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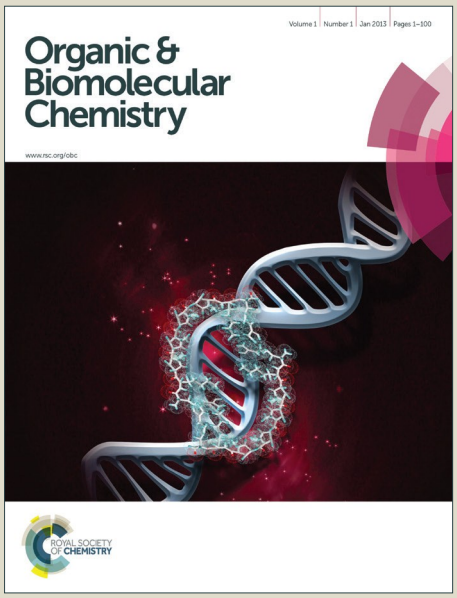

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PAPER

A practical and scalable synthesis of carbohydrate based oxepines

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An efficient, seven-step synthesis of carbohydrate based oxepines is reported using per-*O*-acetyl septanoses as key intermediates. The scope of the synthesis was evaluated by varying both the pyranose starting materials and protecting groups incorporated into the oxepine products. The practicality of the method make it amenable to scale up as demonstrated by the gram-scale synthesis of the D-glucose derived oxepine.

Introduction

Carbohydrate based oxepines (oxepines)[1] are ring-expanded glycals (e.g., **1** vs **2** in Fig. 1).[2] Glycals are six-membered cyclic enol ethers with a lengthy track record as starting materials for oligosaccharides[3] and as building blocks in small molecule target synthesis (e.g., natural products).[4] Their value in these roles comes from the enol ether functionality and the stereogenic centers; oxidation, addition, and rearrangement reactions deliver useful intermediates en route to individual targets. Likewise, oxepines have played a key role in the synthesis of seven-membered ring carbohydrates, called septanoses.[5,6,7] Our overarching strategy for septanose synthesis has been to apply methods established for the formation of pyranosyl glycosides to septanose glycosylations.[8] For example, DMDO epoxidation of oxepines resulted in the formation of 1,2-anhydroseptanoses, which were then opened with a variety of nucleophiles to give the corresponding septanosyl derivatives.[9,10] Due to their use as starting materials, carbohydrate based oxepines have become important synthetic targets in their own right.[8,11,12] If oxepines are to be used as ring expanded glycals in other contexts, the current limitation of ready access to this class of compounds must be overcome.

Several methods for the preparation of glycals have been co-opted towards the synthesis of carbohydrate based oxepines. They include the ring closing metathesis of dienes,[10,13] cycloisomerization of alkynols,[11,12,14] and a sequential cyclization and elimination of hydroxy acetals.[15,16] These syntheses have some drawbacks, however, such as using expensive catalysts, intricate reaction protocols, low efficiency, and limited protecting group scope. The desire to utilize oxepines in synthesis and the shortcomings of the current methods for their preparation prompted us to search for a practical alternative. Here we report a simple, seven-step route for the synthesis of per-*O*-actetyl protected carbohydrate based oxepines that is scalable. Akin to their glycal congeners, we expect that these compounds will serve as valuable starting materials in the synthesis of a variety of target molecules.

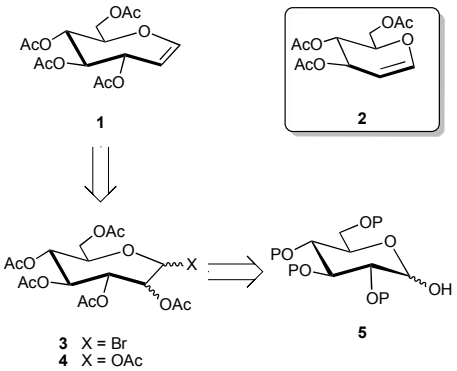

Fig. 1 Retrosynthetic analysis of oxepine using key intermediate

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† Footnotes relating to the title and/or authors should appear here.
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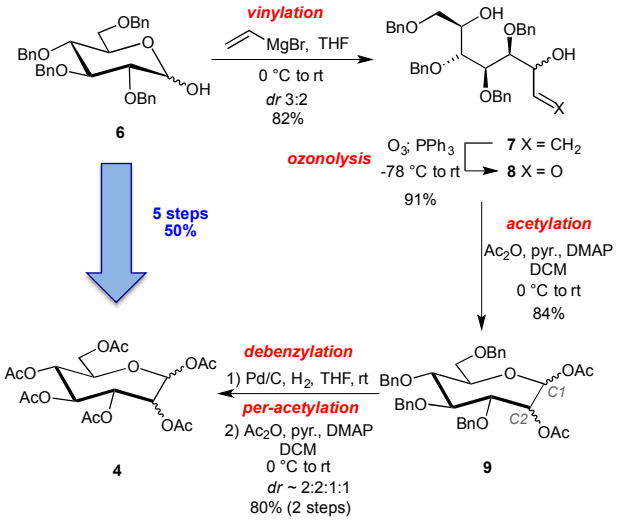
Glycals have traditionally been synthesized via a reductive elimination of acetylated glycosyl bromides using elemental zinc in acetic acid (Fischer-Zach method).[17,18] Over the years the route has been modified in terms of reducing agents used or the leaving groups on the anomeric carbon. Nonetheless, due to its efficiency, affordability and low toxicity, the Fischer-Zach method is used to synthesize glycals on a multi-kilogram scale.[19] These attributes led us towards the development of a reductive elimination approach for the synthesis of oxepines (e.g.,conversion of **3** to **1** in Fig. 1).



