Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 911–914

TETRAHEDRON: *ASYMMETRY*

Enantio- and diastereoselective synthesis of 4′-α-substituted carbocyclic nucleosides

Keisuke Kato*,[a,*] Hisaki Suzuki,[b] Hiromichi Tanaka[b] and Tadashi Miyasaka*[b]

[a]*School of Pharmaceutical Science, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274, Japan*

[b]*School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan*

Received 16 January 1998; accepted 2 February 1998

Abstract

Enantio- and diastereoselective synthesis of 4-α-alkylcarbovir derivatives **5** were achieved based on Sakai's asymmetric alkylation of β-keto esters. The key carbocyclic intermediate **14** was synthesized from **8** *via* an eleven-step sequence. Coupling of **14** with 2-amino-6-chloropurine followed by desilylation and subsequent hydrolysis gave the target compounds **5** in moderate yields.

In recent years, carbocyclic nucleoside analogues have emerged as a promising group of compounds for antiviral and antitumor agents. Carbovir **1** and other 2-cyclopentenyl nucleoside analogues have been extensively investigated for their potential as anti-HIV agents.[1] The numerous syntheses of carbovir and other carbocyclic nucleosides have been reported.[2] The most common approach to carbocyclic nucleosides is a convergent synthesis which couples a purine or pyrimidine base with a cyclopentene moiety, thus the former is easy to modify[3] but the latter is generally little functionalized. Recently, Magg[4] and Meguro[5] reported the anti-HIV activity of various 4-α-substituted nucleosides **2** and **3** (Fig. 1).

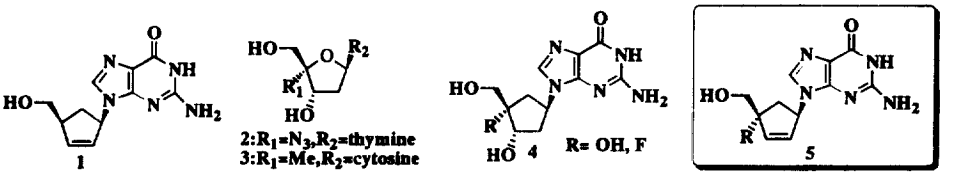


Fig. 1.

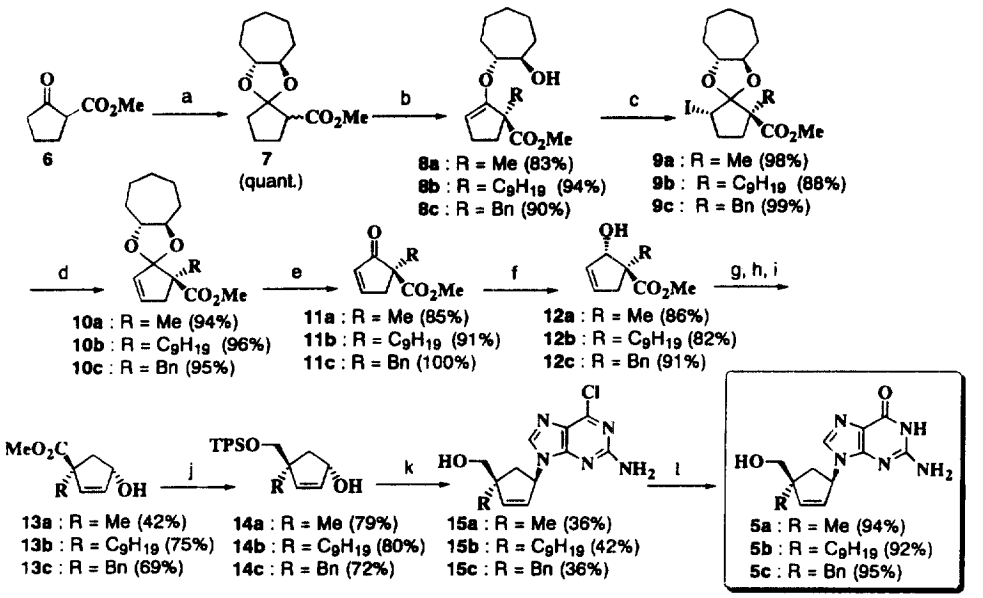
On the other hand, few examples have been reported for the synthesis and biological evaluation of 4′-α-substituted carbocyclic nucleosides.[6] For example, 4′-α-hydroxyl and 4′-α-fluoro derivatives **4** have been synthesised by aristeromycin, which show potent anti-herpetic activity.[6b] The most common synthesis of the 4′-α-substituted carbocyclic nucleosides is transformation from a natural product,[6a–d]

