# Synthesis of a 6-aryloxymethyl-5-hydroxy-2,3,4,5-tetrahydro-[1H]-2-benzazepin-4-one: a muscarinic (M<sub>3</sub>) antagonist<sup>†</sup>

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A synthesis of the racemic 6-aryloxymethyl-5-hydroxy-2,3,4,5-[1*H*]-2-tetrahydrobenzazepin-4-one **2**, for evaluation as a muscarinic ( $M_3$ ) antagonist, is described. 2-[2-*tert*-Butyldimethylsilyloxymethyl-6-(2,6-dimethoxyphenoxymethyl)phenyl]propan-2-ol **10** was prepared from 2,6-dimethyl-1bromobenzene **5** and taken through to *N*-[3-(2,6-dimethoxyphenoxymethyl)-2-(propen-2-yl)phenyl]methyl-*N*-prop-2-enyl 2-nitrobenzene sulfonamide **4**. However, attempts to cyclise this diene by alkene metathesis were unsuccessful, the open-chain alkene **15** being the only product isolated in yields of up to 70%. In a second approach to the 6-aryloxymethyl-5-hydroxytetrahydrobenzazepin-4-one, methyl (*Z*)-3-[2-(1-*tert*-butyldimethylsilyloxymethyl)-6-(1,6-dimethoxyphenoxymethyl)phenyl]but-2-enoate **24** was converted into (*Z*)-3-[2-hydroxymethyl-6-(2,6-dimethoxyphenoxymethyl)phenyl]but-2-enoid 2-nitrobenzene sulfonamide **17** which was cyclised under Mitsunobu conditions to the corresponding 2,3-dihydro-[1*H*]-2-benzazepine **3**. The structure of this was confirmed by an X-ray crystal structure of its 2-(4-bromophenylsulfonyl) analogue **28**, and functional group modification including hydroxylation, attachment of the requisite side-chain at C(2) and further oxidation gave the target compound **2** which was assayed for muscarinic ( $M_3$ ) activity.

### Introduction

In the preceding paper,<sup>1</sup> the synthesis of a series of 5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-ones **1** and their activities as selective muscarinic ( $M_3$ ) antagonists<sup>2</sup> are reported. Further modelling studies<sup>3</sup> based on *a*-helices of the bacteriorhodopsin receptor structure<sup>4</sup> using *ab initio* methods, suggested that the incorporation of a 6-aryloxymethyl substituent would lead to an improvement in the selectivity of these compounds towards the  $M_3$  receptor by providing two points of contact with the moiety at position 151 (Ala,  $M_1$ ,  $M_3$ ,  $M_5$ ; Val  $M_2$ ,  $M_4$ ). We now describe a synthesis of the racemic 6-aryloxymethyl-5-hydroxy-2,3,4,5-tetrahydro-2-benzazepin-2-one **2** together with aspects of its biological activity.

During the syntheses of the tetrahydro-[1H]-2-benzazepin-4-ones 1,<sup>1</sup> ring-closing metathesis<sup>5</sup> had been used to prepare the seven-membered rings. As applied to a synthesis of the target compound 1, this would entail metathesis of the diene 4 to give the 1,2-dihydro-[1H]-2-benzazepine 3. The preparation of 1,2-dihydro-[1H]-2-benzazepines by ring-closing metathesis is known<sup>1,6,7</sup> although an attempt to prepare a 5-phenyl-6-prop-2-yloxy substituted derivative was unsuccessful.<sup>6</sup> Nevertheless, if the dihydrobenzazepine 3 were available, hydroxylation and functional group modification would give the required hydroxybenzazepinone 2. The diene 4 was therefore synthesized but attempted ring-closing metathesis gave the open-chain alkene 15, not the required 1,2-dihydrobenzazepine 3, and so an alternative synthesis had to be developed with formation of the 2,3-dihydro-[1H]-2-benzazepine **3** being achieved using a Mitsunobu reaction.<sup>8</sup>



### Discussion

### An approach to the 6-aryloxymethyl-5-hydroxytetrahydrobenzazepin-4-one 2 using metathesis

The synthesis of the metathesis precursor 4 is outlined in Scheme 1. Free-radical bromination of 1-bromo-2,6-dimethylbenzene 5 gave the tribromide  $6^{\circ}$  which with 2,6-dimethoxyphenol under basic conditions gave the ether 7. Hydrolysis then gave the alcohol 8which was converted into the diol 9 by halogen-metal exchange

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Scheme 1 Reagents and conditions: i, NBS, AIBN (trace), CCl<sub>4</sub> (54%); ii, 2,6-dimethoxyphenol, NaH, THF, 80 °C, 16 h (51%); iii,  $K_2CO_3$ , water-dioxane (50 : 50), reflux, 16 h (99%); iv, *n*-BuLi, THF, -78 °C, 30 min, then propanone, -78 °C, 1 h (75%); v, *t*-BuMe<sub>2</sub>SiCl, imid., CH<sub>2</sub>Cl<sub>2</sub> (99%); vi, CH<sub>3</sub>SO<sub>2</sub>Cl, Et<sub>3</sub>N, DMAP, rt, 16 h (66%); vii, *n*-Bu<sub>4</sub>NF, THF, rt, 1 h (86%); viii, (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub> (87%); ix, prop-2-enylamine, CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h then NaBH<sub>4</sub>, MeOH, 0 °C, 1 h (90%); x, 2-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>Cl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h (92%).

using *n*-butyllithium followed by the addition of propanone. Following selective protection of the primary alcohol, dehydration of the tertiary benzylic alcohol was effected using mesyl chloride and triethylamine to give the alkene **11**. Desilylation gave the alcohol **12** which on oxidation gave the aldehyde **13**. Finally, reductive amination using prop-2-enylamine gave the amine **14** which was converted into its 2-nitrophenylsulfonamide (nosyl) derivative **4**.<sup>10</sup>

Interestingly, the <sup>1</sup>H NMR spectra of the styrene derivatives 4 and 11–14 indicated that these compounds were chiral since their benzylic methylene groups appeared as pairs of doublets characteristic of diastereotopic protons. Presumably there is hindered rotation about the aryl carbon–vinyl carbon bond due to the bulky *ortho*-substituents.<sup>6</sup>

However, in contrast to cyclisations of analogous substrates which lacked the 2,6-dimethoxyphenoxymethyl group,<sup>1</sup> all attempts to convert the diene **4** into the 2,3-dihydro-[1*H*]-2benzazepine **3** were unsuccessful. Only an open-chain alkene, assumed to be the (*E*)-isomer **15**, was isolated in up to 70% yield using the Grubbs' II catalyst,<sup>11</sup> even under vigorous conditions. Denosylation of the alkene **15** gave the free amine **16** which appeared to be predominantly the (*E*)-geometrical isomer perhaps containing just a small amount, *ca*. 5%, of its (*Z*)-diastereoisomer. The methylene groups of the trienes **15** and **16** also appeared as **AB**-systems characteristic of diastereotopic hydrogens, although the *syn*- and *anti*-atropisomers were not distinguished. It would appear that ring-closing metathesis is unfavourable in this system.<sup>6</sup> Perhaps the 2,6-dimethoxyphenoxymethyl group forces the isopropenyl group out of the plane of the benzene ring so disfavouring the conformation required for ring-closing metathesis to occur.

### Synthesis of the 6-aryloxymethyl-5-hydroxy-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one 2 using a Mitsunobu cyclisation

It was decided that an irreversible ring-closing procedure would have to be used to assemble the seven-membered ring in the 2,3-dihydro-[1H]-2-benzazepine **3**. Cyclisation of the 2-nitrobenzene sulfonamide **17** *via* a Mitsunobu reaction was considered an alternative approach to the dihydrobenzazepine **3**.<sup>8</sup> The alkyne **18** was identified as a suitable precursor of the sulfonamide **17** since the alkyne should be accessible despite the steric hindrance of the two neighbouring substituents.

Attempts to effect a Sonogashira coupling<sup>12</sup> of the *tert*butyldimethylsilyl derivative of the bromobenzene **8** with trimethylsilylethyne or similar alkynes were unsuccessful, perhaps because of steric hindrance due to the two *ortho* substituents. Therefore, a less direct synthesis of alkyne **18** had to be investigated, see Scheme 2. Reaction of the aryllithium, prepared from the bromide **8** by halogen–metal exchange using *n*-butyllithium, with ethanal, gave the diol **19** which was selectively protected to





**Scheme 2** *Reagents and conditions:* i, *n*-BuLi, THF, -78 °C, 30 min, then ethanal, -78 °C, 1 h (81%); ii, *t*-BuMe<sub>2</sub>SiCl, imid., CH<sub>2</sub>Cl<sub>2</sub> (99%); iii, (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub> (81%); iv, LDA, THF, -78 °C, 30 min then (EtO)<sub>2</sub>P(O)Cl, -78 °C to rt, 16 h; v, LDA, THF, -78 °C, 1 h (81% from **21**); vi, *n*-BuLi, THF, -78 °C, 30 min then CICO<sub>2</sub>Me, -78 °C, 30 min (94%); vii, LiCuMe<sub>2</sub> (5 eq.), THF, -78 °C to -50 °C, 20 h (99%); viii, DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C to -40 °C, 1 h (81%); ix, *o*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>NH<sub>2</sub>, DIAD, PPh<sub>3</sub>, THF, rt, 16 h (82%); x, *n*-Bu<sub>4</sub>NF, THF, rt, 1 h (97%); xi, DIAD, PPh<sub>3</sub>, THF, rt, 1 h (99%); xii, PhSH, K<sub>2</sub>CO<sub>3</sub>, MeCN, rt, 16 h (99%); xiii, 4-BrC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>Cl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h (55%).

give the silyl ether 20. Oxidation gave the methyl ketone 21 which was converted to the alkyne 18 by elimination of diethyl phosphate from the enol phosphate 22.<sup>13</sup> The alkyne 18 then gave the (Z)unsaturated ester 24 by methoxycarbonylation followed by the stereoselective addition of a methyl cuprate.<sup>14</sup> Shorter routes to the ester 24 from the ketone 21 were less successful, for example Wittig reactions on the ketone 21 gave recovered starting material, perhaps because of steric hindrance to nucleophilic attack on the carbonyl carbon of the ketone. Reduction of the ester 24 gave the alcohol 25 which was converted into the 2-nitrobenzene sulfonamide 26 via a Mitsunobu reaction. Desilylation then gave the alcohol 17 which was cyclised very efficiently, again using Mitsunobu conditions,<sup>8</sup> to give the required 2,3-dihydro-[1H]-2benzazepine 3, and removal of the 2-nitrobenzenesulfonyl group using thiophenol under basic conditions,<sup>10</sup> gave the parent 2,3dihydro-[1H]-2-benzazepine 27.

