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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-β-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′-deoxy-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-β-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-β-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 E_2 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 β side on the sp^2 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-β-D-*threo*-

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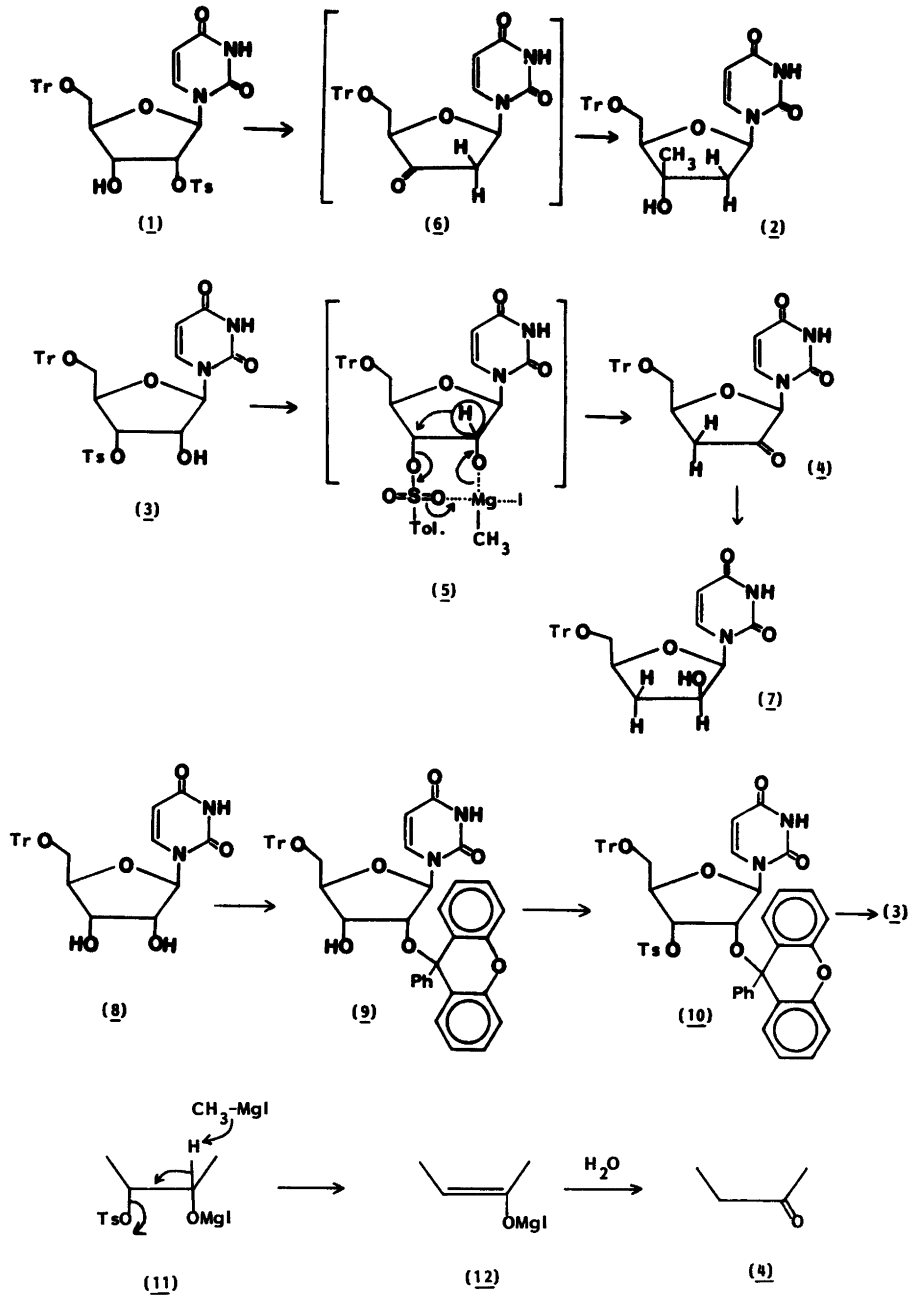
Tr
NH
O
N
HO
OTs
(1)
(6)
CH3 H
(2)
Ts O
OH
(3)
O=S=O
Mg---I
Tol.
CH3
(5)
(4)
(7)
(8)
Ph
(9)
(10)
(3)
CH3-MgI
TsO
OMgI
(11)
(12)
H2O
(4)

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*-triphenylmethyl uridine *8*. The 2'-hydroxyl function of (*8*) was selectively blocked with 9-phenylxanthen-9*H*-9-yl- (pixyl) group[7] 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 solution[5] 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. ^{13}C NMR spectra were measured at 23.7 kHz using tetramethylsilane as the internal standard. IR spectra was measured using a Perkin-Elmer 298 spectrometer.

Reactions were monitored by using Merck pre-coated silica gel 60 F_{254} 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-triphenylmethyl-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 methylmagnesium iodide (5 eq.) was added to a dry dioxan 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 %). ^{1}H NMR ($CDCl_3$+ 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. ^{13}C NMR ($CDCl_3$+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 (chloroform): ν_{max} 1773, 1710 and 1690 cm^{-1}; $M^{\cdot+}$ at *m/z* 468 (12.7 %).

Preparation of 1-(5'-O-triphenylmethyl-3'-deoxy-β-D-threopentofuranosyl)uracil (7). Sodium borohydride reduction[6] of *4* gave *7* in 86 % yield as a glass. ^{1}H NMR ($CDCl_3$+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'. ^{13}C NMR ($CDCl_3$+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 $M^{\cdot+}$ at *m/z* 470 (23 %).

Preparation of 5'-O-triphenylmethyl-2'-O-(9-phenylxanthen-9-yl)uridine (9). Crystalline 9-phenylxanthen-9-yl[7] (2.2 g, 7.4 mmol) was added to a dry pyridine solution (40 ml) of 5'-*O*-triphenylmethyluridine *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 %).

^{1}H NMR ($CDCl_3$+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'-CH_2;

Preparation of 5'-O-triphenylmethyl-3'-O-(4-toluenesulfonyl)-2'-O-(9-phenylxanthen-9-yl)uridine (10). 4-Toluenesulfonyl chloride (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 %). ^{1}H NMR ($CDCl_3$+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-triphenylmethyl-3'-O-(4-toluenesulfonyl)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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