Short Communications

An Efficient Conversion of a Ribonucleoside to the Corresponding 2'-Keto-3'-deoxyribonucleoside by a Grignard Reagent

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There are only two reports of branched-deoxysugar nucleosides. One is by Acton and his co-workers 1 on the synthesis of 2',3'-dideoxy-3'-hydroxymethyl thioguanosine and the second is on the synthesis of 1-(3'-amino-2',3'-dideoxy-beta-D-glucopyranosyl)uracil by Ueda et al. 2. In view of the interesting biological properties of such branched-chain sugar nucleosides, 3,4 we have been interested in their synthesis through more convenient routes. We have thus reported 5 a new stereospecific synthesis of an unknown nucleoside: 2'-dideoxy-3'-erythro-C-methyl-5'-O-(triphenylmethyl)uridine 2 in 37% yield via a one-step preparation involving a Grignard reaction with 2'-O-(4-toluenesulfonyl)-5'-O-(triphenylmethyl)uridine 1 and methylmagnesium iodide.

We herein report that a similar treatment of methylmagnesium iodide and 3'-O-(4-toluenesulfonyl)-5'-O-(triphenylmethyl)uridine 3 gave 1-(5'-O-triphenylmethyl-3'-deoxy-beta-D-glycero-pentofuran-2-ulosyl)uracil 4 in 79% yield. Such ketosugar nucleosides are considered potentially useful 6 for the preparation of a variety of sugar-modified products for evaluation as specific inhibitors of viral enzymes.

The above facile preparation of (4), starting from a ribonucleoside 3, constitutes its first report. Earlier, 9-(5'-O-triphenylmethyl-3'-deoxy-beta-D-glycero-pentofuran-2-ulosyl)adenine was obtained in 67% yield starting from 5'-O-triphenylmethyl-3'-deoxyadenosine. 6 We have subsequently compared the product 4 with an authentic sample prepared by the oxidation of 5'-O-triphenylmethyl-3'-deoxy uridine. 8

The reaction mechanism for the formation of (4) from (3) may involve an intermediate 5 which undergoes a [1,2]-hydride shift with accompanying inversion of both C-2' and C-3' centers which is very similar to what Robins and his co-workers have proposed for their reaction with lithium triethylborohydride. 8 Alternatively, one may conceive of an E2 elimination of toluenesulfonic acid from iodomagnesium alcoholate 11 to produce iodomagnesium enolate 12. Such an intermediate like 12 would resist the action of excess methylmagnesium iodide but would generate the ketone 4 on work up. Further work is now in progress to delineate the actual mechanism for the formation of 4.

It should be noted that during the preparation 5 of (2) from (1) and methylmagnesium iodide we did not detect any expected ketosugar 6 in the reaction mixture; while in the very similar reaction with 3, the ketosugar 4 is the only product formed despite the fact that an excess of the Grignard reagent was used in the latter reaction condition. This observation may be explained by the assumption that a nucleophilic attack from the beta side on the sp² hybridized 2'-carbon is sterically much less favoured than a corresponding attack on the C-3' in 6.

However, it should be added that it has been possible to carry out a reduction at C-2' of (4) with sodium borohydride 6 to obtain 1-(5'-O-triphenylmethyl-3'-deoxy-beta-D-threo-
Scheme 1.
pentofuranosyl)uracil 7 in 86 % isolated yield. None of the corresponding 2'-erythro epimer of (7) was detected in the purified reaction product.

The substrate 3 has been synthesized through a new route, as shown in scheme 1, starting from 5'-O-triphosphoryl uridine 8. The 2'-hydroxyl function of (8) was selectively blocked with 9-phenylxanthen-9H-9-yl (pixyl) group1 to give 9 in 78 % yield which was tosylated quantitatively at the 3'-position to obtain 10. Subsequently, the 2'-pixyl group of (10) was removed with zinc bromide and anthranilic acid in nitromethane solution3 at room temperature to give 3 in 70 % yield.

Experimental.1 H NMR spectra were measured at 60 MHz with a Perkin-Elmer R 600 and at 90 MHz with a Jeol FX 90Q spectrometer using tetramethylsilane as an internal standard.13C NMR spectra were measured at 25.7 kHz using tetrakis(methyl) as the internal standard. IR spectra were measured using a Perkin-Elmer 298 spectrometer.

Reactions were monitored by using Merck pre-coated silica gel 60 F254 plates using 10 % methanol–chloroform (v/v). Merck Kieselgel G was used for short column chromatography.10 Dried solvents were prepared using our literature procedures.10

Preparation of 1-(5'-O-triphosphoryl-3'-O-deoxy-β-D-glycero-pentofuran-2-ulosyl)uracil (4). A typical procedure for the preparation of 4 is as follows: A diethyl ether solution (10 ml) of methylammagnesium iodide (5 eq.) was added to a dry dioxane solution (5 ml) of 3 (480 mg, 0.75 mmol) at 0 °C under argon, it was then stirred for 1 h at room temperature followed by heating at 65 °C for 15 h. After cooling, 10 % aqueous ammonium chloride (7 ml) was added. Standard work-up gave a glass which was chromatographed on a short column of silica gel using first dichloromethane and then with a 2 % ethanol - chloroform mixture to afford 4 as a glass (227 mg; 79 %).1H NMR (CDCl3 + TMS): δ 7.3 (m, 16 H); 5.59 (d, 7.8 Hz, 1 H), H-5; 5.34 (s, 1 H), H-1; 4.54 (m, 1 H), H-4; 3.39 (m, 2 H), H-5; 2.68 (m, 2 H), H-3; all assignments have been made by homodecoupling experiments.13C NMR (CDCl3 + TMS): δ 206.3 (C-2); 163.49 (C-4); 150.0 (C-2); 143.4 and 143.2 (C-5 & C-6); 128.66, 127.85 and 127.17 (trityl); 85.9 (C-1'); 75.3 (C-4'); 65.5 (C-5'); 36.6 (C-3'). IR (chlooroform): νmax 1775, 1710 and 1690 cm⁻¹; M+ at mlz 468 (12.7 %).

