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Preparation of cyclic ethers for polyether synthesis by catalytic ring-closing enyne metathesis of alkynyl ethers

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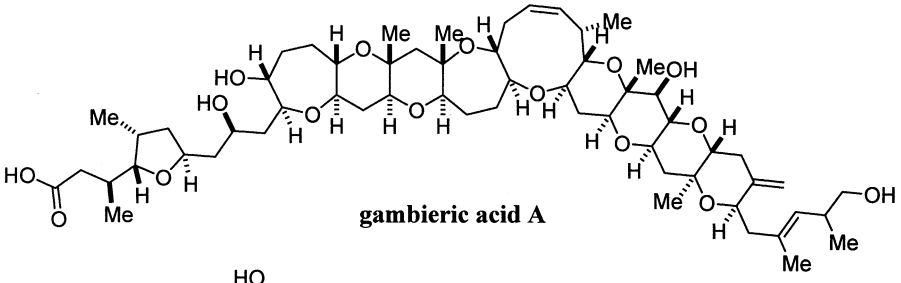
Abstract—Alkenyl-substituted six- and seven-membered cyclic enol ethers, which are potential building blocks for the synthesis of marine polyether natural products, can be prepared in high yield (70–97%) from alkynyl ethers by ruthenium-catalysed ring-closing enyne metathesis. The carbene-bearing ruthenium complex **9** is generally the most efficient catalyst for the reaction.

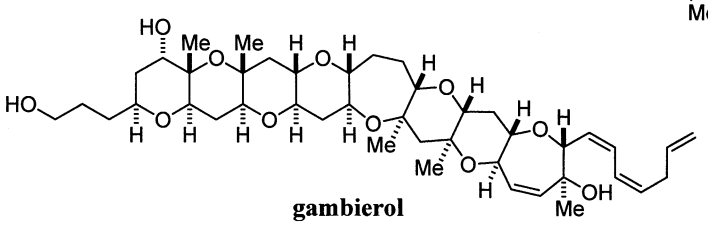
1. Introduction

Polycyclic ethers of marine origin, such as the brevetoxins and the ciguatoxins, continue to be highly attractive synthetic targets because of their structural complexity and the significant biological activities they display.[1,2] These marine natural products possess extended arrays of *trans*-fused cyclic ethers and their size coupled with the high proportion of medium-sized rings and the large number of stereogenic centres they contain makes them formidable targets. In addition, marine polyethers of the brevetoxin and the ciguatoxin families are of interest because of their potent neurotoxicity; most of them interfere with the function of voltage-sensitive sodium channels in vertebrates at very low concentrations.[1]

Two typical marine polyether natural products are gambierol[3] and gambieric acid A,[4] both of which are produced by *Gambierdiscus toxicus*, a dinoflagellate organism responsible for ciguatera poisoning in humans.[1] Gambierol and the gambieric acids are notable for the predominance of six- and seven-membered ether rings in their polyether structures. The gambieric acids are of particular pharmacological significance because they display potent anti-fungal activity against a variety of filamentous fungi.[4,5]



gambieric acid A



gambierol

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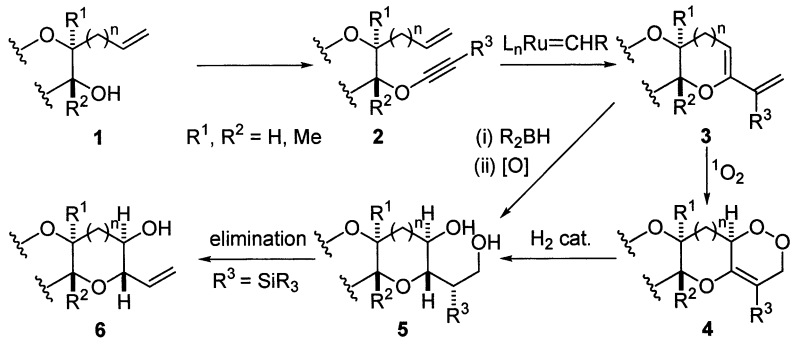


Scheme 1.

In recent years, we[6] and other workers[7] have reported that ring-closing metathesis[8] is a powerful reaction for the synthesis of cyclic ethers of the type found in polyether natural products of marine origin. We have demonstrated that ring-closing metathesis of acyclic enol ethers and hydroboration of the resulting cyclic enol ethers can be used to prepare six- and seven-membered cyclic ethers,[6a,e] and that ring-closing metathesis of allylic ethers can be used to prepare seven-, eight- and nine-membered cyclic ethers in excellent yield.[6b,c] In addition, we have demonstrated that ring-closing metathesis can be employed as the key reaction for two-directional assembly of polycyclic ethers.[6f]

As part of our ongoing research programme directed towards the synthesis of marine polyethers in general and the gambieric acids in particular, we have investigated enyne metathesis as a method for cyclic ether construction to complement our recently developed enol ether and allylic ether ring-closing metathesis approaches.[6] Our strategy for the preparation of *trans*-fused polyethers using ring-closing enyne metathesis is summarised in Scheme 1. We envisaged preparing the suitably functionalised alkynyl ethers **2** from the functionalised alcohols **1** and then converting them into the alkenyl-substituted cyclic enol ethers **3** by catalytic ring-closing metathesis.[6d,8] Elaboration of these products by hydroboration or by cycloaddition with $^1O_2$ followed by hydrogenation of the resulting cyclic *endo*-peroxides **4**,[9] would provide the diols **5**. In the case where R^3 is a trialkylsilyl group, ring-closing metathesis would deliver a vinylic silane (**3**, R^3=SiR_3). Subsequent hydroboration and oxidative work-up would produce a β-hydroxy silane (**5**, R^3=SiR_3) which would then undergo immediate Peterson elimination to deliver the alcohol **6**.[10] Attachment of an unsaturated chain to the secondary hydroxyl group of the alcohol **6** would then allow an additional cyclic ether to be constructed by ring-closing diene metathesis of the alkene with the pendant vinylic group.

2. Results and discussion

In initial studies we sought to establish whether alkynyl ethers would undergo metathesis using a variety of catalysts (**7**–**9**, Fig. 1).[6d] Preliminary work revealed that the Schrock molybdenum complex **7** is not a suitable metathesis catalyst in this context, and so we concentrated on using the ruthenium complexes **8** and **9** as catalysts.[11] In previous

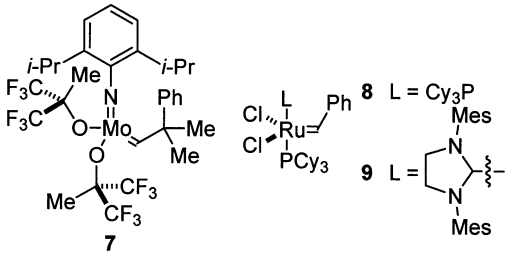
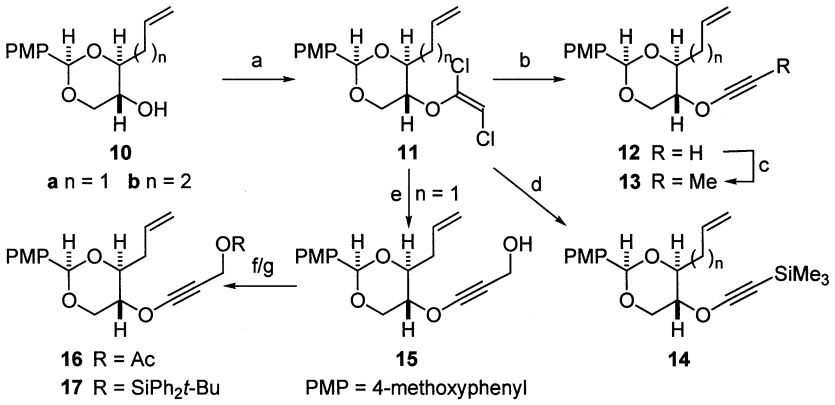


Figure 1. Candidate catalysts for ring-closing enyne metathesis of alkynyl ethers.

work we had found that substituted enol ethers are less reactive metathesis partners than alkenes and are usually poor substrates for the ruthenium catalyst **8**.[6,12] At the outset it was not clear whether alkynyl ethers would display an analogous decrease in reactivity compared to alkynes. It was also necessary to establish whether terminal alkynyl ethers would undergo efficient ring-closing metathesis because literature data suggested that ring-closing enyne metathesis reactions of terminal alkynes were sometimes problematic.[13]

