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Pure α-linked products can be obtained in high yields in glycosylation with glucosyl trichloroacetimidate donors with a C2 ester capable of neighboring group participation

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Abstract—Predominant or even pure (1→3)-α-linked products can be generated in glycosylation with glucosyl trichloroacetimidate donors with a C2 ester capable of neighboring group participation. Benzoylation of either the donors or acceptors gave more β-linkage, while 4,6-*O*-benzylidenation of the acceptor gave exclusive β-glucosylation. 3-*O*-Glycosylation of the donor and the presence of a (1→3)-β-linkage in the oligosaccharide acceptor gave sole α-glucosylation.

Neighboring group participation has been frequently used in organic synthesis. In carbohydrate chemistry, generally, it is believed that glycosyl donors possessing an acyloxyl group with a participating function at C-2 exclusively give the corresponding 1,2-*trans* glycoside with quite high stereoselectivity in glycosylation reactions. Therefore, the most widely used approach for achieving stereochemical control in the formation of β-glucosidic linkages involves the use of a C2 ester capable of neighboring group participation.[1] In this type of chemistry, *ortho* esters are frequent intermediates[2] or undesired byproducts[3] owing to trapping of the intermediate bridging cation by the nucleophile as opposed to attack at the anomeric carbon. Whitfield has published calculations that address the mechanism of neighboring group participation that support the notion of a bridging cation as an intermediate.[4] The orthoesters formed during glycosylation, in the absence of a buffer, subsequently rearrange to the corresponding 1,2-*trans* glycosidic products under the action of protic or Lewis acids.[3b–d,5] This transformation has recently been put into good use.[6]

As part of our program to develop an immune stimulant, we are dealing with synthesis of (1→3)-β-D-glucooligosaccharides. These oligosaccharides, which are the fragments of the natural (1→3)-β-D-glucan homopolysaccharides isolated from the inner cell wall of *Saccharomyces cerevisiae*,[7] stimulate immunity and belong to the class of drugs known as biological response modifiers (BRMs). For an investigation of structure–immunity relationships, we needed a series of (1→3)-β-D-glucooligosaccharides. Thus, we prepared 3-*O*-allyl-2,4,6-tri-*O*-acetyl-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-D-glucopyranosyl trichloroacetimidate (**1**) as the donor and lauryl 2,4,6-tri-*O*-benzoyl-β-D-glucopyranoside (**2**) as the acceptor (entry 1, Fig. 1). We expected that the coupling of **1** with **2** in the presence of TMSOTf[8] would give a β-linked trisaccharide. However, to our surprise, the donor and acceptor were linked with a pure α-bond. Similar anomalous stereoselectivity was observed by Hashimoto and Izumi when they carried out the glycosylation with peracetylated 5-thio-D-arabinopyranosyl and 5-thio-L-fucopyranosyl trichloroacetimidates.[9] To explore the stereoselectivity–structure relationship, a variety of donors and acceptors were used for coupling. Fig. 1 shows that the stereoselectivity of the glycosylation was dependent on the structures of both the acceptor and the donor.

It was found, see Fig. 1, that 4,6-*O*-benzylidenation of the acceptor favored β-linkage formation (entry 2), while benzoylation of the donor and acceptor instead of acetylation tended to give more β-glycosylation as indicated from entry 3 versus entries 4 and 5. The former entry gave sole β-linkage, while the latter two entries gave α- and β-linked mixtures (α:β = 1:2 and 1:1, respectively). However, 3-*O*-allylation of the donor substan-

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tially changed the stereoselectivity yielding predominant α-linkage (α:β 4:1) as indicated in entry 6. Moreover, 3-*O*-glycosylation completely changed the stereoselectivity to sole α-linkage as shown in entries 1 and 7. A (1→3)-β-linked disaccharide as the acceptor also gave α-glycosylation (entry 8). Similarly, condensation of a (1→3)-β-linked disaccharide donor **18** with a trisaccharide acceptor **19** having a (1→3)-β-linkage at the non-reducing end yielded sole α-linked pentasaccharide **21** (entry 9).

