A CHEMICAL SYNTHESIS OF 1-*O*-INDOMETHACIN-β-D-GLUCOSYLURONIC ACID

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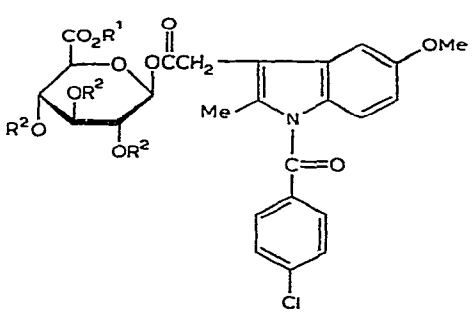
ABSTRACT

A new synthetic route to labile acyl D-glucosyluronic acids was developed by using 2,2,2-trichloroethoxycarbonyl as the hydroxy-protecting group. Condensation of 2,2,2-trichloroethyl 2,3,4-tri-*O*-(2,2,2-trichloroethoxycarbonyl)-β-D-glucopyranuronate with indomethacin, followed by treatment with zinc dust in acetic acid, afforded the zinc salt of indomethacin-β-D-glucosyluronic acid.

INTRODUCTION

The β-D-glucosyluronic acid of indomethacin (**1**) is a major urinary metabolite of indomethacin in man and in animals[1]. It was isolated as a 65% preparation and its structure was established by conversion into a fully acetylated methyl ester (**2**) that was identical with a synthetic specimen[2]. However, attempts to regenerate pure **1** from **2** under mild hydrolytic conditions were thwarted by the chemical sensitivity of the acylglycosyl linkage and particularly, in this case, by the labile *p*-chlorobenzoyl group in indomethacin[3]. Recently, in support of some clinical pharmacogenetic studies, it became desirable to obtain a pure specimen of the glucosyluronic acid as a reference compound. The feasibility of a chemical synthesis was therefore reinvestigated.



1 $R^1 = R^2 = H$

2 $R^1 = Me$, $R^2 = Ac$

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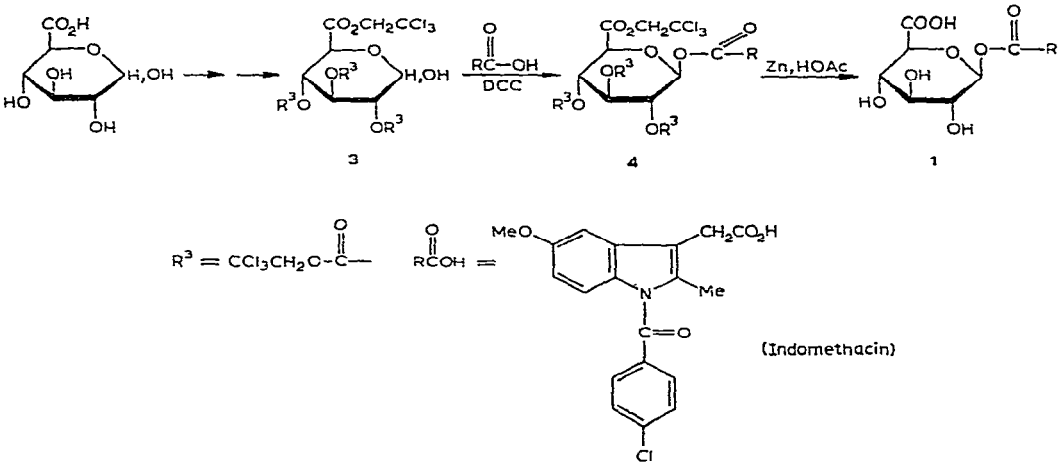
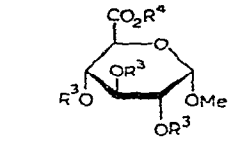
DISCUSSION

