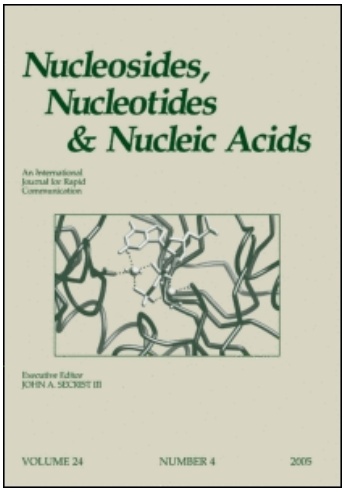

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Synthesis of 2',3'-Dideoxyuridine Via the Corey-Winter Reaction

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SYNTHESIS OF 2',3'-DIDEOXYURIDINE VIA THE COREY-WINTER REACTION.

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Abstract—*Heating of 5'-protected uridine cyclic 2',3'-O-thiocarbonates in trimethyl phosphite in an inert atmosphere gives 5'-protected 2',3'-didehydro-2',3'-dideoxyuridines in nearly quantitative yield.*

Recent interest in development of efficient methods for the synthesis of 2',3'-dideoxy- and 2',3'-didehydro-2',3'-dideoxy-ribonucleosides has resulted from potential application of these compounds in HIV (human immunodeficiency virus) chemotherapy [1]- [4]. Active analogues appear to be converted in cells to 5'-triphosphates that, like the approved anti-HIV drug 3'-azido-3'-deoxythymidine, inhibit the HIV reverse transcriptase [2].

Routinely used multistep synthetic methods for the 2',3'-dideoxynucleosides involve base-catalyzed elimination of 3'-sulfonyl derivatives of 2'-deoxyribonucleosides [5,6]. The methods are rather laborious and expensive, and lack the necessary efficiency for large scale production. Reductive elimination of halogen and acetate from trans-2'(3')-O-acetyl-3'(2')-deoxy-3'(2')-halogeno nucleosides by a chromous complex at low temperature provides 2',3'-didehydro-2',3'-dideoxy analogs but only in a moderate yield, due to glycosidic bond cleavage and reductive dehalogenation [7]. Recently, M.J.Robins' group reported an efficient modification of that method, in which treatment of trans-2'(3')-O-acetyl-3'(2')-bromo-3'(2')-deoxyadenosines with zinc-copper couple in DMF [8] produced 2',3'-didehydro-2',3'-dideoxyadenosine in 81% yield.

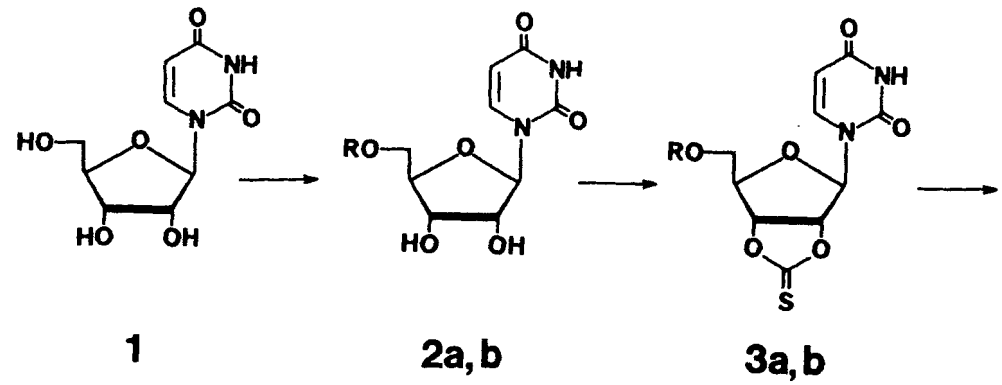
This paper presents an efficient route for the synthesis of 2',3'-didehydro-2',3'-dideoxyuridine (uridinene, **5**). The product itself is not biologically active, but the method illustrates a potentially useful strategy in the synthesis of 2',3'-unsaturated

nucleosides and, by catalytic hydrogenation, 2′,3′-dideoxynucleosides. The method is based on the olefin synthesis of Corey and Winter [9] using the readily prepared cyclic thiocarbonates of cis-diol systems. The cyclic thiocarbonates heated in trialkyl phosphite react with the solvent giving olefins and, as side-products, trialkyl thiophosphate and carbon dioxide [9].

