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DIBENZ[de,g]ISOQUINOLINE DERIVATIVES—I

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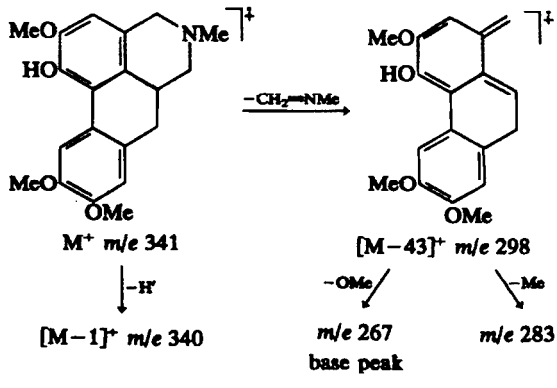
Abstract—The oxidation of certain derivatives of 2-methyl-4-benzyl-1,2,3,4-tetrahydroisoquinoline with VOF_3 results in the formation of dibenz[de,g]isoquinolines in moderate to good yields, thus making these substances available for the first time.

Intramolecular oxidative C–C coupling of phenols is a key step in the biosynthesis and synthesis of alkaloids, especially of the isoquinoline group, and of other polycyclic compunds.[1-3] However, the synthetic potential of this reaction has been severely limited by extremely low yields, and furthermore, the method is limited by the fact that a diphenolic moiety is required. Recently a number of reports has appeared describing efficient intramolecular oxidative aryl–aryl coupling of monophenolic and non-phenolic substrates using a variety of newer chemical reagents. Successful syntheses, in high yields of a number of natural and un-natural products have been realised.[4-11] In particular, Kupchan *et al.*,[12-17] have developed useful syntheses of aporphinoids, by oxidising 1-benzyl-1,2,3,4-tetrahydroisoquinolines with VOF_3. The mechanism of the coupling reaction elucidated by them is summarised in Scheme I for tetrahydropapaverine derivatives (**1a–1c**). Aryl migration from the morphinandienone (**2**) to give successively the neoproaporphine (**3**) and the aporphine (**4**) appears to be favoured in reactions involving substrates and conditions which may enhance the participation of the nitrogen lone pair of electrons. However use of BF_3/etherate appears to reinforce the alkyl migration to **5**. A monophenolic precurser, (**1d**), should undergo oxidative coupling very readily; this was found[17] to be the case.

It seemed to us that a synthesis of the dibenz[de,g]-isoquinoline ring system should be possible by oxidation of suitable 4-benzyl-1,2,3,4-tetrahydroisoquinolines with VOF_3; a mechanism for the oxidative coupling can be written (Scheme II) entirely analogous to that in Scheme I. However, in this case the availability of the nitrogen lone pair would not be expected to play a major role in determining the mode of rearrangement of the dienone **7** to **8** or to **10**, but subsequent cleavage of the N-containing ring of **10**, the product of alkyl migration to form **11**, should be facile in non-acidic solvents.

The readily available[18] 4-benzyl-1,2,3,4-tetrahydroisoquinolines studied were prepared as indicated in Scheme III. Some of these substances have been described elsewhere (**12b**, **12c**, and **12e**,[19] **13b**,[18] and **15g**[20]). The concomitant formation of **16** with **13a** is not unexpected.[21] After some initial difficulties, the reduction of methiodides (**14**, R_4 = Me) with $NaBH_4$ gave high yields of the required 4-benzyl-1,2,3,4-tetrahydroisoquinoline derivatives (**15**) (Experimental).

Influenced by the probable mechanistic pathway (Scheme II), the first compound chosen for oxidation was the 6-hydroxy-4-benzyltetrahydroisoquinoline (**15a**). Oxidation was achieved by using VOF_3 in CH_2Cl_2|TFA|TFAA|ethyl acetate solution under conditions that were established after considerable experimentation.[22] The reaction was followed by UV spectroscopy; it was anticipated that the UV spectrum of the hoped for product (**9a**) (Scheme II) would be very similar to that of the isomeric thaliporphine (**4**, R_1 = H, R_2 = Me Scheme I) [λ_{max}^{EtOH}: 220, 280 and 305 nm]. After 5 hr no further change in UV absorption occurred. Column chromatography over silica yielded *a base* (70% yield), shown by spectroscopic data to be the expected compound (**9a**); none of the isomeric ortho–ortho coupled product was detected by tlc. The UV spectrum (λ_{max} 233, 281 and 305 nm) is very similar to that expected[23,24] for aporphines. The use of ^{1}H NMR[23,24] in the structural elucidation of aporphines is concerned, essentially, with the fact that methoxy groups at C_1 or C_{11} appear at higher fields (3.4–3.72 δ) than the signals due to other OMe groups (3.7–3.9 δ) while C_{11}—H resonates at lower field (7.6–8.1 δ) than other aromatic protons (6.38–7.0 δ). By analogy it was expected that C_{11}—H of **9a** would absorb at a lower field than the other aromatic protons, and this was found to be the case; singlets at 8.21, 6.83 and 6.55 δ were recorded. The low resolution mass spectral fragmentation of (**9a**) was compatible with the Scheme:



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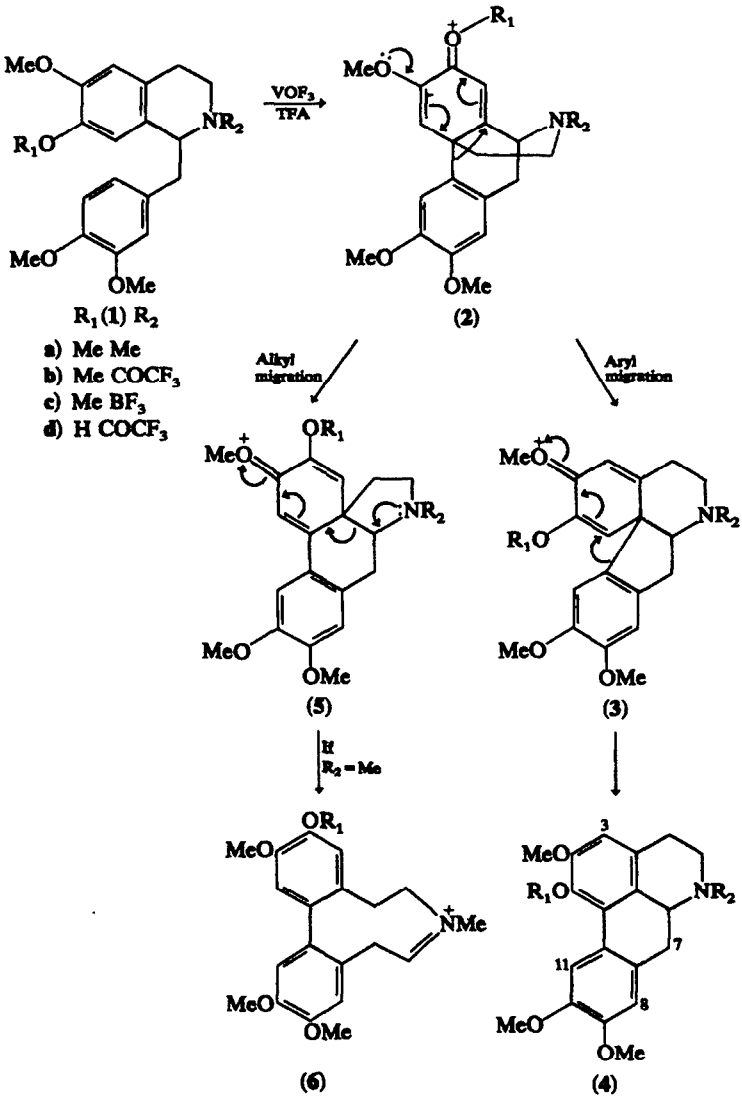
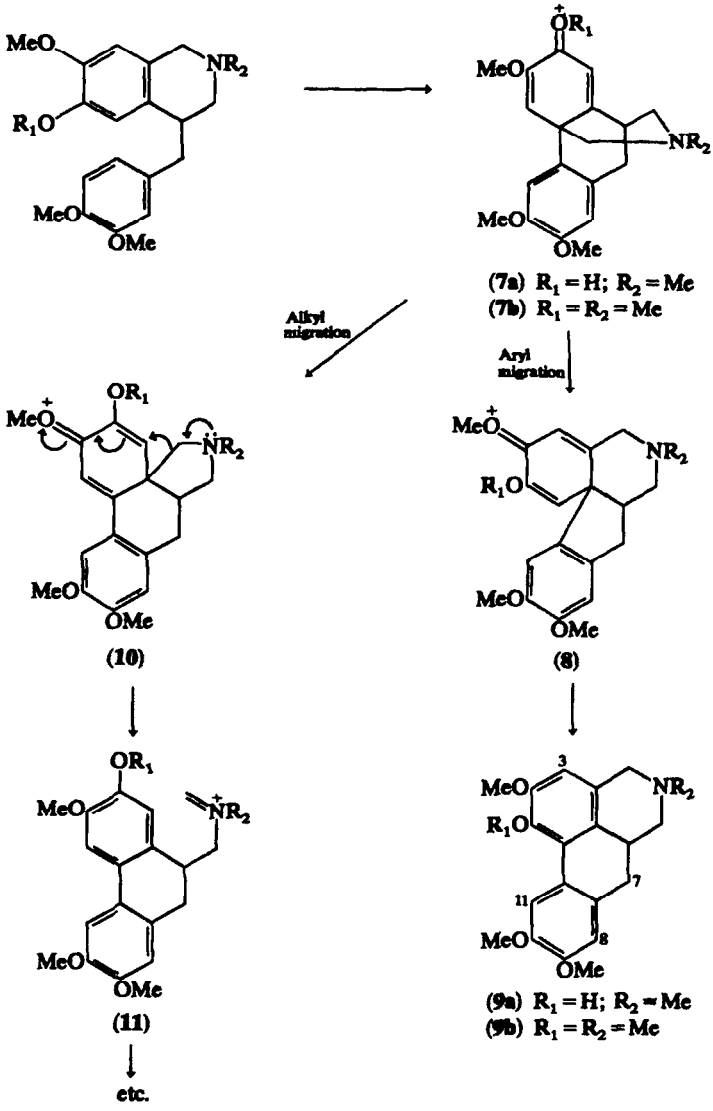


Scheme I. Oxidative coupling of 1-benzyltetrahydroisoquinolines

Although the presence of several minor components was suggested by tlc, further elution of the column from which **9a** was obtained did not provide pure compounds, although it was established that an orange quaternary salt was present. However, this materal was more easily isolated in a pure state when shorter reaction times were used (see below).

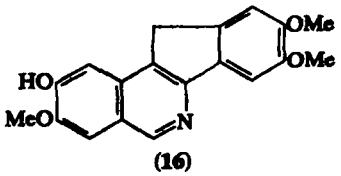
By analogy with oxidations in the 1-benzyltetrahydroisoquinoline series a dienone (**7a**) might be anticipated, and several attempts were made to isolate this substance. Thus, the phenol (**15a**) was again treated with VOF_3, but the reaction was quenched after 10 min, and the pH adjusted to 8–9 immediately in the hope of supressing any rearrangements of **7a**. Chromatography of the mixture over alumina instead of silica led to the isolation of **9a** once more, again in 70% yield, together with an orange crystalline solid (12% yield), $C_{20}H_{22}ClNO_4$. The IR spectrum is devoid of absorption in the CO region, thus precluding the sought for dienone. The ^{1}H NMR spectrum exhibited four singlets in the aromatic region resonating at 8.8, 7.13, 6.5 and 6.21 δ, together with singlets attributable to three O-methoxyls at about 4.0 δ. The N-Me resonance appeared at 3.14 δ, indicating a quaternary salt rather than a tertiary amine. The base peak in the mass spectrum at *m/e* 339 can be assigned to a structure such as **17**, formed from the parent compound by loss of HCl. This may also be responsible for the unusual behaviour observed when the orange solid was heated; it softened at 96–100° to a red gum which solidified over 130–140°, and then finally melted at 145–146°. Structures **18** and **19** are compatible with these data, the latter being preferred since very little change was observed in the UV spectrum of the compound upon the addition of base. The signal at 8.8 δ in the ^{1}H NMR spectrum is probably due to C_{11}—H, and since, in structure **18**, C_4—H would be expected to resonate at lower field than 7.13 δ, the alternative structure **19** is again preferred. That this minor product of the oxidation of **15a** arises from over-oxidation is supported by the fact that when **9a** itself was subjected



Scheme II. Probable course of oxidation of 4-benzyltetrahydroisoquinolines

to the conditions of the oxidation with VOF_3 the orange solid was obtained in high yield. Conversely, reduction of the orange solid with $NaBH_4$ gave the dibenz[de,g]isoquinoline (**9a**). Further attempts to isolate the dienone (**7a**) by carrying out the oxidation of **15a** with VOF_3 in the absence of acid failed; no oxidation occurred at all. So, either the sought for dienone is too unstable to isolate under the reaction conditions, or aryl–aryl coupling occurs directly and not through the intermediacy of the dienone.

