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Short Note

1,3,4,5-Tetra-*O*-benzoyl-α-D-tagatopyranose

Yiming Hu, Akihiro Iyoshi, Yui Makura, Masakazu Tanaka and Atsushi Ueda *

Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan; ym-hu@nagasaki-u.ac.jp (Y.H.); matanaka@nagasaki-u.ac.jp (M.T.)
* Correspondence: aueda@nagasaki-u.ac.jp

Abstract

D-Tagatose, a rare sugar, is recognized as a low-calorie sweetener, used in daily life. Although D-tagatose exhibits intriguing biological activities, the synthesis of its derivatives has rarely been reported. In this study, we developed a method for synthesizing 1,3,4,5-tetra-*O*-benzoyl-α-D-tagatopyranose through the regioselective benzoylation of D-tagatose in a single step, achieving an 88% yield on a gram scale. Additionally, 1,2,3,4,5-penta-*O*-benzoyl-α-D-tagatopyranose and 1,2,3,4,6-penta-*O*-benzoyl-α-D-tagatofuranose were synthesized in 50% yield as a 7:1 mixture. The structures of the three new benzoylated D-tagatose derivatives were confirmed by ^{1}H, ^{13}C NMR, 2D NMR, FT-IR, and HRMS analyses.

Keywords: tagatose; benzoylation; pyranose; furanose; regioselective

1. Introduction

D-Tagatose is a rare sugar found in limited quantities in nature [1,2]. The chemical structure of D-tagatose is similar to that of naturally occurring sugars. For example, D-tagatose is the C4 epimer of D-fructose and the C1/C2-isomer of D-galactose. Owing to its intriguing biological activities that offer multiple health benefits to patients with type 2 diabetes [3,4] and its role as a low-calorie sweetener [5,6], D-tagatose is produced in large quantities from D-galactose through an enzymatic process [7–9]. Although carbohydrates serve as excellent chiral building blocks [10,11], the synthesis of D-tagatose derivatives has rarely been reported [12–16]. Due to its mutarotation, D-tagatose exists in five different structures, namely, α-D-tagatopyranose, β-D-tagatopyranose, α-D-tagatofuranose, β-D-tagatofuranose, and acyclic D-tagatose (open-chain form). Therefore, the control of the conformation of these structures is essential for the development of D-tagatose derivatives.

The regioselective acylation of monosaccharides is a valuable approach for the preparation of derivatives such as glycosides. Benzoyl protection, in particular, serves as an important acyl protecting group due to its ease of introduction and removal, greater stability compared to the acetyl group, strong UV absorbance, and wide commercial availability. Tetrabenzoylated hexoses can be transformed into various glycosyl donors [17], while pentabenzoylated hexoses can function as glycosyl donor themselves [18,19] and as photocatalytic C-glycosidation precursors [20]. Consequently, regioselective benzoylation has been explored in the literature [21]. However, there are limited reports on the benzoylation of rare sugars. Yamanoi et al. reported the benzoylation of D-allulose (D-psicose) and l-fructose [22]. The benzoylation of D-allulose mainly yielded 1,3,4,6-tetra-*O*-benzoyl-D-allulofuranose (54%) along with 1,3,4,5-tetra-*O*-benzoyl-D-allulopyranose (12%, Scheme 1). Similarly, the benzoylation of L-fructose resulted in 1,3,4,6-tetra-*O*-benzoyl-l-fructofuranose (64%) as the major product, accompanied by 1,3,4,5-tetra-*O*-

