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Stereoselective synthesis of amino-substituted apio dideoxynucleosides through a distant neighboring group effect

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Abstract—Novel amino-substituted apio nucleoside (2*R*,4*R*)-LJ-45 as a potential anti-HBV agent was stereoselectively synthesized from the known oxazolidine **1** through a distant neighboring group effect. It is believed that this synthetic method using a chiral template, (−)-L-serine methyl ester can be generally applied to the synthesis of other chiral amino-substituted nucleosides.

Hepatitis B is a viral disease which afflicts about 350 million people worldwide,[1] but effective chemotherapeutics are still not available for the treatment of hepatitis B virus (HBV) infected individuals except L-β-1,3-oxathiolanyl cytosine (3TC, lamivudine)[2] approved by the Food and Drug Administration (FDA).

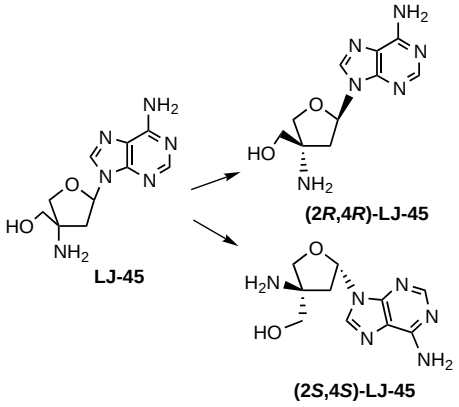

Figure 1.

Since the discovery of lamivudine as an anti-HBV drug, many nonclassical types of nucleosides such as 1,3-dioxolanyl nucleosides,[3] L-nucleosides,[4] isonucleosides,[5] apio nucleosides[6] and carbocyclic nucleosides[7] have been synthesized and found to be active against HBV.

Recently, we have reported the synthesis of racemic amino and azido substituted apio nucleosides[8] as potential antiviral agents, among which adenine derivative, LJ-45 was found to be active (EC_{50} = 3.5 M in 2.2.15 cells)[6] against hepatitis B virus (HBV) (Fig. 1).

Since biological activity of racemic mixture generally resides in one enantiomer, it was of interest to synthesize each enantiomeric pure form of LJ-45 and to find out which enantiomer is responsible for anti-HBV activity. In this communication, we report the asymmetric synthesis of one of the enantiomers, (2*R*,4*R*)-LJ-45 and its anti-HBV activity. For the synthesis of enantiomeric pure stereoisomer, (2*R*,4*R*)-LJ-45, we utilized Seebach's chemistry[9] to fix the stereochemistry of C3′ position.

Our initial attempt to synthesize the desired (2*R*,4*R*)-LJ-45 started from the known oxazolidine **1**[9] prepared from (−)-L-serine methyl ester (Scheme 1).

Reaction of **1** with LDA at −78°C followed by treatment with allyl bromide gave **2** as a single stereoisomer (55%). Treatment of allyl ester **2** with Super-hydride at −78°C afforded the alcohol **3** which was subjected to

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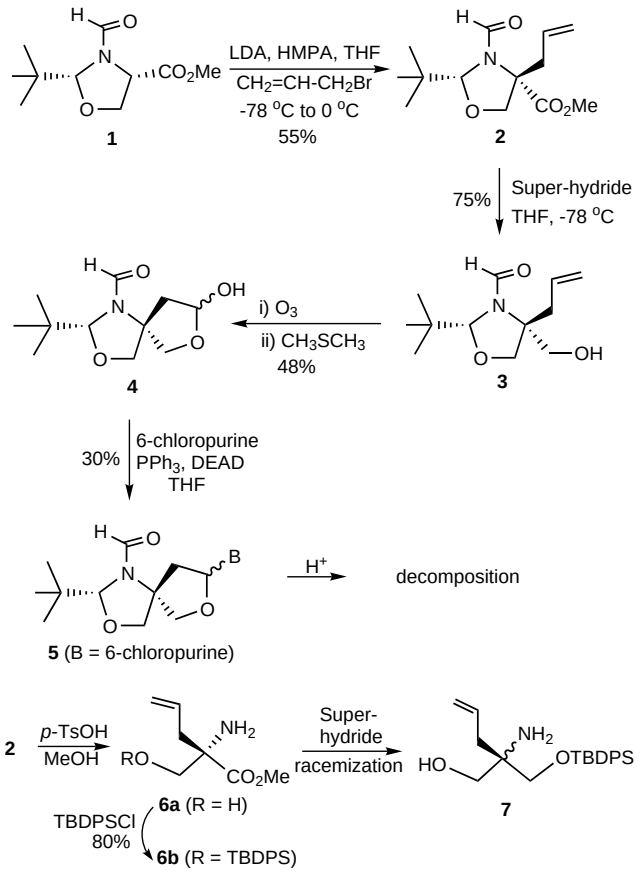


