The synthesis of mono- and bicyclic ethers *via* acid catalysed ring-opening cyclisation of tetrahydropyranyl ether derivatives

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A range of monocyclic and bicyclic alkenols were synthesised *via* acid catalysed ring-opening cyclisation of homoallylic tetrahydropyranyl ether derivatives in excellent yield. Upon palladium catalysed hydrogenation these products were reduced with excellent diastereoselectivity to the corresponding saturated cyclic alcohols in essentially quantitative yield.

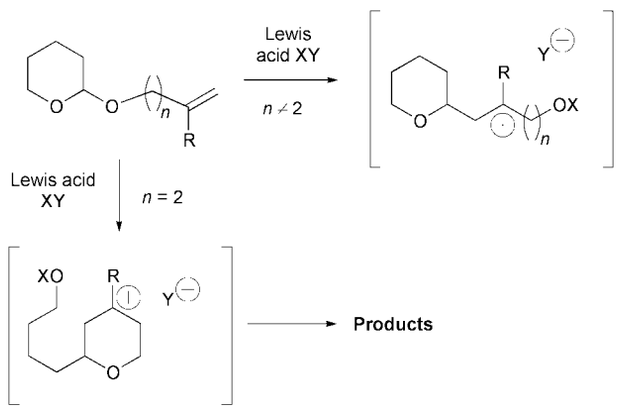
Introduction

The profusion of bioactive natural products containing pyran and furan ring systems exhibiting carbon linked substituents adjacent to the heteroatom has led to the development of several methods for their synthesis in recent years.[1] In the previous paper we described our work on the oxygen to carbon rearrangement of anomerically linked alkenols as a method useful for introducing carbon functionality directly at the anomeric centre.[2] Here we discuss our findings on a related but distinct methodology, the acid catalysed ring-opening-cyclisation of tetrahydropyran ring systems by anomerically linked homoallylic alcohols.

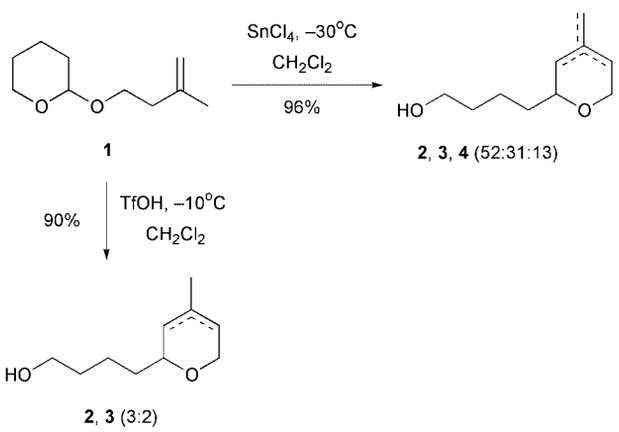
Prins-type cyclisations[3] of this type have been known in the literature for many decades and rely on the formation of an oxocarbenium cation intermediate derived from a homoallylic alcohol which is subsequently attacked by the alkene appendage. The oxocarbenium cation intermediates can be formed through direct condensation of the homoallylic alcohol with a carbonyl compound[4] or from acid promoted cleavage of a linked acetal.[5] Upon cyclisation, the fate of the generated carbocationic intermediate depends upon the nature of the substrate and/or the reaction conditions employed. Elegant variations of this reaction, in which the homoallylic alcohol is generated *in situ* prior to oxocarbenium cation formation and cyclisation have been reported.[6] Unsurprisingly, this type of cyclisation has been used widely in synthesis.[7]

The work presented here stems from our studies on anomerically linked alkenols and is based on the observation that Lewis acid mediated anomeric oxygen to carbon rearrangement is superseded by a Prins-type cyclisation when the alkenol is homoallylic (Scheme 1).

In this paper we show that treatment of a variety of homoallylic tetrahydropyranyl ether substrates with Brönsted acid suffices to drive this reaction to completion, and results in the formation of pyranyl products. Finally, we discuss our findings on an unexpected diastereoselective palladium catalysed hydrogenation of these alkenic products, resulting in a simple procedure for the diastereoselective production of substituted mono- and bicyclic ethers.



Scheme 1



Scheme 2

Cyclisation reactions

In the course of our studies on the oxygen to carbon rearrangement of a series of anomerically linked alkenols we synthesised substrate **1** *via* the tetrahydropyranylation of 3-methylbut-3-en-1-ol (Scheme 2). Compound **1** underwent a rearrangement reaction on treatment with tin tetrachloride in dichloromethane at −30 °C. Careful NMR analysis of the product and that of a derivative[8] led us to the conclusion that, rather than the substrate undergoing an anomeric oxygen to carbon rearrangement, cyclisation of the alkene to the anomeric centre had occurred to give a mixture of three regioisomeric alkenols **2**, **3** and **4** in the ratio 52 : 31 : 13, in near quantitative yield. This reaction is of the Prins-type, and such reactions may generally be performed with either Lewis or protic acid with trapping of the intermediate carbocation by solvent or counter-ion as a commonly observed side-reaction.[3–7] In this case, however, regeneration of the alkene occurs *via* an

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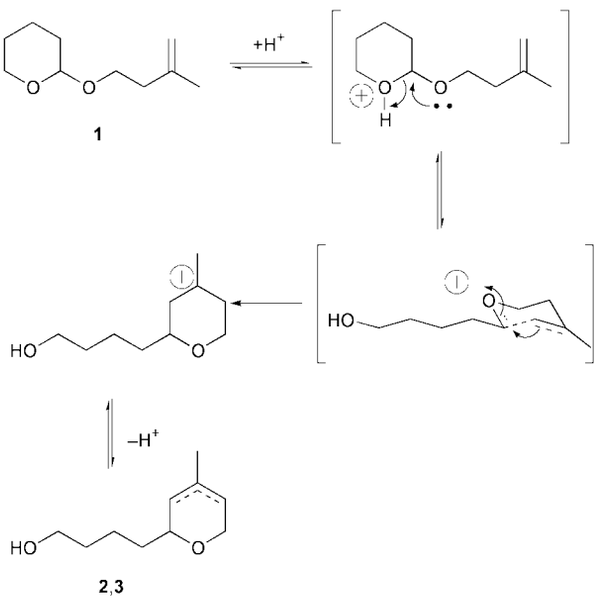
elimination process. A protic acid promoted cyclisation of **1** was then attempted, and indeed treatment with one equivalent of trifluoromethanesulfonic acid in dichloromethane at −10 °C gave alkenols **2** and **3** in 90% yield in the ratio 3:2. It is precedented that in the presence of protic acid, concurrent isomerisation of the *exo*-double bond into the ring system can occur, resulting in only two regioisomers.[9]

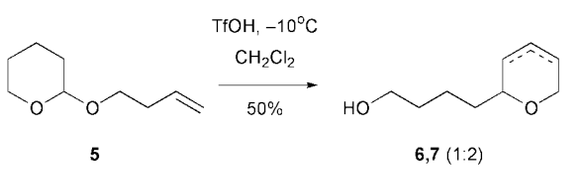
The reaction proceeds by reversible acid promoted ring-opening to give an acyclic oxonium species followed by irreversible ring closure to the cyclic ether (Scheme 3). Apparently this



Scheme 3

reaction pathway is favoured to the complete exclusion of the previously observed anomeric oxygen to carbon rearrangement, and it seems likely that ring-opening is a general feature of such tetrahydropyranyl ether systems in the presence of Lewis or protic acids. In this case the incipient oxocarbenium cation is trapped by the alkene due to the favourable nature of the six-member ring transition state.[10] Subsequent acid catalysed alkene isomerisation then occurs to give the final products, and the overall process is in principle catalytic in protic acid.

