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A neighboring group participation strategy: facile synthesis of 3,5-di-*O*-benzoyl-2-*C*-methyl-D-arabino-γ-lactone

Yuanchao Xie [a], Jian Zhang [b], Guanghui Tian [b], Mingshuo Xu [a], Tianwen Hu [a], Xiangrui Jiang [a], Jingshan Shen [a,*]

[a] Shanghai Institute of Materia Medica, Chinese Academy of Sciences (CAS), 555 Zuchongzhi Road, Shanghai 201203, PR China
[b] Topharman Shanghai Co., Ltd, 1088 Chuansha Road, Pudong, Shanghai 201209, PR China

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ABSTRACT

A simple and efficient approach for the synthesis of 3,5-di-*O*-benzoyl-2-*C*-methyl-D-arabino-γ-lactone through a neighboring group participation mechanism is reported. This compound could be a useful precursor for the synthesis of nucleoside antiviral agents.

3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-D-ribono-γ-lactone **1** is an important intermediate for the preparation of sofosbuvir **2**, a highly effective drug recently approved for treating chronic hepatitis C.[1] Some other nucleoside HCV NS5B polymerase inhibitors currently under preclinical or clinical studies are also synthesized through this intermediate.[2–6] By now, there have been several routes reported for preparing **1** (Fig. 1), but most of them are not industrially acceptable.[7–11]

Scheme 1 describes a route for the industrial production of **1**, characterized by two common starting materials, 2,3-*O*-isopropylidene-D-glyceraldehyde **L1** and 2-(triphenyl-phosphanylidene)-propionic acid ethyl ester **L2**.[8] In this route, there usually exist two byproducts, 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-D-arabino-γ-lactone **12** and 3,5-di-*O*-benzoyl-2-deoxy-2-chloro-2-*C*-methyl-D-ribono-γ-lactone **13** (their structures are shown in Scheme 6), which are difficult to be removed and have a great influence on the product quality.[12] 3,5-Di-*O*-benzoyl-2-*C*-methyl-D-arabino-γ-lactone **4**, prepared with the same starting materials can also be used to synthesize **1**. However, due to the low yield, the high cost and risk of diethylaminosulfurtrifluoride (DAST), its application is only restricted to small scale preparation in the lab.[7] For the synthesis of 2-*C*-methyl-D-arabino-γ-lactone **3**, an alternative method with L-erythronolactone as the starting material is also available, but also hardly applied to the synthesis of **1**.[13]

2-*C*-Methyl-D-ribono-γ-lactone **5** is a useful pharmaceutical intermediate in the synthesis of bioactive 2′-*C*-methyl nucleosides,[14,15] and could be easily prepared from D-glucose.[13] The only difference between lactones **3** and **5** is the steric configuration of the C2 hydroxyl or methyl group. We considered that if the configuration of the hydroxyl group was able to be changed from α to β, **4** would be obtained from **5**. To our knowledge, there is no relevant study about the conversion. Being interested in this new idea, we devoted ourselves to make the synthesis of **4** from **5**, and also exploit efficient methods for preparing **1** without using DAST.

The three hydroxyl groups of **5** present varied reactivity, which is as follows: C5-OH ⩾ C3-OH > C2-OH. Accordingly, selective benzoylation of C5 and C3 hydroxyl groups with benzoyl chloride efficiently gave **6** in a yield of 80%, Scheme 2. The following sulfonylation of **6** was performed with trifluoromethanesulfonic anhydride (Tf_2O), and the reaction went smoothly to afford **7**. When **7** was treated with *N*,*N*-dimethylformamide (DMF), a new product was rapidly generated, and subsequently identified as **9** by the ^1H NMR, ^{13}C NMR, and HRMS spectrum. This intermediate was stable in air or neutral water, but in the presence of bases, such as Et_3N, it could be easily converted to **4**.

