Pergamon

Tetrahedron Vol. 51, No. 36, pp. 9995-10012, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00572-2

Synthesis of Bis-2,5-Linked Tetrahydrofurans via Iodoetherification

Margaret A. Brimble[1]* and Michael K. Edmonds[2]

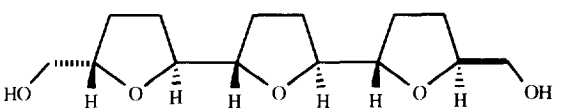
1. Department of Chemistry, University of Sydney, NSW 2006, Australia.

2. Department of Chemistry and Biochemistry, Massey University, Palmerston North, New Zealand.

Abstract: Iodoetherification of alcohol **4** and several ether derivatives **12-15** afforded bis-tetrahydrofurans **8** and **9**. The ratio of **8**:**9** depended on the nature of the ether substituent with **8** being the major product for R=H, $SiMe_3$, and Si^tBuPh_2 whereas **9** was favoured when R=dichlorobenzyl. Attempts to effect ring expansion of **8** afforded ketone **16** wherein hydride migration had occurred. Iodoetherification of trisubstituted hydroxyalkene **17** afforded predominantly iodoether **21**. Attempts to increase the amount of iodoether **22** formed led to a 1:1 ratio of **21**:**22** using trimethylsilyl ether **23**. Treatment of iodoether **21** and **22** with Ag_2CO_3 in aqueous acetone proceeded stereospecifically affording the ring expansion products **27** and **28** respectively. Pyran **28** possesses the same stereochemistry as that present in the polyether antibiotic salinomycin.

INTRODUCTION

2,5-Disubstituted tetrahydrofuran units are present in many monocarboxylic acid ionophores commonly known as polyether antibiotics.[1] These naturally occurring polyether antibiotics are podand-like structures which bind cations and transport them across lipid bilayers. Recent effort has therefore been directed towards the synthesis of neutral podands which structurally resemble the poly-tetrahydrofuran / tetrahydropyran substructures of the polyether antibiotics.[2] In particular, oligo-2,5-linked tetrahydrofurans (oligo-THFs) assembled out of 2,5-*trans*-THF units e.g. **1**[3] have received considerable interest as THF-podands. Furthermore, the oligo-THF moiety is well-represented in the acetogenin class of natural products which exhibit antineoplastic properties.[4]



(**1**)

Several synthetic strategies for the assembly of 2,5-disubstituted tetrahydrofurans have been developed and are summarized in recent reviews.[5-8] One such strategy developed by Bartlett[9] involves electrophilic cyclization (in particular, halocyclization) of γ,δ-unsaturated alcohols, wherein treatment of a γ,δ-unsaturated alcohol with iodine in acetonitrile at 0°C affords a *trans*-2,5-disubstituted-THF ring whereas treatment of the 2,6-dichlorobenzyl ether of the alcohol affords the *cis*-isomer.

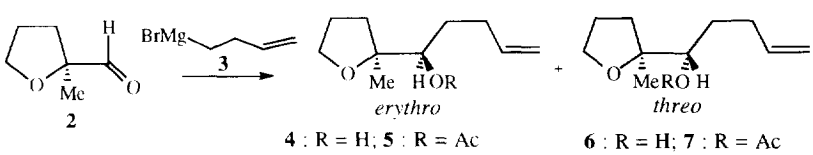
The work described herein provides an extension to Bartlett's methodology to the synthesis of bis-2,5-linked tetrahydrofurans as a foundation for the construction of oligo-THF podands *via* iterative iodoetherification of γ,δ-unsaturated alcohols. The iodomethyl substituent formed in the iodoetherification reaction offers two further synthetic transformations. Firstly, conversion of the iodine to an aldehyde allows

introduction of an additional γ,δ-unsaturated alcohol unit required for introduction of an additional THF unit. Secondly, silver(I) assisted solvolysis of the iodine may provide a method for ring expansion to a tetrahydropyran ring, thereby offering the possibility of preparing mixed THF-THP podands as found in several polyether antibiotics e.g. salinomycin[10] and lasalocid.[11]

DISCUSSION

Our initial attention focussed on the iodoetherification of γ,δ-unsaturated alcohol **4**. Addition of the Grignard reagent of 4-bromo-1-butene **3** to aldehyde **2** afforded a 4:1 *erythro-threo* mixture of alcohols **4** and **6** (Scheme 1) for which the spectral data were in agreement with the literature.[12] The most significant feature in the nmr spectra of alcohols **4** and **6** centred on the two chiral centres at C2' and C1. The ^{1}H nmr chemical shift of the 1-H proton of the *erythro* alcohol **4** (δ 3.53) was further downfield than that of the *threo* alcohol **6** (δ 3.40). A similar pattern was observed in the ^{13}C nmr spectra with the chemical shift of the 2'-Me carbon of *erythro* alcohol **4** (δ 22.9) appearing further downfield from that of the 2'-Me carbon of the *threo* alcohol **6** (δ 19.9).

Conversion of the mixture of alcohols **4** and **6** to the corresponding acetates which were separable by flash chromatography afforded pure *erythro* alcohol **4** upon hydrolysis of the purified *erythro* acetate **5**. Iodoetherification of *erythro*-alcohol **4** produced a 5:1 ratio of the *erythro trans* iodoether **8** and *erythro cis* iodoether **9** (Scheme 2) in 93% overall yield. Similarly, iodoetherification of the *threo* alcohol **6** purified *via* hydrolysis of *threo* acetate **7**, produced a 5:1 ratio of the *threo trans* and *threo cis* iodoethers **10** and **11** (Scheme 3). The stereoselectivity of the iodoetherification was investigated in the *erythro* series upon conversion of the hydroxy group to various ether derivatives. The *erythro* silyl ethers **12** and **13** afforded a 5:1 ratio of *trans : cis* ethers **8**:**9** whereas use of a 4-bromobenzyl (BBN) ether **14** gave a slight preference for formation of the *cis*-isomer and the bulkier 2,6-dichlorobenzyl ether (DCB) **15** results in a much larger 10:1 *cis trans* ratio.



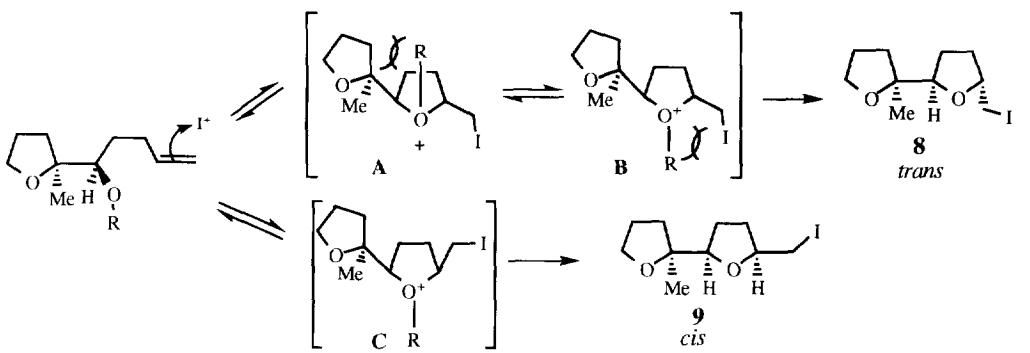
Scheme 1

These observations were consistent with Bartlett's rationalization[9] of the observed selectivity in the simpler case wherein the initial THF ring was a simple alkyl group. Thus, in the case where R is a bulky group, the intermediate cations A and B which lead to the *trans* isomer suffer from severe 1,2-non-bonded interactions whereas the transition state C leading to the *cis* isomer lacks such non-bonded interactions. In the case of the alcohol **4** (R=H), the *trans* isomer **8** is formed due to the absence of the 1,3-non-bonded interactions present in the transition state C leading to the *cis* isomer **9**.

The *erythro-trans* : *erythro-cis* ratio was obtained by isolation of the individual isomers after purification by flash chromatography. However, due to the inability to separate iodoethers **10** and **11**, the *threo*

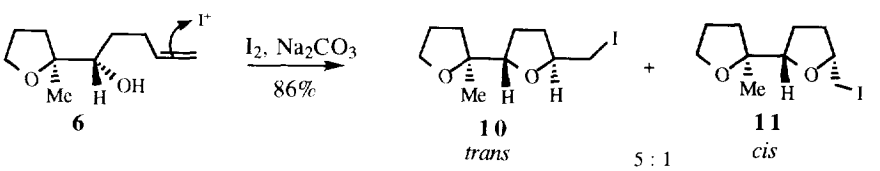
trans : *threo-cis* ratio was determined by integration of the resonances assigned to 5-H in the ^{1}H nmr spectrum of the product mixture.

In both the *erythro* and *threo* series the assignment of the major and minor iodoetherification products as the *trans* and *cis* iodides respectively was made on the basis of their ^{1}H nmr spectra. The most significant feature in the ^{1}H nmr spectra was the difference in the chemical shift of the 5-H and 2-H protons. In the ^{1}H nmr spectra of the *trans* isomers **8** and **10** both the 5-H and 2-H protons have chemical shifts further downfield than the corresponding protons in the *cis* isomers **9** and **11** (Table 1). Work by Cassady *et al* [13] has indicated that a *trans* relationship between the C-2 and C-5 positions of 2,5-disubstituted tetrahydrofuran rings will result in a chemical shift (δ) of between 4.00-4.11 for the 5-H proton, whilst a *cis* relationship will exhibit a 5-H chemical shift between 3.89-3.93.



Compound	R	(**8**) : (**9**)	Yield	Conditions
(**4**)	H	5 : 1	93%	I_2, Na_2CO_3, MeCN, 0^{0}C, 15 min.
(**5**)	Ac	-	no reaction	I_2, MeCN, 0^{0}C, 15 min.
(**12**)	$SiMe_3$	5 : 1	68%	I_2, MeCN, 0^{0}C, 15 min.
(**13**)	Si^tBuMe_2	5 : 1	57%	I_2, MeCN, 0^{0}C, 15 min.
(**14**)	BBN	2 : 3	46%	I_2, MeCN, 0^{0}C, 15 min.
(**15**)	DCB	1 : 10	63%	I_2, MeCN, 0^{0}C, 15 min.

