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Stereoselective Synthesis of Carbocyclic L-4′-Fluoro-2′,3′-dideoxyadenosine

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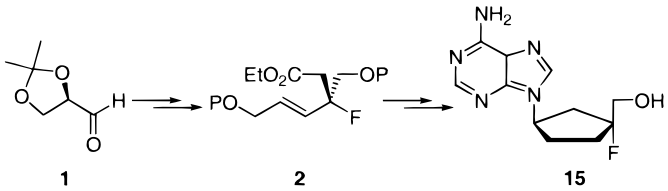
ABSTRACT



L-(1′*S*,3′*S*)-9-[3-Fluoro-3-(hydroxymethyl)cyclopentan-1-yl]adenine 15 has been synthesized from ester 2, which can be conveniently prepared from 2,3-isopropylidene-D-glyceraldehyde 1 in six steps. The key ring closure has been accomplished through an intramolecular nucleophilic substitution reaction.

Carbocyclic nucleosides have played an important role in the search for useful antiviral or antitumoral agents in the past 15 years.[1] An outstanding achievement in this field has been the recent approval of abacavir[2] (Figure 1) for the treatment of AIDS. From a chemical point of view, the nonglycosidic nature of carbocyclic nucleosides has made them a challenging target for synthetic chemists.

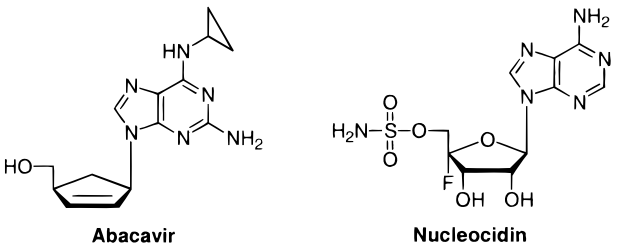


Figure 1. Structures of anti-HIV drug abacavir and natural antibiotic nucleoside nucleocidin.

Among "classical" nucleoside analogues bearing a glycosidic bond, a variety of substitutions have been made on the sugar moiety in the attempt to improve the biological activity as well as to obtain metabolically stable derivatives. In some cases, an electron-withdrawing substituent such as fluorine has conferred favorable pharmacological properties, and we[3] and others[4] have reported the synthesis and biological evaluation of several 2′- and 3′-fluorinated nucleosides.

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Since the discovery of nucleocidin[5] (Figure 1), several 4′-substituted analogues have been synthesized and their biological activities have been assessed.[6]

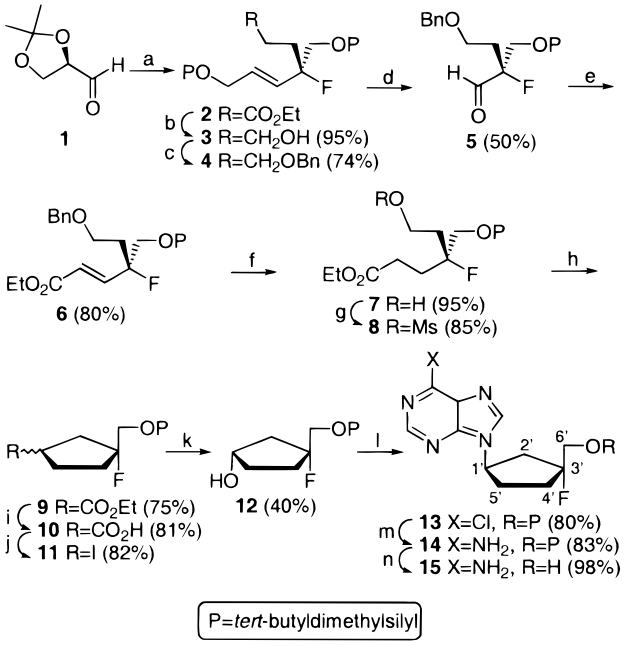
In the case of carbocyclic analogues, however, only a few examples have been reported, such as the synthesis of carbocyclic 4′-fluoro-2′-deoxyguanosine from aristeromycin[7] and the synthesis of carbocyclic 2′-*ara*-4′-α-fluoroguanosine.[8] Carbocyclic 4′-fluoro-3′-deoxythymidine has been identified as a side product in the synthesis of the 3′-fluoro analogue, though it could not be purified and fully characterized.[9]

The importance of carbocyclic nucleosides as antiviral agents as well as the potential advantage of fluorine substitution prompted us to combine these two features into novel L-4′-fluoro-2′,3′-dideoxy nucleosides. In view of the fact that several carbocyclic adenosine analogues are *S*-adenosylhomocysteine hydrolase inhibitors,[10] we decided to synthesize the adenosine analogue as part of a feasibility study.

