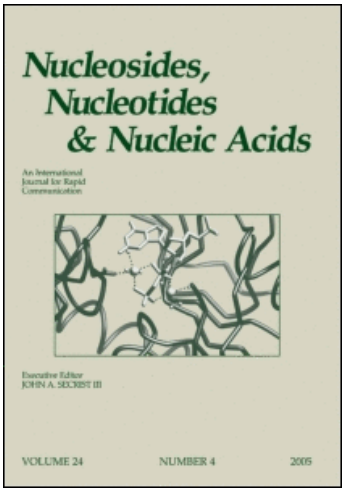

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SYNTHESIS OF ENANTIOPURE PSEUDO-L-VINYLCYCLOPROPYL NUCLEOSIDES BEARING QUATERNARY CARBON AS POTENTIAL ANTI-HERPESVIRUS AGENT

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□ *Pseudo-L-vinylcyclopropyl adenine and guanine nucleosides **11** and **12** were designed and enantiopurely synthesized starting from (S)-epichlorohydrin using tandem alkylation, regioselective oxirane-ring opening, and chemoselective reduction as key steps.*

Keywords Pseudo-L-vinylcyclopropyl; anti-herpesvirus agent; tandem alkylation; chemoselective reduction

INTRODUCTION

Since the discovery of acyclovir (**1**, Figure 1),[1] which is an acyclic nucleoside and has shown very potent and selective anti-herpes simplex virus (HSV) and anti-varicella-zoster virus (VSV) activities, medicinal chemists have paid their attentions to the synthesis of acyclic nucleosides and cyclic nucleoside derivatives bearing three- and four-membered sugar ring. As a result of their endeavors, acyclic nucleosides such as ganciclovir (**2**)[2] and its carbanucleoside, penciclovir (**3**)[3] were approved as a clinically useful antiviral drug, and cyclobut-G (**4**),[4] carbocyclic counterpart of oxetanocin G has been found to exhibit a highly potent and broad spectrum against herpesviruses including HSV-1 and 2, VZV, and human cytomegalovirus (HCMV). In particular, penciclovir (**3**), one of carbanucleosides in which the ethereal oxygen of normal nucleosides is replaced by a carbon atom exhibited a broad antiviral spectrum. Carbocyclic nucleosides such as

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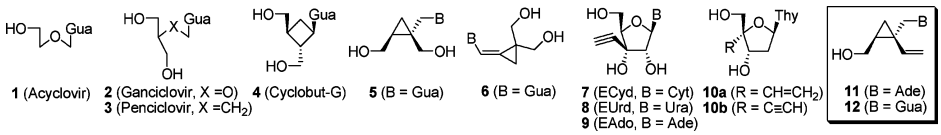


FIGURE 1 The rationale for the design of the desired nucleosides, **11** and **12**.

penciclovir (**3**) and cyclobut-G (**4**) obtain the benefit to be more stable under acidic conditions or to enzymes that cleave normal nucleosides. It is of interest to note that in cases of acyclic nucleosides or small sugar-ring sized nucleosides, guanine nucleoside usually has been found to exhibit the most potent and selective antiviral activity against HSV-1 and 2, VZV and other herpes viruses (HCMV and Epstein-Barr virus). Up to now, 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. Recently, cyclopropyl guanine nucleoside **6**[6] bearing exo-methylene group has been found to show a potent inhibition against herpesviruses including HCMV and MCMV (murine cytomegalovirus).

