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Strict Stereocontrol by 2,4-*O*-Di-*tert*-butylsilylene Group on β-Glucuronylations

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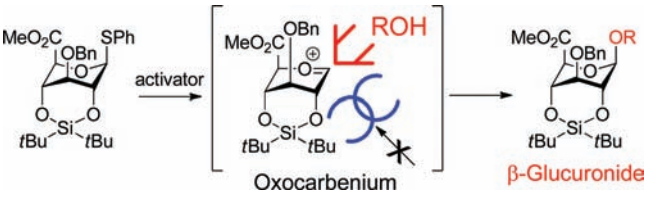
ABSTRACT



Strict β-controlled glucuronylations without classical neighboring-group participation were achieved by the assistance of a 2,4-*O*-di-*tert*-butylsilylene group. Comparison of activation conditions and conformational analysis indicated that the strict β-selectivity was achieved by steric hindrance of the 2,4-*O*-di-*tert*-butylsilylene group and not by complex glycosyl intermediates.

β-Glucuronides, abundant in polysaccharides and metabolites, have been chemically constructed using classical neighboring group participation (NGP) to form a 1,2-*cis*-type cyclic oxonium intermediate in the glycosylation process.[1,2] NGP can be a very reliable strategy for strict stereocontrolled glycosylation, and reactions that proceed by way of an orthoester intermediate also react analogously.[3] However, the low reactivity of the orthoesters often becomes problematic in the glycosylation of less reactive acceptors such as secondary or tertiary alcohols or the 4-OH group of hexopyranosides,[2,3] and an alternative methodology that did not generate such stable intermediates could have many advantages. Generally, 1,2-*trans* glycoside formation without NGP requires consideration of many different pathways; solvent effects of ethers and nitriles,[4] S_N2-type reactions,[5] formation of triflate intermediates,[6] and torsional strain in fused-ring systems[2,7] have all provided high stereoselectivities. However, the stereoselectivity of these strategies for *gluco*-conformers is affected by the reaction conditions, and the product is often contaminated with small amounts of the anomeric isomer.[1,4,8] To our knowledge, there are no reports in the literature regarding strict β-selective glucuronylations[9,10] without NGP.

To achieve strict stereoselectivity without the action of an O(2) participating group, bicyclic ring systems[11,12] have

(1) (a) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926. (b) Crich, D.; Li, L. *J. Org. Chem.* **2007**, *72*, 1681. (c) Crich, D.; Subramanian, V.; Hutton, T. K. *Tetrahedron* **2007**, *63*, 5042. (d) Crich, D.; Vinogradova, O. *J. Org. Chem.* **2006**, *71*, 8473.

(2) (a) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144. (b) Mydock, L. K.; Demchenko, A. V. *Org. Biomol. Chem.* **2010**, *8*, 497.

(3) (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155. (b) Furukawa, T.; Hinou, H.; Shimawaki, K.; Nishimura, S.-I. *Tetrahedron Lett.* **2011**, *52*, 5567.

(4) (a) Fraser-Reid, B.; Udodong, U. E.; Wu, Z.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett* **1992**, 927. (b) Schmidt, R. R.; Rücker, E. *Tetrahedron Lett.* **1980**, *21*, 1421. (c) Schmidt, R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694.

(5) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731.

(6) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435.

(7) (a) Okada, Y.; Mukae, T.; Okajima, K.; Taira, M.; Fujita, M.; Yamada, H. *Org. Lett.* **2007**, *9*, 1573. (b) Okada, Y.; Nagata, O.; Taira, M.; Yamada, H. *Org. Lett.* **2007**, *9*, 2755.

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(9) (a) Garegg, P. J.; Olsson, L.; Oscarson, S. *J. Org. Chem.* **1995**, *60*, 2200. (b) Dinkelaar, J.; de Jong, A. R.; van Meer, R.; Somers, M.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 4982. (c) Krog-Jensen, C.; Oscarson, S. *Carbohydr. Res.* **1998**, *308*, 287. (d) van den Bos, L. J.; Codée, J. D. C.; Litjens, R. E. J. N.; Dinkelaar, J.; Overkleeft, H. S.; van der Marel, G. A. *Eur. J. Org. Chem.* **2007**, 3963.

(10) Poláková, M.; Pitt, N.; Tosin, M.; Murphy, P. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2518.

