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Stereoselective Synthesis of Methyl *trans*-Chrysanthemate and Related Derivatives

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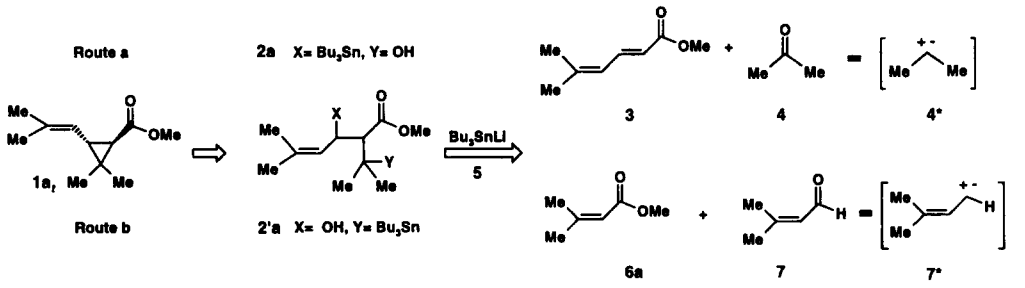
Abstract: γ-hydroxyalkenylstannanes, readily available from α,β-unsaturated esters, α,β-unsaturated aldehydes and tri(*n*-butyl)stannyllithium, react with boron trifluoride etherate to produce vinyl cyclopropane carboxylic esters. An original highly convergent synthesis of chrysanthemic acid is reported. © 1998 Elsevier Science Ltd. All rights reserved.

We previously described a short synthesis of methyl *trans*-chrysanthemate **1a**$_t$ from methyl 5-methyl-2,4-hexadienoate **3** and acetone **4** which formally involves the insertion of the 2-propylidene moiety **4***, derived from the deoxygenation of acetone, regioselectively on the C,C double bond closer to the ester group (Scheme 1, route a).[1] The key step of this process implies the 1,3-elimination[1,2] of the tributylstannyl- and hydroxyl-groups on the γ-hydroxyalkenylstannane **2a** ($SOCl_2$, Et_3N, CH_2Cl_2 , 0°C, 0.5 h), obtained by trapping, with acetone, the enolate derived from the 1,4 addition of tri(*n*-butyl)stannyllithium **5** on **3** (Scheme 1, route a).

We now report an even more convenient route to the same compound **1a**$_t$ (Scheme 1, route b) which uses a closely related strategy, the same key step involving the same leaving groups *(the hydroxyl and the stannyl ones)*, but attached in a reverse order, on the same carbon framework (compare the γ-stannylalkenol **2a** to the γ-hydroxyalkenylstannane **2'a**, Scheme 1).

Scheme 1



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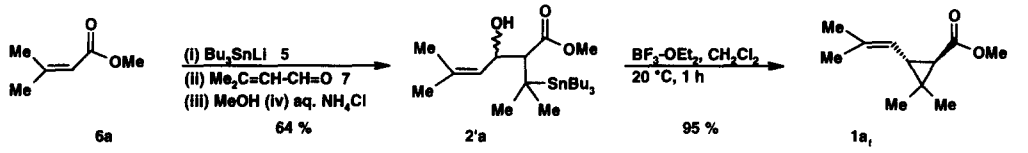
The desired γ-hydroxyalkenylstannane **2'a** was readily synthesized, as a mixture of two diastereoisomers by sequential addition of tri(*n*-butyl)stannyllithium **5**[3] and 3-methyl-2-butenal **7** (THF, -78°C, 64% yield, **2'a$_a$/2'a$_b$**, 67/33), it is interesting to notice the successful addition of tri(*n*-butyl)stannyllithium to the highly hindered carbon of **6a**.

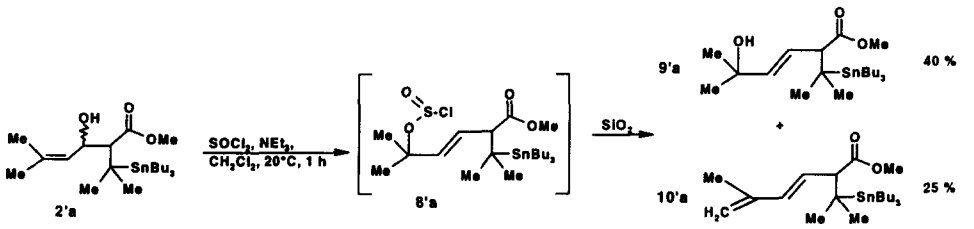
Scheme 2



6a **2'a** **1a$_f$**

The cyclization step involves the 1,3-elimination of the hydroxyl- and tri(*n*-butyl)stannyl-group from **2'a**. We expected from our previous work[1] that thionyl chloride-triethylamine would be the most successful combination for that purpose, but that proved not to be the case. We in fact got a quite unstable compound , whose structure was tentatively assigned to be **8'a**, which decomposes on silica gel to provide the ε-hydroxy-γ-alkenyl stannane **9'a** and the dienylstannane **10'a**, resulting from the rearrangement and the dehydration of **2'a** respectively (Scheme 3).

Scheme 3



2'a **8'a** **9'a** **10'a**

Use of boron trifluoride etherate (1.5 eq., CH_2Cl_2, 20 °C, 1h), which did not worked properly on the γ-hydroxyalkenylstannane **2a**,[1] allows however the synthesis of methyl *trans*-chrysanthemate **1a$_f$** in very good yield and reasonably high stereocontrol from each of the two stereoisomers (95% yield, d.e. 80%, Scheme 2).

We nevertheless suspected, because the 1,3-elimination reaction is not stereospecific as usual,[2d] that a non concerted mechanism is taking place and we therefore tried to identify an intermediate on which the stereochemical information present in **2'a** is lost.

We in fact proved that ε-hydroxy-γ-alkenyl stannane **9'a** was produced, besides methyl *trans*-chrysanthemate **1a$_f$** (**9'a** / **1a$_f$** ratio : 40 / 60 (d.e. 84 %), Scheme 4), if the reaction was carried out at lower temperature (1.5 eq. BF_3-OEt_2, CH_2Cl_2, -78 °C). We also proved that this intermediate reacts with the same reagent at 20°C to generate, as in the case for **2'a**, the methyl *trans*-chrysanthemate **1a$_f$** in very good yield and high stereocontrol (95% yield, d.e. 78%, Scheme 4).