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Enantioselective Synthesis of Tetrahydroprotoberberines and Bisbenzylisoquinoline Alkaloids from a Deprotonated α-Aminonitrile

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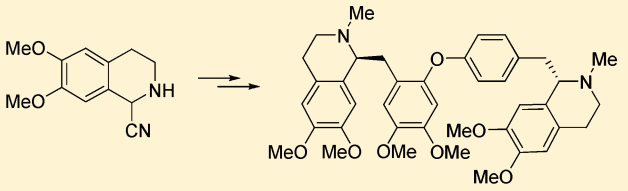
Supporting Information

ABSTRACT: Under controlled conditions, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile can be quantitatively deprotonated in the α-position. Its alkylation directly furnishes 3,4-dihydroisoquinolines which can serve as starting materials for the preparation of various alkaloids. Here, the preparation of the benzylisoquinolines (+)-laudanidine, (+)-armepavine, and (+)-laudanosine as well as the tetrahydroprotoberberines (−)-corytenchine and (−)-tetrahydropseudoepiberberine using Noyori's asymmetric transfer hydrogenation are described. The dimeric alkaloids (+)-*O*-methylthalibrine and (+)-tetramethylmagnolamine were obtained from nonracemic precursors in Ullmann diaryl ether syntheses.



INTRODUCTION

Benzylisoquinoline alkaloids represent a large and important class of natural products.[1−3] The simple tetrahydrobenzylisoquinolines can be isolated mainly from angiosperms.[4] However, they may also serve their producers as the biogenetic precursors of more complex alkaloid families such as the morphinanes, the aporphines, the phthalide isoquinolines, the berbines, or bisbenzylisoquinolines.[4,5] Many representatives of these classes show potent biological activities in both vertebrates and insects, and plants producing such secondary metabolites are believed to benefit from their antifeedant action.

Here, we describe a short enantioselective synthesis[6−9] of several N-methylated benzylisoquinolines, tetrahydroprotoberberines, and two dimeric benzylisoquinolines which uses the alkylation of a deprotonated α-aminonitrile as the key step.

The powerful anion-stabilizing capacity of the cyano group allows Strecker products derived from aromatic or heteroaromatic aldehydes and secondary amines to be deprotonated under relatively mild conditions.[10−13] More surprisingly, even those α-aminonitriles derived from primary amines or ammonia can be α-deprotonated without inducing the impending retro-Strecker reaction, i.e., the base-induced dehydrocyanation, if a proper base such as KHMDS is employed at low temperatures.[14] The resulting keteneiminates can serve as stabilized α-aminocarbanion equivalents in one-pot syntheses of highly substituted α-branched amines, 1,2-diamines, β-amino alcohols, γ-amino acids, or N-heterocycles.[13,15] After the reaction with a suitable electrophile, the nitrile substituent can be removed under mild conditions as delocalization of the amine nitrogen lone pair into the σ*-orbital of the C−CN bond leads to its scission under formation of a protonated imine which can subsequently be trapped by suitable C-nucleophiles or hydride.[16,17]

RESULTS AND DISCUSSION

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile **1** is available in three steps and 52−59% yield from homoveratrylamine.[18−20] Its quantitative deprotonation with KHMDS in THF at −78 °C furnishes a potassium keteneiminate which can be α-alkylated with primary alkyl halides.[19] Surprisingly, the dehydrocyanation of the primary alkylation product occurs spontaneously under the reaction conditions and leads to the consumption of 2 equiv of base. This behavior permits cyanide to be effectively removed from the resulting 3,4-dihydroisoquinolines **3** by washing the organic phase with a $NiCl_2$ solution. Transfer hydrogenation with Noyori's Ru-Ts-DPEN catalyst[21] therefore becomes a viable option for the enantioselective reduction of their C=N double bond and synthesis of *N*-unsubstituted tetrahydroisoquinoline alkaloids[19] as remaining cyanide ions would poison the ruthenium catalyst by ligand exchange. Since secondary amines are produced in the reduction step, subsequent N-alkylations or Pictet−Spengler cyclizations[22] may be used to enhance the structural diversity of the products accessible by this modular strategy. As an example, the alkaloids (+)-laudanidine (**5a**), (+)-armepavine (**5b**), and (+)-laudanosine (**5d**) have been prepared from the corresponding nor-alkaloids **4** by reductive methylation. Similarly, cyclization of compounds **4** with formaldehyde yields (−)-corytenchine (**6a**) and (−)-tetrahydropseudoepiberberine (**6c**), respectively (Scheme 1).[23]

Since the triisopropylsilyl (TIPS) protecting group is labile against the trifluoroacetic acid used in the Pictet−Spengler reaction, complete O-desilylation occurs during cyclization and no additional deprotection step is required. The TIPS group appears to be particularly well suited for the protection of phenolic groups in the presented sequence and the crude

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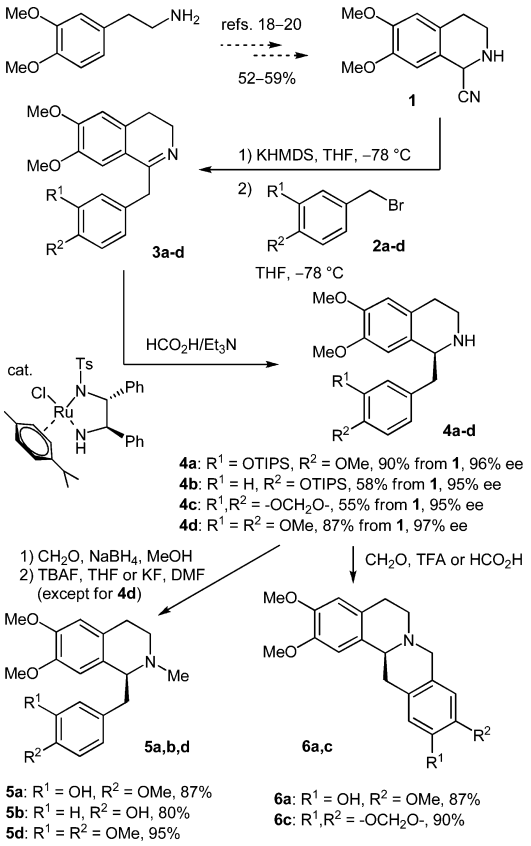
Scheme 1

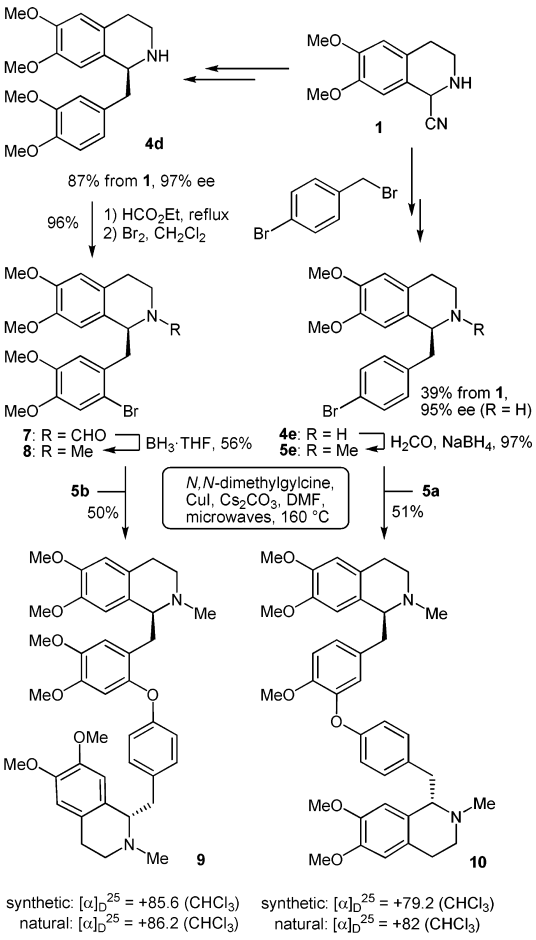


dihydroisoquinolines **3** were generally obtained in high purity. Due to their sensitivity toward aerial oxidation at the α-methylene group, the chromatographic purification of these compounds is not advisable.[24] The development of a one-step procedure for the conversion of **4a**/**4b** to **5a**/**5b** was not undertaken since the overall yields were acceptable.

With a reliable procedure for the preparation of nonracemic benzylisoquinolines at hand, the synthesis of the bisbenzylisoquinolines (+)-tetramethylmagnolamine (**9**)[25] and (+)-*O*-methylthalibrine (**10**)[26] was attempted. Both alkaloids contain a diaryl ether linkage, the formation of which in an Ullmann reaction was chosen as the key step.[25,27−32] Test reactions in the racemic series revealed that formation of the diaryl ether worked best on N-methylated precursors while the coupling of *N*-formyl derivatives gave inferior results with respect to purity and yield. Consequently, bromides **5e** and **8** were selected as key intermediates. While compound **5e** could be obtained by alkylation of **1** with 4-bromobenzyl bromide and subsequent reductive methylation, an *o*-bromine substituent in the benzyl bromide led to a diminished yield of the alkylation reaction. Therefore, norlaudanosine (**4d**) was *N*-formylated and brominated followed by BH_3 reduction to furnish **8** in 54% yield over three steps. Reduction of the formamide with $LiAlH_4$ led to substantial debromination instead. Among the various ligands and conditions tested for the final Ullmann diaryl ether synthesis, the *N*,*N*-dimethylglycine ligand introduced by Ma in combination with microwave heating turned out to give the highest yields.[33] Following this procedure, the synthesis of the dimers **9** and **10** could be completed in 50% and 51% yield, respectively (Scheme 2).

