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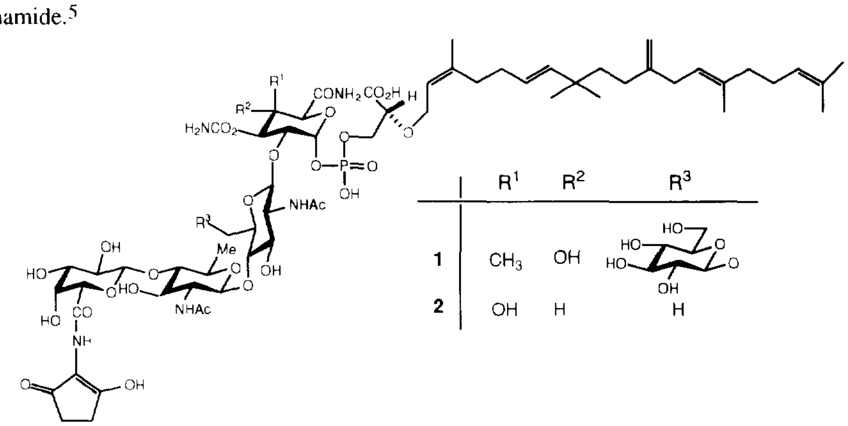
Synthesis of 2-(Trimethylsilyl)ethyl 4-C-methyl-β-D-glucopyranuronamide. A Derivative Suitable as Building Block in Synthesis of Phosphoglycolipid Antibiotics

Thomas G. Hansson*[1] and Niklas A. Plobeck*[2]

Astra Arcus AB, S-151 85 Södertälje Sweden.

Abstract: The title compound, a protected derivative of a unique component in the moenuronamide group of phosphoglycolipid antibiotics has been synthesised in eleven steps and 30 % total yield from 2-(trimethylsilyl)ethyl-β-D-galactopyranoside (**6**). The key step was a stereroselective addition of methylmagnesium chloride to ketone **11** to form the 4-C-methyl-glucopyranoside **12**.

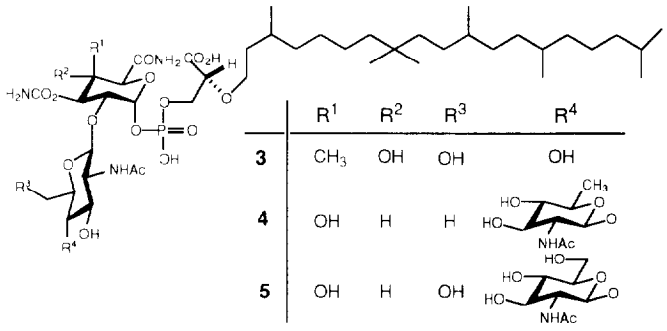
The phosphoglycolipid group of antibiotics have been isolated mainly from various *Streptomyces* cultures and are very efficient inhibitors of bacterial cell wall peptidoglycan biosynthesis.[3] So far the full structure has been elucidated for six such antibiotics, including four which have a derivative of the unique carbohydrate 4-C-methyl-β-D-glucuronamide (**19**) (moenuronamide) in a central position.[4] The most thoroughly studied member is moenomycin A (**1**).[4a] Recently the structures were elucidated for two phosphoglycolipid antibiotics, for example moenomycin C_1 (**2**), where moenuronamide is replaced by galacturonamide.[5]



Scheme 1

Much of the structural basis for the biological activity of the phosphoglycolipid antibiotics has been revealed by Welzel and co-workers. Thus the disaccharide **3** is the smallest unit of moenomycin A (**1**) which still retains biological activity.[6] Similar studies on moenomycin C_1 (**2**) showed that in this case the

trisaccharide **4** was necessary to obtain similar biological activity.[5a] A synthetic program focusing on the galacturonamide group of antibiotics, recently led to the synthesis of the first synthetic bacterial transglycosylation inhibitor **5**.[7] No publications have appeared so far on the synthesis of antibiotics incorporating 4-C-methyl-D-glucuronamide.[8]



Scheme 2

In order to gain synthetic access to the 4-C-methyl-D-glucuronamide group of phosphoglycolipid antibiotics, an efficient synthesis of a suitably protected form of this carbohydrate was needed. Although no synthesis of **19** has been reported, two syntheses of derivatives of 4-C-methyl-D-glucuronic acid[9] and several syntheses of derivatives of 4-C-methyl-D-glucose have been reported,[10,11] all starting from glucose or galactose. However for various reasons, none of these derivatives is well suited to be used in the synthesis of phosphoglycolipid antibiotics. We now report an efficient synthesis of a protected 4-C-methyl-β-D-glucuronamide derivative, suitable for this purpose.

