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The Synthesis of 2-Arylmethyltetrahydroisoquinolines from Bis(Aminol) Ethers Involving Two Iminium Salt Intermediates

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Abstract: The bis(aminol) ether derived from 3,4-dimethoxy-b-phenylethylamine, methanol, and formaldehyde reacts with trichloromethylsilane to afford an equilibrium mixture of N-chloromethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and its related iminium chloride. Interaction with electron rich aromatic compounds afford good yields of N-arylmethyl derivatives, including sendaverine methyl ether. Reactions of the bis(aminol) ether in the presence of the aromatic substrate allows the formation of the N-arylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives in a one pot reaction.

Introduction

The frequent occurrence of the isoquinoline nucleus in a range of natural products has led to considerable interest in the synthesis of that ring system. The synthesis of tetrahydroisoquinolines from β-arylethylamines by the Pictet-Spengler reaction is well documented.[1] β-Arylethylamines that have an electron releasing substituent at the 3-position form imines with aldehydes, which are sometimes isolated, and undergo intramolecular Mannich type reactions upon protonation with hydrochloric acid when heated to 100°C. These somewhat harsh conditions, however, are not favoured when labile functional groups are present. Some modifications employing milder reaction conditions have been developed.[2] Thus, condensation of phenethylamine derivatives with paraformaldehyde in formic acid at 40 °C gives rise to *N*-formyltetrahydroisoquinoline derivatives. The use of three mole equivalents of paraformaldehyde in this system allows *N*-methyltetrahydroisoquinolines to be prepared in one step. In this case formic acid can function as the solvent and acidic catalyst in the Pictet-Spengler reaction as well as the reducing agent in the Eschweiler-Clarke *N*-methylation process.

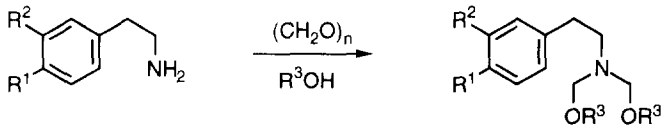
The preparation of 2-formyl-1,2,3,4-tetrahydroisoquinolines has been reported by the reaction of *N*-formylphenethylamines with a variety of aldehydes.[3] 2-Arylsulphonyl-1,2,3,4-tetrahydroisoquinolines have been prepared from the imines derived from β-phenylethylamines in reaction with sulphonyl chlorides.[4] Similarly, 2-acyl-1,2,3,4-tetrahydroisoquinolines have been prepared using acyl chlorides.[5] It has been reported that *N*-alkylamines, derived from piperonal, in reaction with glycidol followed by periodate oxidation and hydrogenation gave simple *N*-alkyl-1,2,3,4-tetrahydroisoquinolines.[6] This method, however, could not be applied for the preparation of *N*-phenyl or *N*-benzyl analogues.

Results and Discussion

Although bis(aminol) ethers have been known for a long time[7] their usage has mainly been concentrated in the formation of benzoxazines[8,9,10] by their reactions with nucleophilic phenols. As far as we are aware there is

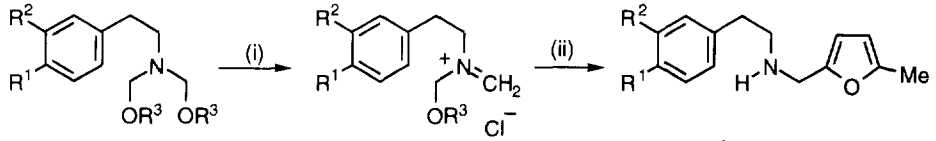
no previous report of the use of bis(aminol) ethers derived from β-phenylethylamines. In the course of our investigations of the reactions of bis(aminol) ethers for the preparation of secondary amines we have prepared three *N,N*-bis(alkoxymethyl)-β-arylethylamines.[11] Some of the results described in this paper have already been disclosed in a preliminary communication.[12] We now provide a detailed account of the work carried out together with full experimental procedures.

N,N-Bis(methoxymethyl)-3-4-dimethoxy-β-phenylethylamine (**1**) was conveniently prepared from 3,4-dimethoxy-β-phenylethylamine in 60% yield by the interaction of methanol and paraformaldehyde in the presence of potassium carbonate at room temperature. Similarly *N,N*-bis(ethoxymethyl)-β-phenylethylamine (**2**) was obtained in 50% yield from β-phenylethylamine, paraformaldehyde and ethanol. However, *N,N*-bis(ethoxymethyl)-4-methoxy-β-phenylethylamine (**3**) was prepared in 80% yield by heating a mixture of 4-methoxy-β-phenylethylamine, paraformaldehyde, ethanol, and benzene under Dean-Stark conditions.



(**1**, $R^1 = R^2 = OMe$; $R^3 = Me$)
(**2**, $R^1 = R^2 = H$; $R^3 = Et$)
(**3**, $R^1 = OMe$; $R^2 = H$; $R^3 = Et$)

In our initial investigations bis(aminol) ethers (**2**) and (**3**) were treated with chlorosilane derivatives or ethereal hydrogen chloride. The corresponding iminium salts, which could either be isolated or reacted *in situ* with 2-methylfuran, gave rise exclusively to the corresponding secondary amines (**4**) and (**5**) in good yields as shown in ***Scheme 1***.



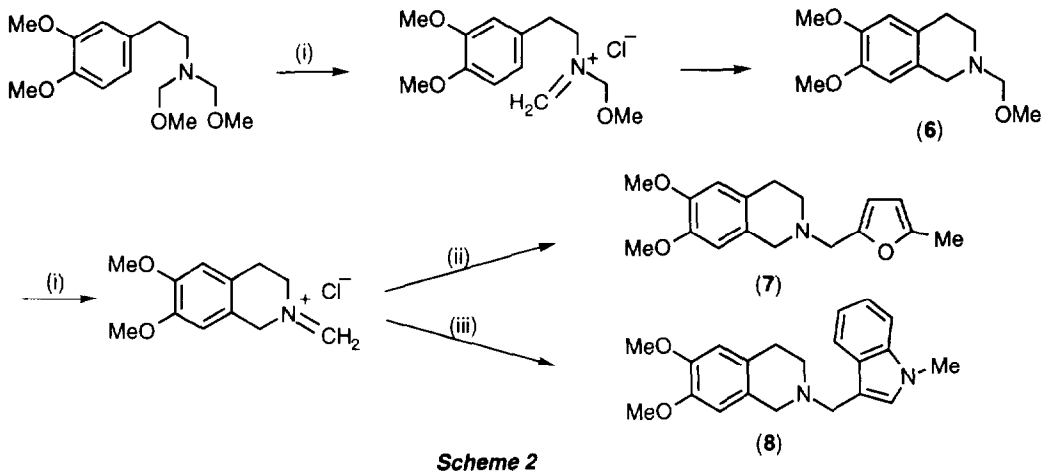
(**2**, $R^1 = R^2 = H$; $R^3 = Et$)
(**3**, $R^1 = OMe$; $R^2 = H$; $R^3 = Et$)

(**4**, $R^1 = R^2 = H$; 55%)
(**5**, $R^1 = OMe$; $R^2 = H$; 59%)

Scheme 1

(i) $MeSiCl_3$ or $Et_2O.HCl$, petroleum ether (40-60 °C); (ii) 2-methylfuran, MeCN

It was anticipated that the increase in electron density at the position *para-* to the methoxy-group located at the 3-position in the bis(aminol) ether (**1**) would facilitate a Pictet-Spengler type cyclisation reaction and that the initial product (**6**), now an aminol ether derived from a secondary amine, would be capable of forming a second iminium salt and hence react in an intermolecular reaction with electron rich aromatic substrates. We were thus in a position to carry out tandem reactions. A solution of the bis(aminol) ether (**1**) and 2-methylfuran in acetonitrile gave, in the presence of trichloromethylsilane, the 2-furylmethyl derivative (**7**) in a 65% yield. Similarly, a reaction in which the 2-methylfuran was replaced by *N*-methylindole resulted in the formation of the indole derivative (**8**) in an 85% yield as shown in ***Scheme 2***.

