Synthetic approaches toward ecteinascidins. Part 1. Preparation of an (*E*)-2-arylidene-3-benzyl-1,5-imino-3-benzazocin-4-one having a protected phenol in the E-ring

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A synthetic strategy for the preparation of ecteinascidins isolated from the Caribbean tunicate *Ecteinascidia turbinata* and an efficient synthesis of a key tricyclic lactam intermediate 32 are described. The key step is the intramolecular cyclization of the allylic alcohol 15 to the (*E*)-1,5-imino-3-benzazocine 16. Cyclization of 15 (R = Me, Bn) afforded the desired product 16 in good yield. However, treatment of 15 (R = MOM) under acidic conditions gave compound 18 in high yield, the structure of which was determined by X-ray crystallography. Finally, 16 was converted into (*E*)-*N*-methyltricyclic lactam 32 that can serve as a synthetic precursor of ecteinascidins.

Introduction

Ecteinascidins, isolated from the Caribbean tunicate *Ecteinascidia turbinata*,[1] are active against P388 lymphoma, B16 melanoma, M5076 ovarian sarcoma, Lewis lung carcinoma, and the LX-1 human lung and MX-1 human mammary carcinoma xenografts. The structures of ecteinascidins were elucidated by detailed analysis of the highfield NMR and FAB mass spectral data. The crystal structures of some ecteinascidin analogues completed the unambiguous assignment of relative stereochemistry.[2] The ecteinascidins are tetrahydroisoquinoline derivatives that are structurally related to safracins and saframycins from microbes.[3] Because treatment of ecteinascidin 597 with $HgCl_2$ followed by $NaBH_4$ and methanolysis gave L-cysteine methyl ester, the absolute configuration of ecteinascidins is probably the same as that of safracins.[4]

We have reported on the total synthesis of (±)-saframycin B–D and (−)-*N*-acetylsaframycin Mx 2.[5] To extend the scope of the synthetic route to saframycin antibiotics, we have focused our attention on the synthesis of ecteinascidins. Our initial strategy for their synthesis was based on the retrosynthetic analysis outlined in Scheme 1. Reaction of the saframycin framework **C** with cysteine would give the compound **B**. Oxidation of the phenol **B** afforded the unsaturated ketone **A**. Intramolecular cyclization by the SH group of compound **A** followed by acetylation gave ecteinascidin 594. The electrophilic ketone in ecteinascidin 594 can be condensed in a Pictet–Spengler reaction with a dopamine derivative to form the third tetrahydroisoquinoline ring in ecteinascidin 743. We would envision formation of the pentacyclic framework **C** from the tricyclic lactam **D**, itself prepared from the allylic alcohol **1** in three steps (Scheme 2). This strategy is supported by the possible biosynthetic pathway recently presented by Rinehart and co-workers.[6]

We describe here a synthetic strategy for the preparation of ecteinascidins which have challenging structural features, and an efficient synthesis of a key tricyclic lactam **32** having a protected phenol in the E-ring.

Results and discussion

Our starting material for the synthesis of the E-ring portion of ecteinascidins was piperonal **3** (Scheme 3), the Baeyer–Villiger oxidation of which followed by hydrolysis under basic conditions gave sesamol **4** (70%).[7] Phenol **4** was then converted almost quantitatively into the methoxymethyl ether **5** using sodium hydride and chloromethyl methyl ether in dry dimethyl-

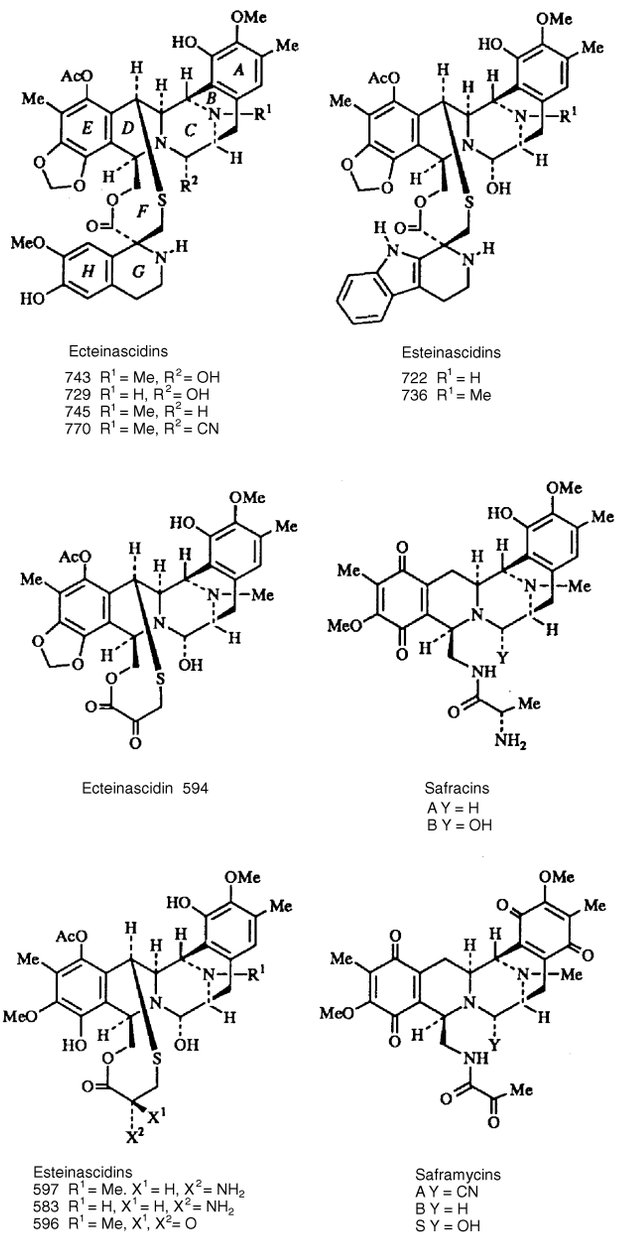
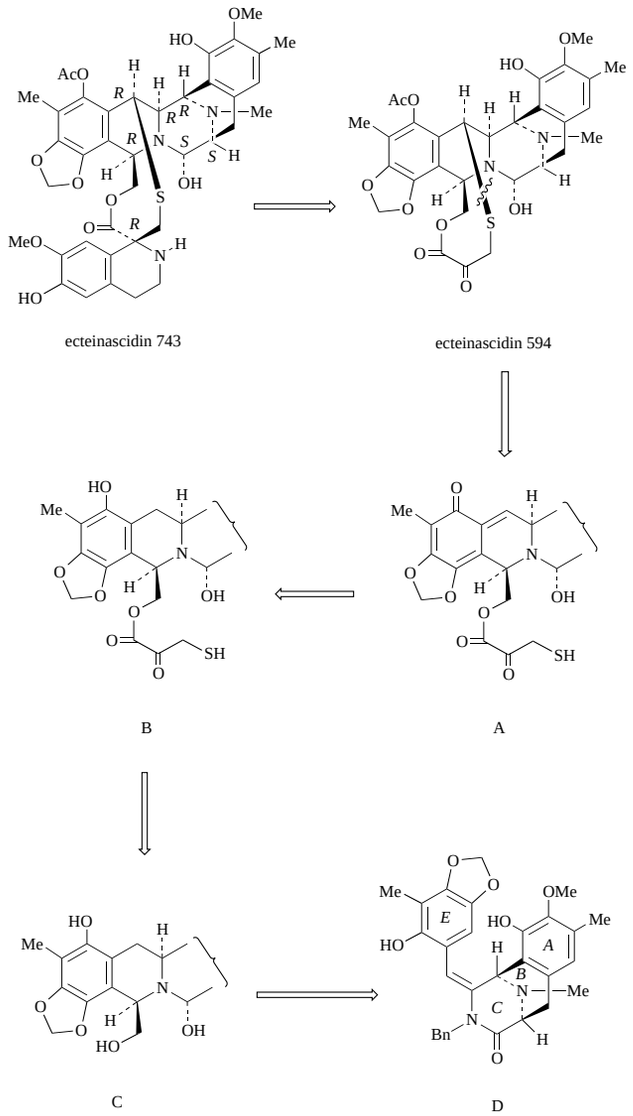
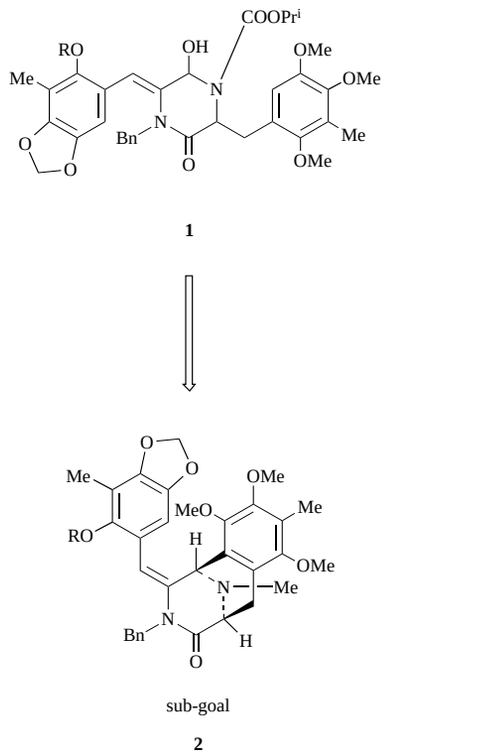


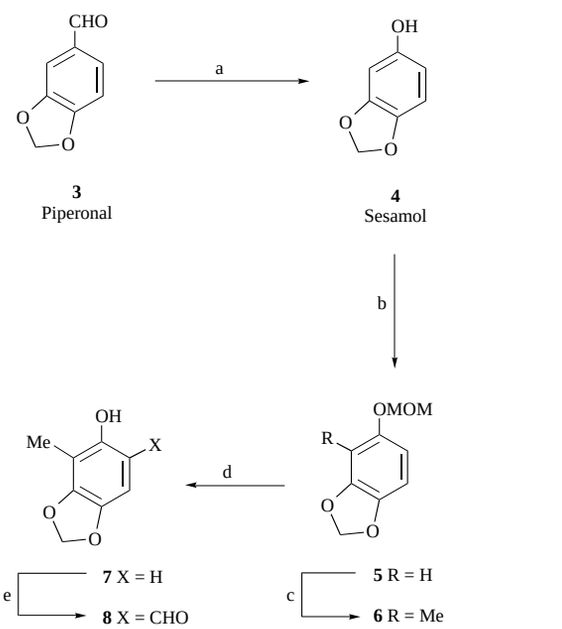
Fig. 1 Structural formulae of ecteinascidins, safracins and saframycins



Scheme 1



Scheme 2



Scheme 3 *Reagents and conditions*: a, *m*-CPBA, CH_2Cl_2, reflux, 4 h and then 10% KOH–H_2O, MeOH, room temp., 2.5 h; b, NaH, DMF, 0 °C, 1 h and then MOMCl, DMF, 0 °C, 3 h; c, BuLi, THF, −17 °C, 1 h and then MeI, THF, −17 °C, 2 h; d, HCl, EtOH, reflux, 3 h; e, hexamethylenetetraamine, AcOH, reflux, 30 min

formamide (DMF). Treatment of **5** with BuLi in THF at −17 °C followed by iodomethane treatment gave **6** (72%). Deprotection of **6** under acidic conditions afforded the phenol **7** (77%). Finally, the Duff formylation[8] of **7** with hexamethylenetetraamine in acetic acid under reflux gave the benzaldehyde **8** (73%).

The phenol **8** was protected with a methoxymethyl group to afford **9a** (Scheme 4), condensation of which with the diacetate **10**[9] in the presence of potassium *tert*-butoxide gave (*Z*)-arylidenepiperazinedione **11a** (84%). Benzylation of **11a** followed by hydrazine hydrate treatment gave the *N*-benzylated derivative **13a** (83%). The regiochemical structure of **13a** was confirmed by X-ray crystallographic analysis (Fig. 2). The piperazine ring of **13a** was activated by introduction of a 2-propyloxycarbonyl group to give the imide **14a** (98%).

Chemoselective reduction of **14a** with lithium tri-*tert*-butoxyaluminium hydride in THF afforded a diastereoisomeric mixture of the alcohol **15a**, which when exposed to formic acid at 60 °C for 1 h was converted into a new compound, the structure of which was not that desired (Scheme 5). Treatment of **15a** with catalytic amount of hydrochloric acid in propan-2-ol under reflux for 1 h gave **18** (73%), the stereochemical structure of which was confirmed by X-ray crystallographic analysis (Fig. 3). The probable mechanistic pathway for the formation of **18** is shown in Scheme 6. The dehydration of **15a** generated (*Z*)-**17** which by isomerization of the *exo*-double bond gave (*E*)-**17**. Cyclization of (*E*)-**17** to **18** (path A) is faster than that of (*E*)-**17** to **16a** (path B).

We then investigated the transformation of **14a** to the corresponding phenol **19**, and were surprised to find that treatment of **14a** with catalytic amount of hydrochloric acid in propan-2-ol under reflux for 2 h gave the coumarin **20** (91%) as a mixture of two rotational isomers. It is proposed that acid-catalysed *O*-deprotection of **14a** affords an intermediate **19**, the double bond of which is isomerized and leads to ring formation to give **20**. Further, treatment of **13a** under similar conditions afforded compound **22** (81%) (Scheme 7). Coumarin **20** had

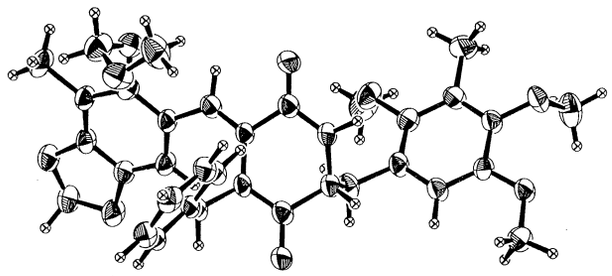
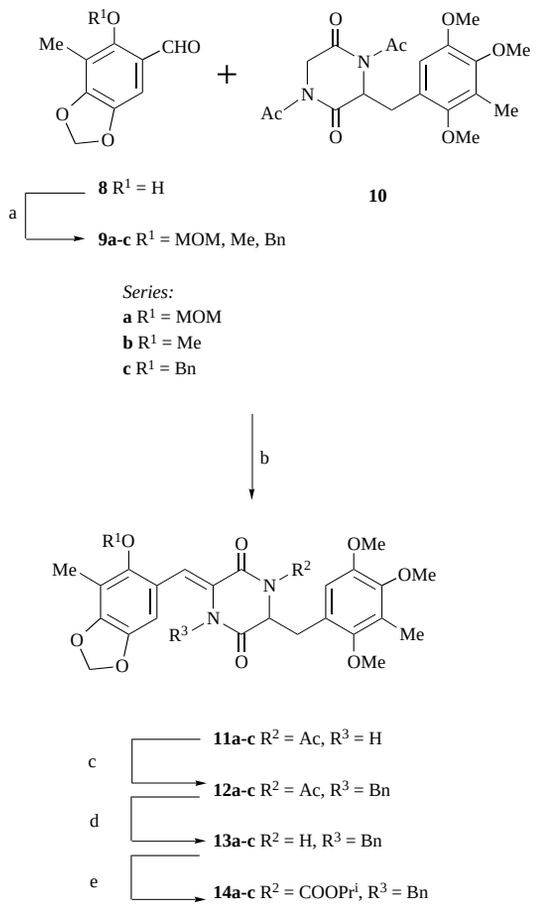


Fig. 2 X-Ray molecular structure of compound **13a**



Scheme 4 *Reagents and conditions*: a, NaH, DMF, 0 °C, 30 min and then R^1X, DMF, 0 °C, 1 h; b, $KOBu^t$, $HOBu^t$, DMF, room temp., 24 h; c, NaH, DMF, 0 °C, 30 min and then BnBr, DMF, room temp., 2 h; d, NH_2NH_2–H_2O, DMF, room temp., 1 h; e, $ClCOOPr^i$, DMAP, NEt_3, CH_2Cl_2, room temp., 3 h

signals for two aromatic protons, in addition to those for the benzyl substituent, together with an alkene singlet. The ^{13}C NMR spectrum of the main rotamer of **20** also showed two doublet signals at δ 103.6 and 111.2 assigned to the aromatic carbon together with an alkene doublet at δ 144.3.†[10] Deprotection of **18** with sodium methoxide in methanol under reflux for 15 h afforded the pyrazinone **23** (39%) and compounds **24**‡ (10%). The ^1H NMR spectrum of **23** displayed a hydroxyl proton which appeared at δ 5.17 together with four methylene signals at δ 3.73, 4.16, 5.22 and 5.85; no methine proton was observed. Acetylation of **23** with acetic anhydride in pyridine gave the acetate **25** (88%) (Scheme 8).

† The ^{13}C NMR spectrum of 3-methylcoumarin showed a C-4 doublet signal at δ 138.8.

‡ The ^1H NMR spectrum of **24** showed a peak at δ 8.51 which was assigned to the *exo*-olefinic proton, thus indicating that **24** has a *Z*-configuration.

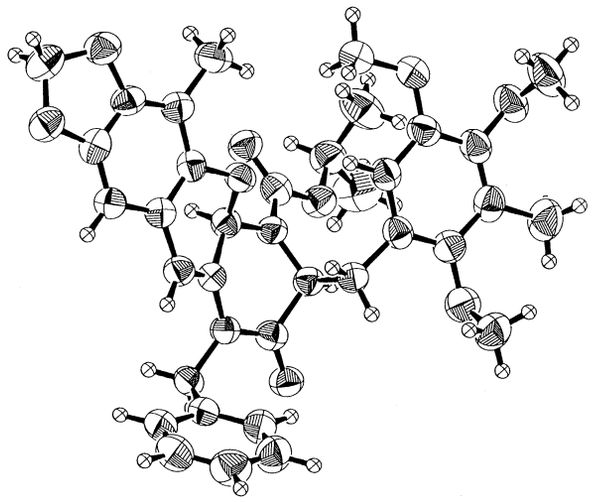
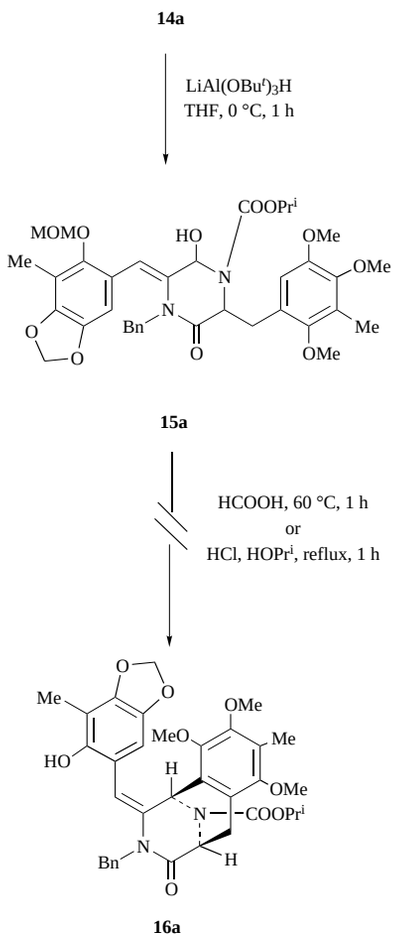
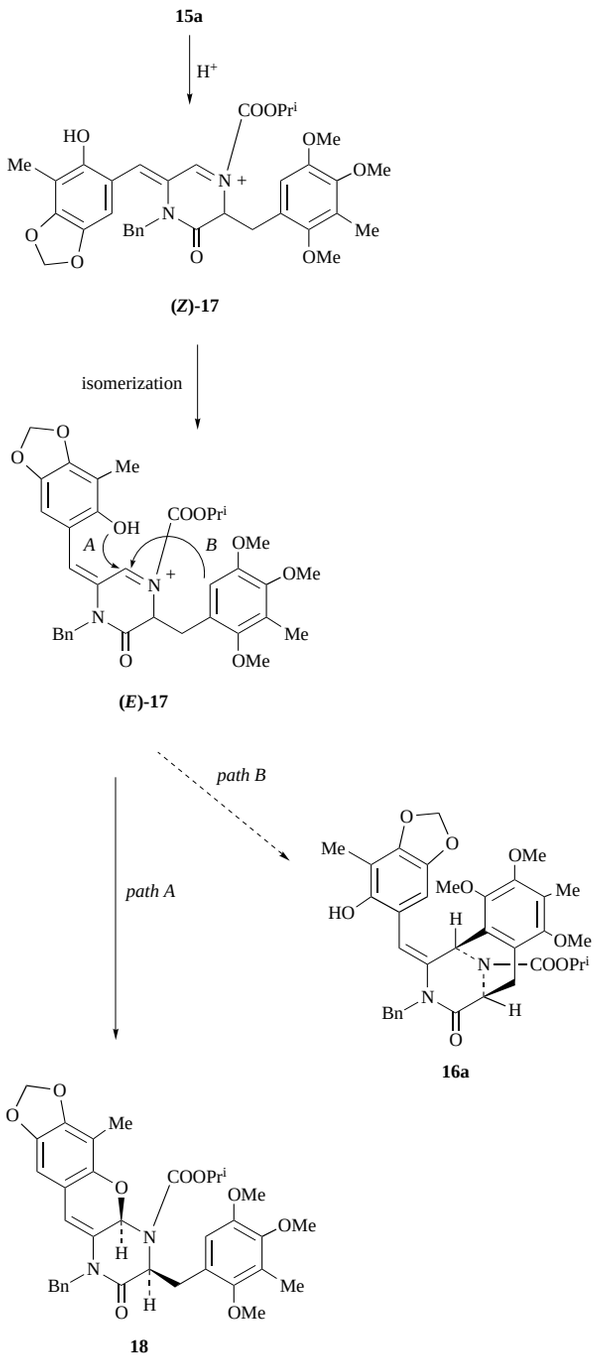


