Block Synthesis of Oligosaccharides under Mild Conditions

Yali Wang, Hong Zhang, Wolfgang Voelter*

Introducion

Because of the fundamental role of carbohydrates in cell function, such as energy storage, structural blocks, modifiers of protein folding and function, immunological determinants or conjugation units to hormones, antibodies or cells, carbohydrate research occupies a more and more important position in biology, biochemistry and organic chemistry [1]. Considerable progress has been achieved in the formation of the glycosidic bond and in the synthesis of quite a number of oligosaccharides [2]. One of the more exciting new developments in glycosylation methodologies is due to Kahne * et al. [3] involving glycosyl sulfoxides as glycosyl donors activated by triflic anhydride and 2,6-di-t-tert-butyl-pyridine at low temperature. Here we report details about the synthesis of the trisaccharide α-D-Glc(1→6)-β-D-Glc(1→6)-D-Glc [4] using this new approach to demonstrate its utility in oligosaccharide block syntheses.

Results and Discussion

As seen from Scheme 1, the desired glycosyl donor 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside sulfoxide (7) was prepared in 4 steps starting from the readily available 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (1) [5]. Treatment of 1 with sodium thiophenolate yielded the phenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (2). The acetyl groups of 2 were removed by sodium methoxide treatment to give the phenyl 1-thio-β-D-glucopyranoside (3). 3 was benzylated to yield phenyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside (4) which upon oxidation with mCPBA afforded the desired glycosyl donor 7. The glycosyl acceptor 6 was prepared as follows: Tritylation of 3 followed by pivaloylation produced phenyl 2,3,4,tri-O-pivaloyl-6-O-trityl-1-thio-β-D-glucopyranoside (5), and after detritylation phenyl 2,3,4,tri-O-pivaloyl-1-thio-β-D-glucopyranoside (6) was obtained. Coupling of phenyl 2,3,4,tri-O-pivaloyl-1-thio-β-D-glucopyranoside (6) and 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside sulfoxide (7) in toluene with triflic anhydride and DtBP afforded the disaccharides 9 and 10 in 58.4% and 29.2% yield respectively. Both compounds (9 and 10) are confirmed by their 13C-nuclear magnetic resonance spectra, which showed C-1a chemical shifts for 9 at 95.8 and for 10 at 104.1 ppm respectively. 9 was oxidized with mCPBA to give the sulfoxide 11. Formation of the β-(1→6) linkage between the glycosyl donor 11 and the acceptor 1,2,3,4-tetra-O-acetyl-1-thio-β-D-glucopyranose (12) was performed in dichloromethane with triflic anhydride and DtBP to give the trisaccharide 13 in 73% yield under complete stereocontrol. The β-configuration at C-1b was assigned according to its 13C NMR data which revealed a signal at 100.3 ppm, allowing the conclusion that the pivaloyl-protected glycosyl sulfoxide (disarmed group) can be activated at low temperature affording specifically a β-linkage.

The same trisaccharide 13 was also synthesized via another route (Scheme 2). Phenyl 2,3,4-tri-O-

* Reprint requests to Prof. Dr. Dr. h.c. W. Voelter.
pivaloyl-6-O-trityl-β-D-glucopyranoside sulfoxide (8), obtained by oxidation of 5 with mCPBA in the presence of one equivalent 2,6-di-tert-butylpyridine (D/BP), was glycosylated with 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (12) in the presence of 2 equivalents of D/BP and one equivalent of triflic anhydride to yield the protected disaccharide 14 in 80.6% yield. No α-glycoside formation was observed during this reaction and the structure of 14 was unambiguously ascertained by $^1$H- and $^{13}$C-nuclear magnetic resonance (NMR) spectroscopy. If one equivalent of D/BP was used for the above mentioned glycosylation reaction, removal of the trityl group was observed and a complex mixture of products was obtained. Treatment of 14 at 0 °C with 15% trifluoroacetic acid in dichloromethane for 20 min yielded the disaccharide 15 which sugosylated with 7 to produce 13 in 46% yield and 16 in 20.3% yield.

