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Silicon-mediated Isoquinoline Synthesis: Preparation and Stereochemical Characterization of 4-Hydroxy-3-phenylisoquinolines

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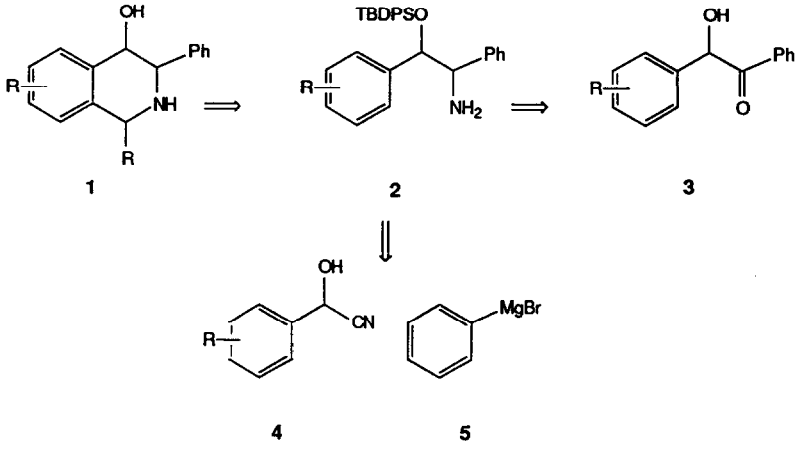
Abstract: The silicon-mediated synthesis of 4-hydroxy-6,7-dimethoxy-3-phenylisoquinoline derivatives is reported. The described procedure implies synthetically useful yields and a high degree of stereoselectivity.

The potent pharmacological activity of simple 4-substituted tetrahydroisoquinolines has generated much interest in their synthesis and in the last years several new naturally-occurring compounds of this type have been isolated.[1] For example, the antidepressant drug Nomifensine[2] has a close relationship to the alkaloid Cherylline,[3] and the 4-phenyl-*N*-methyl-1,2,3,4-tetrahydroisoquinoline is an agonist of dopamine receptors.[4] Besides, an analogue of Nomifensine, racemic 4-hydroxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (PI-OH), has showed a potent potentiating effect on the response of rat anococcygeus muscle to noradrenaline without any side effect at higher concentrations, such as postsynaptic inhibition.[5]

The 4-hydroxy-tetrahydroisoquinoline derivatives are of interest, as it has been proposed that these alkaloids could be involved in the development of alcohol dependence and withdrawal symptoms. Besides, they could also contribute, in general, to the pharmacologic actions of ethanol.[6] On the other hand, Grunewald and co-workers[7] have examined the activity of the 4-hydroxy-tetrahydroisoquinoline on *in vitro* activity as substrate or inhibitor of phenylethanolamine *N*-methyltranferase (PNMT), probing that it inhibited the PNMT-catalyzed methylation of ß-phenylethanolamine by a competitive kinetic mechanism denoting direct active-site interactions for each ligand. In the same context, 4-hydroxytetrahydroisoquinoline was detected as a metabolite of a possible parkinsonism-inducing substance, tetrahydroisoquinoline, in rat liver microsomes and rat urine.[8]

As a consequence of the importance of this type of compound, several synthetic approaches have been developed in order to obtain 4-hydroxyisoquinoline derivatives.[9] On the other hand, during the last years as part of a program of research oriented toward the synthesis of different isoquinoline alkaloids, we have been involved

in the preparation, reactivity, spectroscopic and stereochemical studies of 3-arylisoquinoline derivatives with excellent results.[10] In this context and considering that, to the best of our knowledge, very few 4-hydroxy-3-arylisoquinoline compounds have been obtained,[11] we decided to carry out the preparation and further studies of this type of derivatives.Toward this end two synthetical routes appeared as the most convenient ones for our proposal as shown in the following retro-synthetical Scheme 1.

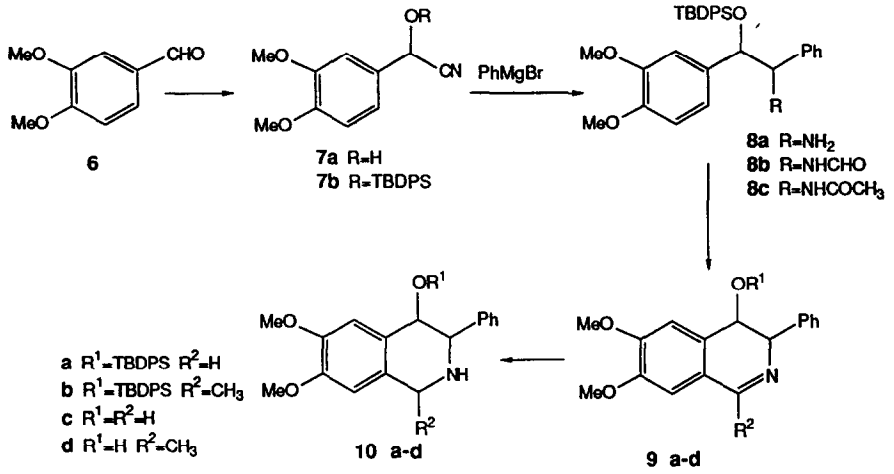


1 2 3 4 5

Scheme 1

With this strategy in mind and in order to avoid side reactions due to the oxygenated function we tried different reagents as alcohol protective groups (TBDPS, TBDMS, TrPS, PDMS and Bn),[12] exploring their use with commercial benzoin. For this purpose, the following factors were evaluated: overall yield for the protection-deprotection process, resistance to different acid-basic media at variable temperatures and stability on storage, thus selecting the TBDPS (t-butyldiphenylsilyl) as the adequate protective group for our proposal. Using the latter reagent the protected benzoin was obtained quantitatively, showing stability in acidic media at room temperature. Nevertheless, under basic reaction conditions the following behaviour was observed: while alcoholic NaOH induced deprotection at room temperature, ammoniacal solutions of the compound under study were stable even under heating. However the subsequent reductive amination ($PrNH_2/TiCl_4/NaBH_4$)[13] afforded the expected amine **2** although with a poor yield (32%). Then, we prepared the corresponding acetyloxime derivative (94%), but different reductive procedures that we carried out, gave negative results. Therefore, we explored the alternative method shown in Scheme 1.

