SYNTHESIS OF SOME NEODIHYDROTHEBAINE AND BRACTAZONINE ISOMERS

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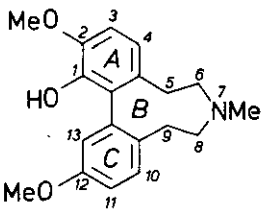
Abstract — The synthesis of four isomeric dibenz[d,f]azonine compounds is described. Neither of these substances may be confused with the natural Papaver bracteatum alkaloids neodihydrothebaine and bractazonine.

Our structural assignments of the dibenz[d,f]azonine alkaloids neodihydrothebaine 1 and bractazonine 2, isolated from Papaver bracteatum[1], were mainly based upon spectroscopical evidence and biosynthetic considerations. Formal proof of their identities was obtained from synthesis[1]. Biosynthetic proposals may give useful indications for the structures of natural products, but are not conclusive. As a matter of fact, biogenetic considerations, based on morphinandienol to dibenz[d,f]azonine transformations (analogous to those proposed for the biosynthesis of protostephanine[2]), indicate that 2,3-disubstituted dibenz[d,f]azonines are not to be excluded, in view of the natural occurrence of some 2,3-disubstituted morphinandienones in Papaveraceous plants[3]. The isolation of such a compound, O-methylflavinantine, from Papaver bracteatum was reported recently[4]. Moreover, it is known, that 2-hydroxy-3-methoxy-dibenz[d,f]azonine compounds display in ^{1}H-NMR the C-3 methoxyl resonance at $\delta \sim 3.90$[5], very close to the value δ 3.904 observed for both natural products. In Pr(fod)$_3$ induced shift experiments in ^{1}H-NMR it was found that the o-hydroxy methoxyl resonances of the two natural alkaloids showed a non-identical behaviour[1]. For these reasons, we decided to synthesize the isomeric compounds 3 - 6.



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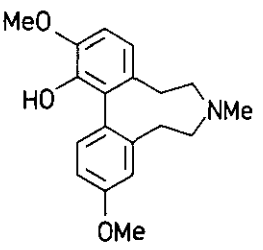

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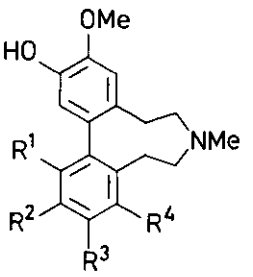
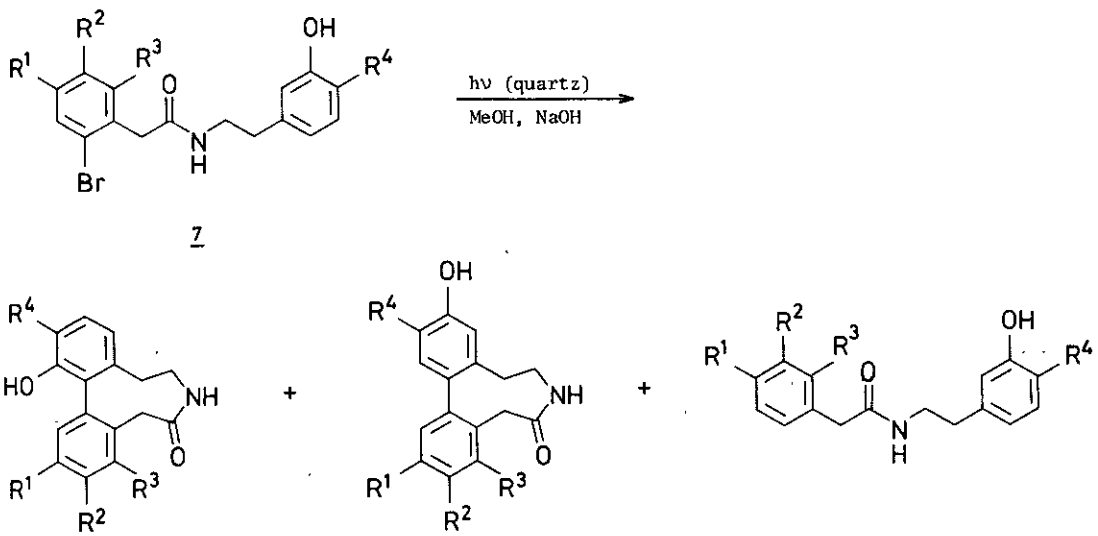


3: $R^1=R^3=R^4=H; R^2=OMe$
4: $R^1=R^2=R^3=H; R^4=OMe$
5: $R^1=R^2=R^4=H; R^3=OMe$
6: $R^1=OMe; R^2=R^3=R^4=H$

The neodihydrothebaine and bractazonine isomers 3 - 6 were synthesised using the photolytic ring closure procedure, used earlier in the total synthesis of the natural alkaloids erybidine[6], laurifinine, laurifonine and laurifine[7]. We also successfully employed this procedure in a total

synthesis of bractazonine[1]. Incidently, the structure 3 was proposed at one time for laurifinine[8]. The ring closure method, used in this work, requires the directive presence of a hydroxyl substituent in ortho- or para-position with respect to the site of aryl-aryl coupling (See Scheme 1). Consequently, suitable protective groups were needed in the construction of compounds 3 and 4, in order to obtain the desired 2-hydroxy-3-methoxy substituted 8-oxodibenz[d,f]azonins from 3-hydroxy substituted aryl-aryl coupling products, having an appropiately shielded 2-hydroxyl function. For the latter purpose protection as an isopropyl ether was chosen. In the synthesis of 3 this functionalization was attained by hydrolysis of a protective benzyl ether, followed by isopropylation, both at the acetamide stage. Such protective group interchange was avoided in the preparation of compound 4, where we proceeded directly from 4-isopropoxy-3-tosyloxyphenethylamine. Compounds 5 and 6 were both derived from a single acetamide substrate, which was prepared from 3-tosyloxyphenethylamine and 2-bromo-4-isopropoxy-5-methoxyphenylacetic acid.

Scheme 1: Photochemical synthesis of products 9A, 9B, 9C and 8C, used in the synthesis of compounds 3, 4, 5 and 6, respectively



7 8 9 10

starting compound	R^1	R^2	R^3	R^4	products (yield)
7A	OMe	H	H	$OCHMe_2$	8A (12%); 9A (32%)
7B	H	H	OMe	$OCHMe_2$	8B (21%); 9B (37%); 10B (14%)
7C	$OCHMe_2$	OMe	H	H	8C (12%); 9C (30%); 10C (17%)

The ^{1}H-NMR chemical shifts of the methoxyl group at C-3 of products 3 - 6 were found at δ 3.91 - 3.92, rather than at δ 3.90, as shown by recording the spectra of compounds 3 - 5 in 1:1 mixtures with neodihydrothebaine 1 (See Table 1). The C-10 and C-11 methoxyl resonances are found at δ 3.83 - 3.84, and the C-12 methoxyl resonance is found at δ 3.78. The C-13 methoxyl resonance of compound 6 is observed at relatively high field (δ 3.70), as anticipated for this substituent,

being in a position strongly influenced by the neighbouring aromatic ring A. Such substitution pattern was already excluded for the P. bracteatum alkaloids[1]. Neither of the four synthetic substances can be confused with the natural P. bracteatum alkaloids neodihydrothebaine and bractazonine, nor with laurifinine[7,8,9].

