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Mini-Review

Evolution of the Synthesis of Remdesivir. Classical Approaches and Most Recent Advances

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Cite This: https://doi.org/10.1021/acsomega.1c03082

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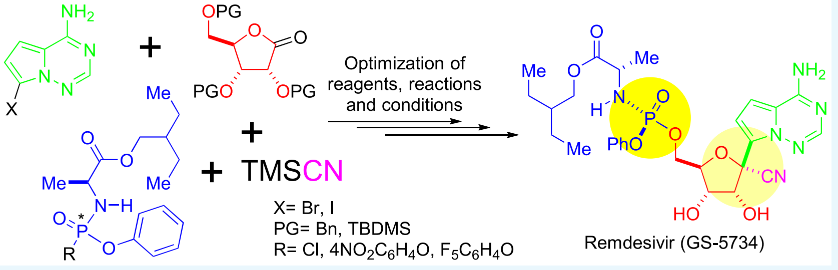


ABSTRACT: The broad-spectrum antiviral Remdesivir, a monophosphate nucleoside analogue prodrug (ProTide), was repurposed. In May 2020, it received emergency approval by the FDA, being the first drug approved to fight the new coronavirus (COVID-19) disease which targets the virus directly. The main synthetic strategies toward Remdesivir, and their relevant modifications, are presented and discussed, to provide a panoramic view of the state-of-the-art and the more important advances in this field. Recent progress, proposed improvements, and uses of novel technologies for the synthetic sequence are also detailed.

1. INTRODUCTION

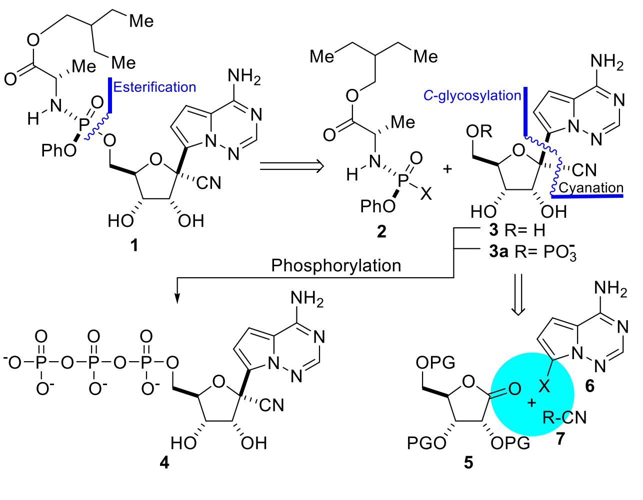
In 2012, Cho et al. discovered that C-nucleotide mimics containing 1′-substituted 4-aza-7,9-dideazaadenosine are analogues of ATP with potent activity against RNA viruses.[1] The concomitant outbreak of the Ebola epidemics of 2014 prompted the development of new specific antivirals.[2]

The incorporation of phosphate groups into drugs is problematic, due to their high metabolic lability and charged nature, which hinder membrane crossing. Therefore, they are synthesized as prodrugs, such as phosphoramidates, where metabolically labile protecting groups replace the acidic oxygens of the phosphate. This results in compounds which are uncharged, more lipophilic, and less prone to phosphoesterase-mediated hydrolysis; they can be converted into the bioactive forms inside the cells.

Remdesivir (**1**, Scheme 1), a phosphoramidate prodrug nucleotide (ProTide), is a result of this approach. Developed by Gilead Sciences Inc. as GS-5734 since 2009 to fight the hepatitis C virus, the drug was later claimed as active against the Ebola virus and others, including those causing SARS and MERS, as well as against the Hendra, Junin, Lassa, Nipah, Marburg, Zika, and respiratory syncytial viruses.[3]

In vitro, **1** blocks virus infection at low micromolar concentration with high selectivity index. These bioactivity data and the preexistence of safety and clinical data eased FDA approval of **1** as a repurposed drug for treatment of severe COVID-19 cases, being the first approved treatment that directly targets the virus.[4]

Scheme 1. Retrosynthetic Analysis of Remdesivir (1), Intermediate 3 (GS-441524), and Bioactive Form 4 (GS-443902)



Received: June 11, 2021
Accepted: July 14, 2021

The pharmaceutical use of **1** instead of compound **3** improves the potency and efficacy of the treatment. The ProTide **1** can enter the cells (passive diffusion or via the nucleoside transporter), while the permeabilities of **3** and its monophosphate derivative GS-704277 (**3a**) are much lower. Inside the cells, **1** undergoes an esterase-mediated *in vivo* bioactivation, ultimately leading to the monophosphate **3a**. Phosphate loss under the action of phosphatase or nucleosidase gives the adenosine analogue GS-441524 (**3**), which has shown *in vivo* efficacy in a veterinary setting. In the cells, the monophosphate **3a** (a species which avoids the rate-limiting first phosphorylation step) can also be in equilibrium with the nucleoside **3**.

