Glycosylations

Deutsche Ausgabe: DOI: 10.1002/ange.201505176
Internationale Ausgabe: DOI: 10.1002/anie.201505176

Stereoselective Synthesis of α-3-Deoxy-D-*manno*-oct-2-ulosonic Acid (α-Kdo) Glycosides Using 5,7-*O*-Di-*tert*-butylsilylene-Protected Kdo Ethyl Thioglycoside Donors

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Dedicated to Professor Feng-Peng Wang on the occasion of his 70th birthday

Abstract: *An efficient methodology for the synthesis of α-Kdo glycosidic bonds has been developed with 5,7-O-di-tert-butylsilylene (DTBS) protected Kdo ethyl thioglycosides as glycosyl donors. The approach permits a wide scope of acceptors to be used, thus affording biologically significant Kdo glycosides in good to excellent chemical yields with complete α-selectivity. The synthetic utility of an orthogonally protected Kdo donor has been demonstrated by concise preparation of two α-Kdo-containing oligosaccharides.*

3-Deoxy-D-*manno*-oct-2-ulosonoic acid (Kdo), a unique acidic eight-carbon sugar, is an essential structural constituent of polysaccharides present in bacteria.[1] Both α- and β-Kdo glycosides are found in nature, with the α-glycosides being a fundamental component of the inner-core oligosaccharides of lipopolysaccharides (LPSs) in Gram-negative bacteria, and the β-linked glycosides being an important component in capsular polysaccharides (CPSs) of Gram-positive and Gram-negative bacteria. It is found that bacterial LPSs and CPSs are closely associated with the pathogenicity and survival of pathogenic bacteria. The chemical synthesis of structurally defined Kdo-containing fragments of LPSs and CPSs is currently appealing, as the synthetic fragments play significant roles in developing potential carbohydrate-based vaccines and diagnostics.[2] From this aspect, numerous efforts have been directed toward the development of Kdo glycosyl donors for efficient glycosylation,[3] including the use of various anomeric leaving groups, such as halides,[4] *N*-phenyltrifluoroacetimidates,[5] thioglycosides,[6] and glycals,[7] as well as the introduction of an auxiliary group at the C3-position.[8] Among the donors employed to date, the 4,5-*O*-isopropylidene acetal or 4,5-di-*O*-*tert*-butyldimethylsilyl(TBS)-protected Kdo fluoride donors, originally developed by Kusumoto and co-workers,[4a–c] showed special validity in the stereoselective synthesis of α-Kdo glycosides.[4d] But an efficient and general Kdo glycosylation with high stereoselectivity still has not been fully achieved. The major problem met in this glycosylation reaction is that the lack of a C3 participating group cannot ensure the stereochemical outcome of glycosylation. Another problem is that the presence of the C1 electron-withdrawing carboxylic group of a typical Kdo donor reduces the reactivity of the tertiary anomeric center, thereby leading to a low yield of the glycosylation product and the formation of a significant amount of undesirable 2,3-glycal byproduct. These inherent properties of Kdo glycosyl donors render the high yielding stereoselective formation of Kdo glycosides as one of the most challenging tasks in synthetic carbohydrate chemistry.

Herein we report a new method for stereospecific synthesis of α-Kdo glycosides using 5,7-*O*-DTBS-protected[9] (DTBS = di-*tert*-butylsilylene) Kdo ethyl thioglycosides as glycosyl donors and its application to the practical preparation of various α-Kdo glycosidic bonds.

Initially, a set of Kdo ethyl thioglycoside derivatives (**1a**–**e**; Table 1), wherein both the C5- and C7-positions were protected by a cyclic acetal functionality, were designed and synthesized (see the Supporting Information). For the purpose of comparison, the thioglycoside **1f**, without a cyclic protecting group, was also prepared. With these compounds, we explored glycosylations with the model glucosyl acceptor **2**[10] to survey the influence of the cyclic acetal protecting groups on the reaction stereoselectivity. All glycosylations were performed by employing 2 equivalents of the donor and 1 equivalent of the acceptor in the presence of *N*-iodosuccinimide (NIS, 4.0 equiv), catalytic trifluoromethanesulfonic acid (TfOH), and 4 Å molecular sieves (M.S.) at −78 to −50 °C in CH_2Cl_2 (Table 1). The product stereochemistry was determined on the basis of the coupling constant between the axial proton at C3 and the ^{13}C carbon atom at the C1-position ($^3J_{C\text{-}1/H\text{-}3ax}$) in the proton-coupled ^{13}C NMR spectra.[4e,11] For the α-anomer, the $^3J_{C\text{-}1/H\text{-}3ax}$ value is $\leq$ 1.0 Hz, while, for the β-anomer, the $^3J_{C\text{-}1/H\text{-}3ax}$ is 5.0–6.0 Hz.[12]

