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Stereoselective Synthesis of Aliphatic 1,5,9,13-Polyols using (δ-Alkoxyallyl)stannanes

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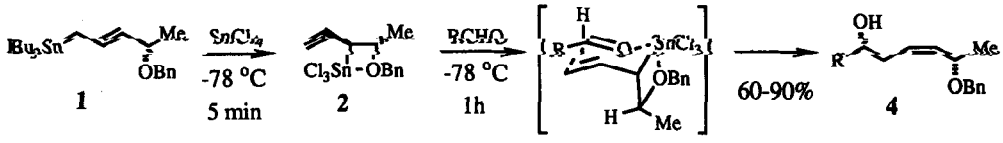
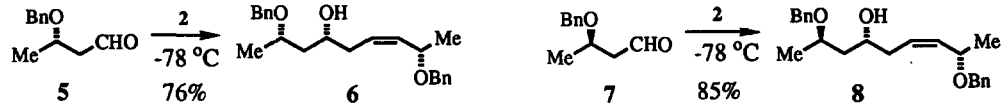
Abstract: Treatment of aliphatic aldehydes with the allyltin trichloride generated from the 4-benzyloxyocta-2,7-dienylstannane **18** and tin(IV)chloride provides stereoselective access to polyhydroxylated compounds with the hydroxyl groups at positions 1,5,9,13- etc. along the aliphatic chain.

The δ-benzyloxyallylstannane **1** undergoes transmetallation with tin(IV)chloride to generate the allyltin trichloride **2** which reacts with aldehydes with excellent 1,5-asymmetric induction to give *syn*-alcohols **4**.[1-3] The stereoselectivity of these reactions is consistent with the participation of the six-membered ring, chair-like transition state **3** for the reaction of the allyltin trichloride with the aldehyde, and is not usually influenced by the chirality of the aldehyde, e.g. the aldehydes **5** and **7** give the homoallyl alcohols **6** and **8**, respectively (de >93%).[2]

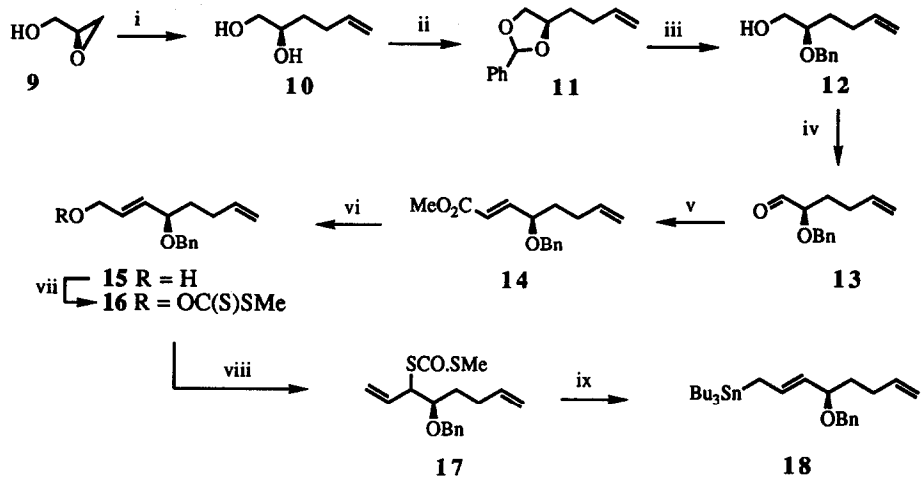




As very few methods exist for effective 1,5-asymmetric induction in aliphatic chemistry, it was decided to investigate the tin(IV)halide induced reactions of other δ-alkoxyallylstannanes. We now report the preparation of the octadienylstannane **18**, and its use for the stereoselective synthesis of polyols with hydroxy substituents at positions 1,5,9,13- etc. along an aliphatic chain.