The stereoselectivity of the glycosylation was readily determined by ^{1}H and ^{13}C NMR spectroscopy. For di- and trisaccharides, ^{1}H NMR usually gave clear

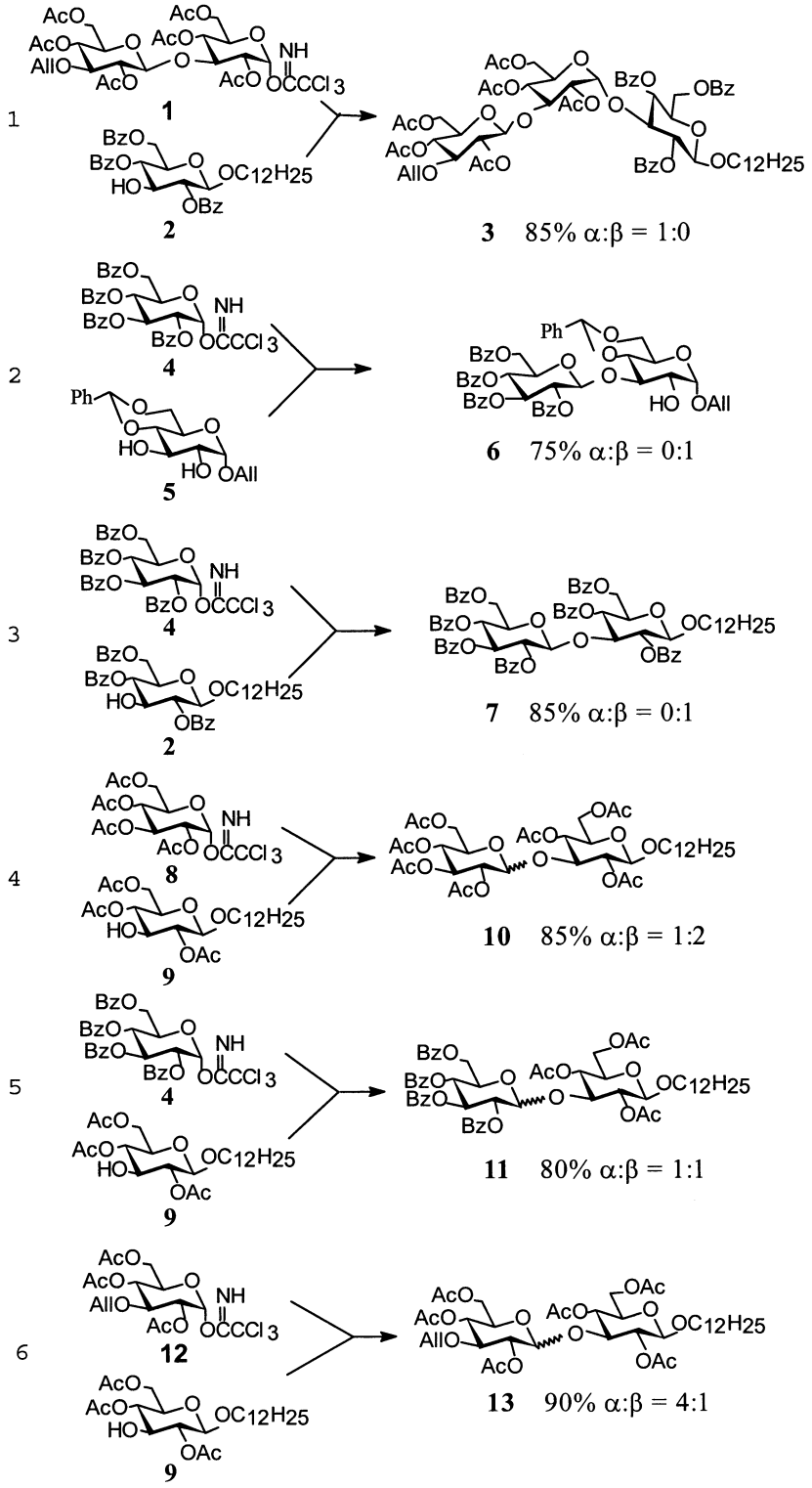

Figure 1. Coupling results with different donors and acceptors.