Then, a kinase-mediated phosphorylation yields the active form, the triphosphate **4** (GS-443902).[5] The latter confuses the RNA-dependent viral RNA polymerase,[6] decreasing viral RNA production;[7] when incorporated into viral RNA, it compromises UTP uptake in the first transcription, causing chain termination in the second transcription.

Remdesivir has low aqueous solubility and suffers fast first pass clearance in the liver. Therefore, it is available in a parenteral dosage form (Veklury), which contains sodium β-cyclodextrin sulfobutyl ether. However, since the SARS-CoV-2 virus infects multiple tissues, its parenteral use ensures higher plasmatic drug levels, improving its exposure and distribution among the target tissues.

2. SYNTHESIS OF THE KEY FRAGMENTS OF REMDESIVIR

Retrosynthetically, **1** can be disconnected into an activated phosphoramidate (**2**) and an adenosine mimic (**3**), which in turn can be further retrosynthetically disassembled to unveil an activated pyrrolo[2,1-*f*][1,2,4]triazin-4-amine (**6**) along with a suitably protected D-ribono-1,4-lactone precursor (**5**) and a cyanide source (**7**).

2.1. Pyrrolo[2,1-*f*][1,2,4]triazine-4-amine Core. Klein et al. (Scheme 2) provided the first concise and efficient approach[8] to this long known heterocycle (**12**).[9] 2-Formylpyrrole (**8**) was treated with hydroxylamine-*O*-sulfonic acid (HOSA) in aqueous KOH to give 1-amino-2-pyrrolonitrile (**10**) in 43% yield, along with 37% yield of 2-pyrrolonitrile (**11**). Next, **10** was cyclocondensed with formamidine acetate in refluxing ethanol under mild basic conditions (K_2CO_3), furnishing **12** in 66% yield.

However, for the synthesis of Remdesivir, **12** was prepared from 2,5-dimethoxytetrahydrofuran (**15**) and *tert*-butyl carbazate in dioxane at 90 °C under HCl catalysis to give **16** (59% yield).[10] This was exposed to chlorosulfonyl isocyanate in MeCN, resulting in 67% yield of nitrile **17** after reaction with DMF, which converted the *N*-chlorosulfonyl amide intermediate into a nitrile moiety.

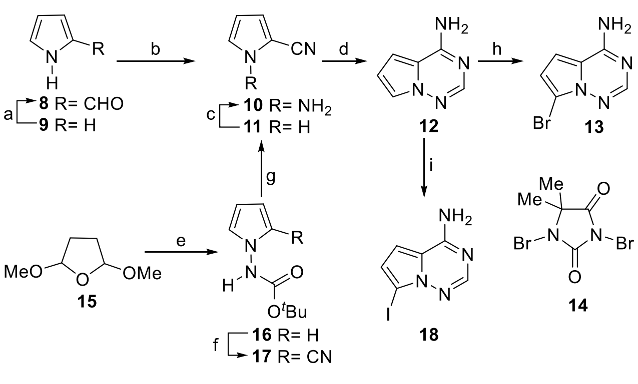
Acid-mediated deprotection of **17** with HCl in dioxane gave an improved yield of **10** (85%),[11] which in turn delivered **12** in 81% yield in three crops, when the cyclocondensation with formamidine acetate was performed using potassium phosphate as base (31% overall yield from **15**).

Finally, the heterocycle was selectively brominated with 1,3-dibromo-5,5-dimethylhydantoin (**14**) in DMF to give **13** in 90% yield.[12] This heterocycle was employed for the first-generation synthesis of Remdesivir. Other Remdesivir generations and their modifications[13] used **18**, obtained in 95% yield by iodination of **12** with *N*-iodosuccinimide (NIS).[14] Alternative procedures toward **18** employed ICl (90% yield)[15] and molecular iodine (85% yield)[16] as iodinating reagents.

Remdesivir sparked renewed interest in the synthesis of **12**. In an improved alternative (39% overall yield),[17] the reaction of **8** and HOSA with $NaHCO_3$ afforded **11** (92% yield), and **10** was obtained in 71% yield by *N*-amination with NaH and $ClNH_2$. However, the approach of Snead et al.[18] is the best one. It is based on a one-pot oxidative Vilsmeier cascade from pyrrole (**9**) to afford **10** through the intermediacy of **8** and further cyclocondensation of **10** to **12** with formamidine acetate (59% overall yield).