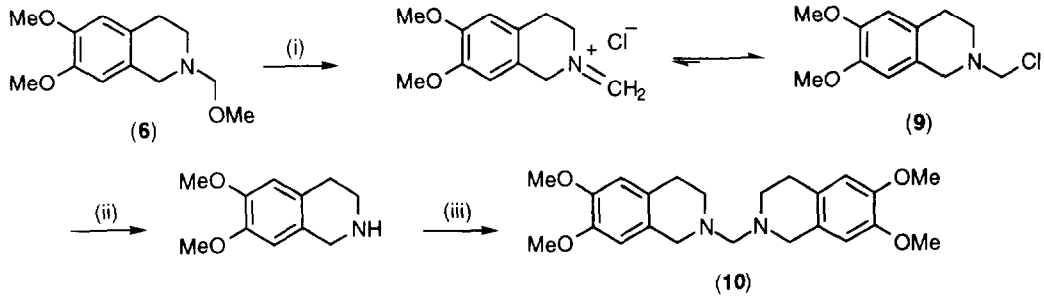


Scheme 2

(i) $MeSiCl_3$, MeCN; (ii) 2-methylfuran, MeCN; (iii) *N*-methylindole

With these novel compounds in hand we embarked on an investigation to identify the second intermediate iminium salt. The aminol ether (**1**) was treated with 2 mole equivalents of trichloromethylsilane, and a relatively stable pale yellow crystalline solid (**9**) was isolated in quantitative yield. The ^{13}C n.m.r. spectra of the solid determined in $CDCl_3$ and CD_3CN, even in the presence of sulphur dioxide, did not reveal the expected iminium resonances. However, a methylene resonance was observed at δ_C = 78.4 ppm which is assigned to a chloromethylamino group.

It is noteworthy that the ^1H decoupled ^{13}C n.m.r. spectrum of *N,N*-dimethyl(methylene)iminium chloride in a mixture of CD_2Cl_2 and SO_2 showed the presence of four different carbons at δ_C = 38.7 (s), 49.4 (t), 79.0 (s), and 168.1 (t) ppm. This indicates that an equilibrium exists between the ionic and covalent species in that solvent system. Similarly the ^{13}C n.m.r. spectrum of *N*-methylene(piperidinium) chloride also showed similar features when recorded in CD_2Cl_2/SO_2. *N*-methylene(piperidinium) iodide,[13] prepared by the interaction of di(*N*-piperidinyl)methane with iodotrimethylsilane showed, in its ^1H decoupled ^{13}C n.m.r. spectrum, no evidence of the iminium carbon. Singlets were observed at δ_C (DMSO-d_6) 21.3, 22.0, 48.3, and 78.0 ppm. It is reasonable to conclude, therefore, that the pale yellow crystalline solid (**9**) is an equilibrium mixture in which the covalent species predominates to the extent that the ionic species cannot be detected by n.m.r. spectroscopy.

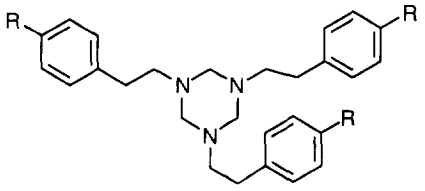


Scheme 3

(i) $MeSiCl_3$,Et_2O; (ii) NaOH (aq.), pH 14; (iii) compound (**9**)

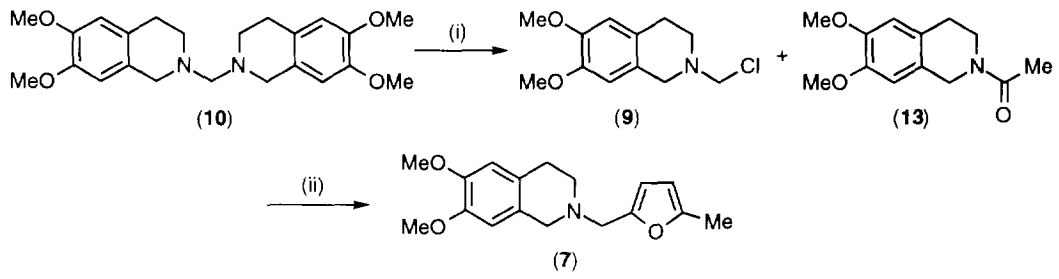
In an attempt to hydrolyse the yellow crystalline solid (**9**) to 6,7-dimethoxytetrahydroisoquinoline we treated the compound with water and adjusted the pH to 14. This resulted in the formation of the aminal (**10**) in 95% yield. Evidently the hydrolysis leads to the formation of 6,7-dimethoxytetrahydroisoquinoline but this is captured either by the *N*-chloromethyl- derivative (**9**) or the iminium salt with which it is in equilibrium. This observation confirms the proposed structure of the yellow crystalline solid. The formation of an aminal from an iminium salt has been observed previously.[14]

It is interesting to note that the iminium salts derived from the bis(aminol) ethers, *N,N*-bis(ethoxymethyl)-β-phenylethylamine (**2**) and *N,N*-bis(ethoxymethyl)-β-4-methoxyphenylethylamine (**3**), under the same hydrolysis conditions did not yield the corresponding aminals. The *N,N′,N′′*-tris[β-arylethyl]hexahydro-*s*-triazine derivatives (**11**) and (**12**) were formed in 70% and 74% yield respectively. This is not unexpected as these iminium salts failed to undergo intramolecular cyclisation and the secondary amines (**4**) and (**5**) were isolated on treatment with 2-methylfuran. An electron-donating substituent at the 3-position on the benzene ring is essential in order to activate the *para* -position for intramolecular Mannich reaction. Condensation of primary amines with formalin under basic aqueous conditions has been reported to give access to 1,3,5-trialkylhexahydrotriazines as Mannich reagents for the formation of secondary amines.[15]



(**11**; R = H)
(**12**; R = OMe)

The aminal (**10**) was fully characterised by elemental analysis and by spectroscopic methods. It was also identified by reaction with acetyl chloride which gave 2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[5] (**13**) in 54% yield together with the *N*-chloromethyltetrahydroisoquinoline (**9**), in 93% yield. Upon reaction with 2-methylfuran the isolated compound (**9**) gave the tetrahydroisoquinoline (**7**) in 95% yield, as shown in ***Scheme 4***.

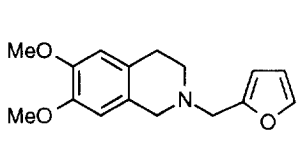


Scheme 4

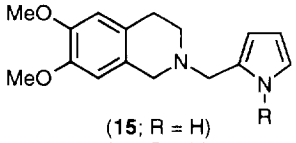
(i) CH_3COCl, Et_2O; (ii) 2-methylfuran, MeCN

Although the "one-pot" reactions of other aromatic heterocycles gave reasonable yields of the corresponding 2- arylmethyltetrahydroisoquinolines, isolation and purification proved somewhat difficult due to the presence of small amounts of basic impurities. We envisaged that it would more profitable to carry out the reactions in two steps. It was argued that reactions using the solid (**9**) should allow the formation of cleaner, and therefore more easily isolable products and in higher yields as was the case of the reaction of 2-methylfuran with the solid isolated from the aminal (**10**).

