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FULL PAPER

Regio/Stereoselective Glycosylation of Diol and Polyol Acceptors in Efficient Synthesis of Neu5Ac-α-2,3-LacNPhth Trisaccharide

Ying Zhang,[a] Fu-Long Zhao,[a] Tao Luo,[a] Zhichao Pei*,[b] and Hai Dong*[a]

Abstract: A concise approach to Neu5Ac-α-2,3-LacNPhth trisaccharide derivative was developed. Firstly, the regio/stereoselective glycosylation between glycoside donors and glucoNPhth diol acceptors was investigated. It was found that the regioselectivity depends not only on the steric hindrance of the C2-NPhth group and the C6-OH protecting group of the glucosamine acceptors, but also on the leaving group and protecting group of the glycoside donors. Under optimized conditions, LacNPhth derivatives were synthesized up to a 92% yield through the regio/stereoselective glycosylation between peracetylated-α-galactopyranosyl trichloroacetimidate and *p*-methoxyphenyl 6-*O*-tert-butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranoside, avoiding the formation of glycosylated orthoesters and anomeric aglycon transfer. Secondly, the LacNPhth derivative was deacylated and then protected on the primary position by TBDPS to form a LacNPhth polyol acceptor. Finally, the Neu5Ac-α-2,3-LacNPhth derivative was synthesized in a 48% yield through the regio/stereoselective glycosylation between the LacNPhth polyol acceptor and a sialyl phosphite donor. Starting from D-glucosamine hydrochloride, the Neu5Ac-α-2,3-LacNPhth derivative was synthesized in a total yield of 18.5% using only 10 steps.

Introduction

The N-Acetylneuraminic acid (Neu5Ac) is widely distributed in the terminals of oligosaccharide chains in a biological system.[1] The Neu5Ac has been demonstrated to be able to promote cell adhesion, to regulate the information exchange between cells and the environment, to control the life cycle of the body glycoprotein, and to induce viral infection. It is thus related to many important diseases, such as influenza and inflammation. In humans, Neu5Ac always exists in the form of α-glycosidic linkage and bonds to galactose and/or N-acetylgalactosamine through an α 2-3-linked and/or α 2-6-linked glycosidic linkage in various glycoconjugates.[2] Therefore, controlling the selectivity to obtain the 2-α-glycosidic linkages during chemical synthesis is one of the most challenging tasks in sialylation chemistry.[3] The electron-withdrawing C-1 carboxyl group and the lack of C-3 neighboring participation groups have restricted the generation of single stereoselective products. In addition, the anomeric elimination can easily occur and lead to the formation of 2,3-dehydro derivatives.

The 3'SLN (Neu5Ac-α-2,3-LacNAc), sialylated oligolactosamine glycan structure being constituted through an α 2-3-linked glycosidic bond to the LacNAc disaccharide, is ubiquitous in influenza infection (Figure 1).[4] The access to this compound is important for studying the potential resistance against influenza. Several methods to synthesize the target trisaccharide analogues (Neu5Ac-α-2,3-LacNAc derivatives) have been developed, which have included enzymatic methods[5] as well as chemical methods.[6,7] Enzymatic methods have the commonly known limitations in that enzymes are usually fragile and expensive. The reported chemical methods usually have two strategies. One strategy is to use a one-pot glycosylation of sialylated disaccharide derivatives.[6] The other strategy is to use the direct sialylation of the lactosamine disaccharide derivatives (Scheme 1a),[7] where the preparation of lactosamine disaccharide acceptors from glucosamine or lactose usually needs multi-steps (11-13 steps) of protection, deprotection and modification, with extremely low total yields (5.5-17.3%). Consequently, the Neu5Ac-α-2,3-LacNPhth derivatives were only obtained in only 4-8% total yields.

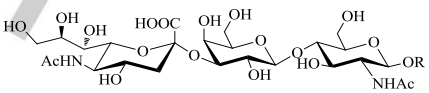

Figure 1. Structure of the Neu5Ac-α-2,3 LacNAc (3'SLN)

In the present study, we developed an efficient approach to synthesize a Neu5Ac-α-2,3-LacNPhth derivative **3** resulting in a total yield of 18.5% over only 10 steps starting from glucosamine hydrochloride (Scheme 1b). The key to the synthesis of this diasaccharide **3** is the highly efficient preparation of lactosamine disaccharide. Hence, the effect of protecting group on glucosamine acceptor, the effect of the leaving group and the protecting group on the galactosyl donor has been studied. Through the improvement on the regio/stereoselective glycosylation between galactosyl donors and glucoNPhth diol acceptors, the LacNPhth polyol acceptor **1** with four unprotected hydroxyl groups was synthesized in total yield of 39% over 8 steps starting from glucosamine hydrochloride. The further sialylation of the LacNPhth polyol acceptor **1** with Neu5Ac donor **2** still showed good selectivity even with four unprotected hydroxyl groups, thus leading to a total 48% isolated yield of the target trisaccharide **3** over 2 steps.

Results and Discussion

Our initial studies on the synthesis of Neu5Ac-α-2,3-lactosamine derivative focused on the highly efficient preparation of LacNPhth acceptor. The Neu5Ac-α-2,3-lactosamine donor with a 2-phthalimido group instead of a 2-acetamido group favored the glycosylation reaction with lipids or proteins.[8] Several methods to synthesize LacNPhth and LacNHAc derivatives have been reported (Entries 1-10 in Table 1).[7b,9] These methods can be categorized into two types: one using acceptors where both the C3-OH and C4-OH are unprotected (Entries 1-10 apart from 4 and 7 in Table 1) and the other using acceptors where only the C4-OH is unprotected (Entries 4 and 7 in Table 1). However, all these methods provided moderate yields of LacNPhth and LacNHAc products.

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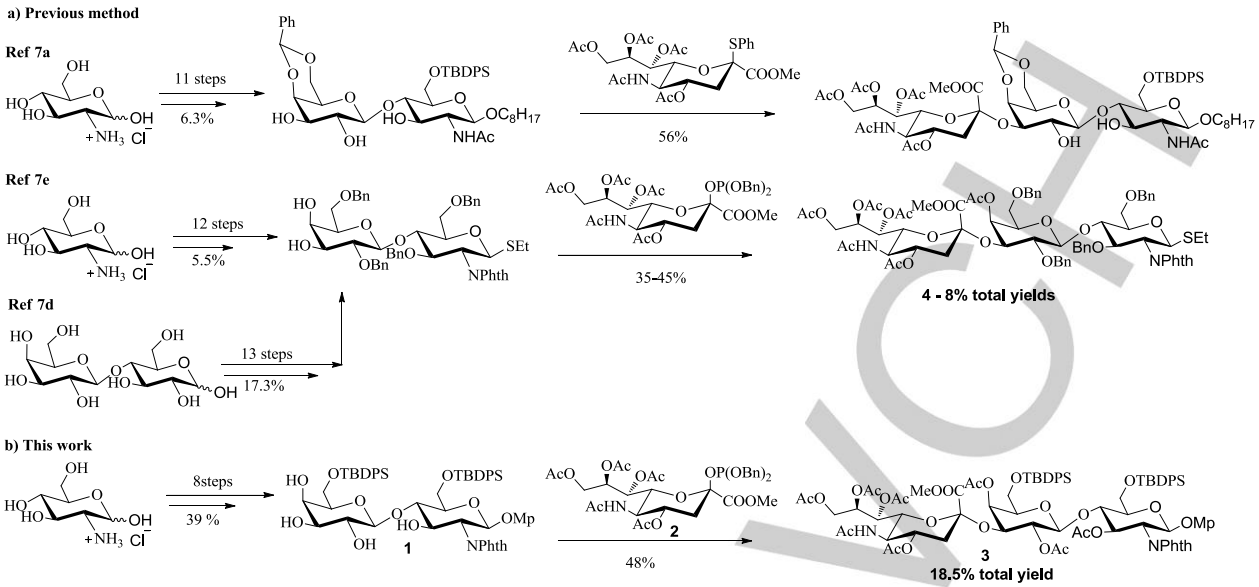

Scheme 1. Comparison of this work with previous methods for the synthesis of Neu5Ac-α-2,3 lactosamine derivatives

In our initially attempt to obtain LacNPhth derivative through glycosylation reaction, peracetylated-α-galactopyranosyl trichloroacetimidate **4a** was chosen as the donor and phenyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside **5i** was chosen as the acceptor (Entry 11 in Table 1). The reactions were carried out in dichloromethane in the presence of 4 Å molecular sieves. Moderate yield of LacNPhth product **6a** (71%) was obtained due to the formation of orthoester **7** (15%) even under the optimized condition (See in supporting information, Table S1). Subsequently, the phenyl 6-O-benzoyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside **5j**, synthesized via regioselective benzoylation in 89% yield starting from phenyl 2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside,[10] was chosen as the acceptor to react with the donor **4a**. Under the optimized condition (Entry 12 in Table 1: 0.1 equiv. of TMSOTf, -20 ºC), LacNPhth product **6b** was isolated in 69% yield (Optimization in supporting information, Table S1). The major byproduct was β-1,3-linked disaccharide as expected. The minor byproduct was phenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranoside likely due to the occurrence of the aglycon transfer as reported by C.Gildersleeve.[11]

Next, phenyl 6-O-tertbutyldimethylsilyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside **5e**, the tert-butyldimethylsilyl (TBS) group instead of the benzoyl group in 6-position, was chosen as the acceptor to react with the donor **4a**. Interestingly, although the LacNPhth product **6c** was isolated in 66% yield (Entry 13 in Table 1), the obtained byproduct **8** (18% yield) was found to be the one that TBS group of **6c** was lost due to the instability of TBS at acidic conditions. The result actually indicated a good regioselectivity (>84%). It is well-known that the TBDPS group was more stable than the TBS group in resisting hydrolysis under acidic conditions. Thus, phenyl 1-thio-β-D-glucopyranoside **5k**, the TBDPS group instead of TBS group, was chosen as the acceptor to react with the donor **4a**. To our delight, the LacNPhth product **6d** was isolated in an 83% yield (Entry 14 in Table 1)**.** Furthermore, in order to completely avoid the possible aglycon transfer of the thiophenyl glycoside **5k**, the thiophenyl group was replaced with *p*-methoxyphenyl (MP) group to form **5l**. The pseudo-orthogonal MP group can be easily transferred to corresponding trichloroacetimidate derivative by treatment with ceric ammonium nitrate (CAN).[12] When **5l** as the acceptor reacted with **4a**, the LacNPhth product **6e** was isolated in an even more increased yield of 92% (Entry 15 in Table 1).

