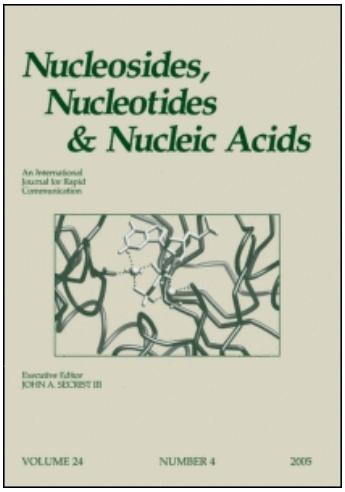

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Synthesis of 3'-4'-α-Propylene-2'-3'-dideoxynucleosides

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CHEMISTRY

SYNTHESIS OF 3',4'-α-PROPYLENE-2',3'-DIDEOXYNUCLEOSIDES

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Abstract *In order to obtain a high degree of rigidity within the sugar moiety of nucleosides, some bicyclic pyrimidine nucleoside analogues where synthesized starting from cyclopentanone. The C-4'-substituent is fused to the C-3'-position via a propylene to give a [3.3.0]-bicyclic ring system.*

Introduction

Over the last decade a large number of modified nucleosides have been synthesised that inhibit the replication of human immunodeficiency virus (HIV).[1] The majority of these compounds are metabolised, *in vivo*, to their corresponding 5'-triphosphates and are, as such, inhibitors of reverse transcriptase and/or chain terminators of viral DNA synthesis.

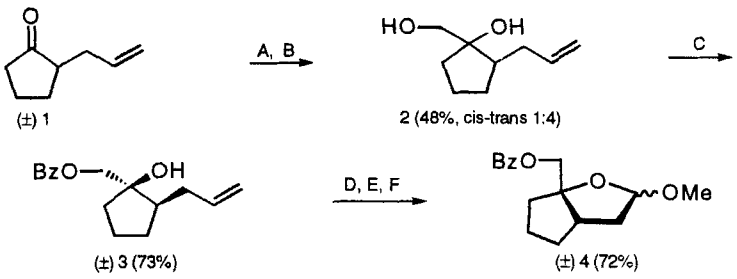
Due to the complexity of nucleoside analogue metabolism, a rationale for structure-activity relationships have been limited to, more or less, empirical generalisations. Analysis of the solid-state conformations of both inactive and active anti-HIV nucleoside analogues have been used in attempts to correlate conformational features with the relative activities of the compounds. Likewise, studies on nucleoside conformations in solutions have been performed using NMR-spectroscopy. In these studies, the flexibility of the sugar ring makes conclusions concerning anti-HIV activity based on conformational analysis very difficult. It has been suggested that a potentially useful strategy for the design of nucleoside analogues involved in metabolic processes could be to study conformationally restricted sugars.[2] In this work we present the synthesis of a bicyclic

pyrimidine nucleoside analogue in which the sugar ring, appended by a α-propylene substituent, is conformationally restricted.

The starting material, 2-(2-propenyl)cyclopentanone (**1**), was obtained from cyclopentanone and allyl alcohol.[3] The introduction of the hydroxymethyl group was achieved by the reaction of the ketone with isopropoxydimethylsilylmethylmagnesium chloride[4] in tetrahydrofuran at 0 °C followed by the treatment with potassium fluoride, potassium hydrogen carbonate and hydrogen peroxide in tetrahydrofuran-methanol to give racemic 1-(hydroxymethyl)-2-(2'-propenyl)-cyclopentanol (**2**) as a cis/trans mixture 1:4 in 48% yield. Alternatively, the hydroxymethyl equivalent was introduced using [(methoxymethoxy)methyl]tributylstannane[5] in tetrahydrofuran at -78 °C giving racemic 1-[(methoxymethoxy)methyl]-2-(2'-propenyl)-cyclopentanol in 60 % yield in a cis/trans ratio of 1:5. Although yields were more favourable using the stannane reagent, the limitations in the defined protecting group made the silyl Grignard reagent the more favourable. Benzoylation of the primary hydroxyl group using benzoyl chloride in pyridine gave **3** in 73% yield after separation of the cis isomer by column chromatography. Cis-hydroxylation of the olefinic bond in **3** using a catalytic amount of osmium tetraoxid and *N*-methylmorpholine-*N*-oxide as reoxidant[6] gave the corresponding diol which was cleaved using sodium periodate in aqueous tetrahydrofuran to produce an unstable furanose. Treatment of this furanose with methanol containing hydrochloric acid (2.5 %, w/w) readily produced the furanoside **4** as an enantiomeric mixture in 72% yield from **3**.

