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Weinreb Amide Approach to the Practical Synthesis of a Key Remdesivir Intermediate

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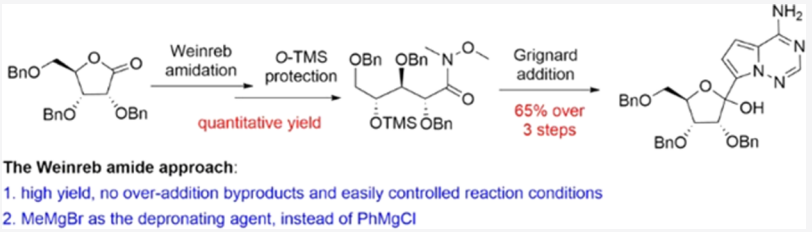

ABSTRACT: Currently, remdesivir is the first and only FDA-approved antiviral drug for COVID-19 treatment. Adequate supplies of remdesivir are highly warranted to cope with this global public health crisis. Herein, we report a Weinreb amide approach for preparing the key intermediate of remdesivir in the glycosylation step where overaddition side reactions are eliminated. Starting from 2,3,5-tri-*O*-benzyl-D-ribonolactone, the preferred route consisting of three sequential steps (Weinreb amidation, *O*-TMS protection, and Grignard addition) enables a high-yield (65%) synthesis of this intermediate at a kilogram scale. In particular, the undesirable PhMgCl used in previous methods was successfully replaced by MeMgBr. This approach proved to be suitable for the scalable production of the key remdesivir intermediate.

INTRODUCTION

The newly emerged coronavirus, SARS-CoV-2, which leads to a severe respiratory disease named COVID-19, has posed a great threat to global public health. As COVID-19 numbers continue to rise around the world, effective treatments are urgently needed to combat this pandemic.[1] Remdesivir (RDV), a 1′-cyano-substituted adenosine nucleotide analogue prodrug that demonstrates broad-spectrum antiviral activity against an array of RNA viruses,[2,3] was found to be a potent SARS-CoV-2 replication inhibitor and approved by the FDA for COVID-19 treatment on October 22, 2020.[4,5]

As a unique C-nucleoside analogue characterized by a 1′-α-CN and an adenine-mimicking pyrrolotriazine base moiety, the synthesis of RDV as well as its parent nucleoside, GS-441524, is a great challenge. In 2016, a scalable approach for the preparation of RDV was reported, involving multistep reactions starting from 2,3,5-tri-*O*-benzyl-D-ribonolactone **3** and 4-amino-7-iodopyrrolo[2,1-*f*][1,2,4]triazine **4a** (Scheme 1).[6] In the first step, the addition reaction between **3** and **4a** needs to be performed under harsh reaction conditions, giving the hemiacetal **5** only in a moderate to low yield (40%). The following two steps suffered from serious disadvantages, such as low reaction temperatures, use of hazardous and corrosive reagents, and cumbersome workup. From **2**, three steps were required to synthesize RDV, with a total yield of 43%. The entire process for the manufacturing of RDV was rather time-consuming and costly, and it became even worse when COVID-19 affected the whole world.

Recently, Gilead scientists reported a large-scale cyanation process to prepare **6** using continuous flow chemistry.[7] Moreover, an optimized synthetic method employing $NdCl_3$/*n*-Bu_4NCl to facilitate the critical C-glycosylation reaction between **3** and **4a** was provided, affording **5** in 69% yield. Compound **5** is an upstream intermediate in RDV synthesis, and its accessibility is fundamental for the bulky supply of RDV. To date, the synthesis of **5** is mainly achieved by coupling **3** with **4a** or the bromide counterpart **4b**. In the case of using **4b** as the starting material, the yield of **5** could reach 60%,[8,9] even up to 75%, reported in a newly published paper.[10] Nevertheless, an uncommon agent, 1,2-bis(chlorodimethylsilyl)ethane, was required to mask the amino group of **4b**, which made this approach unsuitable for large-scale production.

In our lab, we had performed an extensive study on the synthesis of **5** using the existing methods but were unable to obtain acceptable yields (40−50%). Two main byproducts

