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A facile synthesis of fused aromatic spiroacetals based on the 3,4,3′,4′-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) skeleton

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Abstract—The facile synthesis of a series of aromatic 6,6-spiroacetals based on the parent 3,4,3′,4′-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) heterocyclic system is reported. Key steps included the use of a Sonogashira coupling for the synthesis of an aryl acetylene that was coupled to an aryl aldehyde to form a propargyl alcohol intermediate. Hydrogenation of the alkynol followed by oxidation produced a masked dihydroxy ketone that upon treatment with trimethylsilyl bromide underwent deprotection and cyclisation to the fused aromatic spiroacetal.

1. Introduction

The presence of spiroacetals as key sub-units in a wide range of biologically active natural products has prompted a range of synthetic methods for their preparation largely based on the acid catalysed cyclisation of dihydroxyketones or compounds containing a masked carbonyl group.[1] However, the occurrence of spiroacetals in which the oxygen atoms are derived from two aromatic hydroxy groups is less common and therefore fewer methods have been reported for their synthesis. The rubromycins **1–3** (Fig. 1) are a class of antibiotics isolated from cultures of *Streptomyces*[2] that exhibit activity against Gram-positive bacteria. β-Rubromycin **2** and γ-rubromycin **3** exhibit potent inhibition of human telomerase[3] with IC_{50} values of 3 μM and are active against the reverse transcriptase of human immunodeficiency virus-1.[4] These compounds possess a unique aromatic spiroacetal ring system in which benzannelated furan and pyran rings share one carbon atom to form a spiroacetal system. The fact that α-rubromycin **1**, which lacks this aryl spiroacetal moiety, exhibits substantially decreased inhibitory potency towards telomerase (IC_{50}>200 μM), suggests that this

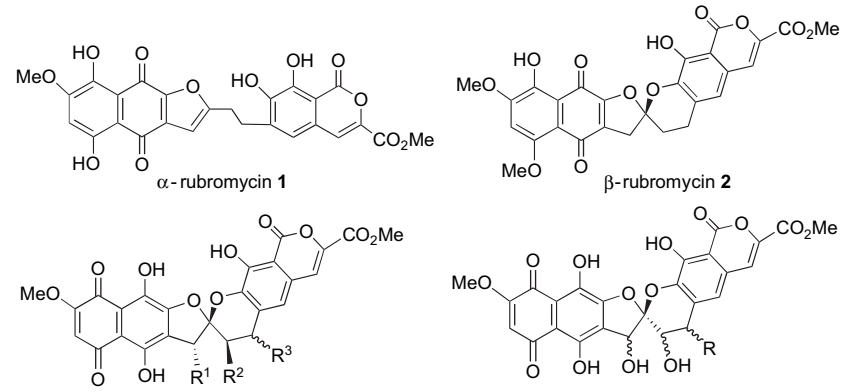

Figure 1. The rubromycin family of antibiotics.

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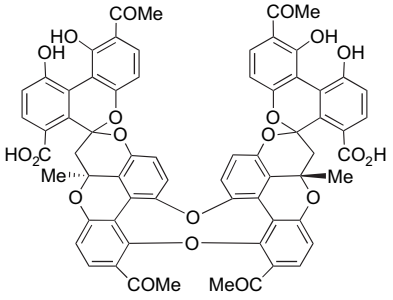
spiroacetal system plays an essential role in the observed inhibition of telomerase. Structurally related to the rubromycins are purpuromycin **4**,[5] a potential topical agent for vaginal infections,[6] heliquinomycin **5**,[7] an inhibitor of DNA helicase and griseorhodin C **6**.[8] All these compounds can act as bioreductive alkylating agents as postulated by Moore.[9]

To date the only synthesis of a naturally occurring bisbenzannelated spiroacetal is the elegant total synthesis of heliquinomycin **5** reported by Danishefsky et al.[10] In this case the key aromatic 5,6-spiroacetal ring system was assembled via electrophilic spiroacetalization of a naphthofuran bearing a phenolic hydroxyl group as the nucleophilic partner. The only other synthesis of the bisbenzannelated spiroacetal ring system present in γ-rubromycin **3** was reported by de Koning et al.[11] in which a Henry reaction allowed union of two aryl moieties and a Nef reaction was used to liberate the masked carbonyl group that induces the spiroacetalization step.

Our research group has also reported[12] the synthesis of several bisbenzannelated aromatic 5,6-spiroacetal analogues of the naturally occurring antibiotic γ-rubromycin **3**. We now herein report the synthesis of a series of aromatic 6,6-spiroacetals as found in the novel cytotoxic acetophenone, cynantetrone **7**.[13] These aryl 6,6-spiroacetals are homologous to the aryl 5,6-spiroacetal present in γ-rubromycin **3**. Extension of the central core spiroacetal ring system provides an opportunity to probe the effect of the conformation of the spiroacetal ring system on the inhibition of human telomerase. Previous syntheses of the 3,4,3′,4′-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) heterocyclic system involved hydrogenation and acid catalysed cyclisation of a disalicylideneacetone,[14] acid catalysed reaction of resorcinol with 2,6-dimethyl-2,5-heptadien-4-one or 1,5-diphenyl-1,4-pentadien-3-one,[15] or Michael reaction between dimedone and a 1,5-diaryl-1,4-pentadien-3-one[16] followed by intramolecular cyclisation of the Michael 1:2 adduct. These latter approaches however, only afforded C_2-symmetric spirochromans where the oxygen atoms were derived from two aromatic hydroxy groups. Our strategy for the synthesis of the 3,4,3′,4′-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) skeleton was amenable to the preparation of unsymmetrical analogues.

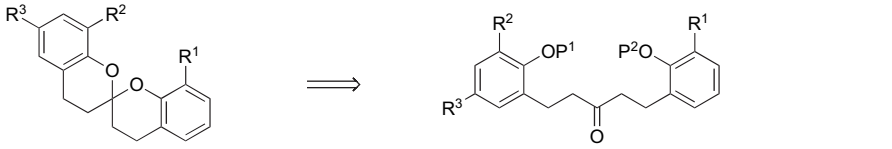


cynantetrone **7**

2. Results and discussion

As a part of our synthetic programme directed towards the synthesis of bioactive spiroacetal-containing natural products we prepared the tetracyclic aryl spiroacetals **8**–**12** via disconnection to the protected diphenolic ketones **13**–**17** (Scheme 1). The strategy for assembly of these spiroacetal precursors **13**–**17** focussed on reaction of the aryl acetaldehydes **18**–**20** with the acetylides derived from acetylenes **21** and **22**.

The synthesis of the aryl aldehydes **18**–**20** required for coupling with the acetylenes **21**,**22** is outlined in Scheme 2. Aldehydes **18**–**20** were prepared from the readily available phenols **23**–**25** via Claisen rearrangement of the derived allylphenols **26**–**28**. After protection of the Claisen rearrangement products **29**–**31** as either a methoxymethyl (MOM), a methoxyethoxymethyl (MEM) or an ethoxymethyl (EM) ether, hydroboration of the alkenes **32**–**34** using borane–dimethylsulfide complex at 0 °C afforded the



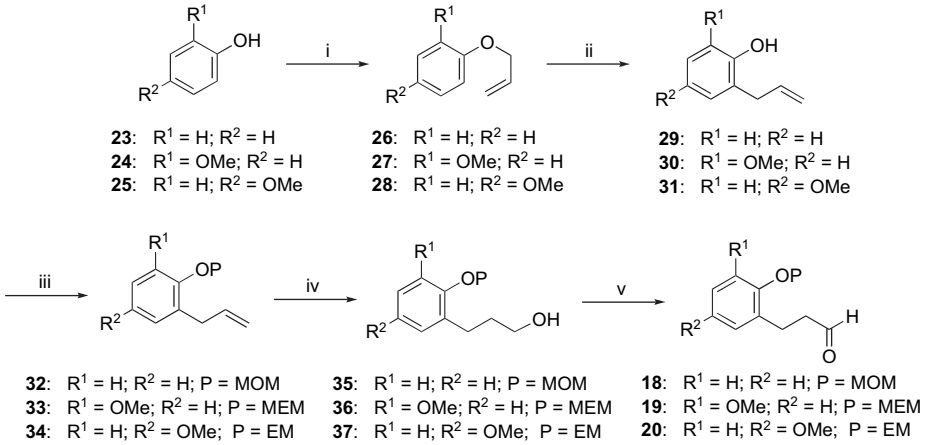
8: R^1 = H; R^2 = H; R^3 = H
9: R^1 = H; R^2 = OMe; R^3 = H
10: R^1 = H; R^2 = H; R^3 = OMe
11: R^1 = OMe; R^2 = H; R^3 = OMe
12: R^1 = OMe; R^2 = OMe; R^3 = H

13: R^1 = H; R^2 = H; R^3 = H; P^1 = MOM; P^2 = MEM
14: R^1 = H; R^2 = OMe; R^3 = H; P^1 = MEM; P^2 = MEM
15: R^1 = H; R^2 = H; R^3 = OMe; P^1 = EM; P^2 = MEM
16: R^1 = OMe; R^2 = H; R^3 = OMe; P^1 = EM; P^2 = MOM
17: R^1 = OMe; R^2 = OMe; R^3 = H; P^1 = MEM; P^2 = MOM

18: R^1 = H; R^2 = H; P = MOM
19: R^1 = OMe; R^2 = H; P = MEM
20: R^1 = H; R^2 = OMe; P = EM

21: R^1 = H; P = MEM
22: R^1 = OMe; P = MOM

Scheme 1.



Scheme 2. Reagents, conditions and yields: (i) allyl bromide, K_2CO_3, acetone, reflux, **26**, 86%; **27**, 83%; **28**, 97%; (ii) 180 °C, N_2, **29**, 72%; **30**, 87%; **31**, 99%; (iii) MOMCl/MEMCl/EMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C, **32**, 50%; **33**, 37%; **34**, 74%; (iv) $BH_3 \cdot SMe_2$, NaOH, H_2O_2, **35**, 60%; **36**, 55%; **37**, 70%; (v) TPAP, NMO, 4 Å MS, CH_2Cl_2, **18**, 51%; **19**, 70%; **20**, 40%.

primary alcohols **35**–**37** that underwent oxidation to the desired aldehydes **18**–**20** in moderate yield using tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO).

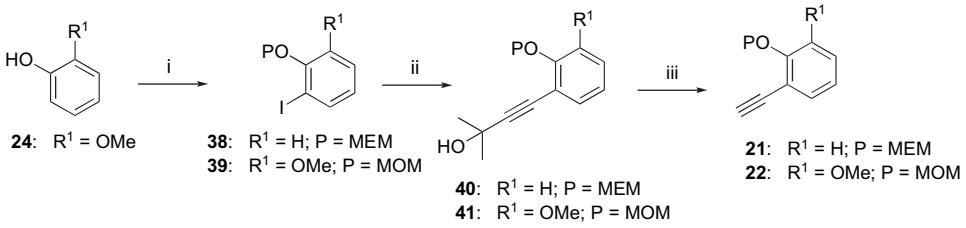
Acetylenes **21** and **22** were prepared (Scheme 3) via Sonogashira reaction of iodides **38** (prepared directly by MEM protection of 2-iodophenol) and **39** (prepared from 2-methoxyphenol **24** via MOM protection followed by ortholithiation and iodination) with 2-methyl-3-butyn-2-ol followed by pyrolysis of the resultant tertiary acetylenic alcohols **40** and **41** under basic conditions.

With both acetylenes **21**, **22** and aldehydes **18**–**20** in hand, the synthesis continued with the coupling of these two sub-units to construct the desired 6,6-spiroacetals **8**–**12** (Scheme 4). The coupling step involved generation of the acetylide by treatment of the appropriate acetylene **21** or **22** with butyllithium at −78 °C under nitrogen. After allowing time for the complete formation of the acetylide (40 min) the appropriate aldehyde **18**, **19** or **20** was added dropwise in tetrahydrofuran. After 1 h the reaction was allowed to warm to room temperature and stirred for a further 2 h. Aqueous workup followed by flash chromatography gave the desired propargyl alcohols **42**–**46** in good yield.

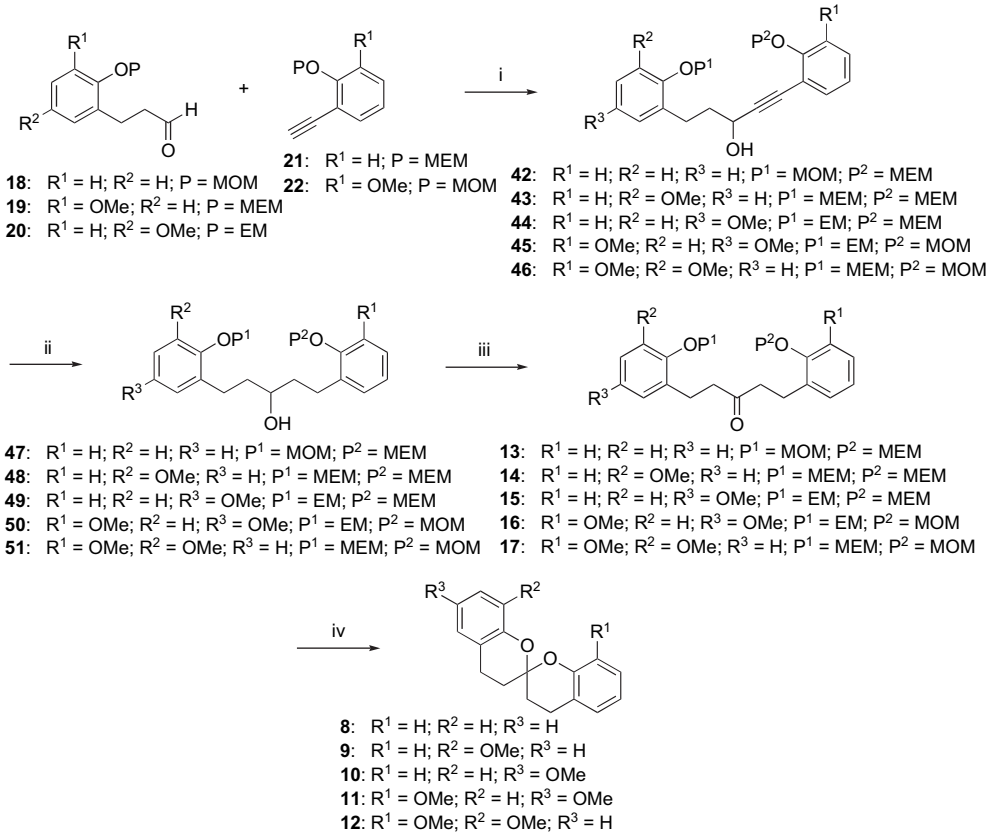
Hydrogenation of the alkyne was then effected by stirring the propargyl alcohols **42**–**46** in ethyl acetate with potassium carbonate over 10% palladium on carbon under hydrogen. The resulting secondary alcohols **47**–**51** were isolated in nearly quantitative yield after purification by flash chromatography. Oxidation of the secondary alcohols **47**–**51** using tetra-*n*-propylammonium perruthenate (TPAP), 4-methylmorpholine *N*-oxide (NMO) and 4 Å molecular sieves in dichloromethane provided the ketones **13**–**17** required for the final spirocyclisation step.

