Tetrahedron Letters 50 (2009) 7283–7285

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Mechanistic studies of rearrangements during the ring expansions of cyclopropanated carbohydrates

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ARTICLE INFO

Article history:
Received 10 September 2009
Revised 6 October 2009
Accepted 7 October 2009
Available online 14 October 2009

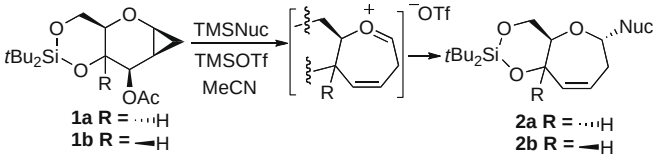
ABSTRACT

Deuterium-labeling studies have been performed on the ring expansion of cyclopropanated carbohydrates. From these studies, mechanisms have been proposed for two unusual rearrangements. In addition, a selective deprotection of the 1,3-di-*tert*-butylsilyl ether protecting group at the secondary position versus the primary position has been observed. This is a high yielding transformation with the potential for general synthetic utility.

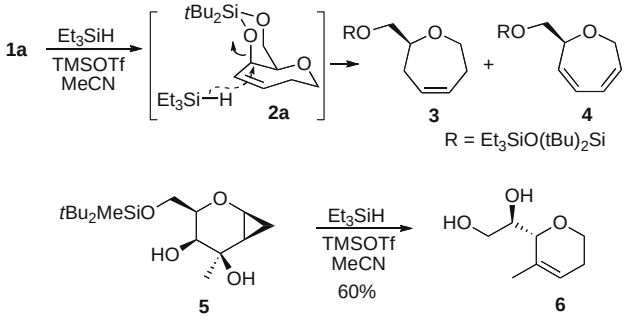
Over a decade ago, we reported on the ring expansion of cyclopropanated sugars of type **1** with both galactal and glucal-based sugars, Scheme 1.[1–4] Since then, recent applications and extensions of this methodology have been reported,[5–8] and have also culminated in the synthesis of oligonucleotides.[9] The heptanoses that result from this ring expansion have become increasingly important in biological settings,[10,11] where examples include protein-binding agents[12,13] and inhibitors of viral replication.[14] During the course of our synthetic studies, we have observed several unusual transformations with both interesting mechanistic and synthetic implications. This Letter describes these transformations and studies on their underlying mechanisms.

In our Letter involving the ring expansion of the galactal-based cyclopropane **1a**, we noted the formation of **3** in 86% yield,[4] Scheme 2; subsequently we have noticed that slight variations in the procedure can produce minor amounts of **4** (~2–5%). The formation of **3** was initially postulated to occur from ring expansion product **2a** (Nuc = H) that underwent displacement of the axial oxygen by a hydride equivalent. Capture or pre-coordination of a Et_3Si cation by the displaced oxygen produces the observed product **3**. Also in the galactal series, we observed the unusual formation of **6** as opposed to the expected seven-membered ring when using the derivative **5**. Again we were intrigued by the appearance of **6** and have performed labeling studies to elucidate the mechanism of its formation.

To investigate the mechanism for the formation of **3**, a deuterium labeling study was performed using Et_3SiD,[15] Scheme 3. Reaction of **1a** with Et_3SiD generated a mixture of deuterated **3** and **4** (designated **3-D** and **4-D**), which are impossible to separate, however separation is unnecessary as the ratio of major to minor products allows for assignments. Analysis of the major product **3-D** using ^{29}Si NMR confirmed the presence of both the Et_3SiO and di-*tert*-butylsilyl groups with chemical shifts at δ_{Si} 9.2 and −21.0 ppm. ^{13}C NMR revealed a one-bond C-D coupling for two carbons at 69.3 and 69.1 ppm, indicating that both epimers were present. Integration of the proton signals associated with this carbon revealed the presence of deuterium and an α:β epimeric ratio



Scheme 1. Ring expansion of **1**.



Scheme 2. Atypical rearrangements of galactal-based cyclopropanes.

