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The Quasi-Homo-Anomeric Interaction in Substituted Tetrahydropyranyl Radicals: Diastereoselectivity

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Abstract: The isomer distribution of products from the reaction of a range of simple cyclohexyl and tetrahydropyranyl radicals (**3** - **7**) with Bu_3SnD and with allyltributyltin, has been determined in order to gauge the influence of the classical anomeric effect and the quasi-homo-anomeric effect on stereoselectivity. In these unencumbered radicals, both anomeric effects caused a strong preference for *trans* deuterated products, but no significant stereoselectivity was observed for the allylation reactions. The difference between the two types of reaction suggests that deuteration is mainly under kinetic control whereas allylation has a greater tendency for thermodynamic control. © 1998 Elsevier Science Ltd. All rights reserved.

An effect known as quasi-homo-anomeric stabilisation was first invoked by Giese and Sustmann to rationalise the behaviour of certain carbohydrate radicals.[1,2] They suggested that a stabilising interaction can occur when a radical centre is flanked by an oxygen lone pair and a β-C–O bond, and that the orbital overlap, and hence stabilisation, will be maximised when the SOMO, an orbital containing an oxygen lone pair, and the σ^* of the C-O bond are coplanar. This hypothesis is consistent with the conformations of both simple acyclic radicals and of complex cyclic species revealed by EPR.[1-3] However, in the case of carbohydrate radicals, such as **1** and **2**, it is not clear what role the many substituents not involved in the quasi-homo-anomeric stabilisation play in determining the overall molecular structure. Very recently we reported our results with the related, but more simple tetrahydropyran-2-yl radicals (**3** and **4**),[4] which, by EPR spectroscopy, showed very similar conformations to that of the mannosyl radical (**2**). We also presented kinetic data for the reactions of the sulfide precursors of **3** and related radicals, showing that the isomers in which C-O bond and C-S were antiperiplanar reacted the fastest with the tributyltin radical. These findings support the existence of the quasi-homo-anomeric interaction in the unencumbered tetrahydropyranyl radicals (**3** and **4**).

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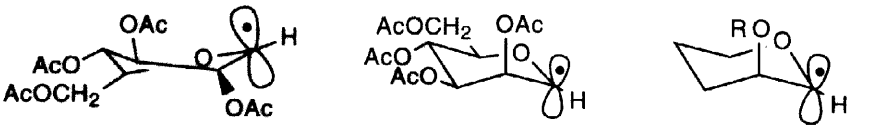


1 **2** **3**; R = C_3H_7CO **4**; R = t-C_4H_9CO

Figure 1: Structures of pyranos-1yl[1,2] and tetrahydropyran-2-yl[4] radicals, as determined by EPR.

The stereoselectivity towards various 1-pyranose radicals of a range of reagents, e.g. *N*-bromosuccinimide, bromine, tributyltin hydride and deuteride, and suitably substituted alkenes, has been studied by a number of workers.[5,6,7] In most of the reported cases, the α-face of the pyranose ring is the preferred side of attack. Such reactions are especially useful for the construction of β-glycosides. It is thought that axial bond formation is preferred because it allows the quasi-homo-anomeric interaction to operate throughout the bond forming process, whereas, due to geometric constraints, equatorial bond formation does not.[8] However, as with the above conformational studies, such attempts to rationalise the observed stereoselectivity of sugar radicals are complicated by the presence of extraneous substituents around the pyranose ring. We have, therefore, examined the stereoselectivity of the simpler cyclic radicals (**3** and **4**) unencumbered by superfluous substituents and compared the results with related radicals in which only the classical anomeric effect,[9] or no anomeric effect at all, can operate.

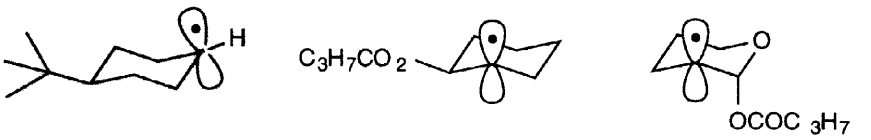
Results and Discussion

A: Reaction with Tributyltin Deuteride. As a preliminary investigation into the stereoselectivity of tetrahydropyranyl radical reactions, a range of substrates was treated with tributyltin deuteride, the results of which are shown in Table 1. As detailed below, standard NMR techniques were used to determine the stereochemical distribution of the products.

Table 1. Stereoselectivity of substituted cyclic radicals towards Bu_3SnD in benzene at 80°C.

