Model studies of the overall 5-*endo-trig* iodocyclization of homoallylic alcohols

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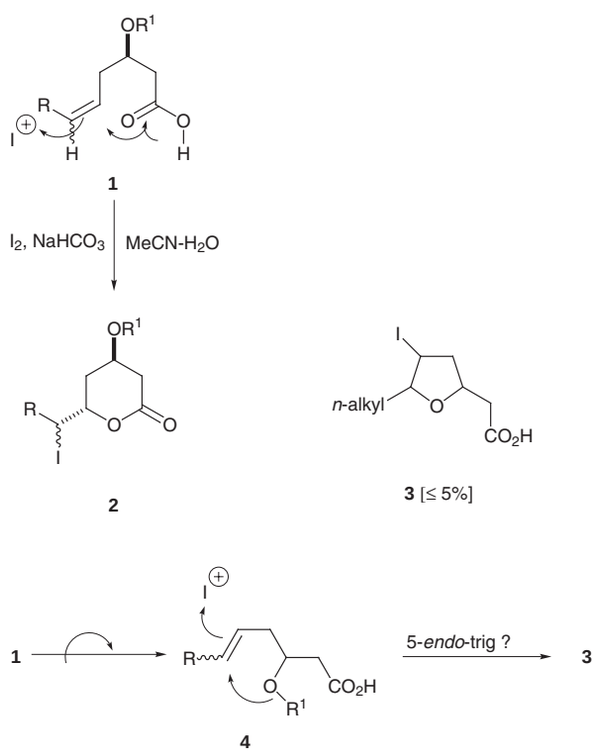
Overall 5-*endo-trig* iodocyclizations of homoallylic alcohols, with a range of substitution patterns, leading to β-iodotetrahydrofurans are usually highly efficient and stereoselective when carried out in anhydrous acetonitrile in the presence of sodium hydrogen carbonate. Such cyclizations, which are not exceptions to Baldwin's rules as they are electrophile-driven, appear to proceed *via* a well-ordered chair-like transition state. The iodine can be replaced by hydroxy, acetoxy and azide groups.

In studies aimed at preparing the valerolactone segment of the Mevinic acids, we have discovered that iodolactonizations of the 3-hydroxyalk-5-enoic acid derivatives **1** gave largely, and somewhat unexpectedly, the *trans*-3,5-disubstituted lactones **2** (Scheme 1).[1,2] Normally, such cyclizations give predominantly



Scheme 1

the corresponding 3,5-*cis* diastereoisomers, *via* a chair-like transition conformation in which the 3-substituent is positioned equatorially.[3] We reasoned that this divergence from the expected could be due to intramolecular hydrogen bonding between the 3-oxygen function and the carboxylic acid, which appeared to be effective even in examples of 3-silyloxy derivatives. During these studies, we noticed the formation of small (≤5%) and variable quantities of by-products which, normally, might well have simply been removed upon purification and not further investigated. However, the richly detailed appearance of many of the resonances in the ^{1}H NMR spectra due to these trace products encouraged us to characterize these because this could assist in defining alterations to the lactonization conditions in order to minimize their formation. In two cases with alkyl substituents (*i.e.* **1**; R = Et or C_5H_{11}), we were surprised to find that these by-products were single diastereoisomers of the β-iodo-tetrahydrofurans **3**; at this stage, no attempts were made to define the exact stereochemistry of these. The structures of these compounds were tentatively secured by NMR and mass spectral analysis and subsequently confirmed, along the lines detailed below. What was remarkable about this finding was that such products appeared to have arisen by a 5-*endo-trig* cyclization, in which the precursor carboxylic acids [**1**; R^1 = H or SiR_3] had undergone cyclization, with loss of either a proton or a silyl group, as depicted in Scheme 1, formula **4**. As this appeared to contravene one of the basic tenets of Baldwin's rules,[4] we were somewhat dubious about this mechanism and wondered if something more subtle was occurring.

A search of the literature did provide some hints that such 5-*endo-trig* cyclizations could indeed be viable. Perhaps not surprisingly, the very well known 5-*exo-trig* mode predominates in iodocyclizations of alk-4-ene-1,2-diols when, in principle, the 2-hydroxy group could compete *via* a 5-*endo-trig* pathway.[5] However, isolated examples of the cyclization of homoallylic alcohols by the latter pathway had been reported previously, but apparently were neither highlighted nor pursued further. In a footnote contained in a paper concerned with iodolactonization, Bartlett and Myerson report in passing that a 2-hydroxyalk-4-enoate cyclises upon exposure to iodine in acetonitrile to give a single stereoisomer of the corresponding β-iodo-tetrahydrofurancarboxylate, presumably by a 5-*endo-trig* cyclization.[6] Two later papers on the chemistry of novel iodonium ion sources both feature an isolated example of a presumed 5-*endo-trig* cyclization, also without additional comment. In the first, a combination of sodium iodide and *m*-chloroperbenzoic acid enabled cyclization of (*E*)-hex-3-en-1-ol to *trans*-2-ethyl-3-iodotetrahydrofuran (see **10** to **14** below),[7] while the same transformation can be effected using bis(*sym*-collidine)iodine(I) perchlorate.[8] With other examples of homoallylic alcohols, the latter reagent led to the formation of iodomethyloxetanes by the alternative 4-*exo* pathway. A related and apparently unique 5-*endo-trig* bromoetherification had been used to prepare intermediates towards the synthesis of the antibiotic mycinamycin, again without comment.[9]

Our own studies began using the (*E*)-hydroxy-acid **5**, a small

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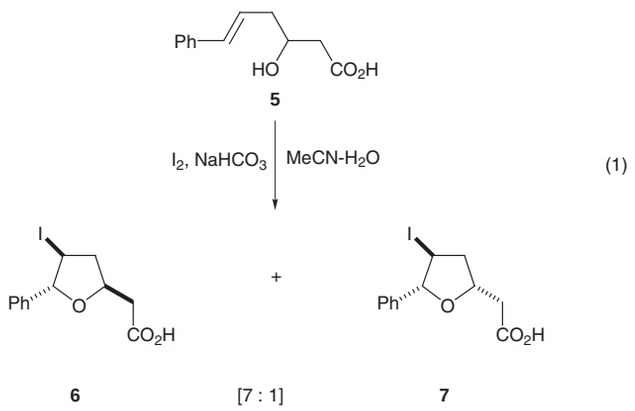
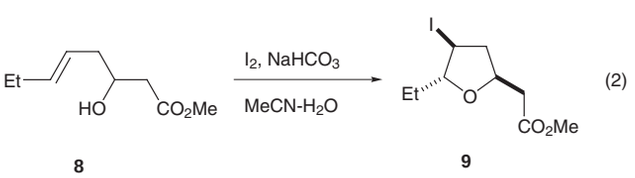
sample of which we had available from our selenolactonization studies.[10] When treated with three equivalents each of iodine and sodium hydrogen carbonate in aqueous acetonitrile, the kinetic iodolactonization conditions developed by Bartlett,[3,6,11] we were surprised to isolate the tetrahydrofuranacetic acids **6** and **7** in a 7:1 ratio, according to ^{1}H NMR integration, in approximately 80% yield [eqn. (1)]. The products were not fully



characterized, but their physical and spectroscopic data clearly indicated the presence of both a tetrahydrofuran ring and a carboxylic acid group. Further, these were clearly not the corresponding valerolactones, which would perhaps be the more expected products.[1,10] However, as other related hydroxy-acids, with alkyl substituents in place of the phenyl group [*i.e.* (*E*)-**1**; R = alkyl; R^1 = H], cyclized to give largely the expected valerolactones and only traces of iodotetrahydrofurans **3**, we reasoned that this was a special case. This is due to the ability of the phenyl group to stabilize an electron deficient benzylic centre and hence favour the overall 5-*endo* cyclization leading to the tetrahydrofurans **6** and **7**, at the expense of the competing 6-*exo* lactonization. Previous studies by the Kurth group[12] have shown that the difference in energy between 5-*exo* iodolactonization and iodoetherification can be very small and hence the effect of the phenyl group in the present case might be sufficient to tip the balance away from a 6-*exo* iodolactonization towards a 5-*endo* iodoetherification.

We reasoned that it ought to be possible to block the lactonization of hydroxy-acids **1** [R = alkyl; R^1 = H] simply by forming the corresponding methyl esters. We were thus pleased to find that exposure of the (*E*)-hydroxy-ester **8** to the Bartlett iodocyclization conditions gave a reasonable yield of the iodotetrahydrofuran **9**, largely as a single isomer [eqn. (2)].



Further studies showed that 10% water in acetonitrile at 0 °C gave a respectable 67% isolated yield of this compound. Wondering if we had discovered a new and simple stereoselective approach to β-iodotetrahydrofurans, we embarked upon a viability study of this type of cyclization, intrigued by the lack of previous reports of such iodoetherifications in general. However, it soon became apparent that the foregoing examples were special cases. Exposure of (*E*)-hex-3-en-1-ol **10** to the Bartlett conditions returned the more familiar 5% yield of the corresponding iodotetrahydrofuran **11**, accompanied by various iodohydrins **12** and **13** (Scheme 2) indicating that the preferred pathway for reaction of the presumed iodonium species formed under these conditions was intermolecular attack by water [Fig. 1], rather than the Baldwin-disfavoured 5-*endo*

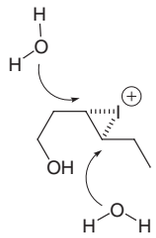
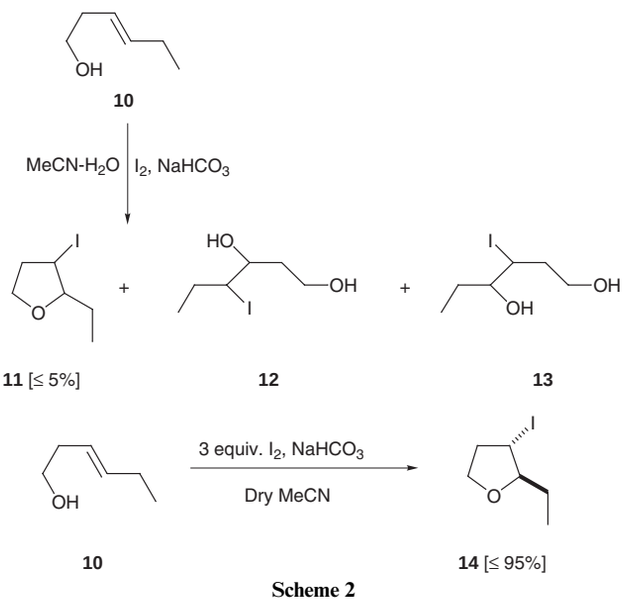


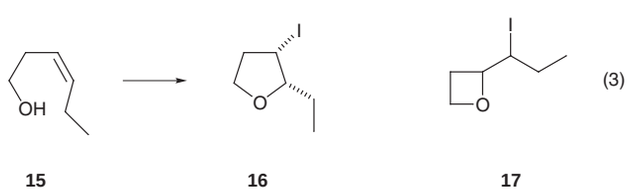
Fig. 1



Scheme 2

cyclization mode. However, consideration of the pathway shown in Fig. 1 suggested that by carrying out the reactions in a dry solvent, and thus in the absence of a competing nucleophile, in this case water, such cyclizations could be viable. We were amazed to find that the homoallylic alcohol **10** underwent cyclization in less than 5 minutes at 0 °C or less than 2 hours at −25 °C, when treated with three equivalents each of iodine and sodium hydrogen carbonate in anhydrous acetonitrile, to give an essentially quantitative yield of the *trans*-iodotetrahydrofuran **14** (Scheme 2). The only loss in yield appeared to be due to the volatility of the product; a ^{13}C NMR spectrum of crude material showed no resonances other than those due to the tetrahydrofuran **14**, the stereochemistry of which was inferred from its spectral data which were identical to those previously reported.[8] Furthermore, no significant NOE enhancement was observed at H-3 upon irradiation of H-2 and *vice versa*. Irradiation of the 1′-CH_2 protons did, however, result in enhancement of H-3 (*ca*. 4%).

