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SHORT AND STEREOCONTROLLED CYCLIC POLYGLYCEROLS SYNTHESIS USING BF_3·OEt_2 MEDIATED INTRAMOLECULAR EPOXIDE-OPENING REACTION

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Abstract – We developed a new method for the stereocontrolled synthesis of cyclic oligoglycerols. Optically pure solketal and epichlorohydrin were coupled with allyl alcohol under aqueous basic conditions to construct a linear triglycerol skeleton. After subsequent steps, the epoxy alcohol (**7**) obtained was treated with a catalytic amount of BF_3·OEt_2 in CH_2Cl_2 to produce in a high yield of the desired cyclic triglycerol through a regioselective, intramolecular epoxide ring-opening reaction.

Polyglycerols are oligomers of glycerol that can be linear, brunched, or cyclic. Cyclic polyglycerol has a cyclic polyether skeleton tethered to three carbon atoms with regularly arranged secondary alcohols. Its unique structure is interesting as a chiral host molecule; however, only a few reports describe its synthesis. Dupuy and co-workers reported the synthesis of cyclic tetraglycerol via intermolecular coupling of diepoxide with monoglycerol under the basic conditions,[1] while Rollin *et al*. reported the synthesis of cyclic tri-, tetra-, and penta-glycerols using Williamson's ether synthesis.[2] We also recently reported the stereocontrolled synthesis of cyclic triglycerol through intramolecular substitution under the basic conditions.[3,4] Our synthetic pathway enable precise control of the stereochemistry; however, it comprises many long steps. Herein, we report a new short synthetic pathway to produce cyclic triglycerol through regioselective, intramolecular epoxide ring opening promoted by BF_3·OEt_2 as a single catalyst.

Optically active solketal (**1**) was coupled with optically active epichlorohydrin (**2**) and allyl alcohol under aqueous basic conditions[5] to obtain linear triglycerol **3** in 65% yield as a single isomer. Deprotection of

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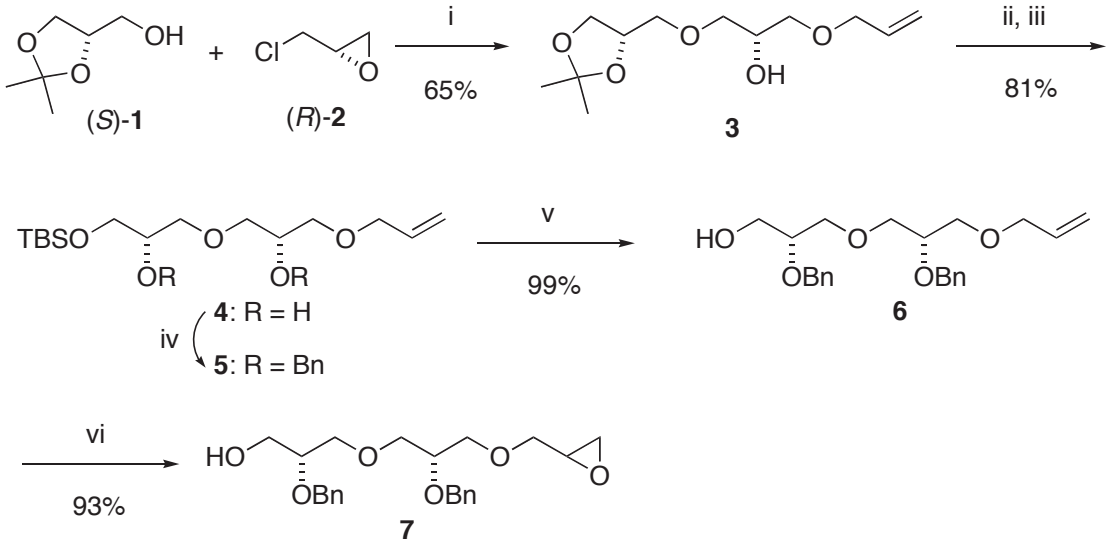
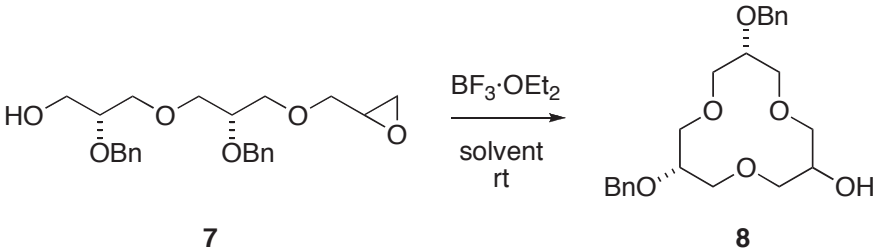
Dedicated with respect to Dr. Ei-ichi Negishi on the occasion of his 77th birthday.

