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NEW AND PRACTICAL SYNTHESIS OF GS-441524, THE KEY INTERMEDIATE OF REMDESIVIR

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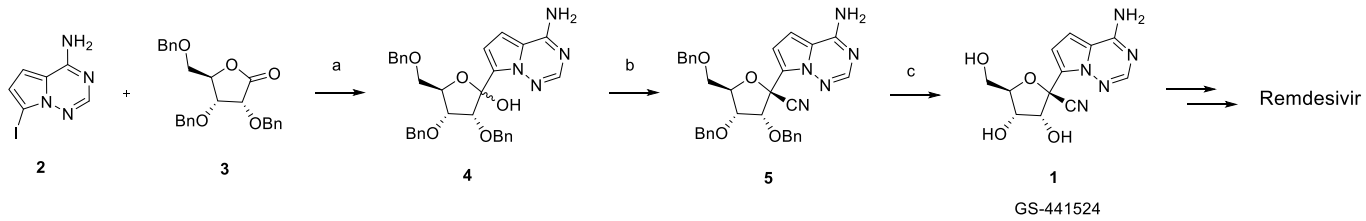
Abstract – A new and practical synthesis of GS-441524, the key intermediate for remdesivir, is developed. 4-Amino-7-iodopyrrolo[2,1-*f*][1,2,4]triazine is protected by DMF-DMA, and reacted with 2,3,5-tri-*O*-benzyl-D-ribonolactone to give the product in 61% isolated yield. The next cyanation and debenzylation are carried out at −30 °C successively in 67% yield over two steps with >99% purity (HPLC). Purification methods of the intermediates and the final product involved in the route are developed.

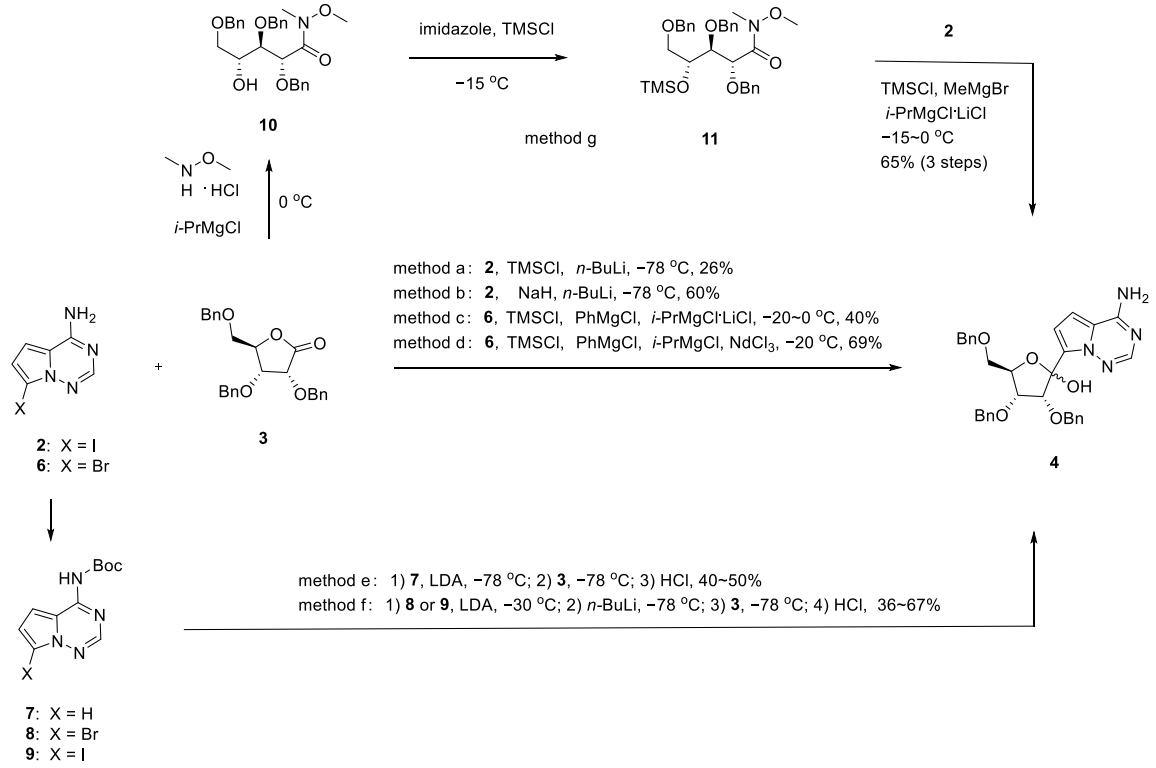
GS-441524 (**1**, Scheme 1) is a potent inhibitor of feline infectious peritonitis (FIP) virus.[1] It is the active metabolite, as well as the key intermediate for the preparation of remdesivir, which is the potent SARS-CoV-2 replication inhibitor and approved by the FDA for COVID-19 treatment on October 22, 2020.[2,3]

