Pergamon

Tetrahedron Vol. 50, No. 7, pp. 2207-2218, 1994

0040-4020/94 $6.00+0.00

0040-4020(93)E0159-D

An Improved Method for the Generation of Imines and Enamides. Application to the Synthesis of 3-Arylisoquinoline Derivatives

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Abstract: The one-pot preparation of hindered 1,2-diarylethylamines **3** and **4** and ethylenenamides **5** is achieved *vía* sodium cyanoborohydride reduction and acylation of the deoxybenzoin imines **2**, respectively. A new methodology for the synthesis of 3-arylisoquinolinium salts by the Bischler-Napieralski reaction of 1,2-diarylethylenenamides and their transformation into 12-methyl substituted benzo[c]phenanthridines has been developed.

The chemistry of imines has received great attention recently because of their ability to provide the amino functionality, responsible for biological activity of many classes of pharmaceutical agents. In general, amines[1] and enamides[2] have been prepared by starting directly from aldehydes and ketones vía imine/enamine intermediates. The Borch reduction[3] has been one the most popular one-pot methods to synthetize amines, but it is less than satisfactory to prepare hindered amines. Thus, the reductive amination of ketones with aromatic amines or that of hindered ketones generally proceeds sluggishly or with very low yields (< 5%).[4] Alternative azeotropic methods to obtain imines are also unsatisfactory in these cases.[5] Titanium (IV) chloride[6] or titanium (IV) isopropoxide and sodium cyanoborohydride[7] have been used as Lewis acid catalyst and water scavenger to promote difficult enamine/imine formation. Several methods have been published to prepare enamides but they are hitherto hampered by the fact that are not general enough, particularly in the case of hindered enamides and the synthetically very useful dienamides. Acylation of pre-formed imines with an acyl chloride or an acid anhydride[2] and acid catalyzed condensation of ketones and amides[2,8] have been successfully used.

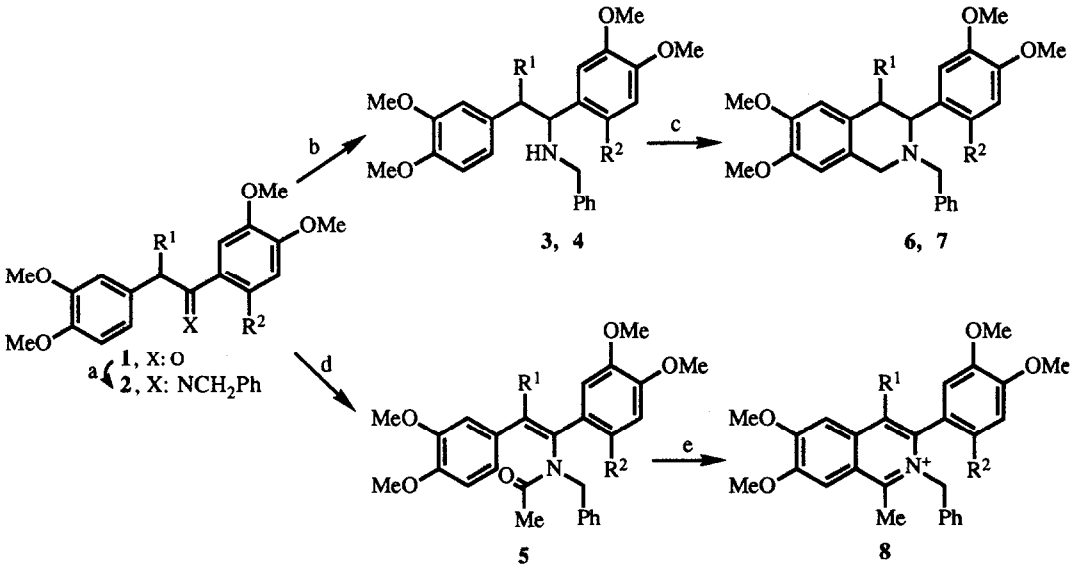
In the present paper, we describe the one-pot preparation and synthetic applications of amines **3** and **4** and enamides **5**, derived from a series of aryl benzyl ketones **1**, *vía* imines **2**. Our strategy has allowed us to develop a new methodology for the synthesis of 3-arylisoquinolines.

The series of α-substituted ketones **1b-1e** was prepared by alkylation of the 3,4-dimethoxybenzyl 3,4-dimethoxyphenyl ketone **1a**[9] with LDA in THF-HMPA, followed by treatment with the corresponding alkyl halide. On the other hand, the ketone **1f** was obtained by reduction of the 2-(3,4-dimethoxyphenylacetyl)-4,5-dimethoxy-phenylacetic acid with $NaBH_4/TiCl_4$ to the corresponding dialcohol, followed by selective silylation of the primary hydroxyl group with $^tBuPh_2SiCl$ and PCC oxidation of the secondary alcohol.[10]

As illustrated in Scheme 1, our approach to amines **3** and **4** and enamides **5** involves respectively formation of imines **2** and subsequent reduction and acylation.The benzyl group was chosen preferentially because of its easy removal under nonhydrolytic conditions. Our first experiments to arrive at *N*-(1,2-diarylethylidene)benzylamines **2** using azeotropic methods were not encouraging since no reaction was observed between ketone **1a** and benzylamine in the presence of potassium carbonate, magnesium sulphate, magnesium perchlorate, molecular sieves (4Å), trifluoroacetic acid, or using a Dean-Stark trap, varying solvent (benzene,

toluene, acetonitrile), temperature, and reaction times. However, the use of *p*-toluenesulphonic acid was most satisfactory and the anticipated imine **2a** was formed (50%). On the other hand, attempts to prepare enamides **5** by direct condensation of **1** with acetamide using a Dean-Stark trap, *p*-toluenesulphonic acid in toluene under reflux, or titanium (IV) chloride as catalyst also failed and unreacted ketone was recovered.

Finally, the synthesis of imines **2**, amines **3** and **4** and enamides **5** was successfully accomplished by using titanium (IV) chloride as catalyst. A variety of experiments were carried out in order to determine the optimum reaction conditions for the preparation of imines **2**. Thus, we found that instead of the excess of amine, the use of stoichiometric amounts of amine, ketone and titanium (IV) chloride in the presence of triethylamine, with dimethoxyethane as solvent provided the best results. Further *in situ* reduction of imines **2** with sodium cyanoborohydride in methanol gave amines *anti*-**3** and *syn*-**4**,[11] which were separated by flash column chromatography (Tables 1 and 4). The *anti* : *syn* ratio could also be determined by ^{1}H NMR spectroscopy by integration of the methinic proton at C-2. The stereochemical assignments were made by comparing the vicinal coupling constants of the two methinic protons (J_{anti} = 9.2-9.6 Hz and J_{syn} = 5.7-5.9 Hz).[12] In representative comparison experiments, reactions with titanium (IV) isopropoxide in dimethoxyethane were consistently slower and gave lower yields. In the case of ketone **1f**, all attempts at reductive amination led to mixtures of the desired amine **3f** and the starting ketone, which could not be separated. Although imine **2f** was quantitatively formed (TLC and NMR monitoring), total conversion could not be achieved in the subsequent reduction. Thus, the isolated ketone seems to derive from hydrolysis of the imine during the aqueous workup.



a: $R^1 = R^2 = H$; b: R^1 = Me, $R^2 = H$; c: R^1 = Et, $R^2 = H$; d: $R^1 = CH_2CH{=}CH_2$, $R^2 = H$; e: $R^1 = CH_2CO_2Me$, $R^2 = H$; f: $R^1 = H$, $R^2 = CH_2CH_2OSiPh_2{}^tBu$

Scheme 1. (a) 1 eq $PhCH_2NH_2$, 3 eq Et_3N, 1 eq $TiCl_4$, DME, -78°C to r.t.; (b) 3 eq.$NaCNBH_3$, MeOH, r.t. 3h; (c) 18% aqueous HCHO (3 eq), HCl 3M (3 eq) reflux, 1h; (d) 3 eq CH_3COCl, r.t., 0.5 h.; then 1 eq $TiCl_4$, r.t., 1-2 h; (e) 8 eq $POCl_3$, CH_3CN, reflux, 3-4 h.

The resulting imines **2** were allowed to react with acetyl chloride and titanium (IV) chloride in dimethoxyethane, and *E* : *Z* mixtures or pure *Z* enamides **5** were obtained in good yields. The *E* : *Z*

ratio determined by ^{1}H NMR spectroscopy by integration of the acetyl protons. The *E* and *Z* enamides **5a** were separated by HPLC (hexane / ethyl acetate 60 : 40). Isomerization of *E* into *Z* isomer occurred when treated with phosphorus pentachloride in acetonitrile at room temperature. Acylation with acetic anhydride provided the enamide **5a** in a lower yield (48%) (conversion 75%). Some examples are given in Tables 1 and 5.