In order to improve the last cyclization reaction, our starting material was 3,4-dimethoxybenzaldehyde **6** which was converted into cyanohydrin **7b**, then reacted with the appropriate organometallic reagent affording, after the corresponding reduction, the 1,2-diarylethylamine derivative **8a** as the *erythro* isomer (^{1}H-NMR), probably due to the formation of an intramolecular chelate which exerts sterical hindrance towards nucleophile attack.[14]



Scheme 2

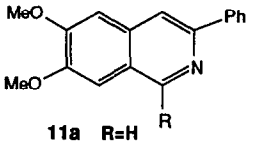
Reaction of the so-obtained compound **8a** with formamide and acetyl chloride afforded amide derivatives **8b** and **8c** respectively in a quantitative yield. Besides, in accordance with the behaviour of similar compounds,[15] we suggest that the formamide derivative **8b** should exist in solution as two amide bond rotamers. In fact, the latter compound is obtained as a mixture of rotamers, as can be deduced from the signals of the ^1H NMR. Amides **8b** and **8c** were submitted to cyclization reaction under Bischler-Napieralski conditions with the results shown in Table 1.

Table 1. Synthetic data of isoquinolines **9** and **11** prepared.

Substrate	Reagent	Solvent	Time (h)	Product	Ratio	Yield[a] (%)
8b	PCl_5	CH_2Cl_2	3	**9a, 11a**	16:1	85
8b	P_2O_5	CH_2Cl_2	3	**11a**		75
8b	PCl_5	CH_3CN	2	**9a, 11a**	2:1	90
8b	P_2O_5	CH_3CN	2	**9a, 11a**	1:5	90
8c	PCl_5	CH_2Cl_2	1	**9b**		85
8c	P_2O_5	CH_2Cl_2	1	**11b**		75
8c	PCl_5	CH_3CN	1	**9b, 11b**	15:1	85
8c	P_2O_5	CH_3CN	1	**11b**		65

a) Total yield of **9** and **11**.

As it can be seen in Table 1, by using PCl_5 as reagent 4-hydroxydihydroisoquinoline derivatives **9a** and **9b** were obtained in good yields. Nevertheless, the use of P_2O_5 as cyclodehydration agent afforded isoquinolines **11a** and **11b**, probably formed by deprotection and subsequent elimination of water, similar to the Pictet-Gams reaction for the synthesis of aromatic isoquinolines.



11a R=H
11b R=Me

It is noteworthy to point out that no rearrangement reaction occurs,as it has been proposed in cyclizations of this type,[16] probably due to the mild reaction conditions employed. In fact, NOE experiments[17] carried out on isoquinolines **11a** and **11b** have shown NOE between H_4 and H_5 protons respectively, thus probing the substitution at C_3. The hypothetical obtention of 4-phenylisoquinoline derivatives should afford products where H_5 could not experiment NOE effect with the vicinal protons. Besides, both isoquinolines **11a** and **11b** showed NOE effect between H_8-H_1 and H_8-CH_3 respectively.

Early investigations developed by our group on the synthesis of 3-aryldihydroisoquinoline derivatives without substitution at C_4, revealed the participation of the solvent in the cyclization process thus avoiding stilbene formation.[18] In the present case such reaction doesn't occur, because the required formation of the intermediate carbocation is not favored, thus the use of CH_2Cl_2 or CH_3CN as solvent is not significant.

With dihydroisoquinolines **9** in hand, and in order to attain our synthetic objetive, reductive reaction conditions were carried out, both with protected and deprotected dihydroisoquinoline derivatives, and the following behaviour was observed: by treatment with $NaBH_4$ dihydroisoquinoline derivative **9a** yielded the expected tetrahydroisoquinoline **10a**, on the contrary the former derivative **9a** underwent simultaneous deprotection/reduction by the action of LAH, thus leading to the 4-hydroxytetrahydroisoquinoline derivative **10c**. It is worthwhile to point out that both reagents show complementary chemical behaviour leading to protected or deprotected tetrahydroisoquinolines (Table 2).

In order to assign the correct stereochemistry to the obtained tetrahydroisoquinolines, NOE experiments were carried out showing that both derivatives **10a** and **10c** exhibited a (*3R*,4S**) configuration as deduced from the observation of no-NOE between H3 and H_4, which must adopt axial and pseudoaxial positions respectively thus confirming the *erythro* configuration already proposed for amine precursor **8a**. Similar behaviour was observed when **9b** was submitted to reduction under the above conditions. However, while the use of $NaBH_4$ as reagent afforded a couple of epimers at C_1, the use of LAH for the same purpose yielded

diastereoselectively only the epimer (*1R*,3R*,4S**) of isoquinoline **10d**, as deduced from selected NOE experiments.