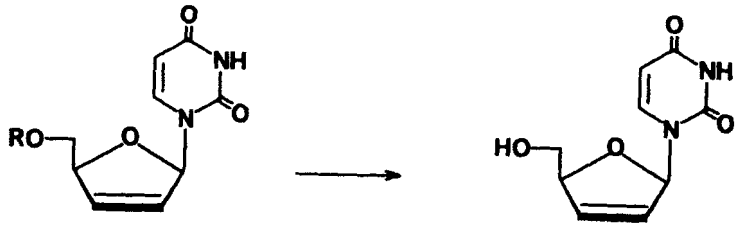
A previous attempt to apply this method to uridine failed, producing 3-methyluridinene instead [10]. This probably occurred because of a work-up procedure where the final reaction mixture was treated with a dilute solution of sodium hydroxide. We found that methylation of the aglycone can be avoided by carrying out the reaction in oxygen-free atmosphere and by elimination of the alkaline work-up. Prolongation of the reaction time to 24 h did not give us different results. Since the elimination reaction is complete after 5 h it was reasonable to assume that only two components of the reaction mixture can be responsible for the methylation of the nucleoside product: trimethyl phosphite and thiophosphate. The third possible component, trimethyl phosphate, can be present due to the presence of oxygen. We tested trimethyl phosphite and phosphate for their ability to methylate 5′-O-TBDMS uridinene and uridinene using methyl iodide as a reference. We found that neither trimethyl phosphite nor phosphate itself methylated uridinene derivatives at 115°C. Only trimethyl phosphate, and not phosphite, can methylate the nucleosides at room temperature in the presence of a base. Therefore we could explain that reported methylation [10] of the compounds is due to the presence of trimethyl phosphate, generated by oxidation of phosphite, or the side-product of the Corey-Winter reaction, trimethyl thiophosphate, during the alkaline work-up.

In our procedure we choose to block the 5′-hydroxyl of **1** with the benzoyl or tert-butyldimethylsilyl group to simplify the synthesis of the cyclic thiocarbonate of uridines, and to avoid acid conditions during deblocking of acid-labile 2′,3′-didehydro-2′,3′-dideoxyuridine. 5′-O-Benzoyl uridine, **2a**, was obtained by the method of Nishino et al. [11]. Use of tert-butyldimethylsilyl chloride in DMF in the presence of imidazole gave 5′-O-TBDMS uridine, **2b**, in 75% yield [12].

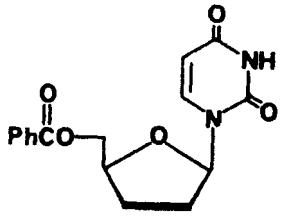
Treatment of **2a** and **2b** under argon with 1,1′-thiocarbonyldiimidazole at room temperature gave quantitatively 5′-O-blocked uridine 2′,3′-O-cyclic thiocarbonates, **3a** and **3b**. The 2′,3′-O-thiocarbonates were converted into 5′-O-blocked uridinene derivatives **4a** and **4b** by heating in trimethyl phosphite during 5 h . The reaction was almost quantitative (90%) when carried out in an inert atmosphere, e.g. argon. The products **4a** and **4b** were obtained in pure form in yields of 70% and 89%, respectively. Uridinene (**5**) was obtained by treatment of **4a** with sodium ethoxide and of **4b** with tetra-n-butylammonium fluoride in THF in high yields. Compounds **4a** and **5** had the same physicochemical properties as previously reported for 5′-O-benzoyluridinene and uridinene, respectively [6]. The ^{1}H NMR spectrum of **5** showed the presence of two adjacent vinyl protons centered at δ 6.40 and δ 5.92. In order to prove that methylation of the aglycone did not occur, compound **5** was treated with 1N HCl at 90°C. The isolated base was unequivocally identified as uracil by melting point and ^{1}H NMR.



1 2a,b 3a,b



4a,b 5



6

a. R = -C(=O)Ph,

b. R = -SiBuMe$_2$.

Compound **4a** reduced in the presence of hydrogen and 5% Pd/C gave a product identical to the previously synthesized 5'-O-benzoyl-2',3'-dideoxyuridine [6]. Its ^{1}H NMR spectrum was characteristic for 2',3'-dideoxynucleosides , showing multiplets at δ 1.87 to 2.57 corresponding to four protons (2', 2", 3' and 3" protons) and a quartet centered at δ 6.08 (1' proton) [5,13].

There are several potential advantages of this procedure for the synthesis of 2',3'-unsaturated nucleosides. Inexpensive reagents, including the readily available ribonucleosides, simple purification steps, and ease of scale up, make it an interesting alternative to present methods of synthesis of 2',3'-dideoxynucleosides. We are continuing studies of this procedure for a direct, general synthesis of other nucleosides, e.g. 2',3'-didehydro-2',3'-dideoxycytidine (cytidinene) and 2',3'-dideoxycytidine, attractive for their potential of being clinically useful inhibitors of HIV [4].

