Stereoselective Thermal Reactions between (*E*)-1-Alkoxymethoxybut-2-enyl-(tributyl)stannanes and Aldehydes

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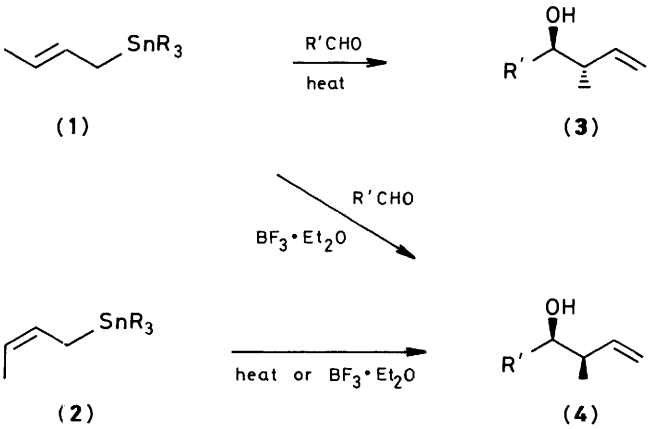
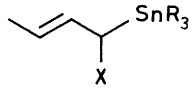
(*E*)-1-Methoxymethoxybut-2-enyl(tributyl)stannane (**6**), readily available by the addition of tributylstannyl-lithium to crotonaldehyde and alkylation of the adduct using chloromethyl methyl ether, reacts on heating with aldehydes to give *anti*-4-hydroxy-3-methyl-*cis*-1,2-enol ethers. These on hydrolysis and oxidation provide *trans*-4,5-disubstituted butyrolactones.

The chemistry of allylic organometallic reagents has been extensively studied over the last few years, and the application of these reagents to acyclic stereochemical control widely investigated.[1] In particular allyl- and but-2-enyl-stannanes have been of some interest because the stereochemistry of the products of their reactions with aldehydes has been found to depend upon the reaction conditions. In the presence of a Lewis acid catalyst, commonly boron trifluoride–diethyl ether, both (*E*)- and (*Z*)-but-2-enyltrialkylstannanes (**1**) and (**2**) react rapidly with aldehydes to give *syn*-adducts (**4**),[2] whereas the uncatalysed, thermal reactions give rise to *anti*-adducts (**3**) from (*E*)-stannanes (**1**), and *syn*-adducts (**4**) from (*Z*)-stannanes (**2**).[3] The stereoselectivity of these thermal reactions parallels those of other but-2-enyl metal compounds, and is consistent with the participation of six-membered ring, chair-like, transition states, the Lewis acid catalysed processes supposedly proceeding *via* acyclic transition states.

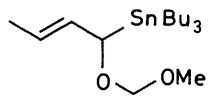
We were interested in developing the chemistry of but-2-enylstannanes to provide an asymmetric synthesis of aldehyde



adducts. It was thought that one way in which this might be achieved would be to incorporate an additional α-substituent into the but-2-enylstannane. For such a substituted stannane, *e.g.* (**5**), the additional substituent would be expected to influence the diastereofacial selectivity of its reactions, and, in particular, would have a preference for either an axial or equatorial position in the cyclic transition state of the thermal aldehyde addition process. The report by Still of the addition of trialkyltin lithium reagents to aldehydes followed by alkylation of the adducts,[4] suggested that α-alkoxybut-2-enylstannanes (**5**; X = OR) should be readily available from



(**5**)



(**6**)

crotonaldehyde and the corresponding trialkyltin lithium. We now describe the synthesis of racemic (*E*)-1-methoxymethoxybut-2-enyl(tributyl)stannane (**6**), together with its thermal reactions with aldehydes.[5–7]

Results and Discussion

Tributylstannyl-lithium (**8**) is known to add to α,β-unsaturated aldehydes and ketones at either the carbonyl group or the β-carbon depending upon steric hindrance.[4] When crotonaldehyde was added at −78 °C to a solution of tributylstannyl-lithium (**8**) in tetrahydrofuran (THF), efficient carbonyl addition occurred to give the unstable alcohol (**9**). This was not

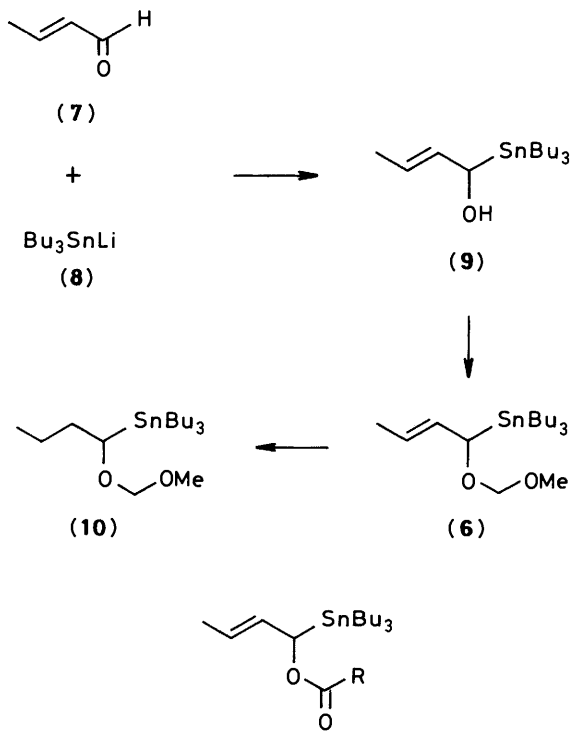


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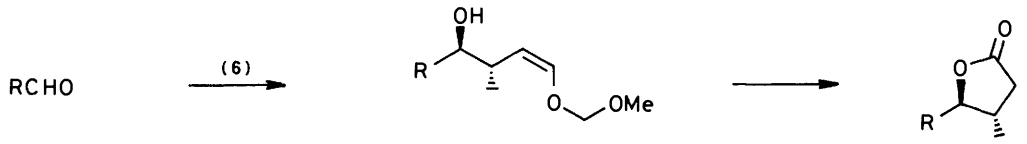
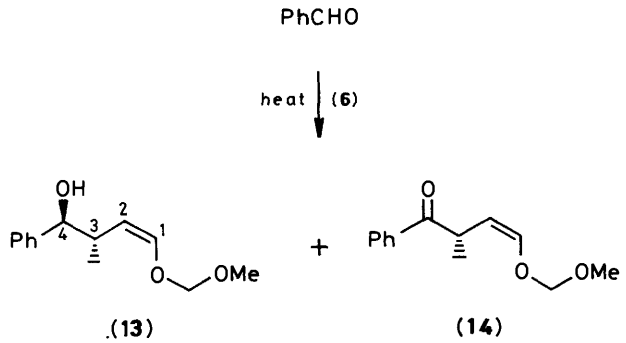
Table.