Oxidation of the tetramethoxy-4-benzyl-1,2,3,4-tetrahydroisoquinoline (**15b**) under the conditions used for **15a** gave a mixture from which a base (38%) and a quaternary salt (10%) were isolated. The spectral characteristics of the base, which analysed for $C_{20}H_{25}NO_4$, are fully in accord with those expected for the dibenz[de,g]isoquinoline derivative



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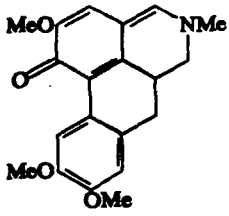

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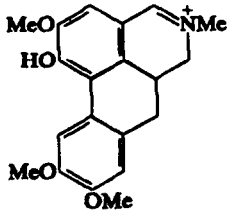

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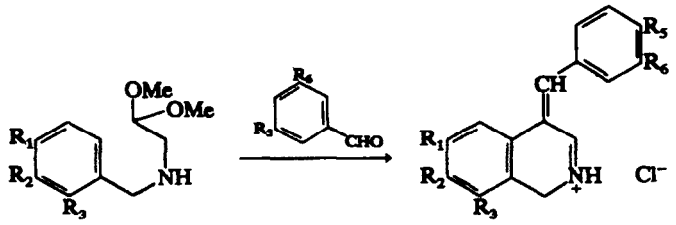
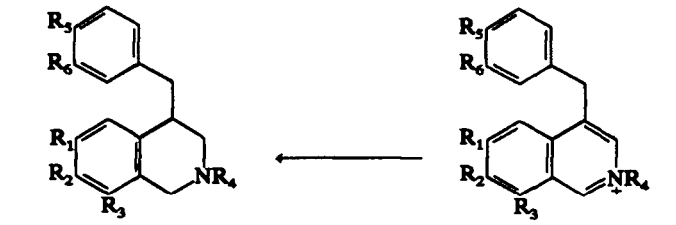


	R_1	R_2	R_3
12a	OBz	OMe	H
12b	OMe	OMe	H
12c	OMe	OH	H
12d	H	OMe	OMs
12e	H	OMe	OH

	R_1	R_2	R_3	R_5	R_6
13a	OH	OMe	H	OMe	OMe
13b	OMe	OMe	H	OMe	OMe
13c	OMe	OH	H	OMe	OMe
13d	H	OMe	OMs	OMe	OMs

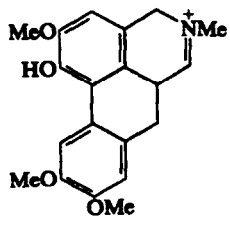


	R_1	R_2	R_3	R_4	R_5	R_6
15a	OH	OMe	H	Me	OMe	OMe
15b	OMe	OMe	H	Me	OMe	OMe
15c	OMe	OMe	H	Me	OMe	OH
15d	OMe	OH	H	Me	OMe	OMe
15e	OMe	OMe	H	Me	OH	OMe
15f	OH	OMe	H	Me	O—CH_2—O	
15g	H	OMe	OH	Me	OMe	OH
15h	H	OMe	OMs	H	OMe	OMs
15i	H	OMe	OMs	Ms	OMe	OMs
15j	H	OMe	OH	Ms	OMe	OH

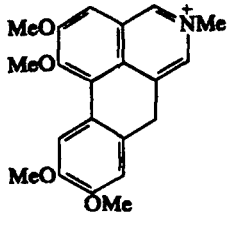
	R_1	R_2	R_3	R_4	R_5	R_6
14a	OH	OMe	H	H	OMe	OMe
14b	OMe	OMe	H	Me	OMe	OMe
14c	OMe	OMe	H	Me	OMe	OH
14d	OMe	OH	H	Me	OMe	OMe
14e	OMe	OMe	H	Me	OH	OMe
14f	OH	OMe	H	Me	O—CH_2—O	
14g	H	OMe	OH	Me	OMe	OH
14h	H	OMs	OMs	H	OMe	OMs

Scheme III. The preparation of the 4-benzyltetrahydroisoquinolines.

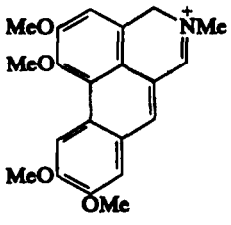
(**9b**) (Experimental). The orange quaternary salt, $C_{20}H_{19}ClNO_4$, exhibited ^1H NMR and mass spectral characteristics consistant with either structure **20** or **21**, but a satisfactory elemental analysis could not be obtained.



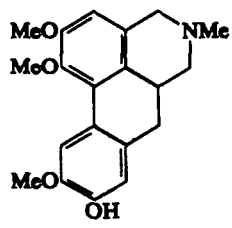
(**19**)



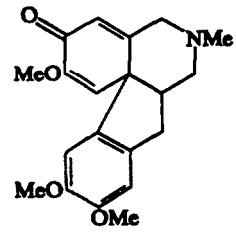
(**20**)



(**21**)

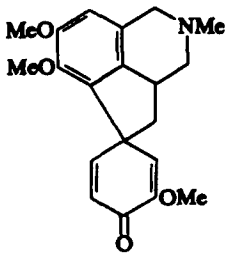


(**22**)



(**23**)

In an effort to develop this synthesis of the dibenz[de,g]isoquinoline ring system further, a number of monophenolic 4-benzyltetrahydroisoquinolines (**15c–15f**) was prepared by the general method (Scheme III). Compound **15c** was chosen because direct para coupling to yield **22** should be a facile process, and some coupling *ortho* to OH might be anticipated. With the substrate **15d** the formation of the dienone (**23**) may be expected to occur, whereas with **15e** the isomeric dienone (**24**) might be produced. In the event only black, tarry, multicomponent mixtures resulted from the oxidation of any of these phenols with VOF_3 under a



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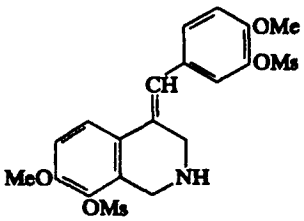
variety of conditions. Evidently the oxidation potential of VOF_3 is too high for these substrates; a study of alternative oxidising agents will be reported subsequently.

