On the Use of *E*-1-Methoxymethoxybut-2-enyl(tri-n-butyl)stannane as a *threo*-Selective, Homo-enolate Equivalent

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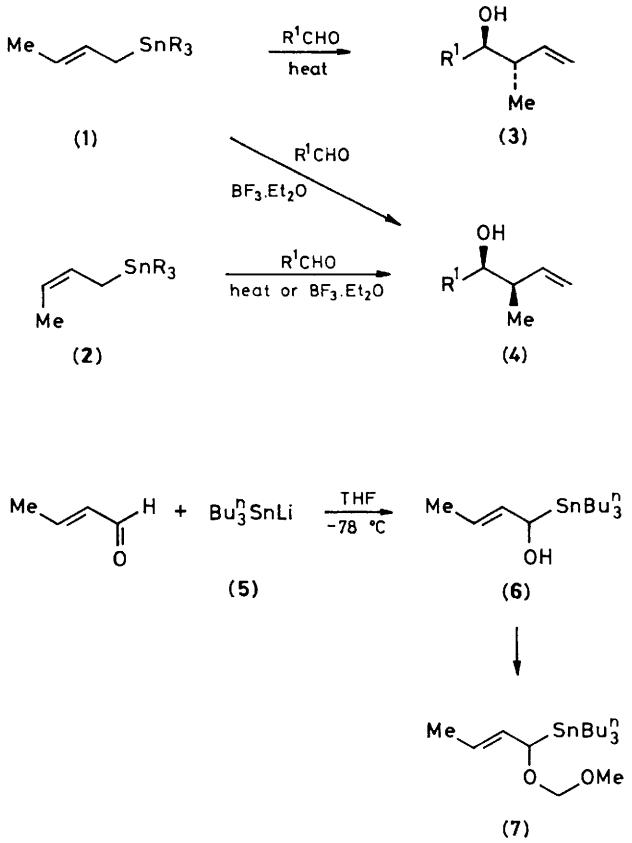
(*E*)-1-Methoxymethoxybut-2-enyl(tri-n-butyl)stannane, readily available by addition of tri-n-butylstannyl-lithium to crotonaldehyde, and protection of the alcohol so formed using chloromethyl methyl ether, reacts on heating with aromatic and aliphatic aldehydes to give *threo*-4-hydroxy-3-methyl-*cis*-1,2-enol ethers, hydrolysis and oxidation of which provides a stereoselective route to *trans*-4,5-disubstituted butyrolactones.

Recently there has been considerable interest in acyclic stereochemical control.[1] One significant development in this field has been the introduction of procedures for *erythro*- and *threo*-selective aldol condensations, either directly using stereoselectively generated (*Z*)- or (*E*)-enolate anions,[2] or indirectly using crotyl metal derivatives,[3] including crotyltrialkylstannanes.[4,5] Recent work has shown that under Lewis acid ($BF_3.Et_2O$) catalysed conditions, both (*E*)- and (*Z*)-crotyltrialkylstannanes (**1**) and (**2**) react rapidly with aldehydes to give *erythro*-adducts (**4**).[4] However an earlier report[5] had suggested that the uncatalysed, thermal, addition of a crotylstannane to an aldehyde is stereoselective, (*E*)-crotyl-(trialkyl)stannanes (**1**) providing *threo*-adducts (**3**), and (*Z*)-crotyl(trialkyl)stannanes (**2**) providing *erythro*-adducts (**4**), after hydrolysis.[6] This stereoselectivity parallels that of other crotyl metal compounds, and is consistent with a 6-membered-ring, chair-like, transition state. We here report that (*E*)-1-methoxymethoxybut-2-enyl(tri-n-butyl)stannane (**7**) reacts with both aromatic and aliphatic aldehydes, in the absence of a Lewis acid catalyst, to give *threo*-4-hydroxy-3-methyl-*cis*-1,2-enol ethers.

