SYNTHESIS OF SUGAR ALLYLTINS AND THEIR APPLICATION IN THE PREPARATION OF CARBOBICYCLES

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Abstract: Sugar allylic alcohols are readily converted into sugar allyltin derivatives of the general formula Sug-CH=CH-CH_2SnBu_3 or Sug-CH($SnBu_3$)-CH=CH_2. Both, primary and secondary allyltins undergo controlled decomposition induced with the Lewis acids (preferably $ZnCl_2$) to the dienoaldehydes with the *trans* configuration of the internal double bond exclusively. Primary allyltins are stable up to 170 °C, while secondary ones are converted into the *cis* dienoaldehydes at 140 °C. The corresponding dienoaldehydes were used for the preparation of highly oxidized bicyclo[4.3.0]nonanes and bicyclo[4.4.0]decanes.

Introduction

Highly oxygenated carbobicyclic derivatives like bicyclo[4.3.0]nonane and bicyclo[4.4.0]decane might possess interesting biological activity. For example, one of the stereoisomers of decalin **2** has shown potent and selective α-glucosidase inhibition at μM concentration against α- and β-glucosidases. However, compounds of this type are available only in racemic form.[1] Optically pure derivatives **2** and **3** might be, eventually, prepared from the precursors **4** and **5**, which could be obtained from the dienoaldehyde **1** accessible in enantiomerically pure form from sugars (Fig. 1).

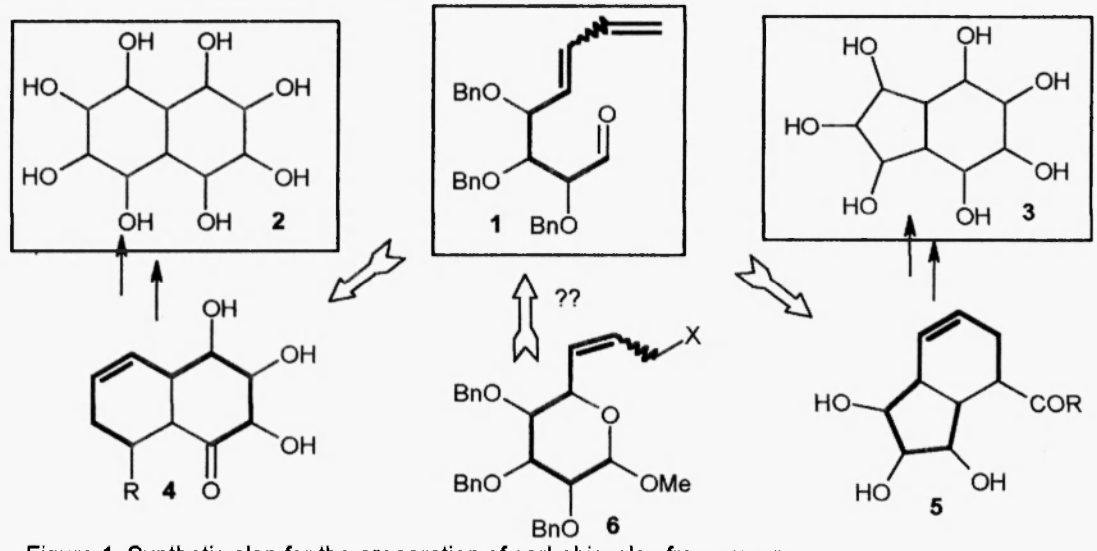


Figure 1. Synthetic plan for the preparation of carbobicycles from sugars

Aldehyde **1** might be prepared from monosaccharides either by a stepwise procedure[2] or by a rearrangement of a sugar skeleton; the latter might offer access to configurationally pure dienes **1** either in the *trans* or *cis* forms. The most promising method for such controlled rearrangement of a sugar skeleton seemed to be a reductive fragmentation of compound **6** (X = halogen) induced with metallic zinc; it might be regarded as an application of the classical Vasella reaction[3] (see Fig. 2) to allylic sugar derivatives.