This behaviour can be explained on the basis that both reduction and deprotection are simultaneous and the nucleophile hydride should attack from the less hindered side of the molecule, thus avoiding steric and electronic effects, consequently we can propose that the reaction behaves under kinetic control. Finally, when we tried the already mentioned reduction conditions on dihydroisoquinoline **9d**, we always obtained diastereoselectively derivative **10d** as the epimer: (*1S*,3R*,4S**)-6,7-dimethoxy-4-hydroxy-1-methyl-3-phenyltetrahydro-isoquinoline.

Table 2. Tetrahydroisoquinolines **10** prepared.

Substrate	Product (Method)[a]	Relative configuration	Yield (%)	M.p.(°C) (solvent)
9a	**10c** (A)	*3R*, 4S**	65	166-7 (EtOAc)
9a	**10a** (B)	*3R*, 4S**	75	88-9 (MeOH)
9b	**10d** (A)	*1R*, 3R*, 4S**	75	104-5 (Hexane/ EtOAc)
9b	**10b** (B)	*1R*, 3R*, 4S** and *1S*, 3R*, 4S** [b]	90	113-4 (MeOH) 132-3 (MeOH)
9d	**10d** (A)	*1S*, 3R*, 4S**	85	123-4 (EtOAc)
9d	**10d** (B)	*1S*, 3R*, 4S**	80	123-4 (EtOAc)

a) Method (A): LAH/THF.Method (B): $NaBH_4$/MeOH.
b) The diastereoisomers, obtained in 1:1 ratio, were separated.

In summary, following the reported strategy 4-hydroxy-3-phenyltetrahydroisoquinoline derivatives can be obtained in good overall yield and high stereoselectivity. Besides, from our results we may propose that the use of LAH allows to obtain diastereoselectively isoquinoline derivatives **10d**. This behaviour can be explained assuming that the reaction proceeds specifically under kinetic control on protected dihydroisoquinolines, while under thermodinamic control on the corresponding deprotected derivatives.

EXPERIMENTAL

General Procedures: Melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were measured in a Perkin-Elmer 1430 spectrophotometer as KBr plates or as neat liquid and peaks are reported in cm^{-1}. ^1H NMR spectra were recorded in a Bruker ACE-250 apparatus at 250 MHz with CHCl3 (7.26 ppm) as an internal reference in CDCl3 solutions. ^{13}C NMR spectra were recorded in the same spectrometer at 62.8 MHz with CHCl3 (77.0 ppm) as an internal reference in CDCl3 solutions. Chemical shifts are given in ppm (d); 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. Tetrahydrofuran (THF) was freshly distilled from benzophenone-sodium ketyl. All other solvents used were technical grade and purified according to standard procedures.[19] Thin layer chromatography was performed on silica gel 60 F254 plates and visualized by UV light or Dragendorf's reagent.[20] Flash column chromatography[21] was performed on Merck kieselgel 60 (70-230 mesh ASTM). The reactions were carried out under an atmosphere of dry, deoxygenated argon unless otherwise indicated. All tranfers of liquid solution and solvents were performed by syringe techniques or *via* canula.[22] Combustion analyses were performed with a Perkin-Elmer 2400 CHN apparatus.

2-(3,4-Dimethoxyphenyl)-2-(tert-butyldiphenylsilyloxy)acetonitrile **7b**: A solution of 3.76 g (19.48 mmol) of 2-(3,4-dimethoxyphenyl)-2-hydroxyacetonitrile **7a**, 2.91 g (43 mmol) of imidazole and 5.55 ml (21.4 mmol) of tert-butyldiphenylsilyl chloride in 15 ml of anhydrous DMF was stirred for 90 minutes. Then, 10 ml of water was added and the mixture was extracted with dichloromethane. Work up gave a pale yellow oil which was purified by flash column chromatography using hexane/ethyl acetate (9/1) as eluent. Cyanohydrin **7b** was obtained as a colorless oil in a nearly quantitative yield. ^1H NMR: δ 7.80-6.70 (m, 13H, arom); 5.31 (s, 1H, CH); 3.82 (s, 3H, CH3O); 3.78 (s, 3H, CH3O); 1.10 (s, 9H, t-C4H9-Si); ^{13}C NMR: δ 149.5, 149.0, 131.5. 131.3, 128.6 (qCarom); 135.5, 135.4, 130.2, 130.0, 127.8, 127.6, 119.0, 110.8, 109.4 (HCarom); 118.8 (CN); 64.4 (C-2); 55.6, 55.5 (CH3O); 26.4 ((CH3)3); 19.0 (SiC); IR (neat liq.) υ 1600, 1520. $C_{26}H_{29}NO_3Si$: Calc. C72.36, H 6.78, N 3.25; Found C 72.42, H 6.65, N 3.42.

