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Tetrahedron Letters 45 (2004) 863–865
Tetrahedron Letters

A new synthetic approach to 2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranose, the fluorofuranose unit of the anti-HIV-active nucleoside, β-FddA

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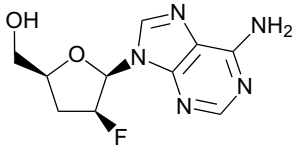
Received 12 August 2003; revised 30 October 2003; accepted 6 November 2003

Abstract—The fluorinated furanose unit of the anti-HIV-active nucleoside (2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine, β-FddA, has been synthesized as its 5-trityl derivative with high stereocontrol from (*S*)-trityl glycidol and phenylthioacetic acid.

The introduction of a fluorine atom into the sugar moiety of some deoxynucleosides has led to the discovery of a group of compounds with significant antiviral activity. One such compound is (2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (β-FddA) **1**.[1] The efficacy of β-FddA has attracted considerable interest, and consequently, there have been a number of attempts to develop efficient synthetic routes to this compound. Two broad strategies have been investigated, one involving the construction of a 2-fluorofuranose unit with the correct stereochemistry prior to coupling with a suitable adenine derivative and the second involving the fluorination of a preformed furanosyl adenine adduct.[1,2] A crucial requirement of either approach is the need to establish the correct (β) configuration of the fluorine substituent. In the most recent synthesis by Choudhury et al.[3] the β-fluoro substituent was introduced via an S_N2 displacement of an α-hydroxy group at the C-2 position. In a contribution from the Marquez group[4] at NIH, who have been particularly active in the area, the stereochemical requirement was addressed by fluorination of a suitable furanosyladenosine intermediate on the preferred alpha face of the sugar ring with a subsequent inversion of configuration at C-2 via an elimination (to a vinyl fluoride)-hydrogenation sequence to produce the β-configuration.[3] Despite the success of this and other approaches to the synthesis of **1**, there is still a need for a route capable of producing multigram quantities of the product.



FddA (1)

In seeking to develop a new route to a fluorofuranose suitable for eventual conversion to β-FddA we had identified a number of specific objectives. Firstly, the route should be amenable to scale-up with the minimum amount of chromatographic methods of purifications. Secondly, we sought a route that was highly enantioselective, and thirdly, access to inexpensive starting materials was highly desirable. These considerations led us to examine a glycidol derivative as the principal building block. Several glycidol derivatives are commercially available in single enantiomer form. The condensation of glycidol derivatives with malonate esters under basic conditions is known to form α-substituted-γ-valerolactones (Eq. 1),[5] which are amenable to further transformations, notably decarboxylation. Diastereoisomeric mixtures are usually obtained

Keywords: Anti-viral; Fluorofuranose; Epoxide ring opening; Phenylthioacetic acid; Stereospecific fluorination.
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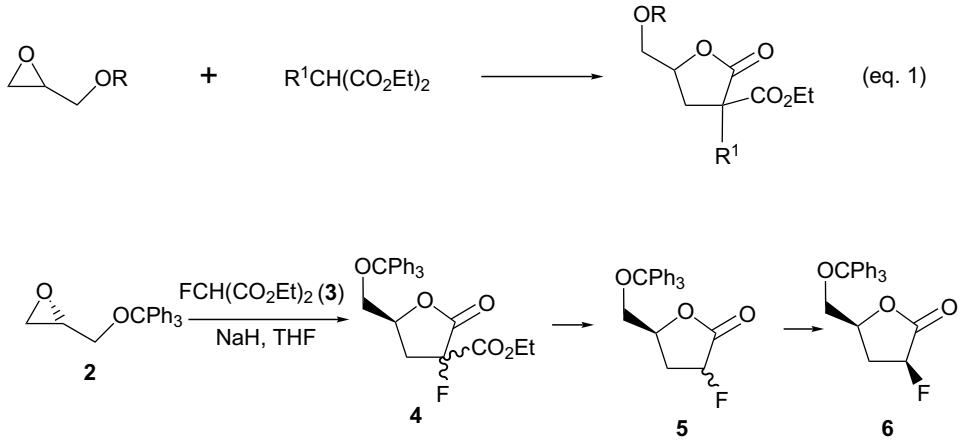
doi:10.1016/j.tetlet.2003.11.020



