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Asymmetric Synthesis of Novel Pseudo-d-Vinylcyclopropyl Nucleosides Bearing Quaternary Carbon as Potential Anti-Herpesvirus Agent

Ah-Young Park^a; Hyung Ryong Moon^a; Kyung Ran Kim^a; Moon Woo Chun^b; Lak Shin Jeong^c

^a College of Pharmacy and Research Institute for Drug Development, Pusan National University, Busan, Korea ^b College of Pharmacy, Seoul National University, Seoul, Korea ^c College of Pharmacy, Ewha Womans University, Seoul, Korea

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ASYMMETRIC SYNTHESIS OF NOVEL PSEUDO-D-VINYLCYCLOPROPYL NUCLEOSIDES BEARING QUATERNARY CARBON AS POTENTIAL ANTI-HERPESVIRUS AGENT

Ah-Young Park, Hyung Ryong Moon and Kyung Ran Kim □ *College of Pharmacy and Research Institute for Drug Development, Pusan National University, Busan, Korea*

Moon Woo Chun □ *College of Pharmacy, Seoul National University, Seoul, Korea*

Lak Shin Jeong □ *College of Pharmacy, Ewha Womans University, Seoul, Korea*

□ *Pseudo-D-vinylcyclopropyl nucleosides 10–12 bearing a quaternary carbon were designed and synthesized starting from (R)-epichlorohydrin using a tandem reaction of double alkylation and lactonization via oxirane-ring opening reaction, a Wittig reaction, and chemoselective reduction as potential anti-herpesvirus agent.*

Keywords Pseudo-D-vinylcyclopropyl nucleosides; anti-herpesvirus agent; oxirane-ring reaction; double alkylation

INTRODUCTION

Acyclovir (**1**, Figure 1)^[1] has become the drug of choice for the treatment of HSV-1 and 2 (herpes simplex virus type-1 and 2) and VZV (varicella-zoster virus) infections as a potent and selective inhibitor. Since acyclovir (**1**), which belongs to acyclic nucleoside class has been found to show a potent antiviral activity, a number of acyclic nucleosides and cyclic nucleosides having a small ring size of their sugar such as three- and four-membered rings were synthesized, and evaluated against a variety of viruses. Among them, acyclic nucleosides such as ganciclovir (**2**)^[2] and penciclovir (**3**)^[3] were launched as new antiviral agents, and cyclobut-G (**4**)^[4] carbocyclic counterpart of oxetanocin G showed a highly potent and broad spectrum against herpesviruses including HSV-1 and -2, varicella-zoster virus (VZV),

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Address correspondence to Hyung Ryong Moon, College of Pharmacy and Research Institute for Drug Development, Pusan National University, San 30 Jangjeon-dong, Geumjeong-gu, Busan 609-735, Korea. E-mail: mhr108@pusan.ac.kr

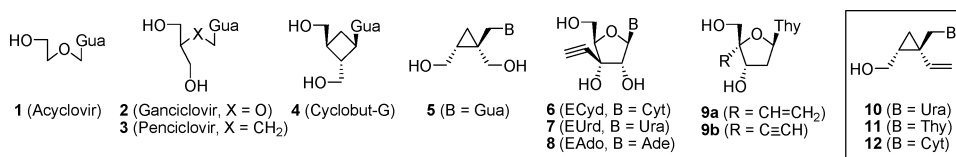


FIGURE 1 The rationale for the design of the desired nucleosides, **10–12**.

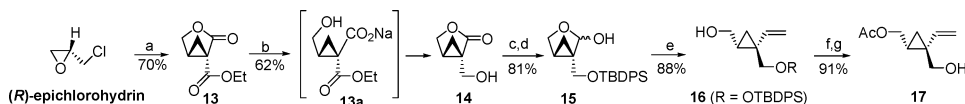
and human cytomegalovirus (HCMV). Specially, penciclovir (**3**) in which the ethereal oxygen of ganciclovir (**2**) is replaced by a carbon atom showed anti-HBV (hepatitis B virus) activity as well as a similar activity spectrum to acyclovir, i.e., anti-HSV-1 and 2 and anti-VZV activities and currently has been approved for the treatment of VZV infection by the FDA. In general, carbanucleosides such as penciclovir (**3**), and cyclobut-G (**4**) are more resistant to enzymatic hydrolysis and chemical degradation than normal nucleosides. These properties confer on carbanucleosides an additional benefit in developing a clinically useful drug. Several structural modifications on cyclopropane ring have been made in the search for antiviral agents with better efficacy and selectivity. 9-[[*cis*-1',2'-Bis(hydroxymethyl)cycloprop-1'-yl]methyl]guanine (**5**),^[5] which retains a cyclopropane ring and a guanine base has been reported to show extremely potent antiviral activity against HSV-1 and VZV with good selectivity.

