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## Facile synthesis of 2-*C*-methyl-D-arabino- $\gamma$ -1,4-lactones and mechanism study

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**Abstract:** In our previous research on the synthesis of 3,5-di-*O*-benzoyl-2-*C*-methyl-D-arabino- $\gamma$ -lactone **4a**, the reaction mechanism of DMSO-mediated configuration inversion of C2 hydroxyl group in the lactone was ambiguous. As a follow-up to this research, we used <sup>18</sup>O-labelled H<sub>2</sub>O and DMSO to investigate the mechanism. It was surprisingly discovered that DMSO served as an oxygen donor to stereoselectively displace the leaving group, and was regenerated in the reaction. The protecting groups had no influence on the inversion, but would significantly affect the yield. We also disclosed another approach for the synthesis of **4a** without using the expensive Tf<sub>2</sub>O, which was more suitable for application.

**Key word:** nucleoside; 2-*C*-methyl-D-arabino- $\gamma$ -lactone; mechanism; SN2 reaction; <sup>18</sup>O-labelled DMSO.

2'-substituted nucleosides which displayed intriguing antiviral and antitumor activities had attracted strong research attention in recent years.<sup>1</sup> 2-substituted 2-*C*-methyl-D-ribo-1,4-lactones were a class of versatile intermediates for such nucleosides synthesis.<sup>2</sup> The most successful anti-HCV drug, sofosbuvir approved in 2013 was manufactured from

3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-*D*-ribo- $\gamma$ -lactone **A**,<sup>3</sup> and the 2'-chloro analog (IDX21437), currently under phase II clinical trial study was also prepared from a chloro lactone **B**,<sup>4</sup> shown in Figure 1. In addition, a growing number of other 2'-substituted nucleosides in clinical or earlier stages of research exhibited various biological activities and some of them were potentially to be new antiviral or antitumor agents.<sup>5</sup>

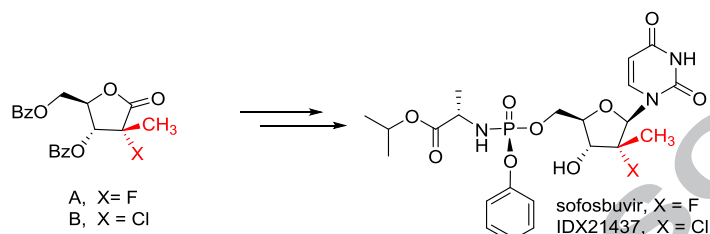
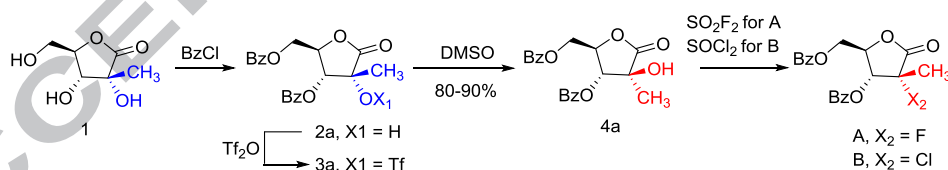


Figure 1. Anti-HCV nucleosides and their synthetic intermediates

Previously, we reported a simple and efficient route for the synthesis of intermediates **A** and **B** starting from 2-*C*-methyl-*D*-ribo- $\gamma$ -lactone **1**, which was a commercially available material, Scheme 1.<sup>6</sup> In this route, the most striking step was the highly selective and efficient DMSO-mediated  $\alpha$  to  $\beta$  inversion of the C2 hydroxyl group. The reaction went very fast and easily gave the product in at least 80% yield by crystallization. However, the inversion mechanism had not been studied. In order to find out the source of the oxygen atom of C2- $\beta$ -OH, herein we investigated the reactions using <sup>18</sup>O-labelled H<sub>2</sub>O and DMSO, respectively. A series of 2-*C*-methyl-*D*-ribo- $\gamma$ -lactones with different protecting groups was also synthesized. With these substrates, we further proved that the reaction didn't rely on the C3 and C5 protecting groups.

