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# Transformation of linear oligoketosides into macrocyclic neoglycoconjugates

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ABSTRACT

The macrocyclization of linear D-*galacto*-2-heptulopyranose-containing oligoketosides has been carried out by intramolecular glycosidation and ring-closing metathesis. The aglycon fragment of the cyclic neglycoconjugates thus formed was an alkylidene or a polyether chain. One of the oligoketoside–crown ethers showed a moderate asymmetric induction in the Cram model phenyl acetate–acrylate addition.



Both natural and synthetic macrocyclic glycoconjugates combining structurally organized carbohydrate moieties and lipophilic subunits have been the targets of numerous synthetic efforts because these compounds offer a great deal of opportunities as chiral amphiphilic receptors in biological studies and in asymmetric synthetic methodologies. Quite notable are the natural product macrocyclic resin glycosides (glycolipids) such as tricolorin A and G, woodrosin, and sophorolipid lactone. The synthesis of these compounds has been carried out in Fürstner laboratory via ring-closing metathesis as the key macrocyclization step of dialkene or dialkyne functionalized oligosaccharide fragments.[1] Moreover, Heathcock and co-workers reported[2] the synthesis of tricolorin F via classical macrolactonization of a heterotrisaccharide-hexadecanoic acid lipid.[3] Biological activities have been described for these lipopolysaccharides including general cytotoxicity against several cancer cell lines and plant toxicity.[1,4] Another abundant class of macrocyclic glycoconjugates is constituted of synthetic carbohydrate–crown ether hybrids.[5] These compounds belong to the vast family of chiral crown ether derivatives[6] which rekindled great interest in the last decades for their potential as catalysts in asymmetric reactions and models of enzymatic systems. Macrocycles displaying oligoketoside fragments are quite uncommon as the only known compounds are cyclic oligomers of fructofuranose, the so-called cyclofructins[7] to emphasize their analogy to cyclodextrins. Cyclofructins have been prepared by enzymatic degradation of the fructose polymer inulin. Hence, we would like to report here on the first synthesis of macrocyclic glycoconjugates whose glycosidic moiety is made up of D-*galacto*-2-heptulopyranose units while the tether is constituted of a polymethylene or polyether chain (Fig. 1).

A few years ago we reported[8] on an iterative glycosylation protocol affording a set of linear α-(2,1)-D-*galacto*-2-heptulopyranose-containing oligoketosides **1** up to the pentameric stage (Scheme 1). These alcohols were suitably equipped with an anomeric *O*-pentenyl group with the aim to transform them into cyclic products via intramolecular glycosylation. Indeed this reaction occurred to a good extent with the linear disaccharide **1a** ($n = 0$) and trisaccharide **1b** ($n = 1$) but failed with the higher oligomers **1c** ($n = 2$) and **1d** ($n = 3$) which instead decomposed under the glycosidation conditions. We suspected that oligomers **1c** and **1d** adopted a spatial arrangement that disfavored the intramolecular process. Hence we thought that this drawback could be avoided by elongation of the alcohol side chain. As shown in Scheme 1, a polyether chain was introduced because the intramolecular glycosidation carried