In our approach, we started from intermediate **2** (Scheme 1), which was synthesized from 2,3-isopropylidene-D-glyceraldehyde **1** in fivw steps by the procedure developed in our laboratory. This procedure was based on the [3,3]-Claisen rearrangement, which allowed us to elaborate the fluorine to the desired position with high stereoselectivity.[11]

Compound **2** was reduced to alcohol **3** by treatment with a solution of lithium aluminum hydride (LAH) in THF at −40 to −35 °C (Scheme 1). Benzylation of **3** gave fully protected triol **4**, which was treated with ozone in methanol at −78 °C, followed by decomposition of the ozonide by dimethyl sulfide, to give aldehyde **5**. The Horner−Emmons-type reaction was performed by treatment of **5** with the sodium salt of triethyl phosphonoacetate in THF. *E*-Alkene

Scheme 1. Synthesis of (1′*S*,3′*S*)-9-[3-Fluoro-3-(hydroxymethyl)cyclopentan-1-yl]adenine[a]



[a] Reagents and conditions: (a) ref 11; (b) LAH, THF, −40 to −35 °C, 90 min; (c) NaH, THF, 0 °C to rt, 1 h, then BnBr, TBAI, 0 °C to rt, overnight; (d) O_3, MeOH, −78 °C, 45 min, then Me_2S, 0 °C, 2 h; (e) [$(EtO)_2P(O)CH_2CO_2Et$/NaHMDS], THF, −78 °C, 1 h; (f) H_2, 10% Pd/C, cyclohexane, rt, 24 h; (g) MsCl, Py, CH_2Cl_2, 0 °C to rt, 24 h; (h) NaH, THF, reflux, overnight; (i) NaOH/H_2O, EtOH, rt, 5 h, then AcOH, 0 °C; (j) $Pb(OAc)_4$, CCl_4, *hν*, reflux, 15 min, then I_2, CCl_4, *hν*, reflux, 2 h; (k) $NaHCO_3$, 15% (v/v) water/HMPA, 100 °C, overnight; (l) 6-chloropurine, [PPh_3/DEAD], rt, 6 h; (m) NH_3/MeOH, 100 °C (steel bomb), 2.5 h; (n) TBAF, THF, rt, 30 min.

6, obtained in 80% yield, was quantitatively converted to intermediate **8** by catalytic hydrogenolysis followed by mesylation of the resulting alcohol **7**. Treatment of **8** with sodium hydride in THF under refluxing conditions generated the enolate which cyclized through an intramolecular nucleophilic substitution reaction to produce epimeric esters **9** in 75% yield. Esters **9** were hydrolyzed to acids **10** by treatment with a solution of sodium hydroxide in water/ethanol 1:1, followed by careful acidification. Attempts to oxidatively decarboxylate **10** to an alcohol or ester derivative by using a number of different oxidants and conditions were not successful. However, a successful oxidative iododecarboxylation could be achieved by the method reported by Barton et al.:[12] a mixture of acids **10** and lead tetraacetate in carbon tetrachloride was stirred under reflux in a nitrogen atmosphere while being illuminated with a 250 W tungsten lamp for 15 min. Using the same conditions of refluxing and illumination, a solution of iodine in carbon tetrachloride was added in small portions until no more discoloration was observed (ca. 1 h). The reaction was continued for 1 h more. Workup and flash chromatography afforded epimeric iodides

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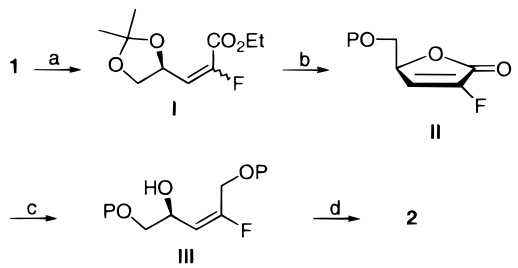


