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ASYMMETRIC SYNTHESIS OF ISOQUINOLINE ALKALOIDS#

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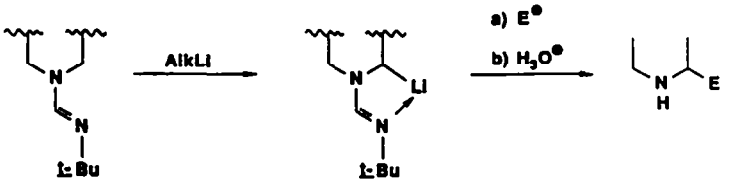
Abstract - The use of chiral formamidines affixed to variously substituted tetrahydroisoquinolines, allows asymmetric C-C bond forming reactions to occur α- to the amino group. In this manner, a wide variety of (S)-1-alkyl-1,2,3,4-tetrahydroisoquinolines were constructed in > 90% enantiomeric excess. Choosing the proper substituents and skeletal features, an efficient entry into the benzylisoquinoline, tetrahydroprotoberberine, aporphine, and isopavine class of alkaloids was achieved.

Over the past several years, we have described a synthetic method which allows metalation adjacent to amine nitrogen by virtue of an appended formamidine moiety (Scheme 1). Alkylation

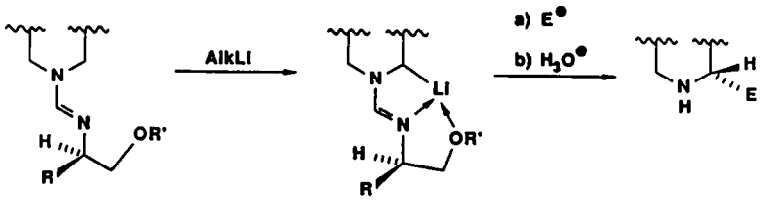
SCHEME 1



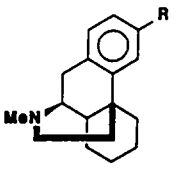
with a variety of electrophiles and hydrolytic removal of the formamidine furnished 2-substituted amines in generally good yields.[1] Although α-lithiated amine derivatives have been reported and shown to have wide synthetic utility,[2] none of these provide for the introduction of a suitable chiral auxiliary such that the alkylated amines obtained would be a single enantiomer. This highly coveted process, without precedent, was recently reported from this laboratory which has to date led to a number of natural and unnatural products in high enantiomeric excess (Scheme 2). We have described, with full details, an asymmetric synthesis of (+)-morphinans (1),[3] (-)-deplancheine (2),[4] (+)-metazocine (3),[5] while reporting in preliminary form, approaches to (+)-anisomycin (4),[6] and several examples of natural isoquinoline alkaloids, 5[7]and 6,[8] as well as other related systems.[8,9] Recent work in our laboratory has also focused on the mechanistic aspects[10] of this important process.

#This work is dedicated to a dear colleague, Professor Hans Wynberg on the occasion of his 65th birthday.

SCHEME 2



We now report full details of our general asymmetric synthesis of isoquinoline alkaloids 5, 6 and others not yet described (vide infra). What is clear from the results is that a powerful method to generate optically pure (or nearly so) natural alkaloids of the isoquinoline class is in hand.



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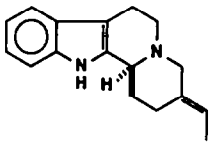

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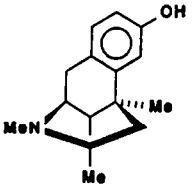

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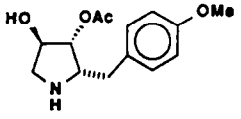

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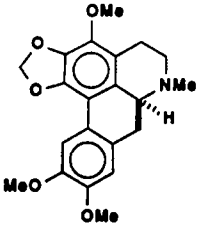

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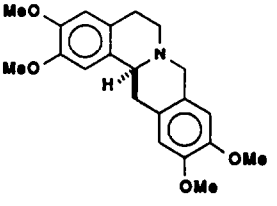

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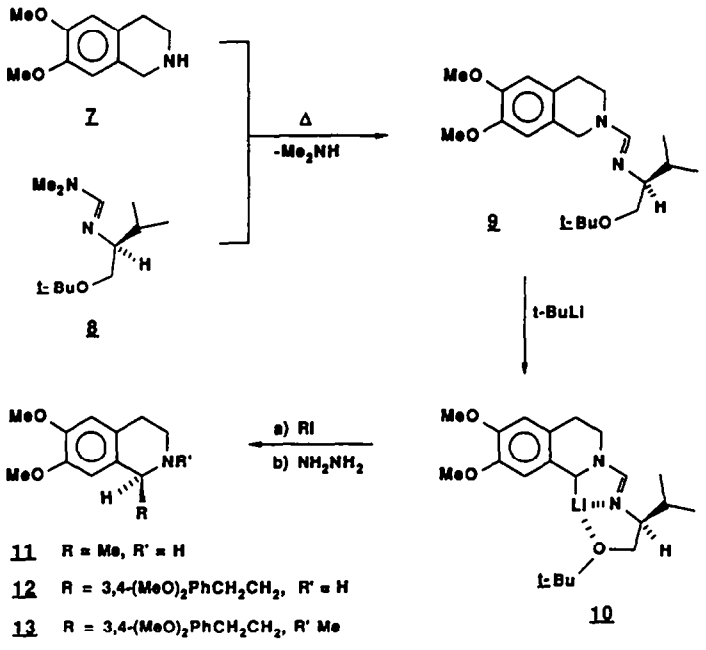
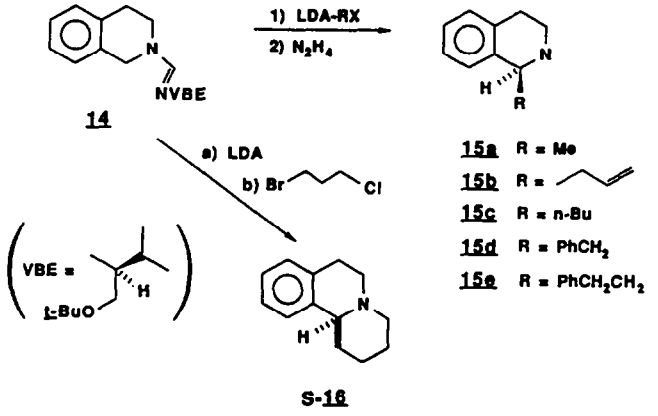
(-)-Salsolidine and (+)-Homolaudanosine

The simple natural isoquinoline alkaloids, salsolidine 11 and homolaudanosine 13 were readily reached by initiating the synthesis with commercially available 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 7. Treatment with the formamidine of valinol tert-butyl ether 8[5] in refluxing toluene resulted in an exchange to 9 and concomitant loss of dimethyl amine. The formamidine equipped isoquinoline could, if necessary, be purified either by chromatography or distillation and completely characterized. However, flash chromatography usually gave material of sufficient purity for metalation-alkylation. When 9 was treated with 1.1 equiv tert-butyllithium (-78°, THF, 30 min) a deep red solution appeared which was rapidly decolorized on addition of methyl iodide. The resulting methylated formamidine was then subjected to hydrazine-acetic acid to remove the formamidine moiety and also release valinol tert-butyl ether. The latter can be recovered[3] and reutilized by transforming it into 8.[5] In this manner, (-)-salsolidine 11 was produced in 61% yield (from 9) and 95% enantiomeric excess. This enantiomeric purity was based on comparison of specific rotation of the natural and synthetic material. Similar alkylation of 10 with 3,4-dimethoxyphenethyl iodide followed by hydrazine treatment gave the 1-substituted isoquinoline 12, which was transformed into the formamide and reduced to the N-methyl derivative, known as (+)-homolaudanosine, 13. The natural isoquinoline alkaloid was obtained in 46-48% overall yield (from 9) and when compared to natural material was found to be 95-96% optically pure.