From 2016, a scalable approach for the preparation of remdesivir, especially focus on it's key intermediate (3*R*,4*R*,5*R*)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)-methyl)tetrahydrofuran-2-ol (**4**) had been reported, involving multistep reactions starting from 4-amino-7-iodopyrrolo[2,1-*f*][1,2,4]triazine (**2**) and 2,3,5-tri-*O*-benzyl-D-ribonolactone (**3**), as shown in Scheme 1.[4,5] The addition reaction between **2** and **3** needs to be performed under harsh reaction conditions, giving **4** only in 20~40% yield (Scheme 2 methods a, b, c). The following two steps suffered low reaction temperatures, use of hazardous and corrosive reagents, and cumbersome workup, to give GS-441524 in 73% yield. An optimized synthetic method employing $NdCl_3$ to facilitate the C-glycosylation reaction between **2** and **3** was provided, affording **4** in 69% yield (Scheme 2 method d).[5–7] The synthesis of **4** is also achieved by coupling the Boc protected compound **7**, **8** or **9** with **3**, in 40~67% overall yield, which led to two more steps (Scheme 2 methods e, f).[8,9] Recently, Shen's group reported a novel method (Scheme 2 method g), consisting of three sequential steps (Weinreb amidation,

O-TMS protection, and Grignard addition) to give **4** in 65% over all yield.[10] While we found the two intermediates **10** and **11** are unstable, which can partially convert to the ribonolactone **3** even at room temperature for several hours, which will restrict the scale-up production.



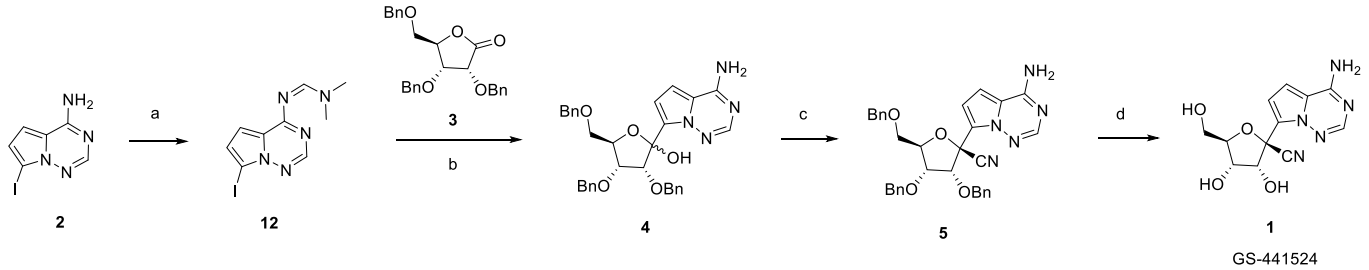
Scheme 1. Reagents and conditions: (a) TMSCl, PhMgCl, *i*-PrMgCl·LiCl, THF, −20 °C, 40%; (b) TfOH, TMSOTf, TMSCN, CH_2Cl_2, −78 °C, 85%; (c) BCl_3, CH_2Cl_2, −78 °C, 86%.