The final step in the synthesis of the aryl 6,6-spiroacetals **8**–**12** involved deprotection of the phenolic hydroxyl groups of the ketones **13**–**17** and subsequent Lewis acid catalysed cyclisation (Scheme 4). The ketones **13**–**17** were treated with trimethylsilyl bromide (10 equiv) in dichloromethane in the presence of 4 Å molecular sieves to effect both deprotection of the methoxyethoxymethyl, or equivalent group, and the cyclisation step.

The ^{1}H NMR spectra of the aryl 6,6-spiroacetals **8**–**12** were much simpler than those of the ketone precursors **13**–**17** due to the symmetrical, or almost, symmetrical nature of the products. The electronic differences induced by the presence of methoxy substituents on the aryl ring did not exhibit an effect on the central spiroacetal ring system. Additionally, the loss of the ether protecting groups led to cleaner NMR spectra. The most characteristic feature in the ^{13}C NMR spectra of the spiroacetals **8**–**12** was the presence of a characteristic quaternary spirocarbon at δ_C 96.2–96.4 ppm. In the ^{1}H NMR spectra four sets of doublets of doublets of doublets could be assigned to the diastereotopic protons of



Scheme 3. Reagents, conditions and yields: (i) MOMCl, $^{i}Pr_2EtN$, CH_2Cl_2, 0 °C then BuLi, THF, rt, 2 h then −45 °C, I_2, 1 h, **39**, 14%; (ii) PPh_3, $PdCl_2(PPh_3)_2$, 2-methyl-3-butyn-2-ol, Et_3N, CuI, **40**, 95%; **41**, 99%; (iii) NaOH, toluene, reflux, **21**, 86%; **22**, 72%.



Scheme 4. Reagents, conditions and yields: (i) ^{n}BuLi, THF, −78 °C to rt, **42**, 57%; **43**, 51%; **44**, 88%; **45**, 73%; **46**, 54%; (ii) 10% Pd/C, K_2CO_3, EtOAc, **47**, 71%; **48**, 77%; **49**, 70%; **50**, 99%; **51**, 83%; (iii) TPAP, NMO, 4 Å MS, CH_2Cl_2, **13**, 99%; **14**, 91%; **15**, 99%; **16**, 95%; **17**, 99%; (iv) TMSBr, CH_2Cl_2, −30 °C to rt, **8**, 97%; **9**, 96%; **10**, 99%; **11**, 96%; **12**, 96%.

the methylene groups in the spiroacetal ring system. The two methylene groups were distinguished using 2D spectroscopy (COSY). Long distance coupling between the aromatic protons of the outer aryl-rings with four protons in the inner spiroacetal rings allowed conclusive assignment of the benzylic CH_2 groups (Fig. 2).

An X-ray crystal structure was also obtained[17] for aryl spiroacetal **11**. The ORTEP diagram for spiroacetal **11** (Fig. 3) clearly shows that the spiroacetal rings adopt a flattened chair–chair arrangement with two anomeric effects stabilising the bis-axial conformation.

In summary five aryl 6,6-spiroacetals that are homologous to the aryl 5,6-spiroacetal ring system present in the telomerase inhibitor γ-rubromycin **3** have been prepared using trimethylsilyl bromide to effect cyclisation of a suitably protected diphenolic ketone precursor. The cyclisation precursors in turn were readily available via coupling of an aryl acetylene to an aryl aldehyde fragment. A Sonogashira reaction was used to prepare the acetylene precursors. The 6,6-spiroacetals thus prepared adopted a flattened chair–chair bis-axial conformation.

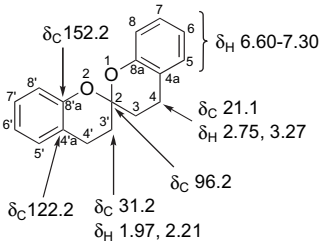


Figure 2. Characteristic ^{1}H and ^{13}C NMR chemical shifts for the parent 6,6-spiroacetal **8**.

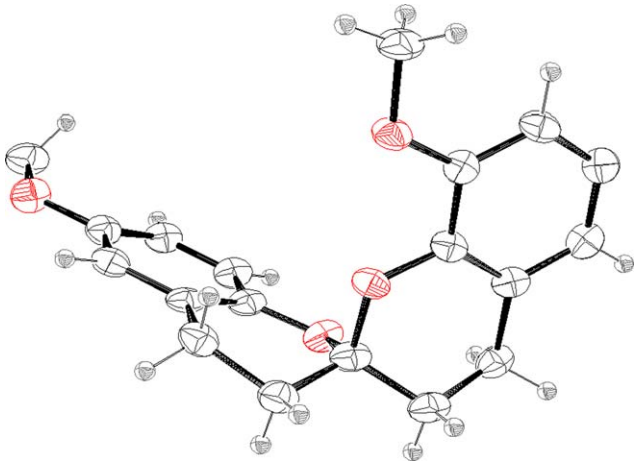


Figure 3. ORTEP diagram for 6,6-spiroacetal **11**.[17]

3. Experimental

3.1. General details

Dichloromethane, toluene and triethylamine were distilled from calcium hydride prior to use. Tetrahydrofuran was dried over sodium/benzophenone and distilled before use. Glassware was oven or flame-dried under an atmosphere of nitrogen. Reactions were carried out under an atmosphere of nitrogen unless otherwise specified. Infrared spectra (IR) were obtained using Perkin Elmer Spectrum 1000 Fourier Transform Infrared spectrometer from thin films between sodium chloride plates. Absorbtion peaks are expressed in wave numbers (cm^{-1}) and were measured between 450 cm^{-1} and 4000 cm^{-1}. The signal strengths are expressed by the abbreviations: s=strong, m=medium, w=weak, and br=broad. NMR spectra were recorded on a Bruker DRX300 spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or on a Bruker DRX400 spectrophotometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are recorded as parts per million (ppm) downfield from tetramethylsilane (TMS) as the internal standard or relative to the ^{1}H in $CDCl_3$. The ^{13}C values were referenced to the residual chloroform peak at δ 77.0 ppm. ^{13}C shifts are reported as chemical shift and assignment. ^{1}H shifts are reported as chemical shift, relative integral, multiplicity, coupling constant and assignment. ^{1}H MNR data are reported as s (singlet); d (doublet); dd (doublet of doublets); dt (doublet of triplets); ddd (doublet of doublets of doublets); t (triplet); q (quartet); m (multiplet); br (broad). *J* values are given in Hertz. All assignments were made with the aid of DEPT 135, COSY and HSQC experiments where required. Low resolution mass spectra were recorded using a VG70-SE spectrometer operating at nominal accelerating voltage of 70 eV. High resolution mass spectra were recorded using a VG70-SE spectrometer operating at nominal resolution of 5000–10,000 as appropriate. Fragmentation was induced using desorptive electron impact (DEI^+), electron impact (EI) or fast atom bombardment (FAB^+). Fast atom bombardment (FAB) mass spectra were obtained using 3-nitrobenzyl alcohol as the matrix. Major and significant fragments are quoted in the form *x*(*y*), where *x* is the mass to charge ratio and *y* is the percentage abundance relative to the base peak. Purification by flash chromatography was performed using Merck silica gel 0.0063–0.10 mm with the solvent systems indicated. Thin layer chromatography (TLC) was run on silica precoated aluminium plates (Merck Kieselgel F_{254}). Compounds were visualised under UV fluorescence and by staining with vanillin in methanolic acid followed by heating. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

3.2. Standard procedures

3.2.1. Allylation of phenols. To a stirred solution of the appropriate phenol (5.0 g, 53 mmol) in acetone (30 mL) were added potassium carbonate (9.23 g, 159 mmol) and allyl bromide (4.58 mL, 54 mmol). The mixture was heated under reflux at 65 °C for 16 h, cooled to room temperature, filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL) and washed sequentially with 1 M aqueous sodium hydroxide (15 mL), water (15 mL) and brine (15 mL). The organic layer was dried over magnesium sulfate and concentrated in vacuo. The resultant residue was purified by flash chromatography using the specified solvent system.

3.2.2. Claisen rearrangement of allyl ether. Neat allyl phenyl ether (475 mg, 3.5 mmol) was placed in an oven dried flask or a sealed tube and heated at 200 °C under a nitrogen atmosphere for 16 h. The reaction mixture changed from colourless oil to pale brown oil. The reaction mixture was allowed to cool and the thick oil was subjected to column chromatography using the specified solvent system.

3.2.3. Protection of allylated phenols as methoxymethyl, methoxyethoxymethyl or ethoxymethyl ethers. A stirred solution of the appropriate 2-allylphenol (344 mg, 2.56 mmol) in dry dichloromethane (5 mL) was cooled to 0 °C under nitrogen. Diisopropylethylamine (0.803 mL, 4.61 mmol) was added followed by methoxyethoxymethyl chloride (0.270 mL, 3.59 mmol) dropwise. The cooling bath was removed after 30 min and the mixture was warmed to room temperature over 12 h. Dichloromethane was removed in vacuo and the residue was taken up in diethyl ether (10 mL) and washed sequentially with water (10 mL), 10% aqueous sodium hydroxide (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate and concentrated in vacuo. The resultant residue was purified by column chromatography using the specified solvent system.

3.2.4. Hydroboration of protected allylphenol. Allylphenol (100 mg, 0.45 mmol) was dissolved in tetrahydrofuran (6 mL) and the solution was cooled to 0 °C. Borane–dimethyl sulfide complex (0.09 mL, 0.9 mmol) was added dropwise and the mixture was stirred at 0 °C for 5 h then warmed to room temperature and stirred overnight. The excess borane was quenched by the addition of methanol (0.5 mL). Sodium hydroxide (1 M, 0.5 mL) was added carefully followed by the dropwise addition of hydrogen peroxide (30%, 0.5 mL) and the resultant mixture stirred overnight. The mixture was extracted with diethyl ether (5 mL) and the combined organic extracts were dried over magnesium sulfate. The solvents were concentrated in vacuo and the resultant residue was purified by flash chromatography using the specified solvent system.

3.2.5. TPAP oxidation of the alcohol. To a mixture of the alcohol (294 mg, 1.5 mmol) in dichloromethane (5 mL) with 4 Å molecular sieves (300 mg) were added tetra-*n*-propylammonium perruthenate (30 mg, 0.075 mmol) and 4-methylmorpholine *N*-oxide (263 mg, 2.25 mmol) and the reaction was stirred at room temperature for 1 h. The mixture was filtered through a plug of flash silica and concentrated in vacuo. The resultant residue was purified by flash chromatography using the specified solvent system.

3.2.6. Sonogashira coupling. A mixture of the protected iodophenol (308 mg, 1.0 mmol), 2-methyl-3-butyn-2-ol (0.154 mL, 1.6 mmol), triphenylphosphine (5 mg, 0.02 mmol) and bis(triphenylphosphine)palladium(II) dichloride (7 mg, 0.01 mmol) in dry triethylamine (5 mL) was stirred under nitrogen at 80 °C for 15 min. Copper(I) iodide (4 mg, 0.002 mmol) was then added and the reaction was heated

overnight at 80 °C. The reaction mixture was filtered through a plug of Celite® and concentrated under reduced pressure. The resultant residue was purified by column chromatography using the specified solvent system.

3.2.7. Pyrolysis of the tertiary alcohol. A mixture of the alcohol (101 mg, 0.384 mmol) and solid sodium hydroxide (468 mg, 1.92 mmol) in dry toluene (10 mL) was heated under reflux for 3.5 h. The reaction was quenched by the addition of saturated ammonium chloride solution (4 mL) and extracted with diethyl ether (10 mL). The solvents were removed under reduced pressure and the resultant residue was purified by column chromatography using the specified solvent system.

3.2.8. Coupling of the acetylene with the aldehyde. *n*-Butyllithium (0.18 mL, 1.6 M in hexane, 0.29 mmol) was added dropwise to a stirred solution of the acetylene (75 mg, 0.31 mmol) in tetrahydrofuran (1 mL) at −78 °C under nitrogen. The solution was stirred at −78 °C for 40 min then a solution of the aldehyde (50 mg, 0.26 mmol) in tetrahydrofuran (0.5 mL) was added dropwise and the mixture was stirred for 1 h. The mixture was allowed to warm to room temperature and stirred for 2.5 h. Water (3 mL) was added and the mixture was extracted with ethyl acetate (3×2 mL). The combined organic extracts were washed with brine (1 mL), dried over magnesium sulfate and concentrated in vacuo. The resultant residue was purified by flash chromatography using the specified solvent system.

3.2.9. Hydrogenation of acetylene. A mixture of the acetylene (80 mg, 0.17 mmol), 10% palladium on carbon (67 mg, 0.63 mmol) and potassium bicarbonate (86 mg, 0.63 mmol) in ethyl acetate (2 mL) was stirred under an atmosphere of hydrogen at room temperature for 2 h. The resulting mixture was filtered through a plug of Celite® and the filtrate was concentrated in vacuo. The resulting residue was purified by flash chromatography using the specified solvent system.

