Synthesis of the bisbenzannelated spiroketal core of the γ-rubromycins. The use of a novel Nef-type reaction mediated by Pearlman's catalyst †

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The synthesis of the bisbenzannelated spiroketal core **6** of γ-rubromycin **1** from the substituted nitrostyrene **20** was achieved by using a novel Nef-type reaction mediated by Pearlman's catalyst. The precursor **28** was synthesised from readily prepared starting materials using Henry condensation chemistry. The product **6** was found to exist in two conformations in solution as shown by NMR spectroscopy.

Introduction

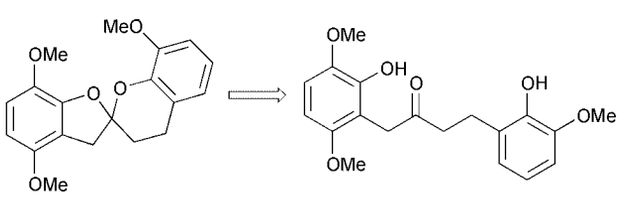
Since the reported isolation of the spiroketal-containing pigment γ-rubromycin **1** from *Streptomyces collinus* in 1969,[1] a number of related compounds have been discovered. These include purpuromycin **2**[2] and heliquinomycin **3**,[3] as well as griseorhodins C **4** and G **5**.[4] All these compounds contain benzannelated furan and pyran rings that share one carbon atom to form a spiroketal system.

Several of these compounds show interesting biological activities. The rubromycins are active against the reverse transcriptase of human immunodeficiency virus-1,[5] while purpuromycin is a potential topical agent for vaginal infections.[6] This has resulted in patents on the use of purpuromycin and related derivatives for vaginal infections.[7] The most recently discovered member of this class of compounds, heliquinomycin, is an inhibitor of DNA helicase.[3] It is believed that these compounds can act as bioreductive alkylating agents.[8]

As a result of the interesting biological activities and structures of these microbial metabolites, several synthetic analogues have been made.[9] However, the total synthesis of these compounds has so far remained elusive. Even more surprisingly, examination of the literature has revealed that there are no reported syntheses of the basic bisbenzannelated dioxa-3*H*-spiro [benzofuran-2,2′-chromane] core of these natural products. As part of our ongoing research programme aimed at the synthesis of biologically active quinones,[10,11] this paper discloses the synthesis of the aromatic spiroketal compound **6**, which forms the core of γ-rubromycin. Part of this work has already been reported as a communication.[12]

Results and discussion

The obvious disconnection of the target system **6** is to the diphenolic ketone **7** (Scheme 1). Three possible strategies for



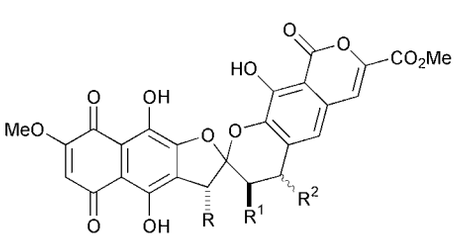
6 **7**

Scheme 1

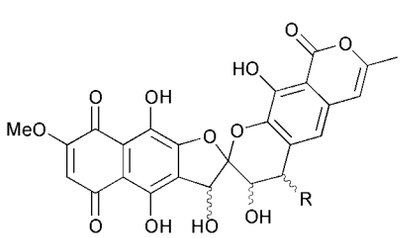
the synthesis of **7** were investigated, all involving the coupling of two arylated moieties with the creation of a carbon–carbon bond to the site destined to become the keto group.

Initially, the use of Corey–Seebach thioacetal "umpolung" methodology[13] was probed. One approach[14] used was to attempt the synthesis of **10** from aromatic thioacetal **8** and the aromatic aldehyde **9** (Scheme 2). Both **8** and **9** were easily prepared from readily available starting materials. Baeyer–Villiger oxidation of 2,5-dimethoxybenzaldehyde **11** with the magnesium salt of monoperoxyphthalic acid (MMPP) followed by chromatography on silica gel gave the required phenol **12**, which was protected as the methoxymethyl (MOM) ether **13**.

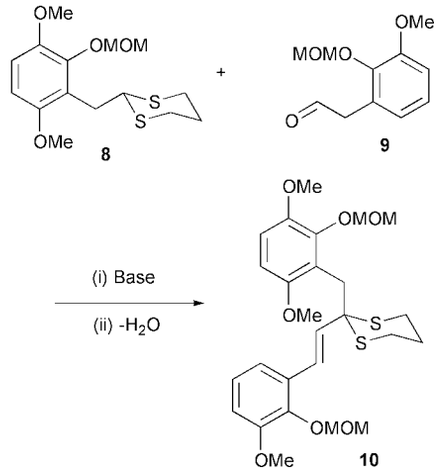
† Experimental data and full characterization of compounds **8** and **12**–**16** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b002984j/



1, γ-Rubromycin, R=H, R^1=H, R^2=H
2, Purpuromycin, R=H, R^1=H, R^2=OH
3, Heliquinomycin, R=O-cymarose, R^1=OH, R^2=H



4, Griseorhodin C, R=OH
5, Griseorhodin G, R=H



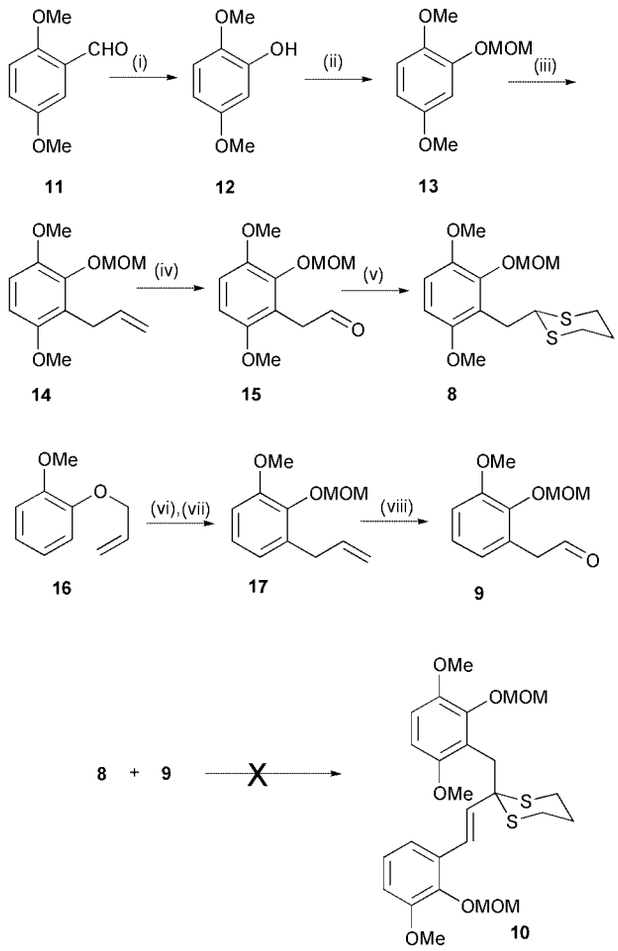
Scheme 2

Treatment of **13** with *n*-butyllithium followed by allyl bromide at −78 °C afforded the desired product **14**. It was clear from ^{1}H NMR spectroscopy that the allyl group was situated *ortho* to both the methoxy and MOM ether as two aromatic protons were visible at δ 6.73 and 6.56 and showed characteristic *ortho*-coupling (J = 8.7 Hz). Ozonolysis of **14** provided aldehyde **15**. In attempted formation of thioacetal **8** by treatment of **15** with propane-1,3-dithiol and boron trifluoride–diethyl ether, the MOM protecting group was lost, but this was easily re-introduced under standard conditions to give **8** in 63% overall yield from **15** (Scheme 3).

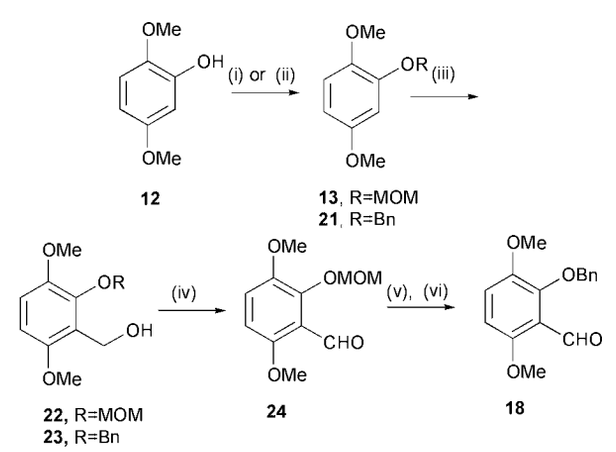
The other compound **9** required for the synthesis of **10** was readily prepared from guaiacol. Treatment of guaiacol with allyl bromide and potassium carbonate gave ether **16** in 99% yield. Careful heating of **16** at 180 °C in the absence of solvent effected Claisen rearrangement (Scheme 3). The required phenolic product was treated immediately with methoxymethyl chloride and diisopropylethylamine to give **17**. Reaction of **17** with ozone afforded the desired aldehyde **9**. However, all attempts to achieve the critical carbon–carbon formation between **8** and **9** to afford **10** proved to be fruitless. The use of alternative "umpolung" methodology using trimethylsilyl derivatives of a cyanohydrin[15] was also unsuccessful in our hands.