Fig. 3 X-Ray molecular structure of compound **18**

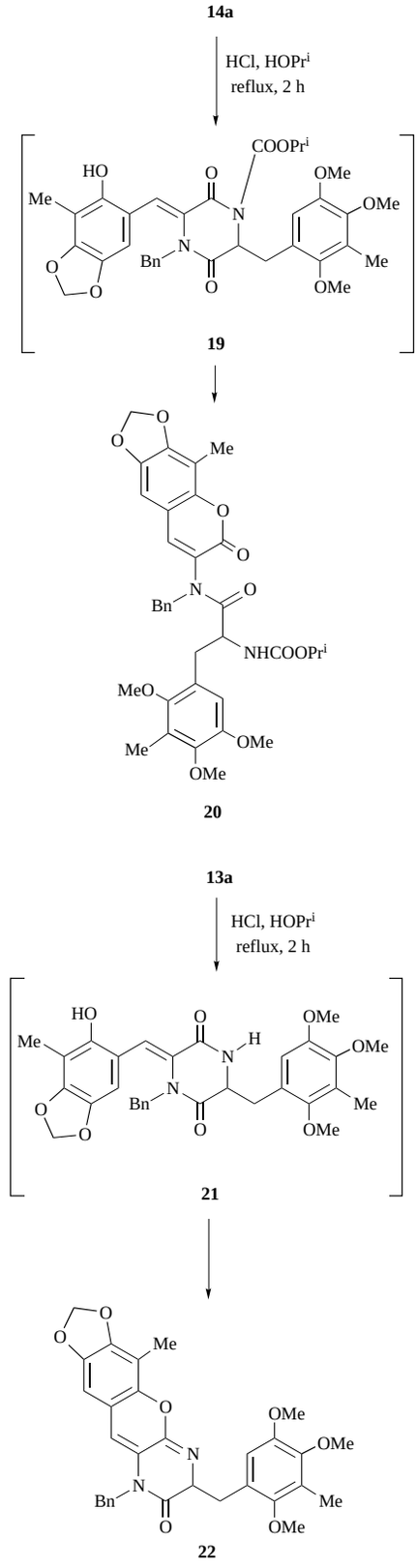


Scheme 5

Since attempts to convert **14a** into 1,5-imino-3-benzazocine **16** were unsuccessful, we sought to induce this transformation by using the methyl and benzyl groups as a hydroxyl protecting group. Alkylation of the phenol **8** gave **9b** (80%) and **9c** (92%) (Scheme 4). Substrates **14b** and **14c** were prepared in four steps by the same procedure as used for **14a** in 63 and 45% overall yields, respectively. Reduction of **14b** with lithium tri-*tert*-butoxyaluminium hydride afforded the allylic alcohol **15b** (contaminated with a small amount of **13b**), which on treatment with formic acid at 70 °C for 16 h afforded the desired cyclization product **16b** with a maximum yield of only 16%. Because molecules that incorporated a methylenedioxyl group were rela-



Scheme 6

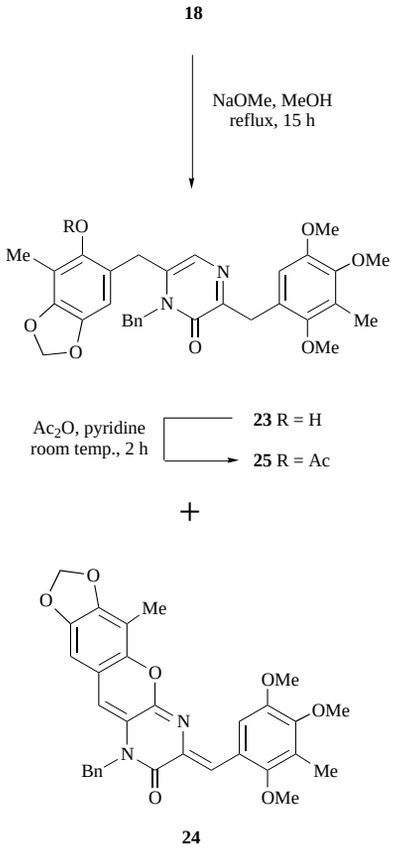


Scheme 7

tively unstable under these conditions, the following procedure required experimentation and optimization.§ Methanesulfonic anhydride in dichloromethane at room temperature for 48 h brought about mild and efficient dehydration/cyclization of **15b** to afford the desired cyclization product **16b** (71%) along with **13b** (8%). Reduction of **14c** followed by cyclization using methanesulfonic acid in dichloromethane under the same conditions afforded **16c** (35%) and **13c** (10%). In this case, our previous procedure[11] using methanesulfonyl chloride and triethylamine in dichloromethane under reflux was effective and generated the desired product **16c** (58%) from **14c** (Scheme 9). It was difficult to determine the geometry of the *exo*-double bond at this stage, because the signals in the ^{1}H NMR spectra of **16b** and **16c** were not split, which indicated that there was a mixture of two rotational isomers.

We then prepared the derivatives of 1,5-imino-3-benzazocine **16d**–**e**. Substrates **14d** and **14e** were prepared from the benzaldehydes **34** and **9c** with the diacetate **35** in four steps, respectively (Scheme 11). Reduction of **14d** afforded the allylic alcohol **15d** (contaminated with a small amount of **13d**), which on treatment with formic acid at 70 °C for 2 h afforded the desired

§ Attempted cyclization with other protic acids instead of methanesulfonic anhydride gave **16b** in low yield: TFA (22%), TFAA (23%), MsOH (15%), CSA (6%), *p*-TsOH (25%).



Scheme 8

product **16d** (63%) along with **26d** (3.2%), **27** (7.0%)¶ and **13d** (5.3%). The signal in the ^{1}H NMR spectrum of **16d** was not split, which also indicated that there was a mixture of two rotational isomers. However, the *Z*-isomer **26d** had signals for four aromatic singlet protons together with an alkene singlet at δ 5.74, 6.47, 6.89, 6.97 and 7.19. The ^{13}C NMR spectrum of **27** showed three methylene signals at δ 30.7, 40.5 and 101.3 together with a quaternary carbon signal at δ 100.5. Attempts under a variety of conditions to cyclize compound **16e** from **14e** *via* **15e** were fruitless; the yield was disappointingly low because of the occurrence of unwanted cyclization to give the indeno[1,2-*b*]pyrazin-2-one **28**.[12,13] After extensive investigation of the reaction conditions, the following procedure was found to be best in terms of product yield and reproducibility of the reaction: treatment of **15e** with 2 equiv. of methanesulfonic anhydride in dichloromethane at room temperature for 72 h gave the desired compound **16e** (36%) along with **29** (5.2%) and **13e** (11.6%).

Finally, we studied removal of the *N*-protecting group of compound **16** to give the secondary amine **30**. Since all attempts to remove the urethane blocking group of **16b** under acidic conditions caused decomposition of the starting material, an alternative approach was used under basic conditions.[14] Deprotection of **16b**–**e** with sodium methoxide in methanol under reflux gave the amines **30b**–**e** (72–95%) (Scheme 10). Similarly, **26d** was converted into **31** (90%). The ^{1}H NMR spectrum of **31** showed the H-1 signal as a singlet at δ 4.39, whereas in the ^{1}H NMR spectrum of **30d** it appeared at δ 4.96. The C-1 signal of **31** appeared at δ 54.5 which was to lower field than that of **30d** (δ 50.7). The δ value observed for the methine proton at the C-1 position of compounds **30b**–**d** (δ 4.91–5.46) indicates that this proton is positioned in the deshielding zone of the aromatic ring of the side chain at the C-2 position. Methylation of **31b**–**e** with formaldehyde and formic acid at 70 °C for 1 h gave the tricyclic lactams **32b-e** (86–99%). The *E* stereochemical assignments for **32b**–**e** are also based on ^{1}H NMR and ^{13}C NMR spectral evidence.

¶ Stereochemistry yet to be determined.

Conclusion

In summary, we have efficiently synthesised a key tricyclic lactam intermediate having a protected phenol in the *E*-ring. Efforts to improve the efficiency of the sequence and apply it to the total synthesis of ecteinascidins are now being made.

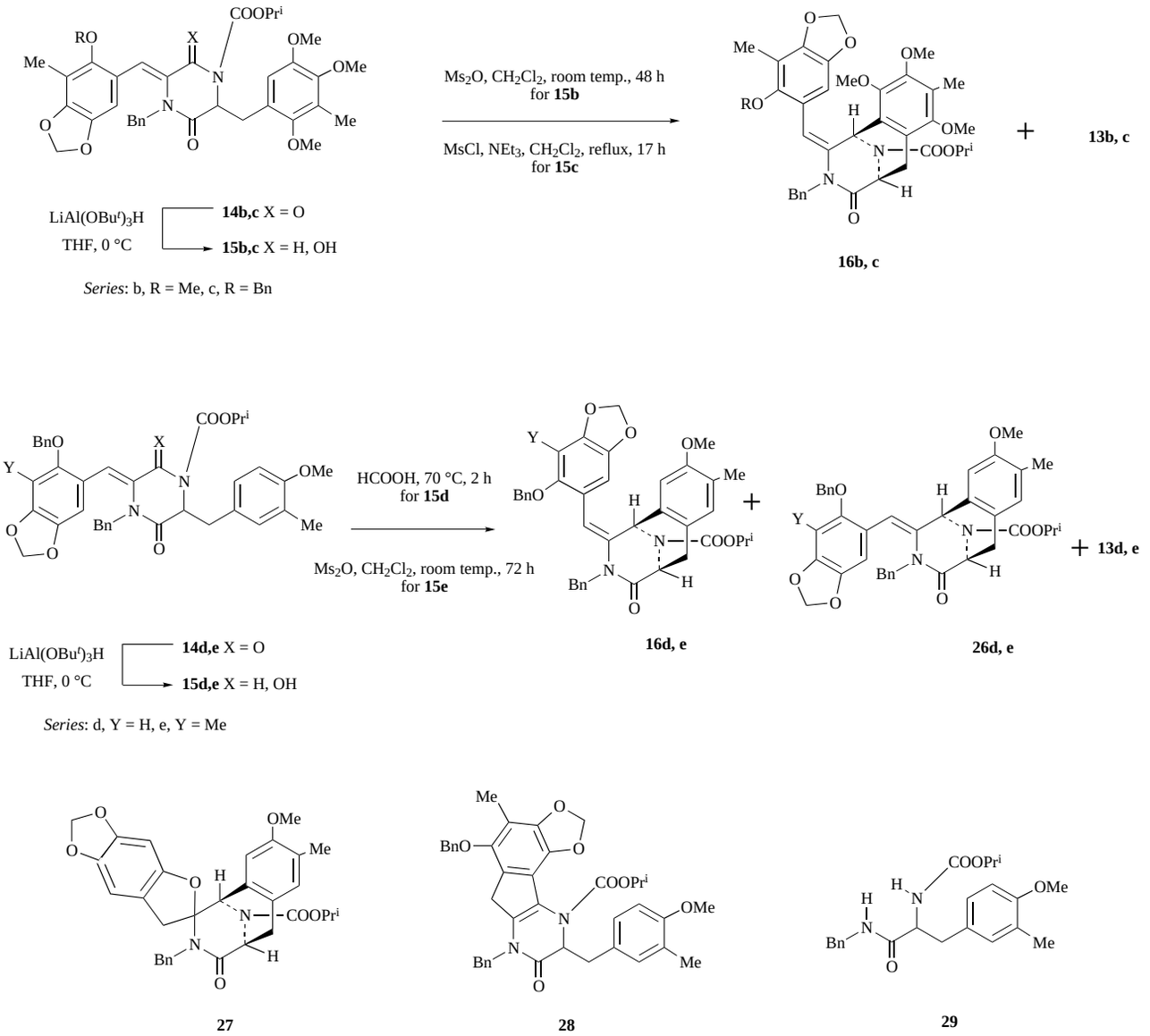
Experimental

All melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded with a Hitachi 260-10 Infra Red Fourier transform spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-EX 270 spectrometer at 270 MHz. Peak multiplicities are denoted by s (single), br s (broad singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet) or by a combination of these, *e.g.* dd (double double) with coupling constants (*J*) given in Hz. ^{13}C NMR spectra were recorded on a JEOL JNM-EX 270 spectrometer at 65 MHz (multiplicity determined from off-resonance decoupled or DEPT spectra). Mass spectra were recorded on a JMS-DX 302 instrument with a direct inlet system operating at 70 eV. Elemental analyses were obtained using a Perkin-Elmer Model 240B elemental analyser. All reactions were conducted under an argon atmosphere. Dry solvents and reagents were obtained using standard procedures. Anhydrous sodium sulfate was used for drying organic solvent extracts, and removal of the solvent was done with a rotary evaporator and, finally, under high vacuum. Column chromatography was performed with Merck silica gel 60 (70–230 mesh). Ether refers to diethyl ether.

6-Hydroxy-5-methyl-3,4-methylenedioxybenzaldehyde 8

(a) Sesamol 4. *m*-Chloroperbenzoic acid (80%; 31.7 g, 147 mmol) was added to a stirred solution of piperonal **3** (15.0 g, 100 mmol) in dry dichloromethane (400 cm^3) at 0 °C, and the resulting solution was heated under reflux for 4 h. The reaction mixture was poured onto ice–water (200 g) and the phases were separated. The aqueous layer was extracted with dichloromethane (2 × 200 cm^3). The combined organic layer and extracts were washed with 5% aqueous sodium hydrogen carbonate (200 cm^3), dried, and concentrated *in vacuo* to give the residue. A solution of this residue in methanol (200 cm^3) and 10% aqueous potassium hydroxide (40 cm^3) was stirred at room temperature for 2.5 h, after which it was diluted with water (800 cm^3), neutralized with 2 M aqueous hydrochloric acid and extracted with chloroform (3 × 400 cm^3). The combined extracts were washed with water (300 cm^3), dried, and concentrated *in vacuo* to give a solid (14.5 g), recrystallization of which from ether gave sesamol **4** (9.6 g, 70%) as colourless needles, mp 62–63 °C (lit.,[7] 65 °C); δ_H($CDCl_3$) 4.81 (1 H, s, OH), 5.81 (2 H, s, OCH_2O), 6.12 (1 H, dd, *J* 2 and 8, 6-H), 6.31 (1 H, d, *J* 2, 2-H) and 6.53 (1 H, d, *J* 8, 5-H).

(b) (3,4-Methylenedioxyphenoxy)methyl methyl ether 5. Sodium hydride (60% oil dispersion, washed with dry hexane three times; 5.76 g, 240 mmol) was added to a stirred solution of sesamol **4** (27.6 g, 200 mmol) in dry DMF (200 cm^3), and the resulting solution was stirred for 30 min at 0 °C. Chloromethyl methyl ether (18.3 cm^3, 240 mmol) was added to the reaction mixture which was then stirred for 3 h at 0 °C. After this the reaction mixture was diluted with water (300 cm^3), and extracted with ether (3 × 300 cm^3). The combined extracts were washed with water, dried, concentrated and the crude oil (49.0 g) was purified by column chromatography (10 : 1, hexane–ethyl acetate) to give **5** (36.2 g, 99%) as a colourless oil, which was used for the next step without further purification; δ_H($CDCl_3$) 3.47 (3 H, s, OCH_3), 5.08 (2 H, s, OCH_2OCH_3), 5.91 (2 H, s,



Scheme 9

OCH_2O), 6.49 (1 H, dd, *J* 8.6 and 2.3, 6-H), 6.62 (1 H, d, *J* 2.3, 2-H) and 6.70 (1 H, d, *J* 8.6, 5-H).

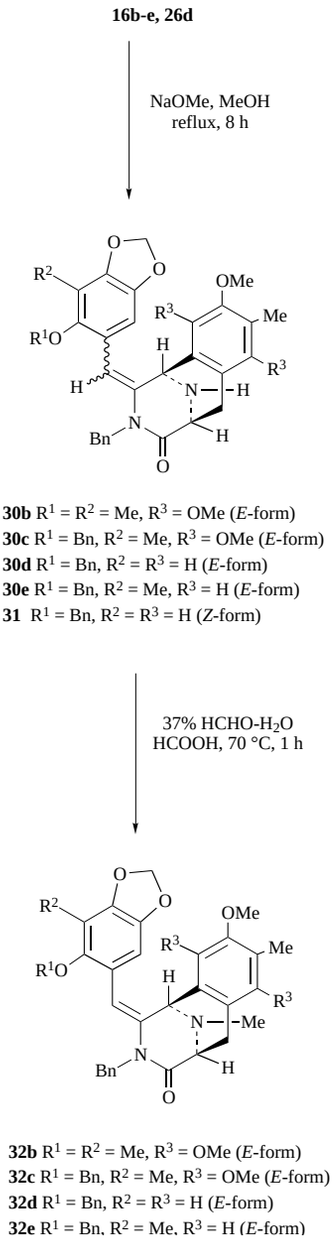
(c) (2-Methyl-3,4-methylenedioxyphenoxy)methyl methyl ether 6. A solution of **5** (36.2 g, 200 mmol) in dry THF (300 cm^3) was added to a solution of BuLi (1.61 mol, 310 cm^3, 500 mmol) in hexane at −17 °C for 1 h. After being stirred for 1 h at the same temperature, the mixture was treated with a solution of iodomethane (37.3 cm^3, 600 mmol) in dry THF (100 cm^3), added over 1 h; stirring was then continued for 2 h. After this the reaction mixture was diluted with water (2000 cm^3) and extracted with ether (3 × 400 cm^3). The combined extracts were washed with saturated aqueous sodium chloride (400 cm^3), dried and concentrated. The resulting crude oil (30.0 g) was purified by column chromatography (200:1, hexane–ethyl acetate) to give **6** (27.9 g, 72%) as colourless oil which was used for the next step without further purification; $\delta_H(CDCl_3)$ 2.13 (3 H, s, CH_3), 3.49 (3 H, s, OCH_3), 5.10 (2 H, s, OCH_2OCH_3), 5.90 (2 H, s, OCH_2O), 6.50 (1 H, d *J* 8.6, ArH) and 6.57 (1 H, d, *J* 8.6, ArH.

(d) 2-Methyl-3,4-methylenedioxyphenol 7. Concentrated hydrochloric acid (0.1 cm^3) was added to a stirred solution **6** (9.80 g, 50 mmol) in ethanol (80 cm^3), and the resulting solution was heated under reflux for 3 h. After this the reaction mixture was concentrated *in vacuo*, and the residue was diluted with 5% aqueous sodium hydrogen carbonate solution (200 cm^3) and extracted with ether (3 × 200 cm^3). The combined extracts were washed with water, dried, and concentrated *in vacuo* to give a solid (7.30 g), recrystallization of which from benzene gave the phenol **7** (5.84 g, 77%) as colourless needles, mp 94.5–95.5 °C; ν_{max}(KBr)/cm^{-1} 3230; $\delta_H(CDCl_3)$ 2.13 (3 H, s, CH_3), 4.65 (1 H, s, OH), 5.90 (2 H, s, OCH_2O), 6.22 (1 H, d, *J* 8.3, ArH) and 6.51 (1 H, d, *J* 8.3 ArH).