Table 1: Chemical shifts and differences in chemical shifts of methoxyl resonances, for 1:1 mixtures of dibenz[d,f]azonines 3 - 5 with neodihydrothebaine 1

Compounds	Chemical shifts and differences of chemical shifts
natural mixture of 1 and 2	a, 3.78(3H) [C-12 OMe 1]; b, 3.84(3H) [C-11 OMe 2]; c, 3.90(6H) [C-2 OMe 1 + C-2 OMe 2]; c-b, 0.067; b-a, 0.057; c-a, 0.124.
1 + 3	a, 3.78(6H) [C-12 OMe 1 + C-12 OMe 3]; b, 3.90(3H) [C-2 OMe 1]; c, 3.92(3H) [C-3 OMe 3]; c-b, 0.018; b-a, 0.125; c-a, 0.143.
1 + 4	a, 3.78(3H) [C-12 OMe 1]; b, 3.84(3H) [C-10 OMe 4]; c, 3.90(3H) [C-2 OMe 1]; d, 3.91(3H) [C-3 OMe 4]; d-c, 0.014; c-b, 0.062; b-a, 0.064; d-b, 0.075; c-a, 0.127; d-a, 0.140.
1 + 5	a, 3.78(3H) [C-12 OMe 1]; b, 3.83(3H) [C-11 OMe 5]; c, 3.90(3H) [C-2 OMe 1]; d, 3.91(3H) [C-3 OMe 5]; d-c, 0.008; c-b, 0.078; b-a, 0.047; d-b, 0.087; c-a, 0.125; d-a, 0.133.

EXPERIMENTAL

GC/MS was carried out using a Hewlett-Packard 5710A / JEOL JMS D-300 or a Carlo Erba GLC / Kratos MS 80 combination of gas chromatograph / mass spectrometer. These combinations were connected to a JMA 2000 and a Kratos DS 55 data system, respectively. Spectra were recorded at 70 eV. High-resolution mass spectra were obtained using a M-80B type Hitachi double beam GC/MS instrument. ^{1}H-NMR spectra were recorded in $CDCl_3$ (unless stated otherwise), at 90 MHz using a Varian EM 390 spectrometer. TMS was internal standard (δ = 0). ^{13}C-NMR Chemical shift assignments of dibenz[d,f]azonine alkaloids form the subject of a forthcoming publication. GC was carried out on a Pye Series 104 gas chromatograph, equipped with a FID, using on-column injection and glass columns, packed with 3% OV-17 on Chrompack SA (80 - 100 mesh), operating at 260°C (system a), or with 3% SE-30 on Chromosorb W-HP (80 - 100 mesh), operating at 260°C (system b). For GC retention times thebaine was chosen as a reference ($RR_t \equiv 1.00$). TLC was performed on Si-gel GF 254 plates using EtOAc - Et_2NH (19:1) (system a), or using C_6H_6 - Me_2CO - MeOH (7:2:1) (system b), or on Al_2O_3 F 254 (type E) plates using $CHCl_3$ - n-heptane - Et_2O (4:5:1) (system c). Alkaloid detection was accomplished using UV light (254 nm). Melting points were corrected.

Synthesis of 5,6,8,9-tetrahydro-3,12-dimethoxy-7-methyl-dibenz[d,f]azonin-2-ol 3. The synthesis of compound 3 starts with 4-benzyloxy-3-tosyloxyphenethylamine 11 and 2-bromo-4-methoxyphenylacetic acid[7].

4-Benzyloxy-3-tosyloxyphenethylamine 11. To a mixture of 4-benzyloxy-3-tosyloxybenzylcyanide[10] (13 g) and $NaBH_4$ (3 g) in dry THF (150 ml) $BF_3.OEt_2$ (4 ml) was added dropwise while stirring at 0°C. The solution was then stirred at room temp. for 5 h, and decomposed with EtOH, H_2O and diluted aq. HCl, respectively, and evaporated. The residue was neutralised with aq. NH_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried (Na_2SO_4), and evaporated to give the amine 11 (11 g, yield 84%) as a colourless oil. Analysis: calcd for $C_{22}H_{23}NO_4S$ m/z 397.1346; found m/z

397.1306. ^{1}H-NMR: δ 2.33 (3H,s,ArMe), 4.78 (2H,s,ArCH$_2$O), 6.68 - 7.38 (10H,m,ArH), 7.58 (2H,d,J=9 Hz, 2 tosyl-H). By treatment of the oil with oxalic acid the crystalline oxalate was obtained. M.p. 192 - 193°C (colourless needles, from MeOH).

N-(4-Benzyloxy-3-tosyloxyphenethyl)-2-(2-bromo-4-methoxyphenyl)acetamide 12. A mixture of compound 11 (7.2 g) and 2-bromo-4-methoxyphenylacetic acid[7] (5.0 g) in decaline (120 ml) was heated under reflux for 2.5 h. After cooling, the mixture was evaporated to dryness and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was shaken thoroughly with 5% aq. HCl, 2% aq. NaOH and H_2O, dried (Na_2SO_4), and evaporated to give the amide 12 (10.2 g, yield 90%). M.p. 100 - 101°C (from Et_2O). Elemental analysis in agreement with $C_{31}H_{30}NO_6BrS \cdot 0.5\ H_2O$. IR ν_{max} ($CHCl_3$): 3430(NH) and 1665 cm^{-1} (CO). ^{1}H-NMR: δ 2.38 (3H,s,ArMe), 2.66 (2H,t,J=7 Hz,ArCH$_2$CH$_2$N), 3.38 (2H,q,J=7 Hz, ArCH$_2$CH$_2$NH), 3.59 (2H,s,ArCH$_2$CO), 3.78 (3H,s,OMe), 4.83 (2H,s,ArCH$_2$O), 5.35 (1H,t,J=7 Hz,NH), 6.64 - 7.40 (13H,m,ArH), 7.66 (2H,d,J=8 Hz,2 tosyl-H).

N-(4-Benzyloxy-3-hydroxyphenethyl)-2-(2-bromo-4-methoxyphenyl)acetamide 13. To a stirred solution of the amide 12 (450 mg) in MeOH (15 ml) and DMF (15 ml) KOH (500 mg) was added, and the reaction mixture was then stirred at 60°C for 3 h. After cooling, the mixture was poured into H_2O, treated with HCl, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried (Na_2SO_4), and evaporated to yield the phenolic compound 13 (280 mg, yield 83%). IR ν_{max} ($CHCl_3$): 3600(OH), 3450 (NH) and 1670 cm^{-1} (CO). ^{1}H-NMR: δ 2.62 (2H,t,J=7 Hz,ArCH$_2$CH$_2$N), 3.39 (2H,q,J=7 Hz,ArCH$_2$CH$_2$NH), 3.55 (2H,s,ArCH$_2$CO), 3.72 (3H,s,OMe), 5.00 (2H,s,ArCH$_2$O), 5.28 (1H,t,J=7 Hz,NH), 6.28 - 7.20 (6H,m, ArH), 7.32 (5H,s,ArH).

N-(4-Hydroxy-3-tosyloxyphenethyl)-2-(2-bromo-4-methoxyphenyl)acetamide 14. A stirred solution of the amide 12 (10 g) in conc. HCl (80 ml) and EtOH (80 ml) was heated at 60°C for 6 h. The volatile materials were removed, H_2O was added, and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated, producing the debenzylated amide 14 (7.9 g, yield 92%) as a colourless oil. IR ν_{max} ($CHCl_3$): 3560(OH), 3430(NH) and 1670 cm^{-1} (CO). ^{1}H-NMR: δ 2.43 (3H,s,ArMe), 2.58 (2H,t,J=7 Hz,ArCH$_2$CH$_2$N), 3.27 (2H,q,J=7 Hz,ArCH$_2$CH$_2$NH), 3.56 (2H,s,ArCH$_2$CO), 3.78 (3H,s,OMe), 5.34 (1H,t,J=7 Hz,NH), 6.44 - 7.30 (8H,m,ArH), 7.62 (2H,d,J=8 Hz,2 tosyl-H). MS m/z (rel.int.): 534,412,332,290,245,200,178(100).