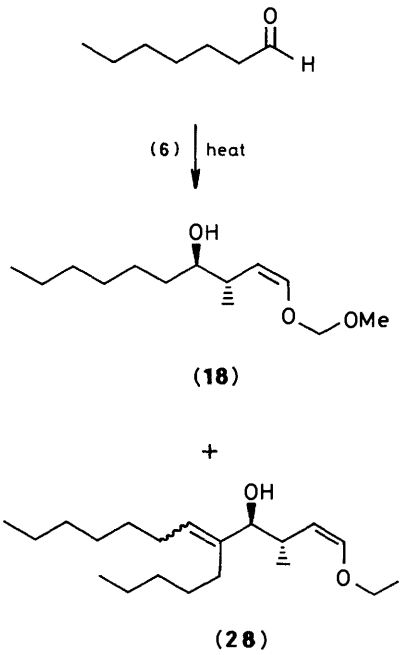


	Stannyl reaction[a]				Hydrolysis–oxidation[b]	
R	Temp (°C)	Time (h)	Product	Yield (%)	Product	Yield (%)
Ph[c]	115	90	(**13**)	79	(**22**)	89
Ph	140	11	(**13**)	70	—	—
PhCH=CH	140	11.5	(**15**)	60	(**23**)	72
p-$NO_2C_6H_4$	60	16	(**16**)	56(66)[d]	(**24**)	71
p-ClC_6H_4	100	36	(**17**)	76	(**25**)	70
C_6H_{13}	140	36	(**18**)	47[e]	(**26**)	95
C_6H_{13}[f]	140	19	(**18**)	66(89)[g]	—	—
Et	140	36	(**19**)	33[h]	—	—
Pr^i	140	36	(**20**)	72	(**27**)	77
Bu^t	140	40	(**21**)	5	—	—

[a] 2 Mol equiv. of (**6**), neat unless otherwise stated. [b] 3M Aqueous HCl–THF, 1:1, 24 h, 20 °C; PCC, NaOAc, CH_2Cl_2, 12 h, 20 °C. [c] Using 1.2 mol equiv. of (**6**) in toluene as solvent. [d] Yield in parenthesis allows for 14% recovered aldehyde. [e] Plus 10% of adduct (**28**). [f] Using 5 mol equiv. of aldehyde relative to stannane (**6**). [g] Yield in parenthesis allows for 26% recovered stannane (**16**). [h] Plus 44% of adduct (**29**).



(**13**) (**14**)



(**18**)

(**28**)

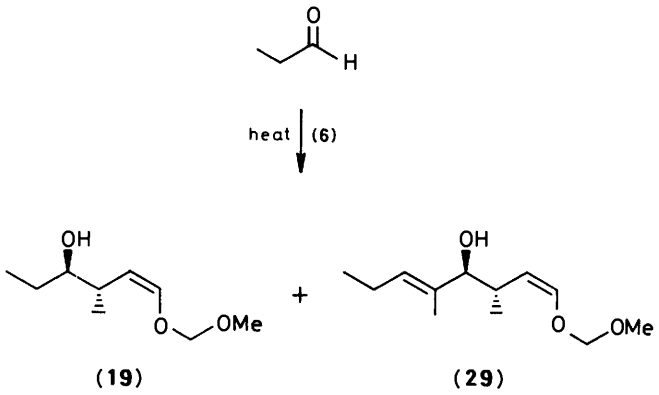
purified, but was immediately alkylated using chloromethyl methyl ether and di-isopropylethylamine to give the (*E*)-1-methoxymethoxybut-2-enyl(tributyl)stannane (**6**) (86% from crotonaldehyde). Acylation of the but-2-enol (**9**) was also achieved using acetyl and benzoyl chlorides to provide the α-acetoxy- and α-benzoyloxy-stannanes (**11**) and (**12**).

The structures of these α-substituted but-2-enylstannanes were consistent with spectroscopic data, the double-bond geometries being confirmed by vinylic coupling constants (*ca.* 16 Hz). Reduction of the alkoxybut-2-enylstannane (**6**) to the saturated alkoxybutylstannane (**10**) was achieved using di-imide.

It was found that heating a solution of the methoxymethoxybut-2-enyl(tributyl)stannane (**6**) and benzaldehyde in toluene under reflux for 90 h gave a single major product which was isolated after chromatography in 79% yield, and identified as the *anti*-4-hydroxy-3-methyl-*cis*-1,2-enol ether (**13**). No other isomers of this product were isolated, the one minor side-product isolated in small amounts (*ca.* 1—2%) from some reactions being identified as the ketone (**14**) also prepared by oxidation of the major alcohol (**13**). The benzaldehyde–stannane addition reaction was also carried out using 2 mol equiv. of stannane as solvent, a 70% yield being obtained after 11 h at 140 °C. Using an excess of benzaldehyde, a 97% yield of adduct based on stannane was obtained under similar conditions.

Other aromatic aldehydes gave analogous products, reaction conditions and yields being shown in the Table. The optimum temperatures for these reactions was found to depend upon the reactivity of the aldehyde towards nucleophilic attack; *p*-chlorobenzaldehyde gave a 76% yield of adduct after 36 h at 100 °C, whereas *p*-nitrobenzaldehyde reacted smoothly at 60 °C.

With aliphatic aldehydes variable results were obtained depending upon the nature of the aldehyde. Treatment of heptanal with 2 mol equiv. of the alkoxystannane (**6**) at 140 °C for 36 h gave the expected *anti*-4-hydroxy-3-methyl-*cis*-1,2-enol ether (**18**) (47%) together with a second product which was identified as the enol ether (**28**) (10%) which would appear to be derived from the aldol dimer of heptanal. Only one isomer of this second product was isolated but the stereochemistry of its C(5)–C(6) double-bond was not established. If an excess of heptanal was used, an improved yield of the desired enol ether (**18**) was obtained, see Table. Propanal behaved similarly giving a 33% yield of the simple adduct (**19**) together with 44% of

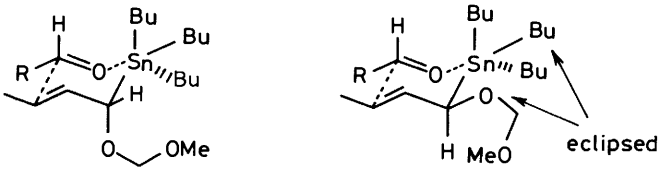


(19) (29)

the aldol adduct (**29**). However isobutyraldehyde gave just the desired adduct (**20**) (72%). In contrast pivaldehyde was too unreactive to give efficient addition, only a 5% yield of adduct (**21**) being obtained after 40 h at 140 °C.

