



The synthesis of carbohydrate-derived acylsilanes and their intramolecular free radical cyclizations with the formation of polyoxygenated cyclopentanes

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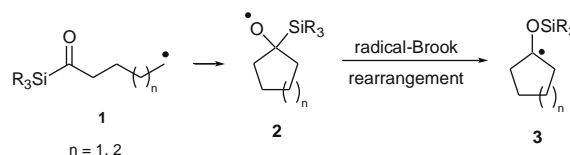
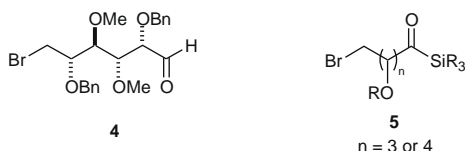
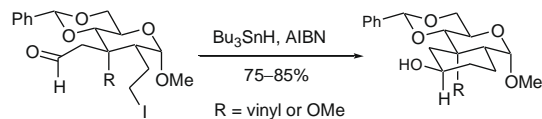
ABSTRACT

A convenient way for the synthesis of acylsilanes from arabinose, lyxose, and ribose is developed. All the chiral centers of the carbohydrate templates are conserved, and only the reducing end is transformed into the acylsilane functional group. The non-reducing end of the templates can be converted into a bromide. These bromo acylsilanes undergo efficient intramolecular radical cyclizations to give polyoxygenated cyclopentanes.

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Acylsilane is a useful functionality which has attracted the attentions of synthetic chemists.¹ The presence of silyl group on the carbonyl not only enhances the reactivity of a carbonyl but also becomes a useful handle for additional transformations.

Several years ago we have initiated a project to study the intramolecular radical cyclizations involving acylsilanes.² As shown in Scheme 1, intramolecular radical cyclization of acylsilane **1** gives a cyclized alkoxy radical intermediate **2** with a silyl group attached at the β -position of the radical. A facile radical-Brook rearrangement^{3,4} successfully drives the reaction toward the formation of a silyloxy-substituted radical **3**. In contrast, similar radical cyclizations involving formyl group are known to be reversible processes in favor of the acyclic radicals.⁵ Therefore, the special feature of the radical cyclizations of acylsilanes made this type of reaction a useful method in the preparation of cyclic alcohols.⁶



Scheme 1.

Carbohydrates are unique sources of chirality in nature and have been extensively used as building blocks for the synthesis of enantiomerically pure and highly oxygenated derivatives.⁷ In particular, the conversion of carbohydrates to carbocycles is an area that has been extensively studied.⁸ Fraiser-Reid and co-workers demonstrated several successful carbohydrate-based free radical cyclizations in which aldehyde groups served as the radical acceptor (Eq. 1).⁹ In these cyclizations, the ω -formylalkyl radicals are immobilized by fusing with a pyranoside ring. However, aldehydes that carry carbohydrate skeleton, such as bromide **4**, are not good substrates for radical cyclizations.^{9f} Thus there is a need to examine whether acylsilane **5** can be suitable substrate for this purpose. Herein we wish to report our synthesis of some pentose-derived acylsilanes and the study of their intramolecular radical cyclizations.

Preparation of carbohydrate-derived acylsilanes has been reported by Plantier-Royon and Portella¹⁰ using the 2-silylated-1,3-dithiane approach developed by Brook¹¹ and Corey.¹² In this approach, all the chiral centers of the carbohydrate substrates are retained and the carbon skeleton is extended by one. However, the α -position of the resulting acylsilanes cannot have a hydroxyl or alkoxy substituent. Although several reports about the construction

