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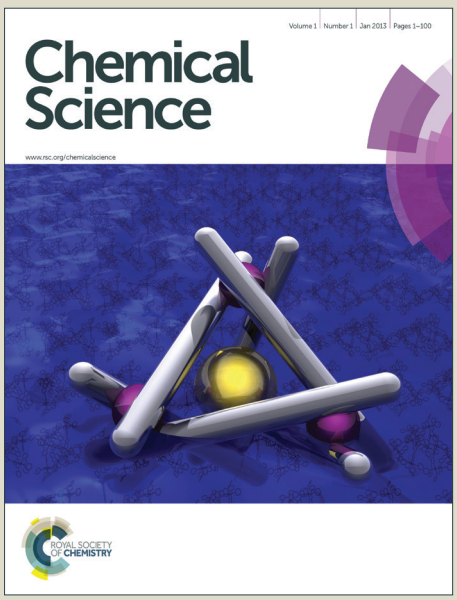

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ARTICLE

A Facile Synthesis of Sialylated Oligolactosamine Glycans from Lactose via the Lafont Intermediate

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The 2-aminophosphonium iodide lactosamine glycoside (Lafont intermediate) readily obtained from lactose has been previously shown not amenable to the derivatization for oligosaccharide synthesis, but now was successfully converted via the salicylaldehyde imine into the suitably protected Lactosamine building blocks (**13**-**16**) for the glycosylation. The titled strategy has enabled us to rapidly synthesize Neu5Ac-α-2,3LacNAc-β-1,3LacNAc pentasaccharide and Neu5Ac-α-2,3LacNAc-β-1,3LacNAc-β-1,3LacNAc heptasaccharide. Furthermore, this strategy has been adopted to synthesize other 2-aminosugars (e.g., **23**-**27**), which provides a useful method to prepare 2-aminosugar building blocks.

Introduction

The pandemic of influenza has posed a serious threat in the public, such as was evidenced by the avian influenza outbreak of H5N1 in 1997 and 2003[1], the spread of H1N1 in 2011[2], and the emergence of H7N9 in 2013.[3] The viral surface glycoprotein, hemagglutinin (HA), recognizes the sialylated glycans present on the host cell, initiating the first step of the viral entry.[4] Sialylated oligolactosamine glycan structures, including Neu5Ac-α-2,3LacNAc (3'SLN), Neu5Ac-α-2,3LacNAc-β-1,3LacNAc (3'SLN-LN), Neu5Ac-α-2,3LacNAc-β-1,3LacNAc-β-1,3LacNAc(3'SLN-LN-LN), Neu5Ac-α-2,6LacNAc (6'SLN) and Neu5Ac-α-2,6LacNAc-β-1,3LacNAc (6'SLN-LN), serve as important determinants for the influenza infection.[5] Recent glycomic analysis of human respiratory tract tissues has revealed the presence of N-glycans with various length of sialylated α2-3 oligoLacNAc extension in the human lung.[6] Regarding the novel H7N9 outbreaks, investigation of H7 receptor preference using biologically relevant glycans found in human respiratory tract will provide important implications on the host adaptation of the H7N9 viruses. In a program aiming to investigate the receptor-binding specificity of HAs from avian and human infecting H7N9 influenza viruses using STD-NMR[7], the sialylated oligolactosamine glycans will be preferably provided by chemical synthesis. Nevertheless, due to the intrinsic structural complexity, the synthesis of these glycans in a large amount is challenging.

The past decades have witnessed great advances in the construction of complex oligosaccharides, thus it is fair to state that almost any glycan could be synthesized now if given enough time and resources.[8] The future efforts are suggested to be oriented to the development of high throughput synthetic strategies and methodologies to generate both small and large quantities of complex glycans.[9] In this regard, the identification of universal building blocks and the rapid and inexpensive access to the necessary building blocks will accelerate the provision of the glycans of biological interests.[9]

In the synthesis of the sialylated oligolactosamine glycans, a bulk of the repeating unit, the lactosamine building block, is required. The lactosamine structure is present in many biologically relevant glycans, including the human milk glycan[10], Lewis X[11], α-Gal-Pentasaccharide[12], and human glycan determinants in N-linked glycoproteins, O-linked glycoproteins and glycolipds[13](Figure 1). Thus, a facile synthesis of the lactosamine building block serving as a universal building block will be of great importance in the assembly of the abovementioned glycans.

