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Synthesis of 2′-β-*C*-methyl toyocamycin and sangivamycin analogues as potential HCV inhibitors

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Abstract—Coupling reaction of 2-β-*C*-methyl-1,2,3,4-tetra-*O*-benzoyl-D-ribofuranose with 4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidine, followed by debromination and debenzoylation, gave the 2′-β-*C*-methyl toyocamycin in high yield. Based on this result, a series of 2′-β-*C*-methyl-4-substituted toyocamycin and sangivamycin analogues were synthesized for biological screening as potential inhibitors of HCV RNA replication.

Heptatitis C virus is the most common blood-borne infection and a major cause of chronic liver disease and liver transplantation in industrialized countries. The prevalence of HCV infection is estimated to be five-fold greater than HIV infection and ranges from 1% to 5% in most developed countries.[1] Current therapy is both poorly tolerated and has limited efficacy, with less than 50% response rates among patients infected with the most prevalent virus genotype. Therefore, there is a need for more efficient and better tolerated anti-HCV agent.

Screens of available nucleosides for HCV inhibitors in the cell-based bicistronic replicon assay have identified 2′-β-*C*-methyl adenosine, which inhibit HCV RNA replication in the absence of cytotoxicity.[2] Toyocamycin and sangivamycin are naturally occurring nucleoside antibiotics.[3] A lot of their derivatives were chemically synthesized to try to increase their biological and chemotherapeutic activity.[4] In view of these interesting results, we initiated a study to design and synthesize 2′-β-*C*-methyl toyocamycin and sangivamycin analogues to look for HCV inhibitors.

2′-β-*C*-Methyl toyocamycin and sangivamycin were synthesized by Takamasa's group in 1992.[5] However, their synthetic strategy was not very practical. The overall yields for both compounds were very low, and the purification of the key intermediate was very difficult. Their coupling reaction gave a mixture of α- and β-anomers, and the structures of the final compounds were confirmed by X-ray analysis. So, it appears that there was need for a more efficient method to synthesize a series of 2′-β-*C*-methyl toyocamycin and sangivamycin derivatives for biological screening. Here, we want to report a new synthetic strategy for the synthesis of 2′-*C*-methyl toyocamycin and sangivamycin, and several of their analogues.

The syntheses of 2′-β-*C*-methyl toyocamycin and sangivamycin derivatives are summarized in Scheme 1. The coupling reaction between 2-β-*C*-methyl-1,2,3,5-tetra-*O*-benzoyl-β-D-ribofuranose (**1**)[6] and 4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]-pyrimidine (**2**)[7] gave the key intermediate **3** in high yield in 5 g scale. A similar approach for the synthesis of compound **3** was reported recently,[8] however, that paper did not provided any solid evidence to support the structure of compound **3**. During our studies, we found that, even starting from compounds **1** and **2** under different conditions, an isomer of compound **3** was isolated from the reaction mixture as a major product. Therefore, it is necessary to report the exact procedure for the synthesis of compound **3** with solid evidence.

Compound **2** was first silylated with 2 equiv of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in anhydrous acetonitrile under argon atmosphere at room temperature, and then reacted with 1 equiv of compound **1** in the

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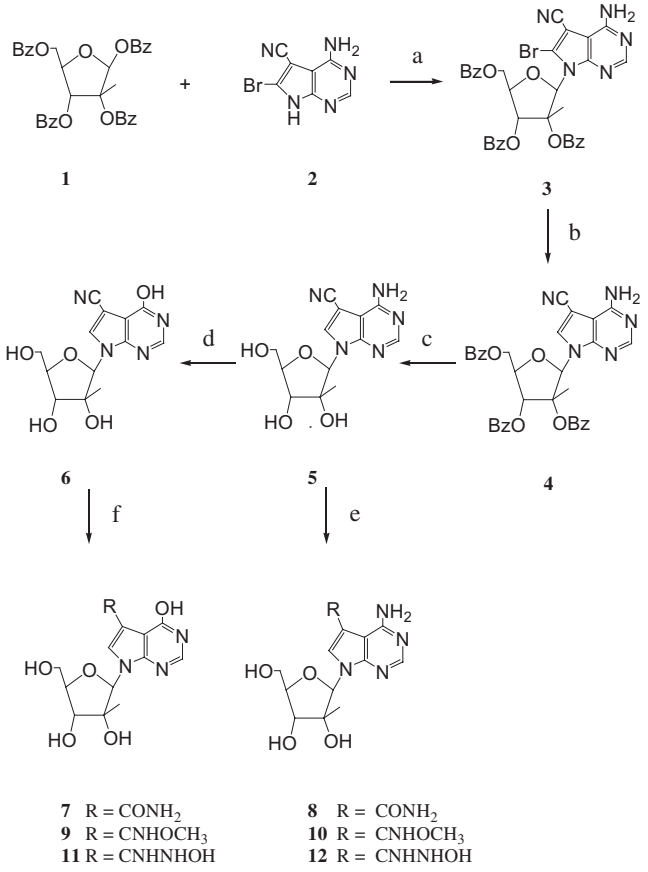


