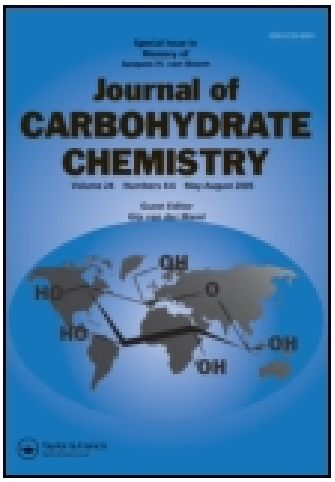

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lcar20

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Published online: 27 Feb 2008.

To cite this article: Barbara Werschkun , Karin Gorziza & Joachim Thiem (1999) Synthesis of β-Glucuronides of Estradiol, Ethynylestradiol and Estrone, Journal of Carbohydrate Chemistry, 18:6, 629-637, DOI: 10.1080/07328309908544025

To link to this article: http://dx.doi.org/10.1080/07328309908544025

J. CARBOHYDRATE CHEMISTRY, 18(6), 629–637 (1999)

SYNTHESIS OF β-GLUCURONIDES OF ESTRADIOL, ETHYNYLESTRADIOL AND ESTRONE

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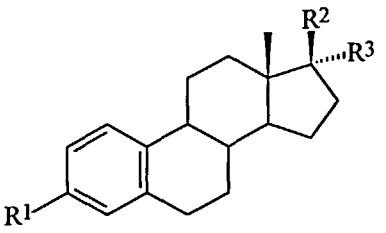
Received November 10, 1998 - Final Form April 7, 1999

ABSTRACT

Improved syntheses for the 3-β-D-glucuronides of the steroidal sex hormones 17β-estradiol, 17α-ethynylestradiol and estrone are reported employing boron trifluoride diethyl etherate catalysis with tetraacetylated glucuronic acid or the corresponding imidate.

INTRODUCTION

In 1971 Conrow and Bernstein published an improved Koenigs-Knorr synthesis of aryl glucuronides using cadmium carbonate as the acid acceptor to give the the 3-β-D-glucuronide of the naturally occurring estrogen, estrone.[1] Previously standard Koenigs-Knorr reactions using silver carbonate gave maximum yields of 10%,[2,3] and by employing unprotected 17β-estradiol only bisglucosiduronate (2%) was found.[2] Hadd *et al.* tried the $CdCO_3$ method with the synthetic component of many oral contraceptive agents, 17α-ethynylestradiol. Contrary to their expectation, they obtained more 17β-glucuronide (5%) than 3-linked glycoside and as the main product (7%) the 3,17-bisglucuronide.[4] Conrow and Bernstein avoided that problem by using the formate-protected 17β-estradiol to achieve 71% of the 3-glucuronidated steroid.[1]



	R1	R2	R3
3	OH	OH	H
4	OH	OAc	H
5	OH	=O	
6	OH	OH	C≡CH
7	OAc	OAc	C≡CH
8	OH	OAc	C≡CH

Scheme 1

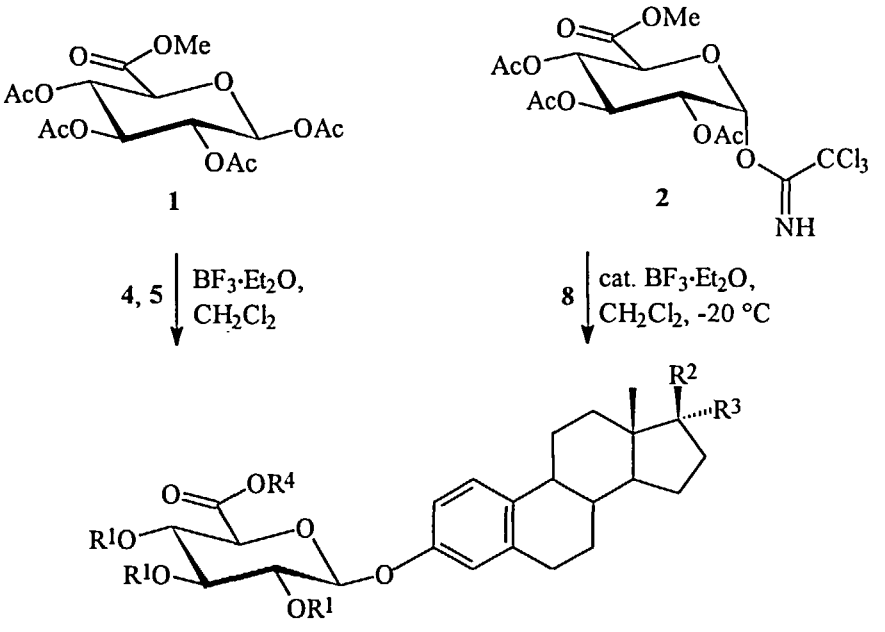
With regard to the particular biological and medical importance of steroidal estrogens and investigation into their glucuronic acid conjugates as significant metabolites a more convenient method for preparing glucuronides of estradiol and ethynylestradiol was required. Recently an alternative access was presented by the enzymatic synthesis of these conjugates on a preparative scale employing UDP-glucuronyl transferase.[5]

