bonds are formed in a "critical range" of ΔpK_a values scattered roughly around 1.0.[12, 13] For substituted pyridine · PCP adducts in CCl_4 solution, an ideal ΔpK_a for "50% proton transfer" is reported as 1.6.[13a] Since a more polar environment generally favors more ionic forms, it must be expected that in crystals, a pyridine · PCP adduct with $\Delta pK_a = 1.6$ is formally ionic (N^+–H···O^-) and adducts with really 50% proton transfer are characterized by $\Delta pK_a < 1.6$. Because the influence of the crystalline environment cannot be predicted quantitatively, one cannot predict the exact hydrogen-bond geometry from a known ΔpK_a value and molecular geometry. In any case, the ΔpK_a of 0.77[12] makes 4-MePy · PCP an interesting candidate in the search for an O–H–N bond with a centered H atom ($pK_a = 5.22$ (Py), 6.03 (4-MePy), 5.26 (PCP)).[12a]

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[17] The observation that the H atom is on time-average closer to the O atom at room temperature, and closer to the N atom at 20 K could have a number of reasons: 1) The substance might be dimorphic, with one crystal form having a different kind of hydrogen bond than the other. 2) There might be gradual proton migration upon cooling; this is the effect that was actually found in the second experiment. 3) The H atom might be disordered over two positions, one closer to the O atom and the other closer to the N atom, and relative occupancies change with temperature; similar effects are known, for example, with the O–H···O hydrogen bond in benzoic acid: C. C. Wilson, N. Shankland, A. J. Florence, *J. Chem. Soc. Faraday Trans.* **1996**, *92*, 5051 – 5057. 4) The difference between the structures at room temperature and at 20 K might be nothing more than an artifact caused by experimental inaccuracies.

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[23] In 4-MePy · PCP, the hydrogen bond is geometrically centered at about 90 K. This H position is singular in geometric terms, but not the one where the O–H and H–N bonds have equal "bond orders" $s = ½$. Free O–H and N–H covalent bonds have different lengths (e.g. 0.957 and 1.012 Å in H_2O and H_3N vapor, respectively), and also O–H and N–H bonds with $s = ½$ should have different X–H distances. Even the most recent parametrization of distance/valence relations is very inaccurate for strong O–H–N bonds, because no experimental data from that region could be used,[11] but suggests that an O–H bond with $s = ½$ is 0.060 Å shorter than an N–H bond with $s = ½$. According to Table 1, this situation occurs in 4-MePy · PCP between 125 and 150 K.

Nitroglycal Concatenation: A Broadly Applicable and Efficient Approach to the Synthesis of Complex O-Glycans**

Gottfried A. Winterfeld and Richard R. Schmidt*

The mucin class of glycopeptides has attracted much attention in recent years, because it subsumes numerous structures of fundamental importance in biological processes such as fertilization, parasitic infection, inflammation, immune defense, cell-growth, and cell – cell adhesion.[1] Synthesis of the characteristic α-glycosidic linkage between 2-acetamido-2-deoxy-D-galactopyranose and the hydroxy groups of L-serine and L-threonine, however, proved difficult. Most syntheses of α-O-linked glycopeptides rely essentially on the methodology introduced by Paulsen in 1978: The glycosylations are carried out with glycosyl donors that have a non-participating azido group at position 2 as latent amino function as well as a leaving group at the anomeric center.[2, 3] Enzymatic syntheses have also been reported, for example the synthesis of Core 1 and the corresponding sialylated Core 1 structure.[4] Core structures are defined as the binding region of the saccharides directly bound to the protein.[19] Recently, we have shown that for the synthesis of the simplest mucin structure, the T_N antigen, Michael addition to 2-nitrogalactal may serve as an efficient alternative approach.[5] This fundamentally new approach has now been developed to a comprehensive and powerful methodology that provides highly stereoselective access to 3-O- and 6-O-branched mucin structures.