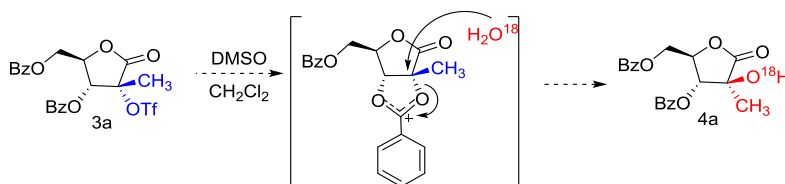


Scheme 1. our previously reported route for the synthesis of **A** and **B**

## Results and Discussion

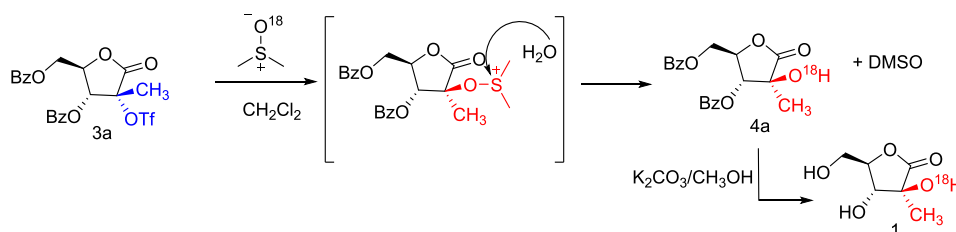
Since the C2- $\alpha$ -OH of intermediate **2a** was activated to be a good leaving group (OTf), neighboring group participation may occur if the leaving group departed. At the beginning, we speculated that H<sub>2</sub>O was the source of the C2- $\beta$ -OH of the product. To validate our assumption, the reaction was carried carefully in the presence of <sup>18</sup>O-labelled H<sub>2</sub>O. However, the result did not agree well with our original idea. The content rate of <sup>18</sup>O in **4a** was no more than 10% based on ESI-MS analyses (Figure S1

in supporting information), indicating that the reaction proceeded not mainly through this way, Figure 2.



**Figure 2.** The original proposed mechanism of H<sub>2</sub>O-mediated inversion

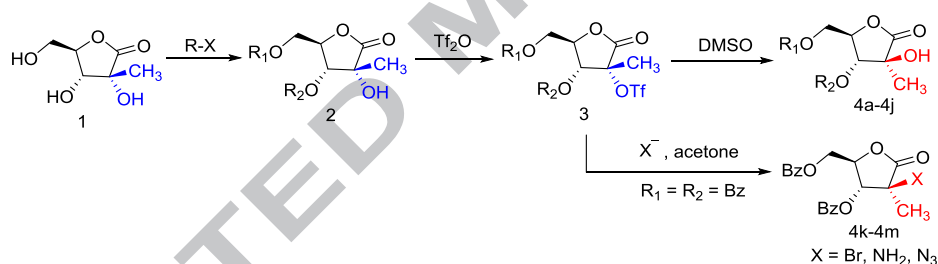
Then, we turned to investigate if DMSO took part in the reaction. <sup>18</sup>O-labelled DMSO could be synthesized from dimethylsulfur dibromide and [<sup>18</sup>O] H<sub>2</sub>O (97 atom% <sup>18</sup>O) in the presence of triethylamine.<sup>7</sup> The purity of prepared [<sup>18</sup>O] DMSO was about 81% roughly judged from the EI-MS. After [<sup>18</sup>O] DMSO was added into a dichloromethane solution of **3a**, it was curiously found that the reaction went much slower, and was completed over 12 hours at room temperature. Not too surprisingly, the [<sup>18</sup>O] was successfully incorporated in the product as well as the debenzoylated product with a high ratio of 74% (Figure S4 and S5 in supporting information). The result convincingly proved that the oxygen atom of C2-β-OH came from DMSO. In the reaction, DMSO likely served as a nucleophile that replaced the leaving group (OTf) in a S<sub>N</sub>2 manner. The transition state was highly unstable, and easily hydrolyzed to afford the C2-β-OH lactone and regenerate DMSO, Figure 3. In an early research, synthesis of bromohydrin using N-bromosuccinimide (NBS) and DMSO shared a similar mechanism with the present reaction.<sup>8</sup> This combination was also welcomed for the synthesis of α-acyloxy ketones and α-amino carbonyl compounds.<sup>9</sup> Swern oxidation was well-known, but Technically, DMSO did not participate in the reaction directly.<sup>10</sup> Indeed, by now there were almost no other cases of demonstrating DMSO or sulfoxide as an oxygen donor in substitution reaction, except a recent study of Zhang's group on the gold-catalyzed intramolecular redox reaction of sulfinyl alkynes.<sup>11</sup>