Fortunately, the approach that ultimately succeeded proceeded through the nitrostyrene **20**, which was prepared from the substituted benzaldehyde **18** and 3-arylnitropropane **19** (see Scheme 6). In this approach our first task was to synthesise the aromatic aldehyde **18**. Treatment of the previously prepared MOM-protected phenol **13** with *n*-butyllithium at −78 °C followed by paraformaldehyde gave the alcohol **22** in good yield (87%).[16] This was oxidised with pyridinium chlorochromate (PCC) supported on Celite to give aldehyde **24**. It was clear from the ^{1}H NMR spectrum that the aldehyde had been formed, as a singlet was evident at δ 10.49. As the more robust benzyl-protected compound **18** was required for future steps, the MOM protecting group of **24** was removed with toluene-*p*-sulfonic acid, and the resulting phenol was protected to give the benzyl ether **18** as shown in Scheme 4. Attempts at direct reaction of the benzyl-protected compound **21** with *n*-butyllithium at −78 °C followed by addition of paraformaldehyde did not give **23**, but gave back mainly starting material as well as a mixture of two uncharacterized products.

The second precursor was made from the previously prepared ether **16**. As before, careful heating of **16** at 180 °C in the absence of solvent effected Claisen rearrangement, but this time the phenolic product was treated immediately with benzyl bromide and potassium carbonate to give **25** (Scheme 5). Ozonolysis of **25** gave aldehyde **26** in 84% yield. Evidence for the conversion came from the singlet at δ 9.51 in the ^{1}H NMR

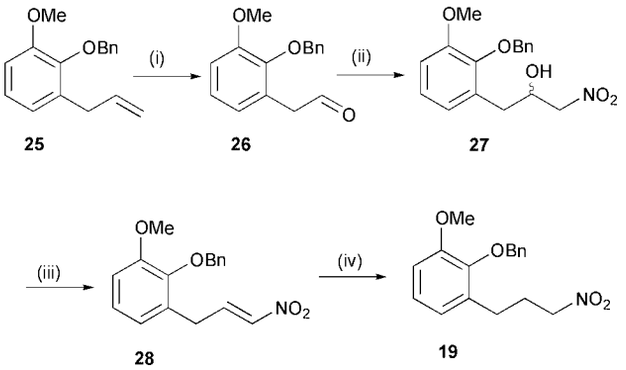


Scheme 3 *Reagents and conditions*: (i) (a) MMPP, MeOH; (b) silica, 94%; (ii) MOMCl, Pr^i_2NH, CH_2Cl_2, 0 °C, 88%; (iii) (a) *n*-BuLi, THF, TMEDA, −78 °C; (b) CH_2=$CHCH_2Br$, 97%; (iv) (a) O_3, MeOH, −40 °C; (b) Me_2S, 89%; (v) (a) $HS(CH_2)_3SH$, *p*-TsOH, PhH; (b) MOMCl, Pr^i_2NH, CH_2Cl_2, 0 °C, 63%; (vi) 180 °C, 91%; (vii) MOMCl, Pr^i_2NH, CH_2Cl_2, 0 °C, 97%; (viii) (a) O_3, MeOH, −40 °C; (b) Zn, AcOH, 90%.



Scheme 4 *Reagents and conditions*: (i) MOMCl, Pr^i_2NH, CH_2Cl_2, 0 °C, 88% (for **12**→**13**); (ii) BnBr, K_2CO_3, Me_2CO, 82% (for **12**→**21**); (iii) (a) *n*-BuLi, THF, TMEDA, −78 °C; (b) $(CH_2O)_n$, 87%; (iv) PCC, Celite, CH_2Cl_2, 86%; (v) *p*-TsOH, dioxane–H_2O, 55 °C, 96%; (vi) BnBr, K_2CO_3, DMF, 70 °C, 97%.

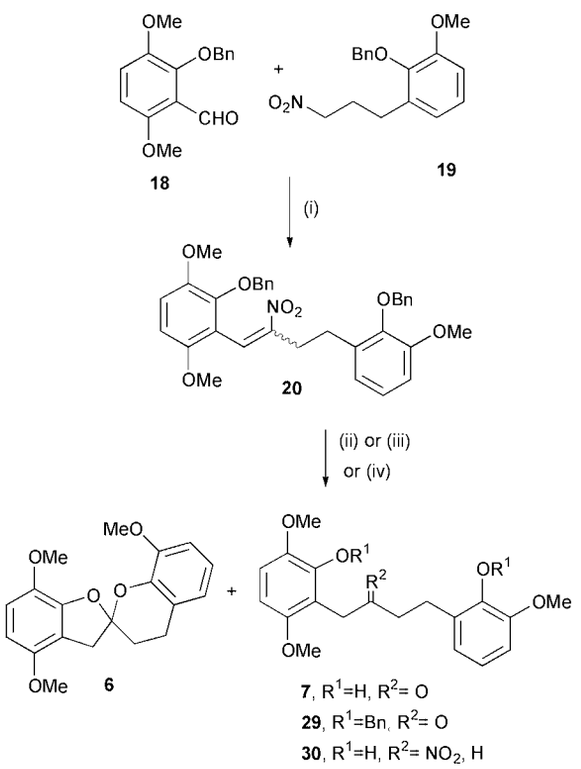
spectrum. Henry condensation of **26** with nitromethane and sodium hydroxide in the presence of cetyltrimethylammonium bromide[17] yielded alcohol **27**. Dehydration of **27** by treatment with methanesulfonyl chloride and diisopropylethylamine[18] afforded alkene **28**. The ^{1}H NMR spectrum showed, *inter alia*, one doublet of doublets at δ 3.43 (J = 6.9 and 1.6 Hz); the other proton on the double bond was obscured by the aromatic



Scheme 5 *Reagents and conditions*: (i) (a) O_3, −40 °C; (b) Zn, AcOH, 84%; (ii) $MeNO_2$, cetyltrimethylammonium bromide (CTABr), 0.025 M NaOH, 100%; (iii) MsCl, Pr^i_2NEt, CH_2Cl_2, 96%; (iv) $NaBH_4$, MeOH–THF, 70%.

protons. Finally, the double bond of **28** was reduced with sodium borohydride[19] to give the desired precursor **19**.

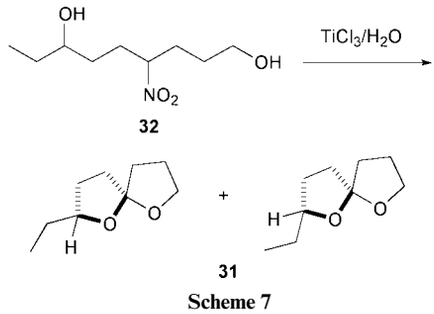
Concurrently with our work an improved protocol for the Henry condensation using microwave irradiation was published in the literature.[20] Gratifyingly, microwave-promoted Henry condensation between **18** and **19** using ammonium acetate in acetic acid as shown in Scheme 6 gave the desired nitroalkene **20**



Scheme 6 *Reagents and conditions*: (i) NH_4OAc, AcOH, 57%; (ii) $TiCl_3$, NH_4OAc, H_2O–MeOH, 29% (for **29**); (iii) Pd/C, H_2, MeOH, 30% (for **30**) and 10% (for **7**); (iv) $Pd(OH)_2$/C, EtOH, conc. HCl, cyclohexene, 64% (for **6**) and 18% (for **7**).

in fair yield (57%) as a mixture of (*Z*)- and (*E*)-isomers.[21] The ratio as determined by ^{1}H NMR spectroscopy differed from experiment to experiment, but this was not an important factor in view of the subsequent fate of the product.