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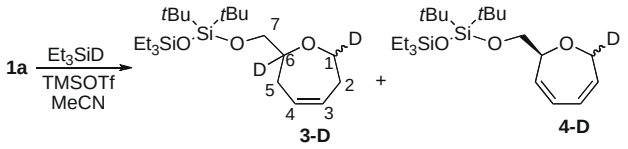
doi:10.1016/j.tetlet.2009.10.031

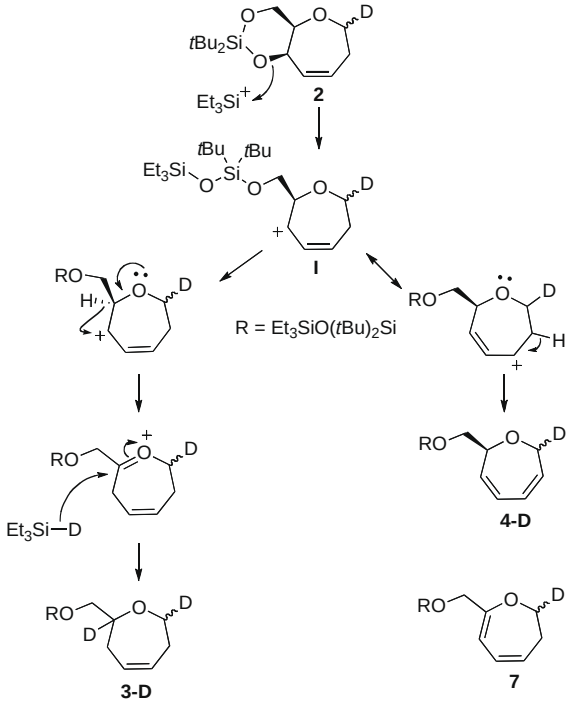


Scheme 3. Labeling studies leading to the formation of **3-D** and **4-D**.

of 1:1. Analysis of the HSQC-DEPT spectrum proved the presence of methylene groups on either side of the double bond with no evidence of C-D coupling in the ^{13}C spectrum. There was also a disconnection observed in both COSY and TOCSY 2D NMR experiments between the methylene at C-5 and the oxymethylene at C-7. Closer examination of the ^{13}C spectrum revealed the presence of a second deuterated carbon at δ_C 80.2 corresponding to C-6, and appearing as a triplet with J = 20.5 Hz. Deuteration at this position also explains the lack of connectivity observed in the COSY and TOCSY data. The connectivity of the ^1H spin system was then constructed from a series of COSY correlations from the C-2 methylene (δ_H 2.49 and 2.18, δ_C 35.6). This signal couples to two different proton resonances: an oxymethine (C-1: δ_H 4.02 and 3.41, δ_C 69.2) and an alkenic methine (C-3: δ_H 5.81, δ_C 130.7). C-3 then couples to a second alkenic methine (C-4: δ_H 5.81, δ_C 129.4), which in turn couples to a methylene (C-5: δ_H 2.49 and 2.16, δ_C 35.6). C-7 appears at 3.83 and 3.54 in the ^1H NMR and 66.3 in the ^{13}C NMR. The HMBC spectrum shows correlations from both the C-5 and C-7 protons into the C-6 carbon, which confirmed this assignment. From this information, it can be deduced that the major compound was **3-D**.

Assignment of the minor component indicated only a single deuterated carbon at δ_C 70.2 in the ^{13}C NMR, which appeared again as a triplet with a coupling constant of 21.1 Hz. ^1H NMR further verified **4-D** as the structure as only a single methylene unit at C-7 was observed (see Experimental for complete discussion).

With this information, a mechanism is proposed as illustrated in Scheme 4. The usual ring expansion of **1a** produces **2** (as in Scheme 1) in both anomeric forms. Formation of allylic cation **I** allows for a divergent pathway that explains both **3-D** and **4-D**. Formation of **3-D** involves a hydride shift with concurrent oxonium ion formation, which undergoes nucleophilic attack by the second deuterium to produce **3-D**. Formation of minor product **4-D** involves a simple elimination to generate the observed product. The alternative diene **7**, was not observed, indicating that the preferred reaction mode for **I** appears to be oxonium ion formation.



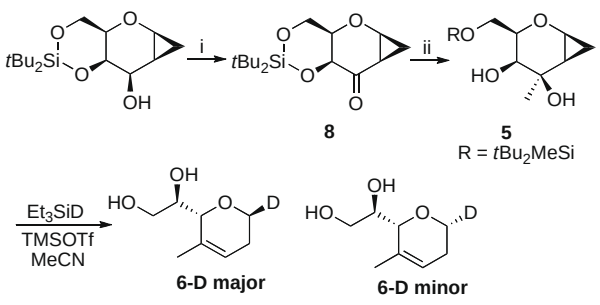
Scheme 4. Proposed mechanism for the formation of **3-D** and **4-D**.