Tri-n-butylstannyl-lithium (**5**) is known to add to α,β-unsaturated aldehydes and ketones at either the carbonyl carbon or the β-carbon depending upon steric hindrance.[7] When crotonaldehyde was added at −78 °C to a solution of tri-n-butylstannyl-lithium (**5**) in tetrahydrofuran (THF), generated at 0 °C from lithium di-isopropylamide and tri-n-butyltin hydride,[7] exclusive carbonyl attack occurred to give the tri-n-butylstannyl alcohol (**6**). This unstable alcohol (**6**) was not purified; instead it was immediately treated with chloromethyl methyl ether and di-isopropylethylamine in CH_2Cl_2 to give (*E*)-1-methoxymethoxybut-2-enyl(tri-n-butyl)-



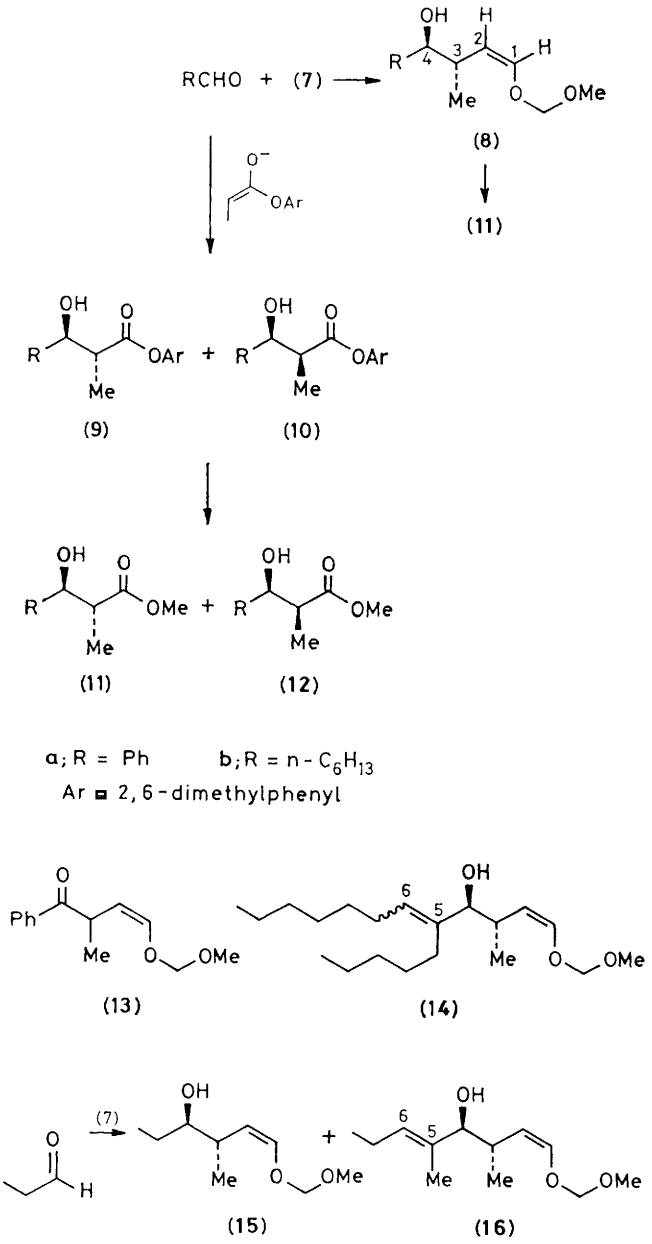


Table 1.

Aldehyde R	Stannyl reaction[a] T/°C	t/h	% yield of (**8**)	Hydrolysis–oxidation[b] % overall yield of (**18**)
Ph[c]	115	90	79	89
Ph	140	11	70	—
PhCH=CH	140	11.5	60	72
p-$NO_2C_6H_4$	60	16	56(66)[d]	71
p-ClC_6H_4	100	36	76	70
Et	140	40	33[e]	—
Pr^i	140	40	72	77
Bu^t	140	40	5	—
n-C_6H_{13}	140	36	47[f]	95
n-C_6H_{13}[g]	140	19	66(89)[h]	—

[a] Two mol. equiv. of (**7**), neat, unless otherwise stated. [b] 3 M aqueous HCl, THF, 1:1, 24 h, 20 °C; PCC, NaOAc, CH_2Cl_2, 12 h, 20 °C. [c] Using 1.2 equiv. of (**7**) in toluene as solvent. [d] Yield in parentheses allows for 14% recovered aldehyde. [e] Plus 44% of adduct (**16**). [f] Plus 10% of adduct (**14**). [g] Using 5 mol. equiv. of aldehyde relative to stannane (**7**). [h] Yield in parentheses allows for 26% recovered stannane (**7**).

