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A Simple Enzymatic Synthesis of (3*S*,4*R*)-(+)-4-Hydroxy-3-phenyltetrahydroisoquinolines

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Abstract. *An efficient versatile method is presented for the stereospecific synthesis of (+)-4-hydroxy-3-phenyltetrahydroisoquinolines **11** and **12** using (R)-arylcyanohydrins as the chiral starting material. From this asymmetric core, the synthetic process proceeds with development of the S absolute stereochemistry for the phenyl group at C-3 and the R configuration at C-1 of the target heterocycle. As the protective group protocol allows the stereospecific deprotection at C-4, (3S,4R)-(+)-4-hydroxy-3-phenyltetrahydroisoquinolines have been prepared using this process.*

Introduction

During the last decade we have been involved in the preparation, stereochemical characterization and synthetic applications of 3-arylisoquinolic derivatives.[1] In fact, one of our latest research programs deals with the synthesis of 4-hydroxyisoquinolines as they have been found to possess important pharmacological activity.[2] As a consequence of our interest in this field, we have recently achieved a novel synthesis of 4-hydroxy-3-phenylisoquinolines from cyanohydrins in good overall yields and high diastereomeric control.[3] However, up to date neither we, nor others as far as we know, had focussed our attention on the enantioselective synthesis of these kind of compounds, moreover, the consulted literature has shown very few examples of the preparation of optically active 4-hydroxytetrahydroisoquinolines and, in all cases reported, kinetic resolution of racemic mixtures was the method of choice.[4]

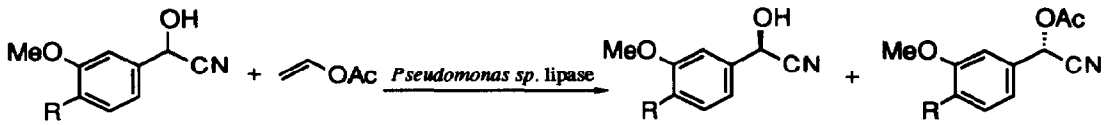
On the other hand, naturally occurring epinephrine (which stimulates the cyclic AMP production) and norepinephrine have the *R* configuration.[5] In addition, only the (*R*)-enantiomer of several natural products with the same β-hydroxyphenethylamine structure, like (-)-ophiocarpine[6], an uterotonic substance, and some synthetic derivatives like racemic 4-hydroxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline, PI-OH, a potentiator on the response of rat anococcygeus muscle to noradrenaline without any side effect at higher concentrations such as postsynaptic inhibition,[7] show biological activity. Consequently, we centered our attention in developing a general asymmetric synthesis of enantiomerically pure (3*S*,4*R*)-(+)-4-hydroxy-3-phenyltetrahydroisoquinolines starting from optically active cyanohydrins with the *R* configuration.

The latter compounds can be obtained by enzyme-catalyzed processes, which have the advantage of high selectivity towards the stereochemistry of the substrate and products, minimal secondary reactions, possibility of recovering the enzymes for a new use without loss of activity and high enantiomeric excess (ee).[8] In this context, and in order to obtain enantiomerically pure arylcyanohydrins using enzymatic catalysts, we have investigated both kinetic resolution of the racemic mixture and asymmetric addition of hydrogen cyanide to the corresponding aldehyde.[9] We now report the completion of such procedures for the preparation of (*R*)-arylcyanohydrins and their use as homochiral starting materials.

Results and Discussion

There have been a number of reports of the use of lipases to resolve racemic cyanohydrins.[10] One recently reported procedure allows the *in situ* preparation and resolution of acetate esters of cyanohydrins,[11] and, more recently, the ability of lipase from *Candida antarctica* (CAL) to catalyze the reaction between alcohols and vinyl carbonates has been communicated.[12]

In our hands, the resolution of (±)-2-hydroxy-2-(3-methoxyphenyl)acetonitrile **1a** and (±)-2-(3,4-dimethoxyphenyl)-2-hydroxyacetonitrile **1b** was carried out by esterification of **1** with vinyl acetate **2**, in the presence of *Pseudomonas sp.* lipase,[13] which can differentiate the acetylation rate of both enantiomers, making the process irreversible and providing the (*R*)-**1** cyanohydrin and the acetylated derivative (*S*)-**3**. The reaction was monitorized by ^{1}H NMR spectroscopy and stopped when the proportion of **1** and **3** was equal. The absolute configuration of the so-obtained cyanohydrins has been assigned on the basis of Kazlaukas's rules.[14]



1a R=H
1b R=OMe

2

(R)-(+)-**1a** R=H
(R)-(+)-**1b** R=OMe

(S)-(+)-**3a** R=H
(S)-(+)-**3b** R=OMe

Figure 1

The ee was measured by studying the ^{1}H NMR signal of the benzylic proton using [Eu(hfc)$_3$] as a chiral shift reagent. The most relevant results of the performed assays are summarized in Table I. It can be seen that the use of the vinyl acetate **2** as solvent (assays 2 and 3 in Table I), instead of CH_2Cl_2, improves the enantioselectivity of the reaction (86 *vs* 76% ee for (+)-**1a**).

Table I. Data obtained from *Pseudomonas sp.* lipase catalyzed resolution.

