Brief Articles

Efficient Preparations of the β-Glucuronides of Dihydroartemisinin and Structural Confirmation of the Human Glucuronide Metabolite

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New and greatly improved preparations of the 12α,1′β- (**5**) and 12β,1′β- (**6**) glucuronides of dihydroartemisinin (DHA, **2**) are reported using anomeric hydroxy and imidate glucuronate intermediates. Comparison of the synthetic and natural materials shows that the human metabolite of DHA is the 12α-epimer **5**.

Introduction

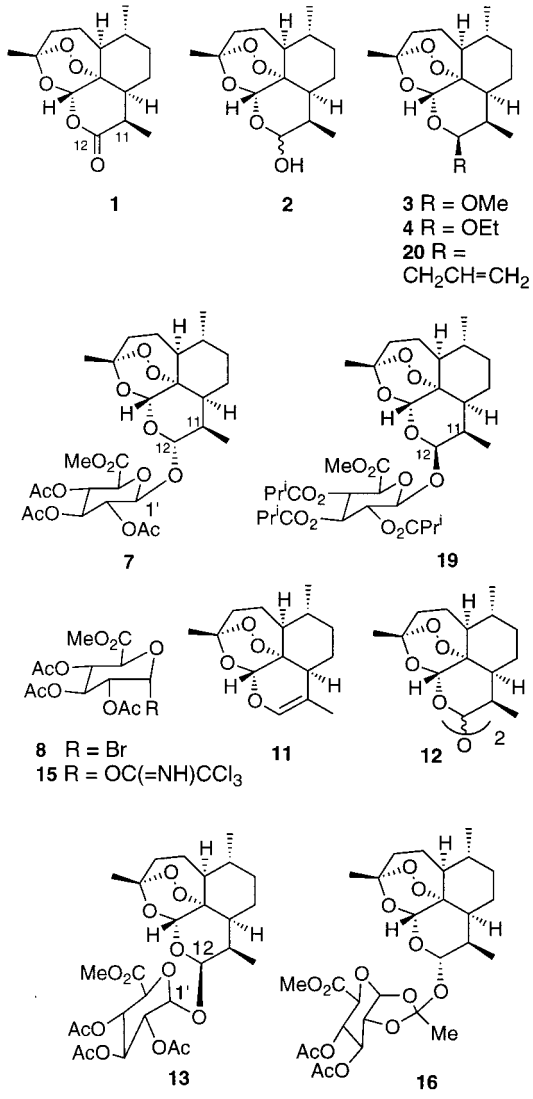
The trioxane derivative artemisinin (**1**), active principle of the medicinal herb *Artemisia annua*, has long been known to be an effective antimalarial agent.[1] Many semisynthetic analogues of **1** based on the derived lactol dihydroartemisinin (DHA, **2**) have appeared, notably the ether derivatives β-artemether (**3**)[2] and β-arteether (**4**).[3] A major drawback of such derivatives is that they undergo rapid metabolism in vivo, yielding initially DHA (**2**) via cytochrome P450-mediated dealkylation. Subsequently **2** is eliminated as a 12-glucuronide.[4] Since DHA (**2**) exhibits neurotoxicity and a short half-life, an important goal in this therapeutic area is the synthesis of derivatives of **2** having enhanced metabolic stability. We have reported[5,6] a series of 12-aryl ethers which satisfy this condition.

It is important to have the human glucuronide metabolite of **2** available as a standard. Low-yielding syntheses of the 12α,1′β- and 12β,1′β-glucuronides **5** and **6** have been reported,[7] without identification of the human metabolite. We therefore sought to establish practical syntheses of both **5** and **6** and to characterize the human metabolite. A valuable bonus was the identification of an ester of **2** which has also proved useful in the preparation of a 12β-carba analogue of DHA.

Discussion and Chemistry

The 12α,1′β-ester **7** had been made before[7] in very low yield (2.5%) by a Koenigs−Knorr reaction between **2** and 3 equiv of bromo sugar **8**; hydrolysis of **7** gave **5**. The 12β,1′β-isomer **9** had been obtained in 17% yield by an acid-mediated condensation between **2** and a large excess (6 equiv) of the 1-hydroxy sugar **10**; hydrolysis of **9** led to **6**.

