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DIFFERENCES IN ANTIVIRAL ACTIVITIES FOR ISOMERS OF A FLUORINATED CYCLOBUTANE NUCLEOSIDE ANALOG

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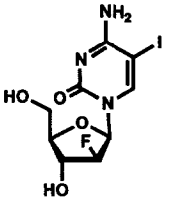
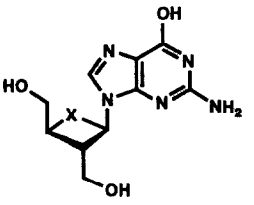
Abstract: Isomeric fluorinated cyclobutane nucleoside analogs (±)-**2** and (±)-**3** were prepared via multi-step syntheses. Compound **2** is a potent inhibitor of herpes viruses in cell culture assays, while the configurational isomer **3** is devoid of antiviral activity.

Fluorine substitution on the furanose ring of nucleosides has led to the discovery of potent antiviral agents, such as 1-(2'-deoxy-2'-fluoro-1'-β-D-arabinofuranosyl)-5-iodocytosine (**FIAC**).[2] Moreover, promising antiviral activity for a number of fluorinated carbocyclic nucleoside analogs has recently been reported.[3] These results, along with our interest in cyclobutane nucleoside analogs,[4] prompted us to study the antiviral effects of fluorine substitution on the cyclobutane ring of (+)-**1**, a potent inhibitor of herpes simplex virus type 1 (HSV-1) and HSV-2. In particular, we chose to investigate the chemical syntheses and antiviral effects of fluorinated analogs **2** and **3**. Herein, we report our results which demonstrate a striking difference in potency for these configurational isomers against a wide range of herpes viruses.



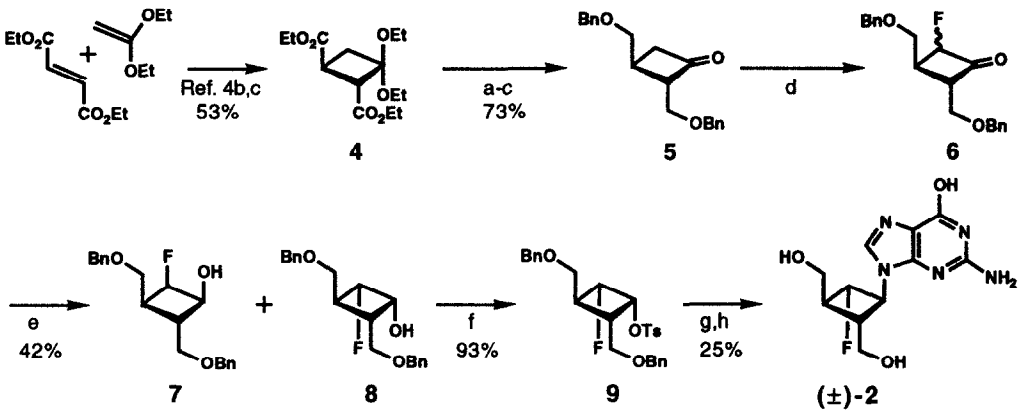
FIAC



1 X = CH_2
2 X = α-FCH
3 X = β-FCH

Synthesis of racemic **2** was carried out as outlined in Scheme 1. Reduction of the readily available cyclobutane derivative **4**,[4b,c] benzylation of the resulting diol and acid hydrolysis of the diethyl ketal afforded cyclobutanone **5**. Several methods for the introduction of fluorine adjacent to the carbonyl group of **5** were considered.[5] Many of these methods require the use of hazardous fluorine gas in the preparation of electrophilic fluorinating agents. Attempts to fluorinate **5** (or a silyl ether derivative of **5**) with the stable, commercially available N-fluoropyridinium triflate were unsuccessful.[5d,6] However, successful fluorination could be achieved by quenching the kinetic enolate of cyclobutanone **5** with perchloryl fluoride[5e] affording a 1:1 mixture of the epimeric α- and β-fluoro ketones **6**. Without purification of **6**, reduction with LS-selectride gave a 1:1 mixture of cyclobutanols **7** and **8** in 42% yield from **5**.[7] As expected in nucleophilic additions to cyclic haloketones,[8] the reduction of fluoroketones **6** was stereoselective, since both diastereomers of **6** gave major products corresponding to hydride delivery on the face opposite the fluorine. The diastereomeric alcohols **7** and **8**

Scheme 1



a) $LiAlH_4$; b) $PhCH_2Br$, NaH; c) 1:3 0.5M H_2SO_4/CH_3CN; d) Lithium 2,2,6,6-tetramethylpiperidide, $FClO_3$; e) LS-Selectride; f) p-TsCl, pyridine; g) 2-amino-6-phenylmethoxypurine, K_2CO_3, 18-Crown-6, DMF, 110°C; h) $Pd(OH)_2$, cyclohexene, ethanol.

