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Improved and large-scale synthesis of different protected D-glucuronals

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ABSTRACT

Although different protected D-glucuronals are used as precursors for the preparation of many compounds, standard procedures and large-scale syntheses are still not described in the literature. In the course of the development of different protected D-glucuronyl donors we developed several versatile methods that can be used for fast and reproducible preparation of large amounts of the key intermediates. D-Glucuronolactone was converted to methyl 3,4-di-*O*-acetyl-D-glucuronal applying a novel one-pot protocol, which allowed for large-scale synthesis. Introduction of silyl and benzyl groups was achieved using optimized procedures. Furthermore 3,4,6-tri-*O*-acetyl-D-glucal was used as starting material for an improved preparation of benzyl protected D-glucuronal, which significantly accelerates and simplifies similar methods described in the literature.

Glycals, systematically named 1,5-anhydro-2-deoxy-1-enitols, are used in organic synthesis as building blocks and precursors for many different types of reactions.[1–5] Several procedures (including one-pot protocols) for the preparation of glycals are described in the literature.[6–10] 1,5-Anhydro-2-deoxy-D-arabino-hex-1-enopyranuronates are derived basically from glucuronic acid and therefore trivially named D-glucuronals. These compounds are applied as starting materials, precursors, and glucuronyl donors many times in the literature. Diastereoselective D-glucuronidation was achieved using different protected D-glucuronals[11–15] and also Ferrier-type reactions as well as rearrangements were done in the past using this type of glycals.[16–18] Durham and Miller used methyl 3,4-di-*O*-acetyl-D-glucuronal (**4**) as starting material for the synthesis of novel bicyclic β-lactams.[19] Nitration of D-glucuronals and subsequent Michael addition lead to C-1 phosphonylated 2-acylamino uronic acids, which was shown very recently.[20] Azidonitration of **4** was used as a key step in the synthesis of amphiphilic poly(sugar amino acid)s as a novel class of glycoclusters for supramolecular materials,[21] whereas double Grignard reaction of **4** with subsequent exchange of protecting groups lead to an effective chiral auxiliary for hydroxyalkyl radicals with application in diastereoselective radical additions to methyl acrylate at −78 °C.[22] Tuwalska et al. applied addition of hydrazoic acid to **4** for the synthesis of novel sugar amino acids[23] and Poláková, O'Brien et al. used an allyl D-glucuronal for the preparation of conformationally inverted donors with application to the diastereoselective synthesis of glucuronides and 2-deoxy-glucuronides.[24,25] Conformational analysis of **4** by X-ray diffraction and high resolution NMR spectroscopy was published by Liberek et al.[26] Furthermore sulfonium mediated oxidative coupling of methyl 4-*O*-acetyl-3-*O*-(*tert*-butyldimethylsilyl)-D-glucuronal (derived from **4**) was used for the synthesis of the trisaccharide subunit of the immunologic adjuvant QS-21A.[27,28]

In the course of designing and investigating novel glucuronyl donors, we became interested in different protected D-glucuronals, since these compounds may be used as key intermediates for the introduction of various leaving and participating groups at the anomeric center and C2, respectively.

Methyl 3,4-di-*O*-acetyl-D-glucuronal (**4**), which is the most commonly used glucuronal, is basically prepared starting from D-glucuronolactone (**1**) within four synthetic steps. After base-catalyzed esterification (step 1) and subsequent acetylation (step 2) to afford methyl 1,2,3,4-tetra-*O*-acetyl-D-glucuronate (**2**), treatment with hydrobromic acid (33% in acetic acid; step 3), followed by reduction with zinc dust in aqueous acetic acid (step 4) provides the desired product. Basically steps 1 and 2 as well as steps 3 and 4, respectively, are usually combined to a one-pot procedure as described by Wyss et al.[29] to afford **4** in an overall yield of 59%. In another described procedure,[30] excess of acetic anhydride is quenched with methanol after acetylation, which may be problematic in terms of large-scale application.

