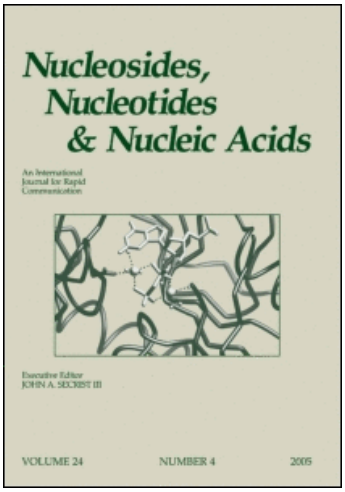

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REACTION OF ANHYDRONUCLEOSIDES WITH MAGNESIUM ALKOXIDES: REGIOSPECIFIC SYNTHESIS OF 2'-O-ALKYLPYRIMIDINE NUCLEOSIDES.

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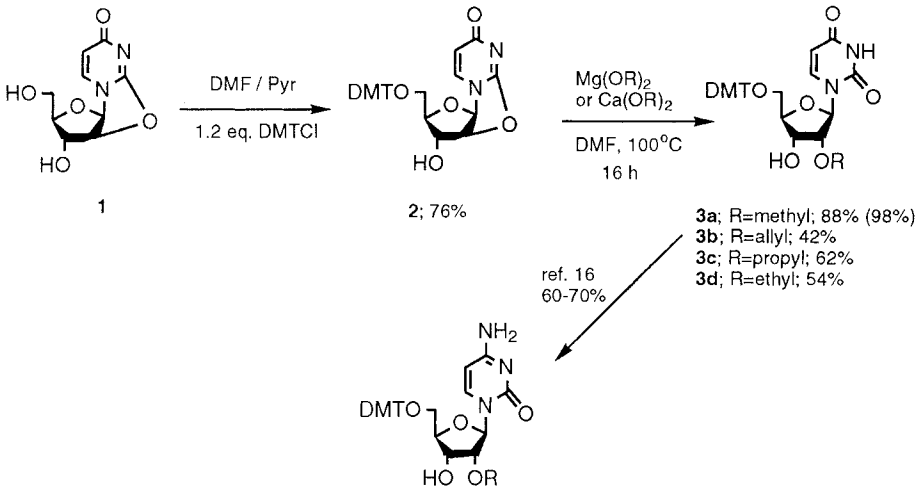
ABSTRACT: A novel approach to 2'-O-alkylpyrimidine nucleosides involving a 3'-hydroxyl assisted intramolecular delivery of a divalent metal alkoxide leads to a regiospecific opening of the anhydropyrimidine linkage at the 2'-position. Thus, reaction of 5'-protected 2,2'-anhydrouridine with magnesium or calcium alkoxides in DMF affords exclusively the corresponding 2'-O-alkyluridines in reasonable yields.

The long-standing interest in 2'-O-alkylnucleosides was initially due to their isolation as minor components of RNA from various organisms and questions concerning the role they play in vivo[1]. A more recent thrust has been the development of oligonucleotides as therapeutic agents encompassing approaches such as antisense[2], ribozymes[3] and selex[4]. The presence of 2'-O-alkyl nucleosides in oligonucleotides have been shown to increase the resistance of the oligonucleotide to both chemical and enzymatic degradation while retaining or potentiating the recognition of a complimentary sequence as measured by melting temperature experiments[5] and to stabilize the C3'-endo form of the ribose[6]. This has prompted a continued interest in developing efficient methods for the synthesis of 2'-O-alkyl nucleosides.

The selective alkylation of the 2'-O-position of ribofuranosylpyrimidines is problematic. Base promoted alkylations of uridine usually afford N^3-alkylated materials as a major product . This has been utilized to position a variety of N^3-protecting groups followed by alkylation of the ribose hydroxyls (order of reactivity 2'-OH > 3'-OH > 5'-OH)[7] and separation of the isomers and deprotection with resulting low overall yields of any one isomer[8]. A significant improvement has been the introduction of a tin catalyzed reaction of unprotected uridine with either alkyl halides[9] or diazomethane[10] yielding directly a mixture of 2'-O and 3'-O-alkyl nucleosides in high yield. The utility of this method is diminished by the difficult separation of the alkylated isomers and the resultant 30-58% isolated yields of 2'-O-alkylated isomer. Alternate approaches have been described involving the glycosylation of pyrimidines with alkylated sugars[11]. Base promoted alkylation of cytidine affords a mixture of O-alkylated products that can be resolved after the addition of protecting groups to afford the 2'-O-alkyl isomer in 25% yield[8e]. High regioselectivity of alkylation of a protected cytidine has recently been reported, where 5'-O-dimethoxytrityl-N^4-(benzoyl or t-butylphenoxyacetyl)cytidine is alkylated with a large excess of alkyl halide and

silver(I) oxide at low temperature, affording the 2'-O-alkylated nucleoside in 50-93% yield. The observation of the influence of a 5'-O-dimethoxytrityl group on the alkylation of the 2'- and 3'-hydroxyls was previously observed in the uridine series[10b].