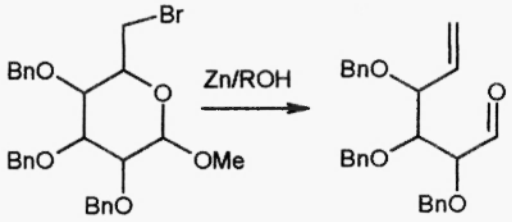


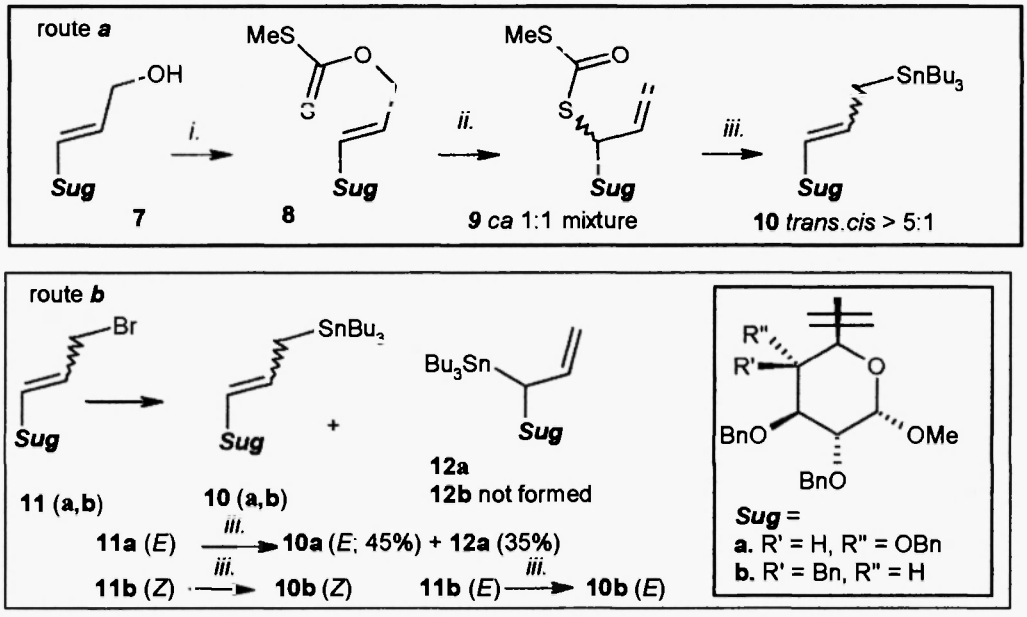
Figure 2. The Vasella reaction

Unfortunately all attempts to prepare the dienoaldehyde **1** *via* a modified Vasella reaction failed. The other methods were, therefore, needed to accomplish conversion of **6** into **1**.

The solution to the problem came from the different field. One of the methods applied by us in the synthesis of higher carbon sugars was based on a coupling of sugar allyltin derivatives **6** (X = $SnBu_3$) with aldehydes catalyzed with a Lewis acid.[4] Besides the expected higher sugar precursor, we isolated also significant amounts of a decomposition product, which, to our surprise, was identified as dienoaldehyde **1**. Moreover, the configuration of the internal double bond was exclusively *trans*. This result, a controlled decomposition of a sugar skeleton induced with a Lewis acid, opened a convenient route to enantiomerically pure carbobicyclic derivatives such as **4** and **5** (as presented schematically in Fig. 1).

Preparation of sugar allyltin derivatives

Although a number of methods for the preparation of allyltin derivatives can be found in the literature[5] they are hardly applicable in sugar chemistry. The best and most reliable method[6,7] for the preparation of sugar allyltins is presented in Scheme 1 (route ***a***). The sugar allylic alcohol **7** is converted into xanthate **8**, which subsequently undergoes a [3,3] rearrangement to thiocarbonate **9** on heating. Surprisingly, this process is completely non-selective.[7] Reaction of **9** with tributyltin hydride under radical conditions result in an S_R2' displacement of a thiocarbonate moiety by the stannyl radical and formation of allyltin **10** as a mixture of the *trans* and *cis* isomers with the former strongly predominating.[7]



