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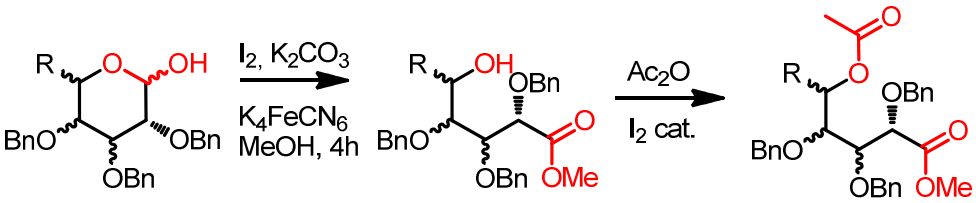


R = H, CH_3, CH_2OBn 6 times faster with K_4FeCN_6 75-93%

Metal-free oxidative esterification of benzylated monosaccharides

Tchambaga Camara, Abed Bil and Vincent Chagnault*

Laboratory LG2A, UMR CNRS 7378, UPJV, 33 rue saint leu, 80000 Amiens, France

Abstract: Methyl glyconates have been attracting considerable attention as intermediates for the preparation of aryl *C*-glycosides, polyphenolic products, aliphatic polyesters, SGLT2 inhibitors, antibiotics etc… In view of the interest in those compounds, we report herein our work on the synthesis of methyl glyconates using an oxidative esterification carried out by molecular iodine. This reaction is catalyzed by non-toxic $K_4Fe(CN)_6$ that releases a small amount of cyanide ion into the reaction mixture. Four benzylated carbohydrates which contain a hemiacetalic functional group have been tested successfully.

Highlights:

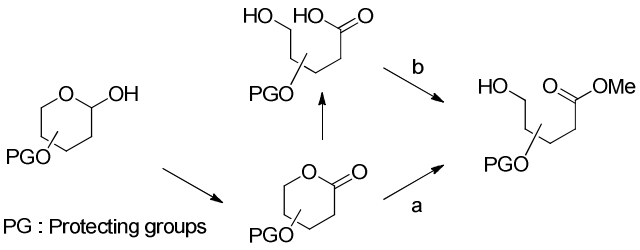
- Synthesis of methyl aldonates from reducing monosaccharides.
- Oxidation catalysis by potassium ferrocyanide.
- Oxidation using molecular iodine

Corresponding author: Phone: +333.22.82.88.12.; fax: +333.22.82.75.60.

E-mail address: vincent.chagnault@u-picardie.fr

1. Introduction

Methyl glyconates have been attracting considerable attention as intermediates for the preparation of aryl *C*-glycosides,[1-2] polyphenolic products,[3] aliphatic polyesters,[4] SGLT2 inhibitors,[5] antibiotics[6] and in a ring-closing reaction type.[7] Depending on the nature of the protecting groups, these esters can be prepared by two different pathways (Scheme 1).



Scheme 1. General scheme for the synthesis of methyl glyconates

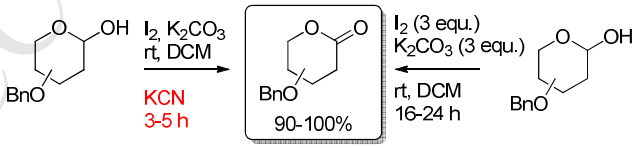
After the oxidation of the hemiacetalic positions to the corresponding lactones, methyl glyconates are generally obtained either by nucleophilic opening by methanol in acidic conditions (Pathway "a") or by alkylation of glyconic acids (Pathway "b"). This alkylation is in most cases carried out using diazomethane in ether.[6]

Lactones are obtained by oxidation *via* various methodologies such as: DMSO/$COCl_2$;[8-9] DMSO/Ac_2O;[10-11] PCC; PDC;[12-14] Dess-Martin's periodinane;[15-16] NMO/TPAP;[17-18] Ag_2CO_3 on Celite;[19-21] $Br_2/H_2O/BaCO_3$;[22-24] MnO_2.[25] Depending on the nature of the functional groups present on the sugar, these lactones become more or less reactive. Thus, the presence of acetate functions allows the direct formation of methyl glyconates (pathway "a").[4-5, 26] However, the presence of benzyl protecting groups leads to a low reactivity of the lactone. Pathway "b" is then very convenient and the corresponding methyl glyconates are obtained in good yields but with longer reaction times.[6-7, 27-28] However, both these methods involve several steps and often the use of diazomethane or metal salts (cadmium chloride, mercuric chloride, magnesium iodide).

In view of the interest in the synthesis of alkyl glyconates, we wish to report here our work on the synthesis of methyl glyconates using a metal-free oxidative esterification reaction. We will present the optimization steps carried out on different substrates protected by benzyl protecting groups.