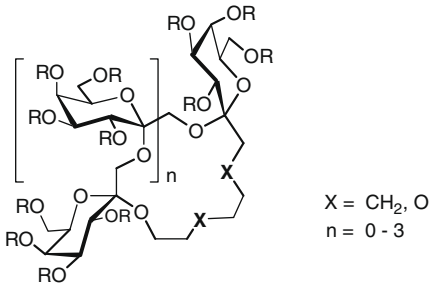


**Figure 1.** General structure of macrocyclic glycoconjugates prepared.

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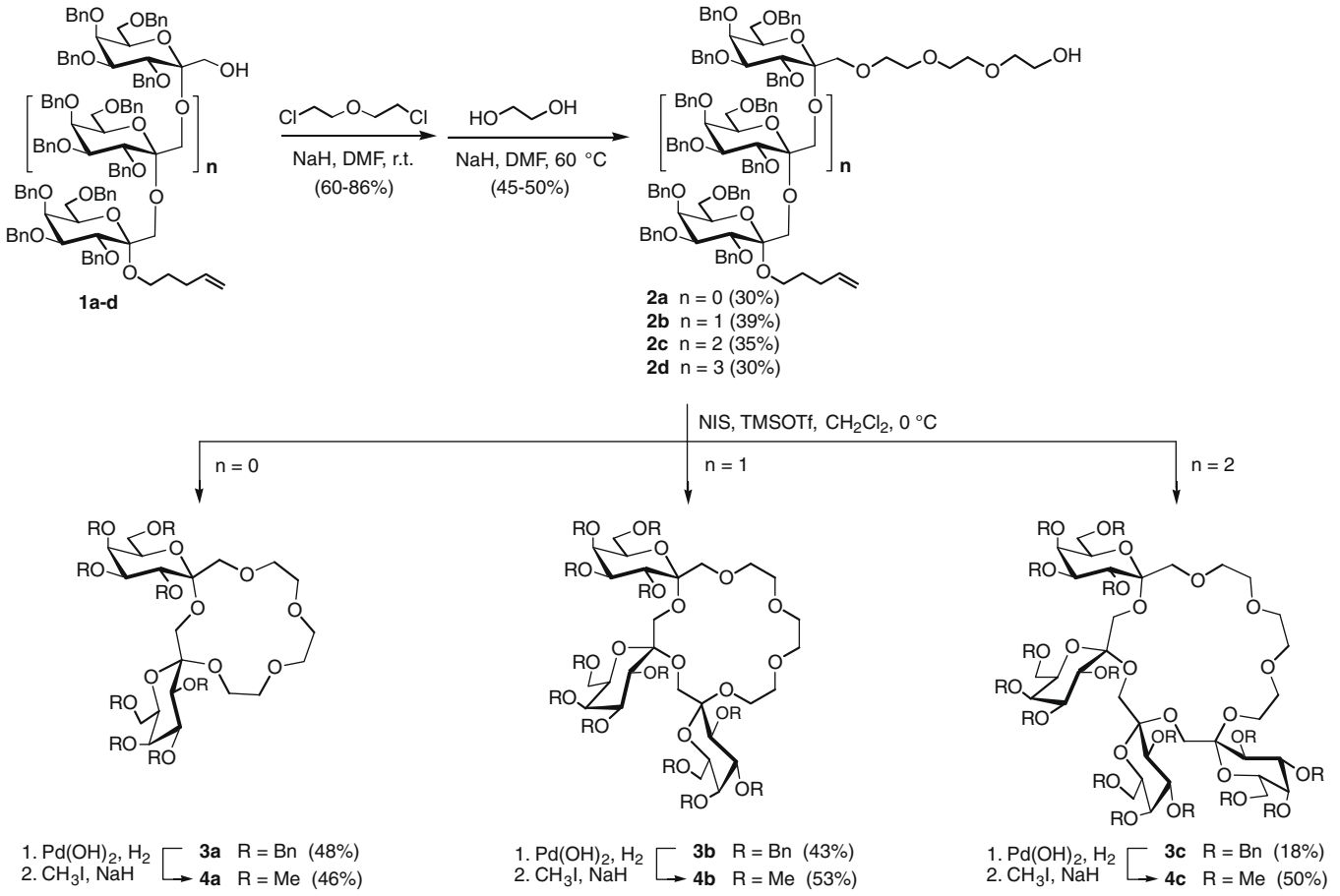