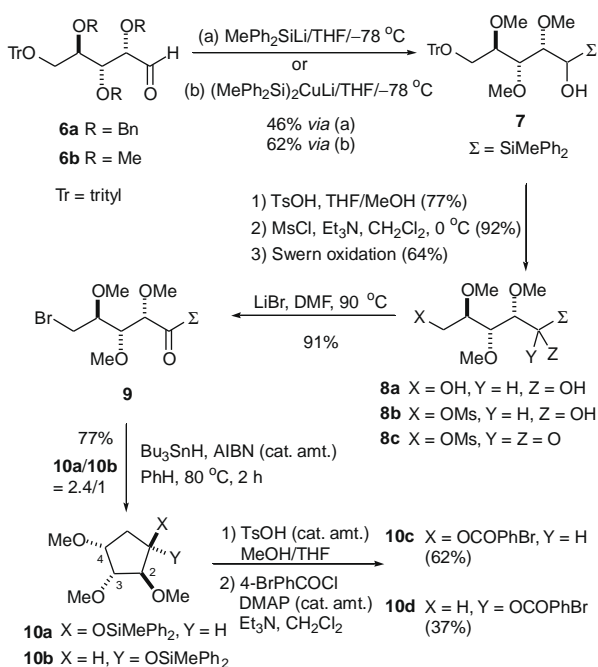
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of α -oxy acylsilanes were known, none of these methods employed carbohydrate starting material directly.¹³ We decided to explore the possibility of adding a silyl anion to the carbonyl end of a carbohydrate to generate an α -silyl alcohol.¹⁴ The resulting α -silyl alcohol can then be oxidized to give an acylsilane with the desired carbohydrate skeleton.

As shown in Scheme 2, aldehyde **6a**¹⁵ derived from arabinose with all the secondary hydroxyl groups protected by benzyl groups did not react with methylphenylsilyl lithium or the corresponding silyl cuprate. With the hypothesis that this aldehyde is quite sterically hindered due to the presence of adjacent bulky substituents, we switched to the methylated analog **6b**.¹⁶ Indeed, aldehyde **6b** reacted with methylphenylsilyl lithium and gave α -silyl alcohol **7** in 46% yield. By using the less basic lithium bis(methylphenylsilyl)cuprate, the yield of α -silyl alcohol **7** was improved to 62%.

The trityl group in alcohol **7** was removed in a mixture of THF and methanol in the presence of *p*-toluenesulfonic acid. The primary hydroxyl group of the resulting diol **8a** was converted to a methanesulfonate **8b**. This material was then oxidized using the Swern method¹⁷ to give acylsilane **8c** in 45% yield over these three steps. Treatment of **8c** with lithium bromide in DMF afforded bromoacylsilane **9** in a 91% yield.

Free radical cyclization of acylsilane **9** using the standard tributyltin hydride method in refluxing benzene² gave successfully the cyclized silyl ether **10** as a mixture of two epimers (**10a/10b** = 2.4/1) in a combined yield of 77%. For the sake of separation, this epimeric mixture was desilylated in a mixture of THF and methanol with catalytic amount of *p*-toluenesulfonic acid. The resulting alcohols were converted to the *p*-bromobenzoates and were separated to afford benzoates **10c** (62%) and **10d** (37%). Difference NOE experiments showed that irradiation of H(1) at δ 5.14 (CDCl₃) in the major isomer **10c** resulted in a 4% enhancement of H(2) at δ 4.03. In contrast, irradiation of H(1) in benzoate **10d** at δ 5.43–5.48 did not show any enhancement of H(2) at δ 3.83–3.89. We therefore assigned the structure of **10c** as having a 1,2-*cis* relationship of the two substituents. This stereochemical outcome indicated that in the radical cyclization step the corre-

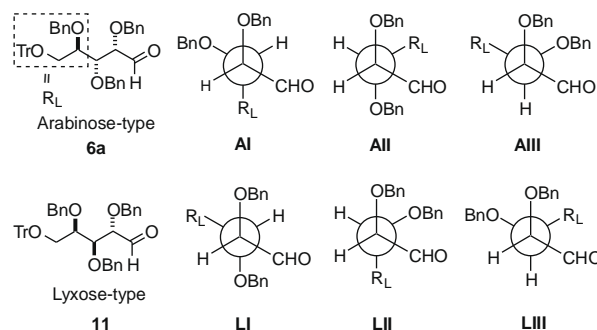


Scheme 2.

