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Intramolecular Hydrogen Transfer Reactions of *o*-(Bromophenyl)dialkylsilyl Ethers. Preparation of Rapamycin-d_1

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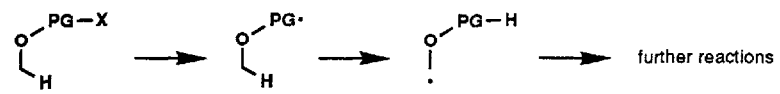
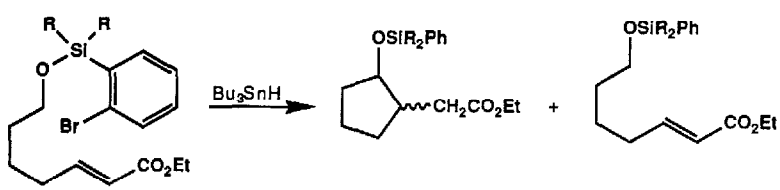
Summary: *Radical translocations of o-(bromophenyl)dimethylsilyl ethers are efficient, but yields of α-silyloxy alkyl radicals formed by 1,5-hydrogen transfer are limited to 65-90% by competing 1,6- and 1,7-hydrogen transfers. Similarities in substituent effects on 1,5-hydrogen transfers and radical cyclizations are identified.*

Synthetic applications of intramolecular hydrogen transfer reactions have taken a new turn with the introduction of protecting groups that function as radical precursors.[3] Generation of a radical within the protecting group is followed by intramolecular hydrogen transfer (radical translocation) to generate a new radical, which can then participate in standard radical addition,[3b] cyclization,[3a-d] and fragmentation[3e] reactions (eq 1). An unactivated C–H bond indirectly serves as a radical precursor in standard radical procedures like the tin hydride method.[4] This radical translocation strategy is presently limited because relatively little is known about the effects of substituents on the rate and regioselectivity of intramolecular hydrogen transfer reactions from carbon-hydrogen bonds to reactive *carbon* radicals.[5,6]



eq 1

We have recently introduced the *o*-(bromophenyl)dimethylsilyl group as an alcohol protecting group and an activating group for the generation of α-silyloxyalkyl radicals.[3a] For example, reduction of ether **1a** (eq 2) by syringe pump addition of tributyltin hydride gave a mixture of cyclized product **2a** (62% yield) and reduced product **3a** (17% yield). Reduction of the *o*-(bromophenyl)cyclopentylsilyl ether **1b** under identical conditions provided **2b** in somewhat improved yield (73%), and **3b** was not isolated.[7] Is the silyl group in **1b** better for hydrogen transfer than that in **1a**, and what is the origin of the reduced product **3a**? We considered two possible pathways for the formation of **3a**: 1) reduction of an aryl radical by tin hydride competes with 1,5-hydrogen transfer, or 2) other (1,6- and 1,7-) hydrogen transfers compete with 1,5-hydrogen transfer.[8] In the first path, translocation fails. In the second; it suceeds, but to the wrong site(s). To differentiate these two possibilities, we have conducted a series of model isotopic labeling experiments with tributyltin deuteride. In addition to the mechanistic information, these experiments provide a route to convert an alcohol to an α-deuterio alcohol without the intermediacy of a ketone. Our results indicate that yields with the *o*-(bromophenyl)dimethylsilyl group will be limited to the range of 65-90% by competing 1,6- (and sometimes 1,7-) hydrogen transfer reactions.



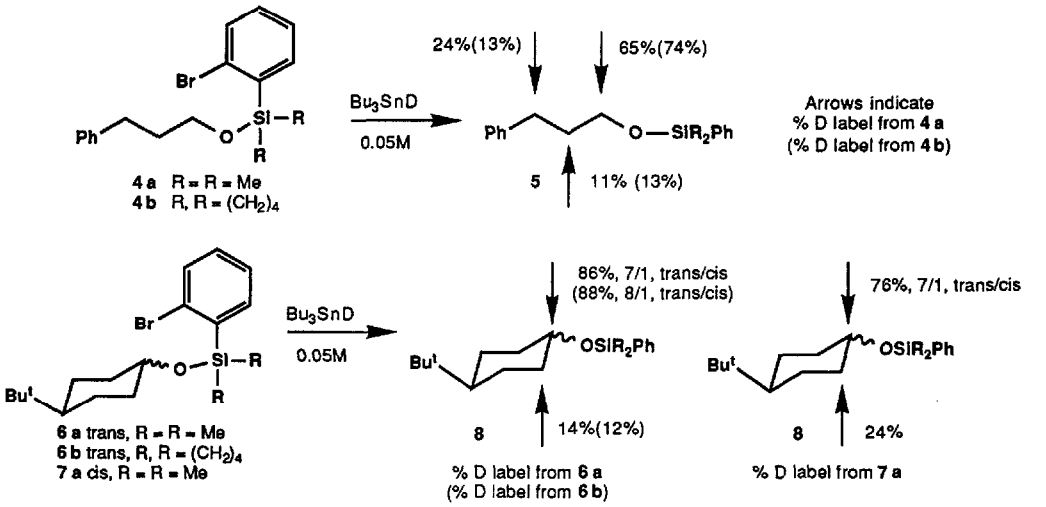
eq 2

1a R = R = Me
1b R,R = $(CH_2)_4$

2a 62% (1/1, cis/trans)
2b 73% (1.8/1, cis/trans)

