

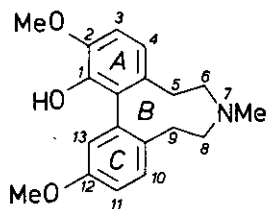
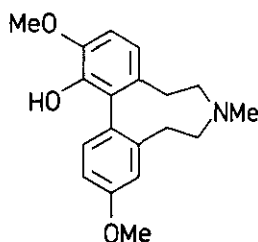
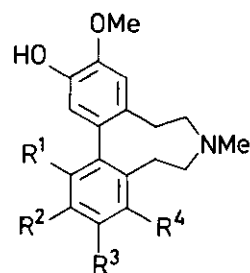
SYNTHESIS OF SOME NEODIHYDROTHERBAINE AND BRACTAZONINE ISOMERS

Hubert G.Theuns*[1], Herman B.M.Lenting[2], Cornelis A.Salemink[2], Hitoshi Tanaka[3], Masayoshi Shibata[3], Kazuo Ito[3] and Robert J.J.Ch.Lousberg[4]

[1] Laboratory of Organic Chemistry, Agricultural University, De Dreijen 5, 6703 BC Wageningen, The Netherlands; [2] Organic Chemical Laboratory, State University of Utrecht, Utrecht, The Netherlands; [3] Laboratory of Natural Products Chemistry, Faculty of Pharmacy, Meijo University, Nagoya, Japan; [4] Ministry of Welfare, Health, and Culture, Leidschendam, The Netherlands

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 bracteatum¹, were mainly based upon spectroscopical evidence and biosynthetic considerations. Formal proof of their identities was obtained from synthesis¹. 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 protostephanine²), 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 Papaveraceae plants³. The isolation of such a compound, O-methylflavinantine, from Papaver bracteatum was reported recently⁴. Moreover, it is known, that 2-hydroxy-3-methoxy-dibenz[d,f]azonine compounds display in ¹H-NMR the C-3 methoxyl resonance at $\delta \sim 3.90^5$, very close to the value $\delta 3.904$ observed for both natural products. In Pr(fod)₃ induced shift experiments in ¹H-NMR it was found that the o-hydroxy methoxyl resonances of the two natural alkaloids showed a non-identical behaviour¹. For these reasons, we decided to synthesize the isomeric compounds 3-6.

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3: R¹=R³=R⁴=H; R²=OMe

4: R¹=R²=R³=H; R⁴=OMe

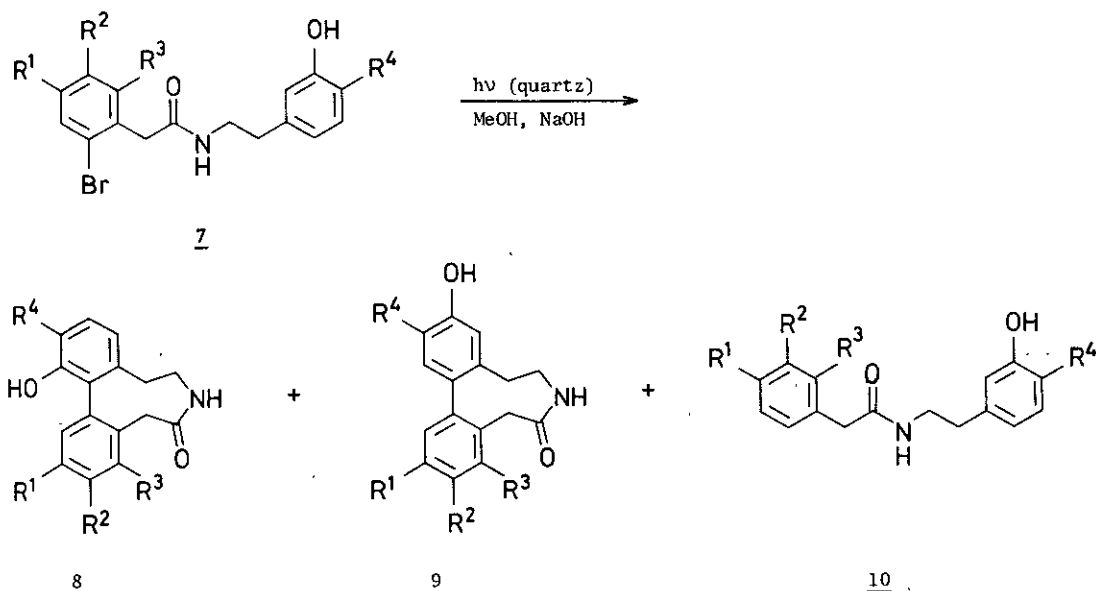
5: R¹=R²=R⁴=H; R³=OMe

6: R¹=OMe; R²=R³=R⁴=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 erybidine⁶, laurifinine, laurifonine and laurifine⁷. We also successfully employed this procedure in a total

