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One-step syntheses of alkyl glycosides and alkyl-substituted DNA oligomers by chemoselective glycosidations using DNA bases

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Dedicated to Professor Kuniaki Tatsuta on the occasion of his 65th birthday

Abstract—The simple and practical synthesis of alkyl glycosides by novel chemoselective glycosidations using natural resources, DNA and RNA nucleosides, was realized, and the one-step synthesis of chemoselectively modified DNA oligomers using the glycosidation method was also demonstrated.

Glycosides, also known as glycosubstances, are found in many biologically important molecules such as glycoproteins, glycolipids and antibiotics. Furthermore, some glycosides have appeared as new functional materials. Typically, certain alkyl glycosides are now expected to be biodegradable surfactants and are in demand in many industrial fields. For these reasons, carbohydrates containing alkyl glycosides continue to be the central focus of research in chemistry, biology and material science.[1] One of the most important and fundamental reactions for preparing such glycosides is chemical glycosidation, which is very useful for synthesizing both natural and unnatural ones.[2] Although many glycosidation methods have been developed to improve the chemical yield and the stereoselectivity, the investigation of efficient and practical glycosidation methods is becoming more and more important in synthetic organic chemistry, and urgently needed both in the laboratory and in industry. One of the most important and challenging tasks confronting chemical glycosidations is the simple preparation of a suitable glycosyl donor and its effective use for chemical glycosidation. In general, the preparation of an appropriately functionalized glycosyl donor for chemical glycosidation is not very easy and usually requires multiple operations. Therefore, if such a glycosyl donor could be easily and directly available from nature, that is, natural resources, it would be a great advantage for an efficient and practical chemical glycosidation. In this study, we used DNA as the glycosyl donor. Large amounts of DNA are readily available from natural resources such as salmon albino, whose effective use has not yet been completely determined. In this letter, we disclose, for the first time, the simple and practical synthesis of alkyl glycosides and alkyl-substituted DNA oligomers by chemoselective glycosidations using DNA bases and DNA oligomers (Fig. 1).

To realize our purpose, we noted the G (guanine)-reaction in the Maxam–Gilbert protocol, which is a well known and widely used DNA sequencing method in molecular biology.[3] In the G-reactions, the G base is selectively modified by dimethylsulfate (Me_2SO_4), followed by treatment using hot piperidine, to afford DNA fragments, which are selectively cleaved at the G sites. Based on this result, we expected that the following chemical reaction must take place during the G-reaction of the Maxam–Gilbert protocol as shown in Figure 2. Thus, the G base is selectively alkylated by dimethylsulfate at the *N*-7 position, whose HOMO level is very high,[4] and then the positively charged methylated G base is formed. Next, release of the resulting positively charged G base as the neutral 7-*N*-methylguanine provides the oxonium cation intermediate. Furthermore, water attacks the oxonium intermediate to give the hemiacetal, which reacts with piperidine to form the imine product. The generating imine is labile under basic

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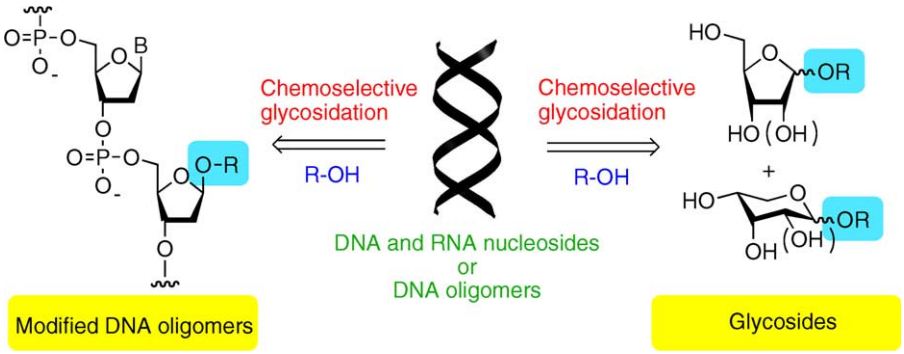

Figure 1. Syntheses of glycosides and modified DNA oligomers by glycosidations using DNA bases and DNA oligomers.

