

percent dope for which a relative increase in the minor peak height could be observed established the detection limit. The same principle was applied in the case of the NMR determination of optical purity for CBZPheValOMe (entry 8). The proton NMR resonances (CDCl_3 , 400 MHz) for the side-chain methyl groups in valine appeared as sets of clearly resolved doublets at δ 0.84 and 0.81 (L,L isomer) and δ 0.75 and 0.72 (D,L isomer). The sweep was narrowed to focus on this region and at maximized digital resolution, the relative increases in the peak heights for the later set of doublets were recorded against the percent dope amounts.

Registry No. 1, 120418-31-7; 3, 99257-94-0; CDI, 530-62-1; $\text{PhCOOCH}_2\text{Ph}$, 120-51-4; CbzPheOEt, 28709-70-8; CbzPheO- $(\text{CH}_2)_{17}\text{CH}_3$, 120418-34-0; CbzPheO-menthol, 98210-62-9; (\pm) -CbzGlyOCH $(\text{CH}_3)\text{COOEt}$, 120418-35-1; CbzAlaO- (S) -CH $(\text{CH}_2\text{Ph})\text{COOMe}$, 120445-32-1; CbzPheOCyt, 120418-36-2; CbzGlyLeuOMe, 17331-93-0; CbzPheLeuOMe, 3850-45-1; CbzPheValOMe, 4818-08-0;

CbzAlaValOMe, 4864-38-4; CbzAlaSerOMe, 19542-34-8; CbzSerLeuOMe, 17331-94-1; CbzAlaAsp $(\text{OMe})_2$, 120418-37-3; CbzPheNMeLeuOMe, 120418-38-4; CbzAibAibOMe, 6671-25-6; BOCAlaAsp $(\text{OMe})_2$, 120418-39-5; BOC(OBn)SerValOMe, 120418-40-8; CbzPheValOMe, 120418-41-9; PhCOOH , 65-85-0; CbzPhe, 1161-13-3; CbzGly, 1138-80-3; CbzAla, 1142-20-7; CbzSer, 1145-80-8; CbzAib, 15030-72-5; BOCAla, 15761-38-3; BOC(OBn)Ser, 23680-31-1; $\text{H}_3\text{C}(\text{C}-\text{H}_2)_{17}\text{OH}$, 112-92-5; (\pm) - $\text{CH}_3\text{CH}(\text{OH})\text{COOEt}$, 2676-33-7; L- $\text{PhCH}_2\text{CH}(\text{OH})\text{COOMe}$, 13673-95-5; HO-Cyt, 120418-42-0; LeuOMe, 2666-93-5; ValOMe, 4070-48-8; SerOMe, 2788-84-3; Asp $(\text{OMe})_2$, 6384-18-5; *N*-MeLeuOMe, 35026-08-5; AibOMe, 13257-67-5; PheValOMe, 80870-38-8; *L*-menthol, 2216-51-5.

Supplementary Material Available: Physical and analytical data for all new compounds not included in the Experimental Section (3 pages). Ordering information is given on any current masthead page.

Stereoselective Nucleophilic Additions to the Carbon–Nitrogen Double Bond. 2. Chiral Iminium Ions Derived from “Second Generation” Chiral Amines[†]

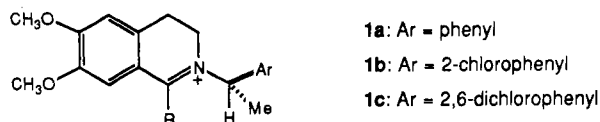
Richard P. Polniaszek* and Craig R. Kaufman

Contribution from the Paul M. Gross Chemical Laboratories, Duke University, Durham, North Carolina 27706. Received September 21, 1988.

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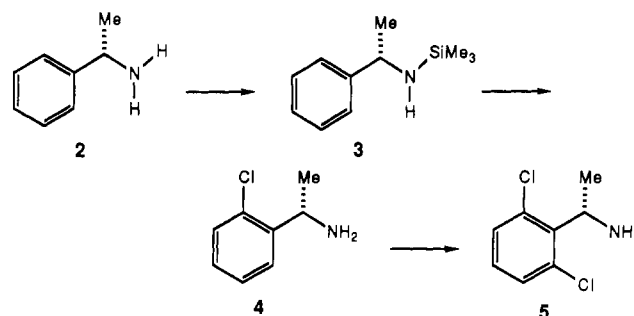
Abstract: “Second generation” chiral amines (1*S*)-(–)-1-(2-chlorophenyl)ethylamine (4) and (1*S*)-(–)-1-(2,6-dichlorophenyl)ethylamine (5) have been prepared from commercially available (*S*)-(–)- α -phenethylamine. These chiral reagents have been incorporated into chiral iminium ions of structural type 1. The iminium ions 1a–c undergo highly diastereoselective hydride reduction to afford chiral, 1-substituted tetrahydroisoquinolines. The sense of asymmetric induction was unambiguously assigned in selected cases by chemical correlation with (*S*)-(–)-salsolidine and (*S*)-(–)-norlaudanosine.

Iminium ions form an important set of electrophiles which participate in carbon–carbon bond forming reactions.¹ We have been interested in obtaining information regarding the transition-state geometry associated with the addition of nucleophiles to chiral iminium ions.² Herein we report highly stereoselective hydride reductions of chiral iminium ions of structural type 1.



The chirality resident in substrates 1 was derived from (*S*)-(–)- α -phenethylamine. Key to this study was the preparation of derivatives of α -phenethylamine which, relative to the parent structure, possess enhanced steric differences between the aryl and methyl groups. It was assumed that the degree of stereoselection observed in reduction of iminium ions 1 would be governed by steric factors. The single stereogenic center appended to the nitrogen atom of the iminium ion moiety in 1a–c creates different steric environments on the two iminium ion diastereofaces in the ground state and/or transition state of the nucleophilic addition reaction. It was anticipated that increasing the relative size difference between methyl and aryl groups in iminium ions 1 would selectively increase the steric crowding of one iminium ion diastereoface and enhance hydride-reduction diastereoselection in the series 1a \rightarrow 1b \rightarrow 1c.

