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SYNTHESIS OF C_3 AND C_S SYMMETRIC CYCLIC TRIGLYCEROLS

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Abstract–Authentic cyclic triglycerol standards have been efficiently synthesized. C_3 and C_S symmetric cyclic glycerols were effectively synthesized using intramolecular cyclization conditions and the stereochemistry of their isomers was confirmed.

Polyglycerols are glycerin oligomers that are easily produced and available in bulk quantities through industrial methods.[1,2] They are classified into linear, branched, and cyclic structures. Cyclic polyglycerols have extra secondary alcohols and consist of several ether groups arranged in a crown ether-like ring.[3] Because the oxygen atoms are well situated to coordinate with a cation located inside the ring, cyclic polyglycerols are expected to serve as a phase transfer catalysts. There are a few representative polyglycerol standards in the literature.[4-10] We previously reported the synthesis and fine structure of highly symmetric cyclic polyglycerols (**1**-**4**) as authentic standards.[11]

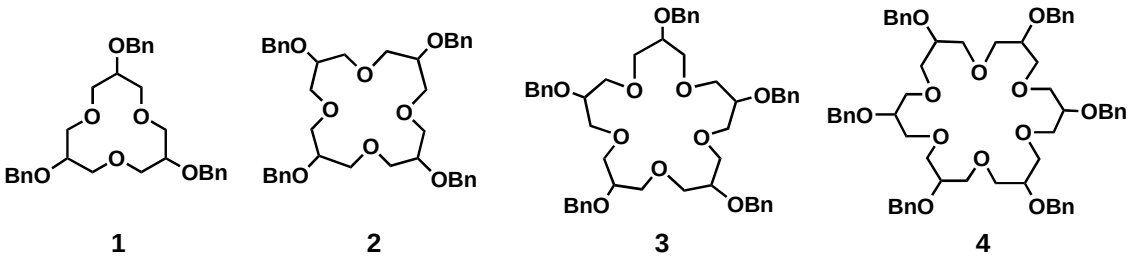
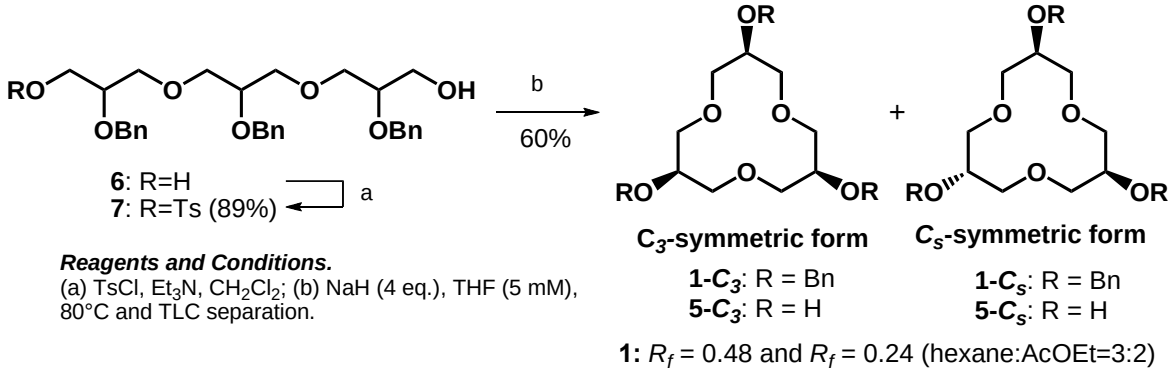


Figure 1. Structure of cyclic polyglycerols **1**-**4**

When the mixture of mono-tosylates (**7**) obtained from the readily available tri-glycerol diol (**6**)[12] were treated with NaH in DMF (4 mM) at 80 °C for 48h, 12-membered cyclic benzyl glycerols (**1**) were obtained in 38%yields.[11] By examining the solvent, THF solvent increased reaction yield up to 60%. Two

