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# Regioselective Esterification of Vicinal Diols on Monosaccharide Derivatives via Mitsunobu Reactions

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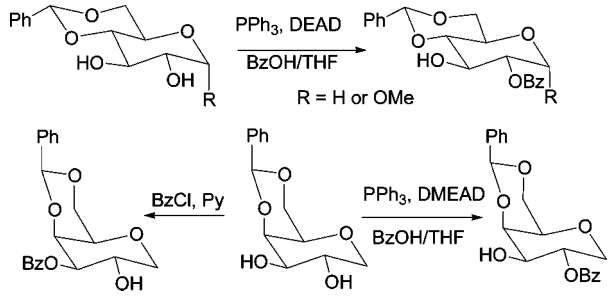
## ABSTRACT




**We have carried out a series of esterification reactions of secondary alcohols derived from D-glucose, D-mannose, and D-galactose via the Mitsunobu reaction. The benzoylation reaction of vicinal diols derived from monosaccharides under Mitsunobu conditions afforded monobenzoates with retention of stereochemistry only. The regioselectivity of these reactions depends on the stereochemistry of the sugar starting material. The Mitsunobu reactions on these diols may be used for the selective protection of other vicinal secondary hydroxyl groups.**

The Mitsunobu reaction is widely used in organic synthesis to introduce various functional groups under mild conditions.[1−3] An especially useful aspect of the reaction is the inversion of stereogenic centers via an $S_N2$ mechanism. Typically, a secondary hydroxyl group can be converted to the corresponding ester with inverted stereochemistry using triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) as shown in Scheme 1.[4,5] The alcohol **1** is converted to the ester **2**, and TPP and DEAD are converted to triphenylphosphine oxide (TPPO) and diethyl hydrazinedicarboxylate ($EtO_2CNHNHCO_2Et$). The normal reaction (mechanism 1) generally involves the formation of an initial complex **3** which can then deprotonate benzoic acid to give intermediate **4**. Compound **4** then reacts with the alcohol **1** to afford the key triphenylphosphonium ion **5**. The benzoate nucleophile then reacts with intermediate **5** to afford the ester **2** with inverted stereochemistry by an $S_N2$ mechanism. Although inversion of stereochemistry is expected in general, retention of configuration has also been reported.[6−10] Mitsunobu reactions can give products with retention of the stereochemistry when the secondary hydroxyl group is in a sterically hindered environment via mechanism 2. In this case, the hydroxyl group acts as the nucleophile, and benzoic acid is activated into a phosphonium ion intermediate with a better leaving group.

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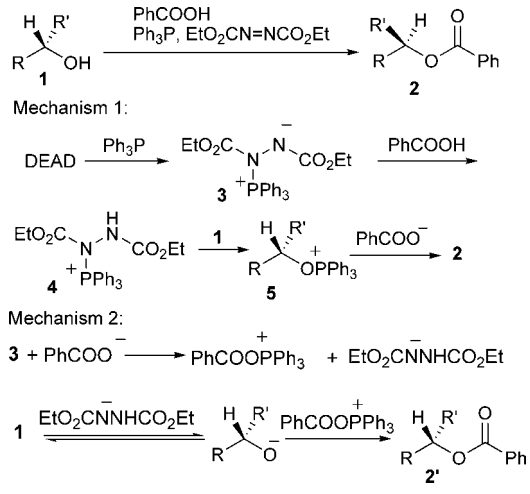
**Scheme 1.** Example of Mitsunobu Reaction and the General Mechanisms to Inversion or Retention of Stereochemistry