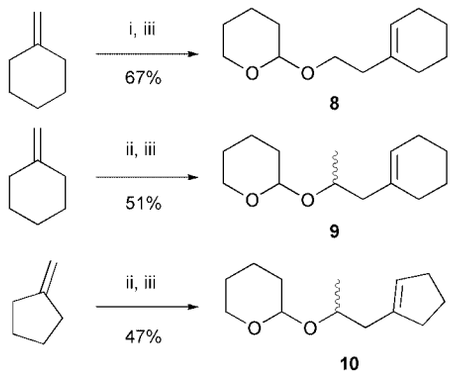
Less electron rich alkenes also readily undergo the cyclisation reaction, and on exposure to the same acidic conditions described above tetrahydropyranyl ether **5** underwent rearrangement to the corresponding cyclic alkenols **6** and **7** in the ratio 1:2, albeit in slightly lower yield (50%), presumably due to the less reactive nature of the alkene (Scheme 4).



Scheme 4

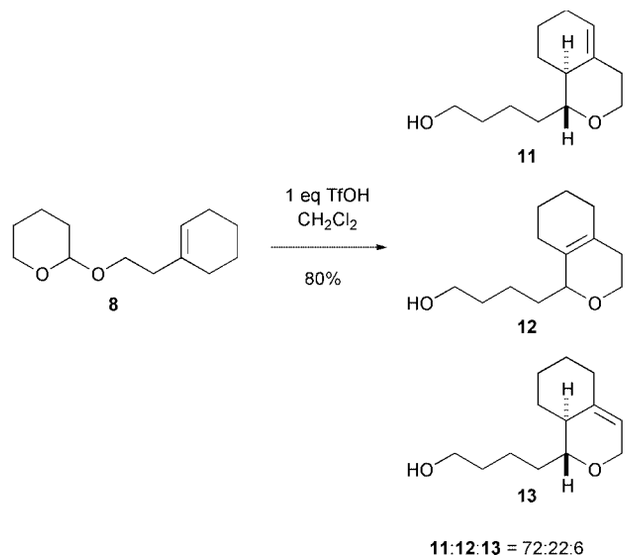
In order to extend the range of the reaction to include highly substituted alkenes, rearrangement substrates **8**, **9** and **10** were prepared from the corresponding cyclic alkenols, synthesised *via* the Lewis acid promoted ene reaction[11] of paraformaldehyde or acetaldehyde with commercially available exocyclic alkenes (Scheme 5).

Trifluoromethanesulfonic acid promoted cyclisation of **8** gave bicyclic ethers **11**, **12** and **13** in 80% combined yield (Scheme 6). Not only does the reaction exhibit moderate regioselectivity, giving a **11**:**12**:**13** ratio of 72:22:6 by proton NMR



i. $(OCH_2)_n$, Me_2AlCl.
ii. CH_3CHO, Me_2AlCl.
iii. DHP, cat. CSA.

Scheme 5



Scheme 6

and gas chromatography, but **11** and **13** are also formed diastereoselectively.

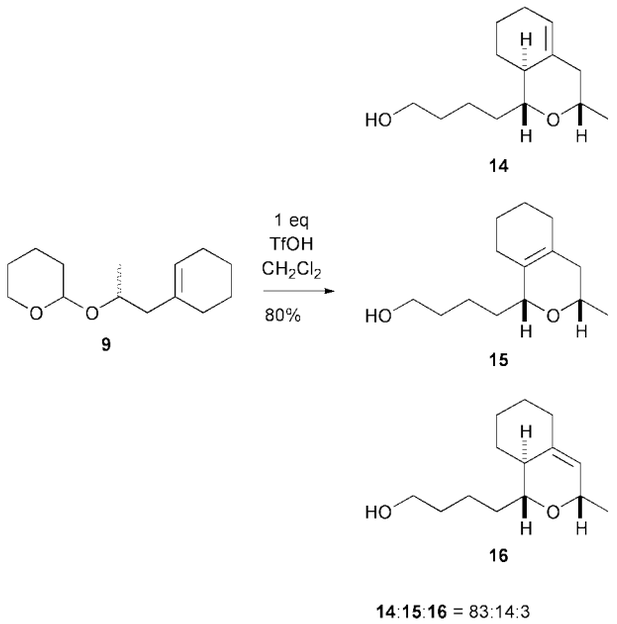
Analogous rearrangement of ether **9** gave a similar ratio of alkene isomers **14**–**16** (**14**:**15**:**16** = 83:14:3) in 80% combined yield. The methyl group in the side chain of **9** exerts a high degree of stereocontrol at the former anomeric position, resulting in isolation of the products as single diastereoisomers (Scheme 7).

Finally, the tetrahydropyranyl cyclopentenyl ether **10** rearranged with 0.5 eq. of acid, and with remarkable diastereo- and regioselectivity resulting in only one product by NMR, the fused six/five member bicycle **17**, in 65% yield, with the alkene in the five member ring (Scheme 8). This result is consistent with the common observation that alkenes tend to isomerise *endo*- rather than *exo*- in five member fused ring systems.

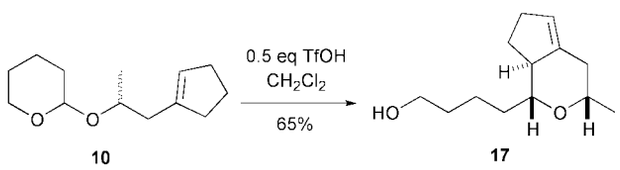
In further experiments we have controlled the elimination/isomerisation pathway with a silyl group β- to the carbocationic centre, allowing individual alkenols to be produced.[12] Trimethylsilyl containing substrates **18** and **19** were synthesised from the corresponding alkenols (Scheme 9); in order to avoid final alkene isomerisation or degradation of the starting materials by protic acid, an excess of tin tetrachloride was used as the promoter, in dichloromethane at −30 °C. In each case the desired Lewis acid promoted rearrangement occurred with smooth elimination of the trimethylsilyl group, to give alkenols **6** (50% yield) and **4** (77% yield) as single regioisomers.

Catalytic hydrogenation studies

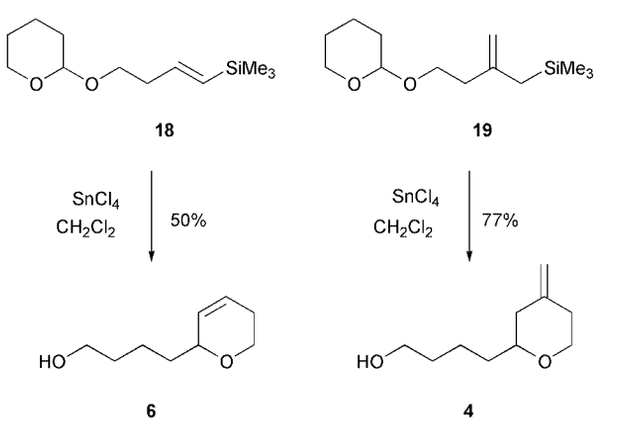
In the rearrangement of **1** presented above it was found expedi-



Scheme 7

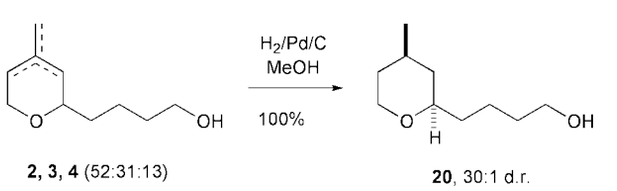


Scheme 8



Scheme 9

ent to simplify the NMR spectra of the products by palladium catalysed hydrogenation of the alkenes in methanol, under 1 atmosphere of hydrogen at room temperature (Scheme 10). The



Scheme 10

fully saturated cyclic ether **20** was produced as a 30 : 1 mixture of diastereoisomers (by proton NMR), separable by column chromatography, in quantitative yield.

