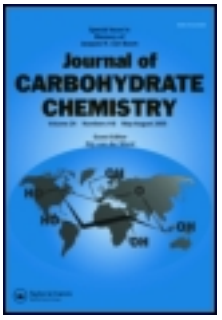

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A CONVENIENT, HIGHLY EFFICIENT ONE-POT PREPARATION OF PERACETYLATED GLYCALS FROM REDUCING SUGARS

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ABSTRACT

A convenient, highly efficient, one-pot, three-step procedure has been developed for the synthesis of peracetylated glycal derivatives from various reducing sugars including D-glucose, D-galactose, L-rhamnose, L-arabinose, D-maltose, D-lactose, and maltotriose. This procedure involves peracetylation of the reducing sugars with acetic anhydride and HBr/acetic acid followed by the transformation of the anomeric acetates to the corresponding bromides with additional HBr/acetic acid and finally reductive elimination of the 1-bromo and 2-acetoxy groups with $Zn/CuSO_4 \cdot 5H_2O$ in acetic acid/water containing sodium acetate. The overall yields of purified peracetylated glycals from the corresponding sugars range from 50 - 98%.

INTRODUCTION

Glycals[1] have been widely employed in the synthesis of various types of glycosides[2] and oligosaccharides.[3] Glycals also serve as the key building blocks in the synthesis of optically active natural products.[4] Therefore, their efficient, cost-effective large scale preparation would be of great value. Typically, the preparation involves three

steps, peracetylation of a carbohydrate,[5] replacement of the anomeric acetate with a halide[6] or sulfide,[7] and reductive elimination[8] to generate the 1,2-double bond. A recent account[9] that employs $(Cp_2TiCl)_2$ to effect the reductive elimination step has prompted us to report a one-pot procedure for the three-step sequence, without the isolation of any intermediates, that has been in use in our labs for some time.[10]