By the comparison of the glycosylation results of entries **12**, **13** and **14**, it became clear that the protecting group at 6-position of the phenyl 2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside has a strong effect on the regioselectivity of 3- and 4-hydroxyl groups in the glycosylation. The silyl groups showed the best regioselectivities in the glycosylation. This finding was further supported by experiments where **5m** (6-OAc), **5n** (6-OBz), **5o** (6-OPiv) and **5p** (6-OBn) were separately used as the acceptors (Entries 16-19 in Table 1). The obtained yields of LacNPhth products **6f**, **6g**, **6h** and **6i** were 59%, 72%, 63% and 66% respectively. Informed by literature, **5m**,[13] **5n**,[10] **5o**,[14] and **5p**[15] were synthesized starting from *p*-methoxyphenyl 2-deoxy-2-phthalimido-β-D-glucopyranoside. However, with TBDPS group protecting the 6-hydroxyl group, acceptors **5q** (1-SEt), **5r** (1-OAll), **5s** (1-OMe) and **5t** (1-OBn) all led to good isolation yields (80-90%) of LacNPhth products (Entries 20-23 in Table 1), indicating good regioselectivities in glycosylation respectively. Acceptor **5q** (1-SEt) led to a relative lower yield (80%) which is likely due to the aglycon transfer. This aglycon transfer commonly occurs in glycosylation of acceptors carrying a thio group at the anomeric position.[11]

In the following experiments, we investigated the regioselectivity of 3- and 4-hydroxyl groups of **5l** in glycosylation where donors other than **4a** were used (Table 2). When the donor **4j** (thiophenyl leaving group instead of trichloroacetimidate leaving group for **4a**) was allowed to react with **5l** in the presence of N-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TfOH), the LacNPhth product **6e** was isolated in 76% yield (Entry 1 in Table 2). When the donor **4l** (acetate leaving group instead of trichloroacetimidate leaving group for **4a**) was allowed to react with **5l** in the presence of TMSOTf, 36% and 67% of the LacNPhth product **6e** were obtained with 0.5 equiv. and 2 equiv. of TMSOTf as the promoter, respectively (Entries 2 and 3 in Table 2). For these reactions, the poor yields are due to poor glycosylation conditions, not due to poor regioselectivity. Thus, in the following investigation, we selected donors with a trichloroacetimidate leaving group to react with **5l**. It was found that the acyl protecting

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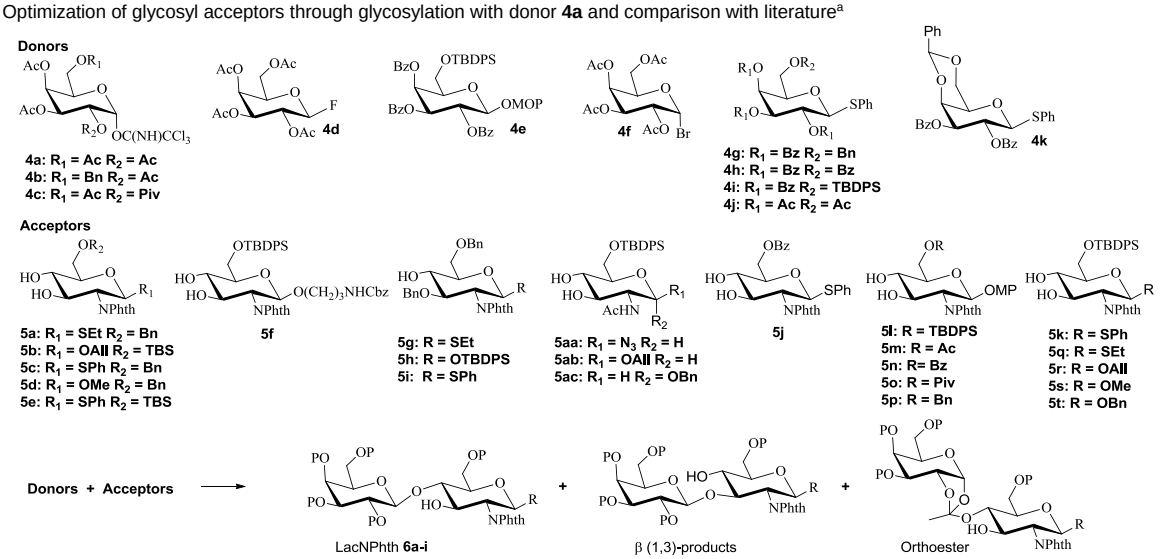
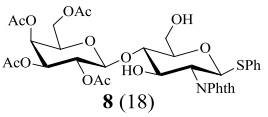
Table 1. Optimization of glycosyl acceptors through glycosylation with donor **4a** and comparison with literature[a]



Entry	Donor	Acceptor	Condition	Product (yield %)[b]	By-product (yield %)
1[9a]	**4a**	**5a**	TMSOTf, -10 ºC	LacNPhth (76)	
2[9b]	**4a**	**5b**	TMSOTf, 0 ºC	LacNPhth (70)	
3[9c]	**4b**	**5c**	TMSOTf, 0 ºC	LacNPhth (77)	
4[7b]	**4c**	**5g**	TMSOTf, -78 ºC	LacNPhth (79)	
5[9d]	**4d**	**5d**	AgOTf-$SnCl_2$, -15 ºC	LacNPhth (73)	
6[9e]	**4e**	**5f**	$Cu(OTf)_2$, r.t.	LacNPhth (64)	β(1,3)-product
7[9f]	**4f**	**5h**	AgOTf, -20 ºC	LacNPhth (70)	Orthoester (20)
8[9g]	**4g-j**	**5aa**	NIS/TfOH, -45ºC	LacNHAc (78, 71, 82, 73)	
9[9g]	**4a**	**5aa, 5ab**	$BF_3{\cdot}Et_2O$	LacNHAc (70, 68)	
10[9h]	**4k**	**5ac**	NIS/TfOH, -50ºC	LacNHAc (78)	
11	**4a**	**5i**	TMSOTf (0.2), -20 ºC	**6a** (71)	Orthoester **7** (15)
12	**4a**	**5j**	TMSOTf (0.2), -20 ºC	**6b** (69)	
13	**4a**	**5e**	TMSOTf (0.1), -20 ºC	**6c** (66)	 **8** (18)
14	**4a**	**5k**	TMSOTf (0.1), -20 ºC	**6d** (83)	
15	**4a**	**5l**	TMSOTf (0.1), -20 ºC	**6e** (92)	
16	**4a**	**5m**	TMSOTf (0.1), -20 ºC	**6f** (59)	
17	**4a**	**5n**	TMSOTf (0.1), -20 ºC	**6g** (72)	
18	**4a**	**5o**	TMSOTf (0.1), -20 ºC	**6h** (63)	
19	**4a**	**5p**	TMSOTf (0.1), -20 ºC	**6i** (66)	
20	**4a**	**5q**	TMSOTf (0.1), -20 ºC	**6j** (80)	
21	**4a**	**5r**	TMSOTf (0.1), -20 ºC	**6k** (90)	
22	**4a**	**5s**	TMSOTf (0.1), -20 ºC	**6l** (88)	
23	**4a**	**5t**	TMSOTf (0.1), -20 ºC	**6m** (86)	

[a] Donor (1 equiv.), acceptor (1.1 equiv.), all the reactions were carried out in the presence of 4 Å MS under argon.
[b] Isolated yield, relative to donor

group of donors was very important for the regioselectivity of 3- and 4-hydroxyl groups of **5l** in glycosylation. For example, when per-acetylated trichloroacetimidate 2-deoxy-2-phthalimido-D-glucopyranoside donor **4m** was allowed to react with **5l**, the 1,4 glycosylation product **6n** and the 1,3 glycosylation product **9a** were isolated in 51% and 42% yields separately (Entry 4 in Table 2), indicating an exceedingly poor regioselectivity. In comparison with donor **4m**, donor **4n** (thiophenyl leaving group instead of trichloroacetimidate leaving group), **4o** (2-OAc instead of 2-NPhth), **4p** (per-benzoylated trichloroacetimidate-D-glucopyranoside) and **4q** (per-benzylated trichloroacetimidate-D-glucopyranoside) were also tested in glycosylation (Entries 5-8 in Table 2). Both **4n** (**6n**/**9a**: 41/34) and **4q** (**6s**/**9b**: 49/42) led to poor regioselectivity (Entries 5 and 8 in Table 2), whereas **4o** and **4p** led to good regioselectivity (Entries 6 and 7 in Table 2), indicating the importance of the acyl group at the 2-position for the regioselectivity. Interestingly, the obtained 1,4 glycosylation product **6s** with **4q** as the donor is a α/β (1:1.5) mixture, whereas the 1,3 glycosylation product **9b** is the absolute β-configuration. The per-acetylated trichloroacetimidate mannoside **4r** and the per-acetylated trichloroacetimidate xyloside **4s** as the donor gave the 1,4 glycosylation products **6p** and **6q** in the yields of 85% and 71% separately (Entries 9, 10 in Table 2). As expected, the glycosylation of **5l** with armed donor gave poor regioselectivity. In comparison of the good regioselectivity with donor **4a** (92% yield of **6e**), the donor **4t** (TBDPS group protecting 6-postion instead of acetyl group for **4a**) led to a significantly low yield of 1,4 glycosylation product **6t** (68%) accompanied by a complex mixture of by-products (Entry 11 in Table 2).

