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A Highly Stereocontrolled Synthesis of 1β,1β-Linked Acetylated Oligosaccharides via Orthoester Formation-Rearrangement

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Abstract: 1β,1β- Linked acetylated di-, tri-, and tetrasaccharides were synthesized in satisfactory yields and good stereoselectivities by a new method—orthoester formation and rearrangement under mild conditions.

1,1-Linked oligosaccharides occur in many bioactive products and are distributed in the plant, fungi, yeast, red alga, lichen, and insect kingdoms.[1] A variety of methods are available for their synthesis, e.g. the Koenigs-Knorr reaction of a 1-hydroxy sugar with a glycosyl halide,[2a-d] perchloric acid catalyzed coupling of 2,3,4,6-tetra-*O*-methyl-[2e] and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1**) with a glycosyl halide,[2f] TMSOTf (1 equiv) promoted coupling of **1** and its manno- and galactose analogues with their corresponding Schmidt glycosyl donors,[2g, 2h, 2l] glycosylation of **1** with its 1-*O*-trimethylsilylated derivative,[2j] and diphenyldichlorosilane-silver triflate[2k] and triflic anhydride[2l] induced coupling of **1**. These methods give 1,1-linked disaccharides as a mixture of αα-, αβ-, and ββ-linkages in variable yields. For glucose, xylose, and galactose dimers, the αβ isomer is usually the major product (30-50%) together with the αα-isomer (18-48%) and the ββ-isomer (5-22%), and only for mannose and rhamnose is the αα- isomer obtained in relatively high yields. 1β,1β-Linked glucose and galactose are important moieties in several biologically important structures.[3a, 3b] However, there have been only very few reports dealing with the synthesis of 1β,1β-linked oligosaccharides. Until now, the most successful preparation of 1β,1β-linked gluco- or galacto-disaccharides was achieved *via* coupling of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose[4] or -α,β-D-galactopyranose[3b] with the corresponding glycosyl trichloroacetimidate which gives products in moderate yields, the latter[3b] as a 1/1 ββ/αβ-anomeric mixture. In our recent research, we have found a new method for regio- and stereoselective synthesis of oligosaccharides using *O*-acetylglycosyl bromides as the glycosyl donors and unprotected or partially protected glycosides as the acceptors through orthoester formation-rearrangement.[5a, 5b, 5c] Here we would like to report a highly effective and stereoselective synthesis of acetylated 1β,1β-linked

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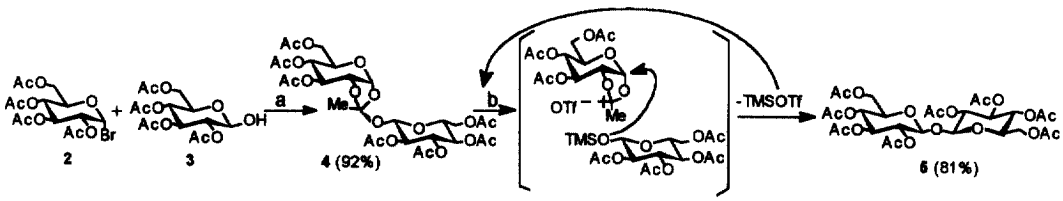
oligosaccharides based on this new method.