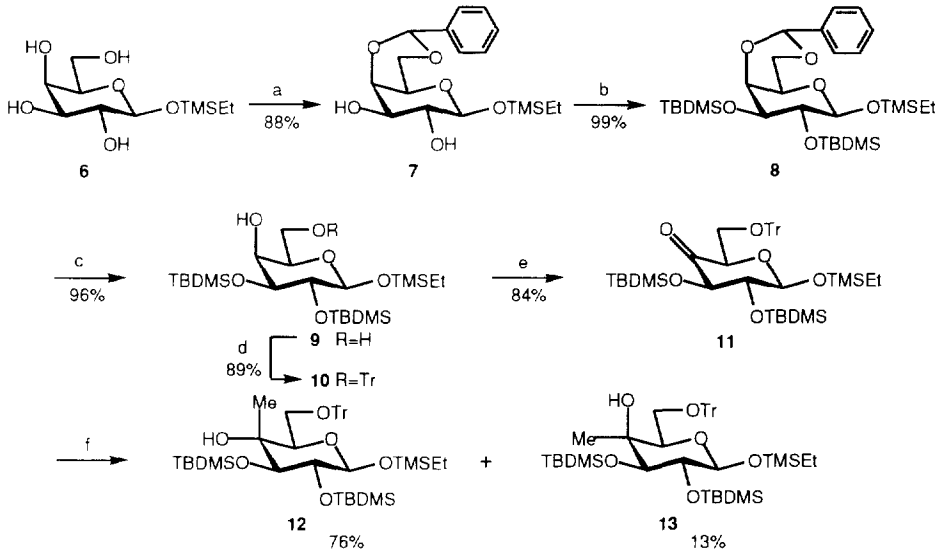
The first problem to be addressed when planning the synthesis, was how to stereoselectively introduce the 4-C-methyl group into a glucopyranose derivative. Previous synthesis of 4-alkyl branched gluco and galactopyranoses have usually relied on addition of organometallics, to various 4-uloses,[9,10,12] although other routes have also been used.[11] Quite often, mixtures of axial and equatorial methyl branched products have been obtained, although high axial stereoselectivity in the addition of various organometallics to 4-uloses of the α series have been reported.[9a,10a,10c]

Our synthesis employs the 2-(trimethylsilyl)ethyl (TMSEt) group as an anomeric blocking group. This protective group has proved its merits in the synthesis of many complex oligosaccharides.[13] It is stable to a large variety of reaction conditions but specific removal is possible under relatively mild acidic conditions.[14] However, there is a difference in stability between α- and β-TMSEt glycosides towards acidic deprotection conditions, only the β TMSEt anomer can be predicted to be cleaved under conditions mild enough to be useful in the synthesis of phosphoglycolipid antibiotics.[14] Although very little is known on the stereoselectivity on addition of organometallics to β glycosidic 4-uloses,[10a] we envisioned that by optimisation of the reaction conditions, stereoselective axial methylation of a suitably protected TMSEt β-D-*xylo*-hexopyranoside-4-ulose could be achieved.

2-(Trimethylsilyl)ethyl β-D-galactopyranoside (**6**), easily made in two steps from commercially available tetra-O-acetyl-α-D-galactopyranosyl bromide, was converted to the benzylidene acetal **7**,[14] using α,α-dimethoxytoluene in acetonitrile. The acetal **7** was treated with an excess of *t*-butyldimethylsilyl chloride

to give the silylated derivative **8**, which underwent catalytic hydrogenation to give the diol **9** in excellent yield. Tritylation of the primary alcohol, employing triphenylmethyl chloride, triethyl amine and 4-dimethylaminopyridine in DMF at room temperature was very slow but eventually led to the triphenylmethylether **10** in good yield. As an alternative tritylation method, 4-dimethylamino-N-triphenylmethylpyridinium chloride in dichloroethane was used, the reaction time was then shortened to a few hours and yields were comparable.[15] Oxidation of the alcohol **10** was accomplished with pyridinium dichromate (PDC)-acetic anhydride to give the ketone **11**.[16]

In order to stereoselectively introduce the C-4-methyl group on the ketone **11** various organometallic reagents and reaction conditions were tried. The best result was obtained when methylmagnesium chloride was added to **11** at -78°C in a 8:1 mixture of toluene / THF. Typically, the ratio between axial and equatorial adducts **12** and **13** was 6:1 and the 4-C-methyl-D-glucose derivative **12** was isolated in 76% yield. On a small scale (< 1 mmol), the selectivity was often as high as 15:1. In accord with previous reports, the reaction showed a notable solvent dependence.[10a,10c] For example, when a similar reaction was attempted in pure THF instead of a 8:1 mixture of toluene / THF no reaction was obtained.