N-(4-Isopropoxy-3-tosyloxyphenethyl)-2-(2-bromo-4-methoxyphenyl)acetamide 15. To a stirred mixture of the amide 14 (7.5 g) and dry K_2CO_3 (2 g) in dry DMF (50 ml) 2-bromopropane (2.5 ml) was added dropwise in a nitrogen atmosphere for 15 min. Stirring was continued at room temp. for 30 min., and then at 100°C for 2 h. After cooling, the mixture was poured into ice-water, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried (Na_2SO_4), and evaporated to yield 15 (7.9 g, yield 98%). M.p. 149°C (from C_6H_6). Elemental analysis in agreement with $C_{27}H_{30}NO_6BrS$. IR ν_{max} ($CHCl_3$): 3430(NH) and 1665 cm^{-1} (CO). ^{1}H-NMR: δ 1.13 (6H,d,J=6 Hz,CMe$_2$), 2.43 (3H,s,ArMe), 2.65 (2H,t,J=7 Hz,ArCH$_2$CH$_2$N), 3.39 (2H,q,J=7 Hz,ArCH$_2$CH$_2$NH), 3.58 (2H,s,ArCH$_2$CO), 3.78 (3H,s,OMe), 4.30 (1H,m,CHMe$_2$), 5.38 (1H,t,J=7 Hz,NH), 6.64 - 7.36 (8H,m,ArH), 7.72 (2H,d,J=8 Hz,2 tosyl-H).

N-(3-Hydroxy-4-isopropoxyphenethyl)-2-(2-bromo-4-methoxyphenyl)acetamide 7A. A mixture of compound 15 (7.5 g) and KOH (3 g) in DMF (40 ml) and MeOH (40 ml) was heated while stirring at 70°C for 3 h. After cooling, the mixture was poured into H_2O, neutralised with HCl, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried (Na_2SO_4), and evaporated to yield 7A (5.1 g, yield 93%) as a colourless oil. IR ν_{max} ($CHCl_3$): 3530(OH), 3420(NH) and 1665 cm^{-1} (CO). ^{1}H-NMR: δ 1.32 (6H,d, J=6 Hz,CMe$_2$), 2.59 (2H,t,J=7 Hz,ArCH$_2$CH$_2$N), 3.38 (2H,q,J=7 Hz,ArCH$_2$CH$_2$NH), 3.54 (2H,s,ArCH$_2$CO), 3.74 (3H,s,OMe), 4.44 (1H,m,CHMe$_2$), 5.50 (1H,t,J=7 Hz,NH), 6.42 (1H,dd,J=3 and 8 Hz,H-6), 6.58 (1H, d,J=3 Hz,H-2), 6.64 (1H,d,J=8 Hz,H-5), 6.73 (1H,dd,J=3 and 8 Hz,H-5'), 7.02 (1H,d,J=3 Hz,H-3'), 7.08 (1H,d,J=8 Hz,H-6'). MS m/z (rel.int.): 422,245,200,178(100).

Photolysis of compound 7A. A solution of compound 7A (500 mg) in MeOH (250 ml) containing NaOH (400 mg) was irradiated with a 100W high-pressure mercury lamp for 2 h in a nitrogen atmosphere. The resulting mixture was concentrated in vacuo, and the crude products were dissolved in H_2O. The aq. solution was washed thoroughly with Et_2O and then neutralised with HCl, followed by extraction with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried (Na_2SO_4), and evaporated to produce a reddish-brown oil. The oil was chromatographed on Si-gel with $CHCl_3$ - Me_2CO (10:1) as eluents. First compound 8A (49 mg, yield 12%) was obtained, and then the desired compound 9A (129 mg, yield 32%). No other debrominated product was observed (See Scheme 1).

5,6,8,9-Tetrahydro-1-hydroxy-2-isopropoxy-12-methoxy-7H-dibenz[d,f]azonin-8-one 8A. Colourless oil. IR ν_{max} ($CHCl_3$): 3530(OH), 3400(NH) and 1650 cm^{-1} (CO). ^{1}H-NMR: δ 1.36 (6H,d,J=6 Hz,C$\underline{Me}_2$), 3.76 (3H,s,O$\underline{Me}$), 4.53 (1H,m,C$\underline{H}Me_2$), 6.44 - 7.16 (5H,m,Ar$\underline{H}$). MS m/z (rel.int.): 341,326,299,270,242(100), 223,211.

5,6,8,9-Tetrahydro-3-hydroxy-2-isopropoxy-12-methoxy-7H-dibenz[d,f]azonin-8-one 9A. M.p. 177 - 178°C (from C_6H_6). Elemental analysis in agreement with $C_{20}H_{23}NO_4 \cdot 0.5\ H_2O$. IR ν_{max} ($CHCl_3$): 3520 (OH), 3380(NH) and 1650 cm^{-1} (CO). ^{1}H-NMR: δ 1.35 (6H,d,J=6 Hz,C$\underline{Me}_2$), 3.78 (3H,s,O$\underline{Me}$), 4.50 (1H,m, C$\underline{H}Me_2$), 6.45 - 7.06 (5H,m,Ar$\underline{H}$). MS m/z (rel.int.): 341,326,299,270,242(100),225,213,211.

5,6,8,9-Tetrahydro-3,12-dimethoxy-2-isopropoxy-7H-dibenz[d,f]azonin-8-one 16. To a suspension of compound 9A (600 mg) and dry K_2CO_3 (300 mg) in absolute EtOH was added dropwise excess MeI (0.3 ml) at room temp. for 10 min. The stirred mixture was heated at 50°C for 6 h, evaporated, and dissolved in warm $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried (Na_2SO_4), and evaporated to produce the O-methyl ether 16 (584 mg, yield 94%) as a colourless oil. IR ν_{max} ($CHCl_3$): 3410(NH) and 1665 cm^{-1} (CO). ^{1}H-NMR: δ 1.35 (6H,d,J=6 Hz,C$\underline{Me}_2$), 3.87 and 3.96 (6H,2 s,2 O$\underline{Me}$), 4.59 (1H,m,C$\underline{H}Me_2$), 6.76 and 6.85 (2H,2 s,H-1 and H-4), 6.83 (1H,d,J=3 Hz,H-13), 7.01 (1H,dd,J=3 and 9 Hz,H-11), 7.35 (1H,d, J=9 Hz,H-10). MS m/z (rel.int.): 355,340,313,284,256(100),241,225.

5,6,8,9-Tetrahydro-3,12-dimethoxy-2-hydroxy-7H-dibenz[d,f]azonin-8-one 17. A solution of compound 16 (400 mg) in HOAc (25 ml) containing conc. HBr (2 ml) was heated with stirring at 80°C for 1.5 h. After cooling the mixture was poured into ice-water, and then extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried (Na_2SO_4), and evaporated to afford compound 17 (281 mg, yield 80%), colourless oil. IR ν_{max} ($CHCl_3$): 3535(OH), 3390(NH) and 1655 cm^{-1} (CO). ^{1}H-NMR: δ 3.80 and 3.92 (6H,2 s,2 O$\underline{Me}$), 6.67 and 6.76 (2H,2 s,H-1 and H-4), 6.74 (1H,d,J=3 Hz,H-13), 6.94 (1H,dd,J=3 and 9 Hz,H-11), 7.30 (1H,d,J=9 Hz,H-10). MS m/z (rel.int.): 313(100),284,257,256,241,225,213.