The structures of all the intermediates in Scheme 2 were consistent with spectroscopic data and the structure of the 1,2-dihydro-[1H]-2-benzazepine 27 was confirmed by an X-ray crystal structure of its 2-(4-bromophenyl) sulfonyl derivative 28, see Fig. 1.

The <sup>1</sup>H NMR spectra of styrenes **17**, **24–26** again showed that these compounds were chiral, but the ketone **21** and the enol phosphate **22** did not exhibit atropisomerism, their benzylic methylene protons being observed as singlets by <sup>1</sup>H NMR. Interestingly,



Fig. 1 ORTEP projection of the 2,3-dihydro-[1H]-2-benzazepine **28** as determined by X-ray crystallography.

the 6-substituted 1,2-dihydro-[1*H*]-2-benzazepines **3** and **28** also appeared to be chiral since their benzylic methylene groups were observed as pairs of diastereotopic protons by <sup>1</sup>H NMR. This was not observed for the analogous 2,3-dihydrobenzazepines lacking a 6-substituent which had been prepared previously,<sup>1</sup> and may be due to steric hindrance between the 4- and 6-substituents preventing racemisation of the non-planar 2,3-dihydrobenzazepines **3** and **28**, see Fig. 1. In contrast, the methylene protons of the 2unsubstituted 1,2-dihydrobenzazepine **27** appeared as broadened singlets.

Having prepared the dihydrobenzazepine **27**, it was now necessary to oxidise the double-bond and attach the C(2)-side-chain to complete a synthesis of the required 5-hydroxy-2,3,4,5-tetrahydro-[1H]-2-benzazepin-4-one **2**.

*N*-Acylation of the dihydrobenzazepine **27** using the acid **35**<sup>1</sup> gave the amide **29** as a mixture of rotamers which on dihydroxylation using osmium tetraoxide-*N*-methyl morpholine *N*-oxide gave the racemic *cis*-diol **30** (Scheme 3).<sup>15</sup> This diol was isolated as a single diastereoisomer and so either the hydroxylation of the amide **29** had been highly selective for one face of the rigid dihydrobenzazepine or, perhaps more likely, the 6-aryloxymethyl-tetrahydrobenzazepine **30** is more flexible, the 6-aryloxymethyl group no longer preventing ring inversion of the non-planar 2,3,4,5-tetrahydrobenzazepine nucleus at ambient temperature.

Before reduction of the amide, it was decided to remove the *N*-nosyl group. Following this deprotection, reduction of the dihydroxyaminoamide **31** using borane in tetrahydrofuran<sup>16</sup> gave the very polar dihydroxyamine **32**. Following reinstatement of the side-chain *N*-nosyl group, a Swern oxidation of the secondary alcohol **33** gave the hydroxyketone **34**, which, on final deprotection gave the target tetrahydrobenzazepine **2**. The carbonyl peak in the IR spectrum of the tetrahydrobenzazepin-4-one **2** was at 1715 cm<sup>-1</sup> which is consistent with the presence of a saturated ketone and indicative of the assigned structure. However, the methylene protons on C-3, seen at  $\delta$  3.3–3.5, were shielded slightly more than the analogous protons in the simpler tetrahydrobenzazepinones prepared previously and may indicate a conformational preference for the dimethoxyphenyl group to lie over the tetrahydrobenzazepine ring.<sup>1</sup>

The biological activity of the racemic tetrahydrobenzazepine **2** was measured against  $M_3$  receptors from guinea pig ileum and  $\log_{10} K_B$  was found to be 6.3, *i.e.* the potency was slightly less

than that found (6.7) for the analogous compound 1 with 2-(3-phenylmethylamino)propyl and 5-cyclobutyl substituents. The activity of the tetrahydrobenzazepine 2 against  $M_2$  receptors in guinea pig left atria was not measured.

### Summary and conclusions

The work outlined in this paper resulted in the synthesis of the tetrahydrobenzazepinone 2 for evaluation as a selective  $M_3$ muscarinic receptor antagonist. Of note is the chirality observed for the 2,6-bis-oxymethyl-1-alkenyl intermediates, e.g. 11, due to hindered rotation about the phenyl carbon-vinyl carbon bond, and the efficient assembly of the 2,3-dihydro-[1H]-2-benzazepine ring system using a Mitsunobu reaction. The potency of tetrahydrobenzazepinone 2 against M<sub>3</sub> receptors in guinea pig ileum was slightly less than had been observed earlier for simpler compounds and may be due to loss of conformational flexibility when bound to the receptor site.3,4 This derivative also showed membrane sensitisation effects at higher doses suggesting that the 2,6-dimethoxyphenyl substituent in an intrinsically potent compound may have advantages. Further work is underway on the preparation of analogous compounds for evaluation as selective muscarinic (M<sub>3</sub>) antagonists.

### Experimental

#### General

Low resolution mass spectra were recorded on a Micromass Trio 200 spectrometer; high resolution mass spectra were recorded on a Kratos Concept IS spectrometer. Modes of ionisation were electron impact (EI), chemical ionisation (CI) using ammonia, or electrospray in positive or negative mode (ES±). For halogenated compounds, characteristic groups of peaks due to different isotopes were observed. Infrared spectra were recorded on a Genesis



Scheme 3 *Reagents and conditions:* i, TBTU, **35**, EtN<sup>1</sup>Pr<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h (83%); ii, OsO<sub>4</sub>, NMO, propanone–*t*-BuOH–water, rt, 16 h (73%); iii, PhSH, K<sub>2</sub>CO<sub>3</sub>, MeCN, rt 16 h (96%); iv, BH<sub>3</sub>·THF, rt, 16 h then aq. HCl, rt, 5 min; v, 2-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>Cl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h (74% from **31**); vi, (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub> (82%); vii, PhSH, K<sub>2</sub>CO<sub>3</sub>, MeCN, rt, 16 h (97%).

FTIR spectrometer as evaporated films (from deuterochloroform or dichloromethane) on sodium chloride plates. Nuclear magnetic resonance spectra were performed using deuterated chloroform (CDCl<sub>3</sub>) as the solvent unless otherwise stated. Proton nuclear magnetic resonance spectra (<sup>1</sup>H NMR) were recorded on Varian INOVA Unity 500 and 300 (500 and 300 MHz) spectrometers. Residual non-deuterated solvent was used as the internal standard. Coupling constants (*J*) are quoted in Hertz (Hz). Carbon nuclear magnetic resonance spectra (<sup>13</sup>NMR) were recorded on a Varian INOVA Unity 300 (75 MHz) spectrometer.

Flash column chromatography was carried out using Merck silica gel 60H (40–60 nm, 230–300 mesh). Thin layer chromatography (TLC) was carried out using plastic plates coated with Merck HF254/366 silica gel. All reagents and solvents were purified by standard techniques and reactions in non-aqueous solvents were carried out under an atmosphere of nitrogen or argon.

### (*E*)-1,4-Bis-{*N*-(2-nitrophenylsulfonyl)-*N*-[3-(2,6-dimethoxyphenoxymethyl)-2-(propen-2-yl)phenylmethyl]} aminobut-2-ene 15

Grubbs' II catalyst (3 mg, 5 mol%) was added to a degassed solution of the diene 4 (37 mg, 0.007 mmol) in dichloromethane (3.5 cm<sup>3</sup>) and the mixture was heated under reflux for 16 h, then cooled and concentrated under reduced pressure. Chromatography of the residue, using ether-light petroleum (1:2) as eluent, gave the *title compound* **15** (24 mg, 67%) as a dark brown oil;  $v_{max}$ 3075, 1640, 1596, 1544, 1493, 1478, 1372, 1296, 1254, 1163, 1112, 908, 773 and 734 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.94 (2 H, m, ArH), 7.67 (8 H, m, ArH), 7.20 (4 H, m, ArH), 7.03 (2 H, t, J 8.5, ArH), 6.61 (4 H, d, J 8.5, ArH), 5.31 (4 H, m, 2-H, 3-H, 2 × 1"-H), 5.01 and 4.89 (each 2 H, d, J 11, 2 × ArHCH), 4.77 (2 H, m, 2 × 1"-H'), 4.55 and 4.49 (each 2 H, d, J 16.5, 2 × ArHCH), 3.84 (12 H, s, 4 × OCH<sub>3</sub>), 3.82 (4 H, m, 1-H<sub>2</sub>, 4-H<sub>2</sub>) and 2.01 (6 H, s,  $2 \times CH_3$ );  $\delta_C$ (75 MHz, CDCl<sub>3</sub>) 154.13, 148.01, 142.32, 142.21, 137.40, 135.65, 134.15, 133.87, 132.19, 131.58, 131.12, 129.19, 128.94, 127.43, 126.82, 124.46, 124.11, 117.03, 105.60, 72.20, 56.31, 48.45, 48.33 and 25.10; *m*/*z* (ES) 1072 (100%) and 1067 (45). Starting material 4 (28%) was also recovered.