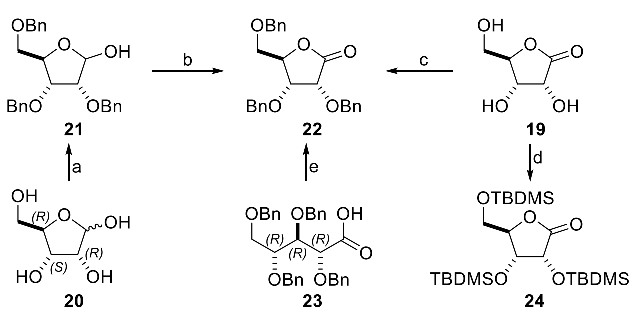
2.2. D-Ribonolactone Moiety. The D-ribono-1,4-lactone (**19**) derivative **22** used for the first-generation synthesis of Remdesivir was obtained employing the Albright−Goldman oxidation (Ac_2O, DMSO) of lactol **21** (96% yield),[19] which in turn can be accessed in high yield from D-ribose (**20**). For the second-generation synthesis, lactone **22** was prepared (~95% yield), using a TEMPO-catalyzed NaClO oxidation (Scheme 3).[20]

Scheme 2



[a]Reagents and conditions: (a) **9**, $POCl_3$, DMF, 20 °C, 1 h; (b) **8**, NH_2OH, Ac_2O, Py, H_2O, 90 °C, 16 h (**11**, 93% from **8**) or **9**, HOSA, KOH, H_2O (**10**, 43%; **11**, 37%) or **9**, HOSA, $NaHCO_3$, H_2O, rt, 1 h (**12**, 92%); (c) NaH, $ClNH_2$ (71%); (d) HC(=NH)NH_2·AcOH, K_2CO_3, EtOH, reflux (66%) or HC(=NH)NH_2·AcOH, K_3PO_4, EtOH, reflux, 18 h (81%); (e) *t*-BuOC(O)$NHNH_2$, HCl, dioxane, 90°C (59%); (f) 1. $ClSO_2NCO$, MeCN, 5 °C, 45 min; 2. DMF, 0 °C, 45 min (77%); (g) 4 N HCl (8 equiv), dioxane, rt, 5 h (85%); (h) **14**, DMF, −20°C, 1.5 h (90%); (i) NIS, 0 °C, 1 h (95%) or ICl, DMF −25 °C → −10 °C, 3 h (90%) or 1. I_2, Py, EtOAc, 10 °C, 1 h; 2. H_2O_2, 20 °C, 10 h (85%).

Scheme 3



[a]Reagents and conditions: (a) 1. MeOH, H_2SO_4, rt (79%); 2. BnBr, NaH, DMF, rt; 3. AcOH, H_2O, 100 °C (95%); (b) DMSO, Ac_2O, rt, 48 h (96%) or NaClO, KBr, K_2HPO_4, TEMPO, MTBE·H_2O (~ 4:1), 1 °C (>95%); (c) $CCl_3C(NH)OBn$, TfOH, dioxane, 0 °C, 3 h (80%); (d) TBDMSCl, imidazole, DMF, 65 °C, 5 h (96%); (e) $SOBr_2$, Py, CH_2Cl_2, rt, 1 h (93%).

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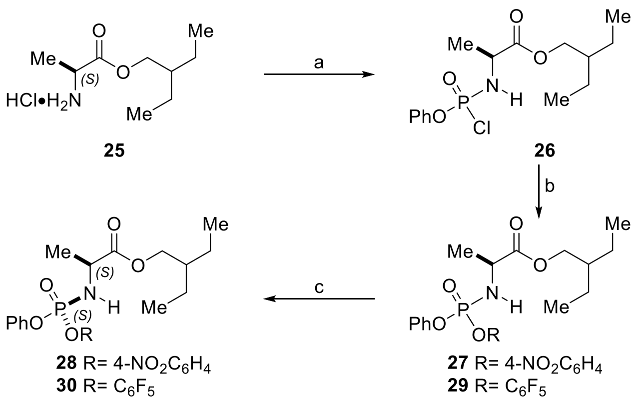
Oxidants such as pyridinium chlorochromate (PCC)[21] have also been used.[22] Given its wide interest, additional syntheses of **22** have been reported, including one which proceeds through the debenzylative lactonization of **23** with $SOBr_2$.[23] On the other hand, compound **24**, used for the third-generation synthesis of Remdesivir, was prepared by conventional silylation of **19**.[24]

2.3. Phosphoramidate Fragment. Three generations of the key phosphoramidate fragment have been reported. The product of the first generation (**26**) was obtained in two steps and 83% yield by reaction of alanine 2-ethylbutylester hydrochloride (**25**) with phenyl dichlorophosphate in CH_2Cl_2 at −78 °C (Scheme 4).

