Practical and Highly Efficient Synthesis of Remdesivir from GS-441524

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ABSTRACT: A three-step sequence for preparing remdesivir, an important anti-SARS-CoV-2 drug, is described. Employing N,N-dimethylformamide dimethyl acetal (DMF-DMA) as a protecting agent, this synthesis started from (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-furan-2-carbonitrile (GS-441524) and consisted of three reactions, including protection, phosphorylation, and deprotection. The advantages of this approach are as follows: (1) the protecting group could be removed under a mild deprotection condition, which avoided the generation of the degraded impurity; (2) high stereoselectivity was achieved in the phosphorylation reaction; (3) this synthesis could be performed successively without purification of intermediates. Moreover, the overall yield of this approach on a gram scale could be up to 85% with an excellent purity of 99.4% analyzed by high-performance liquid chromatography (HPLC).

INTRODUCTION

Remdesivir (1), an inhibitor of RNA-dependent RNA polymerase of the SARS-CoV-2 virus developed by Gilead Sciences,1−4 is the first drug to treat hospitalized patients with COVID-19.5−7 Recent study showed that the risk of hospitalization or death of COVID-19 outpatients with high risk could be reduced by 87% after receiving a three-day course of remdesivir.8 Moreover, the FDA authorized its emergency use in Covid-19 nonhospitalized patients based on the encouraging result of the clinical trial (NCT04501952).9 Therefore, enough supply of remdesivir is crucial to conquer the global health crisis caused by SARS-CoV-2.

Structurally, remdesivir is a monophosphoramidate prodrug of a C-nucleoside analogue GS-441524. Given the great clinical demand, the synthesis of this antiviral prodrug has attracted chemists’ interest.10−15 The gram-scale synthesis of remdesivir from 2,3,5-tri-O-benzyl-D-ribonolactone (6) was reported by Gilead’s chemists (Scheme 1) and consisted of a six-step sequence.16 The low 48% overall yield of the last two reactions, including the phosphorylization and the deprotection, might be the Achilles’ heel for the sufficient supply of remdesivir. Researchers have been studying the problem to address it. Recently, Zhang’s group reported the stereoselective synthesis of remdesivir by the coupling of phosphoramidoyl chloride (7) and acetonide-protected nucleoside 4 catalyzed by chiral imidazole derivatives with 73% overall yield (Scheme 2), which avoided the preparation of enantiomerically pure phosphorylated agent.17 Soon after, Hung’s group reported a similar approach to remdesivir with 70% yield by a one-pot method.18 Nonetheless, the instability of 7 posed a challenge to its purification and storage according to the study of phosphoramidate derivatives reported previously,19 which might limit its application for commercial production.

As far as our group was concerned, intensive efforts were devoted to investigate those two reactions. In our study, methylmagnesium chloride (MeMgCl) could be used instead of MgCl2 and DIPEA in the phosphorylation reaction; moreover, the p-nitrophenylphosphoramidate 3 could be replaced with the pentafluorophenyl phosphoramidate 10 that had been used in the preparation of remdesivir in the literature.20,21 In the deprotection of acetonide, many reaction conditions, such as the concentration of hydrochloric acid, the solvents used, and the temperature, were screened, but no better result was obtained. Meanwhile, we found that the monophosphate impurity 8 was gradually produced before the compound 2 was consumed.
completely, which resulted from the hydrolysis of the phosphoramidate moiety of 1 in the presence of hydrochloric acid. Clearly, the side reaction caused by the harsh reaction condition resulted in the moderate 69% yield of this reaction. Therefore, a suitable protecting group at 2′,3′-dihydroxyls is key to achieve the high-efficient synthesis of remdesivir from GS-441524.

According to our previous study, N,N-dimethylformamide dimethyl acetal (DMF-DMA) is a good protecting agent that could mask 2′,3′-dihydroxyls and C4-amine of cytidine selectively to facilitate the esterification at 5′-hydroxyl group,
Furthermore, the formed dimethylaminomethylene (DMAM) group at the 2′,3′-dihydroxyls could be deprotected easily in the protic solvents, such as ethanol and isopropanol. Hence, employing DMF-DMA as a protecting agent, instead of 2,2-dimethoxypropane, might avoid the production of the by-product 8. Herein, we developed a highly efficient approach for preparing remdesivir from GS-441524 (Scheme 3).