Scheme 1. *i.* NaH, CS_2, MeI; *ii.* 110 °C, 2-3 h; Bu_3SnH, 110 °C, 2 h; *iii.* i. 'Bu_3SnCu', THF

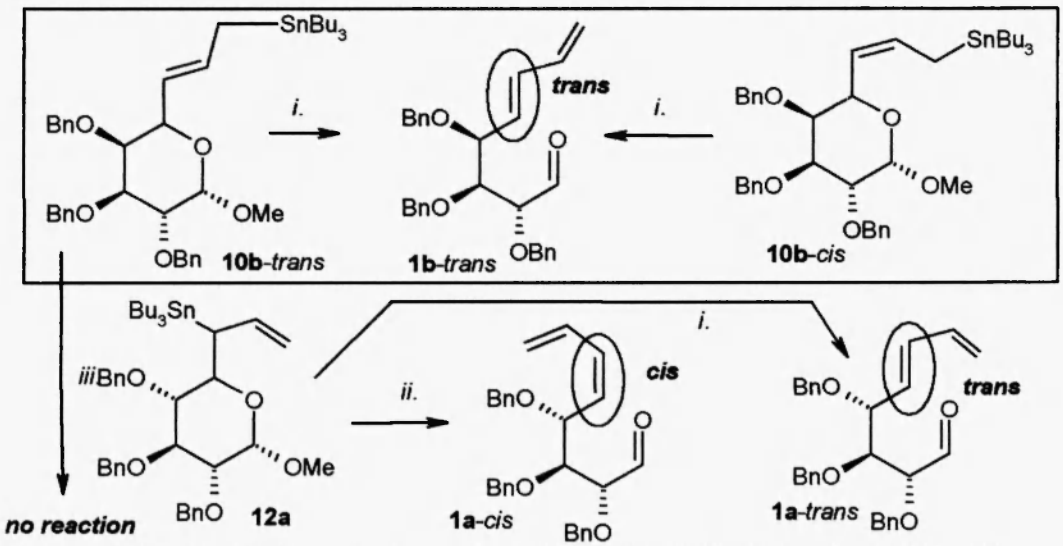
Another, although not so general, method consisted in the reaction of sugar allylic bromides (or mesylates) with tributyltin cuprate[8] (route ***b*** in Scheme 1). The D-*gluco*-configurated allylic bromide **11a** reacted with 'Bu_3SnCu' providing the primary allyltin derivative **10a** together with the secondary one (single isomer of unknown configuration at the newly created stereogenic center) **12a** in the ratio 1.3:1. More sterically hindered D-*galacto*-derivative **11b** led only to the primary allyltins **10b**. It has to be pointed out that the products arising from the nucleophilic displacement of the bromide with the stannyl anion are formed with full retention of the configuration across the double bond.[9]

Transformation of the sugar allyltin derivatives into dienoaldehydes

On treatment with Lewis acids, sugar allyltin derivatives undergo controlled decomposition to dienoaldehydes **1** with elimination of a tributylstannyl moiety. The configuration of the internal double bond in compound **1**, is ***independent*** of the configuration of unsaturated organometallics. The primary allyltins with different geometry across the double bond (*E* or *Z*)[9] as well as the secondary ones[10] are converted ***exclusively*** into the *trans* dienoaldehydes.

For reactions of primary sugar allyltins with zinc chloride (leading to the *trans* dieno-aldehydes) two possible mechanisms may be postulated: first involving a trans-metallation process (route ***a***, Fig. 3-I) and a second one involving a complexation (route ***b***, Fig. 3-I). It is not easy to distinguish between these two alternatives. However, the results of the reaction performed with boron trifluoride etherate (instead of $ZnCl_2$), in which also ***only*** the *trans* dienoaldehyde is formed, support rather the mechanism depicted in route ***b***. However, still, it is not clear why decomposition of the primary sugar allyltins induced with a Lewis acid leads only to the *trans* isomer of **1**, regardless of the configuration of the double bond of starting organometallic derivative.

