One-Step Stereocontrolled Synthesis of α-Anomeric Carboxylic Acid Esters from Unprotected Glycosyl Donors: A Water-Soluble Aspirin Pro-Drug Analogue

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Dedicated to Professor Dieter Seebach for his seminal contributions to organic synthesis.

Abstract: The reaction of 2-(3-methoxypyridyl) β-D-gluco- and D-galactopyranosides with various carboxylic acids affords the corresponding α-1-esters in high yields. Aspirin can be solubilized in water as the α-D-galactopyranosyl ester.

Key words: carbohydrates , aspirin, pro-drugs, esters, stereoselectivity

The chemistry of anomerically substituted sugars occupies a central role in the realm of biologically relevant carbohydrates.[1] In this regard, glycosyl 1-esters (1-*O*-acyl aldoses) are of great interest as valuable intermediates in synthesis, as probes for enzymatic reactions, and as industrially important compounds. Glycosyl 1-esters are abundant in nature, particularly as 1,2-*trans* (or β-D)-isomers.[2]

The traditional methods for the chemical synthesis of glycosyl 1-esters have relied on a protocol where the anomeric hydroxyl group of a suitably protected sugar derivative is esterified. In order to gain access to the unprotected glycosyl 1-ester, the removal of the protective group must be mild enough so as not to cleave the ester, cause migration or lead to anomerization. For example, the lithio salt of 2,3,4,6-tetra-*O*-benzyl D-glucopyranose can be esterified, and the product subjected to hydrogenolysis to give a mixture of α- and β-D-glucopyranosyl carboxylic acid esters.[3] The α- or β-ester can predominate depending on the solvent. A related method relies on the esterification of 2,3,4,6-tetra-*O*-benzyl D-glucopyranose with acyl chlorides in the presence of amine bases.[4,5] Glycosyl 1-esters have been prepared as peracetates from the reaction of the corresponding glycosyl halides with silver[6] or cesium[7] carboxylates, or from the reaction of l-trichloroacetimidates with carboxylic acids.[8] The selective cleavage of ester protecting groups while maintaining the anomeric ester in the products of the above reactions can be problematic because of anomerization and ester migration.[9] Other methods of anomeric esterification utilize the Mitsunobu reaction,[2a,10] carbodiimide mediated esterification,[11] and acylation of tetra-*O*-benzyl-D-glucopyranosyloxy 1-tributylstannane.[12] 1-*O*-Acetyl-β-D-glucopyranose is produced by fermentation.[13]

There are two methods for the direct esterification of free sugars that lead predominantly to 1,2-*trans* glycosyl 1-esters. In the first,[14] β-D-glucopyranose was treated with *N*-acyl 1,2,4-triazole or 1,3-imidazole in the presence of a catalytic amount of sodium hydride to give β-D-glucopyranosyl 1-esters. Simple carboxylic esters as well as various polyenecarboxylates were prepared by this method.[14] The regioselectivity was attributed to the comparatively higher acidity of the anomeric hydroxy group. The slow mutarotation of β-D-glucopyranose in pyridine[15] was considered to contribute to the stereoselectivity of these 1,2-*trans* anomeric esterifications. A second method[16] for the direct esterification of free hexoses and disaccharides relies on *N*-acyl heterocycles such as mercaptobenzothiazole as acylating agents in pyridine in the presence of sodium hydride.

To the best of our knowledge, there are no methods for the direct preparation of 1,2-*cis* glycosyl esters from unprotected glycosyl donors. It is known that the nature of the solvent can influence the ratio of anomeric esters in the reaction of 2,3,4,6-tetra-*O*-benzyl D-glucopyranose with acyl chlorides, favoring the β-esters in benzene, and the α-esters in tetrahydrofuran. Although hydrogenolysis under neutral conditions should be compatible with the presence of an anomeric ester, their propensity to migrate via intramolecular transesterification[17] may lead to mixtures.

We describe herein a general method for the synthesis of α-D-glycopyranosyl 1-esters from unprotected donors, or donors in which only the primary hydroxyl carries a *tert*-butyldiphenylsilyl ether group. We have previously reported that 1,2-*trans* 2-(3-methoxypyridyl) D-hexopyranosides (MOP glycosides) are excellent glycosyl donors with and without hydroxyl protection in a variety of contexts.[18] For example, 2-(3-methoxypyridyl) β-D-galactopyranoside and its D-gluco analogue can be converted to 1,2-*cis* glycosides and oligosaccharides by treatment with excess alcohol as an acceptor in the presence of catalytic quantities of methyl triflate.[19] The same donors can be converted to 1,2-*cis* glycosyl phosphates and nucleotides with phosphoric acid or UDP free acid respectively without the need for *O*-protection.[20] 1,2-*cis*-Glycosyl azides can be prepared from unprotected MOP-donors and $TMSN_3$.[21]

Treatment of the readily available and crystalline MOP donors **1** and **2**[19,22] in acetonitrile or DMF with an excess

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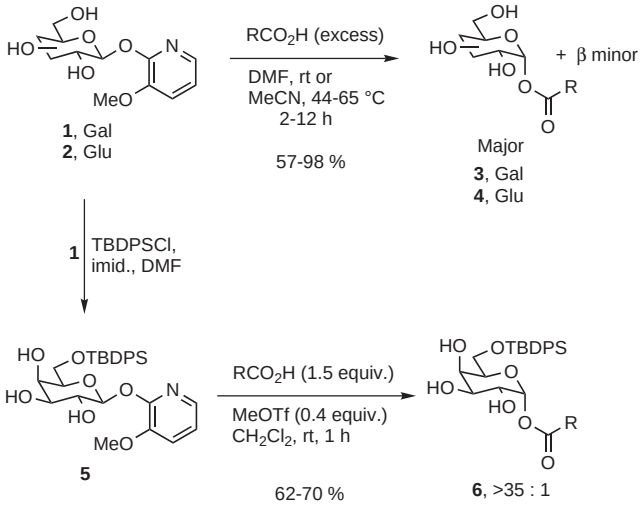
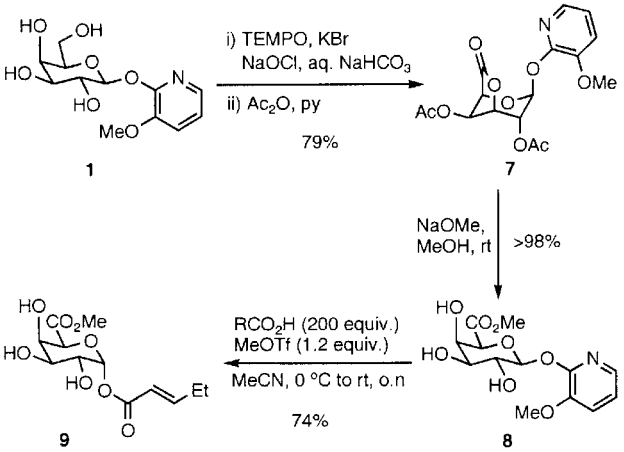
of a carboxylic acid under anhydrous conditions led to the corresponding α-D-gluco- and D-galactopyranosyl 1-carboxylates **3** and **4** respectively in excellent yields (Scheme 1). Table 1 lists the various products and the uniformly good to excellent ratios. Due to the relatively low solubility of the MOP donors in acetonitrile the reactions were done at slightly elevated temperatures. The configuration of the glycosyl esters was ascertained by ^{1}H and ^{13}C NMR spectroscopy. *N*-Acetyl neuraminic acid ester MOP donor was converted to the corresponding 2-acetate or 2-propionate ester in quantitative yield within 2 hours in DMF (Table 1). Aromatic and α,β-unsaturated acids, as well as pivalic acid required longer reaction times, but led to the 1,2-*cis* glycosyl esters as major products (6:1 to 30:1 respectively, Table 1).

The selective cleavage of acetates from methyl 2,3,4-tri-*O*-acetyl-1-*O*-pivaloyl β-D-glucopyranosid-uronate has not been possible.[23] It was therefore of interest to explore the reactivity of methyl 2-(3-methoxypyridyl)-β-D-galactopyranosid-uronate vis-à-vis a carboxylic acid as shown in Scheme 2. The MOP group in **1** was compatible with



Scheme 1



Scheme 2

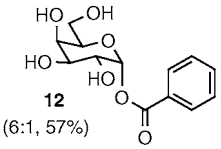
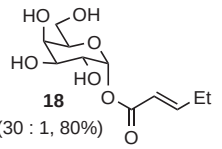
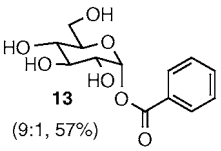
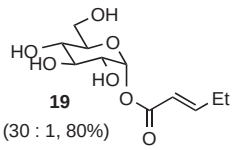
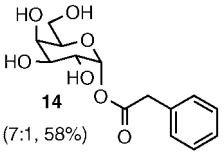
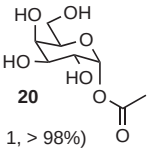
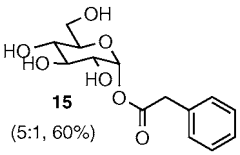
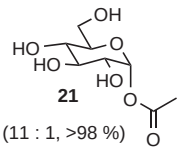
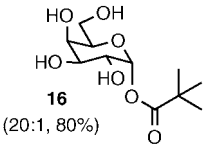
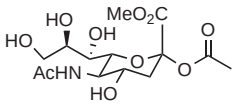
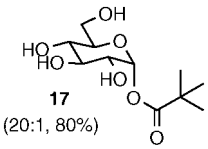
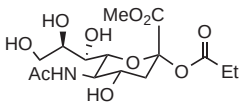
the conditions of oxidation required to form the lactone **7**. Methanolysis afforded the methyl ester **8** which when treated with excess *trans*-2-pentenoic acid in the presence of methyl triflate in acetonitrile gave the α-(2-*trans*-pentenoate)ester **9** in 74% yield. Again, selective MOP activation in the presence of free hydroxyl groups in an intrinsically less reactive glycosyl uronate donor and acid acceptor partner is noteworthy.

