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Exocyclic vinyl ethers of ketofuranosides

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Abstract

Exocyclic vinyl ether derivatives of sugars are found in biosynthetic pathways and may serve as useful synthetic intermediates. The ketose subfamily of sugars is the least characterized in this field. Thus, the synthesis of exocyclic vinyl ether derivatives of ketohexoses via β-elimination was studied with respect to the nature of the 6-*O* leaving group and the protection of the 4-hydroxy group. We applied this study to protected L-sorbofuranoside and D-tagatofuranoside sugar derivatives in which the 4-hydroxy group and the 6-*O*-leaving group are in the *syn* configuration. Some reactions involving deprotection and reductive rearrangement of the tagatose-derived vinyl ether product were also studied.

Keywords: β-Elimination; Enol ether; Ketose; Sugar derivatives

1. Introduction

Exocyclic vinyl ether derivatives of sugars are found as intermediates in various metabolic pathways, such as the hydrolysis of *S*-adenosylhomocysteine by the enzyme SAHC hydrolase,[1] the 2-deoxy-*scyllo*-inosose synthase catalytic reaction,[2] and the formation of dehydroquinate in the shikimic pathway[3] (Fig 1). They also serve as intermediates in the synthesis of enzyme inhibitors and biologically related compounds[4] or as monomers for polymerization.[5] It was demonstrated that a compound of this family could undergo biomimetic rearrangement to the corresponding carbocyclic derivative.[6] Most of the available data refer to aldohexopyranose and aldopentofuranose derivatives, whereas only a few examples of ketofuranose derivatives have been described. Among the latter is the natural antibiotic angustmycin A (Fig. 1D).[7] Labeling studies suggested that the biosynthesis of the carbocyclic moiety of the natural products neplanocin A and aristeromycin involves a key intramolecular aldol condensation,[8] in analogy with the cyclization of glucose-6-phosphate to myo-inositol-1-phosphate.[9] We hypothesize that neplanocin A and aristeromycin biosyntheses may involve a common exocyclic vinyl derivative of fructose-6-phosphate (Scheme 1), in analogy with DHQ biosynthesis.[3]

The synthesis of such vinyl fructofuranoid derivatives proceeds either by β-elimination of the corresponding 6-tosyl- or 6-deoxy-6-halo protected furanoside[10] or by reductive elimination of 6-*O*-acyl-5-halo-fructofuranoside.[6] As part of our studies on 'locked' fructofuranosides,[11] we further explored the β-elimination reaction, with respect to the leaving group and the 4-*O* protecting group. We demonstrate successful preparation of exocyclic vinyl ether ketofuranoside derivatives and present some unexpected reactions of these products.

2. Results and discussion

2.1. Synthesis

The strategy we used relied on locking a ketohexose sugar in its furanose form, proper protection of the sugar hydroxy groups, and activation of the primary C-6 hydroxy group as a good leaving group (Scheme 2).

Our first target was the commercially available 2,3-*O*-isopropylidene-L-sorbofuranose **1** (Scheme 3), previously studied by Hough and Otter.[10] They demonstrated that 4-*O*-acetyl-1-*O*-benzoyl-6-deoxy-6-iodo-2,3-*O*-isopropylidene-L-sorbofuranose

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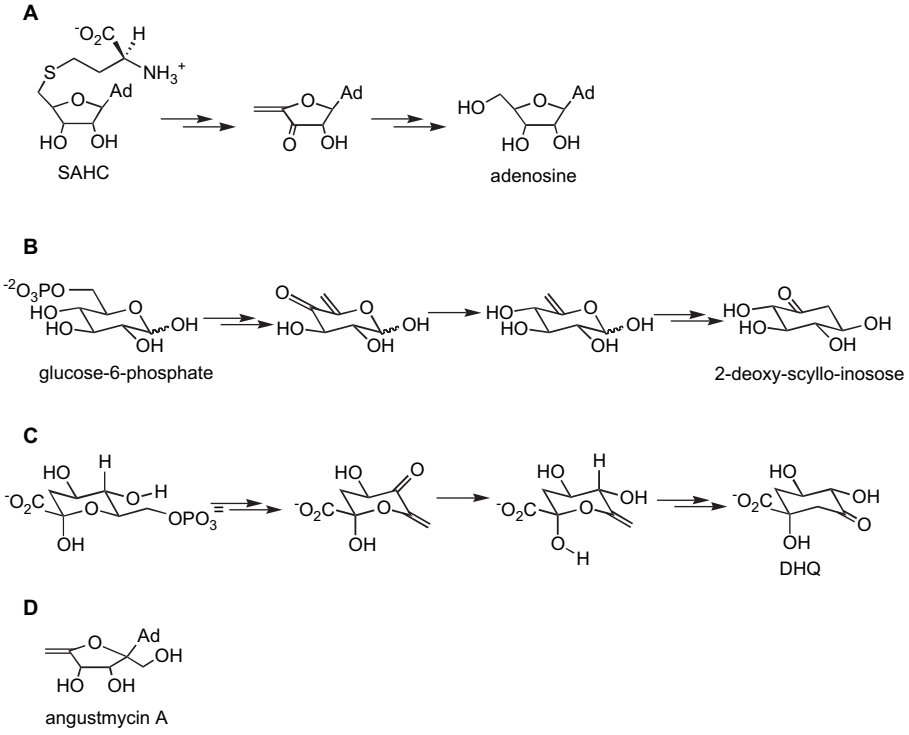
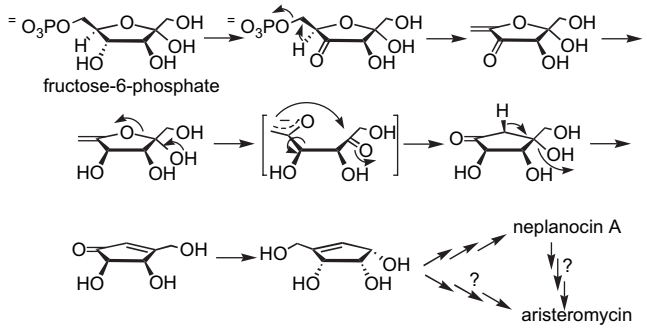
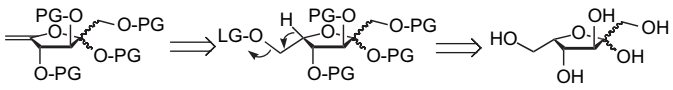


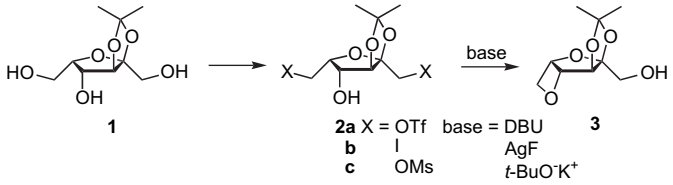
Figure 1. Biological reactions involving exocyclic vinyl ether sugar derivatives. (A) The catalytic activity of SAHC hydrolase. (B) The catalytic activity of 2-deoxy-*scyllo*-inosose synthase. (C) The catalytic activity of DHQ synthase. (D) The angustmycin A antibiotic.



Scheme 1. Suggested biosynthetic pathway for the carbocyclic moiety of neplanocin A and aristeromycin. This pathway involves an exocyclic vinyl furanose intermediate.



Scheme 2. Retrosynthetic analysis of the vinyl ether derivatives of ketohexoses.

