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Efficient synthesis of novel carbocyclic nucleosides via sequential Claisen rearrangement and ring-closing metathesis

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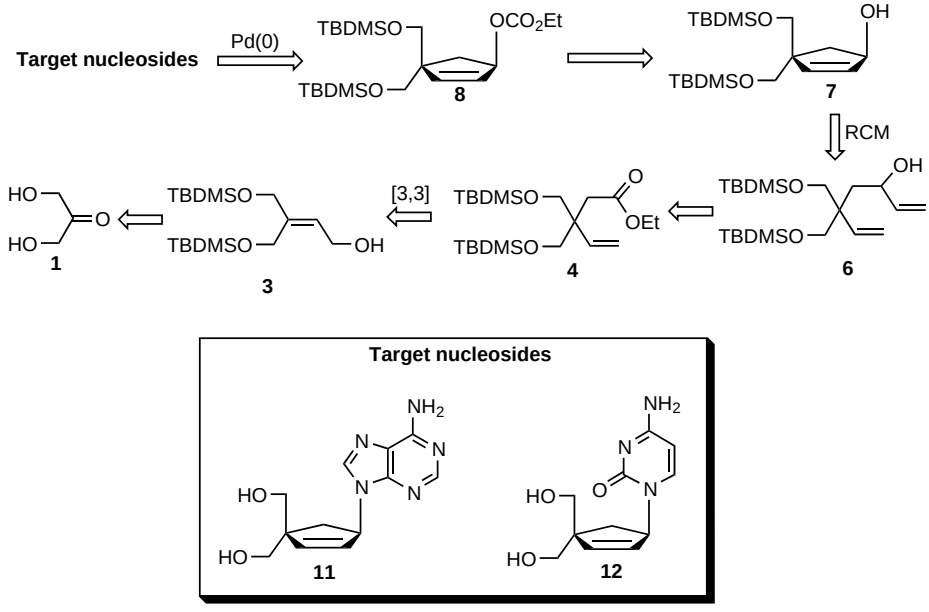
Abstract—Very efficient synthetic route to novel 4′α-*C*-hydroxymethyl branched carbocyclic nucleosides was described. The stereocontrolled synthesis of target nucleosides was successfully achieved by Johnson orthoester–Claisen rearrangement, ring-closing metathesis (RCM) starting from a simple acyclic precursor 1,3-dihydoxy acetone **1**. Nucleosidic bases (adenine and cytosine) were coupled by Pd(0)-catalyzed allylic alkylation in a highly regiocontrolled manner. © 2002 Elsevier Science Ltd. All rights reserved.

Emerging drug resistant virus strains as well as toxicity are major problems in antiviral chemotherapy. Therefore, a number of structurally modified nucleosides have been synthesized to overcome these drawbacks. Among them, carbocyclic nucleosides have attracted great interest, as they show interesting chemical and metabolic features. Carbocyclic nucleosides are a unique class in which a methylene group replaces the oxygen in the furan, which results in metabolic stability to endogenous phosphorylase.[1] The biologically active natural carbocyclic nucleosides such as aristeromycin[2] and neplanocin[3] were found to possess interesting biological properties including antiviral and antitumor activity. Furthermore, the recent approval of abacavir by FDA as an anti-HIV agent strongly warranted the further exploration of carbocyclic nucleosides as chemotherapeutic agents.[4]



Scheme 1.

Keywords: Johnson orthoester–Claisen rearrangement; ring-closing metathesis; Pd(0)-catalyzed reaction; carbocyclic nucleoside.

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Recently, a number of 4′α-substituted nucleoside[5] analogues have been synthesized and showed significant antitumor or antiviral activities. Among them, 4′α-*C*-methyl-2′-deoxycytidine,[6] 4′α-*C*-fluoromethyl-2′-deoxycytidine,[7] 4′α-*C*-hydroxymethylthymidine[8] and 4′α-*C*-azidomethylthymidine[9] demonstrated very potent biological activities, but their high toxicity rendered them ineffectual as drugs.

On the basis of these interesting results and as part of our drug discovery programs, we have designed novel 4′α-hydroxymethyl substituted carbocyclic nucleosides which hybrid the properties of enzyme resistant carbocyclic as well as biologically active 4′α-*C*-branched furanose nucleosides. Herein, we disclose their de novo synthetic routes employing very versatile three step sequences ([3,3]-sigmatropic rearrangement, ring-closing metathesis (RCM), and Pd(0)-catalyzed allylic alkylation) from very simple acyclic precursor '1,3-dihydroxyl acetone'.

