ORGANIC LETTERS

2012
Vol. 14, No. 8
2134–2137

Stereoselective Synthesis of Fluoro-homoneplanocin A as a Potential Antiviral Agent

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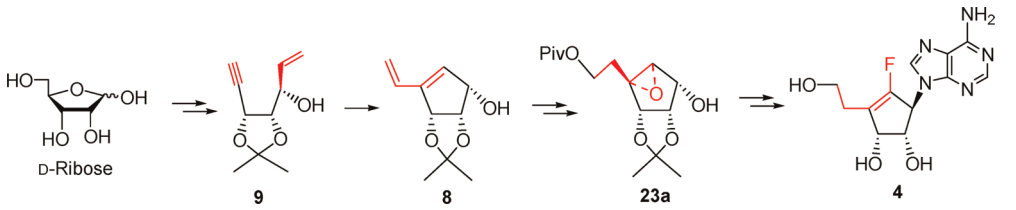
Received March 16, 2012

ABSTRACT



Fluoro-homoneplanocin A (4) was synthesized from D-ribose, via the enyne ring-closing metathesis of 9, the stereoselective opening of epoxide 23a with fluoride, and a simultaneous oxidation–elimination reaction. The key intermediate 8 is expected to serve as a versatile intermediate for the synthesis of carbanucleosides.

Neplanocin A (**1**, Figure 1),[1] isolated from *Aspergillus niger*, is one of the representative carbocyclic nucleosides that inhibits *S*-adenosylhomocysteine (SAH) hydrolase. SAH hydrolase catalyzes the hydrolysis of *S*-adenosylhomocysteine to adenosine and L-homocysteine. The inhibition of SAH hydrolase results in the accumulation of SAH in the cell, which in turn inhibits *S*-adenosyl-L-methionine (SAM)-dependent transmethylase.[2] Because SAM-dependent transmethylase is essential for the formation of the capped methylated structure at the 5′-terminus of viral mRNA, SAH hydrolase is an attractive target for the development of broad-spectrum antiviral agents.[3] Neplanocin A showed potent antiviral activities against several RNA and DNA viruses but could not be further developed as a clinical agent because of high cytotoxicity due to the phosphorylation by adenosine kinase. Neplanocin A is also metabolized by adenosine deaminase, yielding an inactive hypoxanthine derivative.[4]

Based on the structure of neplanocin A (**1**), fluoroneplanocin A (**2**) was designed and synthesized as a mechanism-based inhibitor of SAH hydrolase.[5]

For the synthesis of **2**, electrophilic vinyl fluorination was utilized as a key step. Compound **2** was two times more potent than neplanocin A (**1**) against SAH hydrolase. Unlike neplanocin A, which reversibly inhibits SAH hydrolase, fluoro-neplanocin A was found to inhibit the enzyme through both mechanism-based irreversible inhibition and mechanism-based reversible cofactor (NAD^+)-depletion.[5] In addition, homoneplanocin A (**3**), a one-carbon homologated analog of neplanocin A (**1**), also exhibited potent inhibitory activity against SAH hydrolase.[6]

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10.1021/ol300667q
Published on Web 04/11/2012