In order to diminish the amount of carboxylic acid and circumvent the low solubility of MOP donors in solvents like acetonitrile, or the need to use DMF as a solvent, we explored the same regioselective esterifications with the 6-*O*-*tert*-butyldiphenylsilyl ether derivative **5** of MOP-gal. The reactions were now complete in dichloromethane within 1 hour at room temperature in the presence of 0.4 mol equivalent of methyl triflate as a promoter (Table 2). Uniformly excellent α-selectivities were observed while using only 1.5 mol equivalent of carboxylic acid rather than the large excesses needed when the reactions were done in acetonitrile or DMF in the case of MOP-gal **1** and MOP-glu **2** (Table 1). Of significance was the esterification with *O*-acetyl salicylic acid (aspirin), which gave the corresponding α-glycosyl ester **10** (Scheme 3, Table 2). Cleavage of the TBDPS group afforded (α-D-galactopyranosyl)-2-acetoxybenzoate (**11**) as a freely water-soluble compound, in contrast to the sparingly soluble aspirin. The hydrolytic stability of **11** at three pH values was studied in order to evaluate the prospects of releasing the active ingredient in the stomach. Thus, at a concentration of 4 mg/mL, **11** was converted into aspirin within 30 min at pH 1, and 12 h at pH 4–6. Thus, it should be possible to use glycosyl 1-esters prepared in one step from the corresponding MOP glycosyl donors as a means of drug delivery and other biomedical applications.[24]

In addition to its solubilizing effect, the 6-*O*-TBDPS group in **5** may also contribute to the much higher proportion of α-anomeric ester by virtue of its steric bulk. It should be noted that in these cases, the reactions were done in dichloromethane in the presence of methyl triflate as an activator. Activation and release of 3-methoxy-2-hydroxypyridine (or the corresponding pyridone) may in fact be due to catalytic triflic acid formed by reaction with one of the alcohol groups or the carboxylic acid.

As previously discussed,[18,19] activation of MOP β-D-glycosyl donors with Lewis acids such as methyl triflate (or promoters such as NBS[18,19]), in the presence of an acceptor alcohol or nucleophile (phosphate, azide) affords the products that result from an S_N2-like reaction (1,2-*cis*). In the case of carboxylic acids and MOP donors **1** and **2**, activation takes place by protonation in the presence of excess acid, which also acts as the nucleophile (Scheme 4). Curiously, the α-anomeric esters predominate even when acetonitrile is used which is known to participate via putative anomeric nitrilium ions.[25] In the event of such solvent participation, the α-ester could also arise from the intermediacy of a β-nitrilium ion (Scheme 4).

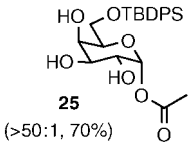
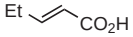
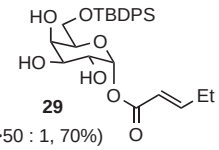
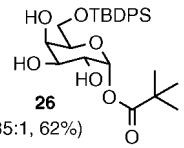
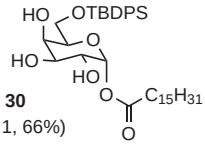
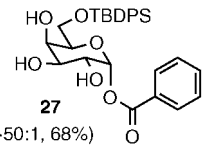
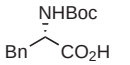
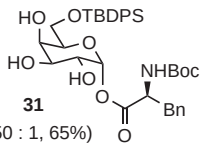
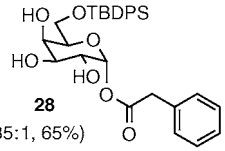
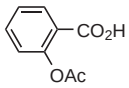
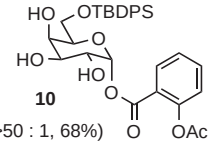
Table 1 Regioselective Esterification with MOP-gal **1**

Acid	Solvent/time (h)	Product (α/β ratio)[a]	Acid	Solvent/time (h)	Product (α/β ratio)[a]
$PhCO_2H$[b]	MeCN[c]/12	 **12** (6:1, 57%)	Et CO_2H[d]	MeCN[f]/12	 **18** (30 : 1, 80%)
$PhCO_2H$[b]	MeCN[c]	 **13** (9:1, 57%)	Et CO_2H[d]	MeCN[f]/12	 **19** (30 : 1, 80%)
$PhCH_2CO_2H$[b]	MeCN[c]	 **14** (7:1, 58%)	HOAc[d]	DMF[f]/2	 **20** (17 : 1, > 98%)
$PhCH_2CO_2H$[b]	MeCN[c]	 **15** (5:1, 60%)	HOAc[d]	DMF[f]/2	 **21** (11 : 1, >98 %)
t-$BuCO_2H$[d]	DMF[e]/12	 **16** (20:1, 80%)	HOAc[d]	DMF[f]/2	 **22** (> 98%)
t-$BuCO_2H$[d]	DMF[e]/12 h	 **17** (20:1, 80%)	$EtCO_2H$[d]	DMF[f]/2	 **23** (> 98%)

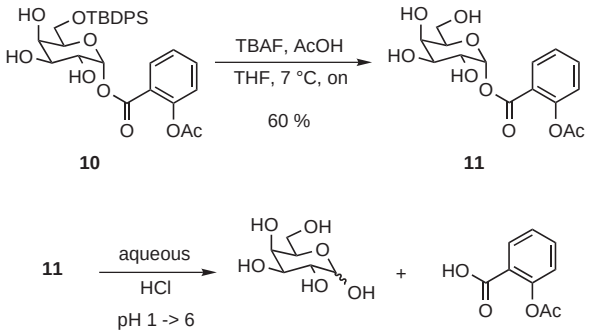
[a] Determined by ^1H NMR at 400 MHz.
[b] 20 equiv.
[c] Reaction done at 44 °C.
[d] 200 equiv.
[e] Reaction done at 65 °C.
[f] Reaction done at r.t.

Previous studies have shown that unprotected MOP α-D-glycopyranosides are much slower to react with alcohols in the presence of methyl triflate as activator[18,19] in nitromethane. The resulting glycosides had a higher proportion of the β-D-anomers indicating an S_N2-like process. It was of interest to extend the anomeric esterification to MOP glycosyl donors with the objective of preparing 1,2-*trans* anomeric esters. Treatment of the α-MOP anomer of **1** (or its pyridyl analogue) with 20 equiv of benzoic acid in acetonitrile at 44 °C for 18 hours afforded a 6:1 mixture of α- and β-galactopyranosyl 1-benzoates. Since ester interchange can be excluded under these thermodynamic conditions, it can be concluded that both α- and β-MOP D-galactopyranosides must be reacting through a common intermediate such as the nitrilium ions as shown in Scheme 4. Evidently, 1,2-*trans*-(β)nitrilium ion reacts faster than the α-anomer to afford the 1,2-*cis*-carboxylate ester. Support for this hypothetical pathway was obtained by conducting the reaction in nitromethane as solvent, where in principle, solvent participation is not likely under the conditions of the reaction. In the event, β-MOP-gal and benzoic acid in nitromethane at 60 °C gave a 3:1 α/β mixture of 1-benzoates, while α-MOP-gal (1,2-*cis* MOP) reversed the ratio to ~1:3 in favor of the 1,2-*trans* (β-) 1-benzoate (Scheme 4). However, α-MOP donors were considerably slower to react under these reactions as observed in *O*-glycosylations.[18,19]

Table 2 Regioselective Esterifications with the 6-*O*-*tert*-Butyldiphenylsilyl Ether MOP-gal, Deriviative **5**

Acid[a]	Solvent/time (h)	Product (α/β ratio)[b]	Acid[a]	Solvent/time (h)	Product (α/β ratio)[b]
$MeCO_2H$	CH_2Cl_2/1	 **25** (>50:1, 70%)		CH_2Cl_2/1	 **29** (>50 : 1, 70%)
t-$BuCO_2H$	CH_2Cl_2/1	 **26** (35:1, 62%)	$C_{15}H_{31}CO_2H$	CH_2Cl_2/1	 **30** (>50 : 1, 66%)
$PhCO_2H$	CH_2Cl_2/1	 **27** (>50:1, 68%)		CH_2Cl_2/1	 **31** (>50 : 1, 65%)
$PhCH_2CO_2H$	CH_2Cl_2/1	 **28** (35:1, 65%)		CH_2Cl_2/1	 **10** (>50 : 1, 68%)

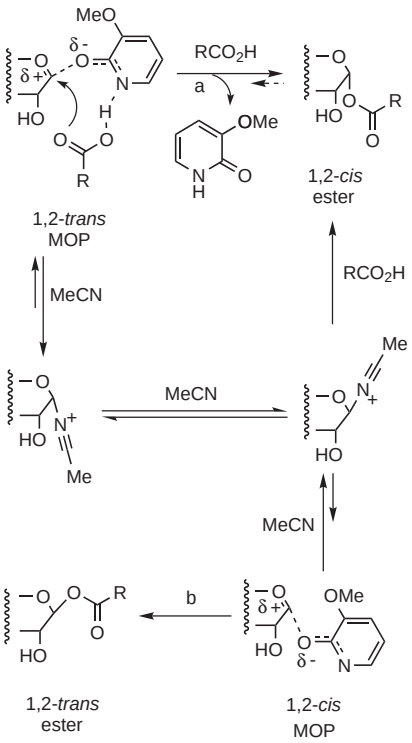
[a] 1.5 equiv of acid and 0.4 equiv of methyl triflate were used.
[b] Determined by ^1H NMR at 400 MHz.