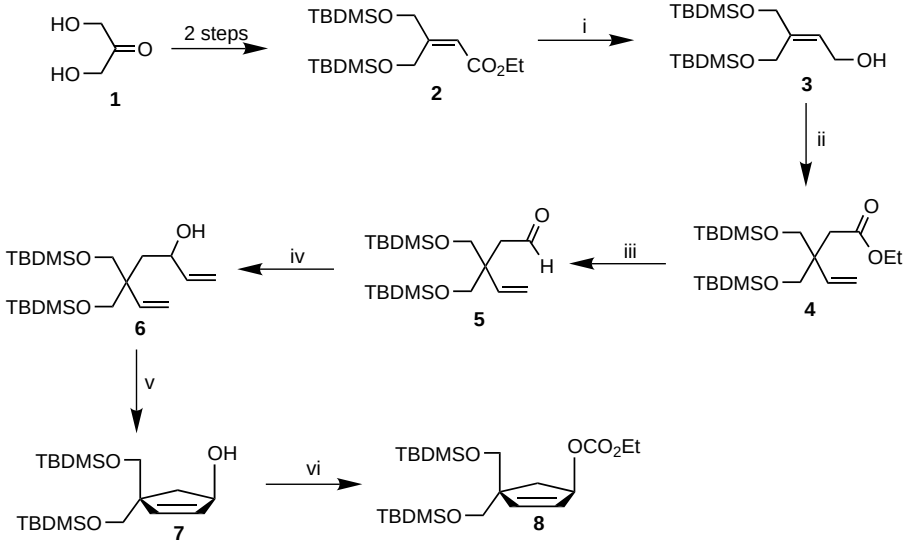
As outlined retrosynthetically in Scheme 1, the synthetic route is straightforward. We envisaged that Johnson orthoester–Claisen rearrangement of **3** would produce the desired quaternary carbon **4** with suitable functional groups, from which cyclopentenol **7** could be installed by successive carbonyl addition and RCM. It is worthwhile that the subjection of **8** to Pd(0)-catalyzed allylic alkylation conditions would produce the desired nucleosides with the correct regiochemistry.

The synthetic route of the key intermediate **8** is illustrated in Scheme 2. 1,3-Dihydroxyacetone was converted to α,β-unsaturated ethyl ester **2**.[10] The α,β-unsaturated ethyl ester **2** was reduced by DIBALH at −20°C in CH_2Cl_2 to give allylic alcohol **3** in 97% yield, which was subjected to standard Johnson's orthoester Claisen rearrangement[11] using triethyl orthoacetate to produce γ,δ-unsaturated ester **4** in 86% yield.[12] Slow addition of DIBALH to solution of the ester **4** in CH_2Cl_2 at −78°C could furnish the desired aldehyde **5**, which was subjected to carbonyl addition by vinyl magnesium bromide to provide divinyl **6** in 74% two-step yield.

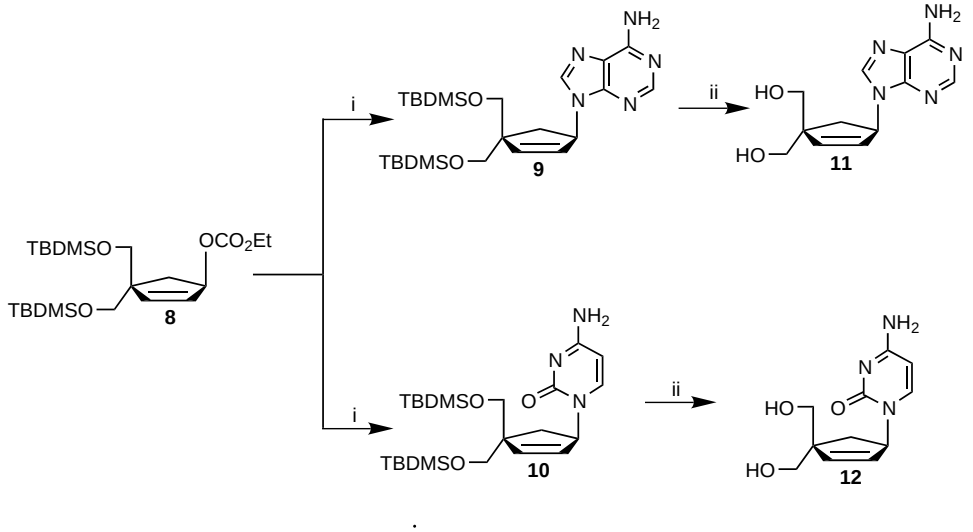
With divinyl **6** in hand, we turned our attention to the formation of five-membered carbocycle. RCM[13] now stands as one of the most powerful tools for the preparation of medium to large ring systems via C–C bond formation. We successfully adopted this powerful procedure for elaboration of our desired five member carbocyclic ring. Thus, divinyl **6** was subjected to normal RCM conditions using [benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium] to afford cyclopentenol **7** in 97% yield. The facile conversion of hydroxyl group of **7** to **8** was made by using ethyl chloroformate in pyridine solvent in 92% yield.