### (*E*)-1,4-Bis-{*N*-[3-(2,6-dimethoxyphenoxymethyl)-2-(propen-2-yl)phenylmethyl]}aminobut-2-ene 16

Thiophenol (22.6 µL, 0.22 mmol) was added to the alkene 15 (86 mg, 0.17 mmol), and K<sub>2</sub>CO<sub>3</sub> (82 mg, 0.59 mmol) in N,Ndimethylformamide (4.25 cm<sup>3</sup>) and the mixture was stirred for 3 h at room temperature. Ethyl acetate (20 cm<sup>3</sup>) and water (20 cm<sup>3</sup>) were added and the aqueous phase was extracted with more ethyl acetate (3  $\times$  20 cm<sup>3</sup>). The organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate-light petroleum  $(75: 25 \rightarrow 100: 0)$  as eluent gave the *title compound* **16** (32 mg, 60%) as an oil (found:  $M^+ - H$ , 677.3590.  $C_{42}H_{49}N_2O_6$  requires M, 677.3585); v<sub>max</sub> 3070, 1640, 1596, 1494, 1478, 1296, 1254, 1216, 1112, 773 and 734 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.67 and 7.37 (each 2 H, dd, J 7.5, 1.5, ArH), 7.31 (2 H, t, J 7.5, ArH), 7.03 (2 H, t, J 8.5, ArH), 6.61 (4 H, d, J 8.5, ArH), 5.76 (2 H, m, 2-H and 3-H), 5.32 (2 H, m,  $2 \times 2''$ -H), 5.05 and 4.93 (each 2 H, d, J 11, 2 × ArHCHO), 4.84 (2 H, m, 2 × 2"-H'), 3.84 (12 H, s, 4 × OCH<sub>3</sub>), 3.82 and 3.74 (each 2 H, d, J 11.5, 2 × ArHCHN), 3.72

(4 H, m, 1-H<sub>2</sub>, 4-H<sub>2</sub>), 2.10 (6 H, s, 2 × CH<sub>3</sub>) and 1.71 (2 H, br. s, 2 × NH);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 154.23, 143.52, 142.35, 137.61, 136.31, 135.31, 130.68, 128.48, 128.30, 127.22, 124.00, 116.36, 105.70, 72.52, 56.35, 50.95, 50.76, 25.55; *m/z* (ES) 696 (M<sup>+</sup> + 18, 100%), 692 (80) and 678 (70).

### 1-[2-(2,6-Dimethoxyphenoxymethyl)-6-(hydroxymethyl)phenyl]ethanol 19

n-Butyllithium (1.6 M in hexanes, 88.04 cm<sup>3</sup>, 140.9 mmol) was added to the bromide 8 (24.54 g, 64.03 mmol, 1 eq) in tetrahydrofuran (320.1 cm<sup>3</sup>) at -78 °C and the solution was stirred for 30 min before acetaldehyde (10.77 cm<sup>3</sup>, 192.1 mmol) was added. After 1 h at -78 °C, saturated methanolic ammonium chloride (40 cm<sup>3</sup>) was added followed by water (300 cm<sup>3</sup>). The mixture was extracted with ether  $(3 \times 340 \text{ cm}^3)$  and the organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ether-light petroleum (60 :  $100 \rightarrow 100$  : 0) as eluent gave the *title compound* **19** (16.50 g, 81%) as a colourless oil (found:  $M^+ + NH_4 - H_2O$ , 318.1698. C<sub>18</sub>H<sub>24</sub>NO<sub>4</sub> requires M, 318.1700); v<sub>max</sub> 3392, 1597, 1478, 1296, 1255, 1111, 774 and 736 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.36 and 7.26 (each 1 H, dd, J 7, 2, ArH), 7.20 (1 H, t, J 7.5, ArH), 7.02 (1 H, t, J 8.5, ArH), 6.60 (2 H, d, J 8.5, ArH), 5.82 (1 H, q, J 6.5, 1-H), 5.18 (1 H, d, J, 11, ArHCH), 5.13 (1 H, d, J 12.5, ArHCH), 5.07 (1 H, d, J 11, ArHCH), 4.58 (1 H, d, J 12.5, ArHCH), 3.82  $(6 \text{ H}, \text{ s}, 2 \times \text{OCH}_3)$ , 3.8 (1 H, br. s, OH) and 1.73 (3 H, d, J 6.5, 2-H<sub>3</sub>); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 153.88, 143.30, 139.78, 136.46, 135.13, 132.02, 131.47, 127.51, 124.28, 105.72, 73.81, 67.64, 64.71, 56.40 and 23.57; *m*/*z* (CI) 319 (M<sup>+</sup> + 1, 6%), 318 (16) and 301 (100).

### 1-[2-(*tert*-Butyldimethylsilyloxymethyl)-6-(2,6dimethoxyphenoxymethyl)phenyl]ethanone 21

tert-Butyldimethylsilyl chloride (8.21 g, 54.46 mmol) was added to the alcohol 19 (16.50 g, 51.86 mmol) and imidazole (7.41 g, 108.9 mmol) in anhydrous dichloromethane (207 cm<sup>3</sup>) at 0 °C and the mixture stirred for 2 h at 0 °C. Saturated aqueous ammonium chloride (250 cm<sup>3</sup>) was added and the mixture was extracted with dichloromethane  $(3 \times 250 \text{ cm}^3)$ . The organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give the silyl ether 20 (23.75 g, ca. 100%) as a pale yellow oil, used without further purification (found:  $M^+ + H$ , 433.2409. C<sub>24</sub>H<sub>37</sub>O<sub>5</sub>Si requires M, 433.2405); v<sub>max</sub> 3468, 1597, 1494, 1478, 1296, 1254, 1215, 1186, 1114, 838, 774 and 733 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.41 and 7.27 (each 1 H, dd, J 7.5, 1.5, ArH), 7.18 (1 H, t, J 7.5, ArH), 6.99 (1 H, t, J 8.5, ArH), 6.56 (2 H, d, J 8.5, ArH), 5.55 (1 H, quin, J 5.5, 1-H), 5.20 and 5.16 (each 1 H, d, J 10.5, ArHCH), 4.97 and 4.85 (each 1 H, d, J 12.5, ArHCH), 4.02 (1 H, d, J 5.5, OH), 3.82 (6 H, s, 2 × OCH<sub>3</sub>), 1.64 (3 H, d, J 6.5, 2-H<sub>3</sub>), 0.94 [9 H, s, OSiC(CH<sub>3</sub>)<sub>3</sub>] and 0.14 and 0.12 (each 3 H, s, OSiCH<sub>3</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 153.97, 142.83, 138.58, 136.47, 134.74, 131.50, 129.33, 126.93, 124.17, 105.49, 73.64, 67.35, 64.01, 56.28, 26.20, 24.26, 18.61, -4.96 and -4.99; m/z (CI) 433 (M<sup>+</sup> + 1, 3%), 415 (50) and 154 (100).

Dimethyl sulfoxide (11.70 cm<sup>3</sup>, 164.8 mmol) in dichloromethane (50 cm<sup>3</sup>) was added to oxalyl chloride (7.19 cm<sup>3</sup>, 82.42 mmol) in dichloromethane (150 cm<sup>3</sup>) at -78 °C and the mixture was stirred for 30 min before the alcohol **20** (23.75 g, 54.95 mmol) in

dichloromethane was added. After a further 30 min, triethylamine (45.91 cm<sup>3</sup>, 329.7 mmol) was added dropwise and the mixture was allowed to warm to 0 °C and then stirred for 30 min. Saturated aqueous ammonium chloride (300 cm<sup>3</sup>) was added and the mixture was extracted with dichloromethane  $(3 \times 300 \text{ cm}^3)$ . The organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ether-light petroleum (10 : 90  $\rightarrow$  30 : 70) as eluent gave the *title* compound 21 (19.15 g, 81%) as a pale yellow oil (found:  $M^+ + H$ , 431.2258. C<sub>24</sub>H<sub>35</sub>O<sub>5</sub>Si requires M, 431.2248); v<sub>max</sub> 1698, 1597, 1494, 1478, 1296, 1255, 1113, 838 and 774 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.56 (1 H, dd, J 5.5, 3, ArH), 7.41–7.39 (2 H, m, ArH), 7.05 (1 H, t, J 8.5, ArH), 6.61 (2 H, d, J 8.5, ArH), 4.90 and 4.72 (each 2 H, s, ArCH<sub>2</sub>), 3.86 (6 H, s, 2 × OCH<sub>3</sub>), 2.74 (3 H, s, 2-H<sub>3</sub>), 0.96 [9 H, s, OSiC(CH<sub>3</sub>)<sub>3</sub>] and 0.13 [6 H, s, OSi(CH<sub>3</sub>)<sub>2</sub>];  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 207.84, 154.09, 141.24, 136.558, 133.04, 129.74, 128.98, 128.61, 127.60, 124.36, 105.37, 72.06, 63.39, 56.19, 33.47, 26.19, 18.68 and -5.13; m/z (CI) 448 (M + 18, 46%), 431 (M<sup>+</sup> + 1, 47) and 299 (100).