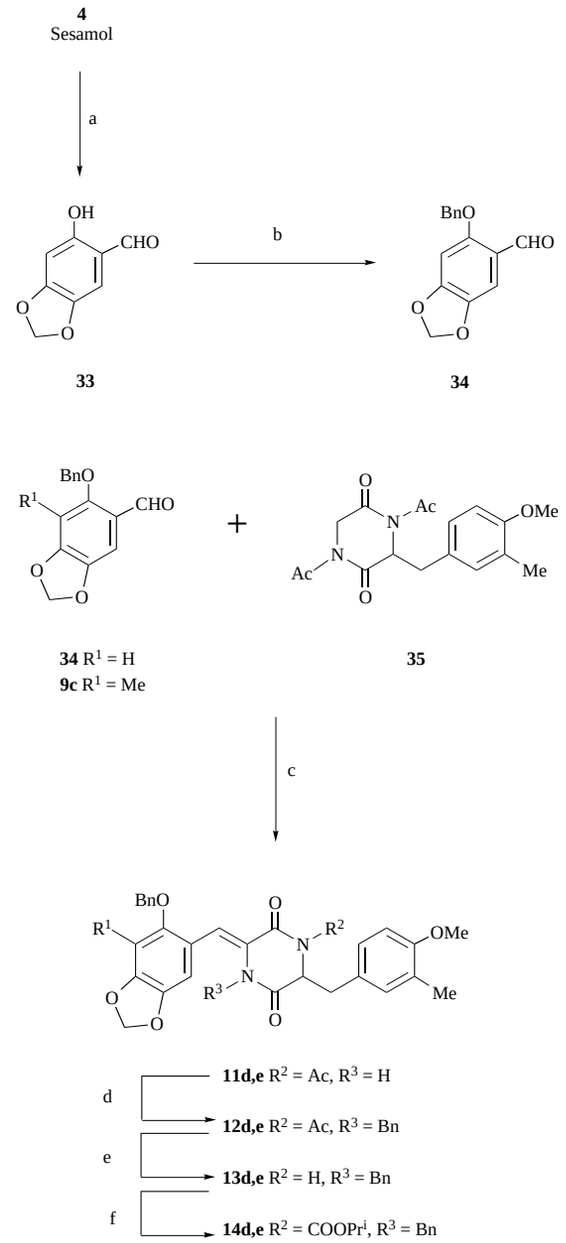
(e) 6-Hydroxy-5-methyl-3,4-methylenedioxybenzaldehyde 8. A solution of **7** (17.2 g, 110 mmol) and hexamethylenetetraamine (154.0 g, 1.1 mol) in acetic acid (650 cm^3) was heated under reflux for 30 min. The reaction mixture was then diluted with water (650 cm^3) and extracted with chloroform (3 × 400 cm^3). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (600 cm^3), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from ethanol gave the title compound **8** (14.5 g, 73%) as colourless needles, mp 93–95 °C; ν_{max}(KBr)/cm^{-1} 3490 and 1630; $\delta_H(CDCl_3)$ 2.13 (3 H, s, CH_3), 6.00 (2 H, s, OCH_2O), 6.72 (1 H, s, 2-H), 9.60 (1 H, s, CHO) and 12.01 (1 H, s, OH); *m/z* 180 (M^+, 100%), 179 (96), 121 (15), 67 (10) and 39 (11) (Found: C, 59.95; H, 4.5. $C_9H_8O_4$ requires C, 60.0; H, 4.48%).

6-Methoxymethoxy-5-methyl-3,4-methylenedioxybenzaldehyde 9a

Sodium hydride (60% oil dispersion, washed with dry hexane



Scheme 10



Scheme 11 *Reagents and conditions*: a, hexamethylenetetraamine, TFA, reflux, 4 h; b, NaH, DMF, 0 °C, 0 °C, 30 min and then BnBr, DMF, 0 °C, 1 h; c, KOBu^t, HOBu^t, DMF, room temp., 24 h; d, NaH, DMF, 0 °C, 30 min and then BnBr, DMF, room temp., 2 h; e, NH_2NH_2–H_2O, DMF, room temp., 1 h; f, ClCOOPr^i, DMAP, NEt_3, CH_2Cl_2, room temp., 3 h

three times; 576 mg, 24 mmol) was added to a stirred solution of the phenol **8** (3.6 g, 20 mmol) in dry DMF (100 cm^3), and the resulting mixture was stirred for 30 min at 0 °C. Chloromethyl methyl ether (1.82 cm^3, 24 mmol) was added to the reaction mixture which was then stirred for 1 h at 0 °C. After this the reaction mixture was diluted with water (100 cm^3) and extracted with ether (3 × 100 cm^3). The combined extracts were washed with water, dried, and concentrated *in vacuo* to give a solid, recrystallization of which from ethyl acetate gave the title compound **9a** (4.19 g, 94%) as colourless needles, mp 93–94 °C; ν_{max}(KBr)/cm^{-1} 1670 and 1615; δ_H($CDCl_3$) 2.20 (3 H, s, CH_3), 3.60 (3 H, s, OCH_3), 5.03 (2 H, s, OCH_2OCH_3), 6.04 (2 H, s, OCH_2O), 7.13 (1 H, s, ArH) and 10.15 (1 H, s, CHO); *m/z* 224 (M^+, 26%), 179 (18), 178 (36) and 45 (100) (Found: C, 59.20; H, 5.44. $C_{11}H_{12}O_5$ requires C, 59.92; H, 5.4%).

6-Methoxy-5-methyl-3,4-methylenedioxybenzaldehyde 9b

This compound was prepared as described above but using iodomethane (1.5 cm^3, 24 mmol) to give a solid, recrystallization of which from ethyl acetate gave the title compound **9b** (3.09 g, 80%) as colourless needles, mp 82–83 °C; ν_{max}(KBr)/cm^{-1} 1670 and 1620; δ_H($CDCl_3$) 2.19 (3 H, s, CH_3), 3.85 (3 H, s, OCH_3), 6.03 (2 H, s, OCH_2OCH_3), 7.11 (1 H, s, ArH) and 10.19 (1 H, s, CHO); *m/z* 194 (M^+, 100%), 179 (31), 178 (12), 177 (26), 176 (24), 151 (15), 149 (10), 148 (48), 147 (33), 134 (14), 121 (48), 107 (14), 96 (13), 67 (17), 65 (21), 53 (12) and 39 (15) (Found: C, 61.63; H, 5.17. $C_{10}H_{10}O_4$ requires C, 61.85; H, 5.19%).

6-Benzyloxy-5-methyl-3,4-methylenedioxybenzaldehyde 9c

This compound was prepared as described above but using benzyl bromide (2.66 cm^3, 24 mmol) to give a solid, recrystallization of which from ethyl acetate gave the title compound **9c** (4.94 g, 92%) as colourless needles, mp 76–77 °C; ν_{max}(KBr)/cm^{-1} 1680; δ_H($CDCl_3$) 2.20 (3 H, s, CH_3), 4.92 (2 H, s, $ArOCH_2$), 5.99 (2 H, s, OCH_2OCH_3), 7.11 (1 H, s, ArH), 7.39 (5 H, s, 5 × ArH) and 10.07 (1 H, s, CHO); *m/z* 270 (M^+, 17%), 178 (20), 91 (100) and 65 (12) (Found: C, 70.94; H, 5.23. $C_{16}H_{14}O_4$ requires C, 71.10; H, 5.22%).

(*Z*)-1-Acetyl-6-(2,4,5-trimethoxy-3-methylbenzyl)-3-(2-methoxymethoxy-3-methyl-4,5-methylenedioxybenzylidene)-piperazine-2,5-dione 11a

A solution of potassium *tert*-butoxide (1.125 g, 10 mmol) in *tert*-butyl alcohol (20 cm^3) was added to a stirred solution of the aldehyde **9a** (2.24 g, 10 mmol) and the acetate **10** (3.92 g, 10 mmol) in dry DMF (20 cm^3) at 0 °C over 30 min. After being stirred for 24 h at room temperature, the reaction mixture was poured into water (50 cm^3), and extracted with benzene (3 × 50 cm^3). The combined extracts were washed with saturated aqueous sodium chloride (50 cm^3), dried and concentrated *in vacuo* to give a solid, recrystallization of which from ethyl acetate–ether gave the title compound **11a** (4.68 g, 84%) as pale yellow prisms, mp 149–150.5 °C; ν_{max}(KBr)/cm^{-1} 3240, 1700 and 1640; δ_H($CDCl_3$) 2.05 and 2.27 (each 3 H, s, CH_3), 2.61 (3 H, s, $COCH_3$), 3.09 (1 H, dd, *J* 13.9 and 3, 6-CHAr), 3.34 (1 H, dd, *J* 13.9 and 5.9, 6-CHAr), 3.49, 3.56, 3.57 and 3.65 (each 3 H, s, OCH_3), 4.71 (1 H, d, *J* 5.9, OC*H*OCH_3), 4.75 (1 H, d, *J* 5.9, OC*H*OCH_3), 5.37 (1 H, dd, *J* 5.9 and 3, 6-H), 6.00 (2 H, s, OCH_2O), 6.31, 6.43 and 6.51 (each 1 H, s) and 8.15 (1 H, s, NH); *m/z* 556 (M^+, 21%), 524 (14), 482 (11), 465 (14), 236 (13), 219 (10), 196 (14), 195 (100), 165 (15) and 45 (10) (Found: C, 60.42; H, 5.89; N, 4.99. $C_{28}H_{32}N_2O_{10}$ requires C, 60.42; H, 5.8; N, 5.03%).

(*Z*)-1-Acetyl-6-(2,4,5-trimethoxy-3-methylbenzyl)-3-(2-methoxy-3-methyl-4,5-methylenedioxybenzylidene)piperazine-2,5-dione 11b

This compound was prepared as described above but using the aldehyde **9b** (1.94 g, 10 mmol) to give a solid, recrystallization of which from ethyl acetate–ether gave the title compound **11b** (3.87 g, 74%) as pale yellow prisms, mp 130–131.5 °C; ν_{max}(KBr)/cm^{-1} 3180, 1690 and 1620; δ_H($CDCl_3$) 2.05 and 2.16 (each 3 H, s, CH_3), 2.61 (3 H, s, $COCH_3$), 3.06 (1 H, dd, *J* 13.5 and 3.3, 6-CHAr), 3.34 (1 H, dd, *J* 13.5 and 5.9, 6-CHAr), 3.53, 3.55, 3.69 and 3.71 (each 3 H, s, OCH_3), 5.37 (1 H, dd, *J* 5.9 and 3.3, 6-H), 6.04 (2 H, s, OCH_2O), 6.30, 6.43 and 6.44 (each 1 H, s) and 8.63 (1 H, s, NH); *m/z* 526 (M^+, 37%), 196 (13), 195 (100) and 165 (11) (Found: C, 64.54; H, 5.77; N, 5.21. $C_{27}H_{30}N_2O_9$ requires C, 61.59; H, 5.74; N, 5.32%).

(*Z*)-1-Acetyl-6-(2,4,5-trimethoxy-3-methylbenzyl)-3-(2-benzyloxy-3-methyl-4,5-methylenedioxybenzylidene)piperazine-2,5-dione 11c

This compound was prepared as described above but using the aldehyde **9c** (2.7 g, 10 mmol) to give a solid, recrystallization of which from ethyl acetate–ether gave the title compound **11c** (4.82 g, 80%) as pale yellow prisms, mp 191–192 °C; ν_{max}(KBr)/cm^{-1} 3490, 1700 and 1620; δ_H($CDCl_3$) 2.04 and 2.07 (each 3 H, s, CH_3), 2.60 (3 H, s, $COCH_3$), 3.04 (1 H, dd, *J* 13.9 and 3, 6-CHAr), 3.12 (1 H, dd, *J* 13.9 and 5.9, 6-CHAr), 3.52, 3.53 and 3.66 (each 3 H, s, OCH_3), 4.62 (2 H, s, OCH_2), 5.32 (1 H, dd, *J* 5.9 and 3, 6-H), 6.00 (2 H, s, OCH_2O), 6.28, 6.42 and 6.45 (each 1 H, s), 7.22–7.33 (5 H, m, 5 × ArH) and 8.63 (1 H, s, NH); *m/z* 602 (M^+, 28%), 511 (23), 469 (56), 250 (17), 235 (10), 224 (10), 219 (13), 218 (14), 196 (13), 195 (100), 192 (12), 165 (18), 150 (11) and 91 (18) (Found: C, 65.96; H, 5.83; N, 4.58. $C_{27}H_{30}N_2O_9$ requires C, 65.77; H, 5.69; N, 4.65%).

(*Z*)-4-Benzyl-6-(2,4,5-trimethoxy-3-methylbenzyl)-3-(2-methoxymethyloxy-3-methyl-4,5-methylenedioxybenzylidene)-piperazine-2,5-dione 13a

Sodium hydride (60% oil dispersion, washed with dry hexane three times; 288 mg, 12 mmol) was added to a stirred solution of the acetate **11a** (5.56 g, 10 mmol) in dry DMF (90 cm^3), and stirring was continued for 30 min at 0 °C. Benzyl bromide (1.43 cm^3, 12 mmol) in dry DMF (10 cm^3) was then added during 30 min after which the reaction mixture was stirred for a further 2 h at room temperature. After the reaction mixture had been concentrated *in vacuo*, the residue was diluted with water (50 cm^3) and extracted with benzene (3 × 50 cm^3). The combined extracts were washed with saturated aqueous sodium chloride (50 cm^3), dried, and concentrated *in vacuo* to give the *N*-benzyl compound **12a** as pale yellow oil, which was used for the next step without further purification. An analytical sample was obtained by crystallization from benzene to give pure **12a** as pale yellow needles, mp 186–187 °C; ν_{max}(KBr)/cm^{-1} 1710, 1690 and 1620; δ_H($CDCl_3$) 2.07 and 2.17 (each 3 H, s, CH_3), 2.53 (3 H, s, $COCH_3$), 3.15 (1. H, dd, *J* 13.5 and 5.6, 6-CHAr), 3.20 (1 H, dd, *J* 13.5 and 7, 6-CHAr), 3.50, 3.51, 3.59 and 3.79 (each 3 H, s, OCH_3), 4.21 (1 H, d, *J* 15.2, NCHAr), 4.59 (1 H, d, *J* 6, OC*H*OCH_3), 4.59 (1 H, d, *J* 6, OC*H*OCH_3), 5.31 (1 H, d, *J* 15.2, NCHAr), 5.48 (1 H, dd, *J* 7 and 5.6, 6-H), 6.04 (2 H, s, OCH_2O), 6.47 and 6.67 (each 1 H, s), 6.91–6.95 (2 H, m), 7.12–7.19 (3 H, m) and 7.36 (1 H, s); *m/z* 646 (M^+, 45%), 615 (16), 614 (35), 586 (14), 585 (31), 559 (18), 555 (21), 543 (23), 309 (16), 305 (12), 277 (11), 235 (11), 196 (14), 195 (100), 165 (15) and 91 (29) (Found: C, 65.38; H, 5.88; N, 4.2. $C_{35}H_{38}N_2O_{10}$ requires C, 65.0; H, 5.92; N, 4.33%). Hydrazine monohydrate (10 cm^3) was added to a stirred solution of the crude acetate **12a** in dry DMF (90 cm^3), and the resulting solution was stirred for 1 h at room temperature. After the reaction mixture had been concentrated *in vacuo*, the residue was diluted with 5% aqueous sodium hydrogen carbonate (100 cm^3) and extracted with benzene (3 × 100 cm^3). The combined extracts were washed with water (100 cm^3), dried and concentrated *in vacuo* to give a solid (6.32 g), recrystallization of which from ethyl acetate gave the title compound **13a** (5.04 g, 83%) as colourless prisms, mp 180–181 °C; ν_{max}(KBr)/cm^{-1} 3300, 1725, 1695 and 1630; δ_H($CDCl_3$) 2.18 and 2.21 (each 3 H, s, CH_3), 3.03 (1 H, dd, *J* 13.9 and 8.6, 6-CHAr), 3.34 (1 H, dd, *J* 13.9 and 4, 6-CHAr), 3.49, 3.70, 3.73 and 3.76 (each 3 H, s, OCH_3), 4.34 (1 H, dd, *J* 8.6 and 4, 6-H), 4.63 (1 H, d, *J* 14.8, NCHAr), 4.68 (2 H, s, OC$H_2$$OCH_3$), 4.93 (1 H, d, *J* 14.8, NCHAr), 6.01 (2 H, s, OCH_2O), 6.32 (1 H, s, NH), 6.58 and 6.61 (each 1 H, s), 6.93–7.00 (2 H, m), 7.16–7.23 (3 H, m) and 7.26 (1 H, s); *m/z* 604 (M^+, 12%), 559 (13), 544 (36), 543 (100), 377 (12), 196 (13), 195 (65), 190 (11), 165 (12) and 91 (36) (Found: C, 65.57; H, 6.04; N, 4.58. $C_{33}H_{36}N_2O_9$ requires C, 65.55; H, 6.0; N, 4.63%).

(*Z*)-4-Benzyl-6-(2,4,5-trimethoxy-3-methylbenzyl)-3-(2-methoxy-3-methyl-4,5-methylenedioxybenzylidene)-piperazine-2,5-dione 13b

This compound was prepared by the two-step reaction as described above from the acetate **11b** (5.26 g, 10 mmol). Recrystallization of the crude reaction mixture from ethyl acetate gave the title compound (5.31 g, 93%) as colourless prisms.

Compound **12b**: mp 169.5–171 °C (ethyl acetate–ether); ν_{max}(KBr)/cm^{-1} 1710, 1700, 1690 and 1620; δ_H($CDCl_3$) 2.06 and 2.15 (each 3 H, s, CH_3), 2.55 (3 H, s, $COCH_3$), 3.16 (1 H, dd, *J* 13.8 and 5.4, 6-CHAr), 3.23 (1 H, dd, *J* 13.8 and 8.1, 6-CHAr), 3.43, 3.50, 3.59 and 3.79 (each 3 H, s, OCH_3), 4.20 (1 H, d, *J* 14.8, NCHAr), 5.36 (1 H, d, *J* 14.8, NCHAr), 5.50 (1 H, dd, *J* 7 and 5.6, 6-H), 6.03 and 6.05 (each 1 H, s, OCHO), 6.47 and 6.64 (each 1 H, s), 6.84–6.91 (2 H, m), 7.12 (1 H, s) and 7.12–7.19 (3 H, m); *m/z* 616 (M^+, 62%), 586 (14), 585 (35), 543 (26), 196 (13), 195 (100) and 165 (11) (Found: C, 66.11; H, 5.96; N, 4.5. $C_{34}H_{36}N_2O_9$ requires C, 66.22; H, 5.88; N, 4.54%).

Compound **13b**: mp 149.5–151 °C; ν_{max}(KBr)/cm^{-1} 3200, 1690 and 1630: δ_H($CDCl_3$) 2.16 and 2.20 (each 3 H, s, CH_3), 3.03 (1 H, dd, *J* 13.9 and 8.9, 6-CHAr), 3.34 (1 H, dd, *J* 13.9 and 3.6, 6-CHAr), 3.47, 3.70, 3.74 and 3.77 (each 3 H, s, OCH_3), 4.33 (1 H, dd, *J* 8.9 and 3.6, 6-H), 4.63 (1 H, d, *J* 15.2, NCHAr), 4.92 (1 H, d, *J* 15.2, NCHAr), 6.01 (2 H, s, OCH_2O), 6.30 (1 H, s, NH), 6.58 and 6.59 (each 1 H, s), 6.92–6.96 (2 H, m) and 7.15–7.19 (4 H, m); *m/z* 574 (M^+, 12%), 544 (36), 543 (100), 195 (49), 165 (11) and 91 (17) (Found: C, 66.91;

H, 6.02; N, 4.8. $C_{32}H_{34}N_2O_8$ requires C, 66.88; H, 5.96; N, 4.88%).

(*Z*)-4-Benzyl-6-(2,4,5-trimethoxy-3-methylbenzyl)-3-(2-benzyloxy-3-methyl-4,5-methylenedioxybenzylidene)-piperazine-2,5-dione 13c

This compound was prepared by the two-step reaction as described above from the acetate **11c** (6.0 g, 10 mmol). Recrystallization of the crude reaction mixture from ethyl acetate gave the title compound (4.0 g, 61%) as colourless prisms.

Compound **12c:** mp 145–146 °C (ethyl acetate–ether), ν_{max}(KBr)/cm^{-1} 1705, 1695, 1630 and 1610; δ_H($CDCl_3$) 2.07 and 2.11 (each 3 H, s, CH_3), 2.58 (3 H, s, $COCH_3$), 3.16 (1 H, dd, *J* 13.9 and 5.9, 6-CHAr), 3.24 (1 H, dd, *J* 13.9 and 6.3, 6-CHAr), 3.49, 3.59 and 3.79 (each 3 H, s, OCH_3), 4.26 (1 H, d, *J* 10.6, ArOCH), 4.27 (1 H, d, *J* 15.2, NCHAr), 4.37 (1 H, d, *J* 10.6, ArOCH), 5.42 (1 H, d, *J* 15.2, NCHAr), 5.52 (1 H, dd, *J* 6.3 and 5.9, 6-H), 6.04 and 6.06 (each 1 H, s, OCHO), 6.47 and 6.64 (each 1 H, s), 6.82–6.91 (2 H, m), 7.10–7.20 (3 H, m), 7.22 (1 H, s) and 7.28–7.36 (5 H, m); *m*/*z* 692 (M^+, 30%), 602 (15), 601 (33), 560 (35), 559 (100), 308 (12), 265 (11), 195 (66), 165 (11) and 91 (33) (Found: C, 69.23; H, 5.97; N, 3.96. $C_{40}H_{40}N_2O_9$ requires C, 69.35; H, 5.82; N, 4.04%).

