DOI: 10.1002/hlca.201900161

FULL PAPER

HELVETICA chimica acta

A Short Sequence for the Iterative Synthesis of Fused Polyethers

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Dedicated to Professor *Philippe Renaud* to mark the occasion of his 60th birthday

A simple and efficient four-step sequence for the synthesis of fused polyether arrays has been developed. Cyclic ethers are installed by sequential alkynyl ether formation, carbocupration, ring-closing metathesis and hydroboration with acidic workup. Crucially, the alkene required for the subsequent ring formation by ring-closing metathesis is present in the substrate but is masked in the form of a vinylic silane, which prevents competitive metathesis of the side chain. Generation of the reactive alkene from the unreactive vinylic silane is accomplished by hydroboration and subsequent acid-mediated *Peterson* elimination of the intermediate hydroxysilane.

Keywords: fused polyether, ring-closing metathesis, hydroboration, latent alkene, *Peterson* elimination.

Introduction

Fused polyether natural products are produced by various marine dinoflagellates and are found in organisms that feed on these algae.[1,2] Members of this family of natural products include the brevetoxins,[3,4] ciguatoxins,[5–8] gambieric acids,[9,10] gymnocins,[11,12] tamulamides,[13] yessotoxin,[14] adriatoxin,[15] gambierol,[16] gambierone,[17] brevenal[18] and maitotoxin,[19] the largest non-polymeric natural product known. Many marine polyethers (*e.g.*, the ciguatoxins) are potent neurotoxins that affect vertebrates at very low concentrations, but some possess little or no neurotoxic activity and are potential lead compounds for the development of therapeutic agents. For example, the gambieric acids exhibit potent anti-fungal activity and brevenal has been identified as a lead for the development of treatments for cystic fibrosis.[20,21]

Marine polyethers are some of the most structurally complex and challenging targets confronting contemporary organic synthesis. They contain arrays of *trans*-fused cyclic ethers, ranging in ring size from six to nine, in which the position of the ether alternates along the backbone. Several of the natural products (*e.g.*, the ciguatoxins and brevetoxins) possess eight- and nine-membered rings embedded within their structures. However, the most common sub-units found in the fused polyethers are six- and seven-membered cyclic ethers, and in many of the natural products (*e.g.*, gymnocin-A and gambierol,[11,16] *Figure 1*) the polycyclic array is composed entirely or almost entirely of fused rings of these sizes.

Marine polyethers are popular targets for total synthesis because of their size, structural complexity and the synthetic challenges they present. They are also of interest because of their potent biological activities. Total syntheses of the brevetoxins,[22–26] ciguatoxins,[27–33] gambieric acids,[34,35] gymnocins,[36,37] gambierol[38–42] and brevenal[43–45] have been accomplished, but syntheses of the larger natural products (*i.e.*, those that possess more than eight rings) are generally extremely lengthy and cannot provide sufficient quantities of the natural products for full biological evaluation or extensive analogue synthesis. Consequently, new strategies for the rapid construction of fused polyethers are required to reduce the step count significantly and improve both synthetic convergence and efficiency.

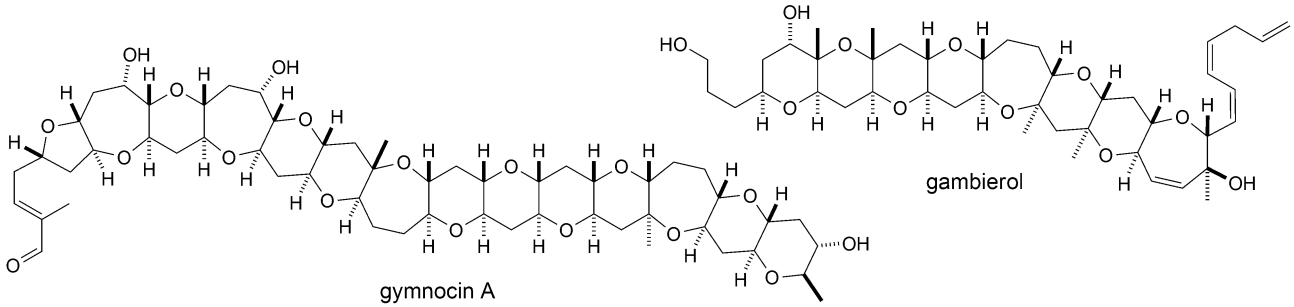
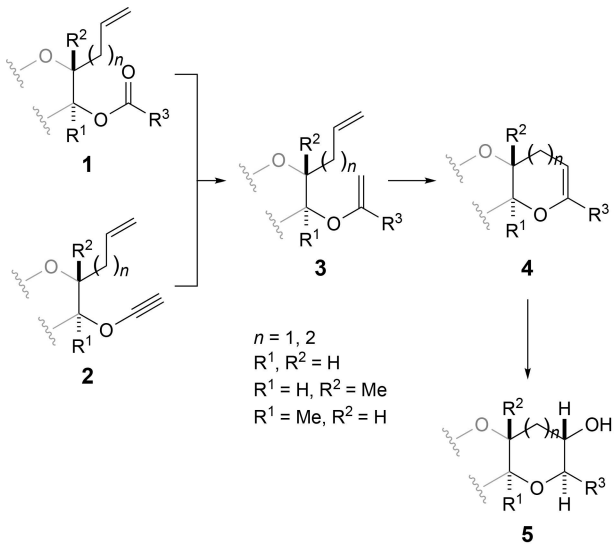


Figure 1. Structures of gymnocin A and gambierol.

In previous work, we have devised several potentially efficient approaches to the synthesis of fused polyether systems.[46–48] Our work has focused on the use of ring-closing metathesis (RCM) reactions of enol ethers,[49,50] allylic ethers[51,52] and alkynyl ethers[53–55] to prepare six- to nine-membered cyclic ether units of the type found in marine fused polyether natural products. We have used these reactions iteratively and in a bidirectional manner to prepare significant portions of the large polyether natural products CTX3C[56] and gambieric acid A.[57,58]

During our work, we have found that RCM reactions of acyclic enol ethers and functionalization of the resulting cyclic enol ethers is a particularly effective sequence for the synthesis of polyether subunits that contain six- and seven-membered rings. In contemporaneous studies, *Rainier* and co-workers have demonstrated the power of RCM reactions of enol ethers[59–62] and have used this method to synthesise and gambierol and brevenal,[42,45] and to construct significant fragments of the larger natural products yessotoxin and adriatoxin.[63]

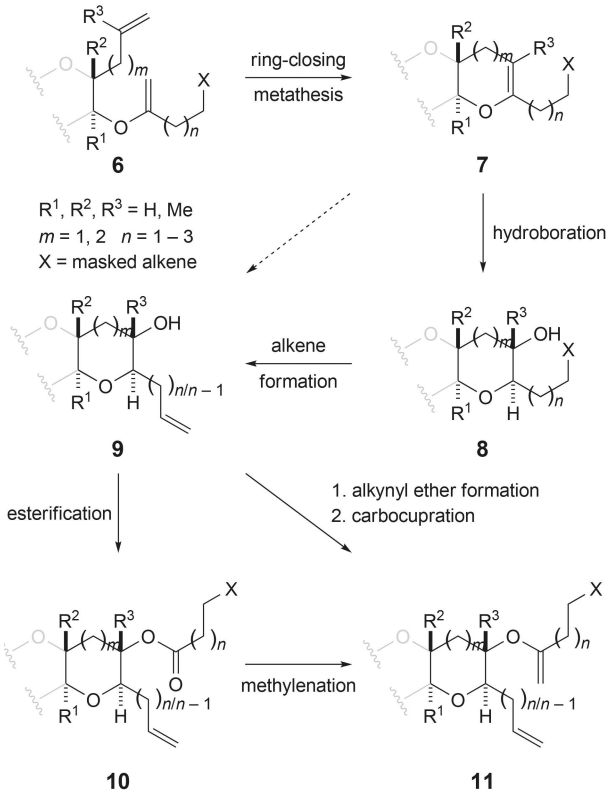
In the approach developed by us previously, an acyclic enol ether **3** is prepared by methylenation of an ester **1** or by carbocupration of an alkynyl ether **2** (*Scheme 1*).[57] The acyclic enol ether **3** is subjected to RCM to provide the cyclic ether **4** that is then hydroborated to give the alcohol **5**. To repeat the sequence and thereby construct a further ring, a series of reactions is required to introduce an alkene into the R^3 substituent because the presence of an unprotected terminal alkene is incompatible with the preceding RCM and hydroboration reactions. Because of the additional functionalisation reactions required to generate an alkene at the R^3 position, a relatively efficient four-step sequence is rendered much less efficient. The additional steps in each iteration would have a deleterious impact on the overall step count when



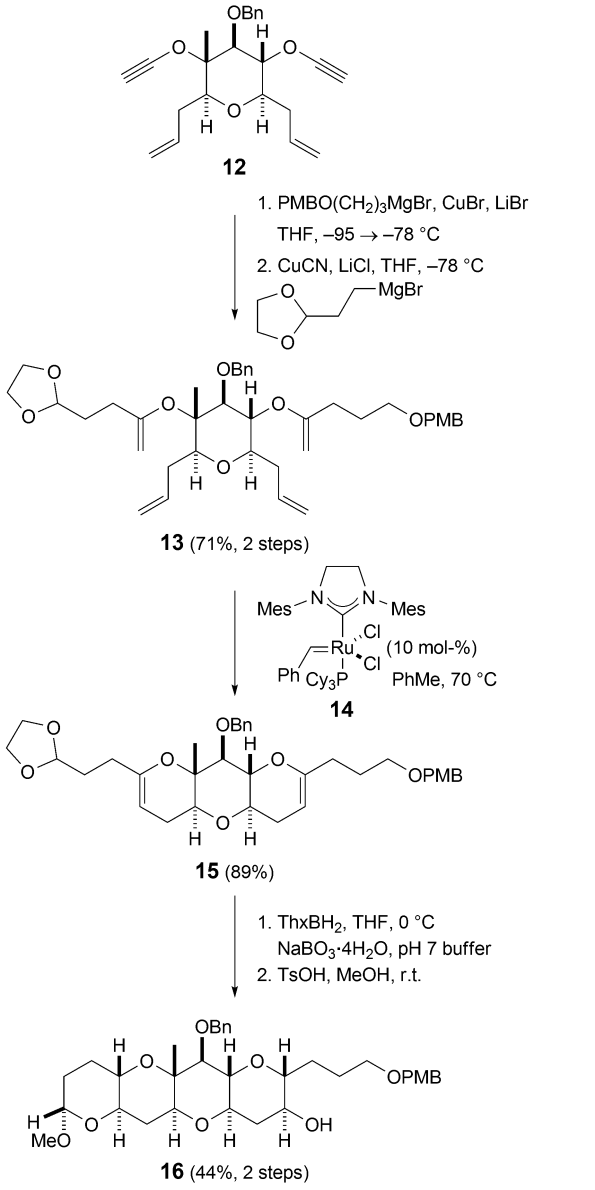
Scheme 1. Synthesis of fused cyclic ethers by sequential RCM and hydroboration.

constructing polyethers that contain 10 or more fused rings.

