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Synthesis of a Structural Analogue of the Repeating Unit from *Streptococcus pneumoniae* 19F Capsular Polysaccharide Based on the Cross-Metathesis–Selenocyclization Reaction Sequence[#]

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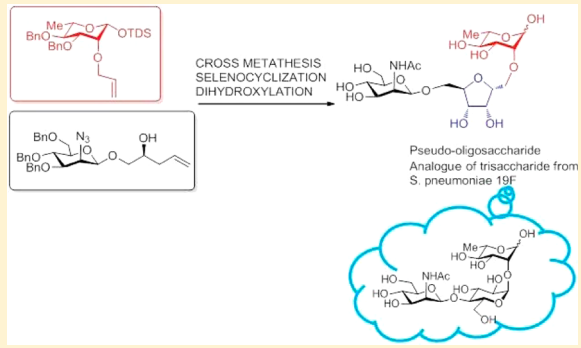
Supporting Information

ABSTRACT: Pseudo-oligosaccharides have attracted much interest as scaffolds for the synthesis of sugar mimics endowed with very similar biological properties but structurally and synthetically simpler than their natural counterparts. Herein, the synthesis of pseudo-oligosaccharides using the cross-metathesis reaction between distinct sugar-olefins followed by intramolecular selenocyclization of the obtained heterodimer as key steps is first investigated. This methodology has been then applied to the preparation of structural analogues of the trisaccharide repeating unit from *Streptococcus pneumoniae* 19F. The inhibition abilities of the synthetic molecules were evaluated by a competitive ELISA assay using a rabbit polyclonal anti-19F serum.



INTRODUCTION

Carbohydrates feature an enormous structural diversity, which makes them the most important mediators in the intercellular interactions and with extracellular matrix components, such as enzyme, hormones, toxins, bacteria, viruses, etc.[1] It follows that oligo- and polysaccharides play a fundamental role in signal transduction and vital molecular recognition phenomena, thus offering exciting new therapeutic opportunities in biomedical fields.[2] Nevertheless, the development of saccharide-based drugs using classical carbohydrate synthesis can still be a difficult task,[3] despite the excellent progresses made by modern carbohydrate chemistry.[4] Sugar mimics endowed with very similar biological properties, but structurally and synthetically simpler than their natural counterparts, may offer a valuable alternative. Thus, there is a strong demand for general and efficient approaches to these structures that would allow circumvention of the typical challenges associated with oligosaccharide synthesis, such as laborious protecting group manipulations and the lack of a general method for the stereoselective formation of glycosidic linkages.

Among the most recent advances in synthetic organic chemistry, transition metal-catalyzed olefin metathesis has undoubtedly gained a prominent role as a highly promising and valuable methodology for the construction of carbon–carbon bonds.[5] In particular, during the past decade, there has been an enormous growth of the metathesis area due to the availability of robust and well-defined ruthenium alkylidene-based precatalysts, endowed with high reactivity, air-stability, and impressive functional group tolerance.[5a,6]

Although most applications of olefin metathesis employ the more entropically favored ring-closing metathesis (RCM), the advent of the new catalysts led to increasing applications of the cross-metathesis (CM) reaction in synthetic organic chemistry.[5] However, there are relatively few examples of selective cross-metatheses applied to carbohydrate chemistry, and they are mostly limited to the homodimerization of *O*-allyl and *C*-allyl glycosides or their cross-linking with various types of aliphatic and aromatic olefins.[7] On the other hand, the selective cross-coupling between unlike sugar olefins to provide the corresponding heterodimer is a very attractive process, because the diversity of accessible carbohydrate derivatives is much higher compared to simple homodimerization. With the purpose to further explore the potential of CM reaction in the field of carbohydrate chemistry, we recently described a preliminary investigation on the synthesis of pseudo-oligosac-

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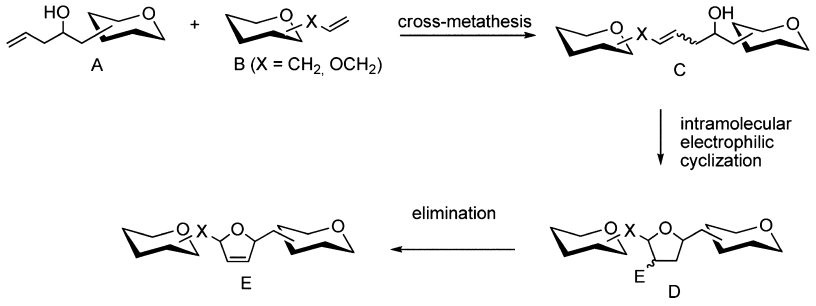
Scheme 1. Synthetic Strategy



charides employing the cross-metathesis reaction between sugar olefins followed by intramolecular cyclization.[8]

In our early investigation, the use of molecular iodine to promote the electrophilic cyclization afforded iodocyclized type D compounds (Scheme 1, E = I) with poor stereoselectivity and as an inseparable mixture of diastereoisomers, thus implying that the monosaccharide units do not exert a significant asymmetric induction on the iodocyclization reaction course.[8] Moreover, the 1,2-elimination of iodine to provide the endocyclic C−C double bond (compound E) required very harsh reaction conditions (DBU in refluxing toluene, 5−7 days), not applicable to substrates containing base-sensitive functional groups.

In the quest for different promoters that could improve the stereoselectivity of the cyclization and/or facilitate the separation of the type D diastereoisomers (Scheme 1), we considered the use of electrophilic organoselenium reagents. The selenocyclization reaction has been frequently applied to unsaturated alcohols[9] and acids.[10] Of particular importance is the possibility of performing either reagent-controlled[11] or substrate-controlled[12] asymmetric cyclization reactions from which enantiomerically enriched or enantiopure heterocycles can be obtained. In addition, once incorporated, the selenium moiety can be easily converted into different functional groups or eliminated.[13] The best known and widely used syn elimination of selenoxides[14] would introduce a new endocyclic C−C double bond that lends itself to further synthetic transformations.

In the present paper, type E pseudo-oligosaccharides are achieved by a strategy based on heterodimerization by CM reaction of suitably elaborated monosaccharides A and B, followed by intramolecular selenocyclization of intermediate C and 1,2-elimination of the electrophile (Scheme 1).

Because type E compounds can be seen as potentially useful scaffolds for the synthesis of mimics of naturally occurring, biologically important carbohydrates, we decided to check the generality and feasibility of our methodology on more complex and functionalized molecular target of biological relevance. We therefore report herein on the synthesis of the pseudotrisaccharides **1a**/**1b** (Figure 1) as potential mimics of the trisaccharide repeating unit of the capsular polysaccharide (CPS) from the Gram+ bacterium *Streptococcus pneumoniae* 19F. Finally, the relative affinities of synthetic compounds **1a**/**1b** (differing in their configurations at C-3 and C-4; see Figure 1) were investigated in comparison with the natural trisaccharide repeating unit and native 19F polysaccharide (positive control) by a competitive ELISA assay using a rabbit polyclonal anti-19F serum.

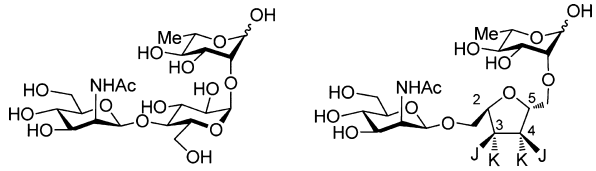


Figure 1. Structures of the trisaccharide repeating unit of *S. pneumoniae* 19F and synthetic analogues **1a**/**1b**.

RESULTS AND DISCUSSION

Synthesis of Pseudotrisaccharides by Selenocyclization. To the best of our knowledge, while the use of selenium nucleophiles has been widely explored in carbohydrate chemistry, only a few synthetic applications of selenium electrophiles in this area have been reported.[15] So our initial effort was devoted to explore the behavior of different electrophilic selenium reagents (compounds **2**−**4**, Figure 2),

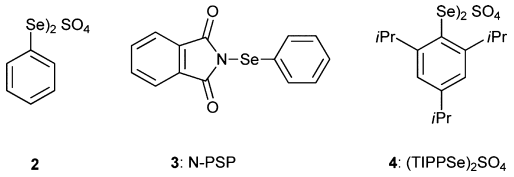


Figure 2. Structures of the selenium reagents employed in the present work.

in the selenocyclization reaction on heterodimers **5**, **6**, and **7** (Scheme 2), prepared as previously described and fully characterized by assignment of the *R* configuration at C-7[8] (corresponding to *S* configuration at C-5 in tricyclic compounds **8**−**19**).

All the selenium reagents reported in Figure 2 were able to promote the cyclization of our substrates, though with different efficiencies.

Preliminary experiments were carried out on diastereoisomerically pure heterodimer **5** using phenylselenyl sulfate **2** (Figure 2) as a promoter, that was easily produced in situ by the reaction of diphenyl diselenide with ammonium persulfate in acetonitrile at 80 °C (Table 1, entry 1) or at room temperature by the addition of trifluoromethanesulfonic acid to a mixture of diphenyl diselenide and ammonium persulfate (Table 1, entry 2).[16] In both cases we obtained the two diastereoisomers **8** and **9** (Scheme 2) in high to excellent yields with a moderate diastereoisomeric ratio (1:2). The best diastereoisomeric ratio was however achieved performing the selenocyclization with *N*-(phenylseleno)phthalimide (N-PSP)

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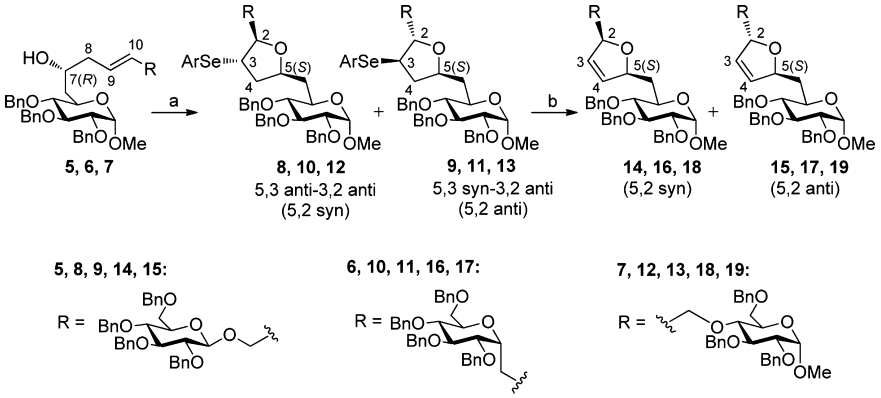
Scheme 2. Synthesis of Pseudotrisaccharides by a Selenocyclization−Elimination Sequence[a]



[a]Key: (a) See Table 1; (b) H_2O_2, MeOH, rt, then $NaHCO_3$, benzene, 80 °C.

Table 1. Selenocyclization of Heterodimers 5, 6, and 7[a]

entry	heterodimer[b]	Se species[c]	exptl conditions	cyclic ether[b] (diast ratio)[d]	yield, %
1	**5**	**2**	method A, 15 min	**8**/**9** (1/2)	82
2	**5**	**2**	method B, 30 min	**8**/**9** (1/2)	92
3	**5**	**3**	method C, 1 h	**8**/**9** (1/3)	79
4	**5**	**4**	method D, 5 h	**8**/**9** (1/1.2)	70
5	**6**	**3**	method C, 1 h	**10**/**11** (1:3.4)[e]	60
6	**6**	**4**	method D, 1 h	**10**/**11** (1:1.9)	79
7	**7**	**3**	method C, 1 h	**12**/**13** (1/1.3)	23
8	**7**	**4**	method B, 1 h	**12**/**13** (1/1.8)	45
9	**7**	**2**	method A, 1 h	**12**/**13** (1/2.3)	45

[a]Method A: $(PhSe)_2$, $(NH_4)_2S_2O_8$, CH_3CN, 80 °C; method B: $(PhSe)_2$ or $(TIPPSe)_2$, $(NH_4)_2S_2O_8$, CF_3SO_3H, CH_3CN, rt; method C: N-PSP, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to rt; method D: $(TIPPSe)_2$, $(NH_4)_2S_2O_8$, CF_3SO_3H, CH_3CN, rt. [b]See Scheme 2 for chemical structures. [c]See Figure 2 for Se species. [d]Diastereoisomeric ratios were calculated from the ^1H NMR spectra of the crude mixture by integration. [e]Only in this case was an inseparable mixture of diastereoisomers obtained.