In summary, a simple protocol for the modular enantioselective synthesis of various N-methylated benzylisoquinoline

Scheme 2



alkaloids and tetrahydroprotoberberines was developed. The nor-alkaloids prepared in the asymmetric transfer hydrogenation were also used for the preparation of two bisbenzylisoquinolines in a microwave-accelerated Ullmann diaryl ether synthesis.

EXPERIMENTAL SECTION

All reactions were carried out under argon. Solvents were dried and distilled before use: THF was distilled from K/benzophenone, Et_2O from Na/benzophenone, and CH_2Cl_2 from CaH_2. Ethyl acetate was distilled from K_2CO_3. 4-Methoxy-3-(triisopropylsilanyloxy)benzyl alcohol, 4-methoxy-3-(triisopropylsilanyloxy)benzyl bromide, 4-(triisopropylsilanyloxy)benzyl alcohol, 4-(triisopropylsilanyloxy)benzyl bromide, as well as 6,7-dimethyoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**1**) were prepared according to known procedures.[18,19,34,35] All other solvents and reagents were purchased from commercial suppliers and were used without further purification. TLC was performed on TLC aluminum sheets (silica gel 60 F_{254}). Flash chromatography was carried out on silica gel (35−70 μm). Analytical HPLC separations were performed on a Superspher Si 60 column (4 μm, 125 × 3 mm) or on a Nucleosil 100-5 column (250 × 4.6 mm) using a low-pressure gradient pump and a UV detector. Determination of the enantiomeric excess was performed as described for each compound. ^{1}H NMR and ^{13}C NMR spectra were recorded using standard pulse sequences on high-resolution FT-NMR spectrometers equipped with inverse or direct observe probes and gradient shim units. Peak assignments were based on gradient-selected two-dimensional NMR experiments using standard pulse programs (COSY, HSQC, HMBC). Chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.0 ppm; CD_3OD: δ_H = 3.31 ppm, δ_C = 49.0 ppm). IR spectra were recorded

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on routine FTIR spectrometers in transmission or using a diamond ATR unit. Melting points were measured on a Dr. Tottoli apparatus or a digital melting point apparatus with electric heating. MS spectra were recorded on double-focusing spectrometers (FD-MS, FAB-MS, EI-MS) or on a linear ion trap LC/MSD detector (ESI-MS). ESI-HRMS spectra were recorded on high resolution Q-TOF spectrometer with an dual source and a suitable external calibrant.

General Procedure for the Preparation of the 1-Benzyl-3,4-dihydroisoquinolines (Step 1).[19] In a flame-dried round-bottom flask equipped with a silicone septum and a magnetic stir bar was dissolved 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile[18] **1** (500 mg, 2.29 mmol) in dry THF (15 mL) under argon atmosphere, and the solution was cooled to −78 °C. In a similar vessel, KHMDS (914 mg, 4.58 mmol) was dissolved in THF (10 mL) under argon atmosphere. The KHMDS solution was slowly added to the solution of the aminonitrile. After 5 min at −78 °C, a solution of the benzyl bromide (2.52 mmol, 1.1 equiv) in dry THF (10 mL) was slowly added. The reaction mixture was stirred for 3−4 h at −78 °C (TLC control). The acetone/dry ice bath was removed, and the mixture was gradually warmed to room temperature. After addition of NaOH (1 M, 60 mL), the reaction mixture was extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with a $NiCl_2$ solution (300 mg $NiCl_2{\cdot}6H_2O$ in 30 mL H_2O), aqueous ammonia (10%, 30 mL), and brine (50 mL). After drying over Na_2SO_4, the solvent was removed in vacuo. Because of the sensitivity of the 1-benzyl-3,4-dihydroisoquinolines toward aerial oxidation, these compounds were subjected to asymmetric reduction without further purification.[24]

General Procedure for the Noyori Asymmetric Transfer Hydrogenation (Step 2).[19,21] For the preparation of the ruthenium catalyst, triethylamine (47.8 μL, 434 μmol), dichloro-*p*-cymene−ruthenium(II) dimer (21.6 mg, 34.3 μmol), and (1*R*,2*R*)-*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine (25.2 mg, 68.8 μmol) were dissolved in dry DMF (1.7 mL). The solution was degassed by ultrasonication under argon and heated to 80 °C for 1 h. To the warm solution was added the 1-benzyl-3,4-dihydroisoquinoline as a degassed solution in dry DMF (10 mL). The mixture was cooled to 0 °C, and HCO_2H/Et_3N-azeotrope (5:2, 2.21 mL) was added. The reaction mixture was stirred for 3.5 h at ambient temperature. Saturated aq K_2CO_3 (10 mL) was added, and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting brown oily residue was filtered over a short pad of silica ($EtOAc/HNEt_2$ 4:1) to remove ruthenium species. The 1-benzyl-1,2,3,4-trtrahydroisoquinolines were purified by column chromatography.

1-[4-Methoxy-3-(triisopropylsilanyloxy)benzyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (3a). A solution of KHMDS (620 mg, 3.10 mmol) in dry THF (6 mL) was added at −78 °C to a solution of **1** (339 mg, 1.55 mmol) in dry THF (10 mL). After 4 min, a solution of **2a** (609 mg, 1.63 mmol) in dry THF (8 mL) was added. After being stirred for 3 h at −78 °C, the mixture was warmed to ambient temperature. The reaction mixture was poured into aq NaOH (1 M, 45 mL), and the organic layer was separated. The aqueous layer was extracted with Et_2O (4 × 15 mL). The combined organic layers were washed with a solution of $NiCl_2{\cdot}6H_2O$ (300 mg) in water (30 mL), 10% ammonia (30 mL), and brine (30 mL). After drying over Na_2SO_4 and filtration, the solvent was removed in vacuo to yield the crude imine **3a** as a pale yellow oil (641 mg): R_f = 0.56 ($cyclohexane/EtOAc/HNEt_2$ = 6:3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.91 (s, 1H, H-8), 6.83 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1H, H-6′), 6.75−6.72 (m, 2H, H-2′, H-5′), 6.64 (s, 1H, H-5), 3.94 (s, 2H, Ar-CH_2), 3.87 (s, 3H, OCH_3), 3.72−3.65 (m, 2 × 3H, 2H, OCH_3, H_2-3), 2.63 (t, ^3J = 7.6 Hz, 2H, H_2-4), 1.12−1.07 (m, 3H, CH), 1.05−0.98 (m, 18H, CH_3) ppm. Because of the instability of dihydroisoquinolines against aerial oxidation, the product was subjected to the asymmetric transfer hydrogenation without further purification.

(*S*)-(−)-1-[4-Methoxy-3-(triisopropylsilanyloxy)benzyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4a). The title compound was prepared according to the general procedure from triethylamine (22.7 μL, 206 μmol), dichloro-*p*-cymene−ruthenium(II) dimer (10.0 mg, 16.4 μmol), and (1*R*,2*R*)-*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine (12.0 mg, 33.3 μmol) in dry DMF (0.8 mL). After addition of **3a** (641 mg) in dry DMF (5 mL) to the preformed catalyst, the mixture was cooled to 0 °C, and HCO_2H/Et_3N (5:2, 1.05 mL) was added. The mixture was stirred for 4 h at room temperature. The brown oily crude product (523 mg) was purified by column chromatography (silica gel, petroleum ether/$EtOAc/Et_2NH$, 8:1:1) to give **4a** (477.4 mg, 90%) as a light orange oil. Determination of the enantiomeric excess was carried out by derivatization with (*S*)-α-methylbenzyl isocyanate (er > 99.5:0.5) and analytical HPLC: eluent hexane/EtOAc 75:25, 1 mL min^{-1}, t_R ((*R*)-derivative) 9.4 min, t_R ((*S*)-derivative) 12.5 min, ee = 96%; R_f = 0.5 ($cyclohexane/EtOAc/HNEt_2$ = 6:3:1); $[\alpha]^{25}_D$ −24.9 (*c* = 1, $CHCl_3$); IR (NaCl) ν = 2942, 2865, 1509, 1463, 1269, 1225, 1111, 1032, 994, 882, 834 cm^{-1}; ^{1}H NMR, COSY (500 MHz, $CDCl_3$) δ = 6.79−6.74 (m, 3H, H-2′,H-5′, H-6′), 6.67 (s, 1H, H-5), 6.57 (s, 1H, H-8), 4.08 (dd, ^3J = 8.8 Hz, ^4J = 4.4 Hz, 1H, H-1), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.20−3.15 (m, 1H, H-3_b), 3.10−3.07 (dd,^3J = 17.0 Hz, ^4J = 4.4 Hz, 1H, Ar-CH_b) 2.90−2.84 (m, 2 × 1H, Ar-CH_a, H-3_a), 2.71−2.67 (m, 2H, H_2-4), 1.80 (br. s, 1H, NH), 1.24−1.17 (m, 3H, CH), 1.07 (d, ^3J = 7.5 Hz, 18H, CH_3) ppm; ^{13}C NMR, HMBC, HSQC (125.8 MHz, $CDCl_3$) δ = 149.7, 147.5, 147.2, 145.6 (C-6, C-7, C 3′, C-4′), 131.3 (C-1′), 130.6 (C-8a), 127.6 (C-4a), 122.5 (C-2′), 121.5 (C-6′), 112.3 (C-5), 111.9 (C-5′), 109.5 (C-8), 56.9 (C-1), 56.1, 55.9, 55.7 (3 × OCH_3), 41.6, 41.1 (Ar-CH_2, C-3), 29.7 (C-4), 18.1 (3 × CH), 13.0 (6 × CH_3) ppm; ESI-MS (*m*/*z*) 486.4 (86) $[M + H]^+$, 971.7 (100) $[2\ M]^+$, 972.7 (51) $[2\ M + H]^+$; ESI-HRMS calcd for $[C_{28}H_{43}NO_4Si + H]^+$ 486.3032, found 486.3032.