Structures were assigned to the *anti*-4-hydroxy-3-methyl-*cis*-1,2-enol ethers on the basis of spectroscopic data and chemical correlation with known compounds. In all cases the ^{1}H n.m.r. coupling constant between the vinylic protons was 5 (±1) Hz which established the *cis*-enol ether geometry since *trans*-enol ethers usually have a vinylic coupling of 12 Hz.[8] The 3,4-*anti* stereochemistry was assigned by analogy with the results obtained for thermal reactions between aldehydes and other (*E*)-but-2-enylstannanes,[3] and was confirmed for the benzaldehyde and heptanal adducts (**13**) and (**18**) by ozonolysis followed by oxidative work-up and esterification to give the *anti*-2,3-disubstituted methyl esters (**34**) and (**35**). Authentic samples of these esters were prepared using the procedure developed by Heathcock.[9] Treatment of benzaldehyde and heptanal with the lithium enolate derived from 2,6-dimethylphenyl propionate gave mixtures of the *anti*- and *syn*-aldol adducts (**30**)/(**32**), and (**31**)/(**33**), *anti*:*syn* *ca.* 7:1 in each case. Hydrolysis and diazomethane esterification then gave 7:1 mixtures of the *anti*- and *syn*-methyl esters (**34**)/(**36**) and (**35**)/(**37**). In both series the major *anti*-methyl ester was identical with the sample prepared from the alkoxystannane adduct, and the minor *syn*-methyl ester was clearly different. *anti*-Configurations were assigned to the other enol ether adducts by analogy.

The stereoselective formation of 3,4-*anti*-1,2-*cis*-enol ethers is consistent with these reactions proceeding *via* six-membered



Axial 1-methoxymethoxy substituent leading to *Z*-enol ether

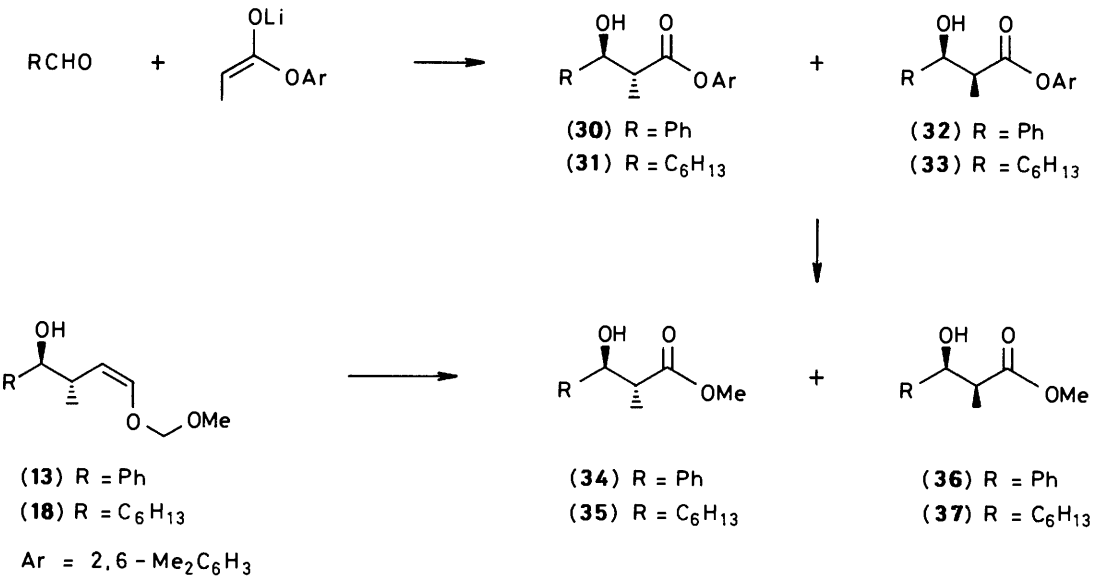
Equatorial 1-methoxy substituent leading to *E*-enol ether

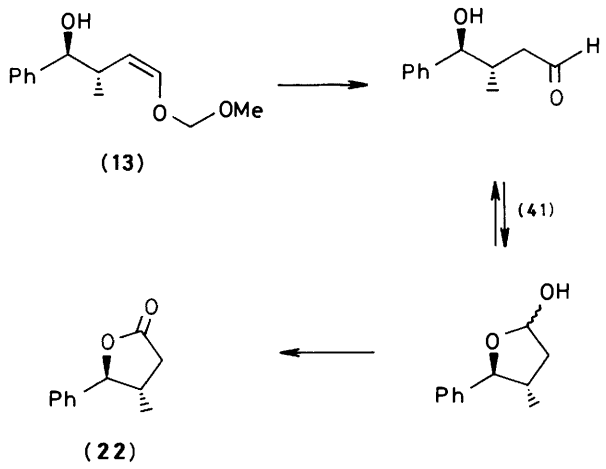
Figure.

ring, chair-like, transition states in which the *anti*-stereochemistry is a consequence of the (*E*)-geometry of the stannane, and the *cis*-enol ether geometry is due to a preference of the α-methoxymethoxy substituent to adopt an axial position (see Figure). Analogous stereoselectivity has been observed before for other butenyl organometallic reagents during their reactions with aldehydes including butenylboranes[10] and the α-methylstannane (**38**),[11] which when generated in the presence of an aldehyde gives a mixture of the adducts (**39**) and (**40**). For the α-substituted butenylboranes, this stereoselectivity has been explained in terms of steric effects involving the α-substituent.[10,12] In the present case, if the tin is a trigonal bipyramid in the transition state,[11] an equatorial α-substituent would experience an eclipsing interaction with one of the butyl groups which could be avoided if the substituent adopted an axial position, see Figure. However this explanation is only tentative and awaits more detailed knowledge of reaction pathways of tin.[13]

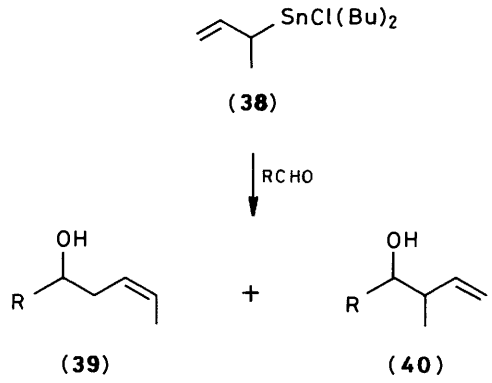
The high stereoselectivity observed for these reactions is interesting, and indicates that the α-substituent does play an important role in the thermal addition process. In particular, the strong preference for the α-substituent to adopt the axial position means that if the reagent could be resolved, it should show efficient enantioface selectivity in its reactions with prochiral aldehydes. An investigation of this possibility is described in the following paper.[14]

Finally the hydrolysis and oxidation of the *anti*-*cis*-enol ethers was examined. Treatment of the benzaldehyde adduct (**13**) with aqueous HCl–THF (24 h, 20 °C) gave the lactol (**41**) which was oxidized by buffered pyridinium chlorochromate to





the *anti*-4,5-disubstituted butyrolactone (**22**). The other *anti-cis*-enol ethers were similarly taken through to the analogous lactones (see Table). In these syntheses of butyrolactones the alkoxybut-2-enylstannane (**6**) is being used as an *anti*-selective, homoenolate equivalent.



