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Cyclic di-*t*-butylsilylenediyl ether group as a convenient protective group for the glycoconjugate synthesis

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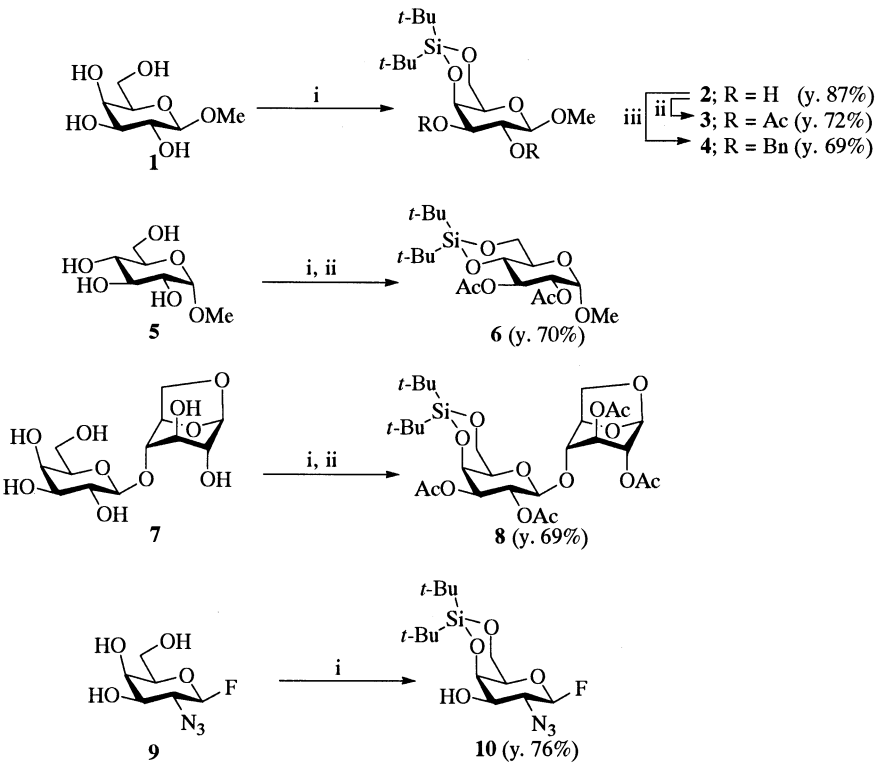
Abstract—Treatment of methyl β-D-glucopyranoside, methyl α-D-glucopyranoside, 2-azido-2-deoxy-β-D-galactopyranosyl fluoride, and 1,6-anhydro-β-lactose with di-*t*-butyldichlorosilane gave the corresponding 4,6-cyclic di-*t*-butylsilylenediyl ether (4,6-CDBS) derivatives in high yields. It was suggested that the 4,6-CDBS group is quite stable under general conditions for further chemical manipulations such as the acetylation, benzylation and glycosylation reactions employed widely in the carbohydrate chemistry. This protective group was readily removed by treatment with tetrabutylammonium fluoride or triethylamine–3HF complex under mild conditions.

Regioselective manipulations of hydroxyl groups in carbohydrate chemistry are crucial steps to achieve a highly selective and efficient synthesis of oligosaccharides and glycoconjugates.[1] The use of some cyclic acetals and ketals such as benzylidene, isopropylidene, *p*-substituted benzylidene and cyclohexylidene groups



Scheme 1. (i) $(t\text{-Bu})_2SiCl_2$, HOBt/Pyr., 95°C; (ii) Ac_2O/Pyr.; (iii) BnBr, NaH/DMF.

Keywords: di-*t*-butyldichlorosilane; 4,6-cyclic di-*t*-butylsilylenediyl ether derivatives; 4,6-CDBS group; T antigenic glycopeptide.