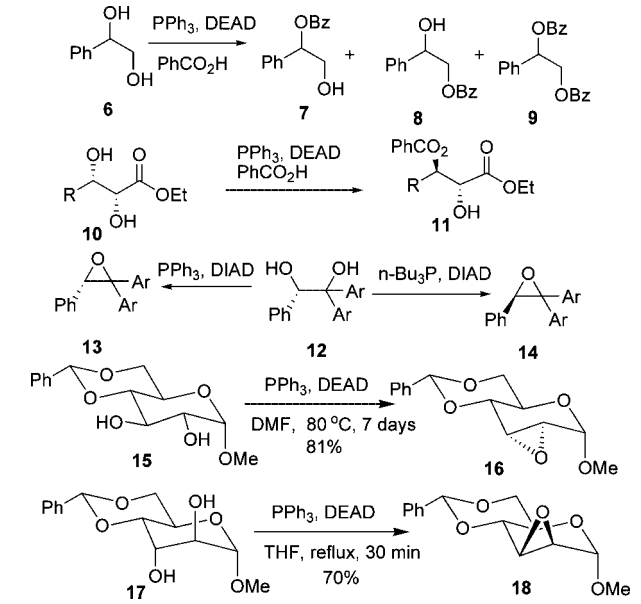




**Figure 1.** Examples of vicinal diols and their Mitsunobu reaction products.

Compared to the vast amount of Mitsunobu reactions performed on compounds containing monohydroxyl groups,[1−3] there are fewer Mitsunobu reactions done on compounds containing multiple hydroxyl groups, especially those with two vicinal chiral hydroxyl groups.[11−17] Two examples of Mitsunobu esterification of diols are shown in Figure 1. The esterification of the 1,2-diol **6** using TPP, DEAD, and benzoic acid afforded ester **7** in 79.7% yield, along with 12% primary ester **8** and 8.3% of diester **9**.[11b] The regioselectivity is such that the esterification occurs primarily at the secondary center. However, butane 1,3- diol was esterified predominantly at the primary center, in over 90% yield. The *syn*-dihydroxy ester **10** gives only the $\beta$-functionalized derivative **11** with inverted stereochemistry.[12]

1,2-Diols have also been shown to form epoxides under Mitsunobu conditions when no additional nucleophiles are used.[15−18] For example, the diol **12** can be converted to either of the epoxides **13** or **14** depending on the type of phosphine agent used (Figure 1). When triphenylphosphine and diisopropylazodicarboxylate (DIAD) were used, the epoxide **13** with retention of configuration was obtained, while tri-*n*-butyl phosphine and DIAD afforded epoxide **14** instead.[17] Cyclic vicinal diols can also be converted to the corresponding epoxides; for example, the monosaccharide derived compounds **15** and **17** can be converted into epoxides **16** and **18**, respectively (Figure 1). While compound **17** with diaxial hydroxyl groups afford the corresponding epoxide **18** with relative ease, compound **15** diequatorial hydroxyl groups is more difficult to convert to the epoxide **16**.[18]

Carbohydrates are useful chiral pool materials and renewable resources. They contain multiple chiral centers and can be used as starting materials for the synthesis of many complex bioactive compounds. Mitsunobu esterification has been applied to the C-6 and C-1 positions of sugars and their derivatives.[19] Previously, we synthesized bicyclic amino acids from D-glucose and D-mannose and organogelators from glucose derivatives.[20−22] During these syntheses, it was necessary for us to differentiate between the hydroxyl groups at the C2 and C3 positions of various D-glucose derivatives. For example, the acylation of compound **15** using acyl chloride and pyridine afforded mainly the 2-ester along with a small amount of the 3-ester and diester. Depending on the choice of acylating agents, the 2-esters and 3-esters are good organo/hydrogelators.[21]

Here we wish to report the results of Mitsunobu benzoylation reactions of alcohols, especially vicinal diols derived from D-glucose, D-mannose, and D-galactose. We studied the acylation reactions of vicinal diols under Mitsunobu conditions using benzoic acid, TPP, and DEAD and found that the benzoylation reactions proceeded with interesting regioselectivity and stereoselectivity. The regioselectivity and

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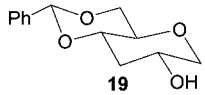
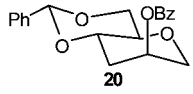
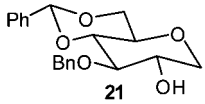
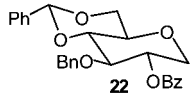
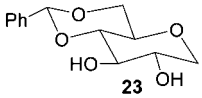
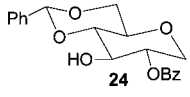
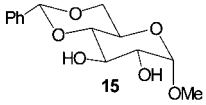
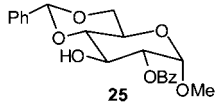
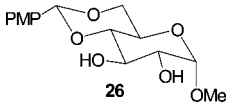
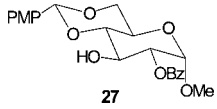
stereochemistry of the reactions are determined by the structures of the monosaccharides. To our surprise, the reactions utilizing vicinal diols produced monobenzoates with retention of stereochemistry only. The results for a series of glucose-derived alcohols are shown in Table 1.

**Table 1.** Mitsunobu Esterification of Various Glucose Derivatives Using TPP and DEAD and the Acylating Agent Is Benzoic Acid for All Compounds

| starting material | product | yield |
|---|---|---|
|  **19** |  **20** | 69% |
|  **21** |  **22** | 90% |
|  **23** |  **24** | 94% |
|  **15** |  **25** | 80%<br>*95% |
|  **26** |  **27** | 75%<br>*90% |

* Estimated conversion based on $^1$H NMR spectrum.