2-(3,4-Dimethoxyphenyl)-1-phenyl-2-(tert-butyldiphenylsilyloxy)ethylamine **8a**: 8.88 g (20.61 mmol) of cyanohydrin **7a** dissolved in 50 ml of anhydrous ether, was added dropwise to a solution of 27.1 mmol of phenylmagnesium bromide in 150 ml of the same solvent under vigorous stirring. The mixture was refluxed for 6 h, then 150 ml of anhydrous methanol was added slowly and 1.9 g (41.2 mmol) of NaBH4 was added in two portions to the crude and the reaction continued overnight. For the elaboration 100 ml of water was 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 was column chromatographed with hexane/ethyl acetate (8/2) to afford ethylamine **8a** as a pale yellow oil. Yield: 80%. ^1H 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, CH3O); 3.55 (s, 3H, CH3O); 1.47 (br s, 2H, NH_2); 0.99 (s, 9H, t-C4H9-Si); ^{13}C NMR: δ 148.0, 147.7, 141.9, 133.6, 133.4, 132.5 (qCarom); 135.9, 129.6, 129.4, 127.9,

127.7, 127.5, 127.3, 127.7, 119.7, 110.6, 110.1 (HCarom); 80.3 (C-2); 61.9 (C-1); 55.8, 55.4 (CH3O); 27.0 ((CH3)3); 19.3 (SiC); **IR** (neat liq.) υ 3400-3300, 1600, 1520. $C_{32}H_{37}NO_3Si$: Calc. C 75.11, H 7.30, N 2.74; Found C 75.05, H 7.41, N 2.81. The corresponding hydrochloric salt was prepared quantitatively by treating an ethanolic solution of amine **8a** with alcoholic HCl. The so-obtained derivative was recrystallized from ethanol. M.p. 219-220°C. **^{1}H NMR**: δ 7.34-7.11 (m, 15H, arom and NH_3); 6.61-6.37 (m, 2H, arom); 6.37 (s, 1H, arom); 4.95 (d, J=6.5, 1H, H-2); 4.19 (d, J=6.5, 1H, H-1); 3.79 (s, 3H, CH3O); 3.55 (s, 3H, CH3O); 0.90 (s, 9H, t-C4H9-Si); **IR** (KBr) υ 3250-3100, 1590, 1510.

N-[2-(3,4-Dimethoxyphenyl)-1-phenyl-2-(tert-butyldiphenylsilyloxy)ethyl]formamide **8b**: A suspension of 5 g (9.13 mmol) of the hydrochloride of **8a** in 10 ml of formamide was stirred at 150°C for 20 minutes, then cooled and 75 ml of water was added. The so-obtained precipitate was filtered and recrystallized from hexane/ethyl acetate (8/2) to afford formamide **8b** as a mixture of two rotamers (ratio 5:2). M.p. 103-104°C. **^{1}H NMR** δ 8.00 (d, J=11.6, 2/7H, CHO); 7.83 (s, 5/7H, CHO); 7.76-6.54 (m, 17H, arom); 6.16 (d, J=1.41, 5/7H,arom); 6.06 (s, 2/7H, arom), 5.81 (m,1H, NH); 5.13 (dd, J=8.8, 3.3, 5/7H, HCN); 5.09 (d, J=3.3, 5/7H, HCO); 4.90 (d, J=2/7H, HCO); 4.47 (d, J=10.2, 3.5, 2/7H, HCN); 3.84 (s, 3H, CH3O); 3.49 (s, 3H, CH3O); 1.10 (s, 9x2/7H, t-C4H9-Si); 1.07 (s, 9x5/7H, t-C4H9-Si); **^{13}C NMR**: δ 164.4, 160.0 (C=0); 148.4, 148.2, 147.9, 147.8, 137.8, 137.2, 135.5, 133.4, 132.8, 132.6, 131.7, 129.8, 129.6 (qCarom); 136.0, 135.8, 130.2, 130.1, 129.7, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 126.7, 119.3, 118.7, 110.4, 110.2, 110.1 (HCarom); 77.8, 77.5 (HCO); 61.6, 57.8 (HCN); 55.7, 55.6, 55.3, 55.2 (CH3O); 27.0, 26.9 ((CH3)3); 19.3, 19.2 (SiC); **IR** (KBr) υ 3220, 1680, 1510. $C_{33}H_{37}NO_4Si$: Calc. C 73.43, H 6.91, N2.60; Found C 73.80, H 6.97, N 2.62.

N-[2-(3,4-Dimethoxyphenyl)-1-phenyl-2-(tert-butyldiphenylsilyloxy)ethyl]acetamide **8c**: A solution of 511 mg (1 mmol) of amine **8a** in 10 ml of dichloromethane was stirred at room temperature. Catalytic amounts of DMAP and 0.17 ml (1.5 mmol) of triethylamine were added. When the solution was cooled on an ice bath, 0.09 ml (1.25 mmol) of acetyl chloride was added and the stirring was continued overnight at room temperature. The crude was poured onto ice and extracted with dichloromethane and dried over sodium sulfate. After evaporation of the solvent under vacuum, the resulting oil was crystallized from ether to afford a white solid which was identified as acetamide **8c** Yield: 95%. M.p. 158-159°C. **^{1}H NMR**: δ 7.76-6.57 (m, 17H, arom); 6.16 (d, J=1.7, 1H, H-2'); 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, CH3O); 3.48 (s, 3H, CH3O); 1.71 (s, 3H, CH3); 1.07 (s, 9H, t-C4H9-Si); **^{13}C NMR**: δ 169.0 (C=0); 148.1, 147.9, 137.7, 133.6, 133.0, 132.3, (qCarom); 136.0, 135.8, 130.1, 129.7, 128.2, 127.9, 127.6, 127.2, 118.8, 110.2 (HCarom); 77.8 (C-0); 59.2 (C-N); 55.7, 55.3 (CH3O); 27.0 ((CH3)3); 23.1 (CH3); 19.4 (SiC); **IR** (KBr) υ 3270, 1680, 1510. $C_{34}H_{39}NO_4Si$: Calc. C 73.74, 7.10, 2.53; Found C 73.72, H 7.14, N 2.55.