As illustrated in Table 1 (entries 1–6), glycosylations of the thioglycosides **1a**–**f** with **2** afforded the corresponding glycoside products in equally excellent yields but with varying degrees of stereocontrol. The coupling between **1a**, protected as a 5,7-*O*-acetonide, and **2** displayed a slight α-selectivity, thus resulting in the disaccharide **3a** in 95 % yield as a mixture of anomers (entry 1). A higher degree of α-selectivity (α/β 6:1) was observed in the reaction with the 5,7-*O*-benzylidene-protected donor **1b** (entry 2). Gratifyingly, the thioglycosides

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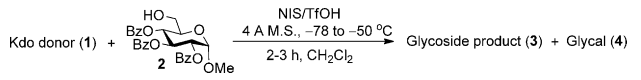
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201505176.

Table 1: Effect of cyclic 5,7-*O*-acetals on glycosylation stereoselectivity.[a]



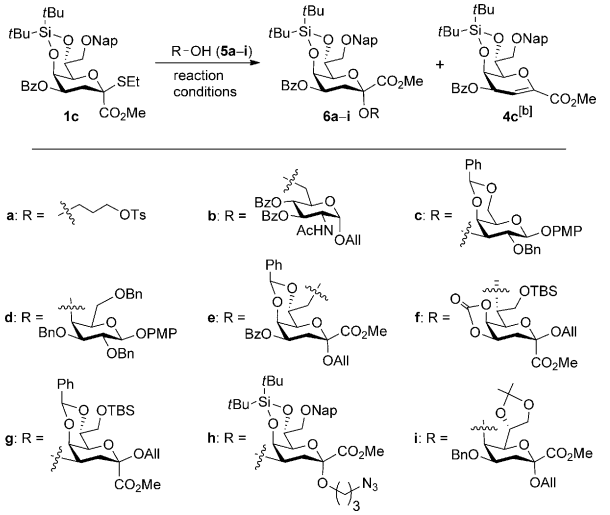
Entry	Donor	Product	Yield[b] (α/β)[c]	Glycal (Yield [%])[d]
1	**1a**: R^1 = isopropylidene, R^2 = Nap	**3a**: R^1 = isopropylidene, R^2 = Nap	95% (1.1:1)	**4a**: R^1 = isopropylidene (50%), R^2 = Nap
2	**1b**: R^1 = benzylidene, R^2 = TBS	**3b**: R^1 = benzylidene, R^2 = TBS	85% (6:1)	**4b**: R^1 = benzylidene (44%), R^2 = TBS
3	**1c**: R = Nap	**3c**: R = Nap	90% (α only)	**4c**: R = Nap (50%)
4	**1d**: R = TBS	**3d**: R = TBS	95% (α only)	**4d**: R = TBS (52%)
5	**1e**: R = Piv	**3e**: R = Piv	88% (α only)	**4e**: R = Piv (45%)
6	**1f**	**3f**	90% (1:2.5)	**4f** (47%)

[a] Glycosylations were conducted with a Kdo thioglycoside donor (**1**; 2 equiv), acceptor (**2**), NIS (4 equiv)/TfOH (0.1 equiv), and 4 Å M.S. in anhydrous CH_2Cl_2 at −78→−50 °C for 2–3 h. [b] Yield of isolated product is based on the acceptor. For entries 1, 2, and 6, the yield is the combined yield of the α/β isomers. [c] Determined by ^{1}H NMR analysis of the corresponding isomer mixture. [d] Based on the donor. Bz = benzoyl, Nap = 2-methylnaphthyl, Piv = pivaloyl, Tf = trifluoromethanesulfonyl.

1c–**e**, bearing a 5,7-*O*-DTBS group, exhibited strong stereocontrol during the condensations with **2** and complete α-anomeric selectivity was obtained for the products **3c**–**e** (entries 3–5). No β-stereoisomers were found even after chromatographic purification in these reactions. In contrast, the reaction of the 4,5,7-tri-*O*-Bz-8-*O*-TBS-protected thioglycoside **1f** showed a reverse β-stereoselectivity (entry 6), which is similar to the findings reported by Oscarson et al. in the glycosylation of the peracylated Kdo thioglycosides.[6d] These results clearly indicate that the cyclic DTBS acetal group at the 5- and 7-positions has an α-stereodirecting effect on the glycosylation of the Kdo thioglycoside donors. Attack on the β-side by the glycosyl acceptor is prevented by the bulky DTBS substituent. Furthermore, it is worth pointing out that, though a large amount of glycal (**4a**–**f**) was formed (44—52 % yield) along with the desired disaccharide products in each glycosylation, these byproducts could be easily separated from the glycoside products by silica gel column chromatography.

