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Syntheses of 4′-spirocyclic phosphono-nucleosides as potential inhibitors of hepatitis C virus NS5B polymerase

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ABSTRACT

To discover novel nucleosides as potential antiviral agents, 4′-spirocyclic phosphono-nucleosides were designed to mimic the monophosphate of R-1479, a known nucleoside inhibitor of HCV NS5B. Bypassing the first kinase step to nucleoside monophosphate is viewed as advantageous since this phosphorylation is often observed as the rate-limiting transformation to the active NTP for many nucleosides. Efficient synthetic routes were developed with a triphenylphosphine–iodine cyclization reaction as the key step to form the tetrahydrofuran 4′-spirocycle. The desired 4′-spirocyclic phosphono-cytidine analogs **12a**, **12b**, and **16** were prepared in 11 steps.

To discover nucleoside inhibitors of HCV NS5B, scientists have primarily focused on the preparation of nucleoside analogs altered on the 2′-position of the ribose moiety. Representative examples include 2′-modified nucleosides which have successfully advanced into clinical trials, such as MK-608,[1] NM-107,[2] PSI-6130,[3] and **17**[4] (Fig. 1), although to date only sofosbuvir[5] reached the market.

In contrast to the numerous nucleoside analogs with 2′-modifications, R-1479 is a cytidine analog with 4′-modification and it is a potent HCV NS5B inhibitor that advanced to clinical trials (Fig. 2).[6] Like all nucleoside inhibitors of HCV NS5B, R-1479 exerts its anti-HCV activity via its triphosphate (TP) which is the actual inhibitor of HCV NS5B.[7] Thus, R-1479 actually is a prodrug of the active metabolite R-1479-TP which is formed in vivo via an initial kinase-mediated phosphorylation step to yield its monophosphate (R-1479-MP) and then two more kinase transformations to form the corresponding triphosphate (R-1479-TP). We envisioned that 4′-spirocyclic phosphononucleoside **12** could potentially mimic R-1479-MP as shown in Figure 2.

The selection of a phosphonic acid group to mimic the phosphate of R-1479-MP was based on the observation that organophosphonates have geometrical and electronic similarities relative to a phosphate group. Furthermore, organophosphonates have been demonstrated as excellent mimics of phosphates, leading to numerous biologically active molecules with some reaching the market.[8] Attachment of a phosphonate group to the 2-position of the 4′-spiro-tetrahydrofuran ring should place the phosphonate in the same vicinity as the phosphate group of R-1479-MP. Kinase phosphorylation of the phosphonate **12** could produce its diphosphate which should mimic R-1479-TP. The successful mimicry of the active nucleoside-MPs should bypass the first kinase step which is often observed as the rate-limiting step for many nucleosides. It is well established that some organophosphonic acids function as substrates for kinases and their corresponding diphosphates are formed in vivo. For example, PMEA,[9] a phosphonate analog of nucleoside 5′-monophosphate, exerts its anti-HBV activity via its diphosphate and its prodrug form is employed clinically to treat HBV infections.[10]

To access the 4′-spirocyclicphosphono nucleoside scaffold, a retrosynthetic plan was devised to prepare the ribose intermediate **8** which should allow rapid exploration of various bases via glycosidic bond formation reactions, Scheme 1 (Nap: 2-naphthylmethyl;[11] TBDPS: *tert*-butyldiphenylsilyl).

The 4′-hydroxymethyl-ribose derivative **1** was prepared according to the Prakash procedures.[12] Treatment of compound **1** with dimethoxytrityl chloride (DMTr-Cl) in pyridine gave the hydroxy-protected compound **2** in 90% yield. Removal of TBDPS protecting group using TBAF gave compound **3** in 66% yield, and subsequent oxidation of the α-hydroxymethyl group gave aldehyde **4** in 95% yield. Wittig reaction of aldehyde **4** gave phos-

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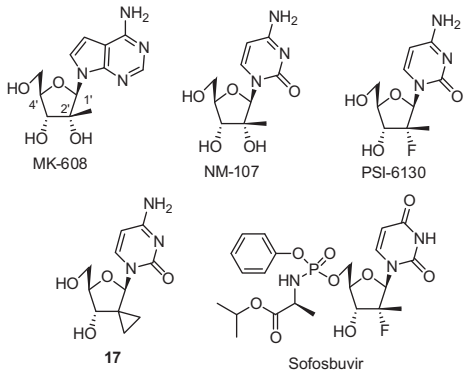


Figure 1. Clinically evaluated nucleoside HCV NS5B inhibitors.