				(R)-1			(S)-3		
Assay	(R)-1/(S)-1 ratio	Solvent	Time (days)	Yield (%)	$[\alpha]_D^{20}$	ee (%)	Yield (%)	$[\alpha]_D^{20}$	ee (%)
1	**1a** (50 / 50)	CH_2Cl_2	4	56	+29	76	44	-	36
2	**1a** (50 / 50)	vinyl acetate	6	50	+33	86	50	-	55
3	**1a** (81 / 19)	vinyl acetate	6	77	+37	97	-	-	-
4	**1b** (50 / 50)	CH_2Cl_2	5	51	+42	91	49	+16	88
5	**1b** (50 / 50)	vinyl acetate	5	48	+46	>98	52	+18	>98

Trying to increase the already mentioned enantioselectivity, we checked a new assay by applying the same procedure to the racemic mixture **1a** after being enantiomerically enriched with the pure (*R*)-alcohol provided by the enzyme. Thus, a mixture of cyanohydrin **1a** (*R*/*S* ratio 81/19) produced the (+)-enantiomer with more than 95% ee, nevertheless the chemical yield remained still low (assay 3). Similar experiments were carried out for cyanohydrin **1b** but, in this case (assay 5), enantiomerically pure cyanohydrin (*R*)-**1b** was

obtained from racemic starting material, as shown in Table I. It was also observed in this assay that the obtained ee was slightly higher when using vinyl acetate as solvent instead of CH_2Cl_2.

Therefore, we tried to improve the yield of the (*R*)-**1a** epimer by the enzymatically catalyzed addition of HCN to *m*-anisaldehyde **4a** in the presence of *oxynitrilase*, which can differentiate between the *re* and *si* faces of some aromatic aldehydes, providing enantioselectively the *R* adduct.[15] Towards this end, the following procedure was performed: defatted almond meal was used as a source of *oxynitrilase* and HCN was added maintaining the enzyme's optimum pH (5.5). This *modus operandi* afforded the cyanohydrin (*R*)-**1a** in 85% yield, with more than 98% of optical yield ($[\alpha]_D^{20} = +38$; c=1, $CHCl_3$). It is noteworthy to point out the fact that both enzymes, *Pseudomonas sp.* lipase and *oxynitrilase*, provide the same enantiomer.

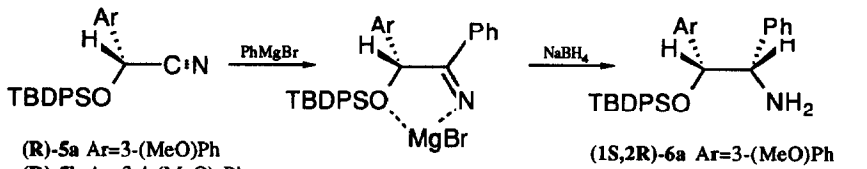
However, veratraldehyde **4b** did not turn out to be a good substrate for *oxynitrilase* enzyme catalyzed reaction, since racemic **1b** was obtained in less than 5% yield under the same experimental conditions.

4a R=H
4b R=OMe

(R)-**1a** R=H, yield=85%, 98% ee
(R)-**1b** R=OMe, yield=5%, 0% ee

Figure 2

Following our synthetic strategy both cyanohydrins, (*R*)-**1a** and (*R*)-**1b**,were protected as the tert-butyldiphenylsilyl ethers (TBDPS), the protection of choice for our synthetic purpose, giving rise to silyl ethers **5a** and **5b** respectively.[3] Subsequent addition of phenylmagnesium bromide to the already obtained derivatives, (*R*)-**5a** and (*R*)-**5b**, followed by reduction ($NaBH_4$) yielded amines **6a** and **6b** in very good yield and without loss of enantiomeric purity[16], as deduced from the ^1H- and ^{19}F-NMR of the Mosher's derivatives. Probably the iminomagnesium intermediate adopts preferentially a chelated conformation which, according to Cram's model, forces addition of the incoming nucleophilic hydride to the less hindered face, leading to the (1*S*,2*R*)-erythro isomer formation.[17] Besides, this stereochemical proposal was confirmed *a posteriori* by measurements of the difference Nuclear Overhauser Effect (NOE),[18] carried out on the target heterocycles **11** and **12**.



(R)-**5a** Ar=3-(MeO)Ph
(R)-**5b** Ar=3,4-$(MeO)_2$Ph

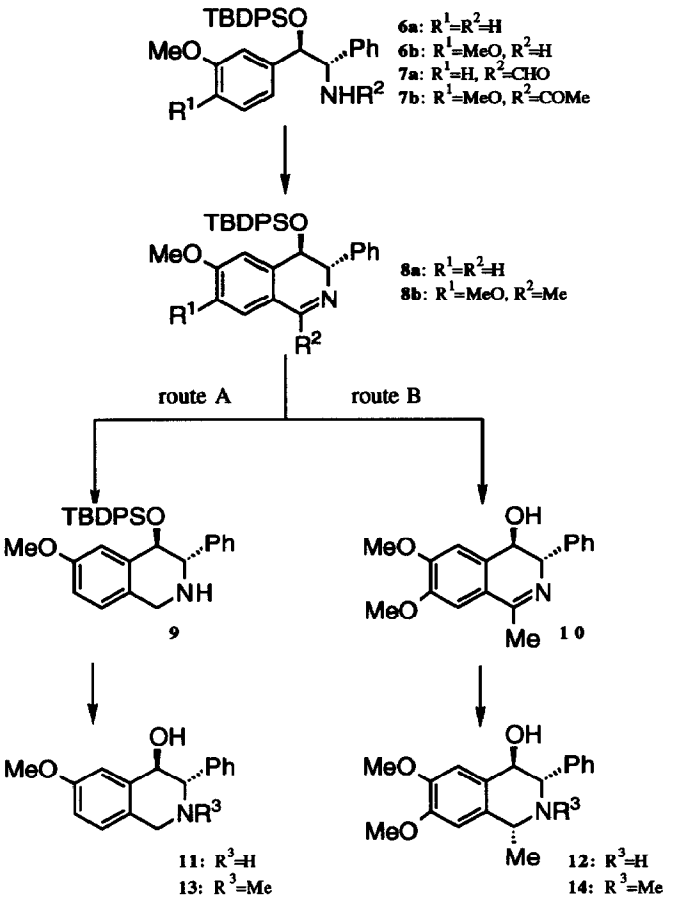
(1S,2R)-**6a** Ar=3-(MeO)Ph
(1S,2R)-**6b** Ar=3,4-$(MeO)_2$Ph