Table 1. Synthesis of Amines **3** and **4**, and Enamides **5** from Deoxybenzoins **1**

Entry	Product (Isomer Ratio)	Yield(%)[a]	Molecular Formula[b]	mp (°C) (MeOH)
1	**3a**	78	$C_{25}H_{29}NO_4$ (407.5)	oil
2	*anti* **3b** +*syn* **4b**[c] (55 : 45)	80	$C_{26}H_{31}NO_4$ (421.5)	140-141/oil
3	*anti* **3c** +*syn* **4c**[c] (75 : 25)	85	$C_{27}H_{33}NO_4$ (435.6)	111-112/oil
4	*anti* **3d** +*syn* **4d**[c] (72 : 28)	82	$C_{28}H_{33}NO_4$ (447.6)	105 / oil
5	**3e**	56[d]	$C_{28}H_{33}NO_6$ (479.6)	100-101
6	**3f**	75[e]		
7	**5a** (*E* : *Z*)[c] (34 : 66)	65	$C_{27}H_{29}NO_5$ (447.5)	oil
8	**5b** (*E* : *Z*)[f] (44 : 56)	98	$C_{28}H_{31}NO_5$ (461.5)	oil
9	**5c** (*Z*)	89	$C_{29}H_{33}NO_5$ (475.6)	oil
10	**5d** (*Z*)	90	$C_{30}H_{33}NO_5$ (487.6)	oil
11	**5e** (*Z*)	55	$C_{30}H_{33}NO_7$ (519.6)	oil
12	**5f** (*Z*)	78	$C_{45}H_{51}NO_6Si$ (729.9)	oil

[a] Yield of isolated, pure products. [b] Satisfactory microanalyses obtained C ± 0.31, H ± 0.17, N ± 0.29. [c] The isomers (*anti* : *syn* or *E* : *Z*) were separated by flash column chromatography. [d] The *anti* amine **3e** was obtained accompanied of the *trans-N*-benzyl-4,5-bis(3,4-dimethoxyphenyl)-2-pyrrolidone in a 26% yield.[13] [e] Determined by ^{1}H NMR (conversion 64%); the amine **3f** and the ketone **1f** could not be separated and hence no analytically pure sample was obtained. [f] The isomeric ratio was determined by ^{1}H NMR.

The reaction conditions described herein are milder than those associated with the previous syntheses of amines and enamides. Our methods proved to be superior for use with complex molecules containing labile functionality, such as esters and silyl ethers. For instance, the drastic reaction conditions required in the classical Leuckart reductive amination of ketones are not compatible with the presence of certain functional groups.[14] Thus, the method failed when applied to ketones **1e** and **1f**. Several procedures for the reduction of oximes were also tested, but in most cases reduction yields were lowered owing to the competing Beckmann rearrangement.[10] On the other hand, although the reductive acetylation of oximes to enamides had been reported some years ago,[8,15] we found that these conditions were not suitable for the synthesis of the more hindered enamides dealt with in the present study. The condensation of deoxybenzoins oximes with acetic anhydride using chromium (II) acetate always failed. Thus, the corresponding acetylated oxime was obtained when dimethylformamide was used as solvent, whereas operating in pyridine the reaction product was a complex mixture of products.

Our next concern was the synthesis of 3-arylisoquinoline derivatives. To our knowledge, few examples have been reported of the application of the Pictet-Spengler reaction to secondary amines.[16] We found that *anti* and *syn N*-benzyl-1,2-diarylethylamines **3** and **4** were diasteroselectively converted (HCHO/HCl) to 3,4-*trans*- **6** and 3,4-*cis*-tetrahydroisoquinolines **7**, respectively (see Tables 2 and 6). The stereochemistry was deduced by Nuclear Overhauser Effect difference spectroscopy and ^{1}H-^{1}H decoupling experiments.

On the other hand, no synthesis of isoquinolines by Bischler-Napieralski cyclization of enamides has been reported so far. Previous approaches to these nitrogen heterocycles implied the cyclization of β-hydroxy or β-alkoxyphenethylamides (Pictet-Gams reaction[16]). Therefore, we turned our attention to the Bischler-Napieralski cyclization of enamides **5**. Thus, we have established that treatment of enamides **5** with phosphorus oxychloride in acetonitrile under reflux provided good yields of the 3-arylisoquinolinium salts **8** (see Tables 2 and 7).

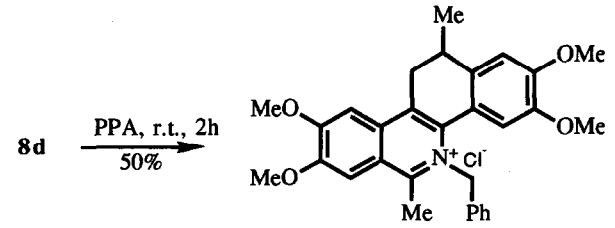
However, it was found that enamide **5f** failed to yield the corresponding isoquinolinium salt under Bischler-Napieralski conditions and afforded as sole product the 1-(3,4-dimethoxybenzylidene)-6,7-dimethoxyisochromane. Formation of this cyclic ether could be explained by assuming that deprotection of the silyl ether and subsequent intramolecular cyclization under reaction conditions has taken place.

Table 2. Synthesis of Tetrahydroisoquinolines **6** and **7** and Isoquinolinium Salts **8**

Entry	Product	Yield(%)[a]	Molecular Formula[b]	mp (ºC) (MeOH)
1	**6a**	83	$C_{26}H_{29}NO_4$ (419.5)	oil
2	*trans* **6b** / *cis* **7b**	95/92	$C_{27}H_{31}NO_4$ (433.5)	148-149 / 140-142
3	*trans* **6c** / *cis* **7c**	90/81	$C_{28}H_{33}NO_4$ (447.6)	114-115 / 124-125
4	*trans* **6d** / *cis* **7d**	95/86	$C_{29}H_{33}NO_4$ (459.6)	198-200[c] / 140-141
5	**6e**	33[d]	$C_{29}H_{33}NO_6$ (491.6)	108-109
6	**6f**	-[e]		
7	**8a**	60	$C_{27}H_{28}ClNO_4$ (466.0)	oil
8	**8b**	40	$C_{28}H_{30}ClNO_4$ (480.0)	oil
9	**8c**	55	$C_{29}H_{32}ClNO_4$ (494.0)	oil
10	**8d**	93	$C_{30}H_{32}ClNO_4$ (506.0)	oil
11	**8e**	72	$C_{30}H_{32}ClNO_6$ (538.0)	oil
12	**8f**	-[f]		

[a] Yield of isolated, pure products. [b] Satisfactory microanalyses obtained C ± 0.37, H ± 0.25, N ± 0.23. [c] Measured as its hydrochloride. [d] Partial hydrolysis of the carboxyl group took place under the acidic reaction conditions and the corresponding 4-carbomethoxymethyl substituted tetrahydroisoquinoline was obtained (21%). [e] A mixture of products was formed, due to desilylation of the substrate under the acidic reaction conditions. [f] The 1-(3,4-dimethoxybenzylidene)-6,7-dimethoxyisochromane was obtained (50%).

It is noteworthy that the above methodology can be extended to the total synthesis of benzophenanthridines by taking advantage of the 3-arylisoquinolinium salt **8d**. Thus, treatment of **8d** with polyphosphoric acid at room temperature for 24 h quantitatively provided the 12-methyl substituted benzo[c]phenanthridine **9**.



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In conclusion, our methodology enlarges the synthetic use of deoxybenzoins **1** and is particularly effective for the one-pot preparation of hindered amines, enamides and dienamides even with acid-sensitive functionality, such us 1,2-diarylethylamines **3** and **4** and ethylenamides **5**. On the other hand, the Bischler-Napieralski reaction of enamides offers attractive synthetic advantages in the preparation of isoquinolinium salts in view of its simplicity and versatility and the avoidance of the alternative methods of oxidation of tetrahydro- and dihydroisoquinolines.[17]

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 ^1H and 62.8 MHz for ^{13}C (solvent $CDCl_3$, internal standard TMS). ^1H-{^1H} NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet.[18] Assignment of individual ^{13}C resonances are supported by DEPT experiments. Elemental analyses were performed on a Perkin-Elmer 2400 CHN apparatus. Mass spectra were recorded by the Universities of Santiago de Compostela and La Laguna (Spain). 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.[19] Flash column chromatography[20] on silica gel was performed with Merck Kieselgel 60 (230-400 mesh). HPLC was accomplished on a Waters 600E apparatus with a Porasil 10M 19 mm x 15 cm column. All solvents used in reactions were anhydrous and purified according to standard procedures.[21] Reactions were carried out under dry, deoxygenated argon atmosphere. Transfers of solvents and solutions were performed by syringe or *via* canula.[22] Ketones **1a**[9] and **1f**[10] were synthesized according to literature methods.

