Pergamon

Tetrahedron Vol. 51, No. 46, pp. 12721-12730, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00827-6

Oxidation Reactions of 2'-Functionalized 3-Aryltetrahydro- and 3,4-Dihydroisoquinolines

Nuria Sotomayor, Esther Domínguez, and Esther Lete*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad del País Vasco, Apdo. 644-48080 Bilbao, Spain.

Abstract: Several 2'-functionalized 3-arylisoquinolines in different oxidation stages have been prepared. Fremy's salt or I_2/NaAcO oxidation of 2'-functionalized 3-aryltetrahydroisoquinolines always stops at the 3,4-dihydroisquinoline stage; however, better yields and shorter reaction times are obtained with iodine. Air/KOH/DMSO oxidation of 3,4-dihydroisoquinolines furnished the aromatic derivatives with concomitant cleavage of the TBDPS group. While 3-arylisoquinolin-1-(2H)-ones are obtained by air oxidation of 3,4-dihydroisquinolinium salts, the use of DDQ in dioxane resulted in a selective dehydrogenation to the corresponding *N*-substituted isoquinolinium salts.

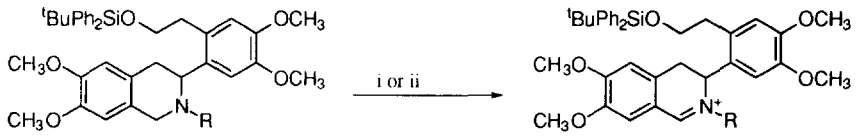
Previous reports from our laboratories have established that Lewis acid-promoted reactions of 1,2-diarylethylamines with paraformaldehyde represent an efficient and regioselective route to 3-aryltetrahydroisoquinolines.[1] Because the fully aromatic or isoquinolinone derivatives can be used as precursors in the synthesis of a number of biologically active natural products,[2] we sought to develop methods to provide this type of derivatives. Synthesis of benzo[c]phenanthridines can be achieved by intramolecular alkylation/acylation reactions at the C-4 position of *N*-substituted-3-aryl-1,2-dihydroisoquinolines or 1-isoquinolinone (enamines or enamides), bearing an appropiately functionalized ethyl side chain at the C-2' position.[3] In a similar fashion, intramolecular *N*-alkylation of the 3,4-dihydro derivatives would furnish 7,8-dehydroberbines.[4] Herein we report our studies on the oxidation of C-2'-functionalized 3-aryltetrahydroisoquinolines, which have resulted in selective methods to prepare 3,4-dihydroisoquinolines, isoquinolines and/or isoquinolinones, with the ability to control the oxidation stage.

1,2,3,4-Tetrahydroisoquinolines can be oxidized to 3,4-dihydroisoquinolines or to the fully aromatic derivatives by chemical or catalytic methods. Catalytic dehydrogenation with Pd, Pt or Raney-Ni has been widely used, though it implies drastic reaction conditions, mostly when applied to *N*-alkyltetrahydroisoquinolines. Some of the more commonly used oxidating agents for tetrahydroisoquinoline aromatization are $KMnO_4$, HNO_3, I_2, $Hg(AcO)_2$, S, Se or $SOCl_2$. However, certain 3,4-dihydroisoquinolines are resistant to further oxidation with with I_2 or $Hg(AcO)_2$, whereas only degradation occurs with $KMnO_4$.[5] Fremy's salt[6] (potassium nitrosodisulfonate) offers a mild alternative for aromatization of 1-unsubstituted tetrahydroisoquinolines[7], though 1-substituted derivatives are oxidized to 3,4-dihydroisoquinolines, giving low yields of the aromatic compounds.[8] Other oxidating agents are NBS, sodium hypochlorite,[9] phenylselenic anhydride[10], iodosylbenzene[11] or MnO_2.[12] Some of these procedures have been applied to 3-

aryltetrahydroisoquinolines. I_2 or $Hg(AcO)_2$ oxidation of 3-aryltetrahydroisoquinolines affords the corresponding 3,4-dihydroderivatives, whereas Pd/C or DDQ oxidation yield the aromatic compounds. Both oxidation stages can be obtained by Fremy's salt oxidation, though reactions are generally slow (days).[13]

With these precedents in mind, we thought that these oxidation agents offered the possiblity to control the selectivity of oxidation reactions of C-2'-functionalized 3-aryltetrahydroisoquinolines. It was expected that Fremy's salt oxidation of the 3-aryltetrahydroisoquinolines would provide the aromatic derivatives in good yields. Thus, potassium nitrosodisulfonate oxidation of tetrahydroisoquinoline **1**, prepared from $TiCl_4$-promoted reaction of the corresponding 1,2-diarylethylamine with paraformaldehyde,[1] was explored and found to give the 3,4-dihydroisoquinoline **3** (as a free base) in a good yield (82%). The reaction did not appear to go to completion even after 6 days (41% conversion) (Scheme 1, Table 1). No aromatization was observed when **3** was further treated under the same reaction conditions for 4 days.

It is known[7, 8] that non-phenolic tetrahydroisoquinolines suffer stepwise oxidation by Fremy's salt. This observation is consistent with the formation of an aminium radical, followed by hydrogen abstraction from an α or δ position.[14] The failure of the 2'-functionalized 3,4-dihydroisoquinolines to be oxidized could not be easily explained. However, examination of molecular models led us to speculate that steric effects of the bulky TBDPS group prevented the approach of the oxidant from face of the molecule where the H-3 proton is oriented. Besides, the deviation of H-3 from the axial position (see spectroscopic discussion below) would also unfavour this hydrogen abstraction.



