# Synthesis of Optically Active (*E*)-1-Alkoxymethoxybut-2-enyl(tributyl)stannanes: Stereochemistry of their Thermal Reactions with Aldehydes

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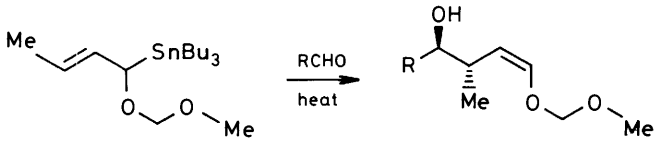
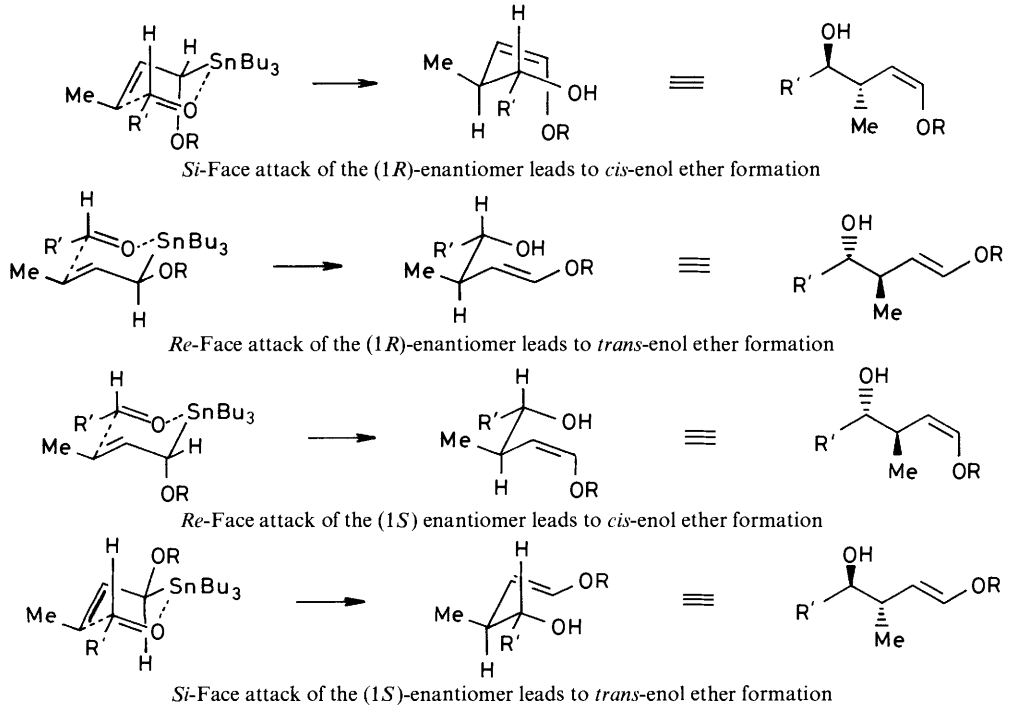
(1*R*)- and (1*S*)-1-[(−)-Menthyloxymethoxy]-(*E*)-but-2-enyl(tributyl)stannanes (**8**) and (**9**), whose configurations were assigned by correlation with (2*R*)- and (2*S*)-pentan-2-ol (**14**) and (**15**), react stereoselectively on heating with benzaldehyde to give (3*S*,4*S*)- and (3*R*,4*R*)-4-hydroxy-3-methyl-(*Z*)-1,2-enol ethers (**16**) and (**18**), respectively, the configurations of these products being established by correlation with pseudoephedrine.

Racemic (*E*)-1-methoxymethoxybut-2-enyl(tributyl)stannane (**1**) has been found to react stereoselectively with aldehydes on heating to give *anti*-4-hydroxy-3-methyl-*cis*-1,2-enol ethers (**2**).[1]




(**1**) (**2**)

These reactions are believed to proceed *via* six-membered ring, chair-like, transition states in which there is a strong preference for the α-methoxymethoxy substituent to adopt an axial position.[1,2] This observation suggests that the enantiomers of a chiral α-alkoxystannane should show high selectivity for the enantiotopic faces of a prochiral aldehyde. This idea is shown in the Scheme where it can be seen that the preference of the 1-alkoxy substituent to adopt an axial position requires the (1*R*)- and (1*S*)-enantiomers of the stannane to choose the *Si*- and *Re*-faces of the aldehyde respectively. We now report confirmation of this prediction.[3]




**Scheme.**

## Results and Discussion

The racemic (tributyl)stannylbutenol (**3**) was prepared by the addition of tributyltin lithium to crotonaldehyde. Treatment of this alcohol with (*S*)-(−)-methoxy(trifluoromethyl)phenylacetyl chloride [(*S*)-MTPA chloride] gave a mixture of the two diastereoisomeric esters (**4**) and (**5**) which could be partially separated by short column chromatography to provide one of the diastereoisomers as a pure compound free from the other. This isomer was heated at 140 °C for several hours, but no epimerization occurred (300 MHz n.m.r.). However when a mixture of the diastereoisomeric esters was heated at 100 °C with *p*-nitrobenzaldehyde for 15 h, no reaction took place, and the stannyl esters were recovered unchanged. This preliminary