The alkynyl ethers required for our study were synthesised from the alcohols **10a** and **10b** (Scheme 2). These alcohols were prepared from (*R*)-2,3-*O*-isopropylidene glyceraldehyde[14] by diastereoselective Grignard addition of allylmagnesium bromide or 3-butenylmagnesium bromide followed by acetonide cleavage and *p*-methoxybenzylidene acetal formation, as described previously by us (Scheme 2).[6,15] The cyclisation substrates **12a** and **12b** were prepared using a modification of Greene's method for the synthesis of alkynyl ethers from hindered secondary alcohols.[16] The original method involves deprotonation of the alcohol, reaction of the resulting alkoxide with trichloroethene, and treatment of the intermediate dichloro enol ethers with *n*-butyllithium in a one-pot fashion.[16] However, modest yields were obtained when we employed this procedure to convert the alcohols **10a** and **10b** directly into the alkynyl ethers **12a** and **12b**. As a consequence, we discovered that it was best to isolate the intermediate enol ethers **11a** and **11b** and generate the alkynyl ethers in a separate reaction. The enol ethers **11a** and **11b** were isolated as stable crystalline solids in high yield, and their subsequent treatment with *n*-butyllithium provided the alkynyl ethers **12a** and **12b** in excellent yield. In fact, the combined yields over two steps were comparable to those obtained by Greene and



Scheme 2. *Reagents:* (a) (i) KH, THF, rt, (ii) Cl_2CCHCl, THF, 0°C (**11a** 81%, **11b** 89%); (b) (i) *n*-BuLi, Et_2O, −78°C (**12a** 88%, **12b** 84%); (c) (i) *n*-BuLi, Et_2O, −78→−10°C, (ii) MeI, DMPU, −10°C→rt (**13a** 80%, **13b** 77%); (d) (i) *n*-BuLi, Et_2O, −78°C, (ii) Me_3SiCl, −78→0°C (**14a** 87%, **14b** 46%); (e) (i) *n*-BuLi, THF, −78→−10°C, (ii) $(CH_2O)_n$, −10°C→rt (66%); (f) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt (83%); (g) *t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2, rt (94%).

co-workers when they used their one-pot procedure to prepare analogous alkynyl ethers.[16]

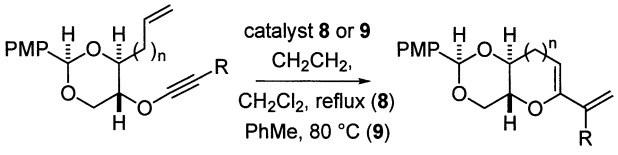
The other substrates required for our studies were prepared from the enol ethers **11a/b** or the alkynyl ethers **12a/b**. The cyclisation precursors **13a** and **13b** were prepared by deprotonation of the alkynyl ethers **12a** and **12b** with *n*-butyllithium and alkylation of the resulting anions with methyl iodide. The substrates **14a**, **14b** and **15** were obtained by treatment of the enol ethers **11a** and **11b** with *n*-butyllithium and reaction of the resulting acetylide anions with either trimethylsilylchloride or paraformaldehyde. Acetylation of the alcohol **15** with acetic anhydride delivered the acetate **16**, and the corresponding silyl ether **17** was prepared by treatment of the same alcohol with *t*-butyldiphenylsilyl chloride in the presence of imidazole.

The ring-closing metathesis reactions of the alkynyl ethers **12**–**17** promoted by the catalysts **8**[17] and **9**[18] were explored (Table 1). Treatment of each substrate with the complex **8** in dichloromethane at reflux or the complex **9** in toluene at 80°C, resulted in ring-closing metathesis to afford the alkenyl-substituted cyclic enol ethers **18**–**23** (Table 1). In general, the highest yields of the required dienes were obtained from those reactions in which the more reactive ruthenium complex **9** was employed as the catalyst.[18] When this complex was used as the catalyst, the yields of the six-membered cyclic ethers (entries 1–6, Table 1) were usually ~90% and yields of the seven-membered cyclic ethers were >70%.

The ruthenium-catalysed ring-closing enyne metathesis reaction was successful with substrates bearing a wide variety of alkyne substituents. In general, the ruthenium complex **9** is a more efficient catalyst than the related complex **8**, especially in cases where the alkyne possesses a bulky substituent or the metathesis reaction delivers a seven-membered cyclic ether as the product. The only case in which the complex **8** proved to be superior to the complex **9** as a metathesis catalyst was the cyclisation reaction of the alcohol **15**. When this reaction was performed using the ruthenium catalyst **9**, only a trace amount of the product **21** was produced after several days, and large amounts of the enyne **15** were recovered. In this case, the ruthenium catalyst **9** appears to complex to the free hydroxyl group of the substrate or product to such an extent that the catalyst is effectively deactivated and the catalytic cycle is not established.

Two other notable findings emerge from the results given in Table 1. Firstly, terminal alkynyl ethers, such as **12a** and **12b**, are good substrates for the ruthenium catalysed

Table 1.



Entry	Substrate	R	*n*	Product	Yield (%; **8**)	Yield (%; **9**)
1	**12a**	H	1	**18a**	65	90
2	**13a**	Me	1	**19a**	77	98
3	**14a**	$SiMe_3$	1	**20a**	20	88
4	**15**	CH_2OH	1	**21**	84	8
5	**16**	CH_2OAc	1	**22**	54	72
6	**17**	$CH_2OTBDPS$	1	**23**	61	91
7	**12b**	H	2	**18b**	33	70
8	**13b**	Me	2	**19b**	27	72
9	**14b**	$SiMe_3$	2	**20b**	–	0

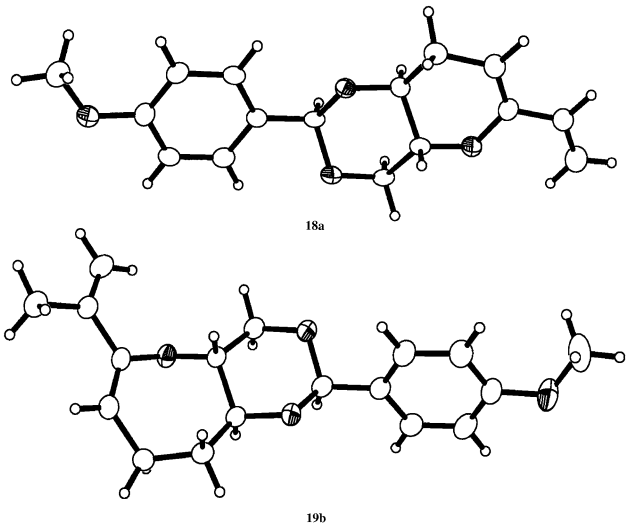


Figure 2. The X-ray crystal structures of the ring-closing enyne metathesis products **18a** and **19b**.[19]

ring-closing enyne metathesis reaction, and secondly, ring-closing enyne metathesis to give the seven-membered cyclic ethers **18b** and **19b** is significantly more difficult to achieve than ring closure to give the corresponding six-membered cyclic ethers **18a** and **19a**.

The ring-closing metathesis products **18a** and **19b** were obtained as crystalline solids and crystals suitable for X-ray crystallography were obtained by slow recrystallisation from petroleum ether. The structures of both of the cyclic ethers **18a** and **19b** were confirmed by X-ray analysis (Fig. 2).[19]

3. Conclusions

Our results demonstrate that ring-closing metathesis reactions of alkynyl ethers promoted by the ruthenium complexes **8** and **9** can be used to prepare six- and seven-membered alkenyl-substituted cyclic enol ethers in high yield. In addition, we have shown that optimum yields are usually obtained using the more reactive carbene-substituted complex **9** as the metathesis catalyst and that ruthenium metathesis catalysts are tolerant of a wide range of alkyne substituents.

We are currently exploring the elaboration of the alkenyl-substituted cyclic enol ethers obtained by ring-closing enyne metathesis, and the conversion of these compounds into polycyclic ethers fragments of the natural products will be reported in due course.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded at ambient temperature using Bruker AM 400, AV 400 and DRX 500 instruments, and samples were dissolved in deuterochloroform. Chemical shifts are quoted in parts per million (ppm) and J values are given in Hertz. ^{1}H NMR signals are described as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m), or broad (br) or a combination of these. Signals in ^{13}C NMR spectra are quoted in parts per million (ppm) with residual chloroform (δ=77.1 ppm) as the internal standard and peaks are given as singlets (s), doublets (d), triplets (t) or quartets (q) indicating the number of protons attached to each carbon atom. IR spectra were recorded using a Perkin–Elmer 1600 series FT-IR spectrometer with internal calibration using solution cells unless otherwise stated. Melting points were determined using a Mel-Temp II melting point apparatus. Elemental analyses were performed by the microanalysis section of the School of Chemistry, University of Nottingham. Mass spectra and accurate mass measurements were recorded using a Fisons VG Autospec or VG Micromass 70E instrument. Optical rotations were determined using a Jasco DIP-370 digital polarimeter. Reactions were monitored by TLC and were performed on Merck Kieselgel 60 F_{254} plates and visualized by a combination of UV light and ethanolic anisaldehyde with heat. Flash column chromatography was performed using Fluka silica gel 60. Solvents and reagents were distilled using standard methods prior to use and air sensitive compounds were handled under nitrogen or argon. The ruthenium complexes **8** and **9** were either purchased from Strem Chemicals or prepared according to the procedures of Grubbs.[17,18a] All reactions were performed in flame-dried glassware under nitrogen or argon unless otherwise indicated.