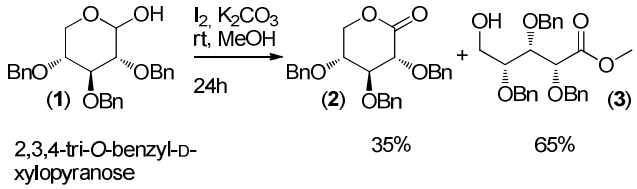
2. Results and discussion

Recently, we described a new chemoselective oxidation method of hemiacetalic groups using molecular iodine.[29] Various benzylated carbohydrates are thus oxidized to lactones in 16-24 hours with a yield of 90-100%. Surprinsigly, we also observed that reaction times can be reduced considerably by the use of potassium cyanide.[30] In this case, the same lactones are obtained in only 3-5 h with similar yields (Scheme 2).



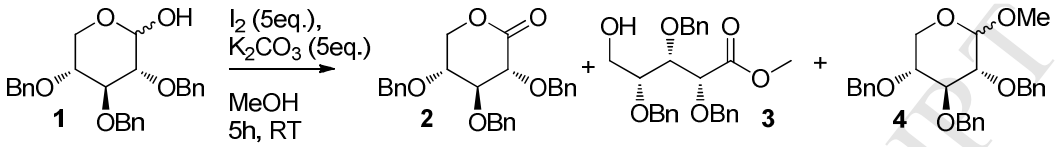
Scheme 2. Oxidative lactonisation of benzylated aldoses.

As in all reactions involving the use of diiodine, the nature of the solvent plays a very important role.[31-33] The substitution of dichloromethane by methanol (Scheme 3) leads to the formation of a mixture of the corresponding lactone (**2)** and methyl glyconate (**3)** with a ratio 35:65 respectively (established by NMR).[29]



Scheme 3. Oxidative lactonisation in methanol.

We chose 2,3,4-tri-*O*-benzyl-D-xylose (TBX) (**1**) as starting material, easily prepared on the scale of several tens of grams.[34] The development of the esterification reaction *via* molecular iodine has thus been explored. As described during our previous researches, when 3 mole equivalents of I_2 and K_2CO_3 are used, the reaction is quantitative after stirring for 16-24 h (Scheme 3). In order to get higher proportions of methyl xylonate (**3**), we tried to increase the amount of both iodine and potassium carbonate. However, when 5 mole equivalents of each reagent are used, the reaction mixture quickly becomes complex after only 5 hours of stirring. In this case, NMR spectroscopic analyses showed the presence of methyl-*O*-xylosides (**4**), lactone (**2**) and the ester (**3**) (Scheme 4).



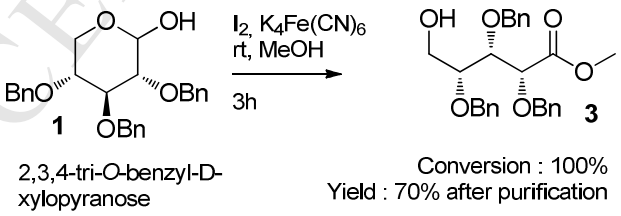
Scheme 4. Effect of large excess of diiodine on the oxidative esterification.

The ratio of **2**, **3** and **4** could not be accurately determined. Nevertheless, we can reasonably estimate the reaction as being composed of 50% methyl-*O*-glycosides (NMR ratio). Despite the quantity of each reagent increased, the presence of a mixture is always observed. Other conditions have therefore been envisaged.

As explained in our previous research on the oxidizing lactonization,[30] we observed that the addition of cyanide ions in the reaction medium clearly speeds up the oxidation significantly. Thus, in order to check the catalytic power of these ions in the oxidative esterification reaction, a third attempt was carried out during which 3 mole equivalents of I_2 and K_2CO_3 were added to a solution of TBX (**1**) in methanol. Then, KCN (3 mole equivalents) was added and the reaction stirred at room temperature and monitored by TLC and mass spectrometry.

The total conversion was reached after only 2 hours of stirring. However, the mixture was still complex and the different analyzes showed the presence of the lactone **2**, the ester **3** as well as methyl-*O*-xylosides **4**. The rapid dissolution of KCN in the reaction medium therefore leads to a too fast catalysis (Solubility of KCN in methanol = 21 $g.L^{-1}$ at 298.2 K).[35]

To overcome this problem and to prevent the manipulation of potassium cyanide, we considered the use of another cyanogenic source. The work of Xinzhe *et al.* indicates that ferrocyanide ions can be used as cyanogenic agents in the presence of diiodine.[36] We therefore tested a fourth protocol replacing KCN by potassium ferrocyanide (Solubility of $K_4Fe(CN)_6$ in methanol = 0.12 $g.L^{-1}$ at 10°C).[37]



Scheme 5. Effect of $K_4Fe(CN)_6$ on the oxidative esterification.

