An Efficient Method for the Refinement of 1,3-Methyleneglycerol via Bridged Acetal Exchange and the Synthesis of a Symmetrically Branched Glycerol Trimer

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Abstract: Acid-catalyzed equilibrium of a mixture of 1,2- and 1,3-methyleneglycerol in 1,4-dioxane affords predominantly the 1,3-isomer via bridged acetal exchange. The minor 1,2-isomer is removed via sequential pivaloylation and tritylation to afford the desired 1,3-isomer in >99.5% purity. A symmetrically branched triglycerol is efficiently synthesized starting from the purified 1,3-isomer.

Key words: alcohols, acylation, isomerization, oligomerization, glycerol

Oligo- and polyglycerols possessing ether linkages (OPGLs) have been studied to improve various properties of medicinal molecules.[1] Among typical OPGLs,[1] our developed series of symmetrically branched oligoglycerols (BGLs), such as the trimer (**BGL003**)[2] and heptamer (**BGL007**),[3] are more versatile for modification of a medicinal molecule than other OPGLs. This is due to the fact that BGLs are chemically pure (non-distributed mixtures), and no asymmetric center is induced when the apex point is connected to the target molecule (Figure 1). In contrast, other OPGLs often exist as a distributed mixture of molecular weights with a number of uncontrolled asymmetric centers (Figure 2).[1]

The strategy for the preparation of the terminus-protected BGLs[2–4] (TP-BGL) is illustrated in Scheme 1. 1,3-Protected glycerol **1** was used as the key starting material for all TP-BGLs.

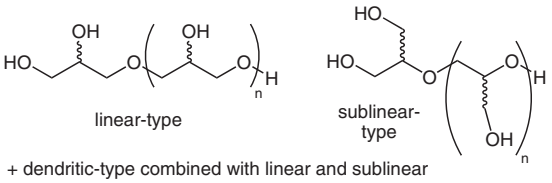
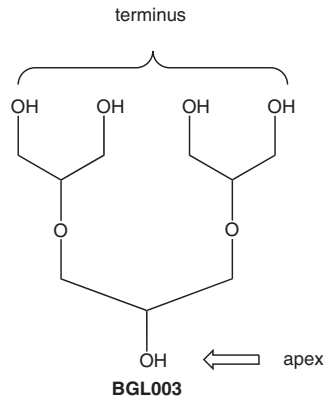


Figure 2 Examples of other OPGLs

Protected glycerol **1** is not only an essential material for the preparation of the BGL family of molecules, but is also a versatile C_3 building block in organic synthesis.[5] As such, many methods for the preparation of **1** have been reported,[2,6–8] which can be classified into two types (Scheme 2). The first type results in the cyclic form **1A**, which is prepared from glycerol and an aldehyde or ketone (R^1COR^2) (method A).[6,7] The second leads to acyclic form **1B**, which is obtained from epichlorohydrin and an alcohol (R^3OH) (method B).[2,8,9]

Method A is more sustainably acceptable than method B due to the following reasons. Industrial-scale production of biofuels (methyl or ethyl esters of fatty acids) from vegetable triglycerides affords a tremendous amount of glycerol as a surplus material.[10] In contrast, epichlorohydrin is prepared from petroleum (e.g., allylic chlorination of pro-



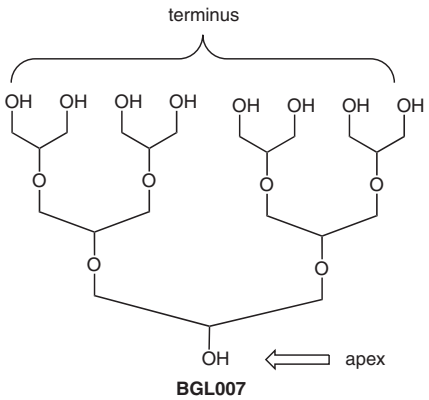


Figure 1 Examples of our developed BGLs as OPGLs

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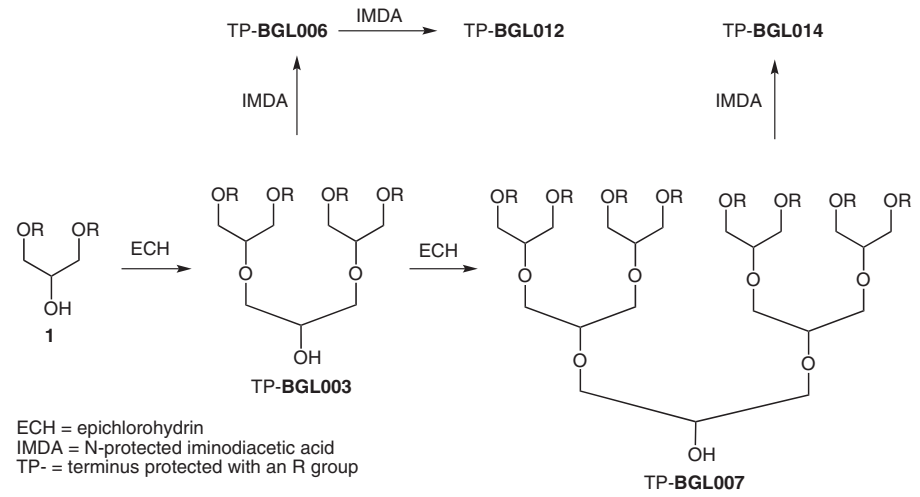
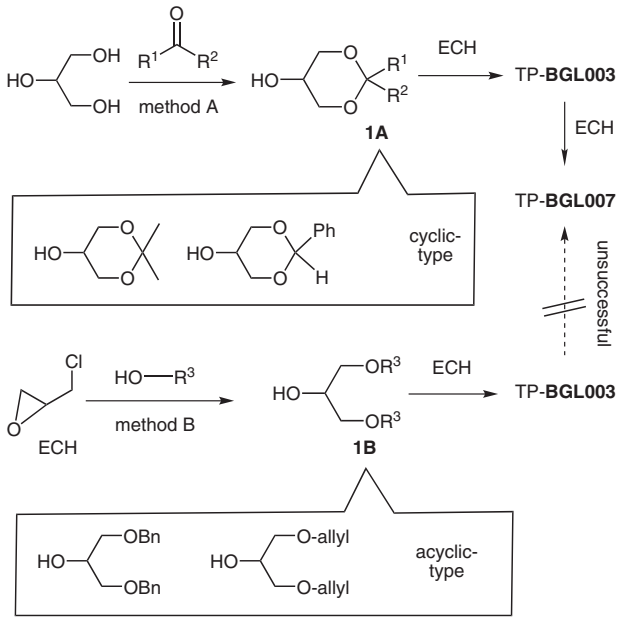