The diphenolic 4-benzyltetrahydroisoquinoline (**15g**) was required to examine the possibility of oxidative coupling with $K_3Fe(CN)_6$. Although **15g** was obtained from **12e** and isovanillin (Scheme III), the yields were very poor, and considerable difficulty was experienced in the purification of a number of the intermediates. In an alternative approach O-mesylisovanillin was condensed with **12d** to yield **13d**, which, with $NaBH_4$ gave **25**. This was



(25)

hydrogenated to **15h**, characterised as the N-mesylate (**15i**). Removal of the O-mesyl groups from the latter with base gave the diphenol (**15j**). However, all attempts to effect aryl–aryl coupling under a variety of conditions using $K_3Fe(CN)_6$, $FeCl_3$ and MnO_2 failed; only complex, tarry mixtures were obtained.

EXPERIMENTAL

UV spectral data refer to EtOH solns unless otherwise stated, and IR spectra were measured on nujol mulls. Proton NMR spectra were measured at 60 or 100 MHz and chemical shifts are measured in ppm downfield from internal TMS. M.ps are uncorrected. Mass spectral measurements were made at low resolution on AEI MS12 and the high resolution mass measurements were carried out with AEI MS902 instrument.

N-(3-Methoxy-4-benzyloxybenzal)aminoacetaldehyde dimethylacetal. O-Benzylvanillin (15 g) and aminoacetaldehyde dimethylacetal(aminoacetal) (6.5 g) were heated together in benzene (80 mL) under a Dean and Stark separator for 5 hr, then the solvent was removed and the residue crystallised from petrol (b.p. 60–80°) to give white prisms (88%) m.p. 57.5–58.0°. ^{1}H NMR($CDCl_3$): 8.15 s [1] (CH=N); 7.5–7.2 complex [6] (C_6H_5 + Ar—H); 7.1 dd [1], J = 8.0 Hz, and 2.0 Hz, (Ar—H); 6.87 d [1], J = 8.0 Hz (Ar—H); 5.17 s [2] (C_6H_5—CH_2); 4.65 t [1], J = 5.0 Hz ($CH(OMe)_2$); 3.92 s [3] (ArOMe); 3.73 d [2], J = 5.0 Hz, (—CH_2—CH); 3.41 s [6] ($CH(OMe)_2$). [Found: C, 69.2; H, 6.8; N, 4.3. $C_{19}H_{23}NO_4$ requires C, 69.4; H, 7.0; N, 4.25%]

N-Benzylaminoacetaldehyde dimethylacetals-general procedure. The benzaldehyde derivative (0.1 mole) and aminoacetal (10.5 g) were stirred in EtOH soln at r.t. for 24 hr $NaBH_4$ (2.0 g) was then added portionwise and the mixture stirred further 24 hr. Water (400 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic extracts were washed with water (50 mL), dried (Na_2SO_4) and evaporated to leave the required acetal and excess of aminoacetal. The latter was removed by distillation at about 70°/1.0 mm.

N-(3-Methoxy-4-benzyloxybenzyl)aminoacetaldehyde dimethylacetal (**12a**) was obtained as a colourless oil (76%) ^{1}H NMR ($CDCl_3$): 7.5–7.2 m [5] ($C_6H_5CH_2$); 6.90 s [1] and 6.79 s [1] (Ar—H's); 5.11 s [2] ($C_6H_5CH_2$); 4.47 t [1], J = 5 Hz ($CH(OMe)_2$) 3.87 s [3] (OMe); 3.72 s [2] (Ar—CH_2N); 3.35 s [6] ($CH(OCH_3)_2$); 2.73 d [2], J = 5 Hz ($CH_2CH(OMe)_2$); 1.76 b.s [1] (NH, removed by D_2O). [Found: C, 69.0; H, 7.7 N, 4.4. $C_{19}H_{25}NO_4$ requires C, 69.0; H, 7.55; N, 4.25%]

N-(3-Hydroxy-4-methoxybenzyl)aminoacetaldehyde dimethylacetal (**12e**) was obtained as a pale yellow solid (81%). ^{1}H NMR ($CDCl_3$): 6.89 b.s. [1] and 6.80 s [2] (Ar—H's); 4.47 t [1], J = 5 Hz ($CH(OMe)_2$); 3.83 s [3] (ArOMe); 3.69 s [2] (Ar—CH_2N); 3.34 s [6] $CH(OCH_3)_2$); 2.72 d [2], J = 5 Hz ($CH_2CH(OMe)_2$); 4.0–3.8 b.s. [2] (OH + NH, removed by D_2O). [Found: C, 59.5; H, 7.5; N, 5.4. $C_{12}H_{19}NO_4$ requires C, 59.7; H, 7.9; N, 5.8%]

N-(2-Mesyloxy-3-methoxybenzyl)aminoacetaldehyde dimethylacetal (**12d**) was obtained as a colourless oil (95%). [Found: C, 48.4; H, 6.5; N, 4.2. $C_{13}H_{21}NO_6S$ requires C, 48.9; H, 6.6; N, 4.4%]