4.1.1. (2*R*,4*S*,5*R*)-4-Allyl-5-[(*E*)-1,2-dichlorovinyloxy]-2-(4-methoxyphenyl)-1,3-dioxane (11a). A solution of the alcohol **10a** (1.07 g, 4.28 mmol) in dry THF (10 mL) was added by cannula to a stirred suspension of KH (345 mg, 8.60 mmol) in dry THF (20 mL) at room temperature. The reaction was stirred for 1 h and freshly distilled trichloroethane (630 mg, 4.79 mmol) in dry THF (5 mL) was then added dropwise at 0°C. The reaction was stirred for 1 h at room temperature and then quenched with methanol (1 mL). The solvent was removed and the residue was dissolved in diethyl ether (100 mL). The solution was washed with water (2×50 mL) and then dried ($MgSO_4$). The solvent was removed in vacuo to give a solid which was purified by flash column chromatography on silica gel (1% Et_3N, diethyl ether–hexane, 1:10) to give the enol ether **11a** as a colourless crystalline solid (1.2 g, 81%): mp 89–91°C; $[\alpha]_D^{26}$=−14.9 (c 0.895, $CHCl_3$); ν_{max} ($CHCl_3$) 3110, 2928, 2865, 1616, 1589, 995, 916 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, d, J=8.8 Hz, *Ar*), 6.91 (2H, d, J=8.8 Hz, *Ar*), 5.99 (1H, dddd, J=6.6, 7.4, 10.1, 17.2 Hz, C*H*=CH$_2$), 5.60 (1H, s, ClC*H*), 5.50 (1H, s, OC*H*O), 5.25–5.18 (1H, m, CH=C*H*$_2$), 5.20–5.16 (1H, m, CH=C*H*$_2$), 4.41 (1H, dd, J=5.2, 10.8 Hz, CH*H*O), 4.27 (1H, ddd, J=5.2, 9.3, 10.0 Hz, C*H*O), 3.95 (1H, ddd, J=3.2, 7.2, 9.3 Hz, C*H*O), 3.83–3.78 (1H, m, CH*H*O), 3.82 (3H, s, OC*H*$_3$), 2.74–2.69 (1H, m, C*H*$_2$CH=CH$_2$), 2.54–2.46 (1H, m, C*H*$_2$CH=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (s), 142.1 (s), 133.3 (d), 129.8 (s), 127.4 (d), 118.1 (t), 113.7 (d), 101.0 (d), 99.2 (d), 78.7 (d), 72.8 (d), 68.3 (t), 55.3 (q), 35.8 (t); LRMS (EI) m/z 344 (M^+, 3), 233 (32), 137 (100), 136 (65), 135 (85), 97 (51); HRMS (EI) Calcd for $C_{16}H_{18}O_4{}^{35}Cl_2$ (M^+): 344.0582. Found 344.0598. Anal.

Calcd for $C_{16}H_{18}O_4Cl_2$: C, 55.67; H, 5.26; Cl, 20.54. Found: C, 55.32; H, 5.14; Cl, 20.33.

4.1.2. (2*R*,4*S*,5*R*)-4-(But-3-enyl)-5-[(*E*)-1,2-dichlorovinyloxy]-2-(4-methoxyphenyl)-1,3-dioxane (11b). A solution of the alcohol **10b** (1.0 g, 3.8 mmol) in dry THF (10 mL) was added by cannula to a stirred suspension of KH (345 mg, 8.60 mmol) in dry THF (15 mL) at room temperature. The reaction was stirred for 1 h and freshly distilled trichloroethane (600 mg, 4.57 mmol) in dry THF (2 mL) was then added dropwise at 0°C. The reaction was stirred for 1 h at room temperature and then quenched with methanol (1 mL). The solvent was removed and the residue was dissolved in diethyl ether (100 mL). The solution was washed with brine (2×50 mL) then dried ($MgSO_4$). The solvent was removed in vacuo to give a solid which was purified by flash column chromatography on silica gel (1% Et_3N, diethyl ether–hexane, 1:10) give the enol ether **11b** as a colourless crystalline solid (1.21 g, 89%): mp 94–95°C; $[\alpha]_D^{25}=-37.3$ (*c* 0.885, $CHCl_3$); ν_{max} ($CHCl_3$) 3110, 2936, 2865, 1665, 1627, 1614, 1589, 1002, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, d, *J*=8.6 Hz, *Ar*), 6.92 (2H, d, *J*=8.6 Hz, *Ar*), 5.87 (1H, dddd, *J*=6.3, 7.0, 10.1, 17.2 Hz, C*H*=CH_2), 5.60 (1H, s, ClC*H*), 5.49 (1H, s, OC*H*O), 5.08 (1H, dddd, *J*=1.7, 1.7, 1.7, 17.2 Hz, CH=CH_2), 5.04–5.00 (1H, m, CH=CH_2), 4.40 (1H, dd, *J*=5.2, 10.8 Hz, CH_2O), 4.22 (1H, ddd, *J*=5.2, 9.2, 10.2 Hz, C*H*O), 3.87 (1H, ddd, *J*=2.6, 9.1, 9.2 Hz, C*H*O), 3.82 (3H, s, OCH_3), 3.81 (1H, dd, *J*=10.2, 10.8 Hz, CH_2O), 2.42–2.31 (1H, m, CH_2CH=CH_2), 2.30–2.18 (1H, m, CH_2CH=CH_2), 2.06 (1H, dddd, *J*=2.6, 7.0, 9.5, 14.0 Hz, OCHCH_2), 1.76 (1H, dddd, *J*=5.1, 9.0, 9.1, 14.0 Hz, OCHCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (s), 142.2 (s), 138.0 (d), 130.0 (s), 127.4 (d), 115.2 (t), 113.7 (d), 101.1 (d), 99.3 (d), 78.5 (d), 73.8 (d), 68.4 (t), 55.4 (q), 30.8 (t), 28.9 (t); HRMS (EI) Calcd for $C_{17}H_{20}O_4{}^{35}Cl_2$ (M^+): 358.0738. Found 358.0739. Anal. Calcd for $C_{17}H_{20}O_4Cl_2$: C, 56.84; H, 5.61; Cl, 19.74. Found C, 56.90; H, 5.79; Cl, 19.33.

4.1.3. (2*R*,4*S*,5*R*)-4-Allyl-5-ethynyloxy-2-(4-methoxyphenyl)-1,3-dioxane (12a). A solution of the dichloroenol ether **11a** (790 mg, 2.29 mmol) in dry ether (10 mL) was added dropwise to a solution of *n*-BuLi (3.1 mL of a 2.2 M solution in hexane, 6.8 mmol) in dry ether (10 mL) at −78°C over a period of 10 min. The reaction mixture was stirred at −78°C for 30 min then warmed to 0°C and stirred for a further 30 min. The reaction was quenched with water and extracted with diethyl ether (2×50 mL) and washed with brine (2×20 mL). The organic extracts were dried ($MgSO_4$) and the solvent was removed in vacuo to give a yellow oil which was purified by flash column chromatography on silica gel (1% Et_3N, diethyl ether–hexane, 1:10) to afford the alkynyl ether **12a** (550 mg, 88%) as a colourless oil: $[\alpha]_D^{25}=-21.7$ (*c* 1.40, $CHCl_3$); ν_{max} ($CHCl_3$) 3322, 2866, 2155, 1615, 968, 912 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (2H, d, *J*=8.8 Hz, *Ar*), 6.90 (2H, d, *J*=8.8 Hz, *Ar*), 5.96 (1H, dddd, *J*=6.7, 7.2, 10.2, 17.1 Hz, C*H*=CH_2), 5.46 (1H, s, OC*H*O), 5.23 (1H, dddd, *J*=1.6, 1.6, 1.6, 17.2 Hz, CH=CH_2), 5.20–5.16 (1H, m, CH=CH_2), 4.55 (1H, dd, *J*=5.3, 10.8 Hz, CH_2O), 4.07 (1H, ddd, *J*=5.3, 9.5, 10.2 Hz, C*H*O), 3.88–3.80 (1H, m, C*H*O), 3.82 (1H, dd, *J*=10.2, 10.8 Hz, CH_2O), 3.82 (3H, s, OCH_3), 2.68–2.75 (1H, m, CH_2CH=CH_2), 2.45–2.53 (1H, m, CH_2CH=CH_2), 1.62 (1H, s, C≡C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (s), 133.0 (d), 129.6 (s), 127.5 (d), 118.4 (t), 113.8 (d), 101.1 (d), 88.6 (d), 78.1 (d), 67.6 (t), 55.4 (q), 35.9 (t), 27.8 (s); HRMS (EI) Calcd for $C_{16}H_{18}O_4$ (M^+): 274.1205. Found 274.1212.