Compound **13c:** mp 168–169 °C; ν_{max}(KBr)/cm^{-1} 3250, 1690, 1675 and 1640; δ_H($CDCl_3$) 2.15 and 2.20 (each 3 H, s, CH_3), 2.99 (1 H, dd, *J* 13.9 and 8.6, 6-CHAr), 3.24 (1 H, dd, *J* 13.9 and 4, 6-CHAr), 3.68, 3.73 and 3.76 (each 3 H, s, OCH_3), 4.08 (1 H, dd, *J* 8.6 and 4, 6-H), 4.38 and 4.45 (each 1 H, d, *J* 10.9, ArOCH), 4.62 (1 H, d, *J* 15.2, NCHAr), 5.04 (1 H, d, *J* 15.2, NCHAr), 6.02 (2 H, s, OCH_2O), 6.38 (1 H, s, NH), 6.52 and 6.60 (each 1 H, s), 6.90–6.94 (2 H, m), 7.14–7.17 (3 H, m), 7.20 (1 H, s), 7.27–7.34 (5 H, m); *m*/*z* 650 (M^+, 20%), 560 (36), 559 (97), 544 (14), 543 (39), 347 (16), 282 (18), 265 (26), 250 (14), 219 (12), 195 (100), 165 (19) and 91 (68) (Found: C, 69.85; H, 5.9; N, 4.16. $C_{38}H_{38}N_2O_8$ requires C, 70.14; H, 5.89; N, 4.31%).

X-Ray structure determination of compound 13a

Crystals of compound **13a** ($C_{33}H_{36}N_2O_9$) belong to the triclinic space group *P*1 (#2) with cell constants $a = 11.037(6)$ Å, $b = 18.169(9)$ Å, $c = 8.370(2)$ Å, $\alpha = 92.95(3)°$, $\beta = 119.92(3)°$, $\gamma = 72.25(4)°$, $Z = 2$, $D_c = 1.46$ g cm^{-3}. All measurements were made on a Rigaku RAXIS II imagine plate area detector with graphite monochromated Mo-Kα radiation. The data were collected at a temperature of 23 ± 1 °C to a maximum 2θ value 46.3°. A total of 2862 reflections was collected. The linear absorption coefficient, μ, for Mo-Kα radiation was 1.07 cm^{-1}. The structure was solved by direct methods[15] and expanded using Fourier techniques.[16] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included, but their positions were not refined; isotropic *B* values were refined. The final cycle of full-matrix least-squares refinement was based on 1960 observed reflections [$I > 4.00\sigma(I)$] and 434 variable parameters and converged (largest parameter shift was 0.33 times its esd) with unweighted and weighted agreement factors of $R = 0.066$ and $R_w = 0.079$. Neutral atom scattering factors were taken from Cromer and Waber.[17] Anomalous dispersion effects were included in F_c[18]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[19] The values for the mass attenuation coefficients are those of Creagh and Hubble.[20] All calculations were performed using the teXsan[21] crystallographic software package of Molecular Structure Corporation. The drawing of the molecule was made by ORTEP. The atomic coordinates, bond lengths and bond angles together with the Hermol parameters for this work have been deposited with the Cambridge Crystallographic Data Centre. Any request for this material should be accompanied by a full bibliographic citation together with the reference number 207/57 [see Instructions for Authors (1997), *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1].

(*Z*)-4-Benzyl-1-isopropyloxycarbonyl-6-(2,4,5-trimethoxy-3-methylbenzyl)-3-(2-methoxymethoxy-3-methyl-4,5-methylenedioxybenzylidene)piperazine-2,5-dione 14a

A solution of **13a** (4.22 g, 7 mmol), triethylamine (1.96 cm^3, 14 mmol), and 4-(dimethylamino)pyridine (1.71 g, 14 mmol) in dry dichloromethane (70 cm^3) was cooled with ice–water, and isopropyl chloroformate (3.22 cm^3, 28 mmol) was added dropwise to it over 10 min. The solution was then stirred at room temperature for 3 h. The organic layer was washed with 1 M aqueous hydrochloric acid (50 cm^3), and then water (50 cm^3), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from ethyl acetate–ether gave the title compound **14a** (4.71 g, 98%) as colourless prisms, mp 104–105 °C; ν_{max}(KBr)/cm^{-1} 1790, 1735, 1710 and 1625; δ_H($CDCl_3$) 1.22 and 1.29 (each 3 H, d, *J* 6.3, CHC*H*$_3$), 2.12 and 2.17 (each 3 H, s, CH_3), 3.17 (1 H, dd, *J* 13.5 and 6.6, 6-CHAr), 3.25 (1 H, dd, *J* 13.5 and 6.6, 6-CHAr), 3.53, 3.60, 3.64 and 3.80 (each 3 H, s, OCH_3), 4.24 (1 H, d, *J* 14.9, NCHAr), 4.63 and 4.72 (each 1 H, s, OC*H*$_2$OCH$_3$), 5.01 (1 H, sept, *J* 6.3, OC*H*CH$_3$), 5.10 (1 H, t, *J* 6.6, 6-H), 5.26 (1 H, d, *J* 14.9, NCHAr), 6.03 (2 H, s, OCH_2O), 6.47 and 6.69 (each 1 H, s), 6.96–7.00 (2 H, m), 7.17–7.21 (3 H, m) and 7.27 (1 H, s); δ_C($CDCl_3$) 9.7 (q), 9.8 (q), 21.5 (q), 21.6 (q), 32.9 (t), 48.1 (t), 55.9 (q), 57.9 (d), 59.8 (q), 60.3 (q), 60.7 (q), 71.7 (d), 100.4 (t), 101.7 (t), 105.3 (d), 111.5 (d), 114.1 (s), 119.1 (s), 121.3 (s), 122.7 (d), 125.7 (s), 127.6 (d), 127.7 (d), 127.8 (s), 128.5 (d), 136.2 (s), 143.4 (s), 147.4 (s), 148.3 (s), 149.2 (s), 151.2 (s), 151.7 (s), 162.0 (s) and 16.9 (s); *m*/*z* 690 (M^+, 11%), 630 (20), 629 (48), 559 (10), 544 (12), 543 (33), 377 (11), 196 (17), 195 (100), 190 (10), 165 (19), 150 (10), 91 (46), 45 (13) and 43 (11) (Found: C, 64.29; H, 6.18; N, 3.97. $C_{37}H_{42}N_2O_{11}$ requires C, 64.34; H, 6.13; N, 4.06%).

(*Z*)-4-Benzyl-1-isopropyloxycarbonyl-6-(2,4,5-trimethoxy-3-methylbenzyl)-3-(2-methoxy-3-methyl-4,5-methylenedioxy-benzylidene)piperazine-2,5-dione 14b

A solution of **13b** (5.45 g, 9.5 mmol), triethylamine (2.66 cm^3, 19 mmol), and 4-(dimethylamino)pyridine (2.32 g, 19 mmol) in dry dichloromethane (100 cm^3) was cooled with ice–water, and isopropyl chloroformate (4.33 cm^3, 38 mmol) was added to it dropwise over 10 min. The solution was then stirred at room temperature for 4 h. The organic layer was then separated, washed with 1 M aqueous hydrochloric acid (50 cm^3) and then water (50 cm^3), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from ethyl acetate–ether gave the title compound **14b** (5.76 g, 92%) as colourless prisms, mp 147.5–148 °C; ν_{max}(KBr)/cm^{-1} 1780, 1720, 1695 and 1625; δ_H($CDCl_3$ 1.25 and 1.31 (each 3 H, d, *J* 6.3, CHC*H*$_3$), 2.11 and 2.15 (each 3 H, s, CH_3), 3.20 (1 H, dd, *J* 13.5 and 6.6, 6-CHAr), 3.26 (1 H, dd, *J* 13.5 and 6.6, 6-CHAr), 3.44, 3.60, 3.65 and 3.85 (each 3 H, s, OCH_3), 4.23 (1 H, d, *J* 14.9, NCHAr), 5.03 (1 H, sept, *J* 6.3, OC*H*CH$_3$), 5.21 (1 H, t, *J* 6.6, 6-H), 5.31 (1 H, d, *J* 14.9, NCHAr), 6.02 and 6.04 (each 1 H, d, *J* 1.3, OCHO), 6.49 and 6.67 (each 1 H, s), 6.90–6.94 (2 H, m), 7.15–7.18 (3 H, m) and 7.26 (1 H, s); *m*/*z* 660 (M^+, 41%), 630 (36), 629 (89), 544 (18), 543 (52), 196 (13), 195 (100), 165 (18) and 91 (21) (Found: C, 65.47; H, 6.11; N, 4.16. $C_{36}H_{40}N_2O_{10}$ requires C, 65.44; H, 6.10; N, 4.24%).

(*Z*)-4-Benzyl-1-isopropyloxycarbonyl-6-(2,4,5-trimethoxy-3-methylbenzyl)-3-(2-benzyloxy-3-methyl-4,5-methylenedioxybenzylidene)piperazine-2,5-dione 14c

A solution of the compound **13c** (1.3 g, 2 mmol), triethylamine (0.56 cm^3, 4 mmol), and 4-(dimethylamino)pyridine (488 mg, 4 mmol) in dry dichloromethane (12 cm^3) was cooled with ice–water, and isopropyl chloroformate (0.92 cm^3, 8 mmol) was added dropwise to it over 10 min. The solution was then stirred at room temperature for 4 h. The organic layer was separated, washed with 1 M aqueous hydrochloric acid (20 cm^3) and then water (20 cm^3), dried and concentrated *in vacuo* to give a solid, recrystallization of which from ethyl acetate–ether gave the title

compound **14c** (1.37 g, 93%) as colourless prisms, mp 127–128.5 °C; ν_{max}(KBr)/cm^{-1} 1780, 1725, 1685 and 1620; δ_H($CDCl_3$) 1.22 and 1.30 (each 3 H, d, *J* 6.3, $CHCH_3$), 2.12 and 2.13 (each 3 H, s, CH_3), 3.17 (1 H, dd, *J* 13.9 and 6.9, 6-CHAr), 3.22 (1 H, dd, *J* 13.9 and 6.9, 6-CHAr), 3.60, 3.63 and 3.79 (each 3 H, s, OCH_3), 4.25 (1 H, d, *J* 15.5, NCHAr), 4.29 and 4.37 (each 1 H, d, *J* 10.6, ArOCH), 5.04 (1 H, sept, *J* 6.3, O*C*HCH_3), 5.22 (1 H, t, *J* 6.9, 6-H), 4.37 (1 H, d, *J* 15.5, NCHAr), 6.02 and 6.05 (each 1 H, d, *J* 1.3, OCHO), 6.48 and 6.69 (each 1 H, s), 6.93–6.95 (2 H, m), 7.12–7.18 (3 H, m), 7.29–7.36 (5 H, m) and 7.36 (1 H, s); *m/z* 736 (M^+, 16%), 645 (19), 629 (15), 560 (30), 559 (82), 543 (11), 527 (20), 308 (14), 282 (12), 265 (14), 250 (11), 195 (100), 165 (20), 91 (69), 44 (14) and 43 (11) (Found: C, 68.46; H, 6.02; N, 3.8. $C_{42}H_{44}N_2O_{10}$ requires C, 68.46; H, 6.10; N, 3.74%).

Attempted conversion of compound 14a to compound 16a

Method A. A stirred solution of **14a** (103.5 mg, 0.15 mmol) in dry THF (5 cm) was cooled in ice–water, and lithium tri-*tert*-butoxyaluminium hydride (152.6 mg, 0.6 mmol) was added to it over 5 min. After continued stirring at the same temperature for 1 h, the reaction mixture was quenched by the addition of water (1 cm^3) and then filtered through a Celite pad. The filtrate was concentrated *in vacuo* to give a crude diastereoisomeric mixture of the allylic alcohols **15a** (120.4 mg) which was used for the next step without further purification. A solution of the above mixture in formic acid (2 cm^3) was heated for 1 h at 60 °C and then was diluted with water (10 cm^3) and extracted with chloroform (3 × 20 cm^3). The combined extracts were washed with 5% aqueous sodium hydrogen carbonate (20 cm^3), dried, and concentrated *in vacuo* to give a residue (121 mg). Chromatography of this on a silica gel (15 g) column with hexane–ethyl acetate (2:1) as the eluent gave compound **18** (35.4 mg, 38%) as a solid, recrystallization of which from ethyl acetate gave the pure compound as pale yellow prisms.

Method B. Reduction of **14a** (690 mg, 1 mmol) with lithium tri-*tert*-butoxyaluminium hydride (1.02 g, 4 mmol) as described above afforded the allylic alcohol **15a** (810 mg). A solution of this residue in propan-2-ol (15 cm^3) was cooled in ice–water, and a propan-2-ol (20 cm^3) solution of hydrochloric acid (0.005 cm^3) was added dropwise to it over 5 min. This mixture was then heated under reflux for 1 h after which it was concentrated *in vacuo*. The residue was diluted with 5% aqueous sodium hydrogen carbonate (30 cm^3) and extracted with ether (3 × 30 cm^3). The combined extracts were washed with water (30 cm^3), dried and concentrated *in vacuo* to give a solid, recrystallization of which from ethyl acetate gave compound **18** (491 mg, 73%) as pale yellow prisms, mp 172–173 °C; ν_{max}(KBr)/cm^{-1} 3120, 1690, 1660 and 1635; δ_H($CDCl_3$: this compound was a mixture of two rotational isomers, ratio, 2:1) 0.78 (3 H, d, *J* 5.9, CHC*H*$_3$), 1.12 (2/3 × 3 H, d, *J* 5.9, CHC*H*$_3$), 1.20 (1/3 × 3 H, d, *J* 5.9, CHC*H*$_3$), 2.19 and 2.25 (each 3 H, s, CH_3), 3.10 (1 H, br t, 6-CHAr), 3.39 (1 H, br d, 6-CHAr), 3.78, 3.81 and 3.81 (each 3 H, s, OCH_3), 4.71 (1 H, sept, *J* 5.9, O*C*HCH_3), 4.85 (1 H, d, *J* 15.8, NCHAr), 5.03 (1/3 × 1 H, br t, CH), 5.16 (1 H, d, *J* 15.8, NCHAr), 5.33 (2/3 × 1 H, br t, CH), 5.87 (2 H, s, OCH_2O), 5.95 (1 H, d, *J* 2.3, C=CH), 6.11 (1/3 × 1 H, br s, OCHN), 6.27 (2/3 × 1 H, br s, OCHN), 6.35 (1 H, s), 6.80 (1/3 × 1 H, s), 6.87 (2/3 × 1 H, s) and 7.23–7.36 (5 H, m); δ_C($CDCl_3$) 8.8 (q), 9.7 (q), 21.1 (q), 21.9 (q), 33.1 (t), 46.8 (t), 56.4 (q), 58.3 (d), 60.2 (q), 60.8 (q), 70.1 (d), 79.8 (d), 101.1 (t), 103.4 (d), 108.7 (d), 112.7 (d), 115.7 (s), 125.3 (s), 126.5 (d), 127.5 (2 × d), 128.9 (2 × d), 136.0 (s), 142.1 (s), 146.0 (s), 147.2 (s), 148.8 (s), 151.3 (s), 153.9 (s) and 167.7 (s); *m/z* 630 (M^+, 84%), 544 (37), 543 (100), 349 (43), 195 (47), 190 (10), 165 (13) and 91 (34) (Found: C, 66.6; H, 6.02; N, 4.43. $C_{35}H_{38}N_2O_9$ requires C, 66.65; H, 6.07; N, 4.44%).

X-Ray structure determination of compound 18

Crystals of **18** ($C_{35}H_{38}N_2O_9$) belong to the monoclinic space group $P2_1/a$ (#14) with cell constants a = 8.798(4) Å, b = 24.625(3) Å, c = 14.765(2) Å, β = 104.42(2)°, Z = 4, D_c = 1.352 g cm^{-3}. All measurements were made on a Rigaku RAXIS II imagine plate area detector with graphite monochromated Mo-Kα radiation. The data were collected at a temperature of 23 ± 1 °C to a maximum 2θ value 44.1°. A total of 3438 reflections was collected. The linear absorption coefficient, μ, for Mo-Kα radiation was 0.98 cm^{-1}. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods[15] and expanded using Fourier techniques.[16] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included, but their positions were not refined; isotropic *B* values were refined. The final cycle of full-matrix least-squares refinement was based on 2915 observed reflections [$I > 3.00\sigma(I)$] and 454 variable parameters and converged (largest parameter shift was 0.29 times its esd) with unweighted and weighted agreement factors of R = 0.064 and R_w = 0.079. Neutral atom scattering factors were taken from Cromer and Waber.[17] Anomalous dispersion effects were included in F_c;[18] the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[19] The values for the mass attenuation coefficients are those of Creagh and Hubble.[20] All calculations were performed using the teXsan[21] crystallographic software package of Molecular Structure Corporation. The drawing of the molecule was made by ORTEP. The detailed crystallographic results for this work have been deposited with the Cambridge Crystallographic Data Centre: see comments under the structural determination for compound **13a**.

Reaction of compound 14a with hydrochloric acid in propan-2-ol

A solution of **14a** (138 mg, 0.2 mmol) in propan-2-ol (4 cm^3) was cooled in ice–water and a propan-2-ol (4 cm^3) solution of hydrochloric acid (0.001 cm^3) was added dropwise to it over 5 min. This mixture was heated under reflux for 2 h after which it was concentrated *in vacuo*. The residue was diluted with 5% aqueous sodium hydrogen carbonate (10 cm^3) and extracted with ether (3 × 10 cm^3). The combined extracts were washed with water (10 cm^3), dried and concentrated *in vacuo* to give a solid (140 mg), recrystallization of which from ethyl acetate gave the compound **20** (117 mg, 91%) as pale yellow prisms, mp 163–164 °C; ν_{max}(KBr)/cm^{-1} 3260, 1735, 1710 and 1635; δ_H($CDCl_3$): this compound was a mixture of two rotational isomers, ratio, 2:1 (major isomer) 1.11 and 1.23 (each 3/4 × 3 H, d, *J* 6.3, CHC*H*$_3$), 2.12 and 2.32 (each 3/4 × 3 H, s, CH_3), 2.80 (3/4 × 1 H, dd, *J* 13.9 and 9.9, 6-CHAr), 2.99 (3/4 × 1 H, dd, *J* 13.9 and 3.6, 6-CHAr), 3.59, 3.70 and 3.74 (each 3/4 × 3 H, s, OCH_3), 4.23 (3/4 × 1 H, d, *J* 14.9, NCHAr), 4.51 (3/4 × 1 H, m, CH), 4.76 (3/4 × 1 H, sept, *J* 6.3, O*C*HCH_3), 5.64 (3/4 × 1 H, d, *J* 14.9, NCHAr), 5.71 (3/4 × 1 H, d, *J* 6.9, NH), 6.04 (3/4 × 2 H, s, OCH_2O), 6.45 and 6.61 (each 3/4 × 1 H, s), 7.18 (3/4 × 2 H, m), 7.21–7.24 (3/4 × 3 H, m) and 7.51 (3/4 × 1 H, s); (minor isomer) 1.17 and 1.23 (each 1/4 × 3 H, d, *J* 6.3, CHC*H*$_3$), 2.18 and 2.27 (each 1/4 × 3 H, s, CH_3), 2.99 (1/4 × 2 H), 3.57, 3.80 and 3.80 (each 1/4 × 3 H, s, OCH_3), 4.08 (1/4 × 1 H, d, *J* 13.9, NCHAr), 4.76 (1/4 × 1 H, m, CH), 4.76 (1/4 × 1 H, sept, *J* 6.3, O*C*HCH_3), 5.46 (1/4 × 1 H, d, *J* 13.9, NCHAr), 5.46 (1/4 × 1 H, d, *J* 6.9, NH), 6.00 (1/4 × 1 H, s), 6.02 (1/4 × 2 H, s, OCH_2O), 6.29 and 6.57 (each 1/4 × 1 H, s), 6.00 (1/4 × 2 H, m) and 7.21–7.24 (1/4 × 3 H, m); δ_C($CDCl_3$) (major isomer) 8.4 (q), 9.7 (q), 22.0 (q), 32.9 (t), 50.2 (t), 53.3 (d), 55.6 (q), 60.1 (q), 60.6 (q), 68.2 (d), 102.2 (t), 103.6 (d), 108.0 (s), 111.2 (d), 123.2 (s), 124.6 (s), 125.3 (s), 127.4 (d), 128.4 (d), 128.7 (s), 136.5 (s), 144.1 (s), 144.3 (d), 146.9 (s), 149.0 (s), 150.4 (s), 150.8 (s), 156.1 (s), 159.1 (s) and 172.8 (s); (minor isomer) 8.4 (q), 9.8 (q), 22.0 (q), 22.0 (q), 35.3 (t), 50.4 (t), 52.0 (d), 55.8 (q), 60.3 (q), 60.5 (q), 68.3 (d), 102.1 (t), 103.0 (d), 108.4 (s), 112.1 (d), 123.2 (s), 124.7 (s), 125.3 (s), 127.5 (d), 128.4 (d), 128.7 (s), 136.3 (s), 142.9 (d), 144.1 (s), 146.9 (s), 149.3 (s), 150.2 (s), 151.1 (s), 155.1 (s), 159.1 (s) and 172.2 (s); *m/z* 646 (M^+, 38%), 543 (45), 512 (54), 397 (41), 309 (100), 235 (77), 195 (94) and 91 (60) (Found: C, 64.68;

H, 5.91; N, 4.18. $C_{35}H_{38}N_2O_{10}$ requires C, 65.0; H, 5.92; N, 4.18%).

