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Synthesis of [(2'*S*, 3'*S*)-Bis(hydroxylmethyl)pyrrolidin-1-yl] Purine and Pyrimidine Nucleosides as Potential Antiviral Agents

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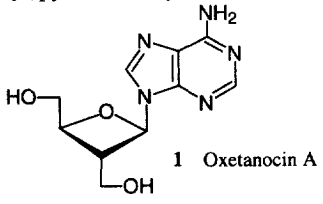
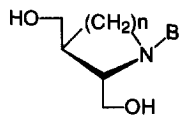
Abstract: The enantiomerically pure synthesis of [(2'*S*, 3'*S*)-bis(hydroxymethyl)pyrrolidin-1-yl] thymine **17** and -adenine **20** was achieved *via* construction of the base on the 1-amino-pyrrolidine **15**, and their anti-HSV-1 and -2, and anti-HIV-1 activities were evaluated.

Keywords: Antivirals, Nucleosides

As part of our continuing studies on the preparation and antiviral evaluation of different types of hydroxymethyl-branched nucleosides as the modified oxetanocin A **1** analogs, we recently reported the synthesis of [(2'*S*, 3'*S*)-bis(hydroxymethyl)azetidin-1-yl] nucleosides **2**.[1] To further evaluate the structure-activity relationship of hydroxymethyl-substituted nucleosides, we have accomplished the first synthesis of [(2'*S*, 3'*S*)-bis(hydroxymethyl)pyrrolidin-1-yl] nucleosides **3**.[2, 3]



1 Oxetanocin A



2 n = 1 azetidine-N-nucleosides
3 n = 2 pyrrolidine-N-nucleosides

The vinyl group of **5** [4] was subjected to hydroboration reaction with 9-BBN to afford alcohol **6**. Compound **6** was converted to pyrrolidine **13** : $[\alpha]^{21}_{D}$ +30.0° (*c* 0.88, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.54 (1H, tdd, J = 6.6, 7.5, 13.2 Hz), 1.94 (1H, m), 2.14 (1H, m), 2.86-3.03 (2H, complex), 3.11 (1H, td, J = 6.6, 4.0 Hz), 3.43 (2H, d, J = 6.6 Hz), 3.45 (1H, dd, J = 6.6, 9.2 Hz), 3.61 (1H, dd, J = 4.0, 9.2 Hz), 4.49 (2H, s), 4.53 (2H, s) and 7.25-7.37 (10H, complex); HRMS, m/z 311.1885 cacld for $C_{20}H_{25}NO_2(M^+)$, found 311.1890: by a seven-step sequence: (1) protection of the primary alcohol by acetylation, (2) desilylation by nBu_4NF, (3) preparation of the mesylate with MsCl, (4) substitution reaction with NaN_3, (5) hydrolysis of the acetate with K_2CO_3 in MeOH, (6) preparation of the mesylate with MsCl, (7) reductive cyclization by hydrogenation of the azido-mesylate. The resulting pyrrolidine compound **13** was nitrosated with excess isoamyl nitrite to give nitroso-pyrrolidine **14** in quantitative yield. Reduction of **14** with lithium aluminum hydride yielded *N*-amino-pyrrolidine **15** (Scheme 1). Treatment of **15** with 3-methoxy-2-methylacryloyl isocyanate in benzene afforded the intermediate acrylamide **16**. Subsequent ring closure of **16** followed by deprotection by transfer hydrogenolysis provided the target compound **17**. The pathway of compound **15** to purine derivatives was *via* an imidazole intermediate. Condensation of **15** with ethyl *N*-

