A CONVENIENT ACCESS TO PROTOBERBERINE DERIVATIVES

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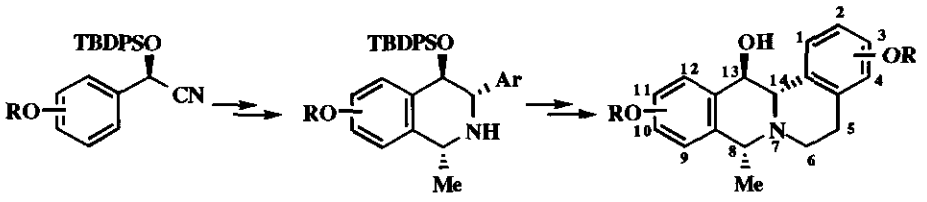
Abstract-A synthesis of protoberberine derivatives starting from (1*R**,3*S**,4*R**)-3-aryl-1-methyl-4-silyloxytetrahydroisoquinolines is presented. The influence of the substitution pattern of the aryl ring at C-3 and the effect of the derivatization of the hydroxyl group at C-4 on the final cyclization reaction is discussed.

INTRODUCTION

The isoquinoline alkaloids, protoberberines *inter alia*, are important in chemistry because of their pharmacological interest.[1] Among them, the 13-hydroxyprotoberberines have attracted our attention, as the consulted literature shows very scarce examples of naturally occurring[2] or synthetically prepared compounds with the already mentioned skeleton. In this context, Pictet-Spengler cyclization of 1-(1-hydroxy-1-phenylmethyl)tetrahydroisoquinolines[3] or transannulation of norphthalideisoquinolines[4] have been used for the synthesis of 13-α-hydroxyxylopinine and ophiocarpine respectively. On the other hand, 13-β-hydroxystylopine has been synthesized in a three-step pathway starting from protopine.[5]

In continuation of our interest in the field of isoquinoline alkaloids, we decided to apply adequately substituted 3-arylisoquinolines for the synthesis of 13-hydroxyprotoberberines. Recently,[6] we have developed a high yielding stereoselective access to 3-aryl-4-hydroxytetrahydroisoquinolines of type **2**, starting from optically active *O*-silylated cyanohydrins (**1**). The former derivatives appear to be a rather convenient starting material for the preparation of the target molecules, the 13-hydroxyprotoberberine derivatives (**3**). For this purpose, the strategy we have optimized includes the *N*-alkylation of tetrahydroisoquinolines (**2**) with bromacetaldehyd diethyl acetal (BADA) followed by intramolecular electrophilic attack to the aryl substituent at C-3 promoted by the adequate acid catalyst.[7]

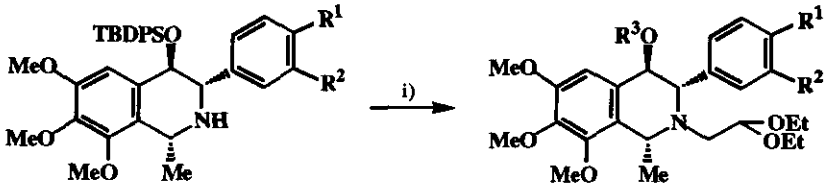


1 **2** **3**

TBDPS: ***tert*-butyldiphenylsilyl**

RESULTS AND DISCUSSION

Although the *N*-alkylated isoquinolines (**5a**) and (**5b**) were easily obtained starting from **4a** and **4b** respectively,[8] nevertheless, we observed that the subsequent cyclization process was highly influenced by the substitution of the aryl ring at C-3 and the derivatization of the hydroxy group at C-4 respectively.



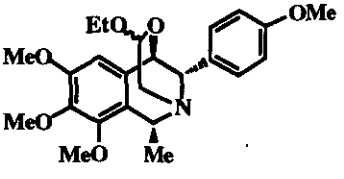
4a: R^1=MeO, R^2=H
4b: R^1=H, R^2=MeO

i) NaH, BADA, dioxane, reflux
ii) TBAF, THF, room temperature
iii) Ac_2O, TEA, DMAP, CH_2Cl_2, room temperature
iv) NaH, MeI, THF, reflux

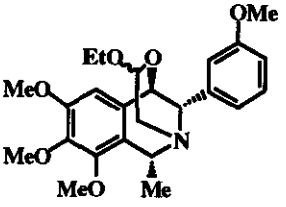
5a: R^1=MeO, R^2=H, R^3=TBDPS
5b: R^1=H, R^2=MeO, R^3=TBDPS
5c: R^1=MeO, R^2=R^3=H
5d: R^1=R^3=H, R^2=MeO
5e: R^1=H, R^2=MeO, R^3=Ac
5f: R^1=H, R^2=MeO, R^3=Me

In fact, during the preliminary assays carried out, no reaction occurred when tetrahydroisoquinolines (**5a**) and (**5b**) were submitted to cyclization conditions (6M HCl, room temperature), probably as a result of the steric hindrance due to the voluminous protecting group. On the contrary, a slow and regioselective *N*-dealkylation process took place when the reaction temperature was raised up to 60°C or, alternatively, when *p*-TsOH/dioxane was used as acid catalyst for the intended carbocyclization.[9]

Consequently, new experiments using hydroxylated isoquinolines (**5c**) and (**5d**) as starting materials were performed. In the first set of assays (6M HCl, room temperature), internal acetals (**6a**) and (**6b**), respectively, were the only compounds formed[10] as a result of typical transacetalization reactions.

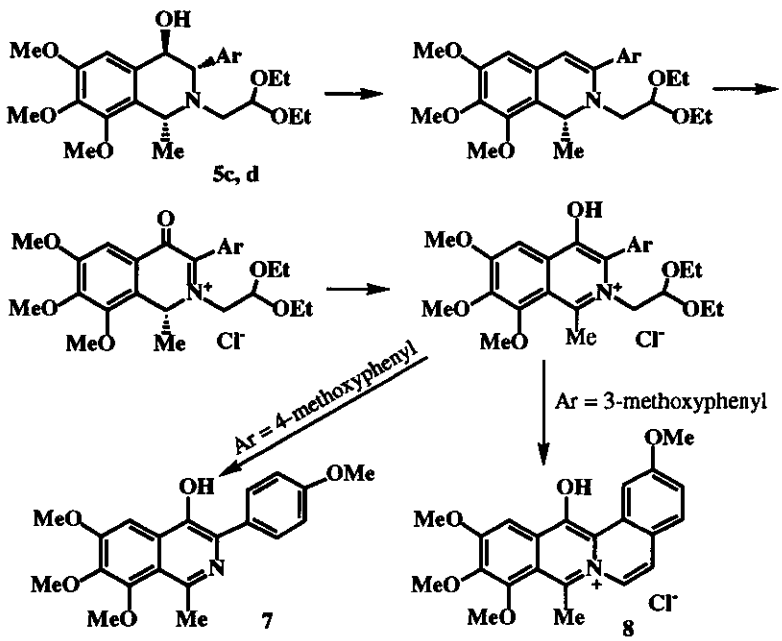


6a



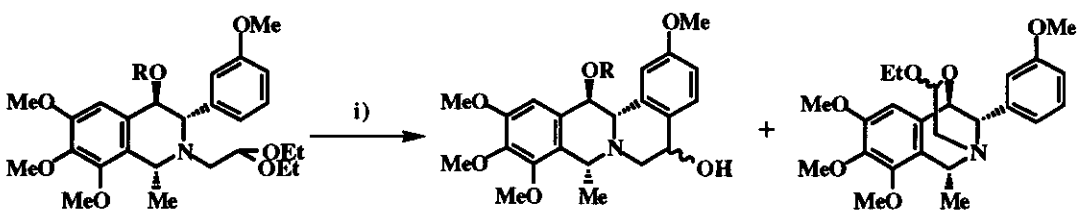
6b

On the other hand, when the reaction was run in refluxing dioxane, probably a dehydration followed by air-oxidation reaction took place affording a 4-hydroxyisoquinolinium hydrochloride, likely through formation of an α-oxoiminium salt.[11] The former intermediate, in turn, suffered an ulterior cyclization process, giving rise to a tetracyclic product (**8**), when the arilyc substituent beared the adequate activation. On the contrary, *N*-dealkylation reaction succeeded in the case of lack of proper activation in the aryl ring thus providing derivative (**7**). (Scheme I).