Scheme 4



[a]Reagents and conditions: (a) $Cl_2P(O)OPh$, Et_3N, CH_2Cl_2, −78 °C → rt, 3 h; (b) 4-$NO_2C_6H_4OH$, Et_3N, 0 °C → rt, 3 h (66% overall); for **30**: C_6F_5OH, Et_3N, 0 °C → rt, 3 h (**30**); (c) for **28**: *i*-Pr_2O (**28**, 39%) or *i*-PrOAc, heptane, DBU (10% *v*/*v*), 0 °C, 21 h; for **30**: *i*-PrOAc, heptane, Et_3N, 0 °C, 10 h.

The second-generation phosphoramidate (**28**) was accessed by *in situ* exposure of **26** to 4-nitrophenol. This furnished **27** in 80% yield, which was fractionally crystallized from di-isopropyl ether to give (S_P,*S*)-**28** in 39% yield, as proven by single-crystal X-ray diffraction.

A third-generation synthesis of phosphoramidates based on a dynamic kinetic resolution approach was first disclosed in a 2016 patent by Gilead, without informing yields.[14,25] The method involved preparation of **26** in *i*-PrOAc at −20 °C and its *in situ* conversion into (R_P/S_P)-**27** by reaction with 4-nitrophenol under Et_3N promotion.

The reaction was quenched and subjected to acid and base washings; next, the organic phase was concentrated and then diluted with heptane and treated with 10% of a base like DBU (0 °C, 21 h), which caused isomerization of the phosphorus stereocenter. Seeding crystals of (S_P,*S*)-**28** induced selective crystallization of this less soluble diastereomer, driving the isomeric conversion to completion. The yield of this scalable process was not reported.

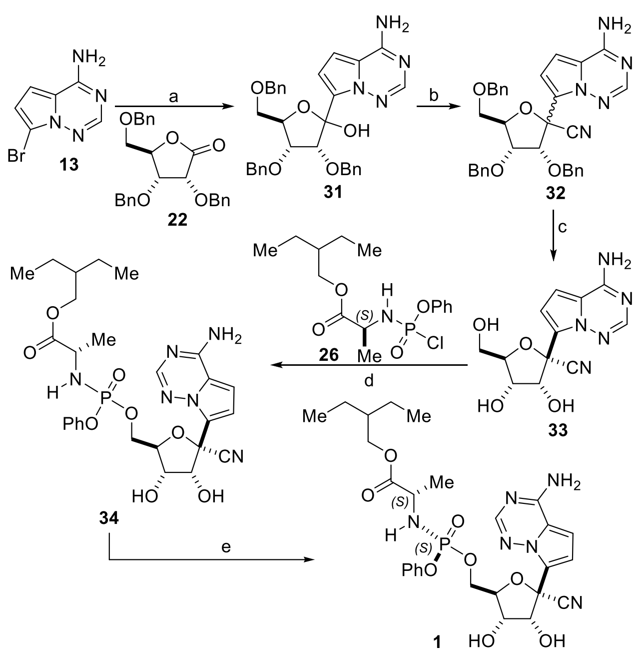
Analogously, exposure of **26** to per-fluorophenol gave **29**.[13] Kinetic resolution of **29** in hexane-isopropyl acetate, to which Et_3N was added to favor isomerization of the phosphorus stereocenter, provided the (S_P,*S*)-isomer (**30**).

3. SYNTHETIC ROUTES TOWARD REMDESIVIR

Gilead devised three main generations of the same strategy toward Remdesivir. They were partially reviewed in contributions with different scopes.[26,27] The approval of the drug for COVID-19 treatment resulted in additional synthetic contributions since the pandemic's outbreak.

3.1. First Generation. A New Antiviral Prodrug. The first synthetic route toward Remdesivir was disclosed in 2012 (Scheme 5).[28] There, **13** was subjected to a temporary *N*,*N*-bis-silylation for *N*-amino protection. Next, metal−halogen exchange in THF at −78 °C and reaction with **22** afforded lactol **31**, as a mixture of anomers. Use of *n*-BuLi and TMSCl gave a meagre 25% yield of **31**.[11]

Scheme 5



[a]Reagents and conditions: (a) *n*-BuLi, TMSCl, THF, −78 °C (26%) or NaH, *n*-BuLi, $ClSi(Me)_2CH_2CH_2(Me)_2SiCl$, THF, −78 °C (60%); (b) TMSCN, TMSOTf, CH_2Cl_2, −78 °C, 5 h (65%; β:α = 89:11); (c) BCl_3, CH_2Cl_2, −78 °C, 1 h (74%); (d) NMI, $(MeO)_3P{=}O$, THF, 0 °C (21%); (e) chiral HPLC.

