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Regioselective glycosylation of 3,6-unprotected mannoside derivatives: fast access to high-mannose type oligosaccharides

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Abstract—A regioselective glycosylation of 3,6-unprotected mannoside acceptors was investigated. With glycosyl trichloroacetimidate donors, when an excess of trimethylsilyl trifluoromethanesulfonate is used as the catalyst, 6-*O*-glycosylation exclusively occurred affording a silylated disaccharide that could be involved in a subsequent glycosylation reaction. As an illustration, the fast synthesis of two trisaccharides and one pentasaccharide was achieved.

As part of our research towards the synthesis of mannosyl mimetic derivatives based on a β-cyclodextrin (β-CD) core,[1] a short and effective route was required for the preparation of high-mannose type oligosaccharides found in the HIV-1 viral surface envelope glycoprotein gp 120.

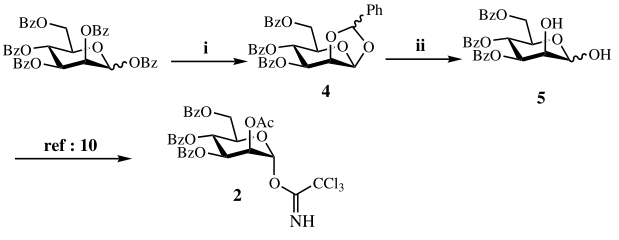
Some successful syntheses of the HIV-1 nonamannoside structure have been achieved, notably by Fraser-Reid,[2] Ley[3] and more recently by Seeberger.[4] The latter presents a powerful linear synthesis based on a simultaneous multi-glycosylation strategy. Nevertheless, the assembly of the starting differentially protected trimannoside requires a relatively long multistep procedure. The use of the trityl-cyanoethylidene condensation as a glycosylation method developed by Backinowsky et al.[5] could circumvent this drawback. This procedure in which selective 3-*O*-glycosylation of 3,6-di-*O*-trityl mannoside acceptors occurs in good yield with 1,2-*O*-[(1-cyano)ethylidene]-β-D-mannopyranose donors, and has been utilised for the convergent synthesis of 'fully-carbohydrate' mannodendrimers.[6]

Nevertheless, the easy access to 3,6-unprotected mannoside derivatives described by Bundle[7] prompted us to investigate a regioselective glycosylation approach. We report here the results of our study which show that 6-*O*-glycosylation can be highly regioselective and effective with glycosyl trichloroacetimidate donors when an excess of trimethylsilyl trifluoromethanesulfonate (TMSOTf) is used as the catalyst.

Owing to the known versatility of glycosyl trichloroacetimidate in glycosylation reactions,[8] we chose to employ 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl trichloroacetimidate[9] **1** and 2-*O*-acetyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranosyl trichloroacetimidate[10] **2**. As methyl α-D-mannopyranose is commercially available, the methyl 2,4-di-*O*-benzoyl-α-D-mannopyranose **3** was chosen as acceptor.

The recently described synthesis of the known 2-*O*-acetyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranosyl trichloroacetimidate **2**,[10] was slightly modified (Scheme 1).

The key intermediate diol, namely 3,4,6-tri-*O*-benzoyl-D-mannopyranose **5**, was obtained in three steps from the per-*O*-benzoyl-D-mannopyranose via the 3,4,6-tri-*O*-benzoyl-1,2-*O*-benzylidene-β-D-mannopyranose **4**.



Scheme 1. *Reagents and conditions*: (i) HBr/AcOH, CH_2Cl_2, 2 h then Bu_4NI, $NaBH_4$, CH_3CN, 36 h; (ii) HBF_4/H_2O, CH_3CN, 4 h, 45% (2 steps).

Keywords: regioselective glycosylation; high-mannose.
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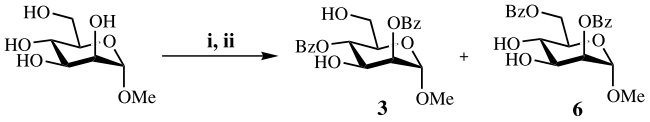
The latter was prepared using the classical method[11] in 45% yield, followed by hydrolysis of the ketal with 50% aq. tetrafluoroboric acid to afford the diol **5** in quantitative yield.

