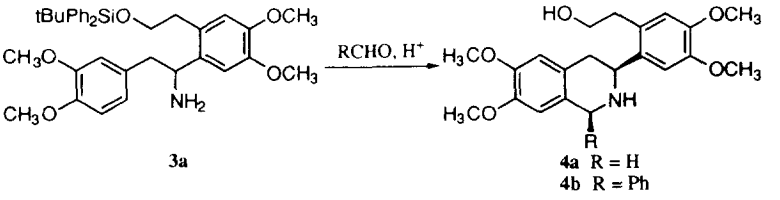



3a

4a R = H
4b R = Ph

**Scheme 2**

The stereochemistry of **4a** and **4b** was established by $^1$H NMR. In both isoquinolines the magnitudes of the coupling constants of the ABX system formed by the H-4 and H-3 protons (Table 1) indicate that the heterocyclic system adopts a preferred half-chair conformation with the aryl group at C-3 in a *pseudo*equatorial position, as decribed for other 3-aryltetrahydroisoquinoline systems.[13] In the case of **4b** the NOE observed between H-1 and H-3 suggests that the phenyl group at C-1 and the aryl group at C-3 are in a *cis* disposition, both in *pseudo*equatorial orientations of the tetrahydroisoquinoline half-chair (Figure 1).

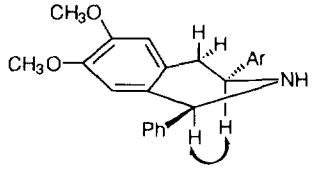
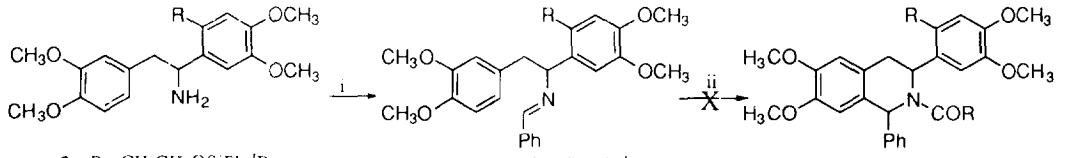



**Figure 1.** NOE observed for **4b**.

These results indicate that the classical Pictet-Spengler methodology fails when acid sensitive groups are present in the amine. Therefore, we decided to apply different reaction conditions in order to improve the yields and avoid deprotection of the hydroxyl group. Several modifications of these classical conditions have been developed in order to achieve the cyclization under milder conditions. Thus, tryptamine derivatives have been successfully cyclized with TFA in dichloromethane[23], acetic acid in dioxane [22] or even in aprotic media[24]. Also, ketals and enol ethers[25] have been used as carbonyl group equivalents. Cyclizations via *N*-acyliminium ions[26] or amine *N*-oxides[27] could also be considered as variations of this Pictet-Spengler reaction.

One of these modifications, described by Venkov and co-workers[28], implies the Lewis acid promoted cyclization of previously prepared Schiff bases in the presence of acyl chlorides.Thus, 2-acyl-1-aryl-tetrahydroisoquinolines are obtained through an intermediate *N*-acyliminium ion. We tried to extend this methodology to the preparation of 2-acetyl-1-phenyl-3-aryltetrahydroisoquinolines. Using the amine **3b** as a model compound (Scheme 3), the imine **5b** was prepared in good yield (86%) by condensation with benzaldehyde. However, treatment with acyl chlorides ($CH_3COCl$, PhCOCl) and Lewis acids ($AlCl_3$, $TiCl_4$, $SnCl_4$) only gave, after work-up, the starting amine.[29] The same procedures applied to **3a** gave identical results.




3a R= $CH_2CH_2OSiPh_2{}^tBu$
3b R= H

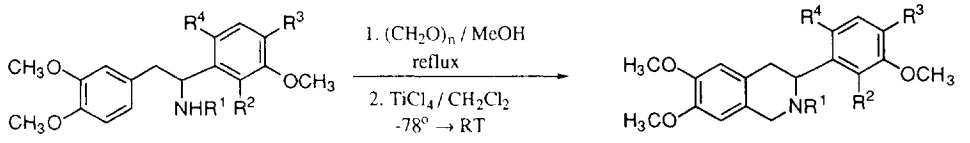
5a R= $CH_2CH_2OSiPh_2{}^tBu$
5b R= H

i: PhCHO, toluene, reflux; ii: RCOCl, Lewis acid, $CH_2Cl_2$, rt

**Scheme 3**

Kubo[30] described the first example of the use of alkoxymethylamines as iminium ions precursors in the synthesis of tetrahydroisoquinolines. This protocol implies the treatment of a secondary phenethylamine with paraformaldehyde in ethanol to yield an ethoxymethyl amine that cyclizes in the presence of TFA. In a similar fashion, Heaney[31] has applied this methodology to a primary amine, the 3,4-dimethoxyphenethylamine, to obtain *N*-arylmethyltetrahydroisoquinolines in a tandem reaction. The first iminium ion formed cyclizes to the tetrahydroisoquinoline in the presence of $CH_3SiCl_3$; then, a second iminium ion reacts with the external nucleophiles, electron rich aromatic compounds. In the absence of nucleophiles, the dimer bis[2-(6,7-dimethoxytetrahydroisoquinolinyl)]methane is obtained. This procedure has also been extended to the synthesis of 1-substituted tetrahydroisoquinolines by reaction of α-alkoxyhalides with *N*-phenethylcarbamates, followed by cyclization.[32] With these precedents in mind, we designed a new procedure for the preparation of 3-aryltetrahydroisoquinolines that implies the Lewis acid promoted cyclization of bis(methoxymethyl) derivatives of primary 1,2-diarylethylamines. We expected that the presence of the 1-aryl group in the amine would avoid the alkylation of the second iminium ion formed, preventing the formation of dimers reported by Heaney.[31]

We chose the 1,2-diarylethylamine **3c** as a model compound. The amine **3c** was refluxed with excess of paraformaldehyde in methanol to yield the corresponding (methoxymethyl)amine that, without further purification, was treated with $TiCl_4$ at -78°C. The reaction mixture was allowed to warm up to room temperature (1 h) and the 3-aryltetrahydroisoquinoline **6c** was obtained in good yield (70%). Under identical conditions the tetrahydroisoquinoline **6a** was also obtained in high yield (Scheme 4, Table 1). As expected, no dimerization product was observed and the mild reaction conditions avoid desilylation. The application of this procedure to the secondary amine **3d** led to the corresponding tetrahydroisoquinoline **6d**, though longer reaction times are required for the cyclization. The best way to prepare the *N*-substituted derivatives is cyclization and subsequent alkylation. Thus, **6a** was *N*-methylated [$(CH_2O)_n$ / MeOH / $NaBH_4$][33] to give **6e** in almost quantitative yield.