The next step in the synthesis was to convert the unsaturated nitro compound **20** into ketone **7** using the Nef reaction.[22] To our surprise, the use of Nef chemistry for the formation of *aromatic* spiroketals has not been previously reported.[23] However, the related formation of simple spiroketal systems such as **31** from intermediate **32** has been documented (Scheme 7).[24] Also in the literature[25] are examples of the conversion of



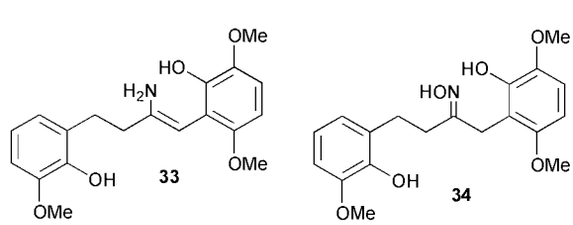
Scheme 7

nitroalkenes into carbonyls, without prior reduction to nitroalkanes, and hence we decided to subject compound **20** to some of the conditions reported in the literature.

Exposure of **20** to titanium trichloride in a mixture of methanol and aqueous ammonium acetate[26] gave the desired product **29**, albeit in low yield (29%). At this stage it was decided to change tactics slightly and remove the benzyl protecting group of **20** before attempting the Nef reaction, as it was believed that the phenolic intermediates formed would be more compatible with the aqueous reaction conditions frequently required for the Nef reaction. It was also suspected that the double bond of the unsaturated nitro functionality would probably be reduced, giving the saturated nitro compound **30**. Catalytic hydrogenation of **20** with activated palladium on carbon (20%) in methanol gave an inseparable mixture of the desired compound **30** as well as a compound that was not completely characterised. Based on NMR spectroscopic evidence in particular, indications were that not only had the benzyl protecting groups been removed, but that the unsaturated nitro group had been converted into a carbonyl group. The most significant diagnostic feature for this was the appearance of a signal at δ 209.3 in the ^{13}C NMR spectrum. Hence it was believed that during the reaction the diphenolic ketone **7** was also being produced.

As a result of this, a series of experiments was conducted to establish reaction conditions that would effect not only the removal of both the benzyl protecting groups, but also the conversion of the unsaturated nitro group of **20** in one step to yield **7** as the sole product. It was also hoped that this product would then spontaneously lose water to give the desired spiroketal **6**. Satisfyingly, exposure of **20** to Pearlman's catalyst [20% $Pd(OH)_2$ on carbon] in 96% ethanol together with one drop of concentrated hydrochloric acid and cyclohexene under an atmosphere of hydrogen[27] afforded the spiroketal **6** directly in 64% yield, together with the carbonyl compound **7** (18% yield) (Scheme 6). On standing **7** slowly converted into **6**.

Two possible mechanisms were envisaged for the conversion of **20** into **6**. The first entails the reduction of the nitro group of **20** to afford enamine **33**, which under aqueous acidic conditions would hydrolyze to the carbonyl compound **7**, and then cyclize to the spiroketal **6**. Alternatively, the nitro group could be reduced to an unsaturated hydroxylamine, tautomerisation would yield the oxime **34**, which could be hydrolyzed to **7**.



Literature precedent[28] shows that reduction of unsaturated nitro groups by palladium on carbon can produce oximes; recent results from our laboratories[29] indicate that oxime intermediates such as **34** are indeed involved in this reaction.

Therefore the mechanism outlined in the preceding communication[12] depicting **33** as an intermediate is probably incorrect.

^{1}H and ^{13}C NMR spectroscopy indicates that **6** adopts two conformations in solution. The evidence for this was that six methoxy signals were observed in the ^{1}H NMR spectrum at ambient temperature. Upon heating the product in toluene-d_8 up to 363 K, coalescence of most of the duplicated signals, including the methoxy singlets was observed. As our spirocyclization was an acid-promoted reaction, with no emphasis on stereocontrol, presumably the thermodynamically favoured isomer should be formed. The preferred conformation around the spiro centre is for both oxygens to benefit from anomeric effects by adopting pseudoaxial positions relative to each other.[30] Therefore we were surprised to find two conformations of the spiroketal in solution. Although one might intuitively expect an equilibrium between axial–axial and axial–equatorial conformations to be responsible for the spectroscopic observations, preliminary results from molecular modelling using HyperChem 5.0 indicate that the pyran ring of the bisbenzannelated spiroketal core seems to be adopting two different conformations while maintaining the mutual axial relationship of oxygen at the anomeric centre.[31]

In conclusion, this work represents the first synthesis of the bisbenzannelated 1,6-dioxaspiro[4.5]decane system. To our knowledge, this is also the first example of Pearlman's catalyst effecting a Nef-type reaction on a conjugated nitroalkene. However this example does not lead to the free carbonyl **7** but leads directly to the spiroketal **6** since free phenolic groups are also liberated in the presence of Pearlman's catalyst. Work in progress includes the synthesis of other spiroketal systems using this new methodology.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on either a Bruker AC-200 or a Bruker DRX 400 spectrometer at the frequency indicated. DEPT, CH-correlated and HMBC spectra were run on some samples to enable complete assignments of all the signals. NMR spectral assignments with the same superscript may be interchanged. *J*-Values are given in Hz. Infra-red spectra were recorded either on a Bruker IFS 25 Fourier Transform spectrometer, or on a Bruker Vector 22 Fourier Transform spectrometer. Mass spectra were recorded on a Kratos MS 9/50, VG 70E MS or a VG 70 SEQ mass spectrometer. Elemental analysis was performed on a Perkin-Elmer 2400 CHN Elemental Analyser. Macherey-Nagel Kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica gel chromatography and Macherey-Nagel Kieselgel 60 (particle size 0.040–0.063 mm) was used for preparative flash chromatography. All solvents used for reactions and chromatography were distilled prior to use.

1-Methoxy-2-methoxymethoxy-3-(prop-2-enyl)benzene 17

Compound **16** (5.779 g, 35.19 mmol) was heated neat at 180 °C under a nitrogen atmosphere. The reaction mixture changed from a clear oil to a dark brown oil. On completion of the reaction as monitored by ^{1}H NMR spectroscopy, the reaction mixture was allowed to cool, and the thick brown oil subjected to column chromatography (5% ethyl acetate–hexane) yielding the intermediate, 2-methoxy-6-(prop-2-enyl)phenol, as a clear oil (5.260 g, 91%). ν_{max}(film)/cm^{-1} 3524 (s, OH), 2974 (w, =CH_2), 2836 (w, Ar-H), 1592 (w, ArC=C), 1270 (s, C-O) and 738 (s, oop ArC-H); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.79–6.70 (3H, m, Ar-H), 5.99–5.91 (1H, m, CH_2CH=CH_2), 5.75 (1H, s, O*H*), 5.13–5.01 (2H, m, CH_2CH=CH_2), 3.83 (3H, s, OCH_3) and 3.42 (2H, dt, *J* 6.5 and 1.5, CH_2CH=CH_2); δ_C (50.32 MHz; $CDCl_3$) 146.3 (C-1[a]), 143.3 (C-2[a]), 136.6 (CH_2CH=CH_2), 125.8 (C-6), 122.2, 119.3 and 115.3 (3 × Ar-C), 108.6 (CH_2CH=CH_2), 55.9 (OCH_3) and 33.8 (CH_2CH=CH_2).

2-Methoxy-6-(prop-2-enyl)phenol (10.394 g, 63.30 mmol) was dissolved in dry dichloromethane (150 cm^3) and cooled to 0 °C under nitrogen. Diisopropylethylamine (27.57 cm^3, 20.45 g, 0.16 mol) was added, followed by methoxymethyl chloride (7.21 cm^3, 7.64 g, 95 mmol). The cooling bath was removed after 30 min, and the reaction allowed to stir for a further 2 h at room temperature. The reaction was monitored by tlc, using Pauly's salt as a spray reagent to detect the phenol, as the phenol and methoxymethyl ether have the same R_f. On completion, the dichloromethane was removed *in vacuo*, and the residue taken up in diethyl ether, and washed sequentially with 100 cm^3 each of aqueous 10% HCl, H_2O, aqueous 10% NaOH and aqueous saturated NaCl. The organic layer was then dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by column chromatography (5% ethyl acetate–hexane) to afford the substituted *benzene* **17** as a clear oil (12.822 g, 97%) (Found: M$^+$, 208.1092. $C_{12}H_{16}O_3$ requires *M*, 208.1099); ν_{max}(film)/cm^{-1} 2938 (w, =CH_2), 2838 (w, Ar-H), 1584 (m, ArC=C), 1270 (s, C-O) and 750 (m, oop ArC-H); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.03–6.95 (1H, m, H-5), 6.79–6.75 (2H, m, H-4 and H-6), 6.05–5.88 (1H, m, CH_2CH=CH_2), 5.11–5.01 (2H + 2H, m + s, CH_2CH=CH_2 + OCH_2OCH_3), 3.80 (3H, s, OCH_3), 3.57 (3H, s, OCH_2CH_3) and 3.47 (2H, dt, *J* 6.6 and 1.4, CH_2CH=CH_2); δ_C (50.32 MHz; $CDCl_3$) 152.05 (C-2[a]), 143.88 (C-1[a]), 136.95 (CH_2CH=CH_2), 134.01 (C-3), 123.97, 121.81 and 115.44 (3 × Ar-C), 110.17 (CH_2CH=CH_2), 98.72 (OCH_2OCH_3), 57.18 (OCH_2OCH_3), 55.46 (OCH_3) and 34.02 (CH_2CH=CH_2); *m*/*z* (EI) 208 (M$^+$, 33%), 163 (31), 131 (10) and 45 (100).