acetonide **3** using 80% aqueous AcOH followed by selective protection of the primary and secondary alcohols gave allyl ether **5**. After desilylation of **5**, the allyl moiety of the resultant **6** was oxidized with *m*CPBA to give epoxy alcohol **7** in 93% yield as an inseparable mixture of diastereomers (Scheme 1).



Scheme 1. *Conditions*: (i) nBu$_4$NHSO$_4$, 50% aq. NaOH, 0 °C, 2 h then allyl alcohol rt, 1 d (65%); (ii) 80% aq. AcOH, rt, 1 d (quant); (iii) TBSCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, rt, 4 h (81%); (iv) NaH, BnBr, THF, rt, 2 h (89%); (v) TBAF, THF, rt, 2 h (99%); (vi) *m*CPBA, CH$_2$Cl$_2$, rt, 3 h (93%).

First, we attempted to cyclize epoxy alcohol **7** using the basic conditions described by us and Dupuy, but the desired compound was not obtained. Therefore, the epoxy alcohol **7** was instead treated with 30 mol% of BF$_3$·OEt$_2$ in CH$_2$Cl$_2$ to obtain the desired cyclic triglycerol (**8**) in a moderate yield as an inseparable mixture of diastereomers (Table 1, entry 1). The solvent is important in this reaction, and only halogenated hydrocarbon solvents afforded the cyclic triglycerol (entries 1-4). The concentration of solvent also influenced the cyclic triglycerol yield (entries 1, 5, and 6). In 5 mM of CH$_2$Cl$_2$, the amount of BF$_3$·OEt$_2$ did not affect to the reaction yield (entries 7 and 8). Interestingly, the use of an equimolecular amount of BF$_3$·OEt$_2$ afforded the desired cyclic triglycerol with only a 58% yield (entry 9).[6]



