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Synthesis of Two Hyaluronic-Acid-Related Oligosaccharide 4-Methoxyphenyl Glycosides Having a β-D-Glucuronic Acid Residue at the Reducing End*

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Synthesis of two hyaluronic-acid-related oligosaccharides, the 4-methoxyphenyl β-glycosides of β-D-Glc*p*A-(1→3)-β-D-Glc*p*NAc-(1→4)-D-Glc*p*A and β-D-Glc*p*A-(1→3)-β-D-Glc*p*NAc-(1→4)-β-D-Glc*p*A-(1→3)-β-D-Glc*p*NAc-(1→4)-D-Glc*p*A, is described. D-Glucopyranosyluronic acid residues were obtained by selective oxidation at C6 of corresponding D-glucopyranosyl residues after construction of the oligosaccharide backbones, using pyridinium dichromate and acetic anhydride.

Key words: hyaluronic acid, oxidation, oligosaccharide synthesis

Hyaluronic acid (HA) is a linear extracellular polysaccharide [1], built up from disaccharide repeating units of 2-acetamido-2-deoxy-D-glucose and D-glucuronic acid: [→4)-β-D-Glc*p*A-(1→3)-β-D-Glc*p*NAc-(1→]$_n$. It is a major component of several soft connective tissues, but it has also been found in certain bacterial strains [2]. Native high-molecular-mass HA is anti-angiogenic [3], whereas HA degradation products of specific size (3–10 disaccharide units) stimulate endothelial cell proliferation and migration [4], and induce angiogenesis in the chick chorioallantoic membrane assay [4,5]. To contribute to the possibilities to study the ability of specific oligosaccharide fragments of hyaluronic acid to induce angiogenesis, a synthetic program was initiated in our laboratory to obtain a wide range of medium-sized, well-defined oligosaccharide elements of HA.

As a result, a series of oligosaccharide fragments constituted of even or odd numbers of monosaccharides have been generated: HA di-, tri-, tetra-, penta-, and hexa-saccharides having a 1-*O*-(4-methoxyphenyl) *N*-acetyl-β-D-glucosamine residue at the reducing end [6–8], and HA di- and tetra-saccharides having a 1-*O*-(4-methoxyphenyl) β-D-glucuronic acid residue at the reducing end [9,10]. In all our synthetic protocols D-glucuronic acid residues were obtained by selective oxidation

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of primary hydroxyl functions of corresponding D-glucose residues. In the course of our work, also the syntheses of HA di-, tri- [11], tetra-, hexa-, and octa-saccharide [12] fragments having a 1-*O*-methyl β-D-glucuronic acid residue at the reducing end, by direct coupling of D-glucuronic acid derivatives with suitably protected 2-deoxy-2-trichloroacetamido-D-glucose residues [13], have been described.

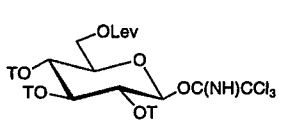
In this paper we report the synthesis of the HA tri- and penta-saccharides **1** and **2**, having a 1-*O*-(4-methoxyphenyl)- β-D-glucuronic acid residue at the reducing end, which were initially excluded from the second series mentioned above.

β-D-Glc*p*A-(1→3)-β-D-Glc*p*NAc-(1→4)-β-D-Glc*p*A-(1→O)MP (**1**)

β-D-Glc*p*A-(1→3)-β-D-Glc*p*NAc-(1→4)-β-D-Glc*p*A-(1→3)-β-D-Glc*p*NAc-(1→4)-β-D-Glc*p*A-(1→O)MP (**2**)

RESULTS AND DISCUSSION

For the synthesis of trisaccharide **1** and pentasaccharide **2** our earlier prepared key mono- and di-saccharide derivatives monosaccharide donor **3** [6], disaccharide acceptor **4** [10], and disaccharide donor **5** [8] were used (Scheme 1).



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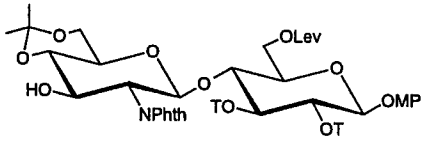

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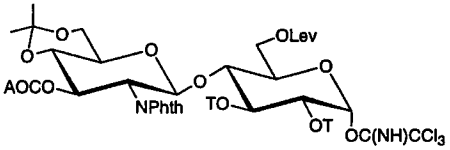

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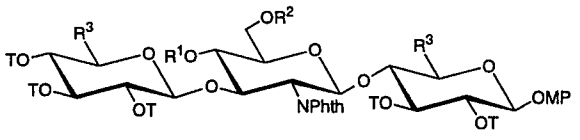
Scheme 1. Earlier synthesized key intermediates.

In order to prepare compound **1**, disaccharide acceptor **4** (Scheme 1) was condensed with monosaccharide donor **3** (Scheme 1) in dichloromethane in the presence of trimethylsilyl triflate (0.05 equiv based on **4**), affording trisaccharide derivative **6** in 87% yield (Scheme 2). Removal of the isopropylidene function under acidic conditions, followed by conventional acetylation of the hydroxyl functions gave **7** (overall yield 76%), which was delevulinoylated using hydrazinium acetate [14,15] to afford diol **8** in 90% yield. Oxidation of the trisaccharide, using pyridinium dichromate and acetic anhydride [8,16] in dichloromethane gave **9** (78%), as established by NMR analysis of the product and of the methyl-esterified derivative. Treatment of **9** with

ethylenediamine in 1-butanol at 90°C [17], followed by re-*N*,*O*-acetylation using acetic anhydride and pyridine in the presence of a catalytic amount of 4-dimethylaminopyridine, and finally de-*O*-acetylation using aq 2 M sodium hydroxide in tetrahydrofuran at 0°C [18] yielded the desired compound **1** (62%).