The solution to a successful synthesis of an acyl D-glucosyluronic acid obviously depends upon the finding of a suitable hydroxyl-protecting group that can be removed under mild and non-hydrolytic conditions. In a series of papers[4,5] Keglević and co-workers have explored the utility of the benzyl group for this purpose, and several 1-*O*-acyl-D-glucopyranuronic acids were synthesized *via* benzyl 1-*O*-acyl-2,3,4-tri-*O*-benzyl-D-glucopyranuronates by catalytic debenzylation. Depending on the reaction conditions and the steric hindrance of the acyl moiety, various mixtures of α- and β-anomers were obtained. In our study we decided to utilize a newly developed hydroxyl-protecting group, 2,2,2-trichloroethoxycarbonyl (Troc), which could be removed by treatment with zinc dust in 90% acetic acid or methanol[6,8]. The synthetic route envisaged was outlined as shown in the following schemes.



Thus, the primary task was to synthesize the fully protected D-glucuronic acid derivative (**3**). To investigate the properties of (Troc)-substituted carbohydrates, methyl (methyl α-D-glucopyranosid)uronate[7] (**5**) was first converted into the 2,3,4-tri-*O*-Troc derivative (**6**) by treatment with 2,2,2-trichloroethoxycarbonyl chloride (Troc chloride, TrocCl)* in pyridine. The Troc group is easily recognized by means of ^{1}H n.m.r. since the protons of the CH_2 group resonate as a singlet at τ 5.25. The ester group in **6** is apparently more susceptible to acid hydrolysis than the glycosidic linkage, since heating with 2.5M hydrochloric acid gave the free acid **7** only. The acid **7** was reesterified with 2,2,2-trichloroethanol and *N,N'*-dicyclohexylcarbodiimide to give a crystalline ester **8** in 47% yield. Attempts to cleave the methyl glycoside with hydrogen bromide in acetic acid or by other strongly acidic conditions again gave the free acid **7** and/or decomposition products. Similarly, treatment of methyl

*This compound is available from both Aldrich Chemical Co., Inc., Milwaukee, Wis., 53210, and Regis Chem. Co., Chicago, Ill.

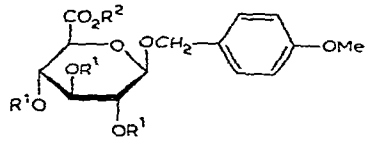


5 $R^3 = H$, $R^4 = CH_3$

6 $R^3 = -C(=O)-OCH_2CCl_3$, $R^4 = Me$

7 $R^3 = -C(=O)-OCH_2CCl_3$, $R^4 = H$

8 $R^3 = -C(=O)-OCH_2CCl_3$, $R^4 = CH_2CCl_3$



11 $R^1 = Ac$, $R^2 = Me$

12 $R^1 = H$, $R^2 = Me$

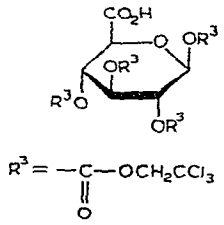
13 $R^1 = -C(=O)-OCH_2CCl_3$, $R^2 = Me$

14 $R^1 = -C(=O)-OCH_2CCl_3$, $R^2 = H$

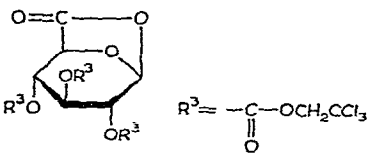
15 $R^1 = -C(=O)-OCH_2CCl_3$, $R^2 = CH_2CCl_3$

17 $R^1 = R^2 = H$

9



$R^3 = -C(=O)-OCH_2CCl_3$



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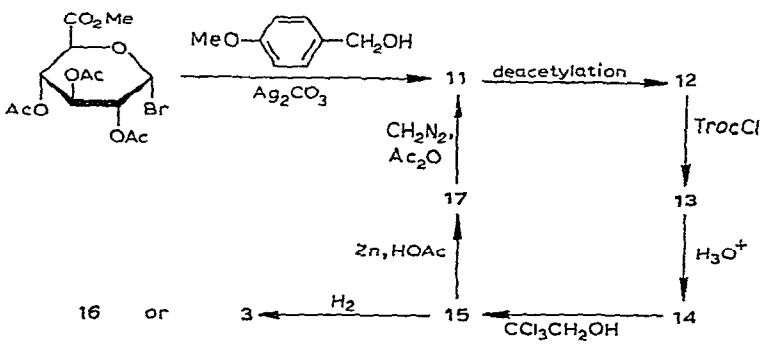
D-glucuronate with TrocCl in pyridine followed by hydrochloric acid yielded the crystalline acid **9**. The acid stability of these glycosides is probably attributable to the presence of the electronegative trichloroethoxycarbonyl groups, which interfere with the protonation step in the acid hydrolysis of glycosides. This observation suggests that treatment of acid-labile glucosyluronic acids with TrocCl might enhance their stability and facilitate their characterization in metabolic studies.