(11) (a) Toshima, K.; Mukaiyama, S.; Nosaki, Y.; Inokuchi, H.; Nakata, M.; Tatsuta, K. *J. Am. Chem. Soc.* **1994**, *116*, 9042. (b) Oscarson, S.; Sehgelmeble, F. W. *J. Am. Chem. Soc.* **2000**, *122*, 8869.

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been employed, including for the formation of 2,6-dideoxyhexopyranosides,[11a] β-fructofuranosides,[11b] and β-galactosides.[12] Among these, we focused on the di-*tert*-butylsilylene group as the second rigidifying ring, and we earlier employed the tactic for the high yielding α-selective glycosylation of a 4,6-*O*-di-*tert*-butylsilylene-2-azidogalactose derivative.[12a] Ando et al. have also reported that this stereocontrol effect is stronger than that of an O(2) NGP effect.[12b] However, 4,6-*O*-di-*tert*-butylsilylene derivatives in *gluco*- or *manno*- configurations did not exert a strong stereocontrolling effect.[13] These results suggested that at least one axially oriented hydroxyl group is required for the silylene protecting group's stereocontrolling effect. Thus, we designed a 2,4-*O*-di-*tert*-butylsilylene-protected glucuronate derivative **1** as a novel glycosyl donor for strict stereocontrol in the formation of β-glucuronides. In addition, donor **1** has a $^1C_4$ conformation which would be expected to exhibit increased reactivity due to cooperative conformational[14] and anomeric effects. A method using steric hindrance as the dominant factor could be a versatile alternative strategy for β-glucuronylation. (Figure 1)

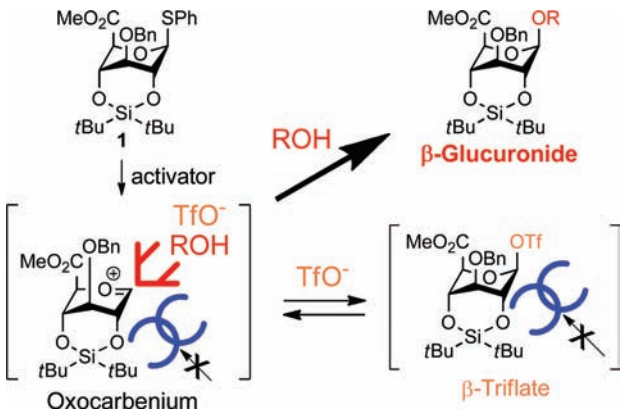
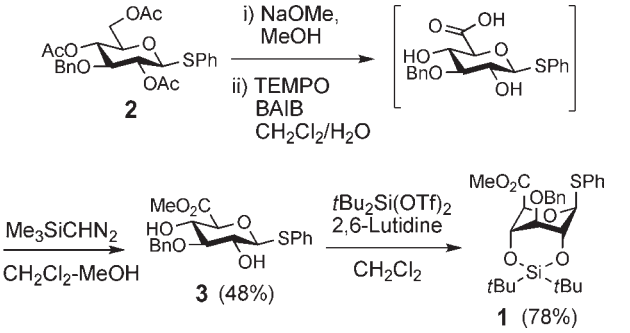


Figure 1. Working hypothesis and designed donor **1**.

The donor **1** was prepared from **2**[15] in four steps as shown in Scheme 1. Acetyl group deprotection, 2,2,6,6-tetramethylpiperidine-1-oxy (TEMPO) radical/[bis-(acetoxy)iodo] benzene (BAIB) oxidation[16] at C-6, and methyl esterification of **2** afforded precursor **3** in 48% yield via a one-pot reaction. The desired compound **1** was obtained in 78% yield from **3** by treatment with di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (tBu$_2$Si(OTf)$_2$) and 2,6-lutidine.

Scheme 1. Synthesis of Glycosyl Donor **1**



To clarify the reactivity of donor **1** in the glycosylation reaction, seven acceptor substrates—benzyl alcohol **4**, cyclohexanol **5**, 1-adamantanol **6**, 6-*O*-unprotected glucoside derivative **7**, 3-*O*-unprotected 2-azidegalactoside derivative **8**, 3-*O*-unprotected glucosaminide derivative **9**, and 4-*O*-unprotected glucosaminide derivative **10**—were selected and reacted with donor **1**, which was activated with diphenylsulfoxide (Ph_2SO)/triflic anhydride (Tf_2O)/2,4,6-tri-*tert*-butylpyrimidine (TTBP).[17] This reagent system is known to control stereoselectivity by the formation of glycosyl triflate type intermediates (Figure 1, Table 1).