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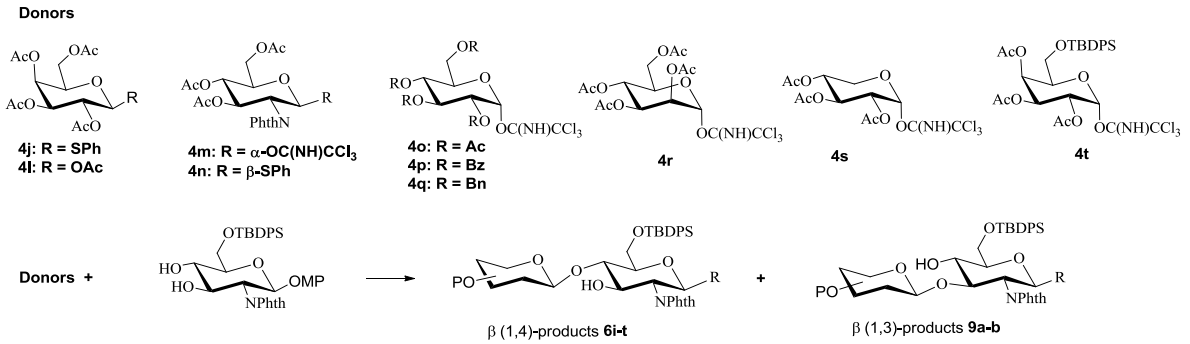
Table 2. Effects of different protecting groups and leaving group of glycosyl donors on the glyosylation with glycosyl acceptor **5l**[a]



Entry	Donor	Acceptor	Promoter	Product(yield %)[b]	By-product(yield %)
1	**4j**	**5l**	NIS (2.0)/TfOH (0.2)	**6e** (76)	
2	**4l**	**5l**	TMSOTf (0.5)	**6e** (36)[c]	
3	**4l**	**5l**	TMSOTf (2)	**6e** (67)	
4	**4m**	**5l**	TMSOTf (0.1)	**6n** (51)	**9a** (42)
5	**4n**	**5l**	NIS (2.0)/TfOH (0.2)	**6n** (41)	**9a** (34)
6	**4o**	**5l**	TMSOTf (0.1)	**6o** (87)	
7	**4p**	**5l**	TMSOTf (0.1)	**6r** (81)	
8	**4q**	**5l**	TMSOTf (0.1)	**6s** (49)[d]	**9b** (42)
9	**4r**	**5l**	TMSOTf (0.1)	**6p** (85)[e]	
10	**4s**	**5l**	TMSOTf (0.1)	**6q** (71)	
11	**4t**	**5l**	TMSOTf (0.1)	**6t** (68)	Complex mixture

[a] Donor (1 equiv.), acceptor (1.1 equiv.), -20°C, all the reactions were carried out in the presence of 4 Å MS under argon.
[b] Isolated yield, relative to donor
[c] Low conversion
[d] α/β = 1/1.5
[e] α(1,4)-product.

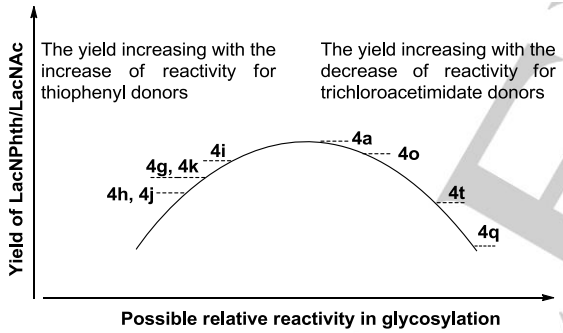
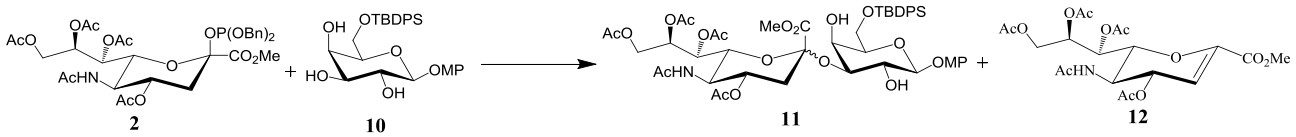


Figure 2. Comparison of the LacNAc yields by the glycosylation of thiophenyl donors with the LacNPhth yields by the glycosylation of trichloroacetimidate donors. Yield of LacNPhth/LacNAc: **4a** (92), **4g** (78), **4h** (71), **4i** (82), **4j** (73), **4k** (78) in Table 1 and **4o** (87), **4t** (68), **4q** (49) in Table 2.

An interesting result was found by comparing the literature[9g,h] with this study. In this study, the obtained yield of LacNPhth with a disarmed trichloroacetimidate donor (**4a** or **4o**) is much higher than that with a trichloroacetimidate donor (**4t** or **4q**) whose 6-position is protected by an armed protecting group. However, in the literature (Entries 8 and 10 in Table 1),[9g,h] the obtained yield of LacNAc with a disarmed thiophenyl donor (**4h** or **4j**) is slightly lower than that with a thiophenyl donor(**4g**, **4k** or **4i**) whose 6-position is protected by an armed protecting group. The reason may be due to that the best yield of LacNPhth/LacNAc depends on the most appropriate reactivity of the donors (Figure 2). The slightly poor yield of LacNAc (71 or 73) with the disarmed thiophenyl donor (**4h** or **4j**) may be caused by the relatively lower reactivity of the donor. Thus, the relatively higher reactivity of the thiophenyl donor (**4g**, **4k** or **4i**) led to the better yield of LacNAc (78, 78 or 82). It is known that trichloroacetimidate donors usually showed higher reactivity than thiophenyl donors in glycosylation reactions. We have shown that the poor yield of LacPhth **6s** or **6t** (Entries 8 and 11 in Table 2) was caused by the poor selectivity in the glycosylation of **5l** with the trichloroacetimidate donor (**4t** or **4q**). The poor selectivity should be attributed to the relatively high reactivity of **4t** or **4q**. Thus, the relatively low reactivity of the disarmed trichloroacetimidate donor (**4a** or **4o**) caused the best regio/stereoselective glycosylation, which resulted in the best yield of LacPhth. Obviously, the best yield of LacPhth/LacNAc was obtained when using a disarmed trichloroacetimidate donor than when using an armed thiophenyl donor.

LacNPhth **1** was easily obtained starting from **6e** through two steps (deacylation, then silylation). Therefore, we hypothesized that the most concise route to synthesize 3'SLN derivative was through straightforward sialylation of the LacNPhth **1** with the Neu5Ac donor, assuming that a good regioselectivty for the 3-OH of **1** could be obtained. The relative good regioselectivity for the straightforward sialylation between galacto-type polyols and sialyl N-phenyl trifluoroacetimidate donor has been previously reported.[16] Since sialyl phosphite donors are much more readily prepared from inexpensive reagents than sialyl N-phenyl-trifluoroacetimidate donors, we choose *p*-methoxyphenyl 6-*O*-TBDPS-β-D-galactoside **10** as a model to test the sialylation with the sialyl phosphite donor **2** (Table 3)**.** Two major products formed in the sialylation: one was the desired product 2,3 disaccharide product **11** and the other was the elimination product **12** from the Neu5Ac donor **2**. Through varying the used amounts of the donor, the temperature and the solvents, it was found that **11** was obtained in a yield up to 63% when 1.5 equiv. of donor **2** was used in acetonitrile at -40 °C (Entry 3 in Table 3). Sialylation with this sialyl phosphite donor **2** showed similar yield of **11** and even high α-selectivity than the reported sialyl N-phenyltrifluoroacetimidates donor.[16] These results indicated that the straightforward sialylation between the LacNPhth **1** and the Neu5Ac donor **2** should be feasible.

Table 3. Straightforward sialylation with *p*-methoxyphenyl 6-*O*-TBDPS-β-D-galactoside 10.[a]



Entry	Donor (equiv.)	Promoter (equiv.)	Additive (equiv.)	Solvent	Time (h)	**11** (yield %)[b]
1	**2** (0.9)	TMSOTf(0.2)	----	CH_3CN	40min→2h	39
2	**2** (1.2)	TMSOTf(0.2)	----	CH_3CN	2h	51
3	**2** (1.5)	TMSOTf(0.2)	----	CH_3CN	2h	63 (α:β = 8.1:1)
4	**2** (1.8)	TMSOTf(0.2)	----	CH_3CN	2h	49
5	**2** (1.5)	TMSOTf(0.2)	----	CH_2Cl_2	2h	N/D
6[c]	**2** (1.5)	TMSOTf(0.2)	----	CH_3CN-CH_2Cl_2 (1:1)	2h	54 (α:β = 5.4:1)

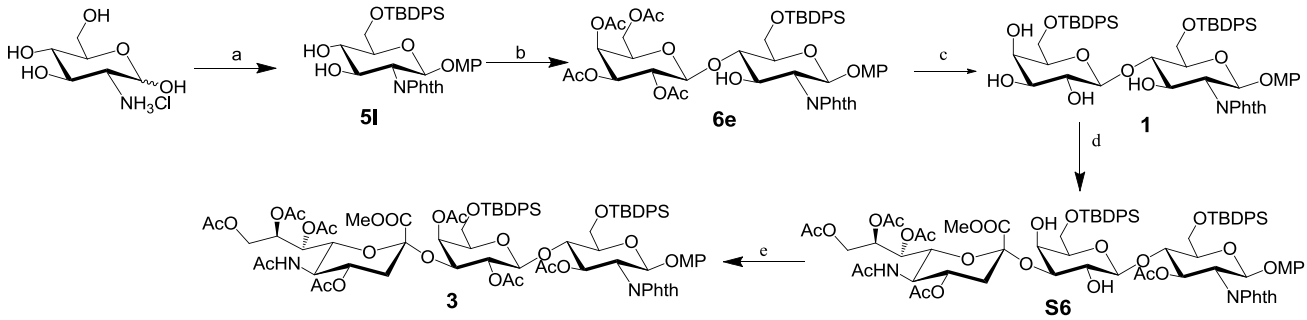
[a] Reagents and conditions: donor **2** (100 mg, 1.5 equiv), acceptors **10** (47.5 mg, 1.0 equiv), and 4 Å molecular sieves in dry CH_3CN(2 mL) was stirred atroom temperature under argon for 30 min and then cooled to -40 °C for 15 min, TMSOTf (3.28 μL, 0.2 equiv) in CH_3CN (0.3 mL) was added with syringe and stirred at -40 °C for 2 h. [b] Isolated yields based on **10** and α/β-ratiodetermined by NMR. [c] Reaction at -70 °C.

