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THE DIRECT CONVERSION OF 5'-O-TRITYL-3'-KETO-2'-DEOXYTHYMIDINE TO 1-(2-DEOXY-3-METHYL-BETA-D-XYLOSYL)THYMINE

Thomas R. Webb
Genentech Inc.
Department of Molecular Biology
460 Point San Bruno Boulevard
South San Francisco, California 94080

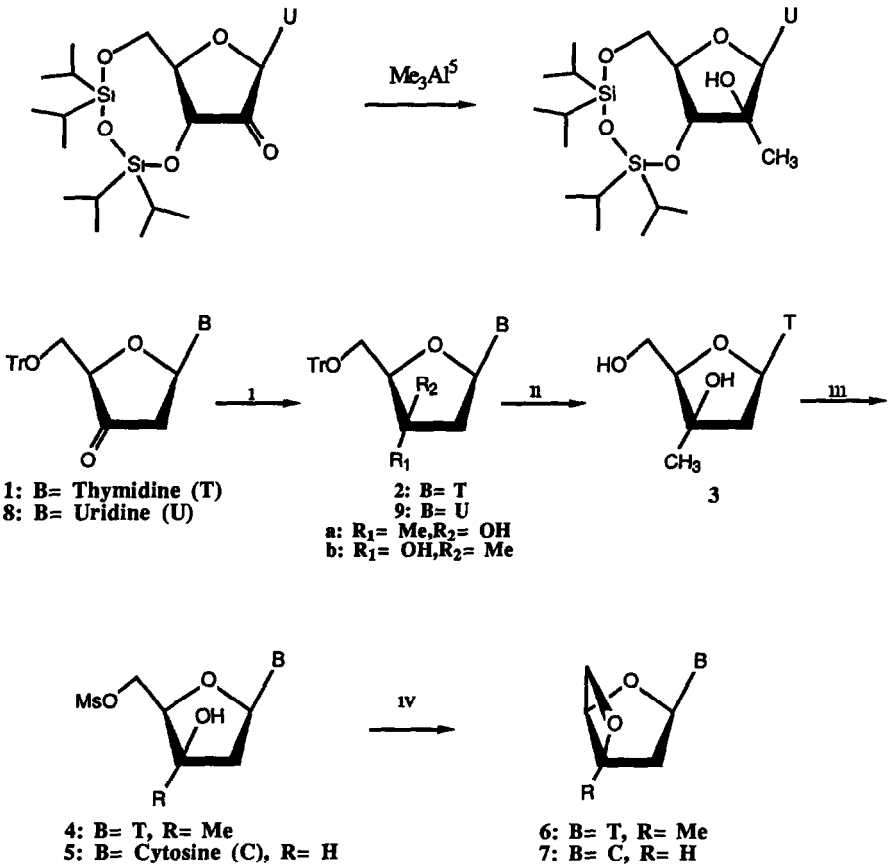
Abstract The first synthesis of 1-(2-deoxy-3-methyl-beta-D-xylosyl)thymine from the unstable 5'-O-trityl-3'-keto-2'-deoxythymidine via a novel organometallic reagent is reported The stereochemistry at the 3' position is conclusively determined by chemical means Some further transformations of the title product are described

Interest has recently been growing in the synthesis of new nucleoside analogs with potential anti-retroviral activity, due to the emergence of the acquired immunodeficiency syndrome as a significant medical problem [1] We have been interested in the development of new synthetic methods for the efficient synthesis of new 3'-substituted 2'-deoxynucleoside analogs. A potential starting material for the synthesis of these derivatives would be the ketone **1**.[2] This compound is however, notoriously unstable to acid and base promoted beta-elimination of thymine. For example, **1** is not stable to analytical thin-layer chromatography We attempted the addition of organometallic reagents such as MeMgCl or methyl lithium to **1** at -78° C in tetrahydrofuran. In these cases thymine could be isolated in high yield indicating that beta-elimination was the major or the exclusive reaction taking place. We observed the same results when **1** was treated with dimethylsulfonium methylide[3] or Tebbe's reagent[4], using the published conditions.

