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A New General Method for the Synthesis of 4-Hydroxylated 3-Aryltetrahydroisoquinolines[1]

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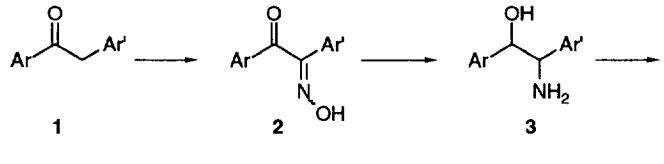
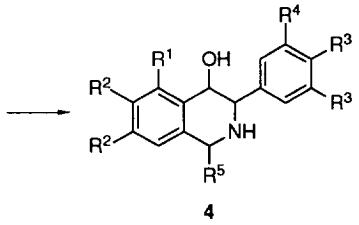
Abstract: 3-Aryl-4-hydroxytetrahydroisoquinolines have been prepared from deoxybenzoins. The nitrosation of the latter derivatives has been improved and the catalytic reduction of the obtained oximinoketones has been carried out with the help of ultrasounds. Heterocyclization to the isoquinoline moiety occurred on the unprotected 1,2-aminoalcohol to give stereoselectively the corresponding hydroxylated heterocycle with good yield.

Related to our investigations on 3-arylisoquinoline alkaloids,[2] we wish to report here the preparation of a series of uncommon[3] 3-aryl-4-hydroxytetrahydroisoquinolines **4**, by means of α-oximinoketone intermediates **2** previously synthesized from deoxybenzoins **1**, according to the following approach.





	R^1	R^2	R^3	R^4	R^5
a	H	H	H	H	H
b	H	OMe	OMe	H	H
c	H	OMe	H	H	H
d	H	OMe	OMe	OMe	H
e	OMe	OMe	OMe	H	H
f	H	OMe	OMe	H	Me

This synthetic proposal involves some key reactions like nitrosation[4] of deoxybenzoin systems, and the subsequent reduction of the so-obtained α-oximinoketones. It is important to note that, as far as we know, the Pictet-Spengler cyclization[5] of aminoalcohols of type **3** to produce straightforward the hydroxylated heterocycle **4** has never been done.

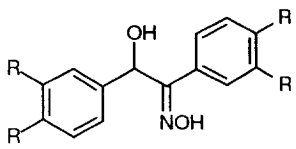
The first step, introduction of the oximino group into the α position to the carbonyl group, can be made by nitrosation with a wide number of reagents like nitrogen oxides, nitrosyl halides, nitrosyl thiocyanate, nitrosyl acetates, acidic solutions of nitrous acid, alkyl nitrites[4,6] and alkylthionitrates[7]. Nitrosation with alkyl nitrites, RONO, occurs both in acidic[8] and in alkaline[9] solution. When the reaction is carried out under basic conditions the mechanism probably involved implies the direct attack of the reagent to the ketone enolate[10], on the contrary under acidic conditions the alkyl nitrite first disocciates into the corresponding alcohol and the highly reactive nitrosonium ion NO^+, which then attacks the enolic form of the ketone[11]. In both reported conditions, the obtained nitroso compound tautomerizes to the expected α-oximinoketone.

In our hands, nitrosation of deoxybenzoin[12] **1a** with ^{t}BuONO/NaOEt supplied the α-oximinoketone **2a** with good yield (90%), but when the same procedure was applied to deoxybenzoin **1b** it failed to produce the expected oxime, thus only starting material and the corresponding diketone were detected. Formation of latter derivatives is a well-known process which happens either by autoxidation of ketones under basic conditions[13] or by treatment of ketones with alkyl nitrites in acidic or basic media.[14]

When LDA or NaH were used instead of ethoxide for the same purpose, only small amounts of the α-oximinoketone **2b** (25% and 10%, respectively) were obtained, along with the already mentioned diketone, deoxybenzoin **1b** and 3,4-dimethoxybenzoic acid, the latter derivative being formed by C-C cleavage, specially favoured when two electron-withdrawing groups are present as in this case.[4]

Consequently we performed the nitrosation of ketone **1b** in acidic medium by slightly modifying Hartung's procedure[15] and although some authors failed to carry out this type of reaction[8c], we succeeded in obtaining the α-oximinoketone **2b** (78%). These acidic nitrosation conditions were also applied to ketones **1c**, **1d**, and **1e**, to give α-oximinoketones **2c** (96%), **2d** (63%) and **2e** (67%) respectively.

Two main procedures are known for the reduction of α-oximinoketones to 1,2-aminoalcohols, the LAH reduction[8c] and the catalytic hydrogenation with the system Pd-C/HCl[15,8a].