For an improved and fast preparation of **4**, we developed a one-pot protocol for all four steps starting from readily available, cheap D-glucuronolactone (**1**). After base-catalyzed esterification

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using NaOH in dry MeOH, the solvent was removed in vacuo and the residue was redissolved in acetic anhydride. Instead of pyridine,[29,31] iodine,[32] or perchloric acid,[31] hydrobromic acid in acetic acid (HBr/HOAc) was used for activation of the acetylation. We observed full conversion to the desired product **2** as well as partial formation to the corresponding bromo sugar **3**. After evaporation of the solvent in vacuo (excess of acetic anhydride can be recovered by subsequent distillation), the residue was treated with pure HBr/HOAc to afford compound **3** nearly quantitatively as indicated by TLC. This solution was dropwise added to a mixture of zinc dust, sodium acetate, and copper(II) sulfate in aqueous acetic acid (cooled to −10 °C). Improved work-up and crystallization from dry ethanol gave **4** in reasonable yields (53–63%). Applying this improved and optimized method we were able to synthesize methyl 3,4-di-*O*-acetyl-D-glucuronal in large scale within 3 days, avoiding very time-consuming isolation and (chromatographic) purification of the intermediate **2** (Scheme 1).

Using compound **4** as starting material we were able to easily synthesize several silyl protected glucuronals (Scheme 2). Compared to already published procedures,[11–13,27,28] a catalytic amount of potassium carbonate gave better results for the deacetylation of **4**. After TBDMS introduction yielding **6**, basic hydrolysis of the methyl ester was achieved using KOH in MeOH to afford 3,4-di-*O*-(*tert*-butyldimethylsilyl)-D-glucuronal (**7**), which was first synthesized by Marcus Tius et al.[14] within six steps (including four chromatographic purifications; poor yields for final two-step 6-OH-glycal oxidation) starting from 3,4,6-tri-*O*-acetyl-D-glucal. For the preparation of a fully silyl protected glucuronal (**8**), a 2-(trimethylsilyl)ethyl ester was introduced at C6 by reaction of **7** with 2-(trimethylsilyl)ethanol, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), and 4-(*N*,*N*-dimethylamino)pyridine (DMAP).

Benzyl protected glucuronals were used for nitration,[20] synthesis of glucuronyl phosphates,[33] or direct glucuronidation.[12] Since benzylation of **5** is not possible (except mono-benzylation using bis(tributyltin) oxide and benzyl bromide[12]) all of these compounds were prepared so far starting from corresponding 6-OH-glucals via Dess–Martin and subsequent Pinnick oxidation.[12,20,34] These 6-OH-glucals are usually prepared starting from D-glucal (**10**) via regioselective O-silylation at C6, subsequent benzylation, and following cleavage of the silyl ether, with chromatographic separations after each step. We were able to accelerate and simplify this procedure significantly, by omitting separations of intermediates, which also led to higher yields of 3,4-di-*O*-benzyl-D-glucal (**13**) compared to already published work.[35,36] To avoid a two-step procedure for oxidation including the use of expensive Dess–Martin periodinane, we applied 2,2,6,6-tetramethyl-1-piperidinyloxyl, free radical (TEMPO)/[bis(acetoxy)iodo]benzene (BAIB)-mediated one-pot oxidation[37] to afford 3,4-di-*O*-benzyl-D-glucuronal (**14**). The TEMPO/BAIB system was shown to be compatible to thioglycosides[37] and could also be applied to glycals in the course of our research work. Glucuronal **14** was directly used without further purification for the synthesis of the methyl ester **15** and benzyl 3,4-di-*O*-benzyl-D-glucuronal (**16**) in reasonable overall yields (Scheme 3).

In summary, two different strategies for the preparation of various protected D-glucuronals were developed and optimized, respectively. An improved procedure was applied for the large-scale synthesis of methyl 3,4-di-*O*-acetyl-D-glucuronal (**4**), which is a common building block and precursor in carbohydrate chemistry. Furthermore this compound was used as a key intermediate for the preparation of silyl protected glucuronals. TEMPO/BAIB was applied for the first time for the oxidation of glycals, and used for the synthesis of benzyl protected glucuronals starting from 3,4-di-*O*-benzyl-D-glucal, which was prepared using an optimized, straightforward protocol, without time-consuming purification of intermediates.