### [2-(*tert*-Butyldimethylsilyloxymethyl)-6-(2,6dimethoxyphenoxymethyl)phenyl]ethyne 18

n-Butyllithium (1.6 M in hexanes, 27.01 cm<sup>3</sup>, 43.22 mmol) was added to di-isopropylamine (6.35 cm<sup>3</sup>, 45.28 mmol) in tetrahydrofuran (41 cm<sup>3</sup>) at 0 °C and the mixture was stirred for 30 min then cooled to -78 °C. The ketone 21 (17.71 g, 41.16 mmol) in tetrahydrofuran (37 cm<sup>3</sup>) was added and the mixture was stirred at -78 °C for 1 h before diethyl chlorophosphate (6.45 cm<sup>3</sup>, 45.28 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 16 h before saturated aqueous ammonium chloride (10 cm<sup>3</sup>) then water (100 cm<sup>3</sup>) were added. Following extraction with ether  $(3 \times 100 \text{ cm}^3)$ , the organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give the enol phosphate 22 (23.3 g) as a pale oil, used without further purification (found:  $M^+ + H$ , 567.2539. C<sub>28</sub>H<sub>44</sub>O<sub>8</sub>PSi requires M, 567.2538); v<sub>max</sub> 1650, 1597, 1478, 1295, 1255, 1113, 1032, 999, 838 and 777 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.69 (1 H, d, J 7.5, ArH), 7.59 (1 H, d, J 8, ArH), 7.44 (1 H, dd, J 8, 7.5, ArH), 7.02 (1 H, t, J 8.5, ArH), 6.60 (2 H, d, J 8.5, ArH), 5.47 (1 H, t, J 2, 2-H), 5.15 (2 H, s, ArCH<sub>2</sub>), 4.99 (1 H, t, J 2, 2-H'), 4.89  $(2 \text{ H}, \text{ s}, \text{ArCH}_2), 4.18-3.94 (4 \text{ H}, \text{m}, 2 \times \text{OCH}_2\text{CH}_3), 3.83 (6 \text{ H}, \text{s}, 2 \times \text{OCH}_2\text{CH}_3)$  $2 \times OCH_3$ , 1.27 (6 H, td, J 7, 1,  $2 \times OCH_2CH_3$ ), 0.98 [9 H, s, OSiC(CH<sub>3</sub>)<sub>3</sub>] and 0.14 [6 H, s, OSi(CH<sub>3</sub>)<sub>2</sub>];  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 154.13, 148.83, 148.72, 140.13, 137.36, 136.70, 131.74, 131.66, 129.24, 127.88, 125.89, 124.00, 105.55, 104.08, 72.34, 64.52, 64.44, 62.70, 56.28, 26.23, 18.65, 16.29, 16.17 and -5.03; m/z (CI) 584  $(M^+ + 18, 8\%)$ , 567  $(M^+ + 1, 21)$  and 172 (100).

*n*-Butyllithium (1.6 M in hexanes, 44.80 cm<sup>3</sup>, 71.68 mmol) was added to di-isopropylamine (10.29 cm<sup>3</sup>, 73.43 mmol) in tetrahydrofuran (77 cm<sup>3</sup>) at 0 °C and the solution was stirred for 30 min then cooled to -78 °C. The enol phosphate **22** (23.3 g, 41.16 mmol) in tetrahydrofuran (137 cm<sup>3</sup>) was added and the mixture was stirred at -78 °C for 1 h then saturated methanolic ammonium chloride (10 cm<sup>3</sup>) was added. After extracting with ether (3 × 200 cm<sup>3</sup>), the organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give the *title compound* **18** (13.69 g, 81% from **21**) as a pale yellow oil (found: M<sup>+</sup> + NH<sub>4</sub>, 430.2414. C<sub>24</sub>H<sub>36</sub>NO<sub>4</sub>Si requires M, 430.2408);

 $v_{\rm max}$  3295, 1598, 1478, 1377, 1298, 1256, 1114, 1044, 839 and 776 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.72 and 7.56 (each 1 H, d, J 7.5, ArH), 7.45 (1 H, dd, J 8, 7.5, ArH), 7.04 (1 H, t, J 8.5, ArH), 6.62 (2 H, d, J 8.5, ArH), 5.27 and 4.96 (each 2 H, s, ArCH<sub>2</sub>), 3.85 (6 H, s, 2 × OCH<sub>3</sub>), 3.55 (1 H, s, 2-H), 1.02 [9 H, s, OSiC(CH<sub>3</sub>)<sub>3</sub>] and 0.17 [6 H, s, OSi(CH<sub>3</sub>)<sub>2</sub>];  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 154.09, 143.97, 140.78, 137.50, 128.91, 126.51, 124.90, 124.05, 117.15, 105.62, 87.10, 74.63, 72.97, 63.59, 56.36, 26.24, 18.70 and -5.05; *m/z* (CI) 430 (M<sup>+</sup> + 18, 25%), 413 (M<sup>+</sup> + 1, 4), 172 (55), 155 (53) and 87 (100).

### Methyl 3-[2-(1-*tert*-butyldimethylsilyloxymethyl)-6-(2,6dimethoxyphenoxymethyl)phenyl]prop-2-ynoate 23

n-Butyllithium (1.6 M in hexanes, 22.83 cm<sup>3</sup>, 36.53 mmol) was added to the alkyne 18 (13.69 g, 33.21 mmol) in tetrahydrofuran  $(565 \text{ cm}^3) - 78 \text{ °C}$  and the solution was stirred for 30 min then methyl chloroformate (17.96 cm<sup>3</sup>, 232.5 mmol) was added. After a further 30 min at -78 °C, saturated methanolic ammonium chloride (10 cm<sup>3</sup>) was added and the mixture was allowed to warm to room temperature. Saturated aqueous ammonium chloride (500 cm<sup>3</sup>) was added and the mixture was extracted with ether  $(3 \times 500 \text{ cm}^3)$ . The organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ether-light petroleum (10:  $90 \rightarrow 40$ : 60) as eluent gave the *title compound* 23 (14.72 g, 94%) as a yellow oil (found: M<sup>+</sup> + NH<sub>4</sub>, 488.2469. C<sub>26</sub>H<sub>38</sub>NO<sub>6</sub>Si requires M, 488.2463); δ<sub>max</sub> 2216, 1713, 1597, 1478, 1283, 1254, 1199, 1172, 1111, 838 and 775 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.77 (1 H, d, J 7, ArH), 7.61-7.51 (2 H, m, ArH), 7.04 (1 H, t, J 8.5, ArH), 6.61 (2 H, d, J 8.5, ArH), 5.26 and 4.94 (each 2 H, s, ArCH<sub>2</sub>), 3.87 (3 H, s, CO<sub>2</sub>CH<sub>3</sub>), 3.86 (6 H, s,  $2 \times OCH_3$ ), 1.00 [9 H, s, OSiC(CH<sub>3</sub>)<sub>3</sub>] and 0.17 [6 H, s, OSi(CH<sub>3</sub>)<sub>2</sub>];  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 154.63, 153.99, 145.54, 142.14, 137.12, 130.94, 127.20, 125.52, 124.19, 114.86, 105.44, 89.55, 81.68, 72.54, 63.36, 56.30, 52.98, 26.21, 18.68 and -5.06; m/z (ES) 488 (M<sup>+</sup> + 18, 100%).

### Methyl (*Z*)-3-[2-(1-*tert*-butyldimethylsilyloxymethyl)-6-(2,6-dimethoxyphenoxymethyl)phenyl]but-2-enoate 24

Methyllithium (1.6 M in ether, 19.9 cm<sup>3</sup>, 31.9 mmol) was added to a suspension of copper(I) iodide (3.04 g, 16.00 mmol) in tetrahydrofuran (55 cm<sup>3</sup>) at 0 °C and the mixture was stirred for 30 min. More tetrahydrofuran (108 cm<sup>3</sup>) was added and the mixture was cooled to -78 °C before the alkyne 23 (1.50 g, 3.19 mmol) was added. The mixture was warmed to -50 °C and stirred for 20 h and allowed to warm to room temperature before the addition of saturated methanolic ammonium chloride (10 cm<sup>3</sup>). The reaction was recooled to -78 °C and methanol (7.5 cm<sup>3</sup>) was added followed by aqueous ammonium chloride (60 cm<sup>3</sup>). The reaction mixture was allowed to warm to room temperature then partitioned between saturated aqueous ammonium chloride (100 cm<sup>3</sup>) and ether (100 cm<sup>3</sup>). The aqueous phase was extracted with ether (100 cm<sup>3</sup>) and the combined organic extracts washed with brine, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the title compound 24 (1.55 g, ca. 100%) as a yellow oil (found:  $M^+$  + NH<sub>4</sub>, 504.2772. C<sub>27</sub>H<sub>42</sub>NO<sub>6</sub>Si requires M, 504.2776); v<sub>max</sub> 1728, 1645, 1596, 1477, 1373, 1296, 1254, 1224, 1160, 1113, 834 and 775 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.63 and 7.52 (each 1 H, d, J 7.5, ArH), 7.38 (1 H, t, J 7.5, ArH), 7.04 (1 H, t, J 8.5, ArH), 6.62 (2 H,

Downloaded by University of Massachusetts - Amherst on 13/04/2013 11:03:51. Published on 18 April 2008 on http://pubs.rsc.org | doi:10.1039/B801208C d, J 8.5, ArH), 6.12 (1 H, q, J 1.5, 2-H), 4.95 and 4.77 (each 1 H, d, J 10.5, ArHC*H*), 4.65 and 4.60 (each 1 H, d, J 13, ArHC*H*), 3.85 (6 H, s,  $2 \times OCH_3$ ), 3.31 (3 H, s,  $CO_2CH_3$ ), 2.34 (3 H, d, J 1.5, 4-H<sub>3</sub>), 0.98 [9 H, s, OSiC(CH<sub>3</sub>)<sub>3</sub>] and 0.13 and 0.12 (each 3 H, s, OSiCH<sub>3</sub>);  $\delta_c$  (75 MHz, CDCl<sub>3</sub>) 165.74, 155.60, 154.22, 138.62, 137.39, 136.11, 132.94, 128.76, 127.45, 126.77, 124.06, 119.36, 105.60, 72.47, 63.09, 56.25, 51.24, 27.31, 26.25, 18.68, -4.99 and -5.05; *m*/*z* (CI) 504 (M<sup>+</sup> + 18, 13%), 488 (15), 355 (36) and 333 (100).

