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Total synthesis of remdesivir [☆]

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ABSTRACT

Remdesivir, the first drug approved by the FDA to treat COVID-19, is in high demand for patients infected with the SARS-CoV-2 virus. Herein, we report a facile approach minimizing the protecting group manipulations to afford remdesivir in good overall yield.

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Introduction

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created a devastating health crisis around the globe [1–6]. To combat this pandemic, effective and affordable treatments are still being urgently sought. In 2020, the FDA approved remdesivir (**1**, GS-5734) as the first drug for the treatment of COVID-19 [7,8], and subsequently, related molecules such as galidesivir (**2**), sofosbuvir (**3**), and molnupiravir (**4**) were also found to be effective (Fig. 1) [9].

Remdesivir (**1**), was initially developed by Gilead Sciences for the treatment of hepatitis C and Ebola virus infections [10,11]. However, the clinical trials against Ebola were not successful [12]. Remdesivir is a prodrug with good cell permeability and hydrolyzes inside the cell to release a nucleotide triphosphate that targets the key RNA dependent RNA polymerase (RdRp) enzyme responsible for viral replication.

The synthetic route developed by Gilead Sciences for the commercial production of remdesivir [10,11], involves protecting group manipulations of the sugar part during the synthesis,

providing an opportunity for further improvements. Conversion of D-ribose (**5**) to 2,3,5-tri-O-benzyl-D-ribonolactone (**6**) followed by addition of modified nucleobase 4-amino-7-iodopyrrolo[2,1-f][1–2,4]triazine (**7**) onto the lactone gave C-glycosylated product **8** in low yield (40%). After cyanation, all three benzyl groups were deprotected using BCl₃ and the two secondary alcohols of the resulting triol were subsequently protected as isopropylidene ketal **10**. Finally, introduction of phosphonate ester **11** to ketal **10** followed by hydrolysis of the ketal leads to the target compound remdesivir (**1**) (Scheme 1) [10]. Later, to improve the yield of the C-glycosylation reaction, expensive NdCl₃ was used as an additive in stoichiometric amounts, which improved the yield to 69% [13,14].

In view of the importance of this being the only FDA-approved drug for COVID-19 mitigation, we reasoned any improvement on the synthetic route would have a large impact on supplies. The opportunities we realized include (a) protecting group manipulations, viz, replacing the benzyl groups with those which could be introduced and removed by catalytic processes avoiding stoichiometric reagents, (b) avoiding the use of NdCl₃, and (c) achieving anomeric selectivity with better yields.

We planned our synthesis from D-ribonolactone (**12**), which is in the correct oxidation form to introduce the heterocyclic fragment at the anomeric carbon. It was also assumed that a bulky protecting group at the C-5 hydroxyl would enable better selectivity at the anomeric position. Thus, the primary hydroxyl group of

[☆] This work is dedicated to the memory of Dr. Surendar Reddy Bathula (Principal Scientist, CSIR-IICT), who lost the battle with COVID-19 infection after a fierce fight.

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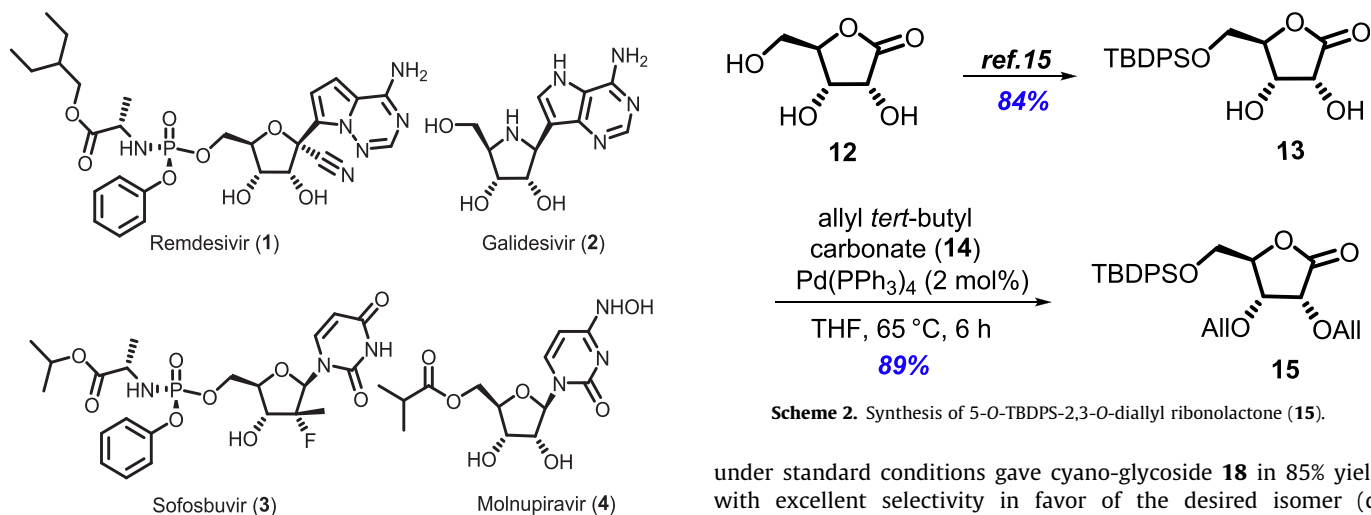