3a 17%
3b —

Eq 3 summarizes the results of the series of isotope labeling experiments with silyl ether derivatives of a representative 1°-alcohol (**4a,b**), and axial and equatorial 2°-alcohols (**6a,b,7a**). We conducted each reduction under a standard set of conditions: an 0.05M benzene solution of the substrate containing Bu_3SnD (1.2 equiv) and AIBN (0.1 equiv) was heated at 80 °C for 4 h. The crude reaction product was analyzed by ^2H NMR to determine the sites of deuteration,[9] prior to chromatography to determine the isolated yield and the % deuteration (both of which were uniformly high).



Reduction of **4a** gave 65% 1,5-hydrogen transfer, 11% 1,6-hydrogen transfer, and 24% 1,7-hydrogen transfer. Reduction of **4b** gave a similar amount of the 1,6-hydrogen transfer product (13%), but more of the 1,5-transfer product (74%) formed at the expense of the 1,7-hydrogen transfer product (13%). Reduction of equatorial silyl ether **6a** gave 86% 1,5-hydrogen transfer and 14% 1,6-hydrogen transfer. The product of 1,5-hydrogen transfer was a 7/1 mixture of equatorial and axial silyl ethers.[10] We obtained very similar results in the reduction of **6b**. Axial silyl ether **7a** gave considerably more 1,6-hydrogen transfer (24%) at the expense of 1,5-hydrogen transfer (76%). The product of the 1,5-hydrogen transfer is again a 7/1 mixture of equatorial/axial isomers (1,5-hydrogen transfer generates the same radical from **6a** and **7a**).

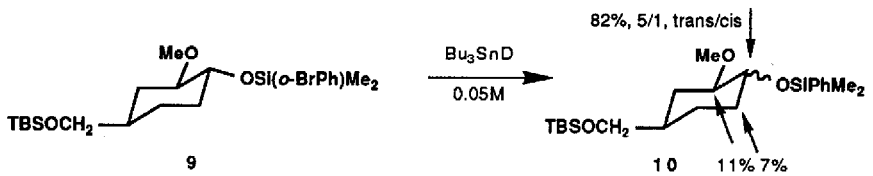
From these model studies, we can draw conclusions about the general effectiveness of *o*-(bromophenyl)dialkylsilyl groups for radical translocation. In eq 2, most of the reduced product **3a** must result from 1,6-hydrogen transfer. The so-formed radical cannot cyclize readily (4-exo), and it simply abstracts a hydrogen from tributyltin hydride. 1,7-Hydrogen transfer may also lead to **3a**, but the benzylic hydrogen atoms probably facilitate 1,7-transfer in the model **4** relative to **1**. Silyl ethers **4b** and **6b** are not significantly more selective for 1,5-hydrogen transfer than **4a** and **6a**. We now believe that **3b** probably was formed in the reduction of **1b**, but it must have hydrolyzed during the workup or chromatography. Like **4a,b** the cyclic 2°-alcohols **6a, 6b** and **7a** show moderate selectivity for 1,5-hydrogen transfer.

Significant amounts of 1,6-hydrogen transfer products form in all the reactions despite the fact that these products (2°-alkyl radicals) must be less stable than the products of 1,5-hydrogen transfer (2°- or 3°-silyloxyalkyl radicals). This is analogous to radical cyclizations, where regioselectivities are not greatly affected by product radical stabilities. Like radical cyclizations, these exothermic hydrogen transfer reactions must have relatively early transition states. The analogy can be extended further. Comparisons of **4, 6,** and **7** with ether analogs[3e] indicate that the nuclear substitution of silicon in the chain favors 1,6-hydrogen transfer relative to 1,5. It is also known that nuclear substitution of silicon in hexenyl[11a] and oxahexenyl[11b,c] radicals permits endo cyclization[8] to occur in competition with exo. The nuclear substitu-

tion of sulfur (SO_2) also permits 1,6- and 1,7-hydrogen transfers to compete with 1,5 transfer,[12a] and endo cyclization becomes favored over exo.[12b] However, even if the analogy between exo/endo cyclization and 1,5/1,6 hydrogen transfer is a good one, it is by no means clear that these trends have similar origins.[13]