To improve the classical synthesis of aryl glycosides by Helferich *et al.*[6] we combined the findings of Bretschneider *et al.*,[7] who converted phenols and glucose pentaacetate into the corresponding aryl β-D-glucopyranosides using boron trifluoride in anisol as catalyst, with the imidate method utilizing $BF_3 \cdot Et_2O$.[8] Similary, the same procedure could be achieved to give morphine and coumarin glucuronide derivatives in good yields.[9,10]

RESULTS AND DISCUSSION

Starting from D-glucuronolactone the peracetylated glucuronic methyl ester **1** could be prepared as the crystalline β-anomer in one step.[11] Conversion of the acetate by a standard method gave the glycosyl bromide and successive treatment with silver(I) oxide and trichloroacetonitrile led to the well-known α-imidate **2**.[8,12]

The 17β-hydroxyl group of estradiol **3** was selectively protected by transesterification with an excess of methyl acetate in cyclohexane to give 17-acetate **4**.[13] For selective protection of the propargyl compound **6** two steps were necessary: First both OH-groups were acetylated to give **7**, then with potassium carbonate in methanol the phenolic acetyl group was removed resulting in **8** with 66% yield (see Scheme 1).



	R1	R2	R3	R4	yield
9	Ac	OAc	H	Me	42%
11	Ac	=O		Me	42%
13	Ac	OAc	C≡CH	Me	61%
10	H	OH	H	H	84%
12	H	=O		H	94%
14	H	OH	C≡CH	H	74%

NaOH, MeOH

Scheme 2

For glucuronation, facile reaction conditions employing equimolar amounts of boron trifluoride etherate in anhydrous dichloromethane were tested. By this method the 3-β-D-glucuronide triacetate methyl ester of estradiol and estrone (**9** and **11**) could be obtained after crystallisation in 42% yield. Convincing yields for such glucuronic acid conjugates were achieved, and the inconvenient use of glycosyl halides and catalysis with heavy metal salts was avoided. With ethynylestradiol **8** as aglycon the same procedure yielded only 11% of the expected product **13**. Better results (61%) were obtained with the activated glucuronic acid imidate **2** and catalytic amounts of $BF_3{\cdot}Et_2O$ (see Scheme 2).

For ester hydrolysis and deacetylation of the products, treatment with sodium hydroxide in methanol gave the corresponding glucuronides **10**, **12** and **14**. The progress of the reaction for ethynyl conjugate **13** could not be monitored by TLC; cleavage of the sugar acetate groups was faster than of the steroid 17-acetyl group, and monoacetylated and fully deblocked compounds had the same R_f values. Therefore, the reaction was stopped after two days, worked up and completion monitored by ^{1}H NMR.

EXPERIMENTAL

General methods. Melting points were determined using an Olympus polarizing microscope with a Mettler FP 82 heating desk and are uncorrected. Optical rotations were measured with Perkin-Elmer polarimeter 243 or 341. NMR spectra were recorded on Bruker AMX-400 NMR spectrometer (400 MHz for ^{1}H and 100.67 MHz for ^{13}C). HRMS spectra were determinded with a VG Analytical 70-250S mass spectrometer, using the FAB ion source, 3-nitrobenzyl alcohol as matrix and polyethylene glycol (average mass of 300 or 600, respectively) as reference. MALDI-TOF spectra were recorded on Bruker Biflex III. TLC were run on precoated plates, silica gel 60 GF_{254} (Merck). Detection was effected by observation under UV light at 254 nm, and by spraying with 10% ethanolic sulfuric acid and subsequent heating. Column chromatography was performed by flash technique using silicagel 60 (0.040-0.063 mm, Merck).