Pleased with the efficient and highly diastereoselective nature of this hydrogenation [13] (de > 93%), we looked at the hydrogenation of several of the other rearrangement products synthesised above. Our findings are detailed in the remainder of this paper.

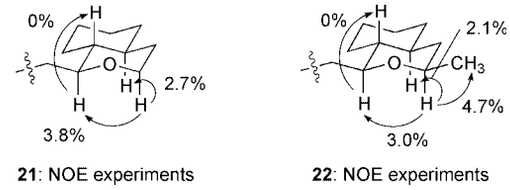
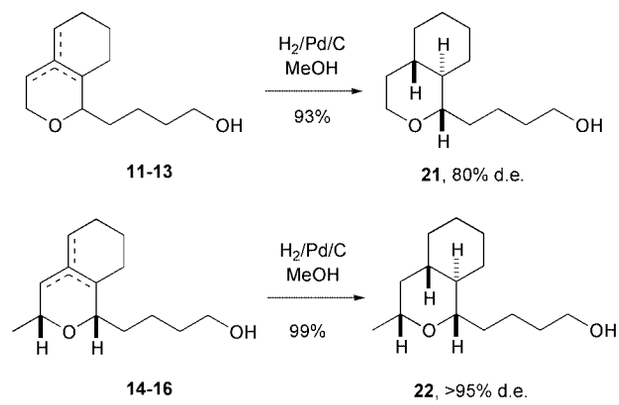


Fig. 1

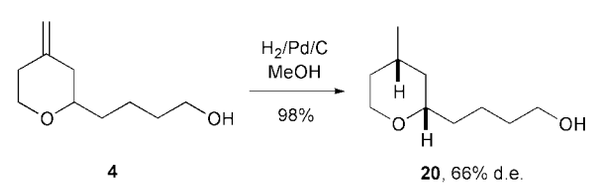
As our starting point we investigated the hydrogenation of the bicyclic alkenols **11**–**13** and **14**–**16**; as we had hoped, hydrogenation of these substrates by catalytic palladium on carbon under 1 atmosphere of hydrogen at room temperature gave saturated fused heterocycles **21** (93% yield, 80% de) and **22** (99%, >95% de) (Scheme 11).[14]



Scheme 11

The full assignment of the relative stereochemistry in **21** and **22** was made possible by observation of the NOE between each of the axial protons (Fig. 1).

The efficiency and selectivity shown by the overall sequence of rearrangement followed by hydrogenation are impressive considering that it results in the controlled formation of up to three new stereogenic centres and a cyclic ether in two high-yielding steps. Interestingly, the *exo*-alkene **4**, hydrogenated under the same conditions, gave saturated cyclic ether **20** in 98% yield but in only 66% diastereoisomeric excess, compared to >93% de for hydrogenation of the *endo*/*exo* alkene mixture **2**–**4** (Scheme 12).



Scheme 12

It is possible that the origin of the selectivity in these hydrogenation reactions arises from co-ordination of the alkene *and* the heterocyclic oxygen atom to the surface of the palladium, holding the substrate in place and resulting in preferential hydrogenation from one face; [15] the increased remoteness of the *exo*-alkene in **4** from the ring oxygen may prevent such a two-point binding, and this could account for the lower diastereoselectivity seen in its hydrogenation. However, the possibility of palladium catalysed alkene isomerisation [16] prior to hydrogenation, leading to the thermodynamically most stable products, could also be a contributing factor to the observed stereoselectivity and should not be ruled out.

Conclusions

In this paper we have shown that a range of homoallylic tetrahydropyranyl ether substrates on treatment with trifluoro-

methanesulfonic acid is prone to undergo a ring-opening cyclisation reaction of the Prins-type resulting in the generation of cyclic alkenol products. Furthermore, we have demonstrated that the products of these reactions may be hydrogenated in excellent yield and with good to excellent diastereoselectivity, resulting in an overall two-step stereoselective sequence of rearrangement/hydrogenation which provides rapid access to substituted mono- and bicyclic ether systems.

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 ($\delta_C = 77.0$ ppm). 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-(3′-Methylbut-3′-enyloxy)tetrahydropyran 1

To a stirred solution of 3-methylbut-3-en-1-ol (3.0 g, 35 mmol) and pyridinium toluene-*p*-sulfonate (10 mg) in dichloromethane (60 mL) at ambient temperature was added 3,4-dihydro-2*H*-pyran (4.6 g, 53 mmol) drop-wise *via* syringe. Stirring was maintained for 6 hours before the reaction mixture was washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a yellow oil. Purification by flash column chromatography, eluting with 10% ethyl acetate–40/60 petroleum ether, gave **1** (5.24 g, 86%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2942, 2871, 1650 (C=C); δ_H (200 MHz; $CDCl_3$): 4.72–4.69 (2H, m, C=CH_2), 4.56 (1H, t, *J* 3.0, OC*H*O), 3.88–3.75 (2H, m, C*H*HO and OC*H*H), 3.53–3.41 (2H, m, CH*H*O and OCH*H*), 2.28 (2H, t, *J* 7.1, CH_2C=CH_2), 1.79 (3H, s, CH_3), 1.91–1.43 (6H, m, 3 × CH_2); δ_C (50 MHz; $CDCl_3$): 134.5 (*C*=CH_2), 111.2 (C=*C*H_2), 98.6 (*C*H), 66.0 (*C*H_2), 62.1 (*C*H_2), 37.7 (*C*H_2), 30.6 (*C*H_2), 25.4 (*C*H_2), 22.7 (*C*H_3), 19.5 (*C*H_2); *m*/*z* (CI) 171 (100%, MH^+). Found (CI): MH^+ 171.1385. $C_{10}H_{18}O_2H^+$ requires 171.1385.

4-(4′-Methyl-5′,6′-dihydro-2*H*-pyran-2′-yl)butan-1-ol 2, 4-(4′-methyl-3′,6′-dihydro-2*H*-pyran-2′-yl)butan-1-ol 3 and 4-(4′-methylenetetrahydropyran-2′-yl)butan-1-ol 4

