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Ruthenium Dioxide in Fluoro Acid Medium III. Application to the Synthesis of Aporphinic, Homoaporphinic and Dibenzazocinic Alkaloids.[1] Studies towards the Preparation of Azafluoranthenic Skeleton.

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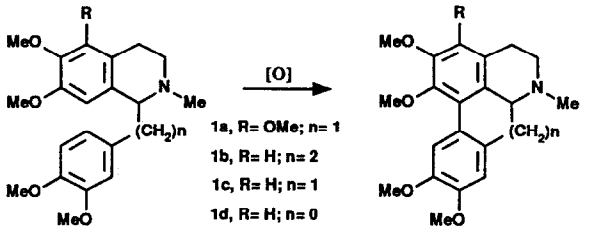
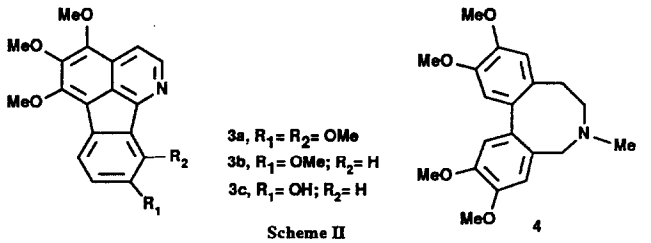
Abstract : *Intramolecular oxidative couplings of phenylalkyltetrahydroisoquinoline precursors in aporphinic and homoaporphinic alkaloids by using $RuO_2,2H_2O$ in fluoro acidic media were performed. A comparative study of our reagent with TTFA has been made with different precursors. The procedure was also extended to the synthesis of one dibenzazocinic alkaloid. Then, we attempted to synthetize the azafluoranthenic ring, using phenolic and non phenolic isoquinoline precursors.*

The successful use of $RuO_2,2H_2O$ as an oxidative biaryl coupling reagent in the lignan series[3] has stimulated efforts in our laboratory to extend the procedure to the synthesis of bridged biaryl alkaloids. We focused our attention towards the biologically active series of aporphines and homoaporphines **2a-c** (Scheme I) which are of considerable interest.[4,5] Kupchan,[6] and Taylor and McKillop[7] have proven that VOF_3 and $Tl(OCOCF_3)_3$ (TTFA) respectively, are very useful reagents for the oxidative coupling of open-chain precursors (such as **1**) into the corresponding aporphinic alkaloids and analogs. We now report the use of ruthenium dioxide in trifluoroacetic acid medium as an efficient oxidative coupling reagent for the synthesis of aporphinic alkaloids. We developed a convenient procedure for the conversion of precursors **1a-c** into aporphines as thalicsimidine **2a**[4b] and glaucine **2c**[4c] and one example of homoaporphine, homoglaucine **2b**[6c] (Scheme I). A successful and generally applicable approach to a dibenzazocine alkaloid **4**, whose phenolic derivatives are direct precursors of alkaloids of *Amaryllidaceae*[6a,8,9] has also been achieved. Finally, we will report our studies toward the synthesis of azafluoranthenic alkaloids **3a-c**[10] (Scheme II).



Scheme I 2a-d

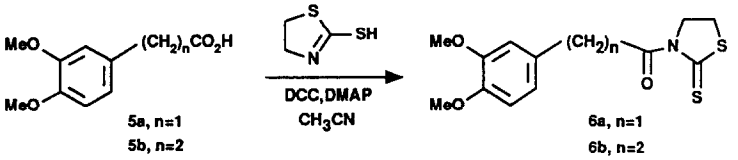


Scheme II 4

Results and discussions

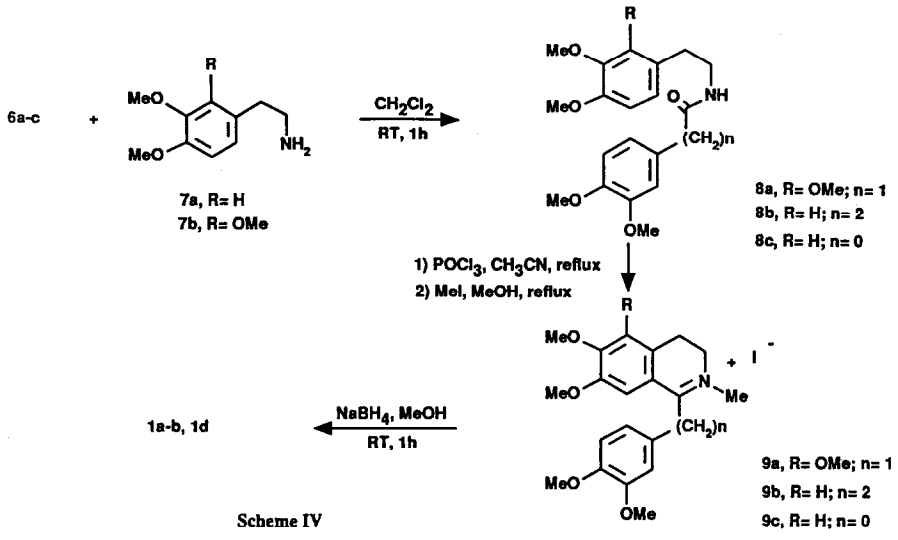
For the synthesis of the parent phenylalkyltetrahydroisoquinolines **1a-d**, as well as for azafluoranthenic alkaloid precursors, we used a well known procedure[7] which involves Bischler-Napieralski cyclisation of suitable amides. These amides are generally prepared by condensation of amines and carboxylic acids by heating them at 190°C. The low yield obtained with these procedures prompted us to examine Brown and Nagao's methods,[11] which used thiazolidinethione derivatives as acylation agents for alcohols and amines.

Thiazolidinethiones **6a-c** were obtained in good yields (80-90%) from the corresponding carboxylic acids **5a-c** by stirring for 16 hours at room temperature with 2-mercaptothiazoline (Scheme III). Addition of **6a-c** to amines **7a-b**[12] in CH_2Cl_2 at room temperature[11b] afforded, after chromatography, the corresponding amides **8a-c** in good yields (60-80%) (Scheme IV).



Scheme III

Cyclisation of amides **8a-c** was carried out with $POCl_3$ in refluxing acetonitrile. Resulting crude imines were transformed into iminium salts **9a-c** (MeI in MeOH), which were subsequently reduced with $NaBH_4$ to give amines **1a-b** in 80% and 87% overall yield respectively (from **8a** and **8b**) and cryptostyline **1d** (isolated from *Cryptostylis fulva schltr*[13]). Precursor **1c** (racemic laudanosine) is commercially available. It is noteworthy that **1b** is a natural product (homolaudanosine) which was firstly synthesised by Kupchan in 1973[6d] and was later discovered in *Dysoxylum lenticellare*.[14]



Scheme IV

Oxidative couplings of non phenolic precursors

Considering the similar behavior of TTFA and $RuO_2,2H_2O$ in fluoro acid medium,[3] we successively oxidized precursors **1a-c** with these reagents (Table I, method A and B). However, unlike in the lignans series[3] where 2 equivalents of $RuO_2,2H_2O$ were sufficient, 4 equivalents were required for the complete oxidation of phenylalkyltetrahydroisoquinolines, using analogous reaction conditions. It was also discovered that the use of ultrasound to accelerate the oxidation in the fluoro acid media[3d] only required 2 equivalents of $RuO_2,2H_2O$ (Table I, method C), affording the expected products in comparable yields.