1-Benzyl-3-(2,4,5-trimethoxy-3-methylbenzyl)-6-(2-hydroxy-3-methyl-4,5-methylenedioxybenzyl)pyrazin-2(1*H*)-one 23

A stirred solution of **18** (56.0 mg, 0.089 mmol) in dry methanol (3 cm_3) was cooled in ice–water, and a methanol solution of sodium methoxide (28%; 1.05 cm^3) was added dropwise to it over 5 min. This mixture was heated under reflux for 15 h after which it was diluted with water (10 cm^3), acidified with 1 M hydrochloric acid, made alkaline with 5% aqueous sodium hydrogen carbonate and extracted with chloroform (3 × 20 cm^3). The combined extracts were washed with water (20 cm^3), dried, and concentrated *in vacuo* to give a residue (50 mg), chromatography of which on a silica gel (8 g) column with benzene–ethyl acetate (9:1) as the eluent gave the compound **24** (4.7 mg, 10%) and with benzene–ethyl acetate (4:1) as the eluent gave the title compound **23** (18.9 mg, 39%) as a pale yellow amorphous powder.

Compound **23**: amorphous powder, $\nu_{max}(CHCl_3)/cm^{-1}$ 3610, 3500–3200, 1645 and 1595; $\delta_H(CDCl_3)$ 2.04 and 2.20 (each 3 H, s, CH_3), 3.63 (3 H, s, OCH_3), 3.73 (2 H, s, $ArCH_2C$), 3.74 and 3.76 (each 3 H, s, OCH_3), 4.16 (2 H, s, $ArCH_2C$), 5.17 (1 H, br s, OH), 5.22 (2 H, s, NCH_2Ar), 5.85 (2 H, s, OCH_2O), 6.23, 6.67 and 6.96 (each 1 H, s), 7.09–7.12 (2 H, m) and 7.24–7.27 (3 H, m); $\delta_C(CHCl_3)$ 8.9 (q), 9.7 (q), 30.5 (t), 33.8 (t), 47.0 (t), 55.8 (q), 60.2 (q), 60.8 (q), 101.0 (t), 106.2 (d), 107.5 (s), 111.4 (d), 113.6 (s), 123.5 (d), 125.4 (s), 126.0 (s), 126.5 (d), 127.5 (d), 128.7 (d), 135.4 (s), 138.2 (s), 141.0 (s), 145.7 (s), 146.5 (s), 146.6 (s), 149.0 (s), 150.7 (s), 156.7 (s) and 156.8 (s); *m/z* 544 (M^+, 100%), 542 (15), 513 (26), 453 (18), 422 (19), 381 (13), 271 (22), 230 (13), 200 (28), 181 (12) and 91 (27) (Found: M^+, 544.2210. $C_{31}H_{32}N_2O_5$ requires *M*, 544.2205).

Compound **24**: mp 236–237 °C; $\nu_{max}(KBr)/cm^{-1}$ 1675, 1650 and 1605; $\delta_H(CDCl_3)$ 2.24 and 2.26 (each 3 H, s, CH_3), 3.76, 3.85 and 3.98 (each 3 H, s, OCH_3), 5.23 (2 H, s, NCH_2Ar), 5.97 (2 H, s, OCH_2O), 6.29 and 6.42 (each 1 H, s), 7.26–7.36 (5 H, m), 7.67 and 8.51 (each 1 H, s); *m/z* 540 (M^+, 100%), 525 (17), 510 (11), 509 (31), 419 (28), 418 (38), 403 (20), 373 (16), 361 (12), 360 (44) and 91 (15) (Found: C, 67.98; H, 5.19; N, 4.99. $C_{31}H_{28}N_2O_7 \cdot 1/2H_2O$ requires C, 67.75; H, 5.32; N, 5.1%).

Acetylation of the phenol 23

Acetic anhydride (0.4 cm^3) was added to a solution of the phenol **23** (32.4 mg, 0.06 mmol) in dry pyridine (1.0 cm^3), and the mixture was set aside at room temperature for 2 h. After being diluted with 5% aqueous sodium hydrogen carbonate (10 cm^3) the mixture was extracted with chloroform (3 × 10 cm^3). The combined extracts were washed with water (10 cm^3), dried, and concentrated *in vacuo* to give a residue (44 mg). Chromatography of this on a silica gel (8 g) column with hexane–ethyl acetate (1:1) as the eluent gave the acetate **25** (31 mg, 88%) as pale yellow amorphous powder; $\nu_{max}(CHCl_3)/cm^{-1}$ 1755, 1645 and 1585; $\delta_H(CDCl_3)$ 2.00 (3 H, s, $COCH_3$), 2.03 and 2.23 (each 3 H, s, CH_3), 3.55 (2 H, s, $ArCH_2C$), 3.72, 3.78 and 3.79 (each 3 H, s, OCH_3), 4.21 (2 H, s, $ArCH_2C$), 5.16 (2 H, s, NCH_2Ar), 5.94 (2 H, s, OCH_2O), 6.23, 6.74 and 7.04 (each 1 H, s) and 7.28–7.35 (3 H, m); *m/z* 586 (M^+, 100%), 555 (21), 464 (16), 406 (16), 271 (14) and 91 (30) (Found: M^+, 586.2319. $C_{31}H_{32}N_2O_5$ requires *M*, 586.2315.)

Reaction of compound 13a with hydrochloric acid in propan-2-ol

A solution of **13a** (90.6 mg, 0.15 mmol) in propan-2-ol (4 cm^3) was cooled in ice–water and a propan-2-ol (4 cm^3) solution of hydrochloric acid (0.001 cm^3) was added dropwise to it over 5 min. After this mixture had been heated under reflux for 2 h it was concentrated *in vacuo* and the residue was diluted with 5% aqueous sodium hydrogen carbonate (10 cm^3) and extracted with ether (3 × 10 cm^3). The combined extracts were washed with water (10 cm^3), dried and concentrated *in vacuo* to give a solid (108 mg), recrystallization of which from ethyl acetate gave compound **22** (66.1 mg, 81%) as pale yellow prisms, mp 146–149 °C; $\nu_{max}(KBr)/cm^{-1}$ 1690, 1675, 1645, 1625 and 1610; $\delta_H(CDCl_3)$ 2.17 and 2.23 (each 3 H, s, CH_3), 3.25 (1 H, dd, *J* 13.5 and 4.3, ArCHC), 3.49 (1 H, dd, *J* 13.5, 5.9, ArCHC), 3.63, 3.68 and 3.71 (each 3 H, s, OCH_3), 4.85 (1 H, d, *J* 16.2, NCHAr), 5.01 (1 H, dd, *J* 5.9 and 4.3, CH), 5.07 (1 H, d, *J* 16.2, NCHAr), 5.92 (1 H, s), 5.93 (2 H, diffuse s, OCH_2O), 6.29 and 6.72 (each 1 H, s), 6.96–6.99 (2 H, m) and 7.21–7.36 (3 H, m); $\delta_C(CDCl_3)$ 8.5 (q), 9.8 (q), 35.4 (t), 44.9 (t), 55.6 (q), 60.2 (q), 61.0 (q), 62.0 (d), 101.5 (t), 102.3 (d), 107.6 (s), 111.0 (d), 111.9 (s), 112.2 (d), 122.4 (s), 124.6 (s), 125.3 (s), 126.2 (d), 127.5 (d), 128.9 (d), 134.8 (s), 143.1 (s), 144.0 (s), 146.8 (s), 147.2 (s), 148.6 (s), 151.5 (s), 151.6 (s) and 167.3 (s); *m/z* 542 (M^+, 15%), 348 (24), 347 (100), 195 (36) and 91 (25) (Found: C, 68.28; H, 5.62; N, 5.04. $C_{31}H_{30}N_2O_7 \cdot 1/10H_2O$ requires C, 68.4; H, 5.59; N, 5.15%).

Isopropyl (*E*)-3-benzyl-1,2,3,4,5,6-hexahydro-2-(2-methoxy-3-methyl-4,5-methylenedioxybenzylidene)-7,9,10-trimethoxy-8-methyl-4-oxo-1,5-imino-3-benzazocine-11-carboxylate 16b

A stirred solution of **14b** (264 mg, 0.4 mmol) in dry THF (15 cm^3) was cooled in ice–water, and lithium tri-*tert*-butoxyaluminium hydride (406.8 mg, 1.6 mmol) was added to it over 5 min. After continued stirring at the same temperature for 1 h, the reaction mixture was quenched by addition of water (1 cm^3) and filtered through a Celite pad. The filtrate was concentrated *in vacuo* to give a crude diastereoisomeric mixture of the allylic alcohols **15b** (458 mg) (along with compound **13b**) which was used for the next step without further purification. Methanesulfonic anhydride (84 mg, 0.48 mmol) was added to a stirred solution of the above mixture in dichloromethane (2 cm^3), and stirring continued for 48 h at room temperature. The reaction mixture was then diluted with water (20 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The combined extracts were washed with 5% aqueous sodium hydrogen carbonate (20 cm^3), dried, and concentrated *in vacuo* to give a residue (316 mg). Chromatography of this on a silica gel (16 g) column with hexane–ethyl acetate (2:1) as the eluent gave the title compound **16b** (183.1 mg, 71%) as a solid, recrystallization of which from ethyl acetate gave the pure compound as pale yellow prisms. Further elution with ethyl acetate gave **13b** (18.8 mg, 8.1%) as prisms whose spectra were identical with those of an authentic sample as above; mp 216.5–218 °C; $\nu_{max}(KBr)/cm^{-1}$ 1740, 1695, 1670, 1640 and 1625; $\delta_H(CDCl_3$: this compound was a mixture of two rotational isomers, ratio, 2:1) 1.32 (2/3 × 6 H, d, *J* 6.3, $CHCH_3$), 1.46 (1/3 × 6 H, d, *J* 6.3, $CHCH_3$), 2.13 and 2.20 (each 3 H, s, CH_3) 2.87 and 3.05 (each 3 H, s, OCH_3), 3.15 (1 H, dd, *J* 16.2 and 5.6, 6-Hα), 3.31 (1 H, d, *J* 16.2, 6-Hβ), 3.47 and 3.70 (each 3 H, s, OCH_3), 4.46 (1 H, d, *J* 16.2, NCHAr), 5.08 (1 H, sept, *J* 6.3, $OCHCH_3$), 5.24 (1/3 × 1 H, d, *J* 5.6, 5-H), 5.26 (2/3 × 1 H, d, *J* 5.6, 5-H), 5.73 (1 H, d, *J* 16.2, NCHAr), 5.93 (2 H, s, OCH_2O), 6.01 (2/3 × 1 H, s), 6.05 (1/3 ×1 H, s), 6.61–6.66 (3 H, m), 6.99–7.08 (3 H, m), 7.20 (2/3 × 1 H, s) and 7.56 (1/3 × 1 H, s); $\delta_C(CDCl_3)$ (major isomer) 9.0 (q, $ArCH_3$), 9.3 (q, $ArCH_3$), 22.3 (q, $CHCH_3$), 27.4 (t, C-6), 43.5 (t, $ArCH_2N$), 46.4 (d, C-1), 52.8 (d, C-5), 59.2, 59.7, 60.0 and 60.1 (q, OCH_3), 70.1 (d, OCH), 101.0 (t, OCH_2O), 105.7 (d, C=CH), 107.4 (d), 113.4 (s), 122.5 (s), 125.3 (s), 125.4 (s), 126.1 (d), 126.6 (d), 128.3 (d), 134.4 (s), 136.4 (s), 142.8 (s), 145.6 (s), 150.2 (s), 152.2 (s), 152.7 (s), 152.9 (s, COO) and 168.4 (s, NCO); (minor isomer) 9.0 (q, $ArCH_3$), 9.3 (q, $ArCH_3$), 21.9 (q, $CHCH_3$), 28.2 (t, C-6), 43.5 (t, $ArCH_2N$), 45.8 (d, C-1), 53.5 (d, C-5), 59.2, 59.7 60.0 and 69.6 (q, OCH_3), 70.1 (d, OCH), 101.0 (t, OCH_2O), 106.3 (d, C=CH), 107.7 (d), 113.4 (s), 122.2 (s), 125.3 (s), 125.4 (s), 126.1 (d), 126.6 (d), 128.3 (d), 134.4 (s), 136.4 (s), 142.8 (s), 146.2 (s), 150.2 (s), 152.2 (s), 152.7 (s), 152.9 (s, COO) and 168.4 (s, NCO); *m/z* 644 (M^+, 100%) and 234 (19) (Found: C, 66.7; H, 6.37; N, 4.17. $C_{36}H_{40}N_2O_9$ requires C, 67.06; H, 6.25; H, 4.35%).

Isopropyl (*E*)-3-benzyl-1,2,3,4,5,6-hexahydro-2-(2-benzyloxy-3-methyl-4,5-methylenedioxybenzylidene)-7,9,10-trimethoxy-8-methyl-4-oxo-1,5-imino-3-benzazocine-11-carboxylate 16c

A stirred solution of **14c** (110.4 mg, 0.15 mmol) in dry THF (5 cm^3) was cooled in ice–water, and lithium tri-*tert*-butoxyaluminium hydride (228.8 mg, 0.9 mmol) was added to it over 5 min. After continued stirring at the same temperature for 1 h, the reaction mixture was quenched by addition of water (1 cm^3) and filtered through a Celite pad. The filtrate was concentrated *in vacuo* to give a crude diastereoisomeric mixture of the allylic alcohols **15c** (140 mg) (along with compound **13c**) which was used for the next step without further purification. A solution of the above mixture and triethylamine (0.038 cm^3, 0.27 mmol) in dichloromethane (6 cm^3) was cooled in ice–water, and methanesulfonyl chloride (0.021 cm^3, 0.27 mmol) was added dropwise to it over 10 min. The mixture was heated under reflux for 17 h after which it was washed with 1 M aqueous hydrochloric acid (20 cm^3) and then with water (10 cm^3), dried, and concentrated *in vacuo* to give a residue (129 mg). Chromatography of this on a silica gel (20 g) column with hexane–ethyl acetate (2:1) as the eluent gave the title compound **16c** (62.1 mg, 57.5%) as a solid, recrystallization of which from ethyl acetate–ether gave the pure compound as pale yellow prisms. Further elution with ethyl acetate gave **13c** (24.4 mg. 10.6%) as prisms whose spectra were identical with those of an authentic sample as above: mp 208–209 °C; ν_{max}(KBr)/cm^{-1} 1740, 1690, 1665, 1640 and 1630; δ_H($CDCl_3$: this compound was a mixture of two rotational isomers, ratio, 2:1) 1.32 (2/3 × 6 H, d, *J* 6.3, CHCH_3), 1.45 (1/3 × 6 H, d, *J* 6.3 CHCH_3), 1.98 and 2.18 (each 3 H, s, CH_3), 3.03 (1 H, br s, 6-Hα), 3.17 (2/3 × 3 H, s, OCH_3), 3.20 (1/3 × 3 H, s, OCH_3), 3.34 (1 H, d, *J* 16.2, 6-Hβ), 3.53 and 3.68 (each 3 H, s, OCH_3), 4.25 and 4.37 (each 1 H, d, *J* 11.6, OCHAr), 4.76 and 5.08 (each 1 H, d, *J* 16.8, NCHAr), 5.08 (1 H, sept, *J* 6.3, OC*H*CH_3), 5.23 (1/3 × 1 H, br s, 5-H), 5.27 (2/3 × 1 H, d, *J* 5.6, 5-H), 5.94 (2 H, s, OCH_2O), 6.11 (2/3 × 1 H, s), 6.15 (1/3 × 1 H, s), 6.60 (2 H, br s), 6.69 (2/3 × 1 H, s), 6.77 (1/3 × 1 H, s), 6.91–6.93 (3 H, m), 7.08–7.11 (2 H, m), 7.24–7.29 (3 H + 2/3 × 1 H, m) and 7.60 (1/3 × 1 H, s); δ_C($CDCl_3$) (only major isomer) 9.3 (q, $ArCH_3$), 9.5 (q, $ArCH_3$), 22.2 (q, CH*C*H_3), 27.3 (t, C-6), 44.6 (t, $ArCH_2N$), 46.4 (d, C-1), 52.8 (d, C-5), 59.5, 60.1 and 60.3 (each q, OCH_3), 70.2 (d, OCH), 74.7 (t, OCH_2), 101.1 (t, OCH_2O), 106.7 (d, C=*C*H), 107.0 (d), 113.9 (s), 122.7 (s), 125.8 (d), 126.8 (d), 127.4 (d), 127.7 (d), 128.3 (d), 136.3 (s), 138.0 (s), 143.0 (s), 145.7 (s), 150.4 (s), 151.5 (s), 152.8 (s, COO) and 168.2 (s, NCO); *m/z* 720 (M^+, 36%), 631 (12), 630 (42), 629 (100), 544 (34), 543 (98), 278 (16), 235 (20), 234 (51), 204 (22) and 91 (32) (Found: C, 69.75; H, 6.25; N, 3.71. $C_{42}H_{44}N_2O_9$ requires C, 69.98; H, 6.15; N, 3.89%).

Isopropyl (*E*)-3-benzyl-1,2,3,4,5,6-hexahydro-2-(2-benzyloxy-4,5-methylenedioxybenzylidene)-9-methoxy-8-methyl-4-oxo-1,5-imino-3-benzazocine-11-carboxylate 16d

A stirred solution of **14d** (331.0 mg, 0.5 mmol) in dry THF (20 cm^3) was cooled in ice–water, and lithium tri-*tert*-butoxyaluminium hydride (762.8 mg, 3.0 mmol) was added to it over 5 min. After continued stirring at the same temperature for 1 h, the reaction mixture was quenched by addition of water (1 cm^3) and filtered through a Celite pad. The filtrate was concentrated *in vacuo* to give a crude diastereoisomeric mixture of the allylic alcohols **15d** (426 mg) (along with compound **13d**) which was used for the next step without further purification. A solution of the above mixture in formic acid (12 cm^3) was heated at 70 °C for 2 h after which it was diluted with water (30 cm^3), and extracted with chloroform (3 × 30 cm^3). The combined extracts were washed with 5% aqueous sodium hydrogen carbonate (30 cm^3), dried, and concentrated *in vacuo* to give a residue (426 mg). Chromatography of this on a silica gel (20 g) column with hexane–ethyl acetate (4:1) as the eluent gave the title compound **16d** (202.3 mg, 63%) as a solid, recrystallization of which from ethyl acetate–methanol gave the pure compound as colourless prisms. Further elution with hexane–ethyl acetate (3:1) as the eluent gave a mixture (41 mg) which showed two major spots on TLC [R_f, 0.46 and 0.42, hexane–ethyl acetate (3:1)]. This mixture was subjected to chromatography on preparative layer silica gel plates [Merck 5715, solvent, hexane–ethyl acetate (3:1)] and gave compound **27** (19.4 mg, 7.0%) as a solid, recrystallization of which from ethyl acetate–ether gave the pure compound as colourless prisms and the (*Z*)-isomer **26d** (10.4 mg, 3.2%) as colourless amorphous powder. Finally, elution with ethyl acetate as eluent gave a solid, recrystallization of which from ethyl acetate afforded **13d** (15.4 mg, 5.3%) as prisms whose spectra were identical with those of an authentic sample as above.

