Organic LETTERS

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Regioselective Ring Opening of Di-isopropylsilylenes Derived from 1,3-Diols with Alkyl Lithium Reagents

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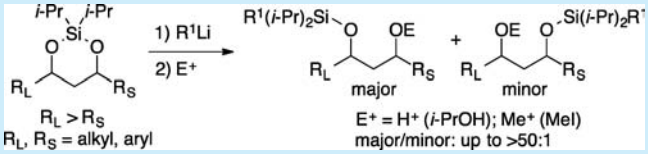
Supporting Information

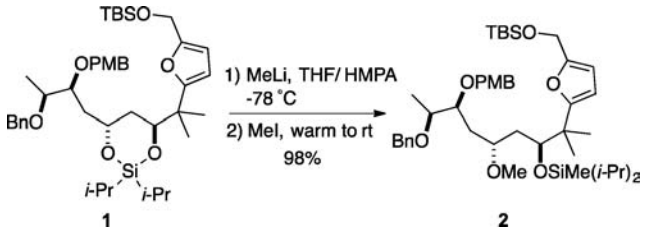
ABSTRACT: The selective alkyl lithium-induced ring opening of 1,3-di-isopropylsilylenes is described. The reaction affords a differentially substituted 1,3-diol bearing a silane that resides at the oxygen in the more sterically demanding position. The reaction can be highly selective with a regiochemical preference up to >50:1 and likely proceeds via an alkoxy-silane intermediate. This intermediate can by trapped by methyl iodide to provide the corresponding silyl methyl ether, wherein the silane again resides at the oxygen in the more sterically demanding position.



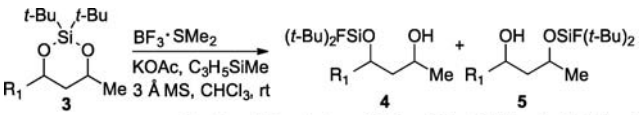
Polyoxygenated natural products, such as the oxo-polyene macrolides, have been popular targets for synthesis due to their biological activity and structural complexity,[1] and have been of long-standing interest to our laboratory.[2] The presence of a 1,3-diol moiety is common in these compounds, and the selective installation or functionalization of this group has been the subject of much research not only for this class of molecules, but for others as well.[3,4] Strategies for accomplishing this include protection of both alcohols followed by selective deprotection of the less hindered alcohol;[5] selective protection of the less hindered alcohol followed by a subsequent protection of the more hindered alcohol with an orthogonal protecting group;[6] or engaging the two hydroxyl groups in a cyclic protecting group followed by selective ring opening. The latter strategy includes protections as acetal[7] or silylene[8] groups, and each offers distinct advantages and complementary conditions for ring opening. In a recent effort directed toward the synthesis of peloruside A,[9] we had a need to selectively differentiate a 1,3-diol unit, and found that the ring opening of the silylene in compound **1** was highly selective (single isomer, Scheme 1).[10] We have since studied the scope of this method, and our results are described herein.

The protection of 1,2-, 1,3-, and 1,4-diols as the corresponding silylene is well-known,[11] and silylenes have been used for a variety of related manipulations. They have been shown to be useful in total syntheses[12] wherein they are typically removed either under acidic conditions[13] or by the use of a fluoride source.[11a,14] Interestingly, Pagenkopf has shown that it is possible to selectively cleave only one of the silicon−oxygen bonds of a dialkylsilylene using a mild fluoride source, $BF_3{\cdot}SMe_2$, in the presence of adjuncts to prevent complete desilylation.[8a] The products of these reactions bear a free hydroxyl group and a fluoro-silane, which Pagenkopf has shown to be stable to common reaction conditions. High selectivity has been observed in this reaction in the cleavage of two secondary 1,3-diols, examples of which are shown in Scheme 2.

Scheme 1. Selective Silylene Ring Opening



Scheme 2. Pagenkopf's Selective Silylene Opening



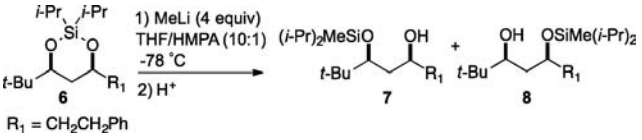
In addition, the selective ring opening of a 1,3-bicyclicsilylene by alkyl lithium reagents has been reported by Mukaiyama in the course of his total synthesis of Taxol and Kuwajima has reported the selective ring opening of primary/secondary 1,2-silylenes with alkyl lithium reagents.[15] Herein we describe the related ring opening of 1,3-silylenes wherein both alcohols are secondary.

