

Communications

New Synthetic Method of Natural Arsenosugar

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Arsenic (As), a metallic substance which is spread widely as a compound of various forms, is a main environmental pollutant with strong toxic nature.^{1,2} Arsenic is gaining attention as a carcinogenic substance which causes lung cancer, skin cancer, liver cancer and others in a human body.³ In a group which drank water with a higher concentration of arsenic, the incidences of skin diseases, lung cancer and liver cancer were appeared high.⁴ In water, arsenic exists in the form of inorganic arsenic such as arsenite (+3) and arsenate (+5).^{5,6} On the other hand, seafood arsenic comprises several organoarsenic compounds such as arsenobetaine ($\text{Me}_3\text{As}^-\text{CH}_2\text{CO}_2^-$) and arsenosugar. In fish and most shellfish, the predominant arsenical is arsenobetaine and in edible seaweed (algae), the arsenic is primarily bound to carbohydrate compounds, collectively termed arsenosugars.^{7,8} The arseno-

sugars occur at significant concentrations in both algae and marine animals feeding on algae, such as scallops.⁹ In terms of toxicology, arsenobetaine, a relatively stable arsenic compound in a living body, is not metabolized and is evaluated as harmless to human body because it is expelled quickly into urine compared to trivalence and pentavalence inorganic arsenic.¹⁰⁻¹² However, the toxicology of arsenosugars has not been fully assessed but it is likely to be more complicated than that of arsenobetaine.¹³ In additions, arsenosugars have a wide fluctuation range in the body of each biological species. As a result, it is hard to measure just what kind of harm an arsenic compound does in a living body. Among 17 identified arsenosugars, four arsenosugars **1a-d** in Figure 1 have been most often identified in the marine environment.¹⁴⁻¹⁵ One of these compounds, (*R*)-2',3'-dihydroxypropyl 5-deoxy-5-dimethyl-

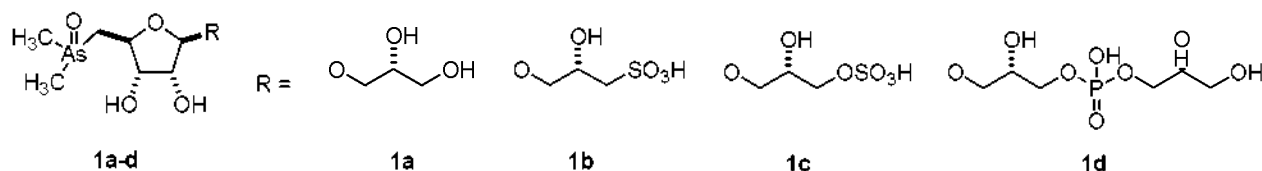
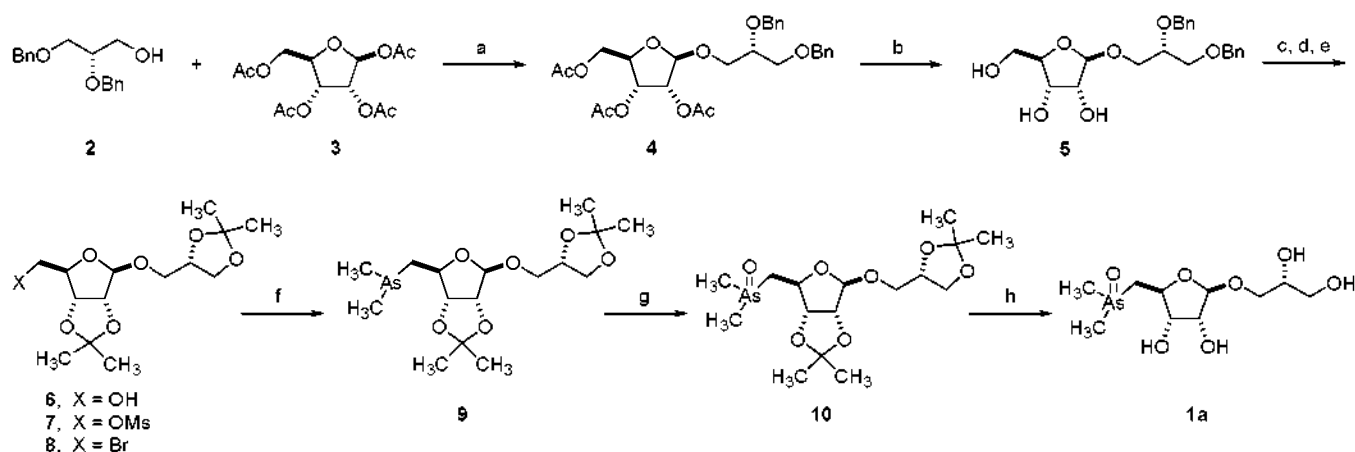


Figure 1. Structures of the four arsenosugars most often identified in the environment.