synthesis of bractazonine¹. Incidentally, the structure 3 was proposed at one time for laurifinine⁶. 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 appropriately 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



starting compound	R ¹	R ²	R ³	R ⁴	products (yield)
<u>7A</u>	OMe	H	H	OCHMe ₂	<u>8A</u> (12%); <u>9A</u> (32%)
<u>7B</u>	H	H	OMe	OCHMe ₂	<u>8B</u> (21%); <u>9B</u> (37%); <u>10B</u> (14%)
<u>7C</u>	OCHMe ₂	OMe	H	H	<u>8C</u> (12%); <u>9C</u> (30%); <u>10C</u> (17%)

The ¹H-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* alkaloids¹. 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 <u>1</u> and <u>2</u>	δ , 3.78(3H) [C-12 OMe <u>1</u>]; δ , 3.84(3H) [C-11 OMe <u>2</u>]; δ , 3.90(6H) [C-2 OMe <u>1</u> + C-2 OMe <u>2</u>]; δ - δ , 0.067; δ - δ , 0.057; δ - δ , 0.124.
<u>1</u> + <u>3</u>	δ , 3.78(6H) [C-12 OMe <u>1</u> + C-12 OMe <u>3</u>]; δ , 3.90(3H) [C-2 OMe <u>1</u>]; δ , 3.92(3H) [C-3 OMe <u>3</u>]; δ - δ , 0.018; δ - δ , 0.125; δ - δ , 0.143.
<u>1</u> + <u>4</u>	δ , 3.78(3H) [C-12 OMe <u>1</u>]; δ , 3.84(3H) [C-10 OMe <u>4</u>]; δ , 3.90(3H) [C-2 OMe <u>1</u>]; δ , 3.91(3H) [C-3 OMe <u>4</u>]; δ - δ , 0.014; δ - δ , 0.062; δ - δ , 0.064; δ - δ , 0.075; δ - δ , 0.127; δ - δ , 0.140.
<u>1</u> + <u>5</u>	δ , 3.78(3H) [C-12 OMe <u>1</u>]; δ , 3.83(3H) [C-11 OMe <u>5</u>]; δ , 3.90(3H) [C-2 OMe <u>1</u>]; δ , 3.91(3H) [C-3 OMe <u>5</u>]; δ - δ , 0.008; δ - δ , 0.078; δ - δ , 0.047; δ - δ , 0.087; δ - δ , 0.125; δ - δ , 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. ¹H-NMR spectra were recorded in CDCl₃ (unless stated otherwise), at 90 MHz using a Varian EM 390 spectrometer. TMS was internal standard (δ = 0). ¹³C-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 ($RR_t \approx 1.00$). TLC was performed on Si-gel GF 254 plates using EtOAc - Et₂NH (19:1) (system a), or using C₆H₆ - Me₂CO - MeOH (7:2:1) (system b), or on Al₂O₃ F 254 (type E) plates using CHCl₃ - n-heptane - Et₂O (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 acid⁷.

4-Benzyloxy-3-tosyloxyphenethylamine 11. To a mixture of 4-benzyloxy-3-tosyloxybenzylcyanide¹⁰ (13 g) and NaBH₄ (3 g) in dry THF (150 ml) BF₃.OEt₂ (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, H₂O and diluted aq. HCl, respectively, and evaporated. The residue was neutralised with aq. NH₃ and extracted with CHCl₃. The CHCl₃ extract was washed with H₂O, dried (Na₂SO₄), and evaporated to give the amine 11 (11 g, yield 84%) as a colourless oil. Analysis: calcd for C₂₂H₂₃NO₅ m/z 397.1346; found m/z