All mucin core structures contain at the reducing end a *N*-acetylgalactosamine α-glycosidically linked to L-serine or L-threonine. Eight core structures of mucin-type glycopeptides have been identified to date; they bear additional glycosyl residues at either position 6 or position 3 or at both positions to form complex O-glycans (Scheme 1). To demonstrate that nitroglycal concatenation is a well-suited tool for the synthesis of all members of the mucin family we strategically chose two target molecules from the 6-O-branched structures (ST_N antigen and Core 7) and one target molecule from the 3-O-branched structures (Core 1). These structures are generated by reaction sequences I – III (Scheme 2 and 3).

For reaction sequences I and II as well as for the synthesis of T_N building blocks, nitroglycal **2** is the key intermediate of our synthesis. Nitroglycal **2** can be obtained in 84% yield from protected galactal **1**[6] by using a two-step, one-pot procedure involving addition of acetyl nitrate to the glycal functionality and subsequent elimination of acetic acid (Scheme 2).[5]

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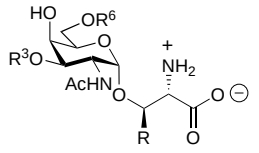


	R^6
Core 6:	GlcNAc β (1-6) →
Core 7:	GalNAc α (1-6) →
ST_N-Antigen:	Neu5Ac α (2-6) →

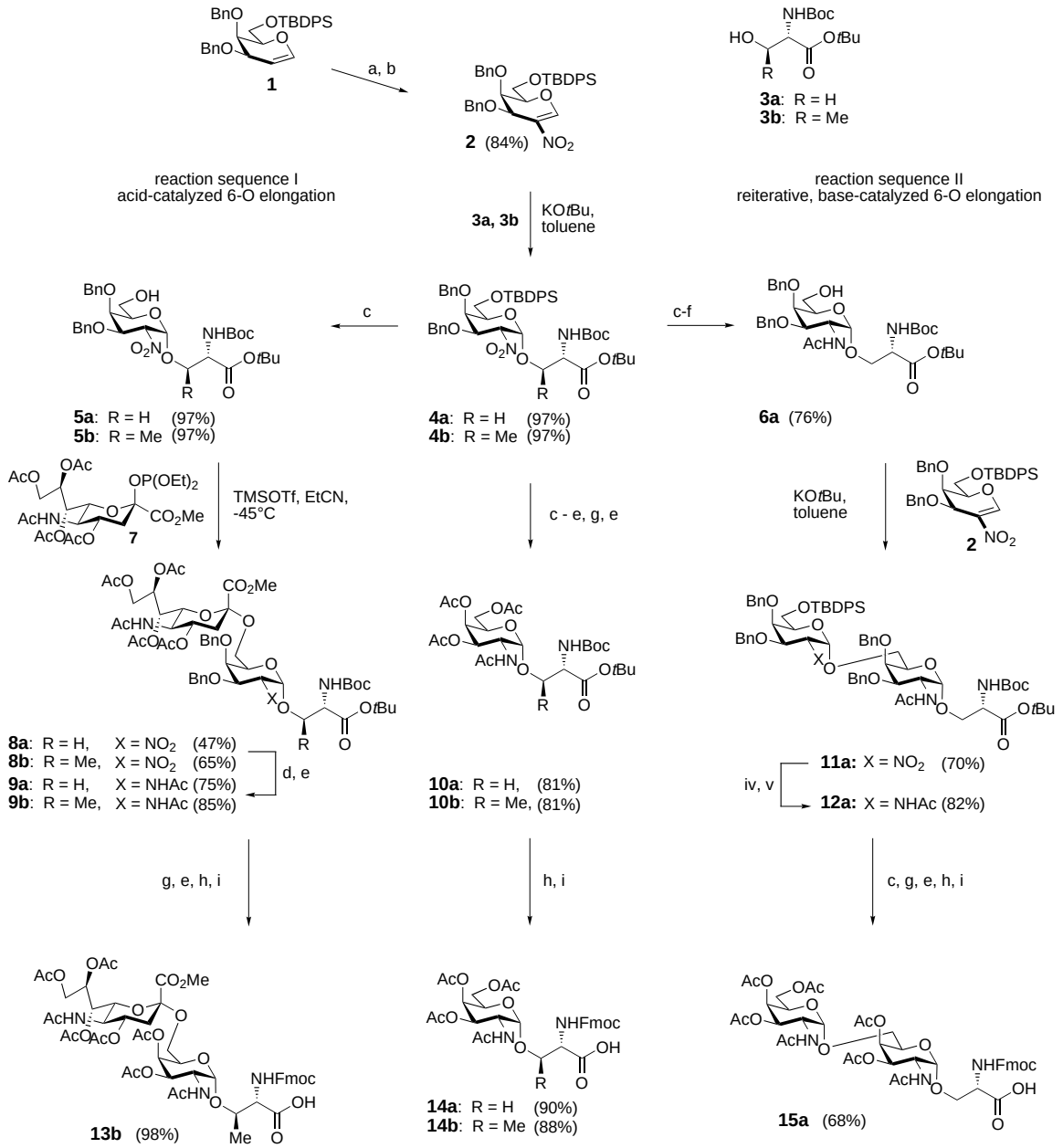
	R^3
Core 1:	Gal β (1-3) →
Core 3:	GlcNAc β (1-3) →
Core 5:	GalNAc α (1-3) →
Core 8:	Gal α (1-3) →