With regard to the formation of **6** from **5**, this anomaly arose following methylation of ketone **8** to produce the unexpected di-*tert*-butylmethylsilyl ether **5**, Scheme 5. Examination of the ^1H and ^{13}C NMR data of cyclopropane **5** revealed the presence of a methyl signal at δ_H 0.10 in the ^1H NMR, indicative of a methyl group attached to a silicon atom. Presumably, during Grignard addition, the silyl ether protecting group had cleaved to produce the tBu$_2$MeSi ether at the C-6 position. It should be noted that the glucal isomer of ketone **8** also undergoes the same methylation reaction in 99% yield (see Supplementary data).

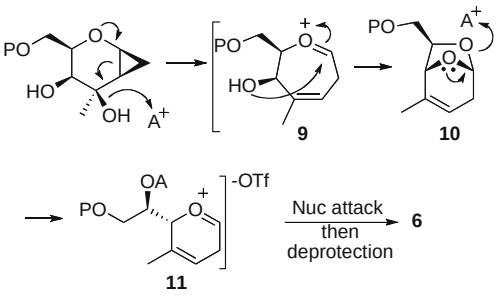
Treatment with MeMgBr is known to convert acetonides to *tert*-butyl ethers by selective deprotection of the secondary oxygen over the primary.[16] However, to our knowledge this has not been reported to occur with di-*tert*-butylsilyl acetals. Nonetheless, given that the desired methylation of the ketone had occurred as needed, we proceeded with the normal sequence of acetylation and ring expansion. However, acetylation of the tertiary alcohol in **5** was unachievable, and given no alternatives, we attempted the ring expansion reaction with Et_3SiH (as in Scheme 2) and subsequently with Et_3SiD (as in Scheme 5) only to discover the formation of **6**. In the reaction with Et_3SiD, diol **6-D** was obtained as a 6:1 mixture of epimers, with the major product having a ß-deuterium. ^{13}C NMR revealed that only C-1 was deuterium labeled with the C-1 carbon signal at δ_C 63.4 resonating as a triplet with a coupling constant of 21.7 Hz, indicative of an attached deuterium.

The stereochemistry of the reaction was confirmed by NOESY data that revealed an enhancement between the C-1 and C-5 protons on the minor alpha isomer diol, which while it was not separated from the mixture, was clearly observable in the ^1H NMR. The minor anomer could also be detected in the ^{13}C NMR spectrum, with the C-1 shift at 63.5 ppm again as a triplet with a coupling constant of 22.2 Hz.

A plausible mechanism, as illustrated in Scheme 6, would involve formation of the expected oxonium intermediate **9** with subsequent internal attack by the C-5 alcohol to produce the 1,6-anhydropyranose **10**. Formation of oxonium ion **11** from such anhydro compounds is well precendented[17] and allows for attack of the nucleophile to produce the observed product. Generation of triflic acid during the reaction leads to deprotection of the silyl ethers producing the observed diol **6**.



Scheme 5. Reagents and conditions: (i) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, 94%; (ii) MeMgBr, THF, rt, 86%.



Scheme 6. Proposed mechanism for the formation of **6**, where A = activating group (presumably TMS).

Ring-expansion of cyclopropanated sugars has become a valuable synthetic route to a number of important heptanoses. We have shown here that additional products can be accessed and the mechanisms for their production have been proposed. The mechanism of formation of **6** opens a new avenue of chemistry for cyclopropanated carbohydrates. This may prove to be especially useful given the configuration at C-5, which is normally difficult to access. The methylation of ketone **8** to produce **5**, with concurrent selective deprotection, is also noteworthy and appears to be a reliable and high-yielding transformation.

Acknowledgments

We are grateful to Associate Professor Peter Northcote and Dr. John Ryan at Victoria University for assistance with NMR experiments.

Supplementary data

Supplementary data (experimental procedures for all reactions and NMR spectra for **3**, **5** (galactal and glucal based diol), **6** and **8**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.031.

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