Scheme I

Therefore, in order to avoid the observed competitive transacetalization reaction, the behaviour of C-4 acetoxylated and methoxylated derivatives (**5e**) and (**5f**) with the adequate activation by electron withdrawing arylic substituent was studied. In the former case, operating under mild cyclization conditions (6M HCl, room temperature) a mixture of derivatives (**9a**) and (**6b**) was obtained. However, derivative (**5f**) under the same reaction conditions, provided protoberberine (**9b**) in good yield without formation of the corresponding internal acetal. Both protoberberines (**9a** and **9b**) were obtained as a mixture of two epimers at C-5 (50% de). Each epimeric derivative was isolated and fully characterized by means of the adequate NOE experiments, allowing us to identify the (5*R**,8*R**,13*R**,14*S**) derivative as the major isomer in every case (Scheme II).



5e: R=Ac
5f: R=Me

9a: R=H
9b: R=Me

6b

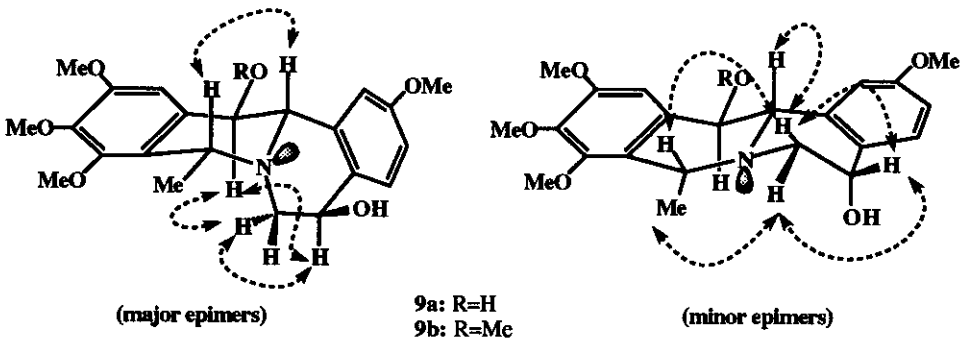
i) 6M HCl, room temperature

Scheme II

In the following figure, it has been represented with dashed arrows a selection of different observed NOE in order to identify not only the relative configuration of C-5 in each diastereomer (**9**) but also the conformation

adopted by the quinolizidinic system. Thus, the absence of NOE between either H-8 or H-14 and the methylenic protons at C-6 suggests a *cis* type fusion for the quinolizidinic system in the major epimers (**9a**) and (**9b**). On the other hand, a *trans* type fusion for the heterocyclic system, in the minor epimers (**9a**) and (**9b**), can be proposed from the observation of a NOE between H-8 and both H-6 along with the absence of NOE between H-13 and the protons in the quinolizidinic system.

The same kind of experiments were performed to determine the relative configuration at C-5. A (5*R**,8*R**,13*R**,14*S**) configuration for the major epimers (**9a**) and (**9b**) can be easily suggested because of the observed NOE between H-5 and H-13. The absence of this effect between the latter protons and the observed NOE between H-5 and both methylenic protons in C-6 are in good agreement with a (5*S**,8*R**,13*R**,14*S**) relative configuration for the minor epimers (**9a**) and (**9b**) respectively.



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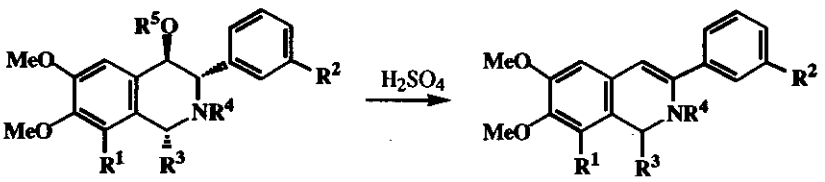
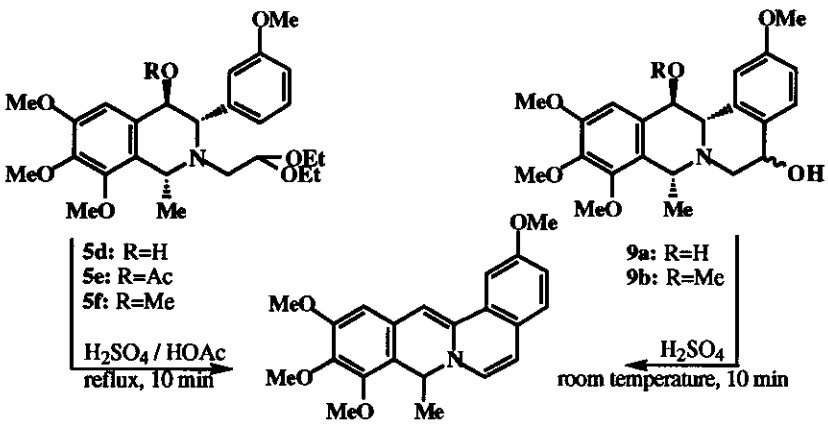


5 / 10	R1	R2	R3	R4	R5
g	H	H	Me	CH_2COOMe	TBDPS
h	MeO	H	H	CH_2COOMe	TBDPS
i	H	H	Me	Me	H
j	MeO	MeO	Me	Me	H

Facing these results, we decided to examine the behaviour of other tetrahydroisoquinolines with a different substitution pattern under carbocyclization conditions using H_2SO_4 as acid catalyst[12] in the hope that the

dehydration ability of this reagent would afford a planar 8*H*-berberinic structure, thus exhibiting an interesting shape for pharmacological studies.[13] In fact, we were able to transform the series of *N*-alkyl-4-alkoxytetrahydroisoquinolines (**5**) shown below into the corresponding 1,2-dihydroisoquinolines (**10**) almost quantitatively by direct treatment with H_2SO_4.[14] No further carbocyclization reactions were observed.

Finally, when we applied other reported annulation conditions,[15] isoquinolines (**5d-f**) were quantitatively transformed in a few minutes to the expected 8*H*-berberine (**11**), which in turn was also obtained from protoberberines (**9a**) and (**9b**) by treatment with H_2SO_4.



11

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 or $CHCl_3$ solutions (oils) and peaks (ν) are reported in cm^{-1}. Nmr spectra were recorded on a Bruker ACE-250 apparatus at 20-25°C running at 250 MHz for ^1H and 62.8 MHz for ^{13}C in $CHCl_3$ (7.26 ppm) as an internal reference in $CDCl_3$ solutions. Chemical shifts (δ) are given in ppm; multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) or dd (doublet of doublets). Coupling constants (J) are reported in hertz (Hz). ^1H-{^1H} NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet in $CDCl_3$ solvent.[16] Assignment of individual ^{13}C resonances were supported by DEPT experiments.[17] Combustion analyses were performed with a Perkin-Elmer 2400 CHN apparatus and are in good agreement with given structure. Mass spectra (EI) were obtained on a MS902 model Kratros apparatus. Data are reported in the form m/z (intensity relative to base = 100). Tetrahydrofuran (THF) was freshly distilled from benzophenone-sodium ketyl. All other solvents used were technical grade and purified according to standard procedures.[18] Thin layer chromatography was performed on silica gel 60 F_{254} plates and visualized by uv light (254 nm) or Dragendorff's reagent.[19] Flash column chromatography[20] was performed on Merck kieselgel 60 (230-400 mesh ASTM). The reactions were carried out under an atmosphere of dry, deoxygenated argon unless otherwise indicated. All transfers of liquid solutions and solvents were performed by syringe techniques or *via canula*.[21] All oily products were purified by HPLC on a Waters 600E apparatus with a Porasil 10M 19 mm x 15 cm column.