We studied *syn*-1,3-diol **6** which bears *tert*-butyl and dihydrocinnamyl groups adjacent to the oxygens as a model to optimize the conditions for ring opening. We first studied the use of excess MeLi in THF/HMPA (10:1, 0.2M) at −78 °C and observed irreproducible results wherein the reaction proceeded with variable selectivity. We attributed this to the conditions used in the quench of the reaction and, therefore, varied the proton source in the workup and observed the following results (Table 1). Aqueous NH_4Cl provided inconsistent results, presumably because the aqueous solution immediately froze upon addition

Received: September 2, 2015
Published: October 23, 2015

DOI: 10.1021/acs.orglett.5b02529
Org. Lett. 2015, 17, 5196−5199

Table 1. Optimization of Reaction Quench



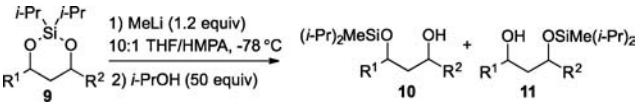
entry	H^+ source	ratio (7:8)[a]
1	xs NH_4Cl	variable up to 8:1
2	0.1 M AcOH·THF	2.5:1[b]
3	*i*-PrOH (5 equiv); 1:1 $NaHCO_3$/hexanes	5:1
4	*i*-PrOH (20 equiv); 1:1 $NaHCO_3$/hexanes	20−50:1
5	*i*-PrOH (50 equiv); 1:1 $NaHCO_3$/hexanes	>50:1

[a]Ratios determined by ^{1}H NMR of crude reaction mixtures. [b]25% cleavage to the diol.

and the reaction quenched upon melting, the rate of which was variable from run to run (Table 1, entry 1). The use of acetic acid provided diminished selectivity (2.5:1) as well as partial cleavage to the diol (Table 1, entry 2). The use of 5 equiv of isopropanol provided a 5:1 ratio of regioisomers, whereas 20 equiv provided a 20−50:1 ratio and 50 equiv proved optimal and consistently provided a ratio of >50:1 (Table 1, entries 3−5). The reaction required excess MeLi (4 equiv) in the absence of additives, but proceeded to completion using 1.2 equiv in the presence of 10:1 THF/HMPA.

The scope of this method using both *syn*- and *anti*- protected 1,3-diols is shown in Table 2. It was found that when one of the

Table 2. Regioselectivity of Silylene Monodeprotection with Proton Trapping



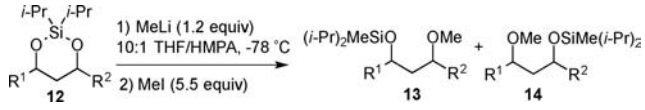
entry	R^1	R^2	*syn*/*anti*	ratio[a] **10:11**	yield[b]
1	*t*-Bu	*i*-Pr	*syn*	>50:1	95%
2	*t*-Bu	*i*-Pr	*anti*	>50:1	89%
3	*t*-Bu	Ph	*syn*	>50:1	94%
4	*t*-Bu	Ph	*anti*	>50:1	92%
5	*t*-Bu	Me	*syn*	>50:1	95%
6	*t*-Bu	Me	*anti*	>50:1	92%
7	*t*-Bu	$Ph(CH_2)_2$	*syn*	>50:1	96%
8	*t*-Bu	$Ph(CH_2)_2$	*anti*	>50:1	94%
9	$Ph(CH_2)_2$	Me	*syn*	5:1	93%
10	$Ph(CH_2)_2$	Me	*anti*	5:1	89%
11	Ph	$Ph(CH_2)_2$	*syn*	4:1	96%
12	Ph	$Ph(CH_2)_2$	*anti*	4:1	92%
13	*i*-Pr	$Ph(CH_2)_2$	*syn*	2:1	95%
14	*i*-Pr	$Ph(CH_2)_2$	*anti*	5:1	93%
15	*i*-Pr	Ph	*syn*	1:2	93%
16	*i*-Pr	Ph	*anti*	2:1	92%

[a]Ratios determined by ^{1}H NMR of crude reaction mixtures. [b]Combined isolated yields of **10** and **11**.

