

HETEROCYCLES, Vol. 69, 2006, pp. 107 - 111. © The Japan Institute of Heterocyclic Chemistry
 Received, 2nd July, 2006, Accepted, 21st August, 2006, Published online, 25th August, 2006. COM-06-S(O)44

SYNTHESIS OF CYCLIC POLYGLYCEROLS

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Abstract – Authentic standards of cyclic polyglycerol, with well-defined structures and degrees of polymerization from 3 to 6 cyclic oligomers, have been efficiently synthesized. The intramolecular cyclization conditions gave cyclic glycerols more effectively than intermolecular coupling conditions.

Polyglycerols are oligomers of glycerol (glycerin). Their fatty acid esters (PGE) are generally dispersible in water and soluble in oil. They are widely using in food additives, cosmetic materials and toiletries as surfactants.¹ Although polyglycerols is readily available in bulk quantities by industrial manufacture, the reaction requires drastic conditions, including high temperature and alkaline media. Therefore, commercially available polyglycerols are very complicated oligomeric mixtures and undefined molecular composition with difficult characterization.²

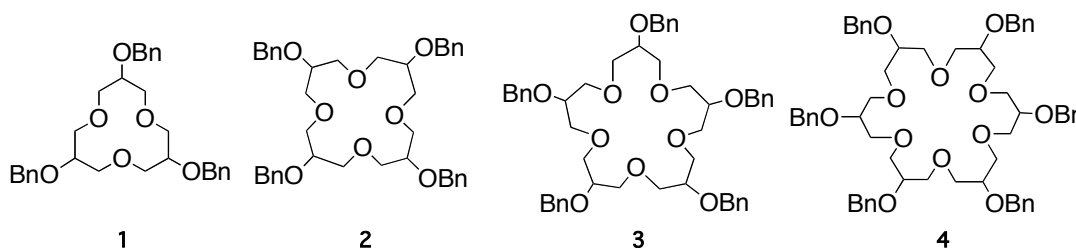
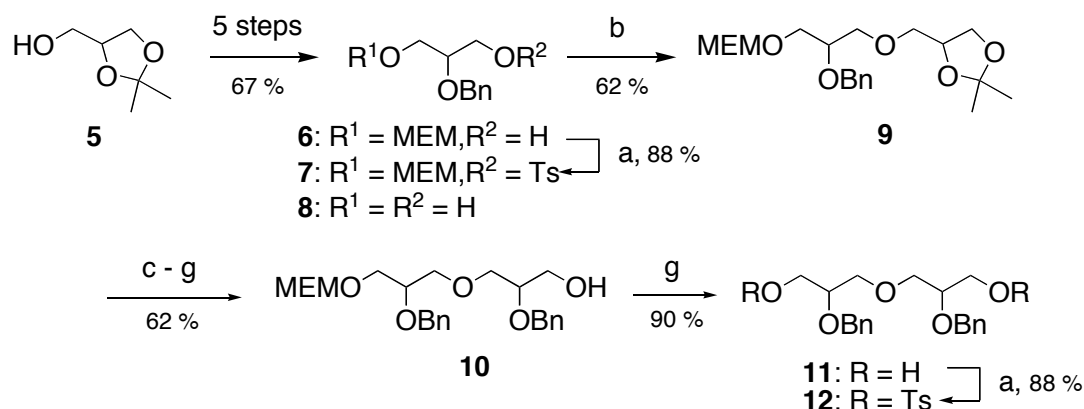


Figure 1. Structure of cyclic polyglycerols

We therefore focused our attention on the synthesis of single and fine structure of highly cyclic polyglycerols (**1-4**) as an authentic standard. There are a few representative standards of polyglycerols in the literature.³⁻⁸ Linear polyglycerols, dimer to pentamer, have previously been prepared either by direct

synthesis involving bishydroxylation of diallyl ether⁵ and 1,3-di-*O*-allylglycerol⁶ or by coupling of D,L- α,β -isopropylidenglycerol (solketal (**5**)) with either its tosylate⁸ or with glycidyl solketal ether.⁹⁻¹¹ Rollin *et al.* reviewed recent synthesis of linear, branched and cyclic polyglycerol standards.¹²