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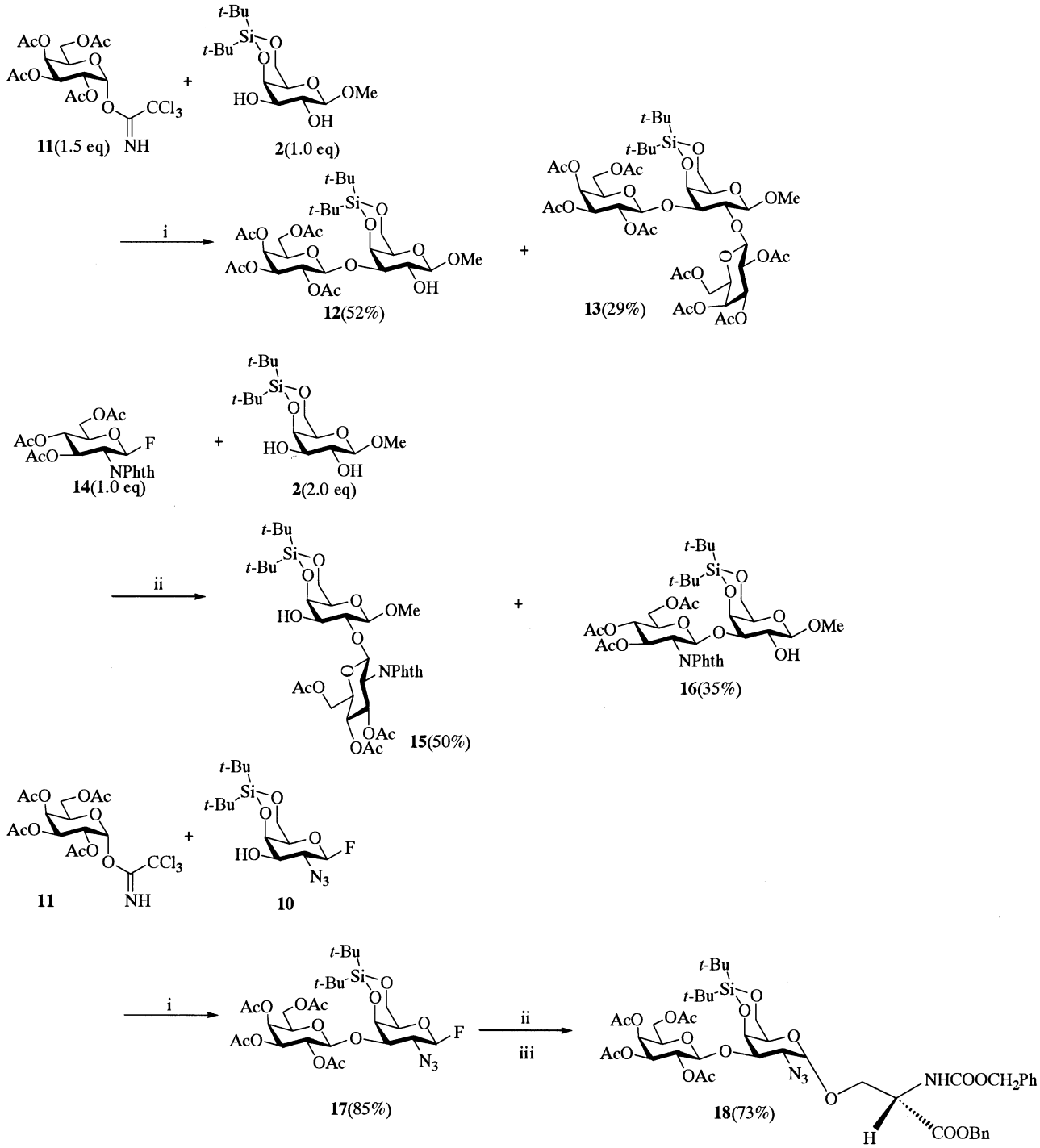
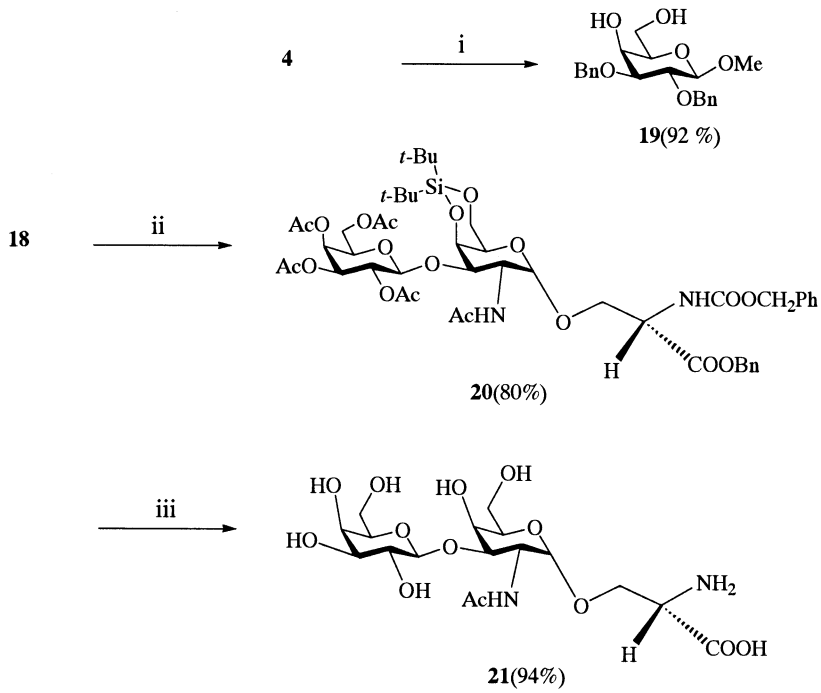
at C-4 and C-6 positions have greatly accelerated further chemical manipulations of the remaining secondary hydroxyl groups at C-2 and C-3 positions.[2–4] The isopropylidene group has also been used for the temporary protection of the 1,2-*cis*-diol groups existing in D-galactopyranose, D-mannopyranose and L-fucopyranose derivatives.[5] However, it has been well known that reagents such as trimethylsilyltrifluoromethane sulfonate (TMSOTf), borane trifluoride etherate, trifluoromethanesulfonic acid and other strong acid-catalysts commonly employed as promoters for the glycoside formation reactions have often caused considerable destruction of these protective groups.