Experimental

I.r. spectra were measured on Perkin-Elmer 257 and 681 spectrophotometers as liquid films unless otherwise stated. N.m.r. spectra were recorded on a Bruker WH 300 spectrometer using deuteriochloroform as solvent, and mass spectra were recorded on a V.G. Micromass 16F spectrometer using either electron impact (e.i.) or chemical ionization (c.i.) modes. Characteristic isotope clusters were observed for organotin compounds. Only those corresponding to ^{120}Sn are quoted. M.p.s were determined on a Buchi 510 apparatus and are uncorrected.

Short column and flash chromatography were carried out on Merck Kieselgel 60 H and Merck silica gel 60, respectively. All solvents were dried and distilled before use. Ether refers to diethyl ether throughout, and light petroleum to the fraction boiling in the range 40—60 °C. Lithium di-isopropylamide (LDA) was prepared from equimolar amounts of butyl-lithium in hexane and di-isopropylamine in THF under nitrogen at 0 °C, and tributyltin hydride was prepared according to the literature procedure[15] and purified by distillation, b.p. 108—110 °C (0.5 mmHg) [lit.,[15] b.p. 68—74 °C (0.3 mmHg)].

(E)-1-*Methoxymethoxybut-2-enyl(tributyl)stannane* (**6**).—Tributyltin hydride (26.5 ml, 100 mmol) was added to a solution of LDA (100 mmol) in THF–hexane (250 ml) at 0 °C under an atmosphere of nitrogen. After 15 min, the green solution was cooled to −78 °C, and crotonaldehyde (7 g, 100 mmol) was added dropwise. The reaction was stirred for 5 min, quenched by the addition of saturated aqueous NH_4Cl (100 ml), and warmed to 20 °C. The mixture was partitioned between light petroleum (200 ml) and water (200 ml), and the organic phase separated, dried ($MgSO_4$), and concentrated under reduced pressure to leave (*E*)-1-(tributylstannyl)but-2-en-1-ol (**9**) as an unstable oil used immediately without purification.

Di-isopropylethylamine (35 ml, 200 mmol) was added to the stirred solution of the butenol (**9**) (*ca.* 100 mmol) in anhydrous dichloromethane (250 ml) at 0 °C, and chloromethyl methyl ether (11.5 ml, 150 mmol) added. After 1 h, the reaction mixture was poured into light petroleum (750 ml), and the resulting mixture washed with ice-cold 0.5M aqueous HCl (2 × 250 ml), water (250 ml), and saturated aqueous $NaHCO_3$. The organic phase was then dried ($MgSO_4$), and concentrated under reduced pressure to leave the *title compound* (**6**) (33.3 g, 82%) as a pale yellow oil which was generally used without purification. For formal characterisation, samples were purified by flash chromatography and by column chromatography over basic alumina, using light petroleum–ether (95:5) as eluant, to give the stannane (**6**), as a colourless oil (Found: C, 53.05; H, 9.15. $C_{18}H_{38}SnO_2$ requires C, 53.35; H, 9.45%); $\nu_{max.}$ 1 456, 1 374, 1 151, 1 092, 1 014, 963, and 920 cm^{-1}; δ_H 0.88—1.73 (30 H, complex m, aliphatic CH), 3.34 (3 H, s, OMe) 4.49 (1 H, d, *J* 6.5 Hz, OHC*H*O), 4.56 (1 H, br d, *J* 7.5 Hz, 1-H), 4.67 (1 H, d, *J* 6.5 Hz, O*H*CHO), 5.39 (1 H, m, 3-H), and 5.58 (1 H, m, 2-H); *m/z* (e.i.) 291 (M^+ − 115, 100%).

(E)-1-*Acetoxybut-2-enyl(tributyl)stannane* (**11**).—A solution of 4-*N*,*N*-dimethylaminopyridine (61 mg, 0.5 mmol) in anhydrous dichloromethane (5 ml) was added to a solution of crude (*E*)-1-(tributylstannyl)but-2-en-1-ol (**9**) (*ca.* 5 mmol; prepared as described above) and triethylamine (0.76 g, 7.5 mmol) in anhydrous dichloromethane (40 ml) at 0 °C followed by acetyl chloride (0.59 g, 7.5 mmol) in anhydrous THF (5 ml). After 1 h the mixture was poured into dichloromethane (50 ml), and the solution so obtained washed with ice-cold 0.5M aqueous HCl (50 ml), water (50 ml), and saturated aqueous $NaHCO_3$ (50 ml). After drying ($MgSO_4$), concentration of the organic phase under reduced pressure gave an oil which was purified by flash chromatography using ether–light petroleum (2:98) as eluant to give the *title compound* (**11**) (1.4 g, 67%) as a colourless oil; $\nu_{max.}$ 1 722, 1 457, 1 367, 1 238, 1 065, 1 015, and 958 cm^{-1}; δ_H 0.79—1.65 (27 H, m, aliphatic H), 1.69 (3 H, br d, *J* 6.5 Hz, 4-Me), 2.05 (3 H, s, MeCO), 5.26 (1 H, br d, *J* 7 Hz, 1-H), and 5.36 and 5.68 (each 1 H, m, vinylic H); *m/z* (e.i.) 293 (M^+ − 111, 100%).

The (*E*)-1-benzoyloxybut-2-enyl(tributyl)stannane (**12**) was similarly prepared; δ_H 0.8—1.9 (30 H, m, aliphatic H), 5.2—6.1 (3 H, m, 1-H and vinylic H), 7.4—7.65 (3 H, m, aromatic H), and 8.0—8.25 (2 H, m, aromatic H).