### (*Z*)-3-[2-(1-*tert*-Butyldimethylsilyloxymethyl)-6-(2,6-dimethoxyphenoxymethyl)phenyl]but-2-enol 25

Di-isobutylaluminium hydride (1 M in toluene, 8.19 cm<sup>3</sup>, 8.19 mmol) was added to the ester 24 (1.66 g, 3.41 mmol) in dichloromethane (18.5 cm<sup>3</sup>) at -78 °C. The mixture was stirred at -40 °C for 1 h, methanol (3.5 cm<sup>3</sup>) was added, and the mixture was allowed to warm to room temperature and partitioned between aqueous Rochelle salt (30 cm<sup>3</sup>) and ether (30 cm<sup>3</sup>). The aqueous phase was extracted with ether  $(3 \times 30 \text{ cm}^3)$  and the combined organic extracts washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ether-light petroleum (30 :  $70 \rightarrow 50$  : 50) as eluent gave the title compound 25 (1.61 g, 81%) as a pale oil (found:  $M^+ + NH_4$ , 476.2822.  $C_{26}H_{42}NO_5Si$  requires M, 476.2827);  $v_{\text{max}}$  3436, 1597, 1478, 1296, 1254, 1113, 1004, 837 and 773 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.60 and 7.54 (each 1 H, d, J 7.5, ArH), 7.39 (1 H, t, J 7.5, ArH), 7.06 (1 H, t, J 8.5, ArH), 6.63 (2 H, d, J 8.5, ArH), 6.02 (1 H, m, 2-H), 4.94 and 4.75 (each 1 H, d, J 10, ArHCH), 4.65 and 4.61 (each 1 H, d, J 13, ArHCH), 3.87  $(6 \text{ H}, \text{ s}, 2 \times \text{OCH}_3), 3.85 - 3.68 (2 \text{ H}, \text{m}, 1 - \text{H}_2), 3.04 (1 \text{ H}, \text{dd}, J 8.5)$ 5, OH), 2.03 (3 H, s, 4-H<sub>3</sub>), 0.99 [9 H, s, OSiC(CH<sub>3</sub>)<sub>3</sub>] and 0.16 and 0.15 (each 3 H, s, OSiCH<sub>3</sub>);  $\delta_{C}$  (75 MHz, CDCl<sub>3</sub>) 153.93, 139.01, 138.27, 137.13, 135.94, 134.17, 129.90, 129.86, 127.59, 127.57, 124.36, 105.48, 72.82, 63.06, 60.05, 56.24, 26.28, 25.78, 18.74, -4.93 and -4.95; m/z (CI) 476 (M<sup>+</sup> + 18, 7%), 459 (M<sup>+</sup> + 1, 13), 458 (5), 441 (45), 309 (53), 172 (100) and 154 (50).

### (*Z*)-3-[2-Hydroxymethyl-6-(2,6-dimethoxyphenoxymethyl)phenyl]but-2-enyl 2-nitrobenzene-sulfonamide 17

Di-isopropyl azodicarboxylate (1.18 cm<sup>3</sup>, 5.98 mmol) was added to the alcohol 25 (1.61 g, 3.51 mmol), 2-nitrobenzene sulfonamide (2.13 g, 10.54 mmol) and triphenylphosphine (1.57 cm<sup>3</sup>, 5.98 mmol) in tetrahydrofuran (88 cm<sup>3</sup>). The mixture was stirred for 16 h and concentrated under reduced pressure. Chromatography of the residue using ether-light petroleum (30 : 70  $\rightarrow$ 60 : 40) as eluent gave a mixture of the sulfonamide 26 and diisopropyl azodicarboxylate [3.32 g, ca. 1.85 g of 26, 82% together with 1,2-(di-isopropoxycarbonyl)hydrazine (<sup>1</sup>H NMR)], as white solid (found:  $M^+$  + Na, 665.2322.  $C_{32}H_{42}N_2O_8SSiNa$  requires M, 665.2323);  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.85 (1 H, dd, J 7.5, 1.5, ArH), 7.62 (1 H, dd, J 8, 1.5, ArH), 7.59–7.46 (4 H, m, ArH), 7.34 (1 H, dd, J 8, 7.5, ArH), 7.07 (1 H, t, J 8.5, ArH), 6.63 (2 H, d, J 8.5, ArH), 6.40 (1 H, dd, J 9, 3, NH), 5.84 (1 H, m, 2-H), 4.89 (1 H, d, J 9.5, ArHCH), 4.58 (1 H, d, J 13.5, ArHCH), 4.58 (1 H, d, J 9.5, ArHCH), 4.54 (1 H, d, J 13.5, ArHCH), 3.88 (6 H, s, 2 × OCH<sub>3</sub>), 3.31 (1 H, m, 1-H), 3.61 (1 H, ddd, J 14, 9.5, 3, 1-H'), 2.00 (3 H, s, 4-H<sub>3</sub>), 0.96 [9 H, s, OSiC(CH<sub>3</sub>)<sub>3</sub>] and 0.12 [6 H, s, OSi(CH<sub>3</sub>)<sub>2</sub>];  $\delta_{C}$ 

(75 MHz, CDCl<sub>3</sub>) 153.82, 148.23, 138.49, 138.40, 137.28, 136.91, 134.46, 133.77, 133.01, 132.38, 130.45, 130.31, 127.88, 127.47, 125.89, 125.06, 124.55, 105.24, 72.95, 62.85, 56.15, 42.93, 26.24, 25.69, 18.69 and -4.99; m/z (ES) 665 (M<sup>+</sup> + 23, 18%), 431 (70), 277 (50) and 145 (100).

Tetra-n-butylammonium fluoride (1 M in tetrahydrofuran, 4.32 cm<sup>3</sup>, 4.32 mmol) was added to a mixture of the silyl ether 26 and di-isopropyl azodicarboxylate (3.32 g, containing ca. 1.85 g of 26, 2.88 mmol) in tetrahydrofuran (14.4 cm<sup>3</sup>) and the mixture was stirred for 1 h at room temperature before being partitioned between saturated aqueous ammonium chloride (30 cm<sup>3</sup>) and dichloromethane (30 cm<sup>3</sup>). The aqueous phase was extracted with ether  $(3 \times 30 \text{ cm}^3)$  and the combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using etherlight petroleum (50 : 50  $\rightarrow$  100 : 0) as eluent gave the *title* compound 17 (1.47 g, 97%) as a pale yellow oil (found: M<sup>+</sup> + Na, 551.1460. C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>8</sub>SNa requires M, 551.1459); v<sub>max</sub> 3306, 1715, 1597, 1544, 1479, 1375, 1254, 1168, 1110, 838 and 775 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.92 (1 H, dd, J 7, 1.5, ArH), 7.70–7.52 (4 H, m, ArH), 7.44 (1 H, d, J 7.5, ArH), 7.36 (1 H, t, J 7.5, ArH), 7.07 (1 H, t, J 8.5, ArH), 6.63 (2 H, d, J 8.5, ArH), 6.49 (1 H, br. m, NH), 5.84 (1 H, tq, J 7, 1.5, 2-H), 4.86 and 4.69 (each 1 H, d, J 10, ArHCH), 4.61 and 4.56 (each 1 H, d, J 13, ArHCH), 3.87  $(6 \text{ H}, \text{ s}, 2 \times \text{OCH}_3)$ , 3.45  $(2 \text{ H}, \text{ m}, 1 \text{ -H}_2)$  and 2.02  $(3 \text{ H}, \text{ s}, 4 \text{ -H}_3)$ ;  $\delta_C$ (75 MHz, CDCl<sub>3</sub>) 153.91, 148.17, 139.46, 137.70, 137.65, 137.00, 134.90, 134.67, 133.14, 132.63, 130.60, 128.98, 128.11, 126.09, 125.10, 124.47, 105.36, 72.67, 63.18, 56.20, 42.75 and 26.08; m/z (ES) 551 ( $M^+$  + 23, 100%).

