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Sequential Cyclization−Elimination Route to Carbohydrate-Based Oxepines

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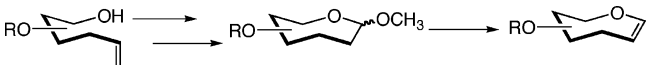
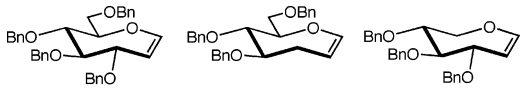
Received October 22, 2004



A five-step preparation of carbohydrate-based oxepines from hept-1-enitols is presented. The hept-1-enitols were subjected to silyl protection and hydroboration/oxidation to give the protected heptan-1-itols. Swern oxidation of the homologated alcohols followed by sequential acetal formation/cyclization provided methyl 2-deoxyseptanosides that underwent elimination reactions to give the carbohydrate-based oxepines. The new sequence is an alternative to the ring-closing metathesis for the synthesis of carbohydrate-based oxepines from protected pyranose sugars. The product oxepines can serve as glycosyl donors in the synthesis of novel septanose carbohydrates. In addition, *C*-methylenealdehydo arabinofuranoside **16** was formed from 2-deoxyseptanoside **10** as the only product during protic acid mediated elimination reactions. This novel ring contraction complements other reported preparations of *C*-methylenaldehydo furanosides and underscores the acid-mediated reactivity introduced by competing eliminations between the C-1/C-2 and C-2/C-3 bonds.

Analogues of natural carbohydrates are important to the development of new tools for understanding glycobiology[1] and as potential therapeutics;[2] septanoses are ring-expanded analogues of pyranoses that are defined by having a seven-membered ring.[3,4] These unnatural carbohydrate homologues are conceptually similar to β-amino acids[5] and size-expanded nucleosides[6] that have been reported. While oligomerization of the latter biopolymer building blocks has led to novel structures[6,7] and biological activity,[8] the preparation of septanose oligomers has received less attention. The development of modular syntheses of septanose carbohydrates represents a major prerequisite to their biological investigation. We have recently described a ring closing metathesis (RCM) based approach for the synthesis of seven-membered cyclic enol ethers, or oxepines, derived from protected pyranoses.[9] Further, we have demonstrated that the reactivity of these carbohydrate-based oxepines is similar to that of glycals.[10,11] Here we report a new preparation of septanosyl donors that can be used in glycosylation reactions for the synthesis of septanose carbohydrates. The route is characterized by the cyclization and elimination of carbohydrate-based hydroxy-acetals and is amenable to the larger scale preparation of these structures.

The choice of carbohydrate-based oxepines as synthetic targets was based on two factors. First, **1**−**3** are cyclic



1 **2** **3**

enol ethers reminiscent of glycals. We have recently shown that the D-xylose-based oxepine (**3**) reacted with DMDO[10] and NIS[11] in glycosylation reactions in a manner similar to that of glycals. Glycals are versatile starting materials for the preparation of various glycosides[12] and can also be used to prepare other donor types.[13] The centrality of glycals in the preparation of pyranose carbohydrates motivated our investigation of oxepines as glycosyl donors in septanose carbohydrate synthesis. Second, attractive synthetic routes for the preparation of enol ethers have been applied to the synthesis of carbohydrate-based oxepines.[14−20] As shown in Figure 1, oxepine **A** could come from precursors **B**−**D**. Our original reported preparation,[9] based on earlier precedents,[14]

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10.1021/jo048128c CCC: $30.25
Published on Web 03/19/2005

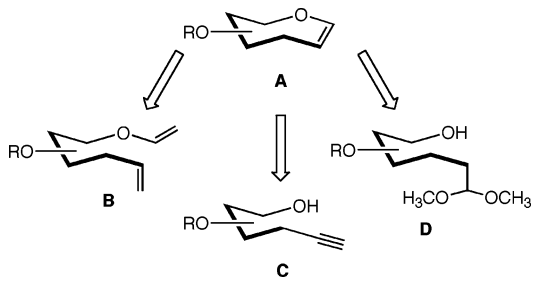

FIGURE 1. Retrosyntheses of carbohydrate-based oxepines.

