Dancing Silanols: Stereospecific Rearrangements of Silanol Epoxides into Silanoxy-Tetrahydrofurans and Silanoxy-Tetrahydropyrans

Harshit Joshi[a], Annu Anna Thomas[a], Joel T. Mague[b], and Shyam Sathyamoorthi[a,*]

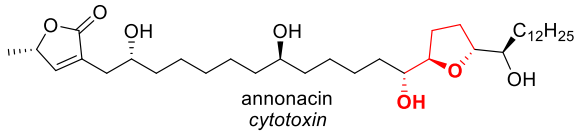
[a] University of Kansas, Department of Medicinal Chemistry, Lawrence, KS, USA (66047)

[b] Tulane University, Department of Chemistry, New Orleans, LA, USA (70118)

ABSTRACT: We have developed highly stereospecific rearrangements of silanol epoxides into 1'-silanoxy-tetrahydrofurans and 1'-silanoxy-tetrahydropyrans. Upon treatment with Ph_3CBF_4 and $NaHCO_3$ in CH_2Cl_2, di-substituted *trans*-epoxide silanols rearrange into products with an *erythro* configuration; di-substituted *cis*-epoxide silanols give products with a *threo* configuration. To our knowledge, this transformation has little literature precedent. Control experiments show that the rearrangement reaction likely proceeds by nucleophilic attack of the proximal silanol oxygen onto the epoxide followed by an intramolecular silyl transfer. We have used these reactions as key steps in the syntheses of (±)-solerone and (±)-muricatacin.

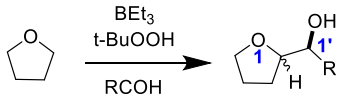
Scheme 1. Current approaches to 1'-hydroxy-tetrahydrofurans contrasted with our own.

Knowledge Gap: 1'-hydroxy-tetrahydrofurans are important motifs in biologically active natural products, but general methodology is lacking for highly regioselective and diastereoselective syntheses.



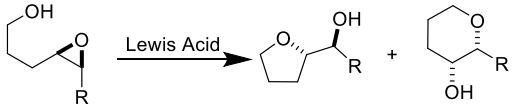
Current Methodology to Access 1'-Hydroxy-Tetrahydrofurans Includes:

1. Radical additions into aldehydes.



Limitations: Mixtures of diastereomers are produced.

2. Ring Opening of Epoxides.

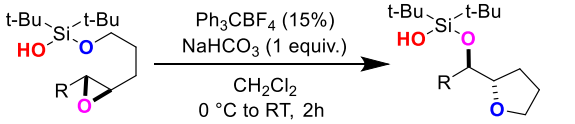


Limitations: Mixtures of regioisomers are produced.

3. Nucleophilic addition into carbonyl compounds

Limitations: Mixtures of diastereomers are produced.

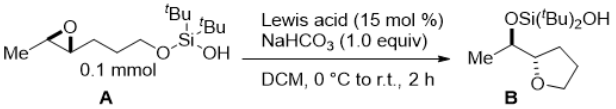
Our Approach: An Unprecedented Stereospecific Rearrangement



single diastereomer
F^+ removes the silanol

1'-hydroxy-tetrahydrofurans are found in many important biologically active natural products and are key structural features of the annonaceous acetogenins[1-3] (**Scheme 1**). The annonaceous acetogenins are known for possessing a range of interesting properties, including neurotoxicity, cytotoxicity, and pesticidal activity. There is a dearth of technology for the direct stereoselective and regioselective synthesis of 1'-hydroxy-tetrahydrofurans. Radical additions into aldehydes,[4, 5] ring opening of epoxides,[6-8] and nucleophilic additions into tetrahydrofuran carbaldehydes[9-11] generally furnish mixtures of diastereomers or regioisomers. Our laboratory has a programmatic focus on the development of the di-*tert*-butyl silanol moiety into a synthetically useful auxiliary.[12-19] During our exploration of epoxide opening reactions by pendant silanols,[15] we serendipitously discovered an unprecedented rearrangement reaction of silanol epoxides into 1'-silanoxy-tetrahydrofurans. The uniqueness of this transformation prompted us to further explore its scope, mechanism, and potential applications. What follows is an account of our discoveries with this remarkable transformation.