* Corresponding author.

0957-4166/98/$19.00
PII: S0957-4166(98)00065-2

therefore the functionalization of the cyclopentene moiety is restricted. We wish to report here the enantio- and diastereoselective synthesis of 4′-α-alkyl carbocyclic nucleosides **5**.

Our synthetic plan is as follows (Scheme 1): (1) The construction of the stereogenic quaternary carbon should be achieved by the asymmetric alkylation of chiral acetal **7**. (2) The double bond of **11** may be introduced utilizing the enol ether moiety of **8**. (3) The hydroxy ester **12** could be stereoselectively prepared from **11** by the regio- and diastereoselective Luche reduction. (4) The key carbocyclic intermediate **14** may be prepared from **12** *via* the stereospecific Pd-catalyzed allylic rearrangement. (5) The target compounds **5** would be obtained by the Mitsunobu reaction of **14**.

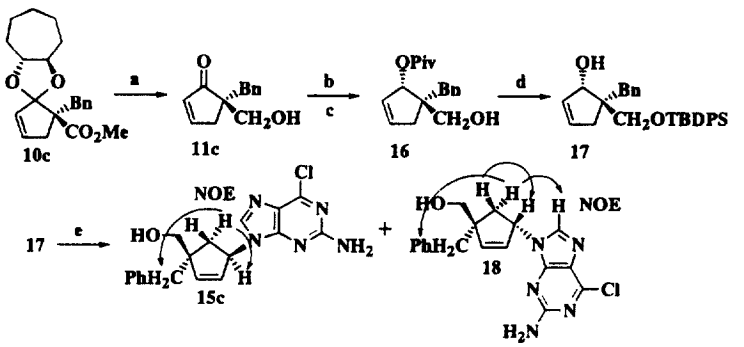


Reagents: a) *(R,R)*-cycloheptane-1,2-diol, TsOH ; b) LDA, MeI for **8a**, $C_9H_{19}Br$ for **8b** and BnBr for **8c** ; c) I_2, Et_3N ; d) DBU ; e)10%HCl, MeOH ; f) $NaBH_4$, $CeCl_3$; g) Ac_2O, pyridine ; h) $PdCl_2(MeCN)_2$, benzoquinone ; i) K_2CO_3, MeOH ; j) i) DHP ii) LAH iii) TBDPS-Cl 4) PPTS ; k) i) 2-amino-6-chloropurine, Ph_3P, $EtO_2CN{=}NCO_2Et$ ii) TBAF ; l) 1 N NaOH

Scheme 1.

