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SYNTHESIS AND ANTIVIRAL EVALUATION OF [(2'*S*, 3'*S*)-BIS(HYDROXYMETHYL)AZETIDIN-1-YL]PYRIMIDINE NUCLEOSIDES: ANALOGS OF OXETANOCIN-A

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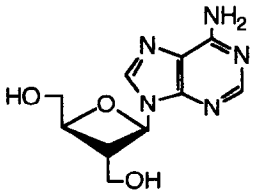
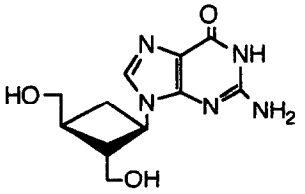
Abstract: The enantiospecific synthesis of [(2'*S*, 3'*S*)-bis(hydroxymethyl)azetidin-1-yl]pyrimidine nucleosides **15**, **18**, and **20**, the first members of a new class of nucleoside analogs in which the oxetane ring in oxetanocin-A **1** is replaced by an azetidine ring linked to a nucleic base through an N-N bond, was achieved *via* construction of the base on the 1-aminoazetidine **11** prepared from (+)-diethyl-L-tartrate. None of these compounds had significant antiviral activity in cell culture tests.

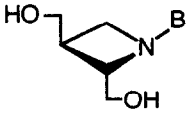
The unique nature of the replicative cycle of HIV-1 provides many potential targets for the discovery of chemotherapeutic intervention, i.e. inhibitors of reverse transcriptase, protease, and HIV-1 nuclear regulatory proteins tat and rev. The design and synthesis of potential these inhibitors therefore constitutes a rational strategy for the development of anti-AIDS agents which is presently being pursued by a large number of research groups. The discovery of the potent antiviral activity of oxetanocin-A **1**,[1] and carbocyclic oxetanocin-G **2**[2] has prompted great interest in this class of compounds. As a part of our continuing studies on the preparation and antiviral evaluation of analogs of **1** and **2**, we became interested in developing a synthesis of (azetidin-1-yl)pyrimidine and purine nucleoside analogs **3**[3] possessing a flexible N-N glycosyl link. In this report we describe the first synthesis of [(2'*S*, 3'*S*)-bis(hydroxymethyl)azetidin-1-yl]pyrimidine nucleosides.



1 Oxetanocin-A



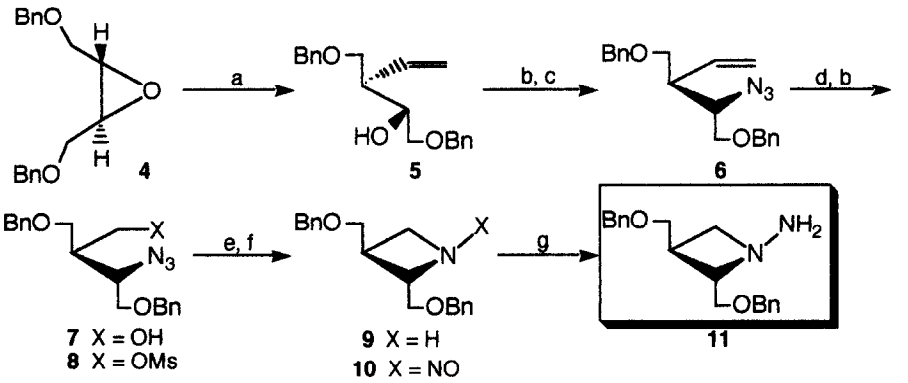
2 COXT-G



3 B = nucleic acid base

As shown in Scheme 1, the synthesis of the key intermediate 1-aminoazetidine **11** began with (*S*, *S*)-1,4-bis(benzyloxy)-2,3-epoxybutane **4** prepared from (+)-diethyl-L-tartrate according to the protocol of Nicolaou *et al.*.[4] Reaction of **4** with vinylmagnesium bromide in the presence of CuI gave the vinyl-alcohol **5** in 94 % yield. Mesylation of **5** with methanesulphonyl chloride followed by an S_N2 substitution with sodium azide in DMF afforded the vinyl-azide **6** in 89 % yield (2 steps). Then **6** was subjected to the following two-step one pot procedure because of the rapid epimerization of the aldehyde obtained during aqueous work-up and/or silica gel

