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A Novel Convergent Strategy for the Construction of Oligosaccharides Using TIPS-Protected Glycosides. Synthesis of Fragments Related to Glycolipids of *Mycobacterium smegmatis*

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Abstract: 4,6-*O*-Pyruvylated glucosides **1** were converted to the corresponding glucosyl fluorides **3** and 2,3-*O*-TIPS-protected glucopyranosides **5**, respectively. Lewis-acid-catalyzed coupling of **3** and **5** afforded the pyruvylated disaccharides **6** one of which was further converted *via* the disaccharide donor **8** to di- and trisaccharide fragments of *Mycobacterium smegmatis*.

Otherwise apathogenic Mycobacteria can cause severe infections (atypical mycobacterioses) in immuno compromized persons especially in those suffering from AIDS[1]. The diagnosis of atypical mycobacterioses is however difficult in an early stage of infection due to the need to identify the bacteria *via* cultivation. Furthermore, some atypical Mycobacteria are ubiquitous environmental germs, for example *Mycobacterium smegmatis* and can thus lead to contamination and false interpretation of the cultivation. Therefore, the development of highly specific diagnostic tools for these atypical infections is quite important, also in order to be able to differentiate unambiguously between distinct mycobacterial diseases. A recent promising approach employed species specific neoglycoantigens[2] and synthetic oligosaccharides[3] of Mycobacteria for that purpose. Thus, effective syntheses of Mycobacterium-related saccharides are highly desirable and novel convenient strategies for their preparation would help to improve significantly further developments.

Recently, we found that TIPS-protected glycosides were regioselectively glycosylated by glycosyl fluorides under Lewis-acid-catalysis[4]. Using glycosyl fluorides having a neighborgroup active acyl substituent at position 2 β-(1→6)-linked saccharides were obtained from 4,6-*O*-TIPS-protected glycosides. Contrarily, from 3,4-*O*- and 2,3-*O*-TIPS-protected glucosides β-(1→3)-linked saccharides were obtained exclusively. Here, we now used the latter β-(1→3)-selective glycosylation protocol for a novel convergent strategy for the synthesis of the complex pyruvylated oligosaccharide fragments AB and ABC of the lipopentasaccharide[5] from *Mycobacterium smegmatis* (Figure 1).

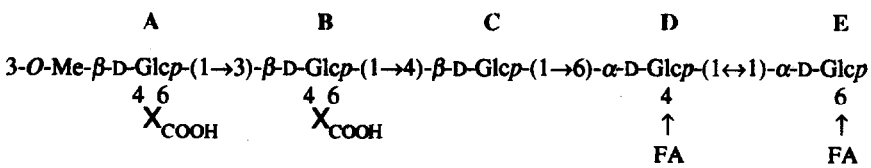
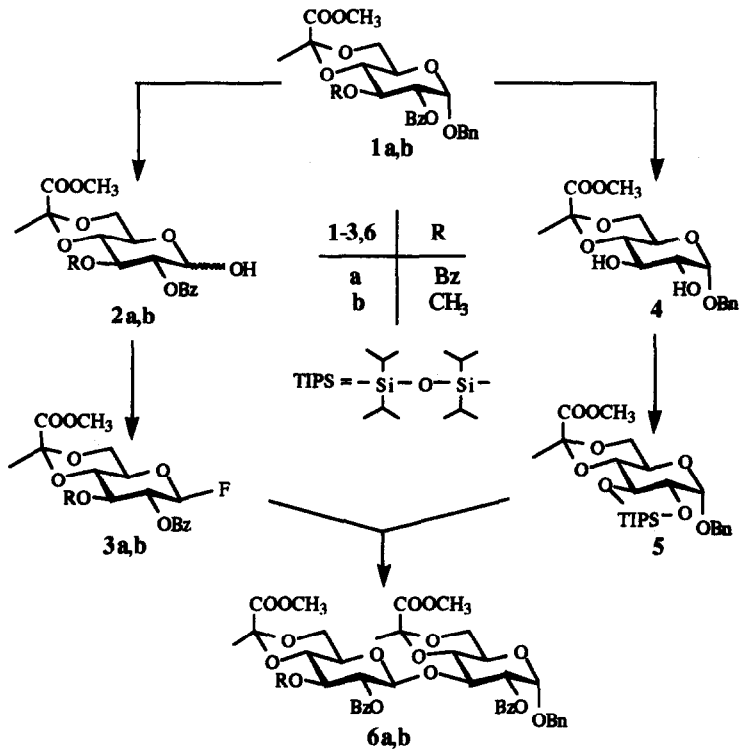