In conclusion, the trisaccharide unit α-D-Glc(1→6)-β-D-Glc(1→6)-D-Glc was successfully synthesized under mild conditions using phenyl 1-thio-glycopyranoside sulfoxides as glycosyl donors. In the coupling process neither thiophenyl nor trityl protecting groups are cleaved from the carbohydrate moieties. The phenyl 1-thio-glycopyrano-
sides can easily be oxidized to the corresponding sulfoxides which act as glycosyl donors for the next step of the block synthesis. The trityl group can be used as temporary protection in block syntheses and then be removed almost quantitatively to produce a new glycosyl acceptor. The results indicated that this method is a rapid glycosylation method with high yield and good selectivity and will be very useful in block synthesis of polysaccharides.

**Experimental**

Melting points were determined uncorrectedly on a Büchi 510 stage apparatus. NMR spectra were obtained on an Ac 250, Bruker and a WM 400, Bruker spectrometer. The mass spectra were measured on a Varian MAT 711 mass spectrometer. Chromatography was performed on Merck silica gel 60 (70–230 mesh).

Phenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (2) [6]

50 g (95%, 0.115 mol) 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (1) [5] in 180 ml chloroform were added to a solution of 18.01 g (0.136 mol) sodium thiophenolate in 180 ml ethanol under stirring. The mixture was refluxed for 45 min and then poured into 400 ml water and extracted with dichloromethane (3×150 ml). The extracts were washed with 10% sodium carbonate (2×200 ml) and water (2×200 ml), dried over sodium sulfate, concentrated and crystallized from methanol to yield 39.8 g of 2 (75% yield). m.p.: 114–115 °C (ref. 117 °C).

Phenyl 1-thio-β-D-glucopyranoside (3) [7]

38.61 g of 2 were dissolved in 150 ml of 0.4% sodium methoxide in methanol and stirred at room temp. for 24 h. Then 2 g of Dowex-50 (H+) resin were added. After filtration the solution was concentrated and the residue was crystallized from methanol and diethyl ether to give 3 in 94% yield. m.p.: 129–130 °C. – FD-MS: 272 (M). – 1H NMR (CD3OD): δ = 7.55 (m, 2H), 7.25 (m, 3H), 4.85 (s, 4H, OH), 4.59 (d, J = 9.64, 1H, H-1), 3.85 (dd, J = 12.2, 1.5, 1H, H-6), 3.65 (dd, J = 12.07, 5.3, 1H, H-6), 3.45–3.15 (m, 4H). – 13C NMR (CD3OD): δ = 135.19, 132.69, 129.84, 128.29 (aromatic), 89.36 (C-1), 81.97, 79.65, 73.73, 71.33, 62.85.

Phenyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside (4) [8]

5.6 g of 3 were dissolved in 60 ml dry THF and 15 ml of benzyl bromide and 3 g of sodium hydride suspension (60–65%) were added under stirring and then the mixture was refluxed for 24 h. After 5 ml methanol was added, the mixture was poured into 100 ml water and extracted with chloroform (3×50 ml). The combined organic extracts were washed with water (2×100 ml) and dried over sodium sulfate, filtered and evaporated. Chromatography with petroleum ether and ethyl acetate (10:1 → 7:1) gave 4 in 70.2% yield as a white solid. m.p.: 86–88 °C. – FD-MS: 633 (M). – 1H NMR (CDCl3): δ = 7.65–7.25 (m, 25H, 5Ph), 5.0–4.5 (m, 9H, H-1, 4CH3Ph), 3.85–3.5 (m, 6H, H-2, H-3, H-4, H-5, 2H-6). – 13C NMR (CDCl3): δ = 138.49–127.47 (m, aromatic), 87.53 (C-1), 86.83, 80.95, 79.18, 77.91, 75.86, 75.45, 75.08, 73.48, 69.12.