**Figure 3.** The possible mechanism of DMSO-mediated inversion

From the mechanism, this inversion reaction seemed to be independent of the protecting groups at C3-OH and C5-OH positions. In confirmation of it, we prepared a series of lactones which had different protecting groups at the two positions,

Scheme 2. Following the same procedure described in Scheme 1<sup>6</sup>, all products were successfully obtained with inverted C2 hydroxyl groups, shown in Table 1. For the acyl groups, the yield was similar among compounds **4a-4e**, and a little lower for compounds **4f-4g**. Notably, the inversion also occurred in the TBS and TIPDS containing substrates (Entry 8 and Entry 9), which strongly supported the proposed mechanism. In Entry 8-10, triflation of **2h-2j** did not go to completion, and the products **3h-3j** were found very labile during purification by column chromatography. As a result, compounds **4h-4j** were obtained in low yields. In contrast, the aroyl protecting triflates were much more stable, such as **3a** which could react with different nucleophiles (tetrabutyl ammonium bromide, aqueous ammonia, sodium azide) in acetone to give 2- $\alpha$ -methyl- $\beta$ -substituted arabino-1,4-lactones **4k-4m**. The two compounds (**4k**, X = Br and **4m**, X = N<sub>3</sub>) were obtained smoothly in about 80% yields with no need of chromatographical purification. As for **4l** (X = NH<sub>2</sub>), the yield was relatively lower (30%), which was largely due to lack of stability of the lactone ring or Bz protecting groups under basic condition. Such lactones were useful building blocks in the synthesis of novel 2'-substituted nucleosides.



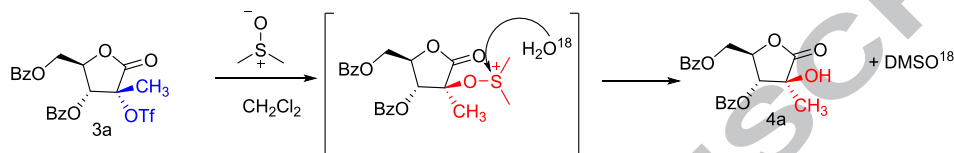
Scheme 2. Synthesis of lactones **4a-4j** and **4k-4m**

Table 1, the results of DMSO-mediated C2-OH inversion for different substrates.

Entry	Product	R <sub>1</sub>	R <sub>2</sub>	yield <sup>a</sup>
1	4a	Bz	Bz	73%
2	4b	4-Cl-Bz	4-Cl-Bz	84%
3	4c	4-Br-Bz	4-Br-Bz	79%
4	4d	3-MeO-Bz	3-MeO-Bz	77%
5	4e	4-Me-Bz	4-Me-Bz	80%
6	4f	Pivaloyl	Pivaloyl	45%
7	4g	furan-2-carbonyl	furan-2-carbonyl	53%
8	4h	TIPDS		10%
9	4i	TBS	TBS	15%
10	4j	Trt	Bz	15%