397.1306. $^1\text{H-NMR}$: δ 2.33 (3H,s,ArMe), 4.78 (2H,s,ArCH₂O), 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 acid⁷ (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 CHCl₃. The CHCl₃ solution was shaken thoroughly with 5% aq. HCl, 2% aq. NaOH and H₂O, dried (Na₂SO₄), and evaporated to give the amide 12 (10.2 g, yield 90%). M.p. 100 - 101°C (from Et₂O). Elemental analysis in agreement with C₃₁H₃₀NO₆BrS. 0.5 H₂O. IR ν_{max} (CHCl₃): 3430(NH) and 1665 cm⁻¹ (CO). $^1\text{H-NMR}$: δ 2.38 (3H,s,ArMe), 2.66 (2H,t,J=7 Hz,ArCH₂CH₂N), 3.38 (2H,q,J=7 Hz, ArCH₂CH₂NH), 3.59 (2H,s,ArCH₂CO), 3.78 (3H,s,OMe), 4.83 (2H,s,ArCH₂O), 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 H₂O, treated with HCl, and extracted with CHCl₃. The CHCl₃ extract was washed with H₂O, dried (Na₂SO₄), and evaporated to yield the phenolic compound 13 (280 mg, yield 83%). IR ν_{max} (CHCl₃): 3600(OH), 3450 (NH) and 1670 cm⁻¹ (CO). $^1\text{H-NMR}$: δ 2.62 (2H,t,J=7 Hz,ArCH₂CH₂N), 3.39 (2H,q,J=7 Hz,ArCH₂CH₂NH), 3.55 (2H,s,ArCH₂CO), 3.72 (3H,s,OMe), 5.00 (2H,s,ArCH₂O), 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, H₂O was added, and the mixture was extracted with CHCl₃. The extract was washed with H₂O, dried (Na₂SO₄), and evaporated, producing the debenzylated amide 14 (7.9 g, yield 92%) as a colourless oil. IR ν_{max} (CHCl₃): 3560(OH), 3430(NH) and 1670 cm⁻¹ (CO). $^1\text{H-NMR}$: δ 2.43 (3H,s,ArMe), 2.58 (2H,t,J=7 Hz,ArCH₂CH₂N), 3.27 (2H,q,J=7 Hz,ArCH₂CH₂NH), 3.56 (2H,s,ArCH₂CO), 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 K₂CO₃ (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 CHCl₃. The CHCl₃ extract was washed with H₂O, dried (Na₂SO₄), and evaporated to yield 15 (7.9 g, yield 98%). M.p. 149°C (from C₆H₆). Elemental analysis in agreement with C₂₇H₃₀NO₆BrS. IR ν_{max} (CHCl₃): 3430(NH) and 1665 cm⁻¹ (CO). $^1\text{H-NMR}$: δ 1.13 (6H,d,J=6 Hz,CMe₂), 2.43 (3H,s,ArMe), 2.65 (2H,t,J=7 Hz,ArCH₂CH₂N), 3.39 (2H,q,J=7 Hz,ArCH₂CH₂NH), 3.58 (2H,s,ArCH₂CO), 3.78 (3H,s,OMe), 4.30 (1H,m,CHMe₂), 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 H₂O, neutralised with HCl, and extracted with CHCl₃. The CHCl₃ extract was washed with H₂O, dried (Na₂SO₄), and evaporated to yield 7A (5.1 g, yield 93%) as a colourless oil. IR ν_{max} (CHCl₃): 3530(OH), 3420(NH) and 1665 cm⁻¹ (CO). $^1\text{H-NMR}$: δ 1.32 (6H,d, J=6 Hz,CMe₂), 2.59 (2H,t,J=7 Hz,ArCH₂CH₂N), 3.38 (2H,q,J=7 Hz,ArCH₂CH₂NH), 3.54 (2H,s,ArCH₂CO), 3.74 (3H,s,OMe), 4.44 (1H,m,CHMe₂), 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 H₂O. The aq. solution was washed thoroughly with Et₂O and then neutralised with HCl, followed by extraction with CHCl₃. The CHCl₃ extract was washed with H₂O, dried (Na₂SO₄), and evaporated to produce a reddish-brown oil. The oil was chromatographed on Si-gel with CHCl₃-Me₂CO (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 $\nu_{\max}$ (CHCl₃): 3530(OH), 3400(NH) and 1650 cm⁻¹ (CO). ¹H-NMR: δ 1.36 (6H,d,J=6 Hz,CMe₂), 3.76 (3H,s,OMe), 4.53 (1H,m,CHMe₂), 6.44 - 7.16 (5H,m,ArH). 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 C₆H₆). Elemental analysis in agreement with C₂₀H₂₃NO₄ · 0.5 H₂O. IR $\nu_{\max}$ (CHCl₃): 3520 (OH), 3380(NH) and 1650 cm⁻¹ (CO). ¹H-NMR: δ 1.35 (6H,d,J=6 Hz,CMe₂), 3.78 (3H,s,OMe), 4.50 (1H,m,CHMe₂), 6.45 - 7.06 (5H,m,ArH). 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 K₂CO₃ (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 CHCl₃. The CHCl₃ solution was washed with H₂O, dried (Na₂SO₄), and evaporated to produce the O-methyl ether 16 (584 mg, yield 94%) as a colourless oil. IR $\nu_{\max}$ (CHCl₃): 3410(NH) and 1665 cm⁻¹ (CO). ¹H-NMR: δ 1.35 (6H,d,J=6 Hz,CMe₂), 3.87 and 3.96 (6H,2 s,2 OMe), 4.59 (1H,m,CHMe₂), 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 CHCl₃. The CHCl₃ extract was washed with H₂O, dried (Na₂SO₄), and evaporated to afford compound 17 (281 mg, yield 80%), colourless oil. IR $\nu_{\max}$ (CHCl₃): 3535(OH), 3390(NH) and 1655 cm⁻¹ (CO). ¹H-NMR: δ 3.80 and 3.92 (6H,2 s,2 OMe), 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 BF₃·OEt₂ (75 μ l) in dry THF was added dropwise in 15 min. to a cold suspension of compound 9A (30 mg) and NaBH₄ (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 H₂O, treated with aq. NH₃, and extracted with CHCl₃. The CHCl₃ extract was washed with H₂O, dried (Na₂SO₄), and evaporated, to afford compound 18 (20 mg, yield 70%) as a colourless oil. IR $\nu_{\max}$ (CHCl₃): 3550 cm⁻¹ (OH). ¹H-NMR: δ 1.32 (6H,d,J=6 Hz,CMe₂), 3.78 (3H,s,OMe), 4.47 (1H,m,CHMe₂), 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 $\nu_{\max}$ (CHCl₃): 3540 cm⁻¹ (OH). ¹H-NMR: δ 1.37 (6H,d,J=6 Hz,CMe₂), 3.77 (3H,s,OMe), 4.52 (1H,m,CHMe₂), 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 $\nu_{\max}$ (CHCl₃): 3550 cm⁻¹ (OH). ¹H-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 NaBH₄ (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 CHCl₃. The CHCl₃ extract was washed with H₂O, dried (Na₂SO₄), and evaporated, to give 3 (150 mg, yield 96%). Colourless needles. M.p. 197°C (from Me₂CO). The elemental analysis was in excellent agreement with C₁₉H₂₃NO₃. IR $\nu_{\max}$ (CHCl₃): 3540 cm⁻¹ (OH). ¹H-NMR: δ 2.33 (3H, s, NMe), 2.3-2.8 (8H, m, 4 CH₂), 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 $\Delta\delta$ (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-isopropoxybenzaldehyde¹¹ and 2-bromo-6-methoxyphenylacetic acid¹.