Scheme 1. Reagents and conditions: (a) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, MeCN, rt, 17 h, 60%; (b) $\text{NH}_3(\text{g})$, MeOH, rt, 24 h, quantitative; (c) H_2 , Pd/C, *p*-TsOH, dimethoxypropane (5 equiv.), acetone, rt, 6 h, 61%; (d) $\text{CH}_3\text{SO}_2\text{Cl}$, DMAP, TEA, rt, 24 h, CH_2Cl_2 , quantitative; (e) Bu_4NBr (3 equiv.), DMF, reflux, 24 h, 62%; (f) $(\text{CH}_3)_2\text{AsI}$ (6 equiv.), Na (12 equiv.), THF, rt, 26 h, 51%; (g) H_2O_2 , THF, rt, 30 min, 84%; (h) TFA, H_2O , rt, 10 min, then 2 N NH_4OH , Sephadex LH-20, 86%.

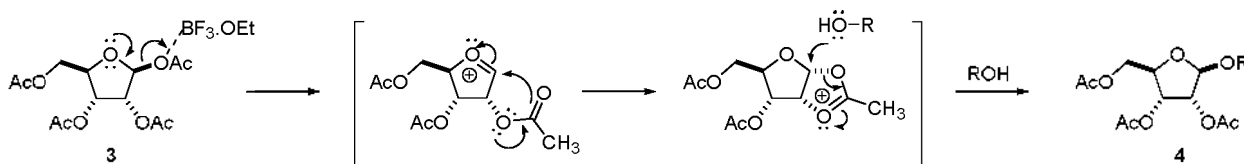


Figure 2. β -Ribofuranoside formation *via* the neighboring-group effect of a nearby acetate.

arsinyl- β -D-ribose **1a**, has proven to be a constant component of most marine flora studied to date.¹⁶ Since Koreans have a habit of eating seafood much, research on the toxicity and biotransformation of arsenosugars is of obvious interest in order to make accurate risk assessments. Therefore, this aim of research is to synthesize and provide the arsenosugar **1a** in gram amounts using new synthetic method for the evaluation of its toxicity and the study of its reaction on primates. Until now, three synthetic methods for arsenosugar **1a** have been reported by Stick group and Irgolic group, respectively.¹⁶⁻¹⁸ Herein, we describe new synthetic method of arsenosugars **1a** starting tetraacetyl- β -D-ribofuranose (**3**) *via* the modification of known methods.

In an initial glycosidation attempt, commercially available tetraacetyl- β -D-ribofuranose **3** was treated with (*S*)-1,2-dibenzyl-oxy glycerol **2** in the presence of Lewis acid ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) to provide the anomericly pure β -ribofuranoside **4** in 60% as expected from the mode of formation as shown in Figure 2. This stereochemical result was found to be very interesting and useful compared to the previously reported literatures, which provided only the anomeric mixture and/or the diastereomeric mixture due to anomerization at C-1 and/or racemization at C-2'.¹⁶⁻¹⁷

The deacetylation of β -ribofuranoside **4** was carried out quantitatively using ammonia in methanol. Tandem debenzylation of C-2' and C-3' and protection of resultant hydroxyl functionalities in **5** was achieved using H_2 , Pd/C, *p*-TsOH and dimethoxypropane (5 equiv.) in one pot condition and this afforded the desired β -ribofuranoside **6** in 61% yield (Scheme 1). For the introduction of an arsenic atom at C-5 of **6**, primary hydroxyl functionality of **6** was transformed into the tosyl functionality, which was again converted into the corresponding bromide functionality of **8** in 62% yield using known better method (Bu_4NBr in DMF).¹⁶ The introduction of dimethylarsenic group at C-5 of **8** was carried out to give the stable arsine **9** in 51% yield using dimethylarsenic iodide (5 equiv.) and excess of sodium in THF solution. The arsine **9** was easily oxidized with H_2O_2 to afford the arsine oxide **10** in 84% yield. Finally, the removal of protecting groups in **10** with aqueous TFA, neutralization with 2 N NH_4OH , and separation on Sephadex-20 column provided the target arsenosugar **1a** in 86% yield. The spectral data of arsenosugar **1a** were all identical to those of the reported compound.¹⁵ In summary, anomericly pure natural arsenosugar, (*R*)-2',3'-dihydroxy-

propyl 5-deoxy-5-dimethylarsinyl- β -D-ribose **1a** was easily synthesized from tetraacetyl- β -D-ribofuranose **3** using new synthetic method.

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- The spectral data of arsenosugar **1a**: ^1H NMR (400 MHz, D_2O) δ 4.89 (1H, s, H-C1), 4.16-4.09 (2H, m, H-C3 & H-C4), 4.00 (1H, m, H-C2), 3.75 (1H, m, H-C2'), 3.62 (1H, m, H-C1'), 3.52-3.42 (3H, m, H-C1' and H-C3'), 2.54 (1H, dd, $J = 14.0$ and 3.2 Hz, H-C5), 2.39 (1H, dd, $J = 14.0$ and 10.4 Hz, H-C5), 1.81 (3H, s, $\text{CH}_3\text{-As}$), 1.77 (3H, s, $\text{CH}_3\text{-As}$); ^{13}C NMR (100 MHz, D_2O) δ 107.30, 76.67, 75.62, 74.10, 70.06, 68.75, 62.30, 35.91, 14.30, 13.97; $[\alpha]_D^{25} = -1.88^\circ$ (c, 8 in MeOH). The natural product had $[\alpha]_D^{25} = -2.0^\circ$ (c, 1.3 in MeOH).¹⁵