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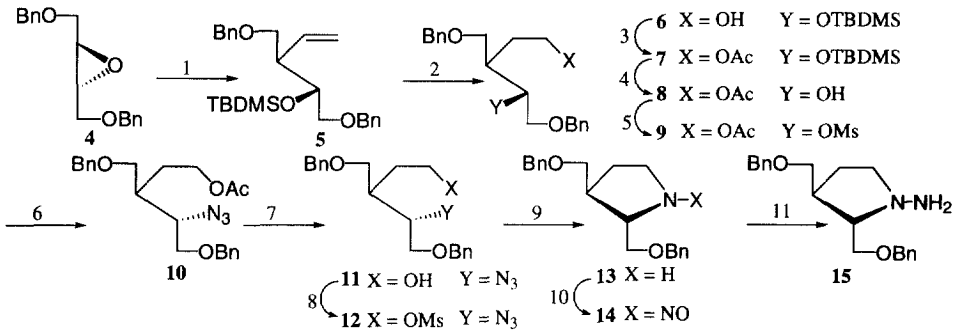
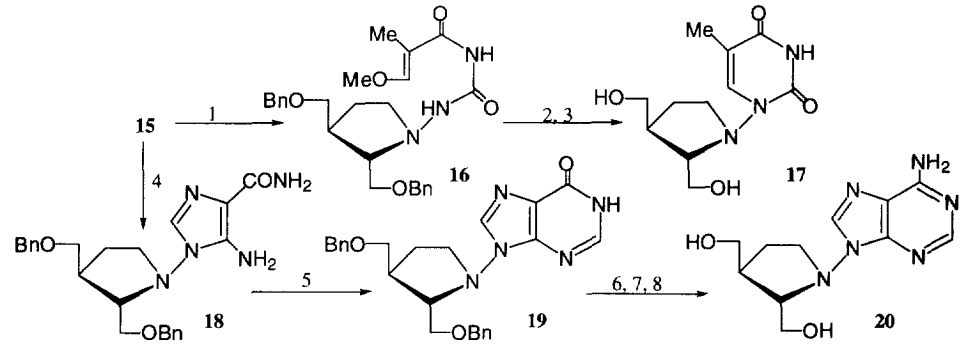
(carbamoylcyanomethyl)formimidate gave imidazole **18**, which was converted into hypoxanthine **19** using triethyl orthoformate. Compound **19** was successfully transformed into the adenine **20** *via* ammonolysis of the intermediate 2,4,6,-triisopropylbenzenesulfonate followed by deprotection by transfer hydrogenolysis (Scheme 2).



Scheme 1 *Reagents and Conditions*: 1) see Ref. 1; 2) a: 9-BBN (0.5 M THF solution), rt, 18.5 h, b: 3N-NaOH, 35 % H_2O_2, rt, 6 h, 74 %; 3) Ac_2O, pyridine, rt, 22 h, 75 %; 4) nBu_4NF, THF, rt, 7 h, 88 %; 5) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2.5 h, 96 %; 6) NaN_3, DMF, 110 °C, 1.5 h, 91 %; 7) K_2CO_3, MeOH, rt, 1.5 h, 96 %; 8) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1.5 h, 91 %; 9) 10 % Pd-C, H_2, EtOH, rt, 1 h, 96 %; 10) isoamyl nitrite, rt, 20 h, 95 %; 11) $LiAlH_4$, THF, -10 °C, 3.5 h, 79 %.



Scheme 2. *Reagents and conditions* : 1) 3-methoxy-2-methylacryloyl isocyanate, benzene, rt, 12 h, 55 %; 2) 7 % NH_4OH, EtOH, 80 °C, 8 h, 43 %; 3) 20 % $Pd(OH)_2/C$, cyclohexene, EtOH, reflux, 3 h, 64 %; 4) EtO-C=N-CH(CN)$CONH_2$, EtOH, reflux, 30 min, 41 %; 5) $HC(OEt)_3$, DMF,120 °C, 20 min, 49 %; 6) 2,4,6-triisopropyl benzenesulphonyl chloride, Et_3N, DMAP, CH_2Cl_2, rt, 2 h, 62 %; 7) NH_3, EtOH, sealed tube, 80 °C, 6 h;, 70 %; 8) 20 % $Pd(OH)_2/C$, cyclohexene, EtOH, reflux, 5h, 68 %.

Evaluation of compounds **17** 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 10 μg/ml revealed these compounds to be devoid of antiviral activity and cytotoxicity.

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

References:

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