3,17β-Diacetoxy-17α-ethynyl-1,3,5[10]-estratriene (7).[14] A solution of ethynyl-estradiol **6** (3.0 g, 10 mmol) in pyridine (30 mL) and acetic anhydride (30 mL) was stirred at 100 °C for 2 d. The solvent was evaporated under reduced pressure to give **7** as a colourless foam (3.81 g, quantitative): $[\alpha]^{20}_D$ -1.1° (*c* 0.5, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3H, Me), 1.31-1.46 (m, 4H), 1.63-1.70 (m, 1H), 1.75-1.83 (m, 3H), 1.93-2.03 (m, 2H), 1.99 (s, 3H, OAc), 2.16-2.23 (m, 1H), 2.21 (s, 3H, OAc), 2.29-2.33 (m, 1H), 2.56 (s, 1H, ≡CH), 2.68-2.80 (m, 3H), 6.72 (d, 1H, Ar), 6.78 (dd, 1H, Ar), 7.22 (d, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ 12.95 (Me), 20.70, 21.02 (2 acetyl-Me), 22.86, 25.73, 26.65, 29.09, 32.67, 36.92 (6 CH_2), 38.33, 43.18, 47.39, 47.42 (4 CH), 74.50, 82.92, 84.01 (3 quart. C), 118.18, 121.07, 126.01 (3 Ar-CH), 137.34, 137.73 (2 quart. Ar-C), 148.01 (Ar-C-O), 169.17, 169.41 (2 CO_2).

17β-Acetoxy-17α-ethynyl-3-hydroxy-1,3,5[10]-estratriene (8). A solution of peracetylated ethynylestradiol 7 (4.01 g, 10.6 mmol) and potassium carbonate (700 mg, 5 mmol) in anhydrous methanol (50 mL) was stirred at room temperature for 0.5 h. After filtration and concentration under reduced pressure, the residual crude product was purified by column chromatography with dichloromethane to give **8** as a colourless foam (2.36 g, 66%): $[\alpha]^{20}_D$ -0.4° (*c* 0.5, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3H, Me), 1.26-1.46 (m, 4H), 1.62-1.70 (m, 1H), 1.74-1.82 (m, 3H), 1.92-2.03 (m, 2H), 1.99 (s, 3H, OAc), 2.11-2.22 (m, 1H), 2.26-2.31 (m, 1H), 2.56 (s, 1H, ≡CH), 2.68-2.78 (m, 3H), 4.66 (bs, 1H, OH), 6.50 (d, 1H, Ar), 6.57 (dd, 1H, Ar), 7.09 (d, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ 12.99 (Me), 21.04 (acetyl-Me), 22.87, 25.92, 26.81, 29.18, 32.69, 36.94 (6 CH_2), 38.69, 42.97, 47.38, 47.46 (4 CH), 74.50, 82.92, 84.12 (3 quart. C), 112.28, 114.80, 126.14 (3 Ar-CH), 132.03, 137.75 (2 quart. Ar-C), 152.94 (Ar-C-O), 169.32 (CO_2).