(*S*)-(−)-1-[4-Methoxy-3-(triisopropylsilanylox)ybenzyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. To a solution of **4a** (49.5 mg, 102 μmol) in MeOH (3.2 mL) was added formalin (37%, 210 μL). After the reaction mixture was stirred for 30 min at room temperature, it was cooled to 0 °C, sodium borohydride (116 mg, 3.07 mmol) was added slowly, and the mixture was allowed to warm to room temperature. Stirring for an additional 30 min and removing the solvent in vacuo furnished a colorless solid which was dissolved in aq NaOH (1 M, 10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give the title compound (45.3 mg, 89%) as a colorless oil: R_f = 0.58 ($cyclohexane/EtOAc/HNEt_2$ = 6:3:1); $[\alpha]^{25}_D$ −28.6 (*c* = 1, $CHCl_3$); IR (NaCl) ν = 3011, 2943, 2866, 1608, 1582, 1515, 1464, 1270, 1227, 1113, 1032, 883, 834 cm^{-1}; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.71−6.69 (m, 2H, H-2′, H-6′), 6.56−6.54 (m, 2H, H-5, H-5′), 6.13 (s, 1H, H-8), 3.83 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.64−3.62 (m, 1H, H-1), 3.61 (s, 3H, OCH_3), 3.15−3.06 (m, 2 × 1H, Ar-CH_a, H-3_a), 2.84−2.69, (m, 3H, Ar-CH_b, H-4_b, H-3_b), 2.61−2.55 (m, 1H, H-4_a), 2.51 (s, 3H, N−CH_3), 1.25−1.18 (m, 3H, CH), 1.06 (d, ^3J = 7.2 Hz, 18H, CH_3) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 149.1, 147.5, 146.5, 145.4 (C-6, C-7, C-3′, C-4′), 132.9 (C-1′), 130.8 (C-8a), 126.0 (C-4a), 122.8 (C-2′), 121.9 (C-6′), 112.0, 111.3, 111.0 (C-5, C-8, C-5′), 65.2 (C-1), 55.9, 55.8, 55.7 (3 × OCH_3), 47.4 (C-3), 42.9 (CH_3), 40.6(Ar-CH_2), 26.0 (C-4), 18.1 (6 × CH_3), 13.0 (3 × CH) ppm; ESI-MS (*m*/*z*) 206.0 (100) $[M - C_{17}H_{29}O_2Si]^+$, 293.0 (18) $[M - C_{12}H_{16}NO_2]^+$, 500.0 (100) $[M]^+$; ESI-HRMS calcd for $[C_{29}H_{45}NO_4Si + H]^+$ 500.3175, found 500.3172.

(+)-Laudanidine, (*S*)-(+)-1-(3-Hydroxy-4-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (5a). A solution of (*S*)-(−)-1-[4-methoxy-3-(triisopropylsilanylox)ybenzyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (37.3 mg, 74.6 μmol) in dry THF (2 mL) was cooled to 0 °C, and TBAF (1 M in THF, 112 μL) was added. The resulting mixture was stirred for 30 min at room temperature, quenched with satd aq NH_4Cl (5 mL), and extracted with CH_2Cl_2 (3 × 5 mL). To remove the remaining silicon compounds, the organic layers were concentrated in vacuo, dissolved in 1 M HCl (5 mL), and extracted with Et_2O (2 × 3 mL). The extract was discarded. The aqueous layers were adjusted to pH 9 with satd aq $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with satd aq NaCl, dried with Na_2SO_4, and

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evaporated to give **5a** (25.1 mg, 98%) as a light yellow solid: mp 182−183 °C (lit.[36] mp 184−185 °C); R_f = 0.23 (cyclohexane/EtOAc/$HNEt_2$ = 6:3:1); $[\alpha]^{25}_D$ +83.7 (*c* 1, $CHCl_3$) (lit.[36] $[\alpha]^{22}_D$ +94.7 (*c* 0.5, $CHCl_3$)); IR (KBr) ν = 3003, 2919, 2849, 1610, 1589, 1512, 1463, 1380, 1268, 1226, 1132, 1100, 1031, 863 cm^{-1}; ^1H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.78 (d, ^4J = 2.0 Hz, 1H, H-2′), 6.73 (d, ^3J = 8.0 Hz, H-5′), 6.56 (s, 1H, H-5), 6.53 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1H, H-6′), 6.05 (s, 1H, H-8), 3.85 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.70 (dd, ^3J = 7.7 Hz, ^4J = 5.3 Hz, 1H, H-1), 3.57 (s, 3H, OCH_3), 3.21−3.17 (m, 1H, H-3_b), 3.12 (dd, *J* = 13.8 Hz, *J* = 5.3 Hz, 1H, Ar-CH_b), 2.87−2.76 (m, 3H, Ar-CH_a H-3_a, H-4_b), 2.66−2.59 (m, H-4_a), 2.52 (s, 3H, N-CH_3) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 147.6 (C-7), 146.6 (C-6), 145.6 (C-4′), 145.2 (C-3′), 133.4 (C-1′), 129.3 (C-4a), 125.2 (C-8a), 121.4 (C-6′), 116.0 (C-2′), 111.4 (C 5′), 111.3 (C-5), 110.6 (C-2′), 65.0 (C-1), 56.2, 55.9, 55.7 (3 × OCH_3), 46.8 (C-3), 42.6 (CH_3), 40.9 (Ar-CH_2), 25.3 (C-4) ppm; ESI-MS *m*/*z* = 242.3 (83), 243.3 (55), 340.3 (34), 344.2 (100) $[M + H]^+$. The spectroscopic data are in accordance with those reported in the literature.[37,38]

(−)-Corytenchine, (*S*)-(−)-11-Hydroxy-2,3,10-trimethoxy-5,8,13,13a-tetrahydro-6*H*-isquino[3,2-*a*]isoquinoline (6a). A suspension of **4a** (46.4 mg, 95.5 μmol), formic acid (88%, 389 μL), and formalin (37%, 264 μL) was stirred at 90 °C for 3.5 h.[39] The resulting yellow reaction mixture was made alkaline with satd aq $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. The yellow solid was triturated with petroleum ether to remove the TIPS group to give **6a** (28.3 mg, 87%) as a yellow solid: mp 243−244 °C (lit.[40] mp 245−246 °C); $[\alpha]^{25}_D$ −251.1 (*c* 1, $CHCl_3$) (lit.[40] $[\alpha]^{25}_D$ −268 (*c* 0.89, $CHCl_3$)); IR (KBr) ν = 3427, 2943, 2866, 1607, 1513, 1463, 1281, 1229, 1138, 1017, 883 cm^{-1}; ^1H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.73 (s, 1H, H-1), 6.71 (s, 1H, H-12), 6.61 (s, 1H, H-4), 6.55 (s, 1H, H-9), 3.95 (d, *J* = 14.4 Hz, 1H, H-8_a), 3.89 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.70 (d, *J* = 14.4 Hz, 1H, H-8_b), 3.64−3.60 (m, 1H, H-13a), 3.23−3.12 (m, 3H, H-5_a, H-6_a, H-13_a), 2.85−2.78 (m, 1H, H-13_b), 2.71−2.61 (m, 2H, H-5_b, H-6_b) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 147.8 (C-2), 147.7 (C-3), 145.3 (C-11), 144.4 (C-10), 129.7 (C-4a), 127.0 (C-8a), 126.7 (C-13b), 125.5 (C-12a), 114.4 (C-12), 111.6 (C-4), 108.8 (C-1), 108.5 (C-9), 59.7 (C-13a), 58.4 (C-8), 56.3, 56.2, 56.0 (3 × OCH_3), 51.4 (C 6), 36.2 (C-13), 29.0 (C-5) ppm; ESI-MS *m*/*z* = 338.2 (100), 340.2 (88) $[M]^+$, 677.4 (29). The spectroscopic data match those reported in the literature.[41]

1-(4-Triisopropylsilanyloxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (3b). The title compound was prepared according to the general procedure from KHMDS (644 mg, 3.23 mmol) in dry THF (8 mL), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile **1** (352 mg, 1.62 mmol) in dry THF (10 mL), and **2b** (610 mg, 1.78 mmol) in dry THF (10 mL). The mixture was stirred for 4 h at −78 °C. After drying over Na_2SO_4, the solvent was removed in vacuo to yield the crude imine **3b** as a yellow oil (1.01 mg): R_f = 0.64 (cyclohexane/EtOAc/$HNEt_2$ = 6:3:1); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.13 (d, ^3J = 8.4 Hz, 2H, H-2′, H-6′), 6.93 (s, 1H, H-8), 6.78 (d, ^3J = 8.4 Hz, 1H, H-3′, H-5′), 6.65 (s, 1H, H-5), 3.98 (s, 2H, Ar-CH_2), 3.88 (s, 3H, OCH_3), 3.74 (t, ^3J = 7.7 Hz, 2H, H_2-3), 3.69 (s, 3H, OCH_3), 2.66 (t, ^3J = 7.7 Hz, 2H, H_2-4), 1.28−1.16 (m, 3H, CH), 1.06 (d, ^3J = 7.5 Hz, 18H, CH_3) ppm.