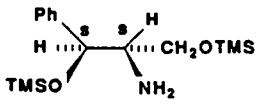


Similarly high levels of enantiomeric purity were found using unsubstituted tetrahydroisoquinolines. The commercially available material was transformed, as above, into the valine-based chiral auxiliary 14. In this instance, metalation took place smoothly with lithium diisopropylamide and was complete in 15 min at -78° in THF. This was verified with methanol-D

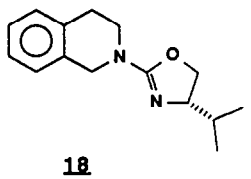


quench experiments. Alkylation with various alkyl iodides or bromides was equally rapid (~ 15 min) at -95° C. The temperature of the lithiated formamidine was always lowered to -95 ± 5° C to maximize stereoselectivity in the alkylation step. Hydrazine treatment afforded the 1-alkyltetrahydroisoquinolines 15 in 93-99% ee and yields of 60-94%, based on 14. All of the enantiomeric determinations are based on chiral HPLC analyses (Pirkle Column)[11] and direct comparisons made with racemic products.[12] With regard to the absolute configuration, the valine-based chiral auxiliary provided products with the same absolute stereochemistry as that obtained earlier with the bis-silylated phenylaminodiol,[9b] 17. Thus, metalation of 14, alkylation with 3-bromo-1-chloropropane, and hydrazine treatment gave the benzoquinolizidine, 16 in 72% yield and 99% optical purity, based on the known, naturally derived material, whose absolute configuration is also known to be S. It may therefore be concluded that the 1-alkyltetrahydroisoquinoline 15 (a-e) also possess the same stereochemical sense, with the alkyl halide entering from the β-face. This has recently been confirmed by two independent studies.[10,13]

In another approach, albeit quite closely related, Gawley[14] has utilized a chiral oxazoline affixed to a tetrahydroisoquinoline (18) to effect metalation and alkylation with a high degree of



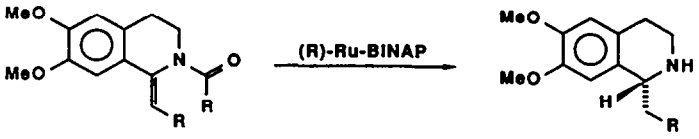
17 (BISPAD)



18

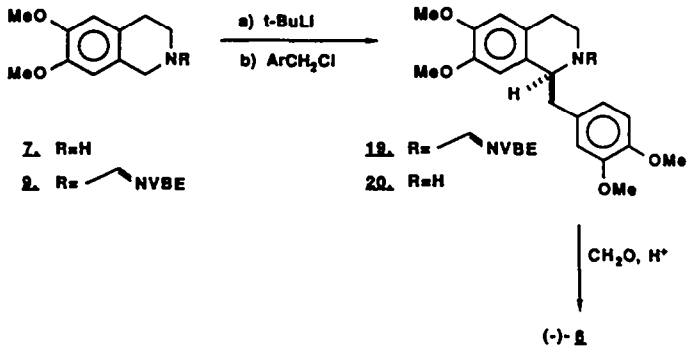
diastereoselectivity (~ 90%). This variation on the formamidine methodology promises to be of considerable synthetic value. In another major advance, Noyori[15] has reported the asymmetric catalytic hydrogenation of unsaturated amides in isoquinoline systems furnishing a variety of alkaloids in >95% ee (Scheme 3).

SCHEME 3

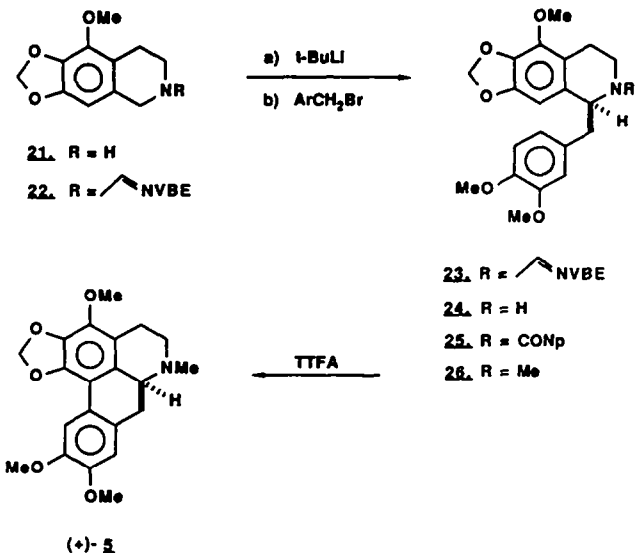


(-)-Norcoralydine and (+)-Ocoteine

An asymmetridc route to the tetrahydroprotoberberine (6) and the aporphine (5) class of alkaloids was also successfully implemented by the ready formation of 1-benzylisoquinolines in high enantiomeric excess. Thus starting from the dimethoxy isoquinoline 7, as before, and transforming it to the chiral formamidine, 9, we were able to metalate with t-butyl lithium and alkylate with the requisite benzyl halide affording 19, which was directly treated with hydrazine to produce 20. Without purification, the latter was treated with formalin solution in the presence of hydrochloric acid to furnish (-)-norcoralydine, 6 in 37% overall yield (from 9) with an enantiomeric purity of 98.5%, when compared to the natural product. This sequence demonstrates the rapid and efficient route to this class of isoquinoline alkaloids, by foregoing purification of the intermediates. This synthesis has not been optimized and future work is expected to lead to higher overall yields.



The route to the aporphine system, (+)-ocoteine (5) basically required the same initial strategy. The appropriately substituted tetrahydroisoquinoline 21 was prepared via literature procedures and transformed into its formamidine 22. Metalation with 1.3 equiv t-butyllithium and addition of 3,4-dimethoxybenzyl bromide at -100° gave the alkylated material 23 which was directly transformed into the 1-benzyltetrahydroisoquinoline 24 in 82% overall yield (from 22). The enantiomeric excess of 24 was determined by chiral HPLC analysis[11] on the α-naphthoyl derivative 25, which indicated a 96.5:3.5 ratio of enantiomers (93% ee). N-methylation of 24 was carried out

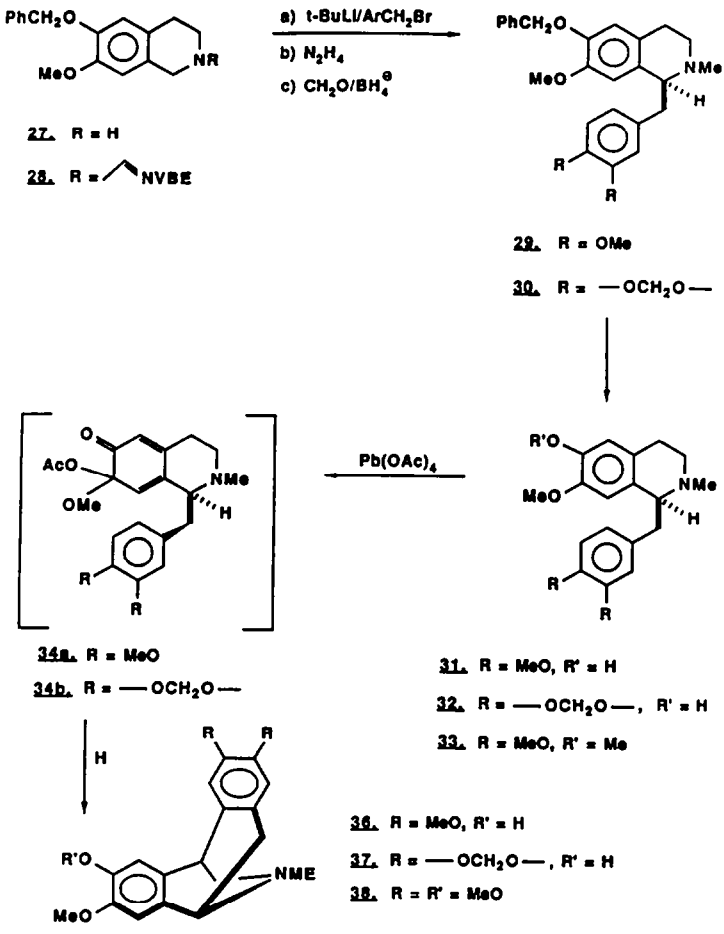


either by formaldehyde-sodium borohydride treatment (76%) or via the lithio salt of 24 and methyl iodide quench (90%) furnishing 26. Non-phenolic biaryl oxidation of 26 into (+)-ocoteine, 5 proceeded in 48-50% yield using 0.6 equiv of thallium (III) trifluoroacetate according to the procedure of Taylor and McKillop.[16] Spectral data were identical to that reported[16] for the racemic material. The specific rotation obtained for (+)-5 (32.1°) was also quite close to the literature[17] value (36-37°) and the sign of rotation supports the fact that the natural S-enantiomer was produced. The "true" enantiomeric purity, we feel, is based on the chiral HPLC analyses (96.5:3.5; 93% ee) whereas the comparison of specific rotations gave only qualitative agreement. More importantly, however, the thallium biaryl coupling proceeded with little or no racemization during the radical cation process.[16]

(-)-Reframoline and (-)-Methylthalisopavine

Further studies on the alkylation of 1,2,3,4-tetrahydroisoquinolines were directed toward the asymmetric synthesis of the isopavine alkaloids, (-)-O-methyl thalisopavine 36, and (-)-reframoline 37. This sequence originated from the properly substituted tetrahydroisoquinoline 27, prepared in high overall yield from isovanillin . The formamidine moiety was affixed as described earlier to afford the key intermediate 28 in 92% yield. Metalation of the latter using tert-butyllithium was performed at -100° C and was complete in 25 min after which the appropriately substituted benzyl bromide was added (-100° C) furnishing the respective 1-benzyl derivatives. The formamidine moiety was removed without purification of the previous product via the hydrazine treatment and the secondary amine transformed immediately, with formaldehyde-sodium borohydride, to the N-methyl derivatives 29 and 30. These tertiary amines were found to be much more stable to air oxidation and could be easily purified by chromatographic means. The overall yields of 29 and 30, based on starting material 27, was 70 and 53%, respectively.