In light of the results displayed in Table 3, LacNPhth **1** was allowed to react with 1.5 equiv. of sialyl phosphite donor **2** in the presence of 0.2 equiv. of TMSOTf in acetonitrile at -40 °C. A similar regioselectivity to the use of **10** was observed. Thus, a concise route to synthesize 3'SLN derivative **3** can be developed starting from glucosamine hydrochloride (Scheme 2). The glucosamine hydrochloride was equipped with Nphth group, OTDPBS group and OMP group at C2, C6, and anomeric carbon respectively to provide **5l** in 47% yield over 5 steps of protections and deprotections. Next, the following glycosylation of the acceptor **5l** with the donor **4a** led to the disaccharide LacNPhth derivative **6e** in 92% yield. The LacNPhth disaccharide **6e** was then deacetylated in methanol with NaOH as a catalyst,[17] followed by the protection of TBDPS group at the primary position to form the polyol disaccharide acceptor **1** in excellent yield (90% over two steps). It should be noted that the phthalimide group is unstable under strong basic conditions (pH > 10). With the disaccharide acceptor **1** in hand, the linear synthesis of 3'SLN derivative was naturally carried out (Scheme 2). Finally, the selective sialylation of the polyol disaccharide acceptor **1** with the sialyl phosphite donor **2** gave the Neu5Ac-2,3 LacNPhth trisaccharides**S6** with high α-selectivity (α:β = 5.2:1). The reaction mixture was further acetylated due to the difficult isolation of the Neu5Ac-2,3 LacNPhth trisaccharides by column chromatography. Consequently, the pure per-acetylated Neu5Ac-a-2,3 LacNPhth trisaccharide **3** was easily isolated by column chromatography in 48% yield over two steps.The trisaccharide **3** can be further equipped with a suitable anomeric leaving group, whichcan be used as a donor to prepare morecomplicated glycoconjugates[6a,18] for biological activity studies (Scheme 3).

Conclusions

In the present study, we developed a concise approach to synthesizing the 3'SLN analogue via regio/stereoselective glycosylation and sialylation of diol and polyol acceptors, thereby avoiding the need for numerous protection/deprotection steps. Firstly, the method through regio/stereoselective glycosylation of per-acylated trichloroacetimidate donors with 6-*O*-tert-butyldiphenylsilyl-2-deoxy-2-phthalimido-β-D-glucoside diol acceptors was developed. The regio/stereoselectivity was found to depend not only on the steric hindrance of the C2-NPhth group and the C6-OH protecting group of the glucosamine acceptors,

Scheme 2. Linear synthesis of the target Neu5Ac-α-2,3 LacNAc (3'SLN) derivative from glucosamine hydrochloride.[a]



[a]Reagents and conditions: a) (1) MeOH, Phthalic anhydride; (2) Py, Ac_2O, DMAP, 65% yield over 2 steps; (3) MPOH or HSPh, $BF_3{\cdot}Et_2O$, DCM; (4) NaOH, MeOH; (5) TBDPSCl, Py, DMAP, 72% yield over 3 steps ; b) **4a**, TMSOTf, DCM, -20°C, 92% yield; c) (1) NaOH, MeOH; (2) TBDPSCl, Py, DMAP, 90% yield over 2 steps; d) **2**, TMSOTf, CH_3CN, -40°C, 4 Å MS; e) Ac_2O, Py, DMAP, 48% yield over 2steps.

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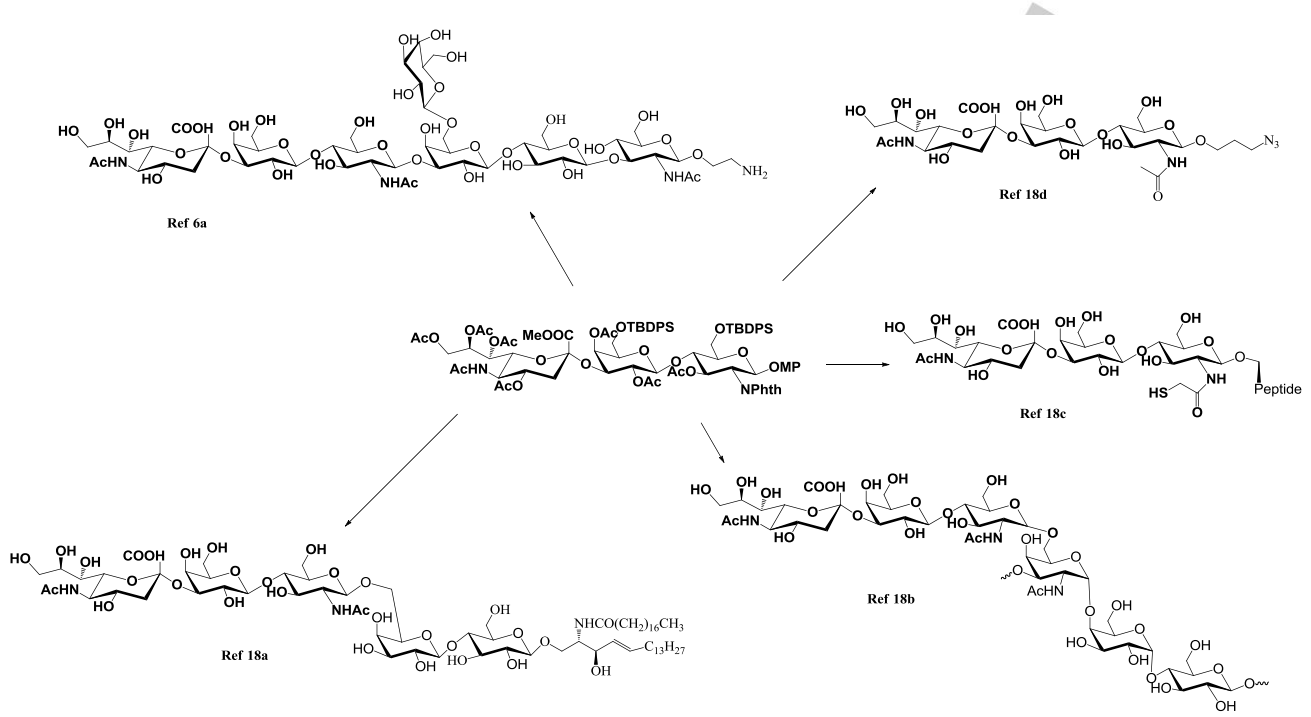
Scheme 3. Reported biologically active compounds containing 3'SLN trisaccharide



but also on the leaving group and protecting group of the glycoside donors. Different from the better yield of LacNAc obtained with an armed thiophenyl donor in the literature,[9g,h] better yield of LacNPhth is obtained when using a disarmed trichloroacetimidate donor in this study. The reason was also discussed and proposed that the best yield of LacNPhth/LacNAc depends on the most appropriate reactivity of the donors. The better yield of LacNPhth/LacNAc can be obtained using the disarmed trichloroacetimidate donor than using the armed thiophenyl donor. Consequently, the highest synthesized yield of 92% of LacNPhth disaccharide product achieved via the glycosylation of trichloroacetimidate peracetylated-α-galactopyranosyl donor with *p*-methoxyphenyl 6-*O*-tert-butyldi-phenylsilyl-2-deoxy-2-phthalimido-β-D-glucopyranoside acceptor. Secondly, the method through regio/stereoselective sialylation of a sialyl phosphite donor with a LacNPhth polyol acceptor was successfully developed, where a Neu5Ac-α-2,3-LacNPhth trisaccharide derivative was synthesized in a 48% yield. By making use of these two strategies, the Neu5Ac-α-2,3-LacNPhth trisaccharide derivative was synthesized in a total yield of 18.5% using only 10 steps starting from D-glucosamine hydrochloride. Further investigation of the coupling of the Neu5Ac-α-2,3-LacNPhth trisaccharide derivative with glycoside building blocks or phosphatides to synthesize natural oligosaccharides and glycoconjugates is currently underway.

Experimental section

General Information: All commercially available starting materials and solvents were of reagent grade and dried prior to use. Chemical reactions were monitored with thin-layer chromatography using precoated silica gel 60 (0.25 mm thickness) plates. High-resolution mass spectra (HRMS) were obtained by electrospray ionization (ESI) and Q-TOF detection. Flash column chromatography was performed on silica gel 60 (0.040-0.063 mm). ^{1}H and ^{13}C spectra were recorded with 400 and 100 MHz instruments respectively at 298 K in $CDCl_3$, using the residual signals from D-chloroform (^{1}H, δ 7.25 ppm; ^{13}C, δ 77.2 ppm), as internal standard. Assignments were made by first-order analysis of the spectra, supported by standard ^{1}H-^{1}H correlation spectroscopy (COSY).

General Procedure A for Glycosylation with Trifluoroacetimidate Donors: A mixture of the trifluoroacetimidate donor (1.0 equiv), acceptors, and 4 Å molecular sieves in dry CH_2Cl_2 was stirred at room temperature under argon for 30 min and then cooled to -20 °C. TMSOTf (0.1 equiv) dissolved in CH_2Cl_2 was added. After being stirred at -20 °C for 2 h, the reaction was quenched with a few drops of triethylamine and warmed to room temperature. The resulting mixture was filtered and concentrated and chromatographed on a silica gel column to afford the desired coupling products.

General Procedure B for Glycosylation with Thiophenyl Donors: A mixture of the thiophenyl donor (1.0 equiv), acceptors, and 4 Å molecular sieves in dry CH_2Cl_2 was stirred at room temperature under argon for 30 min and then cooled to -20 °C. NIS (2.0 equiv) and TfOH (0.2 equiv) was added. After being stirred at -20 °C for 2 h, the reaction was quenched with a few drops of triethylamine and warmed to room temperature. The resulting mixture was filtered and concentrated and chromatographed on a silica gel column to afford the desired coupling products.