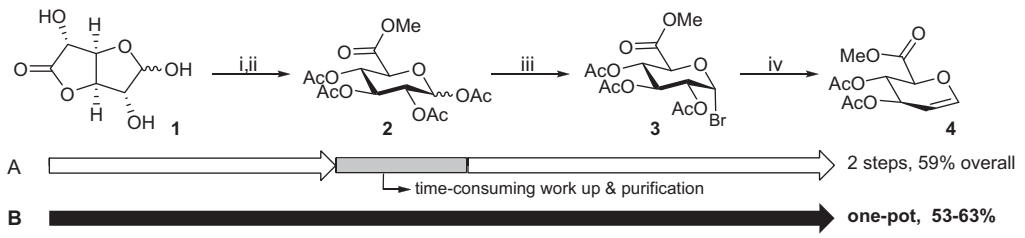
1. Experimental

1.1. General methods

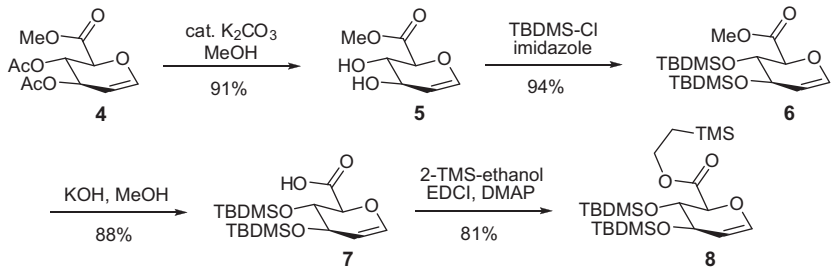
All reactions were performed under an argon atmosphere. The progress of the reactions was monitored by thin-layer chromatography (TLC) over silica gel 60 F254 (Merck). The chromatograms were visualized by irradiation with ultraviolet light or by heat staining with ceric ammonium molybdate in ethanol/sulfuric acid. Column chromatography was performed on silica gel 60 (Merck, 40–63 μm) using a Büchi SepacoreTM Flash System. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-200 MHz or Avance DRX-400 MHz spectrometer. Data were recorded and evaluated using TOPSPIN 1.3 (Bruker Biospin). All chemical shifts are given in ppm relative to tetramethylsilane. The calibration was done using residual solvent signals. Multiplicities are abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), and b (broad signal). All chemicals were purchased from ABCR or Sigma–Aldrich.

1.2. Improved large-scale preparation of methyl 3,4-di-*O*-acetyl-D-glucuronal (4)

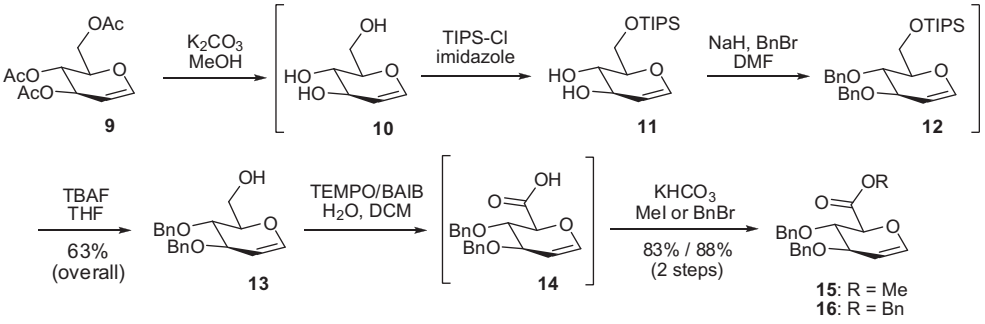
NaOH (0.15 g, 3.8 mmol) was added to a solution of D-glucuronolactone (50 g, 284 mmol) in dry MeOH (360 mL) at room temperature. The mixture was stirred for 1 h and then concentrated in vacuo at 30 °C. The residue was dissolved in Ac_2O (350 mL), and HBr (40 mL, 33 wt.% in HOAc) was added dropwise at 0 °C. The temperature was gradually elevated to ambient level, and the mixture was kept stirring for approximately 10 h. TLC showed the formation of the acetylated product **2** (R_f 0.35, hexanes/EtOAc = 1:1) and traces of bromo sugar **3** (R_f 0.75, hexanes/EtOAc = 1:1). The reaction mixture was concentrated (evaporated Ac_2O may be recovered by subsequent distillation) in vacuo at 40 °C and the resulting residue was dissolved in ice cold HBr (350 mL, 33 wt.% in HOAc). The resulting mixture was slowly warmed to room temperature, stirred for 5 h and then dropwise added to a solution of NaOAc (250 g, 3.05 mol) and $CuSO_4{\cdot}5H_2O$ (31.2 g, 126 mmol) in aqueous HOAc (600 mL, 50%). After slow addition of zinc dust (100 g, 1.53 mol) stirring was continued for 3 h at −10 °C. The reaction mixture was filtrated and poured onto 1.5 L ice water. After extraction with CH_2Cl_2 (3 × 600 mL), the combined organic phases