Preparation of Reagents 4 and 5. The strategy employed in preparing “second generation” chiral amines 4 and 5 involved



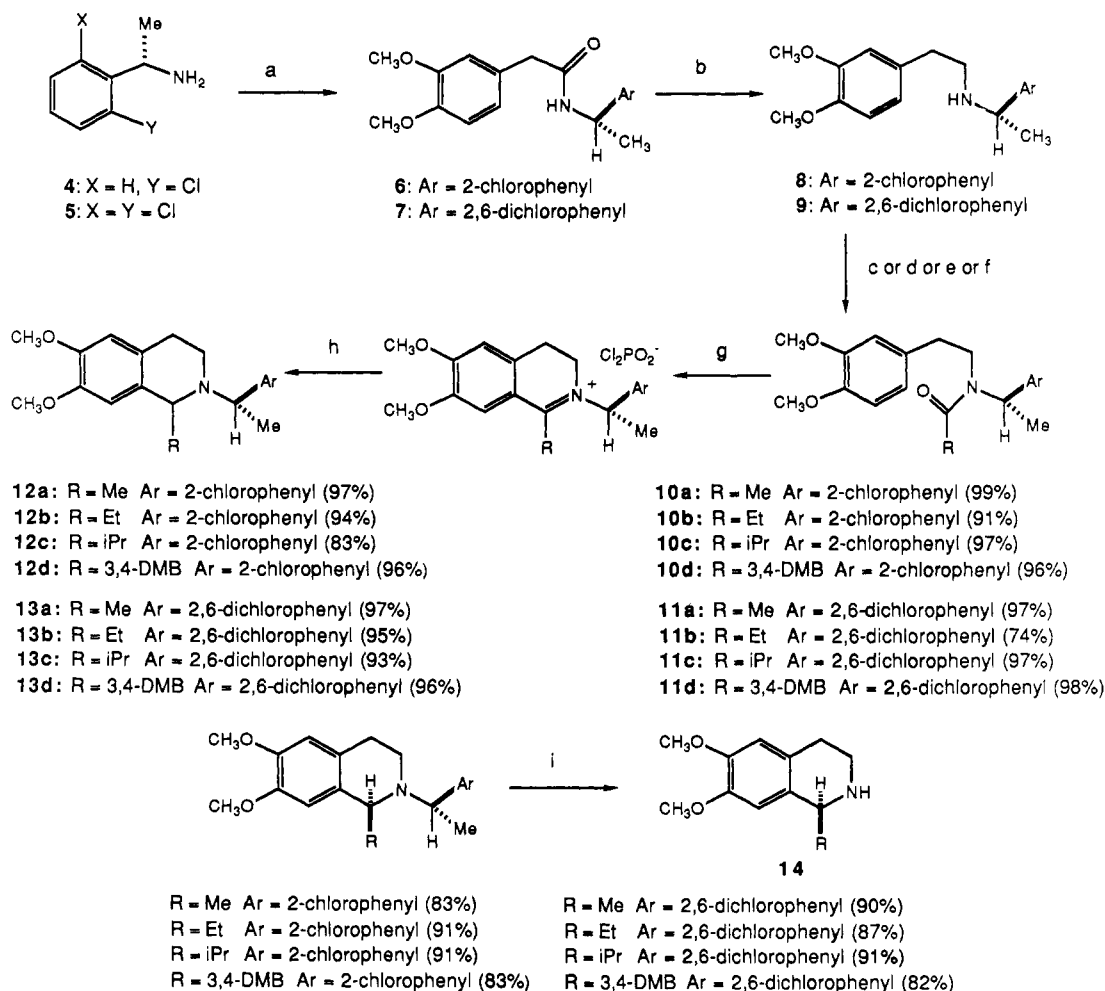
functionalization of the 2- and 2,6-positions of the aromatic ring of α -phenethylamine via directed-metalation reactions. (*S*)-(–)- α -Phenethylamine (2) ($[\alpha]_D = -39^\circ$ (neat), 96.5% ee)³ was monosilylated⁴ (2 equiv of $(\text{TMS})_2\text{NH}$, 0.04 equiv of $(\text{NH}_4)_2\text{SO}_4$,

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(2) Polniaszek, R. P.; McKee, J. A. *Tetrahedron Lett.* **1987**, 28, 4511. Kametani first reported the reduction of 1a (*R* = Me) with NaBH_4 at 0°C to proceed with a diastereoselectivity of 72:28. This material was subsequently converted to *S*-(–)-salsolidine by hydrogenolysis: Kametani, T.; Okawara, T. *J. Chem. Soc. Perkin Trans. 1* **1977**, 579.

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[†] Taken in part from the M.S. thesis of Kaufman, C. R., Duke University, 1988.

Scheme 1^a

^aReagents: (a) 1.2 equiv 1,1'-carbonyldiimidazole, 1.2 equiv 3,4-dimethoxyphenylacetic acid, THF, 0–25 °C, 24 h; (b) 2.5 equiv BH₃–THF, 0.4 equiv BF₃·Et₂O, THF, reflux, 2–4 h; (c) 1.5 equiv Ac₂O, 0.1 equiv DMAP, CH₂Cl₂, 1.2 equiv NEt₃; (d) 2 equiv propionyl chloride, 0.5 equiv DMAP, 2.2 equiv NEt₃, CH₂Cl₂; (e) 2 equiv isobutyryl chloride, 0.1 equiv DMAP, 2.2 equiv NEt₃, CH₂Cl₂; (f) 2.5 equiv DCC, 2.5 equiv (3,4-dimethoxyphenyl)acetic acid, CH₂Cl₂, 25 °C; (g) 2:1 benzene–POCl₃, 90 °C, 4–72 h; (h) 4–5 equiv NaBH₄, added in portions, 3 h, –78 °C; (i) H₂, 10% Pd/C, EtOH–EtOAc, 10% HCl, 8–24 h.

125 °C, 24 h, then 0.1 equiv of TMSCl, 125 °C, 24 h; 86%) and the resultant silylamine 3 was dilithiated (3 equiv of *n*-BuLi, 25 °C, 24 h) according to the general method of Corriu.⁵ Reaction of the *N*-lithio-2-lithiosilylamine with hexachloroethane⁶ (–78 to –40 °C) afforded (1*S*)-(–)-1-(2-chlorophenyl)ethylamine (4), 65%, [α]_D = –43.6° (*c* 3.2, CH₂Cl₂), after aqueous workup. The amine 4 was then monosilylated⁴ as above (83%) and dilithiated⁵ (3 equiv of *n*-BuLi, 0 °C, 40 min), and the dilithiosilylamine was reacted with hexachloroethane⁶ (–78 to –40 °C) to produce (1*S*)-(–)-1-(2,6-dichlorophenyl)ethylamine (5), 45%, [α]_D = –7.6° (*c* 2.9, CH₂Cl₂). The three chiral amines 2, 4, and 5 represent a series of compounds which possess a monotonic increase in steric size difference between aryl and methyl groups.

Generation and Reduction of Chiral Iminium Ions 1b–c. (1*S*)-(–)-1-(2-chlorophenyl)ethylamine (4) and (1*S*)-(–)-1-(2,6-dichlorophenyl)ethylamine (5) were reacted (Scheme I) with (3,4-dimethoxyphenyl)acetic acid and 1,1'-carbonyldiimidazole⁷ to afford amides 6 (97%, mp 138.5–139 °C) and 7 (94%, oil). The amides were reduced to amines 8 (97%, [α]_D = –33.4° (*c*

1.1, CHCl₃)) and 9 (95%, [α]_D = 1.6° (*c* 2.6, CH₂Cl₂)) with BH₃–THF and BF₃·Et₂O in refluxing THF.⁸ The amines 8 and 9 were acylated with either acetic anhydride, propionyl chloride, or isobutyryl chloride in the presence of 4-dimethylaminopyridine and triethylamine. Amides 10d and 11d were most efficiently prepared by reaction of amines 8 and 9 with (3,4-dimethoxyphenyl)acetic acid in the presence of dicyclohexylcarbodiimide.^{9,10} The chiral amides 10a–d and 11a–d were cyclized¹¹ with excess POCl₃ in benzene at 90 °C. The resultant chiral iminium ions were isolated by evaporative removal of solvent under reduced pressure. The unpurified iminium ions were simply dissolved in anhydrous methanol and reacted with excess solid NaBH₄ at –78 °C. These reductions proceeded with a very high precision of stereoselection (Table I), and the difference in free energy of activation between the lowest energy competing transition states ($\Delta\Delta G^\ddagger$) responsible for the formation of D₁ and D₂ is greater than 1.6 kcal/mol for all iminium ions derived from amine 5. The corresponding values for reduction of iminium ions 1 derived from amine 4 and (S)-(–)- α -phenethylamine² (2) are presented in Table