1-*Methoxymethoxybutyl(tributyl)stannane* (**10**).—A mixture of the 1-methoxymethoxybut-2-enylstannane (**6**) (1 g, 2.47 mmol), anhydrous NaOAc (820 mg, 10 mmol), and toluene *p*-sulphonohydrazide (1.86 g, 10 mmol) in anhydrous ethanol was heated under reflux for 2 h under an atmosphere of argon. After the mixture had cooled to room temperature, the ethanol was removed under reduced pressure, and the residue partitioned between light petroleum (200 ml) and water (200 ml). The organic layer was separated, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure to leave the *title compound* (**10**) (800 mg, 80%), as a

colourless oil; $\delta_{max.}$ 1 460, 1 378, 1 146, 1 095, 1 039, and 921 cm^{-1}; δ_H 0.85—1.91 (34 H, complex m, aliphatic H), 3.35 (3 H, s, OMe), 4.07 (1 H, dd, *J* 6, 7.5 Hz, 1-H), and 4.54 and 4.59 (each 1 H, d, *J* 6.5 Hz, OHC*H*O); *m/z* (e.i.) 351 ($M^+ - 57$, 20%).

Reactions of 1-*Methoxymethoxybut*-2-*enyl*(*tributyl*)*stannane* (**6**) *with Aldehydes.—With benzaldehyde.* A solution of the stannane (**6**) (2.7 g, 6.7 mmol) and benzaldehyde (0.25 ml, 2.5 mmol) in anhydrous toluene (20 ml) was heated under reflux under a nitrogen atmosphere for 90 h. After cooling, the mixture was concentrated under reduced pressure to give a residue which was purified by short-column chromatography using ether–light petroleum (gradient elution) to give (3RS,4RS,1Z)-4-*hydroxy*-1-*methoxymethoxy*-3-*methyl*-4-*phenylbut*-1-*ene* (**13**) (435 mg, 79%) as a colourless oil (Found: C, 70.35; H, 8.3. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.15%); $\nu_{max.}$ 3 460, 3 025, 1 670, 1 450, 1 380, 1 305, 1 155, 1 040, and 920 cm^{-1}; δ_H 0.84 (3 H, d, *J* 7 Hz, CHMe), 2.3—2.4 (1 H, br s, OH), 3.04 (1 H, m, 3-H), 3.40 (3 H, s, OMe), 4.33 (1 H, d, *J* 8.5 Hz, 4-H), 4.49 (1 H, dd, *J* 6.5, 9.5 Hz, 2-H), 4.82 (2 H, s, OCH_2O), 6.30 (1 H, d, *J* 6.5 Hz, 1-H), and 7.25—7.40 (5 H, m, aromatic H); *m/z* (c.i.) 205 ($M^+ - 17$, 40%). In some cases a second product was isolated (*ca.* 1%) and was identified as (3Z)-4-*methoxymethoxy*-2-*methyl*-1-*phenylbut*-3-*en*-1-*one* (**14**), as a colourless oil; $\nu_{max.}$ 3 046, 1 680, 1 593, 1 575, 1 241, 1 200, 1 156, 1 030, 969, and 920 cm^{-1}; δ_H 1.31 (3 H, d, *J* 6.5 Hz, CH*Me*), 3.42 (3 H, s, OMe), 4.54—4.65 (2 H, complex m, 2-H and 3-H), 4.87 (2 H, s, OCH_2O), 6.19 (1 H, d, *J* 6 Hz, 4-H), 7.40—7.58 (3 H, m, aromatic H), and 8.07 (2 H, m, aromatic H); *m/z* (c.i.) 221 ($M^+ + 1$, 100%).

With cinnamaldehyde. A mixture of the stannane (**6**) (4.05 g, 10 mmol) and cinnamaldehyde (0.66 g, 5 mmol) was heated at 140 °C for 11.5 h under an atmosphere of argon. After cooling, the mixture was dissolved in acetonitrile (100 ml) and the resulting solution washed with light petroleum (2 × 50 ml) before being concentrated under reduced pressure.[16] Flash chromatography of the residue using ether–light petroleum (1:2) as eluant gave (3RS,4SR,1Z,5E)-4-*hydroxy*-1-*methoxymethoxy*-3-*methyl*-6-*phenylhexa*-1,5-*diene* (**15**) (750 mg, 60%) as a colourless oil; $\nu_{max.}$ 3 440, 3 020, 1 665, 1 158, 1 100, 1 040, 966, 920, 750, and 692 cm^{-1}; δ_H 1.07 (3 H, d, *J* 6.5 Hz, CH*Me*), 2.11 (1 H, d, *J* 3 Hz, OH), 2.94 (1 H, m, 3-H), 3.43 (3 H, s, OMe), 4.05 (1 H, m, 4-H), 4.49 (1 H, dd, *J* 6, 9.5 Hz, 2-H), 4.86 (2 H, s, OCH_2O), 6.28 (1 H, dd, *J* 7, 16 Hz, 5-H), 6.31 (1 H, d, *J* 6 Hz, 1-H), 6.65 (1 H, d, *J* 16 Hz, 6-H), and 7.24—7.45 (5 H, m, aromatic H); *m/z* (c.i.) 249 ($M^+ + 1$, 2%).

With p-*nitrobenzaldehyde.* Following the procedure outlined above for cinnamaldehyde, *p*-nitrobenzaldehyde (76 mg, 0.5 mmol) and the stannane (**6**) (405 mg, 1 mmol) after being heated for 16 h at 60 °C and flash chromatographed gave recovered *p*-nitrobenzaldehyde (11 mg, 14%) together with (3RS,4RS,1Z)-4-*hydroxy*-1-*methoxymethoxy*-3-*methyl*-4-(4-*nitrophenyl*)*but*-1-*ene* (**16**) (75 mg, 56%) as a pale yellow oil (Found: C, 58.5; H, 6.6; N, 5.2. $C_{13}H_{17}NO_5$ requires C, 58.4; H, 6.4; N, 5.2%); $\nu_{max.}$ 3 450, 3 055, 1 661, 1 595, 1 515, 1 345, 1 155, 1 104, and 1 030 cm^{-1}; δ_H 0.88 (3 H, d, *J* 6.5 Hz, CH*Me*), 2.65 (1 H, br s, OH), 3.00 (1 H, m, 3-H), 3.37 (3 H, s, OMe), 4.42 (1 H, dd, *J* 6, 9.5 Hz, 2-H), 4.48 (1 H, d, *J* 7.5 Hz, 4-H), 4.79 (2 H, s, OCH_2O), 6.29 (1 H, d, *J* 6 Hz, 1-H), and 7.54 and 8.19 (each 2 H, m, aromatic H); *m/z* (c.i.) 250 ($M^+ - 17$, 5%).