5,6,8,9-Tetrahydro-2-isopropoxy-12-methoxy-7H-dibenz[d,f]azonin-3-ol 18. A solution of $BF_3.OEt_2$ (75 µl) in dry THF was added dropwise in 15 min. to a cold suspension of compound 9A (30 mg) and $NaBH_4$ (15 mg) in dry THF. After stirring at room temp. for 6 h, excess diborane was destroyed by slow addition of EtOH. A stream of HCl gas was passed through the mixture, and the volatile materials were removed. The residue was poured into H_2O, treated with aq. NH_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried (Na_2SO_4), and evaporated, to afford compound 18 (20 mg, yield 70%) as a colourless oil. IR ν_{max} ($CHCl_3$): 3550 cm^{-1} (OH). ^{1}H-NMR: δ 1.32 (6H,d,J=6 Hz,C$\underline{Me}_2$), 3.78 (3H,s,O$\underline{Me}$), 4.47 (1H,m,C$\underline{H}Me_2$), 6.60 and 6.66 (2H,2 s,H-1 and H-4), 6.65 (1H,d,J=3 Hz,H-13), 6.80 (1H,dd,J=3 and 8 Hz,H-11), 7.04 (1H,d,J=8 Hz,H-10). MS m/z (rel.int.): 327(100),312, 285,284,256,255,243,225.

5,6,8,9-Tetrahydro-2-isopropoxy-12-methoxy-7H-dibenz[d,f]azonin-1-ol 19. A similar reaction of the amide 8A (30 mg) with in situ prepared diborane afforded compound 19 as an amorphous solid (21 mg, yield 73%). IR ν_{max} ($CHCl_3$): 3540 cm^{-1} (OH). ^{1}H-NMR: δ 1.37 (6H,d,J=6 Hz,C$\underline{Me}_2$), 3.77 (3H,s,O$\underline{Me}$), 4.52 (1H,m,C$\underline{H}Me_2$), 6.61 (1H,d,J=10 Hz,H-3 or H-4), 6.68 (1H,d,J=3 Hz,H-13), 6.70 (1H,d,J=10 Hz,H-3 or H-4), 6.83 (1H,dd,J=3 and 8 Hz,H-11), 7.09 (1H,d,J=8 Hz,H-10). MS m/z (rel.int.): 327(100),312,

285,284,256,255,243,225.

5,6,8,9-Tetrahydro-3,12-dimethoxy-7H-dibenz[d,f]azonin-2-ol 20. A similar reaction of the amide 17 (200 mg) with in situ prepared diborane gave product 20 (135 mg, yield 71%). M.p. 198°C (from MeOH). IR ν_{max} ($CHCl_3$): 3550 cm^{-1} (OH). ^{1}H-NMR: δ 3.78 (3H,s,OMe), 3.90 (3H,s,OMe), 6.65 (1H,d,J=3 Hz, H-13), 6.66 and 6.69 (2H,2 s,H-1 and H-4), 6.84 (1H,dd,J=3 and 9 Hz,H-11), 7.08 (1H,d,J=9 Hz,H-10).

5,6,8,9-Tetrahydro-3,12-dimethoxy-7-methyl-dibenz[d,f]azonin-2-ol 3. A 37% aq. HCHO solution (0.15 ml) was added to a solution of compound 20 (150 mg) in MeOH (40 ml) and the mixture was stirred at room temp. for 0.5 h. The mixture was cooled to 5 - 10°C, and $NaBH_4$ (150 mg) was added in small portions during 10 min. After continued stirring for 30 min. at room temp., the mixture was evaporated to dryness, and dissolved in $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried (Na_2SO_4), and evaporated, to give 3 (150 mg, yield 96%). Colourless needles. M.p. 197°C (from Me_2CO). The elemental analysis was in excellent agreement with $C_{19}H_{23}NO_3$. IR ν_{max} ($CHCl_3$): 3540 cm^{-1} (OH). ^{1}H-NMR: δ 2.33 (3H,s,NMe), 2.3 - 2.8 (8H,m,4 CH_2), 3.78 (3H,s,OMe), 3.92 (3H,s,OMe), 4.90 (1H,br s,OH), 6.68 (1H,d,J=2.7 Hz,H-13), 6.71 and 6.73 (2H,2 s,H-1 and H-4), 6.84 (1H,dd,J=2.7 and 8.4 Hz,H-11), 7.11 (1H,d,J=8.4 Hz,H-10). GC/MS m/z (rel.int.): 314(22),313(100),257(35), 256(73),255(74),225(26),223(12),195(11). The Δδ (OMe) observed was 0.143 (See Table 1).

Synthesis of 5,6,8,9-tetrahydro-3,10-dimethoxy-7-methyl-dibenz[d,f]azonin-2-ol 4. The starting materials for the preparation of the substrate for the photolytic ring closure reaction, ultimately leading to compound 4, were 3-hydroxy-4-isopropoxybenzaldehyde[11] and 2-bromo-6-methoxyphenylacetic acid[1].

4-Isopropoxy-3-tosyloxybenzaldehyde 21. 3-Hydroxy-4-isopropoxybenzaldehyde[11] was stirred with tosyl chloride (1 equivalent) in pyridine for 18 h. The solvent was removed in vacuo, and the residue was divided between H_2O and $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, 3N HCl, and H_2O. After drying over $MgSO_4$, the $CHCl_3$ was evaporated, giving compound 21 in 98% yield. M.p. 98°C (from Et_2O). ^{1}H-NMR: δ 1.23 (6H,d,J=6 Hz,CMe_2), 2.46 (3H,s,ArMe), 4.54 (1H,m,J=6 Hz,$CHMe_2$), 6.96, 7.73 and 7.76 (3H,ABC-pattern,$J_{2,6}$=2 Hz,$J_{5,6}$=8 Hz,H-5, H-2 and H-6, respectively), 7.32 and 7.79 (4H,2 d,J=8.7 Hz,tosyl-H), 9.87 (1H,s,CHO). GC/MS m/z (rel.int.): 334(3),292(16),157(5),156(9), 155(100),138(3),137(13),109(5),92(10),91(87),81(4).

4-Isopropoxy-3-tosyloxybenzylalcohol 22. $LiAlH_4$ (0.8 g) was added to ice-cold pyridine (50 ml) in a nitrogen atmosphere, and stirred at room temp. for 24 h. Compound 21 (5.3 g) was cooled at 0°C, and stirred, while the yellow solution of lithium tetrakis(N-dihydropyridyl)aluminate[12,13] in a nitrogen atmosphere was filtered and added. Stirring was continued for 2 days. MeOH (2 ml) was added, changing the colour of the solution from light-orange into yellowish. The reaction mixture was poured on ice (400 g) and conc. HCl (100 ml). The ice-cold solution was extracted with $CHCl_3$ (5x200 ml). The extract was washed with 2.5 N HCl (150 ml), dried ($MgSO_4$) and concentrated in vacuo. The crude products were chromatographed on Al_2O_3 (activity III), using $CHCl_3$, saturated with H_2O. The yield of 22 was 50%. Oil. ^{1}H-NMR: δ 1.11 (6H,d,J=6 Hz,CMe_2), 1.90 (1H,br s,OH), 2.42 (3H,s,ArMe), 4.38 (1H,m,J=6 Hz,$CHMe_2$), 4.57 (2H,s,ArCH_2OH), 6.82, 7.18 and 7.24 (3H,ABC-pattern, $J_{2,6}$=2.4 Hz,$J_{5,6}$=8.4 Hz,H-5,H-6 and H-2,respectively), 7.29 and 7.78 (4H,2 d,J=8.4 Hz,tosyl-H). GC/MS m/z (rel.int.): 336(15),294(30),155(50),139(36),123(14),122(100),111(73),93(59),92(15), 91(83).

