# Diastereoselective oxygen to carbon rearrangements of anomerically linked enol ethers and the total synthesis of (+)-(*S*,*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid, a component of civet

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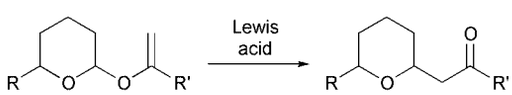
A range of enol ethers, linked *via* their oxygen atom to the anomeric centre of a pyran ring system, was shown to undergo oxygen to carbon rearrangement upon treatment with a Lewis acid to give the corresponding 2-carbon substituted products. At low temperature, trimethylsilyl trifluoromethanesulfonate catalysed rearrangements of anomerically linked 6-substituted tetrahydropyranyl enol ethers gave selectively the *trans*-pyranyl ketones, whereas at higher temperatures selective formation of the *cis*-pyranyl ketones was observed. In a simple application of the methodology the *cis*-selective rearrangement was used as the key step in a concise total synthesis of a constituent of civet.

## Introduction

Bioactive natural products which contain tetrahydropyran and furan ring systems exhibiting carbon substituents adjacent to the heteroatom are abundant in the biosphere. The stereoselective formation of carbon–carbon bonds at anomeric sites presents an important challenge in total synthesis, and a variety of attractive solutions to this problem have evolved.[1] We have recently shown that oxygen to carbon rearrangements of anomerically linked nucleophiles are powerful reactions for the introduction of carbon substituents at anomeric sites. This methodology encompasses the rearrangement of alkenes,[2] alkynyl stannanes,[3] and silyl enol ethers[4] as the nucleophilic component, and has also seen utility in total synthesis.[5] In this paper we present our investigations into the rearrangement of anomerically linked enol ethers,[6] and show how they may be applied to the total synthesis of a constituent of civet.

Enol ethers represent an attractive nucleophile in an anomeric rearrangement approach to functionalised heterocycles; the product is a ketone or aldehyde, which may be further elaborated by a diverse range of methods, or used intact as part of a total synthesis (Scheme 1).



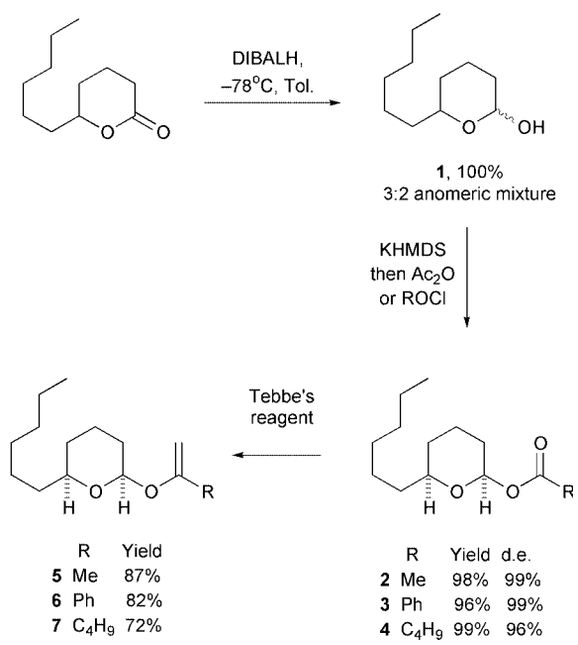

**Scheme 1**

Their drawbacks, when compared to other nucleophiles, include intolerance of protic acid and the need for involved synthetic routes for their formation. Enol ethers have been used as external nucleophiles for the formation of carbon–carbon bonds at anomeric centres,[7,8] and as anomerically linked nucleophiles in pioneering studies by Suzuki,[9] Menicagli[10] and Degl'Innocenti.[11,12] The investigations described below build on this work by probing *cis* and *trans* ring stereoselectivity, facilitating wider application of the methodology in total synthesis.

## Results and discussion

### Preparation of the anomerically linked enol ethers

Recent developments in organic synthesis have provided methods for the formation of enol ethers from esters *via* the Tebbe,[13] Grubbs[14] or Petasis[15] reagents. Incorporating the methodology of Tebbe, an efficient and flexible route towards anomerically linked enol ethers was developed, starting from commercially available undecano-5-lactone (Scheme 2).




**Scheme 2**

Reduction using diisobutylaluminium hydride (DIBALH) at −78 °C in toluene gave a quantitative yield of lactol **1** (1.05 equiv.). Formation of the anomeric alkoxide with potassium hexamethyldisilylazide (KHMDS) in tetrahydrofuran at −78 °C and subsequent acylation with acetic anhydride or an acid chloride afforded anomeric esters **2**–**4** in excellent yield after purification on silica gel deactivated with triethylamine. Interestingly, these esters are formed almost exclusively as the *cis*-isomers (95–99% de). Other chemists working on low-temperature *O*-glycosidation with alkoxides have observed similar results,[16] and have suggested that this phenomenon arises

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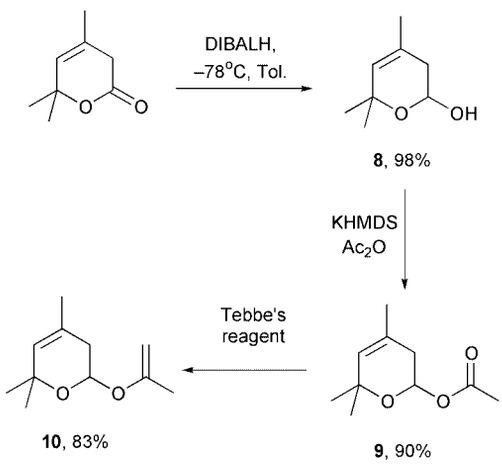
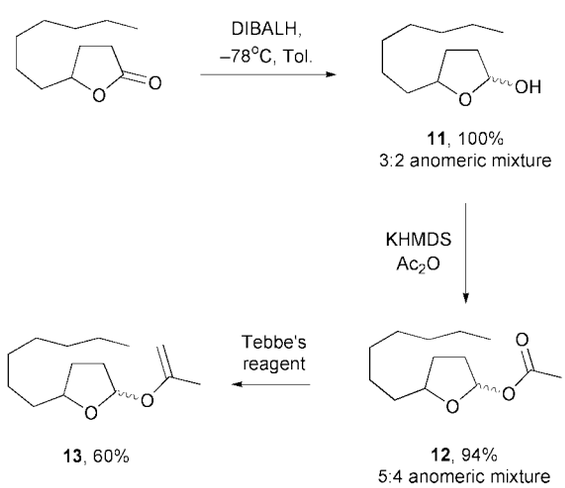
from dipolar interactions between the oxygen lone pairs which increase the reactivity of the *cis*-alkoxide. To complete the synthesis of the desired enol ethers, the esters were treated with Tebbe reagent in tetrahydrofuran (THF) at −30 °C, which after aqueous sodium hydroxide quench gave the corresponding enol ethers **5**–**7** in good yield after filtration through alumina. Fresh Tebbe reagent (purchased from Alrich Chemical Co.) was found to be crucial for obtaining a high yield of the enol ether without degradation. Older samples of reagent often resulted in low yields, and additionally some *in situ* rearrangement, probably as a result of its Lewis acidic nature. Another commercially available alkenic lactone was readily converted to anomeric enol ether **10**, *via* lactol **8** and anomeric acetate **9**, using the same route in 73% overall yield (Scheme 3). In this case there is a




**Scheme 3**

*gem*-dimethyl group in the 6-position, removing any complications of diastereoselectivity.

The same sequence was equally applicable to five-membered ring systems: starting from commercially available undecano-4-lactone, reduction gave lactol **11**, acetylation yielded acetate **12**, and treatment with Tebbe reagent as before gave enol ether **13** in 56% overall yield (Scheme 4). In this case a 5:4 mixture of

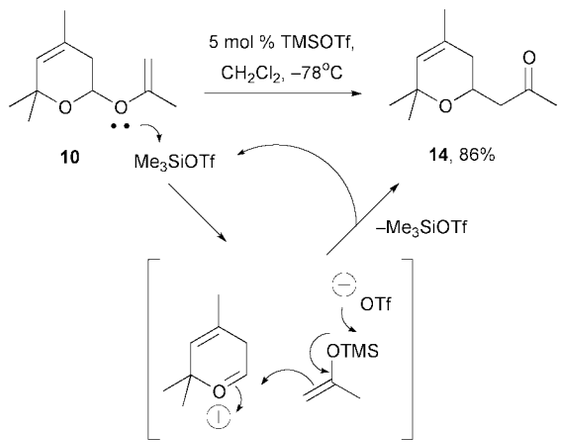



**Scheme 4**

anomers was formed; the low selectivity may be accounted for by the lower conformational rigidity of five-membered rings, which reduces the steric difference between axial and equatorial substituents.

### Anomeric oxygen to carbon rearrangements

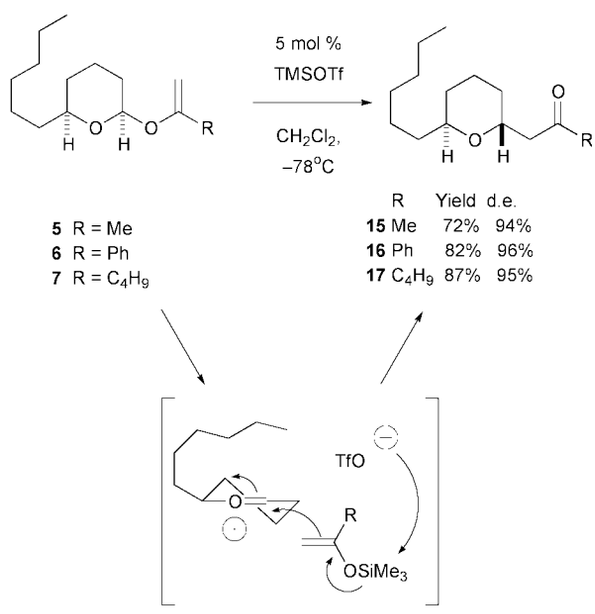
With a range of anomeric enol ethers in hand, their rearrangements were studied initially under catalytic Lewis acid activation. In the first example, enol ether **10** gave the ketonic rearrangement product **14** in 86% yield when treated with 5 mol% trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloromethane at −78 °C for 5 minutes (Scheme 5). The




**Scheme 5**

ability to activate the rearrangement with only a catalytic quantity of Lewis acid is an attractive feature of anomerically linked enol ethers, and is the result of a mechanism whereby TMSOTf activates the leaving group leading to formation of the oxonium ion and a silyl enol ether *in situ*. These components then recombine with concurrent loss of the trimethylsilyl group which rejoins the catalytic cycle.