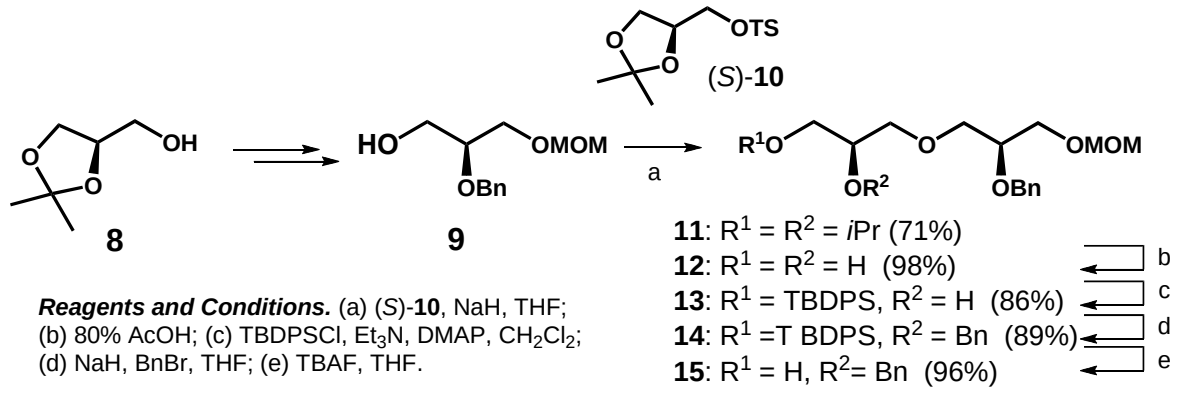
This paper is dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday

cyclic triglycerol benzyl ethers (**1-C$_3$** and **1-Cs**) displayed different *Rf* values at 0.48 and 0.24 by TLC analysis, were isolated with 1/3 ratio; however, the stereochemistry of the triols, was unclear. In this paper, the stereocontrolled synthesis of both diastereomers was performed to confirm the stereochemistry of their isomers.



Scheme 1. Synthesis of cyclic triglycerols **1-C**$_3$ and **1-Cs**

Starting from the (*R*)-solketal (**8**), a monoglycerol unit (**9**) was synthesized in five steps which consisted of methoxymethyloxy (MOM) protection, hydrolysis in 80% acetic acid (AcOH), *tert*-butyldiphenylsilyl (TBDPS) protection, benzyl (Bn) protection and silyl deprotection by tetrabutylammonium fluoride (TBAF). The monoglycerol unit (**9**) was coupled with (*S*)-tosyl glycigyl ether ((*S*)-**10**) to provide diglycerol (**11**) in 71% yield. Acid treatment with 80% AcOH removed the acetonide group in 98% yield and TBDPS protection of the primary alcohol gave alcohol (**13**) in 86% yield. Protection of the secondary hydroxy group with Bn group afforded benzyl ether (**14**) in 89% yield. The silylgroup of **14** was removed using TBAF to give diglycerol unit (**15**) in 96% yield.



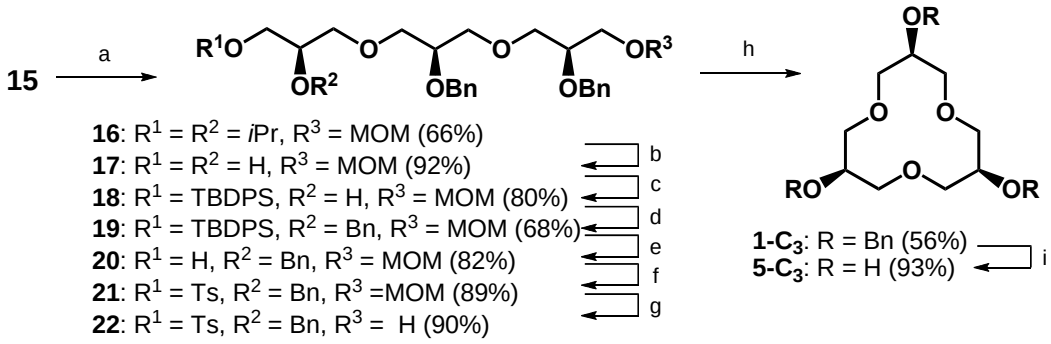
Scheme 2. Synthesis of the cyclic diglycerol unit

Coupling between **15** and (*S*)- and (*R*)-**10** produced triglycerol units **16** in 66% yield and **23** in 64% yield, which were converted to tri-benzyl ethers (**20** and **27**) in 41% and 50% yields, respectively, in four steps.

Tosylation of the alcohols (**20** and **27**), followed by acidic hydrolysis of the MOM group gave the desired intermediates (**22** and **29**) in 90 and 88% yields, respectively.