(a) $(EtO)_2P(O)CHFCO_2Et$, NaHMDS, 80%; (b) (i) concd HCl, EtOH, (ii) TBDMSCl, 70%; (c) (i) DIBAL-H, (ii) $NaBH_4$, $CeCl_3$, 80%, (iii) TBDMSCl, 80%; (d) $(EtO)_3CCH_3$, propionic acid, 130 °C, 70%.

(12) Barton, D. H. R.; Faro, H. P.; Serebryakov, E. P.; Woolsey, N. F. *J. Chem. Soc.* **1965**, 2438.

11, which were smoothly hydrolyzed by heating at 100 °C in a solution of sodium bicarbonate in 15% water/HMPA.

Surprisingly, only the α-alcohol could be isolated from hydrolysis of the mixture **11** (epimeric ratio ≈ 1:1). In the reaction conditions, the α-iodide was probably not hydrolyzed and longer reaction times or higher temperatures caused its decomposition. Under our best conditions, alcohol **12**[13] was obtained in 40% yield, and traces of the β-isomer could be detected by proton NMR.

The selectivity of the hydrolysis reaction might result from the pseudoequatorial preference of the bulky iodide groups in **11**α and **11**β (Figure 2). The attack of the water molecule

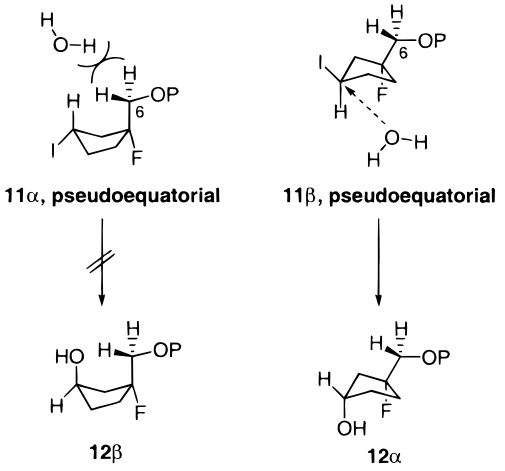


Figure 2. Proposed mechanism for the hydrolysis of iodides **11**.

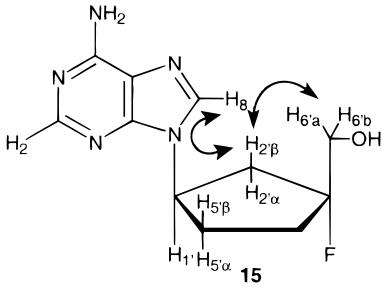
to **11**α may be hampered by the hindered exocyclic methylene (P = trimethyldimethylsilyl), whereas the **11**β conformer undergoes nucleophilic substitution by the water molecule.

Alcohol **12** was condensed with 6-chloropurine under Mitsunobu conditions to give adduct **13**. The success of Mitsunobu reactions in the synthesis of nucleoside analogues often depends on the conditions employed. In our case, a solution of the alcohol was added to the mixture containing 6-chloropurine and the preformed complex triphenylphosphine/DEAD in THF,[14] and the reaction was performed at room temperature in the dark for 6 h. Removal of the solvent and flash chromatography gave the product in 80% yield. The 6-chloro derivative **13** was converted into protected adenosine analogue **14** by treatment with a saturated solution of ammonia in methanol in a steel bomb at 100 °C for 2.5 h. Desilylation of the primary alcohol by treatment with tetrabutylammonium fluoride (TBAF) in THF resulted in the desired carbocyclic L-4′-fluoro-2′3′-dideoxyadenosine **15**[15] in 98% yield.

In summary, we have described a de novo synthesis of key intermediate cyclopentanol **12**. Condensation of this intermediate with 6-chloropurine, followed by ammonolysis and deprotection, readily provided carbocyclic L-4′-fluoro-2′,3′-dideoxyadenosine. Furthermore, intermediate **12** can be utilized for the syntheses of other nucleosides with the natural as well as the unnatural heterocyclic moieties, which are in progress.

