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Di-*tert*-butylsilylene (DTBS) group-directed α-selective galactosylation unaffected by C-2 participating functionalities

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Abstract—We have discovered an unusual α-galactosylation using phenylthioglycoside of 4,6-*O*-di-*tert*-butylsilylene (DTBS)-protected galactose derivatives as a glycosyl donor, which was not hampered by the neighboring participation of C-2 acyl functionality such as NTroc and OBz. The power of the DTBS effect has been exemplified by the coupling reaction with various glycosyl acceptors.

In view of the increasing attention in the biological field being paid to multi-functional carbohydrates,[1] which for example serve as an interface in cell–cell, pathogen–cell and toxin–receptor recognition and also as modulator in cell signaling, the procurement of homogeneous targeting carbohydrates has been a matter of great importance for investigation at the molecular level. In this context, the chemical fabrication of fine oligosaccharides incorporated with peptide, protein or lipid scaffolds has sustained the molecular biological study.

The feasibility of oligosaccharide synthesis, in general, mainly relies on the stereoselectivity in the glycoside formation where the α- and β-glycoside outcome would be produced simultaneously. In the situation of *gluco*- and *galacto*-type glycoside formation incorporated within oligosaccharide synthesis, β (1,2-*trans*)-selectivity can be efficiently accomplished by the neighboring effect of various acyl functionalities mounted on the C-2 hydroxyl or amino group of the glycosyl donor, by nitrile solvent effect[2] under thermodynamically controlled condition, or by tethering of the glycosyl donor to the glycosyl acceptor.[3] For α (1,2-*cis*)-selective glycosylation, on the contrary, the glycosyl donors with non-neighboring functionality on C-2 have been commonly exploited in order to maximize the anomeric effect, often with the aid of ethereal solvent effect.[4] Recently, several research groups have reported alternative approaches to α-predominant glycosylation utilizing a tethering method,[3,5] a carboxyphenylthio group as a leaving group,[6] remote participating groups[7] and conformational locking of the sugar acceptor,[8] in which, however, the participating functionalities on C-2 will be ill-suited to the α-anomeric selectivity. In this paper we report a novel methodology of α-selective *galacto*-type glycoside formation, in which C-2 acyl groups on the donor are permissible.[9]

The key feature of our approach is the 4,6-*O*-di-*tert*-butylsilylene (DTBS) group[10] on the *galacto*-type donors, which is responsible for α-selective galactosylation compatible with the neighboring functionality on the C-2 position, e.g. NTroc and OBz.

The potential of DTBS group as α-galactosylation enhancer was found by chance during a synthetic study on b-series gangliosides, in which phenyl 2-deoxy-4,6-*O*-di-*tert*-butylsilylene-3-*O*-(2,2,2-trichloroethoxycarbonyl)-2-(2,2,2-trichloroethoxycarbonylamino)-1-thio-β-D-galactopyranoside **1**,[†] used as a surrogate of

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[†] This compound was synthesized from phenyl 2-deoxy-1-thio-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-galactopyranoside in one-pot manner: 4,6-*O*-DTBS formation with $^{t}Bu_2Si(OTf)_2$ and DMAP in pyridine at room temperature, and successive addition of TrocCl to the reaction mixture gave objective compound in 65 % yield. Other DTBS-protected glycosyl donors used in this study were also prepared in a similar manner. For DTBS formation, see: Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett*. **1982**, *25*, 4871.

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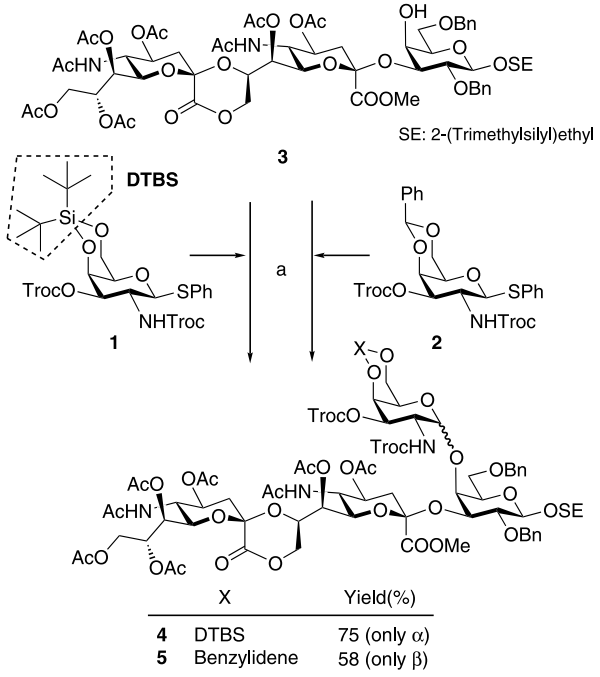
4,6-*O*-benzylidene type donor **2**, exhibited excellent α-selectivity in the iodonium-promoted coupling reaction[11] in CH_2Cl_2 at 0°C with trisaccharide acceptor **3**[12] to afford tetrasaccharide **4** despite the presence of the neighboring Troc group on the C-2 amino functionality. On the other hand, the corresponding 4,6-*O*-benzylidenated donor **2** gave β-glycosyl product **5** exclusively (Scheme 1). The stereochemistry of the new glycosides in compounds **4** and **5** was confirmed to be α and β from ^{1}H NMR spectra, δ 5.09 (d, $J_{1,2}=3.4$ Hz, H-1^{GalN}) in **4** and δ 5.05 (d, $J_{1,2}=8.6$ Hz, H-1^{GalN}) in **5**, respectively. This unexpected and unusual result has prompted us to examine the power of the DTBS effect on various coupling reactions (Fig. 1).

