

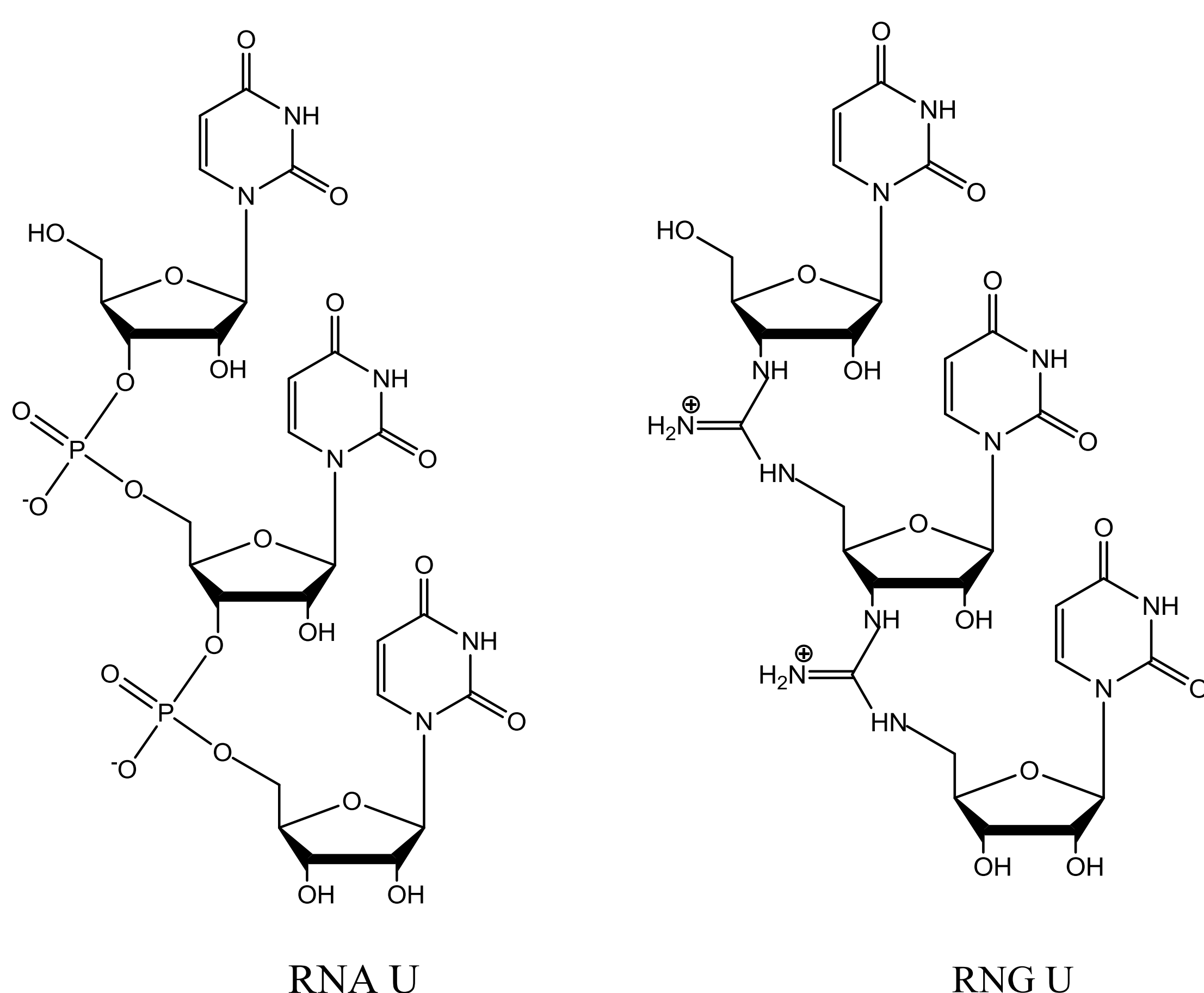


Solid-phase synthesis of positively charged uridyl ribonucleic guanidine (RNG U)

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Introduction

Synthetic oligonucleotides have been investigated for inhibition of gene expression by either antisense or RNAi mechanisms. Several nucleic acid drugs are at different stages of clinical trial for treatment of cancer and viral diseases. Replacement of the negatively charged phosphodiester linkages of RNA with positively charged guanidium linkages provides the polycationic ribonucleic acid guanidine (RNG). Key goals in the design of such agents include increasing the binding affinity while maintaining the sequence specific, resistance to degradation by cellular nucleases, and increased membrane permeability. Synthesis of 3'-end, middle, and 5'-end monomers is required for the synthesis of an RNG. In this work we described some steps needed for the synthesis of the 5'-end monomer.



