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Highly Stereoselective Access to 2,4- and 2,4,5-Substituted Tetrahydrofurans from α-Silylacetic Esters. A Study of Homoallylic Stereocontrol.

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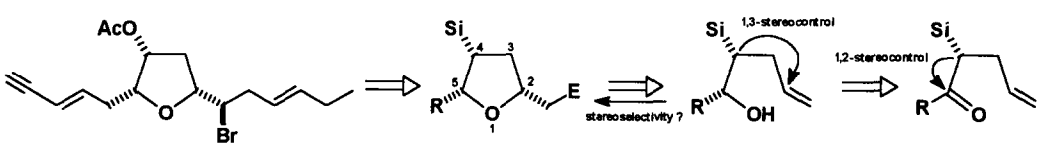
Abstract: *Cis*-2,4- and *cis-cis*-2,4,5-substituted tetrahydrofurans have been prepared stereoselectively using electrophile-mediated cyclization of β-hydroxyhomoallylsilanes, readily available from α-silylacetic esters.

Natural compounds containing tetrahydrofurans have been of special interest due to their wide spread occurrence and theirs varied biological activities.[1,2] The electrophile-mediated cyclizations of chiral hydroxy-alkenes is one of the most straightforward routes to the tetrahydrofuran skeleton, since the method usually allows excellent stereocontrol over the relative stereochemistry of the new chiral centres and produces compounds containing functionalities which can be elaborated further.[2] Several investigations have demonstrated that the stereocontrol arising from electrophilic activation of olefins is generally good with hydroxy-alkenes possessing an allylic substituent.[3] In contrast, few examples of homoallylic asymmetric induction have been reported to date.[4] Herein we report the electrophilic cyclofunctionalization of a number of hydroxy-alkenes possessing a homoallylic silyl group.

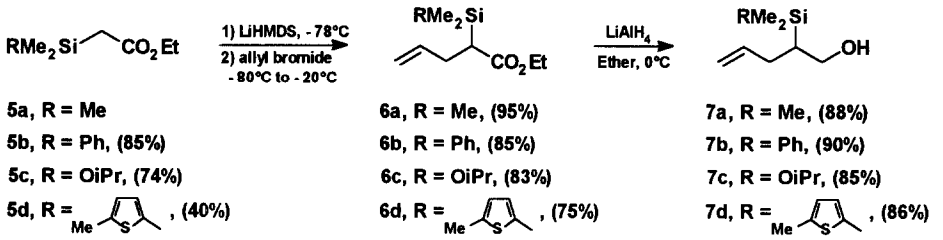
Marine tetrahydrofurans such as **1**, isolated from red algae of the genus *Laurencia*, are presumed to be formed by halocyclization of corresponding polyene-alcohols.[1,5] The challenging structure of these natural compounds prompted us to devised a general approach (Scheme 1), where the heterocycle moiety is formed by a stereocontrolled cyclization of homoallylsilane (e.g. **3**). The silicon group is expected to control the stereochemistry at both prochiral centres, first during the reduction of the ketone (1,2-stereocontrol),[6] then during the cyclofunctionalization (1,3-stereocontrol). Finally, the silyl moiety can be unmasked with retention of configuration revealing an hydroxyl group.[7]



trans **- kumausyne 1** **2** **3** **4**

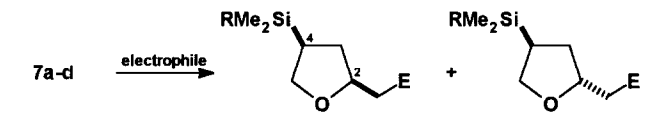
Scheme 1

We decided to study first the homoallylic stereocontrol arising from the electrophilic cyclization of simple β-hydroxy silanes **7**. These compounds are easily available in 3 steps from the corresponding α-silylacetic esters **5**, prepared by Si-H insertion of carbenes generated by $Rh_2(OAc)_4$ catalyzed decomposition of ethyl diazoacetic ester.[8,9] Alkylation of the latter using LiHMDS and allyl bromide, followed by reduction of the ester group with $LiAlH_4$ afforded the desired homoallylic alcohols **7a-d** in good overall yields (Scheme 2).



