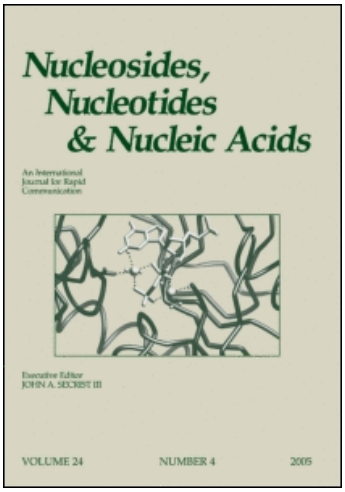

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Synthesis of 5-Formyluridines

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SYNTHESIS OF 5-FORMYLURIDINES

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Abstract: 5-Formyl-2',3'-*O*-isopropylideneuridine and 5-formyl-2',3',5'-tri-*O*-acetyluridine were prepared by a new procedure involving palladium-catalyzed coupling of 5-iodouridine with styrene, followed by reaction with acetic anhydride or acetone and ozonolysis of the resulting 5-styryluridine derivatives.

The synthesis of modified nucleosides as potential antimetabolites has received much attention over the past decade. Some pyrimidine nucleosides carrying substituents at the 5-position have shown potent antiviral activity. [1] 5-Carbon substituted pyrimidine nucleosides have been typically prepared by palladium catalyzed coupling of a suitably protected 5-iodo or 5-mercurated uridine or 2'-deoxyuridine with alkenes and terminal alkynes. [2] As part of our program aimed at the synthesis of 5-carbon substituted uridine derivatives we proposed targets which were not easily accessible *via* palladium catalyzed coupling methodology. Our synthetic strategy required suitably protected 5-formyluridine as a key intermediate.

The synthesis of 5-formyluridine has been reported in low yield (46%) from the oxidation of 5(hydroxymethyl)uridine with platinum oxide. [3] An alternative procedure involves the oxidation of 5-(hydroxymethyl)-2',3'-*O*-isopropylideneuridine with active manganese dioxide, to give 5-formyl-2',3'-*O*-isopropylideneuridine (in 37% yield) followed by acid hydrolysis of the

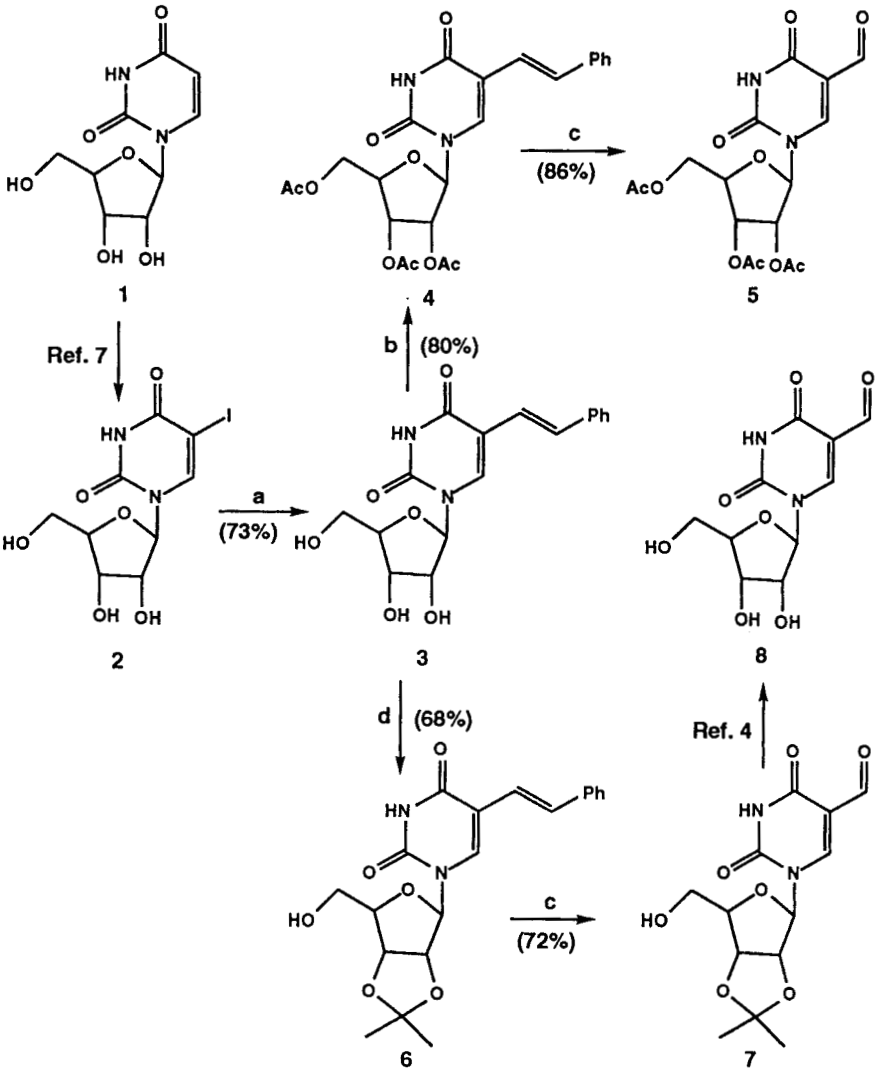
isopropylidene group. [4] Recently, Whale et al. have reported a better yield (63%) for the above oxidation using pyridinium dichromate. [5]

