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NUCLEIC ACID RELATED COMPOUNDS. 43. A CONVENIENT PROCEDURE FOR THE SYNTHESIS OF 2' AND 3'-KETONUCLEOSIDES[1]

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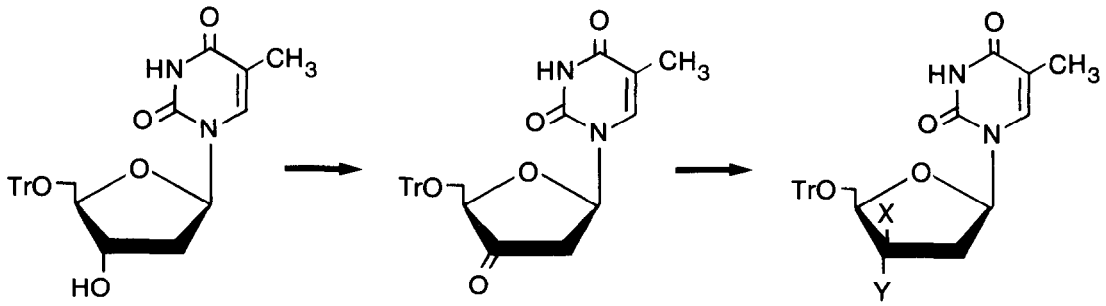
Chromium trioxide/pyridine/acetic anhydride effects smooth oxidation of selectively protected nucleosides to give high yields of 2' or 3'-keto-nucleosides, whose reduction provides the inverted nucleoside epimers.

Although ketonucleosides are potentially very useful synthetic intermediates, they have been considered to be rather inaccessible owing to their reported lability (especially under basic conditions) and the difficulty in obtaining suitably protected precursor nucleosides.[2] Oxidation of 5'-O-acetylthymidine using the mild Pfitzner-Moffatt conditions resulted in spontaneous β-elimination of the thymine base.[3] Attempted oxidation of 5'-O-tritylthymidine with chromium trioxide/pyridine also had been reported to result in loss of thymine.[4] Moffatt and co-workers separated mixtures of 3',5' and 2',5'-di-O-trityl uridine[5] and cytidine[6] derivatives and subjected them to oxidation to obtain the corresponding pyrimidine 2' and 3'-keto-nucleosides. Ruthenium tetroxide was employed to oxidize a xylofuranosyl-adenine derivative to give a purine 2'-ketonucleoside.[7] Examples of theophylline hexopyranose 2'-ketonucleosides were obtained using chromium and Pfitzner-Moffatt oxidants.[8] The first successful synthesis of a 3'-keto-2'-deoxynucleoside was reported in 1977 by Binkley and co-workers, who employed a novel photochemical cleavage of the pyruvate ester of 5'-O-tritylthymidine.[9]

A recently described chromium(VI) reagent, chromium trioxide/pyridine/acetic anhydride (1:2:1), was reported to oxidize selectively protected carbohydrate derivatives smoothly.[10] We now wish to report use of this complex to give high yields of 2' and 3'-ketonucleosides from conveniently protected precursors. Reduction of the carbonyl function using sodium borohydride allows an easy overall inversion to give the nucleoside epimer.

Oxidation of 485 mg (1 mmol) of 5'-O-tritylthymidine (1) with 3 molar equivalents of the pre-mixed complex of CrO_3/pyridine/Ac_2O (300 mg/0.5 mL/0.3 mL) in 7 mL of dichloromethane was allowed to proceed for 45 min at ambient temperature. The dark brown solution was poured into 50 mL of ethyl acetate, and the resulting mixture was filtered using a 1 cm layer of Woelm neutral



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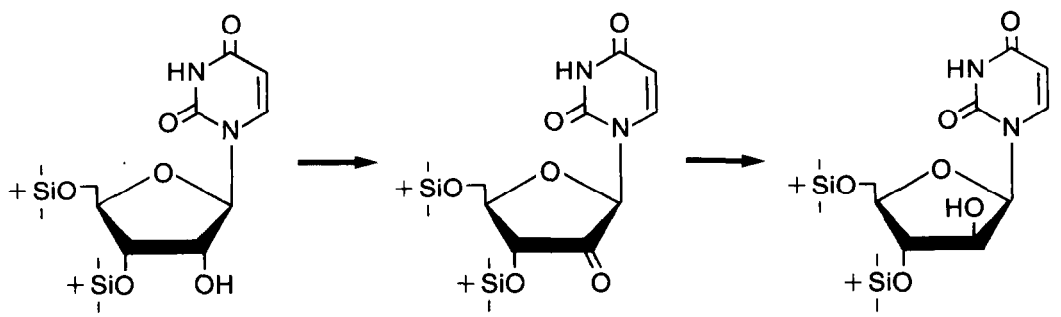
silica gel (0.2-0.5 mm) in a 4 cm diameter column. The precipitated solids and silica were washed with ethyl acetate and the combined filtrate was evaporated (<25°C). Toluene (25 mL) followed by chloroform (25 mL) were added and evaporated to leave a colorless crystalline solid. This product was dissolved in 4 mL of chloroform and cooled. Carbon tetrachloride (~18 mL) was added with stirring at 0°C and two crops of analytically pure crystals[11] were collected to give 419 mg (87%) of 1-(5-O-trityl-β-D-glycero-pentofuran-3-ulosyl)thymine (2) with mp 171-174°C (Lit.[9] mp 171-174°C). This represents the first successful chemical oxidation of a 2'-deoxynucleoside to its 3'-keto analogue and gives 2 in over 25% higher yield than the photochemical procedure.[9]