We proposed a possible mechanism for the conversion of **7** to **4**, shown in Figure 2. In DMF, the C2-OTf of **7** should first leave to generate an α-carbonyl carbocation, which facilitated the occurrence of an atypical neighboring group participation. The C3

* Corresponding author. Tel.: +86 21 20231962.
E-mail address: shenjingshan@simm.ac.cn (J. Shen).

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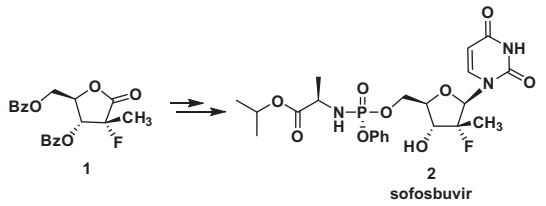


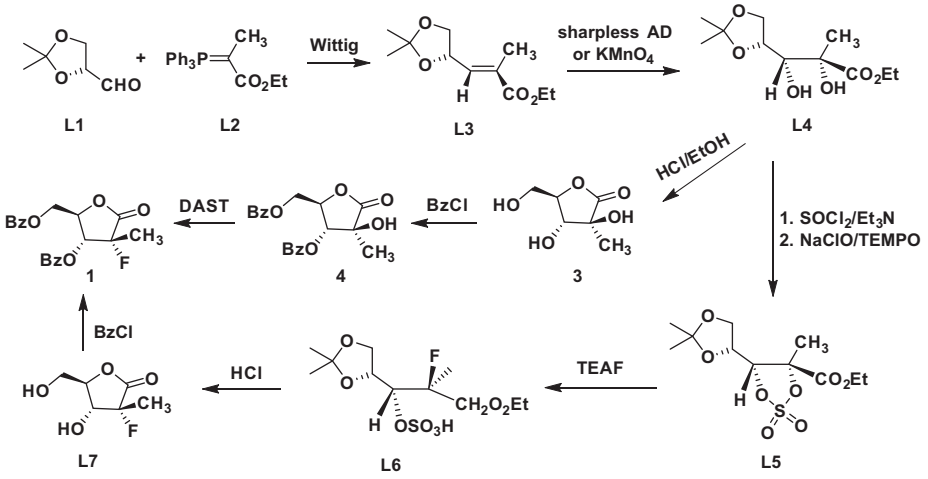
Figure 1. Structures of **1** and **2**.

benzoate carbonyl attack on the α-carbonyl carbocation led to the formation of an active intermediate **7-I**. DMF served as a nucleophilic reagent to attack the benzyl cation of **7-I**. The derived intermediate **7-II** was very unstable in the presence of water, and quickly hydrolyzed to afford **9**. An extension of the Vilsmeier–Haack reaction for the synthesis of formic acid esters was also achieved through the imidate ester.[16] The last step from **9** to **4** was hard to proceed without the addition of bases. The base, such as Et_3N would consume the produced formic acid, therefore promoting the reaction.

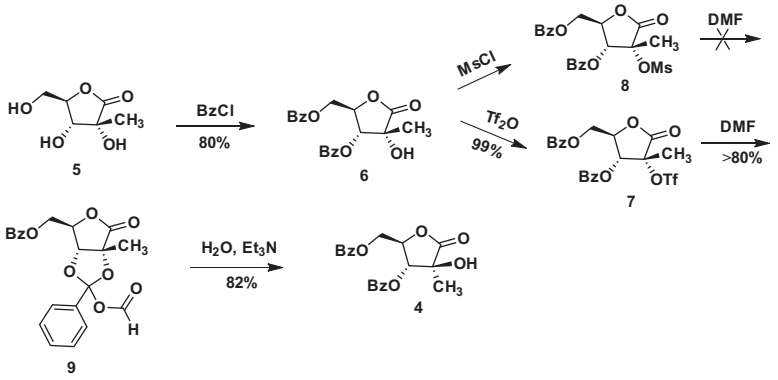
The participation of the C3 benzoate carbonyl group should take place after the departure of the C2 leaving group. In Scheme 2, we had found that stirring of **8** in a solution of DMF and water did not give any product, even under high temperature conditions. Since –OMs is a much weaker leaving group than –OTf, the departure of –OMs at the C2 position of **8** would not easily happen. As a result, the following neighboring group participation did not happen too. In order to validate that DMF served as a reactant in the reaction, *N*,*N*-dimethylacetamide (DMAC) was used to replace DMF (Scheme 3). As expected, intermediate **10** was produced.