(3-Methoxy-2-methoxymethoxyphenyl)acetaldehyde 9

1-Methoxy-2-methoxymethoxy-3-(prop-2-enyl)benzene **17** (1.506 g, 7.221 mmol) was dissolved in methanol (90 cm^3) and cooled to −40 °C. Ozone was bubbled through the solution until an indicator solution of aqueous potassium iodide turned yellow (~10 min). Zinc dust (0.94 g, 14.4 mmol) and acetic acid (1.65 cm^3, 1.73 g, 28.8 mmol) were added and the cooling bath removed. The reaction mixture was stirred at room temperature for 1 h, after which the excess zinc was removed by filtration. The solvent was removed *in vacuo*, leaving a solid yellow residue. This was taken up in H_2O (50 cm^3) and washed with diethyl ether (3 × 75 cm^3). The ethereal extracts were dried ($MgSO_4$) and evaporated. The yellow oil was purified by silica gel column chromatography (10–15% ethyl acetate–hexane) to afford the desired *acetaldehyde* **9** (1.161 g, 90% based on starting material converted, 85% conversion) as a pale yellow oil, and starting material (0.225 g) (Found: M$^+$, 210.0891. $C_{11}H_{14}O_4$ requires *M*, 210.0892); ν_{max}(film)/cm^{-1} 2838 (m, OCH_3), 2727 (w, C-H of CHO), 1721 (s, C=O), 1586 (s, ArC=C), 1268 and 1223 (m, C-O) and 752 (m, oop ArC-H); δ_H (200 MHz; $CDCl_3$; Me_4Si) 9.71 (1H, t, *J* 2.2, H-1), 7.07–7.03 (1H, m, H-5′), 6.88 (1H, dd, *J* 8.3 and 1.5, H-4′), 6.77 (1H, dd, *J* 7.7 and 1.5, H-6′), 5.09 (2H, s, OCH_2OCH_3), 3.84 (3H, s, OCH_3), 3.73 (2H, d, *J* 2.2, H-2) and 3.52 (3H, s, OCH_2OCH_3); δ_C (50.32 MHz; $CDCl_3$) 199.8 (C-1), 152.2 (C-2′[a]), 144.8 (C-3′[a]), 126.8 (C-1′), 124.5, 122.8 and 111.7 (3 × Ar-C), 98.9 (OCH_2OCH_3), 57.3 (OCH_2OCH_3), 55.6 (OCH_3) and 45.2 (C-2); *m*/*z* (EI) 210 (M$^+$, 35%), 180 (29), 178 (45), 150 (29), 136 (34), 135 (12) and 45 (100).

(3,6-Dimethoxy-2-methoxymethoxyphenyl)methanol 22

Ether **13** (4.229 g, 21.34 mmol) was dissolved in dry tetrahydrofuran (200 cm^3) and cooled to −78 °C under a nitrogen atmosphere. TMEDA (6.44 cm^3, 4.96 g, 42.7 mmol) was added, followed by the dropwise addition of *n*-butyllithium (28.45 cm^3 of a 1.50 M solution in hexane, 42.7 mmol). This caused the colourless solution to turn yellow. After 90 min, paraformaldehyde (1.278 g, 42.6 mmol, pre-dried in a drying oven under high vacuum at 70 °C for 2 h) was added, causing the reaction mixture to go pale yellow, and cloudy. The reaction was allowed to warm to room temperature 1 h after the addition of para-

formaldehyde, and left stirring for 18 h. Water (100 cm^3) was added, and the mixture extracted with diethyl ether (3 × 100 cm^3), and the ethereal extracts dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was purified on a silica column (15–30% ethyl acetate–hexane) to afford the *alcohol* **22** as a pale oil (3.581 g, 87% based on starting material converted, 84% conversion), as well as recovered starting material **13** (0.671 g, 3.387 mmol). (Found: M^+, 228.0992. $C_{11}H_{16}O_5$ requires *M*, 228.0998); ν_{max}(film)/cm^{-1} 3476 (s, OH), 2996 (s, Ar-H), 1594 (s, ArC=C), 1260 (s, C-O) and 798 (s, oop ArC-H); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.81 (1H, d, *J* 9.0, H-5′), 6.61 (1H, d, *J* 9.0, H-4′), 5.10 (2H, s, OCH_2OCH_3), 4.75 (2H, s, CH_2OH), 3.80 and 3.79 (each 3H, s, OCH_3), 3.58 (3H, s, OCH_2OCH_3) and 3.05 (1H, br s, CH_2OH); δ_C (50.32 MHz; $CDCl_3$) 152.1 (C-2′[a]), 146.3 (C-3′[a]), 145.4 (C-6[a]), 124.2 (C-1′), 111.9 and 106.2 (2 × Ar-C), 99.2 (OCH_2OCH_3), 57.4 (OCH_2OCH_3), 56.2 and 55.9 (each OCH_3) and 54.6 (CH_2OH); *m*/*z* (EI) 228 (M^+, 10%), 167 (19), 166 (100), 165 (15), 137 (27), 136 (19), 123 (35) and 45 (84).

3,6-Dimethoxy-2-(methoxymethoxy)benzaldehyde 24

Pyridinium chlorochromate (4.06 g 18.8 mmol) and Celite (4.0 g) were suspended in dry dichloromethane (150 cm^3). A solution of **22** (2.543 g, 11.14 mmol) in dry dichloromethane (150 cm^3) was added, changing the reaction mixture from a bright orange suspension to a dark brown suspension. The reaction was stirred at room temperature under an inert nitrogen atmosphere for 19 h. The reaction mixture was poured onto a silica plug (CH_2Cl_2, then 30% ethyl acetate–hexane) to afford the *benzaldehyde* **24** (2.162 g, 86%) as an orange oil (Found: M^+, 226.0838. $C_{11}H_{14}O_5$ requires *M*, 226.0841); ν_{max}(film)/cm^{-1} 2951 (m, Ar-H), 1690 (s, C=O), 1579 (s, ArC=C), 1273 (s, C-O) and 747 (m, oop ArC-H); δ_H (200 MHz; $CDCl_3$; Me_4Si) 10.49 (1H, s, C*H*O), 7.10 (1H, d, *J* 9.1, H-4), 6.68 (1H, d, *J* 9.1, H-5), 5.19 (2H, s, OCH_2OCH_3), 3.86 and 3.83 (each 3H, s, OCH_3) and 3.56 (3H, s, OCH_2OCH_3); δ_C (50.32 MHz; $CDCl_3$) 189.8 (*C*HO), 155.0 (C-2[a]), 148.6 (C-3[a]), 146.4 (C-6[a]), 112.0 (C-1), 119.0 and 106.7 (2 × Ar-C), 99.8 (OCH_2OCH_3), 57.7 (OCH_2OCH_3) and 56.7 and 56.1 (each OCH_3); *m*/*z* (EI) 226 (M^+, 41%), 195 (17), 181 (25), 180 (77), 166 (52), 151 (15), 137 (15), 124 (20), 107 (9) and 45 (100).

2-Benzyloxy-3,6-dimethoxybenzaldehyde 18

Benzaldehyde **24** (0.746 g, 3.30 mmol) was dissolved in a mixture of 1,4-dioxane (18 cm^3) and water (6 cm^3). Toluene-*p*-sulfonic acid (0.070 g, 0.37 mmol) was added, and the reaction mixture heated at 55 °C for 20 h. Water (30 cm^3) was added, and the mixture extracted with diethyl ether (3 × 30 cm^3), the organic extracts dried ($MgSO_4$), and the solvent removed *in vacuo*. The orange–brown solid was purified by chromatography on silica (20% ethyl acetate–hexane) to afford the intermediate, 3,6-dimethoxy-2-hydroxybenzaldehyde (0.575 g, 96%), as bright yellow needles mp 67–67.5 °C (from ethyl acetate–hexane) (Found: M^+, 182.0588; C, 59.20. H, 5.45%. $C_9H_{10}O_4$ requires C, 59.30; H, 5.50; *M*, 182.0579); ν_{max}($CHCl_3$)/cm^{-1} 3019 (s, OH), 2839 (w, Ar-H), 1647 (s, C=O), 1591 (ArC=C), 1227 and 1197 (s, C-O) and 723 (m, oop ArC-H); δ_H (200 MHz; $CDCl_3$; Me_4Si) 12.18 (1H, s, O*H*), 10.29 (1H, s, C*H*O), 7.02 (1H, d, *J* 8.9, H-4), 6.26 (1H, d, *J* 8.9, H-5) and 3.84 and 3.83 (each 3H, s, OCH_3); δ_C (50.32 MHz; $CDCl_3$) 194.7 (*C*HO), 155.6 (C-3[a]), 153.3 (C-6[a]), 141.8 (C-2[a]), 120.1 (Ar-C), 110.8 (C-1), 99.2 (Ar-C), 56.6 and 55.5 (each OCH_3); *m*/*z* (EI) 182 (M^+, 100%), 167 (24), 163 (19), 139 (54), 136 (6), 121 (7), 107 (27), 93 (2), 79 (13), 69 (8), 55 (5), 51 (10) and 39 (8).

