AN EFFICIENT SYNTHESIS OF 3'-FLUORO-3'-DEOXYTHYMIDINE (FLT)

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Summary: A synthetic route which permits the regioselective introduction of fluoride into an FLT precursor under mild conditions and the subsequent conversion of that intermediate into FLT is reported.

The AIDS epidemic has spurred a worldwide search for effective antiviral agents. Although many different therapies have been explored (e.g., soluble CD4, HIV protease inhibitors, glycosidase inhibitors, nucleoside and non-nucleoside reverse transcriptase (RT) inhibitors, immunostimulators, etc.), at present only the nucleoside RT inhibitors (e.g., AZT, DDI, DDC, etc.) have been shown to exhibit any real clinical efficacy.1 As a consequence, the development of general synthetic protocols which permit efficient syntheses of both known and potential antiviral nucleosides has taken on increased importance.

One of the more potent antiviral nucleosides which is currently undergoing clinical evaluation is 3'-fluoro-3'-deoxythymidine (FLT, 12).1 Although several syntheses of this compound have been reported, all of them have proven to be unsuitable for scale-up. In large part this is because each of them makes use of fluorinating reagents, such as anhydrous HF and DAST, which are difficult to handle on a large scale.2 Herein, we report a synthetic route which permits: (a) the regioselective introduction of fluoride into an FLT precursor (see Scheme 1) using a very mild reagent, tetrabutylammonium dihydrogentrifluoride (Bu$_4$NH$_2$F$^+$) and (b) the subsequent conversion of that intermediate to FLT.

Scheme 1

The synthesis of the 2,3-epoxy alcohol 1 is similar to the one reported in our synthesis of AZT.4 Although commercially available, we have found it to be more cost-effective to synthesize our starting
material, ethyl 3,3-diethoxypropionate, using literature procedures. Conversion of this material to 1 was accomplished using the sequence shown in Scheme 2. This involves: (a) acetal exchange; (b) reduction of the ester functionality to its corresponding aldehyde; (c) two carbon Horner-Emmons homologation; (d) reduction of the resulting α,β-unsaturated ester to produce prochiral allylic alcohol 4; and (e) Sharpless asymmetric epoxidation.

Scheme 2

Not surprisingly, the regioselective ring opening of the 2(S),3(R)-epoxy alcohol 1 proved to be a difficult transformation to achieve. In attempting to convert 1 to 2 using literature methods (e. g., SiF₄, anhydrous n-Bu₄NF, KHF₂-AlF₃, HF-pyridine, etc.), we observed either significant decomposition of the starting epoxy alcohol or no reaction. Since all of these reagents required vigorous conditions to effect the epoxide opening, it was apparent that a number of unwanted processes were competing favorably for reaction with the substrate. The most important of these proved to be cleavage of the bis-benzyloxy acetal functionality. However, by employing phase transfer conditions similar to those developed by Landini et al. (solid-liquid phase transfer catalysis with KHF₂ and Bu₄NH₂F₃), the 2(S),3(R)-epoxy alcohol 1 could be converted to the corresponding fluorohydrin in 57% yield. By switching to homogeneous catalysis (i. e., eliminating the KHF₂ additive) and increasing the mole % of Bu₄NH₂F₃, we further improved the outcome, observing both a reduction in reaction times and an increase in the yield of fluorohydrin (72% yield).

Both ¹³C NMR and capillary GC analysis indicated that the regioselectivity of this hydrofluorination reaction was 5 : 1 in favor of the desired fluorohydrin 2. Since the fluorohydrin regioisomers are difficult to separate on a large scale, this level of regioselectivity, while encouraging, still remained unacceptable. Fortunately, we found that by simply employing the same reaction conditions with acetate 5, the regioselectivity for the desired isomer increased to 25 : 1.