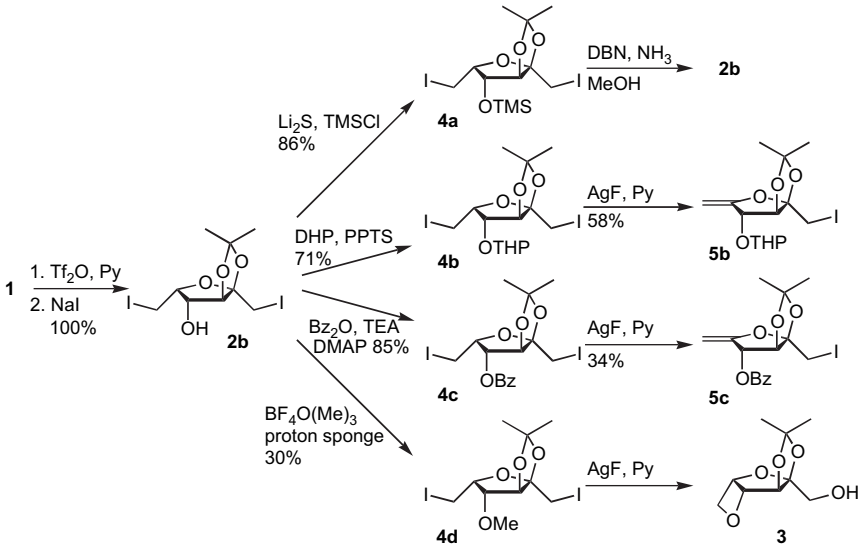


Scheme 3. Oxetane formation from the unprotected 4-hydroxy, 6-activated L-sorbofuranoside.

can be transformed to the corresponding vinyl ether in good yield. On the other hand, 5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-xylofuranose, in which the unprotected 4-hydroxy group is *syn* to the 5-iodo leaving group, undergoes an intramolecular substitution reaction to form the corresponding oxetane. Thus, we studied the fate of the 6-activated-4-unprotected derivatives **2** under basic conditions. Three activating groups were tested, triflate, iodo, and mesyl, with pK_a values of the conjugated acids of −13, −10, and −2, respectively. All three compounds yielded the oxetane product **3**, with no traces of the β-elimination products (Scheme 3).

Next, we examined various protecting groups for the 4-hydroxy group. 1,6-Dideoxy-1,6-diiodo-2,3-*O*-isopropylidene-L-sorbofuranose was prepared via a one-pot two-step procedure in quantitative yield. It was then subjected to several protecting protocols and subsequent β-elimination reaction (Scheme 4). An attempt to protect the 4-hydroxy group with the bulky *tert*-butyl dimethyl silyl group failed, probably due to steric hindrance. On the other hand, the smaller trimethyl silyl protecting group was efficiently introduced at the 4-hydroxy position. Unfortunately, this protecting group was not stable under the basic elimination conditions, yielding the unprotected starting material **2b**. Protection with either THP or benzoyl protecting groups was also efficient, yielding **4b** (as a nearly 1:1 diastereomeric mixture) and **4c**, respectively. Elimination from either of these compounds proceeded in a moderate yield, providing the desired exocyclic vinyl ethers **5b** (as nearly 1:1 mixture of two diastereomers) and **5c** (Scheme 4).

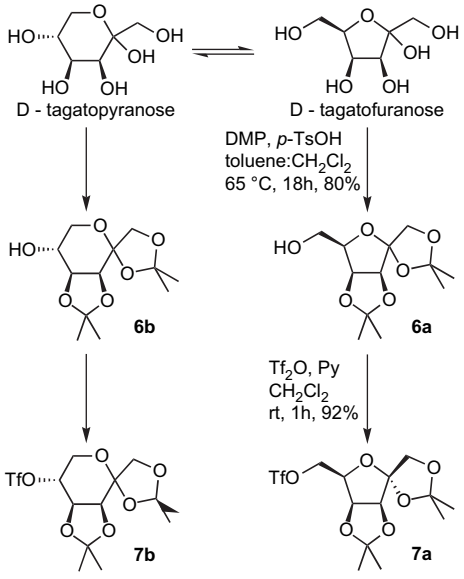
Of special interest is our attempt to protect the 4-hydroxy group by methylation (**4d**). To our surprise, treatment of the



Scheme 4. Synthesis of exocyclic vinyl ether derivatives of L-sorbofuranoside. Effect of the 4-hydroxy protecting group.

methyl-protected **4d** with AgF did not produce the desired elimination product but rather the oxetane **3**, probably via an oxonium intermediate. Thus, protection of the hydroxy group as an ether does not prevent oxetane formation when the hydroxy and the leaving group are in *syn* configuration.

Our next target was the ketohexose D-tagatose (Scheme 5). It too was expected to have a *syn* configuration between the 4-hydroxy and the leaving groups, necessitating protection of the former. Ketohexoses are more stable in aqueous solution in their pyranose form, rather than in the furanose form,[12] but the equilibrium shifts toward the furanose form in less polar solvents.[12a] Thus, the outcome of tagatose protection in terms of configuration and anomeric composition is not straightforward. Only the furanose form will have a free 6-hydroxymethyl group available for activation and elimination to the exocyclic enol ether.



Scheme 5. Structure of the 1,2:3,4-diisopropylidene-D-tagatofuranoside versus D-tagatopyranoside.

Put into practice, D-tagatose was protected as the 1,2:3,4-diacetonide, yielding a single isomer in 80% yield. This reaction was very sensitive to the conditions, being optimal in toluene–CH_2Cl_2, 4:5, at 60–65 °C for 18 h with 3.8 equiv of dimethoxypropane (DMP) and a catalytic amount of *p*-TsOH. Deviation from the optimal temperature or extension of the reaction time led to significant reduction in the reaction yield. The identification of the single isomer product was not trivial. In principle, it could be any of the four possible isomers, α- and β-furanose, and α- and β-pyranose (**6a** and **6b**, Scheme 5). Therefore, the product of unknown configuration was further triflated, providing a single isomer that was fully characterized by NMR (including 2D COSY, NOESY, and HMQC). The hydroxy to triflate transformation was accompanied by a shift of two geminal methylene protons from δ ~3.8 to ~4.7 ppm in the ^{1}H NMR spectrum and a shift of the corresponding methylene carbon from δ 68 to 76 ppm in the ^{13}C NMR spectrum. This confirmed triflation of the 6-hydroxy group of the furanoside form **6a**. NOESY data established α configuration of both the free hydroxy furanoside **6a** and its triflate product **7a** (Fig. 2). Thus, this reaction provided both the desired furanose configuration, required for the β-elimination reaction, and the protection of the 4-hydroxy group, to prevent the competing oxetane formation.

Having established the furanose configuration for the D-tagatose diacetonide **6a** and its 6-triflate **7a**, we studied the

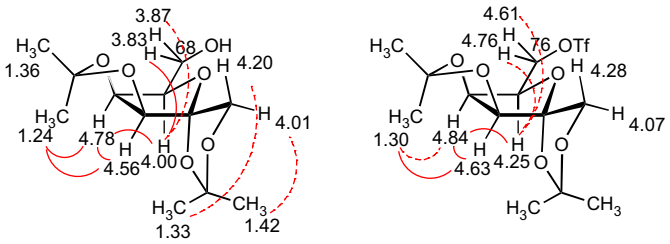
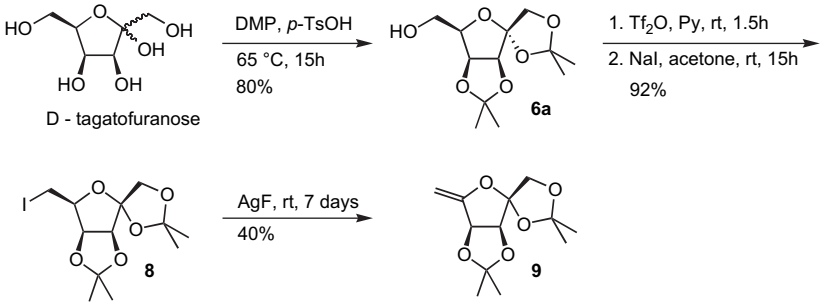


Figure 2. NOESY correlation support for the structural determination of the diacetonide furanosides **6a** and **7a**. Solid and dashed lines represent medium and weak correlations, respectively. The strong geminal correlations are not marked.