The study clearly indicated that the oxidation was very regioselective, since no other aporphinic isomers were isolated during the reaction. This work also revealed that for such oxidative intramolecular biaryl couplings, $RuO_2,2H_2O$ in fluoro acid medium is a very effective and mild reagent.

Table I. Reaction of $RuO_2,2H_2O$ in trifluoroacetic medium with representative non phenolic precursors

Starting material	Product	Conditions[a]	Time h	Yield[b]%
1a	2a	A	12	57
1b	2b	A	2	47
1c	2c	A	8	65
1a	2a	B	12	66
1b	2b	B	8	60
1c	2c	B	24	76
1a	2a	C	16	68
1b	2b	C	12	60
1c	2c	C	22	75

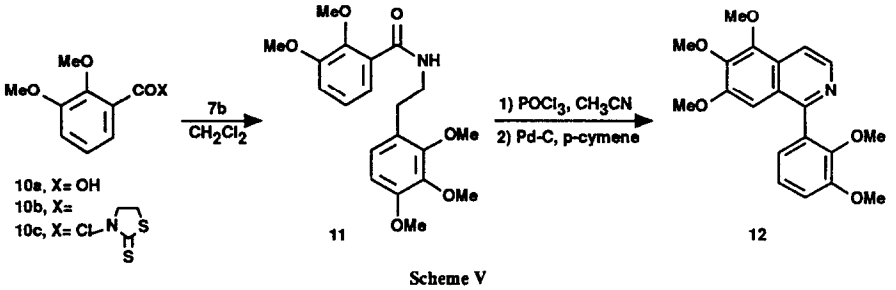
[a] A: Tl_2O_3 (0.54 eq.), CH_2Cl_2-TFA-TFAA- BF_3-Et_2O, T=18-20°C.
B: RuO_2. $2H_2O$ (4 eq.), CH_2Cl_2-TFA-TFAA- BF_3-Et_2O, T= 18-20°C.
C: RuO_2. $2H_2O$ (2eq.), CH_2Cl_2-TFA-TFAA- BF_3-Et_2O, Ultra-sound, T= 18-20°C.

[b] Yields in isolated product after chromatography on silica (CH_2Cl_2-MeOH 99:1).

Attempted synthesis of the azafluoranthenic skeleton and its derivatives

Azafluoranthenic alkaloids **3a-c** incorporate an unusual strained five membered ring in combination with an isoquinoline moiety. These alkaloids, isolated from *Abuta Imene* and *A. rufescens*,[10a,15] were used by South America indians in the preparation of curare. Synthesis in azafluoranthenic family was initiated by M.P. Cava et al.[10a,14] who used as key-step, a Pschorr ring closure of a diazonium salt. More recently, D.L. Boger et al[10b] devised an approach involving a Diels-Alder reaction to form the suitable aromatic system.

We attempted first the cyclisation of cryptostyline II **1d**, which possesses a suitable structure, as we wanted to minimize the strain of the expected five membered ring.



Scheme V

Unfortunately, numerous attempts to cyclize precursor **1d** resulted in recovered starting material under the following conditions, TTFA in CH_2Cl_2-TFA-TFAA or $RuO_2,2H_2O$ in different fluoroacid media.

Finally, we noted that, while the benzyl- and phenethyltetrahydroisoquinoline were reactive in the above oxidation conditions, phenyl analogs are not affected in this medium. Since the geometry of the nitrogen ring had no effect on the orientation of the oxidative biaryl coupling, we thought that the presence of methoxyl groups *"para"* to the future biaryl bond should influence favorably the coupling. Thus, we developed a synthesis of the fully unsaturated phenyl-1-isoquinoline **12** with the ultimate objective to prepare imeluteine **3a** (Scheme V).

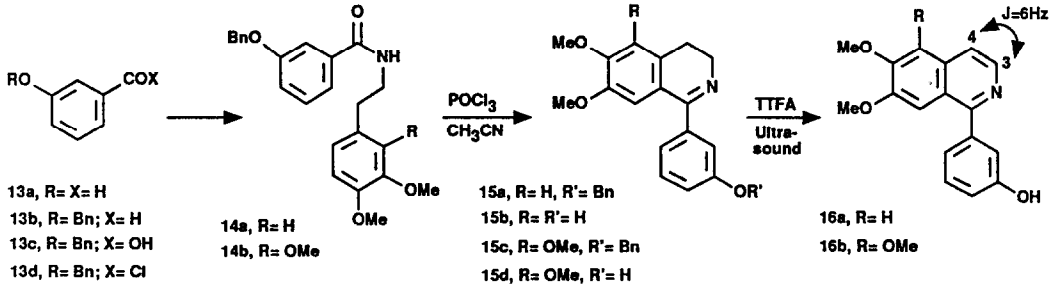
We tried to repeat the generally applicable approach to amides that we described previously, but benzoylthiazolidinethione **10b** failed to react with amine **7b** as before. Thus, we considered another approach which involved the reaction of acyl chloride **10c** (prepared from acid **10a**: $SOCl_2$-ether/pyridine) with the suitable amine,[16] affording the amide **11** in quantitative yield. **11** was then readily converted into isoquinoline **12** by the two-step sequence illustrated in scheme V (66% overall yield).[10a]

Unfortunately, as before, the different attempts to cyclize the open precursor **12b** into imeluteine **3a**, with 1.1 equivalent of TTFA or 2 eq. of $RuO_2,2H_2O$ in CH_2Cl_2-TFA-TFAA resulted in recovered starting material. We noticed that after addition of BF_3-Et_2O a deep blue coloration appeared, which reveals the formation of radical species.[17] According to the literature[6e,18] and our observations, we can formulate two hypothesis to explain these failures. Appearance of a deep coloration could be explained by the formation of a very stable charge transfer complex (CTC) which did not lead to the expected radical cation, nor consequently to the desired biaryl bond. The second possibility was the formation of the radical cation from the CTC, which was probably delocalized over the whole conjugated system. According to the low ionization potential of isoquinolines,[7] we can assume that the radical cation was certainly localized on the nitrogen ring, due to the electronegativity of the nitrogen moiety.

Attempted synthesis of the phenolic azafluoranthenic skeleton

Isolation of norrufescine **3c** by M.P. Cava et al.[15] led these authors to suggest a possible biogenetic relation between **3c** and open-chain precursors, which possess a phenolic moiety in *"para"* position (to the future biaryl bond), as previously proposed by Barton in aporphinic series.[19]

We investigated the coupling reaction of open phenolic precursors, whose synthesis was readily achieved as illustrated in scheme VI. The amides were prepared from the commercially available aldehyde **13a**, which was protected with benzyl chloride in ethanol (to give **13b** in 88% yield) and then oxidized in acid **13c** with $KMnO_4$ in an H_2O-acetone mixture.[16] Acyl chloride **13d** was prepared as before and used with the suitable amines **7a-b** to give **14a-b** in 65% and 81% overall yields respectively (from **13c**). **14a-b** were converted into imines **15a** and **15c** (with $POCl_3$ in CH_3CN), which were further deprotected using BCl_3 in CH_2Cl_2,[20] to give the corresponding phenolic imines **15b** and **15d** (Scheme VI). Attempted hydrogenolysis with palladium on charcoal resulted in an extensive decomposition of **15a** and **15c**.