4-Isopropoxy-3-tosyloxybenzaldehyde 21. 3-Hydroxy-4-isopropoxybenzaldehyde¹¹ was stirred with tosyl chloride (1 equivalent) in pyridine for 18 h. The solvent was removed in vacuo, and the residue was divided between H₂O and CHCl₃. The CHCl₃ extract was washed with H₂O, 3N HCl, and H₂O. After drying over MgSO₄, the CHCl₃ was evaporated, giving compound 21 in 98% yield. M.p. 98°C (from Et₂O). ¹H-NMR: δ 1.23 (6H, d, J=6 Hz, CMe₂), 2.46 (3H, s, ArMe), 4.54 (1H, m, J=6 Hz, CHMe₂), 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. LiAlH₄ (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 CHCl₃ (5x200 ml). The extract was washed with 2.5 N HCl (150 ml), dried (MgSO₄) and concentrated in vacuo. The crude products were chromatographed on Al₂O₃ (activity III), using CHCl₃, saturated with H₂O. The yield of 22 was 50%. Oil. ¹H-NMR: δ 1.11 (6H, d, J=6 Hz, CMe₂), 1.90 (1H, br s, OH), 2.42 (3H, s, ArMe), 4.38 (1H, m, J=6 Hz, CHMe₂), 4.57 (2H, s, ArCH₂OH), 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 Et₂O, containing a catalytic amount of pyridine, was treated with SOCl₂ in dry Et₂O, and stirred at room temp. for 20 min. The solution was washed with H₂O and diluted aq. NH₃, dried (MgSO₄), and evaporated. Yield 83%. M.p. 71°C. ¹H-NMR: δ 1.14 (6H, d, J=6 Hz, CMe₂), 2.44 (3H, s, ArMe), 4.41 (1H, m, J=6 Hz, CHMe₂), 4.50 (2H, s, ArCH₂Cl), 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. $97^\circ C$ (from MeOH). 1H -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. 1H -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 acid¹ in decaline in the usual way gave product 26 in 75% yield. The yield, corrected for recovered acid, was 100%. Oil. 1H -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. 1H -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. $161^\circ C$. 1H -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. $171^\circ C$. 1H -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-one¹. 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.