Aryl Benzyl Ketones **1b-e**; *General Procedure:*

A solution of the ketone **1a** (3 g, 9.5 mmol) in dry THF (150 mL) was added dropwise to a cold (-78°C) solution of lithium diisopropylamide (LDA) (10.4 mmol) in dry THF (150 mL) under Ar. To this solution HMPA (1.7 mL, 9.5 mmol) and then the alkyl halide (19 mmol) were added dropwise. After additional stirring for 1 h, the mixture was warmed to r. t., quenched with sat. aq NH_4Cl (30 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine (4 x 50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was recrystallized to give the corresponding deoxybenzoins **1** (Table 3).

N-benzyl-N-1,2-diarylethylamines anti **3a-f** *and syn* **4b-d**; *General Procedure:*

To a stirred mixture of deoxybenzoins **1a-f** (2.6 mmol), *N*-benzylamine (2.6 mmol) and Et_3N (7.7 mmol) in dry dimethoxyethane (15 mL) kept at -78°C under Ar, $TiCl_4$ (2.6 mmol, 2.6 mL of a 1M solution of $TiCl_4$ in CH_2Cl_2) was added dropwise. The resulting dark orange suspension was allowed to warm to r.t., and stirred until all the starting ketone had disappeared (TLC). To the black suspension of imines **2a-f**, a methanolic solution (12 mL) of $NaCNBH_3$ (0.46 g, 7.4 mmol) was added. The now yellow reaction mixture was stirred for 3h, quenched with sat. aq K_2CO_3 (20 mL), and extracted with Et_2O (3 x 30 mL); the organic extracts were washed with brine (3 x 50 mL), dried (K_2CO_3), and concentrated. The crude mixture of the *N*-benzyl-1,2-diarylethyl-amines **3** and **4** was separated by flash column chromatography (SiO_2, hexane/AcOEt, 6:4). (Tables 1 and 4).

With ketone **1e** the methyl 2,3-*anti*-3-benzylamine-2,3-bis(3,4-dimethoxyphenyl)propionate **3e** (56 %) was obtained along with the *trans-N*-benzyl-4,5-bis(3,4-dimethoxyphenyl)-2-pyrrolidone (26 %), as a white solid of mp 150-151°C (MeOH).

Anal.: Found C 72.11; H 6.62; N 3.05.$C_{27}H_{29}NO_5$ requires: C 72.46; H 6.53; N 3.13.

IR: ν = 1680 (C=O) cm^{-1}.

^1H NMR: δ = 2.61 (dd, 1H, J_{AB} = 17, J_{AX} = 8.1, H_{3A}), 2.96 (dd, 1H, J_{AB} = 17, J_{AX} = 9.2, H_{3B}), 3.23-3.33 (m, 1H, H_4), 3.51 (d, 1H, J_{AB} = 14.4, $PhC\underline{H}_AH_BN$), 3.60 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.14 (d, 1H, J = 6.2, H_5), 5.03 (d, 1H, J_{AB} = 14.5, $PhCH_A\underline{H}_BN$), 6.34 (d, 1H, J_m = 1.9, $H_{2'}$), 6.47-6.55 (m, 3H, H_{arom}), 6.64 (d, 1H, J_o = 8.2, $H_{5'}$), 6.75 (d, 1H, J_o = 8.1, $H_{5''}$), 7.01-7.04 (m, 2H, Ph), 7.11-7.26 (m, 3H, Ph).

^{13}C NMR: δ = 38.3 (C_3), 44.6 (Ph$\underline{C}H_2N$), 47.0 (C_4), 55.7, 55.8, 55.9, 56.0 (4 x OCH_3), 69.5 (C_5), 109.5, 110.0, 111.1, 118.8, 119.7 127.5, 128.5, 128.7 (C_{arom}-H), 131.6, 134.1, 136.3 ($\underline{C}_{arom}$-C), 148.0, 148.9, 149.4 (C_{arom}-O), 174.0 (C=O).

MS (70 eV): *m/z* (%): 448 (13), 447 (M^+, 40), 356 (13), 300 (18), 255 (14), 192 (8), 191 (10), 165 (12), 164 (41), 91 (23), 65 (100).

Table 3. Deoxybenzoins **1** Prepared.

Compound	Yield (%)[a]	mp (°C) (solvent)	^1H NMR[b] δ, J (Hz)	^{13}C NMR δ
1b	78	126-127 (MeOH)	1.44 (d, 3H, J = 6.85, $C\underline{H}_3CH$), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.53 (q, 1H, J = 6.85, $C\underline{H}CH_3$), 6.70-6.79 (m, 4H, H_{arom}), 7.47 (d, 1H, J_m= 2.0, $H_{2'}$), 7.53 (dd, 1H, J_o= 8.4, J_m= 2.0, $H_{6'}$)	19.6 ($\underline{C}H_3CH$), 47.0 ($CH_3\underline{C}H$), 55.8, 55.9, 56.0 (4 x OCH_3), 109.9, 110.5, 111.0, 111.5 ($C_{2'}$, $C_{5'}$, $C_{2''}$, $C_{5''}$), 119.9, 123.3 ($C_{6'}$, $C_{6''}$), 130.0, 134.5 ($C_{1''}$, $C_{1'}$), 147.9, 148.9, 149.3, 153.0 (C_{arom}-O), 199.0 (C=O).
1c	72	78-79 (MeOH)	0.83 (t, 3H, J = 7.4, $C\underline{H}_3CH_2$), 1.73-1.79 (m, 1H, $CH_3C\underline{H}_AH_B$), 2.06-2.12 (m, 1H, $CH_3CH_A\underline{H}_B$), 3.73 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.82 (s, 6H, 2 x OCH_3), 4.27 (t, 1H, J = 7.3, $CH_2C\underline{H}$), 6.69-6.80 (m, 4H, H_{arom}), 7.40 (d, 1H, J_m= 2.0, $H_{2'}$), 7.55 (dd, 1H, J_o= 8.4, J_m= 2.0, $H_{6'}$)	12.3 ($\underline{C}H_3CH_2$), 27.1 ($CH_3\underline{C}H_2$), 54.5 ($CH_2\underline{C}H$), 55.8, 55.9, 56.0 (4 x OCH_3), 109.9, 110.7, 110.8, 111.3 ($C_{2'}$, $C_{5'}$, $C_{2''}$, $C_{5''}$), 120.5, 123.2 ($C_{6'}$, $C_{6''}$), 130.1, 132.7 ($C_{1''}$, $C_{1'}$), 148.0, 148.9, 149.2, 153.0 (C_{arom}-O), 198.8 (C=O).
1d[c]	88	80-81 (MeOH)	2.45-2.56 (m, 1H, CH_2=$CHC\underline{H}_AH_B$), 2.81-2.90 (m, 1H, CH_2=$CHCH_A\underline{H}_B$), 4.49 (t, 1H, J = 7.3, $CH_2C\underline{H}$), 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.85 (s, 6H, 2 x OCH_3), 4.90-5.09 (m, 2H, $C\underline{H}_2$=CH), 5.65-5.72 (m, 1H, CH_2=$C\underline{H}$), 6.73-6.83 (m, 4H, H_{arom}), 7.50 (d, 1H, J_m= 2.0, $H_{2'}$), 7.58 (dd, 1H, J_o= 8.4, J_m= 2.0, $H_{6'}$).	38.2 (CH_2=$C\underline{H}CH_2$), 52.6 ($CH_2\underline{C}H$), 55.7, 55.8, 55.9, 56.0 (4 x OCH_3), 109.9, 110.8, 110.9, 111.3 ($C_{2'}$, $C_{5'}$, $C_{2''}$, $C_{5''}$), 120.5, 123.2 ($C_{6'}$, $C_{6''}$), 116.4 ($\underline{C}H_2$=CH), 129.8, 132.1 ($C_{1''}$, $C_{1'}$), 136.4 (CH_2=$\underline{C}H$), 148.0, 148.9, 149.2, 153.1 (C_{arom}-O), 197.9 (C=O).
1e[d]	90	117-118 (Hexane AcOEt)	2.63 (dd, 1H, J_{AB} = 16.8, J_{AX} = 5.2, $C\underline{H}_AH_BCO_2$), 3.26 (dd, 1H, J_{AB}= 16.8, J_{BX}= 9.5, $CH_AH_BCO_2$), 3.58 (s, 3H, CO_2CH_3), 3.75 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.92 (m, 1H, $C\underline{H}CH_2$), 6.69-6.79 (m, 4H, H_{arom}), 7.46 (d, 1H, J_m= 2.0, $H_{2'}$), 7.57 (dd, 1H, J_o= 8.4, J_m= 2.0, $H_{6'}$).	38.5 ($\underline{C}H_2CO_2$), 48.7 ($\underline{C}HCH_2$), 51.8 ($CO_2\underline{C}H_3$), 55.7, 55.8, 55.9, 56.0 (4 x OCH_3), 110.0, 110.6, 111.0, 111.6 ($C_{2'}$, $C_{5'}$, $C_{2''}$, $C_{5''}$), 120.4, 123.6 ($C_{6'}$, $C_{6''}$), 129.2, 131.1 ($C_{1''}$, $C_{1'}$), 148.4, 148.9, 149.4, 153.2 (C_{arom}-O), 172.6 ($\underline{C}O_2CH_3$), 197.1 (C=O).