It is important to note that the use of potassium ferricyanide ($K_3Fe(CN)_6$) led to similar results but also to purification difficulties. After stirring for 3 hours at RT, the reaction was quantitative and NMR analyzes showed the exclusive presence of the methyl ester **3** (Scheme 5). Purification by silica gel chromatography gave the desired product with 70% yield. The loss of product can be explained by the relative instability of this class of compounds. Indeed, as described by Bowles *et al.*, a non-negligible balance exists (Scheme 6) between the lactone **2** and the ester **3** in the presence of silica.[5]

Scheme 6. Equilibrium between methyl esters and lactones on silica gel.

In the case of benzylated sugars, the formation rate of the lactone from the corresponding methyl ester is relatively slow and allows purification on silica gel. Once the product is stored dry at less than 4 °C, the ester **3** may be kept several days without any problems. To facilitate the NMR analyzes, the deuterated chloroform was previously stored on potassium carbonate. Otherwise, the acidity of this solvent leads to the progressive presence of the lactone signals in the spectra.

Thus, our methodology was applied on other benzylated sugars: 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**5**), 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (**6**) and 2,3,4-tri-*O*-benzyl-L-fucopyranose (**7**), these compounds being commercially available. The results are summarized in the table below.

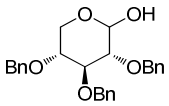
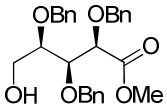
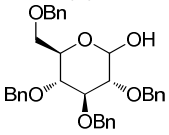
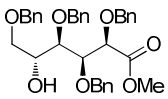
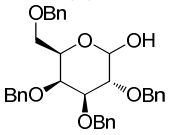
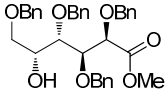
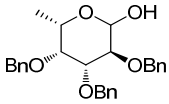
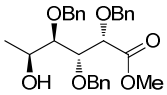
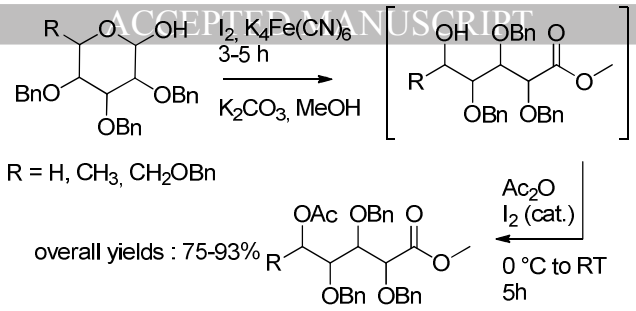
Entry	Substrat	Product	Time	Yield*
1	 (**1**)	 (**3**)	3h	70%
2	 (**5**)	 (**8**)	5h	55%
3	 (**6**)	 (**9**)	3h	87%
4	 (**7**)	 (**10**)	3h	84%

Table 1: Oxidative esterification catalyzed by potassium ferrocyanide. Reaction conditions : 3 mol. Equiv. K_2CO_3, 3 mol. Equiv. I_2, 3 mol. Equiv. $K_4Fe(CN)_6$, MeOH, 3-5 h, RT. *After purification by silica gel chromatography.

The substrates **1**, **6**, **7** lead to the formation of the corresponding methyl esters **3**, **9** and **10** respectively after only 3 hours of stirring. The reactivity of glucose derivatives being lower than the other substrates,[29-30] 5h were needed for a complete conversion. To overcome the loss of product during the purification step (Scheme 6), we decided to derivatize the crude reaction mixtures by acetylation of the remaining free hydroxyl group.

With the objective of a rapid acetylation to prevent lactonization of methyl esters, we carried out the reaction using molecular iodine as a catalyst in acetic anhydride.[38-40] Thus, methyl glyconates were engaged in an acetylation reaction without prior purification. The different crude reaction mixtures were dissolved in acetic anhydride and a catalytic amount of diiodine was added at 0 °C. After stirring for 2 h, the ice bath is removed so that the temperature rises gradually over 3 h. After appropriate workup, the acetylated glyconates were purified on silica gel chromatography (Scheme 7).



Scheme 7. Oxidative esterification of aldose hemiacetals followed by acetylation.