4-Isopropoxy-3-tosyloxybenzyl chloride 23. Compound 22 in dry Et_2O, containing a catalytic amount of pyridine, was treated with $SOCl_2$ in dry Et_2O, and stirred at room temp. for 20 min. The solution was washed with H_2O and diluted aq. NH_3, dried ($MgSO_4$), and evaporated. Yield 83%. M.p. 71°C. ^{1}H-NMR: δ 1.14 (6H,d,J=6 Hz,CMe_2), 2.44 (3H,s,ArMe), 4.41 (1H,m,J=6 Hz,$CHMe_2$), 4.50 (2H,s, ArCH_2Cl), 6.82, 7.20 and 7.25 (3H,ABC-pattern,$J_{2,6}$=2.1 Hz,$J_{5,6}$=9.3 Hz,H-5,H-6 and H-2,respectively),

7.30 and 7.78 (4H,2 d,J=8.4 Hz,tosyl-H). GC/MS m/z (rel.int.): 356(4),354(12),314(11),313(5),312 (22),277(7),159(16),158(5),157(54),156(11),155(100),123(18),122(77),94(7),93(7),92(11),91(86).

4-Isopropoxy-3-tosyloxybenzylcyanide 24. Compound 23 was stirred with KCN (1.25 eq.) in DMSO at room temp. for 18 h. The reaction mixture was poured into H_2O, and extracted with Et_2O. The Et_2O extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The yield of compound 24 was 95%. M.p. 97°C (from MeOH). ^{1}H-NMR: δ 1.13 (6H,d,J=6 Hz,CMe_2), 2.43 (3H,s,ArMe), 3.65 (2H,s, $ArCH_2CN$), 4.39 (1H,m,J=6 Hz,$CHMe_2$), 6.84, 7.13 and 7.25 (3H,ABC-pattern,$J_{5,6}$=9.3 Hz,the $J_{2,6}$ being obscured by the tosyl resonance,H-5,H-2 and H-6,respectively), 7.31 and 7.79 (4H,2 d,J=8.4 Hz, tosyl-H). GC/MS m/z (rel.int.): 345(5),303(17),157(5),156(9),155(100),149(5),148(18),92(10),91(65).

4-Isopropoxy-3-tosyloxyphenethylamine 25. Reduction of 24 with in situ prepared diborane gave a quantitative yield of 25. Oil. ^{1}H-NMR: δ 1.10 (6H,d,J=6 Hz,CMe_2), 2.42 (3H,s,ArMe), 2.4 - 3.1 (4H,m, 2 CH_2), 3.33 (2H,br s,NH_2), 4.33 (1H,m,J=6 Hz,$CHMe_2$), 6.7 - 7.4 (5H,m,ArH), 7.77 (2H,d,J=8 Hz, tosyl-H). GC/MS m/z (rel.int.): 349(3),320(15),279(5),278(31),277(5),166(4),156(4),155(30),124(19), 123(100),122(8),94(4),92(7),91(35).

N-(4-Isopropoxy-3-tosyloxyphenethyl)-2-(2-bromo-6-methoxyphenyl)acetamide 26. Heating compound 25 with 2-bromo-6-methoxyphenylacetic acid[1] in decaline in the usual way gave product 26 in 75% yield. The yield, corrected for recovered acid, was 100%. Oil. ^{1}H-NMR: δ 1.10 (6H,d,J=6 Hz,CMe_2), 2.41 (3H,s,ArMe), 2.62 (2H,t,J=7 Hz,$ArCH_2CH_2N$), 3.36 (2H,double t,J=6 and 7 Hz,$ArCH_2CH_2NH$), 3.78 (5H,s, OMe + $ArCH_2CO$), 4.32 (1H,m,J=6 Hz,$CHMe_2$), 5.66 (1H,t,J=6 Hz,NH), 6.6 - 7.8 (10H,m,ArH).

N-(3-Hydroxy-4-isopropoxyphenethyl)-2-(2-bromo-6-methoxyphenyl)acetamide 7B. Detosylation of compound 26 using KOH in DMF - MeOH gave product 7B in 100% yield. Yellow oil. ^{1}H-NMR: δ 1.31 (6H,d, J=6 Hz,CMe_2), 2.61 (2H,t,J=7 Hz,$ArCH_2CH_2N$), 3.40 (2H,double t,J=6 and 7 Hz,$ArCH_2CH_2NH$), 3.75 (3H,s, OMe), 3.78 (2H,s,$ArCH_2CO$), 4.49 (1H,m,J=6 Hz,$CHMe_2$), 5.72 (1H,t,J=6 Hz,NH), 6.31 (1H,s,OH), 6.4 - 7.2 (6H,m,ArH). GC/MS m/z (rel.int.): 423(2),421(2),246(3),244(3),201(15),199(15),179(10),178(60), 176(7),171(4),169(4),150(3),137(16),136(100).

Photolysis of compound 7B. Compound 7B (500 mg) in MeOH (250 ml), containing NaOH (400 mg) was irradiated for 45 min using a 125W high-pressure mercury lamp (Philips HPLN 57236 E/74, from which the outer bulb was removed) in a quartz immersion apparatus, while a stream of nitrogen was passed through the solution. The solvent was removed in vacuo, and the residue was dissolved in H_2O, whereupon Et_2O extraction was performed. The aq. phase was neutralised using conc. HCl, and extracted with $CHCl_3$. The extract was washed with H_2O, dried ($MgSO_4$), and evaporated. The crude products from 5.13 g 7B were separated on a Si-gel column, eluted with $CHCl_3$. First a mixture of compounds 8B and 10B (1.42 g) was eluted, and then compound 9B (1.51 g, yield 37%). The mixture of 8B and 10B was separated on Si-gel, with toluene - EtOAc (3:1). First product 10B (0.56 g, yield 14%) was eluted, and then product 8B (0.84 g, yield 21%). (See Scheme 1).

5,6,8,9-Tetrahydro-1-hydroxy-2-isopropoxy-10-methoxy-7H-dibenz[d,f]azonin-8-one 8B. M.p. 161°C. ^{1}H-NMR: δ 1.32 and 1.34 (6H,2 d,J=6 Hz,CMe_2), 2.48 (2H,m), 3.06, 3.55 and 4.5 (3H,broad bands), 3.06 and 4.18 (2H,AB-pattern,J=17 Hz,$ArCH_2CO$), 3.85 (3H,s,OMe), 4.54 (1H,m,J=6 Hz,$CHMe_2$), 5.69 (1H, s,OH), 6.6 - 7.0 (4H,m,ArH), 7.2 - 7.45 (1H,m,H-12). In the pattern, obtained for the aromatic protons, the AB-pattern for H-3 and H-4 (δ 6.68 and 6.86,J=8.5 Hz) was well recognisable. GC/MS m/z (rel.int.): 342(22),341(72),299(42),270(50),254(11),243(34),242(100),241(14),227(14),225(11),223 (15),152(12).