1 R = H
2 R = CH_3

i: $(KSO_3)_2NO$ / 4% Na_2CO_3, rt
ii: I_2 / NaAcO / EtOH, reflux

3 R = H
4 R = CH_3

Scheme 1

Table 1. Synthetic Data of the 3,4-Dihydroisoquinolines Prepared

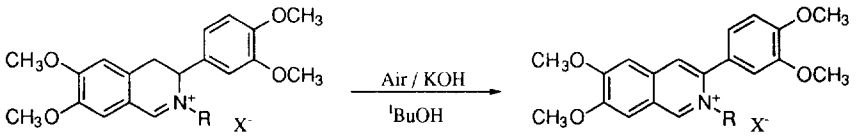
Substrate	Method	Product	Time	Yield (%)
1	$(KSO_3)_2NO$	**3**	6 days	82[a]
1	I_2 / NaOAc	**3**	1 h	97
2	I_2 / NaOAc	**4**	1h	96

[a] Based on a 41% conversion

However, reactions of **1** and its *N*-methylated derivative **2** with 2 equivalents of I_2 / NaAcO in refluxing ethanol gave excellent yields of the 3,4-dihydroderivative **3** (as a free base) and the iodomethylate **4** ($X^- = I^-$), respectively. The use of iodine as oxidizing agent resulted in a great rate enhancement and complete reaction was attained in only one hour (Scheme 1, Table 1). As described for other 3-aryl-tetrahydroisoquinolines[13], no aromatization was observed. These results could be explained assuming that a charge transfer complex is formed by interaction of the axial lone pair of the nitrogen atom in the preferred conformation[15] and the iodine molecule. This complex would facilitate the *anti* H-1 elimination, forming the 3,4-dihydroderivative that could not tautomerize, thus preventing further oxidation.[16]

Having obtained the 3,4-dihydro derivatives **3** and **4**, we looked for suitable methods to introduce the 3,4-double bond and to prepare 1-oxygenated derivatives. It has been reported[17] that oxidation of 3,4-dihydroisoquinolines with oxygen in the presence of KOH and using *tert*-butanol as solvent gives the corresponding 1-isoquinolinones, probably by oxidation of the *pseudo*base formed in basic media. However, when this procedure was applied to 3-aryl-3,4-dihydroisoquinoline derivatives, only dehydrogenation to the aromatic compounds was observed.[18] These results prompted us to investigate this oxidation method on our substrates **3** and **4**, in order to study the competition between aromatization and isoquinolinone formation.

To optimize the reaction conditions, we first tested the procedure using the unfunctionalized 3,4-dihydroisquinoline **5** (as a free base) and the iodomethylate **6** as model compounds (Scheme 2). The choice of the solvent turned out to be an important factor in these oxidation reactions. Treatment of **5** and **6** with 3 equivalents of KOH in ^{t}BuOH at 55°C, keeping a continuous bubbling of pre-dried air through the reaction mixture, led to the formation of the desired aromatic isoquinolines **7** and **8**, respectively. In both cases, long reaction times are required and the conversions are low, recovering most of the starting material (Table 2). Oxidation in ethanol, under otherwise identical reaction conditions, gave similar results, while in DMSO the reaction rate was increased and excellent yields were obtained. Thus, air oxidation of **5** with KOH in DMSO furnished **7** in a 90% yield in only 45 minutes. The results are summarized in Table 2.



5 R = H
6 R = CH_3

7 R = H
8 R = CH_3

Scheme 2

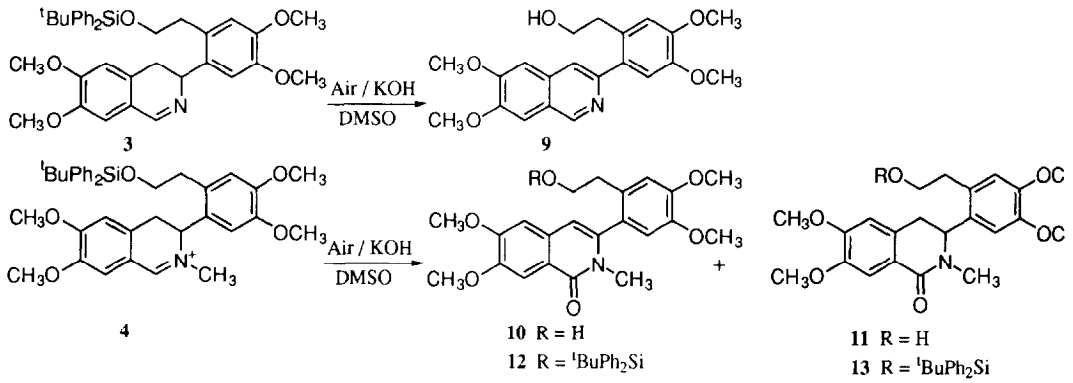
Table 2. Oxidation Reactions of the 3,4-Dihydroisoquinolines Prepared

Substrate	Procedure	T (°C)	Time (h)	Product	Conversion (%)	Yield (%)
5	KOH/DMSO	50-55	0.75	**7**	100	90
	KOH/^{t}BuOH	50-55	39	**7**	35	56
6	KOH/^{t}BuOH	50-55	20	**8**	62	88
	DDQ/toluene	110-111	5	-[a]	-	-
	DDQ/dioxane	100-102	3	**8**	85	68
3	KOH/DMSO	50-55	2	**9**	100	98
4	KOH/DMSO	50-55	2	**10+11**[b]	100	60
	DDQ/dioxane	100-102	6	**14**	66	87

[a] Starting material was recovered (94%).
[b] The **10** : **11** ratio was 1 : 6.5 (^{1}H NMR).

