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An approach to highly oxygenated monocyclic derivatives with large rings

Anna Osuch-Kwiatkowska, Sławomir Jarosz *

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

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ABSTRACT

Coupling of the D-glucose and D-xylose derivatives via a phosphonate methodology provided a C12 higher sugar enone, which was converted into the protected dodecitol with both terminal free OH groups. This compound was used as a starting material for the preparation of highly oxygenated macrocyclic derivatives.

1. Introduction

Highly functionalized macrocyclic derivatives with a large ring are interesting synthetic targets. In general, they can be divided into two classes: carbo- and heterocyclic. The synthesis of such derivatives can be carried out by several routes. One of the most common methods for the preparation of heterocyclic derivatives is macrolactonization.[1,2] Many natural macrocyclic compounds contain double bond(s); this allows us to plan their synthesis based on a Wittig type reaction, McMurry reaction,[3] or other similar reactions in which this double bond is created during the cyclization step. A classical version for the preparation of such systems is the intramolecular Horner–Wadsworth–Emmons (HWE) reaction, which has been applied to the synthesis of 16-,[4] 17-,[5] 18-,[6] 28-,[7] and 36-[8] membered rings. In all cases, this reaction was highly stereoselective and afforded macrocyclic olefins with an *E*-configuration across the double bond. In 2010, a method for the construction of macrocyclic olefins with a *Z*-geometry was proposed.[9]

Another route to the synthesis of unsaturated macrocyclic compounds is the ring closing metathesis (RCM) reaction.[1,10] The pioneering work of Fürstner was particularly important in the preparation of such complex structures via RCM.[11,12] The key-aspect of the construction of the new double bond is in the *E*/*Z*-selectivity.[13] It has been reported that the temperature and the solvent have great influence on the selectivity of this process.[11,14] The nature of the catalyst plays also a crucial role.[15,16] The configuration of the olefin is also dependent on the substituents of the compound involved in the RCM process.[17]

Recently we became interested in the synthesis of carbocyclic polyhydroxylated derivatives with large rings. Higher carbon sugars (HCS) seem to be convenient starting materials for the preparation of such targets. A general route to HCS is shown in Figure 1.

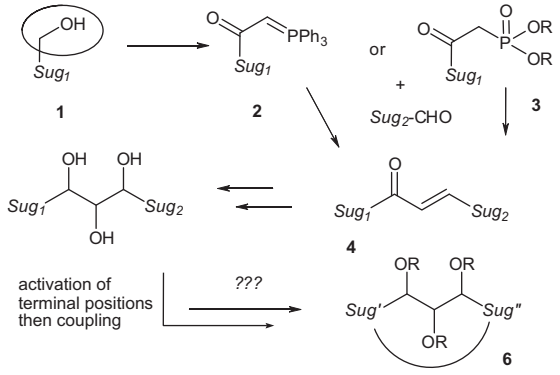

Figure 1. Synthesis of higher sugar precursors by Wittig type methodology and (possible) route to carbocycles.

The monosaccharide-derived phosphoranes **2** or phosphonates **3** upon reaction with sugar aldehydes provided the higher enones, which were then converted into fully hydroxylated compounds **5**.[18] Proper functionalization of both terminal positions should allow us to 'close' the molecule and obtain the polyhydroxylated carbocylic derivative with a large ring. Herein we report a model synthesis of such compounds.

2. Results and discussion

As a starting material for the model synthesis of polyhydroxylated carbocyclic compounds with large rings, the known[19] C12 alcohol **10** was chosen.

The target compound was obtained by the stereoselective transformation of the higher sugar enone **9**, previously prepared by the phosphorane methodology[20] or (more conveniently and in higher yield) by coupling of phosphonate **7**[21] with the corresponding aldehyde **8**[22] under mild PTC conditions (Fig. 2).

* Corresponding author. Tel.: +48 22 343 23 22; fax: +48 22 632 66 81.
E-mail address: slawomir.jarosz@icho.edu.pl (S. Jarosz).

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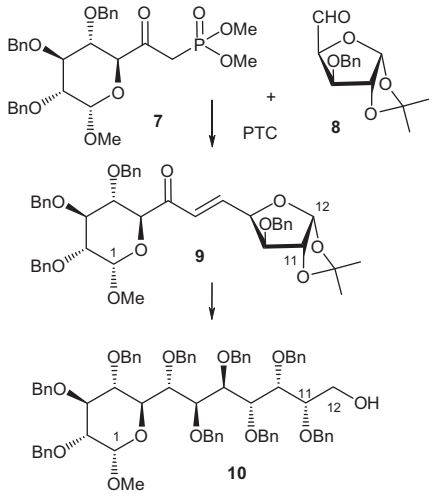


Figure 2. Synthesis of the key-starting material for the preparation of cyclic polyhydroxylated compounds with large ring.

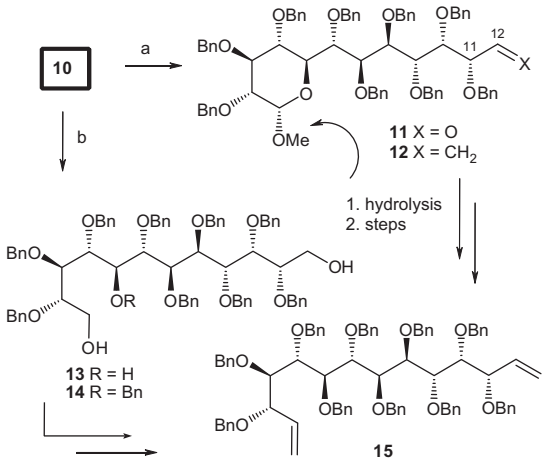
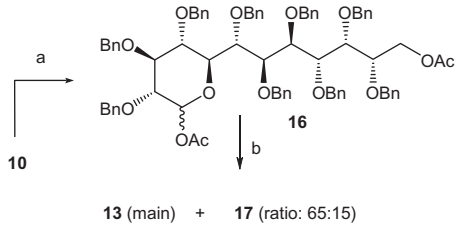


Figure 3. Synthetic strategies to polyhydroxylated di-olefin **15**, 75%.