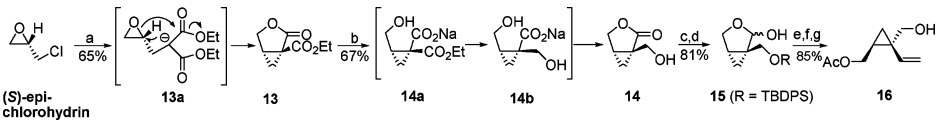
On the other hand, nucleosides bearing unsaturated functional groups such as vinyl and acetylenyl at 3′ or 4′ position have been reported to show potent antiviral and antitumor activities. Among them, 1-(3-*C*-ethynyl-β-D-*ribo*-pentofuranosyl)cytosine (ECyd, **7**)[7] and its uracil congener (EUrd, **8**) have exhibited potent antitumor activity. ECyd (**7**) has also shown potent anti-HIV (human immunodeficiency virus) activity with its adenine congener, EAdo (**9**). In addition, 4′α-*C*-ethenyl- and ethynylthymidines, (**10a** and **10b**)[8] also have been found to show very potent anti-HSV-1 and anti-HIV-1 activities.

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 synthesize novel pseudo-L-vinylcyclopropyl nucleosides **11** and **12**, combining properties of nucleosides bearing cyclopropane ring and vinyl substituent, respectively. Herein, we wish to report the synthesis of pseudo-L-vinylcyclopropyl adenine and guanine nucleosides **11** and **12** starting from (*S*)-(+)-epichlorohydrin.

CHEMISTRY

It was envisioned that analog of cyclopropyl alcohol **16** could be an appropriate glycosyl donor for the condensation with various natural bases.

Synthesis of the vinyl-substituted glycosyl donor **16** is shown in Scheme 1. Formation of bicyclolactone **13**[9] was accomplished by a tandem reaction of

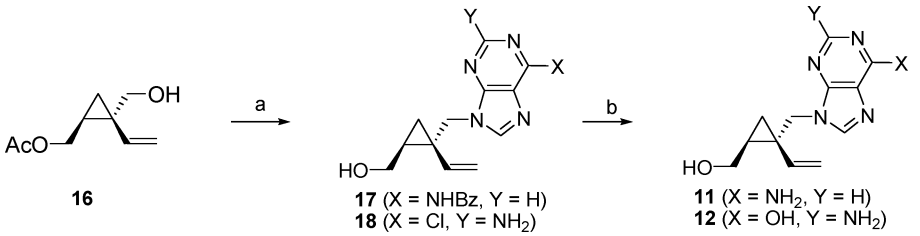


SCHEME 1 Reagents and conditions: (a) $(EtO_2C)_2CH_2$, Na, EtOH, 80°C, 24 hours; (b) i) 1 eq. NaOH, EtOH, rt, 16 hours; ii) $NaBH_4$, reflux, 3 hours then 2 *N* HCl, rt, 18 hours; (c) TBDPSCl, imidazole, CH_2Cl_2,rt, overnight; (d) Dibal-H, CH_2Cl_2, −78°C 50 minutes;(e) CH_3PPh_3Br, *t*-BuOK, THF, rt 2 hours; (f) Ac_2O. pyridine. rt, overnight; (g) *n*-Bu_4NF, THF, rt, 1 hour.

double alkylations and lactonization. Reaction of (*S*)-(+)-epichlorohydrin with diethyl malonate in the presence of sodium metal in EtOH first formed alkylated compound **13a**, which was deprotonated by sodium ethoxide to give **13a** anion. The enolate anion attacked more substituted oxirane carbon to open the epoxide ring and the resulting oxide anion formed lactone compound **13** in 65% yield by attacking carbonyl group of ester functional group. The regioselectivity in oxirane ring-opening reaction appears to result from more favorable formation of three-membered ring than four-membered ring. Chemoselective reduction of ester group of **13** in the presence of lactone functional group was accomplished by successive hydrolysis, reduction and cyclization reaction.[10] Protection of hydroxyl group of **14** as the silyl ether followed by lactone reduction with Dibal-H afforded the corresponding lactol **15**. A Wittig reaction of lactol **15** gave vinyl-substituted cyclopropyl analog. Successive acetylation and desilyation gave glycosyl donor **16**.