Methodology

All chemical reactions were carried out under nitrogen atmosphere and in anhydrous solvents. After the reactions were completed, **Rota-vapor** was used to remove solvents, and **TLC** was used to determine the purity of our compound. **Column chromatography** was performed to purify and isolate our product. The chemical structure was then confirmed by **NMR spectroscopy**.



Performing column chromatography: Cynthia Rodriguez, Andrew Mahler and Ismael Espinoza

Results

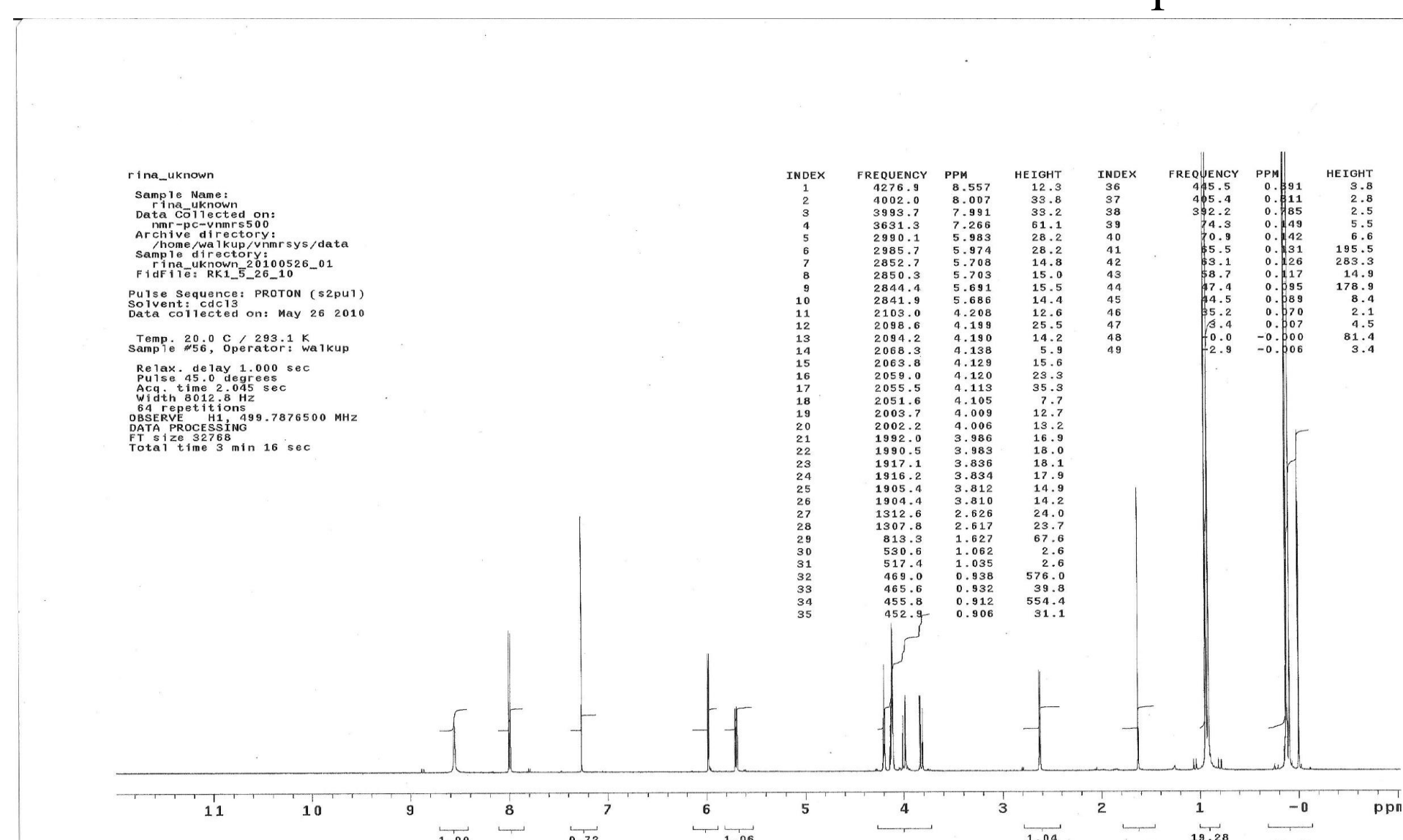
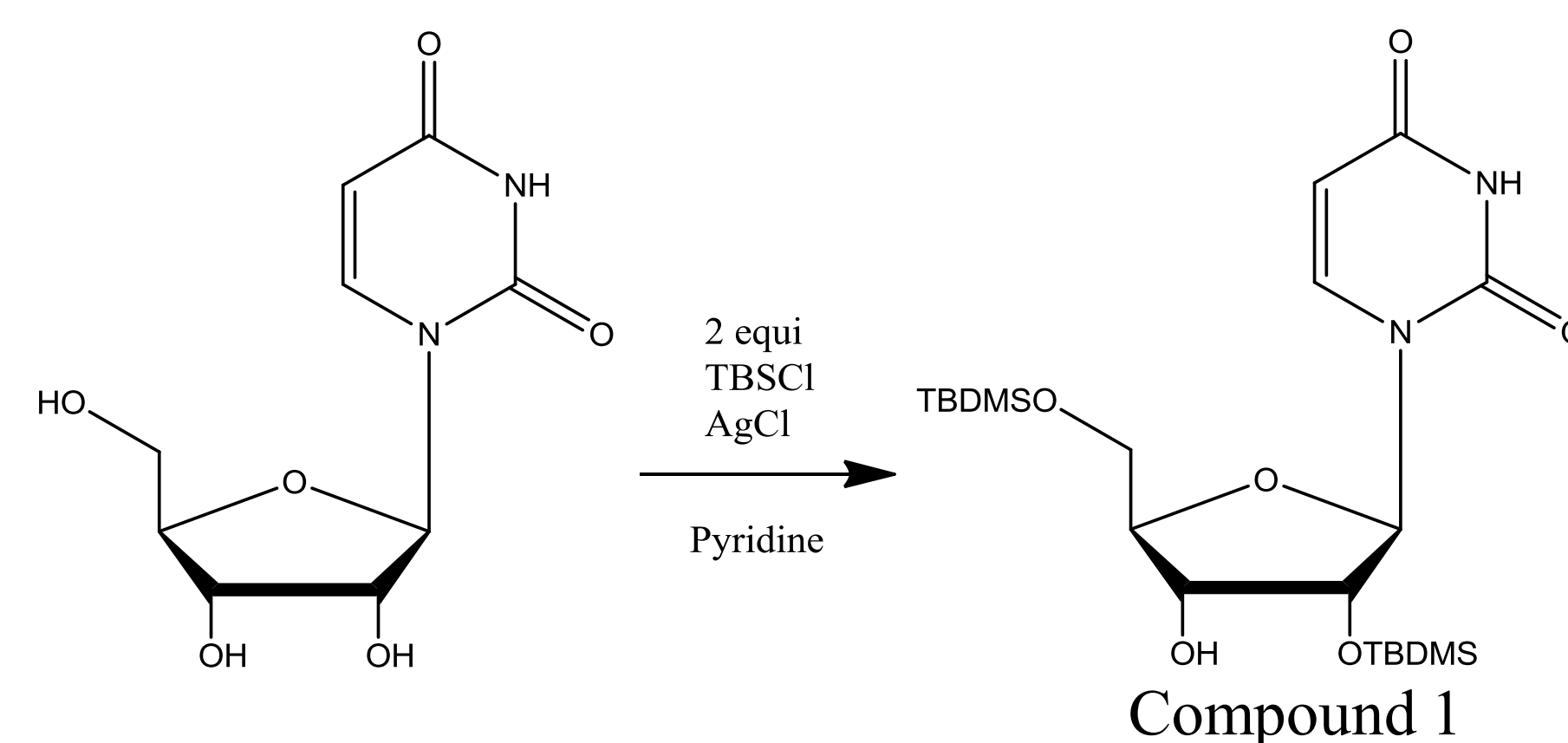