Scheme 1 Preparation of the BGL family of compounds



Scheme 2 Methods for the preparation of 1,3-protected glycerol **1**

pene followed by epoxidation). Furthermore, method A comprises a dehydrating process while method B includes a substitution reaction that essentially wastes a halogen atom.

In addition, for our BGL project, method A is more synthetically acceptable than method B because we can successfully prepare TP-**BGL007** bearing cyclic protecting groups from the precursor TP-**BGL003**,[3] while the reaction of acyclic TP-**BGL003** to give TP-**BGL007** proved unsuccessful. Additionally, the deprotecting conditions for **1A** are generally milder than those required for **1B**.[11] Accordingly, the use of method A is not only essential for our BGL project, but is also advisable for synthetic studies using the glyceryl skeleton as a C_3 building block.[5,12]

To prepare **1A** on large scale, the selectivity in favor of the 1,3-protected isomer versus the 1,2-protected isomer should be as high as possible. Thus, a simple procedure for the separation of the isomers would need to be developed. As shown in Scheme 3, however, undesired selectivities using acetone (**3**:**4** = >99:<1)[13] and benzaldehyde (**5**:**6** = 50:50)[7] were reported.

Based on the reported selectivities,[7,13] we hypothesized that the selectivity for **1A** versus **2A** would be very low if both the R^1 and R^2 groups were large, due to 1,3-diaxial repulsions[13] in **1A** (Figure 3).

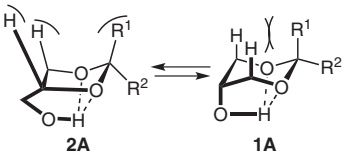
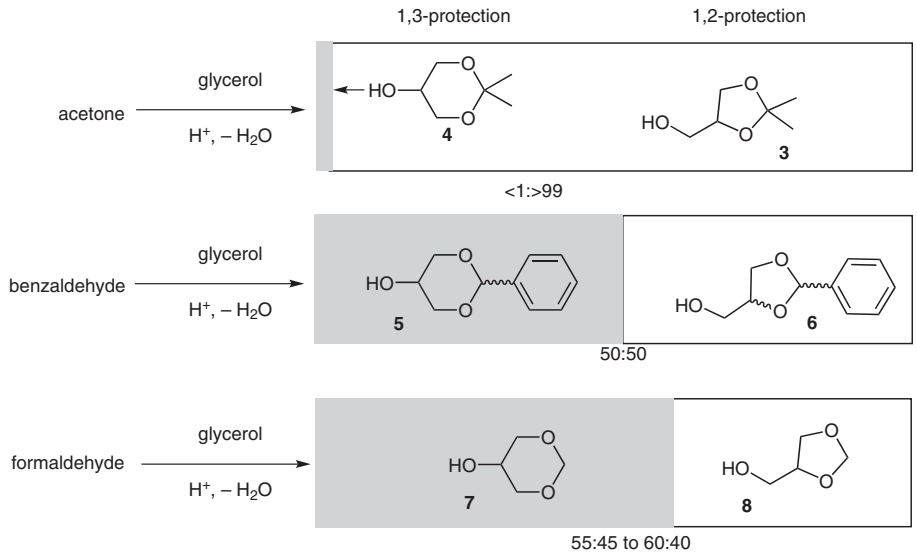


Figure 3 Steric effects on the synthesis of 1,2- and 1,3-protected glycerols

Therefore, the selectivity for **1A** might, in theory, be high when both R^1 and R^2 are small (e.g. a hydrogen atom). Initially, however, we were disappointed to find that the molar ratios of both a literature reported mixture,[14] and a commercially available mixture of **7** and **8** were much lower than expected.

Despite this, we focused our attention on protected glycerol **7** because the methylene-bridged protecting group is the smallest of all the versatile protecting groups for diols, and demonstrates advantages of economy and sustainability. Thus, we planned to separate isomer **7** from **8**, on large scale, using an acceptable procedure such as distillation or recrystallization. These two attempts were, however, immediately abandoned because the boiling point of **7** (193.8 °C) was very similar to that of **8** (192.5 °C),[15] and neither of their melting points were accessible (their melting points must be impractically low).