Figure 1. Structure of the lipopentasaccharide isolated from *Mycobacterium smegmatis*[5]. Fatty acid residues: FA (D) = 2,4-dimethyl-2-eicosenoic acyl; FA (E) = tetra- or hexadecanoic acyl. The pyruvate acetals of residues A and B have the (*S*)-configuration as can be concluded from the proton NMR spectra.

Starting from the readily prepared benzyl 2,3-di-*O*-benzoyl-4,6-*O*-(*S*)-(1-methoxycarbonyl)ethylidene-α-D-glucopyranoside[6] (**1a**) and its 3-*O*-methyl analogue[6] **1b** Pd-catalyzed hydrogenolysis gave the 1-*O*-unprotected glucoses **2a**[6] and **2b** in a practically quantitative yield. The latter two compounds were subsequently converted[7] (1.1 equiv. DAST in THF, -30°C → room temp., 1h) to the fluorides **3a** (76%) and **3b** (73%), respectively. The fluoride **3a** was obtained as crystalline β-anomer, whereas amorphous **3b** contained a small amount of the α-fluoride, according to the NMR spectra[8], that could not be removed by chromatography. On the other hand, compound **1a** was debenzoylated (Zémplen: cat. NaOMe in MeOH, room temp., 24h), to give the derivative **4** (85%) having positions 2 and 3 free. Upon silylation[4] (1.2 equiv. $TIPSCl_2$, 4.8 equiv. imidazole, DMF, room temp., 1h) the diol **4** furnished benzyl 4,6-*O*-(*S*)-(1-methoxycarbonyl)ethylidene-2,3-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-D-glucopyranoside (**5**) in 77% yield (Scheme 1).

Scheme 1. Synthesis of the laminaribioside derivatives **6** from pyruvylated benzyl glucosides **1**.