Scheme 2

Our first attempts of halocyclization using Bartlett's kinetic conditions[2c,4a] (I_2, $NaHCO_3$) were disappointing due to the low conversion and degradation of the starting material. This is probably because a large excess of I_2 had to be used,[10] and therefore we decided to look for electrophiles that could be used in stoechiometric amount. Our first results, using various electrophiles, are summarised in table 1. The cyclization took place, as expected, through a *5-exo-trig* process leading to tetrahydrofurans in generally good yields (Scheme 3). It is noteworthy that under these conditions, the silyl moiety remained untouched and no tetrahydropyran was detected in the ^1H NMR of the crude mixture. Subsequent separation by flash chromatography afforded the pure diastereoisomeric tetrahydrofurans **8** and **9**. The *cis*-2,4-stereorelationship of the major diastereoisomers have been unambiguously assigned using NOESY experiments.[11] Phenylselenoetherification was found to be poorly selective (entry 1) in agreement with some observations made by Reitz and co-workers on related cyclofunctionalizations.[3a] Whereas I_2 gave poor results, iodoetherification with N-iodosuccinimide (NIS) provided the corresponding tetrahydrofurans in excellent yields and good selectivity (entry 2-3). We then examined the reactions of **7a-d** with Hg(II) salts, and found that the reaction was highly stereoselective, but also that the high homoallylic stereocontrol was salt (entry 7 and 11), solvent (entry 7-8 and 11-12) and to a lesser extent, temperature dependent (entry 7 and 9).[12] Surprisingly, when the reaction was carried out in the absence of a base (entry 10), the diastereoselectivity remained very high.[13]



Scheme 3 **8** **9**

Table 1. **Electrophilic cyclizations of homoallylic silanes 7a-d (Scheme 3).**

Entry	Substrate[a]	Electrophiles[b]	Solvent	T (°C)	E	Yield (%)[c]	ratio 8 : 9[d]
1	7d	PhSeCl, K_2CO_3	Et_2O	- 70°	PhSe	70	**69 : 31**
2	7b	NIS	CH_2Cl_2	+ 20°	I	89	**83 : 17**
3	7d	NIS	CH_2Cl_2	- 20°	I	89	**86 : 14**
4	7a	$Hg(OAc)_2$, $CaCO_3$	THF	- 20°	HgBr	88	**91 : 9**
5	7b	$Hg(OAc)_2$, $CaCO_3$	THF	- 20°	HgBr	82	**94 : 6**
6	7c	$Hg(OAc)_2$, $CaCO_3$	THF	- 20°	HgBr	71	**92 : 8**
7	7d	$Hg(OAc)_2$, $CaCO_3$	THF	- 20°	HgBr	81	**94 : 6**
8	7d	$Hg(OAc)_2$, $CaCO_3$	CH_3CN	- 20°	HgBr	78	**86 : 14**
9	7d	$Hg(OAc)_2$, $CaCO_3$	THF	+ 20°	HgBr	82	**88 : 12**
10	7d	$Hg(OAc)_2$.	THF	- 20°	HgBr	88	**95 : 5**
11	7d	$Hg(TFA)_2$, $CaCO_3$	THF	- 20°	HgBr	87	**80 : 20**
12	7d	$Hg(TFA)_2$, $CaCO_3$	CH_3CN	- 20°	HgBr	77	**57 : 43**
13	7d	$Hg(NO_3)_2$, $CaCO_3$	THF	- 20°	HgBr	81	**90 : 10**

[a] 0.1M solution (1mmol scale); [b] Electrophile (1.1 eq.), $CaCO_3$ (2.2 eq.), then saturated aqueous KBr; [c] Isolated yields after flash chromatography; [d] Determined by 400 MHz ^1H NMR.

The high selectivity we obtained may be rationalised using a transition state close to the one proposed by Harding and Burks for the mercury-cyclization of olefinic amides.[14] It is reasonable to assume that a similar chair-like transition state is involved in our case and that the silicon group adopts an equatorial position (fig-1). Further evidence for such a transition state has been put forward by Labelle et al. for the iodoetherification of homoallylic alcohols.[4a] Interestingly, semiempirical calculations, supported by experimental results, showed that electronegative substituents (*i.e.* F, OH, OMe) on the homoallylic center prefer the axial position in the transition state.[3g,4a,4b] Also noteworthy is that a slight decrease in the steric bulk around silicon did not alter the selectivity (entry 4). This could indicate the presence of an electronic effect. However, the Me_3Si is a bulky group and hence steric effects cannot be completely ruled out.

