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An Efficient and Practical Method for the Preparation of a Branched Oligoglycerol with Acetonide Protection Groups

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A novel method for the preparation of 1,3-bis(2,2-dimethyl-1,3-dioxan-5-yloxy)propan-2-ol, a branched oligoglycerols (BGL), was developed from 1,3-diallylated glycerol in excellent yield.

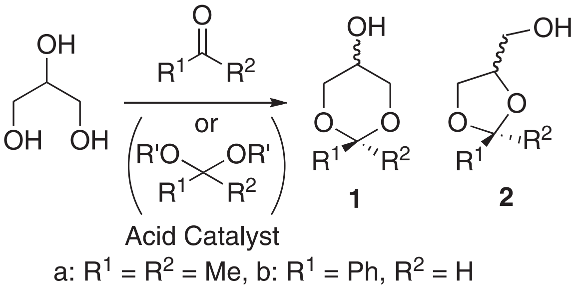
Preparation of 5-hydroxy-1,3-dioxanes **1** was previously carried out by acetalization or ketalization of glycerol, which generally produced a mixture of **1** and the isomer(s) **2** (Scheme 1).[1]

We recently reported that protected branched glycerol trimers **3** (BGL003) and heptamers **4** (BGL007),[2] which convert very lipophilic molecules into water-soluble derivatives, were synthesized starting from **1a**[1] and **1b**[3] (Scheme 2).

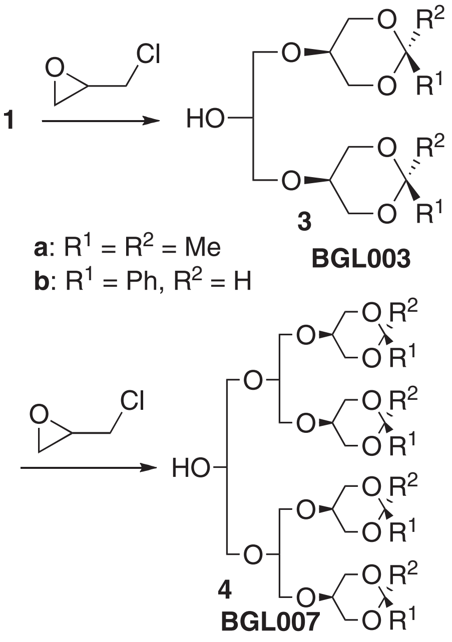
The protecting groups of **3a** and **3b** are deprotectable under mild acidic conditions and under hydrogen atmosphere in the presence of palladium catalysts to produce the volatile deprotected residues, acetone and toluene, respectively. Thus, it is important to develop a facile and efficient method for the large-scale preparation of small units of glycerol such as **1a**, **1b**, **3a**, and **3b** for various projects concerning the synthesis of linear, branched, and dendron oligo- and polyglycerols,[4] including our BGL-related projects.

First, we report the successful large-scale preparation of **1b**[3] (1.2 kg) from glycerol (1.0 kg) and benzaldehyde (1.0 kg). The dioxane **1b** was isolated from a mixture of **1b**, its *trans*-diastereomer and a diastereomeric mixture of **2b** by recrystallization. All the reagents for this reaction and the subsequent isolation (toluene as a reaction solvent, hexane and ethyl acetate for recrystallization, and sulfonic acid for acetalization catalyst) were reasonably priced and/or easily recoverable.

When the benzaldehyde dimethyl acetal was used instead of benzaldehyde in the presence of various acids, ^{1}H NMR analysis of the crude product indicated that the molar ratio of the undesired **2b** was increased. Furthermore, isolation of **1b** via recrystallization was unsuccessful probably because of the high molar ratio of **2b** and contamination of the remaining benzaldehyde dimethyl acetal. Accordingly, use of benzaldehyde was more suitable to prepare pure **1b** than use of the dimethyl acetal.



Scheme 1.