Instead, we examined chemoselective acylation using pivaloyl chloride (PvCl); it is known that pivaloylation of a primary hydroxy functionality is much faster than that of a secondary one.[16,17] Furthermore, the undesired piv-



Scheme 3 Previously reported acid-catalyzed dehydration reactions of glycerol with an aldehyde or a ketone

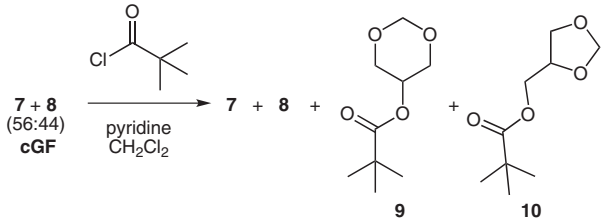
aloylated esters can be easily recycled to the original alcohols by alkaline hydrolysis (Table 1).[17,18]

Since we used commercially available glycerol formal (**cGF**), which exists as a 56:44 mixture of **7** and **8**, the ideal results for our purpose based on the sum of **7** and **8** would be yields of **7** (56%), **8** (0%), **9** (0%) and **10** (44%) using 0.44 equivalents of pivaloyl chloride. After several attempts on small scale, we found satisfactory conditions that afforded **7** (59%, within error limits, or including the isomerization process from **8** into **7**), **8** (7%), **9** (0%), and **10** (33%), using pivaloyl chloride (0.55 equivalents) and pyridine (0.68 equivalents) in dichloromethane (0.15 M) at 0 °C to room temperature over 18 hours. All the yields were determined by calculation of the ^{1}H NMR spectroscopic peak areas based on mesitylene as an internal standard. Next, the large-scale pivaloylation of **cGF** (1.81 mol) was carried out under the same conditions to afford a mixture of **7** and **8** (95:5) in 50% isolated yield and a mixture of **9** and **10** (9:91) in 33% isolated yield after distillation. We carried out the alkaline hydrolysis of the above mixture of **9** and **10** (9:91) to afford a mixture of **7** and **8** in almost quantitative yield in a 9:91 ratio, along with sodium pivalate in 98% isolated yield. Accordingly, this method for the efficient separation of **8** from **cGF** to prepare **7** in high purity proved successful, and included the recycling of isomer **8** as well as the recovered sodium pivalate.

Next, as shown in Scheme 4, we attempted the acid-catalyzed isomerization between **7** and **8** via intermediate **11** and related species, primarily because such bridged acetal exchange reactions in organic synthesis are often reported in good to excellent yields.[6,15,19] However, the reported conditions were not applicable for our purposes due to an unusual problem for small molecules such as **7** and **8**.

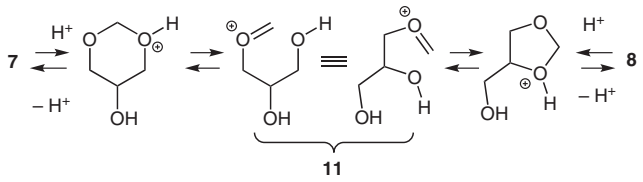
This problem was the low stoichiometry of the recovered mixture of **7** and **8**, as non-trivial amounts of unidentified by-products remained in the flask after distillation. Although it was difficult to analyze all the components of the distillation residue, oligomeric compounds such as **12**, **13**

Table 1 Pivaloylation of **cGF**



Method	7	8	9	10
Small scale[a]	59%	7%	0%	33%
Large scale (1.81 mol)[b]	50% (**7**:**8** = 95:5), (**7** = 48%, **8** = 2%)		33% (**9**:**10** = 9:91), (**9** = 3%, **10** = 30%)	
Ideal case	56%	0%	0%	44%

[a] Determined by ^{1}H NMR spectroscopy.
[b] Yield of isolated materials after distillation.



Scheme 4 A typical route for isomerization between **7** and **8**

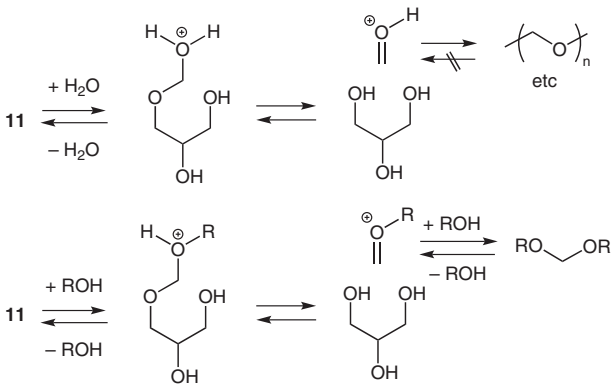
and further oligomers were present in the inseparable mixture (Scheme 5).

Even under strict anhydrous conditions, oligomers such as **12** and **13** can theoretically be produced because both **7** and **8** leave behind protic residues. Therefore, methylene bridges can be randomly transferred throughout to produce fully dehydrated compounds such as **13** with no free hydroxy groups, and partially dehydrated compounds such as **12** with two hydroxy groups. Furthermore, oligomerization is generally fast when the molecule is small.

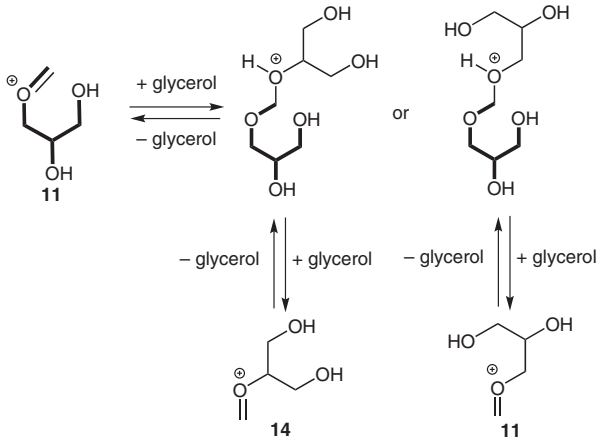
Although addition of protic molecules such as water or alcohols (ROH) may prevent oligomerization reactions, this leads to the formation of problematic by-products as illustrated in Scheme 6, and a non-protected triol (i.e., glycerol).

