Reversal of the Apparent Regiospecificity of NAD(P)H-Dependent Hydride Transfer: The Properties of the Difluoromethylene Group, A Carbonyl Mimic

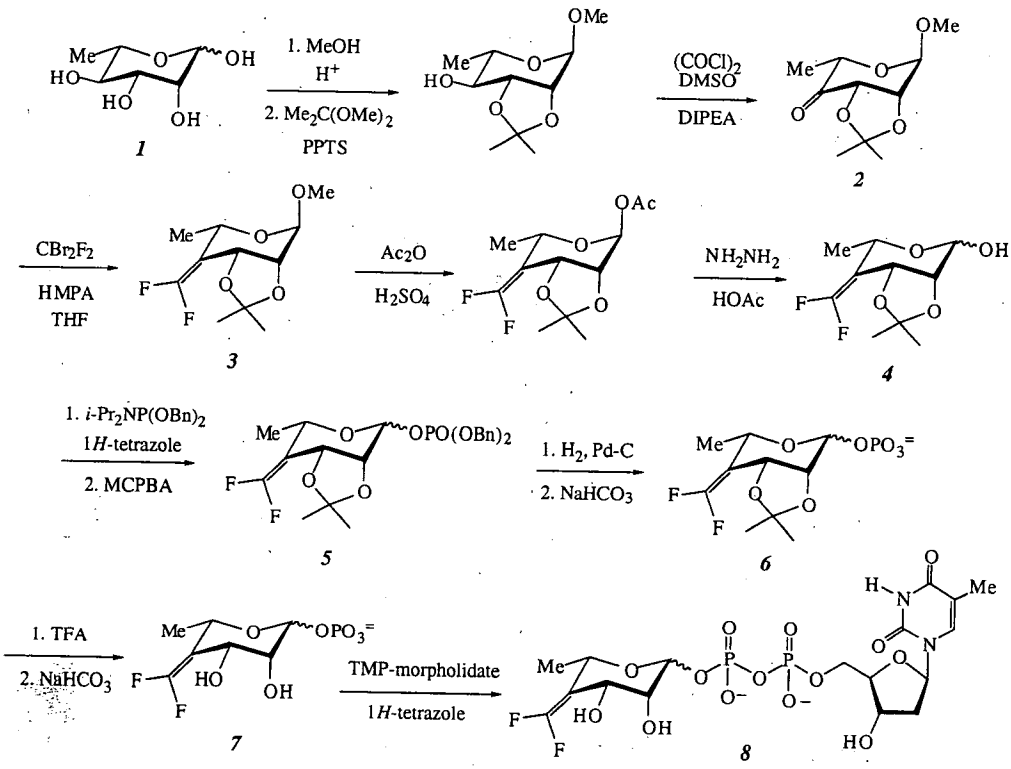
Caroline Leriche, Xuemei He, Cheng-wei T. Chang and Hung-wen Liu*

Division of Medicinal Chemistry, College of Pharmacy, and Department of Chemistry and Biochemistry, University of Texas, Austin, Texas 78712

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Supporting Information

Scheme A



The C_2-and C_3-OH groups of methyl L-rhamnose, derived from L-rhamnose (**1**), were first selectively protected,[1] and the C_4-OH was oxidized. The exocyclic difluoromethylene moiety was introduced by reacting the resultant 4-hexulose (**2**) with dibromodifluoromethane and hexamethylphosphoramide.[2] Selective deprotection of the anomeric-OH was achieved by the

treatment of **3** with acetic anhydride/sulfuric acid,[3] followed by hydrazine acetate.[4] A two-step sequence with *N,N*-diisopropyldibenzyl phosphoramidite and *m*-CPBA[5] was used to convert **4** to its C-1 phosphate (**5**). Subsequent hydrogenation (10% Pd/C) followed by treatment with a stoichiometric amount of bicarbonate afforded **6** in quantitative yield.[6] The isopropylidene moiety in **6** was removed by 25% aqueous trifluoroacetic acid,[7] and the product **7** was converted to its triethylammonium salt by passage through a cation-exchange column (BioRad AG 50W-X2, Et_3NH^+ form). It should be noted that condensation of **7** with the 4-morpholine *N,N'*-dicyclohexylcarboxamidine salt of thymidine 5'-monophosphate in the presence of 1*H*-tetrazole[8] afforded the desired product **8** as a mixture of α and β anomers (**8**α:**8**β = 3:1). Due to the instability of **8** upon further purification and lyophilization, this mixture was used directly in the subsequent experiments.

1. Tadano, K. I.; Maeda, H.; Hoshino, M.; Limura, Y.; Suami, T. *J. Org. Chem.* **1987**, *52*, 1946.
2. Houlton, J. S.; Motherwell, W. B.; Ross, B. C.; Tozer, M. J.; Williams, D. J.; Slawin, A. M. Z. *Tetrahedron* **1993**, *49*, 8087.
3. Watanabe, S.; Kavai, I.; Bobek, M. *J. Carbohydr. Chem.* **1995**, *14*, 685.
4. Excoffier, G.; Gagnaire, D.; Utille, J.-P. *Carbohydr. Res.* **1975**, *39*, 368.
5. Yu, K. L.; Fraser-Reid, B. *Tetrahedron Lett.* **1988**, *29*, 979.
6. Leriche, C.; René, L.; Derouet, F.; Rousseau, B.; Badet, B. *J. Labelled Compd. Radiopharm.* **1995**, *36*, 1115.
7. Lewbart, M. L.; Schneider, J.-J. *J. Org. Chem.* **1969**, *34*, 3505.
8. Murray, B. W.; Wittmann, V.; Burkart, M. D.; Hung, S.-C.; Wong, C.-H. *Biochemistry* **1997**, *36*, 823.