In order to cyclize these 1-benzyl isoquinolines to the isopavine alkaloids, a free hydroxyl in the isoquinoline ring was required. Thus, hydrogenolysis of 29 and 30 gave 31 and 32 in over 90% yield using palladium on carbon. In order to assess the extent of asymmetric alkylation in 29 and 30, it was necessary to transform one of these compounds into a known naturally occurring isoquinoline alkaloid and compare their optical rotations. It was easiest to take 31, with the three methoxyl groups and simply methylate the free hydroxyl to acquire natural (+)-laudanosine, 33. Thus, diazomethane treatment of 31 gave (+)-laudanosine 33, $[\alpha]_D$ +92° which compared with the literature rotation[19] of $[\alpha]_D$ +107°. Based on this value, the optical purity of 31, 32, and 33 can be assumed to be at least 86-90% which is roughly typical of the range of optical purity seen for the other derivatives in this study (ca 90-95% ee). However, as is generally agreed among workers in this field, specific rotations are only of semiquantitative value, and the enantiomeric purity could indeed be higher by 5-10%.



The next and last stage of the synthesis to reach the isopavines (36, 37) was to oxidize the respective 1-benzylisoquinolines with lead tetraacetate to their ortho quinol acetates as described earlier[20,21] and then, without any attempt at isolation, cyclize with acid. In this manner (-)-3-desmethyl-O-methylthalisopavine 36 was obtained in 50% yield from the isoquinoline 31, whereas (-)-reframoline 37 was obtained in only 9-10% yield from 32. Based on the literature rotations, reframoline (37) was found to be 98-99% optically pure, while desmethyl-O-methylthalisopavine, 36 and its methylated analog 38, both known in the literature (but no specific rotations are reported[22]) could not be compared. However, based upon the chiral HPLC behavior and the enantiomeric purity of 31 considered to be 86-90% ee we feel justified in assigning 36 and 38 as possessing this range as a minimum. The poor yield of 37 in our sequence may only be the result of a single, unoptimized reaction with the lead tetraacetate and deserves to be studied further. However, our goal at this time is to demonstrate the asymmetric synthesis and its application to a wide range of isoquinoline alkaloids.

EXPERIMENTAL

General

All laboratory glassware was flame-dried under vacuum and purged with dry argon. The vacuum-argon purge was repeated twice to ensure an inert atmosphere. All solvents were distilled before use, including hexanes, ethyl acetate, chloroform and dichloromethane. Triethylamine, diisopropylamine, and hexamethyl-phosphoramide (HMPA) were distilled from calcium hydride and stored over activated 3A sieves. Toluene and benzene were distilled and stored over sodium. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl and were withdrawn from the collection vessel via syringe and used immediately to prevent moisture contamination.

Low temperature reactions were run using different cooling baths depending on the desired temperature: 0°C (ice-water), -40° C (acetonitrile, Dry ice), -78° C (acetone, Dry ice), -100° C (methanol, liquid nitrogen). In the case of reactions requiring prolonged cooling times, they were immersed in a methanol bath cooled by a Flexi Cool (FTS Systems, Inc) refrigeration unit.

Organolithium reagents were purchased from either Aldrich, Lithium Corporation of America, or Alfa-Ventron and were titrated monthly with s-butanol (distilled from and stored over calcium hydride) using N-phenyl-1-naphthylamine as an indicator. The solutions of organolithium reagents were transferred using oven dried syringes. Lithium diisopropyl amide (LDA) was prepared by addition of 1.0 equiv of n-butyllithium to a 10% solution of diisopropylamine in THF at -78° C followed by warming to 0° C. The desired amount was then transferred via syringe to a given reaction mixture.

Chromatographic separation and purification were performed by a number of methods. Column chromatography and flash chromatography were performed using silica gel (Woelm, 32-63) or aluminum oxide (Baker, neutral, powder). Analytical HPLC was performed with a Waters (6000A) instrument on a Baker chiral phase column (Bakerbond, DNBPG, 5 m covalent) fitted with an ultraviolet (254nm) detector. VPC analyses (where indicated) were performed on a Hewlett Packard 5750 instrument, fitted with a 2m x 2mm column using 10% SE-30 on Chromosorb P.

(S)-N,N-Dimethyl-N'-(1-t-butoxy-3-methyl-2-butyl) Formamidine 8

S-Valinol tert-butyl ether prepared as previously described[5] was treated with N,N-dimethylformamide dimethyl acetal (Aldrich, 25.0 g, 210 mmol), and the reaction mixture was heated under argon at 40° C for 1 h. The solution was concentrated in vacuo and the crude product was bulb-to-bulb distilled (0.05 mm, 55-65° C) yielding 8 (26.0 g, 87% from 3) as a colorless liquid; $[\alpha]^{25}_D$ -18.2° (c 0.98, THF). IR (film) cm^{-1}: 2980, 1160, 1368, 1203, 1082; ^1H NMR (270 MHz, $CDCl_3$) δ: 7.23(s, 1H), 3.54-3.48(m, 1H), 3.21-3.15(m, 1H), 2.81(s, 6H), 2.74-2.69(m, 1H), 1.89-1.72(m, 1H), 1.16(s, 9H), 0.86(d, 3H, J=6.76Hz), 0.85(d, 3H, J=6.68Hz). HRMS, calc for: $C_{12}H_{26}N_2O$: 214.2045. Found: 214.20497.

Preparation of 8 via Gold's Reagent

To anhydrous methanol (23 mL) was added sodium metal (0.39 g, 16.9 mmol). After evolution of hydrogen had ceased, S-valinol-tert-butylether (2.00 g, 12.6 mmol) was added. The solution was cooled to 0°C and Gold's reagent[23] (Aldrich, 2.78 g, 16.9 mmol), was added and the solution stirred for 4 h at 0° C. The mixture was poured into sat. $NaHCO_3$ (150 mL) and the resultant mixture was extracted with dichloromethane (4 x 40 mL). The combined organic extracts were washed with brine (80 mL) and dried over K_2CO_3. Concentration gave a residue which was flash filtered through a small amount (1-2 g) of silica gel (Woelm 32-63 μ) with 8% Et_3N, 30% ethyl acetate and 62% hexane. Evaporation of the eluent gave dimethylamino-valinol-tert-butylether formamidine 8 (2.49 g, 92%); $[\alpha]^{25}_D$ -16.0-18.5° (c 0.99, THF). (NOTE: The rotations vary due to polarimeter, temperature, solvent purity, but all samples were of equal purity by VPC and NMR).