[a] Yield of isolated, pure products. Satisfactory microanalyses obtained: C ± 0.40, H ± 0.28. [b] IR (KBr) cm^{-1}: 1665-1675 (C=O, ketone) and in **1e**, 1740 (C=O, ester). [c] MS (70 eV): *m/z* (%) **1d**: 356 (M^+, 26), 287 (12), 192 (18), 191 (100), 165 (98), 160 (28), 151 (13), 137 (17), 122 (17), 77 (30). [d] MS (70 eV): *m/z* (%) **1e**: 388 (M^+, 21), 223 (12), 181 (24), 166 (29), 165 (100), 137 (110, 77 (17).

Table 4. Spectral Data for 3,4-*anti*-Amines **3**.[a, b]

Compound	^{1}H NMR δ, J (Hz)	^{13}C NMR δ
3a	1.72 (br s, 1H, NH), 2.79 (dd, 1H, J_{AB} = 13.5, J_{AX} = 8.5, CH_AH_BCH), 2.88 (dd, 1H, J_{AB}= 13.5, J_{AX}= 5.6, CH_AH_BCH), 3.45 (d, 1H, J = 13.6, $PhCH_AH_BN$), 3.45 (d, 1H, J = 13.6, $PhCH_AH_BN$), 3.74-3.79 (m, 1H, CH_2CH), 3.77 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.88 (s, 6H, 2 x OCH_3), 6.55 (d, 1H, J_m= 1.6, $H_{2'}$), 6.66 (dd, 1H, J_o= 8.1, J_m= 1.6, $H_{6'}$), 6.76 (d, 1H, J_o= 8.1, $H_{5'}$), 6.83-7.03 (m, 5H, H_{arom}), 6.93-7.11 (m, 2H, Ph), 7.20-7.29 (m, 3H, Ph).	44.8 (CH_2CH), 51.1 ($PhCH_2N$), 55.5, 55.6, 55.7 (4 x OCH_3), 63.0 (CH_2CH), 110.0, 110.8, 111.0, 112.1, 119.6, 121.2, 126.4, 127.9, 128.1 (C_{arom}-H), 133.1, 136.0, 140.3 (C_{arom}-C), 147.4, 147.9, 148.5, 148.9 (C_{arom}-O).
3b	0.92 (d, 3H, J = 7, CH_3CH), 1.72 (br s, 1H, NH), 2.73-2.85 (m, 1H, CH_3CH), 3.27 (d, 1H, J_{AB} = 13.9, $PhCH_AH_BN$), 3.46 (d, 1H, J = 9.6, CHN), 3.56 (d, 1H, J_{AB} = 13.6, $PhCH_AH_BN$), 3.82 (s, 3H, OCH_3), 3.90 (s, 6H, 2 x OCH_3), 3.91 (s, 3H, OCH_3), 6.67 (d, 1H, J_m = 1.6, $H_{2'}$), 6.77 (dd, 1H, J_o= 8.2, J_m= 1.8, $H_{6'}$), 6.82 (s, 1H, H_{arom}), 6.86 (s, 2H, H_{arom}), 6.92-6.97 (m, 3H, H_{arom}, Ph), 7.17-7.26 (m, 3H, Ph).	19.1 (CH_3CH), 46.9 (CH_3CH), 50.8 ($PhCH_2N$), 55.6, 55.7, 55.8 (4 x OCH_3), 67.2 (CHN), 110.0, 110.4, 111.1, 119.7, 121.1, 126.6, 128.0, 128.8 (C_{arom}-H), 134.8, 137.1, 140.3 (C_{arom}-C), 147.6, 148.1, 148.9, 149.0 (C_{arom}-O).
3c	0.52 (t, 3H, J = 7.3, CH_3CH_2), 1.22-1.31 (m, 2H, CH_3CH_2), 1.80 (br s, 1H, NH), 2.52 (dt, 1H, J = 9.8, J = 4.7, CH_2CH), 3.24 (d, 1H, J_{AB} = 13.9, $PhCH_AH_BN$), 3.49 (d, 1H, J = 9.8, CHN), 3.56 (d, 1H, J_{AB} = 13.9, $PhCH_AH_BN$), 3.75 (s, 3H, OCH_3), 3.83 (s, 6H, 2 x OCH_3), 3.85 (s, 3H, OCH_3), 6.61 (d, 1H, J_m= 1.8, $H_{2'}$), 6.77 (dd, 1H, J_o= 8.2, J_m= 1.8, $H_{6'}$), 6.81-6.96 (m, 6H, H_{arom}, Ph), 7.18-7.26 (m, 3H, Ph).	12.0 (CH_3CH_2), 26.0 (CH_3CH_2), 50.6 ($PhCH_2N$), 54.7 (CH_2CH), 55.7, 55.8, 55.9 (4 x OCH_3), 66.4 (CHN), 110.6, 111.1, 120.9, 121.2, 126.7, 128.0, 128.1 (C_{arom}-H), 134.7, 134.9, 140.0 (C_{arom}-C), 148.1, 149.0, 149.1 (C_{arom}-O).
3d[c]	1.62 (br s, 1H, NH), 2.03-2.09 (m, 2H, CH_2=$CHCH_2$), 2.69-2.78 (m, 1H, CH_2=$CHCH_2CH$), 3.27 (d, 1H, J_{AB} = 13.8, $PhCH_AH_BN$), 3.54 (d, 1H, J_{AB} = 9.2, CHN), 3.57 (d, 1H, J_{AB} = 13.8, $PhCH_AH_BN$), 3.81 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.91 (s, 6H, 2 x OCH_3), 4.67-4.74 (m, 2H, CH_2=CH), 5.30-5.46 (m, 1H, CH_2=CH), 6.59 (d, 1H, J_m= 1.6, $H_{2'}$), 6.72 (dd, 1H, J_o= 8.2, J_m= 1.6, $H_{6'}$), 6.80-6.85 (m, 3H, H_{arom}), 6.93-6.97 (m, 3H, H_{arom}, Ph), 7.19-7.27 (m, 3H, Ph).	37.4 (CH_2=$CHCH_2$), 50.6 ($PhCH_2N$), 52.7 (CH_2=$CHCH_2CH$), 55.5, 55.6, 55.7 (4 x OCH_3), 65.8 (CHN), 115.5 (CH_2=CH), 110.4, 110.8, 120.7, 121.0, 126.5, 127.8, 127.9 (C_{arom}-H), 134.0, 134.5, 140.1 (C_{arom}-C), 136.5 (CH_2=CH), 147.5, 148.1, 148.7, 148.9 (C_{arom}-O).
3e[d]	1.62 (br s, 1H, NH), 2.37-2.41 (m, 2H, CH_2CO_2), 3.21-3.33 (m, 2H, $PhCH_ACH_BN$, CH_2CH), 3.40 (s, 3H, CO_2CH_3), 3.56-3.61 (m, 2H, $PhCH_ACH_BNCH$), 3.80 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.90 (2s, 6H, 2 x OCH_3), 6.61 (d, 1H, J_m= 1.7, $H_{2''}$), 6.75 (dd, 1H, J_o= 8.2, J_m = 1.7, $H_{6''}$), 6.78-6.86 (m, 3H, H_{arom}), 6.92-6.99 (m, 3H, H_{arom}, Ph), 7.19-7.25 (m, 4H, Ph).	38.2 (CH_2CO_2), 48.4 (CH_2CH), 50.6 ($PhCH_2N$), 51.1 (CO_2CH_3), 55.6, 55.7 (4 x OCH_3), 65.4 (CHN), 110.5, 110.8, 111.0, 120.3, 121.0, 126.5, 127.8, 128.0 (C_{arom}-H), 133.2, 133.5, 140.0 (C_{arom}-C), 147.8, 148.2, 148.7, 149.0 (C_{arom}-O), 172.3 (C=O).