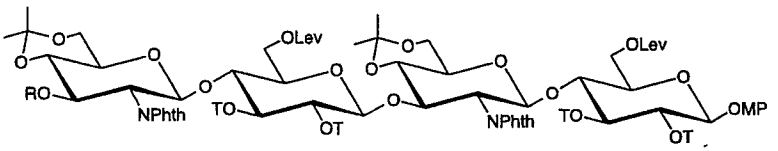


	R^1	R^2	R^3
6	CMe_2		CH_2OLev
7	Ac	Ac	CH_2OLev
8	Ac	Ac	CH_2OH
9	Ac	Ac	COOH

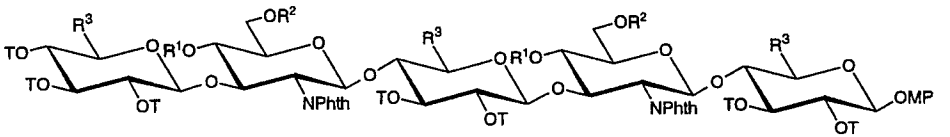
Scheme 2. Synthetic intermediates towards trisaccharide **1**.

For the preparation of pentasaccharide **2**, disaccharide acceptor **4** (Scheme 1) and disaccharide donor **5** (Scheme 1) were condensed in dichloromethane using trimethylsilyl triflate (0.05 equiv based on **4**) as a catalyst to afford **10** in 68% yield (Scheme 3). Transformation of **10** into tetrasaccharide acceptor **11** was readily achieved by removal of the allyloxycarbonyl function using tetrakis(triphenylphosphine)palladium and morpholine [19,20] in tetrahydrofuran (91%). Condensation of **11** with monosaccharide donor **3** (Scheme 1) in dichloromethane using trimethylsilyl triflate (0.05 equiv based on **11**) as a catalyst gave pentasaccharide derivative **12** (65%). Removal of the isopropylidene functions with trifluoroacetic acid and water in dichloromethane, followed by acetylation of the hydroxyl functions, using acetic anhydride and pyridine in the presence of a catalytic amount of 4-dimethylaminopyridine, provided **13** (82%). Delevulinoylation of **13** using hydrazinium acetate (→ **14**, 77%), followed by oxidation as described for the preparation of **9**, afforded **15** in 70% yield, as verified by ^{1}H NMR analysis of the methyl-esterified derivative. Finally, deprotection using ethylenediamine in 1-butanol at 90°C, followed by re-*N*,*O*-acetylation with acetic anhydride and pyridine in the presence of a catalytic amount of 4-dimethylaminopyridine and de-*O*-acetylation using aq. 2 M sodium hydroxide in tetrahydrofuran at 0°C gave target compound **2** (75%).

The synthesized 4-methoxyphenyl glycosides **1** and **2** will be tested in biological assays for their ability to affect the angiogenesis.



	R
10	AOC
11	H



	R^1	R^2	R^3
12	CMe_2		CH_2OLev
13	Ac	Ac	CH_2OLev
14	Ac	Ac	CH_2OH
15	Ac	Ac	COOH

Scheme 3. Synthetic intermediates towards pentasaccharide **2**.

EXPERIMENTAL

General: Reactions were monitored by TLC on Kieselgel 60 F_{254} (Merck); compounds were visualized by charring with aq 50% H_2SO_4, after examination under UV light. In the work-up procedures of reaction mixtures, organic solutions were washed with appropriate amounts of the indicated aqueous solutions, then dried ($MgSO_4$), and concentrated under reduced pressure at 20–40°C (water-bath). Column chromatography was performed on Kieselgel 60 F_{254} (Merck, 70–230 mesh). Optical rotations were measured at 20°C for solutions in $CHCl_3$ with a Perkin-Elmer 241 polarimeter, using a 10-cm 1-ml cell. ^1H NMR spectra were recorded with Bruker AC 300, Bruker AMX 500 or Bruker AMX 600 spectrometers; the values of δ_H are given in ppm relative to the signal for internal Me_4Si ($\delta = 0$) for solutions in $CDCl_3$, or by reference to acetone ($\delta = 2.225$) for solutions in D_2O. ^{13}C (APT, 75 MHz) NMR spectra were recorded at 27°C with a Bruker AC 300 or a Varian Gemini-300 instrument; indicated ppm values for δ_C are relative to the signal of $CDCl_3$ ($\delta = 76.9$) for solutions in $CDCl_3$. Two-dimensional double-quantum filtered ^1H-^1H correlation spectra (2D DQF ^1H-^1H COSY) were recorded using a Bruker AMX 500 apparatus (500 MHz) at 27°C. Fast-atom-bombardment mass spectrometry (FABMS) was performed on a JEOL JMS SX/SX 102A four-sector mass spectrometer, operated at 10 kV accelerating voltage, equipped with a JEOL MS-FAB 10 D FAB gun, operated at 10 mA emission current, producing a beam of 6 keV Xe atoms. Elemental analyses were carried out by H. Kolbe Mikroanalytisches Laboratorium (Mülheim an der Ruhr, Germany).

4-Methoxyphenyl(6-*O*-levulinoyl-2,3,4-tri-*O*-*p*-toluoyl-β-D-glucopyranosyl)-(1→3)-(2-deoxy-4,6-*O*-isopropylidene-2-phthalimido-β-D-glucopyranosyl)-(1→4)-6-*O*-levulinoyl-2,3-di-*O*-*p*-toluoyl-β-D-glucopyranoside (6): To a solution of 6-*O*-levulinoyl-2,3,4-tri-*O*-*p*-toluoyl-β-D-glucopyranosyl