Table 1. Effect of Lewis Acids on Reaction Performance.



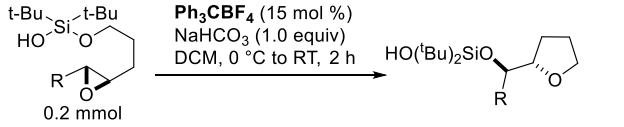
Entry	Lewis acid	Product yield (%)
1	$Ph_3C^+BF_4^-$	83
2	Tropylium BF_4	0
3	$Al(OTf)_3$	82
4	$Sc(OTf)_3$	85
5	BF_3•Et_2O	90
6	$In(OTf)_3$	82
7	$Zn(OTf)_2$	10

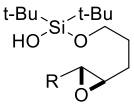
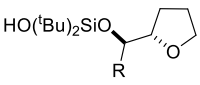
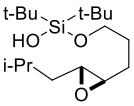
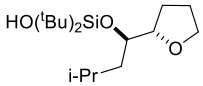
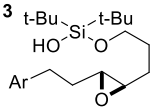
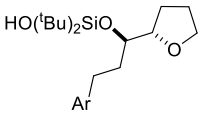
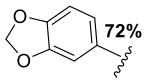
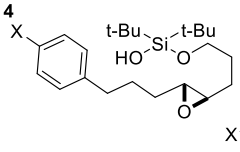
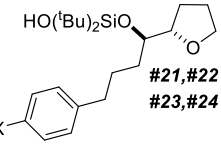
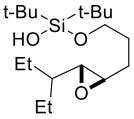
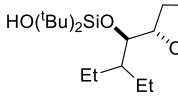
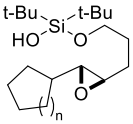
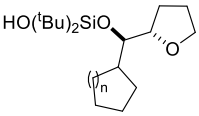
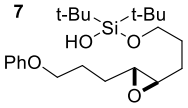
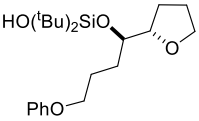
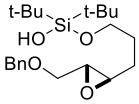
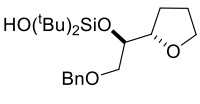
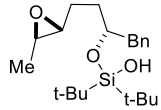
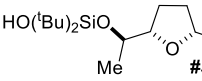
Our initial investigations were conducted with Ph_3CBF_4, an unusual Lewis acid catalyst (**Table 1**, **Entry 1**). We wondered if other Lewis acids were capable of transforming silanol epoxide **A** into silanoxy-tetrahydrofuran **B**. Interestingly, with the related catalyst tropylium tetrafluoroborate, the reaction shut down completely (**Table 1**, **Entry 2**). With strong Lewis acids such as $Al(OTf)_3$, $Sc(OTf)_3$, BF_3•OEt_2, and $In(OTf)_3$, the yield of the rearrangement was comparable to that with Ph_3CBF_4 (**Table 1**, **Entries 3–6**). With $Zn(OTf)_2$, a markedly weaker Lewis acid,[20, 21] the yield of **B** was only 10% with starting material accounting for the remaining mass balance (**Table 1**, **Entry 7**). A solvent screen (See **Supporting Information**, **Additional Optimization Section**) revealed that none were better than CH_2Cl_2.

