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1,6-Asymmetric Induction in Reactions between 6-Hydroxy-5-methylhex-2-enyl(tributyl)stannane and Aldehydes Promoted by Tin(IV) Bromide

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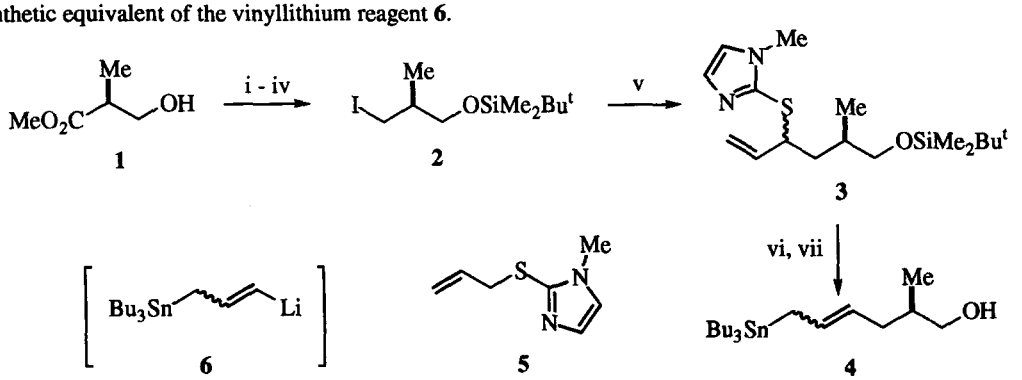
Abstract: (*R*)-6-Hydroxy-5-methylhex-2-enyl(tributyl)stannane **4** transmetallates on treatment with tin(IV) bromide to give an intermediate allyltin tribromide which reacts with aldehydes to give 1-substituted (*Z*)-6-methylhept-2-ene-1,7-diols **7** with excellent *anti*-1,6-asymmetric induction.

Transmetallation of allylstannanes which have heteroatom containing substituents at the 4-, 5- or 6-positions using tin(IV) halides generates allyltin trihalides which react with aldehydes with useful levels of remote asymmetric induction.[1,2] We now report reactions of the (*R*)-6-hydroxy-5-methylhex-2-enyl-(tributyl)stannane **4** with aldehydes which proceed with useful levels of 1,6-asymmetric induction.

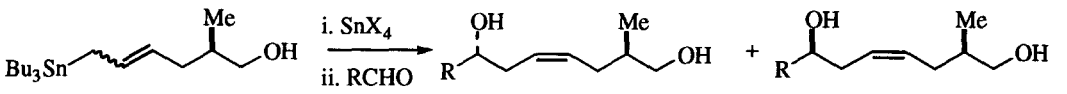
The stannane was prepared by alkylation of the thioether **5**[3] with (*S*)-3-*tert*butyldimethylsilyloxy-2-methylpropyl iodide **2**, which is available from methyl (*S*)-3-hydroxy-2-methylpropanoate **1**, **Scheme 1**. Treatment of the alkylated sulphide **3** with tributyltin hydride under free radical conditions[4] gave the 6-hydroxyhexenylstannane **4**, as a mixture of *E*- and *Z*-isomers, ratio *ca.* 75 : 25, after deprotection using tetrabutylammonium fluoride. In this synthesis, the lithiated derivative of the sulphide **5** is being used as the synthetic equivalent of the vinyllithium reagent **6**.



Scheme 1 ***Reagents:*** i, Bu^{t}Me$_2$SiCl, imid. (100%); ii, DIBAL-H (100%); iii, MesCl, Et$_3$N; iv, NaI, acetone (70% over two steps); v, **5**-Li, HMPA (42%); vi, Bu$_3$SnH, AIBN (79%); vii, Bu$_4$NF (79%).

Reactions of the 6-hydroxyhexenylstannane **4** with aldehydes were carried out by adding a solution of tin(IV) bromide in dichloromethane to a solution of the stannane in dichloromethane at -78 °C, stirring at this temperature for 10 minutes, and addition of the aldehyde. After work-up, the products were isolated and

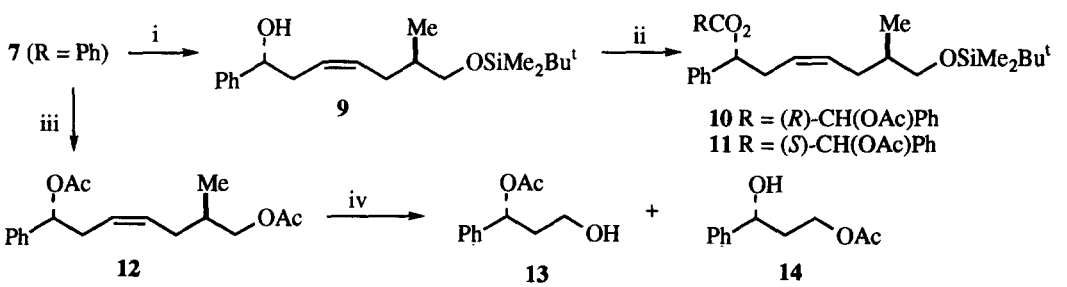
purified by chromatography. In all cases the reactions were found to proceed with useful levels of 1,6-induction in favour of the 1,6-*anti*-products **7**. The use of tin(IV) chloride resulted in lower stereoselectivity.