trichloroacetimidate [6] (**3**; 0.535 g, 0.69 mmol) and 4-methoxyphenyl (2-deoxy-4,6-*O*-isopropylidene-2-phthalimido-β-D-glucopyranosyl)-(1→4)-6-*O*-levulinoyl-2,3-di-*O*-*p*-toluoyl-β-D-propyranoside [10] (**4**; 0.327 g, 0.34 mmol) in dry CH_2Cl_2 (5 ml), containing 3 Å molecular sieves (0.35 g), was added Me_3SiOTf (6.2 μl). After stirring for 10 min, TLC (CH_2Cl_2-acetone, 93:7) showed the disappearance of **4**, and the formation of **6** (R_f = 0.49). Then, the solution was neutralized with Et_3N, and the mixture was diluted with EtOAc (200 ml), filtered through Celite, washed with aq 5% NaCl, and the organic layer was dried, filtered, and concentrated. Column chromatography (CH_2Cl_2-acetone, 93:7) of the residue gave **6**, isolated as a white foam. Yield 0.467 g (87%), $[\alpha]_D$ +23° (c = 1). ^1H NMR ($CDCl_3$): δ = 7.919, 7.794, 7.724, 7.525, 7.279, 7.238, 7.119, 7.098, 6.981, and 6.959 (10d, each 2H, 5 $COC_6H_4CH_3$), 6.79–6.65 (m, 4H, $C_6H_4OCH_3$), 5.444 and 5.134 (2dd, each 1H, $J_{1,2/1'',2''}$ = 7.6 and 7.9, $J_{2,3/2'',3''}$ = 9.1 and 9.4, H2,2''), 5.147 (d, 1H, $J_{1',2'}$ = 8.3, H1'), 4.959 and 4.931 (2d, each 1H, H1,1''), 4.437 (dd, 1H, $J_{2',3'}$ = 10.3, H2'), 3.687 (s, 3H, $C_6H_4OCH_3$), 2.398, 2.373, 2.337, 2.305, and 2.241 (5s, each 3H, 5 $COC_6H_4CH_3$), 2.174 and 2.170 (2s, each 3H, 2 $COCH_2CH_2COCH_3$), 1.326 and 1.315 (2s, each 3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ = 172.1 and 171.4 (2 $COCH_2CH_2COCH_3$), 165.4, 165.0 (2C), and 164.9 (2C) (5 $COC_6H_4CH_3$), 100.2, 99.9, and 98.5 (C1,1',1''), 99.2 [$C(CH_3)_2$], 62.6, 61.7, and 61.0 (C6,6',6''), 55.5 (C2' and $C_6H_4OCH_3$), 37.8 (2C), 29.2, 29.0, 27.8, and 27.5 (2 $COCH_2CH_2COCH_3$), 21.5 ($COC_6H_4CH_3$), 29.6 and 18.8 [$C(CH_3)_2$]. Anal. Calcd. for $C_{86}H_{87}NO_{27}$: C, 65.93; H, 5.60. Found: C, 65.84; H, 5.71.

4-Methoxyphenyl (6-*O*-levulinoyl-2,3,4-tri-*O*-*p*-toluoyl-β-D-glucopyranosyl)-(1→3)-(4,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→4)-6-*O*-levulinoyl-2,3-di-*O*-*p*-toluoyl-β-D-glucopyranoside (**7**): To a solution of **6** (0.45 g, 0.29 mmol) in CH_2Cl_2 (5 ml) and H_2O (35 μl) was added CF_3CO_2H (318 μl). The mixture was stirred for 30 min, when TLC (CH_2Cl_2-acetone, 85:15) showed the disappearance of **6** (R_f = 0.89) and the formation of a slower moving spot (R_f = 0.33). Then, the mixture was diluted with EtOAc (150 ml) and washed with aq 10% $NaHCO_3$ and aq 5% NaCl. The aqueous layers were extracted twice with EtOAc, and the combined organic layers were dried, filtered, and concentrated. To a solution of the residue in pyridine (8 ml) were added Ac_2O (8 ml) and a catalytic amount of 4-dimethylaminopyridine. After stirring overnight at room temperature, TLC (CH_2Cl_2-acetone, 9:1) showed the acetylation to be complete (**7**; R_f = 0.60). The mixture was concentrated and co-concentrated with toluene, EtOH, and CH_2Cl_2 (3 x 20 ml). Column chromatography (CH_2Cl_2-acetone, 9:1) of the residue gave **7**, isolated as a glass. Yield 0.35 g (76%), $[\alpha]_D$ +16° (c = 1). ^1H NMR ($CDCl_3$): δ = 7.842, 7.769, 7.688, 7.522, 7.419, 7.159, 7.131, 7.102, 7.023, and 6.967 (10d, each 2H, 5 $COC_6H_4CH_3$), 6.80–6.67 (m, 4H, $C_6H_4OCH_3$), 5.406 and 5.168 (2dd, each 1H, $J_{1,2/1'',2''}$ = 7.4 and 7.8, $J_{2,3/2'',3''}$ = 8.9 and 9.6, H2,2''), 5.121 (d, 1H, $J_{1',2'}$ = 8.5, H1'), 4.961 and 4.529 (2d, each 1H, H1,1''), 4.203 (dd, 1H, $J_{2',3'}$ = 10.8, H2'), 3.690 (s, 3H, $C_6H_4OCH_3$), 2.382, 2.349, 2.339, 2.315, and 2.221 (5s, each 3H, 5 $COC_6H_4CH_3$), 2.185 and 2.159 (2s, each 3H, 2 $COCH_2CH_2COCH_3$), 2.028 and 1.977 (2s, each 3H, 2 Ac); ^{13}C NMR ($CDCl_3$): δ = 171.9 and 171.4 (2 $COCH_2CH_2COCH_3$), 170.2 and 168.9 (2 $COCH_3$), 165.4, 164.9 (2C), 164.8, and 164.6 (5 $COC_6H_4CH_3$), 100.5, 99.9, and 97.3 (C1,1',1''), 62.3, 61.9, and 61.7 (C6,6',6''), 55.3 (C2' and $C_6H_4OCH_3$), 37.6, 37.5, 29.6, 29.2, 27.6, and 27.4 (2 $COCH_2CH_2COCH_3$), 21.4, 21.3 (2C), and 21.2 (2C) (5 $COC_6H_4CH_3$), 20.5 ($COCH_3$). Anal. Calcd. for $C_{87}H_{87}NO_{29}$: C, 64.88; H, 5.45. Found: C, 64.71; H, 5.48.