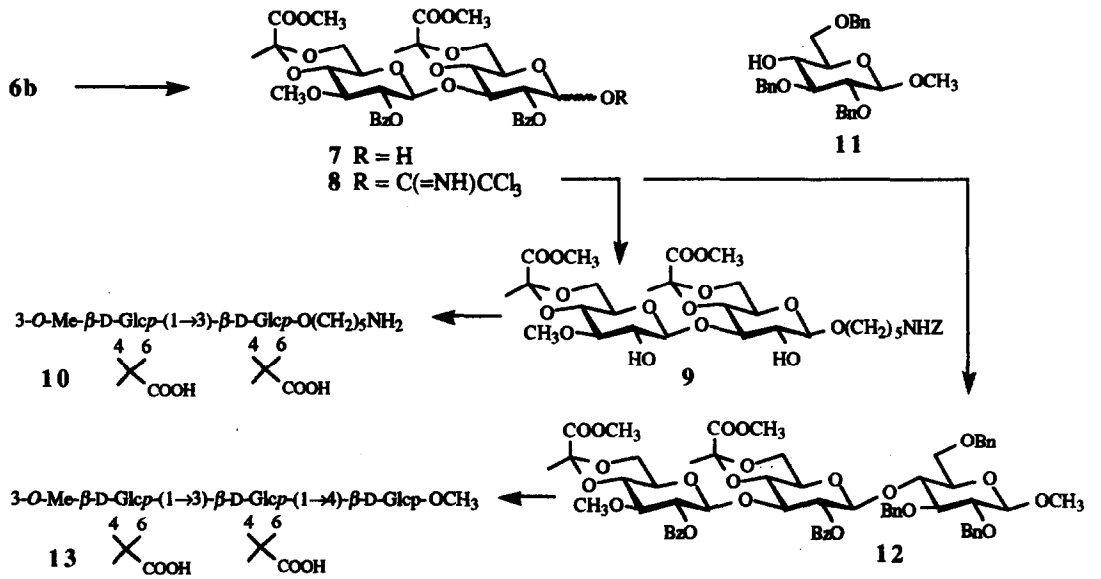


BF_3-etherate-catalyzed glycosylation of compound **5** (50 mol-% BF_3OEt_2, CH_2Cl_2) with **3a** (room temp., 24h) and **3b** (0°C→room temp., 48h), respectively proceeded smoothly and afforded first the corresponding addition products that still contained the fluorinated TIPS residue (3-fluoro-1,1,3,3-tetraisopropyldisiloxane-1-yl) at position 2^1 of the disaccharides. A small amount of already desilylated disaccharide could be detected on TLC as was previously described for other examples[4]. Therefore, the latter intermediates were not isolated and characterized here but were directly desilylated in a one-pot-procedure (cat. $Bu_4NF{\cdot}3H_2O$, THF, room temp. 1h), followed by rebenzoylation (BzCl, pyridine, room temp. 1-2h) of thus formed 2^1-OH compounds. Finally, the pyruvylated disaccharides **6a** (50%) and **6b** (81%) were obtained (Scheme 1). Their NMR spectra[8] clearly showed the presence of a β-(1→3)-linkage. The above outlined one-pot-

procedure had the advantage that the somehow difficult isolation of the apolar silylated intermediates was circumvented and the fully benzoylated products **6** could be easily separated from contaminant byproducts by simple chromatography. The achieved moderate to good yields of this method and the convenient isolation of compounds **6** justified to proceed this way. The glycosylation protocol presented here should be also suitable for other oligosaccharide syntheses and further extensions of the method are now under investigation.

Compounds **6** are useful intermediates for the construction of higher oligosaccharides related to *Mycobacterium smegmatis* that contain two adjacent pyruvylated glucose residues (Scheme 2). For example, the benzyl laminaribioside **6b** was transformed to the complex disaccharide donor **8** *via* hydrogenolysis (10 % Pd-C, H_2, HOAc, room temp., 3d) to give first crude **7**. Without further purification, the latter was treated with trichloroacetonitrile (Cl_3CCN, K_2CO_3, CH_2Cl_2, room temp., 5h) to give the trichloroacetimidate **8** (90%) as an anomeric mixture (α:β=1:1.4)[8]. TMSOTf-catalyzed condensation (1 mol-% TMSOTf, CH_2Cl_2, -20°C, 1h) of donor **8** and 5-benzyloxycarbonylamido pentanol was somehow sluggish and the resulting aminopentyl laminaribioside had to be partially deblocked (Zémplen) in order to obtain pure **9** (59%). The deblocking of the latter was then achieved by saponification of the two acetal-bound methyl pyruvates (4 equiv. 1 N NaOH, H_2O, room temp., 24h) and hydrogenolytic debenzylation (cat. 10% Pd-C, H_2, H_2O, room temp. 12h) to afford the AB-fragment **10** (46%).

Scheme 2. Synthesis of the mycobacterial fragments AB and ABC from the laminaribiose derivative **6b**.



Condensation of donor **8** and methyl 2,3,6-tri-*O*-benzyl-β-D-glucopyranoside **11** as described above proceeded smoothly and gave the trisaccharide **12** in 79% yield. The deblocking of **12** was then performed by first removing the benzoyl groups (Zémplen) followed by saponification and hydrogenolysis as described for **10**, to furnish the ABC-fragment **13** in 98% yield.