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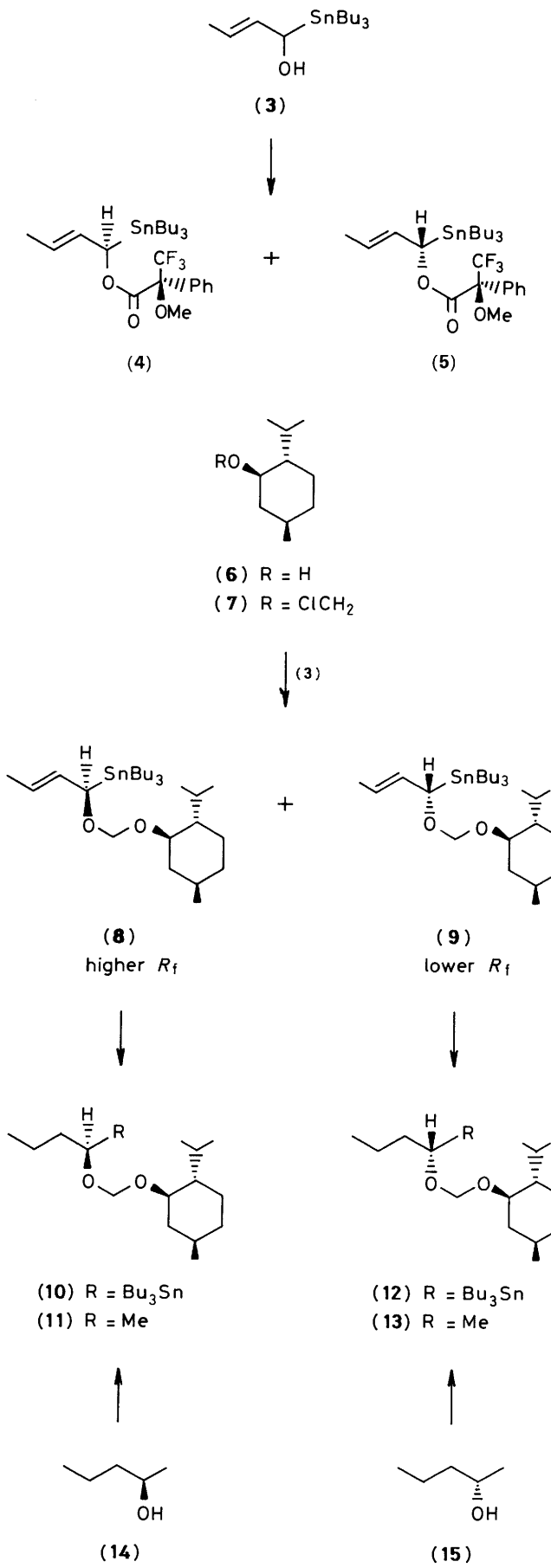
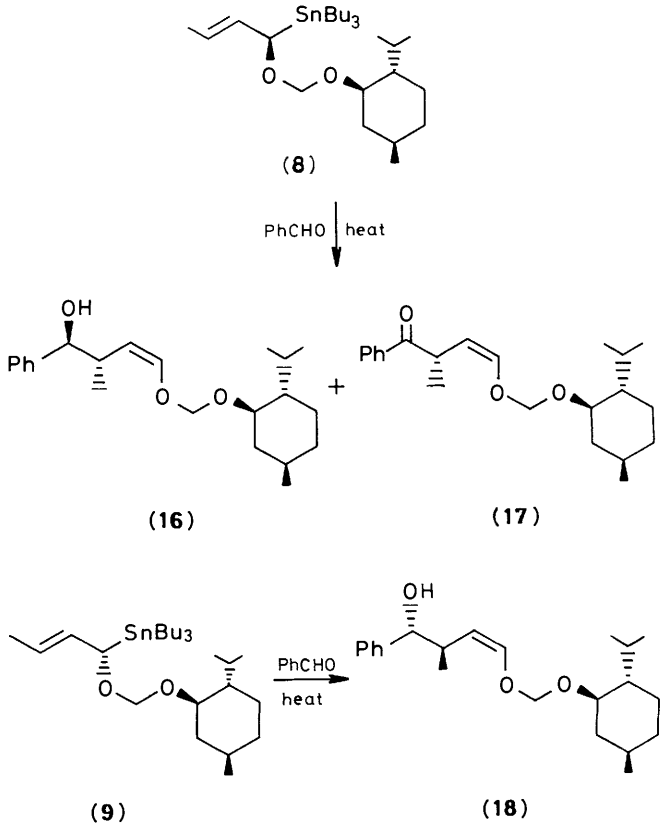
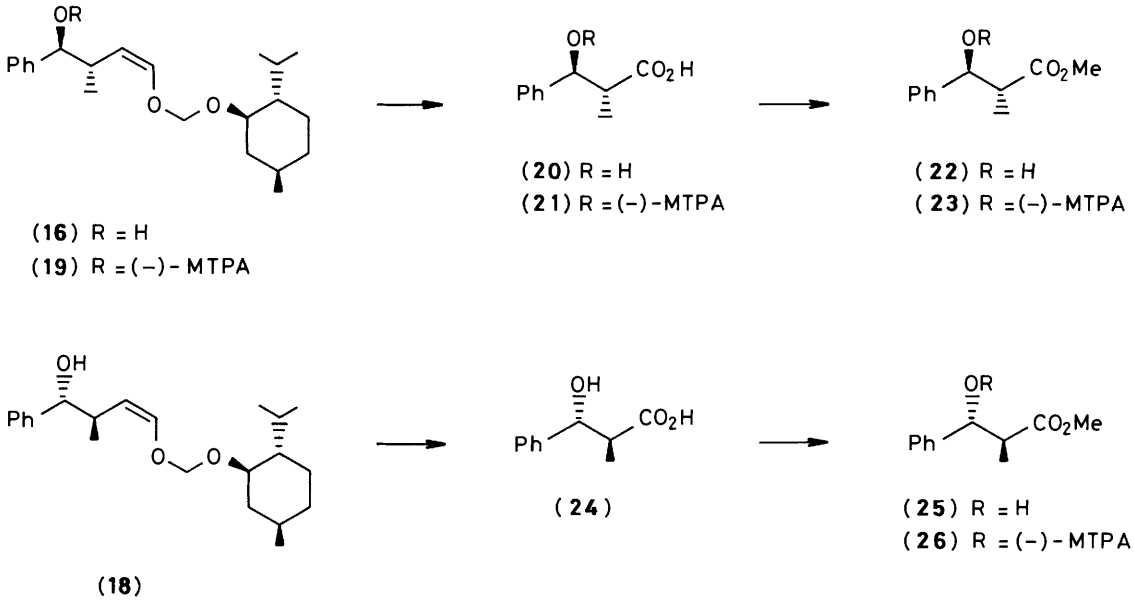



investigation showed that the α-acyloxy compounds were insufficiently reactive for addition to occur even with reactive aldehydes. Attempts to reduce the esters (**4**) and (**5**) to release the separate enantiomers of alcohol (**3**) were unsuccessful. It was then decided to attempt to prepare and separate the 1-alkoxymethoxy(but-2-enyl)stannanes derived from a chiral alcohol, (−)-menthol (**6**) being found to be a suitable chiral auxiliary.

(−)-Menthol (**6**) was converted into the chloromethyl (−)-menthyl ether (**7**)[4] by treatment with 1,3,5-trioxane and HCl in dichloromethane containing $MgSO_4$ (54%). The crude racemic stannol (**3**) was then treated with the chloromethyl menthyl ether (**7**), in the presence of di-isopropylethylamine, to provide the diastereoisomeric but-2-enylstannanes (**8**) and (**9**) isolated as a mixture by flash chromatography (59%). Careful short-column chromatography separated the two diastereoisomers giving the (1*R*)-isomer (**8**) as the less polar component, followed by the (1*S*)-isomer (**9**), as the more polar component.