To a stirred solution of **1** (400 mg, 2.28 mmol) in dichloromethane (8 mL) at −10 °C was added trimethylsilyl trifluoromethanesulfonate (504 mg, 2.28 mmol) drop-wise *via* syringe. Stirring was maintained at this temperature for 30 minutes, before the reaction mixture was diluted with ether (30 mL), washed with phosphate buffer (20 mL, pH 7.5), extracted into ether (3 × 20 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 **2**, **3** and **4**, an inseparable mixture of alkenes in the ratio 52:31:13 **2**:**3**:**4** by 200 MHz proton NMR spectroscopy and GC analysis (3 compounds with retention times 13.68, 14.18 and 14.45 minutes in the ratio 13:31:52) (362 mg, 96%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3382 (br, O–H), 2933, 1680, 1656 (C=C); δ_H (200 MHz; $CDCl_3$): 5.37 (1H **2**, s, C=C*H*), 5.29 (1H **3**, s, C*H*=C), 4.70 (1H **4**, s, C=C*H*H), 4.69 (1H **4**, s, C=CH*H*), 4.05 (1H **4**, ddd, *J* 10.8, 5.4 and 1.6, OC*H*), 3.99–3.90 (2H **2** and 2H **3**, m, C*H*HO and C*H*HOH), 3.63 (2H **4**, t, *J* 6.2, CH_2OH), 3.60–3.40 (3H **2** and 3H **3**, m, CH*H*O, OC*H* and CH*H*OH), 3.34 (1H **4**, td, *J* 11.7 and 3.1, CH*H*O), 3.26–3.16 (1H **4**, m, CH*H*O), 2.29–1.34 (11H **2**, 11H **3** and 10H **4**, m, 5 × CH_2 (**4**), CH_3 and 4 × CH_2 (**2** and **3**); δ_C (50 MHz; $CDCl_3$): 144.64 (*C*=CH$_2$, **4**), 132.2 (*C*=CH, **2**), 131.7 (CH=*C*, **3**), 123.8 (C=*C*H, **2**), 119.6 (*C*H=C, **3**), 108.2 (C=*C*H$_2$, **4**), 78.7 (O*C*H, **4**), 73.8 (O*C*H, **2**), 73.7 (O*C*H, **3**), 68.6 (*C*H$_2$, **4**), 63.4 (*C*H$_2$, **3**), 62.7 (*C*H$_2$, **4**), 62.6 (*C*H$_2$, **3**), 62.5 (*C*H$_2$, **2**), 62.4 (*C*H$_2$, **2**), 41.1 (*C*H$_2$, **4**), 35.8 (*C*H$_2$, **2** and **4**), 35.4 (*C*H$_2$, **3**), 35.2 (*C*H$_2$, **4**), 35.1 (*C*H$_2$, **2**), 32.6 (*C*H$_2$, **2**, **3** and **4**), 30.0 (*C*H$_2$, **3**), 23.0 (*C*H$_3$, **2**), 22.9 (*C*H$_3$, **3**), 21.4 (*C*H$_2$CH$_2$OH, **3**), 21.6 (*C*H$_2$CH$_2$OH, **2** and **4**); *m*/*z* (CI) 171 (100%, MH^+). Found (CI): MH^+ 171.1385. $C_{10}H_{18}O_2H^+$ requires 171.1385.

4-(4′-Methyl-5′,6′-dihydro-2*H*-pyran-2′-yl)butan-1-ol 2 and 4-(4′-methyl-3′,6′-dihydro-2*H*-pyran-2′-yl)butan-1-ol 3

To a stirred solution of 3-methylbut-3-en-1-ol tetrahydropyranyl ether **1** (100 mg, 0.59 mmol) in dichloromethane (2 mL) at −10 °C was added trifluoromethanesulfonic acid (0.050 mL, 0.59 mmol) drop-wise *via* syringe. Stirring was maintained at this temperature for 10 minutes before the reaction mixture was quenched by the addition of phosphate buffer (10 mL, pH 7.5), and extracted with ether (3 × 10 mL). The combined extracts were 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, gave a mixture of **2** and **3**, 3:2 ratio of **2**:**3**, by integration of the singlets at 5.37 (major) and 5.29 (minor) in the proton NMR spectrum and GC analysis (2 compounds with retention times 14.19 and 14.46 minutes in the ratio 3:2) (90 mg, 90%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3279 (br, O–H), 2937, 1659 (C=C); δ_H (200 MHz; $CDCl_3$): 5.37 (1H **2**, s, C=C*H*), 5.29 (1H **3**, s, C*H*=C), 3.99–3.90 (2H **2** and 2H **3**, m, C*H*HO and C*H*HOH), 3.60–3.40 (3H **2** and 3H **3**, m, CH*H*O, OC*H* and CH*H*OH), 2.29–1.34 (11H **2** and 11H **3**, m, 4 × CH_2 and CH_3); δ_C (50 MHz; $CDCl_3$): 132.2 (*C*=CH$_2$, **2**), 131.7 (CH=*C*, **3**), 123.9 (C=*C*H, **2**), 119.8 (*C*H=C, **3**), 73.7 (O*C*H, **2**), 73.6 (O*C*H, **3**), 63.7 (*C*H$_2$, **3**), 62.5 (*C*H$_2$, **3**), 62.6 (*C*H$_2$, **2**), 62.4 (*C*H$_2$, **2**), 35.8 (*C*H$_2$, **2**), 35.4 (*C*H$_2$, **3**), 35.1 (*C*H$_2$, **2**), 32.6 (*C*H$_2$, **2** and **3**), 30.2 (*C*H$_2$, **3**), 23.0 (*C*H$_3$, **2**), 22.9 (*C*H$_3$, **3**), 21.4 (*C*H$_2$CH$_2$OH, **3**), 21.5 (*C*H$_2$CH$_2$OH, **2**); *m*/*z* (CI) 171 (100%, MH^+). Found (CI): MH^+ 171.1385. $C_{10}H_{18}O_2H^+$ requires 171.1385.

4-(4′-Methylenetetrahydropyran-2′-yl)butan-1-ol 4

To a stirred solution of **19** (150 mg, 0.61 mmol) in dichloromethane (6 mL) at −30 °C was added a solution of tin tetrachloride in dichloromethane (1.0 M, 0.61 mL, 0.61 mmol) drop-wise *via* syringe. Stirring was maintained at this temperature for 30 minutes before the reaction mixture was quenched by the rapid addition of sodium hydroxide solution (2.5 M, 2.0 mL), and diluted with dichloromethane (10 mL). The organic

layer was 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 50% diethyl ether–40/60 petroleum ether gave **4** (80 mg, 77%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3394 (br, O–H), 2937, 2859, 1654 (C=C); δ_H (200 MHz; $CDCl_3$): 4.70 (1H, s, C=C*H*H), 4.69 (1H, s, C=CH*H*), 4.05 (1H, ddd, *J* 10.8, 5.4 and 1.6, OC*H*), 3.63 (2H, t, *J* 6.2, CH_2OH), 3.34 (1H, td, *J* 11.7 and 3.1, C*H*O), 3.26–3.16 (1H, m, C*H*HO), 2.29–1.34 (10H, m, 5 × CH_2); δ_C (50 MHz; $CDCl_3$): 144.6 (*C*=CH$_2$), 108.2 (C=*C*H$_2$), 78.7 (O*C*H), 68.6 (*C*H$_2$), 62.7 (*C*H$_2$), 41.1 (*C*H$_2$), 35.8 (*C*H$_2$), 35.15 (*C*H$_2$), 32.6 (*C*H$_2$), 21.6 (*C*H$_2$); *m*/*z* (CI) 171 (100%, MH$^+$). Found (CI): MH$^+$ 171.1385. $C_{10}H_{18}O_2H^+$ requires 171.1385.