Synthesis of 3-aryl-tetrahydroisoquinolines (5a) and (5b).

General procedure. A mixture of tetrahydroisoquinoline (**4**) (0.59 g, 1 mmol) and 0.12 g (3 mmol) of NaH (60% suspension in oil) in 40 ml of dioxane was refluxed for 4 h, then cooled to room temperature, BADA (1.18 g, 6 mmol) was added and the new solution was heated under reflux during 4 d. After cooling with an ice bath, 25 ml of water were slowly added and the mixture was extracted with CH_2Cl_2 (3x20 ml). Work up gave an oil which was purified by flash column chromatography using hexane/ethyl acetate (7:3) as eluent.

(*1R*,3S*,4R)-4-(*tert*-Butyldiphenylsilyloxy)-*N*-(2,2-diethoxyethyl)-6,7,8-trimethoxy-3-(4-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (5a).**

Following the general procedure, isoquinoline (**5a**) was obtained from **4a** as a colorless oil (0.53 g, 75%). Pmr: δ 7.55-7.20 (m, 12H, Harom); 6.74 (d, J=8.5, 2H, H-3', H-5'); 6.59 (s, 1H, H-5); 5.09 (d, J=8.4, 1H, H-4); 4.40 (m, 1H, $\underline{H}C(OEt)_2$); 4.36 (q, J=6.9, 1H, H-1); 3.86 (s, 3H, OCH_3); 3.79 (s, 6H, $2xOCH_3$); 3.68 (d, J=8.4, 1H, H-3); 3.66-3.56 (m, 1H, $OC\underline{H}CH_3$); 3.41 (m, 3H, $3xOC\underline{H}CH_3$); 3.26 (s, 3H, OCH_3); 2.70 (m, 2H, NCH_2); 1.20-1.13 (m, 9H, $3xCH_3$); 0.84 (s, 9H, $(CH_3)_3$). Cmr: δ 158.8, 151.2, 148.7, 140.3 (qCarom); 135.8, 135.7 (tCarom); 134.8, 134.4, 134.0, 133.0 (qCarom); 130.7, 129.4, 129.2, 127.3 (tCarom); 125.0 (qCarom); 113.3 (tCarom); 105.1, 102.8 (C-5, $H\underline{C}(OEt)_2$); 73.2 (C-4); 62.2, 61.4 ($2xOCH_2$); 60.9, 60.5 ($2xOCH_3$); 58.4 (NCH_2); 55.3, 55.2 ($2xOCH_3$); 52.0 (C-1); 26.7 ($C(\underline{C}H_3)_3$); 25.2 ($C_1\underline{C}H_3$); 19.5 ($\underline{C}(CH_3)_3$); 15.2 ($2xOCH_2\underline{C}H_3$). Ms: (m/z, %): 698 (M^+-15, 35); 610 (65); 462 (76); 301 (30); 199 (42); 197 (39); 135 (100); 75 (56). Anal. Calcd for $C_{42}H_{55}NO_7Si$: C, 70.65; H, 7.76; N, 1.96. Found: C, 70.70; H, 7.68; N, 1.90.

(*1R*,3S*,4R)-4-(*tert*-Butyldiphenylsilyloxy)-*N*-(2,2-diethoxyethyl)-6,7,8-trimethoxy-3-(3-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (5b).**

Following the general procedure, isoquinoline (**5b**) was obtained from **4b** as a colourless oil (0.53 g, 75 %). Pmr: δ 7.58-6.73 (m, 14H, Harom); 6.56 (s, 1H, H-5); 5.11 (d, J=8.6, 1H, H-4); 4.41 (t, J=5.2, 1H, $\underline{H}C(OEt)_2$); 4.34 (q, J=6.9, 1H, H-1); 3.85 (s, 3H, OCH_3); 3.79 (s, 3H, OCH_3); 3.74 (s, 3H, OCH_3); 3.70 (d, J=8.6, 1H, H-3); 3.66-3.25 (m, 4H, $2xOCH_2$); 3.22 (s, 3H, OCH_3); 2.71 (d, J=5.2, 2H, NCH_2);1.16 (t, J=7.0, 3H, $OCH_2C\underline{H}_3$); 1.15 (d, J=6.9, 3H, C_1CH_3); 1.05 (t, J=7.0, 3H, $OCH_2C\underline{H}_3$); 0.82 (s, 9H, $(CH_3)_3$). Cmr: δ 159.3, 151.1, 148.5, 144.4, 140.2 (qCarom); 135.7 (tCarom); 134.3, 133.9, 132.7 (qCarom); 129.4, 129.1, 128.7, 127.2, 122.3, 115.1, 112.7 (tCarom); 104.9, 102.7 (C-5, $H\underline{C}(OEt)_2$); 73.2, 71.9 (C-4, C-3); 62.2, 61.2 ($2xOCH_2$); 60.8, 60.4 ($2xOCH_3$); 58.4 (NCH_2); 55.2, 54.8 ($2xOCH_3$); 51.9 (C-1); 26.5 ($C(\underline{C}H_3)_3$); 25.2 ($C_1\underline{C}H_3$); 19.4 ($\underline{C}(CH_3)_3$); 15.1 (2x $OCH_2\underline{C}H_3$). Anal. Calcd for $C_{42}H_{55}NO_7Si$: C, 70.65; H, 7.76; N, 1.96. Found: C, 70.72; H, 7.72; N, 1.95.

Synthesis of 3-aryl-4-hydroxytetrahydroisoquinolines (5c) and (5d).

General procedure. A solution of silyl derivative (**5a**) or (**5b**) (0.71 g, 1 mmol) in THF (25 ml) was treated with $^nBu_4NF$ (4 ml of a 1M solution in THF, 4 mmol). After stirring overnight at room temperature the solution was diluted with 10 ml of water and extracted with CH_2Cl_2 (3x20 ml) and dried over anhydrous sodium sulfate. After evaporation of the solvent under vacuum, the resulting crude was purified by flash column chromatography using hexane/ethyl acetate (6:4) as eluent affording the desilylated tetrahydroisoquinolines (**5c**) and (**5d**).

(*1R*,3S*,4R)-*N*-(2,2-Diethoxyethyl)-4-hydroxy-6,7,8-trimethoxy-3-(4-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (5c).**

Following the general procedure, derivative (**5c**) was obtained from **5a** as a colourless oil (0.40 g, 85%). Ir ($CHCl_3$): ν 3580-3300 (OH st.); 1130 (COC st.). Pmr: δ 7.35 (d, J=8.6, 2H, H-2', H-6'); 6.93 (s, 1H, H-5); 6.88 (d, J=8.6, 2H, H-3', H-5'); 4.59 (dd, J=8.2, 3.6, 1H, H-4); 4.49 (t, J=5.2, 1H, C<u>H</u>$(OEt)_2$); 4.40 (q, J=6.7, 1H, H-1); 3.91 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.63-3.30 (m, 5H, H-3, 2xOCH_2); 3.57 (d, J=8.2, 1H, H-3); 2.77 (d, J=5.2, 2H, NCH_2); 1.23 (d, J=6.7, 3H, C_1CH_3); 1.14 (t, J=7.1, 3H, $OCH_2C\underline{H}_3$); 1.07 (t, J=7.1, 3H, $OCH_2C\underline{H}_3$).Cmr: δ 158.9, 151.8, 148.9, 140.5, 133.3, 133.2 (qCarom); 129.8 (tCarom); 125.0 (qCarom); 113.5 (tCarom); 102.8, 101.8 (C-5, H<u>C</u>$(OEt)_2$); 70.9 (C-4); 69.3 (C-3); 62.1, 61.3 (2xOCH_2); 60.6, 60.4 (2xOCH_3); 55.9 (NCH_2); 55.6, 54.9 (2xOCH_3); 52.2 (C-1); 24.4 ($C_1\underline{C}H_3$); 15.0, 14.9 (2x$OCH_2\underline{C}H_3$). Anal. Calcd for $C_{26}H_{37}NO_7$: C, 65.66; H, 7.84; N, 2.94. Found: C, 65.72; H, 7.85; N, 2.96.