**3a** $R^1$, $R^2$ = H, $R^3$ = $OCH_3$, $R^4$ = $CH_2CH_2O^tBuPh_2Si$
**3c** $R^1$, $R^3$, $R^4$ = H, $R^2$ = $OCH_3$
**3d** $R^1$ = $CH_2Ph$, $R^2$, $R^4$ = H, $R^3$ = $OCH_3$

**6a** $R^1$, $R^2$ = H, $R^3$ = $OCH_3$, $R^4$ = $CH_2CH_2O^tBuPh_2Si$
**6c** $R^1$, $R^3$, $R^4$ = H, $R^2$ = $OCH_3$
**6d** $R^1$ = $CH_2Ph$, $R^2$, $R^4$ = H, $R^3$ = $OCH_3$
**6e** $R^1$ = $CH_3$, $R^2$ = H, $R^3$ = $OCH_3$, $R^4$ = $CH_2CH_2O^tBuPh_2Si$

**Scheme 4**

The titanium tetrachloride promoted cyclization of *N*-methoxymethyl-*N*-1,2-diarylethylamines *via* iminium ions constitutes an efficient approach to 2'-functionalized-3-aryltetrahydroisoquinolines. No nitrogen protection is required to apply this procedure to primary amines, since the 1-aryl group prevents dimerization of the so-obtained tetrahydroisoquinoline. This method has the advantage over the classical protic acid promoted Pictet-Spengler cyclization of being compatible with the presence of acid sensitive groups in the molecule.

**Table 1.** Synthetic and Selected Spectroscopic Data of Tetrahydroisoquinolines **4** and **6**

| | | | | $^1$H NMR [δ,ppm (mult.[c]), J, Hz] | | |
|---|---|---|---|---|---|---|
| Entry | Product | Method[a] | Yield (%)[b] | H-3 | H-4ax | H-4eq |
| 1 | **4a** | A | 14 | 4.22 (dd) (10.1, 4.0) | 3.15 (dd) (16.2, 10.1) | 2.87 (dd) (16.2, 4.0) |
| 2 | **4b** | B | 58 | 4.35 (dd) (11.5, 3.2) | 3.30-3.59 (m) | 2.86-2.94 (m) |
| 3 | **6a** | C | 85 | 3.86-3.92 (m) | 2.72-2.84 (m) | 2.52 (dd) (16.0, 3.6) |
| 4 | **6c** | C | 70 | 4.51 (t) (7.2) | 2.85 (d) (7.2) | |
| 5 | **6d** | C | 69 | 3.59-3.78 (m) | 2.82-3.10 (m) | |
| 6 | **6e** | D | 96 | 3.75-3.90 (m) | 3.83-2.98 (m) | 2.52 (dd) (16.6, 3.8) |

[a] Method A: 37% aq.HCHO / 3M HCl, reflux; Method B: PhCHO / 85% $H_3PO_4$, 40°C; Method C: 1.$(CH_2O)n$/MeOH, reflux, 2. $TiCl_4/CH_2Cl_2$, -78°C→RT: Method D: 1.$(CH_2O)n$/MeOH, reflux, 2. $NaBH_4$, from **6a**.

[b] Yield of pure, isolated compounds.

[c] Multiplicity: d: doublet; dd: doublet of doublets; m: multiplet.

## EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were obtained by using a Perkin-Elmer 1430 spectrophotometer on KBr pellets (solids) or $CHCl_3$ solution (oils). NMR spectra were recorded on a Bruker AC-250 spectrometer at 20-25°C, running at 250 MHz for $^1$H and 62.8 MHz for $^{13}$C in $CDCl_3$, solutions. $^1$H NMR chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane ($\delta_{TMS}$ = 0.00 ppm) as internal standard. Assignments were confirmed by homonuclear spin-spin decoupling experiments. $^1$H-{$^1$H} NOE experiments were carried out in the difference mode[34] by irradiation of all the lines of a multiplet.[35] The $^{13}$C NMR chemical shifts are reported in ppm downfield from TMS and referenced with respect to internal $CDCl_3$ (δ = 77.00 for the center line). Assignment of individual $^{13}$C resonances are supported by DEPT experiments. Elemental analyses were determined on a Perkin-Elmer 2400 CHN apparatus. Mass spectra were recorded by the Universities of La Laguna and Santiago de Compostela. TLC was carried out with 0.2 mm thick silica gel plates (Merck Kieselgel $GF_{254}$). Visualization was accomplished by UV light or by spraying with Dragendorff's reagent.[36] Flash column chromatography[37] on silica gel was performed with Merck Kieselgel 60 (230-400 mesh). All solvents used in reactions were anhydrous and purified according to standard procedures.[38] Amines **3a**, **3b**, **3c** and **3d** were prepared according to literature procedures.[39]

*Synthesis of 3-[2-(2-hydroxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxytetrahydroisoquinoline* **4a**

A solution of the amine **3a** (200 mg, 0.33 mmol) and 37% aq. HCHO (0.15 mL) in 3M HCl (1mL) was refluxed over 2 hours. The reaction mixture was cooled down to room temperature, water was added and the aqueous phase was washed with ether. After basifying with 40% NaOH, the aqueous layer was extracted with $CH_2Cl_2$ (3 x 10 mL) and the resulting organic phase was dried over $Na_2SO_4$, filtered and evaporated. The residue was purified by column chromatography (silicagel, 1-5% $CH_2Cl_2$/MeOH), affording the tetrahydroisoquinoline **4a** (14%, 18 mg). Mp (methanol): 207-208°C (dec.); IR $\nu_{max}$ (KBr): 3420, 3200, 1610 $cm^{-1}$; $^1H$ NMR (δ, ppm): 2.74 (td, J = 14.1, J = 3.9, 1H, Ar-C$\underline{H}_a$H$_b$-CH$_2$-OH), 2.87 (dd, J = 16.2, J = 4.0, 1H, H-4eq), 2.94-2.03 (m, 1H, Ar-CH$_a$$\underline{H}_b$-CH$_2$-OH), 3.15 (dd, J = 16.2, J = 10.1, 1H, H-4ax), 3.64-3.73 (m, 2H, Ar-CH$_a$H$_b$-C$\underline{H}_2$-OH), 3.77 (s, 3H, OCH$_3$), 3.82 (s, 6H, 2 x OCH$_3$), 3.84 (s, 3H, OCH$_3$)*, 3.90 (d, J = 16.0, 1H, H-1)*, 4.09 (d, J = 16.0, 1H, H-1), 4.20 (broad s, 2H, NH y OH)**, 4.22 (dd, J = 10.1, J = 4.0, 1H, H-3)**, 6.51 (s, 1H, H-6'), 6.61 (s, 1H, H-3'), 6.72 (s, 1H, H-5), 6.94 (s, 1H, H-8) (*, **: overlapped signals); $^{13}C$ NMR (δ, ppm): 33.38 (Ar-$\underline{C}$H$_2$-CH$_2$-OH), 35.32 (C-4), 46.82 (C-1), 55.29 (C-3), 55.76, 55.83, 55.89 (4 x OCH$_3$), 63.55 (Ar-CH$_2$-$\underline{C}$H$_2$-OH), 108.77, 109.11 (C-5 and/or C-3'), 111.59 (C-8), 113.21 (C-6'), 125.57, 125.99 (C-8a and/or C-2'), 131.17, 132.17 (C-4a and/or C-1'), 147.36, 147.57, 147.66, 148.36 (C-6, C-7, C-5', and/or C-4'); MS(EI) m/z (%): 373 ($M^+$, 3), 165 (26), 164 (100), 121 (26), 91 (15), 83 (12), 77 (19), 69 (19), 67 (11), 57 (23), 55 (29), 43 (31), 41 (23), Anal. Calcd for $C_{21}H_{27}NO_5$ (373.19): C 67.53, H 7.29, N 3.75; Found: C 67.59, H 7.32, N 3.68.

*Synthesis of 1-phenyl-3-[2-(2-hydroxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxytetrahydroisoquinoline* **4b**

To a mixture of the amine **3a** (200 mg, 0.33 mmol) and benzaldehyde (40 mg, 0.36 mmol), 2.5 mL of 85% $H_3PO_4$ were added dropwise and the resulting suspension was stirred at 40°C for 36 hours. Water was added and the aqueous phase was washed with ether. After basifying with 40% NaOH, the aqueous phase was extracted with $CH_2Cl_2$ (3 x 10 mL) and the resulting organic layer dried over $Na_2SO_4$, filtered and evaporated. The residue was purified by column chromatography (silicagel, 1-3% $CH_2Cl_2$/MeOH), affording the tetrahydroisoquinoline **4a** (58%, 86 mg). Mp: oil; IR $\nu_{max}$($CHCl_3$): 3520, 3300, 1615$cm^{-1}$; $^1H$ NMR (δ, ppm): 2.81-2.86 (m, 1H, Ar-C$\underline{H}_a$H$_b$-CH$_a$H$_b$-OH), 2.86-2.94 (m, 1H, H-4eq), 3.01-3.10 (m, 1H, Ar-CH$_a$$\underline{H}_b$-CH$_a$H$_b$-OH), 3.30-3.59 (m, 1H, H-4ax), 3.63 (s, 3H, OCH$_3$), 3.67-3.82 (m, 2H, Ar-CH$_a$H$_b$-C$\underline{H}_a$H$_b$-O$\underline{H}$), 3.86 (s, 3H, OCH$_3$), 3.87 (s, 3H, OCH$_3$), 3.88 (s, 3H, OCH$_3$), 3.91-3.97 (m, 1H, Ar-CH$_a$H$_b$-CH$_a$$\underline{H}_b$-OH), 4.35 (dd, J = 11.5, J = 3.2, 1H, H-3), 5.29 (s, 1H, H-1), 6.27 (s, 1H, H-8), 6.67 (s, 1H, H-3'), 6.73 (s, 1H, H-6'), 7.06 (s, 1H, H-5), 7.22-7.34 (m, 5H, Ph); $^{13}C$ NMR (δ, ppm): 34.99 (Ar-$\underline{C}$H$_2$-CH$_2$-OH), 35.51 (C-4), 53.34 (C-3), 55.84, 56.04 (4 x OCH$_3$), 62.99 (C-1), 64.05 (Ar-CH$_2$-$\underline{C}$H$_2$-OH), 109.08, 110.50, 111.20, 113.27 (C-5, C-8, C-3', and/or C-6'), 127.70, 127.79 (Ph$\underline{C}_{arom}$-H), 128.57, 128.91, 129.05, 130.83 (C-1', C-2', C-4a, C-8a, and/or Ph$\underline{C}_{arom}$-C), 147.42, 147.57, 147.70, 148.34 (C-6, C-7, C-5' and/or C-4'); MS(EI) m/z (%): 449 ($M^+$, 5), 266 (26), 421(18), 240 (62), 239 (35), 225 (10), 210 (21), 209 (100), 208 (17), 194 (14), 192 (28), 178 (14), 165 (23), 152 (10), 150 (11), 77 (8); Anal. Calcd for $C_{27}H_{31}NO_5$ (449.55): C 72.14, H 6.95, N 3.12; Found: C 71.84, H 7.02, N 3.01.

