Transacetalization Reaction of D-Glucuronic Acid with α,α-Dimethoxytoluene

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D-Glucuronic acid, α,α-dimethoxytoluene, and a strongly acidic cation-exchange resin in the H^+ form were used in a modified transacetalization reaction. Methyl [methyl 3,5-*O*-benzylidene-2-*O*-(1-methoxybenzyl)-α-D-glucofuranosid]uronate was formed as a major product. Its structure was proved with combination of ^1H and ^{13}C NMR spectroscopy and mass spectrometry.

Transacetalization reactions are available methods for protecting free hydroxyl groups in carbohydrate chemistry. The acetalization reaction between D-glucuronic acid and benzaldehyde catalyzed with $ZnCl_2$ has been used for preparation of 1,2:3,5-di-*O*-benzylidene-α-D-glucofuranuronic acids and diastereoisomeric mixtures of (*endo*-1,2)- and (*exo*-1,2)-*O*-benzylidene-α-D-glucofuranurono-6,3-lactones. Low yields of products are obtained from this reaction [1].

The transacetalization reactions of methyl α- and β-D-glucopyranosides with α,α-dimethoxytoluene for the protection of the 4,6-position were performed by *Evans* at higher temperature and *in vacuo* [2]. Here we report on application of a modified Evans transacetalization reaction using D-glucuronic acid and α,α-dimethoxytoluene catalyzed by strongly acidic cation-exchange resin in H^+ form affording different products than we expected.

EXPERIMENTAL

Melting points were determined on a Kofler hotstage. Optical rotations were measured using a Perkin—Elmer automatic polarimeter, model 141. ^1H and ^{13}C NMR spectra were recorded with a Bruker AM-300 spectrometer in chloroform-*d* or methanol-d_4 using TMS as an internal standard. Thin-layer chromatography on silica gel coated glass slides was carried out using the system A (chloroform—methanol, φ_r = 98 2), system B (ethyl acetate—heptane, φ_r = 3 2). EI MS were measured on FINNIGAN MAT SSQ 710 by direct probe (70 eV, current filement 100 μA).

Transacetalization Procedure

D-Glucuronic acid (2 g; 10 mmol), α,α-dimethoxytoluene (6.05 cm^3, 40 mmol), and strongly acidic cation-exchange resin (0.1 g, Amberlite IR-120, H^+ form) were stirred for 3 h at 50 °C. After reaction, the resin was filtered, then the mixture was evaporated to dryness. Crystallization from methanol gave methyl [methyl 3,5-*O*-benzylidene-2-*O*-(1-methoxybenzyl)-α-D-glucofuranosid]uronate (*Ia*), which was recrystallized from propan-2-ol. Yield of *Ia* was 2 g (48 %). Methanolic mother liqueur was evaporated *in vacuo*, yellow sirup was crystallized from chloroform and product, methyl α-D-glucofuranosiduronic acid (*IIa*), 0.7 g (32 %) was isolated. Residue was evaporated *in vacuo* and crystallization of the residue from ethyl acetate—heptane (system B) gave pure (*exo*-1,2)-*O*-benzylidene-α-D-glucofuranurono-6,3-lactone (*IIIa*). Yield of *IIIa* was 0.13 g (5 %). From the mother liqueur a mixture of *IIIa* and (*endo*-1,2)-*O*-benzylidene-α-D-glucofuranurono-6,3-lactone (*IIIb*) was obtained. Yield = 0.1 g (3.8 %).

Methyl [Methyl 3,5-*O*-Benzylidene-2-*O*-(1-methoxybenzyl)-α-D-glucofuranosid]uronate (*Ia*)

M.p. = 141—143 °C, [α](D, 20 °C, ρ = 10.1 g dm^{-3}, $CHCl_3$) = + 15.8° EI mass spectrum, *m/z* (I_r/%): 430 (12, $[M]^+$), 371 (11), 324 (12), 249 (16), 121 (22), 75 (100). ^1H NMR spectrum, δ: 3.46, 3.47 (2s, 6H, 2 × OCH_3), 3.86 (s, 3H, $COOCH_3$), 3.91 (dd, 1H, H-4, $J_{4,3}$ = 2 Hz, $J_{4,5}$ = 8 Hz), 4.04 (dd, 1H, H-3, $J_{3,2}$ = 1.4 Hz, $J_{3,4}$ = 2 Hz), 4.28 (t, 1H, H-2, $J_{2,1}$ < 1.0 Hz, $J_{2,3}$ = 1.4 Hz), 4.69 (d, 1H, H-5, $J_{5,4}$ = 8 Hz), 4.84 (d, 1H, H-1, $J_{1,2}$ < 1.0 Hz), 5.62 (s, 1H, H_a), 5.91 (s, 1H, H_b), 7.42—7.55 (m, 10H, 2 × C_6H_5). ^{13}C NMR spectrum, δ: 52.6, 54.8, 56.4 (3 × OCH_3), 76.3, 76.6, 77.1, 77.4 (C-2, C-3, C-4, C-5), 97.5, 100.9, 102.1 (2 × $\underline{C}HC_6H_5$, C-1), 126.3—132.4 (C_6H_5), 169.6 (COO).