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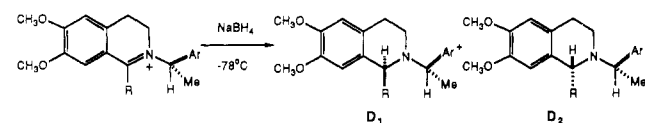
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(10) Amides 10a–d and 11a–d were obtained as a mixture of *E* and *Z* configurational isomers. High-field ¹H NMR spectra were obtained in *p*-xylene-*d*₁₀ at 120 °C, where amide rotation was fast relative to the NMR time scale.

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Table I. Product Ratios and Differences in Free Energy for the Reduction of Iminium Ions


	Ar = phenyl		Ar = 2-chlorophenyl		Ar = 2,6-dichlorophenyl	
	D ₁ :D ₂ ^a	ΔΔG [‡]	D ₁ :D ₂ ^a	ΔΔG [‡]	D ₁ :D ₂	ΔΔG [‡]
R = Me	91:9	0.87	100:0 ^b	>1.8	98.4:1.6	1.6
R = Et	92:8	0.94	95:5	1.1	100:0 ^b	>1.8
R = iPr	88:12	0.77	98.6:1.4	1.7	98.6:1.4	1.7
R = 3,4-DMB ^c	94:6	1.1	87:13	0.73	99:1	1.8

^a Unless stated otherwise, all diastereomeric ratios were determined by HPLC on an ISCO 5 mm × 25 cm 5-μm silica column with UV detection (254 nm). ^b In these cases only one diastereomer could be detected by HPLC and 500-MHz ¹H NMR in both the presence and absence of shift reagents. The diastereomeric purity was further checked by comparison of the optical rotations of hydrogenolysis products **14** (R = Me,¹² R = 3,4-DMB¹³). ^c DMB = dimethoxybenzyl.

I for comparison. The configuration of the newly generated asymmetric center in tetrahydroisoquinolines **12** and **13** was assigned by selective hydrogenolysis of **12a** and **13a** to (*S*)-(-)-salsolidine¹² and **12d** and **13d** to (*S*)-(-)-norlaudanosine.¹³ Stereochemical assignments for **12b,c** and **13b,c** were made by analogy. The chemistry realized in this reaction sequence is very efficient and highly stereoselective.

Discussion

The nucleophilic addition reactions reported in Table I represent examples of 1,3 asymmetric induction. These reactions are ionic in nature. A reasonable first step may be ion metathesis and formation of an iminium ion–borohydride ion pair prior to hydride reduction. Iminium ions **1a–c** possess a carbon–nitrogen double bond embedded in a rather rigid six-membered ring. It appears that only two conformational degrees of freedom are accessible to these structures: rotation about the C–N single bond linking the nitrogen atom to the stereogenic center and rotation about the C–C single bond linking the chloro aromatic moiety to the stereogenic center. The data in Table I indicate that iminium ions **1** tend to prefer transition-state conformations in which the re diastereoface is more hindered to nucleophile approach than the si diastereoface. Upon substitution of the phenyl moiety with chlorine substituents, the net steric shielding of the iminium ion re diastereoface increases, and hence reaction stereoselection increases.

Assuming the reduction reaction proceeds by a polar process, interpretation of the stereoselection data in Table I reduces to determining those iminium ion conformers which participate in the hydride-reduction reaction, the extent to which they contribute, and the diastereofacial preference of each “reactive conformation.” At this point in time, we have not acquired enough data to provide a definitive description of the transition-state topology of this reaction. We are systematically probing the question of the transition-state topology associated with the addition of nucleophiles to the carbon–nitrogen double bond, both experimentally and computationally, and will describe these results in due course. In addition, we are currently applying the synthesis methodology described in this report to the enantioselective construction of antiviral and antitumor agents.

The stereoselective reduction of iminium ions **1** affords chiral, 1-substituted tetrahydroisoquinolines. Chiral electrophiles **1** complement the elegant stereoselective alkylation reactions of chiral formamidine¹⁴ and oxazoline¹⁵ nucleophiles, the catalytic

asymmetric reduction of enamides,¹⁶ and other protocols¹⁷ which also provide methodology for constructing chiral, 1-substituted tetrahydroisoquinolines.

Experimental Section

(1*S*)-(-)-1-(2-Chlorophenyl)ethylamine (4). A dry, 100-mL round-bottomed flask was charged with a stir bar, (*S*)-(-)-α-phenethylamine (6.1 g, 50 mmol), ammonium sulfate (228.0 mg, 2 mmol), and a reflux condenser and the system was purged with nitrogen. Hexamethyldisilazane (21.1 mL, 100 mmol) was added via a syringe, and the reaction mixture was heated to 100 °C. After 5 h, the mixture was heated to 125 °C. After 19 h, the mixture was cooled to 25 °C, an aliquot was dissolved in dry hexane, and capillary GC analysis (DB-5, 15 psi, 150 °C) revealed 90% conversion to the monosilylamine. Neat trimethylsilyl chloride (0.5 mL) was added and the mixture was reheated to 125 °C. After 12 h, capillary GC analysis indicated nearly complete conversion to the silylamine **3**. After cooling of the mixture to 0 °C for 1 h to precipitate ammonium salts, the liquid was transferred via a cannula under N₂ to a 100-mL flask. The oil was fractionally distilled on a Kugelrohr apparatus; first at 1 mmHg to remove excess hexamethyldisilazane followed by venting the system to argon from a mercury over-pressure bubbler, changing receiver bulbs, and distilling the residue at 50–60 °C, 0.1 mmHg, to afford (*S*)-*N*-trimethylsilyl-1-phenylethylamine (**3**) as a clear colorless oil: 8.2 g, 86%. On occasion the silylation reaction required longer thermolysis times to go to completion. The reaction was always checked by capillary GC prior to distillation. The reactions tend to proceed to completion faster in the presence of 4 equiv of hexamethyldisilazane.