Scheme 2



Scheme 3

Another notable difference between the *cis* and *trans* iodides is the diastereotopicity exhibited by the CH_2I protons. With both the *erythro* and *threo* iodides, the difference in the chemical shifts of the CH_2I protons of the *trans* isomers is greater than that of the *cis* isomers, although this difference is particularly noticable with

erythro iodides. While the individual diastereotopic CH_2I protons of the *erythro trans* iodide **8** exhibit a significant difference in chemical shift ($\Delta\delta = 0.16$) the resonances for these same protons in the *erythro cis* iodide **9** have merged into a complex multiplet ($\Delta\delta < 0.02$).

One further difference in the ^1H nmr spectra of the two *trans* isomers **8** and **10** compared to the *cis* isomers **9** and **11** is that the *trans* isomers **8** and **10** have a multiplet equivalent to 1 proton ($1/2 \times CH_2$) at δ~2.25.while the chemical shifts of the CH_2 protons of the corresponding *cis* isomers **9** and **11** are all below δ2.07.

Table 1

^1H NMR Chemical Shifts (δ) for 2-(Iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofurans **8**, **9**, **10** and **11**

Assignment	**8** *erythro trans*	**9** *erythro cis*	**10** *threo trans*	**11** *threo cis*
CH_3	1.15	1.17	1.12	1.15
$4 \times CH_2$	1.56 - 2.28	1.57 - 2.07	1.57 - 2.28	1.61 - 2.06
CH_AI	3.15	3.24 - 3.28	3.18	3.18
CH_BI	3.31	3.24 - 3.28	3.28	3.25
CH_2O	3.85	3.86	3.77 - 3.91	3.83 - 3.92
5-H	4.07	3.93	4.03	3.83 - 3.92
2-H	4.05 - 4.16	3.89 - 3.99	4.00 - 4.10	4.02 - 4.13

Table 2

^{13}C NMR Chemical Shifts (δ) for 2-(Iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofurans **8**, **9**, **10** and **11**

assignments	**8** *erythro trans*	**9** *erythro cis*	**10** *threo trans*	**11** *threo cis*
CH_2I	10.7	10.7	10.7	10.2
2'-Me	22.7	23.3	22.9	23.2
CH_2	26.1	26.3	26.3	26.2
CH_2	28.0	27.0	27.4	26.3
CH_2	32.9	31.4	33.0	31.4
CH_2	33.4	33.2	34.6	34.8
CH_2O	68.1	68.2	68.4	68.6
C-2	79.1	78.2	79.0	79.0
C-2'	84.3	83.9	84.1	83.1
C-5	85.4	85.9	85.6	86.2

Similarities in the ^{13}C NMR spectra of the *cis* and the *trans* iodides proved less obvious (Table 2). However, general patterns were observed in the chemical shifts of the C5, C2' and 2'-Me carbon atoms with the C5 and 2'-Me carbon atoms of the *cis* iodides **9** and **11** exhibiting larger chemical shifts than those of the corresponding *trans* iodides **8** and **10**, while the C2' carbon atoms of the *trans* iodides **8** and **10** possess larger chemical shifts than those of the corresponding *cis* iodides **9** and **11**.

Attempts to corroborate the *cis* and *trans* assignments of the iodides **8** and **9** using NOESY and NOE difference experiments were problematic. Hence iodides **8** and **9** were converted to the methyl compounds using tributyltin hydride and AIBN for which nmr analysis supported the stereochemical assignment in that an NOE effect was observed between 5-H and 2-Me (Figure 1) for the *trans* isomer.

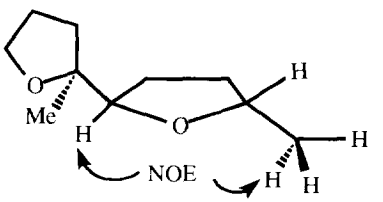
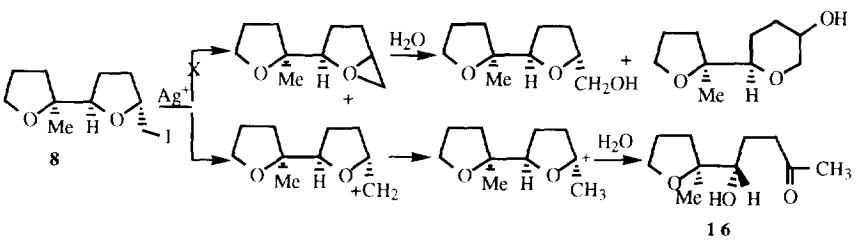


Figure 1

It is interesting to note that the mercuric acetate induced cyclisation of the *erythro* alcohol **4** followed by reduction with sodium borohydride as carried out by Amouroux *et al*[12] afforded a 7:1 ratio of the *trans* : *cis* methyl ethers which is comparable to the 5 : 1 ratio observed in the iodoetherification reported herein.

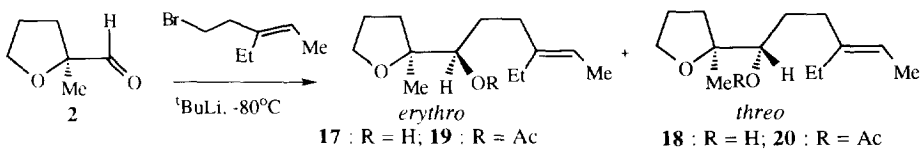
Ring expansion of tetrahydrofurans to tetrahydropyrans have been documented *via* solvolysis of a mesylate using silver carbonate[14] or *via* thallium-induced cyclization of a hydroxyolefin.[15] Treatment of iodide **8** with silver carbonate, however, leads to formation of ketoalcohol **16** rather than ring expansion suggesting that successful ring expansion requires a tetrasubstituted carbon at C-2 on the bis-THF, thereby eliminating the possibility of hydride migration (Scheme 4).



Scheme 4

Our attention therefore focussed on the iodoetherification of γ-substituted-γ,δ-unsaturated alcohol **17** which was prepared in 54% yield by inverse addition of the organolithium reagent derived from (*E*)-1-bromo-3-ethyl-3-pentene to aldehyde **2** (Scheme 5). This provided a 3:1 mixture of the *erythro* **17** and *threo* **18** isomers which were readily separated upon conversion to their acetate derivatives **19** and **20**. Assignment of the alcohols **17** and **18** as the *erythro* and *threo* isomers respectively was made by comparison of the ^1H nmr spectra with those for recorded for the alcohols **4** and **6**.

Alcohol **17** provides C-2 disubstituted tetrahydrofurans **21** and **22** upon iodoetherification. Examination of the stereoselectivity of this iodoetherification of *erythro* alcohol **17** is of particular interest in that ring expansion of **22** affords the appropriately substituted THF-THP system with the same stereochemistry as that present in the right hand portion of the polyether antibiotics salinomycin and lasalocid.



Scheme 5

Treatment of alcohol **17** with iodine in acetonitrile afforded predominantly iodoether **21** (Scheme 6) with the exact ratio depending on the temperature used. Assignment of the relative configurations of iodides **21** and **22** was made on the basis of their ^{1}H and ^{13}C nmr spectra. The ^{1}H nmr spectra of iodide **21** possessed a 5-H chemical shift of δ 4.02 compared with δ 3.94 for the 5-H chemical shift of iodide **22**. Tentative assignment of the major iodide **21** as the *trans* isomer and the minor iodide as the *cis* isomer **22** was made on the basis of the chemical shifts of the 5-H protons, using work by Cassady *et al*[13] which established that the chemical shift for the 5-H proton of the *trans* isomer should be in the range δ 4.00 - 4.11 while that of the *cis* isomer should be at δ 3.89 - 3.93. The ^{13}C nmr spectra of iodides **21** and **22** reflected the difference in configuration at the C2 and C1' atoms with the chemical shifts of the C-1' of iodide **21** (δ 40.2) exhibiting a chemical shift significantly downfield of the corresponding C-1' atom of iodide **22** (δ 35.6). The chemical shifts of the carbon atoms at 2'-Me, C-2 and C-2''' of the two iodides **21** and **22** also differed, albeit to a lesser extent. NOESY and NOE difference spectra of the two iodides were recorded in order to support this assignment however, this did not prove fruitful. Nevertheless subsequent ring expansion of the iodides **21** and **22** provided confirmation of this assignment (*vide infra*).

Individual treatment of each iodide **21**, **22** with silver carbonate in wet acetone afforded in each case a single, but different, ring expanded product (**21** → **27** 68%; **22** → **28**, 77%). The ring expanded products **27**, **28** were readily purified by column chromatography. Assignment of relative configurations of the ring expanded products **27**, **28** was made on the basis of their ^{1}H and ^{13}C nmr spectra. Thus in the ^{1}H nmr spectra the chemical shift of the 2-Me of pyran **28** (δ 1.24) was significantly downfield from that observed for 2-Me of pyran **27** (δ 1.11). The 2-H and 6-H protons of pyran **28** (δ 3.75 - 3.89 and 3.46, respectively) also possessed chemical shifts downfield of the corresponding 2-H (δ 3.35) and 6-H (δ 3.25) protons of pyran **27**. Similarly the ^{13}C spectra of pyrans **27** and **28** exhibited differences in the chemical shifts of the C-2 and C-6 carbons with those of pyran **28** (δ 74.0 and 74.8) being significantly upfield of the C-2 and C-6 carbons of pyran **27** (δ 80.8 and 82.9). NOE analysis of the pyrans **27**, **28** proved fruitful with an interaction observed between the 2-Me and 6-H of the pyran **28** confirming the relative configuration of the C-2 and C-6 atoms to be the same as that found in the terminal THF-THP rings of salinomycin and lasalocid (Figure 2).