### 6-[(2,6-Dimethoxyphenoxy)methyl]-5-methyl-2-(2-nitrophenyl)sulfonyl-2,3-dihydro-[1*H*]-2-benzazepine 3

Di-isopropyl azodicarboxylate (2.03 cm<sup>3</sup>, 10.30 mmol) was added to the sulfonamide 17 (1.47 g, 2.78 mmol) and triphenylphosphine (2.03 cm<sup>3</sup>, 10.30 mmol) in tetrahydrofuran (284 cm<sup>3</sup>) and the mixture was stirred for 1 h then concentrated under reduced pressure. Chromatography of the residue using ether-light petroleum  $(40: 60 \rightarrow 70: 30)$  as eluent gave the *title compound* **3** (1.55 g, 99%) as a yellow gum (found:  $M^+ + NH_4$ , 528.1806.  $C_{26}H_{30}N_3O_7S$ requires M, 528.1799); v<sub>max</sub> 1727, 1596, 1545, 1478, 1373, 1296, 1255, 1166, 1112, 852, 773 and 733 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 8.00 (1 H, dd, J 7, 2, ArH), 7.81 (1 H, dd, J 7.5, 1.5, ArH), 7.76-7.63 (3 H, m, ArH), 7.36 (1 H, t, J 7.5, ArH), 7.34 (1 H, dd, J 7.5, 2, ArH), 7.04 (1 H, t, J 8.5, ArH), 6.60 (2 H, d, J 8.5, ArH), 6.02 (1 H, td, J 8, 1.5, 4-H), 5.08 and 4.96 (each 1 H, d, J 11, HCHO), 4.62 (1 H, d, J 13, 1-H), 4.04 (1 H, dd, J 13, 8, 3-H), 3.96 (1 H, d, J 13, 1-H'), 3.84 (6 H, s, 2 × OCH<sub>3</sub>), 2.99 (1 H, dd, J 13, 8, 3-H') and 2.24 (3 H, s, 5-CH<sub>3</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 154.02, 148.43, 143.44, 140.17, 137.10, 135.88, 133.66, 133.42, 132.42, 131.86, 131.37, 130.74, 129.45, 128.51, 124.37, 124.27, 121.85, 105.45, 72.48, 56.25, 49.59, 43.15 and 23.22; m/z (CI) 528 (M<sup>+</sup> + 18, 42%), 511 (M<sup>+</sup> + 1, 7), 324 (92) and 172 (100).

### 6-[(2,6-Dimethoxyphenoxy)methyl]-5-methyl-2,3-dihydro-[1*H*]-2benzazepine 27

Thiophenol (0.89 cm<sup>3</sup>, 8.64 mmol) was added to a suspension of the dihydrobenzazepine 3 (1.47 g, 2.88 mmol) and potassium

carbonate (1.59 g, 11.53 mmol) in acetonitrile (48 cm<sup>3</sup>) and the mixture was stirred for 16 h at room temperature then concentrated under reduced pressure. Chromatography of the residue using methanol–dichloromethane (0 : 100  $\rightarrow$  10 : 90) containing triethylamine (1%) as eluent gave the *title compound* **27** (937 mg, *ca*. 100%) as an oil (found: M<sup>+</sup> + H, 326.1751. C<sub>20</sub>H<sub>24</sub>NO<sub>3</sub> requires M, 326.1751);  $\nu_{max}$  3313, 1596, 1494, 1478, 1296, 1254, 1111, 1036, 773 and 734 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.79 (1 H, d, *J* 7.5, ArH), 7.35 (1 H, t, *J* 7.5, ArH), 7.26 (1 H, d, *J* 7.5, ArH), 7.03 (1 H, t, *J* 8.5, ArH), 6.60 (2 H, d, *J* 8.5, ArH), 6.08 (1 H, td, *J* 6, 1, 4-H), 5.07 (2 H, br. s, OCH<sub>2</sub>), 3.85 (6 H, s, 2 × OCH<sub>3</sub>), 3.70 (2 H, br. s, 1-H<sub>2</sub>), 3.07 (2 H, br. s, 3-H<sub>2</sub>) and 2.26 (3 H, d, *J* 1, 5-CH<sub>3</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 154.12, 140.93, 140.89, 137.45, 136.96, 135.48, 130.08, 128.62, 127.89, 125.01, 124.06, 105.55, 72.80, 56.30, 49.12, 41.78 and 23.20; *m/z* (CI) 326 (M<sup>+</sup> + 1, 100%) and 172 (28).

### 2-(4-Bromophenylsulfonyl)-6-[(2,6-dimethoxyphenoxy)methyl]-5methyl-2,3-dihydro-[1*H*]-2-benzazepine 28

4-Bromobenzene sulfonyl chloride (19 mg, 0.07 mmol) was added to the dihydrobenzazepine 27 (20 mg, 0.06 mmol), triethylamine (13  $\mu$ L, 0.09 mmol) and 4-dimethylaminopyridine (0.15 mg, 2 mol%) in anhydrous dichloromethane (0.6 cm<sup>3</sup>) and the mixture was stirred for 16 h at room temperature. Water (10 cm<sup>3</sup>) was added and the mixture was extracted with dichloromethane  $(4 \times 10 \text{ cm}^3)$ . The organic extracts were washed with brine, dried  $(MgSO_4)$ , and concentrated under reduced pressure. Chromatography of the residue using ether-light petroleum (25 :  $75 \rightarrow 80$  : 20) as eluent gave the title compound 28 (18 mg, 55%) as a pale yellow solid, m.p. 143-145 °C (found: C, 57.25; H, 5.05; N, 2.45; Br, 14.45; S, 5.45%. C<sub>26</sub>H<sub>26</sub>BrNO<sub>5</sub>S requires C, 57.35; H, 4.8; N, 2.55; Br, 14.7; S, 5.9%. Found:  $M^+$  + Na, 566.0603.  $C_{26}H_{26}NO_5^{79}BrSNa$ requires M, 566.0607); v<sub>max</sub> 1597, 1575, 1494, 1478, 1357, 1343, 1296, 1255, 1162, 1111, 1092, 1069, 911, 773, 749 and 733 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.77 (1 H, dd, J 8, 1.5, ArH), 7.72–7.63 (4 H, m, ArH), 7.25 (1 H, t, J 7.5, ArH), 7.05 (1 H, dd, J 7.5, 1.5, ArH), 7.03 (1 H, t, J 8.5, ArH), 6.58 (2 H, d, J 8.5, ArH), 5.82 (1 H, tq, J 8, 1.5, 4-H), 5.03 and 4.95 (each 1 H, d, J 10.5, OHCH), 4.55 (1 H, d, J 12.5, 1-H), 3.99 (1 H, dd, J 12.5, 8, 3-H), 3.87–3.75 (7 H, m, 1-H' and 2 × OCH<sub>3</sub>), 2.77 (1 H, dd, J 12, 8, 3-H'), 2.67 (3 H, s, 5-CH<sub>3</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 154.00, 143.25, 139.98, 138.74, 136.97, 135.78, 132.55, 131.99, 131.26, 129.39, 129.15, 128.21, 127.66, 124.22, 121.46, 105.39, 72.36, 56.22, 49.92, 43.08 and 23.18; *m*/*z* (ES) 568 (M<sup>+</sup> + 23, 90%) and 566 (M<sup>+</sup> + 23, 100).

### (4RS,5SR)-4,5-Dihydroxy-6-[(2,6-dimethoxyphenoxy)methyl]-5methyl-2-[3-(N-2-nitrophenyl-sulfonyl-N-phenylmethyl)aminopropanoyl]-2,3,4,5-tetrahydro-[1H]-2-benzazepine 30

*O*-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (1.11 g, 3.46 mmol) was added to the acid **35** (1.15 g, 3.17 mmol), the 2,3-dihydrobenzazepine **27** (937 mg, 2.88 mmol) and di-isopropylethylamine (1.20 cm<sup>3</sup>, 6.92 mmol) in dichloromethane (25 cm<sup>3</sup>) and the reaction mixture was stirred for 16 h at room temperature. Dichloromethane (50 cm<sup>3</sup>) was added and the organic layer was washed with saturated aqueous sodium bicarbonate (50 cm<sup>3</sup>), water (50 cm<sup>3</sup>), saturated aqueous ammonium chloride (50 cm<sup>3</sup>) then water (50 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ether–light petroleum (50 : 50  $\rightarrow$  100 : 0) as eluent gave the *N*-acyldihydrobenzazepine **29** (1.6 g, 83%), a mixture of rotamers, as a white foam (found: M<sup>+</sup> + Na, 694.2191). C<sub>36</sub>H<sub>37</sub>N<sub>3</sub>O<sub>8</sub>SNa requires M, 694.2194);  $\nu_{max}$  1636, 1596, 1542, 1494, 1478, 1436, 1372, 1296, 1254, 1163, 1111, 852 and 772 cm<sup>-1</sup>; m/z (ES) 694 (M<sup>+</sup> + 23, 100%).