Scheme VI

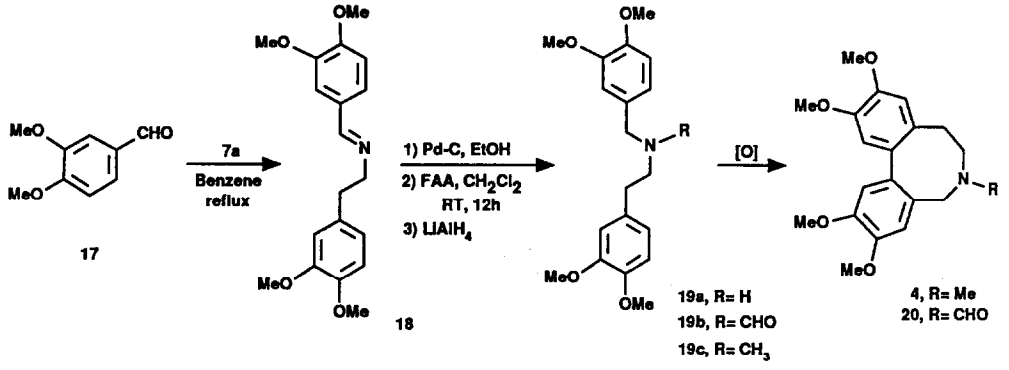
Different attempts to cyclise precursors **15b** and **15d** with 2 eq. of $RuO_2,2H_2O$ in CH_2Cl_2-TFA-TFAA were unsuccessful. However, when the reaction was carried out with 1.5 eq. of TTFA and ultra-sound assistance in the same medium, we observed the formation of a slightly more polar compound in each case. ^1H NMR spectra of these products exhibited two doublets at nearly 8 ppm (J= 6 Hz) assignable to the protons 3 and 4 of the fully aromatic structures **16a** and **16b** (Scheme VI). No traces of azafluoranthenic skeletons were detected under these conditions. Moreover, comparison of ^1H NMR spectra of **16a-b** and the one of **12** confirms the aromatization of imines **15b** and **15d**. This behaviour of TTFA had already been demonstrated by Taylor and McKillop during the oxidation of a 1,2-diphenylethane model.[7] The particular behaviour of 1-phenylisoquinoline and analogs, during the oxidation with TTFA or $RuO_2,2H_2O$ in CH_2Cl_2-TFA-TFAA was reported, during the course of this work, by McKillop et al.[21] who displayed the importance of the radical attached to the nitrogen atom ($COCF_3$ or tosyl instead of CH_3 in cryptostyline **1d**). Whatever the substituent they used, no trace of azafluoranthenic skeleton was detected during the oxidation.

Synthesis of the dibenzazocinic skeleton by oxidative coupling

We propose here a general and easy approach to dibenzazocines such as **4** (Scheme II), which are analogs of dibenzazonines and dibenzazecines alkaloids (respectively nitrogen 9 and 10 membered ring analogs), precursors of complex alkaloids of *erythrina* and *homoerythrina*.[22]

Open precursors **19b-c** were prepared respectively in 3 and 4 steps from commercially available veratraldehyde **17** and the amine **7a**, as illustrated in scheme VII. The formylation sequence was carried out with

formic-acetic anhydride (FAA) in CH_2Cl_2,[24] affording the crystalline formamide **19b** in 89% yield. Finally, reduction of **19b** by $LiAlH_4$ in ether[25] gave the corresponding tertiary amine **19c** in 50% overall yield from **17**. Oxidation of the precursor **24b** was carried out as usual by the mixture of CH_2Cl_2-TFA-TFAA with 0.54 eq. of Tl_2O_3. After 15 minutes, a complex mixture was obtained from which none of the required compound was isolated. Holton et al.[9] have simultaneously observed the same features with a phenolic derivative of **19c**. The electron rich amine probably reacts with the intermediate formed during the oxidation as suggested by Schwartz[8] and Kupchan,[6a,b] who performed their oxidation with $VOCl_3$ and VOF_3 on deactivated amine (the methyl was generally replaced by a $COCF_3$ group).



Scheme VII

Precursor **19b** was oxidized, using 1.08 eq. of TTFA (generated *in situ* as above), and gave, after 6 hours at room temperature, the biaryl **20** in 37% yield. It is interesting to note that no trace of other regioisomers were detected, but only the *"para-para"* product **20**. Encouraged by these results, we examined the reaction with RuO_2,$2H_2O$ (2 eq.) in CH_2Cl_2-TFA-TFAA. As previously described[3] the study clearly indicated that this reagent was more efficient than the conventional reagent, TTFA, as summarized in table II.

Table II. Comparative results of the oxidative coupling of precursors **19b** and **19c**.

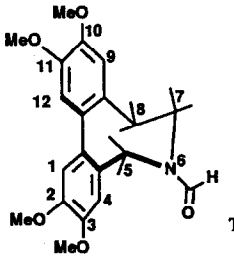
Starting material	Product	Conditions[a]	Time h	Yield[b] %
19c	4	A	0.25	0
19c	4	B	6	0
19b	20	A	6	37
19b	20	B	24	40
19b	20	C	8	45

[a] A: Tl_2O_3 (0.54 eq.), CH_2Cl_2-TFA-TFAA- BF_3-Et_2O, T=18-20°C.
B: RuO_2, $2H_2O$ (2 eq.), CH_2Cl_2-TFA-TFAA- BF_3-Et_2O, T= 18-20°C.
C: RuO_2, $2H_2O$ (2eq.), CH_2Cl_2-TFA-TFAA- BF_3-Et_2O, Ultra-sound, T= 18-20°C.

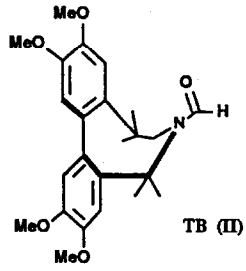
[b] Yield in isolated product after chromatography on silica (CH_2Cl_2/MeOH 99:1→97:3).

As in the bisbenzocyclooctadiene lignan series,[27] dibenzazocines show an atropoisomeric feature. We noticed, with molecular models, the possibility of a twist-boat-chair isomer I (rigid) and a more flexible one,

the twist-boat isomer II (Scheme VIII). A prominent feature in ^1H NMR spectrum of **20** is the AB system for the two protons H-5α and H-5β respectively located at 5.11 ppm and 3.15 ppm, with a coupling constant of 13.5 Hz. Another characteristic of this structure is the chemical shift of H-4 located around 7.35 ppm. This deshielding effect, having a magnitude of about 0.5-0.6 ppm (compared to the chemical shift of the other aromatic protons) is due to the position of H-4 in the plane of the carbonyl. The same effect is observed on the two protons H-5α and H-5β. So, all these observations are in favour of atropoisomer I. It is also interesting to note that the same conclusion, had been drawn in bisbenzocyclooctadiene lignan series,[27] the oxidative coupling leading in most cases to the more rigid TBC atropoisomer (called *"iso"* in lactonic BBCOD lignans).



TBC (I)



TB (II)

Scheme VIII

Conclusion

Several synthetic routes have been described that have permitted the preparation of the aporphinic ring system as well as their parent, the homoaporphinic ring. Procedures are dependent on a non phenolic oxidative coupling of precursors involving the reagent $RuO_2,2H_2O$ in fluoro acid medium. These studies indicated that this reagent should provide a new, fast, and easy way for the preparation of important families of alkaloids such as *Erythrina* and *Homoerythrina*. The easy availability of dibenzazocinic precursors offers a very promising extension of applicability of our reagent in oxidative coupling of phenolic dibenzazocine, leading to *Amaryllidaceae* alkaloids.[6,9,22]

Experimental

Most of the organic compounds used in this study were commercial products of very high purity. $RuO_2,2H_2O$, Tl_2O_3, trifluoroacetic acid and anhydride were used without purifications. Dichloromethane and acetonitrile were dried through a column of alumina and stored over 4Å molecular sieves. All glassware were dried thoroughly in a drying oven and cooled in a desiccator containing P_2O_5 and silicagel. Melting points determined on a Reichert microscope are reported in °C (uncorrected). Infrared spectra (IR) were recorded on a FT Nicolet 5DX spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM 90 or on a Brucker 500 spectrometers using as internal standard tetramethylsilane (Me_4Si), and $CDCl_3$ as solvent unless otherwise indicated. Mass spectra were obtained on a Varian Mat 311 spectrometer. Elemental analysis were performed by analysis centre of CNRS in Lyon-Vernaison. Since the reactions performed are all similar in many respects, typical reactions will be described as specific examples.