Figure 3

To attempt the final heterocyclization process, the so-obtained amino derivatives **6a** and **6b** were acylated affording amide derivatives **7a** and **7b** which, in turn, were submitted to Bischler-Napieralski

cyclization providing the corresponding dihydroisoquinolines **8a** and **8b** respectively. The outcomes for the subsequent steps, which are summarized below, reveal that the desired final tetrahydroisoquinolines can be obtained in good overall yields without epimerization, starting from enantiomerically pure (*R*)-cyanohydrins **1**. (Table II)

Scheme 1



Finally, in order to establish unambiguously the correct stereochemistry of the prepared tetrahydroisoquinolines, NOE experiments were accomplished on derivatives **9** and **11** showing, for each of them, the expected (3*S*,4*R*) configuration. In the same manner a (1*R*,3*S*,4*R*) configuration for isoquinoline **12** could be proposed. Besides, diagnostic data were obtained from the observation of no-NOE between the H-3 and H-4 protons, thus probing the erythro configuration already assigned to protected β-ethanolamines **6**, on the basis of theoretical data.

The enantiomeric excesses of the target isoquinolines **11** and **12** were deduced from the ^{1}H- and ^{19}F-NMR spectra of the Mosher's salts of the corresponding N-methyl derivatives **13** and **14** respectively.

Table II. Selection of synthetic and physical data of all compounds prepared.

Compound	Yield (%)	$[\alpha]_D^{20}$ (c=1)[a]	Time (h)	M.p. (°C)	Absolute configuration
1a	85	+ 38	36	oil	2*R*
1b	48	+ 46	120	88-89	2*R*
5a	95	- 20	2	oil	2*R*
5b	98	- 35	2	oil	2*R*
6a	91	- 29	5 / on	70-72[b]	1*S*,2*R*
6b	87	- 42	5 / on	210-211	1*S*,2*R*
7a	94	- 40	0.3	123-124	1'*S*,2'*R*
7b	95	- 64	on	118-119	1'*S*,2'*R*
8a	96	- 33°	3	157-158	3*S*,4*R*
8b	94	- 290	2	131-132	3*S*,4*R*
9	87	- 97	on	158-159	3*S*,4*R*
11	82	+ 101	22	197-198	3*S*,4*R*
12	85	+106	on	150-151	1*R*,3*S*,4*R*
10	88	+49	24	192-193	3*S*,4*R*
13	95	+59	on	87-88	3*S*,4*R*
14	92	+60	on	118-119	1*R*,3*S*,4*R*

a) In degassed $CHCl_3$ except for compound **11** (THF).

b) Melted with decomposition.

Conclusion

In summary, the use of chiral cyanohydrins for the synthesis of optically active 4-hydroxy-3-phenyltetrahydroisoquinoline derivatives, **11** and **12**, is very efficient because the former substrate induces an enantioselective synthesis of the ethanolamine precursors **6**, thus introducing the second stereogenic center at the C-3 of the target heterocycle. On the other hand, the subsequent reactions carried out from **6** occur without epimerization of either stereogenic center. Besides, enantiomerically pure 1-methyl substituted tetrahydroisoquinoline **12** can be obtained from dihydroisoquinoline **8b** through a high diastereoselective sequence of deprotection / reduction (route B in Scheme 1). Otherwise, reduction of dihydroisoquinoline **8b** would afford the corresponding 1:1 diastereomeric mixture of (1*S*,3*S*,4*R*)- and (1*R*,3*S*,4*R*)-4-(tert-butyldiphenylsilyloxy)-1-methyl-3-phenyltetrahydroisoquinolines.[3]

EXPERIMENTAL SECTION

General Procedures: Melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were measured on a Perkin-Elmer 1430 spectrophotometer as KBr plates or as neat liquid films; bands are reported in cm^{-1} and only noteworthy absorptions are given. ^1H NMR spectra were recorded at ambient temperature on a Bruker ACE-250 apparatus at 250 MHz with $CHCl_3$ (7.26 ppm) as an internal reference in $CDCl_3$ solutions. ^1H-^1H NOE experiments were carried out in the difference mode by irradiation of all the lines

of a multiplet.[18] ^{13}C NMR spectra were recorded in the same spectrometer at 62.8 MHz with $CHCl_3$ (77.0 ppm) as an internal reference in $CDCl_3$ solutions and were completely decoupled. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), dd (doublet of doublets) or dq (doublet of quadruplets). Coupling constants, *J*, are reported in hertz. HPLC purifications were carried out on a Waters 600E apparatus, with a P/N 91648 Waters column and a Waters R 401 differential refractometer as detector. Flash column chromatography[19] was performed with Merck Kieselgel 60 (230-400 mesh). Analytical thin-layer chromatography (TLC) was done with 0.2 mm thick silica gel plates (Merck Kieselgel GF_{254}) and products were visualized by ultraviolet absorptions or by spraying with Dragendorff's reagent.[20] PH values were measured with a Crison 507 pHmeter. Specific optical rotations (10 mg/ml chloroformic solutions except otherwise stated) were recorded on a Perkin Elmer 241 polarimeter at 20 °C, using a 1 dm cell and the Na lamp. The reactions were carried out under an atmosphere of dry, deoxygenated argon unless otherwise indicated. All tranfers of liquid solutions and solvents were performed by syringe techniques or *via canula*.[21] Tetrahydrofuran was freshly distilled from benzophenone-sodium ketyl. All other solvents used were technical grade and purified according to standard procedures.[22] Defatted almond meal was commercially available from Sigma Chemical Company and *Pseudomonas sp.* lipase was courteously given by Amano Pharmaceutical Company. Combustion analyses were performed on a Perkin-Elmer 2400 CHN apparatus.