The intermediate 3,6-dimethoxy-2-hydroxybenzaldehyde (1.421 g, 7.80 mmol) was dissolved in dry DMF (25 cm^3). Benzyl bromide (1.39 cm^3, 2.00 g, 11.7 mmol) and potassium carbonate (1.82 g, 13.2 mmol) were added, and the reaction mixture was heated at 70 °C for 18 h under an inert nitrogen atmosphere. Water (50 cm^3) was then added and the mixture extracted with diethyl ether (6 × 50 cm^3). The organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The brown oil was purified by chromatography on silica (hexane, 20% ethyl acetate–hexane) yielding the *product* **18** (2.060 g, 97%) as an orange oil (Found: M^+, 272.1056. $C_{16}H_{16}O_4$ requires *M*, 272.1049); ν_{max}(film)/cm^{-1} 2940 (m, Ar-H), 1696 (s, C=O), 1582 (s, ArC=C), 1267 (s, C-O) and 751 (m, oop ArC-H); δ_H (200 MHz; $CDCl_3$; Me_4Si) 10.37 (1H, s, C*H*O), 7.47–7.29 (5H, m, Ph-H), 7.10 (1H, d, *J* 9.1, H-4), 6.63 (1H, d, *J* 9.1, H-5), 5.11 (2H, s, CH_2Ph) and 3.84 and 3.82 (each 3H, s, OCH_3); δ_C (50.32 MHz; $CDCl_3$) 189.8 (*C*HO), 154.5 (C-3[a]), 150.7 (C-6[a]), 146.7 (C-2[a]), 136.5 (C-1), 128.5, 128.3, 128.2 and 127.8 (4 × Ar-C), 119.1 (C-5[b]), 106.5 (C-4[b]), 76.0 (CH_2Ph) and 56.6 and 56.1 (each OCH_3); *m*/*z* (EI) 272 (M^+, 12%), 244 (8), 180 (14), 167 (3), 149 (10), 137 (3), 122 (2), 107 (4), 92 (8), 91 (100), 79 (3), 65 (10), 51 (4) and 39 (5).

2-Benzyloxy-1,4-dimethoxybenzene 21

Phenol **12** (0.554 g, 3.59 mmol) was dissolved in acetone (25 cm^3). Benzyl bromide (0.674 cm^3, 0.969 g, 5.67 mmol) was added, followed by potassium carbonate (0.90 g, 6.51 mmol), causing the reaction mixture to change from colourless to pink–yellow. The reaction was heated under reflux under an inert atmosphere of nitrogen for 18 h. The reaction was cooled, and the potassium carbonate removed by filtration. The solvent was removed *in vacuo* and the residue subjected to column chromatography (hexane, 10% ethyl acetate–hexane) to afford the *product* **21** (0.716 g, 82%) as a clear oil which formed a waxy solid (mp 37–37.5 °C) on standing (Found: M^+, 244.1105. $C_{15}H_{16}O_3$ requires *M*, 244.1099); ν_{max}(film)/cm^{-1} 3023 (m, Ar-H), 1612 and 1610 (s, ArC=C), 1205 (s, C-O) and 723 (m, oop ArC-H); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.43–7.27 (5H, m, Ph-H), 6.79 (1H, d, *J* 8.8, H-6), 6.53 (1H, d, *J* 2.8, H-3), 6.39 (1H, dd, *J* 8.8 and 2.8, H-5), 5.10 (2H, s, OCH_2Ph), 3.81 and 3.68 (each 3H, s, OCH_3); δ_C (100.625 MHz; $CDCl_3$) 154.1 (C-2[a]), 149.0 (C-1[a]), 144.0 (C-3[a]), 136.9, 128.4, 127.7, 127.2, 112.8, 103.9 and 102.6 (7 × Ar-C), 70.9 (OCH_2Ph) and 55.7 and 55.5 (each OCH_3); *m*/*z* (EI) 244 (M^+, 31%), 153 (11), 125 (17), 91 (100) and 65 (11).

Attempted synthesis of (2-benzyloxy-3,6-dimethoxyphenyl)-methanol 23

2-Benzyloxy-1,4-dimethoxybenzene **21** (0.637 g, 2.61 mmol) was dissolved in dry tetrahydrofuran (50 cm^3) and cooled to −25 °C. TMEDA (0.787 cm^3, 0.606 g, 5.21 mmol) was added, followed by *n*-butyllithium (1.74 cm^3 of a 1.50 M solution in hexane, 2.61 mmol), causing the colourless reaction mixture to turn yellow, then orange, and then black. After 1 h, paraformaldehyde (0.162 g, 5.41 mmol) was added. The black colour faded slowly, until the solution was clear, and a white precipitate had formed. The reaction was allowed to warm to room temperature and stirred overnight. Water (50 cm^3) was added, and the mixture extracted with diethyl ether (3 × 50 cm^3). The ether extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by column chromatography (hexane, 10% ethyl acetate–hexane) to afford the starting material **21** (0.243 g, 38% recovery), as well as two uncharacterizable products.

2-Benzyloxy-1-methoxy-3-(prop-2-enyl)benzene 25[32]

2-Methoxy-6-(prop-2-enyl)phenol (11.56 g, 70.42 mmol), prepared as described for the synthesis of **17**, was dissolved in distilled acetone (250 cm^3). Benzyl bromide (20.94 cm^3, 30.11 g, 0.18 mol) and potassium carbonate (24.81 g, 0.18 mol) were added with acetone (250 cm^3). The reaction mixture was heated under reflux under a nitrogen atmosphere for 16 h, after which tlc analysis with Pauly's salt as a spray reagent showed completion of reaction. The reaction mixture was cooled, and the

inorganic solids removed by filtration, and the solvent removed *in vacuo*. The pale yellow oil was purified by column chromatography (hexane, 5% ethyl acetate–hexane) to yield the *product* **25** (15.08 g, 86%) as a pale yellow oil (Found: M^+ 254.1308. $C_{17}H_{18}O_2$ requires *M*, 254.1306); ν_{max}(film)/cm^{-1} 2936 (w, =CH_2), 2836 (w, Ar-H), 1584 (m, ArC=C), 1271 (s, C-O) and 750 (m, oop ArC-H); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.49–7.31 (5H, m, Ar-H), 7.04–6.74 (3H, m, Ar-H), 5.97–5.84 (1H, m, H-2′), 5.05–4.96 (4H, m, CH_2Ph and H-3′), 3.84 (3H, s, OCH_3) and 3.36 (2H, dt, *J* 6.6 and 1.4, H-1′); δ_C (50.32 MHz; $CDCl_3$) 152.8 (C-2[a]), 145.7 (C-1[a]), 137.9 (Ar-C), 137.2 (C-3′), 134.2 (C-3), 128.2, 128.0 and 127.7 (3 × Ar-C), 123.9, 121.9 and 115.5 (C-4, C-5 and C-6), 110.4 (C-2′), 74.5 (*C*H_2Ph), 55.6 (O*C*H_3) and 34.1 (C-1′); *m*/*z* (EI) 254 (M^+, 22%), 163 (15), 137 (7), 103 (5), 92 (10), 91 (100) and 65 (8).