Scheme 1.

after decarboxylation when $R^1 \neq H$. Examples are known with $R^1 =$ a benzenoid substituent where subsequent deprotonation to form the enolate followed by kinetic reprotonation at low temperature has been employed to transform a diastereoisomeric mixture into a single isomer, the *cis*-lactone.[6] On the strengths of these precedents the route summarized in Scheme 1 was designed. We chose (*S*)-tritylglycidol **2** and diethyl fluoromalonate **3** as the reaction partners. (*S*)-Tritylglycidol is readily available in bulk with high enantiopurity (~98% ee). Step 1 involves condensation of the epoxide with the fluoromalonate anion to form the fluorinated lactone **4**. Step 2 requires decarboxylation to form **5**, and step 3, epimerization of the latter, if necessary, to produce the *cis*-fluorolactone **6**. A literature survey revealed that whereas there are many examples of the reaction of malonate ions with epoxides, the corresponding process with fluoromalonate was unknown, though this anion has been alkylated with other electrophiles. In the event, treatment of (*S*)-tritylglycidol with diethyl fluoromalonate in the presence of sodium hydride in THF furnished a mixture of products, which contained the *cis*- and *trans*-fluorolactones **5** to the extent of 20%.

Evidently, decarboxylation, or its equivalent, had occurred in the course of the reaction.

Although we had succeeded in preparing the *cis*-fluorolactone in a one-pot process, there were significant shortcomings in the chemistry, principally the reaction yield, which could not be improved beyond 40% and an inability to raise the *cis*-content of the isomer mixture above 75% via low temperature deprotonation–reprotonation treatment.

Repeated recrystallizations of the mixture did not further enhance the *cis* content. The *cis* and *trans* isomers could readily be separated by chromatography, though this was not considered an acceptable solution to the problem.

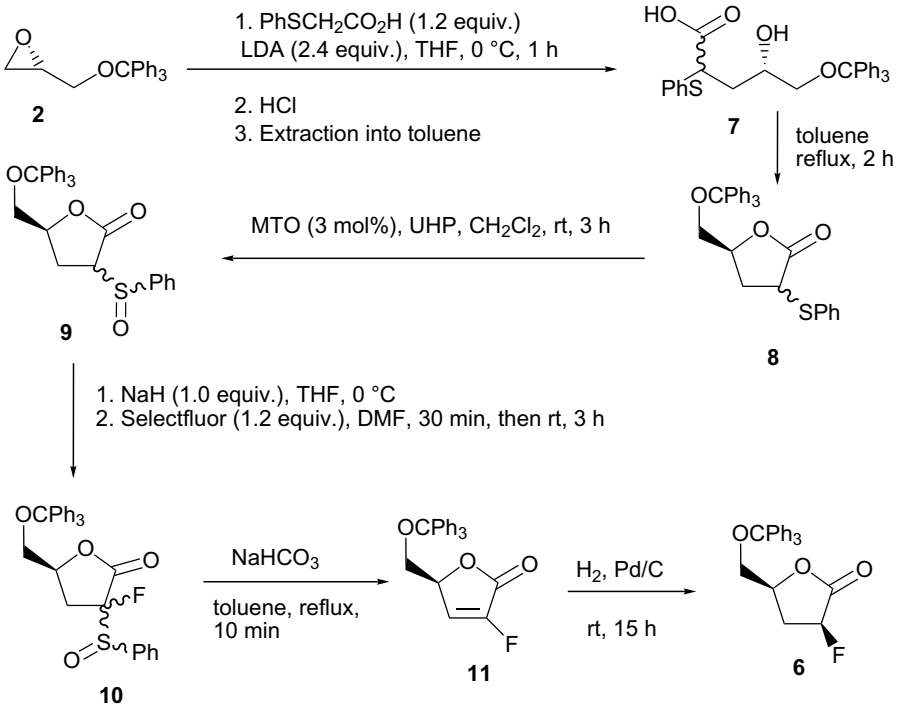
In an attempt to address these limitations we devised a modified route based on (*S*)-trityl glycidol, which is summarized in Scheme 2. The new route commenced with addition of the dianion of phenylthioacetic acid, efficiently generated in THF with 2.4 equiv of LDA, to (*S*)-tritylglycidol.