Coupling of **16** with N^6-benzoyladenine and 2-amino-6-chloropurine under Mitsunobu conditions smoothly generated protected purine nucleosides **17** and **18**, respectively (Scheme 2). Treatment of **17** with 1 M NaOMe afforded the final adenine nucleoside **11** in 63% yield from **16**. Conversion of **18** into the final guanine nucleoside **12** was accomplished by treating with 2-mercaptoethanol and 1 M NaOMe at 80°C[11] in 42% yield from **16**.

Now, biological evaluation of the synthesized final compounds **11** and **12** is in progress against various herpesviruses and their antiviral activities will be compared with those of D-counterparts of the final compounds.



SCHEME 2 Reagents and conditions: (a) PPh. DEAD, N^6-benzoyladenine, or 2-amino-6-chloropurine, THF, rt, 2 hours for **17** and **18**; (b) 1 *N* NaOMe, rt, 5 hours, 63% from **16** for **11**, 2 -mercaptoethanol, 1 *N* NaOMe, MeOH, 80°C, 7 hours 42% from **16** for **12**.

CONCLUSION

On the basis of facts that cyclopropyl nucleosides and nucleosides having substituent of multiple bond such as vinyl and acetylenyl groups showed highly potent anti-herpesvirus inhibition and in particular, guanine nucleosides have shown higher anti-herpesvirus potency than nucleosides with other natural bases, vinyl-substituted cyclopropyl nucleoside derivatives **11** and **12** with adenine and guanine bases were designed and enantiopurely synthesized starting from (*S*)-(+)-epichlorohydrin employing 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. Schaeffer, H.J.; Beauchamp, L.; De Miranda, P.; Elion, G.B.; Bauer, D.J; Collines, P. 9-(2-Hydroxyethoxymethyl)guanine activity against viruses of the herpes group, *Nature* **1978**, 272, 583–585.
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.V.; Cheng, Y.C. The mode of action of penciclovir. *Antiviral Chem. Chemother.* **1994**, 5, 31–37.
4. Nishiyama, Y.; Yamamoto, N.; Yamada, Y.; Daikoku, T.; Ichikawa, Y.; Takahashi, K. Anti-herpesvirus activity of carbocyclic oxetanocin G in vitro. *J. Antibiot.* **1989**, 42, 1854–1859.
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. Zhou, S.; Breitenbach, J.M.; Borysko, K.Z.; Drach, J.C.; Kern, E.R.; Gullen, E.; Cheng, Y.-C.; Zemlicka, J. Synthesis and antiviral activity of (*Z*)- and (*E*)-2,2-[bis(hydroxymethyl) cyclopropylidene]methylpurines and –pyrimidines: second-generation methylenecyclopropane analogues of nucleosides, *J. Med. Chem.* **2004**, 47, 566–575.
7. 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.
8. Sugimoto, I.; Shuto, S.; Mori, S.; Shigeta, S.; Matsuda, A. Nucleosides and Nucleotides. 183. Synthesis of 4′α-branched thymidines as a new type of antiviral agent. *Bioorg. Med. Chem. Lett.* **1999**, 9, 385–388.
9. Pirrung, M.C.; Dunlap, S.E.; Trinks, U.P. Synthesis and study of racemic, (1*R*,2*S*)-, and (1*S*,2*R*)-1-amino-2-(hydroxymethyl)cyclopropanecarboxylic acid. *Helv. Chim. Acta* **1989**, 72, 1301–1310.
10. Onishi, T.; Matsuzawa, T.; Nishi, S.; Tsuji, T. A practical synthesis of antiviral cyclopropane nucleoside A-5021. *Tetrahedron Lett.* **1999**, 40, 8845–8847.
11. Yoo, B.N.; Kim, H.O.; Moon, H.R.; Seol, S.K.; Jang, S.K.; Lee, K.M.; Jeong, L.S. Synthesis of 2-C-hydroxymethylribofuranosylpurines as potent anti-hepatitis C virus (HCV) agents. *Bioorg. Med. Chem. Lett.* **2006,** 16, 4190–4194.