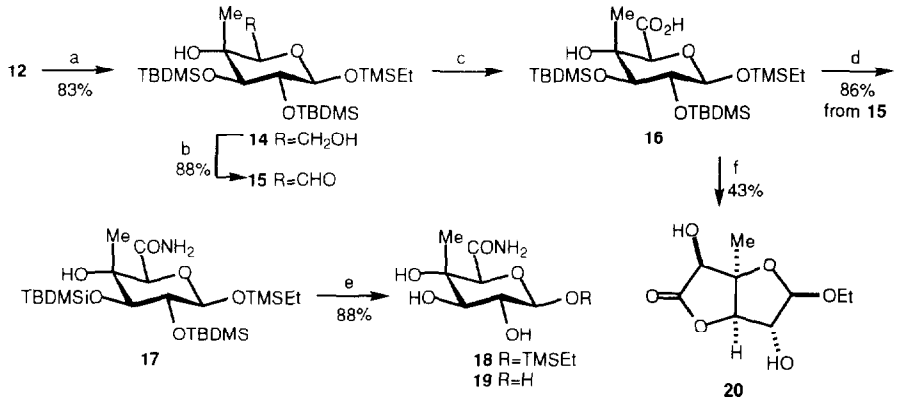


Reagents and Conditions; (a) $PhCH(OMe)_2$, PTSA, MeCN, RT. (b) $^tBuMe_2SiCl$, Imidazole, DMF, RT. (c) H_2/Pd, AcOH, RT. (d) TrCl, Et_3N, DMAP, DMF, RT. (e) PDC, Ac_2O, CH_2Cl_2, 40°C. (f) MeMgCl, 1:8 THF-Toluene, -70°C→RT.

Scheme 3

The configuration of C-4 in **12** and **13** was determined by the difference in ^{13}C NMR chemical shift of the C-4-methyl carbons, corresponding to observations made in NMR studies of related 4-C-methyl-branched sugars where axial methyl groups were found to have significantly higher chemical shift.[17] The assignment was later corroborated by conversion of the C-4-methyl-glucuronic acid derivative **16** into ethyl 4-C-methyl-D-glucurono-6,3 lactone (**20**),[9] which previously has been isolated from moenomycin A by acidic ethanolysis.[18]

Oxidation of the C-6 position was accomplished after cleavage of the trityl group from **12** with formic acid in diethylether affording **14**.[19] This alcohol was oxidized with PDC-acetic anhydride to give the aldehyde **15**, which underwent further oxidation with Ag_2O to give the 4-C-methyl-glucuronic acid derivative **16** in high yield. Alternatively the alcohol **14** could be oxidized to the aldehyde **15** with dimethyl sulfoxide / acetic anhydride, however, prolonged reaction time resulted in transformation of the tertiary 4-OH of **15** into the corresponding methylthiomethyl ether.[20] The 4-C-methyl-glucuronic acid derivative **16** was converted to the amide **17** with isobutyl chloroformate and ammonia in dichloromethane (86% from **15**). Finally, cleavage of the silyl groups with tetrabutylammonium fluoride in THF afforded 2-(trimethylsilyl)ethyl 4-C-methyl-β-D-glucuronamide (**18**). The synthesis of **18** required 11 steps from **6** in 30% total yield.



Reagents and conditions;(a) HCO_2H, Et_2O, RT. (b) PDC, Ac_2O, CH_2Cl_2, 40°C. (c) AgO_2, $EtOH/H_2O$, RT. (d) i) i-BuOCOCl ii) NH_3, CH_2Cl_2, -15°C (e) TBAF, THF, RT. (f) 0.1M HCl, EtOH, 80°C.

Scheme 4

In summary, an efficient synthetic route to various TMSEt protected 4-C-methyl glucopyranoses has been developed. The 2-(trimethylsilyl)ethyl anomeric protecting group can be selectively transformed to other derivatives and removed by treatment with trifluoroacetic acid in methylene chloride at -20°C. Under these relatively mild conditions, glycosidic and amide bonds are stable making these derivatives suitable for synthesis of phosphoglycolipid antibiotics.

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EXPERIMENTAL.

General Procedures. All moisture sensitive reactions were performed in flame-dried glassware with rubber septa under a positive pressure of dry nitrogen. Organic extracts were dried over Na_2SO_4. TLC was performed on Merck Kieselgel 60 F_{254}. Preparative liquid chromatography was performed on Merck Kieselgel 60 (0.040-0.063 mm). ^1H and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz respectively. Chemical shifts are referenced to $CDCl_3$ (7.26 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR) and CD_3OD (3.30 ppm for ^1H NMR and 49.0 ppm for ^{13}C NMR). IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The benzylidene

acetal **7** was prepared from **6** by a modification of a published method,[14] using α,α-dimethoxytoluene in acetonitrile with toluene-p-sulfonic acid as catalyst in 88% yield.

