STRUCTURE ELUCIDATION AND SYNTHESIS OF A METABOLITE OF ANTIINFLAMMATORY DRUG DUP 697

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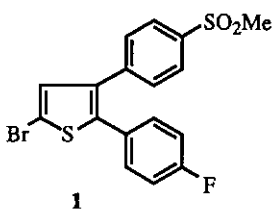
Abstract - Structure of the *O*-glucuronide (**2**), one of the metabolites of antiinflammatory drug DUP 697 (**1**), has been elucidated on the basis of spectral data and a total synthesis of it has been accomplished. Since the synthetic route to **2** is an unambiguous one, completion of the synthesis established the assigned structure.

DUP 697[1] [5-bromo-2-(4-fluorophenyl)-3-(4-methanesulfonylphenyl)thiophene] (**1**) has been shown to be an orally active cyclooxygenase II inhibitor[2] which is expected to have a potent antiinflammatory activity without a remarkable ulcerogenic action. This drug has a unique diarylthiophene skeleton which is a quite different structural feature from the conventional nonsteroidal antiinflammatory drugs. During the course of our project concerning drug disposition[3] of DUP 697, we have searched its metabolites in the bile of rat and isolated the *O*-glucuronide (**2**). The structure of the metabolite has been deduced mainly on the basis of ^{1}H-nmr and mass spectral studies. Because not only of a need for biological evaluation but also of a confirmation of the structure, there is a need for an efficient and unambiguous synthetic route to **2**. In this paper, we report a full account of the structure elucidation and the total synthesis, which established the assigned structure, of the *O*-glucuronide (**2**). (Figure 1)



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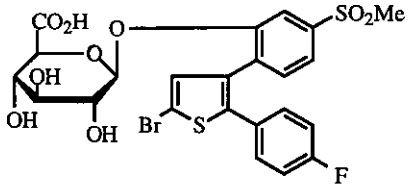

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Figure 1

Structre of the Glucuronide (2)

A very small amount (480 μg) of the glucuronide (**2**) was isolated as an oily stuff from the acidic ethyl acetate extract of the bile (1250 ml) of rat by a combination of Silica-gel $60F_{254}$ and RP-18 preparative thin layer chromatographies. The structure of the metabolite was assumed to be the *O*-glucuronide of the phenolic analog of **1** by the mass spectral data[4] [positive FABms: *m/z* 602, 604 (M^+) and 425, 427 (M - glucuronide)$^+$; negative FABms: *m/z* 601, 603 $(M-H)^-$]. Observations of the NOEs between the methyl protons of SO_2Me at 4' position and the *ortho*-aromatic protons (3'-H and 5'-H) and of the diagnostic coupling patterns of 3', 5' and 6'-H (Table 1) revealed that the sugar moiety would be connected at the C2' position. The configuration of the anomeric center (C1''') of the sugar was deduced to be β by a characteristic ^{1}H-nmr signal at δ 5.23 as a doublet with *J*=7.3 Hz. Based on the above-mentioned evidences and the ^{1}H-nmr data (Table 1), the structure of **2** was elucidated as shown in Figure 2.