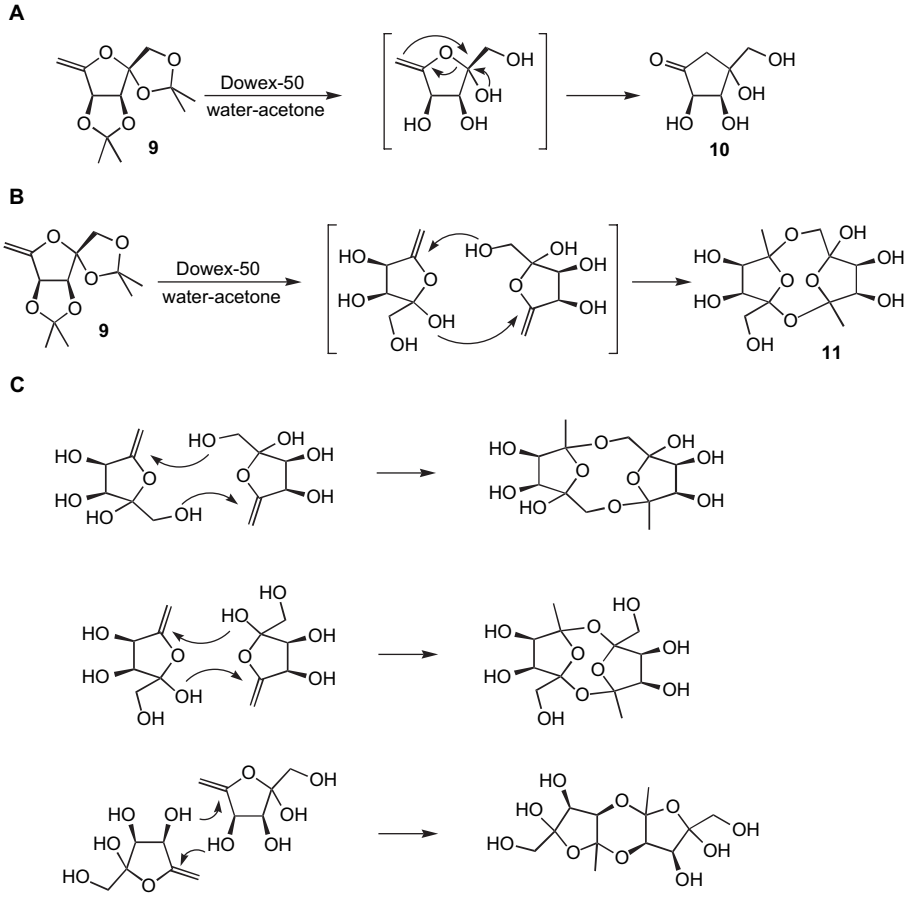


Scheme 6. Synthesis of the exocyclic vinyl ether derivative of D-tagatofuranoside.

β-elimination reaction. Attempts to eliminate the triflate under various basic conditions (2–10 equiv of DBU, rt to 85°C, 15–72 h) did not provide the desired exocyclic vinyl ether **9**. Direct iodination of **6a** (PPh_3, I_2, imidazole) yielded mainly starting material, with only 2% traces of the desired iodide **8**. Therefore, the diacetonide **6a** was quantitatively iodinated via the one-pot two-step procedure mentioned above. Treatment of iodide **8** with AgF finally afforded the desired vinyl ether **9** in moderate yield (Scheme 6).

2.2. Reactions

One possible application of the exocyclic vinyl ether derivatives, related to our studies on 'locked' fructofuranose derivatives,[11] is their transformation to carbocyclic sugar analogs. We anticipated that deprotection of the diacetonide vinyl ether **9** might lead to rearrangement to the corresponding cyclopentanone **10** (Scheme 7A). This assumption was based on the analogous spontaneous rearrangement of a vinyl pyranose derivative to the corresponding cyclohexanone, as a model reaction for the final step of the complex reaction catalyzed by the enzyme DHQ synthase.[6] Thus, diacetonide **9** was treated with acidic Dowex-50 in a water–acetone mixture. To our surprise, the only product, obtained in quantitative yield, was the nine-membered ring dimer **11** (Scheme 7B).[13] The same product was efficiently obtained even at high dilution. We assigned structure **11** to the dimer (with a central 9-membered ring) rather than a central 6-, 8-, or 10-membered



Scheme 7. Dimerization of the deprotected exocyclic vinyl ether derivative of D-tagatofuranose. (A) The anticipated rearrangement reaction. (B) The nine-membered ring product of the dimerization. (C) Other possible dimerization reactions, which were rejected based on NMR analysis.

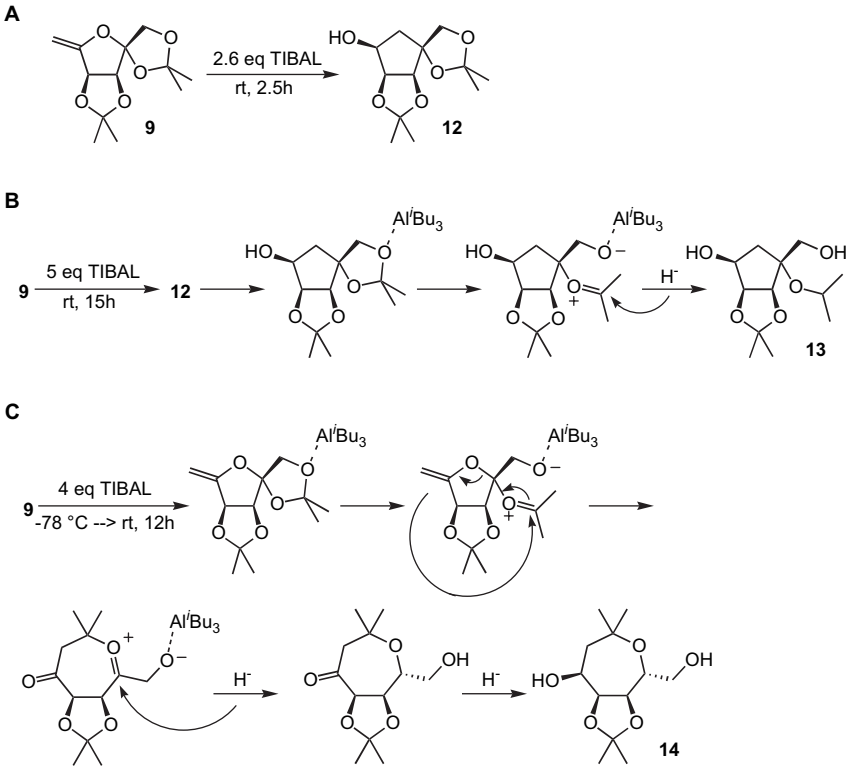
ring structure (Scheme 7C). This assignment was based on the analysis of the dimer's ^{1}H NMR spectrum: each of the monomers in the dimer had a discrete set of resonances in the spectrum, indicating an asymmetric structure. The spectrum exhibited two sets of methylene protons: one pair of protons resonated at δ 3.83 and 3.86 ppm, while the other at δ 3.71 and 4.15 ppm. The fact that one pair of protons resonated at two very close frequencies ($\Delta\delta$=0.03 ppm) while the other pair was split ($\Delta\delta$=0.44 ppm) may indicate that one methylene is part of a ring and the other is not. This distinction supports only the 9-membered ring dimer structure, but not the 6, 8-, and 10-membered ring alternatives.

Another approach we examined was the glycoside-to-carbocycle reductive rearrangement, promoted by triisobutylaluminum (TIBAL).[14] It was applied in some rearrangements of vinyl glucopyranosides to cyclohexane derivatives,[4b,14a] but not to vinyl furanosides. Unfortunately, treatment of **9** with 2.6 equiv TIBAL in toluene at rt for 2.5 h afforded mainly tar, from which the desired cyclopentanol diacetonide **12** was isolated, though at a low 7% yield. The structure was fully characterized by 2D NMR, demonstrating that the 1,2-acetonide retained its configuration and that the hydride transfer occurred from the less hindered α face (Scheme 8A).

