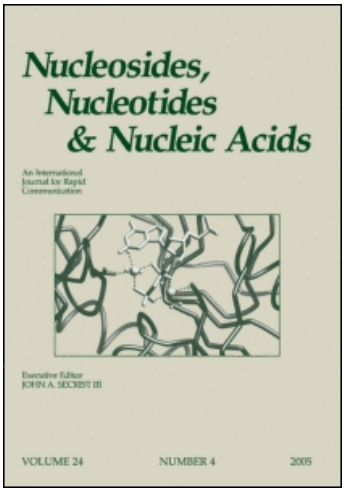

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Synthesis of Homo-C-D4T and Homo-C-Thymidine

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SYNTHESIS OF HOMO-C-D4T AND HOMO-C-THYMIDINE

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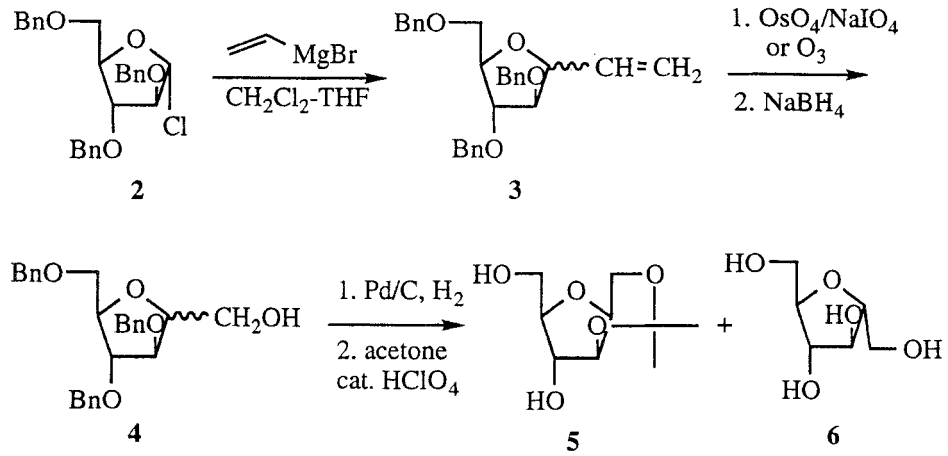
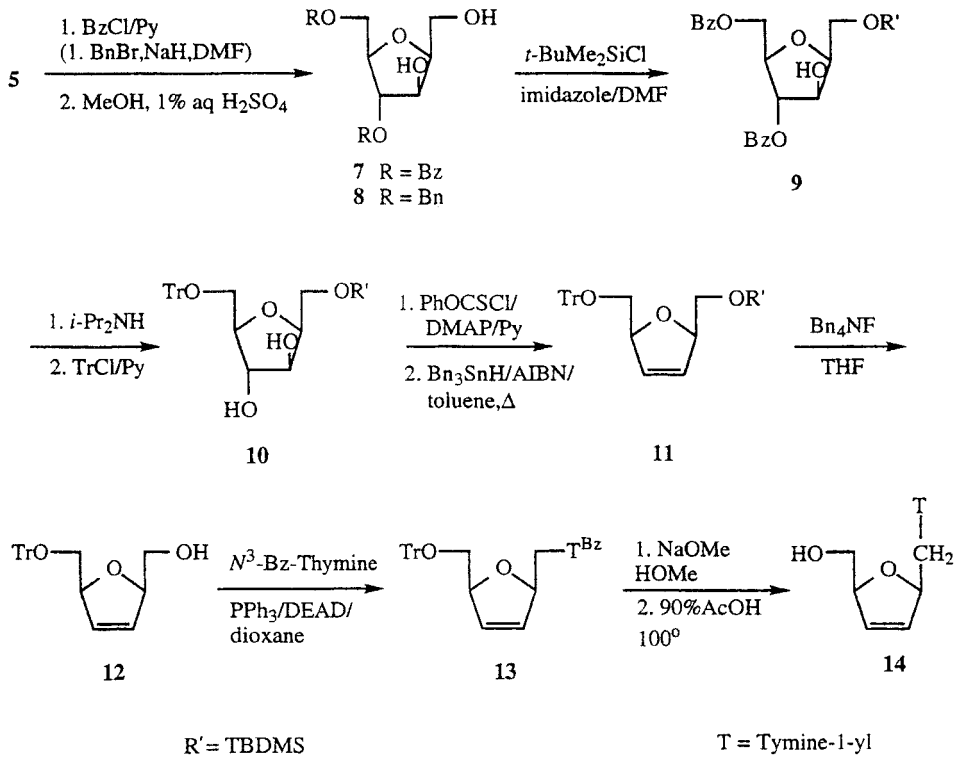
ABSTRACT: ß-C-Vinyl glycoside of D-arabinofuranose was converted to the β-C-hydroxymethyl glycoside **12** which was condensed with N-3-benzoyl thymine under Mitsunobu conditions to furnish homo-C-analog **14** of the 2',3'-dideoxy-2',3'-didehydrothymidine (D4T). Synthesis of the homo-C-thymidine **18** was accomplished by the same procedure from compound **15**.