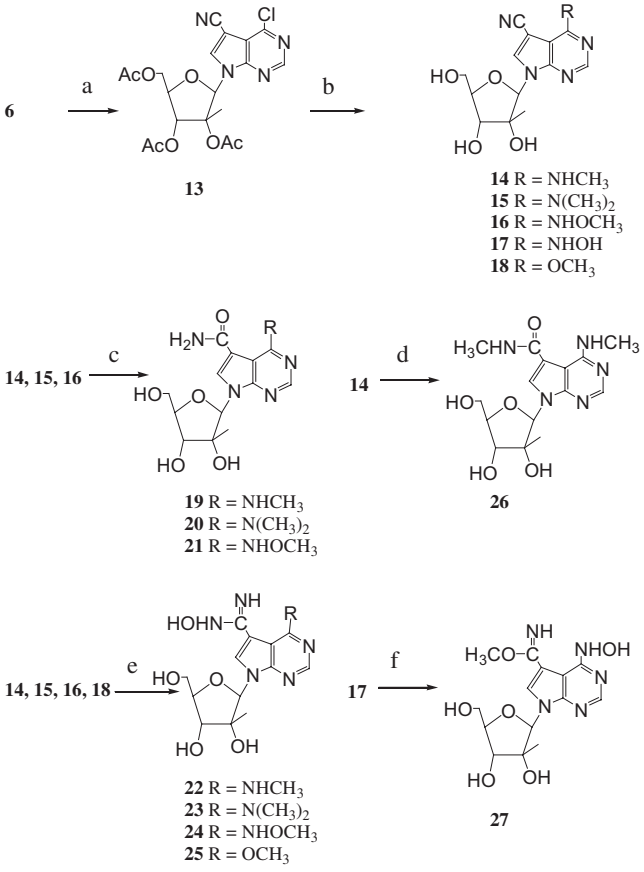
Scheme 1. Reagents and conditions: (a) BSA, CH_3CN, TMSOTf, 80 °C, 3 h, 75%; (b) Pb/C, H_2, CH_3OH, 90%; (c) NH_3/MeOH, 85%; (d) $NaNO_2$, CH_3CO_2H/H_2O, 65%; (e) NH_4OH, H_2O_2, room temperature, 5 h; or NaOMe/MeOH, room temperature, 10 h, or NH_2OH, ethanol, room temperature, 10 h; (f) NH_4OH, H_2O_2, room temperature, 5 h, or NaOMe/MeOH, room temperature, 10 h, or NH_2OH, ethanol, room temperature, 10 h.

presence of 3 equiv of trimethylsilyl trifluoromethanesulfonate at 80 °C for 3 h. After a simple workup, 4-amino-6-bromo-5-cyano-7-(2-β-*C*-methyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-pyrrolo[2,3-*d*]-pyrimidine (**3**) was obtained in 75% yield. Debromination of **3** was accomplished by hydrogenation with 10% Pd/C to afford 4-amino-5-cyano-7-(2-β-*C*-methyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (**4**) in 90% yield. Compound **4** was deprotected with saturated methanolic ammonia to give 2′-β-*C*-methyl toyocamycin **5** in 85% yield. Its structure was confirmed by comparing its NMR spectrum with the same compound reported in the literature,[5] which was confirmed by X-ray analysis.

By using this synthetic strategy, we were able to obtain compound **5** in large scale, and to synthesize a series of 2′-β-*C*-methyl toyocamycin and sangivamycin analogues for biological screening. Oxidation of compound **5** with sodium nitrite in a 4:1 mixture of acetic acid and water gave compound **6** in 65% yield. Conversion of the cyano group of compounds **5** and **6** to an amide group (H_2O_2, concentrated NH_4OH) afforded 2′-β-*C*-methyl sangivamycin **8** and its derivative **7**. Treatment of compounds **5** and **6** with sodium methoxide in methanol gave the 2′-β-*C*-methyl sangivamycin derivatives **9** and **10**. Treatment of compounds **5** and **6** with an excess of hydroxylamine furnished the 5-carboxamide oxime derivatives **11** and **12**.