4.1.4. (2*R*,4*S*,5*R*)-4-(But-3-enyl)-5-ethynyloxy-2-(4-methoxyphenyl)-1,3-dioxane (12b). A solution of the dichloroenol ether **11b** (370 mg, 1.03 mmol) in dry ether (10 mL) was added dropwise to a solution of *n*-BuLi (1.25 mL of a 2.5 M solution in hexane, 3.1 mmol) in dry ether (10 mL) at −78°C over a period of 10 min. The reaction mixture was stirred at −78°C for 30 min then warmed to 0°C and stirred for a further 50 min. The reaction was quenched with methanol (1 mL), extracted with diethyl ether (2×20 mL) and washed with brine (2×20 mL). The organic extracts were dried ($MgSO_4$) and the solvent was removed in vacuo to give a yellow oil which was purified by flash column chromatography on silica gel (1% Et_3N, diethyl ether–hexane, 1:1) to afford the alkynyl ether **12b** (250 mg, 84%) as a colourless solid: mp 30–35°C; $[\alpha]_D^{20}=-48.9$ (*c* 0.986, $CHCl_3$); ν_{max} ($CHCl_3$) 3322, 2935, 3865, 2154, 1641, 1615, 1589, 967, 913 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, d, *J*=8.6 Hz, *Ar*), 6.90 (2H, d, *J*=8.6 Hz, *Ar*), 5.86 (1H, dddd, *J*=6.3, 6.9, 10.2, 17.1 Hz, C*H*=CH_2), 5.45 (1H, s, OC*H*O), 5.09 (1H, dddd, *J*=1.6, 1.6, 1.6, 17.1 Hz, CH=CH_2), 5.03 (1H, m, CH=CH_2), 4.56 (1H, dd, *J*=5.2, 10.8 Hz, CH_2O), 4.00 (1H, ddd, *J*=5.2, 9.4, 10.2 Hz, C*H*O), 3.84–3.75 (2H, m, C*H*O, CH_2O), 3.82 (3H, s, OCH_3), 2.41–2.32 (1H, m, CH_2CH=CH_2), 2.30–2.17 (1H, m, CH_2CH=CH_2), 2.12–2.03 (m, 1H, OCHCH_2CH$_2$), 1.83–1.72 (1H, m, OCHCH_2CH$_2$), 1.61 (1H, s, C≡C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (s), 137.8 (d), 129.7 (s), 127.4 (d), 115.3 (t), 113.7 (d), 101.1 (d), 88.7 (d), 79.1 (d), 78.0 (d), 67.6 (t), 55.4 (q), 30.9 (t), 28.8 (t), 27.5 (s); HRMS (EI) Calcd for $C_{17}H_{20}O_4$ (M^+): 288.1362. Found 288.1363. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found C, 70.39; H, 7.10.

4.1.5. (2*R*,4*R*,5*S*)-4-Allyl-2-(4-methoxyphenyl)-5-(prop-1-ynyloxy)-1,3-dioxane (13a). A solution of the alkyne **12a** (200 mg, 0.729 mmol) in dry diethyl ether (10 mL) was added dropwise to a solution of *n*-BuLi (1.0 mL of a 2.2 M solution in hexane, 2.2 mmol) in dry diethyl ether (1 mL) at −78°C. The mixture was stirred at −78°C for 20 min and then allowed to warm at −10°C and stirred for a further 10 min. Freshly distilled methyl iodide (426 mg, 3.00 mmol) in dry DMPU (5 mL) was then added dropwise and the resulting solution allowed to warm slowly to room temperature. After 1 h, the reaction was quenched with water (5 mL) and diluted with diethyl ether (50 mL). The mixture was washed with brine (2×50 mL) and then dried ($MgSO_4$). The solvent was removed in vacuo to afford a yellow oil which was purified by flash column chromatography on silica gel (1% Et_3N, diethyl ether–hexane, 1:10) to give the alkynyl ether **13a** (168 mg, 80%) as a colourless oil: $[\alpha]_D^{23}=-25.8$ (*c* 1.16, $CHCl_3$); ν_{max} ($CHCl_3$) 2937, 2922, 2862, 2839, 2282, 1642, 1616, 1589, 987, 915 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (2H, d, *J*=8.7 Hz, *Ar*), 6.90 (2H, d, *J*=8.7 Hz, *Ar*), 5.95 (1H, dddd, *J*=6.7, 7.3, 10.2, 17.1 Hz, C*H*=CH_2), 5.44 (1H,

s, OC*H*O), 5.23 (1H, dd, *J*=1.0, 17.1 Hz, CH=CH_2), 5.15 (1H, dd, *J*=1.0, 10.2 Hz, CH=CH_2), 4.52 (1H, dd, *J*=5.2, 10.8 Hz, CH_2O), 3.92 (1H, ddd, *J*=5.3, 9.3, 10.2 Hz, C*H*O), 3.81–3.74 (2H, m, C*H*O, CH_2O), 3.81 (3H, s, OCH_3), 2.72–2.67 (1H, m, CH_2CH=CH_2), 2.46 (1H, dddd, *J*=0.9, 7.3, 7.3, 14.7 Hz, CH_2CH=CH_2), 1.73 (3H, d, *J*=1.0 Hz, CCH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 160.0 (s), 133.1 (d), 129.7 (s), 127.3 (d), 118.0 (t), 113.5 (d), 100.9 (d), 86.1 (s), 78.3 (d), 77.3 (d), 67.7 (t), 55.2 (q), 35.8 (t), 33.4 (s), 1.4 (q); HRMS (EI) Calcd for $C_{17}H_{20}O_4$ (M^+): 288.1362. Found 288.1357. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 71.20; H, 7.41.

4.1.6. (2*R*,4*S*,5*R*)-4-(But-3-enyl)-2-(4-methoxyphenyl)-5-(prop-1-ynyloxy)-1,3-dioxane (13b). A solution of the alkyne **12b** (160 mg, 0.555 mmol) in dry diethyl ether (1 mL) was added dropwise to a solution of *n*-BuLi (0.67 mL of a 2.5 M solution in hexane, 1.7 mmol) in dry diethyl ether (5 mL) at −78°C. The reaction was stirred at −78°C for 30 min and then allowed to warm to −10°C and stirred for a further 30 min. Freshly distilled methyl iodide (315 mg, 2.22 mmol) in dry DMPU (2 mL) was added dropwise and the resulting solution allowed to warm slowly to room temperature. After 1 h, the reaction was quenched with water (5 mL) and diluted with diethyl ether (50 mL). The mixture was washed with brine (2×20 mL) and then dried ($MgSO_4$). The solvent was removed in vacuo to give a yellow oil which was purified by flash column chromatography on silica gel (1% Et_3N, diethyl ether–hexane, 1:10) to afford the alkynyl ether **13b** (130 mg, 77%) as a colourless solid: mp 33–36°C; $[\alpha]_D^{20}$=−40.5 (*c* 1.13, $CHCl_3$); ν_{max} ($CHCl_3$) 3082, 2923, 2861, 2282, 1640, 1616, 1589, 990, 914 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, d, *J*=8.6 Hz, *Ar*), 6.92 (2H, d, *J*=8.8 Hz, *Ar*), 5.88 (1H, dddd, *J*=6.2, 6.9, 10.2, 17.1 Hz, C*H*=CH$_2$), 5.44 (1H, s, OC*H*O), 5.12 (1H, dddd, *J*=1.6, 1.6, 1.6, 17.1 Hz, CH=CH_2), 5.09–5.01 (1H, m, CH=CH_2), 4.54 (1H, dd, *J*=5.0, 10.6 Hz, CH_2O), 3.89 (1H, *J*=5.0, 9.5, 10.0 Hz, C*H*O), 3.84–3.72 (2H, m, CH_2O, C*H*O), 3.83 (3H, s, OCH_3), 2.43–2.32 (1H, m, CH_2CH=CH$_2$), 2.28–2.17 (1H, m, CH_2CH=CH$_2$), 2.02–2.11 (1H, m, OCHCH_2CH$_2$), 1.83–1.72 (1H, m, OCHCH_2CH$_2$), 1.75 (3H, s, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (s), 137.9 (d), 129.8 (s), 127.4 (d), 115.1 (t), 113.6 (d), 100.9 (d), 86.2 (s), 78.2 (d), 78.1 (d), 67.9 (t), 55.3 (q), 33.4 (s), 30.8 (t), 28.8 (t), 1.6 (q); HRMS (EI) Calcd for $C_{18}H_{22}O_4$ (M^+): 302.1518. Found 302.1517.

