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RING CONTRACTION AND REARRANGEMENT OF 4-THIOFURANOSE DERIVATIVES OBSERVED DURING DAST FLUORINATION IN THE SYNTHESIS OF L-2'-"UP"-FLUORO-4'-THIOTHYMIDINE†

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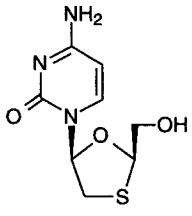
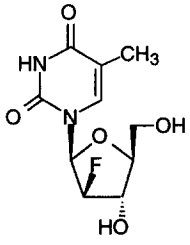
Abstract : Ring contraction and rearrangement of 4-thiofuranose derivatives were observed through the regioselective opening of the episulfonium ion formed during DAST fluorination in the synthesis of L-2'-"up"-fluoro-4'-thiothymidine.

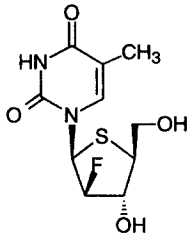
Hepatitis B is a viral disease which afflicts about 350 million people worldwide.[1] Although vaccines which target hepatitis B virus (HBV) are now being used as prophylactic agents, effective therapeutics are still not available for the treatment of HBV-infected individuals.



3TC



L-FMAU



L-SFMAU

Several families of compounds have recently been synthesized and evaluated for anti-HBV activity. Among these compounds, (-)-L-β-1,3-oxathiolanylcytosine (3TC, lamivudine)[2] is clinically used for HBV-infected patients in China and will soon be approved by the Food and Drug Administration (FDA) for use in the USA. Another L-nucleoside, 2'-fluoro-5-methyl-β-L-arabinofuranosyluracil (L-FMAU)[3] also showed potent anti-HBV activity with a favorable therapeutic index. L-FMAU is currently undergoing preclinical toxicological studies. In an effort to discover analogues to L-FMAU based on a "bioisosteric replacement" rationale, we sought to prepare the 4-thio congener (L-SFMAU) and to compare its anti-HBV activity with the parent L-nucleoside. En route to our target compound, we encountered an unusual ring contraction-rearrangement of some thiofuranose intermediates via a regioselective opening of a transient episulfonium ion produced during attempted fluorination with diethylaminosulfur trifluoride (DAST). Here, we report the total synthesis of L-SFMAU and expound upon the interesting chemistry we observed in the process.