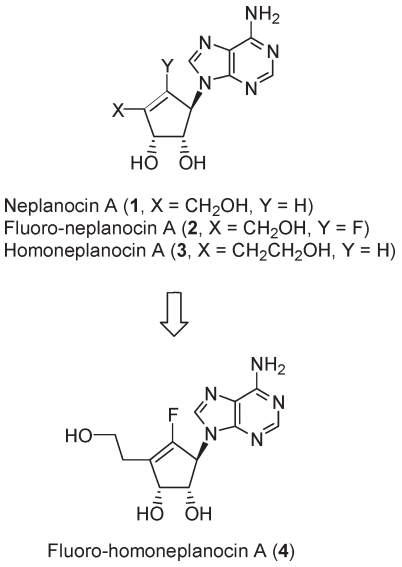


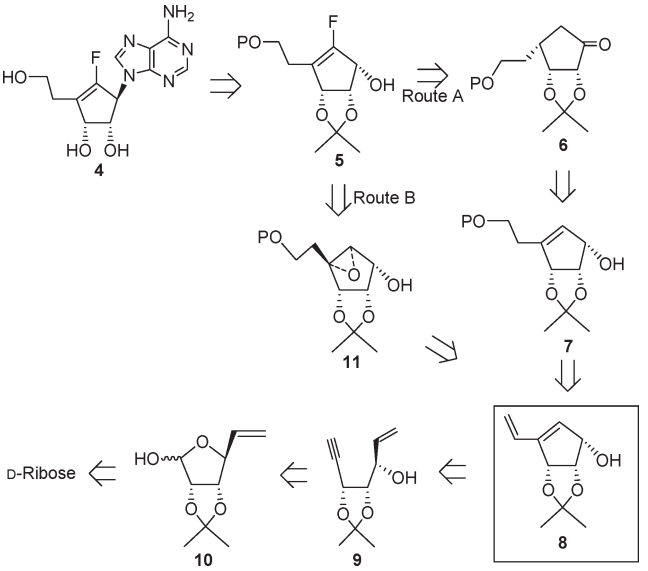
Figure 1. Rationale for the design of the target nucleoside **4**.

Compound **3** exhibited potent antiviral activity against hepatitis B virus (HBV) without apparent cytotoxicity.[7]

Based on these results, it was of great interest to synthesize fluoro-homoneplanocin A (**4**), which combines the properties of fluoro-neplanocin A (**2**) and homoneplanocin A (**3**). In the synthesis of the target nucleoside, enyne ring-closing metathesis (RCM), nucleophilic fluorination to an epoxide, and simultaneous oxidation–elimination were the key steps. Herein, we report the highly efficient synthesis of fluoro-homoneplanocin A (**4**) from D-ribose, along with the synthesis of homoneplanocin A (**3**).

Scheme 1 illustrates the retrosynthetic analysis for desired nucleoside **4**. Fluoro-homoneplanocin A (**4**) could be synthesized by condensing allylic alcohol **5** with a purine base under the Mitsunobu conditions. It was envisaged that fluoroallylic alcohol **5** might be synthesized by two routes. In Route A, compound **5** is derived from ketone **6** using electrophilic fluorination[8] and phenylseleneylation followed by syn-elimination. The oxidation of allylic alcohol **7** followed by reduction could lead to ketone **6**. Compound **7** might be easily derived from the chemoselective hydroboration–oxidation of **8** followed by protection of the resulting hydroxyl group. The cyclopentenol **8** could be derived from **9** via ring-closing metathesis (RCM). Compound **9** could be synthesized by reacting lactol **10** with trimethylsilyl diazomethane ($TMSCHN_2$) under basic conditions. The lactol **10** could be easily synthesized from D-ribose using a known procedure.[9] The other route for the synthesis of fluoroallylic alcohol **5** involves the regioselective opening of epoxide **11** with fluoride followed by the elimination of the tertiary alcohol (Route B). Epoxide **11** would be synthesized from cyclopentenol **8** by manipulation of the vinyl group followed by epoxidation.

Scheme 1. Retrosynthetic Analysis of the Desired Nucleoside **4**



We first synthesized the common intermediate **8**, which is utilized in both Routes A and B, as shown in Scheme 2. D-Ribose was converted into known lactol **10**[9] in three steps. The conversion of D-ribose into 2,3-acetonide **12** under acidic conditions followed by treatment with vinylmagnesium bromide gave triol **13**. The oxidative cleavage of **13** with $NaIO_4$ yielded lactol **10**.[9] The nucleophilic addition of **10** with $TMSCHN_2$[10a] in the presence of *n*-BuLi and *N*,*N*-diisopropylamine (DIPA) afforded enyne **9** (65%) and its TMS-protected derivative **14** (16%). The TMS group in compound **14** was removed with tetra-*n*-butylammonium fluoride (TBAF) to give **9**. It is worth noting here that the use of $TMSCHN_2$/LDA provided the desired derivative **9** without any epimerization at C-5, which is usually observed when using the Bestmann–Ohira reagent/condition.[10b] The structure of **9** was confirmed by the coupling constant ($J_{H4,H5}$ = 5.6 Hz) between H-4 and H-5 and the NOE enhancement (2.11%) that indicated the *cis*-orientation of these two protons. The ring-closing metathesis (RCM)[11] of enyne **9** with a first generation Grubbs catalyst afforded cyclopentenol **8** (60%), which can serve as a