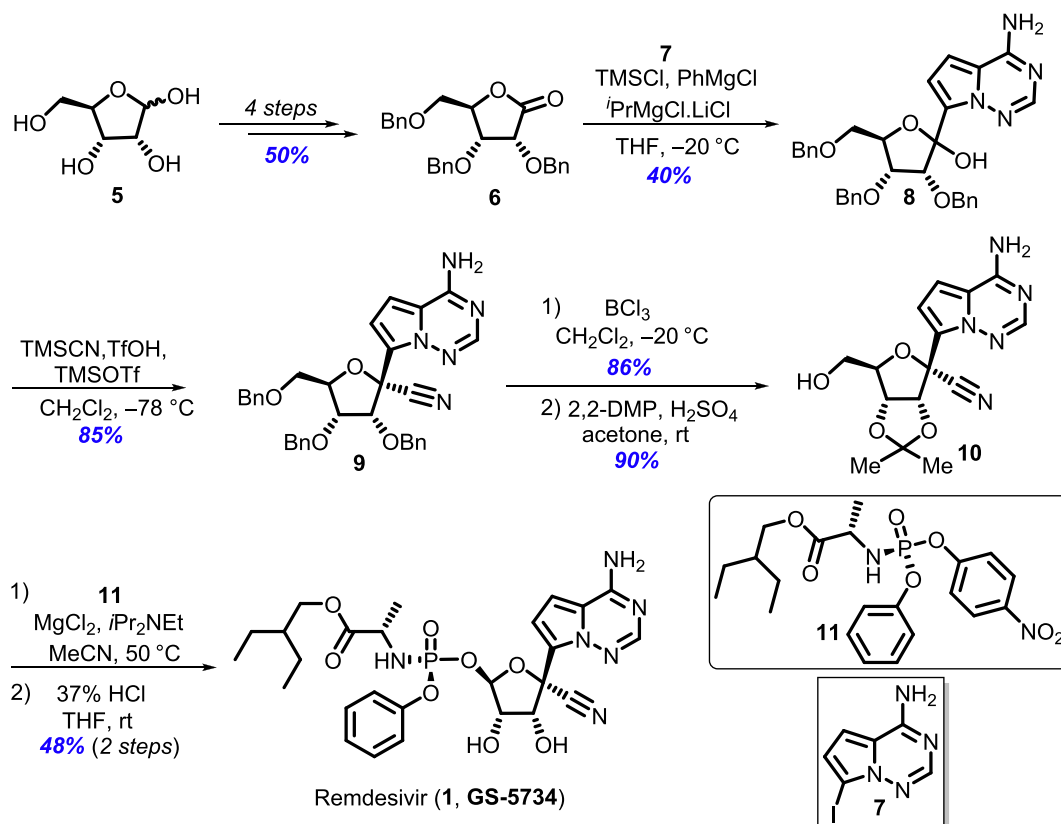
Fig. 1. Structures of remdesivir and other related antiviral drugs.

commercially available *D*-ribonolactone (12, can also be synthesized from *D*-ribose in one step) was silylated with *tert*-butyldiphenyl silyl (TBDPS) group to afford the corresponding silyl ether (13) in 84% yield [15]. Further protection of the remaining two secondary alcohols using allyl *tert*-butyl carbonate (14) in the presence of 2 mol% Pd(PPh₃)₄ furnished diallylated ribonolactone (15) in 89% yield (Scheme 2) [16].