In this paper we report an alternative route to 5-formyl-2',3'-*O*-isopropylidneuridine [4] and 5-formyl-2',3',5'-tri-*O*-acetyluridine. [6] Both of these 5-formyluridine derivatives were obtained from 5-iodouridine [7] in good overall yield. Thus, reaction of 5-iodouridine with styrene under Heck coupling conditions catalyzed by palladium in refluxing dioxane gave (*E*)-5-styryluridine (**3**) in 73% yield. [8] Reaction of **3** with aceteic anhydride in pyridine gave the triacetyl derivative **4** in 80% yield. Reaction of **4** with ozone in methylene chloride at -78 °C followed by treatment with methyl sulfide provided 5-formyl-2',3',5'-tri-*O*-acetyluridine in very good (86%) yield. Also, reaction of (*E*)-5-styryluridine with acetone in the presence of sulfuric acid gave (*E*)-2',3'-*O*-isopropylidene-5-styryluridine (**6**) in 68% yield. This was smoothly converted to the 5-formyl derivative **7** in good yield (72%) again by ozonolysis. Conversion of **7** to 5-formyluridine (**8**) by treatment with 50% aqueous acetic acid at 100 °C has been described by Armstrong et al.[4c] The 5-formyluridine derivatives **5** and **7** are potentially useful intermediates for further synthetic transformations.

EXPERIMENTAL

Melting points were determined in open capillary tubes using a Electrothermal apparatus and are uncorrected. The proton (300 MHz) NMR spectra were recorded on a Varian VXR-300 spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from internal tetramethylsilane. Column chromatography was performed on Merck silica gel 60 (240-400) mesh; silica gel plates were routinely used for tlc determinations. Elemental analyses were performed by Desert Analytics, Tucson, AZ, and were within ±0.4% of the theoretical values.

(*E*)-5-Styryluridine (3): A mixture of palladium acetate (140 mg, 0.63 mmol), triphenylphosphine (350 mg, 1.35 mmol), triethylamine (6 ml) and dioxane (15 ml) was heated under nitrogen until the solution was a deep red color. A mixture of 5-iodouridine [7] (5.0 g, 13.5 mmol) and styrene (4.1 ml, 35.7 mmol) was added, and the reaction mixture was heated at reflux for 5 h then filtered while hot



(a) $Pd(OAc)_2$, PPh_3, Et_3N, dioxane, styrene, reflux, 5h.
(b) Ac_2O, pyridine, reflux, 24h.
(c) O_3, CH_2Cl_2, -78 °C then Me_2S.
(d) acetone, $CuSO_4$ (anh.), H_2SO_4 (cat), RT, 24h.