On the other hand, nucleosides bearing unsaturated functional groups such as vinyl and acetylenyl at 3' or 4' position have been reported to show potent antiviral and antitumor activities. Among them, 1-(3-*C*-ethynyl- β -D-ribo-pentofuranosyl)cytosine (ECyd, **6**)^[6] and its uracil congener (EUrd, **7**)^[7] have exhibited potent antitumor activity. ECyd (**6**) also have shown potent anti-HIV (human immunodeficiency virus) activity with its adenine congener, EAdo (**8**). In addition, 4' α -C-ethynyl- and ethynylthymidines (**9a** and **9b**)^[8] also have been found to show very potent antiviral activities against HSV-1 and HIV-1.

On the basis of these findings, as a part of our efforts to search for novel antiviral agents with better potency and selectivity, it was interesting to design and asymmetrically synthesize novel pseudo-D-vinylcyclopropyl pyrimidine nucleosides **10–12**, combining properties of nucleosides bearing cyclopropane ring and vinyl substituent, respectively. Herein, we wish to report the synthesis of pseudo-D-vinylcyclopropyl nucleosides having natural bases (Ura, Thy, and Cyt) starting from (*R*)-(-)-epichlorohydrin.

CHEMISTRY

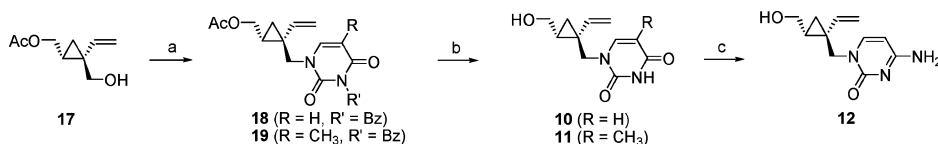
Synthesis of the vinyl-substituted glycosyl donor **17** is shown in Scheme 1. Reaction of (*R*)-(-)-epichlorohydrin with diethyl malonate in the presence of sodium metal in EtOH gave bicycrolactone **13** via a tandem reaction of



SCHEME 1 Reagents and conditions: (a) $(\text{EtO}_2\text{C})_2\text{CH}_2$, Na, EtOH, 80°C , 20 hours; (b) i) 1 eq. NaOH, EtOH, rt, 16 hours; ii) NaBH_4 , reflux, 3 hours, then 2 M HCl, rt, 18 hours; (c) TBDPSCl, imidazole, CH_2Cl_2 , rt, overnight; (d) Dibal-H, CH_2Cl_2 , -78°C , 30 minutes; (e) $\text{CH}_3\text{PPh}_3\text{Br}$, *t*-BuOK, THF, rt, 3 hours; (f) Ac_2O , pyridine, rt, overnight; (g) $n\text{-Bu}_4\text{NF}$, THF, rt, overnight.

double alkylations and lactonization in 70% yield.^[5] Chemoselective reduction of ester group of **13** in the presence of lactone functional group was accomplished by successive hydrolysis, reduction and cyclization reaction. Treatment of **13** with 1 eq. of NaOH cleaved only the lactone ring over ester group to give sodium carboxylate **13a**, probably due to high ring strain of the lactone group. Treatment of **13a** with NaBH_4 produced the corresponding alcohol formed by reduction of ester. Finally, acidic conditions by 2 M HCl induced a cyclization, resulting in the formation of lactone **14**. Protection of hydroxyl group of **14** as the silyl ether followed by reduction with Dibal-H afforded the corresponding lactol **15**. Compound **15** was converted to vinyl-substituted cyclopropyl analog **16** by a Wittig reaction. Acetylation of primary hydroxyl group of **16** and then removal of TBDPS group with TBAF gave compound **17**, which was glycosyl donor for the condensation with various nucleobases.

Synthesis of pyrimidine nucleoside derivatives **10–12** is shown in Scheme 2. Condensation of glycosyl donor **17** with *N*⁴-benzoyluracil and *N*⁴-benzoylthymine under Mitsunobu conditions smoothly gave protected *N*⁴-benzoyluracil nucleoside **18** and protected *N*⁴-benzoylthymine nucleoside **19** in 94% and 95% yield, respectively. Removal of acetyl and benzoyl groups of **18** and **19** was accomplished by 1 M NaOMe to afford the final nucleosides, **10** and **11**, respectively. In order to synthesize cytosine nucleoside, the methodology converting uracil nucleoside **10** into cytosine nucleoside **12** was tried. Uracil compound **10** was converted into cytosine nucleoside **12** via acetylation of the hydroxyl group followed by successive three conventional steps (1,2,4-triazole, POCl_3 , pyridine; 1,4-dioxane, NH_4OH ; NH_3 , MeOH)^[9] in overall 57% yield.