(*S*)-(−)-1-(4-Triisopropylsilanyloxy)benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4b). The title compound was prepared according to the general procedure from triethylamine (33.7 μL, 306 μmol), dichloro-*p*-cymene−ruthenium(II) dimer (14.8 mg, 24.2 μmol), and (1*R*,2*R*)-*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine (17.7 mg, 49.1 μmol) in dry DMF (1.2 mL). After addition of **3b** (1.61 mmol) in dry DMF (7.2 mL) to the preformed catalyst, the mixture was cooled to 0 °C, and HCO_2H/Et_3N (5:2, 1.56 mL) was added. The mixture was stirred for 4 h at room temperature. The brown oily crude product (1.00 g) was purified by column chromatography (cyclohexane/EtOAc/$HNEt_2$ = 8/1/0.5). Yield over two steps: 430.6 mg (0.94 mmol, 58%), light brown oil. The enantiomeric excess was determined by HPLC after derivatization with (*S*)-α-methylbenzyl isocyanate (er > 99.5:0.5): eluent *n*-hexane/2-propanol = 100/0 → 95/5 (20 min), 1 mL min^{-1}, t_R ((*R*)-derivative) 17.6 min, t_R ((*S*)-derivative) 18.3 min, ee = 95%; R_f = 0.65 (cyclohexane/EtOAc/$HNEt_2$ = 6:3:1); $[\alpha]^{25}_D$ = −6.3 (*c* = 1, $CHCl_3$); IR (NaCl) ν = 2944, 2866, 1608, 1508, 1464, 1260, 1226, 1114, 1012, 883, 854 cm^{-1}; ^1H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.08 (d, ^3J = 8.0 Hz, 2H, H-2′, H-6′), 6.83 (d, ^3J = 8.0 Hz, 2H, H-3′, H-6′), 6.82 (s, 1H, H-8), 6.58 (s, 1H, H-5), 4.12 (dd, ^3J = 12 Hz, ^4J = 4 Hz, 1H, H-1), 3.86 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.23−3.17 (m, 1H, H-3_b), 3.13 (dd, *J* = 12 Hz, *J* = 4 Hz, 1H, Ar-CH_b), 2.91−2.85 (m, 2H, Ar-CH_a, H-3_a), 2.75−2.71 (m, 2H, H_2-4), 2.08 (br s, 1H, NH), 1.29−1.20 (m, 3H, CH), 1.10 (d, ^3J = 7.1 Hz, 18H, CH_3) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 155.1 (C-4′), 147.8 (C-6), 147.3 (C-7), 131.5 (C-1′), 130.6 (C-2′, C-6′), 129.6 (C-4a), 127.6 (C-8a), 120.3 (C-2′, C-5′), 112.1 (C-5), 109.9 (C-8), 57.2 (C-1), 56.3, 56.2 (2 × OCH_3), 42.2 (Ar-CH_2), 41.0 (C-3), 29.7 (C-4), 18.3 (6 × CH_3), 13.0 (3 × CH) ppm; ESI-MS *m*/*z* = 456.29 (100) $[M + H]^+$ ESI-HRMS calcd for $[C_{27}H_{41}NO_3Si + H]^+$ 456.2928, found 456.2928.

(*S*)-(+)-1-(4-Triisopropylsilanyloxy)benzyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (9). To a solution of **4b** (200 mg, 430 μmol) in MeOH (13.7 mL) was added formalin (37%, 903 μL), and the mixture was stirred for 3 h at room temperature. After the mixture was cooled to 0 °C, $NaBH_4$ (498 mg, 13.2 mmol) was added portionwise. The ice bath was removed, and the mixture was stirred for 2 h at room temperature. The solvent was removed in vacuo, and the resulting solid was dissolved in NaOH (1 M, 10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed in vacuo to furnish the title compound (206 mg, quant) as a colorless oil: R_f = 0.58 (cyclohexane/EtOAc/$HNEt_2$ = 6:3:1); $[\alpha]^{25}_D$ = +46.3 (*c* = 1, $CHCl_3$); IR (NaCl) ν = 2945, 29.41, 2868, 1611, 1509, 1465, 1262, 1229, 1104, 1016, 915, 883 cm^{-1}; ^1H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.93 (d, ^3J = 8.0 Hz, 2H, H-2′, H-6′), 6.83 (d, ^3J = 8.0 Hz, 2H, H-3′, H-5′), 6.54 (s, 1H, H-5), 6.04 (s, 1H, H-8), 3.83 (s, 3H, OCH_3(6)), 3.66 (dd, ^3J = 7.6 Hz, ^4J = 4.8 Hz, 1H, H-1), 3.56 (s, 3H, OCH_3(7)), 3.19−3.11 (m, 2H, Ar-CH_b, H-3_b), 2.84−2.71 (m, 3H, Ar-CH_a, H-3_a, H-4_b), 2.60 (dt, ^2J_d = 16 Hz, ^3J_t = 4.8 Hz, 1H, H-4_a), 2.53 (s, 3H, N−CH_3), 1.28−1.19 (m, 3H, CH), 1.09 (m, 18H, CH_3) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 154.5 (C-4′), 147.3 (C-6), 146.4 (C-7), 132.4 (C-1′), 130.8 (C-2′, C-6′), 129.6 (C-4a), 126.0 (C-8a), 119.6 (C-3′, C-5′), 111.3 (C-8), 111.2 (C-5), 65.2 (C-1), 55.9, 55.6 (2 × OCH_3), 47.2 (C-3), 42.9 (N−CH_3), 40.8 (Ar-CH_2), 25.9 (C-4), 18.1 (6 × CH_3), 12.8 (3 × CH) ppm; ESI-MS *m*/*z* = 470.2 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{28}H_{43}NO_3Si + H]^+$ 470.3090, found 470.3094.

(+)-Armepavine, (*S*)-(+)-1-(4-Hydroxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (5b). To a solution of (*S*)-(+)-1-(4-triisopropylsilanyloxy)benzyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (203 mg, 432 μmol) in DMF (11 mL) was added KF (50.2 mg, 863 μmol) in water (1.1 mL). After the mixture was stirred for 30 min at room temperature, HCl (1 M, 10 mL) was added. After extraction with EtOAc (3 × 5 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The yellowish oily crude product was purified by column chromatography (cyclohexane/EtOAc/$HNEt_2$ = 8:6:1) to furnish the title compound (108 mg, 345 μmol, 80%) as a colorless solid: mp 142.5−143 °C (lit.[42] 142−144 °C); R_f = 0.33 (cyclohexane/EtOAc/$HNEt_2$ = 6:4:1); $[\alpha]^{25}_D$ = +94.2 (*c* = 1, $CHCl_3$) (lit.[43] $[\alpha]_D^{22}$ = +96 (*c* = 1, $CHCl_3$)); IR (NaCl) ν = 2937, 2854, 1613, 1513, 1454, 1253, 1227, 1135, 1117, 1015, 861, 830 cm^{-1}; ^1H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.93 (d, ^3J = 8.5 Hz, 2H, H-2′, H-6′), 6.67 (d, ^3J = 8.5 Hz, 2H, H-3′, H-5′), 6.56 (s, 1H, H-5), 6.02 (s, 1H, H-8), 3.83 (s, 3H, OCH_3(7)), 3.71 (dd, ^3J = 7.7 Hz, ^4J = 5.3 Hz, 1H, H-1), 3.57 (s, 3H, OCH_3(6)), 3.26−3.20 (m, 1H, H-3_b), 3.13 (dd, *J* = 13.6 Hz, *J* = 5.3 Hz, 1H, Ar-CH_b), 2.90−2.79 (m, 2H, H-3_a, H-4_b), 2.75 (dd, *J* = 13.6 Hz, *J* = 7.7 Hz, 1H, Ar-CH_a), 2.64−2.62 (m, 1H, H-4_a), 2.53 (s, 3H, N−CH_3) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 154.8 (C-4′), 147.5 (C-7), 146.5 (C-6), 131.0 (C-1′), 130.9 (C-2′, C-6′), 128.7 (C-4a), 125.4 (C-8a), 115.5 (C-3′, C-5′), 111.3 (C-5, C-8), 65.1 (C-1), 55.9, 55.6 (2 × OCH_3), 46.3 (C-3), 42.2 (N−CH_3),

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40.6 (Ar-CH_2), 24.8 (C-4) ppm; ESI-MS m/z = 314.2 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{19}H_{23}NO_3 + H]^+$ 314.1756, found 314.1767. The spectroscopic data match those reported in the literature.[44]

6,7-Dimethoxy-1-(3,4-methylenedioxybenzyl)-3,4-dihydroisoquinoline (3c). The title compound was prepared according to the general procedure from KHMDS (729 mg, 3.66 mmol) in dry THF (8 mL), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile **1** (400 mg, 1.83 mmol) in dry THF (10 mL), and 3,4-methylenedioxybenzyl bromide (414 mg, 1.93 mmol) in dry THF (8 mL). The reaction mixture was stirred for 3.5 h at −78 °C. Extractive workup furnished the title compound (682 mg) as a light yellow oil: R_f = 0.48 (cyclohexane/EtOAc/$HNEt_2$ = 6:4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.06 (s, 1H, H-8), 6.81−6.69 (m, 4H, H-5, H-2′, H-5′, H-6′), 5.91 (s, 2H, OCH_2O), 4.00 (s, 2H, Ar-CH_2), 3.91, 3.90 (s, 2 × 3H, OCH_3), 3.84−3.78 (m, 3H, 2H, OCH_3, H_2-3), 2.76 (t, ^3J = 7.8 Hz, 2H, H_2-4) ppm.