Phenyl 6-O-*tert*-butyldimethylsilyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-1-thio-β-gluco-pyranoside 6cand**Phenyl 4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-1-thio-β-gluco-pyranoside8**

The reaction was performed by following the general procedure A using the donor **4a** (100 mg, 0.204 mmol), acceptor **5e** (115.53 mg, 0.224 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6c** as a colorless oil (113.8 mg, 66%) and **8** (26.8 mg, 18%). **6c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.22 (m, 9H, Nphth, SPh), 5.60 (d, *J* = 10.8 Hz, 1H), 5.36 (d, *J* = 2.8 Hz, 1H), 5.23 (dd, *J* = 10 Hz, 8 Hz, 1H), 4.96 (dd, *J* = 10 Hz, 8 Hz, 1H), 4.60 (d, *J* = 8 Hz, 1H), 4.40 (t, *J* = 9.2 Hz, 1H), 4.17 (t, *J* = 10.4 Hz, 1H), 4.06 (t, *J* = 6.4 Hz, 3H), 3.97 (t, *J* = 6.8 Hz, 1H), 3.90 (d, *J* = 11.6 Hz, 1H), 3.76 (dd, *J* = 11.2 Hz, 3.2 Hz, 1H), 3.68 (t, *J* = 9.2 Hz, 1H), 3.53 (dd, *J* = 9.2 Hz, 1.6 Hz, 1H), 2.12, 2.08, 1.98, 1.90 (4s, 12H, 4OAc), 0.94 (s, 9H, $C(CH_3)_3$), 0.14 (d, *J* = 22.8 Hz, 6H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.1, 170.0, 169.1, 168.1, 167.4, 134.1, 132.8, 132.2, 131.8, 131.7, 128.8, 127.9, 123.6, 123.3, 101.6, 83.4, 81.5, 78.8, 77.3, 71.2, 70.9, 70.8, 68.7, 66.8, 61.7, 61.4, 55.2, 25.9, 20.7, 20.6, 20.5, 20.3, 18.3, -4.9, -5.2; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{40}H_{51}NO_{15}SSiNa$868.2646; found 868.2645.**8:** ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.93-7.23 (m, 9H, Nphth, SPh), 5.67 (d, *J* = 10.4 Hz, 1H), 5.36 (d, *J* = 3.2 Hz, 1H), 5.23 (dd, *J* = 10.4 Hz, 8.4 Hz, 1H), 5.04 (dd, *J* = 10.4 Hz, 3.2 Hz, 1H), 4.63 (d, *J* = 8 Hz, 1H), 4.45 (dd, *J* = 10.0 Hz, 8.4 Hz, 1H), 4.24 (d, *J* = 10.4 Hz, 1H), 4.06 (m, 3H), 3.89 (dd, *J* = 12.0 Hz, 2.0 Hz, 1H), 3.71 (t, *J* = 9.2 Hz, 1H) 3.65 (dd, *J* = 11.6 Hz, 3.2 Hz, 1H), 3.60 (dt, *J* = 10.0 Hz, 2.4 Hz, 1H), 2.13, 2.11, 1.98, 1.86 (4s, 12H, 4OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.0, 169.9, 169.4, 168.1, 167.5, 134.2, 132.5, 131.8, 131.7, 131.6, 129.0, 128.1, 123.7, 123.3, 101.9, 83.5, 81.8, 78.1, 77.2, 71.3, 70.8, 70.7, 68.8, 66.8, 61.6, 61.0, 55.1, 20.7, 20.6, 20.5, 20.2; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{34}H_{37}NO_{15}Sna$ 754.1782; found 754.1762.

***p*-Methoxyphenyl 6-O-*tert*-butyldiphenylsilyl-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside 6e**

The reaction for the donor **4a** (100 mg, 0.204 mmol), acceptor **5l** (146.3 mg, 0.224 mmol)was performed by following the general procedure A. Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6e** as a colorless oil (184.5 mg, 92%).

The reaction forthe donor **4j** (100 mg, 0.227 mmol), acceptor **5l** (163.3 mg, 0.25 mmol)was performed by following the general procedure B. Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6e** as a colorless oil (168.6 mg, 76%).

A mixture of the donor penta-O-acetyl-D-galactopyranosyl **4l**(100 mg, 0.26 mmol), acceptors **5l** (184.2 mg, 0.28 mmol), and 4 Å molecular sieves in dry CH_2Cl_2 (3 mL) was stirred at room temperature under argon for 30 min and then cooled to -20 °C. Subsequently, TMSOTf (2 equiv) dissolved in CH_2Cl_2 was added. After being stirred at -20 °C for 2 h, the mixture was quenched with a few drops of triethylamine and warmed to room temperature. The resulting mixture was filtered and concentrated. The residue was chromatographed (Ethyl acetate/Petroleum ether, 1:2) on a silica gel column to afford **6e** (171.2 mg, 67%).

6e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.20 (m, 14H, Nphth, $Si(Ph)_2$), 6.90-6.70 (m, 4H, Ar-H in OMP), 5.78 (d, *J* = 8.4 Hz, 1H, H-1), 5.36 (d, *J* = 2.8 Hz, 1H), 5.22 (dd, *J* = 10.4 Hz, 8.8 Hz, 1H), 4.99 (dd, *J* = 10.4 Hz, 3.2 Hz, 1H), 4.72 (d, *J* = 8 Hz, 1H, H-1'), 4.53 (dd, *J* = 10.4 Hz, 8.0 Hz, 1H), 4.43 (dd, *J* = 10.8 Hz, 8.8 Hz, 1H), 4.11 (m, 2H), 3.94 (m, 5H), 3.73 (s, 3H, OCH_3), 3.68 (dd, *J* = 10.8 Hz, 2.8 Hz, 1H), 2.13, 1.99, 1.98, 1.65 (4s, 12H, 4OAc), 1.09 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.1, 169.9, 169.1, 155.4, 150.9, 135.9, 135.6, 134.1, 133.5, 132.4, 131.8, 129.9, 129.8, 127.9, 127.7, 118.8, 114.4, 101.3, 97.4, 80.9, 77.3, 74.8, 71.3, 70.8, 69.5, 68.7, 66.9, 61.7, 61.3, 56.2, 55.7, 26.9, 20.6, 20.5, 20.4, 20.2, 19.4; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{51}H_{57}NO_{17}SiNa$ 1006.3293; found 1006.3283.

***p*-Methoxyphenyl 6-O-acetyl-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside 6f**

The reaction was performed by following the general procedure A using the donor **4a** (100 mg, 0.204 mmol), acceptor **5m** (103.4 mg, 0.224 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6f** as a colorless oil (94.7 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.73 (m, 4H, Nphth), 6.87-6.72 (m, 4H, Ar-H in OMP), 5.76 (d, *J* = 8.0 Hz, 1H, H-1), 5.37 (d, *J* = 2.8 Hz, 1H), 5.26 (dd, *J* = 10 Hz, 8.0 Hz, 1H), 5.02 (dd, *J* = 10.4 Hz, 3.2 Hz, 1H), 4.61(d, *J* = 8.0 Hz, 1H, H-1'), 4.42 (m, 4H), 4.10 (m, 4H), 3.85 (ddd, *J* = 7.2 Hz, 5.2 Hz, 2.0 Hz, 1H), 3.73 (s, 3H, OCH_3), 3.66 (t, *J* = 8 Hz, 1H), 2.15, 2.13, 2.10, 1.98, 1.87 (5s, 15H, 5OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.4, 170.0, 169.9, 169.5, 155.6, 150.7, 134.2, 131.7, 123.5, 118.7, 114.4, 102.0, 97.5, 83.3, 77.2, 72.0, 71.4, 70.8, 69.9, 68.7, 66.8, 62.6, 61.7, 55.6, 20.8, 20.6, 20.6, 20.5, 20.2; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{37}H_{41}NO_{18}Na$810.2221; found 810.2226.

***p*-Methoxyphenyl 6-O-benzoyl-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside 6g**

The reaction was performed by following the general procedure A using the donor **4a** (100 mg, 0.204 mmol), acceptor **5n** (114.7 mg, 0.224 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6g** as a colorless oil (124.7 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-7.47 (m, 9H, Nphth, OBz), 6.89-6.66 (m, 4H, Ar-H in OMP), 5.81 (d, *J* = 8.4 Hz, 1H, H-1), 5.37 (d, *J* = 3.2 Hz, 1H), 5.27 (dd, *J* = 10.4 Hz, 8.4 Hz, 1H), 4.98 (dd, *J* = 10.4 Hz, 2.8 Hz, 1H), 4.63 (m, 2H, H-1'), 4.47 (m, 4H), 4.03 (m, 4H), 3.73 (t, *J* = 6.4 Hz, 1H), 3.70 (s, 3H, OCH_3), 2.15, 2.13, 1.97, 1.87 (4s, 12H, 4OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.0, 169.9, 169.6, 166.1, 155.6, 150.6, 134.2, 133.4, 131.7, 129.7, 129.6, 128.5, 123.5, 118.8, 114.4, 102.1, 97.5, 83.7, 77.3, 72.2, 71.4, 70.9, 70.1, 68.7, 66.8, 63.2, 61.8, 55.7, 55.6, 20.7, 20.6, 20.5, 20.2; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{42}H_{43}NO_{18}Na$ 872.2378; found 872.2359.

***p*-Methoxyphenyl 6-O-pivaloyl-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside 6h**

The reaction was performed by following the general procedure A using the donor **4a** (100 mg, 0.204 mmol), acceptor **5o** (111.8 mg, 0.224 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6h** as a colorless oil (106.5 mg, 63%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.73 (m, 4H, Nphth), 6.88-6.70 (m, 4H, Ar-H in OMP), 5.76 (d, *J* = 8.4 Hz, 1H, H-1), 5.37 (d, *J* = 3.2 Hz, 1H), 5.29 (dd, *J* = 10 Hz, 8 Hz, 1H), 5.00 (dd, *J* = 10.4 Hz, 3.2 Hz, 1H), 4.60 (d, *J* = 8 Hz, 1H, H-1'), 4.43 (m, 4H), 4.05 (m, 4H), 3.89 (m, 1H), 3.72 (s, 3H, OCH_3), 3.60 (t, *J* = 8.4 Hz, 1H), 2.15, 2.10, 1.96, 1.88 (4s, 12H, 4OAc), 1.23 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 170.4, 170.0, 169.9, 169.5, 155.5, 150.7, 134.2, 131.7, 123.5, 118.7, 114.4, 102.1, 97.4, 83.8, 77.2, 72.2, 71.5, 70.9, 70.0, 68.6, 66.8, 63.0, 61.7, 55.7, 55.6, 38.8, 27.2, 20.6, 20.6, 20.5, 20.2; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{40}H_{47}NO_{18}Na$852.2691; found 852.2671.