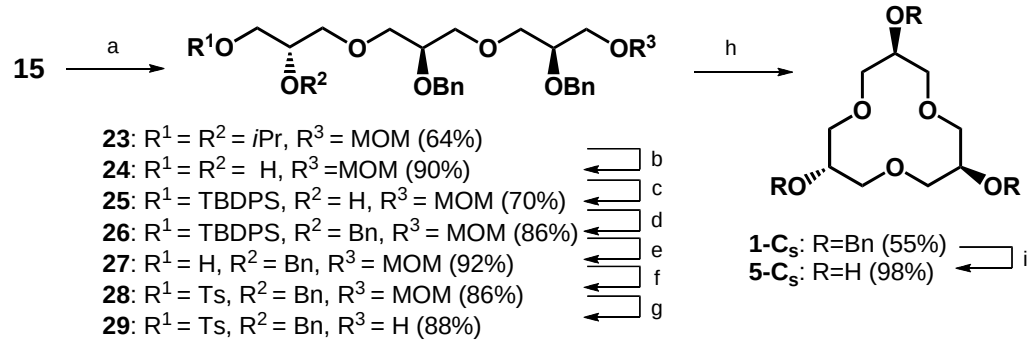
The mono-tosylates (**22** and **29**) were treated with NaH (4 eq.) in refluxing THF (4 mM) to afford 12-membered C_3- and Cs symmetric benzyl glycerols (**1-C$_3$** and **1-Cs**) in 56% and 55% yields, respectively.[13]

Comparison between the TLC *Rf* values of pure C_3 and C_S forms and their mixtures allowed the compound observed at an *Rf* of 0.24 to be identified as the C_3 isomer and the other compound (*Rf* = 0.48) as the C_S form. Hydrogenation of the benzyl group smoothly proceeded to give the desired triols (**5-C$_3$** and **5-Cs**) in 93% and 98% yields, respectively.



Reagents and Conditions. (a) (*S*)-**10**, NaH, DMF; (b) 80% AcOH; (c) TBDPSCl, Et_3N, DMAP, CH_2Cl_2; (d) NaH, BnCl, THF; (e) TBAF, THF; (f) TsCl , Et_3N, DMAP, CH_2Cl_2; (g) 1*N* HCl, MeOH; (h) NaH (4 eq), THF (5 mM), reflux, 17h; (i) Pd-C, H_2, THF/EtOH=1/2.

Scheme 3. Synthesis of the C_3-symmtric cyclic tri-glycerol



Reagents and Conditions. (a) (*R*)-**10**, NaH, THF; (b) 80% AcOH; (c) TBDPSCl, Et_3N, DMAP, CH_2Cl_2; (d) NaH, BnCl, THF; (e) TBAF, THF; (f) TsCl , Et_3N, DMA, CH_2Cl_2; (g) 1*N* HCl, MeOH; (h) NaH (4 eq), THF (5 mM), reflux, 17h; (i) Pd-C, H_2, THF/EtOH=1/2.

Scheme 4. Synthesis of the Cs-symmetric cyclic triglycerol

The ^{1}HNMR spectrum of tri-glycerol **5-C$_3$** displayed three simple sets of peaks s at 3.81, 3.67 and 3.50 ppm in ^{1}H NMR and ^{13}C NMR spectrum showed two sets of peaks at 74.0 and 69.2 ppm suggesting that this isomer was highly symmetric. On the other, the **5-Cs** showed complicated ^{1}H and ^{13}CNMR spectra.
In conclusion, we established the first synthesis of cyclic polyglycerols as pure compound based on an intramolecular cyclization method. Aiming at the synthesis of optically active polyglycerols, we adopted a synthetic approach based on convergent coupling using glycerol units.

EXPERIMENTAL

All reagents used were of commercial quality. Anhydrous THF and CH_2Cl_2 (Kanto Chemical) were used without purification. All air- and moisture-sensitive reactions were performed under an inert gas (nitrogen or argon). Analytical TLC was conducted on precoated TLC plates (silica gel 60F$_{254}$, Merck) and column chromatography was performed using silica gel 60N (70-230 mesh, Kanto Chemical). ATR-IR spectra were measured using a PerkinElmer Spectrum 100 spectrometer equipped with a Universal ATR accessory. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Biospin AVANCE II 400 spectrometer and a JEOL JNM LA-400 spectrometer using TMS or a solvent peaks as an internal standard (chemical shift in ppm). LR-ESI-MS spectra were recorded on an Agilent Technology 1100 LC-MSD spectrometer using MeOH or MeCN solutions in water or 0.5% HCO_2H as effluents. HR-ESI-MS spectra were acuired on a Bruker Dartonics micrOTOFfocus spectrometer. Specific rotation values were measured with a Horiba polarimeter.