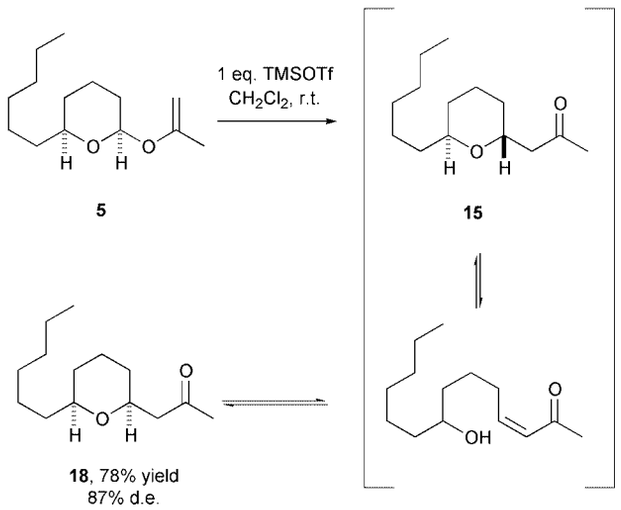
When anomeric enol ethers **5**–**7** were individually treated with 5 mol% TMSOTf in dichloromethane at −78 °C for 30 minutes, they underwent the desired anomeric oxygen to carbon rearrangement to afford *trans*-pyranyl ketones **15**–**17** in 72–87% yield (Scheme 6). The *trans* products were favoured over the *cis*




**Scheme 6**

products **18**–**20** (as shown by gradient NOE experiments) in 94–96% de, and they were easily separated by flash column chromatography. Following the proposed mechanism of Deslongchamps,[17] attack on an oxonium species will occur *trans* to a 6-substituent as a result of the greater stability of the chair-like transition state that is formed *vs*. the boat-like state from attack *cis* to the side-chain. Thus the rearrangement proceeds under kinetic control, directed by the 6-alkyl chain, to give a large preponderance of the *trans*-ketone.

We have also shown that Lewis acid mediated rearrangement may be accompanied by reversible ring-opening β-elimination, and this gives selective access to the *cis*-ketones (Scheme 7). For

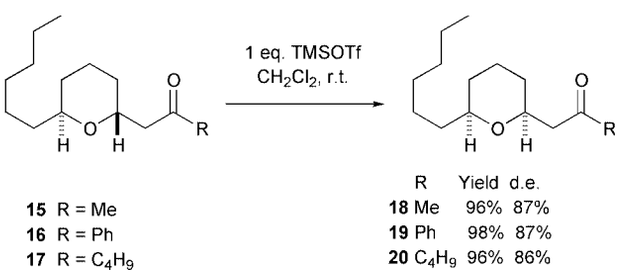



**Scheme 7**

example, when enol ether **5** was exposed to 1 equivalent of TMSOTf at room temperature for 30 minutes the selectivity of the rearrangement reaction was reversed, and *cis*-methyl ketone **18** was isolated in 78% yield and 87% de.

It is well established that the *cis* form is the lowest energy ring system, due to reduced diaxial interactions relative to the *trans* diastereoisomer, a feature which has long been utilised in the synthesis of *cis*-tetrahydropyrans;[18] exploiting the thermodynamics of the system thus allows selective formation of the *cis*-ketone.

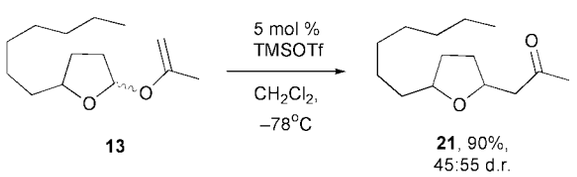
The *trans*-products **15**–**17**, when individually treated with 1 equivalent of TMSOTf at room temperature in dichloromethane, can also be equilibrated to their *cis*-isomers **18**–**20** respectively (Scheme 8). The same ratio of products was




**Scheme 8**

produced regardless of whether the starting material was the pure *cis*-ketone or the *trans*-ketone, which both supports the proposed mechanism, and indicates that the observed de is the ratio at equilibrium.

The rearrangement was also applicable to the tetrahydrofuranyl ring system **13**. In this case, performing the rearrangement under kinetic control resulted in ketone **21** in 90% yield, but with low diastereocontrol (45:55 ratio of isomers, stereochemistry not determined) (Scheme 9). Subsequent attempts to isomerise under the conditions described above did not affect

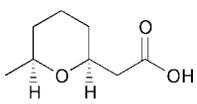



**Scheme 9**

the de of the product. This lower de is in accordance with our previous observations on the selectivity of anomeric rearrangement reactions on related tetrahydrofuranyl systems.[3,4]

### Total synthesis of (+)-(*S*,*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid, a component of civet

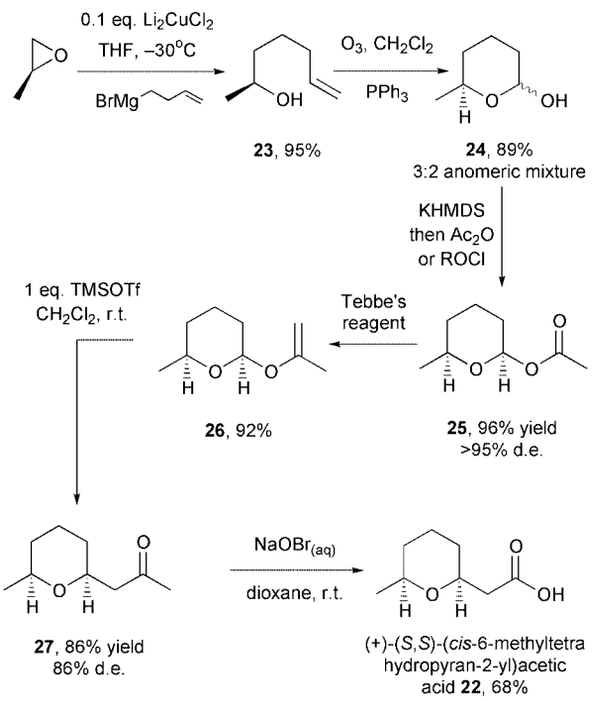
(+)-(*S*,*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid **22** was isolated by Maurer *et al.* in 1978 from civet, a glandular secretion of the civet cat (*Viverra civetta*).[19] Together with ambergis, eastoreum and musk, civet is amongst the few very expensive animal-derived perfumes. Acid **22** has no recorded biological



**22**

activity, and has only a faint odour, described by Maurer as "sour-fatty" in nature! Nevertheless, the rearrangement of an anomerically linked enol ether is ideally suited to the construction of compounds such as **22**, and consequently this compound constitutes an ideal target to test the methodology in a synthetic context.

The simple structure of **22** has made it the target of several successful synthetic strategies.[19,20] Our strategy for the enantiopure synthesis of **22** incorporates an anomeric oxygen to carbon rearrangement as the key step and commences from commercially available (−)-(*S*)-propylene oxide (Scheme 10).




**Scheme 10**

Ring-opening of (−)-(*S*)-propylene oxide with butenyl Grignard (1.2 equiv.) gave alkenol **23** in 95% yield. It was found that this reaction could be effectively catalysed by 10 mol% dilithium tetrachlorocuprate (prepared from copper(II) chloride and lithium chloride).[21] Ring-opening of this epoxide by magnesium or lithium organometallic reagents was extremely slow or impossible to achieve in the absence of a catalyst, and also resulted in the degradation of the starting material. Conversion of **23** to lactol **24** (89% yield) *via* the open-chain aldehyde was performed by ozonolysis at −78 °C, and acylation gave anomeric *cis*-methyl ester **25** (96%, >95% de). Treatment of **25** with Tebbe reagent led to the rearrangement substrate, enol ether **26**,

in 92% yield. The key rearrangement reaction was performed under the conditions described above (1 equiv. TMSOTf, room temperature, 30 minutes) providing the desired *cis*-methyl ketone **27** in 86% yield (86% de) under thermodynamic control. Fortunately, the selectivity of the reaction was equal to that seen for the analogous case where there is a $C_6$ alkyl chain in the 6-position, despite the reduced steric requirement of the methyl substituent in **26**. The *trans*-isomer **28** was also isolated and characterised, allowing the de of the rearrangement to be accurately determined by integration of the crude proton NMR spectrum.

The final step to form **22** required the oxidative degradation of ketone **27** to the corresponding acid *via* the haloform reaction. Side reactions are a common problem with this reaction, especially when applied to a substrate such as **27** where enolisable protons lie on both sides of the ketone, but it was hoped that in this case the bulk of the ring system would inhibit halogenation at the more substituted position. Indeed, when **27** was treated with an aqueous solution of sodium bromite (prepared from sodium hydroxide solution and bromine[22]) at room temperature for 2 hours the natural product **22** was isolated in an unoptimised yield of 68%. The synthetic sample of **22** was identical in all respects (IR, optical rotation, NMR spectra, mass spectrum, odour) to the published data for the natural product.[20u,23,24]

## Conclusion

The methodology described above extends the scope of anomeric oxygen to carbon rearrangements in organic synthesis allowing ready access to either *cis*- or *trans*-substituted tetrahydropyranyl ring systems, in high yields and with good to excellent diastereoselectivities. The short and efficient synthesis of **22** described above features the rearrangement of an anomerically linked enol ether as its key step, giving the natural product in 52% yield over six steps from (−)-(*S*)-propylene oxide. It demonstrates how an anomeric oxygen to carbon rearrangement may be smoothly incorporated into a total synthesis, where it provides a simple and effective method for forming functionalised tetrahydropyrans.

## 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 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.

### 6-Hexyltetrahydropyran-2-ol 1

To a stirred solution of undecano-5-lactone (11.60 g, 63 mmol) in toluene (120 mL) at −78 °C was added a solution of $^iBu_2AlH$ in toluene (1.0 M, 66 mL, 66 mmol). After 120 min the reaction mixture was quenched by the careful addition of MeOH (10 mL) and allowed to warm to ambient temperature, whereupon it was treated with a saturated aqueous solution of Rochelle's salt (100 mL) and stirred for about 60 min until the phases separated. The aqueous phase was extracted with $Et_2O$ (2 × 80 mL) and the combined organic extracts were dried ($Na_2SO_4$), filtered and the solvent evaporated *in vacuo* to give **1**, as a 3 : 2 mixture of anomers by proton NMR (11.65 g, 100%) (Found: C, 70.85; H, 11.90%. $C_{11}H_{22}O_2$ requires: C, 70.91; H, 11.91%); $\nu_{max}$ (thin film)/cm$^{-1}$ 3393, 2928, 2857, 1460, 1440, 1378, 1352, 1193, 1105, 1068, 1028, 970; $\delta_H$ (400 MHz; $CDCl_3$): 5.24 (1H major, br s, C*H*OH), 4.64 (1H minor, t, *J* 6.9, C*H*OH), 4.43 (1H major, d, *J* 6.2, O*H*), 3.88 (1H minor, m, C*H*OCHOH), 3.82 (1H minor, br s, O*H*), 3.35 (1H major, m, C*H*OCHOH), 1.85–1.06 (16H minor and 16H major, m, 8 × C$H_2$), 0.82 (3H minor and 3H major, t, *J* 6.9, $CH_3$); $\delta_C$ (100 MHz; $CDCl_3$): 96.5 (*C*OH, major), 91.6 (*C*OH, minor), 76.5 (*C*HOCHOH, major), 68.7 (*C*HOCHOH, minor), 36.1 (*C*$H_2$, major), 35.9 (*C*$H_2$, minor), 32.8 (*C*$H_2$, major), 31.7 (*C*$H_2$, minor), 30.2 (*C*$H_2$, major), 29.8 (*C*$H_2$, minor), 29.6 (*C*$H_2$, major), 29.4 (C*H*$_2$, minor), 29.3 (C*H*$_2$, major), 28.4 (*C*$H_2$, minor), 25.4 (*C*$H_2$, minor), 25.3 (*C*$H_2$, major), 22.6 (*C*$H_2$, minor), 22.5 (*C*$H_2$, major), 22.1 (*C*$H_2$, major and minor), 17.4 (*C*$H_3$, minor), 14.0 (*C*$H_3$, major); *m*/*z* 209 (100%, $MNa^+$). Found (FAB): $MNa^+$ 209.1508. $C_{11}H_{22}O_2Na$ requires 209.1517.

