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A Ring Contraction of 2,3-Di-*O*-Silylated Thiopyranosides To Give Thiofuranosides under Mildly Acidic Conditions

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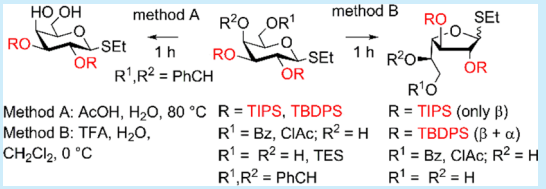
Supporting Information

ABSTRACT: A pyranose ring contraction of ethyl 1-thio-β-D-galactopyranosides has been discovered that proceeds with retention of aglycon under mildly acidic conditions (aq TFA in CH_2Cl_2). Key factors for success of this rearrangement are the presence of bulky silyl (TIPS or TBDPS) substituents at *both* O-2 and O-3 and a free hydroxy group at C-4 (derivatives with acid-labile protective groups at O-4 will also engage in this reaction). The rearrangement cleanly proceeds for 2,3-di-*O*-TIPS derivatives with two hydroxy groups at C-4 and C-6, acid-labile TES groups at O-4 and O-6, or one acyl substituent (Bz, ClAc) at O-6. A possibility to switch the direction of the debenzylidenation reaction in 4,6-*O*-benzylidene-2,3-di-*O*-TIPS/TBDPS derivatives by the choice of an acid (TFA, which cleanly gives furanose, versus AcOH, which cleaves benzylidene acetal only) may present an advantage in the divergent synthesis of selectively protected glycosyl donors (either in furanose or pyranose form) useful for the synthesis of biologically important oligosaccharides.



The synthesis of furanose-containing oligosaccharides is an important area of current research because monosaccharides in the furanose form are frequent constituents of the polysaccharides of pathogenic microorganisms, such as extracellular galactomannan of *Aspergillus fumigatus*,[1,2] the arabinogalactan of *Mycobacterium tuberculosis* and other *Mycobacterium* species,[3−8] the galactan of *Actinobacillus pleuropneumoniae*,[9] and the galactan of *Bifidobacterium catenulatum*.[10] Several methods to access furanosyl building blocks have been reported.[11] Because of the lower number of strategies available for the preparation of furanosides, in comparison to pyranosides, the search for simple efficient and reliable methods for the synthesis of selectively functionalized furanoside glycosyl donors still presents a challenge.

Bulky silyl substituents in a glycosyl donor are known to significantly alter the geometry of the pyranose ring, which can affect the outcome of glycosylation.[12] Recently, we have reported that a *single* triisopropylsilyl (TIPS) group at O-2 in glycosyl donors with *galacto*-configuration (L-fucose and D-galactose) may favor an efficient 1,2-*cis*-glycosylation.[13,14] During these studies, we noticed that an attempted *O*-trifluoroacetylation of ethyl 1-thio-α-L-thiofucopyranoside with *two* TIPS groups at O-2 and O-3 led to rearrangement and formation of a furanose derivative lacking ethylthio aglycon.[13] Here, we report the ability of bulky silyl groups at O-2 and O-3 in derivatives of ethyl 1-thio-β-D-galactopyranoside to favor contraction of the pyranose ring, leading to the formation of furanose derivatives with *retention* of aglycon under mildly acidic conditions.

Selective cleavage of the 4,6-*O*-benzylidene group[15,16] in various carbohydrate derivatives is commonly achieved by acidic hydrolysis[17] (heating with aq AcOH,[18] treatment with TFA in CH_2Cl_2−ethylene glycol[19] or aq TFA in CH_2Cl_2 at room temperature (rt)[18] or at 0 °C[14,20]), which leads to formation of the corresponding 4,6-diol. These procedures are considered to be robust and efficient and are widely used in protective group strategies.[21,22]