Monohydroxyl compound **19** was synthesized from D-glucose[22] and can be cleanly converted to the corresponding benzoate **20** with inversion of stereochemistry. Compound **21**[21] also has one free secondary hydroxyl group, but under similar conditions afforded the ester **22** with retention of stereochemistry. The structure of **22** was confirmed by hydrolysis of the benzoate ester, and the hydrolyzed product of **22** was found to have the same structure as the starting material according to NMR spectra. It is reasonable to view compound **21** as a sterically hindered secondary alcohol, and retention of configuration was expected when the hydroxyl group is in a hindered environment in accordance to the results reported by several researchers.[6−10] The 1,3-dideoxy derivative **19** is less sterically hindered compared to **21** and therefore produced the inverted ester.

The 1-deoxy-glucose derivative **23** was converted exclusively to the 2-*O*-benzoate **24** with retention of stereochemistry using 2 equiv of benzoic acid, TPP and DEAD. No other regioisomers were observed. The structure of the product was confirmed by NMR spectra of the product and the hydrolysis of ester **24**. Hydrolysis of **24** with NaOMe in MeOH gave a single product whose $^1$H and $^{13}$C NMR spectra exactly match those of compound **23**, not the compound with inverted C-2 configuration. For the 1-methoxy glucoside **15**, a similar pattern was observed. The 2-*O*-benzoate **25** was formed with retention of configuration. On the basis of $^1$H NMR, the starting material is converted to the 2-ester in over 95% yield, but the product is difficult to separate from the byproduct of DEAD. We found that the solvent system using hexane:DCM:THF (30:1:1) gave the best separation. The 4-methoxyphenyl acetal **26** also gives the 2-ester exclusively with over 90% conversion (estimated from $^1$H NMR spectrum).

These results indicate that the esterification of compounds **15**, **21**, **23**, and **26** proceeds via a different mechanism from the classical Mitsunobu reaction (mechanism 2 shown in Scheme 1). This mechanism was also postulated for other Mitsunobu esterification reactions.[5,6,23] Here the nucleophile is the 2-alkoxide or 2-hydroxyl group of the diol, which undergoes acylation with the activated acid to form the benzoate with retention of configuration. The 2-hydroxyl group of compound **19** is in a less hindered environment compared to other substrates in Table 1, thus it proceeds via mechanism 1 shown in Scheme 1, leading to inversion of the C-2 stereocenter. It seems that an epoxide intermediate is not formed when the diol was subjected to the same Mitsunobu conditions in the absence of an acid for 2 days, and no reaction took place.

To confirm the mechanism and further understand the reaction, we also used thiobenzoic acid (PhCOSH) as the acylating agent for compound **26**. The same product, 2-*O*-benzoate **27**, was obtained, and no incorporation of thio group (**28**, Figure 2) was observed. This reaction outcome supports

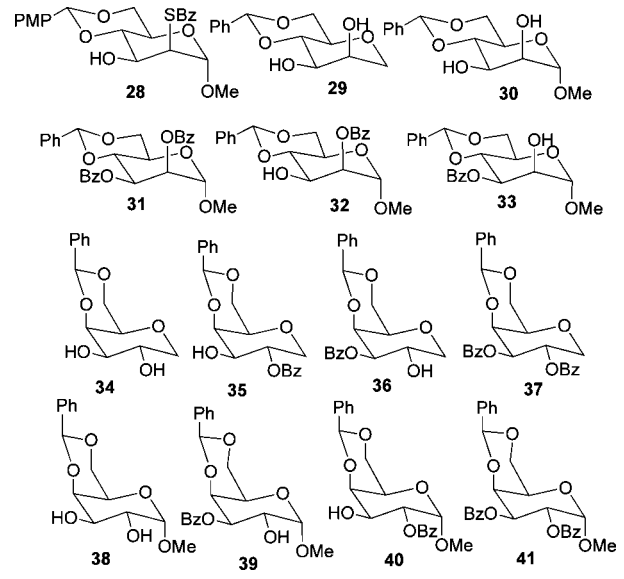



**Figure 2.** Structures of compound **28** and D-mannose and D-galactose derivatives and their acylation products **29**−**41**.

the mechanism 2 in Scheme 1 where the nucleophile is the 2-hydroxy group, not the benzoate. However, the reaction conversion was only around 35%, with about 65% of unreacted starting materials. The reason for the lower conversion was perhaps due to the bulkiness of the sulfur group compared to

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an oxygen atom. In addition, the elimination of $Ph_3P{=}S$ is not as thermodynamically favorable as that of $Ph_3P{=}O$, as the phosphorus−sulfur double bond is not as strong as the phosphorus−oxygen double bond (P═O bond energy ∼ 544 kJ/mol, whereas P═S ∼ 335 kJ/mol).[24]

The regioselectivities of **15**, **23**, and **26** can be rationalized by stereoelectronic factors. In the diol **23**, the 2-OH is less hindered than the 3-OH since it is next to a primary carbon. Therefore, the regioselectivity favors the formation of the 2-ester. In compounds **15** and **26**, the cis relationship with the methoxyl group presumably promotes hydrogen bonding and leads to the enhanced nucleophilicity of the 2-hydroxyl group. This makes the 2-hydroxyl group more reactive, and under mild Mitsunobu conditions, the 2-ester is the major product.

