Synthesis and Absolute Configuration of Optically Active *E*-1-Alkoxymethoxybut-2-enyl(tri-n-butyl)stannanes: Stereoselective Reactions with Aldehydes

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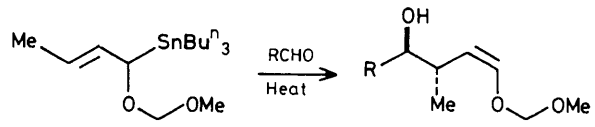
(1*R*)- and (1*S*)-1-[(−)-menthoxymethoxy]-*E*-but-2-enyl(tri-n-butyl)stannanes (**5**) and (**6**), whose configurations at C(1) were assigned by correlation with (2*R*)- and (2*S*)-pentan-2-ol, react stereoselectively on heating with benzaldehyde to give (3*S*,4*S*)- and (3*R*,4*R*)-4-hydroxy-3-methyl-*cis*-1,2-enol ethers (**11**) and (**13**), respectively.

(±)-*E*-1-Methoxymethoxybut-2-enyl(tri-n-butyl)stannane (**1**) reacts stereoselectively with aldehydes on heating to give (±)-*anti*-4-hydroxy-3-methyl-*cis*-1,2-enol ethers (**2**).[1]† We report here the preparation and characterization of optically active 1-[(−)-menthoxymethoxy]-*E*-but-2-enyl(tri-n-butyl)-stannanes (**5**) and (**6**) together with details of their reactions with aldehydes.

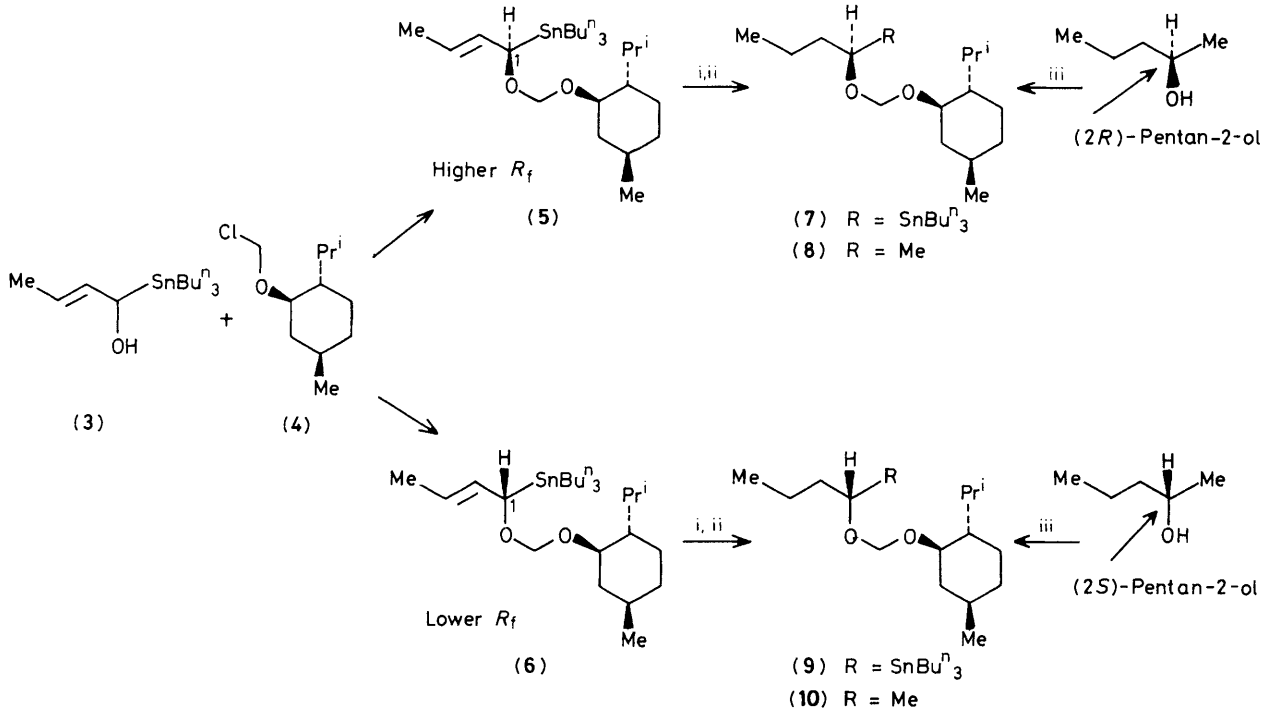
Chloromethyl (−)-menthyl ether (**4**)[3] was prepared by bubbling anhydrous HCl through a solution of (−)-menthol and trioxane in CH_2Cl_2 in the presence of anhydrous $MgSO_4$ (b.p. 82—84 °C at 0.8 mm Hg, 54%), and was added to a mixture of racemic stannol (**3**)[1] and di-isopropylethylamine in CH_2Cl_2 to give, after 2 h at 0 °C and 2 h at 20 °C, a mixture of the diastereoisomeric but-2-enylstannanes (**5**) and (**6**), isolated as a mixture by flash chromatography (59%). Careful short-column chromatography (eluted with 40/60 petroleum–benzene, 5:1) gave the (1*R*)-diastereoisomer (**5**), $[\alpha]_D^{20}$ +12.1° ($CHCl_3$), followed by the (1*S*)-diastereoisomer (**6**), $[\alpha]_D^{20}$ −91.1° ($CHCl_3$), which could be distinguished by t.l.c. and by high field (300 MHz) ^{1}H n.m.r. spectroscopy.‡