Scheme 1. Reagents: (a) Ac_2O/AcOEt, cat. H_2SO_4; (b) $NaBH_4$, THF/MeOH.

Our synthetic strategy required the conversion of this derivative into linear di-olefin **15** either stepwise or simultaneously (Fig. 3 route a or b respectively). The first route involves the elaboration of an efficient method for the synthesis of mono-olefin **12** (by olefination of the aldehyde **11**), followed by further transformations of the molecule. The most demanding step is the hydrolysis of the glycosidic bond in **12**.

Oxidation of alcohol **10** was achieved almost quantitatively by PCC; the Swern oxidation,[23] commonly used in our laboratory for the oxidation of such complex systems, was not effective. The reaction of **11** with $Ph_3P{=}CH_2$ provided the corresponding olefin **12** in only 35% yield. Replacement of this simplest phosphorane for other reagents (e.g., Tebbe reagent[24]) was unsuccessful.

As expected, hydrolysis at the C-1 position (removal of methyl group) in **12** caused a large problem. We have already reported that the hydrolysis of the glycosidic bond in higher sugars can be performed most conveniently under acetolysis conditions; however, when unsaturation is placed at the terminal position, such a reaction was not effective.[25] This was also the case here; that is, compound **12** was completely resistant towards hydrolysis (Ac_2O/H_2SO_4) even after 24 h.

We therefore decided to synthesize di-olefin **15** via route b. Acetolysis of compounds **10** afforded diacetate **16** as a mixture of α/β anomers (in the ratio ~4.5:1 as detected by integration of the acetate signals in the ^{1}H NMR spectrum) in good yield.

Treatment of **16** with $LiAlH_4$ or DIBAL-H led only to the decomposition of the starting material. However, reduction of **16** with a large excess of sodium borohydride provided the desired diol **13** together with the side product **17** (Scheme 1; ratio **13**:**17** = 65:15).

The determination of the structure of **17** was not easy. The MS spectrum indicated the elimination of one molecule of benzyl alcohol during the reduction stage; this suggests that the product has a double bond or cyclic structure. Our first assumption is that it was an olefin that was excluded, since **17** was resistant towards ozone.

Acetylation of crude **17** gave a product containing two acetate groups: one primary and one secondary as assigned by the signals at δ: 3.93 (dd, H-12a), 4.11 (H-12b) and 5.85 (dd, H-3) ppm respectively. Furthermore, we found (with help of 2D correlation: COSY, HSQC, HMBC and DEPT experiments), characteristic signals at δ: 3.80 (dd, H-1a) and 4.14 (H-1b) in the ^{1}H NMR, and in the ^{13}C NMR spectra at δ: 20.8 and 21.2 [2 × C(O)*Me*], 64.2 (C-12), 71.53 (C-3), 71.55 (C-1), 169.4 and 170.5 (2 × C=O). On the basis of these data, structure of **17-Ac** was proposed for this compound. Plausible mechanism of its formation is shown in Figure 4.

The first step involved the hydrolysis of the acetates with the formation of the free sugar **18a**, which is in equilibrium with the open-chain derivative **18b**. Reduction of the carbonyl group and attack of the free C5–OH (or its anion) at the C3-position (with elimination of BnOH) affords the oxetane **19**. Next, opening of the 4-membered ring with the C1–$O^{(-)}$ provided derivative **17**, which was finally converted into the di-acetate **17-Ac**.

Compound **13** was transformed into diol **14** using the standard sugar methodology: protection of the primary OH (at the C1 and C12 positions) as trityl ethers to give **21** followed by benzylation of the C5–OH to give **22** and deprotection (Scheme 2).

Oxidation of both terminal hydroxyl groups was achieved with PCC and provided the di-aldehyde **23** in good yield. Double olefination was carried out with $Ph_3P{=}CH_2$ and afforded the di-olefin **15** in excellent yield (Scheme 3).

Attempts to cyclize di-olefin **15** in the presence of Grubbs (I and II generation; **A** and **B** in Figure 5), Hoveyda-Grubbs (II generation; **C** in Figure 5) catalysts, as well as modified complex: **D** or **E** were unsuccessful. After 24 h (in CH_2Cl_2 at rt or in toluene at 80 °C), no product **24** was formed.

It is reported that conducting the 'challenging' RCM cases in perfluorinated solvents can solve the problem of the low reactivity of certain olefins.[26] However, cyclization of di-olefin **15** in per-fluorobenzene was not effective either. The same failure was noted in the McMurry cyclization of the dialdehyde **23** (Scheme 4).

We cannot explain why the RCM for **15** and McMurry for **23** cyclizations did not. One of the reasons may be the size of the target ring; because there are ten benzyl groups present in the molecule, and the 12-membered ring could be too small to form easily.

We decided, therefore, to enlarge the size of the ring. Alcohol **14** was allylated and the resulting di-olefin **25** was subjected to the RCM reaction (Scheme 5). In order to avoid the cross-metathesis, this reaction was performed under high dilution conditions.