N-Methylmorpholine-N-oxide (2.62 g, 22.34 mmol) and osmium tetraoxide (57 mg, 0.22 mmol) were added to the dihydrobenzazepine 29 (1.50 g, 2.23 mmol) in a mixture of acetone (36 cm<sup>3</sup>), *tert*-butanol (36 cm<sup>3</sup>) and water (18 cm<sup>3</sup>). The mixture was stirred for 96 h with addition of more osmium tetraoxide (57 mg) every 24 h. Saturated aqueous sodium sulfite (50 cm<sup>3</sup>) was added and the mixture was stirred for 30 min before being extracted with ethyl acetate (4  $\times$  50 cm<sup>3</sup>). The organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ether-light petroleum (75:  $25 \rightarrow 100$ : 1) as eluent gave the *title compound* **30** (1.15 g, 73%), a 60 : 40 mixture of rotamers, as a pale yellow gum (found: M<sup>+</sup> + Na, 728.2244. C<sub>36</sub>H<sub>39</sub>N<sub>3</sub>O<sub>10</sub>SNa requires M, 728.2248); v<sub>max</sub> 3468, 1634, 1544, 1478, 1373, 1296, 1254, 1163, 1113, 1033, 992, 939, 852, 772 and 735 cm<sup>-1</sup>;  $\delta_{\rm H}$  (500 MHz, CDCl<sub>3</sub>) 7.82 (1 H, m, ArH), 7.60-7.49 (2.4 H, m, ArH), 7.43 (0.6 H, m, ArH), 7.29 (0.4 H, dd, J 7.5, 1.5, ArH), 7.25-7.11 (6.2 H, m, ArH), 7.06 (0.6 H, t, J 7.5, ArH), 7.03 (0.4 H, t, J 7.5, ArH), 6.93 (0.6 H, t, J 8.5, ArH), 6.92 (0.4 H, t, J 8.5, ArH), 6.73 (0.4 H, dd, J 7.5, 1.5, ArH), 6.50 (1.2 H, d, J 8.5, ArH), 6.48 (0.8 H, d, J 8.5, ArH), 5.70 (0.6 H, br. s, OH), 5.29 (0.6 H, d, J 9.5, OHCH), 5.27 (0.8 H, s, OCH<sub>2</sub>), 5.22 (0.6 H, d, J 9.5, OHCH), 4.93 (0.6 H, d, J 15, 1-H), 4.67 (0.4 H, d, J 16.5, 1-H), 4.45 and 4.44 (each 0.6 H, d, J 14, NHCHPh), 4.42 and 4.41 (each 0.6 H, d, J 14, NHCHPh), 4.15 (0.4 H, d, J 16.5, 1-H'), 3.95–3.36 (11.8 H, m, 4-H, 3-H<sub>2</sub>, 3'-H<sub>2</sub>,  $2 \times OH$  and 2 × OCH<sub>3</sub>), 2.61 (0.6 H, br. s, OH), 2.56–2.33 (2 H, m, 2'-H<sub>2</sub>), 1.58 (1.8 H, s, 5-CH<sub>3</sub>) and 1.40 (1.2 H, s, 5-CH<sub>3</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 170.26, 170.17, 153.76, 153.55, 148.25, 143.15, 142.71, 138.51, 137.44, 136.46, 136.36, 136.10, 135.18, 134.73, 134.25, 133.97, 133.69, 133.58, 133.19, 132.11, 132.04, 131.04, 130.65, 129.08, 129.03, 128.96, 128.67, 128.54, 128.27, 128.21, 127.45, 127.34, 124.53, 124.45, 105.52, 105.49, 80.57, 79.78, 79.72, 78.77, 77.09, 76.95, 75.48, 66.90, 56.35, 56.32, 55.50, 53.31, 53.05, 51.69, 50.57, 46.84, 44.69, 44.61, 32.70, 32.34, 26.74 and 26.65; m/z (ES) 728 (M<sup>+</sup> + 23, 53%), 251 (69) and 139 (88).

### (4*RS*,5*SR*)-4,5-Dihydroxy-6-[(2,6-dimethoxyphenoxy)methyl]-5methyl-2-[3-(*N*-phenylmethyl)-aminopropanoyl]-2,3,4,5tetrahydro-[1*H*]-2-benzazepine 31

Thiophenol (0.218 cm<sup>3</sup>, 2.23 mmol) was added to the 2nitrobenzene sulfonamide **30** (500 mg, 0.71 mmol) and potassium carbonate (392 mg, 2.84 mmol) in acetonitrile (11.8 cm<sup>3</sup>) and the reaction mixture was stirred at room temperature for 16 h. After concentration under reduced pressure, water (30 cm<sup>3</sup>) was added and the aqueous phase was extracted with ethyl acetate (4 × 30 cm<sup>3</sup>). The organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using methanol–dichloromethane (10 : 90) containing triethylamine (1%) gave the *title compound* **31** (344 mg, 96%), a 7 : 3 mixture of rotamers, as a pale yellow foam (found: M<sup>+</sup> + H, 521.2653. C<sub>30</sub>H<sub>37</sub>N<sub>2</sub>O<sub>6</sub> requires M, 521.2646);  $v_{max}$  3419, 1632,

1595, 1544, 1478, 1372, 1296, 1255, 1163, 1111, 772 and 733 cm<sup>-1</sup>;  $\delta_{\rm H}$  (500 MHz, CDCl<sub>3</sub>) 7.38 (0.3 H, dd, J 7.5, 1.5, ArH), 7.29 (0.7 H, dd, J 7.5, 1.5, ArH), 7.24–7.1 (5.7 H, m, ArH), 7.08 (1 H, t, J 7.5, ArH), 7.01 (0.3 H, m, ArH), 6.93 (0.7 H, t, J 8.5, ArH), 6.92 (0.3 H, t, J 8.5, ArH), 6.50 (1.4 H, d, J 8.5, ArH), 6.49 (0.6 H, d, J 8.5, ArH), 5.35 (0.7 H, d, J 9.5, HCHO), 5.33 and 5.26 (each 0.3 H, d, J 10.5, HCHO), 5.24 (0.7 H, d, J 9.5, HCHO), 5.08 (0.7 H, d, J 15, 1-H), 4.87 and 4.39 (each 0.3 H, d, J 16.5, 1-H), 4.05 (0.7 H, d, J 15, 1-H'), 4.00–3.53 (11 H, m, 3-H<sub>2</sub>, 4-H, NCH<sub>2</sub>Ph, and 2  $\times$ OCH<sub>3</sub>), 3.2 (2 H, br. s, OH), 2.78–2.27 (4 H, overlapping m, 2'-H<sub>2</sub> and 3'-H<sub>2</sub>), 1.64 (2.1 H, s, 5-CH<sub>3</sub>) and 1.50 (0.9 H, s, 5-CH<sub>3</sub>);  $\delta_c$ (125 MHz, CDCl<sub>3</sub>) 171.88, 171.49, 153.59, 153.37, 142.74, 139.80, 139.06, 138.88, 137.50, 136.13, 136.08, 134.97, 133.75, 133.28, 133.12, 128.41, 128.39, 128.35, 128.22, 127.11, 127.06, 126.91, 124.06, 124.01, 105.23, 80.24, 79.53, 78.64, 76.51, 56.08, 56.05, 53.86, 53.63, 51.63, 50.81, 46.91, 46.05, 44.88, 44.59, 32.96, 32.35, 26.21 and 26.11; m/z (ES) 521 (M<sup>+</sup> + 1, 7%), 196 (69), 192 (56), 169 (29), 153 (94) and 110 (100).

### (4RS,5SR)-4,5-Dihydroxy-6-[(2,6-dimethoxyphenoxy)methyl]-5methyl-2-[3-(N-2-nitrophenyl-sulfonyl-N-phenylmethyl)aminopropyl]-2,3,4,5-tetrahydro-[1H]-2-benzazepine 33

The amide **31** (318 mg, 0.61 mmol) in tetrahydrofuran (5.1 cm<sup>3</sup>) was added to borane (1 M in tetrahydrofuran, 3.06 cm<sup>3</sup>, 3.06 mmol) at 0 °C, and the mixture was stirred at room temperature for 16 h then cooled to 0 °C and aqueous hydrogen chloride (1 M, 5.1 cm<sup>3</sup>) was added. The mixture was heated under reflux for 45 min and aqueous sodium hydroxide (1 M, 10 cm<sup>3</sup>) was added followed by dichloromethane (20 cm<sup>3</sup>). The layers were separated and the aqueous phase was extracted with dichloromethane  $(3 \times 20 \text{ cm}^3)$ . The organic extracts were washed with water, brine, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the amine 32 (304 mg) as a colourless gum (found:  $M^+$  + H, 507.2856.  $C_{30}H_{39}N_2O_5$  requires M, 507.2853); v<sub>max</sub> 3480, 3302, 1596, 1494, 1478, 1372, 1296, 1254, 1223, 1111, 1034, 910, 772, 733 and 700 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CD<sub>3</sub>OD) 7.63 (1 H, dd, J 7.5, 2, ArH), 7.34–7.23 (3 H, m, ArH), 7.23–7.11 (4 H, m, ArH), 7.06 (1 H, t, J 8.5, ArH), 6.71 (2 H, d, J 8.5, ArH), 5.58 and 5.29 (each 1 H, d, J 11, HCHO), 3.94–3.81 (3 H, m, 4-H and NCH<sub>2</sub>Ph), 3.86 (6 H, s,  $2 \times \text{OCH}_3$ ), 3.82 and 3.76 (each 1 H, d, J 13, 1-H), 3.06 (1 H, dd, J 12.5, 2, 3-H), 2.93 (1 H, br. dd, J 13, 4.5, 3-H'), 2.79 (2 H, t, J 6.5, 3'-H<sub>2</sub>), 2.68 (2 H, t, J 6.5, 1'-H<sub>2</sub>), 1.84 (2 H, m, 2'-H<sub>2</sub>) and 1.69 (3 H, s, 5-CH<sub>3</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 153.77, 144.05, 138.24, 137.00, 135.58, 134.80, 133.38, 132.23, 129.27, 129.06, 128.36, 127.07, 123.97, 105.58, 80.14, 78.63, 75.80, 64.76, 58.62, 56.39, 52.35, 47.80, 25.58 and 25.07; m/z (ES) 545  $(M^+ + 39, 2\%)$ , 529  $(M^+ + 23, 16)$  and 507  $(M^+ + 1, 100)$ .

