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NEODIHYDROTHEBAINE AND BRACTAZONINE, TWO DIBENZ[d,f]AZONINE ALKALOIDS OF *PAPAVER BRACTEATUM**

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Key Word Index—*Papaver bracteatum*; Papaveraceae; alkaloids; dibenz[d,f]azonines; neodihydrothebaine; bractazonine; biosynthetic pathway; synthesis; 5,6,8,9-tetrahydro-2-methoxy-7-methyl-dibenz[d,f]azonin-1,12-diol; 5,6,8,9-tetrahydro-2,10-dimethoxy-7-methyl-dibenz[d,f]azonin-1-ol; 5,6,8,9-tetrahydro-2,11-dimethoxy-7-methyl-dibenz[d,f]azonin-1-ol; 5,6,8,9-tetrahydro-2,12-dimethoxy-7-methyl-dibenz[d,f]azonin-1-ol.

Abstract—Two new dibenz[d,f]azonine alkaloids, neodihydrothebaine and bractazonine were isolated from *Papaver bracteatum*. Their possible biosynthesis from thebaine is discussed. The structures of both new alkaloids are proven by synthesis. An isomeric dibenz[d,f]azonine compound was also prepared.

INTRODUCTION

Several minor morphinane-type alkaloids were earlier reported to be present in *Papaver bracteatum*: codeine [1], neopine [1], the isomeric *N*-oxides of thebaine [2], oripavine [3], 14-β-hydroxycodeine [4], 14-β-hydroxycodeinone [4] and thebaine methochloride [5]. They can all be considered to be structurally derived from thebaine [6], the major alkaloid of this plant.

We now wish to report on the presence of two new alkaloids in *P. bracteatum*, both having a basic skeleton different from thebaine, but nevertheless probably biogenetically related to it. Neither of these two substances was earlier reported to occur in nature. One of them was identified as the synthetically derived compound 5,6,8,9-tetrahydro-2,12-dimethoxy-7-methyl-dibenz[d,f]azonin-1-ol (neodihydrothebaine, **1**). The other one is hitherto unknown in literature, and we propose the name bractazonine for it. Bractazonine is shown to be isomeric to neodihydrothebaine, and is 5,6,8,9-tetrahydro-2,11-dimethoxy-7-methyl-dibenz[d,f]azonin-1-ol, **2**. Possible biosynthetic pathways for both new alkaloids are discussed. The structures of neodihydrothebaine and bractazonine are confirmed by synthesis. In doing so, another trisubstituted dibenz[d,f]azonine was prepared and its synthesis is also described. This is the first report on the natural occurrence of dibenz[d,f]azonine alkaloids within the Papaveraceae.

RESULTS AND DISCUSSION

Crude extracts of *P. bracteatum* were separated by counter-current fractionation [1]. GC/MS screening [4] revealed the presence of two MW *m/z* '313' alkaloids in fractions 99–127. The mass spectrometrical fragmentations of these two compounds showed strong resemblances to those reported for the naturally occurring Menispermaceae dibenz[d,f]azonine alkaloids laurifonine (**3**), laurifinine (**4**) and laurifine (**5**) [8, 9]. Therefore, dibenz[d,f]azonine skeletons were assumed for the two alkaloids.

For further purification, subfractions 112–118 were submitted to preparative GC and TLC. Capillary GC/MS showed the isolated material to consist of a 1 : 1 mixture of the two unknown compounds. The ^{1}H NMR spectrum of this mixture was fully compatible with the proposed dibenz[d,f]azonine skeleton. Biogenetic considerations, as discussed below, suggested neodihydrothebaine (**1**) as a likely structure for one of the compounds. Therefore, neodihydrothebaine was prepared according to methods described in the literature [10, 11]. Capillary GC/MS measurements provided evidence for the identity of synthetic neodihydrothebaine with one of the isolated compounds. For the unknown second alkaloid in the isolated mixture the name bractazonine is proposed.

Insight into the structure of bractazonine was obtained from its ^{1}H NMR spectrum. Two methoxyl resonances at δ 3.90 and 3.78 could be ascribed to neodihydrothebaine, whereas a second resonance at δ 3.90 and one at 3.84 could be ascribed to bractazonine. The *N*-methyl signals of the two compounds at δ 2.28 were barely separated from each other. All data suggested bractazonine to have an isomeric structure differing from **1** only in substitution pattern.

The location of the methoxyl groups in bractazonine was studied by ASIS-effects. In $CDCl_3$–C_6D_6 (1 : 1) the methoxyl resonances of synthetic **1** showed strong upfield shifts (δ 3.56 and 3.53). For the mixture of the natural alkaloids the same upfield shifts were observed for all methoxyl resonances. At this stage, it was convenient to know the chemical shift and ASIS-effect of a methoxyl located at position C-1. For this purpose, synthetic **1** was methylated. The newly introduced C-1 methoxyl was found at relatively high field (δ 3.54), most likely due to the

*Part 6 in the Series; for part 5 see ref. [7].

experience of an anisotropy effect executed by the aromatic C-ring as a result of a twisting around the central bond of the biphenyl system. The ASIS-effect on this newly introduced methoxyl was virtually nil, whereas the two other methoxyl resonances of *O*-methylneodihydrothebaine (**6**) were affected to an equal extent as those in the parent compound **1**. These results strongly suggested that methoxyl substitution at C-1 or C-13 could be excluded for bractazonine [12, 13].

$Pr(fod)_3$ induced shifts in ^1H NMR studies were expected to allow conclusive assignments of the position of methoxyl groups in the unknown alkaloid. As model substances 1,2-dimethoxybenzene and 2-methoxyphenol were studied first. The former compound showed large shifts of the methoxyl resonance upon addition of $Pr(fod)_3$, and moderate line-broadening. For the latter substance, however, the induced shift of the methoxyl resonance was much smaller, and subject to considerable line broadening. The isolated methoxyl groups of 1,3-dimethoxybenzene showed only small induced shifts in comparison to those of 1,2-dimethoxybenzene, while little line broadening occurred.

Clearly, the induced shifts of methoxyl resonances are dependent upon the aromatic substitution patterns: *o*-dimethoxy compounds experience large shifts; methoxyl resonances with a hydroxyl *ortho* to it show smaller shifts, accompanied with more distinct line broadening. Isolated methoxyl resonances exhibit negligible shifts and the line width remains virtually uninfluenced. The line broadening in the model compounds in the case of *o*-hydroxy methoxy substitution vs *o*-dimethoxy substitution was quite striking.

For neodihydrothebaine (**1**), the methoxyl resonance at low field shifted upon addition of small amounts of $Pr(fod)_3$ to higher field, with considerable line broadening (disappearance of wiggles, loss of height), while the other methoxyl resonance remained virtually unchanged. Completely in line with the above data from model compounds it can be concluded that the resonance found at lower field can be assigned to the methoxyl group at C-2. This result was further substantiated by the synthesis of compound **7**, which showed its C-2 methoxyl resonance at δ 3.88.

The methoxyl group at C-12 (δ 3.78) in *O*-methylneodihydrothebaine (**6**) remained virtually unchanged upon addition of $Pr(fod)_3$. The induced upfield shift of the C-1 methoxyl resonance was twice that of the C-2 methoxyl group. This result may be explained by the supposition that chelation takes place with the two oxygen atoms at C-1 and C-2, thus forcing the methyl protons of the methoxyl group at C-1 in a steric position over ring C. Protons in such a position experience the combined upfield shifts, caused by the shift reagent and by the anisotropy effect of ring C.

For laurifonine (**3**) synthesized from *O*-methylflavinantine, the methoxyl resonances at δ 3.83 and 3.91 shifted to higher field upon addition of the shift reagent, while the other methoxyl resonance at δ 3.78 was virtually uninfluenced. Hence, the latter resonance in the ^1H NMR spectrum of laurifonine must be assigned to the C-12 methoxyl group.

Laurifinine, which was earlier believed to have either structure **4** [8] or structure **8** [9], could be proven to be identical to compound **4**, by comparison with a synthetic reference sample [14]. The methoxyl resonance at δ 3.82 in the ^1H NMR spectrum of authentic laurifinine shifted upon addition of $Pr(fod)_3$ to higher field, with considerable line broadening, while the other methoxyl group at δ 3.78 remained almost uninfluenced. As a consequence the methoxyl at C-2 must be located at δ 3.82.

For the isolated alkaloid mixture both methoxyl resonances at higher field remained virtually uninfluenced upon addition of $Pr(fod)_3$. The coinciding methoxyl resonance at lower field (integrating for six protons) shifted to higher field, and slightly separated into two singlets, both with considerable line broadening. From these results bractazonine was considered to be a dibenz[d, f]azonine, possessing an isolated methoxyl group (δ 3.84) next to an *o*-hydroxy methoxyl function (δ 3.90).

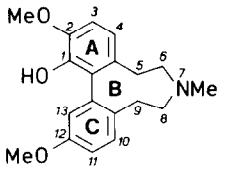
Further examination of the chemical shifts of the isolated methoxyl groups in the compounds studied showed that the C-12 methoxyl resonance was invariably found at *ca* δ 3.78. Therefore a substitution pattern, which differs from those of the 1,2,12- and 2,3,12-trisubstituted compounds studied, should be considered for bractazonine.

The similarity of the natural alkaloids neodihydrothebaine and bractazonine in their chromatographic and extraction behaviours suggested an identical position of the phenolic function in these compounds. On the other hand, the different behaviour of the *o*-hydroxy methoxyl resonances in the $Pr(fod)_3$ induced shift experiment on the isolated material suggested otherwise. The most likely substitution pattern of ring C, from the biogenetic point of view, is a C-11 substitution for bractazonine (see below). Such considerations lead to the proposition of structure **2** for bractazonine. Although biogenetic considerations may provide useful indications for structural elucidations, they are not conclusive. Therefore it was necessary to prepare compound **9** as well. The need to compare bractazonine with the 10-substituted product **9** was further stressed by the finding that the C-10 methoxyl group of protostephanine (**10**) showed its resonance at δ 3.82, as revealed by $Pr(fod)_3$ induced shift studies in ^1H NMR (see Experimental). For the synthesis of compounds **2** and **9** a photolytic cyclization procedure [14, 15] was employed.

In several chromatographic systems neodihydrothebaine (**1**), product **2** and product **9** showed identical R_f values. In ^1H NMR the synthetic compounds **2** and **9** were compared, each in 1 : 1 mixture with neodihydrothebaine, with the isolated natural mixture of alkaloids (see Experimental). Comparison of these data, with those obtained for the isolated mixture of natural alkaloids shows that the artificial mixture of products **1** and **2** is fully compatible with the data obtained for the isolated mixture of *P. bracteatum* alkaloids. The differences with the mixture of products **1** and **9**, however, are minimal, which stressed the need for further structural evidence. For this purpose GC/MS analysis was chosen.

In the mass spectra of 10-methoxy-dibenz[d, f]azonine alkaloids a substantially more intense $[M-OMe]^+$ fragment ion was observed than in the spectra of 11-methoxy- or 12-methoxy-dibenz[d, f]azonines. Both neodihydrothebaine and bractazonine showed no intense fragment ion at *m/z* 282. Consequently, structure **9** could be excluded as possible structure for bractazonine. These results indicated bractazonine to be identical with compound **2**.

Next, the behaviour of the artificial mixture of neodihydrothebaine (**1**) and compound **2**, tentatively identified as bractazonine, was studied in a $Pr(fod)_3$ shift experiment



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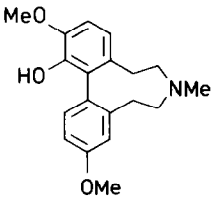

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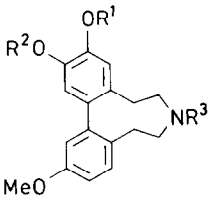
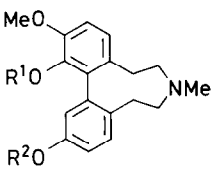
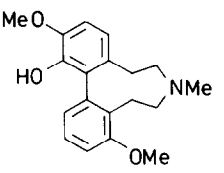


3 $R^1=R^2=R^3=Me$
4 $R^1=H; R^2=R^3=Me$
5 $R^1=R^2=Me; R^3=H$
8 $R^1=R^3=Me; R^2=H$



6 $R^1=R^2=Me$
7 $R^1=R^2=H$



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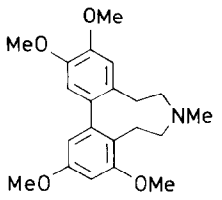

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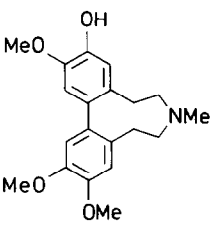

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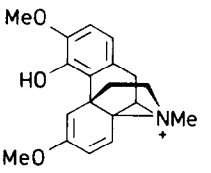


12

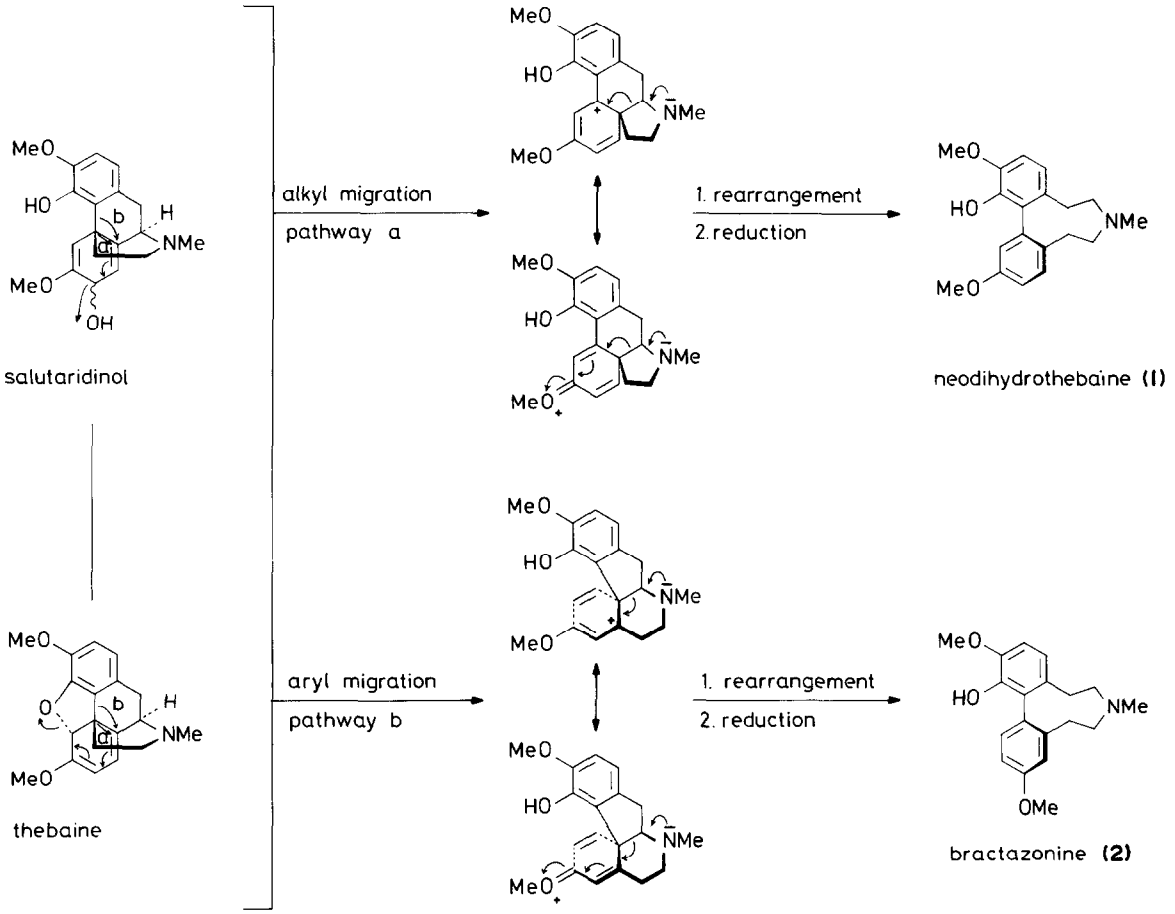
in ^{1}H NMR. The results, obtained for the latter mixture, were in full agreement with those, originally obtained from the isolated mixture of natural neodihydrothebaine and bractazonine. Obviously, there is some preference for the shift reagent to chelate with one of these alkaloids, thus causing the differences observed among the *o*-hydroxy methoxyl resonances. A capillary GC/MS comparison of the natural and synthetical mixtures of alkaloids confirmed their identity.

The possible formation of neodihydrothebaine (**1**) and bractazonine (**2**) as artifacts, resulting from acidic extraction conditions [16], can be excluded since both compounds were also detected in basic extracts.

The dibenz[d,f]azonine skeleton is rarely encountered in nature. Apart from the three alkaloids laurifonine (**3**) laurifinine (**4**) and laurifine (**5**), isolated from the leaves of *Cocculus laurifolius* (Menispermaceae) [8,9], only two other structurally related natural alkaloids have been found before: protostephanine (**10**) isolated from *Stephania japonica* (Menispermaceae) [17], and erybidine (**11**), in several *Erythrina* species (Leguminosae) [18–23]. The finding of the naturally occurring dibenz[d,f]azonine alkaloids neodihydrothebaine (**1**) and bractazonine (**2**) in *P. bracteatum* (Papaveraceae) adds two more representatives of this structural class to the small number of compounds already known.

The biosynthetic formation of 11- and 12-substituted dibenz[d,f]azonine alkaloids in *P. bracteatum* may be rationalized in terms of aryl and alkyl migrations, respectively, in the common precursor thebaine. These steps are also conceivable starting with salutaridinol, the immediate precursor of thebaine. The biosynthetic pathways, proposed here, are depicted in Scheme 1.

The pathway involving alkyl migration (pathway a), through the intermediary neospirinedienone methoxonium ion, is identical to the pathway followed in the synthesis of neodihydrothebaine from thebaine [10]. We now propose that the biosynthesis of **1** proceeds according to a similar route. The first step of pathway b (Scheme 1) is analogous to some known reactions of morphinandienones [24,25], whereas the conversion of proerythrinadienone intermediates into dibenz[d,f]azonines, the next step in pathway b, was realized chemically [26], and is beyond question in the biosynthesis of *Erythrina* alkaloids [27]. A similar biosynthetic pathway, proceeding through an intermediary proerythrinadienol,



Scheme 1. Proposed biosynthesis of dibenz[d,f]azonines in *Papaver bracteatum*.

was proposed for the *in vivo* formation of the dibenz[d,f]azonine alkaloids laurifonine (**3**), laurifinine (**4**) and laurifine (**5**) [28]. The formation of a proerythrinadienone methoxonium ion, as proposed in pathway b, is likely to proceed through participation of the nitrogen lone pair, giving intermediate **12**, in which stereoelectronic factors favour aryl migration [25].

In view of the finding of both neodihydrothebaine (**1**) and bractazonine (**2**) as natural alkaloids (most likely biogenetically derived from thebaine), it is imperative to refer to the classical exposé on the structural elucidation of thebaine, by R. Robinson [29]: "But the star performers in the team of molecular acrobats are undoubtedly the alkaloids of the morphine group and I shall speak especially of thebaine."

EXPERIMENTAL

GC/MS were recorded at 70 eV. Capillary GC/MS analyses were performed using a capillary CP Sil-5 (Chrompack) GC column (50 m glass; carrier gas He 5 ml/min; 5 min isothermal at 200°, then +4°/min temp programmed to 300°) with an open split coupling (all glass system) linked to a double focussing mass spectrometer (electron impact, at 70 eV; source temperature 240°; cathode emission 0.7 mA; acceleration voltage 800 V; scan speed 1 decade/min; interval 0.8 sec; mass range 22–520), connected to a data system.

^{1}H NMR spectra were recorded in $CDCl_3$ (unless given otherwise), at 90 MHz in the CW mode or at 100 MHz in the FT mode. TMS was int. standard ($\delta = 0$). ASIS-effects were studied by gradual addition of C_6D_6 to a $CDCl_3$ soln of the alkaloid, until a *ca* 1:1 composition was reached. Shift expts were performed by addition of small vols of a soln of *tris*(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)praseodymium [Pr(fod)$_3$] in $CDCl_3$ to a soln of the compounds in $CDCl_3$, and recording spectra after each addition, until a *ca* 1 : 10 complex was reached. The resulting straight line graphs are expressed as normalized shielding gradients $d\delta$ (calculated induced shifts in ppm for equimolar complexes). Differences in chemical shifts are given as $\Delta\delta$ in ppm.

GC was carried out on a FID chromatograph using on-column injection and glass columns, packed with 3% OV-17 on Chrompack SA (80–100 mesh), operating at 260° (system a), or with 3% SE-30 on Chromosorb W-HP (80–100 mesh), operating at 260° (system b). For GC R_ts thebaine was chosen as ref. ($RR_t \equiv 1.00$). TLC was performed on silica gel GF 254 plates using EtOAc–Et_2NH (19:1) (system a), or C_6H_6–Me_2CO–MeOH (7:2:1) (system b), or on Al_2O_3 F 254 (type E) plates using $CHCl_3$–heptane–Et_2O (4:5:1) (system c). Alkaloid detection was accomplished using UV light (254 nm). Mps are corr.

Plant extraction and concentration of alkaloids. (i) Capsules of *P. bracteatum* Lindl., cv 'Arya I', cultivated by Franco-Pavot Industries, France, were extracted as reported earlier [1]. The concn of neodihydrothebaine plus bractazonine (**1** + **2**) in the

crude extract was 0.036% dry wt. (ii) Capsules of *P. bracteatum*, cv 'Arya II', cultivated at the Agricultural University Wageningen, Wageningen, The Netherlands, were extracted by elution using 5% aq. HOAc for 2 hr, and after adjustment of the pH of the eluate to 8.9 using an NH_3–NH_4Cl buffer soln, extracted with $CHCl_3$–*iso*-PrOH (3:1). Solvents were removed *in vacuo* at low temp and the residue analysed by GC. The concn of thebaine was 2.66% and the concn of (**1** + **2**) was 0.11% dry wt. In the non-phenolic alkaloid fraction of an (H_2O–K_2CO_3–*n*-BuOH–C_6H_6) extract of the same plant material, the presence of (**1** + **2**) was demonstrated.

Isolation of a mixture of neodihydrothebaine (**1**) *and bractazonine* (**2**). Counter-current fractions 112–118 [1] were submitted to prep. GC (3% OV-17, 270°), yielding 3.1 mg of material, homogeneous by TLC. In order to remove some starting point material in TLC, this material was submitted to prep. TLC (system a), yielding 1.7 mg of a 1:1 mixture of neodihydrothebaine and bractazonine. ^{1}H NMR: δ 2.28 (6H, 2 × *s*, 2 × NMe), 2.3–2.7 (16H, *m*, 8 × CH_2), 3.78 (3H, *s*, OMe), 3.84 (3H, *s*, OMe), 3.90 (6H, *s*, 2 × OMe), 6.7–7.2 (10H, *m*, aromatic H). Accurately determined δ values of the OMe resonances in ^{1}H NMR of the natural mixture (using FT-NMR) were δ 3.780, 3.837 and 3.904. In $CDCl_3$–C_6D_6 (1:1) the OMe resonances were found at δ 3.50–3.56. The normalized shielding gradients in a Pr(fod)$_3$ shift expt were for δ 2.28 dδ 4.3 and 5.1, for δ 3.78 dδ 0.5, for δ 3.84 dδ 0.7, and for δ 3.90 dδ 12 and 16.

Pr(fod)$_3$ shift experiments on model compounds. The normalized shielding gradients were for 1,2-dimethoxybenzene dδ 30, for 2-methoxyphenol dδ 9.3, and for 1,3-dimethoxybenzene dδ 0.20.

Pr(fod)$_3$ shift experiments on alkaloids **1**, **3**, **4**, **6** *and* **10**. *Neodihydrothebaine* (**1**): δ 2.28 (NMe) dδ 7.9, δ 3.78 (C-12 OMe) dδ 0.6, δ 3.90 (C-2 OMe) dδ 14; *Laurifonine* (**3**): δ 2.31 (NMe) dδ 3.8, δ 3.78 (C-12 OMe) dδ 0.7, δ 3.83 (C-2 OMe) dδ 19, δ 3.91 (C-3 OMe) dδ 20; *Laurifinine* (**4**): δ 2.32 (NMe) dδ 1.4, δ 3.78 (C-12 OMe) dδ ~ 0, δ 3.82 (C-2 OMe) dδ 2.6; *O-Methylneodihydrothebaine* (**6**): δ 2.28 (NMe) dδ 4.7, δ 3.54 (C-1 OMe) dδ 7.3, δ 3.78 (C-12 OMe) dδ 0.2, δ 3.89 (C-2 OMe) dδ 4.0; *Protostephanine* (**10**): δ 2.30 (NMe) dδ 4.7, δ 3.78 (C-12 OMe) dδ 0.8, δ 3.82 dδ 1.2 (C-10 OMe) and 15 (C-2 OMe), δ 3.91 (C-3 OMe) dδ 16.

Laurifinine (**4**). ^{1}H NMR: δ 2.32 (3H, *s*, NMe), 2.3–2.8 (8H, *m*, 4 × CH_2), 3.78 (3H, *s*, OMe), 3.82 (3H, *s*, OMe), 5.0 (1H, *br s*, OH), 6.67 and 6.80 (2H, 2 × *s*, H-1 and H-4), 6.72 (1H, *d*, J = 2.7 Hz, H-13), 6.87 (1H, *dd*, J = 2.7 and 8.4 Hz, H-11), 7.15 (1H, *d*, J = 8.4 Hz, H-10). The $\Delta\delta$(OMe) observed was 0.041. In $CDCl_3$–C_6D_6 (1:1) the OMe resonances were found at δ 3.42 and 3.54. GC/MS *m/z* (rel. int.): 314 (23), 313 (100), 312 (14), 311 (23), 298 (15), 270 (10), 257 (26), 256 (71), 255 (71), 239 (14), 226 (10), 225 (40), 195 (12).

Protostephanine (**10**). ^{1}H NMR: δ2.30 (3H, *s*, NMe), 2.0–3.0 (8H, *m*, 4 × CH_2), 3.78 (3H, *s*, OMe), 3.82 (6H, *s*, 2 × OMe), 3.91 (3H, *s*, OMe), 6.32 and 6.45 (2H, 2 × *d*, J = 2.4 Hz, H-11 and H-13), 6.66 and 6.73 (2H, 2 × *s*, H-1 and H-4). The observed $\Delta\delta$ (OMe) were 0.042, 0.087 and 0.128. GC/MS *m/z* (rel. int.): 358 (23), 357 (100), 355 (19), 342 (12), 326 (16), 313 (13), 302 (16), 301 (91), 300 (82), 299 (88), 283 (11), 270 (14), 269 (12), 268 (11), 255 (11).

Synthesis of **1** *from thebaine. Method a.* This synthesis was accomplished starting from thebaine (4.4 g), using freshly prepared MgI_2, and subsequent reduction of the resulting imine by the action of $LiAlH_4$, as recorded in ref. [10]. Florisil chromatography (eluent Et_2O) yielded a yellow solid, which was further purified by prep. TLC (system a). Yield 57%. Mp 100° (from MeOH). *Method b.* Thebaine (1.08 g) was dissolved in TFA (5 ml) [11]. The dark-red soln discoloured quickly, and after stirring for 0.5 hr at room temp the pink soln was evaporated *in vacuo*. MeOH (60 ml) was added to the yellow syrup, and $NaBH_4$ (large excess) was added portionwise. The reaction mixture was stirred for 0.5 hr and, after addition of H_2O, concd *in vacuo*. $CHCl_3$ extraction was performed and the extract dried over Na_2SO_4. After evaporation of solvent, the residue was chromatographed on an Al_2O_3 column (activity III, $CHCl_3$ satd with H_2O), affording pure **1** (1.03 g; yield 95%). Mp 107°. ^{1}H NMR: δ 2.28 (3H, *s*, NMe), 2.3–2.7 (8H, *m*, 4 × CH_2), 3.78 (3H, *s*, OMe), 3.90 (3H, *s*, OMe), 5.08 (1H, *br s*, OH), 6.73 and 6.84 (2H, AB-pattern, J = 8.1 Hz, H-3 and H-4), 6.74, 6.90 and 7.18 (3H, ABC-pattern, $J_{10,11}$ = 8.3 Hz, $J_{11,13}$ = 2.7 Hz, H-13, H-11 and H-10, respectively). The $\Delta\delta$ (OMe) was determined as 0.125. In $CDCl_3$–C_6D_6 (1:1) the OMe resonances were found at δ 3.53 and 3.56. GC/MS *m/z* (rel. int.): 314 (22), 313 (100), 312 (11), 298 (11), 296 (16), 270 (14), 257 (30), 256 (66), 255 (48), 239 (10), 225 (17), 223 (26), 195 (11).

Synthesis of O-methylneodihydrothebaine (**6**). Compound **1** (50 mg) was treated with excess CH_2N_2 in Et_2O for 3 days at room temp. Evaporation of solvent gave the *O*-Me ether. This product was purified by TLC (system a). Yield 83%. Oil. ^{1}H NMR: δ 2.26 (3H, *s*, NMe), 2.3–2.7 (8H, *m*, 4 × CH_2), 3.54 (3H, *s*, OMe), 3.78 (3H, *s*, OMe), 3.89 (3H, *s*, OMe), 6.90 (2H, A2-pattern, J = 8.7 Hz, H-3 and H-4), 6.68, 6.85 and 7.13 (3H, ABC-pattern, $J_{10,11}$ = 8.4 Hz, $J_{11,13}$ = 2.7 Hz, H-13, H-11 and H-10, respectively). In $CDCl_3$–C_6D_6 (1:1) the OMe resonances were found at δ 3.48, 3.50 and 3.61. GC/MS *m/z* (rel. int.): 328 (22), 327 (100), 326 (10), 325 (15), 297 (11), 296 (54), 271 (36), 270 (40), 269 (21), 256 (10), 255 (15), 254 (25), 253 (71), 240 (14), 239 (28), 238 (30), 225 (12), 165 (13), 152 (10).

Synthesis of 5,6,8,9-tetrahydro-2-methoxy-7-methyl-dibenz-[d,f]azonin-1,12-diol (**7**). Thebaine. HCl (1.08 g) was dissolved in TFA (5 ml) and stirred at room temp for 0.5 hr. The soln retained its red colour. The TFA was removed *in vacuo*, MeOH (20 ml) and $NaBH_4$ (large excess) was added to the yellow residue and the reaction mixture stirred for 0.5 hr at room temp. H_2O was added and the MeOH removed *in vacuo*. $CHCl_3$ extraction, drying over $MgSO_4$ and concn afforded the crude product (1.02 g). This was separated on Al_2O_3 (activity III). Elution with hexane–Et_2O (1:1) and $CHCl_3$–Et_2O mixtures afforded first fractions, which on further purification were shown to contain **1** (10 mg, yield 1%), neopine (169 mg, yield 18%), isoneopine (150 mg, yield 16%) and codeine (10 mg, yield 1%). Finally compound **7** was eluted (oil, 233 mg, yield 25%). ^{1}H NMR: δ 2.24 (3H, *s*, NMe), 2.2–2.8 (8H, *m*, 4 × CH_2), 3.88 (3H, *s*, OMe), 5.6 (2H, *br s*, 2 × OH), 6.58 (1H, *d*, J = 2.7 Hz, H-13), 6.72 and 6.82 (2H, AB-pattern, J = 8.4 Hz, H-3 and H-4), 6.73 (1H, *dd*, J = 2.7 Hz, J = 8.4 Hz, H-11), 7.10 (1H, *d*, J = 8.4 Hz, H-10). GC/MS *m/z* (rel. int.): 300 (20), 299 (100), 298 (12), 284 (10), 282 (18), 256 (14), 243 (19), 242 (44), 241 (42), 225 (10), 211 (16), 209 (30), 181 (15).

Synthesis of laurifonine **3** *from O-methylflavinantine.* This synthesis was performed in an analogous manner to that of protostephanine from protostephanone [30, 31]. O-Methylflavinantine (**13**, 299 mg) was stirred with excess $NaBH_4$ (430 mg) in MeOH (30 ml) for 4 hr at 0°. The reaction was monitored by TLC (silica gel C_6H_6–EtOAc–Et_2NH (7:2:1) R_f **13** 0.44; R_f *O*-methylflavinantinol-I (**14**) 0.37; R_f *O*-methylflavinantinol-II (**15**) 0.23—detection by conc H_2SO_4 spray, giving bright orange spots for the dienols). Upon addition of H_2O (30 ml) the MeOH was removed *in vacuo* at room temp and the products extracted into CH_2Cl_2 (6 × 30 ml). The soln was dried (Na_2SO_4) and evaporated, yield 238 mg. The intermediary dienols were isolated in one prepn using the above TLC system.

O-Methylflavinantinol-I (**14**). ^{1}H NMR: δ 2.47 (3H, *s*, NMe), 3.74 (3H, *s*, OMe), 3.85 (3H, *s*, OMe), 3.88 (3H, *s*, OMe), 4.70 (1H, *d*, J = 3.9 Hz, H-7), 5.32 (1H, *s*, H-5), 5.81 (1H, *d*, J = 3.9 Hz, H-8), 6.59 (1H, *s*, H-1), 6.79 (1H, *s*, H-4) [32].

O-Methylflavinantinol-II (**15**). ^{1}H NMR: δ 2.47 (3H, *s*, NMe), 3.74 (3H, *s*, OMe), 3.85 (3H, *s*, OMe), 3.88 (3H, *s*, OMe), 4.56 (1H, *d*, J = 3.1 Hz, H-7), 5.30 (1H, *s*, H-5), 5.76 (1H, *d*, J = 3.1 Hz, H-8), 6.60 (1H, *s*, H-1), 6.77 (1H, *s*, H-4) [32]. The above dienols **14** and **15** (238 mg) were stirred for 18 hr in TFA (20 ml) under N_2, giving instantaneously a red colour. The TFA was removed *in vacuo* and the residue in MeOH was treated portionwise with excess $NaBH_4$ at 0°. After stirring for 2 hr, H_2O was added, and the MeOH removed *in vacuo*. Extraction into CH_2Cl_2 yielded after drying (Na_2SO_4) upon evaporation compound **3** (oil, 209 mg, yield 73%). ^{1}H NMR: δ 2.31 (3H, *s*, NMe), 2.4–2.8 (8H, *m*, 4 × CH_2), 3.78 (3H, *s*, OMe), 3.83 (3H, *s*, OMe), 3.91 (3H, *s*, OMe), 6.68 and 6.73 (2H, 2 × *s*, H-1 and H-4), 6.72 (1H, *d*, J = 2.7 Hz, H-13), 6.86 (1H, *dd*, J = 2.7 Hz, J = 8.4 Hz, H-11), 7.14 (1H, *d*, J = 8.4 Hz, H-10). GC/MS *m/z* (rel. int.): 328 (23), 327 (100), 312 (17), 284 (13), 271 (58), 270 (79), 269 (69), 254 (12), 253 (16), 240 (18), 239 (11), 238 (15), 165 (13), 152 (11).

Total synthesis of **2**. Bractazonine was synthesized using a procedure involving a photolytic aryl coupling reaction [14, 15]. The substrate for this photolytic reaction was prepared from 2-bromo-3-hydroxy-4-methoxybenzaldehyde and 3-hydroxybenzaldehyde.

2-Bromo-3-isopropoxy-4-methoxybenzaldehyde (**16**). 2-Bromo-3-hydroxy-4-methoxybenzaldehyde [33] (0.05 mole) and dry K_2CO_3 (3.8 g) in dry DMF (50 ml) were stirred in an N_2 atmosphere, while 2-bromopropane (0.06 mole) was added dropwise in 15 min. After another 30 min stirring at room temp, the reaction mixture was heated at 100° for 2 hr. After cooling, the reaction mixture was poured on ice-H_2O (250 g) and extracted with Et_2O (4 × 300 ml). The extract was washed with H_2O (50 ml), dried ($MgSO_4$), and concd *in vacuo* giving product **16** in 91% yield. Mp 48°. ^{1}H NMR: δ 1.33 (6H, *d*, J = 6 Hz, CMe_2), 3.93 (3H, *s*, OMe), 4.61 (1H, *m*, J = 6 Hz, C<u>H</u>Me_2), 6.96 and 7.72 (2H, 2 × *d*, J = 8.6 Hz, H-5 and H-6), 10.32 (1H, *s*, CHO). GC/MS *m/z* (rel. int.): 274 (9), 272 (9), 233 (9), 232 (94), 231 (75), 230 (100), 229 (69).

2-Bromo-3-isopropoxy-4-methoxybenzylalcohol (**17**). Compound **16** in EtOH was treated portionwise with $NaBH_4$ (1.2 equivalent). After stirring for 1 hr, H_2O was added and the EtOH removed *in vacuo*. After acidification using conc HCl, $CHCl_3$ extraction was performed. The extract was washed with H_2O, aq. HCl (3 N) and H_2O, dried ($MgSO_4$) and concd *in vacuo*. Yield 100%. Oil. ^{1}H NMR: δ 1.32 (6H, *d*, J = 6 Hz, CMe_2), 2.23 (1H, *br s*, OH), 3.85 (3H, *s*, OMe), 4.59 (1H, *m*, J = 6 Hz, C<u>H</u>Me_2), 4.70 (2H, *s*, $ArCH_2O$), 6.84 and 7.14 (2H, 2 × *d*, J = 8 Hz, H-5 and H-6). GC/MS *m/z* (rel. int.): 276 (20), 274 (20), 234 (95), 233 (18), 232 (100), 231 (11), 217 (15), 215 (15), 153 (31), 125 (24), 124 (29), 110 (16).

2-Bromo-3-isopropoxy-4-methoxybenzylchloride (**18**). Compound **17** (38 g) in dry Et_2O (380 ml) and pyridine (1.4 ml) was treated with $SOCl_2$ (27 ml) in dry Et_2O (90 ml). The reaction mixture was stirred at room temp for 20 min. The soln was washed with H_2O (2 × 150 ml) and with dil. aq. NH_3 and dried ($MgSO_4$). Evaporation of solvent gave **18** (39 g, yield 96%). Oil. ^{1}H NMR: δ 1.31 (6H, *d*, J = 6 Hz, CMe_2), 3.83 (3H, *s*, OMe), 4.58 (1H, *m*, J = 6 Hz, C<u>H</u>Me_2), 4.70 (2H, *s*, $ArCH_2Cl$), 6.84 and 7.18 (2H, 2 × *d*, J = 8 Hz, H-5 and H-6). GC/MS *m/z* (rel. int.): 296 (3), 294 (14), 292 (10), 259 (3), 257 (3), 254 (11), 253 (4), 252 (45), 251 (4), 250 (35), 218 (8), 217 (97), 216 (9), 215 (100), 202 (4), 200 (4).

2-Bromo-3-isopropoxy-4-methoxybenzylcyanide (**19**). KCN (10.7 g) was added to **18** (39 g) in DMSO (250 ml) and stirred at room temp for 18 hr. The reaction mixture was poured into H_2O (1.5 l.) and extraction with Et_2O (5 × 400 ml) was performed. The Et_2O extracts were washed with brine (2 × 150 ml), dried ($MgSO_4$) and concd *in vacuo*. Yield 36 g (95%). Mp 45°. ^{1}H NMR: δ 1.31 (6H, *d*, J = 6 Hz, CMe_2), 3.79 (2H, *s*, $ArCH_2CN$), 3.86 (3H, *s*, OMe), 4.60 (1H, *m*, J = 6 Hz, C<u>H</u>Me_2), 6.86 and 7.22 (2H, 2 × *d*, J = 9 Hz, H-5 and H-6). GC/MS *m/z* (rel. int.): 285 (7), 283 (8), 244 (10), 243 (99), 242 (12), 241 (100), 228 (17), 226 (18), 162 (27).

2-Bromo-3-isopropoxy-4-methoxyphenylacetic acid (**20**). Compound **19** (0.4 mol), ethylene glycol (500 ml) and KOH (100 g) in H_2O (150 ml) were refluxed for 2 hr. The reaction mixture was poured into H_2O (2 l.) and extracted with EtOAc (3 × 300 ml). The aq. phase was acidified (6 N HCl) and extracted with $CHCl_3$ (4 × 500 ml). The extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. Yield 90%. Mp 99°. ^{1}H NMR: δ 1.31 (6H, *d*, J = 6 Hz, CMe_2), 3.78 (2H, *s*, $ArC\underline{H}_2COOH$), 3.82 (3H, *s*, OMe), 4.57 (1H, *m*, J = 6 Hz, C<u>H</u>Me_2), 6.79 and 6.97 (2H, AB-pattern, J = 8.5 Hz, H-5 and H-6, respectively), 9.90 (1H, *br s*, COOH). GC/MS *m/z* (rel. int.): 304 (25), 302 (25), 263 (8), 262 (66), 261 (8), 260 (67), 218 (9), 217 (98), 216 (10), 215 (100), 182 (9), 181 (64), 137 (9).

3-Tosyloxybenzaldehyde (**21**). 3-Hydroxybenzaldehyde (20 g) was stirred with tosylchloride (1 equivalent) in pyridine (225 ml) for 18 hr. The solvent was removed *in vacuo* and the residue divided between H_2O (250 ml) and $CHCl_3$ (4 × 300 ml). The extracts were washed with H_2O (100 ml), 3 N HCl (100 ml) and H_2O (100 ml). After drying over $MgSO_4$ the solvent was removed *in vacuo*, giving compound **21** (42 g, yield 92%). Mp 63°. ^{1}H NMR: δ 2.44 (3H, *s*, ArMe), 7.2–7.9 (8H, *m*, ArH), 9.96 (1H, *s*, CHO). GC/MS *m/z* (rel. int.): 276 (14), 155 (47), 92 (9), 91 (100).

3-Tosyloxybenzylalcohol (**22**). To compound **21** (41.6 g) in cold dry THF (750 ml), $NaBH_4$ (17.1 g) was added. In an N_2 atmosphere $BF_3 \cdot OEt_2$ (76.1 ml) in dry THF (100 ml) was added dropwise in 1 hr at 0°. After stirring for 15 min at 0°, excess borane was destroyed by cautious addition of H_2O. After addition of cold 3 N HCl, $CHCl_3$ extraction was performed. The extract was dried ($MgSO_4$) and concd *in vacuo*, giving product **22** in 100% yield. Mp 65°. ^{1}H NMR: δ 2.06 (1H, *br s*, OH), 2.44 (3H, *s*, ArMe), 4.63 (2H, *s*, $ArCH_2O$), 6.7–7.4 (6H, *m*, ArH), 7.72 (2H, *d*, J = 8.7 Hz, tosyl-H). GC/MS *m/z* (rel. int.): 278 (26), 155 (59), 123 (12), 92 (10), 91 (100).

3-Tosyloxybenzylchloride (**23**). Compound **22** was treated with $SOCl_2$ as reported for the synthesis of **18**. The yield of **23** was 95%. Mp 59°. ^{1}H NMR: δ 2.43 (3H, *s*, ArMe), 4.48 (2H, *s*, $ArCH_2Cl$), 6.8–7.4 (6H, *m*, ArH), 7.72 (2H, *d*, J = 8.7 Hz, tosyl-H). GC/MS *m/z* (rel. int.): 298 (11), 296 (26), 155 (98), 91 (100), 77 (10).

3-Tosyloxybenzylcyanide (**24**). Compound **23** was treated with KCN in DMSO, as in the synthesis of **19**. The yield of **24** was 86%. Mp 69°. ^{1}H NMR: δ 2.44 (3H, *s*, ArMe), 3.69 (2H, *s*, $ArCH_2CN$), 6.7–7.5 (6H, *m*, ArH), 7.72 (2H, *d*, J = 8.7 Hz, tosyl-H). GC/MS *m/z* (rel. int.): 287 (25), 155 (78), 92 (8), 91 (100).

3-Tosyloxyphenethylamine (**25**). To a mixture of **24** (5.74 g) and $NaBH_4$ (0.43 g) in dry THF (60 ml) $BF_3 \cdot OEt_2$ (1.9 ml) was added dropwise while stirring at 0°. The soln was then stirred at room temp for 6 days and decomposed with EtOH, H_2O and dil. aq. HCl, respectively, and evaporated. The residue was neutralized 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 **25** (5.82 g, yield 100%). Oil. ^{1}H NMR: δ 1.27 (2H, *br s*, NH_2), 2.43 (3H, *s*, ArMe), 2.5–3.0 (4H, *m*, 2 × CH_2), 6.7–7.4 (6H, *m*, ArH), 7.72 (2H, *d*, J = 9 Hz, tosyl-H). GC/MS *m/z* (rel. int.): 292 (3), 291 (11), 262 (2), 155 (30), 136 (35), 107 (26), 92 (11), 91 (100), 90 (10).

N-(3-Tosyloxyphenethyl)-2-(2-bromo-3-isopropoxy-4-methoxyphenyl)acetamide (**26**). A mixture of **20** (6.06 g) and **25** (5.82 g) in decalin (135 ml) was heated under reflux for 2.5 hr. After cooling, the mixture was evaporated to dryness and the residue dissolved in $CHCl_3$. The $CHCl_3$ soln was shaken thoroughly with 5% aq. HCl, 2% aq NaOH and H_2O. The soln was dried (Na_2SO_4) and

evaporated to give the amide **26** (9.68 g, yield 84%). Oil. Acidification of the basic washings and $CHCl_3$ extraction recovered some **20**. When corrected for recovered acid **20**, the yield of **26** was 100%. ^{1}H NMR: δ 1.31 (6H, *d*, J = 6 Hz, CMe_2), 2.43 (3H, *s*, ArMe), 2.64 (2H, *t*, J = 7 Hz, $ArCH_2\underline{CH_2}N$), 3.33 (2H, double *t*, J = 6 Hz, J = 7 Hz, $ArCH_2\underline{CH_2}NH$), 3.63 (2H, *s*, $ArCH_2CO$), 3.84 (3H, *s*, OMe), 4.57 (1H, *m*, J = 6 Hz, $C\underline{H}Me_2$), 5.36 (1H, *br t*, J = 6 Hz, NH), 6.6–7.8 (10H, *m*, ArH).

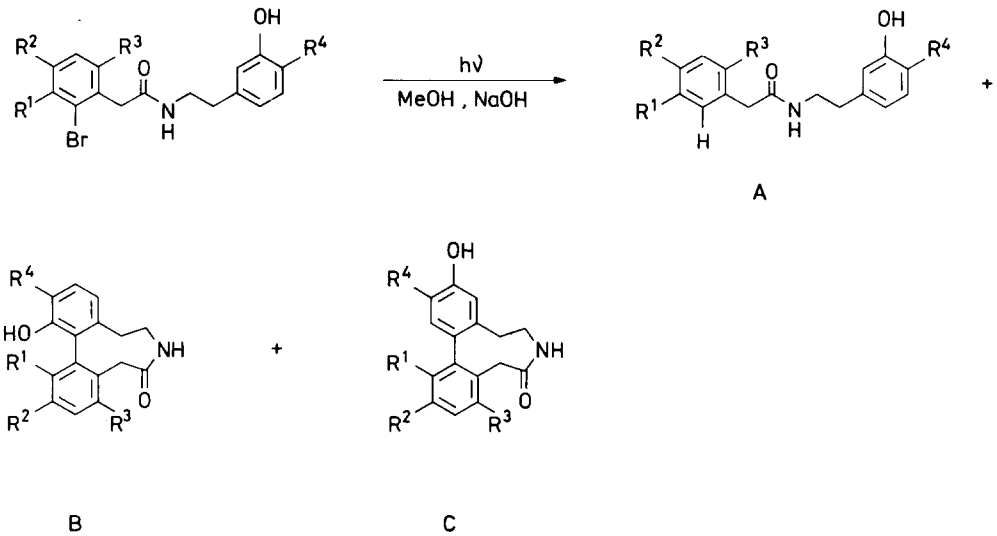
N-(3-*Hydroxyphenethyl*)-2-(2-*bromo*-3-*isopropoxy*-4-*methoxyphenyl*) *acetamide* (**27**). To a stirred soln of **26** (9.1 g) in MeOH (50 ml) and DMF (50 ml) KOH (3.64 g) was added and the reaction mixture stirred at 60° for 3 hr. After cooling, the mixture was poured into H_2O, treated with HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried (Na_2SO_4), and evaporated to give the phenolic compound **27** in 92% yield. Colourless oil. ^{1}H NMR: δ 1.32 (6H, *d*, J = 6 Hz, CMe_2), 2.60 (2H, *t*, J = 7 Hz, $ArC\underline{H_2}CH_2N$), 3.43 (2H, double *t*, J = 6 Hz, J = 7 Hz, $ArCH_2\underline{CH_2}NH$), 3.65 (2H, *s*, $ArCH_2CO$), 3.83 (3H, *s*, OMe), 4.63 (1H, *m*, J = 6 Hz, $C\underline{H}Me_2$), 5.46 (1H, *br t*, J = 6 Hz, NH), 6.5–7.3 (6H, *m*, ArH). GC/MS *m/z* (rel. int.): 423 (9), 421 (10), 342 (31), 300 (58), 217 (48), 215 (48), 180 (100), 121 (67), 120 (40), 77 (30).

Photolysis of **27**. Compound **27** (500 mg) in MeOH (250 ml), containing NaOH (400 mg), was irradiated for 50 min using a 125 W high-pressure Hg lamp (Philips HPLN 57236 E/74, from which the outer bulb was removed) in a quartz immersion apparatus, while a stream of N_2 was passed through the soln. The solvent was removed *in vacuo* and the residue dissolved in H_2O, whereupon Et_2O extraction was performed. The aq. phase was neutralized (conc HCl) and extracted with $CHCl_3$. The extract was washed with H_2O, dried ($MgSO_4$) and evaporated. From a $CHCl_3$ soln of the products from 4.45 g **27** upon cooling some **29** crystallized. Recrystallization from $CHCl_3$ gave 1.33 g **29**. Mp 256°. The mother liquors were separated by silica gel chromatography, using $CHCl_3$–MeOH mixtures (0–15% MeOH). This yielded a mixed fraction of **28** and **30** (421 mg) and finally crude **29** (1.10 g). The latter fraction was crystallized and further purified by silica gel chromatography using EtOAc–*n*-hexane–MeOH (75:25:1). The yield of **29** was 2.06 g (58%). The fraction containing **28** and **30** was chromatographed in a similar manner giving first **28** (230 mg, yield 6%), and then **30** (87 mg, yield 2.4%) (see Scheme 2).

N-(3-*Hydroxyphenethyl*)-2-(3-*isopropoxy*-4-*methoxyphenyl*) *acetamide* (**28**). ^{1}H NMR: δ 1.31 (6H, *d*, J = 6 Hz, CMe_2), 2.63 (2H, *t*, J = 7 Hz, $ArC\underline{H_2}CH_2N$), 3.41 (2H, '*q*', J = 6 Hz, J = 7 Hz, $ArCH_2C\underline{H_2}NH$), 3.46 (2H, *s*, $ArCH_2CO$), 3.82 (3H, *s*, OMe), 4.46 (1H, *m*, J = 6 Hz, $C\underline{H}Me_2$), 5.80 (1H, *t*, J = 6 Hz, NH), 6.4–7.2 (7H, *m*, ArH), 7.7 (1H, *br s*, OH). GC/MS *m/z* (rel. int.): 344 (10), 343 (42), 301 (5), 182 (15), 181 (87), 166 (11), 138 (37), 137 (100), 123 (12), 122 (11), 121 (16), 120 (15).

5,8,9-*Trihydro*-1-*isopropoxy*-2-*methoxy*-6-*oxo*-7*H*-*dibenz*[*d*,*f*]-*azonin*-11-*ol* (**29**). ^{1}H NMR: δ 0.72 and 1.04 (6H, 2 × *br d*, J = 6 Hz, CMe_2), 2.1–4.7 (7H, *m*), 3.87 (3H, *s*, OMe), 3.98 (1H, *m*, J = 6 Hz, $C\underline{H}Me_2$), 5.9 (1H, *br s*, OH), 6.5–7.2 (5H, *m*, all resonances being broadened, ArH). GC/MS *m/z* (rel. int.): 342 (14), 341 (56), 300 (18), 299 (100), 270 (18), 242 (40), 241 (13), 211 (15), 209 (13), 181 (14).

5,8,9-*Trihydro*-1-*isopropoxy*-2-*methoxy*-6-*oxo*-7*H*-*dibenz*[*d*,*f*]-*azonin*-13-*ol*- (**30**). Mp 158–170°. ^{1}H NMR: δ 0.8 and 1.05 (6H, two very broad bands, CMe_2), 3.88 (3H, *s*, OMe), 4.03 (1H, *m*, J = 6 Hz, $C\underline{H}Me_2$), 6.2–7.3 (5H, *m*, ArH). In CD_3OD at 200 MHz the CMe_2 resonances were observed as four doublets, at δ 0.73, 0.86, 0.98 and 1.08, together integrating for 6H. This integral was divided in the *ca* proportion 5:4:4:5, respectively. The peak heights of the outer two resonances were 1.7 times those of the inner resonances. J was 6 Hz. The OMe resonance was a sharp *s*



Substrate	Products A	B	C	R^1	R^2	R^3	R^4	Final product
27	**28**	**30**	**29**	$OCHMe_2$	OMe	H	H	**2**
39	**40**	**41**	**42**	H	H	OMe	OMe	**9**

Scheme 2. Substrates for and products of the photolytic aryl-aryl coupling reaction.

at δ 3.87. At 50° the CMe_2 resonances were broadening, and at 75° almost complete collapse to a broad unresolved band was observed. GC/MS *m/z* (rel. int.): 342 (18), 341 (59), 300 (21), 299 (100), 270 (30), 242 (52), 181 (18).

5,8,9-*Trihydro*-2,11-*dimethoxy*-1-*isopropoxy*-6-*oxo*-7*H*-*dibenz*-[*d,f*]*azonin* (**31**). To a suspension of **29** (600 mg) and dry K_2CO_3 (300 mg) in dry EtOH was added dropwise excess MeI (0.3 ml) at room temp during 10 min. The stirred mixture was heated at 50° for 6 hr, evaporated and dissolved in warm $CHCl_3$. The $CHCl_3$ soln was washed with H_2O, dried (Na_2SO_4) and evaporated. The crude yield was 97%. The products, obtained by methylation of 1.63 g **29** were purified by silica gel chromatography, using $CHCl_3$–EtOAc (3:1), which yielded 1.21 g **31** (yield 71%). ^{1}H NMR: δ 0.80 and 0.97 (6H, two very broad bands, CMe_2), 3.85 (3H, *s*, OMe), 3.87 (3H, *s*, OMe), 6.33 (1H, *br*), 6.6–7.5 (5H, *m*, ArH). GC/MS *m/z* (rel. int.): 356 (10), 355 (46), 314 (19), 313 (100), 284 (18), 256 (27), 225 (10).

5,8,9-*Trihydro*-2,11-*dimethoxy*-6-*oxo*-7H-*dibenz*[*d,f*]*azonin*-1-*ol* (**32**). A soln of **31** (840 mg) in HOAc (53 ml) containing conc HBr (4.2 ml) was heated with stirring at 80° for 1.5 hr. After cooling the mixture was poured into ice-H_2O and then extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried (Na_2SO_4) and evaporated to afford **32** (691 mg, yield 93%). ^{1}H NMR: δ 3.79 (3H, *s*, OMe), 3.88 (3H, *s*, OMe), 5.9 (1H, *br s*, OH), 6.7–7.3 (5H, *m*, ArH).

5,6,8,9-*Tetrahydro*-2,11-*dimethoxy*-7H-*dibenz*[*d,f*]*azonin*-1-*ol* (**33**). To a cold suspension of **32** (326 mg) and $NaBH_4$ (227 mg) in dry THF (30 ml) $BF_3 \cdot OEt_2$ (0.8 ml) was added dropwise in 15 min. After stirring at room temp for 6 hr, excess borane was destroyed by slow addition of EtOH (2 ml), followed by addition of H_2O (3 ml) and conc HCl (1 ml). The reaction mixture was concd *in vacuo* and the residue treated with H_2O and conc aq. NH_3 until pH 8–9 was reached, and then extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried ($MgSO_4$) and evaporated. Yield 96%. Mp 212°. ^{1}H NMR: δ 2.0–3.2 (10H, *m*), 3.84 (3H, *s*, OMe), 3.91 (3H, *s*, OMe), 6.6–6.93 (4H, *m*, ArH), 7.0–7.2 (1H, *m*, ArH). GC/MS *m/z* (rel. int.): 300 (21), 299 (100), 257 (26), 256 (13), 255 (16), 253 (26), 242 (12), 240 (19), 226 (11), 225 (36), 223 (12).

Bractazonine (**2**). A 37% aq. HCHO soln (0.15 ml) was added to a soln of **33** (109 mg) in MeOH (20 ml) and the mixture stirred at room temp. for 0.5 hr. The mixture was cooled to 5–10° and $NaBH_4$ (144 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 **2** (107 mg, yield 94%). Mp 101°. ^{1}H NMR: δ 2.28 (3H, *s*, NMe), 2.3–2.7 (8H, *m*, 4 × CH_2), 3.84 (3H, *s*, OMe), 3.90 (3H, *s*, OMe), 5.3 (1H, *br s*, OH), 6.70 and 6.84 (2H, AB-pattern, J = 8.3 Hz, H-3 and H-4), 6.82 (1H, *d*, J = 2.7 Hz, H-10), 6.82 (1H, *dd*, J = 2.7 Hz, J = 9.2 Hz, H-12), 7.09 (1H, *d*, J = 9.2 Hz, H-13). The observed $\Delta\delta$ (OMe) was 0.068. GC/MS *m/z* (rel. int.): 314 (22), 313 (100), 312 (14), 298 (15), 296 (24), 270 (27), 257 (15), 256 (28), 255 (32), 239 (15), 225 (14), 223 (30).

Synthesis of **9**. The starting materials for the preparation of the substrate for the photolytic coupling reaction, leading ultimately to **9**, were 2-bromo-6-methoxybenzoic acid and 3-benzyloxy-4-methoxyphenethylamine.

2-*Bromo*-6-*methoxybenzylalcohol* (**34**). 2-Bromo-6-methoxybenzoic acid [34] in dry THF was reduced in an N_2 atmosphere at room temp using excess borane in THF. The reaction proceeded slowly as monitored by GC. After 3 days, excess hydride was destroyed by cautious addition of a mixture of THF and H_2O (1:1). The aq. phase was satd with K_2CO_3, whereupon the THF layer was separated and the H_2O layer extracted with Et_2O. The combined extracts were dried ($MgSO_4$) and concd *in vacuo*. The yield of **34** was 66%, while 30% starting material was recovered upon acidification of the aq. phase. Mp 75° (Et_2O and MeOH). ^{1}H NMR: δ 2.53 (1H, *br s*, OH), 3.86 (3H, *s*, OMe), 4.88 (2H, *s*, Ar$C\underline{H}_2$OH), 6.7–7.3 (3H, *m*, ArH). Upon computer simulation of the ABC pattern obtained for the aromatic protons excellent agreement was obtained for δ 6.84 (H-5), 7.11 (H-4) and 7.18 (H-3), with $J_{3,4}$ = 7.9 Hz, $J_{3,5}$ = 2.3 Hz and $J_{4,5}$ = 7.1 Hz. GC/MS *m/z* (rel. int.): 218 (77), 217 (14), 216 (79), 203 (13), 201 (28), 199 (16), 187 (16), 185 (30), 183 (15), 171 (11), 169 (10), 137 (66), 136 (14), 109 (100), 108 (13), 94 (33), 91 (15), 90 (11).

2-*Bromo*-6-*methoxybenzylchloride* (**35**). Compound **34** was treated with $SOCl_2$, as in the synthesis of **18**, which gave compound **35** in 96% yield. Mp 47°. ^{1}H NMR: δ 3.88 (3H, *s*, OMe), 4.83 (2H, *s*, ArCH_2Cl), 6.83, 7.15 and 7.20 (ABC-pattern for H-5, H-4 and H-3, respectively, very similar to that observed in **34**). GC/MS *m/z* (rel. int.): 238 (10), 236 (40), 234 (31), 202 (9), 201 (99), 200 (9), 199 (100), 171 (40), 169 (39), 90 (27).

2-*Bromo*-6-*methoxybenzylcyanide* (**36**). Treatment of **35** with KCN in DMSO afforded **36** in 96% yield. Mp 49°. ^{1}H NMR: δ 3.85 (2H, *s*, ArCH_2CN), 3.87 (3H, *s*, OMe), 6.7–7.3 (3H, *m*, ArH, very similar to **34** and **35**). GC/MS *m/z* (rel. int.): 227 (99), 225 (100), 212 (22), 210 (23), 187 (37), 185 (39), 146 (28).

2-*Bromo*-6-*methoxyphenylacetic acid* (**37**). Hydrolysis of **36** in a similar way to the preparation of **20**, gave **37** in 88% yield. Mp 180°. ^{1}H NMR: δ 3.82 (3H, *s*, OMe), 3.93 (2H, *s*, Ar$C\underline{H}_2$COOH), 6.7–7.3 (3H, *m*, ArH, pattern similar to that mentioned above), 8.7 (1H, *br s*, COOH). GC/MS *m/z* (rel. int.): 246 (53), 244 (54), 202 (34), 201 (47), 200 (36), 199 (45), 171 (53), 169 (53), 165 (100).

N-(3-*Benzyloxy*-4-*methoxyphenethyl*)-2-(2-*bromo*-6-*methoxyphenyl*)*acetamide* (**38**). Heating 3-benzyloxy-4-methoxyphenethylamine [35] and 2-bromo-6-methoxyphenylacetic acid (**37**) in decalin, afforded **38** in 70% yield. Acidification of the basic washings, followed by $CHCl_3$ extraction, recovered unreacted **37**, making the corrected yield of **38** 100%. Mp 136° (decomp. from MeOH). ^{1}H NMR: δ 2.62 (2H, *t*, J = 7 Hz, Ar$C\underline{H}_2CH_2N$), 3.39 (2H, double *t*, J = 6 Hz, J = 7 Hz, Ar$CH_2C\underline{H}_2$NH), 3.73 (3H, *s*, OMe), 3.75 (2H, *s*, ArCH_2CO), 3.85 (3H, *s*, OMe), 5.07 (2H, *s*, ArCH_2O), 5.42 (1H, *br t*, J = 6 Hz, NH), 6.5–7.5 (11H, *m*, ArH), GC/MS *m/z* (rel. int.): 485 (1.6), 483 (1.6), 241 (7), 240 (40), 201 (6), 199 (6), 166 (6), 150 (11), 92 (9), 91 (100), 90 (5).

N-(3-*Hydroxy*-4-*methoxyphenethyl*)-2-(2-*bromo*-6-*methoxyphenyl*)*acetamide* (**39**). A stirred soln of **38** (4.0 g) in conc HCl (40 ml) and EtOH (40 ml) was heated at 60° for 6 hr. The volatile materials were removed, H_2O was added, and the mixture extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated, producing the debenzylated amide **39** (3.22 g, yield 99%). Mp 118° (decomp. from MeOH–Et_2O). ^{1}H NMR: δ 2.62 (2H, *t*, J = 7 Hz, Ar$C\underline{H}_2CH_2N$), 3.42 (2H, double *t*, J = 6 Hz, J = 7 Hz, Ar$CH_2C\underline{H}_2$NH), 3.78 (5H, *s*, OMe + Ar$C\underline{H}_2$CO), 3.85 (3H, *s*, OMe), 5.46 (1H, *br t*, NH), 5.65 (1H, *br s*, OH), 6.45–7.4 (6H, *m*, ArH). GC/MS *m/z* (rel. int.): 395 (1.6), 393 (1.6), 246 (1.4), 244 (1.4), 201 (12), 199 (12), 151 (13), 150 (100), 137 (11), 135 (8), 91 (8), 90 (5).

Photolysis of **39**. Compound **39** (6.7 g) was irradiated in 500 mg aliquots for 25 min, similarly to the photolysis of **27**. The products were chromatographed on silica gel, first using $CHCl_3$, followed by $CHCl_3$–Me_2CO (99:1). The elution order was **40**, then **41** and finally **42**. The products were not fully separated. Fractions containing mainly **41**, respectively **42**, were crystallized from Et_2O–MeOH, yielding pure **41** (0.77 g) and pure **42** (1.2 g). The mother liquor and the fractions containing mainly **40** were combined (1.67 g), and chromatographed on Al_2O_3 (activity III), eluted with $CHCl_3$ satd with H_2O, followed by $CHCl_3$–MeOH mixtures, up to 19:1. This yielded **41** (0.3 g), then a mixture of **40** and **39** (0.78 g, *ca* 25% **39** by ^{1}H NMR), and finally **42** (0.32 g). The yield of **41** was 32%, that of **42** was 28%. The yield of **40** was

ca 10%, while *ca* 3% starting material was present (see Scheme 2).

N-(3-*Hydroxy*-4-*methoxyphenethyl*)-2-(6-*methoxyphenyl*)*acetamide* (**40**). ^{1}H NMR: δ 2.59 (2H, *t*, J = 7 Hz, $ArCH_2CH_2N$), 3.40 (2H, double *t*, J = 6 Hz, J = 7 Hz, $ArCH_2CH_2NH$), 3.51 (2H, *s*, $ArCH_2CO$). GC/MS *m/z* (rel. int.): 315 (5), 222 (6), 166 (5), 151 (12), 150 (100), 137 (10), 135 (8), 122 (6), 121 (28).

5,6,9-*Trihydro*-2,10-*dimethoxy*-8-*oxo*-7H-*dibenz*[*d,f*]*azonin*-1-*ol* (**41**). Mp 238° (from Et_2O–MeOH). ^{1}H NMR: δ 2.50 (2H, *m*), 3.08 and 4.22 (2H, AB-pattern, J = 17 Hz, $ArCH_2CO$), 3.1, 3.6 and 4.4 (3H, *br*), 3.86 (6H, *s*, 2 × OMe), 5.53 (1H, *s*, OH), 6.65–7.05 (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 6.72 and 6.88, J = 8.4 Hz) was recognisable, though somewhat obscured by the resonances of H-11 and H-13. GC/MS *m/z* (rel. int.): 314 (19), 313 (100), 284 (41), 257 (21), 256 (72), 255 (11), 241 (18), 225 (21), 223 (17).

5,6,9-*Trihydro*-2,10-*dimethoxy*-8-*oxo*-7H-*dibenz*[*d,f*]*azonin*-3-*ol* (**42**). Mp 216° (from Et_2O–MeOH). ^{1}H NMR: δ 2.50 (2H, *m*), 3.17 and 4.20 (2H, AB-pattern, J = 18 Hz, $ArCH_2CO$), 3.15, 3.7 and 4.3 (3H, *br*), 3.79 (3H, *s*, OMe), 3.88 (3H, *s*, OMe), 5.83 (1H, *br s*, OH), 6.46 (1H, *s*, H-4), 6.74 (1H, *s*, H-1), 6.7–7.0 (2H, *m*, H-11 and H-13), 7.15–7.4 (1H, *m*, H-12). In DMSO-d_6 the resonances of the aromatic protons were better resolved: δ 6.43 and 6.60 (2H, 2 × *s*, H-4 and H-1, respectively), 6.69 (1H, *dd*, J = 1.3 Hz, J = 7.2 Hz, H-11), 7.04 (1H, *dd*, J = 1.3 Hz, J = 8.4 Hz, H-13), 7.27 (1H, *dd*, J = 7.2 Hz, J = 8.4 Hz, H-12). GC/MS *m/z* (rel. int.): 314 (19), 313 (100), 284 (42), 257 (21), 256 (59), 255 (16), 241 (18), 225 (27).

5,6,8,9-*Tetrahydro*-2,10-*dimethoxy*-7H-*dibenz*[*d,f*]*azonin*-1-*ol* (**43**). Compound **41** was treated with *in situ* prepared diborane, similar to the synthesis of **33**, giving **43** in 100% yield. Mp 100°. ^{1}H NMR: δ 1.8–4.0 (10H, *m*), 3.84 (3H, *s*, OMe), 3.91 (3H, *s*, OMe), 6.6–7.0 (4H, *m*, ArH), 7.27 (1H, *dd*, J = 7.5 Hz, J = 8.4 Hz, H-12). GC/MS *m/z* (rel. int.): 300 (21), 299 (100), 282 (10), 268 (25), 257 (22), 256 (23), 255 (29), 253 (22), 240 (16), 239 (11), 226 (11), 225 (40), 223 (14).

5,6,8,9-*Tetrahydro*-2,10-*dimethoxy*-7-*methyl*-*dibenz*[*d,f*]*azonin*-1-*ol* (**9**). Compound **43** was *N*-methylated in the manner, described for the synthesis of **2** from **33**, giving a quantitative yield of **9**. Mp 166°. ^{1}H NMR: δ 2.27 (3H, *s*, NMe), 2.0–3.1 (8H, *m*, 4 × CH_2), 3.83 (3H, *s*, OMe), 3.90 (3H, *s*, OMe), 5.2 (1H, *br s*, OH), 6.73 and 6.86 (2H, AB-pattern, J = 8.3 Hz, H-3 and H-4), 6.81 (1H, *dd*, J = 1.5 Hz, J = 7.2 Hz, H-11 or H-13), 6.88 (1H, *dd*, J = 1.5 Hz, J = 8.4 Hz, H-11 or H-13), 7.25 (1H, *dd*, J = 7.2 Hz, J = 8.4 Hz, H-12). The observed $\Delta\delta$ (OMe) was 0.075. GC/MS *m/z* (rel. int.): 314 (22), 313 (100), 298 (13), 296 (28), 282 (36), 270 (14), 257 (19), 256 (45), 255 (52), 241 (13), 239 (19), 225 (18), 223 (31), 165 (12), 152 (10), 71 (12).

Chemical shifts and differences in chemical shifts of methoxyl resonances, for 1:1 *mixtures of dibenz*[*d,f*]*azonine alkaloids. Natural mixture of* **1** *and* **2**: *a*, 3.78 (3H), *b*, 3.84 (3H), *c*, 3.90 (**6H**), *c* − *b*, 0.067, *b* − *a*, 0.057, *c* − *a*, 0.124. **1**: *a*, 3.78 (3H) [C − 12 OMe], *b*, 3.90 (3H) [C − 2 OMe], *b* − *a*, 0.125. *Artificial 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*, 0.068, *b* − *a*, 0.057, *c* − *a*, 0.125. **1** *and* **9**: *a*, 3.78 (3H) [C-12 OMe **1**], *b*, 3.83 (3H) [C-10 OMe **9**], *c*, 3.90 (6H) [C-2 OMe **1** + C-2 OMe **9**], *c* − *b*, 0.075, *b* − *a*, 0.050, *c* − *a*, 0.125.

GC data. **1**, a 0.68, b 0.80; **2**, a 0.70, b 0.82; **3**, a 0.68, b 0.82; **4**, a 0.71, b 0.82; **6**, a 0.52, b 0.62; **7**, a 0.95, b 0.99; **9**, a 0.64, b 0.80; **10**, a 1.19, b 1.23; Isolated mixture of natural alkaloids **1** + **2**, a 0.69 (broad), b 0.80 (sharp); artificial mixture of **1** + **2**, a 0.69 (broad) b 0.80 (sharp); **1** + **9**, a 0.64 and 0.68, b 0.80 (sharp).

TLC data. **1**, a 0.83, b 0.17, c 0.10; **2**, a 0.83, b 0.17, c 0.10; **3**, a 0.85, b 0.22, c 0.32; **4**, a 0.50, b 0.11, c 0.01; **6**, a 0.83, b 0.35, c 0.38; **7**, a 0.37, b 0.07, c 0.00; **9**, a 0.83, b 0.17, c 0.10; **10**, a 0.87, b 0.17, c 0.23; **11**, a 0.51, b 0.10, c 0.01.

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