3 (Figure 2) in the presence of $BF_3{\cdot}OEt_2$ (Table 1, entry 3). On the other hand, the use of the more sterically demanding (2,4,6-triisopropylphenyl)selenium sulfate $(TiPPSe)_2SO_4$ **4** (Figure 2), derived by addition of ammonium persulfate to the corresponding diselenide[17] in the presence of trifluoromethanesulfonic acid in acetonitrile, led to a reasonable yield but poor diastereoselectivity (Table 1, entry 4). The obtained cyclic ethers were separated by column chromatography and examined by NMR spectroscopy using mono- and bidimensional (H,H-COSY, HMQC) techniques. In all cases we observed the exclusive formation of 2,3-anti diastereoisomers, in agreement with the widely accepted mechanism of selenium electrophilic addition to alkenes, i.e., the intramolecular nucleophilic attack of the hydroxy group occurs by the backside at the bridged selenonium ion, giving overall anti addition. In particular, the structures of tricyclic compounds **8** and **9** (Ar = Ph, Scheme 2) were assigned on the basis of NOESY experiments (see Supporting Information). In compound **8** a strong dipolar interaction was observed between H-5 and H-2, indicating the 5,2-syn relationship in the minor diastereoisomer, while in pseudotrisaccharide **9** the dipolar interaction between H-5 and H-3 confirmed their 5,2-anti relative configuration in the major diastereoisomer. This allowed the assignment of *S* configuration at C-2 of the major isomer **9**, and the *R* configuration at the same carbon of the minor isomer **8**.

The selenocyclization of heterodimer **6** was carried out using *N*-(phenylseleno)phthalimide, but an inseparable mixture of diastereoisomers was obtained (Table 1, entry 5). The use of $(TIPPSe)_2SO_4$ **4** provided a mixture 1:1.9 of two diastereoisomers **10** and **11** (Scheme 2, Ar = TIPP), that were easily separated by column chromatography (Table 1, entry 6). Although both diastereoisomers were fully characterized by NMR, we could not determine the absolute configuration at C-2, due to overlapping of the signals corresponding to H-5 and H-2 protons (both in $CDCl_3$ and C_6D_6). However, the structure assignment for compounds **10** and **11** was later deduced on the basis of the NMR characterization of the corresponding elimination products **16** and **17** (see below).

The cyclization of heterodimer **7** with the selenium reagents **2**, **3**, and **4** (Figure 2) led in all cases to modest yields and stereoselectivities. The best result was achieved using phenylselenyl sulfate (Table 1, entry 9), that afforded a 1:2.3 ratio of the cyclized products **12** and **13** in 45% yield (Scheme 2, Ar = Ph). The stereochemical structures reported in Scheme 2 were derived by a tentative attribution comparing the ^{13}C NMR chemical shifts of C-3 and C-4 with the corresponding values measured for the same carbons in compounds **8** and **9**, whose configurations were unambiguously determined.[18]

All the selenocyclized pseudotrisaccharides **8**−**13** were next subjected to the elimination reaction by oxidation with hydrogen peroxide in methanol at room temperature (Scheme 2). The subsequent syn elimination occurred by refluxing the obtained selenoxides in benzene containing 10% of sodium hydrogencarbonate. In all cases the elimination products were purified by column chromatography and fully characterized by NMR spectroscopy. Following this procedure, compounds **14** and **15** were obtained from pseudotrisaccharides **8** and **9** in 77% and 96% yield, respectively. 1D NOE experiment carried out in C_6D_6 on compound **14** showed a strong dipolar interaction between H-5 and H-2, confirming their syn relationship previously determined on **8**. On the other hand, NMR analysis by rotating-frame Overhauser spectroscopy (2D ROESY experiment) of compounds **16** and **17**, derived by

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oxidative elimination of compounds **10** (90% yield) and **11** (98% yield), respectively, allowed the determination of the absolute configuration at C-2, which was unfeasible for the selenocyclized precursors (see Supporting Information for a detailed NMR analysis).

Finally, oxidative elimination of compounds **12** and **13** afforded pseudotrisaccharides **18** and **19** in 77% and 93% yield, respectively (Scheme 2). An analogous trend with fully characterized elimination products **14** and **15** was observed in the ^{1}H NMR analysis of compounds **18** and **19**, further supporting our previous attributions of the absolute configuration at C-2 indicated in Scheme 2 on selenocyclized precursors **12** and **13**.[19]

Altogether these results indicate that, in comparison to the iodocyclization, the use of selenium electrophiles for the cyclization reaction leads to higher, even if moderate, stereoselectivity. Moreover, the possibility to change the R group in the selenium electrophile (RSe^+) permits in all cases the separation of the two diastereoisomers. A second apparent and more convincing advantage is the very mild conditions required for the elimination step, which allows us to considerably extend the feasibility of the selenium protocol also on highly functionalized and delicate substrates.

Synthesis of a Structural Analogue of the Trisaccharide from *S. pneumoniae* 19F Capsular Polysaccharide. The Gram-positive bacterium *Streptococcus pneumoniae*[20] is a major cause of death and disability throughout the world,[21] causing meningitis, otitis, septicemia, and pneumonia, both in developed and in developing countries.[22] Although vaccination against pneumococcal diseases has become a global health priority,[23] between 800 000 and one million children under five years of age still die annually from *Streptococcus pneumoniae* infections.[24] Serotype 19F of *Streptococcus pneumoniae*, whose CPS is composed of (→4)-β-D-Man*p*NAc-(1→4)-α-D-Glc*p*-(1→2)-α-L-Rha*p*-(1-OPO$_3^-$→) repeating units (Figure 1), is one of the most commonly isolated serotypes causing pneumococcal disease. Some of us have a long established experience on the synthesis of *S. pneumoniae* 19F CPS fragments[25] and structural analogues.[26] We therefore considered the 19F trisaccharide repeating unit the ideal candidate as a proof-of-concept for our synthetic methodology illustrated in Scheme 1 to verify whether it could be a potentially useful approach to target biologically important oligosaccharides.

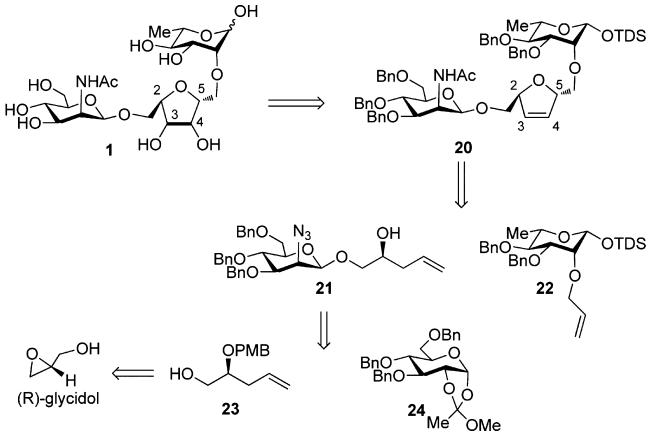
As outlined in Scheme 3, we envisaged compound **20** as a suitable precursor of our synthetic target **1**. Synthesis of pseudotrisaccharide **20** could be achieved by CM reaction between sugar olefins **21** and **22** followed by electrophilic cyclization and elimination.

The synthesis of the rahmnoside unit **22** was accomplished by sequential silylation (thexyldimethylsilyl chloride and imidazole in CH_2Cl_2) and 2-O-allylation (AllBr, NaH in DMF) of 3,4-di-*O*-benzyl-L-rhamnopyranose, which in turn was easily obtained from known 3,4-di-*O*-benzyl-1,2-*O*-(1-methoxyethylidene)-β-L-rhamnopyranose.[27]

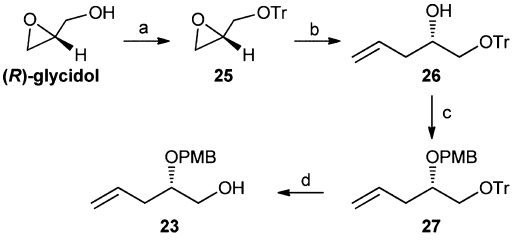
The β-mannoside **21** can be derived by glycosylation with the glucose-derived orthoester **24**[28] of the enantiopure alcohol **23**, which in turn can be prepared starting from the commercially available (*R*)-glycidol.

Our synthesis of alcohol **23** began with the protection of the (*R*)-glycidol hydroxyl as triphenylmethyl (trityl, Tr) ether followed by epoxide ring-opening with an organocopper reagent generated in situ from vinylmagnesium bromide and copper(I) iodide at −30 °C (Scheme 4). According to the

Scheme 3. Retrosynthetic Strategy for the Synthesis of the Pseudotrisaccharide 1



Scheme 4. Synthesis of Alcohol 23[a]



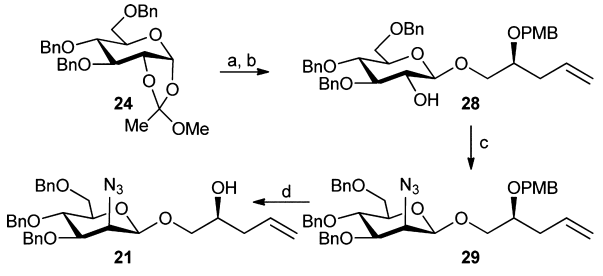
[a]Key: (a) TrCl, TEA, CH_2Cl_2, 81%; (b) vinylMgBr, CuI, THF, −30 °C; (c) PMBBr, NaH, DMF; (d) PTSA, MeOH, 88% over three steps.

procedure reported by Mulzer and co-workers,[29] alcohol **26** was obtained in enantiopure form. The 2-OH was then protected as a *p*-methoxybenzyl (PMB) ether (compound **27**), and the subsequent hydrolysis of the trityl group with a catalytic amount of *p*-toluensulfonic acid (PTSA) in methanol cleanly furnished alcohol **23** in 88% yield over three steps.

Glycosylation of alcohol **23** with orthoester **24** was carried out using TMSOTf as acidic promoter at −40 °C and afforded a mixture of 2-OH and 2-OAc derivatives, which was subjected to deacetylation under Zemplen conditions to provide glucoside **28** in 66% yield over two steps (Scheme 5).

The 2-OH of **28** was then activated as a triflate with trifluoromethanesulfonic anhydride in dichloromethane at −40 °C, followed by nucleophilic displacement with freshly prepared tetrabutylammonium azide in toluene at 60 °C, providing β-2-azidomannopyranoside **29**. Finally, removal of

Scheme 5. Synthesis of Mannoside 21[a]



[a]Key: (a) **23**, TMSOTf, CH_2Cl_2, −40 °C ; (b) Na, MeOH, 66% over two steps; (c) Tf_2O, Py, CH_2Cl_2, −40 °C, then Bu_4NN_3, toluene, 60 °C; (d) DDQ, H_2O:CH_2Cl_2 19:1, 55% over three steps.

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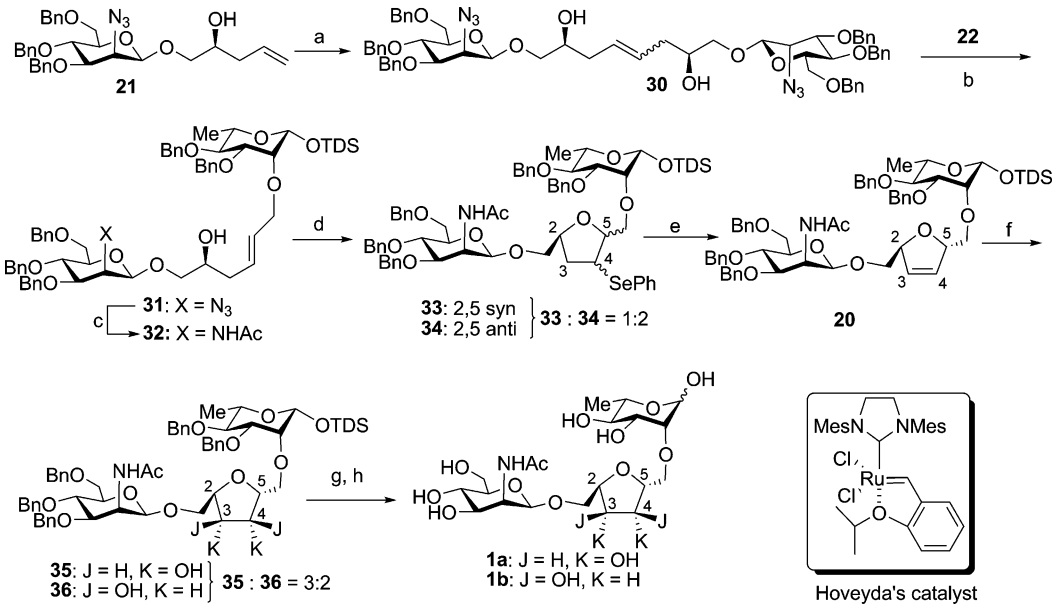
Scheme 6. Assembly of Pseudotrisaccharides 1a/1b[a]



[a]Key: (a) 5 mol % Hoveyda's catalyst, refluxing CH_2Cl_2, 77%; (b) 10 mol % Hoveyda's catalyst, CH_2Cl_2; 94% (c) PPh_3, THF, then H_2O, Ac_2O, MeOH, 80% over two steps; (d) Ph_2Se_2, $(NH_4)_2S_2O_8$, CH_3CN, 80 °C, 75%; (e) **34**, H_2O_2, MeOH, rt, then $NaHCO_3$, C_6H_6, 80 °C, 88%; (f) OsO_4, NMO, H_2O:acetone 1:1, 62%; (g) TBAF, THF; (h) H_2 over 10% Pd/C: 60% (**1a**), 48% (**1b**), over two steps.

the PMB group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded fragment **21** in 55% yield over three steps.