4.1.7. (2*R*,4*S*,5*R*)-4-Allyl-2-(4-methoxyphenyl)-5-[(trimethylsilyl)ethynyloxy]-1,3-dioxane (14a). *n*-BuLi (1.7 mL of a 2.5 M solution in hexane, 4.3 mmol) was added dropwise over a 2 min period to a solution of the enol ether **11a** (500 mg, 1.45 mmol) in dry diethyl ether (25 mL) at −78°C. The reaction was stirred for 30 min at −78°C and a solution of freshly distilled chlorotrimethylsilane (470 mg, 4.33 mmol) in dry diethyl ether (8 mL) was added dropwise. The mixture was allowed to warm to 0°C and stirred for 2 h 30 min and then quenched with water (5 mL). The mixture was extracted with diethyl ether (70 mL) and the organic extract washed with brine (2×25 mL) then dried ($MgSO_4$). The solvent was removed in vacuo to give a yellow oil which was purified by flash column chromatography on silica gel (1% Et_3N, diethyl ether–hexane, 1:30) to afford the alkynyl ether **14a** (410 mg, 87%) as a colourless oil: $[\alpha]_D^{22}$=−16.4 (*c* 1.05, $CHCl_3$); ν_{max} ($CHCl_3$) 2956, 2183, 1615, 967 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (2H, d, *J*=8.8 Hz, *Ar*), 6.91 (2H, d, *J*=8.8 Hz, *Ar*), 5.96 (1H, ddd, *J*=6.9, 7.1, 10.2, 17.2 Hz, C*H*=CH$_2$), 5.45 (1H, s, OC*H*O), 5.23 (1H, dddd, *J*=1.6, 1.6, 1.6, 17.2 Hz, CH=CH_2), 5.20–5.15 (1H, m, CH=CH_2), 4.54 (1H, dd, *J*=5.3, 10.8 Hz, CH_2O), 4.08 (1H, ddd, *J*=5.3, 9.6, 10.0 Hz, C*H*O), 3.87–3.76 (2H, m, C*H*O, CH_2O), 3.82 (3H, s, OCH_3), 2.76–2.68 (1H, m, CH_2CH=CH$_2$), 2.53–2.44 (1H, m, CH_2CH=CH$_2$), 0.00 (9H, s, Si[CH_3]$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (s), 133.0 (d), 129.7 (s), 127.5 (d), 118.4 (t), 113.7 (d), 107.2 (s), 101.1 (d), 78.4 (d), 78.2 (d), 67.5 (t), 55.3 (q), 38.0 (s), 35.9 (t), 0.6 (q); HRMS (FAB) Calcd for $C_{19}H_{27}O_4Si$ (M^++H): 347.1679. Found 347.1706. Anal. Calcd for $C_{19}H_{26}O_4Si$: C, 65.86; H, 7.56. Found: C, 65.59; H, 7.62.

4.1.8. (2*R*,4*S*,5*R*)-4-(But-3-enyl)-2-(4-methoxyphenyl)-5-[(trimethylsilyl)ethynyloxy]-1,3-dioxane (14b). *n*-BuLi (1.4 mL of a 2.4 M solution in hexane, 3.4 mmol) was added dropwise to a solution of the enol ether **11b** (400 mg, 1.11 mmol) in dry THF (10 mL) cooled to −78°C. The mixture was stirred at −78°C for 30 min, allowed to warm at 0°C and stirred for another 30 min at this temperature. Freshly distilled chlorotrimethylsilane (480 mg, 4.42 mmol) was added in one portion and the reaction was warmed to room temperature and stirred for 2 h. The reaction was quenched with water (5 mL) and the THF was removed in vacuo. The residual material was extracted with ether (2×50 mL) and the organic extracts were washed with brine (2×50 mL) and then dried ($MgSO_4$). The solvent was removed in vacuo to give a pale yellow solid which was purified by flash column chromatography on silica gel (1% Et_3N, diethyl ether–hexane, gradient 1:10→1:1) to afford the alkynyl ether **14b** (203 mg, 46%) as a colourless oil: $[\alpha]_D^{20}$=−29.5 (*c* 0.895, $CHCl_3$); ν_{max} ($CHCl_3$) 2958, 2966, 1640, 1615, 1592, 993, 943, 915 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, d, *J*=8.7 Hz, *Ar*), 6.91 (2H, d, *J*=8.7 Hz, *Ar*), 5.86 (1H, dddd, *J*=6.3, 6.9, 10.2, 17.1 Hz, C*H*=CH$_2$), 5.49 (1H, s, OC*H*O), 5.08 (1H, dd, *J*=1.7, 17.1 Hz, CH=CH_2), 5.03–4.98 (1H, m, CH=CH_2), 4.37 (1H, dd, *J*=5.2, 10.6 Hz, CH_2O), 4.28 (1H, ddd, *J*=5.2, 9.2, 10.0 Hz, C*H*O), (1H, ddd, *J*=2.6, 9.0, 9.2 Hz, C*H*O), 3.82 (3H, s, OCH_3), 3.82 (1H, dd, *J*=10.0, 10.6 Hz, CH_2O), 2.42–2.31 (1H, m, CH_2CH=CH$_2$), 2.30–2.17 (1H, m, CH_2CH=CH$_2$), 2.10–2.00 (1H, m, OCHCH_2CH$_2$), 1.75 (1H, m, *J*=5.1, 9.0, 9.0, 14.1 Hz, OCHCH_2CH$_2$), 0.30 (9H, s, Si[CH_3]$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (s), 145.9 (s), 138.1 (d), 130.1 (s), 127.4 (d), 115.1 (t), 113.7 (d), 101.0 (d), 78.7 (d), 73.4 (d), 68.6 (t), 55.4 (q), 30.8 (t), 29.0 (t), −0.9 (q).

4.1.9. (2*R*,4*S*,5*R*)-4-Allyl-2-(4-methoxyphenyl)-5-[(3-hydroxy)prop-1-ynyloxy]-1,3-dioxane (15). The enol ether **11a** (700 mg, 2.03 mmol) was dissolved in dry THF (10 mL) and the solution was cooled at −78°C. *n*-BuLi (2.5 mL of a 2.4 M solution in hexane, 6.0 mmol) was added dropwise over a 5 min period to the solution and the mixture was stirred at −78°C for 30 min. The reaction was warmed to −10°C and stirred for a further 30 min, and then paraformaldehyde (1 g, predried by azeotropic removal of water with toluene) in dry THF (5 mL) was added in one

portion. The mixture was warmed to room temperature and then stirred at reflux for 2 h. The reaction was quenched with water (5 mL) and the THF was removed in vacuo. The residual material was extracted with diethyl ether (2×100 mL) and the organic extracts were washed with brine (2×50 mL) then dried ($MgSO_4$). The solvent was removed in vacuo to give a pale yellow solid which was purified by flash column chromatography on silica (1% Et_3N, diethyl ether–hexane, gradient 1:5→1:1) to afford the alcohol **15** (410 mg, 66%) as a colourless solid: mp 85–87°C; $[\alpha]_D^{26}=-20.1$ (*c* 0.820 in $CHCl_3$); ν_{max} ($CHCl_3$) 3611, 2937, 2867, 2839, 2271, 1642, 1615, 1589, 980, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (2H, d, *J*=8.7 Hz, *Ar*), 6.90 (2H, d, *J*=8.7 Hz, *Ar*), 5.95 (1H, dddd, *J*=6.9, 7.0, 10.2, 17.2 Hz, C*H*═CH_2), 5.45 (1H, s, OC*H*O), 5.22 (1H, dd, *J*=1.5, 17.2 Hz, CH═CH_2), 5.17 (1H, d, *J*=10.2 Hz, CH═CH_2), 4.53 (1H, dd, *J*=5.3, 10.8 Hz, OCH_2), 4.26 (2H, s, CH_2OH), 4.03 (1H, ddd, *J*=5.3, 9.7, 9.8 Hz, C*H*O), 3.87–3.74 (2H, m, C*H*O, CH_2O), 3.81 (3H, s, OCH_3), 2.73–2.64 (1H, m, CH_2CH═CH_2), 2.52–2.43 (1H, m, CH_2CH═CH_2) 1.81 (1H, br, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (s), 133.0 (d), 129.6 (s), 127.4 (d), 118.3 (t), 113.7 (d), 101.1 (d), 92.4 (s), 78.2 (d), 78.2 (d), 67.6 (t), 55.3 (q), 50.6 (t), 37.7 (s), 35.9 (t); HRMS (EI) Calcd for $C_{17}H_{20}O_5$ (M^+): 304.1311. Found 304.1300. Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found C, 66.82; H, 6.67.