Scheme

through a pad of Celite. The solvent was removed by evaporation under reduced pressure and the residue was triturated with a little methylene chloride. The resulting solid was filtered, washed well with water, and dried to give 3.4 g (73%) of a colorless solid. A sample was recrystallized from water. The R_f, mp, and ^1H nmr data were identical with that reported by Bergstrom and Ogawa. [8]

(*E*)-2',3',5'-Tri-*O*-acetyl-5-styryluridine (4): A mixture of (*E*)-5-styryluridine (1.0 g, 2.92 mmol), acetic anhydride (1.0 ml, 10. 6 mmol), and dry pyridine (5 ml) was heated at reflux under nitrogen for 24 h. The solvent was removed by evaporation under reduced pressure, and the residue was dissolved in methylene chloride and washed with 1% hydrochloric acid followed by water. The organic layer was dried over anhydrous magnesium sulfate, filtered, and the solvent was evaporated. The residue was chromatographed on silica gel, eluting with 80% ethyl acetate in hexane to give 1.1 g (80%) of a colorless solid, mp: 132-134 °C. ^1H NMR ($CDCl_3$): δ 2.11, 2.15 (2 overlapping s, 9H), 4.4 (m, 3H), 5.4 (m, 2H), 6.18 (d, J = 2 Hz, 1H), 6.82 (d, J = 16 Hz, 1H), 7.2-7.6 (m, 6H), 9.0 (s, 1H). Anal. Calcd. for $C_{23}H_{24}N_2O_9$: C, 58.47; H, 5.12; N, 5.93. Found: C, 58.25; H, 5.13; N, 5.57.

2',3',5'-Tri-*O*-acetyl-5-formyluridine (5): Ozone was bubbled through a solution of (*E*)-2',3',5'-tri-*O*-acetyl-5-styryluridine (0.25 g, 0.529 mmol) in methylene chloride (10 ml) which was cooled to -78 °C, for 10 min. Oxygen was then bubbled through this solution for 5 min, and methyl sulfide (0.5 ml) added. The mixture was allowed to warm to room temperature and stirred for a further 0.5 h. The solvent was removed by evaporation under reduced pressure, and the residue was chromatographed on a short pad of silica gel, eluting with 1-2% methanol in chloroform to give 0.18 g (86%) of a colorless foam. The ^1H nmr data was identical to that reported by El-Barbary et al. [6]

(*E*)-2',3'-*O*-Isopropylidene-5-styryluridine (6): A mixture of (*E*)-5-styryluridine (1.0 g, 2.92 mmol), acetone (100 ml), anhydrous copper(II) sulfate (280 mg, 1.73 mmol) and concentrated sulfuric acid (1 drop) was stirred under nitrogen for 24 h at room temperature. The mixture was filtered through a short pad of calcium hydroxide, and the filtrate mixed with 5g of calcium hydroxide, stirred for 1 h, and filtered. The solvent was evaporated and the residue was

dissolved in methylene chloride, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed by evaporation. The residue was chromatographed on silica gel, eluting with 5-10% methanol in methylene chloride to give 0.75 g (68%) of a colorless solid, mp: 195-196 °C. ^{1}H NMR (DMSO-d_6): δ 1.25 (s, 3H), 1.45 (s, 3H), 3.63 (m, 2H), 4.18 (m, 1H), 4.85 (m, 1H), 5.0 (m, 1H), 5.3 (br s, 1H), 5.92 (d, J = 2 Hz, 1H), 6.85 (d, J = 16 Hz, 1H), 7.2-7.5 (m, 6H), 8.19 (s, 1H), 11.6 (br, 1H). Anal. Calcd. for $C_{20}H_{22}N_2O_6$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.02; H, 5.66; N, 6.98.

5-Formyl-2',3'-*O*-isopropylideneuridine (7): Ozone was bubbled through a solution of (*E*)-2',3'-*O*-isopropylidene-5-styryluridine (0.25 g, 0.647 mmol) in methylene chloride (10 ml) which was cooled to -78 °C for 10 min. Oxygen was then bubbled through this solution for 5 min, and methyl sulfide (0.5 ml) added. The mixture was allowed to warm to room temperature and stirred for a further 0.5 h. The solvent was removed by evaporation under reduced pressure, and the residue was chromatographed on a short pad of silica gel, eluting with 80% ethyl acetate in hexanes to give 0.14 g (72%) of a colorless solid; mp 155-158 °C (lit mp 157-159 °C). [4c] The ^{1}H NMR data was identical with that reported by Armstrong et al.[4c]

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