Phenyl 2,3,4-tri-O-pivaloyl-6-O-trityl-1-thio-β-D-glucopyranoside (5)

A solution of 5 g of 3 (0.0184 mol) and 5.38 g of trityl chloride (0.0193 mol) in 14 ml pyridine was
stirred at room temp. for 16 h [9], then 10 ml of pivaloyl chloride were added and the mixture was stirred at 95–100 °C for 6 h. After cooling to room temp., the mixture was poured into 300 ml water and extracted with dichloromethane (3×100 ml). The combined extracts were washed with water (3×300 ml), dried over sodium sulfate, filtered and evaporated. Chromatography (petroleum ether/dichloromethane, 3:1→1:1) gave 5 in 72% yield as an oil. – FD-MS: 766.8 (M), 1533.5 (2M). – 1H NMR (CDCl3): δ = 7.5–7.1 (m, 15H), 5.2 (t, J = 9.2, 1H), 5.05 (t, J = 9.5, 1H), 4.92 (t, J = 9.8, 1H), 4.77 (d, J = 10.1, 1H, H-1), 3.68 (m, J = 9.4, 7.3, 1.7, 1H, H-5), 3.2 (dd, J = 10.4, 1.7, 1H, H-6), 2.98 (dd, J = 10.4, 1.7, 1H, H-6), 1.15, 1.0, 0.76 (3s, 27H, 3 Piv).

Phenyl 2,3,4-tri-O-pivaloyl-1-thio-β-D-glucopyranoside (6)

The crude product 5 which was prepared from 4 g of 3 without chromatography was dissolved in 20 ml dichloromethane under stirring at 0 °C, then 20 ml of 50% TFA in dichloromethane were added. The mixture was stirred at 0 °C for 8 min, poured into 300 ml water and extracted with dichloromethane (3×100 ml). The combined extracts were washed with 7% K2CO3 (2×100 ml), dried over sodium sulfate, filtered and evaporated. Chromatography with petroleum ether and ethyl acetate gave a mixture of anomers 7a and 7b in 89.4% yield. 7a: – FD-MS: 1172 (2M-SOPh), 523.3 (M-SOPh). – 1H NMR (CDCl3): δ = 7.6–7.1 (m, aromatic, 25H), 4.05 (t, J = 9.5, 1H), 3.9 (d, J = 9.8, 1H, H-1), 3.73 (t, J = 9.0, 1H), 3.5 (t, J = 9.7, 1H), 3.45 (m, 2H, H-6), 3.25 (dd, J = 9.7, 4.7, 2.2, 1H, H-5). – 13C NMR (CDCl3): δ = 138–128 (m, aromatic), 93.74 (C-1), 86.82, 80.92, 78.29, 77.54, 76.05, 75.89, 75.34, 73.72, 69.02. 7b: – FD-MS: 1172 (2M-SOPh), 523 (M-SOPh). – 13C NMR (CDCl3): δ = 140.43–125.90 (m, aromatic), 95.77 (C-1), 86.44, 79.53, 77.96, 77.01, 75.56, 75.07, 74.21, 73.78, 68.82.

Phenyl 2,3,4-tri-O-pivaloyl-6-O-trityl-1-thio-β-D-glucopyranoside sulfoxide (8)

To a solution of 1.243 g 5 (1.623 mmol) and 377 mg di-tert-butyl pyridine (1.97 mmol) in 30 ml dichloromethane, 0.509 g of 55% mCPBA (1.623 mmol) in 8 ml dichloromethane was added under nitrogen at −78 °C. After warming to 10 °C, 10 ml of saturated sodium bicarbonate solution containing 5% sodium sulfite were added. The mixture was washed with saturated sodium bicarbonate (2×30 ml) and water (2×30 ml), dried over sodium sulfate, filtered and evaporated. Chromatography with dichloromethane and ethyl acetate (35:1) gave anomers 8a and 8b in 89.5% yield. 8a: – FD-MS: 782 (M), 657 (M-SOPh). – 1H NMR (CDCl3): δ = 7.7–7.05 (m, 20H, aromatic), 5.15 (t, J = 8.9, 1H), 5.10 (t, J = 8.9, 1H), 4.77 (m, J = 9.5, 1H), 4.37 (d, J = 9.7, 1H, H-1), 3.55 (dd, J = 10.1, 1.9, 1H, H-1), 2.97 (dd, J = 10.6, 1.9, 1H, H-6), 2.89 (dd, J = 10.6, 5.7, 1H, H-6), 1.07, 0.93, 0.65 (3s, 27H, 3 Piv). – 13C NMR (CDCl3): δ = 177.28, 176.98, 176.11 (3C-O), 143.59–126.98 (m, aromatic), 92.94 (C-1), 86.79 (CPh3), 78.80, 73.81, 68.90, 67.79, 61.63. 8b: – FD-MS: 782 (M), 657 (M-SOPh), 1440 (2M-SOPh). – 1H NMR (CDCl3): δ = 7.7–7.05 (m, 20H, aromatic), 5.41 (t, J = 9.5, 1H), 5.24 (t, J = 9.1, 1H), 4.77 (m, J = 9.4, 1H), 4.2 (d, J = 9.2, 1H, H-1), 3.5 (m, 1H, H-5), 3.16 (dd, J = 10.5, 8.3, 1H, H-6), 2.62 (dd, J = 10.5, 1.3, 1H, H-6). – 13C NMR (CDCl3): δ = 177.55, 176.32, 143.62–125.28 (aromatic), 91.68 (C-1), 86.84 (CPh3), 79.25, 73.63, 68.31, 67.82, 62.94.