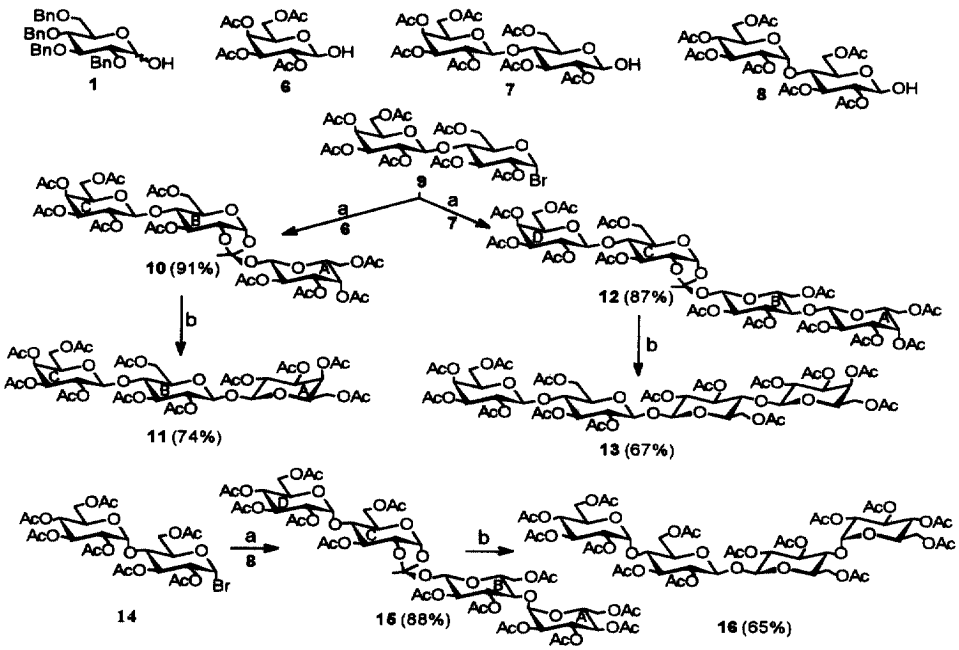
As shown in Scheme 1, coupling of acetobromoglucose **2** with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**3**) in the presence of AgOTf (1 equiv.) and 2,4-lutidine (1 equiv.) with dichloromethane as the solvent furnished orthoester (*exo*) **4** as the sole product in a very high yield (92%). Subsequent rearrangement of **4** with a catalytic amount of TMSOTf (0.1 equiv) afforded the pure 1β,1β-linked Glu-Glu **5** in a yield of 81%. We rationalized that an attack of the trimethylsilylated acceptor from the C-1 back side of the acyloxonium ion ensured the β stereoselectivity of the rearrangement, while the mild reaction conditions used in both orthoester formation and rearrangement excluded anomerization of both starting material **3** and the resultant 1β,1β-linked disaccharide **5**.

Scheme 1



Reagents and conditions: a. AgOTf (1 equiv), 2,4-lutidine (1 equiv), CH_2Cl_2, M.S.(4 Å), RT, N_2, 2 h. b. TMSOTf (0.1 equiv), CH_2Cl_2, M.S.(4 Å), -20 °C, N_2, 1 h.

Scheme2



Reagents and conditions: see Scheme 1 for a,b.

The success in the synthesis of isotrehalose **5** encouraged us to explore synthesis of more complex 1β,1β-linked oligosaccharides. Thus, coupling of acetobromolactose **9** with acceptor **6** under the same conditions as described above yielded 1β,1β-linked trisaccharide **11** *via* an intermediate trisaccharide orthoester (*exo*) **10**[6] in an overall yield of 67% (see the Scheme 2). Furthermore, 1β,1β-linked lactosyl-lactoside **13** and maltosyl-maltoside **16** were readily obtained in satisfactory yields from coupling of acetobromolactose **9** and acetobromomaltose **14** with **7** and **8** followed by rearrangement respectively.

In summary, we provide a general and very effective method for the synthesis of 1β,1β-linked oligosaccharides *via* orthoester formation and rearrangement under mild conditions. The use of the acetyl protecting group and the readily available *O*-acetylglycosyl bromides substantially simplified the procedures. Further investigation of the application of this new method to the synthesis of special 1,1-linked oligosaccharides is in process.

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6. The yields of orthoesters and the final products after rearrangement were shown in parentheses of Scheme 2. Optical rotation and ^{1}H NMR ($CDCl_3$, 400MHz) data of new compounds are as follows. **10**: $[\alpha]_D^{20}$ +30.1° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 5.60 (d, 1 H, $J_{1B,2B}$ 5.3 Hz, H-1_B), 5.44 (bs, 1 H, H-3_B), 5.35 (bs, 2 H, H-4_A, 4_C), 5.15, 5.11 (2 dd, 2 H, $J_{1A,2A}$, $J_{1C,2C}$ 8.1 Hz, $J_{2A,3A}$, $J_{2C,3C}$ 9.8 Hz, H-2_A, 2_C), 4.99, 4.97 (2 dd,