Radical	Product	Stereoselectivity	
		trans	*cis*
5	**9**	1.0	3.3
6	**12**	1.4	1.0
7	**15**	8.0[a]	1.0
3	**18**	4.6	1.0
4	**20**	8.1	1.0
1	**26**	1.0	4.6[b]
2	**27**	19	1.0[b]

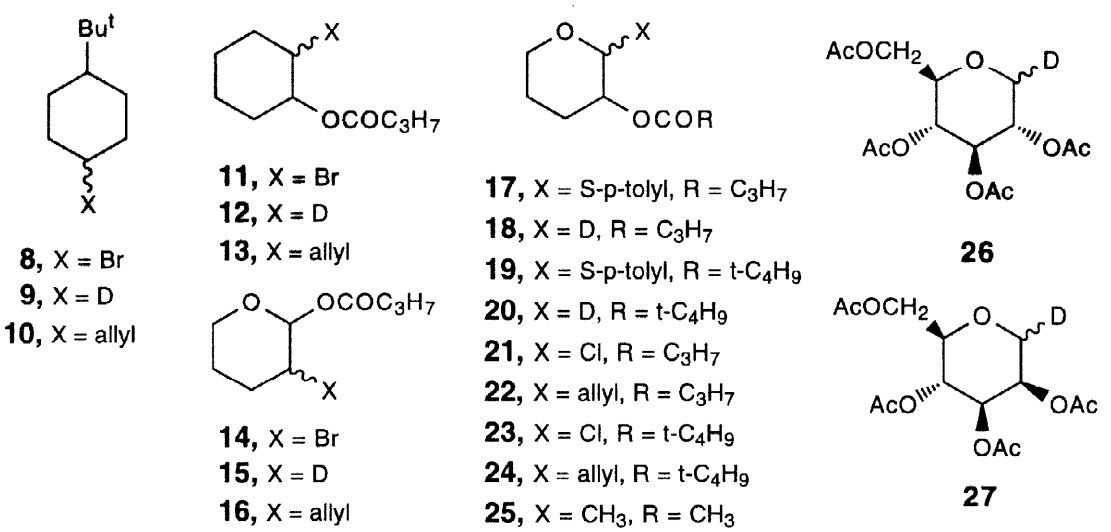
Footnotes: a; Lower limit. b; Data taken from ref 10.



5 **6** **7**

Figure 2: The structures of cyclohexyl and tetrahydropyran-3-yl radicals, as determined by EPR.[4]

To establish the stereoselectivity of ordinary, conformationally locked cyclohexyl radicals, 1-bromo-4-*t*-butylcyclohexane (**8**)[11] was treated with tributyltin deuteride at 80°C in benzene in the presence of AIBN, and the deuterated product (**9**) was distilled out of the product mixture. The ^{13}C NMR spectrum of this compound contained two sets of triplets due to C-1, one at 26.16 ppm and the other at 26.21 ppm (J = 18.8 Hz). The former had the greater intensity. A ^{2}H NMR spectrum of the product was also recorded, and it contained two peaks, one at 1.59 ppm and the other at 1.69 ppm, in a ratio of 3.30 : 1 respectively. The upfield signal was assumed to be due to the axially substituted *cis* deuteride.[12] As axial substituents are believed to shield their attached carbon atoms relative to equatorially substituted carbons,[13] the results from the two different spectra are consistent. A similar result (2.33 : 1) was obtained by Giese's group from the same reaction performed under virtually identical conditions.[14]



8, X = Br
9, X = D
10, X = allyl

11, X = Br
12, X = D
13, X = allyl

14, X = Br
15, X = D
16, X = allyl

17, X = S-p-tolyl, R = C_3H_7
18, X = D, R = C_3H_7
19, X = S-p-tolyl, R = t-C_4H_9
20, X = D, R = t-C_4H_9
21, X = Cl, R = C_3H_7
22, X = allyl, R = C_3H_7
23, X = Cl, R = t-C_4H_9
24, X = allyl, R = t-C_4H_9
25, X = CH_3, R = CH_3

26

27

Figure 3

Similar treatment of 2-bromocyclohexyl butyrate (**11**)[4] with tributyltin deuteride afforded 2-deuterocyclohexyl butyrate (**12**) which gave peaks in its ^{2}H NMR spectrum at 1.25 ppm and 1.70 ppm in a ratio of 1 0 : 1.4 respectively. Assuming that the upfield signal was due to the axial deuterium, and that the ester was in an equatorial orientation, we concluded that *trans*-**12** was the major product.