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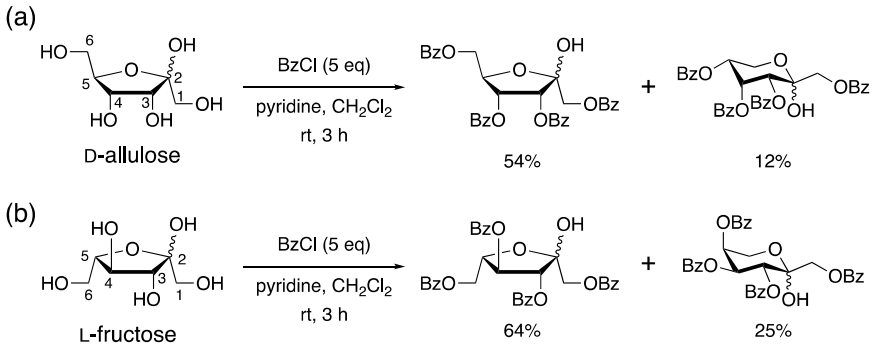
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benzoyl-l-fructopyranose (25%). Therefore, the development of regioselective benzoylation methods for rare sugars, overcoming mutarotation, is necessary. Fortunately, D-tagatose predominantly exists as α-pyranose and β-pyranose in aqueous solutions [23]. Indeed, Machinami et al. reported the tetraacetylation of D-tagatopyranose in 72%yield [24], and Mahrwald et al. described the synthesis of pentaacetylated Dl-tagatopyranose as a 1:1 mixture with acetylated Dl-sorbopyranose in 75% yield [25]. Herein, we report the synthesis of 1,3,4,5-tetra-*O*-benzoyl-D-tagatopyranose (**2**), 1,2,3,4,5-penta-*O*-benzoyl-α-D-tagatopyranose (**3**), and 1,2,3,4,6-penta-*O*-benzoyl-α-D-tagatofuranose (**4**) in a single step through the regioselective benzoylation of D-tagatose.



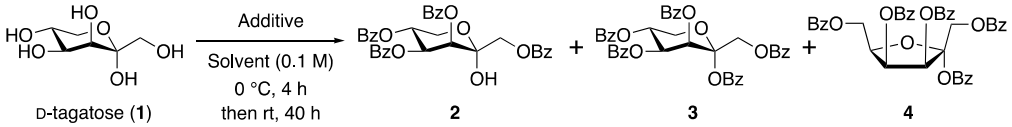
Scheme 1. Benzoylation products of rare sugars: (**a**) benzoylation of D-allulose and (**b**) benzoylation of l-fructose [22].

2. Results and Discussion

We initially investigated the synthesis of 1,3,4,5-tetra-*O*-benzoyl-D-tagatopyranose (**2**) via the regioselective benzoylation of D-tagatose (**1**), as detailed in Table 1. The optimal result was obtained by gradually adding five equivalents of benzoyl chloride (BzCl) to a solution of D-tagatose (**1**) in pyridine/CH_2Cl_2 over one hour at 0 °C, yielding tetrabenzoate **2** on a gram scale in 88% yield (entry 1). The ^{1}H NMR spectrum revealed that tetrabenzoate **2** existed as an α-anomer in $CDCl_3$. In this reaction, 1,2,3,4,5-penta-*O*-benzoyl-α-D-tagatopyranose (**3**) and 1,2,3,4,6-penta-*O*-benzoyl-α-D-tagatofuranose (**4**) were also produced in a 5% yield as an inseparable mixture with a ratio of 1.5:1. Initiating the reaction at a lower temperature (e.g., 0 °C) is crucial for preventing the formation of other conformers, such as furanose and open-chain forms. When pyridine was used as the solvent, the formation of **3** was suppressed, although the yield of **2** decreased (entry 2). Conversely, the use of seven equivalents of BzCl along with 4-dimethylaminopyridine (DMAP) enhanced the formation of **3**, resulting in 32% yield (**3**:**4** = 1.3:1, entry 3). The optimal yield and proportion of **3**, at 50% (**3**:**4** = 7:1), was achieved by conducting the reaction at 50 °C following the addition of DMAP (entry 4).

Subsequently, the conversion of tetrabenzoate **2** to pentabenzoate **3** was carried out as shown in Table 2. Under standard benzoylation conditions, pentabenzoate **3** was obtained in modest NMR yields of 10% at room temperature (entry 1) and 21% at 50 °C (entry 2) using three equivalents of BzCl in the presence of DMAP. Notably, only pyranose **3** was produced in this reaction, albeit in low yield, indicating the poor reactivity of the anomeric hydroxy group. Consequently, Yamanoi's acylation conditions (*n*-BuLi, BzCl, THF, –30 °C), typically used for the acetylation of the anomeric hydroxy group of ketoses, were employed for the benzoylation of **2** at the anomeric position [22,26]. Ultimately, tetrabenzoate **2** was transformed into pentabenzoate **3** with a 61% NMR yield. These findings suggest that compound **2** is unlikely to be an intermediate in the formation of compound **4** via acyl migration.