In the present study, our interest is focused on the availability of a cyclic silyl ether protective group, di-*t*-butylsilylenediyl group,[6] as a convenient and versatile protective group for oligosaccharide synthesis. Although this protective group has often been utilized for the syntheses of the anthracyclines[7,8] and nucleotide



Scheme 2. (i) $TMSOTf/CH_2Cl_2$, −20°C, 3 h; (ii) Cp_2ZrCl_2, $AgClO_4/CH_2Cl_2$, 25°C, 2 h; (iii) *N*-benzyloxycarbonyl L-serine benzyl ester, Cp_2ZrCl_2, $AgClO_4/CH_2Cl_2$, 25°C, 2 h.



Scheme 3. (i) $(n\text{-Bu})_4NF$/THF, 0°C, 24 h; (ii) AcSH/Pyr., 16 h; (iii) a. Et_3N–3HF/THF, 0–25°C, 4 h, b. 0.1N NaOH aq./MeOH, 0°C, 20 min, c. Pd-C/MeOH, H_2, 1.5 h.

derivatives,[9] there has been no example for this group being used for oligosaccharide synthesis. Since silyl ether groups show satisfactory stability under strong acidic conditions and they can be removed selectively by treating with fluoride ions under mild conditions, use of the cyclic dialkylsilylene ether groups[10] might become a potential and versatile procedure for the diol-protections of sugar residues.