(*1R*,3S*,4R)-*N*-(2,2-Diethoxyethyl)-4-hydroxy-6,7,8-trimethoxy-3-(3-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (5d).**

Following the general procedure, derivative (**5d**) was obtained from **5b** as a colourless oil (0.41 g, 86%). mp: 144-145°C (hydrochloride, HCl-dioxane). Ir ($CHCl_3$): ν 3600-3500 (OH st.); 1130 (COC st.). Pmr: δ 7.27 (dd, J=7.6, 7.6, 1H, H-5'); 7.04-7.00 (m, 2H, Harom); 6.95 (s, 1H, H-5); 6.85 (dd, J=7.0, 1.2, 1H, Harom); 4.61 (d, J=8.4, 1H, H-4); 4.51 (t, J=5.2, 1H, C<u>H</u>$(OEt)_2$); 4.42 (q, J=6.6, 1H, H-1); 3.92 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.58 (d, J=8.4, 1H, H-3); 3.61-3.34 (m, 4H, 2xOCH_2); 2.78 (d, J=5.2, 2H, NCH_2); 1.26 (d, J=6.6, 3H, C_1CH_3); 1.14 (t, J=7.0, 3H, $OCH_2C\underline{H}_3$); 1.07 (t, J=7.0, 3H, $OCH_2C\underline{H}_3$). Cmr: δ 159.6, 151.0, 149.0, 143.4, 140.7, 133.1 (qCarom); 129.2 (tCarom); 125.0 (qCarom); 121.3, 114.4, 112.9 (tCarom); 102.8, 101.9 (tCarom, H<u>C</u>$(OEt)_2$); 70.9, 70.8 (C-4, C-3); 62.2, 61.4 (2xOCH_2); 60.7, 60.4 (2xOCH_3); 56.3 (NCH_2); 55.7, 54.9 (2xOCH_3); 52.2 (C-1); 24.7 ($C_1\underline{C}H_3$); 15.1, 15.0 (2x$OCH_2\underline{C}H_3$). Anal. Calcd for $C_{26}H_{37}NO_7$: C, 65.66; H, 7.84; N, 2.94. Found: C, 65.76; H, 7.81; N, 2.89.

(1*R,3*S**,4*R**)-4-Acetoxy-*N*-(2,2-diethoxyethyl)-6,7,8-trimethoxy-3-(3-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (5e).**

A solution of tetrahydroisoquinoline (**5d**) (0.47 g, 1 mmol) in 25 ml of CH_2Cl_2 was stirred at room temperature. Catalytic amounts of DMAP and TEA (0.15 g, 1.5 mmol) were added. When the solution was cooled on an ice bath, Ac_2O (0.13 g, 1.25 mmol) was added and the stirring was continued overnight at room temperature. The crude was poured into ice and extracted with CH_2Cl_2. After evaporation of the solvent under vacuum, the resulting oil was purified by flash column chromatography using hexane/ethyl acetate (7:3) as eluent affording a colourless oil (0.44 g, 85%) which was identified as the tetrahydroisoquinoline (**5e**). Ir ($CHCl_3$): ν 1740 (C=O st.); 1130 (COC st.). Pmr: δ 7.19 (dd, J=7.9, 7.9, 1H, H-5'); 7.01-6.97 (m, 2H, Harom); 6.79-6.75 (m, 1H, Harom); 6.47 (s, 1H, H-5); 5.99 (d, J=9.0, 1H, H-4); 4.51-4.45 (m, 2H, H-1, C<u>H</u>$(OEt)_2$); 3.91 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3); 3.79 (s, 3H, OCH_3); 3.74 (d, J=9.0, 1H, H-3); 3.63-3.30 (m, 4H, 2xOCH_2); 2.78 (d, J=5.1, 2H, NCH_2); 1.91 (s, 3H, $COCH_3$); 1.30 (d, J=6.7, 3H, C_1CH_3); 1.14 (t, J=7.0, 3H, $OCH_2C\underline{H}_3$); 1.06 (t, J=7.0, 3H, $OCH_2C\underline{H}_3$). Cmr: δ 169.5 (COO); 159.2, 151.9, 149.4, 142.6, 141.3, 129.8 (qCarom); 128.6 (tCarom); 125.9 (qCarom); 121.3, 114.4, 112.7 (tCarom); 102.7, 102.2 (C-5,

HC(OEt)$_2$); 72.2 (C-4); 67.8 (C-3); 62.3, 61.6 (2xOCH$_2$); 60.7, 60.5 (2xOCH$_3$); 56.7 (NCH$_2$); 55.8, 55.0 (2xOCH$_3$); 52.5 (C-1); 24.9 (C$_1$CH$_3$); 20.5 (COOCH$_3$); 15.1, 15.0 (2xOCH$_2$CH$_3$). Anal. Calcd for $C_{28}H_{39}NO_8$: C, 64.97; H, 7.59; N, 2.71. Found: C, 64.94; H, 7.57; N, 2.67.

(1*R,3*S**,4*R**)-*N*-(2,2-Diethoxyethyl)-4,6,7,8-tetramethoxy-3-(3-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (5f).**

A mixture of tetrahydroisoquinoline (**5d**) (0.47 g, 1 mmol) and MeI (0.71 g, 5 mmol) in 15 ml of THF was added dropwise to 0.04 g (1 mmol) of NaH (60% suspension in oil) in 25 ml of THF cooled to 0°C. After being refluxed for 6 h, the mixture was cooled with an ice bath, 25 ml of water were slowly added and the mixture was extracted with CH_2Cl_2 (3x20 ml). Standard work up gave an oil which was purified by flash column chromatography using hexane/ethyl acetate (7:3) as eluent affording tetrahydroisoquinoline (**5f**) as a colourless oil (0.45 g, 92%). Ir ($CHCl_3$): ν 1130 (COC st.). Pmr: δ 7.25 (dd, J=7.9, 7.9, 1H, H-5'); 7.13-7.09 (m, 2H, Harom); 6.85 (s, 1H, H-5); 6.84-6.80 (m, 1H, Harom); 4.48-4.42 (m, 2H, H-1, CH(OEt)$_2$); 4.16 (d, J=9.5, 1H, H-4); 3.92 (s, 3H, OCH$_3$); 3.88 (s, 3H, OCH$_3$); 3.86 (s, 3H, OCH$_3$); 3.82 (s, 3H, OCH$_3$); 3.64-3.52 (m, 2H, H-3, OCHCH$_3$); 3.43-3.26 (m, 3H, 3xOCHCH$_3$); 3.05 (s, 3H, OCH$_3$); 2.72 (d, J=5.2, 2H, NCH$_2$); 1.34 (d, J=6.8, 3H, C$_1$CH$_3$); 1.13 (t, J=7.0, 3H, OCH$_2$CH$_3$); 1.03 (t, J=7.0, 3H, OCH$_2$CH$_3$). Cmr: δ 159.4, 151.9, 149.1, 144.5, 140.7, 132.8 (qCarom); 128.7 (tCarom); 125.4 (qCarom); 121.5, 114.4, 112.5 (tCarom); 102.3, 102.2 (C-5, HC(OEt)$_2$); 81.5, 69.7 (C-4, C-3); 62.3, 61.5 (2xOCH$_2$); 60.8, 60.5, 60.0 (3xOCH$_3$); 56.8 (NCH$_2$); 55.8, 55.0 (2xOCH$_3$); 52.2 (C-1); 25.7 (C$_1$CH$_3$); 15.3, 15.2 (2x OCH$_2$CH$_3$). Anal. Calcd for $C_{27}H_{39}NO_7$: C, 66.23; H, 8.03; N, 2.86. Found: C, 66.34; H, 8.06; N, 2.83.