Phenyl 2,3,4-tri-O-pivaloyl-6-O-trityl-1-thio-β-D-glucopyranosyl-1-thio-β-D-glucopyranoside (9) and phenyl 2,3,4-tri-O-pivaloyl-6-O-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (10)

175 mg of triflic anhydride (0.62 mmol) were dissolved in 3 ml of toluene, cooled to −78 °C un-
under nitrogen atmosphere. 400 mg of phenyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside sulfoxide (7) (0.62 mmol) in 1.5 ml of toluene were added and then 118 mg of 2,6-d-tert-butylpyridine (0.62 mmol) in 0.3 ml of toluene were brought into the reaction vessel. After increasing the temperature to −70 °C, 405 mg of phenyl 2,3,4-tri-O-pivaloyl-1-thio-β-D-glucopyranoside (6) (0.77 mmol) in 2 ml toluene were added and the mixture was allowed to warm to 10 °C. Then 3 ml of a saturated NaHCO₃ solution were added and the mixture was poured into water (30 ml) and extracted with dichloromethane (3×20 ml), dried over Na₂SO₄, filtered and evaporated. Chromatography on a silica gel column (dichloromethane/ethyl acetate 40:1) gave 435 mg of 9 and 218 mg of 10 in 58.4% and 29.2% respectively. 9: -FD-MS: 1047 (M). - 1H NMR (400 MHz, CDCl₃): δ = 7.4–7.08 (m, 25 H, aromatic), 5.24–3.24 (m, 22 H, H-1a–H-6a, H-1b–H-6b, 4 CH₂Ph). 1.09 (s, 9 H, Piv), 1.08 (s, 9 H, Piv), 1.00 (s, 9 H, Piv). - 13C NMR (100.6 MHz, CDCl₃): δ = 175.6, 175.0, 174.9 (COCMe₂), 137.5, 137.0, 136.7, 136.5 (Cq, aromatic), 131.6–123.6 (aromatic), 95.8 (C-1a), 85.7 (C-1b), 80.6, 78.6, 76.3, 75.2, 74.2, 73.4, 72.1, 71.9, 71.8, 68.7, 68.2, 67.1, 67.0, 65.7 (C-2a–C-6a, C-2b–C-6b, CH₂Ph), 37.3 (CMe₂), 28.6–28.2 (CH₃). 10: -FD-MS: 1047 (M), 956 (M–CH₂Ph). - 1H NMR (400 MHz, CDCl₃): δ = 7.28–6.93 (m, 25 H, aromatic), 5.15–3.15 (m, 22 H, H-1a–H-6a, H-1b–H-6b, 4 CH₂Ph), 1.06 (s, 9 H, Piv), 1.00 (s, 9 H, Piv), 0.96 (s, 9 H, Piv). - 13C NMR (100.6 MHz, CDCl₃): δ = 177.0, 176.8, 176.4 (COCMe₂), 138.6, 138.4, 138.1, 138.0 (Cq, aromatic), 131.6–123.6 (aromatic), 104.1 (C-1a), 86.3 (C-1b), 84.8, 82.5, 78.4, 77.9, 76.0, 75.2, 75.1, 75.0, 73.8, 73.6, 69.8, 69.1, 68.9, 68.9 (C-2a–C-6a, C-2b–C-6b, CH₂Ph), 39.0–38.9 (CMe₂), 27.4–27.3 (CH₃).