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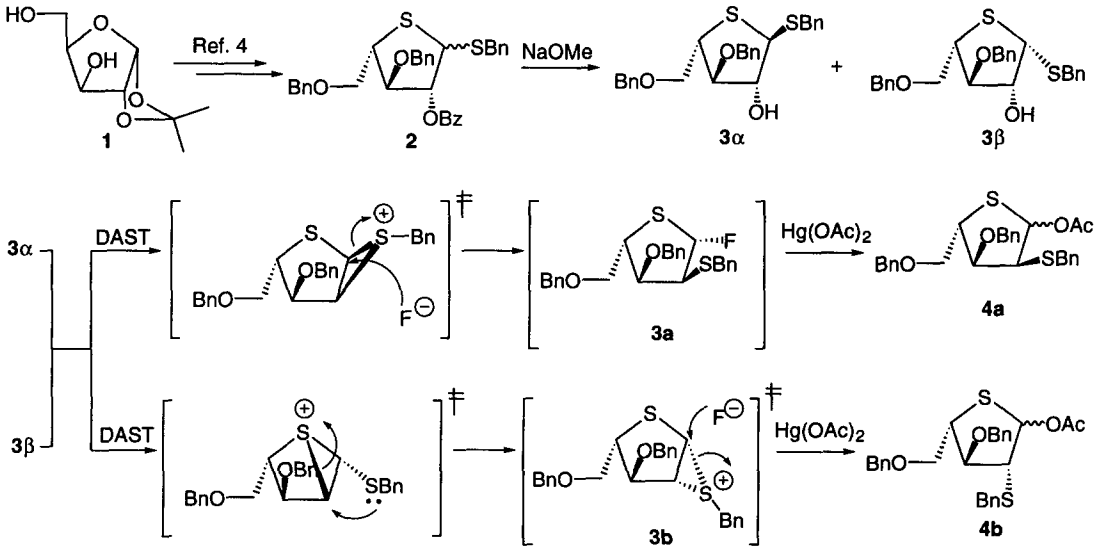
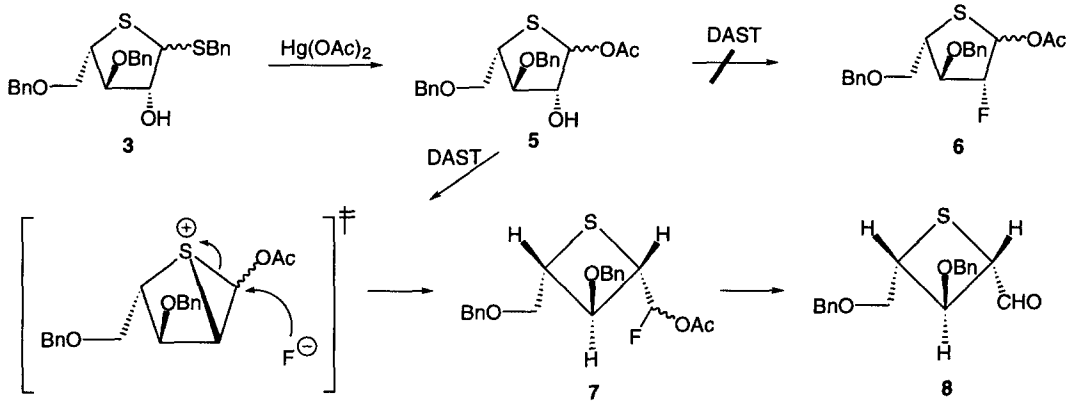
Our synthetic plan was to synthesize a 2-deoxy-2-fluoro-4-thiofuranose as a glycosyl donor and condense with thymine as an acceptor. As seen in Scheme 1, 1,2-isopropylidene-D-xylose (**1**) was easily converted to compound **2** according to the efficient method developed by our laboratory.[4] The benzoyl group of **2** was removed by treating with NaOMe to give an anomeric mixture (95%) of **3**α and **3**β in 10 to 1 ratio.

