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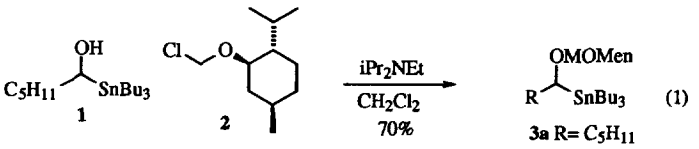
PREPARATION OF ENANTIOMERICALLY ENRICHED α-ALKOXYSTANNANES BY REGIOSELECTIVE ACETAL EXCHANGE OR ACETAL HYDROLYSIS

Russell J. Linderman*, Kevin P. Cusack and Mohamad R. Jaber
Department of Chemistry, North Carolina State University
Raleigh, NC 27695-8204

Abstract α-Alkoxyorganostannanes can be resolved via the methoxymenthyl ethers with subsequent regioselective acetal exchange or cleavage of the acetal group to the α-hydroxyalkylstannane.

α-Alkoxystannanes have become versatile reagents in organic synthesis, serving as a precursor for α-alkoxylithio anions [1] and the derived organocopper reagents. [2] Recently direct Pd or Cu catalyzed coupling reactions of α-alkoxystannanes with a variety of electrophiles has also been reported. [3] We have illustrated the utility of α-alkoxystannanes as nucleophilic [4a] and electrophilic [4b] synthetic equivalents to a carbonyl ylide. However, applications of α-alkoxystannanes in asymmetric synthesis have been impeded by the difficulty in obtaining these reagents in enantioenriched form. Although a number of methods for the synthesis of enantioenriched α-alkoxystannanes have been devised, these methods are not generally applicable to the synthesis of functionalized stannanes. Chromatographic resolution by means of a Mosher ester derivative, [1c] and menthyl [5a] or 8-phenylmenthyl [5b] acetal derivatives has been reported. Other methods for the preparation of enantioenriched α-alkoxystannanes have included enzymatic resolution of an acetate, [6a] nucleophilic addition reactions to stannyl substituted cyclic acetals, [6b,c] and the addition of a silylstannane reagent to an aldehyde in the presence of a chiral amine. [6d] The most useful method to date is the asymmetric reduction of acyl stannanes reported independently by Chong and Marshall. [7] Although this method has provided a number of enantioenriched stannanes, the asymmetric reduction of the sensitive acyl stannane precursor is often difficult to carry out reproducibly. We now report a method for resolution of an acetal derivative which allows for regeneration of the unstable enantioenriched α-hydroxyalkylstannane or a novel direct exchange reaction of the chiral acetal.

We surmised that acetal cleavage would be facilitated by a stereoelectronic effect imparted by the tin substituent. [8] The most efficiently separated acetal derivative of those examined was the methoxymenthyl (MenOM) ether **2** obtained by protection of racemic **1** with chloromethylmenthyl ether **2** [9] (1). The MenOM derivative **3** was resolved by flash chromatography using 10%CH_2Cl_2/pet ether as eluent. A single flash column run can achieve 80-85%de. Somewhat better results were obtained using MPLC, but resolution greater than 90-95%de still required two passes (compare entries 1 and 2 with 3 and 4 in the Table). Nevertheless, this resolution procedure ultimately provides both enantiomers of the α-hydroxystannane (see



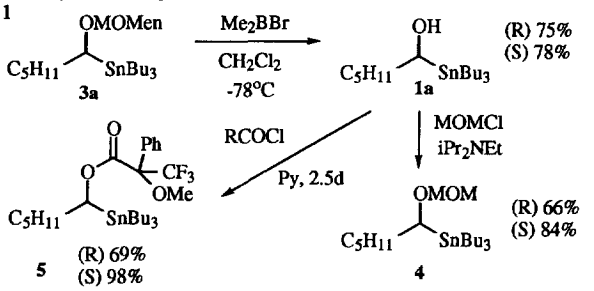
below) and therefore is very practical in comparison to existing techniques. Other examples of MenOM ether derivatives that were resolved are given in the Table. The resolution method obviates potential problems associated with the asymmetric reduction of an intermediate acyl stannane and can be scaled up (>2g range).

Table Resolution of α-Methoxymenthyl Stannanes **3**

Entry	R=	%Yield, %de	
		High Rf	Low Rf
1	C_5H_{11}, **3a**	70, 96	72, 92
2	$TBSOC_5H_{10}$, **3b**	60, 96	64, 90
3	$PhCH_2CH_2$, **3c**	90, 84	88, 82
4	C_6H_5, **3d**	81, 86	78, 84

The best results for acetal cleavage were obtained using Me_2BBr [10] at -78°C. The enantioenriched α-hydroxyalkylstannanes thus obtained were each reprotected as the MOM ether and as the Mosher ester [11] as shown in Scheme 1 (the chemical yields are given for each enantiomer). The absolute configuration of MOM