After acidification, but without purification, the resulting adduct **7** was taken up in toluene and heated under reflux for 2 h to form the phenylsulfenyl lactone **8** in 70% yield over the two steps. Oxidation of **8** to the corresponding sulfoxides **9** (a mixture of diastereoisomers) proceeded smoothly in quantitative yield through the action of urea–hydrogen peroxide (UHP) in the presence of methyltrioxorhenium (MTO) (3 mol%) in dichloromethane at room temperature.

Introduction of the 2-fluoro substituent was achieved in 70% yield by treatment of the sulfoxides **9** with Selectfluor in the presence of sodium hydride in THF at 0 °C to form fluorosulfoxide **10** (also a mixture of diastereoisomers). Thermolysis of **10** for 10 min in hot toluene containing sodium bicarbonate caused a smooth elimination reaction, furnishing the unsaturated fluorolactone **11** in quantitative yield. To complete the synthesis, hydrogenation of **11** over palladium on carbon afforded the target molecule **6** in quantitative yield with a diastereoselectivity of >98%.[7]

In summary, an efficient synthesis of a key intermediate for β-FddA has been developed with an overall yield of ca. 50% via readily accessible starting materials and easily purified intermediates. The main advantage over the approach of Confalone and co-workers[3] is the use of Selectfluor at room temperature to introduce the fluoro substituent in place of the less convenient DAST at low temperature. Our approach also avoids the Horner–Emmons chemistry, which forms the basis of the Patrick and Wei[7] approach. Another significant feature of our synthesis, which enhances its scalability is the minimal use of chromatography with only one intermediate, **11**, requiring purification in this way to remove a trace amount of precursor **9**.

Fluorination of phenylsulfinyl lactone **9** *with Selectfluor.* To a three-necked round-bottomed flask fitted with a



Scheme 2.

septum and a nitrogen inlet was added sodium hydride (60% in mineral oil, 0.5 g, 12.4 mmol) followed by dry THF (20 mL).The suspension was cooled to 0 °C. A solution of lactone **9** (4.0 g, 8.2 mmol) in dry THF (40 mL) was then added via a syringe over 10 min. The resulting mixture was stirred at 0 °C for 1 h then at room temperature for 1/2 h. The color had meanwhile turned from light yellow to orange to yellow. It was then transferred in portions via a cannula over 10 min to a cooled (ice bath) solution of Selectfluor (2.84 g, 8.7 mmol) in dry DMF. When the addition was completed, the solution was stirred at room temperature for 3 h. It was then poured into a 500 mL separating funnel containing aqueous saturated ammonium chloride (200 mL) and extracted with ether (2×150 mL). The combined ethereal extracts were washed with water (6×150 mL), dried over magnesium sulfate, filtered, and concentrated at reduced pressure to yield the fluorinated lactone **10**, a white foam (3.8 g), which was used without purification. The 300 MHz NMR spectrum measured immediately after completion of the reaction workup revealed the presence of a small amount of starting material, which was not removed prior to the next step. The NMR spectrum measured 24 h later revealed the presence of a new component, indicating that elimination to form unsaturated lactone **10** was already taking place to a small extent.

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