[a]Only spectral data of **3** are reported, because those of **4** showed no significant differences [b]IR (KBr) cm^{-1}: 3340-3350 (N-H) and in **3e** 1730 (C=O, ester). [c]MS (70 eV): *m/z* (%) **3d**: 447 (M^+, < 1), 446 (2), 300 (12), 258 (47), 257 (100), 256 (99), 255 (28), 254 (44), 214 (13), 191 (37), 165 (50), 164 (32), 160 (24), 159 (14), 151 (45), 150 (29), 145 (12), 129 (12), 119 (11), 117 (18), 116 (23), 115 (25), 107 (10), 106 (31), 105 (10), 92 (99), 91 (99), 77 (33), 65 (65). [d]MS (70 eV): *m/z* (%) **3e**: 479 (M^+, <1), 478 (1), 448 (6), 447 (11), 257 (23), 256 (100), 164 (22), 92 (18), 91 (99).

N-Benzyl-N-1,2-diarylethyleneamides **5a-f**; *General Procedure:*

To the black suspensions of imines **2a-f** (2.6 mmol), prepared as described above, acetyl chloride (7.8 mmol) was added at r.t. under Ar. The mixture was stirred for 30 min and after further dropwise addition of $TiCl_4$ (2.6 mmol, 2.6 mL of a 1M solution of $TiCl_4$ in CH_2Cl_2), the stirring was continued for the required period of time. The progress of the reaction was monitored by TLC using hexane / EtOAc (6 : 4) as eluent. After the same workup described above, purification by flash column chromatography (SiO_2, hexane / EtOAc, 6 : 4) gave the enamides **5**, as a mixture of *E* and *Z* isomers or as a single *Z* diastereomer (Tables 1 and 5).

Table 5. Spectral Data for Enamides **5**.[a]

Compound	^{1}H NMR δ, J (Hz)	^{13}C NMR δ
5a (Z)[b]	1.91 (s, 3H, CH_3CO), 3.67 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.53 (d, 1H, J = 13.6, $PhCH_ACH_BN$), 4.88 (d, 1H, J = 13.6, $PhCH_ACH_BN$), 6.62 (d, 1H, J_m= 2.1, $H_{2'}$), 6.67 (s, 1H, CH=CN), 6.76-6.87 (m, 4H, $H_{2''}$, $H_{5''}$, $H_{6''}$, $H_{5'}$), 6.95 (dd, 1H, J_o = 8.4, J_m = 2.1, $H_{6'}$), 7.18-7.38 (m, 5H, Ph).	22.2 (CH_3CO), 50.8 ($PhCH_2N$), 55.8, 56.0 (4 x OCH_3), 109.0, 110.1, 111.1, 111.2, 118.7, 122.3, 124.5, 127.8, 128.3, 130.4 (C_{arom}-H, CH=CN), 127.7 (CH=CN), 131.3, 137.1, 137.8 (C_{arom}-C), 149.0, 149.1 (C_{arom}-O), 171.5 (C=O).
5b[c]	1.56 (E) , 1.89 (Z) (2s, 6H, CH_3C), 2.21 (Z) , 2.22 (E) (2s, 6H, CH_3CO), 3.45 (E) (s, 3H, OCH_3), 3.47 (E) (s, 3H, OCH_3), 3.62 (Z) (s, 3H, OCH_3), 3.79 (Z) (s, 3H, OCH_3), 3.80 (Z) (2s, 6H, 2 x OCH_3), 3.84 (E) (s, 3H, OCH_3), 3.86 (E) (s, 3H, OCH_3), 3.79-3.86 (m, 2H, $PhCH_AH_BN$), 4.87 (Z), 5.25 (E) (2d, 1H, J = 13.9; 1H, J = 13.9, $PhCH_AH_BN$), 6.25 (Z) , 6.38 (E) (2d, 1H, J_m= 1.8; 1H, J_m= 1.7, $H_{2''}$), 6.43 (E) (d, J_m= 1.9, $H_{2'}$), 6.55 (E) (dd, J_o= 8.2, J_m= 1.9, $H_{6'}$), 6.62-6.83 (m, H_{arom}), 7.16-7.29 (m, 5H, Ph).	21.2 (E), 21.6 (Z) (CH_3C), 22.3 (E), 23.0 (Z) (CH_3CO), 48.6 (E), 51.5 (Z) ($PhCH_2N$), 55.5, 55.7, 55.8 (4 x OCH_3), 110.2, 110.4, 110.5, 110.9, 111.1, 111.8, 111.9, 113.2, 119.8, 120.8, 121.9, 122.9, 127.2, 127.4, 128.2, 128.2, 129.9, 130.0, 128.7, 132.4 (C_{arom}-H), 133.8, 134.3, 134.7, 136.0, 136.4, 137.0, 138.1 (C_{arom}-C, C=CN), 148.0, 148.1, 148.2, 148.4, 148.5, 148.6, 148.8 (C_{arom}-O), 170.5 (Z) , 171.5 (E) (C=O)
5c[d]	1.01 (t, 3H, J = 7.4, CH_3CH_2), 1.92 (s, 3H, CH_3CO), 2.57 (q, 2H, CH_3CH_2), 3.48 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.82-3.88 (m, 1H, $PhCH_ACH_BN$), 4.84 (d, 1H, J = 14.0, $PhCH_ACH_BN$), 6.31 (d, 1H, J_m= 2.1, $H_{2''}$), 6.76-6.87 (m, 5H, H_{arom}), 7.19-7.22 (m, 5H, Ph).	13.7 (CH_3CH_2), 23.1 (CH_3CO), 27.7 (CH_3CH_2), 51.3 ($PhCH_2N$), 55.5, 55.7, 55.8, 55.9 (4 x OCH_3), 110.4, 110.9, 111.2, 111.6, 120.1, 121.8, 127.2, 128.2, 129.9 (C_{arom}-H), 131.0, 132.1, 136.4, 138.1, 139.1 (C_{arom}-C, C=CN), 148.4, 148.6, 148.9 (C_{arom}-O), 171.5 (C=O).
5d[e]	1.9 (s, 3H, CH_3CO), 3.33-3.35 (m, 2H, CH_2=CHCH_2), 3.48 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.79-3.83 (m, 1H, $PhCH_ACH_BN$), 4.86 (d, 1H, J =14.0, $PhCH_ACH_BN$), 5.01-5.09 (m, 2H, CH_2=CH), 5.70-5.86 (m, 1H, CH_2=CH), 6.39 (d, 1H, J_m = 1.9, $H_{2''}$), 6.69-6.78 (m, 5H, H_{arom}), 7.19-7.20 (m, 5H, Ph).	23.0 (CH_3CO), 38.8 (CH_2=CHCH_2), 51.1 ($PhCH_2N$), 55.5, 55.6, 55.7, 55.9 (4 x OCH_3), 110.4, 111.0, 111.2, 111.7, 120.2, 121.9, 127.3, 128.2, 129.9 (C_{arom}-H), 116.4 (CH_2=CH), 130.7, 132.1, 134.4, 137.9, 138.0 (C_{arom}-C, C=CN), 136.0 (CH_2=CH), 148.5, 148.6, 148.8, 148.9 (C_{arom}-O), 171.5 (C=O).
5e[f]	1.96 (s, 3H, CH_3CO), 3.52 (s, 3H, CO_2CH_3), 3.61 (s, 3H, OCH_3), 3.63 (m, 2H, CH_2CO_2), 3.81 (s, 3H, OCH_3), 3.80-3.90 (m, 1H, $PhCH_ACH_BN$), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.90 (d, 1H, J= 13.9, $PhCH_ACH_BN$), 6.50 (br d, 1H, $H_{2''}$), 6.73-6.89 (m, 5H, H_{arom}), 7.22-7.33 (m, 5H, Ph).	23.2 (CH_3CO), 40.6 (CH_2CO_2), 51.2 ($PhCH_2N$), 52.0 (CO_2CH_3), 55.6, 55.8, 55.9, 56.0 (4 x OCH_3), 110.7, 111.0, 111.3, 111.9, 120.1, 122.2, 127.4, 128.3, 129.9 (C_{arom}-H), 129.5, 130.3, 131.6, 138.1, 140.2 (C_{arom}-C, C=CN),148.8, 149.0, 149.2(C_{arom}-O),171.5, 172.0 (C=O)
5f	0.99 (s, 9H, $C(CH_3)_3$), 3.42 (s, 3H, OCH_3), 3.55 (t, 2H, J = 6.6, 2H, CH_2CH_2O), 3.67 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.77 (s, 3H. OCH_3), 3.73-3.78 (m, 2H, CH_2CH_2O), 4.46 (br s, 2H, $PhCH_2N$), 6.26 (s, 1H, CH=CN), 6.30 (d, J = 1.8, 1H, $H_{2''}$), 6.47 (dd, J = 8.4, 1.8, 1H, $H_{6''}$), 6.49 (s, 1H, $H_{3'}$), 6.55 (d, J = 8.4, 1H, $H_{5''}$), 6.79 (s, 1H, $H_{6'}$), 7.12-7.39 (m, 10H, 2 x PhSi), 7.51-7.59 (m, 5H, Ph).	19.1 ($C(CH_3)_3$), 22.5 (CH_3CO) 26.8 ($C(CH_3)_3$), 35.0 (CH_2CH_2O), 48.2 ($PhCH_2N$), 55 2, 55 7, 55 8, 55 9 (4 x OCH_3), 63.8 (CH_2CH_2O), 110.6, 111.0, 112.8, 113.1, 122.4, 126.9, 127.6, 128.2, 129.1, 129.6, 135.5 (C_{arom}-H), 126.4, 127.8, 131.6, 133.5, 137.8 (C_{arom}-C, CH=CN), 147.8, 148.2, 148.4, 149.3 (C_{arom}-O), 171.0 (C=O).