Compound **16d**: mp 216–218 °C; ν_{max}(KBr)/cm^{-1} 1705, 1665, 1635 and 1620; δ_H($CDCl_3$: this compound was a mixture of two rotational isomers, ratio, 3:1) 1.25 (3/4 × 6 H, d, *J* 6.6, CHCH_3), 1.29 (1/4 × 6 H, d, *J* 6.6, CHCH_3), 2.15 (3 H, s, CH_3), 3.08 (1 H, d, *J* 16.8, 6-Hβ), 3.21 (1 H, m, 6-Hα), 3.43 (3 H, s, OCH_3), 4.78–4.85 (3 H, br s, OCH_2Ar and NCHAr), 4.97–5.11 (2 H, d like, OCH and NCHAr), 5.18 (1/4 × 1 H, br s, 5-H), 5.29 (3/4 × 1 H, br s, 5-H), 5.82 (1 H, s), 5.93 (3/4 × 2 H, s, OCH_2O), 5.96 (1/4 × 2 H, s, OCH_2O), 6.05 (3/4 × 1 H, s), 6.08 (1/4 × 1 H, s), 6.37 (1 H, br s), 6.53 (1 H, br s), 6.69 (2 H, br s), 6.88 (1 H, s), 6.98–7.07 (3 H, m), 7.12 (2 H, m) and 7.23–7.34 (4 H, s); δ_C($CDCl_3$) (major isomer) 15.9 (q, $ArCH_3$), 22.1 (q, CH*C*H_3), 22.6 (q, CH*C*H_3), 31.5 (t, C-6), 44.7 (t, $ArCH_2N$), 49.6 (d, C-1), 53.4 (d, C-5), 54.8 (q, OCH_3), 69.5 (d, OCH), 71.2 (t, OCH_2), 96.6 (d), 101.4 (t, OCH_2O), 105.4 (d, C=*C*H), 107.8 (d), 109.9 (d), 117.6 (s), 123.5 (s), 126.1 (d), 126.7 (d), 128.2 (d), 131.0 (d), 132.3 (s), 136.0 (s), 137.9 (s), 141.6 (s), 147.5 (s), 152.1 (s), 153.0 (s, COO), 156.4 (s) and 168.6 (s, NCO); (minor isomer) 14.1 (q, $ArCH_3$), 22.3 (q, CH*C*H_3), 22.6 (q, CH*C*H_3), 31.3 (t, C-6), 44.7 (t, $ArCH_2N$), 49.1 (d, C-1), 53.2 (d, C-5), 54.8 (q, OCH_3) 69.4 (d, OCH), 70.1 (t, OCH_2), 96.4 (d), 101.4 (t, OCH_2O), 105.4 (d, C=*C*H), 108.1 (d), 110.4 (d), 117.4 (s), 123.0 (s), 126.9 (d), 127.2 (d), 128.5 (d), 130.8 (d), 132.4 (s), 136.0 (s), 137.9 (s), 141.6 (s), 147.5 (s), 151.9 (s), 153.2 (s, COO), 156.4 (s) and 168.6 (s, NCO); *m/z* 646 (M^+, 55%), 556 (18), 555 (32), 513 (16), 470 (26), 469 (82), 268 (14), 266 (15), 260 (14), 220 (11), 219 (11), 218 (32), 176 (16), 175 (20), 174 (100), 159 (14), 91 (54) and 43 (16) (Found: C, 72.56; H, 5.94; N, 4.32. $C_{39}H_{38}N_2O_7$ requires C, 72.43; H, 5.92; N, 4.33%).

Compound **27**: mp 180–181.5 °C; ν_{max}(KBr)/cm^{-1} 1705, 1655 and 1620; δ_H($CDCl_3$ at 55 °C) 1.26 [6 H, d, *J* 5.9, CH(CH_3)$_2$], 2.22 (3 H, s, $ArCH_3$), 3.04 (1 H, d, *J* 16.5, ArCHC), 3.11–3.18 (2 H, br s, ArCHC and ArC*H*CH), 3.48 (1 H, m, ArC*H*CH), 3.78 (3 H, s, OCH_3), 4.42 and 4.50 (each 1 H, d, *J* 15.5, ArCHN) 4.99 (1 H, sept, *J* 5.9, OCH), 4.99 (1 H, m, ArCHC*H*), 5.32 (1 H, br s, CH), 5.92 (2 H, s, OCH_2O), 6.30, 6.59 and 6.62 (each 1 H, s), 6.75 (2 H, d, *J* 7.6), 6.91 (1 H, s) and 7.00–7.11 (3 H, m); δ_C($CDCl_3$ at 25 °C) (major isomer) 15.9 (q, $ArCH_3$), 22.1 (q, CH*C*H_3), 31.1 (t, Ar*C*H_2CH), 40.8 (t, $ArCH_2C$), 44.1 (t, $ArCH_2N$), 53.7 (d, CH), 55.5 (q, OCH_3), 56.0 (d, $ArCH_2CH$), 70.0 (d, OCH), 92.8 (d), 100.8 (s), 101.3 (t, OCH_2O), 105.3 (d), 112.1 (d), 115.8 (s), 124.3 (s), 126.6 (d), 126.9 (d), 128.0 (d), 130.6 (d), 137.8 (s), 142.6 (d), 147.8 (s), 151.3 (s), 153.9 (s), 155.9 (s) and 168.4 (s, NCO); (minor isomer) 15.9 (q, $ArCH_3$), 22.2 (q, CH*C*H_3), 30.7 (t, Ar*C*H_2CH), 40.5 (t, $ArCH_2C$), 43.9 (t, $ArCH_2N$), 52.9 (d, CH), 55.5 (q, OCH_3), 56.9 (d, $ArCH_2CH$), 69.9 (d, OCH), 92.9 (d), 100.5 (s), 101.3 (t, OCH_2O), 105.0 (d), 111.9 (d), 115.7 (s), 124.9 (s), 126.6 (d), 127.0 (d), 128.3 (d), 130.8 (d), 137.8 (s), 142.4 (s), 147.9 (s), 151.3 (s), 153.1 (s), 155.9 (s) and 168.1 (s, NCO); *m/z* 556 (M^+, 100%), 465 (32), 380 (13), 379 (48), 268 (24), 261 (20), 246 (31), 220 (11), 219 (22), 218 (15), 175 (11), 174 (67) and 91 (23) (Found: C, 68.9; H, 5.86; N, 4.92. $C_{32}H_{32}N_2O_7$ requires C, 69.05; H, 5.8; N, 5.03%).

Compound **26d**: amorphous powder, ν_{max}($CHCl_3$)/cm^{-1} 1710, 1690, 1675 and 1615; δ_H($CDCl_3$) 0.85 and 0.97 (each 3 H, d, *J* 6.3, CHCH_3), 2.10 (3 H, s, $ArCH_3$), 3.14 (1 H, d, *J* 16.2 and 1.7,

6-Hβ), 3.23 (3 H, s, OCH_3), 3.40 (1 H, dd, *J*16.2 and 5.6, 6-Hα), 4.52 (1 H, d, *J* 15.5, NCHAr), 4.73 (1 H, sept, *J* 6.3, OCH), 4.95 (2 H, s, OCH_2Ar), 5.03 (1 H, d, *J* 15.5, NCHAr), 5.44 (1 H, dd, *J* 5.6 and 1.7, 5-H), 5.62 (1 H, s, 1-H), 5.66 (1 H, d, *J* 1.0, OCHO), 5.74 (1 H, s), 5.79 (1 H, d, *J* 1.0, OCHO), 6.47 (1 H, s), 6.58 (2 H, d, *J* 6.9), 6.89 (1 H, s), 6.97 (1 H, s), 6.94–7.07 (3 H, m), 7.19 (1 H, s) and 7.20–7.30 (5 H, m); *m/z* 646 (M^+, 94%), 557 (21), 556 (24), 555 (44), 513 (22), 470 (33), 469 (100), 268 (14), 266 (15), 260 (12), 248 (21), 219 (10), 218 (30), 176 (13), 175 (18), 174 (82), 159 (12), 91 (48) and 43 (10) (Found: M^+, 646.2677. $C_{31}H_{32}N_2O_5$ requires *M*, 646.2679).

Isopropyl (*E*)-3-benzyl-1,2,3,4,5,6-hexahydro-2-(2-benzyloxy-3-methyl-4,5-methylenedioxybenzylidene)-9-methoxy-8-methyl-4-oxo-1,5-imino-3-benzazocine-11-carboxylate 16e

Method A. A stirred solution of **14e** (405.6 mg, 0.6 mmol) in dry THF (25 cm^3) was cooled in ice–water, and lithium tri-*tert*-butoxyaluminium hydride (915 mg, 3.6 mmol) was added to it over 5 min. After continued stirring at the same temperature for 1 h, the reaction mixture was quenched by addition of water (1 cm^3) and filtered through a Celite pad. The filtrate was concentrated *in vacuo* to give a crude diastereoisomeric mixture of the allylic alcohols **15e** (498 mg) (along with compound **13e**) which was used for the next step without further purification. A solution of the above mixture in formic acid (12 cm^3) was heated at 70 °C for 2 h after which it was diluted with water (30 cm^3) and extracted with chloroform (3 × 30 cm^3). The combined extracts were washed with 5% aqueous sodium hydrogen carbonate (30 cm^3), dried, and concentrated *in vacuo* to give a residue (431 mg). Chromatography of this on a silica gel (40 g) column with hexane–ethyl acetate (3 :1–2 : 1) as the eluent gave a mixture (187 mg) which showed three major spots on TLC [R_f, 0.30, 0.25 and 0.13, hexane–ethyl acetate (2 : 1)]. This mixture when subjected to chromatography on preparative layer silica gel plates [Merck 5715, solvent, hexane–ethyl acetate (3 : 1)] gave the title compound **16e** (56.4 mg, 14.2%, as colourless amorphous powder), the (*Z*)-isomer **26e** (33.2 mg, 8.4%, as a solid, recrystallized from ethyl acetate–ether) and compound **28** (34.5 mg, 8.7%) as colourless amorphous powder. Finally, elution with ethyl acetate as an eluent gave the compound as a solid, recrystallization of which from ethyl acetate gave **13e** (28.5 mg, 8.1%) as prisms whose spectra were identical with those of an authentic sample as above.

Method B. Reduction of **14e** (405.6 mg, 0.6 mmol) with lithium tri-*tert*-butoxyaluminium hydride (915 mg, 3.6 mmol) as described above afforded the allylic alcohol **15e** (422 mg). A solution of the above mixture and triethylamine (0.837 cm^3, 6 mmol) in dichloromethane (20 cm^3) was cooled in ice–water, and methanesulfonyl chloride (0.465 cm^3, 6 mmol) was added dropwise to it over 10 min. The mixture was heated under reflux for 38 h after which it was washed with 1 M aqueous hydrochloric acid (20 cm^3) and then with water (10 cm^3), dried, and concentrated *in vacuo* to give a residue (531 mg). Chromatography of this on a silica gel (40 g) column with hexane–ethyl acetate (3 : 1–2 : 1) as the eluent gave a mixture (86 mg) which showed two major spots on TLC [R_f, 0.30 and 0.13, hexane–ethyl acetate (2 : 1)]. This mixture was subjected to chromatography on preparative layer silica gel plates [Merck 5715, solvent, hexane–ethyl acetate (3 : 1)] and gave the title compound **16e** (27.9 mg, 7.0%, as a colourless amorphous powder) and compound **28** (40.9 mg, 10.3%) as colourless amorphous powder. Finally, elution with ethyl acetate as an eluent gave a solid, recrystallization of which from ethyl acetate afforded **13e** (38.9 mg, 11.0%).

Method C. Reduction of **14e** (405.6 mg, 0.6 mmol) with lithium tri-*tert*-butoxyaluminium hydride (915 mg, 3.6 mmol) as described above afforded the allylic alcohol **15e** (427 mg). Methanesulfonic anhydride (209 mg, 1.2 mmol) was added to a stirred solution of the above mixture in dichloromethane (10 cm^3), which was then stirred at room temperature for 72 h. It was then diluted with water (20 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The combined extracts were washed with 5% aqueous sodium hydrogen carbonate (20 cm^3), dried, and concentrated *in vacuo* to give a residue (422 mg). Chromatography of this on a silica gel (40 g) column with hexane–ethyl acetate (2 : 1) as the eluent gave the title compound **16e** (141.4 mg, 35.7%) as a solid, recrystallization of which from ethyl acetate gave the pure compound as pale yellow prisms. Further elution with ethyl acetate–hexane (2 : 1) gave a solid which was recrystallized from methanol to afford compound **29** (11.9 mg, 5.2%) and elution with ethyl acetate as the eluent gave **13e** (41.0 mg, 11.6%) as prisms.

Compound **16e**: amorphous powder, $\nu_{max}(CHCl_3)/cm^{-1}$ 1702, 1692, 1635 and 1620; $\delta_H(CDCl_3$: this compound was a mixture of two rotational isomers, ratio 2 : 1) 1.27 (3 H, d, *J* 6.3, $CHCH_3$), 1.37 (3 H, d, *J* 6.3, $CHCH_3$), 2.06 and 2.16 (each H, s, CH_3), 3.08 (1 H, d, *J* 15.2, 6-Hβ), 3.22–3.28 (1 H, m, 6-Hα), 3.53 (3 H, s, OCH_3), 4.38 (2 H, s, OCH_2Ar), 4.82 and 4.96 (each 1 H, d, *J* 16.5, NCHAr), 5.02 (1 H, sept, *J* 6.3, OCH), 5.21 (1/3 × 1 H, br s, 5-H), 5.28 (2/3 × 1 H, br s, 5-H), 5.78–5.96 (1 H, br), 5.97 (2/3 × 2 H, s, OCH_2O), 5.98 (1/3 × 2 H, s, OCH_2O), 6.19 (1 H, br s), 6.24 (2/3 × 1 H, s), 6.29 (1/3 × 1 H, s), 6.62–6.64 (2 H, br d), 6.89–7.15 (5 H, m) and 7.26–7.37 (5 H, m); $\delta_C(CDCl_3)$ (major isomer) 9.6 and 15.9 (q, $ArCH_3$), 22.2 (q, $CHCH_3$), 22.2 (q, $CHCH_3$), 31.1 (t, C-6), 44.6 (t, $ArCH_2N$), 49.9 (d, C-1), 53.4 (d, C-5), 55.1 (q, OCH_3), 70.1 (d, OCH), 74.9 (t, OCH_2), 101.3 (t, OCH_2O), 105.8 (d, C=CH), 107.2 (d), 108.1 (d), 114.0 (s), 121.5 (s), 123.6 (s), 125.8 (d), 126.8 (d), 127.5 (d), 127.9 (d), 128.3 (d), 128.4 (d), 131.2 (d), 132.3 (s), 135.9 (s), 137.1 (s), 138.8 (s), 143.2 (s), 146.3 (s), 151.8 (s), 153.0 (s, COO), 156.5 (s) and 168.8 (s, NCO); (minor isomer) 9.6 and 15.9 (q, $ArCH_3$), 22.0 (q, $CHCH_3$), 22.0 (q, $CHCH_3$), 31.6 (t, C-6), 44.6 (t, $ArCH_2N$), 49.3 (d, C-1), 54.2 (d, C-5), 55.1 (q, OCH_3), 69.6 (d, OCH), 74.9 (t, OCH_2), 101.3 (t, OCH_2O), 105.7 (d, C=CH), 107.4 (d), 108.3 (d), 114.0 (s), 121.5 (s), 123.6 (s), 125.8 (d), 126.8 (d), 127.5 (d), 127.9 (d), 128.3 (d), 128.4 (d), 131.0 (d), 132.3 (s), 135.9 (s), 137.2 (s), 137.3 (s), 143.1 (s), 146.3 (s), 151.8 (s), 153.1 (s, COO), 156.4 (s) and 168.8 (s, NCO); *m/z* 660 (M^+, 57%), 570 (46), 569 (85), 484 (32), 483 (97), 282 (12), 260 (12), 218 (23), 175 (22), 174 (100), 159 (12), 91 (59) and 43 (19) (Found: M^+, 660.2837. $C_{40}H_{40}N_2O_7$ requires *M*, 660.2836.

Compound **26e**: mp 190–191.5 °C; $\nu_{max}(KBr)/cm^{-1}$ 1680, 1670 and 1615; $\delta_H(CDCl_3)$ 0.96 and 1.07 (each 3 H, d, *J* 6.3, $CHCH_3$), 2.17 (6 H, s, 2 × ArCH), 3.20 (1 H, dd, *J* 16.2 and 2.0, 6-Hβ), 3.34 (3 H, s, OCH_3), 3.47 (1 H, dd, *J* 16.2 and 5.9, 6-Hα), 4.53 (1 H, d, *J* 15.8, NCHAr), 4.76 (2 H, s, OCH_2Ar), 4.81 (1 H, sept, *J* 6.3, OCH), 5.06 (1 H, d, *J* 15.8, NCHAr), 5.45 (1 H, s, 1-H), 5.51 (1 H, dd, *J* 5.9 and 2.0, 5-H), 5.75 (1 H, d, *J* 1.0, OCHO), 5.81 (1 H, s), 5.88 (1 H, d, *J* 1.0, OCHO), 6.62 (2 H, d, *J* 6.9), 6.95 (1 H, s), 6.99–7.10 (3 H, m), 7.21 (1 H, s), 7.30 (1 H, s) and 7.35 (5 H, m); *m/z* 660 (M^+, 30%), 570 (45), 569 (100), 174 (82) and 91 (18) (Found: C, 72.64; H, 5.85; N, 4.17. $C_{40}H_{40}N_2O_7$ requires C, 72.71; H, 6.1; N, 4.24%).

Compound **28**: mp 184.5–185 °C; $\nu_{max}(KBr)/cm^{-1}$ 1715 and 1660; $\delta_H(CDCl_3)$ 1.08 and 1.18 (each 3 H, d, *J* 6.3, $CHCH_3$), 2.03 and 2.17 (each 3 H, s, $ArCH_3$), 2.75–2.95 (3 H, m, ArCH-C=C and $ArCH_2CH$), 3.19 (1 H, d, *J* 21.8, ArCHC=C), 3.69 (3 H, s, OCH_3), 4.79 (4 H, s, NCH_2Ar and OCH_2Ar), 4.86 (1 H, sept, *J* 6.3, OCH), 5.15 (1 H, br s, CH), 5.96 (2 H, s, OCH_2O), 6.50 (1 H, d, *J* 8.3), 6.83 (1 H, br s), 6.86 (1 H, dd, *J* 8.3 and 2.0) and 7.21–7.38 (10 H, m); $\delta_C(CDCl_3)$ 9.3 (q, $ArCH_3$), 15.7 (q, $ArCH_3$), 21.6 (q, $CHCH_3$), 21.9 (q, $CHCH_3$), 31.1 (t), 36.3 (t), 46.7 (q, NCH_3), 55.3 (q, OCH_3), 60.3 (d, CH), 70.2 (d, OCH), 74.7 (t, OCH_2Ar), 100.9 (t, OCH_2O), 109.1 (s), 109.7 (d), 118.6 (s), 119.9 (s), 122.2 (s), 126.0 (s), 127.6 (2 × d), 127.7 (d), 127.8 (2 × d), 127.9 (s), 128.1 (2 × d), 128.5 (2 × d), 128.8 (2 × d), 131.2 (s), 131.9 (d), 135.0 (s), 136.7 (s), 137.8 (s), 147.0 (s), 147.7 (s), 156.6 (s) and 167.1 (s); *m/z* 660 (M^+, 100%), 483 (12), 481 (13), 440 (19), 439 (60), 349 (10), 348 (18), 347 (15), 257 (10),

135 (71) and 91 (57) (Found: C, 72.66; H, 6.17; N, 4.18. $C_{40}H_{40}N_2O_7$ requires C, 72.71; H, 6.1; N, 4.24%).

Compound **29**: mp 175–176 °C; ν_{max}(KBr)/cm^{-1} 3300, 3250, 1685 and 1610; δ_H[$CDCl_3$–CD_3OD (3:1), at 50 °C] 1.17 [6 H, d, *J* 5.9, $CH(CH_3)_2$], 2.15 (3 H, s, $ArCH_3$), 2.92 (1 H, dd, *J* 13.5 and 7.6, CHC*H*Ar), 3.03 (1 H, dd, *J* 13.5 and 5.9, CHC*H*Ar), 3.78 (3 H, s, OCH_3), 4.26–4.42 (3 H, m, NCH_2Ar and C*H*CH_2Ar), 4.81 (1 H, sept, *J* 5.9, OCH), 5.18 and 6.15 (each 1 H, br s, NH), 6.68 (1 H, d, *J* 8.6), 6.95 (2 H, br s), 7.07 (2 H, br s) and 7.23 (3 H, br s); δ_C[$CDCl_3$–CD_3OD (3:1), at 50 °C] 15.8 (q, $ArCH_3$), 21.8 (q, $CHCH_3$), 37.8 (t, CH*C*H_2Ar), 43.2 (t, NCH_2Ar), 55.2 (q, OCH_3), 56.3 (d, *C*HCH_2Ar), 68.8 (d, OCH), 110.2 (d), 126.7 (s), 127.2 (d), 127.4 (d), 127.4 (d), 128.1 (s), 128.4 (d), 131.5 (d), 137.6 (s), 156.8 (s, NCOO) and 171.5 (s, NCO); *m/z* 384 (M^+, 4%), 282 (22), 281 (100), 176 (12), 175 (11), 164 (11), 148 (30), 136 (11), 135 (77), 106 (4) and 91 (21) (Found: C, 68.66; H, 7.35; N, 7.24. $C_{22}H_{28}N_2O_4$ requires C, 68.72; H, 7.34; N, 7.29%).