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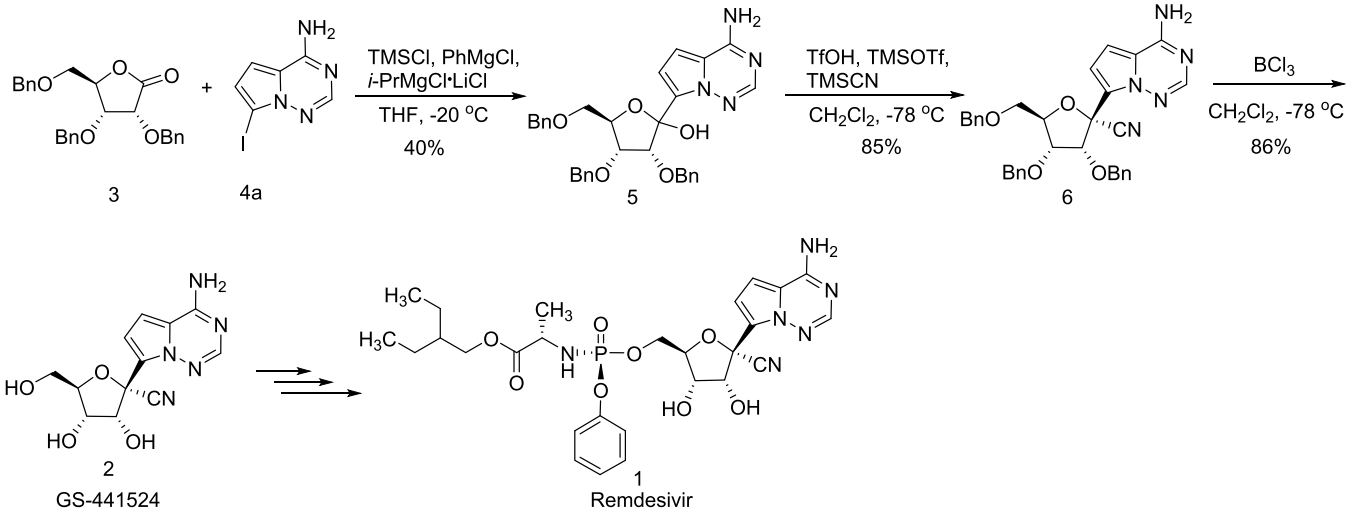
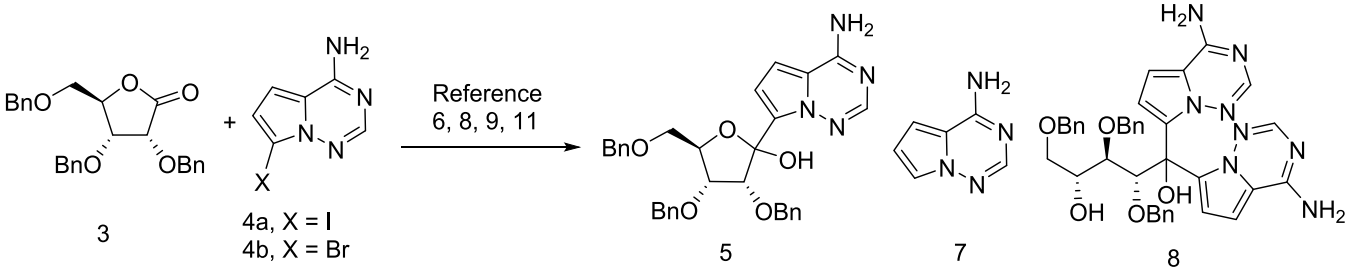
Scheme 1. Gilead's Method for the Scalable Synthesis of RDV



Scheme 2. Two Main Byproducts (7 and 8) Identified in the Synthesis of 5 Using the Existing Methods



were identified, the deiodinated pyrrolotriazine **7** and the overaddition product **8** (Scheme 2), accounting for at least 30% in the reaction mixture, as reported in recent research that elaborately investigated the impurities of this glycosylation step.[11] **4a** bearing a free primary amino group makes this addition reaction complicated, and lactone **3** has an ester functionality, which inevitably leads to the overaddition side reactions. Use of PhMgCl as the deprotonating agent for in situ TMS protection of the amino group of **4a** could lead to an equivalent amount of benzene that is undesirable from an application perspective, as well as the potential impurities associated with the addition of PhMgCl to **3** or **5**. These issues still remain in the optimized process for preparing **5**.

As is known, Weinreb amides are excellent substrates for the diverse synthesis of ketones by reaction with Grignard or organolithium reagents. This approach is highly efficient, and importantly, it could minimize or even preclude over-addition.[12−14] Hence, we envisaged that using a Weinreb amide, instead of lactone **3**, may gain superiority in accessing the key intermediate of RDV. Herein, we describe our discovery of a new approach for the preparation of **5**. To our surprise, this approach not only offers a high yield but also eliminates the use of PhMgCl, which allows for an efficient and practical synthesis of **5** at a large scale.

RESULTS AND DISCUSSION

Given the commercial availability, we still used **3** as the starting material, and the original route is shown in Scheme 3. Transforming **3** into Weinreb amide **10** was readily achieved in a quantitative yield (100%) using 1.5 equiv of *N,O*-dimethylhydroxylamine hydrochloride **9** in the presence of 3.0 equiv of *i*-PrMgCl. This intermediate possessed a free 4-hydroxyl group, which was supposed to be protected before proceeding to the following step. Initially, TBS was chosen as the protecting group in view of its tolerance to organometallic reagents. This reaction was conducted in dimethylformamide (DMF) with a combination of TBSCl and imidazole at 0 °C. Unexpectedly, the product mixture contained a high level of **3** that was possibly derived from **10** due to the tendency to form a stable five-membered ring. After purification, **11a** was obtained in 58% yield, and it proved to be stable under an ambient atmosphere for weeks. With **11a** in hand, the literature glycosylation conditions were employed (**4a** was first in situ silylated with TMSCl and PhMgCl, followed by magnesium−iodide exchange in the presence of *i*-PrMgCl·LiCl to form the heteroaryl Grignard reagent, and then reacted with **11a**), and it was encouraging to find that the reaction was clean, except for the deiodinated byproduct **7**, accounting for ∼20% in the mixture. Compound **12a** was obtained by chromatographic purification on silica gel in 52% yield, and the TBS protecting group was removed by trifluoroacetic acid (TFA) to furnish **5** in a yield of 80%.

The favorable outcome of the Weinreb amide-based approach for the synthesis of **5** prompted us to optimize this new method. First, to shorten the synthetic route that consisted of four steps, we intended to directly prepare **5** in the addition step by using an excess of hydrochloric acid as the quenching agent to remove the TBS protecting group of **11a**. However, this group exhibited good stability and remained unchanged for at least 2 h in the acidic solution (pH = 1) at ambient temperature. We thought that TMS or TES that had much lower acid stability may be removed automatically