Asymmetric alkylation [LDA (3 equiv.), THF/HMPA (5 equiv.), RX (3 equiv.), −78 to −40°C] of chiral acetal **7** derived from readily available methyl 2-oxocyclopentanecarboxylate **6** and (*R,R*)-cycloheptane-1,2-diol,[7] with methyl iodide, nonyl bromide, and benzyl bromide afforded the corresponding alkylated enol ethers **8** in a completely diastereoselective manner (d.e.>99%).[8] Iodoacetalization of the enol ethers **8** using iodine (2 equiv.) in the presence of triethylamine (1 equiv.) in THF at −40°C for 12 h gave the iodoacetals **9** as a single diastereomer.[9] Treatment of the iodoacetals **9** with DBU at 95–100°C for 1 h afforded the olefinic acetals **10**. Acid hydrolysis of **10** gave the chiral enone esters **11**, accompanied by (*R,R*)-cycloheptane-1,2-diol (71–81%). Luche reduction[10] of **11** using $NaBH_4/CeCl_3$ in MeOH gave the hydroxy esters **12** in highly regio- and diastereoselective manner. Acetylation of **12** followed by treatment with Pd-catalyst in the presence of benzoquinone in THF gave the desired rearranged products.[11] Subsequent methanolysis of these products gave **13** as a single diastereomer. The hydroxy esters **13** were converted into the key intermediate **14** by a four-step sequence [(i) DHP, PPTS in CH_2Cl_2, r.t.; (ii) LAH in THF, r.t.; (iii) TBDPS-Cl, imidazole in DMF, r.t.; (iv) PPTS in MeOH, 40°C]. The Mitsunobu reaction[12] of **14** with 2-amino-6-chloropurine followed by desilylation afforded **15**,[13] which when hydrolyzed with 1 N NaOH gave the target compounds **5** in 34–39% yields.[14] The attachment of carbo-sugar to the base at N_9 is confirmed by the HMBC spectrum of **15**, which showed

long range coupling between the $C_{1'}$–H and the purine carbons C_4 and C_8. The biological activity studies are in progress.



Reagents: a) i) LAH, THF ii) 10% HCl, MeOH (90%); b) $NaBH_4$, $CeCl_3$ (70%); c) Me_3CCOCl, DMAP (80%); d) i) TBDPSCl, imidazole ii) KOH, MeOH (90 %); e) i) 2-amino-6-chloropurine, Ph_3P, $EtO_2CN{=}NCO_2Et$ ii) TBAF (36%)

Scheme 2.

Acknowledgements

Useful comments and suggestions by Professor H. Suemune (Kyushu University) are gratefully acknowledged.

References

1. (a) Vince, R., Hua, M., Brownell, J., Daluge, S., Lee, F., Shannon, W. M., Lavelle, G. C., Qualls, J., Weislow, O. S., Kiser, R., Canonico, P. G., Schultz, R. H., Narayanan, V. L., Mayo, J. G., Shoemaker, R. H., Boyd, M. R., *Biochem. Biophys. Res. Com.* **1988**, 156, 1046. (b) Vince, R., Hua, M., *J. Med. Chem.*, **1990**, 33, 17. (c) Peel, M. R., Sternbach, D. D., Johnson, M. R., *J. Org. Chem.*, **1991**, 56, 4990. (d) Jones, M. F., Myers, P. L., Robertson, C. A., Storer, R., Williamson, C., *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2479.
2. (a) Agrofoglio, L., Suhas, E., Farese, A., Condom, R., Challard, S. R., Earl, R. A., Guedj, R., *Tetrahedron*, **1994**, 50, 10611. (b) Borthwick, A. D., Biggadike, K., *Tetrahedron*, **1992**, 48, 571. (c) Huryn, D. M., Okabe, M., *Chem., Rev.*, **1992**, 92, 1745. (d) Tanaka, M., Norimine, Y., Fujita, T., Suemune, H., Sakai, K., *J. Org. Chem.*, **1996**, 61, 6952. (e) Borthwick, A. D., Crame, A. J., Exall, A. M., Weingarten, G. G., Mahmoudian, M., *Tetrahedron Lett.*, **1995**, 36, 6929. (f) Taylor, S. J. C., McCague, R., Wisdom, R., Lee, C., Dickson, K., Ruecroft, G., O'Brien, F., Littlechild, J., Bevan, J., Roberts, S. M., Evans, C. T., *Tetrahedron: Asymmetry*, **1993**, 4, 1117.
3. Popescu, A., Hornfeldt, A.-B., Gronowitz, S., *Nucleosides Nucleotides*, **1995**, 14, 1639.
4. Maag, H., Rydzewski, R. M., McRoberts, M. J., Crawford-Ruth, D., Verheyden, J. P. H., Prisbe, E. J., *J. Med. Chem.*, **1992**, 35, 4098.
5. Waga, T., Ohrui, H., Meguro, H., *Nucleosides Nucleotides*, **1996**, 15, 287.
6. (a) Biggadike, K.; Borthwick, A. D., *J. Chem. Soc., Chem. Commun.*, **1990**, 1380. (b) Borthwick, A. D., Biggadike, K. Eur. Pat. Appl. 0 345 076, 1989. (c) Caamano, O., Fernandez, F., Neito, M. I., *Nuclesides Nucleotides*, **1995**, 14, 295. (d) Bianco, A., Mazzei, R. A., *Tetrahedron Lett.*, **1997**, 38, 6433. (e) Chao, Q., Nair, V., *Tetrahedron Lett.*, **1995**, 36, 7375.
7. (*R*,*R*)-Cycloheptane-1,2-diol can be prepared by enzymatic procedure. See Xie, Z.-F., Nakamura, I., Suemune, H., Sakai, K. *J. Chem. Soc., Chem. Commun.*, **1988**, 966.
8. Kato, K., Suemune, H., Sakai, K. *Tetrahedron*, **1994**, 50, 3315.
9. The stereochemistry of **9** was determined by NOE experiments.
10. Luche, J. L., Genal, A. L. *J. Am. Chem. Soc.*, **1979**, 101, 5848.
11. Oehlschlager, A. C., Mishra, P., Dhami, S., *Can. J. Chem*, **1984**, 62, 791.
12. Jenny, T. F., Previsani, N., Benner, S. A., *Tetrahedron Lett.*, **1991**, 36, 7029.