chromatography. Ozonolysis of **6** in methanol and subsequent *in situ* reduction of the ozonide with sodium borohydride yielded the azido-alcohol **7** in 77 % yield. Several attempts to get the azetidine **9** by a reductive cyclization of **7** with triphenylphosphine [5] failed. Subsequently, compound **9** could be obtained as follows: mesylation of **7** with methanesulphonyl chloride gave the azido-mesylate **8**, which smoothly cyclized *in situ* during hydrogenation with Raney-Ni (W-2) as the catalyst to yield **9**[8] in 86 % yield (2 steps). **9** was nitrosated with excess isoamyl nitrite to give the nitroso-azetidine **10** in quantitative yield. Lithium aluminum hydride reduction of **10** gave the 1-aminoazetidine **11**[6] in 83 % yield.



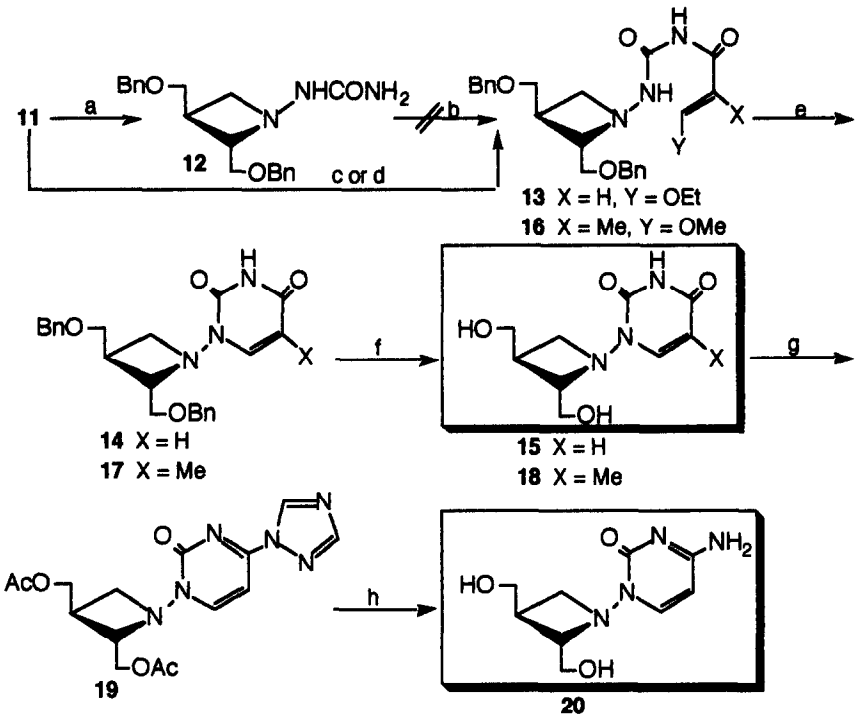
Scheme 1. *Reagents and conditions* : (a) CH_2=CHMgBr, CuI, Et_2O, -10 °C, 4.5 h. (b) MsCl, Et_3N, 0 °C, 4 h. (c) NaN_3, DMF, 100 °C, 1 h. (d) O_3, MeOH, -20 °C, then $NaBH_4$, rt, 10 h. (e) Raney-Ni W-2, EtOH, rt, 15 h. (f) isoamyl nitrite, 0 °C → rt, 20 h. (g) $LiAlH_4$, THF, -10 °C, 3.5 h.

In order to obtain the uracil nucleoside **15** compound **11** was treated with trimethylsilyl isocyanate in dichloromethane to afford the urea **12**[8] as a stable solid in 55 % yield. Attempted condensations of compound **12** with 3-ethoxyacryloyl chloride to give the intermediate acrylamide **13** were unsuccessful. Alternatively, treatment of **11** with 3-ethoxyacryloyl isocyanate generated *in situ* from 3-ethoxyacryloyl chloride and silver cyanate[7] in benzene readily afforded **13** in 64 % yield, which cyclized smoothly upon treatment with 7 % NH_4OH in EtOH at 80 °C to provide the uracil **14** in 92 % yield. Deprotection of **14** by transfer hydrogenolysis with 20 % $Pd(OH)_2$ on carbon and cyclohexene afforded the target compound **15**[8] in 64 % yield.