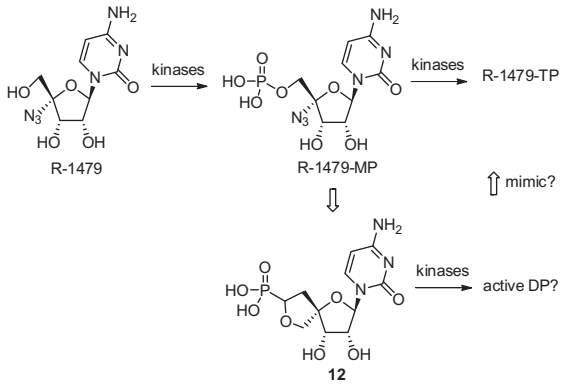
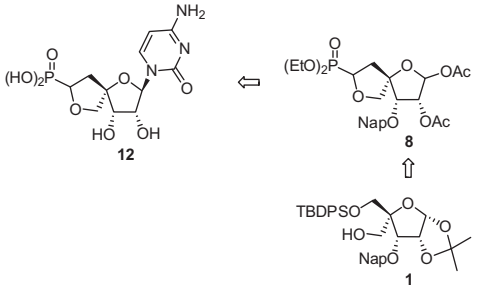


Figure 2. Novel 4′-spirocyclic phosphono-nucleosides.

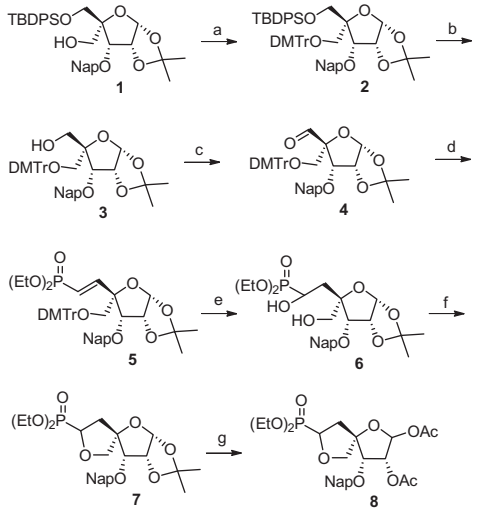
phonate ester **5** in 65% yield. Hydroboration of olefin **5** under Negishi conditions[13] gave diol **6** in 36% yield (note: the newly formed chiral center α to the phosphorus is racemic; the DMTr protecting group fell off). Cyclization of the diol **6** to form the tetrahydrofuran ring was carried out using the Mandal procedure:[14] treatment of diol **6** with triphenylphosphine and iodine in the presence of imidazole gave the 4′-spiro-tetrahydrofuan **7** in 26% yield (note: the newly formed chiral center α to the phosphorus is racemic). Treatment of compound **7** with a mixture of acetic acid, acetic anhydride, and sulfuric acid (5.5:2:0.2, v/v) gave the desired key ribose derivative **8** (52%), which is ready for Vorbruggen couplings with various bases (Scheme 2).

With the key ribose **8** in hand, we demonstrated its utility by coupling with a cytidine base, as illustrated in Scheme 3.

Under Vorbruggen coupling conditions, ribose **8** was reacted with the silylated N-Ac cytidine in the presence of tin(IV) chloride to give the nucleoside **9** in 40% yield. Removal of the Nap protecting group was achieved under DDQ oxidation conditions[15] to give compound **10** in 22% yield. Treatment of compound **10** with



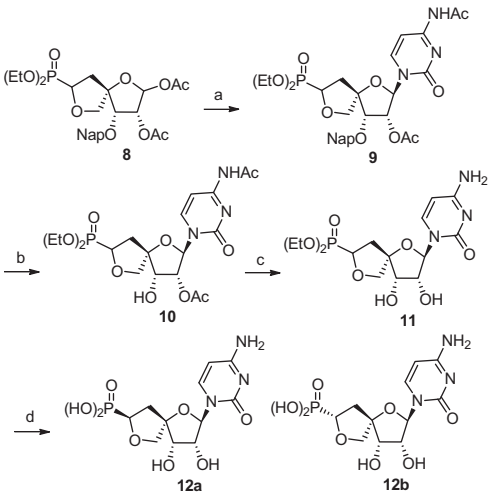
Scheme 1. Retrosynthetic analysis.



Scheme 2. Synthesis of **8**. Reagents and conditions: (a) DMTrCl (1.06 equiv), pyridine, 25 °C, 16 h, 90%; (b) TBAF (2.07 equiv), THF, 25 °C, 48 h, 66%; (c) nBu$_4$NBr (0.05 equiv), TEMPO (0.05 equiv), $KHCO_3$ (2.1 equiv), NBS (1.57 equiv), CH_2Cl_2/H_2O (1:1), 0 °C, 1 h, 95%; (d) $Ph_3P{=}CH\text{-}PO(OEt)_2$ (1.06 equiv), DMF, 90 °C, 16 h, 65%; (e) (i) BH_3–THF (12 equiv), THF, 25 °C, 12 h; (ii) H_2O_2 (56 equiv), NaOAc (excess), H_2O, 55 °C, 0.5 h, 36%; (f) (i) PPh_3 (1.12 equiv), imidazole (2.55 equiv), toluene, reflux, 5 min.; (ii) I_2 (1.04 equiv), reflux, 0.5 h, 26%; (g) $AcOH/Ac_2O/H_2SO_4$ (5.5:2.0:0.2, v/v, 0.08 M solution), 25 °C, 20 h, 52%.

ammonium hydroxide in methanol removed both the N-Ac and 2′-OAc protecting groups to produce **11** in 43% yield, and a final TMSBr mediated-removal of the phosphonate diethyl ester gave the desired 4′-spirocyclic phosphono nucleosides, which were separated by HILIC Silica HPLC to give compounds **12a** and **12b**. The stereochemistry of the 4′-carbon for compounds **12a** and **12b** was established via NOESY experiments, and the data are summarized in Figure 3.