The two diastereoisomers (**8**) and (**9**) could be distinguished by t.l.c. and by high field (300 MHz) $^1$H n.m.r. spectroscopy with the chemical shifts of the diastereotopic $OCH_2O$ protons being a particularly clear distinguishing feature. The configurations of these compounds at C-1 were established by correlation with the (2*R*)- and (2*S*)-pentan-2-ols (**14**) and (**15**). Di-imide reduction of the less polar stannane, followed by transmetallation (BuLi, −78 °C, 5 min) and methylation ($Me_2SO_4$, −78 °C, 1.75 h), a procedure known to involve retention of configuration,[5] gave the (2*R*)-pentan-2-ol derivative (**11**) which was also prepared from authentic (2*R*)-pentan-2-ol (**14**).[6] Similarly the more polar stannane was converted into the (2*S*)-pentan-2-ol derivative (**13**) also prepared from (2*S*)-pentan-2-ol (**15**). The two pentan-2-ol derivatives (**11**) and (**13**) were clearly different by high field (300 MHz) $^1$H n.m.r. spectroscopy, in particular the diastereotopic $OCH_2O$ protons were observed as doublets at δ 4.73 and 4.83 for the (2*R*)-isomer (**11**) and at δ 4.69 and 4.85



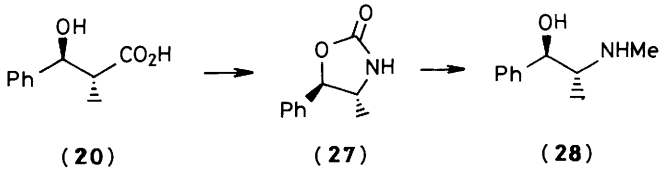



for the (2*S*)-isomer (**13**), and enabled the less polar, higher $R_F$ stannane to be identified as the (1*R*)-isomer (**8**), with the more polar, lower $R_F$ stannane being identified as the (1*S*)-isomer (**9**).

The (−)-menthoxymethoxystannanes (**8**) and (**9**) were then separately heated with an excess of benzaldehyde at 130 °C for 14—15 h under an atmosphere of argon. These reactions gave rise to the formation of different products. Short column chromatography of the reaction mixture from the (1*R*)-stannane (**8**) gave a single major product identified as the (3*S*,4*S*)-4-hydroxy-3-methyl-*cis*-1,2-enol ether (**16**) (81%), together with a small amount (1—2%) of the analogous ketone formed by adventitious oxidation of the initially formed alcohol. In contrast chromatography of the product mixture obtained from the (1*S*)-stannane (**9**) gave a single product identified as the (3*R*,4*R*)-adduct (**18**) (67%). The two major products (**16**) and (**18**) could be clearly distinguished by $^1$H n.m.r. spectroscopy, with the $OCH_2O$ and vinylic protons being particularly useful in this respect, and examination of the crude reaction mixtures from these reactions showed that no appreciable cross-over had occurred, only the (3*S*,4*S*)-diastereoisomer (**16**) being obtained from the (1*R*)-stannane (**8**) and only the (3*R*,4*R*)-diastereoisomer (**18**) being obtained from the (1*S*)-stannane (**9**) (sensitivity 2—3%).

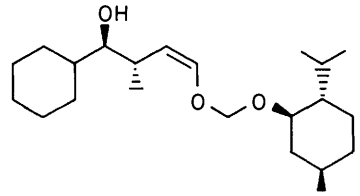
Structures were assigned to the products from these reactions on the basis of spectroscopic data with the stereochemical assignments shown being established by conversion of the adducts (**16**) and (**18**) into the enantiomeric hydroxy esters (**22**) and (**25**) whose absolute configurations were established by correlation with pseudoephedrine. Thus ozonolysis of the enol ethers (**16**) and (**18**), followed by a dimethyl sulphide work-up, oxidation ($Ag_2O$), and esterification ($CH_2N_2$) gave the esters (**22**) and (**25**), respectively (40% overall). The enantiomeric excesses of each of these esters was >90% as measured by optical rotation,[7] and by conversion into (−)-methoxy(trifluoromethyl)phenylacetyl [(−)-MTPA] derivatives (**23**) and (**26**), but in each case a small amount of racemization (2—3%) was detected. This was unexpected since the starting enol ethers (**16**) and (**18**) appeared to be single diastereoisomers within the limits of detection by $^1$H n.m.r. (300 MHz) spectroscopy, and the optical purity of the menthol used was high (>98%) as judged by conversion into its [(−)-MTPA] derivative. This inconsistency was resolved when it was found that the (−)-MTPA derivative (**19**) of enol ether (**16**) gave, after ozonolysis, oxidation, and esterification, the ester (**23**) containing <1% of the other isomer (**26**). This showed that the small amount of C(3)–C(4) equilibration observed earlier had occurred during the ozonolysis or subsequent steps, perhaps *via* reversible aldol equilibration.

To assign absolute configurations to the hydroxy esters (**22**) and (**25**), the corresponding (−)-hydroxy acid, readily available by cinchonidine resolution[7] of the racemic acid,[8] was converted into (−)-pseudoephedrine (**28**) by a Schmidt rearrangement and reduction. (−)-Pseudoephedrine (**28**) is known[9] to have the absolute configuration shown so establishing the absolute configuration of the (−)-acid as that in formula (**20**). Esterification of the (−)-acid (**20**) with diazomethane gave the (−)-ester (**22**), which in turn had been obtained from the enol ether derived from the (1*R*)-stannane (**8**).




This correlation established that the enol ether obtained using the (1*R*)-stannane had the stereochemistry shown in formula (**16**) with the diastereoisomeric adduct from the (1*S*)-stannane being (**18**). Thus these reactions had taken place with the stereoselectivity predicted in the Scheme. The (1*R*)-alkoxybut-2-enylstannane (**8**) had reacted selectively with benzaldehyde *via* *Si*-facial attack, and the (1*S*)-isomer (**9**) had reacted selectively *via* *Re*-facial attack. No epimerization at C-1 of these stannanes had taken place during the course of these reactions.

Similar stereoselectivity was observed with other aldehydes. The (1*R*)-stannane (**8**) reacted stereoselectively on heating with excesses of cyclohexanecarbaldehyde and cinnamaldehyde to produce adducts (**29**) (80%) and (**30**) (68%). The stereochemistry of these products was assigned by analogy with the benzaldehyde series, and the structure of the cyclohexanecarbaldehyde adduct (**29**) was confirmed by ozonolysis, oxidation, and esterification which gave the (−)-hydroxy ester (**31**) whose absolute configuration had been assigned by Meyers.[10] The optical purity



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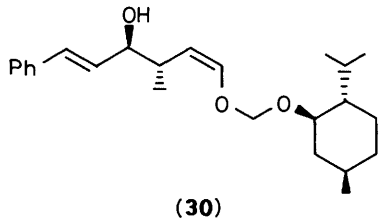

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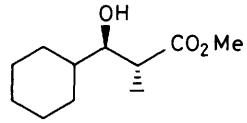
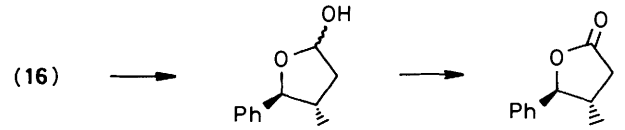


(31)

of the ester (**31**) was shown to correspond to an e.e. of 93% by $^1$H n.m.r. in the presence of the chiral shift reagent Eu(hfc)$_3$.*

Finally the (3*S*,4*S*)-enol ether (**16**) was hydrolysed using aqueous HCl, and the resulting lactol (**32**) oxidized using pyridinium chlorochromate buffered with sodium acetate to provide the *trans*-4-methyl-5-phenylbutyrolactone (**33**). This was identical with a sample prepared earlier,[1] but was found to be racemic. The mechanism of this racemization was not investigated but may have occurred at the oxidation stage.