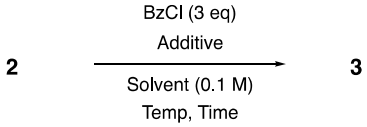
Table 1. Synthesis of 1,3,4,5-tetra-*O*-benzoyl-D-tagatopyranose (**2**) and 1,2,3,4,5-penta-*O*-benzoyl-D-tagatopyranose (**3**).



Entry	BzCl (eq) [1]	Additive	Solvent	Yield	
				2	3 + 4 (ratio) [2]
1	5	none	pyridine/CH_2Cl_2 (1:1)	88%	5% (1.5:1)
2	5	none	pyridine	82%	trace
3 [3]	7	DMAP (0.3 eq)	pyridine/CH_2Cl_2 (1:1)	46%	32% (1.3:1)
4 [3,4]	7	DMAP (0.3 eq)	pyridine/CH_2Cl_2 (1:1)	13%	50% (7:1)

[1] BzCl was introduced using a syringe pump over one hour. [2] The ratio was determined by ^{1}H NMR. [3] DMAP was added after four hours. [4] Instead of stirring at room temperature, the reaction mixture was heated to 50 °C for 40 h.

Table 2. Conversion of tetrabenzoate **2** to pentabenzoate **3**.



Entry	Additive	Solvent	Temp	Time (h)	NMR Yield [1]
1	DMAP (0.3 eq)	pyridine/CH_2Cl_2 (1:1)	rt	26	10%
2	DMAP (0.3 eq)	pyridine/CH_2Cl_2 (1:1)	50 °C	26	21%
3	*n*-BuLi (1.3 eq)	THF	−30 °C	4	61%

[1] The NMR yield was determined by ^{1}H NMR.

For D-tagatofuranoses, comparing the chemical shifts in the anomeric positions ($\delta_{C\text{-}2}$) in the ^{13}C NMR spectra is a convenient method to determine the anomeric configuration ($\delta_{C\text{-}2}$ = 107–109 ppm for α-anomers vs. $\delta_{C\text{-}2}$ = 103–105 ppm for β-anomers) [15]. In contrast, tagatopyranoses exhibit only small differences in the ^{13}C NMR chemical shifts between the α- and β-anomers [23]. However, the coupling constants in the ^{1}H NMR spectra show significant differences between the anomers. Due to the anomeric effect, α-D-tagatopyranose adopts a $^5C_2$-conformation, while β-D-tagatopyranose forms a $^2C_5$-conformation. Consequently, the coupling constants of compounds **2**–**4** were compared with those of 1-deoxy-D-tagatose (Table 3) [27]. The large coupling constants (approximately 10 Hz) of the $J_{4,5}$ and $J_{5,6b}$ values in compounds **2** and **3** confirmed the presence of consecutive diaxial protons, clearly indicating the $^5C_2$-conformation of α-D-tagatopyranose. On the other hand, the *J* values of furanose **4** were similar to that of 1-deoxy-D-tagatofuranoses and the chemical shifts in the anomeric carbon of **4** was 108.4 ppm, identical to that of α-D-tagatofuranoses [15]. The nuclear Overhauser effect spectroscopy (NOESY) spectra further support this assignment by showing correlations between H-4 and H-6 in pyranoses **2** and **3**, while furanose **4** exhibits correlations between H-3 and H-5 (Figure 1).

Table 3. Coupling constants of compounds **1**–**3** [1].

Compound	$J_{1a,1b}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
2	12.0	3.4	10.2	5.9	10.7	10.7
3	12.2	3.3	10.3	5.9	10.5	11.3
4	11.9	5.4	4.6	6.5	5.6	11.7
1-deoxy-α-D-tagatopyranose [2]	–	3.3	9.6	5.6	10.8	10.8
1-deoxy-β-D-tagatopyranose [2]	–	3.3	4.6	2.0	2.7	13.1
1-deoxy-α-D-tagatofuranose [2]	–	5.3	5.3	N.D. [3]	N.D. [3]	N.D. [3]
1-deoxy-β-D-tagatofuranose [2]	–	4.5	4.5	N.D. [3]	N.D. [3]	N.D. [3]

[1] The *J* values of coupling constants are shown in Hz. [2] The coupling constants of 1-deoxy-D-tagatoses were obtained from the literature [27]. [3] N.D. = not determined.