We have found that the choice of acid used for the removal of the 4,6-*O*-benzylidene group can determine the size of the ring in the product formed. Heating of 4,6-*O*-benzylidene derivatives **1** and **9** obtained from the known 2,3-diol[19,23] (see the Supporting Information (SI) for full experimental details) containing TIPS or TBDPS groups at O-2 and O-3 with 80% aq AcOH at 80 °C for 1 h (method A) gave the normally expected diols **2** and **10** in pyranose form (68% and 75% yields, respectively), accompanied by trace amounts (∼1%) of the corresponding thiofuranosides **3** and **11**. However, treatment of **1** with ca. 50% aq TFA in CH_2Cl_2 (TFA−H_2O−CH_2Cl_2, 4:1:3 (v/v)) at 0 °C for 1 h (method B) resulted in the isolation of considerable amounts of partially protected thiofuranoside **3** (25%), along with thiopyranoside **2** (40%). Surprisingly, treatment of **1** with more dilute (ca. 9%) aq TFA in CH_2Cl_2 (TFA−H_2O−CH_2Cl_2, 9:1:100, v/v) at 0 °C for 1 h (method C) led *exclusively* to the β-thiofuranoside **3** in 76% yield, thiopyranoside **2** being absent (see Schemes 1 and 4 (shown later in this work)).

The influence of acid and its concentration on the outcome of the debenzylidenation reaction deserves a comment. At first

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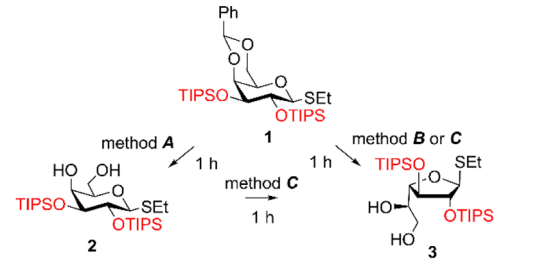
Scheme 1. Choice of the Acid Determines the Ring Size in the Product of Debenzylidenation



Method ***A***: 80% aq AcOH, 80 °C; **2** (68%) and **3** (1%)
Method ***B***: TFA-H_2O-CH_2Cl_2 (4:1:3), 0 °C; **2** (40%), **3** (25%)
Method ***C***: TFA-H_2O-CH_2Cl_2 (9:1:100), 0 °C; **3**: 76% from **1**, 75% from **2**

glance, the stronger the acid (TFA (pK_a = 0.23) versus AcOH (pK_a = 4.76)), the more prominent the ring contraction.

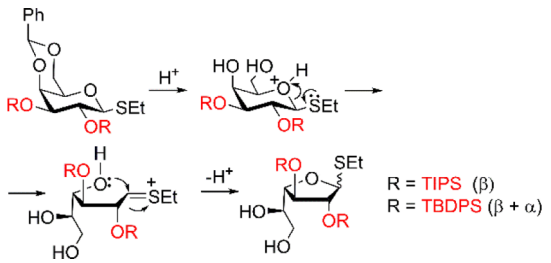
However, the complete ring contraction observed in more *dilute* TFA is puzzling. Clearly, the concentration of protons is not the only factor that determines the success of the pyranose ring contraction. Indeed, the proportions of water differ considerably under the conditions of methods B and C, and different protonating species[24,25] might be present in the reaction solutions, probably causing changes in balance between general and specific acid catalysis thus favoring different reaction pathways. Apparently, one must consider differences in the structures of reaction solutions in each case, which could include differences in structures of supramers[26] (and references cited therein) formed by both acid reagent[24,25] and carbohydrate substrate. This issue deserves a special physico-chemical study, similar to those we conducted[26−28] for other systems.

From a purely preparative point of view, the possibility to switch the course of the debenzylidenation reaction by an appropriate choice of acid (TFA versus AcOH) may present an advantage in the divergent synthesis of selectively protected glycosyl donors (either in furanose or pyranose form) useful for the synthesis of biologically important oligosaccharides. For example, the repeating unit of the galactan of *A. pleuropneumoniae*[9] comprises galactose residues both in pyranose and furanose forms.

