Easy and Stereoselective Approach to α , β -Unsaturated γ -Lactones Fused to Pyranoses from Furanose Scaffolds

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ABSTRACT



The first facile and efficient route to pyranose-fused butenolides from furanose scaffolds, convenient for scaling up production, is described. Wittig olefination of 1,2-*O*-isopropylidene pentofuranos- or hexofuranos-3-uloses with a resonance-stabilized ylide led to the stereoselective formation of the (*Z*)- α , β -unsaturated ester. In the presence of acid labile 5-*O*- or 5,6-di-*O*-protecting groups, acid hydrolysis of the Wittig product resulted in isomerization to the pyranose form and spontaneous lactonization to give the target molecules in good overall yield.

The α , β -unsaturated γ -lactone motif is found in many natural products exhibiting a wide range of biological properties, namely, phytotoxic, antibacterial, or anti-inflammatory activities, with some of those compounds being described as potential anticancer agents, phospholipase A2 and cyclooxygenase inhibitors.¹ Furthermore, sugars comprising this structural moiety have been reported as fungicides or highly potent and selective insecticides (Figure 1).² This biological profile encourages the search for efficient and straightforward approaches leading to new sugar-based butenolides.

Five-membered ring lactones fused to carbohydrate templates are known mainly in furanose systems. These compounds are useful intermediates for the preparation of nucleosides and branched-chain sugars.³ Concerning sugar-

10.1021/oI071351m CCC: \$37.00 © 2007 American Chemical Society Published on Web 07/26/2007 fused α,β -unsaturated γ -lactones, only a few were reported, and those are fused to six-membered rings at positions 2



Figure 1. Structure of sugar-based α , β -unsaturated γ -lactones possessing fungicidal (A) and insecticidal properties (B).

and 3 of the sugar.⁴ However, their synthesis was implemented in a very low global yield using pyranos-2-uloses as starting materials, which are in general obtained in low yield by chemical synthesis.

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We report herein an easy and direct method to prepare pyranose-fused butenolides starting from readily available pentofuranos- or hexofuranos-3-uloses.

Butenolides fused to hexopyranoses were synthesized as illustrated in Scheme 1.



The 3-keto sugar **1** was obtained by oxidation of commercially available 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose with pyridinium dichromate/acetic anhydride in dry methylene chloride in nearly quantitative yield,^{5a} using a different workup than that described in the literature.^{5b}

It was subjected to Wittig reaction with [(ethoxycarbonyl)methylene]triphenylphosphorane in refluxing chloroform, affording the known (*E*)- and (*Z*)- α , β -unsaturated esters **2a** and **2b**,⁶ in 12% yield and 68% yield, respectively. The 5,6-*O*-isopropylidene group of **2b** was selectively removed by treatment with aqueous acetic acid (60%) affording the 5,6diol **3b** in 95% yield.

Selective protection of the primary hydroxyl group of **3b** was successful even when the substrate was treated with pivaloyl chloride in excess (2.4 equiv) in pyridine/methylene

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chloride at 0 °C. The 6-O-pivaloyl derivative 4 was the major reaction product, isolated in 57% yield, and the 5,6-di-Opivaloyl-protected derivative 5 was obtained in only 27% yield. However, benzoylation afforded under similar conditions the 5,6-di-O-benzoyl derivative 6 in 83% yield, and no monoprotection was observed. The 6-O-pivaloyl (Z)- α , β unsaturated ester 4 was then submitted to hydrolysis with aqueous acetic acid (70%) under reflux to give the target molecule 7 as a mixture of both anomers (α/β ratio 1:0.7) in 83% yield, resulting from deprotection of the 1,2acetonide, furanose ring opening, its closure into the pyranose form, and intramolecular lactonization, in one single step. When compound **3b** was subjected to similar hydrolytic conditions, followed by acetylation with acetic anhydride in pyridine, the triacetate-derived butenolide 9 was obtained in 78% overall yield (ratio α/β , 2:1). Direct synthesis of the intermediate deprotected butenolide 8 was successfully and readily achieved (90% yield) by acid hydrolysis of 2b with IR-120 H⁺ resin⁷ in refluxing methanol (ratio α/β , 3:1). Moreover, the butenolide fused to positions 3 and 4 of a pyranose moiety 10 was successfully obtained by resin acid hydrolysis of the (E)- α , β -unsaturated ester **2a**, which after acetylation gave the triacetate derivative 11 as a 1:1 mixture of α,β -anomers in 63% overall yield.