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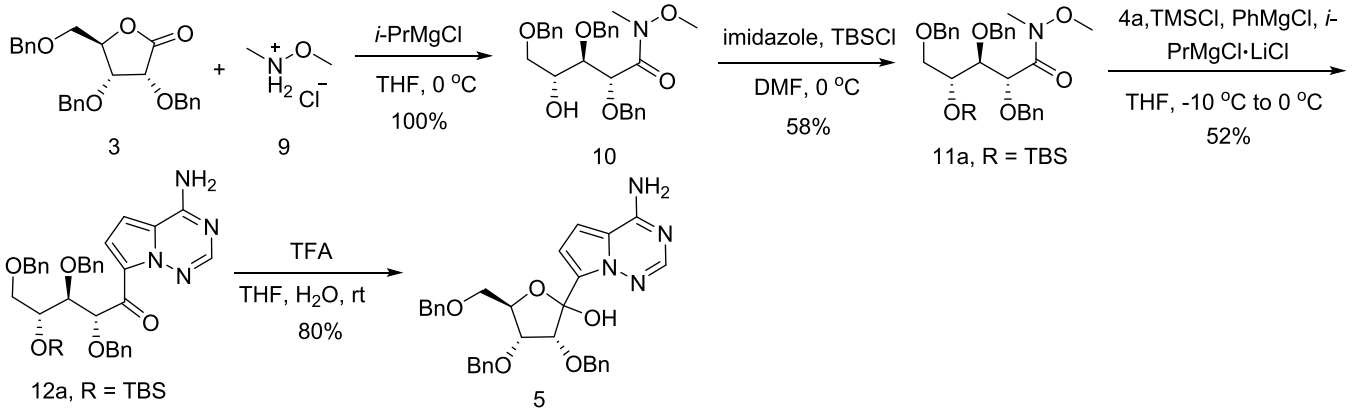
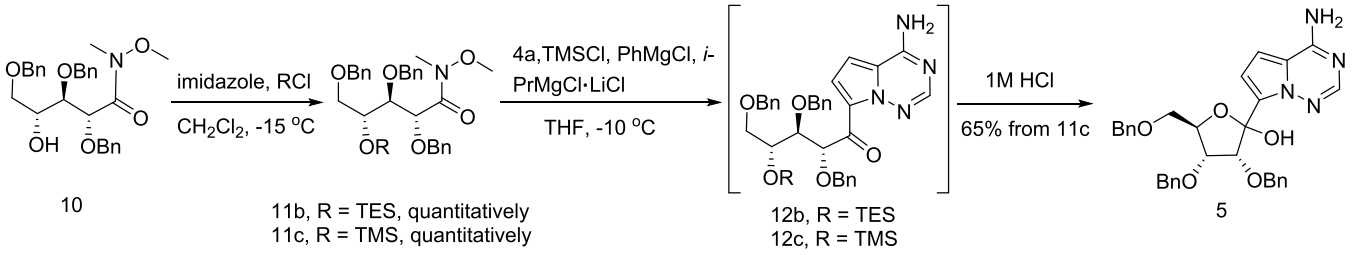
Scheme 3. Original Weinreb Amide-Based Approach for the Synthesis of 5



Scheme 4. Modified Weinreb Amide-Based Approach for the Synthesis of 5



during the workup. Along this line, we performed the addition reaction using TES- and TMS-protected Weinreb amides (**11b** and **11c**), respectively, shown in Scheme 4. As we expected, the reactions afforded **5** directly after being quenched with 1 M HCl to a final pH of 1−2. In this way, the TMS-containing adduct **11c** could be easily (within 20 min to 1 h depending on the scale) converted into **5** at ambient temperature in an isolated yield of 65%, while prolonged reaction time (at least 4 h) was required to remove the TES group of **11b**. Therefore, TMS was identified as the best protecting group.

Subsequently, we optimized the reaction condition of the silylation step. With imidazole as the base, solvent screening was done, including DMF, CH_2Cl_2, tetrahydrofuran (THF), and methyl *tert*-butyl ether (MTBE). For DMF and CH_2Cl_2, the reaction proceeded well at 0 °C with 1.2 equiv of TMSCl and 1.8 equiv of imidazole. However, the cyclization byproduct **3** was also produced, accounting for approximately 10% in the reaction mixture. THF and MTBE were found to be unfavorable for this reaction due to the incomplete conversion of compound **10**. Considering that the remaining DMF would be detrimental to the addition reaction, CH_2Cl_2 was chosen as the solvent for further condition optimization. It was discovered that when the reaction was conducted at a lower temperature (−15 °C), there was no or only a slight amount of **3** in the product, which could be directly used for the following addition reaction.

Coupling of **11c** with **4a** involved a complicated process and constituted the most crucial step in the synthesis of **5**. In principle, total protection of the amino group of **4a** was favorable, as evidenced by the application of bis-(chlorodimethylsilyl)ethane for *N*-protection, which provided a high yield for the addition step.[10] With regard to the *N*-TMS protection of **4a**, we assumed that disilylation of the amino group would be beneficial for the Mg−I exchange and the subsequent addition reaction. PhMgCl has been considered as the optimal deprotonating agent for in situ TMS protection of **4a** to perform the addition reaction.[6,11] However, this reagent could lead to toxic benzene, which is obviously a concern in large-scale production. In another aspect, Grignard reagents bearing bulky nucleophilic components may hamper the deprotonation or the silylation process. Taking these considerations into account, we chose three common Grignard reagents (CH_2=CHMgCl, EtMgCl, and MeMgBr) for condition optimization of this step, and the result is shown in Table 1. CH_2=CHMgCl bearing a vinyl anion is similar to PhMgCl in the aspects of alkalinity and nucleophilicity. It was observed that in the presence of 1.0 equiv of TMSCl, the two reagents gave acceptable yields (~65%, entries 1 and 3). However, when the amount of TMSCl was increased to 2.0 equiv, PhMgCl led to a decreased yield (entry 2), and CH_2=CHMgCl provided a relatively better result, with byproduct **7** reduced to 14% (entry 4).

EtMgCl was recently investigated as an alternative deprotonating agent but found to be inferior to PhMgCl for the addition reaction.[11] Similarly, in this study, we found that EtMgCl gave a poor result with **5** and **7** in a ratio of nearly 1:1 (entries 5 and 6). MeMgBr is the simplest Grignard reagent and supposed to be highly reactive to deprotonate the amino group of **4a**. When it was used, to our surprise, the reaction went smoothly over an easily controlled temperature range (−15 to 0 °C), and was completed within 1.5 h after transferring **11c** into the nascent Grignard reagent solution. In the case of 2.0 equiv of TMSCl, the yield was up to 76% at a 10.0 mmol scale (entry 9), which was a little better than that of the 1.0 equiv of TMSCl (entry 8). We further performed the reactions at a larger scale (192 mmol) starting from **3**, and the product was obtained by crystallization in MTBE in a yield of 65% (entry 10). It is noteworthy that **7** was the primary byproduct in the reaction and could be recycled by an acid−base workup.

