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Synthesis of 3′,3′-Difluoro-2′-hydroxymethyl-4′,5′-Unsaturated Carbocyclic Nucleosides

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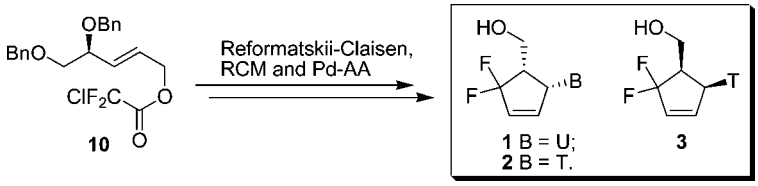
ABSTRACT



3′,3′-Difluoro-2′-hydroxymethyl-4′,5′-unsaturated carbocyclic nucleosides 1–3 have been stereoselectively synthesized from ester 10, which can be conveniently prepared from 2,3-isopropylidene-D-glyceraldehyde 7 in five steps. The whole synthesis highlighted the stereoselective Reformatskii–Claisen rearrangement, ring-closing metathesis (RCM), and palladium-catalyzed allylic alkylation, in which the regioselectivity was reversed from that of nonfluorinated substrates.

Carbocyclic nucleosides (CNAs) have received considerable attention because they possess greater metabolic stability toward the nucleoside phosphorylases and higher lipophilicity, two properties that are potentially beneficial in terms of increased in vivo half-life, oral efficiency, and cell-wall penetration.[1] In the past two decades, a large number of CNAs have been synthesized and biologically evaluated.[2,3] The best known CNAs are the anti-HIV (−)-carbovir,[4] abacavir,[5] and entecarvir[6] (Figure 1); all of them are already in clinical use. Now modifications to some bioactive CNAs

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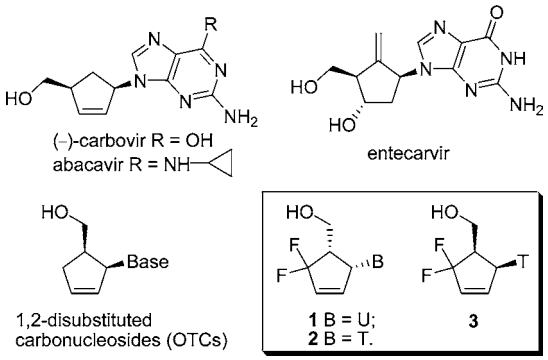
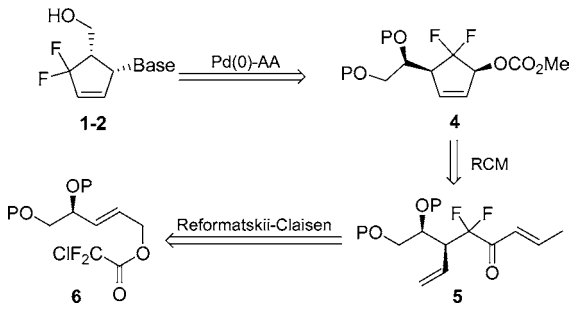


Figure 1. Some highly bioactive CNAs and rational design of 3′,3′-difluoro-4′,5′-unsaturated OTCs **1**−**3**.

represent an important active area in search for compounds with improved biological property. Based on CNAs skeletons, 1,2-disubstituted carbocyclic nucleosides (OTCs), recently attracted more and more attention,[7] especially after De Clercq et al. found that some OTCs showed moderate to good activity against murine leukemia cells L1210/0, human T-lymphocyte cells Molt4/C8, and CEM/0 via topological substructural approach to molecular design (TOSS-MODE).[8] On the other hand, it is well-known that the introduction of fluorine atom(s), especially *gem*-difluoromethylene (CF_2) group, into an organic compound can bring about remarkable changes in the physical, chemical, and biological properties.[9] However, to the best of our knowledge, only a few *gem*-difluorinated CNAs have been developed,[10] which was attributed to the limitation of fluorination method.[11] In the reported syntheses of *gem*-difluorinated CNAs, all the *gem*-difluoromethylene groups (CF_2) were introduced via direct fluorination of carbonyl groups with DAST, which has been limited to wide use not only for its frequently low yield but also for its invalidity to stereo-hindered cyclopentones. To break through this limitation and continue our ongoing efforts to develop new antiviral and anticancer agents, we would like to explore an efficient synthetic route to optically pure *gem*-difluorinated CNAs utilizing commercially available fluorinated building blocks. Herein we describe the stereoselective synthesis of 3′,3′-difluoro-4′,5′-unsaturated OTCs **1**−**3**.

Our retrosynthetic analysis of target molecules **1**−**2** highlighted three key steps, as outlined in Scheme 1.

