Deoxyglycoside Synthesis

Synthesis of 2,3,6-Trideoxysugar-Containing Disaccharides by Cyclization and Glycosidation through the Sequential Activation of Sulfoxide and Methylsulfanyl Groups in a One-Pot Procedure**

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Deoxysugars are often found in the polysaccharide domains of biologically active (anticancer, antibiotic, and cardiotonic) natural products.[1] The important role that the oligosaccharide moiety plays in this class of natural products has become apparent.[1,2] Like many deoxysugars, 2,3,6-trideoxysugars exist in important antibiotics,[3] such as landomycin A[4] and PI-080.[5] Several problems arise in the synthesis of 2,3,6-trideoxyglycosides.[6] Glycosyl donors with a leaving group at the anomeric center are quite sensitive compounds, and the 2,3,6-trideoxyglycosidic linkage formed by glycosylation is also labile under the acidic conditions used. Generally, the fewer oxygen atoms present in the pyranoside, the lower its acid stability.[7] Thus, the glycosylation method chosen should be applicable to the glycosylation of other deoxysugars and take into account their acid lability. 2,3,6-Trideoxysugars are not commercially available, as is true for deoxysugars in general. Therefore, the development of an efficient synthetic strategy, including the preparation of deoxysugars, introduction of the leaving group, and glycosylation, is particularly important.

Our attention has been focused on a strategy based on the idea that a sulfur atom can stabilize a carbanion at the α position, whereas a sulfenium ion can be used to generate a carbocation at the same position. Hanessian et al. and Trost et al. elegantly utilized these features in the synthesis of nucleosides.[8] We recently demonstrated that alkylation of an α-phenylsulfanyllactone followed by intramolecular acetal formation (glycosylation) provided a sialyl glycolactone.[9] Herein we report a novel and convenient one-pot method for the synthesis of disaccharides that contain 2,3,6-trideoxysugars, from acyclic compounds with a sulfoxide and a methylsulfanyl group.[10]

The synthetic strategy is illustrated in Scheme 1. Alkylation of methyl (methylsulfanyl)methyl sulfoxide (formaldehyde mercaptal sulfoxide; FAMSO) (**4**)[11] with 3,4-dialkoxy-1-iodopentane **5**, followed by selective deprotection, provides

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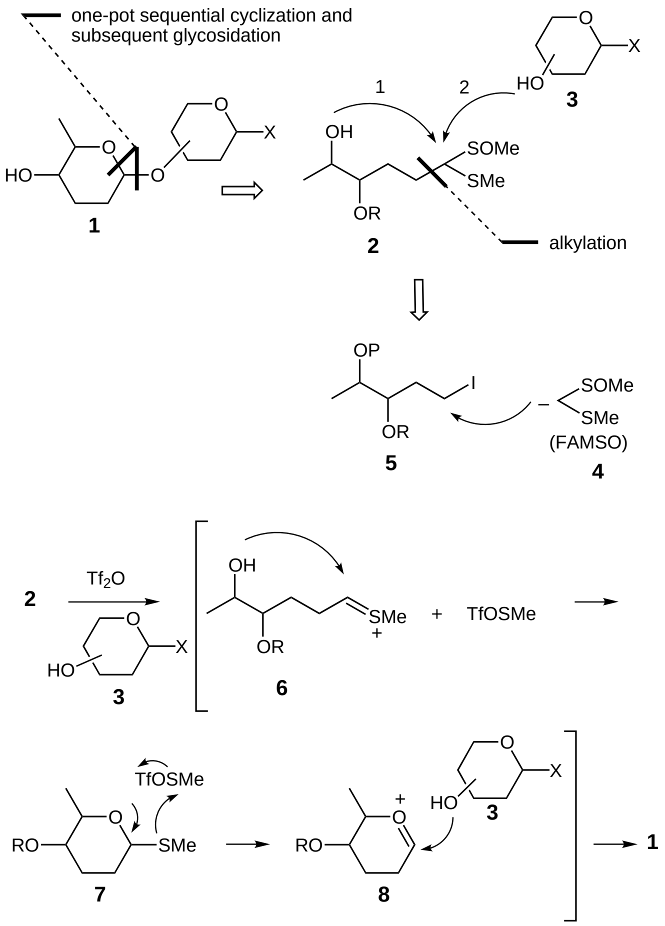
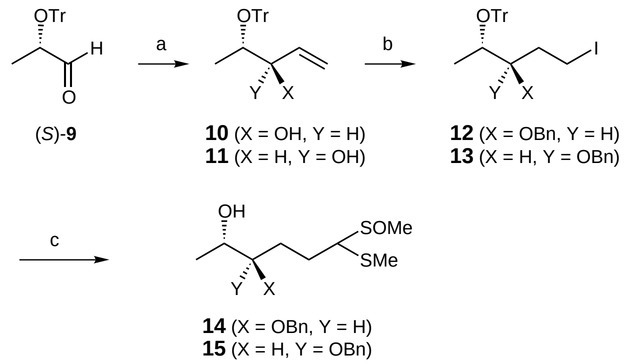
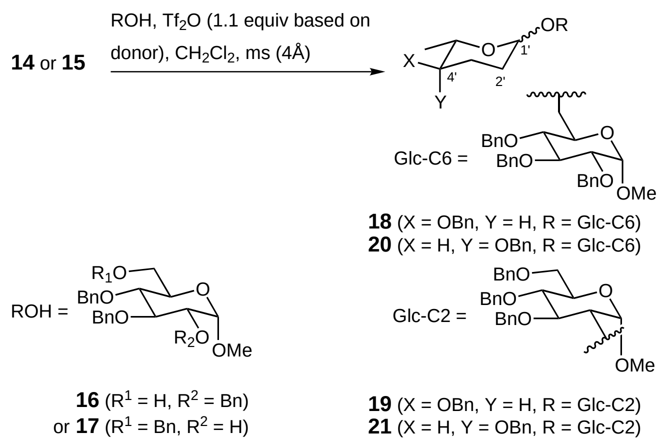