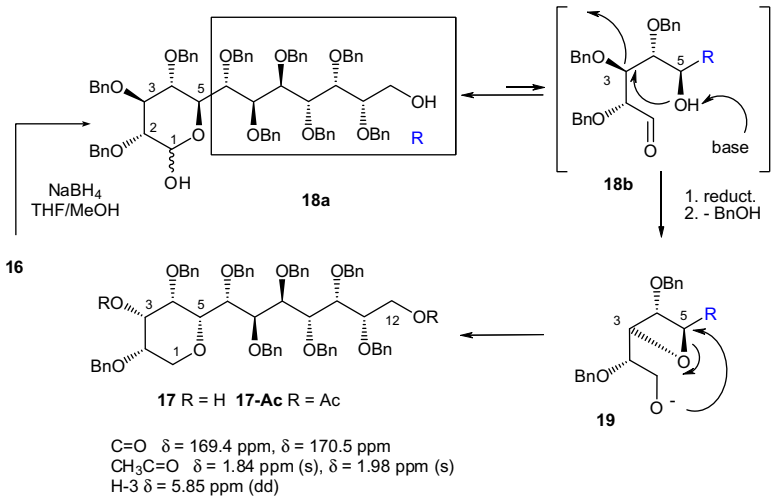
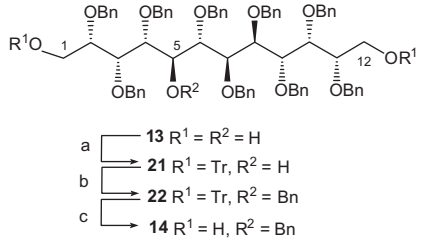
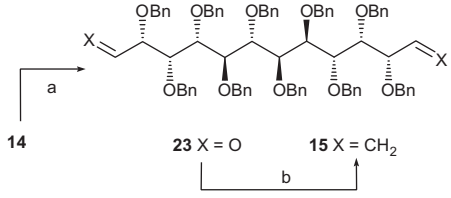


Figure 4. The (proposed) mechanism for the formation of compound **17**.



Scheme 2. Reagents: (a) TrCl, py; (b) BnCl/Bu_4NCl/50% NaOH; (c) *p*-TsOH/MeOH–ether (78% overall).



Scheme 3. Reagents: (a) PCC, CH_2Cl_2, 72%; (b) $Ph_3P{=}CH_2$, 75%.

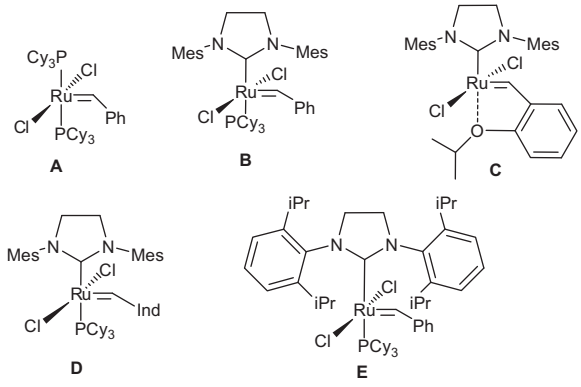
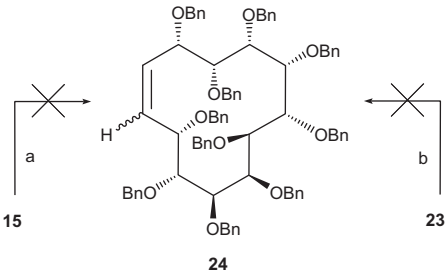
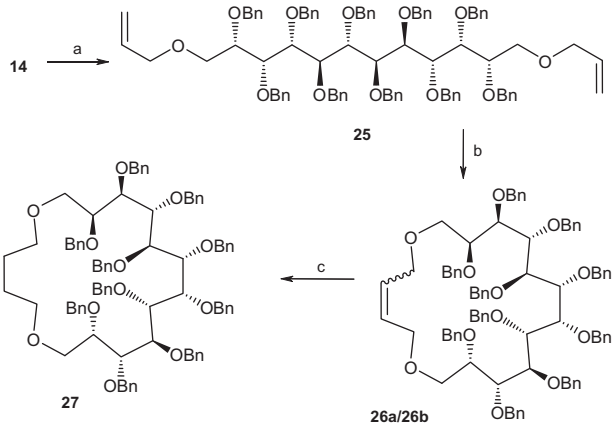


Figure 5. Catalysts used for RCM reaction.



Scheme 4. Reagents: (a) RCM (see: Section 4); (b) $TiCl_4$/Zn, THF, reflux.



Scheme 5. Reagents: (a) AllBr, toluene/50% NaOH/Bu_4NCl, 80 °C, 80%; (b) RCM (see: Table 1); (c) H_2NNH_2, O_2, cat. AcOH, EtOH, 60 °C, 72–77%.

Table 1
The RCM reaction of di-allyl derivative **25**

cat. (mol %)	Concn (10^{-3} M)	Temp	Time (h)	Yield **26a**/**26b** (%)
A, 20 mol %	4.5	rt	24	9/50
A, 20 mol %	0.7	85 °C	4.5	9/56
A, 30 mol %	0.7	rt	9	20/65
B, 20 mol %	0.7	rt	24	6/40[a]

[a] 16% of isomerized starting material was isolated.

