Original Synthesis of Linear, Branched and Cyclic Oligoglycerol Standards

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Dedicated to Professor Joachim Thiem on the occasion of his 60th birthday

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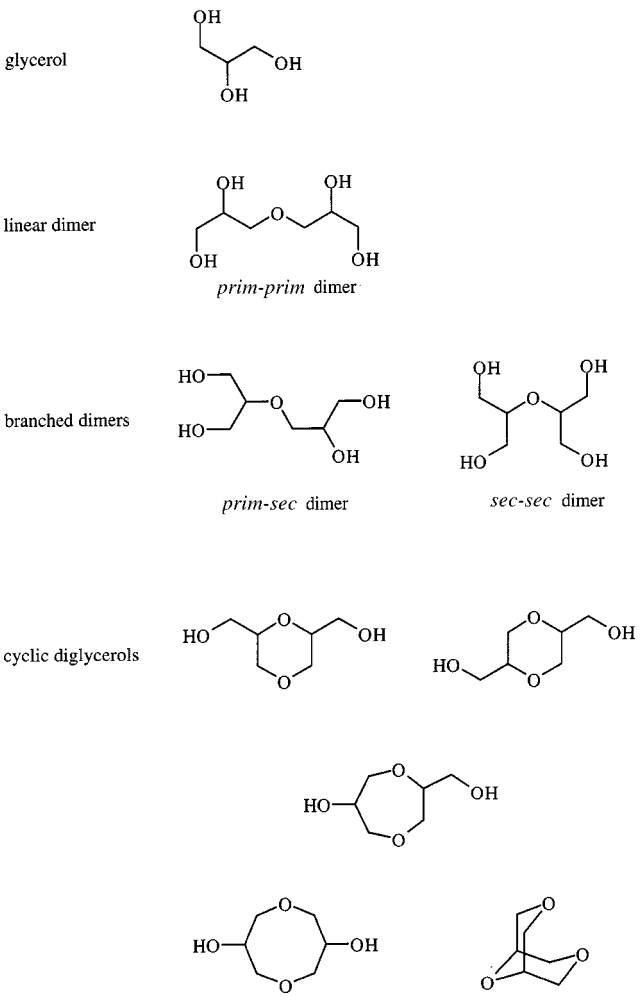
A variety of authentic standards of linear, branched and cyclic oligomers of glycerol, with well-defined structures and degrees of polymerisation from 2 to 5, have been efficiently synthesised. Linear oligomers were obtained by means of a convergent approach based on regioselective opening of bis(epoxides) with solketal; branched compounds were synthesised using oxidative cleavage of the corresponding anhydrohexitols as the key step. A 6-*exo*-*trig* halocyclisation reaction involving heteroatom-tethered unsaturated alcohols permitted an efficient synthesis of the precursors of selected cyclic dimers; larger cyclic oligomers were prepared by two one-pot Williamson reactions using a ditriflate derived from diglycerol. All these methodologies permitted further scaling up.

Introduction

Glycerol is readily available in bulk quantities as a by-product from oleochemistry,[1] and is therefore becoming an attractive renewable raw material, notably as the hydrophilic component of neutral surfactants and emulsifiers for food, cosmetics and pharmacy.[2] Nevertheless, glycerol itself is not suitable for this purpose and oligomers are needed[3] for increasing the hydrophilic component and for adjusting the hydrophilic-hydrophobic balance (HLB) of the products.

Until now, industrial manufacture of polyglycerols required drastic conditions, including high temperature and caustic media, therefore providing complex mixtures of oligomers, of undefined molecular composition.[4] Indeed, only a few representative standards of oligoglycerols are described in the literature[5–8] and physicochemical properties have been investigated on mixtures of oligomeric derivatives.[4,9,10]

Nevertheless, determination of correlations between molecular structures of polyglycerol-based surfactants, performance, environmental impact and ecotoxicity accordingly calls for the synthesis of authentic samples with determined degrees of oligomerisation and well-defined structures. Coupling of two glycerol units may occur: (i) between primary positions, providing a dimer referred to as the *prim-prim* compound, or (ii) between a secondary and either a primary or a secondary position, resulting in either a *prim-sec* or a *sec-sec* dimer, respectively. A second etherification process may occur, thus giving access to a variety of cyclic dimers (Scheme 1).



Scheme 1. Various dimers of glycerol

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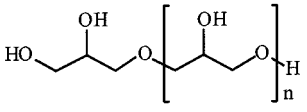
In this context, we describe here a new means of access to authentic standards of linear, branched and cyclic oligomers of glycerol, with well-defined structures and determined degrees of polymerisation from 2 to 5.

Results and Discussion

Synthesis of Linear Oligomers

Linear di- and triglycerols **1** and **2** are known compounds[5−7] that have previously been prepared either by direct syntheses involving bis(hydroxylation) of diallyl ether[7] and 1,3-di-*O*-allylglycerol[11] or by coupling of D,L-α,β-isopropylideneglycerol (solketal) with either its tosylate[12] or with glycidyl solketal ether,[13−16] furnishing either **1** or **2** after the removal of acetonide groups.

We therefore focused our attention on the synthesis of linear tetra- and pentaglycerols **3** and **4** (Scheme 2). Our strategic plan involved the preparation of dimeric or trimeric precursors containing orthogonal protecting groups and functionalities that could allow efficient convergent synthesis of either polyglycerols **3** and **4** or their monoesters,[17] characterised as well-defined structures.



1: n = 1

2: n = 2

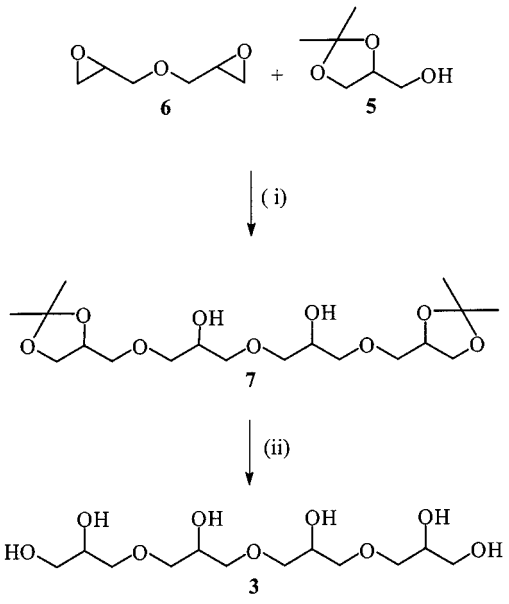
3: n = 3

4: n = 4

Scheme 2. Linear oligoglycerols

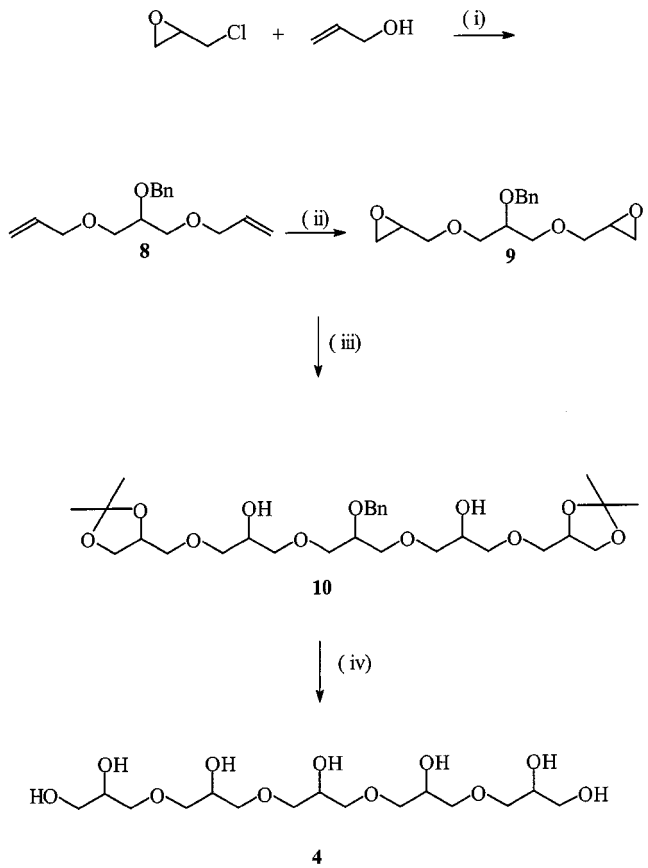
Bis(glycidyl) ether **6** was able to provide linear oligomers with an even number of glycerol units, whereas the use of bis(epoxide) **9** allowed access to oligoglycerols containing an odd number of glycerol units.

Linear tetraglycerol **3** was generated from precursor **6**,[7,18] which was easily prepared in 93% yield by oxidation of commercially available allyl 2,3-epoxypropyl ether. After some experimentation, we found that treatment of an excess of solketal (5 equiv.) with the bis(epoxide) **6** in a biphasic system composed of 50% aqueous sodium hydroxide and *n*-hexane in the presence of a catalytic amount of Aliquat® 336 resulted in the formation of the expected tetramer **7** in 46% yield after purification by column chromatography. Subsequent acid-catalysed hydrolysis of bis(dioxolane) **7** furnished the expected, unprotected linear tetraglycerol **3** (Scheme 3).



Scheme 3. Synthesis of linear tetraglycerol **3**: (i) aq. 50% NaOH, Aliquat®336, *n*-hexane, 80 °C (46%); (ii) Dowex-H 50W×8, MeOH, reflux (73%)

A procedure similar to that described for the synthesis of **3** was used to prepare pentamer **4**, starting from the bis(epoxide) **9** (Scheme 4). Compound **9** was efficiently produced by treatment of allyl alcohol with epichlorohydrin,



Scheme 4. Synthesis of linear pentaglycerol **4**: (i) a) 18 M aq. NaOH, TBAB, *n*-hexane; b) BnBr, TBAB, THF (65% 2 steps); (ii) *m*CPBA, CH_2Cl_2 (63%); (iii) solketal, 25 M aq. NaOH, Aliquat®336, *n*-hexane (53%); (iv) H_2, Pd/C, MeOH (66%)

followed by sequential protection of the free hydroxy group as a benzyl ether and the epoxidation of both double bonds with *m*CPBA (41% overall yield). Treatment of bis(epoxide) **9** with solketal under phase transfer conditions generated compound **10** in reasonably good yield (53%). Finally, protected pentaglycerol **10** was converted into the target pentamer **4** by a one-pot procedure, using palladium on activated charcoal in methanol under hydrogen. Linear pentaglycerol **4** was isolated as an oil after purification by column chromatography and characterised by elemental analysis and mass spectrometry.

We have therefore developed a general means of access to linear oligoglycerols with defined degrees of oligomerisation, with provision for further efficient scaling up.

Synthesis of Branched Oligomers

Unlike the linear oligoglycerols, branched compounds cannot easily be synthesised using a general convergent method. As the number of possible structures corresponding to each degree of polymerisation (Scheme 5) rapidly becomes high (12 isomeric compounds for $n = 3$, 360 for $n = 5$), a selection of targets had to be decided upon and different strategies had to be developed in order to synthesise the branched oligomers.

$$I_n = (n+1)\,!\,/\,2$$

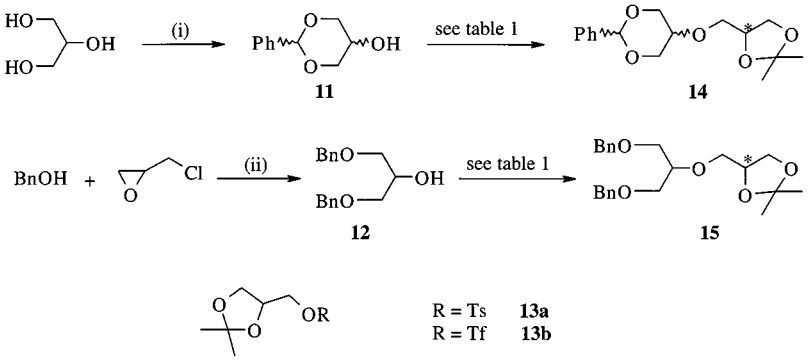
I_n is the number of possible structures corresponding to the degree of polymerisation **n**

Scheme 5

In an initial approach to the synthesis of branched dimers, a large number of nucleophilic displacements by diverse alkoxides and openings of epoxides under various conditions were tested in parallel to the strategy used for the synthesis of linear oligomers (Scheme 6, Table 1).

When racemic solketal was used, this method yielded at most 60% of the desired racemic mixture of the *prim-sec* dimer **18a** (Scheme 7).

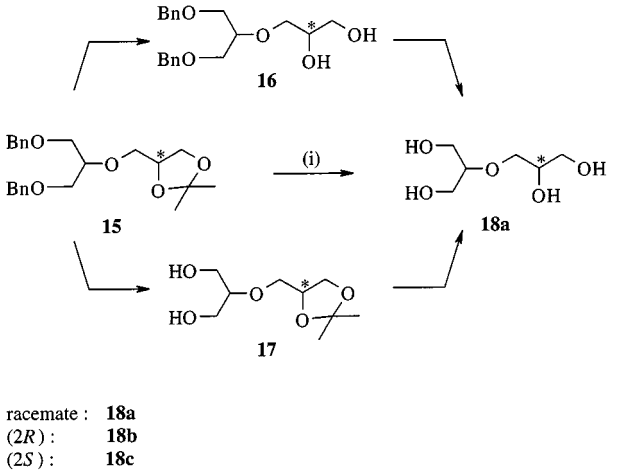
Should attempts be made here to increase the degree of oligomerisation, the yields for the coupling step would probably decrease and might even come close to zero for coupling between two secondary positions. We therefore



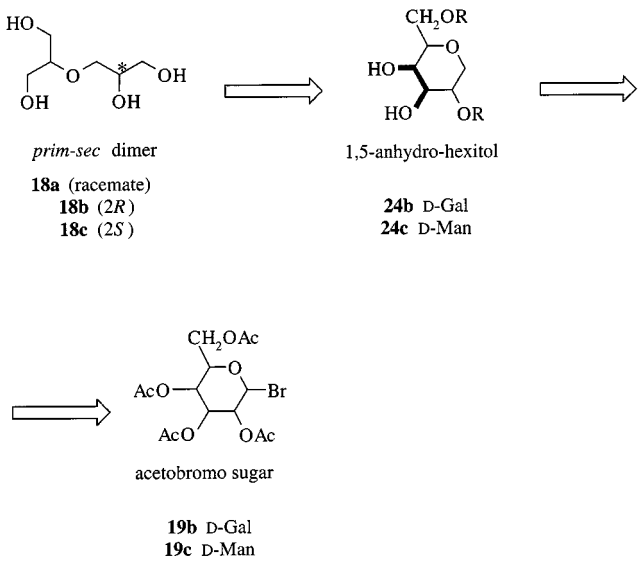
Scheme 6. Synthesis of *prim-sec* dimer precursors **14** and **15**: (i) benzaldehyde, DMF, CSA, 70 °C, 1 h (68%); (ii) KOH, H_2O, TBAI, 80 °C, 48 h (80%)[19]

Table 1. Coupling test conditions for protected and activated units of glycerol

Alcohol	Reagent	Conditions		*T* [°C]	Reaction time	Product	Yield (%)
11	**13a** 1.2 equiv.	NaH 2.0 equiv. DMF	TBAB 0.04 equiv.	room temp.	24 h	**14**	40
11	glycidol 3.0 equiv.	phase transfer 50% NaOH/ cyclohexane	TBAB 0.1 equiv.	60	24 h	**14**	traces
12	epichlorohydrin 1.2 equiv.	NaH 1.5 equiv. DMF	TBAB 0.2 equiv.	80	20 h	**15**	9
12	**13b** 1.5 equiv.	NaH 1.5 equiv. DMF	TBAB 0.2 equiv.	room temp.	20 h	**15**	54
12	**13a**	CsOH 1.4 equiv. DMF	TBAI 0.5 equiv.	room temp.	24 h	**15**	54
12	**13a**	NaH 1.5 equiv. DMF	TBAB 0.2 equiv.	80−100	48 h	**15**	60
12	**13a**	NaH 2.2 equiv. THF	15-crown-5	room temp.	20 h	**15**	traces



Scheme 7. Synthesis of racemic *prim-sec* dimer **18a** from protected precursor **15**: (i) MeOH, 10% Pd/C, H_2, room temp., 1 atm, 24 h (88%)



Scheme 8. Retrosynthetic scheme for enantiomerically pure *prim-sec* dimers **18b** and **18c**

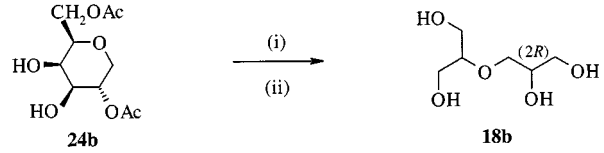
switched to a different strategy, based on the oxidative cleavage of judiciously selected anhydroalditols.

Synthesis of the *prim-sec* Dimer

For the synthesis of the *prim-sec* dimer, two different 1,5-anhydroalditols **24b** and **24c** were selected, allowing separate elaboration of both enantiomers **18b** and **18c**, respectively (Scheme 8). The method chosen for the preparation of the 1,5-anhydro-itol[20] requires the hydrogenolysis of the corresponding bromoacetyl sugar. The main difficulty was then to isolate and protect the hydroxy group in position 2 selectively and efficiently.

In a D-galacto-type compound, the relative positioning of the 3- and 4-hydroxy groups provides for formation of the 3,4-isopropylidene ketal. This ketal could be selectively prepared in high yields (90%) and with good regioselectivity (the 4,6-isopropylidene ketal was formed only in trace amounts).[21] Positions 2 and 6 have to be acetylated; then the ketal can be selectively cleaved, yielding the suitably protected diol **24b**, ready to undergo the oxidative cleavage.

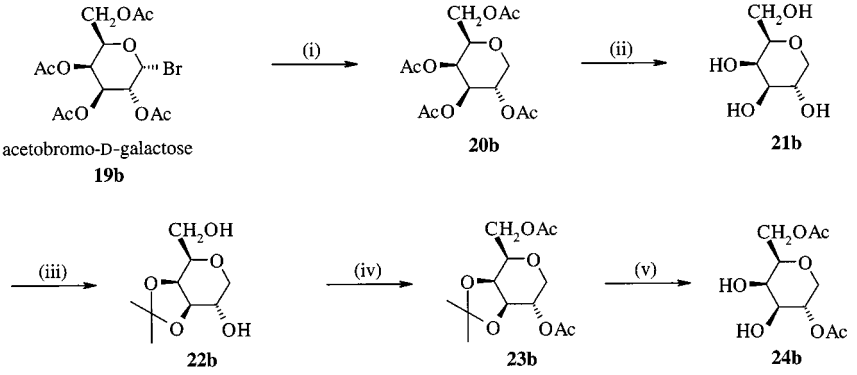
The hydrogenolysis of commercially available acetobromogalactose **19b** under basic conditions results in 1,5-anhydro-D-galactitol **21b** (Scheme 9), which − after protection as convenient − can in turn be transformed into the (2*R*)-*prim-sec* dimer **18b** (Scheme 10).



Scheme 10. Oxidative cleavage of diol precursor **24b**: (i) aq. 0.1 M $NaIO_4$ solution, room temp., 30 min; (ii) H_2O, $NaBH_4$, room temp., 30 min (quantitative)

It should be noted that the excess of sodium borohydride used in the reduction of the dialdehyde is sufficient to deprotect the hydroxy groups in positions 2 and 6.

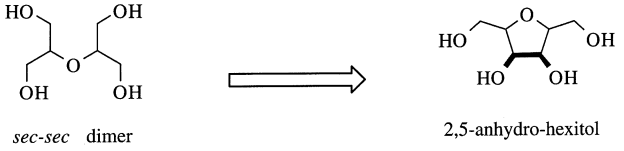
For the synthesis of the (2*S*) enantiomer **18c**, D-mannose may be used as starting material. The strategy for the protection of the hydroxy group in position 2 can be performed according to the methodology of Deferrari et al. and Kovác et al.[22]



Scheme 9. Elaboration of diol precursor **24b**: (i) AcOEt, Et_3N, 10% Pd/C, H_2, room temp., 1 atm, 3 h (96%); (ii) MeOH, NaOMe, room temp., overnight (90%); (iii) a) 2,2-dimethoxypropane, CSA, room temp., 48 h; b) MeOH/H_2O (10:1), cat. AcOH, 50 °C, 30 min (89%); (iv) Ac_2O, pyridine, room temp., 20 h, (quantitative); (v) 60% aq. AcOH, 50−60 °C, 2 h (82%)

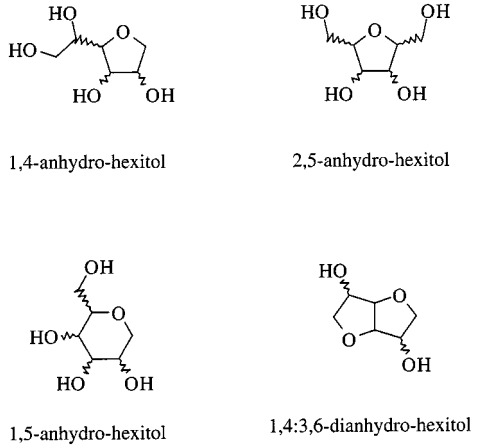
Synthesis of the *sec-sec* Dimer

In this case, the synthesis relies on the oxidative cleavage[23] of the vicinal diol moiety of a 2,5-anhydroalditol (Scheme 11).