As shown in Table 1‡, both donors **1** and **2** gave predominantly α and β glycosyl product in the coupling reaction with relatively high reactive acceptor **11** in high yield again, respectively (entries 1 and 2), by which



Scheme 1. First encounter with unusual α-galactosylation. *Reagents and conditions*: (a) **1** or **2**, NIS-TfOH/CH_2Cl_2, MS 4 Å, 0°C.

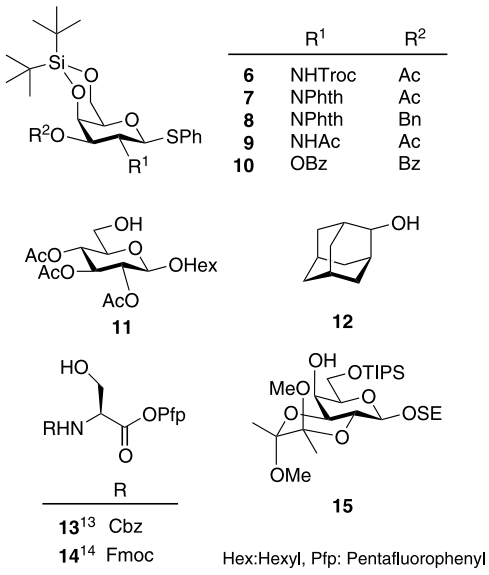


Figure 1. Donors and acceptors used in this study.

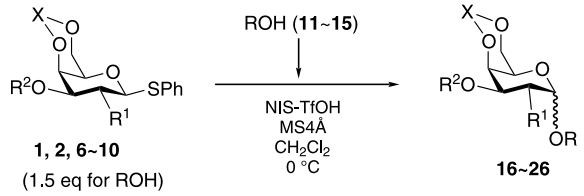
it turned out to be apparent that the aforesaid result of the incorporation with acceptor **3** is not just a case for α-selective glycosidation of donor **1**. Furthermore, donor **1** has also enjoyed the coupling reactions with acceptor **12**–**14**[13,14] in α-selective and high-yielding manner (entries 3–5). Gratifyingly, α-anomeric products were preferentially afforded by the condensation of 3-*O*-Ac-GalNTroc (**6**), 3-*O*-Ac-GalNPhth (**7**) and 3-*O*-Bn-GalNPhth (**8**) donor with acceptor **11** in good yields as well (entries 6–8). In addition, it is of note that even the C-2 acetamide group was accepted to furnish the α-product exclusively (entry 9). These results strongly suggest that the 4,6-*O*-DTBS group is a dominant factor in these α-selective galactosylations.

Phenylthioglycoside of a galactose derivative having the 4,6-*O*-DTBS and benzoyl group on both C-2 and C-3 hydroxyl, **10**, has also come up to our anticipation. In entries 10 and 11, α-selective and high-yielding coupling reaction of the donor **10** has been accomplished, unaffected by the reactivity of the acceptor hydroxyls.

In summary, we have established a 4,6-*O*-DTBS-directed α-galactosylation methodology, in which the neighboring participation of the NHTroc, NPhth, NHAc and OBz groups was ineffectual to selectively produce β-glycoside. Although, very recently, a similar kind of α-galactosylation methodology using 4,6-*O*-benzylidene-protected donor has been first reported by Kong's group,[15] stereoselectivity in their method appears to be influenced by the reactivity of acceptor to some extent. In this regard, our DTBS-directed approach can be tolerant toward any type of acceptors as shown above.[16] However, the mechanism of the α-galactosylation is ambiguous at the moment. The X-ray crystallographic analysis of compound **7**[17] showed that

‡ A typical experimental procedure for α-galactosylation (actual scale): To a solution of 4,6-*O*-DTBS-protected donor (192 μmol) and acceptor (128 μmol) in dry CH_2Cl_2 (3.2 mL) was added pre-activated 4 Å molecular sieves (200 mg) under an Ar atmosphere, then the mixture was stirred for 1 h. After addition of NIS (384 μmol) and TfOH (38 μmol) at 0°C, the reaction mixture was continuously stirred at 0°C until the donor was completely consumed on TLC analysis (actual duration time ranges from 30 min to 5 h). The mixture was filtered through Celite®, washed with $CHCl_3$, and the combined filtrate and washings were washed with satd Na_2CO_3 aq., satd $Na_2S_2O_3$ aq. and brine, dried over Na_2SO_4 and concentrated in vacuo. Silica gel (80 mesh; product of Fuji Silysia Co.) column chromatography of resulting syrup gave glycosyl products.