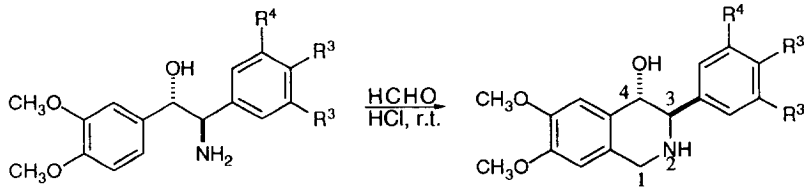


5 a R=H
b R=OMe

When we tried the reduction of oximinoketones **2a** and **2b** with complex hydrides like $NaBH_4$ and LAH we obtained the corresponding α-oximinoalcohols **5** instead of the expected aminoalcohols **3**. Nevertheless, complete reduction was achieved by catalytic (Pd-C) hydrogenation of the oximinoketone **2a** (95%) and, in spite of the literature reports, there was not necessary to use HCl. Surprisingly, this method was not satisfactory enough when applied to oximinoketone **2b**, since lower yields (about 50%) of the aminoalcohol and many undesired products were obtained after long reaction time.

We were able to overcome the problem by performing the hydrogenation in an ultrasound bath[16], adding small amounts of chloroform to the reaction mixture[17], so that the yield of 1,2-aminoalcohol **3b** was improved up to 95%. According to the large coupling constant (6.3 Hz) measured between protons at C-1 and C-2, and assuming that the preferred conformation is the one with both aryl groups in *anti*, we may tentatively propose an *erythro* relative configuration for the so-obtained aminoacohol **3b**, but doubtless assignment could not be made until cyclization took place. The same procedure was successfully applied to the preparation of aminoalcohols **3c** (94%), **3d** (90%) and **3e** (91%), for which the coupling constants were 5.9, 6.4 and 5.9 Hz respectively.

The last part of our research program was the Pictet-Spengler cyclization of amine derivatives **3**. Even though several examples are known for the preparation of 4-hydroxytetrahydroisoquinolines starting from phenolic substrates,[18] nevertheless we only found one such heterocyclization starting from a methoxy-substituted precursor (yield 30%).[18d] The diphenylaminoalcohol **3a** did not produce any cyclization product under the typical acidic conditions, clearly due to lack of activation towards the electrophilic substitution on the benzene ring. Although under the already mentioned reaction conditions dehydration to produce stilbenic derivatives could happen, nevertheless when the aminoalcohol **3b** was submitted to such conditions with formaldehyde, tetrahydroisoquinoline **4b** was obtained stereoselectively, making unnecessary previous alcohol protection. Similar results were encountered from **3c** and **3d**, giving rise to isoquinolines **4c** and **4d**, respectively.



3b, c, d

4b R^4=H, R^3=OMe 95%
c R^4=R^3=H 92%
d R^4=R^3=OMe 89%

As could be deduced from the coupling constants between H-3 and H-4 (7.9, 7.8 and 8.3 Hz respectively), the isoquinolines show an *anti* relative stereochemistry for the C-3 and C-4 substituents. Therefore, the starting aminoalcohols **3** must have the *erythro* relative configuration previously proposed.

Nevertheless, reaction of aminoalcohol **3e** with formaldehyde under different conditions did not produce any cyclization product but a complex mixture of compounds. Taking into account the excellent yields obtained for the other cyclization reactions previously performed, we deduced that disfavourable steric interactions between the methoxy group and the hydroxy groups at C-2' and C-1 respectively were responsible for the observed failure in cyclization. In fact, to the best of our knowledge, 4-hydroxy-5-methoxy substituted isoquinolines have not been described in the literature.

On the other hand, the cyclization is also efficient when using acetaldehyde instead of formaldehyde. For instance the 1-methyltetrahydroisoquinoline **4f** was obtained as a mixture of two epimers at C-1, and according to NOE experiments, the major isomer (9:1 ratio) was the one having the 1-methyl substituent in the pseudoequatorial position.[3c,19] In fact, NOE effect can be observed between H-3 and H-1, which suggests a *cis*-1,3-diaxial relationship between these protons and, therefore, pseudoequatorial and equatorial positions for the substituents at C-1 and C-3, respectively. Furthermore, this proposal is confirmed by the fact that no NOE can be seen between the methyl group at C-1 and H-1.

In summary, we have developed a short and efficient access to 4-hydroxylated 3-aryltetrahydroisoquinolines **4** starting from deoxybenzoins in three steps with good overall yield (50-83%). Our approach was based on the following attainments: we have improved nitrosation of deoxybenzoins thus obtaining oximinoketone derivatives which, in turn, have been advantageously reduced by sonication-assisted hydrogenation. Finally, in our hands the so-obtained aminoalcohols cyclized to the target isoquinolines regio- and stereoselectively avoiding hydroxyl protection.