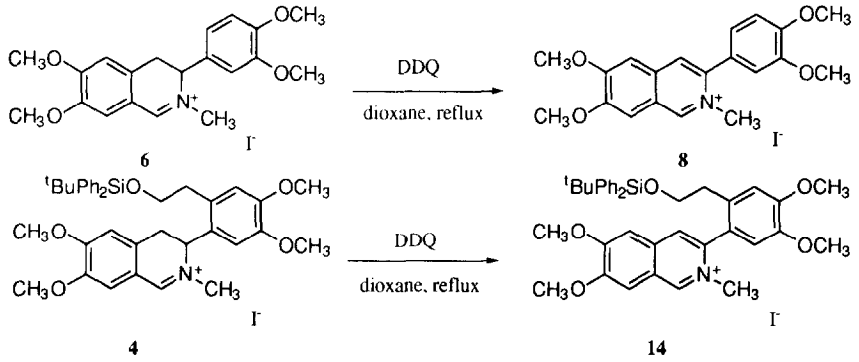
These improved reaction conditions were applied to the 2'-functionalized 3,4-dihydroisoquinolines **3** and **4** as a convenient route to prepare isoquinolines. The dihydroisoquinoline **3** was quantitatively oxidized with air/KOH/DMSO to the aromatic derivative **9**, where concomitant deprotection had ocurred. However, when the dihydroisquinolinium salt **4**, having a more electrophilic C-1, was used, a 1 : 6.5 mixture of the 1-isoquinolinone **10** and the 3,4-dihydro-1-isoquinolinone **11** was obtained in a 60% overall yield. During the

oxidation of **4**, the TBDPS group was also cleaved in the reaction media. Both isoquinolinones could not be separated by chromatographic means (column chromatography or HPLC), so their ratio was determined by ^{1}H NMR spectroscopy by integration of the aromatic protons. It is worth to mention that the iodomethylate **4** is spontaneously and quantitatively oxidized by air to a 1 : 2.5 mixture of the isoquinolinones **12** and **13**, even in the absence of solvent. These isoquinolinones could not be separated either, and their ratio and structures were also established from the ^{1}H NMR spectrum of the mixture.



Scheme 3

Since air oxidation of 3,4-dihydroisoquinolinones affords the corresponding isquinolinones and, on the other hand, aromatic 3-arylisoquinolines are known to be resistant to *N*-alkylation,[5] we needed to find an alternative route to prepare *N*-substituted fully aromatic derivatives. We decided to test the aromatization of 3,4-dihydroisoquinolinium salts with DDQ. In a preliminary study to optimize the reaction conditions, the 3,4-dihidroisoquinolinium salt **6** was chosen as model compound. When this was subjected to DDQ oxidation in refluxing toluene, again, no significant evolution of the starting material was observed (tlc, ^{1}H NMR) after 5 h. However, using 1,4-dioxane as solvent, the isoquinolinium salt **8** was obtained in a 68% yield.(Scheme 4, Table 2). When the iodomethylate **4** was used, the corresponding aromatic derivative **14** was obtained in a good yield (87%), though total conversion of the starting material could not be achieved (66%), even increasing the reaction time or using an excess of the reactant.



Scheme 4

The ^1H NMR spectroscopic data confirmed the structures proposed for the 3,4-dihydroisoquinolines, isoquinolines, and 1-isoquinolones, whose stereochemistry was deduced by measurements of the difference NOE[19] and selective ^1H-^1H decoupling experiments.

The analysis of the coupling constants values of the ABX system formed by H-3 and the diasterotopic H-4 protons in the ^1H NMR spectra of the 3,4-dihydroisoquinolines and 3,4-dihydroisoquinolin-1-[2H]-ones prepared (Table 3) is consistent with a half-chair conformation of the heterocyclic ring with the aryl C-3 group in a *pseudo*equatorial disposition, as in the parent tetrahydroisoquinolines.[15] However, due to the presence of an imine function (in **3** and **4**) or a carbonyl group (in **11** and **13**), the heterocyclic system is rather planar, resulting in a deviation of the 3-aryl group from the equatorial position. This is reflected in a larger value of the H-3 - $H\text{-}4_{eq}$ coupling constant and a smaller value of the H-3 - $H\text{-}4_{ax}$ coupling constant[20], compared with the values observed in tetrahydroisoquinoline derivatives ($J_{ax\text{-}ax}$ = 10.0 - 11.0 Hz; $J_{ax\text{-}eq}$ = 2.5 - 4.0 Hz)[15]. Besides, the dihydroisoquinoline **3** shows a long range allylic coupling between H-3 and H-1 (J = 2.8 Hz).

Table 3. ^1H NMR Chemical Shift and Coupling Constants of the ABX systems in **3**,**4**,**11** and **13**.