Figure 1: ¹H NMR for compound 1

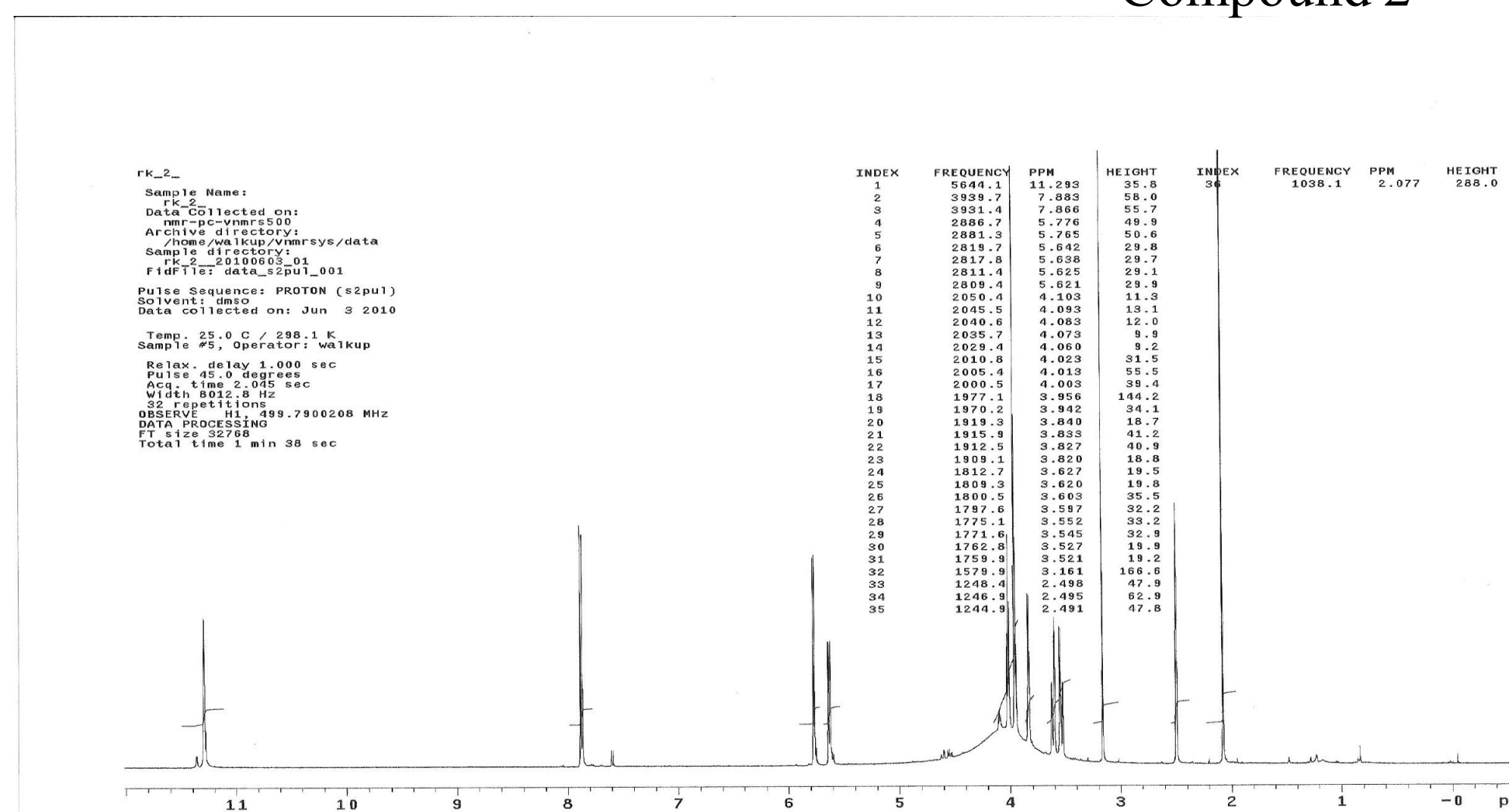