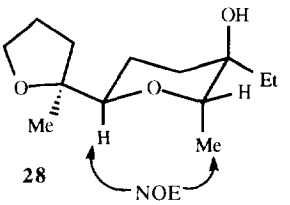
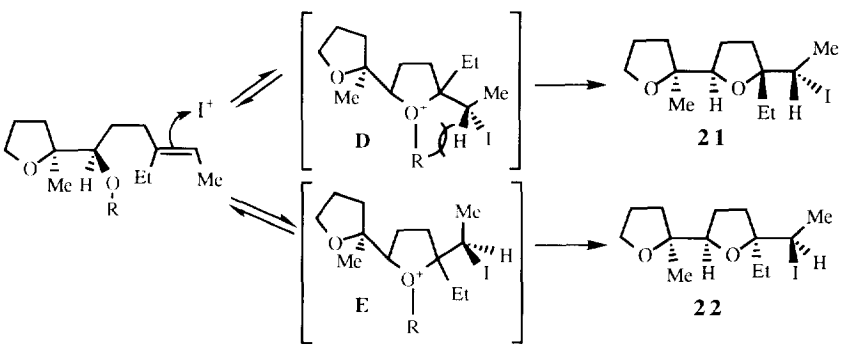


Figure 2

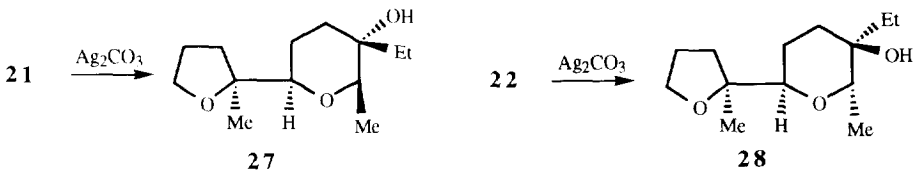
In order to improve the yield of iodoether **21**, which forms pyran **28** with the same stereochemistry as several naturally occurring polyether antibiotics upon ring expansion, an investigation into the stereocontrol involved in the iodoetherification was carried out. Upon examination of the two most stable oxonium ions D and E formed in the iodoetherification of alcohol **17**, cation D leading to **21** is more favourable than E since the 2,2-disubstituted THF ring is 1,3-*syn* to an ethyl group rather than the bulkier CHIMe group. In order to increase the amount of iodoether **22** formed a bulky ether substituent R must be introduced resulting in unfavourable steric interactions between R and the CHIMe group such that reaction takes place *via* transition state E.



Compound	R	(**21**) : (**22**)	Yield	Conditions
(**17**)	H	1.8 : 1	19%	I_2, MeCN, 60^0C, 20 min.
(**17**)	H	2 : 1	70%	I_2, Na_2CO_3, MeCN, 0^0C, 50 min.
(**17**)	H	3.2 : 1	78%	I_2, Na_2CO_3, MeCN, -43^0C, 15 min.
(**17**)	H	2.5 : 1	88%	I_2, MeCN, -32^0C, 10 min.
(**23**)	$SiMe_3$	1 : 1	75%	I_2, MeCN, -5^0C, 15 min.
(**24**)	$SiEt_3$	1 : 1	46%	I_2, MeCN, 0^0C, 15 min.
(**25**)	Si^iPr_3	1 : 1	47%	I_2, MeCN, 0^0C, 15 min.
(**26**)	Si^tBuMe_2	1 : 1	27%	I_2, MeCN, 0^0C, 15 min.

Scheme 6

Conversion of alcohol **17** to bulkier benzyl, 2,6-dichlorobenzyl, and *tert*-butyldiphenylsilyl ethers met with little success in that attempted iodoetherification of these derivatives required higher temperatures which led to decomposition. Concluding that the benzyl group was too bulky to allow iodoetherification of the trisubstituted hydroxyalkene, it was hoped that the trimethylsilyl ether **23** might allow selective formation of the *cis*-iodide **22** but not be too bulky such that cyclization would be prevented.



Scheme 7

Use of trimethylsilyl ether **23**, however, afforded a 1:1 mixture of iodethers **21** and **22** in 75% yield. The observed increase in the amount of **22** formed in this case suggests that by using a larger R group the 1,2-*syn* interactions between R and the bulkier CHIMe group in D become more significant thus reaction *via* E becomes more competitive. Increasing the size of the silyl ether to a triethylsilyl ether **24**, a triisopropylsilyl ether **25** and a *tert*-butyldimethylsilyl ether **26**, however, led to the same 1:1 ratio of the iodoethers **21**:**22** with diminished overall yield.

Thus, it appears that little improvement in the yield of the desired iodoether **22** (and hence pyran **28**) can be achieved upon conversion of alcohol **17** to an ether derivative. Pyran **28** is of particular interest to us in that it has the same stereochemistry as that present in the D and E rings of the polyether antibiotic salinomycin. It was hoped that the work described herein might have provided the framework for extension of our synthesis[16] of the central bis-spiroacetal portion of salinomycin to incorporate the E ring.

EXPERIMENTAL

General Methods

Infrared spectra were recorded on a BIO-RAD FTS ora BIO-RAD FTS-40 spectrophotometer as Nujol mulls or thin films between sodium plates. ^{1}H nmr spectra were obtained at 400 MHz using a Bruker AM400 spectrometer or at 270 MHz using a Jeol GX 270 spectrometer. ^{13}C nmr spectra were obtained at 100 MHz using a Bruker AM400 spectrometer or at 67.8 MHz using a Jeol GX270 spectrometer. Microanalyses were performed at the microanalytical laboratory, University of Otago, Dunedin. Mass spectra were recorded on a Varian VG70-250S double focusing magnetic sector mass spectrometer with an ionization potential of 70eV. Merck Kieselgel 60 (230-400 mesh) was used for flash chromatography. All solvents were purified and dried before use.

(1R, 2'S*)- and (1S*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-4-penten-1-ol (**4**) and (**6**) [erythro and threo].* To a suspension of magnesium filings (230 mg, 9.46 mmol) in freshly distilled tetrahydrofuran (3 ml) was added 4-bromo-1-butene (214 mg, 1.59 mmol) and the reaction was initiated by scratching the surface of the magnesium with a glass rod. A solution of 4-bromo-1-butene (856 mg, 6.31 mmol) in tetrahydrofuran (5 ml) was then added slowly over 20 min. The reaction was stirred for 30 min. then freshly prepared 2-methyl-2-tetrahydrofuraldehyde **2**[16] (900 mg, 7.89 mmol) was added. After stirring for a further 20 min. the reaction was quenched with saturated aqueous ammonium chloride (10 ml) and left to stir for 16 h. The reaction mixture was extracted with diethyl ether (3 × 40 ml) and the combined organic layers were dried over

magnesium sulphate. Removal of the solvent at reduced pressure and purification of the residue by flash chromatography, using hexane/ethyl acetate (4:1) as eluant, afforded the title compounds **4** and **6** as an inseparable (4:1, ^{1}H NMR) mixture of the *erythro* **4** and *threo* **6** products as a colourless oil (917 mg, 68%).

Separation of the isomers was effected by formation of the acetates **5** and **7**, which are separable by flash chromatography, followed by deprotection to afford pure samples of the *erythro* and *threo* alcohols **4** and **6** (*vide infra*).

(1R, 2'S*) and (1S*, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-pent-4-enyl acetate (5) and (7) [erythro and threo].* To a solution of (1R*, 2'S*)- and (1S*, 2'S)-1-(2-methyltetrahydrofur-2-yl)-4-penten-1-ol (4:1, **4:6**) (1.50 g, 8.81 mmol) in dry dichloromethane (110 ml) under nitrogen were added triethylamine (1.62 ml, 11.6 mmol), acetic anhydride (0.91 ml, 9.64 mmol) and a catalytic quantity of 4-dimethylaminopyridine (~5 mg). After stirring for 24 h. the solvent was removed under reduced pressure to afford a cloudy yellow residue which was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant to afford:
(1R, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-1-pent-4-enyl acetate* **5** [*erythro*] (1.29 g, 69%) (Found: (CI, NH_3) M + H, 213.1503. $C_{12}H_{21}O_3$ requires M + H, 213.1491.); υ_{max}/cm^{-1} (film) 3068 (m, =C-H), 2967, 2863 (s, C-H), 1738 (vs, C=O), 1637 (m, C=C), 1442, 1370 (s, C-H), 1235 (vs, C-O-C) and 911 (vs, $=CH_2$); δ_H (270 MHz; $CDCl_3$) 1.10 (3H, s, CH_3), 1.55-1.67 (2H, m, CH_2), 1.68-1.80 (1H, m, CH_2), 1.86-1.92 (3H, m, CH_2), 1.95-2.03 (2H, m, CH_2), 2.08 (3H, s, CH_3CO), 3.80-3.86 (2H, m, CH_2O), 4.83-4.91 (2H, m, CHOAc, 5_A-H), 4.94 (1H, d, $J_{5B,4}$ 17.2, 5_B-H) and 5.81 (1H, ddt, $J_{4,5B}$ 17.2 $J_{4,5A}$ 10.3 $J_{4,3}$ 6.6, 4-H); δ_C (67.8 MHz; $CDCl_3$) 21.1 (CH_3, CH_3CO), 22.4 (CH_3), 25.9 (CH_2), 29.0 (CH_2), 30.3 (CH_2), 34.5 (CH_2), 68.3 (CH_2O), 77.0 (CHOAc), 83.5 (quat., C-2'), 114.8 ($=CH_2$), 137.8 (=CH) and 170.7 (C=O); *m/z* 213 (M + H, 2%), 153 (M - CH_3COO, 6), 111 (2), 98 (4), 85 (C_5H_9O, 100) and 55(2).
(1S, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-1-pent-4-enyl acetate* **7** [*threo*] (319 mg, 17%) (Found: (CI, NH_3) M + H, 213.1503. $C_{12}H_{21}O_3$ requires M + H, 213.1491); υ_{max}/cm^{-1} (film) 3066 (m, =C-H), 2966, 2862 (s, C-H), 1739 (vs, C=O), 1637 (m, C=C), 1445, 1370 (s, C-H), 1237 (vs, C-O-C) and 915 (vs, $=CH_2$); δ_H (270 MHz; $CDCl_3$) 1.19 (3H, s, CH_3), 1.59-1.69 (3H, m, CH_2), 1.75-1.80 (1H, m, CH_2), 1.85-1.96 (2H, m, CH_2), 1.98-2.09 (2H, m, CH_2), 2.10 (3H, s, CH_3CO), 3.79-3.89 (2H, m, CH_2O), 4.91-4.99 (2H, m, CHOAc, 5_A-H), 5.02 (1H, d, $J_{5B,4}$ 17.2, 5_B-H) and 5.80 (1H, ddt, $J_{4,5B}$ 17.2 $J_{4,5A}$ 10.3 $J_{4,3}$ 6.6, 4-H); δ_C (67.8 MHz; $CDCl_3$) 21.1 (CH_3, Ac), 22.4 (CH_3), 26.2 (CH_2), 29.5 (CH_2), 30.4 (CH_2), 34.6 (CH_2), 67.7 (CH_2O), 77.1 (CHOAc), 83.6 (quat., C-2'), 115.0 ($=CH_2$), 137.8 (=CH) and 170.9 (C=O); *m/z* 213 (M + H, 2%), 153 (M - CH_3COO, 6), 111 (2), 98 (4), 85 (C_5H_9O, 100) and 55(2).