When benzyl alcohol **4** was employed as an acceptor, the desired product **11** was obtained in high yield with strict β-selectivity (Table 1, entry 1). The relatively high yield and strict β-selectivity of donor **1** were reproduced with acceptors **5**–**10** (Table 1, entries 2–7). Even for hindered acceptors 1-adamantanol **6** and 4-OH unprotected glucosaminide derivative **10**, donor **1** gave the desired products **13** and **17**, respectively, in good yields (Table 1, entries 3, 7). The hydroxyl group at *O*-4 in **10** is notorious for its poor nucleophilicity and is known to be a difficult glycosyl acceptor.[18] Yamada et al. reported that 2,3,4-tri-*O*-silyl-protected glucose donors exhibit β-selective glucosidation, but strict stereoselectivity and the glycosylation of a 4-OH were not achieved.[7a] Thus, successful reactions with acceptors **6** and **10** clearly indicate the high reactivity of donor **1** even with hindered acceptors.

In the $^1C_4$ conformation, anomeric configurations cannot be determined by ^{1}H NMR spectroscopy because the α and β anomers have similar coupling constants ($J_{1,2}$) at the anomeric proton. To confirm the stereoselectivity of donor **1**, deprotections of 2,4-*O*-di-*tert*-butylsilylene groups were

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(13) (a) Ohnishi, Y.; Ando, H.; Kawai, T.; Nakahara, Y.; Ito, Y. *Carbohydr. Res.* **2000**, *328*, 263. (b) Jensen, H. H.; Pedersen, C. M.; Bols, M. *Chem.—Eur. J.* **2007**, *13*, 7576. (c) Dinkelaar, J.; Gold, H.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 4208.

(14) (a) Pedersen, C. M.; Marinescu, L. G.; Bols, M. *C. R. Chimie* **2011**, *14*, 17. (b) Pedersen, C. M.; Nordstrøm, L. U.; Bols, M. *J. Am. Chem. Soc.* **2007**, *129*, 9222.

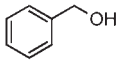
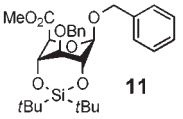
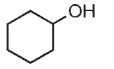
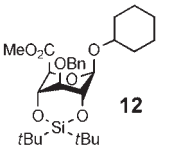
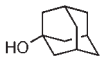
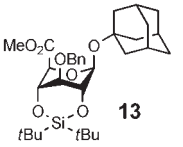
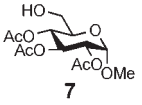
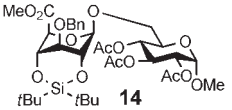
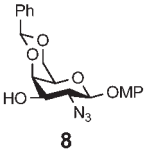
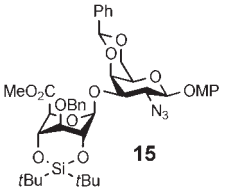
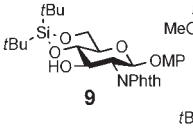
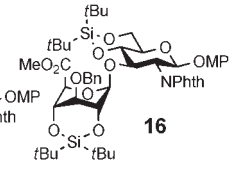
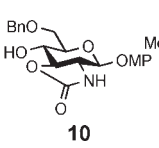
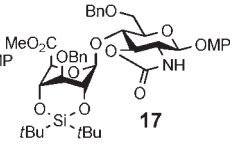
(15) Codée, J.; Stubba, B.; Schiattarella, M.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H.; van der Marel, G. A. *J. Am. Chem. Soc.* **2005**, *127*, 3767.

(16) van den Bos, L. J.; Litjens, R. E. J. N.; van den Berg, R. J. B. H. N.; Overkleeft, H. S.; van der Marel, G. A. *Org. Lett.* **2005**, *7*, 2007.

(17) (a) Garcia, B.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269. (b) Codée, J. D. C; Litjens, R. E. J. N.; den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1519.

(18) (a) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *123*, 6819. (b) Miermont, A.; Zeng, Y.; Jing, Y.; Ye, X.-S.; Huang, X. *J. Org. Chem.* **2007**, *72*, 8958.