We eventually discovered that these problems could be solved by the addition of glycerol as a source of protons. As illustrated in Scheme 7, the alcoholysis of **11** using glycerol was no longer a side reaction. Repeat bond formation and cleavage between **7**, **8**, **11**, **14** and glycerol can occur smoothly to achieve equilibrium between **7** and **8**. At the same time, the formation of oligomers, especially fully dehydrated molecules such as **13**, is strongly inhibited since sufficient protons are available from the additional glycerol.

Based on the idea described above, we examined the acid-catalyzed isomerization of a mixture of **7** and **8** (9:91 ratio) in the presence of glycerol. As anticipated, the material balance between the input and output of **7** and **8** was greatly improved. Additionally, we made another unexpected and positive discovery: the ratio of **7** and **8**, after the acidic treatment, was often much more than 56:44 as

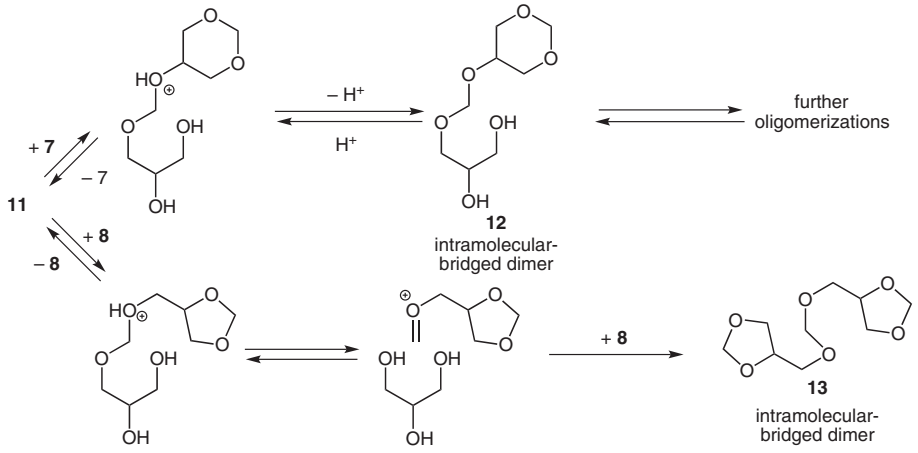


Scheme 6 Mechanism for the formation of by-products and glycerol in the presence of a large excess of protic molecules



Scheme 7 Strong inhibition of hydrolysis and oligomerization in the presence of glycerol

listed in Table 2. Accordingly, we hypothesized that **cGF** (56:44 ratio) may not be a thermodynamically controlled mixture.[14,20] We first examined the reaction of **cGF** (2.0 M in diethyl ether) at reflux for 18 hours in the presence of 0.5 equivalents of glycerol and a catalytic amount of sulfuric acid (Table 2, entry 1). However, the mass balance was still low (51%) in diethyl ether, probably because of the low solubility of glycerol in this solvent. At a



Scheme 5 Typical examples of side reactions (self-oligomerization) due to the presence of protic residues in **7** and **8**

low reaction temperature (17 °C), the ratio of **7**:**8** was unchanged, probably due to the reason that no deprotection or re-protection processes occurred (Table 2, entry 2). Other aromatic and ethereal solvents[21] were examined under the same conditions (18 h, sulfuric acid, 60 °C) (Table 2, entries 3–8). In each case, the molar ratio of **7** was increased, thus verifying our hypothesis. Accordingly, 1,4-dioxane was chosen as the most suitable solvent (Table 2, entry 8) because it gave the highest mass balance of the product.

As anticipated, the reaction in the absence of glycerol gave a decreased chemical yield (Table 2, entry 9), whereas almost the same yields were obtained when 0.5, 1.0, and 2.0 equivalents of glycerol were used (Table 2, entries 8, 10 and 11). Therefore, 0.5 equivalents of glycerol with respect to **cGF** were used in subsequent reactions.

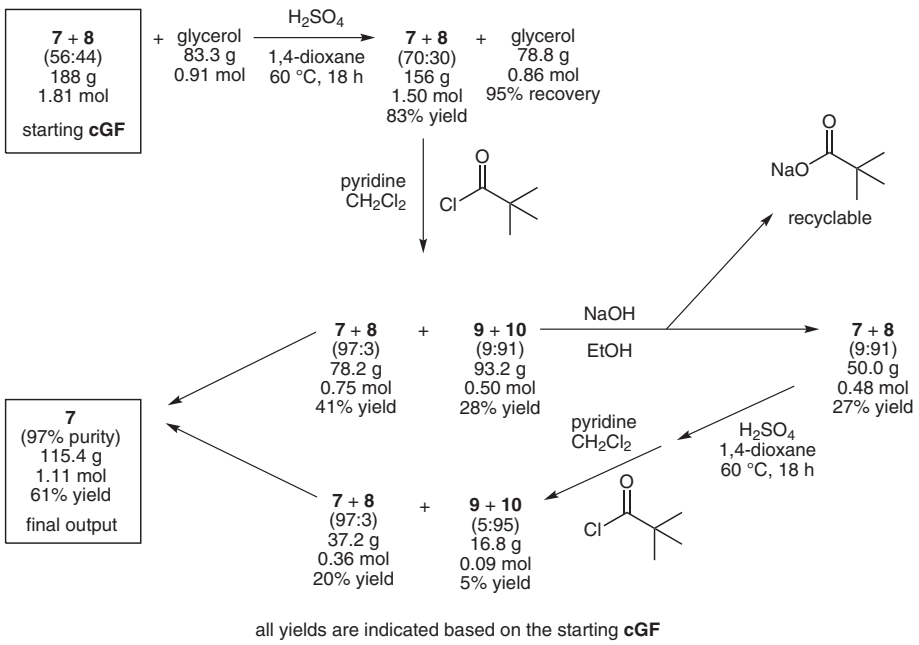
In entries 8, 12 and 13 (Table 2), the final molar ratios of **7**:**8** were the same within error limits, even for different initial molar ratios of **7**, that is, medium (56:44, Table 2, entry 8), high (97:3, Table 2, entry 12) and low (30:70, Table 2, entry 13). Therefore, the thermodynamic balance between **7** and **8** at 60 °C in 1,4-dioxane was estimated to be approximately 77:23.[20] In addition, various reaction periods were examined (3, 6, 18, and 48 h, Table 2, entries 14, 15, 8 and 16). The results indicated that a reaction time between 18 and 48 hours was long enough to reach thermodynamic equilibrium. Finally, reactions at various temperatures were examined (not all results are shown in Table 2). Below 50 °C, acid-catalyzed isomerization starting from **cGF** was too slow (e.g., at 17 °C over 48 h, **7**:**8** = 59:41, Table 2, entry 17). Above 70 °C, the mass balance was low and the ratio of **7** decreased (e.g., at 95 °C over 18 h, **7**:**8** = 64:36, Table 2, entry 18). Thus, a temperature around 60 °C was considered optimum to maximize the amount of the desired compound **7**.