As shown in Scheme 2, the acceptor **3** was prepared in a one-pot procedure. Methyl α-D-mannopyranose was reacted with triethyl orthobenzoate in the presence of camphorsulfonic acid (CSA) as a catalyst. The 2,3,4,6-di-*O*-orthoester intermediate thus obtained was hydrolysed with aq. trifluoroacetic acid (1:9) to give a mixture of the corresponding 2,4- and 2,6-di-*O*-benzoates, namely methyl 2,4-di-*O*-benzoyl-α-D-mannopyranoside **3** and methyl 2,6-di-*O*-benzoyl-α-D-mannopyranoside **6** in 29% and 24% yields, respectively. Both compounds were readily separated by flash chromatography.



Scheme 2. *Reagents and conditions*: (i) triethyl orthobenzoate, CSA, CH_3CN, 2 h; (ii) 90% CF_3CO_2H, CH_3CN, 10 min, 29% of **3** (2 steps).

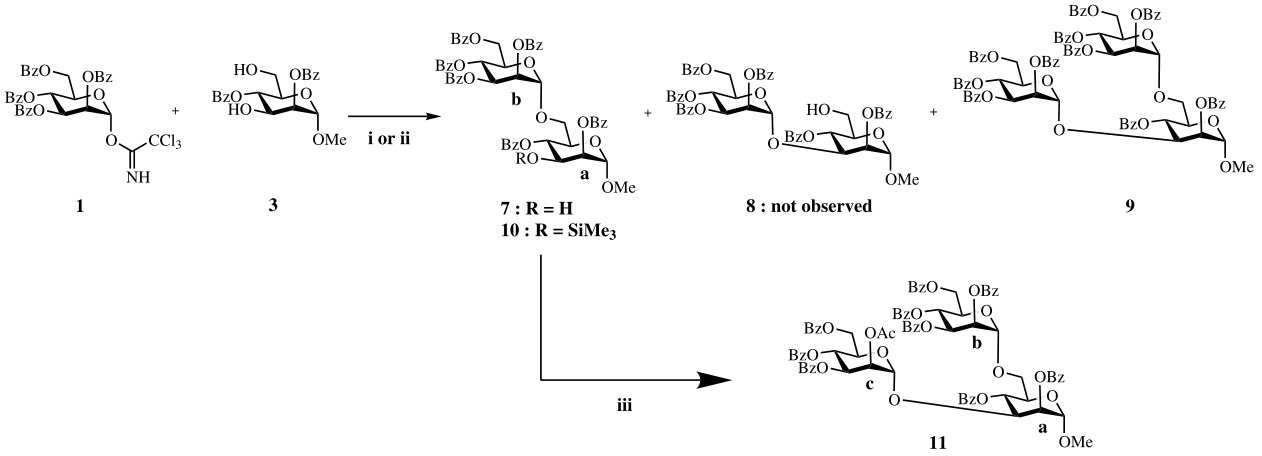
First attempts at glycosylation between the donor **1** and the acceptor **3** were performed using standard conditions (low temperature, 0.5 equiv. of TMSOTf, CH_2Cl_2, N_2 atmosphere, 1.2 equiv. of **1**). We presumed that using a low temperature would increase the difference in reactivity between the primary hydroxy group and the secondary one. Very low temperatures (–80°C and –60°C) afforded only traces or poor yields (25% at –60°C) of the expected α-1,6-disaccharide **7** (Scheme 3). The best yield was obtained at –40°C (47%). Glycosylation only occurred on the primary hydroxy group. The α-1,3-disaccharide **8** and the trisaccharide **9** were not observed even at higher temperature.

Because of these relatively disappointing results, we decided to investigate the influence of the amount of the catalyst. Using a large excess of TMSOTf (3.5 equiv.) at –80°C led to the methyl 2,4-di-*O*-benzoyl-3-*O*-trimethylsilyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-α-D-mannopyranose[12] **10** in 70% yield. It is notable that the silylation occurred after the quenching of the reaction mixture with triethylamine. Therefore, the amount of the promotor did not play a part in the regioselectivity but only increased the rate of the reaction. Under these conditions, a small amount of trisaccharide **9** was formed (10%).

