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Synthesis of stereodefined vinyl-tetrahydropyran and vinyl-octahydrochromene derivatives via acetalization–cyclization of allylsilanes with aldehydes. Origin of the high stereoselectivity

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Abstract—Functionalized allylsilanes **1**–**5** and aldehydes **6**–**8** undergo Lewis-acid mediated ring closure to afford 2,3,5- or 6-substituted tetrahydropyrans (**8**–**15**) and 2,3-substituted octahydrochromenes (**16a**–**b**) with excellent stereoselectivity. According to DFT calculations the high stereoselectivity arises from electronically induced steric effects occurring in the key-intermediate of the cyclization.

Stereodefined tetrahydropyran and octahydrochromene structural motifs occur in many important natural products and biologically active molecules.[1] In particular, functionalized allylsilanes have proved to be useful reagents for stereoselective preparation of tetrahydropyran derivatives.[2] Based on acid-catalyzed cyclization of allylsilanes with acetals Mohr[2a] reported a very efficient method for the preparation of stereodefined vinyl-tetrahydropyran derivatives. Ito and co-workers[2b] have improved this methodology by using the so-called acetalization–intramolecular allylsilane cyclization protocol. We have studied the possibilities to extend the synthetic scope of this procedure to various functionalized allylsilanes and aldehydes (Eq. (1)). It was found that the stereoselectivity of the reaction is remarkably high even for different R^1 and R^2 substituents involving cyclic allylsilyl precursors. In order to understand the origin of the high stereoselectivity we have carried out density functional (DFT) calculations to study the interplay of the steric and electronic effects in the cyclization process. In a typical reaction the allylsilyl substrate (**1**–**5**) was reacted with the corresponding aldehyde (**6**–**8**) in the presence of trimethylsilyl trifluoroacetate (TMS–OTf) in dry CH_2Cl_2 under argon at −78°C (Table 1). The allylsilanes can be prepared by a recently reported efficient palladium(0)-catalyzed process[3a] followed by reduction.[3b,c]

All reactions proceeded with a remarkably high stereoselectivity. Reaction of **1** with *iso*-butyraldehyde (**6**) provided **9** and the corresponding *cis*-isomer in a ratio of 15:1 (entry 1), while formation of a single diastereomer (**10**–**16**) was observed for the rest of the reactions (entries 2–9). The only side-reaction found in these cyclizations was protodesilylation of **1**–**5**, which

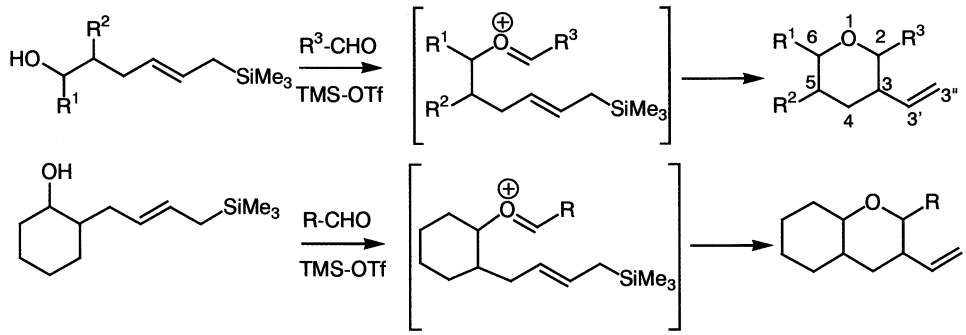

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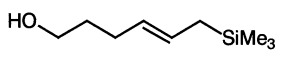
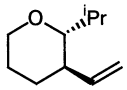
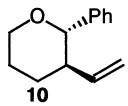
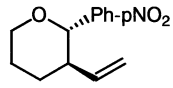
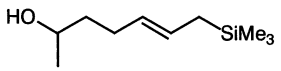
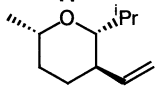
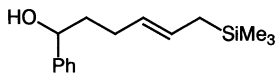
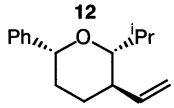
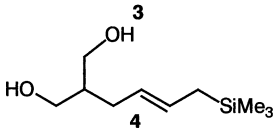
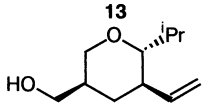
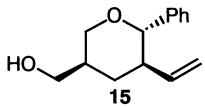
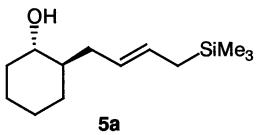
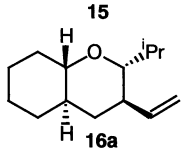
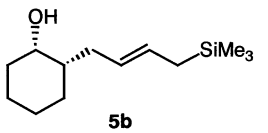
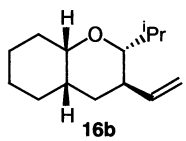
Table 1. Cyclization of allylsilanes **1–5** with aldehydes **6–8** [a]