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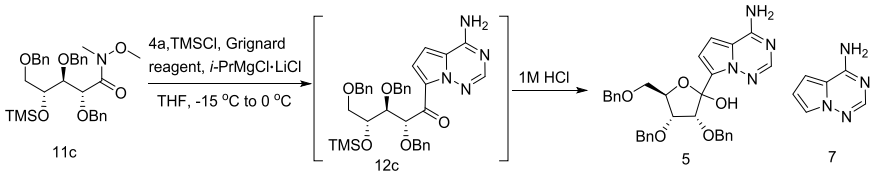
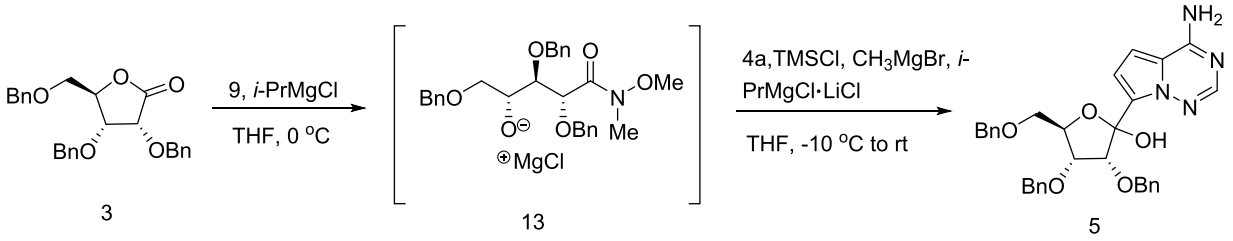
Table 1. Summary of Results for the Coupling of 11c with 4a Using Different Deprotonating Grignard Reagents



entry	scale of **4a** (mmol)	Grignard reagent	equiv of TMSCl	yields [%] **5**[a]	yields [%] **7**[b]
1	2.0	PhMgCl	1.0	65	22
2	2.0	PhMgCl	2.0	47	31
3	2.0	CH_2=CHMgCl	1.0	64	24
4	2.0	CH_2=CHMgCl	2.0	72	14
5	2.0	EtMgCl	1.0	42	37
6	2.0	EtMgCl	2.0	44	36
7	2.0	MeMgBr	1.0	66	16
8	10.0	MeMgBr	1.0	72[c]	15
9	10.0	MeMgBr	2.0	76[c]	12
10	192.0	MeMgBr	2.0	65[d]	

[a]Determined by column chromatographic purification on silica gel unless otherwise specified. [b]7 was obtained from the acidic aqueous phase by neutralization. [c]5 was synthesized from 3 in three steps. The majority of 5 was obtained by crystallization in MTBE, and the remaining portion was obtained by column chromatography from the filtrate. [d]Crystallization yield.

Scheme 5. More Simplified Weinreb Amide-Based Approach for the Synthesis of 5



In the course of the Weinreb amidation step, the product was obtained in the form of magnesium alkoxide (proposed structure **13**), which was converted into **10** upon aqueous workup. Because the hydroxyl group of **13** was deprotonated, this intermediate could be used directly for the addition reaction, therefore possibly further simplifying the synthetic method. At first, we conducted the reaction by adding **13** into the nascent heteroaryl Grignard reagent THF solution. However, it went very slowly, affording only a very small amount of **5** in the reaction mixture by thin-layer chromatography (TLC) analysis. After quenching with 1 M HCl, the predominant product was **7**. We also attempted to add the nascent Grignard reagent to the solution of **13** and it gave a similar result. By accident, we discovered that when an additional 1.0 equiv of *i*-PrMgCl was added to the freshly prepared **13** (a total of 4.0 equiv of *i*-PrMgCl was used) and on transferring the mixture into the Grignard reagent solution, the reaction proceeded well and gave a remarkably increased yield (60% yield). However, the reaction took a relatively long time (5−6 h) even at room temperature.

Considering that the excess of magnesium ion may facilitate the addition reaction, we conducted the reaction using 1.0 equiv of $MgCl_2$ instead of the additional *i*-PrMgCl. Disappointingly, it did not afford the desired product, which was contrary to our expectations. The role of the additional *i*-PrMgCl in the reaction was confusing. Nevertheless, efforts were still made to improve the reaction yield or shorten the reaction time, such as further increasing the amount of *i*-PrMgCl, adding the additional *i*-PrMgCl to the final reaction mixture, and increasing the addition reaction temperature, but no improvement was observed. Generally, this method did not show an obvious advantage over the TMS-protection process for the preparation of **5** despite being more simplified (Scheme 5).

Based on the above result, a three-step process for the synthesis of **5** was finalized: Weinreb amidation, *O*-TMS protection, and Grignard addition. Using the optimized conditions, preparation of **5** at scales from 50 grams to kilograms was successfully achieved in a stable yield (65%). The overall yield was highly dependent on the quality of **13c** in the silylation step, where the cyclization impurity **3** should be strictly controlled.

CONCLUSIONS

In summary, we explored a Weinreb amide approach for the synthesis of a key RDV intermediate in the C-glycosylation step with the aim of eliminating the overaddition side reactions. Initially, this idea was implemented in a four-step sequence with compound **7** as the main byproduct. After process optimizations, the synthesis of **5** was achieved in three steps, and the crystallization yield could reach 65% at a kilogram scale. In particular, the undesirable PhMgCl was replaced by MeMgBr, which provided a superior yield for the addition reaction. Besides, a more simplified route consisting of two steps was developed and worthy of further optimization.