Synthesis of 3-Aryl-4,2-(2-ethoxyepoxyethano)tetrahydroisoquinolines (6a-b).

General procedure: A solution of 1 mmol of tetrahydroisoquinolines (**5c**) or (**5d**) in 6M HCl (15 ml) was stirred overnight at room temperature. The mixture was cooled on an ice bath, basified with 10% aqueous NH_4OH (50 ml) and extracted with CH_2Cl_2. The crude material was purified as depicted for each compound.

2,4-(2-Ethoxyepoxyethano)-6,7,8-trimethoxy-3-(4-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (6a).

Following the general procedure, the derivative (**6a**) was obtained from (**5c**) as a colourless oil in 75% yield. This oil showed by tlc (hexane/ethyl acetate 3:7) the presence of two diastereoisomers, which were separated and purified by column chromatography and hplc respectively thus affording (***1R*,3S*,4R*,1'S****)-**6a**/(***1R*,3S*,4R*,1'R****)-**6a**, in a 2:1 ratio.

(***1R*,3S*,4R*,1'S****)-**6a**: colourless oil. Ir ($CHCl_3$): ν 1130 (COC st.). Pmr: δ 7.07 (d, J=8.7, 2H, H-2aryl, H-6aryl); 6.76 (s, 1H, H-5); 6.72 (d, J=8.6, 2H, H-3aryl, H-5aryl); 6.94 (s, 1H, H-4); 4.62 (s, 1H, H-3); 4.44 (dd, J=9.8, 3.2, 1H, H-1'); 4.00 (q, J=7.1, 1H, H-1); 3.95 (s, 3H, OCH$_3$); 3.88 (s, 3H, OCH$_3$); 3.85 (s, 3H, OCH$_3$); 3.76 (m, 1H, OCH$_2$CH$_3$); 3.73 (s, 3H, OCH$_3$); 3.36-3.27 (m, 2H, OCH$_2$CH$_3$, H-2'); 3.14 (dd, J=13.8, 3.2, 1H, H-2'); 1.13 (t, J=7.1, 3H, OCH$_2$CH$_3$); 0.73 (d, J=7.1, 3H, C-1CH$_3$). Cmr: δ 158.5, 152.8, 149.3, 142.1, 131.7 (qCarom); 129.8 (tCarom); 127.8, 127.3 (qCarom); 113.3 (tCarom); 107.9 (C-5); 92.4 (C-1'); 70.2 (C-4); 64.6 (OCH$_2$CH$_3$); 62.8 (C-2'); 60.6, 60.4 (2xOCH$_3$); 59.5 (C-3); 56.0 (OCH$_3$); 55.1 (OCH$_3$, C-1); 23.1 (C-1CH$_3$); 15.2 (OCH$_2$CH$_3$). Anal. Calcd for $C_{24}H_{31}NO_6$: C, 67.11; H; 7.27, N, 3.26. Found: C, 66.84; H, 7.12; N, 2.95.

***(1R*,3S*,4R*,1'R*)*-6a:** oil. Ir ($CHCl_3$): ν (cm^{-1}) 1130 (COC st.). Pmr: δ 7.09 (d, J=8.6, 2H, H-2aryl, H-6aryl); 6.81 (s, 1H, H-5); 6.72 (d, J=8.6, 2H, H-3aryl, H-5aryl); 4.73 (s, 1H, H-4); 4.54 (s, 1H, H-3); 4.48 (d, J=4.0, 1H, H-1'); 4.13 (q, J=7.1, 1H, H-1); 3.94 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 3.85-3.79 (m, 1H, $OC\underline{H}_2CH_3$); 3.77 (s, 3H, OCH_3); 3.74 (s, 3H, OCH_3); 3.30-2.96 (m, 3H, $OC\underline{H}_2CH_3$, 2xH-2'); 0.79 (d, J=7.1, 3H, C-1CH_3); 0.58 (t, J=7.0, 3H, $OCH_2C\underline{H}_3$). Cmr: δ 158.6, 151.7, 149.9,142.4, 132.1 (qCarom); 129.8 (tCarom); 128.5 (qCarom); 113.2 (tCarom); 107.5 (C-5); 93.3 (C-1'); 66.7 (C-4); 62.0 ($O\underline{C}H_2CH_3$); 61.6 (C-2'); 60.7, 60.1 (2xOCH_3); 59.2 (C-3); 56.3 (OCH_3); 55.5 (C-1); 55.1 (OCH_3); 22.8 (C-1$\underline{C}H_3$); 14.7 ($OCH_2\underline{C}H_3$). Anal. Calcd for $C_{24}H_{31}NO_6$: C, 67.11; H, 7.27; N, 3.26. Found: C, 67.22; H, 7.16; N, 3.25.

4,2-(2-Ethoxyepoxyethano)-6,7,8-trimethoxy-3-(3-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (6b).

Following the general procedure, the derivative (**6b**) was obtained from (**5d**) as a colourless oil in 81% yield. This oil showed by tlc (hexane/ethyl acetate 3:7) the presence of two diastereoisomers, which were separated and purified by column chromatography and hplc respectively thus affording ***(1R*,3S*,4R*,1'S*)*-6b/*(1R*,3S*,4R*,1'R*)*-6b**, in a 1:1 ratio.

***(1R*,3S*,4R*,1'S*)*-6b:** mp 85-86°C (hexane). Ir ($CHCl_3$): ν 1130 (COC st.). Pmr: δ 7.11 (dd, J=7.1, 7.1, 1H, H-5aryl); 6.80-6.70 (m, 4H, Harom); 4.96 (d, J=1.4, 1H, H-4); 4.63 (d, J=1.4, 1H, H-3); 4.44 (dd, J=9.8, 3.3, 1H, H-1'); 4.01 (q, J=7.1, 1H, H-1); 3.94 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3); 3.72 (s, 3H, OCH_3); 3.77-3.71 (m, 1H, $OC\underline{H}_2CH_3$); 3.31-3.26 (m, 2H, $OC\underline{H}_2CH_3$, H-2'); 3.15 (dd, J=13.8, 3.3, 1H, H-2'); 1.13 (t, J=7.1, 3H, $OCH_2C\underline{H}_3$); 0.76 (d, J=7.1, 3H, C-1$\underline{C}H_3$). Cmr: δ 159.1, 152.8, 149.3, 142.0, 141.2 (qCarom); 128.7 (tCarom); 127.5, 127.1 (qCarom); 120.9, 114.7, 112.6 (tCarom); 107.5 (C-5); 92.4 (C-1'); 70.4 (C-4); 64.5 ($O\underline{C}H_2CH_3$); 62.9 (C-2'); 60.6, 60.3 (2xOCH_3); 59.9 (C-3); 56.0 (OCH_3); 55.3 (C-1); 55.1 (OCH_3); 23.0 ($OCH_2\underline{C}H_3$); 15.1 (C-1$\underline{C}H_3$). Anal. Calcd for $C_{24}H_{31}NO_6$: C, 67.11; H, 7.27; N, 3.26. Found: C, 67.35; H, 7.05; N, 3.12.