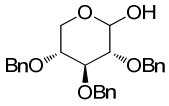
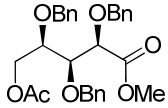
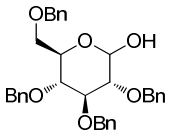
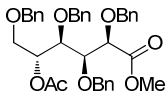
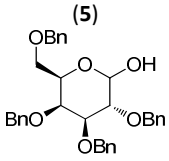
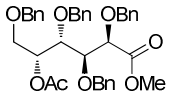
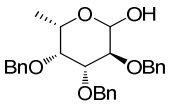
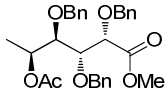
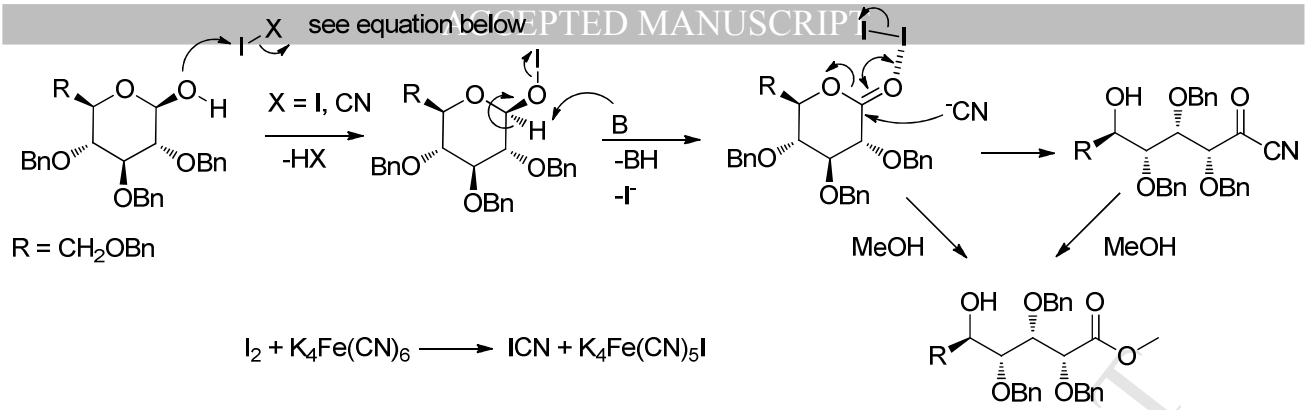
Entry	Substrat	Product	Yield*
1	 (**1**)	 (**11**)	85%
2	 (**5**)	 (**12**)	75%
3	 (**6**)	 (**13**)	93%
4	 (**7**)	 (**14**)	80%

Table 2: Optimized oxidative esterification followed by acetylation. Reaction conditions for acetylation: I_2 cat., 15 mol. Equiv. Ac_2O, 0 °C to RT, 5 h. *overall yields after purification

Good overall yields ranging from 75 to 93% were obtained (Table 2). These values demonstrate the effectiveness of the oxidative esterification step as well as the possibility to functionalize the free remaining hydroxyl group. All these structures were characterized by NMR spectroscopic analyses and mass spectrometry. The NMR analyses confirm the presence of a singlet at 3.6 ppm corresponding to the OCH_3 protons and a singlet at 2 ppm corresponding to the acetyl group. NMR ^{13}C brings out the occurrence of two carbonyls at 170 and 172 ppm corresponding to the carbon C1 and the carbon of the acetyl group respectively.

3. Mechanism of oxidative esterification reaction

The chemoselective oxidation of aldoses has been described in our previous work.[29-30, 33] However, the role of the cyanide ion in this process remains uncertain. A mechanistic pathway is suggested herein (Scheme 8). We assume that the reaction of diiodine in the presence of potassium ferrocyanide leads to the formation of ICN. This molecule is a better iodizing agent than the diiodine itself. The formation of the O-I species is probably faster when ICN is present in the medium. Further investigations will be carried out in a future research work to better understand the role of ferrocyanide ions in this type of oxydation.



Scheme 8. Role of cyanide ions in the oxidative esterification.

4. Conclusion

Molecular iodine is a formidable tool which, once coupled with the use of potassium ferrocyanide, makes it possible to obtain methyl glyconates from benzylated aldoses. This soft method is fast and flexible. We also demonstrated the possibility to acetylate the free hydroxyl group with good yields and without returning to the corresponding lactones.

5. Experimental Section

All reagent-grade chemicals were obtained from commercial suppliers and were used as received. Characterizations of known compounds were in accordance with literature. Optical rotations were recorded in CH_2Cl_2 solution. FTIR spectra were obtained using ATR and are reported in cm^{-1}. ^1H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded in $CDCl_3$. The proton and carbon signal assignments were determined from decoupling experiments, COSY spectra and HSQC spectra. TLC were performed on Silica F_{254} and detection by UV light at 254 nm or by charring with cerium molybdate reagent. Column chromatography was performed on Silica Gel 60 (230 mesh). High-resolution electrospray mass spectra in the positive ion mode were obtained on a Q-TOF Ultima Global hybrid quadrupole/time-of-flight instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source and an additional sprayer (Lock Spray) for the reference compound. The source and desolvation temperatures were kept at 80 and 150 °C, respectively. Nitrogen was used as the drying and nebulizing gas at flow rates of 350 and 50 L/h, respectively. The capillary voltage was 3.5 kV, the cone voltage 100 V and the RF lens1 energy was optimized for each sample (40 V). For collision-induced dissociation (CID) experiments, argon was used as collision gas at an indicated analyser pressure of 5.10^{-5} Torr and the collision energy was optimized for each parent ion (50-110 V). Lock mass correction, using appropriate cluster ions of sodium iodide $(NaI)_nNa^+$, was applied for accurate mass measurements. The mass range was typically 50-2050 Da and spectra were recorded at 2 s/scan in the profile mode at a resolution of 10000 (FWMH).