Scheme 3

In conclusion, we have developed a one-step anomeric esterification of unprotected or 6-*O*-protected 2-(3-methoxypyridyl) β-D-gluco- and galactopyranosides. In acetonitrile, the preponderant products are 1,2-*cis*-(α)-D-gluco- and galactopyranosyl 1-esters. 1,2-*trans*-(β)-D-Galactopyranosyl 1-benzoate can be obtained as a major product from the corresponding 1,2-*cis*-(α)-D-galactopyranosyl donor, but reactions are slower. Aspirin can be solubilized as its α-D-galactopyranosyl ester, and released at pH 1–6.

Solvents were distilled under a positive pressure of dry nitrogen before use and dried by standard methods: THF and Et_2O, from Na/benzophenone and CH_2Cl_2, from CaH_2. All commercially available reagents were used without further purification. Reactions were performed under nitrogen atmosphere. NMR (^1H, ^{13}C) spectra were recorded on AMX-300 and ARX-400 spectrometers. All ^1H were assigned by COSY45 using ARX400 spectrometer. Low- and high-resolution mass spectra were recorded on VG Micromass, AelMS902 or Kratos MS-50 spectrometers using fast atom bombard-



a. in nitromethane, 60°C, 24 h, α/β = 3/1.
b. in nitromethane, 60°C, 24 h, α/β = 1/3.

Scheme 4

ment (FAB) or electrospray techniques. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter in a 1 dm cell at r.t. Analytical TLC was performed on Merck $60F_{254}$ pre-coated silica gel plates. Visualization was performed by UV light and/or by staining with ceric ammonium molybdate. Flash column chromatography was performed using (40–60 μM) silica gel at increased pressure. Carboxylic acids were dried by azeotropic distillation of toluene, then stored under reduced pressure in the presence of P_2O_5.

α- and β-D-Galactopyranosyl 1-Benzoate (12)

To a solution of benzoic acid (425 mg, 20 equiv) in MeCN (2.2mL, 0.08 M) heated at 44 °C was added **1** (50 mg, 174 μmol) The mixture was stirred overnight at 44 °C and concentrated. Purification by flash chromatography of the residue (silica gel; CH_2Cl_2–MeOH, 8:1) gave the title compound.

Yield: 28 mg (57%); syrup; α:β = 6:1. When the reaction was done in nitromethane at 60 °C, the α:β ratio was 3:1.

For Major Isomer (α)

IR (film): 3369, 1722 cm^{-1}.

^1H NMR (CD_3OD, 400 MHz): δ = 8.09 (m, 2 H, 2 CH-phenyl), 7.62 (m, 1 H, CH-phenyl), 7.5 (m, 2 H, 2 CH-phenyl), 6.41 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H-1), 4.1–3.97 (br m, 4 H, H-5, H-4, H-3, H-2), 3.71 (d, 2 H, H-6a, H-6b).

^{13}C NMR (CD_3OD, 100 MHz): δ = 166.9 (CO), 134.6 (CH-phenyl), 131.2 (C_4-phenyl), 130.8 (2 CH-phenyl), 129.6 (2 CH-phenyl), 94.6 (C1), 75.1 (CH-sugar), 71.4 (CH-sugar), 70.7 (CH-sugar), 69 (CH-sugar), 62.5 (C6).

HR-FABMS: *m*/*z* calcd for $C_{13}H_{17}O_7$: 285.09744; found: 285.09640.

α- and β-D-Glucopyranosyl 1-Benzoate (13)

To a solution of benzoic acid (425 mg, 20 equiv) in MeCN (2.2mL, 0.08 M) heated at 44 °C was added **2** (50 mg, 174 μmol), the mixture was stirred overnight at 44 °C and concentrated. Purification by flash chromatography of the residue (silica gel; CH_2Cl_2–MeOH, 8:1) gave the title compound.

Yield: 28 mg (57%); syrup; α:β = 9:1.

For Major Isomer (α)

IR (film): 3369, 1722 cm^{-1}.

^1H NMR (CD_3OD, 400 MHz): δ = 8.09 (m, 2 H, 2 CH-phenyl), 7.53 (m, 1 H, CH-phenyl), 7.51 (m, 2 H, 2 CH-phenyl), 6.38 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1), 3.88 (t, $J_{2,3} = J_{3,4}$ = 9.2 Hz, 1 H, H-3), 3.83–3.71 (br m, 2 H, H-5, H-4), 3.69 (dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.6 Hz, 1 H, H-2), 3.48 (t, $J_{gem} = J_{5,6a} = J_{5,6b}$ = 9.3 Hz, 2 H, H-6a, H-6b).

^{13}C NMR (CD_3OD, 100 MHz, 293 K): δ = 166.8 (CO), 134.6 (CH-phenyl), 131.1 (C_4-phenyl), 130.8 (2 CH-phenyl), 129.6 (2 CH-phenyl), 94.2 (C1), 76.3 (CH-sugar), 74.9 (CH-sugar), 72.4 (CH-sugar), 71.1 (CH-sugar), 62.2 (C6).

HR-FABMS: *m*/*z* calcd for $C_{13}H_{17}O_7$: 285.09744; found: 285.09640.

α- and β-D-Galactopyranosyl 1-Phenylacetate (14)

To a solution of phenylacetic acid (474 mg, 20 equiv) in MeCN (2.2mL, 0.08 M) heated at 44 °C was added **1** (50 mg, 174 μmol), the mixture was stirred overnight at 44 °C and concentrated. Purification by flash chromatography of the residue (silica gel; CH_2Cl_2–MeOH, 8:1) gave the title compound.

Yield: 30 mg (58%); syrup; α:β = 7:1.

For Major Isomer (α)

IR (film): 3402, 1728 cm^{-1}.

^1H NMR (CD_3OD, 400 MHz): δ = 7.31 (s, 5 H, 5 CH-phenyl), 6.17 (d, $J_{1,2}$ = 3.8 Hz, 1 H, H-1), 3.95 (dd, $J_{2,3}$ = 10.9 Hz, $J_{1,2}$ = 3.8 Hz, 1 H, H-2), 3.89 (m, 1 H, H-sugar), 3.75–3.62 (br m, 6 H, H-3, 3 H-sugar, CH_2-benzylic).

^{13}C NMR (CD_3OD, 100 MHz): δ = 172.4 (CO), 135.4 (C_4-phenyl), 130.5 (2 CH-phenyl), 129.5 (2 CH-phenyl), 128.0 (CH-phenyl), 94.1 (C1), 74.7 (C-sugar), 71.2 (C-sugar), 70.6 (C-sugar), 68.8 (C-sugar), 62.4 (C6), 41.8 (CH_2-benzylic).

HR-FABMS: *m*/*z* calcd for $C_{14}H_{18}O_7Na$: 321.09503; found: 321.09650.

α- and β-D-Glucopyranosyl 1-Phenylacetate (15)

To a solution of phenylacetic acid (474 mg, 20 equiv) in MeCN (2.2 mL, 0.08 M) heated at 44 °C was added **2** (50 mg, 174 μmol). The mixture was stirred overnight at 44 °C and concentrated. Purification by flash chromatography of the residue (silica gel; CH_2Cl_2–MeOH, 8:1) gave the title compound.

Yield: 31 mg (60%); syrup; α:β = 5:1.

For Major Isomer (α)

IR (film): 3402, 1728 cm^{-1}.

^1H NMR (CD_3OD, 400 MHz): δ = 7.31 (s, 5 H, 5 CH-phenyl), 6.14 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1), 3.9–3.35 (br m, 4 CH-sugar, CH_2-sugar, CH_2-benzylic).

^{13}C NMR (CD_3OD, 100 MHz): δ = 172.4 (CO), 135.3 (C_4-phenyl), 130.5 (2 CH-phenyl), 129.5 (2 CH-phenyl), 128.0 (CH-phenyl), 93.8 (C1), 75.9 (CH-sugar), 74.8 (CH-sugar), 72.2 (CH-sugar), 70.8 (CH-sugar), 62 (C6), 41.9 (CH_2-benzylic).

HR-FABMS: *m*/*z* calcd for $C_{14}H_{19}O_7$: 299.11307; found: 299.1250.