5,6,8,9-Tetrahydro-3-hydroxy-2-isopropoxy-10-methoxy-7H-dibenz[d,f]azonin-8-one 9B. M.p. 171°C. ^{1}H-NMR: δ 1.30 and 1.32 (6H,2 d,J=6 Hz,CMe_2), 2.50 (2H,m), 3.13, 3.6 and 4.45 (3H,broad bands), 3.16 and 4.19 (2H,AB-pattern,J=16.5 Hz,$ArCH_2CO$), 3.89 (3H,s,OMe), 4.46 (1H,m,J=6 Hz,$CHMe_2$), 6.20 (1H,br s,shifting upon dilution,OH), 6.50 (1H,s,H-4), 6.74 (1H,s,H-1), 6.7 - 7.0 (2H,m,H-11 + H-13),

7.15 - 7.4 (1H,m,H-12). The pattern, obtained for the aromatic protons, was practically superimposable on the one obtained for 5,6,8,9-tetrahydro-2,10-dimethoxy-3-hydroxy-7H-dibenz[d,f]azonin-8-one[1]. GC/MS m/z (rel.int.): 342(22),341(76),300(10),299(51),271(14),270(72),243(32),242(100),241 (32),227(12),225(13),211(11).

N-(3-Hydroxy-4-isopropoxyphenethyl)-2-(2-methoxyphenyl)acetamide 10B. Slightly yellowish oil. ^{1}H-NMR: δ 1.34 (6H,d,J=6 Hz,CMe_2), 2.58 (2H,t,J=7 Hz,$ArCH_2CH_2N$), 3.40 (2H,double t,J=6 and 7 Hz, $ArCH_2CH_2NH$), 3.52 (2H,s,$ArCH_2CO$), 3.74 (3H,s,OMe), 4.50 (1H,m,J=6 Hz,$CHMe_2$), 5.82 (1H,br t,J=6 Hz, NH), 6.0 (1H,br s,OH), 6.35 - 7.4 (7H,m,ArH). GC/MS m/z (rel.int.): 343(9),179(8),178(52),166(6), 137(13),136(100),123(15),121(42),91(22).

5,6,8,9-Tetrahydro-3,10-dimethoxy-2-isopropoxy-7H-dibenz[d,f]azonin-8-one 27. Compound 9B was treated with MeI, as in the synthesis of 16, giving a quantitative yield of 27 (foam). ^{1}H-NMR: δ 1.28 and 1.30 (6H,2 d,J=6 Hz,CMe_2), 2.53 (2H,m), 3.13 (1H,broad band), 3.63 (1H,broad band), 3.11 and 4.18 (2H,AB-pattern,J=17 Hz,$ArCH_2CO$), 3.87 (6H,2 s,separated by only 0.85 Hz,2 OMe), 4.4 (1H, broad band), 4.43 (1H,m,J=6 Hz,$CHMe_2$), 6.53 (1H,s,H-4), 6.68 (1H,s,H-1), 6.77 (1H,dd,J=1.4 and 7.4 Hz, H-11 or H-13), 6.92 (1H,dd,J=1.4 and 8.3 Hz,H-11 or H-13), 7.27 (1H,dd,J=7.4 and 8.3 Hz,H-12). GC/MS m/z (rel.int.): 356(25),355(100),313(32),285(19),284(93),257(31),256(88),255(32),254(15), 241(38),225(17),181(11),165(10),152(11).

5,6,8,9-Tetrahydro-3,10-dimethoxy-2-hydroxy-7H-dibenz[d,f]azonin-8-one 28. Compound 27 (615 mg) was treated with HBr in HOAc, as in the synthesis of 17, giving 28 in 93% yield (506 mg). Semi-solid oil. ^{1}H-NMR: δ 2.51 (2H,m), 3.12, 3.56 and 4.4 (3H,broad bands), 3.14 and 4.18 (2H,AB-pattern,J=17 Hz,$ArCH_2CO$), 3.87 (3H,s,OMe), 3.89 (3H,s,OMe), 5.7 (1H,broad), 6.55 and 6.63 (2H,2 s, H-1 and H-4), 6.74 (1H,dd,J=1.4 and 7.4 Hz,H-11 or H-13), 6.90 (1H,dd,J=1.4 and 8.4 Hz,H-11 or H-13), 7.24 (1H,m,H-12). GC/MS m/z (rel.int.): 314(21),313(100),285(10),284(53),257(21),256(66), 255(18),242(10),241(41),225(15).

5,6,8,9-Tetrahydro-3,10-dimethoxy-7H-dibenz[d,f]azonin-2-ol 29. The reduction of compound 28 was performed in the way, described for the synthesis of 18. In the work-up, however, addition of aq. NH_3 produced an intense violet colour, and the crude product showed only broadened resonances in ^{1}H-NMR. Purification was attained by Al_2O_3 chromatography [activity III, $CHCl_3$ - MeOH - H_2O (93:5:2)] followed by crystallisation from MeOH. Yield 52%. M.p. 214°C. ^{1}H-NMR ($CDCl_3$ - CD_3OD/4:1): δ 1.8 - 3.1 (9H,m), 3.86 (3H,s,OMe), 3.92 (3H,s,OMe), 6.68 and 6.70 (2H,2 s,H-1 and H-4), 6.75 (1H,dd,J=1.2 and 7.5 Hz,H-11 or H-13), 6.87 (1H,dd,J=1.2 and 8.4 Hz,H-11 or H-13), 7.21 (1H,dd,J=7.5 and 8.4 Hz, H-12). GC/MS m/z (rel.int.): 300(23),299(100),269(11),268(29),257(28),256(40),255(28),226(12),225 (46),197(15).

5,6,8,9-Tetrahydro-3,10-dimethoxy-7-methyl-dibenz[d,f]azonin-2-ol 4. Reductive N-methylation of product 29 was performed in the usual way. Yield 100%. M.p. 197°C. ^{1}H-NMR: δ 2.31 (3H,s,NMe), 2.0 - 3.1 (9H,m), 3.84 (3H,s,OMe), 3.91 (3H,s,OMe), 6.73 (2H,s,H-1 and H-4), 6.76 (1H,dd,J=1.2 and 7.5 Hz, H-11 or H-13), 6.84 (1H,dd,J=1.2 and 8.1 Hz,H-11 or H-13), 7.19 (1H,dd,J=7.5 and 8.1 Hz,H-12). The Δδ (OMe) observed was 0.075 (See Table 1). GC/MS m/z (rel.int.): 314(24),313(100),298(19), 282(32),257(22),256(66),255(66),241(13),225(23),223(14),195(11),71(27).

Synthesis of compound 5. The synthesis of the substrate for the photolytic construction of model compound 5 started with 2-bromo-4-isopropoxy-5-methoxybenzaldehyde[14] and 3-tosyloxyphenethylamine[1].

2-Bromo-4-isopropoxy-5-methoxybenzylalcohol 30. Reduction of 2-bromo-4-isopropoxy-5-methoxybenzaldehyde[14] with $NaBH_4$ in EtOH gave compound 30 in 98% yield. M.p. 45°C. ^{1}H-NMR: δ 1.35 (6H,d, J=6 Hz,CMe_2), 2.16 (1H,s,OH), 3.84 (3H,s,OMe), 4.49 (1H,m,J=6 Hz,$CHMe_2$), 4.67 (2H,s,$ArCH_2OH$), 7.01 and 7.04 (2H,2 s,ArH). GC/MS m/z (rel.int.): 276(33),274(35),234(94),233(18),232(100),231(11), 217(15),215(14),153(39),152(11),125(33),124(34),110(36),109(12),94(10),93(75).

2-Bromo-4-isopropoxy-5-methoxybenzyl chloride 31. In a procedure, analogous to the synthesis of 23, compound 30 was converted into product 31 in 97% yield. M.p. 72°C. ^{1}H-NMR: δ 1.34 (6H,d,J=6 Hz, CMe_2), 3.85 (3H,s,OMe), 4.50 (1H,m,J=6 Hz,$CHMe_2$), 4.65 (2H,s,$ArCH_2Cl$), 6.96 and 7.05 (2H,2 s,H-3 and H-6). GC/MS m/z (rel.int.): 296(4),294(16),292(12),254(10),253(4),252(39),251(4),250(30), 218(10),217(94),216(10),215(100),202(3),185(3).