We carried out several attempts; in all cases, two products **26a** and **26b** were formed. The results are shown in Table 1. Cyclization of **25** with Grubbs-I catalyst **A** at room temperature in toluene at low concentrations (4.5×10^{-3} M) afforded two cyclic products (as detected by MS) in 9% yield for **26a** and 50% yield for **26b**. After 24 h, complete conversion of the di-olefin and decomposition of the catalyst was achieved.

The same results were obtained at a higher temperature (entry 2), although the time of the reaction was shortened significantly. The reaction was more effective when 30 mol % of the catalyst was used (entry 3). Changing the catalyst to **B** (Grubbs-II) resulted in a decreased yield; significant isomerization of the starting material was also observed.

Although isomeric olefins **26a** and **26b** could be easily separated, we were unable to assign the geometry across the double bond. Even the high resolution ^{1}H NMR spectra (600 MHz) were not clear enough; the signals (especially in the olefinic region at δ: 5.52–5.75 ppm) were broadened, which did not allow us to precisely assign the coupling constants.

This might be due to the presence of trace amounts of ruthenium species in the product, which can cause significant broadening of the lines in the spectrum. However, using known methods for oxidative termination of the RCM process[27] (which should remove traces of the catalyst) did not improve the spectra. Moreover, the spectrum of di-olefin **25** (recovered from post-reaction mixture), which did contain trace amounts of the catalyst did not show significant broadening of the lines.

A possible explanation for the phenomenon of the broad lines in the NMR spectra may be connected with the large number of conformers of the macrocyclic skeleton (substituted with ten bulky benzyloxy groups), which may be relatively stable. However, the ^{1}H NMR spectrum recorded at a higher temperature (80 °C) in DMSO-d_6 did not improve the quality of the spectrum. Recording at a low temperature (−40 °C in $CDCl_3$ or −60 °C in CD_2Cl_2) was also not helpful for obtaining a spectrum of good quality.

These cyclic compounds were therefore characterized by HRMS and elemental analysis, as well as, their conversion into the saturated product **27**. Compound **26a** or (separately) **26b** upon treatment with hydrazine in the presence of air afforded the same compound **27**.

The NMR spectra (^{1}H and ^{13}C), also in case of **27**, were also unclear; most of the signals were broadened. However, in the ^{13}C NMR spectrum recorded in CD_2Cl_2 at −60 °C, two signals of the secondary carbons (CH_2–) at δ: 26.2 and 27.1 ppm were seen. Moreover, in the ^{1}H NMR spectra the olefinic signals at δ: 5.52–5.75 observed for unsaturated products **26a** and **26b** disappeared.

3. Conclusion

The higher sugar dodecitol with ten *O*-benzyl groups at the C2–C11 positions was converted into the C14-di-olefin, which was completely resistant towards RCM reactions most likely due to the steric hindrance created by ten benzyl units. Allylation of this dodecitol provided another di-olefin, which did undergo RCM cyclization. However, the cyclic products were very difficult to characterize even using 600 NMR spectroscopy.

4. Experimental

4.1. General

The NMR spectra were recorded with a Varian 600 MHz or Bruker 500 MHz in $CDCl_3$ at 25 °C unless otherwise stated. The structures were assigned, whenever necessary, with help of 2D correlation experiments (COSY, HSQC and HMBC). Chemical shifts (in most cases only diagnostic signals were shown) were reported with reference to TMS. Optical rotations were measured with a Jasco P 1020 polarimeter (sodium light) in chloroform at room temp. The MS spectra were recorded with a Mariner PerSeptive Biosystems spectrometer. Thin layer chromatography was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}). Column chromatography was carried out with silica gel (230–400 mesh).

4.1.1. Methyl 2,3,4,6,7,8,9,10,11-nona-*O*-benzyl-L-*threo*-L-*manno*-α-D-*gluco*-dodeca-1,5-pyranoside 10

This compound was prepared according to the literature;[19] $[\alpha]_D^{rt} = +14$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (600 MHz) δ: 4.59 (d, $J_{1,2}$ = 3.5, H-1), 4.23 (d, H-5), 3.97 (t, H-3), 3.83 (dd, $J_{3,4}$ = 9.1, $J_{4,5}$ = 10.2, H-4), 3.79 (t, H-10), 3.57 (m, H-12a i H-11), 3.45 (m, H-12b), 3.40 (dd, $J_{2,3}$ = 9.6, H-2), 3.30 (s, OMe), 1.68 (br s, OH); ^{13}C NMR (150 MHz) δ: 97.8 (C-1), 82.8 (C-3), 80.5 (C-10), 80.1 (C-2), 79.3 (C-11), 78.5 (C-4), 69.6 (C-5), 61.6 (C-12), 55.0 (OMe); HR-MS (ESI) *m*/*z*: 1207.5558; calcd for $C_{76}H_{80}O_{12}$ [M+Na$^+$]: 1207.5542; analysis: calcd for $C_{76}H_{80}O_{12}$: C, 77.00; H, 6.80; found: C, 77.11; H, 6.76.

4.1.2. Methyl 2,3,4,6,7,8,9,10,11-nona-*O*-benzyl-L-*threo*-L-*manno*-α-D-*gluco*-dodeca-1,5-pyranosid-12-ulose 11

This compound was prepared previously[19] in lower yield and was not characterized. Alcohol **10** (0.51 g, 0.43 mmol) was dissolved in methylene chloride to which PCC (1.4 g, 6.5 mmol) was added and the mixture was stirred for 7 h. The excess oxidant was filtered off and the filtrate was concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate, 8:1 to 6:1) to yield **11** in 0.49 g (95%). LR–MS (ESI) *m*/*z*: 1205.7; calcd for $C_{76}H_{78}O_{12}$ [M+Na$^+$]: 1205.

