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Stereoselective synthesis of 1-*O*-β-feruloyl and 1-*O*-β-sinapoyl glucopyranoses

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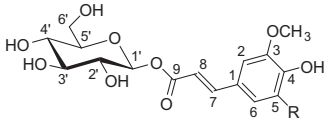
ABSTRACT

1-*O*-β-Feruloyl and 1-*O*-β-sinapoyl glucopyranoses are two common substrates for serine carboxypeptidase-like acyltransferases and serve as acyl donors in the biosynthesis of numerous secondary metabolites. In addition, they are involved in plant cell wall cross-linking and are also ideal substrates for studying the kinetics of lignification involving hydroxycinnamates. We report the first chemical (and multi-gram scale) synthesis of 1-*O*-β-feruloyl and 1-*O*-β-sinapoyl glucopyranoses.

1. Introduction

First isolated in 1960, 1-*O*-β-feruloyl and 1-*O*-β-sinapoyl glucopyranoses, **1** and **2**, are ubiquitous in plants (Fig. 1).[1] Instead of the coenzyme A-activated hydroxycinnamates, these hydroxycinnamoyl glucopyranoses are the common substrates for a class of acyltransferases known as serine carboxypeptidase-like (SCPL) acyltransferases, and serve as acyl donors for the biosynthesis of numerous plant secondary metabolites.[2] It is generally believed that these enzymes were adapted from serine carboxypeptidase to take over the acyl transfer function, making them an ideal system to study principles of functional adaption and molecular evolution of plant genes.[3] The roles of SCPL acyltransferases in plant metabolism remain largely elusive, with research on this class of enzymes only recently reported.[4] There is also evidence that 1-*O*-β-feruloyl glucopyranose, but not feruloyl-CoA, is the acyl donor for feruloylation of arabinoxylan.[5] Feruloylated arabinoxylan is involved in arabinoxylan cross-linking in grass cell walls (via ferulate dehydrodimerization) and has been implicated as an initiation or nucleation site for lignification in grass cell walls (via radical coupling between ferulate and monolignols);[6] ferulate thus serves as a powerful plant cell wall cross-linking agent. Understanding the nature and scope of ferulate–polysaccharide–lignin interactions may provide a basis for selection or genetic modification of plants aimed at improved utilization of plant cell walls.[7] The hydrophilic nature of 1-*O*-β-feruloyl and 1-*O*-β-sinapoyl glucoses also makes them ideal substrates for studying the kinetics of lignification involving hydroxycinnamates,[8] and we are exploring their use as hydrophilic monolignol (partial) replacements.[9]

Access to 1-*O*-β-feruloyl and 1-*O*-β-sinapoyl glucopyranoses is needed to study the biological and biochemical processes in which they are involved. 1-*O*-β-Feruloyl and 1-*O*-β-sinapoyl glucopyranoses are usually obtained by extraction and purification from plant materials. However, these methods are tedious and only a small amount is obtained even from a large amount of plant materials. An alternative approach is developed through an enzymatic reaction using recombinant proteins of sinapate glucosyltransferase derived from globe amaranth (*Gomphrena globasa*) cDNA.[10] Although the yield has been improved by coupling with a recycling system of UDP-glucose by sucrose synthase from *Arabidopsis thaliana* and using a relatively large amount of starting materials and enzymes, only small amounts of 1-*O*-β-feruloyl and 1-*O*-β-sinapoyl glucoses are produced, presumably due to product inhibition. Given the low yields of these approaches, chemical synthesis is the only route to obtain 1-*O*-β-feruloyl and 1-*O*-β-sinapoyl glucopyranoses in moderate quantities.



1 R = H, 1-O-β-feruloyl glucopyranose
2 R = OCH_3, 1-O-β-sinapoyl glucopyranose

Figure 1. Structures of 1-*O*-β-feruloyl and 1-*O*-β-sinapoyl glucopyranoses.

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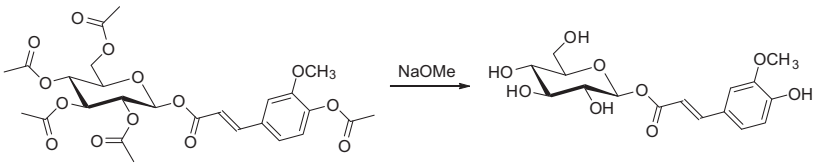

Figure 2. Deacetylation as a key step in claimed syntheses of 1-*O*-β-feruloyl glucopyranose.[11]

