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Synthesis of 4′-*C*, 3′-*O* bicyclic thymidine analogues using ring closure metathesis†

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Abstract—We have developed a route to the synthesis of new six-membered ring bicyclic nucleoside analogues. The synthesis of 4′-*C*, 3′-*O* bicyclic thymidine analogues is presented as first examples of this new family. Six-membered ring construction was efficiently achieved by the application of ring closure olefin metathesis on a diene intermediate using Grubbs' catalyst.

Since the approval of 3′-azido-3′deoxy-thymidine (AZT, Zidovudine, Retrovir) as the first drugs for the clinical treatment of acquired immunodeficiency syndrome (AIDS) by the Food and Drugs Administration,[1] a considerable amount of work has been devoted towards the synthesis and biological evaluation of nucleoside analogues. This intensive research was dedicated to the discovery of more effective, more selective and nontoxic new therapeutic agents, as well as new agents for other viral infections.[2] These efforts provided a number of drugs and drug candidates,[3] and, in this context, considerable attention has been particularly focused on the synthesis of *C*-branched sugar nucleosides,[4] carbocyclic sugar nucleosides,[5] acyclic sugar nucleosides,[6] and bicyclic sugar nucleosides.[7]

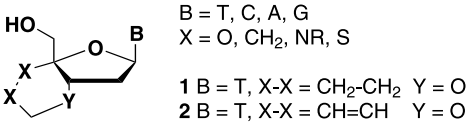
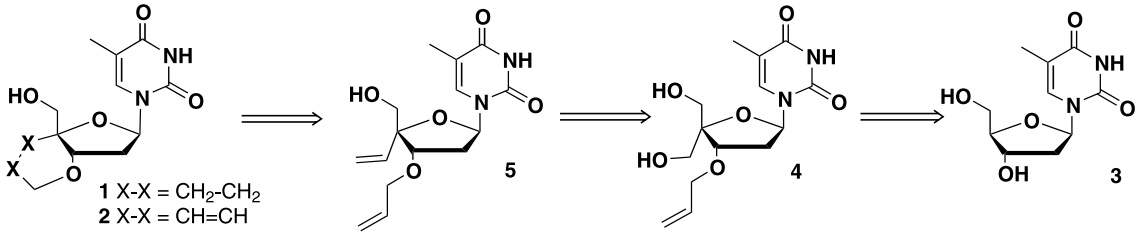


Figure 1.

In the course of our ongoing research on the synthesis and biological evaluation of modified sugar ring nucleosides, we became interested in an efficient and flexible strategy for the preparation of 4′,3′-six-membered ring bicyclic nucleoside analogues, as presented in Fig. 1, to provide novel analogues for biological studies.

Surprisingly, although considerable work has been done in the synthesis of nucleoside analogues, to the best of our knowledge, no synthetic work has been reported to provide any member of this family of bicyclic nucleoside analogues.[8,9] This fact prompted us to devise



Scheme 1. Retrosynthetic scheme.

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† The authors wish to dedicate this paper to Dr. Jean Villiéras, an outstanding chemist and a great teacher, on the occasion of his retirement.

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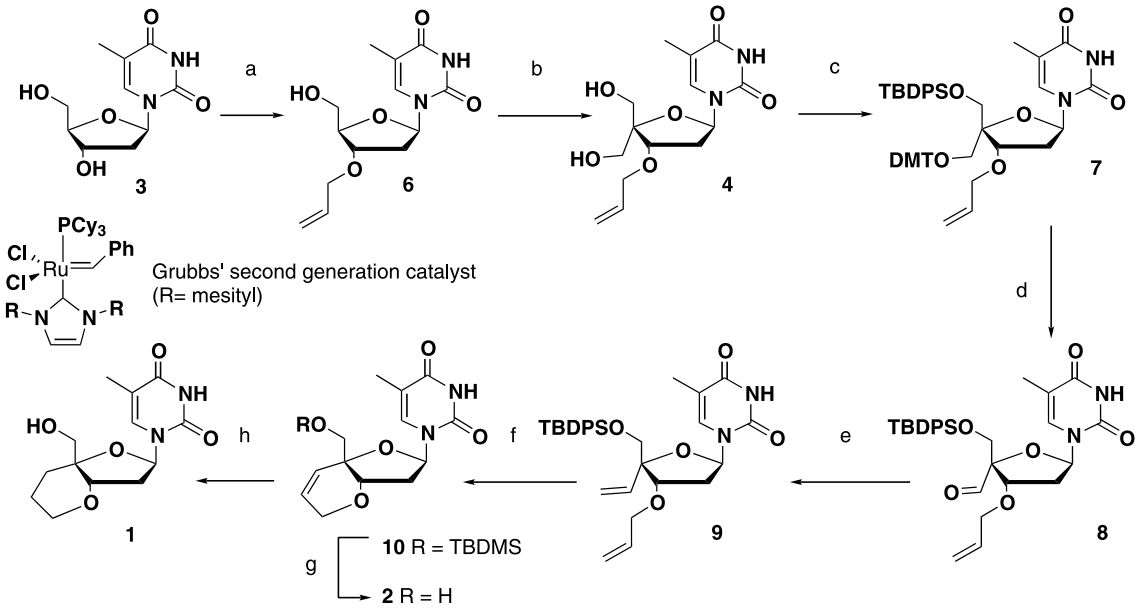