13. In a preliminary experiment, the S_N1'-type Mitsunobu reaction of **17** derived from **10c** *via* six-step sequence [(i) LAH, (ii) H^+, (iii) $NaBH_4/CeCl_3$, (iv) pivaloyl chloride, (v) TBDPSCl, (vi) KOH, MeOH] with 2-amino-6-chloropurine, followed by desilylation afforded the β-isomer **15c** (18%) accompanied by the α-isomer **18** (18%). The relative stereochemistry of **15c** and **18** was determined by NOE experiments (Scheme 2). In the case of **15a** and **15b**, the similar results of NOE experiments with **15c** were observed.
14. Satisfactory analytical data were obtained for all new compounds. **5a**: white crystalline solid, m.p. 280–290°C (dec.); $[\alpha]_D^{22}$ −4.7 (c 0.2, MeOH); λ_{max}(MeOH)/nm 206.0 (ε=19310), 253.4 (ε=10211); ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.05 (3H, s, Me), 1.87 (1H, dd, *J*=13.4, 5.8 Hz, $C_{5'}$–H-β), 2.12 (1H, dd, *J*=13.4, 8.5 Hz, $C_{5'}$–H-α), 3.26 (1H, d, *J*=10.4 Hz, $C_{6'}$–H), 3.34 (1H, d, *J*=10.7 Hz, $C_{6'}$–H), 4.72 (1H, s, $C_{6'}$–O*H*), 5.43 (1H, m, $C_{1'}$–H), 5.73 (1H, dd, *J*=5.5, 2.1 Hz, $C_{2'}$–H), 5.93 (1H, dd, *J*=5.5, 2.1 Hz, $C_{3'}$–H), 6.39 (2H, br s, NH_2), 7.59 (1H, s, C_8–H), 10.54 (1H, s, N*H*); ^{13}C-NMR (500 MHz, DMSO-d_6): δ 23.4 (q, Me), 41.5 (t, $C_{5'}$), 50.9 (s, $C_{4'}$), 58.3 (d, $C_{1'}$), 68.2 (t, $C_{6'}$), 116.4 (s, C_5), 127.7 (d, $C_{2'}$), 134.7 (d, C_8), 143.6 (d, $C_{3'}$), 150.6 (s, C_4), 153.4 (s, C_2 or C_6), 156.6 (s, C_2 or C_6); FAB-MS *m/z*: 262 (M^++1). **5b**: White crystalline solid, m.p. 280–290°C (dec.); $[\alpha]_D^{23}$ +59.9 (c 0.2, MeOH); λ_{max}(MeOH)/nm 206.2 (ε=18953), 254.8 (ε=9731); ^{1}H-NMR (500 MHz, DMSO-d_6): δ 0.87 (3H, t, *J*=6.7 Hz, C_8H_{16}–C*H*$_3$), 1.25 (14H, m, CH_2–C_7H_{14}–C*H*$_3$), 1.36 (2H, t, *J*=7.9 