General procedure for the preparation of Phenylalkylthiazolidinethiones. N-[2-(3,4-dimethoxyphenyl)acetyl]-2-thiazolidine-2-thione (6a). Typically, to a stirred solution of 1 g (5.1 mmol) of the acid **5a** in 300 ml of dry CH_3CN, was added at room temperature (RT), 0.61 g (5.1 mmol) of 2-mercaptothiazoline and 0.025 g (0.205 mmol) of 2-dimethylaminopyridine (DMAP). Then, 1.26 g (6.1 mmol) of dicyclohexylcarbodiimide (DCC) in 10 ml of CH_3CN was added dropwise at RT. Stirring was maintained overnight and the excess of DCC was eliminated by addition of oxalic acid. The white precipitate of dicyclohexylurea (DCU) was removed by filtration and the solvent evaporated in vacuo. The residue was dissolved in CH_2Cl_2 and filtered again in order to remove all traces of DCU. Evaporation and recrystallization from ether

gave **6a** (1.4 g, 93%) as yellow prisms: mp 92-94°C (ether); IR (nujol) 1701 (C=O), 1611, 1591 (C=C) cm^{-1}; ^{1}H-NMR δ 3.27 (t, 2H, NCH_2), 3.90 (s, 6H, 2 OCH_3), 4.50- 4.80 (m, 4H, SCH_2 and CH_2O), 6.87 (s, 3H, aromatic protons). Anal. Calcd for $C_{13}H_{15}NO_3S_2$: C, 52.50; H, 5.08; O, 16.14; N, 4.71. Found: C, 52.40; H, 5.16; O, 16.93; N, 4.30.

N-[3-(3,4-dimethoxyphenyl)propionyl]-2-thiazolidine-2-thione (6b). **6b** was obtained as a yellow crystalline solid (1.23 g, 83%), recrystallized from ether: mp 101-103°C; IR (nujol) 1699 (C=O), 1607 (C=C) cm^{-1}; ^{1}H-NMR δ 2.98 (t, 2H, aliphatic protons), 3.26 (t, 2H, NCH_2), 3.62 (t, 2H, aliphatic protons), 3.92 (s, 6H, 2 OCH_3), 4.60 (t, 2H, SCH_2), 6.87 (s, 3H, aromatic protons). Anal. Calcd for $C_{14}H_{17}NO_3S_2$: C, 53.99; H, 5.50; O, 15.40; N, 4.50. Found: C, 53.96; H, 5.58; O, 15.29; N, 4.34.

N-(3,4-dimethoxybenzoyl)-2-thiazolidine-2-thione (6c). **6c** was obtained as yellow needles (6.2 g, 80%), recrystallized from CH_2Cl_2-ether: mp 137-139°C; IR (nujol) 1670 (C=O), 1593 (C=C) cm^{-1}; ^{1}H-NMR δ 3.52 (t, 2H, NCH_2), 3.97 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.58 (t, 2H, SCH_2), 6.95 (d, 1H, J= 8 Hz, H-5), 7.43 (d, 1H, J= 2 Hz, H-2), 7.58 (dd, 1H, J= 2 Hz, 8 Hz, H-6). Anal. Calcd for $C_{12}H_{13}NO_3S_2$: C, 50.86; H, 4.62; O, 16.94; N, 4.94. Found: C, 50.90; H, 4.76; O, 17.99; N, 4.92.

General procedure for the preparation of amides from Phenylalkylthiazolidinethiones. N-[2-(2,3,4-trimethoxyphenyl)ethyl]-2-(3,4-dimethoxyphenyl)acetamide (8a). Typically, to a stirred solution of 2.8 g (9.4 mmol) of **6a** in 50 ml of anhydrous CH_2Cl_2 was added dropwise at RT, 2.4 g (11.3 mmol) of amine **7b**[12] in 50 ml of dry CH_2Cl_2. Stirring was maintained for 1 h and the solution was washed with 10% HCl, saturated brine and dried ($MgSO_4$). Evaporation of the solvent gave a mixture of amide **8a** and mercaptothiazoline, which was removed by flash chromatography on silica (CH_2Cl_2-ether 8:2), affording **8a** (3 g, 82%) as white needles: mp 104-105°C [lit.[26] mp 102-103°C (Benzene-hexane)] ; IR (nujol) 3286 (NH), 1639 (C=O), 1608, 1592 (C=C) cm^{-1}; ^{1}H-NMR δ 2.72 (t, 2H, aliphatic protons), 3.30-3.60 (m, 4H, aliphatic protons), 3.85 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.88 (s, 1H, NH), 6.55-6.95 (m, 5H, aromatic protons). Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64.77; H, 6.99; O, 24.65; N, 3.60. Found: C, 64.53; H, 6.99; O, 24.87; N, 3.59.

N-[2-(3,4-dimethoxyphenyl)ethyl]-3-(3,4-dimethoxyphenyl)propionamide (8b). **8b**[6e] was obtained as a white crystalline solid (0.9 g, 75%), recrystallized from CH_2Cl_2-ether: mp 94-96°C; IR (nujol) 3339, 3307 (NH), 1638 (C=O), 1605, 1591 (C=C) cm^{-1}; ^{1}H-NMR δ 2.30-3.10 (m, 6H, aliphatic protons), 3.35-3.70 (m, 2H, aliphatic protons), 3.87 (s, 12H, 4 OCH_3), 6.60-7.00 (m, 6H, aromatic protons).

N-[2-(3,4-dimethoxyphenyl)ethyl]-3,4-dimethoxybenzamide (8c). **8c** was obtained as white needles (3.7 g, 60%), recrystallized from CH_2Cl_2-ether: mp 140-142°C; IR (nujol) 3291 (NH), 1628 (C=O), 1601 (C=C) cm^{-1}; ^{1}H-NMR δ 2.93 (t, 2H, aliphatic protons), 3.50-3.90 (m, 2H, aliphatic protons), 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.98 (s, 6H, 2 OCH_3), 6.35-6.65 (m, 1H, NH), 6.80-7.05 (m, 4H, aromatic protons), 7.25-7.75 (m, 2H, aromatic protons). Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; O, 23.16; N, 4.06. Found: C, 66.11; H, 6.51; O, 23.29; N, 3.97.