2-(But-3′-enyloxy)tetrahydropyran 5

To a stirred solution of but-3-en-1-ol (1.00 g, 13.87 mmol) and camphorsulfonic acid (5 mg) in dichloromethane (20 mL) at ambient temperature was added 3,4-dihydro-2*H*-pyran (1.16 g, 13.87 mmol) drop-wise *via* syringe. Stirring was maintained for 2 hours before the reaction mixture was diluted with ether (30 mL), washed with saturated sodium bicarbonate (40 mL), dried (K_2CO_3), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography eluting with 5% ethyl acetate–40/60 petroleum ether gave pure **5** (1.37 g, 64%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2901, 1640 (C=C), 1140, 1051, 1030; δ_H (200 MHz; $CDCl_3$): 5.82–5.62 (1H, m, C*H*=CH$_2$), 5.02–4.86 (2H, m, CH=C*H*$_2$), 4.47 (1H, t, *J* 3.2, OC*H*), 3.79–3.59 (2H, m, OC*H*H and OC*H*H), 3.41–3.26 (2H, m, OCH*H* and OCH*H*), 2.22 (2H, qt, *J* 6.8 and 1.3, OCH$_2$C*H*$_2$-CHCH$_2$), 1.73–1.36 (6H, m, 3 × CH_2); δ_C (50 MHz; $CDCl_3$): 135.1 (CH$_2$*C*H), 115.9 (*C*H$_2$CH), 98.4 (O*C*H), 66.5 (*C*H$_2$), 61.8 (*C*H$_2$), 34.0 (*C*H$_2$), 30.5 (*C*H$_2$), 25.3 (*C*H$_2$), 19.3 (*C*H$_2$); *m*/*z* (CI) 174 (100%, MNH$_4^+$). Found (CI): MNH$_4^+$ 174.1494. $C_9H_{16}O_2\cdot NH_4^+$ requires 174.1494.

4-(5′,6′-Dihydro-2*H*-pyran-2′-yl)butan-1-ol 6 and 4-(3′,6′-dihydro-2*H*-pyran-2′-yl)butan-1-ol 7

To a stirred solution of but-3-en-1-ol tetrahydropyranyl ether **5** (100 mg, 0.64 mmol) in dichloromethane (6 mL) at −15 °C was added trifluoromethanesulfonic acid (0.050 mL, 0.64 mmol) drop-wise *via* syringe. Stirring was maintained at this temperature for 2 hours, before the reaction mixture was diluted with ether (10 mL), washed with sodium bicarbonate (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a yellow oil. Purification by flash column chromatography, eluting with 30% ethyl acetate–40/60 petroleum ether, gave **6** and **7**, 1 : 2 ratio of inseparable isomers **6**:**7** by integration of the C*H*=C*H* signals at 3.72–3.52 (**7**) and 3.50–3.39 (**6**) in the 200 MHz proton NMR spectrum (50 mg, 50%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3388 (br, O–H), 2924, 1648 (C=C), 1083, 1034; δ_H (200 MHz; $CDCl_3$) 5.88–5.50 (2H **7** and 2H **6**, m, CH=C*H* and C*H*=CH), 4.22–3.85 (2H **7** and 2H **6**, m, CHOC*H* and C*H*HO), 3.72–3.52 (3H **7** CH_2OH and CH*H*O), 3.50–3.39 (3H **6**, m, CH_2OH and CH*H*O), 2.30–1.20 (8H **7** and 8H **6**, m, 4 × CH_2); δ_C (50 MHz; $CDCl_3$) 130.4 (CH=*C*HCH, **6**), 126.3 (CH=*C*HCH, **7**), 124.8 (*C*H=CHCH, **6**), 124.3 (*C*H=CHCH, **7**), 73.8 (O*C*H, **6**), 73.6 (O*C*H, **7**), 66.0 (*C*H$_2$, **7**), 63.5 (*C*H$_2$, **6**), 62.9 (*C*H$_2$, **7** and **6**), 35.6 (*C*H$_2$, **7**), 35.0 (*C*H$_2$, **6**), 32.7 (*C*H$_2$, **7** and **6**), 31.1 (*C*H$_2$, **7**), 25.4 (*C*H$_2$, **6**), 21.7 (*C*H$_2$, **7**), 21.4 (*C*H$_2$, **6**); *m*/*z* (CI) 157 (100%, MH$^+$). Found (CI): MH$^+$ 157.1231. $C_9H_{16}O_2H^+$ requires 157.1229.

4-(5′,6′-Dihydro-2*H*-pyran-2′-yl)butan-1-ol 6

To a stirred solution of **18** (51 mg, 0.24 mmol) in dichloromethane (6 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 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 50% diethyl ether–40/60 petroleum ether, gave **6** (50 mg, 50%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3280 (br, O–H), 2920, 1651 (C=C), 1078, 1031; δ_H (600 MHz; $CDCl_3$) 5.84–5.81 (1H, m, CH$_2$C*H*=CH), 5.62–5.60 (1H, m, CH=C*H*CH), 4.07 (1H, br s, CHOC*H*), 3.98–3.94 (1H, m, C*H*HO), 3.66–3.62 (3H, m, CH_2OH and CH*H*O), 2.30–2.23 (1H, m, C*H*H), 1.89–1.30 (7H, m, CH*H* and 3 × CH_2); δ_C (50 MHz; $CDCl_3$) 130.3 (CH=*C*HCH), 124.7 (CH$_2$*C*H=CH), 73.7 (O*C*H), 63.4 (*C*H$_2$), 62.7 (*C*H$_2$), 34.9 (*C*H$_2$), 32.6 (*C*H$_2$), 25.3 (*C*H$_2$), 21.3 (*C*H$_2$); *m*/*z* (CI) 179 (100%, MNa$^+$), 157 (80%, MH$^+$). Found (CI): MH$^+$ 157.1232. $C_9H_{16}O_2H^+$ requires 157.1229.

2-(2′-Cyclohex-1′-enylethoxy)tetrahydropyran 8

To a stirred solution of 2-cyclohex-1-enylethanol (1.00 g, 8.00 mmol) and camphorsulfonic acid (5 mg) in dichloromethane (10 mL) at ambient temperature was added 3,4-dihydro-2*H*-pyran (0.87 g, 8.80 mmol) drop-wise *via* syringe. Stirring was maintained for 1 hour before the dark purple reaction mixture was diluted with ether (20 mL), washed with saturated sodium bicarbonate (30 mL) and then brine (30 mL), dried (K_2CO_3), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography eluting with 10% diethyl ether–40/60 petroleum ether gave **8** (1.48 g, 88%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2933, 2657, 1667 (C=C), 1067, 1030 (C–O); δ_H (200 MHz; $CDCl_3$): 5.46 (1H, s, C=C*H*), 4.59 (1H, t, *J* 3.0, OC*H*), 3.92–3.73 (2H, m, C*H*HO and OC*H*H), 3.54–3.40 (2H, m, CH*H*O and OCH*H*), 2.23 (2H, t, *J* 7.3, CH_2CCH), 1.98–1.27 (14H); δ_C (50 MHz; $CDCl_3$): 134.7 (*C*=CH), 122.4 (C=*C*H), 98.6 (O*C*H), 66.4 (*C*H$_2$), 62.1 (*C*H$_2$), 38.0 (*C*H$_2$), 30.7 (*C*H$_2$), 28.7 (*C*H$_2$), 25.4 (*C*H$_2$), 25.2 (*C*H$_2$), 22.9 (*C*H$_2$), 22.3 (*C*H$_2$), 19.5 (*C*H$_2$); *m*/*z* (CI) 233 (100%, MNa$^+$). Found (CI): MNa$^+$ 233.1522. $C_{13}O_2H_{22}Na^+$ requires 233.1518.