A dry, 500-mL single-necked round-bottomed flask was equipped with a rubber septum and a stir bar and purged with nitrogen. The flask was charged with amine **3** (8.20 g, 42.8 mmol) and diethyl ether (62 mL) and cooled to 0 °C. A solution of *n*-BuLi (58.3 mL, 3 equiv, 2.2 M in hexane) was added dropwise via a syringe, the ice bath was removed, and the mixture was stirred at 25 °C for 24 h. The mixture was cooled to –78 °C, and a solution of hexachloroethane (20.3 g, 2 equiv) in ether (52 mL) was added via a cannula over a 1-h period. The internal temperature of the reaction was not allowed to rise above –65 °C during the addition. Upon completion of addition, the temperature was raised to –40 °C, and after 1 h, 2.25 N HCl (150 mL) was added. The mixture was allowed to warm to room temperature and the ether layer was extracted twice with 2.25 N HCl. The combined aqueous layers were cooled to 0 °C, basified with solid KOH to pH 13, and extracted four times with dichloromethane. The combined organic extracts were dried (Na₂SO₄), filtered, concentrated, and flash chromatographed on silica gel¹⁸ with a gradient of ethyl acetate → 5:95 → 10:90 methanol–ethyl acetate. The amine (*R*_f 0.1 in 5:95 MeOH–EtOAc) was isolated as a yellow oil (4.7 g). Kugelrohr distillation (40–45 °C at 0.1 mmHg) afforded a clear colorless oil (4.4 g, 67%): IR (NaCl) 3450 (m), 3170 (m), 758 (m) cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 7.52 (dd, 1 H, *J* = 1.8, 7.8 Hz), 7.31 (dd, 1 H, *J* = 1.4, 7.8 Hz), 7.26 (td, 1 H, *J* = 1.3, 7.6 Hz), 7.14 (td, 1 H, *J* = 1.7, 7.6 Hz), 4.52 (q, 1 H, *J* = 6.6 Hz, ArCHCH₂NH₂), 1.54 (br s, 2 H, NH₂), 1.38 (t, 1 H, *J* = 6.6 Hz, ArCHNH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 144.6, 132.6, 129.6, 127.8, 127.2, 126.3, 47.6, 23.7; mass spectrum (CI, NH₃) *m/e* 156 (MH⁺, base peak) Cl³⁵; [α]_D = –43.6° (c 3.2, CH₂Cl₂). Anal. Calcd for C₈H₁₀ClN: C, 61.7; H, 6.4. Found: C, 61.6; H, 6.3.

(1*S*)-(-)-1-(2,6-Dichlorophenyl)ethylamine (5). A mixture of amine **4** (3.2 g, 20.4 mmol), (NH₄)₂SO₄ (270.0 mg, 0.1 equiv), and hexamethyldisilazane (17.2 mL, 4 equiv) was treated according to the procedure described above. Fractional Kugelrohr distillation afforded (*S*)-*N*-trimethylsilyl-1-(2-chlorophenyl)ethylamine as a clear oil: bp 80 °C at 0.1 mmHg, 3.8 g, 83%.

To an ice-cold solution of (*S*)-*N*-trimethylsilyl-1-(2-chlorophenyl)ethylamine (4.6 g, 20.2 mmol) in ether (50 mL) was added *n*-BuLi (27.5 mL, 60.6 mmol, 2.2 M in hexane) dropwise via a syringe over a period of 20 min. The resultant straw yellow solution was stirred at 0 °C for 40 min and cooled to –78 °C, and a solution of hexachloroethane (9.6 g, 2 eq) in ether (28 mL), was added via a cannula over 1 h. The internal reaction temperature was maintained below –66 °C during the addition. The stirred mixture was warmed to –40 °C and, after 1 h, quenched with 2.25 N HCl. The reaction mixture was worked up and flash chromatographed¹⁸ as described above for **4**. A yellow oil (1.75 g) was obtained. Kugelrohr distillation (80 °C at 0.1 mmHg) afforded a colorless oil: 1.7

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g, 45%; IR (NaCl) 3400 (m), 3300 (m), 3060 (w), 790 (s), 770 (s) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.26 (d, 2 H, $J = 7.8$ Hz), 7.07 (t, 1 H, $J = 7.8$ Hz), 4.89 (q, 1 H, $J = 7.1$ Hz, $\text{NCHCH}_3\text{ArCl}_2$), 2.08 (s, 2 H, NH_2), 1.54 (d, 3 H, $J = 7.1$ Hz, NCHCH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 140.8, 133.9, 129.2, 127.6, 48.7, 20.8; mass spectrum (CI, NH_3) m/e 190 (MH^+) Cl^{35} ; $[\alpha]_D = -7.6^\circ$ (c 2.9, CH_2Cl_2). Anal. Calcd for $\text{C}_8\text{H}_9\text{Cl}_2\text{N}$: C, 50.6; H, 4.8. Found: C, 50.7; H, 4.8.

(S)-N-[1-(2-Chlorophenyl)ethyl]-2-(3,4-dimethoxyphenyl)acetamide (6). A solution of 1,1'-carbonyldiimidazole (197 mg, 1.2 equiv) in THF (8 mL) was cannulated into an ice-cold solution of (3,4-dimethoxyphenyl)acetic acid (235 mg, 1.2 equiv) in THF (8 mL). The solution was stirred at 25°C for 20 h and cooled to 0°C , and a solution of (1S)-(-)-1-(2-chlorophenyl)ethylamine (155 mg, 1 equiv) in THF (2 mL) was cannulated into the ice-cold solution of the acylimidazole. The solution was stirred at 25°C for 20 h, concentrated to a small volume, and placed directly on a prepacked column ($1'' \times 6''$) of silica gel¹⁸ and eluted with 25:75 \rightarrow 50:50 EtOAc-hex. The amide **6** (R_f 0.22, 50:50 EtOAc-hexane) was obtained as a white, crystalline solid, 324 mg, 97%, mp $138.5\text{--}139^\circ\text{C}$. IR 3425 (m), 1660 (s) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.28–7.35 (m, 1 H, ArClH), 7.11–7.23 (m, 3 H, ArClH), 6.74–6.88 (m, 3 H, $(\text{MeO})_2\text{ArH}$), 5.87 (br d, 1 H, $J = 7$ Hz, NH), 5.38 (qn, 1 H, $J = 7$, NCHMeArCl), 3.89 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.53 (2 H, s, $(\text{MeO})_2\text{ArCH}_2\text{CO}$) 1.40 (d, 3 H, $J = 7$ Hz, $\text{NCHCH}_3\text{ArCl}$); ^{13}C NMR (75 MHz, CDCl_3) δ 20.8, 43.3, 47.3, 55.86, 55.93, 111.5, 112.3, 121.6, 127.0, 127.2, 127.3, 128.4, 130.1, 132.7, 140.4, 148.3, 149.2, 170.2; mass spectrum (CI, NH_3) m/e 334 (MH^+) Cl^{35} ; $[\alpha]_D = 21.8^\circ$ (c 1.0, CHCl_3). Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{ClNO}_3$: C, 64.8; H, 6.0. Found: C, 64.8; H, 6.0.