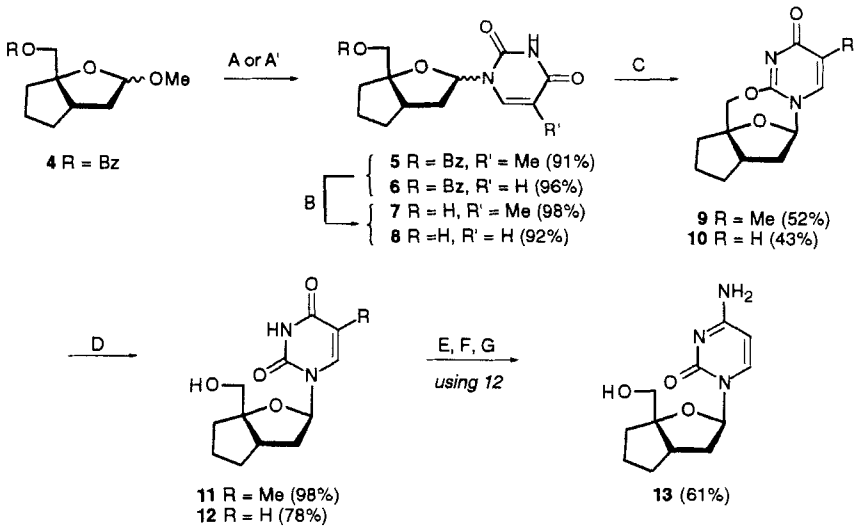
Glycosylation of **4** with bis(trimethylsilyl)thymine gave 1-[5'-*O*-benzoyl-3'-deoxy-3',4'-α-propano-α,β-D,L-*erythro*-pentofuranosyl]thymine (**5**) in 93% yield with an α/β ratio of 1:2.8. Glycosylation of **4** with bis(trimethylsilyl)uracil gave 1-[5'-*O*-benzoyl-2',3'-dideoxy-3',4'-α-propano-α,β-D,L-*erythro*-pentofuranosyl]uracil (**6**) in 96% yield with an α/β ratio of 1:1.2.

Separation of the two anomers by column chromatography or HPLC was unsuccessful and, as a consequence, separation was accomplished by chemical differentiation. Deprotection of the 5'-hydroxyl group in **5** and **6** by sodium methoxide in methanol gave compounds **7** and **8** in 98% and 92% yield, respectively. Converting the primary hydroxyl groups to the corresponding tosylate using *p*-toluenesulfonyl chloride in pyridine followed by refluxing in acetonitrile containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the 2-5'-anhydro compounds **9** and **10** in 52% and 43% yield, respectively. The 2-5'-anhydro compounds could easily be isolated by column chromatography. The anhydro compounds were hydrolysed using 2 M aqueous sodium hydroxide in dioxane to give the (+/-) form of 3'-deoxy-3',4'-α-propanothymidine (**11**) in 98% yield and the (+/-) form of 2',3'-dideoxy-3',4'-α-propanouridine (**12**) in 78%



A isopropoxydimethylsilylmethyl magnesium chloride, THF B: MeOH, THF, KF, $KHCO_3$, H_2O_2 C: BzCl, pyridine D:OsO_4, N-methylmorpholine N-oxide E: $NaIO_4$ F: HCl-MeOH

Scheme I



A: silylated thymine, CH_3CN/CH_2Cl_2, TBDMSOTf A': silylated uracil, CH_3CN/CH_2Cl_2, TMSOTf B: NaOMe C: DBU, CH_3CN, Δ D: NaOH, dioxan E: BzCl, pyridine F: triazole, $POCl_3$, Et_3N, CH_3CN G: Triazole, $POCl_3$, MeOH/NH_3

Scheme II

yield. (+/-) 2',3'-Dideoxy-3',4'-α-propanocytidine (**13**) was prepared, in 61% yield, by reacting the benzoylated **12** with triazole, phosphorus oxychloride and triethyl amine followed by methanolic ammonia at 40 °C (scheme II).[7]

Biological Results

Compounds **11**, **12** and **13** were tested in an *in vitro* assay[8] for HIV-1 RT inhibition and in a XTT assay for anti-HIV-1 cytopathic effects.[9] All compounds were found to be inactive in the assays.

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