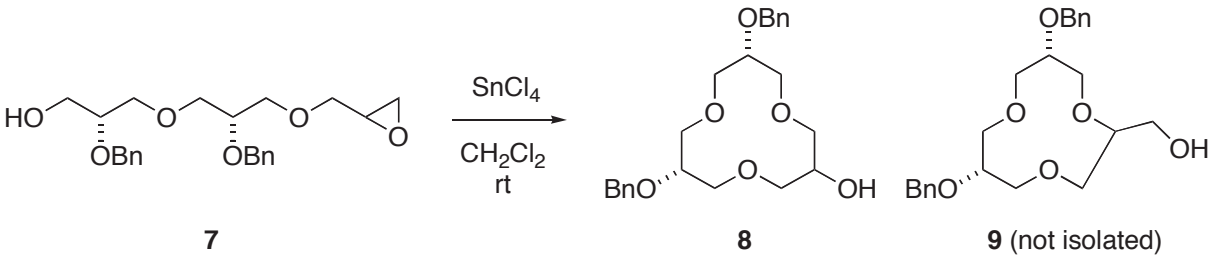
Scheme 2

Table 1. $BF_3{\cdot}OEt_2$-mediated intramolecular epoxide ring opening

Entry	$BF_3{\cdot}OEt_2$ (eq)	Solvent (mM)	Time (h)	**8** (Yield, %)[a]
1	0.3	CH_2Cl_2 (30)	24	41
2	0.3	DMF (10)	9	0
3	0.3	toluene (10)	24	0
4	0.3	1,2-DCE (10)[b]	11	40
5	0.3	CH_2Cl_2 (20)	12	56
6	0.3	CH_2Cl_2 (10)	5	81
7	0.2	CH_2Cl_2 (5)	3	79
8	0.5	CH_2Cl_2 (5)	7	86
9	1.1	CH_2Cl_2 (10)	4	58

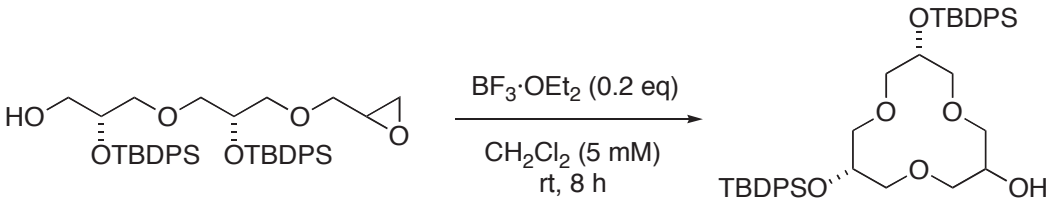
[a] Isolated yield. [b] 1,2-dichloroethane.

The use of $SnCl_4$ or $TiCl_4$ as a Lewis-acidic catalyst decreased the regioselectivity and resulted in a complex mixture including trace amounts of undesired primary alcohol **9** (Scheme 3). In contrast, epoxy alcohol **10**, which is protected by a *t*-butykdiphenylsilyl (TBDPS) group rather than a benzyl (Bn) group in the secondary alcohol, produced cyclic triglycerol **11** (Scheme 4) with a 63% yield after treatment under standard conditions (Table 1, entry 6).



7 **8** **9** (not isolated)

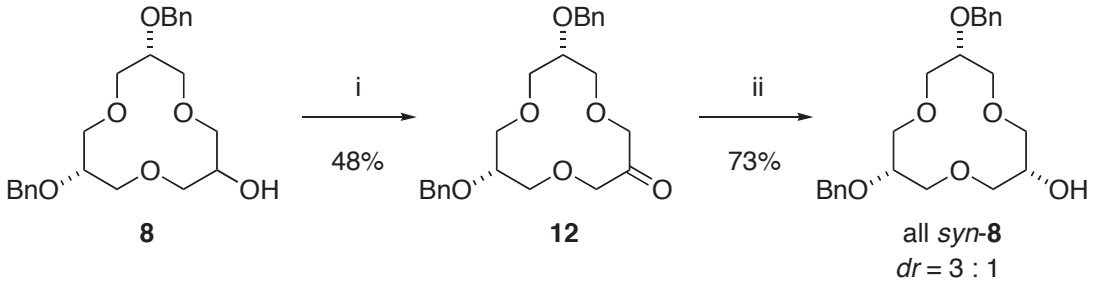
Scheme 3



10 **11** (63%)

Scheme 4

Subsequently, the synthesized cyclic trigricerol **8** was oxidized with Dess-Martin periodinane (DMP) to give the corresponding ketone **12** with a 48% yield. Ketone **12** was reduced by L-selectride to regenerate alcohol **8** as a 3:1 mixture of diastereomers (Scheme 5). The major product had an all-*syn* (C_3-form) configuration, which was determined by HPLC analysis[7] and inspection of the ^{1}H-NMR spectrum after benzylation of the hydroxy group.



Scheme 5. *Conditions*: (i) DMP, CH_2Cl_2, rt, 1 d (48%); (ii) L-selectride, THF, -78 °C, 2 h (73%).