***p*-Methoxyphenyl 6-O-benzyl-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside 6i**

The reaction was performed by following the general procedure A using the donor **4a** (100 mg, 0.204 mmol), acceptor **5p** (113.1 mg, 0.224 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6i** as a colorless oil (111.6 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.32 (m, 9H, Ar-H in OBn, Nphth), 6.89-6.71 (m, 4H, Ar-H in OMP), 5.74 (d, *J* = 8 Hz, 1H, H-1), 5.34 (d, *J* = 2.8 Hz, 1H), 5.20 (dd, *J* = 10.4 Hz, 8.4 Hz, 1H), 4.96 (dd, *J* = 10.4 Hz, 3.6 Hz, 1H), 4.72 (d, *J* = 12 Hz, 1H, H-1'), 4.48 (m, 4H), 4.02 (m, 4H), 3.77 (m, 3H), 3.72 (s, 3H, OCH_3), 2.13, 2.01, 1.98, 1.93 (4s, 12H, 4OAc).^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.1, 169.9, 169.1, 155.5, 150.8, 138.0, 134.1, 131.7, 128.5, 127.9, 127.8, 118.8, 114.4, 101.5, 97.6, 81.9, 77.3, 74.3, 73.7, 71.2, 70.7, 69.7, 68.7, 67.8, 66.8, 61.5, 55.9, 55.6, 20.7, 20.6, 20.5, 20.3; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{42}H_{45}NO_{17}Na$ 858.2585; found 858.2565.

Ethyl 6-O-*tert*-butyldiphenylsilyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside 6j

The reaction was performed by following the general procedure A using the donor **4a** (100 mg, 0.204 mmol), acceptor **5q** (132.4 mg, 0.224 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6j** as a colorless oil (150.3 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.33 (m, 14H, Nphth, $Si(Ph)_2$), 5.35 (d, *J* = 10.4 Hz, 1H, H-1), 5.34 (d, *J* = 3.2 Hz, 1H), 5.21 (dd, *J* = 10.0 Hz, 8.0 Hz, 1H), 4.96 (dd, *J* = 10.4 Hz, 3.2 Hz, 1H), 4.72 (d, *J* = 8 Hz, 1H, H-1'), 4.49 (dd, *J* = 10.4 Hz, 8.4 Hz, 1H), 4.27 (t, *J* = 10.4 Hz, 1H), 4.06 (m, 3H), 3.90 (m, 4H), 3.60 (d, *J* = 9.2 Hz, 1H), 2.70 (m, 2H, SCH_2-), 2.13, 1.99, 1.99, 1.70 (4s, 12H, 4OAc), 1.21 (t, *J* = 7.2 Hz, 3H, -CH_3), 1.12 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.1, 169.9, 169.1, 168.1, 167.8, 136.0, 135.6, 134.1, 134.1, 133.5, 132.6, 131.9, 131.7, 129.9, 129.9, 127.9, 127.7, 123.7, 123.2, 101.2, 80.7, 80.4, 78.5, 77.3, 71.2, 70.8, 70.4, 68.7, 66.8, 61.9, 61.2, 55.4, 26.9, 23.3, 20.6, 20.5, 20.4, 20.3, 19.4, 14.8; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{46}H_{55}NO_{15}SSiNa$ 944.2959; found 944.2963.

Allyl 6-O-*tert*-butyldiphenylsilyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside 6k

The reaction was performed by following the general procedure A using the donor **4a** (100 mg, 0.204 mmol), acceptor **5r** (131.3 mg, 0.224 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6k** as a colorless oil (168.4 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.37 (m, 14H, Nphth, $Si(Ph)_2$), 5.77 (m, 1H, -CH=), 5.35 (d, *J* = 3.2 Hz, 1H), 5.28 (d, *J* = 8.8 Hz, 1H, H-1), 5.21 (dd, *J* = 10.4 Hz, 8.4 Hz, 1H), 5.14 (m, 1H, CH_2=), 5.08 (dd, *J* = 10.4 Hz, 1.2 Hz, 1H, CH_2=), 4.98 (dd, *J* = 10.4 Hz, 3.2 Hz, 1H), 4.74 (d, *J* = 8.0 Hz, 1H, H-1'), 4.46 (dd, *J* = 10.4 Hz, 8.4 Hz, 1H), 4.29 (m, 1H, OCH_2-), 4.20 (dd, *J* = 10.8 Hz, 8.8 Hz, 1H), 4.14-3.73 (m, 8H, OCH_2-), 3.57 (dd, *J* = 10.0 Hz, 2.2 Hz, 1H), 2.13, 1.98, 1.97, 1.69 (4s, 12H, 4OAc), 1.12 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.1, 169.9, 169.1, 136.0, 135.6, 134.0, 133.8, 133.6, 132.6, 131.8, 129.9, 129.9, 127.9, 127.7, 117.2, 101.3, 96.8, 81.1, 77.3, 74.6, 71.2, 70.8, 69.5, 69.3, 68.8, 66.9, 61.9, 61.3, 56.2, 26.9, 20.6, 20.5, 20.4, 20.3, 19.3; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{47}H_{55}NO_{16}SiNa$ 940.3188; found 940.3169.

Methyl 6-O-*tert*-butyldiphenylsilyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside 6l

The reaction was performed by following the general procedure A using the donor **4a** (100 mg, 0.204 mmol), acceptor **5s** (125.4 mg, 0.224 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6l** as a colorless oil (159.9 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.91-7.36 (m, 14H, Nphth, Si(Ph)$_2$), 5.36 (d, *J* = 3.2 Hz, 1H), 5.22 (dd, *J* = 10.4 Hz, 8.4 Hz, 1H), 5.13 (d, *J* = 8.4 Hz, 1H, H-1), 4.99 (dd, *J* = 10.4 Hz, 3.2 Hz, 1H), 4.74 (d, *J* = 8.0 Hz, 1H, H-1'), 4.46 (dd, *J* = 10.4 Hz, 8.8 Hz, 1H), 4.19 (dd, *J* = 10.4 Hz, 8.8 Hz, 1H), 4.08 (m, 2H), 3.91 (m, 5H), 3.59 (dd, *J* = 10.4 Hz, 2.8 Hz, 1H), 3.44 (s, 3H, OMe), 2.13, 1.99, 1.97, 1.69 (4s, 12H, 4OAc), 1.11 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.4, 170.1, 169.9, 169.1, 136.0, 135.6, 134.0, 133.6, 132.6, 131.9, 129.9, 129.9, 127.9, 127.7, 101.3, 98.8, 81.1, 77.3, 74.6, 71.2, 70.9, 69.4, 68.8, 66.9, 61.8, 61.3, 56.4, 56.2, 26.9, 20.6, 20.5, 20.4, 20.3, 19.4; HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{45}H_{53}NO_{16}SiNa$ 914.3031; found 914.3041.

Benzyl 6-O-*tert*-butyldiphenylsilyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside 6m

The reaction was performed by following the general procedure A using the donor **4a** (100 mg, 0.204 mmol), acceptor **5t** (142.5 mg, 0.224 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6m** as a colorless oil (169.6 mg, 86%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.90-7.33 (m, 14H), 7.18-7.05 (m, 5H), 5.35 (d, *J* = 2.8 Hz, 1H), 5.25 (d, *J* = 8.4 Hz, 1H, H-1), 5.21 (dd, *J* = 10.0 Hz, 8.0 Hz, 1H), 4.98 (dd, *J* = 10.4 Hz, 3.2 Hz, 1H), 4.85 (d, *J* = 12.4 Hz, 1H, PhCH$_2$), 4.74 (d, *J* = 8.0 Hz, 1H, H-1'), 4.53 (d, *J* = 12.4 Hz, 1H, PhCH$_2$), 4.46 (dd, *J* = 10.8 Hz, 8.4 Hz, 1H), 4.26 (dd, *J* = 10.8 Hz, 8.4 Hz, 1H), 4.09 (m, 2H), 3.99 (d, *J* = 10.8 Hz, 1H), 3.89 (m, 4H), 3.59 (dd, *J* = 10.0 Hz, 2.8 Hz, 1H), 2.12, 1.98, 1.98, 1.72 (4s, 12H, 4OAc), 1.13 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.4, 170.1, 169.9, 169.1, 137.2, 136.0, 135.6, 133.9, 133.6, 132.6, 131.8, 129.9, 129.9, 128.2, 127.9, 127.7, 127.6, 127.5, 101.3, 96.8, 81.1, 77.3, 74.7, 71.3, 70.9, 70.2, 69.4, 68.8, 66.9, 61.9, 61.3, 56.9, 26.9, 20.6, 20.5, 20.4, 20.3, 19.4; HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{51}H_{57}NO_{16}SiNa$ 990.3344; found 990.3357.

***p*-Methoxyphenyl 6-O-*tert*-butyldiphenylsilyl-2-deoxy-4-O-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside 6n** and

***p*-Methoxyphenyl 6-O-*tert*-butyldiphenylsilyl-2-deoxy-3-O-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside 9a**