Preparation of 1-(5'-O-triphosphoryl-3'-O-deoxy-β-D-threopentofuranosyl)uracil (7). Sodium borohydride reduction of 4 gave 7 in 86 % yield as a glass.1H NMR (CDCl3 + TMS): δ 7.81 (d, 7.8 Hz, 1 H), H-6; 7.4 (m, 15 H); 6.02 (d, 3.4 Hz, 1 H), H-1'; 5.35 (d, 7.8 Hz, 1 H), H-5; 4.64 (m, 1 H), H-2'; 4.22 (m, 1 H), H-4'; 3.41 (m, 2 H), H-5'; 2.17 (m, 2 H), H-3'.13C NMR (CDCl3 + TMS): δ 165.22, 151.26, 143.73, 142.86, 128.97, 128.16, 127.42, 87.5, 87.22, 77.2, 70.66, 65.47 & 34.4 M+ at mlz 470 (23 %).

Preparation of 5'-O-triphosphoryl-2'-O-(9-phenylxanthen-9-yl)uridine (9). Crystalline 9-phenylxanthen-9-yl72 (2.2 g, 7.4 mmol) was added to a dry pyridine solution (40 ml) of 5'-O-triphosphoryluridine 8 (3 g, 6.2 mmol) at 20 °C and the reaction mixture was stirred for 121 h. It was then poured into a saturated solution of sodium bicarbonate and was extracted by chloroform (4×100 ml). The organic phases were combined and evaporated and chromatographed over a short column of silica gel using first dichloromethane for elution and then with chloroform giving 9 as a glass; yield: 3.4 g (74 %).

1H NMR (CDCl3 + TMS): δ 7.92-7.1 (m, 29 H), aromatic protons and H-6 of uracil residue; 6.33 (d, 5.5 Hz, 1 H), H-1'; 4.81 (d, 6.2 Hz, 1 H), H-5 of uracil residue; 4.03 (m, 2 H), H-2' & H-4'; 3.45 (m, 1 H), H-3'; 3.07 (m, 2 H), 5'-CH22.

Preparation of 5'-O-triphosphoryl-3'-O-(4-toluensulfonyl)-2'-O-(9-phenylxanthen-9yl)uridine (10). 4-Toluensulfonl fluoride (7.4 g, 39 mmol) and 4-N,N-dimethylaminopyridine (2.3 g, 19.5 mmol) were added to a dry pyridine solution (35 ml) of 9 (2.9 g, 3.9 mmol) at 20 °C and stirred for 36 h when the reaction was found to be complete. The reaction mixture was worked up using a procedure which is identical to the one used for the preparation of 9. Subsequently, the crude mixture was chromatographed on a short column of silica gel using dichloromethane as an eluent giving 10 as a glass; yield: 3.3 g (94 %).1H NMR (CDCl3 + TMS): δ 7.82 (d, 6.3 Hz, 1H), H-6 of uracil residue; 7.65-6.8 (m, 33H), aromatic protons; 6.22 (d, 5.2 Hz, 1 H), H-1'; 4.76 (m, 2 H), H-5 of uracil and H-3'; 4.28 (m, 1 H), H-2'; 4.14 (m, 1 H), H-4'; 3.06 (m, 2 H), H-5'; 2.44 (s, 3 H), tosyl-methyl.

Preparation of 5'-O-triphosphoryl-3'-O-(4-toluensulfonyl)uridine (3) 10 was dissolved in dry nitromethane containing anhydrous zinc bromide (113 mg/5 ml; 199 ml; 9 eq. with respect to 10) at 20 °C followed by an addition of dry anthranilic acid (5.5 g, 18 eq.). The reaction mixture was quenched after 160 min (half-life is ca. 15 min) by pouring the reaction

mixture into a stirring solution of saturated sodium bicarbonate solution. The reaction mixture was then worked up in a usual way and chromatographed over a short column of silica gel, using first dichloromethane as an eluent and then with chloroform giving 3 as a glass; yield: 0.95 g (67%).

$^1$H NMR (CDCl$_3$ + TMS); δ 7.75 (d, 7.7 Hz, 1 H), H-6; 7.67 (d, 9 Hz, 2 H), tosyl; 7.5 (m, 15 H), trityl; 5.95 (d, 5.5 Hz, 1 H), H-1'; 5.35 (d, 7.7 Hz, 1 H), H-5; 5.01 (dd, 2 & 5.5 Hz, 1 H), H-3'; 4.48 (dd, 1 H), H-2'; 4.29 (m, 1 H), H-4'; 3.39 (m, 2 H), 5'-H; 2.41 (s, 3 H), tosyl methyl-.

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