Treatment of the sulphide (**17**)[15] with tributyltin deuteride (0.02M) and AIBN in benzene at 80°C afforded a mixture of the reduced (**18**) and the rearranged product (**15**). The latter arises by the β-acyloxyalkyl rearrangement[16] of the initially formed radical (**3**) to give **7**. The ^{2}H NMR spectrum (77MHz, 50K) of **15** contained a single major peak at 1.80 ppm. Integration against a peak at 1.77 ppm gave a lower limit for the diastereoselectivity of the deuteration of **7** to be 8 : 1, assumed to be in favour of *trans*-**15**. A sample of **15** prepared by treatment of 3,4-dihydro-2H-pyran with monodeuterated butyric acid gave the same two peaks in

an approximately 1 : 1 ratio. The reduced compound (**18**) showed two peaks in its ^{2}H NMR spectrum at 3.3 ppm and 3.5 ppm, in a ratio of 1 : 4.6 respectively. The ester was again assumed to be in an equatorial orientation and the upfield signal due to the axial deuterium. Thus, the *trans* isomer was found to be the predominant component. Support for this conclusion came from its ^{1}H NMR spectrum which revealed that the downfield signal due to equatorial H-2 (3.80 ppm) had virtually disappeared and the upfield signal due to axial H-2 (3.58 ppm) had collapsed from a doublet of doublets to a broad singlet.

Similar methods were applied and similar results were obtained when the pivalate (**19**) reacted with tributyltin deuteride. The ^{2}H NMR spectrum of the reduced compound (**20**) suggested that it had a *trans* to *cis* ratio of 8.1 : 1.

The preference for axial attack by tin deuteride on the 4-*t*-butylcyclohexyl radical (**5**) is consistent with the results of Gruselle.[17] This natural tendency for axial attack by Bu_3SnD can be counteracted, however, by the incorporation of a β-ester substituent, as shown by the result of the deuteration reaction of **6**. The result of the reaction of Bu_3SnD with **3** clearly suggests that the quasi-homo-anomeric effect can significantly influence the stereochemical outcome of such reactions. Increasing the bulk of the ester (**4**) has the expected effect of increasing the stereoselectivity. The high selectivity of the deuteration of **7** shows that the classical anomeric effect[9] has an even stronger influence on stereochemical preference.

It is interesting to compare the above results with the deuteration reactions of the glycosyl radicals (**1** and **2**).[10] As mentioned earlier, these radicals tend to react on the α-face. When the 2-substituent is on the β-face (**2**), steric effects in this rigid system appear to induce a very high deuteration stereoselectivity. The stereoselectivity is much lower when the 2-substituent is on the α-face (**1**).

B. Carbon-Carbon Bond Formation. Encouraged by the results of the tin deuteride experiments, we decided to extend our investigation to a synthetically important C-C bond forming process. Allyltributyltin was chosen for this purpose as it has previously shown some stereoselectivity in radical reactions.[7,18]As with the deuteration reactions, it was initially necessary to determine the preferred direction of approach of allyltributyltin to unsubstituted cyclohexyl radicals. When 1-bromo-4-*t*-butylcyclohexane (**8**) was treated with allyltributyltin (1.2 eq) at 80°C in the presence of AIBN the purified product was found to contain the two diastereoisomers of the allylated compound (**10**).[19] The ^{1}H NMR spectrum of **10** showed resonances centred at 2.10 ppm, 4.19 ppm and 5.04 ppm, which confirmed the presence of the allyl moiety, but there were no peaks that could be readily used to determine the distribution of the stereoisomers. The stereoisomers of **10** were also found to be unresolvable by gas chromatography (capillary column), but the ^{13}C NMR spectrum showed a separate set of peaks for each diastereomer. The resonances at 48.1 ppm and 48.4 ppm assigned to C-1, i.e. the carbons attached to the *t*-butyl group, were considered to be the most indicative of product ratio because their shift difference is small and they are identically substituted, and thus would be expected to have virtually identical relaxation rates. A measurement of the relative intensities of these peaks indicated that the isomers were in equal proportion.

Table 2. **Stereoselectivity of substituted** cyclic radicals towards reaction with allyltributyltin at **80°C**.

Radical	Product	Stereoselectivity	
		trans	*cis*
5	**10**	1.0	1.0[a]
6	**13**	3.2	1.0[b]
7	**16**	3.7	1.0[b]
3	**22**	1.0	1.0[b]
4	**24**	1.0	1.0[b]

Footnote: a; No solvent used. b; Solvent was benzene.