Finally, the corresponding *p*-methoxybenzyl D-glucopyranoside (**15**) was selected as the intermediate of choice, and was synthesized by the following route.

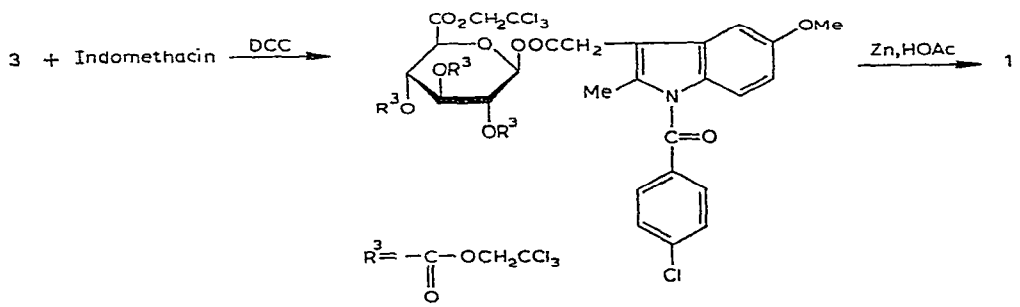


Interestingly, even the *p*-methoxybenzyl glycoside was relatively stable during the acid hydrolysis of the methyl ester group in **12**. Catalytic hydrogenation of **15** gave the desired key intermediate **3** in 66% yield. In one instance, when the hydrogenation

was effected in an acidic medium, the lactone **16** was obtained as a secondary product. The glycoside **12** has a specific rotation of $-18.5 \pm 2.8°$, strongly suggestive of the β-D-configuration by comparison with the rotations of closely related glycosides[10].

To establish the conditions for removing the protecting groups, the glucopyranosiduronate **15** was treated with zinc in acetic acid for 4 h at room temperature, and the reaction was monitored by t.l.c. The reaction mixture was deionized to yield a syrupy acid (**17**) in very good yield. The crude acid **17** was identified by conversion into the fully acetylated methyl ester (**11**), thus completing a protecting and deblocking cycle.

Encouraged by this model experiment, indomethacin was uneventfully condensed with the reagent **3** by *N*,*N*′-dicyclohexylcarbodiimide in tetrahydrofuran at room temperature to give the crystalline conjugate **18** in 50% yield.



18

The cleavage of 2,2,2-trichloroethoxycarbonyl groups in **18** by zinc dust in acetic acid was found by t.l.c. monitoring to be completed in *ca.* 1.5 h. After filtration and evaporation a crystalline glucosyluronic acid having m.p. 183° (decomp) was isolated. The i.r. spectrum of this product showed all of the expected bands but the sample was persistently contaminated with inorganic zinc salts, which could not be removed despite repeated attempts. Richards and Williams[9] have noted that zinc chloride forms complexes with vicinal hydroxyl groups at C-2 and C-3 of several D-glucopyranosides. Similar complex-formation could explain the incomplete deionization in our product. Because of the poor solubility of the zinc complex and the ease of decomposition of the glucosyluronic acid in solution, which precluded the use of ion-exchange column chromatography, no further attempt was made when a final purity of *ca.* 95% (as the zinc salt) was reached. The structure of this product was confirmed by methylation and acetylation to the crystalline derivative **2**, identical with an authentic specimen.