2-Bromo-4-isopropoxy-5-methoxybenzylcyanide 32. Treatment of compound 31 with KCN in DMSO, as in the synthesis of 24, gave 32 in 95% yield. M.p. 58°C. ^{1}H-NMR: δ 1.34 (6H,d,J=6 Hz,CMe_2), 3.76 (2H, s,$ArCH_2CN$), 3.86 (3H,s,OMe), 4.50 (1H,m,J=6 Hz,$CHMe_2$), 6.98 and 7.07 (2H,2 s,H-3 and H-6). GC/MS m/z (rel.int.): 285(17),283(17),244(11),243(100),242(13),241(99),228(29),226(30),162(25),119(11).

2-Bromo-4-isopropoxy-5-methoxyphenylacetic acid 33. Compound 32 (0.4 mole), ethylene glycol (500 ml), and KOH (100 g) in H_2O (150 ml) were refluxed for 2 h. The reaction mixture was poured into H_2O (2 l) and extracted with EtOAc (3x300 ml). The aq. phase was acidified using 6N HCl, and extracted with $CHCl_3$ (4x500 ml). The extracts were dried ($MgSO_4$), and the solvent removed in vacuo. Yield 86%. M.p. 118°C. ^{1}H-NMR: δ 1.34 (6H,d,J=6 Hz,CMe_2), 3.76 (2H,s,$ArCH_2COOH$), 3.82 (3H,s,OMe), 4.48 (1H,m,J=6 Hz,$CHMe_2$), 6.80 and 7.06 (2H,2 s,H-3 and H-6), 9.6 (1H,br s,COOH). GC/MS m/z (rel. int.): 304(31),302(31),262(69),260(71),217(99),215(100),182(11),181(78),137(11).

N-(3-Tosyloxyphenethyl)-2-(2-bromo-4-isopropoxy-5-methoxyphenyl)acetamide 34. Heating 3-tosyloxyphenethylamine[1] and compound 33 in decaline gave product 34 in 84% yield. The yield, corrected for recovered acid, was 100%. Oil. ^{1}H-NMR: δ 1.34 (6H,d,J=6 Hz,CMe_2), 2.43 (3H,s,ArMe), 2.69 (2H,t,J=7 Hz,$ArCH_2CH_2N$), 3.37 (2H,double t,J=6 and 7 Hz,$ArCH_2CH_2NH$), 3.57 (2H,s,$ArCH_2CO$), 3.81 (3H,s,OMe), 4.50 (1H,m,J=6 Hz,$CHMe_2$), 5.49 (1H,br t,J=6 Hz,NH), 6.7-7.8 (10H,m,ArH).

N-(3-Hydroxyphenethyl)-2-(2-bromo-4-isopropoxy-5-methoxyphenyl)acetamide 7C. The detosylation of compound 34, performed analogous to the synthesis of compound 7A, gave a quantitative yield of 7C. M.p. 144°C (from MeOH). ^{1}H-NMR: δ 1.33 (6H,d,J=6 Hz,CMe_2), 2.67 (2H,t,J=7 Hz,$ArCH_2CH_2N$), 3.45 (2H, double t,J=6 and 7 Hz,$ArCH_2CH_2NH$), 3.59 (2H,s,$ArCH_2CO$), 3.77 (3H,s,OMe), 4.46 (1H,m,J=6 Hz,$CHMe_2$), 5.73 (1H,t,J=6 Hz,NH), 6.5-7.2 (6H,m,ArH + OH). GC/MS m/z (rel.int.): 423(7),421(7),343(30), 342(100),301(11),300(45),218(10),217(37),216(10),215(36),181(23),180(50),164(9),138(14),137(44), 136(15),135(7).

Photolysis of compound 7C. Substrate 7C (5.0 g) was photolysed in 500 mg aliquots, in a manner similar to the one used in the photolysis of compound 7B. Irradiation time 50 min. The products were separated on Si-gel, using $CHCl_3$, followed by $CHCl_3$-Me_2CO mixtures, up to 1:1. First mixtures of compounds 8C and 10C (1.507 g) were eluted, and finally the product desired 9C (1.21 g, yield 30%). The mixtures of compounds 8C and 10C were separated on a Si-gel column, eluted with toluene-EtOAc (4:1). This first yielded 10C (0.7 g, yield 17%), and then 8C (493 mg, yield 12%). (See Scheme 1).

5,6,8,9-Tetrahydro-13-hydroxy-2-isopropoxy-3-methoxy-7H-dibenz[d,f]azonin-6-one 8C. M.p. 220°C (from EtOAc). ^{1}H-NMR: δ 1.33 (6H,d,J=6 Hz,CMe_2), 2.2-4.0 (6H,br m,3 CH_2), 3.92 (3H,s,OMe), 4.49 (1H,m,J=6 Hz,$CHMe_2$), 5.4 and 6.1 (2H,2 br s,OH and NH), 6.75 (1H,s,H-1), 7.23 (1H,dd,$J_{10,11}$= $J_{11,12}$=7.8 Hz,H-11), 6.65-7.0 (3H,m,all broad unresolved bands,ArH). GC/MS m/z (rel.int.): 342 (18),341(80),300(21),299(100),270(31),242(35),227(25),211(12),181(13).

5,6,8,9-Tetrahydro-11-hydroxy-2-isopropoxy-3-methoxy-7H-dibenz[d,f]azonin-6-one 9C. M.p. 211°C (from MeOH). ^{1}H-NMR ($CDCl_3$-CD_3OD/5:1): δ 1.34 (6H,2 d,separated by only 1.2 Hz,J=6 Hz,CMe_2), 3.92 (3H,s,OMe), 4.51 (1H,m,J=6 Hz,$CHMe_2$), 6.64, 6.76 and 7.06 (3H,ABC-pattern,$J_{10,12}$=2.2 Hz,$J_{12,13}$=8.4 Hz,H-10,H-12 and H-13,respectively), 6.74 (1H,s,H-1), 6.75 (1H,br s,OH), 7.23 (1H,br s,H-4). The methylene and NH resonances were not well resolved, δ 2.1-4.0 (7H). GC/MS m/z (rel.int.): 342 (14),341(65),300(19),299(100),270(21),242(11),227(23),211(10).

N-(3-Hydroxyphenethyl)-2-(4-isopropoxy-3-methoxyphenyl)acetamide 10C. M.p. 129°C. ^{1}H-NMR: δ 1.34 (6H,d,J=6 Hz,CMe_2), 2.56 (2H,t,J=7 Hz,ArCH_2CH_2N), 3.44 (2H,double t,J=6 and 7 Hz,ArCH_2CH_2NH), 3.47 (2H,s,ArCH_2CO), 3.78 (3H,s,OMe), 4.49 (1H,m,J=6 Hz,$CHMe_2$), 5.55 (1H,t,J=6 Hz,NH), 6.45 - 7.2 (7H,m, ArH), 8.18 (1H,br s,OH). GC/MS m/z (rel.int.): 344(9),343(36),301(5),182(10),181(63),166(8),164(7), 138(33),137(100),136(4),123(7),122(8),121(14),120(13),107(10),94(5),91(5),77(8).