Experimental

Solvents were either purified according to methods described by Perrin *et al.*,[20] or used as received from the manufacturers, depending on their purity. Thin layer chromatography (tlc) was performed on plates coated to a thickness of 0.2 mm with Merck Kieselgel 60 F_{254} using UV light (254 nm) and Dragendorff's reagent[21] as developing agents. Flash column chromatography[22] was performed on Merck kieselgel 60 (230-400 mesh ASTM); air-pressure chromatography was carried out on kieselgel 60 (70-230 mesh ASTM) or on neutral alumina 90 (activity I, 70-230 mesh ASTM). Evaporation of solvents under reduced pressure was performed in a Heidolph VV 60 rotatory evaporator. Melting points were measured in a Büchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer R-1430 infrared spectrophotometer as KBr plates, as neat liquid or in $CHCl_3$ and peaks are reported in cm^{-1}. NMR spectra were recorded on a Bruker ACE-250 (250 MHz for ^1H and 62.83 MHz for ^{13}C). Chemical shifts (δ) were measured in ppm relative to tetramethylsilane (δ 0.00) or chloroform (δ 7.26 for ^1H or 77.00 for ^{13}C) as internal standards; dimethylsulfoxide-d_6 (δ 2.49 for ^1H or 39.5 for ^{13}C) has been used when indicated. Multiplicities are indicated by s (singlet), b s (broad singlet) d (doublet), t (triplet), m (multiplet), or dd (doublet of doublets). Coupling constants, J, are reported in hertz. ^1H-{^1H} NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet in $CDCl_3$ solvent[23]. ^{13}C DEPT experiments were used to assist with the assignation of the signals. Mass spectra (EI) were obtained on a MS902 model Kratos apparatus. Data are reported in the form m/z (intensity relative to base =100). Combustion analyses were performed on a Perkin-Elmer 2400 CHN apparatus. Sonication was performed in a Selecta Model Ultrasons (15 x 30 x 23 cm; ~50 Hz; 200 W), sonication bath filled with water at room temperature.

Synthesis of α-oximinoketones.

1,2-Diphenyl-2-oximinoethanone **2a**. Typical procedure. ^{t}BuONO (0.31 cm^3, 2.58 mmol) was added dropwise to an ice cooled stirred solution of commercial benzyl phenyl ketone **1a** (0.5 g, 2.54 mmol) in dry ethanol (50 cm^3) under nitrogen. After three minutes, a stirred suspension of sodium ethoxide (0.21 g, 3.08 mmol) in dry ethanol (50 cm^3) was added slowly. After stirring overnight the solvent was removed *in vacuo*.

The residue was dissolved in water, extracted with diethyl ether, acidified with HCl (10 cm^3 of a 1 mol dm^{-3} solution in water) and extracted with dichloromethane. Organic extracts were dried over anhydrous sodium sulfate and evaporated to give a colourless oil which was purified by air-pressure column chromatography (alumina, 10% EtOAc/hexane) to give a mixture of cis- and trans-isomers of 1,2-*diphenyl*-2-*oximinoethanone* **2a**[24] (0.51 g, 90 %) as a white powder, m.p. 81-85°C (ethanol); δ_C[25] 126.4, 128.2, 128.4, 128.9, 129.0, 129.4, 129.8, 130.4, and 134.5 (C_{arom}-H), 134,6 (*C*$_{arom}$-C), 157.0 (C=NOH), 194.1 (CO); m/z 225 (M^+, 23), 195 (2), 165 (4), 105 (100), 77 (30), 51 (6); (Found: C,74.70; H, 4.68; N, 6.40. $C_{14}H_{11}O_2N$ requires C, 74.99; H, 4.50; N, 6.25%).

The same procedure on diarylketone **1b** (1 g, 3.16 mmol) afforded the following products:

1,2-*Bis*-(3,4-*dimethoxyphenyl*)*ethanodione* **6** (0.93 g, 90%), m.p.182-184°C (diethyl ether) (Lit [26] 183-184°C (methanol)), R_f (CH_2Cl_2-EtOAc, 9:1) 0.9; δ_C 56.0, 56.1 (OMe), 110.2, 126.2, 126.4 (C_{arom}-H), 149.4 (*C*$_{arom}$-C), 154.7 (C_{arom}-O), 193.4 (CO) (Found: C, 65.23; H, 5.61. $C_{18}H_{18}O_6$ requires C, 65.45; H, 5.49%), and

3,4-*Dimethoxybenzoic acid* **7** (*veratric acid*) (0.03 g, 6%), m.p. 178-180°C (diethyl ether) (Lit[27] 180-181°C (methanol)).

1,2-*Bis*-(3,4-*dimethoxyphenyl*)-2-*oximinoethanone* **2b**. Typical procedure. ^{t}BuONO (0.4 cm^3, 3.25 mmol) was added dropwise to an ice cooled stirred solution of deoxybenzoin **1b** (1.0 g, 3.16 mmol) in dry THF (50 cm^3) under nitrogen. After three minutes, an EtOH-HCl mixture (26 cm^3) previously prepared by bubbling hydrogen chloride in dry ethanol, was added very slowly. The mixture was allowed to stand three hours at room temperature, and then the solvent was removed *in vacuo* to give a brown oil which was dissolved in water and extracted with dichloromethane. The aqueous layer was basified to pH 8 and extracted with dichloromethane. Combined organic layers were dried over anhydrous sodium sulfate and evaporated to give a yellow oil which was purified by flash column chromatography using 10% EtOAc/CH_2Cl_2 as eluent. 1,2-*Bis*-(3,4-*dimethoxyphenyl*)-2-*oximinoethanone* **2b** was obtained (0.85 g, 78%) as a yellow powder, m.p. 115-116°C (diethyl ether), R_f (CH_2Cl_2-EtOAc, 9:1) 0.5; ν_{max} 3430 (O-H), 1730 (C=O), 1660 (C=N); δ_H 3.88 (3H, s, OMe), 3.90 (3H, s, OMe), 3.92 (3H, s, OMe), 3.93 (3H, s, OMe), 6.76 (1H, d, *J* 8.4, H-5'$_{arom}$), 6.8-6.9 (2H, m, H $_{arom}$), 7.47 (1H, dd, *J* 8.4, *J* 1.9, H-6'$_{arom}$), 7.5-7.6 (2H, m, H$_{arom}$), 8.4 (1H, bs, O-H); δ_C 55.8, 55.9, 56.0 (OMe), 107.9, 110.4, 110.7, 112.8, 120.5, 123.2 (C_{arom}-H), 149.2, 149.5 (*C*$_{arom}$-C), 151.0, 154.5 (C_{arom}-O), 156.1 (C=NOH), 192.7 (C=O); m/z 345 (M^+, 6), 195 (5), 165 (100), 139 (12), 77 (6) (Found: C, 62.44; H, 5.50; N, 4.30. $C_{18}H_{19}O_6N$ requires C, 62.60; H, 5.55; N, 4.06%).