Scheme 1 Synthesis of D-glucose derived per-*O*-acetylseptanose.

Results and discussion

Synthesis of per-*O*-acteylseptanoses

Our investigation began with the development of a five-step route to per-*O*-acetyl septanoses as illustrated in Scheme 1 using 2,3,4,6-tetra-*O*-benzyl D-glucose **6** as starting material. It should be noted that **6** is commercially available, although somewhat expensive. Nonetheless we have considered it the starting material for synthesis; the per-*O*-benzyl lactols have systematically been considered the starting materials for our synthesis for ease of comparison. We appreciate that these lactols are not uniformly available and that places a limitation on the practicality of the method described here. Vinylmagnesium bromide addition to **6** gave a 3:2 diastereomeric mixture of allylic alcohols **7** in 82% yield.[20,21] Without separating the diastereomers, the alkene moiety of **7** was cleaved via ozonolysis giving hydroxy-aldehydes **8** (91%). As had been reported previously, **8** was in equilibrium with the seven-membered ring hemiacetal as observed by NMR spectroscopy.[21,22] To avoid isomerization of the α-hydroxy aldehyde to the corresponding hydroxymethyl ketone,[23] **8** was directly acetylated to trap it in its cyclic form, providing di-*O*-acetyl-tetra-*O*-benzyl septanoses **9** in 84% yield. Di-*O*-acetyl septanoses **9** were a relatively complex mixture based on the ratio of stereoisomers at C2 (based on vinyl Grignard addition) and the mixture of anomers. Quantifying the ratio of these isomers was consequently difficult. The ^{13}C spectrum of **9** suggested, however, that each C2 stereoisomer existed primarily as one anomer.[23] Hydrogenolysis of the benzyl groups was a crucial step in this synthesis. Some standard catalyst-solvent combinations to conduct the reaction were unsuccessful.[24,25] To our delight, however, we found that hydrogen and 10% Pd/C in THF proved to be an effective combination for the reaction. Debenzylation was followed by acetylation, providing per-*O*-acetyl septanoses **4** in 80% yield over two steps. The per-*O*-acetyl compounds were isolated as a mixture of four diastereomers, based on the possible configurations at both C1 and C2. The fact that **4** existed as a mixture of four diastereomers was of little concern because their stereogenicity would be removed in the reductive elimination step when forming oxepines such as **1**. The per-*O*-acetylseptanoses themselves (e.g., **4**) are useful starting materials for the synthesis of novel septanose glycoconjugates. Overall, the five-step route to the per-*O*-acetylseptanoses was simple and efficient and afforded the septanose **4** in 50% yield from the pyranose **6**.

The five-step route, established with D-glucose, was applied towards the preparation of per-*O*-acetylseptanoses starting from D-xylose **10**, D-mannose **15**, and D-galactose **20** to probe the generality of the approach (Fig. 2). Whereas the diastereoselectivity of vinyl addition to benzyl protected pyranose lactols is known for glucose, galactose, and mannose, the selectivity for addition to xylose has not been reported, to the best of our knowledge. In the case of the former examples, the diastereomeric mixtures of allylic alcohol products **7**, **16**, and **21** (Scheme 1 and Fig. 2) reflected the values previously reported in the literature. For xylose, the formation of the *R* configuration at C2 was preferred, being the major diastereomer in a 10:1 ratio. This diastereomer was likely preferred based on Cram-chelate model. Following the same sequence depicted in Scheme 1, the per-*O*-acetylseptanoses derived from xylose and mannose, **13** (34%, five steps) and **18** (57%, five steps), respectively, largely proceeded without incident (Fig. 2). Their ^{13}C NMR spectra were complex because mixtures of stereoisomers (C1 and C2) were being carried through the sequence but they were, nonetheless, similar to those observed previously in the glucose series, including the preference for one anomeric configuration for each C2 stereoisomer, as was observed for **9**.

In the galactose series, however, there were extra signals in the acetal region of the ^{13}C NMR[23] spectra of the material that came about from hydrogenolysis and per-acetylation of di-*O*-acetylseptanose **22** (Fig. 2). The data suggested that more than the standard four isomers of this compound were present in the mixtures. Our explanation for this observation relied on our characterization of the oxepines that arose in this series as described in the proximal section. We propose that **24** came about via migration of the acetyl group from C1 to C3 and subsequent equilibration of the resulting septanose to a pyranose during the debenzylation step (Fig. 3) of the hydrogenolysis/per-acetylation sequence. Formation of **24** is yet another example of rearrangements that occur with seven membered ring sugars.[5,22]

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Formation of oxepines via reductive elimination

Anomeric acetates are useful precursors for the introduction of other leaving groups at the C1 position under acidic conditions. Treatment of per-*O*-acetylseptanoses **4** with HBr in AcOH gave a pair of diastereomeric α-septanosyl bromides **3** differing only in their configuration at C2.[26] By ^{13}C NMR, only two signals for anomeric carbons (C1), at 87 and 84 ppm, were observed. With the anomeric bromides in hand, we subjected them to standard Fischer-Zach reductive elimination conditions (Table 1, Entry 1). Oxepine **1** was obtained in 45% yield over two steps under these conditions. NMR analysis allowed the assignment of all the protons H1-H7 and corresponding carbons C1-C7 of oxepine **1**. Further, HMBC spectra contained a diagnostic cross peak between C6 and H1 confirming the oxepine structure.[23] We also evaluated other reductive elimination conditions reported for glycal formation. Using a zinc-copper couple[27] (Entry 2) provided **1** in 42% yield; under neutral conditions[28] (Entry 3) **1** was obtained in 44% yield. We next tried zinc in the presence of a catalytic amount of vitamin B_{12}[29] (Entry 4), which yielded only 31% of **1**. Reductive elimination with Cp_2TiCl_2 following Schwartz conditions[30] (Entry 5) gave **1** in higher yield (64%). Despite its higher yield, we considered the reaction protocols required to generate Ti(III) to be cumbersome for the gain in yield. We opted for the traditional Fischer-Zach protocol in subsequent syntheses because of its balance of yield and ease of execution.