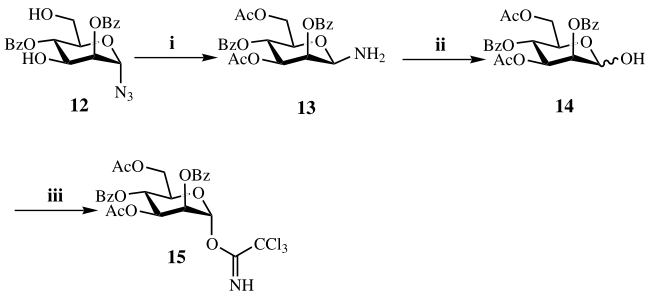
Moreover, glycosylation of the disaccharide **10** with the donor **2** in the presence of an excess of TMSOTf (3.5 equiv.) can be performed without prior deprotection of the silylated hydroxy group in quite good yield (55%) to give the differentially protected trimannoside derivative[13] **11** (Scheme 3). It should be pointed out that under these conditions, but in the absence of donor, the disaccharide **10** led to the desilylated derivative **7**. We concluded that the glycosylation of **10** with the donor **2** followed an in situ cleavage of the silyl ether with the Lewis acid.

The utility of our approach was demonstrated through the synthesis of a pentasaccharidic fragment of a high-mannose type oligosaccharide (see Scheme 5).

Keeping in mind that the oligosaccharidic part of our mannosyl mimetic derivatives based on a β-cyclodextrin core is linked through a peptidic bond to the β-CD,[1] the 2,4-di-*O*-benzoyl-α-D-mannopyranosyl azide **12** was chosen as acceptor and was obtained as previously described.[1] The azide **12** was also designed as starting material in order to obtain a differentially protected donor. It is known that a glycosyl azide can be converted into a glycosyl fluoride donor in two steps (40–50% overall yields) via a triazole intermediate.[14] Nevertheless, we developed an alternative procedure to obtain the 3,6-di-*O*-acetyl-2,4-di-*O*-benzoyl-α-D-mannopyranosyl trichloroacetimidate **15** from the azide **12**, in three steps with a good overall yield (55%) (Scheme 4).



Scheme 3. *Reagents and conditions*: (i) 0.5 equiv. TMSOTf, CH_2Cl_2, –40°C, 30 min, 47% of **7**; (ii) 3.5 equiv. TMSOTf, CH_2Cl_2, –80°C, 30 min, 70% of **10**; (iii) **10**, 1.5 equiv. donor **2**, 3.5 equiv. TMSOTf, CH_2Cl_2, 0°C to rt, 1 h, 55%.



Scheme 4. *Reagents and conditions*: (i) Ac_2O, pyridine then H_2, Pd/C, EtOH, 20 bar, 83%; (ii) HCl 2N, $NaNO_2$, acetone, 0°C to rt, 40 min, 73%; (iii) CCl_3CN, DBU, 0°C to rt, 1 h, 90%.

After acetylation of the free hydroxy groups, the azide group was reduced by classical hydrogenation in quantitative yield. Then, the resulting amine **13** was hydrolysed under nitrous acid catalysis to afford the desired 3,6-di-*O*-acetyl-2,4-di-*O*-benzoyl-D-mannopyranose **14**. Subsequent reaction of **14** with trichloroacetonitrile under DBU catalysis gave the donor **15**.

Condensation of **12** with donor **15** in the presence of a catalytic amount of TMSOTf (0.5 equiv.) afforded the disaccharide **16**, namely 2,4-di-*O*-benzoyl-6-*O*-(3,6-di-*O*-acetyl-2,4-di-*O*-benzoyl-α-D-mannopyranosyl)-α-D-mannopyranosyl azide, in 50% yield. Once again, using an excess of TMSOTf increased the yield up to 90% leading to the trimethylsilylated disaccharide derivative **17**. Deacetylation of **16** or simultaneous deacetylation and desilylation of **17** were performed by acid-catalysed methanolysis[15] to afford the triol[16] **18** in around 65% from both compounds. Simultaneous tri-glycosylation of **18** with 6 equivalents of the trichloroacetimidate donor **2** afforded the expected pentasaccharide[17] **19** in 70% yield. Moreover, condensation of the trimethylsilylated disaccharide derivative **17** and **2** with an excess of TMSOTf led to the trisaccharide[18] **20** in good yield (62%).

The structures of compounds **10**, **11**, **18**, **19** and **20** and other intermediates were established using 1D- and 2D-NMR spectroscopy (COSY, Relays, HMQC). The spin–spin coupling constants of vicinal protons have values indicative of α-D-mannopyranose residues ($J_{1,2}$ = 1–2 Hz, $J_{2,3}$ = 3–3.5 Hz).[5,6] Moreover, the chemical shifts of the anomeric C atoms are consistent with those reported in the literature:[6] around 97.5 ppm for the α-(1→6) linked units and around 99.2 ppm for the α-(1→3) linked ones.