2-(2′-Cyclohex-1′-enyl-1′-methylethoxy)tetrahydropyran 9

To a stirred solution of 1-cyclohex-1-enylpropan-2-ol (0.25 g, 1.95 mmol) and camphorsulfonic acid (10 mg) in dichloromethane (3 mL) at ambient temperature was added 3,4-dihydro-2*H*-pyran (180 mg, 2.15 mmol) drop-wise *via* syringe. Stirring was maintained for 30 minutes before the reaction mixture was diluted with ether (20 mL), washed with saturated sodium bicarbonate (30 mL) and then brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography eluting with 10% diethyl ether–40/60 petroleum ether gave **9**, a 1 : 1 mixture of diastereoisomers by integration of the CH_3 doublets at δ_H = 1.16 and 1.04 in the 200 MHz proton NMR spectrum, assigned as isomer 1 and isomer 2, (0.304 g, 70%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2927, 1042 (C–O); δ_H (200 MHz; $CDCl_3$): 5.43 (1H isomer 1 and 1H isomer 2, s, C=C*H*), 4.71–4.66 (1H isomer 1, m, OC*H*O), 4.63–4.58 (1H isomer 2, m, OC*H*O), 3.94–3.80 (2H isomer 1 and 2H isomer 2, m, C*H*HO and OC*H*CH$_3$), 3.47–3.42 (1H isomer 1 and 1H isomer 2, m, CH*H*O), 2.33–2.13 (1H isomer 1 and 1H isomer 2, m, OCH-(CH$_3$)C*H*H), 2.04–1.50 (15H isomer 1 and 15H isomer 2, m, 5 × CH_2 and OCH(CH$_3$)CH*H*), 1.16 (3H isomer 1, d, *J* 6.3, CH_3), 1.04 (3H isomer 2, d, *J* 6.1, CH_3); δ_C (50 MHz; $CDCl_3$): 134.9 and 134.6 (*C*=CH isomer 1 and isomer 2), 123.7 and 123.5 (C=*C*H, isomer 1 and isomer 2), 98.2 and 95.2 (O*C*HO, isomer 1 and isomer 2), 71.9 and 69.6 (O*C*HCH$_3$, isomer 1 and isomer 2), 62.6 and 61.7 (O*C*H$_2$, isomer 1 and isomer 2), 46.2 and 45.4 (*C*H$_2$, isomer 1 and isomer 2), 31.0 (*C*H$_2$, isomer 1 and isomer 2), 28.8 and 28.7 (*C*H$_2$, isomer 1 and isomer 2), 25.6 and 25.4

(CH_2, isomer 1 and isomer 2), 25.3 (CH_2, isomer 1 and isomer 2), 23.0 (CH_2, isomer 1 and isomer 2), 22.4 (CH_2, isomer 1 and isomer 2), 21.4 and 18.7 (CH_3, isomer 1 and isomer 2), 19.9 and 19.3 (CH_2, isomer 1 and isomer 2); *m*/*z* (CI) 247 (MNa^+), 225 (MH^+). Found (CI): MNa^+ 247.1683. $C_{14}O_2H_{24}Na^+$ requires 247.1674.

2-(2′-Cyclopent-1″-enyl-1′-methylethoxy)tetrahydropyran 10

To a stirred solution of 1-cyclopent-1-enylpropan-2-ol (0.8 g, 6.35 mmol) and camphorsulfonic acid (20 mg) in dichloromethane (20 mL) at 0 °C was added 3,4-dihydro-2*H*-pyran (0.87 mL, 9.60 mmol) drop-wise *via* syringe. Stirring was maintained for 2 hours before the reaction mixture was diluted with ether (20 mL), washed with saturated sodium bicarbonate (30 mL), then brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography eluting with 10% diethyl ether–40/60 petroleum ether gave **10**, 1:1 mixture of diastereoisomers by integration of the C*H*$_3$ doublets at $\delta_H = 1.07$ (isomer 1) and 0.96 (isomer 2) in the proton NMR spectrum, (1.1 g, 83%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2926, 1600 (C=C), 1049 (C–O); δ_H (200 MHz; $CDCl_3$): 5.30–5.25 (1H isomer 1 and 1H isomer 2, m, CC*H*), 4.60 (1H isomer 1, t, *J* 3.5, OC*H*), 4.51 (1H isomer 2, t, *J* 4.6, OC*H*), 3.94–3.80 (2H isomer 1 and 2H isomer 2, m, OC*H*H and OC*H*CH$_3$), 3.41–3.31 (1H isomer 1 and 1H isomer 2, m, OCH*H*), 2.37–1.37 (14H isomer 1 and 14H isomer 2, m, 7 × C*H*$_2$), 1.07 (3H isomer 1, d, *J* 6.3, C*H*$_3$), 0.96 (3H isomer 2, d, *J* 6.8, C*H*$_3$); δ_C (50 MHz; $CDCl_3$): 141.3 and 141.1 (*C*CH, isomer 1 and isomer 2), 125.8 and 125.7 (C*C*H, isomer 1 and isomer 2), 97.9 and 95.3 (O*C*HO, isomer 1 and isomer 2), 71.8 and 69.7 (O*C*HCH$_3$, isomer 1 and isomer 2), 62.2 and 61.7 (O*C*H$_2$, isomer 1 and isomer 2), 39.2 and 38.1 (*C*H$_2$, isomer 1 and isomer 2), 35.3 and 35.2 (*C*H$_2$, isomer 1 and isomer 2), 32.3 and 32.2 (*C*H$_2$, isomer 1 and isomer 2), 31.0 and 30.9 (*C*H$_2$, isomer 1 and isomer 2), 25.5 and 25.4 (*C*H$_2$, isomer 1 and isomer 2), 23.4 (*C*H$_2$, isomer 1 and isomer 2), 21.3 and 18.8 (*C*H$_3$, isomer 1 and isomer 2), 19.7 and 19.3 (*C*H$_2$, isomer 1 and isomer 2); *m*/*z* (FIB) 211 (100%, MH^+). Found (FIB): MH^+ 211.1696. $C_{13}H_{22}O_2H^+$ requires 211.1698.

Hexahydroisochromenyl alcohols 11–13

To a stirred solution of **8** (55 mg, 0.26 mmol) in dichloromethane (5 mL) at −15 °C was added trifluoromethanesulfonic acid (0.029 mL, 0.26 mmol) drop-wise *via* syringe. Stirring was maintained at this temperature for 10 minutes before the reaction mixture was diluted with ether (20 mL), washed with sodium bicarbonate (20 mL), 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, gave **11**–**13**, as an inseparable mixture of 3 isomers, ratio of **11**:**12**:**13** estimated at 72:22:6 by integration of the signals at $\delta_H = 5.46$–5.45 (**11**), 5.39 (**13**) and 3.91–3.84 (**12**) in the 400 MHz proton NMR, (44 mg, 80%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3412 (br, O–H), 2928, 2854, 1641 (C=C), 1104, 1059 (C–O); NMR data for **11**: δ_H (400 MHz; $CDCl_3$): 5.46–5.45 (1H, m, C=C*H*), 3.97 (1H, dd, *J* 10.8 and 5.2, *eq*-C*H*HO), 3.62 (2H, t, *J* 6.0, C*H*$_2$OH), 3.31 (1H, ddd, *J* 10.8, 9.5 and 2.3, *ax*-CH*H*O), 2.84 (1H, td, *J* 8.6, and 2.3, OC*H*), 2.31–2.27 (1H, m, *ax*-C*H*HC), 2.01 (1H, br d, *J* 13.7, *eq*-CH*H*C), 1.97–1.17 (12H, m, CH*H*, C*H* and 5 × C*H*$_2$), 1.01 (1H, qd, *J* 13.0 and 2.8, CH*H*); δ_C (150 MHz; $CDCl_3$): 136.1 (*C*=CH), 121.4 (C=*C*H), 83.3 (O*C*H), 68.6 (*C*H$_2$), 62.70 (*C*H$_2$), 41.6 (C*C*HCHO), 35.5 (*C*H$_2$C), 32.8 (*C*H$_2$), 32.7 (*C*H$_2$), 26.0 (*C*H$_2$), 25.1 (*C*H$_2$), 21.6 (*C*H$_2$), 21.5 (*C*H$_2$); selected signals for minor isomers: δ_H (400 MHz; $CDCl_3$): 5.39 (1H **13**, br s, C=C*H*), 3.91–3.84 (2H **12**, m, C*H*$_2$); further signals for the minor isomers could not be resolved; *m*/*z* (CI) 211 (100%, MH^+). Found (CI): MH^+ 211.1703. $C_{13}H_{22}O_2H^+$ requires 211.1698.