To the best of our knowledge, the chemical synthesis of 1-*O*-β-sinapoyl glucopyranose has not been reported before. Although the chemical synthesis of 1-*O*-β-feruloyl glucopyranose, via two routes, has been claimed recently,[11] one reference provides no characterization to support the contention, and the other presents *^{1}H NMR spectra that are inconsistent with those of 1-O-β-feruloyl glucopyranose!*[12] These reported syntheses proceeded via a common intermediate, 1-*O*-β-acetylferuloyl 2,3,4,6-tetra-*O*-acetylglucose (the yields for synthesizing this key intermediate were not reported in either paper), followed by deacetylation of this intermediate with sodium methoxide to give 1-*O*-β-feruloyl glucose in extremely low yields (Fig. 2). We found key steps in both routes to be irreproducible. Here, we report an effective procedure that results in the preparation of 1-*O*-β-feruloyl and 1-*O*-β-sinapoyl glucopyranoses stereoselectively and reproducibly at a multi-gram scale.

2. Results and discussion

Similarly to the two reported protocols, our strategy is to couple a proper glucosyl donor with protected hydroxycinnamic acids. To ensure high β-stereoselectivities in the glucosylation steps, we accommodate a neighboring group participation approach and protect the 2-hydroxyl group of the glucosyl donor as an ester. Since the glucosyl ester is activated by the acetal oxygen and is thus very labile under normal deacylation conditions, the key to the synthesis is to find a superior acyl group that can be selectively removed in the presence of the labile glucosyl ester bond. To fulfill this goal, we chose chloroacetyl as the protecting group. The rate of alkaline hydrolysis of the chloroacetyl group was found to be 760 times faster than that of acetyl.[13] Furthermore, the chloroacetyl group is susceptible to nucleophilic attack at the methylene position. We envisioned that S_N2 substitution at this methylene position might allow further activation of the ester toward hydrolysis, which would enhance the selectivity of deacylation.

Our synthesis of both **1** and **2** proceeds via intermediates 2,3,4,6-tetra-*O*-chloroacetylglucose **4** and 2,3,4,6-tetra-*O*-chloroacetylglucosyl trichloroacetimidate **5** (Scheme 1). Several protocols to access **4** have been previously reported.[14] After surveying a series of reaction conditions, we found the optimum was to add chloroacetyl chloride in methylene chloride slowly to a suspension of glucose in methylene chloride at 0 °C, producing 1,2,3,4,6-penta-*O*-chloroacetylglucose **3** in 98% yield as an inseparable mixture of α- and β-anomers (94:6). Selective removal of the anomeric chloroacetyl group reproducibly was unexpectedly troublesome. *N*-Benzylamine did selectively cleave the glucosyl ester bond. However, the following purification was found difficult, especially at a relatively large scale. In our hands, hydrazine acetate in THF left the starting material **3** intact, probably due to the insolubility of hydrazine acetate in THF.[14c] Changing the solvent to DMF did give the desired product **4**, but the yield varied significantly from batch to batch.[14b] This is not surprising since hydrazine acetate has been used to cleave chloroacetyl esters of sugar derivatives.[15] When the reaction was carried out at 0 °C for 3 h, 2,3,4,6-tetra-*O*-chloroacetylglucose **4** was obtained in good yield reproducibly, with the α-anomer as the major product. In the presence of a catalytic amount of 1,8-diazabicycloundec-7-ene, 2,3,4,6-tetra-*O*-chloroacetylglucose **4** reacted with trichloroacetonitrile to give the glucosyl donor, 2,3,4,6-tetra-*O*-chloroacetylglucosyl trichloroacetimidate **5** in 87% yield.[14c]

In one of the previous routes, acetylferulic acid was used as a glycosyl acceptor.[11a] We envisioned that it might be difficult to cleave the aryl acetate selectively in the presence of a labile glucosyl ester (vide supra). *O*-Benzyl protected hydroxycinnamic acids have been previously used in the synthesis of caffeoyl glucose.[14c] However, not surprisingly, the yield of debenzylation was low, probably due to the hydrogenation of the unsaturated ester. Chloroacetylferulic acid **6**, and chloroacetylsinapic acid **7**, were chosen as the glycosyl acceptors and prepared in one step following the literature procedure.[16] Under strictly anhydrous conditions, the glycosyl donor, **5**, was activated by trimethylsilyl triflate, and coupled with the glycosyl donors, **6** and **7**, to form the desired glucosyl esters in 72% and 51% yields, respectively. The glucosylations were highly β-stereoselective—no α-products were detected. The chloroacetates **8a** and **9a** were partially cleaved to give **8b** and **9b** during the aqueous work up. However, both hydrolyzed and non-hydrolyzed products were readily used for the final deprotection.