<sup>a</sup>: The yield was calculated from **2**

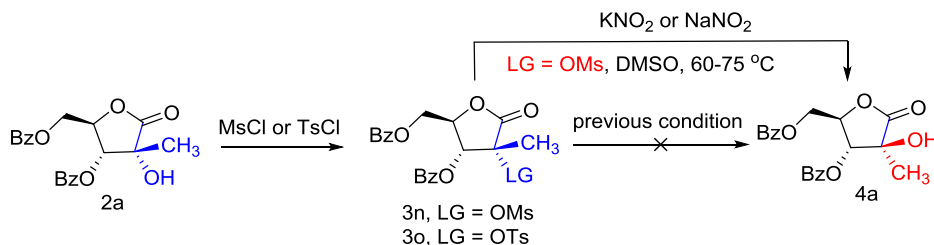
With the collecting results, the DMSO-mediated inversion mechanism became much clear. To further validate it, we performed the reactions with  $^{18}\text{O}$ -labelled  $\text{H}_2\text{O}$  (5 eq) and unlabelled DMSO (2 eq) again, and specifically analyzed the DMSO. It was found that [ $^{18}\text{O}$ ] DMSO was produced obviously, accounting for nearly 40% in the mixture (Figure S6 in supporting information). This result agreed well with the proposed mechanism, Figure 4. The newly generated [ $^{18}\text{O}$ ] DMSO would also take part in the reaction, so it was reasonable to observe a small amount of  $^{18}\text{O}$ -labelled **4a** in the aforementioned reaction using  $^{18}\text{O}$ -labelled  $\text{H}_2\text{O}$ .



**Figure 4.** The mechanistic course revealed by the generated DMSO

In our previous study, the DMSO-mediated conversion of C2-OH was achieved only through the triflate **3a**, instead of the mesylate **3n** or tosylate **3o** even under high temperature. This could be well explained on account of the significant difference in the leaving ability between OTf and OMs or OTs. However, because trifluoromethanesulfonic anhydride was expensive and not atom-economic, from an application perspective, this route was not suitable for large-scale production of pharmaceutical intermediates **A** or **B**.

It was important to note that the leaving groups of **3n** or **3o** were located at the  $\alpha$ -position of the lactone, so it was feasible to make the conversion by some nucleophilic reagent. After many attempts, we found that reaction of the mesylate **3n** with  $\text{KNO}_2$  or  $\text{NaNO}_2$  also gave the desired product, but no reaction was detected for **3o**, Scheme 3. We had screened the reaction conditions, such as the solvent, temperature, ratio of reagents and catalysts. Finally, DMSO was found to be the preferred solvent, and the result was better with  $\text{KNO}_2$  relative to  $\text{NaNO}_2$  in aspect of reaction time and impurities. In addition, catalytic amount of  $\text{Bu}_4\text{NI}$  would improve the yield to 70%, but still lower compared with the former approach.



**Scheme 3.** A new route for the synthesis of compound **4a**

## Conclusion

In the present research, using  $^{18}\text{O}$ -labelled  $\text{H}_2\text{O}$  and DMSO, we determined that DMSO acted as a nucleophile and played a crucial role in the synthesis of 2-*C*-methyl-*D*-arabino- $\gamma$ -lactones. The mechanism was special because DMSO participated in the reaction directly. We also synthesized some 2-substituted 2-*C*-methyl-*D*-arabino-1,4-lactones, which may be useful for the construction of novel nucleosides. In addition, a new approach for the preparation of **4a** avoid using the expensive  $\text{Tf}_2\text{O}$  was disclosed, and potentially to be applied for the scalable synthesis.

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### Supplementary data

Supplementary data (experimental procedures, spectral data, copies of  $^1\text{H}$ -NMR,  $^{13}\text{C}$ -NMR spectra) can be found in the supporting information.

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- A DMSO-participating reaction mechanism for the synthesis of 2-*C*-methyl-D-arabino- $\gamma$ -1,4-lactones
- The mechanism relying on the C2 leaving groups, but not the C3 or C5 protecting groups
- A novel approach suitable for the scalable preparation of 3,5-di-*O*-benzoyl-2-*C*-methyl-D-arabino- $\gamma$ -lactone **4a**