Using the same procedure the following compounds were prepared:

1-(3,4-*dimethoxyphenyl*)-2-*phenyl*-2-*oximinoethanone* **2c**, (flash chromatography in 20% EtOAc/hexane) 96%, m.p. 155-156°C (hexane/EtOAc), R_f (10% EtOAc/CH_2Cl_2) 0.41; ν_{max} 3440 (O-H), 1740 (C=O), 1670 (C=N); δ_H 3.79 (3H, s, OMe), 3.80 (3H, s, OMe), 6.76 (1H, d, *J* 8.4, H-5'$_{arom}$), 7.22-7.29 (3H, m, H $_{arom}$), 7.43 (1H, d, *J* 8.4, H-6'$_{arom}$), 7.49-7.62 (3H, m, H$_{arom}$), 9.81 (1H, bs, O-H); δ_C 55.5, 55.7 (OMe), 109.2, 110.2, 125.7, 125.9, 127.5 (C_{arom}-H), 129.8, 131.0 (*C*$_{arom}$-C), 149.0, 154.1 (C_{arom}-O), 154.6 (C=NOH), 192.9 (C=O); (Found: C, 67.25; H, 5.40; N, 4.87. $C_{16}H_{15}O_4N$ requires C, 67.36; H, 5.30; N, 4.91%) ;

1-(3,4-*dimethoxyphenyl*)-2-(3,4,5-*trimethoxyphenyl*)-2-*oximinoethanone* **2d**, (flash chromatography in 10% EtOAc/CH_2Cl_2) 63%, m.p. 134-137°C ($CHCl_3$), R_f (10% EtOAc/CH_2Cl_2) 0.3; ν_{max} 3420 (O-H), 1680 (C=O, C=N); δ_H 3.72 (6H, s, 2 × OMe), 3.79 (3H, s, OMe), 3.88 (3H, s, OMe), 3.89 (3H, s, OMe), 6.74 (2H, s, H-2"$_{arom}$, H-6"$_{arom}$), 6.82 (1H, d, *J* 8.4, H-5'$_{arom}$), 7.43 (1H, dd, *J* 8.4, 1.9, H-6'$_{arom}$), 7.56 (1H, d, *J* 1.9, H-2'$_{arom}$), 9.2 (1H, bs, O-H); δ_C 55.8, 56.0 (OMe), 103.6, 109.5, 110.3, 125.8, 126.5 (C_{arom}-H), 127.8, 139.8 (*C*$_{arom}$-C), 149.3, 153.2, 154.5 (C_{arom}-O), 156.7 (C=NOH), 192.6 (C=O); (Found: C, 60.65; H, 5.50; N, 3.55. $C_{19}H_{21}O_7N$ requires C, 60.80; H, 5.64; N, 3.73%; and

1-(2,3,4-*trimethoxyphenyl*)-2-(3,4-*dimethoxyphenyl*)-2-*oximinoethanone* **2e**, (flash chromatography in 5% EtOAc/CH_2Cl_2) 67%, m.p. 157-158°C (hexane/EtOAc), R_f (10% EtOAc/CH_2Cl_2) 0.4; ν_{max} 3460 (O-H), 1730 (C=O) 1655 (C=N); δ_H 3.74 (3H, s, OMe), 3.77 (3H, s, OMe), 3.81 (3H, s, OMe), 3.83 (3H, s, OMe), 3.90 (3H, s, OMe), 6.75 (1H, d, *J* 9.1, H-5'$_{arom}$), 6.76 (1H, d, *J* 8.3, H-5"$_{arom}$), 6.93 (1H, dd, *J* 8.3, 1.9, H-6"$_{arom}$), 7.22 (1H, d, *J* 1.9, H-2"$_{arom}$), 7.75 (1H, d, *J* 9.1, H-6'$_{arom}$), 8.56 (1H, bs, O-H); δ_C 55.7, 55.8, 56.1, 60.6, 61.1 (OMe), 107.3, 108.2, 110.6, 120.2, 126.2 (C_{arom}-H), 123.3, 124.1 (*C*$_{arom}$-C),

141.6, 149.0, 150.5, 155.3, 158.7 (C_{arom}-O), 159.1 (C=NOH), 191.0 (C=O); (Found: C, 60.63; H, 5.50; N, 3.58. $C_{19}H_{21}O_7N$ requires C, 60.80; H, 5.64; N, 3.73%.