It should be pointed out that the acetyl groups of **19** as well as **20** can be selectively removed and free hydroxy groups again simultaneously multi-glycosylated opening a short route to hexa-, octa- and nonamannoside derivatives of high-mannose type.

In summary, we have demonstrated that the glycosylation of 3,6-unprotected mannoside acceptors occurred on the primary hydroxy group in high yield when an excess of TMSOTf is used. This regioselective glycosylation approach leads to silylated disaccharides which can be used as starting materials for the fast and efficient synthesis of high-mannose type oligosaccharides of variable size.

Acknowledgements

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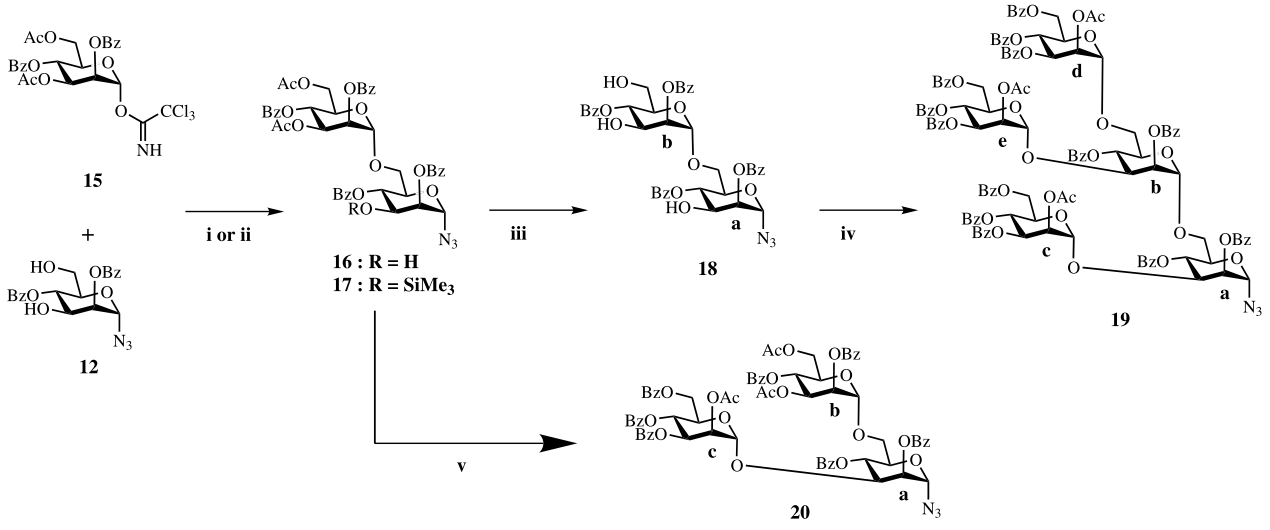

Scheme 5. *Reagents and conditions*: (i) 0.5 equiv. TMSOTf, CH_2Cl_2, −40°C, 30 min, 50% of **16**; (ii) 3.5 equiv. TMSOTf, CH_2Cl_2, −80°C, 30 min, 90% of **17**; (iii) **16** or **17**, CH_3COCl, CH_3OH, CH_2Cl_2, 24 h, 65%; (iv) 6 equiv. donor **2**, 0.5 equiv. TMSOTf, CH_2Cl_2, −20°C to rt, 90 min, 70%; (v) **17**, 3 equiv. donor **2**, 3.5 equiv. TMSOTf, CH_2Cl_2, 0°C to rt, 1 h, 62%.