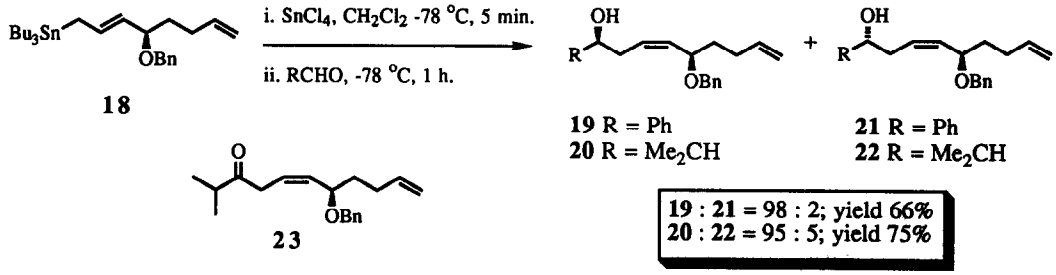
The stannane **18** was prepared as outlined in **Scheme 1**. (*S*)-Glycidol **9** was treated with allylmagnesium chloride to give the diol **10** which was protected as its monobenzyl ether **12**.[4] Oxidation of **12** gave the aldehyde **13** which was converted into the allyl alcohol **15**, (*E*) : (*Z*) = 8 : 1, by condensation with methoxycarbonyltriphenylphosphorane and reduction of the ester **14** using DIBAL-H. 3,3-Rearrangement of

the xanthate **16** prepared from the alcohol **15** gave the dithiocarbonate **17**, as a mixture of diastereoisomers, which reacted with tributyltin hydride to give the allylstannane **18**.[5]



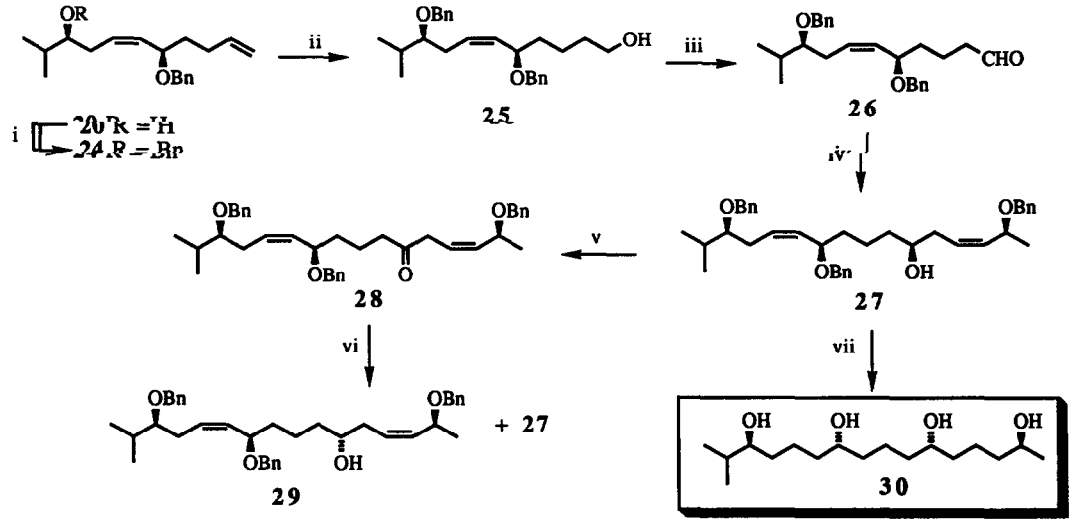
Scheme 1: *Reagents;* i, CH_2=CH-CH_2MgCl, THF, -20 °C (99%); ii, $PhCH(OMe)_2$, TFA (cat.) (80%); iii, DIBAL-H, 0 °C (71% of **12**); iv, DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N (99%); v, $MeO_2C.CHPPh_3$ (97%); vi, DIBAL-H, -78 °C (81%); vii, NaH, CS_2, then MeI (95%); viii, toluene, heat (98%); ix, Bu_3SnH, AIBN, benzene, heat (82%).