Methyl {(17β-Acetoxy-3-hydroxy-1,3,5[10]-estratrien-3-yl)-2,3,4-tri-*O*-acetyl-β-D-glucopyranosid}uronate (9). A solution of estradiol 17-acetate **4** (2.30 g, 7.3 mmol) and peracetylated glucuronic methyl ester **1** (2.75 g, 7.3 mmol) in anhydrous dichloromethane (50 mL) was treated with boron trifluoride diethyl etherate (1.85 mL, 15 mmol) and stirred at room temperature overnight. The mixture was washed twice with saturated sodium hydrogen carbonate solution, dried over magnesium sulfate and concentrated under reduced pressure. Recrystallization (twice) from acetone gave **9** as colourless crystals (1.82 g, 42%): mp 225-227 °C; $[\alpha]^{20}_D$ +3.9° (*c* 0.5, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.75 (s, 3H, Me), 1.17-1.51 (m, 7H), 1.64-1.70 (m, 1H), 1.81 (d, 2H), 1.97, 1.98, 1.98, 1.99 (4s, 12H, 4 OAc), 2.13-2.22 (m, 3H), 2.75-2.77 (m, 2H), 3.67 (s, 3H, OMe), 4.09 (d, 1H, H-5, $J_{4,5}$ = 9.5 Hz), 4.61 (dd ~ t, 1H, H-17'), 5.03 (d, 1H, H-1, $J_{1,2}$ = 7.6 Hz), 5.18-5.27 (m, 3H, H-2, H-3, H-4), 6.64 (d, 1H, Ar), 6.70 (dd, 1H, Ar), 7.13 (d, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ 11.61 (Me), 20.09, 20.20, 20.76 (4 acetyl-Me), 22.80, 25.69, 26.64, 27.11, 29.25, 36.41 (6 CH_2), 37.95 (CH), 42.44 (quart. C), 43.42, 49.33 (2 CH), 52.53 (OMe), 68.80, 70.02, 71.51, 72.24, 82.22 (5 CH-O), 98.87 (O-CH-O), 113.88, 116.67, 126.09 (3 Ar-CH), 135.08, 137.85 (2 quart. Ar-C), 154.19 (Ar-C-O), 166.47, 168.80, 168.92, 169.72, 170.80 (5 CO_2); MALDI-TOF-MS: *m/z* 653.10 $[M+Na]^+$, 669.08 $[M+K]^+$.

Anal. Calcd for $C_{33}H_{42}O_{12}$ (630.69): C, 62.85; H, 6.71. Found: C, 62.83; H, 6.78.

(3,17β-Dihydroxy-1,3,5[10]-estratrien-3-yl) β-D-Glucopyranosiduronic Acid (10). Glucuronide **9** (1.72 g, 2.7 mmol) was suspended in methanol (200 mL) and 2N sodium hydroxide solution (15 mL). The clear solution was stirred at room temperature overnight, the reaction being monitored by TLC (butan-1-ol/water/acetone/glacial acetic acid/25% aq. ammonia 70:60:50:18:1.5). After acidifying with ion-exchange resin Amberlite IR 120 H^+, filtration and concentration under reduced pressure, the residue obtained was recrystallized from methanol/water to give **10** as colourless crystals (1.03 g, 84%): mp 193-195 °C; $[\alpha]^{20}_D$ -9.0° (*c* 1, methanol); ^{1}H NMR (DMSO-d_6) δ 0.69 (s, 3H, Me), 1.12-1.38 (m, 7H), 1.60 (m, 1H), 1.85-1.92 (m, 3H), 2.12 (m, 1H), 2.28 (m, 1H), 2.77 (m, 2H), 3.25-3.35 (m, 2H), 3.42 (dd ~ t, 1H), 3.54 (dd ~ t, 1H), 3.86 (d, 1H, H-5, $J_{4,5}$ = 9.7 Hz), 4.95 (d, 1H, H-1, $J_{1,2}$ = 7.6 Hz), 6.71 (d, 1H, Ar), 6.78 (dd, 1H, Ar), 7.19 (d, 1H, Ar); ^{13}C NMR (methanol-d_4) δ 9.14 (Me), 21.47, 24.95, 25.84, 28.14, 28.18, 35.44 (6 CH_2), 37.75 (CH), 41.78 (quart. C), 42.85, 48.75 (2 CH), 70.45, 72.07, 74.79, 79.91 (5 CH-O), 100.27 (O-CH-O), 112.81, 115.50, 124.72 (3 Ar-CH), 133.42, 136.50 (2 quart. Ar-C), 154.17 (Ar-C-O, 169.63 (CO_2); HRMS: *m/z* 449.2149 $[M+H]^+$ ($C_{24}H_{33}O_8$ requires 449.2175).