Scheme 1



Scheme 2

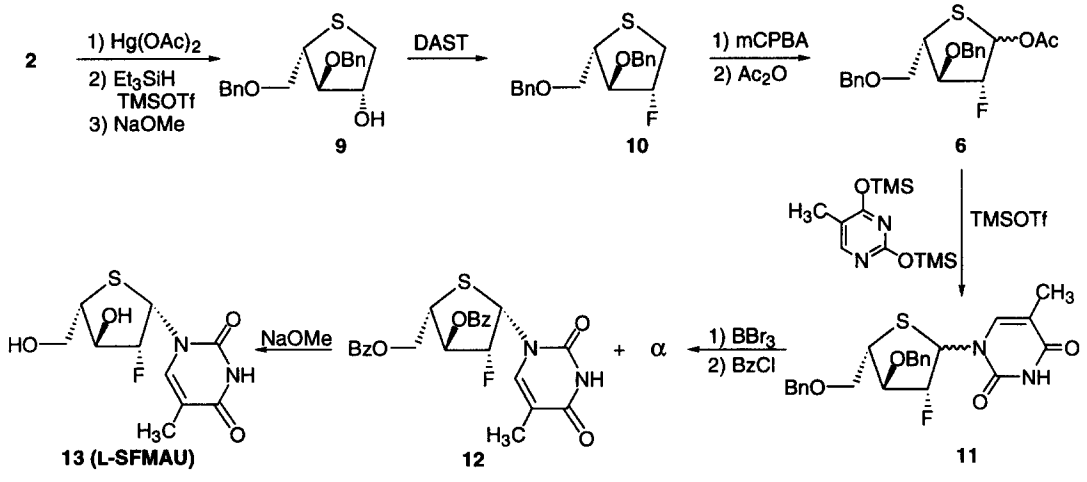


Treatment of **3** did not give the desired fluoro-substituted thiofuranose, but yielded a rearranged product. Scheme 1 outlines the proposed mechanism of this transformation. The anomeric thiobenzyl group of **3**α forms an episulfonium ion by displacement of the trans-disposed C2 derivatized hydroxyl faster than attack by the ring sulfur atom. Opening with fluoride ion at C1 leads to the unstable intermediate **3a** which was treated without purification with $Hg(OAc)_2$ to give a mixture (of which the β anomer predominates) of stable acetates **4a**

(38%).[5] In case of **3β**, initial assistance by the ring sulfur atom forms the bicyclic episulfonium ion which is reopened by the thiobenzyl group to give **3b** which, after similar treatment as for **3a**, gave **4b** as a mixture of anomers.

In an attempt to prevent participation from the anomeric center, the thiobenzyl group was converted to an acetate to give **5** (98%). However, the major product isolated after treatment of **5** with DAST was not the rearranged product as seen in Scheme 1, but the ring-contracted byproduct **7**[6] (63%) instead of the desired **6**. It was thought that the 4-sulfur atom forms an episulfonium ion followed by fluoride ion attack at the electron deficient C1 position, resulting in the ring-contracted product **7**. Treatment of **7** with NaOMe in MeOH afforded the aldehyde **8** in 58% yield.

Scheme 3



To prevent the participation of the thiobenzyl group or the ring contraction induced by the acetoxy group, the substituent at the anomeric position was removed as shown in Scheme 3. Treatment of compound **2** with $Hg(OAc)_2$ produced the anomeric acetate, which was reduced with triethylsilane and trimethylsilyl trifluoromethanesulfonate (TMSOTf)[7] followed by deprotection of the benzoate with sodium methoxide to afford **9** (73%). Reaction of **9** with DAST gave the 2-fluoro-4-thiosugar **10** (73%) with retention of configuration.[8,9] Rearranged or ring-contracted products were not detected in this reaction. Compound **10** was reacted with mCPBA to give the sulfoxide which was converted easily to the acetate **6** (72%) by refluxing with acetic anhydride. Condensation of the acetate **6** with silylated thymine in the presence of TMSOTf as the Lewis acid afforded the inseparable anomeric mixture **11**. Removal of the benzyl group with boron tribromide at -78 °C produced a mixture of diols which remained inseparable by chromatography on silica gel. Fortunately, benzoylation of the mixture gave **12** and its α anomer which were readily separated on silica gel. The benzoyl groups of **12** were removed to afford the final target L-SFMAU (**13**) in 99% yield.

L-SFMAU was assayed against HIV-1 and HSV types 1 and 2. Preliminary results indicated that **13** did not exhibit anti-HIV-1 activity in MT-4 cells but showed moderate activity against both HSV-1 and HSV-2. Anti-HBV activity is being assayed in our laboratory and the results will be reported elsewhere.

In summary, we accomplished the synthesis of L-SFMAU (**13**) from the key intermediate **2** which could be efficiently synthesized from 1,2-isopropyilidene-D-xylose (**1**). During the synthesis, we uncovered some novel nucleophilic sulfur chemistry related to this modified thiofuranose template during DAST fluorination. It was learned that fluorination of this ring system in a manner described here required the removal of substituents at the anomeric position and reintroduction of a suitable glycosyl donor afer fluorine substitution.