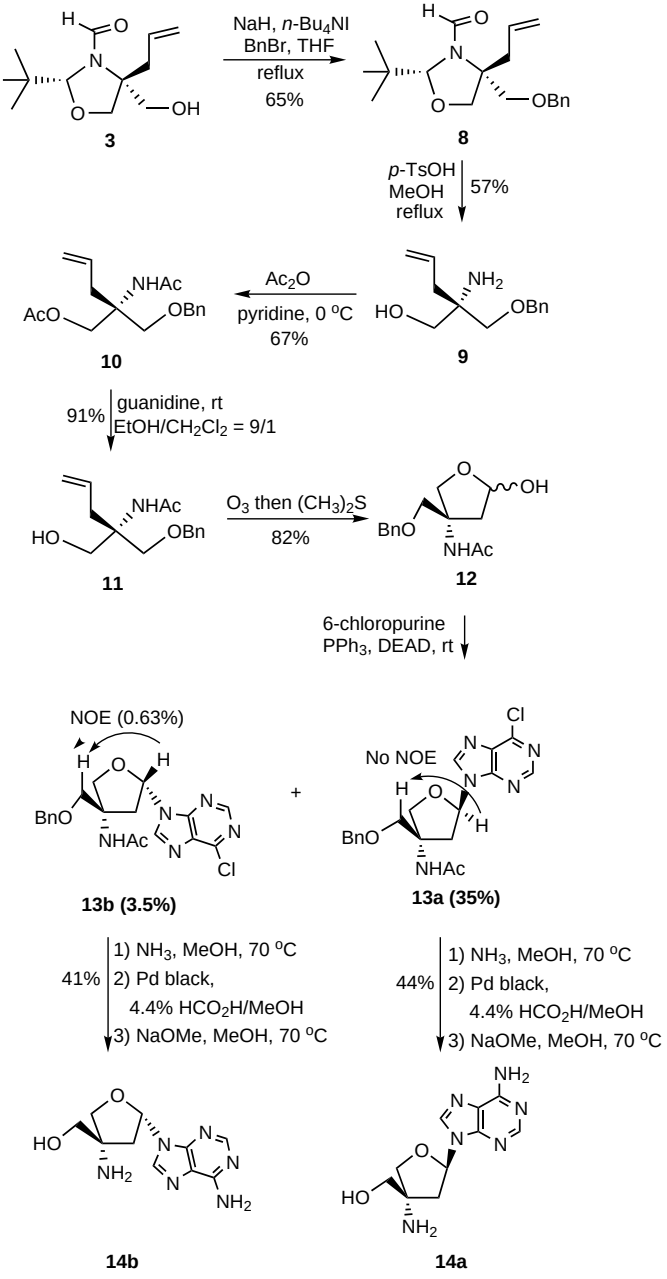
Scheme 1.

ozonolysis to give spiro lactol **4**. Spiro lactol **4** was condensed with 6-chloropurine under the Mitsunobu conditions[10] to give the spiro nucleoside **5** in 30% yield with high β-diastereoselectivity (β/α = 20/1). This coupling method turned out to be better than the acid-catalyzed coupling method of the spiro lactol acetate prepared from acetylation of **4** with silylated 6-chloropurine. Unfortunately, hydrolysis of **5** under the various acidic conditions could not afford the desired nucleoside, but resulted in deglycosylation.