Therefore, NaH and $ClSi(Me)_2CH_2CH_2(Me)_2SiCl$ were employed for the *N*-amino protection step, and then *n*-BuLi executed the metal−halogen exchange.[1,29,30] The modification notably improved the efficiency (up to 60% yield) of this poorly reliable *C*-glycosylation step. Qin et al. demonstrated that replacing NaH with the reagent couple *n*-BuLi/*i*-Pr_2NH afforded **31** (75%), in a hectogram-scale process.[31]

Cyanation was next performed with TMSOTf and TMSCN at 0 °C, through the intermediacy of an oxocarbenium ion. This gave **32** as an anomeric mixture (β:α = 57:43, 80% yield). A β:α = 89:11 ratio was observed when the reaction was performed for 5 h at −78 °C (65% yield). Interestingly, using $BF_3{\cdot}Et_2O$[1] as disclosed by Metobo et al.[29] gave 58% yield of **32** (β:α = 85:15) after 5 h at −78 °C. Other approaches toward **32** have been reported.[32]

Next, a BCl_3-mediated exhaustive debenzylation gave a diastereoisomeric mixture of nitriles in 74% combined yield, which was separated by preparative reverse-phase HPLC to afford **33** in optically pure form. This set the stage for the coupling with the key fragment **26**, in the presence of trimethyl phosphate and *N*-methylimidazole (NMI).

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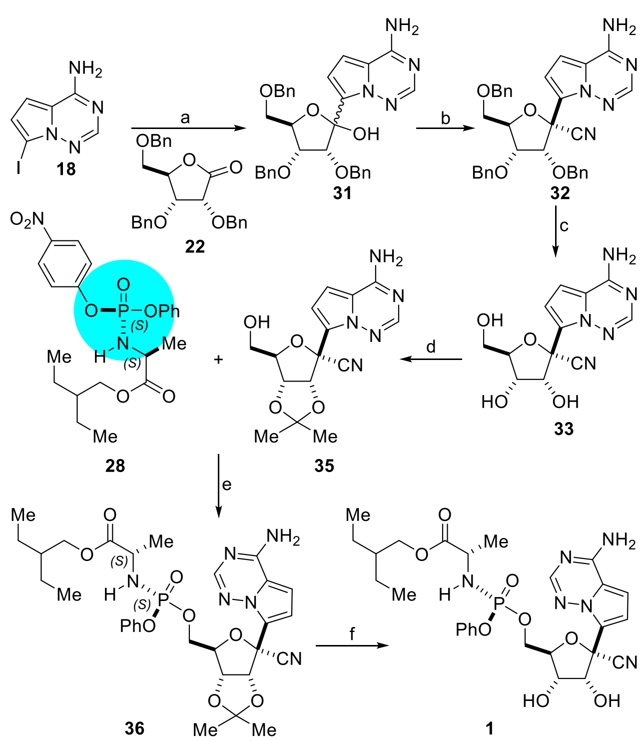
The transformation gave 21% yield of an ∼1:1 mixture of diastereomers (**34**), which was resolved by chiral HPLC to afford Remdesivir (**1**). Overall, the synthetic sequence was straightforward but required several HPLC separations (including chiral HPLC in the final step) and proceeded in low overall yield (0.6−1.5% from **13** and **22**).

3.2. Second Generation. The Optically Pure Phosphoramide Alternative. In 2016, a multigram synthesis of the drug was disclosed (Scheme 6),[13,33] and a 2017 patent included additional details.[34] This new generation synthesis comprised several improvements, including a TEMPO-catalyzed NaClO oxidation to access **22**[20] and a *C*-glycosylation which was executed with iodide **18** and Grignard reagents. This combination proved to be superior to that of the first-generation synthesis (based on **13** and *n*-BuLi, NaH, or *n*-BuLi/*i*-PrNH$_2$). In a modification of this reaction, the LaCl$_3$·2LiCl complex was added to generate a less basic carbanion intermediate, which avoids deprotonation of lactone **22**.[35]

Scheme 6



^{a}Reagents and conditions: (a) TMSCl, PhMgCl, *i*-PrMgCl·LiCl, THF, −20 °C, 1 h (42%); (b) TMSCN, TMSOTf, TfOH, CH$_2$Cl$_2$, −78 °C, 2 h (85%); (c) 1. BCl$_3$, CH$_2$Cl$_2$, −40 °C, 2 h; 2. Et$_3$N, MeOH, −78 °C → rt (86%); (d) 2,2-DMP, H$_2$SO$_4$, Me$_2$CO, rt, 0.5 h; 45 °C, 0.5 h (99%); (e) MgCl$_2$, DIPEA, MeCN, 50 °C, 0.5 h (70%); (f) 12 N HCl, THF (1:5), rt, 5 h (69%).

The efficiency of this 1,2-addition was improved, and intermediate **31** was obtained in 42% yield, consistently, with less costly reagents and under milder conditions (−20 °C), ensuring scalability. Other lanthanide salts (CeCl$_3$, NdCl$_3$, YCl$_3$) seem to have been tested, without disclosing product yields.[14] However, NdCl$_3$ was preferred for process scale up (68% yield of **31** from 282 kg of **22**).[36]

Another modification was the addition of an acid (TfOH, TFA) to the original reagent couple TMSCN/TMSOTf, to carry out the required stereoselective cyanation. This change improved the access to **32** (85% yield; β:α > 95:5). The exhaustive debenzylation step was refined, being performed at −40 °C to give triol **33** in 86% yield.