First, silylation of methyl β-D-galactopyranoside **1** in pyridine was performed at 95°C with 1.5 equiv. of di-*t*-butyldichlorosilane in the presence of 0.5 equiv. of 1-hydroxybenzotriazole (HOBt). The reaction proceeded selectively at 1,3-diol groups of C-4 and C-6 positions and gave a cyclic di-*t*-butylsilylenediyl ether (CDBS) derivative **2** in 87% yield. Compound **2** was subsequently converted into the 2,3-di-*O*-acetylated derivative **3** and 2,3-di-*O*-benzylated derivative **4**. Similarly, methyl α-D-glucopyranoside **5**, 1,6-anhydro-β-lactose **7** and 2-azido-2-deoxy-β-D-galactopyranosyl fluoride **9**[11] were employed for the same procedure and converted to the corresponding CDBS derivatives **6** (70%), **8** (69%) and **10** (76%). In all cases, the formation of the five-membered CDBS derivatives of 1,2-diols was not observed by TLC monitoring during the reaction and all products could be isolated by using general silica gel chromatography (Scheme 1).

Stability of the CDBS derivatives in the glycosylation reactions was demonstrated by using compounds **2** and **10** as shown in Scheme 2. When the diol **2** was employed as an acceptor for the glycosylation reaction with the known 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl imidate **11**[12] (1.5 equiv.) in the presence of TMSOTf as a promoter, disaccharide **12** and trisaccharide **13** were obtained in 52 and 29% yields, respectively.[13] On the other hand, the reaction of **2** (2.0 equiv.) with 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl fluoride **14** (1.0 equiv.) under Suzuki's conditions[14] gave 2-*O*-substituted disaccharide **15** and 3-*O*-substituted **16** in 50 and 35%, respectively. This result suggests that the steric hindrance between the 4,6-CDBS protection of the acceptor **2** and the 2-phthalimido group of the donor **14** seems to interrupt the glycoside bond formation at C-3 position of compound **2**. Moreover, a disaccharide–amino acid intermediate **18** was also synthesized by means of compound **10** as a key starting material. Here, compound **10** was first employed as an acceptor for the coupling with an imidate **11**. This orthogonal-type glycosidation also proceeded smoothly and gave disaccharide **17** in 85% yield. Subsequently compound **17** was allowed to react with *N*-benzyloxycarbonyl L-serine benzyl ester to afford the sugar–amino acid derivative **18** in 73% yield. As demonstrated in these examples, CDBS protection of carbohydrates seems to be widely applicable for the preparation of the common glycosyl donors as well as glycosyl acceptors.

Deprotection of the CDBS derivatives could be accomplished satisfactorily with fluoride ions under mild conditions (Scheme 3). Treatment of CDBS derivative **4** with 1.0 equiv. of tetra-*n*-butylammonium fluoride in tetrahydrofuran for 24 h at 0°C afforded the deprotected diol **19** in 92% yield. Intermediate **18** can also be converted into compound **21**, which is known to be a key component of the T antigenic glycopeptides.[15] After the transformation of the 2-azido group to the *N*-acetyl group, protected derivative **20** was treated with triethylamine–3HF complex (2.0 equiv.) in tetrahydrofuran at

0°C for 4 h, saponified and finally hydrogenolized to afford the target compound (**21**) in 94% overall yield.

In summary, the ease of formation, stability to Lewis acids and mild conditions for the deprotection of the CDBS group suggest that this protecting group will be useful in the selective transformation and assembly of a variety of functional carbohydrates.