4-Methoxyphenyl (2,3,4-tri-*O*-*p*-toluoyl-β-D-glucopyranosyl)-(1→3)-(4,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→4)-2,3-di-*O*-*p*-toluoyl-β-D-glucopyranoside (**8**): To a solution of **7** (296 mg, 0.184 mmol) in EtOH (26 ml) and toluene (13 ml) was added $NH_2NH_2 \cdot HOAc$ (169 mg, 1.84 mmol). The mixture was stirred for 40 min, when TLC (CH_2Cl_2-acetone, 85:15) showed the conversion of **7** into **8** (R_f = 0.40). Then, the mixture was concentrated, and column chromatography (CH_2Cl_2-acetone, 9:1) of the residue afforded **8**, isolated as a glass. Yield 233 mg (90%), $[\alpha]_D$ +32° (c = 1). ^1H NMR ($CDCl_3$): δ = 7.860, 7.765, 7.747, 7.550, 7.454, 7.171, 7.121, 7.113, 7.032, and 6.963 (10d, each 2H, 5 $COC_6H_4CH_3$), 6.79–6.65 (m, 4H, $C_6H_4OCH_3$), 5.398 and 5.166 (2dd, each 1H, $J_{1,2/1'',2''}$ = 7.7 and 7.8, $J_{2,3/2'',3''}$ = 9.3 and 9.8, H2,2''), 5.216 (d, 1H, $J_{1',2'}$ = 8.4, H1'), 5.010 and 4.624 (2d, each 1H, H1,1''), 4.246 (dd, 1H, $J_{2',3'}$ = 10.8, H2'), 3.686 (s, 3H, $C_6H_4OCH_3$), 2.382, 2.375, 2.330, and 2.221 (4s, 3,3,6,3H, 5 $COC_6H_4CH_3$), 2.039 and 1.993 (2s, each 3H, 2 Ac); ^{13}C NMR ($CDCl_3$): δ = 170.4 and 169.6 (2 $COCH_3$), 165.9, 165.6, 165.1, 164.8, and 164.7 (5 $COC_6H_4CH_3$), 100.3, 99.9, and 97.7 (C1,1',1''), 61.7, 61.1, and 60.7 (C6,6',6''), 55.7 and 55.5 (C2' and $C_6H_4OCH_3$), 21.4 ($COC_6H_4CH_3$), 20.6 ($COCH_3$). Anal. Calcd. for $C_{77}H_{75}NO_{25}$: C, 65.39; H, 5.35. Found: C, 65.42; H, 5.46.

4-Methoxyphenyl (2,3,4-tri-*O*-*p*-toluoyl-β-D-glucopyranosyluronic acid)-(1→3)-(4,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→4)-2,3-di-*O*-*p*-toluoyl-β-D-glucopyranosyluronic acid (9): To a solution of **8** (50 mg, 36 μmol) in dry CH_2Cl_2 (2 ml), containing Ac_2O (35 μl), was added pyridinium dichromate (54 mg, 143 μmol). After stirring for 1 h, the brown suspension became a brown solution, and after 6 h TLC (CH_2Cl_2-EtOAc-HOAc, 5:5:1) showed the conversion of **8** (R_f = 0.90) into **9** (R_f = 0.23). After the addition of EtOAc (25 ml), the suspension was applied to column chromatography (EtOAc-HOAc, 98:2) to give **9**, isolated as a glass. Yield 39 mg (78%), $[\alpha]_D$ +3° (c = 1). ^{13}C NMR ($CDCl_3$): δ = 170.6 and 169.7 (2 $COCH_3$), 165.5, 165.0 (2C), 164.9, and 164.6 (5 $COC_6H_4CH_3$), 100.8, 100.3, and 97.6 (C1,1′,1″), 61.9 (C6′), 55.5 and 55.4 (C2′ and $C_6H_4OCH_3$), 21.5 ($COC_6H_4CH_3$), 20.6 ($COCH_3$).

A small amount of **9** was esterified with diazomethane in ether, and analyzed by ^{1}H NMR ($CDCl_3$): δ = 7.855, 7.778, 7.719, 7.569, 7.416, 7.152, 7.143, 7.125, 7.031, and 7.001 (10d, each 2H, 5 $COC_6H_4CH_3$), 6.80–6.67 (m, 4H, $C_6H_4OCH_3$), 5.449 and 5.183 (2dd, each 1H, $J_{1,2/1'',2''}$ = 6.9 and 7.8, $J_{2,3/2'',3''}$ = 8.8 and 9.6, H2,2″), 5.042 (d, 1H, $J_{1',2'}$ = 8.4, H1′), 5.024 and 4.563 (2d, each 1H, H1,1″), 4.154 (dd, 1H, $J_{2',3'}$ = 10.8, H2′), 4.098 and 3.844 (2d, each 1H, $J_{4,5/4'',5''}$ = 9.7 and 8.9, H5,5″), 3.698 (s, 3H, $C_6H_4OCH_3$), 3.615 and 3.421 (2s, each 3H, 2 $COOCH_3$), 2.394, 2.366, 2.351, 2.334, and 2.224 (5s, each 3H, 5 $COC_6H_4CH_3$), 2.119 and 1.948 (2s, each 3H, 2 $COCH_3$). FABMS (positive-ion mode; $C_{79}H_{75}NO_{27}$): *m/z* 1492 $[M+Na]^+$, 1470 $[M+H]^+$.

4-Methoxyphenyl (β-D-glucopyranosyluronic acid)-(1→3)-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-β-D-glucopyranosyluronic acid (1): To a solution of **9** (31 mg, 24 μmol) in 1-BuOH (5 ml) was added ethylenediamine (1 ml). The mixture was stirred overnight at 90°C under Ar, when TLC (1-BuOH-EtOH-H_2O-HOAc, 4:2:2:0.5) showed the disappearance of **9**. After concentration and co-concentration with toluene (5 × 10 ml), the residue was dissolved in dry pyridine (5 ml), and Ac_2O (5 ml) and a catalytic amount of 4-dimethylaminopyridine were added. The mixture was stirred overnight at room temperature, then concentrated and co-concentrated with toluene and EtOH (2 × 20 ml). The yellow, amorphous solid was dissolved in THF (5 ml), and at 0°C under vigorous stirring, aq 2 M NaOH (1 ml) was added. After stirring for 6 h at 0°C, TLC (1-BuOH-EtOH-H_2O-HOAc, 4:2:2:0.5) showed the conversion into **1** (R_f = 0.31), and the solution was neutralized with aq 1 M HCl. The solution was concentrated and co-concentrated with toluene-MeOH (1:1; 3 × 10 ml), and gel filtration on Sephadex G-10 (water) of the residue afforded **1**, isolated after lyophilization as a white, amorphous powder. Yield 10 mg (62%), $[\alpha]_D$ +22° (c = 0.5, H_2O). ^{1}H NMR (D_2O): δ = 7.11–6.97 (m, 4H, $C_6H_4OCH_3$), 4.996 (d, 1H, $J_{1,2}$ = 7.7, H1), 4.597 (d, 1H, $J_{1',2'}$ = 8.6, H1′), 4.471 (d, 1H, $J_{1'',2''}$ = 7.9, H1″), 3.867 (dd, 1H, $J_{2',3'}$ = 10.2, H2′), 3.802 (s, 3H, $C_6H_4OCH_3$), 3.604 (dd, 1H, $J_{2,3}$ = 9.3, H2), 3.559 (dd, 1H, $J_{2'',3''}$ = 9.9, H2″), 2.071 (s, 3H, $NHCOCH_3$). FABMS (negative-ion mode; $C_{27}H_{37}NO_{19}$): *m/z* 700 $[M+Na-H]^-$, 678 $[M-H]^-$.