To further explore the mechanism, we discovered that compound **4** could be also converted to intermediate **9** using the similar method, Scheme 4. Differently, reaction of compound **4** with Tf_2O or MsCl did not give any new product, but with acetyl chloride produced the corresponding ester. We supposed that the β hydroxyl group at C2 position of compound **4** could be sulfonated with Tf_2O, but the neighboring group participation happened fast due to the favorable steric configuration. Therefore, we added DMF in the reaction to 'catch' the active intermediate. When DMF was present in the reaction solvent, we successfully obtained intermediate **9** in a high yield. Following the previous procedure, compound **4** was also obtained.

Even though **4** could be easily synthesized, the complicated procedure in Scheme 2 was not suitable for a large-scale preparation. The reaction conditions still needed to be optimized. Similar to DMF, dimethyl sulfoxide (DMSO) is another polar aprotic solvent. When DMSO was chosen as the solvent, surprisingly, **7** was found to be fast converted to **4** in less than ten minutes without using any base. Importantly, **4** could be prepared in large quantities. The reaction was exothermic, and also gave a small amount of **11**. **11** was the elimination product which could be minimized within 1% by lowering the reaction temperature and diluting DMSO with dichloromethane.



Scheme 1. Industrial route for the synthesis of **1**.



Scheme 2. Synthesis of **3** from **15**.

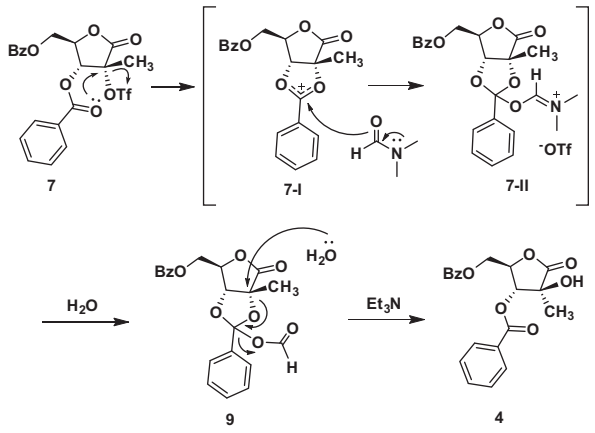
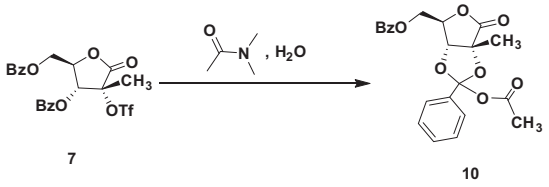
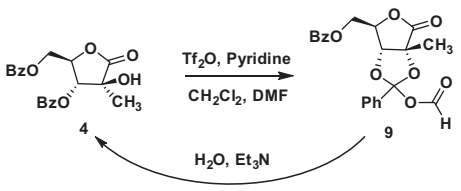


Figure 2. A proposed mechanism of DMF-mediated reaction.



Scheme 3. Synthesis of **20**.



Scheme 4. Synthesis of **9** from **4**.

Sulfuryl fluoride (SO_2F_2) is a common gas used for insect control and has been reported as an efficient dehydroxylating fluorinating agent of alcoholic compounds.[17,18] Previously, **4** was not conveniently prepared which restricted the application of this fluorinating agent. Our study enabled the synthesis of **1** using **4** and SO_2F_2 in the presence of triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$) and Et_3N, Scheme 5. The method was highly practicable and also applicable to large-scale production of the key medicinal intermediate.