[a] IR (KBr) cm^{-1}: 1650-1665 (C=N) , in **5e** 1750 (C=O). [b] Only spectral data of **5a** (Z) are reported, because those of 5a (E) showed no significant differences. [c] MS (FAB): *m/z* (%) **5b**: 462 (MH^+, 100), 461 (47), 420 (15), 419 (8), 418 (18), 329 (27), 328 (15), 314 (17), 313 (39), 299 (10), 298 (12), 297 (12), 227 (27), 165 (39), 164 (23), 151 (19), 92 (17). [d] MS (FAB): *m/z* (%) **5c**: 476 (MH^+, 100), 475 (44), 474 (13), 446 (20), 434 (16), 432 (25), 384 (10), 343 (18), 342 (15), 328 (14), 327 (24), 326 (10), 312 (11), 296 (15), 227 (10), 189 (16), 179 (25), 177 (12), 166 (10), 165 (23), 164 (18), 163 (12), 152 (10), 151 (24), 133 (15), 115 (12), 105 (14). [e] MS (FAB): *m/z* (%) **5d** : 488 (MH^+, 100), 487 (36), 447 (25), 446 (51), 444 (12), 355 (17), 354 (12), 340 (14), 339 (18), 191 (14), 177 (21), 167 (19), 166 (12), 164 (27), 163 (14), 151 (24), 141 (15), 139 (20), 135 (23), 133 (20), 123 (22), 121 (18), 115 (16), 109 (29), 107 (24), 105 (27), 103 (31), 93 (29). [f] MS (70 eV): *m/z* (%) **5e**: 520 (21), 519 (M^+, 62), 476 (17), 447 (24), 446 (81), 418 (23), 387 (18), 386 (26), 355 (18), 327 (12), 326 (21), 227 (12), 91 (100).

N-benzyl-3,4-disubstituted tetrahydroisoquinolines **6a-e** *and* **7b-d**; *General Procedure:*

The amines **3a-e** (1 mmol) and 1M HCl (40 mL) were heated under reflux for 1 h. Formaldehyde (17 mmol, 1.25 mL of 37% aq solution) was added and the heating was continued for an additional hour. Then the mixture was cooled to r.t. and the resulting suspension was basified (1M NaOH) and extracted with CH_2Cl_2 (3 x 30 mL); the combined organic extracts were washed with brine (4 x 50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was recrystallized from methanol to give the corresponding tetrahydroisoqunolines **6a-e** (Tables 2 and 6).

Table 6. Spectral Data for *Trans*-tetrahydroisoquinolines **6**.[a]

Compound	^{1}H-NMR δ, J (Hz)	^{13}C-NMR δ
6a	2.88-3.10 (m, 2H, 2 x H_4), 3.39 (d, 1H, J_{AB}= 15.4, H_{1A}),# 3.59-3.78 (m, 4H, H_{1B}, PhC$\underline{H_2}$N, and 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_o = 8.2, $H_{5'}$), 6.87 (dd, 1H, J_o = 8.2, J_m = 1.85, $H_{6'}$), 6.99 (d, 1H, J_m = 1.85, $H_{2'}$), 7.14-7.46 (m, 5H, Ph).	37.0 (C_4), 54.2 (Ph$\underline{C}H_2$N), 55.8, 55.8, 55.9 (4 x OCH_3), 58.6 (C_1), 64.0 (C_3), 109.1, 110.5, 110.9, 120.0 (C_{arom}-H), 126.8, 128.2, 128.6 ($\underline{PhC}_{arom}$-H), 126.1, 126.3, 135.5, 139.5 (C_{4a}, C_{8a}, $C_{1'}$, $\underline{PhC}_{arom}$-C), 147.3, 147.5, 148.2, 149.2 (C_{arom}-O).
6b	1.30 (d, 3H, J = 6.9, C$\underline{H_3}C_4$), 3.09-3.16 (m, 2H, H_4 and H_{1A}#), 3.30 (d, 1H, J = 6.6, H_3), 3.45 (d, 1H, J = 14.9, PhC$\underline{H_A}H_B$N),# 3.63 (d, 1H, J = 14.9, PhC$H_A\underline{H_B}$N),# 3.72 (d, 1H, J = 13.35, H_{1B}),# 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.47 (s, 1H, H_8), 6.75 (s, 1H, H_5), 6.82-6.90 (m, 3H, H_{arom}), 7.23-7.38 (m, 5H, Ph).	20.9 ($\underline{C}H_3C_4$), 39.8 (C_4), 53.6 (Ph$\underline{C}H_2$N), 55.7, 55.8, 55.9 (4 x OCH_3), 59.6 (C_1), 70.9 (C_3), 108.8, 1103, 110.5, 111.0, 121.2 (C_{arom}-H), 126.8, 128.1, 128.6 ($\underline{PhC}_{arom}$-H), 126.3, 131.3, 133.9, 139.4 (C_{4a}, C_{8a}, $C_{1'}$, $\underline{PhC}_{arom}$-C), 147.1, 147.7, 148.1, 148.9 (C_{arom}-O).
6c	0.92 (t, 3H, J = 7.4, C$\underline{H_3}$CH_2), 1.64-1.75 (m, 1H, CH$_3$C$\underline{H_A}H_B$), 1.93-2.00 (m, 1H, CH$_3$C$H_A\underline{H_B}$), 2.83-2.90 (m, 1H, H_4), 3.36-3.65 (m, 5H, 2 x H_1, H_3, PhC$\underline{H_2}$N), 3.71 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.50 (s, 1H, H_8), 6.61-6.82 (m, 4H, H_5, $H_{2'}$, $H_{5'}$, and $H_{6'}$), 7.24-7.40 (m, 5H, Ph).	11.4 ($\underline{C}H_3CH_2$), 26.8 ($CH_3\underline{C}H_2$), 46.08 (C_4), 51.7 (Ph$\underline{C}H_2$N), 55.5, 55.6, 55.7, 55.9 (4 x OCH_3), 59.4 (C_1), 64.2 (C_3), 108.7, 110.4, 111.1, 111.4, 120.9 (C_{arom}-H), 126.8, 128.1, 128.6 ($\underline{PhC}_{arom}$-H), 127.0, 130.3, 132.7, 139.3 (C_{4a}, C_{8a}, $C_{1'}$, $\underline{PhC}_{arom}$-C), 147.0, 147.5, 147.9, 148.5 (C_{arom}-O).
6d	2.38-2.44 (m, 1H, C$\underline{H_A}H_B$CH=CH_2), 2.69-2.80 (m, 1H, CH$_A\underline{H_B}$CH=CH_2), 3.00-3.02 (m, 1H, H_4), 3.37-3.59 (m, 4H, 2 x H_1 and PhC$\underline{H_2}$N), 3.71 (s, 3H, OCH_3), 3.74 (d, 1H, J = 3.7, H_3), 3.81 (s, 3H, OCH_3), 3.86 (s, 6H, 2 x OCH_3), 4.99-5.05 (m, 2H, CH=C$\underline{H_2}$), 5.70-5.86 (m, 1H, C$\underline{H}$=CH_2), 6.47 (s, 1H, H_8), 6.65-6.79 (m, 4H, H_5, $H_{2'}$,$H_{5'}$, and $H_{6'}$), 7.21-7.39 (m, 5H, Ph).	40.5 ($\underline{C}H_2$CH=CH_2), 44.3 (C_4), 51.6 (Ph$\underline{C}H_2$N) 55.6, 55.8, 56.0 (4 x OCH_3), 59.5 (C_1), 64.5 (C_3), 108.7, 110.6, 111.2, 111.6, 121.4 (C_{arom}-H), 126.9, 128.2, 128.8 ($\underline{PhC}_{arom}$-H), 116.7 (CH=$\underline{C}H_2$), 126.9, 127.1, 129.8, 139.4 (C_{4a}, C_{8a}, $C_{1'}$, $\underline{PhC}_{arom}$-C), 137.1 ($\underline{C}$H=CH_2), 147.2, 147.7, 148.1, 148.6 (C_{arom}-O)
6e[b]	2.69 (dd, 1H, J_{AB} = 16.0, J_{AX} = 4.7, C$\underline{H_A}H_BCO_2CH_3$), 3.08 (dd, 1H, J_{AB} = 16.0, J_{AX} = 8.5, CH$_A\underline{H_B}CO_2CH_3$), 3.38-3.48 (m, 3H, 2 x H_1 and H_4), 3.54 (s, 2H, PhC$\underline{H_2}$N), 3.62 (s, 3H, $CO_2\underline{C}H_3$), 3.68 (s, 3H, OCH_3), 3.79-3.82 (m, 1H, H_3), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.48 (s, 1H, H_8), 6.58-6.62 (m, 2H, $H_{2'}$, $H_{6'}$), 6.69 (s, 1H, H_5), 6.75 (d, 1H, J_o = 8.7, $H_{5'}$), 7.25-7.40 (m, 5H, Ph).	41.1 (C_4), 41.9 ($\underline{C}H_2CO_2CH_3$), 50.7 (Ph$\underline{C}H_2$N), 51.5 ($CO_2\underline{C}H_3$), 55.6, 55.7, 55.8, 55.9 (4 x OCH_3), 59.2 (C_1), 65.4 (C_3), 108.8, 110.6, 110.8, 111.8, 121.1 (C_{arom}-H), 127.0, 128.3, 128.8 ($\underline{PhC}_{arom}$-H), 127.1, 128.92, 130.8, 139.1 (C_{4a}, C_{8a}, $C_{1'}$, $\underline{PhC}_{arom}$-C), 147.5, 147.8, 148.1, 148.4 (C_{arom}-O), 173.2 (C=O).