In conclusion, we developed a short synthetic pathway to the stereocontrolled cyclic triglycerol. The key reaction is the $BF_3{\cdot}OEt_2$-mediated intramolecular epoxide opening. Our method provides a very simple, highly regioselective route to medium-sized polyether skeletons. This reaction is a synthetic tool for the synthesis of natural and synthetic products containing macro polyether rings.

EXPERIMENTAL

^{1}H NMR spectra were recorded in $CDCl_3$ with TMS as an internal reference using a Bruker Biospin AVANCE-II 400 operating at 400 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ with remnant solvent as an internal reference using the Bruker Biospin AVANCE-II 400 operating at 100 MHz. IR spectra were measured using a PerkinElmer FT-IR Spectrum 100 spectrometer. Low-resolution (LR) and high-resolution (HR) electrospray ionization (ESI) mass spectra (MS) were measured using Agilent LC-MSD 1100 series and Bruker Daltonics micrOTOF forcus spectrometers, respectively. Thin-layer chromatography (TLC) was performed on a Merck Silica gel $60F_{254}$ plate. Column chromatography was performed using Kanto Chemical Silica gel 60N (0.063-0.230 mm). All of the organic solvents used in this study were obtained dehydrated from Kanto Chemical and were used. All chemicals used in this study were commercially obtained. All air- and moisture-sensitive reactions were carried out under argon atmosphere.

(2*S*,6*S*)-1,2-*O*-Isopropylidene-4,8-dioxaundeca-10-en-6-ol (3). To a mixture of (*R*)-epichlorohydrin (**2**, 4.14 g, 44.7 mmol) and nBu$_4$NHSO$_4$ (1.01 g, 2.98 mmol) in 50% aqueous NaOH (20 mL) was added (*S*)-solketal (**1**, 3.94 g, 29.8 mmol) at 0 °C. The mixture was stirred for 2 h at the same temperature before allyl alcohol (8.65 g, 0.15 mol) was added. The mixture was stirred for 1 day at rt, and then diluted with ice water. The mixture was extracted with EtOAc. The combined extracts were washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed by evaporation. The residue was purified by column chromatography on silica gel (hexane : EtOAc = 3 : 2 then 1 : 1) to give **3** (4.83 g, 65%) as a colorless oil; R_f 0.39 (hexane : EtOAc = 2 : 3); IR (neat) cm^{-1} 3466, 2986, 2873, 1719, 1455, 1371, 1253, 1213, 1076, 1050, 974, 909, 839, 793, 759; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H), 1.43 (s, 3H), 2.59 (br d, J =

3.5 Hz, 1H), 3.44-3.61 (m, 6H), 3.74 (dd, *J* = 8.3 and 6.4 Hz, 1H), 3.98 (br d, *J* = 3.2 Hz, 1H), 4.02 (dt, *J* = 5.6 and 1.4 Hz, 2H), 4.06 (dd, *J* = 8.3 and 6.5 Hz, 1H), 4.28 (quint, *J* = 5.5 Hz, 1H), 5.20 (dq, *J* = 10.4 and 1.4 Hz, 1H), 5.28 (dq, *J* = 17.2 and 1.6 Hz, 1H), 5.90 (ddt, *J* = 17.2, 10.5, and 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.39, 26.74, 66.59, 69.50, 71.10, 72.37, 72.47,72.87, 74.69, 109.50, 117.31, 134.46; LRMS *m/z* 264 (M^++Na, 38), 247 (M^++H, 100), 189 (31); HRMS calcd for $C_{12}H_{35}O_5$ 247.1540: Found 247.1544.

(2*S*,6*S*)-1-*tert*-Butyldimethylsilyloxy-4,8-dioxaundeca-10-ene-2,6-diol (4). Acetonide **3** (4.30 g, 17.5 mmol) was treated with 80% aqueous AcOH (40 mL) for 7 h at rt. The mixture was concentrated by evaporation to give the corresponding triol (3.70 g, quant.) as a colorless oil. This compound was used in next step without further purification.