(1R, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-4-penten-1-ol* ***(4)*** *[erythro].* To a solution of (1R*, 2'S*)-1-(2-methyltetrahydrofur-2-yl)-1-pent-4-enyl acetate **5** (454 mg, 2.14 mmol) in 95% aqueous methanol (40 ml) was added potassium carbonate (1.18 g, 8.54 mmol). After stirring for 16 h. the reaction mixture was filtered and the solvent was removed under reduced pressure. Saturated aqueous sodium chloride solution (5 ml) was added and the mixture was extracted with dichloromethane (6 × 30 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. The residue was purified by flash chromatography, using hexane/ethyl acetate (9:1) as eluant, to afford (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol **4** as a colourless oil (291 mg, 80%); υ_{max}/cm^{-1} (film) 3451 (br, vs, OH), 3075 (m, =CH), 2973, 2869 (s, C-H), 1077 (s, C-O-C), 1044 (vs, C-O), 1000 (m, =CH) and 910 (s, $=CH_2$); δ_H (270 MHz; $CDCl_3$) 1.12 (3H, s, CH_3), 1.31-1.81 (4H, m, CH_2), 1.87-2.05 (2H, m, CH_2), 2.07-2.12 (1H, m, CH_2), 2.30-

2.44 (1H, m, CH_2), 2.73 (1H, s, OH), 3.53 (1H, dd, $J_{1,2A}$ 10.3, $J_{1,2B}$ 4.0, C<u>H</u>OH), 3.85 (2H, m, CH_2O), 4.97 (1H, d, $J_{5A,4}$ 10.1, 5_A-H), 5.05 (1H, d, $J_{5B,4}$ 17.2, 5_B-H) and 5.85 (1H, ddt, $J_{4,5B}$ 17.2 $J_{4,5A}$ 10.1 $J_{4,3}$ 6.6, 4-H); δ_C (67.8 MHz; $CDCl_3$) 22.9 (CH_3), 26.2 (CH_2), 30.7 (CH_2), 30.9 (CH_2), 34.3 (CH_2), 67.7 (CH_2O), 75.6 (CHOH), 85.6 (quat., C-2'), 114.5 (=CH_2) and 138.4 (=CH); *m/z* 171 (M + H, 4%), 153 (M - OH, 15), 111 (35), 85 (C_5H_9O, 75) and 43 (100). NMR data was in agreement with those reported in the literature.[12]

(1S, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-4-penten-1-ol (**6**) [threo].* Using a similar procedure to that described above *threo* alcohol (**6**) was prepared as a colourless oil (272 mg, 85%); υ_{max}/cm^{-1} (film) 3450 (br, vs, OH), 3074 (m, =CH), 2973, 2869 (s, C-H), 1075 (s, C-O-C), 1045 (vs, C-O), 1000 (m, =CH) and 911 (s, =CH_2); δ_H (270 MHz; $CDCl_3$) 1.14 (3H, s, CH_3), 1.39-1.52 (2H, m, CH_2), 1.57-1.79 (2H, m, CH_2), 1.87-2.05 (2H, m, CH_2), 2.07-2.15 (1H, m, CH_2), 2.32-2.41 (1H, m, CH_2), 2.73 (1H, s, OH), 3.40 (1H, dd, $J_{1,2A}$ 8.4 $J_{1,2B}$ 4.0, C<u>H</u>OH), 3.83 (2H, m, CH_2O), 4.97 (1H, d, $J_{5A,4}$ 10.1, 5_A-H), 5.05 (1H, d, $J_{5B,4}$ 17.0, 5_B-H) and 5.84 (1H, ddt, $J_{4,5B}$ 17.2, $J_{4,5A}$ 10.1, $J_{4,3}$ 6.6, 4-H); δ_C (67.8 MHz; $CDCl_3$) 19.9 (CH_3), 26.3 (CH_2), 30.7 (CH_2), 31.0 (CH_2), 34.4 (CH_2), 67.3 (CH_2O), 75.8 (CHOH), 85.2 (quat., C-2'), 114.6 (=CH_2) and 138.4 (=CH); *m/z* 171 (M + H, 4%), 153 (M - OH, 15), 111 (35), 85 (C_5H_9O, 75) and 43 (100). NMR data was in agreement with those reported in the literature.[12]

(1R, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-(trimethyl-silyloxy)-4-pentene (**12**).* To a solution of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol **4** (170 mg, 1.00 mmol) in dry dichloromethane (1 ml) was added 1-(trimethylsilyl)-imidazole (0.29 ml, 2.0 mmol). After 15 min. the reaction was quenched with water (2 drops), the solvent was removed under reduced pressure, and the residue was purified by flash chromatography, using hexane/ethyl acetate (20:1) as eluant, to afford the *title compound* **12** as a colourless oil (225 mg, 93%) (Found: (CI, NH_3) M + H, 243.1786. $C_{13}H_{27}O_2Si$ requires M + H, 243.1780.); υ_{max}/cm^{-1} (film) 3069 (m, =C-H), 2962, 2864 (vs, C-H), 1637 (m, C=C), 1447 (s, C-H), 1371 (s, C-H), 1248 (s, Si-CH_3), 1106 (vs, C-O-C), 908 (s, =CH_2) and 838 (vs, Si-CH_3); δ_H (270 MHz, $CDCl_3$) 0.01 (9H, s, CH_3Si), 0.98 (3H, s, CH_3), 1.21-1.55 (4H, m, CH_2), 1.69-1.93 (3H, m, CH_2), 2.07-2.13 (1H, m, CH_2), 3.42 (1H, dd, $J_{1,2A}$ 9.9 $J_{1,2B}$ 2.6, CHO), 3.67 (2H, t, $J_{5',4'}$ 6.6, CH_2O), 4.84 (1H, d, $J_{5A,4}$ 10.3, 5_A-H), 4.91 (1H, d, $J_{5B,4}$ 17.2, 5_B-H) and 5.71 (1H, ddt, $J_{4,5B}$ 17.2 $J_{4,5A}$ 10.3 $J_{4,3}$ 6.6, 4-H); δ_C (67.8 MHz; $CDCl_3$) 0.80 (CH_3, Si<u>Me</u>), 22.8 (CH_3), 26.2 (CH_2), 30.9 (CH_2), 32.4 (CH_2), 32.9 (CH_2), 67.5 (CH_2O), 77.5 (CHO), 85.4 (quat., C-2'), 114.4 (=CH_2) and 138.8 (=CH); *m/z* 243 (M + H, 25%), 207 (29), 171 (32), 153 (M - $OSiMe_3$, 51), 95 (26), 85 (C_5H_9O, 100), 74 (Me_3SiH, 73).

(1R, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-(tert-butyl-dimethylsilyloxy)-4-pentene (**13**).* To a stirred solution of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol **4** (170 mg, 1.00 mmol) in dry dichloromethane (1 ml) were added 2,6-lutidine (0.23 ml, 2.0 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulphonate (397 mg, 1.50 mmol). The reaction was stirred at room temperature for 2 h. after which time water (1 ml) was added. The aqueous layer was extracted with diethyl ether (3 × 5 ml) and the combined organic layers were dried over magnesium sulphate. After removal of the solvent under reduced pressure the residue was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford the *title compound* **13** as a colourless oil (191 mg, 67%) (Found: (CI, NH_3) M + H, 285.2259. $C_{16}H_{32}O_2Si$ requires M + H, 285.2250.); υ_{max}/cm^{-1} (film) 3069 (m, =C-H), 2926, 2853 (vs, C-H), 1636 (m, C=C), 1465 (s, C-H), 1102 (vs, C-O-C), 908 (vs, =CH_2) and 835 (vs, Si-CH_3); δ_H (270 MHz; $CDCl_3$) 0.05 (3H, s, SiMe), 0.06 (3H, s, SiMe), 0.88 (9H, s, ^tBu), 1.09 (3H, s, 2'-Me), 1.35-1.72 (4H, m, CH_2), 1.80-2.09

(4H, m, CH_2), 2.17-2.22 (1H, m, CH_2), 3.52 (1H, dd, $J_{1,2B}$ 8.1 $J_{1,2A}$ 3.3, C<u>H</u>OSi), 3.74-3.83 (2H, m, CH_2O), 4.93 (1H, d, $J_{5A,4}$ 10.3, 5_A-H), 5.00 (1H, dd, $J_{5B,4}$ 17.2 $J_{5B,5A}$ 1.8, 5_B-H) and 5.80 (1H, ddt, $J_{4,5B}$ 17.2 $J_{4,5A}$ 10.3 $J_{4,3}$ 6.6, 4-H); δ_C (67.8 MHz; $CDCl_3$) -4.1 (CH_3, SiMe), 18.2 (quat., ^{t}Bu), 22.3 (CH_3, 2'-Me), 26.0 (CH_3, ^{t}Bu), 26.0 (CH_2), 30.7 (CH_2), 33.1 (CH_2), 33.5 (CH_2), 67.2 (CH_2O), 77.0 (CHO), 85.5 (quat., C-2'), 114.1 (=CH_2) and 139.0 (=CH); *m/z* 285 (M + H, 100%), 269 (M - CH_3, 10), 227 (M - ^{t}Bu, 27), 153 (M - OSi^{t}BuMe$_2$, 81) and 85 (C_5H_9O).