To circumvent the deglycosylation, we decided to hydrolize oxazolidine ring before condensation with 6-chloropurine. Allyl ester **2** was treated with *p*-TsOH in methanol to give **6a** and the resulting alcohol was protected as *t*-butyldiphenylsilyl ether to give **6b**. Reduction of **6b** with Super-hydride at −78°C gave the alcohol derivative, but racemization occurred under the reaction conditions.

To avoid the racemization, the hydroxyl group of **3** was protected as benzyl ether **8** which was hydrolyzed under the same acidic conditions to give amino alcohol **9** without racemization (Scheme 2).

Since ozonolysis of **9** under the presence of free amino group did not give the satisfactory yield, **9** was treated with acetic anhydride in pyridine to give **10**, in which acetate was selectively removed by treating with guanidine[11] to afford amide **11**. Ozonolysis of **11** followed by reductive work-up gave the lactol **12** as a diastereomeric mixture in 82% yield. Lactol **12** was converted to the corresponding acetate. However, the Vorbrüggen coupling of this acetate did not yield the glycosylated product. Hence, the lactol **12** was directly condensed with 6-chloropurine under standard Mitsunobu conditions to give **13a** (35%) and **13b** (3.5%) in 10:1 ratio after flash silica gel column chromatography with recovered lactol **12** (18%). High stereoselectivity obtained during the condensation may be attributed to the neighboring group effect by acetamido group because the condensation using the corresponding free amino sugar gave no stereoselectivity. It is very interesting to note that neighboring group effect by distant acetamido group, not by vicinal acetamido group can exist although Mukaiyama et al.[12] reported the elegant



Scheme 2.

and highly stereoselective synthesis of β-deoxyribonucleosides using similar distant neighboring group participation. However, they obtained high β-stereoselectivity by using thiocarbamate group, but low β-selectivity by using the benzoyl group, while we obtained the very high β-selectivity by using acetamido group. To our best knowledge, it is the first example of neighboring group participation by the distant acetamido group. Anomeric configurations of **13a** and **13b** were easily assigned by ^{1}H NOE experiments. Treatment of **13a** and **13b** with methanolic ammonia at 70°C gave the adenine derivatives which were reacted with palladium black in 4.4% formic acid/methanol followed by sodium methoxide solution to afford the final adenine derivatives **14a**[13] and **14b**, respectively.

Anti-HBV activity and cytotoxicity of the final nucleosides **14a** and **14b** were determined in 2.2.15 cells, but both compounds exhibited neither significant anti-HBV activity nor cytotoxicity up to 100 μM, indicating that anti-HBV activity of LJ-45 may reside in (2*S*,4*S*)-LJ-45. Further biological evaluation and asymmetric synthesis of the other enantiomer, (2*S*,4*S*)-LJ-45 are in progress in our laboratory.

In summary, we have accomplished the stereoselective synthesis of amino-substituted apio nucleoside (2*R*,4*R*)-LJ-45 from oxazolidine **1**, through a distant neighboring group effect. It is believed that this synthetic method using a chiral template, (−)-L-serine methyl ester can be generally applied to the synthesis of other chiral amino-substituted nucleosides.

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13. Compound **14a**: mp 165.1–165.7°C; MS (FAB) *m*/*z* 251 (*M*+H$^+$); UV (MeOH) λ_{max} 260 nm (ε=13 040); $[\alpha]_D^{25}$ −42.7 (*c* 0.1, MeOH); ^{1}H NMR (CD_3OD, 400 MHz) δ 2.39 (dd, 1H, *J*=6.8, 14.0 Hz, 2′-H_a), 2.74 (dd, 1H, *J*=6.8, 14.0 Hz, 2′-H_b), 3.69 (dd, 2H, *J*=10.8, 19.6 Hz, CH_2OH), 4.03 (dd, 2H, *J*=8.8, 20.8 Hz, 4′-*H*), 6.49 (t, 1H, *J*=7.2 Hz, anomeric *H*), 8.20 (s, 1H, H-8), 8.30 (s, 1H, H-2); ^{13}C NMR (CD_3OD, 100 MHz) δ 41.692, 62.803, 66.369, 77.097, 85.655, 139.825, 149.173, 152.570, 156.098. Anal. calcd for $C_{10}H_{14}N_6O_2$: C, 47.99; H, 5.64; N, 33.58. Found: C, 47.86; H, 5.28, N, 33.20%.