	^1H NMR, δ (ppm), mult.[a], J (Hz)			
Proton	**3**	**4**	**11**	**13**
H-3	4.55 ddd 13.5, 8.5, 2.8	5.03 distorted t	4.98 dd 7.0, 4.2	4.54 dd 6.7, 4.3
$H\text{-}4_{eq}$	2.57-2.62 m	3.14 dd 17.2, 7.6	2.78-2.87 m	2.69 dd 15.8, 4.3
$H\text{-}4_{ax}$	2.57-2.62 m	3.33 dd 17.2, 8.0	3.43 dd 16.0, 7.0	3.22 dd 15.8, 6.7

[a] Multiplicity: dd: doublet of doublets; ddd: double doublet of doublets; m: multiplet

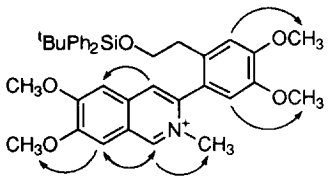


Figure 1. Selected NOEs observed for **14**

In addition, the data of the NOE experiments have allowed us to assign unequivocally the resonances of the aromatic and methoxyl protons of the 3-arylisoquinolines. As an example, the observed NOE for **14** are depicted in Figure 1. In fact, an enhancement upon irradiation was observed between the signals of the following protons: H-1 - H-8, H-4 - H-5, and H-1 - NCH_3, while the H-3' and H-6' signals only presented positive NOE with the methoxyl groups at C-4' and C-5', respectively.

In summary, it has been demonstrated that selective oxidation reactions of 2´-functionalized 3-aryltetrahydro- and 3,4-dihydroisoquinolines can be accomplished by choosing the appropriate oxidation agent. Thus, a variety of 3-arylisoquinoline derivatives in different oxidation stages are avalaible. The utility of these type of isoquinolines as building blocks for alkaloid synthesis (benzo[c]phenanthridines and protoberines) has already been demonstrated in our laboratories and others.

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 20-25ºC, running at 250 MHz for ^1H and 62.8 MHz for ^{13}C, in $CDCl_3$ solutions. ^1H NMR chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (δ_{TMS} = 0.00 ppm) as internal standard. Assignments were confirmed by homonuclear spin-spin decoupling experiments. ^1H-{^1H} NOE experiments were carried out in the difference mode.[19] 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.[21] Flash column chromatography[22] 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.[23] Tetrahydroisoquinolines **1**, **2**, **5** and **6** were prepared according to literature procedures.[24]

Fremy's salt oxidation: synthesis of 3-[2-(2-^{t}butyldiphenylsilyloxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxy-3,4-dihydroisoquinoline ***3***

Tetrahydroisoquinoline **1** (247 mg, 0.41 mmol) was added over a solution of freshly prepared[6] Fremy's salt (443 mg, 1.6 mmol) in 4% aqueous K_2CO_3 (15 mL). The resulting suspension was stirred at room temperature, always keeping an excess of the Fremy's salt, judging by the purple colour of the reaction mixture. After 6 days, the crude was extracted with CH_2Cl_2, the organic phase was washed with brine, dried over anhydrous Na_2SO_4 and the solvent evaporated. The residue was purified by column chromatography (silicagel, 0,5-2% CH_2Cl_2/MeOH), recovering 145 mg (59%) of unreacted tetrahydroisquinoline **1** and the 3-[2-(2-^{t}butyldiphenylsilyloxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxy-3,4-dihydroisoquinoline **3**. (41% conversion, 82%, 84 mg). Mp (hexane/ethyl acetate): 145-147ºC; IR ν_{max} (KBr): 1635, 3200 cm^{-1}; ^1H NMR (δ, ppm): 0.95 [s, 9H, C(C$\underline{H}_3$)$_3$], 2.57-2.62 (m, 2H, 2 x H-4), 2.79 (t, J = 7.2, 2H, Ar-C$\underline{H}_2$-CH$_2$-OPG), 3.72 (s, 3H, OCH$_3$)*, 3.72-3.77 (m, 2H, Ar-CH$_2$-C$\underline{H}_2$-OPG)*, 3.77 (s, 3H, OCH$_3$), 3.83 (s, 3H, OCH$_3$), 3.87 (s, 3H, OCH$_3$), 4.55 (ddd, J = 13.5, J = 8.5, J = 2.8, 1H, H-3), 6.48 (s, 1H, H-6'), 6.52 (s, 1H, H-3'), 6.82 (s, 1H, H-5), 6.89 (s, 1H, H-8), 7.18-7.26 (m, 6H, Ph), 7.49-7.54 (m, 4H, Ph), 8.26 (d, J = 2.8, 1H, H-1) (*: overlapped signals); ^{13}C NMR (δ, ppm): 19.05 [$\underline{C}$(CH$_3$)$_3$], 26.81 [C($\underline{C}$H$_3$)$_3$], 35.51 (Ar-$\underline{C}$H$_2$-CH$_2$-OPG), 35.41 (C-4), 55.74, 55.80, 56.00, 56.14 (4 x OCH$_3$), 57.57 (C-3), 65.20 (Ar-CH$_2$-$\underline{C}$H$_2$-OPG), 110.20, 110.50, 113.02 (C-5, C-8, C-3', and / or C-6'), 121.12 (C-2'), 127.42, 129.53, 133.54, 133.61 (C-1', C-4a, C-8a, and / or Ph$\underline{C}_{arom}$-C), 127.52, 129.49, 135.44 (Ph$\underline{C}_{arom}$-H), 147.44, 147.49, 147.96, 151.36 (C-6, C-7, C-5', and / or C-4'), 159.56 (C-1); MS (EI) m/z (%): 609 (M^+, 10), 353 (27), 352 (34), 351 (20), 350 (20), 340 (16), 338 (24), 276 (12), 206 (12), 200 (15), 199 (72), 191 (19), 190 (100), 165 (25), 164 (23), 160 (75), 151 (22), 146 (22), 135 (71), 121 (32), 105 (43), 77 (54), 57 (70), 41 (48); Anal. Calcd for: $C_{37}H_{43}NO_5Si$ (609.84): C 72.87, H 7.11, N 2.29; Found: C 72.59, H 6.99, N.2.30.

I_2 oxidation. General procedure.