5.1. General procedure for the preparation of methyl glyconates:

Benzylated carbohydrate (0.476 mmol) was suspended in methanol (4.8 mL) in a 10 mL round bottom flask (The use of a too large flask is not recommended to keep each solid in suspension) and potassium carbonate (3 mol. equiv.; 1.427 mmol), diiodine (3 mol. equiv.; 1.427 mmol) and $K_4Fe(CN)_6$ (3 mol. equiv.; 1.427 mmol) were added successively. The reaction mixture was then stirred at room temperature for 3-5 hours and monitored by TLC. Excess of diiodine was reduced using a saturated solution of sodium thiosulfate until a white color is obtained (~1-2 mL). Water was added (5 mL) and the organic layer separated. The aqueous phase was extracted 3 times with dichloromethane or ethyl acetate and the combined organic phases were dried over magnesium sulfate. After evaporation under reduced pressure, the solid residue can be quickly purified by silica-gel column chromatography (Cyclohexane / Ethyl acetate; 8/2). However, cyclisation of these products being favored when dissolved in a solvent, purification should be avoided and the solid should be directly engaged in the next step.

*Methyl 2,3,4-tri-O-benzyl-D-xylonate (**3**).*

Yield 69% (147.9 mg, colorless oil from 0.476 mmol of 2,3,4-tri-*O*-benzyl-D-xylopyranose): ^1H NMR (400 MHz, Methanol-d_4) δ 7.47 – 7.19 (m, 15H, Ar), 4.72 (d, *J* = 11.3 Hz, 1H, CH_2-OPh), 4.67 (d, *J* = 11.5 Hz, 2H), 4.56 (dd, *J* = 11.4, 2.5 Hz, 2H, CH_2-OPh), 4.41 (d, *J* = 11.2 Hz, 1H, CH_2-OPh), 4.27 (d, *J* = 3.9 Hz, 1H, H-2), 4.06 (dd, *J* = 6.0, 3.9 Hz, 1H, H-3), 3.82 – 3.72 (m, 2H, H-4, H-5a), 3.60 (s, 3H, OCH_3), 3.58 – 3.48 (m, 1H, H-5b). ^{13}C NMR (101 MHz, Methanol-d_4) δ 172.8

(C=O), 139.8 (CH-Ar), 139.5 (CH-Ar), 138.6 (CH-Ar), 129.7 – 128.5 (Ar), 81.6 (C_4), 80.6 (C_3), 79.3 (C_2), 75.6 (OCH_2Ph), 74.1 (OCH_2Ph), 74.0 (OCH_2Ph), 62.0 (C_5), 52.4 (OCH_3). IR (ATR) ν = 2929.9; 1745.6; 1209.4; 1051.2 cm^{-1}. $[\alpha]_D^{20}$ +22 (c 0.1, CH_2Cl_2). HRMS [M+Na^+]: calcd. for $C_{27}H_{30}NaO_6$ 473.1940, found 473.1937.

*Methyl 2,3,4,6-tetra-O-benzyl-D-gluconate (**8**)*

Yield 55% (116.1 mg, colorless oil from 0.37 mmol of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose): ^{1}H NMR (400 MHz, Methanol-d_4) δ = 7.42 – 7.16 (m, 20H, Ar), 4.73 (d, *J*=11.2, 1H, OCH_2Ph), 4.68 (d, *J*=11.3, 1H, OCH_2Ph), 4.62 (d, *J*=11.2, 1H, OCH_2Ph), 4.58 (d, *J*=11.1, 1H, OCH_2Ph), 4.57 (d, *J*=11.3, 1H, OCH_2Ph), 4.50 (d, *J*=11.9, 1H, OCH_2Ph), 4.45 (d, *J*=11.9, 1H, OCH_2Ph), 4.43 (d, *J*=11.2, 1H, OCH_2Ph), 4.33 (d, *J*=4.4, 1H, H-2), 4.14 (dd, *J*=4.5, 1H, H-3), 3.96 – 3.81 (m, 2H, H-5), 3.68 (dd, *J*=9.9, 4.0, 1H, H-6a), 3.57 (s, 3H, OCH_3), 3.54 (dd, *J*=9.8, 4.8, 1H, H-6b). ^{13}C NMR (101 MHz, Methanol-d_4) δ 172.8 (C-1), 139.9 (Ar), 139.6 (Ar), 139.5 (Ar), 138.7 (Ar), 130.4 – 127.6 (Ar), 81.4 (C-3), 80.6 (C-4), 79.9 (C-2), 75.9 (OCH_2Ph), 75.4 (OCH_2Ph), 74.3 (OCH_2Ph), 74.1 (OCH_2Ph), 72.2 (C-6), 72.0 (C-5), 52.3 (OCH_3). IR (ATR) ν = 1747.5; 1209.4; 1092.6 cm^{-1}. $[\alpha]_D^{20}$ +43 (c 0.1, CH_2Cl_2). HRMS [M+Na^+]: calcd. for $C_{35}H_{38}NaO_7$ 593.2515, found 593.2510.