It is well known that the palladium-catalyzed allylic alkylations[14] have been the cornerstone in synthetic organic chemistry because of their reliable high fidelity of regio- and stereochemistry. We have successfully adopted this methodology for the synthesis of desired nucleosides (Scheme 3). The adenine and cytosine anion generated by NaH/DMSO in THF/DMSO at 60°C was successfully condensed with **8** using tris(dibenzylideneacetone)-dipalladium(0)-chloroform adduct as a coupling catalyst to give **9** and **10** in 64 and 46% yield, respectively, without their regioisomers. The deprotected 2′,3′-olefinic nucleosides **11**[15] and **12**[16] were readily obtained by the treatment of **9** and **10** with tetrabutylammonium fluoride (TBAF) in THF solvent in high yield (91–93%).

Also, it should be noted the synthesized nucleosides **11** and **12** are novel compounds based on extensive literature searching. Antiviral activities of synthesized compounds against HIV-1, HBV, HSV-1, HSV-2, and



Scheme 2. *Reagents and conditions*: (i) DIBALH, CH_2Cl_2, −20°C, 2 h, 97%; (ii) triethyl orthoacetate, propionic acid, overnight, 130°C, 86%; (iii) DIBALH, toluene, −78°C, 2 h, 79%; (iv) vinylMgBr, THF, −78°C, 1 h, 94%; (v) $Cl_2(Cy_3P)_2Ru{=}CHC_6H_6$, benzene, reflux, 1 h, 97%; (vi) $ClCO_2Et$, pyridine, DMAP, rt, overnight, 92%.



Scheme 3. *Reagents and conditions*: (i) adenine, and cytosine, $Pd_2(dba)_3{\cdot}CHCl_3$, $P(O\text{-}i\text{-}Pr)_3$, NaH, THF/DMSO, reflux, overnight, 46–64%; (ii) TBAF, THF, rt, 3 h, 91–93%.

HCMV were evaluated. However, none of them showed any significant activity or cytotoxicity up to 100 μM.

In summary, we have developed a very efficient synthetic route to the novel 4′α-*C*-hydroxymethyl substituted carbocyclic nucleosides starting from a simple 1,3-dihydroxy acetone. The required stereochemistry was successfully elaborated by sequential Johnson orthoester–Claisen rearrangement, RCM, and Pd(0)-catalyzed allylic alkylation reactions. In our laboratory, these reiterative three-step sequences have been widely applied for the de novo stereoselective syntheses of novel nucleosides having diverse functionality and stereochemistry.

Acknowledgements

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15. **(±)-9-[4,4-Bis(hydroxymethyl)-cyclopent-2-en-1-yl] adenine (11):** mp 179–180°C; UV (H_2O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.14 (s, 1H), 7.94 (s, 1H), 7.19 (br s, 2H, D_2O exchangeable), 5.97 (dd, $J=5.4$, 1.8 Hz, 1H), 5.89 (dd, $J=6.0$, 2.1 Hz, 1H), 5.63 (dd, $J=8.4$, 5.7 Hz, 1H), 4.71 (br s, 2H, D_2O exchangeable), 3.49 (d, $J=10.5$ Hz, 1H), 3.41 (d, $J=10.5$ Hz, 1H), 2.41 (dd, $J=13.8$, 9.0 Hz, 1H), 1.78 (dd, $J=13.5$, 5.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.96, 152.25, 149.18, 140.55, 138.75, 129.87, 118.92, 65.06, 64.73, 58.97, 57.59, 37.20. Anal. calcd for $C_{12}H_{15}N_2O_5$: C, 55.16; H, 5.79; N, 26.80. Found: C, 55.22; H, 5.83; N, 26.69%.
16. **(±)-1-[4,4-Bis(hydroxymethyl)-cyclopent-2-en-1-yl] cytosine (12):** mp 166–169°C; UV (H_2O) λ_{max} 271.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.45 (d, $J=7.8$ Hz, 1H), 7.22 (br s, 1H, D_2O exchangeable), 6.99 (br s, 1H, D_2O exchangeable), 5.89 (d, $J=3.9$ Hz, 1H), 5.74 (d, $J=6.9$ Hz, 1H), 5.60–5.54 (m, 2H), 4.73 (br s, 2H, D_2O exchangeable), 3.43 (d, $J=9.6$ Hz, 1H), 3.32 (d, $J=9.6$ Hz, 1H), 2.21 (dd, $J=14.1$, 9.0 Hz, 1H), 1.36 (dd, $J=13.2$, 6.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.39, 155.96, 142.13, 141.01, 130.58, 93.88, 65.14, 64.62, 57.19, 48.58, 36.78. Anal. calcd for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.69; H, 6.30; N, 17.59%.