The thermal behavior of both regioisomers is different; the primary sugar allyltins are stable up to 170 °C, while the secondary ones undergo controlled decomposition on heating to 140 °C (Scheme 2).[10] The product of this rearangement arising from elimination of the tributylstannyl moiety, dienoaldehyde **1**, has, however, the ***opposite*** *cis*-geometry across the internal double bond![10] For example compound **12a** on heating to 140 °C rearranges into the *cis*-dienoaldehydes (**1**-*cis*, Fig. 3-II).



Scheme 2. *i.* $ZnCl_2$, CH_2Cl_2, rt; *ii.* xylene, reflux (140 °C, 4 h); *iii.* ^{t}-BuC_6H_5, reflux (170°C, 4 h)

Two possible mechanisms can be proposed for this thermal decomposition. First postulates a cleavage of the carbon–metal bond with formation of radical **13** which further is converted into *cis*-**1**. This transformation requires a homolytic cleavage of the C–O bond (route ***a***, Fig. 3-II), a process which is not very likely;[11] this mechanism was excluded also experimentally. The intermediate radical **13**, if formed, should be trapped with tributyltin hydride to afford (besides the dienoaldehyde) also the reduced product **14**. No such product was detected in the post-reaction mixture. We postulate, therefore, that the tin atom present