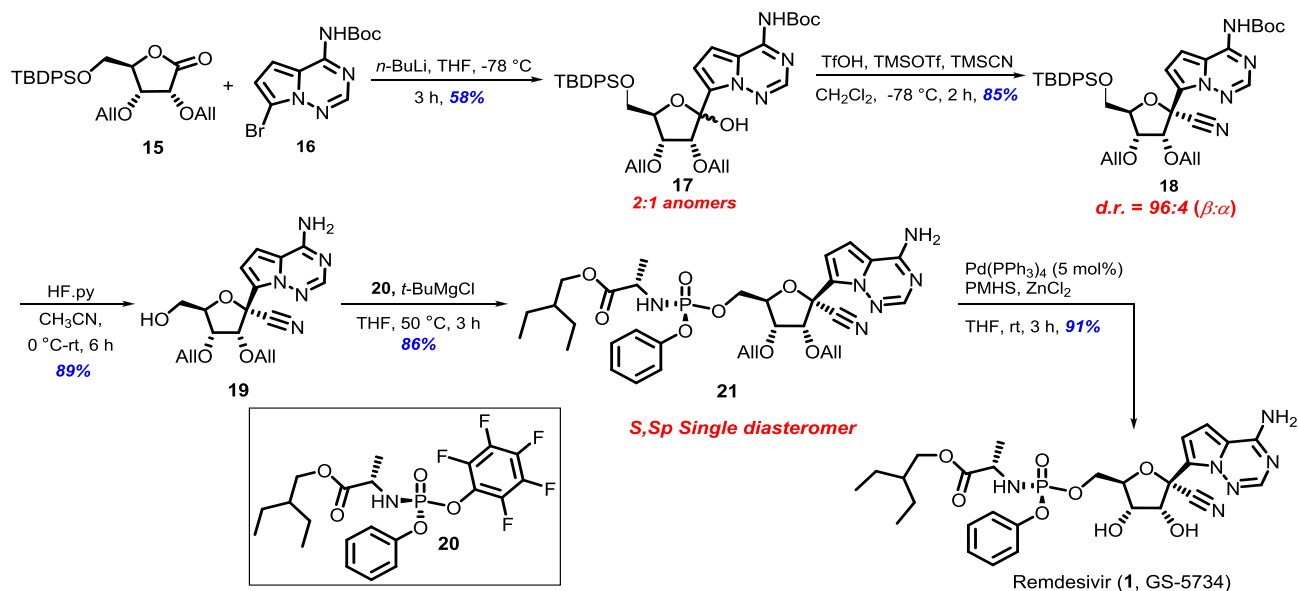
Next, lactone (15) was subjected to C-glycosylation [10,11,13,14,17] with the protected nucleobase *tert*-butyl(7-bromopyrrolo[2,1-*f*] [1-2,4] triazin-4-yl) carbamate (16) which in presence of *n*-BuLi provided an anomeric mixture (2:1) of C-glycosylated product (17) in 58% yield. The cyanation [10–11,13,18] of 17

under standard conditions gave cyano-glycoside (18) in 85% yield with excellent selectivity in favor of the desired isomer (d. r. = 96:4; β:α). To introduce the desired phosphonate on the primary hydroxyl group, deprotection of the silyl group and Boc group was achieved under HF, pyridine conditions in one-pot to afford amino-alcohol (19) in 89% yield [19]. The next task was to carry out the P-chiral phosphorylation, a key step in the synthesis of remdesivir [20]. Coupling of (19) with the known chiral pentafluoro-phosphoramidate (20) [21] in the presence of *t*-BuMgCl gave phosphoramidate ester (21) in 86% yield as a single diastereoisomer. Finally, removal of the diallyl groups from (21) was accomplished by Pd-catalyzed reductive deallylation, using a method developed by our group [22], to obtain the target molecule remdesivir (1) in 91% yield, whose spectral data were in good agreement with the reported data (Scheme 3).

In conclusion, a short synthetic approach to access remdesivir has been developed in seven longest linear steps (LLS) with 25%



Scheme 1. Gilread route for the synthesis of remdesivir (1, GS-5734).



Scheme 3. Total synthesis of remdesivir (1, GS-5734).

overall yield starting from *D*-ribose (12). The present strategy using a silyl/allyl protected sugar 15 has advantages including (i) avoiding the use of hazardous BCl₃ for benzyl deprotection, (ii) improvement in the coupling yield without any additive, (iii) use of catalytic methods for protection and deprotection of the allyl groups. We believe that the present approach is scalable and can be used for the synthesis of novel analogues in addition to remdesivir as anti-viral agents.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Srivari Chandrasekhar reports financial support was provided by Science and Engineering Research Board.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tetlet.2021.153590>.

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