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Overall, our work provides an alternative method for the preparation of the key remdesivir intermediate.

EXPERIMENTAL SECTION

General Experimental Details. 2,3,5-Tri-*O*-benzyl-D-ribonolactone **3** and 4-amino-7-iodopyrrolo[2,1-*f*][1,2,4]triazine **4a** were provided by Topharman Shanghai Co., Ltd. with a purity of ≥95%. The other materials and reagents, including *N*,*O*-dimethylhydroxylamine hydrochloride **9**, *tert*-butyldimethylsilyl chloride (TBSCl), chlorotriethylsilane (TESCl), chlorotrimethylsilane (TMSCl), imidazole, 2.0 M isopropylmagnesium chloride (*i*-PrMgCl) THF solution, 1.3 M isopropylmagnesium chloride−LiCl complex (*i*-PrMgCl·LiCl) THF solution, 2.0 M phenylmagnesium chloride (PhMgCl) THF solution, 1.0 M vinylmagnesium chloride (CH_2=CHMgCl) THF solution, 3.4 M ethylmagnesium chloride (EtMgCl) 2-methyl-THF solution, and 3.0 M methylmagnesium bromide (MeMgBr) 2-methyl-THF solution, were commercially available. Extra dry THF (with molecular sieves, water ≤ 50 ppm) was purchased from Energy Chemical. CH_2Cl_2 (AR) and DMF (AR) were used as received. The melting points were recorded using a melting point apparatus in capillary tubes and uncorrected. ^{1}H NMR and $^{13}C\{^1H\}$ NMR spectra were determined on a Brucker 500 Hz or 600 Hz instrument in DMSO-d_6 or $CDCl_3$ with TMS as a reference. High-resolution mass spectra (HRMS) were recorded on a Q-TOF mass spectrometer (Agilent Technologies 6520) using the electron spray ionization mode. All reactions were monitored by thin-layer chromatography (TLC) on 25.4 mm × 76.2 mm silica gel plates (GF-254).

*(2R,3R,4R)-2,3,5-Tris(benzyloxy)-4-hydroxy-N-methoxy-N-methylpentanamide (**10**).* To a mixture of 2,3,5-tri-*O*-benzyl-D-ribonolactone **3** (20.0 g, 47.8 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride **9** (7.0 g, 71.7 mmol) in extra dry THF (70 mL), 2 M *i*-PrMgCl THF solution (71.7 mL, 143.4 mmol) was slowly added in an ice bath over 30−40 min under a nitrogen atmosphere using a balloon. Note that obvious gas generation was observed if the dropping speed was too fast. After that, the mixture was continuously stirred in the ice bath for 3 h, and TLC showed that the reaction was completed. The mixture was poured into a saturated NH_4Cl aqueous solution (150 mL) and extracted with ethyl acetate (200 mL). The organic phase was separated, washed with water, brine, dried over Na_2SO_4, and evaporated to give **10** (24.1 g, yield 100%) as an oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.39−7.20 (m, 15H), 5.09 (d, J = 4.9 Hz, 1H), 4.71 −4.62 (m, 2H), 4.51−4.42 (m, 4H), 4.38 (d, J = 11.5 Hz, 1H), 4.12−4.04 (m, 1H), 3.82 (dd, J = 7.8, 2.9 Hz, 1H), 3.66 (dd, J = 9.9, 4.5 Hz, 1H), 3.53 (s, 3H), 3.49 (dd, J = 9.9, 6.5 Hz, 1H), 3.12 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 171.2, 139.0, 138.2, 128.6, 128.5, 128.1, 128.0, 127.90, 127.87, 127.77, 82.1, 74.4, 73.7, 72.8, 71.8, 71.5, 69.9, 61.5, 32.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{34}NO_6^+$, 480.2381; found 480.2392.

*(2R,3S,4R)-2,3,5-Tris(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-N-methoxy-N-methylpentanamide (**11a**).* Compound **10** (7.19 g, 15.0 mmol) and imidazole (1.84 g, 27.0 mmol) were dissolved in DMF (20 mL) in an ice bath, followed by the addition of TBSCl (2.71 g, 18.0 mmol) in one portion. The mixture was allowed to warm to room temperature and stirred for about 6 h. TLC showed that the reaction was completed. The reaction mixture was poured into water (150 mL) and extracted with ethyl acetate (150 mL). The organic layer was washed with water, brine, dried over Na_2SO_4, and evaporated to give a mixture of **11a** and **3**, which were subjected to column chromatography on silica gel using acetone and petroleum ether as the eluent (acetone/petroleum ether = 1:20−1:8) to give **11a** (5.17 g, yield 58%) as an oil, and **3** (2.0 g, yield 32%) as a solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.33−7.15 (m, 15H), 4.71−4.63 (m, 1H), 4.60 (d, J = 11.4 Hz, 1H), 4.46−4.38 (m, 3H), 4.36−4.30 (m, 2H), 4.22−4.17 (m, 1H), 3.74 (d, J = 8.6 Hz, 1H), 3.62 (dd, J = 10.0, 4.1 Hz, 1H), 3.49−3.41 (m, 4H), 3.06 (s, 3H), 0.82 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 170.7, 138.3, 138.2, 137.6, 128.13, 128.11, 128.0, 127.6, 127.43, 127.35, 127.33, 127.26, 81.7, 73.12, 73.06, 72.3, 72.0, 71.8, 71.1, 61.1, 31.7, 25.7, 17.8, −4.7, −5.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{48}NO_6Si^+$, 594.3245; found 594.3252.