***Asymmetric synthesis of cyanohydrin* (*R*)-1a.**

(*R*)-(+)-2-Hydroxy-2-(3-methoxyphenyl)acetonitrile **1a**:

Defatted almond meal (3 g) was swollen by stirring with 5 ml of a 0.02 M citrate buffer pH=5.5 for 15 min. After addition of a solution of 2.72 g (20 mmol) of commercially available *m*-anisaldehyde in 5 ml of ethyl acetate, 75 ml of a HCN saturated solution in ethyl acetate were added and the suspension was stirred for 36 h. The enzyme was filtered under vacuum and the crude material was washed with aqueous sodium bisulfite. The organic layer was dried over Na_2SO_4 and, after solvent evaporation, cyanohydrin (*R*)-**1a** was obtained as a colorless oil in 85% yield; $[\alpha]_D^{20}$= +38[23]; **^1H NMR**: δ 7.35 (dd, *J*=8.0, 8.0, 1H, H-5'); 7.11-6.93 (m, 3H, Harom); 5.49 (d, *J*=7.0, 1H, H-2); 3.82 (s, 3H, CH_3O); 3.14 (d, *J*=7.0, 1H, OH); **^{13}C NMR**: δ 159.8 (C-3'); 136.5 (C-1'); 130.1 (tCarom); 118.9 (CN); 118.7, 115.3, 111.9 (tCarom); 63.1 (C-2); 55.3 (CH_3O); **IR** (neat liq.) υ 3580 (free OH), 3500-3300 (asoc. OH), 2250 (CN); **Anal. Calcd for $C_9H_9NO_2$:** C, 66.23; H, 5.56; N, 8.58. **Found:** C, 66.08; H, 5.66; N, 8.72.

***Pseudomonas sp. lipase-catalyzed resolution of cyanohydrin* (*R*)-1b.**

(*R*)-(+)-2-(3,4-Dimethoxyphenyl)-2-hydroxyacetonitrile **1b**:

Racemic cyanohydrin **1b**[3] (0.2 g, 1.23 mmol) was dissolved in 15 ml of vinyl acetate and 0.12 g of the enzyme were added. After stirring for 5 d (50% conversion) the enzyme was filtered, the solvent was evaporated on a rotatory evaporator and the resulting oil was column chromatographed to give acetate **3b** (hexane/ethyl acetate 7/3) and cyanohydrin (*R*)-**1b** (hexane/ethyl acetate 1/1).

Yield=48%; $[\alpha]_D^{20}$= +46; M.p.: 88-89°C (ether); **^1H NMR**: δ 7.08 (dd, *J*=8.3, 2.1, 1H, H-6'); 7.02 (d, *J*=2.1, 1H, H-2'); 6.88 (d, *J*=8.3, 1H, H-5'); 5.48 (d, *J*=6.7, 1H, H-2); 3.90 (s, 3H, CH_3O); 3.89 (s, 3H, CH_3O); 2.96 (d, *J*=6.7, 1H, OH); **^{13}C NMR**: δ 150.2, 149.5, 127.8 (qCarom); 119.4 (tCarom); 118.8 (CN);

111.2, 109.6 (tCarom); 63.6 (C-2); 56.0 (2xCH3O); **IR** (KBr) υ 3460 (free OH); **Anal. Calcd for** $C_{10}H_{11}NO_3$**:** C, 62.15; H, 5.74; N, 7.25. **Found:** C, 61.92; H, 5.93; N, 7.40.

General procedure for protection of cyanohydrins .

A solution of 1 mmol of (*R*)-(+)-**1**, 102 mg (1.5 mmol) of imidazole and 0.29 ml (1 mmol) of tert-butyldiphenylsilyl chloride in 25 ml of anhydrous DMF was stirred for 2 h. Then, the solution was diluted with 25 ml of EtOAc and washed with water. The organic layer was dried over Na_2SO_4, evaporated, and the resulting yellow oil was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent to obtain cyanohydrins **5** as colorless oils.

(*R*)-(-)-2-(tert-Butyldiphenylsilyloxy)-2-(3-methoxyphenyl)acetonitrile **5a**:

Yield=95%; $[\alpha]_D^{20}$= -20; **^{1}H NMR**: δ 7.70-7.63 (m, 2H, Harom); 7.48-7.15 (m, 9H, Harom); 6.83-6.81 (m, 3H, Harom); 5.22 (s, 1H, H-2); 3.70 (s, 3H, CH_3O); 1.02 (s, 9H, t-C_4H_9-Si); **^{13}C NMR**: δ 159.9, 137.7 (qCarom); 135.8, 135.7 (tCarom); 131.6, 131.4 (qCarom); 130.5, 130.3, 129.9, 128.0, 127.9 (tCarom); 118.9 (CN); 118.7, 115.2, 111.7 (tCarom); 64.7 (C-2); 55.3 (CH_3O); 26.4 ((CH_3)$_3$); 19.3 (SiC); **IR** (neat liq.) υ 1110 (Si-O), 820 (Si-O-C); **Anal. Calcd for** $C_{25}H_{27}NO_2Si$**:** C, 74.78; H, 6.78; N, 3.49. **Found:** C, 74.60; H, 6.75; N, 3.51.

(*R*)-(-)-2-(tert-Butyldiphenylsilyloxy)-2-(3,4-dimethoxyphenyl)acetonitrile **5b**:

Yield=98%; $[\alpha]_D^{20}$= -35; **^{1}H NMR**: δ 7.80-6.70 (m, 13H, arom); 5.31 (s, 1H, H-2); 3.82 (s, 3H, CH_3O); 3.78 (s, 3H, CH_3O); 1.10 (s, 9H, t-C_4H_9-Si); **^{13}C NMR**: δ 149.5, 149.0, (qCarom); 135.5, 135.4, (tCarom); 131.5, 131.3 (qCarom); 130.2, 130.0 (tCarom); 128.6 (qCarom); 127.8, 127.6, 119.0, 110.8, 109.4 (tCarom); 118.8 (CN); 64.4 (C-2); 55.6, 55.5 (2xCH3O); 26.4 ((CH_3)$_3$); 19.0 (SiC); **IR** (neat liq.) υ 1120 (Si-O), 830 (Si-O-C); **Anal. Calcd for** $C_{26}H_{29}NO_3Si$**:** C, 72.36; H, 6.78; N, 3.25. **Found:** C, 72.30; H, 6.90; N, 3.41.