Scheme 11. Retrosynthetic scheme for the *sec-sec* dimer

The preparation of such a 2,5-anhydroalditol is problematic. Thermally induced dehydration of an itol (sorbitol, mannitol or dulcitol) in acidic medium was expected to produce the 2,5- and 1,5-anhydro isomers simultaneously. Unfortunately, this method − which would have been cheap and applicable to large-scale synthesis − predominantly gave 1,4:3,6-dianhydro-itols, concomitantly with the 1,4-anhydro-itol (Scheme 12).[24]

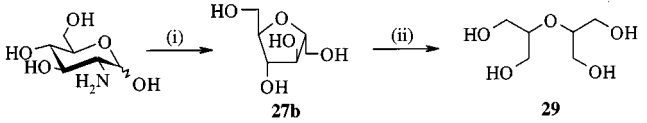


Scheme 12. Possible anhydrohexitols

In the case of sorbitol, only 3% of the expected 2,5-anhydro-L-iditol[25] **27a** was obtained (Scheme 13). Even though sorbitol is a cheap starting material, this is not satisfactory for multigram-scale synthesis.

In the case of dulcitol (galactitol), the expected 1,5-anhydro-D-galactitol could not even be detected in the mixture of products resulting from the dehydration.

We therefore used a method previously developed for the structural study of heparin; it consists of nitrous deamination, with ring contraction, of 2-amino-2-deoxy-D-glucopyranose in aqueous medium (Scheme 14).[26]



Scheme 14. Synthesis of *sec-sec* dimer **29** via 2,5-anhydro-D-mannitol **27b** from D-glucosamine hydrochloride: (i) a) H_2O, room temp., 24 h; b) $NaNO_2$, AcOH, $T < 2$ °C, 2 h; c) $NaBH_4$, H_2O, 0 °C to room temp., overnight (80% overall); (ii) a) aq. 0.1 M $NaIO_4$ solution, room temp., 30 min; b) H_2O, $NaBH_4$, room temp., 30 min (quantitative)

The desired *sec-sec* dimer **29** was obtained in 80% yield from D-glucosamine hydrochloride, through the intermediate formation of 2,5-anhydro-D-mannitol **27b**. The synthesis of this precursor has previously been described in the literature; however we have improved the procedure so as to allow repeatable preparation of 20 gram-scale batches.

Synthesis of *sec-prim prim-sec* Trimer

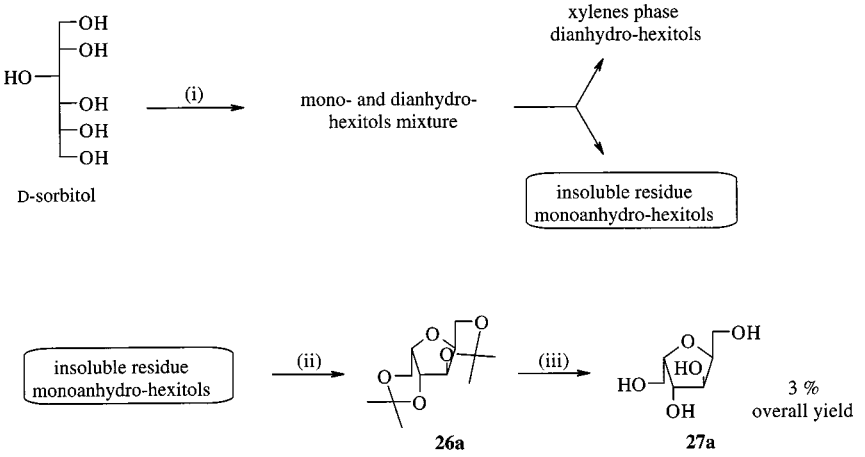
A strategy based on the double opening of epichlorohydrin by an alcohol can be imagined. This methodology, with use of benzyl alcohol, resulted in 1,3-dibenzylglycerol,[19] which could in turn be utilised to yield protected trimer **30** (Scheme 15).

One can imagine repeating this step to give higher degree oligomers (pentamer, heptamer, ...) with dendrimer-like structures.

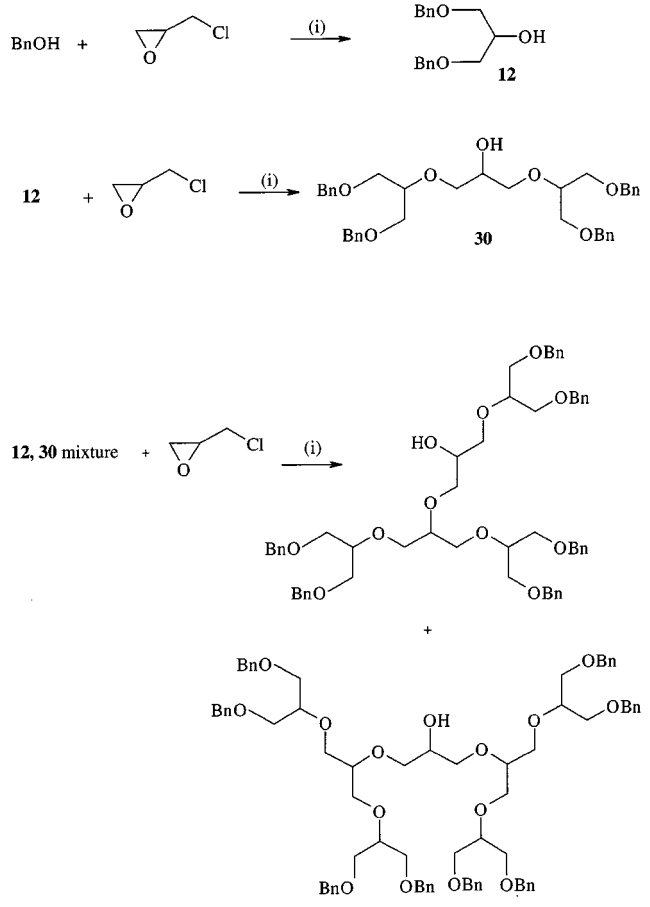
As the palladium-catalysed hydrogenolysis of the benzyl groups was not found satisfactorily repeatable on scaled-up batches, a route using acetolysis was successfully developed (Scheme 16).

Synthesis of *sec-sec prim-prim* Trimer

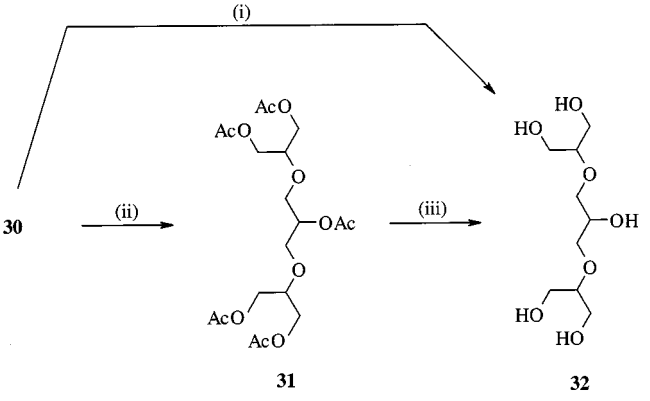
A strategy based on coupling of 2,5-anhydro-D-mannitol − either with an activated form of 2,5-anhydro-D-mannitol



Scheme 13. Synthesis of 2,5-anhydro-L-iditol **27a** from D-sorbitol: (i) xylenes, methanesulfonic acid, reflux, Dean-Stark, 2.5 h; (ii) acetone, H_2SO_4, room temp., overnight (3%); (iii) THF/H_2O, Amberlite® IR-120 (H^+), room temp., overnight (79%)



Scheme 15. Preparation of *sec-prim prim-sec* protected trimer **30**: (i) KOH, H_2O, TBAI, 80 °C, 48 h (80%)



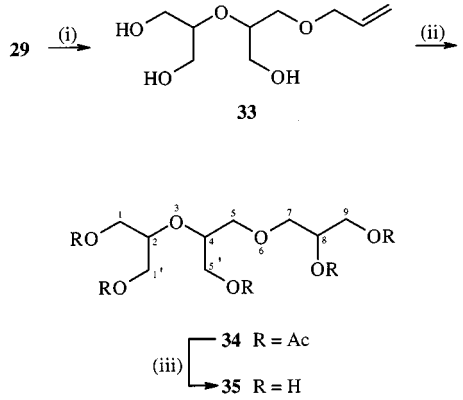
Scheme 16. Deprotection of *sec-prim prim-sec* trimer **30**: (i) H_2, 10% Pd/C, MeOH, room temp., 1 atm, 24 h; (ii) AcOH, Ac_2O, H_2SO_4, 0 °C to room temp., overnight; (iii) MeOH, NaOMe, room temp., overnight (69%)

or with a protected and activated form of glycerol – prior to the oxidative cleavage of the diol was initially envisaged.

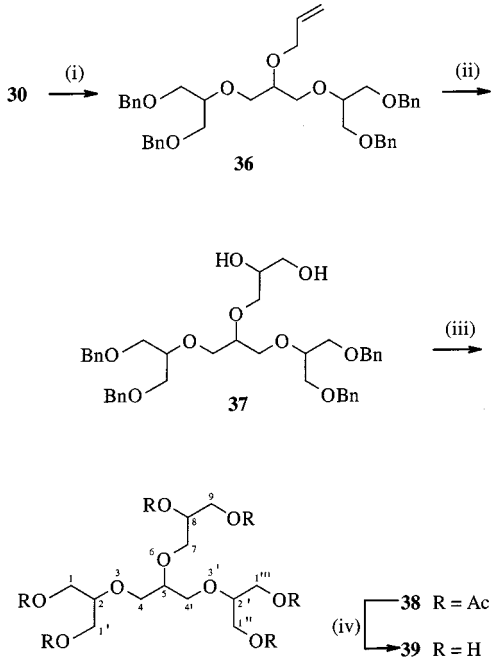
Considering the difficulties – inseparable mixtures of coupling products on both primary and secondary alcohols, lack of reactivity of the solketal tosylate, versatility of the isopropylidene protective group, formation of di- and tri-anhydro-itols on attempting to activate the 2,5-anhydro-D-mannitol as a tosylate in basic medium – a direct coupling of the *sec-sec* dimer with an activated monomeric counterpart was investigated.

Allyl bromide was selected as the activated monomeric moiety to add. It gave satisfying coupling yields and was found stable under the reaction conditions. Moreover, the unavoidable di-, tri- and tetraallyl derivatives formed concomitantly during the condensation reaction could easily be separated by silica gel column chromatography. These can be used as precursors in the elaboration of two different tetramers, one pentamer and one hexamer after the dihydroxylation step.

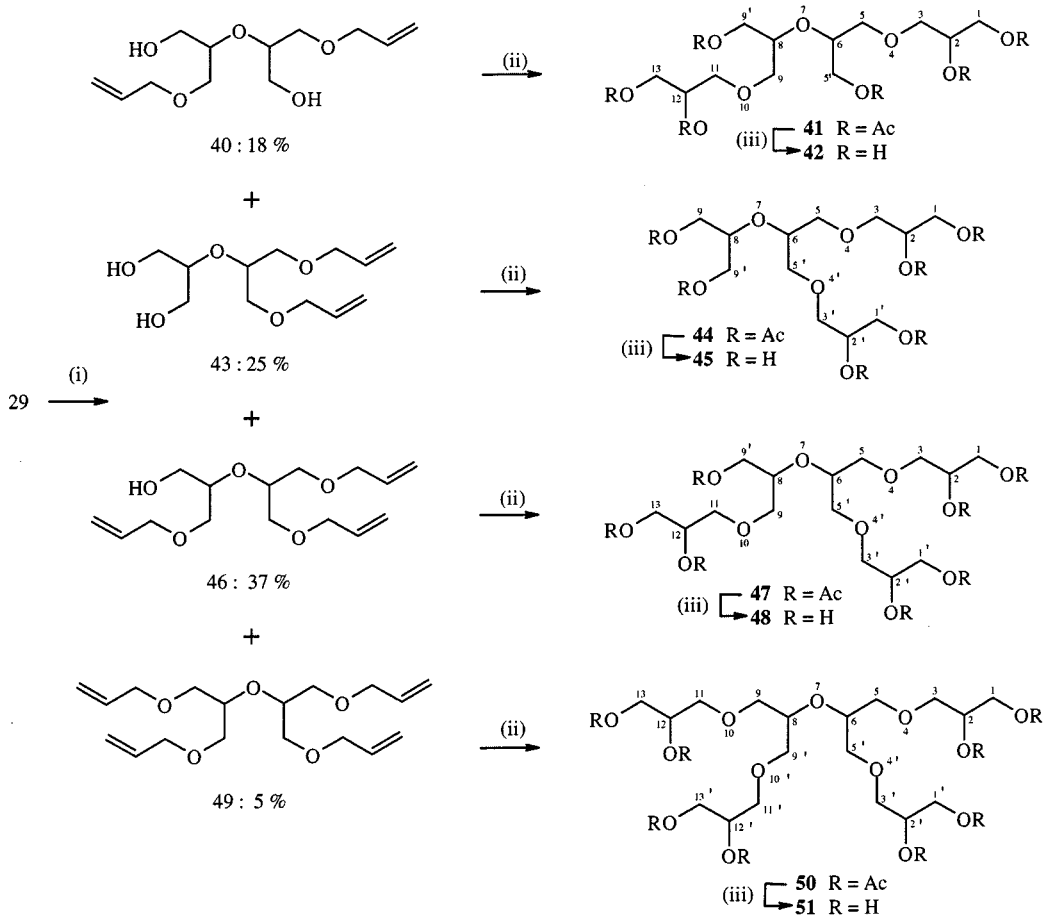
Dihydroxylation of the monoallyl compound was performed using potassium permanganate – cheaper and far less toxic than osmium tetroxide – in water[7,11] to give trimer **34** in good yield (77%, Scheme 17).



Scheme 17. Preparation of *sec-sec prim-prim* trimer **34**: (i) allyl bromide (1.0 equiv.), DMF, NaH, room temp., overnight (49%); (ii) a) $KMnO_4$, H_2O, 0 °C to room temp., 2 h; b) Ac_2O, pyridine, room temp., overnight; (iii) MeOH, NaOMe, room temp., overnight (77%, 3 steps)



Scheme 18. Synthesis of tetramer **39**: (i) allyl bromide, NaH, DMF, room temp., 48 h (41%); (ii) OsO_4 (2 mol-%), H_2O/acetone (1:10), NMO, room temp., 24 h (50%); (iii) AcOH, Ac_2O, H_2SO_4, 0 °C to room temp., overnight; (iii) MeOH, NaOMe, room temp., overnight (74%)



Scheme 19. Preparation of tetramers **42** and **45**, pentamer **48** and hexamer **51**: (i) allyl bromide, DMF, NaH, room temp., overnight; (ii) a) $KMnO_4$ (**40** and **43**: 2.02 equiv.; **46**: 3.03 equiv.; **49**: 4.04 equiv.), H_2O/acetone, 0 °C to room temp., 2 h; b) Ac_2O, pyridine, room temp., overnight; (iii) MeOH, NaOMe, room temp., overnight (**42**: 44%; **45**: 67%; **48**: 50%; **51**: 26%, 3 steps)

Tetramers, Pentamers and Hexamers

Synthesis of *prim-sec* Bis(*prim-sec*) Tetramer

It was also possible to add allyl bromide to the benzylated trimer **30** to give a tetrameric precursor **36**. This, after dihydroxylation followed by removal of the benzyl groups, would afford tetramer **39**.

Dihydroxylation using $KMnO_4$ proved inefficient in this particular case, even under phase transfer conditions. Catalytic OsO_4 and NMO as co-oxidant had to be used to perform this reaction (Scheme 18).

Synthesis of *prim-prim sec-sec prim-prim* Tetramer, *sec-sec* Bis(*prim-prim*) Tetramer, *prim-prim sec-sec* Bis(*prim-prim*) Pentamer, Bis(*prim-prim*) *sec-sec* Bis(*prim-prim*) Hexamer

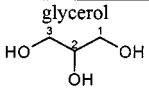
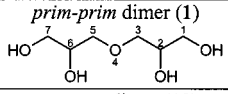
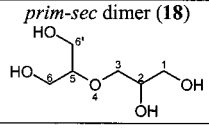
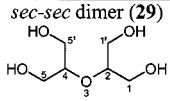
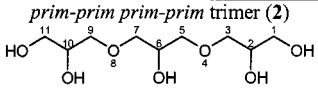
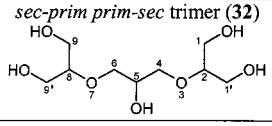
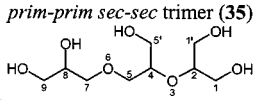
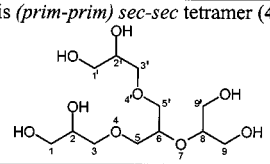
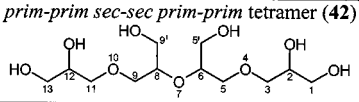
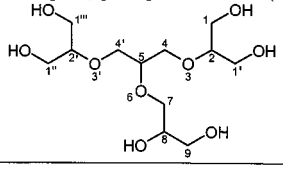
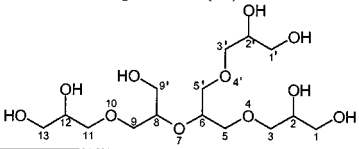
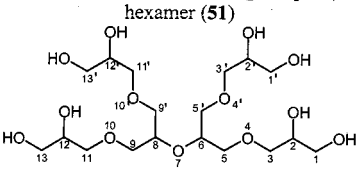
The number and position of the allyl groups could easily be determined by MS and ^1H NMR, and the regioisomeric diallyl compounds **35** and **37** could readily be separated by silica gel column chromatography. Dihydroxylation using 1 equiv. of $KMnO_4$ per double bond to be treated, in water or in a water/acetone mixture according to the solubility of the starting material, afforded the expected tetramers, pentamer and hexamer in reasonable yields (Scheme 19). Acetylation of all compounds in Ac_2O/pyridine permitted the removal of residual salts and thus made purification easier. Transesterification with sodium methoxide in methanol yielded the free oligomers.

