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METHYL 3,4-di-O-ACETYL-2-DEOXY-2(R)-[1H,3H-2,4-DIOXO-1-PYRIMIDINYL]-2-FLUORO-β-D-ARABINOPYRANOSIDE: NOVEL NUCLEOSIDE ANALOGUES VIA CONDENSATION OF GEM-2,2-DIFLUORO METHYL GLYCOSIDES WITH SILYLATED HETEROCYCLIC BASES.

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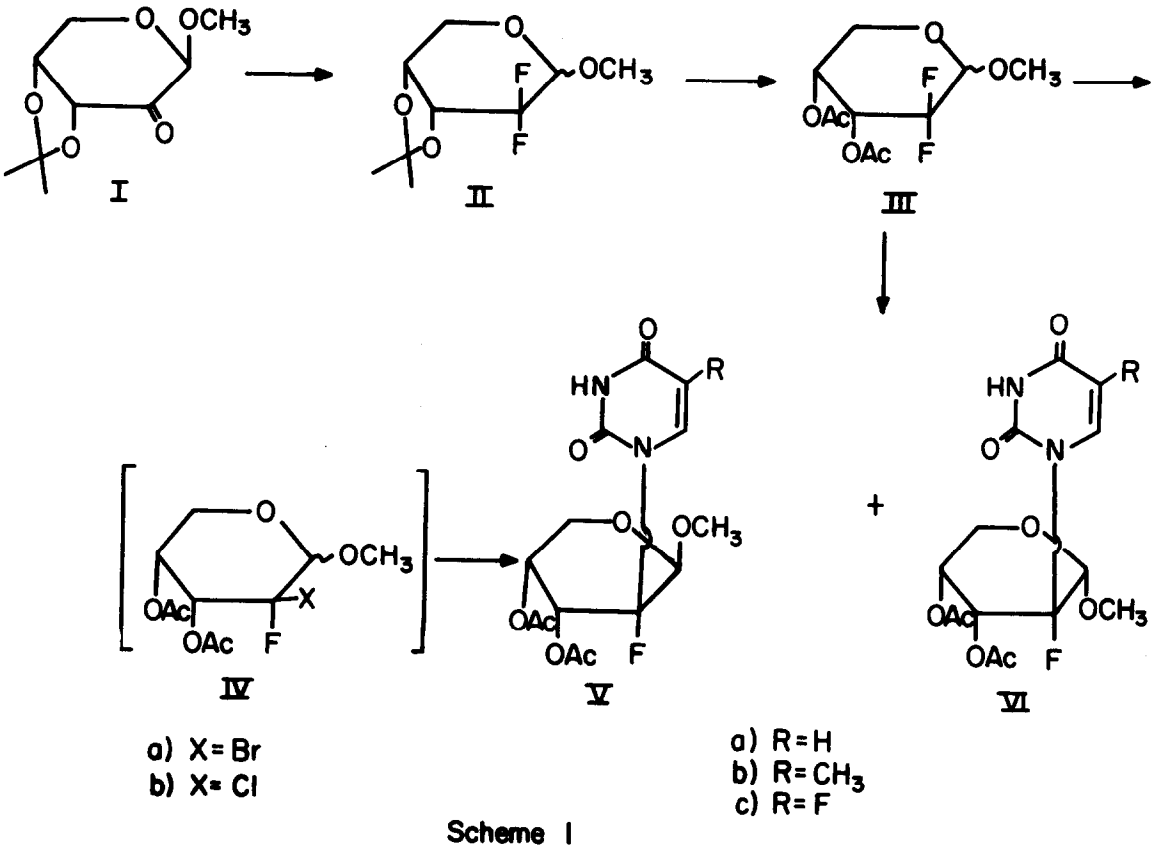
Abstract: Methyl 3,4-di-O-acetyl-2-deoxy-2,2-difluoro-D-erythro-pentopyranoside(III) reacts, in the presence of boron trifluoride etherate, with the trimethylsilyl derivative of uracil to form a novel nucleoside analogue bearing the heterocyclic moiety and fluorine at the 2-position.