Scheme 1. Synthetic strategy and mechanism of formation of deoxy-sugar-containing disaccharide **1**.



Scheme 2. Preparation of the key intermediates. a) 1) vinyl magnesium bromide, THF, 92% (*syn* (**11**)/*anti* (**10**) = 2:3); b) 1) BnBr, NaH, THF, quant. (**12** and **13**); 2) BH_3·THF, then NaOH, H_2O_2, 53% (**12**), 48% (**13**); 3) I_2, PPh_3, benzene, imidazole, 93% (**12**), 94% (**13**); c) 1) FAMSO, NaH, THF, 75 °C; 2) CSA, MeOH, 2 steps, 70% (**14**), 80% (**15**). Tr = triphenylmethyl (trityl), Bn = benzyl, CSA = camphorsulfonic acid.



Scheme 3. One-pot sequential cyclization and glycosidation. ms = molecular sieves.

2. Selective activation of the sulfoxide group[12] in **2** with trifluoromethanesulfonic anhydride (Tf_2O)[13] leads to the formation of a sulfenium species **6**, which undergoes intramolecular acetalization to form thioglycopyranoside **7**. Concomitant activation of the methylsulfanyl group in **7** with the TfOSMe present affords the oxonium intermediate **8**, which undergoes glycosidation with **3**, leading to disaccharide **1** (Scheme 1).[14] As the labile glycosyl donor **7** is formed in situ, the need for its tedious isolation is avoided. If this reaction is carried out in the presence of a leaving group X on the glycosyl acceptor **3**, then further elongation of the glycoside is feasible, that is, orthogonal glycosylation,[15] one-pot glycosylation,[16,17] or two-directional glycosylation.[18]

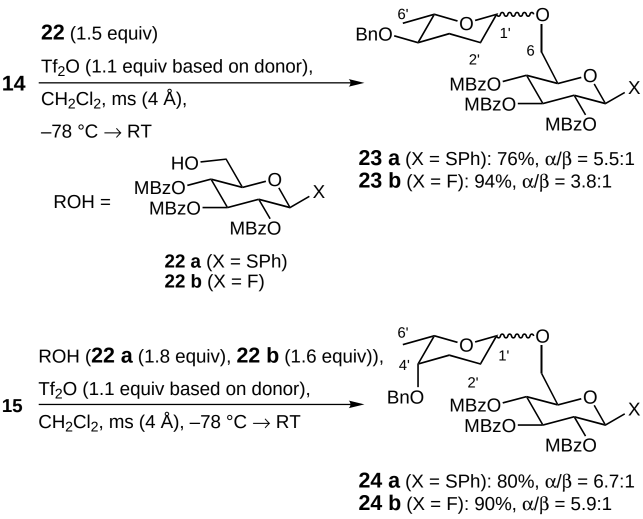
1,2-Addition of a vinyl Grignard reagent to aldehyde (*S*)-**9**, prepared from ethyl (*S*)-lactate, afforded the diastereomers **10** and **11** (3:2, 92%), and these were separated on silica gel.[19] After benzylation of **10**, hydroboration, followed by iodination, afforded iodide **12** (Scheme 2). Alkylation of FAMSO with **12** was performed at 75 °C in the presence of NaH. Removal of the trityl group provided the key intermediate **14** in 70% yield for the two steps.[20] The *syn* diastereomer **15** was prepared from **11** by a similar procedure (Scheme 2).

