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SYNTHESIS OF NONRACEMIC γ-ALKOXY ALLYLSTANNANES BY STEREOSPECIFIC ANTI [1,3]-STANNYL MIGRATION

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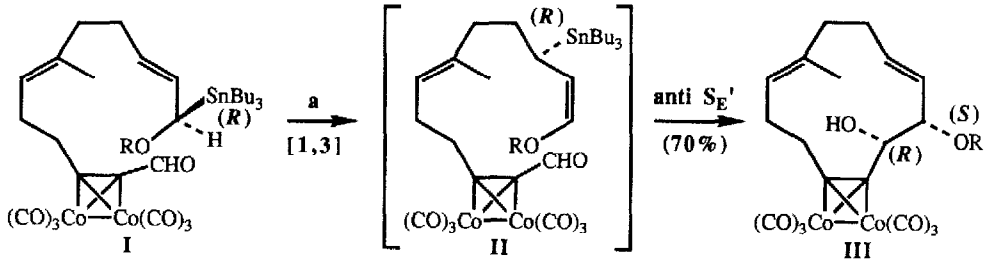
Summary: The γ-alkoxy allylstannane **5b**, prepared in high yield by $BF_3 \cdot OEt_2$ promoted [1,3] rearrangement of the (*S*)-α-alkoxy allylstannane **4b**, affords the syn 1,2-diol derivatives **8** and **9** in high yield and excellent ee upon condensation with various aldehydes.

In the course of studies directed toward the synthesis of macrocyclic and medium-ring natural products, we subjected the racemic allylstannane aldehyde I to $BF_3 \cdot OEt_2$ in CH_2Cl_2 at -78°C. The cyclododecadienol III, a single diastereoisomer, was isolated in 70% yield along with a small amount of the isomerized allylstannane II. None of the cyclodecadienol derived from S_E' cyclization of I was formed.[2] Subsequently, we found that the (*R*)-α-alkoxy allylstannane I afforded the (*S*,*R*) product III with essentially complete chirality transfer. These findings suggest that I isomerizes to II stereospecifically en route to III. In order to clarify the course and scope of this reaction sequence we undertook the studies described herein.



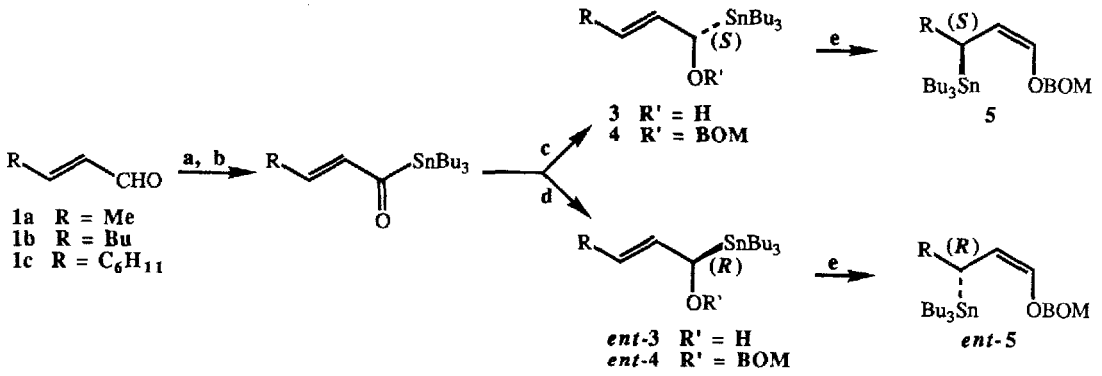
(a) $BF_3 \cdot OEt_2$, CH_2Cl_2, -78°C, 0.001 *M*

Sequential addition of Bu_3SnLi to unsaturated aldehydes **1a-1c** and oxidation of the resultant unstable alcohols with ADD[4] afforded the stannyl ketones **2a-2c**.[5] These ketones were conveniently reduced with the $LiAlH_4$-Darvon alcohol (Chirald®) complex to the (*R*)-alcohols *ent*-**3a**-*ent*-**3c** of greater than 60% ee.[6] Reduction of ketone **2b** with the experimentally more capricious (*R*)-BINAL-H reagent afforded the (*S*)-alcohol **3b** with greater than 95% ee under carefully controlled conditions (Table I).[7]