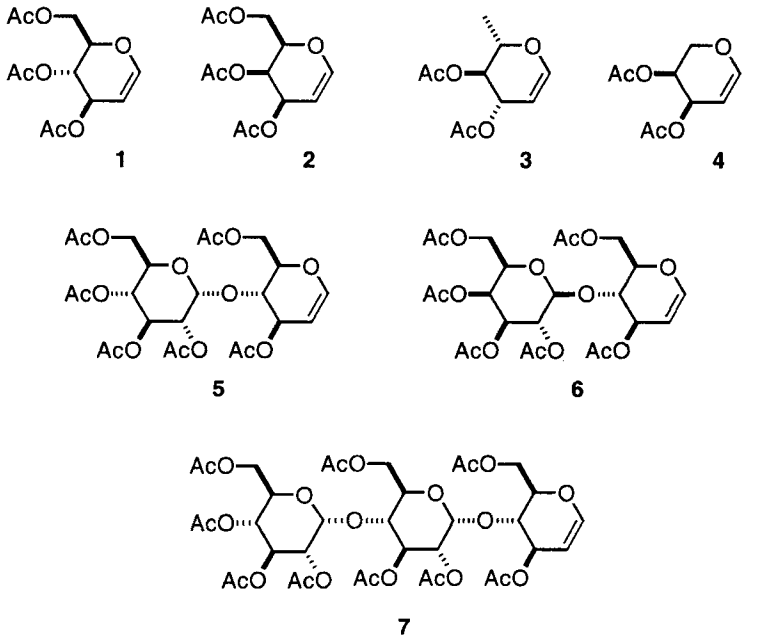
RESULTS AND DISCUSSION

A one-pot preparation of peracetylated glycosyl bromides from reducing sugars has been reported[11] using acetic anhydride and a catalytic amount of HBr/acetic acid to effect peracetylation, followed by the addition of several more equivalents of HBr/acetic acid to complete the formation of the anomeric peracetylglycosyl bromides. However, upon delving anew into details, it was noted that quite frequently the products from this treatment have been described as being accompanied with furanosyl acetate type of byproducts. It has been our observation that the problem of this byproduct formation could be effectively circumvented by maintaining the reaction temperature at or slightly below room temperature. Moreover, in virtually all cases a 1.8 - 2.3-fold excess of acetic anhydride is employed, i.e., ca. 4 excess equivalents for monosaccharides such as glucose, rhamnose, and galactose and 9 excess equivalents for disaccharides maltose and lactose. This is followed by the addition of between approximately 9 and 18 mol equivalents of HBr. It has been observed that the amount of HBr required for the completion of the conversion of the anomeric acetates to the corresponding bromides needs to be several equivalents above that of the remaining acetic anhydride. Therefore, it was concluded that the amount of HBr necessary for the bromide formation might be curtailed by limiting the amount of excess acetic anhydride used for the preceding peracetylation step. We have found that only 1 equivalent excess of acetic anhydride is needed to drive the peracetylation to completion, thereby the necessary amount of HBr can be limited to only between 5 and 6 equivalents. The one-step sequence was completed by first neutralizing the excess HBr of the peracetylation mixture with sodium acetate, followed by pouring the resulting solution into a suspension of $Zn/CuSO_4$ in water and acetic acid buffered with sodium acetate. After work-up, crude yields from various free carbohydrates were good to excellent and the peracetylated glycal products thus obtained were in many cases sufficiently pure to be used for synthetic reactions. When needed, the crude glycals can be purified by silica gel flash column chromatography to their highly pure peracetyl glycals as judged by the results of spectroscopic and combustion analyses (Table 1). For the preparation of peracetyl

TABLE 1. Preparation of Peracetylated Glycals from Reducing Sugars

Reducing Sugars	Glycal Products	Yield (%)[a]
D-glucose	tri-*O*-acetyl-D-glucal (**1**)	98
D-galactose	di-*O*-acetyl-D-galactal (**2**)	58
L-rhamnose	di-*O*-acetyl-D-rhamnal (**3**)	71
L-arabinose	di-*O*-acetyl-L-arabinal (**4**)	51
D-maltose	hexa-*O*-acetyl-D-maltal (**5**)	86
D-lactose	hexa-*O*-acetyl-D-lactal (**6**)	61
D-maltotriose	nona-*O*-acetyl-D-maltotrial (**7**)	50

a. Yield of chromatographically and spectroscopically pure, isolated peracetylated products.



glycals **5** and **7** from D-maltose and maltotriose, respectively, it was found that the yields of the byproducts **1** (from D-maltose) and **1** and **5** (from D-maltotriose) increase as the reaction time for the anomeric bromide formation step is prolonged. Accordingly, it is paramount to limit the reaction time for this step to several hours or less so that the

cleavage of the axial α-glycoside linkage can be suppressed. In contrast, such a problem of by-product formation was not encountered for D-lactose having the β–equatorial glycoside linkage which is less subject to a facile HBr/acetic acid hydrolysis.

The one-pot, three-step preparation of glycals described herein involves the use of only inexpensive, readily available reagents and represents one of the most efficient and convenient procedures to access diverse types of peracetylated glycals.

EXPERIMENTAL SECTION

General. All carbohydrates except maltose were purchased from Aldrich Chemical Company, Milwaukee, WI: D-glucose (monohydrate, 96%), D-galactose (97%), L-rhamnose (monohydrate, 98%), L-arabinose (98%), α-D-lactose (monohydrate, 97%), maltotriose (monohydrate, 95%). D-Maltose monohydrate (97%) was purchased from Fluka Chemical Corp., Ronkonkoma, NY. All of these carbohydrates were dried under vacuum in the presence of P_2O_5 at room temperature for 1 day prior to use. Acetic acid was distilled from acetic anhydride and CrO_3.[12] HBr/acetic acid was either purchased from Fisher Scientific Company, Chicago, IL, or prepared by bubbling dry HBr gas, generated by adding 48% HBr to P_2O_5, through dried acetic acid.[13] The zinc used in the present study was zinc dust (<10 micron), purchased from Aldrich Chemical Company. For flash column chromatography, silica gel 60, 230-400 mesh from Mallinckrodt was used. The progress of each step in the reaction sequence was monitored by ^1H NMR spectroscopy. Typically, an aliquot from the reaction mixture was dissolved in a small (ca. 2 mL) amount of ether or ethyl acetate, the solution was washed successively with saturated aqueous $NaHCO_3$ and brine, the solvent removed under vacuum, and the residue in $CDCl_3$ analyzed by ^1H NMR spectroscopy.

Warning: It is strongly urged that the precipitates collected by filtration during the work-up of the one-pot reaction be washed with water immediately following the washing with ethyl acetate while the precipitates still contain some ethyl acetate. This is necessary since dried precipitates, containing activated zinc with trace organic solvents can readily combust.