*Methyl 2,3,4,6-tetra-O-benzyl-D-galactonate (**9**)*

Yield 87% (181 mg, colorless oil from 0.37 mmol of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose): ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.17-7.37 (m, 20H, Ar), 4.80 (d, 1H, J = 11.4 Hz, OCH_2Ph), 4.71 (d, 1H, J = 11.0 Hz, OCH_2Ph), 4.52 (d, 1H, J = 11.0 Hz, OCH_2Ph), 4.47 (d, 1H, J = 11.8 Hz, OCH_2Ph), 4.41 (d, 2H, J = 8.4 Hz, OCH_2Ph), 4.37 (d, 1H, J = 2.6 Hz, H_2), 4.33 (d, 1H, J = 11.3 Hz, OCH_2Ph), 4.26 (d, 1H, J = 11.2 Hz, OCH_2Ph), 4.26 (dd, 1H, J = 8.7, 2.6 Hz, H_3), 4.11 (td, 1H, J = 6.9, 1.5 Hz, H_5), 3.90 (dd, 1H, J = 8.9, 1.6 Hz, H_4), 3.63 (s, 3H, OCH_3), 3.53 (d, 2H, J = 6.8, 1.4 Hz, H_6). ^{13}C NMR (101 MHz, Methanol-d_4) δ 173.4 (C=O), 139.6 (C_q-Ar), 139.4 (C_q-Ar), 139.31 (C_q-Ar), 138.8 (C_q-Ar), 128.5 – 129.4 (CH-Ar), 80.6 (C_3), 79.2 (C_2), 78.5 (C_4), 75.3 (OCH_2Ph), 75.1 (OCH_2Ph), 74.1 (OCH_2Ph), 73.5 (OCH_2Ph), 72.1 (C_6), 69.8 (C_5), 52.4 (OCH_3). IR (ATR) ν = 1751.4, 1209.4, 1068.6 cm^{-1}. $[\alpha]_D^{20}$ +58 (c 0.1, CH_2Cl_2). HRMS [M+Na^+]: calcd. for $C_{35}H_{38}NaO_7$ 593.2515, found 593.2515.

*Methyl 2,3,4-tri-O-benzyl-L-fuconate (**10**)*

Yield 84% (180 mg, colorless oil from 0.46 mmol of 2,3,4-tri-*O*-benzyl-L-fucopyranose): ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.24-7.38 (m, 15H, CH-Ar), 4.74 (d, H, J_1 = 11.4 Hz, OCH_2Ph), 4.69 (d, 1H, J = 10.8 Hz, OCH_2Ph), 4.59 (d, 1H, J = 11.5 Hz, OCH_2Ph), 4.525 (d, 1H, J = 10.9Hz, OCH_2Ph), 4.445 (d, 1H, J = 11.5 Hz, OCH_2Ph), 4.395 (d, 1H, $J_{2,3}$ = 2.6 Hz, H_2), 4.30 (d, 1H, J = 11.2Hz, OCH_2Ph), 4.205 (dd, 1H, , $J_{4,3}$ = 8.6 Hz, $J_{4,5}$ = 2.6 Hz, H_4), 4.03-4.09 (m, 1H, H_5), 3.68 (s, 3H, OCH_3), 3.55 (dd, 1H, $J_{3,4}$ = 8.6Hz, $J_{3,2}$ = 1.9 Hz, H_3), 1.275 (d, 3H, J = 4 Hz, CH_3). ^{13}C NMR (101 MHz, Methanol-d_4) δ 172.9 (C=O), 139.2 (C_q-Ar), 138.7 (Cq-Ar), 130.01, 138.3 (C_q-Ar), 128.9 (CH-Ar), 128.8 (CH-Ar), 128.7 (CH-Ar), 128.7 (CH-Ar), 128.7 (CH-Ar), 128.6 (CH-Ar), 128.3 (CH-Ar), 128.2 (CH-Ar), 128.2 (CH-Ar), 127.9 (CH-Ar), 81.9 (C_3), 80.5 (C_4), 78.70 (C_2), 75.3 (OCH_2Ph), 74.6 (OCH_2Ph), 73.0 (OCH_2Ph), 66.8 (C_5), 51.8 (OCH_3), 20.1 (CH_3). IR (ATR) ν = 1745.6, 1207.4, 1068.6 cm^{-1}. $[\alpha]_D^{20}$ -64 (c 0.1, CH_2Cl_2). HRMS [M+Na^+]: calcd. for $C_{28}H_{32}NaO_6$ 487.2097, found 487.2090.