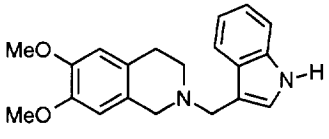
Reactions of a number of aromatic heterocycles and electron-rich benzenoid derivatives afforded the 2-arylmethyltetrahydroisoquinolines (**14**)-(**21**) in excellent yields, when treated with the solid (**9**) in acetonitrile at room temperature. Furthermore it is noted that the tetrahydroisoquinoline derivatives (**7**) and (**8**) were obtained in improved yields of 95 % and 89% respectively when the two step procedure was applied.



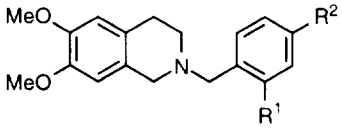
(**14**)



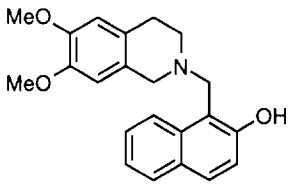
(**15**; R = H)
(**16**; R = Me)



(**17**)



(**18**; R^1 = H, R^2 = OMe)
(**19**; R^1 = R^2 = OMe)
(**20**; R^1 = R^2 = OH)



(**21**)

The yields of products obtained from these reactions indicate the high reactivity of the chloromethyltetrahydroisoquinoline (**9**). 1,3-Dimethoxybenzene, however, the least nucleophilic substrate reported to undergo the Mannich reaction,[16] afforded the tetrahydroisoquinoline derivative (**19**) 77% yield when the reaction mixture was heated under reflux. As expected, aryltributylstannane derivatives are able to undergo *ipso*- electrophilic substitution reactions with the chloromethyltetrahydroisoquinoline (**9**), and afford the products in good yields. The tetrahydroisoquinoline derivative (**19**) was obtained from 2,4-dimethoxyphenyltributylstannane in 87% yield at room temperature. It is of interest to note that the product (**18**) is the methyl ether of the optically inactive phenolic alkaloid sendaverine,[17] isolated from *Corydalis aurea* Willd. (Fumariaceae) by Manske in 1938.[18] *N*-(4´-Methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**18**) was obtained in a 73% yield by the reaction of 4-methoxybenzyltributylstannane with the chloromethyltetrahydroisoquinoline (**9**). The present methodology demonstrates the potential applicability of the Mannich reaction for the preparation of naturally occurring *N*-benzyltetrahydroisioquinoline alkaloids.

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Experimental

Liquid starting materials were freshly distilled before use and solids recrystallised from appropriate solvents. Solvents were dried by conventional methods and solutions of products were dried over anhydrous magnesium sulphate. Oxygen-free nitrogen was dried by passing successively through concentrated sulphuric acid, sodium hydroxide pellets and silica gel. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer; only selected absorbances are reported. Spectra were taken as thin films (film), potassium bromide discs (KBr) or nujol mulls (nujol). N.m.r. Spectra were recorded in $CDCl_3$ unless otherwise stated using TMS as reference. ^1H n.m.r. Spectra were recorded on Varian EM 360 A (60 MHz) or Bruker AC-250 (250 MHz) spectrometers. ^{13}C N.m.r. Spectra were recorded on Bruker WP 80 (20.1 MHz), together with of resonance decoupling, or Bruker ACF-250 (62.9 MHz) spectrometers. Multiplicities are reported as broad singlet (br.s), singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). High field ^{13}C n.m.r. - Distortionless Enhancement by Polarisation Transfer (DEPT) spectra; methyl and methine carbon signals upwards, methylene carbon signals downwards, and quaternary carbon signals absent. Mass Spectra were recorded by electron impact using a Kratos (M.S.80) spectrometer or by fast atom bombardment (FAB) using a V.G.70-250 S spectrometer. Melting Points were recorded using a Kofler hot stage apparatus and are uncorrected. Microanalyses were carried out by Fisons plc, (Pharmaceutical Division, Loughborough).

***N,N*-Bis(methoxymethyl)-3,4-dimethoxy-β-phenylethylamine (1)**

3,4-Dimethoxy-β-phenyl-ethylamine (181.24 g, 1 mol), paraformaldehyde (60.06 g, 2 mol), methanol (400 ml), and potassium carbonate (276.42 g, 2 mol) were stirred vigorously for 2 days at room temperature. The solid was removed by filtration and washed with dried ether. The filtrate was concentrated under reduced pressure and then fractionally distilled affording *N,N-bis(methoxymethyl)-3,4-dimethoxy-β-phenylethylamine* (**1**) as a viscous oil (161.63 g, 60%), b.p. 125 °C /0.01 mmHg; ν_{max} (film) 2928, 2832, 2064, 1606, 1590, 1514, 1464, 1416 cm^{-1}; δ_H (60 MHz) 2.63-3.13 (4H, m, $PhCH_2CH_2$), 3.23 (6H, s, $2xOCH_3$), 3.80 and 3.83 (6H, s, 3-OCH_3 and 4-OCH_3), 4.27 (4H, s, $2xNCH_2O$), and 6.75 (3H, s, Ph-H) ppm; δ_C (20.1 MHz) 35.3 (q, OCH_3), 51.8 (q, 3 and 4-OCH_3), 54.8 (t, $PhCH_2$), 55.8 (t, $PhCH_2CH_2$), 86.7 (t, NCH_2O), 111.5 (d, C-5), 112.3 (d, C-2), 120.7 (d, C-6), 133.1 (s, C-1), 147.5 (s, C-4), and 149.0 (s, C-3) ppm; m/z 269 (M^+, 4.8%), 206 (22), 151 (31.5), 118 (73.5), 42 (100), M^+ measured 269.1604, $C_{14}H_{23}NO_4$ requires 269.1627.

***N,N*- Bis(ethoxymethyl)-β-phenylethylamine (2)**

β-Phenylethylamine (24.24 g, 0.2 mol), paraformaldehyde (12.01 g, 0.4 mol), ethanol (100 ml) and potassium carbonate (27.16g, 0.2 mol) were treated as described for the preparation of (**1**) to give *N,N-Bis(ethoxymethyl)-β-phenylethylamine* (**2**) as an oil (23.77 g, 50%), b.p. 86 °C/0.25 mmHg; ν_{max} (film) 3084, 3060, 3024, 2932, 2860, 1602, 1496, 1454 cm^{-1}; δ_H (60 MHz) 1.17 (6H, t, J = 7.5 Hz, $2xCH_2CH_3$), 2.67-3.17 (4H, m, $PhCH_2CH_2$), 3.40 (4H, q, J = 7.5 Hz, $2xOCH_2CH_3$), 4.30 (4H, s, $2xNCH_2O$), and 7.23 (5H, s, Ph-H) ppm; δ_C (20.1 MHz) 34.5 (q, CH_2CH_3), 34.8 (t, $PhCH_2$), 54.4 (t, $PhCH_2CH_2N$), 74.4 (t, OCH_2CH_3), 84.7 (t, NCH_2O), 126.0 (d, C-4), 128.3 (d, C-3 and C-5), 128.7 (d, C-2 and C-6), and 140.4 (s, C-1) ppm; m/z 237 (M^+, 0.2%), 146 (100), M^+ measured 237.1704, $C_{14}H_{23}NO_2$ requires 237.1729.