(S)-Valinol-tert-butyl ether formamidine of 1, 2, 3, 4-tetrahydroiso-quinoline 14

To a stirred solution of dimethyl formamidine 8 (3.21 g, 15.0 mmoles) in toluene (20 mL) was added 1,2,3,4-tetrahydroisoquinoline (Aldrich, 3.00 g, 22.5 mmol). The solution was heated at reflux under an argon atmosphere for 48 h. It was concentrated in vacuo, chromatographed (5% Et_3N-hexane) and distilled (80° C, 0.03 mm) yielding 14 (3.86 g, 85%) as a yellow oil; $[\alpha]^{25}_D$ -3.96° (c 1.06, THF).[9b] IR (film) cm-1: 2965, 2862, 1648, 1382, 1191, 1075, 739. ^1H NMR (270 MHz, $CDCl_3$) δ: 7.41(s, 1H), 7.20-7.12(m, 4H), 4.54(ABq, 1H, J=17.1Hz), 4.46(ABq, 1H, J=17.0Hz), 3.56-3.48(m, 3H), 3.23-3.17(m, 1H), 2.86(t, 2H, J=5.7Hz), 2.79-2.71(m, 1H), 1.87-1.78(m, 1H), 1.14(s, 9H), 0.87(d, 3H, J=6.8Hz), 0.85(d, 3H, J=6.5Hz). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 153.4, 134.5, 133.7, 128.5, 126.1, 125.8, 125.6, 72.1, 71.2, 64.7, 46.8, 43.9, 30.1, 28.9, 27.4, 20.1, 18.0.

Alkylation of Chiral Formamidine 14-General Procedure[24]

To a dry 3-necked 50 mL round-bottomed flask fitted with a stir bar, thermometer, and rubber septum, under an Argon or N_2 atmosphere, was added formamidine 14 (302 mg, 1.0 mmol). The flask was then placed under a vacuum to remove any trapped oxygen followed by introduction of Ar or N_2 at which time 14 was diluted with THF (20 mL) and cooled to -78°C (Dry ice/acetone), where it was treated with 1.05 equiv of a 0.28 M solution of LDA in THF via syringe. The mixture became red on stirring and was kept at -78°C for 0.3 h. It was then cooled to -100°C (methanol/liquid N_2) and the alkyl halide (1.05 equiv, 50% THF solution) was added to the rapidly stirring solution slowly enough to maintain the internal temperature of the flask at -100°C. Termination of the reaction was usually accompanied by loss of the red solution color. The reaction was allowed to stir at -100° C for 0.5 h and was quenched with methanol. The mixture was then partitioned between water (30

mL) and dichloromethane (30 mL). After an additional extraction with dichloromethane (30 mL), the combined organic layers were washed with brine (30 mL), and dried over K_2CO_3. Concentration in vacuo, yielded the alkylated formamidine as a yellow oil, which was cleaved by hydrazine-acetic acid without further purification. The crude alkylated product (1.0 mmol) was dissolved in 60% aqueous ethanol (5 mL) to which was added hydrazine (0.25 mL, 8.0 mmol) and acetic acid (0.17 mL, 3.0 mmol). The mixture was heated at 50° C under an argon atmosphere overnight and was partitioned between sat. $NaHCO_3$ (30 mL) and dichloromethane (40 mL). After extraction with dichloromethane (2 x 40 mL), the combined organic layers were washed with brine (30 mL), dried over K_2CO_3, and concentrated in vacuo yielding the substituted isoquinoline 15 and O-tert-butyl valinol. The products were separated by distilling slowly at 0.03 mm, where the substituted isoquinolines distilled from 60-90° C with the O-tert-butyl valinol being trapped into a liquid N_2 vessel. For storage purposes, the substituted isoquinolines were converted to their HCl salts. These salts were optically enriched to >99.9% ee (determined by chiral HPLC analysis) by recrystallizing them from ethanol and ether, and the rotations listed for the free amines (15a-15e) are those enriched by crystallization of their HCl salts, and are therefore considered to be optically pure.

Optical Purity Determination via Chiral HPLC (Pirkle Column) Preparation of the α-Naphthamide of the 1-Substituted-1,2,3,4-tetrahydro Isoquinolines (15a-15e)

To the 1-substituted isoquinoline 15 (1.0 mmol) dissolved in dichloromethane (5 mL), and Et_3N (0.2 mL) was added α-naphthoyl chloride[9b] (0.3 g, 1.5 mmol). The mixture was allowed to stir at room temperature for 0.5 h and was transferred to a separatory funnel containing 20% NaOH (10 mL). The organic layer was separated and concentrated to yield the α-naphthamide as a yellow solid, which was purified by radial chromatography or PTLC (5:4:1 dichloromethane:hexane:ethyl acetate). To determine the optical purity, the α-naphthamide was injected onto a covalent phenylglycine-modified spherisorb S5NH column (Regis Chemical Co.), 10% isopropanol in hexane as the elution solvent, incorporated on a Waters 440 HPLC instrument with a flow rate of 5 mL/min.

Physical Properties and Chemical Yields of Optically Pure (S)-1-Alkyl-1,2,3,4-tetrahydroisoquinolines (15a-15e, 16)

(S)-1-Methyl-1,2,3,4-tetrahydroisoquinoline 15a

Oil, (b.p. 60°C, 0.03 mm (pot temp.), 64 mg (45%) was obtained from 14 (301 mg) and methyl iodide(1.05 equiv); $[\alpha]^{25}_D$ -71.3° (c 0.64, THF). IR (film) cm^{-1}: 3650-3160 (broad, 3080, 3040, 2980, 2940, 1490, 750. Hydrochloride salt: mp 208° C. ^1H NMR (270 MHz, $CDCl_3$) δ: 10.60-10.16(brs, 1H), 10.06-9.64(brs, 1H), 7.19-7.00(m, 4H), 4.74-4.56(m, 1H), 3.62-3.00(m, 4H), 1.83(d, 3H, J=6.9Hz).
Anal. Calc for: $C_{10}H_{14}NCl$: C,65.38; H, 7.70; N, 7.62. Found: C, 65.27; H, 7.76; N, 7.55.

(S)-1-Allyl-1,2,3,4-tetrahydroisoquinoline 15b

Oil, b.p. 90° C, 0.03 mm (pot temp.), 86 mg (63%) was obtained from 14 (260 mg) and allyl bromide (1.05 equiv). Spectral characteristics of the free amine were identical to those reported[25]; $[\alpha]^{25}_D$ -83.1° (c 0.61, THF). Hydrochloride salt: mp 194° C. ^1H NMR (270 MHz, $CDCl_3$) δ: 10.60-10.20 (brs, 1H), 9.80-9.40 (brs, 1H), 7.4-7.1 (m, 4H), 6.20-5.85 (m, 1H), 5.45-5.20 (m, 2H), 4.68-4.57 (m, 1H), 3.78-3.58 (m, 1H), 3.5-2.9 (m, 5H).

(S)-1-n-Butyl-1,2,3,4-tetrahydroisoquinoline 15c

Oil, b.p. 108° C, 0.08 mm (pot temp.), 124 mg (61%) was obtained from 14 (324 mg) and n-butyl iodide (1.05 equiv); $[\alpha]^{25}_D$ -78.4° (c 0.61, THF). IR (film) cm^{-1}: 3600-3160(broad), 3060, 3020, 2930, 2860, 1500, 1460, 740. Hydrochloride salt: mp 142-143° C. ^1H NMR (270 MHz, CDCl3) δ: 10.7-10.2 (brs, 1H), 9.83-9.42 (brs, 1H), 7.40-7.10 (m, 4H), 4.61-4.41(brs, 1H), 3.72-3.50 (brs, 1H), 3.45-3.05 (m, 3H), 2.29-2.00 (m, 2H), 1.79-1.56 (m, 2H), 1.56-1.29 (m, 2H), 0.98 (t, 3H, J=7.05Hz).
Anal. Calc for $C_{13}H_{20}NCl$: C, 69.15; H, 8.95; N, 6.20. Found: C, 69.08; H, 9.10; N, 6.23.

(S)-1-Benzyl-1,2,3,4-tetrahydroisoquinoline 15d

Oil, b.p. 105° C, 0.02 mm (pot temp.), 490 mg (94%) was obtained from 14 (713 mg) and benzyl chloride (1.05 equiv). Spectral characteristics of the free amine were identical to those reported;[26] $[\alpha]^{25}_D$ -62.2° (c 1.24, THF). Hydrochloride salt: mp 187° C; lit[26] 170-172° C (racemic material). ^1H NMR (270 MHz, $CDCl_3$) δ: 10.38-10.07 (brs, 1H), 10.06-9.85 (brs, 1H), 7.30-4.72(m, 1H), 3.63 (dd, 1H, J_1=13.8Hz, J_2=4.5Hz), 3.40-2.90 (m, 5H).