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References and notes

1. Tiollais, P.; Pourcel, C.; Dejean, A. *Nature* **1985**, *317*, 489.
2. (a) Schinazi, R. F.; Chu, C. K.; Peck, A.; McMillan, A.; Mathis, R.; Cannon, D.; Jeong, L. S.; Beach, J. W.; Choi, W.-O.; Yeola, S. Liotta, D. C. *Antimicrob. Agents Chemother.* **1992**, *36*, 672. (b) Beach, J. W.; Jeong, L. S.; Alves, A. J.; Pohl, D.; Kim, H. O.; Chang, C.-N.; Doong, S.-L.; Schinazi, R. F.; Cheng, Y.-C.; Chu, C. K. *J. Org. Chem.* **1992**, *57*, 2217.
3. Ma, T.; Pai, S. B.; Zhu, Y. L.; Lin, J. S.; Shanmuganathan, K.; Du, J. F.; Wang, C. W.; Kim, H.; Newton, M. G.; Cheng, Y.-C.; Chu, C. K. *J. Med. Chem.* **1996**, *39*, 2835.
4. (a) 214th American Chemical Society National Meeting, Division of Medicinal Chemistry, Poster No. 166, September 7-11, 1997, Las Vegas, USA. (b) Jeong, L. S.; Moon, H. R.; Choi, Y. J.; Chun, M. W.; Kim, H. O. *J. Org. Chem. in press.*
5. β-isomer: ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3 H, CH_3CO), 3.42 (dd, 1 H, J = 4.4, 10.0 Hz, 2-H), 3.48-3.56 (m, 2 H, 5-H), 3.60-3.67 (m, 1 H, 4-H), 3.80 (d, 1 H, J = 13.2 Hz, SCH_aPh), 3.86 (d, 1 H, J = 13.2 Hz, SCH_bPh), 4.11 (dd, 1 H, J = 6.0, 10.0 Hz, 3-H), 4.56 (s, 2 H, OCH_2Ph), 4.70 (d, 1 H, J = 11.1 Hz, OCH_aPh), 4.79 (d, 1 H, J = 11.1 Hz, OCH_bPh), 5.84 (d, 1 H, J = 4.4 Hz, 1-H), 7.20-7.56 (m, 15 H, 3 x Ph); α-isomer: ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3 H, CH_3CO), 3.41 (dd, 1 H, J = 3.8, 6.0 Hz, 2-H), 3.47 (dd, 1 H, J = 6.6, 9.6 Hz, 5-H_a), 3.68 (dd, 1 H, J = 5.9, 9.6 Hz, 5-H_b), 3.71-3.79 (m, 1 H, 4-H), 3.83 (s, 2 H, SCH_2Ph), 3.91 (t, 1 H, J = 6.0 Hz, 3-H), 4.45 (d, 1 H, J = 11.3 Hz, OCH_aPh), 4.49 (s, 2 H, OCH_2Ph), 4.56 (d, 1 H, J = 11.3 Hz, OCH_bPh), 5.95 (d, 1 H, J = 3.8 Hz, 1-H), 7.22-7.33 (m, 15 H, 3 x Ph).
6. One isomer: ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3 H, CH_3CO), 3.49 (dd, 1 H, J = 6.1, 10.2 Hz, 5-H_a), 3.59 (dd, 1 H, J = 5.9, 6.1 Hz, 5-H_b), 3.81-3.90 (m, 2 H, 2-H, 4-H), 4.22 (t, 1 H, J = 6.3 Hz, 3-H), 4.48 (d, 1 H, J = 11.9 Hz, OCH_aPh), 4.52 (s, 2 H, OCH_2Ph), 4.58 (d, 1 H, J = 11.9 Hz, OCH_bPh), 6.32 (dd, 1 H, J = 6.6, 56.6 Hz, 1-H), 7.29-7.35 (m, 10 H, 2 x Ph).
7. Nair, V.; Jeffery, A. *Tetrahedron Lett.* **1995**, *36*, 3627.
8. Jeong, L. S.; Nicklaus, M. C.; George, C.; Marquez, V. E. *Tetrahedron Lett.* **1994**, *35*, 7569.
9. Yoshimura, Y.; Kitano, K.; Yamada, K.;Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 3140.