Cyclization reaction. Typical procedure: To a stirred solution of the corresponding amide in dichloromethane, small amounts of PCl5 were added until total consumption of the starting material (tlc, dichloromethane/ethyl acetate, 9/1). The additions were made at 0°C and the mixture was allowed to reach room

temperature. 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 purified as specified for each compound.

(3*S**,4*R**)-6,7-Dimethoxy-3-phenyl-4-(tert-butyldiphenylsilyloxy)-3,4-dihydroisoquinoline **9a**: Following the typical procedure, the isoquinoline derivative **9a** was obtained and purified by flash column chromatography (dichloromethane/ethyl acetate, 9/1) to furnish compound **9a** as an oil (yield 80%) which crystallized from hexane/ethyl acetate (7/1) as a white solid. M.p. 82-84°C. ^{1}H NMR: δ 8.62 (d, J=1.5, 1H, H-1); 7.81-6.67 (m, 16H, arom); 6.16 (s, 1H, arom); 5.43 (s, 1H, H-4); 4.71 (d, J=1.7, 1H, H-3); 3.94 (s, 3H, CH3O); 3.50 (s, 3H, CH3O); 0.99 (s, 9H, t-C4H9-Si); ^{13}C NMR: δ 158.6 (C-1); 151.0, 149.1, 136.9, 133.9, 133.8, 121.0, 112.2 (qCarom); 136.1 135.9, 129.9, 129.6, 128.2, 127.9, 127.4, 127.1, 127.0, 109.8 (HCarom); 71.4 (C-4); 68.9 (C-3); 56.0, 55.6 (CH3O); 26.7 ((CH3)3); 19.3 (SiC); IR (KBr) υ 3600-3300, 1700, 1600, 1520. $C_{33}H_{35}NO_3Si$: Calc. C 75.97, H 6.77, N 2.69; Found C 75.78, H 6.68, N 2.72.

(3*S**,4*R**)-6,7-Dimethoxy-1-methyl-3-phenyl-4-(tert-butyldiphenylsilyloxy)-3,4-dihydroisoquinoline **9b**: Following the typical procedure, the isoquinoline derivative **9b** was obtained chromatographically pure (t.l.c., dichloromethane/ethyl acetate, 9/1). Crystallization was accomplished from ether affording a white solid. Yield 88%. M.p. 126-127°C. ^{1}H NMR: δ 7.79-6.67 (m, 16H, arom); 6.16 (s, 1H, arom); 5.38 (s, 1H, H-4); 4.72 (d, J=2.0, 1H, H-3); 3.93 (s, 3H, CH3O); 3.47 (s, 3H, CH3O); 2.60 (s, 3H, CH3); 0.99 (s, 9H, t-C4H9-Si); ^{13}C NMR: δ 162.4 (C-1); 150.5, 148.6, 137.8, 133.9, 133.8, 128.3, 121.9 (qCarom); 136.0, 135.8, 129.4, 128.0, 127.8, 127.3, 127.2, 126.8, 112.1, 108.3 (HCarom); 72.0 (C-4); 68.1 (C-3); 56.0, 55.5 (CH3O); 26.7 ((CH3)3); 23.1 (CH3); 19.2 (SiC); IR (KBr) υ 1630, 1600, 1580. $C_{34}H_{37}NO_3Si$: Calc. C 75.94, H 7.32, N 2.62; Found C 76.48, H 6.91, N 2.70.

(3*S**,4*R**)-6,7-Dimethoxy-4-hydroxy-3-phenyltetrahydroisoquinoline **10c**: To a cooled stirred suspension of 52 mg (1.38 ml) of LAH in 5 ml of dry THF, a solution of 120 mg (0.23 mmol) of dihydroisoquinoline **9a** in 5 ml of THF was added and the reaction was completed in 4 days. The excess of hydride was filtered and the filtrate was diluted with water and extracted with dichloromethane. After evaporation of the solvent the crude was crystallized from ethyl acetate to afford tetrahydroisoquinoline derivative **10c** as a white solid. Yield 65%. M.p. 166-167°C. ^{1}H NMR: δ 7.44-7.42 (m, 5H, Ph); 7.08 (s, 1H, H-5); 6.54 (s, 1H, H-8); 4.73 (d, J=7.8, 1H, H-4); 4.16 (d, J=15.1, 1H, H-1a); 3.94 (d, J=15.1, 1H, H-1e); 3.88 (s, 3H, CH3O); 3.86 (s, 3H, CH3O); 3.77 (d, J=7.8, 1H, H-3); ^{13}C NMR: δ 148.3, 148.0, 141.0, 129.4, 127.5 (qCarom); 128.7, 128.8, 127.7, 109.8, 108.3 (HCarom); 71.9 (C-4); 65.9 (C-3); 56.0, 55.9 (CH3O); 47.9 (C-1); IR (KBr) υ 3280, 1610, 1515. $C_{17}H_{19}NO_3$: C 71.55, H 6.72, N 4.56; Found C 71.70, H 6.80, N 4.49.