When the 2-butanoyloxycyclohexyl bromide (**11**) was treated with allyltributyltin and AIBN, gas chromatography of the crude reaction mixture indicated that the ratio of diastereoisomers of **13** was 3.2 : 1. The allylated product (**13**) was separated from other contaminants by flash chromatography, but its ^{1}H NMR spectrum was not useful in the elucidation of the stereochemistry of the most abundant isomer. However, the ^{13}C NMR spectrum of **13** contained a signal for C-1 of the major isomer at 76.0 ppm, which was situated significantly downfield from the corresponding signal of the minor isomer at 71.7 ppm. This implies that in the minor component, the ester was in an axial orientation, whereas in the major component the ester was equatorially disposed.[13] Hence it was assumed that the major product was the *trans*-diequatorial isomer (*trans*-**13**) and the minor product the *cis* isomer (*cis*-**13**).

Treatment of the bromide (**14**) with allyltributyltin gave a moderate yield of allylated compound (**16**). The isomeric ratio of 1: 3.7 was determined by gas chromatography and ^{1}H NMR spectroscopy. The *trans* isomer (*trans*-**16**) was identified as the major component by virtue of its larger coupling between H-2 and H-3 in its ^{1}H NMR spectrum (7 Hz compared with 2 Hz for the *cis* compound).

The sulphide (**17**) was found to be quite unreactive towards allyltributyltin and it was therefore necessary to employ the corresponding chloride (**21**).[4] The allylated product (**22**) was still only obtained in low yield, presumably because of a short radical chain length and the thermal instability of the chloride. Gas chromatography (capillary column) of the crude reaction mixture showed the ratio of the diastereoisomers of **22** to be *ca* 1:1. This ratio did not change with prolonged heating of the reaction mixture. The corresponding pivalate (**23**)[4] gave identical results when treated allyltributyltin.

The allylation data are summarised in Table 2. By and large they are consistent with the view that the reactions of the various substituted cyclohexyl and tetrahydropyranyl radicals with allyltributyltin are more sensitive to steric effects in the product, and less sensitive to stereoelectronic effects, than the corresponding tributyltin deuteride reactions. This is reasonable since the former reactions have much lower rate constants than the latter (~4×10^4 M^{-1} s^{-1} at 80°C for addition of primary alkyl radicals to allyltributyltin[20] cf. 6×10^6 M^{-1} s^{-1} for the reaction between tributyltin hydride and cyclohexyl radicals at 80°C[21]). The transition structures of the allylation reactions are therefore expected to be more product-like, and consequently the reactions should show a greater tendency for thermodynamic control. Thus, for the simple 4-substituted cyclohexyl radical (**5**), axial and equatorial attack are equally favoured (*cf* axial : equatorial = 3.3 : 1.0 for Bu_3SnD). Giese's group also found that alkenes unsubstituted at the terminal end reacted with **5** to give an approximately 1 : 1 ratio of axial

to equatorial substitution products.[14] The reactions of the 2-substituted cyclohexyl radical (**6**) with allyltributyltin and with Bu_3SnD both show a preference for the *trans* product, but the selectivity for allylation is much higher. Once again, it appears that the thermodynamic factors favouring equatorial attack play a more significant role in the addition to allyltributyltin. Similar results were observed when the corresponding benzoate[18] and alcohol[7] were treated with allyltributyltin.

The lack of selectivity exhibited by the reactions of the radicals **3** and **4** with allyltributyltin is disappointing in terms of the potential of the quasi-homo-anomeric effect as a tool to control the stereoselectivity of C-C bond forming radical reactions. However, the results are consistent with the mechanistic principles outlined above. Because of the stabilisation arising from the quasi-homo-anomeric effect, the rate constant for the addition step is likely to be even lower with these radicals than it is for simple alkyl radicals and hence product distribution is heavily influenced by thermodynamic factors. Molecular mechanics calculations performed on a similar substrate (**25**) suggested that if the ester were axial, the most stable product would be *cis* by approximately 2.2 kcal mol^{-1}, whereas if the ester was equatorial, the most stable product would be *trans* by approximately 3.5 kcal mol^{-1}. It is reasonable to assume that the ester might be oriented somewhere between these two extremes in the transition structures that lead to **22** and **24**, since the quasi-homo-anomeric effect would be gradually reduced in strength as the amount of bond formation at C-2 increased.