Scheme 2. Graphical synthetic routes of compound 4

In order to develop an efficient and practical method for preparing of **1**, a new synthetic route was developed successfully, as shown in Scheme 3. *N'*-(7-Iodopyrrolo[2,1-*f*][1,2,4]triazin-4-yl)-*N*,*N*-dimethylformimidamide (**12**) was prepared by heated 7-iodopyrrolo[2,1-*f*][1,2,4]triazin-4-amine (**2**) and *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) in ethanol with >90% isolated yield. Compound **12** was firstly treated with *i*-PrMgCl at −20~−10 °C, then reacted with ribonolactone **3** to give the product **4** after quenched by ammonium chloride aqueous solution to remove the protecting group, in

>60% yield by recrystallization from MTBE and heptane. The active amino group in compound **2** will block the Grignard reaction, so the protection methods of NH_2 has been widely examined.[4–9] The reported protective groups included -TMS, 1,2-bis(dimethylsilyl)ethane, -Boc, and so on. The N-Si bond is unstable and it should be partly destroyed during the Grignard reaction and the residual NH will consume Grignard reagent, as well as gives side products. The *N*,*N*-dimethylformimidamide group used as the protective group has advantages. There is no NH group in compound **12** so the side product was lower, and the protective group can be deprotected easily during the work-up operation to give **4** directly. Compound **4** should be a mixture of 1′-isomers, while we had not established the method or identified the ratio by HPLC. It was taken into the subsequent 1′-cyanation reaction to give compound **5**, by reacted with TFA, TMSOTf and TMSCN in CH_2Cl_2 respectively at −40~−30 °C in 81% yield and >99% anomeric ratio after purified from toluene. At the last step, compound **5** was added into BCl_3 in CH_2Cl_2 solution at −40~−30 °C to give the final GS-441524 in 83% yield and >99% purity (HPLC). Purification methods of the intermediates and the final product involved in the route were developed, which make it as a process of cost effective, environmental friendly, and feasible for scale-up operation.



Scheme 3. Reagents and conditions: (a) DMF-DMA, EtOH, 70~75 °C, 93%; (b) *i*-PrMgCl, −20~−10 °C, 61%; (c) TFA, TMSOTf, TMSCN, CH_2Cl_2, −40~−30 °C, 81%; (d) BCl_3, CH_2Cl_2, −40~−30 °C, 83%.

EXPERIMENTAL

All commercially available chemicals and solvents were used as received without any further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker UltraShield 400 Plus spectrometer using TMS as an internal standard. Mass spectra were obtained from a Finnigan MAT-95/711 spectrometer. Melting points were measured on a Shenguang WRS-1B melting point apparatus and uncorrected. The HPLC data were acquired using a Waters 2487 UV/Visible Detector and Waters 515 Binary HPLC Pump. The purity of the compounds was based on the areas of HPLC UV.

***N′*-(7-Iodopyrrolo[2,1-*f*][1,2,4]triazin-4-yl)-*N*,*N*-dimethylformimidamide (12).** A mixture of 7-iodopyrrolo [2,1-*f*][1,2,4]triazin-4-amine (**2**) (130 g, 0.5 mol), DMF-DMA (65.5 g, 0.55 mol) in EtOH (1 L) was heated and stirred at 70~80 °C for 2 h to give a suspension. After cooling to room temperature,

the reaction solution was stirred at 0~5 ℃ for 1 h, the resulting solid was collected by suction filtration, washed with EtOH (60 mL × 2), and dried at 50 ℃ for 8 h to obtain **12** (145 g, 93%), as a light-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.16 (s, 3H), 3.22 (s, 3H), 6.93 (dd, J = 13.6, 4.4 Hz, 2H), 8.15 (s, 1H), 8.92 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.4, 41.5, 72.0, 105.3, 120.2, 124.2, 148.6, 158.7, 160.1. HRMS (ESI) calcd for: $C_9H_{11}IN_5$ $[M+H]^+$ 316.00591, Found: 316.00540.