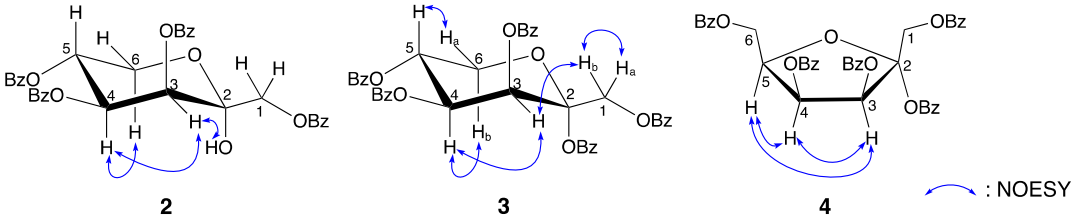


Figure 1. Key NOESY correlations of compounds **2**–**4**.

3. Materials and Methods

3.1. General Procedure and Method

Optical rotations were measured on a JASCO DIP-370 polarimeter (JASCO Corporation, Tokyo, Japan) using $CHCl_3$ as a solvent. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL JNM-ECZ400R (400 MHz and 100 MHz) spectrometers (JEOL Ltd., Tokyo, Japan). Chemical shifts (δ) are reported in parts per million (ppm). Tetramethylsilane was used as the internal reference (0.00 ppm in $CDCl_3$) for ^{1}H NMR spectra, while the central solvent peak acted as the reference (77.0 ppm in $CDCl_3$) for ^{13}C NMR spectra. The IR spectra were recorded on a Shimadzu IRAffinity-1 FT-IR spectrophotometer (Shimadzu Corporation, Kyoto, Japan). High-resolution mass spectra (HRMS) were obtained on a JEOL JMS-T100TD using electrospray ionization (ESI) (JEOL Ltd., Tokyo, Japan) in time-of-flight (TOF) mode. Analytical thin layer chromatography (TLC) was performed with Merck Millipore precoated TLC plates (MilliporeSigma, Burlington, VT, USA), silica gel 60 F_{254}, and layer thicknesses of 0.25 mm. Compounds were observed in UV light at 254 nm and then visualized by staining with *p*-anisaldehyde stain. Flash column chromatography separations were performed on Kanto Chemical silica gel 60N, spherical neutral, with particle sizes of 40–50 µm. All moisture-sensitive reactions were conducted under an inert atmosphere. Reagents and solvents were of commercial grade and were used as supplied, unless otherwise noted.

3.2. 1,3,4,5-Tetra-O-benzoyl-α-D-tagatopyranose (2), 1,2,3,4,5-penta-O-benzoyl-α-D-tagatopyranose (3), and 1,2,3,4,6-penta-O-benzoyl-α-D-tagatofuranose (4)

3.2.1. Synthesis of 2, 3, and 4 from 1 (Table 1, Entry 1)

A solution of D-tagatose (**1**: 1.80 g, 10.0 mmol) in pyridine/CH_2Cl_2 (50 mL each) was prepared, to which benzoyl chloride (5.81 mL, 50.0 mmol) was added at 0 °C over 1 h using a syringe pump. The resulting mixture was stirred at 0 °C for 3 h and at room temperature for 40 h. The reaction was quenched by adding MeOH (10 mL) and stirred at room temperature for 10 min. After solvent removal, the residue was diluted with 50% EtOAc in *n*-hexane, washed with 1 M HCl, sat. $NaHCO_3$ aq, water, and brine, and then dried over anhydrous $MgSO_4$. The residue was purified by flash column chromatography

on silica gel (20% EtOAc in *n*-hexane) to yield **2** (5.28 g, 88%) as an off-white amorphous solid along with a mixture of **3** and **4** (328 mg, 5%, **3**:**4** = 1.5:1) as a colorless syrup.

3.2.2. Synthesis of 3 and 4 from 1 (Table 1, Entry 4)

A solution of D-tagatose (**1**: 180 mg, 1.00 mmol) in pyridine/CH_2Cl_2 (1:1, 10 mL) was prepared and benzoyl chloride (0.813 mL, 7.00 mmol) was added at 0 °C over 1 h using a syringe pump. The resultant mixture was stirred at 0 °C for 3 h before adding 4-dimethylaminopyridine (36.6 mg, 0.300 mmol). The reaction mixture was heated at 50 °C for 40 h and then quenched by adding MeOH (1 mL). After stirring for 10 min at room temperature and evaporating the solvents, the residue was dissolved in 50% EtOAc in *n*-hexane, washed successively with 1 M HCl, sat. $NaHCO_3$ aq, water, and brine, and dried over anhydrous $MgSO_4$. The residue was purified by flash column chromatography on silica gel (15% EtOAc in *n*-hexane) to give **3** along with **4** (348 mg, 50%, **3**:**4** = 7:1) as a white solid.