	R^3, R^6
Core 2:	GlcNAc β (1-6) → Gal β (1-3) →
Core 4:	GlcNAc β (1-6) → GlcNAc β (1-3) →

Scheme 1. Core structures of mucin-type O-glycans.

Protected serine **3a** and threonine **3b** add to this glycosyl donor **2** in virtually quantitative yield and under complete stereocontrol to form the desired α-linked 2-nitroglycosides **4a** and **4b**, respectively. The base-catalyzed glycosylation, which requires 0.1 equivalents of potassium *tert*-butoxide, is performed at room temperature and reaches completion within 10 min in the serine case and within 120 min in the threonine case. Compared to our previous observations with a perbenzylated nitrogalactal,[5] glycosyl donor **2** bearing a sterically demanding protective group at position 6 shows significantly enhanced reactivity and stereocontrol.

The peracetylated T_N antigens **10a** and **10b** are accessible from glycosides **4a** and **4b** in 81% yield after removal of silyl protective groups, reduction of the nitro group with Raney



Scheme 2. Synthesis of T_N antigen, ST_N antigen, and Core 7 building blocks for glycopeptide synthesis; a) HNO_3, Ac_2O; b) Et_3N, CH_2Cl_2; c) TBAF, AcOH, THF; d) Raney-Ni T4 (Pt), H_2, EtOH; e) Ac_2O, pyridine; f) NaOMe, MeOH; g) Pd/C, H_2, AcOH, MeOH; h) TFA, CH_2Cl_2; i) Fmoc-ONSu, $NaHCO_3$, MeCN, H_2O. Ac = acetyl, Bn = benzyl, Boc = *tert*-butoxycarbonyl, Fmoc = fluoren-9-ylmethoxycarbonyl, Su = succinimidyl, TBDPS = *tert*-butyldiphenylsilyl, TFA = trifluoroacetic acid.