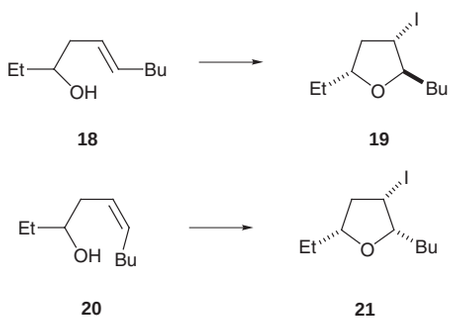
A similar cyclization of the corresponding (*Z*)-hex-3-enol **15** proceeded much more slowly at 0 °C; after 72 h, work-up and column chromatography did, however, provide a 60% isolated yield of a non-polar iodinated product which was clearly different to the *trans*-diastereomer **14**, and hence was the *cis*-isomer **16** [eqn. (3)], or a different ring system. In common with all



other such products, the gross structure, as well as the stereochemistry, was proven in the following manner. Firstly, a ^{1}H–^{13}C correlation spectrum allowed a definite assignment of the respective resonances due to the CHI group: while the proton

resonance occurred at an expected position around δ_H 4.0, the carbon resonance was spectacularly shifted to the region of δ_C 20–35 ppm, due to the heavy atom effect,[13] and hence appeared well removed from the diagonal position of the other features in the spectrum. A subsequent COSY spectrum then allowed all of the other proton resonances to be assigned. Hence, the product was identified as the iodotetrahydrofuran **16** and not the iodooxetane **17**, which could arise from a 4-*exo*-*trig* cyclization. Thus, it was clear that the CHI proton was coupled only to a β-CH_2 and H-2 around a tetrahydrofuran ring. The former methylene was also clearly coupled only to a second methylene which was adjacent to oxygen. This again ruled out the alternative oxetane structure **17**, wherein the CHI proton would be coupled to the methylene of the pendant ethyl group; other correlations confirmed these assignments. An unexpected feature of such 2,3-*cis*-iodotetrahydrofurans is the appearance of H-2, vicinal to the iodine, at δ_H 2.80, somewhat removed from the normal position of a proton in a methine group bonded to an ether oxygen, presumably, due to its *trans*-disposition with the iodine atom.

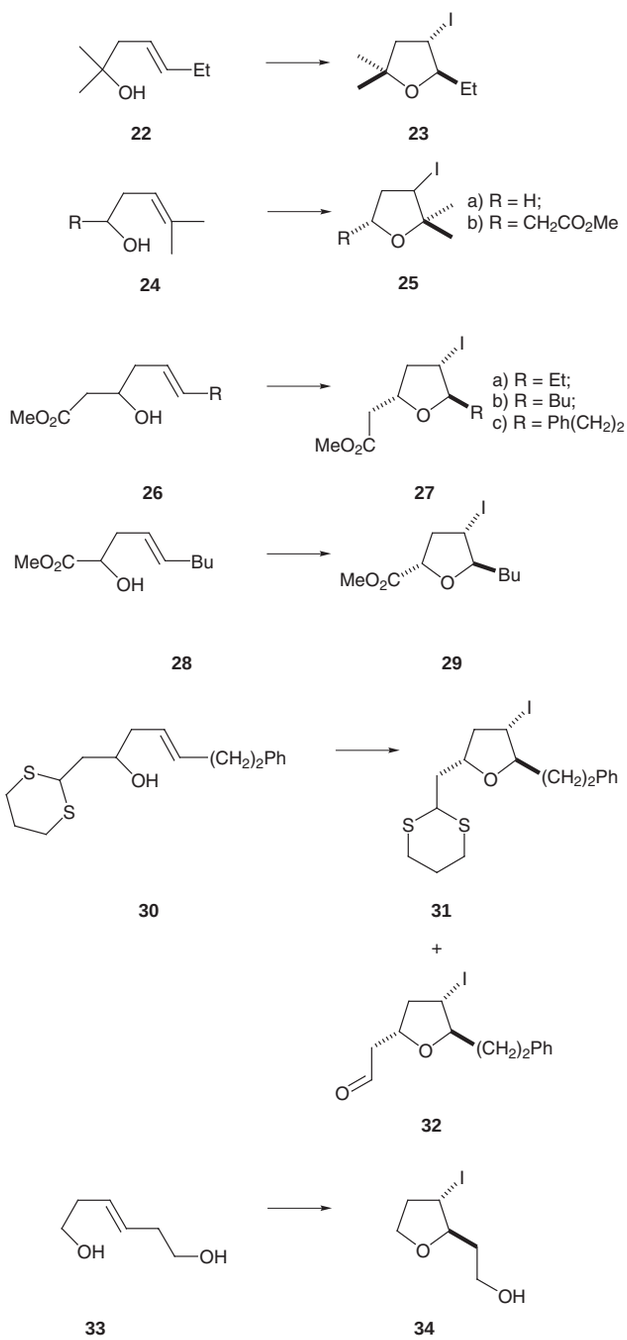
Cyclisations of secondary homoallylic alcohols followed a similar pattern. Thus, (*E*)-dec-5-en-3-ol **18** underwent rapid and very efficient cyclization to give a single iodotetrahydrofuran **19** (Scheme 3), the structure of which was determined as



Scheme 3

outlined above. Correlation spectra identified the two resonances for the CHI group at δ_H 3.94 and δ_C 23.4; a COSY spectrum showed all the expected correlations of the tetrahydrofuran rather than an oxetane structure. Finally, difference NOE measurements showed strong enhancements between H-3 and H_β-4 along with H_β-4 and H-5. Little or no enhancement was observed between H-2 and both H-3 and H-5, confirming that these were in a *trans* relationship and hence establishing the stereochemistry shown (**19**). These data contrasted markedly with those observed for the product **21** obtained from a much slower and less efficient cyclization of the corresponding (*Z*)-dec-5-en-3-ol **20**. Again, the structure of the product **21** was based on a detailed analysis of its spectral data. Thus, in the ^1H–^{13}C correlation spectrum, the heavy atom effect caused one of the features to be well removed from the diagonal and hence was assignable to the CHI array, whose resonances occurred at δ_H 4.43 and δ_C 32.4 respectively. In the ^1H–^1H COSY spectrum, this proton was coupled strongly to resonances at δ_H 2.76 and 2.92 and less strongly to one at 2.31, ruling out an oxetane structure in which these would have included couplings to a side-chain methylene, the resonances for which all occurred at $\delta_H < 2.0$. The resonances at 2.92 and 2.31 ppm were clearly part of the same methylene (δ_C 43.9), according to ^1H–^{13}C correlation and DEPT spectra, and both coupled to a second methine at δ_H 3.86 which correlated to a ^{13}C resonance at 81.4 ppm, and hence was adjacent to the ring oxygen and was therefore due to the 5-CH group. In the ^1H–^1H COSY spectrum, only the resonances at δ_H 2.76 and 3.86 coupled with methylenes in the two side chains. These assignments were consistent with the multiplicities observed in the richly detailed proton spectrum. Finally, NOE difference spectra showed strong enhancements between H-2 and H-3, H-3 and H_β-4, the latter and 5-H and also between H-2 and H-5. No transannular enhancements were observed, for example between H-2 and H_β-4 or H-3 and H-5, but there were no other significant enhancements, such as between H-3 and H_α-4 or H_α-4 and H-5. These data, together with comparisons with those for the corresponding *trans* isomer **19**, confirmed the all-*cis* stereochemistry **21** for this product. Once again, the *trans* disposition of the iodine and H-2 caused the latter to resonate at the unexpected position of δ_H 2.76.

This type of cyclization also worked well both with a tertiary alcohol and with examples of trisubstituted alkenes. Thus, iodocyclizations of the hept-4-en-2-ol **22** led to a 90% isolated yield of the 2,3-*trans*-iodotetrahydrofuran **23** while the two prenyl-containing alcohols **24** gave the corresponding iodotetrahydrofurans **25** in 85 and 81% isolated yields respectively, the latter also as essentially a single 2,4-*trans* stereoisomer (Scheme 4). These cyclizations are perhaps the least surprising, as a late transition state would result in the formation of a

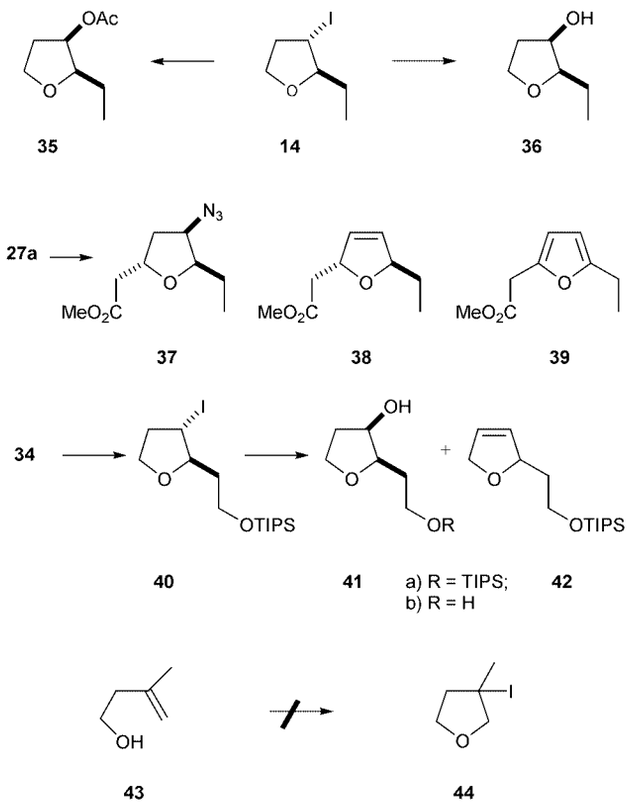


Scheme 4

favourable electron-deficient tertiary carbon, similar to the successful cyclization of the hydroxy-acid **5**. There was no evidence of interference from the ester function in the latter cyclization and thus it was not surprising that similar iodocyclizations of the β-hydroxy esters **26** gave the tetrahydrofuranacetates **27** in around 75% isolated yields. Under anhydrous conditions, the cyclization yield from one of the original precursors **8** was 86%, an improvement on the original return of 67% under aqueous conditions (see above). Hence, although yields are better with these hydroxy-esters under anhydrous conditions, at this stage it was curious to note that acceptable, if lower yields could also be obtained from these substrates even in the presence of water; a rationale for this is outlined below. Cyclisation of an α-hydroxy ester was also viable: thus, the nonenoate **28** gave the corresponding iodotetrahydrofuran **29** in 83% isolated yield [*cf*. ref. 6]. An attempt to incorporate a 1,3-dithiane function met with partial success: when the hydroxydithiane **30** was exposed to the standard cyclization conditions, the hoped-for heterocycle **31** was isolated in 34% yield along with the deprotected aldehyde **32** (15%). In retrospect, it might be possible to optimize this reaction, particularly in terms of an abbreviated reaction time. In all of the foregoing cases, the identity of the products as tetrahydrofurans and not the corresponding oxetanes, together with the relative stereochemistries, were determined in exactly the same manner as described above and were substantiated by comparisons with the foregoing data. Finally, we have established that free hydroxy groups can be included in such cyclization substrates: the symmetrical enediol **33** was readily converted into the hydroxyethyltetrahydrofuran **34** in 87% isolated yield. However, in other competition experiments, iodocyclizations of alk-4-ene-1,2-diols led exclusively to hydroxytetrahydrofurans through 5-*exo-trig* reaction of the 1-hydroxy group, even when this was blocked by a trialkylsilyl- or a benzyl group. Others have noted the exceptional ease with which such 5-*exo*-cyclizations can proceed.[14]

We have briefly examined some displacement chemistry of the iodine in the iodotetrahydrofurans. These proved to be quite difficult, presumably in part because the substrates were secondary halides, and also due to the β-halo-ether effect,[15] and are all unoptimized. Exposure of the *trans*-2-ethyl-3-iodotetrahydrofuran **14** to caesium acetate in hot dimethylformamide[16] for 14 h gave a 35% isolated yield of the *cis*-acetate **35** (Scheme 5). Similarly, the corresponding alcohol **36** was obtained in poor yield using potassium superoxide and 18-crown-6 in DMF.[17] Displacement with azide was somewhat more efficient: reaction between the ester **9** and sodium azide in DMF in the presence of 15-crown-5 at 40 °C gave a 52% return of the inverted azide **37**. Although not fully characterized, the corresponding Boc-protected amine was obtained in excellent yield by reduction over a pre-hydrogenated palladium on carbon catalyst in the presence of di-*tert*-butyl dicarbonate.[18] After prolonged heating at a higher temperature (70 °C), the major product was the corresponding dihydrofuran **38** (79%), accompanied by small amounts of the furan **39**, which presumably arose by aerial oxidation. It is unclear whether this was due to direct elimination or by loss of hydrazoic acid from the azide. That the poor yield of alcohol **36** obtained from the foregoing superoxide displacement was due to the volatility and/or water-solubility of the product was indicated by a much better yield of the alcohol **41a**, which was obtained from the triisopropylsilyl-protected tetrahydrofuran **40** under similar conditions. In this case, a small amount of the corresponding dihydrofuran **42** was also isolated. In the foregoing example leading to alcohol **36**, such a product would have been too volatile to isolate from a relatively small-scale reaction. Subsequent deprotection of the initial product **41a** provided a good yield of the corresponding diol **41b**.