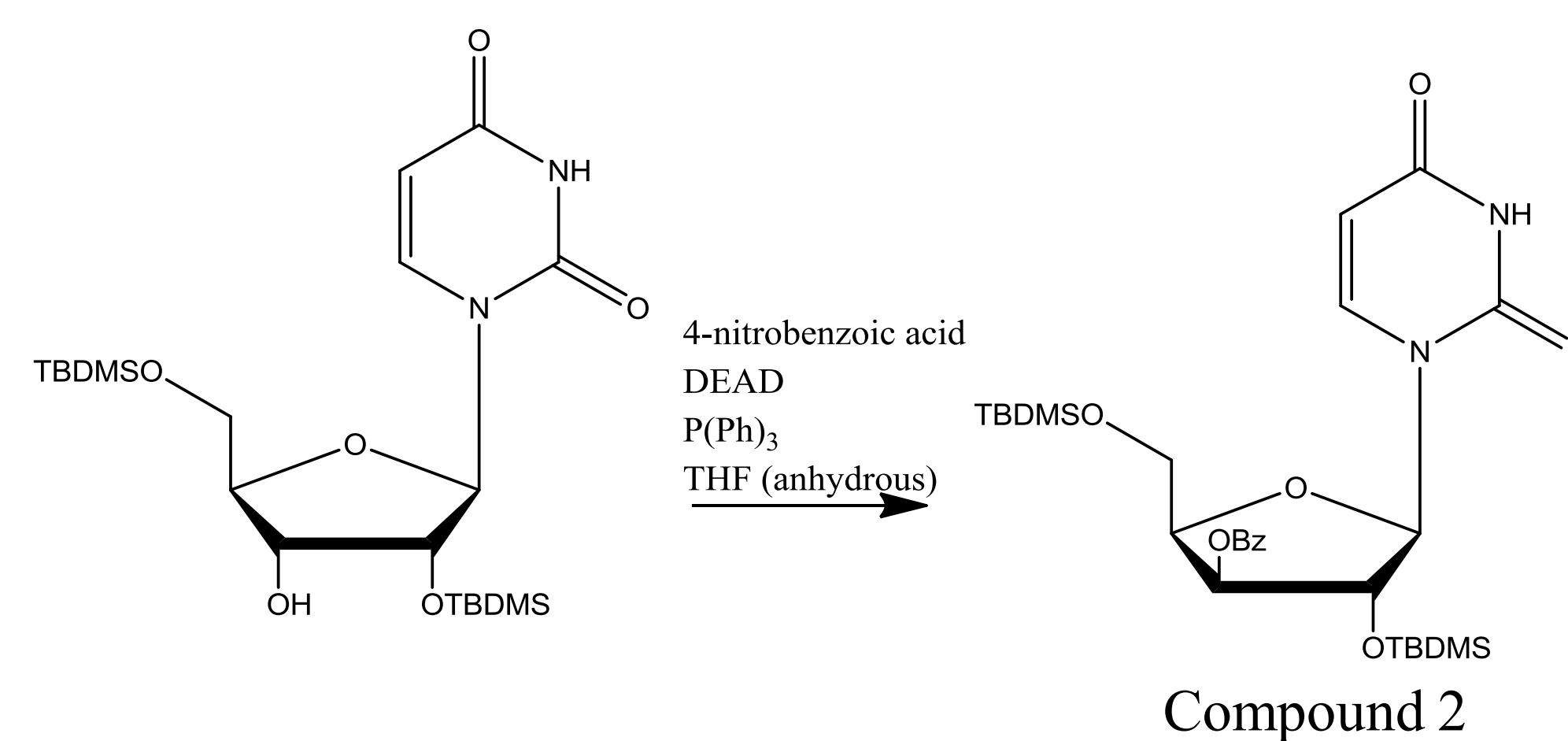