To a solution of the triol (3.60 g, 17.4 mmol), Et_3N (8.83 g, 87.3 mmol), and DMAP (426 mg, 3.49 mmol) in CH_2Cl_2 (170 mL) was added TBDMSCl (3.95 g, 26.2 mmol) at 0 °C. The mixture was stirred for 23 h at rt before saturated aqueous NH_4Cl was added. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated by evaporation. The residue was purified by column chromatography on silica gel (hexane : EtOAc = 1 : 1) to give the title compound **4** (4.51 g, 81%) as a colorless oil; R_f 0.50 (hexane : EtOAc = 3 : 7); IR (neat) cm^{-1} 3405, 2953, 2928, 2857, 1472, 1463, 1361, 1252, 1084, 1005, 926, 834, 775, 667; ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 2.72 (br s, 1H), 2.79 (br s, 1H), 3.45-3.67 (m, 9H), 3.83 (br, 1H), 3.99 (br, 1H), 4.02 (dt, *J* = 5.6 and 1.3 Hz, 2H), 5.20, (dq, *J* = 10.4 and 1.3 Hz, 1H), 5.28 (dq, *J* = 15.7 and 1.5 Hz, 1H), 5.90 (ddt, *J* = 17.2, 10.4, and 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ -5.41, 18.29, 25.87, 63.93, 69.56, 70.72, 71.18, 72.38, 72.44, 72.79, 117.33, 134.45; LRMS *m/z* 321 (M^++H, 14), 207 (100); HRMS calcd for $C_{15}H_{32}O_5SiNa$ 343.1911 : Found 343.1889.

(6*S*,10*S*)-11-*tert*-Butyldimethylsilyloxy-6,10-dibenzyloxy-4,8-dioxaundecene (5). To a suspension of NaH (60% in oil, 2.25 g, 56.2 mol) in THF (50 ml) was added a solution of **4** (4.50 g, 14.0 mmol) in THF (20 mL) at 0 °C. The mixture was stirred for 40 min at rt before BnBr (7.20 g, 42.1 mmol) was added at 0 °C. The reaction mixture was stirred for 2 h at rt. The reaction was quenched with 50% aqueous THF, and concentrated by evaporation. The residue was diluted with water, and the organic materials were extracted with EtOAc. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated by evaporation. The residue was purified by column chromatography on silica gel (hexane : EtOAc = 15 : 1) to give **5** (6.23 g, 89%) as a colorless oil; R_f 0.38 (hexane : EtOAc = 4 : 1); IR (neat) cm^{-1} 2928, 2856, 1496, 1471, 1454, 1252, 1091, 1027, 923, 834, 776, 733, 695, 668; ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 3.49-3.66 (m, 8H), 3.68 (s, 1H), 3.69 (d, *J* = 1.0 Hz, 1H), 3.75 (quint, *J* = 5.1 Hz, 1H), 3.99 (dt, *J* = 5.5 and 1.5 Hz, 1H), 4.686 (s, 2H), 4.695 (s, 2H), 5.16 (dq, *J* = 10.4 and 1.4 Hz, 1H), 5.26 (dq, *J* = 17.2 and 1.7 Hz, 1H), 5.89 (ddt, *J* =17.2, 10.4, and 5.5 Hz, 1H), 7.24-7.36 (m, 2H); ^{13}C NMR ($CDCl_3$) δ -5.42, -5.37, 18.29, 25.91, 63.19, 70.42, 71.68, 71.77, 72.29, 72.33, 77.17, 77.22, 78.89,

116.86, 127.44, 127.48, 127.68, 127.72, 128.28, 134.77, 138.74, 138.86; LRMS *m/z* 520 (M^++H_2O, 100); HRMS calcd for $C_{29}H_{45}O_5Si$ 501.3031: Found 501.3029.

