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Studies towards 1,3-diol units starting from *syn* β-hydroxy acylsilanes

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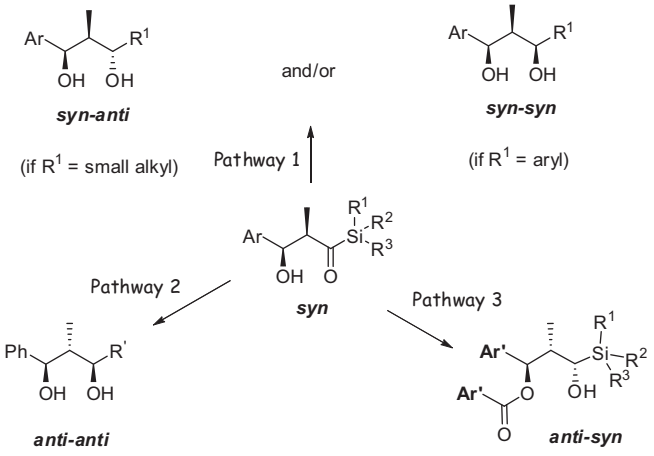
ABSTRACT

Three complementary strategies have been explored to obtain stereodefined 1,3 diols starting from easily accessible *syn* β-hydroxy acylsilanes: fluoride induced migrations of substituents on silicon, a Grignard addition followed by protodesilylation and Tischenko-type reactions. Preliminary data on scope and limitations of these processes are presented.

The acylsilane is a highly versatile functionality and many elegant applications in organic synthesis have been already reported, based on the use of this group.[1] However only a few studies have been described, to date, on the synthesis and the applications of β-hydroxy acylsilanes,[2] although such units appear as potentially very useful building blocks. We have reported recently a new, efficient and stereoselective, synthesis of *syn* β-hydroxy acylsilanes by using a tandem isomerization–aldolisation process,[3] and their use for the preparation of several oxygen-containing heterocycles.[4]

As part of a programme dealing with the total synthesis of bioactive natural products and structural analogues, we were interested in the development of methods to access the important propionate-type 1,3-diol units starting from such *syn* β-hydroxy acylsilanes.

The purpose of this Letter is to report our preliminary results indicating that, by using three complementary approaches, latter silanes can be used for the synthesis of various 1,3-diols with a good stereochemical control (Scheme 1). The first route (pathway 1) involves the migration of substituents from silicon onto the vicinal carbonyl group. The second (pathway 2) utilizes a Grignard addition, followed by a protodesilylation pathway. In the third route (pathway 3), we consider a sequence involving Tischenko-type reactions.



Scheme 1. Three complementary pathways to stereoisomers of 1,3-diol units.

The alkoxide-induced migrations of alkyl or aryl groups on simple acylsilanes have been first reported by Brook,[5] and this process has been extended later to fluoride-mediated reactions by the groups of Ricci and Walton.[6] On the other hand, starting from β-hydroxy acylsilanes, highly stereoselective migrations of phenyl groups have been reported by Oshima and Utimoto.[7] More recently it has been successfully extended to *anti* β-alkoxy

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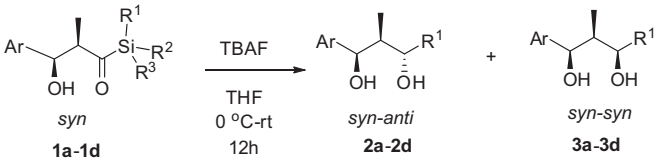


Scheme 2. Fluoride induced migration of alkyl and aryl groups starting from *syn* β-hydroxy acylsilanes **1a-1d**.

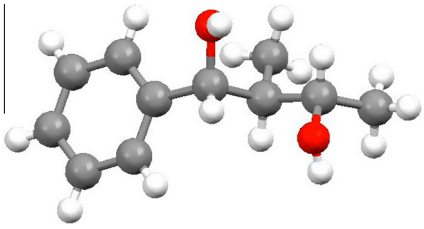
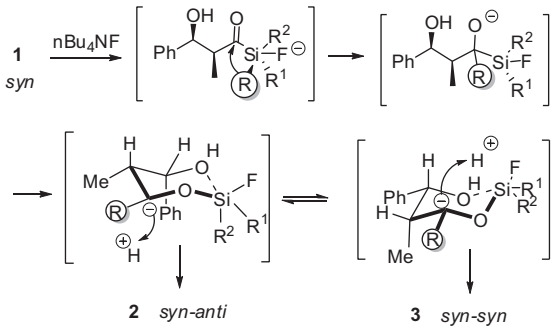