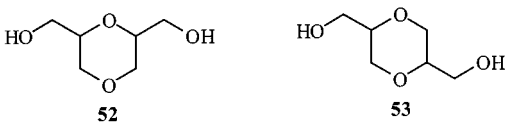
Synthesis of Cyclic Dimers of Glycerol

As with branched oligoglycerols, for cyclic structures a large number of isomers can be envisaged for each degree of oligomerisation. As far as dimers are concerned, five cyclic derivatives can be expected, as shown in Scheme 1. In this work, we have considered efficient synthetic routes towards 1,4-dioxanes **52** and **53**[8] (Scheme 20), which are expected to be present in industrial polyglycerol mixtures.[28]

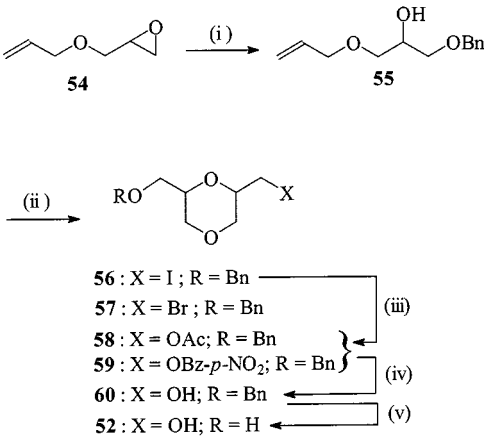
Our strategy was based upon a 6-*exo*-trig halocyclisation reaction involving heteroatom-tethered unsaturated alcohols **55** and **66**. Alcohol **55** was readily produced in 88% yield by opening the oxirane ring of commercially available allyl 2,3-epoxypropyl ether (allyl glycidyl ether) **54** with benzyl alcohol in the presence of sodium hydride as a base (Scheme 21). Similar results were obtained for the preparation of alcohol **66**, produced in 75% yield by (i) alkylation of 1,3-benzylideneglycerol with allyl bromide in the presence of sodium hydride and tetra-*n*-butylammonium brom-

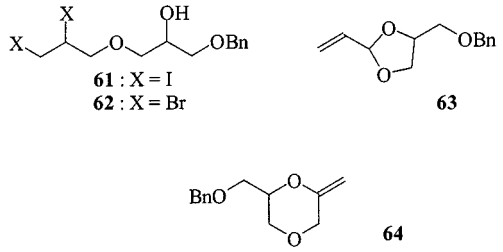
Table 2. ^{13}C NMR chemical shifts of glycerol up to hexameric oligomer

Compound in [D$_6$]DMSO (δ ^{13}C in ppm)	-CH_2OH	δ	-CHOH-	δ	-CH_2-O-	δ	-CH-O-	δ
glycerol 	C-1, C-3	**63.8**	C-2	**73.2**				
prim-prim dimer (**1**) 	C-1, C-7	**63.9**	C-2, C-6	**71.3**	C-3, C-5	**73.7**		
prim-sec dimer (**18**) 	C-1	**63.9**	C-2	**71.6**	C-3	**72.5**	C-5	**82.8**
	C-6, C-6'	**61.7**						
sec-sec dimer (**29**) 	C-1, C-1', C-5, C-5'	**62.5**					C-2, C-4	**82.6**
prim-prim prim-prim trimer (**2**) 	C-1, C-11	**63.9**	C-2, C-10	**71.3**	C-3, C-9	**73.6**		
			C-6	**69.4**	C-5, C-7	**73.7**		
sec-prim prim-sec trimer (**32**) 	C-1, C-1', C-9, C-9'	**61.7**	C-5	**70.1**	C-4, C-6	**72.4**	C-2, C-8	**82.8**
prim-prim sec-sec trimer (**35**) 	C-1, C-1', C-5'	**62.3** **62.4**	C-8	**71.3**	C-7	**72.1**	C-2	**82.1**
	C-9	**63.8**			C-5	**73.6**	C-4	**79.8**
bis *(prim-prim) sec-sec* tetramer (**45**) 	C-1, C-1'	**63.9**	C-2, C-2'	**71.3**	C-3, C-3'	**72.2**	C-6	**82.0**
	C-9, C-9'	**62.1**			C-5, C-5'	**73.7**	C-8	**77.6**
prim-prim sec-sec prim-prim tetramer (**42**) 	C-1,C-13	**63.9**	C-2,C-12	**71.3**	C-3,C-11	**72.2**	C-6, C-8	**79.7**
	C-5', C-9'	**62.2**			C-5, C-9	**73.6**		
bis *(sec-prim) prim-prim* tetramer (**39**) 	C-1, C-1', C-1", C-1"'	**61.6**	C-8	**71.5**	C-4, C-4'	**70.2**	C-2, C-2'	**82.7**
					C-7	**72.3**	C-5	**79.3**
	C-9	**63.9**						
bis *(prim-prim) sec-sec prim-prim* pentamer (**48**) 	C-1, C-1', C-13	**63.9**	C-2, C-2', C-12	**71.3**	C-3, C-3', C-11	**72.1**	C-6	**79.9**
	C-9'	**62.1**			C-5, C-5', C-9	**73.6**	C-8	**77.6**
bis *(prim-prim) sec-sec* bis *(prim-prim)* hexamer (**51**) 	C-1, C-1', C-13, C-13'	**63.9**	C-2, C-2', C-12, C-12'	**71.3**	C-3, C-3', C-11, C-11'	**72.1**	C-6, C-8	**82.1**
					C-5, C-5', C-9, C-9'	**73.7**		



Scheme 20. Cyclic diglycerols

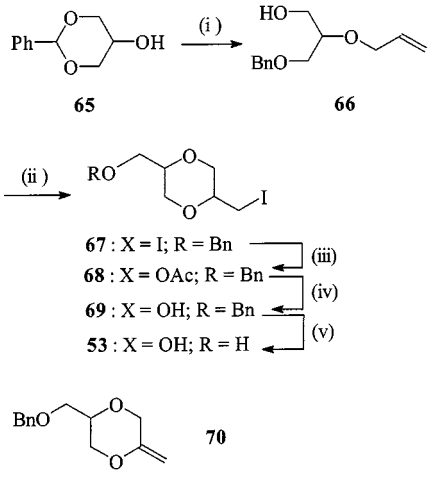




Scheme 21. Synthesis of 2,6-bis(hydroxymethyl)-1,4-dioxane (**52**): (i) BnOH, NaH (88%); (ii) NIS (or NBS), CH_3CN, reflux (50%); (iii) CH_3CO_2K, DMF, 18-crown-6, 80 °C (63%) or potassium *p*-nitrobenzoate, DMSO, 18-crown-6, 90 °C (74%); (iv) MeOH, HCl (85−90%); H_2, Pd/C, MeOH (92%)

ide (TBAB), followed by (ii) opening of the 1,3-dioxane ring with DIBAL-H (Scheme 22).

Halocyclisation of unsaturated alcohols can be carried out using a variety of electrophilic agents, such as iodine, *N*-halosuccinimides or bis(*sym*-collidine)iodonium(I) salts.[29−31] A systematic study of the haloetherification of compounds **55** and **66** was carried out, both for optimisation of yields and for minimisation of side-product formation (Table 3). Treatment of **55** with iodine in diethyl ether in the presence of an aqueous solution of sodium hydrogen carbonate (Table 3, Entry 1) yielded the expected 1,4-dioxane **56** in low yield, together with a major compound (**61**) resulting from the electrophilic addition of iodine to the double bond. The use of *N*-iodosuccinimide (NIS) in dichloromethane at room temperature resulted in the production of dioxolane **63** as the major product (25% yield), in addition to diiodide **61** and the expected 1,4-dioxane **56** (4% yield). The structure of dioxolane **63** was assigned by ^1H and ^{13}C NMR spectroscopy ($CDCl_3$; $CH_2{=}CH{-}CH$: δ = 5.15, d, *J* = 6.1 Hz; $CH_2{=}CH{-}CH$: δ = 5.3, dd, *J* = 17.3 Hz; *J* = 10.2 Hz; $CH_2{=}CH{-}CH$: δ = 5.75, ddd, 1 H; and $=CH{-}CH$: δ = 104.4). The formation of this dioxolane **63** may be explained by a Wohl−Ziegler-type allylic iodination, followed by an intramolecular nucleophilic displacement. In order to minimise the undesirable allylic iodination, a polar solvent was substituted. Thus, when the reaction was performed in refluxing acetonitrile (Table 3, Entry 3), 1,4-dioxane **56** was isolated in 50% yield after chromatographic separation from dioxolane **63**. Under the same conditions, *N*-bromosuccinimide furnished the brominated 1,4-dioxane **57**, albeit in lower yield (Table 3, Entry 4). The optimised reaction conditions were further applied to the iodocyclisation of unsaturated alcohol **66**. 1,4-Dioxane **67** could be isolated in 40% yield (Table 3, Entry 5) after flash chromatographic separation from dioxolane **63**. Cyclic compound **56** was obtained as a mixture of *cis* and *trans* isomers, which could not be separated by chromatography and which were therefore characterised by NMR (^{13}C: $CH_2{-}I$: δ = 2.34 and 3.66; $CH_2{-}OBn$: δ = 67.83 and 69.52) and by positive-ion FAB high resolution MS (calculated for $[M - H]^+$: 347.0144; found for $[M - H]^+$: 347.0146). In contrast, the *cis* and *trans* isomers of **67** were separable by flash chromatography (see Exp. Sect.).



Scheme 22. Synthesis of 2,5-bis(hydroxymethyl)-1,4-dioxane (**53**): (i) a) $CH_2{=}CH{-}CH_2{-}Br$, NaH, TBAB, THF; b) DIBAL-H, CH_2Cl_2 (75%; 2 steps); (ii) NIS, CH_3CN reflux (40%); (iii) CH_3CO_2K, DMF (60%); (iv) MeOH, HCl (98%); (v) H_2, Pd/C, MeOH (98%)

The next step involved the displacement of iodine in **56** and **67**, with installation of an oxygen functionality. Nucleophilic substitution of the iodide function in **56** appeared quite difficult, probably due to the electron-withdrawing oxygen group in the β-position. After some experimentation, we found that treatment of **56** with 10 equiv. of potassium acetate in the presence of 18-crown-6 in DMF at 80 °C gave a mixture of the expected acetate **58** (63% yield), together with the elimination product **64** (25% yield), easily separated by flash chromatography. In order to reduce the basicity of the reagent, we examined potassium *p*-nitrobenzoate. When the reaction was carried out in DMSO at 90 °C using 18-crown-6, the *p*-nitrobenzoate **59** was obtained in 74% yield.

Acetate **68** was obtained under the same conditions from iodide **67**. Treatment of acetates **58** and **68** or *p*-nitrobenzo-

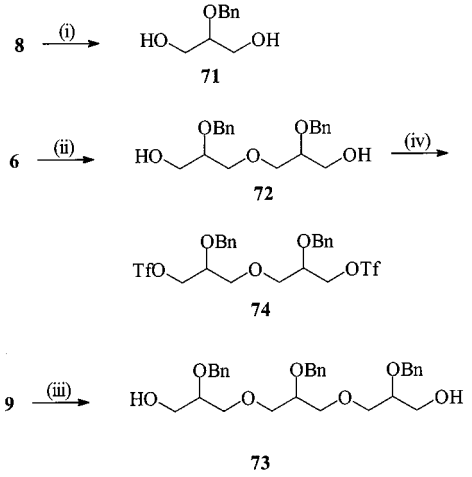
Table 3. Haloetherification reaction involving alcohols **55** and **66**

Entry	Unsaturated alcohol	Halonium donor	Reaction conditions	Product (Yield)	Side products
1	**55**	I_2, $NaHCO_3$	Et_2O/H_2O 5:2, 3 h at 0 °C then 1 h at room temp.	**56** (8%)	**61** (> 25%)
2	**55**	NIS	CH_2Cl_2, room temp., 5 days	**56** (4%)	**61** (9%) **63** (25%)
3	**55**	NIS	CH_3CN, reflux, 3h	**56** (50%)	**63** (15%)
4	**55**	NBS	CH_3CN, reflux, 5h	**57** (27%)	**61** (15%) **63** (traces)
5	**66**	NIS	CH_3CN, reflux, 2h	**67** (40%)	**63** (15%)

ate **59** with hydrochloric acid in methanol, followed by hydrogenolysis of the benzyloxy groups under standard conditions, gave the corresponding diols **52** and **53**, respectively, in nearly quantitative yields. These cyclic diglycerols were purified by flash chromatography and characterised by NMR spectrometry [^{13}C NMR (CD_3OD): diol **52**: CH_2-OH: δ= 61.59 and 62.95; diol **53**: CH_2-OH: δ = 61.21 and 62.82].

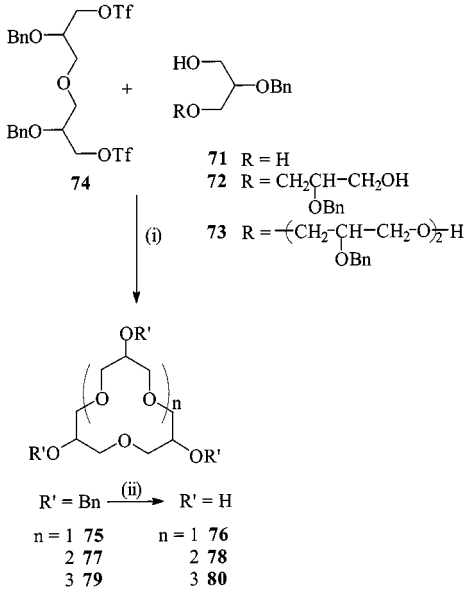
Synthesis of Cyclic Trimer, Tetramer and Pentamer of Glycerol

The synthesis of the cyclic trimer, tetramer and pentamer of glycerol (**76**, **78** and **80**) was envisaged as proceeding through two one-pot Williamson coupling reactions between two bifunctional fragments: ditriflate **74** derived from diglycerol and mono-, di-, or tri-glycerols **71**−**73**, with their secondary hydroxy groups protected as benzyl ethers (Scheme 23). Preparation of compound **74** was achieved by treatment of dibenzylated diglycerol **72** with triflic anhydride in the presence of the weakly nucleophilic 2,6-lutidine.



Scheme 23. Synthesis of linear diols **71**−**73** and ditriflate **74**: (i) Pd/C, APTS, MeOH/water 8:2, reflux (50%); (ii) a) allyl alcohol, NaH, room temp.; b) NaH, BnBr, TBAB, THF, room temp.; c) Pd/C, APTS, MeOH/water 8:2 (37%); (iii) a) allyl alcohol, NaH, room temp.; b) NaH, BnBr, TBAB, THF, room temp.; c) Pd/C, APTS, ethanol/MeOH/water 10:4:2 (56%); (iv) 2,6-lutidine, triflic anhydride, CH_2Cl_2, 0 °C (70%)

Alkylation of diols **71**−**73** with ditriflate **74**, using sodium hydride as a base and without high dilution condition, furnished the corresponding macrocyclisation products **75**, **77** and **79** in 35% yield for each oligomer (Scheme 24). These benzylated cyclic oligoglycerols were fully characterized by ^1H and ^{13}C NMR spectroscopy, high resolution MS and elemental analysis. A similar procedure, based upon the use of the ditosylate of diglycerol instead of the ditriflate **74**, was found to be ineffective and the major proportion of the starting materials was recovered. After hydrogenolysis of the benzyloxy groups, the 12-, 16- and 20-membered rings **76**, **78** and **80** were isolated in virtually quantitative yields.



Scheme 24. Synthesis of cyclic tri-, tetra- and pentaglycerols **77**, **78** and **80**: (i) NaH, THF, room temp. (35%); (ii) Pd/C, H_2, MeOH or MeOH/ethyl acetate, room temp. (83−98%)

Experimental Section

General: Melting points [°C] were determined with a Kofler hot-stage apparatus and are uncorrected. − Optical rotations were measured at 20 °C with a Perkin−Elmer 141 polarimeter. − NMR spectra were recorded with a Bruker DPX 250 spectrometer (250 MHz for ^1H and 62.89 MHz for ^{13}C) or with a Bruker ARX 400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C). Chemical shifts are expressed in ppm downfield from TMS. − Mass spectra were recorded with an API-300 spectrometer [Ionspray® (IS) or heated nebulizer (HN) ionisation mode]. − Thin layer chromatography (TLC) was performed on aluminium sheets precoated with

60 F_{254} silica gel (E. Merck, Darmstadt, Germany); detection was effected by observation under short-wavelength UV light (254 nm) and charring after application of a solution of 5% H_2SO_4 in ethanol or 6% phosphomolybdic acid in ethanol, or vanillin in a 1:1 mixture of sulfuric acid/water or $KMnO_4$ 5 g/K_2CO_3 33 g/AcOH 8.5 mL/H_2O 500 mL. − Column chromatography was performed using silica gel 60 (0.063−0.200 mm, 70−230 mesh ASTM, E. Merck) or silica gel 60H (5−40 μm, E. Merck). Anhydrous reactions were performed in predried flasks, using anhydrous solvents (which were distilled when necessary according to D. D. Perrin, W. L. F. Armarego, D. R. Perrin in *Purification of Laboratory Chemicals*, Pergamon, Oxford, **1986**) and under argon. HRMS was carried out by Technologie Servier (Orléans, France) (Instrument LCT, ES+ ionisation mode, capillary 3000.0 V, sample cone 40.0 V, mass range 80−800). − Microanalyses were carried out by the Service de Microanalyses de l'ICSN (Gif sur Yvette, France). Commercially available chemicals were used without further purification.

1,2:6,7-Diepoxy-4-oxaheptane (6): 70% *m*CPBA (21.2 g, 126 mmol), dissolved in dichloromethane (180 mL), was added dropwise to a solution of allyl glycidyl ether (10 mL, 84.2 mmol) in dichloromethane (20 mL). After stirring the solution for 24 h at room temperature, the mixture was treated with 1 M $Na_2S_2O_3$ and extracted with dichloromethane. The combined extracts were washed with 0.5 M NaOH, dried with $MgSO_4$ and concentrated to yield **6** (10.3 g, 93%) as a colourless oil. − TLC (petroleum ether/ethyl acetate, 8:2): R_f = 0.2. − ^{1}H NMR ($CDCl_3$): δ = 2.63 (m, 2 H, H-1a and H-7a), 2.81 (m, $J_{1a,1b}$ = $J_{7a,7b}$ = 5.1 Hz, 2 H, H-1b and H-7b), 3.18 (m, 2 H, H-2 and H-6), 3.45 (m, 2 H, H-3a and H-5a), 3.85 (m, $J_{3a,3b}$ = $J_{5a,5b}$ = 11.7 Hz, 2 H, H-3b and H-5b). − ^{13}C NMR ($CDCl_3$): δ = 44.15 (2 C, C-1 and C-7), 50.8 (2 C, C-2 and C-6), 71.8 and 72.1 (2 C, C-3 and C-5); see ref.[3,11]

1,2:14,15-Di-*O*-isopropylidene-4,8,12-trioxapentadecane-1,2,6,10,14,15-hexaol (7): Solketal (1.91 mL, 15.3 mmol), Aliquat® 336 (124 mg, 0.307 mmol) and *n*-hexane (5 mL) were added to a 50% aq. solution of NaOH (1.2 g, 30.7 mmol). Compound **6** (400 mg, 3.07 mmol) was then added and the mixture was vigorously stirred at 80 °C for 2 h. The mixture was diluted with water (15 mL) and a 2:1 ethyl acetate/butyl alcohol mixture; the aqueous layer was extracted with 2:1 ethyl acetate/butyl alcohol. The organic extracts were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Traces of butyl alcohol and the major proportion of excess solketal were removed by means of a kugelrohr apparatus. Compound **7** (557 mg, 46%) was isolated after purification by column chromatography (dichloromethane/acetone, 7:3 then 1:1) as a yellow oil. − TLC (dichloromethane/acetone, 1:1): R_f = 0.48. − ^{1}H NMR ($CDCl_3$): δ = 1.36 and 1.42 (2 s, 12 H, CH_3), 3.10 (s, 2 H, OH), 3.48−3.60 (m, 12 H, H-1, H-5, H-7, H-9, H-11 and H-15), 3.72 (m, 2 H, H-3a and H-13a), 3.97 (m, 2 H, H-6 and H-10), 4.05 (dd, $J_{3a,3b}$ = 8.6 Hz, 2 H, H-3b and H-13b), 4.28 (m, $J_{2,3a}$ = 6.1 Hz, $J_{2,3b}$ = 6.1 Hz, 2 H, H-2 and H-14). − ^{13}C NMR ($CDCl_3$): δ = 25.3 and 26.7 (2 C, CH_3), 66.5 (2 C, C-3 and C-13), 69.5 (2 C, C-6 and C-10), 72.5, 72.6 and 72.7 (6 C, C-1, C-5, C-7, C-9, C-11 and C-15), 74.7 (2 C, C-2 and C-14), 109.5 [1 C, $C(CH_3)_2$]. − $C_{18}H_{34}O_9$ (394.46): calcd. C 54.81, H 8.69; found C 54.42, H 8.53.

4,8,12-Trioxapentadecane-1,2,6,10,14,15-hexaol (3): Compound **7** (4.5 g, 11.4 mmol) was stirred overnight in refluxing methanol in the presence of Dowex 50WX8 acidic resin. The resin was then removed by filtration and the filtrate was concentrated and purified by column chromatography (dichloromethane/methanol, 8:2, then 7:3) to yield tetraglycerol **3** (2.6 g, 73%). − TLC (dichloromethane/methanol, 8:2): R_f = 0.11. − ^{1}H NMR (CD_3OD): δ = 3.44−3.56 (m, 16 H, H-1, H-3, H-5, H-7, H-9, H-11, H-13 and H-15), 3.73−3.77 (m, 2 H, H-2 and H-14), 3.90 (m, 2 H, H-6 and H-10). − ^{13}C NMR (CD_3OD): δ = 64.3 (2 C, C-1 and C-15), 72.2 (2 C, C-2 and C-14), 70.6 (2 C, C-6 and C-10), 73.8 (6 C, C-3, C-5, C-7, C-9, C-11 and C-13). − $C_{12}H_{26}O_9$·0.5H_2O (323.38): calcd. C 44.57, H 8.41; found C 44.65, H 8.22.