*General Procedure. Synthesis of the Schiff Bases* **5a** *and* **5b**

A solution of the amine **3a** or **3b** (1 mmol) and benzaldehyde (0.2 mL, 2.2 mmol) in anhydrous toluene (15 mL) was refluxed for 5 hours using a Dean-Stark apparatus. The solvent was evaporated under reduced pressure and the residue was chromatographed (silicagel, 30% hexane/ethyl acetate) to afford the following products:

*N-benzylidene-1,2-bis(3,4-dimethoxyphenyl)ethylamine* **5a**. (86%, 345 mg)

Mp: 103-105°C (Lit.[13a] 102-104°C)

*N-benzylidene-1-[2-(2-ᵗbutyldiphenylsilyloxyethyl)-4,5-dimethoxyphenyl]-2-(3,4-dimethoxyphenyl)-ethylamine* **5b** (75 %, 516 mg). Mp: oil; IR $\nu_{max}$ ($CHCl_3$): 1650 $cm^{-1}$; $^1H$ NMR (δ, ppm): 0.96 [s, 9H, $C(C\underline{H}_3)_3$], 2.68-2.90 (m. 2H, Ar-$C\underline{H}_2$-$CH_2$-OPG), 2.92-2.97 (m, 2H, Ar-$C\underline{H}_2$-CH-N), 3.47 (s, 3H, $OCH_3$), 3.65-3.73 (m, 2H, Ar-$CH_2$-$C\underline{H}_2$-OPG)*, 3.70 (s, 3H, $OCH_3$)*, 3.74 (s, 3H, $OCH_3$), 3.84 (s, 3H, $OCH_3$), 4.38 (dd, J = 7.9, J = 4.9, 1H, Ar-$CH_2$-$C\underline{H}$-N), 6.39 (d, J = 1.8, 1H, H-2'), 6.49 (s, 1H, H-3)*, 6.51 (dd, J = 8.1, J = 1.8, 1H, H-6')*, 6.62 (d, J = 8.1, H-5'), 7.17-7.30 (m, 10H, Ph, N=C$\underline{H}$Ph and H-6), 7.51-7.57 (m, 7H, Ph) (*: overlapped signals); $^{13}C$ NMR (δ, ppm): 19.10 [$\underline{C}(CH_3)_3$], 26.80 [$C(\underline{C}H_3)_3$], 35.59 (Ar-$\underline{C}H_2$-$CH_2$-OPG), 45.29 (Ar-$\underline{C}H_2$-CH-N), 55.39, 55.74, 55.80, 55.94 (4 x $OCH_3$), 65.06 (Ar-$CH_2$-$\underline{C}H_2$-OPG), 72.44 (Ar-$CH_2$-$\underline{C}$H-N), 110.84, 113.32, 113.36, 121.51 (C-3, C-6, C-2', C-5', and/or C-6'), 127.19, 127.63, 128.06, 129.59, 131.59, 133.70 (Ph$\underline{C}_{arom}$-H), 128.37, 130.43, 133.55, 135.28, 136.27 (C-2, C-1, C-1', and/or Ph$\underline{C}_{arom}$), 147.27, 147.58, 148.11 (C-4, C-5, C-3', and/or C-4'), 159.97 (N=$\underline{C}$HPh); Anal. Calcd for $C_{43}H_{51}NO_5Si$ (689.35): C 74.85, H 7.45, N 2.03; Found: C 75.32, H 7.12, N 1.99.

*General procedure. Synthesis of the tetrahydroisoquinolines* **6a-6d**

A suspension of the amine **3a**, **3c** or **3d** (1 mmol) and paraformaldehyde (240 mg, 8.3 mmol) in anhydrous methanol (10 mL) was refluxed for 1 hour. The reaction mixture was cooled down to room temperature and the excess of paraformaldehyde filtered off. The filtrate was evaporated to afford the corresponding methoxymethylamine as a yellowish oil. Without further purification, the so-obtained amine was dissolved in anhydrous $CH_2Cl_2$ (10 mL) under argon atmosphere and $TiCl_4$ (0.2 mL, 2.8 mmol) was added dropwise at -78°C. The reaction mixture was allowed to warm up to room temperature over 1 hour (for **3a** and **3c**) or 24 hours (for **3d**), and was quenched by addition of saturated $K_2CO_3$ (4 mL). The mixture was stirred for 20 min, decanted and the aqueous layer extracted with $CH_2Cl_2$ (3 x 20 mL). The organic phase was dried over $Na_2SO_4$, filtered and the solvent evaporated.The residue was chromatographed (see below) to afford the following products:

*3-[2-(2-ᵗbutyldiphenylsilyloxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxytetrahydroisoquinoline* **6a** (85%, 520 mg). Column chromatography: silicagel, 1% $CH_2Cl_2$/MeOH; Mp: oil; IR $\nu_{max}$ ($CHCl_3$): 3320, 1615 $cm^{-1}$; $^1H$ NMR (δ, ppm): 0.94 [s, 9H, $C(C\underline{H}_3)_3$], 2.52 (dd, J = 16.0, J = 3.6, 1H, H-4eq), 2.72-2.84 (m, 3H, Ar-$C\underline{H}_2$-$CH_2$-OPG and H-4ax), 3.70-3.72 (m, 2H, Ar-$CH_2$-$C\underline{H}_2$-OPG)*, 3.72 (s, 3H, $OCH_3$)*, 3.77 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 3.86-3.92 (m, 3H, 2 x H-1 and H-3), 6.42 (s, 1H, H-6'), 6.48 (s, 1H, H-3'), 6.64 (s, 1H, H-5), 6.99 (s, 1H, H-8), 7.17-7.27 (m, 7H, Ph), 7.45-7.55 (m, 3H, Ph) (*: overlapped signals); $^{13}C$ NMR (δ, ppm): 18.99 [$\underline{C}(CH_3)_3$], 26.74 [$C(\underline{C}H_3)_3$], 35.47 (Ar-$\underline{C}H_2$-$CH_2$-OPG), 36.64 (C-4), 48.56 (C-1), 53.87 (C-3), 55.61, 55.76, 55.87 (4 x $OCH_3$), 65.15 (Ar-$CH_2$-$\underline{C}H_2$-OPG), 108.96, 109.10 (C-5 and/or C-3'), 111.50 (C-8), 113.26 (C-6'), 126.50 (C-8a), 127.47, 129.47 (Ph$\underline{C}_{arom}$-H), 128.09 (C-2'), 133.36, 133.40 (C-1', C-4a, and /or Ph$\underline{C}_{arom}$-C), 135.37 (Ph$\underline{C}_{arom}$-H), 147.30, 147.45, 147.53, 147.74 (C-6, C-7, C-5', and/or C-4'); MS(EI) m/z (%): 611 ($M^+$, <1), 476 (4), 338 (4), 206 (10), 199 (25), 198 (14), 197 (21), 192 (14), 190 (21), 183 (14), 181 (13), 178 (12), 177 (11), 165 (40), 164 (88), 154 (33), 149 (20), 134 (100), 121 (33), 105 (16), 77 (27), 57 (27); Anal. Calcd for $C_{37}H_{45}NO_5Si$ (611.86): C 72.63, H 7.42, N 2.29; Found: C 72.71, H 7.36, N 2.20.

*3-(2,3-dimethoxyphenyl)-6,7-dimethoxytetrahydroisoquinoline* **6c**, (70%, 230 mg); column chromatography: silicagel, 1% $CH_2Cl_2$/MeOH; mp: oil; IR $\nu_{max}$ ($CHCl_3$): 3400, 1605 $cm^{-1}$; $^1H$ NMR (δ, ppm): 2.85 (d, J = 7.2, 2H, 2 x H-4), 3.76 (s, 3H, $OCH_3$), 3.77 (s, 3H, $OCH_3$), 3.80 (s, 6H, 2 x $OCH_3$), 4.01 (d, J = 15.5, 1H, H-1), 4.13 (d, J = 15.5, 1H, H-1), 4.51 (t, J = 7.2, 1H, H-3), 6.51 (broad s, 2H, $H_{arom}$), 6.77-6.81 (m, 2H, $H_{arom}$), 6.99-7.00 (m, 1H, $H_{arom}$); $^{13}C$ NMR (δ, ppm): 35.37 (C-4), 48.11 (C-1), 52.51, 55.69 , 55.84, 55.89 (4 x $OCH_3$), 61.00 (C-3), 108.99, 111.48, 111.60, 118.61, 124.33 (C-5, C-7, C-4', C-5', and/or C-6'), 125.75, 126.45, 136.27 (C-4a, C-8a, and/or C-1'), 146.39, 147.42, 147.57, 152.49

(C-6, C-7, C-2', and/or C-3'); Anal. Calcd for $C_{19}H_{23}NO_4$ (329.40): C 69.27, H 7.04, N 4.25; Found: C 69.59, H 7.12, N 4.32

*N-benzyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxytetrahydroisoquinoline* **6d** (69%, 284 mg); column chromatography: silicagel, 40% hexane/ethyl acetate; mp : oil; $^1$H NMR (δ, ppm): 2.88-3.10 (m, 2H, 2 x H-4), 3.39 (d, 1H, J = 15.4, H-1), 3.59-3.78 (m, 4H, H-1, PhC$\underline{H}_2$N and/or H-3), 3.72 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 6.39 (s, 1H, H-8), 6.54 (s, 1H, H-5), 6.77 (d, 1H, J = 8.2, H-5'), 6.87 (dd, 1H, J = 8.2, J = 1.85, H-6'), 6.99 (d, 1H, J = 1.85, H-2'), 7.14-7.46 (m, 5H, Ph), $^{13}$C NMR (δ, ppm): 37.03 (C-4), 54.23 (Ph$\underline{C}H_2$N), 55.84, 55.87, 55.91 (4 x $OCH_3$), 58.66 (C-1), 64.03 (C-3), 109.18, 110.52, 110.94, 120.05, 126.88, 128.23, 128.65 (C-2', C-5', C-6', C-5, C-8 and/or Ph$\underline{C}_{arom}$-H), 126.13, 126.30, 135.56, 139.50 (C-4a, C-8a, C-1', Ph$\underline{C}_{arom}$-C), 147.34, 147.51, 148.27, 149.23 (C-6, C-7, C-3', and/or C-4'); Anal. Calcd for $C_{26}H_{29}NO_4$ (419.52): C 74.43, H 6.97, N 3.34; Found: C 74.28, H 7.10, N 3.40.

*Synthesis of 3-[2-(2-$^t$butyldiphenylsilyloxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxy-N-methyltetrahydroisoquinoline* **6e**