### *cis*-6-Hexyltetrahydropyran-2-yl acetate 2

To a stirred solution of **1** (2.4 g, 12.9 mmol) in tetrahydrofuran (20 mL) at −78 °C was added a solution of potassium hexamethyldisilylazide in toluene (0.5 M, 27 mL, 13.5 mmol) dropwise, and the reaction mixture warmed to 0 °C over 5 min before cooling to −78 °C. A solution of acetic anhydride (3.8 mL, 38.7 mmol) in tetrahydrofuran (10 mL) was added dropwise, and the reaction mixture stirred for 2 hours at −78 °C before quenching with saturated aqueous ammonium chloride solution (20 mL). Distilled water was added (20 mL), the aqueous layer extracted with diethyl ether (3 × 40 mL), and the combined organic extracts dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to leave a slightly yellow oil. The ratio *cis* : *trans* was found to be >200 : 1 by integration of the signals in the 400 MHz proton NMR spectrum at $\delta_H = 5.56$ (*cis*) and 5.52 (*trans*). Purification by flash column chromatography, eluting with 20% diethyl ether–petroleum ether (bp 40–60 °C) gave **2** (2.88 g, 98%) as a colourless oil. $\nu_{max}$ (thin film)/cm$^{-1}$ 2930, 2858, 1755, 1459, 1442, 1365, 1313, 1233, 1190, 1142, 1114, 1033; $\delta_H$ (400 MHz; $CDCl_3$): 5.59 (1H, dd, *J* 9.6 and 2.2, OC*H*O), 3.47–3.41 (1H, m, C*H*OCHO), 2.05 (3H, s, COC$H_3$), 1.87–1.82 (1H, m, C*H*H), 1.76–1.72 (1H, m, CH*H*), 1.58–1.13 (14H, m, 7 × C$H_2$), 0.83 (3H, t, *J* 6.2, $CH_2CH_3$); $\delta_C$ (100 MHz; $CDCl_3$): 169.2 (*C*OCH$_3$), 94.9 (O*C*HO), 77.1 (*C*HOCHO), 35.9 (*C*$H_2$), 31.7 (*C*$H_2$), 30.2 (*C*$H_2$), 30.0 (*C*$H_2$), 29.2 (*C*$H_2$), 25.3 (2 × *C*$H_2$), 22.5 (*C*$H_2$), 21.7 (CO*C*H$_3$), 14.0 ($CH_2$*C*H$_3$); *m*/*z* (FAB) 228 (M, 75%), 169 (100%). Found (FAB): $M^+$ 228.1725. $C_{13}H_{24}O_3$ requires 228.1725.

### *cis*-6-Hexyltetrahydropyran-2-yl benzoate 3

To a stirred solution of **1** (1.0 g, 5.40 mmol) in tetrahydrofuran

(8 mL) at −78 °C was added a solution of potassium hexamethyldisilylazide in toluene (0.5 M, 11.34 mL, 5.67 mmol) dropwise, and the reaction mixture warmed to 0 °C over 5 min before cooling to −78 °C. Benzoyl chloride (0.66 mL, 5.67 mmol) was added dropwise, and the reaction mixture stirred for 2 hours at −78 °C before quenching with saturated aqueous ammonium chloride solution (8 mL). Distilled water was added (8 mL), the aqueous layer extracted with diethyl ether (3 × 10 mL), and the combined organic extracts dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to leave a slightly yellow oil. The ratio *cis*:*trans* was found to be >200:1 by integration of the signals in the 400 MHz proton NMR spectrum at $\delta_H$ = 3.60–3.55 (*cis*) and 3.38–3.32 (*trans*). Purification by flash column chromatography, eluting with 30% diethyl ether–petroleum ether (bp 40–60 °C) gave **3** (1.5 g, 96%) as a colourless oil (Found: C, 74.67; H, 9.03%. $C_{18}H_{26}O_3$ requires: C, 74.45; H, 9.02%); $\nu_{max}$ (thin film)/cm$^{-1}$ 2932, 2857, 1730, 1602, 1452, 1314, 1176, 1091, 1030; $\delta_H$ (400 MHz; $CDCl_3$): 8.10–8.08 (2H, m, *o*-Ph), 7.54 (1H, t, *J* 7.4, *p*-Ph), 7.42 (2H, t, *J* 7.8, *m*-Ph), 5.90 (1H, br dd, *J* 8.6 and 2.1, OC*H*O), 3.60–3.55 (1H, m, C*H*OCHO), 1.95–1.90 (2H, m, C$H_2$), 1.70–1.26 (14H, m, 7 × C$H_2$), 0.86 (3H, t, *J* 6.9, C$H_3$); $\delta_C$ (100 MHz; $CDCl_3$): 165.0 (O*C*OPh), 133.1 (Ph), 130.0 (Ph, quat.), 129.9 (Ph), 128.2 (Ph), 95.5 (O*C*HO), 77.4 (*C*HOCHO), 35.9 (*C*$H_2$), 31.7 (*C*$H_2$), 30.2 (*C*$H_2$), 30.1 (*C*$H_2$), 29.2 (*C*$H_2$), 25.4 (*C*$H_2$), 22.6 (*C*$H_2$), 21.7 (*C*$H_2$), 14.0 (*C*$H_3$); *m*/*z* (FAB) 291 (100%); Found (FAB): $MH^+$ 291.1961. $C_{18}H_{27}O_3$ requires 291.1960.

### *cis*-6-Hexyltetrahydropyran-2-yl pentanoate 4

To a stirred solution of **1** (1.0 g, 5.4 mmol) in tetrahydrofuran (8 mL) at −78 °C was added a solution of potassium hexamethyldisilylazide in toluene (0.5 M, 11.3 mL, 5.65 mmol) dropwise, and the reaction mixture warmed to 0 °C over 5 min before cooling to −78 °C. Valeric anhydride (1.3 mL, 6.5 mmol) was added dropwise, and the reaction mixture stirred for 2 hours at −78 °C before quenching with saturated aqueous ammonium chloride solution (8 mL). Distilled water was added (8 mL), the aqueous layer extracted with diethyl ether (3 × 10 mL), and the combined organic extracts dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to leave a slightly yellow oil. The ratio *cis*:*trans* was found to be 98:2 by integration of the signals in the 400 MHz proton NMR spectrum at $\delta_H$ = 5.61 (*cis*) and 5.52 (*trans*). Purification by flash column chromatography, eluting with 20% diethyl ether–petroleum ether (bp 40–60 °C) gave **4** (1.45 g, 99%) as a colourless oil (Found: C, 71.07; H, 11.18%. $C_{16}H_{30}O_3$ requires: C, 71.05; H, 11.17%); $\nu_{max}$ (thin film)/cm$^{-1}$ 2933, 2860, 1754, 1460, 1379, 1333, 1244, 1159, 1105, 1034; $\delta_H$ (400 MHz; $CDCl_3$): 5.61 (1H, dd, *J* 9.8 and 2.2, OC*H*O), 3.47–3.42 (1H, m, C*H*OCHO), 2.31 (2H, br t, *J* 7.3, $COCH_2$), 1.87–1.72 (2H, m, C$H_2$), 1.62–1.12 (18H, m, 9 × C$H_2$), 0.87 (3H, t, *J* 7.3, $CH_3$), 0.83 (3H, t, *J* 7.0, $CH_3$); $\delta_C$ (100 MHz; $CDCl_3$): 172.1 (O*C*OCH$_2$), 94.8 (O*C*HO), 77.0 (*C*HOCHO), 35.9 (*C*$H_2$), 34.1 (*C*$H_2$), 31.7 (2 × *C*$H_2$), 29.2 (*C*$H_2$), 26.7 (2 × *C*$H_2$), 25.3 (*C*$H_2$), 22.5 (*C*$H_2$), 22.1 (*C*$H_2$), 21.7 (*C*$H_2$), 14.0 (*C*$H_3$), 13.6 (*C*$H_3$); *m*/*z* (FAB) 271 (100%, $MH^+$). Found (FAB): $MH^+$ 271.2258. $C_{16}H_{30}O_3H^+$ requires 271.2273.

### *cis*-6-Hexyl-2-isopropenyloxytetrahydropyran 5

To a stirred solution of **2** (1.0 g, 4.4 mmol) in tetrahydrofuran (10 mL) at −30 °C was added a solution of Tebbe reagent in toluene (0.5 M, 9.2 mL, 4.6 mmol) dropwise over 10 min. After stirring at the same temperature for 60 min the reaction mixture was quenched by careful dropwise addition of 10% aqueous sodium hydroxide solution (1.0 mL), anhydrous $MgSO_4$ was added (2 g) and the precipitated residues removed by filtration through a pad of Celite, eluting with diethyl ether (500 mL). Evaporation of the volatile components *in vacuo* left an orange oil which was purified by passage through a short column of activated alumina, eluting with 50% diethyl ether–petroleum ether (bp 40–60 °C), to give **5** (0.87 g, 87%) as a colourless oil. $\nu_{max}$ (thin film)/cm$^{-1}$ 2928, 2857, 1662, 1617, 1458, 1443, 1368, 1270, 1190, 1143, 1074, 1033; $\delta_H$ (400 MHz; $CDCl_3$): 4.84–4.82 (1H, m, OC*H*O), 4.12 (1H, s, OC(CH$_3$)C*H*H), 3.98 (1H, s, OC(CH$_3$)CH*H*), 3.40–3.35 (1H, m, C*H*OCHO), 1.88–1.14 (19H, m, C$H_3$ and 8 × C$H_2$), 0.86 (3H, t, *J* 4.2, $CH_2CH_3$); $\delta_C$ (100 MHz; $CDCl_3$): 157.6 (O*C*CH$_3$), 98.8 (O*C*HO), 85.3 (C(CH$_3$)*C*H$_2$), 76.3 (*C*HOCHO), 35.9 (*C*H$_2$), 31.8 (*C*H$_2$), 30.7 (2 × *C*H$_2$), 29.2 (*C*H$_2$), 25.6 (*C*H$_2$), 22.6 (*C*H$_2$), 22.1 (*C*H$_2$), 20.8 (C(CH$_2$)*C*H$_3$), 14.0 (CH$_2$*C*H$_3$); *m*/*z* (FAB) 227 (100%). Found (FAB): $MH^+$ 227.2013. $C_{14}H_{26}O_2H^+$ requires 227.2011.