α- and β-D-Galactopyranosyl 1-Pivaloate (16)

To pivalic acid (4 mL, 200 equiv) in DMF (2.2 mL, 0.08 M) heated at 65 °C was added **1** (50 mg, 174 μmol), the mixture was stirred overnight at 65 °C and concentrated. Purification by flash chromatography of the residue (silica gel; CH_2Cl_2–MeOH, 8:1) gave the title compound.

Yield: 37 mg (80%); syrup; (α:β = 20:1).

For Major Isomer (α)

IR (film): 3402, 1726 cm^{-1}.

^1H NMR (CD_3OD, 400 MHz): δ = 6.12 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H-1), 3.97 (m, 2 H, H-2, H-4), 3.89 (t, $J_{5,6a} = J_{5,6b}$ = 6 Hz, 1 H, H-5), 3.8 (dd, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 3.1 Hz, 1 H, H-3), 3.68 (dd, 2 H, H-6a, H-6b), 1.25 (s, 9 H, Me).

^{13}C NMR (CD_3OD, 100 MHz): δ = 178.9 (CO), 93.8 (C1), 74.9 (CH-sugar), 71.4 (CH-sugar), 70.6 (CH-sugar), 68.8 (CH-sugar), 62.5 (C6), 27.4 (3 Me).

HR-FABMS: *m*/*z* calcd for $C_{11}H_{20}O_7Na$: 287.11069; found: 287.10970.

α- and β-D-Glucopyranosyl 1-Pivaloate (17)

To a solution of pivalic acid (4 mL, 200 equiv) in DMF (2.2 mL, 0.08 M) heated at 65 °C was added **2** (50 mg, 174 μmol). The mixture was stirred overnight at 65 °C and concentrated. Purification by flash chromatography of the residue (silica gel; CH_2Cl_2–MeOH, 8:1) gave the title compound.

Yield: 37 mg (80%); syrup; α:β = 20:1.

For Major Isomer (α)
IR (film): 3402, 1726 cm^{-1}.

^1H NMR (CD_3OD, 400 MHz): δ = 6.09 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1), 3.80–3.61 (br m, 3 H, H-5, H-4, H-3), 3.58 (dd, $J_{2,3}$ = 9.7 Hz, $J_{1,2}$ = 3.6 Hz, 1 H, H-2), 3.41–3.39 (d, 2 H, H-6a, H-6b), 1.26 (s, 9 H, 3 Me).

^{13}C NMR (CD_3OD, 100 MHz): δ = 178.8 (CO), 93.4 (C1), 76.2 (CH-sugar), 74.8 (CH-sugar), 72.3 (CH-sugar), 71 (CH-sugar), 62.3 (C6), 27.5 (3 Me).

HR-FABMS: *m*/*z* calcd for $C_{11}H_{21}O_7$: 265.12872; found: 265.12960.

α-D-Galactopyranosyl 1-(*trans*-2-Pentenoate) (18)
To a solution of *trans*-2-pentenoic acid (3.5 mL, 200 equiv) in MeCN (2.2 mL, 0.08 M) was added **1** (50 mg, 174 μmol). The mixture was stirred overnight at r.t. and concentrated. Purification by flash chromatography of the residue (silica gel; CH_2Cl_2–MeOH, 6:1), gave the title compound.

Yield: 37 mg (80%); syrup; α:β = 30:1; $[\alpha]_D$ + 125.5 (*c* 5.5, MeOH).

IR (film): 3370, 1722 cm^{-1}.

^1H NMR (CD_3OD, 400 MHz): δ = 7.13 (dt, $J_{\alpha,\beta}$ = 15.7 Hz, $J_{\beta,\,CH2}$ = 6.4 Hz, 1 H, H-β), 6.2 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H-1), 5.9 (dt, $J_{\alpha,\beta}$ = 15.7 Hz, $J_{\alpha,\,CH2}$ = 1.7 Hz, 1 H, H-α), 4.05–3.95 (br m, 2 H, H-4, H-2), 3.89 (t, $J_{5,6a}$ = $J_{5,6b}$ = 6.1 Hz, 1 H, H-5), 3.83 (dd, $J_{2,3}$ = 10.3 Hz, $J_{3,4}$ = 3.3 Hz, 1 H, H-3), 3.69 (d, $J_{5,6a}$ = $J_{5,6b}$ = 6.1 Hz, 2 H, H-6a, H-6b), 2.28 (m, 2 H, CH_2), 1.1 (t, $J_{Me,\,CH2}$ = 7.4 Hz, 3 H, Me).

^{13}C NMR (CD_3OD, 100 MHz): δ = 167.1 (CO), 153.6 (CH-olefin), 121 (CH-olefin), 93.8 (C1), 74.7 (CH-sugar), 71.3 (CH-sugar), 70.6 (CH-sugar), 68.9 (CH-sugar), 62.5 (C6), 26.3 (CH_2), 12.4 (Me).

HR-FABMS: *m*/*z* calcd for $C_{11}H_{19}O_7$: 263.11307; found: 263.11200.

α-D-Glucopyranosyl 1-(*trans*-2-Pentenoate) (19)
To a solution of *trans*-2-pentenoic acid (3.56 mL, 200 equiv) in MeCN (2.2mL, 0.08 M) was added **2** (50 mg, 174 μmol). The mixture was stirred overnight at r.t. and concentrated. Purification by flash chromatography of the residue (silica gel; CH_2Cl_2–MeOH, 6:1) gave the title compound.

Yield: 37 mg (80%); syrup; α:β = 30:1; $[\alpha]_D$ + 104.9 (*c* 5.1, MeOH).

IR (film): 3370, 1722 cm^{-1}.

^1H NMR (CD_3OD, 400 MHz): δ = 7.13 (dt, $J_{\alpha,\beta}$ = 15.7 Hz, $J_{\beta,CH2}$ = 6.4 Hz, 1 H, H-β), 6.16 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H-1), 5.9 (dt, $J_{\alpha,\beta}$ = 15.7 Hz, $J_{\alpha,CH2}$ = 1.7 Hz, 1 H, H-α), 3.8–3.61 (br m, 4 H, H-4, H-5, H-6a, H-6b), 3.59 (dd, $J_{2,3}$ = 8 Hz, $J_{1,2}$ = 3.7 Hz, 1 H, H-2), 3.4 (t, $J_{2,3}$ = $J_{3,4}$ = 8 Hz, 1 H, H-3), 2.28 (m, 2 H, CH_2), 1.1 (t, $J_{Me,\,CH2}$ = 7.4 Hz, 3 H, Me).

^{13}C NMR (CD_3OD, 100 MHz): δ = 166.9 (CO), 153.7 (CH-olefin), 120.9 (CH-olefin), 93.5 (C1), 76 (CH-sugar), 74.8 (CH-sugar), 72.3 (CH-sugar), 71.0 (CH-sugar), 62.3 (C6), 26.3 (CH_2), 12.4 (Me).

HR-FABMS: *m*/*z* calcd for $C_{11}H_{19}O_7$: 263.11307; found: 263.11420.

α- and β-D-Galactopyranosyl 1-Acetate (20)
A solution of **1** (90 mg, 0.3 mmol) in DMF (0.8 mL) and HOAc (3.6 mL, 200 equiv) was stirred at r.t. for 2 h and concentrated. Column chromatography of the residue (silica gel; CH_2Cl_2–MeOH, 6:1) gave the title compound.

Yield: 67 mg (quant); syrup; α:β = 17:1.

For Major Isomer (α)
IR (film): 3362, 1747 cm^{-1}.

^1H NMR (CD_3OD, 400 MHz): δ = 2.10 (s, 3 H, AcO), 3.66 (d, 2 H, $J_{5,6}$ = 6.1 Hz, H-6a, H-6b), 3.75 (dd, 1 H, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 3.2 Hz, H-3), 3.85 (t, 1 H, $J_{5,6}$ = 6.1 Hz, H-5), 3.91 (dd, 1 H, $J_{1,2}$ = 3.9 Hz, $J_{2,3}$ = 10.2 Hz, H-2), 3.92 (d, 1 H, $J_{3,4}$ = 3.2 Hz, H-4), 6.11 (d, 1 H, $J_{1,2}$ = 3.9 Hz, H-1).

^{13}C NMR (CD_3OD, 100 MHz): δ = 22.69 (CH_3CO), 64.28, 70.54, 72.40, 76.43, 95.52 (C-1), 173.57 (CH_3CO).

HR-FABMS: *m*/*z* calcd for $C_8H_{14}O_7$: 222.07396; found: 222.06512.

α- and β-D-Glucopyranosyl 1-Acetate (21)
A solution of **2** (60 mg, 0.2 mmol) in DMF (0.5 mL) and HOAc (2.4 mL, 200 equiv) was stirred at r.t. for 2 h and concentrated. Column chromatography of the residue (silica gel; CH_2Cl_2–MeOH, 6:1) gave the title compound.

Yield: 44 mg (quant); syrup; α:β = 11:1).

For Major Isomer (α)
IR (film): 3362, 1743 cm^{-1}.

^1H NMR (CD_3OD, 400 MHz): δ = 2.10 (s, 3 H, AcO), 3.52 (dd, 1 H, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 9.7 Hz, H-2), 3.74 (dd, 1 H, $J_{5,6a}$ = 1.9 Hz, $J_{6a,6b}$ = 11.7 Hz, H-6a), 6.08 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1).