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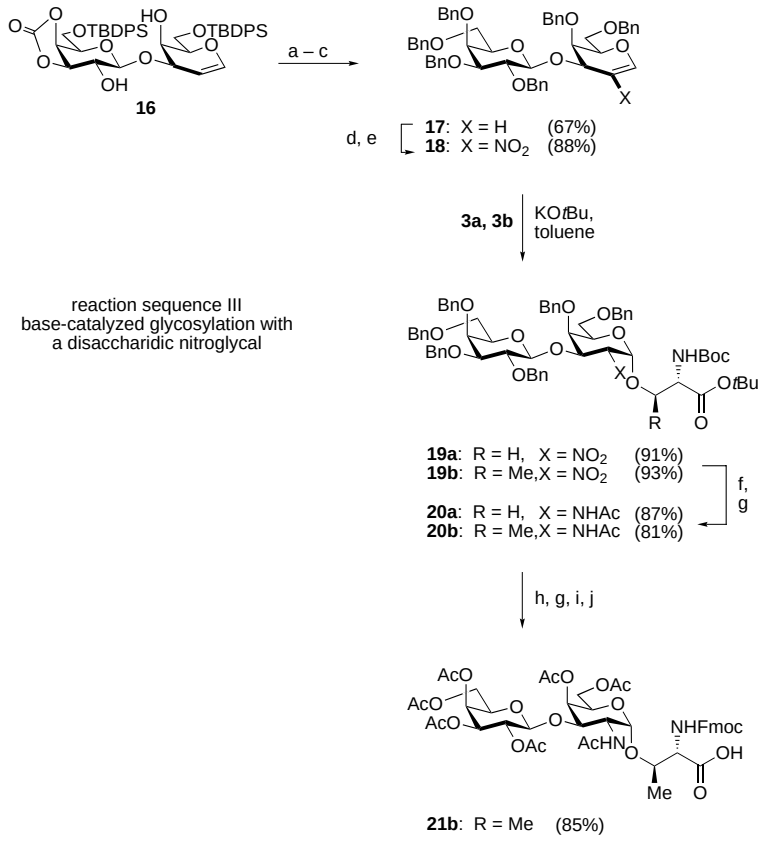

Scheme 3. Synthesis of a Core 1 building block for glycopeptide synthesis; a) NaOMe, MeOH; b) TBAF, THF; c) BnBr, NaH, DMF; d) Ac_2O, HNO_3; e) Et_3N, CH_2Cl_2; f) Raney-Ni T4 (Pt), H_2, EtOH; g) Ac_2O, pyridine; h) Pd/C, H_2, AcOH, MeOH; i) TFA, CH_2Cl_2; j) Fmoc-ONSu, $NaHCO_3$, MeCN, H_2O.

nickel T4/H_2,[5] N-acetylation, and protective group manipulations (Scheme 2). Known[7] building blocks for glycopeptide synthesis **14a** and **14b**[8] are obtained after cleavage of Boc and *tert*-butyl protective groups on the amino acid moiety and installation of the Fmoc protective group.

The ST_N antigen **13b** displays an α-linked *N*-acetylneuraminic acid unit at the 6-O position of the T_N structure. To arrive at a suitable glycosyl acceptor for the acid-catalyzed sialylation reaction, silyl protection at position 6 was removed by using a buffered tetrabutylammonium fluoride (TBAF) solution in THF (Scheme 2, reaction sequence I).[9] Nitroglycosides **5a** and **5b** can be applied to a sialylation reaction with neuraminic acid phosphite **7**[10] under Lewis acid catalysis. At $-45\,^{\circ}C$ in propionitrile the reaction affords α-linked sialosides **8a** and **8b**. The nitro group of these disaccharides can then be reduced to the amine and N-acetylated to afford derivatives **9a** and **9b**. Removal of the benzyl protective groups, peracetylation, removal of the *tert*-butyl protective group and exchange of the Boc for the Fmoc protective group affords the known ST_N building block **13b**[11, 12] suitable for glycopeptide synthesis.

Core 7 bears a second α-linked galactosamine moiety at position 6 of the T_N structure. This second unit may be installed by using a reiterative Michael-addition approach (Scheme 2, reaction sequence II). The 6-position of nitroglycoside **4a** is unmasked as mentioned before and the nitro group reduced to the amine and N-acetylated. Glycosyl acceptor **6a** is glycosylated making repeated use of nitrogalactal **2**. Again the glycosylation affords stereoselectively the α-glycoside **11a**. The second glycosylation cycle is completed by reduction of the nitro group and N-acetylation of the resulting amine to afford **12a**. The synthesis of building block **15a**[13] is achieved after exchange of all protective groups on the carbohydrate moiety of **12a** for acetyl groups, removal of both Boc and *tert*-butyl groups, and installation of the Fmoc protective group.