(**16**) (**32**) (±)-(**33**)

The extremely efficient enantiofacial selectivity exhibited by the tin reagents (**8**) and (**9**) suggests that such α-substituted allylstannanes may be useful in asymmetric synthesis. However the high temperatures required for their thermal reactions with the aldehydes so far investigated, limits their application. If catalytic procedures could be found which enabled the reactions to be carried out under milder conditions without altering their stereoselectivity, then wide use of these reagents could be expected.[11,12]

## Experimental

For general experimental details see the preceding paper. Chloromethyl menthyl ether (**7**) was prepared by bubbling gaseous HCl through a solution of (−)-menthol (**6**) (25.6 g, 164 mmol) and 1,3,5-trioxane (5.7 g, 63 mmol) in dichloromethane (50 ml) containing $MgSO_4$ (45 g) for 8 h. After filtration and concentration under reduced pressure, distillation of the residue gave the desired ether (**7**) (17.8 g, 54%), b.p. 82—84 °C (0.8 mmHg) [lit.[4] b.p. 78—80 °C (0.5 mmHg)]. Pentan-2-ol was resolved by recrystallization of its mandelate esters.[13] Treatment of (±)-pentan-2-ol with (*R*)-mandelic acid in the presence of a trace of toluene-*p*-sulphonic acid in benzene heated under reflux with a Dean–Stark trap, gave a mixture of diastereoisomeric esters. Recrystallization of this mixture gave (2*R*,2′*S*)-pentan-2′-yl 2-hydroxyphenylacetate, m.p. 48—49 °C (lit.,[13] 52—53 °C); $[\alpha]_D^{20}$ +118 ° (*c* 1 in $CHCl_3$). Saponification of this ester using KOH gave (2*S*)-pentan-2-ol (**15**); b.p. 118 °C (lit.,[14] 118.5—119.5 °C); $[\alpha]_D^{20}$ +13.5° (*c* 1.3 in EtOH) {lit.[14] $[\alpha]_D^{20}$ +16.1° (neat)}. The (2*R*)-pentan-2-ol (**14**) was similarly prepared using (*S*)-mandelic acid, and had $[\alpha]_D^{20}$ −14.6° (*c* 1.26 in EtOH). (2*RS*,3*SR*)-3-Hydroxy-2-methylpropionic acid[8] was partially resolved by recrystallization of its cinchonidine salt, $[\alpha]_D^{20}$ −84° (*c* 0.085 in EtOH) {lit.[7] $[\alpha]_D^{25}$ −87.6° (*c* 0.083 in EtOH)}; m.p. 159—163 °C (lit.[7] 170—172 °C). This gave the (2*R*,3*S*)-acid (**20**), a white powder; $[\alpha]_D^{20}$ −12.8° (*c* 0.094 in EtOH) {lit.[7] $[\alpha]_D^{20}$ −19.7° (*c* 0.094 in EtOH)}; m.p. 96—97 °C (lit.[7] 106—107 °C).

(2E,2′S)-1-[*Methoxy(trifluoromethyl)phenylacetoxy*]*but*-2-*enyl(tributyl)stannanes* (**4**) *and* (**5**).—(*S*)-Methoxy(trifluoromethyl)phenylacetyl chloride (631 mg, 2.5 mmol) in dichloromethane (2.5 ml) was added to a solution of the stannylbutenol (**3**) (0.9 g, 2.5 mmol), triethylamine (0.53 ml, 3.8 mmol), and 4-*N*,*N*-dimethylaminopyridine (30 mg, 0.25 mmol), in dichloromethane (20 ml) at 0 °C, and the mixture stirred under an atmosphere of argon. After 2.5 h, the mixture was partitioned between dichloromethane (25 ml) and ice-cold 0.5M aqueous HCl (25 ml). The dichloromethane layer was washed with water (25 ml) and saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure to leave a yellow oil. Flash chromatography using ether–light petroleum (2:98) as eluant gave a mixture of the 1-acetoxystannanes (**4**) and (**5**) (1.31 g, 91%). The less polar diastereoisomer was separated by short column chromatography using ethyl acetate–light petroleum (2:98) as eluant; $\nu_{max.}$(film) 1 762, 1 665, 1 595, 1 451, 1 342, 1 260, 1 173, 1 022, 807, 767, 723, and 700 cm$^{-1}$; $\delta_H$ 0.77—1.60 (27 H, m, 3 × Bu), 1.70 (3 H, d, *J* 6 Hz, CH*Me*), 3.57 (3 H, narrow d, *J* ≈ 1 Hz, OMe), 5.47 (1 H, m, vinylic H), 5.63—5.77 (2 H, m, vinylic H + 1-H), 7.4 (3 H, m, aromatic H), and 7.56 (2 H, m, aromatic H); *m*/*z* (e.i.) 467 ($M^+$ − 111, 3%). Samples enriched in the more polar diastereoisomer showed $\nu_{max.}$(film) 1 760, 1 658, 1 595, 1 341, 1 261, 1 171, 1 123, 1 023, 806, 767, 721, and 699 cm$^{-1}$; $\delta_H$ 0.84—1.53 (27 H, m, 3 × Bu), 1.66 (3 H, d, *J* 6 Hz, CH*Me*), 3.52 (3 H, narrow d, *J* 1 Hz, OMe), 5.35 (1 H, m, vinylic H), 5.59—5.71 (2 H, m, vinylic H + 1-H), 7.4 (3 H, m, aromatic H), and 7.53 (2 H, m, aromatic H); *m*/*z* (e.i.) 467 ($M^+$ − 111, 3%).

(2E,1R,1′R,2′S,5′R)- *and* (2E,1S,1′R,2′S,5′R)-1-(2-*Isopropyl*-5-*methylcyclohexyloxymethoxy*)*but*-2-*enyl(tributyl)stannanes* (**8**) *and* (**9**).—Di-isopropylethylamine (21 ml, 0.12 mol) and chloromethyl menthyl ether (10.36 ml, 50 mmol) were added to a solution of the crude stannylbutenol (**3**) (17.2 g, 48 mmol) in dichloromethane (100 ml) at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 2 h and then at room temperature for 2 h. After being poured into light petroleum (750 ml), the mixture was washed with ice-cold 0.5M aqueous HCl (250 ml), water (250 ml), and saturated aqueous $NaHCO_3$ (250 ml), dried ($MgSO_4$) and concentrated under reduced pressure to leave a pale yellow oil. Flash chromatography using light petroleum–benzene (5:1) as eluant gave a mixture of the alkoxymethoxystannanes (**8**) and (**9**) (14.2 g, 59%). Repeated chromatography separated the two isomers to provide the less polar component identified as the *title compound* (**8**), a colourless oil (Found: C, 60.9; H, 10.4. $C_{27}H_{54}O_2Sn$ requires C, 61.2; H, 10.3%); $[\alpha]_D^{20}$ +12.1° (*c* 1.95 in $CHCl_3$); $\nu_{max.}$(film) 1 455, 1 373, 1 145, 1 092, 1 009, 981, and

* Tris[3-(heptafluoropropylhydroxymethylene)camphorato]europium (III) derivative.