involved ring-closing metathesis (RCM) of dienes such as **B**. A cycloisomerization route with alkynols (**C**) has been very effective in the preparation of glycals[19] and a recent report details the synthesis of some carbohydrate-based oxepines with use of a cycloisomerization reaction.[20] Here we report another synthesis of oxepines (**A**) via the cyclization and elimination of hydroxy acetals **D**.[15,16]

The expense associated with the use of Schrock catalayst[21] at relatively high (20 mol %) loading in our RCM-based approach to oxepines spurred a search for an alternate route to these building blocks of septanose carbohydrates. A reported one-pot sequential cyclization−elimination of hydroxy acetals under acidic conditions[15] was attractive because the starting hept-1-enitols (**4**−**6**) used in our RCM route could be used in the cyclization−elimination route. Also, the cyclization−elimination sequence had been successfully used in the preparation of oxepine intermediates during the synthesis of fused polycyclic ethers. It would also be amenable to modification whereby cyclization to form the mixed acetal could be followed by elimination under alternative conditions such as Lewis acid/base combinations,[17] or by refunctionalization to the thiophenyl septanoside followed by oxidation and elimination.[18]

The known hept-1-enitols (**4**−**6**)[22] were converted to the methyl 2-deoxyseptanosides (**10**−**12**) via the hydroxy acetals (**13**−**15**) by using straightforward transformations as shown in Scheme 1. Protection of the C-6 hydroxy group on hept-1-enitols **4** and **5** as their triethylsilyl (TES) ethers was followed by hydroboration−oxidation of the olefin and gave alcohols **7** and **8** (58% and 59%, 2 steps). In the conversion of **6** to **9** (54%, 2 steps), the C-6 hydroxyl of hept-1-enitol **6** was protected as the *tert*-butyldimethylsilyl (TBDMS) (54%, two steps) ether rather than the TES ether to avoid oxidation of this primary silyl ether in the subsequent Swern reaction. The modest efficiency in the hydroboration/oxidation step is comparable to that observed in other systems where side products included the regioisomeric alcohol and the hydrogenated material.[14d,e,23]

Oxidation of the resultant alcohols **7**−**9** was attempted by using both PCC[24] and the Bobbitt reagent[25] with limited efficiency. Swern oxidation[26] of **7**−**9** gave the corresponding aldehydes in 60−77% yield. They were then submitted to acetalization conditions with use of *p*-toluenesulfonic (*p*TsOH) acid in methanol. Methyl 2-deoxyseptanosides **10**−**12** (50−70%) were the major products isolated from the reactions; here the sequential deprotection of the silyl ethers and cyclization/acetal formation occurred in one pot. Methyl 2-deoxyseptanoside **10** was prepared exclusively as the α-anomer[27] while **11** and **12** were isolated as mixtures favoring (3:2 α:*β*) the α-configuration. Preference for the α-configuration is presumably due to the anomeric effect, which has been demonstrated in mixed acetals of other seven-membered-ring systems.[28,29] Acyclic hydroxy-acetals **13**−**15** (Scheme 1) were also isolated from the acetalization reactions in low (11−32%) yield and could be efficiently cyclized to **10**−**12** by using *p*TsOH in toluene (84−95% yield).

Previous examples of the acid-mediated elimination of methanol from methyl acetals to form cyclic enol ethers was highly regiospecific. The added functionality of the C-3 benzyloxy group in **10** and **12**, however, presented the possibility of a competing elimination of benzyl alcohol across the C-2/C-3 bond. Under the reported pyridinium tosylate (PPTS) conditions,[15] methyl 2-deoxyseptanoside **10** gave a 2:1 (α:*β*) mixture of *C*-methylene-aldehydo arabinofuranosides **16** in 65% yield (Scheme