Methyl {(17-Oxo-1,3,5[10]-estratrien-3-yl)-2,3,4-tri-*O*-acetyl-β-D-glucopyranosid}uronate (11). Glucuronidation [estrone **5** (2.0 g, 5.31 mmol), compound **1** (2.78 g, 7.39 mmol), CH_2Cl_2 (40 mL), BF_3·Et_2O (2 mL, 14.8 mmol)], as described for **9**, afforded **11** as colourless crystals (1.34 g, 42%): mp 213-215 °C; $[\alpha]^{20}_D$ +56.4° (*c* 1, chloroform), {lit,[2] $[\alpha]^{23}_D$ +53.6°±0.4}; ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 3H, Me), 1.37-1.64 (m, 7H), 1.92-1.99 (m, 2H), 2.02, 2.04, 2.05 (3s, 9H, 3 OAc), 2.06-2.13 (m, 1H), 2.14-2.18 (m, 1H), 2.20-2.27 (m, 1H), 2.35-2.40 (m, 1H), 2.45-2.53 (m, 1H), 2.85-2.89 (m, 1H), 3.72 (s, 3H, OMe), 4.13-4.17 (m, 1H, H-5), 5.09 (d, 1H, H-1, $J_{1,2}$ = 7.1 Hz), 5.22-5.33 (m, 3H, H-2, H-3, H-4), 6.72 (d, 1H, Ar-H), 6.78 (dd, 1H, Ar-H), 7.19 (d, 1H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 14.25 (Me), 20.92, 21.00, 21.03 (3 acetyl-Me), 21.99, 26.27, 26.82, 29.99, 31.98, 36.26 (6 CH_2), 38.62, 44.47 (2 CH), 48.37 (quart. C), 50.84 (CH), 53.36 (OMe), 69.67, 71.52, 72.38, 73.14 (C-2, C-3, C-4, C-5), 99.71 (C-1), 114.85, 117.63, 126.93 (3 Ar-CH), 135.46, 138.55 (2 quart. Ar-C), 155.17 (Ar-C-O), 167.32, 169.62, 169.74, 170.54 (4 CO_2); MALDI-TOF-MS: *m/z* 609.07 $[M+Na]^+$.

Anal. Calcd for $C_{31}H_{38}O_{11}$ (586.64): C, 63.47; H, 6.53. Found: C, 63.30; H, 6.60.

(17-Oxo-1,3,5[10]-estratrien-3-yl) β-D-Glucopyranosiduronic Acid (12). Compound **11** (204 mg, 0.339 mmol) was deacetylated by the same procedure [MeOH (40 mL), 2N NaOH solution (2 mL), stirred overnight] as for compound **10**. The obtained residue was recrystallized from methanol/water to give **12** as colourless crystals (142 mg, 94%): mp 144-147 °C, {lit,[1] mp 150-170 °C}; $[\alpha]^{20}_D$ +35.5° (*c* 1, methanol), {lit,[1] $[\alpha]^{20}_D$ +63° (*c* 0.72, methanol)}; ^{1}H NMR (methanol-d_4) δ 0.85 (s, 3H, Me), 1.31-1.65 (m, 6H), 1.80-1.85 (m, 1H), 1.92-2.13 (m, 3H), 2.15-2.22 (m, 1H), 2.32-2.28 (m, 1H), 2.39-2.47 (m, 1H), 2.78-2.84 (m, 2H), 3.38-3.44 (m, 2H), 3.52-3.58 (m, 1H), 3.87 (d, 1H, H-5, $J_{4,5}$ = 9.7 Hz), 4.84 (d, 1H, H-1, $J_{1,2}$ = 7.6 Hz), 6.74 (d, 1H, Ar-H), 6.79 (dd, 1H, Ar-H), 7.14 (d, 1H, Ar-H); ^{13}C NMR (methanol-d_4) δ 14.70 (Me), 22.91, 27.45, 28.05, 31.01, 33.23, 37.14 (6 CH_2), 40.16, 45.80 (2 CH), 48.37 (quart. C), 52.08 (CH), 73.46, 75.06, 77.02, 77.81 (C-2, C-3, C-4, C-5), 103.22 (C-1), 115.90, 118.53, 127.69 (3 Ar-CH), 135.83, 139.40 (2 quart. Ar-C), 157.31 (Ar-C-O); HRMS: *m/z* 447.1990 $[M+H]^+$ ($C_{24}H_{31}O_8$ requires 447.2019).