4.1.3. Methyl 2,3,4,6,7,8,9,10,11-nona-*O*-benzyl-12,13-dideoxy-12,13-didehydro-L-*threo*-L-*manno*-α-D-*gluco*-tridec-1,5-pyranoside 12

To a cooled (−78 °C) suspension of Ph_3PCH_3I (0.182 g, 0.45 mmol) in dry THF (20 mL), BuLi (0.17 mL 2.5 M solution in hexane, 0.43 mmol) was added and the mixture was stirred for 30 min. Next, aldehyde **11** (0.18 g, 0.15 mmol) in THF (4 mL) was added dropwise over 5 min, and the stirring was prolonged for another 30 min, after which the mixture was allowed to reach room temperature. After 24 h, saturated ammonium chloride was added, after which the mixture was stirred for 10 min and partitioned between water (10 mL) and ether (25 mL). The organic phase was separated and the aqueous phase extracted with ether (3 × 10 mL). The combined organic solutions were washed with water (10 mL), dried and concentrated; column chromatography (hexane/ethyl acetate, 99:1 to 8:1) of the crude product afforded pure **12** (62 mg, 35%). ^{1}H NMR (600 MHz) δ: 5.72 (ddd, $J_{11,12}$ = 7.4, $J_{12,13}$ = 10.2, $J_{12,13'}$ = 17.5, H-12), 5.11 (m, H-13 i H-13′), 4.59 (d, $J_{1,2}$ = 3.6, H-1), 4.23 (d, H-5), 3.97 (t, H-3), 3.82 (m, H-4), 3.40 (dd, $J_{2,3}$ = 9.7, H-2), 3.30 (s, OMe); ^{13}C NMR (150 MHz) δ: 135.5 (C-12), 118.7 (C-13), 97.8 (C-1), 82.8 (C-3), 80.1 (C-2), 78.5 (C-4), 69.7 (C-5), 55.0 (OMe); HR-MS (ESI) *m*/*z*: 1203.56059; calcd for $C_{77}H_{80}O_{11}$ [M+Na$^+$]: 1203.55929.

4.1.4. 1,12-Di-*O*-acetyl-2,3,4,6,7,8,9,10,11-nona-*O*-benzyl-L-*threo*-L-*manno*-D-*gluco*-dodeca-1,5-pyranose 16

Methyl glycoside **10** (1.83 g, 1.54 mmol) was dissolved in ethyl acetate (12 mL) to which acetic anhydride (24 mL) and sulfuric acid [4.3 mL of the solution: conc. H_2SO_4 (0.05 mL) in ethyl acetate (100 mL)] were added. The mixture was then stirred at rt until completion [3 d; TLC monitoring in hexane/ethyl acetate, 3:1; also ^{1}H NMR (200 MHz)]. The mixture was then diluted with ether (50 mL), washed with satd aq $NaHCO_3$ (5 × 40 mL) and water (40 ml), dried and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate, 95:5 to 8:1) to yield 1.64 g (85%) of **16** (mixture of α/β anomers in the ratio 4.5:1).

^{1}H NMR (600 MHz) δ: 6.34 [d, $J_{1,2}$ = 3.6, H-1(α)], 5.63 [d, $J_{1,2}$ = 8.2, H-1(β)], 3.89 [t, H-3(α)], 3.66 [t, H-3(β)], 3.46 [dd, H-2(α)], 3.42 [t, H-2(β)], 1.97 and 1.83 [2s, 2 × OAc(α)], 1.96 and 1.82 [2s, 2 × OAc(β)]; ^{13}C NMR (150 MHz) δ: 170.6 and 169.5 [2 × C=O(α)], 169.6 and 168.9 [2 × C=O(β)], 94.2 [C-1(β)], 89.6 [C-1(α)], 85.3 [C-3(β)], 82.3 [C-3(α)], 81.2 [C-2(β)], 79.1 [C-2(α)],

64.3 [C-12(α)], 64.1 [C-12(β)], 21.1 and 20.7 [2 × OC(O)CH_3(β)], 21.0 and 20.8 [2 × OC(O)CH_3(α)]; HR-MS (ESI) *m*/*z*: 1277.55987; calcd for $C_{79}H_{82}O_{14}$ [M+Na^+]: 1277.55968.

4.1.5. 2,3,4,6,7,8,9,10,11-Nona-*O*-benzyl-L-*threo*-L-*manno*-D-*gluco*-dodecitol 13