Table I. Isomerization of α-Alkoxy Allylstannanes

		% ee		% yield			
R	**series**	**3**	*ent*-**3**	**4**	**5**	*ent*-**4**	*ent*-**5**
Me	a		60			62	75
n-Bu	b	>95	62	65	80	64	81
C_6H_{11}	c		61			65	80

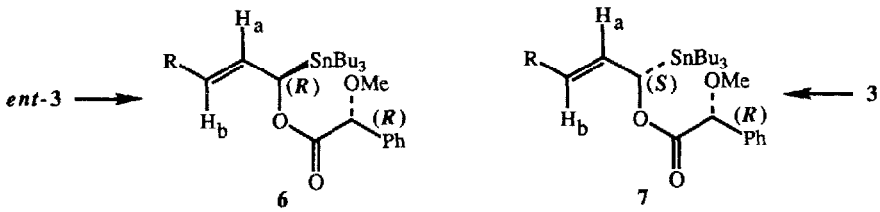
The configurational assignments for these alcohols were based upon distinctive chemical shift differences of the vinylic protons of the (*R*)-O-methyl mandelates **6** and **7** (Table II).[8,5]



(a) Bu_3SnLi, THF; (b) ADD, *t*-BuOMgBr, THF; (c) (*R*)-(+)-BINAL-H, THF; (d) $LiAlH_4$-Chirald®, THF; (e) $BF_3 \bullet OEt_2$, CH_2Cl_2, -78°C

The benzyloxymethyl (BOM) ether derivatives **4b** and *ent*-**4a-4c** readily isomerized to **5b** and *ent*-**5a-5c** upon treatment with $BF_3 \bullet OEt_2$ in CH_2Cl_2 at -78°C for 1-3 h.[9] The double bond geometry of **5** was assigned from the characteristic coupling constants (J ~6 Hz) of the vinylic protons. The absolute configuration of these allylstannanes can be tentatively assigned from the transformations described below pending rigorous proof. As expected, **5b** and *ent*-**5b** showed opposite and roughly equal rotations after correcting for ee.

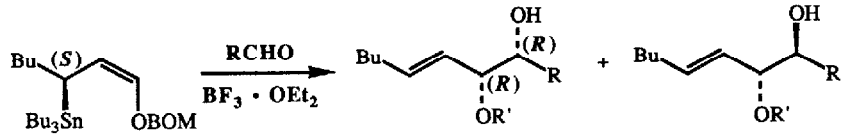
Table II. Vinyl Proton Shifts for (*R*)-O-Methyl Mandelates



	6		7	
R	H_a	H_b	H_a	H_b
Me	5.56	5.09	5.61	5.38
n-Bu	5.51	5.00	5.58	5.26
C_6H_{11}	5.52	5.04	5.59	5.29

Allylstannane **5b** underwent facile addition to representative aldehydes affording the syn diol derivatives **8** and **9** as major products along with a small amount of the anti products **10** (Table III).[10] Both **8** and **9** were formed with virtually complete transfer of chirality according to ^1H NMR analysis of the O-methyl mandelate derivatives. These derivatives could also be used to assign the absolute configuration to **8** and **9**.[8,5]

Table III. Addition of γ-Alkoxy Allylstannane **5b** to Aldehydes

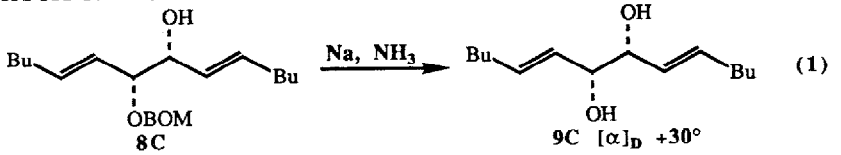


5b (>95% ee) **8** R' = BOM, **9** R' = H, **10**

		8		**9**		**10**[a]	
R	**series**	% **yield**[b]	**ee**[c]	% **yield**[b]	**ee**[c]	% **yield**[b]	**syn/anti**
n-C_6H_{13}	A	58	>95	20	>95	12	87:13
BuC≡C	B	65	>95	7	>95	12	86:14
(*E*)-BuCH=CH	C	61	>95	26	>95	3	97:3
C_6H_{11}	D	62	>95	10	>95	3	96:4
Ph	E	52	>95	20	>95	13	85:15

[a] ee not determined; [b] isolated yield not optimized; [c] ^1H NMR analysis of O-methyl mandelate

The relative stereochemistry of the mono protected syn diol **8C** was confirmed by reductive cleavage to the optically active diol **9C** (eq. 1) of comparable rotation to material directly isolated from the allylstannane condensation.[10] Control experiments indicated that diols **9A-9E** were formed by cleavage of the BOM ethers **8A-8E** in the condensation reaction.