The preferred formation of the *trans* diaxial product from the radical **7** can be similarly rationalised since in this case there appears to be no anomeric stabilisation of the radical centre and hence the transition structure should be more reactant like than is the case for the formation of **22** and **24**. Furthermore, molecular mechanics calculations show that the strain energy of the *trans* diaxial stereoisomer of **16** is only about 0.6 kcal mol^{-1} more than that of *cis* axial-equatorial form. Hence the stereoelectronically preferred formation of the axial C-C bond involves a very small thermodynamic penalty. Nevertheless, comparison with the data in table 2 shows that the reaction is less selective than the corresponding deuteration process. Although this hypothesis appears reasonable, there is also the possibility that boat like transition structures such as that proposed for the glucopyranosyl radical (**3**) may be involved.

Conclusions

Consistent with previous studies,[14] tributyltin deuteride has been found to have a natural tendency to react with a cyclohexyl radical (**5**) from an axial direction. This can be counteracted by the adjacent butyrate substituent in **6**. Importantly, the classical anomeric effect and the quasi-homo-anomeric effect both cause the otherwise unencumbered tetrahydropyranyl radicals (**3**, **4** and **7**) to react with tributyltin deuteride in a highly stereoselective fashion, favouring the *trans* products by up to 8 : 1. By contrast, **3**, **4**, and **5** show no diastereoselectivity on reaction with allyltributyltin, whereas **6** and **7** show moderate preference for the *trans* products. The contrast in stereochemical outcome of the two radical reactions is likely to be due to the allylation operating *via* a much later transition state which, in that case, increases the significance of thermodynamic control.

Experimental

General. ^1H and ^{13}C NMR spectra were recorded as $CDCl_3$ solutions on either a VARIAN XL-200 spectrometer (200 MHz for ^1H) or a VARIAN VXR-300 spectrometer (300 MHz for ^1H) and are reported in parts per million downfield from the tetramethylsilane internal reference (δ). Deuterium (^2H) NMR spectra

were recorded in benzene on a VARIAN VXR-300 spectrometer operating at 46 MHz unless otherwise stated. They were performed with a trace of D_6-benzene as an internal reference (δ 7.26 ppm). Low resolution mass spectra were recorded on a VG MICROMASS 7070 F mass spectrometer operating at 70 eV for electron impact ion generation (EI) or using ammonia for chemical ionisation (CI). High resolution mass spectra were obtained on an AEI MS 902 high resolution mass spectrometer.

3-(2,2-Dimethylpropanoyloxy)-2-(p-tolythio)tetrahydropyran (19). Pivaloyl chloride (320 μL, 2.7 mmol), DMAP (300 mg, 1.3 mmol) and *N,N*-dimethylaniline (320 μL, 2.8 mmol) were heated with 2-(p-tolythio)tetrahydropyran-3-ol[15] in dry chloroform (1.5 mL) at 60°C overnight. The resulting deep blue coloured solution was allowed to cool and was then diluted with diethyl ether, washed with HCl (1M, 2x) and saturated $NaHCO_3$ (3x), and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded a colourless oil which was purified by flash chromatography (5% ethyl acetate / hexane). The product (**19**) (260 mg, 62%) thus obtained partially crystallised on standing. ^{1}H NMR (200 MHz) d 1.00-2.10 (m, 13H, -C(CH_3)$_3$, H-4, 5), 2.31 (s, 3H, ArCH_3), 3.18-3.53 (m, 1H, H-6), 4.12-4.26 (m, 1H, H-6), 4.97-5.10 (m, 1H, H-3), 5.35 (d, 1H, J = 5 Hz, H-2), 7.10 (d, 2H, J = 8 Hz, *o*-ArH), 7.36 (d, 2H, J = 8 Hz, *m*-ArH); ^{13}C NMR (75 MHz) d 20.7 (ArCH_3), 22.7 (C-5), 25.9 (C-4), 26.8 (-C(*C*H_3)$_3$), 62.4 (C-6), 69.7 (C-3), 88.0 (C-2), 129.8, 131.1, 132.0, 137.3 (aromatic C), 177.9 (C=O); IR (film) 1730 (C=O) cm^{-1};
MS (EI) *m/z* 308 (weak, M$^+$), 207 (weak), 185 (28%), 91 (6), 85 (28), 57 (100); HRMS *m/z* 308.1446 (M$^+$), calcd for $C_{17}H_{24}O_3S$ 308.1446.