Chart 1



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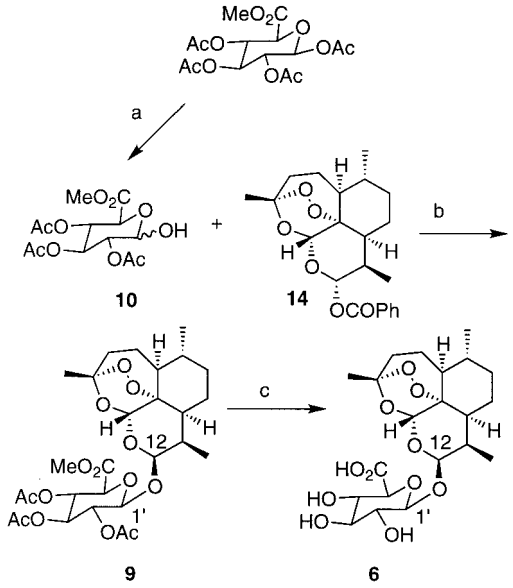
Scheme 1. Synthesis of DHA 12β,1′β-Glucuronide **6**[a]



[a] Reagents: (a) ref 11; (b) $ZnCl_2$; (c) Na_2CO_3, aq MeOH.

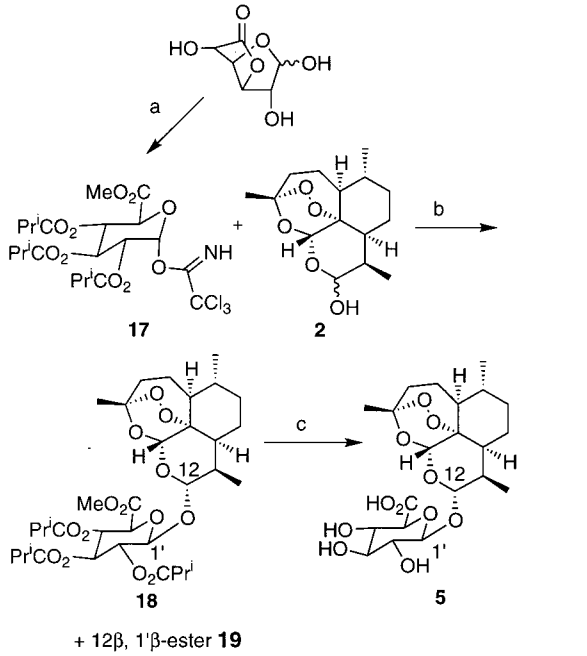
We first studied the synthesis of **6**. In our hands, reaction between **2** and **10** catalyzed by $BF_3{\cdot}Et_2O$ in benzene at 20 °C[7] gave only traces (<5%) of **9**; the main products arose from degradation of **2**, namely anhydro-DHA (**11**) and the ether-bridged dimer **12**. When a near-solution of **2** in 1,2-dichloroethane (DCE) was added to a mixture of **10** and $BF_3{\cdot}Et_2O$ in the same solvent, a conjugate was obtained, but by NMR this was the 12β,1′α-isomer **13**[7] (10% yield).

Using carbohydrate terminology, in the reaction of **2** with **10** either component may be donor or acceptor. Glucuronidation of alcohols using **10** as acceptor component[8] may work well if the donor can generate a highly stabilized carbonium ion, though at low temperature the α-glucuronide may predominate. Though the 1β-epimer of **10**, as an equatorial alcohol, is intrinsically more reactive, the α-epimer is the major component (ca. 5:1), and at low temperature the α to β conversion is too slow to generate significant β-glucuronide. A milder Lewis acid operating at higher temperature should be more suitable. An activated form of DHA could only act as donor and would at least cut down on the loss of two molecules at once in forming the ether dimer **12**.

We therefore prepared the 12α-benzoate **14** of **2**, previously mentioned without preparative details.[9] Reaction of **2** with benzoyl chloride and pyridine in CH_2Cl_2 at 0 °C generated only the 12α-anomer **14**, in high yield: clearly the epimers of **2** equilibrate faster than the rate of acylation.