two alkyl groups adjacent to the diol is a *tert*-butyl group, the reaction is highly selective providing a ratio of greater than 50:1 (Table 2, entries 1−8). This is presumably due to the steric differentiation provided by the bulky *tert*-butyl group. Surprisingly, significant levels of selectivity, 5:1, were observed between methyl and methylene with the methylene substituent serving as the larger group (Table 2, entries 9 and 10). Further, phenyl proved to be a larger substituent than methylene and provided selectivities of 4:1 in the corresponding ring openings (Table 2, entries 11 and 12). The isopropyl and phenyl substituents proved near equal in size with the isopropyl group acting as the larger substituent for the *anti*-substrate and phenyl acting as the larger substituent for the *syn*-substrate (Table 2, entries 15 and 16). Finally, substrates bearing isopropyl and methylene substituents provided diminished selectivities with the isopropyl serving as the larger substituent (5:1 to 2:1; Table 2, entries 13 and 14).

In addition to opening the silylene to afford a monoprotected diol, it is possible to add a methyl iodide in situ to trap the resulting alkoxide thereby forming the silyl methyl ether. As before, the silyl ether resides on the more hindered oxygen. The scope of the methyl iodide trapping reaction was elucidated using the same *syn*- and *anti*-silylene substrates, and the results are shown in Table 3. The reaction demonstrated similar

Table 3. Regioselectivity of Silylene Monodeprotection with Methyl Iodide Trapping



entry	R^1	R^2	*syn*/*anti*	ratio[a] **13:14**	yield[b]
1	*t*-Bu	*i*-Pr	*syn*	>50:1	93%
2	*t*-Bu	*i*-Pr	*anti*	>50:1	96%
3	*t*-Bu	Ph	*syn*	>50:1	92%
4	*t*-Bu	Ph	*anti*	>50:1	94%
5	*t*-Bu	Me	*syn*	>50:1	96%
6	*t*-Bu	Me	*anti*	>50:1	92%
7	*t*-Bu	$Ph(CH_2)_2$	*syn*	>50:1	93%
8	*t*-Bu	$Ph(CH_2)_2$	*anti*	>50:1	92%
9	$Ph(CH_2)_2$	Me	*syn*	6:1	96%
10	$Ph(CH_2)_2$	Me	*anti*	6:1	88%
11	Ph	$Ph(CH_2)_2$	*syn*	3:1	97%
12	Ph	$Ph(CH_2)_2$	*anti*	3:1	88%
13	*i*-Pr	$Ph(CH_2)_2$	*syn*	2:1	96%
14	*i*-Pr	$Ph(CH_2)_2$	*anti*	5:1	92%
15	*i*-Pr	Ph	*syn*	1:2	90%
16	*i*-Pr	Ph	*anti*	2:1	90%

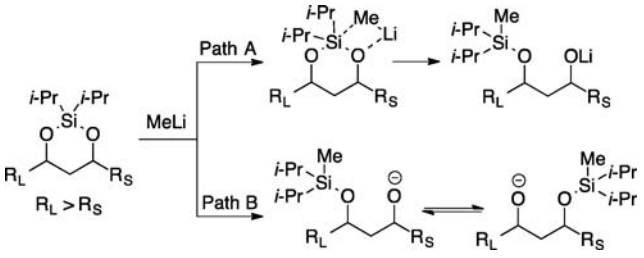
[a]Ratios determined by ^{1}H NMR of crude reaction mixtures. [b]Combined isolated yields of **13** and **14**.

regioselectivity trends as with the isopropanol quench; the effective size of substituents followed the order *tert*-butyl > phenyl ≈ isopropyl > methylene > methyl. These reactions proceeded in high yields ranging from 85−97%.

We wished to study the origin of the regioselectivity of the reaction. If the selectivity is based on the preferential binding of the lithium to the least sterically hindered oxygen, the opening of the silylene would provide a silyl ether on the oxygen in the sterically more demanding position and a lithium alkoxide on the other. Assuming that this intermediate does not undergo silyl migration, reaction of the lithium alkoxide with the electrophile (isopropanol or methyl iodide) would provide the observed product (Scheme 3, Path A). This explanation is essentially the same as that provided by Kuwajima for the selective ring opening of 1,2-silylenes[8b] and related to that of Pagenkopf for the BF_3·SMe_2 opening of 1,3-silylenes.[8a] In another possible mechanism, a nonselective opening of the silylene would provide a silyl ether/alkoxide species that undergoes rapid equilibration followed by selective trapping of the electrophile at the less hindered alkoxide (Path B).