The above 5,7-silylene-tethered Kdo donors may prove useful for preparation of α-Kdo-conjugated oligosaccharides. Of particular promise was the reagent **1c** for it is functionalized with a set of orthogonal protecting groups, that is, the 2-methylnaphthyl (Nap) ether is used for the protection of the C8–OH group and the benzoyl (Bz) ester for the C4-position. We then planned to explore its usefulness for creating diverse α-Kdo glycosides. A series of representative alcohols (**5a**–**i**; Table 2) were therefore synthesized (see the Supporting Information) and examined in the glycosylation with **1c** under suitable reaction conditions (2 equiv donor, 1 equiv

Table 2: α-Selective glycosylations between **1c** and a variety of acceptors.[a]



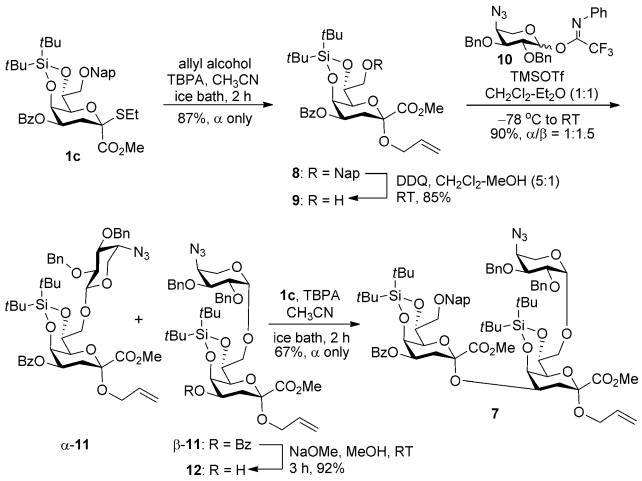
Entry	Acceptor	Conditions	Product	Yield [%][c] (α/β)[d]
1	**5a**	NIS/TfOH, CH_2Cl_2 −78→−50 °C	**6a**	95 (α only)
2	**5b**	NIS/TfOH, CH_2Cl_2 −78→−50 °C	**6b**	92 (α only)
3	**5c**	NIS/TfOH, CH_2Cl_2 −78→−50 °C	**6c**	79 (α only)
4	**5d**	NIS/TfOH, CH_2Cl_2 −78→−50 °C	**6d**	98 (α only)
5	**5e**	NIS/TfOH, CH_2Cl_2 −78→−50 °C	**6e**	80 (α only)
6	**5f**	NIS/TfOH, CH_2Cl_2 −78→−50 °C	**6f**	75 (α only)
7	**5g**	NIS/TfOH, CH_2Cl_2 −78→−50 °C	**6g**	75 (α only)
8[e]	**5h**	NIS/TfOH, CH_2Cl_2 −78→−50 °C	–	–
9	**5h**	TBPA, CH_3CN ice bath	**6h**	73 (α only)
10[e]	**5i**	NIS/TfOH, CH_2Cl_2 −78→−50 °C	**6i**	40 (α only)
11[e,f]	**5i**	NIS/TfOH, CH_2Cl_2 −78→−50 °C	**6i**	50 (α only)
12	**5i**	TBPA, CH_3CN ice bath	**6i**	71 (α only)

[a] Glycosylations were conducted with a Kdo thioglycoside donor (**1**; 2 equiv) and acceptor (**2**) using NIS (4 equiv)/TfOH (0.1 equiv) in CH_2Cl_2 at −78→−50 °C for 2–3 h (for entries 1–8, 10, and 11); TBPA (1.2 equiv) in CH_3CN at 0 °C for 2–3 h was used for entries 9 and 12. [b] The yield of **4c** was based on **1c** and was about 40–60% unless otherwise noted. [c] Yield of isolated product based on the acceptor. [d] Determined by ^{1}H NMR analysis of the corresponding isomer mixtures. [e] The yields of **4c** for entries 8, 10, and 11 were 85%, 67%, and 84%, respectively. [f] 4 equivalents of **1c** were used. All = allyl, PMP = 4-methoxyphenyl, Ts = *p*-toluenesulfonyl.