(S)-N-[1-(2,6-Dichlorophenyl)ethyl]-2-(3,4-dimethoxyphenyl)acetamide (7). A solution of 1,1'-carbonyldiimidazole (195 mg, 1.2 equiv), in THF (8 mL) was reacted with (3,4-dimethoxyphenyl)acetic acid (235 mg) in THF (8 mL) and (1S)-(-)-1-(2,6-dichlorophenyl)ethylamine (190 mg, 1 equiv) according to the procedure described above to afford amide **7** as an oil: 367 mg, 94%; IR (CHCl_3) 3400 (m), 1650 (s) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.20 (d, 2 H, $J = 8$ Hz, $\text{NCHCH}_3\text{ArCl}_2\text{H}$), 7.04 (t, 1 H, $J = 8$ Hz, $\text{NCHCH}_3\text{ArCl}_2\text{H}$), 6.71–6.84 (m, 3 H, $\text{C}_6\text{H}_3(\text{OMe})_2$), 6.55 (d, 1 H, $J = 8.6$ Hz, NH), 5.94 (m, $\text{NCHCH}_3\text{ArCl}_2$), 3.85 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.48 (s, 2 H, $(\text{MeO})_2\text{ArCH}_2\text{CO}$), 1.50 (d, 3 H, $J = 7.1$ Hz, $\text{NCHCH}_3\text{ArCl}_2$); ^{13}C NMR (75 MHz, CDCl_3) δ 170.1, 149.2, 148.3, 137.2, 129.2, 128.6, 127.0, 112.5, 111.4, 55.9, 55.8, 45.9, 43.3, 18.6; mass spectrum (CI, NH_3) m/e 368 (MH^+) Cl^{35} ; $[\alpha]_D = 45.4^\circ$ (c 1.6, CH_2Cl_2). Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{Cl}_2\text{NO}_3$: C, 58.7; H, 5.2. Found: C, 58.8; H, 5.3.

(S)-N-[2-(3,4-Dimethoxyphenyl)ethyl]-1-(2-chlorophenyl)ethylamine (8). A 100-mL round-bottomed flask was charged with a stir bar, amide **6** (1.0 g, 3 mmol) and a reflux condenser, and the system was purged with nitrogen. THF (20 mL) and then $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.6 mL) were added via a syringe. The solution was heated to a gentle reflux, and $\text{BH}_3\cdot\text{THF}$ (7.6 mL, 1 M) was added dropwise. The solution was refluxed for 2 h, cooled to 0°C , and quenched with 4.5 N HCl (20 mL). The mixture was stirred at 0°C for 1 h and then at 25°C for 1 h and concentrated on a rotary evaporator. The mixture was cooled to 0°C and basified to pH 13 with solid KOH. In the latter stages water and CH_2Cl_2 were added to solubilize the potassium salts and the amine. The mixture was extracted four times with CH_2Cl_2 , and the organic extracts were combined, dried (Na_2SO_4), filtered, and concentrated, and the residue was Kugelrohr distilled (210°C at 0.1 mmHg) to afford the amine **8** as a colorless oil: 927.5 mg, 97%; IR 3340 (w) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.39 (dd, 1 H, $J = 7.5$, 2 Hz, ArClH), 7.34 (dd, 1 H, $J = 7.5$, 1.5 Hz, ArClH), 7.26 (td, 1 H, $J = 7.5$, 1.5 Hz, ArClH), 7.17 (td, 1 H, $J = 7.5$, 2.0 Hz, ArClH), 6.70–6.86 (m, 3 H, $(\text{MeO})_2\text{ArH}$), 4.32 (q, 1 H, $J = 6.5$ Hz, $\text{NCHCH}_3\text{ArCl}$), 3.89 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 2.63–2.90 (m, 4 H, $(\text{MeO})_2\text{ArCH}_2\text{CH}_2\text{N}$), 1.48 (br s, 1 H, NH), 1.33 (d, 3 H, $J = 6.5$ Hz, $\text{NCHCH}_3\text{ArCl}$); ^{13}C NMR (75 MHz, CDCl_3) δ 22.6, 35.8, 48.6, 53.9, 55.7, 55.8, 111.1, 111.8, 120.5, 127.0, 127.1, 127.7, 129.4, 132.4, 133.1, 142.4, 147.3, 148.8; mass spectrum (CI, isobutane) m/e 320 (MH^+) Cl^{35} ; $[\alpha]_D = -33.4^\circ$ (c 1.1, CHCl_3). Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{ClNO}_2$: C, 67.6; H, 6.9. Found: C, 67.6; H, 7.0.

(S)-N-[2-(3,4-dimethoxyphenyl)ethyl]-1-(2,6-dichlorophenyl)ethylamine (9). Amide **7** (603.9 mg, 1.6 mmol) in THF (11 mL) was reduced with $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.33 mL) and borane-THF (4.5 mL, 1 M) according to the procedure for **6**. The reflux time was 6 h. The reduction initially produced a mixture of diastereomeric amine-borane complexes. In the case of amine **9**, these complexes are very stable to aqueous acid. Consequently, after quenching the reaction mixture with 4.5 N HCl, the mixture was vigorously stirred for 12 h to decompose the amine-borane complexes. Purification was achieved by flash chromatography¹⁸ on silica gel ($1'' \times 6''$) with 30:70 \rightarrow 40:60 EtOAc-hexane. A clear colorless oil was obtained: 551.5 mg, 95.3%; IR (CHCl_3) 3350 (w) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.42 (br s, 2 H, ArCl_2H), 7.05 (t, 1 H, $J = 8$ Hz,

ArCl_2H), 6.79–6.66 (m, 3 H, $(\text{MeO})_2\text{ArH}$), 4.78 (q, 1 H, $J = 7.1$ Hz, $\text{NCHCH}_3\text{ArCl}_2$), 3.86 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 2.56–2.82 (m, 4 H, $(\text{MeO})_2\text{ArCH}_2\text{CH}_2$), 2.30 (br s, 2 H, NH_2), 1.50 (d, $J = 7.1$ Hz, 3 H, $\text{NCHCH}_3\text{ArCl}_2$); ^{13}C NMR (75 MHz, CDCl_3) δ 148.7, 147.4, 138.3, 132.5, 128.6, 128.2, 120.7, 111.9, 111.1, 55.9, 55.8, 55.0, 49.0, 36.2, 19.4; mass spectrum (EI) m/e 353 (M^+) Cl^{35} ; $[\alpha]_D = 1.6^\circ$ (c 2.6, CH_2Cl_2). Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{Cl}_2\text{NO}_2$: C, 61.0; H, 5.9. Found: C, 61.1; H, 5.2.

(S)-N-[1-(2,6-Dichlorophenyl)ethyl]-N-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (11a). Acetic anhydride (20 μL) was added dropwise to an ice-cold solution of amine **9** (52.3 mg, 0.15 mmol), 4-dimethylaminopyridine (10.0 mg), and triethylamine (38 μL) in dichloromethane (2 mL). After stirring of the mixture at 25°C for 24 h, Ac_2O (10 μL) was added, and the solution was stirred for 3 h, concentrated, and placed on a prepacked column of silica gel ($1'' \times 10''$) with 30:70 EtOAc-hexane. Flash chromatography¹⁸ with 30:70 \rightarrow 40:60 \rightarrow 50:50 EtOAc-hexane, afforded the amide as a clear oil: 58.2 mg, 99%; IR (CHCl_3) 1640 (s) cm^{-1} ; ^1H NMR (500 MHz, p -xylene- d_{10} , 120°C) δ 6.98 (d, 2 H, $J = 8.0$ Hz, ArCl_2H), 6.56–6.66 (m, 4 H, $(\text{MeO})_2\text{ArH}$ and ArCl_2H), 5.85 (br, unresolved dd, 1 H, $\text{NCHCH}_3\text{ArCl}_2$), 3.63 (s, 3 H, OCH_3), 3.59–3.66 (m, 1 H, $(\text{MeO})_2\text{ArCH}_2\text{CHHN}$), 3.57 (s, 3 H, OCH_3), 3.45–3.51 (m, 1 H, $(\text{MeO})_2\text{ArCH}_2\text{CHHN}$), 2.64–2.70 (m, 1 H, $(\text{MeO})_2\text{ArCHHCH}_2\text{N}$), 2.46–2.52 (m, 1 H, $(\text{MeO})_2\text{ArCHHCH}_2\text{N}$), 1.87 (s, 3 H, CH_3CON), 1.49 (d, 3 H, $J = 7.4$ Hz, $\text{NCHCH}_3\text{ArCl}_2$); mass spectrum (CI, NH_3) m/e 396 (MH^+) Cl^{35} ; $[\alpha]_D = 68.9^\circ$ (c 1.8, CH_2Cl_2). Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{Cl}_2\text{NO}_3$: C, 60.6; H, 5.8. Found: C, 60.7; H, 5.9.