**RESULTS AND DISCUSSION**

The study started with the synthesis of the DMAM-protected nucleoside analogue 9. This intermediate was synthesized from the compound 5 with a quantitative yield in the presence of DMF-DMA (4.0 equiv.) in pyridine at 25 °C for 18 h. In view of the instability of the DMAM group at the 2′,3′-dihydroxyls, the progress of this reaction was indicated by the consumption of the starting material (monitored by thin layer chromatography (TLC)); to prepare the TLC sample, the reaction mixture was added to methanol and the resulting solution was used as the sample). Meanwhile, compound 9 was used in the next step directly after concentration under reduced pressure. Subsequently, using methylmagnesium chloride (MeMgCl) (1.5 equiv.) as the deprotonating agent, the 9 was reacted with 10 (1.1 equiv.) to furnish the unstable intermediate 11. When the phosphorylation reaction was quenched with saturated NH₄Cl solution, the DMAM group at 2′,3′-dihydroxyls of the compound 11 was concomitantly decomposed to provide the stable intermediate 12 with an 85% isolated yield, and the hydrolyzed impurity 8 was not observed by TLC analysis. With 12 in hand, the deprotection of the DMAM group at C6-amine was performed with AcOH (20 equiv.) in alcohol for 18 h at 50 °C and the product was afforded in 90% yield by chromatography purification. Overall, the yield of product 1 prepared from compound 5 was up to 76%, which was much higher than that of 43% reported by Gilead.

Encouraged by the favorable outcome, we tried to optimize this new approach. Given the risk of the ester-transfer reaction in the amino acid ester moiety of compound 12 or 1 in ethanol, the deprotection reaction was conducted in isopropanol with lower reactivity, which proceeded smoothly as well and provided nearly the same result as using ethanol as the solvent. To simplify this synthesis, we quenched the phosphorylation reaction with a solution of AcOH (20 equiv.) in THF or isopropanol and the resulting mixture was warmed to 50 °C to remove the DMAM protection; however, this reaction progressed much slower than that using the pure compound 12 as the starting material. We speculated that the existence of magnesium ion (Mg²⁺) might affect the speed of the deprotection reaction. According to this hypothesis, the reaction mixture was extracted with ethyl acetate (EA) to remove Mg²⁺ after the phosphorylation reaction was quenched with saturated aq. NH₄Cl solution. As expected, the reaction of crude 12 obtained from the workup of extraction and concentration with AcOH was continued for 18 h in isopropanol. Additionally, the protected nucleoside 9, because of its instability, was directly subjected to the next reaction after simple workup. Therefore, this synthesis could be conducted successively, which not only avoided the purification of intermediates but also greatly improved the synthetic efficiency.

Having the simplified synthesis in hand, the optimizations of reaction conditions were investigated. Because of the stability of product 1 and its isomer 13 in the conditions of the deprotection reaction, the ratio of two P-chiral isomers could be used to indicate the stereoselectivity of the phosphorylation reaction. To reduce the solvent type in the synthesis, we tried to replace pyridine with THF in the first step. The condensation reaction of compound 5 and DMF-DMA was performed in THF at 60 °C for 3 h. When the starting material 5 was consumed completely, the solvent was removed under reduced pressure and the resultant mixture was processed by solvent exchange with toluene once to remove the unreacted DMF-DMA and the methanol generated from the condensation reaction. The coupling of the obtained crude 9 and 10 (1.2 equiv.) in the presence of MeMgCl (1.5 equiv.) was conducted at −10 °C for 2 h. After simple posttreatment, the obtained 12 was used with AcOH in the deprotection reaction at 50 °C for 18 h. Disappointedly, this attempt provided the final product 1 with much lower d.r. (Table 1, entry 2, 36/1 d.r.) than that using pyridine as the solvent of the condensation reaction (entry 1, 161/1 d.r.). The obvious decrease in the stereoselectivity indicated that the remained pyridine in the crude 9 might exert a special effect on the phosphorylation reaction of 10 and 9. Subsequently, 1 equiv. of pyridine was added to the phosphorylation reaction but the ratio of 1 and 13 was only
feasibility for the synthesis of remdesivir on the gram-scale. In a 5 reaction was finished in only 2 h.

improved to 783/1 with comparable LCAP of 94.1%, and the (entry 5). Surprisingly, the stereoselectivity was significantly chloride ( entry 1). Notably, the lower reaction temperature resulted in the lower reactivity. In addition, using 1 compound needed to be studied further. Although pyridine was an infrequently used solvent, it was still chosen as the solvent of the condensation reaction in consideration of its benefit to the isopropanol to furnish product 1 with 85% yield in 99.9:0.1 d.r. by chromatography purification.

### CONCLUSIONS

In summary, facilitated by DMF-DMA as the protecting agent, a highly efficient synthesis of remdesivir from GS-441524 was developed. Compared to the 43% overall yield reported in the literature, this method provided remdesivir with 85% overall yield through a three-step sequence. Moreover, this synthesis could avoid the generation of the degraded impurity and be conducted successively without purification of intermediates. These advantages improved the synthetic efficiency of remdesivir greatly.