Scheme 1. Preparation of methyl 3,4-di-*O*-acetyl-D-glucuronal **4** (method A: most commonly used procedure;[29] method B: novel improved one-pot protocol); (i) NaOH, MeOH; (ii) Ac_2O, pyridine or Ac_2O, $HClO_4$ (both used for method A) or HBr/HOAc (method B); (iii) HBr/HOAc; (iv) Zn, NaOAc, $CuSO_4$.



Scheme 2. Synthesis of several silyl protected D-glucuronals.



Scheme 3. Preparation of benzyl 3,4-di-*O*-benzyl-D-glucuronal using TEMPO/BAIB-mediated oxidation as a key step.

were washed with water (2 × 800 mL) and satd. $NaHCO_3$ (3 × 800 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was recrystallized from dry EtOH to yield the desired D-glucuronal **4** (46.2 g, 63%, R_f 0.63, hexanes/EtOAc = 1:1) as a white solid: mp 88–90 °C, lit.[29] 88–91 °C; $[\alpha]_D^{25}$ −64.5 (*c* 1.0, $CHCl_3$), lit.[26] −67; ^1H and ^{13}C NMR spectral data matched that reported;[26] ESI-MS: *m*/*z* 281.3 $[M+Na]^+$; Anal. Calcd for $C_{11}H_{14}O_7$: C, 51.16; H, 5.46; O, 43.37. Found: C, 51.04; H, 5.50.

1.3. Methyl D-glucuronal (5)

K_2CO_3 (4.15 g, 30 mmol) was added to a solution of **4** (38.7 g, 150 mmol) in dry MeOH (300 mL). The reaction mixture was stirred at room temperature for 6 h, then treated with HOAc (3 mL) and concentrated. The resulting residue was purified by column chromatography (980 g SiO_2, 200 mL/min, hexanes/EtOAc = 1:2 to 1:5 gradient elution) to give methyl D-glucuronal (**5**) as slightly yellow colored solid (23.8 g, 91%): R_f 0.07 (hexanes/EtOAc = 1:1); mp 147–149 °C, lit.[13] 148–151 °C; $[\alpha]_D^{25}$ −35.0 (*c* 1.0, $CHCl_3$), lit.[13] −34.1; ^1H and ^{13}C NMR spectral data matched that reported;[13] ESI-MS: *m*/*z* 197.3 $[M+Na]^+$; Anal. Calcd for $C_7H_{10}O_5$: C, 48.28; H, 5.79; O, 45.94. Found: C, 48.24; H, 5.91.

1.4. Methyl 3,4-di-*O*-(*tert*-butyldimethylsilyl)-D-glucuronal (6)

To a solution of **5** (20.9 g, 120 mmol) and imidazole (49.0 g, 720 mmol) in dry DMF (200 mL) was added TBDMS-Cl (120 mL, 360 mmol, 3 M in THF) at 0 °C. The resulting solution was stirred at room temperature over-night, poured onto ice water (1 L), and extracted with Et_2O (3 × 600 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Column chromatography (980 g SiO_2, 200 mL/min, hexanes/EtOAc = 50:1 to 10:1 gradient elution) afforded **6** (45.4 g, 94%) as a colorless syrup: R_f 0.50 (hexanes/EtOAc = 20:1); $[\alpha]_D^{25}$ −26.4 (*c* 1.0, $CHCl_3$), lit.[13] −27.2 (*c* 1.05, $CHCl_3$); ^1H and ^{13}C NMR spectral data matched that reported;[13] ESI-MS: *m*/*z* 425.5 $[M+Na]^+$; Anal. Calcd for $C_{19}H_{38}O_5Si_2$: C, 56.67; H, 9.51; O, 19.87; Si, 13.95. Found: C, 56.38; H, 9.87.