A suspension of the tetrahydroisoquinoline **6a** (317 mg, 0.52 mmol) and paraformaldehyde (125 mg, 4.16 mmol) in anhydrous methanol (10 mL) was refluxed for 1 hour. The reaction mixture was cooled down to room temperatute, $NaCNBH_3$ (100 mg, 1.6 mmol) was added and the resulting suspension stirred 1 hour. Water was added and the mixture extracted with $CH_2Cl_2$ (3 x 20 mL) The organic phase was dried over $Na_2SO_4$, filtered, and the solvent evaporated. The residue was chromatographed (silicagel, ethyl acetate), to afford the tetrahydroisoquinoline **6e** (96%, 310 mg); mp: oil; IR $\nu_{max}$($CHCl_3$): 1610 cm$^{-1}$; $^1$H NMR (δ, ppm): 1.03 [(s, 9H, C(C$\underline{H}_3$)$_3$], 2.03 (s, 3H, $NCH_3$), 2.52 (dd, J = 16.6, J = 3.8, 1H, H-4eq), 2.83-2.98 (m, 3H, Ar-C$\underline{H}_2$-$CH_2$-OPG and H-4ax), 3.36-3.42 (m, 2H, Ar-$CH_2$-C$\underline{H}_2$-OPG), 3.75-3.96 ( m, 3H, H-3 and 2 x H-1)*, 3.80 (s, 3H, $OCH_3$)*, 3.83 (s, 3H, $OCH_3$)*, 3.84 (s, 3H, $OCH_3$)*, 3.87 (s, 3H, $OCH_3$)*, 6.44 (s, 1H, H-6'), 6.57 (s, 1H, H-3'), 6.58 (s, 1H, H-5), 6.99 (s, 1H, H-8), 7.23-7.37 (m, 6H, Ph), 7.52-7.62 (m, 4H, Ph) (*: overlapped signals ); $^{13}$C NMR (δ, ppm): 19.07 [$\underline{C}$(C$H_3$)$_3$], 26.82 [C(C$\underline{H}_3$)$_3$], 35.79 (Ar-$\underline{C}H_2$-$CH_2$-OPG), 38.32 (C-4), 42.97 (N-$CH_3$), 55.64, 55.81, 55.97 (4 x $OCH_3$), 58.92 (C-1), 60.99 (C-3), 65.02 (Ar-$CH_2$-$\underline{C}H_2$-OPG), 108.87, 109.78, 110.68, 113.18 (C-5, C-8, C-3', and/or C-6'), 126.30, 128.28, 133.51, 133.59, 135.48 (C-4a, C-8a, C-1',C-2', and/or Ph$\underline{C}_{arom}$-C), 127.55, 129.53, 135.43 (Ph$\underline{C}_{arom}$-H), 147.34, 147.58, 148.15 (C-6. C-7, C-5', and/or C-4'); MS(EI) m/z (%): 626 ($M^+$+1, 21), 625 ($M^+$, 42), 624 (15), 610 (23), 594 (8), 568 (8), 537 (26), 460 (14), 369 (10), 338 (35), 206 (55), 204 (29), 192 (23), 190 (14), 177 (10), 165 (35), 164 (100), 151 (8); Anal. Calcd for $C_{38}H_{47}NO_5Si$ (625.88): C 72.92, H 7.57, N 2.24; Found: C 72.80, H 7.43, N 2.27.

## ACKNOWLEDGMENTS

Financial support from the Basque Government (Project PI9370) and the University of the Basque Country (Project 170.310-EA107/92) is gratefully acknowledged.

## REFERENCES AND NOTES

1. For a review on isoquinoline reactivity see: Dyke, S. F.; Kinsman, R. G.: Properties and Reactions of Isoquinolines and their Hydrogenated Derivatives. In I*soquinolines, Part 1. Heterocyclic Compounds, vol. 38*, Grethe, G., Ed.; John Wiley & Sons: New York, 1981; pp 29.
2. Sainsbury, M.; Brown, D. W.; Dyke, S. F.; Clipperton, R. D. J.; Tonkin, W. R. *Tetrahedron* **1970**, *26*, 2239; Dyke, S. F; Bather, P. A.; Garry, A. B.; Wiggins, D. W. *Tetrahedron* **1973**, *29*, 3881; Gensler,

W. J.; Shanasundar, K. T. *J. Org. Chem.*. **1975**, *40*, 123; Minter, D.; Re, M. A. *J. Org. Chem.* **1988**, *53*, 2653.

3. Onda, M.; Yonezagua, K; Abe, K. *Chem. Pharm. Bull.* **1969**, *17*, 404.
4. Kametani, T.; Ogasawara, K. *Chem. Pharm. Bull.* **1973**, *21*, 893; Kametani, T.; Irata, S.; Ogasawara, K. *J. Chem. Soc. Perkin Trans. I*, **1973**, 1466; For a review on isopavine synthesis see: Gözler, B.: Pavine and Isopavine Alkaloids. In *The Alkaloids, Chemistry and Pharmacology*, vol. 31, Brossi, A., Ed.; Academic Press: Orlando, 1987; pp 317.
5. Dyke, S. F.; Brown, D. W.; Sainsbury, M.; Hardy, G. *Tetrahedron* **1971**, *27*, 3495; Dyke, S. F.; Tiley, E. P. *Tetrahedron* **1975**, *31*, 561; Badía, D.; Domínguez, E.; Lete, E.; Villa, M. J.; Castedo, L.; Domínguez, D. *Heterocycles* **1988**, *27*, 867 and references cited therein; Vicente, T.; Martínez de Marigorta, E.; Domínguez, E.; Carrillo, L.; Badía, D. *Heterocycles* **1993**, *36*, 2067.
6. For reviews on benzo[c]phenanthridine synthesis see: Simánek, V.: Benzo[c]phenanthridine Alkaloids. In *The Alkaloids. Chemistry and Pharmacology*, vol.26, Brossi, A., Ed.; Academic Press: Orlando, 1985; pp 185; Zenk, M. H. *Pure Appl. Chem.*, **1994**, 66, 2023.
7. Onda, M.; Yamaguchi, H.; Hariyaga, Y. *Chem. Pharm. Bull.* **1980**, *28*, 866; Onda, M.; Hatano, A.; Yamaguchi, H.; Saito, N. *Chem. Pharm. Bull.* **1984**, *32*, 2503.
8. Hanaoka, M.; Motonishi, T.; Mukai, C. *J. Chem. Soc., Chem.Commun.* **1984**, 718; Hanaoka, M.; Yamagishi, H.; Marutani, M.; Mukai, C. *Tetrahedron Lett.* **1984**, *25*, 5169; Hanaoka, M.; Kobayashi, N.; Mukai, C. *Heterocycles* **1987**, *26*, 1499.
9. Carty, A. J.; Elliott, I. W.; Lenior, G. N. *Can. J. Chem.* **1984**, *62*, 2435.
10. Beugelmans, R.; Bois-Choussy, M. *Tetrahedron* **1992**, *48*, 8285.
11. Clark, R. D.; Jahangir *J. Org. Chem.* **1989**, *54*, 174.
12. Couture, A.; Cornet, H.; Grandclaudon, P. *Tetrahedron Lett.* **1993**, *34*, 8097.
13. a) Domínguez, E.; Lete, E. *An. Quím.* **1984**, *80C*, 13; b) Domínguez, E.; Lete, E.; Badía, M. D.; Villa, M. J.; Castedo, L.; Domínguez, D. *Tetrahedron* **1987**, *43*, 1943; c) Badía, M. D.; Domínguez, E.; Tellitu, I. *Tetrahedron* **1992**, *48*, 4419; d) Sotomayor, N.; Vicente, T.; Domínguez, E.; Lete, E.; Villa, M. J. *Tetrahedron* **1994**, *50*, 2207.
14. Domínguez, E; Lete, E. *Heterocycles* **1983**, *20*, 1247; Badía, M. D.; Carrillo, L.; Domínguez, E.; Cameno, A. G.; Martínez de Marigorta, E.; Vicente, T. *J. Heterocycl. Chem.* **1990**, *27*, 1287; Tellitu, I.; Badía, M. D.; Domínguez, E.; García, F. J.; *Tetrahedron: Assymetry* **1994**, *5*, 1567.
15. Sotomayor, N.; Domínguez, E.; Lete, E. *Tetrahedron Lett.* **1994**, *35*, 2973; see also ref. 13d.
16. Sotomayor, N.; Domínguez, E.; Lete, E. *Synlett* **1993**, 431.
17. Bhatacharjya, A.; Chattopadhyay, P.; Bahumik, M.; Pakrashi, S. C.; *J. Chem. Res. (S)* **1989**, 228.
18. When the *N*-[1,2-bis(3,4-dimethoxyphenyl)ethyl]formamide, used as a model compound, was refluxed with $PPh_3$ (2.5 eq.) in $CCl_4$ for 5 h, only *trans*-1,2-bis(3,4-dimethoxyphenyl)ethene was isolated in a 50% yield. For spectroscopic data, see: Battersby, A. R.; Binks, R. *J. Chem. Soc.* **1958**, 4333.
19. Nagubandi, S.; Fodor, G. *Heterocycles* **1981**, *15*, 165.
20. Greene, T. W. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1981; pp 47.
21. No deprotection of *tert*-butyldiphenylsilyloxyethylbenzene was observed when treated under the same reaction conditions.
22. Magnus, P.; Thurston, L. S. *J. Org. Chem.* **1991**, *56*, 1166.

23. Kodato, S.; Nakagawa, M.; Hongu, M.; Kawate, T.; Hino, T. *Tetrahedron* **1988**, *44*, 359; Nakagawa, M.; Fukushima, H.; Kawate, T.; Hongu, M.; Kodato, S.; Une, T.; Taniguchi, M.; Ino, T. *Tetrahedron Lett.* **1986**, *27*, 3235; Hermkens, P. H. H.; Van Maarsveen, J. H.; Cobben, P. L. H. M.; Ottenheijm H. C. J.; Kruse, C. G.; Scheeren, H. V. *Tetrahedron* **1990**, *46*, 833.
24. Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, S.; Yamanaka, E.; Hutchins, L.; Di Piero, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535; Jawdosiuk, M.; Cook, J. M. *J. Org. Chem.* **1984**, *49*, 2699
25. Yamato, E. *Chem. Pharm. Bull.* **1970**, *18*, 2038.
26. Walker, G. N.; Kempton, R. J. *J. Org. Chem.* **1971**, *30*, 1413; Hubert, J. C.; Speckamp, W. N.; Huisman, H. O. *Tetrahedron Lett.* **1972**, 4493; Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367, and references cited therein; Moller, K. D.; Wong, P. W.; Tarazi, S.; Marzabadi, M. R.; Wong, P. L. *J. Org. Chem.* **1991**, *56*, 1058.
27. Bather, P. A.; Lindsay Smith, J. R.; Norman, R. O. C. *J. Chem. Soc. (C)* **1971**, 3060.
28. Mollov, N.; Venkov, A. P. *Synthesis* **1978**, 62; Venkov, A. P.; Lukanov, L. K. *Synthesis* **1989**, 59.
29. Acetyl chloride or benzoyl chloride (1 mmol) was added dropwise to a stirred solution of the imine (1 mmol) in $CH_2Cl_2$ (3 mL) at room temperature. After 15 min, the Lewis acid was added ($TiCl_4$, $AlCl_3$ or $SnCl_4$) (1 mmol) and the resulting mixture stirred for 24 h. After standard work up, the starting amines were recovered.
30. Kubo, A.; Saito, N.; Kawakami, N.; Matsuyama, Y. *Synthesis* **1987**, 824.
31. Cooper, M. S.; Earle, M. J.; Fairhurst, R. A.; Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Synlett.* **1990**, 617.
32. Cheung, G. K.; Earle, M. J.; Fairhurst, R. A.; Heaney, H.; Shuhaibar, K. F.; Eyley, S. C.; Ince, F. *Synlett* **1991**, 721.
33. Kapnang, H. *Tetrahedron Lett.* **1977**, 17, 3469.
34. Hall, D. L.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703.
35. Kinns, M.; Sanders, J. K. M. *J. Magn. Res.* **1984**, *56*, 518.
36. Stahl, E. *Thin-Layer Chromatography;* 2nd ed.; Springer-Verlag: Berlin, 1969; pp 873.
37. Still, W. C.; Kann, H.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
38. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed.; Pergamon Press: Berlin, 1988.
39. Preparation of **3a**, see ref. 16; preparation of **3b**, see ref. 13a ; **3c** was prepared by Leuckart reductive amination of the 2,3-dimethoxyphenyl 3,4-dimethoxybenzyl ketone: Badía, M. D.; Domínguez, E.; Galarza, J.; Lete, E.; Martínez de Marigorta, E.; Villa, M. J. *Bull. Soc. Chim. Belg.* **1989**, *98*, 77; preparation of **3d**, see ref. 13d.

(*Received in UK* 27 *June* 1995; *revised* 8 *September* 1995; *accepted* 15 *September* 1995)

Pergamon

*Tetrahedron* Vol. 51, No. 44, pp. 12169-12178, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4020/95 $9.50+0.00

0040-4020(95)00771-7

# New Cyclohexyl-Based Chiral Auxiliaries: Enantioselective Synthesis of α-Hydroxy Acids†

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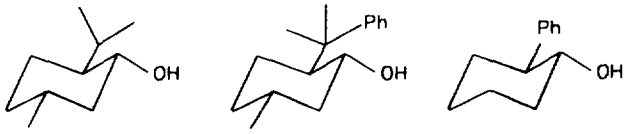
**ABSTRACT:** (1R,2R)-2-(4-*tert*-Butylphenoxy)cyclohexan-1-ol (**5**) and (1R,2R)-2-(4-phenylphenoxy)cyclohexan-1-ol (**6**) have been used for the first time as chiral auxiliaries. Addition of alkylzinc chlorides to the corresponding glyoxylates **5a**, **6a**, after hydrolysis, provided (R)-α-hydroxy acids in high optical purities.

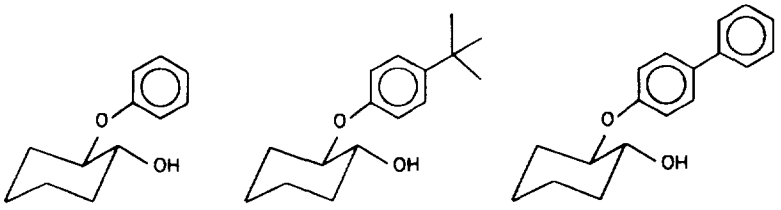
The exponential growth of asymmetric synthesis in the last two decades resulted mainly from the rational design of a large number of chiral auxiliaries and their applications in a large number of stereoselective processes.[1-5] Practical application of asymmetric synthesis requires that the chiral auxiliaries not only be recoverable in reusable form but they can also be readily obtained in the first place. Among the various chiral auxiliaries, the molecules based on cyclohexane frame[5] such as menthol[6] (**1**), Corey's 8-phenylmenthol[7] (**2**) and Whitesell's *trans*-2-phenylcyclohexanol[8] (**3**) occupy a special place because of high potential they offer in a variety of enantioselective processes. With a




**1** **2** **3**

view that structurally similar cyclohexane frame based molecules, *trans*-2-aryloxycyclohexan-1-ols **4**-**6**, would be of interest as chiral auxiliaries, we have developed a convenient simple methodology for obtaining these chiral *trans*-2-aryloxycyclohexan-1-ols in high enantiomeric purities ***via*** enantioselective hydrolysis of the corresponding racemic acetates using pig liver acetone powder (PLAP) as a biocatalyst.[9,10]

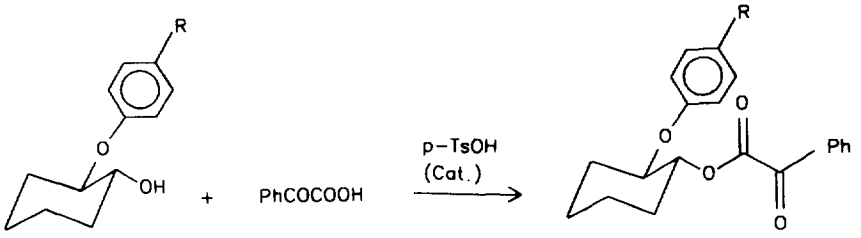
† Dedicated to Professor Gurbakhsh Singh on the occasion of his 75th birthday



**4** **5** **6**

Chiral α-hydroxy acids and their derivatives possessing tertiary hydroxy stereogenic centre, are important synthons for the synthesis of biologically active molecules.[11-13] Recently menthol[6] (**1**) and 8-phenylmenthol[12] (**2**) have been used as chiral auxiliaries for the synthesis of α-hydroxy acids containing tertiary hydroxy stereogenic centre. We have recently examined the applicability of (1R,2S)-2-phenylcyclohexanol[14] (**3**) and (1R,2R)-2-phenoxycyclohexan-1-ol[15] (**4**) as chiral auxiliaries for obtaining α-hydroxy acids in high enantiomeric purities. With a view to examine the effect of sterically more demanding group on the phenyl ring of 2-phenoxycyclohexanol, we have selected the alcohols **5** and **6** as chiral auxiliaries.

We have first studied the applications of (1R,2R)-2-(4-*tert*-butylphenoxy)cyclohexan-1-ol (**5**) as chiral auxiliary for the synthesis of chiral α-hydroxy acids. The required [(1R,2R)-2-(4-*tert*-butylphenoxy)-cyclohex-1-yl] phenylglyoxylate (**5a**) was prepared by treating the alcohol **5** with benzoylformic acid in the presence of *p*-TsOH (eq 1).




**R = $^{t}$Bu, 5**
**R = Ph, 6**

**R = $^{t}$Bu, 5a**
**R = Ph, 6a**

**(1)**

Reaction of keto ester **5a** with a variety of alkylzinc chlorides afforded chiral α-hydroxy esters **7a-11a**. Subsequent saponification provided (R)-2-hydroxy-2-phenylalkanoic acids **7-11** in 86-97% enantiomeric purities (Scheme 1, Table 1).

Similarly, alcohol **6** was converted into the glyoxylate **6a** (eq 1). Subsequent reaction with alkylzinc chlorides provided, after hydrolysis, the desired (R)-α-hydroxy acids **7-11** in 83-89% optical purities (Scheme