Deuteration Experiments. In a typical experiment, a solution of **17**[15] (0.4 g, 1.3 mmol), Bu_3SnD (0.6 g, 85%, 1.7 mmol) and AIBN (cat.) in benzene (85 mL) was deoxygenated with a slow stream of N_2. After the resulting solution was heated at reflux for 1-2 h, it was allowed to cool and the solvent removed to give a colourless oil. The reduced (**18**) and rearranged (**15**) products were isolated from the reaction mixture by flash chromatography (2.5% ethyl acetate / hexane). They were obtained in an approx. 1 : 1 ratio (0.2g, 89%). A similar procedure and work up was employed with the reactions of **8**,[11] *trans*-**11**[4] and **19**. In the case of **8** however, the product (**9**) was distilled out of the reaction mixture (bp 160-170°C).

A sample of **15** with a 1:1 ratio of diastereoisomers was prepared by treatment of 3,4-dihydro-2H-pyran (1.0g, 12 mmol) with monodeuterated butyric acid, at 0°C for 30 min. The deuteroacid had previously been synthesised by the hydrolysis of butyryl chloride (1.3 mL, 12 mmol) with D_2O (240 μL, 12 mmol). The product (**15**) was isolated by means of flash chromatography (0.2 g, 10%).

The spectroscopic and chromatographic properties of the deuterated products (**9**, **12**, **15**, **18** and **20**) were identical to the corresponding hydrogen analogues, except where the presence of deuterium could be detected (eg in ^{1}H and ^{2}H NMR spectra). The ^{2}H NMR data the deuterated compounds are detailed in the text.

1-(1,1-Dimethylethyl)-4-(2-propenyl)cyclohexane (10).[19] The bromide (**8**)[11] (0.5 g, 2.3 mmol) was heated at 80°C with allyltributyltin (0.9 g, 2.7 mmol) for several days. AIBN (cat.) was added twice a day until the reaction was approximately 80% complete, as determined by capillary gas chromatographic analysis of the reaction mixture. The allylated product (**10**) was isolated as a colourless oil (110 mg, 27%) by preparative gas chromatography (OV-17 packed column, thermal conductivity detection). ^{1}H NMR (300 MHz) δ 0.80-1.84 (m, 19H, C(CH_3)$_3$, H-1, 4, H_2-2, 3, 5, 6), 1.90-1.98 (m, 1H, -CH_2CHCH_2), 2.06-2.14 (m, 1H, -CH_2CHCH_2), 4.13-4.25 (m, 2H, -CHCH_2), 4.89-5.08 (m, 1H, -C*H*CH_2); ^{13}C NMR (75 MHz) δ 27.2 (-C(*C*H_3)$_3$), 27.4 (C-2, 6), 27.5 (-*C*(CH_3)$_3$), 30.1, 33.4 (C-3, 5), 35.6 (-*C*H_2CHCH), 37.7 (C-4), 48.1, 48.4 (C-1), 115.0, 115.1 (-CHCH_2), 137.8, 138.6 (-*C*HCH_2).

Butanoyloxy-2-(2-propenyl)cyclohexane (13). The bromide (**11**)[4] (200 mg, 0.8 mmol) was treated with allyltributyltin (330 mg, 1.0 mmol) and AIBN (cat.) in benzene in a similar manner to that used for the preparation of **22**. The usual work up and isolation yielded **13** (85 mg, 50%) as a colourless oil: ^{1}H NMR (300 MHz) δ 0.92-2.08 (m, 16H, -C*H*$_2$C*H*$_3$, -C*H*$_2$CHCH$_2$, H-2, H$_2$-3, 4, 5, 6), 2.27 (t, 2H, *J* = 7 Hz, -COCH$_2$-), 4.57 (d of t, 1H, $J_{1,6}$ = 5, $J_{1,2}$ =12 Hz, H-1), 4.93-5.03 (m, 2H, -CHC*H*$_2$), 5.67-5.83 (m, 1H, -C*H*CH$_2$); ^{13}C NMR (50 MHz) δ 13.6, 14.0 (-CH$_2$*C*H$_3$), 18.5 (-*C*H$_2$CH$_3$), 20.8, 22.6, 24.5, 25.1 (C-4, 5), 27.1, 30.0 (C-3), 31.5, 31.8 (C-6), 36.6, 36.7 (-CO*C*H$_2$-, -*C*H$_2$CHCH$_2$), 40.1, 41.7 (C-2), 71.7, 76.0 (C-1), 115.9, 116.1 (-CHCH$_2$), 136.4, 136.7 (-*C*HCH$_2$), 173.2 (C=O); MS (EI) *m/z* 168 (1%), 2 (32), 81 (65), 71 (94). (CI) *m/z* 228 (15%, (M + NH4)$^+$), 211 (31, (M + H)$^+$); IR (film) 3080 (C=CH$_2$), 1735 (C=O), 1640 (C=C) cm^{-1}; HRMS *m/z* 168.1149 [(M - CH$_3$CH=CH$_2$)$^+$], Calcd for C$_{10}$H$_{16}$O$_2$ 168.1150.