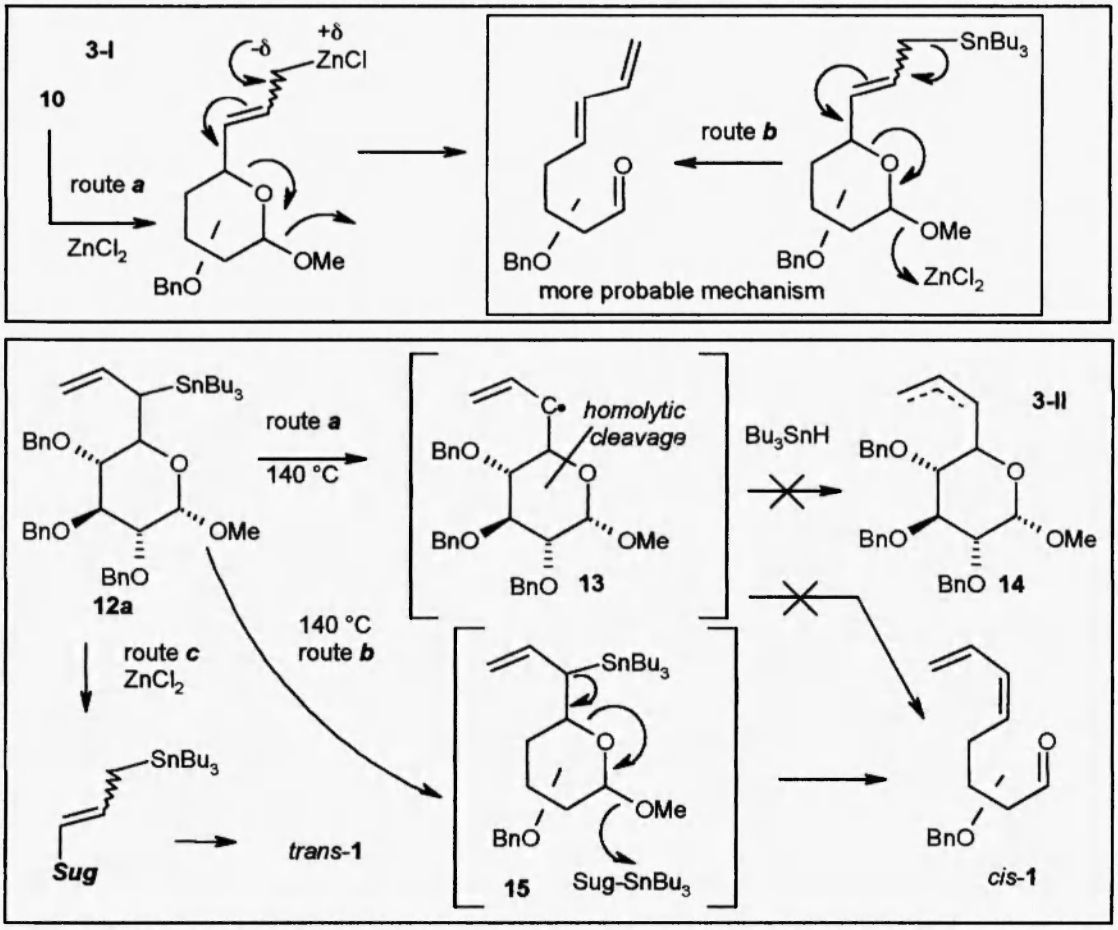


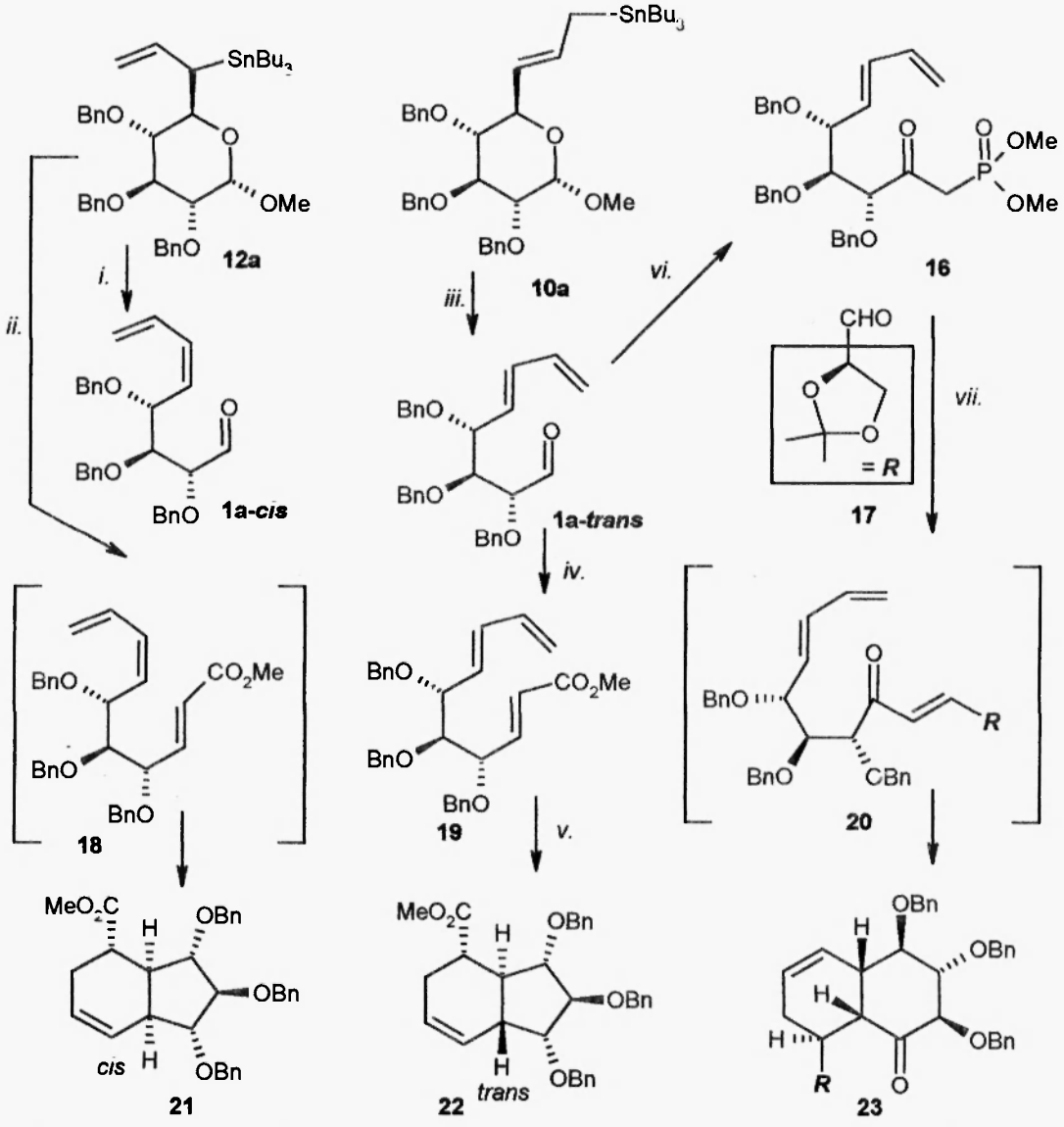
Figure 3. The possible mechanisms for reaction of sugar allyltins with $ZnCl_2$ (**3-I**) and for decomposition of secondary sugar allyltins(**3-II**)