Use of TMS triflate−$AgClO_4$ at −10 °C[5,6,10] gave only the 12β,1′α-isomer **13** (in 40% yield) when applied to the reaction of **14** and **10**, while use of $BF_3{\cdot}Et_2O$ at 20 °C gave anhydro-DHA (**11**) as the main product. However, $ZnCl_2$ proved an effective catalyst (Scheme 1). Thus reaction of **14** with just 2 equiv (cf. above) of **10** (DCE, $ZnCl_2$) for 20 h at 20 °C afforded a very satisfactory yield (31%) of crystalline **9** after chromatography, with identical proton NMR to that reported[7] [in particular, δ 4.82 (1 H, d, J = 8 Hz, 1′-H) and 5.02 (1 H, d, J = 3 Hz, 12-H)]; no 11-*epi* product[7] was observed. Mild hydrolysis of ester **9** (Na_2CO_3, aq MeOH)[11] afforded the free glucuronide **6** having consistent NMR data.[7] However,by LC−MS analysis this product was resolvable from the human DHA metabolite.

Scheme 2. Synthesis of DHA 12α,1′β-Glucuronide **5**[a]



[a] Reagents: (a) ref 15; (b) $BF_3{\cdot}Et_2O$; (c) Na_2CO_3, NaOH, aq MeOH.

It was therefore necessary to synthesize unambiguously the 12α,1′β-isomer **5**. We opted to use the imidate **15**[11] as the donor and DHA now as the acceptor, hoping to exploit the greater reactivity of the 12α-(equatorial) alcohol of **2**. When **2** and **15** were condensed using $BF_3{\cdot}Et_2O$ (0.5 equiv), warming from −10 to +10 °C over 2 h, an impure product was isolated in 6% yield which by NMR was largely the 12α,1′β-glucuronide ester **7**. This would have been sufficient for the preparation of **5**, but the synthesis was improved as follows. Using $ZnCl_2$ as catalyst,[12,13] brief reaction of **2** and **15** gave initially the orthoester **16** in 78% isolated yield. Further exposure of **16** to $ZnCl_2$ led to rearrangement, with **7** being produced in 11% yield [δ_H, inter alia, 2.40 (2 H, m, including 11-H), 4.10 (1 H, m, 5′-H), 4.83 (1 H, d, J = 9 Hz, 12-H) and 5.10 (2 H, m, 1′-H + 2′-H)], along with much degradation leading in particular to **12**. Hydrolysis of **7** led to the desired free glucuronide **5**, which on LC−MS analysis coeluted with the human glucuronide metabolite of DHA. Glucuronidation of DHA in vivo is evidently a highly stereospecific reaction since β-DHA administered as an ester prodrug (namely sodium artesunate, the succinate half-ester of DHA), which would epimerize rapidly following its deesterification, is excreted only as **5**.[4]

The tri-*O*-isobutyryl imidate **17**[13,14,15] shows improved stability and reduced transacylation compared to **15**, and here too it proved the reagent of choice (Scheme 2). Thus reaction of **2** and **17** (1.1 equiv) in DCE with $BF_3{\cdot}Et_2O$ (0.5 equiv) for 1 h at −10 to −5 °C gave complete reaction of **2** with noticeably less of the DHA degradation products **11** and **12** than seen when using **15**. By chromatography, the 12α,1′β-glucuronide ester **18** was isolated in excellent purity and 32% yield; further elution gave the 12β,1′β-glucuronide ester **19**

(15%). Both new esters **18** and **19** gave microanalytically pure material on recrystallization. The slower hydrolysis of the isobutyrates is not a problem, and **5** is now accessible in substantial amounts for biological evaluation.

The 12α-benzoate **14** also proved valuable in the synthesis of 12*β*-allyl-12-deoxo-DHA (**20**), a versatile synthetic intermediate which has been made from DHA (**2**) itself or from 12-deoxofluoro-DHA.[16,17] We found that $ZnCl_2$-catalyzed reaction of **14** with allyltrimethylsilane afforded **20** in excellent yield (80%) with very little contamination by degradation products: anhydro-DHA (**11**) in particular is difficult to separate from **20**. Full details will be described in a forthcoming publication.

In conclusion, we have confirmed the structure of the human DHA glucuronide metabolite as **5**, demonstrated a viable synthesis of this substance in substantial amounts, and shown the 12α-benzoate **14** to be a useful synthetic intermediate.