Hz, C*H*$_2$–C_8H_{17}), 1.79 (1H, dd, *J*=14.0, 5.8 Hz, $C_{5'}$–H-β), 2.19 (1H, dd, *J*=14.0, 8.9 Hz, $C_{5'}$–H-α), 3.28 (1H, dd, *J*=10.4, 5.2 Hz, $C_{6'}$–H), 3.38 (1H, dd, *J*=10.4, 5.1 Hz, $C_{6'}$–H), 4.79 (1H, t, *J*=5.2 Hz, $C_{6'}$–O*H*), 5.35 (1H, m, $H_{1'}$), 5.75 (1H, dd, *J*=5.8, 2.1 Hz, $C_{2'}$–H), 5.87 (1H, dd, *J*=5.8, 2.1 Hz, $C_{3'}$–H), 6.77 (2H, s, NH_2), 7.57 (1H, s, H_8), 10.90 (1H, s, N*H*); ^{13}C-NMR (500 MHz, DMSO-d_6): δ 13.9 (q, C_8H_{16}–*C*H$_3$), 22.0, 23.9, 28.7, 29.0, 29.8, 31.2, 35.9 (each as t, *C*$_8H_{16}$–CH$_3$), 39.3 (t, $C_{5'}$), 54.8 (s, $C_{4'}$), 58.5 (d, $C_{1'}$), 67.2 (t, $C_{6'}$), 116.5 (s, C_5), 128.6 (d, $C_{2'}$), 134.7 (d, C_8), 142.2 (d, $C_{3'}$), 150.6 (s, C_4), 153.7 (s, C_6), 156.6 (s, C_2); FAB-MS *m/z*: 374 (M^++1). **5c**: White crystalline solid, m.p. 290–295°C; $[\alpha]_D^{23}$+112.0 (c 0.410, MeOH); λ_{max}(MeOH)/nm 206.8 (ε=23555), 255.2 (ε=9222); ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.78 (1H, dd, *J*=14.0, 5.5 Hz, $C_{5'}$–H-β), 2.31 (1H, dd, *J*=14.0, 9.0 Hz, $C_{5'}$–H-α), 2.66, 2.77 (2H, each as d, *J*=13.2 Hz, C*H*$_2$–Ph), 3.34 (1H, dd, *J*=10.6, 5.5 Hz, $C_{6'}$–H), 3.41 (1H, dd, *J*=10.6, 5.1 Hz, $C_{6'}$–H), 4.93–4.98 (2H, m, $C_{1'}$–H and $C_{6'}$–O*H*), 5.71 (1H, dd, *J*=5.5, 2.2 Hz, $C_{2'}$–H), 5.94 (1H, dd, *J*=5.5, 2.1 Hz, $C_{3'}$–H), 6.71 (2H, s, NH_2), 7.15–7.30 (5H, m, Ph), 7.55 (1H, s, C_8–H), 10.83 (1H, s, N*H*); ^{13}C-NMR (500 MHz, DMSO-d_6): δ 38.3(t, $C_{5'}$), 41.4 (t, *C*H$_2$–Ph), 55.9 (s, $C_{4'}$), 58.2 (d, $C_{1'}$), 67.0 (t, $C_{6'}$), 116.5 (s, C_5), 129.4 (d, $C_{2'}$), 125.9, 127.7, 130.3 (each as d, Ph), 134.8 (d, C_8), 138.5 (s, Ph), 141.8 (d, $C_{3'}$), 150.6 (s, C_4), 153.6 (s, C_2 or C_6), 156.7 (s, C_2 or C_6), FAB-MS *m/z*: 376 (M^++K)