With p-*chlorobenzaldehyde.* Following the procedure outlined above for cinnamaldehyde, *p*-chlorobenzaldehyde (70 mg, 0.5 mmol) and stannane (**6**) (446 mg, 1.1 mmol) after being heated for 36 h at 100 °C gave (3RS,4RS,1Z)-4-(4-*chlorophenyl*)-4-*hydroxy*-1-*methoxymethoxy*-3-*methylbut*-1-*ene* (**17**) (97 mg, 76%) as a colourless oil; $\nu_{max.}$ 3 440, 3 030, 1 663, 1 490, 1 155, 1 087, 1 035, and 920 cm^{-1}; δ_H 0.84 (3 H, d, *J* 7 Hz, CH*Me*), 2.51 (1 H, br s, OH), 2.97 (1 H, m, 3-H), 3.38 (3 H, s, OMe), 4.31 (1 H, br d, *J* 8 Hz, 4-H), 4.43 (1 H, dd, *J* 6, 9.5 Hz, 2-H), 4.80 (2 H, s, OCH_2O), 6.28 (1 H, d, *J* 6 Hz, 1-H), and 7.3 (4 H, s, aromatic H); *m/z* (c.i.) 239 ($M^+ - 17$, 10%).

With heptanal. A mixture of heptanal (0.336 ml, 2.5 mmol) and the stannane (**6**) (3 g, 7.4 mmol) was heated for 36 h at 140 °C under an atmosphere of argon. Short column chromatography of the product using ether–light petroleum (gradient elution) as eluant gave three fractions. The least polar fraction comprised unchanged stannane (**6**). The second fraction was identified as (3RS,4RS,1Z)-4-*hydroxy*-1-*methoxymethoxy*-3-*methyl*-5-*pentyldodeca*-1,5-*diene* (**28**) (43 mg, 11%) as a colourless oil; $\nu_{max.}$ 3 410, 1 709, 1 662, 1 157, 1 040, and 921 cm^{-1}; δ_H 0.83—1.8 (22 H, complex m, aliphatic H + OH), 2.03 and 2.32 (each 2 H, t, *J* 7 Hz, allylic H), 2.88 (1 H, m, 3-H), 3.41 (3 H, s, OCH_3), 3.64 (1 H, d, *J* 8 Hz, 4-H), 4.40 (1 H, dd, *J* 6, 9.5 Hz, 2-H), 4.81 (2 H, s, OCH_2O), 5.36 (1 H, br t, *J* 7 Hz, 6-H), and 6.25 (1 H, d, *J* 6 Hz, 1-H); *m/z* (c.i.) 265 ($M^+ - 61$, 40%). The most polar fraction was identified as (3RS,4SR,1Z)-4-*hydroxy*-1-*methoxymethoxy*-3-*methyldec*-1-*ene* (**18**) (270 mg, 47%), a colourless oil; $\nu_{max.}$ 3 440, 1 665, 1 458, 1 372, 1 158, and 1 040 cm^{-1}; δ_H 0.9 (3 H, m, CH_2Me), 1.01 (3 H, d, *J* 7 Hz, CH*Me*), 1.28—1.53 (10 H, complex m, 5 × CH_2), 2.0 (1 H, br s, OH), 2.73 (1 H, m, 3-H), 3.36 (1 H, m, 4-H), 3.39 (3 H, s, OMe), 4.40 (1 H, dd, *J* 6, 9.5 Hz, 2-H), 4.80 (2 H, s, OCH_2O), and 6.22 (1 H, d, *J* 6 Hz, 1-H); *m/z* (c.i.) 169 ($M^+ - 61$, 40%).

With propanal. A mixture of propanal (87 mg, 1.5 mmol) and the stannane (**6**) (1.22 g, 3 mmol) was heated in a sealed tube for 36 h at 140 °C. It was then cooled and partitioned between light petroleum and acetonitrile, and the latter phase concentrated under reduced pressure to give a residue. This was flash chromatographed using ether–light petroleum (1:2) as eluant to give a colourless oil (162 mg) shown to be a mixture of two components by t.l.c. Short column chromatography of this mixture eluting with ether–benzene (1:2) gave two fractions. The less polar fraction was identified as (3RS,4RS,1Z,5E)-4-*hydroxy*-1-*methoxymethoxy*-3,5-*dimethylocta*-1,5-*diene* (**29**) (70 mg, 44%) as a colourless oil; $\nu_{max.}$ 3 470, 1 664, 1 450, 1 370, 1 305, 1 230, 1 156, 1 103, 1 035, and 920 cm^{-1}; δ_H 0.84 (3 H, d, *J* 7 Hz, CH*Me*), 0.97 (3 H, t, *J* 7.5 Hz, CH_2Me), 1.64 (3 H, br s, CMe), 2.01—2.11 (3 H, m, CH_2 + OH), 2.87 (1 H, m, 3-H), 3.42 (3 H, s, OMe), 3.59 (1 H, br d, *J* 9 Hz, 4-H), 4.40 (1 H, dd, *J* 6, 9.5 Hz, 2-H), 4.82 (2 H, s, OCH_2O), 5.38 (1 H, br t, *J* 7 Hz, 6-H), and 6.27 (1 H, d, *J* 6 Hz, 1-H); *m/z* (c.i.) 197 ($M^+ - 17$, 5%). The more polar fraction was identified as (3RS,4SR,1Z)-4-*hydroxy*-1-*methoxymethoxy*-3-*methylhex*-1-*ene* (**19**) (86 mg, 33%), a colourless oil; $\nu_{max.}$ 3 450, 3 040, 1 665, 1 305, 1 235, 1 159, 1 100, 1 039, 971, and 921 cm^{-1}; δ_H 0.98 (3 H, t, *J* 7.5 Hz, CH_2Me), 1.01 (3 H, d, *J* 7 Hz, CH*Me*), 1.37–1.73 (3 H, m, CH_2 + OH), 2.76 (1 H, m, 3-H), 3.32 (1 H, m, 4-H), 3.40 (3 H, s, OMe), 4.41 (1 H, dd, *J* 6, 9.5 Hz, 2-H), 4.80 (2 H, s, OCH_2O), and 6.22 (1 H, d, *J* 6.2 Hz, 1-H); *m/z* (c.i.) 157 ($M^+ - 17$, 10%).

With 2-*methylpropanal.* Following the procedure described above for propanal, 2-methylpropanal (108 mg, 1.5 mmol) and the stannane (**6**) (1.22 g, 3 mmol) after being heated for 36 h at 140 °C and the resulting mixture flash chromatographed gave (3RS,4SR,1Z)-4-*hydroxy*-1-*methoxymethoxy*-3,5-*dimethylhex*-1-*ene* (**20**) (203 mg, 72%) as a colourless oil; $\nu_{max.}$ 3 460, 1 665, 1 162, and 1 040 cm^{-1}; δ_H 0.91—1.01 (9 H, 3 overlapping d, 3 × CH*Me*), 1.67—1.76 (2 H, m, 5-H and OH), 2.87 (1 H, m, 3-H), 3.08 (1 H, br t, *J* 6 Hz, 4-H), 3.39 (3 H, s, OMe), 4.43 (1 H, dd, *J* 6, 10 Hz, 2-H), 4.79 (2 H, s, OCH_2O), and 6.20 (1 H, d, *J* 6 Hz, 1-H); *m/z* (c.i.) 127 ($M^+ - 61$, 65%).