The thymine derivative **18** was produced by treatment of **11** with 3-methoxy-2-methylacryloyl isocyanate[7] in benzene to afford the intermediate acrylamide **16** in 51 % yield. Subsequent ring closure with 7 % NH_4OH in EtOH at 80 °C gave the thymine **17** in 41 % yield, which was then deblocked under the same reaction conditions tried for compound **14** to afford the target compound **18**[8] in 40 % yield.

To obtain the cytosine nucleoside **20** the diacetate of **15** was treated with *o*-chlorophenyl phosphorodichloridate and 1,2,4-triazole in pyridine to provide the 4-triazolylpyrimidinone **19**[8] in 26 % yield. Subsequent treatment of **19** with 35 % ammonium hydroxide in MeOH produced the target compound **20**[8] in 56 % yield (Scheme 2).

Biological Activity: Evaluation of compounds **15**, **18**, and **20** against HSV-1 and HSV-2 in Vero cells by a plaque reduction assay at concentrations up to 10 μg/ml, and HIV-1 in MT-4 cells by an indirect immunofluorescence assay at concentrations up to 100 μg/ml revealed these compounds to be devoid of antiviral activity and cytotoxicity .



Scheme 2. *Reagents and conditions* : (a) TMSNCO, THF, rt, 15 h. (b) 3-ethoxyacryloyl chloride, pyridine. (c) 3-ethoxyacryloyl isocyanate, benzene, rt, 12 h. (d) 3-methoxy-2-methylacryloyl isocyanate, benzene, rt, 12 h. (e) 7% NH_4OH, EtOH, 80 °C, 8 h. (f) 20% $Pd(OH)_2/C$, cyclohexene, EtOH, refluxing temp., 3 h. (g) i: Ac_2O, pyridine, rt, 10 h, ii: *o*-$ClC_6H_4OPOCl_2$, 1,2,4-triazole, pyridine, -30 °C→ rt, 12 h. (h) 35% NH_4OH, MeOH, rt, 15 h.

In summary we have developed the first synthesis of [(2'*S*, 3'*S*)-bis(hydroxymethyl)azetidin-1-yl]pyrimidine nucleosides as novel analogs of oxetanocin-A.[9] The synthetic strategy outlined in this report seems to be efficient and applicable to the chiral synthesis of a number of potential antiviral pyrimidine derivatives of this new class.[10]

References and Notes:

1. *Isolation*: Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, A.; Takita, T. *J. Antibiot.* **1986**,*39*, 1623. *Antiviral activities*: Hoshino, H.; Shimizu, N.; Shimada, N.; Takita, T.; Takeuchi, T. *J. Antibiot.* **1987**, *40*, 1077. Nishiyama, Y.; Yamamoto, N.; Yamada, Y.; Fujioka, H.; Shimada, N.; Takahashi, K. *J. Antibiot.* **1989**, *42*, 1308. *Synthesis*: Niitsuma, S.; Ichikawa, Y.; Kato. K.; Takita. T. *Tetrahedron Lett.* **1987**, *28*, 3967 and 4713. Nishiyama, S.; Yamamura, S.; Kato, K.; Takita, T. *Tetrahedron Lett.* **1988**, *29*, 4739 and 4743. Norbeck, D. W.; Kramer, J. B. *J. Am. Chem. Soc.* **1988**, *110*, 7217. Wilson F. X.; Fleet, G. W. J.; Vogt, K.; Wang, Y.; Witty, D. R.; Choi, S.; Storer, R.; Meyers, P. L.; Wallis, C. J. *Tetrahedron Lett.* **1990**, *31*, 6931. Humbalek, R.; Just, G. *Tetrahedron Lett.* **1990**, *31*, 5445. Nagai, M.; Kato, K.; Takita, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron*, **1990**, *46*, 7703.
2. *Synthesis*: Honjo, M.; Maruyama, T.; Sato, Y.; Horii, T. *Chem Pharm. Bull.* **1989**, *37*, 1413. Ichikawa, Y.; Narita, A.; Shiozawa, A.; Hayashi, Y.; Narasaka, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1919.