With both sugar olefins **21** and **22** in our hands, the stage was set for their condensation via cross-metathesis reaction. The results of our previous study[8] suggested that the two-step procedure (self-metathesis followed by cross-metathesis, SM-CM) developed by Grubbs et al.[30] is a favorable approach over the classical, straightforward CM reaction.[31] Accordingly, fragment **21** was first homodimerized using 5 mol % of Hoveyda's catalyst[6c,d] in refluxing dichloromethane, affording homodimer **30** in 77% yield (3:1 *E*/*Z* ratio, Scheme 6). The isomers mixture of **30** was then metathesized with fragment **22** using 10 mol % of Hoveyda's catalyst in refluxing dichloromethane affording the heterodimer **31** in excellent yield (94%) with 9:1 *E*/*Z* ratio. The major *E* stereoisomer was purified by column chromatography and used in the following steps. Reduction of the azide on **31** was carried out under Staudinger's condition[32] followed by N-acetylation (MeOH, Ac_2O), to afford heterodimer **32** in 80% yield over two steps.

The subsequent intramolecular cyclization was accomplished using in situ-generated phenylselenyl sulfate **2** (Figure 2) and furnished compounds **33**/**34** as a 1:2 mixture of diastereoisomers in 75% yield. After careful separation by medium pressure chromatography on silica gel, NOESY experiments were performed on the two diastereoisomers. In the major diastereoisomer **34** the dipolar interaction between H-2 and H-4 confirmed the 2,4-syn and 2,5-anti relative configurations. Only the major diastereoisomer **34** was subjected to the oxidative elimination step to yield compound **20** in 88% yield (Scheme 6).

The next stage of our endeavor has been the dihydroxylation of the C−C double bond in the inner ring of pseudotrisaccharide **20**. In a first attempt, the dihydroxylation reaction was carried out using either AD-α or AD-β mix according to the Sharpless protocol[33] to obtain a single pure diastereoisomer. However, the reaction did not occur, and unreacted substrate **20** was fully recovered. We conjectured that the presence of bulky substituents on both allylic positions (C-2 and C-5) of the five-membered ring might hamper the correct folding of the substrate into the phathalazine pocket active site. On the other hand, dihydroxylation with catalytic OsO_4 and *N*-methylmorpholine-*N*-oxide (NMO) afforded *syn*-diols **35**/**36** in 62% overall yield as a 3:2 mixture of diastereoisomers. The challenging separation of the two stereoisomers was achieved by HPLC on a chiral column (250 × 10 mm ID). The absolute configuration at the newly formed stereogenic centers at C-3 and C-4 of **35** and **36** was determined for both compounds by detailed NMR analysis (see Supporting Information).

Eventually, diols **35** and **36** were fully deprotected by desilylation of the rhamnose unit with TBAF in THF followed by hydrogenolysis of the benzyl ethers, affording pseudotrisaccharides **1a** and **1b** in 60% and 48% yield over two steps, respectively. Complete NMR characterization of compound **1a** confirmed absolutely our previous structural assignments performed on protected precursor **35**. Because compound **1b** was obtained from **36** in a very small amount (about 1 mg), it was identified only by HRMS analysis (ESI source).

ELISA Assay. The ability of increasing concentrations (from 10^{-7}mg/mL to 10^{0} mg/mL) of the pseudotrisaccharides **1a** and **1b** to inhibit the binding between the 19F polysaccharide, coated onto plates and used as positive control, and the anti-19F human polyclonal antibody was evaluated by competitive ELISA assay. The inhibition capacity of the synthetic compounds was determined in comparison with the natural trisaccharide repeating unit previously synthesized by our group.[25] Table 2 shows the relative efficacy of each compound calculated by measuring the maximum effect elicited in this system (relative efficacy), while the concentration that produces 50% of the maximum effect (EC_{50}) was taken as indirect index of its relative potency. As expected, the 19F native polysaccharide exhibited both higher efficacy (100% of

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Table 2. Results of Competitive ELISA Assay

compound	EC_{50} (mg/mL)	maximum inhibition (%)[a]
19F polysaccharide	8.9×10^{-5}	100
natural trisaccharide repeating unit	6.74×10^{-2}	43
1a	–	–
1b	–	–

[a]Measured at 1 mg/mL.

inhibition at 1 mg/mL) and affinity ($EC_{50} = 8.9 \times 10^{-5}$ mg/mL) compared with that of the natural trisaccharide repeating unit, confirming that high molecular weight polysaccharides have a conformational specificity (conformational epitopes) more suitable for antibody binding. On the contrary, both the synthetic repeating unit analogues **1a** and **1b** did not exhibit any inhibition of binding between 19F polysaccharide and the specific antibody at all concentrations tested. This result suggests that the replacement of the inner glucose moiety of the trisaccharide with the five-membered ring strongly affects the biological properties of the trisaccharide repeating unit.

CONCLUSION

Different pseudo-oligosaccharides were obtained by a strategy based on the cross-metathesis reaction between distinct sugar-olefins, followed by intramolecular cyclization of the obtained heterodimer promoted by selenium electrophiles. The following mild syn elimination of the selenocyclized products allowed the introduction of a new endocyclic carbon−carbon double bond, suitable for further functionalization and synthesis of more elaborated molecular targets. The feasibility of our methodology for target molecules of biological significance is demonstrated by the synthesis of a structural analogue of the trisaccharide repeating unit from the capsular polysaccharide of *Streptococcus pneumoniae* 19F.

Despite the poor stereoselectivity obtained in some transformations, the described strategy is however a novel and promising approach for future developments, as the use of sugar partners featuring various structural motifs should allow the introduction of further molecular diversity into the pseudo-oligosaccharide products. Work is in progress in our laboratories to further explore the scope and potential of this methodology.

EXPERIMENTAL SECTION

General Experimental Methods. All commercially available reagents including dry solvents were used as received. Nonvolatile materials were dried under high vacuum. Reactions were monitored by thin-layer chromatography on precoated silica gel plates and visualized by staining with a solution of cerium sulfate (1g) and ammonium heptamolybdate tetrahydrate (27 g) in water (469 mL) and concentrated sulfuric acid (31 mL). Flash chromatography was performed on silica gel. NMR spectra were recorded at 300 K (unless otherwise stated) on spectrometers operating at 400 and 500 MHz. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm). Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm). Optical rotations were obtained on a polarimeter at 589 nm using a 5 mL cell with a length of 1 dm. High resolution mass spectra (HRMS) were performed with an ESI source.

Typical Procedures for Selenocyclization. Method A: To a stirred solution of diphenyl diselenide (0.5 equiv) in acetonitrile was added ammonium persulfate (1 equiv). The resulting solution was warmed to 80 °C, and after 30 min heterodimer (1 equiv) was added and the reaction was further stirred until its complete consumption (TLC hexane:diethyl ether 1:1). The solution was poured into a saturated solution of aq $NaHCO_3$ and extracted twice with CH_2Cl_2. The organic layers were collected, dried (Na_2SO_4) and evaporated to dryness. The crude was purified by medium pressure silica gel column chromatography affording the pure diastereoisomers.

Method B: To a stirred solution of diphenyl diselenide (0.5 equiv) in acetonitrile were added ammonium persulfate (1 equiv) and a catalytic amount of trifluoromethanesulfonic acid. After 30 min, the heterodimer (1 equiv) was added and the reaction was further stirred until its complete consumption (TLC hexane:diethyl ether 1:1). The solution was poured into a saturated solution of aq $NaHCO_3$ and extracted twice with CH_2Cl_2. The organic layers were collected, dried (Na_2SO_4), and evaporated to dryness. The crude was purified by medium pressure silica gel column chromatography, affording the pure diastereoisomers.

Method C: Heterodimer (1 equiv) was dissolved in dry CH_2Cl_2 (0.01 M) and cooled to 0 °C. *N*-Phenylselenylphthalimide (1.4 equiv) and a catalytic amount of $BF_3{\cdot}Et_2O$ were added. The reaction was slowly warmed to room temperature and stirred until complete consumption of the heterodimer (TLC hexane:diethyl ether 1:1). The solution was diluted in diethyl ether and washed twice with 5% NaOH aq solution. The organic layer was dried (Na_2SO_4) and evaporated to dryness. The crude was purified by medium pressure silica gel column chromatography, affording the pure diastereoisomers.

Method D: To a stirred solution of bis(2,4,6-triisopropylphenyl) diselenide [$(TIPP)_2Se_2$] (0.5 equiv) in acetonitrile were added ammonium persulfate (1 equiv) and a catalytic amount of trifluoromethanesulfonic acid. After 30 min, the heterodimer (1 equiv) was added and the reaction was further stirred until its complete consumption (TLC hexane:diethyl ether 1:1). The solution was poured into a saturated solution of aq $NaHCO_3$ and extracted twice with CH_2Cl_2. The organic layers were collected, dried (Na_2SO_4), and evaporated to dryness. The crude was purified by medium pressure silica gel column chromatography, affording the pure diastereoisomers.

2-{Methyl-*O*-[2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl]}-5-{methyl-[methyl 2,3,4-tri-*O*-benzyl-α-D-xylopyranosyl]}-3-(phenylselenyl)tetrahydrofuran, 8/9. Compound **5** (1.07 g, 1.00 mmol) was cyclized following method C as described above, affording a mixture of diastereoisomers in 1:3 dr. After workup, medium pressure chromatography (hexane:diethyl ether 7:3 to 1:1 in gradient elution) afforded **8** (242 mg) and **9** (726 mg) as pure diastereoisomers in 79% overall yield.

Minor Stereoisomer ***8.*** Colorless oil; $[\alpha]^{25}_D$ = +15.2 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.07 (m, 40H), 4.93−4.48 (m, 14H, OCH_2Ph), 4.46 (d, *J* = 3.1 Hz, 1H), 4.27 (d, *J* = 7.8 Hz,1H), 4.19−4.14 (m, 1H), 4.03 (q, *J* = 4.8 Hz, 1H) 3.90 (dd, *J* = 4.6, 11.8 Hz, 1H), 3.86 (t, *J* = 9.2 Hz, 1H), 3.68−3.40 (m, 8H), 3.37−3.33 (m, 2H), 3.24 (t, 1H), 3.23 (s, 3H), 2.13−1.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.6, 138.5, 138.4, 138.2, 138.1, 134.3, 129.1, 128.4−127.5, 103.9, 97.8, 84.5, 83.7, 82.0, 81.9, 81.7, 80.0, 75.7, 75.6, 75.5, 75.0, 74.9, 74.8, 74.6, 73.4, 73.3, 70.9, 68.8, 68.0, 55.1, 40.8, 39.5, 36.9; HRESI MS *m*/*z* calcd $C_{73}H_{78}O_{12}SeNa$ $[M + Na]^+$ 1249.4556, found 1249.4563, error 0.6 ppm.

Major Stereoisomer ***9.*** Colorless oil; $[\alpha]^{25}_D$ = −41.8 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 77.60−7.10 (m, 40H), 5.05−4.55 (m, 14H, OCH_2Ph), 4.46 (d, *J* = 7.9 Hz, 1H), 4.45 (d, *J* = 3.1 Hz, 1H), 4.25−4.17 (m, 1H), 4.15−4.10 (dt, *J* = 3.8, 7.9 Hz, 1H), 3.99 (dd, *J* = 3.8, 11.2 Hz, 1H), 3.93 (t, *J* = 9.4 Hz, 1H), 3.80−3.60 (m, 7H), 3.50−3.40 (m, 3H), 3.30 (s, 3H), 3.24 (t, *J* = 9.0 Hz, 1H), 2.48−2.37 (m, 1H), 1.95−1.80 (m, 2H), 1.78−1.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.6, 138.5, 138.3, 138.2, 138.1, 134.9, 129.1, 128.4−127.5, 103.6, 97.8, 84.7, 83.4, 82.2, 81.9, 81.8, 80.0, 76.2, 75.7, 75.6, 75.2, 74.9, 74.9, 74.7, 73.5, 73.3, 69.0, 68.8, 68.2, 55.2, 40.8, 39.6, 37.4; HRESI MS *m*/*z* calcd $C_{73}H_{78}O_{12}SeNa$ $[M + Na]^+$ 1249.4556, found 1249.4533, error 1.8 ppm.

2-{Methyl-[2,3,4,6-tetra-*O*-benzyl-1-deoxy-α-D-1-*C*-glucopyranosyl]}-5-{methyl-[methyl 2,3,4-tri-*O*-benzyl-α-D-xylopyra-

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nosyl]}-3-(1,2-bis(2,4,6-triisopropylphenyl)selenyl)tetrahydrofuran, 10/11. Compound **6** (1.05 g, 1.00 mmol) was cyclized following method D as described above, affording a mixture of diastereoisomers in 1:1.9 dr. After workup, medium pressure chromatography (hexane:diethyl ether 7:3) afforded **10** (545 mg) and **11** (182 mg) as pure diastereoisomers in 79% overall yield.