4-(3,4-Dimethoxybenzylidene)-6-Hydroxy-7-methoxy-1,4-dihydroisoquinoline (**13a**). Compound **12a** (17.3 g) and veratraldehyde (10.8 g) were dissolved in EtOH (100 mL) and conc HCl (100 mL) was added. The mixture was heated under reflux for 0.5 hr, diluted with water (60 mL), washed with benzene (2 × 50 mL) and left at r.t. 48 hr. The red crystals of **13a** hydrochloride (59%) were collected. Attempts to record m.p. caused isomerisation. $\lambda_{max}(\varepsilon_{max})$: 236(15,900); 275(11,300); 305(10,400); 366(11,300). ^{1}H NMR (TFA): 8.95 d [1], J = 9 Hz (C_3—H); 8.39 b.s. [1] (ArCH=C<); 7.54 s [1], 7.18 s [3] and 6.88 s [1] (Ar—H's); 5.17 b.s. [2] (CH_2—$\overset{+}{N}$); 4.02 s [9] (3 × OMe). [Found: C, 62.9; H, 5.1; N, 3.6. $C_{19}H_{20}NO_4Cl$ requires C, 63.2; H, 5.5; N, 3.9%] Evaporation of the EtOH/H_2O filtrate and trituration of the residue with EtOH gave a second crop of **13a** hydrochloride. The EtOH-soluble materal remaining was heated under reflux in EtOH, cooled, and the yellow crystals of *2-hydroxy-3,8,9-trimethoxy-11H-indeno[1,2-c]isoquinoline* (**16a**) hydrochloride (1.5 g) collected, m.p. 268–270° $\lambda_{max}(\varepsilon_{max})$ 243(23,600); 277(31,400); 308(17,600); 330(15,500). ^{1}H NMR (TFA): 9.05 d [1] (C_5—H); 7.71 s [1] (C_4—H); 7.58 s [2] (C_1—H + C_7—H); 7.4 s [1] (C_{10}—H); 4.21 and 4.10 [11] (3 × OMe + Ar—CH_2Ar). [Found: C, 63.1; H, 4.8; N, 3.6. $C_{19}H_{18}NO_4Cl$ requires: C, 63.5; H, 5.0; N, 3.9%]

4-(3-Mesyloxy-4-methoxybenzylidene)-7-methoxy-8-mesyloxy-1,4-dihydroisoquinoline (**13d**). Compound **12d** (25.0 g) in conc HCl (250 mL) was warmed to 60°, then O-Mesylisovanillin (18.0 g) was added, and the temp was allowed to rise to 90°. After 0.75 hr the mixture was cooled and the orange solid (**13d**) hydrochloride was collected and washed with cold EtOH. Attempts to measure m.p. caused isomerisation. [Found: C, 46.5; H, 4.5; N, 3.2; S, 13.0; Cl, 7.15;. $C_{20}H_{21}NO_8S_2Cl$ requires C, 47.7; H, 4.4; N, 3.1; S, 12.7; Cl, 7.05%].

4-(3,4-Dimethoxybenzyl)-6-hydroxy-7-methoxyisoquinoline (**14a**). Compound **13a** (5.0 g) was heated under reflux in EtOH (100 mL) until no further change in UV spectrum occurred. Evaporation left a yellow solid which

was dissolved in water (100 mL), pH adjusted to 8 with NH_3 soln, and the resultant ppt was collected and crystallised from EtOH to give beige plates (100%) m.p. 194–195° (dec) of the required **14a**; $\lambda_{max}(\varepsilon_{max})$ 242(69,700); 283(15,150); 313(8,300); 327(6,400). After addition of NaOH: 222(54,500); 253(62,100); 340(15,100). ^{1}H NMR ($CDCl_3$/d_6 DMSO): 8.9 s [1] (C_1—H); 8.16 s [1] (C_3—H); 7.36–6.64 m [5] (Ar—H^{1}s); 4.16 s [2] (—CH_2—); 3.99 s [3] (OMe); 3.77 s [6] (2×OMe). Methiodide m.p. 208–210° (dec) [Found: C, 51.9; H, 4.8, N, 2.9. $C_{20}H_{22}NO_4I$ requires C, 51.4; H, 4.7; N, 2.9%]

4-Benzylisoquinoline (**14**) *methiodides—General procedure.* Compound **12** (0.02 mole) and the required benzaldehyde derivative (0.024 mole) were dissolved in EtOH (40 mL), and conc HCl (40 mL) was added. The mixture was heated under reflux for 1.5 hr, cooled and poured into H_2O (400 mL). After washing with benzene (3×50 mL), the aqueous soln was made strongly basic (30% NaOH) and warmed. After cooling the pH was adjusted to 8–9 and the mixture extracted with CH_2Cl_2 (3×100 mL). Evaporation of the dried (Na_2SO_4) combined extracts gave the 4-benzylisoquinolines as brown gums. These, without purification, were dissolved in acetone (150 mL), heated to boiling and MeI (100% excess) was added. After 5 mins the mixtures were cooled to r.t. and the crystalline methiodides were collected.

4-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline (**14b**) *methiodide* was obtained as an orange solid, m.p. 204–208° from EtOH [Found: C, 52.45; H, 5.1; N, 2.8. $C_{21}H_{24}NO_4I$ requires: C, 52.4; H, 5.0; N, 2.9%]

4-(3-Hydroxy-4-methoxybenzyl)-6,7-dimethoxyisoquinoline (**14c**) *methiodide.* Yellow needles ^{1}H NMR ($CDCl_3$/d_6 DMSO): 9.7 s [1] (C_1—H); 8.5–6.6 m [7] (6×Ar—H^{1}s+OH removed by D_2O); 4.48 s [3] (N—Me); 4.36 s [2] (C_4—CH_2); 4.05 s [6] (2×OMe); 3.83 s [3] (OMe) [Found: C, 51.3; H, 4.9; N, 2.9; I, 26.8. $C_{20}H_{22}NO_4I$ requires: C, 51.4; H, 4.7; N, 3.0; I, 27.2%]

4-(3,4-Dimethoxybenzyl)-6-methoxy-7-hydroxyisoquinoline (**14d**) *methiodide.* Green-brown needles m.p. 156–157° (dec) ^{1}H NMR ($CDCl_3$/d_6 DMSO): 9.57 b.s. [1] (C_1—H); 8.4–6.7 m [7], (6×Ar—H+OH removed by D_2O); 4.47 b.s. [5] (N—Me+C_4—CH_2); 4.07 s [3] OMe); 3.85 s [6] (2×OMe). [Found: C, 51.6; H, 5.1; N, 3.0; I, 27.0. $C_{20}H_{22}NO_4I$ requires: C, 51.4; H, 4.7; N, 3.0; I, 27.2%]