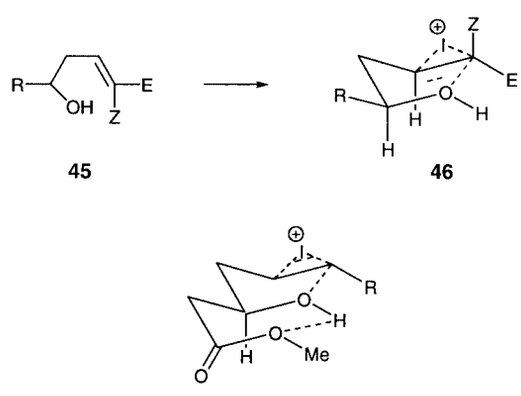
A single attempt to effect an iodocyclization to give a tertiary iodotetrahydrofuran **44**, starting from an internally substituted homoallylic alcohol **43**, gave a complex and rather unstable



Scheme 5

mixture, which did not appear to contain substantial amounts of a tetrahydrofuran. Subsequently, it has been reported that such cyclizations proceed instead along a 4-*exo-trig* pathway to give oxetanes, in examples where there are more substituents than in the present case.[19,20] Again, this would be consistent with a late transition state in which the internal tertiary carbon becomes electron deficient [*cf*. formation of iodotetrahydrofurans **25**].

We do not regard the present cyclizations, which are formally 5-*endo-trig* processes, as exceptions to Baldwin's rules,[4] because these are electrophile- rather than nucleophile-driven, suggesting a late transition state. Further, if there are alternative pathways available, then these will usually be taken.[5,14] The requirement for anhydrous conditions in most of the present examples is a manifestation of this: if water is present, then iodohydrins are the major products rather than iodotetrahydrofurans from a 5-*endo-trig* cyclization. The excellent levels of stereoselection can be explained by assuming the intermediacy of a partial chair-like transition state **46**, arising by the addition



of iodine across the alkene bond in the generalized structure [**45**; 'E' and 'Z' represent (*E*)- or (*Z*)-alkene geometry], followed by rearside attack by the oxygen. A controlling feature is the

substituent 'R', which will be positioned equatorially rather than axially. The conformation **46** also explains why cyclizations of (*Z*)-homoallylic alcohols are slower and less efficient: the necessity of positioning the alkene substituent 'Z' in an axial position is much less favourable and presumably allows intermolecular attack by water, formed in sub-stoichiometric amounts by neutralization of hydrogen iodide by the hydrogen carbonate, to compete. The high stereoselectivity is also consistent with a relatively unfavourable process which will, necessarily, be much more demanding in terms of transition state geometry; in contrast, favoured 5-*exo-trig* cyclizations are often quite non-stereoselective.[21] In 5-*endo* cyclizations, the extra strain involved in accessing transition state **46** explains why water can compete successfully in giving iodohydrins **12** and **13**. In the special cases of the β-hydroxy esters **26** and the phenyl-substituted hydroxyacid **5**, which undergo 5-*endo* cyclizations even in the presence of water, hydrogen bonding between the ester (or acid) and hydroxy groups, as in conformation **43**, may assist O–H bond cleavage such that cyclization competes successfully with intermolecular attack by water. A similar idea has recently been proposed by us to explain the unexpected *trans*-stereoselectivity of halo-lactonizations of the derived hydroxy- and silyloxy-acids **1**, outlined above.[1] Throughout, three equivalents of iodine were found to be necessary to achieve complete conversion into the iodotetrahydrofurans, along the same lines as iodolactonizations developed by the Bartlett group.[3,6,11] The reason for this is unclear but, presumably, a polyiodine species is essential for the first step of the reaction.

Since our first paper on this subject,[22] a number of additional reports have attested both to the viability and synthetic utility of this type of cyclization. Indeed, prior to this, extensive studies by the Warren group[23] had indicated this during their work on the overall 5-*endo-trig* cyclization of episulfonium ions[24] leading to β-sulfenyltetrahydrofurans although, in these cases, the key intermediates are generated by intramolecular displacement of a vicinal halide or tosyloxy group by divalent sulfur. Around the same time, Lipshutz reported very efficient and generally highly stereoselective 5-*endo* iodo- and seleno-cyclizations of a representative range of substituted homoallylic alcohols[25] and subsequently[26] an alternative, more sterically encumbered selenium reagent which delivers even better stereoselectivities from such selenocyclizations. Kang and Lee also reported similar selective iodo- and seleno-cyclizations of 5-(3-furyl)pent-4-ene-1,2-diols.[27] The presence of the furan residue may well be highly influential in directing these cyclizations *via* a 5-*exo* mechanism, despite the operation of an apparent 5-*endo* pathway.[28] The balance between the 5-*endo* and 4-*exo* pathways[20] is also evidently quite subtle, as indicated by some recent examples wherein iodocyclizations of penta-1,4-diene-3-methanols give almost exclusively iodomethyloxetanes by the latter pathway.[29] During the present work, we did not detect any oxetane formation (>5%) in any of the examples studied. We have also shown that 5-*endo* iodocyclizations leading to perhydrobenzofurans are viable and usually highly stereoselective.[30] A silicon group, specifically $PhMe_2Si$ (a synthetic equivalent of OH), has been shown to be effective in directing the stereochemical outcome of both seleno- and sulfeno-induced 5-*endo* cyclizations, thus further enhancing the synthetic potential of this method.[31] In the case of seleno-cyclizations, the original model studies by Nicolaou[32] on the applications of this electrophile in lactonizations and cyclic ether formation indicated that the 5-*endo* pathway was viable, although this has only been further exploited much more recently, as indicated above. Similar cyclizations, when applied to homoallylic sulfonamides, also have much potential in pyrrolidine synthesis.[33] All of these generally highly stereoselective cyclizations should have considerable synthetic potential, especially in asymmetric synthesis, given the number of options to access chiral, non-racemic homoallylic alcohols.

Experimental

General details

Melting points were determined on a Köfler hot stage apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 1600 series Fourier transform spectrometer using thin films between sodium chloride plates, unless otherwise stated. ^{1}H NMR spectra were determined using a Perkin-Elmer R32 operating at 90 MHz, a Bruker WM-250, a JEOL EX-270 or a Bruker AM-400 spectrometer, operating at the frequencies indicated (*i.e.* (90) refers to 90 MHz *etc*.). ^{13}C NMR spectra were determined using any of the later three instruments, operating at 62.5, 67.8 and 100.1 MHz respectively, as indicted after δ_C. Unless otherwise stated, all spectra were determined using dilute solutions in deuteriochloroform and tetramethylsilane as internal standard. *J* Values are expressed in Hz. Mass spectra were measured using either an AEI MS902 or a VG 7070E instrument, both operating in the electron impact mode, unless otherwise stated; FAB spectra were obtained using the latter instrument or were obtained from the EPSRC Mass Spectrometry Service, Swansea University.

Unless otherwise stated, all reactions were carried out in anhydrous solvents which were obtained by the usual methods.[34] All organic solutions from work-ups were dried by brief exposure to anhydrous magnesium sulfate followed by filtration. Solvents were removed by rotary evaporation. CC refers to column chromatography over Sorbsil silica gel using the eluants specified.

A variety of known methods were used to prepare the required starting homoallylic alcohols; these are detailed below, along with references to the original source of the particular method.

(*E*)-3-Hydroxy-6-phenylhex-5-enoic acid 5

Methyl 3-hydroxy-6-phenylhex-5-enoate was prepared by a Wittig condensation between benzyltriphenylphosphonium bromide and methyl 5-oxo-3-triisopropylsilyloxypentenoate followed by desilylation, as previously described.[1,2] The ester (0.25 g, 1.1 mmol, as a 3:1 *E*–*Z* mixture) was stirred at ambient temperature with aqueous 2 M sodium hydroxide (4 ml) for 16 h. The resulting solution was washed with chloroform (2 × 5 ml), acidified to pH 2 using 2 M hydrochloric acid and extracted with chloroform (3 × 10 ml). The combined extracts were dried and evaporated to leave crude hydroxy-acid (0.23 g, *ca* 100%) as a 3:1 *E*–*Z* mixture. Careful crystallization from ether–hexane gave a pure sample of the (*E*)-*acid* **5** (0.11 g, 41%) as a colourless, microcrystalline powder, mp 73–75 °C; ν_{max}/cm^{-1} 3480 and 1714; δ_H (400) 2.45 (2H, br t, *J* 6.4, 4-CH_2), 2.54 (1H, dd, *J* 16.6 and 8.8, 2-CH_aH$_b$), 2.63 (1H, dd, *J* 16.6 and 3.6, 2-CH$_a$$H_b$), 4.18 (1H, dddd, *J* 8.8, 6.3, 6.0 and 3.6, 3-CH), 5.05 (2H, br, 2 × OH), 6.21 (1H, dt, *J* 15.8 and 7.3, 5-CH:), 6.48 (1H, br d, *J* 15.8, 6-CH:) and 7.20–7.40 (5H, m, Ph); δ_C (270) 40.2, 40.6 (both CH_2), 67.7 (3-CH), 125.0 (CH), 126.2 (2 × CH), 127.5 (CH), 128.7 (2 × CH), 133.7 (CH), 137.1 (C) and 177.3 (CO); *m*/*z* 188 ($M^+ - H_2O$, 29%), 129 (11), 128 (31), 118 (90), 117 (100) and 91 (29) [Found: C, 69.8; H, 7.1. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%].

(2*RS*,4*SR*,5*RS*)- and (2*SR*,4*SR*,5*RS*)-(4′-Iodo-5′-phenyltetrahydrofuran-2′-yl)acetic acid 6 and 7

The foregoing (*E*)-acid **5** (14 mg, 0.07 mmol) and sodium hydrogen carbonate (0.17 g, 2 mmol) were stirred together in ice-cold acetonitrile (0.5 ml) and water (0.2 ml). After 5 min, solid iodine (51 mg, 0.2 mmol) was added and the resulting mixture stirred at 0 °C for 5 h. Excess iodine was destroyed by the addition of saturated aqueous sodium thiosulfate, the mixture was made acidic using 2 M hydrochloric acid and extracted with chloroform (3 × 3 ml). The combined extracts were dried and evaporated to leave the iodotetrahydrofurans **6** and **7** (18

mg, *ca*. 80%), in a ratio of 7:1, ν_{max}/cm^{-1} 3400 and 1704. The major isomer **6** showed δ_H (400) 2.27 (1H, ddd, *J* 13.1, 10.3 and 8.6, 3-H$_a$), 2.71 (1H, dd, *J* 15.9 and 6.1, C*H*$_a$H$_b$CO), 2.88 (1H, dd, *J* 15.9 and 7.1, CH$_a$*H*$_b$CO), 2.93 (1H, ddd, *J* 13.1, 7.1 and 6.1, 3-H$_b$), 4.00 (1H, ddd, *J* 10.3, 8.7 and 7.1, 4-H), 4.68 (1H, m, 2-H), 5.08 (1H, d, *J* 8.7, 5-H) and 7.28–7.44 (5H, m, Ph). The minor isomer **7** was detected and the isomer ratio determined by a first-order resonance at δ_H 5.19 (1H, d, *J* 7.1, 5-H). All other resonances due to this isomer were partly or completely obscured, except for δ_H 2.74 (1H, dd, *J ca*. 16.0 and 6.1, C*H*$_a$H$_b$CO).

(*E*)-Dec-5-en-3-ol 18

A solution of hex-1-yne (0.49 g, 6.0 mmol) in dry tetrahydrofuran (10 ml) was stirred under nitrogen and cooled to −5 °C. Diisobutylaluminium hydride (6 ml of a 1.0 M solution in hexane, 6.0 mmol) was added dropwise and, after 0.5 h, the mixture was heated to 55 °C and maintained at this temperature for 3 h then cooled to ambient temperature. Butyllithium (3.8 ml of a 1.6 M solution in hexanes, 6.0 mmol) was added dropwise and the resulting solution stirred for 0.5 h before the dropwise addition of 1,2-epoxybutane (0.43 g, 6.0 mmol) in tetrahydrofuran (3 ml).[35] The resulting solution was stirred for 3 h then quenched by the addition of 2 M hydrochloric acid (20 ml). The mixture was extracted with ether (3 × 15 ml) and the combined extracts washed with saturated aqueous sodium hydrogen carbonate (2 × 10 ml) then dried and evaporated. CC (20% ethyl acetate–hexane) of the residue gave the *alkenol* **18** (0.38 g, 41%) as a colourless oil; ν_{max}/cm^{-1} 3500 and 1401; δ_H (250) 0.91 (3H, t, *J* 7.3, 10-CH$_3$), 0.95 (3H, t, *J* 7.5, 1-CH$_3$), 1.26–1.37 (4H, m, 8- and 9-CH$_2$), 1.43–1.55 (2H, m, 2-CH$_2$), 1.75 (1H, br s, OH), 2.03 (2H, td, *J* 7.3 and 5.8, 7-CH$_2$), 2.22–2.32 (2H, m, 4-CH$_2$), 3.51–3.59 (1H, m, 3-H), 5.43 (1H, dtt, *J* 15.0, 5.8 and 1.2, 6-H) and 5.49 (1H, dtt, *J* 15.0, 6.4 and 1.2, 5-H); δ_C (270) 10.1, 14.0 (both CH$_3$), 22.2, 29.1, 31.3, 31.9, 39.5 (all CH$_2$), 70.4 (3-CH), 121.6 and 130.1 (both CH); *m*/*z* 156 (M$^+$, 1%), 141 (10), 138 (19), 113 (8), 97 (100) and 59 (22) [Found: M$^+$, 156.1509. $C_{10}H_{20}O$ requires *M*, 156.1514].