We have developed and reported[13] on a new approach to the synthesis of 2'-substituted ribopyrimidines that involves opening of 5'-protected 2,2'-anhydrouridine **2** with nucleophiles, delivered regiospecifically to the 2'-position by tethering to the 3'-OH, affording an alternate route to the synthesis of 2'-amino pyrimidines. We sought to extend this approach to the synthesis of 2'-O-alkylpyrimidine nucleosides.



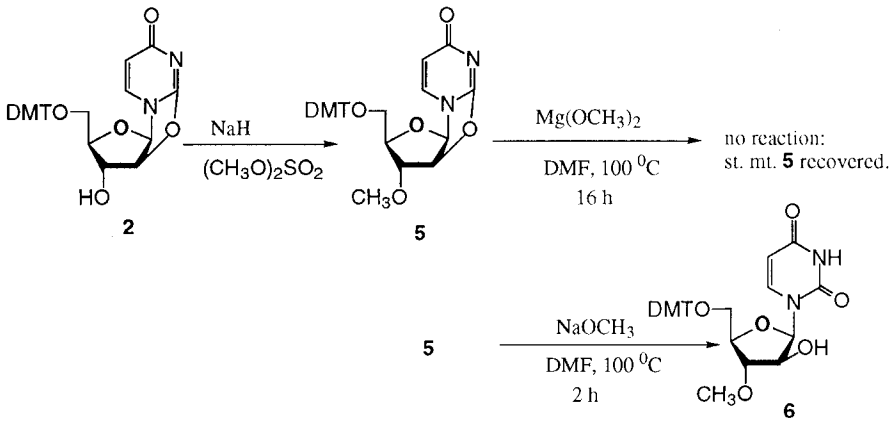
1 2; 76%

4

We reasoned that the free 3'-hydroxyl of compound **2** might direct the attack of divalent metal alkoxides, via complexation and resultant delivery of the alkoxide intramolecularly, leading to a regiospecific opening of the anhydro linkage at the 2'-position of the sugar. 2,2'-Anhydro-1-(β-D-arabinofuranosyl)uracil (anhydrouridine, **1**) obtained by base catalyzed reaction of diphenyl carbonate and uridine[14] was obtained by an improved procedure[13a] in 84% yield. Compound **1** was dimethoxytritylated[13a] and compound **2** obtained in 76% isolated yield. Reaction of compound **2** with ~4 mol eq. of magnesium methoxide for 4 hr at 100 °C lead to the isolation of 5'-O-DMT-2'-O-methyluridine **3a** as the only product in 88% yield. Similar reaction of compound **2** with either magnesium ethoxide or propoxide afforded the corresponding 2'-O-alkyl nucleoside products **3d** and **3c** in 54% and 62% yield. Our inability to prepare magnesium allyloxide lead us to use calcium allyloxide, inefficiently prepared by reaction of the alcohol and calcium hydride, which upon reaction with compound **2** gave 2'-O-allyl uridine **3b** in 42% yield. We have looked at a number of commercially available divalent metal alkoxides i.e.. Ca, Sr, Fe, Cu and found that the respective 2'-O-alkylated products were formed in all instances with some variations in isolated yield. Reaction of compound **2** with sodium methoxide gave 5'-O-DMT-arabinofuranosyluridine[15] as the only product. Compound **3a** was converted by known methods[16] to the cytidine[17] analog **4** in 50% yield.

During the dimethoxytritylation of compound **1** we observed that the yield of compound **2** before chromatography was ~95% by HPLC analysis. This observation lead

us to attempt a two step sequence where compound **1** was converted to compound **2** and, after trituration-decantation and fractional precipitation were used to remove some ditritylated material, the residue was reacted with magnesium methoxide to give a 98% yield of compound **3a** which was 95% pure by NMR and HPLC after a simple extractive workup. Attempts to react unprotected anhydrouridine **1** with magnesium methoxide under the reaction conditions described gave no reaction. This may be due to a combination of the poor solubility of the magnesium methoxide-anhydrouridine complex in DMF and possibly the intrinsic stability of the complex involving presumably the 5'- and 3'-hydroxyls.