Under the most suitable conditions (Table 2, entry 8), isomerization of **cGF** (**7**:**8** = 56:44, 188 g, 1.81 mol) was carried out in the presence of glycerol (83.3 g, 0.91 mol) at a higher concentration (5.0 M of **cGF** in 1,4-dioxane) than the small-scale reaction in preparation for a future large-scale reaction (Scheme 8). After distillation, a mixture of **7** and **8** (70:30, 156 g, 1.50 mol) was afforded in 83% isolated yield. Glycerol was also recovered in 95% yield by distillation. The resulting distillate (156 g of a mixture of **7** and **8**) was pivaloylated to afford **7** and **8** (97:3, 78.2 g, 0.75 mol, 41% yield based on starting **cGF**)

Table 2 Acid-Catalyzed Bridged Acetal Exchange between **7** and **8**[a]

Entry	Initial ratio (**7**:**8**)	Additional glycerol (vs **7** + **8**)	Solvent[b]	Time (h)	Temp (°C)	Yield[c] (%) of **7** + **8**	Ratio (**7**:**8**)
1	56:44	0.5 equiv	Et_2O	18	36	51	82:18
2	56:44	0.5 equiv	Et_2O	18	17	99	56:44
3	56:44	0.5 equiv	neat	18	60	67	81:19
4	56:44	0.5 equiv	toluene	18	60	62	79:21
5	56:44	0.5 equiv	THF	18	60	84	77:23
6	56:44	0.5 equiv	MTBE	18	60	45	78:22
7	56:44	0.5 equiv	CPME	18	60	71	77:23
8	56:44	0.5 equiv	1,4-dioxane	18	60	**90**	**74:26**
9	56:44	–	1,4-dioxane	18	60	82	71:29
10	56:44	1.0 equiv	1,4-dioxane	18	60	92	77:23
11	56:44	2.0 equiv	1,4-dioxane	18	60	90	76:24
12	97:3	0.5 equiv	1,4-dioxane	18	60	99	77:23
13	30:70	0.5 equiv	1,4-dioxane	18	60	80	75:25
14	56:44	0.5 equiv	1,4-dioxane	3	60	85	63:37
15	56:44	0.5 equiv	1,4-dioxane	6	60	86	71:29
16	56:44	0.5 equiv	1,4-dioxane	48	60	94	77:23
17	56:44	0.5 equiv	1,4-dioxane	18–48	17	98	59:41
18	56:44	0.5 equiv	1,4-dioxane	18	95	85	64:36

[a] Reaction conditions: methyleneglycerols **7** and **8** (1.0 equiv), solvent (2.0 M based on methyleneglycerols), glycerol (0.5 equiv), H_2SO_4 (4 mol%) unless otherwise noted.
[b] MTBE = methyl *tert*-butyl ether, CPME = cyclopentyl methyl ether.
[c] Determined by ^1H NMR spectroscopy using mesitylene as an internal standard.

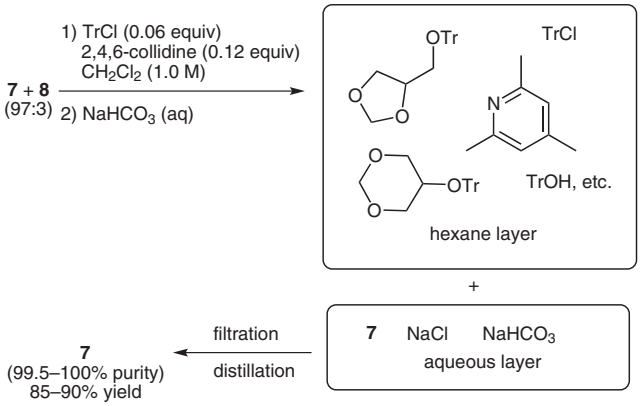


Scheme 8 Preparation of compound **7** on large scale

after distillation. A mixture of **9** and **10** (9:91, 93.2 g, 0.50 mol, 28% isolated yield based on starting **cGF**) was also obtained by distillation. After alkaline hydrolysis of the mixture of **9** and **10** with sodium hydroxide (1.0 M) in ethanol, a mixture of **7** and **8** (9:91) was obtained in 27% yield based on starting **cGF** (95% yield from the mixture of **9** and **10**). Repeated isomerization–pivaloylation afforded a mixture of **7** and **8** (97:3, 37.2 g, 0.36 mol, 72% yield from the mixture of **9** and **10**, 20% yield based on starting **cGF**). A second portion of a mixture of **9** and **10** (5:95, 16.8 g, 89.3 mmol, 5% yield based on starting **cGF**) was also obtained. Accordingly, **cGF** (1.81 mol) was converted into **7** in 61% [= (0.75 + 0.36)/1.81] yield and 97% purity.