We next endeavored to convert each of the other per-*O*-acetyl species to their corresponding oxepines by bromination and reductive elimination. Compounds **14** and **19** in the xylose and mannose series, respectively, were made in 35% and 48% by the two-step sequence (Fig. 2). When the per-*O*-acetyl mixture from the galactose series was treated to the same conditions, a 1:1 mixture of products was obtained in a combined yield of 55%. The same products also arose under

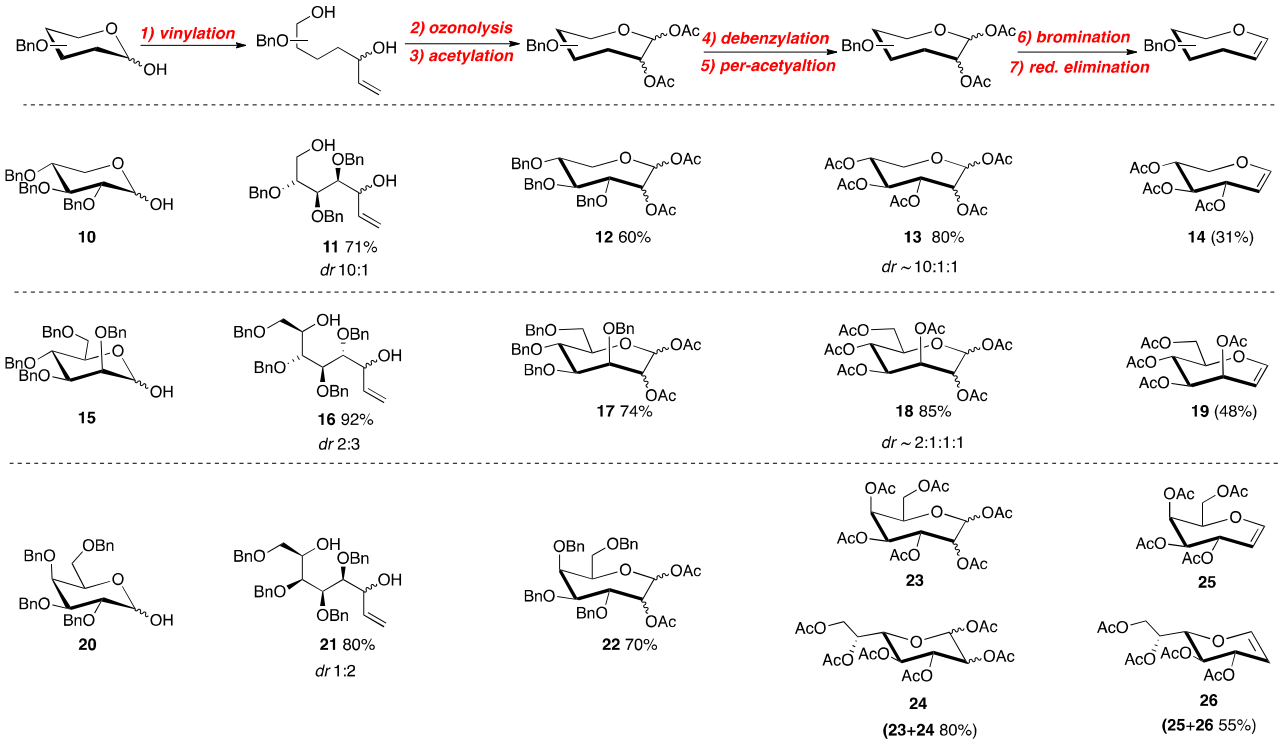
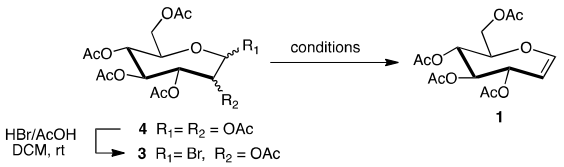


Fig. 2. Starting materials, intermediates and oxepines of xylose, mannose and galactose series.

Table 1. Conversion of per-*O*-acetyl septanose to oxepine via bromination and reductive elimination.



Entry	Conditions	Yield[a]
1	Zn, AcOH:H_2O, Et_2O, 0 °C to rt,12 h	45%
2	Zn, $CuSO_4$, NaOAc, AcOH:H_2O, Et_2O, 0 °C to rt, 10 h	42%
3	Zn, NaH_2PO_4, acetone, rt, 6 h	44%
4	Zn, vitamin B_{12}, NH_4Cl, MeOH, rt, 1 h	31%
5	Zn, Cp_2TiCl_2, CaH_2, dioxane, rt, 1 h	64%

[a]Yields reported are after two steps from **4**.