Experimental Section

General. Ether refers to diethyl ether. Organic extracts were finally washed with saturated brine and dried over anhydrous sodium sulfate prior to rotary evaporation at below 40 °C. Analytical TLC was performed on aluminum-backed Merck kieselgel 60 plates; Merck silica gel 60 (art. 7729) was used for preparative chromatography. Artemisinin derivatives were conveniently visualized using anisaldehyde. Melting points were determined on a Kofler block and are uncorrected. NMR spectra were measured on a Varian Inova instrument at 300 MHz (V) or on a Bruker AC Spectrospin instrument at 250 MHz (B) except where stated, using a deuterium lock on $CDCl_3$ solutions except where noted; δ values are δ_H. Mass spectra were recorded on a Kratos MS 25 instrument working in the chemical ionization (CI) or fast-atom bombardment (FAB) mode, or on a Waters ZMD instrument operating in the electrospray (ES) mode. LC−MS analyses were performed with a 5-μL C_8 column linked to the ES source of a Micromass Quattro II mass spectrometer. Analytes were eluted with a gradient of acetonitrile (20−35% over 15 min, 35−70% over 10 min) in ammonium acetate (0.1 M, pH 6.9) at 0.9 mL/min.

The systematic name of **1** is [3*R*-(3α,5α*β*,6*β*,8α*β*,9α,12*β*,12α-*R**)]-octahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one; the trivial name artemisinin is used here and dihydroartemisinin (DHA) for **2**, and the numbering system regards the lactol carbon of **2** as position 12.

Dihydroartemisinin 12α-Benzoate (14). Benzoyl chloride (0.49 cm^3, 0.59 g, 4.2 mmol) was added to DHA **(2)** (1.12 g, 4.0 mmol) in dichloromethane (12 cm^3) and pyridine (2 cm^3) with stirring at 0 °C. The temperature was allowed to rise to 20 °C; after stirring for 16 h, the mixture was quenched with 7% aq citric acid and extracted twice with ethyl acetate (EtOAc), then the total organic phase was washed with 7% aq citric acid (2×), satd aq $NaHCO_3$, water and evaporated to a clear foam (1.61 g) which was triturated with isohexane and a few drops of ether. Crystals of highly pure product **14** (1.07 g) separated; chromatography of the mother liquors gave further product of equal purity (in all 1.30 g, 83%): mp 111−112 °C (from EtOAc−isohexane); *m/z* 406.2236, $C_{22}H_{28}O_6NH_4$ requires MNH_4^+, 406.2229; δ (V), inter alia, 0.94, 1.03 (6 H, 2 d, 2×*CH*$_3$ CH), 2.44 (1 H, m), 2.78 (1 H, m, 11-H), 5.57 (1 H, s, 5-H), 6.06 (1 H, d, J = 10 Hz, 12-H), 7.49 (2 H, m, ArH), 7.61 (1 H, m, ArH) and 8.16 (2 H, approximately d, ArH); *m/z* (CI) 406 (MNH_4^+, 30%). Anal. ($C_{22}H_{28}O_6$) C,H.

Methyl 1-(Dihydroartemisinin-12*β*-yl)-2,3,4-tri-*O*-acetyl-*β*-D-glucopyranuronate (9). $ZnCl_2$(0.1 g, 0.74 mmol) was stirred with freshly activated 4A molecular sieves in DCE (4 cm^3) under argon at 20 °C for 1 h.The 1-hydroxy sugar **10** (1.33 g, 4 mmol) and the benzoate **14** (0.78 g, 2 mmol) were added and stirring continued for 16 h. Water was added and the mixture extracted with EtOAc (2×), then the combined extracts were washed with satd aq $NaHCO_3$ (2×),water and evaporated to a crude product (1.73 g) which was chromatographed, eluting with 20−50% EtOAc−isohexane. Appropriate fractions were evaporated to give the conjugate **9** (0.38 g, 32%): mp 146−148 °C (from EtOAc−isohexane) (lit.[7] mp 151 °C); δ (V), inter alia, 0.87, 0.97 (6 H, 2 d, 2×*CH*$_3$ CH), 2.00−2.10 (9 H, 3 s, 3×CH_3CO), 2.63 (1 H, m, 11-H), 3.77 (3 H, s, CH_3O), 4.16 (1 H, d, 5′-H), 4.82 (1 H, d, J = 8 Hz, 1′-H), 5.02 (1 H, d, J = 3 Hz, 12-H) and 5.62 (1 H, s, 5-H). Anal. ($C_{28}H_{40}O_{14}$) C,H. This was consistent with the published[7] NMR data: in addition, irradiation of the δ 2.63 multiplet caused both the δ 0.87 and 5.02 signals to collapse to singlets.