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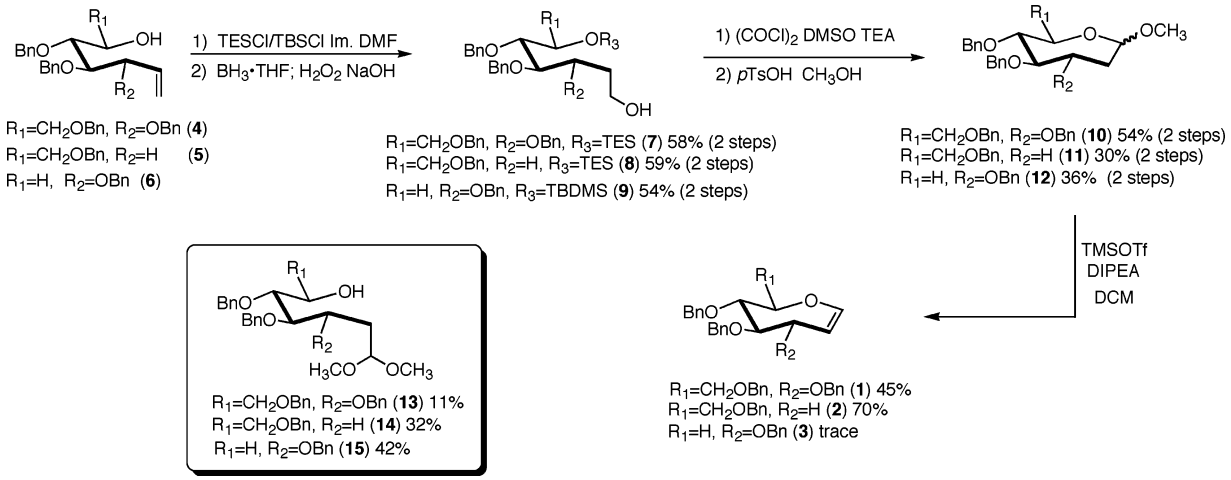
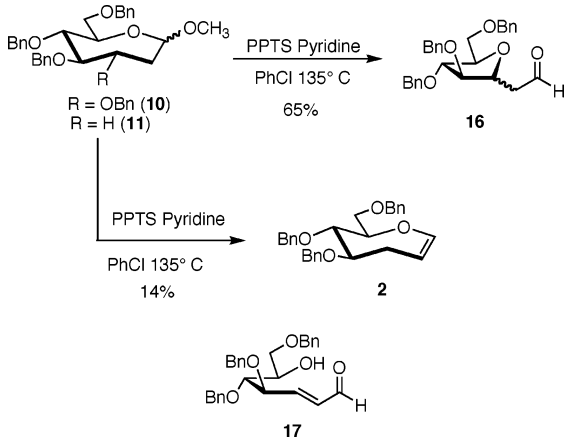
SCHEME 1



SCHEME 2



2).[30] The product presumably arose via intramolecular 1,4 attack by the C-5 oxygen on α,β-unsaturated aldehyde **17** to give the observed products. This intermediate (**17**) resulted from ring opening of **10** to the aldehdye and elimination of benzyl alcohol to provide the α,β-unsaturation. The ring contraction of septanoside **10** to form **16** is the first reported synthesis of a *C*-methylenealdehydo arabinofuranoside. The synthetic route complements other preparations of *C*-methylenealdehydo furanosides from *C*-pyrrolidinone and *C*-allyl furanosides.[31] Reaction of methyl 2,3-dideoxyseptanoside **11** under the PPTS/pyridine conditions gave oxepine **2** in 14% yield (Scheme 2) with 80% recovered starting material. The ability to affect elimination in **11** under the PPTS conditions suggested that the C-3 benzyloxy functionality played a key role in the observed reactivity of **10**. Overall, these results indicated that alternative conditions to affect the desired elimination more efficiently must be identified.