To accomplish ring construction as efficiently as possible, we sought to develop a synthetic sequence in which the alkene required for the subsequent RCM reaction would be present in a masked form and would be revealed after hydroboration but without requiring additional steps. In the proposed sequence of reactions, an acyclic enol ether **6**, which contains a group (X) in the side chain that could be converted into an alkene, would be subjected to RCM to produce the cyclic enol ether **7** (*Scheme 2*). Instead of the cyclic enol ether **7** being subjected to hydroboration to give the alcohol **8** followed by a multistep sequence to produce the terminal alkene **9**, the group X would be chosen so that hydroboration and alkene formation would be accomplished concurrently to give the hydroxyalkene **9** directly from the enol ether **7**. The



Scheme 2. General scheme for iterative fused cyclic ether construction.



Scheme 3. Bidirectional synthesis of the G–I fragment of the gambieric acids.

alcohol **9** would be converted into the enol ether **11** either by esterification to give **10** and subsequent methylenation, or by sequential alkynyl ether formation and carbocupration. Thus, ring construction would be complete in just four steps and the sequence (**6**→**7**→**9**→**11**) could be repeated.

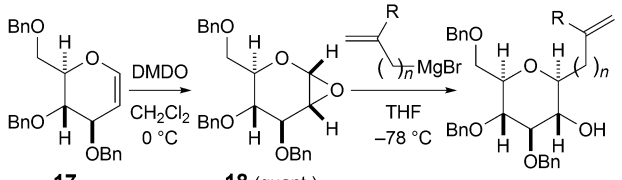
The power of the proposed iterative ring construction procedure could be further amplified by its application in a bidirectional manner. We have demonstrated that bidirectional synthesis can be used to prepare the G–I fragment of the gambieric acids (*Scheme 3*).[57] In course of this work, carbocupration of the bis-alkynyl ether **12** was performed to give the bis-enol ether **13** and a subsequent double RCM reaction mediated by the *Grubbs* second generation pre-catalyst (**14**) delivered the tricyclic bis-enol ether **15**. Final double hydroboration and acetal formation afforded the tetracyclic alcohol **16**. Application of the new synthetic procedure in an analogous bidirectional manner would allow construction of fused polycyclic ethers to be accomplished at the rate of just two steps per ring.

Results and Discussion

As outlined in *Scheme 2*, the development of a four-step sequence for the construction of six- and seven-membered cyclic ethers requires a group (X) that can function as a latent alkene in the side chain during RCM and then be converted into a terminal alkene upon hydroboration so that additional steps are avoided. These requirements led us to select a vinylic silane as a latent terminal alkene because bulky, electron-rich 2-trialkylsilyl-1-alkenes would be relatively unreactive in metathesis reactions but could

undergo subsequent hydroboration.[64] The resulting hydroxysilane would then undergo *Peterson* elimination to reveal the unfunctionalised terminal alkene required for the next iteration of the reaction sequence.

The proposed new annulation sequence was explored using tetrahydropyranols derived from commercially available 3,4,6-tri-*O*-benzyl-D-glucal (**17**; *Scheme 4*). Epoxidation of the enol ether **17** with



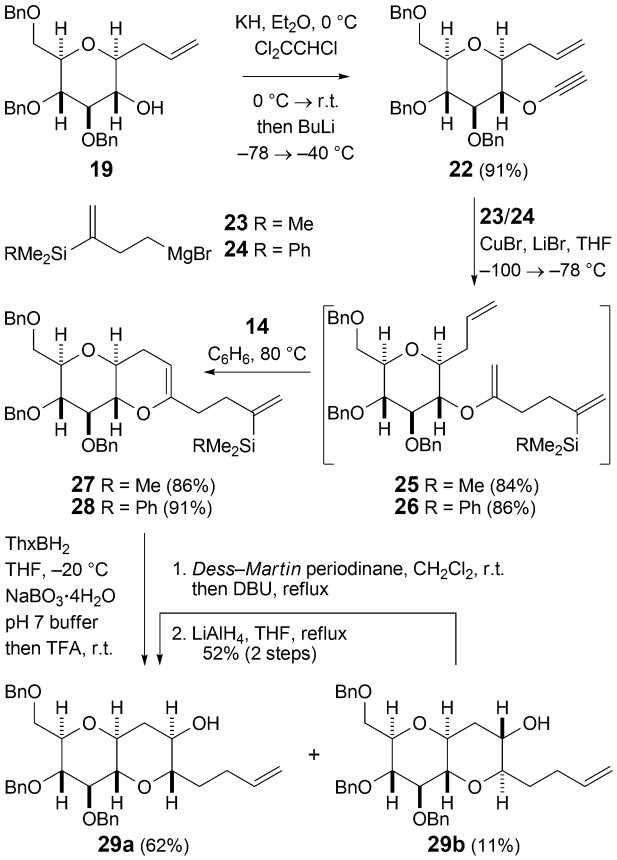
	R	*n*	Yield [%]
19	H	1	92
20	Me	1	52
21	H	2	33

Scheme 4. Synthesis of the alcohols **19**–**21** from 3,4,6-tri-*O*-benzyl-D-glucal (**17**).

dimethyldioxirane (DMDO)[65,66] afforded the epoxide **18** with high diastereofacial selectivity and subsequent reaction with allylmagnesium bromide afforded the alcohol **19** in excellent yield. Reaction of the epoxide **18** with either 2-methyl-2-propen-1-ylmagnesium bromide or 3-buten-1-ylmagnesium bromide afforded the alcohols **20** and **21** in modest yield.[67,68]

The alcohol **19** was the first substrate to be subjected to the four-step annulation sequence (*Scheme 5*). *Greene*'s one-pot method was used to convert the alcohol **19** into the alkynyl ether **22** in excellent yield.[69] Carbometallation of the alkynyl ether using organocopper reagents prepared from the *Grignard* reagents **23** and **24** afforded the enol ethers **25** and **26** in high yield.[1] The key RCM reactions were then effected by treatment of the enol ethers **25** and **26** with the ruthenium complex **14** in benzene at reflux. In both cases, very high yields of the cyclic enol ethers **27** and **28** were obtained. The vinylic silane was unreactive under the RCM conditions and so the silyl substituent did provide a high level of protection to the side-chain alkene, as anticipated.

The final step in the sequence involved hydroboration of both the enol ether and vinylic silane in

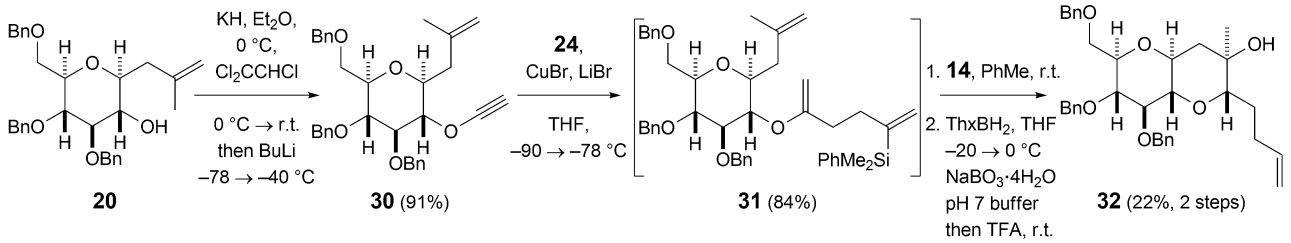


Scheme 5. Four-step sequence for the synthesis of the bicyclic ether **29a** from the cyclic ether **19**.

the RCM products **27** and **28** and then immediate acid-mediated *Peterson* elimination. Hydroboration was accomplished by treatment of each RCM product (**27** and **28**) with excess thexylborane followed by oxidation under mild conditions. *Peterson* elimination was performed simply by dissolving the crude hydroboration products in trifluoroacetic acid as part of the workup procedure.[71] In the case of the enol ether **27**, the hydroboration and *Peterson* elimination sequence delivered the alcohol **29a** in 45% yield. The enol ether **28** was found to be an even better substrate; in this case, the alcohol **29a** was obtained in 62% yield along with the diastereomeric alcohol **29b** in 11% yield after sequential hydroboration and *Peterson* elimination. The alcohol **29b** was converted into the required diastereomeric alcohol **29a** by sequential oxidation, base-mediated epimerization and ketone reduction.

Most polyether natural products possess at least one methyl substituent at a ring junction position, and so we wanted to discover whether the annulation sequence could accommodate this structural feature (*Scheme 6*). The alcohol **20** was converted into the

[1]The Grignard reagent **24** was prepared from the corresponding bromide, see ref. [70].

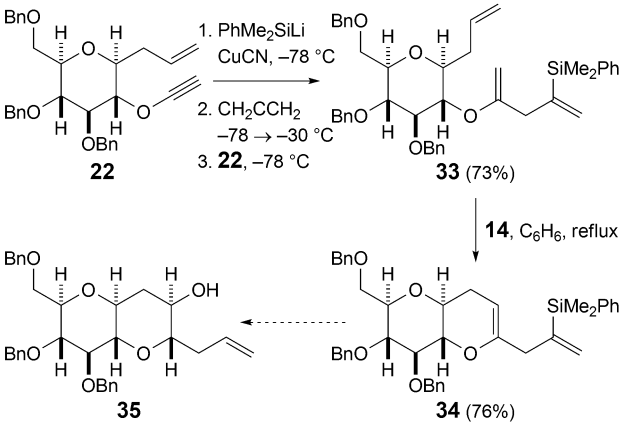


Scheme 6. Four-step sequence for synthesis of the bicyclic ether **32** from the cyclic ether **20**.

alkynyl ether **30** using the one-pot procedure that had been employed to prepare alkynyl ether **22** from the alcohol **19** (*Scheme 5*).[69] Carbometallation of the alkynyl ether **30** using an organocopper reagent prepared from the *Grignard* reagent **24** was performed to give the enol ether **31**.[70] The RCM reaction of the acyclic enol ether **31** to give the tetrasubstituted cyclic enol ether was challenging and a complex mixture of products was obtained from the reaction mediated by the complex **14**. The mixture was then subjected to immediate hydroboration using thexylborane and the resulting crude hydroxysilane was dissolved in trifluoroacetic acid to facilitate *Peterson* elimination. The required alcohol **32** was obtained in modest yield after sequential RCM, hydroboration and *Peterson* elimination.