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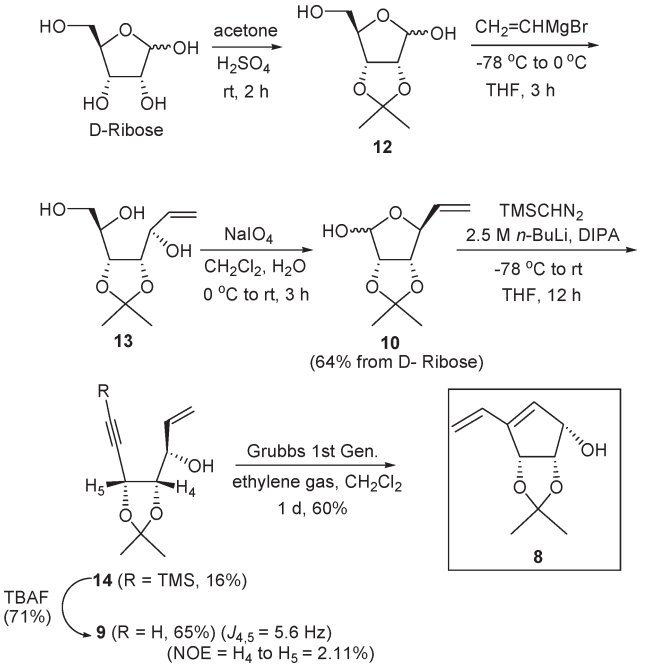
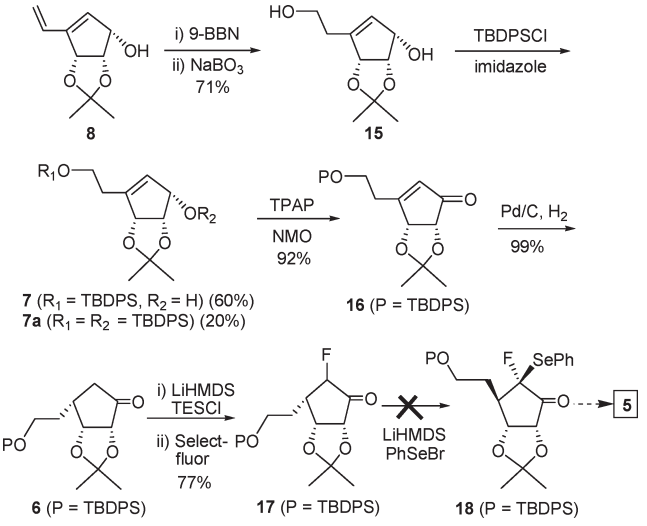
Scheme 2. Synthesis of the Key Intermediate **8** via Enyne Ring-Closing Metathesis



Scheme 3. Synthetic Approach to the Glycosyl Donor **5** via Route A



versatile intermediate for the synthesis of carbocyclic nucleosides.

Several novel methods have been developed for the synthesis of fluorovinyl compounds, including the Horner–Wadsworth–Emmons condensation of fluorophosphonates with carbonyls, Julia olefination, electrophilic fluorination of vinyllithium or stannane, Peterson olefination, fluoro-olefination via a Reformatsky-type reaction, and the fluorodesilylation of vinylsilanes.[12] Despite there being various methods for the synthesis of fluorovinyl compounds, a universal method to produce these compounds remains elusive. Thus, for the synthesis of glycosyl donor **5**, Route A was used starting from the key intermediate **8**, as shown in Scheme 3. The chemoselective hydroboration–oxidation of **8** was achieved with 9-BBN and sodium perborate to give desired diol **15**. Selective TBDPS protection of **15** gave **7** (60%) with concomitant formation of disilyl derivative **7a** (20%).

The oxidation of the resulting allylic alcohol **7** with TPAP/NMO[13] afforded cyclopentenone **16**. The reduction of **16** in the presence of Pd/C yielded cyclopentanone **6** as the single stereoisomer. The treatment of **6** with LiHMDS followed by trapping with TESCl gave a silylenol ether, which was treated with Selectfluor to give fluoroketone **17**.[8] However, the phenylseleneylation of **17** under various reaction conditions did not give the desired fluoroselenide **18**, which could be smoothly converted into glycosyl donor **5** by syn-elimination and reduction.