962 cm$^{-1}$; $\delta_H$ 0.76 (3 H, d, *J* 6 Hz, CH*Me*), 0.8—1.73 (43 H, complex m), 2.06—2.29 (2 H, m, 2 × CH), 3.28 (1 H, dt, *J* 4, 10.5 Hz, 1′-H), 4.58 (1 H, d, *J* 6.5 Hz, OHC*H*O), 4.63 (1 H, br d, *J* 8 Hz, 1-H), 4.81 (1 H, d, *J* 6.5 Hz, O*H*CHO), and 5.36 and 5.52 (each 1 H, m, vinylic H); *m/z* (e.i.) 473 ($M^+ - 57$, 2%). The more polar component was identified as the *title compound* (**9**), a colourless oil; $[\alpha]_D^{20}$ −91.1° (*c* 0.83 in $CHCl_3$); $\nu_{max.}$($CCl_4$) 1 660, 1 451, 1 376, 1 180, 1 010, 909, and 680 cm$^{-1}$; $\delta_H$ 0.79 (3 H, d, *J* 7 Hz, CH*Me*), 0.82—1.74 (43 H, complex m), 2.11—2.27 (2 H, m, 2 × CH), 3.33 (1 H, dt, *J* 4, 10.5 Hz, 1′-H), 4.59 (1 H, br d, *J* 8.5 Hz, 1-H), 4.65 and 4.75 (each 1 H, d, *J* 6.5 Hz, OHC*H*O), and 5.40 and 5.58 (each 1 H, m, vinylic H); *m/z* (e.i.) 473 ($M^+ - 57$, 2%).

(1R,1′R,2′S,5′R)- *and* (1S,1′R,2′S,5′R)-1-(2-*Isopropyl*-5-*methylcyclohexyloxymethoxy*)*butyl*(*tributyl*)*stannanes* (**10**) *and* (**12**).—Anhydrous sodium acetate (381 mg, 4.6 mmol) and toluene-*p*-sulphonohydrazide (860 mg, 3.3 mmol) were added to a solution of the (1*R*)-stannane (**8**) (324 mg, 0.6 mmol) in ethanol (20 ml), and the mixture was heated at reflux, under an argon atmosphere, for 2 h. Concentration under reduced pressure gave a residue which was partitioned between light petroleum (25 ml) and water (25 ml). The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue using ether–light petroleum (2:98) gave the *title compound* (**10**) (266 mg, 82%) as a colourless oil, $[\alpha]_D^{20}$ −58.3° (*c* 1.2 in $CHCl_3$); $\nu_{max.}$(film) 1 452, 1 375, 1 142, and 1 029 cm$^{-1}$; $\delta_H$($CDCl_3$) 0.75—1.87 (50 H, complex m), 2.07—2.30 (2 H, m, 2 × CH), 3.33 (1 H, dt, *J* 4, 10.5 Hz, 1′-H), 4.18 (1 H, t, *J* 7 Hz, 1-H), and 4.53 and 4.86 (each 1 H, d, *J* 7 Hz, O*H*CHO); *m/z* (e.i.) 475 ($M^+ - 57$, 6%). Following the above procedure the (1*S*)-stannane (**9**) (476 mg, 0.9 mmol) was treated with sodium acetate (561 mg, 6.8 mmol) and toluene-*p*-sulphonohydrazide (1.26 g, 4.8 mmol) to provide the *title compound* (**12**) (358 mg, 75%) as a colourless oil: $[\alpha]_D^{20}$ ≈0° (*c* 1.38 in $CHCl_3$); $\nu_{max.}$(film) 1 450, 1 369, 1 139, and 1 020 cm$^{-1}$; $\delta_H$ 0.78 (3 H, d, *J* 7 Hz, CH*Me*), 0.85—1.9 (47 H, complex m), 2.05—2.3 (2 H, m, 2 × CH), 3.25 (1 H, dt, *J* 4, 10.5 Hz, 1′-H), 4.14 (1 H, t, *J* 7 Hz, 1-H), and 4.67 and 4.68 (each 1 H, d, *J* 7 Hz, O*H*CHO); *m/z* (e.i.) 475 ($M^+ - 57$, 12%).

(2R,1′R,2′S,5′R)- *and* (2S,1′R,2′S,5′R)-2-(2-*Isopropyl*-5-*methylcyclohexyloxymethoxy*)*pentanes* (**11**) *and* (**13**).—*From alkylstannanes* (**10**) *and* (**12**). Butyl-lithium (0.21 ml of a 2.2M solution in hexane, 0.46 mmol) was added to a stirred solution of the (1*R*)-stannane (**10**) (245 mg, 0.46 mmol) in THF (3 ml) under argon at −78 °C. After 5 min, dimethyl sulphate (0.43 ml, 4.6 mmol) was added, and the reaction mixture stirred at −78 °C for 1.75 h before being quenched by the addition of water (1 ml) and warmed to room temperature. The mixture was partitioned between light petroleum and water, and the organic phase separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residual oil was flash chromatographed using ether–light petroleum (1:50) as eluant to give the *title compound* (**11**) (93 mg, 79%) as a colourless oil; $[\alpha]_D^{20}$ −80.2° (*c* 1.1 in $CHCl_3$) (Found: C, 74.8; H, 12.5. $C_{16}H_{32}O_2$ requires C, 74.95; H, 12.6%); $\nu_{max.}$(film) 1 448, 1 365, 1 143, 1 087, 1 030, 905, and 835 cm$^{-1}$; $\delta_H$ 0.78 (3 H, d, *J* 7 Hz, CH*Me*), 0.92 (6 H, overlapping d, *J* 7 Hz, 2 × CH*Me*), 0.84—1.75 (14 H, complex m), 1.17 (3 H, d, *J* 7 Hz, CH*Me*), 2.05—2.30 (2 H, m, 2 × C*H*), 3.35 (1 H, dt, *J* 4, 10.5 Hz, 1′-H), 3.76 (1 H, m, 2-H), and 4.73 and 4.83 (each 1 H, d, *J* 7 Hz, O*H*CHO); *m/z* (c.i.) 274 ($M^+ + 18$, 100%). Similarly the (1*S*)-stannane (**12**) (168 mg, 0.32 mmol) was treated with butyl-lithium (0.15 ml of a 2.2M solution in hexane, 0.32 mmol) and dimethyl sulphate (0.3 ml, 3.2 mmol) to give, after chromatography, the *title compound* (**13**) (48 mg, 59%), a colourless oil: $[\alpha]_D^{20}$ −69.2° (*c* 0.76 in $CHCl_3$) (Found: C, 74.8; H, 12.6%); $\nu_{max.}$(film) 1 460, 1 448, 1 378, 1 140, 1 082, and 1 028 cm$^{-1}$; $\delta_H$ 0.8 (3 H, d, *J* 7 Hz, CH*Me*), 0.91 (6 H, d, *J* 7 Hz, 2 × CH*Me*), 1.16 (3 H, d, *J* 7 Hz, CH*Me*), 0.84—1.74 (14 H, complex m), 2.05—2.3 (2 H, m), 3.35 (1 H, dt, *J* 4, 10.5 Hz, 1′-H), 3.77 (1 H, m, 2-H), and 4.69 and 4.85 (each 1 H, d, *J* 7 Hz, O*H*CHO); *m/z* (c.i.) 274 ($M^+ + 18$, 100%).