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mild and neutral reductive elimination conditions, albeit in variable yields (46% and 52%).[23] Characterization of the products revealed that one was the expected oxepine, **25** (28%). The other product (27%) was assigned structure **26** through analysis of NMR spectra of the compound, particularly through a C5-H1 correlation in the HMBC spectrum. The structure of product **26** and the peculiarities in the NMR spectra of the per-*O*-acetyl species mentioned above confirmed that **24** was likely the precursor to **26**. We propose that **24** came about via migration of the C1 acetyl group to C3 and subsequent re-equilibration of the resulting septanose to a pyranose during the debenzylation, per-acetylation sequence.

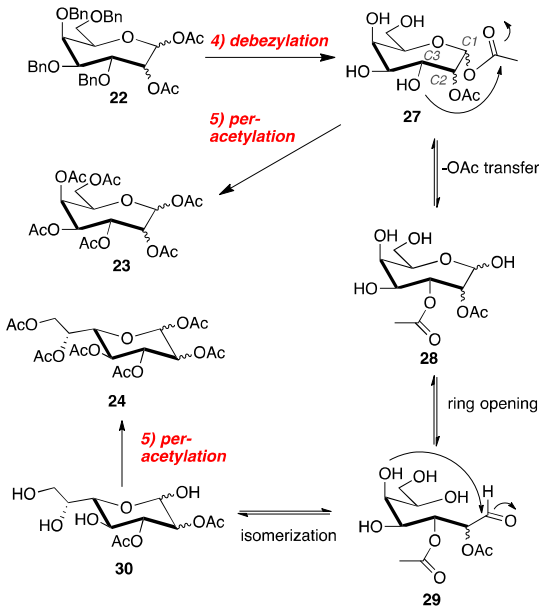
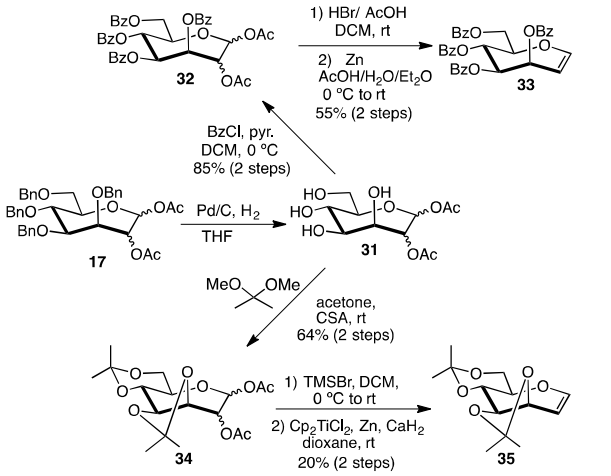


Fig. 3. Proposed mechanism of intramolecular acetate transfer during debenzylation reaction in the galactose series

To expand the scope of the method, we modified the synthetic sequence to incorporate different protecting groups into the oxepine. A logical place to change protecting groups was at the 1,2-di-*O*-acetyl septanose that arose from hydrogenolysis (e.g., **17** in Scheme 2). Benzoylation of the free hydroxyls of **31** gave **32** in 85% yield; subsequent bromination and reductive elimination resulted in per-*O*-benzoyl oxepine **33** in 55% yield after two steps. Likewise, acetonide protection of **31** gave **34** (64%). To avoid cleavage of the acid-labile acetonide groups on **34**, we chose TMS bromination and Schwartz reductive elimination conditions in this series. Bromination of **34** with TMSBr followed by reductive elimination with Ti(III) gave 20% yield of oxepine **35**. The inefficiency of the reaction may be attributed to other eliminations that were possible during the course of the reaction. Nonetheless, these investigations led us to believe that this synthetic sequence is viable for protecting group diversification.

Scheme 2. Synthesis of benzoyl and acetonide protected oxepines



Scaled up synthesis of oxepine 1

We also sought to develop a scalable synthesis of oxepines in order to improve the low to medium throughput of material that can be prepared by RCM of enol ethers.[13] We scaled up the synthesis of oxepine **1** to illustrate the method (Scheme 3). We began the scaled up synthesis with 20 g of tetra-*O*-benzyl-D-glucopyranose **6**. The Grignard addition step went in 91% yield to give intermediate **7**. We then took half of the product material from the Grignard reaction (approximately 10 g) and completed the synthesis through to **1**. Due to safety concerns, we capped the scale of the ozonolysis reactions at two 5 g batches, obtaining **8** in 80% combined yield. Acetylation of the resulting diol gave di-*O*-acetate **9** in 87% yield. Debenzylation and per-acetylation was straightforward, although the hydrogenolysis of benzyl ethers was run at greater catalyst loading (35 wt% of 10% Pd/C relative to 20 wt%) that was used on smaller scale. Subsequent per-acetylation gave **4** in 80% yield over two steps. Anomeric bromide formation and reductive elimination (using Fischer-Zach conditions) of per-*O*-acetyl septanoses yielded 70% of oxepine **1**. Total yield over the seven-step sequence was 35% from the pyranose, greater than 85% average yield per step. The method has allowed the preparation of oxepine **1** on a multi-gram scale, where 10 g of allylic alcohol **7** was converted to >2.5 g of oxepine **1**. Moreover, it is anticipated that yields could be further optimized when the synthesis is conducted on even larger scale.