Minor Stereoisomer ***10***. Colorless oil; $[\alpha]^{25}_{D}$ = +6.7 (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.22 (m, 33H), 7.16−7.11 (m, 2H), 7.03−7.01 (m, 2H), 5.00−4.76 (m, 7H, OCH_2Ph), 4.68−4.57 (m, 5H, OCH_2Ph), 4.48 (d, *J* = 3.8 Hz, 1H), 4.46 (d, *J* = 10.8 Hz, 1H), 4.43 (d, *J* = 10.8 Hz, 1H), 4.45−4.39 (m, 1H), 4.15−4.07 (m, 2H), 3.92 (t, *J* = 9.3 Hz, 1H), 3.90 (sext, *J* = 6.7 Hz, 2H), 3.75−3.51 (m, 7H), 3.49 (dd, *J* = 3.5, 9.6 Hz, 1H), 3.35−3.29 (m, 1H), 3.27 (s, 3H), 3.25 (t, *J* = 9.3 Hz, 1H), 2.86 (sext, *J* = 6.9 Hz, 1H), 2.23 (ddd, *J* = 6.2, 6.6, 12.1 Hz,1H), 2.11 (dt, *J* = 4.2, 15.2 Hz, 1H), 2.02 (ddd, J = 5.5, 10.1, 15.2 Hz, 1H), 1.91−1.78 (m, 2H), 1.65−1.55 (m, 1H), 1.24 (d, *J* = 6.9 Hz, 6H), 1.21 (d, *J* = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 149.8, 138.7, 138.4, 138.3, 138.1, 128.4−127.5, 125.6, 121.7, 97.8, 82.3, 82.0, 81.9, 81.7, 80.0, 79.7, 75.7, 75.3, 75.2, 75.1, 74.9, 73.4, 73.2, 72.5, 71.5, 71.4, 68.7, 68.1, 55.1, 44.6, 40.8, 37.6, 34.4, 34.1, 28.2, 24.5, 23.9; HRESI MS *m*/*z* calcd $C_{82}H_{96}O_{11}SeNa$ $[M + Na]^+$ 1359.6049, found 1359.6011, error 2.8 ppm.

Major Stereoisomer ***11***. Colorless oil; $[\alpha]^{25}_{D}$ = +23.2 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.21 (m, 33H), 7.20−7.15 (m, 2H), 7.03−6.99 (m, 2H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.97−4.70 (m, 6H, OCH_2Ph), 4.73−4.49 (m, 7H, OCH_2Ph), 4.50 (d, *J* = 3.8 Hz, 1H), 4.47−4.40 (m, 1H), 4.29−4.21 (m, 1H), 4.01−3.84 (m, 4H), 3.80−3.60 (m, 6H), 3.60−3.58 (m, 1H), 3.52 (dd, *J* = 3.5, 9.8 Hz, 1H), 3.29 (s, 3H), 3.28 (t, *J* = 9.3 Hz, 1H), 3.16−3.10 (m, 1H), 2.86 (sext, *J* = 6.8 Hz, 1H), 2.15−2.01 (m, 1H), 2.0−1.81 (m, 4H), 1.81−1.70 (m, 1H), 1.24 (d, *J* = 6.9 Hz, 6H), 1.21 (d, *J* = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 149.7, 138.8, 138.7, 138.4, 138.3, 138.2, 138.1, 128.4 −127.5, 126.4, 121.7, 97.8, 82.3, 82.1, 81.8, 80.7, 80.1, 79.5, 75.7, 75.2, 75.1, 74.9, 73.5, 73.3, 72.4, 71.4, 70.8, 68.9, 68.1, 55.1, 45.5, 39.8, 37.3, 34.4, 34.0, 29.9, 24.6, 24.5, 23.9, 23.8; Anal. Calcd for $C_{82}H_{96}O_{11}Se$: C, 73.69; H, 7.24; O, 13.17; found: C, 73.73; H, 7.28; O, 13.15; HRESI MS *m*/*z* calcd $C_{82}H_{96}O_{11}SeNa$ $[M + Na]^+$ 1359.6049, found 1359.6028, error 1.6 ppm.

2-{Methyl-*O*-[methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl]}-5-{methyl-[methyl 2,3,4-tri-*O*-benzyl-α-D-xylopyranosyl]}-3-phenylselenyltetrahydrofuran, 12/13. Compound 7 (0.995 g, 1 mmol) was cyclized following method A, affording a mixture of distereoisomers in 1:2.3 dr. After workup, medium pressure chromatography (hexane:diethyl ether 7:3 to 1:1 in gradient elution) afforded **12** (157 mg) and **13** (360 mg) as pure diastereoisomers in 45% overall yield.

Minor Stereoisomer ***12***. Colorless oil; $[\alpha]^{25}_{D}$ = +12.8 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.40 (m, 2H), 7.35−7.15 (m, 33H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.90,4.84 (2 d, each 1 H, *J* = 10.8 Hz, OCH_2Ph), 4.82−4.75 (m, 3H, OCH_2Ph), 4.70−4.50 (m, 6H, OCH_2Ph), 4.59 (d, *J* = 3.5 Hz, 1H), 4.51 (d, *J* = 3.7 Hz, 1H), 4.22−4.12 (m, 1H), 3.96−3.84 (m, 4H), 3.73−3.55 (m, 5H), 3.52−3.48 (m, 2H), 3.41 (t, *J* = 9.1 Hz, 1H), 3.40−3.38 (m, 1H), 3.37 (s, 3H), 3.29 (s, 3H), 3.21 (t, *J* = 9.3 Hz, 1H), 2.07−1.98 (m, 1H), 1.96−1.78 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.7, 138.3, 138.2, 138.1, 134.3, 129.1, 128.4−127.5, 98.2, 97.8, 83.7, 81.9, 81.8, 80.0, 79.5, 78.1, 75.8, 75.7, 75.5, 75.0, 73.9, 73.4, 73.3, 73.2, 69.9, 68.6, 68.0, 55.2, 55.1, 40.5, 39.8, 36.9; HRESI MS *m*/*z* calcd $C_{67}H_{74}O_{12}Se$ $[M + Na]^+$ 1173.4243, found 1173.4240, error 0.25 ppm.

Major Stereoisomer ***13***. Colorless oil; $[\alpha]^{25}_{D}$ = +4.3 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.20 (m, 35H), 4.95 (d, *J* = 10.8 Hz, 1H), 4.88−4.73 (m, 5H, OCH_2Ph), 4.70−4.46 (m, 6H, OCH_2Ph), 4.57 (d, *J* = 3.5 Hz, 1H), 4.45 (d, *J* = 3.2 Hz, 1H), 4.11−4.03 (m, 1H), 4.03−3.95 (m, 1H), 3.94−3.80 (m, 3H), 3.70−3.52 (m, 4H), 3.50−3.37 (m, 4H), 3.34 (s, 3H), 3.31−3.28 (m, 1H), 3.26 (s, 3H), 3.21 (t, *J* = 9.3 Hz, 1H), 2.36 (dt, *J* = 6.2, 12.5 Hz, 1H), 1.90−1.84 (m, 2H), 1.67 (dt, *J* = 9.4, 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.7, 138.3, 138.2, 138.1, 134.9, 129.1, 128.5−127.5, 98.2, 97.9, 82.9, 81.9, 81.6, 80.0, 79.5, 78.0, 75.8, 75.7, 75.6, 75.2, 73.6, 73.4, 73.3, 70.0, 68.6, 68.1, 55.2, 55.1, 40.8, 40.0, 37.6; HRESI MS *m*/*z* calcd $C_{67}H_{74}O_{12}Se$ $[M + Na]^+$ 1173.4243, found 1173.4222, error 1.8 ppm.

Typical Procedure for Elimination. Method E: Selenocyclized compound (1 equiv) was dissolved in MeOH. Then H_2O_2 30% v/v (3 equiv) was added, and the mixture was stirred at room temperature. The reaction was monitored by TLC (hexane:diethyl ether 6:4). When the oxidation step was finished, the solvent was removed under reduced pressure. The crude was dissolved in C_6H_6 (3 mL) and a solution of $NaHCO_3$ 10% (m/m) was added (1 mL). The resulting solution was heated at 80 °C. The reaction was monitored by TLC (hexane:diethyl ether 6:4). After 3 h, the reaction was stopped and poured into water. The organic phase was extracted with CH_2Cl_2, dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. The crude product was purified by medium pressure flash chromatography (hexane:diethyl ether 6:4), affording elimination compound.

(2*R*,5*S*)-2-{Methyl-*O*-[2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl]}-5-{methyl-[methyl 2,3,4-tri-*O*-benzyl-α-D-xylopyranosyl]}-2*H*,5*H*-dihydrofuran, 14. Compound **8** (100 mg, 0.082 mmol) was subjected to the elimination step following the typical procedure (method E) reported above, affording compound **14** (67 mg, 0.063 mmol) in 77% yield as a colorless oil. $[\alpha]^{25}_{D}$ = +66.3 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.01 (m, 35H), 5.82 (dt, *J* = 1.0, 5.7 Hz, 1H), 5.77 (dt, *J* = 1.0, 5.7 Hz, 1H), 4.95−4.90 (m, 2H), 4.89−4.41 (m, 14H, OCH_2Ph), 4.47 (d, *J* = 3.5 Hz, 1H), 4.32 (d, *J* = 7.8 Hz, 1H), 3.87 (t, *J* = 9.3 Hz, 1H), 3.81 (dd, *J* = 5.0, 10.0 Hz, 1H), 3.66−3.44 (m, 6H), 3.43 (dd, *J* = 3.5, 9.3 Hz, 1H), 3.36−3.32 (m, 2H), 3.28 (s, 3H), 3.22 (t, *J* = 9.5 Hz, 1H), 1.89−1.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.6, 138.5, 138.4, 138.2, 138.1, 131.4, 128.4−127.6, 121.6, 104.2, 97.9, 84.9, 84.6, 83.2, 82.1, 82.0, 81.7, 80.1, 75.7, 75.6, 75.1, 74.9, 74.8, 74.6, 73.6, 73.4, 73.3, 68.8, 67.7, 55.4, 38.8; HRESI MS *m*/*z* calcd $C_{67}H_{72}O_{12}Na$ $[M + Na]^+$ 1091.4916, found 1091.4879, error 3.4 ppm.

(2*S*,5*S*)-2-{Methyl-*O*-[2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl]}-5-{methyl-[methyl 2,3,4-tri-*O*-benzyl-α-D-xylopyranosyl]}-2*H*,5*H*-dihydrofuran, 15. Compound **9** (100 mg, 0.08 mmol) was subjected to the elimination step following the typical procedure (method E) reported above, affording compound **15** (82 mg, 0.077 mmol) in 96% yield as a colorless oil. $[\alpha]^{25}_{D}$ = +58.2 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.10 (m, 35H), 5.90 (dt, *J* = 1.0, 6.1 Hz, 1H), 5.86 (dt, *J* = 1.0, 6.1 Hz, 1H), 5.10−5.01 (m, 2H), 5.00−4.52 (m, 14H, OCH_2Ph), 4.51 (d, *J* = 3.6 Hz, 1H), 4.43 (d, *J* = 7.7 Hz, 1H), 4.0 (dd, *J* = 4.3, 10.5 Hz, 1H), 3.95 (t, *J* = 9.3 Hz, 1H) 3.76−3.64 (m, 3H), 3.63−3.56 (m, 3H), 3.51 (dd, *J* = 3.5, 9.7 Hz, 1H), 3.47−3.43 (m, 2H), 3.32 (t, *J* = 9.0 Hz, 1H), 3.31 (s, 3H), 1.96 (ddd, *J* = 2.5, 6.0, 13.6 Hz, 1H), 1.82 (ddd, *J* = 5.0, 8.3, 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.6, 138.5, 138.4, 138.2, 138.1, 138.0, 131.6, 128.4−127.6, 127.4, 104.0, 98.0, 84.6, 84.4, 83.3, 82.1, 82.0, 81.7, 80.0, 75.7, 75.6, 75.1, 75.0, 74.9, 74.6, 73.4, 73.3, 71.9, 68.9, 67.9, 55.3, 37.7; HRESI MS *m*/*z* calcd $C_{67}H_{72}O_{12}Na$ $[M + Na]^+$ 1091.4916, found 1091.4905, error 1.0 ppm.