Having demonstrated the efficiency of nitroglycal concatenation for the synthesis of unsubtituted and 6-O-substituted O-glycans by elongation of a preformed T_N structure, we devised a Core 1 synthesis to open the methodology towards 3-O-branched structures and to the use of disaccharidic glycals in the nitration/Michael addition protocol. We started from known disaccharide glycal **16**,[14] which was converted to the per-O-benzylated derivative **17** (Scheme 3, reaction sequence III). Glycal **17** undergoes addition of acetyl nitrate and elimination of acetic acid as described for **1**[5] to afford the corresponding nitroglycal **18**. This Michael acceptor was glycosylated under standard conditions with **3a** and **3b** to give the corresponding α-glycosides **19a** and **19b**. Reduction of the nitro groups proceeded similarly to all previous examples and afforded the acetamido glycosides **20a** and **20b** after N-acetylation. Benzyl protective groups were exchanged for acetyl protective groups, the protective groups on the amino acid moiety were removed, and finally the Fmoc protective group was introduced to give the known[7b,g, 15] target building block **21b**.[16]

In conclusion, the syntheses of T_N and ST_N antigens as well as Core 7 and Core 1 structures have been achieved by using Michael addition reactions to nitroglycals as the key reaction. Nitroglycal concatenation has been applied reiteratively and combined with either anomeric leaving-group-based glycosylations[17] or the glycal assembly method,[18] demonstrating its versatility. The readily available starting nitroglycals as well as the stereochemically defined outcome of all base-catalyzed glycosylations shown here highlight this new methodology.

Experimental Section

2: Concentrated nitric acid (24 mL, 0.38 mol) was added dropwise to acetic anhydride (240 mL) at $10\,^{\circ}C$ under constant stirring. The external temperature was further lowered to $-10\,^{\circ}C$ to keep the internal temperature in the range of $10-20\,^{\circ}C$ during the addition. Once the addition was complete, the solution was cooled further to $-50\,^{\circ}C$ upon which a precipitate formed. Then a solution of galactal **1** (30 g, 0.053 mol) in acetic anhydride (120 mL) was added over a period of 10–15 min, and the mixture stirred at this temperature for 30 min. After the reaction mixture had been allowed to warm to $-22\,^{\circ}C$, it became clear. The reaction mixture was poured into iced water (500 mL), brine (250 mL) was added, and the aqueous layer extracted with diethyl ether (3×300 mL). The combined organic extracts were dried over sodium sulfate and the solvents removed by coevaporation with toluene. The crude intermediate 2-nitrogalactopyranose was dissolved in dichloromethane (50 mL) and slowly added to an ice-cold, stirred solution of triethylamine (22 mL, 0.159 mol) in dichloromethane (50 mL). After complete addition the cooling bath was removed and stirring

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continued for 20 min. The organic phase was washed with 2 N HCl solution and dried over sodium sulfate. Removal of the volatiles and column chromatographic purification (toluene/ethyl acetate 98:2) of the residue furnished **2** as a light yellow oil (27 g, 84 %). $[\alpha]_D^{25} = -7.5$ ($c = 12$, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.77$ (s, 1H; 1-H), 7.61 – 7.60 (m, 3H; arom. H), 7.41 – 7.40 (m, 2H; arom. H), 7.34 – 7.14 (m, 15H; arom. H), 4.78 (d, $^3J_{3,4} = 3.5$ Hz, 1H; 3-H), 4.75 (d, $^2J = 10.9$ Hz, 1H; benzyl. H), 4.68 (d, $^2J = 10.9$ Hz, 1H; benzyl. H), 4.59 – 4.57 (m, 2H; 5-H, benzyl. H), 4.51 (d, $^2J = 12.0$ Hz, benzyl. H), 4.22 – 4.14 (m, 2H; 6-H, H6′), 3.81 (t, $^3J_{4,3} = 4.6$, $^3J_{4,5} = 4.6$ Hz, 1H; 4-H), 1.05 (s, 9H; C_4H_9); MS (FAB): *m*/*z*: 610 $[M+H]^+$, 632 $[M+Na]^+$.