(*Z*)-Dec-5-en-3-ol 20

A solution of dec-5-yn-3-ol (0.92 g, 6.0 mmol)[36] in dry ethyl acetate (25 ml) containing Lindlar catalyst (0.10 g) was hydrogenated under 1 atmosphere of hydrogen until gas uptake (157 ml) was complete (*ca*. 1 h). The suspension was filtered and the filtrate evaporated. The residue was dissolved in 20% ethyl acetate–hexane and the resulting solution passed through silica. Evaporation of the filtrate left the *alkenol* **20** (0.89 g, 95%) as a colourless oil; ν_{max}/cm^{-1} 3470 and 1414; δ_H (400) 0.90 (3H, t, *J* 7.1, 10-CH$_3$), 0.96 (3H, t, *J* 7.5, 1-CH$_3$), 1.25–1.39 (4H, m, 8- and 9-CH$_2$), 1.42–1.60 (2H, m, 2-CH$_2$), 1.80 (1H, br s, OH), 2.05 (2H, td, *J* 7.5 and 7.1, 7-CH$_2$), 2.22 (2H, dd, *J* 7.3 and 7.0, 4-CH$_2$), 3.54 (1H, tt, *J* 7.0 and 5.5, 3-H), 5.40 (1H, dtt, *J* 10.9, 7.5 and 1.5, 6-H) and 5.46 (1H, dtt, *J* 10.9, 7.3 and 1.5, 5-H); δ_C (270) 10.1, 14.0 (both CH$_3$), 22.4, 27.2, 29.6, 31.9, 34.9 (all CH$_2$), 72.9 (3-CH), 125.2 and 133.4 (both CH); *m*/*z* 156 (M$^+$, 5%), 141 (9), 138 (19), 113 (8), 97 (100) and 59 (23) [Found: M$^+$, 156.1510. $C_{10}H_{20}O$ requires *M*, 156.1514].

(*E*)-2-Methylhept-4-en-2-ol 22

Ethereal diazomethane was added to a solution of (*E*)-hex-3-enoic acid (5.70 g, 50 mmol) until a yellow colouration persisted. After 1 h at ambient temperature, the excess diazomethane was removed in a stream of dry nitrogen and the resulting solution of the methyl ester added dropwise to a solution of methylmagnesium iodide [prepared from magnesium (4.80 g, 200 mmol) and iodomethane (28.4 g, 200 mmol)] in ether (200 ml). The resulting mixture was refluxed for 1 h then quenched by the successive addition of ethyl acetate (1 ml) and saturated aqueous ammonium chloride (50 ml). The mixture was separated and the aqueous layer extracted with ether (3 × 50 ml). The combined organic solutions were dried and carefully evaporated. Distillation of the residue gave the *homoallylic alcohol* **22** (3.90 g, 59%) as a colourless oil, bp 60 °C at 14 mmHg; ν_{max}/cm^{-1} 3376; δ_H (270) 1.00 (3H, t, *J* 7.1, 7-CH$_3$), 1.20 (6H, s, 2 × CH$_3$), 2.00–2.20 (4H, m, 3- and 6-CH$_2$) and 5.40–5.63 (2H, m, 4- and 5-H).

Methyl 6-methyl-3-oxohept-5-enoate

1,1′-Carbonyldiimidazole (4.36 g, 27 mmol) was added to a stirred solution of 4-methylpent-3-enoic acid (3.0 g, 26 mmol)[37] in dry tetrahydrofuran (20 ml) and the resulting solution stirred for 16 h at ambient temperature then added dropwise to a solution of the magnesium chelate of methyl hydrogen malonate dianion (27 ml of a 1 M solution in tetrahydrofuran).[38] The resulting mixture was stirred for 24 h at ambient temperature then quenched with saturated aqueous ammonium chloride (50 ml) and extracted with ethyl acetate (3 × 100 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (50 ml) and brine (50 ml) then dried and evaporated. CC (15% EtOAc in petrol) of the residue gave methyl 6-methyl-3-oxohept-5-enoate (1.05 g, 45%) as a colourless oil; ν_{max}/cm^{-1} 1750, 1438, 1377 and 1108; δ_H (250) 1.40 (3H, s, CH$_3$), 1.36 (3H, s, CH$_3$), 1.65–1.80 (2H, m, 4-CH$_2$), 2.41–2.60 (2H, m, 2-CH$_2$), 3.75 (3H, s, OCH$_3$) and 5.10–5.15 (1H, m, 5-H); δ_C (400) 25.6 (CH$_3$), 29.2 (CH$_3$), 30.7 (4-CH$_2$), 45.2 (2-CH$_2$), 51.5 (OCH$_3$), 125.4 (5-CH), 132.0 (6-C), 173.6 (1-CO) and 200.9 (3-CO); *m*/*z* 170 (M$^+$, 2%), 143 (46), 101 (39), 97 (69) and 69 (100).

Methyl 6-methyl-3-hydroxyhept-5-enoate 24b

Butylamine–borane complex (0.502 g, 10 mmol) was added to a solution of the foregoing methyl 6-methyl-3-oxohept-5-enoate (1.70 g, 10 mmol) and 1 M aqueous citric acid (7 ml) in methanol (30 ml) and the resulting solution stirred at ambient temperature for 1 h, then diluted with water (30 ml) and extracted with ether (3 × 100 ml).[39] The combined extracts were dried and evaporated to leave a brown oil, CC (20% EtOAc in hexane) of which gave the *hydroxy-ester* **24b** (1.37 g, 80%) as a colourless oil; ν_{max}/cm^{-1} 3490, 1744 and 1643; δ_H (250) 1.63 (3H, s, CH$_3$), 1.65 (3H, s, CH$_3$), 2.20–2.43 (2H, m, 4-CH$_2$), 2.46 (1H, dd, *J* 15.1 and 8.7, 2-H$_a$), 2.51 (1H, dd, *J* 15.1 and 6.3, 2-H$_b$), 3.72 (3H, s, OCH$_3$), 4.02–4.05 (1H, m, 3-H) and 5.23–5.34 (1H, m, 5-H); δ_C (400) 25.6 (CH$_3$), 29.3 (CH$_3$), 31.6 (4-CH$_2$), 42.1 (2-CH$_2$), 51.6 (OCH$_3$), 63.9 (3-CH), 126.0 (5-CH), 131.5 (6-C) and 172.6 (CO); *m*/*z* 172 (M$^+$, 1%), 154 (30), 101 (100), 70 (64) and 55 (43) [Found: M$^+$, 172.1096. $C_9H_{16}O_3$ requires *M*, 172.1099].

Methyl (*E*)-3-hydroxydec-5-enoate 26b

Diisobutylaluminium hydride (27 ml of a 1 M solution in hexane, 27 mmol) was added to a solution of hex-1-yne (3.1 ml, 27 mmol) in dry hexane (91 ml) cooled to 0 °C and the resulting solution stirred and heated to 50 °C for 2 h before cooling to −30 °C. Methyllithium (18.5 ml of a 1.4 M solution in ether, 26 mmol) and ether (90 ml) were then added successively.[35] The resulting suspension was stirred at 0 °C for 0.5 h then cooled to −78 °C. Methyl (±)-3,4-epoxybutanoate (3.0 g, 26 mmol),[40] followed by boron trifluoride etherate (3.18 ml, 26 mmol), were then added and stirring at this temperature continued for 0.75 h. The reaction mixture was quenched by the addition of methanol (10 ml) followed, after 10 min, by 1 M hydrochloric acid (60 ml), then extracted with ethyl acetate (3 × 50 ml). The combined extracts were dried and evaporated. CC (15% EtOAc in petrol) gave the *hydroxy-ester* **26b** (3.28 g, 63%) as a colourless oil; ν_{max}/cm^{-1} 3417 and 1732; δ_H (250) 0.90 (3H, t, *J* 6.4, 10-CH$_3$), 1.20–1.40 (4H, m, 8- and 9-CH$_2$), 2.01–2.05 (2H, m,

7-CH_2), 2.10–2.14 (2H, m, 4-CH_2), 2.45 (1H, dd, *J* 15.7 and 9.8, 2-H_a), 2.52 (1H, dd, *J* 15.7 and 3.8, 2-H_b), 3.71 (3H, s, OCH_3), 4.05–4.20 (1H, m, 3-H), 5.35–5.45 (1H, m, 5-H) and 5.55–5.65 (1H, m, 6-H); δ_C (270) 13.9 (10-CH_3), 22.2, 31.6, 32.3 (all CH_2), 39.9 (4-CH_2), 40.4 (2-CH_2), 51.8 (OCH_3), 67.8 (3-CH), 124.8 (5-CH), 138.7 (6-CH) and 173.3 (CO); *m/z* [NH_3-CI] 218 ($M^+ + NH_4$, 84%), 201 (20), 183 (100), 169 (5) and 151 (10) [Found: C, 65.4; H, 9.9. $C_{11}H_{20}O_3$ requires C, 65.9; H, 10.1%].

Methyl (*E*)-3-hydroxyoct-5-enoate 8

Commercial (*E*)-hex-3-enoic acid (6.04 g) was used to alkylate the magnesium chelate of methyl hydrogen malonate dianion, after activation by coupling with 1,1′-carbonyldiimidazole,[38] exactly as described above for the preparation of methyl 6-methyl-3-oxohept-5-enoate. The final *keto-ester* (5.67 g, 63%), a colourless oil, showed ν_{max}/cm^{-1} 1733 and 1724; δ_H (250) 0.98 (3H, t, *J* 7.4, 8-CH_3), 2.06 (2H, qdd, *J* 7.4, 6.2 and 1.0, 7-CH_2), 3.22 (2H, dd, *J* 6.6 and 0.9, 4-CH_2), 3.48 (2H, s, 2-CH_2), 3.73 (3H, s, OCH_3), 5.51 (1H, dtt, *J* 15.3, 6.6 and 1.3, 5-H) and 5.54 (1H, dtt, *J* 15.3, 6.2 and 1.0, 6-H); δ_C (400) 13.4 (8-CH_3), 25.6, 46.8, 48.2 (all CH_2), 52.2 (OCH_3), 120.0, 137.7 (both CH), 167.6 (1-CO) and 201.1 (3-CO); *m/z* 170 (M^+, 36%), 155 (6), 139 (8), 101 (100), 97 (15) and 69 (25).

A solution of the foregoing keto-ester (5.10 g, 30 mmol) in dry methanol (60 ml) was treated portionwise with sodium borohydride (1.14 g, 30 mmol). The resulting mixture was stirred until TLC indicated the reaction to be complete (*ca*. 0.5 h), then water (15 ml) was added. The bulk of the methanol was evaporated and the residue partitioned between water (60 ml) and ethyl acetate (100 ml). The organic phase was separated, dried and evaporated. CC (20% ethyl acetate–hexane) of the residue separated the *hydroxy-ester* **8** (4.54 g, 88%) as a colourless oil; ν_{max}/cm^{-1} 3422, 1735 and 1648; δ_H (250) 0.98 (3H, t, *J* 7.5, 8-CH_3), 2.04 (2H, qdd, *J* 7.5, 6.2 and 1.1, 7-CH_2), 2.22 (2H, ddd, *J* 6.8, 6.5 and 1.0, 4-CH_2), 2.51–2.63 (2H, m, 2-CH_2), 2.57 (1H, br s, OH), 3.71 (3H, s, OCH_3), 4.04–4.13 (1H, m, 3-H), 5.43 (1H, dtt, *J* 15.3, 6.8 and 1.4, 5-H) and 5.56 (1H, dtt, *J* 15.3, 6.2 and 1.1, 6-H); δ_C (400) 13.4 (8-CH_3), 25.3, 39.4, 40.1 (all CH_2), 51.4 (OCH_3), 67.4 (3-CH), 123.5, 136.0 (both CH) and 179.7 (CO); *m/z* 154 ($M^+ - H_2O$, 9%), 141 (5), 103 (100) and 69 (22) [Found: C, 62.5; H, 9.6. $C_9H_{16}O_3$ requires C, 62.7; H, 9.4%].