(2*R*,5*S*)-2-{Methyl-[2,3,4,6-tetra-*O*-benzyl-1-deoxy-α-D-1-*C*-glucopyranosyl]}-5-{methyl-[methyl 2,3,4-tri-*O*-benzyl-α-D-xylopyranosyl]}-2*H*,5*H*-dihydrofuran, 16. Compound **10** (100 mg, 0.082 mmol) was subjected to the elimination step following the typical procedure (method E) reported above, affording compound **16** (78 mg, 0.074 mmol) in 90% yield as a colorless oil. $[\alpha]^{25}_{D}$ = +100.0 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.22 (m, 35H), 5.98−5.94 (m, 1H), 5.85−5.79 (m, 1H), 4.95−4.93 (m, 1H), 4.95−4.45 (m, 14H, 7 OCH_2Ph), 4.95−4.93 (m, 1H), 4.55 (d, *J* = 3.8 Hz, 1H), 4.38−4.30 (m, 1H), 3.96 (t, *J* = 8.9 Hz, 1H), 3.80−3.55 (m, 7H), 3.52 (dd, *J* = 3.5, 9.6 Hz, 1H), 3.39 (s, 3H), 3.28 (t, *J* = 9.0 Hz, 1H), 2.12−1.93 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.7, 138.3, 138.2, 138.1, 138.0, 130.7, 129.9, 128.4−127.5, 97.9, 83.6, 82.6, 82.3, 82.0, 81.4, 80.0, 79.5, 78.1, 75.7, 75.4, 75.1, 75.0, 73.5, 73.3, 72.6, 71.6, 71.4, 69.2, 67.9, 55.4, 39.1, 32.3; HRESI MS *m*/*z* calcd $C_{67}H_{72}O_{11}Na$ $[M + Na]^+$ 1075.4967, found 1075.4961, error 0.6 ppm.

(2*S*,5*S*)-2-{Methyl-[2,3,4,6-tetra-*O*-benzyl-1-deoxy-α-D-1-*C*-glucopyranosyl]}-5-{methyl-[methyl 2,3,4-tri-*O*-benzyl-α-D-xy-

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lopyranosyl]}-2*H*,5*H*-dihydrofuran, 17. Compound **11** (150 mg, 0.123 mmol) was subjected to the elimination step following the typical procedure (method E) reported above, affording compound **17** (126 mg, 0.12 mmol) in 98% yield as a colorless oil. $[\alpha]^{25}_{D}$ = +9.3 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.26 (m, 33H), 7.14−7.01 (m, 2H), 5.89−5.85 (m, 2H), 5.09−5.02 (m, 2H), 5.01 (d, *J* = 10.8 Hz, 1H, 1/2 OCH_2Ph), 4.95, 4.90 (2 d, each 1H, *J* = 10.8 Hz, OCH_2Ph), 4.86−4.78 (m, 4H, OCH_2Ph), 4.71−4.60 (m, 5H, OCH_2Ph), 4.51 (d, *J* = 3.5 Hz, 1H), 4.45−4.40 (2 d, each 1H, *J* = 10.8 Hz, OCH_2Ph), 4.24−4.18 (m, 1H), 3.97 (t, *J* = 9.3 Hz, 1H), 3.80−3.58 (7H), 3.54 (dd, *J* = 3.6, 9.7 Hz, 1H), 3.37 (s, 3H), 3.36 (t, *J* = 9.4 Hz, 1H), 2.15−2.05 (m, 1H), 1.97 (ddd, *J* = 2.9, 5.9, 13.9 Hz, 1H), 1.91 (ddd, *J* = 3.1, 6.8, 14.8 Hz, 1H), 1.90−1.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.7, 138.4, 138.3, 138.2, 138.0, 130.1, 129.6, 128.4−127.5, 98.0, 82.8, 82.6, 82.4, 82.1, 82.0, 80.0, 80.3, 78,4, 75.7, 75.4, 75.1, 75.0, 73.4, 73.3, 72.9, 71.4, 71.3, 68.8, 68.0, 55.3, 37.7, 31.0; HRESI MS *m*/*z* calcd $C_{67}H_{72}O_{11}Na$ $[M + Na]^+$ 1075.4967, found 1075.4970, error 0.3 ppm.

(2*R*,5*S*)-2-{Methyl-*O*-[methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl]}-5-{methyl-[methyl 2,3,4-tri-*O*-benzyl-α-D-xylopyranosyl]}-2*H*,5*H*-dihydrofuran, 18. Compound **12** (200 mg, 0.173 mmol) was subjected to the elimination step following the typical procedure (method E) reported above, affording compound **18** (133 mg, 0.134 mmol) in 77% yield as a colorless oil. $[\alpha]^{25}_{D}$ =+8.1 (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.21 (m, 30H), 5.88 (d, *J* = 5.6 Hz, 1H), 5.65 (d, *J* = 5.6 Hz, 1H), 5.03−4.95 (m, 2H), 4.88−4.75 (m, 7H), 4.68−4.50 (m, 7H), 3.93−3.82 (m, 3H), 4.76−4.64 (m, 3H), 4.60−4.62 (m, 1H), 3.51−3.43 (m, 4H), 3.36 (s, 3H), 3.35 (s, 3H), 3.22 (t, *J* = 9.4 Hz, 1H), 1.90−1.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.7, 138.3, 138.2, 138.0, 131.4, 128.4−127.5, 127.4, 98.2, 97.9, 84.6, 83.2, 82.0, 81.8, 81.7, 80.0, 79.6, 78.0, 76.2, 75.6, 75.5, 75.0, 73.4, 73.3, 73.2, 70.0, 68.5, 67.8, 55.4, 55.1, 38.9; HRESI MS *m*/*z* calcd $C_{61}H_{68}O_{12}Na$ $[M + Na]^+$ 1015.4608, found 1015.4626, error 1.8 ppm.

(2*S*,5*S*)-2-{Methyl-*O*-[methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl]}-5-{methyl-[methyl 2,3,4-tri-*O*-benzyl-α-D-xylopyranosyl]}-2*H*,5*H*-dihydrofuran, 19. Compound **13** (250 mg, 0.217 mmol) was subjected to the elimination step following the typical procedure (method E) reported above, affording compound **19** (200 mg, 0.202 mmol) in 93% yield as a colorless oil. $[\alpha]^{25}_{D}$ = +28.5 (*c* 1.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.18 (m, 30H), 5.77 (d, *J* = 6.0 Hz, 1H), 5.49 (d, *J* = 6.0 Hz, 1H), 4.95−4.87 (m, 1H), 4.82, 4.79 (2 d, each 1H, *J* = 11.0 Hz, OCH_2Ph), 4.73−4.66 (m, 5H), 4.57−4.47 (m, 5H), 4.42−4.38 (m, 1H), 3.83 (t, *J* = 9.0 Hz, 1H), 3.79 (t, *J* = 9.0 Hz, 1H), 3.72−3.53 (m, 5H), 3.43−3.31 (m, 5H), 3.28−3.23 (m, 7H), 3.20 (t, *J* = 9.2 Hz, 1H), 1.86 (ddd, *J* = 2.4, 7.0, 13.9 Hz, 1H), 1.74 (ddd, *J* = 5.6, 8.6, 14.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.8, 138.3, 138.2, 138.1, 138.0, 131.6, 128.4−127.5, 126.9, 98.2, 98.0, 84.8, 82.9, 82.0, 81.9, 81.8, 80.0, 79.6, 78.2, 75.7, 75.6, 75.5, 75.1, 73.5, 73.4, 73.3, 70.0, 68.4, 67.8, 55.3, 55.1, 37.7; HRESI MS *m*/*z* calcd $C_{61}H_{68}O_{12}Na$ $[M + Na]^+$ 1015.4608, found 1015.4615, error 0.7 ppm.

(*S*)-1-Trityloxypent-4-en-2-ol, 26. Vinylmagnesium bromide (1 M) (63.30 mL, 63.30 mmol) in THF was added dropwise to a slurry of CuI (1.21 g, 6.33 mmol) in dry THF (50 mL) at −40 °C. The mixture was stirred for 30 min, and then a solution of **25**[29] (6.67 g, 21.08 mmol) in dry THF (50 mL) was added dropwise over 30 min. The reaction was stirred at −40 to −30 °C for 1 h and then poured into a cold mixture of sat. aq NH_4Cl (100 mL), NH_4OH (100 mL), and Et_2O (100 mL) with vigorous stirring. The phases were separated, and the aqueous phase was further extracted with Et_2O (3 × 100 mL). The organic solution was washed with brine, dried ($NaSO_4$), and filtered through a short pad of silica gel. The solvent was removed under reduced pressure. An analytical sample of **26** was obtained by flash chromatography (hexane:ethyl acetate 9:1). $[\alpha]^{25}_{D}$ = +79.5 (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.25 (m, 15H), 5.77 (dd, *J* = 13.1, 8.8 Hz, 1H), 5.11−5.05 (m, 2H), 3.87−3.85 (m, 1H), 3.20 (dd, *J* =9.4 *J* 3.9 Hz, 1H), 3.11 (dd, *J* = 9.4 *J* 6.9, 1H), 2.28−2.24 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 134.4, 128.7, 127.9, 127.2, 117.6, 70.3, 67.1, 38.2; HRESI MS *m*/*z* calcd $C_{24}H_{24}0_2Na$ $[M + Na]^+$ 367.1669, found 367.1668, error 0.27 ppm.

(2*S*)-1-Trityloxy-2-(4-methoxybenzyloxy)-4-pentene, 27. Compound **26** (14.46 g, 41.98 mmol) was dissolved in dry DMF (50 mL) under nitrogen atmosphere. Under stirring, PMBBr (7.20 mL, 50.40 mmol) was added and then 95% NaH (1.16 g, 45.95 mmol) in small amounts, and the stirring was continued overnight. The reaction was monitored by TLC (hexane:ethyl acetate 95:5). The reaction was quenched with MeOH after 18 h. DMF was evaporated under reduced pressure, and the crude was dissolved in CH_2Cl_2 (100 mL) and washed with brine (2 × 50 mL). The organic layers were collected, and dried (over Na_2SO_4), and the solvent was removed under reduced pressure. An analytical sample of **27** was obtained by flash chromatography (hexane:ethyl acetate 95:5). $[\alpha]^{25}_{D}$ = −55.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.39 (m, 6H), 7.23−7.14 (m, 11H), 6.79 (d, *J* = 8.6 Hz, 2H), 5.66 (ddt, *J* = 17.2, 10.2, 7.2 Hz, 1H), 4.98−4.89 (m, 2H), 4.52 (d, *J* = 11.3 Hz, 1H), 4.42 (d, *J* = 11.3 Hz, 1H), 3.73 (s, 3H), 3.55−3.48 (m, 1H), 3.13 (dd, *J* = 9.8, 3.9 Hz, 1H), 3.13 (dd, *J* = 9.3, 6.9 Hz, 1H),2.29−2.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 144.2, 134.8, 131.3, 129.4, 128.7, 127.7, 126.9, 116.9, 113.7, 86.6, 71.6, 65.5, 55.3, 36.6; HRESI MS *m*/*z* calcd $C_{32}H_{32}O_3Na$ $[M + Na]^+$ 487.2244, found 487.2239, error 1.0 ppm.

(2*S*)-2-(4-Methoxybenzyloxy)-4-pentenol, 23. To a solution of crude compound **27** in MeOH (100 mL) was added PTSA in a catalytic amount. The reaction was monitored by TLC (hexane:ethyl acetate 8:2). The reaction was stopped after 3 h by addition of solid $NaHCO_3$ and filtered over a short pad of Celite. The solvent was removed under reduced pressure. The crude was purified by flash chromatography (hexane:ethyl acetate 8:2), affording the alcohol **23** (7.83 g, 88% over three steps) as a colorless liquid. $[\alpha]^{25}_{D}$ = −4.5 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J*=8.7 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 5.83 (ddt, *J*=15.5, 10.7, 7.2 Hz, 1H), 5.14 (d, *J*= 15.5 Hz, 1H), 5.11 (d, *J* = 10.7 Hz, 1H), 4.62 (d, *J*= 11.1 Hz, 1H), 4.49 (d, *J* = 11.1, 1H), 3.89 (s, 3H), 3.69−3.67 (m, 1H), 3.59−3.52 (m, 2H), 2.44−2.32 (m, 2H); 2.10 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 134.8, 131.1, 130.1, 118.2, 114.6, 79.5, 71.9, 64.7, 55.9, 36.1. HRESI MS *m*/*z* calcd $C_{13}H_{18}0_3Na$ $[M + Na]^+$ 245.1148, found 245.1140, error 3.3 ppm.