Although the purity of **7** obtained according to Scheme 8 was high enough for some purposes, a further procedure to afford **7** in 99.5–100% purity is described. A solution of **7** (97% purity) in dichloromethane was treated with trityl chloride[22] (0.06 equiv) and 2,4,6-collidine (0.12 equiv) in dichloromethane (1.0 M). After several hours (depending on the reaction scale), water containing 1% sodium hydrogen carbonate was added and the dichloromethane was removed under reduced pressure. Since both **7** and **8** are soluble in water, tritylated compounds and 2,4,6-collidine were removed by extraction with hexane.[23] After concentration of the aqueous layer and removal of inorganic salts such as sodium chloride and sodium hydrogen carbonate by filtration, simple distillation then gave the desired product **7** in 85–90% yield and in over 99.5% purity (Scheme 9).

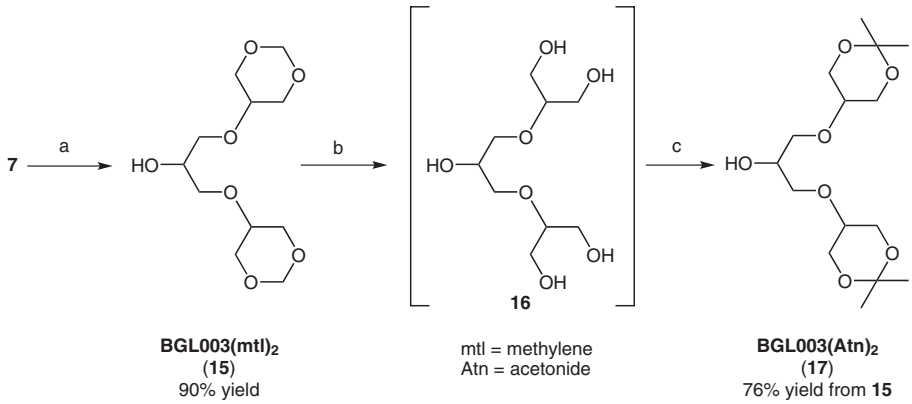
Finally, dendritic-generation growth of **7** was carried out to afford the bis(methylene)-protected symmetrically branched triglycerol **15**. Purified **7** was reacted with epichlorohydrin in the presence of tetrabutylammonium bro-



Scheme 9 Final treatment to afford **7** in 99.5–100% purity

mide and wet potassium hydroxide with vigorous stirring[2,3] to afford **15** in 90% yield. Subsequent hydrolysis of **15** with hydrochloric acid (1.0 M) in methanol gave the pentaol **16**, which was easily protected with 2,2-dimethoxypropane [$Me_2C(OMe)_2$] in the presence of a catalytic amount of Amberlyst 15® in *N*,*N*-dimethylformamide to give **17**[9] in 76% overall yield from **15**. The final product **17** was purified both by silica gel column chromatography and by recrystallization from diethyl ether–hexane (1:3) at –10 °C (Scheme 10).

In conclusion, we have developed an efficient method for the large-scale preparation of highly purified 1,3-methyleneglycerol **7**. The main reagents (the pivaloyl moiety, the sodium cation and additional glycerol) were recovered in excellent yields. The synthesis of two different symmetrically branched trimers (TP-**BGL003**) was also successful. At the same time, problematic side reactions



Scheme 10 Synthesis of TP-**BGL003 15** and **17**. *Reagents and conditions*: (a) ECH, TBAB, KOH, neat, 60 °C, 48 h, 90%; (b) 1 M HCl, MeOH, reflux, 24 h; then Amberlite IRA-96™ (c) $Me_2C(OMe)_2$, cat. Amberlyst 15®, DMF, r.t., 12 h, 76% from **15**.

involving acid-catalyzed exchange of acetal bridges in small molecules were addressed, and a novel solution (addition of the fully deprotected original alcohol if readily available) was demonstrated.

All reactions were carried out under an argon atmosphere unless otherwise described. Toluene, Et_2O, 1,4-dioxane, DMF, CH_2Cl_2 and 2,2-dimethoxypropane were distilled using standard methods prior to use. Glycerol formal (**cGF**) was purchased from Tokyo Chemical Industry Co., Ltd., and was found to contain 56% of 1,3-methyleneglycerol (4-hydroxy-1,3-dioxane) (**7**) and 44% of 1,2-methyleneglycerol (4-hydroxymethyl-1,3-dioxolane) (**8**) according to ^{1}H NMR spectroscopic analysis. Column chromatography was performed using Silica gel 60N purchased from Kanto Chemical Co., Inc. (63–210 μm). IR spectra were obtained using a Jasco FT-IR 6200 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded using JEOL-EX400 or Bruker AV400n instruments and were referenced to tetramethylsilane. High-resolution mass spectra were obtained on a Waters LCT Premier spectrometer.