Table 1. α-Selective coupling of GalN and Gal donors with various acceptors[a]



Entry	Donor	Acceptor	Time	Product	Yield (α:β) (%)[b]
1	**1**	**11**	5 h	**16**	96:3
2	**2**	**11**	30 min	**17**	<7[c]:93
3	**1**	**12**	1 h	**18**	91:7
4	**1**	**13**	30 min	**19**	90:0
5	**1**	**14**	30 min	**20**	78:0
6	**6**	**11**	30 min	**21**	96:0
7	**7**	**11**	30 min	**22**	90:5[d]
8	**8**	**11**	30 min	**23**	94:0
9	**9**	**11**	30 min	**24**	50:0
10	**10**	**11**	3 h	**25**	71:0
11	**10**	**15**	30 min	**26**	74:0

[a] NIS (2.0 equiv. for donor) and TfOH (0.2 equiv. for donor).
[b] Isolated yield.
[c] Including inseparable impurity.
[d] Ratio was calculated from relative signal intensity in ^{1}H NMR spectra.

the six-membered ring comprised of a 4,6-*O*-DTBS acetal moiety and a C4–C5–C6 bond took near half-chair conformation, which resulted in the *tert*-butyl group being positioned closer to the anomeric carbon (Fig. 2). Although it could be one indirect evidence of the steric effect of the DTBS group in the α-selective galactosylation, further study on the transient state of the oxocarbenium intermediate should be carried out for precise discussion regarding the reaction mechanism. Now we are also undertaking the synthesis of biologically relevant carbohydrates including *O*-glycans and globo-series oligosaccharides as a practical extension of this DTBS-directed α-galactosylation.

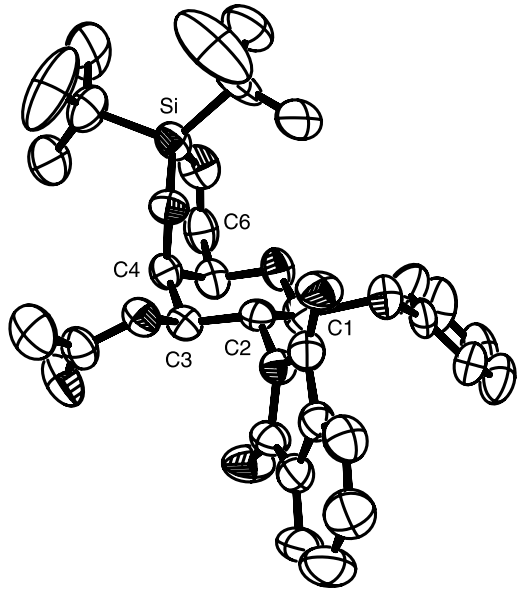


Figure 2. Structure of donor **7** (ORTEP plot).

