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# A contribution to the asymmetric synthesis of isoquinolines: Concise stereoselective approach to (3*S*,4*S*)-6,7-dimethoxy-4-hydroxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline

Luisa Carrillo, Dolores Badía*, * Esther Domínguez*, Fátima Ortega and Imanol Tellitu

*Departamento de Química Orgánica, Facultad de Ciencias, Universidad del País Vasco, PO Box 644, 48080 Bilbao, Spain*

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**Abstract**

A highly efficient stereoselective synthesis of (3*S*,4*S*)-6,7-dimethoxy-4-hydroxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline **8** (e.e.=96%) starting from enantiomerically pure imine **3** is reported. 

The potent physiological activity of simple 4-hydroxytetrahydroisoquinolines has attracted the attention of the research community because of, for example, (1) their involvement in the development of alcohol dependence and withdrawal symptoms and other pharmacological actions of ethanol[1]; (2) racemic 4-hydroxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (PI-OH) has been shown to have a potentiating effect on the response of rat anococcygeus muscle to noradrenaline without any side effects, such as postsynaptic inhibition, at higher concentrations[2]; (3) 4-hydroxytetrahydroisoquinolines act as substrates or inhibitors of phenylethanolamine *N*-methyltransferase (PNMT)[3]; (4) the derivatives under study are metabolized to tetrahydroisoquinolines, possible parkinsonism-inducing substances[4]; (5) this type of compound shows anti-proliferative activity against human mammary and nasopharyngeal carcinomas.[5]

Despite their interest, very few reports on the stereoselective synthesis of chiral 4-hydroxy-tetrahydroisoquinolines have been published and, as far as we know, in all of them kinetic resolution of racemic mixtures was the method of choice.[6] On the other hand, in a previous paper we reported the preparation of enantiopure (3*S*,4*R*)-4-hydroxy-3-phenyl-1,2,3,4-tetrahydroisoquinolines starting from enantiomerically pure (*R*)-cyanohydrins via erythro-1,2-diarylethanolamine formation.[7] In the present paper we would like to report a concise stereoselective approach to the corresponding (3*S*,4*S*)-diastereoisomer **8**.

This synthetic proposal involves a route that includes the $C_4$–$C_{4a}$ bond formation in the final step, as depicted in Scheme 1 and, to that end, the chiral imine **3** was selected as the starting material. This

* Corresponding author. E-mail: qopdopee@lg.ehu.es

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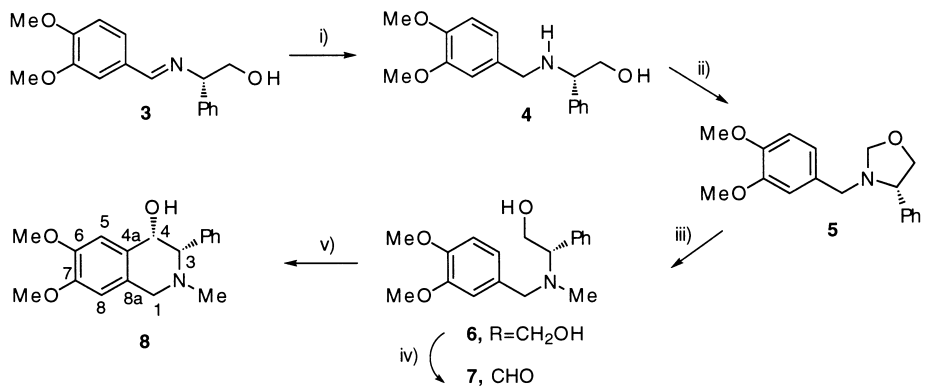
building block, (−)-(1′*S*)-(*E*)-*N*-(1-phenyl-2-hydroxyethyl)-3,4-dimethoxybenzylideneimine **3**, easily accessible by condensation of (*S*)-phenylglycinol with veratraldehyde,[8] was stable and consisted of the typical imine–oxazolidine tautomeric mixture.[9] An *E* configuration has been proposed for this compound based upon the report by Hine and $^{13}$C-NMR studies, which showed only a single resonance for the amino carbon (163 ppm).[10] Imine **3** was first reduced with $NaBH_4$ to aminoalcohol **4** which, in turn, was N-methylated in a one-pot two-step reaction, via formation of the isolable oxazolidine intermediate **5** by reaction with HCHO, followed by a ring opening process, which takes place employing $NaBH_3CN$.