With the glucosyl esters at hand, we screened conditions for global deacylation. Chloroacetates can be hydrolyzed under much milder conditions than those required for acetate removal. We found 1:1 pyridine/water ideal to selectively remove the chloroacetyl groups; the desired products, **1** and **2**, were obtained in 78–85% yields.[17] Interestingly, 1-carboxymethyl pyridinium betaine was isolated as the byproduct. Control experiments showed **8b** was not decomposed or even partially hydrolyzed in sodium phosphate buffer at a similar pH for more than 4 days. These results strongly suggest that the chloroacetyl group was activated by S_N2 attack by pyridine to form Kröhnke salts,[18] followed by the hydrolysis of the corresponding ester bonds.[19] As a result of this synthetic approach, 1-*O*-β-feruloyl and 1-*O*-β-sinapoyl glucopyranoses were obtained on multi-gram scales in 35% and 25% overall yields, respectively.

3. Conclusion

We have devised a total synthesis of 1-*O*-β-feruloyl and 1-*O*-β-sinapoyl glucopyranoses. Our protocol involves stereoselective glycosylation of a chloroacetyl-protected sugar donor and 4-*O*-chloroacetylated hydroxycinnamic acids followed by removal of the chloroacetyl groups under mild conditions. The dual reactivity of the chloroacetyl group used here eliminated the cleavage of the labile glucosyl ester bond. With this protocol, we have synthesized 1-*O*-β-feruloyl and 1-*O*-β-sinapoyl glucopyranoses on multi-gram scales. We anticipate that the results presented here will facilitate the preparation of general β-glycosyl esters for chemical and biological studies.

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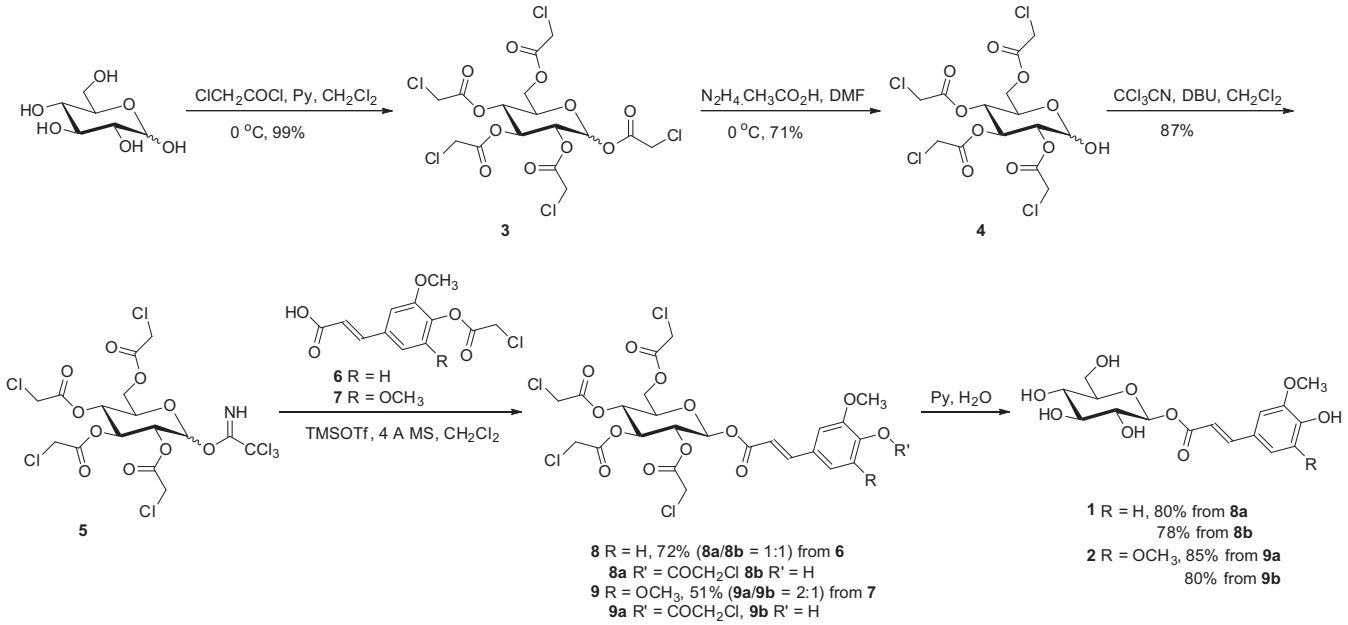

Scheme 1. Synthesis of 1-*O*-β-feruloyl and 1-*O*-β-sinapoyl glucopyranoses.

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Supplementary data

Supplementary data (experimental procedures and ^{1}H and ^{13}C NMR spectra for the complete synthesis of compounds **1** and **2**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.038.

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