Scheme 1. Retrosynthetic Analysis of **1**−**2**



As for regio- and stereoselective installation of the base moiety of carbocyclic nucleosides, one of the most convenient methods was palladium-catalyzed allylic substitution.[12] Konno and Okano have reported that the nucleophile would attack at the carbon remote from the electro-withdrawing fluoroalkyl groups,[13] so compound **1**−**2** may be prepared from allylic carbonate **4** through palladium-catalyzed allylic alkylation. The special backbone of **4** could be built from diene **5** via ring-closing metathesis (RCM), which was considered as a potential tool to build five-membered carbasugar.[14] Compound **5** could be derived from chlorodifluoroacetic ester **6** through silicon-induced Reformatskii−Claisen rearrangement. According to Lewis's report,[15] the

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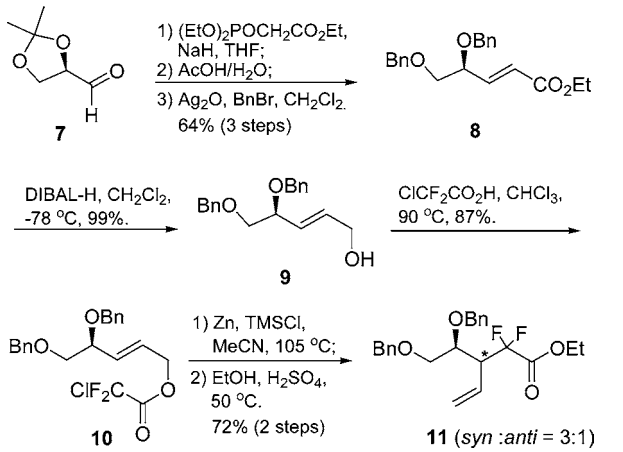
chiral auxiliary of **6** may induce the rearrangement and resulted in the desired product. The target molecule **3** could also be prepared by the same synthetic route.

The required *gem*-difluorinated ester was synthesized in a straightforward manner (Scheme 2). Aldehyde **7** was

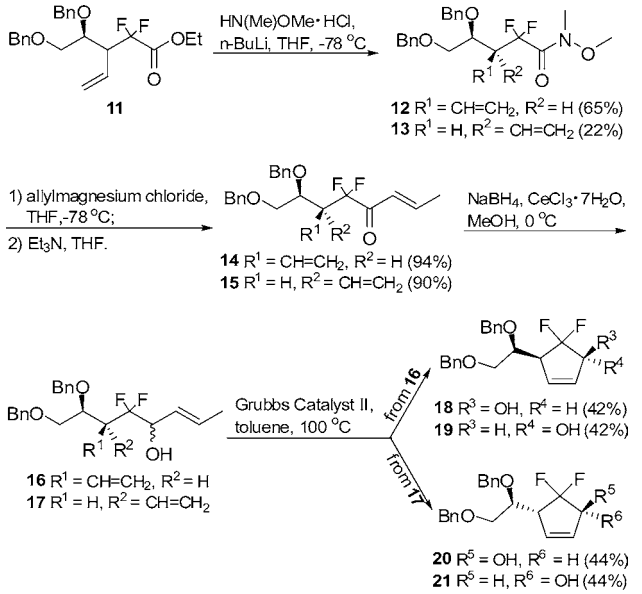
Scheme 2



subjected to Wadsworth−Emmons condensation with ethyl diethylphosphonoacetate to provide the corresponding ester, of which the protecting group was changed to give ester **8**. Reduction of the ester **8** with DIBAL-H gave the allyl alcohol **9** in good yield. Upon treatment of **9** with the excess chlorodifluoroacetic acid in refluxing $CHCl_3$, the esterification took place to deliver the chlorodifluoroacetic ester **10** in 87% yield. Then, ester **10** underwent a silicon-induced Reformatskii−Claisen reaction.[16] A mixture of ester **10**, chlorotrimethylsilane and freshly activated zinc dust was heated in dry acetonitrile at 105 °C for 24 h. The resulting crude product was further esterified with ethanol catalyzed by H_2SO_4 to give our desired *gem*-difluorinated ester **11** (syn/anti = 3:1, determined by ^{19}F NMR) in 72% yield.

After the access to the optically active ester **11** was accomplished, the ring-closing metathesis (RCM) reaction was implemented to establish the cyclopentene ring (Scheme 3). Ester **11** was converted to the Weinreb amides **12** and **13** by treatment with HN(Me)OMe·HCl/*n*-BuLi in 87% yield. Gratifyingly, diastereoisomers **12** and **13** could be readily separated by flash chromatography. Subjecting the isomers **12** and **13** to 2 equiv allylmagnesium chloride at −78 °C in THF followed by Et_3N-mediated double bond migration gave the α,β-unsaturated ketone **14** (94%) and **15** (90%), respectively. When the diene **14** was treated with the Grubbs II catalyst (5 mol %) in toluene at 100 °C, 40% starting material was recovered. In our opinion, the low conversion of the RCM reaction of compound **14** was mainly ascribed to the strong electron-withdrawing effect of *gem*-difluoromethylene group and carbonyl group. Reduction of

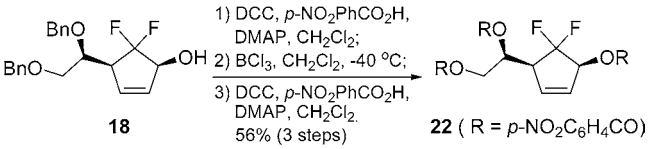
Scheme 3



the carbonyl group into hydroxyl group should alleviate the electron-deficient status. Thus, reduction of the ketones **14** and **15** with $NaBH_4/CeCl_3$ provided the alcohols **16** and **17**, respectively. As expected, subjecting of the alcohols **16** and **17** to RCM reaction using 2.5 mol % Grubbs II catalyst smoothly caused the complete conversion of the starting materials, and the cyclic alcohols **18**−**19** and **20**−**21** were provided, respectively. The diastereoisomers **18** and **19**, **20** and **21** were readily separated by column chromatography.