With 2,2-*dimethylpropanal.* Following the procedure outlined above for propanal, 2,2-dimethylpropanal (129 mg, 1.5 mmol) and the stannane (**6**) (1.22 g, 3 mmol) after being heated for 40 h at 140 °C and the resulting mixture flash chromatographed gave (3RS,4RS,1Z)-4-*hydroxy*-1-*methoxymethoxy*-3,5,5-*trimethylhex*-1-*ene* (**21**) (15 mg, 5%) as a colourless oil; $\nu_{max.}$ 3 490, 1 663, 1 304, 1 236, 1 156, 1 090, 1 040, 987, and 920 cm^{-1}; δ_H 0.94 (9 H,

s, 3 × Me), 1.10 (3 H, d, *J* 7 Hz, CH*Me*), 3.03 (1 H, m, 3-H), 3.15 (1 H, d, *J* 2 Hz, OH), 3.39 (1 H, m, 4-H), 3.41 (3 H, s, OMe), 4.62 (1 H, dd, *J* 6, 9.5 Hz, 2-H), 4.81 (2 H, s, OCH_2O), and 6.08 (1 H, d, *J* 6 Hz, 1-H); *m/z* (c.i.) 141 ($M^+ - 61$, 40%).

Methyl (2RS,3SR)-3-*Hydroxy*-2-*methyl*-3-*phenylpropionate* (**34**).—*From the enol ether* (**13**). Ozonised oxygen was bubbled through a solution of the enol ether (**13**) (280 mg, 1.25 mmol) in methanol (5 ml) and dichloromethane (1 ml) at −78 °C for 1 h. A solution of NaOH (200 mg, 5 mmol) in 27.5% aqueous hydrogen peroxide (1 g) was added, and the mixture warmed to room temperature under a stream of oxygen. It was then acidified to pH 1 with 3M aqueous HCl, extracted with ether (3 × 15 ml), and the extract dried ($MgSO_4$) and concentrated under reduced pressure to give an oil (230 mg). To ensure complete oxidation to the propionic acid, this oil (200 mg) was added to a suspension of silver oxide prepared by the addition of 0.25M aqueous silver nitrate (10 ml, 2.5 mmol) to NaOH (200 mg, 5 mmol) in water (1 ml). This mixture was stirred at 20 °C for 15 min, filtered, and acidified to pH 1 using 3M aqueous HCl. It was then extracted with ether (3 × 15 ml) and the extract dried ($MgSO_4$), and concentrated under reduced pressure to give (2*RS*,3*SR*)-3-hydroxy-2-methyl-3-phenylpropionic acid (154 mg, 79%) as a yellow oil. A solution of an excess of diazomethane in ether was added to a solution of this acid in ether at 0 °C. After 15 min, glacial acetic acid was added until the yellow colour was discharged. After being neutralized by saturated aqueous $NaHCO_3$, the aqueous layer was extracted with ether, and the ether extracts dried ($MgSO_4$), and concentrated under reduced pressure to leave the title methyl ester (**34**) (130 mg, 78%) as a white solid, m.p. 47—50 °C (lit.,[17] 50.5—51.5 °C).

From benzaldehyde. 2,6-Dimethylphenyl propionate was condensed with benzaldehyde as described in the literature[9] to provide a mixture of *anti*- and *syn*-adducts (**30**) and (**32**) [(**30**):(**32**), 7:1]. This mixture was saponified using methanolic KOH to give a mixture of the corresponding acids which were esterified using an excess of diazomethane as described above to give the *anti*-methyl ester (**34**) containing *ca.* 15% of its diastereoisomer (**36**). The *anti*-methyl esters (**34**) prepared by the two routes were identical, and had $J_{2,3}$ 8.5 Hz consistent with the assigned stereochemistry.[18]

Methyl (2RS,3RS)-3-*Hydroxy*-2-*methylnonanoate* (**35**).—*From enol ether* (**18**). The enol ether (**18**) (140 mg, 0.61 mmol) was ozonolysed following the procedure described above. Basic hydrogen peroxide work-up gave (2*RS*,3*RS*)-3-hydroxy-2-methylnonanoic acid (104 mg) as a yellow oil. The crude acid was esterified using diazomethane to provide, after chromatography, *methyl* (2RS,3RS)-3-*hydroxy*-2-*methylnonanoate* (**35**) (20 mg, 19% overall) as a colourless oil; $\nu_{max.}$ 3 415, 1 719, 1 455, 1 372, 1 195, and 1 168 cm^{-1}; δ_H 0.89 (3 H, br t, *J* 7 Hz, CH_2Me), 1.21 (3 H, d, *J* 7 Hz, CH*Me*), 1.15—1.58 (10 H, complex m, 5 × CH_2), 2.5 (1 H, br s, OH), 2.53 (1 H, dq, *J* 6.5, 7 Hz, 2-H), 3.65 (1 H, m, 3-H), and 3.71 (3 H, s, OMe); *m/z* (c.i.) 203 ($M^+ + 1$, 45%).

From heptanal. A solution of 2,6-dimethylphenyl propionate[9] (765 mg, 4.3 mmol) in THF (8 ml) was added to LDA (4.3 mmol) in THF–hexane at −78 °C under an atmosphere of argon. After 20 min, heptanal (0.58 ml, 4.3 mmol) was added, and after 1 min the reaction was quenched by the addition of saturated aqueous NH_4Cl (5 ml) and water (10 ml). The resulting mixture was extracted with ether (4 × 15 ml), and the ethereal extracts dried ($MgSO_4$), and concentrated under reduced pressure to give 2′,6′-dimethylphenyl (2*RS*,3*RS*)-3-hydroxy-2-methylnonanoate (**31**) (1.3 g) used without purification; δ_H(60 MHz) 0.7—1.9 (17 H, complex m, aliphatic H + OH), 2.12 (6 H, s, 2 × aromatic Me), 2.5—3.0 (1 H, m, 2-H), 3.6—3.9 (1 H, m, 3-H), and 7.0 (3 H, s, aromatic H). This ester was stirred overnight at 20 °C with 5% methanolic KOH (35 ml) and water (7 ml). Acidification to pH 9 with 3M aqueous HCl and ether extraction (3 × 50 ml) gave 2,6-dimethylphenol. Further acidification to pH 1 with 3M aqueous HCl, followed by ether extraction (3 × 50 ml) then gave the crude (2*RS*,3*RS*)-3-hydroxy-2-methylnonanoic acid (495 mg). This was esterified using diazomethane as described above to give the *anti*-methyl ester (**35**) containing *ca.* 15% (^1H n.m.r.) of its *syn*-isomer (**37**).