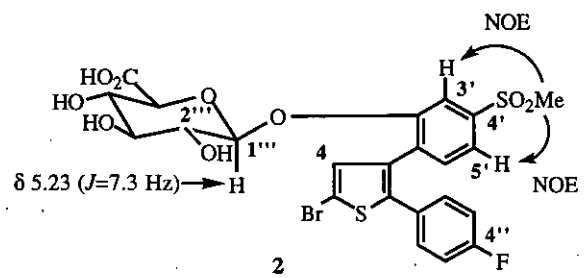

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Figure 2

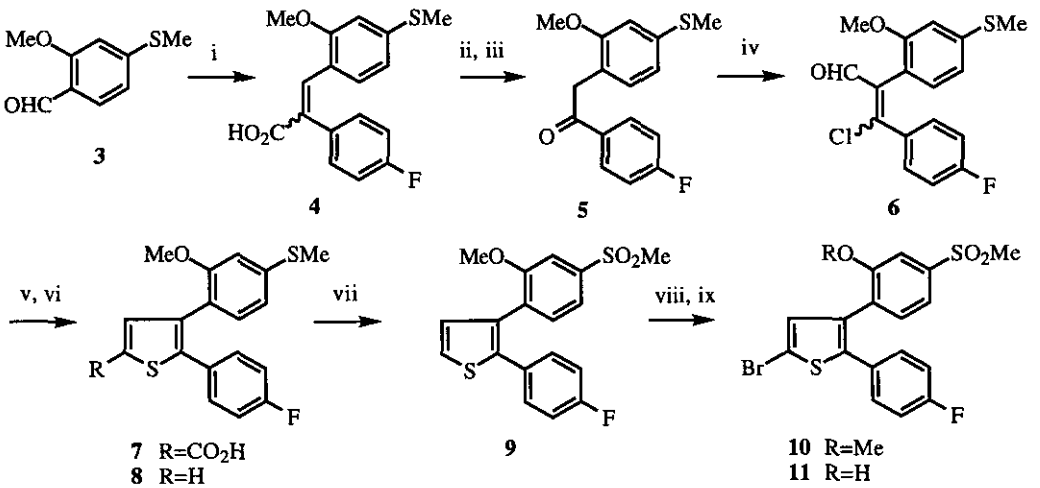
Table 1. ^{1}H-Nmr Data for **2**

Proton	δ in CD3OD
4-H	7.33 (1H, s)
3'-H	7.75 (1H, d, *J*=1.7 Hz)
4'-SO2Me	3.13 (3H, s)
5'-H	7.46 (1H, dd, *J*=8.0 and 1.7 Hz)
6'-H	7.17 (1H, d, *J*=8.0 Hz)
2"and 6"-H	7.19-7.26 (2H, m)
3"and 5"-H	6.95-7.03 (2H, m)
1'''-H	5.23 (1H, d, *J*=7.3 Hz)
2'''-4'''-H	3.37-3.70 (3H, m)
5'''-H	3.98 (1H, d, *J*=9.2 Hz)

Synthesis of the Aglycone (11) and the Glucuronide (2)

According to a procedure for the synthesis[5] of DUP 697 (**1**), the phenolic aglycone (**11**) was prepared by the route shown in Scheme 1. 2-Methoxy-4-methylthiobenzaldehyde (**3**),[6] which was derived from a commercially available 2-methoxy-4-methylthiobenzoic acid *via* a three-step sequence, was condensed with

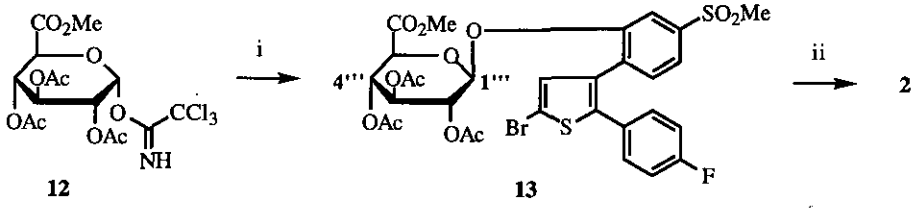
4-fluorophenylacetic acid in the presence of acetic anhydride and triethylamine to give the cinnamic acid derivative (**4**) in 73% yield. Conversion of the α,β-unsaturated carboxylic moiety in **4** to the ketone (**5**) was accomplished in 85% yield by the Shioiri-Curtius rearrangement[7] followed by treatment of the resulting *enamine with aqueous sulfuric acid in methanol*. Vilsmeier-Haack reaction[8] of **5** with dimethylformamide and phosphorous chloride provided an inseparable stereoisomeric mixture of the chloro aldehyde (**6**), which was then treated with thioglycolic acid and triethylamine in 3-picoline at room temperature to 140 °C[9] to afford an inseparable mixture of the requisite thiophene (**8**) and the corresponding carboxylic acid (**7**) in a ratio of 5:1 (from ^{1}Hnmr). The crude mixture in quinoline was immediately heated at 240 °C for 4.5 h in the presence of copper powder to provide **8** in 62% overall yield from **6** after chromatographic purification. Oxidation of the sulfide moiety in **8** with sodium perborate[10] produced 82% yield of the corresponding *sulfone* (**9**), which was then treated with bromine to provide the bromide (**10**) in 89% yield. Cleavage of the methyl ether in **10** was achieved by treatment with boron tribromide to give the requisite phenolic aglycone (**11**) in 63% yield. The tlc behavior of our synthetic compound was identical with that of a sample obtained by the enzymatic hydrolysis of the metabolite (**2**) with β-glucuronidase.[4] (Scheme 1)



Scheme 1. ***Reagents and Conditions***: i, 4-fluorophenylacetic acid, Ac_2O, Et_3N, room temperature; *ii*, $(PhO)_2PON_3$, Et_3N, CH_2Cl_2, *room temperature*; *iii*, *aq.* H_2SO_4, *MeOH, room temperature*; iv, DMF, $POCl_3$, $CHCl_3$, 60 °C; v, $HSCH_2CO_2H$, Et_3N, 3-picoline, room temperature → 140 °C; vi, Cu, quinoline, 240 °C; vii, $NaBO_3$•$4H_2O$, AcOH, room temperature; viii, Br_2, CH_2Cl_2, 0 °C; ix, BBr_3, CH_2Cl_2, -78 °C.

With the aglycone (**11**) in hand, we next turned our attention to a diastereoselective β-glucuronidation, which is a final task for the completion of the synthesis. Attempted conversions of **11** to the glucuronide employing a standard Koenigs-Knorr[11] method as well as the procedures using $SnCl_4$[12] or TMSOTf[13] were

either unsuccessful or met with only limited success. The problem was solved by using the imidate method developed by Schmidt.[14] Thus, treatment of the phenol (**11**) with the protected imidate (**12**)[13] in the presence of boron trifluoride etherate and 4A molecular sieves[15] produced the glucuronide (**13**) as a single product in 33% yield. At this stage, the stereochemistry at an anomeric center (C1''') could not be determined by ^{1}Hnmr spectra, because four methine protons (1'''-4'''-H) on the sugar moiety were observed in a narrow range (δ 5.06-5.38) as a multiplet. However, it was deduced from the literature precedents[14] that the requisite β-isomer would be obtained. Finally, alkaline hydrolysis[10] of **13** produced the glucuronide (**2**), whose ^{1}Hnmr spectra and the tlc behavior were completely identical with those of the material isolated from the bile of rat, and the assigned structure for **2** could be established. (Scheme 2)



Scheme 2. ***Reagents and Conditions*****:**
i, **11**, BF_3•OEt_2, 4A MS, CH_2Cl_2, -25 °C → -10 °C; ii, aq. NaOH, acetone, room temperature

In conclusion, we have described the structure elucidation of the *O*-glucuronide (**2**), one of the metabolites of an antiinflammatory drug DUP 697, and a total synthesis of it. The accomplishment of the synthesis, which is efficient and unambiguous, has enabled us to carry out the biological evaluation and to confirm the assigned structure of **2**.

EXPERIMENTAL SECTION

Melting points were determined by a Yamato mp-2 apparatus and are uncorrected. Ir spectra were recorded on a Hitachi 270-30 spectrophotometer. ^{1}HNmr spectra were recorded at 270 MHz on a JEOL JNM-GX270 and at 400 MHz on a JEOL GSX-400 spectrometer in deuteriochloroform solutions or deuteriomethanol solutions with tetramethylsilane as an internal standard. Chemical shifts are reported in ppm (from TMS). When peak multiplicities are reported, the following abbreviations are used : s, singlet; d, doublet; t, triplet; m, multiplet. Ordinary mass spectra was measured with Hitachi M-80A, JEOL JMS-DX303 and JEOL JMS-700 mass spectrometers. Optical rotations were determined on a JASCO DIP-4 polarimeter. Tlc was carried out with E. Merck silica gel GOF-254 (0.25 mm thickness) precoated tlc plates. Column chromatography was carried out with silica gel (Kieselgel 60, 70 - 230 mesh, E. Merck). All reactions were

run under an atmosphere of argon. Solvents were freshly distilled prior to use: dichloromethane (CH_2Cl_2) and chloroform ($CHCl_3$) were distilled from phosphorus pentoxide and kept over 4A molecular sieves: *N, N*-dimethylformamide (DMF) was distilled under reduced pressure after stirring with calcium hydride for 14-15 h. Unless otherwise noted, all reaction mixture were dried, after workup, over anhydrous magnesium sulfate.

Isolation of the Glucuronide (2). A group of 24 male Sprague-Dawley rats (weight 220-300 g, age 7-8 weeks), fasted for 12 h, was anaesthetized with ether and the bile ducts were cannulated. DUP 697 (300 mg / kg) was administered orally and animals were housed in appropriate metabolic cage with free access to water and food. The bile was collected for about 72 h after administration. The collected bile (1250 ml) was adjusted to pH 3 with 1N HCl and extracted with ethyl acetate (1 l x 3). The extracts were evaporated to dryness under reduced pressure and the residue was purified by preparative tlc (ptlc)(silica gel $60F_{254}$, $CHCl_3$-MeOH-H_2O, 67:33:5, v/v), using MeOH as extraction solvent to give the fractions I-V. Fraction III obtained was further purified successively by ptlc (silica gel $60F_{254}$, $CHCl_3$-MeOH-H_2O, 67:33:5, v/v), ptlc (silica gel $60F_{254}$, $CHCl_3$-MeOH-AcOH, 65:33:1, v/v), and ptlc (RP-18, MeOH-H_2O, 7:3, v/v). Final extracts (AcOEt solution) were concentrated under reduced pressure to give the oily glucuronide (**2**) (480 μg). ^{1}H-Nmr (270 MHz, CD_3OD) δ 3.13 (3H, s, CH_3SO_2), 3.37-3.70 (3H, m, 2'''-4'''-H), 3.98 (1H, d, *J*=9.2 Hz, 5'''-H), 5.23 (1H, d, *J*=7.3 Hz, 1'''-H), 6.95-7.03 (2H, m, 3'', 5''-H), 7.17 (1H, d, *J*=8.0 Hz, 6'-H), 7.19-7.26 (2H, m, 2'', 6''-H), 7.33 (1H, s, thiophene 4-H), 7.46 (1H, dd, *J*=8.0 and 1.7 Hz, 5'-H), 7.75 (1H, d, *J*=1.7 Hz, 3'-H); positive FABms *m/z* 602 and 604 (M^+); negative FABms *m/z* 601 and 603 $(M-H)^-$.

2-(4-Fluorophenyl)-3-(2-methoxy-4-methylthiophenyl)acrylic acid (4). 4-Fluorophenylacetic acid (30.3 g, 0.20 mol) was added to a stirred solution of 2-methoxy-4-(methylthio)benzaldehyde (**3**) (35.8 g, 0.20 mol), triethylamine (60.5 ml, 0.43 mol) and acetic anhydride (62 ml, 0.66 mol) at 0 °C. After being stirred at room temperature for 19 h, the reaction mixture was warmed to 60 °C. Water (200 ml) was added dropwise and the mixture was allowed to cool to room tempeature. The resulting precipitates were collected by filtration and washed with water. After being dried at 60 °C for 10 h, the product was recrystallized from benzene-hexane to provide **4** (45.4 g, 73 %) as pale yellow plates. mp 184-187 °C; ir (KBr) 1664 cm^{-1} (C=O); ^{1}H-nmr (270 MHz, $CDCl_3$) δ 2.44 (3H, s, CH_3S) 3.86 (3H, s, CH_3O), 6.47 (1H, dd, *J*=8.4 and 1.7 Hz, 5-H), 6.62 (1H, d, J=8.4 Hz, 6-H), 6.71 (1H, d, J=1.7 Hz, 3-H), 6.99-7.10 (2H, m, 3', 5'-H), 7.17-7.28 (2H, m, 2', 6'-H), 8.25 (1H, s, olefinic H); ms *m/z* 318 (M^+). Anal. Calcd for $C_{17}H_{15}O_3FS$: C, 64.13; H, 4.75. Found : C, 64.12; H, 4.77.

4-Fluorophenyl (2-methoxy-4-methylthio)benzyl ketone (5). Diphenylphosphoryl azide (39.1 g, 0.14 mol) was added dropwise to a stirred solution of **4** (43 g, 0.14 mol) and triethylamine (21 ml, 0.15 mol) in dry CH_2Cl_2 (300 ml) at 0 °C. After being stirred at room temperature for 24 h, MeOH (15 ml) and 15 % aqueous (aq.) H_2SO_4 (47 ml) were successively added dropwise at the same temperature to the resulting mixture and stirring was continued for 12 h. After addition of water, the mixture was extracted with CH_2Cl_2 and the extracts were washed with aq. 2N-NaOH (50 ml x 2) and brine and dried. Evaporation of the solvent followed by recrystallization from benzene-hexane gave the ketone (**5**) (34.6 g, 85 %) as a white powder. mp 89 - 91 °C; ir (KBr) 1666 cm^{-1} (C=O); ^{1}Hnmr (270 MHz, $CDCl_3$) δ 2.48 (3H, s, CH_3S) 3.78 (3H, s, CH_3O), 4.19 (2H, s, CH_2), 6.80 (1H, d, *J*=1.8 Hz, 3-H), 6.82 (1H, dd, *J*=8.4 and 1.8 Hz, 5-H), 7.09 (1H, d, *J*=8.4 Hz, 6-H), 7.06-7.18 (2H, m, 3', 5'-H), 8.00-8.11 (2H, m, 2', 6'-H); ms *m/z* 290 (M^+). Anal. Calcd for $C_{16}H_{15}O_2FS$: C, 66.18; H, 5.21. Found: C, 66.02; H, 5.19.

2-(4-Fluorophenyl)-3-(2-methoxy-4-methylthiophenyl)thiophene (8). Phosphorus oxychloride (32 ml, 0.34 mol) was added dropwise to a stirred solution of **5** (31 g, 0.11 mol) and DMF (32 ml, 0.41 mol) in dry $CHCl_3$ (250 ml) at 0 °C. After being stirred at 60 °C for 12 h, the mixture was quenched by the addition of water and extracted with $CHCl_3$. The extracts were washed with saturated (sat.) aq. $NaHCO_3$ and brine and dried. Evaporation of the solvent gave the crude **6** (35.8 g, 100 %) as a light brown oil, which was used to the next reaction without further purification. Thioglycolic acid (13 g, 0.14 mol) and triethylamine (38 ml, 0.27 mol) were added successively to a suspension of crude **6** (35 g, 0.10 mol) in 3-picoline (130 ml) at 0 °C. After being stirred at room temperature for 1 h and at 140 °C for 2 h, the mixture was quenched by the addition of water and extracted with AcOEt. The extracts were washed successively with 5% aq. HCl, sat. aq. $NaHCO_3$ and brine and dried. Evaporation of the solvent gave the crude mixture of the carboxylic acid (**7**) and the thiophene (**8**). Copper powder (16 g) was then added to a suspension of the crude mixture of **7** and **8** (38.9 g) in quinoline (130 ml) at room temperature. After being stirred at 240 °C for 4.5 h, the mixture was filtered and the filtrate was taken up into AcOEt. The organic phase was successively washed with 5 % aq. HCl, water, sat. aq. $NaHCO_3$ and brine and dried. Evaporation of the solvent followed by chromatography on silica gel ($CHCl_3$-hexane, 1:1, v/v) gave **8** (21.6 g, 62 %) as colorless needles, mp 81- 82 °C (from n-hexane). ^{1}HNmr (270 MHz, $CDCl_3$) δ 2.50 (3H, s, CH_3S), 3.57 (3H, s, CH_3O), 6.76 (1H, dd, *J*=8.6 and 1.7 Hz, 5-H), 6.78 (1H, d, *J*=1.7 Hz, 3-H), 6.87-6.98 (2H, m, 3', 5'-H), 7.04 (1H, d, *J*=8.6 Hz, 6-H), 7.10 (1H, d, *J*=5.3 Hz, thiophene

4-H), 7.17-7.27 (2H, m, 2', 6'-H), 7.29 (1H, d, *J*=5.3 Hz, thiophene 5-H); ms *m/z* 330 (M^+). Anal. Calcd for $C_{18}H_{15}OFS_2$: C, 65.43; H, 4.58. Found: C, 65.76; H,4.58.

2-(4-Fluorophenyl)-3-(2-methoxy-4-methanesulfonylphenyl)thiophene (9). Sodium perborate tetrahydrate ($NaBO_3 \cdot 4H_2O$) (22.4 g, 0.15 mol) was added in portions to a stirred solution of **8** (19.2 g, 0.06 mol) in acetic acid (250 ml) at room temperature and stirring was continued for 3 h at the same temperature. After addition of water, the resulting precipitates were collected by filtration and washed with water. After being dried at 75 °C for 10 h, the product was recrystallized from ethyl acetate-hexane to provide **9** (17.2 g, 82 %) as a white powder, mp 132-134 °C. ^{1}HNmr (270 MHz, $CDCl_3$) δ 3.10 (3H, s, CH_3SO_2), 3.66 (3H, s, CH_3O), 6.89-7.03 (2H, m, 3', 5'-H), 7.12 (1H, d, *J*=5.3 Hz, thiophene 4-H), 7.13-7.24 (2H, m, 2', 6'-H), 7.31 (1H, d, *J*=7.9 Hz, 6-H), 7.35 (1H, d, *J*=5.3 Hz, thiophene 5-H), 7.41 (1H, d, *J*=1.7 Hz, 3-H), 7.46 (1H, dd, *J*=7.9 and 1.7 Hz, 5-H); ms *m/z* 362 (M^+). Anal. Calcd for $C_{18}H_{15}O_3FS_2$: C, 59.65; H, 4.17. Found: C, 59.86; H,4.13.

5-Bromo-2-(4-fluorophenyl)-3-(2-methoxy-4-methanesulfonylphenyl)thiophene (10). A solution of Br_2 (930 mg, 5.8 mmol) in dry CH_2Cl_2 (3 ml) was added dropwise to a stirred solution of **9** (2.0 g, 5.6 mmol) in dry CH_2Cl_2 (25 ml) at 0 °C. After being stirred for 0.5 h at the same temperature, the mixture was quenched by the addition of 10 % aq. $Na_2S_2O_3$ and extracted with CH_2Cl_2. The extracts were washed with brine and dried. Evaporation of the solvent followed by recrystallization from ethyl acetate-hexane gave the bromide (**10**) (2.0 g, 83%) as a white powder, mp 183-185 °C. ^{1}HNmr (270 MHz, $CDCl_3$) δ 3.09 (3H, s, CH_3SO_2), 3.69 (3H, s, CH_3O), 6.90-7.01 (2H, m, 3', 5'-H), 7.08 (1H, s, thiophene 4-H), 7.09-7.16 (2H, m, 2', 6'-H), 7.25 (1H, d, *J*=7.9 Hz, 6-H), 7.40 (1H, d, *J*=1.7 Hz, 3-H), 7.44 (1H, dd, *J*=7.9 and 1.7 Hz, 5-H); ms *m/z* 440 and 442 (M^+). Anal. Calcd for $C_{18}H_{14}O_3BrFS_2$: C, 48.98; H, 3.20. Found: C, 49.23; H, 3.19.

5-Bromo-2-(4-fluorophenyl)-3-(2-hydroxy-4-methanesulfonylphenyl)thiophene (11). Boron tribromide (1.0 M in CH_2Cl_2, 8.5 ml, 8.5 mmol) was added dropwise to a stirred solution of **10** (1.5 g, 3.4 mmol) in dry CH_2Cl_2 (2 5ml) at -78 °C. The mixture was allowed to warm to room temperature under stirring for 10 h. After addition of sat. aq. $NaHCO_3$, the resulting precipitates were collected by filtration and washed with water. After being dried at 75 °C for 10 h, the product was recrystallized from methanol to provide **11** (910 mg, 63 %) as a white powder. mp 235-237 °C; ir (KBr) 3448 cm^{-1} (OH);

^{1}Hnmr (270 MHz, $CDCl_3$) δ 3.08 (3H, s, CH_3SO_2); 5.72 (1H, s, OH, D_2O disappeared), 6.93-7.02 (2H, m, 3', 5'-H), 7.08 (1H, s, thiophene 4-H), 7.12-7.21 (2H, m, 2', 6'-H), 7.29 (1H, d, *J*=7.9 Hz, 6-H), 7.45 (1H, dd, *J*=7.9 and 2.0 Hz, 5-H), 7.46 (1H, d, *J*=2.0 Hz, 3-H); ms *m/z* 426 and 428 (M^+). Anal. Calcd for $C_{17}H_{12}O_3BrFS_2$: C, 47.78; H, 2.83. Found: C, 47.92; H, 2.80.