Even though the regioselectivity for hydrofluorination of epoxy acetate 5 was acceptable, the reaction conditions employed resulted in the hydrolysis of approximately 10% of 5 which under the reaction conditions afforded fluorodiol 2 (4 : 1 regioisomeric ratio) as a by-product. In an attempt to circumvent this problem, several other oxygen protecting groups were examined. Under the same reaction conditions, use of benzyloxy epoxide 7 led to a 1 : 1 mixture of fluorohydrin regioisomers 8 in a 65.5% yield. However, the corresponding benzoate derivative 9 afforded fluorohydrin 10 in 71%
yield with a regioisomer ratio of 15 : 1 (Table 1) and with very little of the unwanted hydrolysis product. Given these few results, the observed regioselectivity in these BU₄NH₂F₃-induced hydrofluorinations appears to be linked more to the relative basicity of the non-epoxide oxygen rather than its local steric environment.

### TABLE 1

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>R=H (1,2)</td>
<td>140°C, 12-24h</td>
<td>72%</td>
<td>5:1</td>
</tr>
<tr>
<td>R=Ac (5,6)</td>
<td>150°C, 3-4h</td>
<td>62%</td>
<td>25:1</td>
</tr>
<tr>
<td>R=BnO (7,8)</td>
<td>150°C, 3.5h</td>
<td>65.5%</td>
<td>1:1</td>
</tr>
<tr>
<td>R=BzO (9,10)</td>
<td>150°C, 3h</td>
<td>71%</td>
<td>15:1</td>
</tr>
</tbody>
</table>

When exposed to Vorbruggen conditions (2 equiv. bis-O-trimethylsilylthymine, 2 equiv. TMSOTf, CH₃CN, 2.75 h), fluorohydrin 6 was converted to FLT acetate, 11, (71% yield, 2.8 : 1, β : α). Deprotection of 11 with NaOMe / MeOH gave FLT, 12, in 85% yield (Scheme 3). Given the high β-selectivity which had been observed for a similar aminal exchange / cyclization procedure used to prepare AZT, we decided to examine the process more carefully. When the reaction was performed under identical conditions but stopped after fifteen minutes, no starting material remained. Instead, the reaction mixture consisted almost exclusively of 13, contaminated with traces amounts of 14. Thus, unlike its azido counterpart, the cyclization of 6 to 13 appears to be much faster than the aminal exchange of 6 to 14. Since 2-deoxyribose derivatives like 13 rarely exhibit any selectivity during N-glycosylation, the low β-selectivity observed for the overall transformation of 6 to 11 comes as no surprise. While we can not rule out the possibility that 13 undergoes an initial ring opening to produce 14 and a subsequent cyclization to produce 11, based on a number of ancillary considerations we consider this to be unlikely.

Further research is being conducted to find conditions which facilitate the aminal exchange of 6 to 14 and thereby presumably result in a more-selective formation of β-FLT.
Scheme 3

\[ \text{Scheme 3} \]

\[ \begin{align*}
\text{O} & \quad \text{OH} \\
\text{O} & \quad \text{OBn} \\
\text{F} & \quad \text{TMSO} \\
\text{OTMS} & \quad \overset{\text{a}}{\text{71\%}} \\
\text{R} & \quad \text{Ac (11)} \\
\text{R} & \quad \text{H (12)} \\
\end{align*} \]

(a) 2 equiv. TMSOTf, CH\text{3CN}, 25°C, 2:8:1 β:α; (b) NaOMe, MeOH.

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References:


7. Reaction Conditions: 0.5 mole% Bu$_4$NH$_2$F$_3$, 3 mole% KH$_2$F, 120°C-140°C, 15h.

8. The typical experimental conditions involved mixing 1.1 to 1.5 equiv. of Bu$_4$NH$_2$F$_3$ with 2(S),3(R)-epoxy alcohol 1 in a round-bottomed flask equipped with magnetic stir bar and argon inlet. The flask containing the substrate and fluorinating salt was immersed in an oil bath (1400-1550°C) and the reaction monitored by TLC. Upon completion of reaction, the resulting black gum was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution. After drying the organic layer with MgSO$_4$ and removing the solvent, the resulting residue was purified by flash chromatography to yield the desired fluoroxydine.


10. The spectral and physical properties of the product were identical to an authentic sample provided by Dr. Raymond F. Schinazi (VA Medical Center / Emory University School of Medicine).

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