Slusarchyk, W. A.; Young, M. G.; Bisacchi, G. S.; Hockstein, D. R.; Zahler, R. *Tetrahedron Lett.* **1989**, *30*, 6453. Katagiri, N.; Sato, H.; Kaneko, C. *Chem. Pharm. Bull.* **1990**, *38*, 288. *Antiviral activities*: Nishiyama, Y.; Yamamoto, N.; Yamada, Y.; Daikoku, T.; Ichikawa, Y.; Takahashi, K. *J. Antibiot.* **1989**, *42*, 1854. Maruyama, T.; Sato, Y.; Horii, T.; Shiota, H.; Nitta, K.; Shirasaka, T.; Mitsuya, H.; Honjo, M. *Chem. Pham. Bull.* **1990**, *38*, 2719. Bissachi, G. S.; Braitman, A.; Cianci, C. W.; Clark, J. M.; Field, A. K.; Terry, B. J.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1991**, *34*, 1415.

3. Very recently nucleoside analogs containing a pyrrolidine ring linked to the base *via* the heteroatom have been developed. Harnden, M. R.; Jarvest, R. L. *Tetrahedron Lett.* **1991**, *32*, 3863. Lee, Y. H.; Kim, H. K.; Youn, I. K.; Chae,Y. B. *Bioorgnic & Medicinal Chemistry Lett.* **1991**, *1*, 287. Mansour, T. K.; Jin, H. *Bioorgnic & Medicinal Chemistry Lett.* **1991**, *1*, 757. Harnden, M. R.; Jarvest, R. L.; Parratt, M. J. *J. Chem. Soc., Perkin Trans.* 1 **1992**, 2259.
4. Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440.
5. Thijs, L.; Porskamp, Jos J. M.; van Loon, Adriaan A. W. M.; Derks, M. P. W.; Feenstra, Rolf W.; Legters Johan; Zwanenburg, Binne.*Tetrahedron* **1990**, *46*, 2611.
6. As compound **11** is unstable at room temperature, it should be kept in a refrigerator and used without purification in the next step.
7. Shaw, G.; Warrener, R. N. *J. Chem. Soc.* **1958**, 157.
8. Selected spectroscopic data; **9**: colorless oil $[\alpha]^{22}_{D}$ +25° (*c* 0.63, $CHCl_3$); υ_{max}(neat)/cm^{-1} 3340, 1600, and 1545; ^1H NMR (270 MHz, $CDCl_3$) δ 2.76 (1H, m, 3-H), 3.43 (1H, t, *J* 7.6 Hz, 4-H), 3.53 (1H, t, *J* 7.6 Hz, 4-H), 3.57 (4H, d, *J* 5.9 Hz, OCH_2x2), 3.91 (1H, q, *J* 5.9 Hz, 2-H), 4.51 (2H, s, $PhCH_2$), 4.56 (2H, s, $PhCH_2$), and 7.30 - 7.35 (10H, complex, Phx2); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 37.3 (d), 47.0 (t), 60.8 (d), 71.7 (t), 73.2 (t), 73.4 (t), 74.0 (t), 127.7 (d), 127.8 (d), 128.5 (d), and 138.4 (s).

12: white crystals mp 84.6 - 85.5 °C (ether); $[\alpha]^{20}_{D}$ -3.7° (*c* 0.21, MeOH); υ_{max}(nujol)/cm^{-1} 3500, 3300, 1680, and 1575; ^1H NMR (270 MHz, $CDCl_3$) δ 2.53 (1H, m, 3-H), 3.16 (1H, t, *J* 7.3 Hz, 4-H), 3.50 (2H, d, *J* 7.3 Hz, OCH_2), 3.53 (2H, d, *J* 4.3 Hz, OCH_2), 3.61 (1H, dt, *J* 7.3 and 4.3 Hz, 2-H), 3.74 (1H, t, *J* 7.3 Hz, 4-H), 4.51 (2H, s, $PhCH_2$), 4.54 (2H, s, $PhCH_2$), 5.76 (1H, broad s, D_2O exchangable, NH), and 7.29 - 7.37 (10H, complex, Phx2); ^{13}C NMR (67.8 MHz, C_6D_6) δ 31.3 (d), 59.0 (d), 59.1 (t), 70.7 (t), 71.7 (t), 73.0 (t), 73.3 (t), 128.0 (d), 128.4 (d), 128.8 (d), 139.0 (s), and 160.7 (s); HRMS, m/z 355.1894 cacld for $C_{20}H_{25}O_3N_3$ (M^+), found 355.1896.