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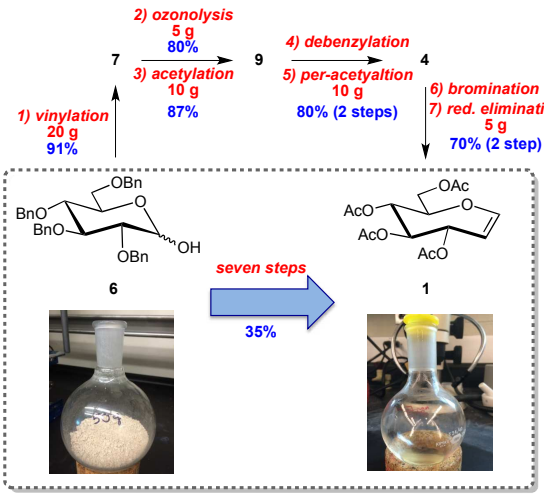

Scheme 3. Scaled-up synthesis of oxepine 1

Conclusions

In conclusion we have developed a simple, seven step route to the synthesis of per-*O*-acetyl oxepines from pyranoses that is readily scalable. The sequential bromination and reductive elimination reactions were successfully applied to synthesize novel oxepines from per-*O*-acetyl septanoses. Interestingly, the per-*O*-acetyl septanoses are likely valuable intermediates in their own right. Our method also allows the synthesis of oxepines with the different protecting groups. Applications and reactions of the new oxepines as well as the per-*O*-acetyl septanose intermediates will be reported in due course.

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Experimental Section

Vinylation (Procedure 1)

To a round bottom flask containing 2,3,4,6-tetra-*O*-benzyl D-pyranose (5.00 g, 9.25 mmol, 1 eq.) in THF (6 mL/g pyranose) was added 0.7M in THF of vinylmagnesium bromide (46.3 mmol, 5 eq.) slowly (7 mL/min) at 0 °C. The reaction mixture was allowed to warm to rt and was allowed to stir for 20-24 h. After, sat. NH_4Cl (10 mL/g of starting material) was added to the reaction mixture at 0 °C to quench it. The mixture was extracted with ethyl acetate (3 x 25 mL/g of starting material). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography using hexanes:ethyl acetate as a solvent system to give respective 1,3,4,5-tetrakis(benzyloxy)oct-7-ene-2,6-diol (70 - 91%).

Ozonolysis and Acetylation (Procedure 2)

Ozonolyis: To a long neck round bottom flask having both an inlet and outlet was added 1,3,4,5-tetrakis(benzyloxy)oct-7-ene-2,6-diol (2.00 g, 3.50 mmol, 1 eq.) in DCM (30 mL/g of starting material). The solution was cooled to -78 °C, ozone gas was bubbled through the reaction mixture by using WELSBACH instrument until a dark blue color persisted. Upon the appearance of the blue color, ozone generation was ceased and the reaction mixture was purged with oxygen gas until the reaction mixture became clear and colorless once again. Still at -78 °C, a solution of triphenylphosphine (2x mass of starting material) in DCM (2 mL/g of PPh_3) was added drop-wise to the reaction mixture. It was allowed to stir as it warmed to rt over 14 h. After, the solvents were concentrated under reduced pressure and the residue was purified by column chromatography using hexanes: ethyl acetate as a solvent system to give respective hydroxyaldehyde as colorless oil (75 - 91%).

Acetylation: To a solution of hydroxyaldehyde (3.00 g, 5.20 mmol, 1 eq.) in DCM (10 mL/g starting material) was added pyridine (4 mL/g starting material) and a catalytic amount of N,N-dimethylaminopyridine (DMAP) (10 mol%). To this mixture was added acetic anhydride (7.2 mL/g of starting material) was added drop by drop at 0 °C. After completion of the reaction (~12 h), ice-cold water (10 mL/g of starting material) was added into the flask. The reaction mixture was extracted with DCM (2 x 30 mL/g of starting material). The solvents were evaporated under reduced pressure and purified by column chromatography using hexane:ethyl acetate as a solvent system to give respective di-*O*-acetyl-tetra-*O*-benzyl septanoses (80 - 90%).

Hydrogenolysis/Acetylation (Procedure 3)

To the di-*O*-acetyl-tetra-*O*-benzyl septanoses (1.00 g, 1.50 mmol, 1 eq.) dissolved in THF (20 mL/g starting material), was added 20% weight of 10% Pd/C (0.20 g) and the mixture was stirred for 12 h at rt under an atmosphere of hydrogen gas. The solution was then filtered through celite, washed with excess methanol and the combined filtrates were concentrated under reduced pressure. After TLC analysis showing the absence of starting material and no UV active spots, the crude reaction mixture was then dissolved in pyridine (5 mL/g starting material), and acetic anhydride (7.2 mL/g) was added at 0 °C and stirred it for 6 h at rt. The mixture was concentrated under reduced pressure and purified by column chromatography using hexane: ethyl acetate as solvent system to give the respective per-*O*-acetyl septanoses (80 - 85%).

Glycosyl Bromide Formation (Procedure 4)

To a solution of per-*O*-acetyl septanose (0.50 g, 1.1 mmol, 1 eq.) in DCM (5 mL) was added a 30% HBr in acetic acid (2.5 mL) solution at 0 °C. After complete consumption of per-O-acetate derivative (usually ~12 h) as observed by TLC (R_f 0.4, 5:2 hexane:ethyl acetate) the resulting solution was poured directly into a 100 mL beaker half full of ice. Additional DCM was added to this mixture and it was then transferred to a

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separatory funnel. The water was removed and the organic phase was washed with cold sat. $NaHCO_3$ (2 x 40 mL), water (40 mL) and brine (40 mL) and dried with Na_2SO_4. The solvents were removed under reduced pressure to give the respective septanosyl bromide.