### *cis*-2-Hexyl-6-(1′-phenylvinyloxy)tetrahydropyran 6

To a stirred solution of **3** (0.80 g, 2.76 mmol) in tetrahydrofuran (8 mL) at −30 °C was added a solution of Tebbe reagent in toluene (0.5 M, 2.9 mL) dropwise over 10 min. After stirring at the same temperature for 60 min the reaction mixture was quenched by careful dropwise addition of 10% aqueous sodium hydroxide solution (1.0 mL), anhydrous $MgSO_4$ was added (2 g) and the precipitated residues removed by filtration through a pad of Celite, eluting with diethyl ether (200 mL). Evaporation of the volatile components *in vacuo* left an orange oil which was purified by passage through a short column of activated alumina, eluting with 50% diethyl ether–petroleum ether (bp 40–60 °C), to give **6** (0.66 g, 82%) as a colourless oil. $\nu_{max}$ (thin film)/cm$^{-1}$ 2927, 2857, 1650, 1620, 1494, 1455, 1281, 1203, 1032; $\delta_H$ (400 MHz; $CDCl_3$): 7.69–7.66 (2H, m, Ph), 7.39–7.26 (3H, m, Ph), 5.03 (1H, dd, *J* 9.1 and 1.8, OC*H*O), 4.86–4.85 (1H, m, C*H*HCOPh), 4.64 (1H, m, CH*H*COPh), 3.53–3.46 (1H, m, C*H*OCHO), 1.97–1.17 (16H, m, 8 × C$H_2$), 0.94 (3H, t, *J* 6.4, $CH_3$); $\delta_C$ (100 MHz; $CDCl_3$): 158.4 (O*C*Ph), 136.3 (quat. Ph), 128.0 (Ph), 125.5 (Ph), 99.9 (O*C*HO), 86.7 (*C*H$_2$CPh), 76.5 (*C*HOCHO), 36.0 (2 × *C*H$_2$), 31.2 (*C*H$_2$), 30.8 (2 × *C*H$_2$), 29.3 (*C*H$_2$), 25.8 (*C*H$_2$), 22.7 (2 × *C*H$_2$), 14.1 (*C*H$_3$); *m*/*z* (EI) 289 (100%, $MH^+$). Found (EI): $MH^+$ 289.2183. $C_{19}H_{29}O_2$ requires 289.2168.

### *cis*-2-(1′-Butylvinyloxy)-6-hexyltetrahydropyran 7

To a stirred solution of **4** (0.80 g, 2.96 mmol) in tetrahydrofuran (8 mL) at −30 °C was added a solution of Tebbe reagent in toluene (0.5 M, 6.2 mL) dropwise over 10 min. After stirring at −30 °C for 60 min the reaction mixture was quenched by careful dropwise addition of 10% aqueous sodium hydroxide solution (1.0 mL), anhydrous $MgSO_4$ was added (2 g) and the precipitated residues removed by filtration through a pad of Celite, eluting with diethyl ether (200 mL). Evaporation of the volatile components *in vacuo* left an orange oil which was purified by passage through a short column of activated alumina, eluting with 50% diethyl ether–petroleum ether (bp 40–60 °C), to give **7** (0.57 g, 72%) as a colourless oil. $\nu_{max}$ (thin film)/cm$^{-1}$ 2930, 2858, 1660, 1620, 1458, 1441, 1265, 1098, 1034; $\delta_H$ (400 MHz; $CDCl_3$): 4.80–4.78 (1H, m, OC*H*O), 4.14 (1H, s, OC(C*H*-H)CH$_2$CH$_2$), 4.00–3.34 (1H, m, C*H*OCHO), 3.96 (1H, s, OC(CH*H*)CH$_2$CH$_2$), 2.10–2.02 (2H, m, OC(CH$_2$)C*H*$_2$CH$_2$), 1.87–1.13 (20H, m, 10 × C$H_2$), 0.87 (3H, t, *J* 7.2, $CH_3$), 0.85 (3H, t, *J* 7.2, $CH_3$); $\delta_C$ (100 MHz; $CDCl_3$): 161.6 (O*C*(CH$_2$)-CH$_2$), 99.1 (O*C*HO), 84.4 (OC(*C*H$_2$)CH$_2$CH$_2$), 76.2 (*C*HOCHO), 35.9 (*C*H$_2$), 34.5 (2 × *C*H$_2$), 31.8 (*C*H$_2$), 29.2 (2 × *C*H$_2$), 29.1 (*C*H$_2$), 25.6 (2 × *C*H$_2$), 22.6 (CH$_2$), 22.2 (*C*H$_2$), 14.0 (*C*H$_3$), 13.8 (CH$_3$); *m*/*z* (EI) 291 (100%, $MNa^+$). Found (EI): $MNa^+$ 291.2283. $C_{17}H_{32}O_2Na$ requires 291.2300.

### 4,6,6-Trimethyl-3,6-dihydro-2*H*-pyran-2-ol 8

To a stirred solution of 4,6,6-trimethyl-3,6-dihydro-2*H*-pyran-2-one (5.0 g, 36 mmol) in toluene (50 mL) at −78 °C was added a solution of diisobutylaluminium hydride in toluene (1.0 M, 38 mL, 38 mmol). After 120 min the reaction mixture was quenched by the careful addition of MeOH (10 mL) and

allowed to warm to ambient temperature, whereupon it was treated with a saturated aqueous solution of Rochelle's salt (50 mL) and stirred for about 60 min until the phases separated. The aqueous phase was extracted with $Et_2O$ (2 × 30 mL) and the combined organic extracts were dried ($Na_2SO_4$), filtered and the solvent evaporated *in vacuo* to give **8** (5.0 g, 98%). $\nu_{max}$ (thin film)/cm$^{-1}$ 3412 (br O-H), 2972, 2927, 1680, 1441, 1381, 1127, 1073; $\delta_H$ (400 MHz; $CDCl_3$): 5.30–5.28 (1H, m, C*H*=C), 5.18–5.13 (1H, m, C*H*OH), 3.70 (1H, br s, O*H*), 2.13–2.00 (2H, m, C$H_2$), 1.67 (3H, s, C$H_3$), 1.28 (3H, s, C$H_3$), 1.25 (3H, s, C$H_3$); $\delta_C$ (100 MHz; $CDCl_3$): 128 (CH=*C*), 127.7 (*C*H=C), 90.1 (*C*HOH), 74.5 ((CH$_3$)$_2$*C*), 36.8 (*C*H$_2$), 29.8 (*C*H$_3$), 27.1 (*C*H$_3$), 22.7 (*C*H$_3$); *m*/*z* (EI) 125 (100%), 143 (35%, MH$^+$), 142 (20%, M$^+$). Found (EI): M$^+$ 142.1004. $C_8H_{14}O_2$ requires 142.0994.

### 4,6,6-Trimethyl-3,6-dihydro-2*H*-pyran-2-yl acetate 9

To a stirred solution of **8** (4.3 g, 30.3 mmol) in tetrahydrofuran (60 mL) at −78 °C was added a solution of potassium hexamethyldisilylazide in toluene (0.5 M, 63.7 mL, 31.8 mmol) dropwise, and the reaction mixture warmed to 0 °C over 5 min before cooling to −78 °C. Acetic anhydride (3.14 mL, 33.3 mmol) was added dropwise, and the reaction mixture stirred for 2 hours at −78 °C before quenching with saturated aqueous ammonium chloride solution (20 mL). Distilled water was added (20 mL), the aqueous layer extracted with diethyl ether (3 × 40 mL), and the combined organic extracts dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to leave a slightly yellow oil. Purification by flash column chromatography, eluting with 20% diethyl ether–petroleum ether (bp 40–60 °C) gave **9** (5.0 g, 90%) as a colourless oil. $\nu_{max}$ (thin film)/cm$^{-1}$ 2939, 1758, 1451, 1119, 1039; $\delta_H$ (400 MHz; $CDCl_3$): 6.10 (1H, t, *J* 4.4, OC*H*O), 5.32–5.31 (1H, m, C*H*=C), 2.17 (1H, br d, *J* 17.0, C*H*H), 2.02–1.97 (4H, m, CH*H* and COC$H_3$), 1.65 (3H, s, C$H_3$), 1.23 (3H, s, C$H_3$), 1.21 (3H, s, C$H_3$); $\delta_C$ (100 MHz; $CDCl_3$): 169.8 (*C*OCH$_3$), 127.8 (CH=*C*), 126.4 (*C*H=C), 90.3 (O*C*HO), 74.1 ((CH$_3$)$_2$*C*), 33.3 (*C*H$_2$), 29.3 (*C*H$_3$), 28.2 (*C*H$_3$), 22.7 (*C*H$_3$), 21.3 (*C*H$_3$); *m*/*z* (FAB) 185 (100%, MH$^+$). Found (FAB): MH$^+$ 185.1172. $C_{10}H_{16}O_3H^+$ requires 185.1178.

### 2-Isopropenyloxy-4,6,6-trimethyl-3,6-dihydro-2*H*-pyran 10

To a stirred solution of **9** (1.0 g, 5.5 mmol) in tetrahydrofuran (10 mL) at −30 °C was added a solution of Tebbe reagent in toluene (0.5 M, 11.4 mL, 5.7 mmol) dropwise over 10 min. After stirring at the same temperature for 60 min the reaction mixture was quenched by careful dropwise addition of 10% aqueous sodium hydroxide solution (1.5 mL), anhydrous $MgSO_4$ was added (2 g) and the precipitated residues removed by filtration through a pad of Celite, eluting with diethyl ether (500 mL). Evaporation of the volatile components *in vacuo* left an orange oil which was purified by passage through a short column of activated alumina, eluting with 50% diethyl ether–petroleum ether (bp 40–60 °C), to give **10** (0.82 g, 83%) as a colourless oil. $\nu_{max}$ (thin film)/cm$^{-1}$ 2920, 2850, 1660, 1610, 1452, 1070, 1039; $\delta_H$ (400 MHz; $CDCl_3$): 5.39 (1H, t, *J* 4.9, OC*H*O), 5.34–5.32 (1H, m, CC*H*=C), 4.24 (1H, s, OC=C*H*H), 3.99 (1H, s, OC=CH*H*), 2.16–2.14 (2H, m, C$H_2$), 1.81 (3H, s, C$H_3$), 1.70 (3H, br s, C$H_3$), 1.28 (3H, s, C$H_3$), 1.27 (3H, s, C$H_3$); $\delta_C$ (100 MHz; $CDCl_3$): 157.5 (O*C*CH$_3$), 127.6 (CH=*C*), 126.5 (*C*H=C), 98.8 (O*C*HO), 85.3 (OC=*C*H$_2$), 74.0 ((CH$_3$)$_2$*C*), 33.6 (*C*H$_2$), 29.0 (*C*H$_3$), 28.1 (*C*H$_3$), 22.4 (*C*H$_3$), 21.4 (*C*H$_3$), 20.7 (CH$_2$=C*C*H$_3$); *m*/*z* (FAB) 183 (100%, MH$^+$). Found (FAB): MH$^+$ 183.1384. $C_{11}H_{19}O_2H^+$ requires 183.1385.