4-Methoxyphenyl (3-*O*-allyloxycarbonyl-2-deoxy-4,6-*O*-isopropylidene-2-phthalimido-β-D-glucopyranosyl)-(1→4)-(6-*O*-levulinoyl-2,3-di-*O*-*p*-toluoyl-β-D-glucopyranosyl)-(1→3)-(2-deoxy-4,6-*O*-isopropylidene-2-phthalimido-β-D-glucopyranosyl)-(1→4)-6-*O*-levulinoyl-2,3-di-*O*-*p*-toluoyl-β-D-glucopyranoside (10): To a solution of (3-*O*-allyloxycarbonyl-2-deoxy-4,6-*O*-isopropylidene--2-phthalimido-β-D-glucopyranosyl)-(1→4)-6-*O*-levulinoyl-2,3-di-*O*-*p*-toluoyl-α-D-glucopyranosyl trichloroacetimidate [8] (**5**; 230 mg, 218 μmol) and 4-methoxyphenyl (2-deoxy-4,6-*O*-isopropylidene--2-phthalimido-β-D-glucopyranosyl)-(1→4)-6-*O*-levulinoyl-2,3-di-*O*-*p*-toluoyl-β-D-glucopyranoside [10] (**4**; 105 mg, 109 μmol) in dry CH_2Cl_2 (4 ml), containing 3 Å molecular sieves (0.10 g), was added at 0°C Me_3SiOTf (2.8 μl). After stirring for 10 min, the water-ice bath was removed and after 90 min, TLC (CH_2Cl_2-acetone, 9:1) showed the disappearance of **4** and the formation of **10** (R_f = 0.57). Then, the solution was neutralized with Et_3N, the mixture was diluted with EtOAc (200 ml), filtered through Celite, and washed with aq 5% NaCl, and the organic layer was dried, filtered, and concentrated. Column chromatography (CH_2Cl_2-acetone, 93:7) of the residue gave **10**, isolated as a glass. Yield 139 mg (68%), $[\alpha]_D$ +24° (c = 1). ^{1}H NMR ($CDCl_3$): δ = 7.864, 7.773, 7.698, 7.239, 7.189, 7.124, 7.119, and 6.964 (8d, each 2H, 4 $COC_6H_4CH_3$), 6.78–6.64 (m, 4H, $C_6H_4OCH_3$), 5.62–5.49 (m, 1H, $COCH_2CH{=}CH_2$), 5.517 (dd, 1H, $J_{3''',4'''}$ = 8.8, H3‴), 5.410 and 4.941 (2dd, each 1H, $J_{1,2/1'',2''}$ = 7.3 and 7.9, $J_{2,3/2'',3''}$ = 9.2 and 9.6, H2,2″), 5.295 and 5.287 (2dd, each 1H, $J_{3,4/3'',4''}$ = 8.9 and 9.7, H3,3″), 5.311 and 5.085 (2d, each 1H, $J_{1',2'/1''',2'''}$ = 7.8 and 8.3, H1,1‴), 5.08–4.94 (m, 2H, $COCH_2CH{=}CH_2$), 4.944 and 4.694 (2d, each 1H, H1,1″), 4.125 and 4.088 (2dd, each 1H, $J_{2',3'/2''',3'''}$ = 10.1 and 9.9, H2′,2‴), 3.676 (s, 3H, $C_6H_4OCH_3$), 2.369, 2.359, and 2.329 (3s, 3,3,6H, 4 $COC_6H_4CH_3$), 2.254 and 2.151 (2s, each 3H, 2 $COCH_2CH_2COCH_3$), 1.209, 1.178, and 1.157

(3s, 3,6,3H, 2 C(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$): δ = 171.7 and 171.4 (2 *C*OCH$_2$CH$_2$COCH$_3$), 164.9, 164.8, 164.7, and 164.4 (4 *C*OC$_6$H$_4$CH$_3$), 154.3 (COCH$_2$*C*H=CH$_2$), 118.3 (COCH$_2$CH=*C*H$_2$), 100.1, 99.5, and 98.2 (2C) (C1,1′,1″,1‴), 99.2 and 98.9 (2 *C*(CH$_3$)$_2$), 68.2 (CO*C*H$_2$CH=CH$_2$), 61.8 and 60.7 (C6,6′,6″,6‴), 55.3 and 55.1 (2C) (C2′,2‴ and C$_6$H$_4$O*C*H$_3$), 37.8, 37.6, 29.7, 29.6, 27.5, and 27.3 (2 CO*C*H$_2$*C*H$_2$CO*C*H$_3$), 21.4 (COC$_6$H$_4$*C*H$_3$), 28.8, 28.5, 18.6, and 18.3 (2 C(*C*H$_3$)$_2$). Anal. Calcd. for $C_{99}H_{102}N_2O_{34}$: C, 63.79; H, 5.46. Found: C, 63.26; H, 5.63.