References

1. Yockot, D.; Moreau, V.; Demailly, G.; Djedaïni-Pilard, F. *Org. Biomol. Chem.* **2003**, *1*, 1810–1818.
2. Merritt, J. R.; Naisang, E.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 4443–4449.
3. Grice, P.; Ley, S. V.; Pietruszka, J.; Osborn, H. M. I.; Priepke, H. W. M.; Warriner, S. L. *Chem. Eur. J.* **1997**, *3*, 431–440.
4. Ratner, D. M.; Plante, O. J.; Seeberger, P. H. *Eur. J. Org. Chem.* **2002**, 826–833.
5. Backinowsky, L. V.; Abronina, P. I.; Nepogodiev, S. A.; Grachev, A. A.; Kochetkov, N. K. *Polish J. Chem.* **1999**, *73*, 955–965.
6. Backinowsky, L. V.; Abronina, P. I.; Shashkov, A. S.; Grachev, A. A.; Kochetkov, N. K.; Nepogodiev, S. A.; Fraser Stoddart, J. *Chem. Eur. J.* **2002**, *8*, 4412–4423.
7. Yu, N. H.; Ling, C. C.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 832–837.
8. Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123.
9. Bien, F.; Ziegler, T. *Tetrahedron: Asymmetry* **1998**, *9*, 781–790.
10. Heng, L.; Ning, J.; Kong, F. *J. Carbohydr. Chem.* **2001**, *20*, 285–296.
11. Betaneli, V. I.; Ovchinnikov, M. V.; Backinowsky, L. V.; Kochetkov, N. K. *Carbohydr. Res.* **1982**, *107*, 285–291.
12. Selected data for **10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08–7.27 (m, 30H, OCOPh), 6.12 (t, 1H, $J_{3,4}=J_{4,5}=9.8$ Hz, H-4b), 6.01 (dd, 1H, $J_{2,3}=3.1$ Hz, H-3b), 5.76 (dd, 1H, $J_{1,2}=1.44$ Hz, H-2b), 5.74 (t, 1H, $J_{3,4}=J_{4,5}=9.9$ Hz, H-4a), 5.48 (dd, 1H, $J_{1,2}=1.2$ Hz, $J_{2,3}=3.5$ Hz, H-2a), 5.14 (d, 1H, H-1b), 4.94 (d, 1H, H-1a), 4.55–4.43 (m, 3H, H-6b, H-5b, H-3a), 4.34 (dd, 1H, $J_{5,6}=4.0$ Hz, $J_{6,6'}=11.9$ Hz, H-6′b), 4.23 (ddd, 1H, $J_{5,6}=5.1$ Hz, $J_{5,6'}=1.9$ Hz, H-5a), 4.12 (dd, 1H, $J_{6,6'}=10.6$ Hz, H-6a), 3.75 (dd, 1H, H-6′a), 3.60 (s, 3H, OMe), 0.03 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 99.1 (C-1a), 97.4 (C-1b). ES-LRMS $m/z=1091.4$ $[M+K]^+$.
13. Selected data for **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32–7.28 (m, 45H, OCOPh), 6.15 (t, 1H, $J_{3,4}=J_{4,5}=10.0$ Hz, H-4b), 6.01 (dd, 1H, $J_{2,3}=3.5$ Hz, H-3b), 5.89 (t, 1H, $J_{3,4}=J_{4,5}=9.9$ Hz, H-4a), 5.80 (t, 1H, $J_{3,4}=J_{4,5}=9.0$ Hz, H-4c), 5.78 (dd, 1H, $J_{1,2}=1.8$ Hz, H-2b), 5.73 (dd, 1H, $J_{1,2}=1.8$ Hz, $J_{2,3}=3.5$ Hz, H-2a), 5.63 (dd, 1H, $J_{2,3}=3.3$ Hz, H-3c), 5.22 (d, 1H, $J_{1,2}=2.0$ Hz, H-1c), 5.20–5.16 (m, 2H, H-1b, H-2c), 5.03 (d, 1H, H-1a), 4.66–4.26 (m, 7H, H-3a, H-5b, H-6b, H-6′b, H-5c, H-6c, H-6′c), 4.21–4.14 (m, 2H, H-5a, H-6a), 3.81 (dd, 1H, $J_{5,6}=1.8$ Hz, $J_{6,6'}=10.6$ Hz, H-6′a), 3.55 (s, 3H, OMe), 1.91 (s, 3H, OCOMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ 99.4 (C-1c), 98.7 (C-1a), 97.4 (C-1b). ES-LRMS $m/z=1519.5$ $[M+Na]^+$.
