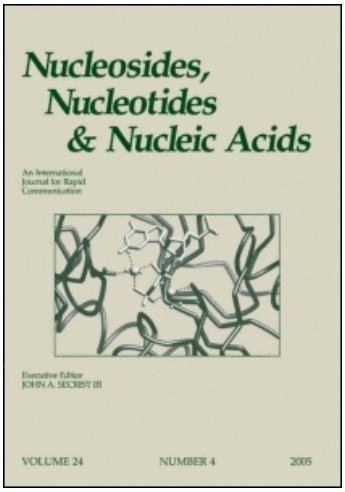

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Synthesis of 1,4-Anhydro-2-deoxy-*D*-ribitol Derivatives from Thymidine

V. Serebryany[ab]; L. Beigelman[a]
[a] Ribozyme Pharmaceuticals Inc., Boulder, Colorado, USA [b] Ribozyme Pharmaceuticals Inc., Boulder, CO, USA

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Synthesis of 1,4-Anhydro-2-deoxy-*D*-ribitol Derivatives from Thymidine[#]

V. Serebryany[*] and L. Beigelman

Ribozyme Pharmaceuticals Inc., Boulder,
Colorado, USA

ABSTRACT

1,2-Dideoxyribose 5-*O*-succinate, a component of solid support employed in the synthesis of ribozymes, was synthesized from thymidine. The key step was elimination of nucleobase from **2** to afford glycal **3**. A number of catalysts for this reaction were tested, resulting in improved and scaleable synthesis. Hydrogenation of the resulting glycal afforded 1,2-dideoxyribose derivative **4** in a high yield.

The intracellular lifetime of synthetic ribozymes is limited due to nuclease digestion. A variety of stabilization techniques have been used to increase nuclease resistance, including the protection of 3′-*termini* by ''abasic'' (1,4-anhydro-2-deoxy-*D*-ribitol or 1,2-dideoxyribose) moiety.[1] Currently, abasic succinate **8** (Sch. 1) is the most expensive component of the solid support used for manufacturing of synthetic ribozymes. Since several ribozymes have entered clinical trials, we needed to develop a scaleable and cost-efficient synthetic method for succinate **8**.

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*Correspondence: V. Serebryany, Ribozyme Pharmaceuticals Inc., 2950 Wilderness Place, Boulder, CO 80301, USA; Fax: +1 303 449 8829; E-mail: serebru@rpi.com.

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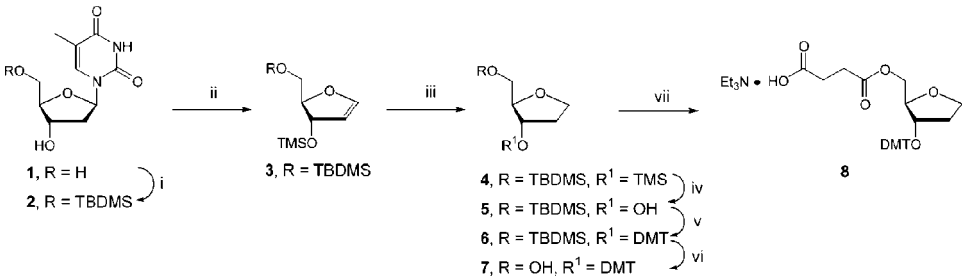
Derivatives of 1,2-dideoxyribose can be synthesized from 2-deoxy-*D*-ribose by a number of methods, however the high cost and poor availability of 2-deoxyribose restricts the use of these approaches. We decided to employ thymidine as a starting material in the preparation of the target compound because it is relatively inexpensive and readily available in bulk quantities due to production of azidothymidine.

It has been shown that thymidine and its 5′-*O*-silylated derivatives undergo elimination of thymine base upon treatment with ammonium sulfate in hexamethyldisilazane (HMDS) under reflux to give cyclic enol ethers, related to dihydrofuran and so called furanoid glycals.[2] Apparently, the double bond in the glycal molecule can be hydrogenated to provide the desired 1,2-dideoxyribose structure. Our synthetic approach is shown in the Sch. 1.

In our initial experiments 5′-*O*-(tert-butyldimethylsilyl) thymidine **2** was reacted with 0.2–0.5 eq. $(NH_4)_2SO_4$ in HMDS under reflux as described[2] to furnish unstable glycal **3**. We observed the yield of this reaction to be variable and highly dependent on reaction conditions and scale. When reactions were performed on more than 10–15 g scale, the yield dropped and decomposition of **3** was detected. The likely reason is instability of **3** in the presence of acidic ammonium sulfate. This prompted us to investigate other compounds that can potentially be used as catalysts for this reaction.

We found that treatment of **2** with trimethylsilyl chloride, trifluoroacetic acid and tin tetrachloride in HMDS did not afford glycal **3,** resulting only in 3′-*O*-silylation of starting compound **2**. Sulfuric acid, *p*-toluenesulfonic acid, methanesulfonic acid and trimethylsilyl methanesulfonate gave results similar to those obtained using ammonium sulfate. Trimethylsilyl triflate and triflic acid furnished fast elimination of nucleobase but gave rise to a complex mixture of products. On the other hand, we have found that treatment of **2** with methanesulfonamide along with a small amount of acidic catalyst, such as methanesulfonic acid furnished fast and clean conversion of **2** to **3**. Under optimized conditions (0.05 mol. eq. of $MeSO_3H$ and 0.5 mol. eq. of $MeSO_2NH_2$) the desired compound **3** was obtained in more than 80% yield. No signs of decomposition of **3** during the reaction were detected. It is worth noting, that increasing the reaction time or scale did not result in reduction of the yield.



Scheme 1. Reagents and conditions: i) TBDMS-Cl, Py, 0°C, 93%; ii) HMDS, $MeSO_3H$ (0.05 eq), then $MeSO_2NH_2$ (0.5 eq), reflux, 2 h; iii) H_2, Pd/C, 1 h; iv) Py·TFA (0.05 eq), MeOH, 30 min 80% from **2**; v) DMT-Cl, Py, DMAP, 87%; vi) NaOH, EtOH-H_2O, reflux; vii) succinic anhydride, Py, DMAP, then Et_3N, 82% overall from **6**.

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Glycal **3** was hydrogenated over Pd/C to give 3,5-di-*O*-protected anhydro-ribitol **4**. Subsequent cleavage of TMS-ether followed by tritylation, desilylation and esterification with succinic anhydride according to standard procedures afforded the target ribitol succinate **8** in a high yield.

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