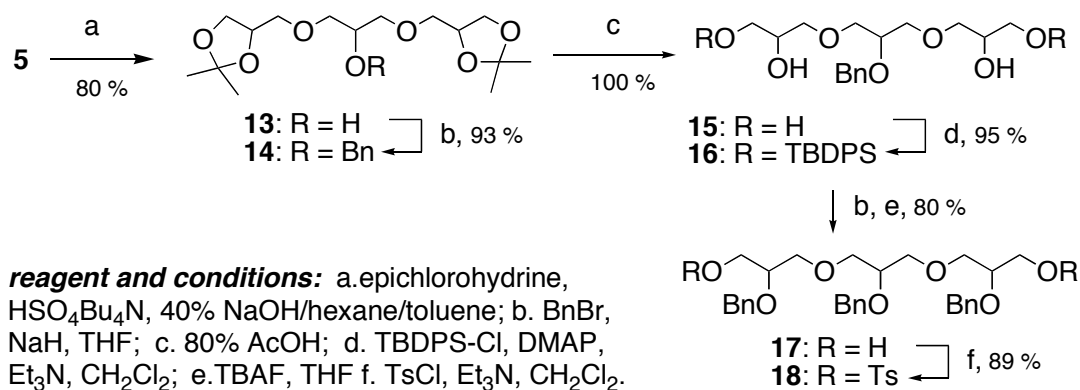
In order to couple only between primary positions, we used three units of glycerol (**8**, **11** and **17**) as the useful synthetic intermediates. Commercially available mono-glycerol unit (**8**) has a benzyl (Bn) group, di-glycerol unit (**11**) has two Bn groups and tri-glycerol unit (**17**) has three Bn groups at each secondary positions. Di-glycerol unit (**11**) was made from solketal (**5**) which was changed to MEM ether (**6**) in 5 steps with 67% overall yield. After methoxyethoxymethyl (MEM) ether (**6**) was converted into tosylate **7** in 88% yield, its coupling with solketal (**5**) provided di-glycerol (**9**) in 62% yield. The acetonide group at terminal position is convertible to Bn group to give **10** in 62% by four steps; hydrolysis in 80% AcOH, *tert*-butyldiphenylsilyl (TBDPS) protection, benzylation and silyl deprotection by tetrabutylammonium fluoride (TBAF). Finally acid hydrolysis of MEM group gave desired di-glycerol unit (**11**) in 90% yield. The corresponding di-tosylate (**12**) was synthesized in 88% yield under usual conditions.



reagent and conditions: a. TsCl, Et₃N, CH₂Cl₂; b. **5**, NaH, DMSO/THF; c. 80% AcOH; d. TBDPS-Cl, DMAP, Et₃N, CH₂Cl₂; e. BnBr, NaH, THF; f. TBAF, THF; g. HCl, MeOH, 80 °C.

Scheme 1. Synthesis of di-glycerol units

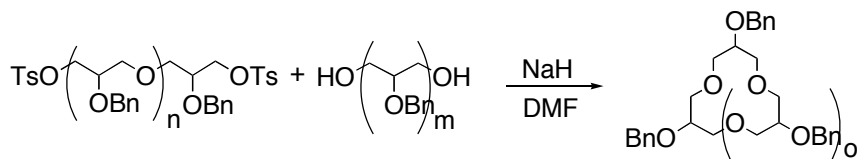
Tri-glycerol unit (**13**) was synthesized from the coupling of solketal (**5**) and epichlorohydrin in the presence of tetrabutylammonium bisulfate in 80% yield. Obtained secondary hydroxy group was protected with Bn group to give **14** in 93% yield, its acetonide groups were removed by acid treatment and following primary alcohols were protected with TBDPS group to give diol (**16**) in 95% yield. Two secondary hydroxy groups were protected with Bn group and TBDPS groups were deprotected to afford desired benzyl tri-glycerol (**17**). The corresponding di-tosylate (**18**) was synthesized in 89% yield under usual conditions.



Scheme 2. Synthesis of tri-glycerol units

Three glycerol (**8**, **11** and **17**) are in hands as the useful synthetic intermediates. We first tried 1:1 condensation of di-tosylates and diols. The synthesis of cyclic trimer to pentamer has been reported by 1:1 condensation of bis-epoxide or di-triflate with di-nucleophiles.¹³

Table 1. Synthesis of cyclic glycerols by intermolecular coupling

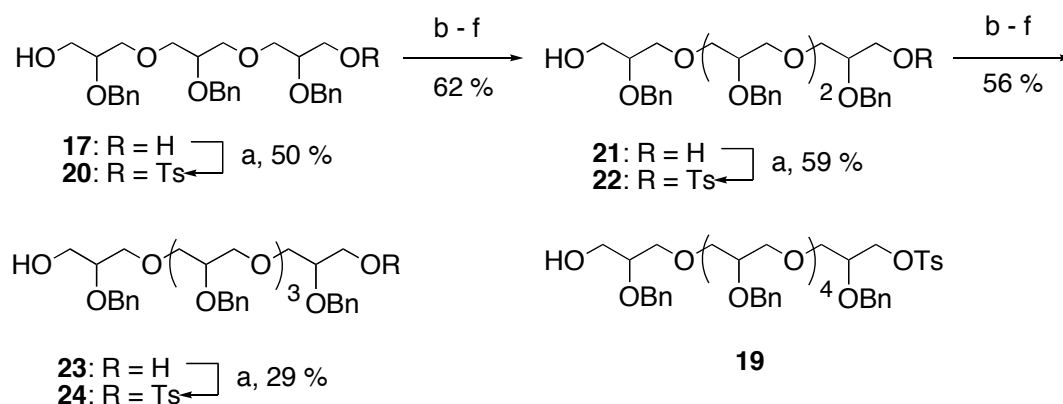


Entry	Tosylate, n	Alcohol, m	oligomer, o	Cyclic oligomer	Yield, %
1	1 : 12	1 : 8	1, Trimer	1	13
2	2 : 18	1 : 8	2, Tetramer	2	19
3	2 : 18	2 : 11	3, Pentamer	3	10
4	2 : 18	3 : 17	4, Hexamer	4	7