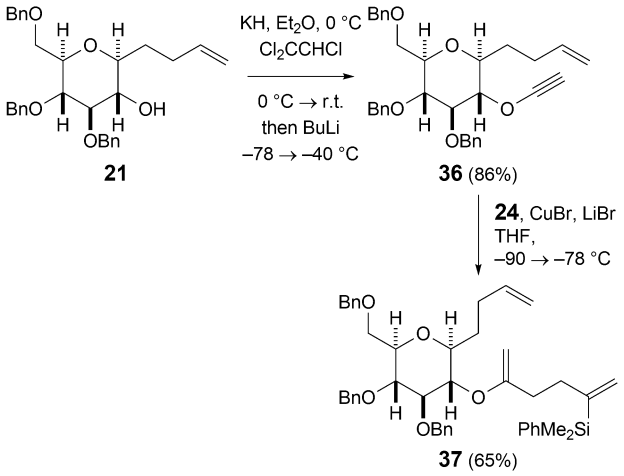
In the annulation sequences shown in *Schemes 5* and *6*, a butenyl side chain had been installed, which would be used to construct a seven-membered cyclic ether in a further iteration of the four-step reaction sequence. However, in many cases a propenyl side chain would be required to construct a six-membered ring in the subsequent RCM reaction. The enol ether **33**, prepared from the alkynyl ether **22** by the route shown in *Scheme 7*, was used to test the reaction sequence. The organocopper reagent used in the carbocupration reaction was prepared by the addition of a higher-order cuprate, generated by the reaction of phenyldimethylsilyl lithium with copper(I) cyanide, to allene.[72] Reaction of the alkynyl ether **22** with an excess of the organocopper reagent delivered the enol ether **33** in 73% yield. Subsequent ring formation by RCM was successful and the bicyclic enol ether **34** was produced in good yield. However, this compound proved to be unstable and so the hydroboration, and *Peterson* elimination sequence was not explored.

We had shown that the four-step sequence could be used to construct fully-functionalised six-membered cyclic ethers and we wanted to establish whether the sequence could be used to construct a seven-membered cyclic ether. The requisite RCM



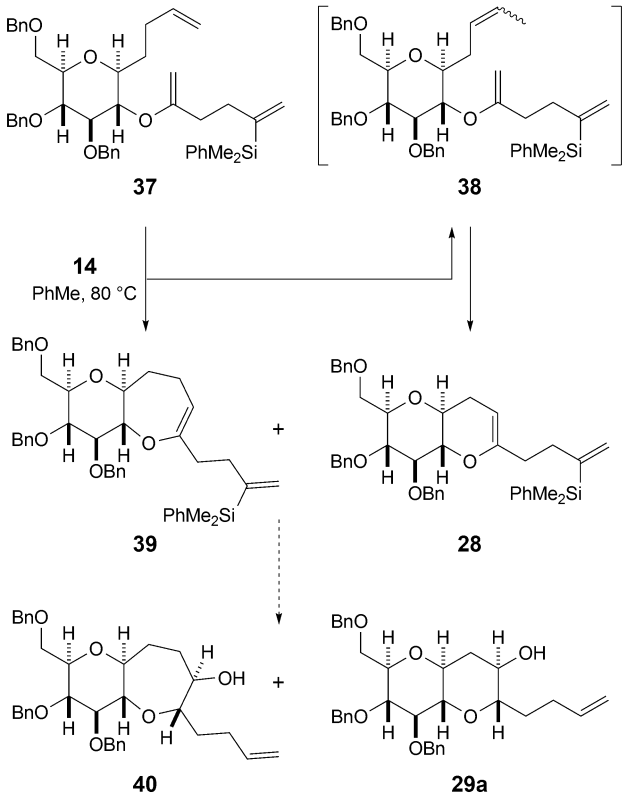
Scheme 7. Synthesis of a fused bicyclic ether with a propenyl side chain.

precursor – enol ether **37** – was prepared from the alcohol **21** by conversion into the alkynyl ether **36** and subsequent carbocupration of the alkyne with an organocopper reagent generated from the *Grignard* reagent **24** (*Scheme 8*).



Scheme 8. Synthesis of cyclisation precursor **37**.

The RCM reaction of the enol ether **37** proved to be more challenging than the RCM reactions of substrates **25**, **26**, **31** or **33**. The RCM reaction was very slow and isomerisation of the substrate **37** to give the alkene **38** occurred in competition with the cyclisation reaction to give the required seven-membered cyclic enol ether **39**.[2] The RCM reaction of the isomerised alkene produced the previously characterized cyclic enol ether **28**, the lower homologue of the required product **39**. Thus, a mixture of the cyclic enol ethers **28** and **39** was obtained, but separation was not possible because the compounds were prone to hydrolysis on extended contact with silica gel. The mixture of enol ethers was subjected to immediate hydroboration and acidic workup to produce the required alcohol **40** and the previously prepared alcohol **29a** (*Scheme 9*). However, neither the alcohol **40** nor homologous compound **29a** could be isolated from the complex mixture of products and attempts to suppress isomerization of the terminal alkene **37** to give 1,2-disubstituted alkene **38** by the inclusion of various additives were unsuccessful.[3][73]



Scheme 9. Synthesis of a bicyclic ether containing an oxepane.

Although it was not possible to suppress isomerization of **37**, the fact that this reaction occurs might offer some advantages, provided the process can be controlled fully. In principle, the ability to perform isomerization or suppress it completely would allow either **29a** or **40** to be prepared from the same substrate (**37**) and would obviate the need to perform the sequence shown in *Scheme 7*, which involves a sensitive intermediate and proved difficult to complete. Work is continuing to discover whether it is possible to accomplish complete *in situ* isomerization of **37** to give **38** prior to RCM when a six-membered cyclic ether is required and suppress the reaction when the construction of a seven-membered ring is required.

Conclusions

A four-step sequence of alkynyl ether formation, carbocupration, ring-closing metathesis and hydroboration with acidic workup, has been used to synthesise fused polyether systems. The alkene required for the further ring construction by a subsequent RCM reaction is present in the substrate but is protected in the form of a vinylic silane, which prevents competitive side-chain metathesis. The four-step sequence can be used to add tetrahydropyranol rings to existing polyether arrays and ring junction methyl groups are tolerated. The use of the reaction for the synthesis of seven-membered cyclic ethers is hampered by competitive isomerization of the terminal alkene in the substrate prior to RCM, which leads to a mixture of the required seven-membered cyclic enol ether and the corresponding six-membered cyclic enol ether.

[2]Competitive isomerization of terminal alkenes during RCM reactions of dienes to form medium-sized rings is well precedented. For examples, see ref. [73].

[3]The following reagents were added to the ring-closing metathesis reaction in unsuccessful attempts to suppress isomerization: triethylamine, water, styrene, tricyclohexylphosphine and tricyclohexylphosphine oxide.

Experimental Section

Materials and Instrumentation

^{1}H-NMR spectra were recorded on *Bruker DRX 500*, *AM 400* and *AV 400* instruments at ambient temperature. All spectra were obtained from samples dissolved in deuterochloroform unless otherwise stated. Chloroform or tetramethylsilane was used as the internal reference (δ 7.27 and 0.0 ppm, resp.). *J* values are given in Hertz. Signals in NMR spectra are described as *singlets* (*s*), *doublets* (*d*), *triplets* (*t*), *quartets* (*q*), *multiplets* (*m*), broad (b) or a combination of these, which refers to the spin–spin coupling pattern observed. ^{13}C-NMR spectra were recorded on either *Bruker DRX 500* (125 MHz) or *AV 400* (100 MHz) instruments at ambient temperature. All spectra were obtained from samples dissolved in deuterochloroform unless otherwise stated, using chloroform as the internal reference (δ 77.1 ppm). IR spectra were recorded in the range 4000–600 cm^{-1} on a *Perkin-Elmer 1600* series FT-IR spectrometer. Melting points were determined using a *Mel-Temp II* melting point apparatus. Elemental analyses were carried out on an *Exeter analytical Inc. CE-440* Elemental analyser. Mass spectra and accurate mass measurements were recorded under EI, FAB, CI and ES conditions on a *FISSONS VG Autospec* instrument. Optical rotations were determined using a *Jasco DIP-370* digital polarimeter.

Synthetic Procedures and Compound Characterisation

(1*S*,3*R*,4*R*,5*S*,6*R*)-4,5-Bis(benzyloxy)-3-[(benzyloxy)-methyl]-2,7-dioxabicyclo[4.1.0]heptane (**18**). To a solution of 3,4,6-tri-*O*-benzyl-D-glucal (=(2*R*,3*S*,4*R*)-3,4-bis(benzyloxy)-2-[(benzyloxy)methyl]-3,4-dihydro-2*H*-pyran; **17**; 5.0 g, 12 mmol) in dichloromethane (20 mL) at 0 °C was added dropwise a solution of freshly prepared dimethyldioxirane (300 mL of a 0.08 M solution in acetone, 24 mmol).[65,66] After the addition, the solvent was removed *in vacuo* (<5 °C). The resulting solid was dissolved in dichloromethane and dried (Na_2SO_4). The solvent was removed *in vacuo* (<5 °C) to give the epoxide **18** as a white solid (5.2 g, quant.). M.p. = 62–64 °C (Lit.[74] 77–78 °C). $[\alpha]_D^{17} = +13.7$ (*c* = 0.42 in $CHCl_3$) (Lit.[74] $[\alpha]_D^{25} = +31.1$ (*c* = 0.5 in $CHCl_3$)). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.42–7.20 (15 H, *m*); 4.98 (1 H, *d*, *J* = 11.4); 4.85 (1 H, br. *s*); 4.79 (1 H, *d*, *J* = 11.4); 4.54 (1 H, *d*, *J* = 11.9); 7.53 (1 H, *d*, *J* = 11.8); 4.44 (1 H, *d*, *J* = 11.9); 4.43 (1 H, *d*, *J* = 11.8); 4.09 (1 H, *d*, *J* = 7.8); 4.00 (1 H, *bd*, *J* = 10.1); 3.92 (1 H, *ddd*, *J* = 10.1, 7.7, 1.7); 3.85 (1 H, *dd*, *J* = 10.8, 3.1); 3.68 (1 H, *dd*, *J* = 10.8, 1.3); 2.81 (1 H, *t*, *J* = 2.4). ^{13}C-NMR (125 MHz, $CDCl_3$): 139.1; 138.7; 138.2; 128.4; 128.3; 128.2; 128.1; 128.0; 127.8; 127.6; 127.4; 127.4; 79.4; 77.5; 74.6; 74.3; 73.3; 71.7; 69.9; 68.5; 52.2. HR-CI–MS (NH_3): 432.1911 (M^+, $C_{27}H_{28}O_5^+$; calc. 432.1937). EI-MS: 359 (10), 181 (17), 91 (100).