6-*O*-Benzyl-4,8-dioxaundecane-1,10-dien-6-ol (8): Allyl alcohol (17.4 mL, 0.256 mol), TBAB (1.03 g, 3.19 mmol) and *n*-hexane (25 mL) were added to 18 M aq. NaOH (25 g, 0.639 mol). Epichlorohydrin (5 mL, 63.9 mmol) was then added and the mixture was vigorously stirred at 65 °C for 6 h. The mixture was diluted with diethyl ether and water; the aq. layer was extracted with diethyl ether. The extracts were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure to remove solvents and residual allyl alcohol, affording 9.9 g of crude 1,3-di-*O*-allylglycerol. This crude residue (9.8 g, 56.9 mmol), in dry THF (10 mL), was added slowly to a suspension of sodium hydride (4.55 g, 0.113 mol) in dry THF (80 mL). After stirring at room temperature for 30 min, TBAB (0.55 g, 1.7 mmol) and benzyl bromide (10.15 mL, 85 mmol) were added. The mixture was stirred for 3 h at room temperature, diluted with diethyl ether, and washed with water and brine. The organic layer was dried with $MgSO_4$, and the solvents were evaporated. Purification of the residue by column chromatography (petroleum ether, then petroleum ether/ethyl acetate, 9:1) yielded **8** (10.9 g, 65% from epichlorohydrin) as a colourless oil. − TLC (petroleum ether/ethyl acetate, 9:1): R_f = 0.4. − ^{1}H NMR ($CDCl_3$): δ = 3.55 (m, 4 H, H-5 and H-7), 3.75 (m, $J_{5,6}$ = 5.1 Hz, 1 H, H-6), 4.00 (m, 4 H, H-3 and H-9), 4.70 (s, 2 H, CH_2−C_6H_5), 5.17 (m, 2 H, H-1a, H-11a), 5.26 (m, $J_{1a,1b}$ = 1.5 Hz, 2 H, H-1b and H-11b), 5.90 (m, $J_{2,3}$ = 5.56 Hz, $J_{2,1a}$ = 10.6 Hz, $J_{2,1b}$ = 16.3 Hz, 2 H, H-2 and H-10), 7.24−7.40 (m, 5 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 70.3 (2 C, C-5 and C-7), 72.2 and 72.3 (3 C, C-3, C-9, CH_2−C_6H_5), 77.1 (1 C, C-6), 116.9 (2 C, C-1 and C-11), 127.0−129.0 (arom. CH), 134.7 (2 C, C-2 and C-10), 138.7 (arom. C). − $C_{16}H_{22}O_3$ (262.35): calcd. C 73.25, H 8.45; found C 73.24, H 8.52.

6-*O*-Benzyl-1,2:10,11-diepoxy-4,8-dioxaundecan-6-ol (9): 70% *m*CPBA (21 g, 85 mmol), dissolved in dichloromethane (190 mL), was added dropwise to **8** (9 g, 34 mmol), in solution in dichloromethane (10 mL). After stirring at room temperature for 24 h, the mixture was treated with 1 M aq. $Na_2S_2O_3$ (100 mL), then extracted with dichloromethane. The extracts were washed with 0.5 M aq. NaOH to remove *m*-chlorobenzoic acid, then dried with $MgSO_4$ and concentrated under reduced pressure to yield **7** (6.2 g, 63%) as a colourless oil, after purification by column chromatography (petroleum ether/ethyl acetate, 1:1). − TLC (petroleum ether/ethyl acetate, 1:1): R_f = 0.54. − ^{1}H NMR ($CDCl_3$): δ = 2.60 (dd, 2 H, H-1a and H-11a), 2.78 (dd, $J_{1a,1b}$ = 5.1 Hz, 2 H, H-1b and H-11b), 3.13 (m, $J_{2,1a}$ = 3.0 Hz, $J_{2,1b}$ = 4.0 Hz, 2 H, H-2 and H-10), 3.40 (m, 2 H, H-3a and H-9a), 3.57−3.70 (m, 4 H, H-5 and H-7), 3.72−3.76 (m, 2 H, H-3b and H-9b), 3.77−3.80 (m, 1 H, H-6), 4.69 (s, 2 H, CH_2−C_6H_5), 7.30−7.40 (m, 5 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 44.2 (2 C, C-1 and C-11), 50.8 (2 C, C-2 and C-10), 71.3 (2 C, C-3 and C-9), 72.1 and 72.3 (3 C, C-5, C-7 and CH_2−C_6H_5), 77.0 (1 C, C-6), 127.0−129.0 (arom. CH), 138.5 (arom. C). − $C_{16}H_{22}O_5$ (294.35): calcd. C 65.29, H 7.53; found C 65.44, H 7.65.

10-*O*-Benzyl-1,2:18,19-di-*O*-isopropylidene-4,8,12,16-tetraoxanonadecane-1,2,6,10,14,18,19-heptaol (10): Solketal (4.25 mL, 34 mmol), Aliquat® 336 (276 mg, 0.68 mmol) and *n*-hexane (10 mL) were added to a 20 M solution of NaOH (2.74 g, 68 mmol). Bis(epoxide) **9** (2 g, 6.8 mmol) was then added, and the resulting

mixture was vigorously stirred at 80 °C for 4 h. The mixture was diluted with water and a ethyl acetate/butyl alcohol mixture (3:1); the aqueous layer was extracted with ethyl acetate/butyl alcohol (3:1). The combined extracts were washed with brine, dried with Na_2SO_4 and concentrated. Excess solketal was removed by distillation with a kugelrohr apparatus. Purification of the residue by column chromatography (dichloromethane/acetone, 9:1 then 7:3) yielded **10** (2 g, 3.58 mmol, 53%) as a yellow oil. − TLC (dichloromethane/acetone, 8:2): R_f = 0.19. − ^{1}H NMR ($CDCl_3$): δ = 2.96 (s, 2 H, OH), 1.35 and 1.42 (2 s, 12 H, CH_3), 3.46−3.56 (m, 12 H H-1, H-5, H-7, H-13, H-15 and H-19), 3.58−3.64 (m, 4 H, H-9 and H-11), 3.71 (m, 3 H, H-3a, H-17a and H-10), 3.95 (m, 2 H, H-6 and H-14), 4.03 (m, 2 H, H-3b and H-17b), 4.28 (m, 2 H, H-2 and H-18), 4.65 (s, 2 H, CH_2−C_6H_5), 7.30−7.34 (m, 5 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 25.3 and 26.7 (4 C, CH_3), 66.5 (2 C, C-3 and C-7), 69.3 (2 C, C-6 and C-14), 71.2 (2 C, C-9 and C-11), 72.2 (1 C, CH_2−C_6H_5), 72.4−72.7 (6 C, C-1, C-5, C-7, C-13, C-15 and C-19), 74.6 (2 C, C-2 and C-18), 76.7 (1 C, C-10), 109.5 [1 C, C$(CH_3)_2$], 127.6 and 128.4 (arom. CH), 138.2 (arom. C). − $C_{28}H_{46}O_{11}$ (558.67): calcd. C 60.20, H 8.30; found C 60.01, H 8.51.

4,8,12,16-Tetraoxanonadecane-1,2,6,10,14,18,19-heptaol (4): Palladium on activated charcoal (10% Pd, 650 mg), was added to a solution of **10** (6.5 g, 11.6 mmol) in methanol (150 mL). After stirring at room temperature under hydrogen for 4 d, the mixture was filtered through Celite® to remove the catalyst. The filtrate was concentrated and purified by column chromatography (dichloromethane/methanol, 8:2) to yield **4** (2.6 g, 66%). − TLC (dichloromethane/methanol, 8:2): R_f = 0.18. − ^{1}H NMR (CD_3OD): δ = 3.61−3.76 (m, 20 H, H-1, H-3, H-5, H-7, H-9, H-11, H-13, H-15, H-17 and H-19), 3.93 (m, 2 H, H-2 and H-18), 4.06 (m, 3 H, H-6, H-10 and H-14). − ^{13}C NMR (CD_3OD): δ = 64.3 (2 C, C-1 and C-19), 70.6 (3 C, C-6, C-10 and C-14), 72.2 (2 C, C-2 and C-18), 73.8 (8 C, C-3, C-5, C-7, C-9, C-11, C-13, C-15 and C-17). − $C_{15}H_{32}O_{11}$ (338.41): calcd. C 46.39, H 8.30; found C 46.01, H 8.59.

1,2-*O*-Isopropylidene-3-*O*-trifluoromethanesulfonylglycerol (13b): To a cooled solution (−15 °C) of solketal (400 mg, 3 mmol) and triethylamine (2.2 equiv.) in dry dichloromethane, was added dropwise triflic anhydride (1.5 equiv.), from a previously rigorously dried syringe. The mixture was stirred for 30 min, keeping the temperature below −10 °C; then the solution was washed with a saturated, aqueous solution of $NaHCO_3$ and with water. The aqueous phases were extracted twice with dichloromethane, the organic phases were collected, dried with $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. The brownish-purple crude product **13b** (684 mg, 86%) was used without further purification and could be kept for a couple of days in a freezer. − ^{1}H NMR ($CDCl_3$): δ = 1.38 and 1.46 (2 s, 6 H, 2 CH_3 *i*Pr), 3.87 (dd, $J_{2,3b}$ = 4.8 Hz, 1 H, H-3b), 4.14 (dd, $J_{2,3a}$ = 6.2 Hz, $J_{3a,3b}$ = 9.0 Hz, 1 H, H-3a), 4.35−4.48 (m, 3 H, H-2, H-1a and H-1b). − MS (IS, MeOH + 5−10% H_2O): *m*/*z* = 265.0 $[M + H]^+$.

6,6′-*O*-Benzylidene-5-hydroxymethyl-1,2-*O*-isopropylidene-4-oxahexane-1,2,6-triol (14): 5-Hydroxy-2-phenyl-1,3-dioxane (**11**) (164 mg, 0.91 mmol) was added to a suspension of NaH (2 equiv.) in DMF. The solution was stirred at room temperature for 30 min to permit the formation of the alcoholate, and TBAB (0.02 equiv.) was added. The solution was stirred for 30 min more, and solketal tosylate (1.2 equiv.) was added. The mixture was stirred at room temperature for 24 h, then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluent petroleum ether/AcOEt (8:2), to give **14** as a colourless gum (40%). − ^{1}H NMR ($CDCl_3$): δ = 1.38 and 1.44 (2 s, 6 H, CH_3), 3.53−3.82 (m, 6 H, H-1b, H-3a, H-3b, H-5, H-6ax and H-6′ax), 4.06 (dd, $J_{1a,1b}$ = 8.3 Hz, $J_{1a,2}$ = 6.4 Hz, 1 H, H-1a), 4.24 (m, 1 H, H-2), 4.36−4.46 (m, 2 H, H-6eq and H-6′eq), 5.40 (s, 1 H, −CH−Ph), 7.35−7.50 (m, 5 H, H-arom). − MS (IS, MeOH + 5−10% H_2O): *m*/*z* = 295.0 $[M + H]^+$, 317.0 $[M + Na]^+$, 333.0 $[M + K]^+$. − $C_{16}H_{23}O_5$: calcd. 295.1545; found 295.1551 (HR-ESI-TOF-MS).

1,3-Di-*O*-benzylglycerol [6972−79−8] (12). − Method A: To a stirred suspension of NaH (60% in mineral oil, 12.78 g, 319.6 mmol) in dry THF (50 mL), was added dropwise benzyl alcohol (29.1 mL, 281.3 mmol). The mixture was stirred at room temperature and tetra-*n*-butylammonium bromide (TBAB) (0.82 g, 2.54 mmol) was added. The mixture was cooled to 0 °C and epichlorohydrin (10 mL, 127.8 mmol) was added dropwise. The mixture was stirred overnight at room temperature and the solvent was evaporated. The residue was dissolved in dichloromethane, then washed 3 times with water. The organic phase was dried with $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. − **Method B:** To a vigorously stirred mixture of benzyl alcohol (1.0 mol), tetra-*n*-butylammonium iodide (0.05 mol), KOH (0.75 mol) and water (3 mL), was added dropwise epichlorohydrin (0.25 mol). The mixture was then stirred at 80 °C for 48 h. After cooling, it was diluted with dichloromethane and water. After decantation, the organic phase was repeatedly washed with water, dried with $MgSO_4$ and filtered, and the filtrate concentrated under reduced pressure. In both cases, the residue was purified by kugelrohr distillation (3−4 Torr): first fraction (60−120 °C): excess benzyl alcohol; second fraction (160−210 °C): expected product **12** as a pale yellow oil (method A: 70%; method B: 80%). − ^{1}H NMR ($CDCl_3$): δ = 3.48−3.62 (m, 4 H, H-1a, H-1b, H-3a and H-3b), 3.99−4.06 (m, 1 H, H-2), 4.56 (s, 4 H, 2 CH_2−Ph), 7.30−7.37 (m, 10 H, H_{Ar} Bn). − MS (Ionspray®, MeOH + 5−10% H_2O): *m*/*z* = 273.0 $[M + H]^+$, 290.0 $[M + NH_4]^+$, 295.0 $[M + Na]^+$.

6-*O*-Benzyl-5-benzyloxymethyl-1,2-*O*-isopropylidene-4-oxahexane-1,2,6-triol (15): To a suspension of NaH (60% in mineral oil, 3.52 g, 88.1 mmol) in DMF (200 mL) was added dropwise 1,3-dibenzylglycerol (20.0 g, 73.5 mmol). The mixture was stirred for 30 min at room temperature and TBAB (4.73 g, 14.7 mmol) was added. The mixture was stirred for additional 30 min, and solketal tosylate **13a** (25.23 g, 88.1 mmol) was added in one portion. The stirred mixture was heated at 100 °C for 40 h, then allowed to cool and concentrated to dryness. The residue was partitioned between dichloromethane and water. The organic phase was successively washed with 5% aqueous $NaHCO_3$ and (twice) with water. The organic phase was dried with $MgSO_4$ and filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography, using petroleum ether/AcOEt (8:2 then 7:3) as eluent, to give 15.74 g (55%) of pure **15** as a pale yellowish oil. − $[\alpha]_D$ = 0 (*c* = 1.0; $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 1.37 and 1.42 (2 s, 6 H, 2 CH_3), 3.58−3.64 (m, 5 H, H-1b, H-6a, H-6b, H-6′a and H-6′b), 3.72−3.80 (m, 3 H, H-1a, H-3a and H-3b), 4.05 (dd, $J_{5,6a}$ = $J_{5,6'a}$ = 6.4 Hz, $J_{5,6b}$ = $J_{5,6'b}$ = 8.3 Hz, 1 H, H-5), 4.27 (m, 1 H, H-2), 4.55 (s, 4 H, 2 CH_2−Ph), 7.31−7.35 (m, 10 H, H_{Ar} Bn). − ^{13}C NMR ($CDCl_3$): δ = 25.8 and 27.2 (2 C, CH_3 *i*Pr), 67.4, 70.6 and 72.0 (4 C, **C**H_2−O-, C-1, C-3, C-6 and C-6′), 73.8 (2 C, 2 **C**H_2 Bn), 75.2 and 79.1 (2 C, **C**H, C-2 and C-5), 109.7 (1 C, quaternary C *i*Pr), 128.0 and 128.8 (10 C, C_{Ar} Bn), 138.6 (2 C, quaternary C_{Ar} Bn). − MS (Ionspray®, MeOH + 5−10% H_2O): *m*/*z* = 387.5 $[M + H]^+$, 404.5 $[M + NH_4]^+$, 409.5 $[M + Na]^+$. − $C_{23}H_{31}O_5$: calcd. 387.2171; found 387.2159 (HR-ESI-TOF-MS).

6-*O*-Benzyl-5-benzyloxymethyl-4-oxahexane-1,2,6-triol (16): A solution of compound **15** (5.0 g, 12.94 mmol) in dry methanol (50 mL)

was refluxed with Dowex 50WX-8 200 ion exchange resin (H^+) (150 mg/g) for 16 h. The resin was filtered off and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography, using petroleum ether/AcOEt (3:7 to 1:9) as eluent, to yield 3.75 g (84%) of pure **16** as a colourless syrup. − $[\alpha]_D$ = 0 (*c* = 1.0; $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 3.52−3.83 (m, 10 H, H-1a, H-1b,H-2, H-3a, H-3b, H-5, H-6a, H-6b, H-6′a and H-6′b), 4.55 (s, 4 H, 2 CH_2−Ph), 7.29−7.36 (m, 10 H, H_{Ar} Bn). − ^{13}C NMR ($CDCl_3$): δ = 64.1, 70.6 and 73.0 (4 C, CH_2, C-1, C-3, C-6 and C-6′), 73.9 (2 C, 2 CH_2 Bn), 71.2 and 79.5 (2 C, CH, C-1 and C-5), 128.2 and 128.9 (10 C, C_{Ar} Bn), 138.1 (2 C, quaternary C_{Ar} Bn). − MS (Ionspray®, MeOH + 5−10% H_2O): *m*/*z* = 347.0 $[M + H]^+$, 364.0 $[M + NH_4]^+$, 369.0 $[M + Na]^+$. − $C_{20}H_{27}O_5$: calcd. 347.1858; found 347.1894 (HR-ESI-TOF-MS).

5-Hydroxymethyl-1,2-*O*-isopropylidene-4-oxahexane-1,2,6-triol (17): A solution of compound **15** (10.0 g, 25.87 mmol) in dry ethyl acetate (100 mL) was treated with palladium on charcoal (10%) (1.0 g, 10 wt-%) under H_2 (1 bar) for 20 h. The catalyst was filtered off through a pad of Celite® and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography, using ethyl acetate as eluent, to yield 3.91 g (73%) of **17** (pale yellowish syrup). − ^{1}H NMR (MeOD): δ = 1.32 and 1.37 (2 s, 6 H, 2 CH_3 *i*Pr), 3.42 (dd, $J_{5,6a}$ = $J_{5,6'a}$ = 5.0 Hz, $J_{5,6b}$ = $J_{5,6'b}$ = 10.1 Hz, 1 H, H-5), 3.57 (d, 2 H, H-3a and H-3b), 3.63 (ddd, $J_{6,OH}$ = 1.6 Hz, $J_{6a,6b}$ = 10.1 Hz, 4 H, H-6a, H-6b, H-6′a and H-6′b), 3.74 (dd, 1 H, H-1b), 4.04 (dd, $J_{1a,1b}$ = 8.3 Hz, 1 H, H-1a), 4.26 (dddd, $J_{1a,2}$ = 6.4 Hz, $J_{1b,2}$ = 6.3 Hz, $J_{2,3}$ = 5.6 Hz, 1 H, H-2). − ^{13}C NMR (MeOD): δ = 26.8 and 28.2 (2 C, 2 CH_3 *i*Pr), 63.7 (2 C, C-6 and C-6′), 68.8 (1 C, C-1), 73.5 (1 C, C-3), 77.6 (1 C, C-2), 84.4 (1 C, C-5); 111.7 (1 C, quaternary C *i*Pr). − MS (Ionspray®, MeOH + 5−10% H_2O): *m*/*z* = 207.0 $[M + H]^+$, 224.5 $[M + NH_4]^+$, 229.0 $[M + Na]^+$, 245.0 $[M + K]^+$.

1,5-Anhydro-D-galactitol [3971−48−0] (21b): 2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-galactitol (**20b**) was deacetylated overnight at room temperature according to Zemplen's methodology, with a solution of sodium methoxide in methanol. The solution was made neutral using Amberlite® IR-120 (H^+ form), and the resin was removed by filtration and the solvents evaporated under reduced pressure. The crude product was purified by silica gel column chromatography, using a CH_2Cl_2/MeOH (20−30%) mixture as eluent. The residue was recrystallised from ethanol to give **21b** as a colourless solid (90%). − $[\alpha]_D$ = + 76 (*c* = 1.0; H_2O) (ref.[20]) + 76.6; *c* = 1.08; H_2O; + 77; +76 to +77; + 80; *c* = 0.8; H_2O). − M.p. 121−122 °C (ref.[20]) 114−115 °C; 113−115 °C; 115−117 °C; 126−128 °C). − ^{1}H NMR (D_2O): δ = 3.10 (dd, $J_{1a,1b}$ = $J_{1b,2}$ = 10.8 Hz, 1 H, H-1b), 3.45−3.63 (m, 2 H, H-3 and H-5), 3.60 (s, 2 H, H-6a and H-6b), 3.73 (ddd, 1 H, H-2), 3.85 (d, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ < 1.0 Hz, 1 H, H-4), 3.91 (dd, $J_{1a,2}$ = 5.5 Hz, $J_{1a,1b}$ = 10.8 Hz, 1 H, H-1a). − ^{13}C NMR (D_2O): δ = 61.7 (C-6), 67.0 (C-2), 69.4 (C-4), 69.5 (C-1), 74.4 and 79.7 (C-3 and C-5). − MS (IS, MeOH + 5−10% H_2O): *m*/*z* = 165.0 $[M + H]^+$, 187.0 $[M + Na]^+$.