### 5-Heptyltetrahydrofuran-2-ol 11

To a stirred solution of undecano-4-lactone (10.4 g, 56.4 mmol) in toluene (100 mL) at −78 °C was added a solution of $^i$Bu$_2$AlH in toluene (1.0 M, 62.0 mL). After 120 min the reaction mixture was quenched by the careful addition of MeOH (5 mL) and allowed to warm to room temperature, whereupon it was treated with a saturated aqueous solution of sodium potassium tartrate (Rochelle's salt) (100 mL) and stirred for about 60 min until the phases separated. The aqueous phase was extracted with diethyl ether (2 × 100 mL) and the combined organic extracts were dried ($Na_2SO_4$), filtered and the solvent evaporated *in vacuo* to give **11** (10.5 g, 100%, an inseparable 3:2 mixture of anomers) as a colourless oil (Found: C, 70.60; H, 11.97%. $C_{11}H_{22}O_2$ requires: C, 70.92; H, 11.90%); $\nu_{max}$ (thin film)/cm$^{-1}$ 3404 (br O-H), 2928, 2856, 1463, 1288, 1193, 1016; $\delta_H$ (400 MHz; $CDCl_3$): 5.53–5.52 (1H major, m, OC*H*O), 5.45 (1H minor, br s, OC*H*O), 4.19–4.14 (1H major, m, C*H*OCHO), 3.98–3.92 (1H minor, m, C*H*OCHO), 3.67 (1H major, d, *J* 2.0, O*H*), 3.57 (1H minor, d, *J* 2.2, O*H*), 2.14–1.26 (16H major and 16H minor, m, 8 × C$H_2$), 0.86 (3H major and 3H minor, t, *J* 6.3, C$H_3$); $\delta_C$ (100 MHz; $CDCl_3$): 98.3 and 98.1 (O*C*HO major and minor), 81.1 and 78.4 (*C*HOCHO major and minor), 37.4 (CH$_2$ major and minor), 35.6 (CH$_2$ major and minor), 32.9 (CH$_2$ major and minor), 31.8 (CH$_2$ major and minor), 29.6 (CH$_2$ major and minor), 29.4 (CH$_2$ minor), 29.2 (CH$_2$ major), 26.0 (CH$_2$ major and minor), 22.6 (CH$_2$ major and minor), 14.0 (*C*H$_3$ major and minor); *m*/*z* (FAB) 186 (80%, M$^+$), 169 (100%). Found (FAB): M$^+$ 186.1619. $C_{11}H_{22}O_2$ requires 186.1620.

### *cis*-5-Heptyltetrahydrofuran-2-yl acetate and *trans*-5-heptyltetrahydrofuran-2-yl acetate 12

To a stirred solution of **11** (1.5 g, 8.06 mmol) in tetrahydrofuran (10 mL) at −78 °C was added a solution of potassium hexamethyldisilylazide in toluene (0.5 M, 17.0 mL, 8.50 mmol) dropwise, and the reaction mixture warmed to 0 °C over 5 min before cooling to −78 °C. Acetic anhydride (0.92 mL, 9.7 mmol) was added dropwise, and the reaction mixture stirred for 2 hours at −78 °C before quenching with saturated aqueous ammonium chloride solution (5 mL). Distilled water (5 mL) was added, the aqueous layer extracted with diethyl ether (3 × 10 mL), and the combined organic extracts dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to leave a slightly yellow oil. Purification by flash column chromatography, eluting with 20% diethyl ether–petroleum ether (bp 40–60 °C) isolated **12**, as a 5:4 mixture of anomers, assigned as isomer 1 and isomer 2 (1.73 g, 94%) as a colourless oil (Found: C, 68.80; H, 10.72%. $C_{13}H_{24}O_3$ requires: C, 68.38; H, 10.59%); $\nu_{max}$ (thin film)/cm$^{-1}$ 2932, 2857, 1748, 1459, 1376, 1237, 1103, 1006; $\delta_H$ (400 MHz; $CDCl_3$): 6.23–6.22 (1H isomer 1, m, OC*H*O), 6.16 (1H isomer 2, br s, OC*H*O), 4.15–4.10 (1H isomer 1, m, C*H*OCHO), 4.03–4.00 (1H isomer 2, m, C*H*OCHO), 2.12–1.23 (19H isomer 1 and 19H isomer 2, m, C$H_3$ and 8 × C$H_2$), 0.82 (3H isomer 1 and 3H isomer 2, br t, *J* 7.0, C$H_3$); $\delta_C$ (100 MHz; $CDCl_3$): 170.4 (*C*OCH$_3$, isomer 1), 170.3 (*C*OCH$_3$, isomer 2), 99.1 (O*C*HO, isomer 1), 98.8 (O*C*HO, isomer 2), 82.1 (*C*HOCHO, isomer 1), 80.3 (*C*HOCHO, isomer 2), 36.8 (*C*H$_2$, isomer 1), 35.3 (*C*H$_2$, isomer 2), 32.9 (*C*H$_2$, isomer 1 and isomer 2), 31.7 (*C*H$_2$, isomer 2), 29.5 (*C*H$_2$, isomer 1 and isomer 2), 29.15 (*C*H$_2$, isomer 1 and isomer 2), 28.6 (*C*H$_2$, isomer 1 and isomer 2), 25.9 (*C*H$_2$, isomer 1 and isomer 2), 22.6 (*C*H$_2$, isomer 1 and isomer 2), 21.1 (CO*C*H$_3$, isomer 1), 19.7 (CO*C*H$_3$, isomer 2), 14.0 (CH$_2$*C*H$_3$, isomer 1 and isomer 2); *m*/*z* (FAB) 251 (20%, MNa$^+$), 169 (100%). Found (FAB): MNa$^+$ 251.1629. $C_{13}H_{24}O_3Na$ requires 251.1623.

### *cis*- and *trans*-2-Heptyl-5-isopropenyloxytetrahydrofuran 13

To a stirred solution of **12** (1.0 g, 4.4 mmol) in tetrahydrofuran (10 mL) at −30 °C was added a solution of Tebbe reagent in toluene (0.5 M, 9.2 mL, 4.6 mmol) dropwise over 10 min. After stirring at the same temperature for 60 min the reaction mixture was quenched by careful dropwise addition of 10% aqueous sodium hydroxide solution (2.0 mL), anhydrous $MgSO_4$ was added (4 g) and the precipitated residues removed by filtration through a pad of Celite, eluting with diethyl ether (400 mL).

Evaporation of the volatile components *in vacuo* left an orange oil which was purified by passage through a short column of activated alumina, eluting with 50% diethyl ether–petroleum ether (bp 40–60 °C), to give an inseparable 5:4 mixture of anomers of **13**, assigned as isomer 1 and isomer 2 (0.60 g, 60%) as a colourless oil. $\nu_{max}$ (thin film)/cm$^{-1}$ 2921, 2856, 1714, 1661, 1621, 1454, 1270, 1087, 1029; $\delta_H$ (400 MHz; $CDCl_3$): 5.58–5.56 (1H isomer 1, m, OC*H*O), 5.51–5.49 (1H isomer 2, m, OC*H*O), 4.09–4.07 (3H isomer 1 and 2H isomer 2, m, C*H*OCHO (isomer 1) and OC($CH_3$)C*H*H (both isomers)), 4.04–4.00 (1H isomer 2, m, C*H*OCHO), 3.94 (1H isomer 1, s, OC($CH_3$)CH*H*), 3.91 (1H isomer 2, s, OC($CH_3$)CH*H*), 2.12–1.16 (18H isomer 1 and 18H isomer 2, m, 9 × C$H_2$), 0.87 (3H isomer 1 and 3H isomer 2, t, *J* 4.6, $CH_2CH_3$); $\delta_C$ (100 MHz; $CDCl_3$): 157.4 (O*C*$CH_3$, isomer 1), 157.2 (O*C*$CH_3$, isomer 2), 101.1 (O*C*HO, isomer 2), 100.7 (O*C*HO, isomer 1), 84.9 (C($CH_3$)*C*$H_2$, isomer 1), 84.7 (C($CH_3$)-*C*$H_2$, isomer 2), 81.2 (*C*HOCHO, isomer 2), 79.1 (*C*HOCHO, isomer 1), 39.2 (*C*$H_2$, isomer 1 and isomer 2), 37.2 (*C*$H_2$, isomer 1 and isomer 2), 33.0 (*C*$H_2$, isomer 1 and isomer 2), 31.8 (*C*$H_2$, isomer 1 and isomer 2), 29.6 (*C*$H_2$, isomer 1 and isomer 2), 29.2 (*C*$H_2$, isomer 1 and isomer 2), 29.0 (*C*$H_2$, isomer 1 and isomer 2), 22.6 (*C*$H_2$, isomer 1 and isomer 2), 21.1 (C($CH_2$)*C*$H_3$, isomer 1 and isomer 2), 14.0 ($CH_2CH_3$ isomer 1 and isomer 2); *m*/*z* (FAB) 185 (30%, M − $C_3H_5$), 169 (100%). Found (FAB): M − $C_3H_5$ 185.1540. $C_{11}H_{21}O_2$ requires 185.1541.

### 1-(4′,6′,6′-Trimethyl-3′,6′-dihydro-2′*H*-pyran-2′-yl)propan-2-one 14

To a stirred solution of **10** (0.132 g, 0.73 mmol) in dichloromethane (2.4 mL) at −78 °C was added TMSOTf (0.006 mL, 0.037 mmol). After stirring at the same temperature for 5 min the reaction mixture was quenched by the addition of phosphate buffer (pH 7.4, 3 mL), the aqueous layer extracted with diethyl ether (3 × 5 mL), and the combined organic extracts dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a slightly yellow oil. Purification by flash column chromatography, eluting with 20% diethyl ether–petroleum ether (bp 40–60 °C) gave **14** (0.113 g, 86%) as a colourless oil. $\nu_{max}$ (thin film)/cm$^{-1}$ 2972, 2916, 1715, 1428, 1361, 1064; $\delta_H$ (400 MHz; $CDCl_3$): 5.28–5.27 (1H, m, C*H*=C), 4.11–4.07 (1H, m, OC*H*), 2.69 (1H, dd, *J* 15.8 and 7.7, C*H*HCOC$H_3$), 2.48 (1H, dd, *J* 15.8 and 5.0, CH*H*COC$H_3$), 2.18 (3H, s, C$H_3$), 1.84–1.79 (2H, m, C$H_2$), 1.64 (3H, s, C$H_3$), 1.19 (3H, s, C$H_3$), 1.17 (3H, s, C$H_3$); *m*/*z* (FAB) 183 (100%, $MH^+$). Found (FAB): $MH^+$ 183.1385. $C_{11}H_{18}O_2H^+$ requires 183.1385.

### 1-(*trans*-6′-Hexyltetrahydropyran-2′-yl)propan-2-one 15 and 1-(*cis*-6′-hexyltetrahydropyran-2′-yl)propan-2-one 18

**Formation under kinetic control.** To a stirred solution of **5** (0.100 g, 0.44 mmol) in dichloromethane (1.5 mL) at −78 °C was added TMSOTf (0.004 mL, 0.022 mmol). After stirring at the same temperature for 5 min the reaction mixture was quenched by the addition of phosphate buffer (pH 7.4, 3 mL), the aqueous layer extracted with diethyl ether (3 × 5 mL), and the combined organic extracts dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a slightly yellow oil. Proton NMR spectroscopic analysis of the crude product showed a 3:97 ratio of **18**:**15** by integration of the signals at $\delta_H$ = 2.64 (**18**) and 2.75 (**15**). Purification by flash column chromatography, eluting with 20% diethyl ether–petroleum ether (bp 40–60 °C), gave **18** (0.002 g, 2%) and then **15** (0.070 g, 70%) as colourless oils.