Recently, we have used the electrophilic fluorination on vinyllithium (from iodovinyl) for the synthesis of fluoroneplanocin A.[5] Using the same strategy, we tried iodination on **16**, but it was found that conventional iodination (I_2/pyridine in CCl_4) was slow. To solve this problem, we tried various iodinating agents and solvents, but the desired iodo compound was obtained in a very low yield (10–15%) (see pp S8–S9 of the Supporting Information). After having trouble with well-known methods, we developed a new method for the synthesis of the fluorovinyl compound via Route B, as depicted in Scheme 4.

The key intermediate **8** was protected with TBDPSCl to give **19**. The chemoselective hydroboration–oxidation produced homoallylic alcohol **20** (78%). The treatment of **20** with pivaloyl chloride followed by the removal of the TBDPS group afforded cyclopentenol **22**. The treatment of allylic alcohol **22** with *m*CPBA at −40 °C to room temperature yielded α-epoxide **23a** (71%) and *β*-epoxide **23b** (8.6%) because of the directing effect of the α-hydroxyl group.

With **23** in hand, we explored the epoxide ring opening using tetra-*n*-butylammonium hydrogenfluoride (*n*-$Bu_4NH_2F_3$) in the presence of KHF_2.[14] The heating of α-epoxide **23a** with *n*-$Bu_4NH_2F_3$ in DMF at 130 °C afforded the desired fluorodiol **24a** in a highly regio- and stereoselective manner. The stereochemistry of the fluorine atom was confirmed by NOE experiments. Under modified Pfitzner–Moffatt conditions,[15] fluorodiol **24a** underwent elimination simultaneously with oxidation to give the α,*β*-unsaturated ketone **25** in good yield. The minor isomer **23b** was also converted into compound **25** under the same reaction conditions. The Luche reduction of **25** yielded glycosyl donor **5** which is ready for condensation with a purine base.

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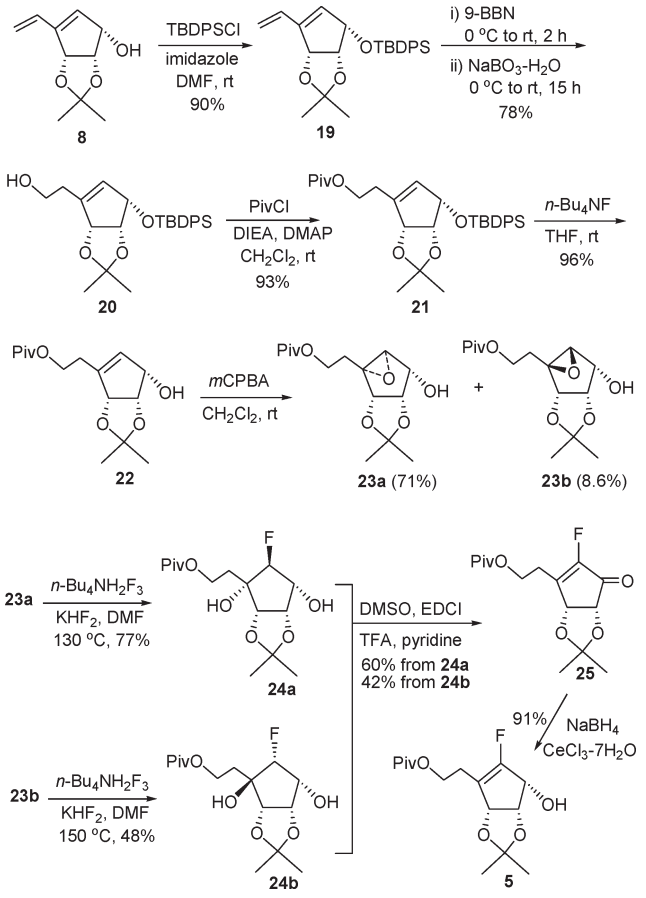
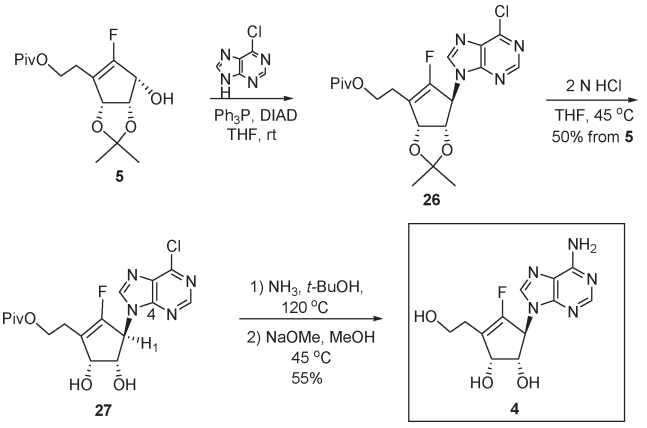
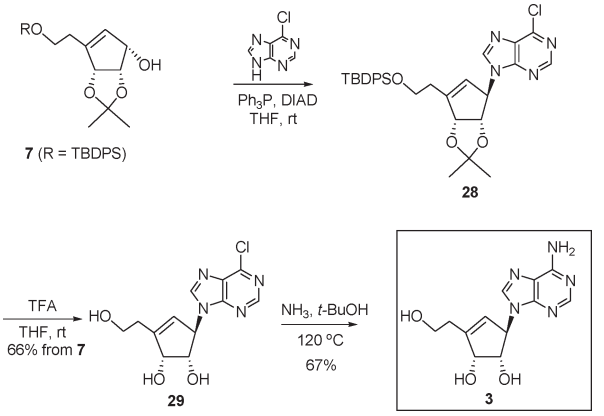
Scheme 4. Synthesis of Glycosyl Donor **5** via Route B