4.1.10. (2*R*,4*S*,5*R*)-4-Allyl-5-[(3-acetoxy)prop-1-ynyloxy]-2-(4-methoxyphenyl)-1,3-dioxane (16). The alcohol **15** (55 mg, 0.18 mmol) was dissolved in dichloromethane (1 mL) and triethylamine (20 mg, 0.20 mmol), DMAP (24 mg, 0.20 mmol) and acetic anhydride (40 mg, 0.39 mmol) were added at room temperature. The reaction was stirred at room temperature overnight. The solvent was removed and the residual material was purified by flash column chromatography on silica gel (1% Et_3N, diethyl ether–hexane, 1:5) to give the acetate **16** (52 mg, 83% yield) as a white solid: mp 95–97°C; $[\alpha]_D^{22}=-22.6$ (*c* 0.980, $CHCl_3$); ν_{max} ($CHCl_3$) 2938, 2866, 2839, 2279, 1738, 1642, 1616, 1589, 981, 915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (2H, d, *J*=8.7 Hz, *Ar*), 6.90 (2H, d, *J*=8.7 Hz, *Ar*), 5.95 (1H, dddd, *J*=6.8, 7.2, 10.2, 17.2 Hz, C*H*═CH_2), 5.45 (1H, s, OC*H*O), 5.21 (1H, dddd, *J*=1.7, 1.7, 1.7, 17.2 Hz, CH═CH_2), 5.16 (1H, m, CH═CH_2), 4.69 (2H, s, CH_2OAc), 4.52 (1H, dd, *J*=5.3, 10.8 Hz, CH_2O), 4.04 (1H, ddd, *J*=5.3, 9.7, 9.8 Hz, C*H*O), 3.86–3.81 (1H, m, C*H*O), 3.81 (3H, s, OCH_3), 3.79 (1H, dd, *J*=10.2, 10.8 Hz, CH_2O), 2.72–2.64 (1H, m, CH_2CH═CH_2), 2.51–2.42 (1H, m, CH_2CH═CH_2), 2.10 (3H, s, O_2CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (s), 160.2 (s), 132.9 (d), 129.6 (s), 127.5 (d), 118.3 (t), 113.7 (d), 101.1 (d), 92.8 (s), 78.4 (d), 78.2 (d), 67.5 (t), 55.3 (q), 52.4 (t), 35.9 (t), 34.0 (s), 20.9 (q); HRMS (EI) Calcd for $C_{19}H_{22}O_6$ (M^+): 346.1416. Found 346.1408. Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found C, 66.01; H, 6.39.

4.1.11. (2*R*,4*S*,5*R*)-4-Allyl-5-[3-(*tert*-butyldiphenylsilyloxy)prop-1-ynyloxy]-2-(4-methoxyphenyl)-1,3-dioxane (17). The alcohol **15** (52 mg, 0.17 mmol) was dissolved in dry dichloromethane (2 mL). Imidazole (23 mg, 0.34 mmol) and *t*-butylchlorodiphenylsilane (51 mg, 0.19 mmol) were added to the solution and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with dichloromethane (10 mL) and then washed with water (2×5 mL). The aqueous layer was washed with additional dichloromethane (5 mL) and the combined organic extracts were dried ($MgSO_4$). Removal of the solvent in vacuo afforded the crude product which was purified by flash column chromatography on silica gel (1% Et_3N, hexane then diethyl ether–hexane, 1:20) to give the protected alcohol **17** (87 mg, 94%) as a viscous oil: $[\alpha]_D^{26}=-15.4$ (*c* 0.920, $CHCl_3$); ν_{max} ($CHCl_3$) 2932, 2860, 2272, 1642, 1615, 1589, 982, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78–7.75 (4H, m, *Ph*), 7.50–7.40 (8H, m, *Ar*, *Ph*), 6.93 (2H, d, *J*=8.8 Hz, *Ar*), 5.95 (1H, dddd, *J*=6.9, 7.0, 10.2, 17.2 Hz, C*H*═CH_2), 5.43 (1H, s, OC*H*O), 5.22 (1H, dddd, *J*=1.7, 1.7, 1.7, 17.2 Hz), 5.17 (1H, br d, *J*=10.2 Hz, C*H*═CH_2), 4.42 (1H, dd, *J*=5.2, 10.7 Hz, CH_2O), 4.40 (2H, s, CH_2OAc), 3.92 (1H, ddd, *J*=5.2, 9.5, 10.2 Hz, C*H*O), 3.83 (3H, s, OCH_3), 3.79 (1H, ddd, *J*=3.3, 7.2, 9.5 Hz, C*H*O), 3.72 (1H, dd, *J*=10.2, 10.7 Hz, CH_2O), 2.72–2.64 (1H, m, CH_2CH═CH_2), 2.48–2.39 (1H, m, CH_2CH═CH_2), 1.02 (9H, s, C[CH_3]$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (s), 135.7 (d), 133.5 (s), 133.0 (d), 129.8 (d), 129.7 (s), 127.7 (d), 127.5 (d), 118.3 (t), 113.7 (d), 101.0 (d), 91.9 (s), 78.2 (d), 77.9 (d), 67.6 (t), 55.3 (q), 52.4 (t), 37.8 (s), 35.9 (t), 26.8 (q), 19.2 (s); HRMS (EI) Calcd for $C_{33}H_{38}O_4Si$ (M^+): 542.2489. Found 542.2486. Anal. Calcd for $C_{33}H_{38}O_4Si$: C, 73.03; H, 7.06. Found C, 73.01; H, 7.10.

4.1.12. (2*R*,4a*R*,8a*S*)-2-(4-Methoxyphenyl)-6-vinyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*]-1,3-dioxine (18a). The ruthenium catalyst **9** (15.2 mg, 17.9 μmol) was dissolved in dry toluene (30 mL) and ethene was bubbled through the solution for 10 min. The alkyne **12a** (90 mg, 0.33 mmol) was dissolved in dry toluene (3 mL) and added to the solution of catalyst at room temperature under an atmosphere of ethene. The solution was then heated at 80°C for 25 min. The solvent was removed in vacuo and the crude product was purified by flash column chromatography on silica (1% Et_3N, diethyl ether–hexane, 1:10) to give the diene **18a** (81 mg, 90%) as white solid which was recrystallised from petroleum ether to afford crystals suitable for X-ray analysis: mp 150–151°C; $[\alpha]_D^{25}=+106$ (*c* 0.770, $CHCl_3$); ν_{max} ($CHCl_3$) 2935, 2911, 2865, 2840, 1654, 1616, 1601, 984, 947, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (2H, d, *J*=8.7 Hz, *Ar*), 6.91 (2H, d, *J*=8.7 Hz, *Ar*), 6.08 (1H, dd, *J*=10.9, 17.2 Hz, C*H*═CH_2), 5.60 (1H, s, OC*H*O), 5.46 (1H, d, *J*=17.2 Hz, CH═CH_2), 5.07 (1H, d, *J*=10.9 Hz, CH═CH_2), 4.84 (1H, dd, *J*=2.6, 5.8 Hz, CH_2C*H*═C), 4.50–4.45 (1H, m, CH_2O), 3.97–3.76 (3H, m, C*H*O, C*H*O, CH_2O), 3.82 (3H, s, OCH_3), 2.49 (1H, ddd, *J*=5.8, 5.8, 17.1 Hz, CH_2CH═C), 2.40–2.32 (1H, m, CH_2CH═C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (s), 150.6 (s), 131.4 (d), 130.0 (s), 127.6 (d), 113.8 (d), 113.2 (t), 101.7 (d), 100.5 (d), 74.9 (d), 69.9 (d), 69.1 (t), 55.4 (q), 27.5 (t); HRMS (EI) Calcd for $C_{16}H_{18}O_4$ (M^+): 274.1205. Found 274.1203. Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found C, 69.83; H, 6.40.