***N,N*-Bis(ethoxymethyl)-4-methoxy-β-phenylethylamine (3)**

4-Methoxy-β-phenylethylamine (15.12 g, 0.1 mol) was added dropwise to a mixture of paraformaldehyde (6.01 g, 0.2 mol), ethanol (50 ml) and benzene (50 ml). The mixture was stirred at room temperature for 15 min before being heated under reflux for 24 h using a Dean-Stark trap. The solvents were then removed by distillation through an 18" Vigreux column and the residue was fractionally distilled under reduced pressure to give *N,N-bis(ethoxymethyl)-4-methoxy-β-phenylethylamine* (**3**) as a viscous oil (21.48 g, 80%), b.p. 118- 124 °C/0.02 mmHg; ν_{max} (film) 2972, 1612, 1582, 1512, 1464, 1376 cm^{-1}; δ_H (250 MHz) 1.19 (6H, t, J = 3.5 Hz, 2xCH_2CH_3), 2.78 (2H, m, $PhCH_2$), 3.07 (2H, m, $PhCH_2CH_2N$), 3.40 (4H, q, J = 3.5 Hz, 2xOCH_2CH_3), 3.78 (3H, s, OCH_3), 4.31 (4H, s, 2xNCH_2O), 6.80-7.14 (4H, AA'BB' , J_{AB} = 5.8 Hz, Ph-H) ppm; δ_C (62.9 MHz) 15.2 (CH_2CH_3), 34.7 ($PhCH_2$), 52.0 ($PhCH_2CH_2$), 55.2 (OCH_3), 62.6 (OCH_2CH_3), 84.8 (NCH_2O), 113.7 (C-3 and C-5), 129.6 (C-2 and C-6), 132.5 (C-1), and 157.9 (C-4) ppm; m/z 267 (M^+, 1.9%), 222 (100), M^+ measured 267.1827; $C_{15}H_{25}NO_3$ requires 267.1834.

***N*-(5′-Methylfurfuryl)-β-phenylethylamine (4)**

A solution of *N,N*-bis(ethoxymethyl)-β-phenyl-ethylamine (**2**) (1.04g, 4.2 mmol) in light petroleum ether (40-60 °C) was treated under nitrogen at 0°C with trichloromethylsilane (0.69 g, 4.6 mmol). After 30 min the mixture was cooled to -60 °C, the solvent was decanted and the precipitated solid was washed with more solvent and then dried under high vacuum. The solid was then dissolved in acetonitrile (30 ml) and 2-methylfuran (0.33 g, 4 mmol) was added. The mixture was stirred at room temperature under nitrogen for 18 h. Water (20 ml) was added, the solvent removed in *vacuo* and the residue was washed with ether (3x30 ml) and then basified to pH14 with 2M NaOH and extracted with ether (3x40 ml). The combined organic extracts from the basic solution were dried and concentrated in *vacuo*. Kugelrohr distillation afforded *N-(5′-methylfurfuryl)-β-phenylethylamine* (**4**) as a colourless oil (0.47 g, 55%), b.p. 120 °C /0.01 mmHg; ν_{max} (film) 3316 (NH), 3100, 3084, 3060, 3024, 2920, 2820, 1602, 1494, 1452 cm^{-1}; δ_H (60 MHz)1.47 (1H, br.s, D_2O ex., NH), 2.27 (3H, s, CH_3), 2.63-3.03 (4H, m, $PhCH_2CH_2$), 3.73 (2H, s, CH_2N), 5.77-6.00 (1H, m, 4'-H), 6.03 (1H, d, J = 3 Hz, 3'-H), and 7.23 (5H, s, Ph-H) ppm; m/z 215 (M^+, 3.5%), 95 (100), M^+ measured 215.1307; $C_{14}H_{17}NO$ requires 215.1310.

***N*-(5′-Methylfurfuryl)-4-methoxy-β-phenylethylamine (5)**

2-Methylfuran (0.74g, 9 mmol) was added to the iminium salt [prepared as described above, from *N,N*-bis(ethoxymethyl)-β-4-methoxyphenyl-ethylamine (**3**) (2.67g, 10 mmol) and 3M $Et_2O.HCl$ (3.7 ml, 11 mmol)] in acetonitrile (50 ml). The mixture was stirred at room temperature for 18 h affording, after work-up as above, *N-(5′-methylfurfuryl)-4-methoxy-1-phenylethylamine* (**5**) as a colourless oil (1.30 g, 59%) b.p. 110-130 °C /0.01 mmHg; ν_{max} (film) 3320 (NH), 3024, 2996, 2920, 2832, 1610, 1582, 1566, 1510, 1462 cm^{-1}; δ_H (250 MHz) 1.10 (1H, br.s D_2O ex., NH), 2.22 (3H, s, 5'-CH_3), 2.67-2.91 (4H, m, $ArCH_2CH_2$), 3.71 (2H, s, 2'-CH_2N), 3.76 (3H, s, OCH_3), 5.84-5.86 (1H, m, 4'-H), 6.00 (1H, d, J = 3 Hz, 3'-H), 6.80-7.13 (4H, AA'BB', J_{AB} = 8 Hz, 2-H, 3-H, 5-H and 6-H) ppm; δ_C (62.9 MHz) 13.5 (CH_3), 35.4 (PhCH2), 46.3 ($PhCH_2CH_2$), 50.5 (2'-CH_2N), 55.0 (OCH_3), 105.9 (C-4'), 107.6 (C-3'), 113.7 (C-3 and C-5), 129.7 (C-2 and C-6), 132.0 (C-1), 151.2 (C-2'), 152.1 (C-5'), and 158.1 (C-4) ppm; m/z 245 (M^+, 3.3%), 95 (100), M^+ measured 245.1396; $C_{15}H_{19}NO_2$ requires 245.1416.

Reaction of 2-methylfuran with *N,N*-bis(methoxymethyl)-3,4-dimethoxy-β-phenylethylamine (1) and trichloromethylsilane

Trichloromethylsilane (0.90 g, 6 mmol) was added dropwise to a mixture of 2-methylfuran (0.49g, 6 mmol) and *N,N*-bis(methoxymethyl)-3,4-dimethoxy-β-phenylethylamine (**1**) (1.62g, 6 mmol) in acetonitrile (30 ml) under nitrogen at 0 °C. The mixture was then stirred at room temperature for 16 h. Water (20 ml) was added and the solvent removed in *vacuo*.. The residue was then washed with ethyl acetate (3x20 ml) and then basified to pH14 with 2M NaOH and extracted with ethyl acetate (3x40 ml). The combined organic washings from the basic solution were dried and concentrated in *vacuo* to a viscous immobile oil. The crude product was triturated with ether/light petroleum ether cooled to -60 °C and allowed to warm up slowly which gave a white solid. Recrystallisation from hexane afforded *N-(5'-methyl-2-furylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**7**) (1.12 g, 65%) as a white solid, m.p. 93-94 °C Found: C, 71.33; H, 7.44; N, 5.05. $C_{17}H_{21}NO_3$ requires C, 71.05; H, 7.37; N, 4.87%; ν_{max} (KBr) 3020, 2984, 2956, 2912, 2836, 2780, 2660, 1610, 1568, 1518 cm^{-1}; δ_H (250 MHz) 2.29 (3H, s, 5'-CH_3), 2.74-2.83 (4H, m, 3-H and 4-H), 3.58 (2H, s, 1-H), 3.65 (2H, s, NCH_2), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 5.91-5.93 (1H, m, 4'-H), 6.14 (1H, d, J = 3 Hz, 3'-H), 6.50 (1H, s, 5-H), and 6.58 (1H, s, 8-H) ppm; δ_C (62.9 MHz) 13.7 (CH_3), 28.5 (C-4), 50.4 (C-3), 54.6 (C-1), 55.1 (NCH_2), 55.9 (OCH_3), 105.9 (C-4'), 109.5 (C-3'), 109.6 (C-8), 111.5 (C-5), 126.7 (C-4a), 127.0 (C-8a), 147.2 and 147.5 (C-6 and 7), 149.2 (C-2'), and 151.9 (C-5') ppm; m/z 287 (M^+, 25.3%), 95 (100), M^+ measured 287.1509; requires 287.1521.