(2*R*,6*S*)-2,6-Dibenzyloxy-4,8-dioxaundeca-10-en-1-ol (6). To a solution of **5** (1.78 g, 3.55 mmol) in THF (12 mL) was added TBAF (1.0 M in THF, 5.33 mL, 5.33 mmol) at 0 °C. The solution was stirred for 2 h at rt, and concentrated by evaporation. The residual oil was purified by column chromatography on silica gel (hexane : EtOAc = 3 : 2) to give **6** (1.37 g, 99%) as a colorless oil; R_f 0.54 (hexane : EtOAc = 2 : 3); IR (neat) cm^{-1} 3457, 3064, 3030, 2866, 1736, 1496, 1454, 1348, 1207, 1087, 1059, 1027, 996,922, 734, 696; ^{1}H NMR ($CDCl_3$) δ 2.21 (br, 1H), 3.48-3.69 (m, 10H), 3.99 (dt, *J* = 4.2 and 1.4 Hz, 2H), 4.54-4.71 (m, 4H, C*H*$_2$Ph), 4.14 (dd, *J* = 10.4 and 1.5 Hz, 1H), 4.21 (dd, *J* =17.3 and 1.6 Hz, 1H), 5.89 (ddt, *J* = 17.2, 10.4, and 5.6 Hz, 1H), 7.24-7.36 (m, 10H, Ph-*H*); ^{13}C NMR ($CDCl_3$) δ 62.78, 70.02, 71.56, 71.65, 71.83, 72.10, 72.27, 72.34, 73.43, 77.85, 117.00, 127.58, 127.70, 127.74, 127.76, 128.32, 128.41, 128.45, 134.63, 138.27, 138.50; LRMS *m/z* 409 (M^++Na, 8), 404 (M^++H_2O, 100), 387 (M^++H, 38); HRMS calcd for $C_{23}H_{30}O_5Na$ 409.1985: Found 409.1996.

(2*R*,6*S*)-2,6-Dibenzyloxy-10,11-epoxy-4,8-dioxaundecan-1-ol (7). To a solution of allyl ether **6** (549 mg, 1.42 mmol) in $CHCl_3$ (7 mL) was added *m*CPBA (294 mg, 1.70 mmol) at 0 °C. The mixture was stirred for 24 h at rt before saturated aqueous $NaHCO_3$ was added at 0 °C in order to quench. The organic materials were extracted with EtOAc, and combined extracts were washed with 1 N HCl, H_2O, and brine, dried over Na_2SO_4, and concentrated by evaporation. The residue was purified by column chromatography on silica gel (hexane : EtOAc = 1 : 1 then 3 : 7) to give **7** (532 mg, 93%) as a colorless oil with inseparable mixture of diastereomers; R_f 0.29 (hexane : EtOAc = 2 : 3); IR (neat) cm^{-1} 3444, 2920, 2870, 1718, 1496, 1454, 1347, 1273, 1208, 1090, 1027, 907, 848, 736, 697; ^{1}H NMR ($CDCl_3$) δ 2.17 (br, 1H), 2.58-2.60 (m, 1H), 2.78 (t, *J* = 4.6 Hz, 1H), 3.11-3.16 (m, 1H), 3.35-3.41 (m, 1H), 3.55-3.68 (m, 8H), 3.71-3.79 (m, 3H), 4.55-4.71 (m, 4H, -C*H*$_2$Ph), 7.25-7.36 (m, 10H, Ph-*H*); ^{13}C NMR ($CDCl_3$) δ 44.14, 50.82, 62.74, 71.22, 71.30, 71.56, 71.60, 72.08, 72.11 72.29, 72.31, 76.96, 77.85, 127.64, 127.77, 128.36, 128.47, 138.26,138.41; LRMS *m/z* 425 (M^++Na, 9), 420 (M^++H_2O, 100), 403 (M^++H, 11); HRMS calcd for $C_{23}H_{30}O_6Na$ 425.1935: Found 425.1948.