^{13}C NMR (CD_3OD, 100 MHz): δ = 22.68 (CH_3CO), 64.01, 72.74, 73,92, 76.50, 77.67, 95.18 (C-1), 173.45 (CH_3CO).

HR-FABMS: *m*/*z* calcd for $C_8H_{14}O_7$: 222.07396; found: 222.07556.

α- and β-Methyl 5-*N*-Acetyl-3,5-dideoxy-2-*O*-(3-methoxy-2-pyridyl)-D-*glycero*-D-*galacto*-2- nonulopyranosonate (α/β-Sialyl MOP)
A solution of *N*-acetyl neuraminic acid (5 g, 15.5 mmol) and Dowex 50(H^+) (3 g) in MeOH (200 mL) was heated at 40 °C for 5 h. The suspension was cooled r.t., filtered and concentrated. The residue was dissolved in pyridine (200 mL) and Ac_2O (30 mL) was added at 0 °C. The solution was stirred at r.t. overnight, then MeOH (1 mL) was added and the solution was concentrated and co-evaporated with toluene. The residue was dissolved in EtOAc (300 mL), washed successively with aq HCl (5%), H_2O, brine, dried (Na_2SO_4) and concentrated to give crude methyl 5-*N*-acetyl-3,5-dideoxy-2,4,7,8,9-penta-*O*-acetyl-D-*glycero*-D-*galacto*-2-nonulopyranosonate.

The above crude methyl ester (5 g, 9.4 mmol) was dissolved in anhyd Et_2O (200 mL) and AcCl (5 mL) was added dropwise. The mixture was cooled to –40 °C and HCl gas was bubbled through for 30 min. The cooling bath was removed and the stirring continued overnight. The solution was concentrated and dried under reduced pressure to give a syrupy chloride. To this chloride dissolved in anhyd nitromethane (200 mL) containing 4 Å molecular sieves (1 g) was added silver 3-methoxy-2-pyridoxide[22] (5 g) at r.t.. The suspension was stirred for 4 h then filtered through Celite and washed with CH_2Cl_2. The residue was concentrated to give a crude 1:1 α:β mixture of methyl 5-*N*-acetyl-3,5-dideoxy-2-*O*-(3-methoxy-2-pyridyl)-4,7,8,9-tetra-*O*-acetyl-D-*glycero*-D-*galacto*-2-nonulopyranosonate.

To a portion of the above crude product (2 g, 3.3 mmol) in anhyd MeOH (20 mL) was added at 0 °C a catalytic amount of freshly prepared NaOMe. The solution was stirred for 4 h at 0 °C, then neutralized with Amberlite resin IR120 (H^+) and filtered. Concentration and purification by flash chromatography (silica gel; CH_2Cl_2–MeOH, 5:1) gave the desired α- and β- methyl 5-*N*-acetyl-3,5-dideoxy-2-*O*-(3-methoxy-2-pyridyl)-D-*glycero*-D-*galacto*-2-nonulopyranosonate.

Yield: 1.3 g (90%); $[\alpha]_D$ –54.7 (*c* 0.3, MeOH).

^1H NMR (CD_3OD, 400 MHz): δ = 7.59 (dd, 1 H), 7.33 (dd, 1 H), 7.01 (dd, 1 H), 4.29–4.19 (m, 1 H), 10.5 (t, 1 H, *J* = 10.5 Hz), 3.90 (t, 1 H, *J* = 10.5 Hz), 3.87 (s, 3 H), 3.71 (s, 1 H), 3.68–3.48 (m, 5

H), 2.62 (dd, 1 H, 3e-H, J = 4.9, 8.4 Hz), 2.04 (dd, 1 H, 3a-H, J = 1.3, 8.4 Hz), 2.01 (s, 3 H).

^{13}C NMR (CD_3OD, 100 MHz): δ = 175.0, 151.7, 146.2, 137.4, 121.0, 120.7, 99.3, 74.0, 72.5, 69.9, 67.7, 64.7, 56.5, 53.6, 50.0, 41.6, 22.9.

HR-FABMS: *m*/*z* calcd for $C_{18}H_{26}N_2O_{10}$: 430.15875; found: 430.15684.

Methyl 2-*O*-Acetyl-5-*N*-acetyl-3,5-dideoxy-α-D-*glycero*-D-*galacto*-2-nonulopyranosonate (22)

A mixture of sialyl MOP (α,β-mixture 430 mg, 1.0 mmol), DMF (2.0 mL) and HOAc (11 mL, 200 equiv) was stirred at r.t. for 2 h and concentrated. Column chromatography (silica gel; CH_2Cl_2–MeOH, 6:1) gave the title compound.

Yield: 290 mg (79%); amorphous mass; $[\alpha]_D$ –54.7 (*c* 0.3, MeOH).

IR (film): 3352, 1754, 1649 cm^{-1}.

^{1}H NMR (CD_3OD, 400 MHz): δ = 4.04 (ddd, 1 H, $J_{3ax,4}$ = 11.3 Hz, $J_{4,5}$ = 10.0 Hz, $J_{3eq,4}$ = 5.0 Hz, H-4), 3.96 (dd, 1 H, $J_{5,6}$ = 10.0 Hz, $J_{6,7}$ = 1.0 Hz, H-6), 3.89 (dd, 1 H, H-5), 3.78 (s, 3 H, OMe), 3.76 (dd, $J_{9a,9b}$ = 10.0 Hz, $J_{8,9a}$ = 2.4 Hz, H-9a), 3.69–3.60 (m, 2 H, H-9b, H-8), 3.50 (dd, 1 H, $J_{7,8}$ = 9.0 Hz, H-7), 2.43 (dd, 1 H, $J_{3ax,3eq}$ = 13.4 Hz, H-3eq), 2.10 (s, 3 H, Ac), 2.02 (s, 3 H, NHAc), 1.74 (dd, 1 H, H-3ax).

^{13}C NMR (CD_3OD, 100 MHz): δ = 178.5, 174.3, 174.0 (C=O), 102.4 (C2), 77.7 (C8), 75.3 (C4), 73.6 (C7), 71.4 (C6), 68.8 (C9), 57.4 (OMe), 57.3 (C5), 44.4 (C3), 26.6 (Ac), 24.3 (NHAc).

HR-FABMS: *m*/*z* calcd for $C_{14}H_{23}NO_{10}$: 365.13220; found: 365.13475.

Methyl 5-*N*-Acetyl-2-*O*-propionyl-3,5-dideoxy-α-D-*glycero*-D-*galacto*-2-nonulopyranosonate (23)

A mixture of sialyl MOP (α,β-mixture 52 mg, 0.12 mmol), DMF (0.4 mL) and propionic acid (1.4 mL, 200 equiv) was stirred at r.t. for 2 h and concentrated. Column chromatography (silica gel; CH_2Cl_2–MeOH, 6:1) gave the title compound.

Yield: 35 mg (78%), amorphous mass; $[\alpha]_D$ –44 (c 0.3, MeOH).

IR (film): 3352, 1754, 1654 cm^{-1}.

^{1}H NMR (CD_3OD, 400 MHz): δ = 4.06 (ddd, 1 H, $J_{3ax,4}$ = 11.8 Hz, $J_{4,5}$ = 10.0 Hz, $J_{3eq,4}$ = 4.8 Hz, H-4), 3.95 (dd, 1 H, $J_{5,6}$ = 10.0 Hz, $J_{6,7}$ = 1.0 Hz, H-6), 3.91 (dd, 1 H, H-5), 3.88 (s, 3 H, OMe), 3.76 (dd, $J_{9a,9b}$ = 10.0 Hz, $J_{8,9a}$ = 2.4 Hz, H-9a), 3.76–3.55 (m, 2 H, H-9b, H-8), 3.49 (dd, 1H, $J_{7,8}$ = 9.0 Hz, H-7), 2.45 (dd, 1 H, $J_{3ax,3eq}$ = 13.0 Hz, H-3eq), 2.41 (q, 2 H, J = 7.0 Hz, propionyl CH_2), 2.01 (s, 3 H, NHAc), 1.75 (dd, 1 H, H-3ax), 1.16 (t, 3 H, J = 7.0 Hz, propionyl CH_3).

^{13}C NMR (CD_3OD, 100 MHz): δ = 174.6, 173.8, 170.1 (C=O), 98.5 (C2), 73.8 (C8), 71.5 (C4), 69.7 (C7), 67.5 (C6), 64.9 (C9), 53.52 (OMe), 53.48 (C5), 40.6 (C3), 28.1 (propionyl CH_2), 22.7 (NHAc), 9.1 (CH_3).

HR-FABMS: *m*/*z* calcd for $C_{15}H_{25}NO_{10}$: 379.14785; found: 379.14520.

2-(3-Methoxypyridyl) 6-(*tert*-Butyldiphenylsilyl)-β-D-*galacto*-pyranoside (5)

To **1** (1 g, 3.48 mmol) and imidazole (474 mg, 2 equiv) in DMF (7 mL, 0.5 M) was added dropwise *tert*-butylchlorodiphenylsilane (1.36 mL, 1.5 equiv). The mixture was stirred overnight at r.t., then diluted with CH_2Cl_2 (20 mL), washed with cold H_2O (2 × 10 mL) and the organic layer was dried (Na_2SO_4). Concentration and purification by flash chromatography of the residue (silica gel; EtOAc–hexanes, 9:1) gave the title compound.