Tri-*O*-acetyl-D-glucal (1). To a suspension of D-glucose monohydrate (1.00 g) in acetic anhydride (3.61 g, 7.0 mol equiv) was added 1.00 g of 31% HBr/acetic acid at room temperature. The temperature of the reaction mixture was maintained at room temperature for 1 h with the use of a water-bath and vigorous stirring, during which time the suspended solid went into solution. This solution was then treated with an additional 6.00 g of 31% HBr/acetic acid (total of 5.3 mol equiv of HBr) and the resulting solution

was stirred overnight at room temperature. Anhydrous sodium acetate (2.00 g) was then added to neutralize the excess HBr, and this mixture was added to a suspension of pulverized $CuSO_4 \cdot 5H_2O$ (0.315 g) and zinc (12.6 g) in a solution of water (10 mL) and acetic acid (15 mL) containing sodium acetate (9.45 g) and the resultant reaction mixture was stirred vigorously at room temperature for 1.5 h. The solid was then removed by filtration and washed first with ethyl acetate (100 mL) and then with water (100 mL). The organic layer of the filtrate was washed with saturated aqueous $NaHCO_3$ (100 mL), then with brine (50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to provide tri-*O*-acetyl-D-glucal (**1**)[1,8a] (1.35 g, 98%) as a colorless oil free of impurities as judged from its ^1H NMR spectrum (300 MHz, $CDCl_3$) which was identical with that of an authentic sample purchased from Aldrich Chemical Company.

Tri-*O*-acetyl-D-galactal (2). To a suspension of D-galactose (10.0 g) in acetic anhydride (34 g, 6.0 mol equiv) was added 1.00 g of 30% HBr/acetic acid and the reaction mixture was stirred overnight at room temperature, after which time an additional 74 g of 30% HBr/acetic acid (total of 5.2 mol equiv HBr) was added. The resulting mixture was stirred for 1 day at room temperature, anhydrous sodium acetate was then added (25 g) to neutralize the excess HBr, and the reaction mixture was added to a suspension of pulverized $CuSO_4 \cdot 5H_2O$ (2.50 g) and zinc (100 g) in a mixture of water (100 mL) and acetic acid (50 mL) containing 125 g of sodium acetate trihydrate and the resultant reaction mixture was stirred vigorously at room temperature for 1.5 h with moderate cooling in a bath of running tap water. The mixture was then filtered and the solid collected washed first with ethyl acetate (1 L) and then with water (1 L). The organic layer of the filtrate was washed successively with water (1 L), saturated aqueous $NaHCO_3$ (1 L), and brine (500 mL) and then dried (Na_2SO_4). The solvent was removed under reduced pressure to provide a crude oil which was purified by silica gel flash column chromatography using 20% ethyl acetate in hexanes as the eluent to afford tri-*O*-acetyl-D-galactal (**2**)[8b] (8.81 g, 58%) as a colorless oil: $[\alpha]_D^{23}$ -16.9° (*c* 1.10, $CHCl_3$) [lit.[8b] $[\alpha]_D^{20}$ -16.5° (*c* 3.0, $CHCl_3$)]; ^1H NMR (300 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.10 (s, 3H), 2.14 (s, 3H), 4.19 - 4.35 (m, 3H), 4.74 (ddd, 1H, J = 6.3, 2.7, 1.5 Hz), 5.44 (ddd, 1H, J = 4.6, 1.5, 1.5 Hz), 5.53-5.56 (m, 1H), 6.47 (dd, 1H, 1H, J = 6.3, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.41 (q), 20.50 (q), 20.56 (q), 61.69 (t), 63.59 (d), 63.70 (d), 72.63 (d), 98.64 (d), 145.09 (d), 169.67 (s), 169.79 (s), 170.05 (s); IR (neat) 1748 (s), 1653 (m), 1436 (m), 1372 (s), 1225 (s), 1149 (m), 1035 (s), 923 (m), 896 (m), 863 (w), 837 (w), 812 (w), 742 (w) cm^{-1}.