2-Butanoyloxy-3-(2-propenyl)tetrahydropyran (16). The bromide (**14**)[4] (140 mg, 0.6 mmol) was treated with allyltributyltin (250 mg, 0.8 mmol) and AIBN (cat.) in benzene (1 mL) at reflux for 7 h (see preparation of **22**). The usual work up and isolation afforded the allylated product (**16**) (60 mg, 47%) as a colourless oil: ^{1}H NMR (300 MHz) δ 0.93-1.02 (m, 3H, -CH$_2$C*H*$_3$), 1.28-2.50 (m, 11H, -COC*H*$_2$C*H*$_2$-, -C*H*$_2$CHCH$_2$, H-3, H$_2$-4, 5), 3.28-4.05 (m, 2H, H$_2$-6), 4.96-5.13 (m, 2H, -CHC*H*$_2$), 5.58 (d, 0.79H, *J* = 7 Hz, H-2 *trans*), 5.64-5.93 (m, 1H, -C*H*CH$_2$), 6.02 (d, 0.21H, *J* = 2 Hz, H-2 *cis*); ^{13}C NMR (75 MHz) δ 13.6, 13.7 (-CH$_2$*C*H$_3$), 18.2, 18.4 (-*C*H$_2$CH$_3$), 22.9, 24.9, 25.1, 25.2 (C-4, 5), 29.3, 34.8 (-*C*H$_2$CHCH$_2$), 35.9, 36.3 (-CO*C*H$_2$-), 37.8, 38.5 (C-3, confirmed by APT), 61.4, 64.8 (C-6), 92.7, 95.9 (C-2), 116.7, 116.8 (-CHCH$_2$), 135.7, 145.1 (-*C*HCH$_2$), 171.8, 172.4 (C=O); MS (EI) *m/z* 212 (weak, M$^+$), 171 (1%), 141 (1), 125 (10), 71 (100); IR (film) 3080 (C=CH$_2$), 1740 (C=O), 1640 (C=C) cm^{-1}; HRMS *m/z* 212.1411 (M$^+$), calcd for C$_{12}$H$_{20}$O$_3$ 212.1412.

3-Butanoyloxy-2-(2-propenyl)tetrahydropyran (22). The crude chloride (**21**),[4] prepared from 2,3-dibutanoyloxytetrahydropyran (200 mg, 0.8 mmol), was dissolved in benzene (1 mL) together with allyltributyltin (330 mg, 1.0 mmol) and AIBN (cat.). The resulting solution was then deoxygenated with a slow stream of N$_2$. After heating at reflux for 12 h under an atmosphere of N$_2$, with the addition of more AIBN after 6 h, the reaction mixture was allowed to cool and was concentrated *in vacuo*. Flash chromatography (2.5% ethyl acetate / hexane) of the residue afforded the product (**22**) (40 mg, 22%) as a colourless oil: *trans* isomer: ^{1}H NMR (200 MHz) δ 0.97 (t, 3H, *J* = 7 Hz, -CH$_2$C*H*$_3$), 1.20-1.84 (m, 6H, -C*H*$_2$CH$_3$, H$_2$-4,5), 2.10-2.50 (m, 4H, -COC*H*$_2$-, -C*H*$_2$CHCH$_2$), 3.25-3.45 (m, 2H, H$_2$-6), 3.85-4.00 (m, 1H, H-2), 4.56 (d of t, 1H, $J_{3,4}$ = 5, $J_{2,3}$ =10 Hz, H-3), 5.00-5.13 (m, 2H, -CHC*H*$_2$), 5.73-6.00 (m, 1H, -C*H*CH$_2$); ^{13}C NMR (50 MHz) δ 13.6 (-CH$_2$*C*H$_3$), 18.5 (-*C*H$_2$CH$_3$), 25.1 (C-5), 29.4 (C-4), 36.4, 36.5 (-CO*C*H$_2$-, *C*H$_2$CHCH$_2$), 67.8 (C-6), 71.3, 78.9 (C-2, 3), 116.9, (-CHCH$_2$), 134.4 (-*C*HCH$_2$), 172.7 (C=O); MS (EI) *m/z* 171 (2%), 124 (8), 83 (3), 71 (100); Anal. Calcd for C$_{12}$H$_{22}$O$_3$: C, 67.89; H, 9.50. Found: C, 68.15; H, 9.58. *cis* isomer: ^{1}H NMR (200 MHz) δ 0.96 (t, 3H, *J* = 7 Hz, -CH$_2$C*H*$_3$), 1.30-2.43 (m, 10H, -COC*H*$_2$C*H*$_2$-, -C*H*$_2$CHCH$_2$, H$_2$-4, 5), 3.40-3.60 (m, 2H, H$_2$-6), 3.96-4.10 (m, 1H, H-2), 4.86 (br s, 1H, H-3), 5.00-5.15 (m, 2H, -CHC*H*$_2$), 5.75-5.90 (m, 1H, -C*H*CH$_2$); ^{13}C NMR (50 MHz) δ 13.7 (-CH$_2$*C*H$_3$), 18.6 (-*C*H$_2$CH$_3$), 20.7 (C-5), 28.0 (C-4), 36.4, 36.4 (-CO*C*H$_2$-, -*C*H$_2$CHCH$_2$), 68.1 (C-6), 68.2, 77.9 (C-2, 3), 117.4, (-CHCH$_2$), 134.0 (-*C*HCH$_2$), 173.3 (C=O).