Synthesis of C-glycosyl compounds received much attention as evidenced by recent books and review articles[1-5] . Intentions of researchers were to obtain the C-glycosyl analogs of naturally occuring substances with a hope to alter a spectrum of their biological activities. In this line of thinking a synthesis of the homo-C-analog **14** of 2',3'-dideoxy-2',3'-didehydrothymidine is described here; synthesis of homo-C-thymidine **18** is also presented.

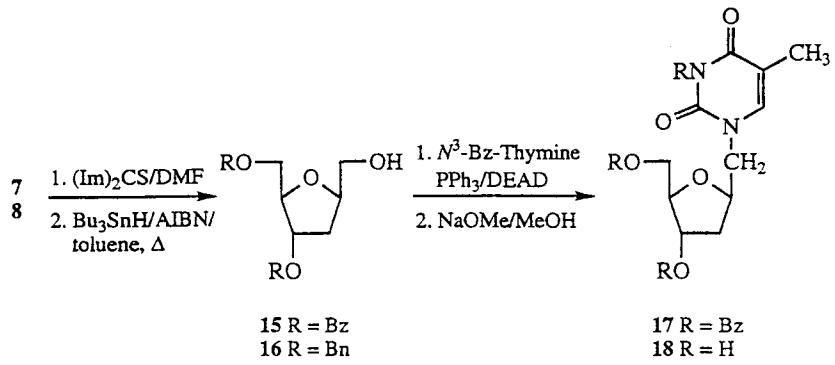
Unstable chloride **2** (predominantly α[6], prepared from α,ß-p-nitrobenzoyl-2,3,5-tri-O-benzylarabinofuranose **1**) was reacted with vinylmagnesium bromide to furnish unseparable C-vinyl-arabinofuranosides **3** in 79% yield (SCHEME 1). Without characterization **3** were converted to hydroxymethyl derivatives **4** by action of OsO_4 -$NaJO_4$ or ozone and $NaBH_4$. Catalytic hydrogenation followed by acetonation furnished pure ß anomer **5** since α anomer **6** is unable to react with acetone.Yield of **5** was 38% counted on **1**. The same acetonide **5** can be prepared by acid catalyzed dehydration of mannitol[7] or 1,6-dibenzoylmannitol[8] and isopropylidenation. **5** was used to synthesize 2'-deoxyshowdomycin[9], L-muscarine[10] and some degradation products of arachidonic acid and antibiotics.[11]



SCHEME 1



SCHEME 2



SCHEME 3

Acetonide **5** was converted to diol **10** via benzoylation and deacetalation (to **7**), selective silylation of the primary hydroxyl group (to **9**), debenzoylation and tritylation (SCHEME 2). Conversion[12] to olefin **11** and desilylation furnished primary alcohol **12**. This was coupled with N-3-benzoylthymine[13] under Mitsunobu conditions to give **13**. Due to difficulties of its purification, **13** was deprotected without characterization to furnish homo-C-analog**14** of the anti-AIDS drug D4T[14] , in 44% yield for three steps. Nucleoside **14** is the first example of such group of compounds.

Synthesis of homo-C-thymidine **18** was also accomplished from diol **7**. Reaction with thiocarbonyldiimidazole followed by reduction with Bu_3SnH/AIBN afforted primary alcohol **15** in cumulative yield 26% (ca twice less than published [9]), SCHEME 3. Dibenzyl derivative **8** gave alcohol **16** in still smaller yield. **15** was condensed with benzoylthymine as described for **13** to furnish **17** (67%). Debenzoylation yielded homo-C-thymidine **18**.

Further work on synthesis of analogs of nucleosides having two and three methylene groups linkers based on C-vinyl and C-allyl glycosides will be published in due course.

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