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CHEMOENZYMATIC SYNTHESIS OF (-)-CARBOCYCLIC 7-DEAZAOXETANOCIN G

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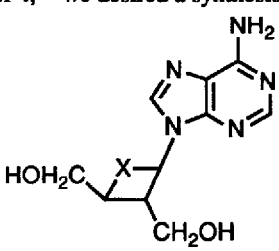
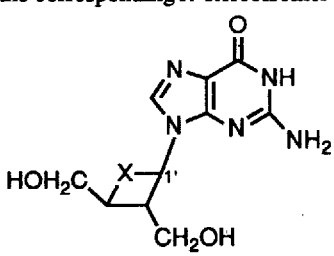
Summary: The enantioselective synthesis of (-)-(1*R*,2*S*,3*S*)-2-amino-7-[2,3-bis(hydroxymethyl)-cyclobutyl]pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**5**) as the 7-deaza analogue of carbocyclic oxetanocin G is described in 13 steps from *trans*-3,3-diethoxy-1,2-bis(hydroxymethyl)cyclobutane (**8**) in an overall yield of 6%. Included in this route is the use of *Pseudomonas cepacia* lipase for enzymatic resolution.

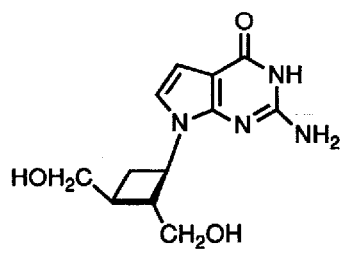
The naturally occurring oxetanocin A (**1**)[1] and synthetic oxetanocin G (**2**)[2] represent a novel class of nucleosides possessing antiviral properties.[3] Modification of the unique oxetanosyl-N-glycoside structural feature of **1** and **2** into the carbocyclic nucleoside framework[4] led to the synthesis of **3** and **4** as racemates[5] and individual enantiomers,[6] which have shown activity against herpesviruses and HIV.[5b,c,6,7] One particular interest to this laboratory is the development of 7-deazapurine carbocyclic nucleosides that can be effective against human cytomegalovirus (HCMV). In view of the potent and selective anti-HCMV properties of the C-1' *R*-stereoisomer of **4**,[6b] we desired a synthesis of the corresponding *R*-stereoisomer **5**.



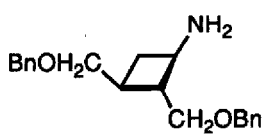
(-)-**1**, X=O
3, X=CH_2



(-)-**2**, X=O
4, X=CH_2



5



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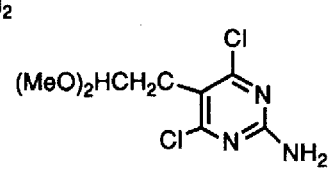