To a solution of compounds **16** (0.41 g, 0.33 mmol) in THF/methanol (3:1 v/v, 40 mL) $NaBH_4$ (3 g, 78 mmol) was added portionwise and the mixture was stirred for 24 h (TLC monitoring in hexane/ethyl acetate, 3:1). Next, the mixture was partitioned between ether (30 mL) and water (15 mL). The organic phase was separated, and the aqueous phase extracted with ether (2 × 15 mL). The combined organic solutions were washed with water (10 mL), dried and concentrated and the residue was subjected to column chromatography (hexane/ethyl acetate, 5:1 to 3:1) to give two products. Compound **13** (0.304 g, 78%) was isolated as an oil; HR-MS (ESI) *m*/*z*: 1195.55420; calcd for $C_{75}H_{80}O_{12}$ [M+Na^+]: 1195.55781; analysis: calcd for $C_{75}H_{80}O_{12}$: C, 76.77; H, 6.87; found: C, 76.84; H, 7.07. This compound was also characterized as a tri-acetate; ^{1}H NMR (600 MHz) δ: 5.82 (dd, *J* = 3.5, *J* = 7.2, H-5), 1.85, 1.82, and 1.81 (3s, 3 × OAc); ^{13}C NMR (150 MHz) δ: 170.6, 170.5, and 169.5 (3 × C═O), 64.1 and 64.0 (C-1 and C-12); HR-MS (ESI) *m*/*z*: 1321.59163; calcd for $C_{81}H_{86}O_{15}$ [M+Na^+]: 1321.59163. 1-Deoxy-2,4,6,7,8,9,10,11-octa-*O*-benzyl-L-*threo*-L-*manno*-α-D-*allo*-dodeca-1,5-pyranoside **17** (0.070 g, 20%); HR-MS (ESI) *m*/*z*: 1087.50165; calcd for $C_{68}H_{72}O_{11}$ [M+Na^+]: 1087.49669; Analysis: calcd for $C_{68}H_{72}O_{11}$: C, 76.67; H, 6.81; found: C, 76.81; H, 6.58.

$[\alpha]_D^{rt} = -28.0$ (*c* 1.3, $CHCl_3$).

4.2. Determination of the structure of 17

Ozonolysis of this derivative under standard conditions was unsuccessful, which excluded the presence of the double bond in the molecule. Acetylation of this compound provided the acetate **17-Ac**. ^{1}H NMR (600 MHz) δ: 5.85 (dd, $J_{2,3}$ = 7.1, $J_{3,4}$ = 3.6, H-3), 4.37 (dd, $J_{4,5}$ = 7.1, H-4), 4.28 (dd, *J* = 3.2, *J* = 9.6, H-6), 4.14–4.07 (m, H-1a, H-12a, H-9, H-2), 3.93 (dd, *J* = 6.6, *J* = 11.8, H-12b), 3.80 (dd, $J_{1b,2}$ = 4.3, $J_{1a,1b}$ = 12.2, H-1b), 3.76 (m, H-11), 3.63 (dd, *J* = 4.3, *J* = 5.8, H-10), 1.99 and 1.84 (2s, 2 × OAc); ^{13}C NMR (150 MHz) δ: 170.5 and 169.4 (2 × C═O), 80.5 (C-5), 80.0 (C-6), 78.5 (C-10), 77.7 (C-2), 77.5 (C-11), 71.5 (C-1 and C-3), 64.2 (C-12), 21.2 and 20.8 (2 × OC(O)CH_3). LR-MS (ESI) *m*/*z*: 1171.6; calcd for $C_{72}H_{76}O_{13}$ [M+Na^+].

4.2.1. 2,3,4,5,6,7,8,9,10,11-Deca-*O*-benzyl-L-*threo*-L-*manno*-D-*gluco*-dodecitol 14

Compound **13** (1.71 g, 1.46 mmol) was dissolved in methylene chloride (25 mL), containing triethylamine (3 mL), trityl chloride (3 g, 10 mmol) and DMAP (25 mg). The mixture was heated at reflux for 5 h (TLC monitoring in hexane/ethyl acetate, 4:1), then cooled to rt and partitioned between ether (50 mL) and water (50 mL). The organic phase was separated and the aqueous phase extracted with ether (2 × 20 ml). The combined organic solutions were washed with water (40 mL) and brine (40 mL), dried and concentrated and the crude product **21** (LR MS; *m*/*z*: 1679.8; calcd for $C_{113}H_{108}O_{12}$ [M+Na^+]: 1679) was used in the next step without purification.

To a solution of crude **21** in toluene (30 mL), benzyl chloride (8.4 mL, 73 mmol) was added, followed by 50% aq NaOH (40 mL) and Bu_4NBr (50 mg). The mixture was vigorously stirred for 5 days (TLC monitoring in hexane/ethyl acetate, 5:1) and partitioned between ether (50 mL) and water (50 mL). The organic phase was separated, dried and concentrated and the crude **22** (LR MS; *m*/*z*: 1769.9; calcd for $C_{120}H_{114}O_{12}$ [M+Na^+]: 1769) was used in the next step without purification.

Crude **22** was dissolved in ether/methanol (v/v 1:1; 40 mL) to which *p*-TsOH·H_2O (3 g, 15 mmol) was added, and the mixture was stirred and heated at reflux for 5 h. After cooling to rt, it was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic phase was separated, and the aqueous phase extracted with ethyl acetate (2 × 25 mL). The combined organic solutions were washed with water (50 mL) and brine (50 mL), dried and concentrated and the product was isolated by column chromatography (hexane/ethyl acetate, 7:1 to 4:1) to afford **14** (1.45 g, 78% after three steps). HR-MS (ESI) *m*/*z*: 1285.5983; calcd for $C_{82}H_{86}O_{12}$ [M+Na^+]: 1285.60115. Analysis: calcd for $C_{82}H_{86}O_{12}$: C, 77.95; H, 6.86; found: C, 78.17; H, 6.46%; $[\alpha]_D^{rt} = +2.0$ (*c* 0.5, $CHCl_3$). This diol was further characterized as a di-acetate **14-Ac**. ^{1}H NMR (600 MHz): 1.79 and 1.78 (2s, 2 × OAc); ^{13}C NMR (150 MHz) δ: 170.6 and 170.5 (2 × C═O), 139.8–138.2 (10 × 4°$C_{aromat.}$), 74.8–71.6 (10 × CH_2Ph), 64.3 and 64.1 (C-1 and C-12), 20.8 and 20.7 [2 × OC(O)CH_3]; HR-MS (ESI) *m*/*z*: 1369.62598; calcd for $C_{86}H_{90}O_{14}$ [M+Na^+]: 1369.62228.