3.2.10. Oxidation of the secondary alcohol to a ketone. Tetra-*n*-propylammonium perruthenate (0.3 mg, 0.008 mmol) was added to a stirred mixture of the secondary alcohol (74 mg, 0.16 mmol), 4-methylmorpholine *N*-oxide (3 mg, 0.24 mmol) and 4 Å molecular sieves (45 mg) in dichloromethane (1 mL). The reaction was stirred at room temperature for 1.5 h then filtered through a plug of silica gel and the filtrate concentrated in vacuo. The resultant residue was purified by flash chromatography using the specified solvent system.

3.2.11. Cyclisation of the ketone to a 6,6-spiroacetal. To a mixture of ketone (70 mg, 0.15 mmol), 4 Å molecular sieves (50 mg) in dichloromethane (1.5 mL) at −30 °C was added trimethylsilyl bromide (0.20 mL, 1.5 mmol) and the reaction was stirred under nitrogen for 1 h. The reaction was warmed to 0 °C stirred for 1 h, then poured into water (1 mL) and extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with brine (1 mL), dried over magnesium sulfate and concentrated in vacuo. The resultant residue was purified by flash chromatography using the specified solvent system.

3.3. Spectroscopic data for individual compounds

3.3.1. Allyl phenyl ether (26). The allylation reaction was carried out according to the standard procedure using phenol **23** (5.0 g, 53 mmol), allyl bromide (4.58 mL, 54 mmol) and potassium carbonate (9.23 g, 159 mmol). The product was purified by column chromatography using hexane–ethyl acetate (90:10) as eluent to give the title compound **26** (6.09 g, 86%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 4.52 (2H, d, *J* 5.5, $OCH_2CH{=}CH_2$), 5.28 (1H, dd, J_{gem} 1.6, *J* 7.8, $OCH_2CH{=}CH_AH_B$), 5.43 (1H, dd, J_{gem} 1.6, *J* 13.8, $OCH_2CH{=}CH_AH_B$), 6.06 (1H, m, $OCH_2CH{=}CH_2$), 7.3–6.9 (5H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 68.6 ($OCH_2CH{=}CH_2$), 117.5 ($OCH_2CH{=}CH_2$), 133.3 ($OCH_2CH{=}CH_2$), 114.7, 120.8, 129.4 (Ar-CH), 158.5 (q, Ar-C). The spectroscopic data were in agreement with the literature.[18]

3.3.2. 2-Allylphenol (29). The Claisen rearrangement reaction was carried out according to the standard procedure using allyl phenyl ether **26** (475 mg, 3.5 mmol). The product was purified by column chromatography using hexane–ethyl acetate (80:20) as eluent to give the title compound **29** (338 mg, 72%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 3.42 (2H, d, *J* 6.7, $CH_2CH{=}CH_2$), 4.95 (1H, br s, O*H*), 5.17 (1H, m, $CH_2CH{=}CH_AH_B$), 5.18 (1H, t, *J* 1.5, $CH_2CH{=}CH_AH_B$), 6.03 (1H, m, $CH_2CH{=}CH_2$), 7.3–6.9 (4H, Ar-H); δ_C (75 MHz, $CDCl_3$) 35.0 ($CH_2CH{=}CH_2$), 116.3 ($CH_2CH{=}CH_2$), 115.7, 120.8 (Ar-CH), 125.2 (q, C2), 127.8, 136.2 (Ar-CH), 136.2 ($CH_2CH{=}CH_2$), 154.0 (q, C1). The spectroscopic data were in agreement with the literature.[19]

3.3.3. 1-Allyl-2-(methoxymethoxy)benzene (32). The protection step was carried out according to the standard procedure using 2-allylphenol **29** (344 mg, 2.56 mmol), diisopropylamine (0.803 mL, 4.61 mmol) and methoxymethyl chloride (0.270 mL, 3.59 mmol). The product was purified by column chromatography using hexane–ethyl acetate (80:20) as eluent to give the title compound **32** (226 mg, 50%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 3.41 (2H, d, *J* 6.2, $CH_2CH{=}CH_2$), 3.48 (3H, s, OCH_3), 5.02 (1H, m, $CH_2CH{=}CH_AH_B$), 5.07 (1H, m, $CH_2CH{=}CH_AH_B$), 5.20 (2H, s, OCH_2O), 5.98 (1H, m, $CH_2CH{=}CH_2$), 7.3–6.9 (4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 34.4 ($CH_2CH{=}CH_2$), 56.0 (OCH_3), 94.4 (OCH_2O), 115.4 ($CH_2CH{=}CH_2$), 137.0 ($CH_2CH{=}CH_2$), 115.4, 121.7, 127.3, 130.0 (Ar-CH), 137.0 (q, C2), 154.0 (q, C1). The spectroscopic data were in agreement with the literature.[20]

3.3.4. 3-(2-(Methoxymethoxy)phenyl)propan-1-ol (35). The hydroboration reaction was carried out according to the standard procedure using 1-allyl-2-(methoxymethoxy)-benzene **32** (100 mg, 0.45 mmol) and borane–dimethyl sulfide complex (0.09 mL, 0.9 mmol). The product was purified by column chromatography using hexane–ethyl acetate (80:20) as eluent to give the *title compound* **35** (65 mg, 60%) as colourless oil. (Found: M^+, 196.1098, $C_{11}H_{16}O_3$ requires 196.1099); ν_{max} (film)/cm^{-1} 3368 (br, O–H), 2934 (s, ArC–H), 2358 (w, O–CH_2–O), 1233 (m, C–O), 1151 (w, C–OH); δ_H (400 MHz, $CDCl_3$) 1.68 (1H, br s, O*H*), 1.86 (2H, quintet, *J* 7.4, 6.2, $CH_2CH_2CH_2OH$), 2.75 (2H, t, *J* 7.4, $CH_2CH_2CH_2OH$), 3.50 (3H, s, OCH_3), 3.64 (2H, t, *J* 6.2, $CH_2CH_2CH_2OH$), 5.21 (2H, s, OCH_2O), 7.3–6.9

(4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 26.1 (CH_2, C-2), 33.0 (CH_2, C-3), 56.0 (OCH_3), 62.0 (CH_2OH), 94.6 (OCH_2O), 113.9, 121.8, 127.2, 130.2 (Ar-CH), 130.6 (q, C1′), 155.2 (q, C2′); *m/z* (EI, %) 196 (M^+, 4), 164 (15), 134 (71), 121 (7), 119 (12), 91 (11), 45 (100).

3.3.5. 3-(2-(Methoxymethoxy)phenyl)propanal (18). The oxidation was carried out according to the standard procedure using [3-(2-(methoxymethoxy)phenyl)]propan-1-ol (**35**) (294 mg, 1.5 mmol), tetra-*n*-propylammonium perruthenate (30 mg, 0.075 mmol), 4-methylmorpholine *N*-oxide (263 mg, 2.25 mmol) and 4 Å molecular sieves (500 mg). The product was purified by column chromatography using hexane–ethyl acetate (70:30) as the eluent to give the *title compound* **18** (148 mg, 51%) as a colourless oil. (Found: M^+, 194.0940, $C_{11}H_{14}O_3$ requires 194.0943); ν_{max} (film)/cm^{-1} 2932 (m, ArC–H), 2826 (m, CH_2–O–CH_2), 2724 (w, CHO), 1722 (s, C=O), 1492 (w, C–O–C), 1235 (w, C–O); δ_H (400 MHz, $CDCl_3$) 2.76 (2H, dt, *J* 7.8, 1.6, CH_2CHO), 2.98 (2H, t, *J* 7.8, ArCH_2), 3.50 (3H, s, OCH_3), 5.20 (2H, s, OCH_2O), 7.3–6.9 (4H, m, Ar-H), 9.83 (1H, t, *J* 1.6, C*H*O); δ_C (75 MHz, $CDCl_3$) 23.5 (*C*H_2CH$_2$CHO), 44.0 (*C*H_2CHO), 56.1 (OCH_3), 114.2 (OCH_2O), 114.0, 121.9, 127.2, 130.2 (Ar-CH), 129.2, (q, C1′), 155.1 (q, C2′), 202.3 (CHO); *m/z* (EI, %) 194 (M^+, 3), 162 (4), 132 (16), 121 (6), 91 (6), 77 (5), 45 (100).

3.3.6. 1-Iodo-2-((2-methoxyethoxy)methoxy)benzene (38). The protection step was carried out according to the standard procedure using 2-iodophenol (1.07 g, 4.9 mmol), diisopropylethylamine (1.65 mL, 9.4 mmol) and methoxyethoxymethyl chloride (0.81 mL, 7.2 mmol). The product was purified by column chromatography using hexane–ethyl acetate (85:15) as the eluent to give the *title compound* **38** (1.14 g, 75%) as a colourless oil. (Found: M^+, 307.9912, $C_{10}H_{13}IO_3$ requires 307.9909); ν_{max} (film)/cm^{-1} 2923 (s, ArC–H), 2879 (m, O–CH_2–O), 1472 (s, C–O–C), 1229 (s, C–O), 644 (w, C–I); δ_H (400 MHz, $CDCl_3$) 3.35 (3H, s, OCH_3), 3.57 (2H, t, *J* 4.7, OCH_2CH$_2$OCH$_3$), 3.87 (2H, t, *J* 4.7, OCH$_2$CH_2OCH$_3$), 5.36 (2H, s, OCH_2O), 6.65–7.80 (4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 58.9 (OCH_3), 68.1 (O*C*H$_2$CH$_2$OCH$_3$), 71.4 (OCH$_2$*C*H$_2$OCH$_3$), 87.1 (q, C-1), 93.9 (OCH_2O), 115.0, 123.7, 129.5, 139.4 (Ar-CH), 156.0 (q, C-2); *m/z* (EI, %) 308 (M^+, 6), 233 (5), 220 (5), 106 (6), 89 (99), 76 (7), 59 (100), 45 (6).

3.3.7. 4-[(2-Methoxyethoxy)methoxy)phenyl]-2-methylbut-3-yn-2-ol (40). The Sonogashira reaction was carried out according to the standard procedure using 1-iodo-2-((2-methoxyethoxy)methoxy) benzene (**38**) (308 mg, 1.0 mmol), 2-methyl-3-butyn-2-ol (0.154 mL, 1.6 mmol), triphenylphosphine (5 mg, 0.02 mmol), bis(triphenylphosphine)palladium(II) dichloride (7 mg, 0.01 mmol), triethylamine (5 mL) and copper(I) iodide (4 mg, 0.002 mmol). The product was purified by column chromatography using hexane–ethyl acetate (70:30) as the eluent to give the *title compound* **40** (247 mg, 95%) as a colourless oil. (Found: M^+, 264.1356, $C_{15}H_{20}O_4$ requires 264.1362); ν_{max} (film)/cm^{-1} 3423 (br, O–H), 2980 (s, ArC–H), 2930 (s, O–CH_2–O), 2228 (w, C=C), 1489 (s, C–O–C), 1449, 1372 (w, geminal CH_3); δ_H (400 MHz, $CDCl_3$) 1.63 (6H, 2×s, 2×CH_3), 3.81 (3H, s, OCH_3), 2.47 (1H, br s, O*H*), 3.59 (2H, t, *J* 4.7, OCH_2CH$_2$OCH$_3$), 3.91 (2H, t, *J* 4.7, OCH$_2$CH_2OCH$_3$), 5.32 (2H, s, OCH_2O), 6.90–7.40 (4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 31.0 (C(*C*H_3)$_2$), 59.0 (OCH_3), 65.6 (q, COH), 67.9 (O*C*H$_2$CH$_2$OCH$_3$), 71.6 (OCH$_2$*C*H$_2$OCH$_3$), 78.3 (q, Ar–*C*≡C), 94.4 (OCH_2O), 97.9 (Ar–C=*C*), 113.7 (q, C1′), 115.8, 122.0, 129.6, 133.4, (Ar–CH), 157.7 (q, C2′); *m/z* (EI, %) 264 (M^+, 0.5), 158 (100), 143 (8), 131 (7), 115 (5), 89 (24), 59 (85), 43 (24).

3.3.8. 1-Ethynyl-2-((2-methoxyethoxy)methoxy)benzene (21). The reaction was carried out according to the standard procedure using 4-(2-((2-methoxyethoxy)-methoxy)-phenyl)-2-methylbut-3-yn-2-ol (**40**) (101 mg, 0.384 mmol) and sodium hydroxide (468 mg, 1.92 mmol). The product was purified by column chromatography using hexane–ethyl acetate (70:30) as the eluent to give the *title compound* **21** (68 mg, 86%) as a colourless oil. (Found: M^+, 206.0941, $C_{12}H_{14}O_3$ requires 206.0943); ν_{max} (film)/cm^{-1} 3235 (s, C≡C–H), 2970 (s, ArC–H), 2930 (m, O–CH_2–O), 2100 (w, C≡C), 1489 (w, C–O–C); δ_H (400 MHz, $CDCl_3$) 3.27 (1H, s, C≡C*H*), 3.37 (3H, s, OCH_3), 3.56 (2H, t, *J* 4.7, OCH_2CH$_2$OCH$_3$), 3.88 (2H, t, *J* 4.7, OCH$_2$CH_2OCH$_3$), 5.32 (2H, s, OCH_2O), 6.90–7.40 (4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 30.9 (C≡*C*H), 59.0 (OCH_3), 67.9 (O*C*H$_2$CH$_2$OCH$_3$), 71.5 (OCH$_2$*C*H$_2$OCH$_3$), 80.0 (q, Ar-*C*≡C), 81.0 (q, C1), 94.4 (OCH_2O), 115.0, 121.7, 130.2, 134.1, (Ar-CH), 158.3 (q, C2); *m/z* (EI, %) 206 (M^+, 3), 131 (15), 118 (5), 103 (4), 89 (70), 77 (8), 100 (85), 45 (5).

