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A ring closing metathesis strategy for carbapyranosides of xylose and arabinose

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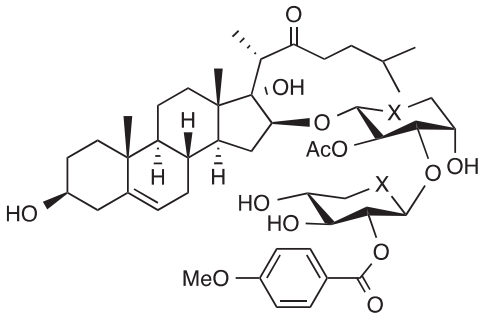
ABSTRACT

The synthesis of β-carba-xylo and arabino pyranosides of cholestanol is described. The synthetic strategy, which is analogous to the Postema approach to *C*-glycosides, centers on the ring closing metathesis of an enol ether–alkene precursor to give a cyclic enol ether that is elaborated to a carba-pyranoside via hydroboration–oxidation on the olefin. The method, which is attractive for its modularity and stereoselectivity, may find wider applications to carba-hexopyranosides and other complex cycloalkyl ether frameworks.

1. Introduction

Carbohydrate residues are present on a wide range of bioactive molecules and invariably, impact on potency and, or specificity.[1–4] Thus, glycodiversification is a popular strategy in the development of carbohydrate-based therapeutics.[5–9] In this context, nonhydrolyzable sugar analogues such as carbasugars, in which the ring oxygen is replaced with a "CH_2", have attracted attention as potentially metabolically stable therapeutic agents and for mechanistic studies.[10] The nuanced conformational properties of carbasugars relative to their parent O-glycosides are of additional relevance to structure activity studies.[11] Consequently, there is much interest in the synthesis and properties of carbasugars. While several methods have been developed for carbasugars in which the pseudo sugar ring is linked to relatively simple alcohol segments or to the primary alcohol oxygen of a sugar, structures with more complex alcohol segments are not as easily accessible because of the challenges associated with fabricating the pseudoglycosidic ether bond.[10,12–14] We envisaged an RCM-based approach to carbasugars that may address this issue and that has further appeal because of its modularity. This strategy is illustrated herein in the synthesis of β-carba-arabino and xylo pyranosides of cholestanol. We were drawn to these frameworks because of the existence of the parent sugars in several antitumor steroidal and triterpenoid saponins, of which OSW-1 1 is a notable example (Fig. 1).[15–18] β-Xylopyranosides also comprise the capsular polysaccharide of fungal pathogens associated with AIDS. Carbaxylosides thereof may be of interest to vaccine development in this area.[19]

Our approach builds on the C-glycoside synthesis from the Postema group, in which the pivotal reaction is the RCM on an enol



1 OSW-1: X = Y = O
2 OSW-1 carbasugars: X/Y = O/CH_2; CH_2/O; CH_2/CH_2

Fig. 1. OSW-1 and carbasugar analogues.

*Chemical compounds studied in this article*Methyl 2,3-O-isopropylidene-beta-D-ribofuranoside (PubChem CID: 96666)Methyl alpha-D-arabinofuranoside (PubChem CID: 11389582)Cholestanol (PubChem CID: 6665)Methyl (triphenylphosphoranylidene)acetate (PubChem CID: 17453)Tebbe reagent (PubChem CID: 91617563)Grubbs catalyst 2nd generation (PubChem CID: 11147261)Dimethyl sulfide borane (PubChem CID: 9833925)

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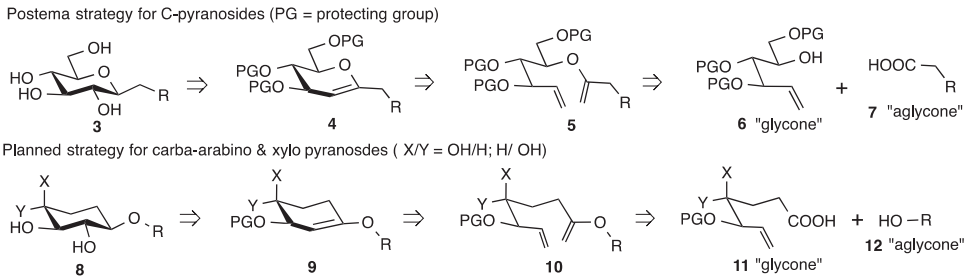
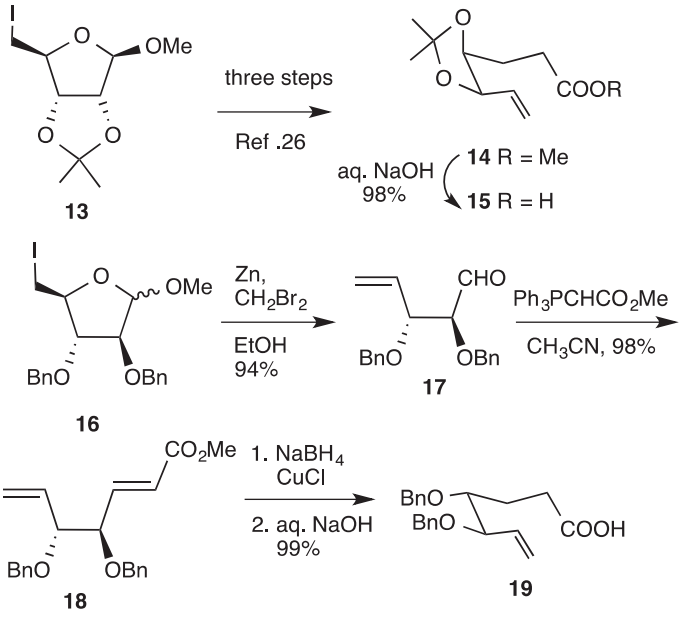