***(1R*,3S*,4R*,1'R*)*-6b:** colourless oil. Ir ($CHCl_3$): ν 1130 (COC st.). Pmr: δ 7.11 (dd, J=7.1, 7.1, 1H, H-5aryl); 6.80-6.70 (m, 4H, Harom); 4.75 (d, J=1.5, 1H, H-4); 4.55 (s, 1H, H-3); 4.46 (m, 1H, H-1'); 4.02 (q, J=7.1, 1H, H-1); 3.92 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 3.79 (s, 3H, OCH_3); 3.72 (s, 3H, OCH_3); 3.36-2.93 (m, 4H, H-2', $OC\underline{H}_2CH_3$); 0.81 (d, J=7.1, 3H, C-1CH_3); 0.62 (t, J=7.1, 3H, $OCH_2C\underline{H}_3$). Cmr: δ 151.7, 149.9, 132.4, 141.8, 129.7 (qCarom); 128.7 (tCarom); 128.6, 127.6 (qCarom); 120.9, 114.7, 114.6, 107.9 (tCarom); 93.3 (C-1'); 66.6 (C-4); 62.2 ($O\underline{C}H_2CH_3$); 61.5 (C-2'); 60.6, 60.1 (2xOCH_3); 59.7 (C-3); 56.2 (OCH_3); 55.7 (C-1); 55.1 (OCH_3); 22.9 ($OCH_2\underline{C}H_3$); 14.6 (C-1$\underline{C}H_3$). Anal. Calcd for $C_{24}H_{31}NO_6$: C, 67.11; H, 7.27; N, 3.26. Found: C, 67.28; H, 7.17; N, 3.07.

4-Hydroxy-6,7,8-trimethoxy-3-(4-methoxyphenyl)-1-methylisoquinoline (7).

A mixture of tetrahydroisoquinoline (**5c**) (0.47 g, 1 mmol) and 2 ml of 6M HCl was heated in 15 ml of refluxing dioxane overnight. After cooling using an ice bath, the mixture was basified with NH_4OH (10 ml of a 10% solution in water), extracted (CH_2Cl_2) and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum affording a syrup which was purified by column chromatography (hexane/ethyl acetate 7:3) and hplc producing an oily compound (0.14 g, 40%). Ir ($CHCl_3$): ν 3600-3500 (OH st.). Pmr: δ 7.58 (d, J=8.1, 2H, H-2', H-6'); 7.32 (s, 1H, H-5); 6.85 (d, J=8.1, 2H, H-3', H-5'); 5.00 (sa, 1H, OH); 3.99 (s, 3H, OCH_3);

3.96 (s, 6H, 2xOCH_3); 3.74 (s, 3H, OCH_3); 2.97 (s, 3H, CH_3). Cmr: δ 159.3, 155.5, 150.5, 147.5, 142.6, 142.1, 133.7 (C-1, qCarom); 130.1 (tCarom); 129.1, 127.4, 119.1 (qCarom); 114.3, 97.2 (tCarom); 61.2, 60.9, 55.9, 55.2 (4xOCH_3); 25.9 (CH_3). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 63.53; H, 5.33; N, 3.36. Found: C, 63.80; H, 5.45; N, 3.40.

13-Hydroxy-2,9,10,11-tetramethoxy-8-methylberberinium salt (8).

A solution of tetrahydroisoquinoline (**5d**) (0.47 g, 1 mmol) and 2 ml of 6 M HCl was heated in 15 ml of refluxing dioxane overnight. Standard work-up afforded a syrup which was purified by column chromatography (hexane/ethyl acetate 3:7) and hplc producing an oily compound (0.12 g, 30%). Pmr: δ 8.35 (d, J=5.2, 1H, H-6); 8.17 (d, J=2.3, 1H, H-1); 7.77 (d, J=9.1, 1H, H-4); 7.69 (d, J=5.2, 1H, H-5); 7.40 (dd, J=9.1, 2.3, 1H, H-3); 7.06 (s, 1H, H-12); 3.99 (s, 3H, OCH_3); 3.97 (s, 3H, OCH_3); 3.93 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 2.34 (s, 3H, CH_3). Cmr: δ 160.5, 154.9, 152.6, 151.4 (qCarom); 138.8 (tCarom); 135.3, 132.7, 128.4 (qCarom); 128.3, 124.4, 123.8, 110.0, 104.0 (tCarom); 61.7, 60.9, 56.2, 55.6 (4xOCH_3); 31.0 (CH_3). Anal. Calcd for $C_{22}H_{22}NO_5Cl$: C, 67.59; H, 5.95; N, 3.94. Found: C, 66.98; H, 5.97; N, 3.90.

Synthesis of protoberberines (9).

General procedure. A suspension of 1 mmol of tetrahydroisoquinolines (**5e**) or (**5f**) in aqueous 6M HCl (25 ml) was stirred at room temperature for 24 h. The mixture was cooled at 0ºC, basified with 10 % aqueous NH_4OH (50 ml) and extracted with CH_2Cl_2. The so-obtained crude material was purified as depicted for each compound.

5,13-Dihydroxy-2,9,10,11-tetramethoxy-8-methylprotoberberine (9a)

Following the general procedure, protoberberine (**9a**) was obtained from **5e** as an oil. This oil showed by tlc the presence of four spots corresponding to the pairs of diastereoisomers for **9a** (40% yield) and **6b** (30% yield) respectively. The mixture of diastereoisomers (**9a**) was separated by column chromatography (hexane/ethyl acetate 1:1). Each diastereoisomer was then isolated and purified by hplc, thus affording (***5R*,8R*,13R*,14S****)-**9a** and (***5S*,8R*,13R*,14S****)-**9a** in a 3:1 ratio.

(***5R*,8R*,13R*,14S****)-**9a:** oil. Ir ($CHCl_3$): ν 3580 (OH st. free), 3520-3200 (OH st. asoc.). Pmr: δ 7.50 (d, J=8.5, 1H, H-4); 7.13 (d, J=2.5, 1H, H-1); 6.96 (s, 1H, H-12); 6.87 (dd, J=8.5, 2.5, 1H, H-3); 4.75 (dd, J=7.0, 4.3, 1H, H-5); 4.55 (d, J=8.6, 1H, H-13); 4.12 (q, J=6.3, 1H, H-8); 3.89 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 3.78 (s, 3H, OCH_3); 3.65 (d, J=8.6, 1H, H-14); 3.31 (dd, J=11.3, 4.3, 1H, H-6); 2.61 (dd, J=11.3, 7.0, 1H, H-6); 1.53 (d, J=6.3, 3H, CH_3). Cmr: δ 158.4, 152.2, 150.5, 141.5, 136.9, 134.5, 131.6 (qCarom); 128.2 (tCarom); 124.7 (qCarom); 113.2, 112.7, 104.5 (tCarom); 70.6, 67.2, 64.2 (C-13, C-14, C-5); 60.7, 60.6, 55.8 (4xOCH_3); 55.3 (C-8); 51.1 (C-6); 21.4 (CH_3). Ms: (m/z, %): 402 (M^++1, 52); 401 (M^++1, 16); 400 (M^+-1, 56); 384 (45); 224 (24); 223 (40); 209 (14); 179 (15); 178 (100); 160 (27). Anal. calcd for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.77, N, 3.49. Found: C, 66.68; H, 6.97; N, 3.55.

(***5S*,8R*,13R*,14S****)-**9a:** oil. Ir ($CHCl_3$): ν 3600-3200 (OH st.).Pmn: δ 7.32 (d, J=8.3, 1H, H-4); 7.29 (d, J=2.6, 1H, H-1); 7.08 (s, 1H, H-12); 6.82 (dd, J=8.3, 2.6, 1H, H-3); 4.52 (s, 1H, H-5); 4.39 (d, J=8.0, 1H, H-13); 4.00-3.96 (m, 1H, H-8); 3.93 (s, 3H, OCH_3); 3.92 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 3.78 (s, 3H, OCH_3); 3.54 (d, J=8.0, 1H, H-14); 3.42 (dd, J=11.5, 3.0, 1H, H-6); 2.70 (d, J=11.5, 1H, H-6); 1.46 (d, J=6.5, 3H, CH_3). Cmr: δ 158.9, 152.2, 150.1, 141.2, 136.0, 134.5 (qCarom); 130.2 (tCarom); 124.5

(qCarom); 113.6, 113.5, 103.3 (tCarom); 83.2 (C-5); 66.5 (C-13); 61.9 (C-14); 60.9, 60.6, 60.5 (3xOCH_3); 55.8 (C-8); 55.2 (OCH_3); 53.4 (C-6); 22.5 (CH_3). Anal. calcd. for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.77, N, 3.49. Found: C, 65.95; H, 6.73; N, 3.45.