(1R, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-(4"-bromo-benzyloxy)-4-pentene* ***(14)***. To a stirred solution of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol **4** (400 mg, 2.35 mmol) in dry tetrahydrofuran (4ml) at 0°C under nitrogen was added sodium hydride (85 mg, 80% oil dispersion, 2.83 mmol). After stirring for 10 min. 4-bromobenzyl bromide (586 mg, 2.34 mmol) and tetrabutylammonium iodide (87 mg, 0.236 mmol) were added and the reaction was stirred for 24 h. The reaction mixture was filtered and washed with dry diethyl ether (50 ml). The solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (20:1) as eluant, to afford the *title compound* **14** as a colourless oil (409 mg, 51%) (Found: M + H, 338.0867, 340.0861. $C_{17}H_{24}O_2{}^{79}Br$, $C_{17}H_{24}O_2{}^{81}Br$ require M + H, 338.0881, 340.0861.); υ_{max}/cm^{-1} (film) 3074 (m, =C-H), 2971, 2866 (s, C-H), 1485 (s, Ar), 1447 (C-H), 1113 (vs, C-O-C), 914 (s, =CH_2) and 802 (vs, Ar); δ_H (270 MHz; $CDCl_3$) 1.15 (3H, s, CH_3), 1.45-1.64 (3H, m, CH_2), 1.85-1.95 (2H, m, CH_2), 2.02-2.13 (2H, m, CH_2), 2.24-2.30 (1H, m, CH_2), 3.36 (1H, dd, $J_{1,2A}$ 9.5 $J_{1,2B}$ 2.9, CHO), 3.73-3.91 (2H, m, CH_2O), 4.55 (1H, d, $J_{HA,HB}$ 11.7, C<u>H</u>$_A$H$_B$Ar), 4.73 (1H, d, $J_{HB,HA}$ 11.7, CH$_A$<u>H</u>$_B$Ar), 4.95-5.04 (2H, m, =CH_2) 5.81 (1H, ddt, $J_{4,5B}$ 16.9 $J_{4,5A}$ 10.3 $J_{4,3}$ 6.6, 4-H), 7.21-7.24 (2H, m, Ar-H) and 7.44-7.47 (2H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 23.9 (CH_3), 26.4 (CH_2), 30.7 (CH_2), 31.1 (CH_2), 32.7 (CH_2), 67.7 (CH_2O, C-5'), 73.8 (CH_2Ar), 84.5 (CHO), 86.1 (quat., C-2'), 114.7 (=CH_2), 121.0 (quat., Ar-Br) 129.2, 131.2 (Ar-H) 138.3 (quat., Ar-CH_2) and 138.5 (=CH); *m/z* 340 (M + H, 1%), 338 (M + H, 1), 171 ($C_7H_6{}^{81}Br$, 34), 169 ($C_7H_6{}^{79}Br$, 36), 85 (C_5H_9O, 100) and 43 (69).

(1R, 2'S*)-1-(2'-Methyltetrahydrofur-2'-yl)-1-(2",6"-dichlorobenzyloxy)-4-pentene* ***(15)***. To a solution of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol **4** (270 mg, 1.59 mmol) in dry tetrahydrofuran (5 ml) at 0°C under nitrogen was added sodium hydride (58 mg, 80% oil dispersion, 1.94 mmol). After stirring for 10 min. 2,6-dichlorobenzyl bromide (400 mg, 1.67 mmol) was added and the reaction was stirred for 24 h. The reaction mixture was filtered and washed with dry diethyl ether (60 ml). The solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford the *title compound* **15** as a colourless oil (409 mg, 78%) (Found: M + H, 329.1061. $C_{17}H_{23}O_2{}^{35}Cl_2$ requires M + H, 329.1075.); υ_{max}/cm^{-1} (film) 3073 (m, =C-H), 2972, 2868 (s, C-H), 1581 (m, Ar-H), 1099 (vs, C-O-C), 993 (s, =CH), 911 (s, =CH_2), 777 and 765 (vs, Ar); δ_H (270 MHz; $CDCl_3$) 1.15 (3H, s, CH_3), 1.40-1.70 (3H, m, CH_2), 1.85-2.00 (2H, m, CH_2), 2.03-2.18 (2H, m, CH_2), 2.22-2.38 (1H, m, CH_2), 3.43 (1H, dd, $J_{1,2A}$ 9.5 $J_{1,2B}$ 2.9, CHO), 3.87 (2H, t, $J_{5',4'}$ 6.4, CH_2O), 4.85 (1H, d, $J_{HA,HB}$ 10.6, C<u>H</u>$_A$H$_B$Ar), 4.88-5.03 (2H, m, =CH_2), 5.05 (1H, d, $J_{HB,HA}$ 10.6, CH$_A$<u>H</u>$_B$Ar), 5.81 (1H, ddt, $J_{4,5B}$ 16.9 $J_{4,5A}$ 10.3 $J_{4,3}$ 6.6, 4-H), 7.13-7.19 (1H, m, Ar-H) and 7.27-7.33 (2H, m, Ar-H); δ_C (67.8 MHz; $CDCl_3$) 23.3 (CH_3), 26.2 (CH_2), 30.6 (CH_2), 31.2 (CH_2), 33.2 (CH_2), 67.4 (CH_2O), 68.8 (CH_2Ar), 84.7 (CHO), 86.0 (quat., C-2'), 114.4 (=CH_2), 128.4, 129.6 (Ar-H), 134.4, 136.8 (Ar-CH_2, Ar-Cl) and 138.9 (=CH); *m/z* 329 (M + H, 1%), 161 (20), 159 ($C_7H_5{}^{35}Cl_2$, 31), 85 (C_5H_9O, 100) and 43 (48).

(2R, 5R*, 2'S*) and (2S*, 5R*, 2'S*)-2-(Iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran* ***(8)*** *and* ***(9)*** *[trans and cis] - from alkene* ***4*** . To a solution of (1R*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol **4** (200 mg, 1.17 mmol) in dry acetonitrile (12 ml) were added sodium carbonate (1.24 g, 1.17 mmol) and iodine (1.49 g, 5.87 mmol). After 1 h. the reaction was extracted with diethyl ether (50 ml) and washed with 10% aqueous sodium sulphite (20 ml), followed by saturated aqueous sodium chloride solution (20 ml). The organic layer was dried over magnesium sulphate and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, afforded: *(2R*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran* **8** [*trans*] as a colourless oil (265 mg, 77%) (Found: M + H, 297.0356. $C_{10}H_{18}O_2I$ requires M + H, 297.0352.); υ_{max}/cm^{-1} (film) 2971, 2867 (s, C-H), 1459 (m, C-H), 1095 (s, C-O-C), 1051 (vs, C-O-C) and 491 (s, C-I); δ_H (270 MHz; $CDCl_3$) 1.15 (3H, s, CH_3), 1.56-1.80 (3H, m, CH_2), 1.86-2.08 (4H, m, CH_2), 2.18-2.28 (1H, m, CH_2), 3.15 (1H, dd, $J_{HA,HB}$ 9.7 $J_{HA,2}$ 8.0, $C\underline{H}_AH_BI$), 3.31 (1H, dd, $J_{HB,HA}$ 9.7 $J_{HB,2}$ 4.4, $CH_A\underline{H}_BI$), 3.85 (2H, t, $J_{5',4'}$ 6.4, CH_2O), 4.07 (1H, dd, $J_{5,4A}$ 8.6 $J_{5,4B}$ 6.4, 5-H) and 4.05-4.16 (1H, m, 2-H); δ_C (67.8 MHz; $CDCl_3$) 10.7 (CH_2I), 22.7 (CH_3), 26.1 (CH_2), 28.0 (CH_2), 32.9 (CH_2), 33.4 (CH_2), 68.1 (CH_2O), 79.1 (CHO, C-2), 84.3 (quat., C-2') and 85.4 (CHO, C-5); *m/z* 297 (M + H, 5%), 279 (M - OH, 2), 211 (5), 111 (2), 85 (C_5H_9O, 100), 55 (13) and 43 (54). *(2S*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran* **9** [*cis*] as a colourless oil (54 mg, 16%) (Found: M + H, 297.0344. $C_{10}H_{18}O_2I$ requires M + H 297.0352.); υ_{max}/cm^{-1} (film) 2963, 2863 (s, C-H), 1455 (m, C-H), 1092 (s, C-O-C), 1057 (vs, C-O-C) and 504 (s, C-I); δ_H (270 MHz; $CDCl_3$) 1.17 (3H, s, CH_3), 1.57-1.78 (3H, m, CH_2), 1.84-2.07 (5H, m, CH_2), 3.24-3.28 (2H, m, CH_2I), 3.86 (2H, t, $J_{5',4'}$ 6.6, CH_2O), 3.93 (1H, dd, $J_{5,4A}$ 8.4 $J_{5,4B}$ 6.6, 5-H) and 3.89-3.99 (1H, m, 2-H); δ_C (67.8 MHz; $CDCl_3$) 10.7 (CH_2I), 23.3 (CH_3), 26.3 (CH_2), 27.0 (CH_2), 31.4 (CH_2), 33.2 (CH_2), 68.2 (CH_2O), 78.2 (CHO, C-2), 83.9 (quat., C-2') and 85.9 (CHO, C-5); *m/z* 297 (M + H, 1%), 211 (2), 85 (C_5H_9O, 100), 55 (12) and 43 (64).

(2R, 5R*, 2'S*) and (2S*, 5R*, 2'S*)-2-(Iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran* ***(8)*** *and* ***(9)*** *[trans and cis] - from ethers* ***12-15*** . To a solution of each of the protected hydroxyalkenes **12-15** (1.0 mmol) in dry acetonitrile (9 ml) at 0°C was added iodine (5.0 mmol). After 10 min. the reaction was extracted with diethyl ether (20 ml) and washed with 10% aqueous sodium sulphite (20 ml). The aqueous layer was extracted with diethyl ether (4 × 25 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, afforded (2R*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran **8** [*trans*] and (2S*, 5R*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetra-hydrofur-2'-yl)tetrahydrofuran **9** [*cis*] with the yield and product ratios as depicted in Table 1.