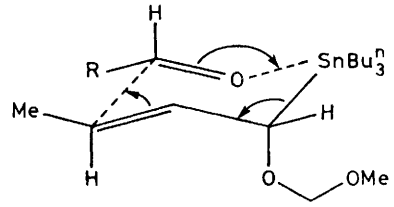


Figure 1

stannane (**7**), 82% overall from crotonaldehyde.† The crude alkoxycrotylstannane (**7**) so obtained was sufficiently pure for most practical purposes, but could be purified either by flash chromatography on silica, or by column chromatography on basic alumina.

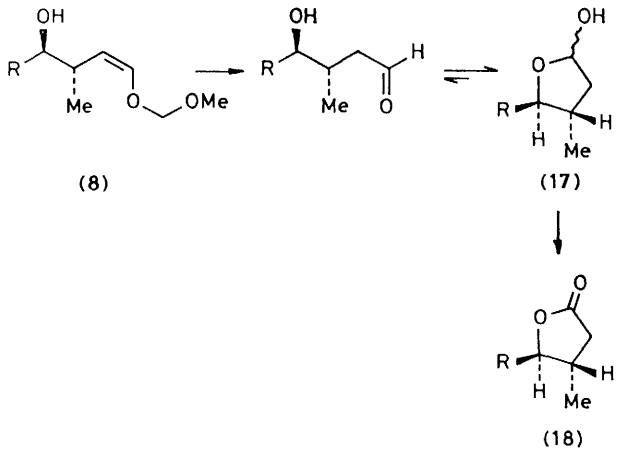
It was found that heating a solution of alkoxycrotylstannane (**7**) and benzaldehyde in toluene under reflux for 90 h gave one major product, isolated after short column chromatography in 79% yield, and identified as the *threo*-4-hydroxy-3-methyl-*cis*-1,2-enol ether (**8a**).† No other isomers of the *threo*-*cis*-enol ether (**8a**) were isolated, the one side-product isolated in 1% yield being identified as ketone (**13**).

† All new compounds were characterised by spectroscopic data, and by analytical or accurate mass data whenever possible.

Subsequently it was found that this condensation reaction could be carried out using 2 mol. equiv. of alkoxycrotylstannane (**7**) as the reaction solvent, a 70% yield of product (**8a**) being obtained after 11 h at 140 °C.

Aliphatic aldehydes were found to behave similarly. Thus treatment of n-heptanal with 2 mol. equiv. of alkoxycrotylstannane (**7**) at 140 °C for 36 h gave the *threo*-4-hydroxy-3-methyl-*cis*-1,2-enol ether (**8b**) (47%). In this case a second product was isolated (10% yield) and identified as enol ether (**14**) on the basis of spectroscopic data. Only one isomer of enol ether (**14**) was isolated; the geometry of its C(5)–C(6) double-bond was not determined. Use of an excess of n-heptanal gave an improved yield of the desired enol ether (**8b**), *e.g.* using 5 mol. equiv. of n-heptanal, an 89% yield of (**8b**) was obtained, based on consumed stannane, after 19 h at 140 °C (Table 1).