For $C_{23}H_{27}O_8$ (M_r = 430.46) w_i(calc.): 64.04 % C, 6.31 % H; w_i(found): 63.9 % C, 6.34 % H.

Methyl α-D-Glucofuranosiduronic Acid (*IIa*)

M.p. = 152—155 °C, [α](D, 20 °C, ρ = 10 g dm^{-3}, MeOH) = +27° ^{1}H NMR spectrum, δ: 3.39 (s, 3H, OCH_3), 4.85—4.97 (m, 3H, H-2, H-3, H-4), 5.49 (s, 1H, H-5), 5.58 (d, 1H, H-1, $J_{1,2}$ = 3.6 Hz). ^{13}C NMR spectrum, δ: 55.8 (OCH_3), 71.7 (C-5), 80.1 (C-3), 80.3 (C-2), 86.4 (C-4), 106.2 (C-1), 177.2 (COO).

For $C_7H_{12}O_7$ (M_r = 208.17) w_i(calc.): 40.35 % C, 5.81 % H; w_i(found): 40.52 % C, 5.86 % H.

(*exo*-1,2)-*O*-Benzylidene-α-D-glucofuranurono-6,3-lactone (*IIIa*)

M.p. = 146—147 °C, [α](D, 20 °C, ρ = 10 g dm^{-3}, CH_3COCH_3) = +61° Ref. [3] gives m.p. = 146.5—148.5 °C, [α](D, 20 °C, ρ = 10 g dm^{-3}, CH_3COCH_3) = +67°

Methyl 3,5-*O*-Benzylidene-2-*O*-(1-methoxybenzyl)-α-D-glucofuranosiduronic Acid (*Ib*)

Ia (0.5 g; 1.16 mmol) was dissolved in acetone (20 cm^3) and 0.05 M sodium hydroxide (5 cm^3) was added to stirred solution. After 1 h at room temperature, the mixture was diluted with 50 cm^3 of acetone and treated with strongly acidic cation-exchange resin (Amberlite IR-120, H^+ form, 0.5 g). The resin was filtered off, and the solvent was evaporated *in vacuo*. Crude product was purified on silica gel (system B) to give pure substance *Ib*. Yield 0.35 g (73 %), m.p. = 107—111 °C.

^{1}H NMR spectrum, δ: 3.46, 3.47 (2s, 6H, 2 × OCH_3), 3.91 (dd, 1H, H-4, $J_{4,3}$ = 2 Hz, $J_{4,5}$ = 8 Hz), 4.04 (dd, 1H, H-3, $J_{3,2}$ = 1.4 Hz, $J_{3,4}$ = 2 Hz), 4.28 (t, 1H, H-2, $J_{2,1}$ < 1.0 Hz, $J_{2,3}$ = 1.4 Hz), 4.69 (d, 1H, H-5, $J_{5,4}$ = 8 Hz), 4.84 (d, 1H, H-1, $J_{1,2}$ < 1.0 Hz), 5.62 (s, 1H, H_a), 5.91 (s, 1H, H_b), 7.42—7.55 (m, 10H, 2 × C_6H_5).

For $C_{22}H_{25}O_8$ (M_r = 417.44) w_i(calc.): 63.24 % C, 6.04 % H; w_i(found): 63.31 % C, 6.01 % H.

Methyl 2,3,5-Tri-*O*-acetyl-α-D-glucofuranosiduronic Acid (*IIb*)

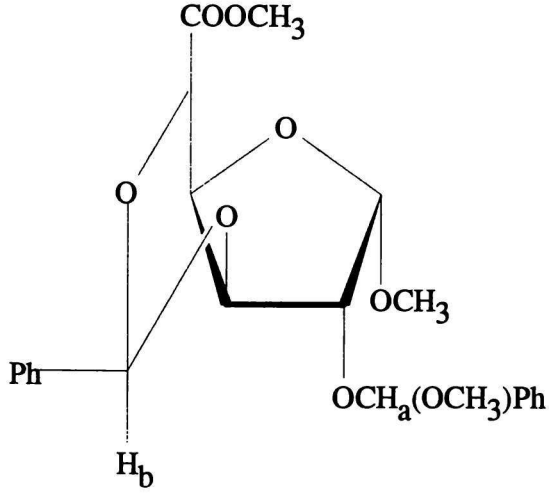
IIa (0.5 g; 2.4 mmol) was dissolved in pyridine (10 cm^3) and acetic anhydride (4.5 cm^3, 4.8 mmol) was added. Mixture was left to stand overnight, then it was evaporated *in vacuo* and the yellow oil was purified by column chromatography (silica gel, system B), yielding 0.75 g (95 %) of yellow sirupy *IIb*.