Reaction of *N*-methylindole with *N,N*-bis(methoxymethyl)-3,4-dimethoxy-β-phenylethylamine (1) and trichloromethylsilane

Trichloromethylsilane (0.90 g, 6 mmol) was added dropwise to a mixture of *N*-methylindole (0.79g, 6 mmol) and *N,N*-bis(methoxymethyl)-3,4-dimethoxy-β-phenylethylamine (**1**) (1.62g, 6 mmol) in acetonitrile (60 ml) under nitrogen at 0 °C. The mixture was then stirred at room temperature for 16 h. After work-up as in the previous experiment the product was isolated as a white solid and recrystallised from hexane / cyclohexane (1:1) to give *N-(1'-methyl-3'-indolylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**8**) (1.71g, 85%) m.p. 109 °C. Found: C, 74.95; H, 7.21; N, 8.27. $C_{21}H_{24}N_2O_2$ requires C, 74.97; H, 7.19; N, 8.33%; ν_{max} (KBr) 2996, 2964, 2904, 2868, 2788, 1674, 1608, 1566, 1468 cm^{-1}; δ_H (250 MHz) 2.79 (4H, br.s, 3-H and 4-H), 3.60 (2H, 1-H), 3.76 (3H, s, NCH_3), 3.79 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.87 (2H, s, CH_2N), 6.47 (1H, s, 5-H), 6.58 (1H, s, 8-H), 7.07 (1H, s, 2'-H), 7.09-7.33 (3H, m, 4'-H, 5'-H, and 6'-H), 7.76 (1H, d, J = 7.8 Hz, 7-H) ppm; δ_C (62.9 MHz) 28.9 (C-4), 32.4 (NCH_3), 50.6 (C-3), 53.2 (C-1), 55.6 (CH_2N), 55.7 (OCH_3), 109.0 (C-7'), 109.5 (C-8), 111.2 (C-5), 111.3 (C-3'), 118.9 (C-6'), 119.5 (C-4'), 121.1 (C-5'), 126.3 (C-4a), 127.1 (C-8a), 128.2 (C-3'a), 128.4 (C-2'), 136.9 (C-7'a), 147.0 (C-7), and 147.3 (C-6) ppm; m/z 336 (M^+, 1.3%), 274 (10), 144 (37.5), 56 (100), M^+ measured 336.1850; requires 336.1838.

***N*-Chloromethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and its Related Iminium Chloride (9)**

Trichloromethylsilane (29.90 g, 0.2 mol) in diethyl ether (100 ml) was added dropwise to a solution of *N,N*-bis(methoxymethyl)-3,4-dimethoxy-β-phenylethylamine (**1**) (26.94 g, 0.1 mol) in diethyl ether (300 ml) cooled to 0 °C under nitrogen. The mixture was then stirred at room temperature for 15 min and the precipitated solid was filtered under nitrogen, washed with dry ether (3x100 ml) and dried in *vacuo*. The equilibrium mixture of

N-chloromethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and its related iminium chloride (**9**) was isolated as a pale yellow crystalline solid in quantitative yield (24.17 g, 100%) and stored under nitrogen.

Bis(*N*-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinyl)methane (10)

Trichloromethylsilane (23.92 g, 120 mmol) in acetonitrile (50 ml) was added dropwise to a solution of *N,N*-bis(methoxymethyl)-3,4-dimethoxy-β-phenylethylamine (**1**) (16.16 g, 60 mmol) in acetonitrile (150 ml) at 0 °C under nitrogen. The mixture was stirred at room temperature for 1 h and the precipitated solid was dissolved in water (100 ml). The aqueous solution was washed with ethyl acetate (3x80 ml) and then basified to pH14 with 2M NaOH and extracted with ethyl acetate (3x100 ml). The combined organic extracts from the basic solution were dried and concentrated in *vacuo* to a yellow solid. Recrystallisation from ethyl acetate/cyclohexane (1:1) gave *bis(N-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinyl)methane* (**10**) (11.35g, 95%) as a white solid, m.p. 131-132 °C, (lit.[19], m.p. 126-127 °C). Found: C, 69.18; H, 7.70; N, 7.10. Calc. for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N; 7.03%; ν_{max} (KBr) 2996, 2780, 1610, 1522, 1464, 1420, 1380, 1368 cm^{-1}; δ_H (250 MHz) 2.84 (8H, s, 3 and 4-H), 3.27 (2H, s, NCH_2N), 3.67 (4H, s, 1-H), 3.82 (6H, s, 2xOCH_3), 3.83 (6H, s, 2xOCH_3), 6.55 (2H, s, 5-H), and 6.61 (2H, s, 8-H) ppm; δ_C (62.9 MHz) 28.6 (C-4), 49.2 (C-3), 54.0 (C-1), 55.92 and 55.95 (OCH_3), 80.6 (NCH_2N), 109.7 (C-8), 111.5 (C-5), 126.7 (C-4a), 127.0 (C-8a), 147.2 (C-7), and 147.5 (C-6) ppm; m/z 398 (M^+ not measured), 206 (22.3%), 192 (24.8), 164 (100); *N*-methylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinium ion $C_{12}H_{16}NO_2$, M^+ measured 206.1101; requires 206.1181. F.A.B. (M^+ + Rb) 483; (398 + 85).

***N,N´,N´´*-Tris(β-phenylethyl)hexahydro-*s*-triazine (11)**

Trichloromethylsilane (2.24 g, 15 mmol) in acetonitrile (30 ml) was added to a solution of *N,N*-bis(ethoxymethyl)-β-phenylethylamine (**2**) (3.56 g, 15 mmol) in acetonitrile (30 ml) at 0 °C. The mixture was then stirred under nitrogen at room temperature for 24 h. Following the work-up procedure described for the preparation of the aminal (**10**), *N,N´,N´´-tris(β-phenylethyl)hexahydro-s-triazine* (**11**), was isolated as a colourless oil (1.40g, 70%), b.p. 130 °C / 0.01 mmHg; ν_{max} (film) 3080, 3060, 3024, 2928, 2860, 2796, 1676, 1602, 1492, 1452 cm^{-1}; δ_H (250 MHz) 2.56-2.87 (12H, m, 3xNCH_2CH_2), 3.42 (6H, br.s, 3xNCH_2N), and 7.10-7.29 (15H, m, 3xPh-H) ppm; δ_C (62.9 MHz) 34.5 ($PhCH_2$), 54.3 ($PhCH_2CH_2N$), 74.3 (NCH_2N), 125.9 (C-4), 128.2 (C-3 and C-5), 128.6 (C-2 and C-6), and 140.2 (C-1) ppm; m/z) 399 (M^+ 0.5%), 132 (100), M^+ measured 399.2665; $C_{27}H_{33}N_3$ requires 399.2674.