3-(2,2-Dimethylpropanoyloxy)-2-(2-propenyl)tetrahydropyran (24). The diester, 2,3-Di-(2,2-dimethylpropanoyloxy)tetrahydropyran (200 mg, 0.7 mmol)[4] was treated with thionyl chloride and zinc chloride in a manner similar to that used to prepare the butyrate (**21**). The crude halide (**23**)[4] was

treated with allyltributyltin (300 mg, 0.9 mmol) according to the method described for the allylation of **21**, and the product (**24**) was isolated by flash chromatography (2.5% ethyl acetate / hexane) as a colourless oil (60 mg, 38%): *trans* isomer: ^{1}H NMR (200 MHz) δ 1.10-1.80 (m, 13H, -C(CH$_3$)$_3$, H$_2$-4, 5), 2.10-2.50 (m, 2H, -C*H*$_2$CHCH$_2$), 3.30-3.48 (m, 2H, H$_2$-6), 3.90-4.02 (m, 1H, H-2), 4.55 (d of t, 1H, $J_{3,4}$ = 5, $J_{2,3}$ =10 Hz, H-3), 5.00-5.17 (m, 2H, -CHC*H*$_2$), 5.77-6.00 (m, 1H, -C*H*CH$_2$); ^{13}C NMR (75 MHz) δ 24.9 (C-5), 26.9 (-C(*C*H$_3$)$_3$), 29.0 (C-4), 36.3 (-*C*H$_2$CHCH$_2$), 39.0 (-*C*(CH$_3$)$_3$), 67.8 (C-6), 71.1, 79.1 (C-2, 3), 117.2 (-CH*C*H$_2$), 134.7, (-*C*HCH$_2$), 177.8 (C=O); MS (EI) *m/z* 185 (9%), 131 (7), 85 (24), 57 (100). (CI) *m/z* 227 (83%, (M + H)$^+$), 185 (100), 125 (73); HRMS: C$_{10}$H$_{17}$O$_3$ (M$^+$ - CH$_2$CH=CH$_2$) requires; 185.1178. Found; 185.1177. *cis* isomer: ^{1}H NMR (200 MHz) δ 1.10-2.50 (m, 15H, C(CH$_3$)$_3$, -C*H*$_2$CHCH$_2$, H$_2$-4, 5), 3.43-3.63 (m, 2H, H$_2$-6), 3.97-4.13 (m, 1H, H-2), 4.81 (br s, 1H, H-3), 5.00-5.20 (m, 2H, -CHC*H*$_2$), 5.64-5.90 (m, 1H, -C*H*CH$_2$); ^{13}C NMR (75 MHz) δ 20.6 (C-5), 27.0 (-C(*C*H$_3$)$_3$), 27.8 (C-4), 36.3 (-*C*H$_2$CHCH$_2$), 39.0 (-*C*(CH$_3$)$_3$), 67.9 (C-6), 68.2, 78.0 (C-2, 3), 117.5 (-CHCH$_2$), 134.4, (-CHCH$_2$), 177.7 (C=O).

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