¹H-NMR: δ 1.34 (6H,d,J=6 Hz,CMe₂), 2.58 (2H,t,J=7 Hz,ArCH₂CH₂N), 3.40 (2H,double t,J=6 and 7 Hz,ArCH₂CH₂NH), 3.52 (2H,s,ArCH₂CO), 3.74 (3H,s,OMe), 4.50 (1H,m,J=6 Hz,CHMe₂), 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). ¹H-NMR: δ 1.28 and 1.30 (6H,2 d,J=6 Hz,CMe₂), 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,ArCH₂CO), 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,CHMe₂), 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. ¹H-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,ArCH₂CO), 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. NH₃ produced an intense violet colour, and the crude product showed only broadened resonances in ¹H-NMR. Purification was attained by Al₂O₃ chromatography [activity III, CHCl₃ - MeOH - H₂O (93:5:2)] followed by crystallisation from MeOH. Yield 52%. M.p. 214°C. ¹H-NMR (CDCl₃ - CD₃OD/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. ¹H-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 $\Delta\delta$ (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-methoxybenzaldehyde¹⁴ and 3-tosyloxyphenethylamine¹. 2-Bromo-4-isopropoxy-5-methoxybenzylalcohol 30. Reduction of 2-bromo-4-isopropoxy-5-methoxybenzaldehyde¹⁴ with NaBH₄ in EtOH gave compound 30 in 98% yield. M.p. 45°C. ¹H-NMR: δ 1.35 (6H,d,J=6 Hz,CMe₂), 2.16 (1H,s,OH), 3.84 (3H,s,OMe), 4.49 (1H,m,J=6 Hz,CHMe₂), 4.67 (2H,s,ArCH₂OH), 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. ¹H-NMR: δ 1.34 (6H,d,J=6 Hz, CMe₂), 3.85 (3H,s,OMe), 4.50 (1H,m,J=6 Hz,CHMe₂), 4.65 (2H,s,ArCH₂Cl), 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. ¹H-NMR: δ 1.34 (6H,d,J=6 Hz,CMe₂), 3.76 (2H,s,ArCH₂CN), 3.86 (3H,s,OMe), 4.50 (1H,m,J=6 Hz,CHMe₂), 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 H₂O (150 ml) were refluxed for 2 h. The reaction mixture was poured into H₂O (2 l) and extracted with EtOAc (3x300 ml). The aq. phase was acidified using 6N HCl, and extracted with CHCl₃ (4x500 ml). The extracts were dried (MgSO₄), and the solvent removed in vacuo. Yield 86%. M.p. 118°C. ¹H-NMR: δ 1.34 (6H,d,J=6 Hz,CMe₂), 3.76 (2H,s,ArCH₂COOH), 3.82 (3H,s,OMe), 4.48 (1H,m,J=6 Hz,CHMe₂), 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-tosyloxyphenethylamine¹ and compound 33 in decaline gave product 34 in 84% yield. The yield, corrected for recovered acid, was 100%. Oil. ¹H-NMR: δ 1.34 (6H,d,J=6 Hz,CMe₂), 2.43 (3H,s,ArMe), 2.69 (2H,t,J=7 Hz,ArCH₂CH₂N), 3.37 (2H,double t,J=6 and 7 Hz,ArCH₂CH₂NH), 3.57 (2H,s,ArCH₂CO), 3.81 (3H,s,OMe), 4.50 (1H,m,J=6 Hz,CHMe₂), 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). ¹H-NMR: δ 1.33 (6H,d,J=6 Hz,CMe₂), 2.67 (2H,t,J=7 Hz,ArCH₂CH₂N), 3.45 (2H,double t,J=6 and 7 Hz,ArCH₂CH₂NH), 3.59 (2H,s,ArCH₂CO), 3.77 (3H,s,OMe), 4.46 (1H,m,J=6 Hz,CHMe₂), 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 CHCl₃, followed by CHCl₃-Me₂CO 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). ¹H-NMR: δ 1.33 (6H,d,J=6 Hz,CMe₂), 2.2-4.0 (6H,br m,3 CH₂), 3.92 (3H,s,OMe), 4.49 (1H,m,J=6 Hz,CHMe₂), 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). ¹H-NMR (CDCl₃-CD₃OD/5:1): δ 1.34 (6H,2 d,separated by only 1.2 Hz,J=6 Hz,CMe₂), 3.92 (3H,s,OMe), 4.51 (1H,m,J=6 Hz,CHMe₂), 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. ¹H-NMR: δ 1.34 (6H,d,J=6 Hz,CMe₂), 2.56 (2H,t,J=7 Hz,ArCH₂CH₂N), 3.44 (2H,double t,J=6 and 7 Hz,ArCH₂CH₂NH), 3.47 (2H,s,ArCH₂CO), 3.78 (3H,s,OMe), 4.49 (1H,m,J=6 Hz,CHMe₂), 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. ¹H-NMR: δ 1.33 (6H,d,J=6 Hz,CMe₂), 2.2-4.0 (6H,br m,3 CH₂), 3.84 (3H,s,OMe), 3.91 (3H,s,OMe), 4.48 (1H,m,J=6 Hz,CHMe₂), 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 CHCl₃-MeOH (99:1). The yield of 36 was 233 mg, while 501 mg 35 was used in this reaction. M.p. 241°C. ¹H-NMR (DMSO-d₆): 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. ¹H-NMR (CDCl₃-CD₃OD/3:1): δ 2.0-3.2 (8H,m,4 CH₂), 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. ¹H-NMR: δ 2.30 (3H,s,NMe), 2.3-2.7 (8H,m,4 CH₂), 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. ¹H-NMR: δ 1.34 (6H,d,J=6 Hz,CMe₂), 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,CHMe₂), 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. ¹H-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. ¹H-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. ¹H-NMR: δ 2.28 (3H, s, NMe), 2.3-2.7 (8H, m, 4 CH₂), 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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REFERENCES