(2S, 5S*, 2'S*) and (2R*, 5S*, 2'S*)-2-(Iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran* ***(10)*** *and* ***(11)*** *[trans and cis].* To a solution of (1S*, 2'S*)-1-(2'-methyltetrahydrofur-2'-yl)-4-penten-1-ol **6** (100 mg, 0.58 mmol) in dry acetonitrile (6 ml) were added sodium carbonate (0.63 g, 0.59 mmol) and iodine (0.75 g, 2.96 mmol). After 1 h. the reaction was extracted with diethyl ether (30 ml) and washed with 10% aqueous sodium sulphite (10 ml), followed by saturated aqueous sodium chloride solution (10 ml). The organic layer was dried over magnesium sulphate and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, afforded an inseparable 5:1 mixture of *(2S*, 5S*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran* **10** [*trans*] and

(2R*, 5S*, 2'S*)-2-(iodomethyl)-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran **11** [*cis*] as a colourless oil (148 mg, 85%) (Found: M + H, 297.0341. $C_{10}H_{18}O_2I$ requires M + H, 297.0352.); υ_{max}/cm^{-1} (film) 2970, 2869 (s, C-H), 1459 (m, C-H), 1095 (s, C-O-C), 1051 (vs, C-O-C) and 491 (s, C-I); δ_H (270 MHz; $CDCl_3$) [*trans* **10**] 1.12 (3H, s, CH_3), 1.57-1.67 (2H, m, CH_2), 1.84-2.04 (5H, m, CH_2), 2.17-2.28 (1H, m, CH_2), 3.18 (1H, dd, $J_{HA,HB}$ 9.9 $J_{HA,2}$ 7.3, $C\underline{H}_AH_BI$), 3.28 (1H, dd, $J_{HB,HA}$ 9.9 $J_{HB,2}$ 4.8, $CH_A\underline{H}_BI$), 3.77-3.91 (2H, m, CH_2O) and 4.00-4.10 (2H, m, 5-H, 2-H) ; δ_C (67.8 MHz; $CDCl_3$) [*trans* **10**] 10.7 (CH_2I), 22.9 (CH_3), 26.3 (CH_2), 27.4 (CH_2), 33.0 (CH_2), 34.6 (CH_2), 68.4 (CH_2O), 79.0 (CHO, C-2), 84.1 (quat., C-2') and 85.6 (CHO, C-5); *m/z* 297 (M + H, 1%), 211 (3), 111 (1), 85 (C_5H_9O, 100), 55 (9) and 43 (39); δ_H (270 MHz; $CDCl_3$) [*cis* **11**] 1.15 (3H, s, CH_3), 1.61-2.06 (8H, m, CH_2), 3.18 (1H, dd, $J_{HA,HB}$ 9.9 $J_{HA,2}$ 5.1, $C\underline{H}_AH_BI$), 3.25 (1H, dd, $J_{HB,HA}$ 9.9 $J_{HB,2}$ 7.7, $CH_A\underline{H}_BI$), 3.83-3.92 (3H, m, CH_2O, 5-H) and 4.02-4.13 (1H, m, 2-H); δ_C (67.8 MHz; $CDCl_3$) [*cis* **11**] 10.2 (CH_2I), 23.2 (CH_3), 26.2 (CH_2), 26.3 (CH_2), 31.4 (CH_2), 34.8 (CH_2), 68.6 (CH_2O), 79.0 (CHO, C-2), 83.1 (quat., C-2') and 86.2 (CHO, C-5); *m/z* 297 (M + H, 1%), 211 (3), 85 (C_5H_9O, 100), 55 (15) and 43 (68).

(5R, 2'S*)-5-(2'-Methyltetrahydrofur-2'-yl)-5-hydroxy-pentan-2-one (**16**).* To a solution of (2R*, 5R*, 2'S*)-2-iodomethyl-5-(2'-methyltetrahydrofur-2'-yl)tetrahydrofuran **8** (118 mg, 0.398 mmol) in acetone (2 ml) and distilled water (2 drops) was added silver carbonate (110 mg, 0.399 mmol). The reaction was heated under reflux for 8 h., during which time additional amounts of silver carbonate (2 × 50 mg) were added. The reaction mixture was filtered, washed with ethyl acetate (10 ml), and dried over magnesium sulphate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (1:1) as eluant, to afford the *title compound* **16** as a colourless oil (18 mg, 24%) (Found: (acetate derivative) M + H 229.1431. $C_{12}H_{21}O_4$ requires M + H, 229.1440.); υ_{max}/cm^{-1} (film) 3402 (br, s, OH), 2971, 2872 (s, C-H), 1713 (s, C=O), 1453 (m, C-H) and 1044 (C-O); δ_H (270 MHz; $CDCl_3$) 1.14 (3H, s, 2'-Me), 1.48-2.04 (6H, m, CH_2), 2.17 (3H, s, CH_3CO), 2.52-2.82 (2H, m, CH_2CO), 2.66 (1H, s, OH), 3.48 (1H, dd, $J_{5,4A}$ 11.0 $J_{5,4B}$ 2.0, $C\underline{H}OH$) and 3.78-3.97 (2H, m, CH_2O); δ_C (67.8 MHz; $CDCl_3$) 22.9 (CH_3, 2'-Me), 25.5 (CH_2), 26.2 (CH_2), 30.1 (CH_3, C-1), 30.7 (CH_2), 40.9 ($\underline{C}H_2C=O$), 67.9 (CH_2O), 75.9 (CHOH), 85.3 (quat., C-2') and 209.4 (C=O); *m/z* 187 (M + H, 3%), 169 (M - OH, 100), 136 (11), 111 (32) and 85 (C_5H_9O) and recovered iodide **8** (42 mg, 36%).

(4E, 1R, 2'S*)- and (4E, 1S*, 2'S*)-4-Ethyl-1-(2'-methyl-tetrahydrofur-2'-yl)-4-hexen-1-ol (**17**) and (**18**) [erythro and threo].* To dry tetrahydrofuran (7 ml) at -90°C under argon was added *tert*-butyllithium (2.10 ml of a 1.7 M solution in pentane, 3.57 mmol). After stirring for 2 min. a solution of (E)-1-bromo-3-ethyl-3-pentene (296 mg, 1.68 mmol) in dry tetrahydrofuran (0.2 ml) was added and the reaction mixture was stirred at -80°C for 10 min. Freshly prepared 2-methyl-2-tetrahydrofuraldehyde **2**[12] (300mg, 2.63 mmol) was then added and the reaction mixture was stirred for 2 h., allowing it to warm to -30°C. The reaction was quenched with saturated ammonium chloride (10 ml) and stirred for 16 h. Water (1 ml) was added and the reaction mixture was extracted with diethyl ether (3 × 20 ml) and dichloromethane (2 × 20 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to give a pale yellow residue which was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford an inseparable (3:1, ^1H NMR) mixture of the *erythro* and *threo* products as a colourless oil (189 mg, 53%).

Separation of the isomers was effected by formation of the acetates, which are separable by flash chromatography, followed by deprotection to afford pure erythro and threo products (*vide infra*).

(4E, 1R, 2'S*)- and (4E, 1S*, 2'S*)-4-Ethyl-1-(2'-methyl-tetrahydrofur-2'-yl)-4-hexen-1-yl acetate (**19**) and (**20**) [erythro and threo].* To a solution of the above 3:1 mixture of alcohols **17** and **18** (117 mg, 0.551 mmol) in dry dichloromethane were added triethylamine (92 μl, 0.66 mmol), acetic anhydride (52 μl, 0.55 mmol) and a catalytic quantity of 4-dimethylaminopyridine (~5 mg). After 3 h. the solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford: *(4E, 1R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-yl acetate* **19** [*erythro*] as a colourless oil (101 mg, 72%) (Found: C, 70.54; H, 10.02. $C_{15}H_{26}O_3$ requires C, 70.83; H, 10.30%); υ_{max}/cm^{-1} (film) 2961, 2865 (vs, C-H), 1739 (vs, C=O), 1452 (m, C-H), 1370 (s, C-H) and 1237 (vs, C-O-C); δ_H (270MHz; $CDCl_3$) 0.94 (3H, t, $J_{2'',1''}$ 7.7, $CH_2\underline{CH_3}$), 1.17 (3H, s, 2'-Me), 1.57 (3H, d, $J_{6,5}$ 7.0, CH_3-C=), 1.53-1.62 (2H, m, CH_2), 1.69-1.75 (1H, m, CH_2), 1.85-2.10 (7H, m, CH_2), 2.07 (3H, s, CH_3CO), 3.74-3.88 (2H, m, CH_2O), 4.90 (1H, dd, $J_{1,2A}$ 10.4 $J_{1,2B}$ 2.4, CHOAc) and 5.18 (1H, q, $J_{5,6}$ 7.0, =CH); δ_C (67.8 MHz; $CDCl_3$) 12.7 (CH_3, C-2''), 12.9 (CH_3, C-6), 21.1 (CH_3, Ac), 22.5 (CH_3, 2'-Me), 25.9 (CH_2), 28.3 (CH_2), 29.4 (CH_2), 33.0 (CH_2), 34.4 (CH_2), 68.3 (CH_2O), 77.8 (CHOAc), 83.6 (quat., C-2'), 118.1 (=CH), 140.9 (quat., C-4) and 170.8 (C=O) and *(4E, 1S*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-yl acetate* **20** [*threo*] as a colourless oil (35.9 mg, 26%) (Found: C, 70.41; H, 9.95. $C_{15}H_{26}O_3$ requires C, 70.83; H, 10.30%); υ_{max}/cm^{-1} (film) 2961, 2865 (vs, C-H), 1739 (vs, C=O), 1451 (m, C-H), 1369 (s, C-H) and 1236 (vs, C-O-C); δ_H (270 MHz; $CDCl_3$) 0.94 (3H, t, $J_{2'',1''}$ 7.7, $CH_2\underline{CH_3}$), 1.19 (3H, s, 2'-Me), 1.57 (3H, d, $J_{6,5}$ 7.0, CH_3-C=), 1.53-1.66 (2H, m, CH_2), 1.71-2.21 (8H, m, CH_2), 2.09 (3H, s, CH_3CO), 3.75-3.90 (2H, m, CH_2O), 4.88-4.93 (1H, m, CHOAc) and 5.19 (1H, q, $J_{5,6}$ 7.0, =CH); δ_C (67.8 MHz; $CDCl_3$) 12.8 (CH_3, C-2''), 13.0 (CH_3, C-6), 21.2 (CH_3, Ac), 22.3 (CH_3, 2'-Me), 26.3 (CH_2), 28.5 (CH_2), 28.8 (CH_2), 33.1 (CH_2), 34.7 (CH_2), 67.8 (CH_2O), 77.6 (CHOAc), 83.7 (quat., C-2'), 118.3 (=CH), 140.9 (quat., C-4) and 170.9 (C=O).