Reduction of oximinoketones 2 with $NaBH_4$ and $LiAlH_4$.

Cis- and *trans-2-hydroxy-1,2-diphenylethanone oxime* **5a** and **5b**.Typical procedure. Dry methanol (50 cm^3) was added dropwise to an ice cooled stirred mixture of oximinoketone **2a** (1 g, 4.4 mmol) and $NaBH_4$ (1.66 g, 0.044 mol). After stirring for 18 hours, water (30 cm^3) was added, followed by HCl (60 cm^3 of a 0.5 mol dm^{-3} solution in water).The mixture was filtered and the filtrate was extracted with dichloromethane, dried over anhydrous sodium sulfate and evaporated to give a colourless oil. Flash column chromatography using dichlomethane-ethyl acetate 9:1 as eluent afforded the following products[28]:
cis-2-hydroxy-1,2-diphenylethanone oxime **5a** (0.57 g, 56%) as a white powder, m.p. 95-99°C (dichloromethane-hexane) (Lit[29] 99°C (diethyl ether)), R_f (CH_2Cl_2-EtOAc, 9:1) 0.4; ν_{max} 3550-3200 (O-H), 1645 (C=N); δ_H [30] (DMSO-d_6) 5.99 (1H, d, *J* 4.9, CH-O*H*), 6.59 (1H, d, *J* 4.9, C*H*-OH), 7.2-7.6 (10H, m, H_{arom}),10.41 (1H, bs, N-OH); δ_C (DMSO-d_6) 64.7 (CHOH), 125.3, 126.7, 127.7, 128.1 (C_{arom}-H), 134.3, 141.9 (C_{arom}-C), 158.6 (C=NOH) (Found: C,73.91; H, 5.72; N, 6.27. $C_{14}H_{13}O_2N$ requires C, 73.99; H, 5.77; N, 6.16%); and
trans-2-hydroxy-1,2-diphenylethanone oxime **5a** (0.32 g, 32%) as a white powder, m.p. 140-142°C (methanol) (Lit[29] 151-152°C (benzene)), R_f (CH_2Cl_2-EtOAc, 9:1) 0.2; ν_{max} 3450-3200 (O-H), 1640 (C=N); δ_H [30] (DMSO-d_6) 5.53 (1H, d, *J* 4.3, CH-O*H*), 5.88 (1H, d, *J* 4.3, C*H*-OH), 7.1-7.3 (10H, m, H_{arom}) 10.70 (1H, bs, N-OH); δ_C (DMSO-d_6) 74.4 (CHOH), 126.1, 127.3, 127.7, 128.6 (C_{arom}-H), 132.2, 141.8 (C_{arom}-C), 157.6 (C=NOH) (Found: C,74.10; H, 5.72; N, 6.29. $C_{14}H_{13}O_2N$ requires C, 73.99; H, 5.77; N, 6.16%).
The same procedure applied to oximinoketone **2b** (1 g, 2.9 mmol) afforded 1,2-*bis*-(3,4-*dimethoxyphenyl*)-2-*hydroxyethanone oxime* **5b** (0.77 g, 76%) as a white powder, m.p. 157-160°C(dichloromethane), R_f (CH_2Cl_2-EtOAc, 9:1) 0.2; ν_{max} 3450-3200 (O-H), 1680 (C=N); δ_H (DMSO-d_6) 3.65 (3H, s, OMe), 3.70 (3H, s, OMe), 3.71 (3H, s, OMe), 5.80 (1H, d, *J* 5.0, CH-O*H*), 6.50 (1H, d, *J* 5.0, C*H*-OH), 6.81 (1H, d, *J* 8.4, H-5"$_{arom}$) 6.90 (2H, m, H-5'$_{arom}$, H-6'$_{arom}$), 7.04 (1H, s, H-2'$_{arom}$), 7.15 (1H, dd, *J* 8.4, *J* 1.9, H-6"$_{arom}$), 7.21 (1H, d, *J* 1.9, H-2"$_{arom}$), 10.71 (1H, bs, N-OH); δ_C (DMSO-d_6) 55.4 (OMe), 64.4 (CHOH), 109.7, 110.5, 111.1, 117.4, 120.9 (C_{arom}-H), 126.8, 134.5 (C_{arom}-C), 147.5, 147.7, 148.5, 148.9 (C_{arom}-O) 158.1 (C=NOH) (Found: C, 62.40; H, 6.01; N, 4.10. $C_{18}H_{21}O_6N$ requires C, 62.24; H, 6.09; N, 4.03%).
Cis-2-hydroxy-1,2-diphenyl ethanone oxime **5a**. Typical procedure. A solution of oximinoketone **2a** (0.8 g, 3.55 mmol) in dry THF (30 cm^3) was added dropwise to an ice cooled stirred suspension of LAH (0.3 g, 7 mmol). After stirring for 4 hours, ethyl acetate (10 cm^3) was added slowly, followed by water (10 cm^3). The mixture was filtered and the aqueous layer was extracted with dichloromethane. Combined organic layers were dried over anhydrous sodium sulfate and evaporated to give a colourless oil. Flash column chromatography using dichloromethane-ethyl acetate 9:1 as eluent afforded cis-oximinoalcohol **5a** (0.39 g, 48%).
The same procedure applied to oximinoketone **2b** (0.9 g, 2.6 mmol) afforded 1,2-*bis*-(3,4-*dimethoxyphenyl*)-2-*hydroxyethanone oxime* **5b** (36%).