We examined the scope of this rearrangement reaction with a range of *trans* (**Scheme 2**) and *cis* (**Scheme 3**) epoxide substrates. Di-substituted *trans*-epoxide silanols rearranged stereospecifically into *erythro* silanoxy-tetrahydrofurans. Analogously, di-substituted *cis*-epoxide silanols gave *threo* silanoxy-tetrahydrofurans. The silanol groups in products **24** and **56** were removed using TBAF, and X-ray crystallography of the resulting hydroxy-tetrahydrofurans (**CCDC 2233480** and **CCDC 2233482**) allowed us to unambiguously confirm product identity and relative stereochemistry (See **Supporting Information**, **Structural Reasoning** and **X-ray Crystallography Sections** for additional details). In our optimization experiments (**Table 1**), rearranged product formed in good yields with a range of Lewis acids. However, as the substrate complexity increased, we observed that the best yields were obtained with Ph_3CBF_4, and our optimized reaction protocol involved stirring silanol epoxide substrate with 15 mol% of Ph_3CBF_4 and 1 equivalent of $NaHCO_3$ in CH_2Cl_2 for 2 hours. The role of $NaHCO_3$ is not entirely clear, but, in the absence of it, we have seen a loss of up to 20% of the product yield. We hypothesize that it quenches adventitious HBF_4 and prevents unproductive decomposition of the Brønsted acid-labile silanol moiety. The functional group compatibility of this rearrangement reaction was quite good; alkyl ethers (**Scheme 2**, **Entries 7–8**), aryl ethers (**Scheme 2**, **Entries 3–4**), halogenated aryl rings (**Scheme 2**, **Entry 3** and **Scheme 3**, **Entry 5**), alkyl bromides (**Scheme 3**, **Entry 6**), and terminal epoxides (**Scheme 3**, **Entry 7**) were all tolerated under the reaction conditions. We have also scaled this rearrangement reaction from 0.2 mmol to 3.87 mmol (19-fold increase, **Scheme 4**), without loss of yield or selectivity.

Our success in preparing tetrahydrofuran products prompted us to examine the analogous preparation of 1'-silanoxy-tetrahydropyrans (**Scheme 5**). With substrate **63**, desired product formed in a modest 10% yield (**Scheme 5**, **Entry 1**). Replacing one of the chain carbons with an oxygen heteroatom increased product formation slightly (**Scheme 5**, **Entry 2**). The principle of Thorpe and Ingold is often applied to dramatically increase the rate of cyclization reactions.[22, 23] In line with their observations, with substrates containing *gem*-dialkyl substitutents (**Scheme 5**, **Entries 3-6**), the corresponding silanoxy-tetrahydropyran products formed in synthetically useful yields.

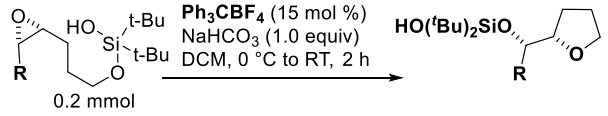
Scheme 2. Substrate Scope (*trans* epoxides).

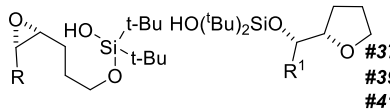
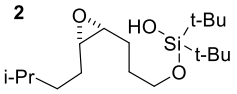
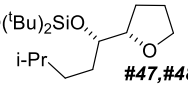
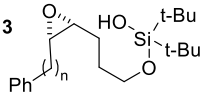
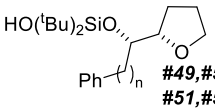
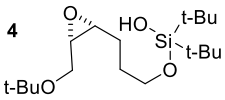
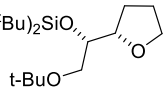
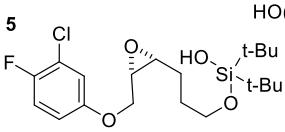
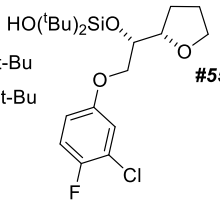
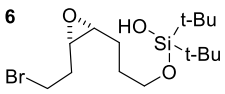
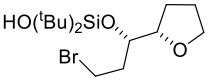
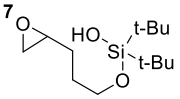
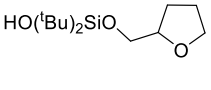
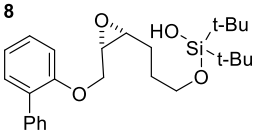
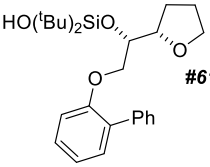


entry	substrate	product	isolated yield (%)
1			***#1,#2***[a] R = Me: **78%** ***#3,#4*** R = C_3H_7: **77%** ***#5,#6*** R = C_6H_{13}: **78%** ***#7,#8*** R = $C_{12}H_{25}$: **80%**
2			***#9,#10*** **71%**
3			***#11,#12*** Ar = Ph: **71%** ***#13,#14*** Ar = 4-F-Ph: **73%** ***#15,#16*** Ar = 3-CF_3-Ph: **67%** ***#17,#18*** Ar = 4-CH_3O-Ph: **72%** ***#19,#20*** Ar =  **72%**
4			***#21,#22*** X = H: **80%** ***#23,#24*** X = OMe: **81%**
5			***#25,#26*** **44%**
6			***#27,#28*** n = 1: **40%** ***#29,#30*** n = 2: **50%**
7			***#31,#32*** **50%**
8			***#33,#34*** **86%**
9			***#35,#36*** **60%**

[a]substrate number, product number; Note: all compounds shown are racemic, and relative stereochemistry is depicted.