SCHEME 2 Reagents and conditions: (a) PPh_3 , DEAD, *N*-benzoyluracil or *N*-benzoylthymine, THF, rt, 5 hours, 94% for **18**, 95% for **19**; (b) 1 N NaOMe, MeOH, rt, 4 hours, 94% for **10**, 87% for **11**; (c) (i) Ac_2O , pyridine, rt, overnight; (ii) 1,2,4-triazole, POCl_3 , pyridine, rt, overnight; (iii) NH_4OH , 1,4-dioxane, rt, overnight; (iv) NH_3/MeOH , rt, overnight, 57% from **10**.

Now, biological evaluation of the synthesized final compounds **10–12** is in progress against various viruses including herpesviruses such as HSV-1 and 2, and VSV and the antiviral activities will be compared with that of L-counterparts of the final compounds in due course.

CONCLUSION

Based on facts that carbanucleosides bearing a small ring size of their sugar showed extremely potent anti-herpesvirus activities and nucleosides having unsaturated functional groups such as vinyl and acetylenyl at their sugar moiety also exhibited potent anti-herpesvirus inhibition, vinyl-substituted cyclopropyl nucleoside derivatives **10–12** were designed and enantiopurely synthesized starting from (*R*)-(-)-epichlorohydrin employing the key steps such as a tandem reaction of double alkylations and lactonization via oxirane-ring opening reaction, a Wittig reaction and chemoselective reduction.

REFERENCES

1. Elion, G.B.; Furman, P.A.; Fyfe, J.A.; de Miranda, P.; Beauchamp, L.; Schaeffer, H.J. Selectivity of action of an antiherpetic agent, 9-(2-hydroxyethoxymethyl) guanine. *Proc. Natl. Acad. Sci. USA* **1977**, *74*, 5716–5720.
2. Spector, S.A.; McKinley, G.F.; Lalezari, J.P.; Samo T.; Andruczk, R.; Follansbee, S.; Sparti, P.D.; Havlir, D.V.; Simpson, G.; Buhles, W.; Wong, R.; Stempien, M. Oral ganciclovir for the prevention of cytomegalovirus disease in persons with AIDS. Roche Cooperative Oral Ganciclovir Study Group. *N. Engl. J. Med.* **1996**, *334*, 1491–1497.
3. Hodge, R.A. Vere; Cheng, Y.C. The mode of action of penciclovir. *Antiviral Chem. Chemother.* **1994**, *5*, 31–37.
4. Norbeck, D.W.; Kern E.; Hayashi, S.; Rosenbrook, W.; Sham, H.; Herrin, T.; Plattner, J.J.; Erickson, J.; Clement, J.; Swanson, R.; Shipkowitz, N.; Hardy, D.; Marsh, K.; Arnett, G.; Shannon, W.; Broder, S.; Mitsuya, H. Cyclobut-A and cyclobut-G: Broad-spectrum antiviral agents with potential utility for the therapy of AIDS. *J. Med. Chem.* **1990**, *33*, 1281–1285.
5. Sekiyama, T.; Hatsuya, S.; Tanaka, Y.; Uchiyama, M.; Ono, N.; Iwayama, S.; Oikawa, M.; Suzuki, K.; Okunishi, M.; Tsuji, T. Synthesis and antiviral activity of novel acyclic nucleosides: Discovery of a cyclopropyl nucleoside with potent inhibitory activity against herpesviruses. *J. Med. Chem.* **1998**, *41*, 1284–1298.
6. Hattori, H.; Tanaka, M.; Fukushima, M.; Sasaki, T.; Matsuda, A. 1-(3-*C*-Ethynyl- β -D-ribo-pentofuranosyl)cytosine (ECyd), 1-(3-*C*-ethynyl- β -D-ribo-pentofuranosyl)uracil (EUrd), and their nucleobase analogues as new potential multifunctional antitumor nucleosides with a broad spectrum. *J. Med. Chem.* **1996**, *39*, 5005–5011.
7. Matsuda, A.; Hattori, H.; Tanaka, M.; Sasaki, T. Nucleosides and nucleotides. 152. 1-(3-*C*-Ethynyl- β -ribo-pentofuranosyl)uracil as a broad spectrum antitumor nucleoside. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1887–1892.
8. Sugimoto, I.; Shuto, S.; Mori, S.; Shigeta, S.; Matsuda, A. Nucleosides and Nucleotides. 183. Synthesis of 4'-branched thymidines as a new type of antiviral agent. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 385–388.
9. Shi, J.; Du, J.; Ma, T.; Pankiewicz, K.W.; Patterson, S.E.; Tharnish, P.M.; McBrayer, T.R.; Stuyver, L.J.; Otto, M.J.; Chu, C.K.; Schinazi, R.F.; Watanabe, K.A. Synthesis and anti-viral activity of a series of D- and L-2'-deoxy-2'-fluororibonucleosides in the subgenomic HCV replicon system. *Bioorg. Med. Chem.* **2005**, *13*, 1641–1652.