^{1}H NMR spectrum, δ: 2.11, 2.13, 2.24 (3s, 9H, 3 × $OCOCH_3$), 3.39 (s, 3H, OCH_3), 5.02 (d, 1H, H-1, $J_{1,2}$ = 3.6 Hz), 5.10—5.36 (m, 4H, H-2, H-3, H-4, H-5).

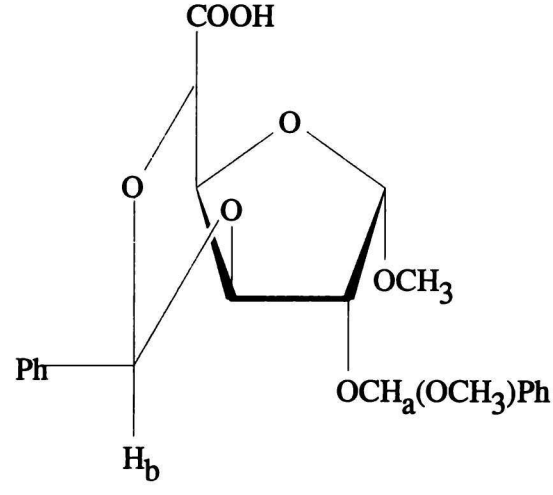
RESULTS AND DISCUSSION

The transacetalization reaction of D-glucofuranurono-6,3-lactone with 2,2-dimethoxypropane in the presence of acid catalysts was studied by *Lee* [4]. All of the functional groups of the carbohydrate have participated in the reaction. The same results as in [4] were obtained when we tried to use the modified Evans reaction for preparation of 1,2:3,5-di-*O*-benzylidene-α-D-glucuronic acid in a higher yield.

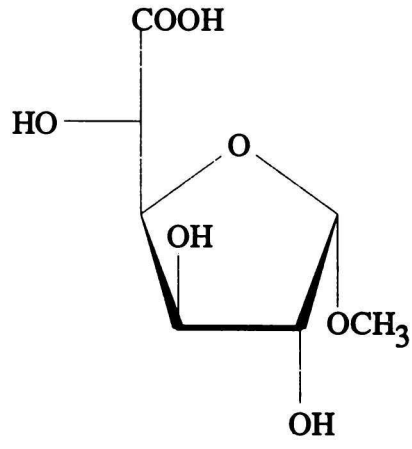
In this reaction we have chosen D-glucuronic acid, α,α-dimethoxytoluene, and strongly acidic cation-exchange resin (Amberlite IR-120, H^+ form) without solvent. Mixture was kept for 3 h at 50 °C. When the reaction between D-glucuronic acid and α,α-dimethoxytoluene proceeded without solvent and at a



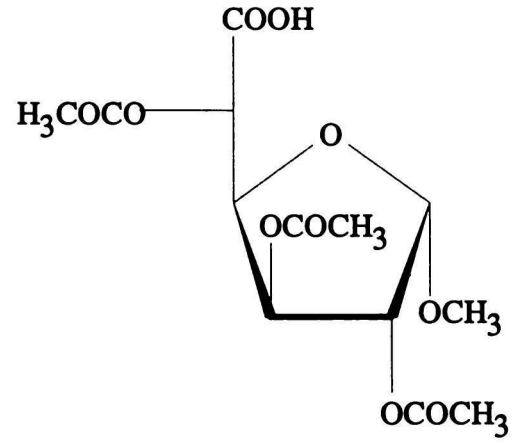
Ia



Ib



IIa



IIb

higher temperature, we obtained different products in comparison with acetalization reaction of D-glucuronic acid, benzaldehyde, and $ZnCl_2$ [1].

Because methanol was not removed from the reaction mixture it might be a reason of formation of these described products.

The major product of this reaction *Ia* was isolated and analyzed by ^{1}H NMR, ^{13}C NMR spectroscopy and mass spectrometry.