The reaction was performed by following the general procedure A using the donor 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranosidetrichloroacetimidate **4m** (100 mg, 0.173 mmol), acceptor **5l** (124.3 mg, 0.19 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 2:3) gave **6n** and **9a** as a colorless oil (172.2 mg, 93%). **6n** (94.4 mg, 51%): ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.86-7.21 (m, 18H, Nphth×2, Si(Ph)$_2$), 6.77-6.54 (m, 4H, Ar-H in OMP), 5.75 (dd, *J* = 10.4 Hz, 8.8 Hz, 1H), 5.69 (d, *J* = 8.4 Hz, 1H, H-1), 5.62 (d, *J* = 8.4 Hz, 1H), 5.08 (t, *J* = 9.6 Hz, 1H), 4.47 (dd, *J* = 10.8 Hz, 8.4 Hz, 1H, H-3), 4.37 (dd, *J* = 10.4 Hz, 8.4 Hz, 1H, H-2), 4.32 (dd, *J* = 10.0 Hz, 8.4 Hz, 1H), 4.17 (m, 2H), 3.97 (m, 2H), 3.87 (t, *J* = 8.8 Hz, 1H, H-4), 3.69 (m, 1H), 3.66 (s, 3H, OCH$_3$), 3.60 (dd, *J* = 8.4 Hz, 3.6 Hz, 1H), 3.52 (dd, *J* = 11.2 Hz, 4.8 Hz, 1H), 2.02, 1.92, 1.81 (3s, 9H, 3OAc), 0.94 (s, 9H, C(CH3)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.4, 169.9, 169.4, 155.1, 150.8, 135.7, 135.6, 135.5, 134.2, 134.0, 133.5, 132.9, 130.7, 129.5, 129.4, 127.8, 127.5, 123.6, 118.5, 118.3, 114.4, 114.3, 98.1, 97.0, 80.4, 77.2, 74.9, 72.0, 70.4, 70.0, 68.9, 62.4, 62.1, 55.9, 55.5, 54.6, 26.8, 26.7, 20.5, 20.3, 20.2, 19.3; HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{57}H_{58}N_2O_{17}SiNa$ 1093.3402; found 1093.3413. **9a** (77.8 mg, 42%): ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.76-7.02 (m, 18H, 2×Nphth, Si(Ph)$_2$), 6.78-6.56 (m, 4H, Ar-H in OMP), 5.55 (t, *J* = 10.4 Hz, 1H), 5.42 (dd, *J* = 10.4 Hz, 8.4 Hz, 1H, H-1), 5.07 (t, *J* = 9.6 Hz, 1H), 4.66 (dd, *J* = 10.4 Hz, 7.6 Hz, 1H, H-3), 4.34 (m, 2H, H-2), 4.21 (m, 2H), 4.09 (m, 2H), 3.93 (m, 2H), 3.67 (m, 2H, H-4), 3.64 (s, 3H, OCH$_3$), 2.04, 1.99, 1.72 (3s, 9H, 3OAc), 1.05 (s, 9H, C(CH$_3$)$_3$);^{13}C NMR (100MHz, CDCl$_3$) δ170.5, 169.9, 169.3, 155.2, 150.9, 135.7, 135.6, 134.1, 133.5, 133.4, 130.8, 129.6, 129.5, 127.6, 123.3, 118.3, 114.3, 98.3, 97.4, 82.2, 77.3, 76.8, 71.9, 70.3, 69.9, 68.7, 63.5, 62.0, 55.5, 55.1, 54.5, 26.8, 20.6, 20.5, 20.2, 19.3; HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{57}H_{58}N_2O_{17}SiNa$ 1093.3402; found 1093.3416.

***p*-Methoxyphenyl 6-O-*tert*-butyldiphenylsilyl-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside 6o**

The reaction was performed by following the general procedure A using the donor 2,3,4,6-tetra-O-acetyl-a-D-glucopyranoside trichloroacetimidate **4o** (100 mg, 0.204 mmol), acceptor **5l** (146.3 mg, 0.224 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6o** as a colorless oil (174.5 mg, 87%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98-7.21 (m, 14H, Nphth, Si(Ph)$_2$), 6.90-6.68 (m, 4H, Ar-H in OMP), 5.77 (d, *J* = 8.4 Hz, 1H, H-1), 5.19 (t, *J* = 9.6 Hz, 1H), 5.04 (m, 2H), 4.81 (d, *J* = 8.4 Hz, 1H, H-1'), 4.51 (dd, *J* = 10.8 Hz, 8.4 Hz, 1H), 4.43 (dd, *J* = 10.8 Hz, 8.4 Hz, 1H), 4.16 (m, 2H), 3.96 (m, 2H), 3.89 (dd, *J* = 11.2 Hz, 2.8 Hz, 1H), 3.76 (m, 1H),3.72 (s, 3H, OCH$_3$), 3.66 (dd, *J* = 10.4 Hz, 2.4 Hz, 1H), 2.03, 2.01, 2.01, 1.67 (4s, 12H, 4OAc), 1.10 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.5, 170.0, 169.3, 168.9, 155.4, 150.8, 135.9, 135.5, 134.1, 133.4, 132.2, 131.7, 129.9, 129.8, 127.9, 127.7, 118.8, 114.4, 100.9, 97.3, 80.9, 77.2, 74.7, 72.7, 72.1, 71.1, 69.4, 68.2, 61.6, 61.5, 56.2, 55.6, 26.8, 20.5, 20.5, 20.4, 20.1, 19.3; HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{51}H_{57}NO_{17}SiNa$ 1006.3293; found 1006.3279.

***p*-Methoxyphenyl 6-O-*tert*-butyldiphenylsilyl-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-β-D-mannopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside 6p**

The reaction was performed by following the general procedure A using the donor 2,3,4,6-tetra-O-acetyl-a-D-mannopyranoside trichloro-acetimidate **4r** (100 mg, 0.204 mmol), acceptor **5l** (146.3 mg, 0.224 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6p** as a colorless oil (170.5 mg, 85%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.86-7.25 (m, 14H, Si(Ph)$_2$, NPhth), 6.92-6.66 (m, 4H, Ar-H in OMP), 5.74 (d, *J* = 8.4 Hz, 1H), 5.35 (m, 2H), 5.24 (m, 2H), 4.60 (dd, *J* = 10.4 Hz, 8.4 Hz, 1H), 4.39 (dd, *J* = 10.4 Hz, 8.4 Hz, 1H), 3.98 (m, 3H), 3.80 (m, 3H), 3.70 (s, 3H, OCH$_3$), 3.69 (m, 1H), 2.04, 2.03, 1.95, 1.88 (4s, 12H, 4OAc), 1.06 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.6, 170.2, 170.2, 169.5, 168.3, 155.3, 151.0, 150.9, 135.7, 135.6, 134.2, 133.2, 132.9, 131.6, 129.7, 127.8, 127.7, 123.5, 118.5, 114.4, 114.4, 98.7, 97.3, 78.6, 77.3, 75.5, 71.8, 69.7, 69.6, 69.0, 65.5, 63.2, 62.1, 56.8, 55.6, 26.8, 26.7, 20.8, 20.7, 20.7, 20.5, 19.2; HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{51}H_{57}NO_{17}SiNa$ 1006.3293; found 1006.3273.

***p*-Methoxyphenyl 6-O-tert-butyldiphenylsilyl-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-β-D-xylopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside 6q**

The reaction was performed by following the general procedure A using the donor 2,3,4-tri-O-acetyl-α-D-xylopyranoside trichloro-acetimidate **4s** (100 mg, 0.238 mmol), acceptor **5l** (171.3 mg, 0.262 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6p** as a colorless oil (153.9 mg, 71%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.86-7.10 (m, 14H, Si(Ph)$_2$, NPhth), 6.92-6.68 (m, 4H, Ar-H in OMP), 5.77 (d, *J* = 7.6 Hz, 1H), 5.20 (t, *J* = 7.6 Hz, 1H), 4.99 (m, 2H), 4.79 (d, *J* = 8.0 Hz, 1H), 4.46 (m, 2H), 4.41 (dd, *J* = 11.6 Hz, 5.2 Hz, 1H), 4.05 (t, *J* = 8.8 Hz, 1H), 3.93 (m, 2H), 3.73 (s, 3H, OCH$_3$), 3.63 (m, 2H), 3.31 (t, *J* = 11.2 Hz, 1H), 2.04, 2.04, 1.73 (3s, 9H, 3OAc), 1.09 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.0, 169.7, 169.1, 155.4, 150.9, 136.0, 135.5, 134.1, 133.4, 132.0, 131.8, 129.9, 129.8, 128.0, 127.7, 118.9, 114.4, 101.3, 97.4, 79.9, 77.3, 74.7, 72.3, 71.3, 69.4, 68.6, 62.9, 61.3, 56.3, 55.7, 26.8, 20.7, 20.3, 19.4; HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{48}H_{53}NO_{15}SiNa$ 934.3082; found 934.3062.

***p*-Methoxyphenyl 6-O-tert-butyldiphenylsilyl-2-deoxy-4-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside 6r**

The reaction was performed by following the general procedure A using the donor 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranosyl trichloroacetimidate **4p** (100 mg, 0.135 mmol), acceptor **5l** (97.2 mg, 0.149 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6r** as a colorless oil (134.6 mg, 81%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.16-7.12 (m, 34H, 4×OBz, Si(Ph)$_2$, NPhth), 6.86-6.61 (m, 4H, Ar-H in OMP), 5.92 (t, *J* = 9.6 Hz, 1H), 5.64 (m, 2H), 5.20 (d, *J* = 8.0 Hz, 1H), 4.82 (dd, *J* = 12.4 Hz, 2.4 Hz, 1H), 4.63 (dd, *J* = 10.8 Hz, 8.4 Hz, 1H), 4.45 (dd, *J* = 10.4 Hz, 8.4 Hz, 1H), 4.32 (dd, *J* = 12.0 Hz, 7.2 Hz, 1H), 4.15 (m, 2H), 3.79 (s, 2H), 3.69 (s, 3H, OCH$_3$), 3.51 (m, 1H), 0.99 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 166.2, 165.6, 165.3, 164.8, 155.4, 150.9, 135.9, 135.4, 134.0, 133.8, 133.7, 133.4, 133.3, 132.2, 130.1, 130.0, 129.9, 129.7, 129.3, 128.7, 128.7, 128.5, 128.4, 128.3, 128.1, 127.7, 119.0, 114.4, 100.9, 97.4, 79.6, 77.3, 74.6, 73.2, 72.6, 71.6, 69.5, 69.3, 62.7, 61.4, 56.4, 55.6, 26.8, 19.4; HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{71}H_{65}NO_{17}SiNa$ 1254.3919; found 1254.3930.

***p*-Methoxyphenyl 6-O-*tert*-butyldiphenylsilyl-2-deoxy-4-O-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside 6s** and

***p*-Methoxyphenyl 6-O-*tert*-butyldiphenylsilyl-2-deoxy-3-O-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside 9b**

The reaction was performed by following the general procedure A using the donor 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosidetrichloroacetimidate **4q** (100 mg, 0.146 mmol), acceptor **5l** (105.2 mg, 0.161 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave

6s and **9b** as colorless oil (156.1 mg, 91%).**6s** (84 mg, 49%, α/β = 1/1.5). **9b** (72.1 mg, 42%, only β): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.12 (m, 34H, 4×OBn, $Si(Ph)_2$, NPhth), 6.86-6.61 (m, 4H, Ar-H in OMP), 5.75 (d, *J* = 8.4 Hz, 1H), 4.89 (d, *J* = 10.8 Hz, 1H), 4.79 (m, 3H), 4.69 (m, 2H), 4.57 (m, 1H), 4.48 (m, 3H), 4.42 (m, 1H), 4.08 (dd, *J* = 11.2 Hz, 3.2 Hz, 1H), 4.03 (t, *J* = 9.2 Hz, 1H), 3.93 (m, 1H), 3.71 (s, 3H, OCH_3), 3.62 (m, 2H), 3.46 (m, 2H), 1.02 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 151.0, 138.4, 138.0, 137.9, 137.7, 135.8, 135.5, 134.0, 133.5, 132.7, 131.9, 129.5, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.6, 127.6, 127.6, 127.5, 118.9, 114.4, 103.2, 97.5, 84.7, 81.8, 79.9, 77.5, 77.2, 75.8, 75.3, 75.2, 75.1, 74.7, 73.4, 73.3, 69.5, 68.4, 61.9, 56.6, 55.6, 31.9, 31.4, 30.2, 29.7, 29.3, 26.8, 22.7, 19.4, 14.1, 0.0; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{71}H_{73}NO_{13}SiNa$ 1198.4749; found 1198.4729.