(S)-1-β-Phenylethyl-1,2,3,4-tetrahydroisoquinoline 15e

Oil, b.p. 135° C, 0.02 mm (pot temp.), 504 mg (91%) was obtained from 14 (716 mg) and phenethyl bromide (1.05 equiv); $[\alpha]^{25}_D$ -23.5° (c 5.71, THF). IR (film) cm^{-1}: 3600-3140 (broad), 3065, 3040, 2960, 1600, 1490, 1450, 740. Hydrochloride salt: mp 200° C. ^1H NMR (270 MHz, $CDCl_3$) δ: 10.60-10.40 (brs, 1H), 10.00-9.70 (brs, 1H), 7.44-7.00 (m, 9H), 4.60-4.42 (m, 1H), 3.73-3.52 (m, 1H), 3.40-3.18 (m, 2H), 3.14-2.90 (m, 3H), 2.61-2.30 (m, 2H).
Anal. Calc for $C_{17}H_{20}NCl$: C, 74.54; H, 7.38; N, 5.12. Found: C, 74.62; H, 7.34; N, 5.00.

(S)-(-)-1,3,4,6,7,11b-Hexahydro-2H-benzo[a]-quinolizine 16

Oil, b.p. 75° C, 0.03 mm (pot temp.) 324 mg (72%) was obtained from 14 (728 mg) and 1-bromo-4-chloropropane (1.05 equiv); $[\alpha]^{25}_D$ -206° (c 0.017, pyridine); lit[27] -208° (c 0.022, pyridine). Spectral characteristics were identical to those reported. IR (film) cm^1: 3040, 3000, 2920, 2840, 2790, 2730, 1490, 1440, 1350, 1295, 1130, 1110, 1050, 725. Hydrochloride salt:mp 263° C (decomp), lit[27] = 260-261° C. ^1H NMR (270 MHz, $CDCl_3$) δ: 10.85-10.60 (brs, 0.25H), 10.25-10.05 (brs, 0.75H), 7.45-7.10 (m, 4H), 4.65-3.95 (m, 2H), 3.70-1.56 (m, 11H).

(S)-Valinol-tert-butyl ether formamidine of 6,7,dimethoxy-1,2,3,4-tetrahydroisoquinoline, 9

To a solution of 5.8 g (30 mmols) of 6,7-dimethoxytetrahydroisoquinoline 7 (obtained from the hydrochloride salt purchased from Aldrich) in 8.0 ml of dry toluene was added 5.0 g (23 mmols) of the dimethyl amino formamidine 8 (which had been stored over CaH_2). The solution was purged with argon and heated to reflux, under a slow stream of argon, for 45-48 h. The toluene and other volatiles were removed under reduced pressure and the viscous residue was bulb-to-bulb distilled to give, as a first fraction, unreacted 7 (110° C; 0.1 mm) followed by 9 (180° C; 0.1 mm). The yield of 9 was 5.10 g. By subjecting the first fraction to chromatography (silica gel, 10% triethylamine-hexane), it was possible to obtain an additional 2.45 g of pure 9. The combined yield of material was 7.55 g (91%); $[\alpha]^{25}_D$ -30.3° (c 2.7, $CHCl_3$); IR (film) 2970s, 2920s, 2870s, 2830s, 1655s, 1620m. ^1H-NMR ($CDCl_3$, 270 MHz) 7.40 (s, 1 H), 6.63 (s, 1 H), 6.60 (s, 1 H), 4.45 (AB-system, J = 17, 1 H), 4.40 (AB-system, J = 17, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.50 (m, 3 H), 3.20 (m, 1 H), 2.76 (m, 3 H), 1.83 (sept, J = 6.7, 1 H), 1.14 (s, 9 H), 0.88 (d, J = 6.7, 3 H), 0.87 (d, J = 6.7, 3 H).
Anal. Calcd for $C_{21}H_{34}N_2O_3$: C, 69.57; H, 10.05; N, 7.73. Found: C, 69.82; H, 9.45; N, 8.02.

General procedure for alkylations of formamidines, 9

To a 0.03 M solution of the formamidine in THF was added 1.1 equiv of a 2.3 M t-butyllithium solution in pentane at -78° C. After 30 min the solution was cooled to -100° C and 1.1 equiv of the electrophile were added. After the mixture was stirred for 30 min at -100° C, it was partitioned between dichloromethane and water. The organic layer was dried over K_2CO_3 and concentrated to give the product which was subjected to hydrazinolysis as described for 14.

S-(-)-Salsolidine 11

Methyl iodide (85 mg, 0.6 mmol) was used to alkylate 200 mg (0.55 mmol) of the formamidine 9 following the general procedure. After hydrazinolysis, the oil was subjected to Kugelrohr distillation (110° C; 0.02 mm) to give 70 mg (61%) (s)-(-)-Salsolidine, 11. ^1H-NMR ($CDCl_3$, 270 MHz): 6.62 (s, 1 H), 656 (s, 1 H), 4.04 (q, J = 6.5 Hz, 1 H), 3.83 (s, 6H), 3.23-2.65 (m, 4 H), 1.69 (s, 1 H), 1.43 (d, J = 6.5 Hz, 3 H); $[\alpha]^{25}_D$ -56.5° (c 4.15, EtOH); lit[28]; $[\alpha]^{25}_D$ -59.5° (c 4.39, EtOH).

(S)-(+)-Homolaudanosine 13

3,4-Dimethoxyphenethyl iodide (430 mg, 1.5 mmol) was used to alkylate 490 mg (1.35 mmol) of the chiral formamidine 9 following the general procedure. After hydrazinolysis, the oil was heated to reflux for 30 min in ethylformate and the solution was concentrated to give the formamide. A solution of the crude formamide in 5 ml THF was treated with 0.3 g (6 mmol) $LiAlH_4$ and the resulting suspension was heated at reflux for 1 h. The mixture was cooled in an ice bath, quenched by addition of water, and filtered. The filter pad was washed with several small portions of THF and the filtrate was concentrated in vacuo. The crude product was purified by tlc (10% Et_3N/ethyl acetate, Rf; 0.5) furnishing 230 mg (46%) of 13 as a yellow oil. Spectroscopic properties were in good agreement with literature values; $[\alpha]^{25}_D$ 10.4° (c 0.2, $CHCl_3$); lit[29]; $[\alpha]^{25}_D$ 11° (c 0.21, $CHCl_3$).

S-(-)-Norcoralydine 6

3,4-Dimethoxybenzyl chloride (240 mg, 1.3 mmol) was used to alkylate 440 mg (1.2 mmol) of the formamidine 9 following the general procedure. After hydrazinolysis the oil was dissolved in 10 ml of 2N HCl and then 2 ml of aqueous formaldehyde solution (37%) was added. The mixture was heated to reflux for 30 min. The solution was rendered alkaline with 10% KOH and extracted with dichloromethane. The organic layer was dried over K_2CO_3 and concentrated to give crude 6. The oil was purified by tlc (10% Et_3N/ethylacetate, Rf: 0.74) to give 160 mg (37%) of colorless crystals

which were recrystallized from methanol, mp = 177° C; $[\alpha]^{25}_D$ -273° (c 1.17, $CHCl_3$); lit[30]; $[\alpha]^{25}_D$ -277° (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 270 MHz): 6.75 (s, 1 H), 6.67 (s, 1 H), 6.62 (s, 1 H), 6.58 (s, 1 H), 4.06-3.65 (m, 3 H), 3.92 (s, 3 H), 3.88 (s, 9 H), 3.28-3.04 (m, 3 H), 2.90-2.70 (m, 1 H), 2.68-3.04 (m, 2 H).

5-Methoxy-6, 7-methylenedioxy-1, 2, 3, 4 tetrahydroiso-quinoline 21

To a stirring solution of 5-methoxy-6,7-methylenedioxy-3,4-dihydroisoquinoline[31] (183 mg, 0.89 mmol) dissolved in MeOH (10 mL), was added NaBH4 (326 mg, 8.9 mmole). The solution was allowed to stir at ambient temperature for 1 h and the solvent was subsequently removed by rotary evaporation. The residue was partitioned between water (40 mL) and dichloromethane (40 mL). After extraction with dichloromethane (2 x 40 mL), the combined organic layers were dried over K_2CO_3. Evaporation of the solvent in vacuo gave a yellow solid that was purified by crystallization (chloroform/hexane) yielding 21 (161 mg, 88%); mp 89-90°C. IR (KBr) cm^{-1}: 3260-3100, 2924, 1620, 1489, 1393, 1046, 820. ^{1}H NMR (270 MHz, CDCl3) δ: 6.23 (s, 1H), 5.86 (s, 2H), 3.99 (s, 3H), 3.90 (s, 2H), 3.09 (t, 2H, J=6.01Hz), 2.62 (t, 2H, J=5.90Hz), 2.25-2.08 (brs, 1H). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 147.7, 141.6, 134.7, 129.9, 120.3, 100.6, 59.4, 48.6, 43.9, 23.8.