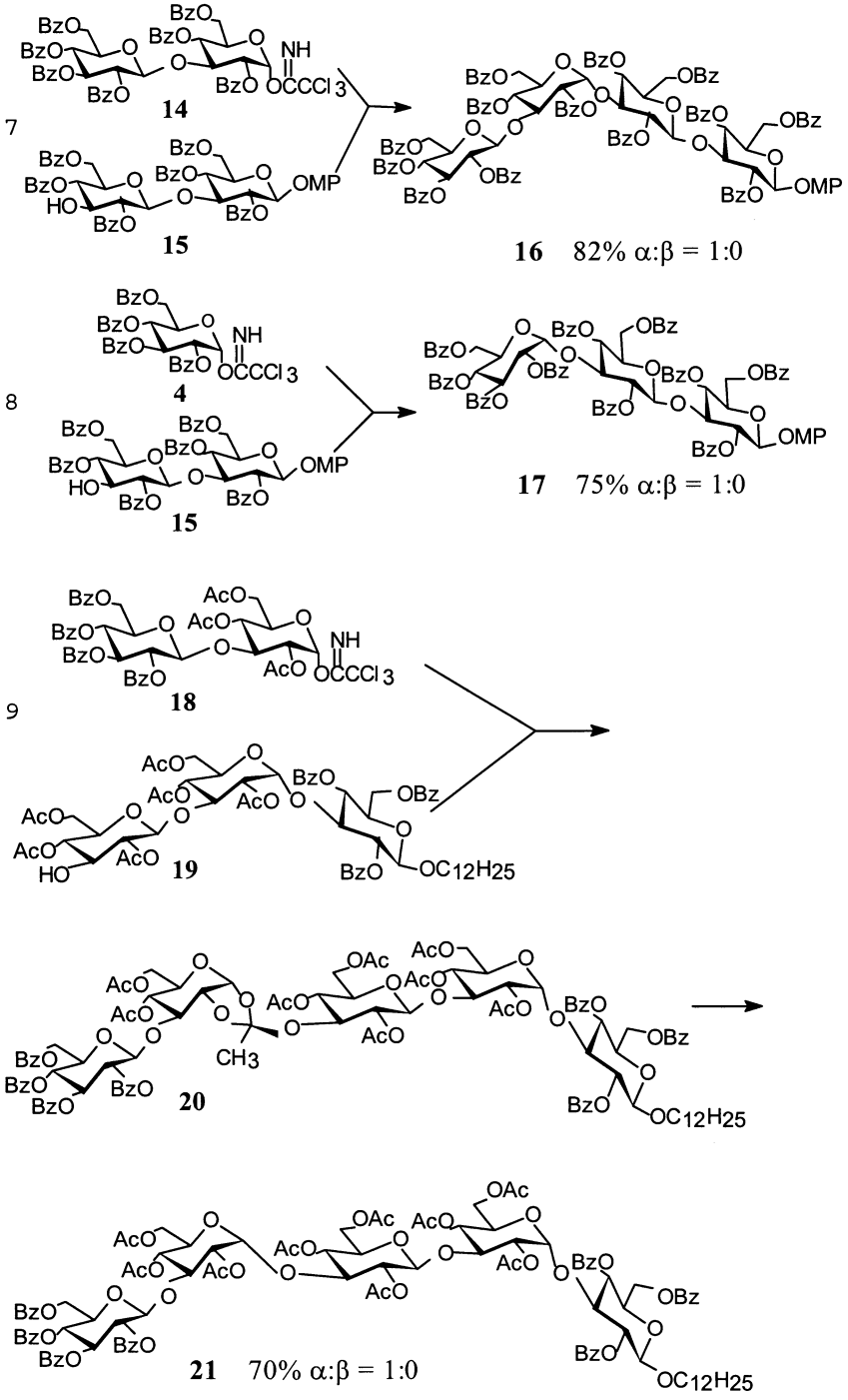

Fig. 1. (*Continued*)

identification since the signals in the 4–6 ppm region were well resolved and H-1α, H-1β showed coupling constants of ~3 and ~8 Hz, respectively. For higher oligosaccharides, ^{13}C NMR spectra were also recorded giving the J_{C1-H1} at δ 173–179 Hz for an α-linkage, and at 159–166 Hz for a β-linkage.[10]

