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# Stereoselective Cyclopropanation in the Synthesis of 3′-Deoxy-3′-*C*-hydroxymethyl-2′,3′-methylene-uridine

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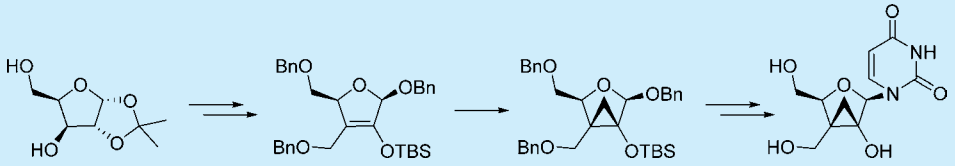
Supporting Information



**ABSTRACT:** The synthesis of the novel 2′,3′-cyclopropane nucleoside 3′-deoxy-3′-*C*-hydroxymethyl-2′,3′-methylene-uridine is described. Stereoselective construction of the cyclopropane ring was achieved via Simmons−Smith cyclopropanation of a benzyl protected silyl enol ether, which was itself derived from 1,2-*O*-isopropylidene-α-D-xylofuranose.

3′-Deoxy-3′-*C*-hydroxymethyl-2′,3′-methylene-uridine **1** was required as part of an investigation into the antihepatitis C virus (HCV) activity of novel nucleoside scaffolds (Figure 1). Although the introduction of four direct-acting antivirals[1] (DAAs) over the past three years has significantly improved patient treatment options, with a prevalence of 2.8% of the world's population,[2] HCV remains a serious global disease concern. Clinical validation of nucleoside inhibitors targeting the HCV NS5B polymerase has been demonstrated with multiple compounds in development over the past decade.[3] In 2013, the 2′-*C*-methyl-uridine prodrug, sofosbuvir,[1d] achieved regulatory approval, and thus further exploration of this important class of DAAs continues.

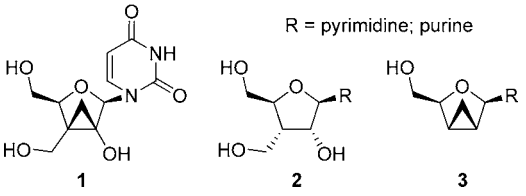
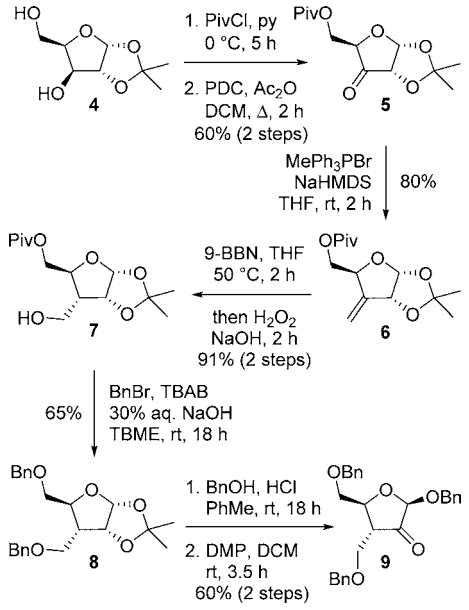



**Figure 1.** Target nucleoside **1** combining 3′-*C*-hydroxymethyl **2** and 2′,3′-dideoxy-2′,3′-cyclopropane **3** structural features.

Incorporation of a 3′-*C*-hydroxymethyl group **2** has historically led to a multitude of diverse sugar-modified nucleoside systems displaying a broad range of antiviral (hepatitis B virus,[4] human immunodeficiency virus,[5] varicella zoster virus[6]), antimicrobial (tuberculosis[7]), and anticancer (leukemia[8]) properties. In contrast, there are relatively few reports concerning nucleosides bearing a 2′,3′-cyclopropane modification **3**, beyond the original 2′,3′-dideoxy analogs.[9] Combination of these structural elements to form 3′-deoxy-3′-*C*-hydroxymethyl-2′,3′-methylene-uridine **1** as a potential anti-HCV agent

**Scheme 1. 2-Ketofuranoside 9 Synthesis**




and the synthesis, characterization, and stereochemical confirmation of this novel ribonucleoside system are described herein.