Compound **6** was then treated with acetic anhydride and pyridine, and the resulting product was refluxed in $POCl_3$ to give the corresponding 4-chloro derivative **13** in 90% yield. The nucleophilic displacement of a chloro group at C-4, followed by the modification of cyano group at C-5, gave the 4,5-disubstituted 2′-β-*C*-methyl sangivamycin derivatives (Scheme 2). Treatment of compound **13** with methylamine, dimethylamine, methoxide, methoxyamine, and hydroxylamine gave the 2′-β-*C*-methyl toyocamycin derivatives **14**, **15**, **16**, **17**, and **18**, respectively. Compounds **14**, **15**, and **16** were then treated with concentrated NH_4OH and H_2O_2, gave 2′-β-C-methyl sangivamycin derivatives **19**, **20**, and **21**, respectively. When compounds **14**, **15**, **16**, and **18** were treated with hydroxylamine, 2′-β-*C*-methyl 5-carboxamide oxime derivatives **22**, **23**, **24** and **25** were obtained, respectively.

Treatment of compound **14** with methylamine in a mixture of methanol and water (10:1) afforded 2′-β-*C*-methyl sangivamycin derivatives **26** in 75% yield. Treat-



Scheme 2. Reagents and conditions: (a) (i) $(Ac)_2O$, pyridine; (ii) $POCl_3$, 70 °C, 1 h, 90%; (b) CH_3NH_2 or $(CH_3)_2NH$ or CH_3ONH_2 or NH_2OH or NaOMe in ethanol, 10 h; (c) NH_4OH, H_2O_2, ethanol, 10 h; (d) CH_3NH_2, MeOH, room temperature, 10 h, 75%; (e) NH_2OH, ethanol, room temperature, 10 h; (f) NaOMe, MeOH, room temperature, 10 h, 67%.

ment of compound **17** with sodium methoxide in methanol gave 4-hydroxylamine of sangivamycin derivative **27** in 67% yield.[9]

Compounds **5**–**12**, **14**–**27** were used for screening in the cell-based bicistronic replicon assay, and some of the compounds showed excellent anti-HCV activities (0.5–100 μM for EC_{50}), and the SAR studies of 2′-β-*C*-methyl related nucleosides for HCV will be reported in due course.

In conclusion, through an efficient synthetic strategy, 2′-β-*C*-methyl toyocamycin was synthesized in high yield, and based on this results, a series of 2′-β-*C*-methyl-4-substituted toyocamycin and 4,5-disubstituted sangivamycin analogues were obtained for biological screening for HCV inhibitors.

