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## Nucleosides, Nucleotides and Nucleic Acids

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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

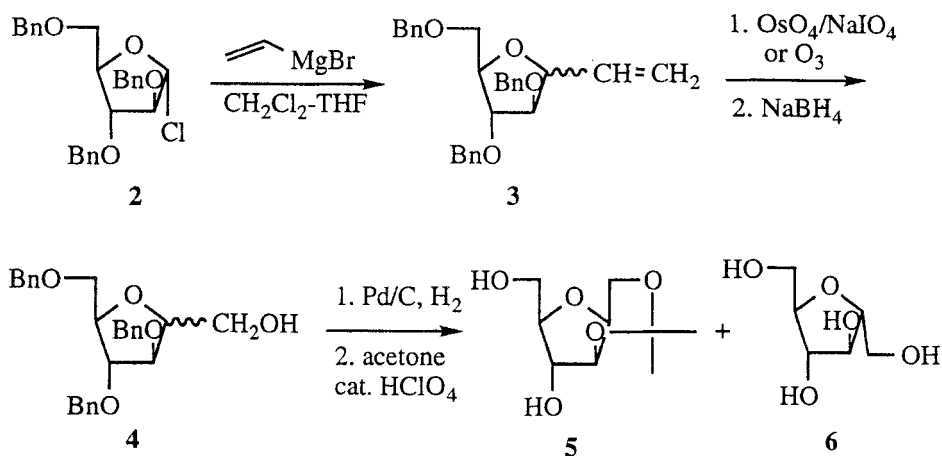
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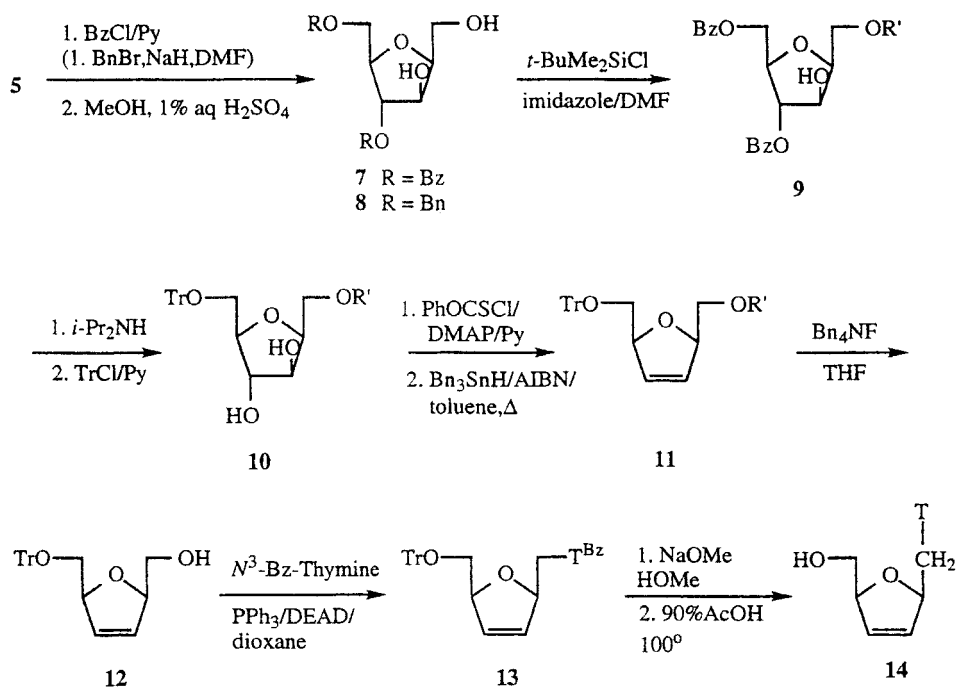
**ABSTRACT:**  $\beta$ -C-Vinyl glycoside of D-arabinofuranose was converted to the  $\beta$ -C-hydroxymethyl glycoside **12** which was condensed with N-3-benzoyl thymine under Mitsunobu conditions to furnish homo-C-analog **14** of the 2',3'-dideoxy-2',3'-didehydrothymidine (D4T). Synthesis of the 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<sup>1-5</sup>. Intentions of researchers were to obtain the C-glycosyl analogs of naturally occurring 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.

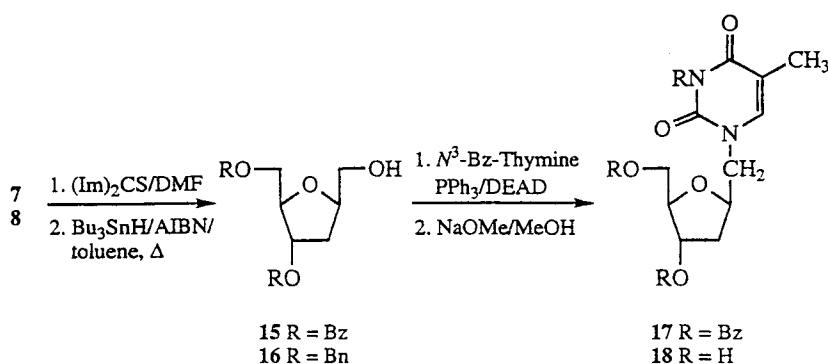
Unstable chloride **2** (predominantly  $\alpha$ <sup>6</sup>, prepared from  $\alpha,\beta$ -p-nitrobenzoyl-2,3,5-tri-O-benzylarabinofuranose **1**) was reacted with vinylmagnesium bromide to furnish unseparable C-vinyl-arabinofuranosides **3** in 79% yield (SCHEME 1). Without characterization **3** were converted to hydroxymethyl derivatives **4** by action of OsO<sub>4</sub>-NaJO<sub>4</sub> or ozone and NaBH<sub>4</sub>. Catalytic hydrogenation followed by acetonation furnished pure  $\beta$  anomer **5** since  $\alpha$  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<sup>7</sup> or 1,6-dibenzoylmannitol<sup>8</sup> and isopropylidenation. **5** was used to synthesize 2'-deoxyshowdomycin<sup>9</sup>, L-muscarine<sup>10</sup> and some degradation products of arachidonic acid and antibiotics.<sup>11</sup>



SCHEME 1

 $\text{R}' = \text{TBDMS}$  $\text{T} = \text{Thymine-1-yl}$ 

SCHEME 2



SCHEME 3

Acetonide **5** was converted to diol **10** via benzylation and deacetalation (to **7**), selective silylation of the primary hydroxyl group (to **9**), debenzylation and tritylation (SCHEME 2). Conversion<sup>12</sup> to olefin **11** and desilylation furnished primary alcohol **12**. This was coupled with *N*-3-benzoylthymine<sup>13</sup> 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<sup>14</sup>, 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  $\text{Bu}_3\text{SnH/AIBN}$  afforded primary alcohol **15** in cumulative yield 26% (ca twice less than published<sup>9</sup>), 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%). Debenzylation 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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Financial support of the Brazilian National Research Council (CNPq) via grant 409211-88 is appreciated.

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