In the coupling reactions, it was found that orthoesters were formed at the initial stage, and they rearranged quickly to the final products. This was readily monitored by TLC since the orthoester intermediates and the final products gave different R_f values. Meanwhile, the orthoesters could be isolated, and they were easily transformed to the final products by treatment with catalytic TMSOTf. In entry 9, the orthoester **20** was isolated and identified by ^1H and ^{13}C NMR, and it was then converted to the pentasaccharide **21** by treatment with catalytic TMSOTf.

Following the literature precedence[4,11] we hypothesize herein a possible mechanism as shown in Fig. 2. Activation of the glycosyl donor **I** with a promoter may lead to irreversible formation of a glycosyl oxocarbenium

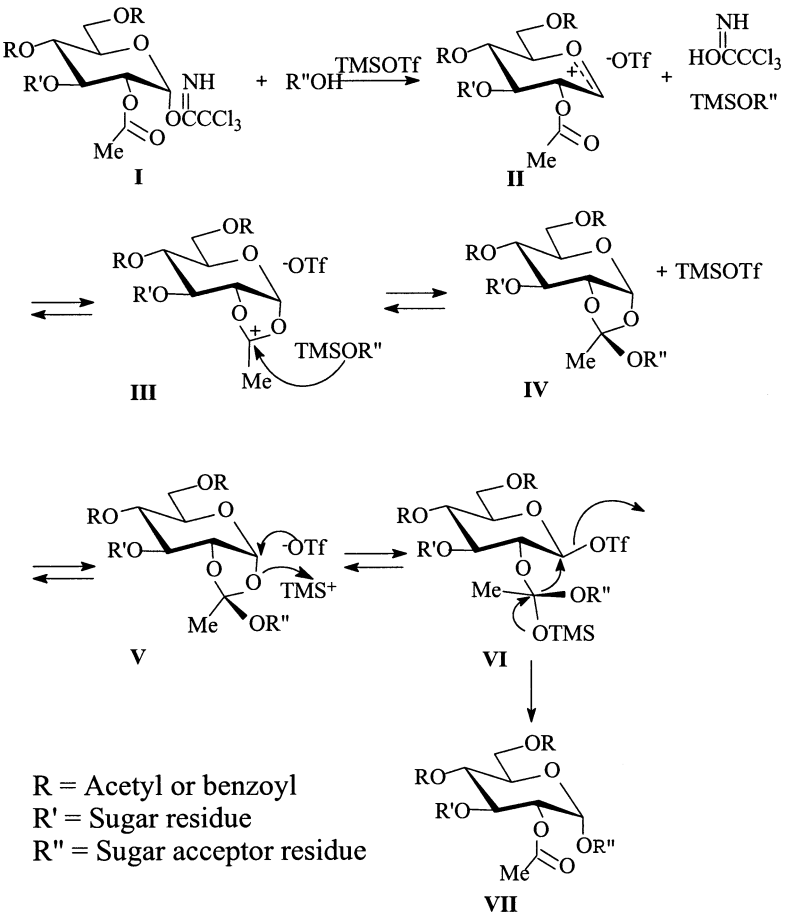

Figure 2. A proposed mechanism for α-linkage formation from an orthoester.

ion **II**. Previous work and the calculations of Whitfield pointed out that the bridging dioxolenium ion **III** is an intermediate, and nucleophiles can react with this ion giving orthoester **IV**. If the nucleophile attacks the C-1 rear side of **III** or the OR′ in **IV** rearranges to reach the C-1 rear side, the normal β-linkage is obtained. However, if TMSOTf promoted C-1–O bond breaking occurs in **V**, an intermediate **VI** will form, and its subsequent rearrangement will give the 1,2-*cis* linked glycoside **VII**.