Yield: 1.5 g (82%); white foam; $[\alpha]_D$ + 28.4 (*c* 0.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.72–7.60 (m, 5 H), 7.49–7.29 (m, 6 H), 7.15 (dd, J = 7.9 Hz, J = 1.6 Hz, 1 H), 6.95 (dd, J = 7.9, 5.1 Hz, 1 H), 5.95 (d, $J_{1,2}$ = 8.1 Hz, 1 H, H-1), 4.2 (t, $J_{3,4}$ = $J_{4,5}$ = 2.9 Hz, 1 H, H-4), 4.05 (t, $J_{1,2}$ = $J_{2,3}$ = 8.1 Hz, 1 H, H-2), 4.0–3.89 (m, 2 H), 3.85 (s, 3 H, OMe), 3.83–3.72 (m, 2 H), 1.04 (s, 9 H, *tert*-Bu-TBDPSi).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.1 (CO-pyridyl), 143.9 (CO-pyridyl), 136.9 (CH-pyridyl), 135.5 (4 CH-aromatic-TBDPSi), 133.2 (C_4-aromatic-TBDPSi), 133.1 (C_4-aromatic-TBDPSi), 129.5 (2 CH-aromatic-TBDPSi), 127.4 (4 CH-aromatic-TBDPSi), 118.5 (CH-pyridyl), 118.2 (CH-pyridyl), 96.2 (C1), 75.2 (CH-sugar), 73.9 (CH-sugar), 70.7 (CH-sugar), 68.7 (CH-sugar), 62.7 (C-6), 55.6 (OMe), 26.6 (*tert*-Bu-TBDPSi), 19.0 (C_4-*tert*-Bu-TBDPSi).

HR-FABMS: *m*/*z* calcd for $C_{28}H_{36}NO_7Si$: 526.22614; found: 526.22520.

6-*O*-(*tert*-Butyldiphenylsilyl)-α-D-galactopyranosyl 1-Esters; General Procedure

To a solution of **5** (100 mg, 190 μmol, 1 equiv) in CH_2Cl_2 (2.4 mL, 0.08 M) and acceptor acid (1.5 equiv) at 0 °C was added methyl triflate (9 μL, 0.4 equiv) and the mixture was stirred for 30 min at this temperature, then for 30 min at r.t.. The solution was diluted with CH_2Cl_2 (10 mL), the organic layer washed (4 × 1 mL) with a cold aq sat. $NaHCO_3$ and dried (Na_2SO_4). Concentration and purification by flash chromatography of the residue (silica gel; EtOAc–hexanes) gave the title compound as a syrup.

6-(*tert*-Butyldiphenylsilyl)-α-D-galactopyranosyl 1-Acetate (25)

Purification by flash chromatography (silica gel; EtOAc–hexanes, 7:3) gave the title compound.

Yield: 61 mg (70%); syrup; α:β >50:1); $[\alpha]_D$ + 37.9 (*c* 1.5, $CHCl_3$).

IR (film): 3402, 2932, 1744, 1428, 1229, 1113, 1091, 1010 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.68–7.64 (m, 5 H), 7.43–7.36 (m, 5 H), 6.22 (d, $J_{1,2}$ = 3.8 Hz, 1 H, H-1), 4.17 (dd, $J_{3,4}$ = 2.8 Hz, 1 H, H-4), 4.07 (dd, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 9.9 Hz, 1 H, H-2), 3.91–3.79 (m, 5 H, H-3, H-5, H-6a, H-6b, 1 OH), 3.78–3.3 (br, 2 H, 2 OH), 2.08 (s, 3 H, Me), 1.04 (s, 9 H, *tert*-Bu-TBDPSi).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.0 (CO), 135.6 (2 CH-aromatic-TBDPSi), 135.5 (2 CH-aromatic-TBDPSi), 132.8 (C_4-aromatic-TBDPSi), 132.6 (C_4-aromatic-TBDPSi), 129.9 (2 CH-aromatic-TBDPSi), 127.8 (4 CH-aromatic-TBDPSi), 92.2 (C1), 71.9 (CH-sugar), 70.6 (CH-sugar), 69.5 (CH-sugar), 68.1 (CH-sugar), 63.3 (C6), 26.8 (*tert*-Bu-TBDPSi), 21 (Me), 19.1 (C_4-*tert*-Bu-TBDPSi).

HR-FABMS: *m*/*z* calcd for $C_{24}H_{32}O_7Si$: 460.19173; found: 460.19205.

6-(*tert*-Butyldiphenylsilyl)-α-D-galactopyranosyl 1-Pivaloate (26)

Purification by flash chromatography (silica gel; EtOAc–hexanes, 65:35) gave the title compound.

Yield: 59 mg (62%); syrup; α:β = 35:1; $[\alpha]_D$ + 53.1 (*c* 1.5, $CHCl_3$).

IR (film): 3402, 2932, 1744, 1428, 1113, 1028 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.69–7.64 (m, 5 H), 7.41–7.37 (m, 5 H), 6.23 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H-1), 4.17 (d, $J_{3,4}$ = 3 Hz, 1 H, H-4), 4.09 (dd, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 9.9 Hz, 1 H, H-2), 3.94–3.82 (m, 3 H, H-5, H-6a, H-6b), 3.8 (dd, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 3 Hz, 1 H, H-3), 3.7–3.1 (br, 3 H, 3 OH), 1.20 (s, 9 H, *tert*-Bu), 1.05 (s, 9 H, *tert*-Bu-TBDPSi).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.2 (CO), 135.6 (2 CH-aromatic-TBDPSi), 135.5 (2 CH-aromatic-TBDPSi), 132.9 (C_4-aromatic-TBDPSi), 132.7 (C_4-aromatic-TBDPSi), 129.9 (2 CH-aromatic-TBDPSi), 127.8 (4 CH-aromatic-TBDPSi), 92 (C1), 72.3 (CH-sugar), 70.8 (CH-sugar), 69.5 (CH-sugar), 68.4 (CH-sugar), 63.5 (C6),

39.2 (C_4-*tert*-Bu), 27.1 (*tert*-Bu), 26.8 (*tert*-Bu-TBDPSi), 19.1 (C_4-*tert*-Bu-TBDPSi).

HR-FABMS: *m*/*z* calcd for $C_{27}H_{38}O_7Si$: 502.23868; found: 502.23756.

6-(*tert*-Butyldiphenylsilyl)-α-D-galactopyranosyl 1-Benzoate (27)

Purification by flash chromatography (silica gel; EtOAc–hexanes, 55:45) gave the title compound.

Yield: 68 mg (68%); syrup (α:β >50:1); $[\alpha]_D$ + 35.2 (*c* 1.4, $CHCl_3$).

IR (film): 3402, 2932, 1732, 1428, 1267, 1113, 1024 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8 (m, 2 H), 7.67–7.61 (m, 5 H), 7.60–7.52 (t, 1 H), 7.44–7.33 (m, 7 H), 6.46 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H-1), 4.23 (d, $J_{3,4}$ = 2.8 Hz, 1 H, H-4), 4.19 (dd, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 9.9 Hz, 1 H, H-2), 3.97 (dd, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 2.8 Hz, 1 H, H-3), 3.93–3.84 (m, 4 H, H-, H-6a, H-6b, 1 OH), 3.6–3.1 (br, 2 H, 2 OH), 1.03 (s, 9 H, *tert*-Bu-TBDPSi).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.7 (CO), 133 (2 CH-aromatic-TBDPSi), 132.9 (2 CH-aromatic-TBDPSi), 131.0 (CH-aromatic), 130.2 (C_4-aromatic-TBDPSi), 130.0 (C_4-aromatic-TBDPSi), 127.4 (2 CH-aromatic-TBDPSi), 127.3 (2 CH-aromatic), 127.0 (C_4-aromatic), 125.9 (2 CH-aromatic), 125.2 (4 CH-aromatic-TBDPSi), 90.3 (C1), 69.5 (CH-sugar), 68.4 (CH-sugar), 66.9 (CH-sugar), 66 (CH-sugar), 60.8 (C6), 24.2 (*tert*-Bu-TBDPSi), 16.5 (C_4-*tert*-Bu-TBDPSi).

HR-FABMS: *m*/*z* calcd for $C_{29}H_{34}O_7SiNa$: 545.19714; found; 545.19880.

6-(*tert*-Butyldiphenylsilyl)-α-D-galactopyranosyl 1-Phenylacetate (28)

Purification by flash chromatography (silica gel; EtOAc–hexanes, 6:4) gave the title compound.

Yield: 66 mg (65%); syrup; α:β = 35:1; $[\alpha]_D$ + 56.6 (*c* 1.3, $CHCl_3$).