Phenyl 2,3,4-tri-O-pivaloyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-1-thio-β-D-glucopyranoside sulfoxide (11)

To 350 ml of 9 (0.335 mmol), dissolved in 10 ml dichloromethane, 105 mg of 55% mCPBA (0.33 mmol) in 10 ml dichloromethane were added under nitrogen. Then the reaction mixture was allowed to warm to 10 °C and 2 ml of a saturated NaHCO₃ solution containing 5% Na₂SO₄ were added under stirring. The mixture was washed with water (3×20 ml), dried over Na₂SO₄, filtered and evaporated. Chromatography with petroleum ether/ethyl acetate (3:1) on a silica gel column gave 11 in 98% yield. This material was directly used in the next step.

1,2,3,4-Tetra-O-acetyl-6-O-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-β-D-glucopyranosyl-β-D-glucopyranosyl (13)

352.6 mg of 11 (0.332 mmol) were dissolved in 2.5 ml dichloromethane and stirred at −78 °C under an atmosphere of nitrogen, then 66.7 mg of DtBP (0.349 mmol) in 0.3 ml of dichloromethane and 98.7 mg of trichlor anhydride (0.349 mmol) in 0.4 ml dichloromethane were added and the mixture was allowed to warm to −65 °C. To this solution 130.5 mg of 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (12) (0.371 mmol) in 0.3 ml of dichloromethane were added and then the temperature was increased to 0 °C. After addition of 2 ml of a saturated NaHCO₃ solution the reaction mixture was poured into water (30 ml) and extracted with dichloromethane (3×20 ml). The combined extracts were washed with water (2×30 ml), dried over Na₂SO₄, filtered and evaporated. Chromatography with dichloromethane/ethyl acetate (40:1–20:1) on a silica gel column gave 310 mg of 13 in 72.7% yield. - FD-MS: 1284 (M). - 1H NMR (400 MHz, CDCl₃): δ = 7.28–7.09 (m, 20 H, aromatic) 5.56 (d, J = 8.2, 1H, H-1c), 5.21–3.33 (m, 28 H, H-1a–H-6a, H-1b–H-6b, H-2c–H-6c, 4 CH₃Ph), 1.97 (s, 3H, Ac), 1.93 (s, 3H, Ac), 1.90 (s, 3H, Ac), 1.85 (s, 3H, Ac), 1.10 (s, 9H, Piv), 1.09 (s, 9H, Piv), 1.03 (s, 9H, Piv). - 13C NMR (100.6 MHz, CDCl₃): δ = 177.3, 176.8, 176.7 (COCMe₂), 170.2, 169.6, 169.4, 169.0 (COMe), 139.2, 138.8, 138.3, 138.2 (Cq, aromatic), 128.7–127.8 (aromatic), 100.3 (C-1b), 97.2 (C-1a), 91.80 (C-1c), 82.2–53.6 (m, C-2a–C-6a, C-2b–C-6b, C-2c–C-6c, CH₂Ph), 38.95 (CMe₃), 27.3 (CH₃), 20.8 (COCH₃).

1,2,3,4-Tetra-O-acetyl-6-O-(2,3,4-tri-O-pivaloyl-6-O-trityl-β-D-glucopyranosyl)-β-D-glucopyranose (14)

To 232 mg of phenyl 2,3,4-tri-O-pivaloyl-6-trityl-1-thio-β-D-glucopyranoside sulfoxide (8) (0.3 mmol), 132.6 mg of DtBP (0.6 mmol) in 3 ml of dichloromethane were added, stirred at −78 °C under an atmosphere of nitrogen, and then 87.7 mg of trichlor anhydride (0.3 mmol) were brought into the reaction vessel. After warming to −65 °C, 116 mg of 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (12) (0.33 mmol) were added and the mixture was allowed to warm to 0 °C. After addition of 2 ml of a saturated NaHCO₃ solution the mixture was poured into 30 ml water and extracted with dichloromethane (3×20 ml). The combined extracts were washed with water (2×30 ml), dried over Na₂SO₄, filtered and evaporated. Chroma-
ography with dichloromethane/ethyl acetate (30:1) on a silica gel column gave 240 mg of 14 in the 80.6% yield. - FD-MS: 1005 (M). - $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.35-7.06 (m, 15H, aromatic), 5.64 (d, J = 9.1, 1H, H-1c), 5.22-4.83 (m, 6H), 4.55 (d, J = 8.1, 1H, H-1b), 4.0-3.55 (m, 6H), 1.93 (s, 3H, Ac), 1.91 (s, 3H, Ac), 1.90 (s, 3H, Ac), 1.87 (s, 3H, Ac), 1.05 (s, 9H, Piv), 0.96 (s, 9H, Piv), 0.73 (s, 9H, Piv). - $^{13}$C NMR (100.6 MHz, CDCl$_3$): (5 = 177.40, 177.28, 176.70 (COMe), 170.17, 169.56, 169.36, 168.85 (COCMe$_3$), 138.14, 137.91, 137.69, 137.46 (Cq, aromatic), 128.19-127.33, 110.04 (C-lb), 91.93 (C-lc), 91.81 (C-lc).