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16. NMR data of selected compounds: for compound **18α**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 and 1.08 (2s, 18H, 2 *t*-Bu), 1.53–1.99 (m, 14H, Adamantane unit), 3.80 (broad t, 1H, H-2^{Adamantane}), 3.83 (s, 1H, H-5^{GalN}), 4.16 (dd, 1H, J_{gem}=12.5 Hz, H-6^{GalN}), 4.28 (dd, 1H, J_{gem}=12.5 Hz, H-6′^{GalN}), 4.57 (ddd, 1H, $J_{1,2}$=3.4 Hz, $J_{2,3}$=11.2 Hz, H-2^{GalN}), 4.70 and 4.78 (2d, 2H, Cl_3CCH_2), 4.75 (d, 1H, $J_{3,4}$=2.7 Hz, H-4^{GalN}), 4.76 and 4.85 (2 d, 2H, Cl_3CCH_2), 4.91 (dd, 1H, $J_{2,3}$=11.2 Hz, $J_{3,4}$=2.7 Hz, H-3^{GalN}), 5.11 (d, 1H, $J_{1,2}$=3.4 Hz, H-1^{GalN}), 5.16 (d, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.83, 23.47, 27.18, 27.26, 27.31, 27.42, 27.65, 30.83, 31.80, 32.01, 33.65, 36.30, 36.73, 37.38, 49.31, 67.09, 67.56, 70.08, 70.18, 74.63, 75.20, 76.31, 76.55, 76.84, 76.93, 79.84, 80.14, 95.91, 154.11, 154.35. For compound **18β**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.95 and 1.02 (2s, 18H, 2 *t*-Bu), 1.22–2.00 (m, 14H, Adamantane unit), 3.62 (s, 1H, H-5^{GalN}), 3.74 (broad t, 1H, H-2^{Adamantane}), 3.94 (q, 1H, $J_{1,2}=J_{2,3}=J_{2,NH}$=8.0 Hz, H-2^{GalN}), 4.04 (dd, 1H, J_{gem}=11.2 Hz, H-6^{GalN}), 4.22 (dd, 1H, J_{gem}=11.2 Hz, H-6′^{GalN}), 4.61 (d, 1H, $J_{1,2}$=8.0 Hz, H-1^{GalN}), 4.64 (d, 1H, $J_{3,4}$=3.4 Hz, H-4^{GalN}), 4.72 (dd, 1H, $J_{2,3}$=8.0 Hz, $J_{3,4}$=3.4 Hz, H-3^{GalN}), 4.77–5.04 (4d, 4H, 2 Cl_3CCH_2), 7.80 (d, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.40, 22.77, 26.56, 26.79, 27.19, 27.41, 29.00, 30.68, 30.83, 30.90, 32.97, 35.68, 35.94, 36.96, 50.98, 55.57, 66.68, 68.96, 69.48, 73.38, 73.67, 75.96, 77.65, 79.10, 79.89, 94.90, 96.16, 98.93, 152.93, 154.34. For compound **25**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, 3H, CH_3CH_2), 0.96 and 1.11 (2s, 18H, 2 *t*-Bu), 1.24–1.31 (m, 6H, $CH_3(CH_2)_3CH_2$), 1.44–1.52 (m, 2H, $CH_2CH_2CH_2O$), 1.98, 2.00 and 2.01 (3s, 9H, 3 Ac), 3.34–3.39 and 3.69–3.73 (2m, 2H, CH_2CH_2O), 3.58 (d, 1H, J_{gem}=11.0 Hz, H-6^{Glc}), 3.62 (m, 1H, $J_{4,5}$=9.1 Hz, H-5^{Glc}), 3.78 (dd, 1H, J_{gem}=11.0 Hz, H-6′^{Glc}), 3.98 (s, 1H, H-5^{Gal}), 4.20 (d, 1H, J_{gem}=12.1 Hz, H-6^{Gal}), 4.31 (d, 1H, J_{gem}=12.1 Hz, H-6′^{Gal}), 4.42 (d, 1H, $J_{1,2}$=8.0 Hz, H-1^{Glc}), 4.84 (dd, 1H, $J_{1,2}$=8.0 Hz, $J_{2,3}$=9.6 Hz, H-2^{Glc}), 4.87 (d, 1H, $J_{3,4}$=2.2 Hz, H-4^{Gal}), 5.01 (t, 1H, $J_{3,4}=J_{4,5}$=9.1 Hz, H-4^{Glc}), 5.16 (near t, 1H, $J_{2,3}$=9.6 Hz, $J_{3,4}$=9.1 Hz, H-3^{Glc}), 5.32 (d, 1H, $J_{1,2}$=3.4 Hz, H-1^{Gal}), 5.59 (dd, 1H, $J_{2,3}$=10.5 Hz, $J_{3,4}$=2.2 Hz, H-3^{Gal}), 5.75 (dd, 1H, $J_{1,2}$=3.4 Hz, $J_{2,3}$=10.5 Hz, H-2^{Gal}), 7.26–8.05 (m, 10H, 2 Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.64, 21.27, 21.41, 23.26, 23.95, 26.21, 27.94, 28.18, 29.28, 30.08, 32.19, 67.21, 67.65, 67.91, 69.27, 69.74, 70.45, 71.68, 71.87, 72.12, 73.64, 73.78, 97.57, 101.29, 129.00, 129.12, 130.01, 130.38, 130.54, 130.68, 133.05, 133.68, 133.84, 166.75, 166.83, 169.78, 170.01, 170.92.
17. Crystal data for **7**: orthorhombic, space group $P2_12_12_1$, a=18.849(5), b=20.083(3), c=8.207(2) Å, V=3106(1) Å^3, Z=4, μ(Mo-Kα)=1.87 cm^{-1}, F(000)=1240, D_c=1.248 g/cm^3, crystal dimensions: 0.32×0.30×0.38 mm. A total of 4049 reflections (4022 unique) were collected using the ω–2θ scan technique to a maximum 2θ value of 55°, and 3197 reflections with $I>0\sigma(I)$ were used in the structure determination. Final R and R_w values (full-matrix least-squares refinement on F^2) were 0.092 and 0.128, respectively. The data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 209522.