3.3.9. 1-[((2-Methoxyethoxy)methoxy)phenyl]-5-[2-(methoxymethoxy)phenyl]-pent-1-yn-3-ol (42). The coupling reaction was carried out according to the standard procedure using 3-(2-(methoxymethoxy)phenyl)propanal (**18**) (25 mg, 0.124 mmol), 1-ethynyl-2-((2-methoxyethoxy)-methoxy) benzene (**21**) (20 mg, 0.102 mmol) and *n*-butyllithium (0.064 mL, 0.122 mmol). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **42** (23 mg, 57%) as a colourless oil. (Found: M^+, 400.1874, $C_{23}H_{28}O_6$ requires 400.1886); ν_{max} (film)/cm^{-1} 3428 (br, O–H), 2925 (s, ArC–H), 2920 (m, O–CH_2–O), 1491 (s, C–O–C), 1078 (m, C–O); δ_H (400 MHz, $CDCl_3$) 2.10 (2H, q, *J* 7.8, 6.2, CH_2CH$_2$Ar), 2.41 (1H, br s, O*H*), 2.89 (2H, t, *J* 7.8, CH$_2$CH_2Ar), 3.31 (3H, s, CH$_2$CH$_2$OCH_3), 3.45 (3H, s, OCH$_2$OCH_3), 3.57 (2H, t, *J* 4.7, OCH_2CH$_2$OCH$_3$), 3.88 (2H, t, *J* 4.7, OCH$_2$CH_2OCH$_3$), 4.61 (1H, t, *J* 6.2, C*H*OH), 5.18 (2H, s, OCH_2OCH$_3$), 5.32 (2H, s, CH$_2$OCH_2O), 6.90–7.5 (8H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 26.2 (CH_2, C-5), 38.0 (CH_2, C-4), 56.1 (OCH_3), 59.0 (OCH$_2$CH$_2$O*C*H$_3$), 62.5 (CHOH), 67.9 (O*C*H$_2$CH$_2$OCH$_3$), 71.6 (OCH$_2$*C*H$_2$OCH$_3$), 81.3 (q, Ar-*C*≡C), 94.1 (q, Ar-C≡*C*), 94.2 (O*C*H$_2$OCH$_2$), 94.5 (O*C*H$_2$OCH$_3$), 112.6 (q, C1′), 113.4 (q, C1″), 114.0, 115.5, 121.8, 121.9, 127.4, 129.8, 130.3, 133.5 (Ar-CH), 155.2 (q, C2″), 157.9 (q, C2′); *m/z* (EI, %) 400 (M^+, <0.5), 262 (20), 250 (18), 131 (19), 121 (15), 89 (44), 59 (100), 45 (65).

3.3.10. 1-[((2-Methoxyethoxy)methoxy)phenyl]-5-[(2-(methoxymethoxy)phenyl]-pentan-3-ol (47). The hydrogenation was carried out according to the standard procedure using 1-[(2-methoxyethoxy)methoxy)phenyl]-5-[2-(methoxymethoxy)-phenyl]-pent-1-yn-3-ol (**42**) (7 mg, 0.0175 mmol), 10% palladium on carbon (7 mg, 0.0063 mmol) and potassium carbonate (9 mg, 0.063 mmol). The product

was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **42** (5 mg, 71%) as a colourless oil. (Found: $M^+(+NH_4)$, 422.2537, $C_{23}H_{32}O_6(+NH_4)$ requires 422.2543); ν_{max} (film)/cm^{-1} 3459 (br, O–H), 2928 (s, ArC–H), 1493 (s, C–O–C), 1078 (m, C–O); δ_H (400 MHz, $CDCl_3$) 1.76 (4H, m, C*H*$_2$CH$_2$Ar), 2.25 (1H, br s, O*H*), 2.75 (4H, m, CH$_2$C*H*$_2$Ar), 3.37 (3H, s, CH$_2$CH$_2$OC*H*$_3$), 3.47 (3H, s, OCH$_2$OC*H*$_3$), 3.47 (1H, m, C*H*OH), 3.58 (2H, m, OC*H*$_2$CH$_2$OCH$_3$), 3.82 (2H, m, OCH$_2$C*H*$_2$OCH$_3$), 5.20 (2H, s, OC*H*$_2$OCH$_3$), 5.29 (2H, s, CH$_2$OC*H*$_2$O), 6.90–7.50 (8H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 26.4 (CH$_2$Ar), 37.8 (*C*H$_2$CHOH), 56.1 (OCH$_2$O*C*H$_3$), 59.0 (OCH$_3$), 67.7 (O*C*H$_2$CH$_2$OCH$_3$), 70.4 (CHOH), 71.6 (OCH$_2$*C*H$_2$OCH$_3$), 93.6 (O*C*H$_2$OCH$_2$), 94.5 (O*C*H$_2$OCH$_3$), 114.0, 114.1, 121.9, 121.9, 127.1, 127.1, 130.1, 130.3 (Ar-CH), 131.1, (q, C1′ and *C*1″), 155.1, 155.1 (q, C2″ and C2′); *m*/*z* (DEI$^+$, %) 422 (M^+, 8), 405 (3), 329 (30), 314 (27), 297 (80), 284 (35), 267 (100), 107 (22).

3.3.11. 1-[((2-Methoxyethoxy)methoxy)phenyl]-5-[2-(methoxymethoxy)phenyl]-pentan-3-one (13). The reaction was carried out according to the standard procedure using 1-[((2-methoxyethoxy)methoxy)phenyl]-5-[2-(methoxymethoxy)phenyl]pentan-3-ol (**47**) (5 mg, 0.0124 mmol), tetra-*n*-propylammonium perruthenate (0.2 mg, 0.0062 mmol), 4-methylmorpholine *N*-oxide (2 mg, 0.0186 mmol) and 4 Å molecular sieves (100 mg). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **13** (5 mg, >99%) as a colourless oil. (Found: $M^+(+NH_4)$, 420.2390, $C_{23}H_{30}O_6(+NH_4)$ requires 420.2386); ν_{max} (film)/cm^{-1} 2925 (s, ArC–H), 1714 (s, C=O), 1494 (m, C–O–C), 1079 (m, C–O); δ_H (400 MHz, $CDCl_3$) 2.70 (4H, m, C*H*$_2$CO), 2.89 (4H, m, CH$_2$C*H*$_2$Ar), 3.37 (3H, s, CH$_2$CH$_2$OC*H*$_3$), 3.46 (3H, s, OCH$_2$OC*H*$_3$), 3.55 (2H, t, *J* 4.4, OC*H*$_2$CH$_2$OCH$_3$), 3.80 (2H, t, *J* 4.4, OCH$_2$C*H*$_2$OCH$_3$), 5.18 (2H, s, OC*H*$_2$OCH$_3$), 5.28 (2H, s, OC*H*$_2$OCH$_2$), 6.80–7.30 (8H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 24.9 (CH$_2$*C*H$_2$Ar), 42.9 (*C*H$_2$CO), 56.0 (CH$_2$CH$_2$O*C*H$_3$), 59.0 (OCH$_3$), 67.7 (O*C*H$_2$CH$_2$OCH$_3$), 71.6 (OCH$_2$*C*H$_2$OCH$_3$), 93.4 (O*C*H$_2$OCH$_2$), 94.3 (O*C*H$_2$OCH$_3$), 113.9, 114.0, 121.7, 125.5, 127.4, 127.5 (Ar-CH), 129.9 (q, C1″ and C1′), 130.0, 130.1 (Ar-CH), 155.08, 155.14 (q, C2″ and C2′), 210.0 (CHO); *m*/*z* (DCI$^+$, %) 420 (68), 297 (44), 295 (25), 282 (28), 265 (100), 253 (62), 131 (24), 89 (14).

3.3.12. 3,4,3′,4′,-Tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) (8). The reaction was carried out according to the standard procedure using 1-[((2-methoxyethoxy)-methoxy)-phenyl]-5-[2-(methoxymethoxy)phenyl]pentan-3-one (**13**) (15 mg, 0.0373 mmol), trimethylsilyl bromide (0.05 mL, 0.373 mmol) and 4 Å molecular sieves (50 mg). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **13** (9 mg, 97%) as a colourless solid, mp 63–65 °C. (Found: M^+, 252.1145, $C_{17}H_{16}O_2$ requires 252.1150); ν_{max} (film)/cm^{-1} 2925 (s, ArC–H), 1455 and 1488 (m, C–O–C), 1094 (w, C–O); δ_H (400 MHz, $CDCl_3$) 1.97 (2H, ddd, J_{gem} 13.0, $J_{3ax,4ax}$ 13.0, $J_{3ax,4eq}$ 5.9, 3 and 3′-H$_{ax}$), 2.21 (2H, ddd, J_{gem} 13.0, $J_{3eq,4ax}$ 5.9, $J_{3eq,4eq}$ 2.6, 3 and 3′-H$_{eq}$), 2.75 (2H, ddd, J_{gem} 16.2, $J_{4eq,3ax}$ 5.9, $J_{4eq,3eq}$ 2.6, 4 and 4′-H$_{eq}$), 3.27 (2H, ddd, J_{gem} 16.2, $J_{4ax,3ax}$ 13.0, $J_{4ax,3eq}$ 5.9, 4 and 4′-H$_{ax}$), 6.60–7.30 (8H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 21.0 (CH$_2$, C-4 and C-4′), 31.2 (CH$_2$, C-3 and C-3′), 96.2 (q, C2), 117.1, 120.8, (Ar-CH), 122.2 (q, C4a and C4a′), 127.2, 129.0 (Ar-CH), 152.2 (q, C8a and C8a′); *m*/*z* (EI, %) 252 (M^+, 60), 158 (14), 145 (40), 131 (100), 107 (40), 77 (13), 57 (6), 43 (4).

3.3.13. 1-(Allyloxy)-2-methoxybenzene (27). The allylation reaction was carried out according to the standard procedure using 2-methoxyphenol (**24**) (5.0 g, 40 mmol), allyl bromide (4.87 mL, 40 mmol) and potassium carbonate (16.58 g, 120 mmol). The product was purified by column chromatography using hexane–ethyl acetate (90:10) as the eluent to give the title compound **27** (5.46 g, 83%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 3.89 (3H, s, OC*H*$_3$), 4.58 (2H, d, *J* 5.5, OC*H*$_2$CH=CH$_2$), 5.27 (1H, m, OCH$_2$CH=C*H*$_A$H$_B$), 5.40 (1H, m, OCH$_2$CH=CH$_A$*H*$_B$), 6.06 (1H, m, OCH$_2$C*H*=CH$_2$), 6.90–7.30 (4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 55.7 (OCH$_3$), 69.7 (O*C*H$_2$CH=CH$_2$), 111.7, 113.5 (Ar-CH), 117.7 (CH=*C*H$_2$), 120.6, 121.1 (Ar-CH), 133.3 (OCH$_2$*C*H=CH$_2$), 147.9 (q, C2), 149.4 (q, C1). The spectroscopic data were in agreement with the literature.[11]

3.3.14. 2-Allyl-6-methoxyphenol (30). The Claisen rearrangement was carried out according to the standard procedure using 1-(allyloxy)-2-methoxybenzene (**27**) (3.664 g, 22.3 mmol). The product was purified by column chromatography using hexane–ethyl acetate (70:30) as the eluent to give the title compound **30** (3.20 g, 87%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 3.40 (2H, m, C*H*$_2$CH=CH$_2$), 3.80 (3H, s, OC*H*$_3$), 4.65 (1H, br s, O*H*), 5.04 (1H, m, CH$_2$CH=C*H*$_A$H$_B$), 5.08 (1H, m, CH$_2$CH=CH$_A$*H*$_B$), 6.00 (1H, m, CH$_2$C*H*=CH$_2$), 6.60–6.80 (3H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 33.6 (*C*H$_2$CH=CH$_2$), 55.6 (OCH$_3$), 108.5 (Ar-CH), 115.1 (CH$_2$CH=*C*H$_2$), 119.2, 122.0 (Ar-CH), 125.8 (q, C2), 136.5 (CH$_2$*C*H=CH$_2$), 143.2 (q, C1), 146.2 (q, C6).[11]

3.3.15. 1-Allyl-3-methoxy-2-((2-methoxyethoxy)methoxy)-benzene (33). The protection step was carried out according to the standard procedure using 2-allyl-6-methoxyphenol (**30**) (1.13 g, 7.9 mmol), diisopropylethylamine (2.48 mL, 14.70 mmol) and methoxyethoxymethyl chloride (0.90 mL, 7.9 mmol). The product was purified by column chromatography using hexane–ethyl acetate (70:30) as the eluent to give the *title compound* **33** (761 mg, 37%) as a colourless oil. ν_{max} (film)/cm^{-1} 3077 (w, CH=CH$_2$), 2934 (s, ArC–H), 1285 (w, C–O), 1150 (m, C–O–C); δ_H (400 MHz, $CDCl_3$) 3.33 (3H, s, CH$_2$CH$_2$OC*H*$_3$), 3.38 (2H, m, C*H*$_2$CH=CH$_2$), 3.54 (2H, m, OC*H*$_2$CH$_2$OCH$_3$), 3.89 (3H, s, OC*H*$_3$), 3.90 (2H, m, OCH$_2$C*H*$_2$OCH$_3$), 5.04 (1H, m, CH$_2$CH=C*H*$_A$H$_B$), 5.04 (1H, m, CH$_2$CH=CH$_A$*H*$_B$), 5.15 (2H, s, OC*H*$_2$O), 5.97 (1H, m, CH$_2$C*H*=CH$_2$), 6.70–7.00 (3H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 33.8 (*C*H$_2$CH=CH$_2$), 55.1 (OCH$_3$), 58.5 (CH$_2$CH$_2$O*C*H$_3$), 68.6 (*C*H$_2$CH$_2$OCH$_3$), 71.3 (CH$_2$*C*H$_2$OCH$_3$), 97.3 (OCH$_2$O), 109.93 (Ar-CH), 115.2 (CH$_2$CH=*C*H$_2$), 121.5, 123.7 (Ar-CH), 133.7 (q, C1), 136.7 (CH$_2$*C*H=CH$_2$), 143.6 (q, C3), 151.8 (q, C2); *m*/*z* (EI, %) 163 (M^+, 5), 131 (25), 93 (52), 63 (100), 51 (9).