(*S*)-(−)-6,7-Dimethoxy-1-(3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydroisoquinoline (4c). The title compound was prepared according to the general procedure from triethylamine (38.2 μL, 279 μmol), dichloro-*p*-cymene−ruthenium(II) dimer (19.4 mg, 31.7 μmol), and (1*R*,2*R*)-*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine (23.3 mg, 62.3 μmol) in dry DMF (1.3 mL). After addition of **3c** (632 mg, 1.70 mmol) in dry DMF (5.9 mL) to the preformed catalyst, the mixture was cooled to 0 °C, and HCO_2H/Et_3N (5:2, 2.05 mL) was added. The mixture was stirred for 4 h at room temperature. The brown oily crude product (612 mg) was purified by column chromatography (cyclohexane/EtOAc/$HNEt_2$ = 8:1:0.5). Yield over two steps: 304 mg (0.93 μmol, 55%), brownish solid. The enantiomeric excess was determined by HPLC after derivatization with (*S*)-α-methylbenzylisocyanate (er > 99.5:0.5): eluent *n*-hexane/2-propanol = 100:0 → 95:5 (15 min), 1 mL min^{-1}, λ = 242 nm, t_R ((*R*)-derivative) 23.8 min, t_R ((*S*) derivative) 25.2 min, ee = 95%; mp 88−90 °C; R_f = 0.5 (cyclohexane/EtOAc/$HNEt_2$ = 6:4:1); $[\alpha]^{25}_D$ = −12.1 (c = 1, $CHCl_3$); IR (NaCl) ν = 3000, 2939, 2838, 1609, 1503, 1488, 1441, 1247, 1223, 1112, 1038, 929, 860, 811 cm^{-1}; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.77 (d, ^3J = 7.9 Hz, 1H, H-5′), 6.75 (d, ^4J = 1.8 Hz, 1H, H-2′), 6.70 (dd, ^3J = 7.9 Hz, ^4J = 1.8 Hz, 1H, H-6′), 6.63 (s, 1H, H-8), 6.59 (s, 1H, H-5), 5.94 (m, 2H, OCH_2O), 4.10 (dd, ^3J = 9.0 Hz, ^4J = 4.2 Hz, 1H, H-1), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.23−3.17 (m, 1H, H-3$_b$), 3.12 (dd, J = 13.8 Hz, J = 4.4 Hz, 1H, Ar-CH_b), 2.96−2.90 (m, 1H, H-3$_a$), 2.84 (dd, J = 13.8 Hz, J = 9.5 Hz, 1H, Ar-CH_a), 2.78−2.69 (m, 2H, H_2-4), 2.04 (br s, 1H, NH) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 147.9 (C-3′), 147.7 (C-6), 147.3 (C-7), 146.3 (C-4′), 132.9 (C-1′), 130.5 (C-4$_a$), 127.5 (C-8$_a$), 122.5 (C-6′), 112.1 (C-5), 109.7 (C-8), 109.7 (C-2′), 108.5 (C-5′), 101.0 (OCH_2O), 57.1 (C-1), 56.2, 56.0 (2 × OCH_3), 42.5 (Ar-CH_2), 40.8 (C-3), 29.6 (C-4) ppm; ESI-MS m/z = 192.1 (27) $[M - C_8H_7O_2]^+$, 328.2 (100) $[M + H]^+$ ESI-HRMS calcd for $[C_{19}H_{21}NO_4 + H]^+$ 328.1543, found 328.1541.

(−)-Tetrahydropseudoepiberberine, (*S*)-(−)-2,3-Dimethoxy-10,11-methylenedioxy-5,8,13,13a-tetrahydro-6*H*-isoquino-[3,2-*a*]isoquinoline (6c). A suspension of **4c** (20.0 mg, 61.1 μmol), TFA (96.6 μL), and formalin (37%, 169 μL) was stirred at 80 °C for 2.5 h.[45] The resulting yellow reaction mixture was made alkaline with satd aq $NaHCO_3$ and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated to yield **6c** (18.6 mg, 90%) as a yellow solid: mp 148−149 °C (lit.[46] mp 154−156 °C); $[\alpha]^{25}_D$ −124.9 (c = 1, $CHCl_3$); IR (NaCl) ν = 3000, 2905, 2830, 2790, 1685, 1610, 1508, 1485, 1257, 1232, 1135, 1037, 935, 857 cm^{-1}; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.72 (s, 1H, H-1), 6.63 (s, 1H, H-12), 6.61 (s, 1H, H-4), 6.55 (s, 1H, H-9), 5.90 (OCH_2O), 3.89 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.92 (d, J = 14.5 Hz, 1H, H-8$_b$), 3.64 (d, J = 14.5 Hz, 1H, H-8$_a$), 3.56 (dd, J = 11.0 Hz, J = 4.0 Hz, 1H, H-13a), 3.21 (dd, J = 15.7 Hz, J = 4.0 Hz, 1H, H-6$_b$), 3.16−3.10 (m, 2H, H-13$_b$, H-5$_b$), 2.80 (dd, J = 15.7 Hz, J = 11.0 Hz 1H, H-6$_a$), 2.69−2.56 (m, 2H, H-13$_a$, H-5$_a$) ppm; ^{13}C NMR, HSQC, HMBC (400 MHz, $CDCl_3$) δ = 147.8, 147.7 (C-2, C-3), 146.4, 146.1 (C-11, C-10), 129.9 (C-4a), 127.6, 127.6 (C-12a, C-8a), 127.0 (C-13b), 111.7 (C-4), 108.8, 108.8 (C-12, C-1), 106.3 (C-9), 100.9 (OCH_2O), 59.8 (C-13a), 58.9 (C-8), 56.4, 56.1 (2 × OCH_3), 51.6 (C 6), 37.12 (C-13), 29.3 (C-5) ppm; ESI-MS m/z = 192.1 (17) $[M - C_8H_7O_2]^+$, 340.2 (100) $[M + H]^+$ ESI-HRMS calcd for $[C_{20}H_{22}NO_4 + H]^+$ 340.1543, found 340.1549. The spectroscopic data match those reported in the literature.[46]

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (3d). The title compound was prepared according to the general procedure from KHMDS (914 mg, 4.58 mmol) in dry THF (10 mL), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile **1** (500 mg, 2.29 mmol) in dry THF (15 mL), and 3,4-dimethoxybenzyl bromide (582 mg, 2.51 mmol) in dry THF (10 mL). The reaction mixture was stirred for 3.5 h at −78 °C. Workup yielded an orange oil (1.031 g): R_f = 0.39 (cyclohexane/EtOAc/$HNEt_2$ = 6:3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.09 (s, 1H, H-8), 6.94 (d, ^4J = 1.9 Hz, 1H, H-2′), 6.85 (dd, ^3J = 8.1 Hz, ^4J = 1.9 Hz, 1H, H-6′), 6.76 (d, ^3J = 8.1 Hz, 1H, H-5′), 6.68 (s, 1H, H-5), 4.16 (s, 2H, Ar-CH_2), 3.87 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.81 (s, 3H,OCH_3), 3.84−3.74 (m, 3H, 2H, OCH_3, H_2-3), 2.75 (t, ^3J = 7.6 Hz, 2H, H_2-4) ppm.