4-(3-Methoxy-4-hydroxybenzyl)-6,7-dimethoxyisoquinoline (**14e**) *methiodide.* Beige microcrystalline solid, m.p. 175–176°. ^{1}H NMR ($CDCl_3$/d_6 DMSO): 9.78 s [1] (C_1—H); 8.63 b.s. [1] (OH, removed by D_2O): 8.38 s [1] (C_3—H); 7.86 s [1] (Ar—H); 7.0–6.6 m [5] (Ar—H^{1}s); 4.50 s [3] (N—Me); 4.43 s [2] (C_4—CH_2); 4.06 s [6] (2×OMe); 3.81 s [3] (OMe). [Found: C, 51.0; H, 4.7; N, 2.7; I, 26.9. $C_{20}H_{22}NO_4I$ requires: C, 51.4; H, 4.7; N, 3.0; I, 27.2%]

4-(3,4-Methylenedioxybenzyl)-6-hydroxy-7-methoxyisoquinoline (**14f**) *methiodide.* Light brown needles, m.p. 182–183° (dec) ^{1}H NMR ($CDCl_3$/d_6 DMSO): 9.51 s [1] (C_1—H); 8.12 s [1] (C_3—H); 7.7 b.s. [1] (Ar—H); 7.4 s [1] (Ar—H); 6.7 d [3] (3×Ar—H); 5.91 s [2] (CH_2O_2); 4.40 s [3] (N—Me); 4.20 s [2] (C_4—CH_2); 4.03 s [3] (OMe). [Found: C, 50.4; H, 4.1; N, 2.8. $C_{19}H_{18}NO_4I$ requires: C, 50.5; H, 4.0; N, 3.1%]

2-Methyl-4-benzyl-1,2,3,4-tetrahydroisoquinolines—General procedure. The 4-benzylisoquinoline methiodide (2.0 g) was dissolved in hot 1:1 EtOH:H_2O (100 mL) and $NaBH_4$ (1.5 g) was added portionwise with stirring. After stirring overnight at r.t., the mixture was made acid (dil HCl) (to decompose excess of $NaBH_4$ and any N-boranes), the pH was adjusted to 8–9 (dilute NH_3) and extracted with benzene (3×50 mL). Evaporation of the combined, dried (Na_2SO_4) extracts left the required tetrahydroisoquinoline as a colourless oil, which crystallised from EtOH.

2-Methyl-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**15b**) was obtained (92%) as white needles, m.p. 96–98°. $\lambda_{max}(\varepsilon_{max})$: 234(17,100); 283(8,000). ^{1}H NMR ($CDCl_3$): 6.9–6.6 m [3] (Ar—H^{1}s); 6.5 s [2] (Ar—H^{1}s); 3.82 s [9] (3×OMe); 3.78 s [2] (C_4—CH_2); 3.71 s [3] (OMe); 3.6—2.4 m [5] (aliphatic-H^{1}s); 2.34 s [3] (NMe): M.S. *m/e* 357 (M^+) (43%) 356 (M^+-1) (27%); 342 (12%); 326 (5%); 314 (8%); 309 (28%); 283 (26%); 268 (9%); 219 (40%); 206 (92%); 205 (100%); 204 (95%); 151 (26%); [Found: C, 70.1; H, 7.3; N, 3.9. $C_{21}H_{27}NO_4$ requires: C, 70.6; H, 7.6; N, 3.9%].

2-Methyl-4-(3,4-dimethoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**15a**). White needles (90%) m.p. 140–142°. $\lambda_{max}(\varepsilon)_{max}$ 230(14,000); 286-(6,500). On addition of NaOH $\lambda_{max}(\varepsilon)_{max}$ 226(18,300); 288(5,000); 304(5,500). ^{1}H NMR ($CDCl_3$): 6.94–6.66 m [4] (Ar—H^{1}s); 6.52 s [1] (Ar—H); 5.8 b.s. [1] (OH, removed by D_2O): 3.88 s and 3.83 s [9] (3×OCH_3); 3.8–2.4 m [7] (aliphatic-H^{1}s); 2.37 s [3] (N—CH_3): M.S. (*m/e*) 343 (M^+) [26%], 342 ($M-1$)$^+$ [15%], 328 [10%], 312 [3%], 300 [5%], 285 [10%], 269 [12%], 254 [4%], 205 [16%], 192 [73%], 191 [91%], 190 [100%], 151 [85%]. [Found: C, 69.9, H, 7.1, N, 4.15. $C_{20}H_{25}NO_4$ requires: C, 70.0; H, 7.3, N, 4.1%].

2-Methyl-4-(3-hydroxy-4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**15c**). White needles (81%). M.p. 139–143° $\lambda_{max}(\varepsilon)_{max}$ 234(11,200); 285-(6,600). On addition of NaOH $\lambda_{max}(\varepsilon)_{max}$ 233(12,700); 293(7,800). ^{1}H NMR ($CDCl_3$), 6.9–6.4 m [5] (Ar—H^{1}s); 3.87 s, 3.85 s and 3.77 s [10] (3×OCH_3+OH removed by D_2O); 3.76–2.44 m [7] (aliphatic-H^{1}s); 2.40 s [3] (N—CH_3). M.S. (*m/e*) 343 (M^+) [8%], 342 (M^+-1) [4%], 312 [2%], 300 [10%], 285 [15%], 269 [6%], 254 [3%], 239 [2%], 225 [4%], 219 [16%], 206 [89%], 205 [100%], 204 [93%], 137 [27%]. [Found C, 70.1; H, 7.2; N, 4.15. $C_{20}H_{25}NO_4$ requires: C, 70.0: H, 7.3; N, 4.1%]

2-Methyl-4-(3,4-dimethoxybenzyl)-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (**15d**). White needles (78%) m.p. 139–140° $\lambda_{max}(\varepsilon)_{max}$ 239(16,100), 285(7,000). On addition of NaOH $\lambda_{max}(\varepsilon)_{max}$ 233-(15,800), 254(14,300), 288(7,200), 300 sh (6,050). ^{1}H NMR ($CDCl_3$), 7.0–6.66 m [3] (Ar—H^{1}s); 6.57 s [1] (Ar—H); 6.54 s [1] (Ar—H); 3.90 s [6] (2×OCH_3); 3.77 s [3] (OCH_3); 3.7–2.4 m [7] (aliphatic-H^{1}s); 2.39 s [3] (N—CH_3). M.S. (*m/e*) 343 (M^+) [7%], 342 (M^+-1) [5%], 328 [3%], 325 [3%], 312 [1%], 310 [1%], 300 [2%], 285 [7%], 269 [7%], 254 [4%], 205 [19%], 192 [78%], 191 [100%], 190 [89%], 151 [24%]. [Found: C, 70.0; H, 7.35; N, 4.1. $C_{20}H_{25}NO_4$ requires: C, 70.0; H, 7.3; N, 4.1%].