1,5-Anhydro-3,4-*O*-isopropylidene-D-galactitol [143697−37−4] (22b): 1,5-Anhydro-D-galactitol (**21b**) (5 g, 30.5 mmol) was suspended in 2,2-dimethoxypropane (10 mL/mmol) containing a catalytic amount of camphorsulfonic acid. The mixture was vigorously stirred under inert atmosphere for 48 h at room temperature to reach equilibrium. The reaction was stopped by addition of a few drops of triethylamine, and the mixture was concentrated under reduced pressure and the crude residue dissolved in a MeOH/H_2O (10:1) mixture (50 mL/g of crude product) containing a catalytic amount of acetic acid. The solution was stirred at 50 °C for 30 min. After addition of a few drops of triethylamine, concentration under vacuum and coevaporation with toluene, the crude product was purified by silica gel column chromatography with AcOEt as eluent. The solid **22b** was recrystallised from an AcOEt/cyclohexane (1:1) mixture to give 89% of a colourless solid. − $[\alpha]_D$ = + 65 (*c* = 1.0; $CHCl_3$) (ref.[21]) +73.0). − M.p. 99−100 °C (ref.[21]) 92−93 °C). − ^{1}H NMR ($CDCl_3$): δ = 1.37 and 1.53 (2 s, 6 H, 2 CH_3 *i*Pr), 3.18 (dd, $J_{1b,2}$ = 10.0 Hz, 1 H, H-1b), 3.97 (m, 5 H, H-2, H-3, H-5, H-6a and H-6b), 4.01 (dd, $J_{1a,2}$ = 5.3 Hz, $J_{1a,1b}$ = 11.3 Hz, 1 H, H-1a), 4.21 (dd, $J_{3,4}$ = 5.7 Hz, $J_{4,5}$ = 2.2 Hz, 1 H, H-4). − ^{13}C NMR ($CDCl_3$): δ = 26.6 and 28.5 (2 C, 2 CH_3 *i*Pr), 63.3 (1 C, C-6), 68.4 (1 C, C-1), 74.5 (1 C, C-4), 69.8, 76.7 and 79.9 (3 C, C-2, C-3 and C-5), 110.5 (1 C, quaternary C *i*Pr). − MS (IS, MeOH + 5−10% H_2O): *m*/*z* = 205.0 $[M + H]^+$, 227.0 $[M + Na]^+$.

2,6-Di-*O*-acetyl-1,5-anhydro-3,4-*O*-isopropylidene-D-galactitol [143916−22−7] (23b): 1,5-Anhydro-3,4-di-*O*-isopropylidene-D-galactitol (**22b**) was acetylated in a pyridine/acetic anhydride mixture at room temperature for 20 h. After methanolysis, the solvents were removed under reduced pressure, then coevaporated with toluene, and the crude product was purified by silica gel column chromatography, with a petroleum ether/AcOEt (1:1) mixture as eluent, to yield **23b** quantitatively, as a colourless solid. − $[\alpha]_D$ = + 63 (*c* = 1.0; $CHCl_3$) (ref.[21]) +70.8). − M.p. 100−102 °C (ref.[21]) 87−92 °C). − ^{1}H NMR ($CDCl_3$): δ = 1.34 and 1.53 (2 s, 6 H, 2 CH_3 *i*Pr), 2.09 and 2.11 (2 s, 6 H, 2 CH_3 acetates), 3.21 (dd, 1 H, H-1b), 3.89 (ddd, $J_{4,5}$ = 2.0 Hz, 1 H, H-5), 4.08 (dd, $J_{1a,1b}$ = 11.5 Hz, 1 H, H-1a), 4.18 (dd or ft, 1 H, H-3), 4.22 (dd, $J_{3,4}$ = 5.4 Hz, 1 H, H-4), 4.24 (dd, $J_{5,6b}$ = 7.9 Hz, 1 H, H-6b), 4.37 (dd, $J_{5,6a}$ = 3.9 Hz, $J_{6a,6b}$ = 11.9 Hz, 1 H, H-6a), 4.97 (ddd, $J_{1a,2}$ = 5.2 Hz, $J_{1b,2}$ = 9.1 Hz, $J_{2,3}$ = 6.2 Hz, 1 H, H-2). − ^{13}C NMR ($CDCl_3$): δ = 21.3 and 21.4 (2 C, 2 CH_3 acetates), 26.4 and 27.9 (2 C, 2 CH_3 *i*Pr), 64.6 (1 C, C-6), 65.5 (1 C, C-1), 70.5 (1 C, C-2), 73.8 (1 C, C-4), 74.0 (1 C, C-5), 75.6 (1 C, C-3), 110.8 (1 C, quaternary C *i*Pr), 170.4 and 171.3 (2 C, 2 quaternary C acetates). − MS (IS, MeOH + 5−10% H_2O): *m*/*z* = 289.0 $[M + H]^+$.

2,6-Di-*O*-acetyl-1,5-anhydro-D-galactitol (24b): 1,5-Anhydro-2,6-di-*O*-acetyl-3,4-di-*O*-isopropylidene-D-galactitol (**23b**) (4 g, 13.9 mmol) was dissolved in dry THF. Removal of the isopropylidene moiety was effected in the presence of an acidic resin (Dowex 50WX8−200, H^+ form) at 50−60 °C for 2 h. The resin was then filtered off and the solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography, with a petroleum ether/AcOEt (2:8) mixture as eluent, to yield **24b** as a colourless solid (82%) . − $[\alpha]_D$ = + 30 (*c* = 1.0; $CHCl_3$). − M.p. 108−110 °C. − ^{1}H NMR ($CDCl_3$): δ = 2.08 and 2.09 (2 s, 6 H, 2 CH_3 acetates), 3.18 (dd, $J_{1b,2}$ = $J_{1a,1b}$ = 11.0 Hz, 1 H, H-1b), 3.56−3.67 (m, 2 H, H-3 and H-5), 3.96 (br. d, $J_{3,4}$ = 2.4 Hz, 1 H, H-4), 4.06 (dd, $J_{1a,2}$ = 6.0 Hz, $J_{1a,1b}$ = 11.0 Hz, 1 H, H-1a), 4.22 (dd, $J_{5,6b}$ = 7.2 Hz, 1 H, H-6b), 4.33 (dd, $J_{5,6a}$ = 5.0 Hz, $J_{6a,6b}$ = 11.8 Hz, 1 H, H-6a), 5.05 (ddd, 1 H, H-2). − ^{13}C NMR ($CDCl_3$): δ = 21.3 and 21.4 (2 C, 2 CH_3 acetates), 64.1 (1 C, C-6), 67.2 (1 C, C-1), 69.8 (1 C, C-4), 70.6 (1 C, C-2), 73.2 (1 C, C-3), 77.0 (1 C, C-5), 171.6 and 172.0 (2 C, quaternary C acetates). − MS (IS, MeOH + 5−10% H_2O): *m*/*z* = 249.0 $[M + H]^+$, 266.0 $[M + NH_4]^+$, 271.0 $[M + Na]^+$. − $C_{10}H_{17}O_7$: calcd. 249.0974; found 249.0952 (HR-ESI-TOF-MS).

1,5,6-Triacetoxy-2-acetoxymethyl-3-oxahexane (25): The protected 1,5-anhydrohexitol **24b** (2.2 g, 8.9 mmol) was treated with a 0.1 M aqueous solution of sodium periodate (5 equiv., 450 mL) over 30 min at room temperature. The mixture was then concentrated to dryness and the crude residue was dissolved in 400 mL of water and treated with 6 equiv. of sodium borohydride. After 30 min of stirring at room temperature, the excess of $NaBH_4$ was decomposed

by addition of Amberlite® IR-120 (H^+ form). The solution was concentrated to dryness to yield the crude *prim-sec*-type dimer, which was acetylated overnight at room temperature using Ac_2O/pyridine. After methanolysis, the solvents were evaporated and co-evaporated with toluene, and the residue was extracted with dichloromethane. The organic phase was washed with a saturated aqueous solution of sodium thiosulfate (in order to remove traces of iodine) and with water. The organic phase was then dried with $MgSO_4$ and filtered, and the filtrate concentrated under reduced pressure. The crude product was purified by silica gel column chromatography, with a petroleum ether/AcOEt (6:4) mixture as eluent, to give the acetylated *prim-sec* dimer **25** as a colourless oil (quantitative). − ^{1}H NMR ($CDCl_3$): δ = 2.04 and 2.06 (2 s, 12 H, 4 CH_3 acetates), 3.67−3.79 (m, 3 H, H-6a, H-6b and H-2), 4.03−4.30 (m, 6 H, H-4a, H-4b, H-1a, H-1b, H-1′a and H-1′b), 5.12 (ddd, 1 H, H-5). − ^{13}C NMR ($CDCl_3$): δ = 21.1 and 21.3 (4 C, 4 CH_3 acetates), 62.9 (1 C, C-4), 63.3 and 63.4 (2 C, C-1 and C-1′), 68.8 (1 C, C-6), 70.6 (1 C, C-5), 76.6 (1 C, C-2), 170.6 and 171.0 (4 C, 4 quaternary C acetates). − MS (IS, MeOH + 5−10% H_2O): *m*/*z* = 275.0 [M − AcOH + H]$^+$, 334.0 [M + H]$^+$, 357.0 [M + Na]$^+$. − $C_{14}H_{22}O_9Na$: calcd. 357.1162; found 357.1178 (HR-ESI-TOF-MS).

2-Hydroxymethyl-3-oxahexane-1,5,6-triol (18): The acetylated *prim-sec* dimer **25** was deacetylated with a sodium methoxide solution in methanol at room temperature over 20 h. The solution was then made neutral with Amberlite® IR-120 (H^+ form) and the resin was removed by filtration. The solvents were evaporated under reduced pressure and the residue was purified by silica gel column chromatography, using a ternary eluent AcOEt/MeOH/H_2O (80:15:5), to give the *prim-sec* dimer **18** as a colourless gum (quantitative). − $[\alpha]_D$ = −5 (*c* = 1.0; H_2O; **18b**). − ^{1}H NMR (D_2O): δ = 3.56−3.77 (m, 9 H, H-1a, H-1b, H-1′a, H-1′b, H-2, H-4a, H-4b, H-6a and H-6b), 3.86−3.96 (m, 1 H, H-5). − ^{13}C NMR (D_2O): δ = 61.0 (2 C, 2 CH_2, C-1 and C-1′), 62.9 (1 C, CH_2, C-6), 71.0 (1 C, CH_2, C-4), 71.1 (1 C, CH, C-5), 81.4 (1 C, CH, C-2). − MS (IS, MeOH + 5−10% H_2O): *m*/*z* = 167.0 [M + H]$^+$,189.0 [M + Na]$^+$, 333.0 [2 M + H]$^+$, 355.0 [2 M + Na]$^+$. − $C_6H_{15}O_5$: calcd. 167.0919; found 167.0926 (HR-ESI-TOF-MS).

2,5-Anhydro-1,3:4,6-di-*O*-isopropylidene-L-iditol [80599−64−0] (26a): To a suspension of 50 g of D-sorbitol in xylenes (250 mL) was added methanesulfonic acid (catalytic amount; 50 μL), and the mixture was refluxed for 2.5 h. The water formed was collected in a Dean-Stark apparatus. The mixture was then allowed to cool and was decanted. The xylenes phase contained dianhydro derivatives, while the residue contained the desired product (among other monoanhydro derivatives). This residue was dissolved in anhydrous acetone (300 mL) containing sulfuric acid (0.5 mL). The mixture was stirred until complete dissolution (ca. 20 h). The reaction was stopped by addition of an excess of sodium bicarbonate in solution in water (4 g in 50 mL water). The inorganic white precipitate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was partitioned between dichloromethane and water. The organic phase was extracted three times with dichloromethane. The organic layers were washed three times with water, combined, dried with $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography with CH_2Cl_2 as eluent and was recrystallised from cyclohexane to give **26a** as glittering white plates (2.04 g, 3%). − $[\alpha]_D$ = +22 (*c* = 1.0; $CHCl_3$) (ref.[25]) +20 to +24; $CHCl_3$). − M.p. 132−134 °C (ref.[25]) 128−130). − ^{1}H NMR (C_6D_6): δ = 1.10 and 1.40 (2 s, 12 H, CH_3 *i*Pr), 3.60 (dd, $J_{1a,1b}$ = $J_{6a,6b}$ = 13.3 Hz, $J_{1b,2}$ = $J_{5,6b}$ = 3.3 Hz, 2 H, H-1b and H-6b), 3.93−3.97 (m, 4 H, H-1a, H-2, H-5 and H-6a), 4.11 (bd, $J_{2,3}$ = $J_{4,5}$ = 2.5 Hz, $J_{3,4}$ < 1.0 Hz, 2 H, H-3 and H-4). − ^{13}C NMR (C_6D_6): δ = 19.8 and 29.5 (CH_3 *i*Pr), 61.8 (C-1 and C-6), 73.4 (C-2 and C-5), 76.0 (C-3 and C-4), 97.6 (quaternary C *i*Pr). − MS (IS, MeOH + 5−10% H_2O): *m*/*z* = 245.0 [M + H]$^+$, 262.0 [M + NH_4]$^+$.

2,5-Anhydro-L-iditol (27a) [28218−55−5]: Hydrolysis of the isopropylidene groups of **26a** was effected using an acidic resin (Amberlite® IR-120, H^+ form) in solution in a THF/water (2:1) mixture at room temperature for 20 h. The resin was then filtered off and the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, with CH_2Cl_2/MeOH (10 to 20%) as eluent, to give **27a** as a yellowish oil (79%). − ^{13}C NMR ([D_6]DMSO): δ = 59.7 (C-1 and C-6), 77.1 (C-3 and C-4), 81.5 (C-2 and C-5). − MS (IS, MeOH + 5−10% H_2O): *m*/*z* = 165.0 [M + H]$^+$, 187.0 [M + Na]$^+$.

1,3,4,6-Tetra-*O*-acetyl-2,5-anhydro-D-mannitol [65729−88−6] (26b): D-Glucosamine hydrochloride (4 g, 18.5 mmol) was stirred in water (11 mL/g) for 20 h at room temperature to reach mutarotational equilibrium. The solution was cooled to 0 °C and 3 equiv. of $NaNO_2$ were added in one portion. While stirring and keeping the temperature below 2 °C, conc. acetic acid (3 equiv.) was added dropwise to form nitrous acid in situ. After additional 2 h of stirring at 0 °C, the temperature was allowed to rise to room temperature under a flow of argon, in order to remove excess nitrous acid. The solution was concentrated to dryness and crude 2,5-anhydro-D-mannose was reduced by sodium borohydride (4 equiv.) in water (10 mL/g) (addition in portions at 0 °C) at room temperature for 1 h. The excess $NaBH_4$ was decomposed using Amberlite® IR-120 (H^+ form), the resin was filtered off, and the filtrate was concentrated under reduced pressure. For better purification, the crude 2,5-anhydro-D-mannitol (**27b**) was acetylated overnight at room temperature, using acetic anhydride/pyridine. After methanolysis, concentration and coevaporation of the solvents with toluene, the product was purified by silica gel column chromatography, with a petroleum ether/AcOEt (6:4) mixture as eluent, to give 80% of **26b** (from D-glucosamine hydrochloride) as a colourless oil. − $[\alpha]_D$ = +26 (*c* = 1.0; $CHCl_3$) (ref.[26] +27.1; *c* = 4.2; $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 2.09 (s, 12 H, 4 CH_3 acetates), 4.24 (s, 6 H, H-1a, H-1b, H-2, H-5, H-6a and H-6b), 5.15 (d, 2 H, H-3 and H-4). − ^{13}C NMR ($CDCl_3$): δ = 21.2 (4 C, 4 CH_3 acetates), 63.5 (2 C, CH_2, C-1 and C-6), 78.5 (2 C, CH, C-3 and C-4), 81.5 (2 C, CH, C-2 and C-5), 170.3 and 171.0 (2 C, quaternary C acetates). − MS (IS, MeOH + 5−10% H_2O): *m*/*z* = 333.5 [M + H]$^+$, 355.0 [M + Na]$^+$. − $C_{14}H_{21}O_9$: calcd. 333.1186; found 333.1174 (HR-ESI-TOF-MS).

2,5-Anhydro-D-mannitol [41107−82−8] (27b): Compound **26b**, dissolved in methanol, was deacetylated overnight at room temperature, with a methanolic 1 M sodium methoxide solution. The solution was made neutral with Amberlite® IR-120 (H^+ form); then the resin was removed by filtration and the solvents were evaporated under reduced pressure. The syrupy 2,5-anhydro-D-mannitol was seeded to induce crystallisation and was recrystallised from anhydrous ethanol to yield the desired product **27b** as colourless crystals (90%). − $[\alpha]_D$ = +50 (*c* = 1.0; H_2O) (ref.[26] +58.2; *c* = 1.37; H_2O; +56.7;[26] *c* = 1.0; H_2O). − M.p. 100−102 °C (ref.[14] 100−101 °C; 101−103 °C[26]). − ^{1}H NMR (D_2O): δ = 3.70 (dd, $J_{1b,2}$ = $J_{5,6b}$ = 5.6 Hz, 2 H, H-1b and H-6b), 3.79 (dd, $J_{1a,2}$ = $J_{5,6a}$ = 3.1 Hz, $J_{1a,1b}$ = $J_{6a,6b}$ = 12.4 Hz, 2 H, H-1a and H-6a), 3.90 (m, 2 H, H-2 and H-5), 4.07 (m, $J_{2,3}$ = 7.3 Hz, 2 H, H-3 and H-4). − ^{13}C NMR (D_2O): δ = 61.5 (2 C, C-1 and C-6), 76.7 (2 C, C-3 and C-4), 82.6 (2 C, C-2 and C-5). − MS (IS, MeOH + 5−10%

H_2O): *m/z* = 165.0 $[M + H]^+$, 187.0 $[M + Na]^+$. − $C_6H_{12}NaO_5$: calcd. 187.0582; found 187.0576 (HR-ESI-TOF-MS).

1,5-Diacetoxy-2,4-bis(acetoxymethyl)-3-oxapentane [92373−25−6] (28): 2,5-Anhydro-D-mannitol (**27b**) [or 2,5-anhydro-L-iditol (**27a**)] (150 mg, 0.914 mmol) was treated with a 0.1 M aqueous solution of sodium periodate (5 equiv., 50 mL). The mixture was stirred for 2 h at room temperature, then concentrated to dryness. The residue was dissolved in water for the reduction step: A solution of the crude dialdehyde in 7.6 mL of water was treated with 6 equiv. of sodium borohydride. After 16 h of stirring at room temperature, the excess of $NaBH_4$ was decomposed using Amberlite® IR-120 (H^+ form). The resin was removed by filtration and the filtrate concentrated under reduced pressure to yield the crude *sec*-*sec*-type dimer, which was acetylated overnight at room temperature in Ac_2O/pyridine. After methanolysis, the solvents were removed under reduced pressure and the residue was extracted with dichloromethane. The organic phase was washed with a saturated, aqueous solution of sodium thiosulfate (in order to remove any trace of iodine), then with water. The organic phase was dried with $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography, with a petroleum ether/AcOEt (6:4) mixture as eluent, quantitatively yielded **28** as a pale yellowish oil. − ^{1}H NMR ($CDCl_3$): δ = 2.06 (s, 12 H, CH_3 acetates), 3.85−3.94 (m, 2 H, CH, H-2 and H-4), 4.11 (d, *J* = 5.3 Hz, 8 H, CH_2, H-1a, H-1b, H-1′a, H-1′b, H-5a, H-5b, H-5′a and H-5′b). − ^{13}C NMR ($CDCl_3$): δ = 21.1 (4 C, 4 CH_3 acetates), 63.9 (4 C, CH_2, C-1, C-1′, C-5 and C-5′), 76.0 (2 C, CH, C-2 and C-4), 171.0 (4 C, 4 quaternary C acetates). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 275.0 $[M - AcOH + H]^+$, 335.0 $[M + H]^+$, 352.0 $[M + NH_4]^+$, 357.0 $[M + Na]^+$. − $C_{14}H_{23}O_9$: calcd. 335.1342; found 335.1314 (HR-ESI-TOF-MS).

Di-2-glyceryl Ether or 2,4-Bis(hydroxymethyl)-3-oxapentane-1,5-diol [100450−00−8] (29): The *sec*-*sec* dimer **28** was deacetylated overnight at room temperature, with a 1 M sodium methoxide solution in methanol. The solution was made neutral with Amberlite® IR-120 (H^+ form) and the resin was removed by filtration. The solvents were evaporated under reduced pressure and the residue was purified by silica gel column chromatography, with a ternary eluent AcOEt/MeOH/H_2O (80:15:5), to give **29** as a colourless solid (quantitative). − M.p. 76−78 °C. − ^{1}H NMR (D_2O): δ = 3.61−3.76 (m, 10 H, H-1a, H-1b, H-1′a, H-1′b, H-2, H-4, H-5a, H-5b, H-5′a and H-5′b). − ^{13}C NMR (D_2O): δ = 61.6 (4 C, CH_2, C-1, C-1′, C-5 and C-5′), 80.6 (2 C, CH, C-2 and C-4). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 167.0 $[M + H]^+$, 189.0 $[M + Na]^+$. − $C_6H_{14}NaO_5$: calcd. 189.0739; found 189.0718 (HR-ESI-TOF-MS). − $C_6H_{14}O_5$ (166.18): calcd. C 43.37, H 8.49, O 48.14; found C 43.60, H 8.44, O 48.29; H_2O, 0.69 (hygroscopic).