IR (film): 3402, 2932, 1748, 1428, 1113, 1015 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.68–7.63 (m, 5 H), 7.42–7.38 (m, 5 H), 7.26–7.24 (m, 5 H), 6.24 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H-1), 4.10 (dd, 1 H, H-4), 4.04 (dd, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 9.9 Hz, 1 H, H-2), 3.83–3.59 (m, 7 H, H-3, H-5, H-6a, H-6b, CH_2-benzylic, 1 OH), 3.55–3.1 (br, 2 H, 2 OH), 1.04 (s, 9 H, *tert*-Bu-TBDPSi).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.4 (CO), 135.6 (2 CH-aromatic-TBDPSi), 135.5 (2 CH-aromatic-TBDPSi), 133.6 (C_4-aromatic), 132.8 (C_4-aromatic-TBDPSi), 132.6 (C_4-aromatic-TBDPSi), 129.9 (2 CH-aromatic-TBDPSi), 129.3 (2 CH-aromatic), 128.6 (2 CH-aromatic), 127.8 (4 CH-aromatic-TBDPSi), 127.2 (CH-aromatic), 92.6 (C1), 71.8 (CH-sugar), 70.7 (CH-sugar), 69.5 (CH-sugar), 68.2 (CH-sugar), 63.3 (C6), 41.3 (CH_2), 26.7 (*tert*-Bu-TBDPSi), 19.1 (C_4-*tert*-Bu-TBDPSi).

HR-FABMS: *m*/*z* calcd for $C_{30}H_{36}O_7Si$: 536.22303; found: 536.22505.

6-(*tert*-Butyldiphenylsilyl)-α-D-galactopyranosyl 1-(*trans*-2-Pentenoate) (29)

Purification by flash chromatography (silica gel; EtOAc–hexanes, 7:3) gave the title compound.

Yield: 67 mg (70%); syrup (α:β >50:1); $[\alpha]_D$ + 52.5 (*c* 1.6, $CHCl_3$).

IR (film): 3402, 2932, 1731, 1652, 1428, 1113, 1018 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.68–7.64 (m, 5 H), 7.44–7.35 (m, 5 H), 7.09 (dt, $J_{\alpha,}$ = 15.7 Hz, $J_{\beta,CH2}$ = 6.4 Hz, 1 H, H-β), 6.29 (d, $J_{1,2}$ = 3.8 Hz, 1 H, H-1), 5.83 (dt, $J_{\alpha,\beta}$ = 15.7 Hz, $J_{\alpha,CH2}$ = 1.7 Hz, 1 H, H-α), 4.19 (dd, 1 H, H-4), 4.11 (dd, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 9.8 Hz, 1 H, H-2), 3.93–3.83 (m, 5 H, H-3, H-5, H-6a, H-6b, 1 OH), 3.78–3.4 (br, 2 H, 2 OH), 2.23 (m, 2 H, CH_2), 1.07 (Me),1.04 (s, 9 H, *tert*-Bu-TBDPSi).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.4 (CO), 152.8 (CH-olefin), 135.6 (2 CH-aromatic-TBDPSi), 135.5 (2 CH-aromatic-TBDPSi), 132.9 (C_4-aromatic-TBDPSi), 132.6 (C_4-aromatic-TBDPSi), 129.9 (2 CH-aromatic-TBDPSi), 127.8 (4 CH-aromatic-TBDPSi), 119.6 (CH-olefin), 92.2 (C1), 71.9 (CH-sugar), 70.8 (CH-sugar), 69.5 (CH-sugar), 68.3 (CH-sugar), 63.4 (C6), 26.8 (*tert*-Bu-TBDPSi), 25.4 (CH_2), 19.1 (C_4-*tert*-Bu-TBDPSi), 11.9 (Me).

HR-FABMS: *m*/*z* calcd for $C_{27}H_{36}O_7Si$: 500.22303; found: 500.22406.

6-(*tert*-Butyldiphenylsilyl)-α-D-galactopyranosyl 1-Palmitate (30)

Purification by flash chromatography (silica gel; EtOAc–hexanes, 55:45) gave the title compound.

Yield: 82 mg (66%); syrup; α:β >50:1); $[\alpha]_D$ + 35 (*c* 1.3, $CHCl_3$).

IR (film): 3402, 2921, 2852, 1754, 1464, 1428, 1113 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.70–7.65 (m, 5 H), 7.45–7.38 (m, 5 H), 6.26 (d, $J_{1,2}$ = 3.8 Hz, 1 H, H-1), 4.22 (d, $J_{3,4}$ = 2.9 Hz, 1 H, H-4), 4.06 (dd, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 9.8 Hz, 1 H, H-2), 3.94–3.86 (m, 3 H, H-5, H-6a, H-6b), 2.34 (m, 2 H), 1.62 (m, 2 H), 1.25 (m, 24 H, CH_2), 1.06 (s, 9 H, *tert*-Bu-TBDPSi), 0.88 (3 H, Me).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.0 (CO), 133.1 (2 CH-aromatic-TBDPSi), 133.0 (2 CH-aromatic-TBDPSi), 130.2 (C_4-aromatic-TBDPSi), 130.0 (C_4-aromatic-TBDPSi), 127.4 (2 CH-aromatic-TBDPSi), 125.3 (4 CH-aromatic-TBDPSi), 89.3 (C1), 69.1 (CH-sugar), 68.3 (CH-sugar), 66.9 (CH-sugar), 66 (CH-sugar), 60.9 (C6), 31.7 (CH_2), 29.4 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 24.2 (*tert*-Bu-TBDPSi), 22.2 (CH_2), 20.1 (CH_2), 16.6 (C_4-*tert*-Bu-TBDPSi), 11.6 (Me).

HR-FABMS: *m*/*z* calcd for $C_{38}H_{60}O_7Si$: 656.41083; found: 656.41154.

6-(*tert*-Butyldiphenylsilyl)-α-D-galactopyranosyl 1-(*N*-Boc)-Phenylalanate (31)

Purification by flash chromatography (silica gel; EtOAc–hexanes, 7:3) gave the title compound.

Yield: 82 mg (65%); syrup; α:β >50:1); $[\alpha]_D$ + 27.6 (*c* 1.7, $CHCl_3$).

IR (film): 3437, 2932, 2859, 1754, 1713, 1498, 1428, 1367, 1164, 1113, 1013 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.71–7.66 (m, 5 H), 7.44–7.40 (m, 5 H), 7.27–7.15 (m, 5 H), 6.27 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1), 5.0 (d, $J_{NH,H\alpha}$ = 7.27 Hz, 1 H, NH), 4.52 (dt, $J_{NH,H\alpha}$ = 7.27 Hz, $J_{CH2,H\alpha}$ = 6.9 Hz, 1 H, Hα), 4.19 (dd, $J_{3,4}$ = 2.2 Hz, 1 H, H-4), 3.98 (dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.9 Hz, 1 H, H-2), 3.92–3.81 (J_{gem} = 10.5 Hz, $J_{5,6a}$ = $J_{5,6b}$ = 5.2 Hz, 2 H, H-6a, H-6b), 3.73 (t, $J_{5,6a}$ = $J_{5,6b}$ = 5.2 Hz, 1 H, H-5), 3.6 (dd, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 2.2 Hz, 1 H, H-3), 3.18–2.99 (J_{gem} = 14 Hz, $J_{CH2,H\alpha}$ = 6.9 Hz, 2 H, CH_2-benzylic), 3.4-2.7 (br, 3 H, 3 OH), 1.41 (s, 9 H, *tert*-Bu-Boc), 1.07 (s, 9 H, *tert*-Bu-TBDPSi).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.6 (CO-ester), 155.6 (CO-Boc), 135.7 (2 CH-aromatic-TBDPSi), 135.5 (2 CH-aromatic-TBDPSi), 132.8 (C_4-aromatic-TBDPSi), 132.4 (C_4-aromatic-TBDPSi), 130 (2 CH-aromatic-TBDPSi), 129.2 (2 CH-aromatic), 128.8 (2 CH-aromatic), 127.8 (4 CH-aromatic-TBDPSi), 127.2 (CH-aromatic), 93.5 (C1), 80.6 (C_4-*tert*-Bu-Boc), 71.8 (CH-sugar), 70.7 (CH-sugar), 69.2 (CH-sugar), 68.5 (CH-sugar), 63.3 (C6), 54.6 (CHN), 37.7 (CH_2), 28.3 (*tert*-Bu-Boc), 26.8 (*tert*-Bu-TBDPSi), 19.1 (C_4-*tert*-Bu-TBDPSi).

HR-FABMS: *m*/*z* calcd for $C_{36}H_{47}O_9Nsi$: 665.30201; found: 665.30402.

α-D-Galactopyranosyl 1-(2-*O*-Acetyl Benzoate) (11)

To a solution of **5** (100 mg, 190 μmol, 1 equiv) in CH_2Cl_2 (2.4 mL, 0.08 M) and 2-*O*-acetyl benzoic acid (1.5 equiv) at 0 °C, was added methyl triflate (9 μL, 0.4 equiv) and the mixture was stirred 30 min at this temperature, then 30 min at r.t.. The mixture was diluted with CH_2Cl_2 (10 mL) and the organic layer washed (4 × 1 mL) with cold aq sat. $NaHCO_3$ and dried (Na_2SO_4). Concentration and purification by flash chromatography (silica gel; EtOAc–hexanes, 80:20) gave 6-(*tert*-butyldiphenylsilyl)-α-D-galactopyranosyl 1-(2-O-acetyl benzoate) **10**.