***N,N´,N´´*-Tris[β-(4´-methoxyphenyl)ethyl]-hexahydro-*s*-triazine (12)**

Trichloromethylsilane (2.99 g, 20 mmol) in diethyl ether (25 ml) was added to a solution of *N,N*-bis(ethoxymethyl)-β-4-methoxyphenylethylamine (**3**) (2.67 g, 10 mmol) in diethyl ether (25 ml) under nitrogen at 0 °C. The mixture was then stirred at room temperature for 1 h. Following the work-up procedure described for the preparation of the aminal (**10**) the crude product was isolated as a viscous immobile oil. The product was then dissolved in ether, triturated with petroleum ether, and cooled and allowed to stand in the freezer overnight, to give pale yellow crystals. Recrystallisation from hexane gave *N,N´,N´´-tris[β-(4´-methoxyphenyl)ethyl]-hexahydro-s-triazine* (**12**) as white crystals (1.21 g, 74%), m.p. 53-54 °C; ν_{max} (Nujol) 3028, 2996, 2932, 2856, 2832, 1610, 1582, 1464 cm^{-1}; δ_H (250 MHz) 2.63-2.73 (12H, m, 3xNCH_2CH_2Ph), 3.48 (6H, br.s, 3xNCH_2N), 3.78 (9H, 3xOCH_3), 6.80-7.13 (12H, AA'BB', J_{AB} = 8 Hz, 3x[2-H, 3-H, 5-H,

and 6-H]) ppm; δ_C (62.9 MHz) 33.6 ($PhCH_2$), 54.7 ($PhCH_2C\ H_2N$), 55.2 (OCH_3), 74.5 (NCH_2N), 113.8 (C-3 and C-5), 129.6 (C-2 and C-6), 132.3 (C-1), and 157.9 (C-4) ppm; m/z) 489 (M^+ not detected), 163 (18%), 121 (100); 4-MeO-C_6H_4-$CH_2CH_2N^+$=CH_2; M^+ measured 163.0986; $C_{10}H_{13}NO$ requires 163.0986.

Reaction of the Aminal (10) with Acetyl Chloride

Acetyl chloride (0.43 g, 5.5 mmol) in diethyl ether (30 ml) was added dropwise to a solution of the aminal (**10**) (1.94 g, 4.8 mmol) in diethyl ether (30 ml). The mixture was stirred for 24 h at room temperature and the precipitated solid was filtered, washed with diethyl ether (3x20 ml) and dried in *vacuo* yielding the solid (**9**) (1.11 g, 95%). Treatment of the solid (**9**) with 2-methylfuran (0.31 g, 3.8 mmol) in acetonitrile (40 ml), at room temperature for 24 h gave the tetrahydroisoquinoline derivative (**7**) (0.98 g, 90%). The filtrate was concentrated in *vacuo* to give a white solid and recrystallised from cyclohexane to afford *N-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**13**) (0.61 g, 54%), m.p. 94-95 °C, (lit.[16], m.p. 94-95 °C). Found: C, 66.46; H, 7.27; N, 6.32. Calc. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95%; ν_{max} (Nujol) 1630 (NC=O), 1610, 1516 cm^{-1}; ^1H n.m.r. showed 2 rotamers, δ_H (250 MHz) 2.18 and 2.19 (3H, s, CH_3), 2.75-2.86 (4H, m, 3-H and 4-H), 3.67 (2H, t, J = 6 Hz, 4-H), 3.81 (2H, t, J = 6 Hz, 3-H), 3.85 and 3.86 (6H, s, 2xOCH_3), 4.55 and 4.66 (2H, s, 1-H), 6.59 and 6.64 (2H, s, 5 and 8-H) ppm; ^{13}C n.m.r. showed 2 rotamers, δ_C (62.9 MHz) 21.59 and 21.94 (CH_3), 28.04 and 28.94 (C-4), 39.46 and 47.76 (C-1), 43.72 and 44.10 (C-3), 55.94 and 56.00 (OCH_3), 108.93 and 109.42 (C-8), 111.27 and 111.64 (C-5), 124.23 and 125.38 (C-4a), 125.76 and 126.97 (C-8a), 147.68 and 147.73 (C-7), 147.90 and 147.96 (C-6), 169.32 and 169.35 (C=O) ppm; m/z 235 (M^+, 100%) measured 235.1213; requires 235.1208.

Preparation of *N*-Arylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines from the Solid (9)—General Method

An aromatic compound (1.0 equiv.) was added to a solution of the solid (**9**) (1.0 equiv.) in acetonitrile under nitrogen at room temperature and the mixture was stirred for a specified period of time. Water (20 ml) was added and the solvent was removed in *vacuo*. The residue was acidified to pH1 with 2M HCl and washed with ethyl acetate (3x30 ml). The aqueous layer was then basified to pH14 with 2M NaOH and extracted with ethyl acetate (3x40 ml). The combined organic washings from the basic solution were dried and concentrated in *vacuo* to a solid or a viscous immobile oil which was triturated with ether to give a solid. The crude products were then purified by recrystallisation from a suitable solvent.

***N* -Furfuryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (14)**

Furan (0.68 g, 10 mmol) was added to the solid (**9**) (2.42 g, 10 mmol) in acetonitrile (70 ml) and the mixture was stirred at room temperature for 72 h. After work-up the title compound was isolated as a viscous oil, crystallised by trituration with ether and recrystallised from hexane to give *N-furfuryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**14**) as a white solid (2.27 g, 83%), m.p. 60-62 °C. Found: C, 70.47; H, 7.02; N, 5.07. $C_{16}H_{19}NO_3$ requires C, 70.31; H, 7.01; N, 5.13%; ν_{max} (KBr) 3128, 2992, 2956, 2916, 1682, 1644, 1610, 1518, 1462 cm^{-1}. δ_H (250 MHz) 2.76-2.83 (4H, m, 3-H and 4-H), 3.58 (2H, 1-H), 3.72 (2H, s, NCH_2), 3.81 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 6.26-6.35 (2H, m, 3'-H and 4'-H), 6.49 (1H, s, 5-H), 6.58 (1H, s, 8-H), and 7.40-7.41 (1H, m, 5'-H) ppm; δ_C (62.9 MHz) 28.5 (C-4), 50.4 (C-3), 54.3 (C-1), 54.9 (CH_2N), 55.7 (OCH_3), 108.5 (C-3'), 109.7 (C-8'), 111.3 (C-5), 125.9 (C-4a), 126.3 (C-8a), 142.0 (C-

5'), 147.1 (C-7), 147.4 (C-6), and 151.8 (C-2') ppm; m/z 273 (M^+, 12.0%), 164 (100), M^+ measured 273.1368; requires 273.1365.

***N*-(5′-Methylfurfuryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7)**

2-Methylfuran (0.49g, 6 mmol) was added to the solid (**9**) (1.45 g, 6 mmol) in acetonitrile (40 ml) and the mixture was stirred at room temperature for 24 hours yielding *N-(5′-methylfurfuryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**7**) as white crystals (1.55 g, 90%), m.p. 93-94 °C, from hexane.