2-(Trimethylsilyl)ethyl 4,6-O-benzylidene-2,3-di-O-*tert*butyldimethylsilyl-β-D-galactopyranoside (8). *tert*Butyldimethylsilyl chloride (3.26 g, 21.7 mmol) was added to a stirred solution of **7** (2.00 g, 5.44 mmol) and imidazole (3.00 g, 44.1 mmol) in DMF (32 mL) at room temperature. After 12 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (2x100 mL). The organic layer was dried and concentrated and the residue purified by chromatography (SiO_2, 1:3 EtOAc-heptane) affording crystalline **8** (3.28 g, 99%) with mp 170-171°C: $[\alpha]^{25}_D$ +8° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.54 (dd, 2H, *J* = 7.6, 1.6 Hz, *o*-ArH), 7.38-7.31 (m, 3H, *p*-ArH, *m*-ArH), 5.47 (s, 1H, PhC*H*), 4.32 (dd, 1H, *J* = 12.4, 1.2 Hz, H-6), 4.17 (d, 1H, *J* = 7.6 Hz, H-1), 4.04 (dd, 1H, *J* = 12.0, 1.6 Hz, H-6), 4.02 (br. d, 1H, *J* = 4.8 Hz, H-4), 3.98 (ddd, 1H, *J* = 11.8, 9.2, 6.4 Hz, C*H*CH_2SiMe_3), 3.76 (dd, 1H, *J* = 9.0, 7.2 Hz, H-2), 3.68 (dd, 1H,*J* = 9.0, 3.4 Hz, H-3), 3.46 (ddd, 1H, *J* = 11.4, 9.2, 6.2 Hz, C*H*CH_2SiMe_3), 3.36 (br. s, 1H, H-5), 1.03 (ddd, 2H, *J* =12.4, 5.8, 5.8 Hz, C*H*$_2$$SiMe_3$), 0.92, 0.91 (2s, each 9H, *Me*$_3$CSi), 0.13, (s, 3H, SiMe), 0.11 (s, 6H, SiMe), 0.09 (s, 3H, SiMe), 0.0 (s, 9H, $SiMe_3$); ^{13}C NMR δ 138.1, 128.6, 128.0, 126.3 (Ar), 103.6 (C-1), 101.0 (Ph*C*H), 77.1 (C-4), 75.2 (C-3), 72.2 (C-2), 69.4 (C-6), 67.0 (CH_2CH_2Si), 66.4 (C-5), 26.2, 26.1 (2 *Me*$_3$CSi), 18.4, 18.3 (2 Me3*C*Si), 18.1 (CH_2Si), -1.48 (Me_3Si), -3.5, -3.6, -3.9, -4.2 (4 MeSi). Anal. Calcd. for $C_{30}H_{56}O_6Si_3$: C, 60.35; H, 9.45. Found: C, 60.21; H, 9.27.

2-(Trimethylsilyl)ethyl 2,3-di-O-*tert*butyldimethylsilyl-β-D-galactopyranoside (9). To a mixture of **8** (2.00 g, 3.40 mmol) in acetic acid (50 mL) was added 10% Pd-C (500 mg). The reaction was degassed and then stirred under a hydrogen atmosphere (1 atm.) for 24 h at room temperature. Upon completion of the reaction, the mixture was filtered through Celite and the solvent was removed. Column chromatography (SiO_2, 1:4, EtOAc-heptane) of the residue afforded **9** (1.62 g, 96%) as a white solid; $[\alpha]^{25}_D$ -7.5° (c 0.90, $CHCl_3$); IR ($CHCl_3$) 3570 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.15 (m, 1H, H-1), 3.97 (dd, 1H, *J* = 11.7, 7.1 Hz, H-6), 3.93 (m, 1H, C*H*CH_2SiMe_3), 3.80 (dd, 1H *J* = 11.7, 4.6 Hz, H-6), 3.78 (m, 1H, H-3), 3.61 (m, 2H, H-2, H-4), 3.50 (m, 2H, H-5, C*H*CH_2SiMe_3), 1.02 (m, 2H, C*H*$_2$$SiMe_3$), 0.92, 0.89 (2s, each 9H, *Me*$_3$CSi), 0.14, 0.12, 0.11, 0.07 (4s, each 3H, MeSi), 0.0 (s, 9H, Me_3Si); ^{13}C NMR ($CDCl_3$) δ 103.3 (C-1), 75.9 (C-2/4), 73.8 (C-5), 72.7 (C-2/4), 70.5 (C-3), 67.2 (CH_2CH_2Si), 62.6 (C-6) 26.1 (2 *Me*$_3$CSi), 18.22 (Me_3CSi), 18.21 (CH_2Si), 18.1 (Me_3CSi), -1.5 (Me_3Si), -3.2, -3.77, -3.83, -4.4 (4 MeSi). Anal. Calcd. for $C_{23}H_{52}O_6Si_3$: C, 54.28; H, 10.30. Found: C, 54.51; H, 10.21.