A solution of the tetrahydroisoquinolines **1** or **2** (1 mmol), I_2 (508 mg, 2 mmol) and NaAcO (107 mg, 1.3 mmol) in dry ethanol (40 mL) was refluxed for 1 h. The reaction mixture was allowed to warm up to room temperature and 10% sodium thiosulphate (10 mL) was added dropwise to destroy the excess of I_2. The resulting yellow solution was extracted with CH_2Cl_2 (3 x 20 mL) and the organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography to afford the following products:

3-[2-(2-^{t}butyldiphenylsilyloxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxy-3,4-dihydroisoquinoline **3** (97%, 590 mg). Column chromatography (silicagel, 0.5-2% CH_2Cl_2/MeOH). (See above for physical data)

3-[2-(2-^{t}butyldiphenylsilyloxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxy-3,4-dihydroisoquinolinium iodomethylate **4** (96%, 720 mg). Column chromatography: silicagel, 3-5% CH_2Cl_2/MeOH; mp (hexane/ethyl acetate): 136-137°C; IR ν_{max} (KBr): 1650 cm^{-1}; ^1H NMR (δ, ppm): 1.02 [s, 9H, C(C<u>H</u>$_3$)$_3$], 2.76-2.98 (m 2H, Ar-C<u>H</u>$_2$-CH$_2$-OPG), 3.14 (dd, J = 17.2, J = 7.6, 1H, H-4_{eq}), 3.33 (dd, J = 17.2, J = 8.0, 1H, H-4_{ax})*, 3.37 (s, 3H, NCH_3)*, 3.71 (s, 3H, OCH_3)**, 3.71-3.90 (m, 2H, Ar-CH$_2$-C<u>H</u>$_2$-OPG)**, 3.76 (s, 3H, OCH_3)**, 3.86 (s, 3H, OCH_3)**, 3.90 (s, 3H, OCH_3)**, 5.03 (distortedt, J = 7.8, 1H, H-3), 6.41 (s, 1H, H-6'), 6.56 (s, 1H, H-3'), 6.65 (s, 1H, H-5), 7.25-7.56 (m, 10H, 2 x Ph), 7.84 (s, 1H, H-8), 10.20 (s, 1H, H-1). (*, **: overlapped signals). ^{13}C NMR (δ, ppm): 19.13 [<u>C</u>(CH$_3$)$_3$], 26.79 [C(<u>C</u>H$_3$)$_3$], 33.72 (Ar-<u>C</u>H$_2$-CH$_2$-OPG), 35.31 (C-4), 45.28 (NCH_3), 55.68, 56.48, 56.75, 56.81 (4 x OCH_3), 59.09 (C-3), 64.88 (Ar-CH$_2$-<u>C</u>H$_2$-OPG), 108.74, 110.61, 113.84, 115.45 (C-5, C-8, C-3', and / or C-6'), 116.94 (C-2'), 124.27, 129.77, 130.53, 133.12, 133.23 (C-1', C-4a, C-8a, and / or Ph<u>C</u>$_{arom}$-C), 127.64, 129.45, 135.31 (Ph<u>C</u>$_{arom}$-H), 148.24, 148.61, 149.47, 157.18 (C-6, C-7, C-5', and / or C-4'), 165.73 (C-1); MS (EI) m/z (%): 625 (28, M^++1), 624 (12, M^+), 623 (10), 611 (8), 610 (9), 537 (21), 460 (10), 369 (10), 339 (15), 338 (29), 206 (43), 204 (49), 192 (22), 182 (13), 177 (9), 164 (100), 151 (22); Anal. Calcd for: $C_{38}H_{46}INO_5Si$ (751.78): C 60.71, H 6.16, N 1.86; Found: C 60.68, H 6.33, N 1.98.

Air / KOH oxidation. General Procedure.

Powdered KOH (168 mg, 3 mmol) was added over a solution of the 3,4-dihydroisoquinolines **3**, **4**, **5** or **6** (1 mmol) in the appropiate solvent (^{t}BuOH or DMSO, 20 mL) and the resulting mixture was stirred at 50-55°C, keeping a continuous bubbling of pre-dried air. Once no further evolution of the starting material was observed (tlc), water was added and the aqueous phase extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and the solvent evaporated. The residue was purified by column chromatography to afford the following products:

3-(3,4-dimethoxyphenyl)-6,7-dimethoxyisoquinoline **7** (35% conversion, 56% yield, 64 mg). Solvent: ^{t}BuOH; reaction time: 39 h; column chromatography: silicagel, 2.5% CH_2Cl_2/MeOH; mp (EtOH) (hydroiodide): 196-197 °C (lit.[13] 197-198 °C). The same procedure using DMSO as solvent gave **7** in 45 minutes. (90%, 292 mg).

3-(3,4-dimethoxyphenyl)-6,7-dimethoxyisoquinolinium iodomethylate **8** (52% conversion, 88% yield, 255 mg). Solvent: ^{t}BuOH; reaction time: 20 h; column chromatography: silicagel, 2-3% CH_2Cl_2/MeOH; mp (EtOH): 202-203 °C (lit.[13] 204-205 °C).