In summary, the findings described above indicated that the (1→3)-α-linked glucosidic bond can be constructed using fully acylated glucosyl trichloroacetimidates as the donors. This can be used in the synthesis of some biologically active glucans containing (1→3)-α-linkages.

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8. Typical glycosylation conditions: the glycosyl donor (0.5 mmol) and acceptor (0.5 mmol) were dried together under high vacuum for 2 h, then dissolved in anhydrous CH_2Cl_2 (30 mL). TMSOTf (15 μL, 0.05 equiv.) was added dropwise at rt. The reaction mixture was stirred for 3 h after which the mixture was neutralized with Et_3N and concentrated to dryness under reduced pressure. Purification by column chromatography afforded the final product.
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10. All new compounds involved in this study were identified by optical rotations, ^1H or ^{13}C NMR spectroscopy, and elemental analyses. Selected spectral data: **3** ^1H NMR ($CDCl_3$): δ 7.99–7.35 (15H), 5.65 (m, 1H, =C*H*-), 5.57 (t, 1H, $J=9.1$ Hz), 5.36 (t, 1H, $J=9.1$ Hz), 5.11 (d, 1H, $J=2.0$ Hz, α-H-1), 5.10 (m, 2H), 4.77 (t, 2H), 4.66 (d, 1H, $J=8$ Hz, β-H-1), 4.61 (dd, 1H, $J=3.6$, 10.4 Hz), 4.50 (m, 1H), 4.42 (d, 1H, $J=8$ Hz, β-H-1), 4.41 (m, 1H), 4.31 (t, 1H, $J=9.2$ Hz), 4.25 (m, 1H), 4.11 (m, 1H), 3.98–3.93 (m, 4H), 3.84 (m, 1H), 3.62 (m, 1H), 3.46–3.39 (m, 2H), 2.12 (s, 3H), 2.09 (s, 3H), 1.97 (s, 3H), 1.94 (s, 3H), 1.87 (s, 3H), 1.75 (s, 3H), 1.53–0.90 (m, 21H), 0.86 (t, 3H). ^{13}C NMR ($CDCl_3$): δ 170.15, 169.91, 169.00, 168.66, 168.17, 168.08, 165.53, 164.57, 164.40, 133.78, 116.20, 100.63 ($J_{C1-H1}=159$ Hz, β-C-1), 100.28 ($J_{C1-H1}=162$ Hz, β-C-1), 95.63 ($J_{C1-H1}=173$ Hz, α-C-1), 79.64, 75.91, 74.58, 71.97, 71.81, 71.59, 71.59, 71.41, 69.68, 69.07, 67.48, 66.89, 62.86, 61.83, 60.69, 31.36, 29.04, 28.95, 28.77, 28.69, 25.29, 22.11, 20.09, 19.97, 19.67, 13.50. **6** (2-OH was benzoylated with BzCl–pyridine). ^1H NMR ($CDCl_3$): δ 8.13–7.21 (25H), 6.92–6.90 (m, 4H), 5.89 (t, 1H, $J=9.6$ Hz), 5.65 (m, 1H), 5.60 (t, 1H, $J=9.2$ Hz), 5.53 (t, 1H, $J=8$ Hz), 5.18–5.12 (m, 3H), 5.07 (d, 1H, $J=3.2$ Hz, α-H-1), 5.04 (d, 1H, 8 Hz, β-H-1), 4.93 (dd, 1H, $J=4.1$, 10.0 Hz), 4.80 (m, 1H), 4.43 (m, 1H), 4.29 (m, 1H), 4.18–4.08 (m, 2H), 3.93–3.73 (m, 5H). **7**. ^1H NMR ($CDCl_3$): δ 5.01 (d, 1H, $J=7.6$ Hz, β-H-1), 4.60 (d, 1H, $J=8$ Hz, β-H-1). **10** (the α and β anomers could not be separated) α anomer ^1H NMR ($CDCl_3$): δ 5.27 (d, 1H, $J=3.2$ Hz, α-H-1), 4.57 (d, 1H, $J=8$ Hz, β-H-1); β anomer: 4.57 (d, 1H, $J=8$ Hz, β-H-1), 4.33 (d, 1H, $J=7.6$ Hz, β-H-1). ^{13}C NMR ($CDCl_3$) of β anomer: 100.99 (β-C-1), 100.85 (β-C-1); α anomer: δ 100.99 (β-C-1), 96.15 (α-C-1). **11** β anomer ^1H NMR ($CDCl_3$): δ 4.97 (d, 1H, $J=7.6$ Hz, β-H-1), 4.29 (d, 1H, $J=7.6$ Hz, β-H-1). ^{13}C NMR ($CDCl_3$): δ 100.74 (β-C-1), 100.41 (β-C-1). α anomer ^1H NMR ($CDCl_3$): δ 5.52 (d, 1H, $J=3.6$ Hz, α-H-1), 5.02 (d, 1H, $J=8.0$ Hz, β-H-1); ^{13}C NMR($CDCl_3$): δ 100.78 (β-C-1), 95.24 (α-C-1). **13** β anomer ^1H NMR ($CDCl_3$): δ 4.59 (d, 1H, $J=8$ Hz, β-H-1), 4.34 (d, 1H, $J=8.0$ Hz, β-H-1); ^{13}C NMR ($CDCl_3$): δ 101.27 (β-C-1), 101.11 (β-C-1); α isomer ^1H NMR ($CDCl_3$): δ 5.20 (d, 1H, $J=3.6$ Hz, α-H-1), 4.66 (d, 1H, $J=8.0$ Hz, β-H-1); ^{13}C NMR ($CDCl_3$): δ 100.98 (β-C-1), 95.94 (α-C-1). **16**. ^1H NMR ($CDCl_3$): δ 5.38 (d, 1H, $J=3.6$ Hz, α-H-1), 5.02 (d, 1H, $J=8$ Hz, β-H-1), 4.97 (d, 1H, $J=6.8$ Hz, β-H-1), 4.45 (d, 1H, $J=7.6$ Hz, β-H-1); ^{13}C NMR ($CDCl_3$): δ 101.00 (β-C-1), 99.98 (β-C-1), 99.88 (β-C-1), 95.67 (α-C-1). **17**. ^1H NMR ($CDCl_3$): δ 5.53 (d, 1H, $J=4$ Hz, α-H-1), 5.13 (d, 1H, $J=8$ Hz, β-H-1), 5.09 (d, 1H, $J=7.6$ Hz, β-H-1). ^{13}C NMR ($CDCl_3$): δ 101.01 (β-C-1), 100.95 (β-C-1), 96.21 (α-C-1). **20**. ^1H NMR ($CDCl_3$): δ 5.51 (d, 1H, $J=4.0$ Hz, α-H-1), 5.14 (d, 1H, $J=3.6$ Hz, α-H-1), 4.68 (d, 1H, $J=8.0$ Hz, β-H-1); ^{13}C NMR ($CDCl_3$): δ 101.60 ($J_{C1-H1}=167$ Hz, β-C-1), 100.67 ($J_{C1-H1}=160$ Hz, β-C-1), 99.87 ($J_{C1-H1}=160$ Hz, β-C-1), 96.52 ($J_{C1-H1}=177$ Hz, α-C-1), 95.71 ($J_{C1-H1}=177$ Hz, α-C-1). **21**. ^1H NMR ($CDCl_3$): δ 5.14 (d, 1H, $J=3.6$ Hz, α-H-1), 5.11 (d, 1H, $J=3.2$ Hz, α-H-1), 4.95 (d, 1H, $J=8.0$ Hz, β-H-1), 4.85 (d, 1H, $J=8.4$ Hz, β-H-1), 4.43 (d, 1H, $J=8.0$ Hz, β-H-1); ^{13}C NMR ($CDCl_3$): δ 100.78 ($J_{C1-H1}=165$ Hz, β-C-1), 100.68 ($J_{C1-H1}=163$ Hz, β-C-1), 99.91 ($J_{C1-H1}=166$ Hz, β-C-1), 95.67 ($J_{C1-H1}=173$ Hz, α-C-1), 94.82 ($J_{C1-H1}=179$ Hz, α-C-1).
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