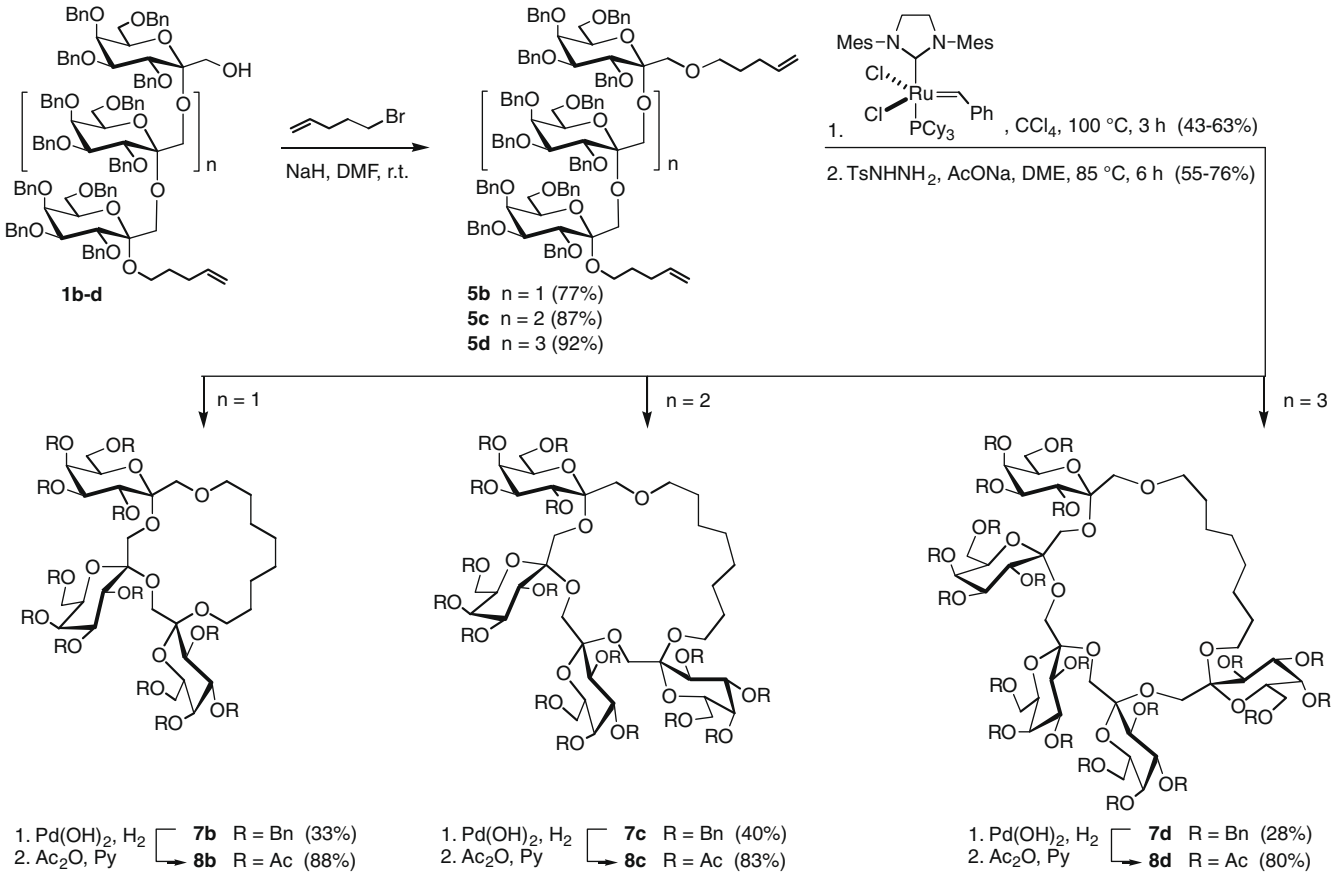

**Scheme 1.**

out afterward will form a macrocyclic oligoketoside–crown ether hybrid. This simple operation was carried out by treatment of the linear oligoketosides **1a–d** with bis(2-chloroethyl) ether and then coupling the resulting alkyl chlorides with ethylene glycol.[9] The new alcohols[10] **2a–d** were then subjected[11] to the standard glycosylation conditions of *O*-pentenyl-armed carbohydrates, that is, activation with *N*-iodosuccinimide-TMSOTf in $CH_2Cl_2$ at 0 °C. The macrocyclization occurred readily with the alcohols **2a–c** to give the corresponding carbohydrate-based crown ethers[10] **3a–c** although in variable yields. The yields decreased substantially by increasing the number of the heptuloside units in the oligoketoside moiety. Therefore, no cyclic product was obtained from pentamer **2d** while this oligomer decomposed under the glycosidation conditions. Macrocycles **3a–c** featuring perbenzylated carbohydrate fragments were readily transformed via debenzylation ($H_2$, $Pd(OH)_2$) and alkylation (NaH, MeI) into the corresponding *O*-methyl derivatives[10] **4a–c**. This new element of diversity can broaden the scope of these compounds as asymmetric molecular receptors. Indeed macrocycles **3** and **4** were tested as chiral hosts in the model Michael addition of methyl phenylacetate to methyl acrylate in the presence of *t*-BuOM (M = $Na^+$ and $K^+$) according to the classical Cram and Sogah procedure.[12] The observed ee values of the formed Michael adduct were in general low or moderate using the tri- and tetraketoside-containing crown ethers **3b**, **4b** and **3c, 4c**, respectively, while higher ee's (55% and 65%) were obtained using the diketoside-based macrocycles **3a** and **4a** (Table 1). Enantioselectivities of the same order of magnitude as those observed here were registered in Michael additions and in other asymmetric reactions using a variety of chiral crown ethers including carbohydrate-based derivatives.[13]