Methylhexahydroisochromenyl alcohols 14–16

To a stirred solution of **9** (60 mg, 0.26 mmol) in dichloromethane (5 mL) at −15 °C was added trifluoromethanesulfonic acid (0.029 mL, 0.26 mmol) drop-wise *via* syringe. Stirring was maintained at this temperature for 10 minutes before the reaction mixture was diluted with ether (20 mL), washed with saturated sodium bicarbonate (20 mL), 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, gave **50a**–**c**, as an inseparable mixture of 3 isomers, ratio **14**:**15**:**16** to minor isomers estimated at 83:14:3 by integration of the signals at $\delta_H = 5.22$ (**16**), 1.18 (**15**) and 1.15 (**14**) in the 600 MHz proton NMR spectrum, (50 mg, 80%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3394 (br, O–H), 2933, 1654 (C=C), 1104, 1059 (C–O); NMR data for **14**: δ_H (600 MHz; $CDCl_3$): 5.42 (1H, m, C=C*H*), 3.62 (2H, t, *J* 6.3, C*H*$_2$OH), 3.34–3.32 (1H, dqd, *J* 11.1, 9.0 and 2.1, CH$_3$C*H*), 2.87 (1H, td, *J* 8.9 and 2.2, CH$_3$CHOC*H*), 2.16 (1H, s, O*H*), 2.07 (1H, d, *J* 13.4, *eq*-CH$_3$CHC*H*H), 1.92–1.23 (13H, m, *ax*-CH$_3$CHCH*H*, C*H*H, OCHC*H* and 5 × C*H*$_2$), 1.15 (3H, d, *J* 6.2, C*H*$_3$), 0.97 (1H, qd, *J* 13.1 and 2.8, CH*H*); δ_C (150 MHz; $CDCl_3$): 136.5 (*C*=CH), 121.2 (C=*C*H), 82.9 (CH$_3$CHO*C*H), 74.0 (CH$_3$*C*H), 62.6 (*C*H$_2$OH), 42.8 (*C*HCHO), 41.0 (*C*H$_2$), 32.7 (*C*H$_2$), 32.6 (*C*H$_2$), 25.9 (*C*H$_2$), 25.1 (*C*H$_2$), 22.0 (*C*H$_3$), 21.7 (*C*H$_2$), 21.6 (*C*H$_2$); selected signals for minor isomers: δ_H (600 MHz; $CDCl_3$): 5.22 (1H **16**, br s, C=C*H*), 1.18 (3H **15**, d, *J* 6.4, C*H*$_3$); *m*/*z* (CI) 225 (100%, MH^+). Found: MH^+ 225.1860. $C_{14}H_{24}O_2H^+$ requires 225.1855.

3-(3′-Methyl-1′,3′,4′,6′,7′,7a′-hexahydrocyclopenta[*c*]pyran-1′-yl)butan-1-ol 17

To a stirred solution of **10** (276 mg, 1.3 mmol) in dichloromethane (10 mL) at −15 °C was added trifluoromethanesulfonic acid (0.058 mL, 0.66 mmol) drop-wise *via* syringe. Stirring was maintained at this temperature for 10 minutes before the reaction mixture was diluted with ether (40 mL), washed with saturated sodium bicarbonate (40 mL), 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, gave **17** (180 mg, 65%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3394 (br, O–H), 2933, 2850, 1663 (C=C), 1442, 1058 (C–O); δ_H (600 MHz; $CDCl_3$): 5.32 (1H, s, C=C*H*), 3.64 (2H, t, *J* 6.3, C*H*$_2$OH), 3.29 (1H, dqd, *J* 12.2, 6.1 and 2.5, CH$_3$C*H*), 2.86 (1H, td, *J* 9.0 and 2.3, CH$_3$CHOC*H*), 2.36 (1H, dd, *J* 2.3 and 13.8, *eq*-CH$_3$CHC*H*H), 2.28–2.26 (3H, m, C*H* and C*H*$_2$), 1.99–1.24 (9H, m, *ax*-CH$_3$CHCH*H* and 4 × C*H*$_2$), 1.22 (3H, d, *J* 6.1, C*H*$_3$); δ_C (150 MHz; $CDCl_3$): 142.3 (*C*=CH), 121.4 (C=*C*H), 85.0 (CH$_3$CHO*C*H), 73.7 (CH$_3$*C*H), 62.7 (*C*H$_2$OH), 49.3 (*C*HCHO), 37.0 (CH$_3$CH$_2$*C*H$_2$), 33.9 (OCH*C*H$_2$), 32.7 (*C*H$_2$CH$_2$OH), 31.31 (CH$_2$CHCH*C*H$_2$), 26.2 (OCHCH$_2$*C*H$_2$), 22.0 (*C*H$_3$), 21.5 (OCHCH*C*H$_2$); *m*/*z* (FIB) 211 (100%, MH^+), 154 (54%). Found (FIB): MH^+ 211.1686. $C_{13}H_{22}O_2H^+$ requires 211.1698.

Trimethyl{2-[2′-(tetrahydropyran-2″-yloxy)ethyl]prop-2-enyl}silane 19

To a stirred solution of 3-(trimethylsilanylmethyl)but-3-en-1-ol[17] (1.00 g, 6.30 mmol) and 3,4-dihydro-2*H*-pyran (2.67 g, 31.60 mmol) in dichloromethane (8 mL) at −10 °C was added camphorsulfonic acid (5 mg) in one portion. Stirring was maintained at this temperature for 10 minutes before the reaction mixture was diluted with dichloromethane (10 mL), washed with saturated sodium bicarbonate (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and finally concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography, eluting with 5% diethyl ether–40/60 petroleum ether gave **19** (0.63 g, 42%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 2942, 1737, 1650 (C=C); δ_H (200 MHz; $CDCl_3$): 4.57–4.50 (3H, m, C=C*H*$_2$ and

OC*H*), 3.84–3.71 (2H, m, C*H*HO and OC*H*H), 3.49–3.37 (2H, m, CH*H*O and OCH*H*), 2.20 (2H, t, *J* 7.2, $CH_2C{=}CH_2$), 1.77–1.46 (8H, m, $4 \times CH_2$), −0.04 (9H, s, $Si(CH_3)_3$); δ_C (50 MHz; $CDCl_3$): 144.3 ($C{=}CH_2$), 108.2 ($C{=}CH_2$), 98.5 (*C*H), 66.2 (CH_2), 62.0 (CH_2), 38.1 (CH_2), 30.6 (CH_2), 27.1 (CH_2), 25.4 (CH_2), 19.4 (CH_2), −1.52 ($SiCH_3$); *m*/*z* (CI) 243 (100%, MH^+). Found (CI): MH^+ 243.1780. $C_{13}H_{26}O_2SiH^+$ requires 243.1780.