1.5. 3,4-Di-*O*-(*tert*-butyldimethylsilyl)-D-glucuronal (7)

KOH (130 mL, 65 mmol, 0.5 M in MeOH) was dropwise added to a solution of **6** (20.2 g, 50 mmol) in dry MeOH (400 mL) at 0 °C. The reaction mixture was stirred over-night at room temperature, diluted with water (400 mL), and acidified by treatment with Amberlite IR120H$^+$. Filtration, evaporation under reduced pressure and lyophilization afforded **7** (17.2 g, 88%) as colorless syrup in sufficient purity: $[\alpha]_D^{25}$ −59.4 (*c* 1.0, $CHCl_3$), lit.[14] −40.0 (*c* 0.64, $CHCl_3$); ^1H and ^{13}C NMR spectral data matched that reported;[14] ESI-MS: *m*/*z* 411.1 $[M+Na]^+$; HRMS (MALDI): *m*/*z* Calcd for $C_{18}H_{37}O_5Si_2$ $[M+H]^+$: 389.2180. Found: 389.2161.

1.6. 2-(Trimethylsilyl)ethyl 3,4-di-*O*-(*tert*-butyldimethylsilyl)-D-glucuronal (8)

To a solution of **7** (11.9 g, 30.6 mmol), DMAP (0.93 g, 7.7 mmol), and 2-(trimethylsilyl)ethanol (5.4 g, 45.9 mmol) in dry CH_2Cl_2 (250 mL) was added EDCI (8.8 g, 45.9 mmol) in small portions at room temperature. The reaction mixture was stirred for 48 h, concentrated on SiO_2 (80 g), and directly applied to column chromatography (440 g SiO_2, 100 mL/min, hexanes to hexanes/EtOAc = 30:1 gradient elution) to yield **8** (12.1 g, 81%) as a colorless oil: $[\alpha]_D^{25}$ −109.4 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.51 (d, $J_{1,2}$ 6.1 Hz, 1H, H-1), 4.80 (ddd, $J_{2,3}$ 5.8, $J_{2,4}$ 1.5 Hz, 1H, H-2), 4.41 (m, 1H, H-5), 4.34 (m, 1H, OCH_2), 4.24 (m, 1H, OCH_2), 4.08 (m, 1H, H-4), 3.75 (dd, $J_{3,4}$ 2.4 Hz, 1H, H-3), 1.05 (dd, J 9.3, 7.5 Hz, 2H, CH_2TMS), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.83 (s, 9H, $SiC(CH_3)_3$), 0.10 (s, 3H, $Si(CH_3)_2{}^tBu$), 0.09 (s, 3H, $Si(CH_3)_2{}^tBu$), 0.05 (s, 9H, $Si(CH_3)_3$), 0.04 (s, 3H, $Si(CH_3)_2{}^tBu$), 0.01 (s, 3H, $Si(CH_3)_2{}^tBu$); ^1H NMR (acetone-d_6): δ 6.50 (d, 1H, $J_{1,2}$ 6.0 Hz, H-1), 4.89 (ddd, 1H, $J_{2,3}$ 5.7, $J_{2,4}$ 1.9 Hz, H-2), 4.39 (m, 1H, H-5), 4.33 (m, 1H, OCH_2Ph), 4.23 (m, 1H, OCH_2Ph), 4.13 (m, 1H, H-4), 3.86 (dd, 1H, $J_{3,4}$ 2.6 Hz, H-3), 1.06 (dd, 2H, J 8.9, 7.5 Hz, CH_2TMS), 0.91 (s, 9H, $SiC(CH_3)_3$),

0.84 (s, 9H, SiC$(CH_3)_3$), 0.16 (s, 3H, Si$(CH_3)_2{}^t$Bu), 0.13 (s, 3H, Si$(CH_3)_2{}^t$Bu), 0.10 (s, 3H, Si$(CH_3)_2{}^t$Bu), 0.08 (s, 9H, Si$(CH_3)_3$), 0.05 (s, 3H, Si$(CH_3)_2{}^t$Bu); ^{13}C NMR (acetone-d_6): δ 169.2 (s, 1C, C-6), 145.5 (d, 1C, C-1), 101.8 (d, 1C, C-2), 73.6 (d, 1C, C-4), 71.7 (d, 1C, C-5), 65.3 (d, 1C, C-3), 63.7 (t, 1C, OCH_2), 26.2 (q, 3C, SiC$(CH_3)_3$), 26.0 (q, 3C, SiC$(CH_3)_3$), 18.51 (s, 1C, SiC$(CH_3)_3$), 18.48 (s, 1C, SiC$(CH_3)_3$), 17.7 (t, 1C, CH_2TMS), −1.4 (q, 3C, Si$(CH_3)_3$), −3.9 (q, 1C, Si$(CH_3)_2{}^t$Bu), −4.3 (q, 1C, Si$(CH_3)_2{}^t$Bu), −4.4 (q, 1C, Si$(CH_3)_2{}^t$Bu), −4.8 (q, 1C, Si$(CH_3)_2{}^t$Bu); ESI-MS: *m/z* 511.6 $[M+Na]^+$; HRMS (MALDI): *m/z* Calcd for $C_{23}H_{49}O_5Si_3$ $[M+H]^+$: 489.2888. Found: 489.2871.