(−)-Norlaudanosine, (*S*)-(−)-1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (4d). The title compound was prepared according to the general procedure from triethylamine (47.8 μL, 346 μmol), dichloro-*p*-cymene−ruthenium(II) dimer (21.1 mg, 34.4 μmol), and (1*R*,2*R*)-*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine (25.2 mg, 68.7 μmol) in dry DMF (1.7 mL). After addition of **3d** (1.031 g, 2.29 mmol) in dry DMF (10 mL) to the preformed catalyst, the mixture was cooled to 0 °C, and HCO_2H/Et_3N (5:2, 2.21 mL) was added. The mixture was stirred for 4 h at room temperature. The brown oily crude product (842 mg) was purified by column chromatography (cyclohexane/EtOAc/$HNEt_2$ = 8/2/0.5): yield over two steps 680 mg (1.98 mmol, 87%), yellowish oil. The enantiomeric excess was determined by HPLC after derivatization with (*S*)-α-methylbenzylisocyanate (er > 99.5:0.5): eluent *n*-hexane/2-propanol = 95/5, 1 mL min^{-1}, λ = 242 nm, t_R ((*R*)-derivative) 30.5 min, t_R ((*S*) derivative) 33.0 min, ee = 97%; R_f = 0.39 (cyclohexane/EtOAc/$HNEt_2$ = 6:3:1); $[\alpha]^{25}_D$ = −21.5 (c = 1, $CHCl_3$); Lit.[19] $[\alpha]^{25}_D$ = −21.9 (c = 1, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.81−6.75 (m, 3H, H-2′, H-5′, H-6′), 6.66, 6.59 (s, 2 × 1H, H-5, H-8), 4.13 (m, 1H H-1), 3.87, 3.86, 3.85, 3.83 (4 s, 4 × 3H, OCH_3), 3.23−3.15 (m, 2H, H_2-3), 2.92−2.66 (m, 4H, Ar-C H_2, H_2-4), 1.80 (br s, 1H, NH) ppm. The spectroscopic data match those reported in the literature.[19]

(+)-Laudanosine, (*S*)-(+)-1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (5d). To a solution of **4d** (70 mg, 204 μmol, 92% ee) in MeOH (6.4 mL) was added formalin (37%, 420 μL). After the reaction mixture was stirred for 30 min at room temperature, it was cooled to 0 °C, sodium borohydride (232 mg, 613 μmol) was added slowly, and the reaction mixture was allowed to warm to room temperature. Stirring for an additional 40 min and removing the solvent in vacuo furnished a colorless solid which was dissolved in 1 M NaOH (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give **5d** (69.2 mg, 95%) as a pale yellow solid: mp 103−105 °C (lit.[30] 89−90 °C); $[\alpha]^{25}_D$ +86.9 (c = 0.41, EtOH) (lit.[47] +96.6 (c = 0.41, EtOH), lit.[48] +93.6 (c = 0.6, EtOH)); IR (NaCl) ν = 3000, 2935, 2905, 2834, 1611, 1590, 1514, 1465, 1262, 1228, 1140, 1102, 1028, 863 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.76 (d, ^3J = 8.2 Hz, 1H, H-5′), 6.63 (d, ^3J = 8.2, ^4J = 2.1 Hz, 1H, H-6′), 6.60 (d, ^4J = 2.1 Hz, 1H, H-2′), 6.55 (s, 1H, H-5), 6.05 (s, 1H, H-8), 3.84, 3.83 (s, 2 × 3H, OCH_3(4′), OCH_3(6)), 3.78 (s, 3H, OCH_3(3)), 3.69 (dd, J = 7.8 Hz, J = 4.5 Hz, 1H, H-1), 3.57 (s, 3H, OCH_3(7)), 3.20−3.12 (m, 2H, Ar-CH_b, H-3$_b$), 2.86−2.73 (m, 3H, Ar-CH_a, H-3$_a$, H-4$_b$), 2.61−2.54 (m, 1H, H-4$_a$), 2.54 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 148.6 (C-4′), 147.4, 147.3 (C-3), (C-6), 146.4 (C-7), 132.6 (C-1′), 129.3 (C-4a), 126.1 (C-8a), 122.0 (C-6′), 113.1 (C-2′), 111.3 (C-5), 111.2 (C-8), 111.1 (C-5′), 65.0 (C-1), 56.0, 55.9, 55.8 (3 × OCH_3), 55.7 (OCH_3(7)), 47.1 (C-3), 42.8 (CH_3), 41.0 (Ar-CH_2), 25.6 (C-4); ESI-MS m/z = 358.2 (100) $[M + H]^+$. The spectroscopic data match those reported in the literature.[38]

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(*S*)-(+)-1-(3,4-Dimethoxybenzyl)-2-formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. Amine **4d** (234 mg, 681 μmol) was dissolved in ethyl formate (30 mL), and the mixture was refluxed for 2 h.[49] The solvent was removed in vacuo, and the crude product was purified by column chromatography (cyclohexane/EtOAc/$HNEt_2$ = 6:6:1) to yield the title compound (252 mg, quant) as a light yellow foam: mp 133.5−134 °C; R_f = 0.30 (cyclohexane/EtOAc/$HNEt_2$ = 6:3:1); $[\alpha]^{25}_D$ = +84.2 (*c* = 0.5, $CHCl_3$) (lit.[48] $[\alpha]^{24}_D$ = +86.3 (*c* = 1.02, $CHCl_3$)); ^1H NMR (400 MHz, $CDCl_3$, 1:1 mixture of rotamers A and B) δ = 8.14 (CHO^B), 7.70 (CHO^A), 6.81 (d, *J* = 8.5 Hz, 1H, H-5′^{B}), 6.74 (d, *J* = 8.2 Hz, 1H, H-5′^{A}), 6.66 (dd, *J* = 8.3 Hz, *J* = 2.3 Hz, 1H, H-6′^{B}), 6.62−6.59 (m, 4H, H-8^B, H-8^A, H-2′^{A}, H-6′^{A}), 6.57 (s, 1H, H-5^B), 6.50 (s, 1H, H-5^A), 6.33 (s, 1H, H-2′^{B}), 5.52 (t, *J* = 6.5 Hz, 1H, H-1^B), 4.57 (dd, *J* = 8.9 Hz, *J* = 5.0 Hz, 1H, H-1^A), 4.48 (ddd, *J* = 12.8 Hz, *J* = 6.3 Hz, *J* = 2.1 Hz, 1H, H-3^A_b), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3,85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.56 (ddd, *J* = 13.0 Hz, *J* = 6.3 Hz, *J* = 2.2 Hz, 1H, H-3^B_b), 3.30−3.23 (m, 1H, Ar-CH^B_b), 3.17−2.77 (m, 7H, H-3^A_a, Ar-CH_2^A, Ar-CH^B_a, H-3^B_a, H-4^A_b, H-4^B_b), 2.70 (mc, 1H, H-4^A_a), 2.60 (mc, 1H, H-4^B_a) ppm; ESI-MS *m*/*z* = 344.1 (100) $[M - CHO + H]^+$, 327.1 (32) $[M + H]^+$, 394.1 (26) $[M + Na]^+$; ESI-HRMS calcd for $[C_{21}H_{25}NO_5 + Na]^+$ 394.1630, found 394.1620. The spectroscopic data match those reported in the literature.[48]

(*S*)-(+)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7). (*S*)-(+)-1-(3,4-Dimethoxybenzyl)-2-formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (252 mg, 679 μmol) was dissolved in CH_2Cl_2 (2 mL), and saturated aq $NaHCO_3$ (0.5 mL) was added. After addition of Br_2 (38.2 μL, 746 μmol) at 0 °C, the mixture was stirred for 4 h while gradually warming to room temperature.[50] The mixture was quenched by saturated aq $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ and brine (25 mL each) and dried over Na_2SO_4. Concentration in vacuo furnished the title compound (294 mg, 653 μmol, 96%) as a light brown oil: R_f = 0.27 (cyclohexane/EtOAc/$HNEt_2$ = 5:3:1); $[\alpha]^{25}_D$ = +129.4 (*c* = 1, $CHCl_3$); IR (NaCl) ν = 3067, 2999, 2939, 2843, 1669, 1508, 1438, 1258, 1220, 1165, 1114, 1030, 859 cm^{-1}; ^1H NMR, COSY (400 MHz, $CDCl_3$, 2:1 mixture of rotamers A and B) δ = 8.10 (s, 1H, CHO^B), 7.64 (s, 1H, CHO^A), 7.06 (s, 1H, H-3′^{A}), 6.97 (s,1H, H-3′^{B}), 6.73 (s, 1H, H-8^A), 6.70 (s, H1, H-6′^{B}), 6.63 (s, 1H, H-5^A), 6.57 (s, 1H, H-5^B), 6.48 (s, 1H, H-6′^{A}), 6.43 (s, 1H, H-8^B), 5.65 (t, *J* = 6.4 Hz, 1H, H-1^B), 4.75−4.71 (dd, *J* = 9.9 Hz, *J* = 4.1 Hz, 1H, H-1^A), 4.53−4.45 (ddd, *J* = 13.0 Hz, *J* = 6.1 Hz, *J* = 2.0 Hz, 1H, H-3^A_b), 3.88 (s, 3H, $OCH_3{}^A$), 3.87 (s, 3H, $OCH_3{}^A$), 3.84 (s, 9H, $OCH_3{}^A$, 2 × $OCH_3{}^B$), 3.80 (s, 3H, $OCH_3{}^A$), 3.73 (s, 3H, $OCH_3{}^B$(C-4′), 3.70 (s, 3H, $OCH_3{}^B$), 3.66−3.62 (m, 1H, H-3^B_b), 3.59−3.51 (m, 1H, H-3^B_a), 3.33−3.26 (m, 1H, Ar-CH^B_b), 3.25−3.19 (m, 2H, Ar-CH^A_b, H-3^A_a), 3.15−3.10 (m, 1H, Ar-CH^B_a), 3.03−2.98 (m, 1H, Ar-CH^A_a), 2.94−2.87 (m, 2H, H-4^A_b, H-4^B_b) 2.78−2.72 (m, 2H, H-4^A_a, H-4^B_a) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$, 2:1 mixture of rotamers A and B) δ = 161.7 (CHO^A), 161.6 (CHO^B), 149.3 (C-5′^{A}), 149.0 (C-4′^{A}), 148.8 (C-7^A), 148.8 (C-5′^{B}), 148.6 (C-4′^{B}), 148.5 (C-7^B), 148.1 (C-6^A), 148.0 (C-6^B), 129.5 (C-1′^{B}), 129.0 (C-1′^{A}), 127.7 (C-4a^A), 127.5 (C-4a^B), 126.7 (C-8a^B), 126.5 (C-8a^A), 116.2 (C-3′^{A}), 115.7 (C-3′^{B}), 115.7 (C-2′^{A}), 115.0 (C-6′^{A}), 114.8 (C-2′^{B}), 114.4 (C-6′^{B}), 112.0 (C-5^A), 111.8 (C-5^B), 110.8 (C-8^B), 110.3 (C-8^A), 57.3 (C-1^A), 56.6, 56.5, 56.3, 56.1 (4 × $OCH_3{}^A$), 56.5, 56.4, 56.3, 56.2 (4 × $OCH_3{}^B$), 51.2 (C-1^B), 43.5 (Ar-$CH_2{}^A$), 41.4 (Ar-$CH_2{}^B$), 40.9 (C-3^B), 34.7 (C-3^A), 29.5 (C-4^B), 28.1 (C-4^A) ppm; ESI-MS *m*/*z* = 451.0 (100) $[M + H]^+$, 472.0 (40) $[M + Na]^+$ ESI-HRMS calcd for $[C_{21}H_{24}BrNO_5 + H]^+$ 450.0916, found 450.0930.