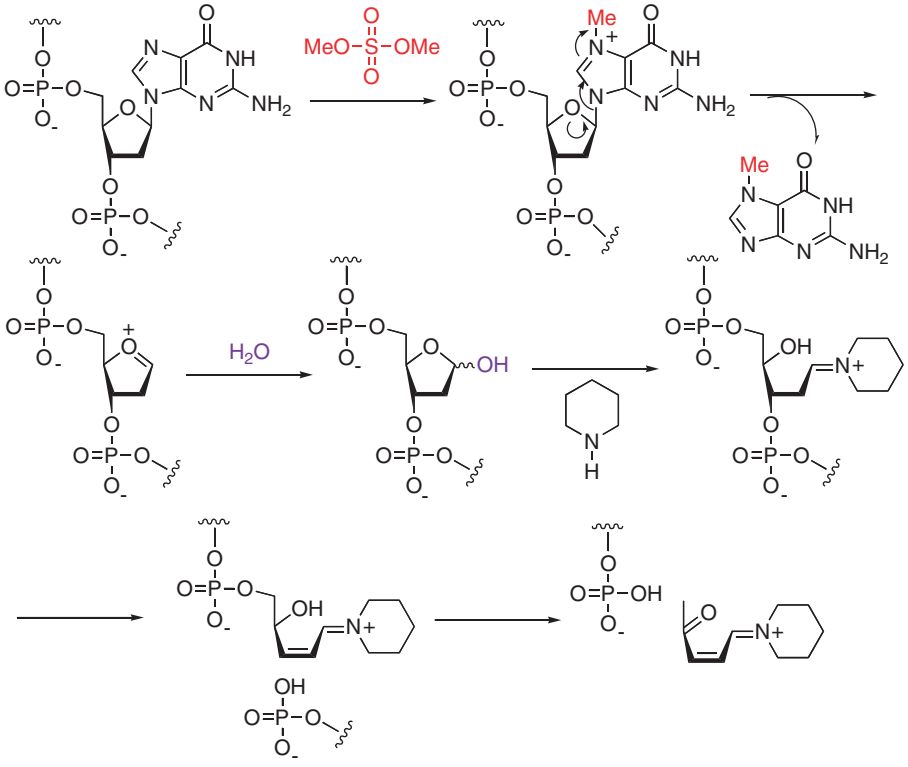

Figure 2. Maxam–Gilbert DNA sequencing method and the presumed mechanism of the G-reaction.

conditions and leads to the DNA cleavage by β-elimination of the phosphate moiety.[3] If this reaction mechanism is correct, when we use an alcohol instead of water under anhydrous conditions, the corresponding glycoside would be obtained in a similar way.

Based on our hypothesis, we first examined the glycosidations using guanosine (**1**), in which the G base is connected with ribose at the C1 position. At this stage, we checked the solubility of the glycosyl donor **1** without any protecting groups in several solvents, and confirmed that **1** is soluble in only DMSO and DMF, and insoluble in PhMe, Et_2O, CH_2Cl_2, MeCN and THF, which were widely used in many conventional chemical glycosidation reactions, due to the high polarity of **1**. For the activating reagents, we tested several alkylating agents such as MeI, MeOTf and BnBr. We found that the glycosidation of **1** and *n*-BuOH (**2**) using MeOTf in DMSO at 80 °C for 5 h smoothly proceeded to give the glycosides **3** together with the corresponding pyranosides **4** in high yield (Fig. 3). It was confirmed that the production of the pyranosides **4** came from the equilibrium between **3** and **4** under the reaction conditions. In addition, we confirmed that MeOTf was superior to the other alkylating agents such as MeI and BnBr, and DMSO was better than DMF as the solvent. In this case, since the unprotected **1** was used as the glycosyl donor, an excess amount of the glycosyl acceptor **2** was needed for obtaining the glycosides **3** and **4** in high yield, because **1** itself has a highly reactive primary hydroxyl group at the C5′-position.

Considering the G+A (adenine)-reaction using formic acid (HCOOH) as the modifying agent in the Maxam–Gilbert protocol,[3] we expected that the glycosidation using **1** would be realized using protic acids. Therefore,