Entry	Substrates	Aldehydes	Time [h]	Product	Yield[b] [%]
1	 **1**	^{i}PrCHO **6**	4	 **9**	70[c]
2	**1**	PhCHO **7**	4	 **10**	66
3	**1**	pNO_2-PhCHO **8**	3.5	 **11**	69
4	 **2**	^{i}PrCHO **6**	4.5	 **12**	69
5	 **3**	PhCHO **7**	6	 **13**	70
6	 **4**	^{i}PrCHO **6**	4	 **14**	64[d]
7	**4**	PhCHO **7**	4	 **15**	62[d]
8	 **5a**	^{i}PrCHO **6**	6	 **16a**	69
9	 **5b**	^{i}PrCHO **6**	6	 **16b**	66

[a]The reactions were conducted in CH_2Cl_2 using 1.2 equiv. of TMS-OTf at -78°C. [b]Isolated yield. [c]6 % of the *cis* isomer was also formed. [d]2.4 equiv. of TMS-OTf was used

lowered the yield by about 5–10%. The stereochemistry of products **9–13** could easily be established on the basis of $^{3}J_{HH}$ coupling constants and comparison with previously reported analogs.[2] The stereochemical assignment of **14–16** is based on a combined analysis of their ^{1}H NMR and NOE spectra. Previous studies by Mohr[2a] have shown that the stereoselectivity of the analogous cyclization reactions is very high when the C6 position of the tetrahydropyran product is substituted ($R^{1} \neq H$). It is interesting that this high stereoselectivity is preserved even for relatively unbulky substituents, such as a methyl group (entry 4). The effects of 5-substitution ($R^{2} \neq H$) has not been investigated previously. We have found that the excellent stereoselectivity can be maintained even for 5-hydroxymethyl substituted tetrahydropyrans (entries 6 and 7). Finally, we have tested the effects of anellated cyclohexyl rings (entries 8 and 9). It was found that the original stereochemistry of the hydroxy and allylsilyl groups determines the *trans*- and *cis*-annulation mode of the cyclohexyl ring in **16a** and **16b**, respectively. The relative stereochemistry of the *i*Pr and vinyl groups in the octahydrochromene derivatives is *trans* similar to the tetrahydropyran products.

In order to understand the origin of the high stereoselectivity we have carried out density functional theory (DFT) calculations at the B3LYP/6-31G(d) level of theory using the Gaussian98 program package.[4] We have studied the ring closure reaction of the oxonium ion intermediate (Eq. (1)), which is the assumed key-intermediate of the reaction.[2b] In these calculations the $SiMe_3$ group was approximated by the SiH_3 functionality.

We found that pre-folded intermediates with a C2–C3 distance of 2.3–2.6 Å occur in the potential energy surface of the cyclization reaction. The relative stability

of these intermediates has an important effect on the stereochemical outcome of the reaction. Intermediate **17a** affording the (e-e)-*trans*-isomer **17c**, is more stable by 1.3 kcal mol^{-1} than intermediate **18a** giving the (e-a)*cis*-isomer **18c** (Fig. 1). The two other isomers which would lead to the (a-a)-*trans*-isomer and the (a-e)-*cis*-isomer have a much higher energy relative to **17a** (5.3 kcal mol^{-1} and 4.0 kcal mol^{-1}, respectively). The activation barrier of the reaction is very low, only 0.2 kcal mol^{-1} (**17b**) and 0.4 kcal mol^{-1} (**18b**). This activation barrier is probably higher in the condensed phase because of solvation of the oxonium ion, however, this solvation effect probably does not affect the relative stability of **17a** and **18a**. The lower stability of **18a** compared to **17a** can be ascribed to the short non-bonding distance between C5–H and C3′–H (2.303 Å), which is clearly shorter than the sum of the van der Waals radii of two hydrogen atoms (2.4 Å).[5] This close van der Waals contact is imposed by hyperconjugative interactions between the π^* orbital of the double bond and the σ MO of the C–Si bond in the allylsilane fragment. This interaction requires that the plane of the C3–C3′ double bond is perpendicular to the C–Si bond rendering the C4–C3–C3′–C3″ atoms to the same plane, which leads to destabilizing steric strain between C5–H and C3′–H. It is interesting to point out that in the cyclic product **18c** this interaction is not present because of the rehybridization of C3. In fact, tetrahydropyran derivative **18c** is only 0.8 kcal mol^{-1} less stable than **17c**. Accordingly, the C5–H and C3′–H non-bonding interaction in **18a** considerably enhances the C5–H–vinyl diaxial interaction, which explains the excellent *trans*-selectivity in the cyclization reactions studied (Table 1).