1,9-Di-*O*-benzyl-2,8-bis(benzyloxymethyl)-3,7-dioxanonan-5-ol (30): 1,3-Di-*O*-benzylglycerol (**12**) (1 equiv., 32.7 g, 120 mmol), tetra-*n*-butylammonium iodide (0.05 equiv., 2.22 g), KOH (0.75 equiv., 5.06 g) and H_2O (0.4 mL) were placed in a three-necked flask equipped with a condenser, a thermometer and a dropping funnel. The mixture was vigorously stirred while adding epichlorohydrin (0.25 equiv., 2.4 mL) dropwise. The mixture was stirred at 60−70 °C for 3 d, then allowed to cool and diluted with dichloromethane. The solution was washed three times with water, the organic phase was dried with $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. The purification of the crude product by silica gel column chromatography, with a petroleum ether/AcOEt (7:3) mixture as eluent, yielded 80% of pure **30** as a pale yellowish oil. − ^{1}H NMR ($CDCl_3$): δ = 3.49−3.84 (m, 14 H, H-1a, H-1b, H-1′a, H-1′b, H-2, H-4a, H-4b, H-6a, H-6b, H-8, H-9a, H-9b, H-9′a and H-9′b), 3.94−4.12 (m, 1 H, H-5), 4.56 (s, 8 H, C*H*$_2$ Ph), 7.29−7.42 (m, 20 H, H−Ar). − ^{13}C NMR ($CDCl_3$): δ = 71.2 (1 C, CH, C-5), 72.5 and 73.2 (6 C, CH_2, C-1, C-1′, C-4, C-6, C-9 and C-9′), 74.7 (4 C, CH_2 Ph), 80.2 (2 C, CH, C-2 and C-8), 129.0 and 129.7 (20 C, C-Ar), 139.3 (4 C, quaternary C-Ar). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 602.0 $[M + H]^+$, 619.0 $[M + NH_4]^+$. − $C_{37}H_{45}O_7$: calcd. 601.3165; found 601.3181 (HR-ESI-TOF-MS).

2,8-Bis(hydroxymethyl)-3,7-dioxanonan-1,5,9-triol (32). − Method A: Compound **30** (2.0 g, 3.33 mmol) in methanol solution (50 mL) was treated with 10% palladium on charcoal (10 wt%) under hydrogen at atmospheric pressure and room temperature for 20 h. The catalyst was removed by filtration through Celite®, and the solvent was evaporated under reduced pressure. − **Method B:** Compound **30** (30.0 g, 49.94 mmol), dissolved in a mixture of 60 mL of glacial acetic acid and 140 mL of acetic anhydride, was cooled in an ice bath while stirring. An ice-cold mixture of concentrated sulfuric acid (8 mL), glacial acetic acid (60 mL) and acetic anhydride (140 mL) was added dropwise over a period of 2−3 h. The solution was then allowed to come to room temperature and was stirred for 14 h. The mixture was cooled to 0 °C, poured onto ice and vigorously stirred until complete melting of the ice. Dichloromethane was added and the mixture was decanted. The organic phase was washed successively with water and a saturated solution of sodium bicarbonate, dried with magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The fully acetylated compound **31** was finally deacetylated overnight at room temperature according to the Zemplen procedure, using sodium methoxide in methanol, after which the solution was neutralised using Amberlite® IR-120 (H^+). The resin was filtered off and the filtrate was concentrated under reduced pressure. In both cases, the crude product **32** was purified by silica gel column chromatography, using ternary AcOEt/MeOH/H_2O (70:25:5) as eluent. − Yield: 69%. − Aspect: colourless oil. − ^{1}H NMR (D_2O): δ = 3.57−3.81 (m, 14 H, H-1a, H-1b, H-1′a, H-1′b, H-2, H-4a, H-4b, H-6a, H-6b, H-8, H-9a, H-9b, H-9′a and H-9′b, 4.02−4.06 (m, 1 H, H-5). − ^{13}C NMR (D_2O): δ = 61.0 and 71.1 (6 C, **C**H_2, C-1, C-1′, C-4, C-6, C-9 and C-9′), 70.0 (1 C, CH, C-5), 81.4 (2 C, CH, C-2 and C-8). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 241.0 $[M + H]^+$, 263.0 $[M + Na]^+$, 503.5 $[2 M + Na]^+$. − $C_9H_{21}O_7$: calcd. 241.1229; found 241.1242 (HR-ESI-TOF-MS).

6,8-bis(hydroxymethyl)-4,7-dioxanon-1-en-9-ol (33): To a suspension of NaH (1.26 g, 31.59 mmol) in DMF (200 mL) was added the *sec*-*sec* dimer **29** (5.0 g, 30.09 mmol). The mixture was stirred at 0 °C (ice bath) while allyl bromide (1.0 equiv., 2.6 mL, 30.09 mmol) was slowly added from a syringe. The mixture was stirred at room temperature for 18 h, then concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, using a dichloromethane/methanol mixture (2 to 10%) as eluent, to yield 3.031 g (49%) of the pure monoallyl compound **33** as a colourless oil. − ^{1}H NMR ([D_6]DMSO): δ = 3.39 (m, 9 H, H-5a, H-5b, H-5′a, H-5′b, H-8, H-9a, H-9b, H-9′a and H-9′b), 3.57 (m, 1 H, H-6), 3.93 (m, 2 H, H-3a and H-3b), 4.39, 4.65 and 4.72 (3 t, 3 H, OH), 5.19 (m, 2 H, H-1a and H-1b), 5.86 (dddd, 1 H, H-2). − ^{13}C NMR ([D_6]DMSO): δ = 62.2, 62.4 and 62.5 (3 C, C-5′, C-9 and C-9′), 71.1 (1 C, C-5), 72.1 (1 C, C-3), 80.1 (1 C, C-6), 82.3 (1 C, C-8), 117.1 (1 C, C-1), 136.0 (1 C, C-2). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 207.5 $[M + H]^+$, 224.5 $[M + NH_4]^+$, 229.5 $[M + Na]^+$, 413.5 $[2 M + H]^+$, 430.5 $[2 M + NH_4]^+$, 435.5 $[2 M + Na]^+$, 451.5 $[2,M + K]^+$. − $C_9H_{19}O_5$: calcd. 207.1232; found 207.1219 (HR-ESI-TOF-MS).

2,4-Bis(hydroxymethyl)-3,6-dioxanonane-1,8,9-triol (35): To a cooled solution (0 °C) of **33** (500 mg, 2.42 mmol) in water (3 mL) was added dropwise a solution of potassium permanganate (387 mg, 2.45 mmol) in water (8 mL), over a period of 1 h. The brown solution was then stirred at room temperature for additional 2 h, and the brownish, insoluble MnO_2 was filtered off through a pad of Celite®. The colourless filtrate was made neutral with concentrated HCl, and then concentrated to dryness. The residue was acetylated overnight at room temperature in pyridine/acetic anhydride; the resulting mixture was concentrated under reduced pressure. The crude acetylated compound **34** was partitioned between water and dichloromethane, decanted, dried with magnesium sulfate and filtered, and the resulting filtrate was concentrated under reduced pressure. Deacetylation with sodium methoxide in methanol in the usual way gave the crude product, which was purified by silica gel column chromatography, using an ethyl acetate/methanol mixture (20−30%) as eluent, to yield 446 mg (77%) of the pure *sec-sec prim-prim* trimer **35** as a colourless oil. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.24−3.46 (m, 13 H, H-1a, H-1b, H-1′a, H-1′b, H-5a, H-5b, H-5′a, H-5′b, H-7a, H-7b, H-8, H-9a, and H-9b), 3.49−3.59 (m, 2 H, H-2 and H-4), 4.49 and 4.56 (2 t, 2 H, OH), 4.71 and 4.77 (3 t, 3 H, OH). − ^{13}C NMR ([D$_6$]DMSO): δ = 62.1, 62.3, 62. 4 and 62.6 (4 C, C-1, C-1′, C-5′ and C-9), 63.9, 72.1 and 73.6 (1 C, C-5), 71.3 and 79.8 (2 C, C-2 and C-4), 82.1 (1 C, C-8). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 207.5 [M + H]$^+$, 224.5 [M + NH_4]$^+$, 229.5 [M + Na]$^+$, 413.5 [2 M + H]$^+$, 430.5 [2 M + NH_4]$^+$, 435.5 [2 M + Na]$^+$, 451.5 [2 M + K]$^+$. − $C_9H_{20}O_7Na$: calcd. 2631107; found 263.1102 (HR-ESI-TOF-MS).

5-Allyloxy-1,9-bis(benzyloxy)-2,8-bis(benzyloxymethyl)-3,7-dioxanonane (36): To a suspension of NaH (1.0 g, 60% in mineral oil, 24.97 mmol) in DMF (200 mL) was added the protected trimer **30** (10.0 g, 16.65 mmol). The mixture was stirred at 0 °C (ice bath) while allyl bromide (2.0 equiv., 2.9 mL, 33.29 mmol) was added slowly from a syringe. The mixture was stirred at room temperature for 48 h and then concentrated under reduced pressure. The residue was dissolved in water/dichloromethane and the resulting mixture was decanted. The organic layer was dried with $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, using a petroleum ether/ethyl acetate mixture (95:5 to 80:20) as eluent, to yield 4.322 g (41%) of the pure compound **36** as a pale yellow oil. − ^{1}H NMR ($CDCl_3$): δ = 3.65−3.76 (m, 8 H, H-1a, H-1b, H-1′a, H-1′b, H-9a, H-9b, H-9′a and H-9′b), 3.82−3.92 (m, 7 H, H-2, H-4a, H-4b, H-6a, H-6b, H-5 and H-8), 4.24−4.28 (m, 2 H, H-11a and H-11b), 4.62 (s, 8 H, 4 CH_2 Bn), 4.20−5.41 (m, 2 H, H-13a and H-13b), 5.94−6.10 (m, 1 H, H-12), 7.34−7.43 (m, 20 H, H-arom Bn). − ^{13}C NMR ($CDCl_3$): δ = 68.8 (4 C, C-1, C-1′, C-9 and C-9′), 69.0 (2 C, C-4 and C-6), 69.8 (1 C, C-11), 71.9 (4 C, 4 CH_2 Bn), 76.3 (1 C, C-5), 77.4 (2 C, C-2 and C-8), 115.0 (1 C, C-13), 126.2 and 126.9 (20 C, CH arom Bn), 134.1 (1 C, C-12), 137.0 (4 C, quat. C Bn). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 675.5 [M + H]$^+$, 692.5 [M + NH_4]$^+$, 697.5 [M + Na]$^+$.

5-(β-Glyceryloxymethyl)-2-hydroxymethyl-3,6-dioxanonane-1,8,9-triol (39): To a solution of compound **36** (1.0 g, 1.56 mmol) in a water/acetone mixture (10:1) was added a solution of osmium tetroxide (315 μL, 0.03 mmol, 2.5 wt-% in *t*BuOH), followed by a solution of *N*-methylmorpholine *N*-oxide (NMO) (243 μL, 2.341 mmol, 50 wt-% solution in water). The mixture was stirred at room temperature for 24 h and the reaction was quenched by addition of an excess of saturated $Na_2S_2O_5$ solution in water. After 30 min of stirring with ethyl acetate, the mixture was decanted and the organic layer was washed twice with water, dried with $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. Purification by silica gel column chromatography, using petroleum ether/ethyl acetate (4:6), yielded the pure dihydroxylation product **37** (526 mg) in 50% yield. Acetolysis overnight at room temperature of 450 mg of **37** (AcOH 2 × 3.4 mL/Ac_2O 2 × 7.9 mL/H_2SO_4 0.45 mL), followed by the usual workup and deacetylation of crude **38** by transesterification in MeOH with sodium methoxide, yielded the crude tetramer **39**, which was purified using octadecyl-bonded silica (Lichroprep® RP-18, Merck), with CH_3CN/water (95:5) as eluent, to yield 90 mg (74%) of the pure tetramer **39** as a colourless syrup. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.22−3.55 (m, 20 H, H-1a, H-1b, H-1′a, H-1′b, H-1′′a, H-1′′b, H-1′′′a, H-1′′′b, H-2, H-2′, H-4a, H-4′a, H-4b, H-4′b, H-5, H-7a, H-7b, H-8, H-9a and H-9b), 4.48 (br. s, 6 H, OH). − ^{13}C NMR ([D$_6$]DMSO): δ = 61.6 (4 C, C-1, C-1′, C-1′′ and C-1′′′), 63.9 (1 C, C-9), 70.2 (2 C, C-4 and C-4′), 71.5 (1 C, C-8), 72.3 (1 C, C-7), 79.3 (1 C, C-5), 82.7 (2 C, C-2 and C-2′). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 315.0 [M + H]$^+$, 332.5 [M + NH_4]$^+$, 337.5 [M + Na]$^+$. − $C_{12}H_{26}NaO_9$: calcd. 337.1475; found 337.1492 (HR-ESI-TOF-MS).

6,8-bis(hydroxymethyl)-4,7,10-trioxatrideca-1,12-diene (40), 6-Allyloxymethyl-8-hydroxymethyl-4,7-dioxanon-1-en-9-ol (43), 6-Allyloxymethyl-8-hydroxymethyl-4,7,10-trioxatrideca-1,12-diene (46), 6,8-Bis(allyloxymethyl)-4,7,10-trioxatrideca-1,12-diene (49): To a suspension of NaH (3.0 g, 75.22 mmol) in DMF (100 mL) was added the *sec-sec* dimer **29** (5.0 g, 30.09 mmol). The mixture was stirred at 0 °C (ice bath), while allyl bromide (2.5 equiv., 6.5 mL, 75.22 mmol) was added slowly from a syringe. The mixture was stirred at room temperature for 18 h, and then concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, using dichloromethane and then a dichloromethane/methanol mixture (2−10%) as eluent, to yield the diallyl regioisomers **40** (18%) and **43** (25%), the triallyl **46** (37%) and the tetraallyl derivative **49** (5%) as colourless oils:

Diallyl Compound 40: (18%). − ^{1}H NMR ([D$_6$]DMSO): δ = 3.34−3.75 (m, 8 H, H-5a, H-5b, H-5′a, H-5′b, H-9a, H-9b, H-9′a and H-9′b), 3.58 (m, 2 H, H-6 and H-8), 3.92−3.95 (m, 4 H, H-3a, H-3b, H-11a and H-11b), 4.45 (t, 2 H, OH), 5.10−5.28 (m, 4 H, H-1a, H-1b, H-13a and H-13b), 5.78−5.94 (m, 2 H, H-2 and H-12). − ^{13}C NMR ([D$_6$]DMSO): δ = 63.0 (2 C, C-5′ and C-9′ *not allylated*), 72.0 (2 C, C-5 and C-9 *bearing the allyl groups*), 73.0 (2 C, C-3 and C-11), 80.7 (2 C, C-6 and C-8), 117.9 (2 C, C-1 and C-13), 136.8 (2 C, C-2 and C-12). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 247.0 [M + H]$^+$, 269.0 [M + Na]$^+$, 493.5 [2 M + H]$^+$, 510.5 [2 M + NH_4]$^+$, 515.5 [2 M + Na]$^+$.

Diallyl Compound 43: 25%. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.36−3.42 (m, 8 H, H-5a, H-5b, H-5′a, H-5′b, H-9a, H-9b, H-9′a and H-9′b), 3.57 and 3.73 (2 m, 2 H, H-6 and H-8), 3.91−3.95 (m, 4 H, H-3a, H-3b, H-3′a and H-3′b), 4.69 (t, 2 H, OH), 5.10−5.27 (m, 4 H, H-1a, H-1b, H-1′a and H-1′b), 5.77−5.93 (m, 2 H, H-2 and H-2′). − ^{13}C NMR ([D$_6$]DMSO): δ = 62.2 (2 C, C-9 and C-9′ *not allylated*), 71.0 (2 C, C-5 and C-5′ *bearing the allyl groups*), 72.1 (2 C, C-3 and C-3′), 77.7, 78.1, 82.1and 82.7 (2 C, C-6 and C-8), 117.1 (2 C, C-1 and C-1′), 136.0 (2 C, C-2 and C-2′). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 247.0 [M + H]$^+$, 266.0 [M + NH_4]$^+$, 269.0 [M + Na]$^+$, 493.5 [2 M + H]$^+$, 515.5 [2 M + Na]$^+$.

Triallyl Compound 46: 37%. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.36−3.47 (m, 8 H, H-5a, H-5b, H-5′a, H-5′b, H-9a, H-9b, H-9′a and H-9′b), 3.58 (m, 1 H, H-8), 3.74 (m, 1 H, H-6), 3.92−3.94 (m, 6 H, H-3a, H-3b, H-3′a, H-3′b, H-11a and H-11b), 4.44 (t, 1 H, OH), 5.10−5.27 (m, 6 H, H-1a, H-1b, H-1′a, H-1′b, H-13a and

H-13b), 5.78−5.93 (m, 3 H, H-2, H-2′ and H-12). − ^{13}C NMR ([D$_6$]DMSO): δ = 62.1 (1 C, C-9′ *not allylated*), 71.0 (3 C, C-5, C-5′ and C-9 *bearing the allyl groups*), 72.1 (3 C, C-3,C-3′ and C-11), 77.8 (1 C, C-6), 80.1 (1 C, C-8), 117.0 (3 C, C-1, C-1′ and C-13), 136.0 (3 C, C-2,C-2′ and C-12). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 287.0 [M + H]$^+$, 309.0 [M + Na]$^+$, 573.5 [2 M + H]$^+$, 595.5 [2 M + Na]$^+$.

Tetraallyl Compound 49: 5%. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.38−3.46 (m, 8 H, H-5a, H-5b, H-5′a, H-5′b, H-9a, H-9b, H-9′a and H-9′b), 3.75 (m, 2 H, H-6 and H-8), 3.92−4.02 (m, 8 H, H-3a, H-3b, H-3′a, H-3′b, H-11a, H-11b, H-11′a and H-11′b), 5.09−5.29 (m, 8 H, H-1a, H-1b, H-1′a, H-1′b, H-13a, H-13b, H-13′a and H-13′b), 5.78−5.94 (m, 4 H, H-2, H-2′, H-12 and H-12′). − ^{13}C NMR ([D$_6$]DMSO): δ = 71.1 (4 C, C-5, C-5′, C-9 and C-9′), 72.1 (4 C, C-3,C-3′, C-11 and C-11′), 77.9 (2 C, C-6 and C-8), 117.0 (4 C, C-1, C-1′, C-13 and C-13′), 135.9 (4 C, C-2,C-2′, C-12 and C-12′). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 327.5 [M + H]$^+$, 344.5 [M + NH_4]$^+$, 349.0 [M + Na]$^+$.

6,8-Bis(hydroxymethyl)-4,7,10-trioxatridecane-1,2,12,13-tetraol (42): To a cooled solution (0 °C) of compound **40** (400 mg, 1.62 mmol) in water (10 mL) was added dropwise a solution of potassium permanganate (518 mg, 3.28 mmol) in water (10 mL), over a period of 1 h. The brown slurry was then stirred at room temperature for additional 2 h, and the brownish insoluble MnO_2 was filtered off through a pad of Celite®. The colourless filtrate was made neutral with concentrated HCl, and then concentrated to dryness. The residue was acetylated overnight at room temperature in pyridine (15 mL) with Ac_2O (15 mL). The mixture was then concentrated under reduced pressure, the residue was partitioned between water and dichloromethane, and the resulting mixture was decanted. The organic layer was dried with $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, using a petroleum ether/ethyl acetate mixture (50:50 to 40:60) as eluent. The pure acetylated compound **41** was then transesterified overnight at room temperature with sodium methoxide in methanol. After neutralisation with Dowex® 50WX-8 200 ion exchange resin (H$^+$) and removal of the resin, the solution was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, using a dichloromethane/methanol mixture (20−30%) as eluent, to yield 223 mg (44%) of the pure *prim-prim sec-sec prim-prim* tetramer **42** as a colourless oil. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.32−3.42 (m, 16 H, H-1a, H-1b, H-3a, H-3b, H-5a, H-5b, H-5′a, H-5′b, H-9a, H-9b, H-9′a, H-9′b, H-11a, H-11b, H-13a and H-13b), 3.54 (m, 4 H, H-2, H-6, H-8 and H-12), 4.49 and 4.65 (2 br. s, 6 H, OH). − ^{13}C NMR ([D$_6$]DMSO): δ = 62.2 (2 C, C-5′ and C-9′), 63.9 (2 C, C-1 and C-13), 71.3 (2 C, C-2 and C-12), 72.2 and 73.6 (4 C, C-3 and C-11, C-5 and C-9), 79.7 (2 C, C-6 and C-8). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 315.5 [M + H]$^+$, 332.5 [M + NH_4]$^+$, 337.5 [M + Na]$^+$. − $C_{12}H_{26}NaO_9$: calcd. 337.1475; found 337.1485 (HR-ESI-TOF-MS).