5.2. General procedure for the methyl glyconates acetylation:

The previous crude reaction mixture was dissolved in acetic anhydride (15 mol. equiv.; 7.14 mmol) a 0 °C (water-ice bath) in a 10 mL round bottom flask. A catalytic quantity of diiodine was added (0.125 mol. equiv.; 0.06 mmol) and the reaction mixture was stirred for 2 hours à 0°C followed with 3 hours at room temperature. Then acetic anhydride was evaporated under reduced pressure and the residue was diluted in dichloromethane. The organic layer was washed using a saturated solution of sodium thiosulfate and separated. The aqueous phase was then extracted 3 times with dichloromethane. Combined organic phases were dried over magnesium sulfate, filtered and evaporated.

*Methyl 5-O-acetyl-2,3,4-tri-O-benzyl-D-xylonate (**11**)*

Yield 72% (414 mg, colorless oil starting from 1.189 mmol of 2,3,4-tri-*O*-benzyl-D-xylopyranose): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 – 7.17 (m, 15H, Ar), 4.84 (d, *J* = 11.5 Hz, 1H, OCH_2Ph), 4.74 (d, *J* = 11.7 Hz, 1H, OCH_2Ph), 4.68 (d, *J* = 11.7 Hz, 1H, OCH_2Ph), 4.62 (s, 2H, OCH_2Ph), 4.50 (d, *J* = 11.5 Hz, 1H, OCH_2Ph), 4.35 (dd, *J* = 12.0, 3.3 Hz, 1H, H-5a), 4.26 (d, *J* = 4.3 Hz, 1H, H-2), 4.14 (dd, *J* = 12.0, 6.3 Hz, 1H, H-5b), 4.03 (dd, *J* = 5.8, 4.4 Hz, 1H, H-3), 3.92 (td, *J* = 6.1, 3.3 Hz, 1H, H-4), 3.65 (s, 3H, $COOCH_3$), 2.03 (s, 3H, CH_3COO). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.1 (C_1), 170.7 (C=O), 138.0 CqAr, 137.9 CqAr, 137.0 CqAr, 129.3 – 127.3 (Ar), 78.6 (C_3), 77.9 (C_2), 77.1 (C_4), 74.4 (OCH_2Ph), 73.3 (OCH_2Ph), 73.2

(OCH$_2$Ph), 63.8 (C$_5$), 52.0 (OCH$_3$), 21.0 (CH$_3$C=O). IR (ATR) ν = 3030.2; 2949.2; 2872.0; 1737.9; 1230.6 cm^{-1}. $[\alpha]_D^{20}$ +20 (c 0.1, CH$_2$Cl$_2$). HRMS [M+Na$^+$]: calcd. for $C_{29}H_{32}NaO_7$ 515.2046, found 515.2040.

*Methyl 5-O-acetyl-2,3,4,6-tetra-O-benzyl-D-gluconate (**12**)*

Yield 62% (66.5 mg, colorless oil starting from 0.1752 mmol of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.09 (m, 20H, Ar), 5.14 – 5.06 (m, 1H, H-5), 4.69 (d, *J* = 11.2 Hz, 1H, CH$_2$OPh), 4.61 (d, *J* = 11.2 Hz, 2H, CH$_2$OPh), 4.55 (d, *J* = 14.3 Hz, 1H, CH$_2$OPh), 4.52 (d, *J* = 14.4 Hz, 1H, CH$_2$OPh), 4.41 (d, *J* = 11.2 Hz, 1H, CH$_2$OPh), 4.36 (d, *J* = 12.0 Hz, 1H, CH$_2$OPh), 4.19 – 4.12 (m, 1H, H-2), 3.98 – 3.93 (m, 2H, H-3, H-4), 3.75 (dd, *J* = 10.5, 4.7 Hz, 1H, H-6a), 3.57 (dd, *J* = 10.5, 5.5 Hz, 1H, H-6b), 3.45 (s, 3H, COOCH$_3$), 1.88 (s, 3H, CH$_3$COO). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.9 (C-1), 170.0 (CH$_3$COO), 138.5 (Ar), 138.1 (Ar), 138.0 (Ar), 137.2 (Ar), 129.7 – 126.9 (Ar), 79.7 (C-3), 78.7 (C-4), 78.6 (C-2), 75.1 (OCH$_2$Ph), 74.7 (OCH$_2$Ph), 73.4 (OCH$_2$Ph), 73.3 (OCH$_2$Ph), 72.7 (C-5), 68.1 (C-6), 51.9 (OCH$_3$), 21.2 (CH$_3$CO). IR (ATR) ν = 3030.2; 2868.2; 1737.9; 1232.5 cm^{-1}. $[\alpha]_D^{20}$ +17 (c 0.1, CH$_2$Cl$_2$). HRMS [M+Na$^+$]: calcd. for $C_{37}H_{40}NaO_8$ 635.2621, found 635.2623.