(2*S*)-2-(4-Methoxybenzyloxy)-1-(3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-4-pentene, 28. Compounds **24**[28] (1.42 g, 2.82 mmol) and **23** (2.97 g, 13.36 mmol) were dissolved with an equal amount of dry CH_2Cl_2 (10 mL), under N_2 atmosphere, and mixed together. Then powdered 4 Å molecular sieves (4.4 g) were added to the resulting solution and stirred at rt for 1 h. Then the mixture was cooled at −40 °C, and a solution of TMSOTf 0.17 M in CH_2Cl_2 (5 mL, 0.85 mmol) was slowly added. The reaction was monitored by TLC (hexane:ethyl acetate 7:3), and after 1.5 h, the reaction was neutralized by adding TEA and the filtered through a short pad of Celite. The organic phase was washed with brine and dried (over Na_2SO_4). Removal of the solvent afforded a crude product as a mixture of 2-hydroxy and 2-O-acetylated derivatives. This crude product was dissolved in dry MeOH (30 mL), under N_2 atmosphere, and a catalytic amount of sodium was added. The reaction was monitored by TLC (hexane:ethyl acetate 4:1). The deacetylation reaction was stopped by neutralization with Amberlite IR-120 resin (H^+) form. The reaction was filtered, and the solvent was removed under reduced pressure. Because the complete chromatographic separation of **28** from unreacted **23** was unfeasible, the crude product was subjected to tritylation (regioselective for primary alcohols) using the same protocol employed for the synthesis of **25**[29] to easily remove the excess of alcohol **23**. In this way, the crude product was purified by flash chromatography (hexane:ethyl acetate 4:1), affording the tritylated alcohol (**27**) and the glucoside **28** (1.21 g, 66% yield) as a colorless oil. $[\alpha]^{25}_{D}$ = +10.1 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.18 (m, 17H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.85 (ddt, *J*= 17.2, 10.1, 7.0 Hz, 1H), 5.18−5.08 (m, 2H), 4.96 (d, *J* = 11.2 Hz, 1H), 4.87−4.82 (m, 2H), 4.64−4.51 (m, 5H), 4.32 (d, *J* = 7.1 Hz, 1H), 3.99 (dd, *J* = 3.5, 10.6 Hz, 1H), 3.81 (s, 3H), 3.77−3.69 (m, 3H), 3.65−3.57 (m, 4H), 3.51−3.46 (m, 1H), 2.37−2.33 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 138.7, 138.1, 134.2, 130.5, 129.5,

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128.4−127.7, 117.5, 113.8, 103.4, 84.4, 75.2, 75.1, 74.9, 73.5, 73.1, 71.9, 71.7, 69.7, 68.9, 55.3, 35.9; HRESI MS *m/z* calcd $C_{40}H_{46}0_8Na$ $[M + Na]^+$ 677.3084, found 677.3078, error 0.9 ppm.

(2*S*)-2-(4-Methoxybenzyloxy)-1-(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-mannopyranosyl)-4-pentene, 29. To a solution of compound **28** (0.500 g, 0.76 mmol) in dry dichloromethane (18 mL) under a nitrogen atmosphere was added pyridine (250 μL, 3.05 mmol). The mixture was cooled to −40 °C, and after 15 min, triflic anhydride (376 μL, 2.34 mmol) was slowly added dropwise. After being stirred 6 h, the solvent was removed under vacuum without heating. The crude 2-*O*-triflate intermediate was dissolved under a nitrogen atmosphere in dry toluene (8 mL), a solution of $Bu_4N^+N_3^-$ (1.085 g, 3.81 mmol) in dry toluene (5 mL) was added quickly, and the reaction was stirred at 55 °C (hexane:ethyl acetate 7:3). After 24 h, the reaction mixture was concentrated with a high vacuum pump. An analytical sample of **29** was purified by flash chromatography. $[\alpha]^{25}_D$ = +2.6 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.19 (m, 15H), 7.11−7.09 (m, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 5.74 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 5.03−4.97 (m, 2H), 4.77 (d, *J* = 10.8 Hz, 1H), 4.61−4.41 (m, 8H), 3.88 (dd, *J* = 10.6, 3.3 Hz, 1H), 3.89 (bd, *J* = 3.3 Hz, 1H), 3.70 (s, 3H), 3.69−3.59 (m, 4H), 3.51−3.42 (m, 2H), 3.31−3.28 (m, 1H), 2.21 (bt, *J*=6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 134.1, 137.6, 134.1, 130.9, 129.3, 128.6−127.6, 117.5, 113.8, 99.9, 80.9, 77.8, 75.7, 75.3, 74.4, 73.6, 72.6, 72.2, 69.1, 62.0, 55.3, 36.1; HRESI MS *m/z* calcd $C_{40}H_{45}N_30_7Na$ $[M + Na]^+$ 702.3150, found 702.3144, error 0.8 ppm.

(2*S*)-1-(2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-mannopyranosyl)-4-penten-2-ol, 21. Crude compound **29** was dissolved in CH_2Cl_2/H_2O (12 mL, 19:1), and DDQ (190 mg, 0.84 mmol) was added. The reaction was monitored by TLC (hexane:ethyl acetate 1:1), and after 2 h, the reaction was diluted with CH_2Cl_2, and the organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude was purified by flash chromatography (hexane:ethyl acetate 6:4), affording compound **21** (220 mg, 55%) as pale yellow solid. $[\alpha]^{25}_D$ = +52.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.11 (m, 15H), 5.78 (ddt, *J* =17.2, 10.1, 7.1 Hz, 1H), 5.10−5.03 (m, 2H), 4.80 (d, *J*=10.8 Hz, 1H), 4.67 (d, *J* =11.8 Hz, 1H), 4.62 (d, *J* =11.8 Hz, 1H), 4.56−4.45 (m, 4H), 3.93 (d, *J*= 3.0 Hz, 1H), 3.84−3.79 (m, 2H), 3.69−3.64 (m, 2H), 3.61−3.50 (m, 3H), 3.39−3.35 (m, 1H), 2.23 (d, *J* = 4.9, 1H), 2.32 (bt, *J* = 6.8, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 137.9, 137.4, 134.2, 128.4−127.9, 117.8, 100.3, 80.9, 75.6, 75.3, 74.4, 73.6, 72.3, 69.9, 69.0, 61.8, 37.8; HRESI MS *m/z* calcd $C_{32}H_{37}N_30_6Na$ $[M + Na]^+$ 582.2574, found 582.2562, error 2.0 ppm.

(2*S*,7*S*)-1,8-Bis(2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-mannopyranosyl)-2,7-dihydroxyoctanediol, 30. Compound **21** (0.372 g, 0.667 mmmol) was dissolved in dry dichloromethane (15 mL), and argon was bubbled through the resulting solution for 10 min. Hoveyda's catalyst (20 mg, 0.033 mmol) was added, and the solution was refluxed and monitored by TLC (hexane:ethyl acetate 2:3). After 3 h, DMSO was added and the stirring was continued overnight at room temperature. The solvent was evaporated, and the crude product was purified by flash chromatography (hexane:ethyl acetate 2:3), affording **30** (*E*/*Z* ratio 3:1, 0.280 g, 77% yield) as yellow pale oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E*/*Z* mixture) δ 7.42−7.20 (m, 30H), 5.56−5.58 (m, 2H), 4.88 (d, *J* = 10.8 Hz, 2H), 4.76 (d, *J* = 11.8 Hz, 2H), 4.71 (d, *J* = 11.8 Hz, 2H), 4.63−4.53 (m, *J* = 12.1 Hz, 8H), 4.02−4.01 (m, 2H), 3.92−3.64 (m, 12 H), 3.59 (dd, *J* = 6.7, 10.3 Hz, 2H), 3.47−3.43 (m, 2H), 2.78 (bs, 2H), 2.28−2.24 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 138.0, 137.5, 129.0, 128.6−127.7, 100.2, 100.2, 80.9, 75.6, 75.3, 74.4, 73.5, 72.2, 70.1, 69.0, 61.8, 36.7; HRESI MS *m/z* calcd $C_{62}H_{70}N_60_{12}Na$ $[M + Na]^+$ 1113.4944, found 1113.4928, error 1.4 ppm.

Thexyldimethylsilyl 2-*O*-Allyl-3,4-di-*O*-benzyl-β-D-rhamnopyranoside, 22. Thexyldimethylsilyl-3,4-di-*O*-benzylrahmnopyranoside[27] (1.01 g, 2.08 mmol) was dissolved in dry DMF (10 mL) under nitrogen atmosphere. Then AllBr (210 μL, 2.5 mmol) and NaH 95% (60 mg, 2.3 mmol) were added. The resulting solution was stirred overnight and monitored by TLC (hexane:ethyl acetate 95:5). The reaction was quenched by addition of 100 μL of MeOH. DMF was evaporated under reduced pressure, and the crude was dissolved in CH_2Cl_2 (100 mL) and washed with brine (2 × 50 mL). The organic phase was dried (over Na_2SO_4) and the solvent evaporated under reduced pressure. The crude was purified by flash chromatography (hexane:ethyl acetate 95:5), affording **22** (850 mg, 77% yield) as a colorless oil. $[\alpha]^{25}_D$ = −37.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.29 (m, 10H), 5.96−5.87 (m, 1H), 5.29 (dd, *J* =18.0, 1.6, 1H), 5.20 (dd, *J*= 10.8, 1.8, 1H), 4.90 (1d, *J*= 10.9, 1H), 4.76 (d, *J* =11.7 Hz,1H), 4.68−4.62 (m, 3H), 4.20−4.16 (m, 1H), 4.10 (bt, *J*= 2.3 Hz, 1H), 4.00−3.95 (m, 1H), 3.83(dd, *J* = 9.3, 2.7 Hz, 1H), 3.75−3.68 (m, 1H), 3.57 (t, *J* = 9.4 Hz, 1H), 1.67 (hept, *J*= 6.9 Hz, 1H), 1.29 (d, *J*= 6.1 Hz, 3H), 0.95 (bt, *J* = 6.1 Hz, 6H), 0.89 (s, 6H), 0.14 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 128.3−127.3, 117.0, 99.6, 80.1, 80.1, 75.2, 72.1, 69.8, 68.4, 67.6, 34.3, 25.0, 20.5, 20.2, 18.8, 18.6, 18.1, −2.7, −2.8; HRESI MS *m/z* calcd $C_{31}H_{46}O_5SiNa$ $[M + Na]^+$ 549.3012, found 549.3005, error 1.3 ppm.

1-*O*-(2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-mannopyranosyl)-6-*O*-(thexyldimethylsilyl-3,4-di-*O*-benzyl-β-D-rhamnopyranosyl)-2-hydroxy-4-hexenediol, 31. Homodimer **30** (400 mg, 0.37 mmol) was dissolved under argon atmosphere in dry dichloromethane (10 mL), and the solution was warmed to 40 °C. Argon was bubbled through the solution for 10 min. Hoveyda's catalyst (11 mg, 0.018 mmol) was added. After 20 min, a solution of allyl derivative **22** (96 mg, 0.18 mmol) in dry dichloromethane (2 mL) was slowly added, and the reaction was monitored by TLC (hexane:ethyl acetate 7:3). After 6 h, DMSO (20 μL) was added and stirring was continued overnight. The solvent was removed under reduced pressure, and the crude was purified by flash chromatography (toluene:acetone 95:5), affording compound **31** (180 mg, 94%) as a colorless oil. $[\alpha]^{25}_D$ = +79.5 (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.20 (m, 25H), 5.75 (dt, *J* = 15.9, 6.6 Hz, 1H), 5.67 (dt, *J* = 15.9, 5.4 Hz, 1H), 4.90 (bt, *J* = 10.1, 10.0 Hz, 2H), 4.78−4.71 (m, 3H), 4.67−4.54 (m, 7H), 4.13 (dd, *J* = 12.2, 5.1 Hz, 1H), 4.09 (m, 1H), 4.01 (d, *J* = 1.5 Hz, 1H), 3.94−3.81−3.61 (m, 10H), 3.58 (t, *J* = 9.4 Hz, 1H,), 3.48−3.44 (m, 1H), 2.77 (bs, 1H), 2.34−2.30 (m, 2H), 1.68 (hept, *J* = 6.9 Hz, 1H), 1.28 (d, *J* = 6.1 Hz, 3H), 0.96 (bt, *J* = 6.3 Hz, 6H), 0.89 (s, 6H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.6, 138.0, 137.9, 137.4, 128.6, 128.4−127.3, 100.3, 99.6, 80.8, 80.2, 75.6, 75.3, 75.2, 74.3, 73.6, 72.3, 72.1, 69.8, 61.8, 36.3, 34.4, 25.0, 20.5, 20.3, 18.2, 18.6, 18.1, −2.7, −2.8; HRESI MS *m/z* calcd $C_{61}H_{79}N_3O_{11}SiNa$ $[M + Na]^+$ 1080.5376, found 1080.5360, error 1.5 ppm.

1-*O*-(2-Acetammido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-mannopyranosyl)-6-*O*-(thexyldimethylsilyl 3,4-di-*O*-benzyl-β-D-rhamnopyranosyl)-2-hydroxy-4-hexenediol, 32. To a solution of compound **31** (220 mg, 0.21 mmol) in dry THF (3 mL) was added PPh_3 (163 mg, 0.62 mmol), and the solution was stirred at 60 °C. The reaction was monitored by TLC (toluene:acetone 9:1). After 4 h, H_2O (100 μL) was added and the solution was stirred overnight. The solvent was evaporated under reduced pressure, the crude amine was dissolved in dry MeOH (3 mL), and Ac_2O (77 μL, 0.83 mmol) was added, stirred for 1 h, and then concentrated to dryness. The crude was purified by flash chromatography (toluene acetone 95:5), affording compound **32** (178 mg, 80% yield) as a colorless oil. $[\alpha]^{25}_D$ = +64.1 (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.20 (m, 25H); 5.87 (d, *J* = 9.7 Hz, 1H), 5.74 (dt, *J* = 15.5, 8.2 Hz, 1H), 5.64 (dt, *J* = 15.5, 5.9 Hz, 1H), 4.92−4.84 (m, 4H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.66−4.59 (m, 4H), 4.54−4.48 (m, 4H), 4.18−4.07 (m, 2H), 3.93−3.86 (m, 2H), 3.82−3.79 (m, 2H), 3.74−3.63 (m, 5H), 3.58−3.46 (m, 3H), 3.04 (bs, 1H), 2.29−2.23 (m, 2H), 2.08 (s, 3H), 1.66 (hept, *J* = 6.8 Hz, 1H), 1.27 (d, *J* = 6.2 Hz, 3H), 0.94 (bt, *J* = 6.3 Hz, 6H), 0.88 (s, 6H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 139.2, 139.0, 138.5, 138.2, 138.0, 128.8−127.5, 101.0, 100.0, 80.6, 75.6, 75.5, 75.1, 74.4, 76.0, 72.5, 71.6, 70.2, 69.1, 68.7, 67.7, 49.8, 36.5, 34.8, 25.3, 24.0, 20.7, 20.6, 19.1, 19.0, −2.3, −2.4; HRESI MS *m/z* calcd $C_{63}H_{83}NO_{12}SiNa$ $[M + Na]^+$ 1096.5577, found 1096.5561, error 1.4 ppm.