Isomerization of 1,2-Methyleneglycerol; Typical Procedure

To a soln of methyleneglycerols **7** and **8** (520 mg, 5.0 mmol) and glycerol (200 mg, 2.5 mmol) in 1,4-dioxane (2.5 mL) was added concd H_2SO_4 (22.0 mg, 0.224 mmol) at r.t. After stirring at 60 °C for 18 h, the mixture was cooled to r.t. and then quenched with powdered Na_2CO_3 (ca. 237 mg, 2.24 mmol) with vigorous stirring. The resulting suspension was filtered through a pad of Celite® which was then rinsed with Et_2O. The filtrate was evaporated under reduced pressure to give a crude material, which was analyzed by ^{1}H NMR spectroscopy after the addition of mesitylene (200 mg, 1.67 mmol) as an internal standard.

Large-Scale Isomerization of Methyleneglycerols; Typical Procedure

To a soln of **cGF** (188 g, 1.81 mol) and glycerol (83 g, 0.90 mol) in 1,4-dioxane (360 mL) was added concd H_2SO_4 (66.0 mg, 0.672 mmol) at r.t. After stirring at 60 °C for 18 h, the mixture was cooled to r.t. and then quenched with powdered Na_2CO_3 (1.42 g, 13.44 mmol). The resulting suspension was filtered through a pad of Celite® which was then rinsed with Et_2O. The filtrate was evaporated under reduced pressure to give a crude residue, which was distilled (65 °C/8 mmHg) to furnish a mixture of **7** and **8** (70:30, 156 g, 1.50 mol, 83% yield). Further distillation (88 °C/0.1 mmHg) afforded glycerol (79.2 g, 0.86 mol, 96% recovered yield) as a colorless oil.

1,3-Methyleneglycerol (7) (in 97% Purity)

To a soln of methyleneglycerols (**7**:**8** = 70:30, 156 g, 1.50 mol) and pyridine (48.0 mL, 0.600 mol) in CH_2Cl_2 (500 mL) was added PvCl (67.7 mL, 0.550 mol) dropwise over 45 min at 0 °C. After stirring at r.t. for 6 h, the mixture was quenched with powdered $NaHCO_3$ (ca. 237 mg, 2.24 mmol), and the resulting suspension filtered. The filtrate was evaporated under reduced pressure to give a colorless oil, which was distilled to furnish **7** in 50% yield with 97% purity (65 °C/8 mmHg, 78.2 g, 0.751 mol), along with a mixture of **9** and **10** as a colorless oil (**9**:**10** = 9:91, 93.2 g, 0.495 mol) (85 °C/8 mmHg) in 33% yield, which was then used for the next hydrolysis procedure without further separation.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.01 (d, *J* = 10.0 Hz, 1 H), 3.63 (dquin, *J* = 10.0, 3.0 Hz, 1 H), 3.88 (dd, *J* = 11.0, 3.0 Hz, 2 H), 3.93 (dd, *J* = 11.0, 3.0 Hz, 2 H), 4.77 (d, *J* = 6.0 Hz, 1 H), 4.94 (d, *J* = 6.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.2 (CHOH), 71.8 (2 × CH_2), 94.1 (OCH_2O).

ESI-HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_4H_8O_3Na$: 127.0366; found: 127.0338.

Hydrolysis of a Mixture of Compounds 9 and 10

To a soln of **9** and **10** (**9**:**10** = 9:91, 29.1 g, 155 mmol) in EtOH (50 mL) was added an aq soln of NaOH (1 M, 233 mL, 233 mmol) at r.t. After stirring at r.t. for 18 h, the mixture was neutralized by the addition of HCl (1 M), and then evaporated under reduced pressure. The resulting suspension containing NaCl and sodium pivalate was filtered through a pad of Celite® which was then rinsed with CH_2Cl_2. The combined organic and aqueous filtrates were evaporated in vacuo to remove CH_2Cl_2 and H_2O to give a colorless oil, which was distilled (65 °C/8 mmHg) to furnish a mixture of **7** and **8** (**7**:**8** = 9:91, 15.3 g, 147 mmol).

Tritylation of a Mixture of 7 and 8

To a stirred soln of a mixture of **7** and **8** (ratio = 97:3, 10.41 g, 0.10 mol) in CH_2Cl_2 (100 mL) in the presence of 2,4,6-collidine (1.09 g, 9.0 mmol) was added slowly a CH_2Cl_2 (10 mL) soln of TrCl (1.67 g, 6.0 mmol) in a dropwise manner at r.t., and then the resulting mixture was stirred for ca. 7 h. The mixture was quenched with an aq soln of $NaHCO_3$ (1 wt%, 500 g, 60.0 mmol). The separated organic layer was concentrated in vacuo to remove CH_2Cl_2. The residue and the separated aq layer were mixed together, and extracted with hexane (2 × 50 mL) to remove lipophilic compounds such as 2,4,6-collidine and tritylated products. The aq layer was concentrated in vacuo in the presence of EtOH (as an azeotrope). [If the inorganic salts (NaCl and $NaHCO_3$) precipitated, filtration was carried out to remove the salts in order to prevent bumping.] The residue was dissolved in CH_2Cl_2 (200 mL), dried over anhyd $MgSO_4$, and concentrated in vacuo. The residue was distilled (66 °C/8 mmHg) to afford **7** in 99.5–100% purity (8.85–9.37 g, 85.0–90.0 mmol, 85–90% yield).