2-(Trimethylsilyl)ethyl 2,3-di-O-*tert*butyldimethylsilyl-6-O-triphenylmethyl-β-D-galactopyranoside (10). A mixture of **9** (10.29 g, 20.2 mmol), triphenylmethyl chloride (13.64 g, 48.8 mmol), 4-dimethylaminopyridine (300 mg, 2.45 mmol) and triethylamine (10.8 mL, 77.6 mmol) in N,N-dimethylformamide (300 mL) was stirred at room temperature. After 5 days the solution was concentrated and the residue was purified by chromatography (SiO_2, 1:9 EtOAc-heptane) affording **10** (13.6 g, 89%) as a white solid with $[\alpha]^{25}_D$ -18.3° (c 0.90, $CHCl_3$); IR ($CHCl_3$) 3572 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50-7.20 (m, 15H, ArH), 4.14 (d, 1H, *J* = 7.0 Hz, H-1), 4.01 (m, 1H, C*H*CH_2SiMe_3), 3.83 (br. s, 1H, H-4), 3.61 (dd, 1H, *J* = 8.6, 7.2 Hz, H-2), 3.58 (dd, 1H, *J* = 8.8, 3.1 Hz, H-3), 3.55-3.46 (m, 3H, H-5, H-6, C*H*CH_2SiMe_3), 3.35 (m, 1H, H-6), 1.05 (m, 2H, C*H*$_2$$SiMe_3$), 0.95, 0.92 (2s, each 9H, *Me*$_3$CSi), 0.16, 0.14, 0.13, 0.09 (4s, each 3H, MeSi), 0.00 (s, 9H, Me_3Si); ^{13}C NMR ($CDCl_3$) δ 144.0, 128.7, 127.8, 126.9 (Ar), 103.2 (C-1), 86.6 (*C*Ph$_3$), 76.7 (C-3), 73.1 (C-5), 72.9 (C-2), 70.1 (C-4), 66.8 (CH_2CH_2Si), 62.8 (C-6), 26.2, 26.1 (2 *Me*$_3$CSi), 18.24, 18.22 (2 Me_3CSi), 18.18 (CH_2Si), -1.5 (Me_3Si), -3.2, -3.8, -4.2 (4 MeSi). Anal. Calcd. for $C_{42}H_{66}O_6Si_3$: C, 67.15; H, 8.85. Found: C, 67.16; H, 8.87.

2-(Trimethylsilyl)ethyl 2,3-di-O-*tert*butyldimethylsilyl-6-O-triphenylmethyl-β-D-*xylo*-hexopyranoside-4-ulose (11). A solution of **10** (9.17 g, 12.2 mmol) in dry CH_2Cl_2 (10 mL) was added to a solution of finely divided pyridinium dichromate (3.25 g, 8.64 mmol) and acetic anhydride (3.42 mL, 36.2 mmol) in dry CH_2Cl_2 (50 mL) The stirred mixture was heated at 40°C for 3h. After the solution was cooled, heptane (ca. 60 mL) was added and the heterogeneous mixture was filtered through a short plug of silica gel. The silica plug was washed with a few more volumes of 1:9 EtOAc-heptane. The combined solutions were concentrated and the residue was subjected to chromatography (SiO_2, 1:20 EtOAc-heptane) to give **11** (7.69 g, 84%) as syrup with $[\alpha]^{25}_D$ -11.1° (c 1.07, $CHCl_3$); IR ($CHCl_3$) 1740 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48-7.20 (m, 15H, ArH), 4.59 (d, 1H, *J* = 6.4 Hz, H-1), 4.13 (d, 1H, *J* = 8.4 Hz, H-3), 4.02 (m, 1H, C*H*CH_2SiMe_3), 3.96 (dd, 1H, *J* = 8.0, 3.3 Hz, H-5), 3.68 (dd, 1H, *J* = 8.4, 6.4 Hz, H-2), 3.62 (m, 1H, C*H*CH_2SiMe_3), 3.56 (dd, 1H, *J* = 10.6, 3.5 Hz, H-6), 3.46 (dd, 1H, *J* = 10.6, 8.3 Hz, H-6), 1.00 (m, 2H, C*H*$_2$$SiMe_3$), 0.92, 0.91 (2s, each 9H, *Me*$_3$CSi), 0.12, 0.09, 0.04, -0.01 (4 s, each 3H, MeSi), 0.00(s, 9H, Me_3Si); ^{13}C NMR ($CDCl_3$) δ 202.3 (C-4), 143.8, 128.7,

127.8, 127.0 (Ar), 103.3 (C-1), 86.9 (CPh_3), 79.5 (C-3), 78.5 (C-2), 76.8 (C-5), 67.0 (CH_2CH_2Si), 62.7 (C-6), 26.0 (2 Me_3CSi), 18.4, 18.15 (2 Me_3CSi), 18.13 (CH_2Si), -1.5 (Me_3Si), -3.7, -4.1, -4.2, -4.7 (4 MeSi). Anal. Calcd. for $C_{42}H_{64}O_6Si_3$: C, 67.33; H, 8.61. Found: C, 67.31; H, 8.58.

Addition of methyl magnesium chloride to 11. A solution of methylmagnesium chloride (3 M solution in THF; 2 mL, 6 mmol) was added dropwise to a stirred solution of **11** (1.46 g, 1.94 mmol) in dry toluene (15 mL) at -78°C. The mixture was allowed to slowly attain room temperature (ca. 12h) and was then quenched by the addition of saturated ammonium chloride (20 mL). This mixture was extracted with diethyl ether (2x30 mL) and the combined organic extracts were dried and concentrated. Column chromatography (SiO_2, 1:20 EtOAc-heptane) of the residue followed by preparative HPLC (APEX PrepSil Si 130, 8 μm, 25-cm x 20-mm i.d.; mobile phase EtOAc-heptane 4:96, flow rate 5 mL/min; UV detection at 254 nm) on fractions containing mixtures of **12** and **13**, provided a total of the exo methyl adduct **12** (oil, 1.12g, 76%) and the endo methyl adduct **13** (oil, 190 mg, 13%).