2 **5** **5** **6**

In order to probe the mechanism of magnesium alkoxide opening of 5'-protected anhydronucleosides we attempted the reaction of compound **2** with magnesium chloride and methanol in DMF to hopefully demonstrate a possible role of the magnesium acting as a Lewis acid on the oxygen's at the 2- and 4-positions of the pyrimidine. No reaction occurred under these conditions. To help determine the role of the 3'-hydroxyl, compound **2** was methylated with dimethyl sulfate and sodium hydride to afford 3'-O-methyl derivative **5**. Attempted reaction of compound **5** with magnesium methoxide lead to recovery of unchanged starting material **5** . Reaction of compound **5** with sodium methoxide readily gave the arabino derivative **6**, the result of attack of alkoxide at the 2-position of the anhydro linkage and subsequent hydrolysis. We conclude from these experiments that magnesium alkoxides are not basic enough to react with the 2,2'-anhydro linkage of uridine. The 3'-hydroxyl may potentiate the reactivity observed by the energy gained in an intramolecular reaction path. The reduced basicity of magnesium alkoxides coupled with its ability to coordinate with electron donors as a Lewis acid has been used to achieve a high degree of selectivity of ester hydrolysis[18a] and resulted in selective reactions when compared to sodium alkoxides[18].

CONCLUSION:

We describe a new and versatile synthesis of 2'-O-alkyl pyrimidine nucleosides from the regiospecific opening of 2,2'-anhydrouridine, an inexpensive and readily available starting material. The wide range of commercially available divalent metal alkoxides and the elimination of the tedious chromatographic separation of 2'-O and 3'-O-aklylated products represent significant improvements over existing prior art and will hopefully encourage commercial utilization. The use of large excesses of hazardous alkylating agents is also eliminated. The 2'-O-alkylated nucleosides are obtained in a

form suitable for conversion to nucleoside phosphoramidite. Compound **1** may be converted to **3a** in 98% yield without the need for chromatography.

EXPERIMENTAL: All NMR spectra were recorded on a 300 MHz instrument in deuterated DMSO. Assignments were based on COESY experiments. Purifications were conducted on either column chromatography using "Baker" silica gel (7024, 40 μM) or a Chromatotron (Harrison Res. Palo Alto, CA).

5'-O-(4,4'-Dimethoxytrityl)-2'-O-methyluridine (3a): A 10% solution of magnesium methoxide (8 ml, 7.78mmol) was evaporated to dryness. To the solid residue was added anhydrous DMF (15 ml) and compound **2** (1.0 g, 1.89 mmol) and the reaction was heated 4 hr at 100 °C then cooled to rt. Acetone was added and the reaction was filtered, the filtrate was evaporated, the residue was redissolved in ethyl acetate and washed with water, the water extracted twice with ethyl acetate and the combined organic phase dried ($MgSO_4$) and evaporated to a pale yellow foam to afford **3a** (0.94 g, 88.7% yield, >95% pure by HPLC). The compound **3a** thus prepared was identical (^1H NMR, TLC) to authentic material[19]. ^1H NMR δ 11.4 (s, 1H), 7.73 (d, J= 8.1 Hz, 1H), 7.39-7.22 and 6.90 (m, 13H), 5.80 (d, J= 3.3 Hz, 1H), 5.29 (d, J= 8 Hz, 1H), 5.23 (d, J=6.9 Hz, 1H), 4.19 (m, 1H), 3.93(m, 1H), 3.81 (m, 1H), 3.73 (s, 6H), 3.40 (s, 3H), 3.23 (m, 2H). Anal. Calcd. for $C_{31}H_{32}N_2O_8$. 0.5 H_2O : C, 65.37; H, 5.84; N, 4.92. Found: C, 65.6; H, 6.02; N, 4.96. MS (M^+560)