However, no intramolecular cyclization was observed by removal of the 1,2-O-isopropylidene group of **5**, which comprises a nonacid labile and bulky pivaloyl protecting group at position 5, being the 1,2-diol **12** isolated in 62% yield. This result suggests that the formation of butenolides 2,3-fused to carbohydrates under these experimental conditions is favored in pyranose systems rather than in furanose forms. Confirmation of this finding was possible when the pentofuranosid-3-ulose **13**⁸ (Scheme 2), with the acid-



resistant 5-*O*-pivaloyl group, was used as starting material. Its synthesis was accomplished by PDC/Ac₂O oxidation of 1,2-*O*-isopropylidene-5-*O*-pivaloyl- α -D-xylofuranose⁹ in 81% yield. Wittig olefination of **13** was stereoselective, leading to the (*Z*)- α , β -unsaturated ester **14b** in 70% yield, with the (*E*)-adduct **14a** being isolated in 12% yield. As expected, intramolecular lactonization to **16** did not occur by treatment

^{(5) (}a) General experimental procedure for PDC/Ac₂O oxidation: A solution of sugar (3.47 mmol) in dry CH₂Cl₂ (6 mL) was added to a mixture of PDC (0.96 g, 2.57 mmol) and Ac₂O (1.1 mL, 11.6 mmol) in dry CH₂Cl₂ (12 mL) under argon. The resulting mixture was stirred under reflux until complete conversion, then cooled to rt. The solvent was removed in vacuo. Diethyl ether (50 mL) was added to the solid residue, and the mixture was filtered over florisil. The solvent was removed under a vacuum to afford the 3-keto sugar. (b) Lee, J.-C.; Chang, S.-W.; Liao, C.-C.; Chi, F.-C.; Chen, C.- S.; Wen, Y.-S.; Wang, C.-C.; Kulkarni, S. S.; Puranik, R.; Liu, Y.-H.; Hung, S.-C. *Chem.-Eur. J.* **2004**, *10*, 399–415.

with aqueous acetic acid, resulting in the 1,2-diol **15** in 70% yield (ratio α/β , 1:0.7), thereby reinforcing that butenolides are difficult to fuse at positions 2,3 of furanose rings with this methodology.

The preparation of butenolides 2,3-fused to pentopyranose units (Scheme 3) was accomplished following a synthetic



pathway similar to that described above for the hexopyranose moieties. The primary hydroxyl group of 1,2-O-isopropylidene- α -D-xylofuranose, easily prepared from D-xylose and commercially available, was selectively protected with

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the acid labile *tert*-butyldimethylsilyl group in quantitative yield, the resulting silyl ether being oxidized to the pentofuranos-3-ulose derivative **17**¹⁰ with PDC/Ac₂O for the first time, in 97% yield. When this 3-keto sugar reacted with [(ethoxycarbonyl)methylene]triphenylphosphorane in chloroform under reflux, stereoselectivity to the (*Z*)- α , β -unsaturated ester **18b**¹¹ was achieved, with this isomer being isolated in 81% yield and the (*E*)-isomer being obtained in 8% yield. Selective hydrolysis of **18b** with aqueous acetic acid (70%) at 70 °C afforded the desilylated derivative **19** in 85% yield, and IR-120 H⁺ resin promoted total hydrolysis with the formation of the butenolide 2,3-fused to the pentopyranose ring **20** in 79% yield in a 1:1 mixture of the α , β -anomers.

In conclusion, a reliable and facile method is described for the stereoselective synthesis of potentially bioactive carbohydrate-based butenolides fused to pento- and hexopyranose rings. The synthetic strategy followed herein involves a short number of steps leading to the target molecules in good overall yield, with the added value of a possible regioselective protection for further derivatization. The readily avaliable starting materials obtained from inexpensive sugars (D-glucose and D-xylose) and the easy and efficient experimental procedures make this methodology useful for the preparation of new sugar derivatives of biological interest.

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Supporting Information Available: New products characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽⁷⁾ **Typical experimental procedure for IR-120 H** + resin promoted **hydrolysis:** To a solution of 3-deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2:5,6-di-*O*-isopropylidene- α -*D*-*ribo*-hexofuranose (0.11g, 0.33 mmol) in MeOH (1.8 mL) was added Amberlite IR-120 H + resin (35 mg). The mixture was moderately stirred under reflux overnight. After filtration of the resin and evaporation of the solvent, the crude was purified by CC on silica gel using AcOEt as eluent to afford **8** (60 mg, 90%) as a white solid.

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