Yield: 75 mg (68%); syrup; α:β >50:1.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.9 (dd, *J* = 7.5, 1.6 Hz, 1 H), 7.70–7.50 (m, 6 H), 7.49–7.27 (m, 6 H), 7.11 (dd, *J* = 7.5, 1.0 Hz, 1 H), 6.40 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H-1), 4.26 (d, $J_{3,4}$ = 3.0 Hz, 1 H, H-4), 4.13 (dd, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 10.1 Hz, 1 H, H-2), 4.00–3.80 (m, 4 H), 3.50–2.50 (br, 3 H, 3 OH), 2.30 (s, 3 H, CH_3CO), 1.03 (s, 9 H, *tert*-Bu-TBDPSi).

To a solution of **10** (100 mg, 172 μmol) in THF (1.8 mL) was added at 0 °C a solution of TBAF (1 M in THF, 207 μL, 1.2 equiv) followed by HOAc (30 μL, 3 equiv) and the mixture was stirred at 7 °C (cold chamber) overnight then concentrated. The crude product was purified by flash chromatography (silica gel; CH_2Cl_2–MeOH, 87:13) to give **11**.

Yield: 36 mg (60%); syrup; α:β >23:1); $[\alpha]_D$ + 90.2 (*c* 0.5, MeOH).

IR (film): 3402, 2932, 1732, 1608, 1371, 1258, 1199, 1092, 1068, 1018 cm^{-1}.

^{1}H NMR (CD_3OD, 400 MHz): δ = 8.09 (dd, *J* = 7.6, 1.7 Hz, 1 H), 7.65 (m, 1 H), 7.39 (m, 1 H), 7.19 (dd, *J* = 8.1, 0.8 Hz, 1 H), 6.35 (d, $J_{1,2}$ = 3.8 Hz, 1 H, H-1), 4.06 (dd, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 10.2 Hz, 1 H, H-2), 4.02 (d, $J_{3,4}$ = 3.2 Hz, 1 H, H-4), 4.00–3.90 (m, 2 H, H-3, H-5), 3.71 (d, *J* = 6.0 Hz, 2 H, H-6a, H-6b), 2.33 (s, 3 H, CH_3CO).

^{13}C NMR (CD_3OD, 100 MHz): δ = 171.4 and 164.6 (CO), 152.3 (C_4-aromatic-O), 135.3, 132.6, 127.2 and 125.0 (4 CH-aromatic), 124.4 (C_4-aromatic), 94.6 (C1), 75.0 (CH-sugar), 71.3 (CH-sugar), 70.6 (CH-sugar), 68.9 (CH-sugar), 62.4 (C6), 21.0 (CH_3).

HR-FABMS: *m*/*z* calcd for $C_{15}H_{18}O_9$: 342.09509; found: 342.09604.

2-(3-Methoxypyridyl) 2,4 Di-*O*-acetyl-β-D-galacturonopyranoside-3,6-lactone (7)

To **3** (500 mg, 1.7 mmol), dissolved in aq $NaHCO_3$ (9.2 mL, 0.19 M), KBr (2.28 g, 11 equiv) and TEMPO (19 mg, 0.07 equiv) were added, followed by dropwise aq sodium hypochlorite (11.8 mL, 100 equiv), and the mixture was stirred at r.t. for 3 h. The mixture was lyophilised and the residue was acetylated in a mixture of pyridine–Ac_2O (1:1; 10 mL) for 2 h at r.t. Pyridine and Ac_2O were removed under reduced pressure, the residue was dissolved in EtOAc (20 mL), washed with H_2O (2 × 10 mL) and processed as usual to give the title compound.

Yield: 505 mg (79%); white foam; $[\alpha]_D$ –65.9 (*c* 6.7, MeOH).

IR (film): 1814, 1754, 1465, 1435, 1371, 1227, 1156, 1123, 1049 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.70 (dd, *J* = 4.9,1.2 Hz, 1 H), 7.13 (dd, *J* = 7.9, 1.2 Hz, 1 H), 6.95 (dd, *J* = 7.9, 4.9 Hz, 1 H), 6.6 (s, 1 H, H-1), 5.57 (d, $J_{2,3}$ = 4.8 Hz, 1 H, H-2), 5.4 (s, 1 H, H-4), 5.01 (d, $J_{2,3}$ = 4.8 Hz, 1 H, H-3), 4.18 (s, 1 H, H-5), 3.86 (s, 3 H, OMe), 2.2 (s, 3 H, Me), 2.12 (s, 3 H, Me).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.7 (CO), 169.4 (CO), 168.9 (CO), 150.6 (CO-pyridyl), 144.5 (CO-pyridyl), 136.6 (CH-pyridyl), 119.7 (CH-pyridyl), 119.0 (pyridyl), 93.1 (C1), 77.3 (CH-sugar), 71.4 (CH-sugar), 70.7 (CH-sugar), 70.6 (CH-sugar), 56.2 (OMe), 20.5 (2 Me).

HR-FABMS: *m*/*z* calcd for $C_{16}H_{18}O_9N$: 368.09814; found: 368.09720.

2-(3-Methoxypyridyl) β-D-Galacturonopyranoside Methyl Ester (8)

A solution of **7** (39 mg, 0.1 mmol) and NaOMe–MeOH (25%; 0.2 mL) in MeOH (5 mL) was stirred until the reaction was completed. The mixture was cautiously neutralized with Amberlite CG-50 (H^+) ion-exchange resin. After filtration and concentration, **8** was obtained.

Yield: 33 mg (quant); syrup; $[\alpha]_D$ –15.17 (*c* 2.9, MeOH).

IR (film): 1814, 1754, 1464, 1435, 1371, 1227, 1156, 1123, 1049 cm^{-1}.

^{1}H NMR (CD_3OD, 400MHz): δ = 7.67 (d, *J* = 4.9 Hz, 1 H), 7.33 (d, *J* = 7.9 Hz, 1 H), 7.01 (dd, *J* = 7.9 Hz, *J* = 4.9 Hz, 1 H), 5.85 (d, $J_{1,2}$ = 8 Hz, 1 H, H-1), 4.47 (s, 1 H, H-5), 4.2 (s, 1 H, H-4), 3.88 (t, $J_{1,2}$ = 9.8 Hz, $J_{2,3}$ = 9.8 Hz, 1 H, H-2), 3.86 (s, 3 H,OMe-pyridyl), 3.75 (s, 3 H, MeO-ester), 3.70 (dd, $J_{2,3}$ = 9.8 Hz, $J_{3,4}$ = 2.7 Hz, 1 H, H-3).

^{13}C NMR (CD_3OD, 100 MHz): δ = 170.3 (CO), 153.7 (CO-pyridyl), 145.8 (CO-pyridyl), 137.6 (CH-pyridyl), 120.6 (CH-pyridyl), 119.8 (CH-pyridyl), 97.1 (C1), 75.8 (CH-sugar), 74.4 (CH-sugar), 71.4 (CH-sugar), 71 (CH-sugar), 56.3 (OMe-pyridyl), 52.6 (OMe-ester).

HR-FABMS: *m*/*z* calcd for $C_{13}H_{18}NO_8$: 316.10324; found: 316.10380.

α-D-Galacturonopyranosyl 1-(*trans*-2-Pentenoate) Methyl Ester (9)

To a solution of **8** (50 mg, 160 μmol) and *trans*-2-pentenoic acid (3.2 mL, 200 equiv) in MeCN (0.5 mL, 0.38 M) was added at 0 °C methyl triflate (22 μL, 1.2 equiv) and the mixture stirred overnight at r.t. and concentrated. Purification by flash chromatography of the residue (silica gel; EtOAc–MeOH, 95:5) gave the title compound.

Yield: 34 mg (74%); syrup; $[\alpha]_D$ + 76.2 (*c* 2.4, MeOH).

IR (film): 1814, 1754, 1465, 1435, 1371, 1227, 1156, 1123, 1049 cm^{-1}.

^{1}H NMR (CD_3OD, 400 MHz): δ = 7.1 (dt, $J_{\alpha,}$ = 15.7 Hz, $J_{\beta,CH2}$ = 6.4 Hz, 1 H, H-β), 6.28 (d, $J_{1,2}$ = 3.7 Hz, 1 H, H-1), 5.9 (dt, $J_{\alpha,\beta}$ = 15.7 Hz, $J_{\alpha,CH2}$ = 1.7 Hz, 1 H, H-α), 4.57 (d, $J_{4,5}$ = 1.2 Hz, 1 H, H-5), 4.27 (dd, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 1.2 Hz, 1 H, H-4), 3.99 (dd, $J_{2,3}$ = 10.2 Hz, $J_{1,2}$ = 3.8 Hz, 1 H, H-2), 3.91 (dd, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 3.3 Hz, 1 H, H-3), 2.28 (m, 2 H, CH_2), 1.09 (t, $J_{Me,CH2}$ = 7.4 Hz, 3 H, Me).

^{13}C NMR (CD_3OD, 100 MHz): δ = 170.6 (CO methyl ester), 166.6 (CO), 154 (CH-olefin), 120.7 (CH-olefin), 93.3 (C1), 74 (CH-sugar), 71.6 (CH-sugar), 70.6 (CH-sugar), 68.3 (CH-sugar), 52.6 (OMe), 26.3 (CH_2), 12.3 (Me).

HR-FABMS: *m*/*z* calcd for $C_{12}H_{17}O_8$: 289.09235; found: 289.09110.

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