in **12a**, may act at high temperature as a (weak) Lewis acid and induce decomposition according to route ***b*** in Fig. 3-II. It is not clear, however, why the geometry of the internal double bond is *cis*.

Treatment of **12a** with $ZnCl_2$ induces its conversion into the *trans*-aldehyde. This might be safely explained assuming the fast rearrangement to the primary analog (a process which is strongly catalyzed with Lewis acids[12]) and decomposition of the latter (route ***c*** in Fig. 3-II). As shown in Scheme 2, the conversion of sugar primary allyltin derivatives catalyzed by a Lewis acid provides exclusively the *trans*-dienoaldehydes ***regardless*** of the geometry of the double bond in the starting organometallics.

Application of sugar allyltins in the synthesis of carbocyclic derivatives

The dienoaldehydes with the *trans* and *cis* geometry across the internal double bond are convenient synthons for the preparation of carbocyclic derivatives. The general methodology is outlined in Scheme 3 for the allyltins derived from D-glucose.



Scheme 3. *i.* xylene, 140 °C, 4 h; *ii.* xylene, 140 °C, $Ph_3P{=}CHCO_2Me$ (**24**); *iii.* $ZnCl_2$, CH_2Cl_2, rt, 1h; *iv.* **24**, C_6H_6; *v.* p = 10 kbar; *vi.* 1.[O], 2. CH_2N_2, 3. $(-)CH_2P(O)(OMe)_2$; K_2CO_3, C_6H_6, rt

The secondary allyltin derivative **12a** on heating to 140 °C is converted into the *cis* aldehyde **1a**-*cis*. If this reaction is performed in the presence of a stabilized ylid ($Ph_3P{=}CHCO_2Me$, **24**) the resulting Wittig product **18** undergoes a spontaneous intramolecular Diels-Alder reaction (IMDA) to provide the bicyclic derivative **21** with the *cis* junction between both rings.[10] The isomeric bicyclo[4.3.0]nonene **22** is available by the (slightly modified) Wittig – IMDA sequence of reactions performed on the *trans*-aldehyde **1**.[13]

Alternatively, dienoaldehyde **1a**-*trans* may-be oxidized to an acid and converted into the methyl ester by reaction with diazomethane. Treatment of this ester with the anion generated from dimethyl methyl phosphonate afforded the Horner-Emmons reagent **16**, which reacted with aldehyde **17** to furnish triene **20**, undergoing spontaneous cyclization to decaline **23** [14]

The very high stereoselectivities observed in all these cyclizations are easily explained assuming the *endo* transition states of reacting species **18 – 20**.

Conclusions

The primary sugar allyltin derivatives are easily available from the corresponding allylic alcohols. The secondary ones are obtained (although as minor products) in reaction of allylic bromides (or mesylates) with tributyltin cuprate. Treatment of both regioiosomers with zinc chloride induces their conversion into the *trans* dienoaldehydes, resulting from a rearrangement of the sugar skeleton with elimination of a tributylstannyl moiety. The configuration across the internal double bond ***is independent*** of the geometry (*E* or *Z*) of the starting organometallic compound. The secondary allyltin derivatives undergo a conversion into the *cis*-dienoaldehydes on heating to 140 °C. Both isomers (*E* and *Z*) of the unsaturated aldehydes are convenient precursors of enantiomerically pure carbobicylic products.

Acknowledgements

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