2-(2′-Hydroxy-7′-phenylhept-4′-yn-1′-yl)-1,3-dithiane

Butyllithium (31.25 ml of a 1.6 M solution in hexanes, 50 mmol) was added dropwise to a stirred solution of 4-phenylbut-1-yne (6.67 g, 50 mmol) in dry tetrahydrofuran (60 ml) maintained at −78 °C. After 0.5 h at this temperature, boron trifluoride etherate (4.10 ml, 33.3 mmol) was added dropwise. After a further 10 min, a solution of 2-(2′,3′-epoxypropyl)-1,3-dithiane (6.02 g, 33 mmol)[41] in tetrahydrofuran (10 ml) was added dropwise and the resulting mixture stirred at −78 °C for 4 h then poured into saturated aqueous ammonium chloride (200 ml). The resulting mixture was extracted with ethyl acetate (3 × 50 ml) and the combined extracts dried and evaporated. CC (10% ethyl acetate–petrol) of the residue (9 g) separated *2-(2′-hydroxy-7′-phenylhept-4′-yn-1′-yl)-1,3-dithiane* (5.80 g, 55%) as a pale yellow oil; ν_{max}/cm^{-1} 3437, 1423, 1276, 1075 and 1030; δ_H (250) 1.85–1.95 (2H, m, 5-CH_2), 2.10–2.20 (2H, m, 1′-CH_2), 2.30 (1H, ddt, *J* 14.7, 6.3 and 2.0, 3′-H_aH_b), 2.40 (1H, ddt, *J* 14.7, 4.0 and 2.0, 3′-H_aH_b), 2.48 (2H, tt, *J* 9.0 and 2.0, 6′-CH_2), 2.81 (2H, t, *J* 9.0, 7′-CH_2), 2.85–2.94 (4H, m, 4- and 6-CH_2), 3.95–4.03 (1H, m, 2′-H), 4.25 (1H, dd, *J* 11.0 and 9.2, 2-H) and 7.20–7.25 (5H, m, Ph); δ_C (270) 20.9, 25.9, 27.7, 29.8, 30.2, 35.1, 41.5 (all CH_2), 43.9 (2-CH), 66.8 (2′-CH), 76.4 (4′-C), 82.7 (3′-C), 126.3, 128.3, 128.4 (all CH) and 140.6 (C); *m/z* [NH_3-CI] 324 ($M^+ + NH_4$, 100%), 307 ($M^+ + H$, 90), 199 (87), 161 (65) and 119 (91) [Found: C, 66.3; H, 7.3; S, 20.5. $C_{17}H_{22}OS_2$ requires C, 66.6; H, 7.2; S, 20.9%].

(*E*)-2-(2′-Hydroxy-7′-phenylhept-4′-en-1′-yl)-1,3-dithiane 30

Lithium aluminium hydride bis(tetrahydrofuran) complex (37.7 ml of a 1 M solution in toluene, 37.7 mmol) was added to a solution of 2-(2′-hydroxy-7′-phenylhept-4′-yn-1′-yl)-1,3-dithiane (4.45 g, 14.5 mmol) in dry toluene (80 ml) and the resulting solution refluxed for 16 h then cooled to ambient temperature. Water (25 ml) was carefully added and the resulting mixture extracted with ethyl acetate (3 × 50 ml). The combined extracts were dried and evaporated to leave the *alkenyldithiane* **30** (3.71 g, 83%) as a colourless oil; ν_{max}/cm^{-1} 3430, 1313, 1147, 1052 and 1030; δ_H (250) 1.80–1.82 (2H, m, 5-CH_2), 1.85–1.93 (2H, m, 1′-CH_2), 2.05–2.25 (2H, m, 3′-CH_2), 2.32–2.40 (2H, m, 6′-CH_2), 2.70 (2H, t, *J* 9.0, 7′-CH_2), 2.80–2.97 (4H, m, 4- and 6-CH_2), 3.82–3.91 (1H, m, 2′-H), 4.27 (1H, t, *J* 8.0, 2-H), 5.32–5.60 (2H, m, 4′- and 5′-H) and 7.20–7.35 (5H, m, Ph); δ_C (270) 26.0, 30.0, 30.4, 34.4, 36.6, 40.7, 42.0 (all CH_2), 44.2 (2-CH), 67.6 (2′-CH), 125.9 (4′(5′)-CH), 126.0, 126.1, 128.3 (all CH), 133.9 (5′(4′)-CH) and 141.7 (C); *m/z* [NH_3-CI] 326 ($M^+ + NH_4$, 63%), 309 ($M^+ + H$, 60), 291 (40), 119 (100) and 91 (75) [Found: C, 66.1; H, 8.0. $C_{17}H_{24}OS_2$ requires C, 66.2; H, 7.9%].

Methyl (*E*)-3-hydroxy-8-phenyloct-5-enoate 26c

Iodomethane (4.4 ml, 70.2 mmol) was added to a stirred mixture of the foregoing alkenyldithiane **30** (2.71 g, 8.8 mmol) and sodium hydrogen carbonate (5.9 g, 70.2 mmol) in acetone (300 ml) and water (15 ml) and the resulting mixture refluxed for 5 h.[42] During this period, further portions of iodomethane were added until the reaction was complete according to TLC analysis. At this point, water (500 ml) was added and the mixture cooled and extracted with ethyl acetate (3 × 300 ml). The combined extracts were dried and evaporated to leave an oil (1.8 g), CC of which (40% ethyl acetate–petrol) separated (*E*)-3-hydroxy-8-phenyloct-5-enal (1.60 g, 87%) as a colourless oil; ν_{max}/cm^{-1} 3400 and 1721; δ_H (250) 2.12–2.21 (2H, m, 4-CH_2), 2.30–2.41 (2H, m, 7-CH_2), 2.47–2.50 (2H, m, 2-CH_2), 2.62–2.73 (2H, m, 8-CH_2), 4.05–4.12 (1H, m, 3-H), 5.30–5.60 (2H, m, 5- and 6-H), 7.15–7.31 (5H, m, Ph) and 9.80 (1H, t, *J* 0.7, 1-H); δ_C (270) 34.4, 35.7, 40.3, 41.0 (all CH_2), 68.0 (3-CH), 125.8 (5-CH), 128.5, 128.6, 129.0 (all CH), 134.7 (6-CH), 141.5 (C) and 200.1 (1-CHO), which was oxidized immediately without further characterization.

Pyridinium dichromate (2.27 g, 6.0 mmol) was added to a solution of the foregoing aldehyde (0.218 g, 1 mmol) in dimethylformamide (2 ml) containing methanol (0.20 ml, 6 mmol).[43] The resulting suspension was stirred for 16 h at ambient temperature then diluted with water (100 ml) and extracted with ether (3 × 25 ml). The combined extracts were dried and evaporated. CC of the residue (40% ethyl acetate–petrol) gave the *methyl ester* **26c** (0.17 g, 69%) as a colourless oil; ν_{max}/cm^{-1} 3420 and 1737; δ_H (250) 2.14 (2H, t, *J* 6.5, 8-CH_2), 2.27–2.41 (4H, m), 2.60–2.76 (3H, m), 3.65 (3H, s, OCH_3), 3.88–4.00 (1H, m, 3-H), 5.37 (1H, dt, *J* 15.3 and 6.8, **:**CH), 5.51 (1H, dt, *J* 15.3 and 7.1, **:**CH) and 7.09–7.25 (5H, m, Ph); δ_C (270) 34.4, 35.8, 39.6, 40.4, (all CH_2), 51.8 (OCH_3), 67.7 (3-CH), 125.9, 126.0, 128.4, 128.5, 133.7 (all CH), 141.8 (C) and 173.2 (CO); *m/z* 230 ($M^+ - H_2O$, 15%), 199 (27), 146 (40), 134 (30) and 91 (100) [Found: $M^+ - H_2O$, 230.1304. $C_{15}H_{18}O_2$ requires *M*, 230.1307].

4-Ethenyl-3-oxaoctanoic acid

A solution of hept-1-en-3-ol (3.08 g, 27 mmol)[44] in dry tetrahydrofuran (10 ml) was added dropwise to a stirred suspension of sodium hydride (2.88 g of a 50% suspension in oil, 60 mmol) in dry tetrahydrofuran (50 ml). After 1 h at ambient temperature, a solution of bromoacetic acid (3.75 g, 27 mmol) in tetrahydrofuran (10 ml) was added over 5 min. The resulting mixture was stirred at reflux for 2 h then cooled and quenched by the careful addition of water (5 ml). The mixture was then

diluted with water (100 ml) and ether (50 ml). The resulting two layers were separated and the aqueous layer washed with ether (3 × 20 ml) then cooled to 0 °C and acidified with 2 M hydrochloric acid. The acidified mixture was extracted with ethyl acetate (3 × 20 ml) and the combined extracts dried, filtered through silica gel and evaporated to leave *4-ethenyl-3-oxaoctanoic acid* (3.48 g, 75%) as a colourless oil; ν_{max}/cm^{-1} 3201–2615 and 1708; δ_H (250) 0.90 (3H, t, *J* 6.9, 8-CH_3), 1.32–1.45 (4H, m, 6- and 7-CH_2), 1.55–1.59 (1H, m, 5-H_a), 1.70–1.78 (1H, m, 5-H_b), 3.75 (1H, app. q, *J* 7.0, 4-H), 4.07 (1H, d, *J* 15.0, 2-H_a), 4.12 (1H, d, *J* 15.0, 2-H_b), 5.19–5.28 (2H, m, **:**CH_2), 5.58–5.69 (1H, m, **:**CH) and 8.50 (1H, br s, OH); δ_C (270) 14.0 (8-CH_3), 22.7, 27.5, 35.0 (all CH_2), 65.2 (2-CH_2), 82.8 (4-CH), 118.5 (**:**CH_2), 137.9 (**:**CH) and 175.7 (CO) [Found: C, 69.0; H, 10.5. $C_9H_{16}O_3$ requires C, 69.2; H, 10.3%].

Methyl (*E*)-2-hydroxynon-4-enoate 28

A stirred solution of lithium diisopropylamide [from diisopropylamine (6.5 ml) and butyllithium (25 ml of a 1.6 M solution in hexanes, 40 mmol)] in tetrahydrofuran (20 ml) was maintained at −78 °C while a solution of the foregoing 4-ethenyl-3-oxaoctanoic acid (3.44 g, 20 mmol) in tetrahydrofuran (10 ml) was added dropwise.[45] The resulting solution was slowly warmed to ambient temperature during 18 h, then acidified with 3 M hydrochloric acid (30 ml) and extracted with ethyl acetate (3 × 10 ml). The combined extracts were dried and evaporated to leave a crude hydroxy-acid (3.03 g, 88%) which was taken up in ice-cold ether (20 ml) and esterified by the addition of a slight excess of ethereal diazomethane at 0 °C followed by warming to ambient temperature during 1 h. The resulting solution was treated with a few drops of acetic acid then washed with 2 M aqueous sodium hydrogen carbonate (3 × 10 ml), dried and evaporated. Rapid column chromatography (20% ethyl acetate–hexane) of the residue gave an isomeric mixture [*E*–*Z* ~ 2 : 1] of the desired hydroxy-ester (3.12 g, 95%) as a colourless oil. Subsequent careful chromatography (15% ethyl acetate–hexane) separated a pure sample of the *(E)-hydroxy-ester* **28** which showed ν_{max}/cm^{-1} 1732; δ_H (250) 0.88 (3H, t, *J* 7.0, 9-CH_3), 1.28–1.35 (4H, m, 7- and 8-CH_2), 2.03 (2H, app q, *J* 6.6, 6-CH_2), 2.41–2.49 (2H, m, 3-CH_2), 3.02 (1H, d, *J* 6.7, OH), 3.77 (3H, s, OCH_3), 4.26 (1H, app pentet, *J* 5.5, 2-H), 5.33–5.43 (1H, m, **:**CH) and 5.55–5.65 (1H, m, **:**CH); δ_C (270) 14.0 (9-CH_3), 22.3, 31.7, 32.4, 37.9 (all CH_2), 52.3 (OCH_3), 70.7 (2-CH), 123.7, 135.3 (both **:**CH) and 175.0 (CO) [Found: C, 64.6; H, 9.8. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.8%].

The (*Z*)-isomer was most easily distinguished by its contrasting ^{13}C NMR data: δ_C (270) 14.0 (9-CH_3), 22.5, 27.2, 31.9, 32.5 (all CH_2), 52.3 (OCH_3), 70.6 (2-CH), 123.0, 134.0 (both **:**CH) and 175.0 (CO).