Scheme 1. Reagents and conditions: (i) $NaBH_4$, MeOH, r.t., 3 h, 98%; (ii) HCHO, $CH_2Cl_2$, r.t., 15 min, 100%; (iii) $NaBH_3CN$, MeCN, r.t., 28 h, 80%; (iv) $(COCl)_2$, DMSO, $^{i}Pr_2EtN$, $CH_2Cl_2$, −60°C, 15 min; (v) HCl (conc), acetone, r.t., 10 min, 70% (two steps).

In order to complete the projected synthesis, we had to perform the transformation of the benzylic β-aminoalcohol **6** into the α-aminoaldehyde **7**. After several experiments, based on the classical Swern oxidation reaction,[11] we found that when diisopropylethylamine was employed instead of the typical, less bulky, triethylamine,[11c] the starting alcohol **6** was completely consumed and aldehyde **7** was obtained in very good yield and then isolated as a colourless oil prone to decomposition.

Finally, with freshly prepared aldehyde **7** in hand, the classical acid catalyzed aromatic electrophilic substitution reaction[12] was performed, affording the expected (3*S*,4*S*)-3-phenyl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline **8** as a single diastereoisomer, as deduced from extensive NMR studies. Thus, the observation of a nuclear Overhauser effect between protons $H_3$ and $H_4$, as well as the value of their coupling constant ($J_{H3/H4}$=2.6 Hz) revealed a *cis* relationship of the substituents at both stereogenic carbons $C_3$ and $C_4$. Moreover, the enantiomeric excess of the target isoquinoline **8**, was determined by chiral HPLC (Chiralcel OD, hexanes:$^{i}$PrOH=75:25, 0.5 mL/min) and calculated to be 96% by comparison with a racemic sample of the derivative under study **8** (retention time for (*R*,*R*)-**8**=18.84 min; retention time for (*S*,*S*)-**8**=24.54 min).

In summary, a new and highly efficient route for the stereoselective preparation of (3*S*,4*S*)-3-phenyl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline **8** from chiral imine **3** has been performed. It is noteworthy to point out some of the advantageous features of the reported synthesis, as follows: (1) the relatively few steps involved; (2) the high overall yield; (3) the complete stereocontrol achieved in the generation of the second stereogenic center at carbon $C_4$; (4) the lack of racemization under the described reactions; and (5) the versatility of the synthetic procedures to be extended to a series of isoquinolines of type **8**.

## 1. Experimental section

### 1.1. 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. $^1$H-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. $^1$H–$^1$H NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet.[13] $^{13}$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), br s (broad singlet), d (doublet), t (triplet), m (multiplet) or dd (doublet of doublets). Coupling constants, J, are reported in hertz. Optical purity was determined by HPLC using a Chiracel OD column and mixtures of hexanes:$^i$PrOH (75:25) as eluent (0.5 mL/min). Flash column chromatography[14] was performed with Merck Kieselgel 60 (230–400 mesh). Analytical thin-layer chromatography (TLC) was performed with 0.2 mm thick silica gel plates (Merck Kieselgel GF254). Specific optical rotations were recorded on a Perkin–Elmer 241 polarimeter at 20°C, using a 1 dm cell and a sodium lamp. The reactions were carried out under an atmosphere of dry, deoxygenated argon unless otherwise indicated. All transfers of liquid solutions and solvents were performed by syringe techniques or via cannula.[15] Tetrahydrofuran was freshly distilled from benzophenone–sodium ketyl. All other solvents used were technical grade and purified according to standard procedures.[16] Combustion analyses were performed on a Perkin–Elmer 2400 CHN apparatus. Mass spectra were recorded under electron impact at 70 eV. GC–MS analyses were performed using an HP-5 column (5% phenyl methyl polysiloxane, 30 m×0.25 mm×0.25 μm).