Reduction of 2 with sodium borohydride was reported to give 1-(2-deoxy-5-O-trityl-β-D-threo-pentofuranosyl)thymine (3, X = OH, Y = H) exclusively.[9a] However, treatment of our crude oxidation product (2) with sodium borodeuteride in absolute ethanol followed by preparative thin layer chromatography resulted in isolation of 9% of 3'-deuterio-5'-O-tritylthymidine (3, X = D, Y = OH) in addition to 77% of 1-(3-deuterio-5-O-trityl-β-D-threo-pentofuranosyl)-thymine (3, X = OH, Y = D). The deuterium label clearly demonstrates that oxidation of 1 to 2 was complete and that attack of borodeuteride at the more hindered β face occurred to give a minor quantity of the erythro isomer.



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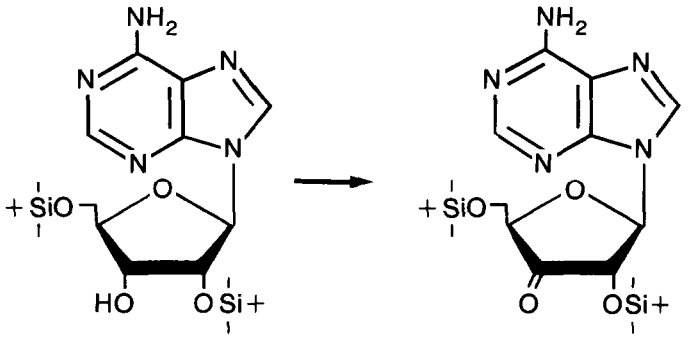
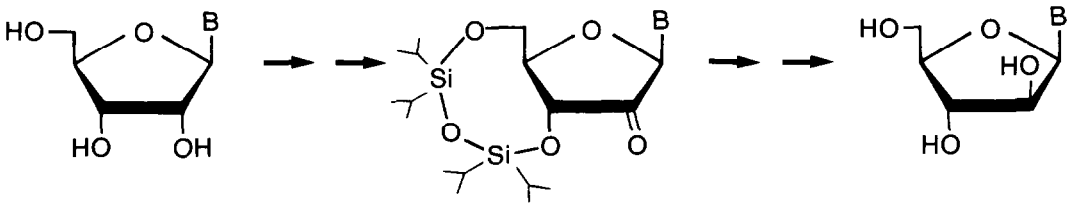
Analogous oxidation of 3',5'-bis-O-(tert-butyldimethylsilyl)uridine[12] (4) gave 1-[3,5-bis-O-(tert-butyldimethylsilyl)-β-D-erythro-pentofuran-2-ulosyl]uracil (5) in 89% yield.[11] Reduction of crude 5 with sodium borohydride gave 1-[3,5-bis-O-(tert-butyldimethylsilyl)-β-D-arabinofuranosyl]-uracil (6) in 95% overall yield[11] from 4.

Treatment of 2',5'-bis-O-(tert-butyldimethylsilyl)adenosine[12] (7) by the general oxidation procedure gave 9-[2,5-bis-O-(tert-butyldimethylsilyl)-β-D-erythro-pentofuran-3-ulosyl]adenine (8) in 88% yield.[11] This represents the first reported example of a purine 3'-ketonucleoside.



7 8

A general sequence has been developed for the 4-stage selective conversion of ribo to arabinonucleosides: (1) protection of a ribonucleoside as its 3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl) derivative;[1,13,14] (2) oxidation of the 2'-hydroxyl group; (3) reduction of the carbonyl function; and (4) deprotection to give the arabinonucleoside (which is separated from a minor amount of the ribo epimer). Adenosine was converted by this sequence to the antiviral agent 9-(β-D-arabinofuranosyl)adenine in 67% overall yield. Other purine-type natural product ribonucleosides have been transformed to their arabino analogues successfully.



The Garegg chromium trioxide/pyridine/acetic anhydride complex in methylene chloride provides a convenient and mild oxidizing system for the secondary hydroxyl functions of selectively protected nucleosides. A variety of 2' and 3'-ketonucleosides are now available in high yields. Experimental details and spectral properties of these compounds will be reported.

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