3.3.16. 3-[(3-Methoxy)-2-((2-methoxyethoxy)methoxy)-phenyl]propan-1-ol (36). The hydroboration reaction was

carried out according to the standard procedure using 1-allyl-3-methoxy-2-((2-methoxyethoxy)methoxy)benzene (**33**) (730 mg, 2.9 mmol) and borane–dimethyl sulfide complex (0.600 mL, 6.0 mmol). The product was purified by column chromatography using hexane–ethyl acetate (10:90) as the eluent to give the *title compound* **36** (430 mg, 55%) as a colourless oil. (Found: M^+, 270.1468, $C_{14}H_{22}O_5$ requires 270.1467); ν_{max} (film)/cm^{-1} 3431 (br, O–H), 2935 (s, ArC–H), 1264 (s, C–O), 1159 (w, C–OH); δ_H (400 MHz, $CDCl_3$) 1.86 (2H, m, $CH_2CH_2CH_2OH$), 2.60 (1H, br s, O*H*), 2.77 (2H, t, *J* 6.3, $CH_2CH_2CH_2OH$), 3.38 (3H, s, CH_2OCH_3), 3.59 (4H, m, CH_2OH and $OCH_2CH_2OCH_3$), 3.80 (3H, s, OCH_3), 3.94 (2H, t, *J* 5.1, $OCH_2CH_2OCH_3$), 5.17 (2H, s, OCH_2O), 6.75–7.00 (3H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 26.1 (CH_2, C-2), 33.0 (CH_2, C-3), 55.5 (OCH_3), 58.9 ($CH_2CH_2OCH_3$), 61.7 (CH_2OH), 69.0 ($CH_2CH_2OCH_3$), 71.70 ($CH_2CH_2OCH_3$), 98.0 (OCH_2O), 109.9, 121.9, 124.2 (Ar-CH), 135.8 (q, C1′), 144.2 (q, C3′), 151.9 (q, C2′); *m*/*z* (EI, %) 270 (M^+, <0.5), 194 (20), 149 (5), 137 (5), 89 (21), 59 (100), 45 (4).

3.3.17. 3-[(3-Methoxy-2-((2-methoxyethoxy)methoxy)-phenyl]propanal (19). The oxidation was carried out according to the standard procedure using [3-(3-methoxy)-2-((2-methoxyethoxy)-methoxy)phenyl]propan-1-ol (**36**) (430 mg, 1.6 mmol), tetra-*n*-propylammonium perruthenate (3 mg, 0.08 mmol), 4-methylmorpholine *N*-oxide (200 mg, 2 mmol) and 4 Å molecular sieves (750 mg). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **19** (301 mg, 70%) as a colourless oil. (Found: M^+, 268.1310, $C_{14}H_{20}O_5$ requires 268.1311); ν_{max} (film)/cm^{-1} 2932 (s, ArC–H), 2838 (m, CH_2–O–CH_2), 2724 (w, CHO), 1722 (s, C=O), 1476 (s, C–O–C), 1265 (m, C–O); δ_H (400 MHz, $CDCl_3$) 2.77 (2H, q, *J* 1.6, 7.0, CH_2CH_2CHO), 3.00 (2H, t, *J* 7.0, $ArCH_2$), 3.38 (3H, s, CH_2OCH_3), 3.57 (2H, t, *J* 6.3 $OCH_2CH_2OCH_3$), 3.81 (3H, s, OCH_3), 3.90 (2H, t, *J* 6.3, $OCH_2CH_2OCH_3$), 5.19 (2H, s, OCH_2O), 6.70–7.00 (3H, m, Ar-H), 9.81 (1H, t, *J* 1.6, C*H*O); δ_C (75 MHz, $CDCl_3$) 23.0 (CH_2, C-3), 44.3 (CH_2, C-2), 55.5 (OCH_3), 58.8 ($CH_2CH_2OCH_3$), 69.0 ($CH_2CH_2OCH_3$), 71.6 ($CH_2CH_2OCH_3$), 97.8 (OCH_2O), 110.5, 121.6, 124.2 (Ar-CH), 134.4 (q, C1′), 144.2 (q, C3′), 152.0 (q, C2′), 201.9 (CHO); *m*/*z* (EI, %) 268 (M^+, 6), 151 (4), 136 (5), 89 (64), 77 (4), 65 (3), 59 (100), 45 (4).

3.3.18. 5-[(3-Methoxy)-2-((2-methoxyethoxy)methoxy)-phenyl]-1-([2-((2-methoxyethoxy)methoxy)phenyl]pent-1-yn-3-ol (43). The coupling reaction was carried out according to the standard procedure using 3-[(3-methoxy)-2-((2-methoxyethoxy)methoxy)phenyl]propanal (**19**) (162 mg, 0.79 mmol), 1-ethynyl-2-((2-methoxyethoxy)methoxy)benzene (**21**) (165 mg, 0.654 mmol) and butyllithium (0.5 mL, 0.785 mmol). The product was purified by column chromatography using hexane–ethyl acetate (20:80) as the eluent to give the *title compound* **43** (152 mg, 51%) as a colourless oil. (Found: M^+, 400.1875, $C_{23}H_{28}O_6$ requires 400.1886); ν_{max} (film)/cm^{-1} 3435 (br, O–H), 2928 (m, ArC–H), 1474 (m, C–O–C), 1077 (m, C–O); δ_H (400 MHz, $CDCl_3$) 2.12 (2H, q, *J* 7.3, 5.9, CH_2CH_2Ar), 2.45 (1H, br s, O*H*), 2.96 (2H, t, *J* 7.3, CH_2CH_2Ar), 3.36, 3.54 (6H, each s, 2×$CH_2CH_2OCH_3$), 3.54 (4H, m, 2×$OCH_2CH_2OCH_3$), 3.81 (3H, s, OCH_3), 3.88 (4H, m, 2×$OCH_2CH_2OCH_3$), 4.65 (1H, t, *J* 5.9, C*H*OH), 5.20 (2H, s, 2″-OCH_2OCH_2), 5.30 (2H, s, 2′-OCH_2OCH_2), 6.70–7.50 (7H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 25.8 (CH_2, C-5), 38.7 (CH_2, C-4), 55.5 (OCH_3), 58.7 (2″-$OCH_2CH_2OCH_3$), 58.8 (CHOH), 62.3 (2′-$OCH_2CH_2OCH_3$), 67.7 (2′-$OCH_2CH_2OCH_3$), 68.9 (2″-$OCH_2CH_2OCH_3$), 71.4 (2′-$OCH_2CH_2OCH_3$), 71.7 (2″-$OCH_2CH_2OCH_3$), 80.7 (q, Ar-C≡C), 94.3 (q, Ar-C≡C), 94.0 (2′-OCH_2OCH_2), 98.0 (2″-OCH_2OCH_2), 110.1 (Ar-CH), 113.4 (q, C1″), 115.3, 121.7, 122.1, 124.1, 129.5, 133.4 (Ar-CH), 135.5 (q, C1′), 144.4 (q, C3′), 152.0 (q, C2′), 157.7 (q, C2″); *m*/*z* (EI, %) 400 (M^+, <0.5), 262 (25), 250 (21), 173 (5), 89 (45), 59 (100), 45 (65).

3.3.19. 1-[(3-Methoxy)-2-((2-methoxyethoxy)methoxy)-phenyl]-5-[2-((2-methoxyethoxy)methoxy)phenyl]-pentan-3-ol (48). The hydrogenation was carried out according to the standard procedure using 5-[(3-methoxy)-2-((2-methoxyethoxy)methoxy)phenyl]-1-[2-((2-methoxyethoxy)methoxy)phenyl]-pent-1-yn-3-ol (**43**) (116 mg, 0.253 mmol), 10% palladium on carbon (100 mg, 0.0912 mmol), potassium carbonate (126 mg, 0.912 mmol). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **48** (90 mg, 77%) as a colourless oil. (Found: M^+, 479.2648, $C_{26}H_{39}O_8$ requires 479.2645); ν_{max} (film)/cm^{-1} 3435 (br, O–H), 2928 (s, ArC–H), 1474 (m, C–O–C), 1077 (m, C–O); δ_H (400 MHz, $CDCl_3$) 1.76 (4H, quintet, *J* 7.6, 13.9, CH_2CH_2Ar), 2.79 (4H, m, CH_2CH_2Ar), 3.36, 3.37 (6H, each s, 2′- and 2″-$CH_2CH_2OCH_3$), 3.55 (5H, m, 2′- or 2″-$OCH_2CH_2OCH_3$ and C*H*OH), 3.80 (3H, s, OCH_3), 3.81 (2H, m, 2′- or 2″-$OCH_2CH_2OCH_3$), 3.93 (2H, m, 2′- or 2″-$OCH_2CH_2OCH_3$), 5.17 (2H, s, 2′-OCH_2OCH_2), 5.27 (2H, s, 2″-OCH_2OCH_2), 6.70–7.20 (7H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 26.2, 26.4 (CH_2-Ar), 37.7, 38.2 (CH_2CHOH), 55.5 ($ArOCH_3$), 58.8, 58.9 ($OCH_2CH_2OCH_3$), 67.6, 69.0 ($OCH_2CH_2OCH_3$), 70.3 (CHOH), 71.4, 71.7 ($OCH_2CH_2OCH_3$), 93.5 (2″-OCH_2OCH_2), 98.0 (2′-OCH_2OCH_2), 109.9, 114.0, 121.7, 121.9, 124.1, 126.9, 130.0 (Ar-CH), 131.2 (q, C3″), 136.2 (q, C1″), 144.2 (q, C1′), 152.0 (q, C2′), 155.0 (q, C2″); *m*/*z* (FAB$^+$, %) 479 (M^+, 3), 402 (2), 372 (4), 219 (3), 165 (5), 154 (100), 136 (70), 89 (46).

3.3.20. 1-[(3-Methoxy)-2-((2-methoxyethoxy)methoxy)-phenyl]-5-[2-((2-methoxyethoxy)methoxy)phenyl]pentan-3-one (14). The oxidation was carried out according to the standard procedure using 1-[(3-methoxy-2-((2-methoxyethoxy)methoxy)phenyl]-5-[2-((2-methoxyethoxy)-methoxy)phenyl] pentan-3-ol (**48**) (90 mg, 0.195 mmol), tetra-*n*-propylammonium perruthenate (0.3 mg, 0.0097 mmol), 4-methylmorpholine *N*-oxide (3.4 mg, 0.29 mmol) and 4 Å molecular sieves (100 mg). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **14** (82 mg, 91%) as a colourless oil. (Found: M^+, 476.2406, $C_{26}H_{36}O_8$ requires 476.2410); ν_{max} (film)/cm^{-1} 2930 (s, ArC–H), 1712 (s, C=O), 1492 (s, C–O–C), 1078 (s, C–O); δ_H (400 MHz, $CDCl_3$) 2.70 (4H, t, *J* 8.1, CH_2CO), 2.91 (4H, m, CH_2Ar), 3.35 (6H, each s, 2×$CH_2CH_2OCH_3$), 3.55 (4H, m, 2×$OCH_2CH_2OCH_3$), 3.80 (3H, s, OCH_3), 3.82 (2H, m, 2′- or 2″-$OCH_2CH_2OCH_3$), 3.93 (2H, m, 2′- or 2″-$OCH_2CH_2OCH_3$), 5.17 (2H, s, 2′-OCH_2OCH_2), 5.27 (2H, s, 2″-OCH_2OCH_2), 6.70–7.35 (7H, m, Ar-H); δ_C (75 MHz,

$CDCl_3$) 24.8, 24.9 (CH_2CH_2-Ar), 42.8, 43.2 (CH_2CH_2-Ar), 55.5 ($ArOCH_3$), 58.8, 58.9 ($OCH_2CH_2OCH_3$), 67.6, 69.0 ($OCH_2CH_2OCH_3$), 71.5, 71.6 ($OCH_2CH_2OCH_3$), 93.3 (2″-OCH_2OCH_2), 97.8 (2′-OCH_2OCH_2), 110.3, 113.9, 121.6, 121.8, 124.1, 127.3, 129.8 (Ar-CH), 129.8 (q, C1″), 135.2 (q, C1′), 144.2 (q, C3′), 152.0 (q, C2′), 155.0 (q, C2″), 209.6 (q, CO); *m/z* (FAB$^+$, %) 476 (M^+, 1), 400 (2), 325 (10), 295 (52), 282 (30), 154 (55), 89 (100), 77 (17).

3.3.21. 8-Methoxy-3,4,3′,4′-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) (9). The cyclisation was carried out according to the standard procedure using 1-[(3-methoxy)-2-((2-methoxyethoxy)-methoxy)phenyl]-5-[2-((2-methoxyethoxy)-methoxy)phenyl]pentan-3-one (**14**) (82 mg, 0.178 mmol), trimethylsilyl bromide (0.23 mL, 1.78 mmol) and 4 Å molecular sieves (50 mg). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **9** (48 mg, 96%) as a colourless solid, mp 125–126 °C. (Found: M^+, 282.1256, $C_{18}H_{18}O_3$ requires 282.1256); ν_{max} (film)/cm^{-1} 3054 (w, ArC–H), 1482, 1421 (w, C–O–C); δ_H (400 MHz, $CDCl_3$) 1.98 (2H, ddd, J_{gem} 13.3, $J_{3ax,4ax}$ 13.1, $J_{3ax,4eq}$ 5.7, 3 and 3′-H_{ax}), 2.31 (2H, ddd, J_{gem} 13.3, $J_{3eq,4ax}$ 5.9, $J_{3eq,4eq}$ 2.6, 3 and 3′-H_{eq}), 2.75 (2H, ddd, J_{gem} 16.2, $J_{4eq,3ax}$ 5.7, $J_{4eq,3eq}$ 2.6, 4 and 4′-H_{eq}), 3.35 (2H, ddd, J_{gem} 16.2, $J_{4ax,3ax}$ 13.1, $J_{4ax,3eq}$ 5.9, 4 and 4′-H_{ax}), 3.63 (3H, s, OCH_3), 6.60–7.20 (7H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 21.0, 21.2 (CH_2CH_2Ar), 30.9, 31.3 (CH_2CH_2Ar), 56.5 (OCH_3), 96.3 (q, C2), 111.0, 117.0, 120.2, 121.3, 122.5 (Ar-H), 122.3, 123.1 (q, C4a and C4a′), 127.0, 128.9 (Ar-CH), 142.14 (q, C8), 148.6 (q, C8a), 152.2 (q, C8a′); *m/z* (EI, %) 282 (M^+, 80), 161 (28), 145 (42), 138 (50), 131 (100), 107 (25), 77 (14), 73 (22).