3-[2-(2-hydroxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxyisoquinoline **9** (98%, 361mg). Solvent: DMSO; reaction time: 2 h; column chromatography: silicagel, 1% CH_2Cl_2/MeOH; mp (EtOH): 98-100°C; IR

ν_{max} (KBr): 3200, 1600 cm^{-1}; ^1H NMR (δ, ppm): 1.63 (broad s, 1H, OH), 2.74 (t, J = 5.5, 1H, Ar-C$\underline{H}_2$-CH_2-OH), 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.92 (t, J = 5.5, 2H, Ar-CH_2-C$\underline{H}_2$-OH)*, 3.96 (s, 6H, 2 x OCH_3)*, 6.80 (s, 1H, H-3'), 6.88 (s, 1H, H-4), 7.04 (s, 1H, H-6'), 7.31 (s, 1H, H-5), 7.62 (s, 1H, H-8), 8.92 (s, 1H, H-1) (*: overlapped signals). ^{13}C NMR (δ, ppm): 34.99 (Ar-$\underline{C}H_2$-CH_2-OH), 55.81, 55.96, 55.99 (4 x OCH_3), 63.74 (Ar-CH_2-$\underline{C}H_2$-OH), 104.52, 105.08 (C-3' and / or C-6'), 112.88, 113.18 (C-5, and / or C-8), 119.22 (C-4), 122.93 (C-2'), 131.01, 132.43, 133.65 (C-1', C-4a, and / or C-8a), 147.38 (C-1), 147.12, 149.30, 150.45, 150.83 (C-6, C-7, C-5', and / or C-4'), 153.57 (C-3); Anal. Calcd for $C_{21}H_{23}NO_5$ (369.42): C 68.27, H 6.27, N 3.79; Found: C 68.32, H 6.30, N 3.72.

3-[2-(2-hydroxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxy-2-methylisoquinolin-1-[2H]-one **10** *and 3-[2-(2-hydroxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolin-1-[2H]-one* **11** (60%, 231 mg). The mixture could not be separated by column chromatography (silicagel, ethyl acetate) or HPLC and the ratio **10/11** was established by ^1H-NMR as 1/6.5. The characterization of **10** was made by comparison with the data reported,[3c] and the spectroscopic data of **11** given below were taken from the spectra of the mixture.

11: IR ν_{max} ($CHCl_3$): 1650 cm^{-1}; ^1H NMR (δ, ppm): 1.74 (bs, 1H, OH), 2.78-2.87 (m, 3H, $H\text{-}4_{eq}$ and Ar-C$\underline{H}_2$-CH_2-OH), 2.91 (s, 3H, NCH_3), 3.43 (dd, J = 16.0, J = 7.0, 1H, $H\text{-}4_{ax}$), 3.49 (s, 3H, OCH_3)*, 3.77 (s, 6H, 2 x OCH_3)*, 3.49-3.77 (m, 2H, Ar-CH_2-C$\underline{H}_2$-OH)*, 3.83 (s, 3H, OCH_3), 4.98 (dd J = 7.0, J = 4.2, 1H, H-3), 6.37 (s, 1H, H-3'), 6.40 (s, 1H, H-6'), 6.64 (s, 1H, H-5), 7.59 (s, 1H, H-8). (* : overlapped signals); ^{13}C NMR (δ, ppm): 29.63 (Ar-$\underline{C}H_2$-CH_2-OH), 33.73 (NCH_3), 34.78 (C-4), 55.65, 56.81, 56.12 (4 x OCH_3), 57.62 (C-3), 68.59 (Ar-CH_2-$\underline{C}H_2$-OH), 109.21, 109.84, 113.17 (C-5, C-8, C-3' , and / or C-6'), 121.57 (C-2'), 127.55, 128.79, 130.64 (C-1', C-4a, and / or C-8a), 147.64, 147.98, 148.21, 151.92 (C-6, C-7, C-4', and / or C-5'), 165.26 (C-1).

By spontaneous air oxidation of the iodomethylate **4,** the isquinolinones **12** and **13** were obtained quantitatively, in a ratio 1:2.5. Their separation was not possible by column chromatography (silicagel, 80% hexane / ethyl acetate) or HPLC. Therefore, the spectroscopic data given below are taken from the spectra of the mixture.

3-[2-(2-^{t}butyldiphenylsilyloxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxy-2-methyl-isoquinolin-1-[2H]-one **12.** IR ν_{max} ($CHCl_3$): 1650 cm^{-1}; ^1H NMR (δ, ppm): 0.98 [s, 9H, C(C$\underline{H}_3$)$_3$], 3.23 (s, 3H, NCH_3), 2.85 (t, J = 7.5, 2H, Ar-C$\underline{H}_2$-CH_2-OPG), 3.84 (s, 3H, OCH_3)*, 3.85 (s, 3H, OCH_3)*, 3.75-3.85 (m, 2H, Ar-CH_2-C$\underline{H}_2$-OPG)*, 3.93 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 6.10 (s, 1H, H-4), 6.66 (s, 1H, H-3'), 6.67 (s, 1H, H-6'), 6.83 (s, 1H, H-5), 7.22-7.64 (m, 10H, Ph), 7.81 (s, 1H, H-8). (* : overlapped signals); ^{13}C NMR (δ, ppm): 19.15 [$\underline{C}(CH_3)_3$], 26.86 [C($\underline{C}H_3$)$_3$], 32.92 (NCH_3), 35.76 (Ar-$\underline{C}H_2$-CH_2-OPG), 55.65 , 56.72, 55.86, 55.96 (4 x OCH_3), 64.15 (Ar-CH_2-$\underline{C}H_2$-OPG), 105.73, 107.18, 107.61, 112.41, 113.09 (C-4, C-5, C-8, C-3', and / or C-6'), 121.64 (C-2'), 127.55, 127.70, 129.55 (Ph$\underline{C}_{arom}$-H), 131.67, 133.40, 133.51, 133.98 (C-1', C-4a, C-8a, C-3, and / or Ph$\underline{C}_{arom}$-C), 135.40 (Ph$\underline{C}_{arom}$-H), 140.91, 147.31, 151.84, 153.31 (C-6, C-7, C-5' , and / or C-4'), 162.40 (C-1).