General procedure for the reaction of isopropyl (*E*)-3-benzyl-2-arylidene-4-oxo-1,5-imino-3-benzazocine-11-carboxylate 16 with sodium methoxide

A stirred solution of **16** (0.4 mmol) in dry methanol (8.0 cm^3) was cooled in ice–water, and a methanol solution of sodium methoxide (28%, 3.0 cm^3) was added dropwise to it over 5 min. This mixture was then heated under reflux for 8 h after which it was diluted with water (20 cm^3), acidified with 1 M aqueous hydrochloric acid, made alkaline with 5% aqueous sodium hydrogen carbonate and extracted with chloroform (3 × 20 cm^3). The combined extracts were washed with water (20 cm^3), dried, and concentrated *in vacuo* to give a residue, which was purified by column chromatography on silica gel to give the corresponding benzazocine derivative **30**.

(*E*)-3-Benzyl-1,2,3,4,5,6-hexahydro-2-(2-methoxy-3-methyl-4,5-methylenedioxybenzylidene)-7,9,10-trimethoxy-8-methyl-1,5-imino-3-benzazocin-4-one 30b. Colourless amorphous powder (210.9 mg, 94.5% yield); ν_{max}($CHCl_3$)/cm^{-1} 3310, 1655, 1635 and 1620; δ_H($CDCl_3$) 2.13 and 2.19 (each 3 H, s, CH_3), 2.24 (1 H, br s, NH), 3.02 and 3.05 (each 3 H, s, OCH_3), 3.06 (1 H, dd, *J* 17.2 and 6.3, 6-Hα), 3.35 (1 H, dd, *J* 17.2 and 1.3, 6-Hβ), 3.50 and 3.70 (each 3 H, s, OCH_3), 4.25 (1 H, dd, *J* 6.3 and 1.3, 5-H), 4.53 (1 H, d, *J* 16.2, NCHAr), 5.46 (1 H, s, 1-H), 5.63 (1 H, d, *J* 16.2, NCHAr), 5.86 (1 H, s, C=CH), 5.91 and 5.92 (each 1 H, diffuse s, OCHO), 6.62 (1 H, s, ArH), 6.68–6.71 (2 H, m) and 7.02–7.05 (3 H, m); δ_C($CDCl_3$) 9.2 (q, $ArCH_3$), 9.3 (q, $ArCH_3$) 29.5 (t, C-6), 43.5 (t, $ArCH_2N$), 46.6 (d, C-1), 53.8 (d, C-5), 58.9, 59.9, 59.9 and 60.1 (each q, OCH_3), 101.1 (t, OCH_2), 105.6 (d, C=CH), 106.3 (d), 113.5 (s), 122.4 (s), 122.8 (d), 124.5 (s), 126.3 (d), 126.4 (d), 126.6 (d), 128.3 (d), 136.8 (s), 138.4 (s), 142.6 (s), 145.4 (s), 146.7 (s), 149.9 (s), 151.8 (s), 152.6 (s) and 170.5 (s, NCO); *m/z* 558 (M^+, 100%), 543 (19), 527 (21), 297 (12), 235 (22) and 234 (91) (Found: M^+, 558.2361. $C_{32}H_{34}N_2O_7$ requires *M*, 558.2368).

(*E*)-3-Benzyl-1,2,3,4,5,6-hexahydro-2-(2-benzyloxy-3-methyl-4,5-methylenedioxybenzylidene)-7,9,10-trimethoxy-8-methyl-1,5-imino-3-benzazocin-4-one 30c Colourless prisms (ethyl acetate–ether) (214.3 mg, 84.5% yield), mp 159–160 °C; ν_{max}(KBr)/cm^{-1} 3320, 1660, 1635 and 1625; δ_H($CDCl_3$) 2.10 (1 H, br s, NH), 2.16 and 2.17 (each 3 H, s, CH_3), 2.94 (1 H, dd, *J* 16.5, 5.9, 6-Hα), 3.05 (3 H, s, OCH_3), 3.21 (1 H, dd, *J* 16.5 and 1.7, 6-Hβ), 3.57 and 3.64 (each 3 H, s, OCH_3), 3.82 (1 H, dd, *J* 5.9, 1.7, 5-H), 4.36 and 4.66 (each 1 H, d, *J* 10.9, OCHAr), 4.71 (1 H, d, *J* 15.8, NCHAr), 5.14 (1 H, s, 1-H), 5.24 (1 H, d, *J* 15.8, NCHAr), 5.77 (1 H, s, C=CH), 5.94 (2 H, diffuse s, OCH_2O), 6.73–6.76 (3 H, m), 7.02–7.04 (3 H, m), 7.26–7.29 (2 H, m) and 7.36–7.40 (3 H, m); δ_C($CDCl_3$) 9.3 (q, $ArCH_3$), 9.6 (q, $ArCH_3$), 29.5 (t, C-6), 44.2 (t, $ArCH_2N$), 46.9 (d, C-1), 53.5 (d, C-5), 59.0, 60.0 and 60.0 (each q, OCH_3), 75.2 (t, OCH_2), 101.0 (t, OCH_2O), 104.2 (d, C=CH), 107.4 (d), 113.7 (s), 122.6 (s), 123.0 (s), 124.3 (s), 126.3 (d), 126.4 (d), 126.7 (d), 128.1 (d), 128.3 (d), 128.3 (d), 128.7 (d), 136.8 (s), 137.4 (s), 140.0 (s), 142.9 (s), 145.4 (s), 146.8 (s), 149.8 (s), 150.0 (s), 152.5 (s) and 170.6 (s, NCO); *m/z* 634 (M^+, 17%), 544 (36), 543 (100), 285 (18), 234 (58), 204 (21), 190 (12) and 91 (25) (Found: C, 71.96; H, 6.2; N, 4.3. $C_{38}H_{38}N_2O_7$ requires C, 71.9; H, 6.03; N, 4.14%).

(*E*)-3-Benzyl-1,2,3,4,5,6-hexahydro-2-(2-benzyloxy-4,5-methylenedioxybenzylidene)-9-methoxy-8-methyl-1,5-imino-3-benzazocin-4-one 30d. Colourless amorphous powder (215.6 mg, 85.0% yield); $\nu_{max.}$($CHCl_3$)/cm^{-1} 3330, 1670 and 1640; δ_H($CDCl_3$) 1.93 (1 H, br s, NH), 2.14 (3 H, s, CH_3), 2.99 (1 H, dd, *J* 16.2 and 1.7, 6-Hβ), 3.14 (1 H, dd, *J* 16.2 and 5.9, 6-Hα), 3.47 (3 H, s, OCH_3), 4.00 (1 H, dd, *J* 5.9, 1.7, 5-H), 4.83 (1 H, d, *J* 15.8, NCHAr), 4.84 and 4.90 (each 1 H, d, *J* 11.6, OCHAr), 4.96 (1 H, s, 1-H), 5.12 (1 H, d, *J* 15.8, NCHAr), 5.51 (1 H, s, C=CH), 5.92 (2 H, s, OCH_2O), 6.03, 6.49 and 6.61 (each 1 H, s, ArH), 6.71–6.74 (2 H, m), 6.84 (1 H, s, ArH), 7.03–7.12 (3 H, m) and 7.27–7.40 (5 H, m); δ_C($CDCl_3$) 15.9 (q, $ArCH_3$), 32.7 (t, C-6), 44.4 (t, $ArCH_2N$), 50.7 (d, C-1), 54.3 (d, C-5), 55.0 (q, OCH_3), 71.8 (t, OCH_2), 97.4 (d), 101.4 (t, OCH_2O), 102.6 (d, C=CH), 108.4 (d), 110.3 (d), 118.3 (s), 124.0 (s), 126.1 (s), 126.7 (d), 127.5 (d), 128.2 (d), 128.7 (d), 130.9 (d), 133.3 (s), 136.4 (s), 141.8 (s), 142.1 (s), 147.3 (s), 150.8 (s), 156.1 (s) and 170.8 (s, NCO); *m/z* 560 (M^+, 37%), 470 (24), 469 (21), 268 (16), 176 (11), 175 (20), 174 (100), 159 (11) and 91 (34) (Found: M^+, 560.2315. $C_{35}H_{32}N_2O_7$requires *M*, 560.2311).

(*E*)-3-Benzyl-1,2,3,4,5,6-hexahydro-2-(2-benzyloxy-3-methyl-4,5-methylenedioxybenzylidene)-9-methoxy-8-methyl-1,5-imino-3-benzazocin-4-one 30e. Colourless amorphous powder (164.3 mg, 71.7% yield); ν_{max}($CHCl_3$)/cm^{-1} 3330, 1670 and 1640; δ_H($CDCl_3$) 1.25 (1 H, br s, NH), 2.14 and 2.18 (each 3 H, s, CH_3), 2.95 (1 H, dd, *J* 16.2 and 1.0, 6-Hβ), 3.14 (1 H, dd, *J* 16.2 and 5.9, 6-Hα), 3.48 (3 H, s, OCH_3), 3.89 (1 H, dd, *J* 5.9, 1.0, 5-H), 4.45 and 4.65 (each 1 H, d, *J* 11.6, OCHAr), 4.81 (1 H, d, *J* 16.2, OCHAr), 4.91 (1 H, s, 1-H), 5.15 (1 H, d, *J* 16.2, NCHAr), 5.53 (1 H, s, C=CH), 5.94 (1 H, s, ArH), 5.99 (2 H, s, OCH_2O), 6.31 (1 H, s, ArH), 6.71 (2 H, d, *J* 6.6), 6.83 (1 H, s, ArH), 7.02–7.10 (3 H, m), 7.26–7.28 (2 H, m) and 7.34–7.38 (3 H, m); δ_C($CDCl_3$) 9.6 (q, $ArCH_3$), 15.9 (q, $ArCH_3$), 32.8 (t, C-6), 44.2 (t, $ArCH_2N$), 50.8 (d, C-1), 54.2 (d, C-5), 55.0 (q, OCH_3), 75.0 (t, OCH_2), 101.2 (t, OCH_2O), 102.2 (d, C=*C*H), 107.1 (d), 108.5 (d), 114.4 (s), 122.2 (s), 124.0 (s), 126.0 (d), 126.4 (d), 126.8 (d), 128.0 (d), 128.2 (d), 128.6 (d), 130.9 (d), 133.3 (s), 136.4 (s), 137.3 (s), 142.3 (s), 143.2 (s), 145.8 (s), 149.5 (s), 156.0 (s) and 171.0 (s, NCO); *m/z* 574 (M^+, 37%), 484 (39), 483 (100), 282 (12), 190 (11), 175 (15), 174 (74) and 91 (29) (Found: M^+, 574.2466. $C_{36}H_{34}N_2O_5$ requires *M*, 574.2468).

(*Z*)-3-Benzyl-1,2,3,4,5,6-hexahydro-2-(2-benzyloxy-4,5-methylenedioxybenzylidene)-9-methoxy-8-methyl-1,5-imino-3-benzazocin-4-one 31

Treatment of (*Z*)-**26d** (32.3 mg, 0.1 mmol) with sodium methoxide (28%, 0.5 cm^3) in dry methanol (2.0 cm^3) as described above gave a residue, which was purified by column chromatography on silica gel with dichloromethane–methanol (100:1) as the eluent to afford the corresponding benzazocine derivative **31** (25.2 mg, 90%) as a solid. Recrystallization of this from ether gave colourless needles, mp 166.5–168 °C; ν_{max}(KBr)/cm^{-1} 3290, 1665, 1635 and 1615; δ_H($CDCl_3$) 1.83 (1 H, br s, NH), 2.17 (3 H, s, CH_3), 2.97 (1 H, dd, *J* 15.8 and 1.7, 6-Hβ), 3.16 (1 H, dd, *J* 15.8 and 5.6, 5-Hα), 3.38 (3 H, s, OCH_3), 3.84 (1 H, dd, *J* 5.6, 1.7, 5-H), 3.92 (1 H, d, *J* 14.8, NCHAr), 4.39 (1 H, s, 1-H), 4.84 and 4.91 (each 1 H, d, *J* 11.0, OCHAr), 5.39 (1 H, d, *J* 14.8, NCHAr), 5.84 (1 H, s, C=CH), 5.97 (2 H, s, OCH_2O), 6.06–6.09 (2 H, m), 6.13 and 6.62 (each 1 H, s, ArH), 6.61–6.68 (2 H, m), 6.71 and 6.82 (each 1 H, s, ArH), 6.89–6.95 (1 H, t like) and 7.35 (5 H, br s); δ_C($CDCl_3$) 16.0 (q, $ArCH_3$), 34.5 (t, C-6), 45.2 (t, $ArCH_2N$), 54.5 (d, C-1), 54.8 (q, OCH_3), 59.2 (d, C-5), 71.3 (t, OCH_2), 95.8 (d), 101.5 (t, OCH_2O), 105.4 (d, C=CH), 108.6 (d), 110.0 (d), 117.3 (s), 124.3 (s), 126.2 (d),

127.2 (d), 127.4 (d), 127.5 (d), 128.1 (d), 128.5 (d), 130.9 (d), 131.7 (s), 136.2 (s), 136.8 (s), 141.3 (s), 147.8 (s), 151.7 (s), 156.0 (s) and 170.2 (s, NCO); *m/z* 560 (M^+, 54%), 470 (35), 469 (98), 268 (17), 175 (21), 174 (100) and 91 (34) (Found: C, 74.69; H, 5.87; N, 4.9. $C_{35}H_{32}N_2O_5$ requires C, 74.98; H, 5.75; N, 5.0%).

General procedure for methylation of (*E*)-3-benzyl-2-arylidene-1,5-imino-3-benzazocin-4-one 30

Formaldehyde (37% wt % solution water, 0.18 cm^3) was added to a stirred solution of the amine **30** (0.2 mmol) in formic acid (0.2 cm^3) at 50 °C. After being stirred for 1 h at 70 °C, the reaction mixture was poured into water (20 cm^3), and extracted with chloroform (3 × 20 cm^3). The combined extracts were washed with 5% aqueous sodium hydrogen carbonate (20 cm^3), dried and concentrated *in vacuo* to give a residue. This was purified by column chromatography on silica gel to give the corresponding *N*-methyl derivative **32**.

(*E*)-3-Benzyl-1,2,3,4,5,6-hexahydro-2-(2-methoxy-3-methyl-4,5-methylenedioxybenzylidene)-7,9,10-trimethoxy-8,11-dimethyl-1,5-imino-3-benzazocin-4-one 32b. Colourless prisms (ethyl acetate–ether) (113.2 mg, 99.0% yield), mp 83–84 °C; ν_{max}(KBr)/cm^{-1} 1655, 1630 and 1615; δ_H($CDCl_3$) 2.12 and 2.20 (each 3 H, s, CH_3), 2.78 (3 H, s, NCH_3), 2.91 and 3.05 (each 3 H, s, OCH_3), 3.16 (1 H, dd, *J* 16.8 and 5.3, 6-Hα), 3.28 (1 H, d, *J* 16.8, 6-Hβ), 3.47 and 3.69 (each 3 H, s, OCH_3), 3.83 (1 H, d, *J* 5.3, 5-H), 4.56 (1 H, d, *J* 16.2, NCHAr), 5.33 (1 H, s, 1-H), 5.68 (1 H, d, *J* 16.2, NCHAr), 5.90 (2 H, s, OCH_2O), 6.13 (1 H, s, C=CH), 6.67–6.69 (2 H, m), 6.81 (1 H, s) and 7.02–7.04 (3 H, m); δ_C($CDCl_3$) 9.0 (q, $ArCH_3$), 9.2 (q, $ArCH_3$), 28.2 (t, C-6), 41.4 (q, NCH_3), 43.1 (t, $ArCH_2N$), 52.2 (d, C-1), 59.0, 59.6, 59.8 and 60.0 (each q, OCH_3), 60.5 (d, C-5), 101.0 (t, OCH_2O), 105.1 (d, C=CH), 109.0 (d), 113.4 (s), 122.0 (s), 122.9 (d), 124.4 (s), 126.1 (d), 126.5 (d), 128.3 (d), 134.4 (s), 136.8 (s), 142.4 (s), 145.3 (s), 146.7 (s), 149.9 (s), 152.0 (s), 152.4 (s) and 169.8 (s, NCO); *m/z* 572 (M^+, 57%), 249 (24), 248 (100) and 218 (21) (Found: C, 68.82; H, 6.61; N, 4.68. $C_{33}H_{36}N_2O_7$ requires C, 69.21; H, 6.34; N, 4.89%).

(*E*)-3-Benzyl-1,2,3,4,5,6-hexahydro-2-(2-benzyloxy-3-methyl-4,5-methylenedioxybenzylidene)-7,9,10-trimethoxy-8,11-dimethyl-1,5-imino-3-benzazocin-4-one 32c. Colourless prisms (acetone–ether) (128.4 mg, 99.1% yield), mp 158–159 °C; ν_{max}(KBr)/cm^{-1} 1670, 1640 and 1625; δ_H($CDCl_3$) 2.02 and 2.18 (each 3 H, s, CH_3), 2.77 (3 H, s, NCH_3), 3.17 (3 H, s, OCH_3), 3.20 (2 H, br s, 6-H_2), 3.53 and 3.69 (each 3 H, s, OCH_3), 3.84 (1 H, s like, 5-H), 4.37 and 4.40 (each 1 H, d, *J* 11.9, OCHAr), 4.88 and 4.99 (each 1 H, d, *J* 16.2, NCHAr), 5.40 (1 H, s, 1-H), 5.93 (2 H, s, OCH_2O), 6.21 (1 H, s, C=CH), 6.71–6.74 (2 H, m), 6.87 (1 H, s), 6.96–6.98 (3 H, m), 7.11–7.14 (2 H, m) and 7.26–7.33 (3 H, m); δ_C($CDCl_3$) 9.3 (q, $ArCH_3$), 9.5 (q, $ArCH_3$), 27.9 (t, C-6), 41.4 (q, NCH_3), 44.6 (t, $ArCH_2N$), 52.2 (d, C-1), 59.3, 60.0 and 60.2 (each q, OCH_3), 60.5 (d, C-5), 74.6 (t, OCH_2) 101.0 (t, OCH_2O), 105.4 (d, C=CH), 108.6 (d), 113.9 (s), 122.2 (s), 123.1 (s), 124.7 (s), 125.9 (d), 126.3 (s), 126.6 (d), 127.4 (d), 127.7 (d), 128.3 (d), 135.7 (s), 136.8 (s), 138.0 (s), 142.6 (s), 145.4 (s), 146.8 (s), 150.1 (s), 151.3 (s), 152.6 (s) and 169.8 (s, NCO); *m/z* 648 (M^+, 27%), 558 (37), 557 (86), 249 (39), 248 (100) and 218 (18) (Found: C, 72.07; H, 6.31; N, 4.26. $C_{39}H_{40}N_2O_7$ requires C, 72.2; H, 6.22; N, 4.26%).