**Table 1**
Michael addition of methyl phenylacetate to methyl acrylate in the presence of *t*-BuOM and crown ethers **3a–c** and **4a–c**

| Host | Metal ion | Isolated yield (%) | ee (%) (*R* or *S*) |
|---|---|---|---|
| **3a** | $Na^{(+)}$ | 60 | 55 (*R*) |
| **3a** | $K^{(+)}$ | 70 | 5 (*R*) |
| **3b** | $Na^{(+)}$ | 65 | 40 (*R*) |
| **3b** | $K^{(+)}$ | 86 | <5 (*S*) |
| **3c** | $Na^{(+)}$ | 85 | 5 (*S*) |
| **3c** | $K^{(+)}$ | 90 | 5 (*R*) |
| **4a** | $Na^{(+)}$ | 86 | 15 (*S*) |
| **4a** | $K^{(+)}$ | 94 | 65 (*S*) |
| **4b** | $Na^{(+)}$ | 60 | 30 (*S*) |
| **4b** | $K^{(+)}$ | 85 | 45 (*S*) |
| **4c** | $Na^{(+)}$ | 72 | 30 (*S*) |
| **4c** | $K^{(+)}$ | 78 | 40 (*S*) |

We envisaged a second way to obtain macrocyclic glycoconjugates from oligoketosides **1** by the introduction of a second *O*-pentenyl appendage at the non-reducing end and then performing a ring-closing metathesis (RCM). Ring-closing alkene or alkyne metathesis has been extensively exploited as a key process toward macrocycle formation[14] including the above-mentioned macrocyclic glycolipids[1] and other carbohydrate containing macrocycles.[15] Hence the linear *O*-alkenyl alcohols **1b–c** were transformed into the bis-*O*-pentenyl derivatives[10] **5b–d** by coupling with pentenyl bromide. These dialkenes were subjected[16] to RCM using the second-generation ruthenium carbene Grubbs catalyst as shown in Scheme 2. The yields of the macrocycle alkenes **6b–d** (*E*/*Z* mixtures) appeared to decrease substantially with the increasing of




**Scheme 2.**

the number of carbohydrate units in the linear ketoside. Nevertheless even the macrocycle **6d** featuring a pentaketoside segment was obtained in satisfactory yield (43%). The double bond of compounds **6b–d** was then reduced[17] using diimide, generated in situ from tosylhydrazide and sodium acetate,[18] to give the corresponding cyclic neoglycoconjugates[10] **7b–d**. All these macrocycles featured a lipophilic moiety constituted of an eight carbon atom alkyl chain. Then, the *O*-benzyl groups of compounds **7b–d** were removed by hydrogenolysis in the presence of $Pd(OH)_2$ and the free hydroxy groups esterified ($Ac_2O$, Py) to give the corresponding *O*-acetyl derivatives[10] **8b–d**. Unlike the crown ether derivatives **3a–c** and **4a–c**, the macrocycles **7b–d** and **8b–d** did not serve as chiral hosts in the model Michael addition because they failed to recognize sodium and potassium cations as proved by $^1H$ NMR complexation experiments.[8]

In conclusion, the synthetic efforts invested in this program culminated in the development of two synthetic routes leading to new classes of macrocyclic neoglycoconjugates. The use of these products as chiral receptors has been so far only scarcely investigated. Hence addressing this issue now becomes of interest.

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9. To a stirred solution of alcohols **1a–d** (0.10 mmol) in dry DMF (2 mL) was added NaH (12 mg, 0.30 mmol, of a 60% suspension in mineral oil) and, after 15 min, bis(2-chloroethyl) ether (120 μL, 1.00 mmol). The mixture was stirred at rt for an additional 3 h, then cooled to 0 °C, diluted with 1 M phosphate buffer at pH 7 (10 mL), and extracted with $Et_2O$ (2 × 50 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated. The residue was eluted from a column of silica gel with 5:1 cyclohexane–AcOEt to give the corresponding alkyl chlorides (60–86%). To a stirred solution of the oligoketoside chlorides (0.05 mmol) and dry 1,2-ethanediol (140 μL) in dry DMF (1 mL) was added NaH (80 mg, 2.00 mmol, of a 60% suspension in mineral oil). The mixture was stirred at rt for 15 min, then warmed to 60 °C, stirred for 14 h, cooled to to 0 °C, diluted with 1 M phosphate buffer at pH 7 (10 mL), and extracted with $Et_2O$ (2 × 30 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated. The residue was eluted from a column of silica gel with cyclohexane–AcOEt (from 3:1 to 1:1) to give **2a–d** (45–50%).
10. Optical rotations were measured at 20 ± 2 °C in $CHCl_3$; values are given in deg mL $g^{-1}$ $dm^{-1}$. MALDI-TOF mass spectra were acquired using α-cyano-4-hydroxycinnamic acid as the matrix. The reported values refer to the sodium and potassium adducts. Compound **2a**: $[\alpha]_D$ +37.3 (*c* 0.3); MS: 1346.3, 1362.3. Compound **3a**: $[\alpha]_D$ +32.2 (*c* 1.6); MS: 1258.4, 1274.8. Compound **4a**: $[\alpha]_D$ +39.1 (*c* 1.0); MS: 650.6, 666.7. Compound **2b**: $[\alpha]_D$ +30.4 (*c* 0.9); MS: 1898.4, 1914.6. Compound **3b**: $[\alpha]_D$ +45.7 (*c* 2.0); MS: 1812.8, 1828.0. Compound **4b**: $[\alpha]_D$ +55.9 (*c* 1.1); MS: 900.6, 915.7. Compound **2c**: $[\alpha]_D$ +32.3 (*c* 1.2); MS: 2451.8, 2467.6. Compound **3c**: $[\alpha]_D$ +31.1 (*c* 0.9); MS: 2365.2, 2381.8. Compound **4c**: $[\alpha]_D$ +35.3 (*c* 1.0); MS: 1148.7, 1164.1. Compound **5b**: $[\alpha]_D$ +36.0 (*c* 1.5);

