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Synthesis of Novel Olefinic Carbocyclic Purine Nucleoside Analogues

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SYNTHESIS OF NOVEL OLEFINIC CARBOCYCLIC PURINE NUCLEOSIDE ANALOGUES

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Abstract: The synthesis of optically pure unsaturated carbocyclic nucleoside analogues is described. (3,4S)-Bis(t-butyldiphenyl silyloxymethyl)-1R and 1S cyclopent-2-en-1-ol were coupled with 6-chloropurine and 2-amino-6-chloropurine respectively, using a modified Mitsunobu reaction. The products were reacted further using standard procedures to give compounds 12, 14, 16 and 18.

Introduction

Carbocyclic nucleosides have emerged as a promising group of compounds for drug discovery in the antiviral field.^{1,2,3} Compounds such as cyclobut A (1) and carbovir (2) are active against human immunodeficiency virus (HIV)^{4,5} and (-) neoplanocin A (3) is active against certain RNA viruses.⁶ A special feature of these compounds is the absence of a glycosidic linkage which increases the metabolic stability against nucleoside phosphorylases and hydrolases, thereby prolonging their half-life *in vivo*.^{7,8} The comparatively higher lipophilicity of carbocyclic nucleosides is potentially beneficial for increasing oral availability and cell wall penetration.



As part of a program to evaluate structure-function relationships for anti-viral activity of hydroxymethyl substituted nucleoside analogues, we have synthezised 3'-hydroxymethyl substitued cyclopentcnyl nucleoside analogues **12**, **14**, **16** and **18**. These

derivatives can be viewed as structurally related to both cyclobut A (1), carbovir (2) and (-)neoplanocin A (3).



Results and Discussion

As starting material the enantiomerically pure (3R,4R)-bis(hydroxymethyl)cyclopentanone ketal $(4)^9$ was used. Reaction with *t*-butyldiphenylsilylchloride in dimethylformamide in the presense of imidazole gave **5** in 98% yield.¹⁰ The ketal was hydrolyzed using a catalytic amount of *p*-toluene sulfonic acid in dioxane-water giving ketone **6** in 92%. To introduce an olefinic bond between C-2 and C-3, compound **6** was reacted with lithium diisopropylamide and subsequently treated with phenylselenylbromide to give selenide **7** which was filtered through a pad of silica gel, concentrated and immediately reacted with hyrogen peroxide in dichloromethane to give 2,3-unsaturated ketone **8** in 72% yield from **6**.^{11,12} Selective reduction of ketone **8** was accomplished in 95% yield using sodium borohydride-cerium trichloride in methanol-dichloromethane.¹³ Separation of the diastereomers by column chromatography yielded the allylic alcohols **9** and **10** in 63% and 32% yield, respectively. Assignments of the configurations of **9** and **10** were based on ¹H-NMR characteristics; **9**: J(H-5 α -B)=12.1 Hz, J(H-5 α -H-1)=7.0 Hz, J(H-



i: tert-Butyldiphenylsilylchloride, imidazole, DMF: *ii*: pTsOH, dioxan, H₂O, 50 °C; *iii*: LDA, phenylselenylbromide, THF, -78 °C; *iv*: H₂O₂, CH₂Cl₂, 0 °C; *v*: NaBH4, CeCl₃ x 7 H₂O, MeOH, CH₂Cl₂



i: 6-Chloropurine, Ph3P-DIAD, THF, 0 °C; ii: NH3, MeOH, dioxan, 80 °C; iii: N(Bu)4F, THF; iv: 2-amino-6-chloropurine, Ph3P-DIAD, THF, 0 °C; v: 80% HCO2H, 80 °C then 25% NH4OH, MeOH

Scheme II

 5_{α} -H-4)=8.7 Hz, J(H-5_{\beta}-H-1)=0.7 Hz and J(H-5_{\beta}-H-4)=0.7 Hz; **10**: J(H-5_{\alpha}-\beta)=13.9 Hz, J(H-5_{\alpha}-H-1)=3.6 Hz, J(H-5_{\alpha}-H-4)=8.2 Hz, J(H-5_{\beta}-H-1)=7.1 Hz and J(H-5_{\beta}-H-4)=4.5 Hz. The stereo selectivity in the reduction can be rationalized from steric repulsion of the C-4 substituent which has a pseudo equatorial orientation making the α -side sterically more accessible.

For the base coupling experiments a modified Mitsunobu reaction with alcohols **9** and **10** using chloropurines produced the best results. *De novo* construction of the bases from the corresponding cyclopentenyl amines was unsuccessful due to instability of the allylic amines. Coupling of adenine or its sodium salt with corresponding cyclopentenyl acetates using various palladium(0) catalysts only produced desired products in low yields.

In the Mitsunobu reaction diisopropylazodicarboxylate (DIAD) and triphenylphosphine in THF were complexed at 0 °C. The mixture was cooled to -78 °C, the alcohol and the chloropurine were added and the temperature was slowly raised to 0 °C and left overnight. This gave after column chromatography compounds **11**, **13**, **15** and **17** in 62%, 57%, 58% and 58% yields, respectively. Further conversions of the base moiety and deprotection of the hydroxyls produced the target compounds **12**, **14**, **16** and **18**.

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