6-(α-Glyceryloxymethyl)-8-hydroxymethyl-4,7-dioxanonane-1,2,9-triol (45): To a cooled solution (0 °C) of compound **43** (400 mg, 1.62 mmol) in water (10 mL) was added dropwise a solution of potassium permanganate (518 mg, 3.28 mmol) in water (10 mL), over a period of 1 h. The brown slurry was then stirred at room temperature for additional 2 h, and the brownish insoluble MnO_2 was filtered off through a pad of Celite®. The colourless filtrate was neutralised with concentrated HCl and was concentrated to dryness. The residue was acetylated overnight at room temperature in pyridine (15 mL) with Ac_2O (15 mL). The mixture was then concentrated under reduced pressure, the residue was partitioned between water and dichloromethane, and the resulting mixture was decanted. The organic layer was dried with $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, using a petroleum ether/ethyl acetate mixture (50:50 to 40:60) as eluent. The pure acetylated compound **44** was then transesterified overnight at room temperature with sodium methoxide in methanol. After neutralisation with Dowex® 50WX-8 200 ion exchange resin (H$^+$) and removal of the resin, the solution was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, using a dichloromethane/methanol mixture (20−30%) as eluent, to yield 343 mg (67%) of the pure bis(*prim-prim*) *sec-sec* tetramer **45** as a colourless oil. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.25−3.69 (m, 20 H, H-1a, H-1b, H-1′a, H-1′b, H-2, H-2′, H-3a, H-3b, H-3′a, H-3′b, H-5a, H-5b, H-5′a, H-5′b, H-6, H-8, H-9a, H-9b, H-9′a and H-9′b), 4.39 (t, 2 H, OH), 4.50 (t, 2 H, OH), 4.63 (d, 2 H, OH). − ^{13}C NMR ([D$_6$]DMSO): δ = 62.1 (2 C, C-9 and C-9′), 63.9 (2 C, C-1 and C-1′), 71.3 (2 C, C-2 and C-2′), 72.2 and 73.7 (4 C, C-3 and C-3′, C-5 and C-5′), 77.6 (1 C, C-8), 82.0 (1 C, C-6). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 315.0 [M + H]$^+$, 337.5 [M + Na]$^+$. − $C_{12}H_{26}NaO_9$: calcd. 337.1475; found 337.1475 (HR-ESI-TOF-MS).

6-(α-Glyceryloxymethyl)-8-hydroxymethyl-4,7,10-trioxatridecane-1,2,12,13-tetraol (48): To a cooled solution (0 °C) of compound **46** (400 mg, 1.40 mmol) in a water (10 mL)/acetone (5 mL) mixture was added dropwise a solution of potassium permanganate (669 mg, 4.23 mmol) in water (13 mL), over a period of 1 h. The brown slurry was then stirred at room temperature for additional 2 h, and the brownish insoluble MnO_2 was filtered off through a pad of Celite®. The colourless filtrate was neutralised with concentrated HCl and was concentrated to dryness. The residue was acetylated overnight at room temperature in pyridine (15 mL) with Ac_2O (15 mL). The mixture was then concentrated under reduced pressure, the residue was partitioned between water and dichloromethane, and the resulting mixture was decanted. The organic layer was dried with $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, using a petroleum ether/ethyl acetate mixture (50:50 to 40:60) as eluent. The pure acetylated compound **47** was then transesterified overnight at room temperature with sodium methoxide in methanol. After neutralisation with Dowex® 50WX-8 200 ion exchange resin (H$^+$) and removal of the resin, the solution was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, using a dichloromethane/methanol mixture (20−30%) as eluent, to yield 272 mg (50%) of the pure bis(*prim-prim*) *sec-sec prim-prim* pentamer **48** as a colourless oil. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.25−3.71 (m, 25 H, H-1a, H-1b, H-1′a, H-1′b, H-2, H-2′, H-3a, H-3b, H-3′a, H-3′b, H-5a, H-5b, H-5′a, H-5′b, H-6, H-8, H-9a, H-9b, H-9′a, H-9′b, H-11a, H-11b, H-12, H-13a and H-13b), 4.59 (m, 7 H, OH). − ^{13}C NMR ([D$_6$]DMSO): δ = 62.1 (1 C, C-9′), 63.9 (3 C, C-1, C-1′and C-13), 71.3 (3 C, C-2, C-2′ and C-12), 72.1 and 73.6 (6 C, C-3, C-3′ and C-11, C-5, C-5′ and C-9), 77.6 (1 C, C-8), 79.9 (1 C, C-6). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 389.5 [M + H]$^+$, 411.5 [M + Na]$^+$. − $C_{15}H_{32}NaO_{11}$: calcd. 411.1842; found 411.1846 (HR-ESI-TOF-MS).

6,8-Bis(α-glyceryloxymethyl)-4,7,10-trioxatridecane-1,2,12,13-tetraol (51): To a cooled solution (0 °C) of compound **49** (200 mg, 0.61 mmol) in acetone (5 mL) was added dropwise a solution of potassium permanganate (391 mg, 2.47 mmol) in water (8 mL), over a period of 1 h. The brown slurry was then stirred at room temperature for additional 2 h and the brownish, insoluble MnO_2

was filtered off through a pad of Celite®. The colourless filtrate was neutralised with concentrated HCl and concentrated to dryness. The residue was acetylated overnight at room temperature in pyridine (15 mL) with Ac_2O (15 mL). The mixture was then concentrated under reduced pressure, the residue was partitioned between water and dichloromethane, and the resulting mixture was decanted. The organic layer was dried with $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, using a petroleum ether/ethyl acetate mixture (50:50 to 40:60) as eluent. The acetylated compound **50** was then transesterified overnight at room temperature with sodium methoxide in methanol. After neutralisation with Dowex® 50WX-8 200 ion exchange resin (H^+) and removal of the resin, the solution was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, using a dichloromethane/methanol mixture (20−50%) as eluent, to yield 74 mg (26%) of the bis(*prim-prim*) *sec-sec* bis(*prim-prim*) hexamer **51** as a colourless oil. − ^{13}C NMR ([D_6]DMSO): δ = 63.9 (4 C, C-1, C-1′, C-13 and C-13′), 71.3 (4 C, C-2, C-2′, C-12 and C-12′), 72.1 and 73.7 (8 C, C-3, C-3′, C-11 and C-11′, C-5, C-5′, C-9 and C-9′), 82.1 (2 C, C-6 and C-8). − MS (IS, MeOH + 5−10% H_2O): *m/z* = 485.5 $[M + Na]^+$. − $C_{18}H_{38}NaO_{13}$: calcd. 485.2210; found 485.2209 (HR-ESI-TOF-MS).

1-*O*-Allyl-3-*O*-benzylglycerol (55): Sodium hydride (3.7 g, 93 mmol) was added slowly at 0 °C under nitrogen to a solution of allyl glycidyl ether (10 mL, 84 mmol) and benzyl alcohol (60 mL). After stirring at room temperature for 4 h, the mixture was diluted with dichloromethane (100 mL), washed with a 5% hydrochloric solution until acidic, then washed with a 5% $NaHCO_3$ solution until neutral. The organic layer was dried with $MgSO_4$ and concentrated. Excess benzyl alcohol was removed by distillation with a kugelrohr apparatus. Purification of the residue by column chromatography (petroleum ether/ethyl acetate, 8:2) afforded **55** (16.4 g, 88%). − TLC (petroleum ether/ethyl acetate, 8:2): R_f = 0.27. − ^1H NMR ($CDCl_3$): δ = 3.50 (m, 4 H, H-1 and H-3), 4.00 (dt, 3 H, H-5 and C*H*−OH), 4.54 (s, 2 H, CH_2−C_6H_5), 5.20 (ddd, 2 H, H-7), 5.80 (m, 1 H, H-6), 7.30 (m, 5 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 69.3 (1 C, CH−OH), 71.3 (2 C, C-1 and C-3), 72.3 (1 C, C-5), 73.4 (1 C, *C*H_2−C_6H_5), 117.3 (1 C, C-7), 127.7 and 128.4 (arom. CH), 134.5 (1 C, C-6), 137.9 (arom. C). − $C_{13}H_{18}O_3$ (222.29): calcd. C 70.25, H 8.16; found C 70.53, H 7.92.

6-Benzyloxymethyl-2-iodomethyl-1,4-dioxane (56): *N*-Iodosuccinimide (17.2 g, 76 mmol) was added to a solution of **55** (10 g, 45 mmol) in dry acetonitrile (150 mL). After 3 h of stirring under reflux, the mixture was washed with a satd. aq. $Na_2S_2O_3$ solution. The organic layer was dried with $MgSO_4$, concentrated and purified by column chromatography (petroleum ether/ethyl acetate, 95:5 then 9:1) to yield **56** (6.95 g, 45%). − TLC (petroleum ether/ethyl acetate, 9:1): R_f = 0.37. − ^1H NMR ($CDCl_3$): δ = 3.07 (ddd, 1 H, CH_2−I, *cis* or *trans*), 3.35 (m, 1 H, CH_2−I), 3.17−3.99 (m, 8 H, H-2, H-3, H-5, H-6 and CH_2−OBn), 4.50 (m, 2 H, CH_2−C_6H_5), 7.30 (m, 5 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 2.3 and 3.7 (CH_2−I, *cis* + *trans*), 67.8 and 69.5 (1 C, *C*H_2−OBn), 68.1, 68.3, 68.7 and 70.3 (2 C, *cis and trans* C-3, C-5), 68.7 and 70.7 (1 C *cis and trans*, C-6), 73.4 (1 C, *C*H_2−C_6H_5), 74.3 and 74.9 (1 C *cis and trans*, C-2), 127.7−127.6, 128.3 (arom. CH), 137.0 (arom. C). − $C_{13}H_{17}IO_3$ (348.18): calcd. C 44.85, H 4.92; found C 44.65, H 4.89.

2-Acetoxymethyl-6-benzyloxymethyl-1,4-dioxane (58): A solution of **56** (0.5 g, 1.44 mmol) in DMF (5 mL) was added to a solution of potassium acetate (1.41 g, 14.4 mmol) and 18-crown-6 (38 mg, 0.14 mmol) in DMF (10 mL). After stirring at 80 °C for 24 h, the mixture was diluted with water and extracted with diethyl ether. The organic layers were washed with water and with brine, dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 9:1 then 8:2) to afford **58** (255 mg, 63%). − TLC (petroleum ether/ethyl acetate, 8:2): R_f = 0.25. − ^1H NMR ($CDCl_3$): δ = 2.07 (d, 3 H, CH_3), 3.30−3.60 (m, 4 H, H-5b, H-3b and CH_2−OBn), 3.72−3.90 (m, 3 H, H-6, H-5a and H-3a), 3.99−4.35 (m, 3 H, H-2 and CH_2−OCO−CH_3), 4.50 (m, 2 H, CH_2−C_6H_5), 7.30 (m, 5 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 20.8 (1 C, CH_3), 62.4 and 63.6 (*C*H_2−OCO−CH_3), 66.9 and 69.6 (1 C, *C*H_2−OBn), 67.7, 68.4, and 68.5 (2 C, C-3, C-5), 68.6 and 69.2 (1 C, C-2), 73.3 and 73.5 (1 C, ***C***H_2−C_6H_5), 73.2 and 74.5 (1 C, C-6), 127.6 and 128.4 (arom. CH), 137.8 (arom. C), 170.7 (C=O). − $C_{15}H_{20}O_5$ (280.32): calcd. C 64.27, H 7.19; found C 64.03, H 7.15.

6-Benzyloxymethyl-2-*p*-nitrobenzoyloxymethyl-1,4-dioxane (59): 18-Crown-6 (38 mg, 0.14 mmol) was added to a solution of compound **56** (0.5 g, 1.44 mmol) and potassium *p*-nitrobenzoate in DMSO (15 mL). The resulting mixture was stirred for 4 h at 90 °C, diluted with water and extracted with diethyl ether. The organic layers were washed with water and with brine, dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 8:2) to afford **59** (412 mg, 74%). − TLC (petroleum ether/ethyl acetate, 8:2): R_f = 0.23. − ^1H NMR (CD_3OD): δ = 3.30−4.20 (m, 8 H, H-2, H-6, H-3, H-5 and CH_2−OBn), 4.27 (s, 2 H, CH_2−C_6H_5), 4.28 and 4.66 (m, 2 H, −CH_2−O−CO−*p*-O_2NBz), 7.30 (m, 5 H, H arom. Bn), 8.10 (m, 4 H, H arom. *p*-nitrobenzoate). − ^{13}C NMR (CD_3OD): δ = 64.5 and 65.9 (1 C, *C*H_2−OCO−), 68.5, 68.8, 69.1 and 69.9 (2 C, C-3 and C-5), 70.0 and 70.8 (1 C, C-2), 67.8 and 70.9 (1 C, *C*H_2−OBn), 74.2 and 74.4 (1 C, *C*H_2−C_6H_5), 74.7 and 76.2 (1 C, C-6), 124.6 and 131.8 (arom. CH, *p*-nitrobenzoate), 128.7 and 129.3 (arom. CH, Bn), 136.5 (arom. C Bn), 139.4 and 152.0 (arom. C, *p*-nitrobenzoate), 165.8 (1 C, C=O). − $C_{20}H_{21}NO_7$ (387.39): calcd. C 62.01, H 5.46; found C 62.03, H 5.45.

2-Benzyloxymethyl-6-hydroxymethyl-1,4-dioxane (60): A few drops of concentrated HCl were added to either **58** (5 g, 17.84 mmol) or **59** (100 mg, 0.26 mmol) in solution in methanol (100 mL or 5 mL). The resulting mixture was stirred at room temperature until the disappearance of starting material. NEt_3 was then added dropwise to the reaction mixture until neutral. Methanol was removed under reduced pressure and the residue was diluted with diethyl ether and water. The aq. layer was extracted with diethyl ether, the organic layers were washed with brine, dried with $MgSO_4$ and concentrated to give **58** (3.85 g, 90% from **58** or 52 mg, 85% from **59**). − TLC (petroleum ether/ethyl acetate, 7:3): R_f = 0.18. − ^1H NMR ($CDCl_3$): δ = 3.30−3.81 (m, 9 H, H-3, H-5, H-6, CH_2−OH, CH_2−OBn), 3.90−4.10 (m, 1 H, H-2), 4.50 (m, 2 H, CH_2−C_6H_5), 7.30 (m, 5 H, H arom). − ^{13}C NMR ($CDCl_3$): δ = 61.1 and 62.2 (1 C, CH_2−OH), 67.0 and 69.7 (1 C, *C*H_2−OBn), 67.2, 67.4, 68.1 and 68.3 (2 C, C-3 and C-5), 69.3 and 70.4 (1 C, C-6), 73.3 (1 C, *C*H_2−C_6H_5), 74.2 and 75.8 (1 C, C-2), 127.6 and 128.3 (arom. CH), 137.6 (arom. C). − $C_{13}H_{18}O_4$ (238.29): calcd. C 65.53, H 7.61; found C 65.59, H 7.61.

2,6-Bis(hydroxymethyl)-1,4-dioxane (52): Palladium on activated charcoal (10% Pd, 350 mg), was added to a solution of **60** (3.5 g, 14.7 mmol) in methanol (50 mL). After stirring at room temperature under hydrogen until all starting material had been consumed, the mixture was filtered through Celite® to remove the catalyst. The filtrate was concentrated and purified by column chromatography (dichloromethane/methanol, 9:1) to afford **52** (2 g, 92%). − TLC (dichloromethane/methanol, 9:1): R_f = 0.3. − ^{13}C NMR

($CDCl_3$): δ = 61.6 and 62.9 (2 C, CH_2−OH), 68.2 and 68.9 (2 C, C-3 and C-5), 72.4 and 77.2 (2 C, C-2 and C-6). − $C_6H_{12}O_4$·0.33H_2O (154.11): calcd. C 46.76, H 8.28, found C 46.57, H 8.22.

2-*O*-Allyl-1-*O*-benzylglycerol (66): Sodium hydride (2.6 g, 65 mmol) was slowly added to a solution of 1,3-*O*-benzylideneglycerol (5.9 g, 32.7 mmol) in DMF (60 mL). After stirring at room temperature for 20 min, TBAB (530 mg, 1.64 mmol) and allyl bromide (4.25 mL, 49 mmol) were added. The resulting mixture was stirred at room temperature for 2 h. It was then diluted with water and extracted with diethyl ether. The extracts were washed with brine, dried with $MgSO_4$ and concentrated. Purification of the residue by column chromatography (petroleum ether/ethyl acetate, 8:2) gave pure 2-*O*-allyl-1,3-benzylideneglycerol (6.6 g, 92%). DIBAL-H (1 M solution in dichloromethane, 59 mL, 59 mmol) was then slowly added to the solution, cooled with an ice bath, of 2-*O*-allyl-1,3-benzylideneglycerol (6.5 g, 29.5 mmol) in dichloromethane (30 mL). After stirring at 0 °C for 2.5 h, the reaction was quenched with 0.5 M NaOH. The organic phase was washed with 0.5 M NaOH, dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 7:3) to afford **66** (5.3 g, 82%) as a colourless oil. −TLC (petroleum ether/ethyl acetate, 7:3): R_f = 0.29. − ^{1}H NMR ($CDCl_3$): δ = 3.49−3.66 (m, 4 H, CH_2−OBn and CH_2−OH), 3.73 (m, 1 H, −O−CH), 4.10 (ddd, 2 H, −CH_2−O−), 4.53 (s, 2 H, CH_2−C_6H_5), 5.16−5.29 (ddd, 2 H, CH_2=CH), 5.90 (m, 1 H, CH_2=C*H*), 7.30 (m, 5 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 62.7 (1 C, CH_2−OH), 69.9 (1 C, −O−CH_2), 73.4 (1 C, *C*H_2−C_6H_5), 77.9 (−O−CH), 117.2 (1 C, *C*H_2=CH), 127.6 and 128.3 (arom. CH), 134.7 (1 C, *C*H=CH_2), 137.9 (arom. C).

5-Benzyloxymethyl-2-iodomethyl-1,4-dioxane (67): *N*-Iodosuccinimide (3.34 g, 14.85 mmol) was added to a solution of **66** (1.65 g, 7.42 mmol) in dry acetonitrile (25 mL). After stirring at reflux for 2 h, the mixture was washed with saturated $Na_2S_2O_3$. The organic layer was dried with $MgSO_4$, concentrated and purified by column chromatography (petroleum ether/ethyl acetate, 95:5 then 9:1) to give **67** (1.03 g, 40%) These chromatographic conditions allowed sufficient separation of the *cis* and the *trans* isomers for NMR studies. − Compound **67** *cis*: TLC (petroleum ether/ethyl acetate, 9:1): R_f = 0.35. − ^{1}H NMR ($CDCl_3$): δ = 3.35 (ddd, 2 H, CH_2−I), 3.50−3.64 (dq, 2 H, CH_2−OBn), 3.67−3.73 (m, 3 H, H-2 and H-6), 3.76−3.85 (m, 3 H, H-5 and H-3), 4.55 (s, 2 H, CH_2−C_6H_5), 7.30 (m, 5 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 3.5 (1 C, CH_2−I), 63.5 (1 C, C-6), 66.1 (1 C, C-3), 68.4 (*C*H_2−OBn), 72.5 (1 C, C-2), 72.7 (1 C, C-5), 73.5 (*C*H_2−C_6H_5), 127.7 and 128.4 (arom. CH), 137.8 (arom. C). − Compound **65** *trans*: TLC (petroleum ether/ethyl acetate, 9:1): R_f = 0.25. − ^{1}H NMR ($CDCl_3$): δ = 3.06 (d, 2 H, CH_2−I), 3.35−3.51 (m, 3 H, CH_2−OBn and H-3a), 3.53−3.59 (m, 2 H, H-2 and H-6a), 3.74 (m, 1 H, H-5), 3.88 (dd, 1 H, H-6b), 4.01 (dd, 1 H, H-3b), 4.54 (s, 2 H, CH_2−C_6H_5), 7.30 (m, 5 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 2.4 (CH_2−I), 68.8 (1 C, C-6), 69.3 (1 C, *C*H_2−OBn), 70.7 (1 C, C-3), 73.5 (1 C, *C*H_2−C_6H_5), 73.9 (1 C, C-5), 74.0 (1 C, C-2), 127.7 and 128.4 (arom. CH), 137.8 (arom. C). − $C_{13}H_{17}IO_3$ (348.18): calcd. C 44.85, H 4.92; found C 44.71, H 4.87.