Reductive Elimination Reactions (Procedure 5)

(A) Zn, 1:1 AcOH: H_2O, diethyl ether, 0 °C to rt, 12 h

A solution of septanosyl bromide (0.50 g, 1.03 mmol, 1 eq.) in diethyl ether (7.5 mL) was quickly added to the flask having 1:1 H_2O: AcOH (10 mL) and Zn (0.470 g, 7.1 mmol, 7 eq.) at 0 °C. The mixture was allowed to warm to rt and the reaction continued for 12 h. The reaction mixture was then filtered through a short pad of celite and more diethyl ether (15 mL) was added to rinse the filtered material. The combined filtrates were washed with H_2O (10 mL), sat. $NaHCO_3$ (10 mL), brine (10 mL) and then dried with Na_2SO_4. Solvent was removed under reduced pressure and the residue was purified by column chromatography using hexane:ethyl acetate as solvent to give the respective per-*O*-acetyl oxepine. Note that in the glucose series, multiple reactions were performed ranging scale 0.05 g to 5.00 g.

(B) Zn, $CuSO_4$, NaOAc, 1:1 AcOH: H_2O, diethylether, 0 °C to rt, 10 h

Septanosyl bromide (0.10 g, 0.021 mmol, 1 eq.) in diethyl ether (0.5 mL) was added to a solution of Zn (0.076 g, 1.17 mmol, 5.6 eq.), NaOAc (0.074 g, 0.9 mmol, 4.3 eq.), $CuSO_4$ (0.002 g, 0.012 mmol, 0.06 eq.) in 1:1 AcOH: H_2O (0.4 mL) at 0 °C. The resulting solution was stirred for 6 h at rt, then it was filtered through a short pad of celite and washed with excess of diethyl ether (15 mL). The combined filtrates were washed with $NaHCO_3$ (5 mL), H_2O (5 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using hexane: ethyl acetate as solvent system to give per-*O*-acetyl oxepine.

(C) Zn, NaH_2PO_4, acetone, rt, 6 h

To a solution of septanosyl bromide (0.095 g, 0.20 mmol, 1 eq.) in acetone (0.25 mL) was added saturated NaH_2PO_4 (0.5 mL) and Zn dust (0.162 g, 2.5 mmol, 12.5 eq.) at rt. The resulting mixture was stirred for 10 h at the same temperature. After, the solution was extracted with EtOAc (2 x10 mL). The organic phase was washed with H_2O (10 mL), $NaHCO_3$ (10 mL) brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using hexane:ethyl acetate as solvent system to give per-*O*-acetyl oxepine.

(D) Zn, vitamin B_{12}, NH_4Cl, MeOH, rt, 1 h

To a solution of vitamin B_{12} (0.0037 g, 1 mol%) in methanol (1 mL) were added Zn (0.275 g, 4.2 mmol, 15 eq.) and NH_4Cl (0.224 g, 4.2 mmol, 15 eq.) respectively, at rt. The resulting mixture was stirred for 0.5 h and then septanosyl bromide (0.130 g, 0.28 mmol, 1 eq.) in methanol (1 mL) was then added to the reaction mixture. TLC was performed after 10 min, which showed completion of the reaction (product R_f 0.45 5:2 hexane:ethyl acetate). The solution was then filtered through celite and the filter was washed using excess methanol (5 mL). Solvent was evaporated from the filtrate under reduced pressure to give crude product, which was redissolved in DCM (15 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried with Na_2SO_4, evaporated under reduced pressure and the residue was purified by column chromatography using hexane:ethyl acetate as solvent system to give per-O-acetyl oxepine.

(E) Zn, Cp_2TiCl_2, CaH_2, dioxane, rt, 1 h

To a 100-mL Schlenk round bottom flask, were added Cp_2TiCl_2 (0.298 g, 1.2 mmol, 3 eq.), Zn (0.156 g, 2.4 mmol, 6 eq.), CaH_2 (0.01 g as trace moisture scavenger), and dioxane (4 mL). The flask was degassed by freeze–pump–thaw cycles and was filled with N_2 (three times). The reduction occurred in less than 5 min. To this solution septanosyl bromide (0.2 g, 0.41 mmol, 1 eq.) in THF (1 mL) was added dropwise at rt. After 1 h, the resulting solution was evaporated under reduced pressure and the residue was purified by column chromatography using hexane:ethyl acetate as solvent system to give per-*O*-acetyl oxepine.

Compound 9. Obtained as colorless oil in 76% yield after two steps using **7** as starting material following general procedure-2. R_f 0.4 (5:1 Hex:EtOAc); ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.43-7.25 (m, 74H), 6.15-6.06 (m, 2.5H), 5.80 (d, *J*= 5.1 Hz, 0.6H), 5.54-5.38 (m, 2.7H), 5.20-5.02 (m, 2.5H), 5.20-4.28 (m, 33H), 4.19-3.59 (m, 20H), 2.27 (s, 1.6H), 2.17 (s, 3.4H), 2.10 (s, 4.2H), 1.96-1.95 (m, 4.7H), 1.94 (s, 3.3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.2, 169.9 (2), 169.8, 169.7, 169.2, 139.0, 138.7, 138.6, 138.4 (2), 138.3, 138.2, 138.1, 137.9, 137.7, 128.7 (2), 128.6 (2), 128.5, 128.4, 128.3, 128.2, 128.1 (2), 128.0 (2), 127.8 (2), 127.2, 95.5, 93.7, 89.8, 88.3, 84.4, 81.0, 80.4, 80.0, 78.9, 78.4, 78.1, 77.1, 76.8, 76.7, 76.3, 76.1, 75.7, 75.4, 75.3, 75.1, 74.8, 73.8, 73.5, 73.4, 72.9, 72.7, 72.6, 72.2, 71.7, 71.4, 70.7, 70.5, 70.3, 21.4, 21.3, 21.2, 21.0 (2); TOF HRMS (DART) m/z calcd for $C_{39}H_{46}O_9N$ $(M+NH_4)^+$ 672.3173, found 672.3170.