5-Hydroxy-2,9,10,11,13-pentamethoxy-8-methylprotoberberine (9b).

Following the general procedure, the derivative (**9b**) was obtained from **5f** as an oil. This oil showed by tlc the presence of two spots corresponding to the expected diastereoisomers (**9b**) which were separated by column chromatography (hexane/ethyl acetate 6:4) and purified by hplc thus affording (***5R*,8R*,13R*,14S****)-**9b** and (***5S*,8R*,13R*,14S****)-**9b** in a 2:1 ratio. Yield:70%.

(***5R*,8R*,13R*,14S****)-**9b:** oil. Ir ($CHCl_3$): ν 3580 (OH st. free), 3520-3200 (OH st. asoc.). Pmr: δ 7.46 (d, J=8.5, 1H, H-4); 7.20 (d, J=2.6, 1H, H-1); 6.86 (dd, J=8.5, 2.6, 1H, H-3); 6.78 (s, 1H, H-12); 4.74 (dd, J=7.2, 4.2, 1H, H-5); 4.20 (d, J=8.2, 1H, H-13); 4.04 (q, J=6.3, 1H, H-8); 3.88 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 3.76 (d, J=8.2, 1H, H-14); 3.87 (s, 3H OCH_3); 3.21 (dd, J=11.2, 4.2, 1H, H-6); 2.54 (dd, J=11.2, 7.2, 1H, H-6); 1.52 (d, J=6.3, 3H, CH_3). Cmr: δ 158.4, 152.0, 150.7, 141.6, 137.0, 133.7, 131.4 (qCarom); 127.7 (tCarom); 124.85 (qCarom); 113.5, 112.7, 104.4 (tCarom); 81.1 (C-5); 67.1 (C-13); 62.1 (C-14); 60.6, 59.4, 55.8 (4xOCH_3); 55.3 (C-8); 55.2 (OCH_3); 51.3 (C-6); 21.4 (CH_3). Ms: (m/z,%): 416 (M^++1, 24); 415 (M^++1, 12); 414 (M^+-1, 43); 398 (31); 238 (100); 223 (26); 178 (15); 160 (10). Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.03, N, 3.37. Found: C, 66.57; H, 6.98; N, 3.36.

(***5S*,8R*,13R*,14S****)-**9b:** oil. Ir ($CHCl_3$): ν 3600-3200 (OH st.). Pmr: δ 7.42 (d, J=2.6, 1H, H-1); 7.30 (d, J=8.3, 1H, H-4); 6.87-6.83 (m, 2H, H-3, H-12); 4.52 (m, 1H, H-5); 4.12 (d, J=8.5, 1H, H-13); 3.95-3.92 (m, 1H, H-8); 3.93 (s, 3H OCH_3); 3.91 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.64 (d, J=8.5, 1H, H-14); 3.47 (s, 3H OCH_3); 3.41 (dd, J=11.6, 3.0, 1H, H-6); 2.71 (d, J=11.6, 1H, H-6); 1.47 (d, J=5.8, 3H, CH_3). Cmr: δ 158.9, 152.2, 150.1, 141.2, 136.0, 134.5 (qCarom); 130.2 (tCarom); 124.5 (qCarom); 113.6, 113.5, 103.3 (tCarom); 83.2(C-5); 66.5 (C-13); 61.9 (C-14); 60.9, 60.6, 60.5 (4xOCH_3); 55.8 (C-8); 55.2 (OCH_3); 53.4 (C-6); 22.5 (CH_3). Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.03, N, 3.37. Found: C, 66.70; H, 7.08; N, 3.25.

Synthesis of 3-Aryl-1,2-dihydroisoquinolines (10g-j).

General procedure. A suspension of tetrahydroisoquinolines (**5g-j**) (1 mmol) in 2 ml of aqueous H_2SO_4 (80%) was stirred at room temperature for 10 min. The mixture was cooled down to 0°C, basified with NH_4OH (15 ml of a 10% solution in water), extracted with CH_2Cl_2 and the extract was dried over anhydrous sodium sulfate. After evaporation of the solvent under vacuum, the resulting oil was purified by flash column chromatography using hexane / ethyl acetate (8:3) as eluent, affording the title derivatives (**10**). Yields: 80-85%.

6,7-Dimethoxy-2-methoxycarbonylmethyl-1-methyl-3-phenyl-1,2-dihydroisoquinoline (10g).

Following the general procedure, the derivative (**10g**) was obtained from **5g** as white crystals (0.28 g, 80%). mp 129-130°C (ether). Ir (KBr): ν 1750 (C=O st); 1610 (C=C st.). Pmr: δ 7.64-7.32 (m, 5H, Ph); 6.70 (s, 1H, H-5); 6.57 (s, 1H, H-8); 6.13 (s, 1H, H-4); 4.25 (q, J=6.7, 1H, H-1); 3.90 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3); 3.73 (d, J= 17.6, 1H, NCH); 3.61 (s, 3H, $COOCH_3$); 3.58 (d, J=17.6, 1H, NCH); 1.35 (d, J=6.7,

3H, C-1$\underline{C}H_3$). Cmr: δ 171.6 (COO); 148.0, 147.8, 142.4, 137.5 (qCarom); 128.4, 128.2, 127.5 (tCarom); 125.8, 125.0 (qCarom); 108.9, 107.4, 107.3 (tCarom); 57.5 (OCH_3); 56.0 (C-1); 55.8 (OCH_3); 53.1 (NCH_2); 51.5 ($COOCH_3$); 21.4 (C-1$\underline{C}H_3$). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.50; H, 6.52; N, 3.96.

6,7,8-Trimethoxy-2-methoxycarbonylmethyl-3-phenyl-1,2-dihydroisoquinoline (10h).
Following the general procedure, the derivative (**10h**) was obtained from **5h** as a yellow oil (0.32 g, 82%). Ir ($CHCl_3$): ν 1750 (C=O st); 1600 (C=C st.). Pmr: δ 7.53-7.49 (m, 2H, Harom); 7.39-7.31 (m, 3H, Harom); 6.40 (s, 1H, H-5); 5.88 (s, 1H, H-4); 4.51 (s, 2H, H-1); 3.87 (s, 3H, OCH_3); 3.85 (s, 6H, 2xOCH_3); 3.84 (s, 3H, OCH_3), 3.66 (s, 2H, NCH_2); 3.64 (s, 3H, $COOCH_3$). Cmr: δ 171.3 (COO); 152.6, 149.2, 147.4, 140.4, 136.9, 130.1 (qCarom); 128.4, 128.1, (tCarom); 113.1 (qCarom); 105.4, 102.8 (tCarom); 61.0, 56.0 (3xOCH_3); 53.1 (NCH_2); 51.7 ($COO\underline{C}H_3$); 47.3 (C-1). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.27; N, 3.79. Found: C, 68.35; H, 6.25; N, 3.76.