Table 1. Glucuronylations[a] Using the Glycosyl Donor **1** for Various Acceptors

entry	acceptors	products	yields[b]	α/β ratio[c]
1	 **4**	 **11**	78%	β-only
2	 **5**	 **12**	98%	β-only
3	 **6**	 **13**	64%	β-only
4	 **7**	 **14**	87%	β-only
5	 **8**	 **15**	71%	β-only
6	 **9**	 **16**	77%	β-only
7	 **10**	 **17**	63%	β-only

[a] Conditions: donor (1.3 equiv), acceptor (1.0 equiv), Ph_2SO (1.5 equiv), Tf_2O (1.5 equiv), TTBP (2.9 equiv), CH_2Cl_2 (0.05 M), −60 to 0 °C, 2 h. MP = *para*-methoxy phenol. [b] Isolated yields. [c] Isolated ratio.

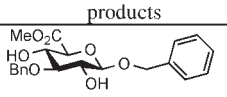
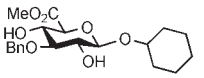
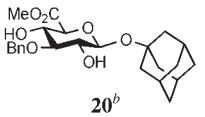
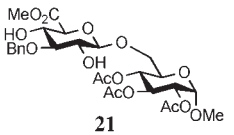
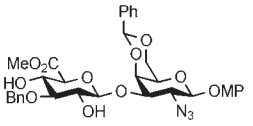
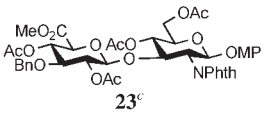
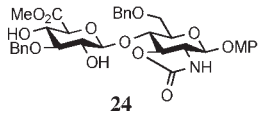
carried out with hydrogen fluoride (HF)/pyridine and each coupling constant was analyzed (Table 2).

As shown in Table 2, the coupling constants of anomeric protons ($J_{1,2}$) converged to approximately 7.5−7.9 Hz, allowing all anomeric configurations to be assigned as β-forms. These results clarify that glycosylation reactions using donor **1** proceed in a β-selective manner.

Next, our interest shifted to the mechanism of the high β-stereoselectivity. Crich et al. reported that anomeric

(19) Crich, D.; de la Mora, M.; Vinod, A. *J. Org. Chem.* **2003**, *68*, 8142.

Table 2. Deprotection of 2,4-*O*-Di-*tert*-butylsilylene Groups[a]

entry	S.M.	products	yields[d]	$J_{1,2}$
1	**11**	 **18**	94%	7.7 Hz (=β)
2	**12**	 **19**	91%	7.8 Hz (=β)
3	**13**	 **20**[b]	88%	7.5 Hz (=β)
4	**14**	 **21**	88%	7.8 Hz (=β)
5	**15**	 **22**	84%	7.7 Hz (=β)
6	**16**	 **23**[c]	94%	7.9 Hz (=β)
7	**17**	 **24**	90%	7.9 Hz (=β)

[a] HF/pyridine, 2 h at rt. S.M. = Starting Material. [b] HF/pyridine, 30 min at rt. [c] HF/pyridine, 2 h at rt, then Ac_2O/pyridine. [d] Isolated yields.

outcomes differ[19] between Ph_2SO/Tf_2O[17] (preactivation conditions to form β-triflate) and *N*-iodo succinimide (NIS)/trifluoromethanesulfonic acid (TfOH) (direct activation condition) mediated activation. These results suggested that the NIS/TfOH direct activation system might show a different stereoselectivity profile than the glucosyl-triflate intermediate of the 1-benzenesulfinyl piperidine[20] and diphenyl sulfoxide reaction conditions.[19]

Table 3. Behaviors of Donor **1** in Different Activation Conditions

entry[a]	acceptors	products	yield[a,b] (yield in Table *1*)	α/β ratio[c]
1	**8**	**15**	80% (71%)	β-only
2	**9**	**16**	46% (77%)	β-only
3	**10**	**17**	70% (63%)	β-only

[a] Conditions: donor (1.5 equiv), acceptor (1.0 equiv), NIS (1.5 equiv), TfOH (0.2 equiv), CH_2Cl_2 (0.07 M), −40 to −10 °C, 2 h, [b] Isolated yields. [c] Isolated ratio.

(20) (a) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198. (b) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015.