2-(Trimethylsilyl)ethyl 2,3-di-O-*tert*butyldimethylsilyl-4-C-methyl-6-O-triphenylmethyl-β-D-glucopyranoside (12). $[\alpha]^{25}_D$ -34.6° (c 1.07, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.50-7.20 (m, 15H, ArH), 4.32 (d, 1H, J = 6.5 Hz, H-1), 4.02 (m, 1H, $CHCH_2SiMe_3$), 3.57 (m, 1H, $CHCH_2SiMe_3$), 3.53 (m, 2H, H-5, H-6), 3.46 (d, 1H, J = 7.9 Hz, H-3), 3.35 (dd, 1H, J = 7.5, 6.0 Hz, H-2), 3.29 (m, 1H, H-6), 2.5 (br. s, 1H, 4-OH), 1.04 (m, 2H, CH_2SiMe_3), 1.00 (s, 3H, Me), 0.94, 0.91 (2s, each 9H, Me_3CSi), 0.16, 0.12, 0.11, 0.10 (4s, each 3H, MeSi), 0.00 (s, 9H, Me_3Si); ^{13}C NMR ($CDCl_3$) δ 143.9, 128.7, 127.8, 127.0 (Ar), 103.1 (C-1), 87.1 (CPh_3), 79.5 (C-3), 77.4 (C-5), 74.0 (C-2), 73.3 (C-4), 66.8 (CH_2CH_2Si), 63.3 (C-6), 26.4, 26.3 (2 Me_3CSi), 18.4, 18.3 (2 Me_3CSi), 18.1 (CH_2Si), 17.2 (Me), -1.5 (Me_3Si), -2.7, -2.9, -3.5, -3.7 (4 MeSi). Anal. Calcd. for $C_{43}H_{68}O_6Si_3$: C, 67.49; H, 8.96. Found: C, 67.28; H, 8.76.

2-(Trimethylsilyl)ethyl 2,3-di-O-*tert*butyldimethylsilyl-4-C-methyl-6-O-triphenylmethyl-β-D-galactopyranoside (13). $[\alpha]^{25}_D$ -18° (c 0.88, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.52-7.18 (m, 15H, ArH), 4.21 (d, 1H, J = 6.8 Hz, H-1), 4.12 (m, 1H, $CHCH_2SiMe_3$), 3.70 (dd, 1H, J = 7.6, 7.0 Hz, H-2), 3.61-3.50 (m, 2H, CH_2SiMe_3, H-6), 3.46 (dd, 1H, J = 10.5, 3.0 Hz, H-6), 3.34 (m, 1H, H-5), 3.32 (d, 1H, J = 7.8 Hz, H-2), 2.57 (d, 1H, J = 0.8 Hz, 4-OH), 1.01 (m, 2H, CH_2SiMe_3), 1.00 (s, 3H, Me), 0.95, 0.92 (2s, each 9H, Me_3CSi), 0.20, 0.16, 0.11, 0.08 (4s, each 3H, MeSi), 0.03 (s, 9H, Me_3Si); ^{13}C NMR ($CDCl_3$) δ 144.1, 128.7, 127.8, 126.9 (Ar), 102.7 (C-1), 87.0 (CPh_3), 79.2 (C-3), 77.7 (C-5), 74.1 (C-2), 73.0 (C-4), 66.2 (CH_2CH_2Si), 63.2 (C-6), 26.6, 26.3 (2 Me_3CSi), 23.1 (Me), 18.5, 18.3 (2 Me_3CSi), 18.0 (CH_2Si), -1.5 (Me_3Si), -2.1, -2.3, -2.8, -3.4 (4 MeSi). Anal. Calcd. for $C_{43}H_{68}O_6Si_3$: C, 67.49; H, 8.96. Found: C, 67.76; H, 8.86.