One-pot sequential cyclization and glycosidation was carried out as follows (Scheme 3, Table 1): Tf_2O (1.1 equiv) was added to a mixture of the acyclic donor **14** and the acceptor **16** in CH_2Cl_2 at −78 °C. After a few minutes, TLC analysis showed that the starting substrate had almost disappeared. After workup and column chromatography the desired disaccharide **18** was obtained in 83% yield (α/β = 1.2:1) (Table 1, entry 1).[21] The glycosidations of donor **14** with acceptor **17**, and donor **15** with acceptors **16** and **17**, were performed under the same conditions to provide the corresponding disaccharides **19, 20**, and **21** in 28%, 72%, and 40% yields, respectively (Table 1, entries 6, 4, and 9). We observed that glycosidations at the C6 hydroxy group occurred in moderate yield, whereas glycosidations at the C2 hydroxy group gave the products in poor yield. We believe that the glycosidation step is the rate-determining step as the substrates disappeared at −78 °C within a few minutes. Therefore, the reaction temperature was allowed to rise slowly from −78 °C to room temperature, which significantly improved the yields of the reactions at both the C6 and C2 hydroxy groups. Under these conditions, anomerization occurred, with dominant formation of the α-glycosides as the reaction temperature increased. When excess donor was used in the

Table 1: One-pot sequential cyclization and glycosidation of acyclic donor precursors **14** and **15** with acceptors **16** and **17**.

Entry	Donor (equiv)	Acceptor (equiv)	Product	T [°C]	Yield [%]	α/β
1	**14** (1.0)	**16** (3.0)	**18**	−78	83	1.2:1[a],[c]
2	**14** (1.0)	**16** (3.0)	**18**	−78→RT	79	1.7:1[a],[c]
3	**14** (1.5)	**16** (1.0)	**18**	−78→RT	92	2.0:1[a],[c]
4	**15** (1.0)	**16** (3.0)	**20**	−78	72	4.5:1[b],[d]
5	**15** (2.0)	**16** (1.0)	**20**	−78→RT	88	3.4:1[b],[d]
6	**14** (1.0)	**17** (3.0)	**19**	−78	28	1.2:1[a],[e]
7	**14** (1.0)	**17** (3.0)	**19**	−78→RT	65	α only[a],[e]
8	**14** (1.5)	**17** (1.0)	**19**	−78→RT	73	22:1[b],[e]
9	**15** (1.0)	**17** (3.0)	**21**	−78	40	α only[b],[f]
10	**15** (1.5)	**17** (1.0)	**21**	−78→RT	74	38:1[b],[f]

[a] The ratio was determined by HPLC analysis. [b] The ratio was determined by integration of the H-4′ signals in the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum. [c] Assignments of the anomeric proton signals for α- and β-L-amicetosides: (400 MHz, $CDCl_3$) $\delta = 4.65$ ppm (br d, $J_{1',2'} = 2.0$ Hz) for **18**α, $\delta = 4.70$ ppm (dd, $J_{1',2'ax} = 9.2$ Hz, $J_{1',2'eq} = 1.9$ Hz) for **18**β. [d] Assignments of the anomeric proton signals for α- and β-L-rhodinosides: (400 MHz, [D$_6$]benzene) $\delta = 4.80$ ppm (br d, $J_{1',2'} = 2.0$ Hz) for **20**α, $\delta = 4.51$ ppm (dd, $J_{1',2'ax} = 9.2$ Hz, $J_{1',2'eq} = 2.0$ Hz) for **20**β. [e] Assignments of the anomeric proton signal for α-L-amicetoside: (400 MHz, $CDCl_3$) $\delta = 4.97$ ppm (br d, $J_{1',2'} = 2.9$ Hz) for **19**α. [f] Assignment of the anomeric proton signal for α-L-rhodinoside: (400 MHz, $CDCl_3$) $\delta = 5.07$ ppm (br d, $J_{1',2'} = 2.9$ Hz) for **21**α.