Elimination of methanol by using the procedure of Gassman[17] provided oxepines **1** and **2** in modest to good yields (Scheme 1). Treatment of **10** or **11** with trimethylsilyl triflate (TMSOTf) in the presence of *N,N*′-diisopropylethylamine (DIPEA) gave **1** and **2** in 45% and 70% yield, respectively. Relative to the PPTS-mediated elimination of **10**, the reaction conditions were mild enough to disfavor the competing C-2/C-3 elimination of benzyl alcohol and allowed formation of oxepine **1**. The conversion of 2,3-dideoxy septanoside **11** to oxepine **2**, observed in low yield with use of the PPTS elimination conditions, was efficient under the TMSOTf/DIPEA conditions. Finally, methyl septanoside **12** showed complex reactivity under the TMSOTf/DIPEA conditions. Oxepine **3** was isolated in low yield (17%) as a mixture with an inseparable side product. This reactivity was unable to be supressed under altered reaction conditions. The inability to prepare oxepine **3** with this procedure suggests a limitation in the route described.

Overall, oxepines **1** and **2** were prepared in five steps from hept-1-enitols **4** and **5** in 16% and 34% yield. The reactions presented allow for the direct and scaleable[32] preparation of carbohydrate-based oxepines by a route that is complementary to the RCM route previously reported. Additional approaches toward carbohydrate-based oxepines are also currently being evaluated. The oxepine products described here are viable glycosyl donors for the synthesis of septanose carbohydrates.

Experimental Section

Silyl Protection: Preparation of 4,5,7-Tri-*O*-benzyl-6-*O*-triethylsilyl-1,2,3-trideoxy-D-glucohept-1-enitol (p8). Imidazole (1.09 g, 16.0 mmol) and DMF (5 mL) were combined in a round-bottom flask under nitrogen. To this mixture was added **5** (2.32 g, 5.36 mmol) followed by the addition of chlorotriethylsilane (TESCl) (1.62 g, 10.7 mmol) dropwise. This solution was stirred at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with H_2O (40 mL). The organic layer was extracted and dried (Na_2SO_4) and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography by using 10:1.5 hexanes−EtOAc as eluent to give **p8** (2.77 g, 95%) as a clear colorless oil.

(30) The α and β isomers of **16** were unable to be separated by chromatography. Reduction of the aldehyde ($NaBH_4/CH_3OH$) to the hydroxymethylene compound provided a similarly inseparable mixture of isomers.

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(32) The route described has been used to prepare up to 1 g of oxepine **2** at a time, for example.

Hydroboration−Oxidation: Preparation of 4,5,7-Tri-*O*-benzyl-6-*O*-triethylsilyl-2,3-dideoxy-D-glucoheptan-1-itol (8). To a solution of **p8** (2.77 g, 5.07 mmol) in THF (20 mL) at 0° C was added dropwise a solution of BH_3·THF (15.2 mL, 1.0 M). The mixture was allowed to warm to room temperature and stirred under N_2. After 3 h, the reaction was quenched with dropwise addition of H_2O. To the mixture was added 4 M NaOH (20 mL) dropwise and then 30% H_2O_2 (5 mL). The mixture was stirred at room temperature overnight. Saturated $NaHCO_3$ (20 mL) was added and the THF was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic phase was washed with H_2O (40 mL) and dried over Na_2SO_4. The solvent was evaporated in vacuo and the products were isolated by silica gel chromatography with hexanes−EtOAc (10:3) as eluent to give **8** (1.77 g, 62%) as a clear colorless oil.

Swern Oxidation: 4,5,7-Tri-*O*-benzyl-6-*O*-triethylsilyl-2,3-dideoxy-D-*glycero*-D-gulose (p11). A solution of CH_2Cl_2 (2 mL) and oxalyl chloride (0.637 g, 5.02 mmol) was placed in a 100-mL round-bottom flask at −60 °C. DMSO (0.784 g, 10.0 mmol) dissolved in CH_2Cl_2 (2 mL) was then added to the mixture. The reaction mixture was stirred for 2 min then **8** (1.42 g, 2.51 mmol) was added and the mixture was allowed to stir for 15 min. TEA (2.538 g, 25.1 mmol) was added and the reaction mixture was stirred for 5 min and then warmed to room temperature over 1 h. Water was added to the mixture and the aqueous layer was extraced with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, washed with saturated NaCl (40 mL), and dried over Na_2SO_4. The solvent was evaporated in vacuo and the products were isolated by silica chromatography, eluting with hexanes−EtOAc (10:3) to give **p11** (1.09 g, 77%) as a clear yellow oil. Aldehydes **10**−**12** were routinely carried on to the acetization/cyclization reaction without further characterization.