2 H, $J_{3A,4A}$, $J_{3C,4C}$ 3.2 Hz, H-3_A, 3_C), 4.73 (d, 1 H, H-1_C), 4.55 (d, 1 H, H-1_A), 4.33 (dd, 1 H, $J_{1B,2B}$ 5.3 Hz, $J_{2B,3B}$ 2.4 Hz, H-2_B), 4.22-3.60 (m, 10 H, H-4_B, 5_A, 5_B, 5_C, 6_A, 6_B, 6_C), 2.14-1.95 (10 s, 30 H, 10 CH_3CO), 1.69 (s, 3 H, CH_3CO$_3$). **11**: $[\alpha]_D^{20}$ -2.5° (*c* 1.3, $CHCl_3$); ^{1}H NMR: δ 5.39 (d, 1 H, $J_{3A,4A}$ 3.3 Hz, H-4_A), 5.36 (d, 1 H, $J_{3C,4C}$ 3.3 Hz, H-4_C), 5.22 (t, 1 H, J 8.8 Hz, H-3_B), 5.14 (dd, 1 H, $J_{1A,2A}$ 7.6 Hz, $J_{2A,3A}$ 9.8 Hz, H-2_A), 5.13 (dd, 1 H, $J_{1C,2C}$ 7.8 Hz, $J_{2C,3C}$ 9.8 Hz, H-2_C), 5.03 (dd, 1 H, $J_{3A,4A}$ 3.3 Hz, H-3_A), 4.97 (dd, 1 H, H-3_C), 4.89 (t, 1 H, J 8.8 Hz, H-2_B), 4.82 (d, 1 H, H-1_B), 4.72 (d, 1 H, H-1_C), 4.53 (dd, 1 H, $J_{5A,6Aa}$ 1.9 Hz, $J_{6Aa,6Ab}$ 12.1 Hz, H-6_{Aa}), 4.50 (d, 1 H, H-1_A), 4.17-4.07 (m, 5 H, H-6_{Ab}, 6_B, 6_C), 3.92 (t, 1 H, $J_{5A,6A}$ 6.7 Hz, H-5_A), 3.87 (t, 1 H, $J_{5C,6C}$ 6.7 Hz, H-5_C), 3.84 (t, 1 H, J 8.8 Hz, H-4_B), 3.70-3.65 (m, 1 H, H-5_B), 2.18-1.98 (11 s, 33 H, 11 CH_3CO). **12**: $[\alpha]_D^{20}$ +2.8° (*c* 0.8, $CHCl_3$); ^{1}H NMR: δ 5.62 (d, 1 H, $J_{1C,2C}$ 5.3 Hz, H-1_C), 5.49 (t, 1 H, J 1.9 Hz, H-3_C), 5.38 (d, 1 H, $J_{3D,4D}$ 3.4 Hz, H-4_D), 5.35 (d, 1 H, $J_{3A,4A}$ 3.4 Hz, H-4_A), 5.19 (t, 1 H, J 9.4 Hz, H-3_B), 5.18 (dd, 1 H, $J_{1D,2D}$ 8.0 Hz, $J_{2D,3D}$ 9.8 Hz, H-2_D), 5.12 (dd, 1 H, $J_{1A,2A}$ 8.2 Hz, $J_{2A,3A}$ 9.6 Hz, H-2_A), 5.01 (dd, 1 H, H-3_D), 4.97 (dd, 1 H, H-3_A), 4.83 (dd, 1 H, $J_{1B,2B}$ 7.9 Hz, $J_{2B,3B}$ 9.4 Hz, H-2_B), 4.73 (d, 1 H, H-1_A), 4.70 (dd, 1 H, $J_{5C,6Ca}$ 1.7 Hz, $J_{6Ca,6Cb}$ 12.2 Hz, H-6_{Ca}), 4.59 (d, 1 H, $J_{1D,2D}$ 8.0 Hz, H-1_D), 4.53 (d, 1 H, H-1_B), 4.39 (dd, 1 H, H-2_C), 4.27 (dd, 1 H, $J_{5C,6Cb}$ 1.8 Hz, $J_{6Ca,6Cb}$ 12.2 Hz, H-6_{Cb}), 4.17-3.60 (m, 12 H, H-4_B, 4_C, 5_A, 5_B, 5_C, 5_D, 6_A, 6_B, 6_D), 2.17-1.97 (13 s, 39 H, 13 CH_3CO), 1.69 (s, 3 H, CH_3CO$_3$). **13**: $[\alpha]_D^{20}$ –8.6° (*c* 0.5, $CHCl_3$); ^{1}H NMR: δ 5.57 (t, 2 H, J 9.7 Hz, 2 × H-3), 5.40 (d, 2 H, $J_{3',4'}$ 3.6 Hz, 2 × H-4'), 5.13 (dd, 2 H, $J_{1',2'}$ 7.8 Hz, $J_{2',3'}$ 9.8 Hz, 2 × H-2'), 4.96 (dd, 2 H, 2 × H-3'), 4.86 (dd, 2 H, $J_{1,2}$ 7.7 Hz, 2 × H-2), 4.50 (d, 2 H, 2 × H-1'), 4.49 (d, 2 H, 2 × H-1), 4.46 (dd, 2 H, $J_{5,6a}$ 1.8 Hz, $J_{6a,6b}$ 12.6 Hz, 2 × H-6_a), 4.27-4.22 (m, 2 H, 2 × H-5), 4.19-4.05 (m, 6 H, 2 × H-6_b, 6'), 3.89 (t, 2 H, $J_{5',6'}$ 6.4 Hz, 2 × H-5'), 3.78 (t, 2 H, J 9.7 Hz, 2 × H-4), 2.16-1.97 (7 s, 42 H, 14 CH_3CO). **15**: $[\alpha]_D^{20}$ +41.8° (*c* 1.2, $CHCl_3$); ^{1}H NMR: δ 5.67 (d, 1 H, $J_{1C,2C}$ 5.5 Hz, H-1_C), 5.46, 5.43 (2 d, 2 H, $J_{1A,2A}$, $J_{1D,2D}$ 4.0 Hz, H-1_A, 1_D), 5.40, 5.36 (2 t, 2 H, $J_{2A,3A}$, $J_{2D,3D}$, 9.9 Hz, $J_{3A,4A}$, $J_{3D,4D}$, 9.9 Hz, H-3_A, 3_D), 5.26 (t, 1 H, J 8.1 Hz, H-3_B), 5.062, 5.061 (2 t, 2 H, J 9.9 Hz, H-4_A, 4_D), 5.03 (t, 1 H, J 1.0 Hz, H-3_C), 4.88, 4.87 (2 dd, 2 H, $J_{1A,2A}$, $J_{1D,2D}$, 4.0 Hz, $J_{2A,3A}$, $J_{2D,3D}$, 9.9 Hz, H-2_A, 2_D), 4.80 (d, 1 H, $J_{1B,2B}$ 8.1 Hz, H-1_B), 4.77 (t, 1 H, J 8.1 Hz, H-2_B), 4.64 (dd, 1 H, $J_{5C,6Ca}$, 1.3 Hz, $J_{6Ca,6Cb}$ 12.3 Hz, H-6_{Ca}), 4.38 (dd, 1 H, $J_{1C,2C}$ 5.5 Hz, $J_{2C,3C}$ 1.0 Hz, H-2_C), 4.35-3.95 (m, 10 H, H-4_B, 4_C, 5_C, 6_A, 6_B, 6_{Cb}, 6_D), 3.88-3.81 (m, 1 H, H-5_B), 3.70-3.63 (m, 2 H, H-5_A, 5_D), 2.12-1.99 (13 s, 39 H, 13 CH_3CO), 1.74 (s, 3 H, CH_3CO$_3$). **16**: $[\alpha]_D^{20}$ +63.7° (*c* 0.7, $CHCl_3$); ^{1}H NMR: δ 5.39 (d, 2 H, $J_{1',2'}$ 3.2 Hz, 2 × H-1'), 5.36 (t, 2 H, J 10.4 Hz, 2 × H-3'), 5.18 (t, 2 H, J 8.4 Hz, 2 × H-3), 5.03 (t, 2 H, 2 × H-4'), 4.89 (d, 2 H, $J_{1,2}$ 7.2 Hz, 2 × H-1), 4.86-4.78 (m, 4 H, 2 × H-2, 2'), 4.47 (m, 2 H, 2 × H-$6'_a$), 4.26-4.21 (m, 4 H, 2 × H-6), 4.07-3.93 (m, 6 H, 2 × H-4, 5', $6'_b$), 3.77-3.75 (m, 2 H, 2 × H-5), 2.17-2.00 (7 s, 42 H, 14 CH_3CO).