(*S*)-(+)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8). In a flame-dried round-bottom flask, **7** (18.2 mg, 40.4 μmol) was dissolved in dry THF (2 mL) under argon atmosphere. BH_3·THF (1 M in THF, 40.4 μL) was slowly added at 0 °C, and the mixture was stirred for 1.5 h at room temperature.[51] After addition of aq HCl (1 M, 5 mL), the mixture was heated to 100 °C for 4 h. The cooled reaction mixture was washed with EtOAc (2 × 5 mL), the aqueous layer was made alkaline by addition of aq NaOH (1 M), and the product was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product (13.8 mg, yellow oil) was purified by preparative TLC (cyclohexane/EtOAc/$HNEt_2$ = 5:3:1) to furnish the title compound (9.8 mg, 0.22 μmol, 56%) as a colorless oil: mp 156.5−158 °C (lit.[30] 146 °C); R_f = 0.36 (cyclohexane/EtOAc/$HNEt_2$ = 6:3:1); $[\alpha]^{25}_D$ = +40.1 (*c* = 0.5, $CHCl_3$) (lit.[52] $[\alpha]_D$ = +44 ($CHCl_3$)); ^1H NMR (400 MHz, $CDCl_3$) δ = 6.98 (s, 1H, H-3′), 6.60 (s, 1H, H-6′), 6.57 (s, 1H, H-5), 5.94 (s, 1H, H-8), 3.86−3.84 (m, 1H, H-1), 3.83, 3.83, 3.72, 3.53 (4s, 4 × 3H, OCH_3), 3.40−3.22 (m, 2H, H-3$_b$, Ar-CH_b), 2.95−2.90 (m, 3H, H-3$_a$, Ar-CH_a, H-4$_a$), 2.79−2.71 (m, 1H, H-4$_b$), 2.60 (s, 3H, N-CH_3) ppm; IR (NaCl) ν = 2999, 2932, 2837, 2797, 1607, 1506, 1462, 1379, 1254, 1218, 1161, 1137, 1101, 1029, 859, 800 cm^{-1}; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 148.3, 148.1, 147.9, 146.7 (C-6, C-7, C-4′, C-5′), 130.5 (C-4a), 125.5 (C-8a), 115.4, 115.2 (C-3′, C-6′), 115.1 (C-2′), 111.3 111.2 (C-5, C-8), 62.1 (C-1), 56.3, 56.2, 56.0, 55.7 (4 × OCH_3), 46.7 (C-3), 42.4 (N−CH_3), 40.6 (Ar-CH_2), 24.8 (C-4) ppm; ESI-MS *m*/*z* = 436.1 (100) $[M + H]^+$ ESI-HRMS calcd for $[C_{21}H_{26}BrNO_4 + H]^+$ 436.1123, found 436.11102.

(+)-*O*-Tetramethylmagnolamine (9). In a flame-dried, argon-flushed microwave reaction glass vessel were suspended (+)-armepavine (**5b**, 10.7 mg. 34.3 μmol), bromide **8** (15 mg, 34,3 μmol), Cs_2CO_3 (33,6 mg, 103 μmol), CuI (0.7 mg, 3.43 μmol), and *N*,*N*-dimethylglycine (1.44 mg, 3,43 μmol) in dry DMF (0.25 mL). The mixture was heated to 160 °C for 1 h by microwave irradiation (monomode, IR-temperature control, maximum power 150 W). After cooling and pressure equilibration, the reaction mixture was coevaporated with toluene. The desired diaryl ether was purified by column chromatography (cyclohexane/EtOAc/$HNEt_2$ = 7:1:0.5). After addition of petroleum ether, the crude product (brow oil) crystallized as a beige solid (11.5 mg, 17.2 μmol, 50%): R_f = 0.4 (cyclohexane/EtOAc/$HNEt_2$ = 6:3:1); mp 145.3−145.9 °C (lit.[30] 148−149.5 °C); $[\alpha]^{25}_D$ = +85.6 (*c* = 1, $CHCl_3$) (lit.[29] $[\alpha]^{25}_D$ = +86.2 (*c* = 1.02, $CHCl_3$)); IR (NaCl) ν = 2999, 2930, 2854, 2836, 1609, 1502, 1464, 1289, 1253, 1217, 1102, 1005, 912, 861 cm^{-1}; ^1H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.01 (d, ^3J = 8.8 Hz, 2H, H-2′, H-6′), 6.76 (d, ^3J = 8.8 Hz, 2H, H-3′, H-5′), 6.58 (s, 1H, H-2‴), 6.54 (s, 2H, H-5, H-5″), 6.51 (s, 1H, H-5‴), 6.13, 6,12 (2 s, 2H, H-8, H-8″), 3.83, 3.82, 3.76, 3.76 (4 s, 12H, 4 × OCH_3), 3.72−3.72, 3.69−3.67 (2 m, 2H, H-1, H-1″), 3.61, 3.58 (2 s, 6H, 2 × OCH_3), 3.20−3.09 (m, 3H, H-3$_b$, H-3$_b$″, Ar-CH_b), 3.00 (dd, *J* = 13.4 Hz, *J* = 6.0 Hz, 1H, Ar-CH_b″), 2.85−2.67 (m, 6H, H-3$_a$, H-3$_a$″, Ar-CH_a, Ar-CH_a″, H-4$_b$, H-4$_b$″), 2.60−2.53 (m, 2H, H-4$_a$, H-4$_a$″) ppm;^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 157.2 (C-1′), 148.2, 147.4, 147.4, 147.2, 146.6, 146.5 (C-6, C-7, C-6″, C-7″, C-3‴, C-4‴), 141.5 (C-1‴), 133.6 (C-4′), 131.0 (C2′, C-6′), 129.8, 129.3 (C-4a, C-4a″), 126.3, 126.3 (C-8a, C-8a″), 123.9 (C-6‴), 116.0 (C-3′, C-5′), 114.8 (C-2‴), 111.3, 111.2, 111.1, 111.0 (C-5, C-5″, C-8, C-8″), 106.1 (C-5‴), 64.9, 63.4 (C-1, C-1″), 56.3, 56.2, 55.9, 55.8 55.7, 55.7 (6 × OCH_3), 47.0, 46.9 (C-3, C-3″), 42.9, 42.8 (2 × N−CH_3), 40.7, 35.0 (Ar-CH_2, Ar-CH_2″), 28.8, 25.4 (C-4, C-4″) ppm; ESI-MS *m*/*z* = 335.1 (100) $[M + 2H]^{2+}$; ESI-HRMS calcd for $[C_{40}H_{48}N_2O_7 + H]^+$ 669.3540, found 669.3533. The spectroscopic data match those reported in the literature.[30]

(*S*)-(−)-1-(4-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4e). The title compound was prepared according to the general procedure from KHMDS (914 mg, 4.58 mmol) in dry THF (10 mL), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile **1** (500 mg, 2.29 mmol) in dry THF (15 mL), 4-bromobenzyl bromide (630 mg, 2.52 mmol) in dry THF (10 mL). The mixture was stirred for 3.3 h at −78 °C. Workup yielded a light yellow oil (1.016 g): R_f = 0.75 (cyclohexane/EtOAc/$HNEt_2$ = 6:3:1);^1H NMR (400 MHz, $CDCl_3$) δ = 7.39 (d, ^3J = 8.0 Hz, 2H, H-3′ H-5′), 7.18 (d, ^3J = 8.0 Hz, 2H, H2′, H-6′), 6.97 (s, 1H, H-5), 6.67 (s, 1H, H-8), 4.17 (s, 2H, Ar-CH_2), 3.91 (s, 3H, OCH_3), 3.76−3.67 (m, 5H, 2H, OCH_3, H_2-3), 2.75 (t, ^3J = 7.5 Hz, 2H, H_2-4) ppm. The asymmetric transfer hydrogenation was performed according to the general procedure using triethylamine (47.8 μL, 434 μmol), dichloro-*p*-cymene-ruthenium(II) dimer (21.6 mg, 34.3 μmol), and (1*R*,2*R*)-*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine (25.2 mg, 68.8 μmol) in