As proven by Gilead scientists, mild coupling of **28** and **35** did not affect the stereochemical integrity of the phosphorus center, suggesting that coupling of **28** and **33** could have the same outcome. However, in order to overcome the poor yields of the coupling stage between **26** and **33**, the vicinal diol moiety of the latter was protected. Hence, **33** was exposed to 2,2-dimethoxy propane/H$_2$SO$_4$, giving the acetonide **35** in 99% yield; interestingly, **35** was synthesized earlier in undisclosed yield, under di-*p*-nitrophenylphosphoric acid catalysis.[11]

Then, **35** was reacted with the second-generation phosphoramidate S_P-**28**, furnishing **36** (70% yield). The process is a nucleophilic substitution, where MgCl$_2$ activates the phosphorus center and DIPEA promotes the coupling, with configurational inversion at the *P*-center. Final deprotection of **36** with concentrated HCl in THF gave optically pure Remdesivir (**1**) in 69% yield.[2] Under the rather mild conditions developed for the coupling, the product exhibited stereochemical integrity of its stereogenic center.

Interestingly, the Gilead 2016 patent[14] also disclosed a *t*-BuMgCl-mediated coupling between unprotected compound **33** and the (R_P/S_P)-diastereomeric mixture of **27** (Scheme 4), which gave (R_P/S_P)-**1** in 43% yield. The resulting diastereomers could barely be separated by gradient reverse-phase HPLC (Kinetex C-18 column); however, they were cleanly separated by chiral HPLC [Lux Cellulose-2 column, eluting with MeCN:MeOH (95:5, *v*/*v*)].

Therefore, the three-step coupling sequence (48% overall yield) for the diastereoselective synthesis of Remdesivir compared favorably with the original coupling-chiral HPLC approach (12.5% overall yield) and the *t*-BuMgCl-mediated coupling (∼21.5% overall yield). Diol protection and use of the enantiopure phosphorylamido derivative (S_P)-**28** were key to this notable improvement.

The whole sequence proceeded in only six linear steps from known lactone **22** and iodide **18** and in 14.7% overall yield. This approach avoided costly, bottleneck HPLC separations and enabled preparation of over 200 g of Remdesivir, to support preclinical efficacy and toxicity studies. The preparation of the radiolabeled analogue [^{14}C]GS-5734 (58.0 mCi/mmol) was carried out with the same strategy, using [^{14}C]TMSCN.

Kappe et al. developed a small-scale flow chemistry approach of the *C*-glycosylation step toward **31**, which afforded the product in a stable 47% yield, with a total residence time of <1 min and a starting material throughput of 51.8 mmol/h (∼690 mg/day).[37] They optimized the reaction stoichiometries to suppress generation of identified impurities arising from onward reaction of the intermediate. The procedure did not provide a significantly higher yield with regard to the original batch conditions (40%), but it offered a marked improvement in processability.

In addition, a manufacturing scale (∼200 kg/run) continuous flow chemistry approach for the cyanation of **31** at −30 °C was reported. The process afforded **32** in 78% yield and 99.9% purity, at a rate of 6 mol/h, comparing favorably with a batch process (71%, 99.2% purity). It also provided improved control over the reaction conditions and increased diastereoselectivity [d.r. (β:α) = 96:4].[36]

Use of large quantities of cyanide derivatives (added in excess) required special conditions for plant design, including detailed written instructions and cyanide detectors as well as

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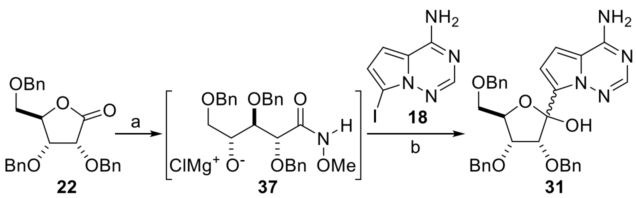
suitable personal training and protective measures. Further, use of cold basic reaction quenching conditions (KOH, H_2O, −10 °C) prevented the generation of HCN gas, whereas the waste streams from the process were treated with bleach until the cyanide levels were below the limit of cyanide test strip detection.[36]

Shen et al.[38] recently reported a simplified and efficient *C*-glycosylation strategy which avoids the formation of over-addition byproducts (Scheme 7). It involves a Weinreb