### EXPERIMENTAL SECTION

#### General Information.

Combustion analysis was performed on a Carlo Erba 1106 elemental analyzer. 1H, 13C, 15N, and 31P NMR spectra were recorded on a Bruker Avance III 500 MHz spectrometer. Mass spectra were measured on a Finnigan LTQ mass spectrometer. Reagents and solvents, such as DMF-DMA, 3.0 M methyl magnesium chloride solution in tetrahydrofuran (THF), 1.7 M t-butyllithium solution in tetrahydrofuran, pyridine, THF, isopropanol, acetic acid, and ethyl acetate, were commercially available. H NMR, 13C(1H) NMR, and 31P NMR spectra were recorded on a Bruker 500 Hz instrument. Low-resolution mass spectra were obtained from Topharman Shanghai Co., Ltd. Other chemical reagents and solvents, such as DMF-DMA, 3.0 M methyl magnesium chloride solution in tetrahydrofuran (THF), 1.7 M t-butyllithium solution in tetrahydrofuran, pyridine, THF, isopropanol, acetic acid, and ethyl acetate, were commercially available. H NMR, 13C(1H) NMR, and 31P NMR spectra were recorded on a Bruker Avance III 500 MHz spectrometer. Mass spectra were measured on a Finnigan LTQ mass spectrometer. Reagents and solvents, such as DMF-DMA, 3.0 M methyl magnesium chloride solution in tetrahydrofuran (THF), 1.7 M t-butyllithium solution in tetrahydrofuran, pyridine, THF, isopropanol, acetic acid, and ethyl acetate, were commercially available. H NMR, 13C(1H) NMR, and 31P NMR spectra were recorded on a Bruker Avance III 500 MHz spectrometer. Mass spectra were measured on a Finnigan LTQ mass spectrometer.

### Table 1. Condition Optimization of the Condensation Reaction (I) and the Phosphorylation Reaction (II)\(^a\)

| entry | solvent | pyridine (equiv.) | deprotonating agent | T (°C) | T (h) | LCAP of 1 (%)\(^e\) | d.r. ratio (1/13)
|-------|---------|------------------|-------------------|--------|------|----------------|----------------|
| 1     | pyridine\(^b\) |                   | MeMgCl            | −10    | 2    | 96.7           | 161/1          |
| 2     | THF\(^c\) |                   | MeMgCl            | −10    | 2    | 93.0           | 36/1           |
| 3     | THF\(^d\) | 1.0              | MeMgCl            | −10    | 2    | 92.7           | 42/1           |
| 4     | pyridine\(^b\) |                   | MeMgCl            | −20    | 2    | 92.9           | 232/1          |
| 5     | pyridine\(^b\) |                   | t-BuMgCl         | −20    | 2    | 94.1           | 783/1          |

\(^a\)General procedure: the condensation reaction of compound 5 (500 mg, 1.72 mmol, 1 equiv.) and DMF-DMA (820 mg, 6.88 mmol, 4.0 equiv.) afforded compound 9. The coupling of the obtained crude 9 and compound 10 (1.02 g, 2.06 mmol, 1 equiv.) was performed in the presence of the deprotonating agent (2.58 mmol, 1.5 equiv.). When crude 9 disappeared, the phosphorylation was quenched with aq. NH₄Cl solution and provided compound 12. After simple aftertreatment, crude 12 was subjected to the solution of acetic acid (2.06 g, 34.4 mmol, 20.0 equiv.). Finally, product 1 was obtained. The condensation was conducted at 25 °C for 3 h. The condensation was conducted at 60 °C for 3 h. LCAP: the area (%) of compound 1 determined by HPLC in the final reaction mixture. The d.r. ratio was determined by HPLC.
1-yl)methoxy)(phenoxy)phosphoryl)-[1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxy-tetrahydrofuran-2-yl)methyl Phe-