3.3.22. 1-(Allyloxy)-4-methoxybenzene (28). The allylation reaction was carried out according to the standard procedure using 4-methoxyphenol (**25**) (5.0 g, 40 mmol), allyl bromide (3.5 mL, 40 mmol) and potassium carbonate (11.0 g, 80 mmol). The product was purified by column chromatography using hexane–ethyl acetate (90:10) as the eluent to give the *title compound* **28** (6.38 g, 97%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 3.74 (3H, s, OCH_3), 4.56 (2H, d, *J* 5.1, $OCH_2CH{=}CH_2$), 5.41 (1H, dq, J_{gem} 1.5, *J* 10.6, $OCH_2CH{=}CH_AH_B$), 5.42 (1H, m, $OCH_2CH{=}CH_AH_B$), 6.10 (1H, m, $OCH_2CH{=}CH_2$), 6.80–6.95 (4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 55.5 (OCH_3), 69.3 ($OCH_2CH{=}CH_2$), 114.5, 115.6 (Ar-CH), 117.4 ($CH{=}CH_2$), 133.5 ($OCH_2CH{=}CH_2$), 152.6 (q, C1), 153.8 (q, C4). The spectroscopic data were in agreement with the literature.[21]

3.3.23. 2-Allyl-4-methoxyphenol (31). The Claisen rearrangement was carried out according to the standard procedure using 1-(allyloxy)-4-methoxybenzene (**28**) (6.37 g, 39 mmol). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **31** (6.37 g, >99%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 3.36 (2H, d, *J* 6.2, $CH_2CH{=}CH_2$), 3.74 (3H, s, OCH_3), 5.10 (1H, dq, J_{gem} 1.5, *J* 10.6, $CH_2CH{=}CH_AH_B$), 5.16 (1H, m, $CH_2CH{=}CH_AH_{2B}$), 5.20 (1H, br s, O*H*), 6.00 (1H, m, 6.2, $CH_2CH{=}CH_2$), 6.60–6.80 (3H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 35.0 ($CH_2CH{=}CH_2$), 55.7 (OCH_3), 112.5, 115.9, 116.3 (Ar-CH), 116.7 ($CH_2CH{=}CH_2$), 126.7 (q, C2), 136.1 ($CH_2CH{=}CH_2$), 147.9 (q, C1), 153.5 (q, C4). The spectroscopic data were in agreement with the literature.[22]

3.3.24. 2-Allyl-1-(ethoxymethoxy)-4-methoxybenzene (34). The protection step was carried out according to the standard procedure using 2-allyl-4-methoxyphenol (**31**) (6.37 g, 39 mmol), diisopropylamine (12.2 mL, 70 mmol) and ethoxymethyl chloride (4.87 mL, 43 mmol). The product was purified by column chromatography using hexane–ethyl acetate (80:20) as the eluent to give the *title compound* **34** (6.41 g, 74%) as a colourless oil. (Found: M^+, 222.1255, $C_{13}H_{18}O_3$ requires 222.1256); ν_{max} (film)/cm^{-1} 3077 (w, $CH{=}CH_2$), 2934 (s, ArC–H), 1285 (w, C–O), 1150 (m, C–O–C); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.0, OCH_2CH_3), 3.37 (2H, d, *J* 6.7, $CH_2CH{=}CH_2$), 3.71 (2H, q, *J* 7.0, OCH_2CH_3), 3.74 (OCH_3), 5.03 (1H, m, $CH_2CH{=}CH_AH_B$), 5.07 (1H, m, $CH_2CH{=}CH_AH_B$), 5.15 (2H, s, OCH_2O), 5.98 (1H, m, $CH_2CH{=}CH_2$), 6.60–7.10 (3H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 15.1 (OCH_2CH_3), 34.4 ($CH_2CH{=}CH_2$), 55.5 (OCH_3), 64.1 (OCH_2CH_3), 94.1 (OCH_2O), 115.8 ($CH_2CH{=}CH_2$), 111.6, 115.4, 115.7 (Ar-CH), 132.7 ($CH_2CH{=}CH_2$), 136.7 (q, C2), 149.2 (q, C1), 154.4 (q, C4); *m/z* (EI, %) 222 (M^+, 65), 192 (22), 163 (36), 149 (31), 103 (11), 77 (10), 59 (100), 41 (10).

3.3.25. 3-[2-(Ethoxymethoxy)-5-methoxyphenyl]propan-1-ol (37). The hydroboration reaction was carried out according to the standard procedure using 2-allyl-1-(ethoxymethoxy)-4-methoxybenzene (**34**) (3.0 g, 13.5 mmol) and borane–dimethyl sulfide complex (2.7 mL, 27 mmol). The product was purified by column chromatography using hexane–ethyl acetate (80:20) as the eluent to give the *title compound* **37** (2.28 g, 70%) as a colourless oil. (Found: M^+, 240.1362, $C_{13}H_{20}O_4$ requires 240.1362); ν_{max} (film)/cm^{-1} 3411 (br, O–H), 2936 (s, ArC–H), 2834 (m, O–CH_2–O), 1278 (w, C–O), 1151 (m, C–OH); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.0, OCH_2CH_3), 1.84 (2H, quintet, *J* 6.2, 7.7, $CH_2CH_2CH_2OH$), 2.60 (1H, br s, O*H*), 2.70 (2H, t, *J* 7.7, $CH_2CH_2CH_2OH$), 3.70 (2H, t, *J* 6.2, CH_2OH), 3.71 (OCH_2CH_3), 3.80 (3H, s, OCH_3), 5.13 (2H, s, OCH_2O), 6.60–7.10 (3H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 15.0 (OCH_2CH_3), 26.1 (CH_2, C2), 32.9 (CH_2, C3), 55.4 (OCH_3), 61.6 (CH_2OH), 64.2 (OCH_2CH_3), 94.0 (OCH_2O), 111.3, 115.5, 115.9 (Ar-CH), 132.6 (q, C1′), 149.3 (q, C2′), 154.3 (q, C5′); *m/z* (EI, %) 240 (M^+, 10), 194 (10), 164 (100), 149 (25), 137 (16), 77 (9), 59 (35), 41 (10).

3.3.26. 3-[2-(Ethoxymethoxy)-5-methoxyphenyl]propanal (20). The oxidation was carried out according to the standard procedure using 3-[2-(ethoxymethoxy)-5-methoxyphenyl]propan-1-ol (**37**) (1.28 g, 5.3 mmol), tetra-*n*-propylammonium perruthenate (100 mg, 0.267 mmol), 4-methylmorpholine *N*-oxide (900 mg, 8.0 mmol) and 4 Å molecular sieves (1 g). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **20** (506 mg, 40%) as a colourless oil. (Found: M^+, 238.1206, $C_{13}H_{18}O_4$ requires 238.1205); ν_{max} (film)/cm^{-1} 2975 (s, ArC–H), 2834 (m, CH_2–O–CH_2), 2724 (w, CHO), 1725 (s, C=O), 1504 (m, C–O–C), 1280 (w, C–O); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.0, OCH_2CH_3), 2.72 (2H, dt, *J* 1.5, 7.6, CH_2CH_2CHO), 2.92 (2H, t, *J* 7.6, $ArCH_2$), 3.67 (2H, q,

J 7.0, OCH_2CH_3), 3.73 (3H, s, OCH_3), 5.17 (2H, s, OCH_2O), 6.70–7.00 (3H, m, Ar-H), 9.80 (1H, t, *J* 1.5, C*H*O); δ_C (75 MHz, $CDCl_3$) 15.0 (OCH_2CH_3), 23.5 (CH_2, C-3), 43.9 (CH_2, C-2), 55.4 (OCH_3), 64.1 (OCH_2CH_3), 93.7 (OCH_2O), 111.7, 115.2, 115.8 (Ar-CH), 130.5 (q, C1′), 149.3 (q, C2′), 154.2 (q, C5′), 202.0 (CHO); *m*/*z* (EI, %) 238 (M^+, 43), 208 (30), 180 (14), 151 (17), 136 (24), 77 (7), 59 (100), 41 (6).

3.3.27. 5-[2-(Ethoxymethoxy)-5-methoxyphenyl]-1-[2-((2-methoxyethoxy)methoxy)phenyl]pent-1-yn-3-ol (44). The coupling reaction was carried out according to the standard procedure using 3-[2-(ethoxymethoxy)-5-methoxyphenyl]propanal (**20**) (40 mg, 0.17 mmol), 1-ethynyl-2-((2-methoxyethoxy)methoxy)benzene (**21**) (42 mg, 0.20 mmol) and *n*-butyllithium (0.13 mL, 0.20 mmol). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **44** (75 mg, 88%) as a colourless oil. (Found: M^+, 444.2146, $C_{25}H_{32}O_7$ requires 444.2148); ν_{max} (film)/cm^{-1} 3428 (br, O–H), 2930 (m, ArC–H), 1495 (m, C–O–C); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, m, OCH_2CH_3), 2.11 (2H, m, CH_2COH), 2.65 (1H, br s, O*H*), 2.87 (2H, m, CH_2CH_2Ar), 3.34 (3H, s, $CH_2CH_2OCH_3$), 3.55 (2H, t, *J* 4.7, $OCH_2CH_2OCH_3$), 3.75 (2H, q, *J* 7.4, OCH_2CH_3), 3.75 (3H, s, OCH_3), 3.88 (2H, t, *J* 4.7, $OCH_2CH_2OCH_3$), 4.61 (1H, t, *J* 6.7, C*H*OH), 5.18 (2H, s, $OCH_2OCH_2CH_3$), 5.32 (2H, s, OCH_2OCH_2), 6.60–7.50 (7H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 15.1 (CH_2CH_3), 26.3 (CH_2, C-5), 38.0 (CH_2, C-4), 55.5 (OCH_3), 58.9 (CH_2CH_3), 60.3 (CHOH), 62.3 ($OCH_2CH_2OCH_3$), 64.17 (2×OCH_2O), 67.8 ($OCH_2CH_2OCH_3$), 71.5 ($OCH_2CH_2OCH_3$), 81.2 (q, Ar-C≡*C*), 94.1 (q, Ar-*C*≡C), 111.4 (Ar-CH), 113.4 (q, C1′), 115.4, 115.6, 116.2, 121.8, 129.7 (Ar-CH), 131.8 (q, C1″), 133.5 (Ar-CH), 149.5 (q, C5″), 154.4 (q, C2′), 157.8 (q, C2″); *m*/*z* (EI, %) 444 (M^+, 1), 292 (20), 277 (8), 222 (29), 180 (25), 89 (27), 59 (100), 45 (4).

3.3.28. 1-[2-(Ethoxymethoxy)-5-methoxyphenyl]-5-[2-((2-methoxyethoxy)methoxy)phenyl]pentan-3-ol (49). The hydrogenation was carried out according to the standard procedure using 5-[2-(ethoxymethoxy)-5-methoxyphenyl]-1-[2-((2-methoxyethoxy)methoxy)phenyl]pent-1-yn-3-ol (**44**) (60 mg, 0.14 mmol), 10% palladium on carbon (51 mg, 0.049 mmol) and potassium carbonate (70 mg, 0.49 mmol). The product was purified by column chromatography using hexane–ethyl acetate (80:20) as the eluent to give the *title compound* **49** (48 mg, 70%) as a colourless oil. (Found: M^+, 448.2461, $C_{25}H_{36}O_7$ requires 448.2461); ν_{max} (film)/cm^{-1} 3584 (br, O–H), 2929 (s, ArC–H), 1495 (m, C–O–C); δ_H (400 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.0, OCH_2CH_3), 1.75 (2H, q, *J* 7.8, CH_2Ar), 2.73 (3H, m, CH_2COH and CHO*H*), 3.37 (3H, s, $CH_2CH_2OCH_3$), 3.55 (2H, m, $OCH_2CH_2OCH_3$), 3.55 (1H, m, C*H*OH), 3.75 (2H, m, CH_2CH_3), 3.75 (3H, s, OCH_3), 3.82 (2H, t, *J* 4.4, $OCH_2CH_2OCH_3$), 5.16 (2H, s, $OCH_2OCH_2CH_3$), 5.29 (2H, s, OCH_2OCH_2), 6.60–7.30 (7H, m, Ar–H); δ_C (75 MHz, $CDCl_3$) 15.1 (CH_2CH_3), 26.3, 26.4 (CH_2Ar), 37.8, 37.8 (CH_2CHOH), 55.5 (OCH_3), 58.9 (CH_2CH_3), 62.3 ($OCH_2CH_2OCH_3$), 67.7 ($OCH_2CH_2OCH_3$), 70.1 (CHOH), 71.6 ($OCH_2CH_2OCH_3$), 93.6, 94.2 (2×OCH_2O), 111.3, 114.1, 115.7, 115.9, 121.8, 127.1, 130.1 (Ar–CH), 131.1 (q, C1′), 132.6 (q, C1″), 149.4 (q, C5″), 154.5 (q, C2′), 155.1 (q, C2″); *m*/*z* (EI, %) 448 (M^+, <0.5), 402 (14), 372 (25), 296 (30), 284 (16), 137 (25), 89 (45), 59 (100).