Figure 1. Structure of 1,3-diol **2a** by X-ray analysis.

acylsilanes by the group of Honda,[8] while some group migrations were reported during thermal rearrangements of α-(acyloxy) silanes.[9]

We studied first the migratory aptitudes and the stereoselectivity of fluoride-induced migrations of the *syn* β-hydroxy acylsilanes **1**. The results are indicated in Scheme 2 and Table 1. For the acylsilanes bearing three small alkyl groups on silicon (Me to *n*-Pr), the migration occurred easily to give, in good to excellent yields and high stereoselectivities, the *syn-anti* diols **2a**–**2c** (entries 1–3). Small amounts (3–10%) of *syn–syn* derivatives **3a**–**3c** were detected by NMR of the crude reaction mixtures. The major *syn-anti* derivatives have been isolated by silica gel chromatography. In the case of bulkier groups on silicon, such as *i*Pr or *t*Bu, complex reaction mixtures were obtained. In order to study the migration of a phenyl group, we started from *syn* aldol **1d** obtained by the tandem isomerization–aldolisation reaction between *p*-bromobenzaldehyde and the allylic alcohol bearing a TBDPS group.[3] In agreement with the literature data,[7] the phenyl group migrates preferentially to *t*Bu and with a *syn* selectivity. However, this selectivity is temperature dependent since the ratio of **2d** to **3d** is ranging from 40:60 to 15:85 (Table 1, entries 4–7) and the highest stereoselectivity is obtained at 40 °C. Both isomers **2d** and **3d** have been isolated after chromatography on SiO_2. The *syn-anti* and *syn–syn* stereochemistry of all 1,3-diols **2** and **3** have been established from the NMR data, by comparison with the literature.[10] Further, the structure of the 1,3-diol **2a** was confirmed by X-ray crystallography analysis (Fig. 1).[11]

In agreement with the literature,[8] we can propose the tentative mechanism indicated in Scheme 3. After fluoride addition on silicon, the Brook rearrangement gives the corresponding carbanion which is protonated at the stereoinducing step. The Si–O interaction allows six-membered type transition states but, due to the *syn* structure of the starting aldol, two conformers can be in equilibrium. The protonation of the one with the methyl group in



Scheme 3. Tentative mechanism for the formation of 1,3-diols **2** and **3**.

equatorial position affords the *syn-anti* derivative **2**, while the second with the phenyl group in equatorial position gives the *syn–syn* diols **3**. Although the mechanistic details of these reactions need further experimental and computational studies, it is clear that the nature of the R group plays a key role in this method and with R = alkyl, compounds **2** are prefered, while for R = Ph the 1,3-diols **3** are obtained.[12]

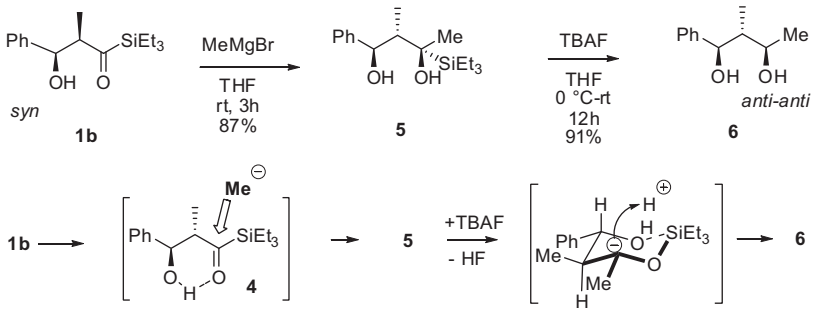
A second route to 1,3-diols (pathway 2) was considered by taking advantage of the stereoselectivity of both the Grignard addition to acylsilanes[13] and the protodesilylation reaction.[13,14] Starting from **1b**, the reaction of methyl Grignard afforded in good yields and as a single isomer, the tertiary alcohol **5** (Scheme 4).