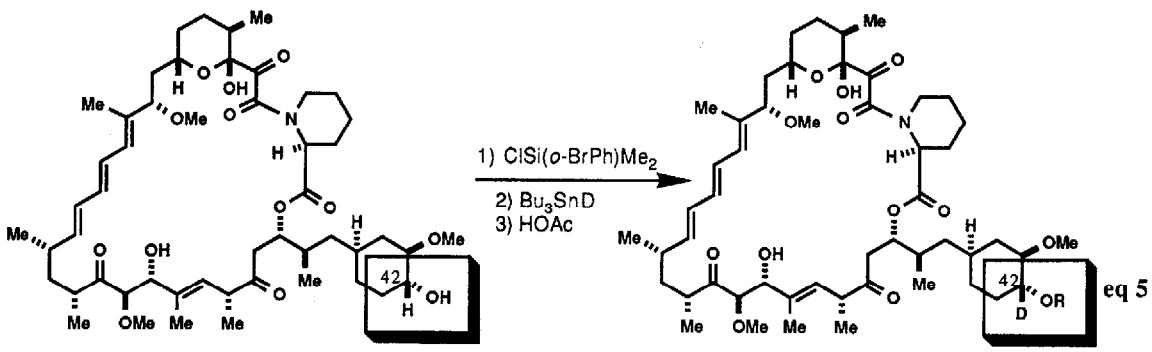
These deuteration reactions have potential use as more than just mechanistic probes because they provide a means to convert an α-protio alcohol to an α-deuterio alcohol without passing through a ketone. To illustrate the potential of this procedure, we chose to selectively deuterate the immunosuppressant rapamycin.[14] This serves as a model for the preparation of tritiated rapamycin, which could be used for radioimmuno assays. Given rapamycin's complexity and instability, its deuteration is not trivial.

We first conducted the model study in eq 4. Reduction of **9**[15] under the standard conditions gave the indicated deuterium distribution in **10** according to ^2H NMR analysis of purified product (97% yield). 1,5-Hydrogen transfer occurs to the extent of 82%, and the subsequent deuterium abstraction then occurs with modest axial selectivity to regenerate the equatorial (trans) alcohol (5/1).[16] Mass spectrometric analysis indicated that **10** was >98% monodeuterated.



9 **10** eq 4

Eq 5 shows the results with rapamycin.[11] Selective monosilylation of the C42 alcohol was followed by reduction with tributyltin deuteride. The ^2H NMR of **12** was very similar to that of the model **10**, so we conclude that a similar labeling pattern was produced. Desilylation under carefully controlled conditions produced labeled rapamycin **13**, which could be separated from the minor C42 axial alcohol by flash chromatography. Due to the complexity of the ^1H NMR spectrum, integration to determine the total %D was not possible. After some experimentation, we finally found that an excellent FAB spectrum of **13** could be obtained in an MNBA matrix containing either NaCl or KCl. Under these conditions, intense peaks corresponding to $(M + Na)^+$ or $(M + K)^+$ were observed. Independent determinations of the % d component from the intensity of the isotopic ions of the above peaks indicated that rapamycin was 61% d_1 and 39% d_0. Apparently, intramolecular hydrogen transfer in rapamycin proceeds with similar efficiency and selectivity to the model, but bimolecular deuterium transfer from tin deuteride is less efficient for rapamycin. The reasons for this reduced efficiency are not clear.



rapamycin **11** **12** R = $SiPhMe_2$

rapamycin-d_1 (major isomer) **13** R = H eq 5

In summary, the *o*-bromophenyldimethylsilyl group is a useful protecting group that doubles as a precursor for silyloxyalkyl radicals by virtue of its ability to perform intramolecular hydrogen abstractions.

Under conditions of moderate to low tributyltin hydride concentrations (≤0.05M), the intramolecular hydrogen transfer is efficient,[9] but the selectivity 1,5-hydrogen transfer is only moderate (65-90%). Because of the unique capabilities of this group to generate radicals from unactivated C–H bonds, these moderate levels of selectivity are useful. However, the design of silyl groups with higher selectivities for 1,5-hydrogen transfer is clearly desirable.

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5. In contrast, much more is known about the hydrogen abstraction reactions of heteroatom-centered radicals. Beckwith, A. L. J.; Ingold, K. U. in "Rearrangements in Ground and Excited States"; de Mayo, P., Ed; Academic: New York, 1980, vol. 1, p 161.
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8. Given that a highly reactive acceptor is employed, we consider as remote the possibility that 1,5-hydrogen transfer succeeds but then hydrogen transfer from tin hydride is faster than cyclization.
9. We usually detected 5-12% deuterium label on the Si-Ar ring, indicating incomplete hydrogen transfer. However, given the deuterium isotope effect and the higher concentrations of the labeling experiments, we do not believe that failed hydrogen transfer is significant under the preparative conditions of syringe pump addition.
10. This stereochemistry of the 1,5-hydrogen transfer product corresponds to the expected axial deuterium abstraction by the intermediate α-silyloxycyclohexyl radical. See, Kulicke, K. J.; Giese, B. *Synlett* **1990**, 91. The configuration of the 1,6-hydrogen transfer product could not be determined.
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13. For example, silicon is usually thought to favor formation of the endo product by decreasing the rate of exo cyclization. However, substitution of silicon in a connecting chain for intramolecular hydrogen transfer does not have an obvious rate decellerating effect.
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16. Deuterium transfer α to the methoxy group was also primarily axial (to regenerate the equatorial methyl ether). The configuration of the other 1,6-transfer product could not be determined.

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