acceptor, 4 equiv NIS/cat. TfOH, −78→−50 °C, CH_2Cl_2). As summarized in Table 2, we were pleased to find that the simple alcohol **5a**,[13] the *N*-acetylglucosamine (GlcNAc) 6-OH acceptor **5b**, as well as the galactose 3-OH (**5c**[14]) and 4-OH (**5d**) acceptors reacted well with **1c**, thus leading to the formation of the corresponding glycosides **6a–d** in 79–98% yields as the α-anomers only (entries 1–4). In the cases of the Kdo glycosyl acceptors, the coupling of Kdo 8-OH (**5e**) and 7-OH (**5f**[15]) substrates with **1c** also proceeded in a high-yielding, α-selective manner, thus affording the α-(2→8)- and (2→7)-linked disaccharides **6e** (80%) and **6f** (75%), respectively (entries 5 and 6). When the Kdo 4-OH alcohols were employed as acceptors, the 5,7-*O*-benzylidene-protected **5g** underwent α-selective glycosylation with **1c**, by using NIS/TfOH, to furnish the dimeric Kdo **6g** having an α-(2→4) linkage in 75% yield (entry 7), whereas the 5,7-*O*-DTBS-protected analogue **5h** did not yield any detectable amounts of product; however, an 85% yield of the glycal **4c** was obtained (entry 8). The difference in glycosylation behavior between these acceptors is probably due to the lower nucleophilicity of the **5h** compared to that of **5g**. Then, a number of thioglycoside promoter systems, such as NIS/silver trifluoromethanesulfonate (AgOTf), iodobromide (IBr)/AgOTf, and dimethyl(thiomethyl)sulfonium triflate (DMTST) were assessed for their ability to realize the facile reaction of the sterically hindered acceptor **5h** with donor **1c**. Ultimately, tris(4-bromophenyl)ammoniumyl hexachloroantimonate (TBPA), known as a one-electron oxidizing agent, and adopted by Sinaÿ et al.[16] and later by Danishefsky et al.[17] for activation of thioglycosides, was found to be the most effective. As a result, when **1c** was activated with 1.2 equivalents of TBPA in acetonitrile (CH_3CN) at 0 °C, and reacted with **5h**, the desired glycoside **6h** was successfully formed in a good 73% yield and with exclusive α-selectivity (entry 9).

Establishing effective glycosylation conditions for the formation of the α-(2→5)-linked Kdo disaccharide proved extremely challenging. As shown in entry 10 of Table 2, for the NIS/TfOH-mediated reaction of **5i** with **1c**, complete α-stereocontrol was maintained but the expected α-(2→5)-Kdo disaccharide **6i** was produced in only 40% yield together with 67% yield of the glycal **4c**. The yield was still modest (50%, α only) even when a large excess (4 equiv) of **1c** was utilized (entry 11). Previously, the difficulty encountered in the synthesis of a Kdo-(2→5)-Kdo linkage was described by Kosma and co-workers. For example, they reported that the glycosylations between a peracetylated Kdo phosphite donor and Kdo 5-OH acceptors did not give any disaccharide products.[8b] It is reasoned that the poor glycosylation efficiency is due mainly to the low reactivity profile for the axial 5-OH group in a Kdo substrate. To our delight, when the glycosylation of **5i** and **1c** was carried out again using the TBPA promoter in CH_3CN, the yield of **6i** (α only) was considerably improved to 71% (entry 12). To the best of our knowledge, this is the first direct assembly of a synthetically difficult α-(2→5) Kdo-Kdo disaccharide unit in high yield with complete stereochemical control.

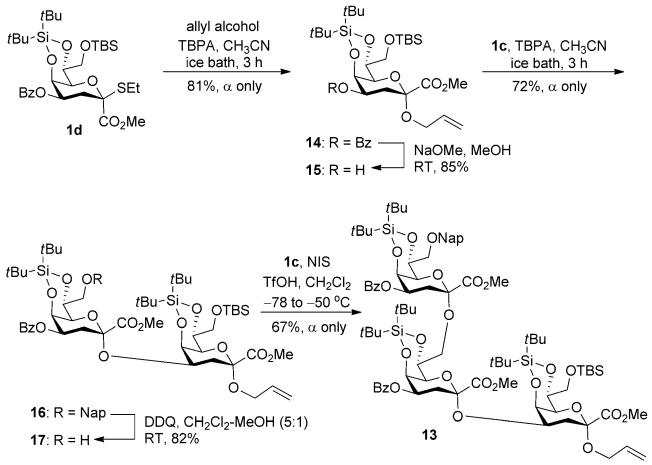
To demonstrate the utilization of this approach in the synthesis of bacterial-related Kdo oligosaccharides, we first



Scheme 1. Synthesis of Kdo-α-(2→4)-[Ara4N-β-(1→8)]-Kdo trisaccharide. TMS = trimethylsilyl.