4b: Nitrogalactal **2** (13 g, 21.3 mmol) and **3b** (7.1 g, 25.6 mmol) were dried under high vacuum and dissolved in dry toluene (250 mL) under argon. Then potassium *tert*-butoxide solution (2.1 mL of a 1 M solution in THF) was added and stirring continued for 120 min. Acetic acid (2 mL) was used to acidify the reaction mixture and all solvents were removed under reduced pressure. The residue was purified by column chromatography (toluene/ethyl acetate 20:1) to furnish **4b** as a colorless oil (18.3 g, 97 %). $[\alpha]_D^{25} = +53.3$ ($c = 5$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.61 - 7.60$ (m, 4H; arom. H), 7.39 – 7.18 (m, 16H; arom. H), 5.32 (d, $^3J_{1,2} = 4.4$ Hz, 1H; 1-H), 4.96 (d, $^3J_{NH,\alpha} = 9.7$ Hz, 1H; NH), 4.93 (dd, $^3J_{2,1} = 4.1$, $^3J_{2,3} = 10.6$ Hz, 1H; 2-H), 4.83 (d, $^2J = 11.0$ Hz, 1H; benzyl. H), 4.77 (d, $^2J = 11.0$ Hz, 1H; benzyl. H), 4.50 (d, $^2J = 11.1$ Hz, 1H; benzyl. H), 4.43 (dd, $^3J_{3,2} = 10.6$, $^3J_{3,4} = 2.9$ Hz, 1H; 3-H), 4.24 – 4.23 (br d, 1H; β-H), 4.06 – 4.05 (m, 2H; α-H, 4-H), 3.88 (br t, $^3J_{5,6} = 6.8$, $^3J_{5,6'} = 6.8$ Hz, 1H; 5-H), 3.74 (dd, $^3J_{6,5} = 7.6$, $^2J_{6,6'} = 10.3$ Hz, 1H; 6-H), 3.68 (dd, $^3J_{6',5} = 5.9$, $^2J_{6',6} = 10.0$ Hz, 1H; 6′-H), 1.49, 1.45 (2s, 18H; $2\,C_4H_9$), 1.04 (s, 9H; C_4H_9). MS (FAB): *m*/*z*: 907 $[M+Na]^+$.

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[8] The NMR data of **14a**, **b** are in excellent agreement with the reported data in ref. [7]. However, varying optical rotation values were reported: **14a**: $[\alpha]_D^{25} = +88.0$ ($c = 0.3$, $CHCl_3$), ref. [7a]: $[\alpha]_D^{20} = +89.9$ ($c = 1$, $CHCl_3$), ref. [7d]: $[\alpha]_D^{22} = +82.3$ ($c = 1$, $CHCl_3$), ref. [7e]: $[\alpha]_D = +87.5$ ($c = 2$, $CHCl_3$), ref. [7f]: $[\alpha]_D^{23} = +74.4$ ($c = 1$, $CHCl_3$); **14b**: $[\alpha]_D^{25} = +61.5$ ($c = 0.2$, $CHCl_3$), ref. [7a]: $[\alpha]_D^{20} = +65.0$ ($c = 1.45$, $CHCl_3$), ref. [7b]: $[\alpha]_D^{20} = +90$ ($c = 0.4 - 0.7$, $CHCl_3$), ref. [7c]: $[\alpha]_D^{25} = +64$ ($c = 1.5$, $CHCl_3$), ref. [7d]: $[\alpha]_D^{22} = +75.8$ ($c = 1$, $CHCl_3$), Ref. [7e]: $[\alpha]_D = +59$ ($c = 0.5$, $CHCl_3$), ref. [7f]: $[\alpha]_D^{23} = +72$ ($c = 0.72$, $CHCl_3$), ref. [7g]: $[\alpha]_D^{23} = +63.7$ ($c = 1.0$, $CHCl_3$), ref. [7 h]: $[\alpha]_D^{23} = +90.6$ ($c = 1.55$, $CHCl_3$).