General procedure for the preparation of iminium salts from amides. 1-(3,4-dimethoxybenzyl)-3,4-dihydro-2-methyl-5,6,7-trimethoxyisoquinolinium iodide (9a). Typically, to a stirred solution of 1.5 g (3.8 mmol) of **8a** in 30 ml of dry CH_3CN was added at RT 4.7 ml (0.05 mol) of freshly distilled $POCl_3$. The mixture was refluxed for 3 h, and the solvent was evaporated in vacuo. The residue was treated with 10% HCl and the pH was adjusted to 9, using a 50% NH_4OH solution. This mixture was carefully extracted under argon with $CHCl_3$ and the resultant organic layer was washed rapidly with brine and dried over $MgSO_4$. The solvent was evaporated and the yellow residue dissolved in 70 ml of anhydrous MeOH. The solution was treated under argon with 4.6 ml (0.074 mol) of methyl iodide and refluxed for 2 h. Evaporation of the solvent in vacuo gave an amorphous yellow solid (2 g, quantitative yield). Recrystallization of an analytical sample from MeOH-ether gave iodide **9a** as yellow needles: mp 162-164°C; IR (KBr) 1636 (N^+-CH_3), 1592 (C=C) cm^{-1}; ^{1}H-NMR δ 3.25-3.45 (m, 2H, aliphatic protons), 3.88 (s, 6H, 2 CH_3), 3.95 (s, 6H, 2 CH_3), 4.03 (s, 3H, CH_3), 4.09 (s, 3H, CH_3), 4.20-4.45 (m, 2H, aliphatic protons), 4.75-5.00 (m, 2H, aliphatic protons), 6.65-7.40 (m, 4H, aromatic protons).

1-[2-(3,4-dimethoxyphenyl)ethyl]-3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium iodide (9b). **9b**[6e] was obtained as a yellow oil (4 g; quantitative yield). IR ($CHCl_3$) 1604 (C=C) cm^{-1}; ^{1}H-NMR δ 2.95-3.40 (m, 4H, aliphatic protons), 3.80 (s, 3H, CH_3), 3.87 (s, 9H, 3 CH_3), 4.05 (s, 3H, CH_3), 3.50-4.30 (m, 4H, aliphatic protons), 6.60-7.0 (m, 5H, aromatic protons).

1-(3,4-dimethoxyphenyl)-3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium iodide (9c). **9c** was obtained as yellow needles (3.9 g, 95%), recrystallized from CH_2Cl_2-ether: mp 221-223°C [lit.[28] mp 242°C (EtOH-ether)]; IR (nujol) 1628 (N^+-CH_3), 1601 (C=C) cm^{-1}; ^{1}H-NMR δ 3.40-3.60 (m, 2H, aliphatic protons), 3.68 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 4.07 (s, 6H, 2 CH_3), 4.12 (s, 3H, CH_3), 4.15-4.65 (m, 2H, aliphatic protons), 6.62 (s, 1H, H-8), 7.10-7.35 (m, 3H, aromatic protons), 7.68 (s, 1H, aromatic proton).

General procedure for the reduction of iminium salts. 1-(3,4-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydro-5,6,7-trimethoxyisoquinoline (1a). To a stirred solution of 1 g (1.94 mmol) of iodide **9a** in 50 ml of anhydrous methanol was added at 0°C, 0.59 g (0.016 mol) of powdered $NaBH_4$. The colorless solution was then stirred for 2 h at RT. After evaporation of the solvent, the residue was dissolved in water and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$) and evaporated in vacuo to give the amine **1a** (0.75 g, quantitative yield) as a pale yellow oil;[4b] IR (nujol) 1602, 1590 (C=C) cm^{-1}; ^{1}H-NMR δ 2.60 (s, 3H, NCH_3), 2.60-3.50 (m, 7H, aliphatic protons), 3.67 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.82 and 3.83 (2s, 9H, 3

OCH_3), 6.05 (s, 1H, aromatic proton), 6.50-7.0 (m, 3H, aromatic protons).

Homolaudanosine (1b).[14] **1b** was obtained as colorless needles (1.3 g, 87%), recrystallized from ether-petroleum ether: mp 77-78°C; IR (nujol) 1609, 1591 (C=C) cm^{-1}; ^{1}H-NMR δ 1.85-2.20 (m, 2H, aliphatic protons), 2.47 (s, 3H, NCH_3), 2.55-2.95 (m, 4H, aliphatic protons), 3.00-3.55 (m, 3H, aliphatic protons) 3.85 (s, 12H, 4 OCH_3), 6.65-6.95 (m, 3H, aromatic protons). Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; O, 17.23; N, 3.77. Found: C, 70.89; H, 7.85; O, 17.21; N, 3.59.

Cryptostyline II (1d). **1d** was obtained as white needles (0.9 g, 82%), recrystallized from ether-petroleum ether: mp 89-90°C [lit.[28] mp 94°C (aq. MeOH)]; IR (nujol) 1609, 1593 (C=C) cm^{-1}; ^{1}H-NMR δ 2.27 (s, 3H, NCH_3), 2.60-2.90 (m, 2H, aliphatic protons), 3.0-3.35 (m, 2H, aliphatic protons), 3.63 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.18 (s, 1H, H-1), 6.24 (s, 1H, H-8), 6.85-7.0 (m, 3H, aromatic protons). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; O, 18.63; N, 4.08. Found: C, 69.76; H, 7.45; O, 18.52; N, 3.99.

General coupling procedure (Method A, table I). Thalicsimidine (2a). To a stirred suspension of 0.134 g (0.292 mmol) of Tl_2O_3 in CH_2Cl_2 (10 ml), TFA (20 ml) and TFAA (4 ml), were added at -10°C, a solution of 0.21 g (0.54 mmol) of **2a** in CH_2Cl_2 (5 ml), then immediately BF_3-Et_2O (0.9 ml). The green mixture was stirred overnight at RT and the solvents were evaporated in vacuo. The residue was dissolved in water and the pH adjusted at 9 by addition of 10% NH_4OH. The solution was extracted with EtOAc and combined extracts were washed with brine and dried over $MgSO_4$. Evaporation of the solvent in vacuo gave a brown oil which was chromatographed on silica (CH_2Cl_2-MeOH 99:1) affording **2a** (0.12 g, 57%) as a colorless oil. An analytical sample was treated by a 65% $HClO_4$ solution, and the perchlorate was recrystallized from MeOH-ether: mp 232-235°C [lit.[4b] mp 220-225°C (MeOH-ether)] ; IR (nujol) 3224 (N-CH_3), 1609 (C=C) cm^{-1}; ^{1}H-NMR δ 2.20-3.20 (m, 7H, aliphatic protons), 2.53 (s, 3H, NCH_3), 3.70 (s, 3H, OCH_3-1), 3.87 (s, 3H, OCH_3), 3.90 (s, 6H, 2 OCH_3), 3.94 (s, 3H, OCH_3), 6.74 (s, 1H, H-8), 7.93 (s, 1H, H-11). MS m/e 385.1875 (M^+).

Homoglaucine (2b). **2b** was obtained as a colorless oil (0.14 g, 47%) which chlorhydrate was recrystallized from MeOH-ether: mp 239-242°C [lit.[6e] mp 242-244°C, dec, (MeOH-ether)]; IR ($CHCl_3$) 1599 (C=C) cm^{-1}; ^{1}H-NMR δ 2.15 (m, 1H, H-7α), 2.41 (m, 1H, H-8α), 2.45 (m, 1H, H-8β), 2.54 (m, 1H, H-7β), 2.56 (s, 3H, NCH_3), 2.81 (dd, 1H, J= 5.5 Hz, 17.4 Hz, H-4β), 3.07 (m, 1H, J= 5.8 Hz, 11.4 Hz, 17.6 Hz, H-5α), 3.13 (m, 1H, J= 6.1 Hz, 12.0 Hz, 17.3 Hz, H-4α), 3.35 (m, 1H, J= 7.4 Hz, 12.0 Hz, H-5β), 3.44 (s, 3H, OCH_3-1), 3.46 (m, 1H, H-6a), 3.86 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.70 (s, 1H, H-3), 6.77 (s, 1H, H-9) 7.08 (s, 1H, H-12).