Our preliminary data have shown a possible limitation of the procedure. For example, N^4-Acetyl-5'-O-TBDMS cytidine 2',3'-O-thiocarbonate undergoes a very fast isomerization at elevated temperatures in aprotic solvents to N^4-acetyl-2'-deoxy-2'-thio-5'-O-TBDMS cytidine 2',3'-S,O-carbonate [14]. The behaviour of this cyclic thiocarbonate is analogous to that of the cyclic thiocarbonate of ethylene glycol [15]. The observed isomerization could be a key explanation of the failure of an early attempt to apply the Corey-Winter procedure to adenosine [16].

Experimental

Melting points were determined on a Mel-temp apparatus and are uncorrected. Ultraviolet spectra were determined with a Gilford Response™ UV-VIS spectrophotometer. Nuclear magnetic resonance spectra were obtained on Bruker WM-250 (250 MHz) or General Electric QE-300 (300 MHz) spectrometers, both operating in the FT mode. Elemental analyses were done by the Microanalysis Laboratory, University of Massachusetts, Amherst, MA. Thin-layer chromatography was performed with Merck Kieselgel 60 F-254 analytical plates. Column chromatography was done with Merck Kieselgel 60 (40-60 μm).

5'-O-Benzoyluridine 2',3'-O-thiocarbonate (**3a**). A solution of 1,1'-thiocarbonyldiimidazole (2.9 g of 90% reagent) in 1,2-dichloroethane (100 ml) was added dropwise during 2 h to a suspension of 5'-O-benzoyluridine (4.94 g; 14.17 mmol) in 1,2-dichloroethane (100 ml) . The reaction mixture was left overnight, and TLC analysis of the resulting solution showed, in addition to the desired compound, a few of percent of the starting material and a more polar component. The reaction mixture was passed through a silica gel column (20x4 cm), and the major product was eluted with 5% methanol in chloroform. During evaporation the product spontaneously crystallized. The crystalline mass was suspended in methanol (50 ml), washed with methanol (3x5 ml) and filtered. The procedure afforded 4.5 g (81%) of pure **3a**, m.p.198°C (softens at 153°; evolution of a gas at 174°C); UV λ_{max}^{EtOH} 233 nm (ϵ 21,140); NMR (DMSO-d$_6$): δ 11.54 (s, 1, H-3), between 7.99 and 7.50 (m, 5, phenyl), 7.75 (d, 1, H-6), 6.11 (bd s, 1, H-2'), 6.10 (d, 1, H-1'), 5.83

(m, 1, H-3'), 5.64 (d, 1, H-5), 4.69 (m, 1, H-4'), 4.56 (m, 2, H-5' and H-5"); $J_{1',2'} < 1.5$ Hz, $J_{2',3'} = 7.3$ Hz. (Found: C, 52.14; H, 3.44; N, 6.98; S, 7.90. Calc. for $C_{17}H_{14}N_2O_7S$: C, 52.30; H, 3.61; N, 7.18; S, 8.21%).

5'-O-(tert-Butyldimethylsilyl)uridine 2',3'-O-thiocarbonate (**3b**). A solution of 1,1'-thiocarbonyldiimidazole (4 g of technical grade reagent; 20 mmol) in chloroform (100 ml) was added dropwise with stirring during 1 h to a solution of compound **2b** (7.5 g; 20 mmol) in 100 ml of ethanol-free chloroform. The product was purified by silica gel chromatography (30x4 cm) by elution with 0.5% ethanol in chloroform. The crystalline residue after evaporation was suspended in toluene and filtered. This yielded 7.4 g (93%) of analytically pure **3b** with m.p.144-147°C; UV λ_{max}^{EtOH} 240 nm (ϵ 27,600); NMR ($CHCl_3$-d): δ 9.37 (broad s, 1, H-3), 7.39 (d, 1, H-6), 5.81 (d, 1, H-1'), 5.78 (d, 1, H-5), 5.65 (dd, 1, H-2'), 5.50 (dd, 1, H-3'), 4.51 (m, 1, H-4'), 3.87 (bd d, 2, H-5' and H-5"), 0.85 (s, 9, $C(CH_3)_3$), 0.10 (s, 6, $SiCH_3$); $J_{1',2'} = 1.6$ Hz, $J_{2',3'} = 7.3$ Hz. (Found: C, 47.91; H, 6.12; N, 7.01; S, 7.91. Calc. for $C_{16}H_{24}N_2O_6SSi$: C, 47.98; H, 6.04; N, 7.00; S, 8.01%).