Synthesis of **1** from the commercially available acetonide protected D-xylose derivative **4** started with the chemistry reported by Suhara et al.[10] to form the 1,2,5-protected 3-*C*-methylene xylofuranoside **6** (Scheme 1). Pivaloyl protection of the primary hydroxyl proceeded selectively, and the oxidation to

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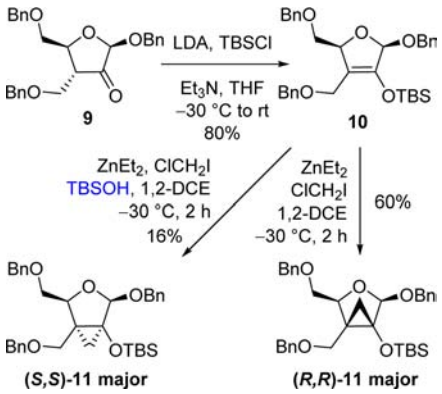
**5** was achieved using pyridinium dichromate in a similar yield to the reported pyridinium chlorochromate oxidation. Non-chromium based oxidation protocols, such as the Swern oxidation or use of the Dess-Martin periodinane, were evaluated but either were less selective or resulted in ketone hydrate formation. Following the Wittig reaction to introduce the exomethylene moiety in **6**, hydroboration was performed using 9-BBN.[10,11] This was achieved in high yield and excellent stereoselectivity with only the 3*R*-isomer observed, and **7** was isolated following treatment with $H_2O_2$ and NaOH. Phase transfer conditions[12] were employed to form the dibenzyl protected intermediate **8** directly from compound **7**. Treatment with 4.0 M HCl in dioxane and BnOH effected acetonide removal, and Fischer glycosylation to give the benzyl glycoside and subsequent oxidation with Dess-Martin periodinane was performed in good yield to give the protected 3-*C*-hydroxymethyl 2-ketofuranoside **9**.

Several examples of the cyclopropanation of pyranose derivatives have been reported in the literature.[13] Open chain cyclopropanations followed by cyclization to give carbohydrate ring systems are also known.[14] However, the formation of cyclopropane rings on carbohydrate substrates in their cyclic furanose form is less well described. An example of Simmons–Smith cyclopropanation on a 4,5-dihydrofuran was found to be highly stereospecific.[15] A high yielding Simmons–Smith type cyclopropanation at the 3,4-position of an L-xylose derived substrate has been described.[16] However, to date, there has been no report of a Simmons–Smith type cyclopropanation at the 2,3-position of a carbohydrate furanose ring. 2,3-Methylene pentofuranose derivatives have been synthesized, although using alternative methods, such as ring contraction, conjugate addition to a phenylselenoid derivative, a displacement approach for *gem*-dimethylcyclopropanes, and via 1,3-dipolar cycloadditions of diazomethane to furanones.[9a,17] 2-Ketofuranoside **9** was transformed into silyl enol ether **10** using LDA and TBSCl (Scheme 2). Cyclopropanation was subsequently performed

**Scheme 2. Stereoselective Cyclopropanation**




using the Simmons–Smith type conditions described by Gerber and Vogel[18] in which the substrate **10** was added to a premixed solution of $ZnEt_2$ and chloroiodomethane in DCE cooled to −30 °C, followed by warming to ambient temperature.

The cyclopropanation reaction was initially found to exhibit remarkably high diastereoselectivity, with a greater than 8:1 ratio of (*R*,*R*)-**11** to (*S*,*S*)-**11**. The desired 2*R*,3*R* stereochemistry in **11** was investigated via 2D-NOESY NMR spectroscopy (Figure 2). An NOE correlation was observed between one of the methylene protons of the cyclopropane ring and the methylene H5 protons

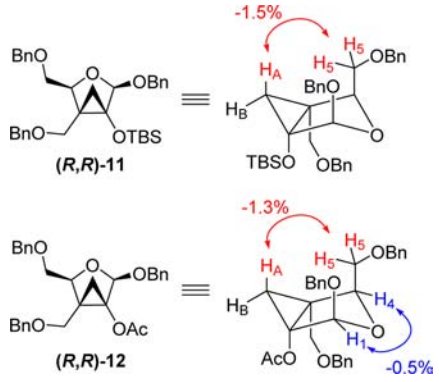



**Figure 2.** Confirmation of stereochemistry by 2D NOESY NMR spectroscopy (performed on a 400 MHz spectrometer; NOE correlations reported from extracted 1D data sets).

confirming their close spatial relationship on the $\beta$-face of the furanose ring.