Acknowledgment

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8. Physical data of compounds **2-13**. All compounds gave satisfactory elemental analyses; NMR spectra and opt. rot. were measured in chloroform: **2b**: m.p. 164-168°C; $[\alpha]_D$=+88.5 (*c* 0.7); NMR δ=5.50 (bd, 1H, H-1α, J=3.7), 4.80 (bd, 1H, H-1β, J=8.3), 3.80 (s, 3H, COOMe), 3.50 (s, 3H, OMe), 1.55 (s, 3H, Me); 99.1 (C_a), 91.1 (C-1α), 96.3 (C-1β), 61.9, 60.0 (OMe), 25.5 (Me). **3a**: m.p. 160-161°C, $[\alpha]_D$=-76.7 (*c* 0.3); NMR δ=5.60 (dd, 1H, H-1, $J_{H,F}$=51.7, $J_{1,2}$=5.4), 3.84 (s, 3H, COOMe), 1.52 (s, 3H, Me); 106.3 (C-1, $J_{C,F}$=220), 99.6 (C_a), 73.8 (C-4,5), 72.2 (C-2, $J_{C,F}$=30), 71.9 (C-3, $J_{C,F}$=6), 65.3 (C-6), 52.8 (COOMe), 25.2 (Me). **3b** (β-anomer): NMR δ=5.73 (dd, 1H, H-1, $J_{H,F}$=50.8, $J_{1,2}$=5.4), 3.87 (s, 3H, COOMe), 3.49 (s, 3H, OMe), 1.57 (s, 3H, Me); 106.2 (C-1, $J_{C,F}$=221), 80.1 (C-3), 75.7 (C-4,5), 72.0 (C-2, $J_{C,F}$=23), 65.1 (C-6), 58.7 (OMe), 52.9 (COOMe), 25.4 (Me). **4**: $[\alpha]_D$=+83.8 (*c* 0.2); NMR δ=4.94 (d, 1H, H-1, $J_{1,2}$=3.9), 4.73, 4.53 (2d, 2H, CH_2Ph, J=11.8), 3.96 (dd, 1H, H-6a, $J_{6a,6b}$=9.7), 3.87 (t, 1H, H-4, $J_{3,4}$=9.3, $J_{4,5}$=9.6), 3.71 (dd, 1H, H-6b, $J_{5,6}$=9.7), 3.62-3.66 (m, 1H, H-5), 3.57 (dd, 1H, H-2, $J_{2,3}$=9.3), 3.31 (t, 1H, H-3), 3.82 (s, 3H, COOMe), 1.55 (s, 3H, Me); 99.2 (C-1), 98.1 (C_a), 76.8 (C-4), 72.8, 71.5 (C-2,3), 70.0 (CH_2Ph), 65.2 (C-6), 62.2 (C-5), 52.9 (COOMe), 25.3 (Me). **5**: $[\alpha]_D$=70.1 (*c* 4.3); NMR δ=4.84 (d, 1H, H-1, $J_{1,2}$=3.8), 4.76, 4.59 (d, 2H, CH_2Ph, J=12.7), 4.03 (dd, 1H, H-6a, $J_{5,6a}$=4.6, $J_{6a,6b}$=9.6), 4.03 (t, 1H, H-4, $J_{3,4}$=9.4, $J_{4,5}$=9.5), 3.78 (dd, 1H, H-5), 3.79 (s, 3H, COOMe), 3.74 (dd, 1H, H-6b), 3.73 (dd, 1H, H-2, $J_{2,3}$=8.5), 3.23 (t, 1H, H-3), 1.51 (s, 3H, Me), 1.02-1.09 (m, 16H, TIPS); 99.1 (C_a), 98.6 (C-1), 77.6 (C-4), 75.7 (C-2), 73.0 (C-3), 69.3 (CH_2Ph), 65.7 (C-6), 61.9 (C-5), 52.4 (COOMe), 25.3 (Me). **6a**: $[\alpha]_D$=+106.7 (*c* 0.3); NMR δ=5.53 (dd, 1H, H-2^2, $J_{1,2}$=7.5, $J_{2,3}$=9.1), 5.18 (d, 1H, H-1^2), 5.08 (d, 1H, H-1^1, $J_{1,2}$=3.8), 4.95 (dd, 1H, H-2^1, $J_{2,3}$=9.9), 4.64, 4.41 (d, 2H, CH_2Ph, J=12.3), 3.77, 3.87 (s, 6H, COOMe), 1.48, 1.44 (s, 6H, Me); 99.7 (C-1^2), 99.3, 99.2 (C_a), 95.8 (C-1^1), 74.8, 74.7, 74.5, 73.3, 72.6, 72.4 (C-2^1,3^1,4^1,2^2,3^2,5^2), 