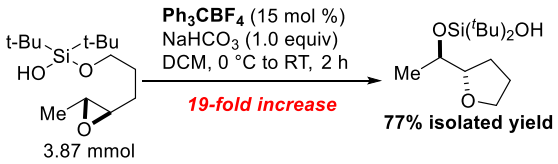
Scheme 3. Substrate Scope (*cis* epoxides).



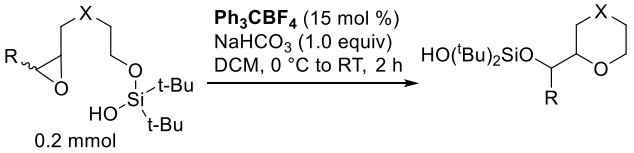
entry	substrate	product	isolated yield (%)
1			***#37,#38***[a] R = Me: **84%** ***#39,#40*** R = t-Bu: **60%** ***#41,#42*** R = C_3H_7: **74%** ***#43,#44*** R = C_6H_{13}: **87%** ***#45,#46*** R = $C_{12}H_{25}$: **80%**
2			***#47,#48*** **80%**
3			***#49,#50*** n = 1: **75%** ***#51,#52*** n = 2: **81%**
4			***#53,#54*** **85%**
5			***#55,#56*** **64%**
6			***#57,#58*** **64%**
7			***#59,#60*** **60%**
8			***#61,#62*** **50%**

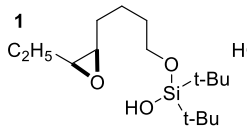
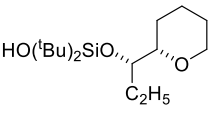
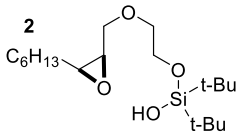
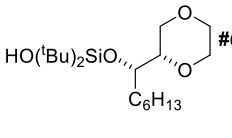
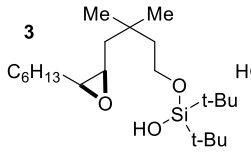
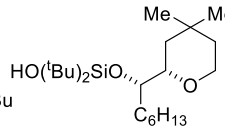
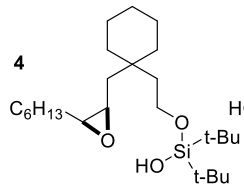
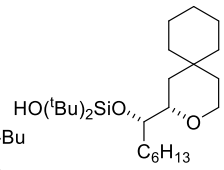
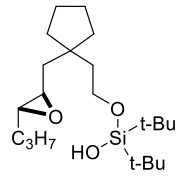
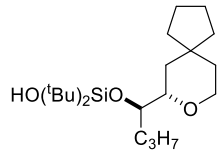
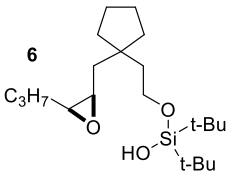
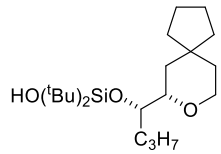
[a]substrate number, product number; Note: all compounds shown are racemic, and relative stereochemistry is depicted

Scheme 4. Scale-up reaction.



Scheme 5. Preparation of Silanoxy-Tetrahydropyrans.