This reaction was very sensitive to the conditions, yielding some unexpected products. When **9** was treated with 5 equiv of TIBAL for 15 h, a second reduction of the 1,2-acetonide protecting group afforded the isopropyl ether **13** in similar low yield (Scheme 8B). Under a different set of conditions, in which 4 equiv of TIBAL was added at −78 °C and then kept at rt for 12 h, a ring expansion/rearrangement reaction with two reductions yielded the seven-membered cyclic ether **14** (Scheme 8C). The relative stereochemistry of **14** at C2 and C5 was assigned unequivocally, based on excellent agreement between measured and calculated[15] ^{1}H NMR coupling constants. The C2−C3, C3−C4, and C4−C5 calculated (and measured) $^3J_{HH}$ values for **14** at the conformation corresponding to its global minimum energy were 9.6 (9.5), 7.9 (7), and 2.6 (3) Hz, respectively. The opposite configuration at C2 and C5 was calculated to exhibit C2−C3 and C4−C5 coupling constants of about 4.6 and 11.2 Hz, respectively. We suggest a mechanism in which the TIBAL Lewis acid interacts with one of the acetonide oxygens, rather than with the 'classic' enol oxygen (Scheme 8C). Another ring expansion reaction was previously observed with *C*-vinyl glycosides.[14a]

A few such rearrangement reactions were previously described, mainly for *exo* vinyl ethers derived from aldopyranosides and also for some aldofuranoside derivatives.[14c] The present study presents the first rearrangement of an *exo* vinyl ether ketofuranoside. It is possible that, whereas the previous studies involve intramolecular aldol condensation on an aldehyde moiety, which is energetically favorable, the present study addresses a corresponding much less favored condensation on a ketone moiety, allowing other side reactions to occur.

It is interesting to compare the above rearrangement reactions to similar reactions on other five-membered ring systems. An exocyclic γ-enollactone, derived from ribonic acid γ-lactone, was reduced to a relatively stable γ-enollactol, which spontaneously isomerized to the corresponding β-hydroxyketone (via ring opening and intramolecular aldol condensation).[16] This isomerization of a γ-enollactol is very similar to that reported



Scheme 8. (A) TIBAL promoted rearrangement, (B) protecting group reduction, and (C) ring expansion of 1,2:3,4-diisopropylidene-D-tagatofuranoside exocyclic vinyl ether derivative **9**.

for the δ-enollactol in the model reaction of the last step catalyzed by DHQ synthase.[6] The lactol led to a single desired rearrangement product. In our case on the other hand, the presence of five different oxygen atoms, involved in three ketal functional groups, may lead to many competing and tandem reactions, providing only a small amount of the desired product.

Another analogous reaction is the palladium(0)-catalyzed isomerization of 5-vinyl-2-alkylidenetetrahydrofurans to the corresponding cyclopentanones.[17] The main limitation of this reaction is its requirement of a substituting vinyl group, in addition to the rearranging exocyclic enol functionality, to serve as a ligand to the palladium complex. Thus, despite its efficiency, this reaction could not be applied to our sugar derivatives.

3. Conclusions

Exocyclic vinyl ether derivatives of sugars are of interest due to their involvement in metabolic processes, and their potential as synthetic intermediates. The least studied of these compounds are the ketose derivatives. Hough and Otter studied their preparation via β-elimination reaction of the corresponding 6-iodo derivatives. Here, we extended these studies, concentrating on ketohexoses in which the leaving group and the 4-hydroxy group are in *syn* configuration. This specific configuration may result in an intramolecular substitution reaction to form an oxetane ring. Therefore, we examined the effect of the nature of the leaving group and the effect of various protecting groups. The most successful procedure involves the preparation of a 6-iodo activating group through an efficient one-pot two-step reaction and AgF-promoted β-elimination with a properly protected 4-hydroxy group.

We further examined some interesting reactions involving deprotection and reductive rearrangement of the exocyclic vinyl ether products. These reactions led to unexpected dimerization, excess reduction, and ring expansion to an oxepane skeleton. Optimization of these reactions may provide an entry to useful synthetic structures.

4. Experimental

4.1. General

Dry solvents were prepared by treatment with 4 Å molecular sieves or by distillation over sodium. ^{1}H NMR spectra were recorded at 200, 300, or 600 MHz in $CDCl_3$, unless otherwise specified. Chemical shifts are expressed in parts per million, relative to TMS as an internal standard. Spectra in D_2O were calibrated by the HOD peak (δ 4.80, ^{1}H NMR) or by the peak of a small amount of added MeOH (δ 49.50, ^{13}C NMR). ^{13}C NMR spectral (at 50, 75, or 150 MHz) assignments were supported by DEPT, HMQC, and HMBC experiments. TLC was performed on E. Merck 0.2 mm pre-coated silica gel F-254 plates, and viewed by UV light and vanillin.[18] Chromatography refers to flash column chromatography,[19] carried out on silica gel 60 (230–400 mesh ASTM, E. Merck or Riedel-de Haën). Manipulated sugar derivatives were named according to the parent carbohydrate structure.

4.2. 2,3-O-Isopropylidene-1,6-di(O-triflate)-L-α-sorbofuranose (**2a**)

To a solution of 2,3-*O*-isopropylidene-L-α-sorbofuranose (1.0 g, 4.54 mmol) in dry CH_2Cl_2 (25 ml) and dry pyridine (1 ml, 2.5 equiv) was added Tf_2O (2 ml, 11.4 mmol) at 0 °C. The mixture was stirred under Ar at rt. After 1 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (25 ml). The mixture was partitioned between water and EtOAc. The organic layer was washed with 1 M HCl and brine, dried over $MgSO_4$, filtered, and evaporated to give pure **2a** (2.20 g, 4.54 mmol, 100%) as a white solid, mp 72–74 °C. ^{1}H NMR δ 1.39 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 4.56 (d, 1H, J=11 Hz, CH_2-1), 4.52 (br s, 1H, C*H*-3), 4.45 (d, 1H, J=2.5 Hz, C*H*-4), 4.63 (d, 1H, J=11 Hz, CH_2-1), 4.63–4.65 (m, 1H, C*H*-5), 4.64 (dd, 1H, J=10, 6.5 Hz, CH_2-6), 4.74 (dd, 1H, J=10, 4.5 Hz, CH_2-6); ^{13}C NMR δ 26.10 (*C*H$_3$), 27.36 (*C*H$_3$), 72.00 (*C*-1), 73.00 (*C*-6), 74.50 (*C*-4), 85.00 (*C*-3), 104.00 (*C*(CH$_3$)$_2$), 105.00 (*C*-2); MS (DCI) *m*/*z* 484 (M^+, 40); HRMS (*m*/*z*) calcd for $C_{11}H_{15}O_{10}S_2F_6$ (MH^+): 485.0013, found: 485.0031.

4.3. 1,6-Dideoxy-1,6-diiodo-2,3-O-isopropylidene-L-α-sorbofuranose (**2b**)

To a solution of 2,3-*O*-isopropylidene-L-α-sorbofuranose (0.64 g, 2.9 mmol) in dry CH_2Cl_2 (16 ml) and dry pyridine (0.5 ml, 2.1 equiv), was added Tf_2O (1.0 ml, 6.1 mmol) at 0 °C under Ar to provide a frozen light pink solution. The cooling bath was removed, and the mixture was allowed to melt and then to stir for 1.5 h. The reaction was quenched by saturated aqueous solution of $NaHCO_3$ (9 ml). The mixture was then partitioned between water and EtOAc and the organic layer was washed with 0.1 M HCl and brine, dried over $MgSO_4$, filtered, and evaporated to give a red oil, which was dissolved in dry acetone (17 ml). NaI (1.74 g, 11.6 mmol) was then added and the mixture was stirred over night in dark. The mixture was then partitioned between saturated aqueous $Na_2S_2O_3\cdot5H_2O$ and EtOAc. The aqueous layer was washed with EtOAc (×2), and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to give pure **2b** (1.276 g, 2.9 mmol, 100%) as a white solid, mp 107–110 °C. ^{1}H NMR δ 1.43 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.25 (t, 1H, J=9 Hz, CH_2-6), 3.30 (dd, 1H, J=9, 6 Hz, CH_2-6), 3.50 (d, 1H, J=11 Hz, CH_2-1), 3.58 (d, 1H, J=11 Hz, CH_2-1), 4.43 (d, 1H, J=3 Hz, C*H*-4), 4.53 (ddd, 1H, J=9, 6, 3 Hz, C*H*-5), 4.55 (s, 1H, C*H*-3); ^{13}C NMR δ −1.10 (*C*-6), 7.40 (*C*-1), 26.54 (*C*H$_3$), 27.59 (*C*H$_3$), 75.10 (*C*-4), 82.36 (*C*-5), 86.26 (*C*-3), 112.56 (*C*-2), 113.10 (*C*(CH$_3$)$_2$) MS (DCI) *m*/*z* 440 (M^+, 34.8), 424 (100); HRMS (*m*/*z*) calcd for $C_9H_{14}O_4I_2$ (M^+): 439.8982, found: 439.8967.