Mechanistically, a rearrangement of pyranoside to furanoside can only occur if O-4 becomes unprotected, i.e., *after* removal of the 4,6-*O*-benzylidene group. Subsequent protonation of the pyranose ring oxygen accompanied by endocyclic cleavage of the pyranose ring creates conditions for recyclization forming the 5-membered furanose ring with retention of both aglycon and anomeric configuration (see Scheme 2).

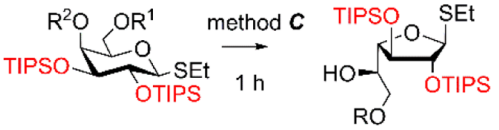
For this reason, it is unsurprising that the presence of the 4,6-*O*-benzylidene group is not critical for the success of the pyranoside to furanoside rearrangement performed under

Scheme 2. Proposed Mechanism of Pyranose Ring Contraction



conditions of method C. Indeed, similar results were obtained for the corresponding 2,3-di-*O*-TIPS derivatives with two hydroxy groups at C-4 and C-6 (**2**) (Scheme 1), acid-labile TES groups at O-4 and O-6 (**4**) (Scheme 3), or one acyl substituent (ClAc or Bz) at O-6 (**5** and **6**, respectively) (Scheme 3).

Scheme 3. The Presence of 4,6-*O*-Benzylidene Group Is Not Required for Ring Contraction

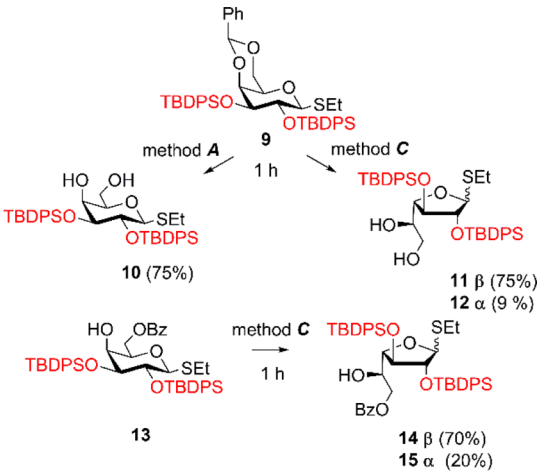


4 $R^1 = R^2$ = TES
5 R^1 = ClAc, R^2 = H
6 R^1 = Bz, R^2 = H

3 R = H (80%)
7 R = ClAc (73%)
8 R = Bz (70%)

For derivatives of ethyl 1-thio-β-D-galactopyranoside containing somewhat less bulky TBDPS groups at O-2 and O-3 (**9**, **13**), ring contraction performed under the conditions of method C led to the expected furanose derivatives **11** (75% from **9**) and **14** (70% from **13**) and was accompanied by partial anomerization of the furanoside formed; the amount of α-anomer in furanose form is dependent on the structure of the starting pyranoside (9% of **12** from **9**, 20% of **15** from **13**) (see Scheme 4).

Scheme 4. Effect of TBDPS Groups on the Outcome of Acidic Treatment: Partial Anomerization of Furanosides



Such differences in stereochemical outcome of the ring contraction between TIPS- and TBDPS-substituted derivatives may be related to differences in their conformations. Indeed, unlike 2,3-di-*O*-TIPS derivatives **2** and **6**, which adopt a slightly distorted $^4C_1$ chair conformation ($J_{1,2} \approx 6.6$ Hz), the corresponding 2,3-di-*O*-TBDPS derivatives **10** and **13** exist in a strongly distorted conformation ($J_{1,2} \approx 3.6$ Hz) that is different from that of phenyl 6-*O*-benzyl-2,3,4-tri-*O*-(*tert*-butyldimethylsilyl)-1-thio-β-D-galactopyranoside ($J_{1,2} \approx 4.9$ Hz),[29] with three bulky silyl groups (see Figure 1).

