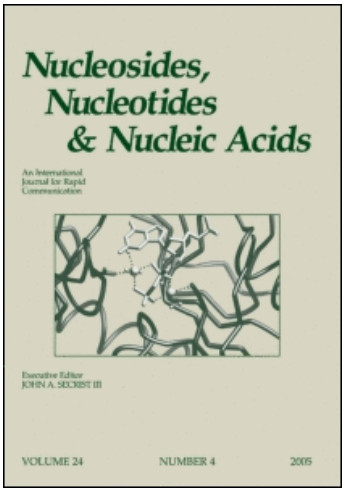

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Some Aspects of Ribonucleoside Chemistry

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SOME ASPECTS OF RIBONUCLEOSIDE CHEMISTRY

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Summary: New routes to the preparations of 2'-deoxy-3'-C-methyl uridine (2c) and 1-(5'-O-trityl-3'-deoxy-ß-D-glycero-pentofuran-2-ulosyl)uracil (4) from 5'-O-trityl-2'-O-tosyl uridine (1) and 5'-O-trityl-3'-O-tosyl uridine (3) respectively are described.

Branched-chain sugar nucleosides constitute an important class of compounds in view of their biological properties[1-3] . All of them have been synthesized, up till now, by the condensation of aglycones with branched-sugars which have been prepared by Grignard reactions with the corresponding pentofuranosuloses[4-7] or by multi-step chemical transformations[3,8].

We herein report[12] a new stereospecific synthesis of 2'-deoxy-3'-erythro-C-methyl-5'-O--trityl uridine (2a), in 37% yield in a one-step preparation involving a Grignard reaction of 2'-O-tosyl-5'-O-trityl uridine (1) , in THF, and a diethylether solution of methylmagnesium iodide (15 equiv.) at 0°C under nitrogen followed by stirring at 20° for 90 min. and then heating at 65°C for 30 min. A study of the reaction conditions has shown that the factors like the order of addition of the reagents, the temperature and the work-up of the reaction are important to avoid the cleavage of the glycosidic linkage.

The structure of the product 2a was determined by spectroscopic evidence. The assignment of erythro configuration to 2a was arrived by analogies of similar reactions in carbohydrate series[4-7,10] and also by a downfield shift (0.3 ppm) of 4'-H in the acetylated product 2b. Finally compound 2a was detritylated to obtain 3'-C-methyl-2'-deoxy uridine (2c) in 54% yield using a mixture of zinc bromide (1.6 equiv.) and anthranilic acid (4 equiv.) in dry nitromethane solution (24 ml/ mmol) for 3h at 20°C A similar treatment[13] of dry diethylether solution of methylmagnesium iodide (5 equiv.) and a dry dioxan solution of 3'-O-tosyl-5'-O-trityl uridine (3) at 0°C, followed by stirring at 20° for 1h and heating at 65° for 15h gave a quantitative (TLC) conversion to 1-(5'-O-trityl-3'-deoxy-ß-D-glycero-pentofuran-2-ulosyl)uracil (4) which was isolated in 79% yield. Such ketosugar nucleosides are considered potentially useful for the preparation of a variety of sugar-modified products for evaluation as specific inhibitors

