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A Novel and Efficient Synthesis of 9-(2-Hydroxyethyl)-7,11-dioxaspiro[5,5] Undecane Useful in the Preparation of Antiviral Acyclonucleosides#

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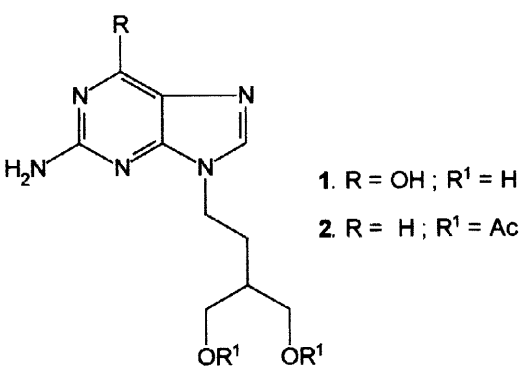
Abstract: An efficient four step route for the synthesis of 9-(2-hydroxyethyl)-7,11-dioxaspiro[5,5] undecane, an intermediate in the preparation of antiviral acyclonucleosides is described. The key transformations, ketalisation, hydroformylation and ring transformation are achieved through catalytic reactions.

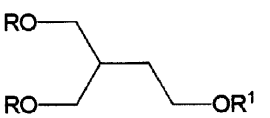
Key words: Antivirals; Hydroformylation; Nucleosides; ring transformation.

The acyclonucleosides [1,2] viz, Penciclovir **1** and Famciclovir **2** are potent antivirals used in the treatment of infections caused by herpes virus and HIV-1. Literature methods for the preparation of 2,2-dimethyl-5(2-hydroxyethyl)-1,3-dioxane **3**, required for 9-N-alkyl substitution of purines involve the reduction of 1,1,2-ethanetricarboxylic ester into 2-(hydroxymethyl)butane-1,4-diol **4** followed by ketalisation[3]. Alternatively, the intermediate **5** was prepared [4] by microbial hydrolysis of **6.**



1. R = OH ; R^1 = H

2. R = H ; R^1 = Ac



3. R = $(CH_3)_2C$; R^1 = H

4. R = H ; R^1 = H

5. R = Ac ; R^1 = H

6. R = R^1 = Ac

We report herein a new and an efficient synthesis of 9-(2-hydroxyethyl)-7,11-dioxaspiro[5,5]undecane **7**, an intermediate for the preparation of these important antiviral nucleosides. We accomplished the preparation of 9-hydroxymethyl-7,12-dixoaspiro[5,6] dodecane **10** starting from cyclohexanone and 2-butene-1,4-diol and rearranged it into **7** taking advantage of the rigidity and stability of the six-membered spiro-1,3-dioxane system, compared to the flexible seven-membered spiro-1,3-dioxepane.

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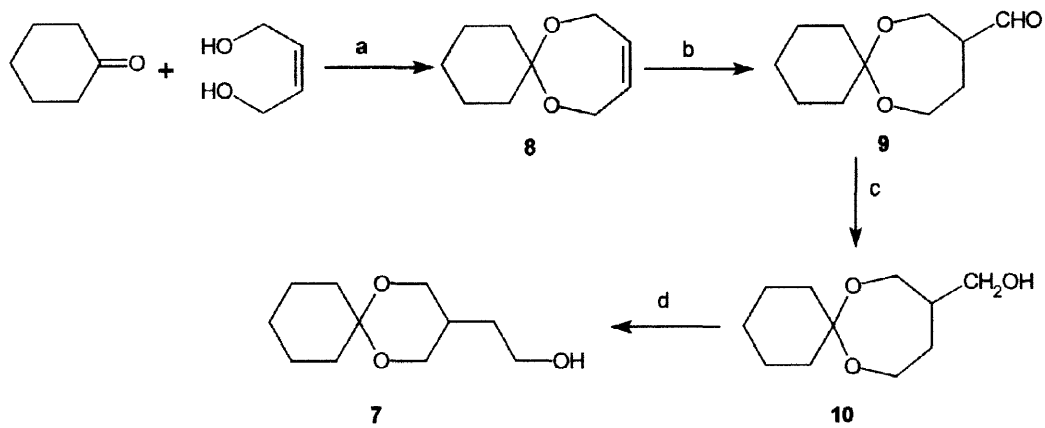

Scheme-I: a) SNCA, toluene, 12h. b) $RhH(CO)(TPP)_3$, CO/H_2,130 bar, 100°C, 4h. c) $NaBH_4$, MeOH,3h, 20°C. d) PTSA, benzene, 10°C, 5h.

The synthetic strategy **(Scheme-I)** consists of the preparation of 7,12-dioxaspiro[5,6]dodec-9-ene **8** in 95% yield starting from cyclohexanone and 2-butene-1,4-diol using a new reusable heterogeneous acid catalyst viz. sulphonated nitrocoal acid (SNCA) prepared by us [5]. Hydroformylation of **8** gave 9-formyl-7,12-dioxaspiro[5,6]dodecane **9** in 93% yield. 9-Hydroxymethyl-7,12-dioxaspiro[5,6]dodecane **10** obtained in 98% yield by $NaBH_4$ reduction of **9**, was rearranged using toluene p-sulphonic acid as catalyst into 9-(2-hydroxyethyl)-7,11-dioxaspiro[5,5]undecane **7** in 90% yield [6]. All the products were characterized by ^1H NMR, ^{13}C NMR, and MS. The ^{13}C NMR signals of carbons bearing oxygen clearly indicated the rearrangement of **10** (101.19, 63.35, 62.56, 59.36) into **7** (97.58, 63.42, 59.48). Compounds **7** and **10** prepared in 78% and 86% overall yields respectively were converted into the corresponding bromides using carbon tetrabromide/triphenyl phosphine or into their tosylates for reaction with purines according to the reported procedures [1,7] to obtain antiviral acyclonucleosides.

In conclusion, we have described the synthesis of novel compounds **7** and **10** in high yields starting from very common reactants through a four step route out of which three are catalytic. This methodology is much superior to the reported route to **3** wherein the selective ketalization itself was 41%. The intermediates **7** and **10** were used for N-alkyl substitution of purines in the synthesis of antiviral acyclonucleosides like penciclovir and famciclovir.

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