General Procedure for the Intramolecular Epoxide-Opening Reaction of 7 (Table 1, Entry 6). To a solution of **7** (402 mg, 1.00 mmol) in CH_2Cl_2 (100 mL) was added BF_3·OEt_2 (42.5 mg, 0.30 mmol) at 0 °C. The solution was stirred for 5 h at rt, and concentrated by evaporation. The residue was purified by column chromatography on silica gel (hexane : EtOAc = 1 : 1 then 2 : 3) to give a 1:1 diastereomeric mixture of **8** (324 mg, 81%) as a colorless oil; R_f 0.33 (hexane : EtOAc = 3 : 7); IR (neat) cm^{-1} 3419, 2867, 1718, 1496, 1453, 1270, 1091, 1070, 1026, 970, 737, 714, 697; ^{1}H NMR ($CDCl_3$) δ 2.34 (br, 1H), 3.49-3.85 (m, 15H), 4.59 (s, 4H), 7.26-7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 68.80, 69.05, 70.13, 70.89,

71.03, 71.06, 71.73, 71.79,72.13, 74.76, 74.83, 127.74, 127.77, 128.42, 138.08, 138.11; LRMS *m/z* 425 (M^++Na, 2), 420 (M^++H_2O, 100), 403 (M^++H, 9); HRMS calcd for $C_{23}H_{31}O_6$ 403.2115: Found 403.2109.

5,10-Dibenzyloxy-3,7,10-trioxacyclododecanone (12). To a solution of **8** (124 mg, 0.31 mmol) in CH_2Cl_2 (3 mL) was added DMP (196 mg, 0.46 mmol) at rt. The mixture was stirred for 2 h at the same temperature before 2-propanol (4 mL) was added in order to quench, and concentrated by evaporation. The residue was diluted with EtOAc, and the solution was washed with saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated by evaporation. The residue was purified by column chromatography on silica gel (hexane : EtOAc = 1 : 1) to give **12** (59 mg, 48%) as a colorless oil; R_f 0.64 (hexane : EtOAc = 3 : 7); IR (neat) cm^{-1} 2869, 1730, 1496, 1454, 1354, 1305, 1267, 1104, 1074, 1027, 982, 949, 916, 735, 696; ^{1}H NMR ($CDCl_3$) δ 3.56-3.70 (m, 9H), 3.76 (dd, *J* = 11.5 and 5.1 Hz, 1H), 4.18 (ABq, J_{AB} = 15.6 Hz, 4H), 4.60 (ABq, J_{AB} = 12.1 Hz, 4H), 7.27-7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 68.96, 69.02, 71.62, 71.79, 73.42, 73.92, 74.90, 75.11, 127.80, 127.87, 127.90, 128.46, 137.86, 208.38; LRMS *m/z* 423 (M^++Na, 2), 418 (M^++H_2O, 100), 401 (M^++H, 2); HRMS calcd for $C_{23}H_{29}O_6$ 401.1959: Found 401.1951.

Stereoselective Reduction of Ketone 12. To a solution of **12** (20 mg, 0.05 mmol) in THF (0.6 mL) was added L-selectride (1.0 M in THF, 0.06 mL, 0.06 mmol) at -78 °C. The mixture was stirred for 2 h at the same temperature before 1 N HCl was added. After warming to rt, the reaction mixture was extracted with EtOAc, and combined extracts were washed with brine, dried over Na_2SO_4, and concentrated by evaporation. The residue was purified by column chromatography on silica gel (hexane : EtOAc = 1 : 1 the 2 : 3) to give **8** (14 mg, 73%) as a colorless oil. All characterized data were corresponded with above data.

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6. In these cases, polymerized products were not observed.
7. HPLC conditions; Cosmosil AR-II (Nacarai Tesque); eluent = MeCN : 0.5% aq. HCO_2H (65 : 35), flow rate = 0.5 mL/min; λ = 254 nm; retention times = 19.5 and 21.8 min (all *syn*).