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[12] **13b**: $[\alpha]_D^{25} = +35.5$ ($c = 2.5$, $CHCl_3$), ref. [11b]: $[\alpha]_D^{22} = +28.9$ ($c = 1.0$, MeOH), ref. [11c]: $[\alpha]_D^{23} = +36.7$ ($c = 1.04$, $CHCl_3$).

[13] **15a**: $[\alpha]_D^{25} = +88.8$ ($c = 1$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta =$ 7.89 (d, $J = 7.5$ Hz, 2H; arom. H), 7.71 (t, $J = 7.7$ Hz, 2H; arom. H) 7.40 – 7.30 (m, 4H; arom. H), 5.45 (d, $^3J_{4,3} = 3.2$ Hz, 1H; 4a-H), 5.33 (d, $^3J_{4,3} = 2.6$ Hz, 1H; 4b-H), 5.21 – 5.17 (m, 2H; 3a-H, 3b-H) 4.88 (d, $^3J_{1,2} = 3.3$ Hz, 1H; 1a-H), 4.77 (d, $^3J_{1,2} = 3.5$ Hz, 1H; 1b-H), 4.55 – 4.42 (m, 4H; β-H, β'-H, 2a-H), 4.35 (t, $^3J_{5,6} = 6.6$, $^3J_{5,6'} = 5.6$ Hz, 1H; 5a-H), 4.28 – 4.23 (m, 3H; 5b-H, α-H, Fmoc-CH), 4.02 (dd, $^3J_{6,5} = 6.0$, $^2J_{6,6'} =$ 11.2 Hz, 1H; 6b-H), 3.95(s, 2H; Fmoc-CH_2), 3.83 (dd, $^3J_{6',5} = 7.0$, $^2J_{6',6} = 11.1$ Hz, 1H; 6b′-H), 3.77 (t, $^3J_{6,6'} = 9.6$ Hz, 1H; 6a-H), 3.34 (dd, $^3J_{6',5} = 5.0$, $^2J_{6',6} = 9.9$ Hz, 1H; 6a′-H), 2.14 – 1.86 (7s, 21H; 5 OAc, 2 NHAc); ^{13}C NMR (150.8 MHz, $CDCl_3$): $\delta = 174.0 - 172.0$ (8C), 145.3 – 121.0 (12C), 100.0 (1a-C), 99.1 (1b-C), 71.5 (Fmoc-CH_2), 70.1 (3a-C), 69.8 (3b-C), 69.3 (4a-C), 68.8 (2-C, 5a-C, 4b-C), 68.0 (5b-C), 67.4 (6a-C), 63.0 (6b-C), 57.7 (Fmoc-CH), 49.0 (2a-C), 48.7 (2b-C), 48.4 (α-C), 22.8, 22.7, 20.7 (2C), 20.5; MS (FAB): *m*/*z*: 966 $[M+Na]^+$, 988 $[M+2Na-H]^+$.

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[16] **21b**: The ^{1}H NMR data are in excellent agreement with reported data in ref. [7b]. Again differences in the optical rotation values were found: $[\alpha]_D^{25} = +25.7$ ($c = 2$, $CHCl_3$), ref. [7b]: $[\alpha]_D^{21} = +67$ ($c = 0.4 - 0.7$, $CHCl_3$), ref. [7g]: $[\alpha]_D^{23} = +69.2$ ($c = 1$, $CHCl_3$).

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