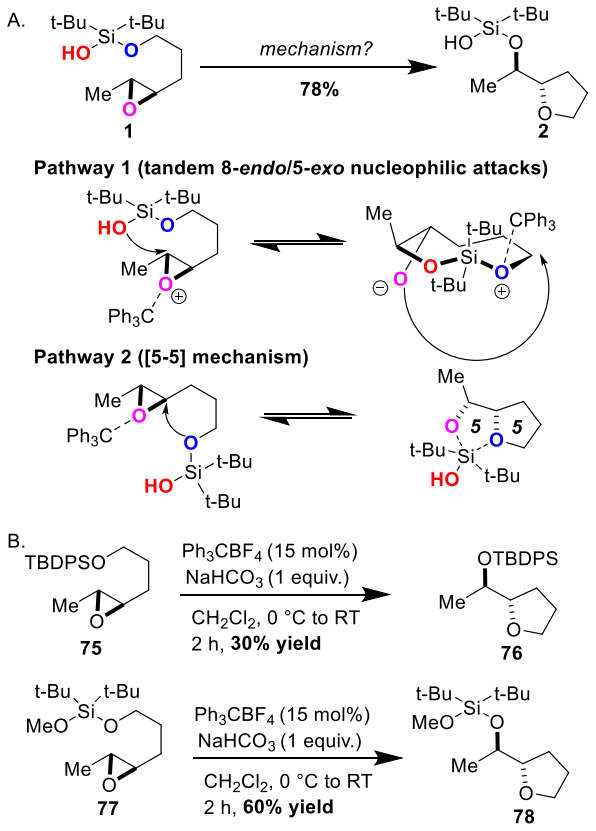
entry	substrate	product	isolated yield (%)
1			***#63,#64***[a] **10%**
2			***#65,#66*** **15%**
3			***#67,#68*** **70%**
4			***#69,#70*** **82%**
5			***#71,#72*** **50%**
6			***#73,#74*** **66%**

[a]substrate number, product number; Note: all compounds shown are racemic, and relative stereochemistry is depicted

We were very interested in determining the mechanism of formation for these 1'-silanoxy-heterocycles (**Scheme 6**), and, for simplicity, we will focus on the formation of 1'-silanoxy-tetrahydrofurans. Which oxygen of the di-*tert*-butyl silanol is responsible for the initial epoxide attack? If the distal oxygen (silanol OH) attacks first, one may draw an 8-membered ring intermediate, which will immediately contract into a five-membered ring upon a second nucleophilic attack (**Scheme 6A, Pathway 1**). If the proximal oxygen attacks first, a [5,5]-mechanism is likely operative, comprised of tetrahydrofuran ring formation followed by a silyl migration[24-28] (**Scheme 6A, Pathway 2**). To distinguish between the two pathways, we designed a series of test substrates (**Scheme 6B**). With TBDPS substrate **75**, rearrangement did occur, albeit in a much lower yield. This experiment established that the distal oxygen of the silanol was not required for a productive reaction, but its presence did promote product formation. With silanoxy methyl

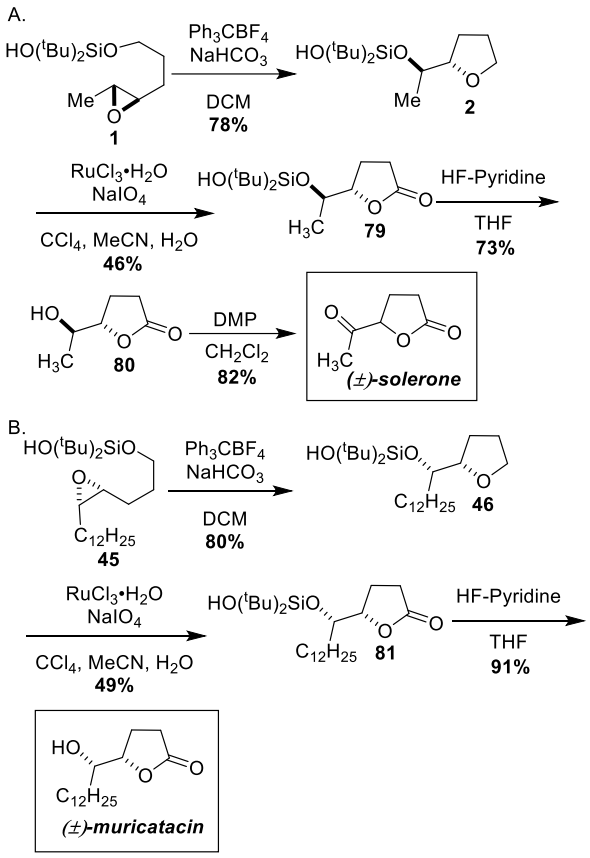
ether substrate **77**, the yield of rearrangement product **78** was higher. Both substrates were outperformed by silanol **1**, which rearranged in a 78% isolated yield. Thus, the performance of the rearrangement reaction was positively correlated to the electrophilicity of the silicon auxiliary, and we hypothesize that the [5,5]-mechanism (**Scheme 6A**, **Pathway 2**) is operative. Analogously, for the formation of 1'-silanoxy-tetrahydropyrans, a [6,5]-mechanism likely underlies product formation.