Scheme 1. RCM strategies to C- and carba-pyranosides.

ether–alkene **5** to give the C1-substituted glycal **4** (Scheme 1).[20] Stereoselective hydroboration–oxidation on **5** leads to the 1,2-*trans*/2,3-*trans* C-glycoside **3**. An attractive feature of this strategy is the modular assembly from "glycone" and "aglycone" precursors **6** and **7**. Through the use of C-branched sugar acids, this method has been applied to C-di- and higher order *C*-glycosides. An analogous strategy for carbasugars calls for an RCM on an enolether alkene **10** to give the cyclic enol ether **9**, which differs from **4**, the corresponding enol ether in the C-glycoside synthesis, in that the enol ether oxygen is exocyclic and not endocyclic. However, while RCMs on enol ether–alkenes like **5** have been successful on a variety of highly substituted substrates, to the best of our knowledge, RCMs on variants like **10**, in which the ether oxygen is exocyclic to the eventual ring, have only been tested on silyl or simple alkyl enol ethers.[21–25]

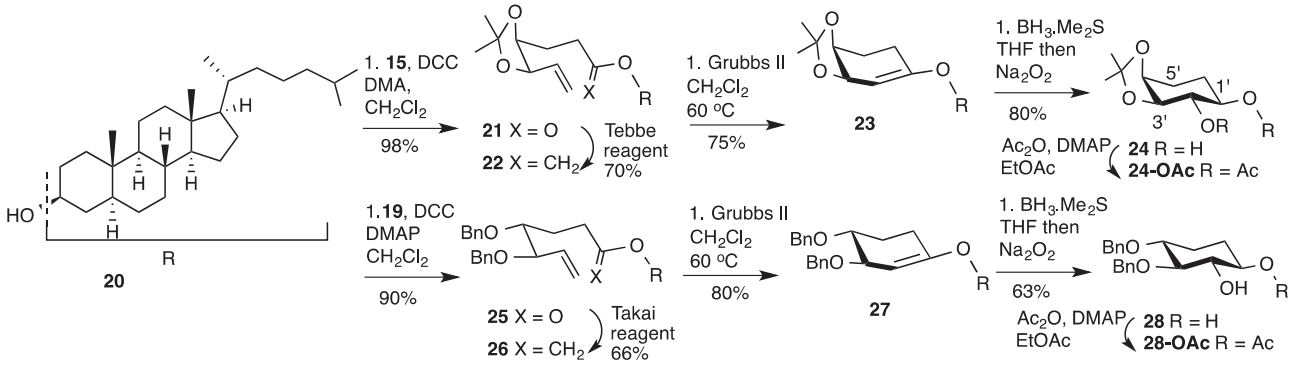


Scheme 2. Synthesis of "glycone" precursors.

2. Results and discussion

Synthesis of "glycone" segments. The unsaturated acid precursor **15** for carba-arabinoses was obtained by hydrolysis of the known ester **14**, which in turn was prepared from 5-deoxy-5-iodo-D-ribofuranoside **13**, via a known procedure (Scheme 2).[26] The carba-xyloside precursor **19**, which was previously prepared from L-tartaric, was prepared here via a more concise route, using a strategy similar to that used for **14**.[27] Thus, zinc mediated reductive opening on the 5-deoxy-5-iodo-D-arabinofuranoside **16** afforded enal **17**.[28,29] Treatment of **17** with methyl(triphenylphosphoranylidene)acetate provided **18** as a single *E*-isomer. Selective hydrogenation of the conjugated alkene followed by hydrolysis of the ester led to **19**.

The feasibility of the key RCM reaction was tested using cholestanol **20** as a model steroidal segment (Scheme 3). Accordingly, DCC promoted esterification of **20** and alkenoic acids **15** and **19** produced esters **21** and **25** in 98% and 90% yields respectively. Next, olefination on **21** and **25** using the Tebbe and Takai reagents afforded the respective enol ethers **22** and **26** in 70% and 66% yields.[30,31] These materials were sensitive to acid and silica gel purification required the presence of triethylamine in the mobile phase. Treatment of **22** and **26** with 10 mole % Grubbs II catalyst in dichloromethane at 60 °C led to the cyclic enol ethers **23** and **27** in 75% and 80% yields respectively. Finally, a hydroboration–oxidation sequence on **23** and **27** afforded the β-carba-arabinoside and xyloside **24** and **28** respectively, as the only observed diastereomers, in 80% and 63% yields. The stereochemistry of **24** and **28** was assigned from ^{1}H NMR analysis of their acetates **24-OAc** ($J_{1',2'} = 9.5$, $J_{2',3'} = 9.9$, $J_{3',4'} = 5.1$ Hz) and **28-OAc** ($J_{1',2'} = J_{2',3'} = J_{3',4'} = 9.5$–9.6 Hz, see Supporting Information for selected ^{1}H NMR assignments).



Scheme 3. Synthesis of carba-3β-cholestanyl pentopyranosides.