*From* (2R)- *and* (2S)-*pentan*-2-*ols* (**14**) *and* (**15**). (2*R*)-Pentan-2-ol (**14**) (250 mg, 2.8 mmol) and chloromethyl menthyl ether (727 mg, 3.6 mmol) were dissolved in dichloromethane (6 ml) at 0 °C, and di-isopropylethylamine (1.19 ml, 6.8 mmol) was added. After stirring at 0 °C for 2 h, and for 2 h at room temperature, the mixture was poured into light petroleum (10 ml), and washed with ice-cold 0.5M aqueous HCl, water, and saturated aqueous $NaHCO_3$. The solution was then dried ($MgSO_4$) and concentrated under reduced pressure, the residue being flash chromatographed using ether–light petroleum (5:95) as eluant to give the (2*R*)-compound (**11**), (442 mg, 61%); $[\alpha]_D^{20}$ −79.9° (*c* 0.9 in $CHCl_3$). (2*S*)-Pentan-2-ol (**15**) (121 mg, 1.4 mmol) was similarly converted into the (2*S*)-derivative (**13**) (47 mg, 13%); $[\alpha]_D^{20}$ −78° (*c* 1.1 in $CHCl_3$).

*Reactions between But*-2-*enylstannanes* (**8**) *and* (**9**) *and Benzaldehyde*.—A mixture of the (1*R*)-alkoxybut-2-enylstannane (**8**) (102 mg, 0.19 mmol) and benzaldehyde (98 μl, 1 mmol) was heated at 130 °C for 14.5 h under an atmosphere of argon. Short-column chromatography of the residue using ether–light petroleum (1:5) as eluant gave (3S,4S,1′R,2′S,5′R,1Z)-4-*hydroxy*-1-(2-*isopropyl*-5-*methylcyclohexyloxymethoxy*)-3-*methyl*-4-*phenylbut*-1-*ene* (**16**) (53 mg, 81%), as a colourless oil; $[\alpha]_D^{20}$ −129.2° (*c* 1.03 in $CHCl_3$); (Found: C, 76.1; H, 10.0. $C_{22}H_{34}O_3$ requires C, 76.3; H, 9.9%); $\nu_{max.}$(film) 3 435, 3 028, 1 665, 1 451, 1 384, 1 110, 1 030, 908, 840, 760, 745, and 700 cm$^{-1}$; $\delta_H$ 0.75, 0.78, 0.91, and 0.96 (each 3 H, d, *J* 7 Hz, CH*Me*), 0.8—1.68 (8 H, complex m), 2.1—2.4 (2 H, m, 2 × CH), 2.98 (1 H, m, 3-H), 3.42 (1 H, dt, *J* 4, 10.5 Hz, 1′-H), 4.29 (1 H, br d, *J* 8.5 Hz, 4-H), 4.39 (1 H, dd, *J* 6, 9.5 Hz, 2-H), 4.85 and 5.02 (each 1 H, d, *J* 7 Hz, O*H*CHO), 6.38 (1 H, d, *J* 6 Hz, 1-H), and 7.27—7.40 (5 H, m, aromatic H); *m/z* (c.i.) 329 ($M^+ - 17$, 6%). In some cases a small amount (*ca.* 5%) of a second product was isolated, this product being identified as (2S,1′R,2′S,5′R,3Z)-4-(2-*isopropyl*-5-*methylcyclohexyloxymethoxy*)-2-*methyl*-1-*phenylbut*-3-*en*-1-*one* (**17**), a colourless oil; $[\alpha]_D^{20}$ +120.5° (*c* 0.81 in $CHCl_3$); $\nu_{max.}$(film) 1 688, 1 598, 1 447, 1 378, 1 243, 1 207, 1 170, 1 150, 1 127, 1 108, 1 030, 970, and 699 cm$^{-1}$; $\delta_H$ 0.78, 0.87, and 0.93 (each 3 H, d, *J* 7 Hz, CH*Me*), 1.28 (3 H, d, *J* 6 Hz, 2-Me), 0.9—1.7 (7 H, complex m), 2.02—2.20 (2 H, m, 2 × CH), 3.42 (1 H, dt, *J* 4, 10.5 Hz, 1′-H), 4.51—4.61 (2 H, m, 2-H and 3-H), 4.87 and 5.06 (each 1 H, d, *J* 7 Hz, OHC*H*O), 6.24 (1 H, d, *J* 5.5 Hz, 4-H), 7.42—7.57 (3 H, m, aromatic H), and 8.07 (2 H, m, aromatic H); *m/z* (e.i.) 326 ($M^+ - 18$, 0.25%).

A mixture of the (1*S*)-alkoxybut-2-enylstannane (**9**) (110 mg, 0.21 mmol) and benzaldehyde (0.3 ml, 2.9 mmol) was heated at 130 °C for 14 h under an atmosphere of argon. Flash chromatography using ether–light petroleum (1:5) as eluant gave (3R,4R,1′R,2′S,5′R,1Z)-4-*hydroxy*-1-(2-*isopropyl*-5-*methylcyclohexyloxymethoxy*)-3-*methyl*-4-*phenylbut*-1-*ene* (**18**) (48 mg, 67%), a colourless oil; $[\alpha]_D^{20}$ −2.0° (*c* 0.7 in $CHCl_3$); $\nu_{max.}$ 3 550, 3 005, 1 661, 1 451, 1 031, and 699 cm$^{-1}$; $\delta_H$ 0.77—1.71 (20 H, complex m), 2.07—2.22 (2 H, m, 2 × CH), 3.03 (1 H, m, 3-H), 3.39 (1 H, dt, *J* 4, 10.5 Hz, 1′-H), 4.32 (1 H, d, *J* 8.5 Hz, 4-H), 4.42 (1 H, dd, *J* 6.5, 9.5 Hz, 2-H), 4.87 and 5.01 (each 1 H, d, *J* 7 Hz, O*H*CHO), 6.37 (1 H, d, *J* 6.4 Hz, 1-H), and 7.24—7.49 (5 H, m, aromatic H).

