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STEREOSPECIFIC SYNTHESIS OF 2'-DEOXY PYRIMIDINE AND 5,6-DIHYDRO 5-HYDROXY THYMIDINE NUCLEOSIDES

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Abstract: An economic and versatile synthesis of 2'-deoxy and 2',3'-dideoxy pyrimidine nucleosides is described. Readily available oxazoline **1** is condensed with glycidate **2** to give anhydro nucleoside **3**. This is converted to the title compounds following established routes. © 1997 Elsevier Science Ltd.

Sugar-modified nucleosides have assumed a major role in antiviral chemotherapy. The successful combination of AZT, ddC, d4T, and 3TC with HIV protease inhibitors[1] has increased the need for efficient and economic syntheses of these 2'-deoxy nucleosides.

Unlike the ribo-counterparts, the synthesis of 2'-deoxy nucleosides from 2-deoxyribofuranose leads to the formation of α,β-mixtures.[2] Efforts to improve stereoselectivity include the use of naturally occurring 2'-deoxynucleosides,[3] 2'- and 2',3'-deoxygenation of β-D-ribofuranonucleosides[4] and the use of 2'-α-phenylseleno[5] and 2'-α-phenylthio[6] functionalities to direct the formation of β-isomers.

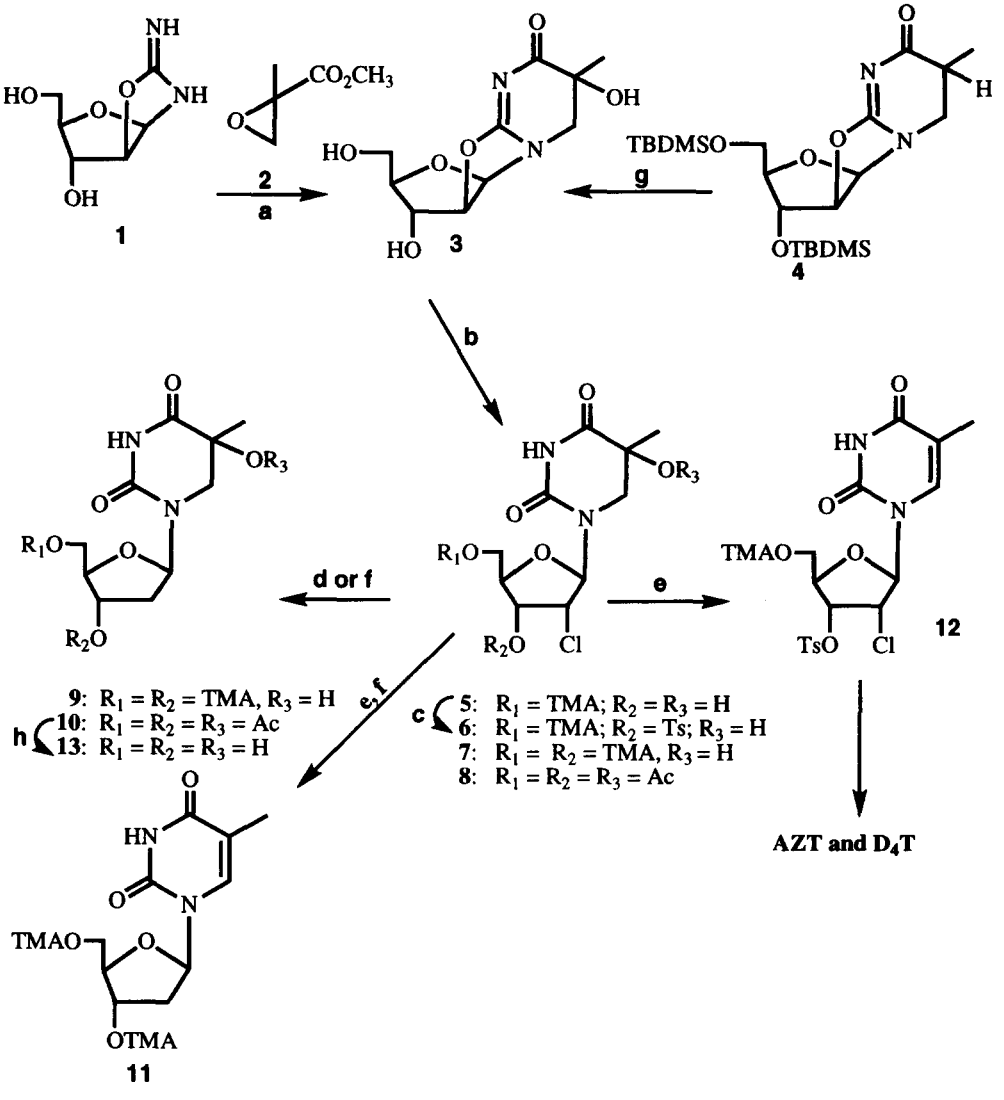
Sugar chirality has also been used to control the stereochemistry of the glycosidic bond. The 3-α- and 3-β-orientations in 2-deoxy-D-ribo-[7] and 2-deoxy-D-xylo-furanosides[8] have been used to control the delivery of the base. Similarly, the chirality at C-4 has been successfully employed for the exclusive formation of β-nucleosides.[9]