***N*-(2′-Pyrrolylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (15)**

Pyrrole (0.54 g, 8 mmol) was added to the solid (**9**) (1.93 g, 8 mmol) in acetonitrile (60 ml) and the mixture was stirred at room temperature for 20 hours. After work-up the title compound was isolated as a viscous oil, crystallised by trituration and recrystallised from cyclohexane/ethyl acetate (1:1), to afford *N-(2′-pyrrolylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**15**) as white crystals (1.82g, 83%) m.p. 146-148 °C. Found: C, 70.86; H, 7.71; N, 10.08. $C_{16}H_{20}N_2O_2$ requires C, 70.56; H, 7.40; N, 10.29%; ν_{max} (KBr) 3396 (NH; pyrrole), 3036, 3000, 2912, 2868, 2832, 2800, 1736, 1692, 1608, 1570, 1518, 1418 cm^{-1}; δ_H (250 MHz) 2.70-2.82 (4H, m, 3-H and 4-H), 3.51 (2H, s, 1-H), 3.67 (2H, s, NCH_2), 3.81 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 6.09-6.15 (2H, m, 3'-H and 4'-H), 6.49 (1H, s, 5-H), 6.60 (1H, s, 8-H), 6.72-6.75 (1H, m, 5'-H), and 8.68 (1H, br.s, D_2O ex. NH) ppm; δ_C (62.9 MHz) 28.4 (C-4), 50.9 (C-3), 55.2 (C-1), 55.3 (CH_2N), 55.8 (OCH_3), 107.5 (C-3'), 107.9 (C-4'), 109.5 (C-8), 111.3 (C-5), 117.9 (C-5'), 125.9 (C-4a), 126.3 (C-8a), 128.0 (C-2'), 147.2 (C-7) and 147.6 (C-6) ppm; m/z 272 (M^+, 1.8%), 192 (97), 164 (100) M^+ measured 272.1531; requires 272.1525.

***N*-(1′-Methyl-2′-pyrrolylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (16)**

N-methylpyrrole (0.65 g, 8 mmol) was added to the solid (**9**) (1.93 g, 8 mmol) in acetonitrile (60 ml) and the mixture was stirred at room temperature for 20 h. After work-up the title compound was isolated as a viscous oil, crystallised by trituration and recrystallised from hexane to afford *N-(1′-methyl-2′-pyrrolylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**16**) (2.00 g, 87%) m.p. 77-78 °C. Found: C, 71.08; H, 7.82; N, 9.40. $C_{17}H_{22}N_2O_2$ requires C, 71.30; H, 7.74; H, 9.78%; ν_{max} (KBr) 2988, 2952, 2928, 2832, 2704, 1652, 1610, 1518, 1494, 1470 cm^{-1}; δ_H (250 MHz) 2.66-2.80 (4H, m, 3-H and 4-H), 3.50 (2H, s, 1-H), 3.59 (2H, s, NCH_2), 3.65 (3H, s, NCH_3), 3.81 (3H, OCH_3), 3.84 (3H, s, OCH_3), 6.05-6.06 (2H, m, 3'-H and 4'-H), 6.50 (1H, s, 5-H), 6.59 (1H, s, 8-H), 6.60-6.61 (1H, m, 5'-H) ppm; δ_C (62.9 MHz) 28.9 (C[4]), 33.8 (NCH_3), 50.3 (C-3), 54.2 (C-1), 55.4 (NCH_2), 55.8 (OCH_3), 106.1 (C-3'), 109.4 (C-4'), 109.6 (C-8), 111.4 (C-5), 122.6 (C-5'), 126.4 (C-4a), 126.9 (C-8a), 128.9 (C-2'), 147.2 (C-7), and 147.4 (C-6) ppm; m/z 286 (M^+ not detected) 192 (93%), 164 (100), F.A.B. 285 (M^+-1, 47%); measured M^+ + Rb 371.239.

***N*-(3'-Indolylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (17)**

Indole (0.82 g, 7 mmol) was added to a solution of the solid (**9**) (1.69 g, 7 mmol) in acetonitrile (70 ml) and the mixture was stirred at room temperature for 22 h. After work-up the title compound was isolated as a viscous oil, crystallised by trituration and recrystallised from cyclohexane / ethyl acetate (1:1) to afford *N-(3'-indolylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**17**) (2.10 g, 93%) m.p. 156-7 °C; ν_{max} (KBr) 3364 (NH), 2948, 2784, 1610, 1556, 1466 cm^{-1}; δ_H (250 MHz) 2.80 (4H, br.s., 3-H and 4-H), 3.62 (2H, s,

1-H), 3.79 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.89 (2H, s, CH_2N), 6.48 (1H, s, 5-H), 6.58 (1H, s, 8-H), 7.10-7.37 (4H, m, 2'-H, 4'-H, 5'-H, and 6'-H]), 7.77 (1H, d, J = 7.7 Hz, 7'-H), and 8.23 (1H, br.s, D_2O ex. NH) ppm; δ_C (62.9 MHz) 28.7 (C-4), 50.7 (C-3), 53.1 (C-1), 55.6 (CH_2N), 55.9 (OCH_3), 109.7 (C-8), 111.1, (C-5) 111.4 (C-7'), 112.3 (C-3'), 119.4 (C-4' and C-6'), 121.6 (C-5'), 123.9 (C-2'), 126.4 (C-4a), 126.9 (C-8a), 128.0 (C-3'a), 136.2 (C-7'a), 147.1 (C-7), and 147.4 (C-6) ppm; m/z 322 (M^+, not detected), 192 (62%), 164 (100), F.A.B. 323 (M^++1, 80.66%); $C_{20}H_{22}N_2O_2$; measured: 323.314.

***N-(1'-Methyl-3'-indolylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (8) from the solid (9)**

N-methylindole (0.79g, 6 mmol) was added to the solid (**9**) (1.45 g, 6 mmol) in acetonitrile (60 ml) and the mixture was stirred at room temperature for 16 h. After work-up the product was isolated as a white solid and recrystallised from hexane / cyclohexane (1:1) to give *N-(1'-methyl-3'-indolylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**8**) (1.79g, 89%) m.p. 109 °C. The spectroscopic data were identical to those obtained previously and reported above.

N-(4'-Methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (18)— Sendaverine methyl ether

4-Methoxyphenyltributylstannane (3.97 g, 10 mmol) was added to the solid (**9**) (2.42 g, 10 mmol) in acetonitrile (100 ml) and the mixture was then stirred at room temperature for 72 h. After work-up the product was isolated as a viscous oil, crystallised by trituration and recrystallised from hexane to afford *N-(4'-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**18**) as white crystals (2.26 g, 73%) m.p.82-84 °C. Found: C, 72.58; H, 7.55; N, 4.36. $C_{19}H_{23}NO_3$ requires C, 72.82; H, 7.40; N, 4.47%; ν_{max} (KBr) 3036, 3004, 2908, 2872, 2836, 2740, 1696, 1630, 1610, 1582, 1518, 1462 cm^{-1}; δ_H (250 MHz) 2.71-2.83 (4H, m, 3-H and 4-H), 3.52 (2H, s, 1-H), 3.61 (2H, s, NCH_2Ar), 3.80, 3.81 and 3.83 (3x3H, s, OCH_3), 6.47 (1H, s, 5-H), 6.58 (1H, s, 8-H), 6.85-7.32 (4H, AA'BB', J_{AB} = 8 Hz, 2'-H, 3'-H, 5'-H, and 6'-H) ppm; δ_C (62.9 MHz) 28.8 (C-4), 50.6 (C-3), 55.2 (C-4'-O*C* H_3), 55.6 (C-1), 55.9 (C-6 and C-7-O*C* H_3), 62.1 (NCH_2Ar), 109.6 (C-8), 111.5 (C-5), 113.6 (C-3' and C-5'), 126.3 (C-4a), 126.9 (C-8a), 130.2 (C-2' and C-6'), 130.5 (C-1'), 147.2 (C-7), 147.5 (C-6), and 158.8 (C-4') ppm; m/z) 313 (M^+, 24.1%), 206 (18), 192 (16), 164 (87), 121(100), M^+ measured 313.1699; requires 313.1678.