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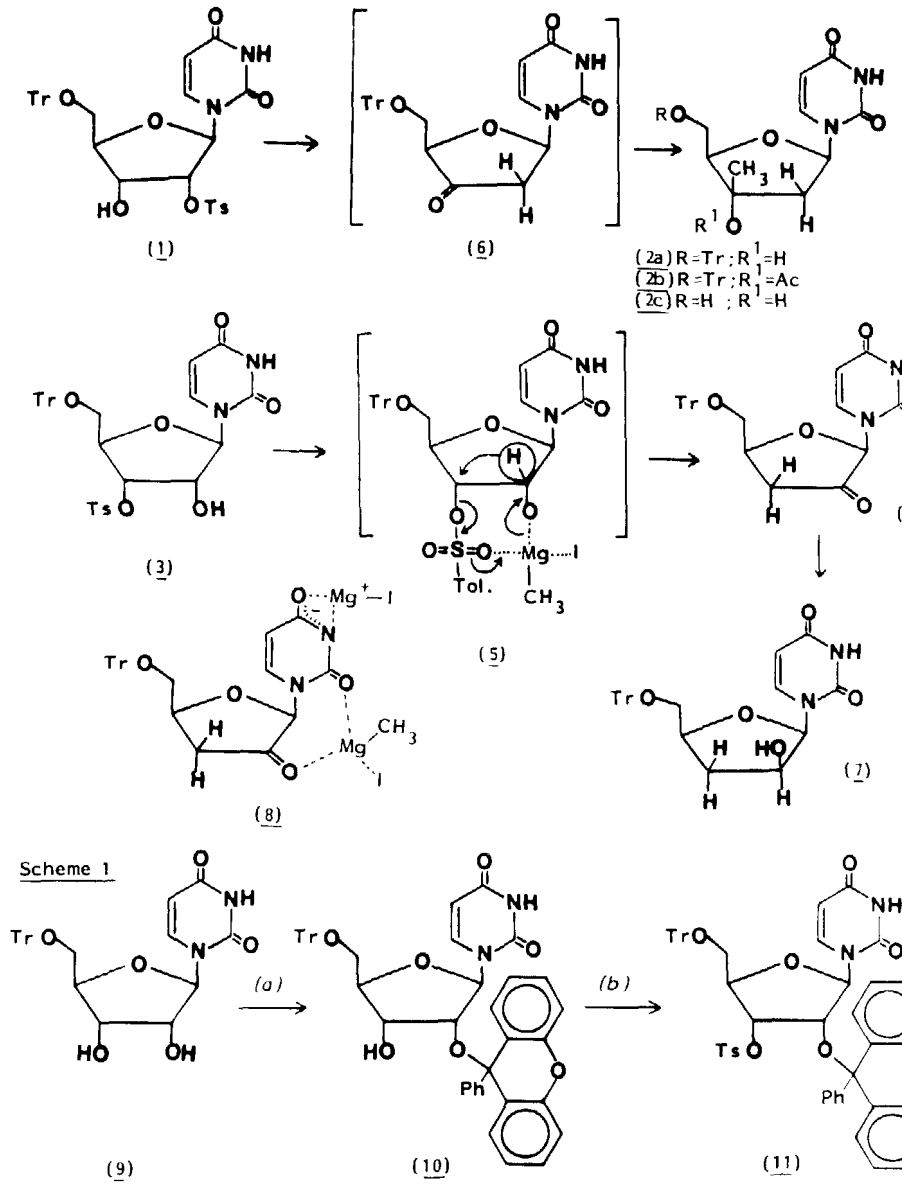

(a) 9-Chloro-9-phenylxanthene (1.1 equiv.) was added to a pyridine solution (5 ml/mmol)
(b) 4-toluenesulfonyl chloride(15 equiv.) and N,N-dimethylaminopyridine (5 equiv.) were added to a pyridine solution (10 ml/mmol)
(c) Zinc bromide (9 equiv.; 0.5 mmol/ 5 ml of acetonitrile) and anthranilic acid (18 equiv.) at RT;half-life of the removal of the pixyl group under this condition is ca. 15 min.

FIG. 1 2D ^{1}H,H-INADEQUATE with HOD suppression for the 3', 4', 5,1, 5'2 sugar proton region of d(ApCpGpT). Double quantum correlations indicated by the diagonals are found equidistant from the skew diagonal.

of viral enzymes. It should be added that the above facile preparation of 4, starting from a ribonucleoside 3, constitutes its first report in the literature.

The mechanism of the formation of (4) from (3) presumably involves an intermediate (5) which undergoes a stereospecific [1,2]- hydride shift with accompanying inversion of both C-2' and C-3' centers which seems to be very similar to what Robins et.al.[9] have proposed for their reaction with lithium triethylborohydride. It should be noted that , during the preparation of (2a) from (1) and methylmagnesium iodide, we have not detected any expected ketosugar (6) in the reaction mixture ; while in a very similar reaction with (3), the ketosugar (4) is the only product formed despite the presence of an excess of the Grignard reagent in the reaction mixture. This observation may be explained by an assumption that a nucleophilic attack from the β side on the sp^2 hybridized 2'-carbon is sterically much less favoured than a corresponding attack on the C-3' in (6). A plausible formation of an intermediate like 8 can be further attributed to a rigid conformation of the carbonyl group which can have a regioselective nucleophilic attack only from the hindered β side. However, it has been possible to carry out a stereoselective reduction at C-2' of (4) with sodium borohydride, using a literature condition[9], to obtain 1-(5'-O-trityl-3'-deoxy-β-D-threo-pentofuranosyl)uracil (7) in 86% isolated yield. None of the corresponding erythro epimer of (7) was detected (NMR) in the purified reaction product. This may be added that the formation of the alcohol 7 necessitates a hydride ion attack from the α side which again supports that the C-2' carbon in 4 is sterically more hindered for an external nucleophilic attack than the C-3' in 6. The substrate (3) has been synthesized through a new route, as shown in scheme 1 , starting from 5'-O-trityl uridine (9). The 2'-hydroxyl function of (9) was selectively blocked with 9-phenylxanthene-9H-9yl- (pixyl)[11] group to give (10) in 78% yield which was tosylated quantitatively at the 3'-position to obtain (11).Subsequently, the 2'-pixyl group from (11) was selectively removed with the help of zinc bromide and anthranilic acid in nitromethane solution at room temperature to give (3) in 70% isolated yield.

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