Di-*O*-acetyl-L-rhamnal (3). To a suspension of L-rhamnose monohydrate (10.0 g) in acetic anhydride (34.0 g, 6.1 mol equiv) was added 1.00 g of 22% HBr/acetic acid

at room temperature (the temperature was kept at room temperature with the use of a cold-water bath). The mixture was stirred for 1 h at room temperature, during which time all of the solid went into solution. More 22% HBr/acetic acid (105 g, thus making an overall total of 5.3 mol equiv of HBr) was added and the resulting mixture was stirred overnight at room temperature. Anhydrous sodium acetate (25 g) was then added to neutralize the excess HBr, and the reaction mixture was poured to a suspension of pulverized $CuSO_4 \cdot 5H_2O$ (2.50 g) and zinc (100 g) in a solution of water (100 mL) and acetic acid (50 mL) containing sodium acetate trihydrate (125 g). The resultant reaction mixture was stirred vigorously at room temperature for 1.5 h with moderate cooling in a bath of running tap water. The mixture was then filtered and the solid collected was washed with ethyl acetate (1 L) and then with water (1 L). The organic layer of the filtrate was washed successively with water (1 L), saturated aqueous $NaHCO_3$ (1 L), and brine (500 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to provide a crude oil which could be purified by silica gel flash column chromatography using 20% ethyl acetate in hexanes as the eluent to afford di-*O*-acetyl-L-rhamnal (**3**)[1b] (8.41 g, 71%) as a colorless oil free of impurities as judged by its ^1H NMR spectrum (300 MHz, $CDCl_3$) which was identical with that of an authentic sample purchased from Aldrich Chemical Company.

Di-*O*-acetyl-L-arabinal (**4**). To a suspension of L-arabinose (4.40 g) in acetic anhydride (15.0 g, 5.0 mol equiv) was added 0.100 g of 30% HBr/acetic acid at room temperature (the temperature was kept at room temperature with the use of a cold-water bath). The mixture was stirred for 4 h at room temperature, during which time all of the solid went into solution. More 30% HBr/acetic acid (42 g, thus making an overall total of 5.3 mol equiv of HBr) was added and the resulting mixture was stirred overnight at room temperature. The reaction mixture was poured onto a suspension of pulverized $CuSO_4 \cdot 5H_2O$ (1.25 g) and zinc (50 g) in a solution of water (50 mL) and acetic acid (25 mL) containing sodium acetate trihydrate (50 g). The resultant reaction mixture was stirred vigorously at room temperature for 1.5 h in a bath of running tap water. The mixture was then filtered and the solid collected was washed with ethyl acetate (500 mL) and then with water (500 mL). The organic layer of the filtrate was washed successively with water (500 mL), saturated aqueous $NaHCO_3$ (500 mL), and brine (250 mL) and then dried (Na_2SO_4). The solvent was removed under reduced pressure to provide a crude oil which was purified by silica gel flash column chromatography using 30% ethyl acetate in hexanes as the eluent to afford di-*O*-acetyl-L-arabinal (**4**)[1b] (2.99 g, 51%) as a colorless oil: $[\alpha]_D^{23}$ -258.2° (*c* 1.07, $CHCl_3$) [lit.[1b] $[\alpha]_D^{23}$ -267° ($CHCl_3$)]; ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.08 (s, 3H), 3.95 - 4.06 (m, 2H), 4.85 (dd, 1H, J = 5.9, 5.2 Hz),

5.19 (ddd, 1H, J = 9.0, 4.0, 4.0 Hz), 5.44 (dd, 1H, J = 5.9, 4.0 Hz), 6.51 (d, 1H, J = 5.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.79 (q), 21.06 (q), 62.85 (t), 62.85 (d), 65.94 (d), 97.49 (d), 147.80 (d), 169.84 (s), 170.45 (s); IR (neat) 1740 (s), 1643 (s), 1453 (m), 1371 (s), 1317 (w), 1231 (s), 1149 (m), 1088 (s), 1056 (s), 1014 (s), 943 (m), 919 (s), 897 (m), 855 (w), 763 (m) cm^{-1}.