Although the exact reasons for preferential retention of anomeric configuration in the thiofuranosides formed (with TIPS groups) and a possibility of their partial anomerization (with TBDPS groups) are yet to be revealed, it is clear that a

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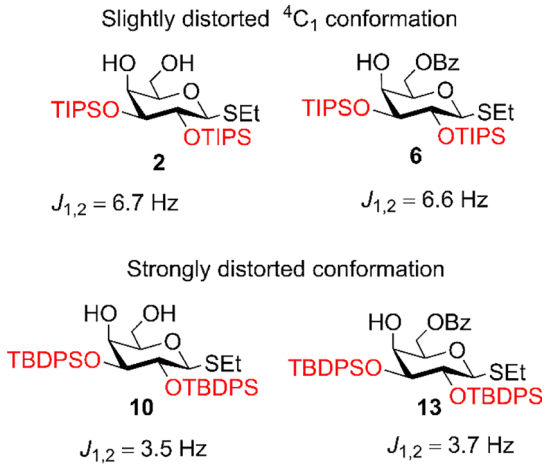


Figure 1. Comparison of coupling constants for TIPS- and TBDPS-containing ethyl 1-thio-β-D-galactopyranosides.

comprehensive mechanism of the reaction should also consider other experimental facts that must be explained. For example, generation of a cationic species, although seemingly required for ring contraction, is not accompanied by the formation of detectable amounts of hydrolysis products that could originate from nucleophilic attack by water present in the reaction mixture. This suggests that C-1 carbon ("anomeric") in such a species is not accessible for an attack by water molecules, probably due to the formation of supramers with special structure, in which molecules of the carbohydrate substrate are isolated from water.[26]

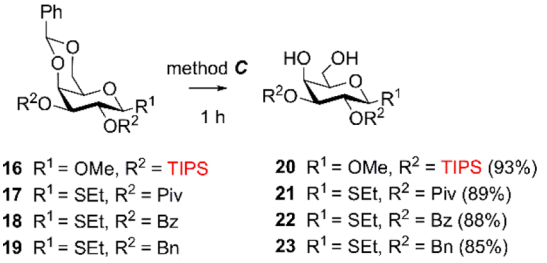
Since the aglycon is retained during the rearrangement, an endocyclic cleavage pathway seems to be operative during the discovered contraction of the pyranose ring (recall Scheme 2). One might speculate that it is steric strain induced by two vicinal bulky silyl groups (TIPS or TBDPS) that facilitates ring opening upon protonation of the pyranose ring oxygen in a way similar to that proposed[30] earlier for endocyclic cleavage in glycosides with 2,3-*trans* cyclic protective groups.

The importance of ring strain induced by *two* bulky silyl groups at O-2 and O-3 for the endocyclic cleavage, hence, for the success of ring contraction, is corroborated by the complete absence of the rearrangement in derivatives with only *one* TIPS at O-2 (compound **24**[14]) or O-3 (compound **26**) in the pyranose ring; the presence of an additional TIPS group at O-6 (compound **29**) does not change the situation (see Scheme 6, shown later in this work).

Although steric strain seems to be critical for the success of the rearrangement, the nature of protective groups at O-2 and O-3 is also very important. Derivative **17** with sterically demanding (although electron-withdrawing) pivaloyl groups at O-2 and O-3 did not undergo ring contraction under conditions of method C and formed diol **21** in pyranose form (89% yield) (see Scheme 5) as did derivative **18** with electron-withdrawing benzoyl groups at O-2 and O-3. Similarly, treatment of derivative **19** with electron-donating benzyl groups at O-2 and O-3 under conditions of method **C** resulted in removal of 4,6-*O*-benzylidene acetal only and formation of the corresponding 4,6-diol **23** in pyranose form (see Scheme 5).