4.1.13. (2*R*,4a*R*,8a*S*)-6-Isopropenyl-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-*d*]-1,3-dioxine (19a). The ruthenium catalyst **9** (9.6 mg, 11.3 μmol) was dissolved in

dry toluene (10 mL) and ethene was bubbled through the solution for 10 min. The alkyne **13a** (66 mg, 0.23 mmol) was dissolved in dry toluene (12 mL) and added to the solution of catalyst at room temperature under an atmosphere of ethene. The solution was then heated at 80°C for 10 min. The solvent was removed in vacuo and the crude product was purified by flash column chromatography on silica (1% Et_3N, diethyl ether–hexane, 1:10) to give the diene **19a** (65 mg, 98%) as white solid which was recrystallised from petroleum ether to afford crystals suitable for X-ray analysis: mp 160–162°C; $[\alpha]_D^{22}$=+88 (*c* 0.61, $CHCl_3$); ν_{max} ($CHCl_3$) 2934, 2864, 2839, 1646, 1615, 1589, 998, 948, 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (2H, d, *J*=8.8 Hz, *Ar*), 6.92 (2H, d, *J*=8.8 Hz, *Ar*), 5.60 (1H, s, OC*H*O), 5.37 (1H, br d, *J*=0.7 Hz, C=CH_2), 4.99 (1H, dd, *J*=2.7, 5.6 Hz, CH_2CH=C), 4.95 (1H, br, C=CH_2), 4.47 (1H, dd, *J*=4.3, 10.0 Hz, CH_2O), 3.96–3.77 (3H, m, C*H*O, C*H*O, CH_2O), 3.83 (3H, s, OCH_3), 2.54–2.46 (1H, m, CH_2CH=C), 2.37 (1H, *J*=2.7, 9.8, 17.1 Hz, CH_2CH=C), 1.88 (3H, s, CH_2=CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6 (s), 152.1 (s), 137.2 (s), 130.4 (s), 127.9 (d), 114.1 (d), 112.5 (t), 102.0 (d), 97.2 (d), 75.2 (d), 70.2 (d), 69.5 (t), 55.7 (q), 27.8 (t), 19.8 (q); HRMS (EI) Calcd for $C_{17}H_{20}O_4$ (M^+): 288.1362. Found 288.1369. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found C, 70.27; H, 6.93.

4.1.14. (2*R*,4a*R*,8a*S*)-2-(4-Methoxyphenyl)-6-(1-trimethylsilyl)vinyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*]-1,3-dioxine (20a). The ruthenium catalyst **9** (52 mg, 61 μmol) was dissolved in dry toluene (60 mL) and ethene was bubbled through the solution for 10 min. The alkyne **14a** (400 mg, 1.15 mmol) was dissolved in dry toluene (60 mL) and added to the solution of catalyst at room temperature under an atmosphere of ethene. The solution was then heated at 80°C for 3 h. The solvent was removed in vacuo and the crude product was purified by flash column chromatography on silica (1% Et_3N, diethyl ether–hexane, 1:10) to give the diene **20a** (350 mg, 88%) as a white solid which was recrystallised from petroleum ether: mp 125–127°C; $[\alpha]_D^{25}$=+88.2 (*c* 0.635, $CHCl_3$); ν_{max} ($CHCl_3$) 2957, 2932, 2864, 1615, 1589, 1463, 994, 946 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (2H, d, *J*=8.7 Hz, *Ar*), 6.92 (2H, d, *J*=8.7 Hz, *Ar*), 6.06 (1H, d, *J*=3.0 Hz, C=CH_2), 5.60 (1H, s, OC*H*O), 5.40 (1H, d, *J*=3.0 Hz, C=CH_2), 4.89 (1H, dd, *J*=2.6, 5.7 Hz, CH_2CH=C), 4.44 (1H, ddd, *J*=5.8, 10.8, 11.2 Hz, C*H*O), 3.96–3.78 (3H, m, C*H*O, CH_2O), 3.83 (3H, s, OCH_3), 2.48 (1H, ddd, *J*=5.7, 5.9, 16.9 Hz, CH_2CH=C), 2.36 (1H, ddd, *J*=2.6, 9.7, 16.9 Hz, CH_2CH=C), 0.19 (9H, s, Si[CH_3]$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (s), 154.1 (s), 145.4 (s), 130.1 (s), 127.6 (d), 125.2 (t), 113.8 (d), 101.7 (d), 97.1 (d), 74.9 (d), 69.9 (d), 69.1 (t), 55.3 (q), 27.6 (t), −0.6 (q); HRMS (FAB) Calcd for $C_{19}H_{27}O_4Si$ (M^++H): 347.1679. Found 347.1659. Anal. Calcd for $C_{19}H_{26}O_4Si$: C, 65.86; H, 7.56. Found: C, 65.76; H, 7.65.

4.1.15. (2*R*,4a*R*,8a*S*)-6-(1-Hydroxymethyl)vinyl-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-*d*]-1,3-dioxine (21). The ruthenium catalyst **8** (15.7 mg, 19 μmol) was dissolved in dry dichloromethane (10 mL) and ethene was bubbled through the solution until the colour changed from purple to orange. The alkyne **15** (58 mg, 0.20 μmol) was dissolved in dry dichloromethane (10 mL) and added to the solution of the catalyst at room temperature under an atmosphere of ethene. The solution was then heated at reflux for 2 h. The solvent was removed in vacuo and the crude product was purified by flash column chromatography on silica (1% Et_3N, diethyl ether–hexane, 1:1) to give the diene **21** (49 mg, 84%) as white solid: mp 185–186°C; $[\alpha]_D^{20}$=+85.5 (*c* 0.490, $CHCl_3$); ν_{max} ($CHCl_3$) 3609, 2934, 2866, 1649, 1615, 1589, 948, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (2H, d, *J*=8.7 Hz, *Ar*), 6.90 (2H, d, *J*=8.7 Hz, *Ar*), 5.60 (1H, s, OC*H*O), 5.52 (1H, s, C=CH_2), 5.24 (1H, s, C=CH_2), 5.08 (1H, dd, *J*=2.6, 5.7 Hz, CH_2CH=C), 4.46 (1H, ddd, *J*=5.8, 10.7, 11.2 Hz, C*H*O), 4.28 (2H, br s, CH_2OH), 3.97–3.78 (3H, m, C*H*O, CH_2O), 3.82 (3H, s, OCH_3), 2.51 (1H, ddd, *J*=5.7, 5.9, 17.2 Hz, CH_2CH=C), 2.38 (1H, ddd, *J*=2.6, 9.7, 17.2 Hz, CH_2CH=C), 1.54 (1H, br s, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (s), 149.5 (s), 140.9 (s), 130.0 (s), 127.6 (d), 113.8 (d), 112.9 (t), 101.7 (d), 97.2 (d), 74.7 (d), 70.0 (d), 69.0 (t), 63.4 (t), 55.4 (q), 27.3 (t); HRMS (EI) Calcd for $C_{17}H_{20}O_5$ (M^+): 304.1311. Found 304.1318. Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.85; H, 6.68.

4.1.16. (2*R*,4a*R*,8a*S*)-6-(1-Acetoxymethyl)vinyl-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-*d*]-1,3-dioxine (22). The ruthenium catalyst **9** (6.2 mg, 7.3 μmol) was dissolved in dry toluene (10 mL) ethene gas was bubbled through the solution for 10 min. The alkyne **16** (50 mg, 0.14 mmol) was dissolved in dry toluene (5 mL) and to the solution of catalyst at room temperature under an atmosphere of ethene. The solution was then heated at 80°C for 2 h. The solvent was removed in vacuo and the crude product was purified by flash column chromatography on silica gel (1% Et_3N, diethyl ether–hexane, 1:5) to give the diene **22** (36 mg, 72%) as a white solid: mp 130–132°C; $[\alpha]_D^{20}$=+76.0 (*c* 0.640, $CHCl_3$); ν_{max} ($CHCl_3$) 2932, 2865, 1733, 1649, 1615, 1590, 997, 947 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (2H, d, *J*=8.7 Hz, *Ar*), 6.91 (2H, d, *J*=8.7 Hz, *Ar*), 5.61 (1H, s, C=CH_2), 5.60 (1H, s, OC*H*O), 5.26 (1H, s, C=CH_2), 5.00 (1H, dd, *J*=2.6, 5.7 Hz, CH_2CH=C), 4.72 (2H, s, CH_2OAc), 4.46 (1H, ddd, *J*=5.8, 10.8, 10.8 Hz, C*H*O), 3.97–3.78 (3H, m, C*H*O, CH_2O), 3.82 (3H, s, OCH_3), 2.50 (1H, ddd, *J*=5.7, 5.9, 17.2 Hz, CH_2CH=C), 2.38 (1H, ddd, *J*=2.6, 9.7, 17.2 Hz, CH_2CH=C), 2.11 (3H, m, O_2CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (s), 160.2 (s), 149.2 (s), 136.2 (s), 130.0 (s), 127.6 (d), 115.4 (t), 113.8 (d), 101.7 (d), 97.6 (d), 74.6 (d), 70.0 (d), 69.0 (t), 64.1 (t), 55.4 (q), 27.3 (t), 21.1 (q); HRMS (EI) Calcd for $C_{19}H_{22}O_6$ (M^+): 346.1416. Found 346.1417. Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found C, 65.90; H, 6.47.