To determine the configuration of compounds **18**−**19** and **12**−**13**, the alcohol **18**, at this stage, was converted to the ester **22** in 56% yield over three steps (Scheme 4).

Scheme 4



The structure of compound **22** was then confirmed by X-ray crystal analysis (see Supporting Information). Furthermore, on the basis of the X-ray structure of compound **22**, the configuration of compounds **20** and **21** was established by COSY and NOESY experiments (Figure 2). The obvious correlations between H1 and H3 was observed in NOESY of compound **21**, whereas there was no considerable correlation between H1 and H3 in NOESY of compound **20**.

With the chiral difluorinated cyclic alcohols in hand, we embarked on installation of base moieties into them (Scheme 5). The intermediate **18** was treated with methyl chloroformate in the presence of pyridine to give the corresponding

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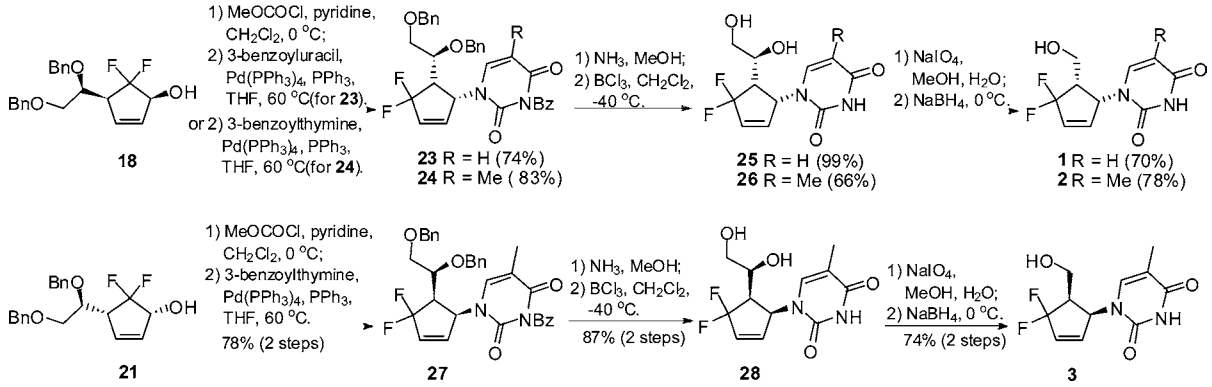
Scheme 5



the allylic carbonate, which reacted with suitably protected nucleobases 3-benzoyl uracil and 3-benzoyl thymine in the presence of catalytic amount of $Pd(PPh_3)_4$ at 60 °C in THF. Just as we predicted in the retrosynthetic analysis, the regioselectivity of these Pd-catalyzed allylic substitution was very high and only γ-substituted compounds **23** and **24** were obtained in good yields, respectively. The outcome of the exclusive regioselectivity was totally different from those of nonfluorinated substrates.[17] The structures of compounds **23** and **24** were elucidated from their NMR spectra and later were further confirmed by the X-ray structure of compound **2** (see Supporting Information). Finally, removal of the benzoyl groups and benzyl groups in compounds **23** and **24** afforded diols **25** and **26**, which were directly converted to the target molecules **1** and **2** by oxidation with $NaIO_4$ and subsequent reduction with $NaBH_4$. The structure of compound **2** was confirmed by X-ray crystal analysis.

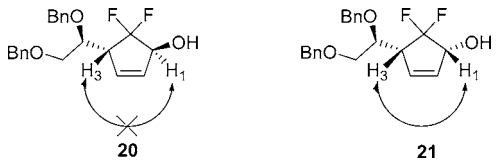


Figure 2. NOESY correlations of compounds **20** and **21**.

In addition, utilizing the identical reaction conditions as described for **2**, the nucleoside analogue **3** was prepared starting from the alcohol **21**. The ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra of product **3** were identical to those of compound **2**, and the optical rotation of compound **3** was opposite to that of compound **2**. Therefore compound **3** was demonstrated as the enantiomer of compound **2**. The stereochemistry of compound **3** and **21** were further confirmed.

In conclusion, we have completed the synthesis of 3′,3′-difluoro-4′,5′-unsaturated OTCs **1**−**3**. The key steps included the Reformatskii−Claisen rearrangement, ring-closing metathesis (RCM), and palladium-catalyzed allylic substitution.

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Supporting Information Available: Experimental procedures and characterization data for all compounds, copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds, and crystallographic data for compounds **2** and **22** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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