Hexa-*O*-acetyl-D-maltal (**5**). To a suspension of D-maltose monohydrate (1.00 g) in acetic anhydride (2.84 g, 10.0 mol equiv) was added 1.00 g of 31% HBr/acetic acid at room temperature (the temperature was kept at room temperature while cooled by a water-bath). The mixture was stirred at room temperature for 1 h, during which time all of the solid went into solution. More 31% HBr/acetic acid (4.00 g, thus making an overall total of 7.0 mol equiv of HBr) was added and the resulting mixture was stirred for 4 h at room temperature. The reaction mixture was poured onto a suspension of pulverized $CuSO_4$•$5H_2O$ (0.182 g) and zinc (7.29 g) in a solution of water (10 mL) and acetic acid (15 mL) containing sodium acetate (5.47 g). The resultant reaction mixture was stirred vigorously at room temperature for 1.5 h in a bath of running tap water. The mixture was then filtered and the solid collected was washed first with ethyl acetate (100 mL) and then with water (100 mL). The organic layer of the filtrate was washed successively with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), and then dried (Na_2SO_4). The solvent was removed under reduced pressure to provide a crude oil which was purified by silica gel flash column chromatography using 50% ethyl acetate in hexanes as the eluent to afford hexa-*O*-acetyl-D-maltal[14] (**5**) (1.34 g, 86%) as a colorless solid: $[\alpha]_D^{23}$ +65.5° (*c* 1.00, $CHCl_3$) [lit.[14] $[\alpha]_D^{20}$ +68° (*c* 0.8, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.04 (s, 3H), 2.06 (s, 3H), 2.11 (s, 3H), 2.13 (s, 3H), 2.14 (s, 3H), 4.03-4.20 (m, 3H), 4.22-4.41 (m, 4H), 4.82 (d, 1H, J = 3.6 Hz), 4.84 (dd, 1H, J = 3.6, 3.6 Hz), 5.06 (dd, 1H, J = 10.0, 9.7 Hz), 5.18 (dd, 1H, J = 4.0, 4.0 Hz), 5.42 (dd, 1H, J = 10.0, 9.7 Hz), 5.51 (d, 1H, J = 4.0 Hz), 6.45 (d, 1H, J = 6.1 Hz); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 20.56 (q), 20.62 (q), 20.68 (q, 2xC), 20.81 (q), 21.10 (q), 61.63 (t), 61.88 (t), 68.18 (d), 68.29 (d), 69.61 (d), 70.44 (d), 72.49 (d), 74.10 (d), 95.83 (d), 98.66 (d), 169.57 (s), 170.04 (s), 170.39 (s), 170.49 (s), 170.60 (s); IR (KBr) 1761 (s), 1747 (s), 1644 (m), 1430 (w), 1367 (m), 1237 (s), 1222 (m), 1172 9w), 1145 (w), 1096 (m), 1048 (s), 1029 (s), 956 (w), 891 (w) cm^{-1}.

Hexa-*O*-acetyl-D-lactal (**6**). To a suspension of D-lactose (1.00 g) in acetic anhydride (2.68 g, 9.0 mol equiv) was added 1.00 g of 31% HBr/acetic acid at room temperature (the temperature was kept at room temperature while cooled by a water-bath). Although the mixture was stirred at room temperature for 4 h, the solid lactose did not completely dissolve. More 31% HBr/acetic acid (4.00 g, thus making an overall total

of 6.7 mol equiv of HBr) was added and the resulting mixture was stirred overnight at room temperature, at which point all of the solid lactose went into solution. The reaction mixture was poured onto a suspension of pulverized $CuSO_4 \cdot 5H_2O$ (0.182 g) and zinc (7.29 g) in a solution of water (10 mL) and acetic acid (15 mL) containing sodium acetate (5.47 g). The resultant reaction mixture was stirred vigorously at room temperature for 1.5 h in a bath of running tap water. The mixture was then filtered and the solid collected was washed with ethyl acetate (100 mL) and then with water (100 mL). The organic layer of the filtrate was washed successively with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), and then dried (Na_2SO_4). The solvent was removed under reduced pressure to provide a crude solid which was purified by silica gel flash column chromatography using 50% ethyl acetate in hexanes as the eluent to afford hexa-*O*-acetyl-D-lactal (**6**)[15] (1.21 g, 86%) as a colorless solid: $[\alpha]_D^{23}$ -16.4° (*c* 1.39, $CHCl_3$) [lit.[15] $[\alpha]_D^{23}$ -18.0° (*c* 0.8, $CHCl_3$)]; ^1H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 3H), 2.06 (s, 3H), 2.07 (s, 3H), 2.09 (s, 3H), 2.12 (s, 3H), 2.16 (s, 3H), 3.91 (dd, 1H, *J* = 6.8, 6.8 Hz), 4.00 (dd, 1H, *J* = 6.2, 6.2 Hz), 3.89 - 4.23 (m, 4H), 4.41 (br d, 1H, *J* = 6.5 Hz), 4.66 (d, 1H, *J* = 7.9 Hz), 4.84 (dd, 1H, *J* = 6.1, 3.3 Hz), 5.01 (dd, 1H, *J* = 10.4, 7.9 Hz), 5.37 (d, 1H, *J* = 3.3 Hz), 5.41 (dd, 1H, *J* = 4.7, 4.2 Hz), 6.42 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 20.56 (q), 20.63 (q, 2xC), 20.66 (q), 20.85 (q), 21.08 (q), 60.98 (t), 61.84 (t), 66.71 (d), 68.85 (d), 68.91 (d), 70.68 (d), 70.82 (d), 74.16 (d), 74.66 (d), 99.00 (d), 101.02 (d), 145.45 (d), 169.30 (s), 169.97 (s), 170.13 (s), 170.22 (s), 170.45 (s, 2xC); IR (KBr) 1751 (s), 1653 (w), 1436 (w), 1372 (m), 1224 (s), 1173 (w), 1141 (w), 1079 (m), 954 (w), 912 (w) cm^{-1}.

