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Oxygen to carbon rearrangements of anomerically linked alkenols from tetrahydropyran derivatives: an investigation of the reaction mechanism *via* a double isotopic labelling crossover study

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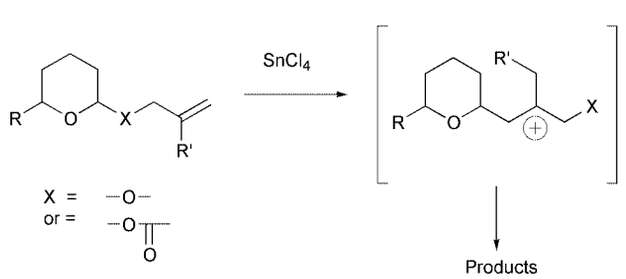
A variety of alkenol tetrahydropyran derivatives were prepared and subjected to a tin tetrachloride promoted anomeric oxygen to carbon rearrangement. Using this methodology many of the corresponding carbon-linked structures were synthesised, including alkenes and bicyclic ethers, in good yields. On the basis of an isotopic labelling study using ^{2}H incorporated into the side chain and ring system it is proposed that these reactions proceed *via* an intermolecular pathway.

Introduction

An abundance of bioactive natural products which contain tetrahydropyran and furan ring systems also exhibit carbon substituents adjacent to the heteroatom. The direct formation of carbon–carbon bonds at anomeric sites still presents a significant challenge to synthetic chemists, and several solutions to this problem have evolved.[1] We have shown recently that Lewis acid promoted oxygen to carbon rearrangement of anomerically linked nucleophiles can be a powerful reaction for the introduction of carbon substituents at anomeric sites. Prior to our work in this area, such rearrangements were restricted to a limited range of alkenic,[2] benzylic[3] and aromatic[4] ether systems, and the potential of a general anomeric oxygen to carbon rearrangement, in which a nucleophile is connected to the anomeric oxygen *via* a carbon chain linker, remained largely untapped. Since we communicated our initial findings on the rearrangements of anomerically linked alkenols[5] the methodology has extended to encompass alkynyl stannanes,[6] enol ethers[7] and silyl enol ethers[8] as the nucleophilic component. Using an anomeric oxygen to carbon rearrangement as the key step we have also completed the total synthesis of the biologically active natural product (+)-Goniodiol.[9]

In this and the following paper[10] we present our investigations into the rearrangement of tetrahydropyran derived alkenols. In particular we describe in detail studies on the tin tetrachloride promoted oxygen to carbon rearrangement of anomeric alkenols, using both ether and ester anomeric linkages (Scheme 1).

In the initial studies we had no clear evidence as to whether such rearrangements proceed through inter or intramolecular pathways or *via* tight ion pair mechanisms. Here we propose a mechanism for these reactions on the basis of a systematic isotopic labelling experiment.



Scheme 1

Anomeric oxygen to carbon rearrangements

The starting materials used throughout this investigation were readily constructed *via* high yielding acid catalysed addition of dihydropyrans to appropriate alkenols, which are either commercially available or can be rapidly accessed through short synthetic routes. For example, for the first rearrangement study we chose to use tetrahydropyranyl ether **1**, which was synthesised by the addition of dihydropyran to a mixture of 2-methylpropen-2-ol and a catalytic amount of camphorsulfonic acid (CSA) in dichloromethane to give **1** in 50% yield. When **1** was exposed to 3.6 equivalents of tin tetrachloride in dichloromethane at −30 °C it underwent a 1,4 oxygen to carbon rearrangement resulting in several distinct carbon-linked products, the diastereoisomeric chlorohydrins **2** (42% yield) and **3** (17% yield), and aldehyde **4** (26% yield, 2 : 1 mixture of diastereoisomers) (Scheme 2).

The formation of these products may be rationalised by considering the initial generation of a carbocationic intermediate **5**. Three possible reaction pathways are open to **5**: i. elimination from one of the surrounding centres to give an alkene; ii. trapping of the cation by chloride ion to give a chlorohydrin; or iii. a 1,2-hydride shift to give an aldehyde (Scheme 2). Reaction pathway (ii) is favoured in this case, in competition with pathway (iii). In a related reaction Herscovici *et al*. have used deuterium labelling studies to prove that a 1,2-hydride shift is indeed the preferred mechanism of aldehyde formation [pathway (iii)] rather than elimination toward the alcohol to form an enol followed by tautomerisation.[11]

With this evidence for a carbocationic intermediate in the rearrangement reaction, it was hypothesised that the presence of a trimethylsilyl group adjacent to the cationic centre would favour the elimination pathway (i) over either (ii) or (iii), leading to clean formation of a disubstituted allylic alcohol containing a pendent tetrahydropyran ring. With this in mind, allylsilylalkenol **6** was prepared[12] and tetrahydropyranylated under the usual conditions to give tetrahydropyranyl ether **7** in 50% yield (Scheme 3). As we anticipated, on exposure to identical rearrangement conditions (3.6 eq. $SnCl_4$, DCM, −30 °C) **7**

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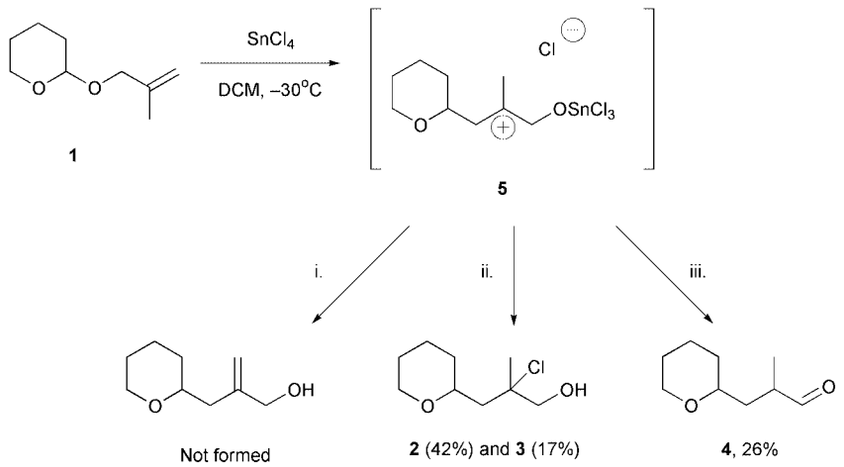
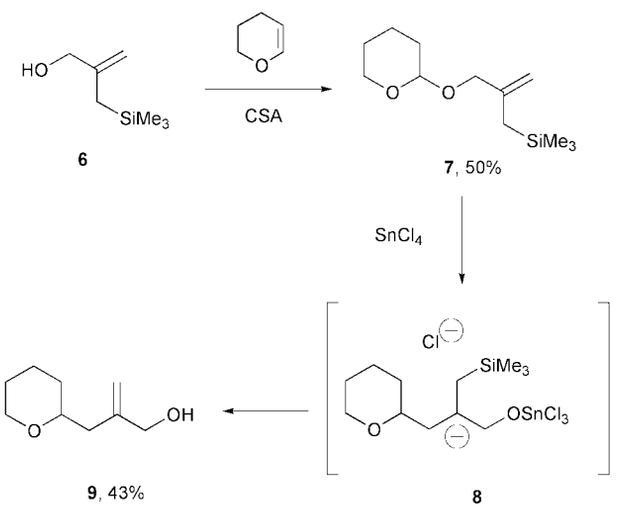


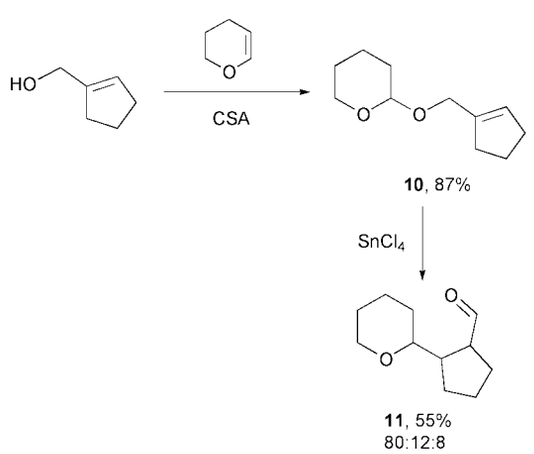
Scheme 2



Scheme 3

underwent a 1,4 anomeric oxygen to carbon rearrangement with concurrent elimination of the silyl group from the carbocationic intermediate **8** to give the desired allyl alcohol **9** in 43% yield as the only rearrangement product isolated.

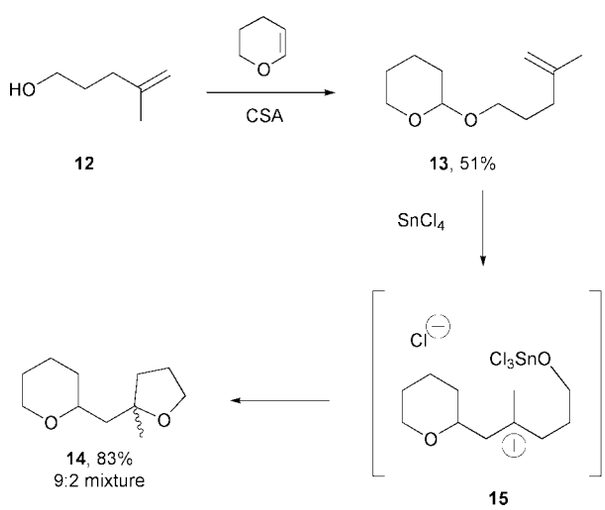
In further experiments we have demonstrated that it is possible to extend this rearrangement to highly substituted alkenes, such as tetrahydropyranyl alkenol ether **10**, synthesised by the standard tetrahydropyranylation of cyclopentenyl methanol in 87% yield (Scheme 4). Rearrangement under



Scheme 4

the usual conditions gave the linked bicyclic aldehyde **11** (3 diastereomers, 80 : 12 : 8 ratio by proton NMR) as the only isolable product.

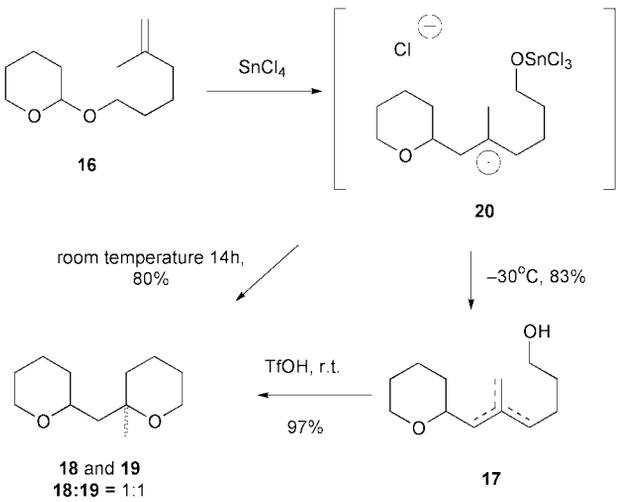
Other experiments have shown that extending the length of the carbon chain linker in this species leads to some interesting changes in the preferred reaction pathway. Alkenol **12** was prepared in 66% overall yield *via* orthoester Claisen rearrangement[13] of 2-methylpropen-1-ol with propanoic acid followed by $LiAlH_4$ reduction, and subsequent tetrahydropyranylation gave ether **13** in 51% yield. When **13** was rearranged under standard conditions, we isolated only the linked 6/5 member bicyclic ether **14** in 83% yield, as an inseparable 9 : 2 mixture of diastereoisomers (by proton NMR and GC analysis) (Scheme 5). It seems that the pendent oxygen bearing the Lewis acid in



Scheme 5

the intermediate carbocation **15** is still sufficiently nucleophilic to undergo *in situ* cyclisation faster than the competing chloride trap or elimination pathways observed in previous examples (a 1,2-hydride shift is precluded in this case); the reason for the diastereoselectivity observed in this reaction remains unclear.

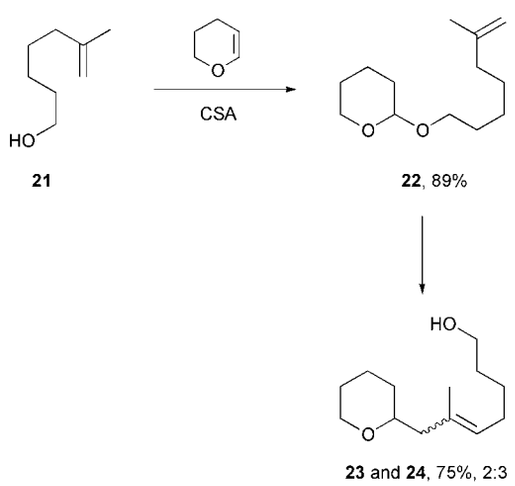
For the next rearrangement we chose to investigate this cyclisation reaction pathway with tetrahydropyranyl ether **16** (Scheme 6). The required precursor, 5-methylhexen-1-ol, was synthesised by the zirconocene dichloride catalysed carbometallation of hexyn-1-ol[14] in quantitative yield, and tetrahydropyranylation gave **16** in 81% yield. Under the usual low temperature conditions **16** undergoes a formal 1,7 oxygen to carbon rearrangement leading to alkenol **17** as a mixture of E/Z isomers in 83% yield, without any evidence of products from cyclisation or trapping by chloride ion. However, treatment of **16** with $SnCl_4$ at room temperature for 14 hours forms exclusively the cyclisation products **18** and **19** in 80% combined yield (**18** : **19** = 1 : 1).



Scheme 6

Intermediate carbocation **20** is presumably the common precursor to both **18/19** and **17**. It is interesting to note that the moderate diastereoselectivity seen in other rearrangements is not observed in this case. Regeneration of intermediate **20** by treating the alkenols **17** with trifluoromethanesulfonic acid in dichloromethane at room temperature leads to clean formation of an equal quantity of the bicycles **18** and **19** in 97% combined yield.

In order to investigate still greater lengths of carbon chain linker, alkenol **21** was synthesised (*via* three-step homologation of 5-methylhex-5-en-1-ol) and tetrahydropyranylated to give ether **22** (Scheme 7). Upon exposure to tin tetrachloride, **22**

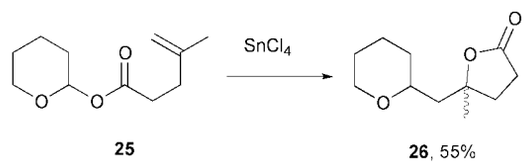


Scheme 7

rearranges in a 1,8 sense to give two alkenols **23** and **24** as the major products in 75% combined yield (2:3 ratio, stereochemistry not determined). In this case formation of a bicyclic product was not observed, presumably due to the unfavoured nature of the required 7 member ring cyclisation.

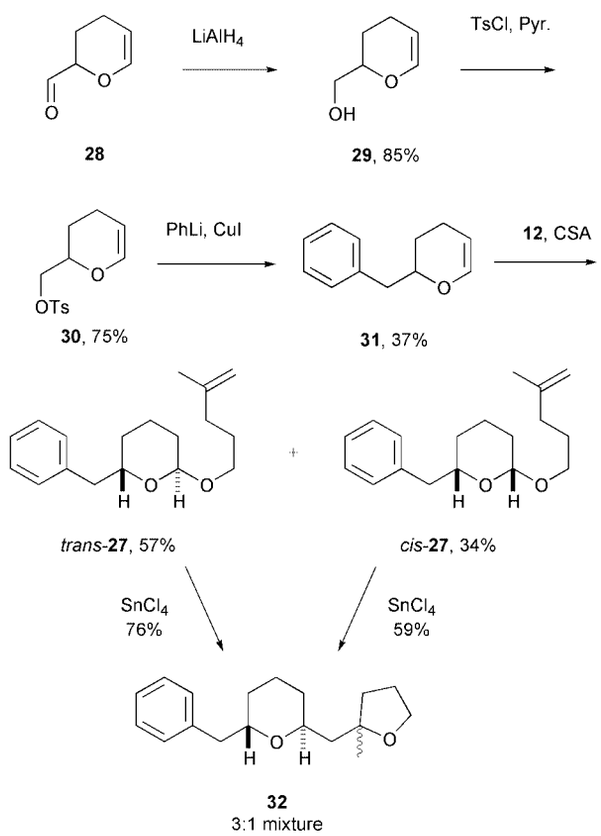
We have discovered that compounds with anomeric leaving groups other than simple ether linkages also undergo oxygen to carbon rearrangement to give structurally interesting products. For example, tetrahydropyranyl ester **25** (synthesised from the corresponding acid) rearranges in a 1,6 sense on exposure to tin tetrachloride to give, after intramolecular cyclisation, lactone **26** in 55% yield (63:37 mixture of diastereoisomers) (Scheme 8).

The extension of oxygen to carbon rearrangements to include *functionalised* tetrahydropyranyl ring systems would lead to synthetically interesting products, and in order to investigate this we selected (±)-*trans*-6-benzyltetrahydropyranyl ether **27** as a suitable rearrangement substrate. In addition to



Scheme 8

introducing further functionality into the system, it is well precedented that a substituent at the 6-position of a pyranyl ring system can exert a substantial degree of diastereocontrol in anomeric oxygen to carbon rearrangements.[6–9] The synthesis of **27** proceeds from acrolein dimer **28** *via* reduction with $LiAlH_4$ to give the alcohol **29** in 85% yield, followed by formation of the unstable tosylate **30**, in 75% yield, by treatment with tosyl chloride and pyridine (Scheme 9). Copper iodide catalysed displace-

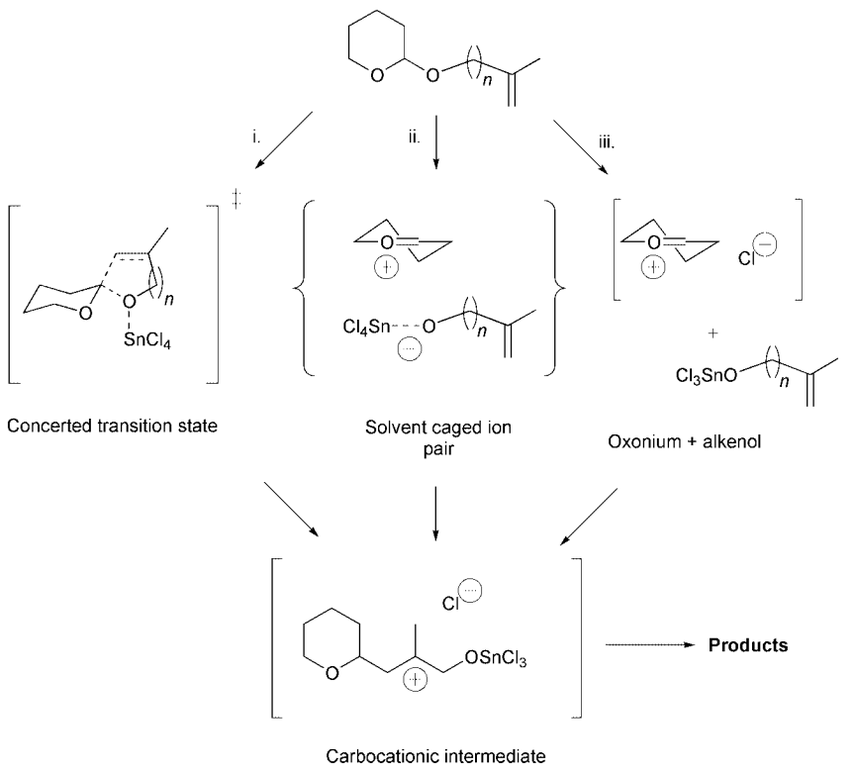


Scheme 9

ment of the tosylate by phenyllithium gave the dihydropyran **31** in an unoptimised 37% yield, accompanied by small amounts of the product resulting from attack by iodide ion. Coupling of **31** with the alkenol **12** under standard acid catalysed conditions gave separable *trans*-**27** and *cis*-**27** in 57% and 34% yield respectively. Tin tetrachloride promoted 1,6 rearrangement of *trans*-**27** is accompanied by clean 5-member ring closure to give bicyclic ethers **32** in 76% isolated yield, in a 3:1 diastereoisomeric ratio. Remarkably, rearrangement of *cis*-**27** also gives ethers **32** (59%), in a 3:1 ratio! In each case only two of the possible four diastereomers are formed, and on the basis of extensive precedent,[15] the ethers **32** are both assigned the *trans*-configuration across the pyran ring, and are therefore epimeric at the tetrahydrofuran ring quaternary centre. The identical ring stereoselectivity in the rearrangement of both *cis*- and *trans*-**27** is discussed in the following section.

Mechanistic studies

We turned our attention next to the detailed mechanism of the rearrangement reaction. Three distinct possibilities present

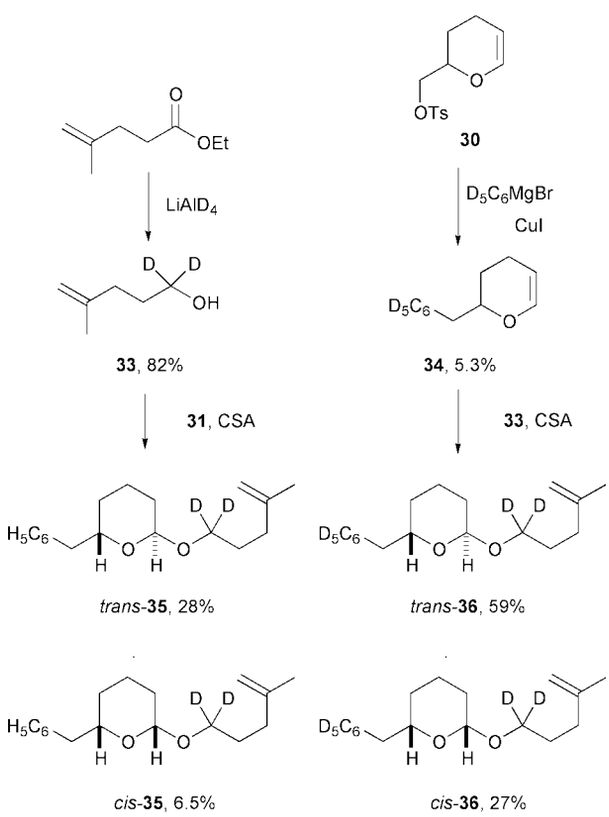


Scheme 10

themselves: i. a concerted process involving simultaneous cleavage of the anomeric bond and formation of the carbon–carbon bond; ii. a stepwise process of initial anomeric bond cleavage to give a solvent-caged ion pair which rapidly recombines in a carbon–carbon bond forming step; or iii. an intermolecular process where anomeric bond cleavage leads to two solvent-separated fragments which then recombine to give the products *via* a carbocationic intermediate (Scheme 10).

With appropriate isotopic tagging of both ring and side chain in the rearrangement substrate, the extent of label crossover in the products directly reflects the degree to which mechanism (iii) (complete scrambling) predominates over mechanisms (i) and (ii) (no scrambling).

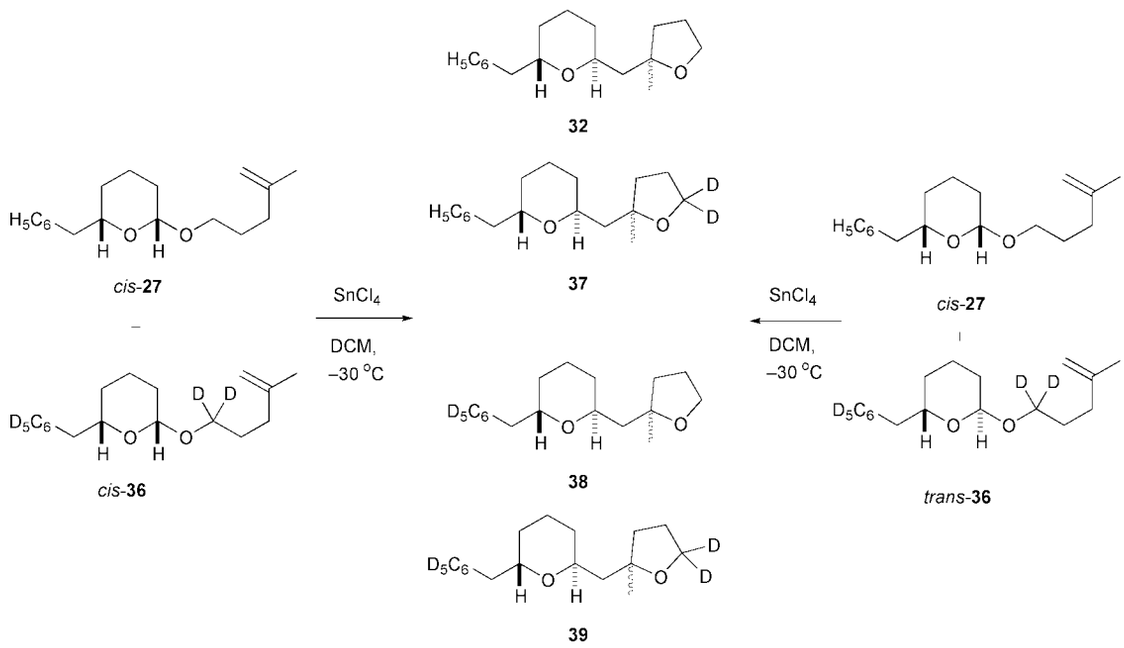
Based on our previous work **27** appears to be a particularly suitable substrate, as the rearrangement of **27** is both high yielding and selective. Furthermore, it was anticipated that deuterium labels could be straightforwardly introduced into both the pendent phenyl ring and the alkenol side chain without significantly influencing the rearrangement reaction rate through kinetic isotope effects. Indeed, the reduction of ethyl 4-methylpent-4-enoate with lithium aluminium deuteride gave the deuterium labelled alkenol **33** in 82% yield, and copper iodide catalysed addition of D_5C_6MgBr to tosylate **30** produced the D_5 labelled dihydropyran **34** in 5.3% yield (Scheme 11). Camphorsulfonic acid catalysed coupling of the undeuterated dihydropyran **31** to the D_2 labelled alkenol **33** resulted in *trans*-**35** (28% yield) along with its *cis* counterpart, isolated in 6.5% yield. The rearrangement products of **35** were used to aid the identification of the crossover rearrangement products. Analogous coupling of **33** and **34** gave tetrahydropyranyl ethers *trans*-**36** (59% yield) and *cis*-**36** (27% yield).



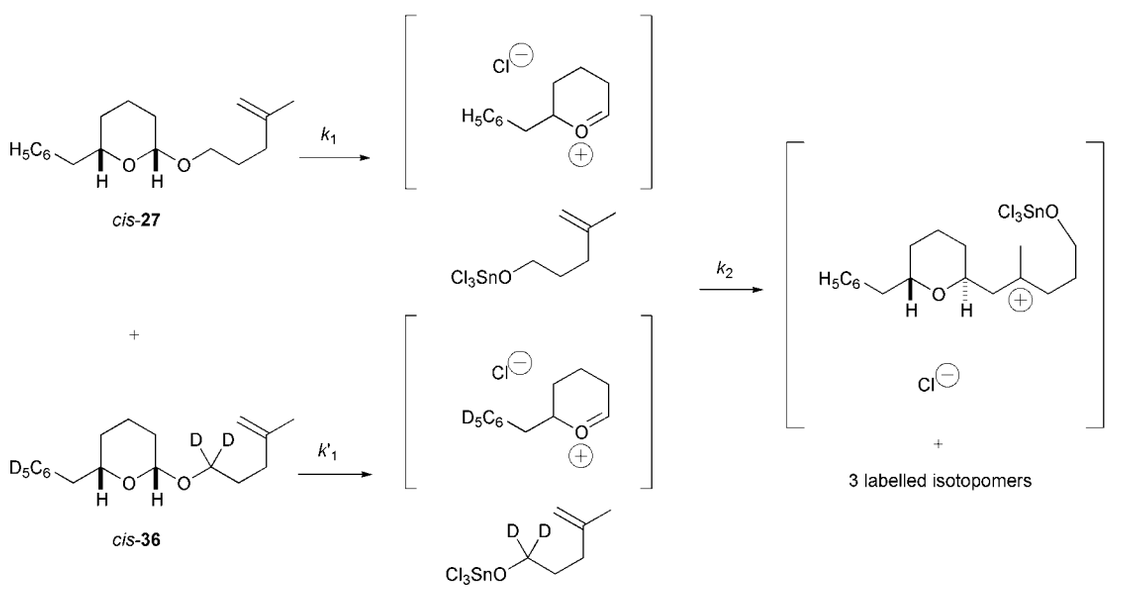
Scheme 11

With *cis*- and *trans*-isomers of both unlabelled **27** and the deuterium labelled **36** in hand, we were in a position to begin our crossover experiments.

As mentioned earlier, independent rearrangement of the unlabelled *trans*-**27** and *cis*-**27** diastereomers gave the same products (*trans*-**32**) with almost identical isomer distributions (approximately 3 : 1); the diastereoisomeric products were partially separable using LiCl doped silica column chromatography, but the relative stereochemistry of the epimeric centre could not be determined. The non-stereospecific nature of the reaction suggests that the reactions proceed through similar intermediates (an oxonium ion or similar species) which eliminates the possibility of concerted anomeric displacement [mechanism (i)]. Two crossover experiments were conducted with the aim of distinguishing between mechanisms (ii) and (iii): equimolar mixtures of a) the unlabelled *cis*-**27** and the deuterium labelled *cis*-**36** acetals, and b) the unlabelled *cis*-**27** and the labelled *trans*-**36** acetals, were treated with tin tetrachloride



Scheme 12



Scheme 13

and the products isolated (Scheme 12). Proton NMR analysis revealed that the reactions had given the usual 1,7 anomeric oxygen to carbon rearrangement coupled with 5-member ring cyclisation. The products had identical spectra to those observed for rearrangement of the unlabelled acetals, the diastereoisomeric ratio being approximately 3 : 1 in each case, but with altered integration as expected from deuterium labelling. Mass spectrometric analysis (FIB) of both mixtures of products gave a complicated pattern where MH^+ ions for the species **32**, **37**, **38** and **39** were present with significant relative abundance.

There was almost complete crossover, as determined by the abundance of the unlabelled **32** and doubly labelled **39** ions compared with the partially labelled **37** and **38** ions. On the basis of this result, we propose that the rearrangement proceeds in two stages: fast (and possibly reversible) fragmentation (with $k_1 \approx k'_1$) into an oxonium ion (or equivalent species) and the alkenol (with the oxygen bound as a tin alkoxide), followed by a much slower (and essentially irreversible) carbon–carbon bond forming process (k_2) (Scheme 13). If k_2 was very large then carbon–carbon bond formation would proceed rapidly within the solvent cage after fragmentation had occurred and levels of crossover would be minimal. However, this step appears to be sufficiently slow to allow for diffusion through the solution, and hence intermolecular crossover occurs. Finally, similar levels of crossover were observed in the rearrangement of a mixture of unlabelled *cis* and the labelled *trans* species suggest that k_1(*trans*) and k_1(*cis*) are of similar magnitude, possibly as a result of the reversibility of the k_1 step, and are in any case large compared with k_2 (Scheme 13).

Whilst explaining the observed results, it should be noted that the mechanism proposed above does not take into account any reversibility of the initial fragmentation, or retardation of reaction rates by kinetic isotope effects. However, it is unlikely that either of these phenomena have significant influence on the crucial carbon–carbon bond forming step.

Conclusions

We have demonstrated that the oxygen to carbon rearrangement of anomerically linked alkenes can be used in the efficient synthesis of an interesting range of ether ring systems bearing

carbon substituents adjacent to the heteroatom. Furthermore, we have proved that the reaction proceeds by an intermolecular mechanism. In the following paper we discuss our related findings on the synthesis of monocyclic and fused ring polycyclic alkenols *via* the intramolecular ring-opening cyclisation of anomerically linked alkenes.

Experimental

All reactions were carried out under an atmosphere of argon, and those not involving aqueous reagents were carried out in oven-dried glassware, cooled under vacuum. Diethyl ether and tetrahydrofuran were distilled over sodium benzophenone ketyl; dichloromethane, methanol and toluene were distilled over calcium hydride. All other solvents and reagents were used as supplied, unless otherwise stated. Flash column chromatography was carried out using Merck Kieselgel (230–400 mesh). Analytical thin layer chromatography was performed on glass plates precoated with Merck Kieselgel 60 F254, and visualised under ultra-violet irradiation, or by staining with aqueous acidic ammonium molybdate(IV) or acidic potassium manganate(VII). Microanalyses were performed in the microanalytical laboratories at the Department of Chemistry, Lensfield Road, Cambridge. Optical rotations were measured on an Optical Activity AA-1000 polarimeter. Infra-red spectra were obtained on Perkin-Elmer 983G or FTIR 1620 spectrometers, from a thin film deposited onto a sodium chloride plate from dichloromethane. Proton NMR spectra were recorded in $CDCl_3$, on Bruker AC-200, Bruker DPX-200, Bruker AM-400, Bruker DPX-400 or Bruker DPX-600 spectrometers, at 200, 400 or 600 MHz, with residual chloroform as the internal reference ($\delta_H = 7.26$ ppm). ^{13}C NMR spectra were recorded in $CDCl_3$, on the same spectrometers, at 50, 100 or 150 MHz, with the central peak of chloroform as the internal reference. Mass spectra and accurate mass data were obtained on Micromass Platform LC-MS, Kratos MS890MS or Bruker BIOAPEX 4.7 T FTICR spectrometers, and at the EPSRC Mass Spectrometry Service, by electron ionisation, chemical ionisation or fast atom/ion bombardment techniques. DEPT135 and two dimensional (COSY, HMQC, HMBC) NMR spectroscopy were used, where appropriate, to aid in the assignment of signals in the proton and ^{13}C NMR spectra.

2-Chloro-2-methyl-3-(tetrahydropyran-2′-yl)propan-1-ols 2 and 3, and 2-methyl-3-(tetrahydropyran-2′-yl)propionaldehyde 4

To a stirred solution of **1** (302 mg, 1.94 mmol) in dichloromethane (3 mL) at −30 °C was added a solution of tin tetrachloride in dichloromethane (1.0 M, 6.98 mL, 6.98 mmol) drop-wise *via* syringe. After stirring at −30 °C for 15 minutes the golden brown reaction mixture was quenched by the addition of aqueous sodium hydroxide solution (2.5 M, 2 mL), diluted with dichloromethane (10 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a yellow oil. Purification by flash column chromatography, eluting with 20% to 50% diethyl ether–40/60 petroleum ether isolated first **4** (80 mg, 26%), then **2** (157 mg, 42%) and finally **3** (62 mg, 17%) as colourless oils. Data for **2**: ν_{max} (thin film)/cm^{-1} 3414 (br, O–H), 2929, 2852, 1084, 1045 (C–O); δ_H (600 MHz; $CDCl_3$): 3.92 (1H, dd, *J* 11.3 and 3.5, C*H*HO), 3.76–3.70 (2H, m, O*H* and C*H*HOH), 3.62 (1H, m, C*H*), 3.46–3.42 (2H, m, CH*H*OH and CH*H*O), 1.99 (1H, dd, *J* 15.7 and 9.1, CHC*H*HC), 1.82–1.80 (1H, m, C*H*H), 1.74 (1H, d, *J* 15.7, CHCH*H*C), 1.55 (3H, s, CH_3), 1.53–1.42 (4H, m, 2 × CH_2), 1.34–1.28 (1H, m, CH*H*); δ_C (150 MHz; $CDCl_3$): 74.8 (*C*H), 71.5 (*C*Cl), 69.3 (CH_2O), 68.2 (CH_2OH), 47.3 ($CHCH_2C$), 32.2 (CH_2CH_2CH), 29.8 (CH_3), 25.4 (CH_2CH_2O), 23.3 (CH_2CH_2-CH); *m*/*z* (CI) 215 (16%), 193 (100%, MH^+), 179 (20%). Found (CI): MH^+ 193.0996. $C_9H_{17}O_2ClH^+$ requires 193.0995. Data for **3**: ν_{max} (thin film)/cm^{-1} 3472 (br, O–H), 2930, 2852 (C–H), 1079, 1040 (C–O); δ_H (600 MHz; $CDCl_3$): 3.94 (1H, dd, *J* 10.6 and 2.2, C*H*HO), 3.61 (3H, m, OH, C*H*HOH and OC*H*), 3.46–3.32 (2H, m, CH*H*OH and CH*H*O), 2.12 (1H, dd, *J* 15.0 and 9.3, OCHC*H*H), 1.99 (1H, dd, *J* 15.0 and 1.7, OCHCH*H*), 1.89–1.78 (1H, m, C*H*H), 1.57 (3H, s, CH_3), 1.54–1.23 (5H, m, 2 × CH_2 and CH*H*); δ_C (150 MHz; $CDCl_3$): 75.0 (O*C*H), 73.1 (*C*CH_3), 71.5 (*C*H_2O), 68.2 (*C*H_2OH), 48.6 (*C*H_2CCl), 32.5 (*C*H_2CH), 25.9 (*C*H_3), 25.3 (*C*H_2CH_2O), 23.4 (*C*H_2CH_2CH); *m*/*z* (CI) 215 (10%), 193 (100%, MH^+), 179 (34%). Found (CI): MH^+ 193.0999. $C_9H_{17}O_2ClH^+$ requires 193.0995. Data for **4**, characterised as a mixture of diastereoisomers in a 2 : 1 ratio by integration of the C*H*O doublets at $\delta_H = 9.62$ (minor isomer) and 9.58 (major isomer): ν_{max} (thin film)/cm^{-1} 2929, 2842, 1723 (C=O), 1084, 1045 (C–O); δ_H (400 MHz; $CDCl_3$): 9.62 (1H minor, d, *J* 1.6, C*H*O), 9.58 (1H major, d, *J* 2.2, C*H*O), 3.94–3.89 (1H major, m, C*H*HO), 3.87–3.83 (1H minor, C*H*HO), 3.42–3.20 (2H major and 2H minor, m, CH*H*O and OC*H*), 2.55 (1H major and 1H minor, m, C*H*CH_3), 1.98–1.23 (8H major and 8H minor, m, 4 × CH_2), 1.10 (3H minor, d, *J* 7.1, C*H*$_3$), 1.08 (3H major, d, *J* 7.0, C*H*$_3$); δ_C (100 MHz; $CDCl_3$): 205.0 (*C*HO, minor), 204.8 (*C*HO, major), 75.2 (O*C*H, minor), 75.0 (O*C*H, major), 68.3 (*C*H_2O, major and minor), 43.5 (*C*HCH_3, minor), 42.7 (*C*HCH_3, major), 37.6 (*C*H_2, major and minor), 32.2 (*C*H_2, minor), 32.1 (*C*H_2, major), 25.9 (*C*H_2, major and minor), 23.4 (*C*H_2, major and minor), 13.8 (*C*H_3, minor), 13.5 (*C*H_3, major); *m*/*z* (CI) 157 (100%, MH^+). Found (CI): MH^+ 157.1231. $C_9H_{16}O_2H^+$ requires 157.1229.

Trimethyl[2-(tetrahydropyran-2′-yloxymethyl)allyl]silane 7

To a stirred solution of **6** (140 mg, 0.98 mmol) and camphorsulfonic acid (10 mg) in dichloromethane (5 mL) at 0 °C was added 3,4-dihydro-2*H*-pyran (98 mg, 1.18 mmol) drop-wise *via* syringe. After stirring for 10 minutes at this temperature the light pink reaction mixture was diluted with ether (20 mL), washed with saturated sodium bicarbonate (20 mL) and brine (20 mL), dried (K_2CO_3), filtered and concentrated *in vacuo* to give a brown oil. Purification by flash column chromatography eluting with 10% diethyl ether–40/60 petroleum ether gave **7** (112 g, 50%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3075, 2948, 2873 (C–H), 1641 (C=C), 1085, 1036 (C–O); δ_H (400 MHz; $CDCl_3$): 4.93–4.91 (1H, m, C=C*H*H), 4.69–4.61 (2H, m, C*H* and C=CH*H*), 4.21–3.80 (3H, m, C*H*HO and OCH_2), 3.56–3.47 (1H, m, CH*H*O), 1.90–1.24 (8H, m, 4 × CH_2), 0.03 (9H, s, Si(CH_3)$_3$); δ_C (100 MHz; $CDCl_3$): 143.7 (quat. *C*), 108.4 (C=*C*H_2), 97.7 (*C*H), 70.7 (*C*H_2), 62.0 (*C*H_2), 30.5 (*C*H_2), 25.4 (*C*H_2), 23.3 (*C*H_2), 19.4 (*C*H_2), −1.4 (Si(*C*H_3)$_3$); *m*/*z* (CI) 251 (30%), 229 (100%, MH^+). Found (CI): MH^+ 229.1630. $C_{12}H_{24}SiO_2H^+$ requires 229.1624.

2-(Tetrahydropyran-2′-ylmethyl)prop-2-en-1-ol 9

To a stirred solution of **7** (72 mg, 0.32 mmol) in dichloromethane (0.6 mL) at −30 °C was added tin tetrachloride (0.13 mL, 1.14 mmol) drop-wise *via* syringe. After stirring at −30 °C for 15 minutes the golden brown reaction mixture was quenched by the addition of sodium hydroxide solution (2.5 M, 2 mL), diluted with dichloromethane (10 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a yellow oil. Purification by flash column chromatography, eluting with 30% to 60% ether–40/60 petroleum ether gave **9** (21 mg, 43%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3420 (br, O–H), 2936, 2850 (C–H), 1648 (C=C), 1086, 1041 (C–O); δ_H (600 MHz; $CDCl_3$): 5.05 (1H, s, C=C*H*H), 4.89 (1H, s, C=CH*H*), 4.05 (2H, s, CH_2OH), 3.99 (1H, d, *J* 11.2, C*H*HO), 3.44–3.41 (2H, m, CH*H*O and OC*H*), 3.26 (1H, s, O*H*), 2.31–2.24 (2H, m, CHCH_2C), 1.84–1.25 (6H, m, 3 × CH_2); δ_C (150 MHz; $CDCl_3$): 146.4 (*C*=CH_2), 113.4 (C=*C*H_2), 77.7 (O*C*H), 68.6 (*C*H_2), 68.5 (*C*H_2), 41.2 (*C*H_2), 31.6 (*C*H_2), 25.7 (*C*H_2), 23.4 (*C*H_2); *m*/*z* (CI) 179 (100%,

MNa^+). Found (CI): MNa^+ 179.1052. $C_9H_{16}O_2Na^+$ requires 179.1048.

2-(Cyclopent-1′-enylmethoxy)tetrahydropyran 10

To a stirred solution of cyclopentenylmethanol (3.13 g, 31.9 mmol) and camphorsulfonic acid (10 mg) in dichloromethane (10 mL) at 0 °C was added 3,4-dihydro-2*H*-pyran (2.95 g, 35.1 mmol) drop-wise *via* syringe. After stirring for 30 minutes at ambient temperature the light pink reaction mixture was diluted with ether (20 mL), washed with saturated sodium bicarbonate (20 mL) and brine (20 mL), dried (K_2CO_3), filtered and concentrated *in vacuo* to give a brown oil. Purification by flash column chromatography eluting with 15% diethyl ether–40/60 petroleum ether gave **10** (5.1 g, 87%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3043, 2938, 2846, 1657 (C=C); δ_H (400 MHz; $CDCl_3$): 5.58–5.57 (1H, m, C=C*H*), 4.56 (1H, t, *J* 3.3, OC*H*O), 4.22–4.15 (1H, m, OC*H*HC), 4.01–3.94 (1H, m, OCH*H*C), 3.87–3.76 (1H, m, C*H*HO), 3.49–3.38 (1H, m, CH*H*O), 2.30–1.43 (12H, m, 6 × CH_2); δ_C (100 MHz; $CDCl_3$): 141.3 (*C*=CH), 126.9 (C=*C*H), 97.5 (O*C*HO), 65.6 (*C*H_2), 61.8 (*C*H_2), 32.9 (*C*H_2), 32.2 (*C*H_2), 30.5 (*C*H_2), 25.4 (*C*H_2), 23.2 (*C*H_2), 19.3 (*C*H_2); *m*/*z* (CI) 205 (100%, MNa^+). Found (CI): MNa^+ 205.1206. $C_{11}H_{18}O_2Na^+$ requires 205.1205.

2-(Tetrahydropyran-2′-yl)cyclopentylmethanal 11

To a stirred solution of **10** (0.10 g, 0.55 mmol) in dichloromethane (6 mL) at −30 °C was added a solution of tin tetrachloride in dichloromethane (1.0 M, 1.98 mL, 1.98 mmol) drop-wise *via* syringe. After stirring at −30 °C for 15 minutes the golden brown reaction mixture was quenched by the addition of sodium hydroxide solution (2.5 M, 2 mL), diluted with dichloromethane (10 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a yellow oil. Purification by flash column chromatography, eluting with 8% diethyl ether–40/60 petroleum ether gave **11**, tentatively assigned as a mixture of three diastereoisomers in a ratio 80 : 12 : 8 as determined by integration of the C*H*O doublets at 9.62 (major isomer), 9.61 and 9.59 (minor isomers 1 and 2) in the 400 MHz proton NMR spectrum (63 mg, 63%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2936, 2852, 1721 (C=O), 1088, 1050 (C–O); δ_H (400 MHz; $CDCl_3$): 9.62 (1H major, d, *J* 2.8, C*H*O), 9.61 (1H minor 1, d, *J* 2.6, C*H*O), 9.59 (1H minor 2, d, *J* 2.1, C*H*O), 3.97–3.91 (1H major, m, C*H*HO), 3.36 (1H major, td, *J* 11.5 and 2.4, OC*H*), 3.07–3.02 (1H major, m, CH*H*O), 2.67–2.63 (1H major, m, C*H*CHO), 2.17–1.13 (13H major, m, C*H* and 6 × CH_2); δ_C (100 MHz; $CDCl_3$): 204.5 (*C*HO, major), 81.5 (O*C*H, major), 68.6 (CH_2O, major), 55.6 (CH, major), 47.4 (CH, major), 30.8 (CH_2, major), 29.1 (CH_2, major), 26.7 (CH_2, major), 26.1 (CH_2, major), 25.3 (CH_2, major), 23.5 (CH_2, major); further signals for the minor isomers could not be resolved; *m*/*z* (CI) 205 (100%, MNa^+), 183 (45%). Found (CI): MNa^+ 205.1209. $C_{11}H_{18}O_2Na^+$ requires 205.1205.

Ethyl 4-methylpent-4-enoate

A solution of methallyl alcohol (10 mL, 8.57 g, 0.12 mol) and propanoic acid (0.6 mL) in triethyl orthoacetate (150 mL) was heated at reflux for 1 h. Ethanol was removed by fractional distillation at atmospheric pressure through a Vigreaux column, and heating was continued for a further hour. The reaction mixture was cooled to ambient temperature and washed with cold water (500 mL) containing camphorsulfonic acid (0.4 g). The organic layer was separated and the aqueous layer extracted with ether (2 × 200 mL). The combined organic extracts were washed with saturated sodium bicarbonate (2 × 300 mL) and brine (300 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Distillation over a short path gave ethyl 4-methylpent-4-enoate as a colourless oil (11.97 g, 71%), bp 156–160 °C (760 mmHg); ν_{max} (thin film)/cm^{-1} 3078, 2980, 2937, 1737, 1651, 1054, 1031; δ_H (200 MHz; $CDCl_3$): 4.73 (1H, s, C=CH*H*), 4.69 (1H, s, C=C*H*H), 4.13 (2H, q, *J* 7.1, CH_3CH_2), 2.33–2.49 (4H, m, 2 × CH_2), 1.73 (3H, d, *J* 0.4, CH_3C), 1.25 (3H, t, *J* 7.1, CH_3CH_2); δ_C (50 MHz; $CDCl_3$): 173.1 (CO), 144.0 (*C*=CH_2), 110.2 (C=*C*H_2), 60.2 (O*C*H_2), 32.6 (*C*H_2), 32.6 (*C*H_2), 22.3 (*C*H_3), 14.1 (*C*H_3); *m*/*z* (CI) 143 (100%, MH^+). Found (CI): MH^+ 143.1095. $C_8H_{14}O_2H^+$ requires 143.1072.

4-Methylpent-4-en-1-ol 12

To a stirred solution of ethyl 4-methylpent-4-enoate (2.0 g, 14.0 mmol) in ether (50 mL) at 0 °C was added lithium aluminium hydride (2.0 M solution in ether, 7.0 mL, 14.0 mmol) drop-wise *via* syringe over a period of 5 minutes. After stirring for 15 minutes the highly viscous reaction mixture was cooled to 0 °C and quenched by the cautious addition of water (10 mL) and aqueous sulfuric acid (1.5 M, 5 mL). The organic residue was extracted with ether (3 × 40 mL) and the combined fractions washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil. Purification by flash column chromatography eluting with 25% ethyl acetate–40/60 petroleum ether gave **12** (1.29 g, 93%) as a colourless oil. δ_H (400 MHz; $CDCl_3$): 4.64–4.62 (2H, m, C=CH_2), 3.54–3.50 (2H, m, HOCH_2), 3.18 (1H, s, O*H*), 2.05–1.97 (2H, m, CH_2CH_2C), 1.66 (3H, s, CH_3), 1.70–1.55 (2H, m, $CH_2CH_2CH_2$); δ_C (100 MHz; $CDCl_3$): 145.3 (*C*=CH_2), 109.9 (C=*C*H_2), 62.1 (HO*C*H_2), 33.9 (*C*H_2), 30.4 (*C*H_2), 22.2 (*C*H_3).

2-(4′-Methylpent-4′-enyloxy)tetrahydropyran 13

To a stirred solution of **12** (0.55 g, 5.5 mmol) and camphorsulfonic acid (5 mg) in dichloromethane (10 mL) at ambient temperature was added 3,4-dihydro-2*H*-pyran (0.54 g, 5.5 mmol) drop-wise *via* syringe. After stirring for 30 minutes the reaction mixture was diluted with ether (20 mL), washed with saturated sodium bicarbonate (20 mL) and brine (20 mL), dried (K_2CO_3), filtered and concentrated *in vacuo* to give a colourless oil. Purification by flash column chromatography eluting with 10% ethyl acetate–40/60 petroleum ether gave **13** (0.52 g, 51%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3073, 2938, 2870, 2730, 2655, 1649 (C=C); δ_H (400 MHz; $CDCl_3$): 4.53 (2H, s, C=CH_2), 4.41 (1H, t, *J* 3.2, C*H*), 3.74–3.51 (2H, m, C*H*HO and OC*H*H), 3.37–3.15 (2H, m, CH*H*O and OCH*H*), 1.97–1.89 (2H, m, CH_2CH_2C), 1.56 (3H, s, CH_3), 1.69–1.32 (8H, m, 4 × CH_2); δ_C (100 MHz; $CDCl_3$): 144.8 (*C*=CH_2), 109.7 (C=*C*H_2), 98.4 (*C*H), 66.7 (CH_2), 61.6 (CH_2), 34.1 (CH_2), 30.5 (CH_2), 27.6 (CH_2), 25.4 (CH_2), 22.1 (*C*H_3), 19.3 (CH_2); *m*/*z* (CI) 185 (100%, MH^+). Found (CI): MH^+ 185.1571. $C_{11}H_{20}O_2H^+$ requires 185.1542.

2-(2′-Methyltetrahydrofuran-2′-ylmethyl)tetrahydropyran 14

To a stirred solution of **13** (100 mg, 0.54 mmol) in dichloromethane (3 mL) at −30 °C was added a solution of tin tetrachloride in dichloromethane (1.0 M, 1.1 mL, 1.1 mmol) drop-wise *via* syringe. After stirring at −30 °C for 15 minutes the light brown reaction mixture was quenched by the addition of sodium hydroxide solution (2.5 M, 2.0 mL), diluted with dichloromethane (10 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a yellow oil. Purification by flash column chromatography eluting with 25% to 50% diethyl ether–40/60 petroleum ether gave **14**, as a 9 : 2 mixture of diastereoisomers by integration of the CH_3 singlets at 1.21 (major) and 1.16 (minor) in the proton NMR, and by GC analysis (2 peaks, retention times 12.52 minutes and 12.78 minutes in a ratio of 2 : 9) (93 mg, 93%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2950, 2850, 1084, 1051, 1009; δ_H (600 MHz; $CDCl_3$): 3.92–3.89 (1H major and 1H minor, m, CH_2C*H*HO), 3.82–3.72 (2H major and 2H minor, m, COCH_2), 3.42–3.36 (2H major and 2H minor, m, CH_2CH*H*O and C*H*),

1.96–1.23 (12H major and 12H minor, m, 6 × CH_2), 1.21 (3H, s, CH_3), 1.16 (3H minor, s, CH_3); δ_C (150 MHz; $CDCl_3$) 81.9 (*C*CH_3, minor), 81.8 (*C*CH_3, major), 75.3 (*C*H, major), 75.1 (*C*H, minor), 68.1 (CH_2CH_2O, major), 66.6 ($COCH_2$, major), 47.5 (CH_2, minor), 47.3 (CH_2, major), 38.2 (CH_2, major), 36.1 (CH_2, minor), 33.2 (CH_2, major), 27.3 (*C*H_3, minor), 25.9 (CH_2, major), 25.8 (CH_2, major), 25.4 (*C*H_3, major), 23.7 (CH*C*H_2C, major); further signals for the minor isomer could not be resolved; *m*/*z* (CI) 269 (70%), 185 (100%, MH^+), 85 (30%). Found (CI): MH^+ 185.1542. $C_{11}H_{20}O_2H^+$ requires 185.1542.

2-(5′-Methylhex-5′-enyloxy)tetrahydropyran 16

To a stirred solution of 5-methylhex-5-en-1-ol (1.5 g, 10.4 mmol) and camphorsulfonic acid (5 mg) in dichloromethane (10 mL) at ambient temperature was added 3,4-dihydro-2*H*-pyran (0.88 g, 10.4 mmol) drop-wise *via* syringe. After stirring for 30 minutes the reaction mixture was diluted with ether (20 mL), washed with saturated sodium bicarbonate (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a colourless oil. Purification by flash column chromatography eluting with 10% ethyl acetate–40/60 petroleum ether gave **16** (1.66 g, 81%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3073, 2944, 2870, 2729, 2656, 1649 (C=C); δ_H (400 MHz; $CDCl_3$): 4.64–4.62 (2H, m, C=CH_2), 4.52 (1H, t, *J* 3.1, C*H*), 3.86–3.61 (2H, m, C*H*HO and OC*H*H), 3.49–3.28 (2H, m, CH*H*O and OCH*H*), 1.98 (2H, t, *J* 7.4, CH_2CCH_2), 1.65 (3H, s, CH_3), 1.79–1.40 (10H, m, 5 × CH_2); δ_C (100 MHz; $CDCl_3$): 145.5 (*C*=CH_2), 109.8 (C=*C*H_2), 98.6 (*C*H), 67.2 (*C*H_2), 62.0 (*C*H_2), 37.4 (*C*H_2), 30.6 (*C*H_2), 29.2 (*C*H_2), 25.4 (*C*H_2), 24.1 (*C*H_2), 22.1 (*C*H_3), 19.5 (*C*H_2); *m*/*z* (CI) 199 (100%, MH^+), 102 (61%), 85 (35%). Found (CI): MH^+ 199.1698. $C_{12}H_{22}O_2H^+$ requires 199.1698.

5-Methylhex-5-en-1-ol

To a stirred solution of zirconocene dichloride (1.75 g, 6.0 mmol) in dichloroethane (40 mL) at ambient temperature was added a solution of trimethylaluminium in hexanes (2.0 M, 37.5 mL, 75.0 mmol) drop-wise *via* syringe. After stirring for 10 minutes a solution of hexyn-1-ol (2.45 g, 25.0 mmol) in dichloroethane (20 mL) was cautiously added drop-wise *via* syringe. The yellow reaction mixture was stirred for 22 hours at ambient temperature and quenched by the addition of saturated sodium bicarbonate (4 mL) at 0 °C. The resulting slurry was diluted with brine (50 mL), extracted with ether (5 × 50 mL) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography, eluting with 50% diethyl ether–40/60 petroleum ether gave 5-methylhex-5-en-1-ol (2.85 g, 100%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3358 (br, O–H), 3073, 2932, 1649 (C=C); δ_H (400 MHz; $CDCl_3$): 4.65–4.62 (2H, m, C=CH_2), 3.55 (2H, t, *J* 6.2, HOCH_2), 2.96 (1H, s, O*H*), 1.97 (2H, t, *J* 7.2, CH_2CH_2C), 1.65 (3H, s, CH_3), 1.59–1.39 (4H, m, $HOCH_2CH_2$ and CH_2CH_2C); δ_C (100 MHz; $CDCl_3$): 145.6 (*C*=CH_2), 109.8 (C=*C*H_2), 62.3 (HO*C*H_2), 37.4 (CH_2), 32.2 (CH_2), 23.6 (CH_2), 22.1 (*C*H_3).

5-Methyl-6-(tetrahydropyran-2′-yl)hex-4-en-1-ol 17

To a stirred solution of **16** (0.10 g, 0.50 mmol) in dichloromethane (6 mL) at −30 °C was added a solution of tin tetrachloride in dichloromethane (1.0 M, 1.98 mL, 1.98 mmol) drop-wise *via* syringe. After stirring at −30 °C for 10 minutes the colourless reaction mixture was quenched by the addition of sodium hydroxide solution (2.5 M, 2 mL), diluted with dichloromethane (10 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil. Purification by flash gel column chromatography, eluting with 30% diethyl ether–40/60 petroleum ether gave **17**, tentatively assigned as a 3 : 1 mixture of *E* and *Z* stereoisomers by integration of the signals in the 400 MHz proton NMR spectrum at δ_H = 5.23 (major) and 5.18 (minor) (86 mg, 86%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3396 (br, O–H), 2935, 2856, 2738, 1666 (C=C); δ_H (400 MHz; $CDCl_3$) 5.23 (1H major, t, *J* 7.3, C=C*H*), 5.18 (1H minor, obs. t, *J* 7.1, C=C*H*), 3.96–3.90 (1H major and 1H minor, m, C*H*HO), 3.63–3.53 (2H major and 2H minor, m, CH*H*O and C*H*HOH), 3.46–3.30 (2H major and 2H minor, m, OC*H* and CH*H*OH), 1.66 (3H major and 3H minor, s, CH_3), 2.47–1.16 (12H major and 12H minor, m, 6 × CH_2); δ_C (100 MHz; $CDCl_3$): 132.4 (*C*=CH_3, major and minor), 126.7 (C=*C*H, major), 126.4 (C=*C*H, minor), 76.3 (O*C*H, minor), 76.0 (O*C*H, major), 68.5 (*C*H_2, major), 68.1 (*C*H_2, minor), 62.7 (*C*H_2, major), 61.0 (*C*H_2, minor), 46.8 (*C*H_2, major), 38.8 (*C*H_2, minor), 32.6 (*C*H_2, major and minor), 31.7 (*C*H_2, major and minor), 26.0 (*C*H_2, major and minor), 24.7 (*C*H_2, major and minor), 23.5 (*C*H_2, major and minor), 16.5 (*C*CH_3, major and minor); *m*/*z* (CI) 199 (100%, MH^+). Found (CI): MH^+ 199.1699. $C_{12}H_{22}O_2H^+$ requires 199.1698.

2-(2′-Methyltetrahydropyran-2′-ylmethyl)tetrahydropyrans 18 and 19

From 16. To a stirred solution of **16** (150 mg, 0.76 mmol) in dichloromethane (6 mL) at ambient temperature was added a 1.0 M solution of tin tetrachloride in dichloromethane (2.73 mL, 2.73 mmol) drop-wise *via* syringe. After stirring at ambient temperature for 14 hours the colourless reaction mixture was quenched by the addition of sodium hydroxide solution (2.5 M, 2 mL), diluted with dichloromethane (10 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave crude **18** and **19** as a 1 : 1 mixture of diastereoisomers by integration of the CH_3 singlets at δ_H = 1.23 and 1.11 in the 600 MHz proton NMR, as a yellow oil. Purification by flash column chromatography, eluting with 10% diethyl ether–40/60 petroleum ether, gave **27** and **28** (120 mg, 80%). ν_{max} (thin film)/cm^{-1} 2933, 2855, 2737, 2668, 1027 (C–O); *m*/*z* (CI) 199 (100%, MH^+). Found (CI) MH^+ 199.1698. $C_{12}H_{22}O_2H^+$ requires 199.1698. Further flash column chromatography, eluting with 10% diethyl ether–40/60 petroleum ether, allowed separation of a small sample of **27** for spectroscopic analysis. Data for **18**: δ_H (600 MHz; $CDCl_3$): 3.93–3.91 (1H, m, C*H*HO), 3.67–3.59 (2H, m, OC*H* and CH*H*O), 3.49–3.45 (1H, m, COC*H*H), 3.40 (1H, td, *J* 11.5 and 2.5, COCH*H*), 1.81–1.37 (14H, m, 7 × CH_2), 1.23 (3H, s, CH_3); δ_C (150 MHz; $CDCl_3$): 74.5 (O*C*H), 72.7 (*C*CH_3), 68.2 (*C*H_2), 61.5 (*C*H_2), 45.7 (*C*H_2), 36.7 (*C*H_2), 33.4 (*C*H_2), 26.0 (*C*H_2), 25.9 (*C*H_2), 23.9 (*C*H_2), 23.6 (*C*H_3), 19.3 (*C*H_2). Data for **19**, isolated as a mixture with **27**: δ_H (600 MHz; $CDCl_3$): 3.96–3.92 (1H, m, C*H*HO), 3.69–3.63 (2H, m, OC*H* and CH*H*O), 3.43–3.37 (2H, m, COCH_2), 1.80–1.34 (14H, m, 7 × CH_2), 1.11 (3H, s, CH_3); δ_C (150 MHz; $CDCl_3$): 74.2 (*C*H), 72.5 (*C*CH_3), 68.1 (*C*H_2), 61.3 (*C*H_2), 45.7 (*C*H_2), 34.2 (*C*H_2), 33.3 (*C*H_2), 26.0 (*C*H_2), 25.9 (*C*H_2), 23.7 (*C*H_2), 19.4 (*C*H_3).

From 17. To a stirred solution of **17** (51 mg, 0.253 mmol) in dichloromethane (2 mL) at −30 °C was added trifluoromethanesulfonic acid (0.022 mL, 0.253 mmol) drop-wise *via* syringe. The reaction mixture was allowed to warm to ambient temperature, stirred for 16 hours, then diluted with ether (10 mL), washed with saturated sodium bicarbonate (10 mL) and extracted into ether (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a colourless oil (49 mg, 97%, 1 : 1 mixture of diastereomers) as a colourless oil. Spectroscopic data for **18** and **19** were identical to those reported previously.

5-Methylhex-5-enyl toluene-*p*-sulfonate

To a stirred solution of 5-methylhex-5-en-1-ol (1.0 g, 8.8 mmol) and toluene-*p*-sulfonyl chloride (2.7 g, 14.1 mmol) in dichloro-

methane (15 mL) at ambient temperature was added triethylamine (8 mL) in one portion. After stirring for 4 hours the reaction mixture was washed repeatedly with 1.5 M aqueous hydrochloric acid until the pH of the aqueous washings measured 1, dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a yellow oil. Purification by flash gel column chromatography eluting with 15% diethyl ether–40/60 petroleum ether gave 5-methylhex-5-enyl toluene-*p*-sulfonate (2.24 g, 95%, containing approximately 15% residual toluene-*p*-sulfonyl chloride by 400 MHz proton NMR). δ_H (400 MHz; $CDCl_3$): 7.71 (2H, d, *J* 8.2, Ar*H*), 7.27 (2H, d, *J* 8.0, Ar*H*), 4.60 (1H, s, C=C*H*H), 4.54 (1H, s, C=CH*H*), 3.97 (2H, t, *J* 6.2, OCH_2), 2.36 (3H, s, ArCH_3), 1.88 (2H, t, *J* 7.4, C=CCH_2), 1.58 (3H, s, CCH_3), 1.56–1.33 (4H, m, 2 × CH_2); δ_C (100 MHz; $CDCl_3$): 144.71 (quat. Ph), 144.63 (quat. Ph), 133.1 (*C*H), 129.8 (*C*H), 127.7 (*C*=CH$_2$), 110.3 (C=*C*H$_2$), 70.4 (O*C*H$_2$), 36.8 (*C*H$_2$), 28.2 (*C*H$_2$), 23.1 (*C*H$_2$), 22.0 (*C*H$_3$), 21.4 (*C*H$_3$).

6-Methylhept-6-enenitrile

To a stirred solution of 5-methylhex-5-enyl toluene-*p*-sulfonate (1.1 g, 4.1 mmol, toluene-*p*-sulfonyl chloride present as 15% impurity) in dimethyl sulfoxide (30 mL) at ambient temperature was added sodium cyanide (400 mg, 8.2 mmol) in one portion. Stirring was maintained for 24 hours before the light yellow reaction mixture was quenched by the addition of water (30 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with aqueous hydrochloric acid (0.1 M, 100 mL), followed by water (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 6-methylhept-6-enenitrile (0.50 g, approximately quantitative yield based on 15% residual toluene-*p*-sulfonyl chloride in starting material) as a yellow oil. δ_H (400 MHz; $CDCl_3$): 4.60 (1H, s, C=C*H*H), 4.56 (1H, s, C=CH*H*), 2.24 (2H, t, *J* 6.7, NCCH_2), 1.93 (2H, t, *J* 7.0, CH_2C=C), 1.59 (3H, s, CH_3), 1.55–1.38 (4H, m, 2 × CH_2); δ_C (100 MHz; $CDCl_3$): 144.4 (*C*=CH$_2$), 119.6 (*C*N), 110.5 (C=*C*H$_2$), 36.6 (*C*H$_2$), 26.2 (*C*H$_2$), 24.7 (*C*H$_2$), 22.0 (*C*H$_3$), 16.8 (*C*H$_2$).

6-Methylhept-6-en-1-ol 21

To a stirred solution of 1-cyano-6-methylheptene (0.50 g, 4.0 mmol) in toluene (10 mL) at −78 °C was added a 1 M solution of diisobutylaluminium hydride in toluene (4.0 mL, 4.0 mmol). Stirring was maintained for 1 hour at this temperature before the reaction mixture was quenched by the addition of potassium carbonate solution (5 mL). The presence of the intermediate aldehyde was tentatively established by thin layer chromatography (R_f = 0.7 in 30% diethyl ether–40/60 petroleum ether), and the reaction mixture was extracted with dichloromethane (3 × 20 mL). After removal of the volatile components *in vacuo*, ethanol (20 mL) was added followed by sodium borohydride (152 mg, 4.0 mmol) and stirring was maintained for 1 hour. The reaction mixture was acidified (concentrated hydrochloric acid) to pH 5, extracted with dichloromethane (3 × 20 mL), and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography, eluting with 50% diethyl ether–40/60 petroleum ether afforded **21** (50 mg, 10%) as a colourless oil. δ_H (400 MHz; $CDCl_3$): 4.69 (1H, s, C=C*H*H), 4.65 (1H, s, C=CH*H*), 3.63 (2H, t, *J* 6.4, HOCH_2), 2.02 (2H, t, *J* 6.8, CH_2C=C), 1.70 (3H, s, CH_3), 1.65–1.29 (6H, m, 3 × CH_2); δ_C (100 MHz; $CDCl_3$): 145.9 (*C*=CH$_2$), 109.7 (C=*C*H$_2$), 62.9 (HO*C*H$_2$), 37.7 (*C*H$_2$), 32.6 (*C*H$_2$), 27.3 (*C*H$_2$), 25.3 (*C*H$_2$), 22.3 (*C*H$_3$).

2-(6′-Methylhept-6′-enyloxy)tetrahydropyran 22

To a stirred solution of **21** (50 mg, 0.40 mmol) and camphorsulfonic acid (3 mg) in dichloromethane (2.5 mL) at ambient temperature was added 3,4-dihydro-2*H*-pyran (37 mg, 0.44 mmol) drop-wise *via* syringe. After stirring for 10 minutes at ambient temperature the purple reaction mixture was diluted with dichloromethane (10 mL), washed with saturated sodium bicarbonate (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a black oil. Purification by flash column chromatography eluting with 10% diethyl ether–40/60 petroleum ether gave **22** (80 mg, 89%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3073, 2936, 2656, 1650 (C=C), 1076 (C–O); δ_H (400 MHz; $CDCl_3$): 4.68–4.66 (2H, m, C=CH_2), 4.57 (1H, t, *J* 3.0, C*H*), 3.92–3.67 (2H, m, C*H*HO and OC*H*H), 3.55–3.33 (2H, m, CH*H*O and OCH*H*), 2.01 (2H, t, *J* 6.7, CH$_2$CH_2C), 1.70 (3H, s, CH_3), 1.92–1.17 (12H, m, 6 × CH_2); δ_C (100 MHz; $CDCl_3$): 146.0 (*C*=CH$_2$), 109.6 (C=*C*H$_2$), 98.8 (*C*H), 67.5 (*C*H$_2$), 62.3 (*C*H$_2$), 37.7 (*C*H$_2$), 30.7 (*C*H$_2$), 29.6 (*C*H$_2$), 27.4 (*C*H$_2$), 25.9 (*C*H$_2$), 25.5 (*C*H$_2$), 22.3 (*C*H$_3$), 19.6 (*C*H$_2$); *m*/*z* (CI) 213 (100%, MH$^+$). Found (CI): MH$^+$ 213.1855. $C_{13}H_{24}O_2H^+$ requires 213.1855.

(*E*)- and (*Z*)-6-Methyl-7-(tetrahydropyran-2′-yl)hept-5-en-1-ol 23, 24

To a stirred solution of **22** (40 mg, 0.19 mmol) in dichloromethane (5 mL) at −30 °C was added a solution of tin tetrachloride in dichloromethane (1.0 M, 0.68 mL, 0.68 mmol) drop-wise *via* syringe. After 10 minutes at this temperature the reaction mixture was quenched by the addition of sodium hydroxide solution (2.5 M, 2 mL), diluted with dichloromethane (10 mL), washed with brine (10 mL) and the organic phase dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a yellow oil. Purification by flash column chromatography, eluting with 50% diethyl ether–40/60 petroleum ether afforded **23** and **24**, tentatively assigned as a 2 : 3 mixture of *E*/*Z* alkene isomers by integration of the signals at 5.23 (minor) and 5.18 (major) in the proton NMR spectrum, (30 mg, 75%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3401 (br, O–H), 2901, 2851, 1650 (C=C); δ_H (600 MHz; $CDCl_3$): 5.23 (1H minor, t, *J* 7.1, C=C*H*), 5.18 (1H major, t, *J* 6.9, C=C*H*), 3.94–3.89 (1H major, m, C*H*HO), 3.85–3.81 (1H minor, m, C*H*HO), 3.66–3.62 (2H major and 2H minor, m, CH*H*O and C*H*HOH), 3.43–3.36 (2H major and 2H minor, m, C*H* and CH*H*OH), 2.29–1.18 (17H major and 17H minor, m, CH_3 and 7 × CH_2); δ_C (150 MHz; $CDCl_3$): 132.2 (quat. *C*, minor), 132.1 (quat. *C*, major), 127.2 (C=*C*H, minor), 126.8 (C=*C*H, major), 76.1 (O*C*H, major), 75.4 (O*C*H, minor), 68.6 (*C*H$_2$, major), 68.2 (*C*H$_2$, minor), 62.9 (*C*H$_2$OH, major and minor), 47.0 (*C*H$_2$, major), 38.9 (*C*H$_2$, minor), 33.1 (*C*H$_2$, minor), 32.6 (*C*H$_2$, major), 32.5 (*C*H$_2$, minor), 31.8 (*C*H$_2$, minor), 31.6 (*C*H$_2$, major), 27.7 (*C*H$_2$, major), 26.1 (*C*H$_2$, major), 25.8 (*C*H$_2$, major), 24.7 (*C*H$_2$, minor), 24.5 (*C*H$_2$, minor), 24.2 (*C*H$_3$, minor), 23.7 (*C*H$_2$, minor), 23.6 (*C*H$_2$, major), 16.3 (*C*H$_3$, major); *m*/*z* (CI) 213 (100%, MH$^+$). Found (CI): MH$^+$ 213.1859. $C_{13}H_{24}O_2H^+$ requires 213.1855.

4-Methylpent-4-enoic acid

To an aqueous solution of lithium hydroxide (1.7 M, 70 mL) at 0 °C was added dropwise a solution of ethyl 4-methylpent-4-enoate (5.6 g, 34.9 mmol) in THF (140 mL). The reaction mixture was allowed to warm to room temperature and stirred vigorously for five hours. The solvent was evaporated, the resulting aqueous solution acidified to pH 1 by the dropwise addition of hydrochloric acid (3 M), and extracted with diethyl ether (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was purified by silica column chromatography eluting with diethyl ether to give 4-methylpent-4-enoic acid (4.0 g, 83%) as a pale yellow oil. ν_{max} (thin film)/cm^{-1} 3200 (br, O–H), 2970, 1709, 1654 (C=C), 1438, 1376, 1290; δ_H (200 MHz; CD_3OD): 5.08 (1H, br s, COO*H*), 4.72–4.69 (2H, m, CCH_2), 3.75–3.31 (2H, m, CH_2CO), 2.47–2.30 (2H, m, CH_2CCH$_2$), 1.73 (3H, s, CH_3CCH$_2$); δ_C (200 MHz;

CD_3OD): 175.7 (*C*OOH), 144.1 (*C*CH_2), 109.4 (C*C*H_2), 32.3 (CH_2), 32.0 (CH_2), 21.3 (*C*H_3).

Tetrahydropyran-2′-yl 4-methylpent-4-enoate 25

3,4-Dihydro-2*H*-pyran (2.4 mL, 26.3 mmol) was added dropwise to a stirred solution of 4-methylpent-4-enoic acid (10.6 g, 5.3 mmol) and camphorsulfonic acid (0.012 g, 0.053 mmol) in dichloromethane (10 mL) at 0 °C and stirred for 30 minutes at room temperature. The reaction mixture was diluted with diethyl ether (10 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was purified by silica column chromatography, eluting with 20% diethyl ether–40/60 petroleum ether, to give **25** (4.5 g, 40%) as a pale yellow oil. ν_{max} (thin film)/cm^{-1} 3078, 2943, 2850, 1712 (CO), 1651 (C=CH_2); δ_H (200 MHz; $CDCl_3$): 4.97–4.93 (1H, m, OC*H*O), 4.83–4.58 (2H, m, CH_2C), 4.05–3.70 (1H, m, *ax*-CH_2O), 3.57–3.37 (1H, m, *eq*-CH_2-O), 2.55–2.46 (2H, m, CH_2CO), 2.37–1.98 (2H, m, CH_2C), 1.87–1.43 (6H, m), 1.74 (3H, s, CH_3); δ_C (200 MHz; $CDCl_3$): 178.8 (*C*O), 143.7 (*C*CH_2), 110.4 (C*C*H_2), 65.8 (*C*H_2O), 62.8 (*C*H_2CO), 32.3 (*C*H_2C), 30.6 (CH_2), 25.4 (CH_2), 19.64 (CH_2), 22.4 (*C*H_3).

2-(5′-Methyl-2′-oxotetrahydrofuran-5′-ylmethyl)tetrahydropyran 26

A solution of tin tetrachloride in dichloromethane (1.0 M, 0.032 mL) was added dropwise to a stirred solution of **25** (0.11 g, 0.59 mmol) in dichloromethane (2.5 mL) at −78 °C, and stirred at this temperature for 10 minutes. The reaction mixture was quenched by the rapid addition of an aqueous solution of sodium hydroxide (2.5 M, 2 mL), diluted with dichloromethane (10 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a brown oil. Purification by silica column chromatography eluting with 20% diethyl ether–40/60 petroleum ether gave **26** (0.05 g, 55%, two diastereoisomers ratio 5 : 3 by integration of the CH_3 singlets at δ_H = 1.42 (major) and 1.38 (minor) in the proton NMR) as an orange oil. ν_{max} (thin film)/cm^{-1} 2936, 1770 (C=O), 1269 (C–O); δ_H (200 MHz; $CDCl_3$): 3.93–3.87 (1H, m, *ax*-CH_2O), 3.50–3.28 (1H, m, *eq*-CH_2O and C*H*O), 2.62–2.37 (2H, m, CH_2CO), 2.29–1.20 (10H, m), 1.42 (3H major, s, CH_3), 1.38 (3H minor, s, CH_3); δ_C (200 MHz; $CDCl_3$): 176.8 (*C*O), 177.2 (*C*O), 86.3 (quat.), 85.6 (quat.), 74.5 (O*C*H), 73.8 (O*C*H), 68.1 (*C*H_2O THP), 46.9 (*C*H_2CO), 46.8 (*C*H_2CO), 34.3 (CH_2), 32.7 (CH_2), 32.0 (CH_2), 29.0 (CH_2), 25.7 (CH_2), 23.4 (CH_2); *m*/*z* (EI) 85 (9%), 199 (27%), 216 (100%).

6-Benzyl-2-[(4-methylpent-4-en-1-yl)oxy]tetrahydropyran *cis*-27 and *trans*-27

A catalytic amount of (±)-camphorsulfonic acid was added to a solution of dihydropyran **31** (0.42 g, 2.4 mmol) and **12** (0.28 g, 2.8 mmol) in anhydrous dichloromethane (10 mL) under an argon atmosphere. The mixture was stirred at room temperature for 1 h, then quenched by the addition of saturated aqueous sodium bicarbonate (50 mL). Additional dichloromethane (50 mL) was added and the organic layer was separated, washed successively with saturated sodium bicarbonate (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a colourless oil; proton NMR analysis indicated that the crude product was a *ca.* 2 : 1 mixture of diastereoisomers. Purification by silica column chromatography eluting with 0% to 8% diethyl ether–40/60 petroleum ether gave first *trans*-**27** as a colourless oil (0.380 g, 57%). Found: C, 79.1; H, 9.6. $C_{18}H_{26}O_2$ requires C, 78.8; H, 9.55%; ν_{max} (thin film)/cm^{-1} 3065, 3027, 2940, 2861, 1649, 1495, 1454, 1441, 1373, 1151, 1071, 1029, 888, 749, 700; δ_H (200 MHz; $CDCl_3$): 7.15–7.31 (5H, m, Ph), 4.78 (1H, br s, 2-*H*), 4.70 (1H, br s, CC*H*H), 4.66 (1H, br s, CC*H*H), 3.87–3.99 (1H, m, 6-*H*), 3.38 (1H, dt, *J* 9.7 and 6.8, CHOC*H*H), 3.22 (1H, dt, *J* 9.7 and 6.5, CHOC*H*H), 2.79 (1H, dd, *J* 13.6 and 7.4, PhC*H*H), 2.64 (1H, dd, *J* 13.6 and 5.9, PhC*H*H), 1.93–2.03 (2H, m, CCH_2), 1.71 (3H, s, CH_3), 1.28–1.86 (8H, m); δ_C (50 MHz; $CDCl_3$): 145.4 (*C*CH_2), 139.0 (q), 129.3 (CH), 128.0 (CH), 126.0 (CH), 109.8 (C*C*H_2), 97.1 (O_2*C*H), 69.8 (O*C*H), 66.2 (O*C*H_2), 42.8 (*C*H_2C), 34.4 (CH_2), 30.9 (CH_2), 29.7 (CH_2), 27.6 (CH_2), 22.4 (CH_3), 18.2 (CH_2). Further elution gave *cis*-**27** as a colourless oil (0.226 g, 34%). Found: C, 79.1; H, 9.45. $C_{18}H_{26}O_2$ requires C, 78.8; H, 9.55%. ν_{max} (thin film)/cm^{-1} 3064, 3028, 2941, 2861, 1648, 1495, 1453, 1435, 1373, 1190, 1151, 1070, 1030, 887, 749, 699; δ_H (200 MHz; $CDCl_3$): 1.21–1.87 (8H, m), 1.72 (3H, s, Me), 2.07 (2H, br t, *J* 7.5, CCH_2), 2.71 (1H, dd, *J* 13.7 and 5.8, PhC*H*H), 2.96 (1H, dd, *J* 13.7 and 7.3, PhC*H*H), 3.38 (1H, dt, *J* 9.6 and 7.0, OC*H*H), 3.48–3.61 (1H, m, 6-*H*), 3.81 (1H, dt, *J* 9.6 and 6.7, OCH*H*), 4.33 (1H, dd, $J_{ax,ax}$ 8.9, $J_{ax,eq}$ 2.3, 2-*H*), 4.68 (1H, br s, CC*H*H), 4.71 (1H, br s, CCH*H*), 7.19–7.32 (5H, m, Ph); δ_C (50 MHz; $CDCl_3$): 145.3 (CH), 138.9 (q), 129.4 (CH), 128.0 (CH), 126.0 (CH), 109.9 (C*C*H_2), 102.2 (O_2*C*H), 77.0 (O*C*H), 68.2 (O*C*H_2), 42.5 (Ph*C*H_2), 34.2 (CH_2), 31.1 (CH_2), 30.4 (CH_2), 27.6 (CH_2), 22.4 (CH_3), 22.1 (CH_2); *m*/*z* (FIB) 273 (M + H, 10%).

2-Hydroxymethyl-3,4-dihydro-2*H*-pyran 29[16]

Lithium aluminium hydride (55 mL of a 1 M solution in ether, 0.055 mol) was added slowly over 30 min to a stirred, cooled (0 °C) solution of acrolein dimer **28** (11.28 g, 0.101 mol) in anhydrous ether (50 mL), and the resultant solution was stirred at 0 °C for a further 30 min, at room temperature for 1 h and finally heated under reflux for 1 h. The mixture was cooled to 0 °C and ethyl acetate (20 mL) was added slowly to consume the excess of $LiAlH_4$. Stirring was continued as the mixture warmed to room temperature over 30 min, and the reaction was quenched by the careful sequential addition of water (2 mL), sodium hydroxide (2 mL of 2.5 M) and water (6 mL), giving a granular white solid. The solution was filtered and the residue was washed with ether. The organic solution was washed with water and brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the alcohol **29** as a colourless oil (9.73 g, 85%). ν_{max} (thin film)/cm^{-1} 3405 br s, 3059, 2924, 1650, 1449, 1241, 1068, 998, 727; δ_H (200 MHz; $CDCl_3$): 6.39 (1H, br d, *J* 6.2, 6-*H*), 4.67–4.74 (1H, m, 5-*H*), 3.92 (1H, ddd, *J* 9.6, 6.6 and 3.4, 2-*H*), 3.55–3.77 (3H, m, CH_2O*H*), 1.59–2.21 (4H, m); δ_C (50 MHz; $CDCl_3$): 143.2 (CH), 100.7 (CH), 75.5 (OCH), 65.1 (CH_2OH), 23.8 (CH_2), 19.3 (CH_2).

2-[(*p*-Tolylsulfonyloxy)methyl]-3,4-dihydro-2*H*-pyran 30

Toluene-*p*-sulfonyl chloride (18.05 g, 95 mmol) was added to a solution of alcohol **29** (8.39 g, 74 mmol) in anhydrous pyridine (90 mL) at 0 °C under an inert atmosphere. The reaction mixture was stirred at 0 °C for 3 h and stirred at room temperature for 3 h, then poured onto ice (300 g). The product was extracted with ether (2 × 200 mL) and the combined ether extracts were washed with ice-cold hydrochloric acid (10%, 4 × 100 mL), saturated sodium bicarbonate (3 × 100 mL), brine (100 mL) and dried ($MgSO_4$). Evaporation of the volatiles *in vacuo* and recrystallisation of the crude product from diethyl ether gave the tosylate **30** as pale yellow crystals (14.86 g, 75%), which were stored at −60 °C. δ_H (200 MHz; $CDCl_3$): 1.50–2.06 (4H, m), 2.44 (3H, s, ArCH_3), 3.93–4.10 (3H, m, OC*H* and CH_2OTs), 4.62–4.70 (1H, m, 5-*H*), 6.25 (1H, dt, *J* 6.2 and 1.8, 6-*H*), 7.34 (2H, d, *J* 8.0, Ar*H*), 7.80 (2H, d, *J* 8.0, Ar*H*); δ_C (50 MHz; $CDCl_3$): 144.9 (q), 142.9 (CH), 132.7 (q), 129.8 (CH), 127.9 (CH), 100.6 (CH), 71.9 (OCH), 71.0 (OCH_2), 23.7 (CH_2), 21.6 (CH_3), 18.7 (CH_2).

2-Benzyl-3,4-dihydro-2*H*-pyran 31

A solution of phenyllithium in hexane–ether (1.8 M, 10 mL) was added dropwise over 10 min to a stirred slurry of copper(I)

iodide (1.46 g, 7.7 mmol) in ether (10 mL) at 0 °C under an argon atmosphere. The dark solution was stirred at this temperature for 10 min, and a solution of the tosylate **30** (1.82 g, 6.8 mmol) in ether (20 mL) was added slowly over 10 min. The reaction mixture was stirred at 0 °C for 2 h, and then at room temperature for 3 h, after which time the mixture was cooled to 0 °C and the reaction was quenched by the addition of water (5 mL). The organics were separated, filtered through Celite and the residue washed with ether (20 mL). The filtrate was washed with cold aqueous ammonium chloride (20 mL), aqueous ammonia (5 × 20 mL), and brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a partially solidified yellow oil. Purification by silica column chromatography eluting with 40/60 petroleum ether gave the dihydropyran **31** as a colourless oil (0.44 g, 37%). A small sample was purified for analysis by bulb-to-bulb distillation (100 °C/0.6 mmHg). Found: C, 82.9; H, 8.1. $C_{12}H_{14}O$ requires C, 82.7; H, 8.1%; ν_{max} (thin film)/cm^{-1} 3060, 3027, 2921, 2848, 1649, 1496, 1454, 1241, 1227, 1068, 1041, 767, 740, 699, 592; δ_H (200 MHz; $CDCl_3$): 1.59 (1H, dddd, *J* 13.3, 9.8, 9.7 and 6.4, 3-H_a), 1.81–1.95 (1H, m, 3-H_b), 1.96–2.07 (2H, m, 4-CH_2), 2.78 (1H, dd, *J* 13.7 and 6.6, PhCH_a), 3.01 (1H, dd, *J* 13.7 and 6.6, PhCH_b), 4.04 (1H, dddd, $J_{ax,ax}$ 9.1, $J_{H2,CH(2a)}$ 6.7, $J_{H2,CH(2b)}$ 6.6, $J_{ax,eq}$ 2.3, 2-*H*), 4.64–4.72 (1H, m, 5-*H*), 6.38 (1H, dt, *J* 6.2 and 1.8, 6-H), 7.22–7.35 (5H, m, Ph*H*); δ_C (50 MHz; $CDCl_3$) 143.7 (CH), 138.1 (q), 129.4 (CH), 128.3 (CH), 126.3 (CH), 100.4 (CH), 75.7 (OCH), 41.6 (Ph*C*H_2), 27.0 (CH_2), 19.6 (CH_2).

Rearrangement of *trans*-27 to *rel*-(2*R*,6*S*,2′*RS*)-2-benzyl-6-[(2′-methyltetrahydrofuran-2′-yl)methyl]tetrahydropyran 32

A solution of tin(IV) chloride in dichloromethane (1.0 M, 1.6 mL) was added dropwise *via* syringe to a solution of acetal *trans*-**27** (117.9 mg, 0.43 mmol) in anhydrous dichloromethane (3.0 mL) at −30 °C under an atmosphere of argon. The reaction mixture was stirred for 15 minutes, quenched by the addition of sodium hydroxide (10%, 2 mL), and stirred vigorously as the mixture warmed to room temperature. Aqueous sodium hydroxide (10%, 20 mL) and dichloromethane (20 mL) were added, the organic layer separated and the aqueous residue extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give a colourless oil. Purification by silica column chromatography eluting with 20% to 75% diethyl ether–40/60 petroleum ether gave the bis-ether **32** as a colourless oil (60.9 mg, 52%, an inseparable 3:1 ratio of diastereoisomers by integration of the CH_3 singlets in the proton NMR spectrum). ν_{max} (thin film)/cm^{-1} 3026, 2934, 2864, 1604, 1496, 1454, 1370, 1196, 1120, 1092, 1041, 700; δ_H (600 MHz; $CDCl_3$): 7.26–7.28 (2H, m, Ph*H* both diastereoisomers), 7.17–7.20 (3H, m, Ph*H* both diastereoisomers), 3.71–3.82 (2H, m, OCH_2 both diastereoisomers), 3.94–4.03 (2H, m, OC*H* both diastereoisomers), 1.33–2.00 (12H, m, both diastereoisomers), 2.88–2.92 (1H, m, PhCH*H* both diastereoisomers), 2.75–2.82 (1H, m, PhC*H*H both diastereoisomers), 1.14 (3H, s, CH_3 major diastereoisomer), 1.09 (3H, s, *C*H_3 minor diastereoisomer); δ_C (50 MHz; $CDCl_3$): 139.1 (quat., both diastereoisomers), 129.3 (CH, both diastereoisomers), 128.1 (CH, both diastereoisomers), 125.9 (CH, both diastereoisomers), 82.1 (quat., both diastereoisomers), 72.2 (CH, major diastereoisomer), 72.0 (CH, minor diastereoisomer), 68.7 (O*C*H_2, major diastereoisomer), 68.7 (O*C*H_2, minor diastereoisomer), 67.1 (CH, minor diastereoisomer), 66.5 (CH, major diastereoisomer), 44.0 (CH_2, major diastereoisomer), 43.7 (CH_2, minor diastereoisomer), 40.4 (CH_2, minor diastereoisomer), 40.2 (CH_2, major diastereoisomer), 37.5 (CH_2, major diastereoisomer), 35.4 (CH_2, minor diastereoisomer), 31.9 (CH_2, minor diastereoisomer), 31.7 (CH_2, major diastereoisomer), 29.3 (CH_2, minor diastereoisomer), 29.0 (CH_2, major diastereoisomer), 27.1 (CH_3, minor diastereoisomer), 26.1 (CH_2, minor diastereoisomer), 25.9 (CH_2, major diastereoisomer), 25.1 (CH_3, major diastereoisomer), 18.6 (CH_2, both diastereoisomers). The diastereomeric bis-heterocycles **32** could be partially separated on silica gel that had been doped with lithium chloride (Merck silica gel 9385 was suspended in a solution of LiCl in methanol; after 1 h the silica was filtered, rinsed with methanol, and dried); while a small sample of the major diastereoisomer could be obtained in good purity, its ^1H NMR spectrum yielded no further information (either in $CDCl_3$ or in C_6D_6) regarding the relative stereochemistry of the molecule. The minor diastereoisomer could not be obtained pure. Major diastereoisomer: ν_{max} (thin film)/cm^{-1} 3062, 3026, 2933, 2864, 1604, 1496, 1454, 1372, 1264, 1197, 1093, 1042, 740, 700; δ_H (200 MHz; C_6D_6): 7.12–7.29 (5H, m, Ph*H*), 4.12–4.23 (1H, m, OC*H*), 3.95–4.06 (1H, m, OC*H*), 3.73–3.81 (2H, m, 2 × OC*H*), 3.00 (1H, dd, *J* 13.4 and 6.9, PhCH*H*), 2.75 (1H, dd, *J* 13.4 and 7.0, PhC*H*H), 2.00 (1H, dd, *J* 14.2 and 8.4), 1.33–1.77 (11H, m), 1.29 (3H, s, CH_3); δ_C (50 MHz; $CDCl_3$): 139.1 (quat.), 129.3 (CH), 128.1 (CH), 125.9 (CH), 82.1 (quat.), 72.2 (CH), 68.73 (OCH_2), 66.5 (CH), 44.0 (CH_2), 40.2 (CH_2), 37.5 (CH_2), 31.7 (CH_2), 29.0 (CH_2), 25.9 (CH_2), 25.1 (CH_3), 18.6 (CH_2).

Rearrangement of *cis*-27

A solution of *cis*-**27** (25.2 mg, 91.8 mmol) in anhydrous dichloromethane (0.7 mL) at −30 °C was treated with a solution of tin(IV) chloride in dichloromethane (1.0 M, 0.34 mL) for 15 minutes and the products isolated and purified according to the procedure described for the rearrangement of unlabelled *trans*-**27** to give the bis-heterocycle **32** as a colourless oil (14.9 mg, 59%, a *ca.* 3:1 mixture of diastereoisomers by integration of the CH_3 singlets), identical (by ^1H NMR spectroscopy) to the products isolated from the rearrangement of *trans*-**27**.

4-Methyl[1,1-$^2H_2$]pent-4-en-1-ol 33

A slurry of lithium aluminium deuteride (4.72 g, 0.122 mol) in anhydrous ether (300 mL) was heated under reflux for 30 min under an argon atmosphere, then cooled to 0 °C. Ethyl 4-methylpent-4-enoate (12.5 g, 0.088 mol) in anhydrous ether (45 mL) was added slowly over 15 min, and the resulting slurry was stirred at room temperature for 30 min and then heated under reflux for 3 h. The reaction mixture was cooled to room temperature and ethyl acetate (10 mL) was added to consume the excess of $LiAlD_4$. Sequential addition of water (5 mL), aqueous sodium hydroxide (10%, 7 mL), and water (15 mL) gave a granular white solid that was separated by filtration. Evaporation of the solvent gave a pale yellow oil which was dissolved in ether (20 mL), washed successively with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Distillation of the residue through a short Vigreaux column gave **33** as a colourless liquid (7.36 g, 82%), bp 150–155 °C. ν_{max} (thin film)/cm^{-1} 3345 (br), 3074, 2969, 2936, 2194, 2088, 1649, 1445, 1374, 1135, 1101, 965, 888; δ_H (200 MHz; $CDCl_3$): 4.68–4.70 (2H, m, CCH_2), 2.07 (2H, br t, *J* 7.6, 3-CH_2), 1.87 (1H, br s, O*H*), 1.72 (3H, s, CH_3), 1.67 (2H, br t, *J* 7.4, 2-CH_2); δ_C (50 MHz; $CDCl_3$): 145.2 (*C*CH_2), 109.8 (C*C*H_2), 61.3 (q, *J* 21.4, *C*D_2OH), 33.8 (CH_2), 30.2 (CH_2), 22.1 (CH_3).

[*phenyl*-$^2H_5$]-2-Benzyl-3,4-dihydro-2*H*-pyran 34

A solution of d_5-bromobenzene (3.12 g, 19.3 mmol) in anhydrous THF (25 mL) was added to a slurry of magnesium powder (1.2 g, 49.4 mmol, preactivated with a crystal of I_2) in THF (10 mL), the mixture heated under reflux for 1 h and cooled to room temperature. The dark supernatant solution was added *via* cannula to a stirred solution of the tosylate **30** (3.14 g, 11.7 mmol) containing copper(I) iodide (2.46 g, 12.9 mmol) in THF (20 mL) at 0 °C, and the mixture stirred at 0 °C

for 3 h and then at room temperature for 6 days. Addition of water (3 mL) and work-up as described for unlabelled **31** followed by purification by silica chromatography eluting with 0% to 8% diethyl ether–40/60 petroleum ether, gave the title dihydropyran **34** as a colourless oil (0.1111 g, 5.3%). ν_{max} (thin film)/cm^{-1} 3058, 2920, 2848, 2360, 2273, 1649, 1447, 1435, 1384, 1241, 1226, 1066, 1042, 728; δ_H (200 MHz; $CDCl_3$): identical to the ^{1}H NMR spectrum for the unlabelled dihydropyran **31** except that the signal 7.22–7.35 (m) was absent as a result of deuterium incorporation; δ_C (50 MHz; $CDCl_3$): 143.7 (CH), 137.9 (q), 129.0 (t, *J* 23.8, CD), 127.8 (t, *J* 24.3, CD), 125.8 (t, *J* 24.3, CD), 100.4 (CH), 75.7 (OCH), 41.5 (Ph*C*H$_2$), 27.1 (CH_2), 19.6 (CH_2); *m*/*z* (EI) 179 (M^+, 1%), 135 (2%), 122 (1%), 96 (3%), 86 (36%), 84 (48%), 51 (35%), 49 (100%). HRMS (EI): 179.1347. Calc. for $C_{12}H_9{}^2H_5O$: 179.1359.

6-Benzyl-2-{[1,1-^{2}H$_2$]-4-methylpent-4-en-1-yl]oxy}tetrahydropyrans *cis*-35 and *trans*-35

Addition of the alcohol **33** (0.294 g, 2.88 mmol) to the dihydropyran **31** (0.310 g, 1.78 mmol) according to the protocol described above for the synthesis of **27** gave, after work-up and purification by silica column chromatography eluting with 0% to 8% diethyl ether–40/60 petroleum ether, first *trans*-**35** (138 mg, 28%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3064, 3027, 2938, 2183, 2085, 1649, 1496, 1454, 1440, 1373, 1170, 1125, 1093, 1017, 951, 887, 747, 699. Proton NMR identical to unlabelled *trans*-**27**, but lacking the signals at 3.38 and 3.22 ppm due to deuterium incorporation. δ_C (50 MHz; $CDCl_3$): 145.4 (*C*CH_2), 139.0 (q), 129.3 (CH), 128.0 (CH), 125.9 (CH), 109.8 (C*C*H$_2$), 97.1 (O_2*C*H), 69.8 (O*C*H), 65.5 (qn, *J* 21.0, O*C*D$_2$), 42.8 (*C*H$_2$C), 34.3 (CH_2), 30.9 (CH_2), 29.7 (CH_2), 27.3 (CH_2), 22.4 (CH_3), 18.2 (CH_2); *m*/*z* (FIB) 275 (MH^+, 10%). HRMS (FIB): 275.1976 (MH^+). Calculated for $C_{18}H_{23}{}^2H_2O_2$: 275.1980. Further elution gave the *cis*-**35** (32.1 mg, 6.5%). δ_H (200 MHz; $CDCl_3$): identical to the ^{1}H NMR spectrum for *cis*-**27** except that the signals 3.38 (dt) and 3.81 (dt) for the diastereotopic OCH_2 were absent as a result of deuterium incorporation; δ_C (50 MHz; $CDCl_3$): identical to the ^{13}C NMR spectrum for *cis*-**27** except that the signal at 68.2 (OCH_2) was absent as a result of deuterium incorporation.

[*phenyl*-^{2}H$_5$]-6-Benzyl-2-{[1,1-^{2}H$_2$]-4-methylpent-4-en-1-yloxy}-tetrahydropyran *cis*-36 and *trans*-36

Addition of the d_2-alcohol **33** (0.301 g, 2.95 mmol) to the d_5-dihydropyran **34** (0.1174 g, 0.655 mmol) according to the protocol described above for the synthesis of acetal **27** gave, after work-up and purification by silica column chromatography eluting with 0% to 8% diethyl ether–40/60 petroleum ether, first the *trans*-**36** as the first-eluting fraction (108.2 mg, 59%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3073, 2938, 2274, 2183, 2086, 1649, 1570, 1440, 1373, 1350, 1262, 1202, 1170, 1125, 1092, 1013, 950, 887, 844, 820; δ_H (200 MHz; $CDCl_3$): identical to the ^{1}H NMR spectrum for *trans*-**27** except that the signals 3.22 (dt) and 3.38 (dt) for the diastereotopic OCH_2, and 7.15–7.31 (m) for PhH, were absent as a result of deuterium incorporation; δ_C (50 MHz; $CDCl_3$): 145.4 (*C*CH_2), 138.8 (q), 129.7 (t, *J* 24.0, CD), 128.3 (t, *J* 24.2, CD), 126.2 (t, *J* 24.0, CD), 109.8 (C*C*H$_2$), 97.1 (O_2*C*H), 69.8 (OCH), 65.9 (qn, *J* 21.5, O*C*D$_2$), 42.7 (CH_2), 34.3 (CH_2), 30.9 (CH_2), 29.7 (CH_2), 27.3 (CH_2), 22.4 (CH_3), 18.2 (CH_2); *m*/*z* (FIB) 280 (MH^+, 11%). Further elution gave *cis*-**36** as a colourless oil (50.5 mg, 27%). ν_{max} (thin film)/cm^{-1} 3073, 2939, 2850, 2274, 2190, 2087, 1649, 1570, 1441, 1392, 1330, 1186, 1156, 1066, 1034, 1022, 932, 887, 845, 821; δ_H (200 MHz; $CDCl_3$): identical to the ^{1}H NMR spectrum for *cis*-**27** except that the signals at 3.38 (dt) and 3.81 (dt) ppm for the diastereotopic OCH_2, and at 7.19–7.32 (m) ppm for PhH, were absent as a result of deuterium incorporation; δ_C (50 MHz; $CDCl_3$): 145.3 (*C*CH_2), 138.7 (quat.), 128.9 (t, *J* 23.5, CD), 128.0 (t, *J* 24.5, CD), 125.5 (t, *J* 24.0, CD), 109.8 (C*C*H$_2$), 102.1 (O_2*C*H), 76.9 (O*C*H), 67.5 (qn, *J* 21.4, O*C*D$_2$), 42.4 (CH_2), 34.1 (CH_2), 31.0 (CH_2), 30.4 (CH_2), 27.4 (CH_2), 22.4 (CH_3), 22.1 (CH_2); *m*/*z* (FIB) 280 (MH^+, 10%).

Rearrangement of *trans*-35

A solution of tin(IV) chloride in dichloromethane (1.0 M, 1.6 mL) was added slowly drop-wise *via* syringe to a stirred solution of D_2 labelled *trans*-**35** (125.5 mg, 0.45 mmol) in anhydrous dichloromethane (3.0 mL) at −30 °C under an argon atmosphere. The reaction mixture was stirred at −30 °C for 30 min, quenched by the addition of aqueous sodium hydroxide (2 M, 1 mL), and stirred vigorously as the mixture warmed to room temperature. Aqueous sodium hydroxide (2 M, 20 mL) and dichloromethane (20 mL) were added and the product was extracted into the organic layer. The organic extract was washed with sodium hydroxide (2 M, 10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by silica column chromatography eluting with 0% to 15% diethyl ether–40/60 petroleum ether gave bicyclic ether **37** as a colourless oil (95.8 mg, 76%, an inseparable of two diastereoisomers in the ratio *ca.* 1 : 2.8 by integration of the CH_3 singlets in the proton NMR). ν_{max} (thin film)/cm^{-1} 3026, 2938, 2865, 2200, 2091, 1604, 1496, 1454, 1371, 1195, 1088, 1038, 1006, 741, 700; δ_H (200 MHz; $CDCl_3$): 7.14–7.32 (5H, m, Ph*H* both diastereoisomers), 3.91–4.04 (2H, m, both diastereoisomers), 2.71–2.96 (2H, m, PhC*H*$_2$ both diastereoisomers), 1.26–2.04 (12H, m, both diastereoisomers), 1.14 (3H, s, CH_3 major diastereoisomer), 1.09 (3H, s, C*H*$_3$ minor diastereoisomer); δ_C (50 MHz; $CDCl_3$): 139.1 (quat., both diastereoisomers), 129.3 (CH, both diastereoisomers), 128.2 (CH, both diastereoisomers), 125.9 (CH, both diastereoisomers), 82.1 (quat., both diastereoisomers), 72.2 (CH, major diastereoisomer), 72.0 (CH, minor diastereoisomer), 68.73 (CH, major diastereoisomer), 68.66 (CH, minor diastereoisomer), 44.0 (CH_2, major diastereoisomer), 43.7 (CH_2, minor diastereoisomer), 40.4 (CH_2, minor diastereoisomer), 40.2 (CH_2, major diastereoisomer), 37.5 (CH_2, major diastereoisomer), 35.4 (CH_2, minor diastereoisomer), 31.9 (CH_2, minor diastereoisomer), 31.7 (CH_2, major diastereoisomer), 29.2 (CH_2, minor diastereoisomer), 29.0 (CH_2, major diastereoisomer), 27.1 (CH_3, minor diastereoisomer), 25.9 (CH_2, minor diastereoisomer), 25.6 (CH_2, major diastereoisomer), 25.1 (CH_3, major diastereoisomer), 18.6 (CH_2, both diastereoisomers); *m*/*z* (FIB) 277 (M + H, 66%). HRMS (FIB): 277.2136 (MH^+). Calc. for $C_{18}H_{25}{}^2H_2O_2$: 277.2137.

Rearrangement of *cis*-35

Treatment of acetal *cis*-**35** (21.0 mg, 76.0 mmol) with a solution of tin(IV) chloride in dichloromethane (1.0 M, 0.3 mL) in anhydrous dichloromethane (0.7 mL) at −30 °C for 30 min followed by isolation and purification of the products as described for *trans*-**35** gave bis-heterocycle **37** as a colourless oil (15.4 mg, 73%, inseparable mixture of two diastereoisomers, dr = 1 : 2.8 by integration of the CH_3 singlets at 1.09 and 1.14 ppm in the proton NMR spectrum), identical by ^{1}H NMR with the sample prepared above except for the slight difference in relative integration between the signals for the major and minor diastereoisomers.

Crossover experiment: rearrangement of a mixture of *cis*-27 and *cis*-36 acetals

A solution of tin(IV) chloride in dichloromethane (1.0 M, 0.90 mL) was added dropwise *via* syringe to a solution of *cis*-**27** (33.7 mg, 0.119 mmol) and *cis*-**36** (33.4 mg, 0.119 mmol) (total acetal: 0.238 mmol) in anhydrous dichloromethane (2.5 mL) at −30 °C under an atmosphere of argon. The reaction mixture

was stirred at this temperature for 1 h, quenched by the addition of aqueous sodium hydroxide (10%, 2.5 mL) and allowed to warm to room temperature. Dichloromethane (20 mL) and aqueous sodium hydroxide (10%, 10 mL) were added and the product was extracted into the organic layer. The aqueous layer was re-extracted with fresh dichloromethane (2 × 20 mL) and the combined organic layers were washed with aqueous sodium hydroxide (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. Purification by silica column chromatography eluting with 5% to 15% diethyl ether–40/60 petroleum ether gave a mixture of the bis-heterocycles **32**, **37**, **38** and **39** as a colourless oil (50.6 mg, 75%, a *ca.* 1:3 mixture of diastereoisomers). *m/z* (FIB) 275 [$M(d_0)H^+$, 26%], 277 [$M(d_2)H^+$, 22%], 280 [$M(d_5)H^+$, 24%], 282 [$M(d_7)H^+$, 18%].

Crossover experiment: rearrangement of a mixture of *cis*-27 and *trans*-36

A solution of *cis*-**27** (37.6 mg, 0.137 mmol) and *trans*-**36** (37.6 mg, 0.134 mmol) (total acetal: 0.271 mmol) in anhydrous dichloromethane (2.9 mL) at −30 °C was treated with a solution of tin(IV) chloride in dichloromethane (1.0 M, 1.0 mL) and the products isolated and purified according to the crossover protocol described above to give the rearranged products **32**, **37**, **38** and **39** as a colourless oil (52.0 mg, 69%, a *ca.* 1:3 mixture of diastereoisomers). *m/z* (FIB) 275 [$M(d_0)H^+$, 27%], 277 [$M(d_2)H^+$, 16%], 280 [$M(d_5)H^+$, 20%], 282 [$M(d_7)H^+$, 18%].

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