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10. 1,1,3,3-Tetraisopropyldisiloxanediyl (TIPDS) has also been used in carbohydrate synthesis for the selective protection of diols. For example: Ichikawa, Y.; Manaka, A.; Kuzuhara, H. *Carbohydr. Res.* **1985**, *138*, 55–64. The protection of mono- or disaccharide derivatives by the TIPDS group often gave a mixture of partially *O*-silylated products due to the flexibility of this protective group.
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13. When the excess amount of glycosyl acceptor (2.0 equiv.) was employed for this reaction, only 3-*O*-substituted disaccharide **12** was obtained as a major product and 2-*O*-substituted disaccharide could not be isolated.
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15. Selected spectral data for compound **17**: δ_H ($CDCl_3$) 5.38 (dd, 1H, *J* 3.3 Hz, H-4′), 5.31 (dd, 1H, *J* 7.8 and 10.0 Hz, H-2′), 5.02 (dd, 1H, *J* 3.3 and 10.4 Hz, H-3′), 5.00 (dd, 1H, *J* 7.6 and 52.5 Hz, H-1), 4.80 (d, 1H, *J* 7.8 Hz, H-1′), 4.61 (t, 1H, *J* 3.0 Hz, H-4), 4.31–4.22 (m, 2H, H-6′a and H-6′b), 4.15–4.04 (m, 2H, H-6a and H-6b), 3.90 (m, 1H, H-5), 3.86 (m, 1H, H-2), 3.42 (m, 1H, H-5′), 3.35 (dd, 1H, *J* 2.9 and 10.4 Hz, H-3), 2.15–2.00 (all s, 12H, 4×Ac), 1.04 (s, 9H, *t*-Bu), and 1.01 (s, 9H, *t*-Bu). Compound **18**: δ_H ($CDCl_3$) 7.38–7.32 (m, 10H, aromatic protons), 5.75 (d, 1H, *J* 8.8 Hz, Ser-N*H*-), 5.38 (d, 1H, *J* 2.9 Hz, H-4′), 5.30 (dd, 1H, *J* 7.4 and 10.3 Hz, H-2′), 5.22–5.12 (m, 4H, 2×PhCH_2), 5.01 (dd, 1H, *J* 2.9 and 10.3 Hz, H-3′), 4.79 (d, 1H, *J* 3.1 Hz, H-1), 4.72 (d, 1H, *J* 7.3 Hz, H-1′), 4.65 (t, 1H, *J*<1.0 Hz, H-4), 4.57 (m, 1H, Ser-α), 4.11–4.06 (m, 4H, H-6a, H-6b, H-6′a, and H-6′b), 4.06–3.96 (dd, 1H, *J* 3.4 and 10.8 Hz, Ser-β), 3.92 (t, 1H, *J* 6.6 Hz, H-5), 3.77 (dd, 1H, *J* 1.4 and 10.3 Hz, H-3), 3.63 (dd, 1H, *J* 3.7 and 10.3 Hz, H-2), 3.54 (br s, 1H, H-5′), 2.14–1.99 (all s, 12H, 4×Ac), 1.04 (s, 9H, *t*-Bu), and 1.01 (s, 9H, *t*-Bu). Compound **21**: δ_H (D_2O) 4.78 (d, 1H, *J* 3.8 Hz, H-1), 4.33 (d, 1H, *J* 7.8 Hz, H-1′), 4.24 (ddd, 1H, *J* 3.7 and 11.0 Hz, H-2), 4.10 (br d, 1H, H-4), 3.99–3.88 (dd, 2H, *J* 3.4 and 10.8 Hz, Ser-β), 3.90 (dd, 1H, *J* 3.1 and 11.1 Hz, H-3), 3.78 (m, 1H, Ser-α), 3.77 (br d, 1H, H-4′), 3.69–3.61 (m, 2H, H-6a and H-6b), 3.66–3.60 (m, 2H, H-6′a and H-6′b), 3.62 (m, 1H, H-5), 3.52 (t, 1H, *J* 2.8 Hz, H-5′), 3.48 (dd, 1H, *J* 3.3 and 10.0 Hz, H-3′), 3.38 (ddd, 1H, *J* 7.8 and 9.9 Hz, H-2′), and 1.9 (s, 3H, NAc).