BF_3-catalyzed additions of nonracemic α-alkoxy allylstannanes **4** to aldehydes have been shown to proceed by an anti S_E' pathway (**A** → IV).[2] Assuming γ-alkoxy allylstannanes follow an analogous pathway, the observed (*R*,*R*) products **8** and **9** must arise from the (*S*)-allylstannane **5b** as in **B** → **8**. Accordingly, the isomerization of allylstannanes **4** and *ent*-**4** to **5** and *ent*-**5** must involve an antarafacial or anti S_E' pathway.[3]

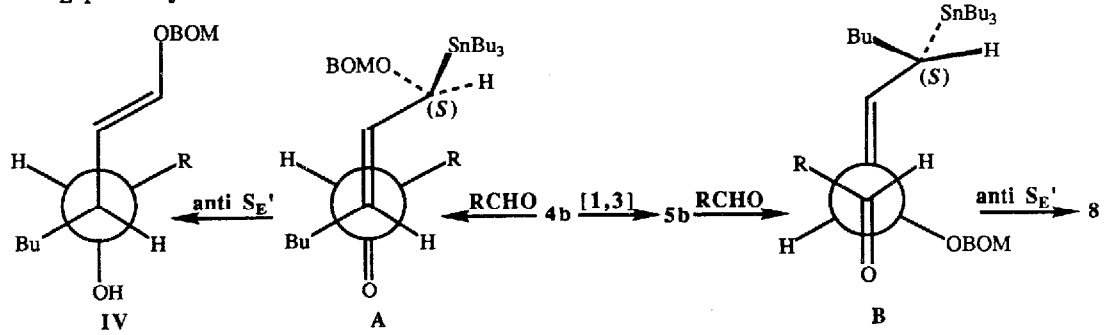
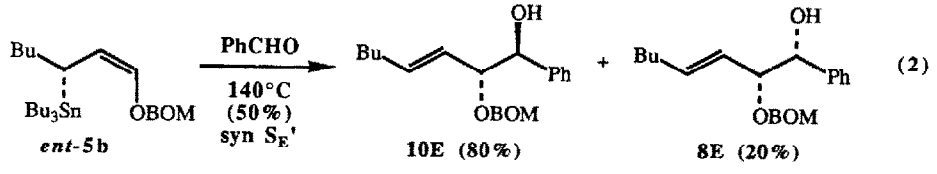
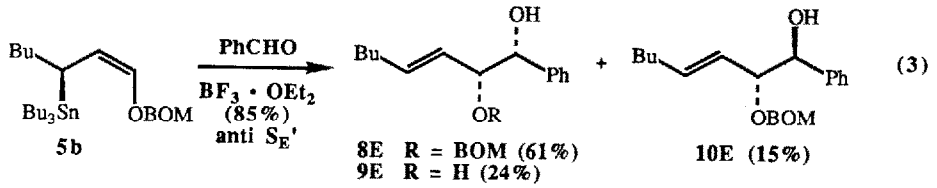


Figure 1. Pathways for BF_3-catalyzed additions of allylstannanes to aldehydes

As additional support for the assigned configuration of the γ-alkoxy allylstannanes **5**, we carried out a thermal addition of *ent*-**5b** to benzaldehyde. Such additions have been shown to proceed in a syn S_E' manner through a chair-like transition state.[11] Consistent with the assigned configuration, *ent*-**5b** afforded an 80:20 mixture of **10E** and **8E** (eq. 2). These same two products were formed in the BF_3-catalyzed addition of **5b** to benzaldehyde (eq. 3).





The ready accessibility of chiral nonracemic γ-alkoxy allylstannanes as exemplified in Table I and the high degree of stereoselectivity exhibited in their addition to aldehydes[10] should be of considerable value for the asymmetric synthesis of polyol systems.

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