1-(Dihydroartemisinin-12*β*-yl)-*β*-D-glucopyranuronic Acid (6). A solution of sodium carbonate (0.045 g, 0.425 mmol) in water (1 cm^3) was added to the ester **9** (0.080 g, 0.133 mmol) in MeOH (3 cm^3) with stirring at 0 °C. The temperature was allowed to rise gradually to 20 °C. After 4 h, when reaction appeared complete by TLC, glacial AcOH was added to pH 6.0 and the solution was evaporated to dryness, then azeotroped with ethanol (3 × 5 cm^3). Trituration of the residue with ethanol−ether gave a hygroscopic solid which was filtered, washed sequentially with 1:1 ethanol−ether and ether, and dried to give the glucuronide **6**[7] as its Na salt (0.036 g, 56%); residual sodium acetate could be removed by chromatography on reverse-phase silica (Lichroprep): δ (V, in D_2O), inter alia, 0.76, 0.83 (6 H, 2 d, 2×*CH*$_3$ CH), 1.24 (3 H, s, CH_3C), 2.34 (1 H, m, 11-H), 3.16, 3.32 (3 H, 2 m, 2′-H + 3′-H + 4′-H), 3.57 (1 H, m, 5′-H), 4.36 (1 H, d, 1′-H), 4.90 (1 H, d, 12-H) and 5.61 (1 H, s, 5-H).

Methyl 1-(Dihydroartemisinin-12α-yl)-2,3,4-tri-*O*-acetyl-*β*-D-glucopyranuronate (7). Zinc chloride (0.136 g, 1 mmol) was added at −15 °C to a solution of imidate **1** (0.72 g, 1.5 mmol) and DHA **(2)** (0.213 g, 0.75 mmol) in DCE (5 cm^3) which had previously been stirred over freshly activated 4A molecular sieves for 0.75 h. Stirring was continued and the temperature allowed to rise to 10 °C over 4 h; then the reaction was worked up as described for **9** to give a clear foam which was purified by chromatography, eluting with 20 to 40% EtOAc−isohexane. Appropriate fractions were evaporated to give a product (0.352 g, 78%) whose proton NMR was consistent with the orthoester **16**: δ (220 MHz), inter alia, 1.85 (3 H, s, CH_3CO_3), 4.60 (1 H, dd, 2′-H), 4.75 (1 H, d, 12-H) and 5.80 (1 H, d, 1′-H).[18] This intermediate was redissolved in DCE (2 cm^3) and stirred at 0 °C with zinc chloride (0.068 g, 0.5 mmol) and freshly activated 4A molecular sieves under argon. The temperature was kept in the range 0−10 °C and after 4 h, when no **16** remained by TLC, the reaction was worked up as for **9**. The crude product (0.345 g) was chromatographed using from 25−40% EtOAc−isohexane. Appropriate fractions were evaporated to give the conjugate **7**[7] (0.038 g, 11%) as a white solid: δ (V), inter alia, 0.92, 0.98 (6 H, 2 d, 2×*CH*$_3$ CH), 2.40 (2 H, m, includes 11-H), 4.10 (1 H, m, 5′-H), 4.83 (1 H, d, J = 9 Hz, 12-H) and 5.10 (2 H, m, 1′-H + 2′-H), consistent with the published data. Irradiation of the multiplet at δ 2.40 caused the doublets at δ 0.92 and 4.82 both to collapse to singlets.

1-(Dihydroartemisinin-12*β*-yl)-*β*-D-glucopyranuronic Acid (5). The ester **7** (0.060 g, 0.10 mmol) was hydrolyzed in aq MeOH using sodium carbonate (0.035 g, 0.33 mmol) as described for **9**. Purification of crude product on Lichroprep reverse-phase silica, eluting with increasing percentages of MeOH in water (from 0 to 80%), afforded the sodium salt of the product **5** (0.021 g, 44%): δ (V, in D_2O), inter alia, 0.75−0.82 (6 H, 2 d, 2×*CH*$_3$ CH), 2.05−2.20 (2 H, m, includes 11-H), 3.14 and 3.38 (3 H, m, 2′-H + 3′-H + 4′-H), 3.57 (1 H, d, 5′-H), 4.65 (1 H, d, 1′-H) and 4.90 (1 H, d, 12-H); *m/z* (ES +ve mode) 483 (MNa^+, 100%); (−ve mode) 459 (M − H^+ for free acid, 100%).