(2*R*,6*R*,10*R*)-2,6,10-*O*-Tribenzyl-1-*O*-(4-toluenesulfonyl)-4,8-dioxaundecane-1,2,6,10,11-pentaol (**22**). To a solution of **21** (16.7 mg, 23.6 μmol) in MeOH (1 mL) was added conc. HCl (50 μL) at 0 °C. The mixture was stirred at 60 °C for 29 h. After completion of the reaction, the mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/1) to give **22** (14.1 mg, 21.2 μmol, 90%) as a colorless oil: *Rf* = 0.24 (hexane/EtOAc, 1/1); $[\alpha]_D^{28}$ −2.8 (*c* 0.50, MeOH): IR (neat, cm^{-1}): 3463, 3064, 3032, 2871, 1722, 1599, 1497, 1454, 1359, 1308, 1293, 1210, 1190, 1175, 1095, 1059, 1028, 983, 922, 814, 793, 735, 696, 666: ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.69 (2H, d, *J*=8.4 Hz), 7.30 -7.16 (17H, m), 4.62 (1H, d, *J*=12.0 Hz), 4.55 (2H, s), 4.53 (1H, d, *J*=12.0 Hz), 4.18 (2H, s), 4.10 (1H, dd, *J*=4.4 Hz, 10.8 Hz), 3.99 (1H, dd, *J*=5.6 Hz, 10.4 Hz), 3.68 (2H, quintet, *J*=5.2 Hz), 3.59 (4H, quintet, *J*=5.2 Hz), 3.55-3.40 (7H, m), 2.34 (3H, s): ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 144.8, 138.4, 138.3, 137.8, 132.9, 129.8, 128.5, 128.4, 128.0, 127.80, 127.75, 127.71, 127.6 (x2), 77.9, 76.9, 76.7, 75.4, 72.4, 72.3, 72.1, 71.63, 71.56, 70.2, 69.5, 62.7, 21.6; LRMS (ESI$^+$): *m/z* (%) = 687 ([M+Na]$^+$, 100); HRMS (ESI$^+$): calcd for $C_{37}H_{44}NaO_9S$: 687.2598; found: 687.2576.

(2*R*,6*S*,10*S*)-2,6,10-*O*-Tribenzyl-1-*O*-(4-toluenesulfonyl)-4,8-dioxaundecane-1,2,6,10,11-pentaol (**29**). Yield: 88% as a colorless oil; *Rf* = 0.24 (hexane/EtOAc, 1/1); $[\alpha]_D^{27}$ −0.3 (*c* 0.66, MeOH): IR (neat, cm^{-1}): 3466, 3064, 3032, 2871, 1731, 1599, 1497, 1455, 1359, 1308, 1210, 1190, 1175, 1094, 1058, 1028, 983, 921, 814, 793, 735, 696, 666; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.69 (2H, dd, *J*=1.6 Hz, 8.0 Hz), 7.33 -7.14 (17H, m), 4.62 (1H, d, *J*=12.0 Hz), 4.55 (2H, s), 4.53 (1H, d, *J*=11.6 Hz), 4.47 (2H, s), 4.10 (1H, dd, *J*=4.0 Hz, 10.4 Hz), 4.00 (1H, dd, *J*=6.0 Hz, 10.4 Hz), 3.70-3.65 (2H, m), 3.63-3.43 (10H, m), 3.44 (2H, dd, *J*=3.2 Hz, 5.6 Hz), 3.40 (1H, dd, *J*=5.6 Hz, 10.0 Hz), 2.34 (3H, s), 2.10-2.00 (1H, brs, OH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 144.8, 138.4, 138.3, 137.8, 132.9, 129.8, 128.5, 128.4, 128.0, 127.80, 127.76, 127.72, 127.70, 127.6, 77.9, 76.9, 76.7, 75.4, 72.4, 72.3, 72.1, 71.6, 71.5, 70.2, 69.4, 62.7, 21.6; LRMS (ESI^+): *m/z* (%) = 687 ($[M+Na]^+$, 100); HRMS (ESI^+): calcd for $C_{37}H_{44}NaO_9S$: 687.2598; found: 687.2615.