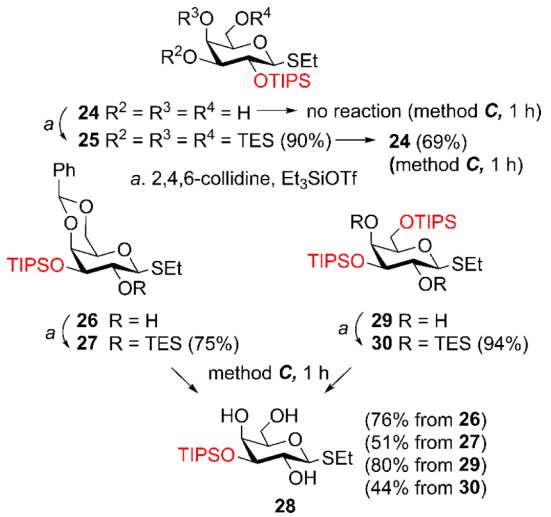
Silyl groups that are stable during the reaction (TIPS and TBDPS) work well, and the corresponding pyranose derivatives readily rearrange to furanose derivatives (Schemes 1−4). However, acid-labile TES groups (compounds **25**, **27**, and **30**)

Scheme 5. *O*-Glycosides and Thioglycoside Derivatives with Nonsilyl Groups Do Not Undergo Ring Contraction



are cleaved under conditions of method C and the pyranose ring remains intact (see Scheme 6).

Scheme 6. Derivatives Lacking Two TIPS Groups at O-2 and O-3 Do Not Undergo Ring Contraction



The found rearrangement seems to be limited to only thioglycosides, since the related *O*-glycoside **16** did not undergo ring contraction under conditions of method C, and gave the corresponding partially protected methyl β-D-galactopyranoside **20** in 93% yield (see Scheme 5). This result suggests the importance of the ethylthio group for stabilization of positive charge that develops during endocyclic cleavage (recall Scheme 2).

The discovered reaction, which is described in this communication, is quite unusual and apparently is not related to the recently developed "pyranoside-into-furanoside (PIF) rearrangement",[31−33] which seems to be limited to *O*-glycosides only and not suitable for ring contraction in thioglycosides. Notably, treatment of ethyl 1-thio-β-D-galactopyranoside with $Py{\cdot}SO_3$ and HSO_3Cl in DMF, the standard conditions used for the PIF rearrangement,[31] was reported to lead to a complex mixture of decomposition products that mainly contained O-sulfated pyranoside derivatives while the formation of the corresponding furanosides was not detected.[34] The discovered pyranose ring contraction of thioglycosides complements the PIF rearrangement of *O*-glycosides, thus facilitating access to furanose glycosyl donors and oligosaccharides.

In conclusion, a pyranose ring contraction of derivatives of ethyl 1-thio-β-D-galactopyranosides is reported that proceeds with retention of aglycon under mildly acidic conditions (aq TFA in CH_2Cl_2). Key factors for success of this rearrangement

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are the presence of bulky silyl (TIPS or TBDPS) substituents at *both* O-2 and O-3 and a free hydroxy group at C-4 (derivatives with acid-labile protective groups at O-4 will also engage in this reaction). The rearrangement cleanly proceeds for 2,3-di-*O*-TIPS derivatives with two hydroxy groups at C-4 and C-6, acid-labile TES groups at O-4 and O-6, or one acyl substituent (Bz, ClAc) at O-6. A possibility to switch the direction of the debenzylidenation reaction in 4,6-*O*-benzylidene-2,3-di-*O*-TIPS/TBDPS derivatives by the choice of an acid (TFA, which cleanly gives furanose, versus AcOH, which cleaves benzylidene acetal only) may present an advantage in the divergent synthesis of selectively protected glycosyl donors (either in furanose or pyranose form) useful for the synthesis of biologically important oligosaccharides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02424.

Experimental procedures and full characterization data for all new compounds (PDF)

Copies of NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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