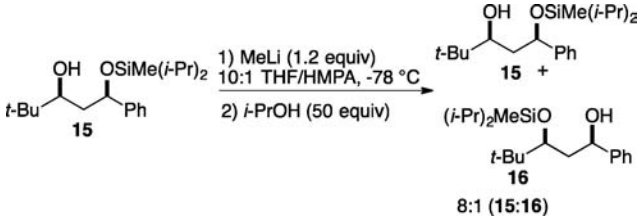
DOI: 10.1021/acs.orglett.5b02529
Org. Lett. 2015, 17, 5196−5199

Scheme 3. Possible Mechanisms



If the silylene opening proceeds via Path B, then it follows that by subjecting the minor regioisomer to the reaction conditions, the silyl ether−alkoxide intermediate would form, which should equilibrate to give identical regioselectivity as observed in the original silylene opening. We, therefore, prepared the minor silyl ether regioisomer **15** and subjected it to the reaction conditions. Only minor amounts of equilibration occurred, and we observed a regioisomeric product ratio of 8:1 (**15**:**16**, Scheme 4). This

Scheme 4. Silyl Ether Equilibration Study

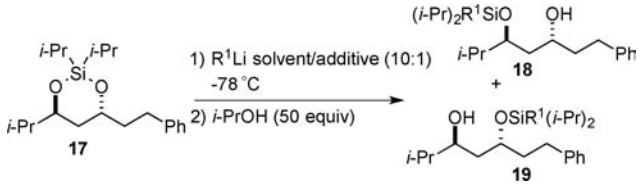


suggests that the selectivity is not due to a rapidly equilibrating intermediate and is consistent with preferential binding of the lithium to the less hindered acetal oxygen.

Given our hypothesis that the reaction proceeds through path A, it follows that increasing the sterics of the lithium reagent should provide greater selectivity, as the selectivity is due to steric interactions between the alkylmetal reagent and environment surrounding the two oxygens. We, therefore, studied the selectivity using alkyl metal reagents with different steric demands on a substrate of moderate selectivity so that changes in selectivity can be readily observed. Substrate **17**, bearing isopropyl and methylene substituents proximal to the secondary alcohols, was chosen for this study. As previously described, this substrate provides a modest selectivity of 2:1 for the *syn*-isomer and 5:1 for the *anti*-isomer using MeLi/HMPA in THF (Table 2, entries 13 and 14). Using the *anti*-silylene substrate (**17**) additives provided little effect in THF (Table 4, entries 1−3),[16] wherein the reagent combination of MeLi/TMEDA provides a selectivity of 9:1, whereas *n*-BuLi/TMEDA provides a selectivity of 25:1 (Table 4, entries 4 and 5).

These newly optimized conditions were applied to several of the silylene substrates that provided selectivities of less than 50:1 using the original conditions (Table 5). In general, the increase in selectivity was more pronounced in the *anti*-series. Even substrates with modest steric differentiation, such as methyl/methylene, provided useful levels of selectivity (9:1, an increase from 5:1; compare Tables 2 and 3, entries 10 with Table 5, entries 5 and 6). Other substrates with greater steric differentiation provided selectivities of 25:1 (Table 5, entries 1−4). In the *syn*-series, an increase in selectivity was observed with the substrate bearing isopropyl/methylene substituents wherein the selectivity increased from 2:1 using the original conditions to 4:1 with the modified conditions (compare Tables 2 and 3, entries 13

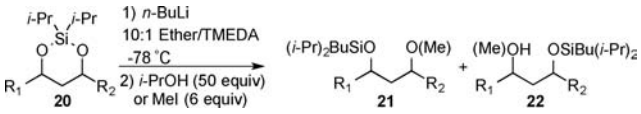
Table 4. Optimization of Reaction Conditions



entry	R^1	solvent	additive	18:19[a]
1	Me	THF	none	5:1
2	Me	THF	HMPA	5:1
3	Me	THF	TMEDA	6.5:1
4	Me	Et_2O	TMEDA	9:1
5	*n*-Bu	Et_2O	TMEDA	25:1