(4E, 1R, 2'S*)-4-Ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol (**17**) [erythro].* To a solution of (4E, 1R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-yl acetate **19** (79.4 mg, 0.312 mmol) in 95% methanol (5 ml) was added potassium carbonate (173 mg, 1.25 mmol). After stirring for 16 h. a saturated solution of sodium chloride (5 ml) was added and extracted with dichloromethane (4 × 10 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to give a residue which was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford the *title compound* **17** as a pale yellow oil (55.2 mg, 83%) (Found: M^+, 212.1776. $C_{13}H_{24}O_2$ requires M, 212.1776.); υ_{max}/cm^{-1} (film) 3451 (vs, OH), 2961, 2865 (vs, C-H), 1454 (s, C-H), 1372 (m, CH_3), 1079 (s, C-O-C) and 459 (vs, C-O-C); δ_H (270 MHz; $CDCl_3$) 0.97 (3H, t, $J_{2'',1''}$ 7.5, $CH_2C\underline{H_3}$), 1.12 (3H, s, 2'-Me), 1.28-1.43 (1H, m, CH_2), 1.59 (3H, d, $J_{6,5}$ 6.6, CH_3-C=), 1.44-1.68 (3H, m, CH_2), 1.87-2.12 (5H, m, CH_2), 2.27-2.36 (1H, m, CH_2), 2.38 (1H, s, OH), 3.52 (1H, dd, $J_{1,2A}$ 10.4 $J_{1,2B}$ 2.0, C<u>H</u>OH), 3.79-3.93 (2H, m, CH_2O) and 5.22 (1H, q, $J_{5,6}$ 6.6, =CH); δ_C (67.8 MHz; $CDCl_3$) 12.8 (CH_3, C-2''), 13.0 (CH_3, C-6), 22.8 (CH_2), 23.0 (CH_3, 2'-Me), 26.3 (CH_2), 30.3 (CH_2), 30.7 (CH_2), 33.6 (CH_2), 67.9 (CH_2O, C-5'), 76.2 (CHO, C-1), 85.8 (quat., C-2'), 118.1 (CH, C-5) and 141.7 (quat., C-4); *m/z* 212 (M^+, 4%), 85 (C_5H_9O, 100), 55 (9) and 43 (26).

(4E, 1R, 2'S*)-4-Ethyl-1-(trimethylsilyloxy)-1-(2'-methyl-tetrahydrofur-2'-yl)-4-hexene* ***(23)***. To a stirred solution of (4E, 1R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol **17** (45 mg, 0.21 mmol) in dry dichloromethane (0.2 ml) was added 1-(trimethylsilyl)imidazole (63 µl, 0.43 mmol). After 15 min. distilled water (1 drop) was added and the solvent was removed under reduced pressure. The residue was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford the *title compound* **23** as a colourless oil (58.4 mg, 98%) (Found: M^+, 284.2184. $C_{16}H_{32}O_2Si$ requires M, 284.2172.); υ_{max}/cm^{-1} (film) 2957, 2864 (s, C-H), 1451 (m, C-H), 1369 (m, C-H), 1247 (s, Si-CH_3), 1107 (vs, C-O-C), 863 (s, Si-C) and 838 (vs, Si-CH_3); δ_H (270 MHz; $CDCl_3$) 0.12 (9H, s, $SiMe_3$), 0.96 (3H, t, $J_{2'',1''}$ 7.5, CH_3), 1.10 (3H, s, 2'-Me), 1.26-1.62 (3H, m, CH_2), 1.58 (3H, d, $J_{6,5}$ 6.6, CH_3-=), 1.82-2.08 (6H, m, CH_2), 2.17-2.25 (1H, m, CH_2), 3.51 (1H, dd, $J_{1,2A}$ 5.9 $J_{1,2B}$ 3.7, CHOSi), 3.78 (2H, t, $J_{5',4'}$ 6.4, CH_2O) and 5.21 (1H, q, $J_{5,6}$ 6.6, =CH); δ_C (67.8 MHz; $CDCl_3$) 0.80 (CH_3Si), 12.8 (CH_3, C-2''), 13.0 (CH_3, C-6), 22.9 (CH_3, 2'-Me), 26.3 (CH_2), 27.6 (CH_2), 32.0 (CH_2), 33.0 (CH_2), 33.9 (CH_2), 67.5 (CH_2O, C-5'), 78.2 (CHO, C-1), 85.5 (quat., C-2'), 117.0 (CH, C-5) and 141.9 (quat., C-4); *m/z* 284 (M^+, 0.5%), 199 (M - C_5H_9O, 9), 109 (17), 101 (4), 85 (C_5H_9O, 100), 73 ($SiMe_3$, 18), 55 (11) and 43 (19).

(4E, 1R, 2'S*)-4-Ethyl-1-(triethylsilyloxy)-1-(2'-methyltetrahydrofur-2'-yl)-4-hexene* ***(24)***. The title compound was prepared in 94% yield by reaction of alcohol **17** (79 µmol) with triethylsilyl trifluoromethanesulphonate (119 µmol) and 2,6-lutidine (163 µmol) in dichloromethane (0.5 ml) as a colourless oil; δ_H (270 MHz, $CDCl_3$) 0.53 (6H, q, *J* 7.9, $SiCH_2$), 0.93 (9H, t, *J* 7.9, $SiCH_2C\underline{H}_3$), 0.97 (3H, t, $J_{2'',1''}$ 7.5, CH_3), 1.10 (3H, s, CH_3), 1.20-1.64 (3H, m, CH_2), 1.58 (3H, d, $J_{6,5}$ 6.6, CH_3-=), 1.86-2.06 (6H, m, CH_2), 2.16-2.28 (1H, m, CH_2), 3.53 (1H, m, CHOSi), 3.79-3.84 (2H, m, CH_2O) and 5.18 (1H, q, $J_{5,6}$ 6.6, =CH); δ_C (67.8 MHz; $CDCl_3$) 6.8 ($SiCH_2$), 7.1 ($SiCH_2C\underline{H}_3$), 12.9 (CH_3, C-2''), 13.0 (CH_3, C-6), 22.9 (CH_3, 2'-Me), 26.0 (CH_2), 27.5 (CH_2), 29.7 (CH_2), 32.5 (CH_2), 33.4 (CH_2), 67.4 (CH_2O, C-5'), 78.2 (CHO, C-1), 85.6 (quat., C-2'), 117.5 (CH, C-5) and 142.2 (quat., C-4).

(4E, 1R, 2'S*)-4-Ethyl-1-(triisopropylsilyloxy)-1-(2'-methyltetrahydrofur-2'-yl)-4-hexene* ***(25)***. The title compound was prepared in 93% yield by the reaction of alcohol **17** (68 µmol) with triisopropyl trifluoromethanesulphonate (100 µmol) and 2,6-lutidine (138 µmol) in dichloromethane (0.5 ml); δ_H 0.97 (3H, t, $J_{2'',1''}$ 7.3, CH_3), 1.09 (21H, m, $SiC(CH_3)$, SiCH) 1.20-2.09 (9H, m, CH_2), 1.58 (3H, d, $J_{6,5}$ 6.6, CH_3-=), 1.20-2.09 (9H, m, CH_2), 2.15-2.30 (1H, m, CH_2), 3.70-3.83 (3H, m, CHOSi, CH_2O) and 5.17 (1H, q, $J_{5,6}$ 6.6, =CH); δ_C (67.8 MHz; $CDCl_3$) 12.9 (CH_3, C-2''), 13.0 (CH_3, C-6), 18.1 (quat., ^tBu), 18.2 (CH_3, ^tBu), 22.8 (CH_3, 2'-Me), 25.9 (CH_2), 27.2 (CH_2), 29.6 (CH_2), 33.3 (CH_2), 34.3 (CH_2), 67.2 (CH_2O, C-5'), 78.0 (CHO, C-1), 86.0 (quat., C-2'), 117.5 (CH, C-5) and 142.3 (quat., C-4).

(4E, 1R, 2'S*)-4-Ethyl-1-(tert-butyldimethylsilyloxy)-1-(2'-methyltetrahydrofur-2'-yl)-4-hexene* ***(26)***. The title compound was prepared in 90% yield by the reaction of alcohol **17** (51 µmol) with *tert*-butyldimethylsilyl trifluoromethanesulphonate (91 µmol) and 2,6-lutidine (103 µmol) in dichloromethane (0.3 ml); δ_H (270 MHz, $CDCl_3$) 0.08 (3H, s, $SiCH_3$), 0.09 (3H, $SiMe_3$), 0.87 (9H, s, ^tBu), 0.96 (3H, t, $J_{2'',1''}$ 7.3, CH_3), 1.11 (3H, s, CH_3), 1.20-2.30 (10H, m, CH_2), 1.58 (3H, d, $J_{6,5}$ 7.0, CH_3-=), 3.51 (1H, dd, $J_{1,2A}$ 5.5 $J_{1,2B}$ 3.3, CHOSi), 3.75-3.82 (2H, m, CH_2O) and 5.18 (1H, q, $J_{5,6}$ 7.0, =CH); δ_C (67.8 MHz; $CDCl_3$) -3.0 ($SiMe_3$), -4.1 ($SiMe_3$), 12.8 (CH_3, C-2''), 13.0 (CH_3, C-6), 18.0 (quat., Si^tBu) 22.7 (CH_3, 2'-Me), 25.7 (CH_2), 26.0 (CH_3, ^tBu), 27.3 (CH_2),

29.7 (CH_2), 32.6 (CH_2), 33.6 (CH_2), 67.3 (CH_2O, C-5'), 77.6 (CHO, C-1), 85.6 (quat., C-2'), 117.4 (CH, C-5) and 142.2 (quat., C-4).