Based on this hypothesis, donor **1** was reacted under the NIS/TfOH conditions to estimate the influence of reaction intermediates[21] such as the glycosyltriflate.[22] We selected sugar hydroxyl groups **8**–**10** as acceptor substrates for practical use (Table 3). The results show that every coupling reaction afforded only β-glycosides and that no significant differences in yield between the acceptors were observed. We thus believe that these results indicate that steric hindrance is the dominant factor and that reaction intermediates have only a small influence on the stereoselectivity of the 2,4-*O*-di-*tert*-butylsilylene group.

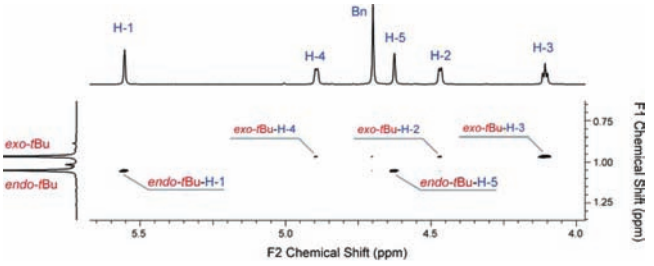


Figure 2. Conformational analysis of donor **1** by NOESY.

We then performed a two-dimensional nuclear Overhauser enhancement spectroscopy (NOESY) measurement to prove the effect of steric hindrance in fixed ring systems. As shown in Figure 2, each ring proton correlates with *tert*-butyl groups. As expected, strong interactions between the *endo*-*t*Bu group and the anomeric proton H-5 were observed. This result indicates that the *endo*-*t*Bu group locates near C-1 and C-5 and shields the α-direction. The structure of **1** was calculated using a macro model (MM)[23] and supported the NOESY analytical data, showing that the ring's α-face was completely covered by the 2,4-*O*-di-*tert*-butylsilylene group (Figure 3).

In conclusion, we have designed and synthesized a novel glucuronyl donor **1** with a 2,4-*O*-di-*tert*-butylsilylene functional group. This donor **1** showed excellent coupling yields and complete β-selectivity for various acceptors, including hindered tertiary alcohols and the 4-OH group of GlcNAc. In addition, the strict β-selectivity is not affected by the activation system. It is thus believed that the *tert*-butyl group steric hindrance plays a significant role in the stereoselectivity. This hypothesis is clearly supported by NMR spectroscopy conformational analysis and donor **1** structural calculations. This stereocontrolled glycosylation method could be applied to the synthesis of other glycosides having gluco-, ido-, allo-, talo-, ribo-, or xylo-type configurations, including β-D-xyloside and α-L-iduronate residues in glycosaminoglycans.

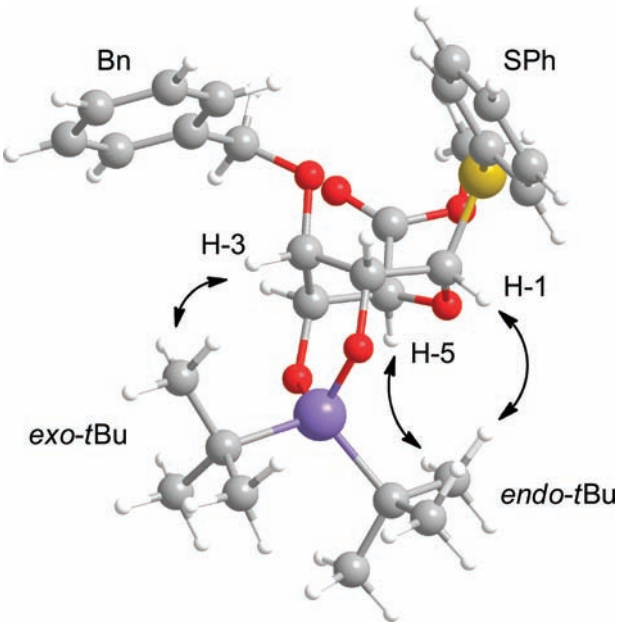


Figure 3. MM calculated structure of donor **1**.

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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(21) Bohé, L.; Crich, D. *C. R. Chimie* **2011**, *14*, 3.

(22) β-Triflate was not directly detected; however it will be more preferential than α-one due to the anomeric effect and the steric reason.

(23) Conformational (distribution) search and energy calculation were carried out with Spartan'10 (Wave function, Inc., Irvine, CA) software using the MMFF molecular mechanics force field.