(S)-N-[1-(2,6-Dichlorophenyl)ethyl]-N-[2-(3,4-dimethoxyphenyl)ethyl]propanamide (11b). IR (CHCl_3) 1640 (s) cm^{-1} ; ^1H NMR (300 MHz, p -xylene- d_{10} , 120°C) δ 7.0 (d, 2 H, $J = 8.1$ Hz, ArCl_2H), 6.57–6.91 (m, 4 H, $(\text{MeO})_2\text{ArH}$ and ArCl_2H), 5.92 (q, 1 H, $J = 7.3$ Hz, $\text{NCHCH}_3\text{ArCl}_2$), 3.64 (s, 3 H, OCH_3), 3.63–3.69 (m, 1 H, $(\text{MeO})_2\text{ArCH}_2\text{CHHN}$), 3.58 (s, 3 H, OCH_3), 3.45–3.59 (m, 1 H, $(\text{MeO})_2\text{ArCH}_2\text{CHHN}$), 2.64–2.69 (m, 1 H, $(\text{MeO})_2\text{ArCHHCH}_2\text{N}$), 2.51–2.56 (m, 1 H, $(\text{MeO})_2\text{ArCHHCH}_2\text{N}$), 2.11–2.30 (m, 2 H, $\text{CH}_3\text{CH}_2\text{CON}$), 1.51 (d, 3 H, $J = 7.3$ Hz, $\text{NCHCH}_3\text{ArCl}_2$), 1.09 (t, 3 H, $J = 7.4$ Hz, $\text{CH}_3\text{CH}_2\text{CON}$); mass spectrum (CI, NH_3) m/e 410 (MH^+) Cl^{35} ; $[\alpha]_D = 68.9^\circ$ (c 1.0, CH_2Cl_2). Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{Cl}_2\text{NO}_3$: C, 61.5; H, 6.1. Found: C, 61.4; H, 6.1.

(S)-N-[1-(2,6-Dichlorophenyl)ethyl]-N-[2-(3,4-dimethoxyphenyl)ethyl]-2-methylpropanamide (11c). IR (CHCl_3) 1640 (s) cm^{-1} ; ^1H NMR (300 MHz, p -xylene- d_{10} , 120°C) δ 6.99 (d, $J = 7.0$ Hz, 2 H, ArCl_2H), 6.58–6.68 (m, 4 H, $(\text{MeO})_2\text{ArH}$ and ArCl_2H), 5.98 (q, 1 H, $J = 7.3$ Hz, $\text{NCHCH}_3\text{ArCl}_2$), 3.65–3.82 (m, 1 H, $(\text{MeO})_2\text{CH}_2\text{CHHN}$), 3.64 (s, 3 H, OCH_3), 3.58 (s, 3 H, OCH_3), 3.47–3.55 (m, 1 H, $(\text{MeO})_2\text{ArCH}_2\text{CHHN}$), 2.65–2.78 (m, 2 H, $(\text{MeO})_2\text{CHHCH}_2\text{N}$ and $\text{NCOCH}(\text{CH}_3)_2$), 2.47–2.60 (m, 1 H, $(\text{MeO})_2\text{CHHCH}_2\text{N}$), 1.51 (d, 3 H, $J = 7.3$ Hz, $\text{NCHCH}_3\text{ArCl}_2$), 1.10 (d, 3 H, $J = 6.5$ Hz, $\text{NCOCH}(\text{CH}_3)_2$), 1.03 (d, 3 H, $J = 6.5$ Hz, $\text{NCOCH}(\text{CH}_3)_2$); $[\alpha]_D = 53.8^\circ$ (c 2.2, CH_2Cl_2). Anal. Calcd for $\text{C}_{22}\text{H}_{27}\text{Cl}_2\text{NO}_3$: C, 62.4; H, 6.4. Found: C, 62.1; H, 6.5.

(S)-N-[1-(2,6-Dichlorophenyl)ethyl]-N-[2-(3,4-dimethoxyphenyl)ethyl](3,4-dimethoxyphenyl)acetamide (11d). A solution of DCC (129 mg, 2.5 equiv) in CH_2Cl_2 (1.5 mL) was cannulated into a solution of amine **9** (80 mg, 0.25 mmol), (3,4-dimethoxyphenyl)acetic acid (123 mg, 2.5 eq) and 4-(dimethylamino)pyridine (10 mg) in CH_2Cl_2 (2 mL). After stirring for 27 h at 25°C , the mixture was filtered through a pipet filled with a plug of glass wool, the filtrate was shaken with saturated aqueous NaHCO_3 , dried (Na_2SO_4), filtered, and concentrated, and the residue was flash chromatographed¹⁸ on silica gel with 40:60 \rightarrow 50:50 EtOAc-hexane. The amide was obtained as a colorless oil: 125 mg, 96%; IR (CHCl_3) 1640 (s) cm^{-1} ; ^1H NMR (500 MHz, p -xylene- d_{10} , 120°C) δ 6.95 (d, 2 H, $J = 8.0$ Hz, ArCl_2H), 6.90 (t, 1 H, ArCl_2H), 6.84 (s, 1 H, $(\text{MeO})_2\text{ArH}$), 6.81 (s, 1 H, $(\text{MeO})_2\text{ArH}$), 6.72 (d, 1 H, $(\text{MeO})_2\text{ArH}$), 6.56–6.66 (m, 3 H, $(\text{MeO})_2\text{ArH}$), 6.03 (br uncoalesced q, 1 H, $\text{NCHCH}_3\text{ArCl}_2$), 3.72–3.77 (m, 1 H), 3.62 (s, 3 H, OCH_3), 3.57 (s, 3 H, OCH_3), 3.55 (s, 3 H, OCH_3), 3.53 (s, 3 H, OCH_3), 3.47–3.60 (m, 5 H), 2.64–2.70 (m, 1 H, $(\text{MeO})_2\text{ArCHHCH}_2\text{N}$), 2.47–2.52 (m, 1 H, $(\text{MeO})_2\text{ArCHHCH}_2\text{N}$), 1.50 (d, 3 H, $J = 7.3$ Hz, $\text{NCHCH}_3\text{ArCl}_2$); mass spectrum (CI, isobutane) m/e 532 (MH^+) Cl^{35} ; $[\alpha]_D = 29.6^\circ$ (c 0.83, CH_2Cl_2).