Scheme 7

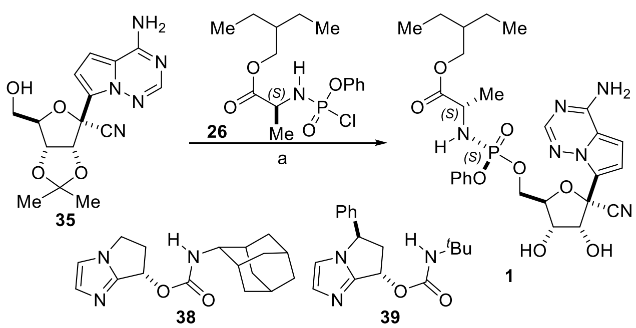


^{a}Reagents and conditions: (a) $MeONH_2·HCl$, *i*-PrMgCl, THF, 0 °C; (b) TMSCl, MeMgBr, *i*-PrMgCl·LiCl, THF, −10 °C → rt (65% overall).

amidation of **22**, followed by *in situ* temporary silylation of **37**, addition of the Grignard reagent derived from **18** (MeMgBr was used instead of PhMgCl), and final cyclization to afford **31** in 65% overall yield at a kilogram scale.

In the absence of additives, it has been shown that the coupling between **26** and the diol **33** gave an ∼1:1 mixture of diastereomers. However, efficient organocatalytic asymmetric *P*-phosphoramidation alternatives to the fragment coupling stage were recently reported by the groups of Zhang[39] and Hung.[40] Their approach involved dynamic kinetic asymmetric transformations (DyKATs) (Scheme 8) with chiral imidazole derivatives (**38** and **39**) as organocatalysts, mimicking the mechanism of the enzyme glucose-6-phosphatase.[40]

Scheme 8



^{a}Reagents and conditions: (a) **38** (10 mol %), CH_2Cl_2, 4 Å MS, −40 °C, 48 h (96% conversion; d.r. = 22.1:1) or 1. **39** (20 mol %), −20 °C, 24 h (97%, d.r. = 96.1:3.9); 2. TsOH, MeOH; 3. recrystallization (70%, d.r. = 99.3:0.7).

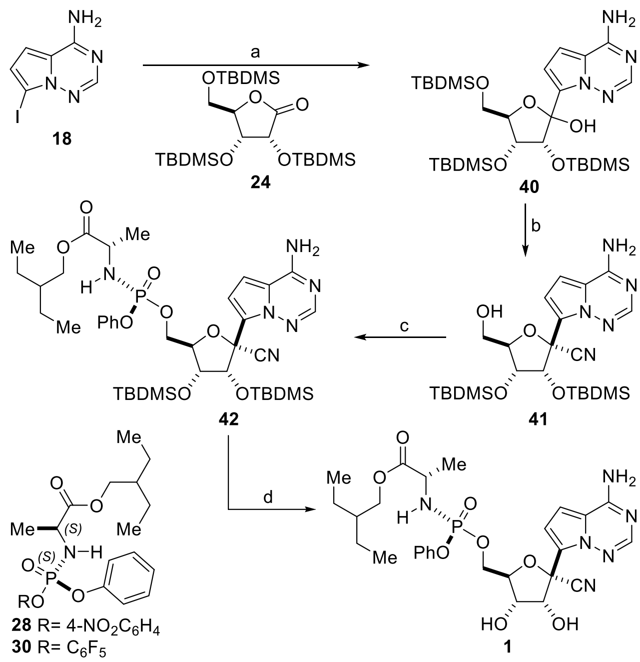
In the procedure devised by Zhang et al., catalyst **38** (10 mol %) was employed under 2,6-lutidine promotion, to diastereoselectively afford the protected intermediate **36** (Scheme 8) after 96% conversion (d.r. = 22.1:1). The improved coupling−deprotection−crystallization sequence of Hung et al. gave **1** in 70% yield (d.r. = 99.3:0.7) under the assistance of **39**, which was recovered (83% yield) for reuse.

The solid-state characteristics of Remdesivir were ascertained employing ssNMR, X-ray powder diffraction, calorimetric (DSC, TGA), and dynamic vapor sorption (DVS) methods. Four polymorphic forms of the drug were differentiated, and a maleate salt was prepared.[41]

3.3. Third Generation. The Silyl Ether Approach.

The sequence was first reported in 2016 without disclosing the yields of any step.[14] There, the silyl lactone **24** was condensed with iodide **18**, using the previously developed Grignard reagents strategy (Scheme 9), and the $LaCl_3·2LiCl$ complex was added to

Scheme 9



^{a}Reagents and conditions: (a) 1. *i*-PrMgCl, TMSCl, 0 °C; 2. *i*-PrMgCl, −15 °C; 3. $LaCl_3·2LiCl$, −15 °C; (b) 1. TMSCN, TMSOTf, TfOH, CH_2Cl_2, −30 °C, 15 min; 2. Et_3N, 0 °C (β:α = 3.8:1); (c) **28**, $MgCl_2$, *i*-Pr_2NEt, THF, 50 °C, 21 h or **30**, *t*-BuMgCl, THF, −10 °C → 5 °C, 16 h; (d) 12 N HCl, 20 °C, 72 h or TBAF or KF or Py·HF.

improve access to **40** and avoid side products. In turn, compound **40** is subjected to cyanation with the TMSCN/TMSOTf reagent system at −30 °C, with the addition of TFA. This selectively affords the monodeprotected nitrile after quenching with Et_3N; however, the product **41** was isolated as a mixture of diastereomers (β:α = 3.8:1), which required a preparative HPLC separation for purification.