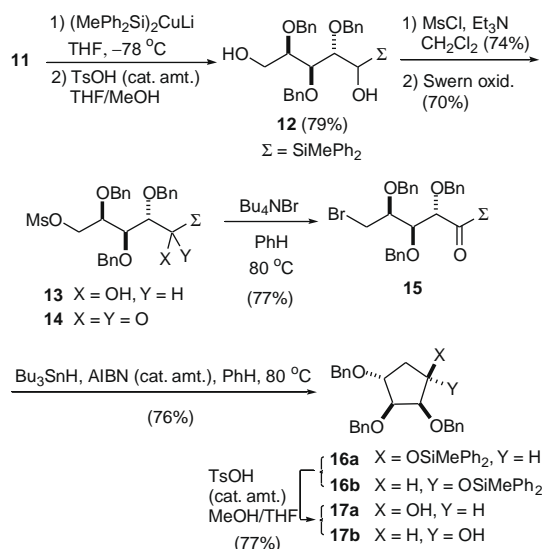
sponding α -silyloxy cyclopentyl radical preferred to abstract a hydrogen from the face opposite to the C(2) methoxy group.

As mentioned above, we attributed the lack of reactivity of alcohol **6a** toward silyl anion to the steric environment around the carbonyl group. Trying to understand the origin of this steric effect, we analyzed the conformation of aldehyde **6a**. As shown in Scheme 3, among the three staggered conformations of **6a**, the carbonyl group in conformers **AI** and **AII** is *gauche* to the large group R_L. Conformer **AIII** has an all *gauche* relationship and presumably also made the carbonyl quite sterically encumbered. Based on this analysis, we felt that the lyxose-derived aldehyde **11**¹⁵ having a C(2)–C(3) *anti* stereo-relationship would contain a low energy conformer **LI**.¹⁸ In which, the two benzyloxy dipoles are *anti* to each other, and the carbonyl group is *anti* to the large group R_L but *gauche* to the smaller benzyloxy group. We therefore hypothesized that the carbonyl group in aldehyde **11** might be less sterically hindered in comparison with aldehyde **6a**.

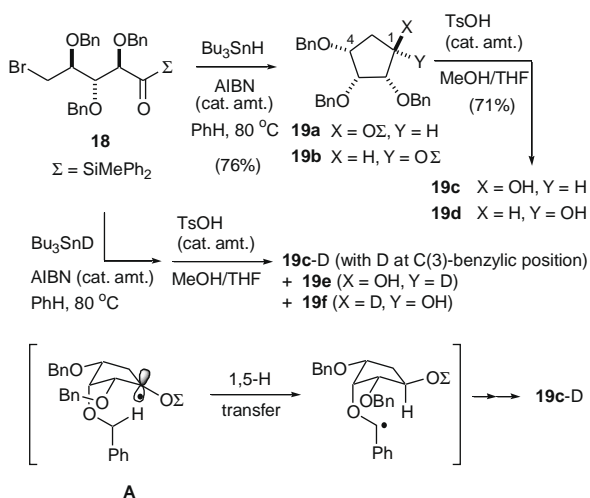
Indeed, aldehyde **11** (Scheme 4) successfully coupled with the silyl cuprate and afforded diol **12** in 79% yield after removal of the trityl group. Diol **12** was converted to mesylate **13** followed by Swern oxidation¹⁷ to give acylsilane **14** in 51% over two steps. Replacing the mesylate group in **14** with bromide using lithium bromide in DMF met with failure. However, this task was accomplished by the reaction of acylsilane **14** with tetrabutylammonium bromide in refluxing benzene¹⁹ and yielded bromoacylsilane **15** (77%).



Scheme 3.



Scheme 4.