Because **11** was an inevitable byproduct in the DMSO-mediated reaction, we thought that the synthesis of **4** was achieved via a similar mechanism (Fig. 3). In the presence of DMSO, the –OTf of **7** had a high ability to leave. With its departure, the participation of both C3 benzoate carbonyl and E2 elimination occurred, but the intramolecular participation was much more dominant than

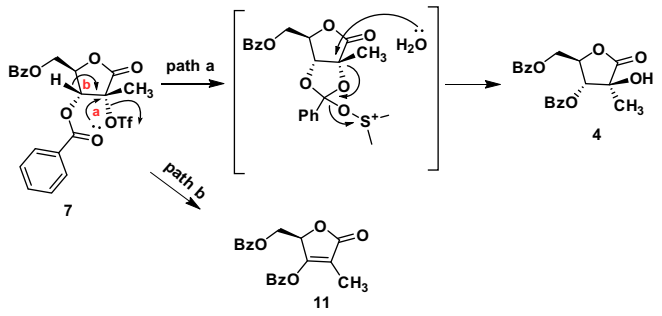
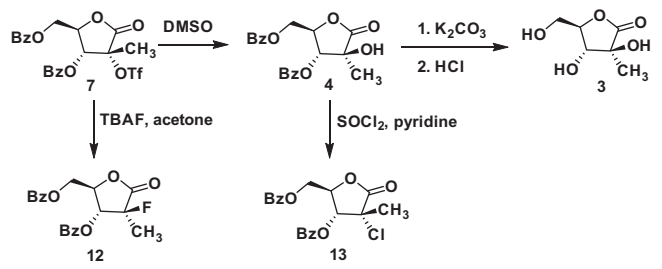


Figure 3. A proposed mechanism of DMSO-mediated reaction.

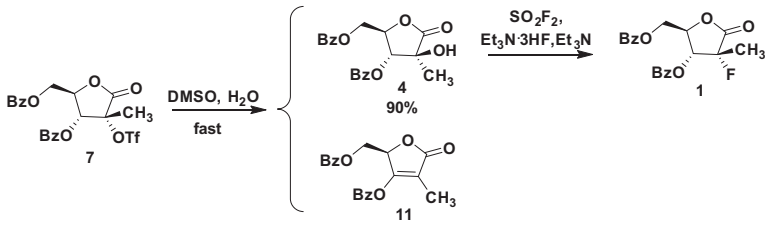


Scheme 6. Synthesis of **3**, **12,** and **13**.

the elimination. Different from the role of DMF in the above mechanism, DMSO served as a catalyst in the reaction. H_2O was an important nucleophile, attacking on the α-carbon to generate the β-OH of **4** at the C2 position.

Another three compounds were also conveniently synthesized from **7** for the first time, shown in Scheme 6. In previous studies, **3** was mainly prepared by the Kiliani reaction of sodiumcyanide with 2,3-*O*-isopropylidene-D-erythronolactone. Though the route is feasible, indeed it is hard to be carried out.[19] Our method enabled the efficient synthesis of **4**, which was an excellent material for the preparation of **3** by removing the benzoyl protecting groups with K_2CO_3, and **13** by chloridization with sulfoxide chloride. With respect to the stereoselective synthesis of diastereomer **12**, at present no pleasurable method is available. We successfully obtained **12** by reaction of **7** with tetrabutylammonium fluoride (TBAF) in a yield of 85%. The reaction not only proceeded fast and but only produced the single diastereomer.

In conclusion, we discovered a simple and efficient method for the synthesis of **4** from **5** by an atypical neighboring-group participation mechanism. DMSO was the preferred solvent and H_2O played an important role in the reaction. Using SO_2F_2 as the fluorating agent, we successfully synthesized **1** in a high yield from **4**. This route held a great potential in industrial application. Besides, several other important intermediates were also conveniently prepared for the first time. The methods in the study would



Scheme 5. Synthesis of **1** and **3** with improved methods.

be of great use in the preparation of various pharmaceutical intermediates.

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Supplementary data

Supplementary data (experimental procedures, NMR HRMS, and IR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.085.

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