- 1 H.G.Theuns, H.B.M.Lenting, C.A.Salemink, H.Tanaka, M.Shibata, K.Ito and R.J.J.Ch.Lousberg, *Phytochemistry*, 1984, 23, 1157
- 2 D.H.R.Barton, *Pure Appl.Chem.*, 1964, 9, 35
- 3 R.H.F.Manske, *The Alkaloids, Chemistry and Physiology*, Volumes 1-20 (Academic Press, New York)
- 4 H.Meshulam and D.Lavie, *Phytochemistry*, 1980, 19, 2633
- 5 K.Ito, H.Furukawa and H.Tanaka, *Chem.Pharm.Bull.*, 1971, 19, 1509
- 6 K.Ito and H.Tanaka, *Chem.Pharm.Bull.*, 1974, 22, 2108
- 7 K.Ito, H.Tanaka and M.Shibata, *Heterocycles*, 1978, 9, 485
- 8 H.Pande and D.S.Bhakuni, *J.Chem.Soc., Perkin Trans. I*, 1976, 2197
- 9 H.Uprety and D.S.Bhakuni, *Tetrahedron Lett.*, 1975, 1201
- 10 B.Hegedüs, *Helv.Chim.Acta*, 1963, 46, 2604
- 11 D.Beke and Cs.Szántay, *Acta Chim.Acad.Sci.Hung.*, 1958, 14, 325
- 12 P.T.Lansbury and J.O.Peterson, *J.Amer.Chem.Soc.*, 1961, 83, 3537
- 13 P.T.Lansbury and J.O.Peterson, *J.Amer.Chem.Soc.*, 1963, 85, 2236
- 14 F.R.Stermitz, J.P.Gillespie, L.G.Amoros, R.Romero, T.A.Stermitz, K.A.Larson, S.Earl and J.E.Ogg, *J.Med.Chem.*, 1975, 18, 708

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