Enzymatic Hydrolysis of the Glucuronide (2) with β-Glucuronidase. β-Glucuronidase (5000 units, Sigma Co.) was added to a solution of the glucuronide (**2**) (100 μg, 0.1 μmol) in a mixture of EtOH (50 μl) and 0.2N AcONa buffer (pH 5)(1 ml). The resulting mixture was incubated at 37 °C for 16 h, then evaporated to give a residue, which was identical with the sample **11**, which was obtained by synthesis as mentioned above, by comparison of the tlc.

5-Bromo-2-(4-fluorophenyl)-3-[2-*O*-(2,3,4-tri-*O*-acetyl-β-D-glucuronopyranosyl)-4-methanesulfonylphenyl]thiophene methyl ester (13). Molecular sieves 4A (300 mg) was added to a solution of **12** (506 mg, 1.1 mmol) and phenol (**11**) (300 mg, 0.7 mmol) in dry CH_2Cl_2 (30 ml) at room temperature. To the stirred mixture, a solution of Et_2O•BF_3 (0.04 ml, 0.33 mmol) in dry CH_2Cl_2 (3 ml) was added dropwise at -25 °C and the resulting mixture was allowed to warm to -10 °C under stirring for 2 h. After filtration through a pad of Celite, the filtrate was washed with sat. aq. $NaHCO_3$ and brine and dried. The solvent was evaporated to give a residue which was chromatographed on silica gel ($CHCl_3$-methanol, 30:1, v/v) to afford **13** (170 mg, 33 %) as a white powder, mp 150-151 °C (from EtOH-Et_2O). $[\alpha]_D$ - 24.8 ° (c=0.58, MeOH); ir (KBr) 1762 cm^{-1} (C=O); ^{1}H-nmr (270 MHz, $CDCl_3$) δ 1.88, 2.01, 2.04 (each 3H, s, OAc x 3), 3.08 (3H, s, CH_3SO_2), 3.75 (3H, s, CO_2CH_3), 4.22 (1H, d, *J*=9.2 Hz, 5'''-H), 5.06-5.38 (4H, m, 1'''-4'''-H), 6.90-7.01 (2H, m, 3'',5''-H), 7.04 (1H, s, thiophene 4-H), 7.07-7.18 (2H, m, 2'',6''-H), 7.21 (1H, d, *J*=7.9 Hz, 6'-H), 7.53 (1H, dd, *J*=7.9 and 1.7 Hz, 5'-H), 7.71 (1H, d, *J*=1.7 Hz, 3'-H); ms *m/z* 742 and 744 (M^+). Anal. Calcd for $C_{30}H_{28}O_{12}BrFS_2$: C, 48.46; H, 3.80. Found: C, 48.65; H, 3.78.

5-Bromo-2-(4-fluorophenyl)-3-[2-*O*-(β-D-glucopyranuronosido)-4-methanesulfonylphenyl]thiophene (2). Aq. 1N NaOH (2.8 ml, 28 mmol) was added dropwise to a stirred solution of **13** (300 mg, 0.4 mmol) in acetone (12 ml) at 0 °C. After being stirried at room temperature for 1 h, the solvent was evaporated to give a residue which was chromatographed on Dowex 50W x 4 (H^+ form) (EtOH-H_2O, 7:3, v/v) to afford **2** (166 mg, 69 %) as colorless plates, mp 199-202 °C (from EtOH-H_2O). $[\alpha]_D$ - 33.5°(c=0.52, EtOH); ir (KBr) 3466 (OH), 1755 cm^{-1} (C=O); ^{1}H-nmr (270 MHz, CD_3OD) δ 3.13 (3H, s,

CH_3SO_2), 3.36-3.70 (3H, m, 2'''-4'''-H), 4.00 (1H, d, *J*=9.2 Hz, 5'''-H), 5.23 (1H, d, *J*=7.3 Hz, 1'''-H), 6.93-7.04 (2H, m, 3'', 5''-H), 7.18 (1H, d, *J*=8.3 Hz, 6'-H), 7.20-7.28 (2H, m, 2'', 6''-H), 7.33 (1H, s, thiophene 4-H), 7.47 (1H, dd, *J*=8.3 and 1.7 Hz, 5'-H), 7.75 (1H, d, *J*=1.7 Hz, 3'-H). Anal. Calcd for $C_{23}H_{20}O_9BrFS_2 \cdot H_2O$: C, 44.45; H, 3.57. Found: C, 44.44; H, 3.47.

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