1,3-Bis[(1,3-dioxan-5-yl)oxy]propan-2-ol [15, BGL003(mtl)$_2$]
To a suspension of TBAB (0.457 g, 1.42 mmol), **7** (2.21 g, 17.7 mmol) and KOH (0.994 g, 17.7 mmol) in H_2O (0.5 mL) was added epichlorohydrin (0.354 mL, 7.09 mmol) dropwise at r.t. with vigorous stirring. After stirring at 60 °C for 48 h, the mixture was neutralized with an aq soln of HCl (1.0 M), and evaporated under reduced pressure to give a suspended material. The suspension containing KCl was filtered through a pad of Celite® which was then rinsed with 1,4-dioxane. The filtrate was evaporated in vacuo to afford a crude oil, which was purified by silica gel column chromatography (CH_2Cl_2–acetone, 3:1) to furnish **15** (1.69 g, 6.40 mol, 90% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.83 (d, *J* = 4.0 Hz, 1 H), 3.42–3.49 (m, 2 H), 3.57 (dd, *J* = 9.0, 6.0 Hz, 4 H), 3.62 (dd, *J* = 9.0, 4.4 Hz, 4 H), 3.74 (dd, *J* = 12.0, 6.0 Hz, 4 H), 3.94 (ddd, *J* = 6.0, 4.4, 4.0 Hz, 1 H), 4.03 (dd, *J* = 12.0, 4.0 Hz, 4 H), 4.75 (d, *J* = 6.0 Hz, 2 H), 4.84 (d, *J* = 6.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.1 (4 × CH_2O), 69.6 (CHOH), 70.1 (2 × CH_2O), 70.6 (2 × CH), 94.1 (2 × OCH_2O).

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{20}O_7Na$: 287.1106; found: 287.1096.

1,3-Bis[(2,2-dimethyl-1,3-dioxan-5-yl)oxy]propan-2-ol [17, BGL003(Atn)$_2$]
A soln of **15** (0.528 g, 2.00 mmol) and HCl (1 M in MeOH; 2 mL) was stirred at reflux for 24 h. The mixture was neutralized by the addition of Amberlite IRA-96™ (0.913 mmol/g; 4.38 g, 4 mmol). The resin was removed by filtration and the filtrate was evaporated under reduced pressure to give crude **16**, which was used without further purification.

To a soln of **16** and 2,2-dimethoxypropane (0.738 mL, 6.00 mmol) in DMF (2 mL) was added Amberlyst 15® (39.5 mg, 0.200 mmol, loading 5.06 mmol/g) portionwise. After stirring at r.t. for 24 h, the mixture was filtered, and evaporated under reduced pressure to give a brownish oil, which was purified by silica gel column chromatography (CH_2Cl_2–acetone, 2:1) to furnish **17** (0.487 g, 1.52 mmol, 76% yield) as a colorless gummy solid. The spectral data of **17** were in complete agreement with those of the same compound reported in our previous work.[3,9]

IR (neat): 3477, 2975, 2917, 2860, 1478, 1460, 1447, 1183, 1155, 1078, 1040, 1017, 974, 942, 912, 802 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 6 H), 1.43 (s, 6 H), 2.68 (br s, 1 H), 3.42–3.49 (m, 2 H), 3.53 (dd, *J* = 9.6, 6.0 Hz, 2 H), 3.60 (dd, *J* = 9.6, 4.4 Hz, 2 H), 3.77 (dd, *J* = 12.6, 4.4 Hz, 4 H), 3.93 (br s, 1 H), 3.98 (dd, *J* = 12.6, 6.0 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5 (2 × CH_3), 23.6 (2 × CH_3), 62.5 (4 × CH_2O), 69.7 (CHOH), 69.8 (2 × CH_2O), 71.1 (2 × CH), 98.3 (2 × C).

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{28}O_7Na$: 343.1733; found: 343.1740.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(16) Ac_2O: Our initial attempt using Ac_2O was unsuccessful as very poor acetylation selectivity between **7** and **8** was observed.
(17) TsCl: Although the use of TsCl for selective tosylation of **8** was reported, the recovered yield of **7** was very low and a serious problem was that tosylated **7** and **8** could not be recycled, see: Gras, J.-L.; Nouguier, R.; Mchich, M. *Tetrahedron Lett.* **1987**, *28*, 6601.
(18) TrCl: The reaction of **cGF** with trityl chloride was abandoned because deprotecting conditions to recycle the reagent must be carefully controlled for tritylated **7** and **8** in the presence of acetal protecting groups. Alternatively, exhaustive hydrolysis to afford glycerol, formaldehyde and trityl alcohol must be performed.
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(20) The hypothesis shown in Figure 3 becomes more credible as a consequence of the results reported herein, because the results of entries 8, 12 and 13 in Table 1 indicate objectively the balanced point of thermodynamic equilibrium. The conditions for the industrial preparation of **cGF** must undoubtedly be different from our reported conditions, although the industrial preparation was not described in detail.
(21) Undesired compound **8** was obtained as the major isomer when halogenated solvents such as CH_2Cl_2 or DCE were chosen for the acid-catalyzed re-bridge reaction of **cGF**. Additionally, wet ethereal solvents and/or wet glycerol afforded less **7** and more **8** than the result obtained in entry 8. Therefore, the thermodynamic ratio (**7**:**8** = 77:23) was reached as long as anhydrous conditions were carefully maintained.
(22) Treatment of compound **7** (of 97% purity) with TrCl afforded **7** in much higher purity than similar treatment with PvCl. Although we pointed out that tritylation of methyleneglycerol was problematic if recycling results of 25–44% of **8** were considered,[18] using TrCl to remove the very small amount of **8** (Scheme 9) was acceptable for our purposes.
(23) Extraction is often more economical and sustainable than distillation since time and energy (electricity for running the vacuum pump and heating equipment) can be saved. Therefore, the separation procedure by extraction with hexane was also examined for removing pivaloylated compounds from **7** and **8**, which proved to be as successful as the tritylation procedure.