In conclusion, 2,2,2-trichloroethyl 2,3,4-tri-*O*-(2,2,2-trichloroethoxycarbonyl)-β-D-glucopyranuronate (**3**) appears to have promising utility in the synthesis of β-glucosyluronic acids that are sensitive to acidic or alkaline conditions. The direct coupling of the 1-hydroxyl group with an aglycon should generally favor the formation of the less-hindered β-anomer. Since formation of β-D-glucosyluronic acids is a com-

mon metabolic pathway, particularly in drug detoxification, the synthetic approach described here may have application in other studies of drug metabolism.

EXPERIMENTAL

General methods. — Melting points were taken in a Thomas–Hoover Unimelt apparatus and are uncorrected. T.l.c. was effected on Analtec silica gel plates, and column chromatography on Baker silica gel. Optical rotations were measured at 27° with a Zeiss polarimeter.

Methyl [methyl 2,3,4-tri-O-(2,2,2-trichloroethoxycarbonyl)-α-D-glucopyranosid]uronate (**6**). — The methyl ester of methyl (methyl α-D-glucopyranosid)uronate[7] (**5**) (29 g, 0.13 moles) was dissolved in 500 ml of pyridine and cooled to 0°. 2,2,2-Trichloroethoxycarbonyl chloride (Troc chloride, see footnote, p. 000) (83 g, 0.39 moles) was added dropwise to the cold solution, which was then stirred overnight at room temperature. After pouring the mixture into water and extracting with dichloromethane, the organic phase was washed with 1.25M sulfuric acid and then with water. The solvent was then evaporated off and the oily residue was chromatographed. The product was eluted with dichloromethane and recrystallized from methanol to give 25.4 g (26%) of **6**, m.p. 121–122°, $[\alpha]_D$ ×37.1° (*c* 1, chloroform).

Anal. Calc. for $C_{17}H_{17}Cl_9O_{13}$: C, 27.28; H, 2.29; Cl, 42.64. Found: C, 27.30; H, 2.35; Cl, 42.34.

Methyl 2,3,4-tri-O-(2,2,2-trichloroethoxycarbonyl)-α-D-glucopyranosiduronic acid (**7**). — Compound **6** (20 g, 0.028 moles) was dissolved in 200 ml of 1,2-dimethoxyethane and then 200 ml of 5M hydrochloric acid was added. The mixture was refluxed for 6 h under nitrogen and then concentrated to dryness, triturated with water and filtered. Chromatography of the residue, with 3% methanol in dichloromethane as eluant, afforded a crude product that was recrystallized from methanol to give 11 g (56%) of **7**, m.p. 92–94°, $[\alpha]_D$ +45.9° (*c* 1, chloroform).

Anal. Calc. for $C_{16}H_{15}Cl_9O_{13}$: C, 26.17; H, 2.06; Cl, 43.45. Found: C, 25.51; H, 2.37; Cl, 43.45.

2,2,2-Trichloroethyl [methyl 2,3,4-tri-O-(2,2,2-trichloroethoxycarbonyl)-α-D-glucopyranosid]uronate (**8**). — A solution of 7.34 g of **7** (10 mmoles) and 1.5 g of 2,2,2-trichlorethanol (10 mmoles) in 60 ml of dichloromethane, containing 0.8 ml of pyridine was stirred at room temperature while *N,N'*-dicyclohexylcarbodiimide (2.06 g, 10 mmoles) was added. The mixture was kept overnight at room temperature. The precipitated *N,N'*-dicyclohexylurea was filtered off and the solution was evaporated to dryness. Chromatography of the crude product, with dichloromethane as eluant, afforded 4.07 g (47%) of **8** after recrystallization from methanol; m.p. 113–115°, $[\alpha]_D$ +44.4° (*c* 1, chloroform).

Anal. Calc. for $C_{18}H_{16}Cl_{12}O_{13}$. C, 24.97; H, 1.86; Cl, 49.14. Found: C, 24.88; H, 1.92; Cl, 48.75.

1,2,3,4-Tetra-O-(2,2,2-trichloroethoxycarbonyl)-β-D-glucopyranorunic acid (**9**). — To an ice-cooled solution of methyl D-glucuronate (18 g, 0.09 mole) in 50 ml of

pyridine was added dropwise Troc chloride (25 g, 0.36 mole). The solution was stirred for 3 h at room temperature and then poured into ice–water and extracted with chloroform. The chloroform layer was washed with cold 1.25M sulfuric acid and then with water. After evaporation of the chloroform the residue was chromatographed, with dichloromethane as an eluant. The initial fractions were combined, and evaporated to give a mixture of α and β anomers, $[\alpha]_D$ +31.8 ±0.7° (*c* 1, chloroform). The mixture was recrystallized from methanol to give a crystalline product (15.1 g), m.p. 130–140°, $[\alpha]_D$ +65 ±0.7° (*c* 1, chloroform), which was characterized by n.m.r. spectroscopy as methyl 1,2,3,4-tetra-*O*-(2,2,2-trichloroethoxycarbonyl)-β-D-glucopyranuronate.

The above derivative (1.8 g, 2 mmoles) was dissolved in 40 ml of 1,2-dimethoxyethane and then 20 ml of 5.5M hydrochloric acid was added. The mixture was refluxed for 18 h under nitrogen and then concentrated to 15 ml and extracted with dichloromethane. The extract was washed with water, dried over sodium sulfate, and evaporated. Crystalline **9** (900 mg, 50%) was obtained from the oily residue upon addition of methanol; m.p. 112–113°, $[\alpha]_D$ +43.6 ±3.2° (*c* 1, chloroform).

Anal. Calc. for $C_{18}H_{14}C_{12}O_{15}$; C, 24.13; H, 1.56; Cl, 47.50. Found: C, 24.09; H, 1.83; Cl, 47.39.

Methyl (p-*methoxybenzyl 2,3,4-tri*-O-*acetyl*-β-D-*glucopyranosid*)*uronate* (**11**). — Methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucopyronurate (**10**) (7.5 g, 1.89 mmoles) was dissolved in 50 ml of dry benzene. To this was added silver carbonate (10.5 g, 3.18 mmoles) and *p*-methoxybenzyl alcohol (4 g, 2.9 mmoles). The mixture was stirred vigorously overnight. Charcoal was added and the mixture was stirred for an additional 10 min, and then filtered through Super-cel. The solution was dried over sodium sulfate and evaporated. The residue was taken up in hot isopropyl alcohol and allowed to crystallize, giving **11** (3.0 g, 35%), m.p. 107–110°, $[\alpha]_D$ −67.1 ±1.5° (*c* 1, chloroform). T.l.c. in 2% methanol in dichloromethane showed a pink spot with ceric sulfate spray. The β-configuration was assigned on the basis of its derivative **12** below. A moderate band at 889 cm^{-1} was also noted[10] in the i.r. spectrum of **11**.

Anal. Calc. for $C_{21}H_{26}O_{11}$; C, 55.50; H, 5.77. Found: C, 56.13; H, 5.91.

Methyl (p-*methoxybenzyl*)-β-D-*glucopyranosid*)*uronate* (**12**). — To a suspension of 9.5 g of **11** in 150 ml of methanol was added 500 mg of sodium methoxide. The yellow slurry turned into a pale solution after 1 h, and Dowex-50 (H^+) ion-exchange resin was added until the solution was neutral. The resin was filtered off and the filtrate was concentrated to dryness. Recrystallization from methanol and a few drops of water gave 3.95 g of **12** (57%), m.p. 119–125° $[\alpha]_D$ −81.5 ±2.8° (*c* 1, chloroform). Comparing with the benzyl analogs[10] the similarity in steric effect and the high negative rotation of **12** strongly suggests the β-configuration.

Anal. Calc. for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14. Found: C, 54.97; H, 6.04.

Methyl [p-*methoxybenzyl 2,3,4-tri*-O-(*2,2,2-trichloroethoxycarbonyl*)-β-D-*glucopyranosid*]*uronate* (**13**). — Compound **12** (3.9 g, 0.02 moles) was dissolved in 50 ml of pyridine at room temperature. To this was added 8.0 g of Troc chloride, with cooling

at 0°. The solution was stirred for 4 h at room temperature, and then poured into ice–water (250 g) and extracted with dichloromethane. The organic layer was washed with M sulfuric acid and then with water, dried over sodium sulfate, and evaporated. The residue was taken up in methanol to yield 8.9 g (88%) of crystalline **13**, m.p. 124–126°, $[\alpha]_D$ −33.0 ±3.5° (*c* 1, chloroform).

Anal. Calc. for $C_{23}H_{24}Cl_9O_{14}$: C, 33.73; H, 2.71; Cl, 37.34. Found: C, 33.85; H, 2.79; Cl, 37.08.

p-*Methoxybenzyl 2,3,4-tri*-O-(*2,2,2-trichloroethoxycarbonyl*)-β-D-*glucopyranosiduronic acid* (**14**). — To a solution of compound **13** (120 g) in 850 ml of 1,2-dimethoxyethane was added 2.5M hydrochloric acid (750 ml) and the mixture was refluxed overnight under nitrogen and then cooled, concentrated to 100 ml, and extracted with dichloromethane. The organic layer was washed twice with water, dried, and evaporated. The residue was placed on a column of silica gel that had been packed in dichloromethane and the product was eluted with 5% methanol in dichloromethane. Recrystallization from methanol gave 40 g (33%) of **14**, m.p. 100–102°, $[\alpha]_D$ −23.6 ±0.7° (*c* 1, chloroform).

Anal. Calc. for $C_{23}H_{21}Cl_9O_{14}$; C, 32.87; H, 2.52; Cl, 37.97. Found: C, 32.78; H, 2.81; Cl, 37.97.

2,2,2-Trichloroethyl [p-*methoxybenzyl-2,3,4-tri*-O-(*2,2,2-trichloroethoxycarbonyl*)-β-D-*glucopyranosid*]*uronate* (**15**). — To 32.62 g of dried **14** in 250 ml of dichloromethane was added 5.85 g of 2,2,2-trichloroethanol and 3 ml of pyridine, and then 8.05 g of *N,N'*-dicyclohexylcarbodiimide was added with stirring at room temperature. After 8 h the precipitate was filtered off and the residue was washed with ether. The filtrate was filtered again after 15 min and was then concentrated to dryness. Addition of acetone and then water gave 33 g (90%) of **15** in two crops (recrystallized from methanol); m.p. 168–170°, $[\alpha]_D$ −44.4 ±2.89° (*c* 1, chloroform).

Anal. Calc. for $C_{25}H_{24}Cl_{12}O_{14}$; C, 30.89; H, 2.28; Cl, 43.78. Found: C, 30.95; H, 2.27; Cl, 43.67.

Deblocking of compound **15**. — To a solution of compound **15** (250 mg) in 5 ml of acetic acid was added 500 mg of zinc dust in small portions during 4 h. The solution was then filtered and diluted with ether to give a precipitate. The precipitate was dissolved in 50 ml of water and put on a Biorad (H^+) ion-exchange column and eluted with water until the eluant was neutral. The fractions were freeze-dried and the residue (**17**, 60 mg) was methylated with diazomethane and then acetylated with pyridine and acetic anhydride to give a sample that was identical with **11** by R_F and mass-spectral comparisons.

2,2,2-Trichloroethyl 2,3,4-tri-O-(*2,2,2-trichloroethoxycarbonyl*)-D-*glucopyranurate* (**3**). — Compound **15** (10.8 g) was hydrogenolyzed in 150 ml of acetic acid containing 0.8 g of potassium acetate and 4 g of palladium chloride. After filtration and concentration, 6.3 g (66%) of **3** was obtained, m.p. 156–158°, $[\alpha]_D$ +8.6° (*c* 1, chloroform), +51.4° (after mutarotation with pyridine overnight).

Anal. Calc. for $C_{17}H_{14}Cl_{12}O_{13}$; C, 23.99; H, 1.66; Cl, 49.95. Found: C, 24.10; H, 1.73; Cl, 49.89.