3.2.3. Conversion of 2 to 3 (Table 2, Entry 3)

Tetrabenzoate **2** (298 mg, 0.500 mmol) was azeotropically dried with toluene three times and then dissolved in anhydrous THF (5 mL). The solution was cooled to −30 °C, and *n*-BuLi (1.6 M in *n*-hexane, 0.406 mL, 0.650 mmol) and benzoyl chloride (0.174 mL, 1.50 mmol) were added to the reaction mixture, which was stirred at the same temperature for 4 h. After adding sat. NH_4Cl aq, the aqueous layer was extracted with EtOAc three times, and the combined organic layers were washed with water and brine. After drying over anhydrous $MgSO_4$ and evaporating of the solvents, the NMR yield of **3** was determined to be 61% using *p*-xylene as an internal standard.

3.2.4. Compound Data of 1,3,4,5-Tetra-*O*-benzoyl-α-D-tagatopyranose (2)

R_f = 0.31 (30% EtOAc in *n*-hexane). $[\alpha]^{25}_D$ –43.1 (*c* 0.99, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15–8.12 (2H, m, Ar*H*), 8.04–7.96 (4H, m, Ar*H*), 7.81–7.79 (2H, m, Ar*H*), 7.66–7.61 (1H, m, Ar*H*), 7.55–7.48 (4H, m, Ar*H*), 7.45–7.35 (5H, m, Ar*H*), 7.26–7.22 (2H, m, Ar*H*), 6.10 (1H, dd, $J_{4,5}$ = 10.2, $J_{3,4}$ = 3.4 Hz, H-4), 6.02 (1H, d, $J_{3,4}$ = 3.4 Hz, H-3), 5.75 (1H, ddd, $J_{5,6b}$ = 10.7, $J_{4,5}$ = 10.2, $J_{5,6a}$ = 5.9 Hz, H-5), 4.76 (1H, d, $J_{1a,1b}$ = 12.0 Hz, H-1a), 4.31 (1H, d, $J_{1a,1b}$ = 12.0 Hz, H-1b), 4.31 (1H, s, O*H*), 4.30 (1H, dd, $J_{6a,6b}$ = 10.7, $J_{5,6a}$ = 5.9 Hz, H-6a), 4.18 (1H, t, $J_{6a,6b}$ = $J_{5,6b}$ = 10.7 Hz, H-6b). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 167.1, 165.9, 165.5, 165.2, 133.7, 133.6, 133.4, 133.1, 130.0 (4C), 129.8 (2C), 129.7 (2C), 129.21, 129.17, 129.1, 128.9, 128.7 (2C), 128.5 (2C), 128.4 (2C), 128.3 (2C), 96.9 (C-2), 69.8 (C-4), 69.7 (C-3), 67.7 (C-5), 65.8 (C-1), 60.5 (C-6). IR (KBr): 3431 (br), 3065, 2961, 1734, 1701 cm^{-1}. HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for $C_{34}H_{28}O_{10}Na$, 619.1591; found, 619.1580.

3.2.5. Compound Data of 1,2,3,4,5-Penta-*O*-benzoyl-α-D-tagatopyranose (3) and 1,2,3,4,6-Penta-*O*-benzoyl-α-D-tagatofuranose (4)