Representative Cyclization-Reduction: 1-Methyl-2-[(1S)-1-(2,6-dichlorophenyl)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13a). A 10-mL round-bottomed flask was charged with a stir bar, amide **11a** (106.2 mg, 0.3 mmol), and a reflux condenser and then purged with nitrogen. Benzene (2 mL) and POCl_3 (1 mL) were added via a syringe, and the solution was heated in an oil bath at 90°C for 4 h. TLC (50:50 EtOAc-hexane, silica) revealed total consumption of the amide. The apparatus was dismantled, the stir bar was removed, and the volatiles were removed from the flask on a rotary evaporator and then on a

high-vacuum rotary evaporator. A stir bar was added to the flask, and the green, viscous oil was dissolved in anhydrous methanol (2.5 mL) under nitrogen. The flask was cooled to -78°C . Solid NaBH_4 (17 mg) was added. In 60 min, 13 mg of NaBH_4 was added. In another 60 min, 15 mg of NaBH_4 was added. In another 60 min, 17 mg of NaBH_4 was added. After an additional 1 h at -78°C , the mixture was quenched by addition of 10% HCl (35 drops) and warmed to room temperature, and the methanol was removed on a rotary evaporator. The residue was basified by adding KOH at 0°C . Water and CH_2Cl_2 were added in the latter stages to solubilize the potassium salts and the amine. The mixture was extracted four times with dichloromethane, the combined extracts were dried (Na_2SO_4), filtered, and concentrated, and the residue was flash chromatographed¹⁸ on silica gel with 20:80 EtOAc–hexane, affording amine **13a** as a colorless oil: 99.4 mg, 97%. HPLC analysis (ISCO 5- μm silica, 2 mL/min, 15:85 EtOAc–hexane) revealed a 98.4:1.6 ratio of diastereoisomers: IR (CHCl_3) 2950 (m) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.25–7.28 (m, 2 H, ArCl_2H), 7.05–7.10 (m, 1 H, ArCl_2H), 6.56 (s, 1 H, $(\text{MeO})_2\text{ArH}$), 6.48 (s, 1 H, $(\text{MeO})_2\text{ArH}$), 4.72 (q, 1 H, $J = 6.9$ Hz, $\text{NCHCH}_3\text{ArCl}_2$), 3.85 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.86–3.93 (q, 1 H, $J = 6.8$ Hz, $\text{NCHCH}_3\text{Ar}(\text{OMe})_2$), 2.82–3.09 (m, 3 H), 2.44–2.37 (m, 2 H), 1.57 (d, 3 H, $J = 6.9$ Hz, $\text{NCHCH}_3\text{ArCl}_2$), 1.29 (d, 3 H, $J = 6.8$ Hz, $\text{NCHCH}_3\text{Ar}(\text{OMe})_2$); ^{13}C NMR (75 MHz, CDCl_3) δ 147.2, 147.0, 139.4, 132.6, 127.9, 126.2, 111.3, 110.5, 56.1, 56.0, 55.8, 53.4, 39.7, 26.0, 18.9, 16.2; mass spectrum (CI, NH_3) m/e 380 (MH^+) Cl^{35} . Anal. Calcd. for $\text{C}_{20}\text{H}_{23}\text{Cl}_2\text{NO}_2$: C, 63.2; H, 6.1. Found: C, 62.6; H, 6.0.

1-Ethyl-2-[(1S)-1-(2,6-dichlorophenyl)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13b). Bischler–Napieralski cyclization required 4 h, 90°C . A white, crystalline solid was obtained: 95%, mp 159–160 $^{\circ}\text{C}$. HPLC analysis (15:85 EtOAc–hexane, 2 mL/min, 5- μm silica) revealed the presence of only one stereoisomer: IR (CHCl_3) 2900 (m) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.26 (d, 2 H, $J = 8$ Hz, ArCl_2H), 7.06 (t, 1 H, $J = 8$ Hz, ArCl_2H), 6.58 (s, 1 H, $(\text{MeO})_2\text{ArH}$), 6.43 (s, 1 H, $(\text{MeO})_2\text{ArH}$), 4.66 (q, 1 H, $J = 7$ Hz, $\text{NCHCH}_3\text{ArCl}_2$), 3.86 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.26–3.30 (m, 2 H), 3.09–3.12 (m, 1 H), 2.86–2.98 (m, 1 H), 2.38–2.45 (m, 1 H), 1.65–1.78 (m, 1 H), 1.61 (d, 3 H, $J = 7$ Hz, $\text{NCHCH}_3\text{ArCl}_2$), 1.39–1.52 (m, 1 H), 0.79 (t, 3 H, $J = 7.3$ Hz, NCH_2CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 147.1, 146.9, 139.9, 136.1, 131.5, 127.8, 126.1, 111.4, 111.3, 61.5, 56.0, 55.7, 38.4, 29.8, 23.4, 15.9, 11.6; mass spectrum m/e 394 (MH^+) Cl^{35} ; $[\alpha]_D = 53.1^{\circ}$ (c 1.2, CH_2Cl_2). Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{Cl}_2\text{NO}_2$: C, 64.0; H, 6.4. Found: C, 64.0; H, 6.3.

1-Isopropyl-2-[(1S)-1-(2,6-dichlorophenyl)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13c). Bischler–Napieralski cyclization required heating at 90°C for 48 h and then at 100°C for 36 h. A colorless oil was obtained which solidified on standing: 94%. HPLC analysis (10:90 EtOAc–hex, 1.5 mL/min, 5- μm silica) revealed a diastereomeric ratio of 98.6:1.4: IR (CHCl_3) 2980 (m) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.22–7.26 (d, $J = 7.8$ Hz, 2 H, ArCl_2H), 7.03–7.08 (t, 1 H, $J = 7.9$ Hz, ArCl_2H), 6.60 (s, 1 H, $(\text{MeO})_2\text{ArH}$), 6.42 (s, 1 H, $(\text{MeO})_2\text{ArH}$), 4.52 (q, 1 H, $J = 7.1$ Hz, $\text{NCHCH}_3\text{ArCl}_2$), 3.87 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.29–3.38 (m, 2 H), 2.77–2.95 (m, 1 H), 2.55–2.62 (m, 1 H), 2.47–2.56 (m, 1 H), 1.64–1.88 (m, 1 H), 1.55 (d, 3 H, $J = 7.1$ Hz, $\text{NCHCH}_3\text{ArCl}_2$), 0.88 (d, 3 H, $J = 6.6$ Hz, $\text{NCHCH}_3(\text{CH}_3)$), 0.75 (d, 3 H, $J = 6.6$ Hz, $\text{NCHCH}_3(\text{CH}_3)$); ^{13}C NMR (75 MHz, CDCl_3) δ 147.3, 145.8, 140.0, 129.7, 127.8, 126.5, 114.0, 111.4, 66.8, 56.0, 55.8, 55.7, 38.2, 33.0, 23.5, 21.2, 20.7, 15.9; mass spectrum (CI, NH_3) m/e 408 (MH^+) Cl^{35} . Anal. Calcd. for $\text{C}_{22}\text{H}_{27}\text{Cl}_2\text{NO}_2$: C, 64.7; H, 6.7. Found: C, 64.8; H, 6.7.

