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Anomeric selectivity in the synthesis of galloyl esters of D-glucose

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ABSTRACT

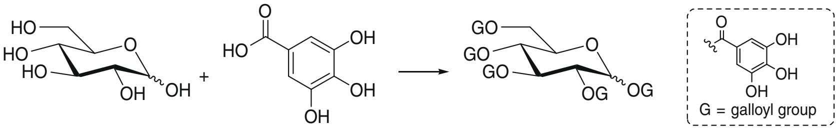
The anomeric selectivity of the ester formation between D-glucopyranose and gallic acid was investigated under a variety of conditions. A new protocol was established that allows performing the reaction under conditions where mutarotation is very slow. Highly α- or β-selective transformations are possible when starting with α- or β-D-glucopyranose, respectively. Due to the kinetic anomeric effect, a high α-selectivity is more difficult to achieve than a high β-selectivity. The new methodology presented in this article was compared with established procedures for the synthesis of gallotannins. In addition to the advantages of a high yield and an easy purification protocol, the new procedure uniquely allowed for a highly selective synthesis of α-products.

The esters of D-glucose (**1**) and gallic acid (**2**) (Scheme 1) occur as natural products in a large number of gallotannins and ellagitannins.[1] Both classes of compounds possess a wide variety of biological activities.[2,3] For example, recent research has established that certain esters of gallic acid with D-glucose and D-glucose analogues possess anti-diabetic properties.[4,5] Derivatives of both D-glucose anomers have been shown to activate D-glucose uptake in adipocytes in the absence of insulin.

Detailed studies of the biological activities of gallotannins and ellagitannins are hampered by a lack of availability of sufficient amounts of pure material. Known syntheses produce mixtures of anomers that are difficult to separated. Some progress in the selective preparation of anomers has been reported recently,[4,6] but the factors that determine selectivity remain obscure. The present study establishes a new protocol for the synthesis of either α- or β-galloate esters of D-glucose. In addition, a comparison with established methodologies is presented.

The anomeric selectivity of esterifications of carbohydrates depends on the rate of mutarotation in a given medium (Scheme 2). A mixture in which the rate of mutarotation is slow relative to the rate of esterification should lead to the selective formation of the α or β anomer when either the pure α or β sugar is used as a starting material. On the other hand, conditions that allow for fast mutarotation can lead to high anomeric selectivity if the equilibrium conditions favor either the α or β anomer, or if the esterification rate of the anomers is significantly different.[7,8]

In order to investigate reaction conditions that lead to high anomeric selectivity, the synthesis of one of the most abundant natural gallotannins, namely penta-*O*-galloyl-D-glucopyranose (**3,** PGG), was used as the model reaction. Gallic acid was introduced as its benzyl-protected derivative (Scheme 3). The benzyl group is most frequently used because it allows for a quantitative removal by hydrogenolysis and a simple workup in the final step of the synthesis of gallotannins.



1 **2** **3**

Scheme 1. Example of a common gallotannin: Penta-*O*-galloyl-D-glucopyranose, PGG, (**3**).

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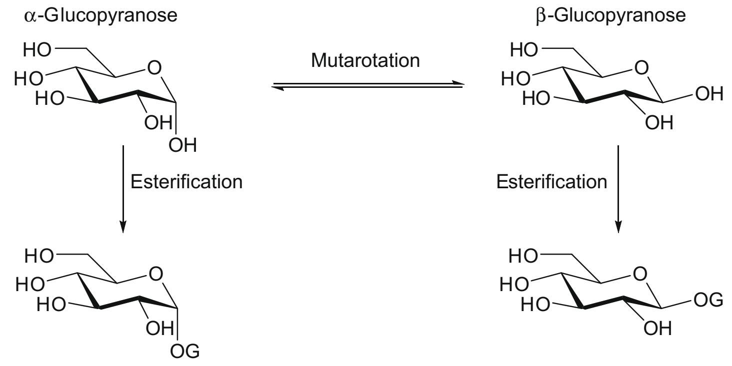
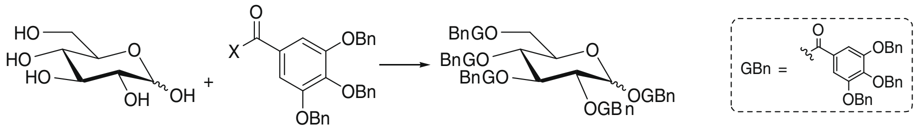


Scheme 2. Transformations that influence the anomeric selectivity of the esterification of D-glucopyranose.