4.2.2. (2*R*,3*S*,4*R*,5*R*,6*R*,7*S*,8*R*,9*R*,10*S*,11*R*)-2,3,4,5,6,7,8,9,10,11-Deca(benzyloxy)-dodecanedial 23

Diol **14** (0.41 g, 0.32 mmol) was dissolved in methylene chloride (60 mL), and then PCC (2.6 g, 12 mmol) was added and the mixture was stirred for 6 h at rt. The inorganic material was filtered off, the filtrate was concentrated and the crude product was isolated by column chromatography (hexane/ethyl acetate, 95:5 to 9:1) to afford pure dialdehyde **23** (0.294 g, 72%) as an oil. ^{1}H NMR (600 MHz) δ: 9.56–9.37 (2 × HC═O); ^{13}C NMR (150 MHz) δ: 201.6–201.3 (2 × HC═O), 139.2–127.2 (10 × 4°$C_{aromat.}$), 75.1–72.0 (10 × CH_2Ph). HR-MS (ESI) *m*/*z*: 1281.57168; calcd for $C_{82}H_{82}O_{12}$ [M+Na^+]: 1281.56985. Analysis: calcd for $C_{82}H_{82}O_{12}$: C, 78.20; H, 6.56; found: C, 78.38; H, 6.62; $[\alpha]_D^{rt} = +20$ (*c* 1.0, $CHCl_3$).

4.2.3. (3*S*,4*R*,5*S*,6*S*,7*S*,8*R*,9*S*,10*S*,11*R*,12*S*)-3,4,5,6,7,8,9,10,11,12-Deca(benzyloxy)-tetradeca-1,13-diene 15

This reaction was conducted under an argon atmosphere. To a cooled (at −78 °C) suspension of Ph_3PCH_3I (0.407 g, 1 mmol) in dry THF (12 mL), BuLi (0.38 mL of a 2.5 M solution in hexane, 0.95 mmol) was added and the mixture was stirred for 45 min. Next, di-aldehyde **23** (0.126 g, 0.1 mmol) in THF (8 mL) was added dropwise (during 15 min) and the mixture was allowed to reach rt. Saturated ammonium chloride (10 mL) was added, stirring was continued another 15 min, after which the mixture was partitioned between ether (20 mL) and water (15 mL). The organic phase was separated and the aqueous phase extracted with ether (3 × 10 mL). The combined organic solutions were washed with water (15 mL), brine (15 mL), dried and concentrated and the product was isolated by column chromatography (hexane/ethyl acetate, 99:1 to 95:5) to afford pure di-olefin **15** (0.0941 g, 75%) as an oil. ^{1}H NMR (600 MHz) δ: 5.74 (m, *J* = 7.6, J_Z = 10.4, J_E = 17.3, H-2 or H-13), 5.63 (m, H-13 or H-2), 5.08–4.92 (m, H-1a, H-1b, H-14a and H-14b), 4.05 (dd, *J* = 5.2, *J* = 7.7, H-3 or H-12), 3.96 (dd, *J* = 5.2, *J* = 7.2, H-3 or H-12), 3.82 (t, H-4 or H-11); ^{13}C NMR (150 MHz) δ: 139.6–138.4 (10 × 4°$C_{aromat.}$), 135.8 and 135.7 (C-2 and C-13), 118.6 and 118.4 (C-1 and C-14), 82.9 (C-4 or C-11), 81.8 and 81.3 (C-3 and C-12), 75.0–70.1 (10 × CH_2Ph). HR-MS (ESI) *m*/*z*: 1277.61071; calcd for $C_{84}H_{86}O_{10}$ [M+Na^+]: 1277.61132. Analysis: calcd for $C_{84}H_{86}O_{10}$: C, 80.35; H, 6.90; found: C, 80.50; H, 6.77 $[\alpha]_D^{rt} = +23$ (*c* 0.5, $CHCl_3$).

4.2.4. (6*S*,7*R*,8*S*,9*S*,10*S*,11*R*,12*S*,13*S*,14*R*,15*S*)-6,7,8,9,10,11,12,13,14,15-Deca(benzyloxy)-4,17-dioxan-icosa-1,19-diene 25

To a solution of diol **14** (107.9 mg, 0.0855 mmol) in toluene (5 mL), allyl bromide (0.3 mL, 3.5 mmol) and 50% aq NaOH (5 mL) were added followed by tetrabutylammonium chloride (30 mg). This heterogeneous mixture was vigorously stirred at

80 °C for 24 h and, after cooling to rt, partitioned between ether (10 mL) and water (10 mL). The organic phase was separated and the aqueous phase extracted with ether (10 mL). The combined organic solutions were washed with water (10 mL) and brine (10 mL), dried and concentrated and the product was isolated by column chromatography (hexane/ethyl acetate, 98:2 to 95:5) to yield pure di-olefin **25** (92 mg, 80%) as an oil. ^{1}H NMR (600 MHz) δ: 5.75 (m, H-2 and H-17), 5.14 (m, J = 1.7, J = 3.1, J_E = 13.9, H-1b or H-18b), 5.11 (m, J = 1.7, J = 3.1, J_E = 13.9, H-1b or H-18b), 5.07 (m, J = 1.0, J = 3.1, J_Z = 10.4, H-1a or H-18a), 5.04 (m, J = 1.0, J = 3.1, J_Z = 10.4, H-1a or H-18a), 3.72 (m, H-3 or H-16) and 3.68 (m, H-3 or H-16); ^{13}C NMR (150 MHz) δ: 139.6–138.4 ($10 \times 4°C_{aro-mat.}$), 135.0 and 134.5 (C-2 and C-17), 116.6 and 116.4 (C-1 and C-18), 72.0 and 71.9 (C-3 and C-16). HR-MS (ESI) m/z: 1365.6691; calcd for $C_{88}H_{94}O_{12}$ [M+Na$^+$]: 1365.66375. Analysis: calcd for $C_{88}H_{94}O_{12}$: C, 78.66; H, 7.05; found: C, 78.45; H, 7.09; $[\alpha]_D^{rt} = -5$ (c 0.25, $CHCl_3$).