14. Bröder, W.; Kunz, H. *Carbohydr. Res.* **1993**, *249*, 221–241.
15. Byramova, N. E.; Ovchinnikov, M. V.; Backinowsky, L. V.; Kochetkov, N. K. *Carbohydr. Res.* **1983**, *124*, C8–C11.
16. Selected data for **18**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13–7.28 (m, 20H, OCOPh), 5.72 (t, 1H, $J_{3,4}=J_{4,5}=9.9$ Hz, H-4a), 5.66 (d, 1H, $J_{1,2}=1.7$ Hz, H-1a), 5.51–5.44 (m, 2H, H-2b, H-4b), 5.35 (dd, 1H, $J_{2,3}=3.4$ Hz, H-2a), 5.11 (d, 1H, $J_{1,2}=1.3$ Hz, H-1b), 4.51 (dd, 1H, $J_{2,3}=3.3$ Hz, $J_{3,4}=9.7$ Hz, H-3b), 4.35–4.31 (m, 2H, H-3a, H-5a), 4.01 (dd, 1H, $J_{5,6}=4.2$ Hz, $J_{6,6'}=11.2$ Hz, H-6a), 3.83–3.76 (m, 2H, H-6′a, H-5b), 3.49–3.41 (m, 2H, H-6b, H-6′b). ^{13}C NMR (75 MHz, $CDCl_3$): δ 97.6 (C-1b), 87.5 (C-1a). ES-LRMS $m/z=806.3$ $[M+Na]^+$.
17. Selected data for **19**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16–7.12 (m, 65H, OCOPh), 6.02 (t, 1H, $J_{2,3}=J_{3,4}=10.0$ Hz, H-4b), 5.90–5.54 (m, 12H, H-1a (5.66 ppm, $J_{1,2}=1.9$ Hz), H-2a, H-2b, H-2c or H-2e, H-2d, H-3c, H-3d, H-3e, H-4a, H-4c, H-4d, H-4e), 5.17 (d, 1H, $J_{1,2}<1$ Hz, H-1b), 5.11 (m, 2H, H-1c or H-1e, H-2c or H-2e), 5.08 (d, 1H, $J_{1,2}=1.8$ Hz, H-1c or H-1e), 4.89 (d, 1H, $J_{1,2}=1.4$ Hz, H-1d), 4.61 (dd, 1H, $J_{2,3}=3.3$ Hz, H-3b), 4.56 (dd, 1H, $J_{2,3}=3.3$ Hz, $J_{3,4}=10.0$ Hz, H-3a), 4.53–4.14 (m, 12H, H-5a, H-5b, H-5c, H-5d, H-5e, H-6a, H-6c, H-6d, H-6e, H-6′c, H-6′d, H-6′e), 4.06 (dd, 1H, $J_{5,6}=4.4$ Hz, $J_{6,6'}=11.2$ Hz, H-6b), 3.79 (dd, 1H, $J_{5,6}<1$ Hz, $J_{6,6'}=10.2$ Hz, H-6′a), 3.62 (dd, 1H, $J_{5,6'}=1.9$ Hz, H-6′b), 1.97, 1.93 and 1.78 (3 s, 9H, $OCOCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 99.4 (C-1c or C), 98.8 (C-1c or C-1e), 97.6 (C-1b), 97.5 (C-1d), 88.5 (C-1a). ES-HRMS $m/z=2354.6443$ $[M+Na]^+$ 2354.6434 required.
18. Selected data for **20**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27–7.28 (m, 35H, OCOPh), 5.81 (t, 1H, $J_{3,4}=J_{4,5}=9.5$ Hz, H-4a), 5.77 (t, 1H, $J_{3,4}=J_{4,5}=10.0$ Hz, H-4c), 5.72–5.69 (m, 2H, H-3b, H-4b), 5.68 (d, 1H, $J_{1,2}=2.0$ Hz, H-1a), 5.59–5.54 (m, 3H, H-2a, H-2b, H-3c), 5.17 (d, 1H, $J_{1,2}=2.0$ Hz, H-1c), 5.14 (dd, 1H, $J_{2,3}=3.3$ Hz, H-2c), 5.05 (d, 1H, $J_{1,2}=1.8$ Hz, H-1b), 4.50 (dd, 1H, $J_{2,3}=3.5$ Hz, H-3a), 4.47–4.38 (m, 4H, H-5a, H-5c, H-6c, H-6′c), 4.30 (m, 1H, H-5b), 4.18 (d, 2H, $J_{5,6}=4.4$ Hz, H-6b, H-6′b), 4.05 (dd, 1H, $J_{5,6}=6.0$ Hz, $J_{6,6'}=11.0$ Hz, H-6a), 3.80 (dd, 1H, $J_{5,6'}=2.2$ Hz, H-6′a), 1.92, 1.89 and 1.88 (3 s, 9H, $OCOCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 99.7 (C-1c), 97.8 (C-1b), 88.0 (C-1a). ES-LRMS $m/z=1406.2$ $[M+Na]^+$.