When the substrates are derivatives from D-mannose (**29**, **30**), the Mitsunobu reaction results are quite different. Unlike the D-glucose derivatives shown in Table 1, here the regioselectivity and yields are low perhaps due to the 2-hydroxy group being in the axial position and more sterically hindered.[25] For the 1-deoxy derivative **29**, using the same conditions utilized in the glucose series, only a very small amount of the starting material was esterified. Two esterification products were obtained in equal ratio, affording no regioselectivity, and the majority (>80%) of the reaction mixture was unchanged starting material.

For the 1-methoxy mannoside **30**, depending on the reaction conditions, different esterification products with retention of stereochemistry were obtained (Figure 2). Under mild conditions, using 2 equiv of reagents, and heating at ∼45 °C for 24 h, the 2-ester was obtained in 38% yield along with 62% unreacted starting materials. Under more harsh conditions, using 3 equiv of each reagent and heating to about 80 °C for 3 days, the starting material was completely converted to three products: the diester **31** in 40%, 2-ester **32** in 45%, and 15% 3-ester **33**. The reaction is no longer regioselective under these conditions; however, both conditions lead to retention of configuration. This is confirmed by analysis of the $^1$H NMR spectra. Additionally, simple hydrolysis of **32** led to the starting material **30** as indicated by $^1$H NMR spectra.

For D-galactose derivatives, an interesting regioselectivity was observed. The direct esterification of 1-deoxy galactose acetal **34** using benzoyl chloride[26] led to the 3-ester **36** as the major product in 85−95% yield along with a small amount of diester **37**. However, under Mitsunobu reaction conditions using TPP and either DEAD or DMEAD,[27] the opposite regioselectivity was observed. The 2-ester **35** was obtained as the major product in 90% yield along with about 5−10% of **36**. Thus, the Mitsunobu reaction provides complementary regioselectivity to standard esterification conditions. The reason for the different regioselectivity is perhaps due to the stereoelectronic differences between the two positions. The 2-position is less hindered in comparison to the 3-hydroxyl group and is acylated more favorably under the mild conditions of the Mitsunobu reaction. The 3-position is favored under normal esterification conditions, perhaps due to the hydrogen bonding of the *cis*-3- and 4-hydroxyl groups, increasing the nucleophilicity of the 3-position.

This exceptional selectivity disappears when using the 1-methoxy derivative **38**. The direct esterification also favors the 3-ester (45% **39**, 12% **40**, and 17% **41**) but to a lesser degree than the 1-deoxy compound **34**. Under Mitsunobu conditions, when using 2 equiv of reagents, the reaction leads to almost equal amounts of the 3-ester **39** and 2-ester **40** and some unreacted starting material. The reaction can reach completion by adding triethylamine as a coreactant giving the 2- and 3-esters in a 1:1 ratio. When a larger excess of reagents was used (4 equiv of each and stirring for 4 days), the reaction gave about 5% diester **41**, 35% 2-ester **40**, and 60% 3-ester **39**. The regioselectivity for the 2-ester decreases probably due to the presence of the large excess of reagents.

In summary, we have carried out a series of esterification reactions on chiral alcohols including vicinal diols derived from monosaccharides under Mitsunobu conditions. The Mitsunobu esterifications of the diols derived from D-glucose, D-galactose, and D-mannose all proceeded with retention of configuration. The glucose based diols **23**, **15**, and **26** and 1-deoxy galactose derivative **34** afforded 2-OBz with high regioselectivity. The D-glucose derivatives regioselectively afforded the 2-benzoate esters with excellent yields. However, D-mannose derivatives and 1-methoxy D-galactose derivatives did not show good regioselectivity. The 1-deoxy D-galactose **34** afforded excellent regioselectivity, and the Mitsunobu esterification gave opposite regioselectivity compared to that of the direct esterification reactions. The stereochemistry of Mitsunobu reactions is very sensitive to the environment, and hindered substrates tend to yield products with retention of configuration. The interesting regioselectivity and stereoselectivity of these Mitsunobu reactions on diols derived from common sugars can be applied to other chiral cyclic diols.

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**Supporting Information Available:** The experimental data for the preparation of **20**, **22**, **24**, **25**, **27**, **35**, **36**, and **39**−**41** are provided. The $^1$H NMR and $^{13}$C NMR spectra of these compounds and some starting materials are also provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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