Iodocyclizations: typical procedure

Sodium hydrogen carbonate (4.11 g, 48.9 mmol) was added to an ice-cold solution of the homoallylic alcohol (16.3 mmol) in dry acetonitrile (66 ml) and the resulting suspension stirred for 5 min. Iodine (12.42 g, 48.9 mmol) was added and stirring continued at 0–5 °C with the exclusion of light for the times specified (TLC monitoring). Ether (100 ml) was added and the resulting mixture washed with saturated aqueous sodium thiosulfate (120 ml). The separated aqueous phase was extracted with ether (3 × 50 ml) and the combined organic solution dried and evaporated. The residue was often essentially pure iodotetrahydrofuran. Filtration through a plug of silica using 10–20% ether in pentane provided analytically pure material; CC using similar solvents was performed as necessary.

An alternative work-up was to use aqueous sodium sulfite to destroy the excess iodine, after dilution with ether. This has the advantage of requiring less water.

trans-2-Ethyl-3-iodotetrahydrofuran 14

Commercial (*E*)-hex-3-en-1-ol **10** (0.37 ml, 3 mmol) was cyclized according to the general procedure during 0.5 h to give the *trans-iodotetrahydrofuran* **14** (0.63 g, 93%) as a colourless oil; ν_{max}/cm^{-1} 1462, 1384, 1164, 1069 and 1023; δ_H (250) 0.99 (3H, t, *J* 7.4, CH_3), 1.49 (1H, dqd, *J* 13.9, 7.4 and 6.8, 1′-H_a), 1.72 (1H, ddq, *J* 13.9, 7.4 and 7.4, 1′-H_b), 2.20–2.36 (1H, m, 4-H_a), 2.46–2.50 (1H, m, 4-H_b), 3.79 (1H, ddd, *J* 6.9, 5.9 and 4.2, 3-H), 3.89 (2H, app dt, *J* 7.1 and 1.2, 5-CH_2) and 3.97 (1H, ddd, *J* 7.4, 6.8 and 4.2, 2-H); δ_C (400) 10.2 (CH_3), 23.4 (3-CH), 25.9 (1′-CH_2), 38.6 (4-CH_2), 66.9 (5-CH_2) and 89.5 (2-CH); *m/z* 226 (M^+, 16%), 156 (37), 91 (61), 85 (100) and 57 (92). These data are identical to those previously reported.[8] An analytical sample was secured by Kugelrohr distillation and showed bp 70–75 °C (oven temp) at 12 mmHg [Found: C, 32.1; H, 5.0. $C_6H_{11}IO$ requires C, 31.9; H, 4.9%].

cis-2-Ethyl-3-iodotetrahydrofuran 16

Commercial (*Z*)-hex-3-en-1-ol **15** (0.37 ml, 3 mmol) was cyclized according to the general procedure for 72 h to give the *cis-iodotetrahydrofuran* **16** (0.41 g, 60%) as a colourless oil; ν_{max}/cm^{-1} 1462, 1384, 1164 and 1023; δ_H (250) 0.93 (3H, t, *J* 7.5, CH_3), 1.50 (1H, dqd, *J* 13.7, 7.5 and 6.6, 1′-H_a), 1.76 (1H, dqd, *J* 13.7, 7.5 and 6.5, 1′-H_b), 2.47 (1H, dddd, *J* 14.2, 7.1, 2.9 and 1.4, 4-H_a), 2.73 (1H, dddd, *J* 14.2, 9.2, 5.6 and 5.6, 4-H_b), 2.80 (1H, ddd, *J* 6.6, 6.5 and 3.2, 2-H), 3.91 (1H, ddd, *J* 9.2, 8.3 and 2.9, 5-CH_a), 4.14 (1H, dddd, *J* 9.2, 8.3, 7.1 and 0.5, 5-CH_b), and 4.48 (1H, ddd, *J* 5.6, 3.2 and 1.4, 3-H); δ_C (270) 10.2 (CH_3), 30.5 (1′-CH_2), 34.2 (3-CH), 39.1 (4-CH_2), 66.0 (5-CH_2) and 83.5 (2-CH); *m/z* 226 (M^+, 10%), 197 (15), 99 (100), 71 (28) and 57 (95). An analytical sample was secured by Kugelrohr distillation and showed bp 70–75 °C (oven temp) at 12 mmHg [Found: C, 32.2; H, 5.1].

(2*RS*,3*SR*,5*RS*)-2-Butyl-5-ethyl-3-iodotetrahydrofuran 19

(*E*)-Dec-5-en-3-ol **18** (0.16 g, 1.02 mmol) was cyclized according to the general procedure for 3 h to give, after CC (10% ether in pentane), the *iodotetrahydrofuran* **19** (0.25 g, 90%) as a colourless oil; ν_{max}/cm^{-1} 1403, 1390, 1154, 1080 and 1020; δ_H (250) 0.92 (6H, app t, *J* 7.5, 2 × CH_3), 1.22–1.47 (5H, m), 1.48–1.53 (1H, m, 5-(1′-H_a)), 1.67–1.72 (1H, m, 5-(1′-H_b)), 1.75–1.85 (1H, m), 1.99 (1H, ddd, *J* 12.8, 10.3 and 8.5, 4-H_a), 2.65 (1H, ddd, *J* 12.8, 7.6 and 6.2, 4-H_b), 3.75 (1H, ddd, *J* 8.7, 7.5 and 3.3, 2-H), 3.89 (1H, dddd, *J* 8.5, 6.4, 6.4 and 6.2, 5-H) and 3.94 (1H, ddd, *J* 10.3, 7.6 and 3.3, 3-H); δ_C (400) 10.2, 14.3 (both CH_3), 23.1 (CH_2), 23.4 (3-CH), 28.5, 29.2, 32.2 (all CH_2), 44.8 (4-CH_2), 79.9 (2-CH) and 86.5 (5-CH); *m/z* 267 (M^+ − Me, 1%), 239 (5), 222 (15), 155 (10) and 125 (100). An analytical sample was secured by Kugelrohr distillation and showed bp 90 °C (oven temp) at 14 mmHg [Found: C, 42.6; H, 7.0. $C_{10}H_{19}IO$ requires C, 42.6; H, 6.8%].

(2*SR*,3*SR*,5*RS*)-2-Butyl-5-ethyl-3-iodotetrahydrofuran 21

(*Z*)-Dec-5-en-3-ol **20** (0.23 g, 1.6 mmol) was cyclized according to the general procedure for 72 h to give, after CC (10% ether in pentane), the *iodotetrahydrofuran* **21** (0.27 g, 60%) as a colourless oil; ν_{max}/cm^{-1} 1463 and 1168; δ_H (250) 0.92 (3H, t, *J* 7.1, CH_3), 0.95 (3H, t, *J* 7.4, CH_3), 1.23–1.39 (4H, m, 2 × CH_2), 1.50–1.83 (4H, m, 2 × CH_2), 2.31 (1H, ddd, *J* 14.6, 6.4 and 3.0, 4-H_a), 2.76 (1H, ddd, *J* 6.4, 6.4 and 4.0, 2-H), 2.92 (1H, ddd, *J* 14.6, 8.0 and 7.0, 4-H_b), 3.86 (1H, dddd, *J* 8.0, 6.4, 6.4 and 6.4, 5-H) and 4.43 (1H, ddd, *J* 7.0, 4.0 and 3.0, 3-H); δ_C (400) 10.6, 14.1 (both CH_3), 22.7, 28.0, 29.3, 31.0 (all CH_2), 32.4 (3-CH), 43.9 (4-CH_2), 81.4 (2-CH) and 81.6 (5-CH); *m/z* 253 (M^+ − Et, 4%), 225 (50), 155 (91), 85 (69) and 69 (100) [Found: M^+ − Et, 253.0072. $C_8H_{14}IO$ requires *M*, 253.0091].

(2*SR*,3*RS*)-5,5-Dimethyl-2-ethyl-3-iodotetrahydrofuran 23

By the general procedure, iodocyclization of (*E*)-2-methylhept-4-en-2-ol **22** (1.00 g, 7.8 mmol) for 1 h gave the *iodotetrahydrofuran* **23** (1.78 g, 90%) as a colourless oil; ν_{max}/cm^{-1} 1453, 1367, 1182, and 1099; δ_H (250) 0.99 (3H, t, *J* 7.5, CH_3), 1.23 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.42–1.58 (1H, m, 1′-H_a), 1.76–1.88 (1H, m, 1′-H_b), 2.18 (1H, dd, *J* 12.9 and 9.9, 4-H_a), 2.39 (1H, dd, *J* 12.9 and 6.9, 4-H_b), 3.79 (1H, ddd, *J* 9.9, 6.9 and 3.4, 3-H) and 4.00 (1H, ddd, *J* 8.9, 6.9 and 3.4, 2-H); δ_C (400) 9.8, (CH_3), 22.5 (3-CH), 24.9 (CH_2), 28.8, 29.5 (both CH_3), 51.3 (4-CH_2) and 81.1 (2-CH) [5-C not observed]; *m*/*z* 239 (M^+ − Me, 7%), 225 (59), 127 (33), 98 (100) and 69 (85) [Found: M^+ − Me, 238.9940. $C_7H_{12}IO$ requires *M*, 238.9935].

2,2-Dimethyl-3-iodotetrahydrofuran 25a

Iodocyclization of 4-methylpent-3-en-1-ol **24a** (1.00 g, 10 mmol) by the general procedure for 1 h gave the *iodotetrahydrofuran* **25a** (1.94 g, 85%) as a colourless oil; ν_{max}/cm^{-1} 1455, 1384, 1370, 1246, 1126 and 1038; δ_H (250) 1.33 (3H, s, CH_3), 1.39 (3H, s, CH_3), 2.18–2.46 (1H, m, 4-H_a), 2.54–2.67 (1H, m, 4-H_b), 3.79–3.98 (3H, m, 3-H and 5-CH_2); δ_C (270) 25.0 (CH_3), 26.4 (CH_3), 31.0 (3-CH), 37.7 (4-CH_2), 65.8 (5-CH_2) and 82.0 (2-C); *m*/*z* 226 (M^+, 8%), 211 (31), 99 (89), 84 (41) and 41 (100) [Found: M^+, 225.9850. $C_6H_{11}IO$ requires *M*, 225.9856].

Methyl (2′*SR*,4′*RS*)-(5′,5′-dimethyl-4′-iodotetrahydrofuran-2′-yl)acetate 25b

The hydroxy-ester **24b** (0.15 g, 0.9 mmol) was cyclized according to the general procedure for 3 h to give, after CC (20% ether in pentane), the *iodotetrahydrofuran* **25b** (0.22 g, 81%) as a colourless oil; ν_{max}/cm^{-1} 1735, 1462, 1384, 1164 and 1023; δ_H (250) 1.64 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.83–1.91 (1H, m, 3′-H_a), 2.22 (1H, ddd, *J* 13.0, 10.8 and 9.1, 3′-H_b), 2.53 (1H, dd, *J* 15.4 and 6.7, 2-H_a), 2.65 (1H, dd, *J* 15.4 and 6.5, 2-H_b), 3.69 (3H, s, OCH_3), 4.02 (1H, dd, *J* 10.8 and 6.8, 4′-H) and 4.33 (1H, dddd, *J* 9.1, 6.7, 6.7 and 6.5, 2′-H); δ_C (400) 25.7, 29.2 (both CH_3), 30.0 (4′-CH), 41.6 (3′-CH_2), 43.7 (2-CH_2), 51.8 (OCH_3), 73.9 (2′-CH), 82.7 (5′-C) and 171.5 (CO) [Found: C, 36.4; H, 5.3. $C_9H_{15}IO_3$ requires C, 36.2; H, 5.1%].