1 **4**: X = OH **5**: X = Cl **6**: α anomer **7**: β anomer

Scheme 3. Esterification of D-glucopyranose with gallic acid derivatives.

The established methods for the synthesis of D-glucose galloates use either gallic acid derivative **4** in conjunction with DCC activation or acid chloride **5** (Scheme 3). Since the reaction using **4** leads to relatively poor anomeric selectivity,[9] the focus of this study is on the use of acid chloride **5**.

In general, all acylation reactions using **5** were found to be rather slow because of the electron-rich nature of the aromatic acylating agent. For example, the standard acylation to prepare the penta-*O*-benzoate of D-glucopyranose from the acid chloride in pyridine[10] failed to yield product after two days at room temperature when **5** was employed instead of benzoyl chloride. The reaction proceeded at a reasonable rate (1 day at room temperature) only after 4-(dimethylamino)pyridine (DMAP) was added.

The preferred reaction conditions avoided the use of excess acid chloride **5** because it led to the formation of small amounts of the anhydride of the benzyl-protected gallic acid, which was difficult to remove. The anhydride may have formed by the reaction of small amounts of hydrolyzed acid chloride with **5** in the presence of DMAP.

The selection of the appropriate solvent for the reaction was of critical importance in order to achieve very high α:β selectivity. The results obtained with five solvents are summarized in Table 1, entries 1–5.

In general, highest selectivities were found when acetonitrile was used as a solvent. The use of α-D-glucose as the starting material led to a product that contained only 3.8% of the β anomer. When β-D-glucose was employed as the carbohydrate reactant, the selectivity switched, and even lower amounts of the minor isomer were formed (1.7% α product). Among the solvents tested, DMF and chloroform led to incomplete conversions (results not shown). Pyridine, traditionally the solvent of choice for the preparation of α esters of D-glucose, did not perform better than several other solvents. Surprisingly, the use of dichloromethane led to poor selectivity in the attempt to prepare the α anomer (Table 1, entry 2). It appears that this solvent accelerates the rate of mutarotation relative to the rate of condensation to the ester.

Since DMAP is used in almost stoichiometric amounts (see Section 1), and since DMAP reacts quickly and completely with the acid chloride to form an acylammonium salt,[11] it can be assumed that the reaction mixture contains very low concentrations of base or acid that could catalyze mutarotation. To test whether a larger excess of base (DMAP) changes the selectivity of the reaction, a conversion using a twofold increase of DMAP in acetonitrile was performed. The result is shown in Table 1, entry 6. The selectivity of the reaction starting with β-D-glucose was found to be unchanged, while the transformation using α-D-glucose showed a small decrease. It appears that the increase in the rate of mutarotation caused by the presence of an excess base is significant only for the less reactive α-D-glucopyranose.

Table 1
Anomeric selectivity in the synthesis of benzyl-protected PGG

Entry	Solvent	Reagents	α:β ratio (**6**:**7**) α-Glc as reactant	α:β ratio (**6**:**7**) β-Glc as reactant
1	Acetonitrile	**5**, DMAP	**96.2**:**3.8**	**1.7**:**98.3**
2	CH_2Cl_2	**5**, DMAP	79.7:20.3	2.8:97.2
3	Ethyl acetate	**5**, DMAP	93.8:6.2	2.9:97.1
4	Pyridine	**5**, DMAP	93.4:6.6	2.6:97.4
5	THF	**5**, DMAP	92.2:7.8	5.1:94.9
6	Acetonitrile	**5**, 2 equiv DMAP	95.3:4.7	1.7:98.3
7	CH_2Cl_2	**4**, DMAP, DCC	70.4:29.6	6.4:93.6
8	CH_2Cl_2	**5**, NEt_3	4.4:95.6	2.3:97.7
9	CH_2Cl_2	**5**, TMEDA	6.9:93.1	**1.3**:**98.7**

Since commercially available α- and β-D-glucopyranose contain small amounts of the opposite isomers, the exact composition of the starting materials had to be determined in order to assess the degree of anomerization occurring during the reaction. The anomeric purity of the respective D-glucose isomers was established by standard methodology using gas chromatography of trimethylsilylated D-glucose.[12] The results are summarized in Table 2.