This product was also obtained as follows: 1 mmol of dihydroisoquinoline **9a** was directly deprotected by treatment with 4 ml of ^{n}Bu$_4$NF (1M in THF) in 15 ml of THF. After stirring overnight at room temperature the solution was diluted with 5 ml of water and extracted with dichloromethane. The so-obtained crude was dissolved in 10 ml of MeOH and 4 mmol of $NaBH_4$ was added. After stirring for 10 h. at room temperature, 5 ml of water was added, the mixture was extracted with dichloromethane and dried over sodium sulfate. The solvent was

evaporated "in vacuo" and the residue was crystallized from ethyl acetate providing isoquinoline **10c** in 60% yield. '

(3*S**,4*R**)-6,7-Dimethoxy-3-phenyl-4-(tert-butyldiphenylsilyloxy)tetrahydroisoquinoline **10a**: 142 mg (0.27 mol) of dihydroisoquinoline **9a** were dissolved in 10 ml of anhydrous methanol. Solid NaBH4 (41 mg, 1.08 mmol) was added in one portion and the stirring was continued overnight at room temperature. The mixture was quenched with 5 ml of water and extracted with dichloromethane. The organic extracts were concentrated and chromatographed (eluent: dichloromethane/ethyl acetate, 9.8/0.2). The resulting oil was crystallized from MeOH to afford tetrahydroisoquinoline **9** as a white solid. M.p. 88-89°C. Yield 75%. ^{1}H NMR: δ 7.73-7.13 (m, 15H, arom); 6.41 (s, 1H, H-8); 6.37 (s, 1H, H-5); 5.01 (d, J=4.5, 1H, H-4); 4.25 (d, J=4.5, 1H, H-3); 3.98 (d, J=16.2, 1H, H-1); 3.79 (s 3H, CH3O); 3.69 (d, J=16.2, 1H, H-1); 3.27 (s, 3H, CH3O); 2.52 (br s, 1H, NH); 0.98 (s, 9H, t-C4H9-Si); ^{13}C NMR: δ 148.2, 147.0, 139.9, 133.9, 133.1, 128.5, 128.2 (qCarom); 136.1, 136.0, 129.8, 129.4, 128.1, 127.7, 127.2, 112.7, 108.0 (HCarom); 70.7 (C-4); 63.7 (C-3); 55.7, 5.2 (CH3O); 45.2 (C-1); 26.7 ((CH3)3); 19.4 (SiC); IR (KBr) υ 3400-3280, 1620. $C_{33}H_{37}NO_3Si$: Calc. C 75.68, H 7.12, N 2.68; Found C 75.75, H 7.01, N 2.82. The deprotection was carried out as described above. The crude was concentrated and crystallized from ethyl acetate giving a white solid which was identified as tetrahydroisoquinoline **10c**. Yield: 77%.

(1*R**,3*S**,4*R**)-6,7-Dimethoxy-4-hydroxy-1-methyl-3-phenyltetrahydroisoquinoline **10d**: To a stirred suspension of 39 mg (1.02 mmol) of LAH in 5 ml of THF cooled with an ice bath, 91 mg (0.17 mmol) of dihydroisoquinoline derivative **9b** dissolved in 5 ml of THF was added. The reaction was carried out as described above for compound **10c**, thus affording after 2 days tetrahydroisoquinoline **10d** which was crystallized from hexane/ethyl acetate (6/4). Yield 75%. M.p. 104-105°C. ^{1}H NMR: δ 7.38-7.25 (m, 5H, Ph); 7.04 (s, 1H, H-5); 6.56 (s, 1H, H-8); 4.68 (d, J=6.7, 1H, H-4); 4.09 (m, 2H, H-3, H-1); 3.98 (s, 3H CH3O); 3.86 (s, 3H, CH3O); 2.11 (br s, NH, OH); 1.49 (d, J=6.7, 3H, CH_3); ^{13}C NMR: δ 148.4, 147.9, 140.9, 132.1, 129.0 (qCarom); 128.6, 127.8, 109.9, 108.8 (HCarom); 71.4 (C-4); 60.2 (C-3); 5.9, 55.8 (CH3O); 49.9 (C-1); 23.4 (CH3); IR (KBr) υ 3600, 3400-3200, 1610. $C_{18}H_{21}NO_3Si$: Calc. C 72.20, H 7.08, N 4.68; Found C 72.15, H 7.13, N 4.60.

(1*R**,3*S**,4*R**)- and (1*S**,3*S**,4*R**)-6,7-Dimethoxy-1-methyl-3-phenyl-4-(tert-butyldiphenylsilyloxy)-tetrahydroisoquinoline **10b**: 96 mg (0.18 mmol) of dihydroisoquinoline **9b** were dissolved in anhydrous methanol and 27 mg (0.72 mmol) of NaBH4 was added in one portion. The crude was stirred for 8 h at room temperature, then quenched with 5 ml of water and extracted with dichloromethane, dried (sodium sulfate) and then concentrated under reduced pressure. Flash column chromatography of the crude (hexane/ethyl acetate, 8/2) afforded tetrahydroisoquinoline derivative **10b** as a mixture of two diastereoisomers in a (1:1) ratio. Both diastereoisomers were separated by fractionated crystallization from methanol. Compound (1*R**,3*S**,4*R**)-**10b** (yield 45%) M.p. 113-114°C. ^{1}H NMR δ 7.60-7.20 (m, 15H, arom); 6.62 (s, 1H, H-8); 6.55 (s, 1H, H-5); 5.17 (d, J=8.0, 1H, H-4); 4.28 (q, J=6.4, 1H, H-1); 4.12 (d, J=8.0, 1H, H-3); 3.84 (s, 3H, CH3O); 3.04 (s,