Procedure from compound 1: To pyridine (60 ml) and DMF (20 ml) was added anhydrouridine **1** (5.0 g, 22.1 mmol), dimethoxytrityl chloride (8.24 g, 24.32 mmol) and catalytic DMAP (~20 mg) and the reaction stirred 16 hr at rt. then a few drops of water were added and the volume reduced by evaporation. The residue was dissolved in dichloromethane and washed with 5% sodium bicarbonate (2X) and the organic phase dried ($MgSO_4$) and evaporated. The oily residue was triturated with ethyl ether (2X) and the ether phase decanted. The yellow solid was twice dissolved in a minimal amount of dichloromethane and the product precipitated with an excess of ethyl ether and the supernatant decanted. The resulting dried yellow solid, crude compound **2** (10.9 g), was used as is in the next step. A 10% solution of magnesium methoxide in methanol (90 ml, 87.58 mmol) was evaporated to dryness. To this white solid was added crude compound **2** obtained above as a DMF (400 ml) solution and the reaction heated 16 hr at 100 °C . The solvent was reduced by evaporation under reduced pressure and the residue dissolved in ethyl acetate and washed with 5% aqueous sodium bicarbonate, the aqueous layer back washed (2X) and the combined organic phase dried ($MgSO_4$) and evaporated to afford **3a** as a yellow foam (12.2 g, 98% yield). ^1H NMR as above. Purity >95% by ^1H MR and HPLC.

2'-O-Allyl-5'-O-(4,4'-Dimethoxytrityl)uridine (3b): Calcium hydride (7g) was ground to a powder and allyl alcohol (300 ml) was added and the suspension refluxed 48 hr, filtered and evaporated under reduced pressure to afford crude calcium allyloxide as a sticky paste. Approximately 1/2 of the crude calcium allyloxide and dimethoxytrityl anhydrouridine **2** (1.0 g, 1.89 mmol) in DMF (30 ml) was heated at 100 °C for 16 hr then evaporated. The residue was partitioned between ethyl acetate and 5% sodium bicarbonate, the organic phase was dried ($MgSO_4$) and evaporated. The residue was purified on silica gel eluting with 50-95% ethyl acetate in hexanes to afford **3b** (470 mg, 42% yield) as a yellow foam. ^1H NMR δ 11.41 (s, 1H), 7.74 (d, J= 8.1 Hz, 1H), 7.39-7.23 and 6.91 (m, 13H), 5.86 (m, 1H), 5.83 (d, J= 3.7 Hz, 1H), 5.25 (m, 4H), 4.20 (m, 1H), 4.17 (m, 1H), 3.97 and 3.88 (m, 3H), 3.74 (s, 6H), 3.26 (ABX, 2H). Anal. Calcd. for $C_{33}H_{34}N_2O_8$. 0.5 H_2O : C, 66.54; H, 5.92; N, 4.78. Found: C, 66.85; H, 6.19; N, 4.52. MS (M+ 586)

5'-O-(4,4'-Dimethoxytrityl)-2'-O-propyluridine (3c): A mixture of compound **2** (1.0 g, 1.89 mmol) and magnesium propoxide (1.62 g, 11.37 mmol) in DMF (30 ml) was heated 16 hr at 100 °C. The reaction was cooled, diluted with ethyl acetate (50 ml) and washed with 5% sodium bicarbonate, the aqueous phase back washed twice and the combined organic phase dried ($MgSO_4$) and evaporated. The residue was purified on silica gel eluting with 20-60% ethyl acetate in hexanes containing 2% triethylamine to afford **3c** (0.69 g, 62% yield) as a light yellow foam. ^{1}H NMR δ 11.39 (s, 1H), 7.75 (d, J= 8.1 Hz, 1H), 7.40-7.24 and 6.9 (m, 13H), 5.78 (d, J= 3.6 Hz, 1H), 5.29 (d, J= 8.1 Hz, 1H), 5.14 (d, J= 6.7, 1H), 4.17 (m, 1H), 3.97 (m, 1H), 3.91 (m, 1H), 3.74 (s, 6H), 3.53 (m, 2H), 3.27 (dd, J= 6.6, 3.5 Hz, 2H), 1.53 (dq, J= 6.9, 7.2 Hz, 2H), 0.86 (t, J= 7.3 Hz, 3H). Anal. Calcd. for $C_{33}H_{36}N_2O_8$: C, 67.33; H, 6.16; N, 4.76. Found: C, 67.28; H, 6.42; N, 4.46.

5'-O-(4,4'-Dimethoxytrityl)-2'-O-ethyluridine (3d): Compound **2** (1.0g, 1.89 mmol) and magnesium ethoxide (1.3 g, 6 eq.) in DMF (20 ml) was heated 16 hr at 100 °C . The reaction was cooled and partitioned with ethyl acetate and 5% sodium bicarbonate and the aqueous phase back extracted twice and the combined organic phase dried ($MgSO_4$) and evaporated. The residue was purified on silica gel eluting with 1% triethylamine / ethyl acetate to afford **3d** (0.67g, 61.5% yield) as a foam. ^{1}H NMR δ 11.40 (s, 1H, NH), 7.75 (d, J= 8.1 Hz,1H, H-6), 7.39-7.23 and 6.90 (m, 13H), 5.80 (d, J= 3.6 Hz,1H, H-1'), 5.29 (d, J= 8.1 Hz,1H, H-5), 5.16 (d, J= 6.9 Hz, 1H, 3'-OH), 4.14 (m, 1H, H-3'), 3.90 (m, 2H, H-2', H-4'), 3.74 (s, 6H), 3.62 (q, J= 6.9 Hz, 2H, OCH_2), 3.2 (m, 2H, H-5'), 1.14 (t, J= 6.9 Hz, 3H, CH_3). Anal. calcd. for $C_{32}H_{34}N_2O_8$: C, 66.89; H, 5.96; N, 4.87. Found: C, 66.72; H, 6.28; N, 4.62.