(S)-Valinol-tert-butyl ether formamidine of 5-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline 22

To a stirring solution of 21 (830 mg, 4.01 mmol) in dry toluene (5 mL), was added 8 (950 mg, 4.40 mmol) and a catalytic amount of camphor sulfonic acid. The solution was heated at reflux under an argon atmosphere for 72 h. The cooled solution was partitioned between chloroform(20 mL) and sat. $NaHCO_3$ (40 mL). After extraction with chloroform (3 x 20 mL), the combined organic layers were dried over K_2CO_3. The solvent was removed in vacuo to give a dark oil. Purification of the oil via flash column chromatography (Merck-MPLC silica-gel, 10% EtOAc, 2% Et3N in hexanes) gave 22(910 mg, 60%) as a green-yellow oil; $[\alpha]^{25}_D$ +0.19° (c 1.57, THF). IR(film) cm^{-1}: 2972, 2870, 1650, 1625, 1480, 1458, 1320, 1265, 1222, 1197, 1042, 940, 912, 885, 809. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 7.38(s, 1H), 6.35 (s, 1H), 5.87(s, 2H), 4.43 (ABq, 1H, J=21.6Hz), 4.34 (ABq, 1H, J=21.0Hz), 3.98 (s, 3H), 3.58-3.14 (m, 3H), 3.24-3.18 (m, 1H), 2.80-2.67 (m, 3H), 1.93-1.78 (m, 1H), 1.14 (s, 9H), 0.87 (d, 6H, J=6.7Hz). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 153.7, 148.0, 141.6, 120.3, 100.8, 72.7, 71.4, 65.1, 59.5, 53.5, 47.5, 44.5, 30.5, 29.8, 27.9, 23.3, 20.4, 18.5.

1-(3,4'-Dimethoxybenzyl)-5-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline 24

To a rapidly stirring solution containing 22 (390 mg, 1.04 mmol), in THF (20.8 mL), at -100°C, was added 1.3 equiv of tert-butyllithium. The solution was allowed to stir at -100°C for 0.3 h, at which time it turned blood-red in color. 3,4-Dimethoxybenzyl bromide (311 mg, 1.31 mmol dissolved in 4 mL THF) was added dropwise, and after an additional 0.3 h, the solution was quenched with excess methanol and immediately partitioned between chloroform (30 mL) and water (30 mL). After extraction with chloroform (2 x 30 mL), the combined organic layers were washed with brine (20 mL) and dried over K_2CO_3. Removal of the solvent via rotary evaporation gave a green-yellow oil. The oil was dissolved in 10% HCl solution (300 mL) and it was washed with ether (3 x 20 mL). The acidic layer was neutralized with NaOH and extracted with chloroform (2 x 40 mL). The combined organic layers were washed with brine (20 mL) and dried over K_2CO_3. Removal of the solvent in vacuo gave a green-yellow oil, 23 which was subjected to the next step without further purification.

To a stirring solution of the 1-(3',4'-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline formamidine, 23 dissolved in a 3:1 ethanol/water solution (5 mL) , was added hydrazine (8.0 mmol, 0.32 mL) and acetic acid (3.0 mmol, 0.24 mL). The solution was allowed to stir overnight at 50°C under an argon atmosphere and then was partitioned between saturated $NaHCO_3$ (30 mL) and chloroform (30 mL). After two additional extractions with chloroform (2 x 30 mL), the combined organic layers were dried over K_2CO_3. Solvent removal by rotary evaporation gave an oil; which was purified by flash chromatography (7% methanol-chloroform), yielding 24 (0.307 g, 83%) as an oil. The enantiomeric excess was determined to be 93% by chiral HPLC analysis (35% isopropanol in hexane) of the 2-α-naphthoyl derivative 25 prepared and characterized by the previously described procedure; $[\alpha]^{25}_D$ -32.9° (c 0.85, THF). IR (film) cm^{-1}: 3700-3080 (broad), 3000, 2940, 2836, 16236, 1590, 1515, 1260, 1138, 1040, 940, 790, 748. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 6.85-6.76 (m, 3H), 6.49 (s, 1H), 5.89 (s, 2H), 4.06 (dd, 1H, J_1=10.17Hz, J_2=3.89Hz), 3.99 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.21-3.12 (m, 2H), 2.90-2.80 (m, 2H), 2.63 (t, 2H, J=5.82Hz), 2.05-1.85 (brs, 1H). ^{13}C NMR (67.9 MHz, CDCl3) δ: 149.50, 148.20, 147.29, 141.05, 134.29, 132.86, 131.91, 121.60, 121.00, 113.50, 112.38, 100.46, 59.12, 57.32, 56.15, 56.07, 42.21, 40.49, 24.29. Hydrochloride salt, mp 223°C (decomp.) (ethanol/ether). It was immediately N-methylated in the next step without further characterization or purification.

1-(3',4'-Dimethoxybenzyl)-2-methyl-5-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline 26

To a solution of 24, (0.311 g, 0.87 mmol) dissolved in methanol (17 mL) was added 37% formalin solution (1.4 mL). The solution was allowed to stir at ambient temperature for 0.2 h and $NaBH_4$ (0.75 g, 19.5 mmol) was cautiously added. The reaction mixture was allowed to stir at ambient temperature for an additional 1.5 h. The solvent was removed in vacuo and the resulting solid was partitioned between water (40 mL) and chloroform (40 mL). After extracting with chloroform (2 x 40 mL), the combined organic layers were washed with brine (40 mL) and were dried over K_2CO_3. Concentration of the solution gave a yellow oil, which was purified by flash chromatography (silica gel, 5% methanol-chloroform), yielding 26 (0.245 g, 76%); $[\alpha]^{25}_D$ -4.7°C (c 0.55, THF). Spectral characteristics were identical to the compound obtained by Taylor and McKillop.[16] IR (film) cm^{-1}: 2930, 2830, 1618, 1594, 1512, 1470, 1260, 1093, 1043, 942, 795, 753. ^1H NMR (270 MHz, $CDCl_3$) δ: 6.79-6.64 (m, 3H), 5.99 (s, 1H), 5.85 (d, 1H, J=1.30Hz), 5.84 (d, 1H, J=0.96Hz), 3.99 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.72-3.68 (m, 1H), 3.24-3.02 (m, 2H), 2.85-2.64 (m, 4H), 2.50 (s, 3H). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 149.13, 147.97, 147.13, 140.68, 134.29, 132.88, 131.75, 121.91, 119.85, 114.14, 112.11, 102.10, 100.40, 65.36, 59.17, 56.21, 46.86, 42.58, 41.10, 20.22. Hydrochloride salt: mp 182-183°; lit[16] 206°C (racemic material).

(+)-Ocoteine

The alkaloid was prepared according to the procedure of Taylor and McKillop.[16] Flash chromatographic purification (silica gel, 2% methanol-chloroform) allowed recovery of starting material in 20% yield. Spectral data obtained for 5 were identical to that of the natural product;[16] $[\alpha]^{25}_D$ +32.1° ± 1.5° (c 0.98, ethanol); lit[17] +37.6°. IR (film) cm^{-1}: 2940, 2840, 2780, 1630, 1608, 1510, 1425, 1398, 1340, 1270, 1246, 860, 742. ^1H NMR (270 MHz, $CDCl_3$) δ: 7.61 (s, 1H), 6.78 (s, 1H), 6.07 (d, 1H, J=1.42Hz), 5.93 (d, 1H, J=1.37Hz), 4.01 (s, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 3.22-3.01 (m, 3H), 2.90-2.78 (m, 2H), 2.78-2.58 (m, 1H), 2.56 (s, 3H), 2.51-2.45 (m, 1H). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 148.57, 143.74, 139.83, 135.33, 128.32, 128.07, 124.40, 119.71, 112.56, 111.71, 100.77, 62.73, 59.49, 56.63, 56.37, 53.62, 43.85, 34.56, 29.83, 23.87. Hydroiodide salt: mp 205°C (decomp); lit[17] 198-200°C - slow rate of heating, 210-212°C fast rate of heating.