Data for **15** (*trans*-isomer) (Found: C, 74.86; H, 11.57%. $C_{14}H_{26}O_2$ requires: C, 74.96; H, 11.60%); $\nu_{max}$ (thin film)/cm$^{-1}$ 2930, 2858, 1715, 1460, 1357, 1203, 1162, 1095, 1041; $\delta_H$ (400 MHz; $CDCl_3$): 4.42–4.19 (1H, m, OC*H*$CH_2$CO), 3.69–3.61 (1H, m, C*H*OCHCH$_2$CO), 2.75 (1H, dd, *J* 15.1 and 8.3, C*H*H-COC$H_3$), 2.42 (1H, dd, *J* 15.1 and 7.4, CH*H*COC$H_3$), 2.17 (3H, s, COC$H_3$), 1.71–1.26 (16H, m, 8 × C$H_2$), 0.87 (3H, t, *J* 6.4, $CH_2CH_3$); $\delta_C$ (100 MHz; $CDCl_3$): 207.4 (*C*OCH$_3$), 71.7 (O*C*H-$CH_2$CO), 67.5 (*C*HOCHCH$_2$CO), 48.2 (*C*H$_2$CO), 33.0 (*C*H$_2$), 31.8 (*C*H$_2$), 30.5 (CO*C*H$_3$), 30.2 (*C*H$_2$), 29.6 (*C*H$_2$), 29.3 (*C*H$_2$), 25.7 (*C*H$_2$), 22.6 (*C*H$_2$), 18.4 (*C*H$_2$), 14.0 ($CH_2$*C*H$_3$); *m*/*z* (FAB) 227 (78%, $MH^+$), 169 (100%). Found (FAB): $MH^+$ 227.2016. $C_{14}H_{26}O_2H^+$ requires 227.2011.

Data for **18** (*cis*-isomer) (Found: C, 74.79; H, 11.58%. $C_{14}H_{26}O_2$ requires: C, 74.96; H, 11.60%); $\nu_{max}$ (thin film)/cm$^{-1}$ 2930, 2858, 1717, 1458, 1356, 1197, 1080; $\delta_H$ (400 MHz; $CDCl_3$): 3.74–3.68 (1H, m, OC*H*CH$_2$CO), 3.26–3.22 (1H, m, C*H*OCHCH$_2$CO), 2.64 (1H, dd, *J* 15.1 and 8.1, C*H*HCOCH$_3$), 2.38 (1H, dd, *J* 15.1 and 4.8), 2.16 (3H, s, COC$H_3$), 1.82–1.11 (16H, m, 8 × C$H_2$), 0.86 (3H, t, *J* 7.0, $CH_2CH_3$); $\delta_C$ (100 MHz; $CDCl_3$): 207.8 (*C*OCH$_3$), 78.0 (O*C*HCH$_2$CO), 74.4 (*C*HOCH-CH$_2$CO), 50.4 (*C*H$_2$CO), 36.4 (*C*H$_2$), 31.8 (*C*H$_2$), 31.6 (*C*H$_2$), 31.3 (*C*H$_2$), 31.0 (CO*C*H$_3$), 29.3 (*C*H$_2$), 25.5 (*C*H$_2$), 23.5 (*C*H$_2$), 22.6 (*C*H$_2$), 14.0 ($CH_2$*C*H$_3$); *m*/*z* (FAB) 227 (40%, $MH^+$), 169 (100%). Found (FAB): $MH^+$ 227.2015. $C_{14}H_{26}O_2H^+$ requires 227.2011.

**Formation under thermodynamic control.** To a stirred solution of **5** (0.080 g, 0.35 mmol) in dichloromethane (1.2 mL) at ambient temperature was added TMSOTf (0.064 mL, 0.35 mmol). After stirring at the same temperature for 30 min the reaction mixture was quenched by the addition of phosphate buffer (pH 7.4, 4 mL), the aqueous layer extracted with diethyl ether (3 × 10 mL), and the combined organic extracts dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a slightly yellow oil. Proton NMR spectroscopic analysis of the crude product showed a 93.5:6.5 ratio of **18**:**15** by integration of the signals at $\delta_H$ = 2.64 (**18**) and 2.75 (**15**). Purification by flash column chromatography, eluting with 20% diethyl ether–petroleum ether (bp 40–60 °C), gave **18** (0.058 g, 73%) and **15** (0.004 g, 5%) as colourless oils. Spectroscopic data for **15** and **18** were identical to those previously described.

**Isomerisation to the equilibrium mixture at ambient temperature.** *From **18***. To a stirred solution of **18** (0.046 g, 0.20 mmol) in dichloromethane (0.67 mL) at ambient temperature was added TMSOTf (0.037 mL, 0.20 mmol). After stirring at ambient temperature for 30 min the reaction mixture was quenched by the addition of phosphate buffer (pH 7.4, 1 mL), the aqueous layer extracted with diethyl ether (3 × 3 mL), and the combined organic extracts dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a slightly yellow oil. Proton NMR spectroscopic analysis of the crude product showed a 93.5:6.5 ratio of **18**:**15** by integration of the signals at $\delta_H$ = 2.64 (**18**) and 2.75 (**15**). Purification by flash column chromatography, eluting with 20% diethyl ether–petroleum ether (bp 40–60 °C), gave **18** (0.042 g, 91%) and **15** (0.003 g, 6%) as colourless oils. Spectroscopic data for **15** and **18** were identical to those previously reported.

*From **15***. To a stirred solution of **15** (0.043 g, 0.19 mmol) in dichloromethane (0.65 mL) at ambient temperature was added TMSOTf (0.034 mL, 0.19 mmol). After stirring at ambient temperature for 30 min the reaction mixture was quenched by the addition of phosphate buffer (pH 7.4, 1 mL), the aqueous layer extracted with diethyl ether (3 × 3 mL), and the combined organic extracts dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a slightly yellow oil. Proton NMR spectroscopic analysis of the crude product showed a 93.5:6.5 ratio of **18**:**15** by integration of the signals at $\delta_H$ = 2.64 (**18**) and 2.75 (**15**). Purification by flash column chromatography, eluting with 20% diethyl ether–petroleum ether (bp 40–60 °C), gave **18** (0.039 g, 90%) and **15** (0.003 g, 6%) as colourless oils. Spectroscopic data for **15** and **18** were identical to those previously described.

### 2-(*trans*-6′-Hexyltetrahydropyran-2′-yl)-1-phenylethanone 16 and 2-(*cis*-6′-hexyltetrahydropyran-2′-yl)-1-phenylethanone 19

**Formation under kinetic control.** To a stirred solution of **6** (150 mg, 0.53 mmol) in dichloromethane (1.8 mL) at −78 °C

was added TMSOTf (5 μL, 0.028 mmol). After stirring at the same temperature for 5 min the reaction mixture was quenched by the addition of phosphate buffer (pH 7.4, 2 mL), the aqueous layer extracted with diethyl ether (3 × 5 mL), and the combined organic extracts dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a slightly yellow oil. Proton NMR spectroscopy of the crude product showed a 2:98 ratio of **19**:**16** by integration of the signals at $\delta_H = 3.02$ (**16**) and 2.92 (**19**). Purification by flash column chromatography, eluting with 20% diethyl ether–petroleum ether (bp 40–60 °C), gave **19** (3 mg, 2%) and then **16** (120 mg, 80%) as colourless oils.

Data for **16** (Found: C, 79.10; H, 9.84%. $C_{19}H_{28}O_2$ requires: C, 79.12; H, 9.78%); $\nu_{max}$ (thin film)/cm$^{-1}$ 2929, 2856, 1687, 1598, 1448, 1376, 1042; $\delta_H$ (400 MHz; $CDCl_3$) 7.96–7.94 (2H, m, *o*-Ph), 7.54 (1H, t, *J* 7.3, *p*-Ph), 7.45 (2H, t, *J* 7.3, *m*-Ph), 4.39–4.33 (1H, m, C*H*$CH_2$COPh), 3.74–3.69 (1H, m, C*H*OCHCH$_2$COPh), 3.30 (1H, dd, *J* 15.4 and 8.7, C*H*HCOPh), 3.02 (1H, dd, *J* 15.4 and 6.6, CH*H*COPh), 1.80–1.61 (5H, m, C*H*H and 2 × C$H_2$), 1.45–1.16 (11H, m, CH*H* and 5 × C$H_2$), 0.86 (3H, t, *J* 6.6, C$H_3$); $\delta_C$ (100 MHz; $CDCl_3$): 198.7 (*C*OPh), 137.4 (Ph, quat.), 132.9 (Ph), 128.5 (Ph), 128.2 (Ph), 72.0 (O*C*HCH$_2$COPh), 67.7 (C*H*OCHCH$_2$COPh), 43.4 (*C*H$_2$COPh), 32.8 (*C*H$_2$), 31.8 (*C*H$_2$), 30.4 (*C*H$_2$), 29.6 (*C*H$_2$), 29.2 (*C*H$_2$), 25.7 (*C*H$_2$), 22.6 (*C*H$_2$), 18.5 (*C*H$_2$), 14.1 (*C*H$_3$); *m*/*z* (FAB) 289 (20%), 169 (21%), 105 (100%). Found (FAB): MH$^+$ 289.2161. $C_{19}H_{29}O_2$ requires 289.2168.

Data for **19** (Found: C, 79.16; H, 9.79%. $C_{19}H_{28}O_2$ requires: C, 79.12; H, 9.78%); $\nu_{max}$ (thin film)/cm$^{-1}$ 2929, 2861, 1688, 1597, 1444, 1348, 1064; $\delta_H$ (400 MHz; $CDCl_3$) 7.98–7.96 (2H, m, *o*-Ph), 7.54 (1H, t, *J* 7.3, *p*-Ph), 7.44 (2H, t, *J* 7.8, *m*-Ph), 3.96–3.89 (1H, m, C*H*CH$_2$COPh), 3.33–3.25 (2H, m, C*H*OCHCH$_2$COPh and C*H*HCOPh), 2.92 (1H, dd, *J* 15.6 and 6.2, CH*H*COPh), 1.85–1.19 (16H, m, 8 × C$H_2$) 0.85 (3H, t, *J* 6.6, C$H_3$); $\delta_C$ (100 MHz; $CDCl_3$): 198.9 (*C*OPh), 137.6 (quat., Ph), 132.9 (Ph), 128.4 (Ph), 128.3 (Ph), 78.1 (O*C*HCH$_2$COPh), 74.6 (C*H*OCHCH$_2$COPh), 45.6 (*C*H$_2$COPh), 36.5 (*C*H$_2$), 31.8 (*C*H$_2$), 31.7 (*C*H$_2$), 29.3 (2 × *C*H$_2$), 25.4 (*C*H$_2$), 23.6 (*C*H$_2$), 22.6 (*C*H$_2$), 14.1 (*C*H$_3$); *m*/*z* (FAB) 289 (87%), 105 (100%). Found (FAB): MH$^+$ 289.2163. $C_{19}H_{29}O_2$ requires 289.2168.

**Isomerisation to the equilibrium mixture at ambient temperature.** Following the procedure described above for isomerisation of **15** to the equilibrium mixture at ambient temperature, **16** (50 mg, 0.174 mmol) was isomerised to a mixture of **19** and **16** in the ratio 93.5:6.5 by integration of the signals at $\delta_H = 3.02$ (**16**) and 2.92 (**19**) in the 400 MHz proton NMR spectrum. The combined isolated yield of **16** and **19** was 49 mg, 98%; spectroscopic data for **16** and **19** were identical to those previously described.

### 1-(*trans*-6′-Hexyltetrahydropyran-2′-yl)hexan-2-one 17 and 1-(*cis*-6′-hexyltetrahydropyran-2′-yl)hexan-2-one 20

**Formation under kinetic control.** To a stirred solution of **6** (200 mg, 0.75 mmol) in dichloromethane (2.5 mL) at −78 °C was added TMSOTf (5 μL, 0.040 mmol). After stirring at the same temperature for 5 min the reaction mixture was quenched by the addition of phosphate buffer (pH 7.4, 3 mL), the aqueous layer extracted with diethyl ether (3 × 5 mL), and the combined organic extracts dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a slightly yellow oil. Proton NMR spectroscopic analysis of the crude product showed a 2.5:97.5 ratio of **20**:**17** by integration of the signals at $\delta_H = 2.75$ (**17**) and 2.64 (**20**). Purification by flash column chromatography, eluting with 20% diethyl ether–petroleum ether (bp 40–60 °C), gave **20** (4 mg, 2%) and **17** (170 mg, 85%) as colourless oils.