2-(Trimethylsilyl)ethyl 2,3-di-O-*tert*butyldimethylsilyl-4-C-methyl-β-D-glucopyranoside (14) Formic acid (90 mL) was added dropwise to a stirred solution of **12** (2.95 g, 3.85 mmol) in dry diethylether (150 mL) at room temperature. After stirring 15 minutes the reaction mixture was slowly poured out into a stirred ice cold mixture of K_2CO_3 (330 g) in water (700 mL) and then extracted with diethylether (700 mL). The etheral extract was washed with brine (400 mL), dried and concentrated. The residue was subjected to column chromatography (SiO_2, 1:9 EtOAc-heptane, then 1:4 EtOAc-heptane) to give **14** (1.67 g, 83%) as an amorphous solid with $[\alpha]^{25}_D$ -19.5° (c 0.87, $CHCl_3$); IR ($CHCl_3$) 3604, 3482 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.30 (d, 1H J = 5.9 Hz, H-1), 3.90 (m, 1H, $CHCH_2SiMe_3$), 3.90-3.76 (m, 2H, H-6), 3.52 (m, 1H, $CHCH_2SiMe_3$), 3.46 (m, Hz, 2H, H-3, H-5), 3.40 (dd, 1H, J = 7.5, 6.0 Hz, H-2), 2.57 (br s, 1H, 4-OH), 2.19 (dd, 1H J = 7.1, 5.2 Hz, 6-OH), 1.19 (s, 3H, Me), 1.00 (m, 2H, CH_2SiMe_3), 0.93, 0.90 (2s, each 9H, Me_3CSi), 0.13, 0.12, 0.11, 0.09 (4s, each 3H, MeSi), 0.00 (s, 9H, Me_3Si); ^{13}C NMR ($CDCl_3$) δ 103.1 (C-1), 78.9 (C-3/5), 78.4 (C-3/5), 73.7 (C-2), 73.4 (C-4), 67.2 (CH_2CH_2Si), 61.8 (C-6), 26.2 (2 Me_3CSi), 18.35, 18.24 (2 Me_3CSi), 18.18 (CH_2Si), 17.7 (Me), -1.5 (Me_3Si), -2.9, -3.0, -3.7, -3.9 (4 MeSi). Anal. Calcd. for $C_{24}H_{54}O_6Si_3$: C, 55.12; H, 10.41. Found: C, 55.05; H, 10.17.

2-(Trimethylsilyl)ethyl 2,3-di-O-*tert*butyldimethylsilyl-4-C-methyl-β-D-glucohexodialdosepyranoside (15). The alcohol **14** (1.60 g, 3.10 mmol) was oxidized with PDC / Ac_2O with the same procedure used for the alcohol **11.** Column chromatography (SiO_2, 1:9 EtOAc-heptane) afforded the aldehyde **15** (1.30g 88%) as a colourless oil with $[\alpha]^{25}_D$ -53.4° (c 1.12, $CHCl_3$); IR ($CHCl_3$) 3474 (OH), 1718 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.98 (d, 1H J = 2.4 Hz, CHO), 4.69 (d, 1H, J = 0.8 Hz, H-1), 4.58 (s, 1H, OH), 3.92 (m, 1H, $CHCH_2SiMe_3$), 3.86 (d, 1H, J = 2.5 Hz, H-5), 3.77 (dd, 1H, J = 3.7, 1.7 Hz, H-2), 3.53 (d, 1H, J = 3.7 Hz, H-3), 3.46 (m, 1H, $CHCH_2SiMe_3$), 1.21 (s, 3H, Me), 0.96-0.84 (m, 2H, CH_2SiMe_3), 0.92, 0.88 (2s, each 9H, Me_3CSi), 0.15, 0.11, 0.08 (3s, 12H, MeSi), 0.02 (s, 9H, Me_3Si); ^{13}C NMR ($CDCl_3$) δ 202.5 (C-6), 100.7 (C-1), 85.7 (C-5), 72.9 (C-3), 72.2 (C-2), 72.1 (C-4), 66.4 (CH_2CH_2Si), 25.7 (2 Me_3CSi), 21.5 (Me), 18.0 (2 Me_3CSi), 17.9 (CH_2Si), -1.5 (Me_3Si), -4.1, -4.5, -4.8 (4 MeSi). Anal. Calcd. for $C_{24}H_{52}O_6Si_3$: C, 55.34; H, 10.06. Found: C, 54.54; H, 9.83.

2-(Trimethylsilyl)ethyl 2,3-di-O-*tert*butyldimethylsilyl-4-C-methyl-β-D-glucopyranosiduronic acid (16). To a stirred solution of **15** (300 mg, 0.57 mmol) in ethanol (3 mL) was added a solution of $AgNO_3$ (230 mg, 1.35 mmol) in water (0.35 mL), then aqueous potassium hydroxide (1.07 M, 3.0 mL, 3.2 mmol) was added. The mixture was stirred at room temperature for 2 h and then filtered through a short plug of silica gel. The silica plug was eluted with ethanol (10 mL) and 9:1 EtOAc-AcOH (10 mL) and the combined eluate was concentrated. The residue was taken up in ether (10 mL) and washed with HCl (aq) (0.01M, 25 mL). The aqueous phase was extracted with ether (3x10 mL) and the combined organic phases were dried and concentrated giving virtually pure **16** (290 mg) as a colourless oil with $[\alpha]^{25}_D$ -25.8° (c 0.77, $CHCl_3$); IR ($CHCl_3$) 3448 (OH), 1744 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.63 (d, 1H, J = 3.1 Hz, H-1), 4.25 (s, 1H, H-5), 4.02 (m, 1H, C*H*CH_2SiMe_3), 3.69 (m, 1H, H-2), 3.60 (m, 2H, H-3, C*H*CH_2SiMe_3), 1.30 (s, 3H, Me), 1.01 (m, 2H, C*H*$_2SiMe_3$), 0.90 (2s, each 9H, *Me*$_3$CSi), 0.20-0.10 (4 s, each 3H, MeSi), 0.05 (s, 9H, Me_3Si). The acid **16** was used in the next step without further purification.