3-Benzyloxy-4-methoxy-1,2,3,4,-tetrahydroisoquinoline 27

To a solution of 2-(3-benzyloxy-4-methoxyphenyl)ethylamine[32] (15.1 g, 58.7 mmol) dissolved in formic acid (64 mL), was added paraformaldehyde (1.76 g, 5.87 mmol). The solution was allowed to stir at 40°C for 24 h. The formic acid was removed in vacuo at low temperature and the remaining oil poured into 20% NaOH (200 mL). Extraction with dichloromethane (2 x 100 mL), after removal of the solvent in vacuo, gave13.3 g (84%) of 27 as a yellow solid. Crystallization from hexane gave colorless needles; mp 78°C. IR (KBr) cm^{-1}: 3330-3160 (broad), 3037, 2935, 2840, 1610, 1515, 1220, 1100, 1010, 841, 749, 690. 1H NMR (270 MHz, $CDCl_3$) δ: 7.44-7.28 (m, 5H), 6.61 (s, 1H), 6.53 (s, 1H), 5.11 (s, 2H), 3.94 (s, 2H), 3.84 (s, 3H), 3.09 (t, 2H, J=5.9Hz), 2.65 (t, 2H, J=5.9Hz). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 148.1, 146.8, 137.3, 128.7, 128.0, 127.3, 127.0, 126.7, 115.7, 110.4, 71.3, 56.0, 47.6, 43.5, 28.3. HRMS Calc for $C_{17}H_{19}NO_2$: 269.1416. Found: 269.14157.

(S)-Valinol tert-butyl ether formamidine of 3-benzyloxy-4-methoxy-1,2,3,4-tetrahydroisoquinoline, 28

To a solution of 27 (2.32 g, 8.59 mmol) in dry toluene (5 mL), was added 8 (5.51 g, 2.58 mmol). The solution was heated at reflux for 16 h. The solvent was removed under aspiratorvacuum and excess 8 (3.16 g, 86%) was removed at 90°C (bulb-to-bulb, 0.03 mm). The remaining oil was flash chromatographed (50% hexanes, 44% ethyl acetate, 5% methanol, 1% Et_3N) to give 28 (3.44 g, 91%) as a yellow oil; $[\alpha]^{25}D$ -28.4° (c 5.63, THF). IR (film) cm^{-1}: 2975, 2872, 1652, 1520, 1260, 1110, 1080, 880, 845, 692. ^1H NMR (270 MHz, $CDCl_3$) δ: 7.48-7.28 m, 5H), 6.66 (s, 1H), 6.63 (s, 1H), 5.11 (s, 2H), 4.46 (ABq, 1H, J=20.1Hz), 4.38 (ABq, 1H, J=20.2Hz), 3.84 (m, 3H), 3.55-3.41 (m, 3H), 3.25-3.13 (m, 1H), 2.81-2.61 (m, 3H), 2.92-2.72 (m, 1H), 1.13 (s, 9H), 0.87 (d, 6H, J=6.4Hz). ^{13}C NMR (67.9 MHz, CDC_{l3}) δ: 153.2, 148.6, 146.9, 137.3, 128.1, 127.4, 127.0, 126.7, 115.4, 110.6, 71.9, 71.4, 71.0, 64.7, 55.9, 46.5, 43.9, 30.2, 28.2, 27.4, 20.0, 17.8.

General Procedure for Conversion of Formamidine 28 to 1-Benzyl-2-methyl-1,2,3,4-tetrahydroisoquinolines, 29 and 30

To a stirring solution of 28 (438 mg, 1.00 mmol) in THF (20 mL), was added 1.05 equiv of tert-butyllithium (2.4 M in pentane). After the solution was allowed to stir at -100°C for 0.5 h, 1.05 equiv of the appropriate benzyl bromide (0.2 g/mL-THF solution) was added dropwise. The mixture was allowed to stir at -100°C for 0.5 h and was quenched with methanol. The solvent was removed

in vacuo and the yellow oil was dissolved in dichloromethane (40 mL) and washed with water (40 mL). After an additional extraction of the aqueous layer with dichloromethane (40 mL), the combined organic layers were washed with brine (40 mL) and dried over K_2CO_3. Concentration in vacuo gave the adduct as an oil that was immediately subjected to the hydrazinolysis procedure.

To a stirring solution of the substituted formamidine adduct in ethanol:water (3.5 mL:1.5 mL) was added hydrazine (0.25 mL, 8 mmol) followed by addition of acetic acid (0.18 mL, 3 mmol). After stirring the solution under an argon atmosphere at 50°C overnight, it was partitioned between saturated $NaHCO_3$ (40 mL) and dichloromethane (40 mL). The aqueous phase was extracted an additional time with dichloromethane (40 mL) and the combined organic layers were washed with brine (40 mL) and dried over K_2CO_3. After solvent removal in vacuo, the remaining yellow oil was heated to 100°C at aspirator vacuum to remove (S)-valinol-t-butyl ether, of which 75% was recovered for further use without loss of optical purity. Due to the ability of the tetrahydroisoquinoline residues to rapidly oxidize, they were immediately converted to their stable N-methyl derivatives, 29 and 30, without additional purification.

To a stirring solution of the crude tetrahydroisoquinoline (1 mmol) in methanol (26.5 mL), 37% formalin solution (1.6 mL) was added and the solution was allowed to stir at ambient temperature for 0.2 h. Sodium borohydride (0.81 g) was slowly added, and after 1 h, the solvent was removed in vacuo and the residue partitioned between 5% aqueous NaOH (40 mL) and dichloromethane (40 mL). The aqueous layer was again extracted with dichloromethane (40 mL) and the combined organic layers were washed with brine (40 mL) and dried over K_2CO_3. Concentration in vacuo, yielded a light yellow oil, which was purified by flash chromatography on silica-gel (0.5% Et_3N, 2% methanol in chloroform), giving the N-methyl 1-alkyl-tetrahydroisoquinolines as yellow oils, which solidified on standing. The physical data follow below.

S(+)-1-(3',4'-Dimethoxybenzyl)-6-benzyloxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline 29

The tetrahydroisoquinoline (2.01 g, 70%) was prepared according to the general procedure from 28 (3.03 g, 6.93 mmol); $[\alpha]^{25}_D$ +40.8° (c 1.14, ethanol). mp 74-76°C (ethanol-ether). IR (film-$CDCl_3$), cm^{-1}: 3075, 2925, 2832, 1610, 1469, 1151, 1135, 1020, 850, 690. ^1H NMR (270 MHz, $CDCl_3$) δ: 7.45-7.29 (m, 5H), 6.78-6.59 (m, 4H), 6.09 (s, 1H), 5.09 (s, 2H), 3.85 (s, 3H), 3.78 (s, 3H), 3.69 (dd, 1H, J_1=4.95Hz, J_2=7.37Hz), 3.58 (s, 3H), 3.17-3.10 (m, 2H), 2.81-2.69 (m, 4H), 2.53 (s, 3H). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 148.8, 147.7, 147.6, 147.2, 137.1, 131.4, 128.5, 128.4, 127.7, 127.3, 124.7, 122.0, 114.3, 113.4, 112.0, 111.4, 71.2, 64.8, 56.0, 55.9, 55.7, 46.3, 41.7, 40.6, 24.4.

S(+)-1-(3',4'-Methylenedioxybenzyl)-6-benzyloxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline 30

The tetrahydroisoquinoline (1.06 g, 53%) was prepared according to the general procedure from 28 (2.08 g, 4.75 mmole); $[\alpha]^{25}_D$ +65.6° (c 2.16, ethanol). mp 86-88oC (ethanol-ether). IR ($CDCl_3$-film) cm^{-1}: 3020, 2920, 1601, 1499, 1432, 1240, 1211, 1125, 1088, 1028, 680. ^1H NMR (270 MHz, $CDCl_3$) δ: 7.45-7.29 (m, 5H), 6.70 (d, 1H, J=7.9Hz), 6.64 (s, 1H), 6.60 (s, 1H), 6.52 (d, 1H, J=7.8Hz), 6.13 (s, 1H), 5.91 (s, 2H), 5.09 (s, 2H), 4.71-4.68 (m, 1H), 3.63 (s, 3H), 3.20-3.18 (m, 2H), 2.81-2.69 (m, 4H), 2.51 (s, 3H). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 147.8, 147.3, 146.9, 145.6, 137.5, 133.8, 130.5, 128.1, 127.4, 127.2, 126.6, 122.4, 115.2, 112.5, 110.0, 107.6, 100.4, 71.5, 64.9, 56.0, 47.2, 42.5., 40.9, 25.5.