***General procedure for the synthesis of β-ethanolamines* 6.**

A solution of 11.29 mmol of cyanohydrin **5** in 25 ml of anhydrous ether was added dropwise to a freshly prepared solution of 16.90 mmol of phenylmagnesium bromide in 50 ml of the same solvent under vigorous stirring. The mixture was refluxed for 5 h and, after cooling, diluted with 50 ml of anhydrous methanol. Then, 0.86 g (25.58 mmol) of $NaBH_4$ were added in two portions and the reaction continued overnight. For elaboration, 100 ml of water were added, the inorganic residue was filtered and the solution was extracted with dichloromethane and dried over sodium sulfate. After evaporation of the solvent, the crude product was column chromatographed with hexane/ethyl acetate (8/2) to afford the following ethanolamines as pale yellow oils.

(1*S*,2*R*)-(-)-2-(tert-Butyldiphenylsilyloxy)-2-(3-methoxyphenyl)-1-phenylethylamine **6a**:

Yield: 91%; $[\alpha]_D^{20}$= -29; M.p.: 70-72°C (as HCl salt in ethanol); **^{1}H NMR**: δ 7.47-6.95 (m, 16H, Harom); 6.71-6.57 (m, 2H, Harom); 6.40 (s, 1H, Harom); 4.73 (d, *J*=5.5, 1H, H-2); 4.08 (d, *J*=5.5, 1H, H-1); 3.59 (s, 3H, CH_3O); 1.00 (s, 9H, t-C_4H_9-Si); **^{13}C NMR**: δ 158.7, 141.8, 141.6 (qCarom), 135.8 (tCarom), 133.5, 133.2 (qCarom); 129.5, 129.3, 128.4, 127.8, 127.5, 127.4, 127.2, 126.9, 119.8, 113.5, 112.4 (tCarom); 80.5 (C-2); 61.8 (C-1); 54.8 (CH_3O); 26.9 ((CH_3)$_3$); 19.2 (SiC); **IR** (neat liq.) υ 3420, 3320 (NH_2); **Anal. Calcd for** $C_{31}H_{35}NO_2Si$**:** C, 77.30; H, 7.33; N, 2.91. **Found:** C, 77.40; H, 7.38; N, 3.01.

(1*S*,2*R*)-(-)-2-(tert-Butyldiphenylsilyloxy)-2-(3,4-dimethoxyphenyl)-1-phenylethylamine **6b**:
Yield: 87%. $[\alpha]_D^{20}$= -42; M.p.: 210-211°C (as HCl salt in ethanol); **^{1}H NMR**: δ 7.50-6.20 (m, 18H, arom); 4.71 (d, *J*=5.4, 1H, H-2); 4.06 (d, *J*=5.4, 1H, H-1); 3.83 (s, 3H, CH_3O); 3.55 (s, 3H, CH_3O); 1.47 (br s, 2H, NH_2); 0.99 (s, 9H, t-C_4H_9-Si); **^{13}C NMR**: δ 148.0, 147.7, 141.9 (qCarom); 135.9 (tCarom); 133.6, 133.4, 132.5 (qCarom); 129.6, 129.4, 127.9, 127.7, 127.5, 127.3, 127.7, 119.7, 110.6, 110.1 (tCarom); 80.3 (C-2); 61.9 (C-1); 55.8, 55.4 (2xCH_3O); 27.0 ((CH_3)$_3$); 19.3 (SiC); **IR** (neat liq.) υ 3400, 3300 (NH_2); **Anal. Calcd for $C_{32}H_{37}NO_3Si$:** C, 75.11; H, 7.29; N, 2.74. **Found:** C, 74.90; H, 7.39; N, 2.75.

***Synthesis of amide derivatives* 7.**

(1'*S*,2'*R*)-(-)-*N*-[2-(tert-Butyldiphenylsilyloxy)-2-(3-methoxyphenyl)-1-phenylethyl]formamide **7a**:
A suspension of 2.72 g (5.26 mmol) of the hydrochloride of the amine **6a** in 25 ml of formamide was stirred at 150°C in an oil bath for 20 min, then cooled and 75 ml of water was added. The so-obtained precipitate was filtered and recrystallized from hexane/ethyl acetate (9/1) to afford formamide **7a** as a mixture of two rotamers[24] (ratio 4:3).
Yield=94%; M.p.: 123-124°C (hexane/ethyl acetate 9:1); $[\alpha]_D^{20}$ = -40; **^{1}H NMR** δ 7.99 (d, *J*=11.0, 3/7H, CHO); 7.83 (s, 4/7H, CHO); 7.77-6.60 (m, 19H, arom); 5.73-5.69 (m, 1H, NH); 5.17 (dd, *J*=8.7, 3.2, 4/7H, HCN); 5.08 (d, *J*=3.2, 4/7H, H-C-O); 4.92 (d, *J*=3.3, 3/7H, H-C-O); 4.50 (dd, *J*=9.5, 3.3, 3/7H, HCN); 3.58 (s, 3x3/7H, CH_3O); 3.56 (s, 3x4/7H, CH_3O); 1.09 (s, 9x3/7H, t-C_4H_9-Si); 1.07 (s, 9x4/7H, t-C_4H_9-Si); **^{13}C NMR**: δ 160.0, 158.8 (2xC=O); 140.7, 138.8, 138.5, 137.6, 137.2 (qCarom); 135.9, 135.7 (tCarom); 133.3, 133.2, 132.7, 132.4 (qCarom); 130.1, 129.9, 129.7, 129.6, 129.4, 128.8, 128.6, 128.5, 128.1, 127.8, 127.7, 127.6, 127.4, 127.2, 126.6, 125.2, 119.3, 119.0, 114.0, 113.8, 112.1, 111.7 (tCarom); 78.0, 77.6 (2xHCO); 61.7, 57.6 (2xHCN); 54.7 (2xCH_3O); 26.9, 26.8 (2x(CH_3)$_3$); 19.2, 19.1 (2xSiC); **IR** (KBr) υ 3240-3200 (N-H), 1680 (C=O); **Anal. Calcd for $C_{32}H_{35}NO_3Si$:** C, 75.41; H, 6.93; N, 2.75. **Found:** C, 75.22; H, 6.92; N, 3.00.