The tin-mediated cyclization of **15** was carried out successfully to give the cyclization products **16** in a 76% yield with a stereoisomeric ratio of 2.8/1 (**16a**/**16b**). The inseparable mixture of **16** was desilylated to afford partially separable alcohols **17** (77%). The stereochemistry of **17** was determined by difference NOE experiments. Specifically, irradiation of H(2) in cyclopentanol **17a** at δ 3.94–3.99 (CDCl₃) resulted in a 16% enhancement of H(1) at δ 4.26–4.37. On the contrary, irradiation of H(2) in **17b** at δ 3.75 only resulted in a 4% enhancement of H(1) at δ 4.16–4.23. These results indicated that the major isomer **17a** exhibited a C(1)–C(2) cis-relationship. Similar selectivity was also observed for the cyclization of acylsilane **9** as mentioned above.

Ribose is another pentose that exhibits a C(2)–C(3) *anti* stereo-relationship. Using similar methods we synthesized the D-ribose-derived acylsilane **18**²⁰ (Scheme 5). Radical cyclization of **18** with tributyltin hydride gave a 76% yield of an inseparable mixture of cyclized products **19a** and **19b** (**19a**/**19b** = 1.6/1). Removal of the silyl group then afforded alcohols **19c** (43%) and **19d** (28%). Difference NOE experiments of **19d** showed that irradiation of H(1) at δ 4.04–4.11 (CDCl₃) resulted in a 6% enhancement of H(2) at δ 3.43. Conversely, irradiation of H(2) resulted in a 14% enhancement of H(1). We therefore assigned **19d** as having a C(1)–C(2) cis-relationship.

Surprisingly, the preference of stereochemical outcome in this system showed that the corresponding α -silyloxy cyclopentyl radical abstracted a hydrogen atom from the same face relative to the benzyloxy group at C(2) on the cyclopentane ring. We suspected that intramolecular hydrogen abstraction might be the cause of this preference. To confirm this suspicion, the cyclization of acylsilane **18** was carried out using tributyltin deuteride followed by desilylation, and we were able to isolate alcohols **19f** (24%) and a mixture (31%) of **19c**-D and **19e** (**19c**-D/**19e** = 45/55).

The complete deuteration at C(1) in the all-cis isomer **19f** is obvious in the ¹H NMR spectrum for the disappearance of the proton signal at C(1) (δ 4.10 in CD₃OD). The ¹³C signal of C(1) also diminished into a very small triplet of equal intensity centered at δ 69.5 (in CDCl₃; J_{C-D} = 23 Hz). In contrast, in the ¹H NMR spectrum of the trans-cis-cis isomer mixture **19c**-D and **19e**, the proton signal at C(1) (δ 4.36 in CD₃OD) only partially disappeared. The ¹³C signal of C(1) of **19e** appeared as a small triplet centered at δ 74.1 (in CDCl₃; J_{C-D} = 23 Hz) coexisted with a signal at δ 74.4 belonging to C(1) of **19c**-D. The ¹³C signal of the benzylic carbon (δ 73.0 in CDCl₃ on the C(3)-side chain also appeared as a singlet overlapped with a triplet indicating the incorporation of a deuterium atom at this carbon.²¹

Therefore, the incorporation of ¹H at C(1) in **19c**-D is most likely occurred through an intramolecular 1,5-hydrogen transfer process from the benzylic position of the C(3)-benzyloxy group. We suggest that the C(3)-substituent is located at a pseudo-axial position (**A**) and is more accessible to deliver the benzylic hydrogen to the radical at C(1). Whereas the C(4)-benzyloxy group adopts a pseudo-equatorial position, it is difficult to reach the corresponding benzylic hydrogen for the radical.

In conclusion, we have developed a convenient way for the synthesis of acylsilanes from carbohydrate templates. All the chiral centers of the templates were conserved, and only the reducing end was transformed into acylsilane. In the meantime, the non-reducing end of the templates can be converted into a bromide. We demonstrated that these bromo acylsilanes can undergo efficient intramolecular radical cyclizations to give polyoxygenated carbocycles with different stereochemical structures. One can expect the silyloxy group to serve as a handle for the conversion of these cyclopentitols to potentially useful compounds such as aminopentitols²² and carbocyclic nucleotides.^{23,24}

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Supplementary data

Supplementary data (compound characterization data of **9**, **10c**, **d**, **15**, **17a**, **b**, **18**, **19c**, and **d**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.032.

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