Methyl (2′*SR*,4′*RS*,5′*SR*)-(5′-ethyl-4′-iodotetrahydrofuran-2′-yl)acetate 9

The (*E*)-3-hydroxyoct-5-enoate **8** (0.21 g, 1.20 mmol) was cyclized according to the general procedure but for 24 h at −4 °C, to give, after CC (20% ethyl acetate in hexane), the *iodotetrahydrofuran* **9** (0.31 g, 86%) as a colourless oil; ν_{max}/cm^{-1} 1740; δ_H (250) 0.99 (3H, t, *J* 7.4, CH_3), 1.51 (1H, m, 1″-H_a), 1.80 (1H, dqd, *J* 14.2, 7.4 and 6.6, 1″-H_b), 2.10 (1H, ddd, *J* 13.1, 5.8 and 3.5, 3′-H_a), 2.55 (1H, dd, *J* 15.5 and 6.5, 2-H_a), 2.74 (1H, dd, *J* 15.5 and 6.9, 2-H_b), 2.79 (1H, ddd, *J* 13.1, 7.1 and 6.6, 3′-H_b), 3.70 (3H, s, OCH_3), 3.79 (1H, ddd, *J* 6.6, 3.8 and 3.5, 4′-H), 4.10 (1H, ddd, *J* 6.6, 6.6 and *ca*. 4, 5′-H) and 4.38 (1H, app dq, *J* 8.3 and *ca*. 6.6, 2′-H); δ_C (400) 10.2 (CH_3), 21.3 (4′-CH), 25.3 (1″-CH_2), 40.8 (3′-CH_2), 44.9 (2-CH_2), 52.0 (OCH_3), 74.6 (2′-CH), 88.1 (5′-CH) and 171.4 (CO); *m*/*z* 298 (M^+, 1%), 269 (46), 237 (15), 225 (13), 171 (56), 142 (30) and 97 (100) [Found: C, 36.7; H, 5.3. $C_9H_{15}IO_3$ requires C, 36.3; H, 5.1%].

A second isomer (<5%) was visible in the crude product and could be detected by δ_C (400) 10.1 (CH_3), 22.8 (4′-CH), 26.4 (1″-CH_2), 40.3 (3′-CH_2), 43.9 (2-CH_2), 52.1 (OCH_3), 74.5 (2′-CH), 90.1 (5′-CH) and 171.4 (CO), along with less well-defined resonances in the ^{1}H NMR spectrum.

When this cyclization was carried out using the same starting hydroxy-ester **8** (1.00 g), but at 0 °C in acetonitrile (20 ml) containing water (2 ml), the isolated yield after chromatography was 67% of iodotetrahydrofuran **9**, which showed spectroscopic and analytical data identical to the foregoing.

Methyl (2′*SR*,4′*RS*,5′*SR*)-(5′-butyl-4′-iodotetrahydrofuran-2′-yl)acetate 27b

The (*E*)-3-hydroxydec-5-enoate **26a** (3.26 g, 16.3 mmol) was cyclized according to the general procedure for 16 h to give, after CC (20% ether in pentane), the *iodotetrahydrofuran* **27b** (3.98 g, 75%) as a colourless oil; ν_{max}/cm^{-1} 1732; δ_H (400; C_6H_6) 1.06 (3H, t, *J* 6.7, CH_3), 1.38–1.90 (6H, m, 3 × CH_2), 2.05 (1H, ddd, *J* 12.6, 5.6 and 3.7, 3′-H_a), 2.39 (1H, dd, *J* 15.5 and 6.5, 2-H_a), 2.45 (1H, ddd, *J* 12.6, 6.7 and 6.4, 3′-H_b), 2.70 (1H, dd, *J* 15.5 and 7.0, 2-H_b), 3.49 (1H, ddd, *J* 6.7, 3.7 and 3.5, 4′-H), 3.51 (3H, s, OCH_3), 4.20 (1H, ddd, *J* 6.7, 6.7 and 3.5, 5′-H) and 4.39 (1H, dddd, *J* 7.0, 6.5, 6.4 and 5.6, 2′-H); δ_C (270; C_6D_6) 14.1 (CH_3), 22.5 (4′-CH), 22.9, 28.3, 32.3 (all CH_2), 40.6 (3′-CH_2), 44.8 (2-CH_2), 51.1 (OCH_3), 74.5 (2′-CH), 86.8 (5′-CH) and 170.6 (CO); *m*/*z* [NH_3-CI] 327 (M^+ + H, 15%), 281 (30), 221 (43), 207 (36) and 147 (100) [Found: C, 40.8; H, 5.9. $C_{11}H_{19}IO_3$ requires C, 40.5; H, 6.0%].

Methyl (2′*SR*,4′*RS*,5′*SR*)-(4′-iodo-5′-phenethyltetrahydrofuran-2′-yl)acetate 27c

The (*E*)-hydroxy-ester **26c** (0.06 g, 0.24 mmol) was cyclized according to the general procedure for 3 h to give, after CC (20% ether in pentane), the *iodotetrahydrofuran* **27c** (0.070 g, 77%) as a colourless oil; ν_{max}/cm^{-1} 1736, 1438, 1202 and 1030; δ_H (250) 1.71 (1H, ddd, *J* 13.8, 4.7 and 3.5, 3′-H_a), 2.01–2.09 (1H, m, 3′-H_b), 2.48 (1H, dd, *J* 15.5 and 6.4, 2-H_a), 2.60–2.85 (5H, m, 2-H_b and 2 × CH_2), 3.64 (3H, s, OCH_3), 3.70 (1H, ddd, *J* 7.4, 3.5 and 3.4, 4′-H), 3.94 (1H, ddd, *J* 8.5, 8.5 and 3.5, 5′-H), 4.35 (1H, ddddd, *J* 6.9, 6.4, 6.4, 4.7 and 1.4, 2′-H) and 7.08–7.25 (5H, m, Ph); δ_C (270) 21.5 (4′-CH), 32.2, 33.9 (both CH_2), 40.7 (3′-CH_2), 44.5 (2-CH_2), 51.8 (OCH_3), 74.5 (2′-CH), 85.9 (5′-CH), 126.0, 128.4, 128.5 (all CH), 141.6 (C) and 170.5 (CO); *m*/*z* 246 (M^+ − HI, 2%), 186 (43), 160 (36), 91 (100) and 55 (95) [Found: C, 48.3; H, 5.2. $C_{15}H_{19}IO_3$ requires C, 48.1; H, 5.1%].

Methyl (2*RS*,4*RS*,5*SR*)-5-butyl-4-iodotetrahydrofuran-2-carboxylate 29[6]

By the general procedure, iodocyclization of the (*E*)-non-4-enoate **28** (0.20 g, 1.08 mmol) during 6 h gave, after CC (20% ethyl acetate–hexane), the *iodotetrahydrofuran* **29** (0.28 g, 83%) as a colourless oil; ν_{max}/cm^{-1} 1735; δ_H (250) 0.92 (3H, t, *J* 7.2, 4′-CH_3), 1.26–1.61 (4H, m, 2′- and 3′-CH_2), 1.61–1.73 (1H, m, 1′-H_a), 1.85–1.92 (1H, m, 1′-H_b), 2.42 (1H, ddd, *J* 13.5, 9.2 and 7.1, 3-H_a), 2.93 (1H, ddd, *J* 13.5, 7.9 and 7.9, 3-H_b), 3.69 (1H, m, 4-H), 3.77 (3H, s, OCH_3), 4.18 (1H, ddd, *J* 8.9, 7.2 and 4.6, 5-H) and 4.49 (1H, dd, *J* 7.9 and 7.1, 2-H); δ_C (270) 14.2 (4′-CH_3), 20.3 (CH_2), 22.9 (4-CH), 28.0, 31.8. 42.4 (all CH_2), 52.6 (OCH_3), 75.9, 88.3 (2- and 5-CH) and 173.0 (CO); *m*/*z* 312 (M^+, 1%), 254 (22), 253 (6), 226 (35), 185 (56), 157 (18) and 55 (100) [Found: C, 38.6; H, 5.5. $C_{10}H_{17}IO_3$ requires C, 38.5; H, 5.5%].

(2*SR*,4*RS*,5*SR*)-5-(1,3-Dithian-2-ylmethyl)-3-iodo-2-(phenethyl)tetrahydrofuran 31 and (2′*SR*,4′*RS*,5′*SR*)-(4′-iodo-5′-phenethyltetrahydrofuran-2′-yl)acetaldehyde 32

The hydroxy-dithiane **30** (1.0 g, 3.24 mmol) was cyclized using the usual method for 16 h, followed by CC (10% EtOAc in petrol) to give (i) the *iodotetrahydrofuryl dithiane* **31** (0.27 g, 34%) as a colourless oil; ν_{max}/cm^{-1} 1602, 1496, 1454, 1422, 1376, 1276, 1144, 1074 and 1031; δ_H (250) 1.70–1.80 (2H, m, CH_2CH_2S), 1.82–2.05 (6H, m, 3 × CH_2), 2.47–2.95 (6H, m, 3 × CH_2), 3.72 (1H, ddd, *J* 6.2, 4.0 and 3.0, 3-H), 3.95 (1H, ddd, *J* 7.0, 7.0 and 3.0, 2-H), 4.20 (1H, dd, *J* 12.0 and 8.0, SCHS), 4.32 (1H, m, 5-H) and 7.15–7.30 (5H, m, Ph); δ_C (270) 21.8, 30.0, 30.3 (all CH_2), 31.9 (3-CH), 32.2, 33.7, 41.7 (all CH_2), 44.1 (4-CH_2), 44.6 (CH_2), 66.4 (SCHS), 74.6 (2-CH), 85.2 (5-CH), 125.8, 128.3, 128.4 (all CH) and 141.6 (C) [Found: C, 46.9 ; H, 5.6. $C_{17}H_{23}IOS_2$ requires C, 47.0; H, 5.3%] and (ii) the *aldehyde*

32 (0.10 g, 15%) as a colourless oil; ν_{max}/cm^{-1} 1725; δ_H (250) 1.75 (1H, ddd, *J* 13.0, 4.7 and 3.5, 3′-H_a), 2.05 (1H, ddd, *J* 13.0, 6.0 and 2.1, 3′-H_b), 2.70–2.90 (6H, m, 3 × CH_2), 3.73 (1H, ddd, *J* 6.2, 4.0 and 3.0, 4′-H), 4.03 (1H, ddd, *J* 7.0, 7.0 and 3.0, 5′-H), 4.42–4.52 (1H, m, 2′-H), 7.15–7.30 (5H, m, Ph) and 9.52 (1H, br s, CHO).

(2*RS*,3*SR*)-3′-Iodotetrahydrofuran-2-ethanol 34

By the general procedure, iodocyclization of (*E*)-hex-3-ene-1,6-diol **33** [prepared by reduction of commercial (*E*)-hex-3-enedioic acid (β-hydromuconic acid) using excess $LiAlH_4$ in refluxing tetrahydrofuran for 24 h] (1.04 g, 9.0 mmol) followed by CC (30% ethyl acetate in hexane) gave the *iodotetrahydrofuran* **34** (1.89 g, 87%) as a colourless oil; ν_{max}/cm^{-1} 3429, 1641 and 1464; δ_H (250) 1.67 (1H, dddd, *J* 14.7, 9.0, 6.0 and 6.0, 4′-H_a), 2.11 (1H, dddd, *J* 14.7, 8.2, 5.1 and 5.1, 4′-H_b), 2.22 (1H, br s, OH), 2.31 (1H, dddd, *J* 13.5, 7.6, 6.0 and 6.0, 1-H_a), 2.55 (1H, dddd, *J* 13.5, 7.6, 6.3 and 6.3, 1-H_b), 3.75–3.87 (3H, m, 3′-H and C*H*$_2$OH), 3.88–4.01 (2H, m, 5′-CH_2) and 4.15 (1H, ddd, *J* 9.1, 7.8 and 3.1, 2′-H); δ_C (250) 23.1 (3′-CH), 34.7, 38.1 (both CH_2), 60.7, 67.3 (both CH_2O) and 87.5 (2′-CH); *m*/*z* 242 (M^+, 100%), 155 (42), 211 (8), 197 (15), 70 (60) and 46 (41) [Found: M^+, 241.9810. $C_6H_{11}IO_2$ requires *M*, 241.9806].

(2*RS*,3*RS*)-3-Acetoxy-2-ethyltetrahydrofuran 35

Caesium acetate (0.127 g, 0.66 mmol) was added to a solution of *trans*-iodotetrahydrofuran **14** (0.100 g, 0.44 mmol) in dry dimethylformamide (1 ml).[16] The resulting mixture was stirred and heated to 80 °C for 14 h then diluted with water (25 ml) and extracted with ether (3 × 20 ml). The combined extracts were dried and evaporated; CC (5% ethyl acetate in petrol) separated the *acetoxytetrahydrofuran* **35** (0.02 g, 35%) as a colourless oil which showed data identical to that previously recorded;[46] specifically ν_{max}/cm^{-1} 1741, 1242, 1106 and 1025; δ_H (250) 0.87 (3H, t, *J* 7.1, CH_3), 1.40–1.55 (2H, m, 1′-CH_2), 1.85–2.03 (1H, m, 4-H_a), 2.18 (3H, s, OAc), 2.17–2.29 (1H, m, 4-H_b), 3.57 (1H, ddd, *J* 7.3, 7.3 and 3.7, 2-H), 3.72 (1H, ddd, *J* 8.7, 8.7 and 5.3, 5-H_a), 3.95 (1H, ddd, *J* 8.7, 7.6 and 7.6, 5-H_b) and 5.23 (1H, ddd, *J* 6.0, 3.7 and 1.5, 3-H).