### 1.2. (+)-(2S)-2-[N-(3,4-Dimethoxybenzyl)]amine-2-phenylethanol **4**

Over a cooled (ice bath) solution of imine **3** (0.28 g, 1 mmol) in MeOH (25 mL), $NaBH_4$ (0.76 g, 2 mmol) was added in three portions. The ice bath was removed and the mixture was stirred at room temperature for 3 h. Then, water (15 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3×25 mL). The combined organic extracts were dried over $Na_2SO_4$ and the solvent was removed under reduced pressure to afford the aminoalcohol **4** as an essentially pure orange oil (0.28 g, 98%), which was crystallized from EtOH as the HCl salt. $[\alpha]_D^{20}$: +63.0 (c=1.0, $CH_2Cl_2$); m.p. (HCl salt, EtOH): 164–166°C; IR (HCl salt, KBr) υ: 3500–3200, 3000–2700; $^1$H-NMR δ: 3.46–3.68 (m, 4H, ArC*H*$_2$, C*H*$_2$OH), 3.78 (dd, J=8.8, 4.2, 1H, PhC*H*), 3.82 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$), 6.77–6.79 (m, 3H, $H_{arom}$), 7.27–7.35 (m, 5H, $H_{arom}$); $^{13}$C-NMR δ: 50.7 (Ar*C*H$_2$), 55.5, 55.6, ($OCH_3$), 63.5 (Ph*C*H), 66.5 ($CH_2OH$), 110.8, 111.2, 120.1, 127.2, 127.4, 128.4 (t $C_{arom}$), 132.3, 140.2, 147.8, 147.9 (q $C_{arom}$); EI-MS *m/z*: 256 ($M^+-31$, 21), 152 (11), 151 (100). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.04; H, 7.37; N, 4.88. Found: C, 71.28; H, 7.43; N, 4.75.

### 1.3. (+)-(4S)-N-(3,4-Dimethoxybenzyl)-4-phenyloxazolidine **5**

A mixture of aminoalcohol **4** (0.28 g, 1 mmol) and 35% aq HCHO (0.4 ml, 5 mmol) in 10 mL of $CH_2Cl_2$ was stirred at room temperature over 15 min in the presence of molecular sieves (4 Å). The molecular sieves were filtered and the solvent was distilled under reduced pressure. The resulting syrup was purified by flash column chromatography (hexanes:EtOAc=6:4) to afford analytically pure

oxazolidine **5** as a colorless oil (yield=100%). $[\alpha]_D^{20}$: +52.6 (c=3.5, $CH_2Cl_2$); $^1$H-NMR δ: 3.48 (d, J=13.2, 1H, ArC*H*), 3.74 (t, J=7.7, 1H, PhC*H*), 3.84 (s, 3H, $OCH_3$), 3.86 (s, 3H, $OCH_3$), 3.88–3.94 (m, 2H, ArC*H*, H-5), 4.26–4.33 (m, 2H, H-5, H-2), 4.60 (d, J=3.7, 1H, H-2), 6.77–6.90 (m, 3H, $H_{arom}$), 7.24–7.46 (m, 5H, $H_{arom}$); $^{13}$C-NMR δ: 55.7, 55.8 ($OCH_3$), 56.3 (C-5), 66.9 (C-4), 73.2 (Ar*C*$H_2$), 86.9 (C-2), 110.8, 111.5, 120.3, 127.3, 127.5, 128.5 (t $C_{arom}$), 131.1, 139.9, 148.0, 148.8 (q $C_{arom}$); EI-MS *m/z*: 152 (82), 151 (100), 148 (24), 137 (11), 121 (15), 118 (15), 197 (10), 91 (22). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.20; H, 7.08; N, 4.68. Found: C, 71.95; H, 7.15; N, 4.46.

### *1.4. (+)-(2*S*)-2-[*N*-(3,4-Dimethoxybenzyl)-*N*-methyl]amino-2-phenylethanol **6***

To a cooled (0°C) solution of oxazolidine **5** (0.30 g, 1 mmol) in 25 mL of MeCN, $NaBH_3CN$ (0.31, 5 mmol) was added in three portions. The ice bath was removed and the mixture was stirred under argon over 28 h. After total consumption of the starting material (TLC, hexanes:EtOAc=7:3), water (5 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3×25 ml). The combined extracts were dried over $Na_2SO_4$, the solvent was distilled under reduced pressure and the resulting oil was flash column chromatographed to afford the aminoalcohol **6** as a colourless oil, which was crystallized from MeOH (yield: 80%). $[\alpha]_D^{20}$: +44.0 (c=1.0, $CH_2Cl_2$); m.p. (MeOH): 117–118°C; IR (KBr) υ: 3400–3300; $^1$H-NMR δ: 2.14 (s, 3H, $CH_3$), 3.20 (br s, 1H, OH), 3.31 (d, J=13.0, 1H, ArC*H*), 3.56 (d, J=13.0, 1H, ArC*H*), 3.67 (dd, J=10.2, 4.9, 1H, PhC*H*), 3.84–3.89 (m, 1H, C*H*OH), 3.88 (s, 6H, $OCH_3$), 4.06 (t, J=10.2, 1H, C*H*OH), 6.82–6.84 (m, 3H, $H_{arom}$), 7.22–7.39 (m, 5H, $H_{arom}$); $^{13}$C-NMR δ: 36.6 ($CH_3$), 55.8 ($OCH_3$), 58.2, 60.6 (Ar*C*$H_2$, *C*$H_2$OH), 67.7 (Ph*C*H), 110.9, 111.8, 120.9, 127.9, 128.2, 129.0 (t $C_{arom}$), 131.3, 135.2, 148.1, 148.9 (q $C_{arom}$); EI-MS *m/z*: 270 ($M^+-31$, 27), 152 (10), 151 (100). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.72; H, 7.70; N, 4.65. Found: C, 71.90; H, 7.58; N, 4.90.