Nona-*O*-acetyl-D-maltotrial (**7**). To a suspension of D-maltotriose monohydrate (1.00 g) in acetic anhydride (2.90 g, 9.0 mol equiv) was added 0.050 g of 31% HBr/acetic acid at room temperature (the temperature was kept at room temperature while cooled by a water-bath). The mixture was stirred at room temperature for 4 h, during which time all of the solid went into solution. More 31% HBr/acetic acid (2.70 g, thus making an overall total of 5.0 mol equiv of HBr) was added and the resulting mixture was stirred for 3 h at room temperature. The reaction mixture was poured onto a suspension of pulverized $CuSO_4 \cdot 5H_2O$ (0.100 g) and zinc (4.00 g) in a solution of water (2 mL) and acetic acid (4 mL) containing sodium acetate (5.00 g). The resultant reaction mixture was stirred vigorously at room temperature for 1.5 h with moderate cooling in a bath of running tap water. The mixture was then filtered and the solid collected was washed first with ethyl acetate (50 mL) and then with water (50 mL). The organic layer of the filtrate was washed successively with saturated aqueous $NaHCO_3$ (50 mL) and brine (25 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to provide a

colorless solid which was purified by silica gel flash column chromatography using 50% ethyl acetate in hexanes as the eluent to afford nona-*O*-acetyl-D-maltotrial (**7**) (0.835 g, 50%) as a colorless solid: $[\alpha]_D^{23}$ +91.2° (*c* 1.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.01 (s, 3H), 2.02 (s, 6H), 2.04 (s, 6H), 2.07 (s, 3H), 2.10 (s, 3H), 2.16 (s, 6H), 3.93 - 4.07 (m, 5H), 4.17-4.33 (m, 3H), 4.39 (br s, 1H), 4.41 (br s, 1H), 4.51 (br d, 1H, *J* = 11.9 Hz), 4.71 (dd, 1H, *J* = 10.3, 3.9 Hz), 4.82 (dd, 1H, *J* = 5.9, 3.4 Hz), 4.87 (dd, 1H, *J* = 10.6, 3.9 Hz), 5.07 (dd, 1H, *J* = 9.7, 9.7 Hz), 5.21 (dd, 1H, *J* = 3.6, 3.6 Hz), 5.31 - 5.48 (m, 4H), 6.46 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 20.52 (q), 20.61 (q, 3xC), 20.68 (q), 20.83 (q, 2xC), 20.95 (q), 21.11 (q), 61.39 (t), 62.02 (t), 62.40 (t), 67.95 (d), 68.50 (d), 68.70 (d), 69.38 (d), 69.85 (d), 70.05 (d), 70.92 (d), 71.96 (d), 72.54 (d), 72.75 (d), 74.10 (d), 95.72 (d, 2xC), 98.61 (d), 145.71 (d), 169.46 (s), 169.75 (s), 169.87 (s), 170.42 (s, 2xC), 170.47 (s), 170.54 (s, 2xC), 170.66 (s); IR (KBr) 1748 (s), 1436 (w), 1371 (m), 1225 (s), 1139 (w), 1039 (m) cm^{-1}.

Anal. Calcd for $C_{36}H_{48}O_{23}\cdot H_2O$: C, 49.89; H, 5.81. Found: C, 49.83; H, 5.85.

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