15: white foam υ_{max}(neat)/cm^{-1} 3440, 1685, and 1650; ^1H NMR (270 MHz, CD_3OD) δ 2.45, (1H, m, 3'-H), 3.59 (1H, dd, *J* 5.6 and 11.9 Hz, OCH), 3.67 (1H, dd, *J* 3.6 and 11.9 Hz, OCH), 3.74 (1H, t, *J* 7.1 Hz, 4'-H), 3.80 (2H, d, *J* 7.1 Hz, OCH_2), 4.29 (1H, t, *J* 7.1 Hz, 4'-H), 4.59 (1H, m, 2'-H), 5.55 (1H, d, *J* 8.1 Hz, 5-H), and 7.69 (1H, d, *J* 8.1 Hz, 6-H).

18: white foam υ_{max}(neat)/cm^{-1} 3420, 1690, and 1660; ^1H NMR (270 MHz, CD_3OD) δ 1.86 (3H, s, 5-Me), 2.46 (1H, m, 3'-H), 3.59 (1H, dd, *J* 5.4 and 11.8 Hz, OCH), 3.66 (1H, dd, *J* 4.0 and 11.8 Hz, OCH), 3.73 (1H, t, *J* 7.1 Hz, 4'-H), 3.80 (2H, d, *J* 6.6 Hz, OCH_2), 4.26 (1H, t, *J* 7.1 Hz, 4'-H), .57 (1H, m, 2'-H), and 7.55 (1H, s, 6-H).

19: white foam υ_{max}(neat)/cm^{-1} 1740, 1690, 1680, 1624, and 1546; ^1H NMR (270 MHz, $CDCl_3$) δ 2.07 (3H, s, OAc), 2.14 (3H, s, OAc), 2.64 (1H, m, 3'-H), 3.70 (1H, dd, *J* 6.7 and 7.9 Hz, 4'-H), 3.99 (1H, dd, J 5.5 and 12.2 Hz, OCH), 4.37 (2H, d *J* 5.5 Hz, OCH_2), 4.39 (1H, dd, *J* 3.1 and 12.2 Hz, OCH), 4.69 (1H, dd, *J* 6.7 and 7.9 Hz, 4'-H), 5.12 (1H, m, 2'-H), 6.91 (1H, d, *J* 7.3 Hz, 5-H), 7.92 (1H, d, *J* 7.3 Hz, 6-H), 8.12 (1H, s, triazolyl 3-H), and 9.24 (1H, s, triazolyl 5-H).

20: white foam υ_{max}(neat)/cm^{-1} 3360, 3200, 1665, and 1610; ^1H NMR (270 MHz, CD_3OD) δ 2.43 (1H, m, 3'-H), 3.53 (1H, dd, *J* 5.5 and 11.7 Hz, OCH), 3.60 (1H, dd, *J* 3.9 and 11.7 Hz, OCH), 3.66 (1H, t, *J* 7.3 Hz, 4'-H), 3.78 (2H, d, *J* 7.3 Hz, OCH_2), 4.30 (1H, t, *J* 7.3 Hz, 4'-H), 4.59 (1H, m, 2'-H), 5.73 (1H, d, *J* 7.6 Hz, 5-H), and 7.64 (1H, d, *J* 7.6 Hz, 6-H).

9. Although two isomers of α and β forms due to inversion at the azetidine nitrogen presumably exist, the NMR spectra of compounds **15**, **18**, and **20** indicate the existence of one isomer, respectively. Detailed discussion of the theoretical and spectroscopic analysis of the stereochemistry will be disclosed in due course.
10. Further studies on the synthesis of purine nucleoside analogs of this class and the results of biological testing will be reported in future publications.

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