1-(3,4-Dimethoxybenzyl)-2-[(1S)-1-(2,6-dichlorophenyl)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13d). Bischler–Napieralski cyclization required heating at 90°C for 23 h. HPLC analysis (20:80 EtOAc–hexane, 2 mL/min, 5- μm silica) revealed a diastereomeric ratio of 99:1. Following chromatography,¹⁸ amine **13d** was obtained as a colorless oil: 96%; IR (CHCl_3) 3000 (m) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.16 (d, 2 H, $J = 8$ Hz, ArCl_2H), 7.03 (t, 1 H, $J = 8$ Hz, ArCl_2H), 6.40–6.65 (m, 3 H, acyclic $(\text{MeO})_2\text{ArH}$), 6.30 (s, 1 H, $(\text{MeO})_2\text{ArH}$), 5.91 (s, 1 H, $(\text{MeO})_2\text{ArH}$), 4.71 (q, 1 H, $J = 7$ Hz, $\text{NCHCH}_3\text{ArCl}_2$), 3.83 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.69–3.78 (m, 1 H), 3.68 (s, 3 H, OCH_3), 3.54 (s, 3 H, OCH_3), 3.20–3.31 (m, 2 H), 2.87–3.02 (m, 2 H), 2.64–2.71 (m, 1 H), 2.41–2.47 (m, 1 H), 1.55 (d, 3

H, $J = 7.1$ Hz, $\text{NCHCH}_3\text{ArCl}_2$); ^{13}C NMR (75 MHz, CDCl_3) δ 149.5, 147.8, 146.2, 140.1, 133.0, 129.9, 127.8, 126.2, 112.5, 111.6, 111.3, 110.9, 61.8, 56.1, 56.0, 55.7, 55.6, 42.2, 39.7, 24.4, 16.0; mass spectrum (CI, isobutane) m/e 516 (MH^+) Cl^{35} . Anal. Calcd. for $\text{C}_{28}\text{H}_{32}\text{Cl}_2\text{NO}_4$: C, 65.1; H, 6.1. Found: C, 65.0; H, 6.1.

General Hydrogenolysis Procedure: (S)-(-)-Salsolidine (**14**, R = Me). A 10-mL round-bottomed flask was charged with a stir bar and 10% Pd/C (99.8 mg). The Pd/C was washed three times with hexane. EtOH (2 mL) and 10% HCl (30 drops) were added, and the mixture was purged with 1 balloonful of hydrogen. The mixture was stirred and prerduced under balloon pressure of hydrogen for 21 h. Amine **13a** (99.2 mg) in EtOH (0.5 mL)–EtOAc (1.5 mL) was added via a syringe. After 29 h, the mixture was filtered through a small pad of Celite, and the flask was washed thoroughly with EtOH and EtOAc, and the washings were filtered through the Celite pad. The filtrate was concentrated on a rotary evaporator. Water was added, and the mixture was cooled in an ice bath and basified with solid KOH. The mixture was extracted three times with dichloromethane, the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated, and the clear oil was chromatographed¹⁸ through a 5 $\frac{3}{4}$ " pipet filled with 1" of silica gel with the gradient 30:70 EtOAc–hexane \rightarrow 5:95 MeOH–EtOAc \rightarrow 20:80 \rightarrow 40:60 MeOH–EtOAc. (S)-(-)-Salsolidine¹² was obtained as a clear oil: 49 mg, 90%; $[\alpha]_D = -58^{\circ}$ (c 2.4, EtOH), 97.5% ee, lit.¹² $[\alpha]_D = -59.5^{\circ}$ (c 4.39, EtOH). We always obtained optical rotations immediately following chromatographic purification. The tetrahydroisoquinolines **14** are very sensitive to air oxidation.

(1S)-1-Ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (14, R = Et). Amine **13b** (84 mg) hydrogenolyzed (23 h) and purified as above afforded the title compound as a colorless oil: 41.2 mg, 87%; IR (CHCl_3) 2950 (m) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 6.62 (s, 1 H, $(\text{MeO})_2\text{ArH}$), 6.56 (s, 1 H, $(\text{MeO})_2\text{ArH}$), 3.81–3.86 (m, 1 H), 3.85 (s, 3 H, OCH_3), 3.18–3.28 (m, 1 H), 2.92–3.05 (m, 1 H), 2.62–2.82 (m, 2 H), 1.82–1.96 (m, 1 H), 1.79 (s, 1 H, NH), 1.64–1.80 (m, 1 H), 1.01 (t, 3 H, $J = 7.5$ Hz, NCH_2CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 127.2, 111.8, 109.3, 56.7, 56.0, 55.8, 41.2, 29.5, 29.1, 10.5; mass spectrum (EI) m/e 221 (M^+) Cl^{35} ; $[\alpha]_D = -51.9^{\circ}$ (c 2.1, CH_2Cl_2), 100% ee.

(1S)-1-Isopropyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (14, R = iPr). Amine **13c** (122 mg) hydrogenolyzed (24 h) and purified as above afforded the title compound as a clear oil: 64.4 mg, 91%; IR (CHCl_3) 2950 (m) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 6.65 (s, 1 H, $(\text{MeO})_2\text{ArH}$), 6.57 (s, 1 H, $(\text{MeO})_2\text{ArH}$), 3.86–3.90 (m, 1 H, $\text{NCHCH}_3(\text{CH}_3)$), 3.85 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.25–3.32 (m, 1 H), 2.76–2.94 (m, 2 H), 2.55–2.61 (m, 1 H), 2.27–2.33 (m, 1 H), 1.69 (br s, 1 H, NH), 1.12 (d, 3 H, $J = 7$ Hz, $\text{NCHCH}_3(\text{CH}_3)$), 0.74 (d, 3 H, $J = 7$ Hz, $\text{NCHCH}_3(\text{CH}_3)$); ^{13}C NMR (75 MHz, CDCl_3) δ 128.3, 111.6, 109.0, 60.5, 56.0, 55.7, 42.6, 32.4, 28.8, 20.2, 15.6; mass spectrum (EI) m/e 236 (MH^+) Cl^{35} ; $[\alpha]_D = -104.3^{\circ}$ (c 0.9, CH_2Cl_2), 97% ee. Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{NO}_2$: C, 71.5; H, 8.9. Found: C, 71.3; H, 9.0.

S-(-)-Norlaudanosine (14, R = 3,4-Dimethoxybenzyl). Amine **13d** (39.9 mg) hydrogenolyzed (24 h) and purified as above afforded (S)-(-)-norlaudanosine: 21.9 mg, 82%; $[\alpha]_D = -28.8^{\circ}$ (c 1.1, CHCl_3); lit.¹³ $[\alpha]_D = -21^{\circ}$ (c 1, CHCl_3).

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Supplementary Material Available: General experimental procedure and characterization data for amides **10a–d** and tetrahydroisoquinolines **12a–d** (4 pages). Ordering information is given on any current masthead page.