(1'*S*,2'*R*)-(-)-*N*-[2-(tert-Butyldiphenylsilyloxy)-2-(3,4-dimethoxyphenyl)-1-phenylethyl]acetamide **7b**:
A solution of 511 mg (1 mmol) of amine **6b** in 10 ml of anhydrous dichloromethane was magnetically stirred at room temperature and then, catalytic amounts of DMAP and 0.17 ml (1.5 mmol) of triethylamine were added. Once the solution was cooled with an ice bath, 0.09 ml (1.25 mmol) of acetyl chloride were added and the stirring was continued overnight at room temperature. The crude reaction mixture was poured onto ice, extracted with dichloromethane and dried over sodium sulfate. After evaporation of the solvent under vacuum, the resulting oil was crystallized from hexane/ethyl acetate 7:3 to afford a white solid which was identified as acetamide **7b**.
Yield: 95%; $[\alpha]_D^{20}$ = -64; M.p.: 118-119°C (hexane/ethyl acetate 7:3); **^{1}H NMR**: δ 7.76-6.57 (m, 17H, arom); 6.16 (d, *J*=1.7, 1H, Harom); 5.84 (d, *J*=8.6, 1H, H-2); 5.10 (m, 1H, NH); 5.07 (d, *J*=8.6, 1H, H-1); 3.85 (s, 3H, CH_3O); 3.48 (s, 3H, CH_3O); 1.71 (s, 3H, CH_3); 1.07 (s, 9H, t-C_4H_9-Si); **^{13}C NMR**: δ 169.0 (C=O); 148.1, 147.9, 137.7 (qCarom); 136.0, 135.8 (tCarom); 133.6, 133.0, 132.3 (qCroam); 130.1, 129.7, 128.2, 127.9, 127.6, 127.2, 118.8, 110.2 (tCarom); 77.8 (C-O); 59.2 (C-N); 55.7, 55.3 (CH_3O); 27.0 ((CH_3)$_3$); 23.1 (CH_3); 19.4 (SiC); **IR** (KBr) υ 3270 (N-H), 1680 (C=O); **Anal. Calcd for $C_{34}H_{39}NO_4Si$:** C, 73.74; H, 7.10; N, 2.53. **Found:** C, 73.80; H, 7.18; N, 2.77.

***Typical procedure for the synthesis of dihydroisoquinolines* 8.**

To a stirred solution of 1.48 mmol of amides **7** in anhydrous dichloromethane, 5x0.092 g (0.44 mmol) of PCl_5 were added every 20 min. The additions were made at 0°C and the mixture was allowed to reach room temperature. The reaction mixture was stirred for 2-3 h, then the solution was made alkaline with 20% NaOH (aq), extracted with CH_2Cl_2 and dried over sodium sulfate. The solvent was evaporated and the residue was crystallized affording pure isoquinolines **8**.

(3*S*,4*R*)-(-)-4-(tert-Butyldiphenylsilyloxy)-6-methoxy-3-phenyl-3,4-dihydroisoquinoline **8a**:

Yield=96%; M.p.: 157-158°C (hexane/ethyl acetate 7:3); $[\alpha]_D^{20}$ = -330; **^{1}H NMR**: δ 8.66 (s, 1H, H-1); 7.80-7.76 (m, 2H, Harom); 7.52-7.04 (m, 12H, Harom); 6.85 (dd, *J*=8.3, 2.4, 1H, H-7); 6.65 (m, 2H, Harom); 6.19 (d, *J*=2.4, 1H, H-5); 5.38 (s, 1H, H-3); 4.69 (s, 1H, H-4); 3.55 (s, 3H, CH_3O); 0.99 (s, 9H, t-C_4H_9-Si); **^{13}C NMR**: δ 161.7 (qCarom); 158.7 (C-1); 136.7 (qCarom); 136.0, 135.9 (tCarom); 133.7, 133.6 (qCarom); 129.9, 129.6, 128.9, 128.1, 127.9, 127.4, 127.1, 127.0, (tCarom); 121.4 (qCarom); 114.8, 114.0 (tCarom); 71.8 (C-4); 68.4 (C-3); 55.1 (CH_3O); 26.8 ((CH_3)$_3$); 19.2 (SiC); **IR** (KBr) υ 1630 (C=N); **Anal. Calcd for $C_{32}H_{33}NO_2Si$:** C, 78.17; H, 6.77; N, 2.85. **Found:** C, 78.10; H, 6.75; N, 3.01.