4 **7** **8**

RCHO	SnX_4	Yield (%)	**7 : 8**
PhCHO	$SnBr_4$	84	93 : 7
4-$O_2NC_6H_4CHO$	"	76	91 : 9
4-$MeOC_6H_4CHO$	"	58	91 : 9
Me_2CHCHO	"	80	91 : 9
CH_3CH_2CHO	"	56	93 : 7
PhCHO	$SnCl_4$	62	84 : 16

The major product from the reaction with benzaldehyde was identified as the *anti*-(*Z*)-isomer **7** (R = Ph) using spectroscopic data and chemical correlation.[5] The double-bond was assigned the *cis*-geometry on the basis of the *ca.* 10 Hz coupling between the vinylic protons in the mono-*tert*butyldimethylsilyl ether **9**. The 1,6-*anti*-configuration was assigned initially using the relative chemical shifts of the (*R*)- and (*S*)-acetylmandelates **10** and **11**, the vinylic protons being significantly more shielded in the (*S*)-acetylmandelate **11** than in the (*R*)-isomer **10**.[6] This was confirmed by ozonolysis, with a reductive work-up, of the bis-acetate **12**, which gave the dextrorotatory 3-acetoxy-3-phenylpropanol known[7] to correspond to the (*R*)-enantiomer **13** together with a small amount of the product **14** of acetyl migration.

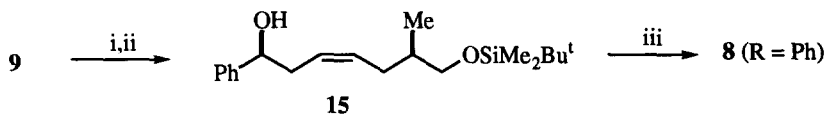


12 **13** **14**

Scheme 2 ***Reagents:*** i, Bu^tMe_2SiCl, Et_3N, 4-dimethylaminopyridine (92%); ii, (*R*)- or (*S*)-acetylmandelic acid, dicyclohexylcarbodiimide, 4-dimethylaminopyridine (80%); iii, Ac_2O, Et_3N, 4-dimethylaminopyridine (90%); iv, O_3, then Me_2S followed by $NaBH_4$ (**13**, 34%; **14**, 16%)

To confirm that the 1,6-*anti*- and 1,6-*syn*-products could be distinguished spectroscopically and to confirm the structure of the minor product from the reaction of the stannane **4** with benzaldehyde, the configuration at C(1) of the mono-*tert*butyldimethylsilyl ether **9** was inverted by treatment with diethyl diazodicarboxylate, triphenylphosphine, and *o*-nitrobenzoic acid followed by saponification and deprotection.[8] This gave the 1,6-*syn*-diastereoisomer **8** (R = Ph) which was clearly different from its 1,6-*anti*-isomer by ^1H

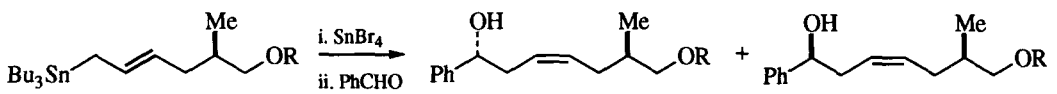
NMR and which was shown to correspond to the minor product from the reaction of the stannane **4** with benzaldehyde. The structures of the other products were assigned by analogy.



15

Scheme 3 ***Reagents:*** i, $EtO_2CN{=}NCO_2Et$, Ph_3P, $O_2NC_6H_4CO_2H$ (69%); ii, NaOH, MeOH (74%); iii, Bu_4NF (88%).