Reactions of the allylstannane **18** with benzaldehyde and 2-methylpropanal were carried out by transmetallation of **18** with tin(IV)chloride in dichloromethane at -78 °C followed by the addition of the aldehyde. Work-up gave the *syn*-alcohols **19** and **20** containing 2% and 5% of the corresponding *anti*-isomers **21** and **22**. Structures were assigned to the major products **19** and **20** on the basis of spectroscopic data, and the configurations of the hydroxy bearing carbons were established by comparison of the ^1H NMR spectra of the (*R*)- and (*S*)-acetoxymandelates.[1,6,7] The structure of the minor product from the reaction with 2-methylpropanal was established by oxidation of the major product **20** to the ketone **23** which was reduced using sodium borohydride to give a mixture of the alcohols **20** and **22** which were separated by chromatography and characterised independently.



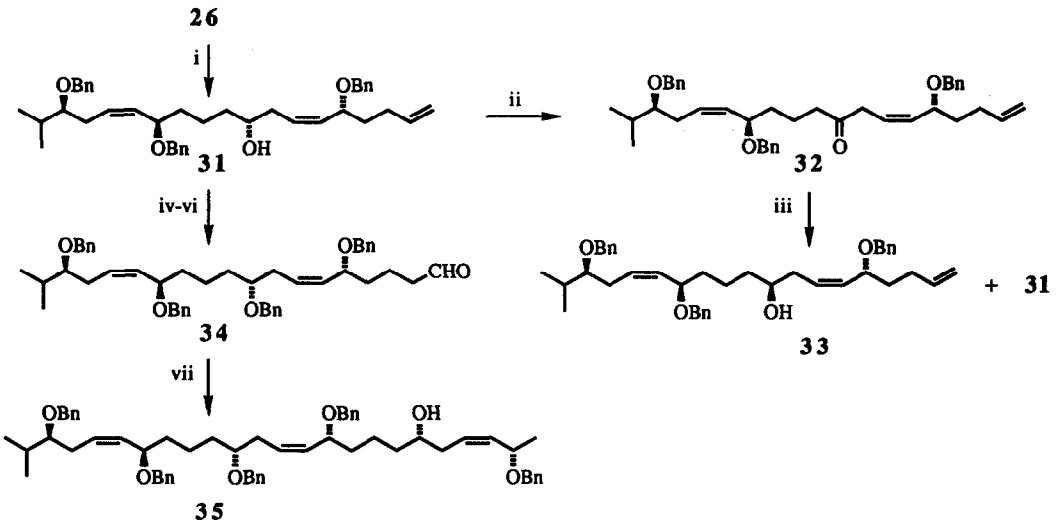
The homoallyl alcohol **20** was then taken through to the aldehyde **26** by *O*-benzylation, regioselective hydroboration, and oxidation, and the reactions of this aldehyde with the δ-alkoxyallylstannanes **1** and **18**

investigated. The tin(IV)chloride mediated reaction of the allylstannane **1** with the aldehyde **26** gave the hexadecadienol **27** in a 76% yield. To check the stereochemical homogeneity of the product, the alcohol **27** was oxidised to the ketone **28** which was reduced non-stereoselectively to give a mixture of the epimers **27** and **29**. These could not be separated by HPLC, but were distinguishable by 500 Mz ^{1}H NMR. Comparison of the NMR spectrum of the mixture with that of **27** obtained from the allylstannnane reaction, failed to detect any of the *anti*-epimer **29**.[8] Hydrogenation of the alcohol **27** using 10% palladium on charcoal as catalyst gave the tetrol **30** (88%),[9] so establishing the use of this tin methodology for the stereoselective synthesis of open-chain polyols with chiral centres dispersed at 1,5,9,13-positions along the carbon chain.