The steric interactions in the pre-folded intermediates also explain the high stereoselectivity in the presence of 6-methyl (**19a–b**) and 5-methyl (**20a–b**) substituents (Fig. 2). Intermediate **19b** is much less stable than **19a** due to a very short non-bonding distance between the axial methyl group and the C2–H atom (2.198 Å). This short distance arises from the contraction of the O1–C2 bond (1.27–1.29 Å) caused by n_{π}–p_{π^*} conjugation between the oxygen lone-pair and the carbocation center at C2. This π-interaction is represented by a double bond in the Lewis-structure of the intermediate (Eq. (1)). In the cyclized product the non-bonding interaction is much weaker, since the π-character of the C2–O bond disappears. Because of the higher stability of **19a** the 6-methyl group strongly prefers an equatorial position, which is in good agreement with the experimental results (entries 4 and 5). An axial 5-methyl group (**20b**) involves an intermediate, which is less stable by 1.4 kcal mol^{-1} than its equatorially substituted counterpart (**20a**). The lower stability is due to the steric interactions between the C3–H atom and the methyl substituent. The C3–H hydrogen atom cannot avoid this destabilizing interaction because of the hyperconjugative interactions in the allylsilane fragment discussed above.

In summary, we have shown that 5- or 6-substituted tetrahydropyran and octahydrochromene derivatives can be prepared from allylsilanes and aldehydes with very high stereoselectivity. The stereoselectivity is determined by the interplay of steric and hyperconjugative/conjugative interactions occurring in the pre-folded reaction intermediates **17–20**.

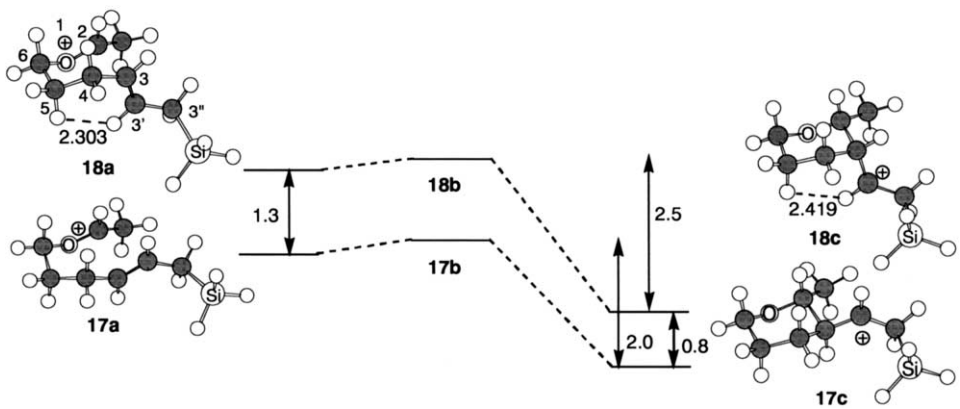


Figure 1. B3LYP/6-31G(d) optimized geometries for pre-folded intermediates **17a–18a** and tetrahydropyran products **17c–18c**. Energies in kcal mol^{-1}, non-bonding distances in Å.

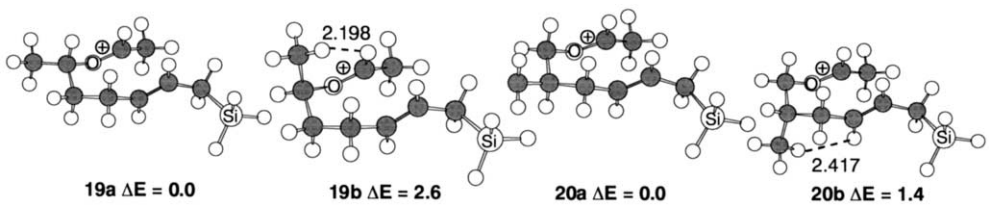


Figure 2. B3LYP/6-31G(d) optimized geometries for 6- and 5-methyl substituted pre-folded intermediates **19a–b** and **20a–b**, respectively. Energies in kcal mol^{-1}, non-bonding distances in Å.

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