Compound 4. Obtained as thick colorless oil in 80% yield from **9** after two steps using general procedure-3. R_f 0.45 (1:1 Hex:EtOAc); ^{1}HNMR (400 MHz, $CDCl_3$) δ 6.20 (d, *J* = 1.1 Hz, 0.5H), 6.11-6.10 (d, *J* = 4.7 Hz, 0.6H), 6.02 (d, *J* = 1.0 Hz, 0.1H), 5.92-5.90 (d, *J* = 7.0 Hz, 1H), 5.83 (d, *J* = 1.0 Hz, 0.3H), 5.72-5.71 (d, *J* = 6.9 Hz, 0.8H), 5.55-5.47 (m, 1.5H), 5.38-5.11 (m, 10H), 5.00-4.93 (m, 4H), 4.45-4.42 (m, 0.7H), 4.27- 4.17(m, 2.2H), 4.10-3.85 (m, 8H), 2.17 (s, 2.2H), 2.03-1.89 (m, 58H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.6, 170.3, 170.2, 169.9, 169.7, 169.5, 169.4, 169.3, 169.2, 169.1, 168.9, 169.8, 168.7, 168.5, 95.7, 95.1, 95.0, 93.2, 92.7, 88.7, 80.5, 77.3, 75.3, 74.1, 72.0, 71.6, 71.4, 71.2,71.0, 70.4, 70.3, 69.9, 69.3, 69.2, 69.0, 68.9, 68.8, 68.7, 68.6, 68.4, 67.4, 63.4, 63.3, 63.2, 62.9, 61.3, 60.2, 27.6, 22.1, 20.9, 20.8, 20.7, 20.5, 20.3, 20.2, 20.1; TOF HRMS (DART) m/z calcd for $C_{19}H_{30}O_8N$ $(M+NH_4)^+$ 480.1717, found 480.1715.

Compound 3. Obtained as colorless oil using general procedure-4 starting from **4**; this material was characterized

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but not routinely isolated. R_f 0.5 (1:1 Hex:EtOAc); ^{1}HNMR (400 MHz, $CDCl_3$) δ 6.43 (d, *J*= 4.6 Hz, 4H), 6.07 (d, *J* = 8.3 Hz, 5H), 5.62-5.50 (m, 16H), 5.39-4.98 (m, 52H), 4.52-4.47 (m, 5H), 4.34-4.30 (m, 8H), 4.22-4.16 (m, 15H), 4.09-3.95 (m, 27H), 2.04-1.92 (m, 183H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.8, 169.9, 169.4, 169.0, 168.3, 87.0, 84.5, 74.4, 73.5, 73.0, 71.9, 71.4, 70.0, 69.5, 68.5, 62.3, 60.6, 21.2, 20.9, 20.7, 20.5, 20.4.

Compound 1. Obtained as colorless oil in 40-70% yield (two steps) using general procedures 4 and 5A. (42%) after 2-steps using general procedures 4 and 5B. (44%) after 2-steps using general procedures-4 and 5C. (31%) after 2-steps using general procedures-4 and 5D. (64%) after 2-steps using general procedures-4 and 5E. R_f 0.45 (1:1 Hex:EtOAc); $[\alpha]_D$ +73.1 (c 1.5, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 6.49 (d, *J* = 6.9 Hz, 1H), 5.39-5.36 (dd, *J* = 5.9 Hz, 1H), 5.24-5.18 (m, 2H), 4.85-4.81 (dd, *J* = 6.9 Hz, 1H), 4.58 - 4.55 (m, 1H), 4.34-4.30 (dd, *J* = 12.2, 5.1 Hz, 1H), 4.20-4.17 (dd, *J* = 12.2, 1.8 Hz, 1H), 2.17 (s, 6H), 2.09 (s, 3H), 2.07 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 169.8, 169.6, 169.0, 150.3, 103.1, 79.0, 73.8, 71.5, 67.5, 63.4, 21.2, 21.0, 20.9; TOF HRMS (DART) m/z calcd for $C_{15}H_{24}O_9N$ $(M+NH_4)^+$ 362.1451, found 362.1458.

Compound 14. Obtained as colorless oil in 35% yield from **13** after two steps using general procedures 4 and 5A. R_f 0.45 (5:2 Hex:EtOAc); $[\alpha]_D$ -111.8 (c 0.6, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 6.50-6.47 (dd, *J* = 6.3, 1.6 Hz, 1H), 5.58-5.56 (m, 1H), 5.47-5.56 (m, 1H), 4.76-4.73 (ddd, *J* = 6.3, 2.6, 1.4 Hz, 1H), 4.36-4.21 (m, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 2.04 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.7, 170.5, 170.3, 145.6, 99.0, 73.0, 64.1, 63.9, 62.1, 21.0, 20.9, 20.8; TOF HRMS (DART) m/z calcd for $C_{12}H_{20}O_7N$ $(M+NH_4)^+$ 290.1240, found 290.1238.