General Procedure to Debenzylate 29, 30 to 31, 32

To a stirring solution of the tetrahydroisoquinoline (29, 30) (1.00 mmol) in methanol (24 mL) and acetic acid (0.24 mL) was added 4% Pd-C (85 mg, 0.04 mmol). The solution was allowed to stir at ambient temperature under hydrogen (50 psi) overnight and then filtered and concentrated in vacuo. The residue was partitioned between sat. $NaHCO_3$ (100 mL) and dichloromethane (50 mL). After an additional extraction with dichloromethane (50 mL), the combined organic layers were washed with brine (100 mL) and concentrated in vacuo yielding the products as bright yellow solids.

S(+)-1-(3', 4'-Dimethoxybenzyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline 31 and Laudanosine 33

The tetrahydro-isoquinoline (1.15 g, 90%) was prepared according to the general procedure from 29 (1.61 g, 3.714 mmol); $[\alpha]^{25}_D$ +48.4° (c 1.89, ethanol); mp 77-79 °C, the material resolidified and melted at 125°C (ethanol-ether); lit[33] 111°C (ethanol, racemic material). The percent enantiomeric excess was determined to be 86% ± 2% by methylation of the 6-hydroxy group with diazomethane[34] to laudanosine, 33: $[\alpha]^{25}_D$ +91.9° +1.9° (c 0.65, ethanol); lit[19] -107±3.0° (c 0.7, ethanol). IR (film-$CHCl_3$) cm^{-1}: 3700-2100 (broad band), 3010, 2835, 1590, 1512, 1150, 1130, 1020, 860, 655. ^1H NMR (270 MHz, $CDCl_3$) δ: 6.78 (d, 1H, J=8.1Hz), 6.66-6.57 (m, 3H), 5.96 (s,

1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.68 (dd, 1H, J_1=4.8Hz, J_2=7.9Hz), 3.56 (s, 3H), 3.19-3.12 (m, 2H), 2.86-2.70 (m, 4H), 2.53 (s, 3H). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 149.0, 147.8, 144.4, 144.3, 132.9, 128.6, 127.0, 122.0, 114.4, 114.1, 111.9, 110.9, 65.1, 56.2, 56.0, 55.8, 47.1, 42.5, 40.9, 25.5.

S(+)-1-(3',4'-Methylenedioxybenzyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline 32

The tetrahydroquinoline (0.23 g, 88%) was prepared according to the general procedure from 28 (0.34 g, 0.81 mmol); $[\alpha]^{25}_D$ +53.4° (c 2.77, ethanol) mp 88-89°C, the material resolidified and melted at 136°C (ethanol-ether); lit[20] 145-145.5°C (racemic material). IR (film-$CDCl_3$) cm^{-1}: 3600-2000 (broad band), 2840, 1605, 1360, 1090, 1042, 858, 802. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 6.72-6.52 (m, 4H), 6.05 (s, 1H), 5.91 (s, 2H), 3.62 (s, 4H, MeO, benzylic H), 3.19-3.06 (m, 2H), 2.86-2.53 (m, 4H), 2.50 (s, 3H). ^{13}C NMR (67.9 MHz, CDCl3) δ: 147.5, 145.8, 144.6, 144.3, 134.1, 129.0, 127.3, 122.6, 114.4, 110.8, 110.2, 107.8, 100.6, 65.2, 55.9, 47.2, 42.6, 41.3, 25.5.

General Procedure for the Conversion of 31 and 32 to 3-Desmethyl-O-methylthalisopavine 36 and Reframoline 37

The procedure used was that of Umezawa[20,21] with the following modifications. To a stirring solution of 31 or 32 (1 mmol) in dry dichloromethane (56 mL) at -8°C (ice-salt water bath), was added lead tetraacetate (0.46 g, 1 mmol) in one portion. After rapid stirring of the solution for five min at -8°C, it was poured into concentrated ammonium hydroxide (80 mL) and extracted with dichloromethane (2 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. Removal of the solvent under aspirator vacuum below 20°C gave diastereomeric mixtures of the ortho quinol acetates 34a, 34b as oils, which were immediately cyclized to isopavines without further purification.

The epimeric crude ortho quinol acetates (1 mmol) were dissolved in concentrated HCl (9 mL) and stirred at ambient temperature for 14 h. Excess acid was neutralized by pouring the solution into a 1000 mL separatory funnel containing saturated aqueous $NaHCO_3$ (200 mL) and the solution was extracted with dichloromethane (2 x 50 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. Solvent removal *in vacuo* gave a yellow oil, which was purified by flash column chromatography (3% methanol-chloroform).

S(-)-3-Desmethyl-O-methylthalisopavine 36

The isopavine (0.158 g, 49%) was prepared according to the general procedure from 31 (0.30 g, 0.82 mmol); $[\alpha]^{25}_D$ -101.4° (c 1.41, ethanol) mp 96 -97°C, the material resolidified and melted again at 133°C, (ethanol-ether); lit[20] oil (racemic material). IR (film-$CHCl_3$) cm^{-1}: 3600-2000 (broad, band), 3010, 2928, 2830, 1606, 1113, 1002, 949, 800, 652. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 6.74 (s, 1H), 6.71 (s, 1H), 6.63 (s, 1H), 6.51 (s, 1H), 4.01-3.97 (m, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H), 3.71-3.52 (m, 4H), 2.96-2.90 (m, 2H), 2.51 (s, 3H). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 148.4, 147.3, 145.6, 145.3, 135.2, 134.5, 128.5, 126.6, 115.4, 112.4, 112.0, 110.0, 62.8, 59.6, 56.3, 56.2, 56.0, 45.3, 44.9, 37.6.

S(-)-Reframoline 37

The isopavine (43 mg, 9%) was prepared according to thegeneral procedure from 32 (5.38 mg, 1.65 mmol). In order to obtain pure material, the crude reaction mixture was purified after chromatography by PTLC (E.Merck silica gel,12% methanol-chloroform); $[\alpha]^{25}_D$ -142° (c 0.38, ethanol); lit[35] -144° (c 0.37, ethanol). mp 154-157°C (ethanol-ether; lit[35] 160°C (ether). IR (film-$CHCl_3$) cm^{-1}: 3600-2000 (broad band), 3010, 2920, 2770, 1600, 1501, 1486, 1370, 1350, 1307, 1260, 1225, 1103, 1035, 930. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 6.72 (s, 1H), 6.71 (s, 1H), 6.61 (s, 1H), 6.47 s, 1H), 5.85 (d, 1H, J=1.32Hz), 5.81 (d, 1H, J=1.08Hz), 6.60-6.31 (brs, 1H), 3.84 (s, 4H, MeO, benzylic H), 3.57-3.45 (m, 3H), 2.92-2.82 (m, 2H), 2.46 (s, 3H). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 146.6, 145.6, 145.3 (2), 136.0, 134.5, 128.9, 127.7, 112.0, 110.9, 109.9, 108.0, 100.7, 62.7, 59.6, 56.4, 45.7, 45.0, 38.3. UV λ_{max} = 292, 248(sh), 230(sh), (ethanol).

S(-)-O-Methylthalisopavine 38

The isopavine (24 mg, 70%) was prepared according to the method of Kupchan,[34] from 36 (32 mg, 0.09 mmol); $[\alpha]^{25}_D$ -72.6° (c 0.65, ethanol); mp 125°, the material[36] resolidified and melted again at 155°C (ethanol-ether); lit[34] 91-92°C (ethanol-ether, synthetic racemate). Another report describes the mp at 163-165°C (methanol) for racemic material.[36] IR (film-$CDCl_3$) cm^{-1}: 3010, 2935, 2835, 1611, 1517, 1467, 1260, 1248, 1238, 1202, 1110. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 6.77 (s, 1H), 6.75 (s, 1H), 6.65 (s, 1H), 6.53 (s, 1H), 3.92-3.89 (m, 1H), 3.88 (s, 3H), 3.87 (s, 6H), 3.77 (s, 3H), 3.64-3.45 (m, 3H), 2.95-2.82 (m, 2H), 2.49 (s, 3H). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 149.0, 148.4, 148.3, 147.1, 133.7, 133.2, 127.1, 125.5, 114.5, 111.5, 110.9, 109.2, 63.1, 59.6, 56.3, 56.1, 55.9, 45.2, 44.8, 36.9, 29.6. Spectral characteristics were identical to those reported.[34]

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