***p*-Methoxyphenyl 6-O-*tert*-butyldiphenylsilyl-2-deoxy-4-O-(6-O-*tert*-butyldiphen-ylsilyl-2,3,4-tri-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside 6t**

The reaction was performed by following the general procedure A using the donor 6-O-*tert*-butyldiphenylsilyl-2,3,4-tri-O-benzoyl-α-D-galacto-pyranosyl trichloroacetimidate **4t** (100 mg, 0.145 mmol), acceptor **5l** (104.5 mg, 0.160 mmol). Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:2) gave **6t** as a colorless oil (116.3 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.12 (m, 24H, 2×$Si(Ph)_2$, NPhth), 6.90-6.65 (m, 4H, Ar-H in OMP), 5.73(d, *J* = 8.4 Hz, 1H), 5.43 (d, *J* = 3.2 Hz, 1H), 5.17 (dd, *J* = 11.2 Hz, 8.8 Hz, 1H), 4.99(dd, *J* = 10.8 Hz, 3.2 Hz, 1H), 4.73 (d, *J* = 7.6 Hz, 1H), 4.57 (dd, *J* = 11.6 Hz, 9.2 Hz, 1H),4.43 (t, *J* = 9.2 Hz, 1H), 3.90 (m, 5H), 3.75 (m,1H), 3.71 (s, 3H, OCH_3),3.67 (m,1H),3.51 (dd, *J* = 10.4 Hz, 6.8 Hz, 1H),1.97, 1.97, 1.61 (3s, 9H, 3OAc),1.09, 0.92 (2s, 18H, 2×$C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 169.9, 169.2, 155.4, 151.0, 135.9, 135.6, 135.5, 134.0, 133.5, 132.5, 132.3, 130.0, 129.9, 129.8, 127.9, 127.9, 127.7, 118.8, 114.4, 101.2, 97.4, 80.7, 77.3, 74.9, 73.9, 71.1, 69.6, 69.1, 66.9, 61.8, 61.2, 56.1, 55.6, 26.8, 26.6, 20.6, 20.5, 20.2, 19.4, 18.8; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{65}H_{73}NO_{16}Si_2Na$ 1202.4366; found 1202.4349.

***p*-Methoxyphenyl6-O-*tert*-butyldiphenylsilyl-2-deoxy-4-O-(6-O-*tert*-butyldiphenylsilyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside 1**

To the solution of **6e** (980 mg, 1.0 mmol) in 5 mL dry MeCN, was added thiourea (114 mg, 1.50 mmol) and refluxed at 80 ℃ for 45 min. The EtI (159 μL, 2 mmol) and Et_3N (554 μL, 4 mmol) were added when the temperature dropped to rt and stirred for 30 min. When the reaction was complete (TLC), the reaction was diluted with ethyl acetate (10 mL), washed with aqueous $NaHCO_3$, and a brine solution. The organic layer was then dried over Mg_2SO_4, filtered, and concentrated. Purified by flash column chromatography (Ethyl acetate/Petroleum ether, 1:3) to afford **1** as a white foam (948 mg, 90% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.24 (m, 24H, 2×$Si(Ph)_2$, NPhth), 6.87-6.68 (m, 4H, Ar-H in OMP), 5.71 (d, *J* = 8.4 Hz, 1H, H-1), 4.54 (dd, *J* = 10.8 Hz, 8.0 Hz, 1H, H-3), 4.42 (m, 2H, H-2,H-1') , 4.00 (m, 2H, H-6), 3.85 (m, 2H, H-5, H-3'), 3.80 (d, *J* = 8.4 Hz, 1H, H-4), 3.72 (m, 1H, H-6'a), 3.71 (s, 3H, OCH_3), 3.69 (m, 1H, H-6'b), 3.59 (m, 2H, H-4',H-2'), 3.45 (dd, *J* = 9.6 Hz, 2.8Hz, 1H, H-5'), 2.68 (brs, 3H), 1.07, 0.88 (2s, 18H, 2×$C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 151.0, 135.9, 135.6, 135.6, 135.5, 133.9, 133.4, 132.8, 132.6, 132.5, 131.8, 129.9, 129.9, 129.8, 127.8, 127.8, 127.7, 118.7, 114.4, 103.9, 97.5, 82.2, 77.3, 75.2, 75.1, 73.5, 71.8, 69.8, 68.5, 63.2, 63.0, 56.0, 55.6, 26.9, 26.6, 19.3, 18.9; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{59}H_{67}NNaO_{13}Si_2Na$ 1076.4049; found 1076.4029.

Target trisaccharide 3'SLN Derivative 3

The solution of sialic acid donor **2** (646 mg, 0.87 mmol), acceptor **1**(617 mg, 0.58 mmol) and activated powdered 4 Å molecular sieves in dry MeCN (20 mL) was stirred at room temperature under an argon atmosphere for 30 min. After being cooled to -40 ℃ for 15 min, TMSOTf (31 μL, 0.18 mmol) in MeCN (0.5 mL) was added and the reaction was stirred at this temperature for 2 h until the consumption of donor monitored by TLC. The reaction was quenched by triethylamine (0.2 mL) and diluted with DCM (50 mL). The solid was filtered off through a pad of Celite and the filtrate was washed with $NaHCO_3$ (aq.) and brine, dried over Na_2SO_4, filtered, and concentrated. The concentration was dissolved in a mixture of pyridine (4 mL) and Ac_2O (2 mL) at room temperature. DMAP (32 mg) was added at 0℃ and the reaction was stirred at room temperature for 4h. After removing the solvent, the residue was finely purified by column chromatography on silica gel (DCM/MeOH, 100:1) to give the pure α-trisaccharide **3** (466 mg, 48% over 2 steps).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.25 (m, 24H, 2×$Si(Ph)_2$, NPhth), 6.92-6.54 (m, 4H, Ar-H in OMP), 5.88 (d, *J* = 8.4 Hz, 1H), 5.76 (dd, *J* = 10.0 Hz, 8.0 Hz, 1H), 5.53 (m, 1H), 5.35 (dd, *J* = 8.8 Hz, 1.6 Hz, 1H), 5.28 (d, *J* = 2.0 Hz, 1H), 5.18 (d, *J* = 10.0 Hz, 1H), 4.93 (dd, *J* = 11.6 Hz, 4.4 Hz, 1H), 4.85 (m, 1H), 4.80 (d, *J* = 7.6 Hz, 1H), 4.58 (dd, *J* = 9.6 Hz, 2.4 Hz, 1H), 4.35 (m, 2H), 4.08 (m, 1H), 4.00 (d, *J* = 10.4 Hz, 1H), 3.91 (m, 4H), 3.85 (s, 3H, OCH_3), 3.71 (m, 1H), 3.65 (s, 3H, OCH_3), 3.55 (dd, *J* = 10.8 Hz, 1.6 Hz, 1H), 3.47 (m, 2H), 2.57 (dd, *J* = 12.4 Hz, 4.4 Hz, 1H), 2.15, 2.08, 2.03, 2.01, 1.98, 1.85, 1.70 (7s, 21H, 6OAc and NHAc), 1.62 (m, 1H), 1.56 (s, 3H, OAc), 1.03, 0.98 (2s, 18H, 2×$C(CH_3)_3$);^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.4, 170.4, 170.4, 169.8, 169.7, 169.3, 167.9, 167.8, 155.2, 150.8, 135.7, 135.7, 135.5, 135.5, 134.2, 133.9, 133.7, 133.1, 132.9, 132.6, 129.9, 129.9, 129.8, 129.7, 129.6, 129.5, 127.8, 127.7, 127.6, 123.7, 123.3, 118.3, 114.4, 100.8, 96.8, 96.7, 77.3, 76.7, 75.8, 72.9, 72.7, 72.0, 71.8, 70.7, 69.6, 67.6, 67.0, 66.8, 63.1, 62.5, 59.9, 55.6, 55.1, 53.1, 49.1, 37.4, 29.8, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 27.2, 26.8, 26.7, 25.6, 23.2, 22.7, 21.5, 20.8, 20.8, 20.8, 20.7, 20.5, 19.9, 19.4, 19.0; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{85}H_{100}N_2O_{28}Si_2Na$ 1675.5899; found 1675.5879.

Conflicts of interest

There are no conflicts to declare.

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Keywords: Neu5Ac-α-2,3-LacNPhth trisaccharide • TBDPS • LacNPhth • D-glucosamine hydrochloride • sialyl phosphite donor

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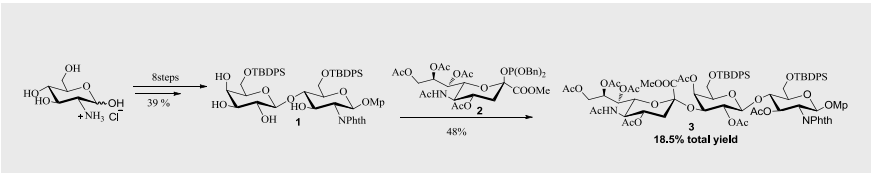

An efficient approach to synthesize a Neu5Ac-α-2,3-LacNPhth derivative **3** was developed, resulting in a total yield of 18.5% over only 10 steps starting from glucosamine hydrochloride.

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Regio/Stereoselective Glycosylation of Diol and Polyol Acceptors in Efficient Synthesis of Neu5Ac-α-2,3-LacNPhth Trisaccharide