2-(2-Benzyloxy-3-methoxyphenyl)acetaldehyde 26

The substituted benzene **25** (2.099 g, 8.254 mmol) was dissolved in methanol (100 cm^3) and the solution was cooled to −40 °C. Ozone was bubbled through the solution for 8 min, after which zinc dust (1.08 g, 16.5 mmol) and acetic acid (1.89 cm^3, 1.98 g, 33.0 mmol) were added, and the cooling bath removed. The reaction mixture was stirred at room temperature for 1 h. Excess zinc was removed by filtration, and the solvent removed *in vacuo*. The solid yellow residue was taken up in H_2O (100 cm^3) and extracted with diethyl ether (3 × 50 cm^3). The organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The yellow oil was subjected to column chromatography (10% ethyl acetate–hexane) to afford the *arylacetaldehyde* **26** (1.787 g, 84%) as a clear oil (Found: M^+, 256.1090. $C_{16}H_{16}O_3$ requires *M*, 256.1098); ν_{max}(film)/cm^{-1} 3031 (w, Ar-H), 2837 (m, C-H of CHO), 1724 (s, C=O), 1586 and 1585 (m, ArC=C), 1269 and 1212 (s, C-O) and 754 (s, oop ArC-H); δ_H (200 MHz; $CDCl_3$; Me_4Si) 9.51 (1H, t, *J* 2.1, CHO), 7.41–7.27 (5H, m, Ph-H), 7.02 (1H, dd, *J* 8.2 and 7.8, H-5′), 6.87 (1H, dd, *J* 8.2 and 1.6, H-4′), 6.70 (1H, dd, *J* 7.8 and 1.6, H-6′), 5.00 (2H, s, CH_2Ph), 3.85 (3H, s, OCH_3) and 3.53 (2H, d, *J* 2.1, CH_2CHO); δ_C (50.32 MHz; $CDCl_3$) 199.4 (CHO), 152.7 (C-2′[a]), 145.9 (C-3′[a]), 137.2 (C-1′), 128.2, 128.2, 127.9 and 126.7 (4 × Ar-C), 124.1 (C-4[b]), 122.6 (C-5[b]), 111.8 (C-6), 74.3 (*C*H_2Ph), 55.5 (O*C*H_3) and 45.0 (*C*H_2CHO); *m*/*z* (EI) 256 (M^+, 46%), 238 (7), 227 (16), 165 (12), 137 (17), 136 (11), 122 (5), 92 (31), 91 (100), 65 (40) and 51 (10).

1-(2-Benzyloxy-3-methoxyphenyl)-3-nitropropan-2-ol 27

The substituted acetaldehyde **26** (1.596 g, 6.23 mmol) and nitromethane (3.37 cm^3, 3.80 g, 62.3 mmol) were suspended in an aqueous 0.025 M sodium hydroxide solution (25 cm^3). Cetyltrimethylammonium bromide (0.249 g, 0.684 mmol) was added, and the reaction mixture stirred vigorously overnight in a stoppered flask. The reaction mixture was then transferred to a continuous extraction apparatus, where it was extracted for 24 h with diethyl ether. Removal of the solvent *in vacuo* afforded a yellow oil which was purified by column chromatography (20% ethyl acetate–hexane) to afford the *3-nitropropan-2-ol* **27** as a clear oil (1.975 g, 100%) (Found: M^+, 317.1260. $C_{17}H_{19}NO_5$ requires *M*, 317.1263); ν_{max}(film)/cm^{-1} 3448 (s, OH), 2838 (w, Ar-H), 1558 (s, ArC=C), 1478 and 1380 (s, NO_2), 1273 and 1212 (s, C-O) and 754 (s, oop ArC-H); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.43–7.25 (5H, m, Ph-H), 7.04 (1H, dd, *J* 8.2 and 7.8, H-5′), 6.89 (1H, dd, *J* 8.2 and 1.6, H-4′), 6.74 (1H, dd, *J* 7.8 and 1.6, H-6′), 5.05 and 4.99 (each 1H, d, *J* 11.4, CH_2Ph), 4.47–4.45 (1H, m, H-2), 4.26–4.23 (2H, m, H-3), 3.89 (3H, s, OCH_3), 3.19 (1H, br d, *J* 4.6, O*H*) and 2.76 (2H, d, *J* 6.2, H-1); δ_C (50.32 MHz; $CDCl_3$) 152.8 (C-2′[a]), 145.8 (C-3′[a]), 137.2 (C-1′), 130.0, 128.5, 128.3 and 128.2 (4 × Ar-C), 124.5 (C-4), 122.8 (C-5), 111.7 (C-6), 79.9 (C-3), 75.0 (*C*H_2Ph), 69.1 (C-2), 55.7 (O*C*H_3) and 35.2 (C-1); *m*/*z* (EI) 317 (M^+, 14%), 265 (9), 257 (19), 256 (46), 238 (11), 227 (25), 165 (14), 164 (8), 162 (7), 161 (9), 137 (23), 122 (5), 92 (30), 91 (100), 77 (8), 65 (28), 51 (6) and 39 (10).

(*E*)-2-Benzyloxy-1-methoxy-3-[3-nitroprop-2-enyl]benzene 28

The substituted nitropropan-2-ol **27** (0.296 g, 0.93 mmol) was dissolved in dry dichloromethane (10 cm^3). Methanesulfonyl chloride (0.087 cm^3, 0.128 g, 1.12 mmol) was added, followed by diisopropylethylamine (0.195 cm^3, 0.144 g, 1.12 mmol). On addition of the base, HCl was evolved as white fumes, and the reaction mixture changed from a colourless solution to pale yellow. The reaction mixture was left to stir under an inert atmosphere of nitrogen for 18 h. The reaction was not complete by tlc analysis, but this reaction does not appear to go to completion. Water (10 cm^3) was added and the mixture extracted with dichloromethane (3 × 15 cm^3). The organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield an orange oil which was subjected to column chromatography (10–30% ethyl acetate–hexane) to afford the *nitropropene* **28** as a yellow oil (0.154 g, 96% based on starting material converted, 57% conversion), as well as recovered starting material (0.126 g) (Found: M^+, 299.1163. $C_{17}H_{17}NO_4$ requires *M*, 299.1157); ν_{max}(film)/cm^{-1} 3032 (w, Ar-H), 1584 and 1556 (s, ArC=C), 1522 and 1354 (m, NO_2), 1081 (s, C-O) and 753 (s, oop ArC-H); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.41–7.34 (5H, m, Ar-H), 7.29–6.68 (5H, m, Ar-H, H-2′ and H-3′), 5.07 (2H, s, CH_2Ph), 3.93 (3H, s, OCH_3) and 3.43 (2H, dd, *J* 6.9 and 1.6, H-1′); δ_C (50.32 MHz; $CDCl_3$) 152.8 (C-2[a]), 145.5 (C-1[a]), 141.0 (C-3′), 134.0 (C-2′), 137.3 (C-3), 129.9, 128.4, 128.2 and 128.1 (4 × Ar-C), 124.3 (C-4[b]), 121.7 (C-5[b]), 111.6 (C-6[b]), 74.7 (*C*H_2Ph), 55.7 (O*C*H_3) and 29.0 (C-1′); *m*/*z* (EI) 299 (M^+, 8%), 265 (10), 162 (26), 161 (27), 119 (5), 92 (35), 91 (100), 77 (6), 65 (30) and 51 (7).

2-Benzyloxy-1-methoxy-3-(3-nitropropyl)benzene 19

The substituted nitropropene **28** (0.818 g, 2.73 mmol) was dissolved in dry tetrahydrofuran (40 cm^3) and dry methanol (10 cm^3). Sodium borohydride (0.282 g, 74.5 mmol) was added portionwise. Effervescence occurred on addition of the hydride, and the reaction mixture changed from a pale yellow to a bright yellow solution. After 30 min, water (15 cm^3) was added and the organic solvents removed *in vacuo*. Diethyl ether was added to the residue, which was neutralized to pH 7 with 3% aqueous HCl. The mixture was then extracted with diethyl ether (2 × 20 cm^3). The organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. Column chromatography (10% ethyl acetate–hexane) yielded the *nitropropane* **19** as a pale yellow oil (0.577 g, 70%) (Found: M^+, 301.1325. $C_{17}H_{19}NO_4$ requires *M*, 301.1314); ν_{max}(film)/cm^{-1} 3032 (w, Ar-H), 1584 and 1559 (m, ArC=C), 1557 and 1380 (m, NO_2), 1082 (s, C-O) and 754 (s, oop ArC-H); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.43–7.30 (5H, m, Ar-H), 7.05–6.97 (1H, m, H-5), 6.84 (1H, dd, *J* 8.2 and 1.6, H-6), 6.72 (1H, dd, *J* 7.5 and 1.6, H-4), 5.00 (2H, s, CH_2Ph), 4.24 (2H, t, *J* 7.2, H-3′), 3.88 (3H, s, OCH_3), 2.61 (2H, t, *J* 7.2, H-1′) and 2.27–2.14 (2H, m, H-2′); δ_C (50.32 MHz; $CDCl_3$) 152.8 (C-2[a]), 145.8 (C-1[a]), 137.7 (C-3), 133.7, 128.4, 128.1 and 128.0 (4 × Ar-C), 124.1 (C-4[b]), 121.8 (C-5[b]), 110.9 (C-6[b]), 74.8 (*C*H_2Ph), 74.7 (C-3′), 55.7 (O*C*H_3), 27.8 (C-2′) and 26.9 (C-1′); *m*/*z* (EI) 301 (M^+, 1%), 267 (2), 163 (21), 149 (10), 131 (2), 103 (3), 92 (11), 91 (100), 77 (3), 65 (9), 51 (2) and 39 (4).