69.8 (CH_2Ph), 66.2 (C-4^2), 65.2 (C-6^1,6^2), 62.4 (C-5^1), 52.8, 52.7 (COOMe), 25.2, 25.1 (Me). **6b**: $[\alpha]_D$=+70.7 (*c* 0.9); NMR δ=5.16 (d, 1H, H-1^2, $J_{1,2}$=7.5), 5.09 (d, 1H, H-1^1, $J_{1,2}$=3.9), 4.63, 4.40 (d, 2H, CH_2Ph, J=12.2), 3.86, 3.82 (s, 6H, COOMe), 3.41 (s, 3H, OMe), 1.55, 1.46 (s, 6H, Me); 99.8 (C-1^2), 99.2, 99.1 (C_a), 95.8 (C-1^1), 80.4 (C-3^2), 77.2 (C-3^1), 75.9 (C-4^2), 74.6 (C-4^1), 73.7, 72.8 (C-2^1,2^2), 69.9 (CH_2Ph), 65.8, 62.4 (C-5^1,5^2), 65.2 (C-6^1,6^2), 58.1 (OMe), 52.8 (COOMe), 25.5, 25.1 (Me). **8** (α:β=1:1,4): $[\alpha]_D$=+35.9 (*c* 0.4); NMR δ=6.48 (d, 1H, H-1^1α, $J_{1,2}$=3.8), 5.98 (d, 1H, H-1^1β, $J_{1,2}$=6.0), 5.20 (d, 1H, H-1^2, $J_{1,2}$=7.6; 93.6 (C-1^1α), 95.6 (C-1^1β), 99.1 (C-1^2), 99.4, 99.1 (C_a), 58.2 (OMe), 53.0, 52.8 (COOMe), 30.9 (CCl_3), 25.5, 25.1 (Me). **9**: $[\alpha]_D$=-20.7 (*c* 0.1); 103.2, 101.7 (C-1^1,1^2), 99.3, 99.1 (C_a), 81.1 (C-3^2), 77.3 (C-3^1), 76.5 (C-4^1), 75.1 (C-4^2), 73.1 (C-2^1), 72.1 (C-2^2), 70.1 (CH_2Ph), 66.7 (C-5^1), 66.6 (CH_2O), 65.9 (C-5^2), 65.2, 64.9 (C-6^1,6^2), 59.8 (OMe), 53.1, 52.9 (COOMe), 40.9 (CH_2N), 29.5, 29.0, 23.1 (CH_2), 25.2, 25.4 (Me). **10**: $[\alpha]_D$=-260 (*c* 0.2, H_2O); NMR δ=105.6, 105.3 (C-1^1,1^2), 104.5, 104, 4 (C_a), 84.1 (C-3^2), 82.7 (C-3^1), 77.7 (C-4^2), 76.8 (C-4^1,5^2), 75.2 (C-5^1), 73.3 (C-2^2), 68.9, 68.6 (C-2^1,6^2), 67.1 (C-6^1), 60.9 (OMe), 42.3 (CH_2N), 31.1, 29.3, 25.0 (CH_2), 27.5, 27.3 (CH_3). **12**: $[\alpha]_D$=-72.2 (*c* 0.1); NMR δ=4.88, 4.56 (d, 2H, H-1^2,1^3, $J_{1,2}$=7.1, 8.0), 4.10 (d, 1H, H-1^1, $J_{1,2}$=7.6), 3.83 (s, 6H, OMe), 3.43, 3.38 (s, 6H, COOMe), 1.53, 1.47 (s, 6H, Me); 104.5 (C-1^1), 100.7 (C-1^3), 99.6 (C-1^2), 99.0, 98.9 (C_a), 82.4 (C-3^3), 81.5 (C-3), 80.4 (C-4), 77.9 (C-2), 76.5 (C-4), 75.9 (C-4), 75.4 (CH_2Ph), 74.7 (CH_2Ph), 74.2 (C-3,5), 73.8 (C-2), 73.4 (CH_2Ph), 72.8 (C-2), 67.5 (C-6), 65.8 (C-5), 65.7 (C-3), 65.3 (C-6), 64.8 (C-6), 58.0 (3^2-OMe), 57.0 (1^1-OMe), 52.8 (COOMe), 52.7 (COOMe), 25.5 (Me), 25.3 (Me). **13**: $[\alpha]_D$=-58.2 (*c* 0.1, H_2O); 84.1 (C-3^3), 82.6 (C-3^2), 81.3 (C-4^1), 78.0, 77.7 (C-3^1,5^1), 77.0, 76.9, 76.8 (C-2^1,4^2,4^3), 75.9 (C-5^2), 75.5 (C-5^3), 68.5, 68.4 (C-2^2,2^3), 67.3, 67.2 (C-6^2,6^3), 62.8 (1-OMe), 61.3 (3-OMe), 60.1 (C-6^1), 27.3 (Me).

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