Glaucine (2c). **2c** was obtained as colorless needles (0.13 g, 65%) recrystallized from CH_2Cl_2-ether: mp 134-136°C [lit.[6d] mp 137-139°C (MeOH-ether)]; IR (nujol) 1600 (C=C) cm^{-1}; ^{1}H-NMR δ 2.45 (m, 1H, H-5β), 2.57 (m, 1H, H-7β), 2.62 (s, 3H, NCH_3), 2.67 (m, 1H, J= 0.63 Hz, 3.2 Hz, H-4β), 3.01 (dd, 1H, J= 13.9 Hz, H-7α), 3.02 (m, 1H, J= 12.6 Hz, H-5α), 3.03 (dd, 1H, J= 3.8 Hz, 13.9 Hz, H-6a), 3.12 (m, 1H, J= 6.3 Hz, 12.6 Hz, 16.4 Hz, H-4α), 3.65 (s, 3H, OCH_3-1), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.59 (s, 1H, H-8), 6.78 (s, 1H, H-3) 8.08 (s, 1H, H-11).

General coupling procedure (Method B, table I). Thalicsimidine (2a). To a stirred suspension of 96 mg (0.72 mmol) of RuO_2,$2H_2O$ in CH_2Cl_2 (11 ml), TFA (1 ml) and TFAA (0.5 ml), were added at -10°C, a solution of 70 mg (0.18 mmol) of **1a** in CH_2Cl_2 (5 ml), then immediately BF_3-Et_2O (0.13 ml). The mixture was stirred vigorously at RT for 12 h and the solvents were evaporated in vacuo. The residue was dissolved in water and the pH adjusted at 9 by addition of 10% NH_4OH. The mixture was extracted with EtOAc and the combined extracts were treated as in method A. Flash chromatography (CH_2Cl_2-MeOH 99:1) afforded **2a** (46 mg, 66%). **2a** was found to be identical with the material prepared above (mp, IR, ^{1}H-NMR). **2b** and **2c** were prepared by the same procedure (results listed in table I) and were found to be identical with the samples prepared precedently.

General coupling procedure (Method C, table I). Thalicsimidine (2a). To a stirred suspension of 69 mg (0.52 mmol) of RuO_2,$2H_2O$ in CH_2Cl_2 (5 ml), TFA (1.5 ml) and TFAA (0.75 ml), were added at -10°C, a solution of 0.1 g (0.26 mmol) of **1a** in CH_2Cl_2 (5 ml), then immediately BF_3-Et_2O (0.15 ml). The flask was immerged in an ultra sound bath (water) thermostated at 18°C (±2°C) and the mixture was stirred for 16 h. The solvents were evaporated in vacuo and the residue was treated as precedently. Flash chromatography (CH_2Cl_2-MeOH 99:1) afforded **2a** (68 mg, 68%), identical in all respects with the materials prepared above (mp, IR, ^{1}H-NMR). **2b** and **2c** were prepared by the same procedure (results listed in table I) and were found to be identical with the samples prepared precedently.

N-(2,3-dimethoxybenzoyl) thiazolidine-2-thione (10b). **10b** was obtained as yellow needles (12.3 g, 79%), recrystallized from CH_2Cl_2-ether: mp 128-129°C; IR (nujol) 1680 (C=O), 1582 (C=C) cm^{-1}; ^{1}H-NMR δ 3.37 (t, 2H, NCH_2), 3.84 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.61 (t, 2H, SCH_2), 6.80-7.15 (m, 3H, aromatic protons).

N-[2-(2,3,4-trimethoxyphenyl)ethyl]-2,3-dimethoxybenzamide (11). To a stirred solution of 2 g (0.011 mol) of acid **10a** in 80 ml of dry ether was added a catalytic amount of anhydrous pyridine (0.1 ml). The mixture was cooled at 0°C and 1.2 ml (16.5 mmol) of freshly distilled $SOCl_2$ was added dropwise. The solution was refluxed for 3 h, then cooled and the solvent was evaporated in vacuo. The solid residue was washed with dry hexane and evaporated in order to remove the excess of $SOCl_2$. The crude acyl chloride **10c** was then dissolved in 20 ml of anhydrous ether and added at RT to a solution of 3.04 g (1.43 mmol) of amine **7b** in a

mixture of 20 ml of ether and 30 ml of a 5% NaOH solution. An efficient stirring was maintained for 1 h at room temperature and the organic layer was decanted. The aqueous layer was extracted with EtOAc and the combined extracts were washed successively with 10% HCl, saturated brine and dried over $MgSO_4$. Evaporation of the solvents afforded **11** as a pale yellow oil (4.1 g, quantitative yield). An analytical sample gave the following data: IR (nujol) 1653 (C=O), 1601 (C=C) cm^{-1}; ^{1}H-NMR (C_6D_6) δ 2.91 (t, 2H, $ArCH_2$), 3.31 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 4.76 (s, 6H, 2 OCH_3), 3.75-4.0 (m, 2H, CH_2NH), 6.45 (d, 1H, J= 8.3 Hz, H-5"), 6.66 (dd, 1H, J= 2Hz, 8.3 Hz, H-4'), 6.90 (d, 1H, J= 8.3 Hz, H-6"), 6.99 (t, 1H, J= 8.3 Hz, H-5'), 8.10 (broad s, 1H, NH), 8.23 (dd, 1H, J= 2 Hz, 8.3 Hz, H-6'). MS m/e 375.1684 (M^+). Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71; O, 25.57; N, 3.73. Found: C, 63.83; H, 7.12; O, 25.75; N, 3.60.

1-(2,3-dimethoxyphenyl)-5,6,7-trimethoxyisoquinoline (12). **12** was obtained as yellow needles (2.5 g, 66%), recrystallized from ether: mp 104-105°C; IR (nujol) 1616, 1581, 1560 (C=C) cm^{-1}; ^{1}H-NMR δ 3.54 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 6.77 (s, 1H, aromatic proton), 6.85-7.35 (m, 3H, aromatic protons), 7.83 (d, 1H, J= 6 Hz, H-4), 8.48 (d, 1H, J= 6 Hz, H-3). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59 ; H, 5.96; O, 22.51; N, 3.94. Found: C, 67.30; H, 5.90; O, 22.50; N, 3.74.

3-Benzoxybenzaldehyde (13b). To a stirred solution of 20 g (0.164 mol) of **13a** in 100 ml of 95% EtOH were added at RT, 25 g (0.18 mol) of K_2CO_3, 1 g (6.57 mmol) of NaI and dropwise 24.3 g (0.192 mol) of freshly distilled benzyl chloride. The mixture was refluxed for 4 h and the suspension was treated with 100 ml of water. The solution was concentrated in vacuo and a mixture of 100 ml of 2N NaOH and 100 g of crushed ice were added. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with saturated $NaHCO_3$, saturated brine and dried over $MgSO_4$. Evaporation of the solvent gave **13b** as white needles (30.6 g, 88%), recrystallized from ether: mp 51-52°C; IR (nujol) 1693 (C=O), 1595 (C=C) cm^{-1}; ^{1}H-NMR δ 5.1 (s, 2H, $ArCH_2O$), 7.05-7.65 (m, 9H, aromatic protons), 10.06 (s, 1H, CHO).