targeted the preparation of the 4,8-branched trisaccharide **7** (Scheme 1), which is from the inner-core region of *Burkholderia* and *Proteus* LPS.[18] In this molecule, the core Kdo moiety is substituted, respectively, at C4 and C8 by an α-Kdo residue and a 4-amino-4-deoxy-β-L-arabinose (Ara4N) subunit. Although the preparation of the trisaccharide sequence was previously fulfilled by Kosma et al., the total synthetic efficiency was very low owing to the poor regioselectivity observed in the coupling reaction of the peracetylated Kdo bromide donor with the Ara4N-Kdo disaccharide 4,5,7-triol acceptor.[4g] Here, we envisioned that the use of the 4,8-orthogonally protected Kdo donor **1c** would facilitate the construction of such 4,8-branched skeleton. Thus, upon activation with TBPA, **1c** was condensed with allyl alcohol to exclusively yield the α-monosaccharide glycoside **8** in 87% yield. After removal of the C8 Nap group of **8** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in a mixture of CH_2Cl_2 and CH_3OH, the obtained Kdo alcohol **9** was reacted with the Ara4N *N*-phenyltrifluoroacetimidate donor **10**[4g] in a CH_2Cl_2/Et_2O (1:1) co-solvent in the presence of TMSOTf (0.03 equiv) to give the disaccharide **11** in 90% yield as a separable 1:1.5 α/β mixture. Then, subjecting pure β-**11** to Zemplén transesterification (NaOMe, MeOH) gave **12**, which contains a free 4-OH group (92% yield). This disaccharide derivative was coupled efficiently and α-stereoselectively to **1c** with a similar TBPA-activated protocol and resulted in the branched trisaccharide target **7** in 67% yield without formation of the β-anomeric product.

This α-selective glycosylation was next applied to the synthesis of the linear Kdo-α-(2→8)-Kdo-α-(2→4)-Kdo trisaccharide **13** (Scheme 2), which is a common LPS epitope of the intracellular human pathogen *Chlamydia*.[19] These parasites are responsible for various diseases in humans and animals. Recently, the group of Kosma group synthesized the same tri-Kdo motif by the use of 3-iodo Kdo-fluoride donors, but the temporary 3-iodo auxiliary group has to be cleaved after the coupling step, thus, further elaboration to the natural Kdo glycoside would be tedious.[8a] In this study, the newly developed Kdo donors **1c** and **1d** were chosen as key building



Scheme 2. Synthesis of Kdo-α-(2→8)-Kdo-α-(2→4)-Kdo trisaccharide.

blocks for the synthesis of the target molecule. Treatment of **1d** and allyl alcohol with TBPA in CH_3CN delivered the allyl glycoside **14** (81%, α only), which upon O-debenzoylation gave **15** in 85% yield. Subsequent reaction of this material with 2 equivalents of **1c**, under the same TBPA conditions outlined above, cleanly generated the α-(2→4)-linked Kdo disaccharide **16** in good yield as a single product. Then, selective removal of the 8′-*O*-Nap group with DDQ liberated the 8′-OH to furnish the disaccharide acceptor **17** (82% yield). At last, a NIS/TfOH catalyzed glycosylation of **17** with **1c** selectively produced the required protected α-Kdo oligomer **13** in 67% yield. Again, no β-isomer was observed in the glycosylation process.

Overall, compared to the existing synthetic routes, our methodology offers a more practical access to both molecules since it not only allows the introduction of the α-Kdo linkage with high selectivity but also simplifies the assembly of the target structures.

In summary, a general and facile synthesis of α-Kdo glycosides is described. The 5,7-*O*-DTBS-substituted Kdo ethyl thioglycoside donor **1c** undergoes stereospecific α-glycosylation to provide a wide variety of Kdo glycosides in high yields, including the major naturally occurring α-(2→6)-linked Kdo-GlcNAc disaccharide and α-(2→4)-, α-(2→5)-, and α-(2→8)-interconnected Kdo dimers. Additionally, the high reactivity of **1c** allows efficient coupling with less reactive acceptors, such as **5i** and the oligosaccharide alcohols **12** and **17**. Further application of the method to the synthesis of biologically relevant Kdo-containing carbohydrates, and extensive investigation into the mechanism of the novel glycosylation are currently underway.

Acknowledgements

This work was supported by the NSFC (21372166, 21172156, 21321061), the 973 program (2010CB833202), and the Ministry of Education (20100181110082) of China. We thank Prof. Qian Wan, Huazhong University of Science & Technology, for helpful discussions.

Keywords: acetals · carbohydrates · glycosylation · silanes · synthesis design

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 10894–10898
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Received: June 6, 2015
Published online: July 23, 2015