4-Methoxyphenyl (2-deoxy-4,6-*O*-isopropylidene-2-phthalimido-β-D-glucopyranosyl)-(1→4)-(6-*O*-levulinoyl-2,3-di-*O*-*p*-toluoyl-β-D-glucopyranosyl)-(1→3)-(2-deoxy-4,6-*O*-isopropylidene-2-phthalimido-β-D-glucopyranosyl)-(1→4)-6-*O*-levulinoyl-2,3-di-*O*-*p*-toluoyl-β-D-glucopyranoside (11): To a solution of **10** (130 mg, 70 μmol) in THF (6 ml), containing morpholine (50 μl), was added tetrakis(triphenylphosphine)palladium (14 mg). The mixture was stirred and boiled under reflux until the de-allyloxycarbonylation was complete (**11**; R_f = 0.66, TLC (CH_2Cl_2-acetone, 6:1)). Then, the mixture was diluted with EtOAc (100 ml) and washed with aq 5% NaCl, and the organic layer was dried, filtered, and concentrated. Column chromatography (CH_2Cl_2-acetone, 7:1) of the residue gave **11**, isolated as a syrup. Yield 114 mg (91%), $[\alpha]_D$ +35° (c = 1). ^{1}H NMR ($CDCl_3$): δ = 7.864, 7.778, 7.689, 7.231, 7.202, 7.128, 7.108, and 6.963 (8d, each 2H, 4 COC$_6$*H*$_4$CH$_3$), 6.78–6.64 (m, 4H, C$_6$*H*$_4$OCH$_3$), 5.515 and 5.303 (2t, each 1H, $J_{2,3/2'',3''} = J_{3,4/3'',4''}$ = 9.0 and 9.3, H3,3″), 5.410 and 4.932 (2dd, each 1H, $J_{1,2/1'',2''}$ = 7.4 and 8.0, H2,2″), 5.208 and 5.087 (2d, each 1H, $J_{1',2'/1''',2'''}$ = 8.2 and 8.3, H1′,1‴), 4.934 and 4.695 (2d, each 1H, H1,1″), 4.085 and 4.016 (2dd, each 1H, $J_{2',3'/2''',3'''}$ = 10.3 and 10.5, H2′,2‴), 3.675 (s, 3H, C$_6$H$_4$OC*H*$_3$), 2.371, 2.358, 2.331, and 2.324 (4s, each 3H, 4 COC$_6$H$_4$C*H*$_3$), 2.248 and 2.148 (2s, each 3H, 2 COCH$_2$CH$_2$COC*H*$_3$), 1.238, 1.191, 1.185, and 1.179 (4s, each 3H, 2 C(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$): δ = 171.6 and 171.3 (2 *C*OCH$_2$CH$_2$COCH$_3$), 164.9, 164.8, 164.7, and 164.3 (4 *C*OC$_6$H$_4$CH$_3$), 99.9, 99.5, 98.4, and 98.2 (C1,1′,1″,1‴), 99.1 and 98.9 (2 *C*(CH$_3$)$_2$), 61.5 and 60.7 (C6,6′,6″,6‴), 56.8, 55.3, and 55.1 (C2′,2‴ and C$_6$H$_4$O*C*H$_3$), 37.8, 37.6, 29.7, 29.6, 27.5, and 27.3 (2 CO*C*H$_2$*C*H$_2$CO*C*H$_3$), 21.4 (COC$_6$H$_4$*C*H$_3$), 28.8, 28.5, 18.6, and 18.4 (2 C(*C*H$_3$)$_2$). Anal. Calcd. for $C_{95}H_{98}N_2O_{32}$: C, 64.11; H, 5.55. Found: C, 63.88; H, 5.68.

4-Methoxyphenyl (6-*O*-levulinoyl-2,3,4-tri-*O*-*p*-toluoyl-β-D-glucopyranosyl)-(1→3)-(2-deoxy-4,6-*O*-isopropylidene-2-phthalimido-β-D-glucopyranosyl)-(1→4)-(6-*O*-levulinoyl-2,3-di-*O*-*p*-toluoyl-β-D-glucopyranosyl)-(1→3)-(2-deoxy-4,6-*O*-isopropylidene-2-phthalimido-β-D-glucopyranosyl)-(1→4)-6-*O*-levulinoyl-2,3-di-*O*-*p*-toluoyl-β-D-glucopyranoside (12): To a solution of 6-*O*-levulinoyl-2,3,4-tri-*O*-*p*-toluoyl-β-D-glucopyranosyl trichloroacetimidate [6] (**3**; 54 mg, 70 μmol) and **11** (50 mg, 28 μmol) in dry CH_2Cl_2 (3 ml), containing 3 Å molecular sieves (75 mg), was added Me_3SiOTf (0.5 μl). After stirring for 90 min, TLC (CH_2Cl_2-acetone, 9:1) showed the disappearance of **11**, and the formation of **12** (R_f = 0.52). Then, the solution was neutralized with Et_3N, diluted with EtOAc (100 ml), filtered through Celite, washed with aq 5% NaCl, and the organic layer was dried, filtered, and concentrated. Column chromatography (CH_2Cl_2-acetone, 9:1) of the residue gave **12**, isolated as a glass. Yield 45 mg (65%), $[\alpha]_D$ +49° (c = 1). ^{1}H NMR ($CDCl_3$): δ = 7.851, 7.771, 7.677, 7.505, 7.253, 7.218, 7.189, 7.122, 7.114, 7.096, 6.969, 6.962, 6.960, and 6.956 (14d, each 2H, 7 COC$_6$*H*$_4$CH$_3$), 6.77–6.64 (m, 4H, C$_6$*H*$_4$OCH$_3$), 5.394, 5.094, and 4.884 (3dd, each 1H, $J_{1,2/1'',2''/1'''',2''''}$ = 7.4, 7.7, and 8.0, $J_{2,3/2'',3''/2'''',3''''}$ = 9.2, 9.4, and 9.6, H2,2″,2‴′), 5.059 and 5.045 (2d, each 1H, $J_{1',2'/1''',2'''}$ = 8.2 and 8.3, H1′,1‴), 4.919, 4.875, and 4.613 (3d, each 1H, H1,1″,1‴′), 4.367 and 4.273 (2dd, each 1H, $J_{2',3'/2''',3'''}$ = 9.9 and 10.4, H2′,2‴), 3.666 (s, 3H, C$_6$H$_4$OC*H*$_3$), 2.356, 2.346, 2.321, 2.301, and 2.225 (5s, 6,3,6,3,3H, 7 COC$_6$H$_4$C*H*$_3$), 2.226, 2.143, and 2.136 (3s, each 3H, 3 COCH$_2$CH$_2$COC*H*$_3$), 1.282, 1.255, 1.139, and 1.133 (4s, each 3H, 2 C(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$): δ = 172.1, 171.6, and 171.4 (3 *C*OCH$_2$CH$_2$COCH$_3$), 165.4, 165.0, 164.9 (2C), 164.7, 164.5, and 164.3 (7 *C*OC$_6$H$_4$CH$_3$), 100.1, 99.8, 99.6, 98.3, and 98.2 (C1,1′,1″,1‴,1‴′), 99.1 and 98.9 (2 *C*(CH$_3$)$_2$), 62.5, 61.6, 61.4, and 60.8 (2C) (C6,6′,6″,6‴,6‴′), 55.4, 55.3, and 55.2 (C2′,2‴ and C$_6$H$_4$O*C*H$_3$), 37.9, 37.3 (2C), 29.6 (2C), 28.9, 27.7, 27.6, and 27.4 (3 CO*C*H$_2$*C*H$_2$CO*C*H$_3$), 21.5 (COC$_6$H$_4$*C*H$_3$), 28.8 and 18.7 (2 C(*C*H$_3$)$_2$). FABMS (positive-ion mode; $C_{130}H_{132}N_2O_{42}$): *m/z* 2416 $[M+Na]^+$, 2394 $[M+H]^+$.