(3*R*,4*R*,5*R*)-2-(4-Aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)-methyl)tetrahydrofuran-2-ol (4). A mixture of compound **12** (78.5 g, 0.25 mol) and anhydrous THF (600 mL) was stirred and cooled to −20 ºC. 2 M *i*-PrMgCl in THF solution (150 mL, 0.30 mol) was added dropwise to the mixture over 30 min and kept the reaction temperature at −20~−10 ºC. A solution of 2,3,5-tri-*O*-benzyl-D-ribonolactone (**3**) (115 g, 0.275 mol) in anhydrous THF (120 mL) was added dropwise to the reaction solution over 30 min and kept the reaction temperature at −20~−10 ºC. Sat. aq. NH_4Cl solution (500 mL) was added slowly to the reaction solution and kept the reaction temperature below 10 ºC. EtOAc (1 L) was added and stirred. The organic layer was separated and washed with water (500 mL × 2). The organic phase was concentrated under reduced pressure to give a light brown oil (145 g). *i*-PrOAc (60 mL) was added to the residue and stirred at 50 ℃ to give a clear solution. Then *t*-BuOMe (580 mL) was added and stirred at 20~30 ℃ for 1 h. Then heptane (58 mL) was added dropwise and stirred at 0~10 ℃ for 6 h. The resulting solid was collected by suction filtration, washed with *t*-BuOMe (30 mL × 2), and dried at 40 ℃ for 6 h to obtain **4** (84 g, 61%) as a white solid. mp 62.4~64.2 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (brs, 2H), 7.99 (s, 1H), 7.37-7.22 (m, 11H), 7.19-7.10 (m, 3H), 7.03-6.97 (m, 2H), 6.95 (d, J = 4.8 Hz, 1H), 5.39 (d, J = 5.9 Hz, 1H), 5.05 (d, J = 5.2 Hz, 1H), 4.61-4.54 (m, 2H), 4.52-4.42 (m, 4H), 4.06-3.98 (m, 1H), 3.93 (dd, J = 5.9, 4.4 Hz, 1H), 3.69 (dd, J = 10.1, 3.4 Hz, 1H), 3.47 (dd, J = 10.0, 6.4 Hz, 1H). ESI-MS (*m/z*) 553.3 $[M+H]^+$.

HPLC Conditions: Column: Agilent InertSustain C18 (250 mm × 4.6 mm × 5 μm); Detection: 210 nm, 244 nm; Flow rate: 0.8 mL/min; Temperature: 30 ℃; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Run time: 30 min; Mobile phase A: water; Mobile phase B: MeOH/HCO_2H = 100/0.1; Gradient program: Mobile phase A/Mobile phase B = 10/90: t_R = 9.175 min, purity: 99.9% (210 nm), 98.2% (244 nm).

(2*S*,3*R*,4*R*,5*R*)-2-(4-Aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)-methyl)tetrahydrofuran-2-carbonitrile (5). A solution of **4** (55.2 g, 0.1 mol) in CH_2Cl_2 (500 mL) was cooled to −40 ºC. TFA (23 g, 0.2 mol) was added dropwise at −40~−30 ºC. After the reaction was stirred for 15 min, TMSOTf (45 g, 0.2 mol) was slowly added and the resulting mixture was stirred for 15 min at −40~−30 ºC. TMSCN (30 g, 0.3 mol) was then added slowly and the mixture was stirred at −40~−30 ºC