3-Benzoxybenzoic acid (13c). To a stirred solution of 10 g (0.047 mol) of **13b** in 400 ml of freshly distilled acetone, was added slowly at RT, 11.2 g (0.07 mol) of $KMnO_4$ in 400 ml of a 1:1 mixture of acetone and water. The mixture was stirred for 10 h at RT and the excess of $KMnO_4$ was removed by addition of a saturated solution of $NaHSO_3$. A solution of 10% HCl was then added until complete dissolution of the brown precipitate of MnO_2. 10 g (93%) of **13c** were precipitated and recrystallized from CH_2Cl_2-ether: mp 130-132°C [lit.[29] mp 134°C, (AcOH)]; IR (nujol) 1701 (C=O), 1604 (C=C) cm^{-1}; ^{1}H-NMR δ 5.12 (s, 2H, $ArCH_2O$), 7.10-8.45 (m, 9H, aromatic protons).

N-[2-(3,4-dimethoxyphenyl)ethyl]-3-benzoxybenzamide (14a). Following the procedure described for the synthesis of **11**, **14a** was obtained as white needles (1.2 g, 70%), recrystallized from MeOH-ether: mp 125-127°C; IR (nujol) 1635 (C=O), 1600 (C=C) cm^{-1}; ^{1}H-NMR δ 2.83 (t, 2H, aliphatic protons), 3.60 (t, 2H, aliphatic protons), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.04 (s, 2H, $ArCH_2O$), 6.37 (broad s, 1H, NH), 6.45 (d, 1H, J= 8.3 Hz, H-5"), 6.60-6.90 (m, 3H, aromatic protons), 6.90-7.85 (m, 8H, aromatic protons), 8.0-8.35 (m, 1H, aromatic proton). Anal. Calcd for $C_{24}H_{25}NO_3$: C, 73.64; H, 6.44; O, 16.35; N, 3.58. Found: C, 72.75; H, 6.33; O, 17.09; N, 3.57.

N-[2-(2,3,4-trimethoxyphenyl)ethyl]-3-benzoxybenzamide (14b). **14b** was obtained as white needles (8 g, 87%), recrystallized from MeOH-ether: mp 73-75°C; IR (nujol) 1645 (C=O), 1601 (C=C) cm^{-1}; ^{1}H-NMR δ 2.85 (t, 2H, aliphatic protons), 3.62 (t, 2H, aliphatic protons), 3.82 (s, 6H, 2 OCH_3), 3.92 (s, 3H, OCH_3), 5.07 (s, 2H, $ArCH_2O$), 6.59 (d, 1H, J= 9 Hz, H-5"), 6.86 (d, 1H, J= 9 Hz, H-6"), 6.95-7.75 (m, 9H, aromatic protons).

1-(3-Benzoxyphenyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (15a). Following the general procedure, **15a** was obtained as pale yellow crystals, recrystal lized from MeOH-ether: mp 116-118°C; IR (nujol) 1604, 1584, 1565 (C=C) cm^{-1}; ^{1}H-NMR δ 2.54-3.02 (broad s, 2H, aliphatic protons), 3.71 (s, 3H, OCH_3), 3.70-4.0 (m, 2H, CH_2N), 4.01 (s, 3H, OCH_3), 5.12 (s, 2H, $ArCH_2O$), 6.55-7.75 (m, 11H, aromatic protons). Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21. Found: C, 76.67; H, 6.08.

3,4-dihydro-6,7-dimethoxy-1-(3-hydroxyphenyl)isoquinoline (15b). To a stirred solution of 0.67 g (1.8 mmol) of imine **15a** in 60 ml of anhydrous CH_2Cl_2, was added dropwise at -10°C, 3.6 ml (3.6 mmol) of a 1M solution of BCl_3 in hexane. The mixture was stirred at 0-5°C for 3 h, then cooled at -10°C and neutralized with a 5% $NaHCO_3$ solution. The organic layer was decanted and the aqueous layer extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$) and the solvents were evaporated in vacuo. The brown oil was chromatographed on silica gel (CH_2Cl_2-MeOH 95:5) to give **15b** (0.4 g, 78%), as white crystals recrystallized from MeOH-ether: mp 208-210°C; IR (nujol) 1636 (C=N), 1601 (C=C), 1576 cm^{-1}; ^{1}H-NMR δ 2.70-3.05 (m, 2H, aliphatic protons), 3.71 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.60-4.0 (m, 2H, CH_2N), 6.55-7.90 (m, 7H, aromatic protons and OH).

1-(3-Benzoxyphenyl)-3,4-dihydro-5,6,7-trimethoxyisoquinoline (15c). **15c** was obtained after chromatography on silica gel (Toluene-EtOAc 92:8), as pale yellow crystals (2.6 g, 91%), recrystallized from CH_2Cl_2-ether: mp 69-71°C; IR ($CHCl_3$) 1634 (C=N), 1600 (C=C) cm^{-1}; ^{1}H-NMR δ 2.94 (m, 2H, aliphatic protons), 3.70 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.60-4.0 (m, 2H, CH_2N), 5.22 (s, 2H, $ArCH_2O$), 6.71 (s, 1H, aromatic proton), 6.95-7.80 (m, 9H, aromatic protons).

3,4-dihydro-1-(3-hydroxyphenyl)-5,6,7-trimethoxyisoquinoline (15d). **15d** was obtained as pale yellow crystals (1.4 g, 72%), recrystallized from CH_2Cl_2-ether: mp 190-192°C; IR (nujol) 1636 (C=N), 1595 (C=C), 1559 cm^{-1}; ^{1}H-NMR δ 2.55-2.90 (m, 2H, aliphatic protons), 3.68 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.93 (s,

3H, OCH_3), 3.60-4.0 (m, 2H, CH_2N), 6.62 (s, 1H, aromatic proton), 6.70-7.35 (m, 4H, aromatic protons), 8.11 (broad s, 1H, OH). MS (m/e) 313.1308 (M^+).

6,7-dimethoxy-1-(3-hydroxyphenyl)isoquinoline (16a). To a stirred suspension of 0.357 g (0.78 mmol) of Tl_2O_3 in 20 ml of anhydrous CH_2Cl_2, was added at RT, 13.1 ml of TFA and 6.5 ml of TFAA. The mixture was cooled at -10°C and 0.295 g (1.04 mmol) of **15b** in 24 ml of dry CH_2Cl_2 was added dropwise, then immediately BF_3-Et_2O (1.1 ml). The flask was immerged in an ultra sound bath (water) thermostated at 18°C (±2°C) and the mixture was stirred for 8 h. Then, the solvents were evaporated in vacuo, and the residue was dissolved in water and treated with a 5% $NaHCO_3$ solution (pH 7-8). The aqueous layer was extracted with EtOAc and the combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave a red oil which was chromatographed on silica gel (CH_2Cl_2-MeOH 98:2) affording **16a** as a yellow oil (0.16 g, 55%): IR ($CHCl_3$) 1593 (C=C) cm^{-1}; ^{1}H-NMR δ 3.78 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.65-7.40 (m, 6H, aromatic protons), 7.47 (d, 1H, J= 6 Hz, H-4), 8.22 (broad s, 1H, OH), 8.35 (d, 1H, J= 6 Hz, H-3).

1-(3-hydroxyphenyl)-5,6,7-trimethoxyisoquinoline (16b). 16b was obtained as yellow crystals (0.14 g, 67%), recrystallized from CH_2Cl_2-ether: mp 174-176°C; IR (nujol) 1590 (C=C) cm^{-1}; ^{1}H-NMR δ 3.78 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 6.60-7.40 (m, 5H, aromatic protons), 7.86 (d, 1H, J= 6 Hz, H-4), 8.42 (d, 1H, J= 6 Hz, H-3), 8.93 (broad s, 1H, OH). MS (m/e) 311.1146 (M^+).