4-Methoxyphenyl (6-*O*-levulinoyl-2,3,4-tri-*O*-*p*-toluoyl-β-D-glucopyranosyl)-(1→3)-(4,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→4)-(6-*O*-levulinoyl-2,3-di-*O*-*p*-toluoyl-β-D-glucopyranosyl)-(1→3)-(4,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→4)-6-*O*-levulinoyl-2,3-di-*O*-*p*-toluoyl-β-D-glucopyranoside (13): To a solution of **12** (45 mg, 19 μmol) in CH_2Cl_2 (5 ml), containing H_2O (15 μl), was added CF_3CO_2H (100 μl). The mixture was stirred for 15 min,

when TLC (CH_2Cl_2-acetone, 3:1) showed the disappearance of **12** (R_f = 0.97) and the formation of a slower moving spot (R_f = 0.36). Then, the mixture was diluted with EtOAc (100 ml) and washed with aq 10% $NaHCO_3$ and aq 5% NaCl. The aqueous layers were extracted twice with EtOAc, and the combined organic layers were dried, filtered, and concentrated. To a solution of the residue in pyridine (5 ml) were added Ac_2O (5 ml) and a catalytic amount of 4-dimethylaminopyridine. After stirring overnight at room temperature, TLC (CH_2Cl_2-acetone, 9:1) showed the acetylation to be complete (**13**; R_f = 0.26). The mixture was concentrated and co-concentrated with toluene, EtOH, and CH_2Cl_2 (3 × 20 ml). Column chromatography (CH_2Cl_2-acetone, 9:1) of the residue gave **13**, isolated as a glass. Yield 38 mg (82%), $[\alpha]_D$ +13° (c = 1). ^{1}H NMR ($CDCl_3$): δ = 7.797, 7.749, 7.678, 7.644, 7.517, 7.406, 7.319, 7.128, 7.121, 7.099, 7.019, 7.011, 6.983, and 6.966 (14d, each 2H, 7 $COC_6H_4CH_3$), 6.77–6.66 (m, 4H, $C_6H_4OCH_3$), 5.370, 5.148, and 4.945 (3dd, each 1H, $J_{1,2/1'',2''/1''',2'''}$ = 7.4, 7.7, and 7.6, $J_{2,3/2'',3''/2''',3'''}$ = 10.2, 9.5, and 8.8, H2,2'',2'''), 5.025 and 4.887 (2d, each 1H, $J_{1',2'} = J_{1''',2'''}$ = 8.4, H1',1'''), 4.918, 4.927, and 4.487 (3d, each 1H, H1,1'',1''''), 4.094 and 4.059 (2dd, each 1H, $J_{2',3'/2''',3'''}$ = 10.6 and 10.7, H2',2'''), 3.716 (s, 3H, $C_6H_4OCH_3$), 2.399, 2.368, 2.332, 2.314, 2.285, and 2.224 (6s, 3,6,3,3,3,3H, 7 $COC_6H_4CH_3$), 2.224, 2.158, and 2.141 (3s, each 3H, 3 $COCH_2CH_2COCH_3$), 1.995, 1.933, 1.873, and 1.805 (4s, each 3H, 4 Ac); ^{13}C NMR ($CDCl_3$): δ = 172.9, 171.5, and 171.4 (3 $COCH_2CH_2COCH_3$), 170.3, 170.2, 168.9, and 168.7 (4 $COCH_3$), 165.5, 164.9, 164.8, 164.7 (2C), and 164.6 (2C) (7 $COC_6H_4CH_3$), 100.7, 100.5, 99.9, 97.4, and 97.3 (C1,1',1'',1''',1''''), 62.2 (2C), 61.8 (2C), and 61.5 (C6,6',6'',6''',6''''), 55.3 and 55.2 (2C) (C2',2''' and $C_6H_4OCH_3$), 37.7, 37.5 (2C), 29.6 (2C), 29.5, 27.5, and 27.4 (2C) (3 $COCH_2CH_2COCH_3$), 21.4 ($COC_6H_4CH_3$), 20.5 (3C) and 20.3 (4 $COCH_3$). FABMS (positive-ion mode; $C_{132}H_{132}N_2O_{46}$): *m/z* 2503 $[M+Na]^+$, 2481 $[M+H]^+$.