5,6,8,9-Tetrahydro-3,11-dimethoxy-2-isopropoxy-7H-dibenz[d,f]azonin-6-one 35. Compound 9C (586 mg) was treated with MeI, as in the synthesis of 16. The yield of 35 was 607 mg (99%). M.p. 171°C. ^{1}H-NMR: δ 1.33 (6H,d,J=6 Hz,CMe_2), 2.2 - 4.0 (6H,br m,3 CH_2), 3.84 (3H,s,OMe), 3.91 (3H,s,OMe), 4.48 (1H,m,J=6 Hz,$CHMe_2$), 6.1 (1H,br s,NH), 6.71 (1H,s,H-1), 6.70 (1H,d,J=2.6 Hz,H-10), 6.82 (1H, dd,J=2.6 and 8.4 Hz,H-12), 7.14 (1H,br d,J=8.4 Hz,H-13), 7.25 (1H,br s,H-4). GC/MS m/z (rel.int.): 356(16),355(72),314(19),313(100),284(21),241(23).

5,6,8,9-Tetrahydro-3,11-dimethoxy-2-hydroxy-7H-dibenz[d,f]azonin-6-one 36. Compound 35 was deisopropylated, as in the synthesis of 17. The reaction time was 3h, in order to achieve completion of the reaction. The products were separated in Si-gel chromatography, using $CHCl_3$ - MeOH (99:1). The yield of 36 was 233 mg, while 501 mg 35 was used in this reaction. M.p. 241°C. ^{1}H-NMR (DMSO-d_6): δ 3.79 (6H,2 s,separated by only 1 Hz,2 OMe), 6.52 (1H,s,H-1), 6.78 (1H,d,J=2.4 Hz, H-10), 6.82 (1H,dd,J=2.4 and 7.5 Hz,H-12), 7.03 (1H,br d,J=7.5 Hz,H-13), 7.10 (1H,br s,H-4), 7.50 (1H,br s,NH), 9.01 (1H,s,OH). GC/MS m/z (rel.int.): 314(20),313(100),284(12),256(6),255(5),242(6), 241(26),225(8),197(6).

5,6,8,9-Tetrahydro-3,11-dimethoxy-7H-dibenz[d,f]azonin-2-ol 37. Compound 36 (210 mg) was treated with diborane, as in the synthesis of 18. The yield of 37 was 185 mg (93%). M.p. 196°C. ^{1}H-NMR ($CDCl_3$ - CD_3OD/3:1): δ 2.0 - 3.2 (8H,m,4 CH_2), 3.86 (3H,s,OMe), 3.93 (3H,s,OMe), 6.65 - 6.9 (4H,m, ArH), 7.0 - 7.15 (1H,m,ArH). GC/MS m/z (rel.int.): 300(21),299(100),257(21),256(14),255(19),227(12), 226(12),225(35),197(26).

5,6,8,9-Tetrahydro-3,11-dimethoxy-7-methyl-dibenz[d,f]azonin-2-ol 5. Compound 37 was N-methylated, as in the synthesis of 3 from 20, giving a 96% yield of compound 5. M.p. 140°C. ^{1}H-NMR: δ 2.30 (3H, s,NMe), 2.3 - 2.7 (8H,m,4 CH_2), 3.7 (1H,br s,OH), 3.83 (3H,s,OMe), 3.91 (3H,s,OMe), 6.69 and 6.70 (2H,2 s,H-1 and H-4), 6.74 (1H,d,J=2.6 Hz,H-10), 6.74 (1H,dd,J=2.6 and 9 Hz,H-12), 7.04 (1H,d,J=9 Hz,H-13). The Δδ (OMe) observed was 0.087. GC/MS m/z (rel.int.): 314(21),313(100),312(10),270(17), 257(12),256(31),255(44),241(14),225(14).

Synthesis of compound 6. Compound 8C was converted into product 6 in four steps.

5,6,8,9-Tetrahydro-3,13-dimethoxy-2-isopropoxy-7H-dibenz[d,f]azonin-6-one 38. The methylation of 8C (381 mg) was performed in the usual way, for 18 h at 60°C. Quantitative yield. M.p. 120°C, resolidifying and remelting at ca. 170°C. ^{1}H-NMR: δ 1.34 (6H,d,J=6 Hz,CMe_2), 2.2 - 4.0 (6H,broad bands, and a sharp 2H s at δ 3.34), 3.70 (3H,s,OMe), 3.92 (3H,s,OMe), 4.48 (1H,m,J=6 Hz,$CHMe_2$), 5.8 (1H,very broad s,NH), 6.71 (1H,s,H-1), 6.82 and 6.85 (2H,2 br d,estimated J's 8.4 and 7.5 Hz, H-12 and H-10), 7.19 (1H,br s,H-4), 7.33 (1H,m,H-11). GC/MS m/z (rel.int.): 356(18),355(79),314 (19),313(100),284(22),256(26),241(18).

5,6,8,9-Tetrahydro-3,13-dimethoxy-2-hydroxy-7H-dibenz[d,f]azonin-6-one 39. Compound 38 was deisopropylated in the usual way. Yield 84% (278 mg). Crystallisation from MeOH afforded 173 mg pure 39. M.p. 233°C. ^{1}H-NMR: δ 3.70 and 3.94 (6H,2 s,2 OMe), 6.73 (1H,s,H-1), 6.7 - 7.0 (2H,m,H-10 and H-12), 7.2 (1H,br s,H-4), 7.31 (1H,'t',H-11). GC/MS m/z (rel.int.): 314(19),313(100),284(11), 256(18),241(19),225(7).

5,6,8,9-Tetrahydro-3,13-dimethoxy-7H-dibenz[d,f]azonin-2-ol 40. Compound 39 was reduced in the usual manner. Yield 100%. M.p. 181°C. ^{1}H-NMR: δ 2.0 - 3.2 (8H,m), 3.72 (3H,s,OMe), 3.91 (3H,s,OMe), 3.8 (2H,br s,NH + OH), 6.65 - 6.9 (4H,m,ArH), 7.29 (1H,'t',H-11). GC/MS m/z (rel.int.): 300(20),299

(100),268(14),257(20),256(13),255(18),239(14),227(12),226(19),225(44),197(11).

5,6,8,9-Tetrahydro-3,13-dimethoxy-7-methyl-dibenz[d,f]azonin-2-ol 6. Reductive N-methylation of the secondary amine 40 afforded a quantitative yield of product 6. M.p. 121°C. ^{1}H-NMR: δ 2.28 (3H, s,NMe), 2.3 - 2.7 (8H,m,4 CH_2), 3.70 (3H,s,OMe), 3.91 (3H,s,OMe), 4.8 (1H,br s,OH), 6.69 and 6.73 (2H,2 s,H-1 and H-4), 6.80 and 6.83 (2H,2 dd,J=1.2 and 8 Hz,H-10 and H-12), 7.25 (1H,dd,J=J=8 Hz, H-11). GC/MS m/z (rel.int.): 314(22),313(100),312(12),282(19),270(16),257(11),256(33),255(29), 241(12),239(17),225(19),71(12).

GC data (relative retention times): 1, a 0.68, b 0.80; 2, a 0.70, b 0.82; 3, a 0.75, b 0.91; 4, a 0.68, b 0.82; 5, a 0.76, b 0.91; 6, a 0.59, b 0.70; Isolated mixture of natural alkaloids 1 + 2, a 0.69 (broad), b 0.80 (sharp); Mixture of 1 + 3, a 0.68 and 0.75, b 0.80 and 0.91; Mixture of 1 + 4, a 0.68 (sharp), b 0.80 - 0.82 (broad); Mixture of 1 + 5, a 0.68 and 0.76, b 0.80 and 0.91.

TLC data (Rf values): 1, a 0.83, b 0.17, c 0.10; 2, a 0.83, b 0.17, c 0.10; 3, a 0.60, b 0.17, c 0.03; 4, a 0.60, b 0.11, c 0.03; 5, a 0.61, b 0.14, c 0.03; 6, a 0.66, b 0.17, c 0.03.

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