Interestingly, this selectivity was not readily reproduced and subsequent cyclopropanations resulted in a mixture of 2*R*,3*R* and 2*S*,3*S* isomers, prompting investigation of the reaction conditions and input materials. The purity of the silyl enol ether substrate **10** was found to be critical to the stereochemical outcome of the reaction. The presence of residual TBSOH due to either its incomplete purging on chromatography or by gradual decomposition of **10** on storage (as observed by proton NMR spectroscopy) was determined to be the influencing factor. Cyclopropanations performed on freshly purified **10** gave exclusively (*R*,*R*)-**11** in 60% yield, whereas a sample of **10** containing 34% w/w (2.2 mol equiv) of TBSOH gave a 1:2.9 mixture of (*R*,*R*)-**11** and (*S*,*S*)-**11** diastereomers with only a 22% combined yield.

One of the major factors influencing the stereochemical outcome of the cyclopropanation reaction is chelation of the zinc carbenoid species.[19] Under normal conditions it is proposed that the zinc carbenoid species chelates to the oxygen atom at the sugar C5-position directing cyclopropanation onto the same ($\beta$) face of the ring to generate the (*R*,*R*)-**11** isomer. If, however, the cyclopropanation is performed in the presence of TBSOH, binding of this impurity to the zinc carbenoid species may compete with substrate chelation resulting in the loss of stereocontrol. Cyclopropanation may then occur preferentially on the less hindered $\alpha$ face to generate (*S*,*S*)-**11** as the major product.

Formation of the desired protected 3-*C*-hydroxymethyl 2,3-methylene furanoside (*R*,*R*)-**11** was achieved in 49% yield from ketofuanose **9** (2 steps). After removal of the silyl group, the tertiary hydroxyl was reprotected as acetate ester (*R*,*R*)-**12** (Scheme 3). A 2D-NOESY NMR experiment performed on (*R*,*R*)-**12** further confirmed the required stereochemistry at C2 and C3 while also indicating the $\beta$ anomeric configuration (Figure 2). Benzyl group removal by hydrogenation and subsequent triacetylation provided nucleosidation substrate (*R*,*R*)-**13** without issue. The (*S*,*S*)-**13** isomer could not be prepared since the debenzylated intermediate following hydrogenation was unstable. Analogous cyclopropanated carbohydrates in their furanose form have been found to behave similarly, and these results will be published in due course.

Nucleosidation of (*R*,*R*)-**13** was performed using silylated uracil and TMS triflate in acetonitrile under Vorbrüggen conditions.[20] Protected uridine **14** was isolated in excellent yield as the $\beta$-anomer only. Acetate deprotection of **14** was,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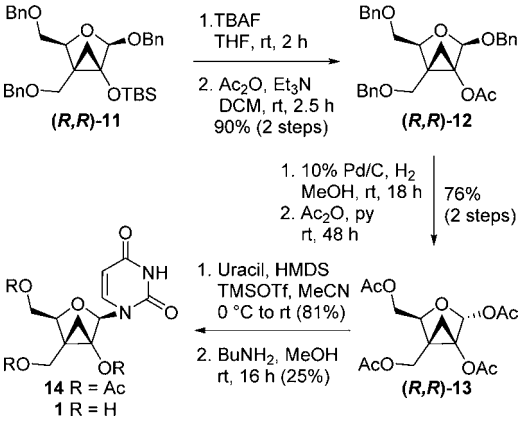
**Scheme 3. Synthesis of Nucleoside 12**




however, challenging due to gradual decomposition under various basic deprotection conditions (NaOMe, $Mg(OMe)_2$, $NH_3$/MeOH). Enzymatic hydrolysis using a range of lipases[21] was ineffective with **14** remaining largely unreacted. Deprotection with *n*-$BuNH_2$ in methanol provided the most suitable reaction profile. Final purification was achieved by reversed phase chromatography in 25% yield to give the target nucleoside **1**.

3′-Deoxy-3′-*C*-hydroxymethyl-2′,3′-methylene-uridine **1** was evaluated in a whole cell-based HCV replicon assay and was not found to possess inhibitory activity ($EC_{50}$ >100 $\mu$M) or cytotoxicity ($CC_{50}$ >100 $\mu$M).

In conclusion, this report is the first example of a stereoselective Simmons−Smith style cyclopropanation performed at the 2,3-positions of a carbohydrate furanose ring system. This key transformation facilitated the 16-step synthesis of the novel nucleoside 3′-deoxy-3′-*C*-hydroxymethyl-2′,3′-methylene-uridine which was evaluated for anti-HCV activity *in vitro*. The synthesis and antiviral evaluation of further structurally diverse 2′,3′-cyclopropane nucleosides is underway and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and spectroscopic characterization (IR, $^1H$, $^{13}C$ NMR, HRMS) of all key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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