3.3.29. 1-[2-(Ethoxymethoxy)-5-methoxyphenyl]-5-[2-((2-methoxyethoxy)methoxy)phenyl]pentan-3-one (15). The oxidation was carried out according to the standard procedure using 1-[2-(ethoxymethoxy)-5-methoxyphenyl]-5-[2-((2-methoxyethoxy)methoxy)phenyl]pentan-3-ol (**49**) (43 mg, 0.096 mmol), tetra-*n*-propylammonium perruthenate (0.2 mg, 0.0048 mmol), 4-methylmorpholine *N*-oxide (17 mg, 0.14 mmol) and 4 Å molecular sieves (100 mg). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **15** (43 mg, >99%) as a colourless oil. (Found: M^+, 446.2303, $C_{25}H_{34}O_7$ requires 446.2305); ν_{max} (film)/cm^{-1} 2931 (s, ArC–H), 1713 (s, C=O), 1495 (s, C–O–C), 1083 (m, C–O); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.1, OCH_2CH_3), 2.69 (2H, t, *J* 8.2, CH_2CH_2Ar), 2.87 (2H, m, CH_2CH_2Ar), 3.37 (3H, s, $CH_2CH_2OCH_3$), 3.55 (2H, t, *J* 4.5, $OCH_2CH_2OCH_3$), 3.73 (3H, s, OCH_3), 3.75 (2H, q, *J* 7.1, CH_2CH_3), 3.80 (2H, t, *J* 4.5, $OCH_2CH_2OCH_3$), 5.15 (2H, s, $OCH_2OCH_2CH_3$), 5.28 (2H, s, OCH_2OCH_2), 6.60–7.20 (7H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 15.1 (CH_2CH_3), 24.9, 25.0 (CH_2Ar), 42.9, 42.9 (CH_2CO), 55.5 (OCH_3), 59.0 ($OCH_2CH_2OCH_3$), 64.1 (CH_2CH_3), 67.7 ($OCH_2CH_2OCH_3$), 71.6 ($OCH_2CH_2OCH_3$), 93.4, 93.9 (2×OCH_2O), 111.6, 113.9, 115.5, 115.9, 121.7, 127.4, 129.9 (Ar-CH), 130.0 (q, C1′), 131.44 (q, C1″), 149.4 (q, C5″), 154.3 (q, C2′), 155.1 (q, C2″), 209.9 (q, CO); *m*/*z* (EI, %) 446 (M^+, 4), 400 (5), 294 (5), 282 (51), 161 (13), 107 (10), 89 (32), 59 (100).

3.3.30. 6-Methoxy-3,4,3′,4′-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) (10). The cyclisation was carried out according to the standard procedure using 1-([2-(ethoxymethoxy-5-methoxyphenyl]-5-[2-((2-methoxyethoxy)methoxy)phenyl]-pentan-3-one (**15**) (40 mg, 0.09 mmol), trimethylsilyl bromide (0.12 mL, 0.9 mmol) and 4 Å molecular sieves (50 mg). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **10** (25 mg, >99%) as a colourless solid, mp 87.5–89.0 °C. (Found: M^+, 282.1252, $C_{18}H_{18}O_3$ requires 282.1256); ν_{max} (film)/cm^{-1} 2958 (w, ArC–H), 1488 and 1455 (w, C–O–C); δ_H (400 MHz, $CDCl_3$) 1.95 (2H, ddd, J_{gem} 13.2, $J_{3ax,4ax}$ 13.2, $J_{3ax,4eq}$ 5.6, 3 and 3′-H_{ax}), 2.19 (2H, ddd, J_{gem} 13.2, $J_{3eq,4ax}$ 6.0, $J_{3eq,4eq}$ 2.6, 3 and 3′-H_{eq}), 2.72 (2H, ddd, J_{gem} 16.5, $J_{4eq,3ax}$ 5.6, $J_{4eq,3eq}$ 2.6, 4 and 4′-H_{eq}), 3.35 (2H, ddd, J_{gem} 16.5, $J_{4ax,3ax}$ 13.2, $J_{4ax,3eq}$ 6.0, 4 and 4′-H_{ax}), 3.74 (3H, s, OCH_3), 6.60–7.30 (7H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 21.3, 22.0 (CH_2CH_2Ar), 31.1, 31.1 (CH_2CH_2Ar), 55.6 (OCH_3), 96.2 (q, C2), 113.1, 113.6, 117.1, 117.6, 120.7 (Ar-CH), 122.2, 122.7 (q, C4a and C4a′), 127.1, 129.0 (Ar-CH), 146.2 (q, C8 and C8′), 152.2 (q, C8a), 153.7 (q, C8a′); *m*/*z* (EI, %) 282 (M^+, 100), 175 (21), 161 (60), 145 (42), 131 (38), 107 (23), 77 (11), 73 (20).

3.3.31. 1-Iodo-3-methoxy-2-(methoxymethoxy)benzene (39). The protection step was carried out according to the standard procedure using 1-methoxyphenol (**24**) (0.996 g, 8.03 mmol), diisopropylethylamine (2.52 mL, 14.4 mmol) and methoxymethyl chloride (0.92 mL, 8.03 mmol). The product was purified by column chromatography using hexane–ethyl acetate (90:10) as the eluent to give the MOM

ether[23] (1.19 g, 88%) as a colourless oil that was used directly in the iodination step; δ_H (400 MHz, $CDCl_3$) 3.50 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.21 (2H, s, OCH_2O), 6.84–7.15 (4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 55.6 (OCH_3), 56.0 (OCH_3), 95.4 (OCH_2O), 111.7, 116.5, 120.8, 122.4 (Ar-CH), 146.5 (q, C-1), 149.8 (q, C-2). To a solution of the MOM ether (1.00 g, 5.93 mmol) in tetrahydrofuran (5 mL) cooled to −15 °C under nitrogen was added *n*-butyllithium (4.08 mL, 6.53 mmol) dropwise with stirring. The reaction mixture was allowed to warm to room temperature over 2 h then cooled to −45 °C and a solution of iodine was (0.825 g, 6.53 mmol) in tetrahydrofuran (1 mL) added dropwise over 1 h. The cooling bath was removed and the solution was warmed to room temperature and stirred for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was taken up with diethyl ether (10 mL) and then washed with 20% sodium thiosulfate (5 mL) and aqueous saturated sodium bicarbonate (5 mL). The organic extract was dried over magnesium sulfate and concentrated under reduced pressure. The resultant residue was purified by flash chromatography using hexane–ethyl acetate (90:10) as eluent to give the *title compound* **39** (0.236 g, 14%) as a colourless oil. (Found: M^+, 293.9755, $C_9H_{11}IO_3$ requires 293.9753); ν_{max} (film)/cm^{-1} 2938 (w, ArC–H), 1569 (C–O), 1580 (O–C–O), 1290 (C–O); δ_H (400 MHz, $CDCl_3$) 3.67 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 5.16 (2H, s, OCH_2O), 6.75–7.37 (3H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 55.9 (OCH_3), 58.3 (OCH_3), 92.6 (q, C1), 98.7 (OCH_2O), 112.8, 125.9, 131.0 (Ar-CH), 145.9 (q, C2), 152.4 (q, C3). *m/z* (EI, %) 294 (M^+, 20), 264 (30), 249 (7), 167 (21), 107 (6), 94 (4), 51 (7), 45 (100).

3.3.32. 4-[(3-Methoxy)-2-(methoxymethoxy)phenyl]-2-methylbut-3-yn-2-ol (41). The Sonogashira reaction was carried out according to the standard procedure using 1-iodo-3-methoxy-2-[(methoxymethoxy)]benzene (**39**) (200 mg, 0.68 mmol), 2-methyl-3-butyn-2-ol (0.106 mL, 1.09 mmol), triphenylphosphine (4 mg, 0.014 mmol), bis(triphenylphosphine)palladium(II) dichloride (5 mg, 0.0068 mmol), triethylamine (5 mL) and copper(I) iodide (2 mg, 0.0013 mmol). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **41** (170 mg, >99%) as a colourless oil. (Found: M^+, 250.1208, $C_{14}H_{18}O_4$ requires 250.1205); ν_{max} (film)/cm^{-1} 3689 (br, OH), 3053 (Ar-CH), 2305 (C≡C), 1469 (OCH_2O), 1265, 1208, 1160 (CO); δ_H (400 MHz, $CDCl_3$) 1.60 (6H, each s, 2×CH_3), 2.88 (1H, br s, O*H*), 3.65 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 5.22 (2H, s, OCH_2O), 6.84–7.00 (3H, m, Ar-C*H*); δ_C (75 MHz, $CDCl_3$) 31.0, 31.4 (C(*C*H_3)$_2$), 55.9 (OCH_3), 57.5 (OCH_3), 65.6 (q, C-2), 84.0 (q, Ar-C≡*C*), 98.0 (q, Ar-*C*≡C-3), 98.5 (OCH_2O), 112.8, 115.4 (Ar-CH), 117.8 (q, C1′), 124.0 (Ar-CH), 146.8 (q, C3′), 152.4 (q, Ar-C2′). *m/z* (EI, %) 250 (M^+, 2), 188 (100), 175 (5), 173 (7), 160 (14), 145 (14), 131 (15), 115 (7), 45 (49), 43 (29).

3.3.33. 1-Ethynyl-3-methoxy-2-(methoxymethoxy)benzene (22). The reaction was carried out according to the standard procedure using 4-[(3-methoxy-2-(methoxymethoxy)phenyl]-2-methylbut-3-yn-2-ol (**41**) (198 mg, 0.79 mmol) and sodium hydroxide (158 mg, 3.96 mmol). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **22** (109 mg, 72%) as a colourless oil. (Found: M^+, 192.0797, $C_{11}H_{12}O_3$ requires 192.0780); ν_{max} (film)/cm^{-1} 3075 (Ar-CH), 2268 (C≡C), 1469 (OCH_2O), 1265, 1208, 1160 (CO); δ_H (400 MHz, $CDCl_3$) 3.25 (1H, s, C≡C*H*), 3.64 (3H, s, OCH_2OCH_3), 3.84 (3H, s, OCH_3), 5.24 (2H, s, OCH_2OCH$_3$), 6.90–7.10 (3H, m, Ar-C*H*); δ_C (75 MHz, $CDCl_3$) 55.9 (OCH_3), 57.5 (OCH_2OCH_3), 80.1 (C≡*C*H), 81.1 (q, *C*≡CH), 98.5 (OCH_2O), 113.4 (Ar-CH), 117.3 (q, *C*-1), 124.1, 125.7 (Ar-CH), 147.6 (q, C-3′), 152.4 (q, C-2′). *m/z* (EI, %) 192 (M^+, 5), 191 (6), 162 (30), 161 (22), 147 (6), 131 (11), 119 (8), 91 (7), 76 (7), 45 (100).

3.3.34. 5-[2-(Ethoxymethoxy)-5-methoxyphenyl]-1-[3-methoxy-2-(methoxymethoxy)phenyl]pent-1-yn-3-ol (45). The coupling reaction was carried out according to the standard procedure using 3-[5-methoxy-2-((2-methoxyethoxy)methoxy)phenyl]propanal (**20**) (75 mg, 0.31 mmol), 1-ethynyl-3-methoxy-2-(methoxymethoxy)benzene (**22**) (50 mg, 0.26 mmol) and *n*-butyllithium (0.18 mL, 0.29 mmol). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **45** (87 mg, 73%) as a colourless oil. (Found: M^+, 430.1985, $C_{24}H_{30}O_7$ requires 430.1992); ν_{max} (film)/cm^{-1} 3435 (br, O–H); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, m, CH_2CH_3), 2.07 (2H, quintet, *J* 6.6, 8.6, CH_2CH$_2$Ar), 2.70 (1H, br s, O*H*), 2.84 (2H, m, CH_2CH_2Ar), 3.63 (2H, m, OCH_2CH$_3$), 3.71 (3H, s, OCH_2OCH_3), 3.73 (3H, s, 5″-OCH_3), 3.83 (3H, s, 3′-OCH_3), 4.60 (1H, t, *J* 6.6, C*H*OH), 5.17 (2H, s, OCH_2OCH$_2$), 5.22 (2H, s, OCH_2OCH$_3$), 6.60–7.30 (7H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 15.1 (CH_2CH_3), 26.2 (CH_2, C-5), 37.9 (CH_2, C-4), 55.5, 55.8 (2×OCH_3), 57.4 (OCH_2OCH_3), 62.3 (CHOH), 64.2 (OCH_2CH_3), 81.3 (q, Ar-*C*≡C), 94.0 (OCH_2OCH_2), 94.1 (q, Ar-C≡*C*), 98.5 (OCH_2OCH_3), 117.8 (q, C1′), 111.6, 112.9, 115.6, 116.0, 124.0, 125.2 (Ar-CH), 131.6 (q, C1″), 147.0 (q, C3′), 149.5 (q, C5″), 152.5 (q, C2′), 154.4 (q, C2″); *m/z* (EI, %) 430 (M^+, 4), 322 (46), 310 (35), 180 (55), 161 (52), 151 (44), 59 (64), 45 (100).

3.3.35. 1-[2-(Ethoxymethoxy)-5-methoxyphenyl]-5-[3-methoxy-2-(methoxymethoxy)phenyl]pentan-3-ol (50). The hydrogenation was carried out according to the standard procedure using 5-[2-(ethoxymethoxy)-5-methoxyphenyl]-1-[3-methoxy-2-(methoxymethoxy)phenyl]pent-1-yn-3-ol (**45**) (80 mg, 0.17 mmol), 10% palladium on carbon (67 mg, 0.063 mmol) and potassium carbonate (86 mg, 0.63 mmol). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **50** (80 mg, 99%) as a colourless oil. (Found: M^+, 434.2309, $C_{24}H_{34}O_7$ requires 434.2305); ν_{max} (film)/cm^{-1} 3584 (br, O–H), 2933 (s, ArC–H), 1499 (m, C–O–C), 1080 (w, C–O); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.1, CH_2CH_3), 1.74 (4H, m, CH_2CH$_2$Ar), 2.70 (1H, br s, O*H*), 2.70 (4H, m, CH_2Ar), 2.80 (1H, m, C*H*OH), 3.70 (2H, q, *J* 7.1, OCH_2CH$_3$), 3.72 (3H, s, OCH_2OCH_3), 3.72 (3H, s, 5′-OCH_3), 3.81 (3H, s, 3″-OCH_3), 5.09 (2H, s, OCH_2OCH$_2$), 5.15 (2H, s, OCH_2OCH$_3$), 6.60–7.10 (6H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 15.0 (CH_2CH_3), 26.1, 26.5 (CH_2Ar), 37.8, 38.2 (*C*H_2CHOH), 55.4, 55.5 (2×OCH_3), 57.5 (OCH_2OCH_3), 64.1 (OCH_2CH_3), 69.9 (CHOH), 94.0 (OCH_2OCH_2), 99.0 (OCH_2OCH_3), 109.9, 111.3, 115.5,

115.7, 121.9, 124.2 (Ar-CH), 132.6 (q, C″), 136.1 (q, C1″), 144.1 (q, C3″), 149.3 (q, C5′), 152.0 (q, C2″), 154.3 (q, C2′); *m/z* (DEI, %) 434 (M^+, 1), 388 (38), 314 (50), 189 (46), 177 (43), 137 (100), 59 (44), 45 (95).