1.7. Improved large-scale preparation of 3,4-di-*O*-benzyl-D-glucal (13)

K_2CO_3 (1.52 g, 11.0 mmol) was added to a solution of **9** (19.98 g, 73.4 mmol) in dry MeOH (140 mL) and the resulting solution was stirred at room temperature for 3 h, until TLC indicated complete conversion (**9**: R_f 0.83, **10**: R_f 0.20, CH_2Cl_2/MeOH = 10:1). After concentration under reduced pressure, the residue was dissolved in dry DMF (110 mL), cooled to 0 °C, and treated with imidazole (15.0 g, 220.2 mmol) and TIPS-Cl (18.39 g, 95.4 mmol). After stirring over-night at room temperature, TLC showed complete consumption of the starting material and formation of the desired product **11** (R_f 0.50, CH_2Cl_2/MeOH = 10:1). The reaction mixture was quenched and diluted with water (400 mL). After extraction with Et_2O (5 × 200 mL), the organic layer was washed with satd NH_4Cl (2 × 250 mL), dried over Na_2SO_4 and evaporated under reduced pressure to afford crude 6-*O*-(triisopropylsilyl)-D-glucal (**11**). This compound was dissolved in dry DMF (180 mL) and treated slowly with NaH (7.0 g, 294 mmol; 60% dispersion in mineral oil was washed with dry hexane and used immediately) at 0 °C. After warming to room temperature within 1 h, the reaction mixture was cooled again to 0 °C, treated dropwise with benzyl bromide (44.0 g, 257 mmol), and stirring was continued over-night. The reaction mixture was quenched and diluted with water (500 mL) and extracted with Et_2O (4 × 250 mL). The organic layer was washed with satd. NH_4Cl (2 × 250 mL), dried over Na_2SO_4, and evaporated in vacuo to yield crude 3,4-di-*O*-benzyl-6-*O*-(triisopropyl)-D-glucal (**12**, R_f 0.18, hexanes/CH_2Cl_2 = 2:1). Column chromatography (980 g SiO_2, 200 mL/min, hexanes/CH_2Cl_2 = 9:1 to 2:1 gradient elution) may be performed at this stage to remove excess of benzyl bromide and side-products (dibenzyl ether, benzyl alcohol) of the benzylation step, but we did not observe significantly higher yields for the following de-silylation.

Tetrabutylammonium fluoride (TBAF, 100 mL, 100 mmol, 1 M in THF) was dropwise added to a solution of crude **12** in dry THF (150 mL) at 0 °C. After stirring for 4 h at room temperature, the solution was diluted with Et_2O (500 mL) and washed with water (2 × 300 mL), which was re-extracted twice. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography (980 g SiO_2, 200 mL/min, hexanes/EtOAc = 5:1 to 3:1 gradient elution) to afford the desired product **13** (15.1 g, 63% over 4 steps) as colorless syrup: R_f 0.36 (hexanes/EtOAc = 3:1); $[\alpha]_D^{25}$ −99.8 (*c* 1.0, $CHCl_3$), lit.[38] −102.0 (*c* 1, $CHCl_3$); ^{1}H and ^{13}C NMR spectral data matched that reported;[35,38] ESI-MS: *m/z* 349.3 $[M+Na]^+$; HRMS (MALDI): *m/z* Calcd for $C_{20}H_{23}O_4$ $[M+H]^+$: 327.1596. Found: 327.1603; Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79; O, 19.61. Found: C, 73.51; H, 6.81.