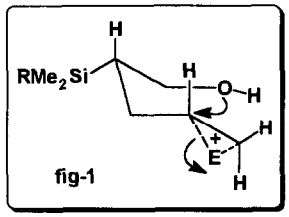
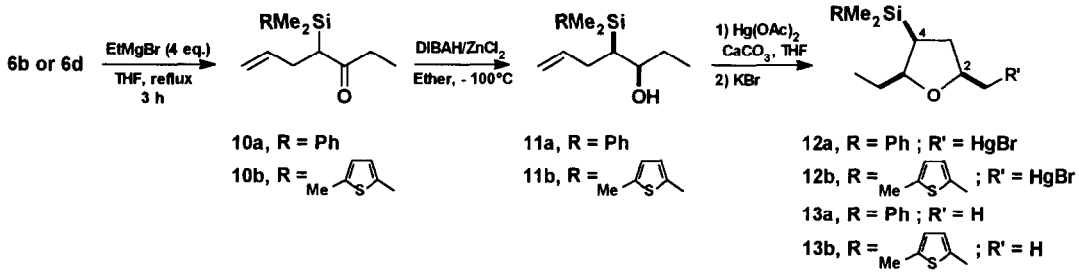


fig-1

This transition state may also explain the intriguing selectivity difference observed between entries 11 and 12 (and between entries 7 and 8), on changing from THF to CH_3CN as solvent. The large dielectric constant of acetonitrile (ε = 38) compared to that of THF (ε = 7.6) may be at the origin of the formation of a localised positive charge (*i.e.* an open cation) instead of a bridged mercurium ion, resulting in a drop in the diastereoselectivity.[15] The less sterically congested *trans*-2,4-disubstituted tetrahydrofuran **9** would thus be obtained in larger amount.

To further establish the usefulness of our methodology, we extended our studies to the synthesis of 2,4,5-trisubstituted tetrahydrofurans. The desired starting alcohols were obtained using a two-step sequence involving transformation of the ester function into the corresponding ketone (*i.e.* **10a-b**) using Larson's procedure,[16] followed by the highly stereoselective reduction[6] of the ketone into β-hydroxy silane using DIBAH/$ZnCl_2$ (45-50% overall yield, *syn*/*anti* >95:5). The alcohols **11a-b** were then cyclized, to give the tetrahydrofurans **12a-b** in 75-80% yields, with selectivities following the trends already observed in the disubstituted series (2,4-*cis*/2,4-*trans* 92:8 for **12a** and 95:5 for **12b**). Finally, the C-Hg bond was readily reduced ($NaBH_4$/NaOH), affording the corresponding tetrahydrofurans **13a-b** in 80-85% yields (Scheme 4).[17]



Scheme 4

In summary, we report an extension of our research concentrated towards the synthetic potential of α-silylacetic esters. Particularly noteworthy is that the cyclization described produces the *cis*-2,4-substituted tetrahydrofurans, complementing the *trans*-2,4 stereoselectivity obtained from the cyclization of chiral homoallylic alcohols.[4a] Since the C-Si to C-OH bond conversion takes place with retention of configuration,[7] our method represents a facile entry to 2,4,5-trisubstituted tetrahydrofurans possessing a stereochemistry analogous to that of *trans*-kumausyne **1**.[5] Further elaboration of this methodology is now under way in this laboratory and will be reported in due course.

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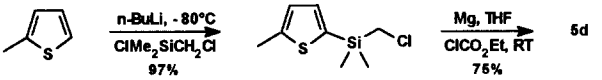
9. Compound **5a** is commercially available (Fluka). The α-silylacetic ester **5d** has also been obtained in better yield using the following two-step procedure:



10. 5 equivalents of I_2 were required to consume the olefin, due to the low solubility of I_2 in organic solvents.
11. Each tetrahydrofuran has also been converted into its 2-methyl analog ($NaBH_4$-NaOH for E=HgBr, Bu_3SnH-benzene for E=I and E=SePh), demonstrating that the same diastereoisomer was obtained, independently from the nature of the electrophile
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17. All new compounds gave satisfactory spectroscopic and microanalytical data. Selected data, **13a**: ^1H NMR ($CDCl_3$, 250MHz) δ ppm: 0.32 (s, 3H, $SiCH_3$), 0.36 (s, 3H, $SiCH_3$), 0.91 (t, 3H, J= 7.2 Hz, $C\underline{H}_3CH_2$), 1.20-1.37 (m, 2H, $CH_3C\underline{H}_2$), 1.26 (d, 3H, J= 6 Hz, CH_3), 1.41 (ddd, 1H, J= 9.3, 11.8, 12.5 Hz, H-3β), 1.84 (ddd, 1H, J= 6.6, 7.8, 12.5 Hz, H-4), 2.01 (ddd, 1H, J= 5.3, 6.6, 11.8 Hz, H-3α), 3.87- 4.05 (m, 2H, H-2 and H-5), 7.31-7.39 (m, 3H, H-arom), 7.50-7,55 (m, 2H, H-arom).

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