2-Acetoxymethyl-5-benzyloxymethyl-1,4-dioxane (68): A solution of **67** (0.5 g, 1.44 mmol) in DMF (5 mL) was added to a solution of potassium acetate (1.41 g, 14.4 mmol) and 18-crown-6 (38 mg, 0.14 mmol) in DMF (10 mL). After stirring overnight at 80 °C, the mixture was diluted with water and extracted with diethyl ether. The organic layers were washed with water and with brine, dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 8:2) to afford **68** (240 mg, 60%). − TLC (petroleum ether/ethyl acetate, 8:2): R_f = 0.28. − ^{1}H NMR ($CDCl_3$): δ = 2.08 (d, 3 H, CH_3), 3.39−3.67 (m, 3 H, H-3 *cis* or *trans* and CH_2−OBn), 3.69−3.88 (m, 5 H, H-2, H-5, H-6 and H-3 *cis* or *trans*), 4.01−4.38 (m, 2 H, CH_2−O−CO−CH_3), 4.50 (m, 2 H, CH_2−C_6H_5), 7.30 (m, 5 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 20.8 (1 C, CH_3), 62.0 and 63.6 (1 C, *C*H_2−OCO−CH_3), 64.0, 64.4, 68.4 and 67.9, (2 C, C-3 and C-6), 68.6 and 69.5 (1 C, *C*H_2−OBn), 70.8 and 72.7 (1 C, C-2), 72.8 and 74.0 (1 C, C-5), 73.5 (*C*H_2−C_6H_5), 127.7 and 128.4 (arom. CH), 137.8 (arom. C), 170.8 (1 C, C=O). − $C_{15}H_{20}O_5$ (280.32): calcd. C 64.27, H 7.19, found C 64.56, H 7.29.

2-Benzyloxymethyl-5-hydroxymethyl-1,4-dioxane (69): A few drops of concentrated HCl were added to **68** (280 mg, 0.99 mmol) in solution in methanol (10 mL). The resulting mixture was stirred at room temperature until the disappearance of starting material. NEt_3 was then added dropwise to the reaction mixture until neutral. Methanol was removed under reduced pressure, and the residue was diluted with diethyl ether and water. The aqueous layer was extracted with diethyl ether, the organic layers were washed with brine, dried with $MgSO_4$ and concentrated to give **69** in quantitative yield. − TLC (petroleum ether/ethyl acetate, 7:3): R_f = 0.10. − ^{1}H NMR ($CDCl_3$): δ = 2.19 (m, 1 H, OH), 3.38−3.90 (m, 10 H, H-2, H-3, H-5, H-6 and CH_2−OH, CH_2−OBn), 4.50 (m, 2 H, CH_2−C_6H_5), 7.30 (m, 5 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 60.9 and 62.3 (CH_2−OH), 63.9, 64.2, 67.9 and 68.1 (2 C, C-3 and C-6), 68.5 and 69.6 (1 C, *C*H_2−OBn), 72.1 and 73.6 (1 C, C-5), 73.5 and 73.6 (1 C, *C*H_2−C_6H_5), 74.0 and 75.2 (1 C, C-2), 127.7 and 128.4 (arom. CH), 137.8 (arom. C). − $C_{13}H_{18}O_4$ (238.29): calcd. C 65.53, H 7.61; found C 65.37, H 7.76.

2,5-Bis(hydroxymethyl)-1,4-dioxane (53): Palladium on activated charcoal (10% Pd, 50 mg) was added to a solution of **69** (120 mg, 0.5 mmol) in methanol (10 mL). After stirring at room temperature under hydrogen until starting material had disappeared, the mixture was filtered through Celite® to remove the catalyst. The filtrate was concentrated and purified by column chromatography (dichloromethane/methanol, 9:1) to afford **53** in quantitative yield. − TLC (dichloromethane/methanol, 9:1): R_f = 0.25. − ^{13}C NMR ($CDCl_3$): δ = 61.2 and 62.8 (2 C, CH_2−OH), 65.0 and 69.5 (2 C, C-3 and C-6), 75.3 and 76.9 (2 C, C-2 and C-5).

2-*O*-Benzylglycerol [14690−00−7] (71): Palladium on activated charcoal (10% Pd, 1 g) and a catalytic amount of APTS (1.5 g, 7.9 mmol) were added to a solution of compound **8** (10.5 g, 40 mmol) in a methanol/water (10:2) mixture (120 mL). After stirring at reflux for 48 h, the mixture was filtered through Celite® and the filtrate was concentrated under vacuum. The residue was diluted with ethyl acetate, washed with water and dried with $MgSO_4$. Solvent was removed under reduced pressure. Purification of the residue by column chromatography yielded **71** (3.65 g, 50%) as a colourless oil. − TLC (petroleum ether/ethyl acetate, 1:1): R_f = 0.11. − ^{1}H NMR ($CDCl_3$): δ = 3.57 (tt, $J_{2,1a}$ = $J_{2,1b}$ = 4.6 Hz, 1 H, H-2), 3.69 (dd, 2 H, H-1a and H-3a), 3.77 (dd, $J_{1a,1b}$ = $J_{3a,3b}$ = 11.7 Hz, 2 H, H-1b and H-3b), 4.63 (s, 2 H, CH_2−C_6H_5), 7.3 (m, 5 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 62.13 (2 C, C-1 and C-3), 71.9 (1 C, *C*H_2−C_6H_5), 79.12 (1 C, C-2), 127.8−129.7 (arom. CH), 137.93 (arom. C).

2,6-Di-*O*-benzyl-4-oxaheptane-1,2,6,7-tetraol (72): Sodium hydride (6.7 g, 0.168 mol) was added slowly under nitrogen to a cooled solution of bis(epoxide) **6** (10 g, 76.8 mmol) in 50 mL of allyl alcohol. After stirring at room temperature for 5 h, the mixture was diluted with dichloromethane, washed with a 5% aqueous solution of HCl, then dried with $MgSO_4$ and concentrated under vacuum.

The residue was purified by column chromatography (petroleum ether/ethyl acetate, 1:1 then 3:7) to give 12.27 g of 4,8,12-trioxapentadecane-1,14-diene-6,10-diol. This compound (12.27 g, 49.8 mmol) was then added slowly under nitrogen to a suspension of sodium hydride (6 g, 0.149 mol) in dry THF. After 30 min of stirring at room temperature, TBAB (1.6 g; 5 mmol) and benzyl bromide (14.9 mL; 0.125 mol) were added. The resulting solution was stirred at room temperature for another 4 h, diluted with diethyl ether and washed with caution with water in order to destroy excess NaH. The organic layer was washed with brine, dried with $MgSO_4$ and concentrated. Purification of the residue by column chromatography (petroleum ether/ethyl acetate, 9:1) afforded 15.9 g of 6,10-di-*O*-benzyl-4,8,12-trioxapentadecane-1,14-diene-6,10-diol as a yellow oil. Palladium on activated charcoal (10% Pd, 1.5 g) and a catalytic amount of APTS (1.6 g; 8.2 mmol) were added to the solution of this product (15.9 g; 37.3 mmol) in a methanol/water (10:2) mixture (250 mL). After stirring at reflux for 3 d, the mixture was filtered through Celite® and the filtrate was concentrated under vacuum. The residue was diluted with ethyl acetate, washed with water and dried with $MgSO_4$. Solvent was removed under reduced pressure. Purification of the residue by column chromatography yielded 2,6-di-*O*-benzyl-4-oxaheptane-1,2,6,7-tetraol (**72**) (9.8 g, 37%) as a colourless oil. − TLC (ethyl acetate): R_f = 0.57. − ^{1}H NMR ($CDCl_3$): δ = 2.4 (br., 2 H, OH), 3.5−3.65 (m, 8 H, H-1, H-3, H-5 and H-7), 3.75 (m, 2 H, H-2 and H-6), 4.6 (ddd, 4 H, C*H*$_2$−C$_6$H$_5$), 7.3 (m, 10 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 62.3 (2 C, C-1 and C-7), 71.4 (2 C, C-3 and C-5), 72.08 (2 C, *C*H$_2$−C$_6$H$_5$), 77.8 (2 C, C-2 and C-6), 127.8−128.4 (arom. CH), 138.0 (arom. C). − $C_{20}H_{26}O_5$ (346.43): calcd. C 69.34, H 7.57; found C 68.92, H 7.59.

2,6,10-Tri-*O*-benzyl-4,8-dioxaundecane-1,2,6,10,11-pentaol (73): Sodium hydride (598 mg, 14.95 mmol) was added slowly under nitrogen to a cooled solution of bis(epoxide) **9** (2 g, 6.79 mmol) in 30 mL of allyl alcohol. After stirring at room temperature overnight, the mixture was diluted with diethyl ether, washed successively with a 5% aqueous solution of HCl and with brine, then dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 1:1) to give 2.3 g of 10-*O*-benzyl-4,8,12,16-tetraoxanonadecane-1,18-diene-6,10,14-triol. This compound (2.2 g, 5.36 mmol) was then added slowly under nitrogen to a suspension of sodium hydride (643 mg, 16.07 mmol) in dry THF (50 mL). After 20 min of stirring at room temperature, TBAB (172 mg; 0.54 mmol) and benzyl bromide (1.6 mL; 13.4 mmol) were added. The resulting solution was stirred overnight at room temperature, diluted with diethyl ether, and washed with caution with water in order to destroy excess NaH. The organic layer was washed with brine, dried with $MgSO_4$ and concentrated. Purification of the residue by column chromatography (petroleum ether/ethyl acetate, 8:2) afforded 2.82 g of 6,10,14-tri-*O*-benzyl-4,8,12,16-tetraoxanonadecane-1,18-diene-6,10,14-triol. Palladium on activated charcoal (10% Pd, 300 mg) and a catalytic amount of APTS (174 mg; 0.92 mmol) were added to a solution of this product (2.7 g; 4.57 mmol) in an ethanol/methanol/water (10:4:2, 100 mL) mixture. After stirring at reflux for 3 d, the mixture was filtered through Celite® and the filtrate was concentrated under vacuum. The residue was diluted with ethyl acetate, washed with water and dried with $MgSO_4$. Solvent was removed under reduced pressure. Purification of the residue by column chromatography (petroleum ether/ethyl acetate, 3:7 then ethyl acetate) yielded the diol **73** (1.75 g, 56%) as a colourless oil. − TLC (ethyl acetate): R_f = 0.56. − ^{1}H NMR ($CDCl_3$): δ = 2.4 (m, 2 H, OH), 3.53−3.65 (m, 12 H, H-1, H-3, H-5, H-7, H-9 and H-11), 3.7 (m, 3 H, H-2, H-6 and H-10), 4.6 (m, 6 H, C*H*$_2$−C$_6$H$_5$), 7.3 (m, 15 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 62.5 (2 C, C-1 and C-11), 71.19−71.48 (4 C, C-3, C-5, C-7 and C-9), 72.0 and 72.2 (3 C, *C*H$_2$−C$_6$H$_5$), 76.8 (1 C, C-6), 77.8 (2 C, C-2 and C-10), 127.7−128.4 (arom CH.), 138.2 (arom. C).

2,6-Di-*O*-benzyl-1,7-di-*O*-trifluoromethanesulfonyl-4-oxaheptane-1,2,6,7-tetraol (74): A solution of 2,6-lutidine (1.27 mL, 10.9 mmol) in 20 mL of dry dichloromethane was cooled to 0−5 °C with an ice bath under nitrogen. Triflic anhydride (1.84 mL, 10.9 mmol) was then added and, after 5 min of stirring, the diol **72** (1 g, 2.88 mmol) in dry dichloromethane (20 mL) was also added. The resulting red solution was stirred for 15 min; then water was added to the mixture. The aqueous layer was extracted with dichloromethane, and the extracts were washed with a 5% HCl solution, dried with $MgSO_4$ and concentrated under reduced pressure. The residue was quickly purified by flash chromatography (petroleum ether acetate, 8:2) to yield ditriflate **74** (1.23 g, 70%) as a brown oil. − TLC (petroleum ether/ethyl acetate 7:3): R_f = 0.78. − ^{1}H NMR ($CDCl_3$): δ = 3.44−3.55 (m, 4 H, H-3 and H-5), 3.73 (m, 2 H, H-2 and H-6), 4.37−4.6 (m, 8 H, H-1, H-7 and C*H*$_2$−C$_6$H$_5$), 7.3 (m, 10 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 68.45 (2 C, C-3 and C-5), 71.58 (2 C, C-1 and C-7), 73.6 (2 C, C-2 and C-6), 74.02 (3 C, *C*H$_2$−C$_6$H$_5$), 112.79, 115.96, 119.14, 122.32 (2 C, CF_3), 126.8−127.6 (arom. CH), 136.0 (arom. C).

3,7,11-Tri-*O*-benzyl-1,5,9-trioxacyclododecane-3,7,11-triol (75): Sodium hydride (53 mg, 1.32 mmol) was added under nitrogen to a solution of diol **71** (100 mg, 0.53 mmol) in dry THF (10 mL). After stirring at room temperature for 20 min, the ditriflate **74** (389 mg, 0.67 mmol) in 5 mL of dry THF was added. The resulting solution was stirred at room temperature until starting ditriflate had disappeared (about 30 min). An aqueous solution of saturated ammonium chloride was then added to the mixture, and the aqueous layer was extracted with diethyl ether. The extracts were washed with brine, dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 8:2) to give the benzylated cyclic triglycerol **75** (91 mg, 35%) as a colourless oil. − TLC (petroleum ether/ethyl acetate, 8:2): R_f = 0.36. − ^{1}H NMR ($CDCl_3$): δ = 3.45−3.65 (m, 15 H, CH_2 and CH of the cycle). 4.51 (s, 6 H, C*H*$_2$−C$_6$H$_5$), 7.3 (m, 15 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 69.51, 69.79 and 70.30 (6 C, CH_2 of the cycle), 71.6 (3 C, *C*H$_2$−C$_6$H$_5$), 74.14 and 74.44 (3 C, *C*H−OBn), 127.8 and 128.5 (arom. CH), 138.05 (arom. C). − $C_{30}H_{36}O_6$ (492.62): calcd. C 73.15, H 7.37; found C 72.92, H 7.31. −MS: $[M + H]^+$: calcd. 493.2590; found 493.2590.

1,5,9-Trioxacyclododecane-3,7,11-triol (76): Palladium on activated charcoal (10% Pd, 50 mg) was added to a solution of **75** (440 mg, 0.89 mmol) in methanol (15 mL). After stirring at room temperature under hydrogen for 6 h, the mixture was filtered through Celite® to remove the catalyst. The filtrate was concentrated and purified by column chromatography (dichloromethane/methanol, 9:1) to give pure 1,5,9-trioxacyclododecane-3,7,11-triol **75** (195 mg, 98%). − TLC (dichloromethane/methanol, 8:2): R_f = 0.26. − ^{1}H NMR (CD_3OD): δ = 3.42−3.57 (m, 12 H, CH_2 of the cycle), 3.76 (m, 3 H, C*H*−OH). − ^{13}C NMR (CD_3OD): δ = 68.35 and 68.71 (3 C, CH−OH), 73.09, 73.30 and 73.42 (6 C, CH_2 of the cycle). − MS: $[M + H]^+$: calcd. 223.1182; found 223.1181; $[M + Na]^+$: calcd. 245.1001; found 245.0997.

3,7,11,15-Tetra-*O*-benzyl-1,5,9,13-tetraoxacyclohexadecane-3,7,11,15-tetraol (77): Sodium hydride (164 mg, 4.1 mmol) was added under nitrogen to a solution of diol **72** (567 mg, 1.64 mmol) in dry THF (30 mL). After stirring at room temperature for 20 min, the ditriflate **74** (1.2 g, 1.96 mmol) in 20 mL of dry THF was ad-

ded. The resulting solution was stirred at room temperature for 1 h. An aqueous solution of saturated ammonium chloride was then added to the mixture, and the aqueous layer was extracted with diethyl ether. The extracts were washed with brine, dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 8:2) to give the benzylated cyclic tetraglycerol **77** (377 mg, 35%) as a colourless oil. − TLC (petroleum ether/ethyl acetate, 7:3): R_f = 0.52. − ^{1}H NMR ($CDCl_3$): δ = 3.42−3.56 (m, 20 H, CH_2 and CH of the cycle), 4.52 (m, 8 H, CH_2−C_6H_5), 7.2 (m, 20 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 68.70, 68.81, 69.05, 69.14, 69.21, 69.49 and 69.62 (8 C, CH_2 of the cycle), 71.39, 71.47, 71.55 and 71.69 (4 C, CH_2−C_6H_5), 75.28, 75.54, 75.62, 75.72 and 75.92 (4 C, *C*H−OBn), 127.55−127.73 and 128.29 (arom. CH), 138.3 (arom. C.). − $C_{40}H_{48}O_8$ (656.82): calcd. C 73.15, H 7.37; found C 73.12, H 7.41. − MS: $[M + H]^+$: calcd. 657.3427; found 657.3435; $[M - H]^+$: calcd. 655.3271; found 655.3264.

1,5,9,13-Tetraoxacyclohexadecane-3,7,11,15-tetraol (78): Palladium on activated charcoal (10% Pd, 50 mg) was added to a solution of **77** (348 mg, 0.53 mmol) in methanol (10 mL). After stirring at room temperature under hydrogen overnight, the mixture was filtered through Celite® to remove the catalyst. The filtrate was concentrated and purified by column chromatography (dichloromethane/methanol, 9:1 then 8:2) to give pure 1,5,9,13-tetraoxacyclohexadecane-3,7,11,15-tetraol (**78**) (130 mg, 83%). − TLC (dichloromethane/methanol, 8:2): R_f = 0.26. − ^{1}H NMR (CD_3OD): δ = 3.44−3.59 (m, 16 H, CH_2 of the cycle), 3.76−3.81 (m, 4 H, C*H*−OH). − ^{13}C NMR (CD_3OD): δ = 69.44, 69.63, 69.72 and 69.86 (4 C, CH−OH), 71.43, 71.58, 71.73, 71.89 and 72.04 (8 C, CH_2 of the cycle). − MS: $[M + Na]^+$: calcd. 319.1369, found 319.1367.

3,7,11,15,19-Penta-*O*-benzyl-1,5,9,13,17-pentaoxacycloicosane-3,7,11,15,19-pentaol (79): Sodium hydride (136 mg, 3.4 mmol) was added under nitrogen to a solution of diol **73** (697 mg, 1.36 mmol) in dry THF (20 mL). After stirring at room temperature for 20 min, the ditriflate **74** (1 g, 1.64 mmol) in 10 mL of dry THF was added. The resulting solution was stirred at room temperature for 1 h. An aqueous solution of saturated ammonium chloride was then added to the mixture, and the aqueous layer was extracted with diethyl ether. The extracts were washed with brine, dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 8:2) to give the benzylated cyclic pentaglycerol **79** (394 mg, 35%) as a colourless oil. − TLC (petroleum ether/ethyl acetate, 8:2): R_f = 0.44. − ^{1}H NMR ($CDCl_3$): δ = 3.48 (m, 20 H, CH_2 of the cycle), 3.57 (m, 5 H, C*H*−OBn), 4.53 (m, 10 H, CH_2−C_6H_5), 7.22 (m, 25 H, H arom.). − ^{13}C NMR ($CDCl_3$): δ = 70.66−71.13 (10 C, CH_2 of the cycle), 71.91−71.96 (5 C, CH_2−C_6H_5), 76.43−76.87 (5 C, *C*H−OBn), 127.5, 127.6 and 128.29 (arom. CH), 138.54 (arom. C). −MS: *m*/*z* = 843.4 $[M + Na]^+$.

1,5,9,13,17-Pentaoxacycloicosane-3,7,11,15,19-pentaol (80): Palladium on activated charcoal (10% Pd, 100 mg) was added to a solution of **79** (480 mg, 0.58 mmol) in a methanol/ethyl acetate (8:2) mixture (20 mL). After stirring at room temperature under hydrogen overnight, the mixture was filtered through Celite® to remove the catalyst. The filtrate was concentrated and purified by column chromatography (dichloromethane/methanol, 9:1 then 8:2) to give pure cyclic pentaglycerol **80** (194 mg, 90%). − TLC (dichloromethane/methanol, 85:15): R_f = 0.14. − ^{1}H NMR (CD_3OD): δ = 3.75 (m, 20 H, CH_2 of the cycle), 4.02 (m, 5 H, C*H*−OH). − ^{13}C NMR (CD_3OD): δ = 69.95, 69.98, 70.01, 70.16, 70.20, 70.38 (5 C, CH−OH), 73.24−73.3 (br., 10 C, CH_2 of the cycle). − MS: $[M + H]^+$: calcd. 371.1917; found 371.1916; $[M + Na]^+$: calcd. 393.1737; found 393.1740.

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