1.8. General procedure for oxidation of glycals and subsequent esterification of D-glucuronals

To a solution of 6-OH-glycal (10 mmol) in CH_2Cl_2 (30 mL) and water (15 mL), TEMPO (0.31 g, 2 mmol) and BAIB (8.1 g, 25 mmol) were added under vigorous stirring at room temperature. After 1 h the reaction mixture was quenched by addition of $Na_2S_2O_3$ solution (100 mL, 10% in H_2O) and extracted with EtOAc (2 × 100 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in dry DMF (70 mL) and treated with $KHCO_3$ (6.0 g, 60 mmol) and R-X (methyl iodide or benzyl bromide, 30 mmol). After stirring for 10 h, the reaction mixture was poured onto water (250 mL) and extracted with EtOAc (3 × 150 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Column chromatography (90 g SiO_2, 60 mL/min, hexanes/EtOAc = 10:1 to 3:1 gradient elution) afforded the pure glucuronals.

1.9. Methyl 3,4-di-*O*-benzyl-D-glucal (15)

Starting from 3,4-di-*O*-benzyl-D-glucal (**13**, 3.3 g, 10 mmol) and following the general procedure described above, compound **15** (2.95 g, 83%) was obtained as colorless syrup: R_f 0.31 (hexanes/EtOAc = 5:1); $[\alpha]_D^{25}$ −26.2 (*c* 1.0, $CHCl_3$); ^{1}H and ^{13}C NMR spectral data matched that reported;[20] ESI-MS: *m/z* 377.7 $[M+Na]^+$; HRMS (MALDI): *m/z* Calcd for $C_{21}H_{25}O_4$ $[M+H]^+$: 355.1545. Found: 355.1546; Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26; O, 22.57. Found: C, 71.01; H, 6.10.

1.10. Benzyl 3,4-di-*O*-benzyl-D-glucal (16)

Starting from 3,4-di-*O*-benzyl-D-glucal (**13**, 3.3 g, 10 mmol) and following the general procedure described above, compound **16** (2.71 g, 88%) was obtained as white solid: mp 50–52 °C, R_f 0.40 (hexanes/EtOAc = 5:1); $[\alpha]_D^{25}$ −36.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.3–7.1 (m, 15H, Ar-H), 6.56 (d, 1H, $J_{1,2}$ 6.3 Hz, H-1), 4.98 (d, 1H, J_{gem} 12.3 Hz, $PhCH_2$-*O*-C_6), 4.94 (ddd, 1H, $J_{2,3}$ 5.7, $J_{2,4}$ 1.4 Hz, H-2), 4.79 (d, 1H, $PhCH_2$-*O*-C_6), 4.74 (dd, $J_{4,5}$ 4.2, $J_{3,5}$ 0.9 Hz, H-5), 4.61 (d, 1H, J_{gem} 12.1 Hz, $PhCH_2$-*O*-C_4), 4.55 (d, 1H, $PhCH_2$-*O*-C_4), 4.34 (d, 1H, J_{gem} 11.6 Hz, $PhCH_2$-*O*-C_3), 4.25 (d, 1H, $PhCH_2$-*O*-C_3), 4.13 (ddd, 1H, $J_{3,4}$ 2.9 Hz, H-4), 3.77 (ddd, 1H, H-3); ^{13}C NMR ($CDCl_3$): δ 168.2 (s, 1C, C-6), 145.2 (d, 1C, C-1), 138.1 (s, 1C, Ar), 137.5 (s, 1C, Ar), 135.4 (s, 1C, Ar), 128.6 (d, 2C, Ar), 128.5 (d, 2C, Ar), 128.41 (d, 2C, Ar), 128.40 (d, 2C, Ar), 128.3 (d, 1C, Ar), 128.1 (d, 1C, Ar), 128.0 (d, 4C, Ar), 127.8 (d, 1C, Ar), 98.7 (d, 1C, C-2), 73.4 (d, 1C, C-4), 72.9 (d, 1C, C-5), 72.1 (t, 1C, $PhCH_2$-*O*-C_4), 69.5 (t, 1C, $PhCH_2$-*O*-C_3), 67.8 (d, 1C, C-3), 67.1 (t, 1C, $PhCH_2$-*O*-C_6); ESI-MS: *m/z* 453.8 $[M+Na]^+$; HRMS (MALDI): *m/z* Calcd for $C_{27}H_{27}O_5$ $[M+H]^+$: 431.1858. Found: 431.1860; Anal. Calcd for $C_{27}H_{26}O_5$: C, 75.33; H, 6.09; O, 18.58. Found: C, 75.50; H, 6.20.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2013.01.007.

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