*(2R,3S,4R)-2,3,5-Tris(benzyloxy)-4-((triethylsilyl)oxy)-N-methoxy-N-methylpentanamide (**11b**).* Following the above procedure of synthesizing **11a**, the reaction of compound **10** (7.0 g, 14.6 mmol) with TESCl (2.6 g, 17.5 mmol) in the presence of imidazole (1.79 g, 26.3 mmol) in DMF afforded crude product **11b**, which could be used in the next step without further purification. Alternatively, the crude product was subjected to column chromatography on silica gel using acetone and petroleum ether as the eluent (acetone/petroleum ether = 1:20−1:8) to give **11b** as an oil (8.1 g, 93%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.38−7.18 (m, 15H), 4.74−4.61 (m, 2H), 4.50−4.44 (m, 3H), 4.42 (d, J = 11.4 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.27−4.22 (m, 1H), 3.82 (d, J = 8.5 Hz, 1H), 3.71 (dd, J = 10.0, 4.5 Hz, 1H), 3.51 (s, 3H), 3.48 (dd, J = 10.0, 6.8 Hz, 1H), 3.12 (s, 3H), 0.91 (t, J = 8.0 Hz, 9H), 0.61−0.54 (m, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 170.7, 138.35, 138.30, 137.7, 128.05, 128.03, 127.97, 127.5, 127.42, 127.38, 127.29, 127.22, 82.0, 73.5, 73.3, 72.4, 72.0, 71.7, 71.1, 61.0, 31.6, 6.6, 4.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{48}NO_6Si^+$, 594.3245; found 594.3247.

*(2R,3S,4R)-2,3,5-Tris(benzyloxy)-4-((trimethylsilyl)oxy)-N-methoxy-N-methylpentanamide (**11c**).* Compound **10** obtained from the reaction of **3** (4.18 g, 10.0 mmol) with **9** (1.56 g, 16.0 mmol) using the above-described procedure was dissolved in CH_2Cl_2 (30 mL) and cooled to −15 °C. Imidazole (1.23 g, 18.0 mmol) was added, followed by the slow addition of TMSCl (1.30 g, 12.0 mmol). The mixture was continuously stirred at −15 °C. About 2 h later, the temperature gradually increased to 0 °C and TLC showed that the material had completely disappeared. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with water. The organic layer was separated and concentrated. The obtained oil product was dissolved in MTBE (60 mL), which was subsequently washed with water and brine. The organic layer was separated, dried over Na_2SO_4, and evaporated to give crude product **11c**, which could be used in the next step without further purification. Alternatively, the crude product was subjected to column chromatography on silica gel using acetone and petroleum ether as the eluent (acetone/petroleum ether = 1:20−1:8) to give **11c** as an oil (5.0 g, 91% over two steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40−7.20 (m, 15H), 4.71−4.64 (m, 1H), 4.61 (d, J = 11.4 Hz, 1H), 4.51−4.45 (m, 3H), 4.43 (d, J = 11.4 Hz, 1H), 4.38 (d, J = 11.7 Hz, 1H), 4.24−4.20 (m, 1H), 3.77 (dd, J = 8.0, 2.1 Hz, 1H), 3.67 (dd, J = 10.1, 4.0 Hz, 1H), 3.53 (s, 3H), 3.49 (dd, J = 10.0, 7.0 Hz, 1H), 3.12 (s, 3H), 0.08 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 138.5, 138.3, 137.7, 128.3, 128.24, 128.17, 127.7, 127.59, 127.56, 127.48, 127.40, 127.37, 81.3, 73.5, 73.0, 72.3, 71.8, 71.6, 71.1, 61.1, 30.8, 0.4. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.9, 138.6, 138.5, 137.7, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 127.4, 82.1, 74.2, 73.4, 73.2, 72.3, 72.1, 72.0, 61.2, 32.1, 0.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{31}H_{42}NO_6Si^+$, 552.2776; found 552.2781.

*Synthesis of **5** from **11a**.* Under nitrogen protection, **4a** (0.52 g, 2.0 mmol) was added in extra dry THF (3.0 mL) and cooled to 0 °C. TMSCl (0.22 g, 2.0 mmol) was added, and about 20 min later, the mixture was cooled to −15 °C; 2.0 M PhMgCl (2.0 mL, 4.0 mmol) in THF was added, and after about 30 min, 1.3 M *i*-PrMgCl·LiCl (1.7 mL, 2.2 mmol) in THF was added. Then, the reaction mixture was stirred at −15 to −10 °C until the material was completely converted into the Grignard reagent (the conversion was monitored using TLC by taking samples in methanol). To this mixture, **11a** (1.19 g, 2.0 mmol) dissolved in extra dry THF (3.0 mL) was slowly added. After the addition, the reaction mixture was stirred at 0 °C for about 1 h and the reaction was quenched with a saturated NH_4Cl aqueous solution and extracted with ethyl acetate. The organic phase was separated, washed with diluted hydrochloric acid and brine, then dried over Na_2SO_4, and concentrated. The residue was subjected to column chromatography on silica gel using ethyl acetate and petroleum ether as the eluent (ethyl acetate/petroleum ether = 1:5−1:1) to give **12a** as a solid (0.69 g, 52% yield); mp 70−73 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.09 (s, 2H), 7.96 (s, 1H), 7.39−7.22 (m, 11H), 7.18−7.07 (m, 3H), 6.96−6.85 (m, 3H), 5.40 (d, J = 7.6

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Hz, 1H), 4.63−4.53 (m, 2H), 4.52−4.42 (m, 3H), 4.34 (d, J = 11.7 Hz, 1H), 4.26−4.17 (m, 1H), 3.91 (dd, J = 7.6, 1.6 Hz, 1H), 3.83 (dd, J = 10.2, 3.5 Hz, 1H), 3.51 (dd, J = 10.2, 7.3 Hz, 1H), 0.83 (s, 9H), 0.02 (s, 3H), −0.05 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 188.4, 155.8, 149.0, 138.5, 138.1, 137.9, 128.6, 128.2, 128.1, 127.8, 127.54, 127.49, 127.3, 127.1, 127.0, 118.9, 117.5, 102.3, 82.6, 79.8, 72.7, 72.42, 72.36, 71.8, 71.4, 25.7, 17.8, −4.6, −5.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{38}H_{47}N_4O_5Si^+$, 667.3310; found 667.3321.