(3*S*,4*R*)-(-)-4-(tert-Butyldiphenylsilyloxy)-6,7-dimethoxy-1-methyl-3-phenyl-3,4-dihydroisoquinoline **8b**:

Yield: 94%; $[\alpha]_D^{20}$ = -290; M.p. = 131-132°C (ether); **^{1}H NMR**: δ 7.79-6.67 (m, 16H, arom); 6.16 (s, 1H, H-5); 5.38 (s, 1H, H-3); 4.72 (d, *J*=2.0, 1H, H-4); 3.93 (s, 3H, CH_3O); 3.47 (s, 3H, CH_3O); 2.60 (s, 3H, CH_3); 0.99 (s, 9H, t-C_4H_9-Si); **^{13}C NMR**: δ 162.4 (C-1); 150.5, 148.6, 137.8 (qCarom); 136.0, 135.8 (tCarom); 133.9, 133.8 (qCarom); 129.4, (tCarom); 128.3 (qCarom); 128.0, 127.8, 127.3, 127.2, 126.8 (tCarom); 121.9 (qCarom); 112.1, 108.3 (tCarom); 72.0 (C-4); 68.1 (C-3); 56.0, 55.5 (CH_3O); 26.7 ((CH_3)$_3$); 23.1 ($C_1\underline{C}H_3$); 19.2 (SiC); **IR** (KBr) υ 1630 (C=N); **Anal. Calcd for $C_{34}H_{37}NO_3Si$:** C, 76.22; H, 6.97; N, 2.61. **Found:** C, 76.48; H, 6.86; N, 2.96.

Reduction of dihydroisoquinolines.

(3*S*,4*R*)-(-)-4-(tert-Butyldiphenylsilyloxy)-6-methoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline **9**:

To a solution of 0.73 g (1.48 mmol) of the dihydroisoquinoline **8a** in 50 ml of anhydrous methanol 0.11 g (2.97 mmol) of $NaBH_4$ were added and the whole was stirred overnight. The reaction was quenched with water and extracted with dichloromethane. The organic solvent was dried over sodium sulfate and evaporated under vacuum. The crude product was purified by flash column chromatography, with hexane/ethyl acetate (8:2) as eluent, to obtain a chromatographically pure colorless oil.

Yield: 87%; M.p.=158-159°C (as HCl salt in ethanol); $[\alpha]_D^{20}$ = -97; **^{1}H NMR**: δ 7.75-7.15 (m, 15H, Harom); 6.87 (d, *J*=8.4, 1H, H-8); 6.68 (dd, *J*=8.4, 2.6, 1H, H-7); 6.44 (d, *J*=2.6, 1H, H-5); 5.06 (d, *J*=4.7, 1H, H-4); 4.23 (d, *J*=4.7, 1H, H-3); 4.04 (d, *J*=14.7, 1H, H-1e); 3.74 (d, *J*=14.7, 1H, H-1a); 3.29 (s, 3H, CH_3O); 0.88 (s, 9H, t-C_4H_9-Si); **^{13}C NMR**: δ 157.5, 140.2, 137.1 (qCarom); 136.1, 135.9 (tCarom); 133.8, 133.0 (qCarom); 129.8, 129.3 (tCarom); 128.4 (qCarom), 128.2, 128.0, 127.7, 127.2, 126.6, 115.1, 113.4 (tCarom); 71.4 (C-4); 63.7 (C-3); 54.7 (CH_3O); 45.2 (C-1); 26.7 ((CH_3)$_3$); 19.4 (SiC); **IR** ($CHCl_3$) υ 3330 (N-H); **Anal. Calcd for $C_{32}H_{35}NO_2Si$:** C, 77.85; H, 7.15; N, 2.84. **Found:** C, 77.77; H, 6.96; N, 2.96.

(1*R*,3*S*,4*R*)-(+)-6,7-Dimethoxy-4-hydroxy-1-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline **12**:

A methanolic solution of 110 mg (0.37 mmol) of dihydroisoquinoline **10** was stirred overnight at room temperature with 43 mg (1.11 mmol) of $NaBH_4$. Then, water was added and the mixture was extracted with

dichloromethane. Solvent was dried over sodium sulfate and evaporated to afford a chromatographycally pure colorless oil, which after crystallization was identified as the tetrahydroisoquinoline **12**.

Yield: 85%; M.p. =150-151°C (hexane/ethyl acetate 1:1); $[\alpha]_D^{20}$ = +106; **^{1}H NMR:** δ 7.52-7.34 (m, 5H, Ph); 7.13 (s, 1H, H-5); 6.68 (s, 1H, H-8); 4.76 (d, *J*=9.0, 1H, H-4); 4.29 (q, *J*=6.5, 1H, H-1); 3.89 (s, 3H, CH_3O); 3.88 (s, 3H, CH_3O); 3.76 (d, *J*=9.0, 1H, H-3); 1.46 (d, *J*=6.5, 1H, CH_3); **^{13}C NMR:** δ 147.8, 147.3, 141.4, 132.4, 130.0 (qCarom); 128.8, 128.2, 127.8, 109.2, 107.8 (tCarom); 72.9 (C-4); 66.6 (C-3); 56.0, 55.9 (2xCH_3O); 53.0 (C-1); 22.7 ($C_1\underline{C}H_3$); **IR** (KBr) υ 3260-3210 (NH, OH); **Anal. Calcd for $C_{18}H_{21}NO_3$:** C, 72.20; H, 7.07; N, 4.68. **Found:** C, 72.27; H, 7.35; N, 4.80.

Deprotection of silylated isoquinolines.

(3*S*,4*R*)-(+)-4-Hydroxy-6-methoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline **11:**

To a stirred solution of 0.69 g (1.40 mmol) of the silylated tetrahydroisoquinoline **9** in 60 ml of dry THF, 3.82 ml of tetrabutylammonium fluoride 1.1M (4.20 mmol) were added at room temperature. After 22 h, water was added and the mixture was extracted with dichloromethane. The combined organic extracts were dried over Na_2SO_4 and evaporated. The resulting yellow oil was column chromatographed with hexane/ethyl acetate (6:4) as eluent, to obtain a white solid which was crystallized from ethyl acetate.