The stereochemistry of this compound was established by X-ray crystallography, as indicated in Figure 2.[11] It is noteworthy that this Grignard addition is occurring with complete epimerisation at the stereocentre bearing the methyl group. Such an epimerisation has been reported with other aldol derivatives and it is occurring via retroaldol-aldol processes.[15] This pathway is likely to be occurring here to afford initially *anti* aldol **4**,[16] and then the

Table 1
Fluorine-induced diastereofacial migration of aryl or alkyl groups from silicon to carbonyl in β-hydroxy acylsilanes **1**

Entry	Aldol	Ar	R^1	R^2	R^3	Temp.	Products	Yield[a,b] (%)	Product diastereoselectivity (*syn-anti*, *syn-syn*)[f]
1	**1a**	Ph	Me	Me	Me	rt	**2a**:**3a**	90[c,d]	97.:03
2	**1**	Ph	Et	Et	Et	rt	**2b**:**3b**	82[d]	87:13
3	**1c**	Ph	*n*-Pr	*n*-Pr	*n*-Pr	rt	**2c**:**3c**	83[d]	90:10
4	**1d**	4Br-Ph	Ph	Ph	*t*-Bu	+40 °C	**2d**:**3d**	13[a], 70[a]	15:85
5	**1d**	4Br-Ph	Ph	Ph	*t*-Bu	rt	**2d**:**3d**	86[e]	20:80
6	**1d**	4Br-Ph	Ph	Ph	*t*-Bu	0 °C	**2d**:**3d**	80[e]	30:70
7	**1d**	4Br-Ph	Ph	Ph	*t*-Bu	−20 °C	**2d**:**3d**	85[e]	40:60

[a] Isolated yield.
[b] All products were characterized by ^{1}H NMR, ^{13}C NMR and mass spectral data.
[c] The product was characterized by X-ray.
[d] Isolated yield of major product.
[e] Isolated yield of **2d**+**3d** mixture.
[f] The diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction mixtures.



Scheme 4. Grignard addition on aldol **1b**, followed by protodesilylation to *anti*,*anti* 1,3-diol **6**.

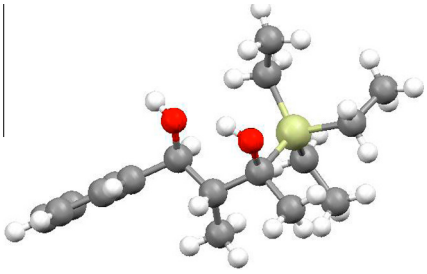


Figure 2. Structure of alcohol **5** by X-ray analysis.

Grignard adduct **5**. In a final step, the protodesilylation of **5** occurs in a fully stereocontrolled fashion to give the *anti–anti* 1,3-diol **6**.

Tentative mechanisms can be proposed in order to explain the stereochemistry of these reactions (Scheme 4). Taking into account the intramolecular hydrogen bond in **4**, the Grignard addition should occur *anti* to the neighbouring methyl group to afford the adduct **5**. On the other hand after fluoride-induced oxygen shift of the silyl group, the protonation of carbanion intermediate furnished the *anti–anti* 1,3-diol **6**. Such protodesilylations have been reported in the literature and their stereoselectivity has been established.[13,14]

The next strategy (pathway 3) was to employ a Tischenko-type process. To the best of our knowledge, it has been reported once starting from acetyltrimethylsilane,[2d] but never from β-hydroxy acylsilanes. On reaction of **7d** with *p*-bromobenzaldehyde under basic conditions, the expected Tischenko product was not obtained. Instead an unexpected product **8**, bearing two *p*-bromobenzaldehyde units, was isolated in good yield together with benzaldehyde (Scheme 5, Table 2). The structure of **8** was established by NMR and MS and the *anti-syn* stereochemistry of the 1,3-diol **8** was confirmed by X-ray analysis, as indicated in Figure 3.[11]

The formation of this compound is very likely due to a retroaldol process followed by an aldolisation with the added *p*-bromobenzaldehyde and completed by a Tischenko-type reaction to give **8** (Scheme 6). In order to study the scope and limitations of such a method, complementary studies have been performed. A similar result was obtained with *p*-nitrobenzaldehyde, affording compound **9**. In the same way, on reaction of **7d** with benzaldehyde, the 1,3-diol **10** was obtained. However, under the same conditions and starting from the same β-hydroxysilane **7d** but using aldehydes with various alkyl subsituents (R′ = *t*-Bu, *i*-Pr), only the corresponding *syn* aldol products **11–12** were isolated in low yields, along with the recovered starting material, without evidence for corresponding Tischenko products. A similar result was obtained with *p*-methoxybenzaldehyde, affording *syn* aldol **13**. The NMR data of derivatives **11–13** were found to be identical with the compounds obtained by the direct tandem isomerization–aldolisation process.[3] Therefore, with such aliphatic aldehydes or less reactive aromatic aldehydes, the reaction

Table 2
Attempts to perform a Tischenko process from β-hydroxy acylsilanes **7d** and **7e**

Entry	Aldol	R	R′	Products	Yield[a,b](%)
1	**7d**	Ph	4Br-Ph	**8**	78[c]
2	**7d**	Ph	4NO_2-Ph	**9**	82
3	**7d**	Ph	Ph	**10**	85
4	**7d**	Ph	*t*-Bu	**11**	40
5	**7d**	Ph	*i*-Pr	**12**	25
6	**7d**	Ph	4OMe-Ph	**13**	32
7	**7e**	*t*-Bu	4Br-Ph	**8**	81

[a] Isolated yield.
[b] All products were characterized by ^{1}H NMR, ^{13}C NMR and mass spectral data.
[c] The product was characterized by X-ray.