Scheme 6. Probe substrates help delineate a possible mechanism of rearrangement.



Our success with the range of substrates shown in **Schemes 2** and **3** prompted us to apply this rearrangement reaction as a key step in the syntheses of (±)-solerone (**Scheme 7A**) and (±)-muricatacin (**Scheme 7B**). Solerone is a natural product which contributes to the aroma of certain wines and has been demonstrated to be a key intermediate in the syntheses of larger chromanones.[29-36] Conversion of silanoxy-tetrahydrofuran **2** into lactone **79** proceeded upon oxidation with $RuCl_3/NaIO_4$. Treatment with HF•pyridine removed the silanol group, and DMP oxidation of the resulting alcohol gave solerone in three steps from **2 (Scheme 7A)**. A similar sequence, commencing with silanoxy-tetrahydrofuran **46**, allowed for a concise preparation of (±)-muricatacin (**Scheme 7B**). We were particularly excited by this result, as muricatacin is a known anti-tumor cytotoxin and is a demonstrated synthetic intermediate for acetogenin natural products.[37-45]

Scheme 7. Application of the rearrangement reaction for the syntheses of (A) (±)-solerone and (B) (±)-muricatacin.



In summary, we have developed highly stereospecific rearrangements of silanol epoxides into 1'-silanoxy-tetrahydrofurans and 1'-silanoxy-tetrahydropyrans. Upon treatment with Ph_3CBF_4 and $NaHCO_3$ in CH_2Cl_2, *trans*-di-substituted silanol epoxides rearrange into products with an *erythro* configuration; *cis*-di-substituted epoxides give products with a *threo* configuration. To our knowledge, this transformation has little literature precedent. Control experiments show that the rearrangement reaction likely proceeds by nucleophilic attack of the proximal silanol oxygen onto the epoxide followed by an intramolecular silyl transfer. We have used these reactions as key steps in the syntheses of (±)-solerone and (±)-muricatacin. Rearrangements have captivated organic chemists for more than a century, and we are pleased to add examples to this storied class of transformations.

ASSOCIATED CONTENT

Supporting Information. Experimental Procedures, Reasoning for Structural Assignments, NMR Spectra, and Crystallographic Information

AUTHOR INFORMATION

Corresponding Author

*E-mail: ssathyam@ku.edu.

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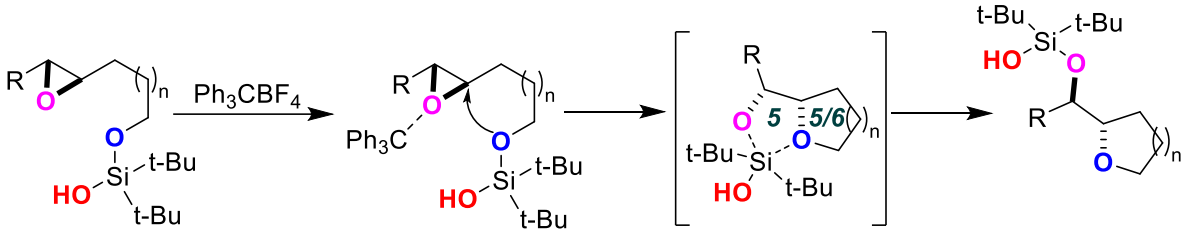
Perfectly Stereospecific Rearrangements of Silanol Epoxides



[5,5]-mechanism *for silanoxy-tetrahydrofuran formation*
[6,5]-mechanism *for silanoxy-tetrahydropyran formation*