Compound 19. Obtained as colorless oil in 48% yield from **18** after two steps using general procedures-4 and 5A. R_f 0.45 (5:2 Hex:EtOAc); $[\alpha]_D$ -33.8 (c 2, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 6.41-6.38 (dd, *J* = 6.8, 1.5 Hz, 1H), 5.77-5.75 (m, 1H), 5.23-5.22 (m, 1H), 5.12-5.09 (dd, *J* = 8.9, 4.1 Hz, 1H), 4.67-4.64 (ddd, *J* = 6.8, 3.4, 1.0 Hz, 1H), 4.27-4.23 (dd, *J* = 11.7, 5.9 Hz, 1H), 4.19-4.10 (m, 2H), 2.06-2.05 (m, 9H), 2.02 (s, 3 H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.7, 170.3, 169.8, 169.1, 148.4, 105.4, 80.5, 73.3, 70.4, 68.4, 63.2, 21.1, 21.0, 20.9; TOF HRMS (DART) m/z calcd for $C_{15}H_{24}O_9N$ $(M+NH_4)^+$ 362.1451, found 362.1456.

Compounds 25 and 26. Obtained as colorless oil with 1:1 mixture of isomers after two steps as follows: (55%) using the general procedures 4 and 5A; (46%) using the general procedures 4 and 5C; (52%) using the general procedures 4 and 5D.

Compound 25. R_f 0.4 (5:2 Hex:EtOAc); $[\alpha]_D$ -71.7 (c 0.5, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 6.36-6.34 (dd, *J* = 7.7, 2.3 Hz, 1H), 5.73- 5.70 (ddd, *J* = 2.7, 2.7, 9.2 Hz, 1H), 5.49 (d, *J* = 2.7 Hz, 1H), 5.09-5.07 (dd, *J* = 9.3, 2.7 Hz, 1H), 4.70-4.68 (dd, *J* = 7.6, 3.1 Hz, 1H), 4.19- 4.15 (m, 2H), 4.07-4.03 (m, 1H), 2.16 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.6, 170.3, 170.2, 170.0, 145.9, 106.9, 76.8, 73.1, 68.5, 68.4, 63.1, 21.1, 20.9 (2), 20.8; TOF HRMS (DART) m/z calcd for $C_{15}H_{24}O_9N$ $(M+NH_4)^+$ 362.1451, found 362.1455.

Compound 26. R_f 0.45 (5:2 Hex: EtOAc); $[\alpha]_D$ -203.7 (c 0.25, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 6.45(dd, *J* = 6.0, 1.2 Hz, 1H), 5.53- 5.50 (ddd, *J* = 1.8, 1.8, 7.2 Hz, 1H), 5.41 (m, 1H), 5.30-5.26 (dd, *J* = 9.8, 7.2 Hz, 1H), 4.82 (dd, *J* = 6.0, 2.5 Hz, 1H), 4.40-4.36 (dd, *J* = 11.8, 4.8 Hz, 1H), 4.25-4.19 (m, 2H), 2.20-2.04 (m, 20H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.9, 170.7, 170.5, 145.8, 100.2, 74.9, 69.7, 66.9, 66.5, 62.5, 21.2, 20.9 (2); TOF HRMS (DART) m/z calcd for $C_{15}H_{24}O_9N$ $(M+NH_4)^+$ 362.1451, found 362.1455.

Compound 33. Obtained as colorless oil in 55% yield from **23** after two steps using the general procedures-4 and 5A. R_f 0.5 (5:2 Hex:EtOAc); $[\alpha]_D$ -263.9 (c 0.7, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.03-7.97 (m, 8H), 7.53-7.50 (m, 4H), 7.41-7.34 (m, 8H), 6.65-6.63 (d, *J* = 6.8 Hz, 1H), 6.24 (m, 1H), 5.82 (m, 2H), 5.02-5.00 (dd, *J* = 6.6, 3.6 Hz, 1H), 4.66-4.54 (m, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 166.3, 165.8, 165.4, 164.9, 149.0, 133.8, 133.5, 133.3, 130.1, 130.0, 129.9, 129.7, 129.6, 129.0, 128.7, 128.6, 128.5,106.4, 81.0, 74.1, 71.0, 69.5, 63.9; TOF HRMS (DART) m/z calcd for $C_{35}H_{32}O_9$ $(M+H)^+$ 610.2077, found 610.2068.

Compound 35. To a solution of **34** (0.10 g, 0.21 mmol, 1 eq.) in DCM (1 mL) was added TMSBr (0.27 mL, 2.1 mmol, 1 eq.) at 0 °C. The mixture was allowed to warm to rt and then stirred for ~24 h. After, the solvent was removed under reduced pressure and followed by reductive elimination general procedure 5E provided **35** in 20% yield as a tan/off-white powder. Characterization data for **35** coincided with that of the material previously reported by us.

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A practical and scalable synthesis of carbohydrate based oxepines

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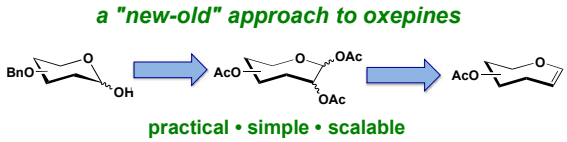

A versatile synthetic route that converts pyranoses to oxepines via reductive elimination of septanosyl bromides is reported.