Yield: 82%; M.p.:197-198°C (ethyl acetate); $[\alpha]_D^{20}$: + 101 (c=1, THF); **^{1}H NMR:** δ 7.47-7.26 (m, 5H, Harom); 7.14 (d, *J*=2.6, 1H, H-5); 6.99 (d, *J*=8.4, 1H, H-8); 6.80 (dd, *J*=8.4, 2.6, 1H, H-7); 4.76 (d, *J*=8.2, 1H, H-4); 4.20 (d, *J*=15.2, 1H, H-1e); 4.02 (d, *J*=15.2, 1H, H-1a); 3.82 (s, 3H, CH_3O); 3.78 (d, *J*=8.2, 1H, H-3); **^{13}C NMR:** δ 158.5, 140.9, 138.5 (qCarom); 128.8, 128.1, 127.7 (tCarom); 127.2 (qCarom); 126.8, 114.1, 111.4 (tCarom); 72.2 (C-4); 65.7 (C-3); 55.3 (CH_3O); 47.8 (C-1); **IR** (KBr) υ 3280 (O-H free), 3200–3140 (asoc. O-H, NH); **Anal. Calcd for $C_{16}H_{17}NO_2$:** C, 75.26; H, 6.71; N, 5.49. **Found:** C, 75.32; H, 6.69; N, 5.78.

(3*S*,4*R*)-(+)-6,7-Dimethoxy-4-hydroxy-1-methyl-3-phenyl-3,4-dihydroisoquinoline **10**:

According to the procedure described above the title compound was obtained from **8b** after 24 h of reaction and purified by crystallization from ethyl acetate.

Yield: 88%; $[\alpha]_D^{20}$ = +49; M.p.: 192-193°C (ethyl acetate); **^{1}H NMR:** δ 7.40-7.20 (m, 5H, Ph); 7.02 (s, 1H, H-5); 6.99 (s, 1H, H-8); 4.68 (d, *J*=10.4, 1H, H-4); 4.52 (dq, *J*=10.4, 1.9, H-3); 3.90 (s, 3H, CH_3O); 3.87 (s, 3H, CH_3O); 2.47 (d, *J*=1.9, 3H, CH_3); **^{13}C NMR:** δ 163.8 (C-1); 151.6, 148.3, 140.8, 132.2 (qCarom); 128.6, 128.1, 127.5 (tCarom); 121.4 (qCarom); 108.9, 108.0 (tCarom); 70.8 (C-4); 68.3 (C-3); 56.2, 56.0 (CH_3O); 23.2 ($C_1\underline{C}H_3$); **IR** (KBr) υ 3500-3200 (free and asoc. OH), 1630(C=N); **Anal. Calcd for $C_{18}H_{19}NO_3$:** C, 72.69; H, 6.44; N, 4.71. **Found:** C, 72.55; H, 6.35; N, 4.95.

Typical procedure for the N-methylation of tetrahydroisoquinolines.

To a stirred solution of 1 mmol of the corresponding tetrahydroisoquinoline **11** and **12** in 25 ml of MeCN, 10 mmol of HCHO (35% aq.) and 2 mmol of $NaBH_3CN$ were added at room temperature. After 12 h, water was added and the mixture was extracted with dichloromethane. The combined organic extracts were dried over Na_2SO_4. After evaporation of the solvent, the resulting solid was crystallized to afford the following pure compounds.

(3*S*,4*R*)-(+)-4-Hydroxy-6-methoxy-N-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline **13:**
Yield: 95%; M.p.:87-88°C (hexane); $[\alpha]_D^{20}$: + 59; ^{1}H **NMR**: δ 7.35-7.22 (m, 5H, Harom); 7.05 (d, *J*=2.6, 1H, H-5); 7.00 (d, *J*=8.5, 1H, H-8); 6.83 (dd, *J*=8.5, 2.6, 1H, H-7); 4.77 (d, *J*=6.5, 1H, H-4); 3.81 (s, 3H, CH_3O); 3.73 (d, *J*=15.2, 1H, H-1e); 3.55 (d, *J*=15.2, 1H, H-1a); 3.43 (d, *J*=6.5, 1H, H-3); 2.20 (s, 3H, NMe); ^{13}C **NMR**: δ 158.3, 137.6, 137.4 (qCarom); 128.9, 128.3, 127.8, 126.7 (tCarom); 126.2 (qCarom); 114.2, 111.8 (tCarom); 72.7, 72.0 (C-4, C-3); 55.5 (C-1); 55.1 (CH_3O); 43.0 (NMe); **IR** (KBr) υ 3280 (O-H free), 3200–3140 (asoc. O-H); **Anal. Calcd for $C_{17}H_{19}NO_2$: C**, 75.80; H, 7.11; N, 5.20. **Found:** C, 75.00; H, 6.99; N, 5.33.

(1*R*,3*S*,4*R*)-(+)-6,7-Dimethoxy-1,N-dimethyl-4-hydroxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline **14:**
Yield: 92%; M.p. =118-119°C (hexane); $[\alpha]_D^{20}$ = +60; ^{1}H **NMR:** δ 7.43-7.26 (m, 5H, Ph); 7.06 (s, 1H, H-5); 6.64 (s, 1H, H-8); 4.75 (d, *J*=8.6, 1H, H-4); 3.87 (s, 3H, CH_3O); 3.85 (s, 3H, CH_3O); 3.61 (q, *J*=6.1, 1H, H-1); 3.23 (d, *J*=8.6, 1H, H-3); !.15 (s, 3H, NMe); 1.46 (d, *J*=6.1, 1H, CH_3); ^{13}C **NMR**: δ 148.1, 147.5, 140.7, 130.7, 129.2 (qCarom); 128.9, 128.6, 127.8, 108.8, 107.6 (tCarom); 73.2, 71.8 (C-4, C-3); 60.8 (C-1); 55.9, 55.7 (2xCH_3O); 41.1 (NMe); 22.9 ($C_1\underline{C}H_3$); **IR** (KBr) υ 3400-3100 (OH); **Anal. Calcd for $C_{19}H_{23}NO_3$:** C, 72.80; H, 7.40; N, 4.47. **Found:** C, 72.09; H, 7.55; N, 4.60.

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