^{1}H NMR spectrum of *Ia* proved a presence of one product which had two benzylidene groups in different alignment than we expected. In the spectrum three methyl proton signals were present: glycosidic and acetalic methyl groups (δ = 3.46 and 3.47) and methyl ester group (three-proton singlet at δ = 3.86). The mass spectrum contained $[M]^+$ = 430. Its structure was presumed to be methyl [methyl 3,5-*O*-benzylidene-2-*O*-(1-methoxybenzyl)-α-D-glucofuranosid]uronate (*Ia*).

Next steps were used to prove the suggested structure. Methyl ester group of *Ia* was removed by basic hydrolysis to give methyl 3,5-*O*-benzylidene-2-*O*-(1-methoxybenzyl)-α-D-glucofuranosiduronic acid (*Ib*). ^{1}H NMR spectrum of this product showed that the signal assigned to the methyl ester group at δ = 3.48 disappeared. Compound *Ia* was reduced with H_2/Pd and ^{1}H NMR spectrum did not show the presence of aromatic hydrogens (signals at δ = 7.42—7.55 disappeared).

Compound *Ia* contains a new chiral centre of substituent on C-2. No attempt was made to find out and assign total configuration on this new chiral atom.

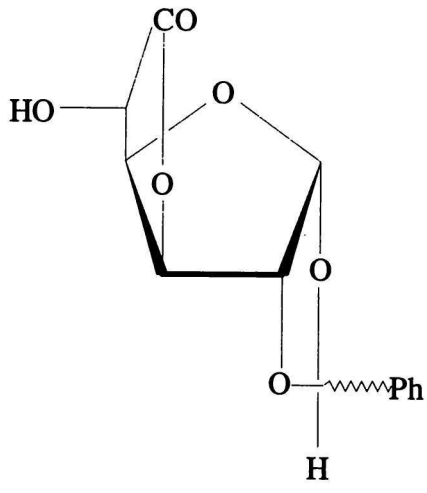
TLC analysis showed that besides of *Ia* secondary products, methyl α-D-glucofuranosiduronic acid (*IIa*) and a diastereoisomeric mixture of (*endo*-1,2)- and (*exo*-1,2)-*O*-benzylidene-α-D-glucofuranurono-6,3-lactones, were formed which were analyzed.

Structure of *IIa* was assigned as methyl α-D-glucofuranosiduronic acid. In literature there are only few publications about *IIa* [5—7]. This assumption may be confirmed by the following data: three-proton singlet of methyl group at δ = 3.39 was assigned as a glycosidic methyl group. It is similar to that of *Ia*. *Lee* [4] assigned this signal to methoxy group on C-1, while methyl ester group gave three-proton singlet at δ = 3.86.

^{13}C NMR spectroscopy [8] of methyl α-D-glucopyranosiduronic acid showed signals C-1—C-5 at δ = 100.7, 71.9, 73.8, 72.5, 71.9 (α-anomer) and δ = 104.3, 73.8, 76.5, 72.3, 75.6 (β-anomer). Signals C-1—C-5 of D-glucofuranurono-6,3-lactone are at δ = 99.1, 74.8, 85.6, 76.7, 70.4 (α-anomer) and δ = 103.7, 74.8, 85.6, 78.4, 70.1 (β-anomer). Product *IIa* has signals for C-1—C-5 at δ = 106.2, 80.3, 80.1, 86.4, 71.7. Comparison of all these ^{13}C NMR data indicated that *IIa* might be a furanoside.

Acetylation reaction of *IIa* gave compound *IIb* with three acetyl groups and one unchanged signal of methoxy group. Three acetyl groups demonstrated that *IIa* was not a lactone. All saccharidic hydrogens had the chemical shift between δ = 5.02—5.36, while in pyranoside structure H-5 is in high field (around δ = 4.3). *Matsui* and *Okada* [9] published the spectrum of methyl (methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosid)uronate, where a characteristic chemical shift for H-5 is at δ = 4.3 (J = 10 Hz, α-anomer) and δ = 4.04 (J = 10 Hz, β-anomer). It is a different result than we obtained, *IIb* had no signals in this region and it supported assumption that product *IIb* is not a pyranoside.

The next minor product was a diastereoisomeric mixture of (*endo*-1,2)- and (*exo*-1,2)-*O*-benzylidene-α-D-glucofuranurono-6,3-lactones (*IIIa, IIIb*) with diastereoisomerism on benzylidene acetal carbon in 1,3-position of dioxolane ring. Their structures have been equal as those of products prepared by the acetaliza-



IIIa, IIIb

tion reaction between D-glucuronic acid and benzaldehyde catalyzed with $ZnCl_2$, reported in [2].

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