For compound **12a**, the 5′-methylene (δ = 2.42–2.49) exhibited an NOE interaction with the 3′-H (δ = 4.28), while the 6′-methylene (δ = 3.90–4.10) did not exhibit any NOE interaction with the 3′-H (δ = 4.28) and the 6-H (δ = 7.77). For compound **12b**, the 5′-methylene (δ = 2.21–2.30) exhibited an NOE interaction with the 6-H



Scheme 3. Synthesis of nucleosides **12a** and **12b**. Reagents and conditions: (a) (i) *N*,*O*-bis(trimethylsilyl)acetamide (7.02 equiv), N-Ac cytidine (2.1 equiv), MeCN, reflux, 2 h; (ii) compound **8** (1.0 equiv), $SnCl_4$ (3.01 equiv), 25 °C, 15 h, 40%; (b) DDQ (20 equiv), CH_2Cl_2/water (20:1, v/v), 25 °C, 48 h, 22%; (c) NH_4OH/MeOH (1:1, v/v), 25 °C, 1.5 h, 43%; (d) TMSBr (15.5 equiv), DMF, 0–25 °C, 4 h, **12a**, 8%, **12b**, 4.4%.

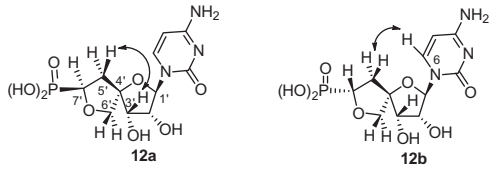
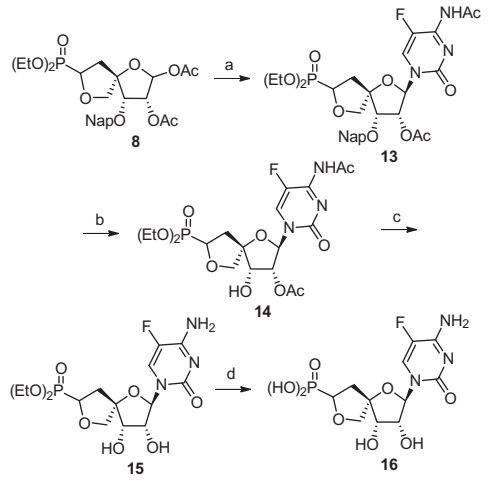


Figure 3. Summary of NOE data for compounds **12a** and **12b**.



Scheme 4. Synthesis of nucleosides **16**. Reagents and conditions: (a) (i) N-Ac-5-F-cytidine (2.11 equiv), *N,O*-bis(trimethylsilyl)acetamide (7.38 equiv), MeCN, reflux, 2 h; (ii) compound **8** (1.0 equiv), $SnCl_4$ (3.16 equiv), 55 °C, 1.5 h, 39%; (b) DDQ (2.1 equiv), CH_2Cl_2/water (20:1, v/v), 25 °C, 6 h, 25%; (c) NH_4OH/MeOH (1:1, v/v), 25 °C, 15 h, 25%; (d) TMSBr (28.4 equiv), DMF, 0–25 °C, 5 h, 26.

(δ = 7.65). On the other hand, the absolute stereochemistry of the 7′-carbon was not determined, instead they were assigned arbitrarily to differentiate the two diastereo-isomers.

Analogously, 5-fluorocytidine nucleoside **16** was also prepared from ribose **8** in four steps, as illustrated in Scheme 4.

In summary, to discover active analogs of the known anti-HCV nucleoside R-1479, a phosphonic acid group was selected as a phosphate mimic of the key metabolite R-1479-MP. A 4′-spirocyclic tetrahydrofuran ring was chosen as the linking group which should provide conformational restriction and partially mimic the steric effect of the 4′-azido group of R-1479. New synthetic routes have been developed to access a versatile ribose 4′-spirocyclic phosphonate diester intermediate **8**, which should allow rapid investigation of various bases via glycosidic bond formation reactions. The utility of compound **8** was demonstrated via the syntheses of novel phosphonic acid-containing cytidine nucleoside analogs **12a**, **12b**, and **16**. Testing of these novel nucleosides against HCV should provide important SAR information to help us to expand the understanding of the field.

Supplementary data

Supplementary data (the experimental procedures and characterization data for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.06.029.

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