(2*S*,3*S*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-[(benzyl-oxy)methyl]-2-(prop-2-en-1-yl)oxan-3-ol (**19**). The crude epoxide **18** (5.2 g, 12 mmol) was dissolved in dry THF (120 mL) and the solution was cooled to −20 °C. Allylmagnesium chloride (12 mL of a 2.0 M solution in THF, 24 mmol) was added dropwise and the mixture was stirred for 2 h. The reaction was quenched by the addition of a saturated solution of NH_4Cl (50 mL) and the resulting mixture was extracted with dichloromethane (3×100 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography over silica gel (Et_2O/hexane 1:1) to give the alcohol **19** (4.95 g, 92%) as a white solid. R_f = 0.52 (Et_2O/hexane 1:1). M.p. = 66–67 °C (Lit.[75] 63–65 °C). $[\alpha]_D^{20} = +40.8$ (*c* = 1.28 in $CHCl_3$) (Lit.[75] $[\alpha]_D = +37.5$ (*c* = 0.9 in $CHCl_3$)). IR ($CHCl_3$): 3610, 2956, 1460, 1047. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.49–7.31 (15 H, *m*); 6.06 (1 H, *dddd*, *J* = 17.1, 10.1, 7.0, 7.0); 5.26 (1 H, *dd*, *J* = 17.1, 1.9); 5.20 (1 H, *d*, *J* = 10.1); 5.08 (1 H, *d*, *J* = 11.5); 4.93 (1 H, *d*, *J* = 10.9); 4.87 (1 H, *d*, *J* = 11.5); 4.76 (1 H, *d*, *J* = 12.3); 4.73 (1 H, *d*, *J* = 10.9); 4.70 (1 H, *d*, *J* = 12.3); 3.88–3.80 (2 H, *m*); 3.72 (1 H, *t*, *J* = 9.3); 3.60 (1 H, *t*, *J* = 8.9); 3.57–3.53 (1 H, *m*); 3.49 (1 H, *t*, *J* = 8.9); 3.39 (1 H, *ddd*, *J* = 8.9, 7.5, 3.3); 2.73–2.67 (1 H, *m*); 2.44 (1 H, *dt*, *J* = 14.6, 7.2); 2.27 (1 H, br. *s*). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.6; 138.3; 138.1; 134.7; 128.7; 128.5; 128.4; 128.0; 127.9; 127.8; 127.6; 117.1; 86.8; 79.2; 78.8; 78.5; 75.2; 74.8; 73.5; 68.9; 36.2. HR-EI-MS: 474.2416 (M^+, $C_{30}H_{34}O_5^+$; calc. 474.2406). EI-MS: 474 (1, M^+), 383 (45), 293 (1), 259 (2), 181 (11), 133 (9), 91 (100). Anal. calc. for $C_{30}H_{34}O_5$: C 75.92, H 7.22; found: C 76.15, H 7.28.

(2*S*,3*S*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-[(benzyl-oxy)methyl]-2-(2-methylprop-2-en-1-yl)oxan-3-ol (**20**). Crude epoxide **18** (5.0 g, 12 mmol) was dissolved in dry THF (100 mL) and the solution was cooled to −20 °C. 2-Methylallylmagnesium chloride (46 mL of 0.50 M solution in THF, 23 mmol) was added dropwise and the mixture was stirred for 2 h. The reaction was quenched by the addition of a saturated solution of NH_4Cl (100 mL) and the resulting mixture was extracted with dichloromethane (3×80 mL). The combined organic extracts were dried ($MgSO_4$) and the

solvent removed *in vacuo*. The resulting residue was purified by flash column chromatography over silica gel (Et_2O/hexane 1:2) to give alcohol **20** (2.9 g, 52%) as a white solid. R_f = 0.67 (Et_2O/hexane 1:1). M.p. = 69–70 °C. $[\alpha]_D^{20} = +30.4$ (c = 1.15 in $CHCl_3$). IR ($CHCl_3$): 3600, 2869, 1602, 1454, 1360, 1075, 992, 895. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.41–7.23 (15 H, *m*); 4.99 (1 H, *d*, *J* = 11.5), 4.87(2 H, br. *s*), 4.85 (1 H, *d*, *J* = 10.8), 4.80 (1 H, *d*, *J* = 11.5), 4.67 (1 H, *d*, *J* = 12.3), 4.65 (1 H, *d*, *J* = 10.8), 4.61 (1 H, *d*, *J* = 12.3), 3.78 (1 H, *dd*, *J* = 11.0, 2.0), 3.72 (1 H, *dd*, *J* = 11.0, 4.3), 3.65 (1 H, *dd*, *J* = 9.6, 9.0), 3.57–3.51 (1 H, *m*); 3.46 (1 H, *ddd*, *J* = 9.6, 4.3, 2.0), 3.41–3.28 (2 H, *m*); 2.58 (1 H, *dd*, *J* = 15.0, 2.3), 2.20 (1 H, *dd*, *J* = 15.0, 7.6), 2.19 (1 H, *d*, *J* = 0.9), 1.84 (3 H, *s*). ^{13}C-NMR (100 MHz, $CDCl_3$): 143.2; 138.7; 138.4; 138.2; 128.7; 128.5; 128.4 (CH); 128.0 (CH); 127.9; 127.9; 127.8; 127.6; 112.6; 86.9; 79.2; 78.5; 78.2; 75.3; 74.8; 74.3; 73.5; 69.1; 40.3; 23.3. HR-EI-MS: 488.2538 (M^+, $C_{31}H_{36}O_5^+$; calc. 488.2563). EI-MS: 488 (1, M^+), 397 (60), 235 (14), 181 (35), 91 (100), 51 (16).

(2*S*,3*S*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-[(benzyloxy)methyl]-2-(but-3-en-1-yl)oxan-3-ol (**21**). Crude epoxide **18** (6.4 g, 15 mmol) was dissolved in dry THF (150 mL) and the solution was cooled to −20 °C. 3-Butenylmagnesium bromide (30 mL of a 0.50 M solution in THF, 60 mmol) was added dropwise and the mixture was stirred for 3 h. The reaction was quenched by the addition of a saturated solution of NH_4Cl (100 mL), and the resulting mixture was extracted with dichloromethane (3×150 mL). The organic extracts were combined and dried ($MgSO_4$) and the solvent was removed *in vacuo*. The resulting residue was purified by flash column chromatography over silica gel (1:1 Et_2O/hexane) to give the alcohol **21** (2.1 g, 33%) as a white solid. R_f = 0.62 (Et_2O/hexane 1:1). M.p. = 60–62 °C. $[\alpha]_D^{23} = +24.8$ (c = 1.01 in $CHCl_3$). IR ($CHCl_3$): 3516, 2868, 1640, 1603, 1454, 1076, 996, 912. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.29–7.14 (15 H, *m*); 5.75 (1 H, *dddd*, *J* = 17.0, 10.2, 6.7, 6.7); 4.96 (1 H, *dddd*, *J* = 17.0, 1.7, 1.7, 1.7); 4.88 (1 H, *dddd*, *J* = 10.2, 1.7, 1.3, 1.3); 4.60 (1 H, *d*, *J* = 11.7); 4.55 (1 H, *d*, *J* = 11.4); 4.51 (1 H, *d*, *J* = 11.7); 4.50 (1 H, *d*, *J* = 12.1); 4.49 (1 H, *d*, *J* = 11.4); 4.44 (1 H, *d*, *J* = 12.1); 3.92 (1 H, *ddd*, *J* = 5.5, 5.1, 4.4); 3.81 (1 H, *dt*, *J* = 9.6, 3.9); 3.72 (1 H, *dd*, *J* = 10.2, 5.7); 3.66 (1 H, *t*, *J* = 5.7); 3.63 (1 H, *dd*, *J* = 10.2, 5.1); 3.60–3.53 (2 H, *m*); 2.74 (1 H, *d*, *J* = 7.9); 2.19–2.08 (1 H, *m*); 2.07–1.96 (1 H, *m*); 1.71 (1 H, *dddd*, *J* = 14.2, 9.3, 9.3, 5.5); 1.58 (1 H, *dddd*, *J* = 14.2, 9.6, 6.8, 4.4). ^{13}C-NMR (125 MHz, $CDCl_3$): 142.1; 141.9; 141.8; 141.3; 132.3; 132.3; 132.2; 131.7; 131.5; 132.4; 131.4; 118.6; 82.1; 81.2; 80.9; 80.7; 79.1; 76.8; 75.1; 73.6; 72.1; 33.4; 31.0. HR-FAB-MS: 489.2667 ($[M+H]^+$, $C_{31}H_{37}O_5^+$; calc. 489.2641). FAB-MS: 489 (9, $[M+H]^+$), 307 (21), 289 (11), 154 (93), 136 (68), 91 (100). Anal. calc. for $C_{31}H_{36}O_5$: C 76.20, H 7.43; found: C 75.98, H 7.28.

(2*R*,3*R*,4*S*,5*S*,6*S*)-3,4-Bis(benzyloxy)-2-[(benzyloxy)methyl]-5-(ethynyloxy)-6-(prop-2-en-1-yl)oxane (**22**). A solution of alcohol **19** (1.0 g, 2.1 mmol) in Et_2O (10 mL) was added slowly by cannula to a suspension of KH (200 mg, 4.99 mmol) in Et_2O (20 mL) at room temperature. The mixture was stirred for 10 min and then cooled to 0 °C. Freshly distilled trichloroethene (320 mg, 2.44 mmol) in Et_2O (2 mL) was added dropwise to the solution. The mixture was allowed to warm to room temperature and stirred for 1 h. The solution was cooled to −78 °C, and BuLi (2.5 mL of a 2.5 M solution in hexanes, 6.3 mmol) was added dropwise. The mixture was stirred at −78 °C for 30 min, then allowed to warm to −40 °C and stirred at that temperature for 45 min. The reaction was quenched by the addition of methanol (5 mL) and the mixture was poured into a saturated solution of NH_4Cl (50 mL). The mixture was extracted with Et_2O (50 mL) and the organic extract was washed with brine (50 mL) and then dried ($MgSO_4$). The solvent removed *in vacuo* and the residue was purified by flash column chromatography over silica gel (Et_2O/hexane 1:9 with 1% Et_3N) to give alkyne **22** (960 mg, 91%) as a colourless oil. R_f 0.45 (Et_2O/hexane 1:9). $[\alpha]_D^{20} = +24.9$ (c = 0.950 in $CHCl_3$). IR ($CHCl_3$) 3322, 2869, 2154, 1642, 1454, 1095, 996, 913. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.40 (2 H, *dd*, *J* = 7.3, 1.2); 7.35–7.23 (6 H, *m*); 7.18–7.15 (2 H, *m*); 5.91 (1 H, *dddd*, *J* = 17.4, 10.5, 7.1, 7.1); 5.21 (1 H, *dd*, *J* = 17.4, 1.3); 5.13 (1 H, *d*, *J* = 10.5); 4.96 (1 H, *d*, *J* = 10.6); 4.81 (1 H, *d*, *J* = 10.8); 4.79 (1 H, *d*, *J* = 10.8); 4.59 (1 H, *d*, *J* = 12.2); 4.55 (1 H, *d*, *J* = 10.6); 4.53 (1 H, *d*, *J* = 12.2); 3.90 (1 H, *dd*, *J* = 9.0, 8.8); 3.85 (1 H, *dd*, *J* = 9.6, 9.0); 3.71 (1 H, *dd*, *J* = 11.2, 2.0); 3.65 (1 H, *dd*, *J* = 11.2, 4.4); 3.61 (1 H, *dd*, *J* = 9.8, 8.8); 3.53 (1 H, *ddd*, *J* = 9.6, 7.1, 3.2); 3.41 (1 H, *ddd*, *J* = 9.8, 4.4, 2.0); 2.68–2.63 (1 H, *m*); 2.40 (1 H, *dt*, *J* = 14.5, 7.1); 1.63 (1 H, *s*). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.2; 138.0; 133.3; 128.5; 128.4; 128.3; 128.0; 127.9; 127.8; 127.7; 118.3; 89.0; 88.0; 83.2; 79.0; 78.1; 76.4; 75.4; 75.2; 73.5; 68.7; 35.6; 28.3. HR-CI–MS (isobutane): 499.2473 ($[M+H]^+$, $C_{32}H_{35}O_5^+$; calc. 499.2484).

(4-{(4a*S*,6*R*,7*R*,8*S*,8a*S*)-7,8-Bis(benzyloxy)-6-[(benzyloxy)methyl]-4,4a,6,7,8,8a-hexahydropyrano[3,2-*b*]pyran-2-yl}but-1-en-2-yl)(trimethyl)silane (**27**). A mixture of copper bromide (213 mg, 1.50 mmol) and lithium bromide (140 mg, 1.50 mmol)

was dried at 60 °C for 4 h under high vacuum (< 1 mbar) and then suspended in THF (10 mL). The suspension was cooled to −90 °C and the *Grignard* reagent **23** (3.0 mL of a 0.50 M solution in THF, 1.5 mmol) was added dropwise over a period of 5 min. The resulting solution was stirred at −90 °C for 5 min. A solution of the alkynyl ether **22** (500 mg, 1.00 mmol) in THF (10 mL) was added dropwise over 5 min at −90 °C and the mixture was warmed to −78 °C then stirred for a further 30 min. The reaction was quenched by the addition of a 10% aqueous solution of NH_4OH (50 mL) and the mixture was extracted with Et_2O (2×50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography over silica gel (hexane→Et_2O/hexane 20:1 with 1% Et_3N) to afford enol ether **25** (530 mg, 84%) as a colourless oil. R_f 0.45 (Et_2O/hexane 1:9). The unstable enol ether was used immediately in the subsequent RCM reaction.

A solution of alkene **25** (530 mg, 0.84 mmol) in toluene (50 mL) was added to a solution of ruthenium complex **14** (40 mg, 46 μmol) in toluene (50 mL) at room temperature under an atmosphere of argon. The solution was heated to 80 °C and stirred at this temperature for 4 h. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography over silica gel (Et_2O/hexane 1:20→1:10 with 1% Et_3N) to give cyclic enol ether **27** (432 mg, 86%) as colourless oil. R_f = 0.42 (Et_2O/hexane 1:9). $[\alpha]_D^{20}$ = +39.0 (*c* = 1.05 in $CHCl_3$). IR ($CHCl_3$): 2913, 2862, 1678, 994, 862, 839. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.61–7.58 (2 H, *m*); 7.54–7.40 (11 H, *m*); 7.37–7.33 (2 H, *m*); 5.79–5.76 (1 H, *m*); 5.54 (1 H, *d*, *J* = 2.7); 5.24 (1 H, *d*, *J* = 11.2); 5.07 (1 H, *d*, *J* = 10.8); 5.00 (1 H, *d*, *J* = 11.2); 4.79 (1 H, *d*, *J* = 12.3); 4.72 (1 H, *d*, *J* = 12.3); 4.71 (1 H, *d*, *J* = 10.8); 4.66 (1 H, *dd*, *J* = 3.5, 1.9); 3.98–3.78 (5 H, *m*); 3.74 (1 H, *ddd*, *J* = 9.7, 4.5, 1.9); 3.68–3.62 (1 H, *m*); 2.60–2.48 (3 H, *m*); 2.43–2.31 (3 H, *m*); 0.28 (9 H, *s*). ^{13}C-NMR (125 MHz, $CDCl_3$): 153.6; 151.4; 138.9; 138.4; 138.2; 128.5; 128.2; 128.1; 128.1; 127.8; 127.8; 124.4; 93.5; 84.5; 79.6; 79.1; 77.6; 75.3; 75.2; 73.6; 72.5; 69.3; 33.5; 27.5; −1.2.

(4-{(4a*S*,6*R*,7*R*,8*S*,8a*S*)-7,8-Bis(benzyloxy)-6-[(benzyloxy)methyl]-4,4a,6,7,8,8a-hexahydropyrano[3,2-*b*]pyran-2-yl}but-1-en-2-yl)(dimethyl)phenylsilane (**28**). A mixture of copper bromide (520 mg, 3.60 mmol) and lithium bromide (320 mg, 3.60 mmol) was dried at 60 °C for 4 h under high vacuum (< 1 mbar) and then suspended in THF (20 mL). The suspension was cooled to −90 °C and the *Grignard* reagent **24** (7.2 mL of a 0.5 M solution in THF, 3.6 mmol) was added dropwise over a period of 5 min. The resulting mixture was stirred at −90 °C for 5 min. A solution of the alkynyl ether **22** (1.5 g, 3.0 mmol) in THF (20 mL) was added dropwise over 5 min at −90 °C, and the mixture was allowed to warm to −78 °C then stirred for a further 30 min. The reaction was quenched by the addition of a 10% aqueous solution of NH_4OH (50 mL) and the mixture was extracted with Et_2O (2×120 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography over silica gel (hexane→Et_2O/hexane 1:20 with 1% Et_3N) to afford enol ether **26** (1.81 g, 86%) as a colourless oil. R_f 0.49 (Et_2O/hexane 1:9). The unstable enol ether was used immediately in the subsequent RCM reaction.

A solution of alkene **26** (1.8 g, 2.6 mmol) in toluene (130 mL) was added to a solution of ruthenium catalyst **14** (110 mg, 130 μmol) in toluene (130 mL) at room temperature under an atmosphere of argon. The solution was heated to 80 °C and stirred at this temperature for 4 h. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography over silica gel (Et_2O/hexane 1:7 with 1% Et_3N) to give cyclic enol ether **28** (1.6 g, 91%) as colourless oil. R_f = 0.45 (Et_2O/hexane 1:1). $[\alpha]_D^{20}$ = +44.7 (*c* = 1.01 in $CHCl_3$). IR ($CHCl_3$): 2912, 2863, 1678, 1454, 1028, 998, 910, 834. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.79–7.74 (2 H, *m*); 7.66–7.62 (2 H, *m*); 7.61–7.48 (14 H, *m*); 7.44–7.40 (2 H, *m*); 6.00 (1 H, *d*, *J* = 1.0); 5.73 (1 H, *s*); 5.26 (1 H, *d*, *J* = 11.3); 5.15 (1 H, *d*, *J* = 10.8); 5.04 (1 H, *d*, *J* = 11.3); 4.86 (1 H, *d*, *J* = 12.3); 4.79 (1 H, *d*, *J* = 12.3); 4.79 (1 H, *d*, *J* = 10.8); 4.62 (1 H, *d*, *J* = 4.5); 4.03–3.93 (2 H, *m*); 3.95 (1 H, *dd*, 10.8, 4.5); 3.90 (1 H, *t*, *J* = 9.3); 3.86 (1 H, *t*, *J* = 9.3); 3.82–3.76 (1 H, *m*); 3.68 (1 H, *ddd*, *J* = 9.5, 9.5, 6.3); 2.65–2.60 (2 H, *m*); 2.57 (1 H, *dt*, *J* = 16.0, 5.9) 2.43–2.32 (3 H, *m*); 0.65 (6 H, *s*). ^{13}C-NMR (125 MHz, $CDCl_3$): 153.1; 149.2; 138.7; 138.2; 138.0; 133.8; 128.9; 128.2; 127.9; 127.8; 127.8; 127.7; 127.5; 127.5; 126.3; 93.3; 84.1; 79.2; 78.8; 77.4; 75.0; 74.9; 73.4; 72.1; 69.0; 33.2; 33.0; 27.2; −3.0.

(2*S*,4a*S*,6*R*,7*R*,8*S*,8a*S*)-7,8-Bis(benzyloxy)-6-[(benzyloxy)methyl]-2-(but-3-en-1-yl)octahydropyrano[3,2-*b*]pyran-2-ol (**29a**) *and* **(2*R*,4a*S*,6*R*,7*R*,8*S*,8a*S*)-7,8-Bis(benzyloxy)-6-[(benzyloxy)methyl]-2-(but-3-en-1-yl)octahydropyrano[3,2-*b*]pyran-2-ol** (**29b**). A solution of thexylborane (30 mL of a 0.50 M solution in THF, 15 mmol) was added dropwise to the

enol ether **28** (1.6 g, 2.4 mmol) in THF (50 mL) at −20 °C. The mixture was stirred at −20 °C for 30 min and then warmed to 0 °C. After a further 30 min, the ice bath was removed, and the mixture stirred for 1 h. The reaction was quenched by the slow addition of methanol (5 mL). After 5 min, pH 7 buffer (20 mL) and $NaBO_3$ (1.64 g, 20 mmol) were added, and the mixture was agitated vigorously for 3 h. AcOEt (100 mL) was added, and the solution was washed with brine (2× 50 mL). The aqueous washings were extracted with AcOEt (2×100 mL), and the combined organic extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was dissolved in AcOEt (200 mL) and filtered through a plug of silica. The solvent was removed *in vacuo* and the residue was dissolved in neat trifluoroacetic acid (5 mL) and stirred for 2 min. The acid was neutralised by slow addition of a saturated aqueous solution of K_2CO_3 and the aqueous mixture was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography over silica gel (Et_2O/hexane 1:4→4:6) to give the alcohol **29a** (805 mg, 62%) as a white solid. Further elution gave the alcohol **29b** (145 mg, 11%) as a white solid.

Data for **29a**. R_f = 0.28 (Et_2O/hexane 1:1). M.p. = 80–81 °C. $[\alpha]_D^{17}$ = −7.3 (*c* = 1.01 in $CHCl_3$). IR ($CHCl_3$): 3617, 3869,1640, 1604, 1454, 996, 913. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.51–7.47 (2 H, *m*); 7.46–7.46 (11 H, *m*); 7.26–7.23 (2 H, *m*); 5.97 (1 H, *ddd*, *J* = 16.9, 10.2, 6.6); 5.18–5.13 (1 H, *m*); 5.13 (1 H, *d*, *J* = 10.9); 5.09 (1 H, *d*, *J* = 10.2); 4.97 (1 H, *d*, *J* = 10.7); 4.88 (1 H, *d*, *J* = 10.9); 4.71 (1 H, *d*, *J* = 12.2); 4.64 (1 H, *d*, *J* = 12.2); 4.60 (1 H, *d*, *J* = 10.7); 3.82 (1 H, *dd*, *J* = 10.7, 1.7); 3.76 (1 H, *dd*, *J* = 10.7, 4.9); 3.74 (1 H, *dd*, *J* = 8.8, 8.4); 3.67 (1 H, *dd*, *J* = 9.2, 8.8); 3.60 (1 H, *ddd*, *J* = 9.4, 4.9, 1.7); 3.48 (1 H, *ddd*, *J* = 10.7, 9.5, 4.7); 3.28 (1 H, *dd*, *J* = 9.4, 9.2); 3.26–3.21 (2 H, *m*); 2.56 (1 H, *ddd*, *J* = 11.8, 4.3, 4.3); 2.51–2.42 (1 H, *m*); 2.35–2.25 (1 H, *m*); 2.08 (1 H, *dddd*, *J* = 16.3, 7.4, 7.0, 2.2); 1.85 (1 H, br. *s*); 1.70–1.58 (2 H, *m*). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.8; 138.3; 138.2; 138.0; 128.4; 128.1; 128.0; 127.9; 127.8; 127.7; 127.7; 115.0; 84.1; 82.2; 81.2; 79.2; 77.6; 75.3; 75.1; 73.9; 73.5; 69.7; 69.2; 38.8; 31.1; 29.8. HR-EI-MS: 544.2833 (M^+, $C_{34}H_{40}O_6^+$; calc. 544.2825). EI-MS: 544 (1, M^+), 454 (42), 363 (6), 209 (19), 181 (26), 91 (100) 65 (18). Anal. calc. for $C_{34}H_{40}O_6$: C 74.97, H 7.40; found C 75.16, H 7.35.

Data for **29b**. R_f = 0.18 (Et_2O/hexane 1:1). M.p. = 92–93 °C. $[\alpha]_D^{23}$ = +15.3 (*c* = 0.63 in $CHCl_3$). IR ($CHCl_3$): 3612, 2926, 2869, 1640, 1454, 1364, 1088, 996, 913. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.40–7.20 (13 H, *m*); 7.13–7.08 (2 H, *m*); 5.85 (1 H, *dddd*, *J* = 16.9, 10.2, 6.6, 6.6); 5.06 (1 H, *dq*, *J* = 16.9, 1.6); 5.05 (1 H, *d*, *J* = 11.0); 5.01 (1 H, *ddt*, *J* = 10.2, 1.6, 1.1); 4.85 (1 H, *d*, *J* = 10.8); 4.77 (1 H, *d*, *J* = 11.0); 4.61 (1 H, *d*, *J* = 12.3); 4.53 (1 H, *d*, *J* = 12.3); 4.47 (1 H, *d*, *J* = 10.8); 3.91–3.85 (2 H, *m*); 3.72 (1 H, *dd*, *J* = 10.7, 2.0); 3.68 (1 H, *t*, *J* = 9.5); 3.67 (1 H, *dd*, *J* = 10.9, 4.0); 3.61 (1 H, *t*, *J* = 9.7); 3.58–3.49 (2 H, *m*); 3.40 (1 H, *t*, *J* = 9.3); 2.35–2.27 (1 H, *m*); 2.23–2.14 (2 H, *m*); 1.99 (1 H, *dddd*, *J* = 14.0, 10.8, 8.9, 5.3); 1.88 (1 H, br. *s*); 1.85 (1 H, *ddd*, *J* = 13.5, 12.0, 2.8); 1.58–1.50 (1 H, *m*). ^{13}C-NMR (100 MHz, $CDCl_3$): 138.9; 138.2; 138.0; 137.6; 128.5; 128.4; 128.4; 128.1; 128.1; 128.1; 127.8; 127.8; 127.7; 116.7; 84.3; 79.4; 77.8; 77.7; 77.4; 75.4; 75.3; 74.7; 73.5; 71.3; 69.7; 69.0; 32.7; 29.5; 27.8. HR-EI-MS: 544.2845 (M^+, $C_{34}H_{40}O_6^+$; calc. 544.2825). EI-MS: 544 (11, M^+), 543 (37), 181 (8), 91 (100). Anal. calc. for $C_{34}H_{40}O_6$: C 74.97, H 7.40; found: C 75.19, H 7.32.

Synthesis of Compound **29a** *from* **29b**. Solid *Dess–Martin* periodinane (18 mg, 0.43 mmol) was added in three portions over 1 h to a solution of alcohol **29b** (20 mg, 0.036 mmol) in dichloromethane (2 mL). The mixture was poured into NaOH (3 M, 5 mL) and stirred for 1 h. Dichloromethane (20 mL) was added and the organic phase was separated and washed with brine (10 mL). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography over silica gel (Et_2O/hexane 1:1) to afford ketone (16.4 mg, 82%). R_f = 0.72 (Et_2O/hexane 1:1). M.p. = 61–62 °C. $[\alpha]_D^{21}$ +1.93 (*c* = 1.05 in $CHCl_3$). IR ($CHCl_3$): 2869, 1726, 1641, 1454, 1363, 1097, 996, 909. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.44–7.27 (13 H, *m*); 7.20–7.16 (2 H, *m*); 5.84 (1 H, *dddd*, *J* = 17.0, 10.3, 6.7, 6.7); 5.10–5.02 (3 H, *m*); 4.92 (1 H, *d*, *J* 10.7); 4.85 (1 H, *d*, *J* = 11.0); 4.63 (1 H, *d*, *J* = 12.2); 4.56 (1 H, *d*, *J* = 12.2); 4.55 (1 H, *d*, *J* = 11.0); 3.85 (1 H, *dd*, *J* = 8.6, 3.6); 3.79–3.68 (4 H, *m*); 3.60–3.51 (3 H, *m*); 3.02 (1 H, *dd*, *J* = 16.1, 5.3); 2.59 (1 H, *dd*, *J* = 16.1, 10.7); 2.34–2.17 (2 H, *m*); 2.09–2.01 (1 H, *m*); 1.73 (1 H, *dddd*, *J* = 14.1, 8.9, 8.5, 5.3). ^{13}C-NMR (100 MHz, $CDCl_3$): 204.9; 138.6; 138.1; 137.9; 137.6; 128.4; 128.0; 128.0; 127.9; 127.8; 127.8; 115.6; 84.0; 82.0; 81.4; 79.2; 77.4; 75.3; 75.3; 74.3; 73.6; 68.9; 45.0; 29.4; 28.4. HR-EI-MS: 542.2680 (M^+, $C_{34}H_{38}O_6^+$; calc. 542.2668). EI-MS: 542 (8), 181 (8, M^+), 91 (100).

(2*R*,3*R*,4*S*,5*S*,6*S*)-3,4-Bis(benzyloxy)-2-[(benzyloxy)methyl]-5-(ethynyloxy)-6-(2-methylprop-2-en-1-yl)oxane (**30**). A solution of alcohol **20** (1.0 g, 2.1 mmol) in Et_2O (10 mL) was added by cannula to a suspension of KH (180 mg, 4.5 mmol) in Et_2O (20 mL)

at room temperature. The mixture was stirred for 10 min and then cooled to 0 °C. Freshly distilled trichloroethene (320 mg, 2.40 mmol) in Et_2O (2 mL) was added dropwise to the solution. The mixture was allowed to warm to room temperature and stirred for 1 h. The solution was then cooled to −78 °C and BuLi (2.5 mL of a 2.5 M solution in hexanes, 6.3 mmol) was added dropwise. The mixture was stirred at this temperature for 30 min and then allowed to warm to −40 °C and stirred for 45 min. The reaction was quenched by the addition of methanol (5 mL), and the resulting mixture was poured into a saturated solution of NH_4Cl (50 mL). The mixture was extracted with Et_2O (50 mL), and the organic phase was washed with brine (50 mL) and then dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by flash column chromatography over silica gel (Et_2O/hexane 1:9 with 1% Et_3N) to give the alkynyl ether **30** (960 mg, 91%) as a colourless oil. R_f = 0.50 (Et_2O/hexane 1:9). $[\alpha]_D^{20}$ = +30.6 (c = 0.960 in $CHCl_3$). IR ($CHCl_3$): 3322, 2959, 2917, 2871, 2154, 1454, 1650, 1361, 1094, 999, 897. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.51 (2 H, *d*, *J* = 7.1); 7.45–7.34 (11 H, *m*); 7.31–7.27 (2 H, *m*); 5.08 (1 H, *d*, *J* = 10.6); 4.97 (2 H, br. *s*); 4.92 (1 H, *d*, *J* = 10.8); 4.91 (1 H, *d*, *J* = 10.6); 4.68 (1 H, *d*, *J* = 12.2); 4.67 (1 H, *d*, *J* = 10.8); 4.64 (1 H, *d*, *J* = 12.2); 4.04 (1 H, *t*, *J* = 9.0); 3.92 (1 H, *t*, *J* = 9.4); 3.81 (1 H, *dd*, *J* = 11.0, 1.7); 3.77–3.70 (3 H, *m*); 3.50 (1 H, *ddd*, *J* = 9.8, 4.4, 1.7); 2.71 (1 H, *dd*, *J* = 14.6, 0.9); 2.41 (1 H, *dd*, *J* = 14.6, 7.7); 1.91 (3 H, *s*); 1.74 (1 H, *s*). ^{13}C-NMR (125 MHz, $CDCl_3$): 141.8; 138.3; 138.2; 138.1; 128.5; 128.4; 128.3; 128.0; 127.9; 127.7; 127.6; 113.3; 88.9; 88.4; 83.2; 79.1; 78.2; 76.1; 75.5; 75.2; 73.5; 68.8; 39.4; 28.5; 23.4. HR-EI-MS: 512.2583 (M^+, $C_{33}H_{36}O_5^+$; calc. 512.2563). EI-MS: 512 (1, M^+), 415 (2), 181 (6), 131 (8), 91 (100).

(2*S*,3*R*,4a*S*,6*R*,7*R*,8*S*,8a*S*)-7,8-Bis(benzyloxy)-6-[(benzyloxy)methyl]-2-(but-3-en-1-yl)-3-methyl-octahydropyrano[3,2-*b*]pyran-3-ol (**32**). A mixture of copper bromide (213 mg, 1.50 mmol) and lithium bromide (140 mg, 1.50 mmol) was dried at 60 °C for 4 h under high vacuum (< 1 mbar) and then suspended in THF (10 mL). The suspension was cooled to −90 °C and the *Grignard* reagent **24** (3.0 mL of a 0.50 M solution in THF, 1.5 mmol) was added dropwise over a period of 5 min. The resulting mixture was stirred at −90 °C for 5 min. A solution of the alkynyl ether **30** (500 mg, 1.00 mmol) in THF (10 mL) was added dropwise at −90 °C and the mixture was warmed to −78 °C then stirred for a further 30 min. The reaction was quenched by the addition of a 10% aqueous solution of NH_4OH (50 mL) and the mixture was extracted with Et_2O (2×50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography over silica gel (hexane→Et_2O/hexane 1:20 with 1% Et_3N) to afford the enol ether **31** (530 mg, 84%) as a colourless oil. R_f = 0.53 (Et_2O/hexane 1:9). The unstable enol ether was used immediately in the subsequent RCM reaction.

A solution of alkene **31** (0.45 g, 0.67 mmol) in toluene (30 mL) was added a solution of ruthenium complex **14** (29 mg, 34 μmol) in benzene (40 mL) at room temperature under an atmosphere of argon, and the mixture was heated at reflux for 4 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography over silica gel (Et_2O/hexane 1:7 with 1% Et_3N) to give a complex mixture of products (323 mg) as colourless oil.

A solution of thexylborane (5.0 mL of a 0.50 M solution in THF, 2.5 mmol) was added dropwise to the mixture of enol ethers (0.32 g, 0.47 mmol) in THF (5 mL) at −20 °C. The mixture was stirred at −20 °C for 30 min, then warmed to 0 °C. After a further 30 min, the ice bath was removed, and the mixture was stirred for 1 h. The reaction was quenched by the slow addition of methanol (1 mL). After 5 min, pH 7 buffer (5 mL) and $NaBO_3$ (430 mg, 5 mmol) were added, and the mixture was agitated vigorously for 3 h. AcOEt (50 mL) was added and the solution was washed with brine (2×25 mL). The aqueous washings were extracted with AcOEt (2×50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was dissolved in AcOEt (100 mL) and filtered through a plug of silica. The solvent was removed *in vacuo* and the residue was dissolved in neat trifluoroacetic acid (2 mL) and stirred for 2 min. The acid was neutralised by slow addition of a saturated solution of K_2CO_3 and the aqueous mixture was extracted with Et_2O (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography over silica gel (Et_2O/hexane 1:4→3:6) to give the alcohol **32** (81 mg, 22% over two steps) as a clear oil. R_f = 0.32 (Et_2O/hexane 1:1). $[\alpha]_D^{24}$ = +9.3 (c = 0.85 in $CHCl_3$). IR ($CHCl_3$): 3610, 2926, 2856, 1640, 1073, 997, 943, 912. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.33–7.22 (13 H, *m*); 7.12–7.09 (2 H, *m*); 5.81 (1 H, *dddd*, *J* = 16.9, 10.2, 6.6, 6.6); 5.01 (1 H, *d*, *J* = 11.2); 5.02–4.97 (1 H, *m*); 4.95 (1 H, *d*, *J* = 10.2); 4.83 (1 H, *d*, *J* = 10.8); 4.74 (1 H, *d*, *J* = 11.2); 4.55 (1 H, *d*, *J* =

12.2); 4.50 (1 H, *d*, *J* = 12.2); 4.44 (1 H, *d*, *J* = 10.8); 3.67 (1 H, *dd*, *J* = 10.7, 1.4); 3.61 (1 H, *t*, *J* = 8.4); 3.60 (1 H, *dd*, *J* = 10.7, 5.2); 3.52 (1 H, *dd*, *J* = 9.8, 8.4); 3.46 (1 H, *ddd*, *J* = 9.8, 4.7, 1.5); 3.18–3.12 (2 H, *m*); 3.10 (1 H, *dd*, *J* = 9.6, 4.2); 2.38–2.29 (1 H, *m*); 2.20 (1 H, *dd*, *J* = 11.3, 4.2); 2.17–2.08 (1 H, *m*); 1.79–1.71 (1 H, *m*); 1.62 (1 H, *t*, *J* = 11.3); 1.66–1.53 (1 H, *m*); 1.49–1.40 (1 H, *m*); 1.19 (3 H, *s*). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.8; 138.3; 138.2; 138.1; 128.4; 128.0; 128.0; 128.0; 127.8; 127.7; 127.7; 115.1; 84.2; 83.8; 83.3; 79.4; 77.7; 75.3; 75.1; 73.9; 73.5; 70.9; 69.2; 45.6; 30.9; 27.8; 21.7. HR-EI-MS: 558.2989 (M^+, $C_{34}H_{42}O_6^+$; calc. 558.2981). EI-MS: 558 (3, M^+), 363 (12), 209 (25), 181 (23), 91 (100) 65 (15).

(4-{[(2*S*,3*S*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-[(benzyloxy)methyl]-2-(prop-2-en-1-yl)oxan-3-yl]oxy}-penta-1,4-dien-2-yl)(dimethyl)phenylsilane (**33**). Copper cyanide (34 mg, 0.38 mmol) was dried at 60 °C for 4 h under high vacuum (< 1 mbar) and then suspended in THF (5 mL). The suspension was cooled to −78 °C and lithium dimethylphenylsilane (0.75 mL of a 1.0 M solution in THF, 0.75 mmol) was added dropwise and the resulting solution stirred at −78 °C for 30 min. Allene (1.5 mL of a 2.0 M solution in THF, 3.0 mmol) was added and the mixture was warmed to −30 °C for 30 min. The mixture was cooled to −78 °C and the alkyne **22** (250 mg, 0.501 mmol) in THF (10 mL) was added dropwise over 5 min at −78 °C. The mixture was stirred for a further 10 min, and the reaction was quenched by the addition of a 10% aqueous solution of NH_4OH (20 mL). The mixture was extracted with Et_2O (2 × 50 mL), and the combined organic extracts were dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by flash column chromatography over silica gel (hexane→Et_2O/hexane 1:10 with 1% Et_3N) to afford enol ether **33** (242 mg, 73%) as a colourless oil. R_f 0.65 (Et_2O/hexane 1:9). $[\alpha]_D^{23} = +2.5$ (*c* = 0.56 in $CHCl_3$). IR ($CHCl_3$): 2232, 2922, 2155, 1095. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.50–7.48 (2 H, *m*); 7.35–7.22 (15 H, *m*); 7.17–7.14 (2 H, *m*); 5.90 (1 H, *dddd*, *J* = 17.1, 10.3, 6.9, 6.9); 5.46 (1 H, *d*, *J* = 1.8); 5.10–5.03 (2 H, *m*); 4.81 (1 H, *d*, *J* = 10.9); 4.78 (1 H, *d*, *J* = 10.7); 4.77 (1 H, br. *s*); 4.64 (1 H, *d*, *J* = 10.7); 4.62 (1 H, *d*, *J* = 11.2); 4.58 (1 H, br. *s*); 4.56 (1 H, *d*, *J* = 11.2); 4.54 (1 H, *d*, *J* = 10.9); 4.46 (1 H, *d*, *J* = 2.8); 4.02 (1 H, *dd*, *J* = 9.1, 9.1); 3.73 (1 H, *dd*, *J* = 10.8, 1.2); 3.70 (1 H, *t*, *J* = 9.1, 9.1); 3.67 (1 H, *dd*, *J* = 10.8, 4.2); 3.61 (1 H, *dd*, *J* = 9.7, 9.1); 3.44 (1 H, *ddd*, *J* = 9.7, 4.2, 1.2); 3.38 (1 H, *ddd*, *J* = 9.1, 8.6, 2.8); 2.46–2.39 (1 H, *m*); 2.19 (1 H, *ddd*, *J* = 14.7, 8.6, 6.9); 1.97 (2 H, *s*); 0.28 (6 H, *s*). ^{13}C-NMR (125 MHz, $CDCl_3$): 159.7; 140.1; 139.1; 138.6; 138.4; 134.8; 134.1; 133.8; 133.7; 131.9; 129.1; 128.4; 128.3; 128.2; 128.0; 127.8; 127.7; 127.6; 117.2; 111.5; 87.7; 86.2; 79.7; 79.1; 79.0; 78.0; 75.2; 73.5; 69.1; 35.8; 22.6; −2.1; −2.6.