Data for **17** (Found: C, 76.18; H, 12.16%. $C_{17}H_{32}O_2$ requires: C, 76.08; H, 12.02%); $\nu_{max}$ (thin film)/cm$^{-1}$ 2934, 2860, 1714, 1461, 1378, 1203, 1033; $\delta_H$ (400 MHz; $CDCl_3$): 4.41–4.15 (1H, m, OC*H*CH$_2$CO), 3.67–3.61 (1H, m, C*H*OCHCH$_2$CO), 2.74 (1H, dd, *J* 15.0 and 8.2, CHC*H*HCOCH$_2$), 2.43 (2H, t, *J* 7.3, CHCH$_2$COC*H*$_2$), 2.37 (1H, dd, *J* 15.0 and 7.4, CHCH*H*-COCH$_2$), 1.74–1.18 (20H, m, 10 × C$H_2$), 0.88 (3H, t, *J* 7.4, CH$_3$), 0.86 (3H, t, *J* 6.4, CH$_3$); $\delta_C$ (100 MHz; $CDCl_3$): 209.6 (CH$_2$*C*OCH$_2$), 71.6 (CHO*C*HCH$_2$COCH$_2$), 67.6 (*C*HOCH-CH$_2$COCH$_2$), 47.3 (CH*C*H$_2$COCH$_2$), 43.2 (CHCH$_2$CO*C*H$_2$), 32.9 (*C*H$_2$), 31.8 (*C*H$_2$), 30.3 (*C*H$_2$), 29.3 (*C*H$_2$), 25.7 (*C*H$_2$), 25.6 (2 × *C*H$_2$), 22.6 (*C*H$_2$), 22.3 (*C*H$_2$), 16.5 (*C*H$_2$), 14.0 (*C*H$_3$), 13.8 (*C*H$_3$); *m*/*z* (FAB) 269 (23%, MH$^+$), 169 (35%), 85 (100%). Found (FAB): MH$^+$ 269.2481. $C_{17}H_{33}O_2$ requires 269.2480.

Data for **20** (Found: C, 76.14; H, 12.03%. $C_{17}H_{32}O_2$ requires: C, 76.08; H, 12.02%); $\nu_{max}$ (thin film)/cm$^{-1}$ 2931, 2856, 1712, 1456, 1370, 1274, 1055; $\delta_H$ (400 MHz; $CDCl_3$): 3.76–3.70 (1H, m, OC*H*CH$_2$CO), 3.27–3.22 (1H, m, C*H*OCHCH$_2$CO), 2.64 (1H, dd, *J* 15.0 and 8.0, CHC*H*HCOCH$_2$), 2.52–2.33 (3H, m, CHCH$_2$COC*H*$_2$ and CHCH*H*COCH$_2$), 1.82–1.08 (20H, m, 10 × C$H_2$), 0.89 (3H, t, *J* 7.3, CH$_3$), 0.87 (3H, t, *J* 6.9, CH$_3$); $\delta_C$ (100 MHz; $CDCl_3$): 210.1 (CH$_2$*C*OCH$_2$), 78.0 (CHO*C*H-CH$_2$COCH$_2$), 74.6 (*C*HOCHCH$_2$COCH$_2$), 49.5 (CH*C*H$_2$-COCH$_2$), 43.7 (CHCH$_2$CO*C*H$_2$), 36.5 (*C*H$_2$), 31.8 (*C*H$_2$), 31.7 (*C*H$_2$), 29.3 (2 × *C*H$_2$), 25.6 (*C*H$_2$), 25.5 (*C*H$_2$), 22.6 (2 × *C*H$_2$), 22.3 (*C*H$_2$), 14.0 (*C*H$_3$), 13.8 (*C*H$_3$); *m*/*z* (FAB) 269 (100%, MH$^+$). Found (FAB): MH$^+$ 269.2481. $C_{17}H_{33}O_2$ requires 269.2480.

**Isomerisation to the equilibrium mixture at ambient temperature.** Following the procedure described above for isomerisation of **15** to the equilibrium mixture at ambient temperature, **17** (0.071 g, 0.27 mmol) was isomerised to a mixture of **20** and **17** in the ratio 93:7 by integration of the signals at $\delta_H = 2.75$ (**17**) and 2.64 (**20**) in the 400 MHz proton NMR spectrum. The combined isolated yield of **17** and **20** was 0.068 g, 96%; spectroscopic data for **17** and **20** were identical to those previously described.

### 1-(*cis*-5-Heptyltetrahydrofuran-2-yl)propan-2-one and 1-(*trans*-5-heptyltetrahydrofuran-2-yl)propan-2-one 21

To a stirred solution of **13** (0.184 g, 0.81 mmol) in dichloromethane (2.7 mL) at −78 °C was added TMSOTf (0.007 mL, 0.04 mmol). After stirring at −78 °C for 5 min the reaction mixture was quenched by the addition of phosphate buffer (pH 7.4, 3 mL), the aqueous layer extracted with diethyl ether (3 × 10 mL), and the combined organic extracts dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a slightly yellow oil. Proton NMR spectroscopic analysis of the crude product showed two products in the ratio of 45:55 by integration of the signals at $\delta_H = 2.64$ (minor isomer) and 2.75 (major isomer). Purification by flash column chromatography, eluting with 20% diethyl ether–petroleum ether (bp 40–60 °C), gave an inseparable mixture of *cis*- and *trans*-**21** (0.166 g, 90%) as a colourless oil. Data for mixture of isomers (Found: C, 73.62; H, 11.61%. $C_{14}H_{26}O_2$ requires: C, 74.29; H, 11.58%); $\nu_{max}$ (thin film)/cm$^{-1}$ 2927, 2857, 1714, 1463, 1358, 1165, 1072; $\delta_H$ (400 MHz; $CDCl_3$): 4.32–4.25 (1H minor, m, OC*H*CH$_2$CO), 4.17–4.13 (1H major, m, OC*H*CH$_2$CO), 3.93–3.85 (1H minor, m, C*H*OCH-CH$_2$CO), 3.78–3.74 (1H major, m, C*H*OCHCH$_2$CO), 2.74–2.67 (1H major and 1H minor, m, C*H*HCOCH$_3$), 2.53–2.45 (1H major and 1H minor, m, CH*H*COCH$_3$), 2.14 (3H major and 3H minor, s, COC$H_3$), 2.11–1.15 (16H major and 16H minor, m, 8 × C$H_2$), 0.84 (3H major and 3H minor, t, *J* 6.4, CH$_2$C$H_3$); $\delta_C$ (100 MHz; $CDCl_3$): 207.4 (*C*OCH$_3$, minor), 207.3 (*C*OCH$_3$, major), 79.6 (O*C*HCH$_2$CO, major), 79.0 (O*C*HCH$_2$CO, minor), 76.7 (*C*HOCHCH$_2$CO, major), 74.9 (*C*HOCHCH$_2$CO, minor), 50.1 (*C*H$_2$CO, major), 49.9 (*C*H$_2$CO, minor), 36.6 (*C*H$_2$, major and minor), 35.9 (*C*H$_2$, major and minor), 31.8 (*C*H$_2$, major and minor), 31.2 (*C*H$_2$, major and minor), 30.6 (CO*C*H$_3$, major and minor), 29.6 (*C*H$_2$, major and minor), 29.2 (*C*H$_2$, major and minor), 26.1 (*C*H$_2$, major and minor), 22.6 (*C*H$_2$, major and minor), 14.0 (CH$_2$*C*H$_3$, major and minor); *m*/*z*

(FAB) 227 (63%, $MH^+$), 169 (100%). Found (FAB): $MH^+$ 227.2007. $C_{14}H_{27}O_2$ requires 227.2011.

### (*S*)-Hept-6-en-2-ol 23

To a stirred solution of (*S*)-propylene oxide (2.0 g, 34.5 mmol) in tetrahydrofuran (60 mL) at −30 °C was added a solution of dilithium tetrachlorocuprate in tetrahydrofuran (0.1 M, 34.5 mL, 3.45 mmol) followed by a solution of butenylmagnesium bromide in tetrahydrofuran (0.5 M, 83 mL, 41.5 mmol). After 30 min the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (10 mL) followed by distilled water (10 mL), and extracted with diethyl ether (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave a yellow oil. Purification by flash column chromatography, eluting with 30% diethyl ether–petroleum ether (bp 40–60 °C) gave **23** (3.73 g, 95%) as a colourless oil. $[\alpha]_D^{31}$ +6.5 (*c* 1.60, $CHCl_3$); $\nu_{max}$ (thin film)/$cm^{-1}$ 3354 (br, O-H), 3077, 2971, 2930, 2860, 1641, 1460, 1374, 1324, 1122; $\delta_H$ (400 MHz; $CDCl_3$): 5.83–5.72 (1H, m, C*H*=$CH_2$), 4.98 (1H, d, *J* 18.1, CH=C*H*H), 4.92 (1H, d, *J* 10.2, CH=CH*H*), 3.78–3.74 (1H, m, C*H*OH), 2.07–2.03 (2H, m, $CH_2$), 1.80 (1H, br s, O*H*), 1.51–1.38 (4H, m, 2 × $CH_2$), 1.15 (3H, d, *J* 6.2, $CH_3$); $\delta_C$ (100 MHz; $CDCl_3$): 138.7 ($CH_2CHCH_2$), 114.5 ($CH_2CH_2CHCH_2$), 67.9 (*C*HOH), 38.7 ($CH_2$), 33.6 ($CH_2$), 25.0 ($CH_2$), 21.1 ($CH_3$); *m*/*z* (EI) 96 (33%, M − $H_2O$), 81 (100%). Found (EI): M − $H_2O$ 96.0939. $C_7H_{12}$ requires 96.0940.

### (*S*)-6-Methyltetrahydropyran-2-ol 24 (anomeric mixture)

To a stirred solution of **23** (3.53 g, 30.96 mmol) in dichloromethane (250 mL) at −78 °C was added anhydrous sodium bicarbonate (1 g), and ozone bubbled through until the reaction mixture became light blue (approximately 30 min). Triphenylphosphine (8.9 g, 34.06 mmol) was added to the reaction mixture, which was allowed to warm to ambient temperature and stirred for 12 hours. The solvent was removed *in vacuo* to leave a slightly creamy oil which was purified by flash column chromatography, eluting with 25% to 35% diethyl ether–petroleum ether (bp 40–60 °C), to give **24** (3.21 g, 89%, a 3:2 mixture of anomers) as a colourless oil. $[\alpha]_D^{31}$ −30.0 (*c* 0.80, $CHCl_3$); $\nu_{max}$ (thin film)/$cm^{-1}$ 3419 (br), 2970, 2936, 1444, 1385, 1163, 1064; $\delta_H$ (400 MHz; $CDCl_3$): 5.26 (1H minor anomer, br s, C*H*OH), 4.67 (1H major anomer, br t, *J* 7.1, C*H*OH), 4.41 (1H major anomer, br s, O*H*), 4.07 (1H minor anomer, br q, *J* 6.1, $CH_3CH$), 3.80 (1H minor anomer, br s, O*H*), 3.56–3.52 (1H major anomer, m, $CH_3CH$), 1.81–1.08 (9H major anomer and 9H minor anomer, m, $CH_3$ and 3 × $CH_2$); $\delta_C$ (100 MHz; $CDCl_3$): 96.4 (*C*HOH, major anomer), 91.8 (*C*HOH, minor anomer), 72.5 ($CH_3CH$, major anomer), 64.9 ($CH_3CH$, minor anomer), 33.0 and 32.5 ($CH_2$, major and minor anomers), 32.4 and 32.2 ($CH_2$, major and minor anomers), 29.5 and 22.1 ($CH_2$, major and minor anomers), 21.7 ($CH_3$, minor anomer), 21.5 ($CH_3$, major anomer), 17.4; *m*/*z* (EI) 116 (24%), 70 (100%). Found (EI): $(M - H_2O)^+$ 98.0735. $C_6H_{10}O$ requires 98.0732.