Methyl Septanoside/Hydroxy-Acetal Formation: Preparation of Methyl 4,5,7-Tri-*O*-benzyl-2,3-dideoxy-α/β-D-*glycero*-D-guloseptanoside (11) and 4,5,7-Tri-*O*-benzyl-6-*O*-triethylsilyl-2,3-dideoxy-D-*glycero*-D-gulose Dimethyl Acetal (14). Compound **11** (0.829 g, 1.47 mmol) was dissolved in methanol (20 mL). To this solution was added *p*-toluenesulfonic acid monohydrate (0.558 g, 2.94 mmol) and the mixture was stirred for 6 h. A saturated solution of $NaHCO_3$ (20 mL) was added and the mixture was extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine, concentrated by rotary evaporation, and purified by column chromatography eluting with 10:3 hexanes:ethyl acetate. Two compounds were isolated, **11** (0.343 g, 50%) as a white solid and **14** (0.231 g, 32%) as a clear oil. In 4:1 hexanes:ethyl acetate, R_f (**11**) 0.69, R_f (**14**) 0.58.

Elimination: Preparation of 1,6-Anhydro-4,5,7-tri-*O*-benzyl-2,3-dideoxy-D-*glycero*-D-gulosept-1-enitol (2). A round-bottom flask was purged with N_2 and to it was added **11** (0.300 g, 0.648 mmol), DIPEA (0.159 g, 1.23 mmol) and CH_2Cl_2 (1.3 mL; 2 mL/mmol of substrate). After the solution was cooled to −50 °C, TMSOTf (0.252 g, 1.14 mmol) was added dropwise via syringe. The solution was allowed to stir at room temperature for 24 h. The reaction was quenched with NaOH (2 mL, 1 M) and extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was washed with brine, dried with Na_2SO_4, concentrated by rotary evaportion, and purified by silica gel column chromatography (10:3 hexanes:ethyl acetate) to give compound **2** (0.196 g, 70%) as a clear yellow oil. Note: For glucose (**10**) and xylose (**12**)-based oxepines, the reaction was run at 0 °C.

***C*-Methylenealdehydo 2,3,5-Tri-*O*-benzyl-α/β-D-arabinofuranoside (16).** To a solution of **10** (0.136 g, 0.227 mmol) and chlorobenzene (20 mL) was added PPTS (0.342 g, 1.36 mmol) and pyridine (0.047 mL, 0.585 mmol). The resulting mixture was heated to 135 °C for 4 h. The reaction was quenched with NaOH (2 mL, 1 M), extracted with ether (3 × 30 mL), washed with brine, dried with Na_2SO_4, concentrated by rotary evaportion, and purified by silica gel column chromatography (10:2 petroleum ether:ethyl acetate) to give **16** (0.107 g, 65%) as a clear oil. The material was isolated as a 2:1 (α: β) mixture of diastereomers that was inseparable by chromatography.

Acknowledgment. The authors thank Martha Morton for help with the acquisition and interpretation of NMR data and Chris Incarvito (Yale University) for collection of X-ray data. Financial support was provided by the Petroluem Research Fund administered by the American Chemical Society, the University of Connecticut, and the University of Connecticut Research Foundation.

Supporting Information Available: General experimental procedures and characterization data for all compounds not previously reported. This material is available free of charge via the Internet at http://pubs.acs.org. Complete crystallographic data for the structural analysis of the methyl 2-deoxyseptanoside derived from hydrogenation of **10** have been deposited in the Cambridge Crystallographic Data Centre (CCDC), No. 259290. Copies of this information may be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax +44-1223-336033; web www.ccdc.cam.ac.uk/conts/retrieving.html; e-mail deposit@ccdc.cam.ac.uk).

JO048128C