We have reported earlier the successful use of D-arabinose to prepare 2'-deoxy-pyrimidine nucleosides. Condensation of oxazoline **1** with methyl methacrylate led to 5,6-dihydrothymidines whose 3',5'-dicarboxylate esters upon oxidation with MnO_2 and DDQ produced less than optimal results in the former and undesirable chlorinated side products in the latter.[10,11] In this letter we report a short, economic, and versatile approach for the synthesis of the title compounds.

Unlike our earlier approaches, the oxidation step was avoided by starting with methyl α-methyl-glycidate **2**, yet another form of an oxidized methacrylate, which could be easily prepared by peracid oxidation of methyl methacrylate.[12] Condensation of oxazoline **1** with glycidate **2** in N,N-dimethyl acetamide furnished the 2,2'-anhydro compound **3** in 80% isolated yield. The reaction proceeded smoothly and, unlike recent reports,[8] produced only the β-isomer. Confirmation of the structure was derived from the conversion of **3** to known derivatives and by an independent synthesis from **4**.[10b] Treatment of **4** with *t*-butoxide[13] followed by bubbling molecular oxygen and subsequent quenching of the peroxide with trimethyl phosphite furnished a product with spectral properties identical to those of **3**.

Conversion of **3** to target compounds followed routine procedures. Treatment of **3** with trimethylacetyl chloride (TMACl) resulted in opening the 2,2'-anhydro bond as well acylation at the 5'-position. Monitoring the esterification reaction allows pereparation of either the mono- or the diester at the 5'- or 3',5'-positions (**5** and **7**), respectively. Reductive dehalogenation of **7** by catalytic

Scheme 1



a) DMA, 90 °C, 16h, 90%; b) TMACl, CH_3CN, 6h, 70%; or AcCl, CH_3CN, reflux, 2h, quant. for **8**; c) TsCl, pyr. rt, 24h, 71%; d) 10% Pd/C, H_2, quant.; e) $SOCl_2$, pyr., 0 °C, 70%; f) *n*-Bu_3SnH, AIBN, toluene, 2h, 90%; g) KOtBu, O_2, $P(OMe)_3$, DMF, 30%; h) $NaOCH_3$, MeOH, quant.

hydrogenation proceeded smoothly to furnish **9** in good yield. It is worth noting that the latter step obviates the need to use existing procedures to produce thymidine derivatives which either suffer the disadvantage of over reduction of the 5,6-double bond or the ecological hazards associated with the disposal of waste zinc metal used for reductive dechlorination. Chloro diester **7** was also easily converted to 3',5'-dipivaloyl thymidine **11** by successive 5,6-dehydration followed by *n*-Bu3SnH reductive dehalogenation at C2'.