(3-{(4a*S*,6*R*,7*R*,8*S*,8a*S*)-7,8-Bis(benzyloxy)-6-[(benzyloxy)methyl]-4,4a,6,7,8,8a-hexahydropyrano[3,2-*b*]pyran-2-yl}prop-1-en-2-yl)(dimethyl)phenylsilane (**34**). A solution of the alkene **33** (202 mg, 0.299 mmol) in toluene (15 mL) was added to a solution of ruthenium catalyst **14** (37 mg, 23 μmol) in benzene (15 mL) at room temperature under an atmosphere argon. The solution was heated at 80 °C for 4 h. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography over silica gel (Et_2O/hexane 1:9 with 1% Et_3N) to give cyclic enol ether **34** (146 mg, 76%) as colourless oil. $R_f = 0.70$ (Et_2O/hexane, 2:8). $[\alpha]_D^{23} = +14.2$ (*c* = 0.950 in $CHCl_3$). IR ($CHCl_3$): 2950, 2869, 1460, 1090. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.48–7.45 (2 H, *m*); 7.37–7.34 (2 H, *m*); 7.31–7.22 (14 H, *m*); 7.13–7.09 (2 H, *m*); 5.27 (1 H, *d*, *J* = 0.9); 5.06 (1 H, *d*, *J* = 11.1); 4.84 (1 H, *d*, *J* = 10.7); 4.81 (1 H, *d*, *J* = 11.1); 4.77 (1 H, *dd*, *J* = 5.3, 2.4); 4.69 (1 H, br. *s*); 4.57 (1 H, *d*, *J* = 12.2); 4.52 (1 H, *d*, *J* = 12.2); 4.48 (1 H, *d*, *J* = 10.7); 3.75 (1 H, *dd*, *J* = 8.8, 8.8); 3.69 (1 H, *dd*, *J* = 10.7, 1.5); 3.64 (1 H, *dd*, *J* = 10.7, 4.7); 3.59 (1 H, *dd*, *J* = 9.5, 9.0); 3.50 (1 H, *dd*, *J* = 9.4, 9.1); 3.48–3.51 (1 H, *m*); 3.37 (1 H, *ddd*, *J* = 9.6, 9.5, 6.4); 2.30 (1 H, *ddd*, *J* = 17.2, 6.4, 5.3); 2.11 (1 H, *ddd*, *J* = 17.2, 9.6, 2.4); 1.91 (1 H, *d*, *J* = 14.0); 1.86 (1 H, *d*, *J* = 14.0); 0.27 (6 H, *s*). ^{13}C-NMR (125 MHz, $CDCl_3$): 151.9; 138.9; 138.9; 138.8; 138.3; 138.0; 134.9; 133.7; 129.3; 129.1; 128.4; 128.1; 128.1; 128.0; 127.7; 110.1; 97.5; 84.4; 79.4; 78.9; 77.5; 75.3; 75.2; 73.6; 69.1; 27.9; 22.5; −2.9; −3.0.

(2*R*,3*R*,4*S*,5*S*,6*S*)-3,4-Bis(benzyloxy)-2-[(benzyloxy)methyl]-6-(but-3-en-1-yl)-5-(ethynyloxy)oxane (**36**). A solution of alcohol **21** (1.5 g, 3.0 mmol) in Et_2O (10 mL) was added by cannula to a suspension of KH (0.28 g, 7.0 mmol) in Et_2O (15 mL) at room temperature. The mixture was stirred for 10 min and then cooled to 0 °C. A solution of freshly distilled trichloroethene (0.48 g, 3.7 mmol) in Et_2O (5 mL) was added dropwise and the mixture was allowed to warm to room temperature then stirred for 1 h. The mixture was cooled to −78 °C and BuLi (4 mL of a 2.5 M solution in hexanes, 10.0 mmol) was added dropwise. The mixture was stirred at this temperature for 30 min and then allowed to warm to −40 °C and stirred for 45 min. The reaction was quenched by the addition of methanol (5 mL), and the resulting mixture was poured into a saturated solution of NH_4Cl (80 mL). The

biphasic mixture was extracted with Et_2O (2×100 mL) and the organic phases were combined and washed with brine (100 mL) then dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by flash column chromatography over silica gel (Et_2O/hexane 1:9 with 1% Et_3N) with to give alkyne **36** (1.35 g, 86%) as a colourless oil. R_f = 0.49 (Et_2O/hexane 1:9). $[\alpha]_D^{21} = +32.3$ (c = 1.85 in $CHCl_3$). IR ($CHCl_3$): 3322, 2913, 2868, 2151, 1641, 1093, 996, 944, 912. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.31–7.13 (13 H, *m*); 7.08–7.04 (2 H, *m*); 5.76 (1 H, *dddd*, *J* = 17.0, 10.2, 6.6, 6.6); 4.98 (1 H, *dddd*, *J* = 17.0, 1.7, 1.7, 1.7); 4.91 (1 H, *dddd*, *J* = 10.2, 1.7, 1.4, 1.4); 4.81 (1 H, *d*, *J* = 10.8); 4.71 (1 H, *d*, *J* = 10.8); 4.64 (1 H, *d*, *J* = 10.8); 4.52 (1 H, *d*, *J* = 12.1); 4.40 (1 H, *d*, *J* = 12.1); 4.38 (1 H, *d*, *J* = 10.8); 4.26–4.20 (2 H, *m*); 3.76 (1 H, *dd*, *J* = 8.3, 8.3); 3.60 (1 H, *dd*, *J* = 10.5, 3.8); 3.59–3.48 (3 H, *m*); 2.21–2.10 (1 H, *m*); 2.08–1.97 (1 H, *m*); 1.77–1.58 (2 H, *m*); 1.51 (1 H, *s*). ^{13}C-NMR (125 MHz, $CDCl_3$): 138.0; 137.9; 137.4; 128.4; 128.4; 128.1; 127.9; 127.8; 127.7; 115.4; 89.7; 87.5; 80.4; 77.5; 75.2; 75.0; 73.5; 72.0; 71.4; 68.7; 29.0; 27.1; 24.1. HR-ESI-MS: 535.2445 ($[M+Na]^+$, $C_{33}H_{36}NaO_5^+$; calc. 535.2455).

(5-{[(2*S*,3*S*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-[(benzyloxy)methyl]-2-(but-3-en-1-yl)oxan-3-yl]oxy}-hexa-1,5-dien-2-yl)(dimethyl)phenylsilane (**37**). Copper bromide (225 mg, 1.59 mmol) and lithium bromide (138 mg, 1.59 mmol) were dried at 60 °C for 4 h under high vacuum (< 1 mbar) and then suspended in THF (15 mL). The suspension was cooled to −100 °C and the *Grignard* reagent **24** (3.2 mL of 0.5 M solution in THF, 1.6 mmol) was added dropwise over a period of 5 min. The resulting mixture was stirred at −90 °C for 5 min and the alkyne **36** (270 mg, 0.53 mmol) in THF (15 mL) was added dropwise over 5 min at −90 °C. The mixture was allowed to warm to −78 °C, and the solution was stirred at this temperature for a further 1 h. The reaction was quenched by the addition of a 10% aqueous solution of NH_4OH (50 mL), and the resulting mixture was extracted with Et_2O (2×80 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography over silica gel (hexane→Et_2O/hexane 1:20 with 1% Et_3N) to afford enol ether **37** (252 mg, 68%) as a colourless oil. R_f 0.5 (Et_2O/hexane 1:4). IR (liquid film): 2950, 2865, 1615, 1090. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.41–7.25 (2 H, *m*); 7.20–7.08 (15 H, *m*); 6.99–6.94 (3 H, *m*); 5.64 (1 H, *ddt*, *J* = 16.9, 10.2, 6.6); 5.54–5.51 (1 H, *m*); 5.27–5.25 (1 H, *m*); 4.86 (1 H, *dd*, *J* = 16.9, 1.8); 4.81 (1 H, *dd*, *J* = 10.2, 1.8); 4.64 (1 H, *d*, *J* = 10.8); 4.64 (1 H, *d*, *J* = 10.8); 4.51 (1 H, *d*, *J* = 11.2); 4.48 (1 H, *d*, *J* = 12.7); 4.34 (1 H, *d*, *J* = 12.2); 4.29 (1 H, *d*, *J* = 10.8); 4.18–4.05 (2 H, *m*); 3.89 (1 H, *d*, *J* = 2.4); 3.75 (1 H, *d*, *J* = 2.4); 3.66 (1 H, *t*, *J* = 8.5); 3.55 (1 H, *dd*, *J* = 10.5, 4.0); 3.53–3.41 (3 H, *m*); 2.20–2.11 (2 H, *m*); 2.10–1.93 (3 H, *m*); 1.92–1.79 (1 H, *m*); 1.61 (1 H, *dddd*, *J* = 14.4, 11.1, 9.3, 5.1); 1.44–1.31 (1 H, *m*); 0.19 (6 H, *s*); ^{13}C-NMR (101 MHz, $CDCl_3$): 161.1; 149.6; 138.8; 138.3; 138.1; 138.1; 138.0; 138.0; 134.0; 129.1; 128.5; 128.4; 128.4; 128.2; 128.0; 128.0; 128.0; 127.9; 127.8; 127.8; 127.7; 125.9; 115.1; 82.6; 81.6; 77.9; 75.3; 75.1; 73.6; 71.6; 71.1; 69.1; 34.9; 33.6; 29.4; 24.3; −3.00. HR-ESI-MS: 725.3609 ($[M+Na]^+$, $C_{45}H_{54}NaO_5Si^+$; calc. 725.3633).

Acknowledgements

This work was supported by studentship funding from the University of Nottingham (*F. E.*) and funding from EPSRC (EP/R035423/1) to support a postdoctoral researcher (*V. C.*).

Author Contribution Statement

J. S. C. conceived the synthetic routes, supervised the project and wrote the paper; *J. S. C.*, *F. E.* and *V. C.* designed the experiments; all synthetic laboratory work was performed by *F. E.* (*Schemes 4–9*) and *V. C.* (*Schemes 8* and *9*).

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Received June 28, 2019
Accepted August 2, 2019