(*E*)-3-Benzyl-1,2,3,4,5,6-hexahydro-2-(2-benzyloxy-4,5-methylenedioxybenzylidene)-9-methoxy-8,11-dimethyl-1,5-imino-3-benzazocin-4-one 32d. Colourless prisms (ethyl acetate–ether) (101.1 mg, 88.0% yield), mp 141.5–143 °C; ν_{max}(KBr)/cm^{-1} 1660 and 1630; δ_H($CDCl_3$) 2.16 (3 H, s, CH_3), 2.60 (3 H, s, NCH_3), 2.97 (1 H, d, *J* 16.2, 6-Hβ), 3.25 (1 H, dd, *J* 16.2 and 6.3, 6-Hα), 3.50 (3 H, s, OCH_3), 3.78 (1 H, d, *J* 6.3, 5-H), 4.84 (3 H, s, OCH_2Ar and 1-H), 4.99 (2 H, s, NCH_2Ar), 5.82 (1 H, s, C=CH), 5.93 (2 H, diffuse s, OCH_2O), 6.11, 6.57 and 6.63 (each 1 H, s, ArH), 6.81–6.84 (2 H, m), 6.86 (1 H, s, ArH), 7.00–7.11 (3 H, m), 7.17–7.20 (2 H, m) and 7.28–7.33 (3 H, m); δ_C($CDCl_3$) 15.9 (q, $ArCH_3$), 31.4 (t, C-6), 41.5 (q, NCH_3), 44.8 (t, $ArCH_2N$), 55.0 (q, OCH_3), 56.6 (d, C-1), 61.0 (d, C-5), 71.6 (t, OCH_2), 97.4 (d), 101.4 (t, OCH_2O), 106.6 (d, C=CH), 108.5 (d), 110.3 (d), 118.3 (s), 123.4 (s), 126.1 (s), 126.3 (d), 126.6 (d), 127.2 (d), 127.9 (d), 128.3 (d), 128.5 (d), 130.5 (d), 133.3 (s), 136.7 (s), 138.9 (s), 141.5 (s), 147.3 (s), 151.5 (s), 156.1 (s) and 169.9 (s, NCO); *m/z* 574 (M^+, 30%), 484 (10), 483 (29), 189 (25) and 188 (100) (Found: C, 75.0; H, 6.08; N, 4.79. $C_{36}H_{34}N_2O_5$ requires C, 75.24; H, 5.96; N, 4.88%).

(*E*)-3-Benzyl-1,2,3,4,5,6-hexahydro-2-(2-benzyloxy-3-methyl-4,5-methylenedioxybenzylidene)-9-methoxy-8,11-dimethyl-1,5-imino-3-benzazocin-4-one 32e. Colourless amorphous powder (101.5 mg, 86.3% yield); ν_{max}($CHCl_3$)/cm^{-1} 1670 and 1630; δ_H($CDCl_3$) 2.08 and 2.15 (each 3 H, s, CH_3), 2.57 (3 H, s, NCH_3), 2.95 (1 H, d, *J* 16.2, 6-Hβ), 3.24 (1 H, dd, *J* 16.2 and 6.3, 6-Hα), 3.54 (3 H, s, OCH_3), 3.79 (1 H, d, *J* 6.3, 5-H), 4.40 and 4.49 (each 1 H, d, *J* 11.2, OCHAr), 4.77 (1 H, s, 1-H), 4.83 and 5.06 (each 1 H, d, *J* 16.2, NCHAr), 5.77 (1 H, s, C=CH), 5.91 and 5.94 (each 1 H, d, *J* 1.0, OCHO), 6.13 and 6.44 (each 1 H, s, ArH), 6.80–6.85 (2 H, m), 6.86 (1 H, s, ArH), 7.05–7.08 (3 H, m), 7.11–7.15 (2 H, m) and 7.24–7.30 (3 H, m); δ_C($CDCl_3$) 9.7 (q, $ArCH_3$), 15.9 (q, $ArCH_3$), 31.1 (t, C-6), 44.4 (q, NCH_3), 44.7 (t, $ArCH_2N$), 55.1 (q, OCH_3), 56.7 (d, C-1), 60.9 (d, C-5), 74.8 (t, OCH_2), 101.2 (t, OCH_2O), 105.9 (d, C=*C*H), 107.4 (d), 108.8 (d), 114.3 (s), 121.9 (s), 123.3 (s), 126.1 (s), 126.2 (d), 126.8 (d), 127.8 (d), 128.2 (d), 128.4 (d), 130.6 (d), 133.1 (s), 136.7 (s), 137.2 (s), 139.7 (s), 142.9 (s), 145.9 (s), 150.2 (s), 156.1 (s) and 170.1 (s, NCO); *m/z* 588 (M^+, 22%), 498 (18), 497 (44), 189 (24), 188 (100) and 91 (10) (Found: M^+, 588.2628. $C_{37}H_{36}N_2O_5$ requires *M*, 588.2624).

6-Benzyloxy-3,4-methylenedioxybenzaldehyde 34

A solution of sesamol **4** (1.1 g, 8 mmol) and hexamethylenetetraamine (11.22 g, 80 mmol) in trifluoroacetic acid (180 cm^3) was heated under reflux for 4 h after which it was diluted with water (400 cm^3), and extracted with dichloromethane (3 × 200 cm^3). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (200 cm^3), dried and concentrated *in vacuo* to give a solid. Recrystallization of this from ethanol gave 6-hydroxy-3,4-methylenedioxybenzaldehyde **33** (740 mg, 56%) as colourless needles, mp 125–126 °C (lit.,[22] 125–126 °C); ν_{max}(KBr)/cm^{-1} 3490, 1650 and 1620; δ_H($CDCl_3$) 5.92 (2 H, s, OCH_2O), 6.34 (1 H, s, 2-H), 6.73 (1 H, s, 5-H), 9.46 (1 H, s, CHO) and 11.53 (1 H, s, OH); *m/z* 166 (M^+, 100%), 107 (14), 79 (11), 53 (16) and 52 (10) (Found: C, 57.44; H, 3.66. $C_8H_6O_4$ requires C, 57.83; H, 3.64%). Sodium hydride (60% oil dispersion, washed with dry hexane three times; 288 mg, 12 mmol) was added to a stirred solution of the phenol **33** (1.66 g, 10 mmol) in dry DMF (12 cm^3), and the resulting solution was stirred at 0 °C for 30 min. After this, benzyl bromide (1.33 cm^3, 11.2 mmol) was added to the reaction mixture which was then stirred at 0 °C for 1 h. After this it was diluted with water (50 cm^3), and extracted with ether (3 × 50 cm^3) The combined extracts were washed with water, dried, and concentrated *in vacuo* to give a solid (3.24 g), recrystallization of which from ethanol gave the title compound **34** (2.26 g, 88%) as colourless needles, mp 97–98 °C; ν_{max}(KBr)/cm^- 1670 and 1620; δ_H($CDCl_3$) 5.01 (2 H, s, OCH_2Ar), 5.87 (2 H, s, OCH_2O), 6.47 (1 H, s, 2-H), 7.13 (1 H, s, 5-H), 7.27 (5 H, s) and 10.14 (1 H, s, CHO); *m/z* 256 (M^+, 18%) and 91 (100) (Found: C, 70.32; H, 4.73. $C_{15}H_{12}O_4$ requires C, 70.3; H, 4.72%).

(*Z*)-4-Benzyl-1-isopropyloxycarbonyl-6-(4-methoxy-3-methylbenzyl)-3-(2-benzyloxy-4,5-methylenedioxybenzylidene)piperazine-2,5-dione 14d

This compound was prepared by the four-step sequence described above but using the benzaldehyde **34** (2.56 g, 10 mmol) and the acetate **35**[13] (3.32 g, 10 mmol).

(*Z*)-1-Acetyl-6-(4-methoxy-3-methylbenzyl)-3-(2-benzyloxy-4,5-methylenedioxybenzylidene)piperazine-2,5-dione 11d. Pale yellow needles (4.12 g, 78%), mp 148–149 °C (ethyl acetate); ν_{max}(KBr)/cm^{-1} 3220, 1695 and 1615; δ_H($CDCl_3$) 1.98 (3 H, s, CH_3), 2.61 (3 H, s, $COCH_3$), 3.07 (1 H, dd, *J* 14.2 and 4, 6-CHAr), 3.14 (1 H, dd, *J* 14.2 and 4, 6-CHAr), 3.71 (3 H, s, OCH_3), 4.94 and 5.05 (each 1 H, d, *J* 11.6, OCHAr), 5.27 (1 H, t, *J* 4, 6-H), 5.97 and 5.98 (each 1 H, d, *J* 1.3, OCHO), 6.36, 6.45 and 6.55 (each 1 H, s), 6.57 (1 H, d, *J* 8), 6.76–6.78 (2 H, m), 7.31–7.37 (5 H, m, 5 × ArH) and 8.58 (1 H, s, NH); *m/z* 528 (M^+, 31%), 437 (14), 396 (12), 395 (47), 225 (16), 190 (28), 178 (23), 176 (11), 175 (13), 135 (100), 91 (35) and 43 (13) (Found: C, 68.2; H, 5.32; N, 5.22. $C_{30}H_{28}N_2O_7$ requires C, 68.17; H, 5.34; N, 5.3%).

(*Z*)-1-Acetyl-4-benzyl-6-(4-methoxy-3-methylbenzyl)-3-(2-benzyloxy-4,5-methylenedioxybenzylidene)piperazine-2,5-dione 12d. Pale yellow needles (4.82 g, 100%), mp 196–197 °C (ethyl acetate); ν_{max}(KBr)/cm^{-1} 1700 and 1620; δ_H($CDCl_3$) 2.11 (3 H, s, CH_3), 2.47 (3 H, s, $COCH_3$), 2.97 (1 H, dd, *J* 13.9 and 6.6, 6-CHAr), 3.06 (1 H, dd, *J* 13.9 and 6.9, 6-CHAr), 3.66 (3 H, s, OCH_3), 4.09 (1 H, d, *J* 14.8, NCHAr), 5.06 (2 H, s, OCH_2Ar), 5.27 (1 H, d, *J* 14.6, NCHAr), 5.42 (1 H, dd, *J* 6.9 and 6.6, 6-H), 6.00 (2 H, s, OCH_2O), 6.55 and 6.62 (each 1 H, s), 6.65 (1 H, d, *J* 8), 6.89–6.94 (4 H, m), 7.15–7.19 (3 H, m), 7.26 (1 H, s) and 7.28–7.39 (5 H, m); *m/z* 618 (M^+, 95%), 528 (11), 527 (27), 486 (32), 485 (100), 295 (13), 294 (17), 268 (36), 251 (15), 190 (15), 135 (95) and 91 (79) (Found: C, 71.68; H, 5.6; N, 4.88. $C_{37}H_{34}N_2O_7$ requires C, 71.83; H, 5.54; N, 4.53%).

(*Z*)-4-Benzyl-6-(4-methoxy-3-methylbenzyl)-3-(2-benzyloxy-4,5-methylenedioxybenzylidene)piperazine-2,5-dione 13d. Pale yellow amorphous powder (3.73 g, 83%); ν_{max}($CHCl_3$)/cm^{-1} 3420, 1695 and 1630; δ_H($CDCl_3$) 2.16 (3 H, s, CH_3), 2.73 (1 H, dd, *J* 13.9 and 9.6, 6-CHAr), 3.06 (1 H, dd, *J* 13.9 and 3.6, 6-CHAr), 3.74 (3 H, s, OCH_3), 3.95 (1 H, dd, *J* 9.6 and 3.6, 6-H), 4.61 and 4.76 (each 1 H, d, *J* 14.9, NCHAr), 4.98 (2 H, s, OCH_2Ar), 5.97 (2 H, s, OCH_2O), 6.03 (1 H, s, NH), 6.56 and 6.57 (each 1 H, s), 6.72 (1 H, d, *J* 8), 6.92 (1 H, s), 6.93–6.96 (2 H, m), 7.14 (1 H, s), 7.16–7.20 (3 H, m), 7.25 (1 H, s) and 7.30–7.37 (5 H, m); *m/z* 576 (M^+, 51%), 485 (59), 469 (14), 457 (11), 333 (16), 268 (23), 251 (11), 190 (15), 176 (18), 135 (85) and 91 (100) (Found: M^+, 576.2260. $C_{35}H_{32}N_2O_6$ requires *M*, 576.2255).

(*Z*)-4-Benzyl-1-isopropyloxycarbonyl-6-(4-methoxy-3-methylbenzyl)-3-(2-benzyloxy-4,5-methylenedioxybenzylidene)-piperazine-2,5-dione 14d. Pale yellow prisms (3.86 g, 90%); ν_{max}(KBr)/cm^{-1} 1775, 1730, 1700 and 1620; δ_H($CDCl_3$) 1.13 and 1.22 (each 3 H, d, *J* 6.3, $CHCH_3$), 2.12 (3 H, s, CH_3), 2.95 (1 H, dd, *J* 14.5 and 6.3, 6-CHAr), 3.03 (1 H, dd, *J* 14.5 and 7.9, 6-CHAr), 3.70 (3 H, s, OCH_3), 4.11 (1 H, d, *J* 14.9, NCHAr), 4.91 (1 H, sept, *J* 6.3, OCH), 5.03 (2 H, s, OCH_2Ar), 5.07 (1 H, dd, *J* 7.9 and 6.3, 6-H), 5.22 (1 H, d, *J* 14.9, NCHAr), 5.99 (2 H, s, OCH_2O), 6.56 and 6.62 (each 1 H, s), 6.68 (1 H, d, *J* 8), 6.91–6.97 (4 H, m), 7.16–7.18 (3 H, m), 7.28–7.39 (5 H, m) and 7.41 (1 H, s); *m/z* 662 (M^+, 36%), 486 (17), 485 (53), 295 (11), 294 (16), 268 (28), 251 (15), 190 (13), 176 (12), 136 (11), 135 (99), 91 (100), 44 (11) and 43 (19) (Found: C, 70.33; H, 5.77; N, 4.13. $C_{39}H_{38}N_2O_8 \cdot 1/10H_2O$ requires C, 70.49; H, 5.79; N, 4.22%).

(*Z*)-4-Benzyl-1-isopropyloxycarbonyl-6-(4-methoxy-3-methylbenzyl)-3-(2-benzyloxy-3-methyl-4,5-methylenedioxybenzylidene)piperazine-2,5-dione 14e

This compound was prepared by the four-step sequence described above but using the benzaldehyde **9c** (6.75 g, 25 mmol) and the acetate **35** (8.30 g, 25 mmol).

(*Z*)-1-Acetyl-6-(4-methoxy-3-methylbenzyl)-3-(2-benzyloxy-3-methyl-4,5-methylenedioxybenzylidene)piperazine-2,5-dione 11e. Pale yellow needles (10.53 g, 78%), mp 175–176 °C (ethyl acetate); ν_{max}(KBr)/cm^{-1} 3200, 1710, 1690, 1660 and 1620; δ_H($CDCl_3$), 1.92 and 2.07 (each 3 H, s, CH_3), 2.62 (3 H, s, $COCH_3$), 3.04 (1 H, dd, *J* 14.2 and 5, 6-CHAr), 3.12 (1 H, dd, *J* 14.2 and 3.6, 6-CHAr), 3.72 (3 H, s, OCH_3), 4.57 and 4.61 (each 1 H, d, *J* 11.2, OCHAr), 5.25 (1 H, dd, *J* 5 and 3.6, 6-H), 6.01 (2 H, s, OCH_2O), 6.22 and 6.32 (each 1 H, s), 6.53 (1 H, d, *J* 8), 6.72–6.74 (2 H, m), 7.21–7.33 (5 H, m) and 8.57 (1 H, s, NH); *m/z* 542 (M^+, 38%), 483 (10), 451 (31), 410 (19), 409 (74), 309 (17), 225 (10), 218 (12), 192 (30), 190 (31), 175 (13), 136 (11), 135 (100) and 91 (20) (Found: C, 68.48; H, 5.69; N, 5.06. $C_{31}H_{30}N_2O_7$ requires C, 68.62; H, 5.57; N, 5.16%).

(*Z*)-1-Acetyl-4-benzyl-6-(4-methoxy-3-methylbenzyl)-3-(2-benzyloxy-3-methyl-4,5-methylenedioxybenzylidene)piperazine-2,5-dione 12e. Pale yellow needles (12.32 g, 100%), mp 159–160 °C (ethyl acetate); ν_{max}(KBr)/cm^{-1} 1720, 1705, 1635 and 1620; δ_H($CDCl_3$) 2.09 and 2.15 (each 3 H, s, CH_3), 2.54 (3 H, s, $COCH_3$), 3.07 (1 H, dd, *J* 14.2 and 6.6, 6-CHAr), 3.12 (1 H, dd, *J* 14.2 and 6.6, 6-CHAr), 3.65 (3 H, s, OCH_3), 4.23 (1 H, d, *J* 15.1, NCHAr), 4.31 and 4.44 (each 1 H, d, *J* 11.0, OCHAr), 5.39 (1 H, d, *J* 15.0, NCHAr), 5.48 (1 H, t, *J* 6.6, 6-H), 6.04 and 6.07 (each 1 H, d, *J* 1.3, OCHO), 6.51 (1 H, s), 6.65 (1 H, d, *J* 8), 6.88–6.99 (4 H, m), 7.14–7.21 (3 H, m), 7.29 (1 H, s) and 7.30-7.39 (5 H, m); *m/z* 632 (M^+, 47%), 542 (25), 541 (65), 500 (34), 499 (100), 309 (12), 308 (18), 282 (28), 265 (12), 190 (17), 135 (75) and 91 (59) (Found: C, 72.05; H, 5.83; N, 4.39. $C_{38}H_{36}N_2O_7$ requires C, 72.13; H, 5.74; N, 4.43%).

(*Z*)-4-Benzyl-6-(4-methoxy-3-methylbenzyl)-3-(2-benzyloxy-3-methyl-4,5-methylenedioxybenzylidene)piperazine-2,5-dione 13e. Pale yellow amorphous powder (11.51 g, 95%); ν_{max}-($CHCl_3$)/cm^{-1} 3420, 1695 and 1630; δ_H($CDCl_3$) 2.15 and 2.16 (each 3 H, s, CH_3), 2.82 (1 H, dd, *J* 13.9 and 9.2, 6-CHAr), 3.18 (1 H, dd, *J* 13.9 and 4, 6-CHAr), 3.74 (3 H, s, OCH_3), 4.02 (1 H, dd, *J* 9.2 and 4, 6-H), 4.36 and 4.41 (each 1 H, d, *J* 11.2, OCHAr), 4.78 and 4.88 (each 1 H, d, *J* 15.5, NCHAr), 6.02 and 6.03 (each 1 H, d, *J* 1.3, OCHO), 6.09 (1 H, s, NH), 6.44 (1 H, s), 6.72 (1 H, d, *J* 8), 6.90–6.97 (4 H, m), 7.09–7.17 (3 H, m), 7.19 (1 H, s) and 7.27–7.39 (5 H, m); *m/z* 590 (M^+, 40%), 500 (36), 499 (99), 483 (27), 471 (25), 347 (21), 282 (25), 281 (18), 190 (39), 135 (97) and 91 (10) (Found: M^+, 590.2411. $C_{36}H_{34}N_2O_6$ requires *M*, 590.2417).

(*Z*)-4-Benzyl-1-isopropyloxycarbonyl-6-(4-methoxy-3-methylbenzyl)-3-(2-benzyloxy-3-methyl-4,5-methylenedioxy-benzylidene)piperazine-2,5-dione 14e. Pale yellow prisms (11.46 g, 87%); ν_{max}(KBr)/cm^{-1} 1780, 1750, 1690 and 1630; δ_H($CDCl_3$) 1.19 and 1.29 (each 3 H, d, *J* 6.3, $CHCH_3$), 2.12 and 2.14 (each 3 H, s, CH_3), 3.09 (1 H, dd, *J* 13.9 and 7.3, 6-CHAr), 3.16 (1 H, dd, *J* 13.9 and 6.6, 6-CHAr), 3.69 (3 H, s, OCH_3), 4.26 (1 H, d, *J* 15.2, NCHAr), 4.30 and 4.40 (each 1 H, d, *J* 10.6, OCHAr), 4.98 (1 H, sept, *J* 6.3, OCH), 5.15 (1 H, dd, *J* 7.3 and 6.6, 6-H), 5.36 (1 H, d, *J* 15.2, NCHAr), 6.03, 6.05 (each 1 H, d, *J* 1.0, OCHO), 6.52 (1 H, s), 6.69 (1 H, d, *J* 8), 6.92–6.95 (4 H, m), 7.12–7.20 (3 H, m), 7.27–7.39 (5 H, m) and 7.44 (1 H, s); *m/z* 676 (M^+, 57%), 586 (32), 570 (13), 569 (37), 558 (11), 557 (30), 500 (28), 499 (81), 471 (14), 347 (17), 309 (12), 308 (12), 282 (29), 265 (18), 190 (22), 136 (10), 135 (100), 91 (78) and 43 (14) (Found: C, 70.80; H, 6.12; N, 4.03. $C_{40}H_{40}N_2O_8$ requires C, 70.99; H, 5.96; N, 4.14%).

Acknowledgements

We are grateful to Professor Kenneth L. Rinehart and Dr Ryuichi Sakai of the University of Illinois who kindly provided us with a preprint of their work and offered helpful comments. We also thank Professor Tohru Fukuyama of Tokyo University for useful suggestions during this work. We thank Misses S. Yoshioka and T. Koseki in the Analytical Center of our college for the NMR and MS data measurements and microanalytical data.

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Paper 6/03292C
Received 10*th May* 1996
Accepted 6*th September* 1996