Methyl {(17β-Acetoxy-17α-ethynyl-3-hydroxy-1,3,5[10]-estratrien-3-yl)-2,3,4-tri-*O*-acetyl-β-D-glucopyranosid}uronate (13). A solution of glycosyl imidate **2** (2.8 g, 5.9 mmol) and ethynylestradiol 17-acetate **8** (2.1 g, 6.2 mmol) in anhydrous dichloromethane (150 mL) was treated with three drops of boron trifluoride diethyl etherate at -20 °C and stirred for 0.5 h. The mixture was washed with saturated sodium hydrogen carbonate solution, dried over magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by column chromatography with petroleum ether/ethyl acetate (3:1) to give **13** as a colourless foam (2.3 g, 61%): $[\alpha]^{20}_D$ -27.2° (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 3H, Me), 1.34-1.51 (m, 4H), 1.68-1.89 (m, 4H), 1.98-2.06 (m, 2H), 2.03, 2.04, 2.06, 2.08 (4s, 12H, 4 OAc), 2.08-2.10 (m, 1H), 2.20-2.37 (m, 1H), 2.62 (s, 1H, ≡CH), 2.73-2.84 (m, 3H), 3.73 (s, 3H, OMe), 4.16 (d, 1H, H-5, $J_{4,5}$ = 9.7 Hz), 5.10 (d, 1H, H-1, $J_{1,2}$ = 7.6 Hz), 5.23-5.35 (m, 3H, H-2, H-3, H-4), 6.70 (d, 1H, Ar), 6.77 (dd, 1H, Ar), 7.20 (d, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ 12.96 (Me), 20.06, 20.18, 21.00 (3 acetyl-Me), 22.84, 25.84, 26.72, 29.27, 32.66, 36.91 (6 CH_2), 38.53, 43.05, 47.39 (3 CH), 52.50 (OMe), 68.80, 70.63, 71.52, 72.21 (C-2, C-3,

C-4, C-5), 74.51, 82.92, 83.99 (3 quart. C), 98.81 (C-1), 113.89, 116.65, 126.10 (3 Ar-CH), 134.94, 137.80 (2 quart. Ar-C), 154.20 (Ar-C-O), 166.46, 168.75, 168.89, 169.11, 169.66 (5 CO_2); HRMS: *m/z* 653.2621 $[M+H]^+$ ($C_{35}H_{41}O_{12}$ requires 653.2598).

(3,17β-Dihydroxy-17α-ethynyl-1,3,5[10]-estratrien-3-yl) β-D-Glucopyranosiduronic Acid (14). Compound **13** (659 mg, 1 mmol) was deacetylated by the same procedure (75 mL MeOH, 5 mL 2N NaOH solution, stirred for 2 d) as for compound **10**. The raw material was purified by column chromatography with chloroform/methanol/acetic acid (25:5:1) to yield **14** as a yellowish solid (349 mg, 74%): $[\alpha]^{20}_D$ -13.5° (*c* 0.5, methanol); ^{1}H NMR (methanol d_4) δ 0.72 (s, 3H, Me), 1.16-1.37 (m, 4H), 1.57-1.65 (m, 3H), 1.71-1.89 (m, 3H), 1.99-2.06 (m, 1 H), 2.08-2.14 (m, 1 H), 2.18-2.26 (m, 1H), 2.65-2.70 (m, 2H), 2.74 (s, 1H, ≡CH), 3.31-3.34, 3.42-3.49 (2m, 2H, 1H, H-2, H-3, H-4), 3.78 (d, 1H, H-5, $J_{4,5}$ = 9.7 Hz), 4.75 (d, 1H, H-1, $J_{1,2}$ = 7.6 Hz), 6.63 (d, 1H, Ar), 6.70 (dd, 1H, Ar), 7.06 (d, 1H, Ar); ^{13}C NMR (methanol-d_4) δ 13.71 (Me), 24.12, 28.03, 28.93, 31.16, 34.46, 40.31 (6 CH_2), 41.33, 45.59, 51.18 (3 CH), 48.63 (quart. C), 73.45, 75.06, 77.81 (4 CH-O), 80.77 (quart. C-O), 103.26 (O-CH-O), 115.85, 118.48, 127.70 (3 Ar-CH), 136.28, 139.47 (2 quart. Ar-C), 157.20 (Ar-C-O), 165.27 (CO_2); MALDI-TOF-MS: *m/z* 495.18 $[M+Na]^+$, 517.16 $[M-H+2Na]^+$ ($C_{26}H_{32}O_8$ requires 472.54).[15]

ACKNOWLEDGEMENTS

Support of this work by the Fonds der Chemischen Industrie and the Schering AG, Berlin is gratefully acknowledged. Thanks go to Kirsten Geisler for laboratory assistance and Lars Kröger for mass spectral analysis.

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15. The structure of **14** could be determined only by NMR and MALDI-TOF-MS data and by characterization of the protected precursor compound **13**.