Later column fractions afforded further solid (0.012 g, 25%) whose NMR was consistent with the free acid form of **5**, in particular the signal at δ 3.85 (1 H, d, 5′-H).

Methyl 1-(Dihydroartemisinin-12α-yl)-2,3,4-tri-*O*-isobutyryl-*β*-D-glucopyranuronate (18). $BF_3{\cdot}Et_2O$ (0.060 cm^3, 0.5 mmol) was added dropwise at −10 °C to a solution of the

triisobutyryl imidate **(17)** (0.56 g, 1 mmol) and DHA **(2)** (0.26 g, 0.9 mmol) in DCE (5 cm^3) which had previously been stirred over freshly activated 4A molecular sieves under argon at 20 °C for 1 h. The temperature was kept in the range −3 to −10 °C for 1 h, then the reaction was worked up as described for **9**. The combined organic extracts were evaporated to an oil (0.80 g) which was chromatographed by eluting with a gradient of 10−30% EtOAc in isohexane. After discarding high R_f material, the first major product fractions were pooled, evaporated and recrystallized from EtOAc−isohexane to give the conjugate **18** as a white solid (0.202 g, 32%): mp 163−165 °C; δ (B), inter alia, 0.90, 0.96 (6 H, 2 d, 2×CH_3 CH), 1.39 (3 H, s, CH_3C), 2.35 (2 H, m, includes 11-H), 2.50−2.60 (3 H, m, 3×CH Me_2), 3.75 (3 H, s, CH_3O), 4.08 (1 H, d, 5′-H), 4.79 (1 H, d, J = 9.5 Hz, 12-H), 5.12 (2 H, m, 1′-H + 2′-H), 5.20−5.40 (2 H, m, 3′-H + 4′-H) and 5.36 (1 H, s, 5-H); *m*/*z* (ES +ve mode) 707 (MNa^+, 100%). Anal. ($C_{34}H_{52}O_{14}$) C,H. The near-coincidence of the 1′- and 2′-signals in the proton NMR is unusual in glucuronide esters (cf. **7**); a more typical pattern is observed on a $(CD_3)_2CO$ solution of **18**; δ (B), inter alia, 4.83 (1 H, d, J = 9.5 Hz, 12-H), 4.99 (1 h, dd, 2′-H) and 5.19 (1 H, d, J = 8 Hz, 1′-H). Later-eluting fractions were pooled and evaporated to give **methyl 1-(dihydroartemisinin-12β-yl)-2,3,4-tri-*O*-isobutyryl-β-D-glucopyranuronate** (**19**) which was recrystallized from EtOAc−isohexane (0.095 g, 15%): mp 126−128 °C (from aq Pr^iOH); δ (B), inter alia, 0.94, 0.96 (6 H, 2 d, 2×CH_3 CH), 1.42 (3 H, s, 15-CH_3), 2.64 (1 H, m, 11-H), 3.73 (3 H, s, CH_3O), 4.18 (1 H, d, 5′-H), 4.83 (1 H, d, J = 8 Hz, 1′-H), 4.99 (1 H, d, J = 3 Hz, 12-H) and 5.63 (1 H, s, 5-H); *m*/*z* (FAB +ve mode, 3-nitrobenzyl alcohol) 707 (MNa^+, 100%). Anal. ($C_{34}H_{52}O_{14}$) C,H.

Characterization of Human DHA Glucuronide Metabolite. Urine samples (2−4 h collections) were obtained from 17 adult male patients administered artesunate (sodium β-DHA hemisuccinate) intravenously (120 mg) for uncomplicated falciparum malaria.[19] The DHA glucuronide found in all of these samples by LC−MS corresponded to **5**; it was chromatographically resolvable from **6** (t_R 13.7 min) and cochromatographed with **5** (t_R 14.2 min). The metabolite and authentic standards yielded identical ES spectra: *m*/*z* 478 (MNH_4^+), 267 (478 − NH_3 − dehydroglucuronic acid − H_2O, 100%), 249, 231, 221, 203, 163.

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