(1.2 g, 3.6 mmol) and racemic

1H NMR (500 MHz, DMSO) δ 8.94 (s, 1H), 8.15 (s, 1H), 7.37–7.32 (m, 2H), 7.21–7.14 (m, 3H), 6.94 (d, J = 4.5 Hz, 1H), 6.80 (d, J = 4.5 Hz, 1H), 6.33 (d, J = 6.2 Hz, 1H), 6.02 (d, J = 13.0, 10.1 Hz, 1H), 5.40 (d, J = 5.6 Hz, 1H), 4.72–4.66 (m, 1H), 4.29–4.21 (m, 2H), 4.10 (dt, J = 12.3, 6.2 Hz, 1H), 3.99 (dd, J = 10.9, 5.6 Hz, 1H), 3.95 (dd, J = 10.9, 5.9 Hz, 1H), 3.86 (dd, J = 10.9, 5.8 Hz, 1H), 3.84–3.77 (m, 1H), 3.24 (s, 3H), 3.18 (s, 3H), 1.45–1.37 (m, 1H), 1.28–1.18 (m, 7H), 0.79 (t, J = 7.5 Hz, 6H). 13C[1H] NMR (126 MHz, DMSO) δ 173.2, 173.2, 160.2, 158.1, 150.8, 150.7, 147.4, 129.6, 124.5, 124.3, 122.6, 120.1, 121.0, 116.8, 111.6, 101.8, 82.4, 82.4, 78.8, 74.0, 70.0, 66.1, 65.5, 65.4, 47.9, 47.1, 41.3, 34.9, 22.6, 22.5, 19.8, 19.7, 10.8, 10.7. 31P NMR (202 MHz, DMSO) δ 3.68. HRMS (ESI) m/z: [M + H]^+ calcd for C_{13}H_{19}N_5O_7P^+ 658.2749, found 658.2739.

2-Ethylbutyl ((S)-((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)-l-alaninate (13). AcOH (1.8 g, 30.0 mmol) was added to the solution of 12 (1.0 g, 1.5 mmol) in ethyl acetate (15.0 mL) in one portion at 25 °C. After that, the reaction mixture was stirred at 25 °C for 18 h under a N_2 atmosphere. When TLC showed that 12 was consumed completely, the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate then washed with saturated aq. NaHCO_3 solution, water and brine. The obtained organic phase was dried over Na_2SO_4 and evaporated. The crude product was purified by chromatography purification using a gradient elution by solution containing CH_2Cl_2 and methanol (the ratio of CH_2Cl_2 and methanol was ranged from 80/1 to 30/1) to afford 12 with 97.5% purity as a foamy solid (1.9 g, 85% yield). 1H NMR (500 MHz, DMSO) δ 8.94 (s, 1H), 8.15 (s, 1H), 7.37–7.32 (m, 2H), 7.21–7.14 (m, 3H), 6.94 (d, J = 4.5 Hz, 1H), 6.80 (d, J = 4.5 Hz, 1H), 6.33 (d, J = 6.2 Hz, 1H), 6.02 (d, J = 13.0, 10.1 Hz, 1H), 5.40 (d, J = 5.6 Hz, 1H), 4.72–4.66 (m, 1H), 4.29–4.21 (m, 2H), 4.10 (dt, J = 12.3, 6.2 Hz, 1H), 3.99 (dd, J = 10.9, 5.6 Hz, 1H), 3.95 (dd, J = 10.9, 5.9 Hz, 1H), 3.86 (dd, J = 10.9, 5.8 Hz, 1H), 3.84–3.77 (m, 1H), 3.24 (s, 3H), 3.18 (s, 3H), 1.45–1.37 (m, 1H), 1.28–1.18 (m, 7H), 0.79 (t, J = 7.5 Hz, 6H). 13C[1H] NMR (126 MHz, DMSO) δ 173.2, 173.2, 160.2, 158.1, 150.8, 150.7, 147.4, 129.6, 124.5, 124.3, 122.6, 120.1, 121.0, 116.8, 111.6, 101.8, 82.4, 82.4, 78.8, 74.0, 70.0, 66.1, 65.5, 65.4, 47.9, 47.1, 41.3, 34.9, 22.6, 22.5, 19.8, 19.7, 10.8, 10.7. 31P NMR (202 MHz, DMSO) δ 3.68. HRMS (ESI) m/z: [M + H]^+ calcd for C_{13}H_{19}N_5O_7P^+ 658.2749, found 658.2739.
**Preparation of 1 from 5 without Purification of Intermediates on a 5 g Scale.** To a suspension of 5 (5.0 g, 17.2 mmol) in pyridine (20.0 mL) was added DMF-DMA (8.2 g, 68.8 mmol). The reaction mixture was stirred for 6 h at 25 °C. When the condensation reaction of 5 and DMF-DMA was finished, pyridine was removed under reduced pressure. The obtained 9 and 10 (10.2 g, 20.6 mmol) were dissolved in THF (50.0 mL). When the resultant solution was cooled to −20 °C, 1.7 M t-butylmagnesium chloride solution in tetrahydrofuran (15.2 mL, 25.8 °C) was added dropwise under a N₂ atmosphere and the temperature was kept under −15 °C. When the coupling reaction of 9 and 10 was completed, the reaction mixture was poured into saturated aq. NH₄Cl solution. After that, the resultant solution was concentrated and then redissolved in ethyl acetate. The obtained solution was washed with water and brine orderly, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column using the mixture of CH₂Cl₂ and methanol (CH₂Cl₂: methanol = 50:1−20:1) to give 1 with 99.4% purity as a foamy solid (8.8 g, 85% yield).

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c02835.

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