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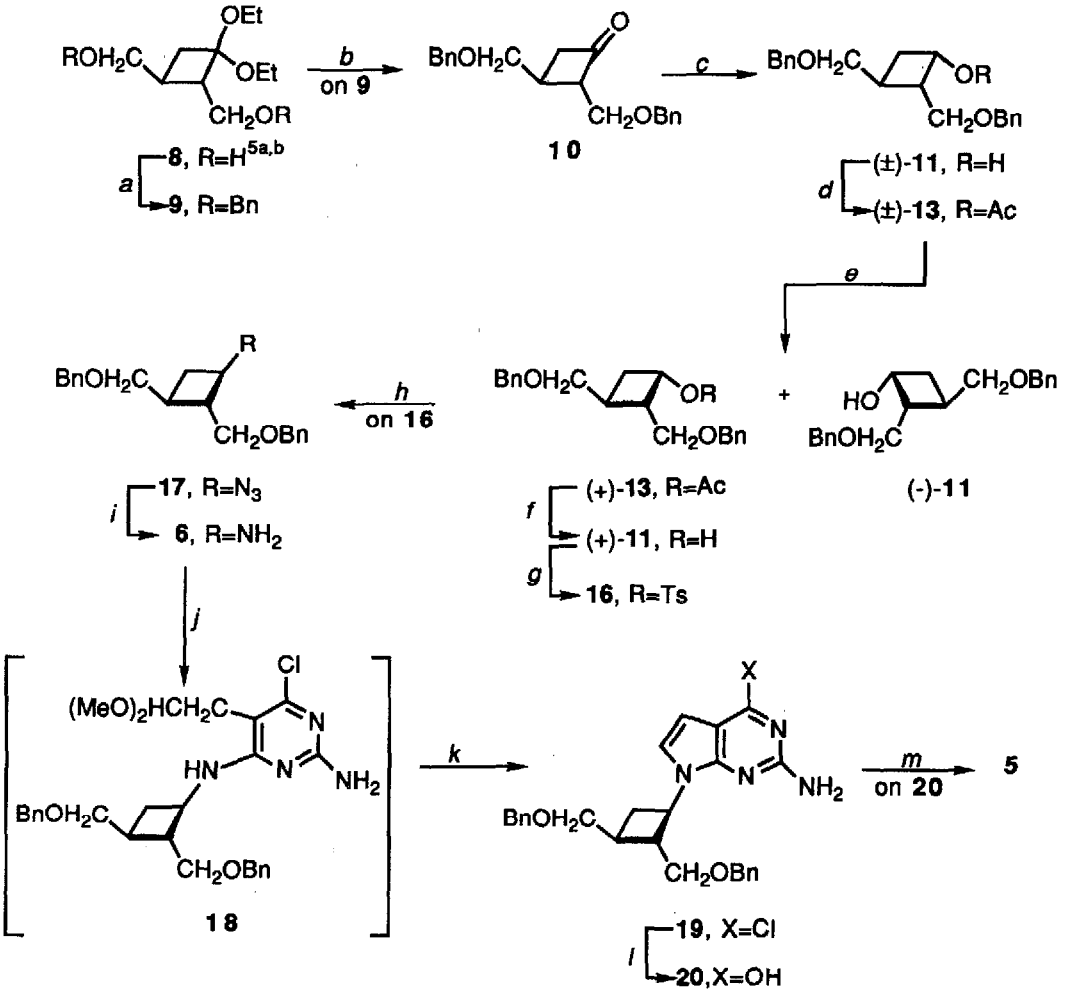
Related 7-deazapurine carbocyclic nucleoside syntheses in our laboratory indicated that the most efficacious route to **5** would be via reaction of the protected chiral amine **6** with the dimethylacetal of 2-(2-amino-4,6-dichloropyrimidin-5-yl)acetaldehyde **7**[8] followed by ring closure, hydrolysis and deprotection. A review of the literature revealed two enantioselective routes to cyclobutyl derivatives used in the synthesis of chiral carbocyclic oxeanocins[6] that seemed suitable for preparing a precursor of **6**. In one case,[6a] however, the initial step involved a [2+2]-cycloaddition reaction of not easily obtainable reagents in the presence of a chiral titanium compound as catalyst. In the other case,[6b] resolution of a chiral mixture of cycloadducts was done through diastereomeric amides that added steps to the synthesis. In view of the ease with which enzymes[9] can produce re-

solution of a racemic mixture, we chose to use *Pseudomonas cepacia* lipase[10] on the (±)-acetate **13** as a more efficient means to **6**.

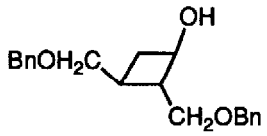
Scheme



Reaction conditions: a, (i) NaH in DMF; (ii) BnBr; *b,* 0.5% H_2SO_4 in MeCN; *c,* LS-Selectride in THF, -78 °C; *d,* Ac_2O/pyridine; *e, Pseudomonas cepacia* lipase in phosphate buffer; *f,* KOH in MeOH; *g,* TsCl/pyridine; *h,* NaN_3 in DMF, 100 °C; *i,* BH_3•THF in THF; *j,* **7** and Et_3N in 1-BuOH, 100 °C; *k,* 2 N HCl; *l,* 5% aq. NaOH in MeOH; *m,* EtSH and BF_3•Et_2O

Thus, benzylation of *trans*-3,3-diethoxy-1,2-bis(hydroxymethyl)cyclobutane (**8**)[5a,b] to *trans*-3,3-diethoxy-1,2-bis[(benzyloxy)methyl]cyclobutane (**9**,[11] 100%, oil) (Scheme) was followed by hydrolysis to *trans*-2,3-bis[(benzyloxy)methyl]cyclobutanone (**10**,[11,12] 100%, oil). Reduction of **10** with LS-Selectride[13] to (±)-(1α,2α,3β)-2,3-bis[(benzyloxy)methyl]cyclobutanol (**11**,[14] 81%, oil) occurred with no indication (by ^1H and ^{13}C nmr) of the diastereomeric alcohol **12** having been formed. Acetylation of **11** gave (±)-(1α,2α,3β)-2,3-