Gem-difluoro nucleosides as analogues of deoxynucleosides are of interest as potential antimetabolites. Having previously developed a method for the preparation of the gem-difluorosugars[1], we attempted to utilize these derivatives in condensation reactions with pyrimidines and purines. In this report we describe a facile nucleophilic displacement of the fluorine in a gem-2,2-difluoro glycoside which can be applied to syntheses of novel functionalized glycosides including nucleoside analogs of potential biological interest.[2,3]

Methyl 3,4-O-isopropylidene-β-D-erythro-pentopyranosid-2-ulose(I) was readily obtained in high yield by chromium trioxide-pyridine-acetic anhydride[4] oxidation of methyl 3,4-O-isopropylidene-β-D-arabinopyranoside[5,6] in methylene chloride, Yield 84%, m.p. 87-88° (Ethyl acetate), $[\alpha]_D^{20}$ -155.80° (c 0.7, $CHCl_3$), IR(KBr), 1740cm^{-1} (C=O). Compound I was previously prepared by oxidation of methyl 3,4-O-isopropylidene-β-D-erythro-pentopyranoside by different reagents[6-8]. Treatment of I with diethylaminosulfur trifluoride[9] (DAST) in benzene at room temperature afforded 78% of an anomeric mixture of methyl 2-deoxy-2,2-difluoro-3,4-O-isopropylidene-D-erythro-pentopyranosides (II)[10] (Scheme I); Oil, b.p. 104-105.5°C at 0.2 mm Hg, m/z 209 (M^+-CH_3).



Scheme I

The presence of the α and β anomers in an approximately 2:1 ratio could be detected by PMR, however, they could not be separated by chromatography. Hydrolysis of the isopropylidene group in II was effected with 95% formic acid to give somewhat labile free methyl glycosides which were acetylated with acetic anhydride-pyridine to afford methyl 3,4-di-O-acetyl-2-deoxy-2,2-difluoro-D-erythro-pentopyranosides (III). Compound III, upon treatment with hydrogen bromide in methylene chloride, gave 2-bromo-2-fluoro sugars IVa, presumably by the attack of HBr at the gem-difluoro group. The bromides IVa, which were not sufficiently stable for purification, were treated with the trimethylsilylated uracil in methylene chloride and in the presence of HgO-$HgBr_2$ catalyst to afford an anomeric mixture (approximately a 1:2 ratio) of nucleosides Va and VIa in 23% yield. This mixture was separated on silica gel ($CHCl_3$/2-pro-

panol, 20:1), the β-anomer Va, methyl 3,4-di-O-acetyl-2-deoxy-2(R)-[1H,3H-2,4-dioxo-1-pyrimidinyl]-2-fluoro-β-D-arabinopyranoside being eluted first. $[\alpha]_D^{20}$ -93.3° (c 0.045, $CHCl_3$), mp 137°C. The α-anomer VIa: $[\alpha]_D^{20}$ +88.6° (c 0.13, $CHCl_3$). The "arabino" configuration of the uracil moiety in both Va and VIa was assigned on the basis of the large coupling constants[11,12] between H-3 and fluorine (17.19 Hz and 19.25, respectively). The anomeric configuration in Va and VIa was inferred from the observed coupling constants for the anomeric protons. ($J_{F-H\ trans}$ 9.8 Hz, $J_{F-H\ cis}$ 2.98 Hz). The chemical shifts for H-4 of V and VI at 5.49 are consistent with those found in other 4'-O-acetyl nucleosides[13], indicating that the reaction of HBr with III was not accompanied by the migration of the 4-O-acetyl group to C_5OH and ring contraction[14,15]. The ability of the fluorine of the gem difluoro group in III to participate in the substitution reaction was further exemplified by the reaction of III with hydrogen chloride which gave IVb. Condensation of IVb with silyated uracil also afforded a mixture of Va and VIa.

In the presence of a Lewis acid catalyst such as boron trifluoride etherate, the fluorine in III is readily displaced by the nitrogen of the silylated uracil giving a mixture of Va and VIa.[16] The gem-difluoro derivative II also gave a mixture of nucleosides in the reaction with silylated uracil and in the presence of BF_3Et_2O. However, in the absence of the stereo-directing effects of the 3-O-acetyl group, two additional isomeric nucleosides could be formed in this reaction and, therefore, the configuration of the products has not been investigated. Condensation of IVa with the silylated derivatives of thymine and/or 5-fluorouracil gave the corresponding nucleosides Vb,c and VI b,c. The anomeric configuration of Vb,c and VIb,c was established on the basis of the coupling constants between the anomeric proton and fluorine which were 8.53 Hz and 10.72 Hz for the α anomers and 2.43 and 4.80 Hz for the β-anomers, respectively.