2-Methyl-4-(3-methoxy-4-hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**15e**). Colourless prisms (100%) m.p. 123–125° $\lambda_{max}(\varepsilon)_{max}$ 237(16,500); 284(10,100). On addition of NaOH $\lambda_{max}(\varepsilon)_{max}$ 241(16,500); 292(10,600). ^{1}H NMR ($CDCl_3$); 6.9–6.6 m [3] (Ar—H^{1}s); 6.47 s [2] (Ar—H^{1}s); 5.88 b.s. [1] (OH, removed by D_2O); 3.78 s [6] (2×OCH_3); 3.70 s [3] (OCH_3); 3.7–2.3 m [7] (aliphatic-H^{1}s), 2.34 s [3] (N—CH_3). M.S. (*m/e*) 343 (M^+) [67%], 342 ($M-1$)$^+$ [21%], 328 [10%], 312 [5%], 300 [13%], 285 [19%], 269 [7%], 254 [2%], 220 [31%], 206 [100%], 205 [66%], 204 [51%] m* 271, 202 [Found: C, 70.1; H, 7.2; N, 4.20. $C_{20}H_{25}NO_4$ requires: C, 70.0; H, 7.3; N, 4.1%]

2-Methyl-4-(3,4-methylenedioxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**15f**). Pale yellow crystalline solid (64%) $\lambda_{max}(\varepsilon)_{max}$ 235(12,000); 289-(10,100). On addition of NaOH $\lambda_{max}(\varepsilon)_{max}$ 235(13,400); 298(10,700). ^{1}H NMR ($CDCl_3$): 6.84–6.56 m [4] (Ar—H^{1}s); 6.5 s [1] (Ar—H); 5.92 s [2] (CH_2O_2); 5.52 b.s. [1] (OH, removed by D_2O); 3.8 s [3] (OCH_3); 3.74–2.40 m [7] (aliphatic-H^{1}s); 2.37 s [3] (N—CH_3), M.S. (*m/e*) 327 (M^+) [41%], 326 (M^+-1) [17%], 312 [77%], 284 [11%], 269 [26%], 254 [9%], 239 [7%], 205 [27%], 192 [78%],

191 [93%], 190 [100%], 135 [39%]. [Found: C, 69.8; H, 6.2; N, 4.3. $C_{19}H_{21}NO_4$ requires: C, 69.9; H, 6.4; N, 4.2%]

4-(3-*Mesyloxy*-4-*methoxybenzyl*)-7-*methoxy*-8-*mesyloxy*-1,2,3,4-*tetrahydroisoquinoline* (**15h**) was obtained as white solid, m.p. 171–173° [Found: C, 50.8; H, 5.1; N, 2.6; S 13.0. $C_{20}H_{25}NO_8S_2$ requires: C, 51.0; H, 5.3; N, 3.0; S, 13.6%].

2-*Mesyl*-4-(3-*mesyloxy*-4-*methoxybenzyl*)-7-*methoxy*-8-*mesyloxy*-1,2,3,4-*tetrahydroisoquinoline* (**15i**). The above tetrahydroisoquinoline (5.0 g) in dry pyridine (50 mL) was treated with methane sulphonyl chloride (1.3 g) and stirred at r.t. 0.75 hr. After addition of dil HCl, the required (**15i**) was collected and washed with dil HCl, then H_2O. Crystallisation from acetone gave white flakes, m.p. 227–228° ^{1}H NMR (d_6DMSO) contained: 7.25 and 7.34 m [5] (Ar—H's); 4.34 d [1] and 4.54 d [1] J = 13 Hz (Ar—$\overset{+}{C}H_2N$); 3.90 s [6] (2×OMe); 3.54 s [3] (O·SO_2—Me); 3.36 s [3] (O·SO_2—Me); 2.96 s [3] (NSO_2Me). [Found: C, 46.4; H, 5.2; N, 2.9; S, 17.65. $C_{21}H_{27}NO_{10}S_3$ requires: C, 45.9; H, 4.9; N, 2.55; S, 17.6%].

2-*Mesyl*-4-(3-*hydroxy*-4-*methoxybenzyl*)-7-*methoxy*-8-*hydroxy*-1,2,3,4-*tetrahydroisoquinoline* (**15j**). The above compound (1.0 g) was boiled with 2 M NaOH (50 mL) and EtOH (10 mL) for 3 hr when a clear soln resulted. After cooling, the feathery white ppt was collected and washed with EtOH. The solid was dissolved in hot water and dil. HCl added slowly when a flocculant white ppt of **15j** was formed. Crystallisation from EtOH gave white needles, m.p. 207–209°. ^{1}H NMR (d_6Me_2CO) contained: 7.28 s [1] (OH, removed by D_2O); 7.63 s [1] (OH, removed by D_2O); 6.75 s [5] (Ar—H's); 4.53 d and 4.17 d, J = 20 Hz [2] (Ar—CH_2—N); 3.82 s [6] (2×OMe); 2.88 s [3] (N—SO_2Me) (Found: C, 58.0; H, 6.0; N, 3.6; S, 7.95. $C_{19}H_{23}NO_6S$ requires: C, 58.0; H, 5.85; N, 3.6; S, 8.1%]

VOF_3 *Oxidations—General procedure.* The tetrahydroisoquinoline (0.5 g) as a 0.05 M soln in CH_2Cl_2 containing 20% TFA–TFAA (20:1) was stirred at −15° under N_2 whilst a solon of VOF_3 (2.5 molar equivs) in the minimum volume of 1:1 EtOAc:TFA–TFAA (20:1) was added dropwise. When reaction was complete (disappearance of starting material) the resultant metallic blue solon was poured into a solon of citric acid (5 g) in water (30 mL) at 0°. The pH was adjusted to 8–9 (NH_3 solon) and the organic layer separated. The blue aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic solons dried (Na_2SO_4) and evaporated to leave a brown gum.