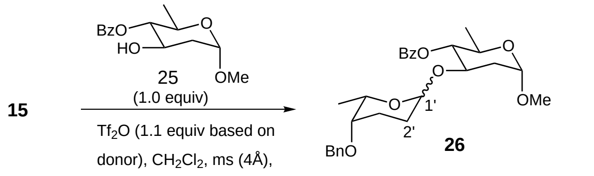
Scheme 4. Chemoselective glycosidation. MBz = 4-methylbenzoyl

reaction, the desired disaccharides were obtained in good yields (92% for **18** (Table 1, entry 3), 73% for **19** (entry 8)).

We next examined chemoselective glycosidation to demonstrate the versatility of this method. Treatment of **14** or **15** with phenylthioglycoside **22a** or glycosyl fluoride **22b** as the glycosyl acceptor, the desired disaccharides were obtained in excellent yields, without decomposition of the phenylsulfanyl group or the fluoride (76% for **23a**, 94% for **23b**, 80% for **24a**, 90% for **24b**) (Scheme 4).[22]

In nature, 2,3,6-trideoxyglycosides are generally linked to deoxyglycosides. We investigated the glycosidation of **15** with

Table 2: One-pot sequential cyclization and glycosidation with methyl 4-*O*-benzoyl-α-D-olivoside (**25**).



Entry	**15** [equiv]	T [°C]	Yield [%]	α/β ratio of **26**
1	1.5	−78	20	3.1:1[a]
2	1.5	−78→RT	dec.[b]	–
3	3.0	−78→−50	63	6.9:1[a]

[a] Ratio determined by HPLC analysis. Assignments of the anomeric proton signals for α- and β-L-rhodinosides: $\delta = 4.88$ ppm (br d, $J_{1',2'} = 2.9$ Hz) for **26**α, $\delta = 4.47$ ppm (dd, $J_{1',2'ax} = 9.2$ Hz, $J_{1',2'eq} = 1.9$ Hz) for **26**β. [b] Decomposed.

methyl 4-*O*-benzoyl-α-D-olivoside (**25**). Glycosidation at −78°C for 1 h gave the desired deoxyglycoside **26** in low yield (20%; Table 2, entry 1). The product decomposed when the reaction mixture was allowed to warm to room temperature (Table 2, entry 2). However, the desired deoxyglycoside **26** was obtained in moderate yield (63%) when the reaction temperature was kept at −50°C for 2 h (Table 2, entry 3).

In summary, we have developed a novel method for the synthesis of 2,3,6-trideoxyglycosides by sequential activation of the sulfoxide and methylsulfanyl groups in a one-pot procedure. This method does not require anomeric deprotection and the activation steps have been incorporated within traditional glycosylation strategies. Only three steps are required for the synthesis of disaccharides from oxygen-functionalized alkyl halides, a variety of which can be readily prepared as building blocks. Furthermore, this reaction proceeds in the presence of a phenylsulfanyl group and glycosyl fluoride, and is applicable to the synthesis of a deoxyglycoside linked to another deoxyglycoside. Thus, the reaction should be extremely useful for the diversity-oriented synthesis of oligosaccharides containing 2-deoxysugars as well as 2,3,6-trideoxysugars.

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[20] The selective deprotection of the trityl group proceeds under mild, acidic conditions (catalytic amount of CSA in methanol at 0 °C) without hydrolysis of the methylsulfanyl–methylsulfoxide moiety.

[21] In an attempt to isolate the methylsulfanylpyranoside, the acyclic donor **14** was treated with Tf_2O in the presence of 4-allyl-1,2-dimethoxybenzene[14a], which can trap TfOSMe. However, this reaction gave a complex mixture.

[22] The α/β ratios were determined by integration after complete assignment of chemical shifts from ^{1}H,^{1}H-COSY spectra: **23a** ((6′-H) α: $\delta = 1.16$ ppm, β: $\delta = 1.20$ ppm); **23b** (6-H) α: $\delta = 3.90$ ppm, β: $\delta = 3.81$ ppm); **24a** (6′-H) α: $\delta = 1.09$ ppm, β: $\delta = 1.55$ ppm; **24b** (6′-H) α: $\delta = 1.09$ ppm, β: $\delta = 1.55$ ppm. Chemical shift assignments for the anomeric protons of α-glycosides: $\delta = 4.71$ ppm (br d, $J_{1',2'} = 2.0$ Hz) for **23a**, $\delta = 3.90$ ppm (br d, $J_{1',2'} = 2.9$ Hz) for **23b**, $\delta = 4.79$ ppm (br d, $J_{1',2'} = 1.9$ Hz) for **24a**, $\delta = 4.78$ ppm (br s) for **24b**.