for 2 h. Triethylamine (50 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature. Sat. aq. $NaHCO_3$ solution (500 mL) was then added and the resulting mixture was stirred for 10 min. The organic layer was separated and washed with brine (500 mL), and concentrated under reduced pressure to give light yellow solid. The solid was dissolved in toluene (150 mL), heated to 70~80 °C to give a clear solution. The solution was stirred at 20~30 °C for 1 h and at 0~10 °C for 2 h. The resulting solid was collected by suction filtration, washed with toluene (30 mL × 1), and dried at 40 °C for 6 h to obtain **5** (46 g, 81%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99-7.82 (m, 3H), 7.37-7.23 (m, 15H), 6.88 (d, J = 4.5 Hz, 1H), 6.76 (d, J = 4.5 Hz, 1H), 4.91 (d, J = 5.0 Hz, 1H), 4.85 (d, J = 11.7 Hz, 1H), 4.77 (d, J = 11.7 Hz, 1H), 4.60-4.45 (m, 4H), 4.40 (q, J = 4.6 Hz, 1H), 4.12 (t, J = 5.4 Hz, 1H), 3.69 (dd, J = 11.1, 3.7 Hz, 1H), 3.59 (dd, J = 11.1, 4.7 Hz, 1H); ESI-MS (*m/z*) 562.3 $[M+H]^+$.

HPLC Conditions: Column: Agilent InertSustain C18 (250 mm × 4.6 mm × 5 μm); Detection: 210 nm, 244 nm; Flow rate: 0.8 mL/min; Temperature: 30 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Run time: 30 min; Mobile phase A: water; Mobile phase B: MeOH/HCO_2H = 100/0.1; Gradient program: Mobile phase A/Mobile phase B = 10/90: t_R = 15.13 min, purity: 100% (210 nm), 100% (244 nm).

Chiral HPLC Conditions: Column: Daicel CHIRALPAK IC; Detection: 220 nm, 237 nm; Flow rate: 0.8 mL/min; Temperature: 30 °C; Injection load: 1 μL; Solvent: *i*-PrOH; Concentration: 0.2 mg/mL; Run time: 20 min; Mobile phase: *n*-hexane/*i*-PrOH = 90/10, t_R = 12.192 min, purity: 99.9% (220 nm), 99.9% (237 nm).

GS-441524 (1). The solution of 1 M BCl_3 in CH_2Cl_2 (250 mL, 0.25 mol) was cooled to −40 °C. A solution of **5** (40 g, 0.071 mol) in CH_2Cl_2 (200 mL) was added dropwise to the BCl_3 solution over 1 h at −40~−30 °C, and stirred at −30 °C for another 1 h. MeOH (80 mL) and triethylamine (60 mL) were added dropwise respectively to the reaction solution below −20 °C. The reaction mixture was allowed to warm to room temperature. The resulting mixture was concentrated under reduced pressure. The solid residue was stirred and heated with heptane (200 mL) at 40~50 °C for 30 min. The resulting solid was collected by suction filtration, washed with heptane (40 mL × 2). The solid was suspended into water (80 mL), 40% aq. NaOH solution was added to adjust the pH ~ 11. The resulting solid was collected by suction filtration, washed with water (15 mL × 2), and dried at 50 °C for 6 h to obtain **1** (17.1 g, 83%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80-7.90 (br s, 3H), 6.80 (d, J = 5.2 Hz, 2H), 6.09 (d, J = 4.8 Hz, 1H), 5.21 (s, 1H), 4.94 (d, J = 5.4 Hz, 1H), 4.62 (d, J = 4.2 Hz, 1H), 4.03 (d, J = 5.0 Hz, 1H), 3.86 (d, J = 3.2 Hz, 1H), 3.55 (t, J = 4.8, 1H), 3.48 (t, J = 4.8, 1H). ESI-MS (*m/z*) 292.1 $[M+H]^+$.

HPLC Conditions: Column: Agilent InertSustain C18 (250 mm × 4.6 mm × 5 μm); Detection: 210 nm,

244 nm; Flow rate: 0.8 mL/min; Temperature: 30 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Run time: 30 min; Mobile phase A: water; Mobile phase B: MeOH/HCO_2H = 100/0.1; Gradient program: Mobile phase A/Mobile phase B = 10/90: t_R = 5.78 min, purity: 99.58% (210 nm), 99.46% (244 nm).

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