Catalytic hydrogenation.

2-*amino*-1,2-*diphenylethanol* **3a**. A mixture of oximinoketone **2a** (1g, 4.4 mmol) and Pd-C catalyst (0.4 g, 10 % Pd) in dry ethanol (60 cm^3) was hydrogenated for 18 hours (P_{H_2}=3 atm). The mixture was filtered and the filtrate was evaporated to afford 1,2-aminoalcohol **3a**[31] (0.90 g, 95%) as a white powder
The same procedure was applied to oximinoketone **2b** to produce 2-*amino*-1,2-*bis*-(3,4-*dimethoxyphenyl*)*ethanol* **3b** (50%), m.p. 155-160°C (methanol) (186-187°C as hydrochloride from methanol), R_f (10% MeOH/CH_2Cl_2) 0.2; ν_{max} 3400 (O-H), 3320, 3210 (N-H); δ_H 1.5-1.9 (3H, bs, NH_2 and OH), 3.80 (3H, s, OMe), 3.83 (3H, s, OMe), 3.87 (6H, s, OMe), 4.07 (1H, d, *J* 6.3, C*H*-NH_2), 4.63 (1H, d, *J* 6.3, C*H*-OH), 6.7-6.9 (6H, m, H_{arom}); δ_C 55.7, 55.8 (OMe), 61.7 ($CHNH_2$), 78.4 (CHOH), 109.8, 110.4, 110.7, 110.8, 119.4, 119.9 (C_{arom}-H), 133.2, 134.0 (C_{arom}-C), 148.5, 148.6, 148.7, 148.9 (C_{arom}-O); (Found: C, 64.75; H, 6.78; N, 4.12. $C_{18}H_{23}O_5N$ requires C, 64.85; H, 6.95; N, 4.20%).

Catalytic hydrogenation assisted by sonication.

2-*Amino*-1,2-*bis*-(3,4-*dimethoxyphenyl*)*ethanol* **3b.** Typical procedure. A mixture of oximinoketone **2b** (1 g, 0.29 mmol), Pd-C catalyst (0.4 g, 10% Pd) and $CHCl_3$ (0.5 cm^3, 6.2 mmol) in dry methanol (70 cm^3) was hydrogenated for 48 hours (P_{H_2}~1.5 atm) in an ultrasound bath. The mixture was filtered and the filtrate was evaporated to give a white powder, which was basified with ammonium hydroxide solution and extracted with dichloromethane. Organic layers were dried over anhydrous sodium sulfate and evaporated to afford chromatographically pure 2-*amino*-1,2-*bis*-(3,4-*dimethoxyphenyl*)*ethanol* **3b** (0.92 g, 95%) as a white powder.

Using the same procedure the following compounds were obtained as yellow oils:

2-*amino*-1-(3,4-*dimethoxyphenyl*)-2-*phenylethanol*, **3c**, 94%, m.p. (as hydrochloride from methanol) 177-178°C, R_f (10% MeOH/CH_2Cl_2) 0.22; ν_{max} 3560 (O-H), 3340, 3280 (N-H); δ_H 2.05 (3H, bs, NH_2 and OH), 3.70 (3H, s, OMe), 3.74 (3H, s, OMe), 4.08 (1H, d, *J* 5.6, C*H*-NH_2), 4.59 (1H, d, *J* 5.9, C*H*-OH), 6.56 (1H, s, H-2'$_{arom}$), 6.68 (1H, m, H-6'$_{arom}$), 6.78 (1H, d, *J* 7.7, H-5'$_{arom}$), 7.12-7.29 (5H, m, H_{arom}); δ_C 55.6, 55.8 (OMe), 61.8 ($CHNH_2$), 77.9 (CHOH), 109.8, 110.5, 119.1, 127.5, 127.6, 128.5 (C_{arom}-H), 133.2, 141.5 (C_{arom}-C), 148.4, 148.5 (C_{arom}-O); (Found: C, 61.85; H, 7.12; N, 4.80. $C_{16}H_{20}O_3ClN$ requires C, 62.03; H, 6.96; N, 4.52%);