3H, CH3O): 2.35 (br s, 2H, NH); 1.37 (d, J=6.4, 3H, CH3); 0.66 (s, 9H, t-C4H9-Si); **^{13}C NMR**: δ 147.6, 142.3, 134.1, 133.5, 132.9, 132.3, 130.4 (qCarom); 136.4, 136.1, 129.5, 129.2, 128.7, 128.5, 127.9, 127.2, 126.9, 112.1, 107.2 (HCarom); 74.3 (C-4); 61.1 (C-3); 55.8, 54.8 (CH3O); 52.5 (C-1); 26.4((CH3)3); 21.9 (CH3); 19.6 (SiC); **IR** (KBr) υ 3600-3300, 1610. $C_{34}H_{39}NO_3Si$: Calc. 75.94, H 7.32, N 2.61; Found C 75.55, H 7.35, N 2.65. Compound (1*S**,3*S**,4*R**)-**10b** (yield 45%). M.p. 132-133°C. **^{1}H NMR** δ 7.80-7.07 (m, 15H, arom); 6.50 (s, 1H, H-8); 6.23 (s, 1H, H-5); 4.99 (d, J=3.2, 1H, H-4); 4.37 (d, J=3.2, 1H, H-3); 3.81 (s, 3H, CH3O); 3.38 (s, 3H, CH3O); 2.35 (br s, 2H, NH); 1.55 (d, J=6.7, 3H, CH3); 0.98 (s, 9H, t-C4H9-Si); **^{13}C NMR**: δ 148.5, 146.9, 139.4, 133.9, 133.5, 133.0, 127.3 (qCarom); 136.1, 136.0, 129.8, 129.5,128.1,127.8, 127.7, 127.3, 126.8, 112.6, 108.3 (HCarom); 70.1(C-4); 61.1 (C-3); 55.7, 55.4(CH3O); 47.8 (C-1); 26.8 ((CH3)3); 23.3 (CH3); 19.3 (SiC); **IR** (KBr) υ 3600-3300, 1620. These tetrahydroisoquinolines were desilylated in the usual way with ^{n}Bu4NF in THF to yield, in 4 hours, tetrahydroisoquinoline(1*R**,3*S**,4*R**)-**10d** and (1*S**,3*S**,4*R**)-**10d** respectively. Yield: 80%.

(3*S**,4*R**)-6,7-Dimethoxy-4-hydroxy-1-methyl-3-phenyldihydroisoquinoline **9d**: According to the procedure described before for deprotection the title compound was obtained from **9b** after 4 hours of reaction (75% yield) and purified by crystallization from ethyl acetate. M.p. 165-166°C. **^{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, 1.95, H-3); 3.90 (s, 3H, CH3O); 3.87 (s, 3H, CH3O); 2.47 (d, J=1.95, 3H, CH3); **^{13}C NMR**: δ 163.8 (C-1); 151.6, 148.3, 140.8, 132.2, 121.4 (qCarom); 128.6, 128.1, 127.5, 108,9, 108.0 (HCarom); 70.8 (C-4); 68.3 (C-3); 56.2, 56.0 (CH3O); 23.2 (CH3); **IR** (KBr) υ 3500-3200, 1630, 1610, 1580. $C_{18}H_{19}NO_3$: Calc. C 72.69, H 6.44, N 4.71; Found C 72.58, H 6.52, N 4.78.

(1*S**,3*S**,4*R**)-6,7-Dimethoxy-4-hydroxy-1-methyl-3-phenyltetrahydroisoquinoline **10d**: 110 mg (0.37 mmol) of dihydroisoquinoline **9d** were stirred overnight at room temperature with 42.1 mg (1.11 mmol) of LAH in 6 ml of THF as solvent to afford tetrahydroisoquinoline **10d** as a unique diastereoisomer (yield 85%). M.p. 123-124°C. **^{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, CH3O); 3.88 (s, 3H, CH3O); 3.76 (d, J=9, 1H, H-3); 1.46 (d, J=6.5, 1H, CH3); **^{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 (HCarom); 72.9 (C-4); 66.6 (C-3); 56.0, 55.9 (CH3O); 53.0 (C-1); 22.7 (CH3); **IR** (KBr) υ 3260, 3210-3060, 1610.

6,7-Dimethoxy-3-phenylisoquinoline **11a**: To a stirred solution of formamide **8b** (200 mg, 0.37 mmol) in dichloromethane (15 ml), small amounts of P_2O_5 (95 mg, 0.66 mmol) were added until total consumption of the starting material (tlc, dichloromethane/ ethyl acetate, 9/1). The additions were made at 0°C and the mixture was allowed to reach room temperature. Elaboration of the crude was carried out following typical procedures thus affording compound **11a** as a yellow oil (yield 75%). **^{1}H NMR**: δ 9.12 (s, 1H, H-1); 8.09-8.06 (m, 2H, arom); 7.93 (s, 1H, H-4); 7.52-7.26 (m, 3H, arom); 7.21 (s, 1H, H-8); 7.11 (s, 1H, H-5); 4.04 (s, 6H, CH3O); **^{13}C NMR**: δ 153.1 (C-3), 150.3, 150.2 (qCarom); 149.8 (C-1); 139.9, 133.3 (qCarom); 128.7,

128.1, 126.7 (HCarom); 123.7 (C-1'); 115.5, 105.2, 104.9 (HCarom); 56.1, 56.0 (CH_3O); IR (neat liq.) ν 1620, 1570, 1500. $C_{17}H_{15}NO_2$: Calc. C 76.95, H 5.70, N 5.28; Found C 76.93, H 5.74, N 5.26.

