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Synthesis of 2-deoxy ribose related disaccharide nucleoside and its phosphoramidite

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ABSTRACT

Synthesis of impurity reference compound of anti-tumor drug ISIS 183750 was achieved. In this process, a general method for synthesis of 2-deoxy ribosyl disaccharide nucleosides was established for the first time.

More than hundred disaccharide nucleosides have been isolated from various natural sources.[1] They display antibacterial, antimycotic, herbicidal, insecticidal, antitumor, and antiviral properties,[2] are structural elements of biopolymers, such as tRNA and poly(ADP-ribose),[3] and can be formed during nucleoside metabolism.[4] Recent studies indicated some disaccharide analogues of thymidine were potential inhibitors of PARPs, which are considered to be promising targets in designing drugs for the treatment of stroke, ischemia, diabetes, arthritis, colitis, cancer, viruses and other inflammatory disorders.[5] Most antiviral drugs are derivatives of nucleosides or nucleotides, anchoring one or two carbohydrate moieties on their sugar portion may increase the activity in comparison with the original drugs.[6] Therefore, disaccharide nucleoside synthesis methods are expected to have wide-spread applications in drug discovery.

Many strategies were developed for the synthesis of disaccharides nucleosides by using aldohexoses and pentose.[7] As a component of DNA, 2-deoxyribose derivatives have an important role in biology. The DNA (deoxyribonucleic acid) molecule, which is the main repository of genetic information in life, consists of a long chain of deoxyribose-containing units called nucleotides, linked via phosphate groups. However, 2-deoxy ribose related disaccharide nucleosides have not reported yet.

Compound **1** is an impurity found in the production of ISIS183750, which is a synthetic oligomer of 20 nucleotides that are connected sequentially by phosphorothioate linkages and a second-generation antisense oligonucleotide drug for advanced lung cancer,[8] and it is needed as a reference compound. In this paper, we would like to report its synthesis while establishing a strategy for synthesizing the 2-deoxy ribose related disaccharide nucleosides and their phosphoramidites.

The central portion of the oligonucleotide ISIS 183750 is composed of ten 2′-deoxynucleotides, and synthesized by introducing DNA or MOE monomers sequentially on solid support, the disaccharide nucleoside phosphoramidite **1** was likely formed during the glycosylation and phosphorylation stages of the monomer synthesis.

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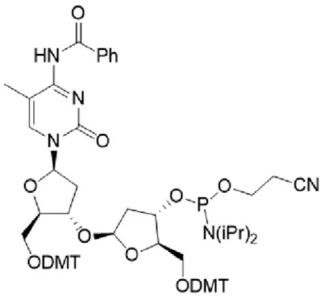

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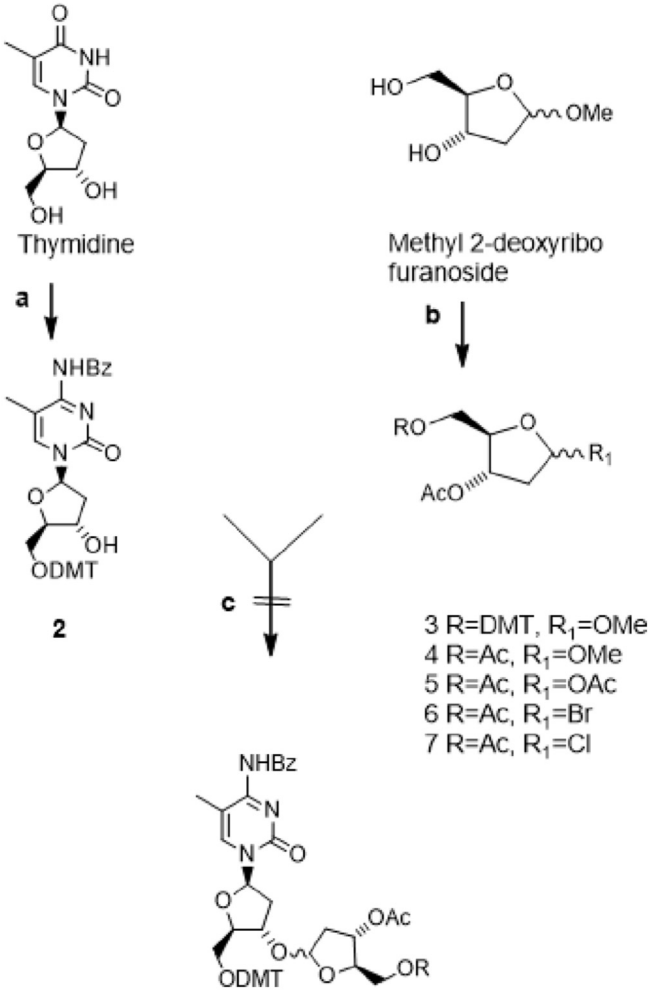
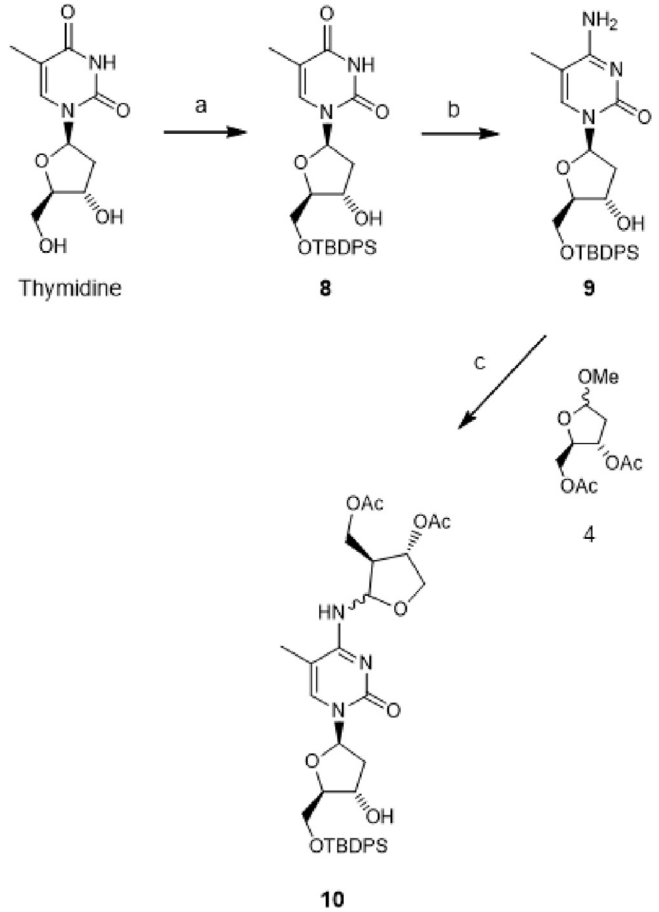
Current reports for the synthesis of disaccharide nucleosides may be classified into two methods. In the first method, N-glycosylation of properly protected disaccharide with a heterocyclic base is employed and this method is not high yielding as disaccharide glycosylation donors are not very stable.[9] The second method involves coupling reaction between a nucleoside and a properly protected monosaccharide donor.[10] As our target compound **1** contains a natural nucleoside, direct glycosylation of the properly protected thymidine **2** with a *p*-dimethoxytrityl (DMT) protected monosaccharide donor **3** under classic glycosylation conditions was considered first as shown in Scheme 1.