The mono ester **5** could be converted to AZT and D4T without the intermediacy of thymidine. Tosylation of **5** gave **6** which was dehydrated to chlorothymidine **12**. Following published procedures, compound **12** can be converted to both AZT[14] and D4T.[4d]

Intermediate **3** was also converted to 5,6-dihydro-5-hydroxythymidine **13**, a compound used in studies aimed at exploring oxidative DNA strand scission.[15] Treatment of **3** with acetyl chloride resulted in opening the 2,2'-anhydro bond and acetylation of all three hydroxyl groups to give **8** in quantitative yields. Reductive dehalogenation with *n*-Bu3SnH followed by methoxide catalyzed deacetylation furnished **13** as a diastereomeric mixture. The ^{1}H NMR data for **13** matched reported literature values.[15,16]

In summary, a short and economic process has been developed for the stereospecific construction of β-D-2'-deoxy pyrimidine nucleosides and their 5,6-dihydro-5-hydroxy derivatives in gram quantities. The availability of chiral glycidate esters makes possible the synthesis of optically pure isomers of the latter compounds. Furthermore, starting with readily available L-arabinose, the preparation of L-enantiomers of the title compounds and studies of their biological activities become feasible.

Current efforts are aimed at further improvement of the process through combination of steps and optimizing yields. The preparation of hydroxylated analogs of clinically useful pyrimidines is also under investigation.

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16. All new compounds had correct elemental analyses. Representative ^{1}H NMR data follow:
3: (300 MHz, D_2O) 1.29 (s, 3H), 3.48-3.68 (m, 4H), 4.25-4.29 (m, 1H), 4.53-4.55 (m, 1H), 5.30 (d, J = 5.7 Hz, 1H), 6.01 (d, J = 5.7 Hz), 6.06 (d, J = 5.7 Hz), (1H).
5: (90 MHz, $CDCl_3$) 1.2 (s, 9H), 1.9 (s, 3H), 3.0 (bs, 2 H, D_2O exchangeable), 3.4 (AB quartet center, Δ_{AB} = 21 Hz, J_{AB} = 23 Hz, 2H), 4.0-4.5 (m, 5H) 6.0-6.2 (m, 1H), 8.8 (bs, 1H, D_2O exchangeable).
6: (90 MHz, $CDCl_3$) 1.3 (s, 9H), 1.5 (s, 3H), 2.8 (bs, 1H, D_2O exchangeable), 3.1-3.4 (m, 2H), 4.1-4.5 (m, 4H), 4.9-5.1 (m, 1H), 5.9 d, J =7.0 Hz, 1H) 7.4 (d, J = 7.0 Hz, 2H), 7.9 (d, J = 7.0 Hz, 2H), 8.4 (bs, 1H, D_2O exchangeable).
7: (300 MHz, $CDCl_3$) d 1.24 (s, 9H), 1.26 (s, 9H), 1.52 (s) 1.66 (s) (3H), 3.36 (AB quartet center, Δ_{AB} = 61.2 Hz, J_{AB} = 12.8 Hz, 2H), 4.16-4.49 (m, 5H, 1H D_2O exchangeable), 5.24 (dd, J = 5.9, 2.7 Hz, 1H), 6.09 (d, J = 7.3 Hz), 6.1 (d, J = 8.1 Hz) (1H), 8.68 (s) 8.84 (s) (1H, D_2O exchangeable).
8: (90 MHz, $CDCl_3$) 1.4-1.6 (m, 3H), 1.8-2.3 (m, 9H), 3.0-3.4 (m, 1H), 3.4-3.82 (m, 2H), 3.9-4.6 (m, 3H), 5.2 (d, J = 7Hz, 1H), 9 (bs, 1H, D_2O exchangeable).
10: (90 MHz, $CDCl_3$)1.6 (s, 3H), 2.1 (s, 11H), 3.0-3.33 (m, 1H), 3.4-3.8 (m, 1H), 3.8-4.5 (m, 3H), 4.8-5.3 (m, 1H), 6.0-6.4 (m, 1H), 8.6 (bs, 1H, D_2O exchangeable.
11: (90 MHz, $CDCl_3$) 1.3 (s, 18H), 1.7-2.6 (m, 5H), 3.9-4.5 (m, 3H), 5.0-5.2 (m, 1H), 6.1-6.3 (dt, 1H), 7.3 (s, 1H), 9.3 (bs, 1H).
13: (90 MHz, D_2O) 1.2 (s, 3H), 1.7-2.2 (m, 2H), 2.9-3.2 (m, 3H), 3.2-3.8 (m, 3H), 4.8-4.3 (m, 1H), 5.8-6.2 (m, 1H).

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