4.4. 2,3-O-Isopropylidene-1,6-di(O-mesyl)-L-α-sorbofuranose (**2c**)

To a solution of 2,3-*O*-isopropylidene-L-α-sorbofuranose (0.5 g, 2.30 mmol) in dry CH_2Cl_2 (3 ml) and dry pyridine

(0.4 ml, 4.60 mmol), was added mesyl chloride (0.3 ml, 4.60 mmol) at 0 °C under Ar. The mixture was stirred at 0 °C for 5 h, and was then partitioned between ice-cold water and EtOAc. The organic phase was washed with 0.1 M HCl, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and evaporated to give pure **2c** (415 mg, 1.1 mmol, 46%) as a white solid, mp 82–85 °C. ^{1}H NMR δ 1.39 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 3.08 (s, 6H, $SO_2CH_3\times2$), 4.34 (d, 1H, J=0.5 Hz, CH-4), 4.35 (d, 1H, J=11.5 Hz, CH_2-1), 4.39 (dd, 1H, J=11, 6.5 Hz, CH_2-6), 4.46 (d, 1H, J=11.5 Hz, CH_2-1), 4.51 (dd, 1H, J=11, 5.5 Hz, CH_2-6), 4.54 (ddd, 1H, J=6.5, 5.5, 0.5 Hz, CH-5), 4.55 (s, 1H, CH-3); ^{13}C NMR δ 26.21 (*C*H_3), 27.25 (*C*H_3), 37.56 (SO_2*C*H_3), 37.99 (SO_2*C*H_3), 66.46 (*C*-6), 68.09 (*C*-1), 74.60 (*C*-4), 77.44 (*C*-5), 85.43 (*C*-3), 111.67 (*C*(CH_3)$_2$), 113.30 (*C*-2); MS (DCI, CH_4) *m/z* 377 (MH^+, 6.9), 205 (100); HRMS (*m/z*) calcd for $C_{11}H_{21}O_{10}S_2$ (MH^+): 377.0576, found: 377.0573.

*4.5. 4,6-Anhydro-2,3-O-isopropylidene-L-α-sorbofuranose (**3**)*

To a solution of **2a** (0.34 g, 0.70 mmol) in dry THF (22 ml) was added DBU (0.3 ml, 2.0 mmol). The mixture was stirred under Ar at rt for 72 h. The mixture was partitioned between water and EtOAc. The organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness. Chromatography (ether–hexane, 2:1) gave **3** as a clear oil. ^{1}H NMR δ 1.42 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 3.90 (d, 1H, J=12 Hz, CH_2-1), 4.00 (d, 1H, J=12 Hz, CH_2-1), 4.18 (dd, 1H, J=8, 2 Hz, CH_2-6), 4.72 (s, 1H, CH-3), 4.79 (dd, 1H, J=8, 4 Hz, CH_2-6), 5.14 (td, 1H, J=4, 2 Hz, CH-5), 5.26 (d, 1H, J=4 Hz, CH-4); ^{13}C NMR δ 27.33 (*C*H_3), 27.89 (*C*H_3), 73.88 (*C*-1), 78.50 (*C*-6), 78.93 (*C*-5), 84.04 (*C*-3), 88.25 (*C*-4), 113.63 (*C*(CH_3)$_2$), 118.51 (*C*-2); MS (DCI, CH_4) *m/z* 203 (MH^+, 9), 187 (100); HRMS (*m/z*) calcd for $C_9H_{15}O_5$ (MH^+): 203.0919, found: 203.0915.

*4.6. 1,6-Dideoxy-1,6-diiodo-2,3-O-isopropylidene-4-O-trimethylsilyl-L-α-sorbofuranose (**4a**)*

To a vigorously stirred suspension of Li_2S (1.52 mmol) in dry acetonitrile (2 ml) was added TMSCl (3.13 mmol) at rt under Ar followed by a solution of **2b** (0.46 g, 1.05 mmol) in dry acetonitrile (5 ml). The mixture was stirred at rt, over night. The mixture was then partitioned between water and EtOAc, and the aqueous layer was washed with EtOAc (×2). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to give pure **4a** as a clear oil (0.90 mmol, 86%). ^{1}H NMR δ 0.23 (s, 9H, Si(CH_3)$_3$), 1.45 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 3.19–3.22 (m, 2H, CH_2-6), 3.42 (d, 1H, J=11 Hz, CH_2-1), 3.56 (d, 1H, J=11 Hz, CH_2-1), 4.37 (d, 1H, J=3 Hz, CH-4), 4.42 (br s, 1H, CH-3), 4.58 (ddd, 1H, J=7, 6, 3 Hz, CH-5); ^{13}C NMR δ −0.33 (*C*-6), 0.18 (Si(*C*H_3)$_3$), 6.74 (*C*-1), 26.73 (*C*H_3), 27.74 (*C*H_3), 74.77 (*C*-4), 83.48 (*C*-3), 85.74 (*C*-5), 112.79 (*C*-2), 113.25 (*C*(CH_3)$_2$); MS (DCI, CH_4) *m/z* 512 (M^+, 22); HRMS (*m/z*) calcd for $C_{12}H_{22}O_4I_2Si$ (M^+): 511.9377, found: 511.9368.

*4.7. 1,6-Dideoxy-1,6-diiodo-2,3-O-isopropylidene-4-O-tetrahydropyranyl-L-α-sorbofuranose (**4b**)*

To a solution of **2b** (1.46 g, 3.31 mmol) and PPTS (19.6 mg) in dry CH_2Cl_2 (35 ml) was added DHP (6 ml, 70 mmol) under Ar at rt. The mixture was stirred at rt for 11 days. The mixture was then partitioned between water and EtOAc, and the aqueous layer was washed with EtOAc (×2). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to give the crude product as a yellow oil. Chromatography (EtOAc–hexane, 1:9) gave nearly 1:1 mixture of two isomers of **4b** as a clear oil (2.36 mmol, 71%). ^{1}H NMR δ 1.44 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.51–1.67 (m, 12H, 2×CH_2-3′–4′–5′), 3.19 (dd, 1H, J=10.2, 9.0 Hz, CH_2-6), 3.21 (dd, 1H, J=10.2, 9.0 Hz, CH_2-6), 3.27 (dd, 1H, J=9.0, 5.1 Hz, CH_2-6), 3.35 (dd, 1H, J=10.5, 5.7 Hz, CH_2-6), 3.455 (d, 1H, J=10.8 Hz, CH_2-1), 3.457 (d, 1H, J=11.4 Hz, CH_2-1), 3.51 (d, 1H, J=11.4 Hz, CH_2-1), 3.57 (d, 1H, J=10.8 Hz, CH_2-1), 3.54–3.65 (m, 2H, CH_2-6′), 3.87–4.0 (m, 2H, CH_2-6′), 4.29 (d, 1H, J=3 Hz, CH-4), 4.63 (ddd, 1H, J=10.2, 5.1, 3.0 Hz, CH-5), 4.69 (ddd, 1H, J=9.0, 5.7, 2.4 Hz, CH-5), 4.72 (s, 1H, CH-3), 4.74–4.76 (m, 2H, 2×CH-2′), 4.81 (s, 1H, CH-3), 5.36 (d, 1H, J=3 Hz, CH-4); ^{13}C NMR δ −4.61 (*C*-1), −0.53 (*C*-1), 4.76 (*C*-6), 6.94 (*C*-6), 19.72 (*C*-4′), 25.21 (*C*-4′), 26.54 (*C*-5′), 26.65 (*C*-5′), 26.71 (*C*H_3), 27.48 (*C*H_3), 27.58 (*C*H_3), 27.68 (*C*H_3), 29.66 (*C*-3′), 30.52 (*C*-3′), 62.71 (*C*-6′), 63.33 (*C*-6′), 80.97 (*C*-4), 81.67 (*C*-4), 82.54 (*C*-5), 84.37 (*C*-5), 84.71 (*C*-3), 87.49 (*C*-3), 95.87 (*C*-2′), 102.45 (*C*-2′), 112.62 (*C*-2), 112.84 (*C*-2), 113.17 (*C*(CH_3)$_2$), 113.84 (*C*(CH_3)$_2$); MS (DCI, CH_4) *m/z* 524 (M^+, 50) 269 (100); HRMS (*m/z*) calcd for $C_{14}H_{22}O_5I_2$ (M^+): 523.9557, found: 523.9556.