Table 2
Anomeric purity of starting materials used in the study

Commercial reactant	α:β ratio
α-D-glucose	97.5:2.5
β-D-glucose	1.5:98.5

A comparison of the results in Tables 1 and 2 shows that under the reaction conditions leading to the α anomer of D-glucose in acetonitrile minimal anomerization of the starting material occurs. Due to the higher nucleophilicity of the β anomer (kinetic anomeric effect[13]), the detected change of α:β ratio from reactant to product was even smaller (0.2%) for the reaction of β-D-glucose.

The new protocol to synthesize anomers of gallotannins with high selectivity was compared with established methods. The most commonly used procedure applies the Steglich methodology.[2,3,9] The carbohydrate is esterified with gallic acid in the presence of *N*,*N*-dicyclohexylcarbodiimide (DCC) and DMAP in dichloromethane. As can be seen in Table 1, entry 7, the method leads to very low anomeric selectivity (70% α product) when using α-D-glucose as the reactant. The selectivity is much improved, but switched (α:β = 6.4:93.6), when starting with β-D-glucose. Again, the improved selectivity can be explained by the kinetic anomeric effect: mutarotation has less of an influence on the outcome of the reaction when β-D-glucose is used as the starting material due to the higher nucleophilicity of this anomer.

Two slightly different methods are commonly employed in the β-selective synthesis of galloyl esters of D-glucose.[6,14] Both use the benzyl-protected acid chloride of gallic acid **5** as the acylating agent and dichloromethane as the solvent. The two procedures only differ in the selection of the base reagent. One uses triethylamine, the other employs *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). As indicated in Table 1, entries 8 and 9, both methods lead to very high selectivities when starting with β-D-glucose (α:β ≈ 2:98). Moreover, the outcome of the transformations is less dependent on the anomeric configuration of the starting material when compared to the results of the transformations in Table 1, entries 1–7. Even when using α-D-glucose as a starting material, both methods deliver a high β selectivity (95.6% and 93.1%, respectively). Since mutarotation is known to be base catalyzed,[15] and since both methods make use of stronger bases than DMAP, an increased rate for the mutarotation can be assumed. The kinetic anomeric effect together with an equilibrium composition that may be shifted toward the β anomer of D-glucose can explain the almost exclusive formation of the β product.

In conclusion, the present study establishes a procedure that allows for a highly α- or β selective synthesis of gallotannins. Further advantages of the methodology are the excellent yield and a simple workup. In general, a high α-selectivity is more difficult to achieve than a high β selectivity due to the kinetic anomeric effect favoring the latter. High β selectivity can also be obtained by starting from the α reactant if tertiary amines are used as bases. The disadvantage of this procedure is that a chromatographic purification of the product is needed. The results of this study will allow for a far more efficient synthesis of the anomers of gallotannins and ellagitannins, which will facilitate the evaluation of the biological activities of these important classes of compounds.

1. Experimental

1.1. Selective synthesis of the anomers of benzyl-protected PGG (6 and 7)

The acid chloride **5** (459 mg, 1.00 mmol) was mixed with α- or β-D-glucose (36 mg, 0.20 mmol) (α-D-glucose: Aldrich 158968; β-D-glucose: Sigma G5250) in 10 mL of solvent. DMAP (128 mg, 0.105 mmol) was added last. After stirring for 48 h at room temperature, the solvent was evaporated. The residue was dissolved in several mL of CH_2Cl_2, and 1 g of silica gel was added. After solvent evaporation, the solid residue was added on top of a 2.5-cm layer of silica gel in a glass filter funnel. The product was eluted with 20 mL of a mixture of 1:1 toluene–EtOAc. After solvent evaporation and drying, a highly viscous, clear oil was obtained. The yield for the reaction in acetonitrile was 441 mg (96%). The product identity was established by NMR spectroscopy.[9] The ratio of anomers was determined by HPLC. The separation of the anomers **6** and **7** on standard RP18 columns failed. A method that employed the use of an RP-Amide column was successful (Ascentis RP-Amide, 5 mm, 25 cm × 4.6 mm, isocratic 71% THF + 29% H_2O, UV detection 254 nm, t_R for **6**: 47.5 min, t_R for **7**: 50.0 min).

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