4.3. General procedure for the RCM reaction of polyhydroxylated di-olefins

This reaction was conducted in dry solvents under an argon atmosphere. To a solution of the corresponding diene in an appropriate solvent the catalyst for the RCM reaction, dissolved in the minimum amount of the same solvent, was added, and the reaction (carried out at given temp.) was monitored by TLC. After completion, the solvent was removed in vacuo, and the residue was purified by column chromatography or preparative TLC.

4.4. Attempts to cyclize the di-olefin

To a solution of diene **15** (15 mg, 0.0119 mmol) in methylene chloride (25 mL; $c = 4.5 \times 10^{-3}$ M/L), Grubbs-I catalyst (or **B**–**D**; 15 mol%) was added and the mixture was kept at rt for 24 h. Only the starting material was recovered.

To a solution of the diene **15** (72 mg, 0.0571 mmol) in toluene (80 mL; $c = 0.7 \times 10^{-3}$ M/L), Grubbs-I catalyst (or **B**, **E**; 20 mol %) was added and the mixture was kept at 80 °C for 72 h. After this time, the unchanged starting material (61.8 mg) was recovered together with small amounts of an isomerized derivative (as detected by MS). Similar results were obtained with cat. **E** in C_6F_6 ($c = 4.5 \times 10^{-3}$ M; t = 75 °C).

4.5. Cyclization of the di-*O*-allyl derivative 25

To a solution of diene **25** (86 mg, 0.0879 mmol) in toluene (14 mL; $c = 4.5 \times 10^{-3}$ M/L) Grubbs-I catalyst (20 mol %) was added and the mixture was kept at rt for 24 h. The products were isolated by preparative TLC (hexane/ethyl acetate, 5:1; 3 dev.) to afford **26a** (7.8 mg, 9%) and **26b** (41.8 mg, 50%). Similar results were obtained after 4.5 h at 85 °C. When this reaction was conducted at lower concentrations (118.1 mg, 0.0879 mmol of **25** in 125 mL of toluene; $c = 0.7 \times 10^{-3}$ M/L) with higher amounts of the catalyst (35%) higher yields of the cyclic products were obtained [(22.7 mg (20%) of **26a** and 74.8 mg (65%) of **26b**].

To a solution of diene **25** (91 mg, 0.0677 mmol) in toluene (125 mL) Grubbs-II catalyst (20 mol%) was added and the mixture was kept at rt for 24 h. The products were isolated by preparative TLC to yield: **26a** (5.7 mg, 6%), **26b** (35.5 mg, 40%) and a mixture of isomerized starting material (as detected by (ESI) MS; m/z; 1365.7; for $C_{88}H_{94}O_{12}$ [M+Na$^+$]: 1365). Data for **26a**: HR-MS (ESI) m/z: 1337.63625; calcd for $C_{86}H_{90}O_{12}$ [M+Na$^+$]: 1337.63245. Data for **26b**: ^{1}H NMR (600 MHz, −40 °C) δ: 5.66 and 5.47 (2 bm, H-1 and H-16); HR-MS (ESI) m/z: 1337.63447; calcd for $C_{86}H_{90}O_{12}$ [M+Na$^+$]: 1337.63245; analysis for **26a/26b**: calcd for $C_{86}H_{90}O_{12}$: C, 78.51; H, 6.90; found: C, 78.49; H, 6.96.

4.6. Reduction of the double bond in 26a

Cyclic olefin **26a** (54 mg, 0.041 mmol) was dissolved in ethanol (5 mL) to which hydrazine hydrate (98%; 0.2 mL) was added followed by 3 drops of acetic acid, and the mixture was stirred at 60 °C for 3 h. After this time, TLC (hexane/ethyl acetate, 5:1) showed the disappearance of the starting material and the formation of a new, slightly less polar product. After cooling to rt, water (5 mL) was added, the organic phase was separated and the aqueous phase extracted with ether (3×5 mL). The combined organic solutions were dried and concentrated, and the product was isolated by preparative TLC (benzene/ether, 100:2) to afford macrocyclic derivative **27** (41.6 mg, 77%). ^{13}C NMR (125 MHz, CD_2Cl_2, −60 °C) δ: 27.1 and 26.2 (C-1 and C-16); HR-MS (ESI) m/z: 1339.64451; calcd for: $C_{86}H_{92}O_{12}$ [M+Na$^+$]: 1339.64810. Analysis: calcd for $C_{86}H_{92}O_{12}$: C, 78.39; H, 7.04; found: C, 78.57; H, 7.05; $[\alpha]_D^{rt} = +7$ (c 0.6, $CHCl_3$). Reduction of **26b** under the same conditions (t = 9 h) provided the same derivative **27** in 72% yield.

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