### (2*R*,6*S*)-6-Methyltetrahydropyran-2-yl acetate 25

To a stirred solution of **24** (3.2 g, 27.6 mmol) in tetrahydrofuran (50 mL) at −78 °C was added a solution of potassium hexamethyldisilylazide in toluene (0.5 M, 58 mL, 29.0 mmol) dropwise, and the reaction mixture warmed to 0 °C over 5 min before cooling to −78 °C. Acetic anhydride (3.13 mL, 33.2 mmol) was added dropwise, and the reaction mixture stirred for 2 hours at −78 °C before quenching with saturated aqueous ammonium chloride solution (10 mL). Distilled water was added (10 mL), the aqueous layer extracted with diethyl ether (3 × 40 mL), and the combined organic extracts dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to leave a slightly yellow oil. Purification by flash column chromatography, eluting with 20% diethyl ether–petroleum ether (bp 40–60 °C) gave **25** (3.89 g, 96%) as a colourless oil. $[\alpha]_D^{31}$ +24.5 (*c* 1.5, $CHCl_3$); $\nu_{max}$ (thin film)/$cm^{-1}$ 2926, 2362, 1714, 1453, 1383, 1263, 1207, 1162, 1097, 1052, 1017; $\delta_H$ (400 MHz; $CDCl_3$): 5.51 (1H, dd, *J* 9.7 and 2.3, OC*H*O), 3.56–3.51 (1H, m, $CH_3CH$), 1.95 (3H, $COCH_3$), 1.78–1.73 (1H, m, $CHCH_2CHH$), 1.67–1.60 (1H, m, $OCH(CHH)O$), 1.49–1.41 (2H, m, $CH_3CHCHH$ and $CHCH_2CHH$), 1.36–1.29 (1H, m, $OCH(CHH)O$), 1.13–1.06 (4H, m, $CH_3CH$ and $CH_3CHCHH$); $\delta_C$ (100 MHz; $CDCl_3$): 169.1 ($COCH_3$), 94.6 (O*C*HO), 73.0 ($CH_3CH$), 31.8 ($CH_3CHCH_2$), 29.6 ($OCH(CH_2)O$), 21.6 ($CH_2CH_2CH_2$), 21.4 ($CH_3CH$), 21.0 ($COCH_3$); *m*/*z* (EI) 158 (100%, $M^+$). Found (EI): $M^+$ 158.0929. $C_8H_{14}O_3$ requires 158.0943.

### (2*R*,6*S*)-2-Isopropenyloxy-6-methyltetrahydropyran 26

To a stirred solution of **25** (1.40 g, 9.6 mmol) in tetrahydrofuran (20 mL) at −30 °C was added a solution of Tebbe reagent in toluene (0.5 M, 23.0 mL, 11.5 mmol) dropwise over 10 min. After stirring at the same temperature for 1 hour the reaction mixture was quenched by careful dropwise addition of 10% aqueous sodium hydroxide solution (1.5 mL), anhydrous $MgSO_4$ was added (2 g) and the precipitated residues removed by filtration through a pad of Celite, eluting with diethyl ether (200 mL). Evaporation of the volatile components *in vacuo* left an orange oil which was purified by passage through a short column of activated alumina, eluting with 50% diethyl ether–petroleum ether (bp 40–60 °C), to give **26** (1.31 g, 92%) as a colourless oil. $\nu_{max}$ (thin film)/$cm^{-1}$ 2931, 2859, 1664, 1616, 1456, 1032; $\delta_H$ (400 MHz; $CDCl_3$): 4.89–4.87 (1H, m, OC*H*O), 4.13 (1H, s, $CH_3CCHH$), 4.01 (1H, s, $CH_3CCHH$), 3.61–3.56 (1H, m, $CH_3CH$), 1.90–1.10 (12H, m, 2 × $CH_3$ and 3 × $CH_2$); $\delta_C$ (100 MHz; $CDCl_3$): 157.5 ($CH_3C(CH_2)O$), 98.6 (O*C*HO), 85.1 ($CH_3C(CH_2)O$), 72.3 ($CH_3CH$), 32.2 ($CH_2$), 30.3 ($CH_2$), 22.1 ($CH_2$), 21.6 ($CH_3$), 20.9 ($CH_3$); *m*/*z* (EI) 156 (100%, $M^+$). Found (EI): $M^+$ 156.1159. $C_8H_{14}O_3$ requires 156.1150.

### (*S*,*S*)-1-(6′-Methyltetrahydropyran-2′-yl)propan-2-one 27 and (2*R*,6*S*)-1-(6′-methyltetrahydropyran-2′-yl)propan-2-one 28

To a stirred solution of **26** (1.31 g, 8.85 mmol) in dichloromethane (30 mL) at ambient temperature was added TMSOTf (0.8 mL, 4.43 mmol). After stirring at ambient temperature for 30 min the reaction mixture was quenched by the addition of phosphate buffer (pH 7.4, 5 mL), extracted with diethyl ether (3 × 10 mL), and the combined organic extracts dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a slightly yellow oil. Proton NMR spectroscopic analysis of this crude product showed a 93:7 ratio of **27**:**28** by integration of the signals at $\delta_H$ = 3.73–3.67 (**27**) and 4.28–4.22 (**28**). Purification by flash column chromatography, eluting with 25% diethyl ether–petroleum ether (bp 40–60 °C), gave **27** (1.05 g, 80%) and **28** (79 mg, 6%) as colourless oils.

Data for **27** (*cis*-isomer) (Found: C, 69.28; H, 10.38%. $C_9H_{16}O_2$ requires: C, 69.17; H, 10.32%); $[\alpha]_D^{31}$ −32.0 (*c* 0.50, $CHCl_3$); $\nu_{max}$ (thin film)/$cm^{-1}$ 2933, 2860, 1714, 1442, 1371, 1204, 1075, 1045, 1017; $\delta_H$ (400 MHz; $CDCl_3$): 3.73–3.67 (1H, m, OC*H*$CH_2$CO), 3.41–3.36 (1H, m, $CH_3CH$), 2.62 (1H, dd, *J* 15.5 and 7.6, C*H*HCO$CH_3$), 2.36 (1H, dd, *J* 15.5 and 5.1, CH*H*CO$CH_3$), 2.12 (3H, s, $COCH_3$), 1.76–1.71 (1H, m, C*H*H), 1.55–1.44 (3H, m, CH*H* and $CH_2$), 1.16–1.06 (5H, m, $CH_3CH$ and 2 × $CH_2$); $\delta_C$ (100 MHz; $CDCl_3$): 207.6 ($COCH_3$), 74.0 (O*C*H$CH_2$CO), 73.9 ($CH_3CH$), 50.3 ($CH_2COCH_3$), 32.9, 31.1, 31.0 ($COCH_3$), 23.4, 22.0 ($CH_3CH$); *m*/*z* (EI) 156 (77%, $M^+$), 143 (86%), 100 (100%). Found (EI): $M^+$ 156.1154. $C_9H_{16}O_2$ requires 156.1150.

Data for **28** (*trans* isomer): $[\alpha]_D^{31}$ +11.6 (*c* 0.90, $CHCl_3$); $\nu_{max}$ (thin film)/$cm^{-1}$ 2934, 1755, 1446, 1369, 1232, 1039; $\delta_H$ (400 MHz; $CDCl_3$): 4.28–4.22 (1H, m, OC*H*$CH_2$CO), 3.92–3.87 (1H, m, $CH_3CH$), 2.79 (1H, dd, *J* 15.2 and 8.0, C*H*HCO$CH_3$), 2.47 (1H, dd, *J* 15.2 and 5.6, CH*H*CO$CH_3$), 2.23 (3H, s,

COC$H_3$), 1.74–1.70 (1H, m, C$H$H), 1.59–1.48 (3H, m, CH$H$ and C$H_2$), 1.12–1.09 (5H, m, C$H_3$CH and 2 × C$H_2$); *m*/*z* (EI) 156 (50%, $M^+$), 143 (100%). Found (EI): $M^+$ 156.1161. $C_9H_{16}O_2$ requires 156.1150.

### (+)-(*S*,*S*)-(*cis*-6′-Methyltetrahydropyran-2′-yl)acetic acid **22**[20u,23]

To a stirred solution of **27** (200 mg, 1.35 mmol) in dioxane (10 mL) at ambient temperature was added 20 mL of a freshly prepared solution of sodium hypobromite (prepared from bromine (3.3 mL), aqueous sodium hydroxide (10%, 85 mL) and dioxane (20 mL)), and the biphasic reaction mixture was stirred vigorously for 3 hours at ambient temperature. The reaction mixture was quenched with aqueous sodium sulfite solution (10%, 5 mL), the aqueous layer acidified to pH 1 with hydrochloric acid (3 M), and the mixture extracted with diethyl ether (2 × 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent evaporated *in vacuo* to leave a yellow oil which was purified by flash column chromatography, eluting with 20% ethyl acetate–petroleum ether (bp 40–60 °C) to give **22** (145 mg, 68%) as a colourless oil. $[a]_D^{31}$ +20.5 (*c* 1.23, $CHCl_3$) [lit.,[23] $[a]_D^{22}$ +18.6 (*c* 2.77, $CHCl_3$)]; $\nu_{max}$ (thin film)/$cm^{-1}$ 3700–2700 (br, O-H), 2934, 1713, 1443, 1295, 1071, 1040; $\delta_H$ (400 MHz; $CDCl_3$): 10.00 (1H, br s, COO$H$), 3.80–3.73 (1H, m, C$H$CH$_2$COOH), 3.55–3.48 (1H, m, CH$_3$C$H$), 2.57 (1H, dd, *J* 15.6 and 7.8, C$H$HCOOH), 2.47 (1H, dd, *J* 15.6 and 5.0, CH$H$COOH), 1.84–1.80 (1H, m, C$H$H), 1.65–1.47 (3H, m, CH$H$ and C$H_2$), 1.30–1.21 (2H, m, C$H_2$), 1.17 (3H, d, *J* 7.2, C$H_3$); $\delta_C$ (100 MHz; $CDCl_3$): 175.6 (*C*OOH), 74.5 (*C*H), 74.0 (*C*H), 41.3 (*C*H$_2$), 32.7 (*C*H$_2$), 30.8 (*C*H$_2$), 23.2 (*C*H$_2$), 22.0 (*C*H$_3$); *m*/*z* (EI) 158 (100%, $M^+$). Found (EI): $M^+$ 158.0943. $C_8H_{14}O_3$ requires 158.0943.

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