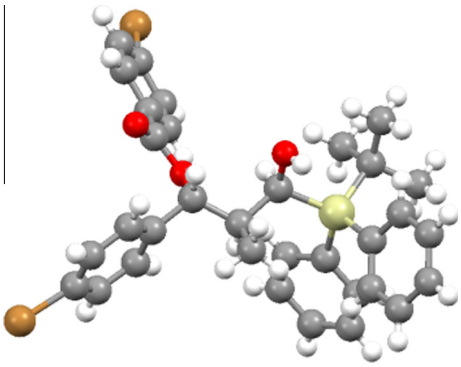
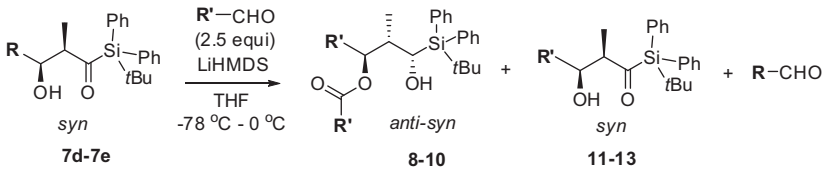
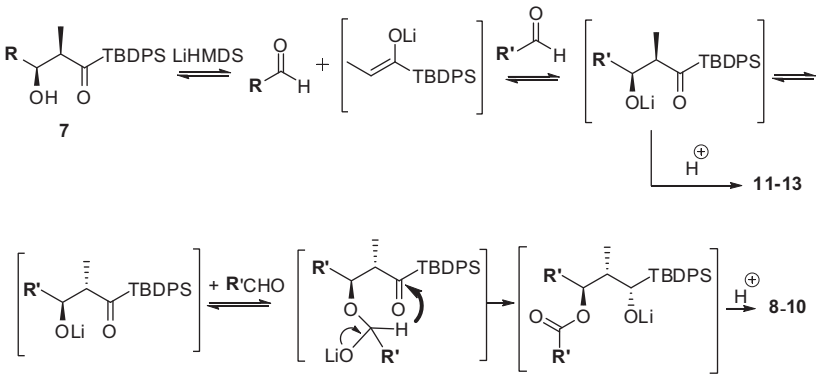


Figure 3. Structure of alcohol **8** by X-ray analysis.



Scheme 5. Attempts to perform a Tischenko sequence starting from *syn* β-hydroxy acylsilanes **7d** and **7e**.



Scheme 6. Proposed mechanism for the formation of 1,3 diols **8**–**10** and *syn* aldols **11**–**13**.

stopped at the retroaldol-aldol step and the Tischenko reaction was not occurring.

In conclusion, these preliminary results demonstrate for the first time that with β-hydroxy acylsilanes the easily occurring retroaldol processes should be taken care of. However starting from the same *syn* β-hydroxy acylsilane and using different reaction pathways, it was possible to obtain three different sets of 1,3 diols:

1. The first, with the *syn*,*anti* (or *syn*,*syn*) structures, by fluoride induced migrations of groups on silicon;
2. The second, with an *anti*,*anti* stereochemistry, by Grignard addition, followed by protodesylilation;
3. The last series, with an *anti*,*syn* stereochemistry, by a retroaldol-aldol-Tischenko sequence. However, the latter method is more limited since it is occurs only with reactive aromatic aldehydes.

Thus, these results confirm the potentialities of the β-hydroxy acylsilanes in synthesis and further studies on the use of these building blocks are under active development in our groups.

Acknowledgements

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Supplementary data

Supplementary data (experimental procedures and compound characterization) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.034.

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11. CCDC 949455 contain the supplementary crystallographic data for compound **2a**. CCDC 949456 contain the supplementary crystallographic data for compound **5**. CCDC 949457 contain the supplementary crystallographic data for compound **8**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
12. As pointed out by a reviewer, the exact structures of the carbanions (conjugated or not) will be very likely different in the two postulated transition states. Therefore, they will induce different electronic interactions with the neighbouring oxygen, as well as different steric effects with the other alkyl and aryl groups in the molecule.
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