Based on the recent report of the addition of Me_3Al to 2',5'-O-di(t-butyldimethylsilyl)-3'-ketouridine or 3',5'-O-tetraisopropyldisiloxan-1,3-diyl-2'-ketouridine to give the corresponding alcohols in good yield,[5] we expected that Me_3Al could add to **1** to give the desired product **2**. The reaction of **1** with three equivalents of Me_3Al in dichloromethane at room temperature however, also gave thymine as the major product isolated, after aqueous work-up The same reaction when performed at -78° C, and allowed to slowly warm to room temperature, gave a 1.2 mixture respectively of thymine and **3** when analyzed by proton NMR. Under these conditions, **2** could not be detected in the crude reaction mixture This experiment showed that the trityl group was being removed by the Me_3Al under these conditions, which is consistent with the observation that

alkylaluminums are strong Lewis acids.[6] This experiment also showed that beta-elimination is a significant side reaction even when using Me_3Al, under these conditions

These results indicated that a highly nucleophilic, near neutral reagent would be needed to give a good yield of **2** from **1**. The fact that alkylaluminums react with alkyllithiums to form the non-acidic lithium tetraalkylaluminates,[6] suggests that MeMgCl would react with Me_3Al to give the less basic magnesium chlorotetramethylaluminate Indeed, when a solution of MeMgCl in tetrahydrofuran (THF) was treated with an equimolar amount of a solution of Me_3Al in toluene, an exothermic reaction took place When the resulting reagent was added to a solution of **1** in dichloromethane at -78° C and the reaction mixture allowed to warm to -40° C, only **2** and a trace of thymine were observed by TLC Aqueous work-up followed by chromatography gave **2** in 80% isolated yield. Thus the magnesium aluminate satisfies the special requirements of this system.



i= $MgAlMe_4Cl$ in CH_2Cl_2, ii= 80% AcOH/ H_2O, iii= MsCl/pyridine, iv= NaOH/EtOH/H_2O

It is notable that the reaction is stereospecific since only a single epimer is observed. Inspection of a molecular model (CPK) clearly shows that the least hindered face of **1** is the alpha face, leading to the prediction that **2a** would be the product observed in this reaction. In order to prove this supposition **2** was treated with mild acid to remove the trityl group, then allowed to react with mesyl chloride/pyridine to give the 5'-O-monomesylate **4**, selectively, in good yield. The mesylate **4** was treated with base, under conditions which are identical to the published conditions for the cyclization of the corresponding mesylate **5** to **7**.[7] Using these conditions **6** could be isolated in 85% yield. The formation of the oxetane ring could only occur if the stereochemistry of the 3'-hydroxyl was as indicated, therefore this reaction sequence proves conclusively the identity of **2** as **2a** and not **2b**

Previously a report has appeared claiming the synthesis of **9b** from 5'-O-trityl-2'-tosyluridine via the addition of MeMgI to *in situ* generated **8**.[8] The alcohol **9b** has the opposite configuration to that of **2a** at the 3' carbon The authors of this report propose that the 5' trityl group should selectively block the alpha face of **8** The only evidence given to support the authors assignment of this stereochemistry is the 0.3 ppm shift of the 4' proton, in the NMR spectum of the 3'-O-acetate of **9** [8] The authors propose that the observed shift is due to a through-space effect of the acetate on this proton On the basis of all of the above data, this literature assignment should be reconsidered. The observed product is in all likelihood **9a**.

In conclusion, ketone **1** has been shown to be a useful intermediate in the synthesis of branched-chain sugar nucleoside analogs. The magnesium halotetraalkylaluminates represent an interesting and useful class of organometallic reagents These reagents may be useful in the synthesis of other compounds related to **2a**. The alcohol **2a** should also be an useful intermediate for the synthesis of other nucleoside analogs with potential anti-retroviral activity.