2-Benzyloxy-3-[(*E*/*Z*)-4-(2-benzyloxy-3-methoxyphenyl)-2-nitrobut-1-enyl]-1,4-dimethoxybenzene 20

Substituted nitropropane **19** (0.604 g, 2.00 mmol) and 2-benzyloxy-3,6-dimethoxybenzaldehyde **18** (0.489 g, 1.80 mmol) were dissolved in glacial acetic acid (3 cm^3) in a wide-necked round bottomed flask. Ammonium acetate (0.040 g, 0.52 mmol) was added. The flask was covered with a watch glass, and placed in a bath containing alumina. The bath was then placed in a conventional microwave oven and heated at 20% power for 5 min. Tlc analysis showed the reaction to be complete. The solvent was removed *in vacuo*, and the brown oil

purified by chromatography on silica gel (hexane, 20% ethyl acetate–hexane), yielding the *product* **20** (0.569 g, 57% based on aldehyde) as a bright yellow oil. This reaction gave different ratios of both geometric isomers on different occasions (it has not been determined which isomer is which) (Found M^+, 555.2246. $C_{33}H_{33}NO_7$ requires *M*, 555.2257); ν_{max}(film)/cm^{-1} 3088 (m, Ar-H), 1585 and 1583 (s, ArC=C), 1480 and 1350 (s, NO_2), 1082 (C-O) and 798 (s, oop ArC-H); δ_H (200 MHz; $CDCl_3$; Me_4Si) (values for the other isomer are given in the second set of NMR spectral data) 7.44–7.22 (10H, m, 2 × Ar-H), 6.95–6.70 (3H, m, H-4″, H-5″ and H-6″), 6.83 (1H, d, *J* 9.1, H-6), 6.52 (1H, d, *J* 9.1, H-5), 6.27 (1H, s, H-1′), 5.02 and 4.89 (each 2H, s, CH_2Ph), 3.84, 3.77 and 3.65 (each 3H, s, OCH_3) and 2.74 (4H, br s, H-3′ and H-4′); δ_C (50.32 MHz; $CDCl_3$) 152.7 (C-1[a]), 151.7 (C-4[a]), 151.0 (C-3″[a]), 146.8 (C-2[a]), 146.3 (C-2″[a]), 145.8 (C-3[b]), 137.7 and 137.2 (2 × Ar-C), 134.1 (C-1″[b]), 128.5, 128.3, 128.2, 128.2, 127.9 and 127.9 (6 × Ar-C), 123.9 (C-5″[c]), 122.1 (C-4″[c]), 120.5 (C-1′), 117.9 (C-2′), 113.3 (C-5[d]), 110.8 (C-6[d]), 105.8 (C-6″[d]), 75.3 (*C*H_2Ph), 74.7 (*C*H_2Ph), 56.4, 55.6 and 55.5 (each O*C*H_3), 34.1 (C-3′) and 28.5 (C-4′); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.67 (1H, s, H-1′), 7.42–7.27 (10H, m, Ar-H), 6.90–6.82 (2H, m, H-6′[a] and H-5″), 6.70 (1H, dd, *J* 8.2 and 1.6, H-6″), 6.60 (1H, dd, *J* 7.6 and 1.6, H-4″), 6.49 (1H, d, *J* 9.1, H-5[a]), 4.85 (2H, s, CH_2Ph), 4.81 (2H, s, CH_2Ph), 3.80, 3.76 and 3.62 (each 3H, s, OCH_3) and 2.76–2.75 (4H, m, H-3′ and H-4′); δ_C (50.32 MHz; $CDCl_3$) 153.3 (C-1[a]), 152.5 (C-4[a]), 151.0 (C-3″[a]), 146.9 (C-3), 146.0 (C-2[b]), 145.8 (C-2″[b]), 137.8 and 136.7 (2 × Ar-C), 134.8 (C-1″), 128.5, 128.2, 128.2, 128.1 and 128.0 (6 × Ar-C), 127.6 (C-1′), 123.7 and 121.7 (2 × Ar-C), 116.9 (C-2′), 113.9, 110.4 and 105.7 (3 × Ar-C), 75.2 and 74.3 (each *C*H_2Ph), 56.4, 55.5 and 55.7 (each O*C*H_3), 29.3 (C-3′[c]) and 26.8 (C-4′[c]); *m*/*z* (EI) 555 (M^+, 67%), 418 (34), 327 (24), 272 (14), 267 (29), 244 (10), 191 (22), 181 (15), 180 (18), 167 (7), 149 (14), 137 (10), 92 (20), 91 (10) and 65 (20).

1-(2-Benzyloxy-3,6-dimethoxyphenyl)-4-(2-benzyloxy-3-methoxyphenyl)butan-2-one 29

Compound **20** (0.095 g, 0.17 mmol) was dissolved in methanol (2 cm^3). A mixture of titanium trichloride (0.68 cm^3 of an aqueous 15% solution, 0.762 mmol) and an aqueous ammonium acetate solution (1.02 cm^3 of a 4 M solution, 4.09 mmol) was added, causing the yellow solution to turn black and stop stirring. A further 10 cm^3 of methanol was added to allow the reaction to stir again. After 6 h, the reaction was saturated with solid sodium hydrogen carbonate and water (10 cm^3) added, and the mixture extracted with chloroform (3 × 30 cm^3). The organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by preparative layer chromatography (25% ethyl acetate–hexane) to afford *1,4-diarylbutan-2-one* **29** (0.026 g, 29%) as a bright yellow oil (Found M^+, 526.2370. $C_{33}H_{34}O_6$ requires *M*, 526.2355); ν_{max}($CHCl_3$)/cm^{-1} 3050 (w, Ar-H), 1700 (s, C=O), 1600 and 1592 (m, ArC=C), 1050 (s, C-O) and 780 (s, oop ArC-H); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.44–7.25 (10H, m, 2 × Ar-H), 6.96–6.52 (5H, m, Ar-H), 4.96 (2H, s, CH_2Ph), 4.95 (2H, s, CH_2Ph), 3.86, 3.82 and 3.63 (each 3H, s, OCH_3), 3.62 (2H, s, H-1), 2.83–2.75 (2H, m, H-3) and 2.62–2.59 (2H, m, H-4); δ_C (50.32 MHz; $CDCl_3$) 208.1 (C-2), 152.8 (C-2′[a]), 152.1 (C-2″[a]), 147.1 (C-3′[a]), 137.9 (C-6′[a]), 137.8 (C-3″[a]), 135.6 (C-1′), 128.6, 128.4, 128.3 (×2), 128.2, 128.1, 128.0, 127.8, 123.9 and 122.0 (10 × Ar-C), 118.9 (C-1″), 111.3, 110.4 and 105.4 (3 × Ar-C), 74.9 and 74.6 (each *C*H_2Ph), 56.3, 55.8 and 55.7 (each O*C*H_3), 42.6 (C-1), 38.6 (C-3) and 24.5 (C-4); *m*/*z* (EI) 526 (M^+, 9%), 508 (3), 418 (14), 281 (14), 269 (11), 191 (11), 167 (22), 137 (11), 92 (12) and 91 (100).