(2*RS*,3*RS*)-2-Ethyl-3-hydroxytetrahydrofuran 36

Potassium superoxide (0.344 g, 4.8 mmol) was added to a stirred solution of *trans*-iodotetrahydrofuran **14** (1.00 g, 4.4 mmol) and 18-crown-6 (0.1 ml) in dry dimethylformamide (10 ml).[17] The resulting mixture was stirred at ambient temperature for 16 h then diluted with water (50 ml) and extracted with ether (3 × 20 ml). The combined extracts were dried and evaporated; CC (20% ethyl acetate in petrol) separated the *hydroxytetrahydrofuran* **36** (0.104 g, 25%) as a colourless oil which showed data identical to that previously recorded;[47] specifically ν_{max}/cm^{-1} 3542, 1375, 1150 and 1023; δ_H (250) 0.94 (3H, t, *J* 7.6, CH_3), 1.40–1.55 (2H, m, 1′-CH_2), 1.84–1.90 (1H, m, 4-H_a), 2.09–2.18 (1H, m, 4-H_b), 3.42 (1H, ddd, *J* 6.8, 6.8 and 3.1, 2-H), 3.79 (1H, ddd, *J* 8.9, 8.9 and 4.6, 5-H_a), 3.97 (1H, m, 5-H_b) and 4.16–4.17 (1H, m, 3-H).

Methyl (2′*SR*,4′*SR*,5′*SR*)-(4′-azido-5′-ethyltetrahydrofuran-2′-yl)acetate 37

A solution of the foregoing iodotetrahydrofuranacetate **8** (0.10 g, 0.34 mmol) in dry dimethylformamide (5 ml) containing sodium azide (0.05 g, 0.64 mmol) and 15-crown-5 (2 drops) was stirred and heated at 40 °C for 8 h. The cooled mixture was diluted with water (20 ml) and pentane (20 ml) and the organic layer separated. The aqueous mixture was extracted with pentane (3 × 10 ml) and the combined pentane solutions dried and evaporated. CC (10% ethyl acetate in hexane) separated the *azide* **37** (0.04 g, 52%) as a colourless oil; ν_{max}/cm^{-1} 2105, 1741 and 1262; δ_H (400) 0.96 (3H, t, *J* 7.4, CH_3), 1.60–1.70 (2H, m, 1″-CH_2), 2.01 (1H, ddd, *J* 13.7, 8.8 and 5.5, 3′-H_a), 2.32 (1H, ddd, *J* 13.7, 7.6 and 6.5, 3′-H_b), 2.50 (1H, dd, *J* 15.4 and 6.5, 2-H_a), 2.66 (1H, dd, *J* 15.4 and 6.6, 2-H_b), 3.70 (3H, s, OCH_3), 3.84 (1H, ddd, *J* 6.9, 6.9 and 3.5, 5′-H), 3.99 (1H, m, 4′-H) and 4.65 (1H, dddd, *J* 8.8, 6.6, 6.5 and 5.5, 2′-H); δ_C (400) 10.7 (CH_3), 23.2, 38.3, 40.8 (all CH_2), 52.0 (OCH_3), 63.8, 73.6, 83.2 (all CH) and 171.4 (CO); *m*/*z* 185 ($M^+ - C_2H_4$, 7%), 170 (3), 157 (8), 84 (19) and 59 (100).

Small traces of the corresponding 2,5-dihydrofuranacetate **38** (see below) were detected in the crude product along with *ca.* 15% of unreacted starting material **8**.

Methyl (2′*SR*,5′*SR*)-(5′-ethyl-2′,5′-dihydrofuran-2′-yl)acetate 38

Repetition of the foregoing experiment on the same scale, but with heating for 24 h at 70 °C, followed by CC using the same solvents gave the *dihydrofuran* **38** (0.09 g, 79%) as a colourless oil; ν_{max}/cm^{-1} 1726 and 1675; δ_H (400) 0.90 (3H, t, *J* 7.4, CH_3), 1.59 (2H, app qd, *J* 7.4 and 5.8, 1″-CH_2), 2.50 (1H, dd, *J* 15.2 and 6.0, 2-H_a), 2.62 (1H, dd, *J* 15.2 and 7.0, 2-H_b), 3.70 (3H, s, OCH_3), 4.85 (1H, ddd, *J* 5.8, 5.8 and 1.2, 5′-H), 5.20 (1H, dddd, *J* 7.0, 6.0, 1.2 and 1.2, 2′-H) and 5.83–5.89 (2H, m, 2 × :CH); δ_C (400) 9.3 (CH_3), 28.9 (1″-CH_2), 41.4 (2-CH_2), 52.0 (OCH_3), 82.3, 87.2 (both CH), 129.4, 130.9 (both CH) and 171.8 (CO); *m*/*z* 170 (M^+, 8%), 141 (27), 139 (10), 111 (9), 110 (17), 97 (100) and 82 (16) [Found: M^+, 170.0946. $C_9H_{14}O_3$ requires *M*, 170.0943].

The product was accompanied by small amounts of the corresponding oxidation product, methyl 5-ethylfuran-2-acetate **39**, the quantity of which increased when a dilute chloroform solution of the dihydrofuran **38** was stored at ambient temperature and which showed, after separation by CC as above, ν_{max}/cm^{-1} 1735, 1555 and 1480; δ_H (250) 1.21 (3H, t, *J* 7.5, CH_3), 2.62 (2H, q, *J* 7.5, 1′-CH_2), 3.64 (2H, s, 2-CH_2), 3.72 (3H, s, OCH_3), 5.91 (1H, ddd, *J* 3.1, 1.1 and 1.1, 4-H) and 6.10 (1H, app d, *J* 3.1, 3-H); δ_C (400) 12.3 (CH_3), 21.6 (1′-CH_2), 34.3 (2-CH_2), 52.5 (OCH_3), 105.0, 108.8 (both CH), 145.8, 157.9 (both C) and 170.5 (CO); *m*/*z* 168 (M^+, 5%), 153 (5) and 139 (100) [Found: M^+, 168.0793. $C_9H_{12}O_3$ requires *M*, 168.0786].

(2*RS*,3*SR*)-3-Iodo-2-(2′-triisopropylsilyloxyethyl)tetrahydrofuran 40

Imidazole (5.83 g, 86 mmol) was added to a stirred solution of the foregoing iodotetrahydrofuran **34** (1.89 g, 7.8 mmol) and triisopropylsilyl chloride (1.75 g, 9.2 mmol) in dry dimethylformamide (10 ml) maintained at 0 °C. The cooling bath was removed and the resulting solution stirred for 48 h, then diluted with pentane (20 ml) and washed with water (3 × 20 ml). The aqueous washings were extracted with pentane (20 ml) and the combined pentane solutions dried and evaporated. CC (10% ethyl acetate in hexane) separated the *silyl ether* **40** (2.33 g, 75%) as a pale yellow oil; ν_{max}/cm^{-1} 1464 and 1384; δ_H (250) 1.02–1.12 (21H, m, 3 × ^{i}Pr), 1.62 (1H, dddd, *J* 13.6, 8.1, 8.1 and 5.5, 4-H_a), 1.95 (1H, dddd, *J* 13.6, 10.1, 7.6 and 3.9, 4-H_b), 2.24 (1H, app dq, *J* 13.7 and 7.4, 1′-H_a), 2.48 (1H, app dq, *J* 13.7 and 7.4, 1′-H_b), 3.72–3.95 (5H, m, 3-H, 5-CH_2 and C*H*$_2$OSi) and 4.15 (1H, ddd, *J* 7.4, 7.4 and 3.9, 2-H); δ_C (250) 12.2 (3 × CH), 18.3 (6 × CH_3), 24.2 (3-CH), 36.4, 38.5 (both CH_2), 60.4, 67.0 (both CH_2O) and 85.7 (2-CH); *m*/*z* 398 (M^+, 100%), 355 (35), 325 (14), 271 (40), 225 (52), 98 (28) and 84 (23) [Found: M^+, 398.1145. $C_{15}H_{31}IO_2Si$ requires *M*, 398.1140].

(2*SR*,3*SR*)-3-Hydroxy-2-(2′-triisopropylsilyloxyethyl)tetrahydrofuran 41a and 2-(2′-triisopropylsilyloxyethyl)-2,5-dihydrofuran 42

A solution of the foregoing silyl ether **40** (2.20 g, 5.53 mmol) in dry dimethylformamide (10 ml) containing potassium superoxide (0.43 g, 6.0 mmol) and 18-crown-6 (2 drops) was stirred at ambient temperature for 10 h then poured into water (30 ml)

and pentane (30 ml).[17] The separated aqueous layer was extracted with pentane (3 × 10 ml) and the combined pentane solutions washed with water (10 ml) then dried and evaporated. CC (30% ethyl acetate in hexane) gave (i) the *dihydrofuran* **42** (0.21 g, 15%) as a colourless oil; ν_{max}/cm^{-1} 1464 and 1385; δ_H (250) 1.02–1.12 (21H, m, 3 × ^iPr), 1.70 (2H, td, *J* 7.2 and 6.8, 1′-CH_2), 3.81 (2H, t, *J* 7.2, CH_2OSi), 4.58–4.62 (2H, m, 5-CH_2), 4.87–4.91 (1H, m, 2-H) and 5.83 (2H, app br s, 3- and 4-H); δ_C (250) 12.1 (3 × CH), 18.2 (6 × CH_3), 39.7 (1′-CH_2), 60.6 (2′-CH_2), 75.0 (5-CH_2), 83.8 (2-CH), 126.2 (**:**CH) and 130.5 (**:**CH); *m*/*z* 270 (M^+, 100%), 227 (85), 197 (18), 185 (22), 141 (8), 97 (9) and 69 (15) followed by (ii) the *hydroxytetrahydrofuran* **41a** (1.20 g, 74%) as a pale yellow oil; ν_{max}/cm^{-1} 3429, 1642 and 1464; δ_H (250) 1.02–1.12 (21H, m, 3 × ^iPr), 1.84–2.32 (4H, m, 4- and 1′-CH_2), 3.66–3.81 (2H, m, CH_2OSi), 3.74 (1H, ddd, *J* 9.5, 9.5 and 4.6, 5-H_a), 3.90 (1H, ddd, *J* 9.5, 4.0 and 4.0, 5-H_b), 4.02 (1H, m, 3-H) and 4.34 (1H, ddd, *J* 5.7, 3.5 and 1.7, 2-H); δ_C (250) 12.2 (3 × CH), 18.3 (6 × CH_3), 32.2, 35.1 (both CH_2), 60.9, 66.4 (both CH_2O), 72.4 (3-CH) and 83.5 (2-CH); *m*/*z* 288 (M^+, 100%), 269 (25), 245 (27), 202 (8), 174 (5) and 115 (7) [Found: M^+, 288.2117. $C_{15}H_{32}O_3Si$ requires *M*, 288.2121].

(2*SR*,3*SR*)-3′-Hydroxytetrahydrofuran-2-ethanol 41b

Tetrabutylammonium fluoride (5 ml of a 1 M solution in tetrahydrofuran, 5 mmol) was added dropwise to a stirred solution of the foregoing hydroxytetrahydrofuran **41a** (1.00 g, 3.5 mmol) in dry tetrahydrofuran (20 ml) maintained at 0 °C. The cooling bath was then removed and the solution stirred for 12 h then evaporated. CC (1:1 ethyl acetate–hexane) separated the *diol* **41b** (0.41 g, 89%) as a colourless oil; ν_{max}/cm^{-1} 3377, 1441 and 1337; δ_H (250) 1.91–2.03 (1H, m, 4′-H_a), 1.97 (1H, dddd, *J* 12.5, 6.7, 6.7 and 1.7, 1-H_a), 1.99 (1H, dddd, *J* 12.5, 6.7, 6.7 and 5.6, 1-H_b), 2.18 (1H, dddd, *J* 11.1, 8.9, 7.8 and 5.6, 4′-H_b), 3.74 (1H, ddd, *J* 15.9, 8.9 and 5.2, 5′-H_a), 3.77 (2H, t, *J* 6.7, C*H*$_2$OH), 3.86 (1H, ddd, *J* 15.9, 10.6 and 5.6, 5′-H_b), 4.05 (1H, m, 3-H) and 4.34 (1H, ddd, *J* 5.6, 3.4 and 1.7, 2′-H); δ_C (250) 31.0, 34.9 (both CH_2), 60.0, 65.9 (both CH_2O), 72.4 (3-CH) and 82.6 (2′-CH); *m*/*z* 132 (M^+, 100%), 114 (27), 87 (18), 83 (62), 69 (7) and 45 (34) [Found: M^+, 132.0782. $C_6H_{12}O_3$ requires *M*, 132.0786].

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