Scheme 2: *Reagents;* i, NaH, BnBr, Bu_4NI, THF (86%); ii, 9-BBN, THF, then H_2O_2, NaOH (64%); iii, DMSO, $(COCl)_2$ then Et_3N (95%); iv, 1-$SnCl_4$ (76%); v, DMSO, $(COCl)_2$ then *n*-Pr_2NEt (74%); vi, $NaBH_4$, EtOH (95%; **27** : **29** = 1 : 1); vii, 10% Pd/C, MeOH, H_2 (88%).

The use of the allylstannane chemistry for preparing longer chain polyols was investigated. The reaction of the aldehyde **26** with allylstannane **18** mediated by tin(IV)chloride gave the alcohol **31** (72%). This appeared to be a single compound, but to check its stereochemical homogeneity, a sample was oxidised to the ketone **32** which was reduced to give a mixture of **31** and its epimer **33**. These could not be separated by HPLC, but were distinguishable by ^{13}C and 500 Mz ^{1}H NMR. Comparison of the NMR spectrum of the alcohol **31** with that of the mixture failed to detect the epimeric alcohol **33**.[8] The alcohol **31** was then converted into the nonadecadienal **34** by *O*-benzylation, hydroboration, and Swern oxidation, although in this long-chain series difficulty was encountered in making these reactions, in particular the hydroboration, go to completion. The aldehyde **34** was then reacted with the allylstannane **1** under the usual conditions to give the tetracosatrienol **35** (67%). The structure of this product was assigned by analogy with the usually observed stereoselectivity of reactions of the allylstannane **1** and was consistent with spectroscopic data including high field NMR.



Scheme 3: *Reagents;* i, 18-$SnCl_4$ (72%); ii, DMSO, $(COCl)_2$ then *n*-Pr_2NEt (85%); iii, $NaBH_4$, EtOH (92%); iv, NaH, DMF, then BnBr, Bu_4NI (68% allowing for recovered **31**); v, 9-BBN then H_2O_2, NaOH (40% allowing for recovered s.m.); vi, DMSO, $(COCl)_2$ then Et_3N (72%); vii, 18-$SnCl_4$ (67%).

This synthesis of alcohol **35**, a protected 1,5,9,13,17,21-hexol, illustrates the potential of the tin(IV)-chloride mediated reactions of the δ-alkoxyallylstannanes for the stereoselective synthesis of open-chain compounds. The stereoselectivity observed for the reactions of the octadienylstannane **18** is consistent with the participation of an allyltin trichloride which reacts with the aldehydes *via* a chair-like six-membered ring, chair-like transition state, *cf.* **2** and **3**.[1-3,10] Further work is in progress to extend the scope of these reactions and to apply them to the synthesis of complex natural products.

ACKNOWLEDGEMENTS. We thank the SERC for a studentship (for A.H.McN.).

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4. Reduction of the dioxolane **11** using DIBAL-H gave a 12 : 1 mixture of **12** and its regioisomer which were separated by flash chromatography.
5. The stannane **18** contained small amounts, *ca.* 5%, of its *cis*-isomer. This mixture was used in reactions with aldehydes since the stereoselectivity of these reactions is independent of the geometry of the double-bond in the allylstannane.
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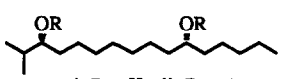
7. ^1H NMR confirmed the *cis*-geometry of the double-bond in all the allylstannane products (*J ca.* 10Hz).
8. It was difficult to estimate accurately the amounts of the minor alcohols **29** and **33** that were present in the products from the allylstannane reactions. The epimeric products were clearly distinguishable by ^1H and ^{13}C NMR, but, because of the complexity of the spectra, small amounts (<5%) could not be measured and the epimers were not separable by HPLC. In all cases where it was possible to estimate the ratio of products accurately, the stereoselectivity was greater than 95 : 5.
9. The hydrogenation was sensitive to the catalyst used. With 5% rhodium on charcoal the diol **i**, characterised as its bis-acetate **ii**, was the major product.



i, R = H; **ii**, R = Ac

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