4-Methoxyphenyl (2,3,4-tri-*O*-*p*-toluoyl-β-D-glucopyranosyl)-(1→3)-(4,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→4)-(2,3-di-*O*-*p*-toluoyl-β-D-glucopyranosyl)-(1→3)-(4,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→4)-2,3-di-*O*-*p*-toluoyl-β-D-glucopyranoside (14): To a solution of **13** (35 mg, 14 μmol) in EtOH (6 ml) and toluene (3 ml) was added NH_2NH_2·HOAc (18 mg, 0.21 mmol). The mixture was stirred for 90 min, when TLC (CH_2Cl_2-acetone, 4:1) showed the conversion of **13** into **14** (R_f = 0.52). Then, the mixture was concentrated and column chromatography (CH_2Cl_2-acetone, 4:1) of the residue afforded **14**, isolated as a glass. Yield 24 mg (77%), $[\alpha]_D$ +15° (c = 1). ^{1}H NMR ($CDCl_3$): δ = 7.886, 7.752, 7.738, 7.674, 7.543, 7.441, 7.408, 7.133, 7.125, 7.117, 7.087, 7.030, 7.009, and 6.972 (14d, each 2H, 7 $COC_6H_4CH_3$), 6.77–6.65 (m, 4H, $C_6H_4OCH_3$), 5.368, 5.146, and 4.841 (3dd, each 1H, $J_{1,2/1'',2''/1''',2'''}$ = 7.7, 7.8, and 7.1, $J_{2,3/2'',3''/2''',3'''}$ = 9.3, 9.8, and 8.6, H2,2'',2''''), 5.136 and 5.052 (2d, each 1H, $J_{1',2'/1''',2'''}$ = 8.2 and 8.4, H1',1'''), 4.986, 4.596, and 4.422 (3d, each 1H, H1,1'',1''''), 4.165 and 4.152 (2dd, each 1H, $J_{2',3'/2''',3'''}$ = 10.9 and 10.8, H2',2'''), 3.682 (s, 3H, $C_6H_4OCH_3$), 2.380, 2.354, 2.329, and 2.222 (4s, 3,6,9,3H, 7 $COC_6H_4CH_3$), 2.009, 1.933, 1.922, and 1.796 (4s, each 3H, 4 Ac); ^{13}C NMR ($CDCl_3$): δ = 170.4 (2 C), 169.6, and 169.3 (4 $COCH_3$), 165.9, 165.6, 165.0, 164.8, and 164.7 (3C) (7 $COC_6H_4CH_3$), 100.2, 99.9, 99.5, 97.8 (2C) (C1,1',1'',1''',1''''), 61.5 (2C), 60.9, and 60.5 (2C) (C6,6',6'',6''',6''''), 55.5 and 55.4 (2C) (C2',2''' and $C_6H_4OCH_3$), 21.5 ($COC_6H_4CH_3$), 20.6 ($COCH_3$). FABMS (positive-ion mode; $C_{117}H_{114}N_2O_{40}$): *m/z* 2209 $[M+Na]^+$, 2187 $[M+H]^+$.

4-Methoxyphenyl (2,3,4-tri-*O*-*p*-toluoyl-β-D-glucopyranosyluronic acid)-(1→3)-(4,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→4)-(2,3-di-*O*-*p*-toluoyl-β-D-glucopyranosyluronic acid)-(1→3)-(4,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→4)-2,3-di-*O*-*p*-toluoyl-β-D-glucopyranosyluronic acid (15): To a solution of **14** (20 mg, 9 μmol) in dry CH_2Cl_2 (1.5 ml), containing Ac_2O (14 μl), was added pyridinium dichromate (21 mg, 55 μmol). After stirring for 1 h, the brown suspension became a brown solution, and after 6 h, TLC (CH_2Cl_2-MeOH-HOAc, 90:10:1) showed the conversion of **14** (R_f = 1) into **15** (R_f = 0.73). After the addition of EtOAc (25 ml), the suspension was applied to column chromatography (EtOAc-HOAc, 99:1) to give **15**, isolated as a glass. Yield 14 mg (70%), $[\alpha]_D$ +32° (c = 0.5).

A small amount of **15** was esterified with diazomethane in ether, and analyzed by ^{1}H NMR ($CDCl_3$): δ = 7.822, 7.760, 7.711, 7.651, 7.561, 7.395, 7.319, 7.129, 7.118, 7.113, 7.035, 7.022, 6.995, and 6.978 (14d, each 2H, 7 $COC_6H_4CH_3$), 6.78–6.65 (m, 4H, $C_6H_4OCH_3$), 5.200 and 4.842 (2d, each 1H, $J_{1',2'/1''',2'''}$ = 8.8 and 8.7, H1',1'''), 5.003, 4.971, and 4.525 (3d, each 1H, $J_{1,2/1'',2''/1''',2'''}$ = 6.8, 8.1, and 7.6, H1,1'',1''''), 3.691 (s, 3H, $C_6H_4OCH_3$), 3.597, 3.436, and 3.377 (3s, each 3H, 3 $COOCH_3$), 2.402, 2.376, 2.339, 2.329, 2.291, and 2.222 (6s, 3,3,3,6,3,3H, 7 $COC_6H_4CH_3$), 2.079, 1.902, 1.878, and 1.737 (4s, each 3H, 4 Ac). FABMS (positive-ion mode; $C_{120}H_{114}N_2O_{43}$): *m/z* 2294 $[M+Na]^+$, 2272 $[M+H]^+$.

4-Methoxyphenyl (β-D-glucopyranosyluronic acid)-(1→3)-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-(β-D-glucopyranosyluronic acid)-(1→3)-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→4)-β-D-glucopyranosyluronic acid (2): To a solution of **15** (7 mg, 3 μmol) in 1-BuOH (5 ml) was added ethylenediamine (1 ml). The reaction mixture was stirred overnight at 90°C under Ar, when TLC (1-BuOH-EtOH-H_2O-HOAc, 4:2:2:0.5) showed the disappearance of **15**. The mixture was concentrated and co-concentrated with toluene (5 × 10 ml), the residue was dissolved in dry pyridine (5 ml), and Ac_2O (5 ml) and a catalytic amount of 4-dimethylaminopyridine were added. The mixture was stirred overnight at room temperature, then concentrated and co-concentrated with toluene and EtOH (2 × 20 ml). The yellow, amorphous solid was dissolved in THF (5 ml), and at 0°C under vigorous stirring, aq 2 M NaOH (1 ml) was added. After stirring for 6 h at 0°C, TLC (1-BuOH-EtOH-H_2O-HOAc, 4:2:2:0.5) showed the conversion into **2** (R_f = 0.56), and the solution was neutralized with aq 1 M HCl. The solution was concentrated and co-concentrated with toluene-MeOH (1:1; 3 × 10 ml), and gel filtration on Sephadex G-10 (water) of the residue afforded **2**, isolated after lyophilization as a white, amorphous powder. Yield 2.5 mg (75%). ^{1}H NMR (D_2O): δ = 7.12–6.96 (m, 4H, $C_6H_4OCH_3$), 4.992 (d, 1H, $J_{1,2}$ 7.8, H1), 4.585 and 4.557 (2d, each 1H, $J_{1',2'/1''',2'''}$ = 8.5 and 8.6, H1',1'''), 4.524 and 4.468 (2d, each 1H, $J_{1'',2''/1'''',2''''}$ = 7.8 and 7.9, H1'',1''''), 3.809 (s, 3H, $C_6H_4OCH_3$), 2.048 and 2.002 (2s, each 3H, $NHCOCH_3$). FABMS (negative-ion mode; $C_{41}H_{58}N_2O_{30}$): *m/z* 1079 $[M+Na-H]^-$, 1057 $[M-H]^-$.

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