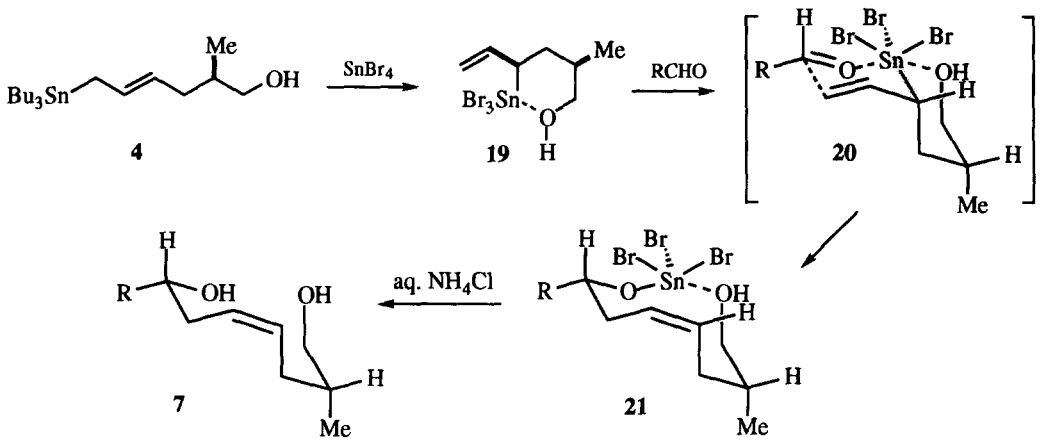
To investigate the influence of the nature of the 6-heterosubstituent on the efficiency of the 1,6-induction, the hydroxystannane **4** was O-alkylated to provide the 6-methoxy, the 6-methoxymethoxy, and 6-benzyloxystannanes **16**. However, the reactions of these with benzaldehyde promoted by tin(IV) bromide were less stereoselective than the corresponding reaction with the 6-hydroxyhexenylstannane **4** and gave mixtures of the 1,6-*anti*- and 1,6-*syn*-products **17** and **18**.



16 **17** **18**

Stannane R	Yield (%)	**17 : 18**
H	84	93 : 7
Me	68	71 : 29
MOM	62	67 : 33
Bn	49	50 : 50

The 1,6-induction observed in the reactions of the 6-hydroxyhexenylstannane **4** and aldehydes promoted by tin(IV) bromide is consistent with stereoselective transmetallation of the stannane to give the allyltin tribromide **19**.[1,2,9] This then reacts with aldehydes *via* the six-membered, chair-like, cyclic transition state **20**, in which the group α to tin is in the axial position giving the *cis*-double-bond in the product. It is suggested that the electron deficient tin atom in the intermediate **19** is co-ordinated to the hydroxyl substituent forming an oxastannane ring, and that this intermediate is formed stereoselectively with the vinyl and methyl substituents *cis* to each other, i. e. both equatorial, about the six-membered ring. Since the chiral centre in the stannane **4** is homoallylic and is unlikely to influence effectively the diastereofacial selectivity of attack of an *external* electrophile on the allylstannane, at least to the levels of 1,6-induction observed for the hydroxystannane **4**, it is suggested that the tin(IV) bromide co-ordinates first to the hydroxyl substituent and is delivered in an *intramolecular* fashion to the allylstannane. The relative stabilities of the possible transition states for this intramolecular transmetallation will reflect the stabilities of the resulting allyltin tribromides with the more stable allyltin tribromide **19**, in which the vinyl and methyl groups are both equatorial, being formed more quickly than its *trans*-diastereoisomer in which one of these substituents would have to be axial. This process parallels that proposed for the reactions of 6-hydroxyallylstannanes with aldehydes which proceed with 1,7-asymmetric induction.[10]



Present work is concerned with the development of alternative procedures for remote asymmetric induction which avoid the use of organostannanes and with the application of this chemistry to the synthesis of natural products.

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5. Data for (1*R*,6*R*,3*Z*)-6-methyl-1-phenylhept-3-ene-1,7-diol **7** (R = Ph), $[\alpha]_D$ +59.8 (*c* 3.2, $CHCl_3$) (Found: $M^+ + NH_4$, 238.1809. $C_{14}H_{24}NO_2$ requires *M*, 238.1807); υ_{max} (film) /cm^{-1} 3346, 1494, 1454, 1035, 876, 759 and 701; δ_H (500 MHz, $CDCl_3$) 0.87 (3 H, d, *J* 7, 6-CH_3), 1.63 (1 H, m, 6-H), 1.88 and 2.18 (each 1 H, dt, *J* 13,7, 5-H), 2.35 (1 H, dt, *J* 15,4, 2-H), 2.58 (1 H, dt, *J* 14,8, 2-H), 2.67 and 3.06 (each 1 H, br s, OH), 3.36 (1 H, dd, *J* 12, 4.5, 7-H), 3.46 (1 H, dd, *J* 11,6, 7-H), 4.65 (1 H, dd, *J* 9,4, 1-H), 5.40-5.55 (2 H, m, 3-H and 4-H), and 7.22-7.32 (5 H, m, aromatic H); δ_C (75 MHz, $CDCl_3$) 17.0, 31.0, 35.7, 37.4, 66.8, 73.8, 125.8, 126.4, 127.5, 128.4, 131.3 and 144.4; *m/z* (CI/NH_3) 238 (M^++18, 5%), 221 (M^++1, 6), 220 (M^+, 22) and 203 (M^+-17, 100).
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