Scheme 5. Synthesis of Fluoro-homoneplanocin A (**4**)



Scheme 6. Synthesis of Homoneplanocin A (**3**)



The glycosyl donor **5** was condensed with 6-chloropurine under the standard Mitsunobu conditions to give the desired N-9 derivative **26** without the concomitant formation of the N-7 isomer (Scheme 5).

After removing the isopropylidene group under acidic conditions, the N-9 isomer was confirmed by comparison of the ^{1}H and ^{13}C NMR spectra reported in the literature[16] and by the HMBC correlation between 1′-H and C-4 of 6-chloropurine. Treatment of **27** with ammonia in *tert*-butanol, followed by the removal of the pivaloyl group with NaOMe, yielded the final fluoro-homoneplanocin A (**4**).

In addition to the synthesis of fluoro-homoneplanocin A (**4**), the synthesis of homoneplanocin A (**3**) was also easily accomplished from compound **7** (Scheme 6). The glycosyl donor **7** was condensed with 6-chloropurine under the standard Mitsunobu conditions to give the desired N-9 derivative **28** as a major isomer along with minor amounts of the N-7 derivative (9%). Careful removal of the protecting groups of **28** with TFA produced the 6-chloropurine derivative **29** which was treated with ammonia in *tert*-butanol gave the final product, homoneplanoicn A (**3**).

In summary, we have accomplished the stereoselective synthesis of fluoro-homoneplanocin A (**4**) along with the synthesis of homoneplanocin A (**3**) from D-ribose as a potential inhibitor of *S*-adenosylhomocysteine hydrolase. For the synthesis of compounds **3** and **4**, enyne ring-closing metathesis (RCM), the regio- and stereoselective opening of the epoxide with fluoride, and a simultaneous oxidation−elimination reaction were employed as key steps. The key intermediate **8** is expected to serve as an excellent template for the synthesis of carbocyclic nucleosides such as neplanocin A, neplanocin C, and aristeromycin. Analysis of the generality, scope, and limitations of the methodology using vinyl fluoride is underway in our laboratory, and the results of these studies will be reported in due course.

Acknowledgment. This work was supported by a grant from the WCU project (R31-2008-000-10010-0) of National Research Foundation (NRF), Korea, and the Ewha Global Top5 Grant 2011 of Ewha Womans University.

Supporting Information Available. Complete experimental procedure and ^{1}H NMR copies of all new compounds and ^{19}F and ^{13}C NMR copies of **4** and **24a** described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.