*Methyl* (2R,3S)-3-*Hydroxy*-2-*methyl*-3-*phenylpropionate* (**22**).—Ozone was bubbled through a solution of the enol ether (**16**) (106 mg, 0.3 mmol) in methanol (3 ml) and dichloromethane (0.5 ml) for 1 h at −78 °C. Excess of ozone was

discharged by bubbling oxygen through the solution after which dimethyl sulphide (150 μl, 3 mmol) was added, and the solution warmed to 20 °C. After 2.5 h, the mixture was concentrated under reduced pressure and the residue taken up in ethanol (1.5 ml). *A solution* of $AgNO_3$ (80 mg, 0.47 mmol) in water (1 ml) was added, followed by a solution of NaOH (80 mg, 2 mmol) in water (3 ml). After 3 h the mixture was filtered, and the filtrate extracted with ether, acidified to pH 1 using 3M aqueous HCl, and re-extracted with ether. The second ether extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to give (2*R*,3*S*)-3-hydroxy-2-methyl-3-phenylpropionic acid (**20**) which was spectroscopically identical with an authentic sample of the racemic compound.[1] An excess of a solution of diazomethane in ether was added to a solution of the acid (**20**) in ether at 0 °C, and after 5 min, the excess of diazomethane was quenched using glacial acetic acid. Saturated aqueous $NaHCO_3$ (50 ml) was added, the layers separated, and the aqueous layer extracted with ether (3 × 25 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave methyl (2*R*, 3*S*)-3-hydroxy-2-methyl-3-phenylpropionate (**22**) (41 mg, 70% overall) which was purified by flash chromatography using ether–light petroleum (gradient elution) as eluant. The chromatographed ester had $[\alpha]_D^{25}$ −52.4° (*c* 1.26 in $CHCl_3$) {lit. $[\alpha]_D^{25}$ −57.1° (*c* 0.123 in $CHCl_3$)}, and was spectroscopically identical with an authentic sample of the racemic ester.[1]

A solution of the methyl ester (**22**) (3 mg), (*S*)-methoxy(trifluoromethyl)phenylacetyl chloride (30 mg), and pyridine (25 μl) in $CCl_4$ was stirred for *ca.* 15 h at 20 °C. The mixture was diluted with ether (10 ml), washed with 3M aqueous HCl, saturated aqueous $NaHCO_3$, and water, and dried. Concentration under reduced pressure and flash chromatography gave *methyl* (2R,3S,2′S)-3-[*methoxy*(*trifluoromethyl*)*phenylacetoxy*]-2-*methyl*-3-*phenylpropionate* (**23**), a white solid, m.p. 70—70.5 °C; $[\alpha]_D^{20}$ −68.3° (*c* 0.185 in $CHCl_3$) (Found: C, 61.5; H, 5.1. $C_{21}H_{21}F_3O_5$ requires C, 61.5; H, 5.2%); $\nu_{max.}$($CCl_4$) 3 080, 3 040, 1 756, 1 460, 1 193, 1 177, 1 125, 1 015, and 700 $cm^{-1}$; $\delta_H$ 0.88 (3 H, d, *J* 7.5 Hz, CH*Me*), 2.99 (1 H, m, 2-H), 3.33 (3 H, d, *J* 1.5 Hz, OMe), 3.46 (3 H, s, $CO_2Me$), 5.99 (1 H, d, *J* 10.5 Hz, 3-H), and 7.15—7.40 (10 H, m, aromatic H); *m*/*z* (e.i.) 379 ($M^+$ − 31, 5%).

A sample of authentic methyl (2*RS*,3*SR*)-3-hydroxy-2-methyl-3-phenylpropionate (**22**)/(**25**) was similarly treated with (*S*)-methoxy(trifluoromethyl)phenylacetyl chloride to provide a 1:1 mixture of the diastereoisomeric esters (**23**) and (**26**). Comparison of this mixture with the crude product from esterification of the sample of the hydroxy ester (**22**) prepared by ozonolysis of the enol ether (**16**) showed that approximately 3—4% of the unwanted diastereoisomer (**26**) was present. Treatment of (−)-(2*R*,3*S*)-3-hydroxy-2-methyl-3-phenylpropionic acid (**20**) obtained by the cinchonidine resolution outlined above, with an excess of diazomethane gave the (2*R*,3*S*)-methyl ester (**22**); $[\alpha]_D^{20}$ −47.7° (*c* 0.145 in $CHCl_3$).

*Methyl* (2S,3R)-3-*Hydroxy*-2-*methyl*-3-*phenylpropionate* (**25**).—The enol ether (**18**) (35 mg, 0.1 mmol) was ozonolysed, oxidised, and esterified using the procedure described above to provide the methyl (2*S*,3*R*)-3-hydroxy-2-methyl-3-phenylpropionate (**25**) (8 mg, 42% overall); $[\alpha]_D^{20}$ +46.6° (*c* 0.206 in $CHCl_3$); spectroscopically identical with an authentic sample of the racemic compound. A sample of this (+)-methyl ester (3 mg) was condensed with (*S*)-methoxy(trifluoromethyl)phenylacetyl chloride (25 mg) as described above to provide methyl (2*S*,3*R*,2′*S*)-3-[methoxy(trifluoromethyl)phenylacetoxy]-2-methyl-3-phenylpropionate (**26**); $\delta_H$ 0.90 (3 H, d, *J* 7.5 Hz, CH*Me*), 2.9—3.05 (1 H, m, 2-H), 3.37 (3 H, d, *J* 1.5 Hz, OMe), 3.62 (3 H, s, $CO_2Me$), 5.93 (1 H, d, *J* 10.5 Hz, 3-H), and 7.15—7.40 (10 H, m, aromatic H). Comparison of the crude product from this reaction with that obtained from the (2*R*,3*S*)-ester (**22**), showed that *ca.* 2% of ester (**23**) was present.

*Conversion of* (2R,3S)-3-*Hydroxy*-2-*methyl*-3-*phenylpropionic Acid* (**20**) *into* (1R,2R)-*Pseudoephedrine* (**28**).—A sample of the laevorotatory acid (**20**) obtained from the cinchonidine resolution (868 mg, 4.82 mmol), triethylamine (0.7 ml, 5.03 mmol), and diphenylphosphoryl azide (1.03 ml, 4.78 mmol), were heated under reflux in benzene (30 ml) for 40 h. After cooling, the reaction mixture was washed with water, saturated aqueous $NaHCO_3$, 1% aqueous HCl, and brine, dried ($MgSO_4$), and concentrated under reduced pressure, to give the urethane (**27**) (841 mg, 99%). Recrystallization from benzene–light petroleum gave the (4*R*,5*R*)-4-methyl-5-phenyloxazolidin-2-one (**27**) as a crystalline solid; m.p. 115—118 °C (lit.,[15] 117.5—119 °C); $[\alpha]_D^{20}$ −15.9° (*c* 0.38 in $CHCl_3$) {lit.,[15] $[\alpha]_D^{20}$ +25.9° (*c* 0.34 in $CHCl_3$) for the (4*S*,5*S*)-enantiomer}. A solution of the oxazolidin-2-one (**27**) (300 mg, 1.69 mmol) in THF (6 ml) was added dropwise to a suspension of $LiAlH_4$ (140 mg, 3.69 mmol) in THF (10 ml) under an atmosphere of argon. The mixture was heated under reflux for 14 h, cooled, and quenched cautiously with water (0.14 ml), 15% aqueous NaOH (0.14 ml), and water (0.42 ml). After filtration, the filtrate was concentrated under reduced pressure to give (1*R*,2*R*)-2-methylamino-1-phenylpropan-1-ol (**28**) as white needles, m.p. 116—119.5 °C (from light petroleum–benzene) (lit.,[16] 118—118.5 °C); $[\alpha]_D^{20}$ −45.3° (*c* 0.97 in EtOH) {lit.[16] $[\alpha]_D^{20}$ −52° (EtOH)}.