Figure 2: ¹H NMR for the compound isolated from the above reaction. The data shows no benzoyl (Bz) group presents.

Literature Cited

Moti L. Jain and Bruce C. Thomas. Solid-phase synthesis of positively charged deoxynucleic guanidine (DNG) oligonucleotide incorporating 7- deazaguanine bases *Bioorg. Med. Chem.* **2006**, *14*, 7333-7346

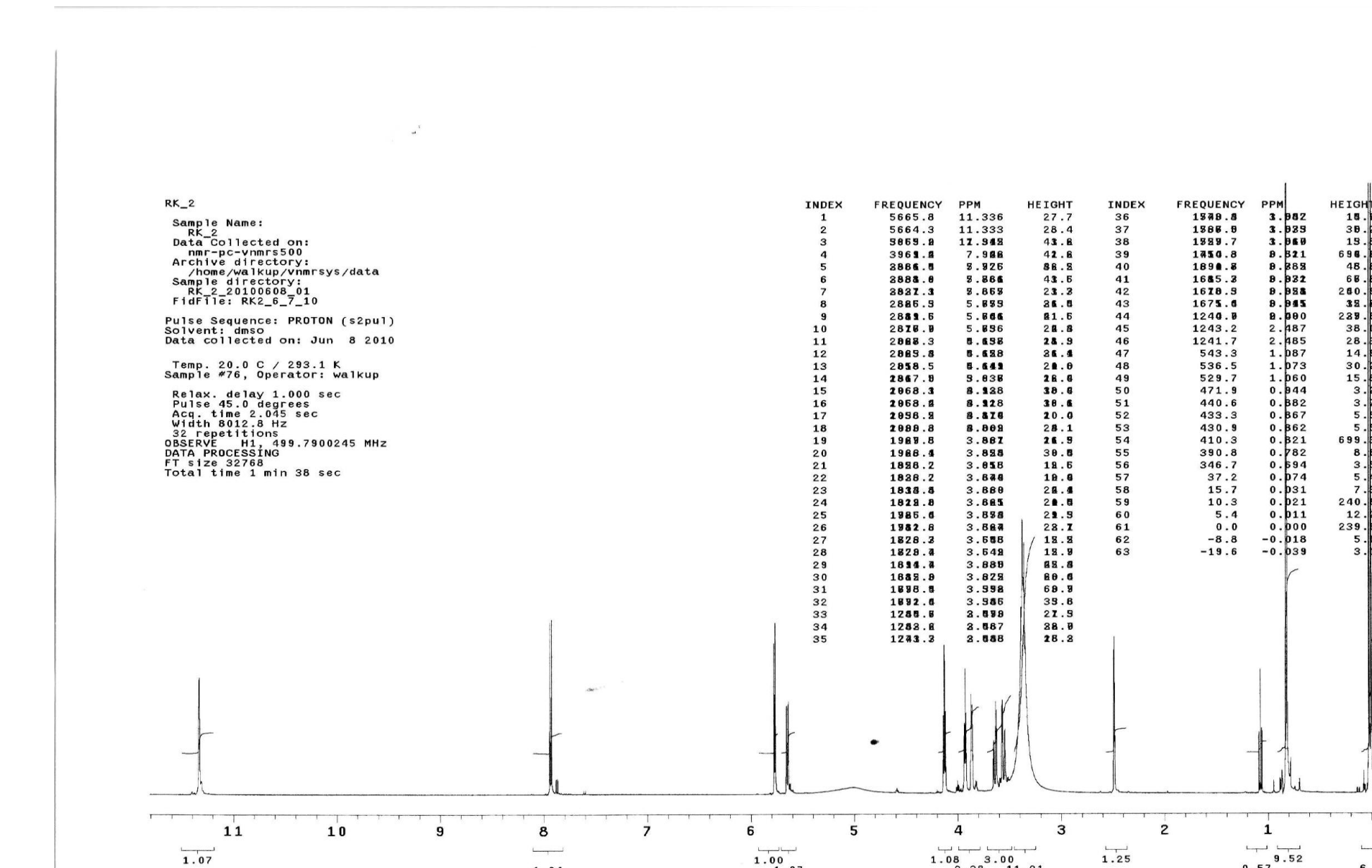
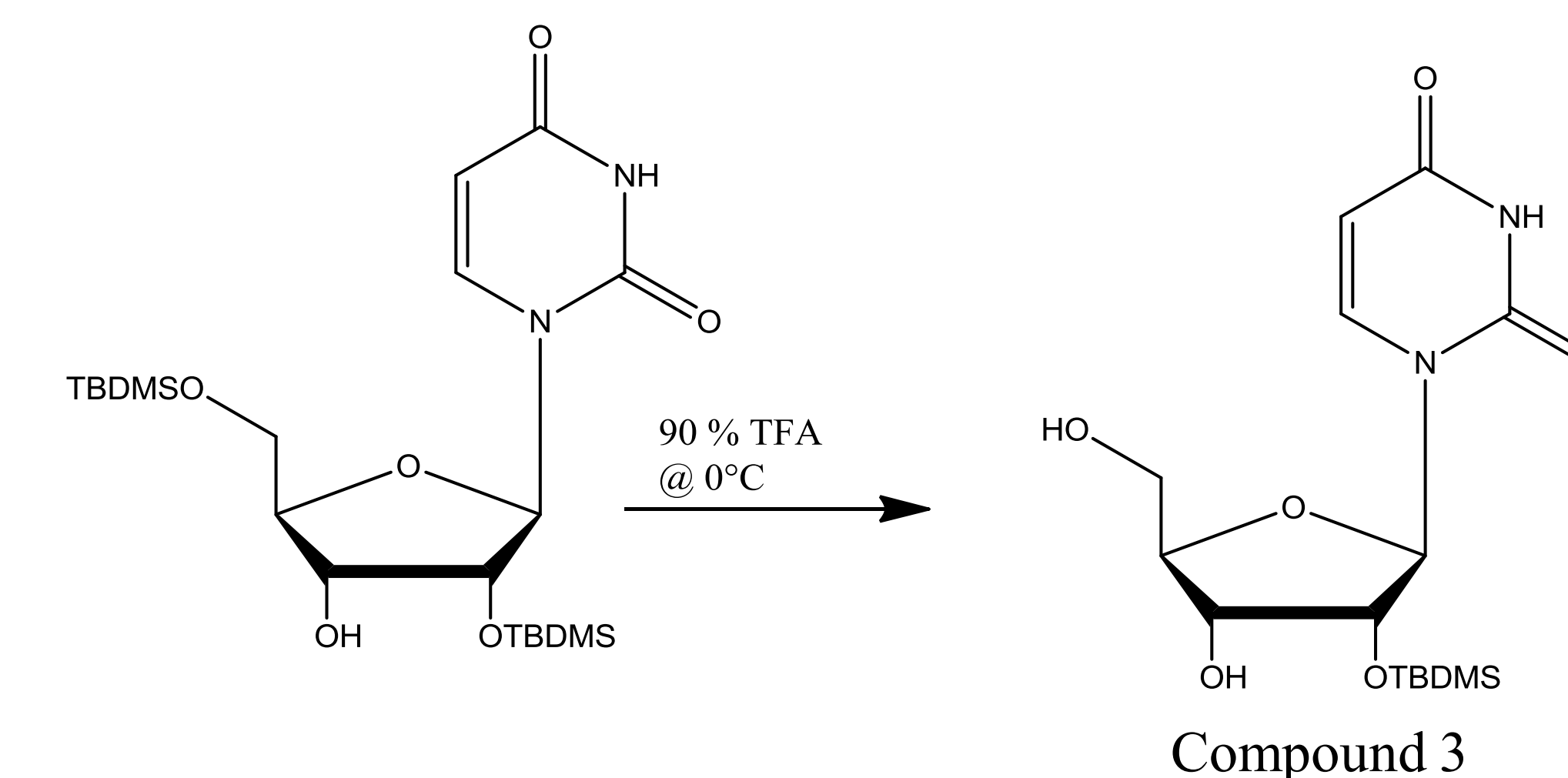


Figure 3: ¹H NMR for compound 3

Conclusions

In this work we designed a scheme for the multi-step synthesis of the 5' building block required for the synthesis of RNG U. We carried out the first reaction, and we have successfully isolated our product 2',5'-bis-O-(tert-Butyldimethylsilyl)uridine. We then used this compound to perform the second reaction in our multi-step synthesis scheme, however we were not able to isolate the desired product. We modified our scheme, and performed a third reaction in which we were successfully able to isolate our product. In future work, the designed synthetic process will continue in an attempt to prepare the 5' terminal monomer required for the synthesis of uridyl ribonucleic guanidine (RNG U). This synthetic oligonucleotides could be tested in biological systems for therapeutically cancer cells.

Acknowledgements

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