To a solution of **12a** (0.69 g, 1.0 mmol) in THF (10 mL), a 50% TFA aqueous solution (1.5 mL) was added. The mixture was stirred at room temperature until the staring material disappeared completely. Water (15 mL) was added, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed successively with water, saturated $NaHCO_3$ solution, and brine, then dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel using methanol and dichloromethane as the eluent (methanol/dichloromethane = 1:50−1:15) to give **5** as a foam (0.44 g, 80% yield); mp 57−59 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.07 (s, 2H), 8.00 (s, 1H), 7.38−7.23 (m, 11H), 7.20−7.13 (m, 3H), 7.04−6.98 (m, 2H), 6.95 (d, J = 4.5 Hz, 1H), 5.39 (d, J = 5.9 Hz, 1H), 5.06 (d, J = 5.3 Hz, 1H), 4.61−4.54 (m, 2H), 4.51−4.43 (m, 4H), 4.05−3.98 (m, 1H), 3.94 (t, J = 5.2 Hz, 1H), 3.70 (dd, J = 10.2, 3.4 Hz, 1H), 3.48 (dd, J = 10.2, 6.4 Hz, 1H).[15] HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{32}H_{33}N_4O_5^+$, 553.2445; found 553.2480.

Synthesis of ***5*** *from* ***11c*** *Using PhMgCl.* Under nitrogen protection, **4a** (0.52 g, 2.0 mmol) was added in extra dry THF (3.0 mL) and cooled to 0 °C. TMSCl (0.22 g, 2.0 mmol) was added, and about 20 min later, the mixture was cooled to −15 °C; 2.0 M PhMgCl (2.0 mL, 4.0 mmol) in THF was added, and after about 30 min, 1.3 M *i*-PrMgCl·LiCl (1.7 mL, 2.2 mmol) in THF was added. Then, the reaction mixture was stirred at −15 to −10 °C until the material was completely converted into the Grignard reagent. To this mixture, **11c** (1.10 g, 2.0 mmol) dissolved in extra dry THF (3.0 mL) was slowly added. The reaction mixture was stirred at 0 °C for about 1 h and quenched with 1 M hydrochloric acid to a final pH of 1−2. The mixture was stirred for 30 min at room temperature and extracted with ethyl acetate. The organic phase was separated, washed with diluted hydrochloric acid and brine, then dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel using methanol and dichloromethane as the eluent (methanol/dichloromethane = 1:50−1:15) to give **5** as a foam (0.72 g, 65% yield). The acidic aqueous phase was neutralized with a saturated Na_2CO_3 solution and extracted with ethyl acetate. The organic phase was separated, washed with brine, and concentrated. The solid residue was slurried with petroleum ether to give **7** as a light gray solid (0.059 g, 22% yield); mp 219−222 °C.

With respect to the reaction with 2.0 equiv of TMSCl (0.43 g, 4.0 mmol), the procedure was the same as described above, but more *i*-PrMgCl·LiCl (3.1 mL, 4.0 mmol) was required for the formation of the Grignard reagent. After workup, **5** (0.52 g, 47% yield) and **7** (0.083 g, 31% yield) were obtained in the same way.

Synthesis of ***5*** *from* ***11c*** *Using* CH_2=CHMgCl. The procedure was the same as described above. The reaction of **4a** (0.52 g, 2.0 mmol) and **11c** (1.10 g, 2.0 mmol) in the presence of TMSCl (0.22 g, 2.0 mmol), 1.0 M CH_2=CHMgCl (4.0 mL, 4.0 mmol), and 1.3 M *i*-PrMgCl·LiCl (2.2 mL, 2.8 mmol) afforded **5** (0.71 g, 64% yield) and **7** (0.064 g, 24% yield), respectively. Another experiment using 2.0 equiv of TMSCl (0.43 g, 4.0 mmol) was conducted in parallel, and gave **5** (0.80 g, 72% yield) and **7** (0.038 g, 14% yield) in the same way.

Synthesis of ***5*** *from* ***11c*** *Using EtMgCl.* The procedure was the same as described above. The reaction of **4a** (0.52 g, 2.0 mmol) and **11c** (1.10 g, 2.0 mmol) in the presence of TMSCl (0.22 g, 2.0 mmol), 3.4 M EtMgCl (1.2 mL, 4.0 mmol), and 1.3 M *i*-PrMgCl·LiCl (2.0 mL, 2.6 mmol) afforded **5** (0.46 g, 42% yield) and **7** (0.099 g, 37% yield), respectively. Another experiment using 2.0 equiv of TMSCl (0.43 g, 4.0 mmol) was conducted in parallel, and gave **5** (0.49 g, 44% yield) and **7** (0.097 g, 36% yield) in the same way.

Synthesis of ***5*** *from* ***11c*** *Using MeMgBr.* A representative procedure at a 10.0 mmol scale was provided. **4a** (2.6 g, 10.0 mmol) was added in extra dry THF (30 mL) under nitrogen protection and cooled to −15 °C. TMSCl (1.1 g, 10.0 mmol) or (2.2 g, 20.0 mmol) was slowly added, and after stirring for about 20 min, 3 M MeMgBr in 2-methyl-THF (20.0 mmol, 6.7 mL) was added slowly. About 30 min later, 1.3 M *i*-PrMgCl·LiCl in THF (10.8 mL, 14.0 mmol) was added. The resulting mixture was stirred at −15 to −10 °C for about 1 h (conversion of **4a** into the Grignard reagent was monitored by taking samples in methanol). When **4a** was completely converted into the Grignard reagent, **11c** (10 mmol) in extra dry THF (20 mL) prepared according to the above-described procedure was transferred into the reaction mixture. The resulting mixture was allowed to warm to 0 °C and stirred for about 1 h; 1 M hydrochloric acid was added to adjust the pH to 1−2. After stirring for 1 h, the organic layer was separated and concentrated. The residue was dissolved in ethyl acetate and washed with water and brine. The organic layer was dried over Na_2SO_4 and evaporated. MTBE was added to give a clear solution, which was held overnight. The solid was obtained by filtration and dried to afford **5** (3.3 g for 1.0 equiv of TMSCl and 3.6 g for 2.0 equiv of TMSCl). The filtrate was concentrated, and the residue was purified by column chromatography on silica gel using methanol and dichloromethane as the eluent (methanol/dichloromethane = 1:50−1:15) to give the remaining portion (0.7 g for 1.0 equiv of TMSCl and 0.6 g for 2.0 equiv of TMSCl). For the experiment with 1.0 equiv of TMSCl, 4.0 g of **5** was obtained, 72% yield; for the experiment with 2.0 equiv of TMSCl, 4.2 g of **5** was obtained, 76% yield.