[a] [b] IR (KBr) cm^{-1}: 1730 (C=O, ester). # interchangeable assignments.

With amine **3e** the desired tetrahydroisoquinoline **6e** (33 %) (Tables 2 and 6) was obtained along with the corresponding 4-carbomethoxymethyl substituted tetrahydroisoquinoline (21 %), as a white solid of mp 105-106°C (MeOH).

Anal.: Found C 70.76; H 6.37; N 2.74. $C_{28}H_{31}NO_6$ requires: C 70.42; H 6.54; N 2.93.

IR: ν = 3550-3000 (O-H), 1730 (C=O) cm^{-1}.

^1H NMR: δ = 3.03 (dd, 1H, J_{AB} = 16.8, J_{AX} = 2.4, $C\underline{H}_AH_BCO_2H$), 3.23 (dd, 1H, J_{AB} = 16.8, J_{AX} = 5.7, $CH_A\underline{H}_BCO_2H$), 3.33-3.34 (m, 1H, H_4), 3.36-3.53 (m, 2H, H_{1A} and $PhC\underline{H}_AH_BN$), 3.64 (s, 3H, OCH_3), 3.73 (d, 1H, J = 15.4, H_{1B}),# 3.80 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.92 (d, 1H, J = 12.8, $PhCH_A\underline{H}_BN$),# 4.21 (br s, 1H, H_3), 6.45 (s, 1H, H_8), 6.56 (d, J_m = 2.0, $H_{2'}$), 6.62 (dd, J_o = 8.2, J_m = 2.0, $H_{6'}$), 6.72 (s, 1H, H_5), 6.80 (d, J_o = 8.2, $H_{5'}$), 7.27-7.40 (m, 5H, Ph) (# interchangeable assignments).

^{13}C NMR: δ = 39.8 (C_4), 44.9 ($\underline{C}H_2CO_2H$), 48.0 ($Ph\underline{C}H_2N$), 55.5, 55.7, 55.8, 55.4 (4 x OCH_3), 58.8 (C_1), 65.9 (C_3), 108.7, 110.8, 112.0, 121.5 (C_{arom}-H), 128.1, 128.7, 129.6 ($\underline{Ph}C_{arom}$-H), 124.2, 126.2, 127.3, 134.5 (C_{4a}, C_{8a}, $C_{1'}$, $\underline{Ph}C_{arom}$-C), 148.1, 148.6, 149.0 (C_{arom}-O), 174.0 (C=O).

This procedure using amines **4a-e** (1 mmol) gave the corresponding 3,4-*cis*-tetrahydroisoquinolines **7a-e** (Table 2). Only spectral data of **6a-e** are reported, because those of **7** showed no significant differences

*N-benzyl-3,4-disubstituted isoquinolinium salts **8a-e**; General Procedure:*

To a stirred solution of enamides **5a-e** (1.1 mmol) in dry CH_3CN (50 mL), freshly distilled $POCl_3$ (9 mmol) was added slowly at r.t. After the addition was complete, the solution was refluxed till total consumption of the starting material (TLC monitoring). The mixture was cooled to r.t., the solvent removed under reduced pressure, and the residue treated with 10% HCl (50 mL). The resulting suspension was extracted with CH_2Cl_2 (3 x 30 mL); the combined organic extracts were washed with H_2O (30 mL), dried (Na_2SO_4), and concentrated to give a pale yellow oil. Purification by column chromatography on silica gel ($MeOH/CH_2Cl_2$) gave the isoquinolinium salts **8a-e** (Tables 2 and 7).

With enamide **5f** the 1-(3,4-dimethoxybenzylidene)-6,7-dimethoxyisochroman was obtained (yield 50%) as a white solid of mp 169-170°C (MeOH).

Anal.: Found: C 70.33; H 6.62. $C_{20}H_{22}O_5$ requires C 70.16; H 6.48.

IR: ν = 1230 (C-O) cm^{-1}.

^1H NMR: δ = 2.87 (t, 2H, J = 5.5, H_4), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.24 (t, 2H, J = 5.5, H_3), 5.90 (s, 1H, C=C$\underline{H}$Ar), 6.59 (s, 1H, H_5), 6.82 (d, 1H, J = 8.4, $H_{5'}$), 7.10 (s, 1H, H_8), 7.24 (dd, 1H, J = 8.4, J = 1.7, $H_{6'}$), 7.39 (d, J = 1.7, $H_{2'}$).

^{13}C NMR: δ = 29.1 (C_4), 55.7, 55.8, 55.9, 56.1 (4 x OCH_3), 64.9 (C_3), 101.4 (C=$\underline{C}$H-Ar), 106.8, 110.6, 111.1, 111.7, 121.2 (C_{arom}-H), 123.0, 126.7, 129.9 (C_{4a}, C_{8a}, $C_{1'}$), 147.0, 148.0, 148.5, 148.8, 149.1 (C_1, C_{arom}-O).

*N-benzyl-6,12-dimethyl-2,3,8,9-tetramethoxybenzo[c]phenanthridinium chloride **9**:*

The isoquinolinium salt **8d** (120 mg, 0.24 mmol) in PPA (5 mL) was stirred for 2h at r.t. After completion (TLC monitoring), water (15 mL) was added to the mixture and extracted with CH_2Cl_2 (3 x 20 mL); the combined organic extracts were washed with HCl (30 ml of 2M HCl), brine (3 x 30 mL), dried (Na_2SO_4), and evaporated under reduced pressure. Purification by column chromatography on silica gel using CH_2Cl_2 to CH_2Cl_2: MeOH 5% afforded **9** as an oil (60 mg, 50%).

Anal.: Found C 71.52; H 6.45; N 2.65. $C_{30}H_{32}ClNO_4$ requires C 71.21; H 6.37; N 2.77.

^1H NMR: δ = 1.41 (d, 3H, J = 6.6, $C\underline{H}_3C_{12}$), 3.10-3.32 (m, 3H, 2 x H_{11} and H_{12}), 3.70 (br s, 3H, $C\underline{H}_3C_6$), 3.94 (s, 6H, 2 x OCH_3), 4.04 (s, 3H, OCH_3), 4.16 (s, 3H, OCH_3), 6.51-6.95 (m, 4H, $PhC\underline{H}_2$ and H_{arom}), 6.84 (s, 1H, H_1), 7.18-7.28 (m, 3H, H_{arom}), 7.33 (s, 1H, H_{10}), 7.44 (s, 1H, H_4), 7.72 (s, 1H, H_7).

^{13}C NMR: δ = 19.3 ($\underline{C}H_3C_6$ and $\underline{C}H_3C_{12}$), 31.5 (C_{12}), 32.8 (C_{11}), 55.9, 56.5, 56.9 (4 x OCH_3), 60.7 (Ph$\underline{C}H_2$N), 101.7, 105.8, 108.2, 112.5 (C_{arom}-H), 125.62, 128.1, 129.3 (Ph$\underline{C}_{arom}$-H), 122.9, 133.8, 135.9, 136.7, 142.1 (C_{1a}, C_{4a}, C_{6a}, C_{10a}, C_{13}, Ph$\underline{C}_{arom}$-C), 147.8, 150.6, 152.1 (C_{arom}-O), 156.01, 157.6 (C_6, C_{14}).