Hydrolysis and Oxidation of the Enol Ethers.—General procedures. The enol ether (0.8—1.3 mmol) was stirred with a 1:1 mixture of THF and 3M aqueous HCl (6 ml total) for 18—24 h at 20 °C. The mixture was then poured into brine (10—15 ml) and extracted with ether (3 × 10—15 ml). The combined extracts were dried ($MgSO_4$), and concentrated under reduced pressure to give the γ-butyrolactol as a mixture of anomers. The crude γ-butyrolactol (0.7—1.1 mmol), pyridinium chlorochromate (2.1—2.5 mmol) and anhydrous sodium acetate (0.4—0.6 mmol) were stirred in dry dichloromethane (1.5—2 ml) for *ca.* 16 h at 20 °C. The reaction mixture was then diluted with ether, filtered through silica, and concentrated under reduced pressure to leave the crude butyrolactone which was purified by recrystallization or flash chromatography.

(4RS,5RS)-4-*Methyl*-5-*phenyldihydrofuran*-2(3H)-*one* (**22**) (89%), a white solid, m.p. 39.0—39.5 °C (from ether) (Found: C, 74.95; H, 6.8. $C_{11}H_{12}O_2$ requires C, 74.95; H, 6.85%); $\nu_{max.}$ 3 060, 3 030, 1 780, 1 278, 1 210, 1 140, 1 090, 1 000, 945, 755, and 700 cm^{-1}; δ_H 1.20 (3 H, d, *J* 6.5 Hz, CH*Me*), 2.35 (1 H, dd, *J* 10, 16 Hz, 3-H), 2.5 (1 H, m, 4-H), 2.80 (1 H, dd, *J* 7, 16 Hz, 3-H′), 4.94 (1 H, d, *J* 8.5 Hz, 5-H), and 7.3—7.45 (5 H, m, aromatic H); *m/z* (e.i.) 176 (M^+, 20%).

(4RS,5RS)-4-*Methyl*-5-[(E)-2-*phenylvinyl*]*dihydrofuran*-2(3H)-*one* (**23**) (72% overall), a white solid, m.p. 57—58.5 °C (from ether) (Found: C, 76.95; H, 7.05. $C_{13}H_{14}O_2$ requires C, 77.2; H, 7.0%); $\nu_{max.}$ 3 055, 3 020, 1 782, 1 700, 1 595, 1 210, 1 163, 990, 968, 939, 752, and 695 cm^{-1}; δ_H 1.18 (3 H, d, *J* 6.5 Hz, CH*Me*), 2.28 (1 H, dd, *J* 10, 16.5 Hz, 3-H), 2.30—2.53 (1 H, m, 4-H), 2.75 (1 H, dd, *J* 7.5, 16.5 Hz, 3′-H), 4.58 (1 H, br t, *J* 7 Hz, 5-H), 6.18 (1 H, dd, *J* 7.5, 16 Hz, 1′-H), 6.70 (1 H, d, *J* 16 Hz, 2′-H), and 7.28—7.44 (5 H, m, aromatic H); *m/z* (e.i.) 202 (M^+, 45%).

(4RS,5RS)-*Methyl*-5-(4-*nitrophenyl*)*dihydrofuran*-2(3H)-*one* (**24**) (71% overall), pale yellow plates, m.p. 76—76.5 °C (from ether) (Found: C, 59.75; H, 5.15; N, 6.35. $C_{11}H_{11}NO_4$ requires C, 59.7; H, 5.0; N, 6.35%); $\nu_{max.}$ 3 110, 3 080, 1 785, 1 603, 1 519, 1 345, 1 279, 1 208, 1 150, 1 020, 1 010, 849, 810, 749, and 698 cm^{-1}; δ_H 1.25 (3 H, d, *J* 6.5 Hz, CH*Me*), 2.35—2.51 (2 H, m, 3-H and 4-H), 2.82 (1 H, m, 3′-H), 5.06 (1 H, d, *J* 8 Hz, 5-H), and 7.52 and 8.24 (each 2 H, br d, *J* 9 Hz, aromatic H); *m/z* (c.i.) 223 ($M^+ + 2$, 15%) and 192 ($M^+ - 29$, 100%).

(4RS,5RS)-5-(4-*Chlorophenyl*)-4-*methyldihydrofuran*-2(3H)-*one* (**25**) (70% overall), a colourless oil which gradually solidified at −30 °C (Found: M^+ 210.0448. $C_{11}H_{11}{}^{35}ClO_2$ requires *M*, 210.0448); $\nu_{max.}$ 1 780, 1 490, 1 283, 1 270, 1 206, 1 140, 1 089, 1 010, and 809 cm^{-1}; δ_H 1.11 (3 H, d, *J* 6.5 Hz, CH*Me*), 2.20—2.42 (2 H, m, 3- and 4-H), 2.71 (1 H, dd, *J* 6, 15 Hz, 3-H′), 4.83 (1 H, d, *J* 8 Hz, 5-H), and 7.2 and 7.3 (each 2 H, br d, *J* 8 Hz, aromatic H); *m/z* (e.i.) 210 (M^+, 25%).

(4RS,5SR)-5-*Hexyl*-4-*methyldihydrofuran*-2(3H)-*one* (**26**) (95% overall), a colourless oil; $\nu_{max.}$ 1 776, 1 460, 1 209, and 1 150 cm^{-1}; δ_H 0.88 (3 H, br t, *J* 7 Hz, CH_2Me), 1.13 (3 H, d, *J* 6.5 Hz, CH*Me*), 1.20—1.70 (11 H, m, 5 × CH_2 + 4-H), 2.18 and 2.66 (each 1 H, m, 3-H), and 4.01 (1 H, m, 5-H); *m/z* (c.i.) 185 ($M^+ + 1$, 100%).

(4RS,5SR)-4-*Methyl*-5-*propan*-2′-*yldihydrofuran*-2(3H)-*one* (**27**) (77% overall), a colourless oil; $\nu_{max.}$ 1 777, 1 467, 1 216,

1 170, 1 004, 979, and 937 cm^{-1}; δ_H 0.99, 1.01, and 1.16 (each 3 H, d, *J* 7 Hz, CH*Me*), 1.87 (1 H, m, 2′-H), 2.18 (1 H, dd, *J* 8, 17 Hz, 3-H), 2.36 (1 H, m, 4-H), 2.70 (1 H, dd, *J* 8.5, 17 Hz, 3-H′), and 3.85 (1 H, dd, *J* 6, 6.5 Hz, 5-H); *m/z* (c.i.) 143 ($M^+ + 1$, 80%).

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