3-[2-(2-^{t}butyldiphenylsilyloxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolin-1-[2H]-one **13**. IR ν_{max} ($CHCl_3$): 1650 cm^{-1}; ^1H NMR (δ, ppm): 1.07 [s, 9H, C(C$\underline{H}_3$)$_3$], 2.69 (dd, J = 15.8, J = 4.3, 1H, $H\text{-}4_{eq}$), 2.75 (s, 3H, NCH_3), 3.84 (t, J = 7.5, 2H, Ar-C$\underline{H}_2$-CH_2-OPG), 3.22 (dd, J = 15.8, J = 6.7, 1H, $H\text{-}4_{ax}$), 3.53 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3)*, 3.79 (s, 3H, OCH_3)*, 3.75-3.85 (m,

2H, Ar-CH_2-C$\underline{H}_2$-OPG)*, 3.92 (s, 3H, OCH_3), 4.54 (dd J = 6.7, J = 4.3, 1H, H-3), 6.33 (s, 1H, H-3'), 6.35 (s, 1H, H-6'), 6.59 (s, 1H, H-5), 7.21-7.64 (m, 11H, 2 x Ph and H-8). (* : overlapped signals); ^{13}C NMR (δ, ppm): 19.15 [$\underline{C}(CH_3)_3$], 26.87 [$C(\underline{C}H_3)_3$], 35.57 (NCH_3), 34.93, 35.32 (Ar-$\underline{C}H_2$-CH_2-OPG , and / or C-4), 55.65, 55.72, 55.86, 56.14 (4 x OCH_3), 57.40 (C-3), 65.02 (Ar-CH_2-$\underline{C}H_2$-OPG), 109.01, 109.79, 109.91, 113.63 (C-5, C-8, C-3', and / or C-6'), 121.65 (C-2'), 127.45, 128.76, 130.26 (C-1', C-4a, and / or C-8a), 127.55, 127.70, 129.80 (Ph$\underline{C}_{arom}$-H), 133.61 (Ph$\underline{C}_{arom}$-C), 135.50 (Ph$\underline{C}_{arom}$-H), 147.57, 147.98, 151.84 (C-6, C-7, C-5', and / or C-4'), 165.07 (C-1).

DDQ oxidation. General procedure.

A solution of DDQ (1.1 mmol) in dioxane (30 mL) was added dropwise over a solution of the correspondig 3,4-dihydrisoquinolinium salt **4** or **6** in dioxane (20 mL), and the resulting mixture was refluxed until no further evlution of the starting material was observed. The solvent was evaporated under reduced pressure, the residue was disolved in CH_2Cl_2 and filtered through an alumina pad. The filtrate was evaporated and the residue purified by column chromatography to afford the following products:

3-(3,4-dimethoxyphenyl)-6,7-dimethoxyisoquinolinium iodomethylate **8** (68% yield, 85% conversion, 269 mg); column chromatography: silicagel, 2-3% CH_2Cl_2/MeOH; mp (EtOH): 202-203 °C (lit.[13] 204-205 °C)

3-[2-(2-^{t}butyldiphenylsilyloxyethyl-4,5-dimethoxyphenyl)-6,7-dimethoxyisoquinolinium iodomethylate **14** (87% yield, 66% conversion, 430 mg). Column chromatography: silicagel, 2-3% CH_2Cl_2/CH_3OH; mp (EtOH): 204-206°C; IR ν_{max} (KBr): 1610 cm^{-1}; ^1H NMR (δ, ppm): 0.98 [s, 9H, $C(C\underline{H}_3)_3$], 2.34-2.42 (m 1H, Ar-$C\underline{H}_aH_b$-CH_2-OPG), 2.66-2.72 (m 1H, Ar-$CH_a\underline{H}_b$-CH_2-OPG), 3.88 (s, 3H, OCH_3)*, 3.88-4.00 (m, 2H, Ar-CH_2-C$\underline{H}_2$-OPG)*,3.90 (s, 3H, OCH_3)*, 4.00 (s, 3H, OCH_3)*, 4.09 (s, 3H, NCH_3)*, 4.14 (s, 3H, OCH_3), 6.79 (s, 1H, H-3'), 6.83 (s, 1H, H-4), 6.89 (s, 1H, H-6'), 7.25-7.55 (m, 10H, 2 x Ph), 7.48 (s, 1H, H-5), 8.17 (s, 1H, H-8), 10.74 (s, 1H, H-1) (*: overlapped signals); ^{13}C NMR (δ, ppm): 19.23 [$\underline{C}(CH_3)_3$], 26.86 [$C(\underline{C}H_3)_3$], 35.70 (Ar-$\underline{C}H_2$-CH_2-OPG), 46.02 (NCH_3), 56.00, 56.64, 57.38 (4 x OCH_3), 64.16 (Ar-CH_2-$\underline{C}H_2$-OPG), 104.36, 107.76 (C-3' , and / or C-6'), 112.45, 112.97 (C-5 , and / or C-8), 123.32 (C-4), 124.09, 124.91, 130.66, 132.99, 133.49 (C-2', C-4a, C-1', C-8a, and / or Ph$\underline{C}_{arom}$-C), 127.74, 129.88, 135.46 (Ph$\underline{C}_{arom}$-H), 143.39, 147.94, 148.77, 150.63 (C-6, C-7, C-5', and / or C-4'), 152.96 (C-3), 158.36 (C-1); Anal. Calcd for $C_{38}H_{44}INO_5Si$ (749.76): C 60.87, H 5.91, N 1.87; Found:C 60.59, H 6.02, N 1.79.