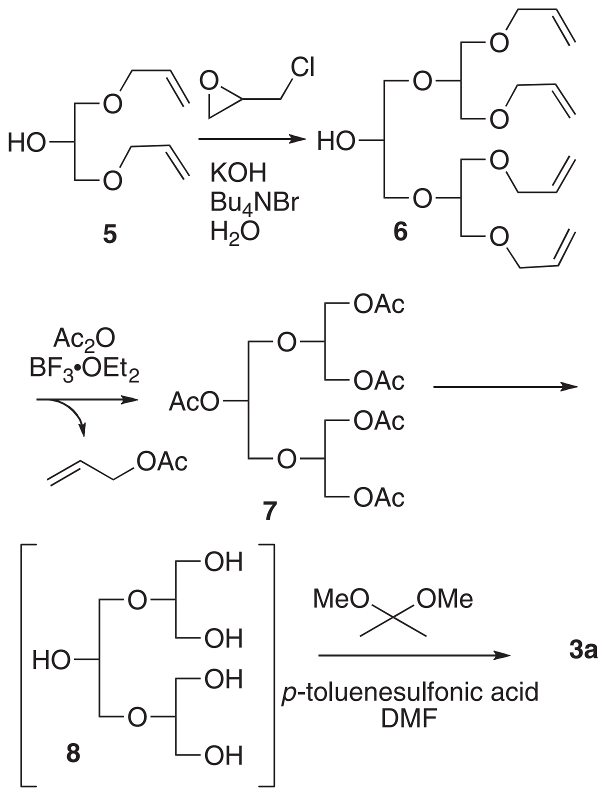


Scheme 2.

In contrast, ketalization of glycerol with acetone (or 2,2-dimethoxypropane) exclusively afforded undesired **2a**, and not even a trace amount of **1a** was detected.[1,5] Therefore, we initially prepared **1a** with the aid of Forbes' contrivable method via three steps,[1] which involved acetonization of 2-amino-2-(hydroxymethyl)propane-1,3-diol, oxidative cleavage of the C–C bond, and reduction of the resulting ketone. However, the method was time-consuming and laborious on a kilogram-scale, due to the presence of uneconomical processes such as reduction immediately after oxidation, loss of 25% of the carbon atoms, requirement for 3.5–4.0 kg of $NaIO_4$ and more than 100–150 g of dangerous $LiAlH_4$ in order to yield 1.0 kg of **1a**.

To avoid this wasteful oxidation–reduction combination and the use of expensive or dangerous reagents, we considered a new synthetic route detouring around **1a**. We herein report an alternative and efficient method for the preparation of **3a** (Scheme 3).

The starting material **5** is commercially available, or was prepared from epichlorohydrin and allyl alcohol in one step according to a method for the preparation of 1,3-dibenzylglycerol.[6] Tetraallylated BGL003 **6**[7] was also prepared from four



Scheme 3.

equivalents of **5** and one equivalent of epichlorohydrin in 86% yield, based on epichlorohydrin, according to the method for the preparation of tetrabenzylated BGL003.[6] Treatment of **6** with BF_3 etherate complex in acetic anhydride at 0 °C[8] afforded pentaacetate **7**[7] in 85% yield. Treatment of **7** with a catalytic amount of sodium methoxide gave the pentaol **8**, which was converted to the desired **3a**[7] using 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid in DMF in 67% overall yield from **7**.

Deallylation generated allyl acetate, which should be removed prior to the process from **7** to **3a**. Otherwise, some unidentified side reactions due to the carbon–carbon double bond under the acidic conditions were observed. Deallylation in the presence of palladium charcoal via double bond isomerization was also successful to produce **8**. However, the palladium-catalyzed procedure was much more dangerous than BF_3-mediated reaction since palladium charcoal easily led to ignition in this case. A second drawback of palladium-catalyzed reaction was the contamination of CH_3CH_2CHO or its dimethyl acetal, generated from the moieties of $–OCH_2CH{=}CH_2$ via double bond isomerization followed by hydrolysis or methanolysis. In this case, an unignorable amount of compound(s) bearing propylidene group(s) was produced. Therefore, a two-step procedure from **6** to **3a** is preferable to one-pot procedure to afford pure **3a**.

All the required reagents for Scheme 3 are reasonably priced, and the reactions are simple. Allyl acetate was recovered in 89% yield by distillation prior to the purification of **7**. Since the allylic moiety has a low molecular weight, the size of the flask as well as the amount of reaction solvent was also curtailed.

In conclusion, we have succeeded in developing an efficient method for preparing a trimer of branched glycerol with acetonide protecting groups **3a**, which is a key compound for BGL-related projects.

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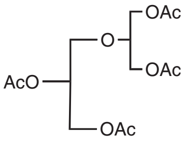
7 Supporting Information of **6**, **7**, and **3a** is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.
8 The first attempted condition (acetic acid, acetic anhydride, sulfonic acid, 0 °C, and 24 h) referred from the following paper, gave **7** in low yield along with glycerol triacetate and **9**. We considered that undesired cleavage of ether-linkage between glycerol units could be due to the presence of water. Therefore, we examined Lewis acids and the first choice ($BF_3{\cdot}OEt_2$) was fortunately successful. Other Lewis acids such as titanium tetrachloride gave a complicated unidentified mixture probably including not only ether-link cleaved by-products but also chlorinated by-products. S. Cassel, C. Debaig, T. Benvegnu, P. Chaimbault, M. Lafosse, D. Plusquellec, P. Rollin, *Eur. J. Org. Chem.* **2001**, 875.



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