4.1.17. (2*R*,4a*R*,8a*S*)-6-[1-(*tert*-Butyldiphenylsilyloxy)-methyl]vinyl-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-*d*]-1,3-dioxine (23). The ruthenium catalyst **9** (3.6 mg, 4.2 μmol) was dissolved in dry toluene (5 mL) and ethene was bubbled through the solution for 10 min. The alkyne **17** (50 mg, 0.092 mmol) was dissolved in dry toluene (4 mL) and added to the solution of catalyst at room temperature under an atmosphere of ethene. The solution was then heated at 80°C for 2 h. The solvent was removed in vacuo and the crude product was purified by flash column chromatography on silica gel (1% Et_3N, diethyl ether–hexane, 1:30) to give the diene **23** (45.3 mg,

91%) as a viscous oil: $[\alpha]_D^{23}=+60.0$ (*c* 0.350, $CHCl_3$); ν_{max} ($CHCl_3$) 2932, 2859, 1614, 1589, 998, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (4H, m, *Ph*), 7.48–7.38 (8H, m, *Ar*, *Ph*), 6.90 (2H, d, *J*=8.8 Hz, *Ar*), 5.59 (1H, s, OC*H*O), 5.54 (1H, s, C=CH_2), 5.44 (1H, s, C=CH_2), 4.80 (1H, dd, *J*=2.6, 5.5 Hz, CH_2CH=C), 4.46 (1H, dd, *J*=4.3, 9.8 Hz, CH_2O), 4.31 (2H, br s, CH_2OSi), 3.99–3.76 (3H, m, C*H*O, C*H*O, CH_2O), 2.41 (1H, ddd, *J*=5.7, 5.9, 17.2 Hz, CH_2CH=C), 2.30 (1H, ddd, *J*=2.6, 9.7, 17.2 Hz, CH_2CH=C), 1.09 (9H, s, C[CH_3]$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (s), 149.4 (s), 140.1 (s), 135.6 (d), 133.5 (s), 130.0 (s), 129.8 (d), 127.8 (d), 127.6 (d), 113.8 (d), 111.2 (t), 101.7 (d), 96.3 (d), 74.8 (d), 69.9 (d), 69.1 (t), 63.1 (t), 55.4 (q), 27.2 (t), 26.9 (q), 19.4 (s); HRMS (EI) Calcd for $C_{33}H_{38}O_5Si$ (M^+): 542.2489. Found 542.2496. Anal. Calcd for $C_{33}H_{38}O_5Si$: C, 73.03; H, 7.06. Found C, 73.15; H, 7.12.

4.1.18. (5a*S*,7*R*,9a*R*)-7-(4-Methoxyphenyl)-2-vinyl-4,5,5a,9a-tetrahydrodioxolo[6,5-*f*]oxepine (18b). The ruthenium catalyst **9** (3 mg, 4 μmol) was dissolved in dry toluene (5 mL) and ethene was bubbled through the solution for 10 min. The alkyne **12b** (20 mg, 69 μmol) was dissolved in dry toluene (3 mL) and added to the solution of catalyst at room temperature under an atmosphere of ethene. The solution was then heated at 80°C for 2 h. The solvent was removed in vacuo and the crude product was purified by flash column chromatography on silica (1% Et_3N, diethyl ether–hexane, 1:10) to give the diene **18b** (14 mg, 70%) as white solid which was recrystallised from petroleum ether: mp 58–59°C; $[\alpha]_D^{25}=+38$ (*c* 0.10, MeOH); ν_{max} ($CHCl_3$) 2928, 2858, 1644, 1615, 1590, 998, 972, 906 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (2H, d, *J*=8.8 Hz, *Ar*), 6.90 (2H, d, *J*=8.8 Hz, *Ar*), 6.11 (1H, dd, *J*=10.6, 17.1 Hz, CH=CH_2), 5.52 (1H, s, OC*H*O), 5.42 (1H, dd, *J*=0.6, 17.1 Hz, CH=CH_2), 5.28 (1H, dd, *J*=5.0, 8.1 Hz, CH_2CH=C), 5.01 (1H, dd *J*=0.6, 10.6 Hz, CH=CH_2), 4.39 (1H, dd *J*=5.4, 10.8 Hz, CH_2O), 3.87–3.77 (2H, m, C*H*O, CH_2O), 3.79 (3H, s, OCH_3), 3.42 (1H, dddd, *J*=0.6, 5.4, 9.3, 10.1 Hz, C*H*O), 2.32–2.18 (2H, m, CH_2CH=), 2.13–2.06 (1H, m, CH_2CH$_2$CH=), 1.59–1.49 (1H, m, CH_2CH$_2$CH=); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0 (s), 155.6 (s), 133.0 (d), 130.1 (s), 127.4 (d), 115.5 (d), 113.7 (d), 112.5 (t), 100.9 (d), 82.7 (d), 75.0 (d), 69.0 (t), 55.3 (q), 31.5 (t), 21.3 (t); HRMS (EI) Calcd for $C_{17}H_{20}O_4$ (M^+): 288.1362. Found 288.1353. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found C, 70.55; H, 7.09.

4.1.19. (5a*S*,7*R*,9a*R*)-2-Isopropenyl-7-(4-methoxyphenyl)-4,5,5a,9a-tetrahydrodioxolo[6,5-*f*]oxepine (19b). The ruthenium catalyst **9** (15 mg, 18 μmol) was dissolved in dry toluene (15 mL) and ethene was bubbled through the solution for 10 min. The alkyne **13b** (106 mg, 0.351 mmol) was dissolved in dry toluene (20 mL) and added to the solution of catalyst at room temperature under an atmosphere of ethene. The solution was then heated at 80°C for 4 h. The solvent was removed in vacuo and the crude product was purified by flash column chromatography on silica gel (1% Et_3N, diethyl ether–hexane, 1:10) to give the diene **19b** (76 mg, 72%) as a white solid which was recrystallised from petroleum ether to afford colourless crystals suitable for X-ray analysis: mp 77–78°C; $[\alpha]_D^{26}=+37.7$ (*c* 0.920, $CHCl_3$); ν_{max} ($CHCl_3$) 2929, 2863, 1644, 1615, 998, 972, 902 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, d, *J*=8.7 Hz, *Ar*), 6.91 (2H, d, *J*=8.7 Hz, *Ar*), 5.54 (1H, s, OC*H*O), 5.50 (1H, dd, *J*=4.9, 9.5 Hz, CH_2CH=C), 5.36 (1H, d, *J*=0.7 Hz, C=CH_2), 4.92 (1H, d, *J*=0.7 Hz, C=CH_2), 4.41 (1H, dd, *J*=5.3, 10.8 Hz, CH_2O), 3.86–3.77 (2H, m, C*H*O, CH_2O), 3.82 (3H, s, OCH_3), 3.39 (1H, ddd, *J*=5.3, 9.1, 10.1 Hz, C*H*O), 2.36–2.20 (2H, m, CH_2CH=), 2.13–2.06 (1H, m, CH_2CH$_2$CH=), 1.87 (3H, s, CH_2=CCH_3), 1.59–1.47 (1H, m, CH_2CH$_2$CH=); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (s), 158.3 (s), 138.2 (s), 130.3 (s), 127.5 (d), 113.7 (d), 112.5 (d), 112.0 (t), 101.1 (d), 82.9 (d), 75.4 (d), 69.1 (t), 55.3 (q), 31.4 (t), 21.3 (t), 19.5 (q); HRMS (CI, CH_4) Calcd for $C_{18}H_{22}O_4$ (M^+): 302.1518. Found 302.1520. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found C, 71.77; H, 7.34.

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19. Crystallographic data (excluding structure factors) for the compounds **18a** and **19b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 172076 (**18a**) and CCDC 172077 (**19b**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk).