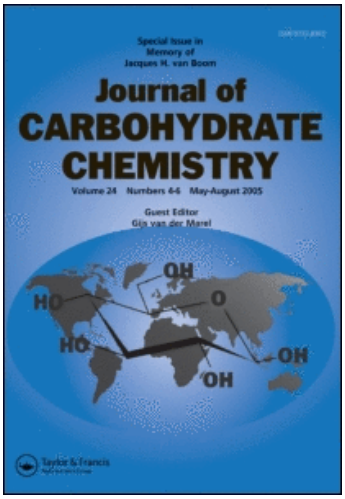

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Synthesis of Urine Drug Metabolites: Glucuronosyl Esters of Carboxymefloquine, Indoprofen, (*S*)-Naproxen, and Desmethyl (*S*)-Naproxen

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ABSTRACT

A general procedure for the synthesis of 1-*O*-acyl-β-D-glucuronic acids using the benzyl 1-*O*-trichloroacetimidoyl-2,3,4-tri-*O*-benzyl-D-glucopyranuronate **6** as donor is exemplified by the synthesis of the urine metabolites of (*S*)-naproxen, desmethyl (*S*)-naproxen, indoprofen, and carboxymefloquine. The key intermediate benzyl 2,3,4-tri-*O*-benzyl-D-glucopyranuronate **5** is easily accessible in four steps (29%) from the peracetylated β-D-glucuronic acid **1**.

Key Words: (*S*)-Naproxen; Desmethyl (*S*)-naproxen; Indoprofen; Carboxymefloquine.

INTRODUCTION

The in vivo formation of β-D-glucuronic acid derivatives plays an important role in the elimination and detoxification of xenobiotics and endogenous compounds in humans.

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Many compounds containing a carboxylic acid group are excreted as 1-*O*-acyl-β-D-glucuronic acids produced via the UDP-glucuronosyl transferase system. A large number of drugs, e.g., (*S*)-naproxen and indoprofen, are known to be metabolised via this pathway. These metabolic products were considered earlier only to be rapidly eliminated from the body without any further biological interaction. Recent results, however, show that adducts are formed both with low-molecular weight nucleophiles and proteins.[1] Detailed metabolism studies including identification, characterisation, and toxicology testing are quite often hampered by the limited access to sample material. Isolation of metabolites from biological material, e.g., urine, is often difficult due to instability of the metabolic products. In vitro biosynthesis affords the metabolites only in small amounts since simultaneous degradation occurs under physiological conditions. Therefore, the preparation of glucuronic acid derivatives of drug metabolites has been a synthetic target for a long time, and a general synthetic route has been desirable. However, the vast majority of these compounds are glucuronides and only a few examples of anomeric ester metabolites have been synthesised.[2–8]

The preparation of anomeric ester derivatives of glucuronic acid is connected to synthetic problems. Although the anomeric hydroxyl group has a higher reactivity as compared to the other hydroxyl groups, this difference is usually not sufficient to produce an acyl glucuronic acid derivative using an unprotected or partially protected glucuronic acid. Consequently, protecting groups have to be chosen, which are removable in the presence of the anomeric ester function. This circumstance excludes the use of many common carboxyl-protecting groups as well as almost all acyl protecting groups, complicating the stereoselective formation of the β-linked anomeric ester, which is normally controlled by using a participating acyl protecting group at O-2. The benzyl ester **5**[9,10] has been found earlier to be a suitable precursor, but different esterification methods, e.g., Mitsunobu conditions and carbodiimide based methods gave anomeric mixtures,[7,8,11] which often were tedious or impossible to separate. Also, the preparation of the perbenzylated glucuronic acid donor is cumbersome. Attempts to alkylate uronic acids directly seemed to be too unpredictable,[12] thus, an oxidising step was required to generate the carboxylic function, a step that can be problematic.

Herein we describe a general procedure for the synthesis of 1-*O*-acyl-β-D-glucuronic acids exemplified by the synthesis of the urine metabolites of (*S*)-naproxen, desmethyl (*S*)-naproxen, a metabolite derived from (*S*)-naproxen via a different pathway, indoprofen, and carboxymefloquine. The acyl uronate of the latter is one of the metabolites of mefloquine hydrochloride, a drug used for the prevention of malaria in areas with chloroquine-resistant parasites.

RESULTS AND DISCUSSION

The methyl peracetyl β-uronate **1** (Sch. 1) was easily prepared by methanolysis of the commercially available 3,6-glucurono lactone, followed by acetylation in Ac_2O and $HClO_4$, and crystallisation.[13] The formation of the thioglycoside glucuronate **2** did not proceed as well and β-stereoselectively as for glycosides. However, with 63% isolated yield the reaction is an attractive alternative to the two step longer routes via the thio orthoester or xanthate rearrangements, which are alternatives if the pure β-anomer is required.[12,14] The acetates were removed with NaOMe in MeOH without any formation

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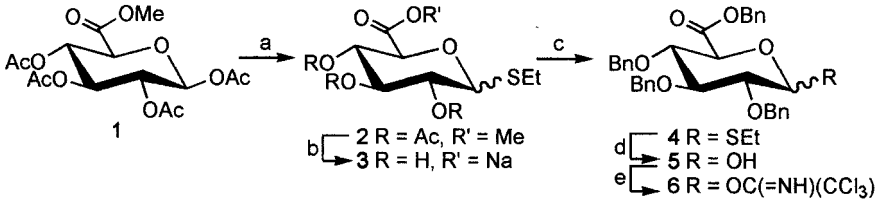


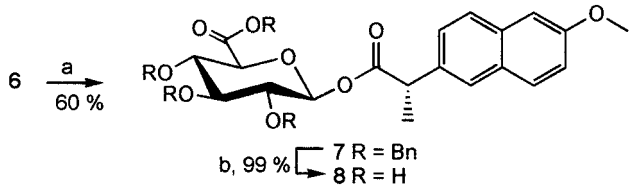
Scheme 1. (a) EtSH, $BF_3{\cdot}Et_2O$,CH_2Cl_2, RT; 63% (b) 1. NaOMe, MeOH; 2. NaOH(aq.), 96% (c) BnBr, NaH, DMSO, 15°C; 57% (d) NIS, wet CH_2Cl_2, RT, 85%; (e) CCl_3CN; cat.NaH, CH_2Cl_2, RT, 91%.

of β-elimination product. Addition of H_2O and NaOH to the reaction mixture yielded the sodium uronate **3**, ready for introduction of the benzyl groups.

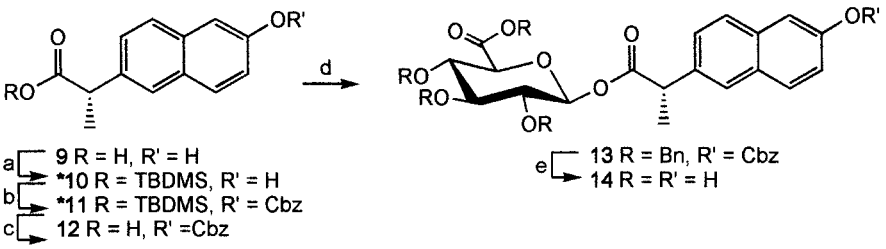
Alkylation of uronates is known to be difficult. However, use of the uronate salt instead of an ester increased the yield[15] as well as replacement of DMF by DMSO[16] along with careful monitoring of the temperature. The yields were acceptable (40–65%), and the procedure is also suitable for oligosaccharic acids.[17] Hence, benzylation of **3** with BnBr and NaH in DMSO produced **4** in 57% yield.

Attempts to activate the thioethyl group with various promoters in the presence of different aglycons did not provide the wanted acyl glucuronic acids.[11] Consequently, the thioethyl group was hydrolysed using NIS and a catalytic amount of AgOTf to produce the benzyl 2,3,4-tri-*O*-benzyl-D-glucopyranuronate **5** (85%).[7,8,11] Conversion to the imidate **6** was accomplished by treatment of **5** with Cl_3CCN in CH_2Cl_2 together with a catalytic amount of NaH (91%, α/β 15 : 1). Compound **6** is known to be an excellent donor for the synthesis of β-alkyl glucuronides, employing S_N2-type coupling conditions,[6,18,19] but has been barely tried for acyl glucuronic acids.[6] (*S*)-Naproxen (Sch. 2) was smoothly converted into its acyl-β-D-glucuronic acid **7** (60%), a minor amount of the α anomer was easily removed by column chromatography. Hydrogenolysis over Pd/C at atmospheric pressure rendered the unprotected metabolite **8**[20,21] in almost quantitative yield.

The acyl glucuronic acids of desmethyl (*S*)-naproxen **14**[20,21] (Sch. 3) is another metabolite of (*S*)-naproxen. A direct transformation of **7** or **8** into their demethylated derivatives is hard to accomplish, therefore, (*S*)-naproxen was modified into the suitable aglycon **12**. The phenolic methyl group was removed with HBr or HI in quantitative yield giving **9**.[21] Attempts to selectively benzylate the phenolic position failed, and dibenzylation led to racemisation in the α position. The coupling with a TBDMS protected desmethyl (*S*)-naproxen was successful, but deprotection of the silyl ether failed, due to many side reactions. Instead, **12** was prepared in a one pot manner. In pyridine, the



Scheme 2. (a) (*S*)-Naproxen, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −30°C; (b) Pd/C, EtOAc, H_2, 1 atm, RT.

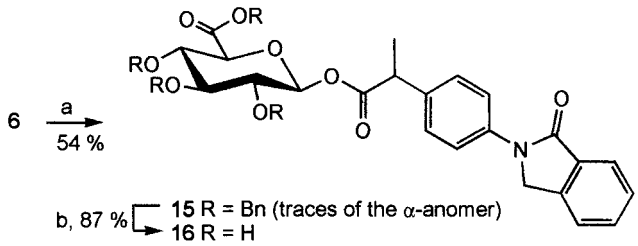


Scheme 3. (a) TBDMSCl, pyridine/CH_2Cl_2, RT; (b) + BnOCCl; (c) + SiO_2, CH_2Cl_2; 36% (for three steps); (d) **6**, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −30°C, 67%; (e) Pd/C, EtOAc, H_2, 1 atm, RT, 99%. (*Not isolated intermediates.)

formation of the labile TBDMS ester with TBDMSCl was faster than the formation of the corresponding phenolic ether, thus, producing intermediate **10**. Addition of benzyl chloroformate formed compound **11**. During aqueous work-up most of the TBDMS ester was cleaved, and after filtration through silica gel **12** was obtained in an overall 36% yield (three steps). Coupling with **6** under the same conditions as above gave, after column chromatography, **13** (67%) as the pure β anomer. **14** was obtained by hydrogenolysis over Pd/C (99%).

The couplings with indoprofen (Sch. 4), which was used as a racemic mixture, and carboxymefloquine (Sch. 5) were more demanding due to their poor solubility in CH_2Cl_2. A good stereoselectivity was achieved by coupling indoprofen and **6** in a CH_2Cl_2–1,4-dioxane mixture (5 : 1) producing **15** containing only a small amount of the α anomer (<3%) in 54% yield. Hydrogenolysis gave **16** (87%). The preparation of the carboxymefloquine acyl glucuronic acid metabolite **17** was tried earlier using Mitsunobu conditions.[11] The best β selectivity was obtained with excess of DIAD and PPh_3 at room temperature (66%, α/β 2 : 1). A lowered reaction temperature increased the total yield, but enhanced the α formation as well (82% α/β 3 : 1). However, the best results were obtained dissolving carboxymefloquine in a small amount of THF and adding a solution of donor **6** in CH_2Cl_2 at 0°C (**17**, 60%, α/β 1 : 3). Deprotection was achieved in EtOAc and Pd/C 5% producing **18** but the reaction was difficult to reproduce due to the concomitant reduction of the aromatic system.

In conclusion, the imidate **6** is a good general donor also for the preparation of β acyl glucuronides. The key intermediate benzyl 2,3,4-tri-*O*-benzyl-D-glucopyranose



Scheme 4. (a) Indoprofen, $BF_3{\cdot}Et_2O$, CH_2Cl_2/1,4-dioxane, −30°C; (b) Pd/C, EtOAc-DMF, H_2, 1 atm, RT.

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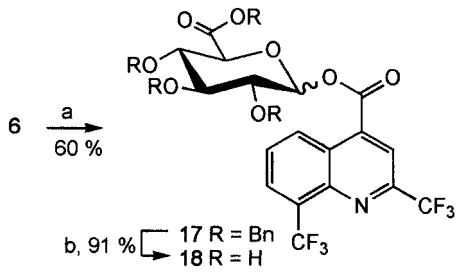

Scheme 5. (a) Carboxymefloquine, $BF_3{\cdot}Et_2O$,CH_2Cl_2/THF, 0°C; (b) Pd/C, EtOAc, H_2, 1 atm, RT.

uronate (**5**) is easily accessible in four steps (29%) from the methyl peracetylated β-uronate **1**.

EXPERIMENTAL

General Methods

All organic solvents were distilled before use, except diethyl ether, which was stored over sodium wire. Organic solutions were dried over magnesium sulphate, before concentration, which was performed under reduced pressure at $<40°C$ (bath temperature). NMR spectra were recorded at 300 or 400 MHz (Varian) (^1H) or at 75 or 100 MHz (^{13}C), respectively, in chloroform-*d*, deuterium oxide or methanol-d_4. Tetramethylsilane was used as internal standard ($\delta = 0$) for ^1H-spectra. ^{13}C-spectra were referred to the chloroform signal ($\delta = 77.17$). Acetone ($\delta = 31.0$, ^{13}C; $\delta = 2.21$, ^1H) was applied as internal standard when deuterium oxide was used as solvent. Silica gel MERCK 60 (0.040–0.063) was used for flash chromatography. Thin-layer chromatography was performed on silica gel 60 F_{254} (Merck) glass plates with detection by UV-light and/or charring with 8% sulphuric acid. Column chromatography was performed on silica gel (Matrix Silica Si 60A, 35–70 μm). MALDI-TOF spectra were recorded on a Bruker Biflex III using PEG 400 and PEG 1000 as calibration reference and 2′,4′,6′-trihydroxy-acetophenone monohydrate (THAP) as matrix.

Benzyl 2,3,4-tri-*O*-benzyl-D-glucopyranuronate (5).[10] Boron trifluoride diethyl etherate (5 mL, 40.0 mmol) was added slowly to a cooled (0 °C) mixture of **1** (9.5 g, 26.6 mmol), ethane thiol (2.4 mL, 32.4 mmol), and molecular sieves (1 g, MS 4 Å) in dry dichloromethane (50 mL) under nitrogen. After stirring at room temperature (12 hr), the solution was poured onto a mixture of cracked ice (≈300 mL) and dichloromethane (200 mL). The organic layer was separated, washed with saturated sodium hydrogencarbonate and brine, dried, and concentrated. The crude product was purified by silica gel chromatography (toluene → 9 : 1, toluene–diethyl ether) to give methyl (ethyl 2,3,4-tri-*O*-acetyl-1-thio-D-glucopyranosid)uronate (**2**) (6.3 g, 16.7 mmol, 63 %) as an α/β mixture. A solution of **2** (6.2 g, 16.4 mmol) in dry methanol (100 mL) was treated with sodium methoxide (30 drops, 1 M in methanol). After 2 hr stirring at room temperature all acetate groups were removed (6 : 1, CH_2Cl_2–MeOH), and water (50 mL) and sodium hydroxide (8 mL, 2 M) were added. After additional 30 min (TLC: 12 : 3 : 3 : 2,

EtOAc–MeOH–H_2O–AcOH), the mixture was neutralised with Dowex 50 (H^+) ion exchange resin, filtered, and concentrated to yield sodium (ethyl 1-thio-D-glucopyranosid)-uronate (**3**)[13] (4.2 g, 16.1 mmol, 96%). Sodium hydride (340 mg, 60 %, ≈2.5 equiv./OH) was added to a stirred solution of **3** (200 mg, 0.77 mmol) and benzyl bromide (1.0 mL, 8.4 mmol, ≈2.5 equiv./OH) in dry dimethyl sulphoxide (2.2 mL) at 15°C (water bath temperature). The water bath was changed to 20°C after the reaction mixture had turned solid (ca. 15 min) and left for 15 min, when the reaction was quenched by addition of toluene (35 mL) and water (15 mL). The organic layer was separated, diluted with ethyl acetate (50 mL), washed with acetic acid (5%, aq.) and brine, dried, concentrated, and filtered through silica gel (toluene → 20 : 1, toluene–ethyl acetate) to give benzyl (ethyl 2,3,4-tri-*O*-benzyl-1-thio-D-glucopyranosid)uronate (**4**) (260 mg, 0.43 mmol, 57%) as an α/β mixture. NMR ($CDCl_3$): ^{13}C[11], anomeric mixture, δ 14.8, 15.1 (SEt), 24.0, 25.1 (SEt), 67.2, 67.3, 75.6–79.3, 81.2, 81.6, 83.7, 85.8, 85.9 C-1–C-5, CH_2Ph), 128.3–128.4, 136.4, 137.8, 138.3 (Ph), 168.2 (C═O). A mixture of **4** (3.6 g, 6.0 mmol) and NIS (1.35 g, 6.0 mmol) in wet dichloromethane (20 mL CH_2Cl_2, 0.5 mL H_2O) was treated with a catalytic amount of silver trifluoromethanesulphonate. After 15 min (TLC: 4 : 1, pentan–ethyl acetate), the mixture was transferred into a separation funnel, washed with sat. sodium thiosulphate and brine, dried and concentrated. The residue was purified by silica gel chromatography (toluene → 10 : 1, toluene–diethyl ether → 6 : 1, toluene–ethyl acetate) to give the title compound **5** (2.8 g, 5.1 mmol, 85%). NMR ($CDCl_3$): ^1H, anomeric mixture δ 3.10 (b, 1H, OH), 3.30–3.95 (m, 3H, H-2, H-3, H-4), 4.35–5.15 (m, 10H, H-1, H-5, 4 × CH_2Ph), 7.00–7.30 (m, 4, Ph); ^{13}C, δ α-anomer 67.5, 70.8, 73.6, 75.1, 75.8, 79.2, 79.4, 80.8 (C-2–C-5, CH_2Ph), 91.7 (C-1), 127.9–128.8, 135.1, 137.7, 137.9, 138.4 (Ph), 168.2 (C═O); β-anomer: 97.8 (C-1).

Benzyl 1-*O*-trichloroacetimidoyl-2,3,4-tri-*O*-benzyl-D-glucopyranuronate (6). The compound was prepared according to the literature.[18] A solution of **5** (800 mg, 1.44 mmol), trichloroacetonitrile (1.5 mL, 14.9 mmol) in dry dichloromethane (15 mL) was treated with sodium hydride (44 mg, 0.11 mmol, 60%). After 30 min the reaction was complete (TLC: 2 : 1, pentane–ethyl acetate). The mixture was concentrated and filtered through silica gel (2 : 1, pentane–ethyl acetate) to obtain **6** (915 mg, 1.31 mmol, 91%, α/β 15 : 1) as a pale yellow syrup. NMR ($CDCl_3$): ^1H, δ 3.85 (dd, 1H, $J = 3.7$ Hz, $J = 9.5$ Hz), 8.89 (t, 1H, $J = 9.5$ Hz), 4.11 (t, 1H, $J = 9.5$ Hz), 4.50 (m, 2H), 4.77 (m, 3H), 4.86 (d, 1H, $J =$ 11.0 Hz), 4.98 (d, 1H, $J = 11.0$ Hz), 5.18, 5.19 (s, 2H), 5.90 (d, 1H, β-H-1, $J = 7.0$ Hz), 6.58 (d, 1H, α-H-1, $J = 3.7$ Hz), 7.15–7.40 (m, 20H, Ph), 8.65 (s, 1H, NH); ^{13}C, δ α-anomer 67.6, 72.9, 73.2, 75.0, 75.5, 75.9, 78.9, 79.0, 80.7 (C-2–C-5, CH_2Ph, —CCl_3), 94.1 (C-1), 127.8–128.7, 135.0, 137.7, 127.8, 137.8, 138.4 (Ph), 161.2 (C═NH), 168.2 (C═O).

Benzyl 1-*O*-[2(*S*)-6-methoxy-2-naphthyl)propionyl]-2,3,4-tri-*O*-benzyl-β-D-glucopyranuronate (7). A boron trifluoride diethyl etherate solution (250 μL, 50 μL $BF_3 \cdot Et_2O$ in 1 mL CH_2Cl_2) was added in five portions to a cooled (−30°C) solution of **6** (460 mg, 0.66 mmol) and (*S*)-naproxen (150 mg, 0.65 mmol) in dry dichloromethane (15 mL). After 1 hr the reaction was complete (TLC: 4 : 1, pentane–ethyl acetate), and sodium hydrogencarbonate (250 mg) was added. The mixture was allowed to attain room temperature, diluted with dichloromethane, filtered and concentrated. Purification on silica gel (20 : 1 → 8 : 1, pentane–ethyl acetate) gave the pure β-anomer **7** (300 mg, 0.39 mmol, 60%). $[\alpha]_D$ −9° (*c* 0.15, MeOH); NMR ($CDCl_3$): ^1H, δ 1.62 (d, 3H, $J = 6.7$ Hz), 3.59 (t, 1H, $J = 8.2$ Hz), 3.71 (t, 1H, $J = 8.9$ Hz), 3.78–3.93 (m, 2H), 3.91 (s, 3H), 4.07 (d, 1H, $J = 9.2$ Hz), 4.41 (d, 1H), 4.48 (d, 1H), 4.58 (d, 1H), 4.65 (d, 1H),

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4.70 (d, 1H), 4.80 (d, 1H), 5.11 (s, 2H), 5.70 (d, 1H, β-H-1, $J = 7.3$ Hz), 6.50–7.14 (m, 6H), 7.20–7.40 (m, 21H), 7.62–7.68 (m, 3H) 18.5 (Me), 45.6 (CH), 55.5 (OMe); ^{13}C, δ 18.5, 45.6, 55.5 (OCH_3), 67.6, 74.9, 75.1, 75.2, 75.8, 79.3, 80.5 (C-2–C-4, CH_2Ph), 84.0 (C-5), 94.3 (C-1), 105.7, 119.2, 126.4–129.5, 134.0, 134.5, 135.1, 137.7, 137.9, 138.2, 157.9 (Ph) 168.2, 173.0 (C═O). Anal. Calcd for $C_{48}H_{46}O_9$ H_2O: C, 73.5; H, 6.2, Found: C, 73.1; H, 6.0.

1-*O*-[2(*S*)-(6-Methoxy-2-naphthyl)propionyl]-β-D-glucopyranuronic acid (8).[20,21] A mixture of **7** (290 mg, 0.38 mmol) and palladium on activated carbon (10%, 30 mg) in ethyl acetate (20 mL) was degassed and set under a hydrogen atmosphere. The hydrogenolysis was carried out at atmospheric pressure over night. The suspension was filtered through a plug of Celite, which was washed with ethyl acetate (100 mL). After concentration, the residue was dissolved in water (10 mL) and washed with diethyl ether (2 × 10 mL). Freeze-drying of the water phase gave **8** (152 mg, 0.38 mmol, 99 %). NMR (D_2O): ^{1}H, 1.57 δ (d, $J = 6.7$ Hz, 3H), 3.40–3.60 (m, 3H), 3.85–4.15 (m, 5H), 5.60 (d, β-H-1, $J = 7.9$ Hz), 7.30–7.50 (m, 3H), 7.75–7.85 (m, 3H);[21] ^{13}C, δ 18.0 (Me), 44.9 (CH), 54.7 (OMe), 66.0, 71.2, 71.9, 75.3 (C-2–C-5), 94.1 (C-1), 105.6, 118.8, 126.0 (2×), 127.3, 128.7, 129.2, 133.4, 134.6, 157.0 (Ph) 171.7, 175.0 (C═O); MS-FAB [M + H]: 411.

2(*S*)-(6-Benzyloxycarbonyloxy-2-naphthyl)propionic acid (12). 2(*S*)-(6-Hydroxy-2-naphthyl) propionic acid (**9**)[21] (600 mg, 2.8 mmol) was dissolved in a solution of butyldimethylsilyl chloride (840 mg, 5.6 mmol) in pyridine (3 mL) and dichloromethane (10 mL) at room temperature. After 30 min the silyl ester was formed according to TLC (9 : 1, toluene–ethyl acetate), and benzyl chloroformate (1.2 mL, 8.4 mmol) was added. To complete the conversion, an additional portion benzyl chloroformate (0.6 mL, 4.2 mmol) was added after 30 min. After 1 hr, the reaction mixture was diluted with dichloromethane (30 mL), washed with water (2 × 15 mL), dried, and concentrated. The residue was filtered through a plug of silica gel (CH_2Cl_2) to cleave any residual silyl ester and purified by flash silica gel chromatography [2 : 1, pentane–diethyl ether (cont. 0.5% AcOH)] to give **12** (460 mg, 1.0 mmol, 36%) as long needles (m.p. 157–158°C). NMR: ^{1}H ($CDCl_3$), δ 1.59 (d, $J = 7.2$ Hz, Me), 3.89 (q, 1H, C*H*), 5.30 (s, 2H, Cbz), 7.30–7.83 (11H, Ph, Cbz); ^{13}C (MeOD), δ 18.2 (PhMe), 45.4 (CH), 70.6 (Cbz), 118.0, 121.0, 126.4, 126.7, 128.4, 128.7, 128.8, 128.9, 129.6, 131.6, 133.0, 134.9, 137.4 (Ph, Cbz), 148.9 (Cbz), 153.8 (Ph), 180.4 (COOH). MALDI-TOF MS: Calcd for $C_{21}H_{18}O_5$ 351.1154 [M]; Found 376.16 $[M + Na]^+$, 389.15 $[M + K]^+$. HRMS: Calcd for $C_{21}H_{19}O_5$ 351.1127 $[M + H]^+$; Found 351.125 $[M + H]^+$.

Benzyl 1-*O*-[2(*S*)-(6-benzyloxycarbonyloxy-2-naphthyl)propionyl]-2,3,4-tri-*O*-benzyl-β-D-glucopyranuronate (13). A solution of **6** (500 mg, 0.72 mmol) and **12** (200 mg, 0.57 mmol) in dry dichloromethane (15 mL) was cooled (−30°C). A 250 μL of a boron trifluoride diethyl etherate solution in dichloromethane (50 μL $BF_3 \cdot Et_2O$ in 1 mL CH_2Cl_2) was added in five portions. After 1 hr the reaction was complete (TLC: 6 : 1, pentane–ethyl acetate), and sodium hydrogencarbonate (250 mg) was added. The mixture was allowed to attain room temperature, diluted with dichloromethane, filtered, and concentrated. Purification on silica gel (20 : 1 → 6 : 1, pentane–ethyl acetate) gave the pure β-anomer **13** (340 mg, 0.38 mmol, 67%). $[\alpha]_D$ −12° (*c* 1.03, CH_2Cl_2); NMR ($CDCl_3$): ^{1}H, δ 1.59 (d, $J = 7.2$ Hz, Me), 3.57 (*t*, $J = 8.7$ Hz, 1H, H-2), 3.70 (t, $J = 8.7$ Hz, 1H, H-3), 3.81 (t, $J = 9.6$ Hz, 1H, H-4), 3.87 (q, 1H, C*H*), 4.07, 4.41, 4.49, 4.60, 4.77, 5.10, 5.30 (CH_2Ph), 5.69 (d, $J = 7.5$ Hz, 1H, H-1), 7.06–7.76 (m, 31H, Ph, Cbz); ^{13}C, δ 18.5 (PhMe), 45.6 (*C*H), 67.5, 70.6, 74.8, 75.0, 75.6, 79.2, 80.5, 84.0, 94.3

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(C-1), 117.8, 121.0, 126.6–129.6, 131.5, 135.0, 134.9, 137.0, 137.7, 137.8, 138.2 (Ph, Cbz), 148.9 (Cbz), 153.8 (Ph), 168.2, 172.6 (C═O). MALDI-TOF MS: Calcd for $C_{55}H_{50}O_{11}$ 886.34 [M]; Found 909.66 $[M + Na]^+$, 925.30 $[M + K]^+$. HRMS: Calcd for $C_{55}H_{50}O_{11}Na$ 909.3245 $[M + Na]^+$; Found 909.288 $[M + Na]^+$.

1-*O*-[2(*S*)-(6-Hydroxy-2-naphthyl)propionyl]-β-D-glucopyranuronic acid (14).[20,21] A mixture of **13** (340 mg, 0.38 mmol) and palladium on activated carbon (10%, 30 mg) in ethyl acetate (20 mL) was degassed and set under a hydrogen atmosphere. The hydrogenolysis was carried out at atmospheric pressure over night. The suspension was filtered through a plug of Celite, which was washed with ethyl acetate (100 mL). After concentration, the residue was dissolved in water (10 mL) and washed with diethyl ether (2 × 10 mL). Freeze-drying gave **14** (150 mg, 0.38 mmol, 99%). $[\alpha]_D + 145^\circ$ (*c* 0.4, H_2O); NMR (D_2O, 25°C): ^1H, δ 1.56 (d, $J = 7.3$ Hz, Me), 3.57 (t, $J = 8.7$ Hz, 1H), 3.50–3.68 (m, 2H), 4.07 (m, 2H), 5.63 (d, $J = 8.0$ Hz, H-1), 7.14 (dd, 1H, PhH), 7.19 (d, 1H, PhH), 7.41 (dd, 1H, PhH), 7.71 (m, 3H, PhH).[21] ^{13}C, δ 17.5 (CH_3), 45.0 (CH), 71.1, 71.7, 75.2 (C2, C3, C4, C5), 94.1 (C1), 109.2, 118.6, 126.3, 126.5, 127.2, 129.9, 133.8, 134.8, 153.8 (Ph), 175.8 (C═O).

Benzyl 1-*O*-indoprofenyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranuronate (15). A solution of boron trifluoride diethyl etherate in dichloromethane (110 μL $BF_3 \cdot Et_2O$ in 1 mL CH_2Cl_2) was added in five portions to a cooled (−30°C) solution of **6** (200 mg, 0.28 mmol) and racemic indoprofen (100 mg, 0.36 mmol) in dry dichloromethane—1,4-dioxane (5 : 1, 10 mL) under argon. Stirring was continued over night, while the mixture slowly attained room temperature TLC: 2 : 1, pentane–ethyl acetate. The reaction mixture was diluted with dichloromethane (10 mL) and neutralized by addition of 10% sodium hydrogencarbonate (20 mL). The organic layer was separated, dried and concentrated. Purification on silica gel (20 : 1 → 8 : 1, pentane–ethyl acetate) gave **13** (150 mg, 0.15 mmol, 54%, $\alpha < 3\%$) as a diastereomeric mixture (1 : 1). NMR ($CDCl_3$, diastereomeric mixture), ^1H, δ 1.55 (d, 3H, Me), 3.44–3.94 (m, 5H, H-2–H-5, CH), 4.00–4.90 (m, 8H, C*H*$_2$Ph, CH_2N), 5.15 (d, 2H, CH_2Ph), 5.86, 5.70 (d, $J = 8.2$ Hz, 1H, H-1, diastereomers), 6.90–7.89 (28H, Ph); ^{13}C, δ 18.2, 18.4 (Me), 45.0, 45.1 (CH), 50.5, 50.8 (C*H*$_2$N), 67.6, 67.7, 74.5, 74.9, 75.1, 75.2, 75.8, 75.9, 79.1, 79.3, 80.5, 80.6, 83.7, 84.0 (*C*H$_2$Ph, C-2–C-5), 94.3, 94.5 (C-1), 119.5, 119.6, 122.7, 122.8, 124.3, 124.4, 127.4–128.8, 132.3–140.2 (Ph), 167.6, 167.7, 168.3, 168.4, 172.8 (C═O). Anal. Calcd for $C_{51}H_{47}NO_9$: C 74.9, H 5.8, N 1.7; Found: C 74.6, H 5.9, N 1.8.

1-*O*-Indoprofenyl-β-D-glucopyranuronic acid (16). A mixture of **15** (60 mg, 73 μmol) and palladium on activated carbon (10%, 50 mg) in ethyl acetate-DMF (9 : 1, 10 mL) was degassed and set under a hydrogen atmosphere for 7 hr at atmospheric pressure. The suspension was filtered through a plug of Celite, washed with ethyl acetate (100 mL). After concentration, the residue was dissolved in water (10 mL) and washed with diethyl ether (2 × 10 mL). Freeze-drying gave **16** (30 mg, 63 μmol, 87%) as a diastereomeric mixture (1 : 1). NMR (MeOD, diastereomeric mixture), ^1H, δ 1.52, 1.54 (d, 3H, Me, diastereomers), 3.32–3.58 (m, 3H), 3.90 (m, 2H), 5.00 (s, 2H), 5.51, 5.52 (d, $J = 7.8$ Hz, H-1), 7.42 (m, 4H), 7.57 (t, 1H), 7.67 (m, 2H), 7.84 (m, 3H); ^{13}C, δ 19.2, 19.3 (Me), 46.1, 46.2 (CH), 52.6 (CH_2N), 73.1, 73.7, 75.6, 75.7 (C-2–C-5), 96.0 (C-1), 121.7, 121.8, 124.3, 124.7, 129.6, 133.7, 133.9, 138.3, 139.7, 142.5 (Ph), 169.9, 174.7, 174.9 (C═O). MS-FAB [M + H]: 458.

Benzyl 1-*O*-carboxymefloquine-2,3,4-tri-*O*-benzyl-D-glucopyranuronate (17). Carboxymefloquine (30 mg, 97 μmol) was dissolved in a small amount of dry THF

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($\approx$75 μL) and **6** (74 mg, 107 μmol) dissolved in dichloromethane (500 μL), was added. The mixture was cooled (0°C) before 50 μL of a boron trifluoride diethyl etherate solution in dichloromethane (50 μL $BF_3 \cdot Et_2O$ in 1 mL CH_2Cl_2) was added under argon. After 10 min, **6** was consumed (TLC: 4 : 1, toluene–ethyl acetate) and Et_3N (50 μL) was added. After concentration the crude material was purified on silica gel (9 : 1, toluene–ethyl acetate) to give **17** (49 mg, 58 μmol, 60%) as an anomeric mixture (α/β 1 : 3). NMR ($CDCl_3$, anomeric mixture): ^{1}H, δ 5.97 (d, $J = 6.6$ Hz, βH-1), 6.62 (d, $J = 3.3$ Hz, αH-1); ^{13}C, δ 67.8, 67.9, 73.4, 74.1,75.1, 75.4, 75.5, 75.7, 76.0, 78.5, 78.9, 79.0, 80.1, 81.0, 83.7, 92.5 (αC-1), 95.0 (βC-1), 118.5, 119.2, 127.7, 129.9, 128.0–129.9, 134.8, 136.0, 137.2–138.0 (Ph), 162.9, 163.5, 168.3, 168.4 (C═O). MALDI-TOF MS: Calcd for $C_{46}H_{37}F_6NO_8$ 845.24 [M]; Found 868.13 $[M + Na]^+$, 884.04 $[M + K]^+$. HRMS: Calcd for $C_{46}H_{37}F_6NO_8Na$ 868.2316 $[M + Na]^+$; Found 868.211 $[M + Na]^+$.

1-*O*-Carboxymefloquine D-glucopyranuronic acid (18). A mixture of **17** (220 mg, 0.26 mmol) and palladium on activated carbon (5%, 20 mg) in ethyl acetate (10 mL) was degassed and set under hydrogen atmosphere for 5 hr at atmospheric pressure. The suspension was filtered through a plug of Celite, washed with ethyl acetate (100 mL). After concentration, the residue was dissolved in water (10 mL) and washed with diethyl ether (2 × 10 mL). Freeze-drying gave **18** (115 mg, 0.24 mmol, 91%, α/β 1 : 2). NMR (acetone-d_6, anomeric mixture): ^{1}H, δ 3.6–4.2 (m, 4H H-2–H-5), 6.01 (d, $J = 7$ Hz, βH-1), 6.62 (sb, αH-1), 8.05 (m, 1H), 8.36 (m, 1H), 8.55 (**18**α, $J = 5.1$ Hz) and 8.58 (**18**β, $J = 5.1$ Hz) (d, 1H), 9.10 (m, 1H); ^{13}C, δ 72.3, 73.0, 73.1, 73.9, 75.0 (C-2–C-5), 96.3 (αC-1), 97.7 (βC-1), 120.7, 121.0, 121.4, 124.0, 124.1, 128.0–132.2, 139.2, 140.1, 145.8, 149.2, 149.5, 165.0, and 165.2 (C═O). MALDI-TOF MS: Calcd for $C_{18}H_{13}F_6NO_8$ 485.05 [M]; Found 486.8 $[M + H]^+$, 508.8 $[M + Na]^+$.

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