(3S,4R,1′R,2′S,5′R,1Z)-4-*Cyclohexyl*-4-*hydroxy*-1-(2-*isopropyl*-5-*methylcyclohexyloxymethoxy*)-3-*methylbut*-1-*ene* (**29**).—A mixture of the but-2-enylstannane (**8**) (188 mg, 0.35 mmol) and cyclohexanecarbaldehyde (0.4 ml, 3.1 mmol) was heated under an atmosphere of argon for 38 h at 130 °C with additional amounts (0.15 ml) of aldehyde being added after 15 and 25 h. Flash chromatography of the reaction mixture using light petroleum–diethyl ether (gradient elution) gave the *title compound* (**29**) (97 mg, 79%) as a colourless oil; $[\alpha]_D^{20}$ −60.1° (*c* 1.23 in $CHCl_3$) (Found: C, 74.75; H, 11.55. $C_{22}H_{40}O_3$ requires C, 74.95; H, 11.45%); $\nu_{max.}$(film) 3 460, 1 665, 1 449, 1 384, 1 110, 1 032, 984, 909, and 736 $cm^{-1}$; $\delta_H$ 0.75 (3 H, d, *J* 7 Hz, CH*Me*), 0.8—1.84 (19 H, complex m), 0.91 (6 H, 2 overlapping d, *J* 7 Hz, 2 × CH*Me*), 0.98 (3 H, d, *J* 7 Hz, CH*Me*), 2.05—2.19 (2 H, m), 2.85 (1 H, m, 3-H), 3.09 (1 H, t, *J* 5.5 Hz, 4-H), 3.39 (1 H, dt, *J* 4.5, 10.5 Hz, 1′-H), 4.36 (1 H, dd, *J* 6.5, 9.5 Hz, 2-H), 4.81 and 4.98 (each 1 H, d, *J* 7 Hz, O*H*CHO), and 6.27 (1 H, d, *J* 6.5 Hz, 1-H); *m*/*z* (c.i.) 370 ($M^+$ + 18, 15%).

A sample of the enol ether (**29**) (75 mg, 0.21 mmol) was ozonolysed, oxidized, and treated with diazomethane as described above to give, after flash chromatography using ether–light petroleum (gradient elution) as eluant, the methyl (2*R*,3*R*)-3-cyclohexyl-3-hydroxy-2-methylpropionate (**31**) (15 mg, 36% overall), as a colourless oil; $[\alpha]_D^{20}$ −8.1° (*c* 0.9 in $CHCl_3$) {lit.,[10] $[\alpha]_D^{23}$ −8.1° (*c* 1.05 in $CHCl_3$)}; $^1H$ n.m.r. in the presence of *ca.* 15% mol equiv. Eu(hfc)$_3$ indicated an e.e. of 93%.

(3S,4R,1′R,2′S,5′R,1Z,5E)-4-*Hydroxy*-1-(2-*isopropyl*-5-*methylcyclohexyloxymethoxy*)-3-*methyl*-6-*phenylhexa*-1,5-*diene* (**30**).—A mixture of the but-2-enylstannane (**8**) (227 mg, 0.43 mmol) and cinnamaldehyde (0.27 ml, 2.1 mmol) was heated at 130 °C for 15 h under an atmosphere of argon. Flash chromatography using light petroleum–ether (5:1) as eluant then gave the *title compound* (**30**) (108 mg, 68%) as a colourless oil; $[\alpha]_D^{20}$ −50.7° (*c* 1.21 in $CHCl_3$); $\nu_{max.}$(film) 3 440, 3 020, 1 665, 1 600, 1 492, 1 448, 1 384, 1 108, 1 030, 965, 908, 841, 750, and 693 $cm^{-1}$; $\delta_H$ 0.76 (3 H, d, *J* 7 Hz, CH*Me*), 0.92 (6 H, overlapping d, *J* 7 Hz, 2 × CH*Me*), 1.0 (3 H, d, *J* 7 Hz, CH*Me*), 0.9—1.68 (8 H, complex m), 2.07—2.20 (2 H, m), 2.85 (1 H, m, 3-H), 3.43 (1 H, dt, *J* 4, 10.5 Hz, 1′-H), 4.01 (1 H, br t,

*J* 7 Hz, 4-H), 4.37 (1 H, dd, *J* 6.5, 9.5 Hz, 2-H), 4.85 and 5.02 (each 1 H, d, *J* 7 Hz, O*H*CHO), 6.23 (1 H, dd, *J* 7, 16 Hz, 5-H), 6.35 (1 H, d, *J* 6.5 Hz, 1-H), 6.61 (1 H, d, *J* 16 Hz, 6-H), and 7.21—7.42 (5 H, m, aromatic H); *m/z* (e.i.) 302 ($M^+ - 70$, 3%).

*Hydrolysis-oxidation of the Enol Ether* (**16**).—A solution of the enol ether (**16**) (77 mg, 0.22 mmol) in THF (1 ml) was stirred with 3M aqueous HCl (1 ml) for 24 h at 20 °C before being poured into brine (10 ml) and extracted into ether (3 × 10 ml). The ethereal extracts were dried ($MgSO_4$), and concentrated under reduced pressure to leave a pale yellow oil (67 mg). This oil was taken up in dichloromethane and pyridinium chlorochromate (240 mg, 0.87 mmol) and anhydrous NaOAc (15 mg, 0.2 mmol) were added. The mixture was stirred for 10 h at 20 °C, and then diluted with ether and filtered through a plug of silica. Flash chromatography using ether–light petroleum (gradient elution) as eluant gave the *trans*-4-methyl-5-phenyldihydrofuran-2(3*H*)-one (**33**) (17 mg, 44% overall), m.p. 51.5—52 °C; $[\alpha]_{889}^{20}$ 0.00°, $[\alpha]_{546}^{20}$ 0.00°, $[\alpha]_{365}^{20}$ 0.00° (all *c* 4.0 in $CHCl_3$); spectroscopically identical with a previously prepared sample of the racemic compound.[1]

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