2-Nitrobenzenesulfonyl chloride (136 mg, 0.61 mmol) was added to the amine **32** (310 mg, 0.61 mmol), triethylamine (0.128 cm<sup>3</sup>, 0.92 mmol), 4-dimethylaminopyridine (1.5 mg) in dichloromethane (8 cm<sup>3</sup>) and the mixture was stirred at room temperature for 16 h. Water (20 cm<sup>3</sup>) was added and the aqueous phase was extracted with dichloromethane (4 × 20 cm<sup>3</sup>). The organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using methanol–dichloromethane (0 : 100  $\rightarrow$  2 : 98) as eluent gave the *title compound* **33** (314 mg, 74% from **31**) as a pale yellow gum (found: M<sup>+</sup> + H, 692.2630. C<sub>36</sub>H<sub>42</sub>N<sub>3</sub>O<sub>9</sub>S requires M, 692.2636); v<sub>max</sub> 3464, 1597, 1543, 1493, 1478, 1370, 1347, 1296, 1254, 1162, 1110, 1034, 774 and 732 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.95 (1 H, d, J 7.5, ArH), 7.73–7.60 (3 H, m, ArH), 7.47 (1 H, dd, J 7.5, 1.5, ArH), 7.40-7.32 (5 H, m, ArH), 7.18 (1 H, t, J 7.5, ArH), 7.03 (1 H, t, J 8.5, ArH), 7.00 (1 H, dd, J 7.5, 1.5, ArH), 6.62 (2 H, d, J 8.5, ArH), 5.47 and 5.46 (each 1 H, d, J 16, HCHO), 5.26 (1 H, br. s, OH), 4.62 and 4.50 (each 1 H, d, J 15.5, NHCHPh), 3.89 (6 H, s,  $2 \times OCH_3$ ), 3.75 (1 H, m, 4-H), 3.62 and 3.51 (each 1 H, d, J 14.5, 1-H), 3.31 (2 H, t, J 7.5, 3'-H<sub>2</sub>), 2.89 (2 H, br. d, J 2.5, 3-H<sub>2</sub>), 2.50 and 2.39 (each 1 H, m, 1'-H), 1.78–1.52 (2 H, m, 2'-H<sub>2</sub>) and 1.61 (3 H, s, 5-CH<sub>3</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 153.75, 148.19, 143.89, 138.06, 136.85, 136.21, 136.04, 133.80, 133.75, 133.64, 132.32, 132.13, 131.26, 129.04, 128.54, 128.28, 127.14, 124.50, 123.98, 105.54, 80.46, 78.74, 75.90, 62.82, 59.79, 56.35, 55.79, 52.34, 46.28, 26.61 and 25.63; m/z (ES) 714  $(M^+ + 23, 15), 692 (M^+ + 1, 15), 179 (12), 133 (12) and 101 (100).$ 

## 6-[(2,6-Dimethoxyphenoxy)methyl]-5-hydroxy-5-methyl-2-[3-(*N*-2-nitrophenylsulfonyl-*N*-phenyl-methyl)aminopropyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one 34

Dimethyl sulfoxide (0.120 cm<sup>3</sup>, 1.70 mmol) in dichloromethane  $(2 \text{ cm}^3)$  was added to oxalyl chloride (89 µL, 1.02 mmol) in dichloromethane (2 cm<sup>3</sup>) at -78 °C and the mixture was stirred for 30 min before the diol 33 (234 mg, 0.39 mmol) in dichloromethane (5 cm<sup>3</sup>) was added. After a further 30 min, triethylamine (0.283 cm<sup>3</sup>, 2.03 mmol) was added and the mixture was allowed to warm to 0 °C and stirred for an additional 30 min. Water (20 cm<sup>3</sup>) was added and the mixture was extracted with ether  $(4 \times 20 \text{ cm}^3)$ . The organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate-light petroleum  $(75: 25 \rightarrow 100: 0)$  as eluent gave the *title compound* 34 (191 mg, 82%) as a pale yellow gum (found: M<sup>+</sup> + H, 690.2477. C<sub>36</sub>H<sub>40</sub>N<sub>3</sub>O<sub>9</sub>S requires M, 690.2480); v<sub>max</sub> 3444, 2360, 1714, 1595, 1544, 1477, 1369, 1296, 1255, 1163, 1113, 1021 and 782 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, CDCl<sub>3</sub>) 7.86–7.77 (2 H, m, ArH), 7.73–7.61 (3 H, m, ArH), 7.38– 7.21 (6 H, m, ArH), 7.05 (1 H, t, J 8.5, ArH), 6.94 (1 H, d, J 7.5, ArH), 6.64 (2 H, d, J 8.5, ArH), 5.60 and 5.29 (each 1 H, d, J 12, HCHO), 4.91 (1 H, br s, OH), 4.59 and 4.48 (each 1 H, d, J 15.5, NHCHPh), 3.88 (6 H, s, OCH<sub>3</sub>), 3.69 (1 H, d, J 16, 3-H), 3.67 (1 H, d, J 18, 1-H), 3.54 (1 H, d, J 16, 3-H'), 3.35-3.25 (3 H, m, 1-H' and 3'-H<sub>2</sub>), 2.50 and 2.37 (each 1 H, m, 1'-H), 1.89 (3 H, s, 5-CH<sub>3</sub>) and 1.80–1.51 (2 H, m, 2'-H<sub>2</sub>);  $\delta_{\rm C}$  (75 MHz, CDCl<sub>3</sub>) 208.90, 154.11, 148.12, 140.39, 138.39, 136.99, 136.25, 134.82, 133.91, 133.44, 132.36, 131.27, 131.21, 129.37, 129.07, 128.54, 128.32, 127.42, 124.44, 124.10, 105.56, 81.79, 73.36, 63.44, 59.90, 56.35, 53.77, 52.48, 46.18, 26.42 and 26.26; m/z (ES) 712 (M<sup>+</sup> + 23, 12%) and  $690 (M^+ + 1, 100).$ 

## 6-[(2,6-Dimethoxyphenoxy)methyl]-5-hydroxy-5-methyl-2-[3-(*N*-phenylmethyl)aminopropyl]-2,3,4,5-tetrahydro-[1*H*]-2-benzazepin-4-one 2

Thiophenol (38  $\mu$ L, 0.37 mmol) was added to a suspension of the sulfonamide **34** (86 mg, 0.13 mmol) and anhydrous potassium carbonate (69 mg, 0.50 mmol) in acetonitrile (2.09 cm<sup>3</sup>) and the mixture was stirred for 16 h at room temperature then concentrated under reduced pressure. The residue was partitioned between

dichloromethane (20 cm<sup>3</sup>) and water (20 cm<sup>3</sup>) and the aqueous phase extracted with dichloromethane  $(4 \times 20 \text{ cm}^3)$ . The organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography of the residue using methanol–dichloromethane (0 : 100  $\rightarrow$  5 : 95) as eluent gave the title compound 2 (61 mg, 97%) as a pale yellow oil (found:  $M^+ + H$ , 505.2699. C<sub>30</sub>H<sub>37</sub>N<sub>2</sub>O<sub>5</sub> requires M, 505.2697); v<sub>max</sub> 3449, 1715, 1596, 1493, 1477, 1365, 1296, 1254, 1217, 1113, 1029, 770 and 733 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, C<sub>6</sub>D<sub>6</sub>) 8.20 (1 H, dd, J 8, 1, ArH), 7.29– 7.08 (5 H, m, ArH), 7.08 (1 H, t, J 7.5, ArH), 6.85 (1 H, t, J 8.5, ArH), 6.69 (1 H, dd, J 7.5, 1, ArH), 6.37 (2 H, d, J 8.5, ArH), 5.98 and 5.70 (each 1 H, d, J 12.5, HCHO), 3.55 (2 H, s, NCH<sub>2</sub>Ph), 3.54–3.30 (3 H, m, 3-H<sub>2</sub> and 1-H), 3.40 (6 H, s, OCH<sub>3</sub>), 3.17 (1 H, d, J 13.5, 1-H'), 2.39 (2 H, t, J 6.5, 3'-H<sub>2</sub>), 2.31 and 2.19 (each 1H, m, 1'-H), 1.97 (3 H, s, 5-CH<sub>3</sub>) and 1.38 (2 H, m, 2'-H<sub>2</sub>);  $\delta_{\rm C}$ (75 MHz, C<sub>6</sub>D<sub>6</sub>) 208.73, 154.52, 141.06, 140.63, 139.30, 138.14, 135.06, 130.68, 128.84, 128.50, 128.28, 127.04, 126.97, 123.60, 106.00, 81.82, 73.52, 63.02, 60.32, 55.78, 54.78, 54.10, 47.18, 28.06 and 25.94; m/z (ES) 527 (M<sup>+</sup> + 23, 6%) and 505 (M<sup>+</sup> + 1, 100).

#### Crystal data for the 2,3-dihydro-[1H]-2-benzazepine 28

 $C_{26}H_{26}BrNO_5S$ , M = 544.45, monoclinic, a = 24.883(2), b = 15.352(2), c = 17.848(2),  $\beta = 133.610(3)$  Å, U = 4936.6(9) Å<sup>3</sup>,  $T = 100(1)^{\circ}$ , space group C2/c (no. 15), Z = 8,  $\mu$ (MoK $\alpha$ ) = 1.787 mm<sup>-1</sup>, 19 599 reflections were measured giving 5171 unique reflection ( $R_{int} = 0.0428$ ). Refinement was carried out on  $F^2$  using all the data. The final R1 = 0.0432 for the 4173 reflections with  $I > 2.00 \sigma(I)$ , wR2 = 0.1203 for all the data.<sup>‡</sup>

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