2-*amino*-1-(3,4-*dimethoxyphenyl*)-2-(3,4,5-*trimethoxyphenyl*)*ethanol*, **3d**, 90%, m.p. (as hydrochloride from methanol) 176-177°C, R_f (10% MeOH/CH_2Cl_2) 0.21; ν_{max} 3550 (O-H, N-H); δ_H 1.88 (3H, bs, NH_2 and OH), 3.78 (3H, s, OMe), 3.79 (3H, s, OMe), 3.80 (3H, s, OMe), 3.81 (3H, s, OMe), 3.82 (3H, s, OMe), 4.01 (1H, d, *J* 6.4, C*H*-NH_2), 4.59 (1H, d, *J* 6.4, C*H*-OH), 6.50 (2H, s, H-5"$_{arom}$, H-6"$_{arom}$), 6.73 (1H, s, H-2'$_{arom}$), 6.79 (1H, d, *J* 8.2, H-5'$_{arom}$), 6.84 (1H, dd, *J* 8.2, 1.1, H-6'$_{arom}$); δ_C 55.7, 55.8, 56.0, 60.7 (OMe), 62.1 ($CHNH_2$), 78.2 (CHOH), 104.4, 109.7, 110.6, 119.3 (C_{arom}-H), 133.2, 137.2 (C_{arom}-C), 148.5, 148.8, 153.0 (C_{arom}-O); (Found: C, 57.26; H, 6.34; N, 3.55. $C_{19}H_{26}O_6ClN$ requires C, 57.07; H, 6.55; N, 3.50%); and

2-*amino*-2-(3,4-*dimethoxyphenyl*)-1-(2,3,4-*trimethoxyphenyl*)*ethanol*, **3e**, 95%, m.p. (as hydrochloride from methanol) 183-184°C, R_f (10% MeOH/CH_2Cl_2) 0.1; ν_{max} 3350 (O-H, N-H); δ_H 1.70 (3H, bs, NH_2 and OH), 3.78 (3H, s, OMe), 3.82 (3H, s, OMe), 3.83 (3H, s, OMe), 3.85 (3H, s, OMe), 3.89 (3H, s, OMe), 4.62 (1H, d, *J* 5.9, C*H*-NH_2), 4.96 (1H, d, *J* 5.9, C*H*-OH), 6.55-6.62 (2H, m, H_{arom}), 6.71-6.86 (3H, m, H_{arom}); δ_C 55.3, 55.5, 55.6, 60.3, 60.7 (OMe), 61.1 ($CHNH_2$), 73.3 (CHOH), 107.1, 110.6, 110.7, 119.6, 122.1 (C_{arom}-H), 126.6, 134.1 (C_{arom}-C), 141.6, 148.2, 148.4, 151.3, 153.0 (C_{arom}-O); (Found: C, 56.85; H, 6.67; N, 3.38. $C_{19}H_{26}O_6ClN$ requires C, 57.07; H, 6.55; N, 3.50%).

Heterocyclization.

(3*R**,4*S**)-3-(3',4'-*Dimethoxyphenyl*)-4-*hydroxy*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* **4b.** Typical procedure. Formaldehyde (0.8 cm^3 of a 40% solution in water, 12 mmol) was added to a stirred solution of 1,2-aminoalcohol **3b** (0.4 g, 1.2 mmol) in HCl (20 cm^3 of a 1 mol dm^{-3} solution in water) under nitrogen at 20°C. After 37 days stirring, water (50 cm^3) was added and the mixture was washed with hexane, the aqueous layer once basified to pH 8 with ammonium hydroxide solution, was washed again with hexane and extracted with dichloromethane. The combined organic extracts were dried over anhydrous sodium sulfate and evaporated to afford tetrahydroisoquinoline **4b** (0.39 g, 95%) as a white powder, m.p.165-168°C (hexane-EtOAc); R_f (10% MeOH/CH_2Cl_2) 0.3; ν_{max} 3480 (O-H), 3260 (N-H); δ_H 1.95 (2H, bs, NH and OH), 3.74 (1H, d, *J* 7.9 Hz, H-3), 3.86 (3H, s, OMe), 3.88 (3H, s, OMe), 3.89 (6H, s, OMe), 3.97 (1H, d, *J* 15.2, H-1$_{pseudo\text{-}eq}$), 4.21 (1H, d, *J* 15.2, H-1$_{pseudo\text{-}ax}$), 4.73 (1H, d, *J* 7.9, H-4), 6.55 (1H, s, H-8$_{arom}$), 6.86 (1H, d, *J* 8.2, H-5'$_{arom}$), 6.93 (1H, dd, *J* 8.1, 1.9, H-6'$_{arom}$), 7.02 (1H, d, *J* 1.9, H-2'$_{arom}$), 7.09 (1H, s, H-5$_{arom}$); δ_C 48.1 (C-1), 55.9 (OMe), 65.7, 72.1 (C-3, C-4), 108.3, 109.7, 110.2, 111.1, 120.1 (C_{arom}-H), 127.3, 129.3, 133.3 (C_{arom}-C), 147.1, 147.9, 148.3, 148.8 (C_{arom}-O); (Found: C, 66.06; H, 6.49; N, 3.77. $C_{19}H_{23}O_5N$ requires C, 66.07; H, 6.71; N, 4.06%).