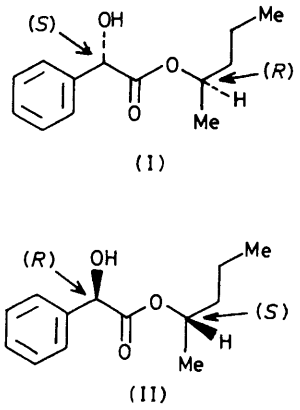
(**1**) (±)-(**2**)

† For the *syn–anti* nomenclature see the discussion by S. Masamune, ref. 2.

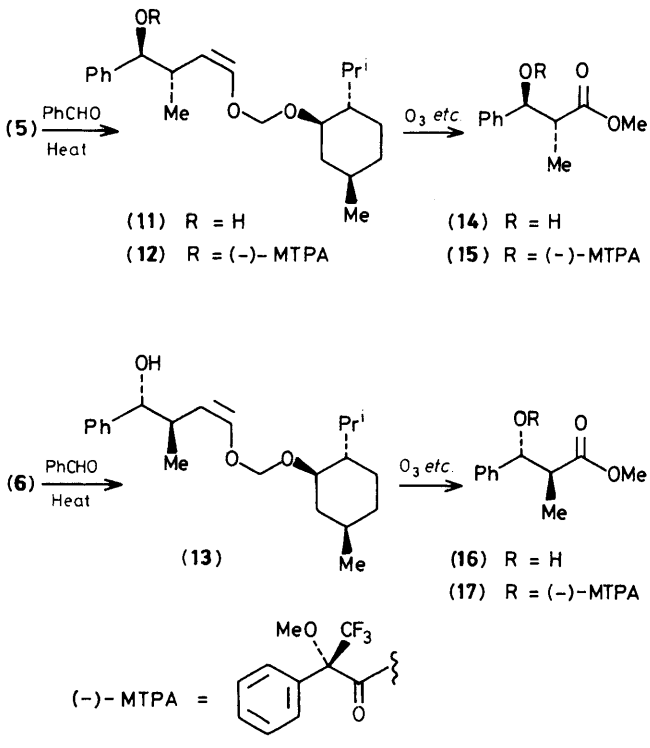
‡ New compounds were fully characterised spectroscopically and by combustion analysis whenever possible.



Scheme 1. *Reagents:* i, $TsNHNH_2$, NaOAc, EtOH; ii, Bu^nLi, tetrahydrofuran, −78 °C, 5 min, then Me_2SO_4, −78 °C, 1¾ h; iii, (**4**), Pr^i_2NEt, 0 °C, 2 h, then 20 °C, 2 h.



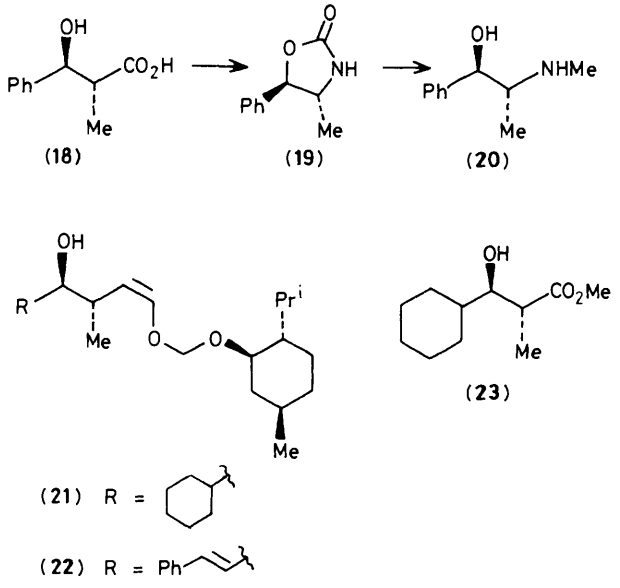
Absolute configurations at C(1) were assigned to stannanes (**5**) and (**6**) by correlation with (2*R*)- and (2*S*)-pentan-2-ol as shown in Scheme 1. Thus di-imide reduction of the higher R_f stannane, followed by transmetallation (Bu^nLi, −78 °C, 5 min) and methylation (Me_2SO_4, −78 °C, 1¾ h), a procedure known to involve retention of configuration,[4] gave the (2*R*)-pentan-2-ol derivative (**8**) which was also prepared from authentic (2*R*)-pentan-2-ol.[5]§ Similarly the lower R_f stannane was converted into the (2*S*)-pentan-2-ol derivative (**10**) which was also prepared from (2*S*)-pentan-2-ol. The pentan-2-ol