Oxidation of 2-*methyl*-4-(3,4-*dimethoxybenzyl*)-6-*hydroxy*-7-*methoxy*-1,2,3,4-*tetrahydroisoquinoline* (**15a**). The crude product (0.43 g) was subjected to column chromatography (Al_2O_3/10% C_6H_6—$CHCl_3$) to afford **9a** as a brown gum (367 mg, 67%) R_f 0.4 (SiO_2, 10% MeOH in $CHCl_3$). The product was dissolved in 2M HCl (5 mL) washed with CH_2Cl_2 (2 mL) and basified to pH 8–9 with dil ammonia and extracted into CH_2Cl_2. Standard work-up afforded the free base **9a** which crystallised from EtOH as colourless prisms m.p. 148–151° $\lambda_{max}(\varepsilon)_{max}$ 233(20,800); 281(12,800); 305(13,300). On addition of NaOH $\lambda_{max}(\varepsilon)_{max}$ 233(21,000); 270(10,900); 311(6,000); 344(8,200). ^{1}H NMR ($CDCl_3$): 8.21 s [1] (Ar—H); 6.83 s [1] (Ar—H); 6.55 s [1] (Ar—H); 3.95 s [6] (2×OCH_3); 3.90 s [3] (OCH_3); 3.9–2.0 m [8] (aliphatic-H's + OH); 2.47 s [3] (N—CH_3). M.S. (*m/e*) 341 (M^+) [86%], 340 (M^+-1) [25%], 298 [90%], 299 [18%], 297 [14%], 283 [28%], 267 [100%], 268 [20%], 266 [20%], m* 260, 230, 240. [Found: C, 70.7; H, 6.7; N, 4.1. $C_{20}H_{23}NO_4$ requires: C, 70.4; H, 6.75; N, 4.1%].

Further elution of the column with 5% MeOH in $CHCl_3$ afforded **18** or **19** (61 mg 12%) R_f 0.16 (SiO_2, 10% MeOH in $CHCl_3$). The product crystallised from $CHCl_3$ as large colourless hexagonal prisms which became opaque orange upon vacuum drying at r.t. The product melted to a red gum over the range 96–100° resolidified over the range 130–140° and then remelted at 145°. $\lambda_{max}(\varepsilon)_{max}$ 231(19,500); 278(16,200); 321(14,700); 331(14,300); 446(22,600). ^{1}H NMR: 8.79 s [1] (C_4—H); 7.13 s [1] 6.50 s [1] and 6.21 s [1] (3×Ar—H); 3.90 s [3], 3.80 s [3] and 3.70 [3] (3×OCH_3); 3.2 s [2] (—$\underline{CH_2}$—$\overset{+}{N}$); 3.13 s [3] ($\overset{+}{N}$—CH_3); 4.39 d J = 9 Hz [2] ($\underline{CH_2}$—CH), 2.42 s [1] (OH, removed by D_2O); M.S. (*m/e*) 341 [48%], 340 [34%], 339 [100%], 338 [45%], 324 [20%], 298 [51%], 283 [11%], 267 [52%]. m* 309.7, 268.75, 260.4, 239.2. [Found: C, 63.7; H, 5.5; N, 3.4. $C_{20}H_{22}NO_4Cl$ requires: C, 64.0; H, 5.85; N, 3.7%].

Oxidation of **9a** *with* VOF_3. The derivative **9a** (30 mg) was subjected to oxidation with VOF_3 as described above to afford a product identical with **18** or **19** (tlc).

Reduction of **18** *or* **19**. The orange solid **18** or **19** (5 mg) was dissolved in 1:1 EtOH:H_2O (1 mL) and $NaBH_4$ (3 mg) was added. The mixture was left at r.t. overnight, then standard work-up gave a base identical with **9a** (tlc, UV and MS).

Oxidation of 2-*methyl*-4-(3,4-*dimethoxybenzyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (**15f**) *with* VOF_3. Column chromatography of the crude product of oxidation (SiO_2:$CHCl_3$) gave the orange solid (48 mg) (**20**) or (**21**) R_f 0.65 (SiO_2/10% MeOH/$CHCl_3$) m.p. 206° (dec) but although pure by tlc, a satisfactory elemental analysis could not be obtained. Further elution of the column afforded **9b** as a brown oil (189 mg; 38%); R_f 0.50 (SiO_2/10% MeOH/$CHCl_3$). Further purification gave **9b** as a beige crystalline solid, m.p. 112–114°. $\lambda_{max}(\varepsilon)_{max}$ 235(19,800); 281(14,600); 305(13,300). ^{1}H NMR ($CDCl_3$): 8.17 s [1] (Ar—H); 6.75 s [1] (Ar—H); 6.74 s [1] (Ar—H); 3.89 s [6] (2×OCH_3); 3.84 s [3] (OCH_3); 3.65 s [3] (OCH_3); 3.9–2.00 m [7] (aliphatic-H's); 2.46 s [3] (NCH_3). M.S. (*m/e*) 355 (M^+) [57%], 313 [15%], 312 [67%], 298 [15%], 297 [70%], 282 [32%], 281 [100%], 269 [11%], 265 [11%], 254 [12%], 250 [14%] m* 283, 274, 253. Treatment of dilute acetone solon of the product with 2 drops of conc HCl afforded the hydrochloride as pale orange needles m.p. 215–218°. [Found: C, 64.55; H, 6.85; N, 3.5. $C_{21}H_{26}NO_4Cl$ requires: C, 64.4; H, 6.6; N, 3.6%].

4-(3-*Mesyloxy*-4-*methoxybenzylidene*)-7-*methoxy*-8-*mesyloxy*-1,2,3,4-*tetrahydroisoquinoline* (**25**). The hydrochloride (**13d**) (20 g) was suspended in EtOH (100 mL) at r.t. and stirred whilst $NaBH_4$ (5 g) was added portionwise. After 1 hr water (200 mL) was added and the white ppt was collected, washed with water and dried. The required base (**25**) was crystallised from EtOH/H_2O m.p. 202–204°. [Found: C, 50.7; H, 5.0; N, 3.3; S, 14.0. $C_{20}H_{23}NO_8S_2$ requires: C, 51.2; H, 4.9; N, 3.0; S, 13.7%].

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