Nitrile **41** was further coupled in THF with the enantiomerically pure phosphoramide **28** under $MgCl_2$/*i*-Pr_2NEt promotion to furnish **42**. In an alternative setup, the use of the phosphoramide **30** carrying a pentafluorophenyl leaving group was also proposed,[42] but the coupling was performed with *t*-BuMgCl in THF at −10 to 5 °C. Incompatibility between the nitro group in **28** with the Grignard reagent may have forced the use of **30**. Acid- (HCl) or fluoride- (TBAF, KF, or Py·HF) mediated desilylation finally provided Remdesivir (**1**).

Since no reaction yields were given, efficiency comparisons with previous syntheses are not possible. However, this route has some clear advantages, such as the selective monodeprotection of the primary silyl ether, which greatly simplifies the last steps (debenzylation, protection, coupling, and deprotection), enabling direct coupling of **41** with the phosphoramide moiety. Another advantage is the milder (room temperature) final deprotection step.

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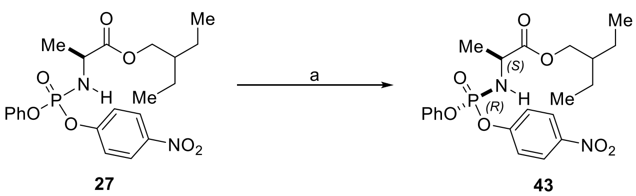
Both the cyanation−monodesilylation step aided by TFA and the use of the pentafluorophenyl derivative **30** for the coupling stage are interesting and novel developments. On the other side, however, the need for preparative HPLC for accessing enantiomerically pure intermediate **41** is a disadvantage.

4. PREPARATION OF (R_P)-REMDESIVIR

The S_P-isomer Remdesivir was originally selected for development due to its greater selectivity and better therapeutic window.[43] However, the R_P-isomer is also active. The enzymes carboxylate esterase 1 (CES1) and cathepsin A (CatA), which have variable expression levels among individual patients, have been identified as the major contributors of the initial activation step inside the cells.

CatA is more widespread and has preference for hydrolysis of (S_P)-Remdesivir, whereas CES1 has a more limited tissue distribution but a strong preference for hydrolysis of the (R_P)-isomer.[44] The new coronavirus affects primarily the lungs, rich in CatA; however, since it attacks multiple tissues, the synthesis of (R_P)-Remdesivir (Scheme 10) becomes relevant.

Scheme 10



[a]Reagents and conditions: (a) In1W variant of phosphotriesterase from *P. diminuta* (In1W-PTE), HEPES (50 mM, pH 8.0), MeOH·H_2O (7:3, v/v), 3 h (48.5%, ee > 95%).

This prompted Raushel et al. to prepare the key intermediate **43** through a chemoenzymatic strategy,[44] employing the In1W variant of the phosphotriesterase from *Pseudomonas diminuta* (In1W-PTE). The product was obtained satisfactorily (97% yield with regards to **27**, ee > 95%), as assessed by ^{31}P NMR. Other strategies toward this end have been reviewed.[45] This group finally achieved the synthesis of R_P-Remdesivir, using the *t*-BuMgCl-mediated coupling conditions (38% yield).

5. SUMMARY AND OUTLOOK

This review highlighted how synthetic efforts have improved the synthesis of Remdesivir in terms of cost, yield, and scalability. It also revealed not only how synthetic organic chemistry and its interaction with other disciplines can give specific responses to nowadays urgent needs but also how difficult it still is for science to come out with state-of-the-art suitable pharmaceutical solutions with regard to small organic molecules, even under the pandemic's pressure. Any specific drug against coronavirus should target the virus and its respiratory and cardiovascular effects. While discovery of this magic bullet is underway, the lessons learned during this pandemic will enhance our preparedness for the next time, when urgency will knock the door again.

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Notes

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■ ACKNOWLEDGMENTS

The authors wish to acknowledge Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) and Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT) for funding our research projects. The authors are indebted to Pharm. Aldana B. Moroni (IQUIR, CONICET-UNR) for revising the text. D.F.V. is also thankful to CONICET for his postdoctoral fellowship.

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https://doi.org/10.1021/acsomega.1c03082
ACS Omega XXXX, XXX, XXX−XXX