*4.8. 1,6-Dideoxy-1,6-diiodo-2,3-O-isopropylidene-4-O-benzoyl-L-α-sorbofuranose (**4c**)*

To a solution of **2b** (1.34 g, 3.04 mmol), triethylamine (1.3 ml, 9.1 mmol), and DMAP (37 mg, 0.3 mmol) in dry THF (30 ml) was added benzoic anhydride (1.04 g, 4.6 mmol) under Ar at rt. The mixture was stirred overnight, and was then partitioned between water and EtOAc. The aqueous layer was washed with EtOAc (×2), and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to give the crude product as a brown oil. Chromatography (EtOAc–hexane, 1:3) gave **4c** as a yellow oil (2.60 mmol, 85%). ^{1}H NMR δ 1.44 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 3.32 (t, 1H, J=9 Hz, CH_2-6), 3.37 (dd, 1H, J=9, 6 Hz, CH_2-6), 3.52 (s, 2H, CH_2-1), 4.69 (s, 1H, CH-3), 4.77 (ddd, 1H, J=9, 6, 3.5 Hz, CH-5), 5.60 (d, 1H, J=3.5 Hz, CH-4), 7.45–7.56 (m, 2H, C_6H_5), 7.60–7.71 (m, 1H, C_6H_5), 8.03–8.07 (m, 2H, C_6H_5); ^{13}C NMR ($CDCl_3$) δ −2.47 (*C*-1), 6.27 (*C*-6), 26.64 (*C*H_3), 27.62 (*C*H_3), 77.03 (*C*-3), 81.22 (*C*-4), 84.95 (*C*-5), 112.90 (*C*-2), 113.00 (*C*(CH_3)$_2$), 128.74

(C_6H_5), 128.88 (C_6H_5), 129.78 (C_6H_5), 130.59 (C_6H_5), 133.77 (C_6H_5), 134.53 (C_6H_5), 165.04 (CO_2); HRMS (*m/z*) calcd for $C_{16}H_{19}O_5I_2$ (MH^+): 544.9322, found: 544.9341.

*4.9. 1,6-Dideoxy-1,6-diiodo-2,3-O-isopropylidene-4-O-methyl-L-α-sorbofuranose (**4d**)*

To a mixture of **2b** (0.72 g, 1.64 mmol), 4 Å molecular sieves (0.8 g), and proton sponge (0.88 g, 4.1 mmol) in dry CH_2Cl_2 (20 ml) was added $BF_4(OMe)_3$ (0.97 g, 6.56 mmol).[20] The mixture was stirred at 40 °C overnight. Filtration and evaporation gave the crude product as a yellow solid. Chromatography (EtOAc–hexane, 1:4) gave **4d** as a clear oil (0.49 mmol, 30%). ^{1}H NMR δ 1.45 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.23 (dd, 1H, J=8.7, 5.4 Hz, CH_2-6), 3.28 (t, 1H, J=9.5 Hz, CH_2-6), 3.41 (d, 1H, J=10.8 Hz, CH_2-1), 3.47 (s, 3H, OCH_3), 3.52 (d, 1H, J=10.8 Hz, CH_2-1), 3.92 (d, 1H, J=3.3 Hz, C*H*-4), 4.59 (ddd, 1H, J=9.6, 5.4, 3.3 Hz, C*H*-5), 4.60 (br s, 1H, C*H*-3); ^{13}C NMR δ −0.87 (*C*-6), 6.78 (*C*-1), 26.72 (*C*H_3), 27.76 (*C*H_3), 58.65 (O*C*H_3), 82.52 (*C*-4), 82.79 (*C*-5), 83.27 (*C*-3), 112.79 (*C*-2), 113.35 (*C*$(CH_3)_2$); MS (DCI, CH_4) *m/z* 454(M^+, 75); HRMS (*m/z*) calcd for $C_{10}H_{16}O_4I_2$ (M^+): 453.9138, found: 453.9102.

*4.10. 1-Deoxy-1-iodo-2,3-O-isopropylidene-4-O-tetrahydropyranyl-5,6-anhydro-L-α-sorbofuranose (**5b**)*

To a solution of **4b** (0.66 g, 1.25 mmol) in dry pyridine (50 ml) was added AgF (18.13 mmol). The mixture was stirred at rt in dark for a week to form a black solution. The mixture was filtered and the filtrate was partitioned between 1 M HCl and EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to give nearly 1:1 mixture of two isomers of **5b** as a brown oil (0.73 mmol, 58%). ^{1}H NMR δ 1.48 (s, 2×3H, 2×CH_3), 1.49 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.57–1.93 (m, 12H, 2×CH_2-3′–4′–5′), 3.48 (d, 1H, J=11 Hz, CH_2-1), 3.50 (d, 1H, J=11 Hz, CH_2-1), 3.52–3.60 (m, 2H, CH_2-6′), 3.65 (d, 1H, J=11 Hz, CH_2-1), 3.68 (d, 1H, J=11 Hz, CH_2-1), 3.80–3.92 (m, 2H, CH_2-6′), 4.21 (d, 1H, J=2 Hz, C*H*-4), 4.27 (d, 1H, J=2 Hz, C*H*-4), 4.57–4.58 (m, 4H, 2×CH_2-6), 4.61 (s, 1H, C*H*-3), 4.65 (s, 1H, C*H*-3), 4.83–4.84 (m, 1H, C*H*-2′), 4.89–4.91 (m, 1H, C*H*-2′); ^{13}C NMR δ 4.70 (*C*-1), 5.02 (*C*-1), 18.81 (*C*-4′), 19.00 (*C*-4′), 25.01 (*C*-5′), 25.29 (*C*-5′), 26.86 (*C*H_3), 26.90 (*C*H_3), 27.09 (*C*H_3), 27.88 (*C*H_3), 30.12 (*C*-3′), 30.43 (*C*-3′), 62.01 (*C*-6′), 62.20 (*C*-6′), 77.00 (*C*-4), 78.36 (*C*-4), 83.82 (*C*-3), 84.52 (*C*-3), 88.16 (*C*-6), 89.17 (*C*-6), 94.99 (*C*-2′), 97.44 (*C*-2′), 114.14 (*C*-2), 114.25 (*C*-2), 114.48 (*C*$(CH_3)_2$), 114.48 (*C*$(CH_3)_2$), 158.27 (*C*-5), 158.71 (*C*-5); MS (DCI, CH_4) *m/z* 297 (MH^+, 5); HRMS (*m/z*) calcd for $C_{14}H_{22}O_5I$ (MH^+): 397.0512, found: 397.0490.

*4.11. 1-Deoxy-1-iodo-2,3-O-isopropylidene-4-O-benzoyl-5,6-anhydro-L-α-sorbofuranose (**5c**)*

To a solution of **4c** (0.32 g, 0.58 mmol) in dry pyridine (50 ml) was added AgF (8.7 mmol). The mixture was stirred at rt in dark for a week to form a black solution. The mixture was then filtered and the filtrate was partitioned between 1 M HCl and EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to give **5c** as a brown oil (0.20 mmol, 34%). ^{1}H NMR δ 1.54 (s, 3H, CH_3), 1.540 (s, 3H, CH_3), 3.57 (d, 1H, J=11 Hz, CH_2-1), 3.74 (d, 1H, J=11 Hz, CH_2-1), 4.49 (d, 1H, J=2 Hz, CH_2-6), 4.66 (dd, 1H, J=2, 0.5 Hz, CH_2-6), 4.79 (s, 1H, C*H*-3), 5.81 (d, 1H, J=0.5 Hz, C*H*-4), 7.42–7.52 (m, 2H, C_6H_5), 7.57–7.65 (m, 1H, C_6H_5), 8.00–8.07 (m, 2H, C_6H_5); ^{13}C NMR δ 4.01 (*C*-1), 26.92 (*C*H_3), 27.89 (*C*H_3), 76.03 (*C*-4), 84.46 (*C*-3), 90.25 (*C*-6), 114.11 (*C*-2), 114.11 (*C*$(CH_3)_2$), 128.56 (C_6H_5), 129.73 (C_6H_5), 133.54 (C_6H_5), 158.33 (*C*-5), 164.97 (*C*OO); MS (DCI, CH_4) *m/z* 417 (MH^+, 32); HRMS (*m/z*) calcd for $C_{16}H_{18}O_5I$ (MH^+): 417.0199, found: 417.0206.