When di-glycerol di-tosylate (**12**) and mono-glycerol (**8**) were treated with NaH in DMF at 60 °C for 12 h, cyclic tri-glycerol (**1**) was obtained in 13% yield. Under the same reaction conditions, tetramer (**2**) was obtained from the coupling of tri-glycerol di-tosylate (**18**) and **8**. Pentamer (**3**) and hexamer (**4**) were obtained in 10% and 7% yields from the coupling of tri-glycerol di-tosylate (**18**) with alcohols (**11** and **17**). Linear hexamer (**19**) was recovered in 9% yield as the by-product of cyclization. When recovered linear hexa-glycerol (**19**) was treated with NaH in DMF at 80 °C for 2 days, cyclic hexa-glycerol (**4**) was obtained in 70% yield (Table 2, Entry 4).

On the base of this result, we made linear glycerols mono-tosylates (**20**, **22** and **24**) to apply NaH-mediated cyclization. After diol (**17**) was selectively converted into tosylate (**20**), which was coupled with **5** and following 4 step sequences (hydrolysis in 80% AcOH, TBDPS protection, benzylation and deprotection by TBAF) to provide tetra-glycerol (**21**). Under the same reaction pathway, penta-glycerol

(**23**) was obtained from tetra-glycerol mono-tosylate (**22**).

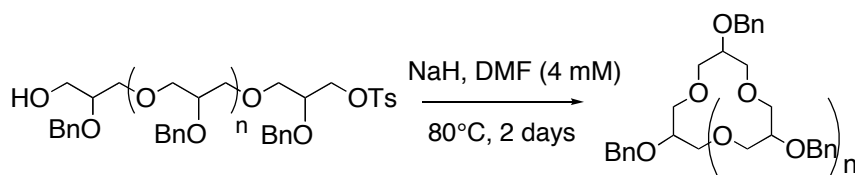


reagent and conditions: a. TsCl, Et₃N, CH₂Cl₂; b. **5**, NaH, DMSO/THF; c. 80% AcOH; d. TBDPS-Cl, DMAP, Et₃N, CH₂Cl₂; e. BnBr, NaH, THF; f. TBAF, THF

Scheme 3. Synthesis of precursors of intramolecular cyclization

When the mono-tosylates (**20**, **22** and **24**) were treated with NaH in DMF¹⁴ (4 mM) at 80 °C for 2 days, 12-, 16-, and 20-membered cyclic benzyl glycerols (**1**, **2**,¹⁵ and **3**¹⁶) were obtained in 38%, 38% and 54% yields, respectively.

Table 2. Synthesis of cyclic glycerols by intramolecular cyclization



Entry	Tosylate, n	oligomer, n	Cyclic oligomer	Yield, %
1	1	20	1	38
2	2	22	2	38
3	3	24	3	54
4	4	19	4	70

We have established cyclic polyglycerol synthesis based on the intramolecular NaH-mediated cyclization method. The intermolecular coupling methodology of di-tosylate and diol was also studied to find efficient synthesis of cyclic polyglycerols. Taking into account the synthesis of optically active polyglycerols as a next project, we adopted the synthetic approach based on convergent coupling by use of glycerol unit.

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14. Cyclization reaction did not proceed using THF as a solvent.
15. The corresponding glycerols of **1**, **2** were synthesized by hydrogenolysis on Pd(OH)₂ in EtOH in 98% and 83% yield, respectively.
16. Typical procedure for the synthesis of **3**: The DMF (10 mL) solution of penta-glycerol monotosylate (**24**) (40 mg, 0.04 mmol) and NaH (60% activity, 9.6 mg, 0.24 mmol) was stirred for 48 h at 80 °C. The reaction mixture was quenched with sat. aq. ammonium chloride. The aq. solution was extracted with EtOAc and the combined organic phase were washed with brine, and dried (Na₂SO₄). Filtration, concentration and silica gel column purification (hexane/EtOAc, 7/3) to give 17.9 mg (54 %) of **3** as a colorless oil. Data for **3**: ¹H-NMR (400 MHz, CDCl₃) 7.32-7.30 (25H, m, HC(Ar)), 4.64(10H, s, CH₂), 3.67-3.57 (25H, m); IR (neat, cm⁻¹) 3854 (w), 3713 (w), 3063 (w), 3031 (w), 2869 (m), 2349 (w), 1497 (w), 1455 (m), 1350 (w), 1306 (w), 1266 (w), 1208 (w), 1109 (s), 1028 (w), 735 (s), 696 (s); FAB-MS (m/z) 847 (17), 846 (74), 845 (100), 844 ([M+Na]⁺, 100), 843 (9), 842 (13), 823 (6), 822 (MH⁺, 13), 821 (3), 820 (4), 752 (42), 735 (53), 615 (66), 451 (29), 409 (11), 289 (32), 181(31), 91(100), 77 (19).