N-(2',4'-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (19)

(a) 1,3-Dimethoxybenzene (5.53 g, 40 mmol) was added to the solid (**9**) (1.93 g, 8 mmol) in acetonitrile (100 ml) and the mixture was heated under reflux for 72 h. After work-up the product was isolated as a white solid and recrystallised from hexane to give *N-(2,'4'-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**19**) (2.11g, 77%) m.p.88-89 °C. Found: C , 69.91; H, 7.57; N, 4.08. $C_{20}H_{25}NO_4$ requires C, 69.95; H, 7.33; N, 4.08%; ν_{max} (KBr) 2996, 2956, 2916, 2836, 2788, 1686, 1610, 1586 cm^{-1}; δ_H (250 MHz) 2.75-2.81 (4H, m, 3- and 4-H), 3.58 (2H, s, 1-H), 3.65 (2H, s, NCH_2), 3.802, 3.806, 3.811, and 3.825 (4x3H, s, OCH_3), 6.46-6.48 (2H, m, 5'-H and 6'-H), 6.49 (1H, s, 5-H), 6.58 (1H, s, 8-H), and 7.31 (1H, d, J = 9 Hz, 3'-H) ppm; δ_C (62.9 MHz) 28.7 (C-4), 50.7 (C-3), 55.3 (C-1), 55.4 (CH_2NAr), 55.5 (C-2'-OCH_3), 55.6 (C-4'-OCH_3), 55.9 (C6 and C7-OCH_3), 98.4 (C-3'), 104.0 (C-5'), 109.6 (C-8), 111.5 (C-5), 116.9 (C-

1'), 126.4 (C-4a), 127.1 (C-8a), 131.2 (C-6'), 147.1 (C-7), 147.4 (C-6), 158.9 (C-4'), and 159.9 (C-2') ppm; m/z 343 (M^+, 21.9%), 151 (100), M^+ measured 343.1749; requires 343.1783.

(b) 2,4-Dimethoxyphenyltributylstannane[20] (1.67 g, 3.9 mmol) was added to the solid (**9**) (0.94 g, 3.9 mmol) in acetonitrile (40 ml). The mixture was stirred at room temperature for 48 h to give the product (**19**) (1.17 g, 87%), m.p.88-89 °C (from hexane).

***N*-(2′,4′-Dihydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (20)**

Resorcinol (0.77 g, 7 mmol) was added to the solid (**9**) (1.69 g, 7 mmol) in acetonitrile (60 ml) and the mixture was then stirred at room temperature for 16 h. Water (20 ml) was added and the solvent was removed in *vacuo*. The residue was acidified to pH1 with 2M HCl and washed with ethyl acetate (3x30 ml). The aqueous layer was then basified to pH9 with saturated $NaHCO_3$ and extracted with ethyl acetate (3x40 ml). The combined organic washings from the basic solution were dried and concentrated in *vacuo* to give a white solid which was recrystallised from ethyl acetate to give *N-(2′,4′-dihydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**20**) (1.76g, 80%) m.p.209-210 °C. Found: C, 68.73; H, 6.68; N, 4.18. $C_{18}H_{21}NO_4$ requires C, 68.55; H, 6.71; N, 4.44%), ν_{max} (KBr) 3428 (OH), 1651, 1622, 1517, 1466 cm^{-1}; δ_H (250 MHz, DMSO-d_6) 2.86 (4H, br.s, 3-H and 4-H), 3.66 (2H, s, 1-H), 3.78 (2H, s, NCH_2Ar), 3.82 and 3.84 (2x3H, s, OCH_3), 6.31-6.34 (2H, m, 5'-H and 6'-H), 6.50 (1H, s, 5-H), 6.59 (1H, s, 8-H), and 6.66 (1H, d, J_{AB} = 8 Hz, 3-H) ppm; (OH-not shown); δ_H (60 MHz), 6.97 (2H, br.s, D_2O ex. OH's) ppm; δ_C (62.9 MHz) 27.9 (C-4), 49.4 (C-3), 54.2 (C-1), 55.4 (OCH_3), 58.3 (NCH_2Ar), 102.6 (C-3'), 106.6 (C-5'), 110.0 (C-8), 111.8 (C-5), 112.8 (C-1'), 125.4 (C-4a), 125.7 (C-8a), 129.8 (C-6'), 147.0 (C-7), 147.4 (C-6), 157.7 (C-4'), and 157.9 (C-2') ppm; m/z 315 (M^+, 0.6%), 164 (100), M^+ measured 315.1439; requires 315.1470.

***N*-(2′-Hydroxy-1′-naphthylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (21)**

2-Naphthol (1.44 g, 10 mmol) was added to the solid (**9**) (2.42 g, 10 mmol) in acetonitrile (80 ml) and the mixture was stirred at room temperature for 16 h. After work-up as described for compound (**20**) the product was isolated as a white solid and recrystallised from cyclohexane /ethyl acetate (9:1) to give *N-(2′-hydroxy-1′-naphthylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**21**) (3.19g, 91%) m.p. 139-140 °C. Found: C, 76.01; H, 6.74; N, 3.85. $C_{22}H_{23}NO_3$ requires C, 75.62; H, 6.63; N, 4.01%; ν_{max} (KBr) 3468 (OH), 2956, 2936, 2832, 1622, 1610, 1520, 1464 cm^{-1}; δ_H (250 MHz) 2.93 (4H, br.s, 3-H and 4-H), 3.79 (2H, s, 1-H), 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.33 (2H, s, NCH_2Ar), 6.50 (1H, s, 5-H), 6.63 (1H, s, 8-H), 7.10 (1H, d, J = 8.9 Hz, 4'-H), 7.26-7.80 (4H, m, 5', 6', 7', and 8'-H), 7.87 (1H, d, J = 8.9 Hz, 3'-H) ppm, (OH not shown); δ_H (60 MHz) 11.03 (1H, br.s, D_2O ex. OH) ppm; , δ_C (62.9 MHz) 28.1 (C-4), 50.3 (C-3), 55.0 (C-1), 55.85 (OCH_3), 55.88 (OCH_3), 55.9 (NCH_2Ar), 109.4 (C-8), 110.8 (C-5), 111.3 (C-1'), 119.3 (C-3), 121.0 (C-8'), 122.4 (C-5'), 125.0 (C-4a), 125.3 (C-8a), 126.3 (C-4'), 128.5 (C-4'a), 128.9 and 129.2 (C-6' and C-7'), 132.7 (C-8'a), 147.5 (C-7), 147.8 (C-6), and 156.7 (C-1') ppm; m/z 349 (M^+, not detected), 206 (3%), 192 (76), 158 (100).

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