The desired cytidine acceptor **2** was synthesized in standard fashion starting from commercially available thymidine, after sequentially treating it with $TMSCl/Et_3N$, triazol/$POCl_3$, NH_3/H_2O and DMT-Cl. Protection of the 5-OH of methyl 2-deoxyribofuranoside with DMT group, followed by acetylation, gave the monosaccharide glycosylation donor **3**. The glycosylation between compounds **2** and **3** was attempted under standard conditions which resulted in a complicate mixture of products. After work up and careful purification, no desired disaccharide nucleoside was isolated. Similarly, we also tried other monosaccharide donors **4**, **5**, **6** and **7** under different glycosylation conditions, the results were same. This may be due to the DMT protecting groups in compounds **2** and **3** which are not stable under the attempted glycosylation conditions, and based on the LCMS analysis, only trace amount of disaccharide without DMT protecting group was detected. Hence, it's felt we should employ protecting groups stable under acidic conditions, such as *t*-butyldiphenylsilyl ether (TBDPS).

Accordingly, thymidine was protected with TBDPS at 5′−OH position to provide the compound **8**, and in three steps, thymidine



Scheme 1. Regents and Conditions: a) 1: DMTCl, DMF, DMAP (2 eq.), room temperature, 3 h; 2: $TMSCl/Et_3N$, triazol/$POCl_3$, NH_3/H_2O; 3: Bz_2O, DMF, 85%; 4: K_2CO_3, THF/MeOH, room temperature, 3 h, 90%; b) for compound **3**, 1: methyl 2-deoxyribofuranoside, DMTCl, DMF, DMAP (2 eq.), room temperature, 4 h; 2: $(Ac)_2O$, pyridine, 0 °C, 4 h, 85% for two steps; for compound **4**: methyl 2-deoxyfuranoside, Ac_2O, pyridine, 90%; for compound **5**: methyl 2-deoxyribofuranoside, H_2SO_4, Ac_2O, 0 °C, 63%; for compound **6**: compound **5** in HBr/AcOH, 0 °C, 30 min., 95%; for compound **7**: compound **5**, CH_2Cl_2 (HCl), 0 °C, 2 h, 85%; c) for compounds **3**, **4** and **5**: compound **2**, compound **3**, or **4**, or **5** CH_2Cl_2, 0 °C, $SnCl_4$, 2 h; for compounds **6** and **7**: compound **2**, compound **6** or **7,** CH_2Cl_2, 0 °C, Ag_2CO_3, dark, 3 h.



Scheme 2. Reagents and Conditions: a) TBDPSCl, pyridine, 90%; b) $TMSCl/Et_3N$, triazol/$POCl_3$, NH_3/H_2O; 85%; c) CH_2Cl_2, 0 °C, $SnCl_4$, 2 h.