5'-O-(4,4'-Dimethoxytrityl)-3'-O-methyl-2,2'-O-anhydrouridine (5): Sodium hydride (60% in mineral oil, 53 mg, 1.2 eq) was added to a stirred solution of compound **2** (0.58 g, 1.1mmol) and dimethyl sulfate (208 ul, 2 eq) in acetonitrile (10 ml). After stirring at rt for 2 hr, the reaction was concentrated and the residue partitioned (2X) between dil. ammonium chloride and dichloromethane, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel eluting with 0-10% methanol/ ethyl acetate containing 1% triethylamine to afford, after evaporation, compound **5** (460 mg, 77%) as a white foam. ^{1}H NMR δ 7.92 (d, J= 7.2 Hz, 1H), 7.28-7.16 and 6.84 (m, 13H), 6.33 (d, J= 5.7 Hz, 1H, H-1'), 5.88 (d, J= 7.5 Hz, 1H), 5.40 (d, J= 6.6 Hz, 1H, H-2'), 4.31 (m, 1H, H-3'), 4.07 (m, 1H, H-4'), 3.73 (s, 6H), 3.34 (s, 1H), 2.95 and 2.85 (ABX, 2H). Anal. calcd. for $C_{31}H_{30}N_2O_7 \cdot 0.5\ H_2O$: C, 67.50; H, 5.66; N, 5.08. Found: C, 67.73; H, 5.88; N, 5.01.

5'-O-(4,4'-Dimethoxytrityl)-3'-O-methyl-arabinouridine (6): A mixture of compound **5** (410 mg, 0.76 mmol) and sodium methoxide (400 mg, 10 eq) in DMF (10 ml) was heated at 100 °C for 2 hr. The reaction was complete at this time but was left at rt overnight. The reaction was evaporated and the residue triturated with dichloromethane and the organic solution applied to a silica gel column which was eluted with 5-10% methanol/ dichloromethane containing 1% triethylamine to afford compound **6** as an off-white foam (350 mg, 82%). ^{1}H NMR δ 11.31 (s, 1H), 7.75 (d, J= 8.07 Hz, 1H), 7.43-7.23 and 6.90 (m, 13H), 5.93 (d, J= 4.2 Hz, 1H), 5.71 (br, 1H), 4.15 (m, 1H), 3.95 (m, 1H), 3.82 (m, 1H), 3.74 (s, 6H), 3.41 (s, 3H), 3.28 (m, 2H). Anal. calcd. for $C_{31}H_{32}N_2O_8 \cdot 0.5\ H_2O$: C, 65.37; H, 5.84; N, 4.92. Found: C, 65.74; H, 6.04; N, 4.87.

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15. 5'-O-Dimethoxytrityl-arabinouridine: ^{1}H NMR δ 11.4 (br, 1H), 7.42-7.22 and 6.90 (m, 14H), 5.76 (d, J= 1.47 Hz, 1H), 5.49 (d, J= 8.16, 1H), 4.31 (m, 1H), 4.16 (s, 1H), 3.73 (s, 6H), 3.68 (m, 1H), 3.24 (m, 2H)

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17. Obtained as an off-white foam: ^{1}H NMR δ 7.80 (d, J= 7.4 Hz,1H), 7.40-7.23 ano 6.91 (m, 15H), 5.84 (d, J= 2.4 Hz, 1H), 5.50 (d, J= 7.38 Hz, 1H), 5.15 (d, J= 7.1 Hz, 1H), 4.20 (m, 1H), 3.93 (m, 1H), 3.74 (s, 6H), 3.64 (m, 1H), 3.45 (s, 3H), 3.25 (m, 2H). Anal. Calcd. for $C_{31}H_{33}N_3O_7$: C, 66.53; H, 5.94; N, 7.51. Found: C, 66.09; H, 6.29; N, 7.26.

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