*Methyl 5-O-acetyl-2,3,4,6-tetra-O-benzyl-D-galactonate (**13**)*

Yield 93% (264 mg, colorless oil starting from 0.46 mmol of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.06 (m, 20H, Ar), 5.39 (td, *J* = 6.3, 2.7 Hz, 1H, H-5), 4.79 (d, *J* = 11.4 Hz, 1H, OCH$_2$Ph), 4.52 – 4.39 (m, 5H, OCH$_2$Ph), 4.36 – 4.28 (m, 3H, OCH$_2$Ph, H-2), 4.05 (dd, *J* = 8.4, 3.2 Hz, 1H, H-3), 3.96 (dd, *J* = 8.4, 2.7 Hz, 1H, H-4), 3.68 – 3.58 (m, 4H, H-6a, COOCH$_3$), 3.55 (dd, *J* = 9.9, 6.4 Hz, 1H, H-6b), 2.01 (s, 2H, CH$_3$CO). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.0 (C-1), 170.7 (COCH$_3$), 138.1 (Ar), 137.9 (Ar), 137.7 (Ar), 137.4 (Ar), 128.5 - 127.6 (Ar), 79.5 (C-3), 78.0 (C-2), 75.7 (C-4), 74.1 (OCH$_2$Ph), 74.0 (OCH$_2$Ph), 73.1 (OCH$_2$Ph), 72.8 (OCH$_2$Ph), 71.3 (C-5), 68.1 (C-6), 52.1 (COOCH$_3$), 21.4 (CH$_3$CO). IR (ATR) ν = 3030.2, 2868.2, 1737.9, 1234.4 cm^{-1}. $[\alpha]_D^{20}$ +20 (c 0.1, CH$_2$Cl$_2$). HRMS [M+Na$^+$]: calcd. for $C_{37}H_{40}NaO_8$ 635.2615, found 635.2620.

*Methyl 5-O-acetyl-2,3,4-tri-O-benzyl-L-fuconate (**14**)*

Yield 70% (80.6 mg, colorless oil starting from 0.23 mmol of 2,3,4-tri-*O*-benzyl-L-fucopyranose): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.13 (m, 15H, Ar), 5.20 (qd, *J* = 6.5, 2.4 Hz, 1H, H-5), 4.81 (d, *J* = 11.3 Hz, 1H, OCH$_2$Ph), 4.54 (d, *J* = 11.4 Hz, 1H, OCH$_2$Ph), 4.46 (d, *J* = 10.6 Hz, 1H, OCH$_2$Ph), 4.42 (d, *J* = 10.7 Hz, 1H, OCH$_2$Ph), 4.38 (d, *J* = 11.5 Hz, 1H, OCH$_2$Ph), 4.35 (d, *J* = 2.9 Hz, 1H, H-2), 4.32 (d, *J* = 11.3 Hz, 1H, OCH$_2$Ph), 4.06 (dd, *J* = 8.7, 2.9 Hz, 1H, H-3), 3.67 (dd, *J* = 8.7, 2.5 Hz, 1H, H-4), 3.65 (s, 3H, COOMe), 2.00 (s, 3H, CH$_3$COO), 1.27 (d, *J* = 6.5 Hz, 3H, H-6). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.0 (C-1), 170.7 (COCH$_3$), 138.0 (Ar), 137.6 (Ar), 137.4 (Ar), 128.7 – 127.3 (Ar), 79.5 (C-4), 79.4 (C-3), 78.0 (C-2), 74.6 (OCH$_2$Ph), 74.0 (OCH$_2$Ph), 72.8 (OCH$_2$Ph), 70.0 (C-5), 52.1 (OCH$_3$), 21.6 (CH$_3$CO), 16.9 (C-6). IR (ATR) ν = 2873.9, 1732.1, 1240.2 cm^{-1}. $[\alpha]_D^{20}$ -18 (c 0.1, CH$_2$Cl$_2$). HRMS [M+Na$^+$]: calcd. for $C_{30}H_{34}NaO_7$ 529.2202, found 529.2196.

AUTHOR INFORMATION

Corresponding Author

* vincent.chagnault@u-picardie.fr

Author Contributions

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