(2R, 5R*, 1'S*, 2"S*)- and (2S*, 5R*, 1'R*, 2"S*)-2-Ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydro-furan (**21**) and (**22**) [trans and cis] - from alkene **17**.* To a solution of (4E, 1R*, 2'S*)-4-ethyl-1-(2'-methyltetrahydrofur-2'-yl)-4-hexen-1-ol **17** (17.5 mg, 82.4 μmol) in dry acetonitrile (1 ml) at -43°C under nitrogen was added sodium carbonate (88 mg, 0.830 mmol), followed by iodine (105 mg, 0.414 mmol). After stirring for 15 min. diethyl ether (5 ml) was added and the resulting solution was washed with 10% aqueous sodium sulphite solution (5 ml). The aqueous layer was extracted with diethyl ether (3 × 10 ml) and the combined organic layers were then dried over magnesium sulphate. The solvent was evaporated at reduced pressure to afford a yellow oil which was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford: *(2R*, 5R*, 1'S*, 2"S*)-2-ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)-tetrahydrofuran* **21** [*trans*] (16.6 mg, 60%) as a colourless oil (Found: M^+, 338.0743. $C_{13}H_{23}O_2I$ requires M, 338.0743.); υ_{max}/cm^{-1} (film) 2966, 2933, 2866 (s, C-H), 1050 (s, C-O), 1458 (m, C-H) and 1370 (m, CH_3); δ_H (270 MHz: $CDCl_3$) 0.92 (3H, t, *J* 7.3, $CH_2C\underline{H}_3$), 1.16 (3H, s, 2"-Me), 1.84 (3H, d, $J_{2',1'}$ 7.3, $C\underline{H}_3CHI$), 1.59-2.07 (10H, m, CH_2), 3.84 (2H, t, $J_{5",4"}$ 6.4, CH_2O), 4.02 (1H, dd, $J_{5,4A}$ 10.6, $J_{5,4B}$ 5.1, CHO) and 4.52 (1H, q, $J_{1',2'}$ 7.3, CHI); δ_C (67.8 MHz; $CDCl_3$) 7.8 (CH_3, C-2"'), 22.5, (CH_3, 2'-Me), 23.9 (CH_3, C-2'), 26.2 (CH_2), 27.9 (CH_2), 28.2 (CH_2), 34.4 (CH_2), 35.2 (CH_2), 40.2 (CH, C-1"), 68.2 (CH_2O), 83.5, 86.6 (quat., C-2, C-2') and 85.0 (CHO); *m/z* 339 (M + H, 10%), 338 (M^+, 1), 111 (9), 85 (C_5H_9O, 100) and 43 (28) and *2S*, 5R*, 1'R*, 2"S*)-2-ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)-tetrahydrofuran* **22** [*cis*] (5.2 mg, 19%) as a colourless oil (Found: (FAB) M + H, 339.0821. $C_{13}H_{24}O_2I$ requires M + H, 339.0821.); υ_{max}/cm^{-1} (film) 2966, 2933, 2866 (s, C-H), 1050 (s, C-O), 1458 (m, C-H) and 1370 (m, CH_3); δ_H (270 MHz; $CDCl_3$) 0.90 (3H, t, *J* 7.4, $CH_2C\underline{H}_3$), 1.14 (3H, s, 2"-Me), 1.89 (3H, d, $J_{2',1'}$ 6.9, $C\underline{H}_3CHI$), 1.59-2.10 (10H, m, CH_2), 3.84 (2H, t, $J_{5",4"}$ 6.5, CH_2O), 3.94 (1H, dd, $J_{5,4A}$ 10.3, $J_{5,4B}$ 5.3, CHO) and 4.41 (1H, q, $J_{1',2'}$ 6.9, CHI); δ_C (67.8 MHz; $CDCl_3$) 7.5 (CH_3, C-2"'), 22.6 (CH_3, 2"-Me), 22.9 (CH_3, C-2'), 26.3 (CH_2), 28.5 (CH_2), 31.7 (CH_2), 32.9 (CH_2), 33.8 (CH_2), 35.6 (CH, C-1'), 68.1 (CH_2O), 83.9, 85.6 (quat., C-2, C-2') and 86.6 (CHO); *m/z* (FAB) 339 (M + H, 31%), 338 (M^+, 7), 213 (25), 211 (17), 139 (22), 111 (18), 85 (C_5H_9O, 100) and 43 (28).

(2R, 5R*, 1'S*, 2"S*)- and (2S*, 5R*, 1'R*, 2"S*)-2-Ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydro-furan (**21**) and (**22**) [trans and cis] - from ethers **23-26*** To a solution of each of the silyl protected hydroxyalkenes **23** - **26** (50 μmol) in dry acetonitrile (0.5 ml) at 0°C under nitrogen was added iodine (250 μmol). After stirring for 15 min. diethyl ether (1 ml) was added and the resulting solution was washed with a 10% aqueous sodium sulphite solution (1 ml). The aqueous layer was extracted with diethyl ether (4 × 1 ml) and the combined organic layers were dried over magnesium sulphate. The solvent was evaporated at reduced pressure to afford a yellow oil which was purified by flash chromatography, using hexane/ethyl acetate (30:1) as eluant, to afford *(2R*, 5R*, 1'S*, 2"S*)-2-ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofuran* **21** and *(2S*, 5R*, 1'R*, 2"S*)-2-ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofuran* **22** with the yield and product ratios depicted in Table 2.

(2R, 3S*, 6R*, 2'S*)-3-Ethyl-3-hydroxy-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran (**27**).* To a solution of (2R*, 5R*, 1'S*, 2"S*)-2-ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofuran **21** (6.0 mg, 18 μmol) in acetone (0.3 ml) were added silver carbonate (5.0 mg, 18 μmol) and distilled water (4

drops). After stirring for 2 h. the reaction mixture was filtered through glass wool, washing with ethyl acetate (30 ml). After drying over magnesium sulphate the solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (1:1) as eluant, to afford the *title compound* **27** (2.8 mg, 68%) as a colourless oil (Found: M^+, 228.1698. $C_{13}H_{24}O_3$ requires M, 228.1725.); υ_{max}/cm^{-1} (film) 3438 (s, OH), 2962, 2863 (s, CH_3), 1100 (s, C-O) and 1452 (s, CH_3); δ_H (270 MHz; $CDCl_3$) 0.90 (3H, t, $J_{2'',1''}$ 7.5, $CH_2C\underline{H}_3$), 1.11 (3H, d, $J_{2\text{-Me},2}$ 6.6, 2-Me), 1.14 (3H, s, 2'-Me), 1.16-2.10 (10H, m, CH_2), 3.25 (1H, dd, $J_{6,5A}$ 5.3, $J_{6,5B}$ 11.0, CHO), 3.35 (1H, q, $J_{2,2\text{-Me}}$ 6.6, CHO) and 3.75-3.88 (2H, m, CH_2O); δ_C (67.8 MHz; $CDCl_3$) 6.65 (CH_3, C-2"), 14.0 (CH_3, 2-Me), 22.3 (CH_3, 2'-Me), 22.5 (CH_2), 24.6 (CH_2), 26.2 (CH_2), 33.9 (CH_2), 34.6 (CH_2), 68.3 (CH_2O), 71.3 (quat., C-3), 80.9, 82.9 (C-2, C-6), 83.7 (quat., C-2'); *m/z* 228 (M^+, 0.1%), 199 (1), 143 (6), 125 (5), 111 (4), 95 (6), 85 (C_5H_9O, 100) and 43 (16).

(2S, 3R*, 6R*, 2'S*)-3-Ethyl-3-hydroxy-2-methyl-6-(2'-methyltetrahydrofur-2'-yl)tetrahydropyran* ***(28)***. To a solution of (2S*, 5R*, 1'R*, 2"S*)-2-ethyl-2-(1'-iodoethyl)-5-(2"-methyltetrahydrofur-2"-yl)tetrahydrofuran **22** (12.9 mg, 38 μmol) in acetone (0.3 ml) were added silver carbonate (12.7 mg, 46 μmol) and distilled water (5 drops). After stirring for 3 h. the reaction mixture was filtered through glass wool, washing with ethyl acetate (25 ml). After drying over magnesium sulphate the solvent was removed under reduced pressure and the residue was purified by flash chromatography, using hexane/ethyl acetate (4:1) as eluant, to afford the *title compound* **28** (6.7 mg, 77%) as a colourless oil (Found: (FAB) M + H, 229.1796. $C_{13}H_{25}O_3$ requires M + H, 229.1804.); υ_{max}/cm^{-1} (film) 3432 (s, OH), 2966, 2867 (s, CH_3), 1457 (m, C-H), 1371 (m, C-H), 1102 (s, C-O) and 1046 (s, C-OH); δ_H (270 MHz; $CDCl_3$) 0.92 (3H, t, $J_{2'',1''}$ 7.5, $CH_2C\underline{H}_3$), 1.24 (3H, d, $J_{2\text{-Me},2}$ 6.7, 2-Me), 1.16 (3H, s, 2'-Me), 1.42-1.95 (10H, m, CH_2), 3.46 (1H, dd, $J_{6,5A}$ 3.5, $J_{6,5B}$ 9.2, CHO) and 3.75-3.89 (3H, m, CH_2O, 2-CHO); δ_C (67.8 MHz; $CDCl_3$) 7.0 (CH_3, C-2"), 13.0 (CH_3, 2-Me), 21.0 (CH_3, 2'-Me), 22.1 (CH_2), 22.8 (CH_2), 25.8 (CH_2), 29.1 (CH_2), 35.5 (CH_2), 68.2 (CH_2O), 71.1 (quat., C-3), 74.0, 74.8 (CH, C-2, C-6); *m/z* 229 (M + H, 63%), 211 (M - OH, 95), 183 (49), 111 (61), 85 (100) and 43 (47).

REFERENCES

1. Westley, J. W. *Polyether Antibiotics: Naturally Occurring Acid Ionophores,*; vol. I,II; Marcel Dekker: New York, 1982.
2. Tang, S.; Still, W. C. *Tetrahedron Lett.*, **1993**, *34*, 6701.
3. Koert, U.; Stein, M.; Harms, K. *Tetrahedron Lett.*, **1993**, *34*, 2299.
4. Rupprecht; J. K.; Hui, Y. H.; McLaughlin, J. L. *J. Nat. Prod.*, **1990**, *53*, 237.
5. Harmange, J.-C.; Figadere, B. *Tetrahedron: Asymmetry*, **1993**, *4*, 1711.
6. Boivin, T. L. B. *Tetrahedron*, **1987**, *43*, 3309.
7. Cardillo, G.; Orena, M. *Tetrahedron*, **1990**, *46*, 3321.
8. Harding, K. E.; Tiner, T. H.*Comprehensive Organic Synthesis* , **1991**, *4*, 363.
9. Rychnovsky, S. D.; Bartlett, P. A. *J. Amer. Chem. Soc.*, **1981**, *103*, 3963.
10. Kinashi, H.; Otake, N.; Yonehara, H.; Sato, S.; Saito, Y. *Tetrahedron Lett.*, **1973**, 4955.
11. Westley, J. W.; Evans, R. H.; Pruess, D. L.; Stempel, A. *Chem. Commun.*, **1970**, *92*, 4428.
12. Amouroux, R.; Amouroux, F.; Chastrette, M.; *Bull. Soc. Chim. Fr.*, **1981**, *18*, 293.
13. Gale, J.B.; Yu, J.g.; Khare, A.; Hu, X.E.; Ho, D.K.; Cassady, J.M. *Tetrahedron Lett.*, **1993**, 5851.
14. Nakata, T.; Schmid, G.; Vranesic, B; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. J. *Amer. Chem. Soc.*, **1978**, *100*, 2933.
15. Michael, J. P.; Ting, P. C.; Bartlett, P. A. *J. Org. Chem.*, **1985**, *50*, 2416.
16. Brimble, M. A.; Williams, G. M. *J. Org. Chem.*, **1992**, *57*, 5818.

(*Received in UK* 15 *May* 1995; *revised* 12 *July* 1995; *accepted* 14 *July* 1995)