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dry DMF (1.7 mL). The dihydroisoquinoline (1.016 g, 2.29 mmol) in dry DMF (10 mL) and HCO_2H/Et_3N-azeotrope (5:2, 2.21 mL) were added. The reaction time amounted to 4 h. The brown oily crude product (1.048 g) was purified by column chromatography (cyclohexane/EtOAc/$HNEt_2$ = 7:1:0.5) to furnish 326 mg (0.90 μmol, 39% over 2 steps) of a yellowish oil. The enantiomeric excess was determined by HPLC after derivatization with (*S*)-methylbenzylisocyanate (er > 99.5:0.5): eluent *n*-hexane/2-propanol = 95:5, 1 mL min^{-1}, λ = 242 nm, t_R ((*R*)-derivative): 12.4 min, t_R ((*S*) derivative): 13.2 min, ee = 95%; R_f = 0.65 (cyclohexane/EtOAc/$HNEt_2$ = 6:3:1); $[\alpha]^{25}_D$ = −8.5 (*c* = 1, $CHCl_3$); IR (NaCl) ν = 2999, 2931, 2830, 1609, 1510, 1487, 1463, 1324, 1259, 1221, 1111, 1011, 857, 801, 781 cm^{-1}; ^1H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.44 (d, ^3J = 8.5 Hz, 2H, H-3′, H-5′), 7.13 (d, ^3J = 8.5 Hz, 2H, H-2′, H-6′), 6.60 (s, 1H, H-5), 6.59 (s, 1H, H-8), 4.15−4.10 (m, 1H, H-1), 3.86 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.22−3.13 (m, 2H, Ar-CH_b, H-3$_b$), 2.95−2.84 (m, 2H, Ar-CH_a, H-3$_a$), 2.79−2.63 (m, 2H, H_2-4) ppm; ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 148.2 (C-7), 147.5 (C-6), 138.1 (C-1′), 132.0 (C-2′, C-6′), 131.6 (C-3′, C-5′), 129.6 (C-4a), 127.3 (C-8a), 120.8 (C-4′), 112.3 (C-5), 109.9 (C-8), 56.9 56.3, 56.2 (C-1, 2 × OCH_3), 42.4 (Ar-CH_2), 40.8 (C-3), 29.3 (C-4) ppm; ESI-MS *m*/*z* = 362.07 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{18}H_{20}BrNO_2 + H]^+$; *m*/*z* = 362.0756, found 362.0756.

(*S*)-(+)-1-(4-Bromobenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5e). To a solution of **4e** (104 mg, 287 μmol) in MeOH (9 mL) was added formalin (37%, 592 μL). The reaction mixture was stirred for 30 min at room temperature. After cooling to 0 °C, $NaBH_4$ (326 mg, 8.62 mmol) was added portionwise.[53] The ice bath was removed, and the mixture was stirred for 1 h at room temperature. After concentration in vacuo and addition of aq NaOH (1 M, 10 mL), the reaction mixture was extracted with CH_2Cl_2 (4 × 10 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo to furnish the title compound (105 mg, 279 μmol, 97%) as a light yellow oil: R_f = 0.48 (cyclohexane/EtOAc/$HNEt_2$ = 6:3:1); $[\alpha]^{25}_D$ = +35.3 (*c* = 0.8, $CHCl_3$); IR (NaCl) ν = 3055, 2935, 2850, 2832, 1509, 1487, 1464, 1253, 1227, 1102, 1010, 860 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.35 (d, ^3J = 8.0 Hz, 2H, H-3′, H-5′), 6.96 (d, ^3J = 8.0 Hz, 2H, H-2′, H-6′), 6.54 (s, 1H, H-5), 6.06 (s, 1H, H-8), 3.84 (s, 3H, OCH_3(7)), 3.68 (t, ^3J = 7.0 Hz, 1H, H-1), 3.61 (s, 3H, OCH_3(6)), 3.41−3.35 (m, 1H, H-3$_b$), 3.19−3.10 (m, 2H, Ar-CH_b, H-3$_a$), 2.84−2.71 (m, 2H, Ar-CH_a, H-4$_b$), 2.57−2.55 (m, 1H, H-4$_a$), 2.51 (s, 3H, N−CH_3) ppm; ^{13}C NMR, HMBC (100.6 MHz, $CDCl_3$) δ = 147.5 (C-7), 146.6 (C-6), 139.0 (C-1′), 131.7 (C-2′, C-6′), 131.2 (C-3′, C-5′), 128.7 (C-4a), 126.2 (C-8a), 120.0 (C-4′), 111.3 (C-5), 110.9 (C-8), 64.8 (C-1), 55.9, 55.7 (2 × OCH_3), 46.0 (C-3), 42.8 (N−CH_3), 40.7 (Ar-CH_2), 25.5 (C-4) ppm; ESI-MS *m*/*z* = 376.09 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{19}H_{22}BrNO_2 + H]^+$ 376.0912, found 376.0927.

(+)-*O*-Methylthalibrine (10). In a flame-dried, argon-flushed microwave reaction glass vessel were suspended (+)-laudanidine **5a** (5.3 mg. 15.4 μmol, 95% ee), bromide **5e** (5.8 mg, 15.4 μmol), Cs_2CO_3 (15.2 mg, 46.6 μmol), CuI (0.29 mg, 1.54 μmol), and *N*,*N*-dimethylglycine (0.65 mg, 4.66 μmol) in dry DMF (0.3 mL). The mixture was heated to 160 °C for 1.5 h by microwave irradiation (monomode, IR-temperature control, maximum power 150 W). After cooling and pressure equilibration, the reaction mixture was coevaporated with toluene. The desired diaryl ether was purified by column chromatography (cyclohexane/EtOAc/$HNEt_2$ = 6:1:0.5). The product crystallized after addition of diethyl ether as a beige solid (5.0 mg, 7.83 μmol, 51%): R_f = 0.33 (cyclohexane/EtOAc/$HNEt_2$ = 6:3:1); mp 126.2−127.4 °C; $[\alpha]^{25}_D$ = +79.2 (*c* = 0.45, $CHCl_3$) (lit.[54] $[\alpha]_D$ = +82 (*c* = 0.36, $CHCl_3$)); IR (NaCl) ν = 2999, 2928, 2854, 2832, 1608, 1507, 1464, 1255, 1226, 1124, 1102, 1015, 860 cm^{-1}. ^1H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.98 (d, ^3J = 8.6 Hz, 2H, H-2′, H-6′), 6.86 (d, ^3J = 8.4 Hz, 1H, H-5‴), 6.81 (dd, ^3J = 8.4 Hz, ^4J = 1.9 Hz, 1H, H-6‴), 6.75 (d, ^3J = 8.6 Hz, 2H, H-3′, H-5′), 6.69 (d, ^4J = H-2‴), 6.54, 6.50 (2 s, 2H, H-5, H.5″), 6.03, 5.96 (2 s, 2H, H-8, H-8″), 3.81, 3.79 (OCH_3(6, 6″)), 3.78 (OCH_3(4‴)), 3.68−3.63 (m, 2H, H-1, H-1″), 3.58, 3.54 (OCH_3(7, 7″)), 3.25−3.08 (m, 4H, H-3$_b$, H-3$_b$″, Ar-CH_b, Ar-CH_b″), 2.87−2.70 (m, 7H, H-3$_a$, H-3$_a$″, Ar-CH_a, Ar-CH_a″, H_2-4, H-4$_b$″), 2.65−2.58 (m, 1H, H-4$_a$″), 2.54, 2.49 (2 s, 6H, 2 × N−CH_3) ppm;^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 156.5 (C-4′), 149.9 (C-4‴), 147.5, 147.0 (C-6, C-6″), 1146.5, 146.5 (C-7, C-7″), 144.6 (C-4‴), 133.0 (C-1‴), 132.8 (C-1′), 131.0 (C-2′, C-6′), 128.6 (C-8a, C-8a″), 126.2 (C-6‴), 125.9 (C-4a, C-4a″), 122.6 (C-2‴), 116.9 (C-3′, C-5′), 112.6 (C-5‴), 111.3, 111.2, 111.1, 111.0 (C-5, C-5″, C-8, C-8″), 65.0, 64.8 (C-1, C-1″), 56.2, 55.9, 55.9, 55.7, 55.6 (5 × OCH_3), 46.8, 46.6 (C-3, C-3″), 42.6, 42.4 (2 × N−CH_3), 40.7, 40.4 (Ar-CH_2, Ar-CH_2″), 25.3, 25.2 (C-4, C-4″) ppm; ESI-MS *m*/*z* = 639.2 (100) $[M + H]^+$; ESI-HRMS calcd for $[C_{39}H_{46}N_2O_6 + H]^+$ 639.3434, found 639.3437. The spectroscopic data match those reported in the literature.[26,54]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of compounds **4**−**10** as well as HPLC chromatograms for the determination of the optical purity. This material is available free of charge via the Internet at http://pubs.acs.org.

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