N-[2-(3,4-dimethoxyphenyl)-ethyl]-3,4-dimethoxybenzaldimine (18). To a stirred solution of 4 g (24 mmol) of **17** in 20 ml of benzene, was added at RT, 6.1 ml (36 mmol) of the amine **7a**. The mixture was refluxed for 3 h and the benzene was evaporated in vacuo. The resultant yellow oil afforded by crystallization from ether **18** as white needles (7 g, 88%), recrystallized from MeOH-ether: mp 80-81°C [lit.[23] mp 83°C (Ether)]; IR (nujol) 1646 (C=N), 1597, 1586 (C=C) cm^{-1}; ^{1}H-NMR δ 2.94 (t, 2H, aliphatic protons), 3.75-4.0 (m, 2H, CH_2N), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.75-7.25 (m, 6H, aromatic protons), 8.04 (s, 1H, CH=N).

N-[2-(3,4-dimethoxybenzyl)(3,4-dimethoxyphenyl)]ethanamine (19a). 10 g (31 mmol) of imine **18** in solution in absolute ethanol (120 ml) were introduced in an hydrogenation flask and 1 g of 10% palladium on charcoal was added. The mixture was stirred for 12 h in a Parr apparatus under H_2 pressure (40 psi) at RT. The black catalyst was removed by filtration and the solvent evaporated in vacuo, affording 9.4 g (93%) of **19a**, as pale yellow crystals recrystallized from CH_2Cl_2-ether: mp 84-86°C [lit.[23] mp 79°C (aq EtOH)]; IR (nujol) 1607, 1590 (C=C) cm^{-1}; ^{1}H-NMR δ 2.65 (s, 1H, NH), 2.75-3.05 (m, 4H, aliphatic protons), 3.76 (s, 2H, aliphatic protons), 3.83 (s, 12H, 4 OCH_3), 6.60-6.95 (m, 6H, aromatic protons).

N-(3,4-dimethoxybenzyl)-N'-formyl-2-(3,4-dimethoxyphenyl)ethanamine (19b). To a stirred solution of 2.2 ml (58.3 mmol) of 99% formic acid, was added dropwise at 0°C, 4.5 ml (47.7 mmol) of freshly distilled acetic anhydride. The mixture was heated at 55-60°C for 1 h, then cooled at RT and diluted with 5 ml of dry CH_2Cl_2. 3 g (9.06 mmol) of amine **19a** in 13 ml of anhydrous CH_2Cl_2 was added dropwise and the mixture was stirred overnight at RT. Solvents were evaporated in vacuo to give a yellow residue which was crystallized from ether, affording **19b** (2.9 g, 89%), as white needles recrystallized from CH_2Cl_2-ether: mp 102-104°C; IR (nujol) 1659 (C=O), 1606, 1593 (C=C) cm^{-1}; ^{1}H-NMR δ 2.55-2.90 (m, 2H, aliphatic protons), 3.20-3.55 (m, 2H, aliphatic protons), 3.79 (s, 12H, 4 OCH_3), 4.15 and 4.44 (2s, 2H, aliphatic protons), 6.45-6.80 (m, 6H, aromatic protons), 7.85 and 8.19 (2s, 1H, CHO).

N-(3,4-dimethoxybenzyl)-N'-methyl-2-(3,4-dimethoxyphenyl)ethanamine (19c).[30] To a suspension of 0.9 g (23.7 mmol) of $LiAlH_4$ in 100 ml of anhydrous THF, was added dropwise at 0°C, 2 g (5.6 mmol) of the formamide **19b** in 50 ml of dry THF. The mixture was refluxed for 4 h and the excess of $LiAlH_4$ was removed by addition of EtOAc at 0°C. Lithium and aluminium salts were precipitated following the Steinhardt procedure[31] (successive addition of 0.9 g of H_2O, 0.9 g of a 15% NaOH solution and 2.7 g of H_2O) and filtered affording a colorless solution which was concentrated in vacuo. **19c** was obtained as a white solid (1.8 g, 94%) recrystallized from ether-petroleum ether: mp 70-72°C; IR (nujol) 1604, 1590 (C=C) cm^{-1}; ^{1}H-NMR δ 2.26 (s, 3H, NCH_3), 2.45-2.90 (m, 4H, aliphatic protons), 3.47 (s, 2H, aliphatic protons), 3.88 (s, 12H, 4 OCH_3), 6.70-6.95 (m, 6H, aromatic protons).

Oxidative coupling of the formyl precursor (19b)(Method A, table II). 6-formyl-5,6,7,8-tetrahydro-2,3,10,11-tetramethoxy-[c,e]dibenzazocine (20). To a stirred suspension of 0.137 g (0.3 mmol) of Tl_2O_3 in CH_2Cl_2 (8 ml), TFA (20 ml) and TFAA (4 ml), were added at -10°C, a solution of 0.2 g (0.56 mmol) of **19b** in CH_2Cl_2 (5 ml), then immediately BF_3-Et_2O (1 ml). The deep blue mixture was stirred overnight at RT and the solvents were evaporated in vacuo. The residue was dissolved in water and the pH adjusted at 9 by addition of a 10% NH_4OH solution. The solution was extracted by EtOAc and the combined extracts were washed with brine and dried over $MgSO_4$. Evaporation of the solvent in vacuo gave a brown oil which was chromatographed on silica gel (CH_2Cl_2-MeOH 99:1 → 97:3) affording **20** (74 mg, 37%), as white needles recrystallized from CH_2Cl_2-ether: mp 189-191°C; IR ($CHCl_3$) 1650 (C=O), 1597 (C=C) cm^{-1}; ^{1}H-NMR δ 2.0-3.0 (m, 4H, aliphatic protons), 3.15 (d, 1H, J= 13.5 Hz, H-5β), 3.90 (s, 6H, 2 OCH_3), 3.93 (s, 6H, 2 OCH_3), 5.11 (d, 1H, J= 13.5 Hz, H-5α), 6.73 (s, 1H, aromatic proton), 6.78 (s, 1H, aromatic proton), 6.81 (s, 1H, aromatic proton), 7.35 (s, 1H, H-4), 8.14 (s, 1H, CHO).

(20) prepared following the method B (table II). As described above, 0.1 g (0.28 mmol) of formamide **19b** were treated by a suspension of 74 mg (0.56 mmol) of RuO_2,$2H_2O$ in 4 ml of dry CH_2Cl_2, 10 ml of TFA, 5 ml of TFAA and 0.5 ml of BF_3-Et_2O. The mixture was stirred for 24 h at RT and treated as described

precedently to give **20** as white needles (40 mg, 40%) identical in many respects with the material prepared by the procedure A.

(20) prepared following the method C (table II). As described precedently, 0.1 g (0.28 mmol) of formamide **19b** were treated by a suspension of 74 mg (0.56 mmol) of $RuO_2,2H_2O$ in 4 ml of dry CH_2Cl_2, 10 ml of TFA, 5 ml of TFAA and 0.5 ml of BF_3-Et_2O. The flask was immerged in an ultra sound bath (water) thermostated at 18°C (±2°C) and the mixture was stirred for 8 h. **20** was obtained as white needles (45 mg, 45%) identical in many respects with the materials prepared before (mp, IR and ^{1}H-NMR).

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