[a]Ratios determined by ^{1}H NMR of crude reaction mixtures

Table 5. Regioselectivity of Silylene Monodeprotection with New Reaction Conditions



entry	R^1	R^2	E^+	21:22[a]	yield
1-*anti*	*i*-Pr	$Ph(CH_2)_2$	*i*-PrOH	25:1	92%
2-*anti*	*i*-Pr	$Ph(CH_2)_2$	MeI	25:1	91%
3-*anti*	*i*-Pr	Ph	*i*-PrOH	25:1	92%
4-*anti*	*i*-Pr	Ph	MeI	25:1	94%
5-*anti*	$Ph(CH_2)_2$	Me	*i*-PrOH	9:1	88%
6-*anti*	$Ph(CH_2)_2$	Me	MeI	9:1	82%
7-*syn*	*i*-Pr	$Ph(CH_2)_2$	*i*-PrOH	4:1	84%
8-*syn*	*i*-Pr	$Ph(CH_2)_2$	MeI	4:1	70%
9-*syn*	*i*-Pr	Ph	*i*-PrOH	8:1	85%
10-*syn*	*i*-Pr	Ph	MeI	8:1	90%
11-*syn*	$Ph(CH_2)_2$	Me	*i*-PrOH	10:1	87%
12-*syn*	$Ph(CH_2)_2$	Me	MeI	10:1	75%

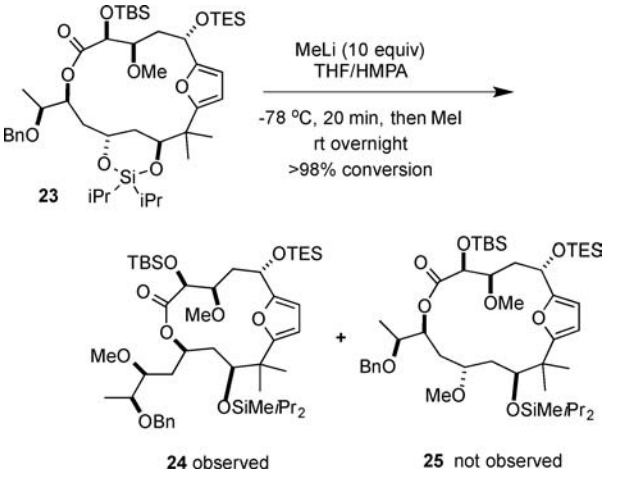
[a]Ratios determined by ^{1}H NMR of crude reaction mixtures

with Table 5, entries 7 and 8). A more dramatic increase was observed in the substrate bearing isopropyl/phenyl substituents wherein the selectivity changed from 1:2 using the original conditions to 8:1 with the modified conditions (compare Tables 2 and 3, entry 15 with Table 5, entries 9 and 10). Finally, an increase in selectivity was observed with the substrate bearing methyl/methylene substituents wherein the selectivity increased from 5:1 using the original conditions to 10:1 with the modified conditions (compare Tables 2 and 3, entry 9 with Table 5 entries 11 and 12).

We were surprised at the electrophilicity of silylenes as illustrated by the transformation shown in Scheme 5. This reaction is related to that shown in Scheme 1 wherein we wished to differentiate the oxygens of the silylene to provide a structure suitable for use in the synthesis of peloruside A, but differs in that the intermediate bears a lactone functionality that is sensitive to nucleophilic addition. We expected addition of MeLi to the lactone to compete with addition to the silylene; however, application of modified reaction conditions (MeLi, 10 equiv; THF/HMPA; −78 °C; then, MeI, warm to rt) provided exclusive addition of MeLi to the silylene in preference to the lactone in >98% conversion! Unfortunately, ring contraction to the 13-membered lactone occurred under the reaction conditions via acyl transfer of the lactone carbonyl to the

DOI: 10.1021/acs.orglett.5b02529
Org. Lett. 2015, 17, 5196−5199

Scheme 5. Electrophilicity of Silylenes



alkoxide. All attempts to prevent this, including rapid quenching of the reaction (addition of an acetic acid solution after 15 s rather than MeI) and studying different solvents and additives, were not successful. Although we could not accomplish the desired transformation, this reaction illustrates the surprisingly high electrophilicity of silylenes and its compatibility with the lactone of **23**.

In conclusion, we have described a new method for the differential functionalization of 1,3-diols via the selective opening of silylenes. The reaction is facile and provides useful levels of selectivity for a broad range of substrates. Our mechanistic studies suggest an origin of selectivity based on the preferential binding of the organolithium reagent to the less hindered oxygen of the silylene. Based on our mechanistic studies, we explored the use of effectively larger organolithium reagents and found that these provide higher levels of selectivity. This method has the potential to be applied to the synthesis of complex molecules in a variety of contexts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02529.

Experimental procedures, characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for partial financial support from NIH-NIGMS (GM48498) and from the NSF (Grant 1266167).

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DOI: 10.1021/acs.orglett.5b02529
Org. Lett. 2015, 17, 5196−5199