MS: 1836.1, 1852.3. Compound **7b**: $[\alpha]_D$ +36.8 (*c* 0.5); MS: 1811.4, 1827.7. Compound **8b**: $[\alpha]_D$ +57.1 (*c* 0.5); MS: 1233.0, 1248.4. Compound **5c**: $[\alpha]_D$ +34.7 (*c* 1.1); MS: 2389.3, 2405.1. Compound **7c**: $[\alpha]_D$ +35.2 (*c* 0.7); MS: 2362.4, 2378.2. Compound **8c**: $[\alpha]_D$ +70.5 (*c* 0.4); MS: 1593.3, 1609.5. Compound **5d**: $[\alpha]_D$ +33.6 (*c* 1.0); MS: 2941.1, 2957.4. Compound **7d**: $[\alpha]_D$ +30.3 (*c* 1.0); MS: 2915.2, 2930.9. Compound **8d**: $[\alpha]_D$ +74.3 (*c* 0.3); MS: 1954.1, 1970.3.

11. To a cooled (0 °C), stirred mixture of alcohols **2a–c** (0.05 mmol), activated 4 Å molecular sieves (0.50 g), finely powdered *N*-iodosuccinimide (22 mg, 0.10 mmol), and dry $CH_2Cl_2$ (5 mL) was added a 0.5 M solution of TMSOTf in dry $CH_2Cl_2$ prepared immediately before the use (100 μL, 0.05 mmol) in four portions during 1 h. The reaction mixture was stirred at 0 °C for an additional 15 min, then diluted with $Et_3N$ (0.1 mL), warmed to rt, filtered through a pad of Celite, and concentrated. A solution of the residue in $CH_2Cl_2$ (50 mL) was washed with 10% aqueous $Na_2S_2O_3$ (2 × 5 mL), dried ($Na_2SO_4$), and concentrated. The residue was eluted from a column of silica gel with cyclohexane–AcOEt (from 2:1 to 1:1) to give **3a–c** (18–48%).
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16. A solution of oligoketoside **5b–d** (0.03 mmol) and commercially available Grubbs catalyst (6.8 mg, 8.0 μmol) in dry $CCl_4$ (1.5 mL) was stirred in a screw-capped vial at 100 °C (oil-bath temperature) for 3 h, then cooled to rt and concentrated. The residue was eluted from a column of silica gel with cyclohexane–AcOEt (from 9:1 to 6:1) to give the corresponding macrocycles **6b–d** as *E*/*Z* mixtures (43–83%).
17. To a warmed (85 °C), stirred solution of alkenes **6b–d** (0.02 mmol) and freshly recrystallized *p*-toluenesulfonyl hydrazide (22 mg, 0.12 mmol) in dimethoxyethane (1 mL) was added 1 M aqueous sodium acetate (120 μL) in six portions during 3 h. After an additional 3 h at 85 °C the mixture was diluted with $H_2O$ (5 mL) and extracted with $CH_2Cl_2$ (2 × 30 mL). The organic phase was dried ($Na_2SO_4$) and concentrated. The residue was eluted from a column of silica gel with cyclohexane–AcOEt (from 9:1 to 6:1) to give **7b–d** (55–76%).
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