2-[Methyl-*O*-(2-acetammido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-mannopyranosyl)]-5-methyl-*O*-(thexyldimethylsilyl 3,4-di-*O*-benzyl-β-D-rhamnopyranosyl)-4-selenylphenyltetrahydrofur-

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an, 33/34. To a stirred solution of 1,2-bis(phenyl) diselenide (32 mg, 0.10 mmol) in CH_3CN (2 mL) at 80 °C was added $(NH_4)_2S_2O_8$ (22.8 mg, 0.10 mmol). After 30 min, compound **32** (214 mg, 0.17 mmol) was added and the reaction mixture was stirred at 80 °C. The reaction was monitored by TLC (hexane:diethyl ether 7:3). The reaction was stopped after 1 h. The reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$, and the organic phase was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The crude was purified by medium pressure flash chromatography (hexane:diethyl ether 7:3 to 1:1), affording selenocyclized compounds **33** (53 mg, 0.044 mmol) and **34** (106 mg, 0.087 mmol) in 75% overall yield and 1:2 dr as a colorless oil.

Minor Stereoisomer ***33***. $[\alpha]^{25}_D$ = −25.5 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.54 (m, 2H), 7.30−7.26 (m, 25H), 7.18−7.16 (m, 2H), 5.92 (d, *J* = 5.9 Hz, 1H), 4.90−4.83 (m, 4H), 4.67−4.43 (m, 9H), 4.23−4.20 (m, 1H), 4.03−3.98 (m, 2H), 3.79−3.42 (m, 13H), 2.03−1.98 (s, 3H), 1.64 (q, *J* = 6.4 Hz, 1H), 1.26 (s, 3H), 1.21 (d, *J* = 4.8 Hz, 3H), 0.92 (t, *J* = 3.6 Hz, 6H), 0.85 (s, 6H), 0.11 (s, 3H), 0.08 (s, 3H); HRESI MS *m*/*z* calcd $C_{69}H_{87}NO_{12}SeSiNa$ [M + Na]$^+$ 1252.5088, found 1252.5116, error 2.2 ppm.

Major Stereoisomer ***34***. $[\alpha]^{25}_D$ = +1.9 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.38−7.28 (m, 25H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.99 (d, *J* = 9.4 Hz, 1H), 4.92−4.85 (m, 3H), 4.77 (d, *J* = 11.7 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.65−4.46 (m, 7H), 4.19−4.12 (m, 2H), 4.08−4.05 (m, 2H), 4.00−3.99 (m, 1H), 3.95−3.89 (m, 2H), 3.83−3.32 (m, 11H), 2.46 (q, *J* = 6.4 Hz, 1H), 2.04 (s, 3H), 1.91−1.83 (m, 1H), 1.65 (q, *J* = 6.8 Hz, 1H), 1.24 (d, *J* = 6.4 Hz, 3H), 0.93 (bt, *J* = 6.7 Hz, 6H), 0.87 (s, 6H), 0.12 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.8, 138.8, 138.5, 138.2, 137.8, 134.8, 129.2, 128.4−127.4, 100.4, 99.6, 83.8, 80.5, 80.0, 79.8, 77.2, 75.2, 75.2, 75.0, 73.5, 72.0, 71.3, 69.6, 68.4, 67.7, 49.3, 40.2, 37.2, 34.3, 24.9, 23.6, 20.4, 20.2, 18.8, 18.6, 18.1, −2.3, −2.4; HRESI MS *m*/*z* calcd $C_{69}H_{87}NO_{12}SeSiNa$ [M + Na]$^+$ 1252.5088, found 1252.5059, error 2.3 ppm.

(2*S*,5*S*)-2-[Methyl-*O*-(2-acetammido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-mannopyranosyl)]-5-methyl-*O*-(thexyldimethylsilyl 3,4-di-*O*-benyl-β-D-rhamnopyranosyl)-2*H*,5*H* dihydrofuran, 20. Compound **34** (100 mg, 0.081 mmol) was subjected to the elimination step following method E reported above, affording compound **20** (76 mg, 0.063 mmol) in 88% yield as a colorless oil. $[\alpha]^{25}_D$ = +32.1 (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.21 (m, 25H), 5.89−5.84 (m, 3H), 5.02−5.01 (m, 1H), 4.99−4.95 (m, 1H), 4.96−4.86 (m, 4H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.66−4.59 (m, 6H), 4.53−4.46 (m, 3H), 4.14−4.12 (m, 1H), 3.85−3.75 (m, 4H), 3.72−3.53 (m, 6H), 3.48−3.40 (m, 2H), 2.06 (s, 3H), 1.67 (q, *J* = 6.8 Hz, 1H), 1.26 (d, *J* = 6.2 Hz, 3H), 0.94 (bt, *J* = 6.8 Hz, 6H), 0.87 (s, 6H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 138.8, 138.5, 138.2, 137.9, 137.8, 128.8−127.2, 100.5, 99.7, 85.4, 85.1, 80.5, 80.1, 80.0, 75.2, 75.0, 74.9, 74.0, 73.5, 72.0, 71.5, 71.3, 69.6, 69.5, 68.8, 68.4, 60.4, 49.3, 34.4, 29.7, 24.9, 23.6, 20.4, 20.2, 18.7, 18.6, 18.1, −2.3, −2.4; HRESI MS *m*/*z* calcd $C_{63}H_{81}NO_{12}SiNa$ [M + Na]$^+$ 1094.5420, found 1094.5439, error 1.7 ppm.

2-[Methyl-*O*-(2-acetammido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-mannopyranosyl)]-5-methyl-*O*-(thexyldimethylsilyl 3,4-di-*O*-benzyl-β-D-rhamnopyranosyl)-3,4-dihydroxytetrahydrofuran, 35/36. Compound **20** (40 mg, 0.037 mmol) was dissolved in H_2O:acetone (1.6 mL, 1:10), and the resulting solution was cooled to 0 °C. *N*-Methylmorpholine *N*-oxide (6 mg, 0.055 mmol) and a solution of 2.5% OsO_4 in *tert*-butyl alcohol (47 μL, 0.0037 mmol) were slowly added dropwise, and the reaction was monitored by TLC (toluene:acetone 7:3). After 3 h, the reaction was diluted with CH_2Cl_2 (5 mL) and washed with sat. aq $NaHSO_3$ (5 mL). The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to dryness, affording a mixture of diastereoisomers in 1:2 dr. The diastereoisomers were completely separated by semipreparative HPLC (chiral column 250 × 10 mm ID, hexane:2-propanol 7:3, flow 2 mL\min, λ 210 nm), affording compound **35** (12 mg, 0.011 mmol) as a major diastereoisomer together with compound **36** (6 mg, 0.0054 mmol) in 62% overall yield.

Compound **35**. $[\alpha]^{25}_D$ = +15.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.28 (m, 25H); 6.09 (d, *J* = 8.3 Hz, 1H), 5.10 (d, *J* = 8.0 Hz, 1H), 4.91−4.84 (m, 3H), 4.78 (d, *J* = 11.1 Hz, 1H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.69 (d, *J* = 1.7 Hz, 1H), 4.65−4.60 (m, 3H), 4.55−4.57 (bs, 1H), 4.51−4.49 (m, 3H), 4.17 (m, 1H), 4.12−4.08 (m, 3H), 4.01−3.99 (m, 1H), 3.93 (dd, *J* = 10.8, 4.6 Hz, 1H), 3.90 (dd, *J* = 10.5, 6.5 Hz, 1H), 3.80−3.67 (m, 8H), 3.65 (dd, *J* = 10.8, 6.7 Hz, 1H), 3.56 (t, *J* = 9.5 Hz, 1H), 3.46−3.44 (m, 1H), 2.07 (s, 3H), 1.66 (hept, *J* = 5.6 Hz, 1H), 1.27 (d, *J* = 6.2 Hz, 3H), 0.95−0.94 (bt, *J* = 6.3 Hz, 6H), 0.87 (s, 6H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 138.8, 138.5, 138.1, 137.7, 137.4, 128.5−124.4, 100.9, 100.1, 80.1, 80.0, 79.7, 75.1, 74.7, 73.9, 73.8, 73.6, 72.1, 71.9, 71.2, 70.5, 69.4, 68.7, 68.5, 66.5, 49.4, 34.4, 24.9, 23.5, 20.4, 20.2, 19.8, 18.8, 18.6, 18.1, −2.7, −2.8; HRESI MS *m*/*z* calcd $C_{63}H_{83}NO_{14}SiNa$ [M + Na]$^+$ 1128.5475, found 1128.5507, error 2.8 ppm.

Compound **36**. $[\alpha]^{25}_D$ = −17.5 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, *T* = 27 °C) δ 7.39−7.28 (m, 25H), 5.97 (d, *J* = 8.3 Hz, 1H), 4.91−4.81 (m, 4H), 4.77−4.45 (m, 8H), 4.23−4.22 (m, 1H), 4.09−3.95 (m, 3H), 3.90−3.83 (m, 2H), 3.77−3.65 (m, 5H), 3.57−3.54 (m, 2H), 3.45−3.41 (m, 1H), 2.05 (s, 3H), 1.66 (q, *J* = 4.5 Hz, 6H), 0.88 (s, 6H), 0.13 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 138.8, 138.6, 138.0, 137.5, 128.8−127.6, 100.5, 100.5, 82.0, 80.2, 79.8, 79.7, 78.7, 75.1, 74.9, 74.8, 74.0, 73.7, 72.1, 71.4, 69.7, 68.5, 68.0, 67.9, 49.2, 34.4, 25.0, 23.7, 20.4, 20.2, 18.7, 18.6, 18.1, −2.6, −2.8; HRESI MS *m*/*z* calcd $C_{63}H_{83}NO_{14}SiNa$ [M + Na]$^+$ 1128.5475, found 1128.5497, error 1.9 ppm.

(2*S*,3*S*,4*R*,5*R*)-2-[Methyl-*O*-(2-acetammido-2-deoxy-β-D-mannopyranosyl)]-5-methyl-*O*-(2-D-rhamnopyranosyl)-3,4-dihydroxytetrahydrofuran, 1a. Compound **35** (11.9 mg, 0.011 mmol) was dissolved in dry THF (0.6 mL) under nitrogen atmosphere, in the presence of 4 Å molecular sieves, and the resulting solution was cooled to 0 °C. A 1 M TBAF solution in THF (0.16 mL, 0.16 mmol) was slowly added, and the reaction mixture was stirred at room temperature. The reaction was monitored by TLC (toluene:acetone 1:1). After the complete consumption of starting compound, 4 mL of brine was added and the solution was extracted (3 × 10 mL) with ethyl acetate. The organic layers were collected and dried (over Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (toluene:acetone 8:2 to 1:1 in gradient elution), affording desilylated compound as an amorphous white solid.

This compound was dissolved in a MeOH/H_2O mixture (0.7:0.7 mL), Pd/C catalyst (10%, 5 mg) was added, and the reaction mixture was vigorously stirred under hydrogen at room temperature. After 48 h, a second portion of the catalyst (5 mg) was added and the mixture was stirred under hydrogen for an additional 12 h. The reaction mixture was diluted with MeOH/H_2O, filtered over a Celite pad, concentrated under reduced pressure to remove MeOH, and finally lyophilized to give **1a** as an amorphous solid (3.3 mg, 60%). ^{1}H NMR (500 MHz, D_2O, *T* = 30 °C) δ 4.82 (d, *J* = 1.5 Hz, 1H), 4.80 (d, *J* = 1.7 Hz, 1H), 4.52 (dd, *J* = 1.5, 4.5 Hz, 1H), 4.23−4.21 (m, 2H), 4.17−4.15 (m, 1H), 4.08 (dd, *J* = 2.5, 11.3 Hz, 1H), 4.02 (m, 1H), 3.96−3.94 (m, 2H), 3.91 (*J* = 12.4, 2.3 Hz, 1H), 3.81 (dd, *J* = 4.6, 3.8 Hz, 1H), 3.80 (dd, *J* = 12.4, 5.9 Hz, 1H) 3.74 (dd, *J* = 9.7, 3.5 Hz, 1H), 3.73−3.68 (m, 2H), 3.59 (dd, *J* = 8.0, 10.6 Hz, 1H), 3.53 (t, *J* = 9.8 Hz, 1H), 3.43 (t, *J* = 9.7 Hz, 1H), 3.42−3.38 (m, 1H), 2.06 (s, 3H), 1.28 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, D_2O, *T* = 30 °C) δ 100.3, 99.7, 80.1, 79.6, 76.4, 72.0, 72.0, 71.8, 71.6, 70.0, 70.0, 69.5, 68.7, 66.8, 66.5, 60.5, 53.1, 22.1, 16.6; HRESI MS *m*/*z* calcd $C_{20}H_{35}NO_{14}Na$ [M + Na]$^+$ 536.1950, found 536.1948, error 0.4 ppm.