R_f = 0.37 (30% EtOAc in *n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of **3** and **4**) δ: 8.21–8.18 (1H, m, Ar*H*), 8.12–8.07 (2H, m, Ar*H*), 8.02–7.93 (3H, m, Ar*H*), 7.90–7.80 (4H, m, Ar*H*), 7.67–7.61 (1H, m, Ar*H*), 7.59–7.20 (14H, m, Ar*H*), 6.67 (0.4H, d, $J_{3,4}$ = 5.4 Hz, **4**-H-3), 6.37 (0.6H, d, $J_{3,4}$ = 3.3 Hz, **3**-H-3), 6.29 (0.4H, t, $J_{3,4}$ = 5.4, $J_{4,5}$ = 4.6, **4**-H-4), 6.13 (0.6H, dd, $J_{4,5}$ = 10.3, $J_{3,4}$ = 3.3 Hz, **3**-H-4), 5.88 (0.6H, ddd, $J_{5,6b}$ = 10.5, $J_{4,5}$ = 10.3, $J_{5,6a}$ = 5.9 Hz, **3**-H-5), 5.56 (0.6H, d, $J_{1a,1b}$ = 12.2 Hz, **3**-H-1a), 5.37 (0.4H, ddd, $J_{5,6a}$ = 6.5, $J_{5,6b}$ = 5.6, $J_{4,5}$ = 4.6 Hz, **4**-H-5), 5.23 (0.4H, d, $J_{1a,1b}$ = 11.9 Hz, **4**-H-1a), 4.93 (0.4H, d, $J_{1a,1b}$ = 11.9 Hz, **4**-H-1b), 4.75 (0.4H, dd, $J_{6a,6b}$ = 11.7, $J_{5,6a}$ = 6.5 Hz, **4**-H-6a), 4.70 (0.6H, d, $J_{1a,1b}$ = 12.2 Hz, **3**-H-1b), 4.68 (0.4H, dd, $J_{6a,6b}$ = 11.7, $J_{5,6b}$ = 5.6 Hz, **4**-H-6b). 4.53 (0.6H, dd, $J_{6a,6b}$ = 11.3, $J_{5,6a}$ = 5.9 Hz, **3**-H-6a), 3.95 (0.6H, t, $J_{6a,6b}$ = 11.3, $J_{5,6b}$ = 10.5 Hz, **3**-H-6b). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, mixture of **3** and **4**) δ: 166.0, 165.7, 165.6, 165.2, 165.1, 164.8, 164.5, 163.3, 133.8, 133.7,

133.6, 133.54, 133.47, 133.3, 133.15, 133.10, 133.0, 130.0, 129.91, 129.85, 129.71, 129.68, 129.6, 129.34, 129.29, 129.0, 128.9, 128.8, 128.74, 128.70, 128.6, 128.56, 128.4, 128.34, 128.30, 128.27, 128.2, 108.4 (**4**-C-2), 103.0 (**3**-C-2), 78.7 (**4**-C-5), 75.3 (**4**-C-3), 72.6 (**4**-C-4), 69.6 (**3**-C-4), 68.2 (**3**-C-3), 66.6 (**3**-C-5), 63.6 (**4**-C-1), 62.3 (**4**-C-6), 62.1 (**3**-C-6), 61.1 (**3**-C-1). IR (KBr): 3065, 3034, 1717 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{41}H_{32}O_{11}Na$, 723.1842; found, 723.1853.

4. Conclusions

The syntheses of 1,3,4,5-tetra-*O*-benzoyl-α-D-tagatopyranose (**2**) and 1,2,3,4,5-penta-*O*-benzoyl-α-D-tagatopyranose (**3**) were accomplished through regioselective benzoylation, achieving 88% and 50% yields, respectively. The structures of **2** and **3** were unambiguously determined by 1D and 2D NMR, which included a comparison of vicinal coupling constants on the pyranose ring, as well as FT-IR and HRMS analyses.

Supplementary Materials: The following supporting information can be downloaded: Figure S1. 1H NMR spectrum of tetrabenzoate 2; Figure S2: 13C NMR spectrum of tetrabenzoate 2; Figure S3: H-H COSY spectrum of tetrabenzoate 2; Figure S4: HSQC spectrum of tetrabenzoate 2; Figure S5: HMBC spectrum of tetrabenzoate 2; Figure S6: NOESY spectrum of tetrabenzoate 2; Figure S7: 1H NMR spectrum of pentabenzoates 3 and 4; Figure S8: 13C NMR spectrum of pentabenzoates 3 and 4; Figure S9: H-H COSY spectrum of pentabenzoates 3 and 4; Figure S10: HSQC spectrum of pentabenzoates 3 and 4; Figure S11: HMBC spectrum of pentabenzoates 3 and 4; Figure S12: NOESY spectrum of pentabenzoates 3 and 4.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Bz	Benzoyl
DMAP	4-Dimethylaminopyridine
THF	Tetrahydrofuran
NOESY	Nuclear Overhauser Effect Spectroscopy

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