*4.12. 1,2:3,4-O-Diisopropylidene-D-α-tagatose (**6a**)*

A suspension of D-tagatose (0.8 g, 4.44 mmol) and *p*-TsOH·H_2O (20 mg) in dry toluene (16 ml) and dry CH_2Cl_2 (20 ml) was heated to reflux (60–65 °C). 2,2-Dimethoxypropane (2.1 ml, 16.9 mmol) was then added and the mixture was refluxed for 18 h to give a clear yellow solution. The mixture was partitioned between water and EtOAc. The aqueous layer was washed with EtOAc (×2), and the combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated to give **6a** as a yellow oil (3.47 mmol, 78%). ^{1}H NMR δ 1.24 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.82 (dd, 1H, J=12, 5 Hz, CH_2-6), 3.87 (dd, 1H, J=12, 5 Hz, CH_2-6), 3.99 (td, 1H, J=5, 4 Hz, C*H*-5), 4.01 (d, 1H, J=10 Hz, CH_2-1), 4.20 (d, 1H, J=10 Hz, CH_2-1), 4.56 (d, 1H, J=6 Hz, C*H*-3), 4.78 (dd, 1H, J=6, 4 Hz, C*H*-4); ^{13}C NMR δ 23.64 (*C*H_3), 24.91 (*C*H_3), 25.42 (*C*H_3), 25.42 (*C*H_3), 59.30 (*C*-1), 68.18 (*C*-6), 78.80 (*C*-5), 80.52 (*C*-4), 85.37 (*C*-3), 110.70 (*C*$(CH_3)_2$), 110.75 (*C*$(CH_3)_2$), 111.90 (*C*-2); MS (DCI, CH_4) *m/z* 261 (MH^+, 9), 203 (75), 245 (100); HRMS (*m/z*) calcd for $C_{12}H_{21}O_6$ (MH^+): 261.1338, found: 261.1301.

*4.13. 1,2:3,4-O-Diisopropylidene-6-O-triflate-D-tagatose (**7a**)*

To a solution of **6a** (0.62 g, 2.40 mmol) and dry pyridine (0.3 ml, 3.6 mmol) in dry CH_2Cl_2 (23 ml) was added Tf_2O (0.6 ml, 3.6 mmol) at 0 °C under Ar. The cool bath was removed and the mixture was allowed to stir for 1 h. The reaction mixture was quenched by saturated aqueous $NaHCO_3$ (13 ml). The mixture was then partitioned between water and CH_2Cl_2. The organic layer was washed with 0.1 M HCl, water, and brine. The organic phase was dried over $MgSO_4$, filtered, and evaporated to give pure **7a** as a yellow oil (2.2 mmol, 92%). ^{1}H NMR δ 1.23 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 4.07 (d, 1H, J=10 Hz, CH_2-1), 4.28 (d, 1H, J=10 Hz, CH_2-1), 4.25 (dt, 1H, J=7, 4 Hz, C*H*-5), 4.61 (dd, 1H, J=11, 7 Hz, CH_2-6), 4.63 (d, 1H, J=6 Hz, C*H*-3), 4.76 (dd, 1H, J=11, 4 Hz, CH_2-6), 4.84 (dd, 1H, J=6, 4 Hz, C*H*-4); ^{13}C NMR δ 25.94 (*C*H_3), 25.98 (*C*H_3), 26.24 (*C*H_3), 26.56 (*C*H_3), 69.30 (*C*-1),

74.22 (*C*-6), 76.34 (*C*-5), 79.70 (*C*-4), 85.13 (*C*-3), 112.30 ($C(CH_3)_2$), 112.35 ($C(CH_3)_2$), 113.61 (*C*-2), 118.73 (q, J=160 Hz, CF_3); HRMS (*m/z*) calcd for $C_{13}H_{20}O_8F_3S$ (MH^+): 393.0518, found: 393.0586.

4.14. 6-Deoxy-6-iodo-1,2:3,4-O-diisopropylidene-D-tagatose (8)

To a solution of crude **7a** (0.15 g, 0.4 mmol) in dry acetone (2 ml) was added NaI (0.8 mmol, 0.8 mmol). The mixture was stirred at rt, over night. The mixture was then partitioned between water and EtOAc. The aqueous layer was washed with EtOAc (×2), and the combined organic layer was washed with saturated aqueous $Na_2S_2O_3\cdot5H_2O$ and brine, dried over $MgSO_4$, filtered, and evaporated to give the crude product as an orange oil. Chromatography (EtOAc–hexane, 1:9) gave **8** as a yellow oil (0.35 mmol, 88%). ^{1}H NMR δ 1.33 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.25 (dd, 1H, J=9.5, 6 Hz, CH_2-6), 3.33 (dd, 1H, J=9.5, 8 Hz, CH_2-6), 4.03 (d, 1H, J=9.5 Hz, CH_2-1), 4.20 (ddd, 1H, J=8, 6, 3.5 Hz, C*H*-5), 4.25 (d, 1H, J=9.5 Hz, CH_2-1), 4.64 (d, 1H, J=6 Hz, C*H*-3), 4.83 (dd, 1H, J=6, 3.5 Hz, C*H*-4); ^{13}C NMR δ −0.1 (*C*-6), 25.01 (CH_3), 26.05 (CH_3), 26.43 (2×CH_3), 69.36 (*C*-1), 79.75 (*C*-5), 79.80 (*C*-3), 85.44 (*C*-4), 111.87 (2×*C*q), 112.93 (*C*q); MS (CI, *i*-Bu) *m/z* 371 (MH^+, 15), 312 (100); HRMS (*m/z*) calcd for $C_{12}H_{19}O_5I$ (M^+): 370.0277, found: 370.0286.

4.15. 1,2:3,4-O-Diisopropylidene-5,6-anhydro-D-tagatose (9)

To a solution of **8** (0.81 g, 2.2 mmol) in dry pyridine (20 ml) and dry CH_2Cl_2 (13 ml) was added AgF (4.2 g, 33 mmol) at rt in the dark. The mixture was stirred at rt, in the dark for a week to form a black solution. The mixture was filtered, and the filtrate was partitioned between 1 M HCl and EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to give the crude product as a dark brown oil. Chromatography (EtOAc–hexane, 0.5:9.5) gave **9** as a light yellow oily-solid (0.88 mmol, 40%). ^{1}H NMR δ 1.36 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 4.16 (d, 1H, J=10 Hz, CH_2-1), 4.362 (d, 1H, J=10 Hz, CH_2-1), 4.364 (dd, 1H, J=2, 1 Hz, CH_2-6), 4.56 (d, 1H, J=5.5 Hz, C*H*-3), 4.58 (ddd, 1H, J=2, 1, 0.5 Hz, C*H*-6), 5.12 (dt, 1H, J=5.5, 1 Hz, C*H*-4); ^{13}C NMR δ 25.95 (CH_3), 26.30 (CH_3), 26.44 (CH_3), 26.84 (CH_3), 69.80 (*C*-1), 79.47 (*C*-4), 83.03 (*C*-3), 88.35 (*C*-6), 112.67 ($C(CH_3)_2$), 112.95 ($C(CH_3)_2$), 113.53 (*C*-2), 160.00 (*C*-5); MS (CI, *i*-Bu) *m/z* 243 (MH^+, 100); HRMS (*m/z*) calcd for $C_{12}H_{18}O_5$ (M^+): 242.1154, found: 242.1171.