MS (FAB): *m/z* (%): 472 (7), 471 (31), 470 (M^+, 100), 468 (8), 456 (7), 380 (14), 379 (30), 378 (15), 365 (6), 364 (15), 350 (5), 348 (6), 177 (8), 133 (14), 109 (20), 93 (13).

Table 7. Spectral Data for Isoquinolinium Salts **8.**

Compound	^{1}H-NMR δ, J (Hz)	^{13}C-NMR δ
8a	3.28 (s, 3H, OCH_3), 3.68 (br s, 3H, $C\underline{H}_3C_1$), 3.90 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 4.13 (s, 3H, OCH_3), 6.12 (s, 2H, Ph$C\underline{H}_2$N), 6.78-7.28 (m, 8H, H_{arom}), 7.44 (s, 1H, H_5), 7.53 (s, 1H, H_4), 7.92 (s, 1H, H_8).	18.9 ($\underline{C}H_3C_1$), 55.9, 56.2, 56.7, 57.3 (4 x OCH_3), 58.0 (Ph$\underline{C}H_2$N), 105.4, 106.6, 111.0, 112.6, 122.2, 124.0 (C_{arom}-H, C_4), 125.4, 128.2, 129.3 (Ph$\underline{C}_{arom}$-H), 123.7, 125.6, 134.6, 135.5 (C_{4a}, C_{8a}, $C_{1'}$, Ph$\underline{C}_{arom}$-C), 146.3, 148.33, 150.5, 152.9 (C_{arom}-O), 156.2, 157.8 (C_1, C_3).
8b[a]	2.35 (s, 3H, $C\underline{H}_3C_4$), 3.25 (s, 3H, OCH_3), 3.49 (br s, 3H, $C\underline{H}_3C_1$), 3.82 (s, 3H, OCH_3), 4.09 (s, 3H, OCH_3), 5.79 (d, 2H, J_{AB} = 17.4, PhC$\underline{H}_A$CH_BN), 5.96 (d, 1H, J_{AB} = 17.4, PhCH_AC$\underline{H}_B$N), 6.66-6.84 (m, 5H, Ph), 7.17-7.19 (m, 3H, H_{arom}), 7.28 (s, 1H, H_5), 7.66 (s, 1H, H_8).	16.9 ($\underline{C}H_3C_4$), 18.9 ($\underline{C}H_3C_1$), 55.7, 56.7, 56.8 (4 x OCH_3), 58.5 (Ph$\underline{C}H_2$N), 103.0, 106.5, 111.2, 112.1, 121.9 (C_{arom}-H), 124.9, 127.9, 129.0 (Ph$\underline{C}_{arom}$-H), 123.1, 124.6, 129.7, 134.1, 135.0 (C_4, C_{4a}, C_{8a}, $C_{1'}$, Ph$\underline{C}_{arom}$-C), 143.7, 148.9, 150.0, 152.3 (C_{arom}-O), 154.4, 157.6 (C_1, C_3).
8c[b]	1.16 (t, 3H, J = 7.4, $C\underline{H}_3CH_2$), 2.12-2.86 (m, 2H, $CH_3C\underline{H}_2$), 3.32 (s, 3H, OCH_3), 3.55 (br s, 3H, $C\underline{H}_3C_1$), 3.86 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 4.12 (s, 3H, OCH_3), 5.84 (d, 1H, J_{AB} = 15.9, PhC$\underline{H}_A$CH_BN), 6.01 (d, 1H, J_{AB} = 15.9, PhCH_AC$\underline{H}_B$N), 6.69-6.72 (m, 3H, H_{arom}), 6.81-6.84 (m, 2H, H_{arom}), 7.21-7.24 (m, 3H, H_{arom}), 7.33 (s, 1H, H_5), 7.72 (s, 1H, H_8).	14.3 ($\underline{C}H_3CH_2$), 19.0 ($\underline{C}H_3C_1$), 23.5 ($CH_3\underline{C}H_2$), 55.8, 56.7, 56.8 (4 x OCH_3), 58.5 (Ph$\underline{C}H_2$N), 102.7, 106.9, 110.1, 112.0, 121.7 (C_{arom}-H), 125.0, 127.9, 129.0 (Ph$\underline{C}_{arom}$-H), 123.8, 124.2, 134.1, 134.3, 135.18 (C_4, C_{4a}, C_{8a}, $C_{1'}$, Ph$\underline{C}_{arom}$-C), 143.7, 148.9, 150.2, 152.4 (C_{arom}-O), 154.8, 157.6 (C_1, C_3).
8d	3.29 (s, 3H, OCH_3), 3.45-3.51 (m, 5H, $C\underline{H}_3C_1$ and $C\underline{H}_2CH{=}CH_2$), 3.82 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 4.80 (d, 1H, J_{AB} = 17.2, PhC$\underline{H}_A$CH_BN), 5.07 (d, 1H, J_{AB} = 10.4, CH=C$\underline{H}_A\underline{H}_B$), 5.77-5.86 (m, 2H, C$\underline{H}$=C$H_A\underline{H}_B$), 5.91 (d, 1H, J_{AB} = 17.2, PhCH_AC$\underline{H}_B$N), 6.67-6.70 (m, 3H, H_{arom}), 6.71-6.80 (m, 2H, H_{arom}), 7.18-7.23 (m, 3H, H_{arom}), 7.29 (s, 1H, H_5), 7.33 (s, 1H, H_8).	19.1 ($\underline{C}H_3C_1$), 34.3 ($\underline{C}H_2CH{=}CH_2$), 55.8, 56.6, 56.8 (4 x OCH_3), 58.6 (Ph$\underline{C}H_2$N), 103.6, 106.6, 110.9, 112.0, 121.6 (C_{arom}-H), 117.5 (CH=$\underline{C}H_2$), 124.9, 127.9, 129.0 (Ph$\underline{C}_{arom}$-H), 123.6, 124.0, 130.7, 134.2, 134.6 (C_4, C_{4a}, C_{8a}, $C_{1'}$, Ph$\underline{C}_{arom}$-C), 134.0 ($\underline{C}H{=}CH_2$), 144.5, 148.7, 150.2, 152.4 (C_{arom}-O), 155.3, 157.54 (C_1, C_3).
8e[c]	3.39 (s, 3H, OCH_3), 3.65 (br s, 3H, $C\underline{H}_3C_1$), 3.69 (s, 3H, $CO_2C\underline{H}_3$), 3.84-3.86 (m, 2H, $C\underline{H}_2CO_2CH_3$), 3.90 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 4.13 (s, 3H, OCH_3), 6.00-6.11 (m, 2H, Ph$C\underline{H}_2$N), 6.75-6.79 (m, 2H, H_{arom}), 6.85-6.92 (m, 3H, H_{arom}), 7.26-7.28 (m, 4H, H_{arom}), 7.73 (s, 1H, H_8).	19.1 ($\underline{C}H_3C_1$), 36.1 ($\underline{C}H_2CO_2CH_3$), 52.3 ($CO_2\underline{C}H_3$), 55.7, 56.8 (4 x OCH_3), 58.7 (Ph$\underline{C}H_2$N), 102.8, 106.8, 111.1, 112.3, 121.8 (C_{arom}-H), 124.9, 127.9, 128.9 (Ph$\underline{C}_{arom}$-H), 123.5, 126.6, 133.9, 134.6 (C_4, C_{4a}, C_{8a}, $C_{1'}$, Ph$\underline{C}_{arom}$-C), 145.2, 148.9, 150.3, 152.5 (C_{arom}-O), 155.9, 158.0 (C_1, C_3), 170.0 (C=O).

[a] MS (FAB): *m/z* (%) **8b**: 445 (32), 444 (M^+, 100), 444 (14), 430 (12), 428 (5), 414 (7), 353 (5), 353 (13), 338 (5), 299 (5), 256 (6), 208 (5), 193 (8), 166 (5), 165 (6), 151 (5), 109 (6), 108 (5). [b] MS (FAB): *m/z* (%) **8c**: 459 (37), 458 (M^+, 100), 457 (7), 455 (13), 445 (5), 444 (15), 441 (7), 428 (7), 367 (6), 366 (13), 352 (7), 336 (5), 109 (5). [c] IR (KBr) cm^{-1} **8e**: 1740 (C=O).

Financial support from the Basque Government (Project nº 9021) and the University of the Basque Country (Project nº 170.310-E102/90) is gratefully acknowledged. We thank the Ministerio de Educación y Ciencia and the Basque Government for fellowships to N.S. and T. V. We are particularly grateful to Dr. G. Tojo (University of Santiago de Compostela) and Dr. R. Pérez Afonso (University of La Laguna) for mass specttra. We also thank Petronor S. A. (Vizcaya, Spain) for kindly supplying hexane during the last years.

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(*Received in UK* 12 *October* 1993; *revised* 15 *November* 1993; *accepted* 19 *November* 1993)