Using the same procedure 3-*phenyl*-4-*hydroxy*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline*, **4c**, was prepared, 92%, m.p.166-167°C (EtOAc); R_f (10% MeOH/CH_2Cl_2) 0.54; ν_{max} 3400 (O-H), 3275 (N-H); δ_H

1.89 (2H, bs, NH and OH), 3.79 (1H, d, *J* 7.8, H-3), 3.86 (3H, s, OMe), 3.88 (3H, s, OMe), 3.95 (1H, d, *J* 15.0, H-$1_{pseudo-eq}$), 4.18 (1H, d, *J* 15.0, H-$1_{pseudo-ax}$), 4.74 (1H, d, *J* 7.8 Hz, H-4), 6.54 (1H, s, H-5_{arom}), 7.08 (1H, s, H-8_{arom}), 7.32-7.44 (5H, m, H_{arom}); δ_C 47.9 (C-1), 55.9 (OMe), 65.8, 71.9 (C-3, C-4), 108.3, 109.8, 127.5, 127.7, 128.8 (C_{arom}-H), 127.5, 129.3, 140.9 (C_{arom}-C), 147.9, 148.4 (C_{arom}-O); (Found: C, 71.42; H, 6.81; N, 5.13. $C_{17}H_{19}O_3N$ requires C, 71.54; H, 6.7; N, 4.91%); and 3-(3',4',5'-*trimethoxyphenyl*)-4-*hydroxy*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* **4d**, 89%, was prepared in the same way as described above for **4b** and **4c**, but stirring during 3 days at 30°C, m.p.163-164°C (methanol); R_f (5% MeOH/CH_2Cl_2) 0.15; ν_{max} 3300 (O-H, N-H); δ_H 1.77 (2H, bs, NH and OH), 3.66 (1H, d, *J* 8.2, H-3), 3.82 (6H, s, OMe), 3.83 (3H, s, OMe), 3.84 (3H, s, OMe), 3.86 (6H, s, OMe), 3.98 (1H, d, *J* 15.0, H-$1_{pseudo-eq}$), 4.20 (1H, d, *J* 15.0, H-$1_{pseudo-ax}$), 4.70 (1H, d, *J* 8.2 Hz, H-4), 6.54 (1H, s, H-8), 6.68 (2H, s, H-2'$_{arom}$, H-6'$_{arom}$), 7.08 (1H, s, H-5_{arom}); δ_C 48.4 (C-1), 55.9, 56.1, 60.8 (OMe), 66.6, 72.4 (C-3, C-4), 104.3, 108.3, 109.5 (C_{arom}-H), 127.2, 129.2, 136.7 (C_{arom}-C), 137.5, 148.0, 148.3, 153.5 (C_{arom}-O); (Found: C, 64.11; H, 6.75; N, 3.92. $C_{20}H_{15}O_6N$ requires C, 64.0; H, 6.67; N, 3.73%).

3-(3',4'-*Dimethoxyphenyl*)-4-*hydroxy*-6,7-*dimethoxy*-1-*methyl*-1,2,3,4-*tetrahydroisoquinoline* **4f**. Acetaldehyde (0.68 cm^3, 12 mmol) was added dropwise to an ice cooled stirred solution of 1,2-aminoalcohol **3b** (0.4 g, 1.2 mmol) in HCl (20 cm^3 of a 1 mol dm^{-3} solution in water) under nitrogen. After stirring overnight at 55°C and cooling, water (50 cm^3) was added and the mixture was washed with hexane, the aqueous layer was basified to pH 8 with ammonium hydroxide solution and extracted with dichloromethane, dried over anhydrous sodium sulfate and evaporated to give an amber oil. Air-pressure column chromatography (silica gel) using 8% methanol/CH_2Cl_2 as eluent afforded the major isomer of tetrahydroisoquinoline **4f** (0.30g, 70%) as a white powder, m.p.116-120°C (hexane-EtOAc); R_f (10% MeOH/CH_2Cl_2) 0.4; ν_{max} 3600-3200 (O-H and N-H); δ_H 1.47 (3H, d, *J* 6.3, CH_3), 1.78 (2H, bs, NH and OH), 3.70 (1H, d, *J* 8.9, H-3), 3.88 (6H, s, OMe), 3.89 (3H, s, OMe), 3.90 (3H, s, OMe), 4.29 (1H, q, *J* 6.3, H-1), 4.75 (1H, d, *J* 8.9, H-4), 6.67 (1H, s, H-8), 6.88 (1H, d, *J* 8.2, H-5'$_{arom}$), 7.03 (1H, d, *J* 8.2 Hz, H-6'$_{arom}$), 7.06 (1H, s, H-2'$_{arom}$), 7.12 (1H, s, H-5); δ_C 22.5 (CH_3), 53.1 (C-1), 55.9 (OMe), 66.5, 72.9 (C-3, C-4), 107.7, 109.2, 110.3, 111.2, 120.1 (C_{arom}-H), 129.9, 132.2, 133.8 (C_{arom}-C), 147.8, 148.2, 148.8, 149.4 (C_{arom}-O); (Found: C, 66.75; H, 7.12; N, 3.95. $C_{20}H_{25}O_5N$ requires C, 66.83; H, 7.01; N, 3.9%); the *minor isomer*, epimer at C-1, could not be isolated, but it was identified in the reaction mixture by means of its ^1H NMR spectral data: δ_H 1.56 (3H, d, *J* 6.4, CH_3), 3.70 (1H, d, *J* 8.9, H-3), 4.18 (1H, q, *J* 6.4, H-1), 4.63 (1H, d, *J* 8.9, H-4), 6.72 (1H, s, H-8), 7.05 (1H, s, H-5).

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