Scheme 2. *Reagents and conditions*: (a) (i) TBDMSCl, imidazole, DMF, rt, 6 h, 87%; (ii) NaH, allyl bromide, 40°C, ultrasound bath, 4 h, 80%; (ii) TBAF, THF, rt, 2 h, 96%; (b) (i) DCC, pyridium trifluoacetate, DMSO, rt, 12 h; (ii) HCHO aq., NaOH aq., dioxane, rt, 6 h then $NaBH_4$, rt, 30 min, 52%; (c) (i) DMTCl, pyridine, rt, 3 h, 64%; (ii) TBDPSCl, imidazole, DMF, rt, 12 h; (d) (i) AcOH/THF/H_2O (7/3/3), rt, 24 h, 67% for the two steps; (ii) DMP, wet CH_2Cl_2, rt, 1 h, 98%; (e) $Ph_3P{=}CH_2$, THF, −78°C, 30 min then 0°C, 2 h, 89%; (f) Grubbs' catalyst second generation, CH_2Cl_2, rt, 4 h, 74%; (g) TBAF, THF, rt, 3 h, 95%; (h) H_2, Pd/C, EtOH, rt, 2 h, 84%.

a synthetic route to reach these compounds and, in this communication, we wish to describe the feasibility of our strategy through the synthesis of the 3′-*O*, 4′-*C* bicyclic thymidine analogues **1** and **2** as the first examples.

Our retrosynthetic analysis is outlined in Scheme 1, and is centered on a ring closing metathesis (RCM) reaction[10] to provide rapid access into 4′-*C*, 3′-*O* bicyclic thymidine analogues.[11] Starting from thymidine **3**, the diene intermediate **5** should be readily available from a known sequence[12] described on the 3′-*O*-silylether thymidine derivative.

Our synthesis is depicted in Scheme 2. Classical protecting group manipulation on thymidine **3**: (i) monosilylation by *tert*-butyldimethylsilyl (TBDMS) group under standard conditions, (ii) *O*-allylation of the C-3′-hydroxyl group[13] performed with NaH (60% suspension in oil) and allyl bromide in THF at 40°C in an ultrasound bath,[14] and (iii) removal of the silyl protecting group using *n*-tetrabutylammonium fluoride (TBAF) furnished the alcohol **6** in 65% overall yield for the three steps. It should be pointed out that the allyl group could serve as a protecting group in the first stage of our synthesis and then as a precursor of the six-membered ring at this end. We next turned our attention to the introduction of a vinyl group into the 4′-α-position as follows.[15]

Thus, the 5′-hydroxyl group of **6** was oxidized, using the Moffatt method, to the corresponding aldehyde which, after purification,[16] was reacted with aqueous NaOH and formaldehyde solutions in dioxane. Then, the resulting reaction mixture was treated by direct addition of $NaBH_4$ to afford, after purification, the diol **4** in 52% overall yield from **6**.

The 5′α-hydroxyl group of **4** was selectively protected as 4,4′-dimethoxytrityl (DMT) ether and the 5′β-hydroxyl group as silyl ether in 64% overall yield to furnish **7**, according to a previously reported procedure.[10] Then, the 5′-α-*O*-DMT group was selectively removed in 88% yield by treating **7** with AcOH in a mixture of THF and water to give the 5′-α-hydroxyl derivative, which was oxidized to the corresponding aldehyde **8** with Dess–Martin periodinane[17] (DMP) in nearly quantitative yield. The key diene intermediate **9** was prepared from the aldehyde **8** by Wittig reaction with methylene triphenylphosphorane to afford the homologated compound in 89% yield after purification.[18] The key diene **9** was subjected to a RCM reaction in dichloromethane with Grubbs' second generation catalyst at room temperature to give the cyclized intermediate **10** in 74% yield.[19] Previous attempts to carry out the RCM reaction with $Cl_2(Cy_3P)_2RuCHPh$ on diene **9** in the same experimental conditions afforded **10** in lower yield (69%). Removal of the TBDMS protecting group from **10** with TBAF afforded the first bicyclic nucleoside analogue **2**.[20] Reduction of the double bond in **2** was accomplished by catalytic hydrogenation on 10% Pd/C in ethanol to give the nucleoside analogue **1** in 84%.[21]

As a first biological evaluation, bicyclic thymidine analogues **1** and **2** were tested in an in vitro assay for *Herpes simplex* virus type 1 (HSV-1) inhibition: these two compounds were found to be inactive.