C_3-symmetric 1,5,9-*O*-Tribenzyl-3,7,11-trioxacyclododecane-1,7,11-triol (**1-C_3**). To a solution of NaH (60% activity, 24.0 mg, 0.6 mmol) in THF (24 mL) was added dropwise with a syringe pump the THF (6 mL) solution of tri-glycerol mono-tosylate (**22**) (100 mg, 0.15 mmol) at 80 ˚C within 3 h. After additional stirring for 14 h, the reaction mixture was quenched with brine. The aq. solution was extracted with EtOAc and the organic phase was washed with water and brine, and dried (Na_2SO_4). Filtration, concentration and preparative silica gel TLC purification (hexane/EtOAc, 3/2) to afford **1-C3** (41.4 mg, 0.084 mmol, 56%) of as a colorless oil: *Rf* = 0.24 (hexane/EtOAc, 3/2); IR (neat, cm^{-1}): 2865, 1497, 1454, 1355, 1304, 1273, 1208, 1099, 1028, 986, 948, 910, 836, 733, 695; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.38-7.25 (15H, m), 4.61 (6H, s), 3.74 (6H, dd, *J* = 3.6, 9.6 Hz), 3.73 (3H, dd, *J* = 3.6, 7.2 Hz), 3.58 (6H, dd, *J* = 7.2, 9.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 138.2, 128.5, 127.8, 127.7, 74.8, 71.7, 71.0; LRMS (ESI^+): *m/z* (%) = 516 (35), 515 ($[M+Na]^+$, 100); HRMS (ESI^+): calcd for $C_{30}H_{36}NaO_6$: 515.2404; found: 515.2421.

Cs symmetric 1,5,9-*O*-Tribenzyl-3,7,11-trioxacyclododecane-1,7,11-triol (**1-Cs**)**.** Yield: 55% as a colorless oi*l; Rf* = 0.48 (hexane/EtOAc, 3/2): IR (neat, cm^{-1}): 2865, 1605, 1497, 1454, 1355, 1305, 1263, 1207, 1090, 1073, 1027, 954, 908, 819, 733, 695; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.28-7.17 (15H, m), 4.53 (6H, s), 3.70-3.47 (15H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 138.1, 128.4, 127.8, 127.7, 74.6, 74.3, 71.7, 70.4, 69.9, 69.6; LRMS (ESI^+): *m/z* (%) = 516 (32), 515 ($[M+Na]^+$, 100); HRMS (ESI^+): calcd for $C_{30}H_{36}NaO_6$: 515.2404; found: 515.2425.

C_3-symmetric 1,5,9-Trioxacyclododecane-3,7,11-triol (**5-C_3**)**.** A solution of **1-C_3** (43.5 mg, 0.088 mmol) in THF/EtOH (1/2, 6 mL) was hydrogenated over 10% Pd-C (88 mg) for 25 h at rt. Filtration and concentration afforded a pale brown solid, which was purified silica gel column chromatography

(CH_2Cl_2/MeOH = 9/1) to give **5-C$_3$** (18.2 mg, 0.082 mmol, 93%) as an oil: *Rf* = 0.39 (CH_2Cl_2/MeOH, 4/1); IR (neat, cm^{-1}): 3308, 2868, 1726, 1653, 1460, 1361, 1261, 1138, 1067, 979; ^{1}H NMR (400 MHz, CD_3OD): δ= 3.81 (3H, ddd, *J* = 3.5, 7.0, 10.4 Hz), 3.67 (6H, dd, *J* = 3.5, 9.7 Hz), 3.50 (6H, dd, *J* = 7.0, 9.7 Hz); ^{13}C-NMR (100 MHz, CD_3OD): δ= 74.0, 69.2; LRMS (ESI^+): *m/z* (%) = 245 ($[M+Na]^+$, 100), 223 ($[M+H]^+$, 6); HRMS (ESI^+): calcd for $C_9H_{19}O_6$: 223.1176; found: 223.1193.

Cs symmetric 1,5,9-trioxacyclododecane-3,7,11-triol (5-Cs). Yield: 98% as an oil; *Rf* = 0.13 (CH_2Cl_2/MeOH, 4/1); IR (neat, cm^{-1}): 3310, 2922, 2866, 1598, 1460, 1361, 1261, 1138, 1072, 979, 948, 837, 785; ^{1}H NMR (400 MHz, CD_3OD): δ=3.93-3.85 (3H, m), 3.67 (2H, dd, *J* = 3.0, 10.0 Hz), 3.69-3.52 (10H, m); ^{13}C-NMR (100 MHz, CD_3OD): δ= 73.7, 73.3, 69.0; LRMS (ESI^+): *m/z* (%) = 245 ($[M+Na]^+$, 100), 223 ($[M+H]^+$, 9); HRMS (ESI^+): calcd for $C_9H_{19}O_6$: 223.1176; found: 223.1179.

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13. The KH base cyclization reaction also proceeded to give **1-C$_3$** and **1-Cs** in 56% and 51% yield, respectively.