6,7-Dimethoxy-1,2-dimethyl-3-phenyl-1,2-dihydroisoquinoline (10i).
Following the general procedure, the derivative (**10i**) was obtained from **5i** as a yellow oil (0.25 g, 85%). Ir ($CHCl_3$): ν 1510 (C=C st.). Pmr: δ 7.58-7.32 (m, 5H, Ph); 6.66 (s, 1H, H-5); 6.60 (s, 1H, H-8); 5.94 (s, 1H, H-4); 4.24 (q, J=6.7, 1H, H-1); 3.89 (s, 6H, 2xOCH_3); 2.66 (s, 3H, NCH_3); 1.28 (d, J=6.7, 3H, C-1$\underline{C}H_3$);.Cmr: δ 148.0, 147.4, 144.6, 138.1 (qCarom); 128.1, 127.8, 127.6 (tCarom); 125.4, 125.1 (qCarom); 109.1, 107.0, 104.6 (tCarom); 58.8 (C-1); 56.1, 55.8 (2xOCH_3); 39.4 (NCH_3); 19.9 (C-1CH_3). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.52; H, 7.16; N, 4.74. Found: C, 77.30; H, 7.17; N, 4.65.

6,7,8-Trimethoxy-1,2-dimethyl-3-(3-methoxyphenyl)-1,2-dihydroisoquinoline (10j).
Following the general procedure, the derivative (**10j**) was obtained from **5j** as a yellow oil (0.29 g, 82%). Ir ($CHCl_3$): ν 1600 (C=C st.). Pmr: δ 7.74-7.70 (m, 1H, Harom); 7.42-7.35 (m, 1H, Harom); 7.13-7.06 (m, 1H, Harom); 6.91-6.87 (m, 1H, Harom); 6.42 (s, 1H, H-5); 5.83 (s, 1H, H-4); 4.61 (q, J=6.6, 1H, H-1); 3.95 (s, 3H, OCH_3); 2.72 (s, 3H, NCH_3); 1.25 (d, J=6.6, 3H, C-1$\underline{C}H_3$). Cmr: δ 159.5, 152.4, 148.9, 145.7, 139.9, 139.5 (qCarom); 129.1 (tCarom); 128.6 (qCarom); 120.2 (tCarom); 118.0 (qCarom); 113.5, 113.3, 103.7, 102.5 (tCarom); 60.9, 60.7, 55.8, 55.1 (4xOCH_3); 53.1 (C-1); 39.6 (NCH_3); 19.0 (C-1CH_3). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09, N, 3.94. Found: C, 70.84; H, 7.08; N, 3.96.

2,9,10,11-Tetramethoxy-8-methyl-8*H*-berberine (11).
Procedure A. A solution of 1 mmol of tetrahydroisoquinolines (**5d-f**) and concentrated H_2SO_4 (9.5 ml, 10 mmol) in 15 ml of HOAc was heated with reflux for 10 min. After evaporation of the solvent under vacuum, the residue was shaked in crushed ice, basified with NH_4OH (30 ml of a 10 % solution in water), extracted with CH_2Cl_2 and the extract was dried over anhydrous sodium sulfate. Final elimination of the solvent in a rotatory evaporator yielded an oil which was purified by hplc affording 8*H*-berberine (**11**) with a quantitative yield.
Procedure B. A solution of 1 mmol of tetrahydroisoquinolines (**9a-b**) in H_2SO_4 (9.5 ml, 10 mmol) was stirred at room temperature for 10 min. The crude was poured into ice, basified with NH_4OH (30 ml of a 10 % solution in water), extracted with CH_2Cl_2 and the extract was dried over anhydrous sodium sulfate. Final elimination of the solvent in a rotatory evaporator yielded an oil which was purified by hplc affording 8*H*-berberine (**11**) with a

quantitative yield. Pmr: δ 7.17 (d, J=1.8, 1H, H-1); 7.04 (d, J=8.6, 1H, H-4); 6.88 (dd, J=8.6, 1.8, 1H, H-3); 6.45 (d, J=7.2, 1H, H-6); 6.37 (s, 1H, H-12); 5.92 (s, 1H, H-13); 5.82 (d, J=7.2, 1H, H-5); 5.18 (q, J=6.5, 1H, H-8); 3.96 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3); 1.29 (d, J=6.5, 3H, CH_3). Cmr: δ 158.4, 153.0, 148.5, 136.7 (qCarom); 131.0 (tCarom); 129.0, 128.0 (qCarom); 126.9 (tCarom); 126.6 (qCarom); 116.8, 114.3, 106.1 (tCarom); 103.5 (qCarom); 101.5, 90.6 (tCarom); 61.0, 60.9, 55.9 (3xOCH_3); 55.6 (C-8); 55.4 (OCH_3); 20.6 (CH_3). Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34, N, 3.83. Found: C, 72.07; H, 6.45; N, 4.07.

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8. A general procedure for the synthesis of tetrahydroisoquinolines (**4a**) and (**4b**) can be found in ref. 6a.

   (1*R,3*S**,4*R**)-4-(*tert*-Butyldiphenylsilyloxy)-6,7,8-trimethoxy-3-(4-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (4a)**: mp 150-151°C (ether). Pmr: δ (ppm) 7.61-7.29 (m, 10H, 2xPh); 7.23 (d, J=8.6, 2H, H-2', H-6'); 6.81 (d, J=8.6, 2H, H-3', H-5'); 6.51 (s,1H, H-5); 5.06 (d, J=8.1, 1H, H-4); 4.30 (q, J=6.4, 1H, H-1); 3.89 (d, J=8.1, 1H, H-3); 3.86 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.79 (s, 3H, OCH_3); 3.05 (s, 3H, OCH_3); 1.32 (d, J=6.4, 3H, C_1CH_3); 0.66 (s, 9H, ($\underline{C}(CH_3)_3$). Cmr: δ (ppm) 159.2, 151.2, 150.2, 140.8 (qCarom); 136.2, 135.9 (tCarom); 134.6, 134.3, 132.7, 132.6 (qCarom); 129.6, 129.2, 127.5,

127.2 (tCarom); 126.4 (qCarom); 113. 9, 107.5 (tCarom); 74.0 (C-4); 64.3 (C-3); 60.4, 55.3, 55.0 (4xOCH_3); 50.3 (C-1); 26.4 ($C(\underline{C}H_3)_3$); 23.3 ($C_1\underline{C}H_3$); 19.6 ($\underline{C}(CH_3)_3$). Ir ($CHCl_3$) ν (cm^{-1}) 3400-3300 (NH st.).

(1*R,3*S**,4*R**)-4-(*tert*-Butyldiphenylsilyloxy)-6,7,8-trimethoxy-3-(3-methoxyphenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (4b):** mp 158-159°C (HCl salt, MeOH). Data for the free base: Pmr: δ (ppm) 7.64-6.82 (m, 14H, Harom); 6.50 (s, 1H, H-5); 5.10 (d, J=8.2, 1H, H-4); 4.31 (q, J=6.3, 1H, H-1); 3.92 (d, J=8.2, 1H, H-3); 3.87 (s, 3H, OCH_3); 3.79 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 3.03 (s, 3H, OCH_3); 1.35 (d, J=6.3, 3H, C_1CH_3); 0.68 (s, 9H, $(CH_3)_3$). Cmr: δ (ppm) 159.7, 151.1, 150.2, 143.7, 140.7 (qCarom); 136.2, 135.9 (tCarom); 134.6, 134.1, 132.3 (qCarom); 129.7, 129.4, 129.1, 127.6, 127.1 (tCarom); 126.3 (qCarom); 121.0, 113.8, 113.7, 107.4 (tCarom); 74.1 (C-4); 65.2 (C-3); 60.4, 60.3, 55.0 (3xOCH_3); 54.8 (C-1); 50.4 (OCH_3); 26.7 ($C(\underline{C}H_3)_3$); 23.2 ($C_1\underline{C}H_3$); 19.6 ($\underline{C}(CH_3)_3$). Ir ($CHCl_3$) ν (cm^{-1}) 3400-3250 (NH st.). Satisfactory combustion analyses were obtained for tetrahydroisoquinolines **(4a)** and **(4b)**.

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