### *1.5. (+)-(3*S*,4*S*)-6,7-Dimethoxy-4-hydroxy-2-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline **8***

To a cooled (−60°C) solution of oxalyl chloride (0.10 mL, 1.16 mmol) in 3 mL of $CH_2Cl_2$, a solution of DMSO (0.16 mL, 2.30 mmol) in 3 mL of the same solvent was added dropwise, and the mixture was stirred for 15 min. Then, a solution of aminoalcohol **6** (0.32 g, 1.06 mmol) in 15 mL of $CH_2Cl_2$ was added dropwise and the stirring was continued for 30 min. Working at the same low temperature, diisopropylethylamine (0.92 mL, 5.30 mmol) was added slowly and, after stirring for 15 min, the solution was allowed to reach ambient temperature. The reaction was quenched with water (10 mL) and extracted with $CH_2Cl_2$ (3×25 ml). The combined organic extracts were dried over $Na_2SO_4$ and the solvent was distilled under reduced pressure to afford (*S*)-2-[*N*-(3,4-dimethoxybenzyl)-*N*-methyl]amine-2-phenylacetaldehyde **7**. A small portion of aldehyde **7** was purified by flash column chromatography (hexanes:EtOAc=3:7). IR (neat) υ: 1730; $^1$H-NMR δ: 2.18 (s, 3H, $NCH_3$), 3.32 (d, J=13.3, 1H, ArC*H*), 3.60 (d, J=13.3, 1H, ArC*H*), 3.87 (s, 3H, $OCH_3$), 3.89 (s, 3H, $OCH_3$), 3.96 (d, J=3.6, 1H, PhC*H*), 6.83–6.88 (m, 3H, $H_{arom}$), 7.39–7.42 (m, 5H, $H_{arom}$), 9.65 (d, J=3.6, 1H, CHO). Crude aldehyde **7** was dissolved in acetone (8 mL) and, after cooling with an ice bath, conc HCl (2 mL) was added and the mixture was stirred for 15 min at room temperature. Then, the crude product was basified with 1 M NaOH and extracted with $CH_2Cl_2$ (3×15 mL). The combined organic extracts were dried over $Na_2SO_4$, the solvent was distilled under vacuum and the resulting oil was purified by flash column chromatography (hexanes:EtOAc=2:8) to afford tetrahydroisoquinoline **8** (yield=70%, two steps) which was obtained as a white solid after crystallization from $Et_2O$. $[\alpha]_D^{20}$: +135.0 (c=1.0, $CH_2Cl_2$); m.p. 165–167°C; IR (KBr) υ: 3650–3300; $^1$H-NMR δ: 2.19 (s, 3H, $NCH_3$), 3.29 (br s, 1H, OH), 3.39 (d, J=15.2, 1H, H-1), 3.52 (d, J=2.6, 1H, H-3), 3.63 (d, J=15.2, 1H, H-1), 3.87 (s, 3H, $OCH_3$), 3.89 (s, 3H, $OCH_3$), 4.49 (br s, 1H,

H-4), 6.51 (s, 1H, H-8), 6.88 (s, 1H, H-5), 7.30–7.43 (m, 5H, Ph); $^{13}$C-NMR δ: 43.4 ($NCH_3$), 55.8, 56.1 ($OCH_3$), 57.8 (C-1), 70.2, 71.9 (C-3, C-4), 108.9, 111.3 (t $C_{arom}$), 126.3 (q $C_{arom}$), 127.4, 127.9, 129.3 (t $C_{arom}$), 129.8, 138.0, 148.0, 148.6 (q $C_{arom}$); EI-MS *m/z*: 180 (34), 179 (18), 121 (10), 120 (100). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.61; H, 7.06; N, 4.48.

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