The stereochemistry of products **12**−**15** has been established by one- and two-dimensional NMR experiments. In particular, NOEDS (1-D NOE difference spectrometry) spectra of **15** were crucial in understanding the geometry of the final product (and, consequently, of the precursors), since proton H-2′β showed net NOE enhancement upon irradiation of protons H-6′ and H-8, clearly indicating that the adenine moiety and the 6′-methylene are in a *cis* relation (Scheme 2). Unfortunately, no correlation between H-1′ and H-2′ could

Scheme 2. NOE Correlations and Stereochemistry of **15**



be studied because of the cluttering of the multiplets corresponding to protons H-2′α, H-2′β, and H-5′α.[16]

Antiviral activity and cytotoxicity evaluations of compound **15** are in progress.

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(13) Colorless oil: $[\alpha]^{27}_D$ 2.21° (*c* 3.13, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.33 (m, 1H, C*H*OH), 3.69 (dd, 1H, $H_{6'}$, *J* = 15.6, 10.7 Hz), 3.65 (dd, 1H, $H_{6'}$, *J* = 16.4, 10.7 Hz), 2.14−1.74 (m, 6H, $H_{2'}$, $H_{4'}$, $H_{5'}$), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 106.3 (J_{C-F} = 175.0 Hz), 73.3, 66.2 (J_{C-F} = 32.0 Hz), 43.7 (J_{C-F} = 21.5 Hz), 34.5, 32.7 (J_{C-F} = 24.1 Hz), 25.8, 18.3, −5.4; HRMS (FAB) obsd, *m*/*z* 249.1699, calcd for $C_{12}H_{26}FO_2Si$, *m*/*z* 249.1686 (MH^+). Anal. Calcd for $C_{12}H_{25}FO_2Si$: C, 58.02; H, 10.14. Found: C, 57.80; H, 9.96.

(14) Jenny, T. F.; Horlacher, J.; Previsani, N.; Benner, S. A. *Helv. Chim. Acta* **1992**, *75*, 1944.

(15) White solid: mp (MeOH) 167−168 °C; $[\alpha]^{29}_D$ −12.73° (*c* 0.37, MeOH); UV (MeOH) λ_{max} 260.0 (ε 20890) (pH 2), 261.5 (ε 19800) (pH 7), 261.5 (ε 17980) (pH 11); ^1H NMR (CD_3OD, 400 MHz) δ 8.12 (s, 1H, H_8), 8.08 (s, 1H, H_2), 5.08 (m, 1H, $H_{1'}$), 3.69 (dd, 1H, $H_{6'}$, *J* = 16.2, 12.1 Hz), 3.65 (dd, 1H, $H_{6'}$, *J* = 17.4, 12.1 Hz), 2.43−2.34 (m, 3H, $H_{2'}$, $H_{5'\alpha}$), 2.33−2.15 (m, 1H, $H_{4'\beta}$), 2.13−2.04 (m, 1H, $H_{5'\beta}$), 2.00−1.86 (m, 1H, $H_{4'\alpha}$); ^{13}C NMR (CD_3OD, 100 MHz) δ 157.3, 153.5, 150.7, 141.2, 120.5, 105.9 (J_{C-F} = 176.6 Hz), 66.7 (J_{C-F} = 27.4 Hz), 56.1, 41.6 (J_{C-F} = 24.1 Hz), 33.7 (J_{C-F} = 23.8 Hz), 31.5; HRMS (FAB) obsd, *m*/*z* 252.1268, calcd for $C_{11}H_{15}FON_5$, *m*/*z* 252.1261 (MH^+). Anal. Calcd for $C_{11}H_{14}FON_5$: C, 52.58; H, 5.62; N, 27.87. Found: C, 52.74; H, 5.73; N, 27.72.

(16) Thus, irradiation of H-1′ resulted in an amorphous multiplet containing protons H-5′α and H2′α (and, maybe, some NOE enhancement from H2′β), whereas protons H-8 and H-6′ correlated only and unequivocally with H-2′β, which showed as a clear double double doublet (*J* = 33.0, 14.2, 10.0 Hz).