In ^{19}F NMR spectra, the chemical shift of fluorine of the α-anomers VIb and VIc appeared at -125.0 ppm (dd, $J_{F,H-3}$ = 16.1 Hz, $J_{F,H-1}$ = 7.0 Hz) and -125.8 ppm (dd, $J_{F,H-3}$ = 18.0 Hz, $J_{F,H-1}$ = 9.3 Hz) from $CFCl_3$, respectively. The fluorine signals of the β anomers Vb and Vc appeared at -122.2 ppm (dd, $J_{F,H-3}$ = 18.1 Hz, $J_{F,H-1}$ = 3.3 Hz) and -122.8 ppm (dd, $J_{F,H-3}$ = 18.1 Hz, $J_{F,H-1}$ = 3.3 Hz), respectively.

The mass spectrum of the uracil derivatives Va and VIa showed characteristic peaks at 360 (M^+) and 112 (uracil). The thymine deriatives Vb and VIb gave peaks at 374 (M^+) and 126 (thymine) while Vc and VIc gave peaks at 378 (M^+) and 130 (5-fluorouracil). While hydrolysis of the acetyl groups in V and VI in the presence of acidic or basic catalysts was accompanied by decomposition, initial experiments utilizing esterases[17,18] indicated that the protective groups were removed. Work on optimizing the conditions, and exploration of nucleosides with protecting groups that are more susceptible[17,18] than the acetyl groups to enzymatic hydrolysis, are in progress.

In preliminary testing the nucleosides Va an VIa showed significant antitumor activity in vivo. At 500 mg/kg/day x 5, Va and VIa increased the life span of mice bearing leukemia L1210 by 55%. These preliminary results indicate that condensation of protected methyl 2,2-difluoro-2-deoxy ribopyranoside with silylated pyrimidines constitutes a useful method for synthesis of novel anticancer nucleosides.

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References

1. R.A. Sharma, I. Kavai, Y.L. Fu and M. Bobek, Tetrahedron Lett., 3433 (1977).
2. J.A. Montgomery, S.D. Clayton and H.J. Thomas, J. Org. Chem., 40, 1923 (1975).
3. J.A. Montgomery and H.J. Thomas, J. Org. Chem., 43, 541 (1978).
4. P.J. Garegg and B. Samuelson, Carbohyd. Res., 67, 267 (1978).
5. J.W. Pratt, N.K. Richtmyer, and C.S. Hudson, J. Amer. Chem. Soc., 74, 2200 (1952).
6. A. Rosenthal and M. Sprinzl, Can. J. Chem., 48, 3253 (1970).
7. K. Onodera, S. Hirano, and N. Kashimura, J. Amer. Chem. Soc., 87, 4651 (1965).
8. W. Sowa and G.H.S. Thomas, Can. J. Chem., 44, 836 (1966).
9. W.J. Middleton, J. Org. Chem., 40, 574 (1975).
10. A similar mixture of gem-difluoro anomers was obtained from the L-enantiomer of I, incorrectly indicated in ref. 1 as the β-anomer only.
11. L.D. Hall and J.F. Manville, Can. J. Chem., 47, 1 (1969).
12. L.D. Hall and J.F. Manville, Can. J. Chem., 47, 361 (1969).
13. B.L. Kam, J.L. Barascut, and J.L. Imbach, Carbohyd. Res., 69, 135 (1979).
14. K. Bock and C. Pedersen, Acta. Chem. Scand., B28, 1041 (1974).
15. K. Bock and C. Pedersen, Carbohyd. Res., 29, 331 (1973).
16. All new compounds were characterized by ^{1}H and ^{19}F NMR, UV, and high resolution mass spectrometry. Satisfactory microanalytical data were obtained for compounds II, V and VI.
17. T. Kawaguchi, Y. Suzuki, Y. Nakahara, N. Nambu, and T. Nagai, Chem. Pharm. Bull., 33, 301 (1985).
18. T. Kawaguchi, M. Saito, Y. Suzuki, N. Nanebu, and T. Nagai, Chem. Pharm. Bull., 33, 1652 (1985).

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