4.16. 6-Deoxytagatoso[2,5-b]-6-deoxytagatose (11)

To a solution of **9** (42 mg, 0.17 mmol) in water (2.5 ml) and acetone (2.5 ml) was added Dowex-50WX8-100 (0.5 g). The mixture was refluxed for 3.5 h, and was then filtered and evaporated to give the crude product as an orange oil. Chromatography (EtOAc–hexane, 1:1) gave **11** as a light yellow oil (0.17 mmol, 100%). ^{1}H NMR (D_2O) δ 1.49 (s, 3H, CH_3-6′), 1.58 (s, 3H, CH_3-6), 3.71 (d, 1H, J=12.5 Hz, CH_2-1), 3.83 (d, 1H, J=12.5 Hz, CH_2-1′), 3.85 (d, 1H, J=3.5 Hz, C*H*-4), 3.86 (d, 1H, J=12.5 Hz, CH_2-1′), 4.07 (d, 1H, J=5.2 Hz, C*H*-4′), 4.15 (d, 1H, J=12.5 Hz, CH_2-1), 4.41 (d, 1H, J=3.5 Hz, C*H*-3), 4.60 (d, 1H, J=5.2 Hz, C*H*-3′); ^{13}C NMR (D_2O) δ 22.47 (CH_3-6), 24.25 (CH_3-6′), 60.98 (*C*-1′), 63.30 (*C*-1), 72.70 (*C*-4), 76.06 (*C*-4′), 76.91 (*C*-3), 80.06 (*C*-3′), 98.52 (*C*-5′), 106.83 (*C*-2), 108.86 (*C*-5), 111.51 (*C*-2′); MS (DCI, CH_4) *m/z* 289 (MH^+-2H_2O, 100); HRMS (*m/z*) calcd for $C_{12}H_{17}O_8$ (MH^+-2H_2O): 289.0923, found: 289.0956.

4.17. 1-Hydroxymethyl-1,1′:2,3-O-diisopropylidene-cyclopentane-1,2,3,4-tetraol (12)

To a solution of **9** (0.57 g, 2.35 mmol) in dry toluene (6 ml) was added TIBAL (6 ml of a 1 M solution in toluene, 6 mmol) at 0 °C under Ar. The cooling bath was removed and the mixture was allowed to stir for 2 h. Water was added dropwise at 0 °C to form a yellow suspension. The mixture was then filtered through Celite and partitioned between water and EtOAc. The aqueous layer was washed with EtOAc (×2) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to give the crude product as a brown oil. Chromatography (EtOAc–hexane, 1:9) gave **12** as a clear oil (0.16 mmol, 7%). ^{1}H NMR δ 1.31 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.54 (dd, 1H, J=13, 10.5 Hz, CH_2-5), 2.32 (dd, 1H, J=13, 6.5 Hz, CH_2-5), 4.02 (d, 1H, J=9.5 Hz, CH_2-1′), 4.25 (d, 1H, J=9.5 Hz, CH_2-1′), 4.24–4.31 (m, 1H, C*H*-4), 4.34 (dd, 1H, J=5.5, 1.5 Hz, C*H*-2), 4.57 (t, 1H, J=5.5 Hz, C*H*-3); ^{13}C NMR ($CDCl_3$) δ 26.07 (CH_3), 26.12 (CH_3), 26.33 (CH_3), 26.55 (CH_3), 37.81 (*C*-5), 69.27 (*C*-1′), 70.93 (*C*-4), 78.71 (*C*-3), 82.86 (*C*-2), 111.31 (*C*-1), 111.67 ($C(CH_3)_2$), 112.64 ($C(CH_3)_2$); HRMS (*m/z*) calcd for $C_{12}H_{21}O_5$ (MH^+): 245.1389, found: 245.1381.

4.18. 4-Hydroxymethyl-4-isopropoxy-2,3-O-isopropylidene-cyclopentane-1,2,3,-triol (13)

To a solution of **9** (0.2 g, 0.83 mmol) in dry toluene (4 ml) was added TIBAL (4 ml of a 1 M solution in toluene, 4 mmol) at 0 °C under Ar. The cooling bath was removed and the mixture was allowed to stir at rt over night. Water was added dropwise at 0 °C to form a yellow suspension. The mixture was then filtered through Celite and partitioned between water and EtOAc. The aqueous layer was washed with EtOAc (×2) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to give the crude product as a brown oil. Chromatography (EtOAc–hexane, 1:9) gave **13** as a clear oil (0.03 mmol, 4%). ^{1}H NMR δ 1.166 (d, 3H, J=6.5 Hz, CHCH_3), 1.169 (d, 3H, J=6.5 Hz, CHCH_3), 1.35 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.52 (dd, 1H, J=12.5, 10.5 Hz, CH_2-5), 1.97 (dd, 1H, J=12.5, 5.5 Hz, CH_2-5), 3.34 (d, 1H, J=9 Hz, CH_2OH), 3.60 (d, 1H, J=9 Hz, CH_2OH), 3.62 (sext, 1H, J=6.5 Hz, C*H*(CH_3)$_2$), 4.26 (dd, 1H, J=5.5, 1.5 Hz, C*H*-3), 4.34 (dt, 1H, J=10.5, 5.5 Hz, C*H*-1), 4.62 (t, 1H, J=5.5 Hz, C*H*-2); ^{13}C NMR δ 22.05 (CHCH_3), 24.31 (CHCH_3), 26.12 (CH_3), 30.83 (*C*-5),

39.98 (CH_3), 69.49 ($CH(CH_3)_2$), 70.75 (CH_2OH), 72.46 (*C*-3), 78.34 (*C*-4), 78.82 (*C*-1), 84.22 (*C*-2). HRMS (*m/z*) calcd for $C_{12}H_{23}O_5$ (MH^+): 247.1546, found: 247.1560.

*4.19. 2-Hydroxymethyl-3,4-O-isopropylidene-7,7-dimethyl-oxepane-3,4,5-triol (**14**)*

To a mixture of **9** (0.43 g, 1.40 mmol) in dry toluene (14 ml) was added TIBAL (5.6 ml of a 1 M solution in toluene, 5.6 mmol) at −78 °C under Ar. The cooling bath was removed and the mixture was allowed to stir at rt over night. Saturated aqueous $NaHCO_3$ (20 ml) was added at 0 °C to form a yellow suspension. The mixture was then filtered through Celite and partitioned between water and EtOAc. The aqueous layer was washed with EtOAc (×2) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to give the crude product as a yellow oil. Chromatography (EtOAc–hexane, 1:5) gave **14** as a clear oil (0.08 mmol, 6%). ^{1}H NMR δ 1.24 (s, 3H, (C-7)–CH_3), 1.25 (s, 3H, (C-7)–CH_3), 1.42 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.92 (dd, 1H, *J*=15, 9 Hz, CH_2-6), 1.99 (dd, 1H, *J*=15, 7 Hz, CH_2-6), 3.37 (dd, 1H, *J*=13, 9 Hz, CH_2OH), 3.95 (dd, 1H, *J*=13, 6 Hz, CH_2OH), 4.08 (ddd, 1H, *J*=9, 7, 3 Hz, C*H*-5), 4.27 (dd, 1H, *J*=9.5, 7 Hz, C*H*-3), 4.51 (td, 1H, *J*=9.5, 6 Hz, C*H*-2), 4.57 (dd, 1H, *J*=7, 3 Hz, C*H*-4); ^{13}C NMR δ 24.46 (CH_3), 26.26 ((C-7)–CH_3), 26.85 (CH_3), 27.96 ((C-7)–CH_3), 43.20 (*C*-6), 63.82 (CH_2OH), 68.02 (*C*-5), 69.64 (*C*-2), 74.19 (*C*-7), 77.90 (*C*-4), 80.29 (*C*-3), 107.64 ($C(CH_3)_2$); MS (DCI, CH_4) *m/z* 247 (MH^+, 42), 189 (66); HRMS (*m/z*) calcd for $C_{12}H_{23}O_5$ (MH^+): 247.1545, found: 147.1554.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.12.049.

References and notes

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