3.3.36. 1-[2-(Ethoxymethoxy)-5-methoxyphenyl]-5-[3-methoxy-2-(methoxymethoxy)phenyl]pentan-3-one (16). The oxidation was carried out according to the standard procedure using 1-[2-(ethoxymethoxy)-5-methoxyphenyl]-5-[3-methoxy-2-(methoxymethoxy)phenyl]pentan-3-ol (**50**) (74 mg, 0.16 mmol), tetra-*n*-propylammonium perruthenate (0.3 mg, 0.008 mmol), 4-methylmorpholine *N*-oxide (3 mg, 0.24 mmol) and 4 Å molecular sieves (20 mg). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **16** (74 mg, 95%) as a colourless oil. (Found: M^+, 432.2148, $C_{24}H_{32}O_7$ requires 432.2148); ν_{max} (film)/cm^{-1} 2931 (s, ArC–H), 1713 (s, C=O), 1495 (s, C–O–C), 1160 (m, C–O); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.0, CH_2CH_3), 2.72 (4H, m, CH_2CO), 2.86, 2.93 (4H, m, CH_2CH_2Ar), 3.54 (3H, s, OCH_2OCH_3), 3.70 (2H, q, *J* 7.0, OCH_2CH_3), 3.71 (3H, s, 5′-OCH_3), 3.82 (3H, s, 3″-OCH_3), 5.08 (2H, s, OCH_2OCH_2), 5.15 (2H, s, OCH_2OCH_3), 6.60–7.30 (6H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 15.1 (CH_2CH_3), 24.7, 25.0 (CH_2CH_2Ar), 42.9, 43.4 (CH_2CO), 55.5, 55.6 (2×OCH_3), 57.4 (OCH_2OCH_3), 64.1 (OCH_2CH_3), 93.8 (OCH_2OCH_2), 98.9 (OCH_2OCH_3), 110.4, 111.7, 115.4, 115.8, 121.9, 124.2 (Ar-CH), 131.4 (q, C1′), 135.3 (q, C1″), 144.3 (q, C3″), 149.4 (q, C5′), 152.1 (q, C2″), 154.3 (q, C2′), 209.7 (q, CO); *m/z* (EI, %) 432 (M^+, 0.5), 386 (38), 312 (50), 187 (46), 175 (43), 137 (100), 59 (44), 45 (95).

3.3.37. 6,8′-Dimethoxy-3,4,3′,4′,-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) (11). The cyclisation reaction was carried out according to the standard procedure using 1-[2-(ethoxymethoxy)-5-methoxyphenyl]-5-[3-methoxy-2-(methoxymethoxy)phenyl]pentan-3-one (**16**) (70 mg, 0.15 mmol), trimethylsilyl bromide (0.20 mL, 1.5 mmol) and 4 Å molecular sieves (50 mg). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **11** (45 mg, 96%) as a colourless solid, mp 146–147 °C. (Found: M^+, 312.1358, $C_{19}H_{20}O_4$ requires 312.1362); ν_{max} (film)/cm^{-1} 2931 (m, ArC–H), 1482 and 1421 (w, C–O–C); δ_H (400 MHz, $CDCl_3$) 1.98 (2H, ddd, J_{gem} 13.1, $J_{3ax,4ax}$ 13.1, $J_{3ax,4eq}$ 5.7, 3 and 3′-H_{ax}), 2.19 (2H, ddd, J_{gem} 13.1, $J_{3eq,4ax}$ 5.9, $J_{3eq,4eq}$ 2.6, 3 and 3′-H_{eq}), 2.90 (2H, ddd, J_{gem} 16.2, $J_{4eq,3ax}$ 5.7, $J_{4eq,3eq}$ 2.6, 4 and 4′-H_{eq}), 3.30 (2H, ddd, J_{gem} 16.3, $J_{4ax,3ax}$ 13.1, $J_{4ax,3eq}$ 5.9, 4 and 4′-H_{ax}), 6.60–7.30 (6H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 20.9, 21.5 (CH_2CH_2Ar), 30.8, 31.2 (CH_2CH_2Ar), 55.6 (6-OCH_3), 56.5 (8′-OCH_3), 96.2 (q, C2), 111.0, 113.0, 113.6, 117.5, 120.2, 121.3 (Ar-CH), 122.8 (q, C4a), 123.2 (q, C4′a), 142.2 (q, C8′a,), 146.2 (q, C8a), 148.6 (q, C8 and C8′), 153.6 (q, C6); *m/z* (EI, %) 312 (M^+, 80), 188 (6), 176 (55), 174 (32), 161 (100), 137 (40), 91 (6), 77 (10).

3.3.38. 5-[(3-Methoxy)-2-((2-methoxyethoxy)methoxy)-phenyl]-1-[3-methoxy-2-(methoxymethoxy)phenyl]pent-1-yn-3-ol (46). The coupling reaction was carried out according to the standard procedure using 3-[(3-methoxy)-2-((2-methoxyethoxy)methoxy)phenyl]propanal (**19**) (50 mg, 0.21 mmol), 1-ethynyl-3-methoxy-2-(methoxymethoxy)-benzene (**22**) (40 mg, 0.21 mmol) and *n*-butyllithium (0.14 mL, 0.23 mmol). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **46** (52 mg, 54%) as a colourless oil. (Found: M^+, 460.2102, $C_{25}H_{32}O_8$ requires 460.2097); ν_{max} (film)/cm^{-1} 3426 (br, O–H), 2934 (s, ArC–H), 1471 (s, C–O–C), 1076 (m, C–O); δ_H (400 MHz, $CDCl_3$) 2.11 (2H, m, CH_2CH_2Ar), 2.92 (2H, m, CH_2CH_2Ar), 2.94, (1H, br s, O*H*), 3.37 (3H, s, $CH_2CH_2OCH_3$), 3.47 (2H, t, *J* 4.5, $OCH_2CH_2OCH_3$), 3.58 (3H, s, OCH_2OCH_3), 3.81, 3.83 (2×OCH_3), 3.92 (2H, m, $OCH_2CH_2OCH_3$), 4.60 (1H, t, *J* 6.0, C*H*OH), 5.19 (2H, s, OCH_2OCH_3), 5.21 (2H, s, CH_2OCH_2O), 6.70–7.10 (6H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 25.9 (CH_2, C-5), 38.7 (CH_2, C-4), 55.6, 55.8 (OCH_3), 57.4 ($OCH_2CH_2OCH_3$), 58.9 (OCH_2OCH_3), 62.3 (CHOH), 69.0 ($OCH_2CH_2OCH_3$), 71.8 ($OCH_2CH_2OCH_3$), 81.0 (q, Ar-C≡C), 94.4 (q, Ar-C≡C), 98.1 (OCH_2OCH_2), 98.5 (OCH_2OCH_3), 110.2, 112.8, (Ar-CH), 117.9 (q, C1′), 122.1, 124.0, 124.2, 125.3 (Ar-CH), 135.4 (q, C1″), 144.5, 147.0 (q, C3′ and C5″), 152.0, 152.5 (q, C2″ and C2′); *m/z* (EI, %) 460 (M^+, <0.5), 322 (14), 310 (31), 174 (20), 161 (23), 89 (25), 59 (100), 45 (50).

3.3.39. 1-[3-Methoxy-2-((2-methoxyethoxy)methoxy)-phenyl]-5-[(3-methoxy)-2-(methoxymethoxy)phenyl]-pentan-3-ol (51). The hydrogenation was carried out according to the standard procedure using 5-[3-methoxy-2-((2-methoxyethoxy)methoxy)phenyl]-1-[(3-methoxy)-2-(methoxymethoxy)phenyl]pent-1-yn-3-ol (**46**) (52 mg, 0.11 mmol), 10% palladium on carbon (43 mg, 0.041 mmol) and potassium carbonate (56 mg, 0.41 mmol). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **51** (43 mg, 83%) as a colourless oil. (Found: M^+, 465.2502, $C_{25}H_{37}O_8$ requires 465.2489); ν_{max} (film)/cm^{-1} 3469 (br, O–H), 2932 (s, ArC–H), 1474 (m, C–O–C), 1072 (w, C–O); δ_H (400 MHz, $CDCl_3$) 1.76 (4H, m, CH_2CO), 2.80 (4H, m, CH_2Ar), 2.80 (1H, m, C*H*OH), 3.37 (3H, s, $CH_2CH_2OCH_3$), 3.57 (3H, s, OCH_2OCH_3), 3.57 (2H, m, $OCH_2CH_2OCH_3$), 3.81, 3.82 (6H, s, 2×OCH_3), 3.93 (2H, m, $OCH_2CH_2OCH_3$), 5.08 (2H, s, OCH_2OCH_3), 5.16 (2H, s, OCH_2OCH_2), 6.70–7.30 (6H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 26.3, 26.3 (CH_2Ar), 38.2, 38.3 (CH_2CHOH), 55.6, 55.6 (OCH_3), 57.4 ($OCH_2CH_2OCH_3$), 59.0 (OCH_2OCH_3), 69.0 ($OCH_2CH_2OCH_3$), 70.1 (CHOH), 71.8 ($OCH_2CH_2OCH_3$), 98.0 (OCH_2OCH_2), 99.0 (OCH_2OCH_3), 109.9, 110.0, 122.0, 122.0, 124.2, 124.2 (Ar-CH), 136.3, 136.3 (q, C1″ and C1′), 144.2, 144.2 (q, C3′ and C5″), 151.0, 152.0 (q, C2″ and C2′); *m/z* (FAB$^+$, %) 465 (M^+, <0.5), 307 (20), 289 (14), 154 (100), 136 (68), 107 (22), 89 (21), 77 (20).

3.3.40. 1-[3-Methoxy-2-((2-methoxyethoxy)methoxy)-phenyl]-5-[3-methoxy-2-(methoxymethoxy)phenyl]pentan-3-one (17). The oxidation was carried out according to the standard procedure using 1-[3-methoxy-2-((2-methoxyethoxy)methoxy)phenyl)]-5-[(3-methoxy)-2-(methoxymethoxy)phenyl)pentan-3-ol (**51**) (43 mg, 0.09 mmol), tetra-*n*-propylammonium perruthenate (0.01 mg, 0.005 mmol), 4-methylmorpholine *N*-oxide (0.1 mg, 0.01 mmol) and 4 Å molecular sieves (50 mg). The product was purified by column chromatography using hexane–ethyl acetate

(50:50) as the eluent to give the *title compound* **17** (43 mg, >99%) as a colourless oil. (Found: $M^+(+NH_4)$, 480.2594, $C_{25}H_{38}NO_8$ requires 480.2597); ν_{max} (film)/cm^{-1} 2936 (s, ArC–H), 1712 (s, CO), 1476 (s, C–O–C), 1073 (s, C–O); δ_H (400 MHz, $CDCl_3$) 2.73 (4H, m, CH_2CO), 2.95 (4H, m, CH_2CH_2Ar), 3.36 (3H, s, $CH_2CH_2OCH_3$), 3.56 (3H, s, OCH_2OCH_3), 3.56 (2H, t, *J* 4.7, $OCH_2CH_2O CH_3$), 3.81, 3.82 (6H, s, 2×OCH_3), 3.89 (2H, t, *J* 4.7, $OCH_2CH_2OCH_3$), 5.08 (2H, s, OCH_2OCH_3), 5.17 (2H, s, CH_2OCH_2O), 6.70–7.30 (6H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 24.6, 24.7 (CH_2CH_2Ar), 43.3, 43.3 (CH_2CO), 55.6, 55.6 (OCH_3), 57.4 ($OCH_2CH_2OCH_3$), 58.9 (OCH_2OCH_3), 69.0 ($OCH_2CH_2OCH_3$), 71.7 ($OCH_2CH_2OCH_3$), 97.8 (OCH_2OCH_2), 98.9 (OCH_2OCH_3), 110.3, 110.4, 121.8, 121.85, 124.1, 124.13 (Ar-CH), 135.2, 135.2 (q, C1″ and C1′), 144.2, 144.3 (q, C3′ and C5″), 152.1, 152.1 (q, C2″ and C2′), 209.6 (CO); *m/z* (DEI, %) 462 (M^+, <0.5), 324 (14), 312 (71), 161 (55), 137 (30), 89 (28), 59 (100), 45 (62).

3.3.41. 8,8′-Dimethoxy-3,4,4′,3′-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) (12). The reaction was carried out according to the standard procedure using 1-[3-methoxy-2-((2-methoxyethoxy)-methoxy)phenyl]-5-[3-methoxy-2-(methoxymethoxy)phenyl]pentan-3-one (**17**) (39 mg, 0.08 mmol), trimethylsilyl bromide (0.11 mL, 0.84 mmol) and 4 Å molecular sieves (50 mg). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **12** (25 mg, 96%) as a colourless solid, mp 195–196 °C. (Found: M^+, 312.1358, $C_{19}H_{20}O_4$ requires 312.1358); ν_{max} (film)/cm^{-1} 2934 (w, ArC–H), 1478 and 1440 (m, C–O–C); δ_H (400 MHz, $CDCl_3$) 2.00 (2H, ddd, J_{gem} 13.1, $J_{3ax,4ax}$ 13.1, $J_{3ax,4eq}$ 5.8, 3-H_{ax}), 2.32 (2H, ddd, J_{gem} 13.1, $J_{3eq,4ax}$ 5.9, $J_{3eq,4eq}$ 2.6, 3-H_{eq}), 2.76 (2H, ddd, J_{gem} 16.2, $J_{4eq,3ax}$ 5.8, $J_{4eq,3eq}$ 2.6, 4-H_{eq}), 3.35 (2H, ddd, J_{gem} 16.2, $J_{4ax,3ax}$ 13.1, $J_{4ax,3eq}$ 5.9, 4-H_{ax}), 3.66 (6H, s, 2×OCH_3), 6.60–7.30 (6H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 21.1 (CH_2CH_2Ar), 31.1 (CH_2CH_2Ar), 56.4 (2×OCH_3), 96.4 (q, C2), 110.9, 120.2, 121.3 (Ar-CH), 123.3 (q, C4a and C4a′), 142.14 (q, C8 and C8′), 148.5 (q, C8a and C8a′); *m/z* (EI, %) 312 (M^+, 75), 295 (5), 188 (12), 175 (44), 161 (100), 137 (44), 115 (3), 77 (8).

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