bis[(benzyloxy)methyl]-1-cyclobutyl acetate (**13**,[14] 92%, oil), which, when subjected to treatment with *Pseudomonas cepacia* lipase yielded (+)-(1*S*,2*S*,3*S*)-bis[(benzyloxy)methyl]-1-cyclobutyl acetate ((+)-**13**,[11] oil, 48%, >99% ee,[15], {$[\alpha]_D^{25}$ +14.57° (*c* 0.508, CH_2Cl_2)} and (-)-(1*R*,2*R*,3*R*)-2,3-bis[(benzyloxy)methyl]-1-cyclobutanol ((-)-**11**,[11] oil, 50%, >99% ee,[15] {$[\alpha]_D^{25}$ -27.06° (*c* 0.436, $CHCl_3$)}). The structural assignments for (+)-**13** and (-)**11** were accomplished by conversion into the enantiomeric alcohols **14** and **15** and comparing the optical rotation data for each product with the reported[16] values for these latter compounds.



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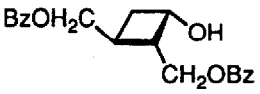
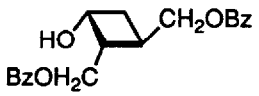


14



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Saponification of (+)-**13** to (+)-(1*S*,2*S*,3*S*)-2,3-bis[(benzyloxy)methyl]cyclobutanol ((+)-**11**,[11] 100%, oil, {$[\alpha]_D^{25}$ +27.14° (*c* 0.7, $CHCl_3$)}) was followed by tosylation to (+)-(1*S*,2*S*,3*S*)-2,3-bis[(benzyloxy)methyl]-1-cyclobutyl tosylate (**16**,[14] 90%, oil). Treatment of **16** with sodium azide (to **17**) followed by reduction provided (+)-(1*R*,2*S*,3*S*)-2,3-bis[(benzyloxy)methyl]cyclobutylamine (**6**,[11] 54% from **16**, oil), which, in turn, upon reaction with **7** gave the desired intermediate **18**. Ring closure of **18** with dilute acid produced (+)-(1*R*,2*S*,3*S*)-2-amino-7-{2,3-bis[(benzyloxy)methyl]cyclobutyl}-4-chloropyrrolo[2,3-*d*]-pyrimidine (**19**,[14] 63% from **6**, oil) that underwent subsequent hydrolysis to the protected 7-deazaguanine derivative (+)-(1*R*,2*S*,3*S*)-2-amino-7-{2,3-bis[(benzyloxy)methyl]cyclobutyl}pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**20**,[14] 78%, oil). Attempted hydrogenolytic debenzylation of **20** produced the 5,6-dihydro derivative of **5**. On the other hand, use of boron trifluoride/ethylthiol on **20** led to the target compound (-)-(1*R*,2*S*,3*S*)-2-amino-7-[2,3-bis(hydroxymethyl)cyclobutyl]pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**5**,[14] 64%, mp 250-252 °C from MeOH, {$[\alpha]_D^{25}$ -12.29° (*c* 0.358, DMSO)}). It should be noted that attempts to react **16** with 2-amino-4-chloropyrrolo[2,3-*d*]pyrimidine[8] resulted in recovery of starting material.

The biological properties of **5** and other uses of (+)-**13** for preparing various carbocyclic oxetanocin derivatives will be reported in the future.

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11. Satisfactory ^{1}H and ^{13}C nmr data was obtained for this compound.
12. Hsiao, C.-N.; Hannick, S.M. *Tetrahedron Lett.* **1990**, *31*, 6609-6612 reports the synthesis of the (+)-enantiomer of **10** in a rather lengthy process.
13. Reference 5b reports LS-Selectride provided the greatest configurational selectivity at the hydroxyl bearing carbon when reducing *trans*-2,3-bis[(benzoyloxy)methyl]cyclobutanone.
14. Satisfactory microanalytical and nmr (^{1}H and ^{13}C) data were obtained for this compound.
15. Enantiomeric purity was determined by HPLC using a Chiracell OJ column (0.46 cm x 25 cm) and eluting with 15% 2-PrOH-hexane.
16. Compound **14**: $[\alpha]_D^{25}$ -12.7° (*c* 1.21, $CHCl_3$); lit.[6b] $[\alpha]_D^{25}$ -13.9° (*c* 1.18, $CHCl_3$). Compound **15**: $[\alpha]_D^{25}$ +12.3° (*c* 1.03, $CHCl_3$); lit.[6b] $[\alpha]_D^{25}$ +12.6° (*c* 1.00, $CHCl_3$).

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