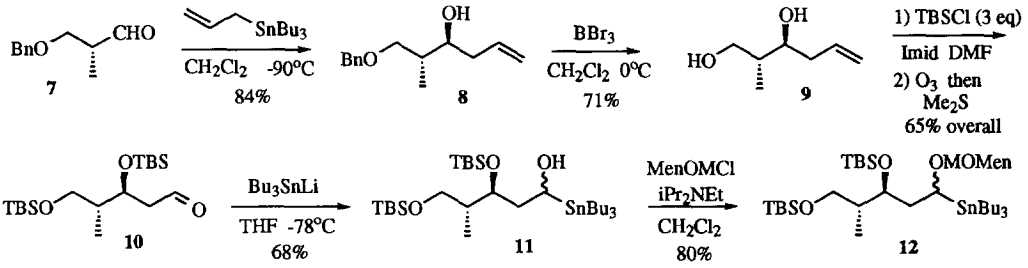
Scheme 1



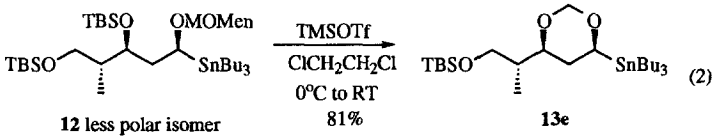
ether **4** was assigned by comparison of rotation data with the known non-racemic compound. [7a] In this case, the MOM ethers were obtained in 91%ee and 90%ee for the (R) and (S) enantiomers, respectively. The Mosher ester **5** of the (R) isomer was shown to be 90%ee (by ^{1}H-NMR) while the (S) isomer ester was obtained in 89%ee. The starting MenOM derivatives were 93%de and 91%de (^{1}H-NMR), respectively. Therefore, no significant loss of optical activity had occurred.

The synthesis of a more functionalized mixed acetal **12**,an intermediate in our approach to phyllanthocin and breynolide, [12] is shown in Scheme 2. Diastereoselective allylation of aldehyde **7** has been reported by Keck and co-workers; [13] however, best results were obtained by carrying out the reaction at -90°C rather than -78°C. In this fashion, alcohol **8** was isolated as a 36:1 mixture of anti:syn alcohols. [14] Removal of the benzyl ether with boron tribromide provided diol **9**. Protection as the bis-TBS ether and ozonolysis of the alkene provided aldehyde **10**. Condensation of the aldehyde with tributyltin lithium then gave the α-hydroxystannane **11**. Conversion of **11** to the separable MenOM ethers **12** was straightforward. The separated diastereomers (yields are for pure diastereomers from a single chromatographic run) were obtained in 46% and 29% yield (along with 5% unresolved mixture) for the less polar and more polar

Scheme 2

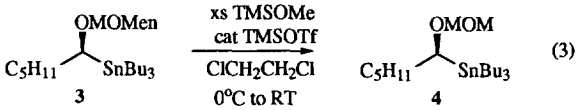


isomers, respectively. Each diastereomer was then carried on independently. Removal of the MenOM ether protecting group was accomplished using Me_2BBr (CH_2Cl_2 at -78°C) without loss of the TBS groups to regenerate enantiopure **11** (73% and 90% yields for low and high Rf isomers, respectively). The absolute configuration of each diastereomer was assigned by direct conversion of the MenOM ether to a dioxane by treatment with catalytic TMSOTf in dichloroethane (2). The stereochemistry of the dioxane substituents was determined by NOESY data and ^{119}Sn-^{13}C coupling constants. [15] The more polar isomer was assigned as dioxane **13e** in which the tin substituent is in the equatorial position. The tributyltin substituent in the less



polar isomer is axial. Note that the free alcohol **11** can now be derivatized as needed with an α-haloether. [12]

The acetal exchange reaction noted above is not limited to the formation of cyclic ethers. Direct treatment of the MenOM ether **3a** (93%de) with 10 eq TMSOMe and catalytic TMSOTf in dichloroethane [16] resulted in the MOM ether **4** in 98% yield. The acetal exchange reaction also occurred without loss of optical purity; **4** was isolated in 91%ee (3). Note that the overall yields of the exchange reaction are significantly higher than those for hydrolysis of the acetal with subsequent reprotection. The acetal exchange reaction of **3** is completely regioselective for formation of the stannyl substituted MOM product, that is none of the MOM



derivative of menthol was isolated. In contrast, the same exchange reaction carried out on the MenOM ether of cyclohexanol results in a 1:1 regioisomeric mixture of MOM protected cyclohexanol and menthol. In both the acetal cleavage and exchange procedures in the tin substituted cases, menthol is recovered in excellent yield.

In summary, we have demonstrated that functionalized stannyl substituted mixed acetals can be readily prepared and resolved to provide highly enantioenriched α-alkoxystannanes. Problems associated with functional group incompatibility and non-reproducible results experienced with other methods for the preparation of these compounds are alleviated by this route. Although the chromatographic resolution of simple stannyl substituted mixed MenOM ethers can be tedious, more functionalized systems such **12** are relatively easy to separate. Note that previous resolution methods [5] using acetals did not provide a method for the regeneration of the α-hydroxyalkylstannane or for acetal exchange.

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14. Aldehyde **7** employed in the formation of **8** was 96%ee (by rotation [13]). After separation, each isomer (as identified by R_f values) of **12** was obtained as a single diastereomer (within analytical detection limits of 1%).

15. For the relationship of ^{119}Sn-^{13}C coupling constants and dihedral angles, see: Olszowy, H. A.; Kitching, W. *Organometallics* **1984**, *3*, 1670-1675.

16. For use of these conditions in a glycosylation reaction, see: Charette, A. B.; Marcoux, J. F.; Cote, B. *Tetrahedron Lett.* **1991**, *32*, 7215-7218. We are not aware of the use of TMSOTf as a catalyst for other acetal exchange reactions. The use of dichloroethane is critical in this transformation. The reaction does not work in other solvents.

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