(2*S*,3*R*,4*S*,5*R*)-2-[Methyl-*O*-(2-acetammido-2-deoxy-β-D-mannopyranosyl)]-5-methyl-*O*-(2-D-rhamnopyranosyl)-3,4-dihydroxytetrahydrofuran, 1b. Compound **36** (5.8 mg, 0.0052 mmol) was fully deprotected as described for major diastereoisomer **35**, affording isomer **1b** as an amorphous solid (1.3 mg, 48%). HRESI MS *m*/*z* calcd $C_{20}H_{35}NO_{14}Na$ [M + Na]$^+$ 536.1950, found 536.1956, error 1.1 ppm.

Competitive ELISA Assay. Flat-bottomed plates (96-well) were incubated overnight at 4−8 °C with a mixture of *S. pneumoniae* 19F

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CPS (1 mg/mL) and methylated human serum albumin (1 mg/mL). A solution of fetal calf serum (5%) in phosphate-buffered saline supplemented with Brij-35 (0.1%) and sodium azide (0.05%) was applied to the plates for blocking of nonspecific binding sites. The plates were incubated overnight at 4−8 °C with a solution (1:200) of rabbit anti-19F, used as reference serum. When compounds **1a** and **1b** were tested, they were added to each well immediately before the addition of the reference serum. The plates were then incubated with alkaline phosphatase conjugate goat antirabbit IgG, stained with *p*-nitrophenyl phosphate, and the absorbance was measured at 405 nm.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

#Dedicated to the memory of Prof. Marcello Tiecco.

■ REFERENCES

(1) (a) Varki, A. *Glycobiology* **1993**, *3*, 97−130. (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683−720. (c) *Comprehensive Glycoscience*, 1st ed; Kamerling, J. P.; Boons, G.-J.; Lee, Y. C.; Suzuki, A.; Taniguchi, N.; Voragen, G. J., Eds.; Elsevier: Oxford, 2007.

(2) (a) Witczak, Z. J.; Nieforth, K. A., Eds. *Carbohydrates in Drug Design*; M. Dekker: New York, 1997. (b) Sharon, N. *Biochim. Biophys. Acta* **2006**, *1760*, 527−537. (c) Balzarini, J. *Nat. Rev. Microbiol.* **2007**, *5*, 583−597. (d) Ernst, B.; Magnani, J. L. *Nat. Rev. Drug Discovery* **2009**, *8*, 661−677.

(3) Sofia, M. J. *Med. Chem. Res.* **1998**, *8*, 362−378.

(4) (a) Boltje, T. J.; Buskas, T.; Boons, G.-J. *Nature Chem* **2009**, *1*, 611−622. (b) Seeberger, P. H. *Chem. Soc. Rev.* **2008**, *37*, 19−28. (c) LepeniesB.Yin, J.; Seeberger, P. H. *Curr. Opin. Chem. Biol.* **2010**, *14*, 404−411 and references cited therein.

(5) (a) Kotha, S.; Dipak, M. K. *Tetrahedron* **2012**, *68*, 397−421 and references cited therein. (b) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746−1787 and references therein. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (d) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923. (e) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117−7140. (f) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490−4527. (g) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243−251.

(6) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039−2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110. (c) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791−799. (d) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179. (e) Scholl, M. S.; Ding, C.; Lee, W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (f) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543−6554.

(7) (a) Dominique, R.; Das, S. K.; Roy, R. *Chem. Commun.* **1998**, 2437−2438. (b) Roy, R.; Das, S. K.; Dominique, R.; Trono, M. C.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *Pure Appl. Chem.* **1999**, *71*, 565−571. (c) Gan, Z.; Roy, R. *Tetrahedron* **2000**, *56*, 1423−1428. (d) Jana, P. K.; Mandal, S. B.; Bhattacharjya, A. *Tetrahedron Lett.* **2011**, *52*, 6767−6771. (e) Liu, Z.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2011**, *76*, 8588−8598. (f) Giguère, D.; Patnam, R.; Juarez-Ruiz, J. M.; Neault, M.; Roy, R. *Tetrahedron Lett.* **2009**, *50*, 4254−4257.

(8) Ronchi, P.; Vignando, S.; Guglieri, S.; Polito, L.; Lay, L. *Org. Biomol. Chem.* **2009**, *7*, 2635−2644.

(9) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D.; Balducci, R. *J. Org. Chem.* **1990**, *55*, 429−434.

(10) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Santi, C. *Synlett* **1993**, *10*, 798−799.

(11) (a) Tiecco, M.; Testaferri, L.; Bagnoli, L.; Marini, F.; Santi, C.; Temperini, A.; Scarponi, C.; Sternativo, S.; Terlizzi, R.; Tomassini, C. *ARKIVOC (Gainesville, FL, U. S.)* **2006**, 186−206. (b) Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Bagnoli, L.; Santi, C.; Temperini, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1493−1502. (c) Tiecco, M.; Testaferri, L.; Bagnoli, L.; Scarponi, C.; Purgatorio, V.; Temperini, A.; Marini, F.; Santi, C. *Tetrahedron: Asymmetry* **2005**, *16*, 2429−2435. (d) Tiecco, M.; Testaferri, L.; Bagnoli, L.; Scarponi, C.; Temperini, A.; Marini, F.; Santi, C. *Tetrahedron: Asymmetry* **2006**, *17*, 2768−2774. (e) Tiecco, M.; Testaferri, L.; Bagnoli, L.; Purgatorio, V.; Temperini, A.; Marini, F.; Santi, C. *Tetrahedron: Asymmetry* **2001**, *12*, 3297−3304.

(12) (a) Tiecco, M.; Testaferri, L.; Bagnoli, L.; Purgatorio, V.; Temperini, A.; Marini, F.; Santi, C. *Tetrahedron: Asymmetry* **2004**, *15*, 405−412. (b) Tiecco, M.; Testaferri, L.; Bagnoli, L.; Terlizzi, R.; Temperini, A.; Marini, F.; Santi, C.; Scarponi, C. *Tetrahedron: Asymmetry* **2004**, *15*, 1949−1955. (c) Tiecco, M.; Testaferri, L.; Bagnoli, L.; Scarponi, C.; Temperini, A.; Marini, F.; Santi, C. *Tetrahedron: Asymmetry* **2007**, *18*, 2758−2767. (d) Tiecco, M.; Testaferri, L.; Bagnoli, L.; Scarponi, C. *Tetrahedron: Asymmetry* **2008**, *19*, 2411−2416.

(13) Tiecco, M. Electrophilic Selenium, Selenocyclizations. In *Topics in Current Chemistry: Organoselenium Chemistry: Modern Developments in Organic Synthesis*; Wirth, T., Ed.; Springer-Verlag: Heidelberg, 2000; pp 7−54.

(14) Back, T. G. Selenoxide eliminations. In *Organoselenium Chemistry. A Practical Approach*; Back, T. G., Ed.; Oxford University Press: Cary, NC, 1999; pp 7−33.

(15) (a) Fournière, V.; Cumpstey, I. *Tetrahedron Lett.* **2010**, *51*, 2127−2129 and references cited therein. (b) Kawai, Y.; Ando, H.; Ozeki, H.; Koketsu, M.; Ishihara, H. *Org. Lett.* **2005**, *7*, 4653−4656. (c) Zbigniew, J.; Witczak, J.; Czernecki, S. *Adv. Carbohydr. Chem. Biochem.* **1988**, *53*, 143−199. (d) Boutureira, O.; Rodríguez, M. A.; Dìaz, Y.; Matheu, I., M.; Castillón, S. *Carbohydr. Res.* **2010**, *345*, 1041−1045. (e) Boutureira, O.; Rodríguez, M. A.; Benito, D.; Matheu, I., M.; Díaz, Y.; Castillón, S. *Eur. J. Org. Chem.* **2007**, 3564−3572.

(16) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Marini, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1989−1993.

(17) Lipshutz, B. H.; Gross, T. *J. Org. Chem.* **1995**, *60*, 3572−3573.

(18) In compound **9**, where H-2 and H-5 are in anti relationship, C-3 was less shielded (40.8 ppm) than C-4 (39.5 ppm), while in stereoisomer **8**, where H-2 and H-5 are in cis relationship, C-3 was more shielded (39.6 ppm) than C-4 (40.8 ppm). A very similar trend was observed for compound **13** (C-3 = 40.5 ppm, C-4 = 39.8 ppm), while for compound **12**, the values were 40.0 ppm for C-3 and 40.8 ppm for C-4. According to this trend, we therefore assumed that H-2 and H-5 are in anti relationship in compound **13** and in syn relationship in compound **12**.

(19) The two protons H-2 and H-5 appeared as a multiplet in the syn elimination products **14** and **18**. On the contrary, in the anti elimination products **15** and **19**, the protons H-2 and H-5 showed different values of chemical shifts and appeared as a doublet of doublet of doublet.

(20) (a) Watson, D. A.; Musher, D. M.; Jacobsen, J. W.; Verhoef, J. *Clin. Infect. Dis.* **1993**, *17*, 913−924. (b) Austrian, R. *Rev. Infect. Dis.* **1981**, *3*, S1−S17. (c) Austrian, R. *Vaccine* **2001**, *19*, S71−S77.
(21) (a) Tikhomirov, E.; Santamaria, M.; Esteves, K. *World Health Stat. Quart.* **1997**, *50*, 170−177. (b) Fedson, D. S.; Anthony, J.; Scott, G. *Vaccine* **1999**, *17*, S11−S18. (c) Poland, G. A. *Vaccine* **1999**, *17*, 1674−1679.
(22) (a) Jones, C. *Carbohydr. Eur.* **1998**, *21*, 10−16. (b) Robbins, J. B.; Austrian, R.; Lee, C. J.; Rastogi, S. C.; Schiffman, G.; Henrichsen, J.; Mäkelä, P. H.; Broome, C. V.; Facklam, R. R.; Tiesjema, R. H.; Parke, J. C. *J. Infect. Dis.* **1983**, *148*, 1136−1159. (c) Musher, D. M. *Clin. Infect. Dis.* **1992**, *14*, 801−807.
(23) (a) Dagan, R.; Klugman, K. P. *Lancet Infect. Dis.* **2008**, *8*, 785−795. (b) Poolman, J. T. *Expert Rev. Vaccines* **2004**, *3*, 597−604. (c) Lockhart, S.; Hackell, J. G.; Fritzell, B. *Expert Rev. Vaccines* **2006**, *5*, 553−564.
(24) Scott, J. A. *Vaccine* **2007**, *25*, 2398−3405.
(25) (a) Bousquet, E.; Khitri, M.; Lay, L.; Nicotra, F.; Panza, L.; Russo, G. *Carbohydr. Res.* **1998**, *311*, 171−181. (b) Soliveri, G.; Bertolotti, A.; Panza, L.; Poletti, L.; Jones, C.; Lay, L. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2174−2181.
(26) Legnani, L.; Ronchi, S.; Fallarini, S.; Lombardi, G.; Campo, F.; Panza, L.; Lay, L.; Poletti, L.; Toma, L.; Ronchetti, F.; Compostella, F. *Org. Biomol. Chem.* **2009**, *7*, 4428−4436.
(27) Bundle, D. R.; Josephson, S. *Can. J. Chem.* **1979**, *57*, 662−668.
(28) Draghetti, V.; Poletti, L.; Prosperi, D.; Lay, L. *J. Carbohydr. Chem.* **2001**, *20*, 813−819.
(29) Ahmed, A. A.; Hoegnauer, K. E.; Enev, V. S.; Hanbauer, M.; Kaehlig, H.; Öhler, E.; Mulzer, J. *J. Org. Chem.* **2003**, *68*, 3026−3042.
(30) (a) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 7427−7430. (b) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58−71.
(31) We found that, when the relative homodimerization rates of the reaction partners are markedly different, the two-step SM-CM sequence provided the best results in comparison to the classical CM reaction. In particular, we observed that sugar-olefins containing nonanomerically linked *O*-allyl groups, such as rhamnoside **22**, have a homodimerization rate much lower than that of homoallyl alcohols, such as *β*-mannoside **21**, and therefore they are the best reaction partners for the SM-CM sequence.
(32) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635−646.
(33) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768−2771.