4-(4′-Methyltetrahydropyran-2′-yl)butan-1-ols *cis*-20 and *trans*-20

From 2, 3 and 4. To a stirred solution of a 52:31:13 mixture of the alkenes **2**, **3**, **4** (100 mg, 0.6 mmol) in methanol (10 mL) at ambient temperature was added palladium on carbon (30 mg, 30% by weight). The reaction mixture was degassed before being placed under an atmosphere of hydrogen gas, and stirred at ambient temperature for 24 hours. The mixture was filtered through Celite and concentrated *in vacuo* to leave only *cis*- and *trans*-**20** as a colourless oil, in a 30:1 ratio of *cis*:*trans* by integration of the CH_3 doublets at $\delta_H = 0.92$ (*cis*) and 0.90 (*trans*) in the 600 MHz proton NMR spectrum, (100 mg, 100%). Flash column chromatography, eluting with 50% ethyl acetate–40/60 petroleum ether, isolated *cis*-**20** as a colourless oil (the trace of *trans*-**20** could not be detected). ν_{max} (thin film)/cm^{-1} 3392 (br, O–H), 2921, 1634 (C=C), 1098, 1066 (C–O); δ_H (600 MHz; $CDCl_3$): 3.97 (1H, dd, *J* 11.4 and 3.5, *eq*-C*H*HO), 3.64 (2H, t, *J* 6.5, CH_2OH), 3.38 (1H, td, *J* 11.4 and 2.1, *ax*-CH*H*O), 3.22 (1H, m, OC*H*), 1.66–1.39 (9H, m, C*H*CH_3, C*H*H, *eq*-C*H*HCH_2O and $3 \times CH_2$), 1.18 (1H, qd, *J* 12.5, 4.6, *ax*-C*H*HCH_2O), 0.92 (3H, d, *J* 6.3, CH_3), 0.90–0.86 (1H, m, CH*H*); δ_C (150 MHz; $CDCl_3$): 77.4 (O*C*H), 68.0 (CH_2O), 62.8 (CH_2OH), 40.6 (CH_2), 36.0 (CH_2), 34.7 (CH_2CH_2O), 32.7 (CH_2CH_2OH), 30.3 (CH_3CH), 22.3 (CH_3), 21.6 ($OCHCH_2CH_2$); *m*/*z* (CI) 173 (100%, MH^+). Found (CI): MH^+ 173.1542. $C_{10}H_{20}O_2H^+$ requires 173.1542. Selected signal for *trans*-**20**: δ_H (600 MHz; $CDCl_3$): 0.90 (3H, d, *J* 6.1, CH_3). Further signals for the *trans* isomer could not be resolved.

From 4. To a stirred solution of alkene **4** (5.0 mg, 0.03 mmol) in methanol (1 mL) at ambient temperature was added palladium on carbon (1 mg, 20% by weight). The reaction mixture was degassed before being placed under an atmosphere of hydrogen gas, and stirred at ambient temperature for 2 hours. The mixture was filtered through Celite and concentrated *in vacuo* to leave *cis*- and *trans*-**20** as a colourless oil, as a 5:1 (*cis*:*trans*) mixture of diastereoisomers by integration of the CH_3 doublets at $\delta_H = 0.90$ (minor) and 0.92 (major) in the 600 MHz proton NMR spectrum, (4.9 mg, 98%).

3-(Octahydroisochromen-1′-yl)butan-1-ol 21

To a stirred solution of **11**–**13** (34 mg, 0.16 mmol) in methanol (4 mL) at ambient temperature was added palladium on carbon (7 mg, 20% by weight). The reaction mixture was degassed before it was placed under an atmosphere of hydrogen gas, and stirred at ambient temperature for 24 hours. The mixture was filtered through Celite and concentrated *in vacuo* to leave a colourless oil. Purification by flash column chromatography, eluting with 50% ethyl acetate–40/60 petroleum ether, gave **21**, as the major component in an inseparable 10:1 mixture of two isomers by integration of the signals at $\delta_H = 3.99$ (minor isomer) and 3.95 (**21**) in the 600 MHz proton NMR spectrum and by GC analysis (2 peaks, retention times: 18.88, 19.65 minutes, ratio 10:1) (32 mg, 93%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3406 (br, O–H), 2920, 2852, 1079, 1055 (C–O); δ_H (600 MHz; $CDCl_3$): 3.95 (1H, dd, *J* 10.8 and 4.5, *eq*-C*H*HOCH), 3.61 (2H, t, *J* 5.5, CH_2OH), 3.43 (1H, td, *J* 10.8 and 2.1, *ax*-CH*H*OCH), 2.93 (1H, br t, *J* 8.1, OC*H*), 1.96–0.77 (18H, m, C*H*CHCHO, C*H*CHO and $8 \times CH_2$); δ_C (150 MHz; $CDCl_3$): 81.5 (O*C*H), 68.1 (CH_2), 62.7 (CH_2), 46.4 (*C*H), 41.0 (*C*H), 33.8 (CH_2), 33.3 (CH_2), 32.8 (CH_2), 32.1 (CH_2), 27.7 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 21.3 (CH_2); selected signal for the minor isomer: 3.99 (1H minor isomer, dd, *J* 12.3 and 3.2, *ax*-C*H*HOCH); further signals for the minor isomer could not be resolved, and the stereochemistry could not be determined; *m*/*z* (CI) 235 (100%, MNa^+). Found (CI): MNa^+ 235.1674. $C_{13}H_{24}O_2Na^+$ requires 235.1674.

3-(3′-Methyloctahydroisochromen-1′-yl)butan-1-ol 22

To a stirred solution of **14**–**16** (20 mg, 0.09 mmol) in methanol at ambient temperature was added palladium on carbon (6 mg, 30% by weight). The reaction mixture was degassed before being placed under an atmosphere of hydrogen gas, and stirred at ambient temperature for 2 hours. The mixture was filtered through Celite and concentrated *in vacuo* to leave a colourless oil. Purification by flash column chromatography, eluting with 50% ethyl acetate–40/60 petroleum ether, gave **22** (20 mg, 99%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3405 (br, O–H), 2919, 2854, 1057, 1029 (C–O); δ_H (600 MHz; $CDCl_3$): 3.63 (2H, t, *J* 5.9, CH_2OH), 3.46 (1H, dqd, *J* 12.3, 6.2 and 1.8, CH_3CH), 2.97 (1H, td, *J* 8.9 and 2.6, CH_3CHOCH), 1.84–1.15 (14H, m, C*H*H, C*H* and $6 \times CH_2$), 1.14 (3H, d, *J* 6.2, CH_3), 0.97–0.76 (4H, m, C*H* and $3 \times CHH$); δ_C (150 MHz; $CDCl_3$): 81.4 ($OCHCH_2$), 73.4 (CH_3CHO), 62.8 (CH_2OH), 46.0 (*C*H), 41.1 (*C*H), 41.2 (CH_2), 33.3 (CH_2), 32.7 (CH_2), 31.9 (CH_2), 27.7 (CH_2), 26.3 (CH_2), 20.1 (CH_2), 22.0 (CH_3), 21.4 (CH_2); *m*/*z* (CI) 227 (100%, MH^+). Found (CI): MH^+ 227.2015. $C_{14}H_{26}O_2H^+$ requires 227.2011.

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