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

1. Sotomayor, N.; Domínguez, E.; Lete, E. *Tetrahedron*, **1995**, in press.
2. 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; 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; For spirobenzylisoquinoline synthesis, see Onda, M.; Yonezagua, K; Abe, K. *Chem. Pharm. Bull.* **1969**, *17*, 404; For protoberberine synthesis, see: Bhakuni, D. S.; Jain, S.: Protoberberine Alkaloids. In

The Alkaloids, Chemistry and Pharmacology, vol. 28, Brossi, A., Ed.; Academic Press: Orlando, 1986; pp 95; see also: Badía, D.; Domínguez, E.; Lete, E.; Villa, M. J.; Castedo, L.; Domínguez, D. *Heterocycles* **1988**, *27*, 867; Vicente, T.; Martínez de Marigorta, E.; Domínguez, E.; Carrillo, L.; Badía, D. *Heterocycles* **1993**, *36*, 2067.

3. For cyclizations on isoquinolin-1-[2H]-one systems, see: a) Onda, M.; Hatano, A.; Yamaguchi, H.; Saito, N. *Chem. Pharm. Bull.* **1984**, *32*, 2503; b) Hanaoka, M.; Kobayashi, N.; Mukai, C. *Heterocycles* **1987**, *26*, 1499; c) Beugelmans, R.; Bois-Choussy, M. *Tetrahedron* **1992**, *48*, 8285; d) Couture, A.; Cornet, H.; Grandclaudon, P. *Tetrahedron Lett.* **1993**, *34*, 8097; For cyclizations on 1,2-dihydroisoquinoline systems see : e) Carty, A. J.; Elliott, I. W.; Lenior, G. N. *Can. J. Chem.* **1984**, *62*, 2435; f) Iwasa, K.; Kamigauchi, M.; Cushman, M.; Wong, W. C.; Chen, J. *Tetrahedron Lett.* **1988**, *29*, 6457; Sotomayor, N; Domínguez, E.; Lete, E. *Synlett* **1993**, 431.
4. Sotomayor, N; Domínguez, E.; Lete, E. *Tetrahedron Lett.* **1994**, 2973.
5. Dyke, S. F.; Kinsman, R. G.: Properties and Reactions of Isoquinolines and their Hydrogenated Derivatives. In *Isoquinolines, Part 1. Heterocyclic Compounds*, vol. 38, Grethe, G., Ed.; John Wiley & Sons: New York, 1981; pp 51.
6. Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229.
7. Wherli, P. A.; Schaer, B. *Synthesis* **1974**, 288.
8. Castedo, L.; Puga, A.; Saá, J. M.; Suau, R. *Tetrahedron Lett.* **1981**, *22*, 2233.
9. Nonaka, G.; Kodera, Y.; Nishioka, I. *Chem. Pharm. Bull.* **1973**, *21*, 1020.
10. Barton,D. H. R.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1982**, *23*, 4949.
11. Muller, P.; Gilabert, D. M. *Tetrahedron* **1988**, *44*, 7171.
12. Burke, T. R.; Russ, P. L.; Márquez, V. E. *Heterocycles* **1992**, *34*, 757.
13. Domínguez, E.; Lete, E. *J. Heterocycl. Chem.* **1984**, *21*, 525.
14. Chow, I. L.; Danen, W. C.; Nelsen, S. F.; Rosenblatt, D. H. *Chem. Rev.* **1978**, *78*, 243.
15. It has been observed that the tetrahydroisoquinoline system adopts a preferred half-chair conformation with the aryl group at C-3 in a *pseudo*equatorial position and the nitrogen lone pair in a *pseudo*axial position: Domínguez, E.; Lete, E. *An. Quím.* **1984**, *80C*, 13; Domínguez, E.; Lete, E.; Badía, M. D.; Villa, M. J.; Castedo, L.; Domínguez, D. *Tetrahedron* **1987**, *43*, 1943; Badía, M. D.; Domínguez, E.; Tellitu, I. *Tetrahedron* **1992**, *48*, 4419; Sotomayor, N.; Vicente, T.; Domínguez, E.; Lete, E.; Villa, M. J. *Tetrahedron* **1994**, *50*, 2207; see also ref.1
16. Suau, R.; Silva, M. V.; Valpuesta, M. *Tetrahedron Lett.* **1991**, *47*, 5841.
17. Ruchirawat, S.; Sukul, S.; Thebtaranonth, Y.; Thirasana, N. *Tetrahedron Lett.* **1977**, *17*, 2335.
18. Badía, D.; Domínguez, E.; Lete, E.; Villa, M.J.: 3-Arylisoquinolines. Synthesis, Stereochemistry and Chemical Behaviour. In *Trends in Heterocyclic Chemistry*, vol. 2; Manon, J. Ed.; Council of Scientific [illegible]
19. Hall, D. L.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703.
20. Cushman, M.; Mohan, P; Smith, E. C. R. *J. Med. Chem.* **1984**, *27*, 544.
21. Stahl, E. *Thin-Layer Chromatography;* 2nd ed.; Springer-Verlag: Berlin, 1969; pp 873.
22. Still, W. C.; Kann, H.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
23. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed.; Pergamon Press: Berlin, 1988.
24. For the preparation of **1** and **2**, see ref. 1; for the preparation of **5** and **6**, see ref.13.

(*Received in UK* 7 *August* 1995; *revised* 22 *September* 1995; *accepted* 28 *September* 1995)