6,7-Dimethoxy-1-methyl-3-phenylisoquinoline **11b**: Following the procedure described above acetamide **8c** was submitted to cyclization reaction thus affording isoquinoline **11b** (yield 75%) which was purified by crystallization from ether. M.p. 121-122 ºC. ^{1}H NMR: δ 8.12-8.09 (m, 2H, arom); 7.78 (s, 1H, H-4); 7.52-7.34 (m, 3H, arom); 7.26 (s, 1H, H-8); 7.09 (s, 1H, H-5); 4.03 (s, 3H, CH_3O); 4.02 (s, 3H, CH_3O); 2.95 (s, 3H, CH_3); ^{13}C NMR: δ 155.8 (C-3); 152.5, 149.6 (qCarom); 149.0 (C-1); 140.1, 133.3 (qCarom); 128.6, 127.9, 126.7 (HCarom); 122.1 (CCarom); 114.3, 105.6, 103.8 (HCarom); 56.0, 55.9 (CH_3O); 22.7 (CH_3). IR (KBr) ν 1620, 1560, 1500, 1240. $C_{18}H_{17}NO_2$: Calc. C 77.38, H 6.13, N 5.01; Found C 77.34, H 6.10, N 4.98.

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REFERENCES

1. Kobayashi, S.; Tokumoto, T.; Taira, Z. *J. Chem. Soc., Chem. Commun.*, **1984**, 1043.
2. Heptner, W.; Schacht, U. *Biochem. Pharmacol.*, **1974**, *23*, 3413.
3. Brossi, A.; Grethe, G.; Teitel, S.; Wildman, W.C.; Bailey, D.T. *J. Org. Chem.*, **1970**, *35*, 1110.
4. Dandridge, P.A.; Kaiser, C.; Brenner, M.; Gaitanopoulos, D.; Davis, L. D.; Webb, R.L.; Foley, J.J.; Sarau, H.M. *J. Med. Chem.*, **1984**, *27*, 28.
5. Ishida, Y.; Koga, N.; Nanbu, T.; Kihara, M.; Kobayashi, S. *Br. J. Pharmacol.*, **1988**, *94*, 19.
6. a) Cohen, G. and Collins, M. *Science*, **1970**, *167*, 1749; b) Bates, H.A.; Garelick, J.S. *J. Org. Chem.*, **1984**, *49*, 4552.
7. Grunewald, G.L.; Ye, Q.; Kieffer, L.; Monn, J.A. *J. Med. Chem.*, **1988**, *31*, 169.
8. Ohta, S.; Tachikawa, O.; Makino, Y.; Tasaki, Y.; Hirobe, M. *Life Sci.*, **1990**, *46*, 599.
9. a) Kihara, M.; Kashimoto, M.;Kobayashi, Y. *Tetrahedron*, **1992**, *48*, 67; b) Tikk, I.; Deák, G.; Tóth, G.; Tamás, J. *J. Chem. Soc. Perkin Trans. I*, **1984**, 619 and references cited therein.
10. See for example: a) Domínguez, E.; Lete, E. *An. Qim.*, **1984**, *80C*, 13; b) Domínguez, E.; Lete, E. *J. Heterocycl. Chem.*, **1984**, *21*, 525; c) Badía, D.; Domínguez, E; Iriondo, C.; Martínez de Marigorta, E. *Heterocycles*, **1986**, *24*, 1871; d) Domínguez, E.; Lete, E.; Badía, D.; Villa, M.J.; Castedo, L.; Domínguez, D. *Tetrahedron*, **1987**, *43*, 1943; e) Badía, D.; Domínguez, E.; Laborra, C. *Bull. Soc. Chim. Belg.*, **1988**, *95*, 207; f) Domínguez, E.; Martínez de Marigorta, E.; Carrillo, L.; Fañanas, R. *Tetrahedron*, **1991**, *47*, 9253.

11. a) Gilchrist, T.L.; Gymer, G.E.; Rees, C.W. *J. Chem. Soc. Perkin Trans. I*, **1974**, 1; b) Whitney, S.E.; Winters, M.; Rickborn, B. *J. Org. Chem.*, **1990**, *55*, 929.
12. Greene, T.W. *Protective Groups in Organic Synthesis*; John Wiley and Sons, Inc., New York, 1981.
13. Badía, D.; Carrillo, L; Domínguez, E.; Cameno, A.G.; Martínez de Marigorta, E.;Vicente, T. *J. Heterocyclic Chem.*, **1990**, *27*, 1287.
14. Krepski, L.R.; Jensen, K.M.; Heilmann, S.M.; Rasmussen, G.K. *Synthesis*, **1986**, 301.
15. Henning, R.; Lerch, U.; Urbach, H. I. *Synthesis*, **1989**, 265.
16. Ardabilchi, N.; Fitton, A.O.; Frost, J.R.; Oppong-Boachie, F. *Tetrahedron Lett.*, **1977**, *47*, 4107.
17. Kinns, M.; Sanders, J.K.M. *J. Magn. Res.*, **1984**, *56*, 518.
18. Domínguez, E.; Lete, E. *Heterocycles* , **1983**, *20*, 1247.
19. Perrin, D.D.; Armarego, W.L.F. *Purification of Laboratory Chemicals*; 3rd Edition, Pergamon Press, Oxford, 1988.
20. Krebs, K.G.,; Heusser, D.; Wimmer, H. *Thin-Layer Chromatography*; eds. Stahl, E.; Springer-Verlag, Berlin, 1969; p. 873.
21. Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.*, **1978**, *43*, 2923.
22. Kramer, G.W.; Levy, A.B.; Midland, M.M. *Organic Synthesis Via Boranes*; John Wiley and Sons, Inc., New York, 1975.