Preparation of **2a**: A solution of 10ml of 3 M MeMgCl in THF (Aldrich) was added to 20 ml of 2 M Me_3Al in toluene (Aldrich) with stirring at 0°C (this solution forms a ppt on setting). A 20 ml portion of this mixture was added to a cooled solution (dry ice/acetone bath) of 2.1 g (4.3 mmol) of **1** in 100 ml of dry CH_2Cl_2, over a 10 minute period, with good stirring. The mixture was allowed to warm to 0°C over a 2h period (TLC,silica 5% MeOH/CH_2Cl_2 shows the reaction to be complete at -40°C) The colorless soln. was treated with 2 ml of acetone and allowed to warm to 20°C, then stirred with 100 ml of 5% aqueous sodium bicarbonate The phases are separated and the aqueous phase reextracted with 100 ml of CH_2Cl_2. The combined organic phase is extracted with water, then dried ($MgSO_4$) and concentrated. This gives 2.1 g of **2a**, which can be used as is for subsequent reactions or purified by silica chromatography (0-5% MeOH /CH_2Cl_2) to give 1 7 g (81%) of pure **2a**. ^1H NMR[9] ($CDCl_3$), 1 32 (s,3H,3'CH_3), 1.85 (s,3H,C5-CH_3), 2 26 (m,2H,H-2'), 3.62 (m,3H, H-4',5'), 6 12 (dd,1H,H-1' J = 2.9, 7 8), 7 32 (m,15H,Tr-H), 7.85 (s,1H,C6-H), 8 35 (s,1H,NH)

Preparation of **3** A soln of 250 mg of the crude **2a** in 15 ml of 80% acetic acid/water was allowed to set for 16 h at 20°C The crystalline trityl alcohol was removed by filtration and the filtrate was conc under vacuum. The product was purified by prep. TLC (10% MeOH/CH_2Cl_2, silica) to give 100 mg (78% yield from **1**) of the

amorphous diol **3**. ^{1}H NMR (D_2O); 1 32 (s,3H,3'CH_3), 1.79 (s,3H,C5-CH_3), 2 3 (m,2H,H-2'), 3.81 (m,3H, H-4',5'), 5.98 (dd,1H,H-1':J = 2 9, 7.8), 7.78 (s,1H,C6-H)

Preparation of **4**: A soln. of 100 mg (0.39 mmol) of **3** in a mixture of 20 ml of CH_2Cl_2 and 20 ml dry pyridine was treated with 0.1 ml (1.29 mmol) MsCl This soln was stirred for 2 h at 20° C, then 1 ml of water was added. The mixture was partitioned between 50 ml of CH_2Cl_2 and 100 ml 5% aqueous sodium bicarbonate The organic phase was dried ($MgSO_4$), concentrated and the residue purified by prep TLC (8% MeOH/CH_2Cl_2, silica). This gave 90 mg (69% yield) of **4**. ^{1}H NMR (CD_3CN), 1 37 (s,3H,3'CH_3), 1.84 (d,3H,C5-CH_3.J =1 2), 2.1 (m,2H,H-2'), 3 06 (s,3H,Ms-CH_3), 3.78 (s,1H,3'-OH), 3.90 (dd,1H,H-4'·J = 4.8, 5 7), 4 4 (m,2H,H-5'.J =2 2, 4.8), 5.98 (dd,1H,H-1'·J = 3 6, 8.1), 7.67 (d,1H,C6-H·J =1 2), 8.88 (bs,1H,NH).

Preparation of **6**. A soln. of 25 mg (0.074 mmol) of **4** in 3 ml of ethanol containing 0 7 ml of water and 0 3 ml of 1M aqueous NaOH was refluxed for 2 h This soln was allowed to cool, then taken to pH 9 with dilute acetic acid and concentrated to dryness. The residue was extracted with ethanol and purified by prep TLC (10% MeOH/CH_2Cl_2, silica) to give 15 mg (85%) of **6** ^{1}H NMR ($CDCl_3$), 1.68 (s,3H,3'CH_3), 1 95 (d,3H,C5-CH_3 J = 1 0), 2 45 (m,2H,H-2'), 4.10 (dd,1H,H-4':J = 1.2, 7 73), 4 62 (m,2H,H-5'), 6 68 (dd,1H,H-1' J = 3 8, 7 0), 8 03 (d,1H,C6-H:J =1 0), 8 80 (bs,1H,NH).

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References and Notes:

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9. All NMR data were recorded on 80 MHz IBM NR/80 spectrometer, and reported as ppm from TMS, except when D_2O was used as a solvent. In the latter case an external reference TMS = 0 00 was used. All new compounds have the expected elemental analysis, UV extinction coefficient and mass spectral fragmentation pattern.

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