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9. Spectral data for some new compounds: **7** ^{1}H NMR (CD_3OD, 300 MHz): δ 8.18 (s, 1H), 8.01 (s, 1H), 6.29 (s, 1H), 4.05 (m, 3H), 3.87 (dd, 1H, J = 13.5, 1.8 Hz); MS: 325 $[M+1]^+$. Compound **8** ^{1}H NMR (CD_3OD, 300 MHz): δ 8.09 (s, 1H), 8.09 (s, 1H), 6.26 (s, 1H), 4.04 (m, 3H), 3.90 (dd, 1H, J = 12.6, 2.7 Hz), 0.85 (s, 3H); MS: 324 $[M+1]^+$. Compound **9** ^{1}H NMR (CD_3OD, 300 MHz): δ 8.44 (s, 1H), 8.12 (s, 1H), 6.26 (s, 1H), 4.13 (d, 1H, J = 10.8 Hz), 4.04 (m, 2H), 3.88 (s, 3H), 3.84 (m, 1H), 0.86 (s, 3H); MS: 339 $[M+1]^+$. Compound **10** ^{1}H NMR (CD_3OD, 300 MHz): δ 8.36 (s, 1H), 7.97 (s, 1H), 6.28 (s, 1H), 4.10 (d, 1H, J = 8.7 Hz), 4.03 (m, 2H), 3.83 (m, 1H), 3.84 (s, 3H), 0.87 (s, 3H); MS: 338 $[M+1]^+$. Compound **11** ^{1}H NMR (CD_3OD, 300 MHz): δ 7.99 (s, 1H), 7.93 (s, 1H), 6.30 (s, 1H), 4.01 (m, 3H), 3.86 (m, 1H), 0.88 (s, 3H); MS: 340 $[M+1]^+$. Compound **12** ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.06 (s, 1H), 7.88 (s, 1H), 6.26 (s, 1H), 4.10 (d, 1H, J = 9.6 Hz), 4.04 (m, 2H), 3.87 (m, 1H), 0.88 (s, 3H); MS: 339 $[M+1]^+$. Compound **14** ^{1}H NMR (CD_3OD, 300 MHz): δ 8.40 (s, 1H), 8.27 (s, 1H), 6.25 (s, 1H), 4.09 (d, 1H, J = 9.0 Hz), 4.04 (m, 2H), 3.86 (dd, 1H, J = 12.6, 2.7 Hz), 3.12 (s, 3H), 0.86 (s, 3H); MS: 320 $[M+1]^+$. Compound **16** ^{1}H NMR (CD_3OD, 300 MHz): δ 8.15 (s, 1H), 7.61 (s, 1H), 6.11 (s, 1H), 4.25 (m, 2H), 4.03 (m, 1H), 3.85 (s, 3H), 3.82 (dd, 1H), 0.89 (s, 3H); MS: 336 $[M+1]^+$. Compound **18** ^{1}H NMR (CD_3OD, 300 MHz): δ 8.60 (s, 1H), 8.51 (s, 1H), 6.34 (s, 1H), 4.18 (s, 3H), 4.13 (d, 1H, J = 9.7 Hz), 4.06 (m, 1H), 4.03 (m, 1H), 3.86 (dd, 1H, J = 12.9, 3.0 Hz), 0.85 (s, 3H); MS: 320 $[M+1]^+$. Compound **19** ^{1}H NMR (CD_3OD, 300 MHz): δ 8.16 (s, 1H), 8.05 (s, 1H), 6.25 (s, 1H), 4.03 (m, 3H), 3.91 (m, 1H), 3.07 (s, 3H), 0.87 (s, 3H); MS: 338 $[M+1]^+$. Compound **20** ^{1}H NMR (CD_3OD, 300 MHz): δ 8.21 (s, 1H), 8.03 (s, 1H), 6.30 (s, 1H), 4.12 (d, 1H, J = 8.7 Hz), 4.03 (m, 2H), 3.86 (dd, 1H, J = 12.6, 3.6 Hz), 0.88 (s, 3H); MS: 352 $[M+1]^+$. Compound **21** ^{1}H NMR (CD_3OD, 300 MHz): δ 7.95 (s, 1H), 7.55 (s, 1H), 6.16 (s, 1H), 4.01 (m, 2H), 3.86 (s, 2H), 3.64 (m, 2H), 0.88 (s, 3H); MS: 354 $[M+1]^+$. Compound **22** ^{1}H NMR (CD_3OD, 300 MHz): δ 8.11 (s, 1H), 7.80 (s, 1H), 6.23 (s, 1H), 4.09 (d, 1H, J = 9.3 Hz), 4.03 (m, 2H), 3.88 (dd, 1H, J = 12.6, 2.8 Hz), 3.05 (s, 3H), 0.86 (s, 3H); MS: 353 $[M+1]^+$. Compound **23** ^{1}H NMR (CD_3OD, 300 MHz): δ 8.17 (s, 1H), 7.76 (s, 1H), 6.30 (s, 1H), 4.12 (d, 1H, J = 8.7 Hz), 4.01 (m, 2H), 3.83 (dd, 1H, J = 12.6, 3.6 Hz), 3.19 (s, 6H), 0.87 (s, 3H); MS: 367 $[M+1]^+$. Compound **24** ^{1}H NMR (CD_3OD, 300 MHz): δ 7.80 (s, 2H), 6.24 (s, 1H), 4.02 (m, 3H), 3.89 (m, 1H), 3.86 (s, 3H), 0.89 (s, 3H); MS: 369 $[M+1]^+$. Compound **25** ^{1}H NMR (CD_3OD, 300 MHz): δ 8.43 (s, 1H), 7.99 (s, 1H), 6.78 (s, 1H), 4.16 (s, 3H), 4.13 (d, 1H, J = 12.6 Hz), 4.03 (m, 2H), 3.83 (dd, 1H, J = 13.2, 3.6 Hz), 0.85 (s, 3H); MS: 354 $[M+1]^+$. Compound **26** ^{1}H NMR (CD_3OD, 300 MHz): δ 8.16 (s, 1H), 7.93 (s, 1H), 6.24 (s, 1H), 4.04 (m, 3H), 3.89 (dd, 1H), 3.08 (s, 3H), 2.90 (s, 3H), 0.86 (s, 3H); MS: 352 $[M+1]^+$. Compound **27** ^{1}H NMR (CD_3OD, 300 MHz): δ 8.47 (s, 1H), 8.25 (s, 1H), 6.28 (s, 1H), 4.11 (d, 1H), J = 9.7 Hz), 4.04 (m, 2H), 3.88 (s, 3H), 3.84 (dd, 1H, J = 12.6, 2.4 Hz), 0.85 (s, 3H); MS: 354 $[M+1]^+$.