The other aldehydes used, together with reaction conditions and yields of products, are shown in Table 1. The selective formation of *threo*-*cis*-enol ethers was found to be quite general, at least for simple aldehydes. For most of these reactions, 2 equiv. of stannane (**7**) were used as reaction solvent, the excess of stannane being removed at the end of the reaction by partition between acetonitrile and light petroleum.[8] Yields refer to chromatographed products. The optimum temperature for the reaction was found to depend upon aldehyde reactivity. Thus *p*-chlorobenzaldehyde gave a 76% yield of product after 36 h at 100 °C, whereas *p*-nitro-



benzaldehyde reacted smoothly at 60 °C. Of the aliphatic aldehydes studied, isobutyraldehyde gave a 72% yield of product at 140 °C, but pivaldehyde was less reactive, only a 5% yield of product being obtained after 40 h at 140 °C, presumably owing to steric hindrance to carbonyl attack. Propanal gave two products, which were separated and identified as the desired *threo-cis*-enol ether (**15**) (37%) together with the analogous product (**16**) (44%) derived from 2-methylpent-2-enal. This behaviour parallels that of n-heptanal. It would seem that primary aliphatic aldehydes undergo aldol condensation–dehydration under the reaction conditions, the aldol products then undergoing reaction with crotylstannane (**7**). Only one isomer of product (**16**) was obtained; in this case the C(5)–C(6) double-bond geometry was assumed.

Structures were assigned to the *threo*-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, consistent with the *cis*-enol ether geometry shown; *trans*-enol ethers normally have a coupling constant between the vinylic protons of *ca.* 12 Hz.[9] The *threo*-configuration was initially assigned by analogy with reactions between aldehydes and other (*E*)-crotyl organometallics. It was confirmed for the benzaldehyde and n-heptanal products (**8a**) and (**8b**) by ozonolysis followed by oxidative work-up and esterification with diazomethane to give the *threo*-methyl esters (**11a**) and (**11b**). These were compared with authentic samples prepared using the procedure developed by Heathcock.[10] Thus treatment of benzaldehyde and n-heptanal with the lithium (*E*)-enolate derived from 2,6-dimethylphenyl propanoate gave mixtures of the *threo*- and *erythro*-aldol products (**9a, b**) and (**10a, b**). *threo*:*erythro* = *ca.* 7:1 for both cases. Hydrolysis and diazomethane esterification of these aldol products gave 7:1 mixtures of the *threo*- and *erythro*-methyl esters (**11a, b**) and (**12a, b**). In both cases the major *threo*-methyl ester was identical to the sample prepared from the corresponding *threo-cis*-enol ether (**8a, b**), and the minor *erythro*-methyl ester was clearly different. The methyl ester (**11a**) in the benzaldehyde series is a known compound; our spectroscopic data agreed with those published. The methyl ester (**11b**) in the n-heptanal series is new; however its 2-H–3-H coupling constant of 6.6 Hz is characteristic of *threo*-isomers, *cf. erythro*-isomers which have analogous coupling constants of 2—4 Hz.[11] The *threo*-configuration was assigned to the other products by analogy.

The stereoselective formation of *threo*-isomers in these reactions is consistent with the 6-membered cyclic chair-like transition state shown in Figure 1. The *threo*-configuration of the product is a consequence of the (*E*)-geometry of the crotylstannane, and a preference for the R-group of the aldehyde to adopt an equatorial position. Of note is the formation of the enol ether with exclusive *cis*-geometry. This implies that the 1-methoxymethoxy-substituent adopted the axial position shown in the transition state. There is some precedent for this stereoselectivity.[12] In our case, it may be due to the bulky n-butyl groups on tin which would provide a substantial *gauche* interaction if the methoxymethoxy-moiety adopted an equatorial position. In the axial position shown in Figure 1, the methoxymethoxy-substituent is involved with only one 1,3-diaxial interaction.

Finally, the hydrolysis and oxidation of the *threo-cis*-enol ethers was examined as a stereospecific route to *trans*-4,5-disubstituted butyrolactones. It was found that hydrolysis of the *threo-cis*-enol ethers (**8**) (3 M aqueous HCl–THF, 1:1; 24 h, 20 °C) gave lactols (**17**) which were oxidised by pyridinium chlorochromate (PCC) (NaOAc buffer, CH_2Cl_2; 12 h, 20 °C) to give butyrolactones (**18**) in good overall yield (Table 1). In the overall conversion of aldehydes into *trans*-4,5-disubstituted butyrolactones (**18**), the alkoxycrotylstannane (**7**) is being used as a *threo*-selective, homo-enolate equivalent.

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