In summary, we have completed a synthesis of two novel 3′-*O*, 4′-*C* bicyclic thymidine analogues **1** and **2** using a ring closure ruthenium-catalyzed olefin metathesis reaction as the key reaction step, providing a new strategy for the synthesis of 4′-*C*, 3′-bicyclic nucleoside analogues with six-membered carbo- and heterocyclic rings. We are currently applying this strategy to the synthesis of the nitrogen and sulfur analogues and this work will be reported in due course as well as the complete biological activities of all these new nucleoside analogues.

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13. Purification on silica gel column led to the desired compound in 80% yield accompanied by the corresponding bis-allyl-2-*N*-, 3′-*O*-derivative in 10% yield and unreacted starting material in 10% yield.
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19. Representative procedure for **10**: To a solution of compound **9** (100 mg, 0.18 mmol) in CH_2Cl_2 (12 mL) was added ruthenium-catalyst (16 mg, 0.019 mmol) in CH_2Cl_2 (8 mL) via cannula transfer, and the reaction mixture was stirred under argon for 4 h at 25°C. The reaction mixture was then diluted with CH_2Cl_2 (30 mL), washed with brine solution, dried over $MgSO_4$ and concentrated. The residue was then purified on a silica gel column, eluting with 40% ethyl acetate/hexane to give the cyclized compound **10** (70 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.83 (s, 1H, NH); 7.38–7.73 (m, 10H, Ph_2-Si); 7.54 (d, 1H, $J=1.2$ Hz, H_6); 6.41 (dd, 1H, $J=5.2$ and 8.9 Hz, $H_{1'}$); 6.08–6.13 (m, 1H, O-CH_2-C*H*=); 5.62–5.67 (m,

1H, O-CH_2-CH=C*H*-C); 4.29 (d, 1H, $J=4.5$ Hz, $H_{3'}$); 4.11–4.18 and 3.85–3.91 (m, 2H, O-CH_2-CH=); 3.58 and 3.83 (AB system, 2H, $J=11.2$ Hz, $H_{5'}$); 2.45–2.51 and 2.32–2.41 (m, 2H, $H_{2'}$); 1.58 (d, 3H, $J=1.2$ Hz, Me_7); 1.10 (s, 9H, ^{t}Bu-Si).^{13}C NMR δ: 158.5; 145.1; 130.3; 130.1; 127.5; 126.9; 125.9; 125.0; 124.9; 122.8; 118.9; 105.8; 79.3; 75.3; 63.0; 57.2; 33.6; 21.8; 14.2; 6.8. HMRS (EI) calcd for $[M-{}^t\text{BuH}]^+$ 461.1533, found 461.1539.

20. Selected spectral data for compound **2**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.40 (s, 1H, H_6); 6.12–6.17 (m, 1H, O-CH_2-C*H*=); 6.07 (dd, 1H, $J=5.5$ and 9.7 Hz, $H_{1'}$); 5.70–5.74 (m, 1H, O-CH_2-CH=C*H*-C); 4.32 (d, 1H, $J=5.2$ Hz, $H_{3'}$); 3.92–3.99 and 4.12–4.19 (m, 2H, O-CH_2-CH=); 3.57 and 3.72 (AB System, $J=11.9$ Hz, 2H, $H_{5'}$); 2.69–2.76 and 2.33–2.38 (m, 2H, $H_{2'}$); 1.91 (s, 3H, Me_7).^{13}C NMR δ: 12.6; 37.4; 62.7; 67.1; 77.6; 81.1; 88.6; 111.3; 124.2; 131.2; 138.2; 150.7; 163.9. HMRS (EI) calcd for $[M^\bullet]^+$ 280.1059, found 280.1060.
21. Selected spectral data for compound **1**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.98 (br s, 1H, NH); 7.54 (s, 1H, H_6); 6.19 (dd, 1H, $J=5.6$ and 8.9 Hz, $H_{1'}$); 4.08–4.14 (m, 1H, $H_{3'}$); 3.82–3.90 and 3.31–3.40 (m, 2H, O-CH_2-CH-); 3.58–3.68 (m, 2H, $H_{5'}$); 3.00 (br s, 1H, -O*H*); 2.52–2.60 and 2.29–2.37 (m, 2H, $H_{2'}$); 1.90 (s, 3H, Me_7); 1.46–1.63 and 1.73–1.93 (m, 4H, O-CH_2-CH_2-CH_2-C). ^{13}C NMR δ: 12.7; 21.0; 28.2; 38.7; 64.9; 68.0; 77.4; 84.3; 88.7; 110.9; 137.7; 150.7; 164.1. HMRS (EI) calcd for $[M^\bullet]^+$ 282.1216, found 282.1218.