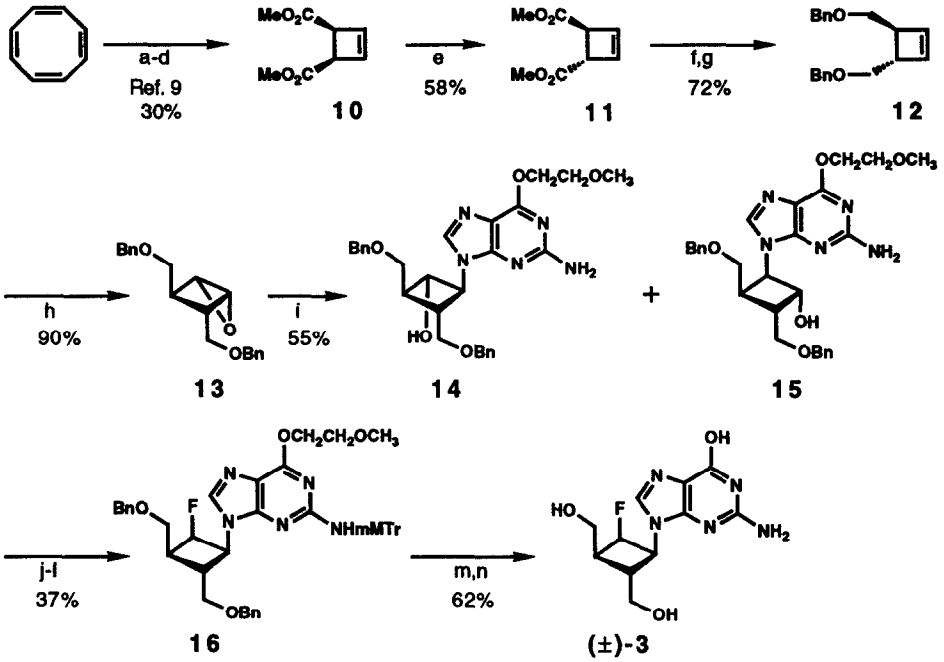
were separated by chromatography, and isomer **8** was converted to tosylate **9**. Nucleophilic substitution with 2-amino-6-phenylmethoxypurine, and protecting group removal afforded (±)-**2**.

Access to the 2'β-fluoro analog (±)-**3** via the same synthetic approach would require inversion of the C(2) hydroxyl group of **7** followed by introduction of the nucleobase; however, attempts to invert the C(2) hydroxyl group of **7** under Mitsunobu conditions failed. Therefore, a different route to the 2'β-isomer **3** was employed (Scheme 2). *Cis*-1,2-dimethyl cyclobutene dicarboxylate **10** was prepared in four steps from 1,3,5,7-cyclooctatetraene via modification of a known sequence.[9] Epimerization of **10** with sodium methoxide provided a 58% yield of the *trans* diester **11**. Reduction of **11**, followed by benzylation of the resulting diol, afforded cyclobutene **12** in 72% yield. Epoxidation of **12** with *m*-chloroperoxybenzoic acid gave **13** in 90% yield. Ring-opening of epoxide **13** with 2-amino-6-methoxyethoxypurine gave a 55% yield of N(9)-alkylated regioisomers **14** and **15** in a 2:1 ratio, respectively. Use of the methoxyethyl protecting group rather than a benzyl protecting group was advantageous for the chromatographic separation of regioisomers in this reaction; however, this protecting group did not lead to a desired enhancement of N(9) versus N(7) alkylation.[10] Next, the 2-amino group of **14** was protected with a mono-methoxytrityl (mMTr) group, and the 2'α-hydroxy group was converted to the corresponding trifluoromethanesulfonate. Subsequent fluoride displacement with tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF) afforded the desired 2'β-fluoro intermediate **16** in 37% yield.[11] Finally, acid hydrolysis of the guanine protecting groups, and boron trichloride removal of the benzyl ethers provided (±)-**3** in 62% yield.

The *in vitro* antiviral effects of (±)-**2** and (±)-**3** are shown in the Table. The 2'α-fluoro analog (±)-**2** exhibits potent antiviral effects against a broad spectrum of herpes viruses in viral plaque reduction assays. In these cell culture-based assays, (±)-**2** is equipotent to acyclovir, the current treatment for HSV-1, HSV-2, and VZV infections. Conversely, the isomeric 2'β-fluoro analog, (±)-**3**, is devoid of antiviral activity. Although fluorine is generally considered to be isosteric with hydrogen, this study provides another example where configurational isomers about a fluoromethylene group result in quite different antiviral properties. In the case of

nucleosides, it is known that **FIAC** is at least 1000 times more active against HSV-1 and HSV-2 than its epimeric 2'α-fluoro isomer.[2] Likewise, similar trends were recently reported for epimeric, fluorocyclopentane nucleoside analogs.[3e,g] Our results underscore the strict stereochemical requirements for biological activity that can be encountered when making fluorine atom substitutions on active compounds.

Scheme 2



a) Br_2; b) O_3, H_2O_2, HCO_2H; c) CH_2N_2; d) Zn-Cu; e) NaOMe; f) $LiAlH_4$; g) BnBr, NaH; h) MCPBA; i) 2-amino-6-(2-methoxyethoxy)purine, LiH, DMF, 110°C; j) mMTrCl, Et_3N; k) $(CF_3SO_2)_2$, pyridine; l) TASF; m) 3M HCl, MeOH; n) BCl_3.

Table

Compd.	IC_{50} (μM)[a,b] HSV-1	HSV-2	VZV	HCMV
(±)-2	0.7-2	0.7	2-4	4-40
(±)-3	>250	>250	>250	>250
(+)-1	0.04-0.08	0.04	0.02-0.08	2
Acyclovir	0.4	0.4	2-4	20-40

a) Viral plaque reduction assay[4d]; b) Concentration for 50% inhibition of plaque formation.

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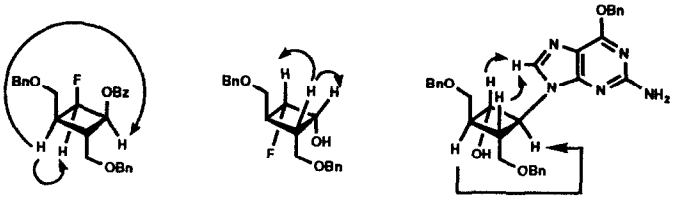

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11. Treatment of mMTr-protected **14** with DAST (diethylaminosulfurtrifluoride) failed to give **16**.