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# Allylic Alcohol Transpositions in the Carbohydrate Moiety of Pyrimidine Nucleosides.

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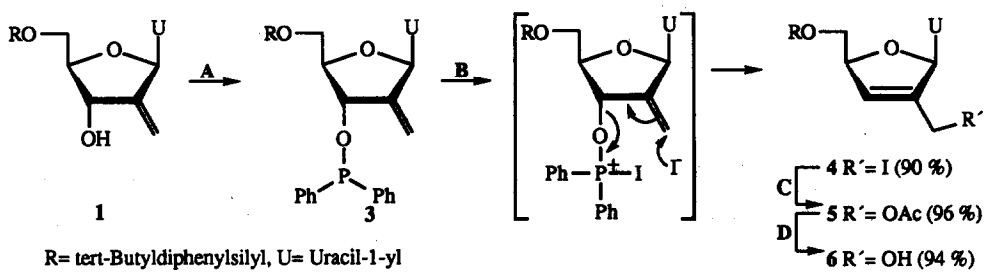
***ABSTRACT.*** *The reagent system chlorodiphenylphosphine, imidazole, and iodine, is shown to be useful in a novel transposition reaction of allylic alcohols to provide access to a new class of 2′,3′-unsaturated nucleoside analogues.*

The nucleosides 2′,3′-dideoxy-2′-*C*-hydroxymethylcytidine[1] and 2′,3′-dideoxy-3′-*C*-hydroxymethylcytidine[2] are reported to show respectively moderate and high anti-HIV activity *in vitro*. As the corresponding 2′,3′-didehydronucleosides would provide valuable insight to the SAR for hydroxymethylsubstituted nucleosides, we have investigated a synthesis for these types of compounds.

A retrosynthetic analysis reveals that an allylic alcohol transposition of **1** and **2** would provide an entry into this class of compounds.

The literature procedures[3] reported for these reaction sequences have inherent limitations when applied to nucleoside substrates *e.g.* requireing unsubstituted olefins,[4] acidic conditions,[5] heat[6] or oxidation-reductions.[7,8] We decided to explore a reagent system previously described for the conversion of primary and secondary hydroxyls to iodides or bromides using chlorodiphenylphosphine, imidazole and iodine or bromine,[9,10] anticipating to carry through an allylic alcohol transposition in three steps as depicted in *Scheme 1*.

Indeed this turned out to work very smoothly with the uridine derivatives **1** and **2** as model compounds. Compound **1**[11] was reacted (*Scheme 1*) with 1.2 equiv. chlorodiphenylphosphine (freshly distilled) and 2.1 equiv. imidazole in toluene-acetonitrile (2:1) at 0 °C under nitrogen. After 2 min, TLC indicated complete conversion of the alcohol **1** to the phosphinate **3** (not isolated).



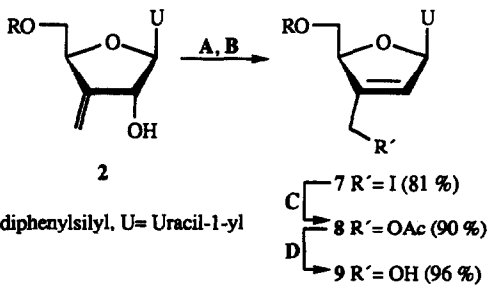

1 3

R= tert-Butyldiphenylsilyl, U= Uracil-1-yl

*Scheme 1.* **A.** $Ph_2PCl$, imidazole, toluene-acetonitrile (2:1), °0 C. **B.** $I_2$ in toluene-acetonitrile (2:1). C. $N(Bu)_4OAc$, $CH_2Cl_2$. **D.** MeOH sat. with $NH_3$.

Addition of 1.2 equiv. iodine dissolved in toluene-acetonitrile (2:1) resulted, after 5 min., in a $S_N2'$ reaction to give **4** in 90 % yield.Reacting **4** with 1.1 equiv. tetrabutylammonium acetate[12] in methylene chloride gave **5** in 96 % yield. De-*O*-acetylation of **6** in methanol saturated with ammonia gave 1-(5-*O*-tert-butyldiphenylsilyl-2,3-didehydro-2,3-dideoxy-2-*C*-hydroxymethyl-β-D-*glycero*-pentofuranosyl)uracil (**6**)[13] in 94 % yield (81 % from **1**).

When **2**[11] was reacted (*Scheme 2*) using the same reaction conditions (*vide supra*) except that 1.2 equiv. imidazole was used and with methylene chloride as solvent, the $S_N2'$ reaction took 2 hours giving **7** in 81 % yield. Compound **8** was obtained in 90 % yield and 1-(5-*O*-tert-butyldiphenylsilyl-2,3-didehydro-2,3-dideoxy-3-*C*-hydroxymethyl-β-D-*glycero*-pentofuranosyl)uracil (**9**)[14] in 96 % yield (70 % from **2**).




*Scheme 2.* **A.** $Ph_2PCl$, imidazole, $CH_2Cl_2$, °0 C. **B.** $I_2$ in $CH_2Cl_2$. **C.** $N(Bu)_4OAc$, $CH_2Cl_2$. **D.** MeOH sat. with $NH_3$.

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13. **6.** $^{13}C$ NMR ($CDCl_3$, 25 °C) δ 19.3 (C-tert), 27.0 (3 x $CH_3$), 59.9 (C-6'), 65.2 (C-5'), 86.4 (C-4'), 89.6 (C-1'), 102.6 (C-5), 127.9-141.1 (8 x ArC, C-2', C-3', C-6), 151.4 (C-4), 164.2 (C-2); $^1H$ NMR ($CDCl_3$, 25 °C) δ 1.06 (s, 9 H, 3 x $CH_3$), 3.88 (m, 2H, H-5', H-5''), 4.21 (m, 2H, H-6', H-6''), 4.85 (m, 1H, H-4'), 5.21 (d, *J*= 8.06 Hz, 1H, H-5), 6.07 (m, 1H, H-1'), 6.99 (m, 1H, H-3'), 7.34-7.65 (m, 10H, ArH), 7.68 (d, *J*= 8.06 Hz, 1H, H-6), 10.21 (s, 1H, H-3).
14. **9.** $^{13}C$ NMR ($CDCl_3$, 25 °C) δ 19.4 (C-tert), 27.1 (3 x $CH_3$), 58.5 (C-6'), 64.3 (C-5'), 86.2 (C-4'), 88.6 (C-1'), 102.65 (C-5), 121.0-148.4 (8 x ArC, C-2', C-3', C-6), 150.6 (C-4), 163.1 (C-2); $^1H$ NMR ($CDCl_3$, 25 °C) δ 1.11 (s, 9 H, 3 x $CH_3$), 3.97 (m, 2H, H-5', H-5''), 4.43 (m, 2H, H-6', H-6''), 4.85 (m, 1H, H-4'), 5.26 (d, *J*= 8.06 Hz, 1H, H-5), 5.77 (m, 1H, H-1'), 6.98 (m, 1H, H-2'), 7.36-7.73 (m, 11H, ArH, H-6), 8.84 (s, 1H, H-3).

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