2,3,4-Tri-O-(2,2,2-trichloroethoxycarbonyl)-β-D-glucopyranurono-1,6-lactone (**16**) — In a reaction carried out as above but without potassium acetate as buffer, the major product obtained was the lactone **16**, m.p. 160–161°. The i.r. spectrum revealed a band at 1820 cm^{-1} in addition to the trichloroethylcarbonyl bands at 1780 cm^{-1}.

Anal. Calc. for $C_{12}H_{11}Cl_9O_6$; C, 25.65; H, 1.58; Cl, 45.43. Found: C, 25.77; H, 1.78; Cl, 45.06.

2,2,2-Trichloroethyl [indomethacin 2,3,4-tri-O-(2,2,2-trichloroethoxycarbonyl)-β-D-glucopyranosyl]uronate (**18**). — To a solution of indomethacin (740 mg) in 10 ml of tetrahydrofuran was added 450 g of *N,N'*-dicyclohexylcarbodiimide. This was stirred for 5 min, and then 1.7 g of **3** in 5 ml of tetrahydrofuran was added. Stirring was continued overnight. After filtration 2 drops of acetic acid was added. Concentration to dryness afforded an oil that was taken up in ether and filtered. Petroleum ether was added and a gel was formed. Filtration gave 1.7 g of crude product. Recrystallization from ether–petroleum ether gave 1.25 g (50%) of **18**, m.p. 121–123°.

Anal. Calc. for $C_{36}H_{28}Cl_{13}NO_{16}$; C, 36.19; H, 2.37; Cl, 38.68; N, 1.17. Found: C, 36.30; H, 2.46; Cl, 37.73; N, 1.32.

Zinc (indomethacin-D-glucosyluronate) (**1**). — To a solution of compound **18** (400 mg) in 6 ml of acetic acid was added zinc dust (600 mg) and the mixture was stirred for 1.5 h. The reaction was monitored by t.l.c. in 10% methanol in dichloromethane. The spot corresponding to **18** at R_F 0.8 was gradually replaced by a new spot at the origin. The mixture was filtered and washed with ether and petroleum ether. The residue was extracted with methanol and the solution was diluted with water. After 18 h the compound was filtered off and dried to give 100 ml of crude material, found to contain zinc chloride. Trituration with water finally led to a product, m.p. 183° decomp., which upon further trituration did not show further purification. The i.r. spectrum was in accordance with the structure. The content of ash (8.85%) (calculated on the basis of zinc oxide), corresponding to 6.88% of zinc. Treatment with dithizone, hydrogen sulfide, or (ethylene dinitrilo)tetraacetic acid to remove the zinc caused partial purification or decomposition.

Anal. Calc. for $C_{50}H_{48}Cl_2N_2O_{21}Zn$+(3% $ZnCl_2 \cdot H_2O$): C, 50.45; H, 4.19; Cl, 7.19; N, 2.56. Found: C, 50.98; H, 4.10; Cl, 7.58. N, 2.37.

Conversion of **1** *into* **2**. — The zinc salt **1** (25 mg) was converted into the methyl ester with methyl iodide in *N,N*-dimethylformamide. After removing the solvent under high vacuum, the amorphous residue was taken up in 1 ml of 50% pyridine in acetic anhydride and kept at 4° overnight. The solution was then poured into ice–water (5 ml) and stirred a few min at room temperature to decompose excess reagent. The precipitated solid was centrifuged, taken up in ether, and the ether solution separated from traces of water by centrifugation. The crude derivative obtained by evaporating the ether solution was identical with an authentic specimen, by t.l.c. in ethyl acetate, 2% methanol in dichloromethane, and chloroform, and by i.r.-spectral comparisons. In the ^1H n.m.r. spectrum of **2** one of the acetyl signals (at τ 8.26) is displaced upfield from the rest. This is in accordance with the observation by Pravdić and Keglević[11] that the signal of 2-acetyl group of 1-*O*-acyl-β-D-glucosyluronic acids usually reso-

nates further upfield than τ 8.23, whereas the 2-*O*-acetyl group of the α anomer resonates below τ 8.18. This evidence tends further to substantiate that our compound is a β-glucosyluronic acid.

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