2-[4-(2-Hydroxy-3-methoxyphenyl)-2-nitrobutyl]-3,6-dimethoxyphenol 30 and 1-(2-hydroxy-3,6-dimethoxyphenyl)-4-(2-hydroxy-3-methoxy)butan-2-one 7

Compound **20** (0.245 g, 0.44 mmol) was dissolved in methanol (12 cm^3). 10% Palladium on carbon (0.025 g, 10% by mass) was added to the solution. The reaction mixture was then placed in an autoclave under 1 atmosphere H_2 for 20 h. The bright yellow solution containing a black suspension lost its yellow colour during this time. The suspension was filtered over Celite, and washed with ethyl acetate (100 cm^3). The solvent was removed *in vacuo*, and the pale brown oil subjected to column chromatography (20–30% ethyl acetate–hexane) to afford a mixture of the *nitrobiphenol* **30** and *ketone* **7** (0.067 g, in a 4 : 1 ratio, ~30% of the nitro compound **30** and 10% of the ketone **7** by NMR spectroscopy) as a yellow oil. Data for compound **30**: (Found: M^+, 377.1489. $C_{19}H_{23}NO_7$ requires *M*, 377.1469); ν_{max}(film)/cm^{-1} 3500 (s, OH), 3080 (m, Ar-H), 1580 and 1579 (s, ArC=C), 1490 and 1363 (s, NO_2), 1073 (C-O) and 760 (s, oop ArC-H); δ_H (400 MHz; $CDCl_3$; Me_4Si) 6.76–6.66 (4H, m, H-5, H-4″, H-5″ and H-6″), 6.29 (1H, d, *J* 8.9, H-4), 5.83 and 5.70 (each 1H, br s, O*H*), 4.87–4.85 (1H, m, H-2′), 3.84, 3.80 and 3.70 (each 3H, s, OCH_3), 3.39–3.44 (1H, m, one of H-3′), 3.21–3.16 (1H, m, one of H-3′), 2.68–2.63 (2H, m, H-1′), 2.38–2.33 (1H, m, one of H-4′) and 2.13–2.08 (1H, m, one of H-4′); δ_C (50.32 MHz; $CDCl_3$) 152.6 (C-1[a]), 146.3 (C-2″[a]), 144.8 (C-6[a]), 143.5 (C-3[a]), 140.9 (C-3″[a]), 126.0 (C-2[b]), 122.2 and 119.3 (2 × Ar-C), 110.9 (C-1″[b]), 109.2, 108.8 and 100.7 (3 × Ar-C), 87.0 (C-2′), 56.3, 55.9 and 55.6 (each O*C*H_3), 32.8 (C-1′), 28.2 (C-4′) and 26.2 (C-3′); *m*/*z* (EI) 377 (M^+, 50%), 346 (13), 328 (42), 209 (41), 193 (57), 191 (51), 178 (16), 177 (30), 167 (63), 166 (28), 161 (27), 151 (14), 137 (100) and 91 (11). For characterisation of ketone **7** see the next experiment.

1-(2-Hydroxy-3,6-dimethoxyphenyl)-4-(2-hydroxy-3-methoxyphenyl)butan-2-one 7 and 4,7,8′-trimethoxy-3*H*-spiro[1-benzofuran-2,2′-chromane)] 6

Compound **20** (0.390 g, 0.700 mmol) was dissolved in 96% ethanol (15 cm^3). Cyclohexene (0.085 cm^3, 0.069 g, 0.84 mmol), 20% palladium hydroxide on carbon (0.170 g of a 50% suspension in water, 120 mg mmol^{-1}) and 1 drop concentrated HCl were added to the solution. The reaction mixture was then placed in an autoclave at 1 atmosphere H_2 for 30 min. The bright yellow solution containing a black suspension loses its original yellow colour during this time. The suspension was filtered through Celite, and washed with ethyl acetate (100 cm^3). The solvent was removed *in vacuo*, and the pale brown oil subjected to column chromatography (20–50% ethyl acetate–hexane) to afford firstly the *ketone* **7** (0.044 g, 18%) as a brown oil (Found: M^+, 346.1421. $C_{19}H_{22}O_6$ requires *M*, 346.1416); ν_{max}(film)/cm^{-1} 3508 (s, OH), 3001 (w, Ar-H), 1707 (s, C=O), 1603 and 1592 (m, ArC=C), 1068 (s, C-O) and 785 (s, oop ArC-H); δ_H (400 MHz; $CDCl_3$; Me_4Si) 6.75–6.71 (3H, m, H-4″, H-5″ and H-6″), 6.70 (1H, d, *J* 8.7, H-4′), 6.32 (1H, d, *J* 8.7, H-5′), 6.01 and 5.88 (each 1H, br s, O*H*), 3.84 and 3.82 (each 3H, s, OCH_3), 3.74 (2H, s, H-1), 3.69 (3H, s, OCH_3), 2.91–2.87 (2H, m, H-3) and 2.82–2.77 (2H, m, H-4); δ_C (50.32 MHz; $CDCl_3$) 209.3 (C-2), 152.3 (C-2′[a]), 146.5 (C-2″[a]), 144.6 (C-3′[a]), 143.5 (C-6′[a]), 141.1 (C-3″[a]), 127.2 (C-1′), 122.2 and 119.2 (2 × Ar-C), 110.5 (C-1″), 109.1, 108.6 and 100.7 (3 × Ar-C), 56.2, 55.8 and 55.6 (each O*C*H_3), 41.6 (C-1), 37.8 (C-3) and 24.0 (C-2); *m*/*z* (EI) 346 (M^+, 4%), 328 (100), 192 (21), 191 (94), 168 (19), 167 (20), 153 (10) and 137 (65).

This was followed by the *spiroketal* **6** (0.147 g, 64%) as a cream-coloured foam (Found: M^+, 328.1303. $C_{19}H_{20}O_5$ requires *M*, 328.1311); ν_{max}(KBr)/cm^{-1} 3006 (w, Ar-H), 1600 and 1590 (m, ArC=C), 1099 and 1070 (m, C-O) and 788 (s, oop ArC-H); δ_H (200 MHz; $CDCl_3$; Me_4Si) (where possible, values for the minor conformer have been given in parentheses) 6.74–6.60 (4H, m, H-6, H-7′, H-5′ and H-6′), 6.33 (1H, d, *J* 8.9, H-5), 3.84–3.62 (2H, m, H-3), 3.81, 3.80 and 3.74 (each 3H, s, OCH_3), 2.86–2.68 (2H, m, H-3′) and 2.49–2.41 (2H, m, H-4′); δ_C (50.32 MHz; $CDCl_3$) 160.4 (160.5) (C-7a), 152.4 (152.5) (C-8′a), 147.2 (146.4) (C-7), 145.3 (145.2) (C-4), 143.6 (143.6) (C-8′), 142.1

(141.4) (C-3a), 127.9 (127.5) (C-4′a), 122.2 (122.1) (Ar-C), 119.3 (119.2) (Ar-C), 111.5 (111.9) (C-8), 109.9 (109.4) (Ar-C), 108.9 (108.7) (Ar-C), 100.7 (100.8) (Ar-C), 56.4 (O*C*H$_3$), 55.9 (55.9) (O*C*H$_3$), 55.6 (55.7) (O*C*H$_3$), 33.6 (28.2) (C-10), 26.2 (27.9) (C-3′) and 21.9 (25.8) (C-3); δ_H (200 MHz; toluene-d$_8$; Me$_4$Si, ambient temp.) 6.84–6.14 (3H, m, H-5′, H-6′ and H-7′), 6.45 (1H, d, *J* 8.9, H-6), 6.10 (1H, d, *J* 8.9, H-5), 4.05 (3.83) (2H, s, H-3), 3.45 (3.51) (3H, s, OC*H*$_3$), 3.40 (3.43) (3H, s, OC*H*$_3$), 3.34 (3.32) (3H, s, OC*H*$_3$), 3.11–3.07 (1H, m, H-3′), 2.95–2.88 (2H, m, H-4′) and 2.61–2.08 (1H, m, H-3′); δ_H (200 MHz; toluene-d$_8$; Me$_4$Si) (300 K) 3.45 (3.52) (OC*H*$_3$), 3.40 (3.43) (OC*H*$_3$), 3.44 (3.32) (OC*H*$_3$) (6 lines); (333 K) 3.45 (3.53), 3.43 (3.44), 3.38 (3.36) (6 lines); (343 K) 3.55, 3.48, 3.48, 3.46, 3.39 (5 lines); (363 K) 3.55, 3.49, 3.47, 3.40 (4 lines); *m*/*z* (EI) 328 (M^+, 47%), 326 (10), 206 (13), 192 (12), 191 (60), 178 (10), 177 (40), 176 (32), 167 (15), 166 (19), 138 (10), 137 (100), 123 (13), 122 (13), 77 (13), 65 (12), 51 (11) and 43 (14); δ_C (50.32 MHz; toluene-d$_8$) 160.2 (160.1) (C-7a), 153.2 (153.4) (C-8′a), 147.8 (147.0) (C-7), 146.4 (146.1) (C-4), 144.5 (144.4) (C-8′), 142.7 (142.1) (C-3a), 137.5 (137.2) (C-4′a), 122.8 (Ar-C), 119.7 (119.5) (Ar-C), 112.6 (112.8) (C-8), 110.6 (109.9) (Ar-C), 109.4 (109.1) (Ar-C), 101.0 (100.1) (Ar-C), 56.4 (56.3) (O*C*H$_3$), 55.6 (55.6) (O*C*H$_3$), 55.4 (55.6) (O*C*H$_3$), 34.2 (28.8) (C-4′), 26.9 (28.7) (C-3′) and 22.7 (26.4) (C-3).

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