2-(Trimethylsilyl)ethyl 2,3-di-O-*tert*butyldimethylsilyl-4-C-methyl-β-D-glucopyranuronamide (17). Isobutylchloroformate (78 μL, 0.59 mmol) was added to a solution of triethylamine (83 μL, 0.59 mmol) in CH_2Cl_2 (2 mL) at -15°C. The mixture was stirred for 10 min and then a dry solution of **16** (290 mg, 054 mmol) in CH_2Cl_2 was added. The solution was stirred for 30 min at -15°C, and then a solution of ammonia in CH_2Cl_2 (1M, 6 mL) was added. After an additional hour, the mixture was allowed to attain room temperature and was then partitioned between water (20 mL) and CH_2Cl_2 (20 mL). The aqueous phase was extracted with CH_2Cl_2 (20 mL), and the combined organic phases were dried and concentrated. Column chromatography (SiO_2, 1:4 EtOAc-heptane) of the residue gave **17** (250 mg, 86% from **15**) as a colourless syrup with $[\alpha]^{25}_D$ -63.6° (c 0.85, $CHCl_3$); IR ($CHCl_3$) 3520, 3402 (NH), 1682 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.59 (br s, 1H, NH), 5.70 (br s, 1H, NH), 4.23 (d, 1H, J ≈ 7.6 Hz, H-1), 4.12 (s, 1H, OH), 3.90 (m, 1H, C*H*CH_2SiMe_3), 3.72 (s, 1H, H-5), 3.58 (m, 2H, H-3, C*H*CH_2SiMe_3), 3.29 (d, 1H, J = 9.1, 7.6 Hz, H-2), 1.17 (s, 3H, Me), 1.03 (m, 2H, C*H*$_2SiMe_3$), 0.93, 0.91 (2s, each 9H, *Me*$_3$CSi), 0.15, 0.13, 0.11, 0.10 (4s, each 3H, MeSi), 0.02 (s, 9H, Me_3Si); ^{13}C NMR ($CDCl_3$) δ 173.2 (CO_2H), 103.9 (C-1), 80.3 (C-3), 76.1 (C-5), 74.0 (C-2), 73.2 (C-4), 67.9 (*C*H_2CH_2Si), 26.6, 26.3 (2 *Me*$_3$CSi), 18.7, 18.32 (2 Me$_3$*C*Si), 18.17 (CH_2Si), 16.4 (Me), -1.5 (Me_3Si), -2.5, -3.4, -3.5 (4 MeSi). Anal. Calcd. for $C_{24}H_{53}NO_6Si_3$: C, 53.78; H, 9.97. Found: C, 53.51; H, 9.56.

2-(Trimethylsilyl)ethyl 4-C-methyl-β-D-glucopyranuronamide (18). Tetrabutylammonium fluoride (1 M solution in THF, 2.0 mL, 2.0 mmol) was added to a stirred solution of **17** (215 mg, 0.40 mmol) in tetrahydrofuran (5 mL) at room temperature. After 12 h the solution was concentrated and the residue purified by column chromatography (SiO_2, EtOAc, then 19:1 EtOAc-HOAc) affording **18** (108 mg, 88%) as white crystals with mp: 153-155°C. $[\alpha]^{25}_D$ -65.6° (c 0.54, MeOH), IR (KBr) 3508, 3434, 3359 (OH), 1687 (C=O) cm^{-1}; ^1H NMR (CD_3OD) δ 4.8 (s, 5H, OH, NH), 4.37 (d, 1H, J = 7.8 Hz, H-1), 4.05 (m, 1H, C*H*CH_2SiMe_3), 3.80 (s, 1H, H-5), 3.66 (m, 1H, C*H*CH_2SiMe_3), 3.48 (d, 1H, J = 9.7 Hz, H-3), 3.17 (dd, 1H, J = 9.7, 7.8 Hz, H-2), 1.16 (s, 3H, Me), 1.02 (m, 2H, C*H*$_2SiMe_3$), 0.05 (s, 9H, Me_3Si); ^{13}C NMR (CD_3OD) δ 174.7 ($CONH_2$), 104.4 (C-1), 79.5 (C-3), 77.3 (C-5), 74.2 (C-4), 73.6 (C-2), 68.5 (*C*H_2CH_2Si), 19.0 (CH_2Si), 16.0 (Me), -1.4 (Me_3Si). Anal. Calcd. for $C_{12}H_{25}NO_6Si$: C, 46.88; H, 8.20. Found: C, 46.61; H, 7.97.

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1. Present Address: Dep. Medicinal Chemistry, Astra Draco AB, Box 34, S-221 00 Lund, Sweden.
2. Present Address: Astra Pain Research Unit, 275 Boul. Armand-Frappier, Laval, Quebec, Canada H7V 4A7.
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