Synthesis of ***5*** *from* ***3*** *in Two Steps.* To a mixture of **3** (24.1 g, 57.7 mmol) and **9** (8.4 g, 86.6 mmol) in extra dry THF (80 mL), 2 M *i*-PrMgCl THF solution (86.5 mL, 173.1 mmol) was slowly added in an ice bath under nitrogen protection. The mixture was stirred in the ice bath until the conversion was completed. Then, an additional 2 M isopropylmagnesium chloride THF solution (29.0 mL, 57.7 mmol) was added, and the resulting mixture was held in the ice bath.

4a (15.0 g, 57.7 mmol) was added in extra dry THF (60 mL) under nitrogen protection and cooled to −10 °C. TMSCl (12.5 g, 115.4 mmol) was slowly added, and after stirring for about 20 min, 3 M MeMgBr in 2-methyl-THF (38.5 mL, 115.4 mmol) was added slowly. About 30 min later, 1.3 M *i*-PrMgCl·LiCl in THF (62.2 mL, 80.8 mmol) was added. The resulting mixture was stirred at −10 °C for about 1 h (conversion of **4a** into the Grignard reagent should be monitored). When **4a** was completely converted into the Grignard reagent, the Weinreb amide **13** solution was transferred into the reaction mixture. The resulting mixture was allowed to warm to room temperature and stirred for 5−6 h; 1 M hydrochloric acid was added to adjust the pH to 1−2. After stirring for 1 h, the organic layer was separated and concentrated. The resulting residue was dissolved in ethyl acetate and washed with water and brine. The organic layer was dried over Na_2SO_4 and evaporated. MTBE was added to give a clear solution, which was held overnight. The solid was obtained by filtration and dried, and combined with the solid obtained from the filtrate to afford **5** (19.1 g, 60% yield).

Procedure for the Scale-Up Synthesis of ***5*** *(50 g, 1 kg, and 20 kg Scales of* ***4a****).* The glass flasks and the reactors were dried before use. The glass flasks were dried using an electric heating air-blowing drier. For the large-scale reactions, the cleaned reactor was charged with extra dry THF, which was evaporated under reduced pressure. The addition and removal of THF were repeated two more times. Then, the reactor was filled with nitrogen gas and held at the indicated temperature; **3** (1.0 equiv) and **9** (1.8 equiv) were mixed in extra dry THF (3.0 vol), and stirred at 0 °C under a nitrogen flow; 2 M isopropylmagnesium chloride tetrahydrofuran solution (3.6 equiv) was added. After the addition, the mixture was continuously stirred at 0 °C for 2 h and was then poured into a saturated NH_4Cl solution. The organic layer was separated, concentrated, and the obtained residue was dissolved in ethyl acetate (6.0 vol). The solution was then washed with water and brine, dried over Na_2SO_4, and evaporated to give compound **10** as an oil.

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The oil product obtained in the first step was dissolved in CH_2Cl_2 (3.0 vol) and cooled to −10 °C. Imidazole (1.8 equiv) was added, followed by the slow addition of TMSCl (1.2 equiv). The mixture was stirred at −10 to −5 °C for 3−4 h. Water (3.0 vol) was added, and the organic layer was separated. After concentration, the oil product was dissolved in MTBE (6.0 vol), which was subsequently washed with water and brine. The organic layer was separated, dried over Na_2SO_4, and evaporated to give **11c** as oil, which was dissolved in extra dry THF (3.0 vol) and held for the next step.

4a (1.0 equiv) was added in extra dry THF (10.0 vol) under a nitrogen flow and cooled to −15 to −10 °C. TMSCl (2.0 equiv) was slowly added, and after stirring for about 20 min, MeMgBr or MeMgCl solution (2.0 equiv) was added slowly. About 30 min later, i-PrMgCl·LiCl (1.4 equiv) was added. After that, the reaction mixture was continuously stirred for about 1 h (conversion of **4a** into the Grignard reagent should be monitored). Then, the reaction temperature increased to −5 to 0 °C, and the **11c** THF solution obtained in the second step was transferred into the reaction mixture. The resulting mixture was stirred for 1−1.5 h at 0 °C, and 1 M hydrochloric acid was added to adjust the pH to 1−2. After stirring for 1 h, the organic layer was separated and concentrated. The resulting residue was dissolved in ethyl acetate (6.0 vol) and washed with water and brine. The organic layer was dried over Na_2SO_4 and evaporated. MTBE (4.0 vol) was then charged and evaporated, followed by the addition of MTBE (4.0 vol) again to obtain a clear solution. Seed crystals of **5** were added, and the mixture was cooled to about 0 °C. After 12 h, the solid was collected by filtration and rinsed with a 1:1 methyl *tert*-butyl ether/*n*-heptane solution. The solid was dried to afford **5** in 65% yield with >99% purity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02986.

Copies of ^{1}H NMR and ^{13}C{^{1}H} NMR spectra (PDF).

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Notes

The authors declare no competing financial interest.

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