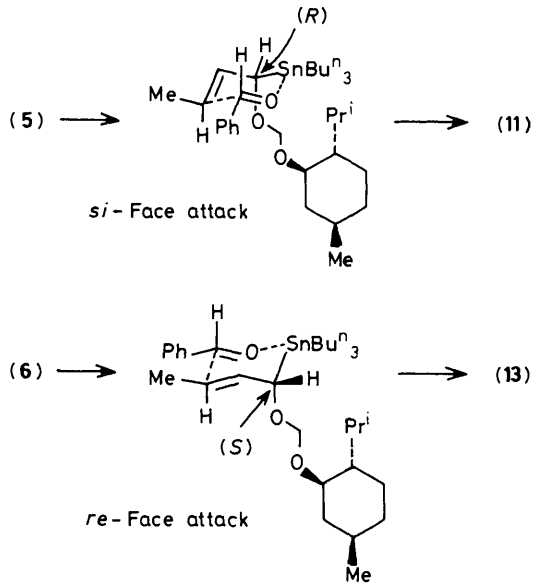


Scheme 2

derivatives (**8**) and (**10**) were clearly distinguished by high field (300 MHz) ^1H n.m.r. spectroscopy, and enabled configurational assignments to be made as shown.

§ (±)-Pentan-2-ol was resolved following the procedure of J. K. Whitesell (ref. 6). Using (*S*)-mandelic acid, the ester (I) of (2*R*)-pentan-2-ol crystallized out which gave (2*R*)-pentan-2-ol, $[\alpha]_D^{20}$ −13.5° ($CHCl_3$) (lit.[5] −16.1°), on hydrolysis. Ester (II) was obtained from (*R*)-mandelic acid.





Scheme 3

The menthoxymethoxystannanes (**5**) and (**6**) were then heated separately with an excess of benzaldehyde (130 °C, 15 h) under an argon atmosphere. The (1*R*)-isomer (**5**) gave the (3*S*,4*S*)-4-hydroxy-3-methyl-*cis*-1,2-enol ether (**11**), whereas the (1*S*)-isomer (**6**) gave the (3*R*, 4*R*)-enol ether (**13**), both isolated in 70—80% yields after flash chromatography. The diastereoisomers (**11**) and (**13**) could be distinguished by ^{1}H n.m.r. spectroscopy, and examination of the crude reaction mixtures showed that no appreciable crossover had occurred, only the (3*S*,4*S*)-isomer (**11**) being obtained from stannane (**5**), and only the (3*R*,4*R*)-isomer (**13**) being obtained from stannane (**6**); see Scheme 2.

Ozonolysis followed by a dimethyl sulphide work up, oxidation (Ag_2O), and esterification (CH_2N_2) of the enol ethers (**11**) and (**13**), gave the enantiomeric hydroxy-esters (**14**) and (**16**), respectively (40% overall). The enantiomeric excess of each of these esters exceeded 90% as measured by optical rotation,[7] and by conversion into their (−)-α-methoxy-α-(trifluoromethyl)phenylacetate [(−)-MTPA] derivatives (**15**) and (**17**).[8] Prior conversion of the enol ether (**11**) into its (−)-MTPA ester (**12**) followed by ozonolysis, oxidation, and esterification gave ester (**15**) with an enantiomeric excess of >98% so showing that the small amount of racemization observed earlier had occurred during the ozonolysis or subsequent steps perhaps *via* reversible aldol equilibration.

Absolute configurations were assigned to the hydroxy-esters by correlation with pseudoephedrine. Thus the (−)-hydroxy-acid, readily available by cinchonidine resolution[7] of the (±)-acid,[9] was found to have the absolute configuration shown in formula (**18**) since Schmidt rearrangement [$(PhO)_2P(O)N_3$] and reduction ($LiAlH_4$) gave (−)-pseudoephedrine (**20**) whose absolute configuration is known.[10] Esterification of the (−)-acid (**18**) with diazomethane gave the (−)-ester (**14**).

The selective transformations of benzaldehyde into *anti*-4-hydroxy-3-methyl-*cis*-1,2-enol ethers (**11**) and (**13**) using the optically active α-alkoxybut-2-enylstannanes (**5**) and (**6**), are consistent with the cyclic transition states shown in Scheme 3. The marked preference for the α-alkoxy group to adopt an axial position in each of these transition states[1,11] ensures that the (1*R*)- and (1*S*)-diastereoisomers (**5**) and (**6**) react selectively with the *si*- and *re*-faces of the benzaldehyde carbonyl group as shown.

Similar discrimination was observed with other aldehydes. Thus the (1*R*)-stannane (**5**) was heated with an excess of cyclohexanecarboxaldehyde and cinnamaldehyde to give adducts (**21**) (80%) and (**22**) (68%). The stereochemistry of these products was assigned by analogy with the benzaldehyde series, and was confirmed for the cyclohexanecarboxaldehyde adduct (**21**) by ozonolysis, oxidation, and esterification, which gave the (−)-hydroxy ester (**23**), $[\alpha]_D^{20}$ −8.1° ($CHCl_3$), the absolute configuration of which has been assigned by Meyers.[12]

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