1,2,3,4-Tetra-O-acetyl-6-O-(2,3,4-tri-O-pivaloyl-$\beta$-D-glucopyranosyl)-$\beta$-D-glucopyranoside (15)

A solution of 195 mg of 14 in 5 ml dichloromethane was stirred at 0°C, then 5 ml 30% TFA in dichloromethane were added. After stirring for 20 min, the mixture was poured into ice-water (20 ml) and the organic phase was washed with saturated NaHCO$_3$ (10 ml), water (2 x 10 ml), dried over Na$_2$SO$_4$ and evaporated. Chromatography with dichloromethane and ethyl acetate (10:1→4:1) gave 130 mg of 15 in the 86.5% yield. - FD-MS: 761 (M-1), 762 (M). - $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 5.41 (d, J = 8.1, 1H, H-1c), 4.34 (d, J = 8.0, 1H, H-1b), 1.83, 1.78, 1.74, 1.73 (4s, 12H, 4Ac), 0.88, 0.86, 0.83 (3s, 27H, 3 Piv). - $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ = 177.40, 177.28, 176.70 (COMe), 170.21, 170.24, 169.42, 169.00 (COMe), 100.58 (C-1b), 91.81 (C-1c).

1,2,3,4-Tetra-O-acetyl-6-O-(6-O-(2,3,4,6-tetra-O-benzyl-$\alpha$-D-glucopyranosyl)-2,3,4-tri-O-pivaloyl-$\beta$-D-glucopyranosyl)-$\beta$-D-glucopyranoside (13) and 1,2,3,4-tetra-O-acetyl-6-O-(6-O-(2,3,4,6-tetra-O-benzyl-$\beta$-D-glucopyranosyl)-2,3,4-tri-O-pivaloyl-$\beta$-D-glucopyranoside) (16)

To a solution of 111 mg triflic anhydride (0.393 mmol) in 2 ml toluene, 255 mg of phenyl 2,3,4,6-tetra-O-benzyl-$\beta$-D-glucopyranoside sulfoxide (7) (0.393 mmol) in 1 ml toluene were added under nitrogen at -78°C, then 76 mg DfBP (0.393 mmol) in 0.5 ml toluene were added. After warming to -65°C, 120 mg (15) (0.157 mmol) in 1 ml toluene was added and the mixture was allowed to warm to -25°C, then 2 ml of saturated NaHCO$_3$ solution were added to it and the mixture was poured into 30 ml water and extracted with dichloromethane (3 x 20 ml), the combined extracts were washed with water (2 x 30 ml), dried over Na$_2$SO$_4$, filtered and evaporated. Chromatography with dichloromethane and ethyl acetate (40:1→20:1) gave 93 mg of 13 and 41 mg of 16 in the yield 46% and 20.3% respectively. 16: - FD-MS: 1284 (M). - $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 5.58 (d, J = 8.0, 1H, H-1c), 1.96, 1.90, 1.89, 1.86 (4s, 12H, 4Ac), 1.09, 1.07, 1.04 (3s, 27H, 3 Piv). - $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ = 177.28, 176.99, 176.74 (COMe), 170.17, 169.56, 169.36, 168.85 (COMe), 138.99, 138.75, 138.53, 138.36 (Cq, aromatic), 104.20 (C-1a), 100.56 (C-1b), 91.84 (C-1c).

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