5'-O-Benzoyl-2',3'-didehydro-2',3'-dideoxyuridine [1-(5-O-benzoyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil] (**4a**). Compound **3a** (3.9 g; 10 mmol) was suspended and heated in 20 ml of trimethyl phosphite under argon. After 5 h at 110°C all starting material dissolved, and TLC showed about 80% transformation into products. The major component was purified by silica gel chromatography (20x4 cm; elution with 2% ethanol in chloroform). The resulting oil was crystallized from ethanol to give 2.2g (70%) of colorless crystals, m.p.140-141°C (lit. [6] m.p.138.5-139°C); NMR ($CHCl_3$-d): δ 9.14 (bd s, 1, H-3), 8.01 and 7.44 (m, 5, phenyl), 7.35 (d, 1, H-6), 7.02 (m, 1, H-1'), 6.40 (d of t, 1, H-3'), 5.90 (bd d, 1, H-2'), 5.34 (d, 1, H-5), 5.17 (m, 1, H-4'), 4.58 and 4.51 (m, 2, H-5' and H-5").

5'-O-tert-Butyldimethylsilyl-2',3'-didehydro-2',3'-dideoxy uridine [1-(5-O-tert-butyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil] (**4b**). Compound **3b** (6.41 g; 16 mmol) was suspended in 50 ml of trimethyl phosphite. The reaction flask was evacuated and then filled with argon. The contents were heated to 118°C, and the suspension disappeared after 5 min of heating. After 4 h, when the evolution of gas ceased, TLC of the reaction mixture show only traces of the substrate and over 95% conversion to the product. After an hour the solvent was removed in a stream of air. The colorless crystalline precipitate was suspended in n-heptane, filtered and washed with n-heptane. The crude product was purified on a silica gel column (20x4 cm) developed with dichloroethane (1.0 L) and 1% ethanol in chloroform(1.5 L). Evaporation of combined fractions containing the pure product yielded 4.61 g (89%) of **4b**, m.p.158-159°C (solidifies above 159°C); NMR ($CHCl_3$-d): δ 8.69 (bd s, 1, H-3), 7.83 (d, 1, H-6), 7.00 (m, 1, H-1'), 6.25 (bd d, 1, H-3'), 5.82 (bd d, 1, H-2'), 5.66 (d, 1, H-5), 4.89 (m, 1, H-4'), 3.86 (m, 2, H-5' and H-5"). (Found: C, 55.36; H, 7.38; N, 8.70. Calc. for $C_{15}H_{24}N_2O_4Si$: C, 55.52; H, 7.46; N, 8.63%).

2',3'-Didehydro-2',3'-dideoxyuridine [1-(2,3-dideoxy-β-D-glycero-pent-2-eno-furanosyl)uracil] (**5**). Compound **4b** (1.38 g; 4.24 mmol) was dissolved in 14 ml of THF and treated with 6.3 ml of 1M tetra-(n-butyl)ammonium fluoride in THF for 2 h. After evaporation of solvent the product was purified on a silica gel column (11x4 cm) using 2% methanol in chloroform as eluent. Crystallization from hot ethanol (14 ml) gave, in two crops, 0.85 g of **5** (95%), m.p.151°C(dec.)[the melt rapidly resolidifies and does not remelt below 250°C]. (lit. [6] m.p.153-4°C; UV λ_{max}^{EtOH} 260 nm (ϵ 9,390); NMR (DMSO-d_6): δ 11.30 (bd s, 1, H-3), 7.76 (d, 1, H-6), 6.82 (m, 1, H-1'), 6.40 (d of t, 1, H-3'), 5.92 (d of q, 1, H-2'), 4.78 (m, 1, H-4'), 3.59 (bd d, 2, H-5' and H-5").
Treatment of **4a** in the standard way with 0.1 M sodium ethoxide in absolute ethanol gave **5** in 85% yield.

5'-O-Benzoyl-2',3'-dideoxyuridine (**6**). A solution of **4a** (628 mg; 2 mmol) in ethanol (120 ml) containing 60 mg of 5% Pd/C was shaken under 50 psi of hydrogen during 3.5 h. The reaction mixture was filtered and evaporated to dryness. Crystallization from ethyl acetate gave 520 mg (82%) of the titled product, m.p.146-147°C (lit. [13] m.p.143-144°C; NMR ($CHCl_3$-d): δ 9.14 (bd s, 1, H-3), 8.03 (d, 1, H-6), between 7.69 and 7.50 (m, 5, phenyl), 6.08 (q, 1, H-1'), 5.55 (d, 1, H-5), 4.61 (m, 2, H-5' and H-5"), 4.45 (m, 1, H-4'), between 2.57 and 1.87 (a complex of m, 4, H-2', H-2", H-3' and H-3").

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