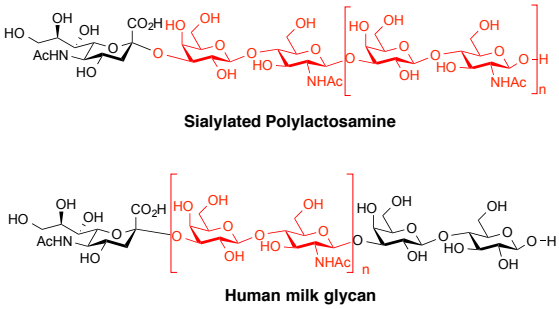
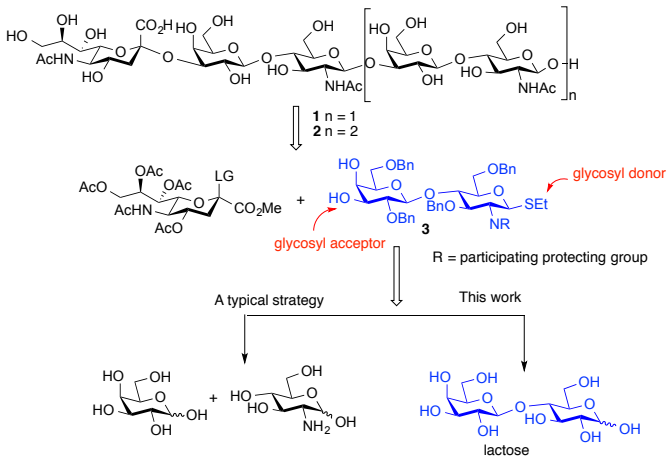


Fig. 1 Glycans containing LacNAc

The conventional strategy for the synthesis of the lactosamine building block involves coupling a suitable galactopyranosyl donor and a suitable glucosamine acceptor (commercially available *N*-acetyl lactosamine, 100 mg, 765 $ Aldrich).[14] In this regard, a lengthy and laborious synthetic route is necessary to obtain the required specific linkage in terms of both regioselectivity and anomeric stereoselectivity, and the installation of orthogonal protecting groups (e.g., 5-6 steps for each building block synthesis). Alternatively, to save efforts in glycosylation, Danishefsky and co-workers have obtained a lactosamine derivative through functionalizing the lactal via iodosulfonamidation.[15] Stütz and co-worker have applied the Heyns rearrangement to convert lactulose into a lactosamine.[16]



Scheme 1 Retrosynthesis of sialylated oligolactosamine glycans

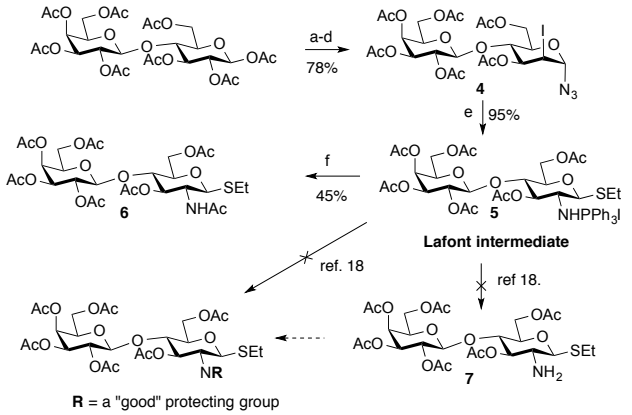
We wished to seek an alternative, robust and easy-handling method to convert inexpensive lactose (1Kg, 147$, Aldrich) into a suitably protected lactosamine building block (i.e. **3,** Scheme 1), which could well serve as both a glycosyl donor and a glycosyl acceptor, thereby enabling one to prepare sialylated oligolactosamine glycans, including 3'SLN-LN and 3'SLN-LN-LN. In our design, the properly protected thiolactosamine building block **3** is attractive, since the thioglycosides are convenient in the preparation and stable during many functional group transformations. Furthermore, in the presence of many thiophilic agents, they become reactive glycosyl donors towards glycosylations.[17] As the glycosyl acceptor, the glycosylation will take place selectively at the equatorial OH.[14c] Thus, the lactosamine building block **3** will allow for the extension of the glycan chain from either the reducing end or the non-reducing end.

Results and discussion

Synthetic plan and conversion of the Lafont intermediate

We initiated our studies by noting an early report by Lafont and co-workers.[18] They have developed an interesting synthesis of *N*-acetyl lactosamine **6** from lactose (Scheme 2). Iodoacetylation of hexa-acylated lactal obtained from lactose in overall 3 steps, followed by the glycosylation with trimethylsilyl azide, afforded compound **4**. Next, the Staudinger reaction with triphenylphosphine at the anomeric azide led *in situ* to an iminophosphorane, followed by the rearrangement with elimination of iodine at C-2. The resultant aziridine intermediate reacted with a suitable thiol (or alcohol) to afford the corresponding 2-aminophosphonium iodide lactosamine β-glycoside **5**. Indeed, the Lafont intermediate **5** could be prepared easily in a multi-gram scale.

However, a critical issue to prevent the potential application of this strategy is that the aminophosphonium intermediate **5** (i.e., Lafont intermediate) appeared very stable and could be isolated and purified by column chromatography. The conversion of this compound to its free-amino counterpart **7** was not successful at all, while the direct conversion into the acetamido compound **6** was successful but in only 45% yield.[18] The acetamido is certainly not a good N-protecting group for glycosylation, due to the formation of stable 1,2-oxazoline intermediate under the glycosylation conditions.[19] However, the direct installation of the suitable N-protecting groups to the Lafont intermediate, including Phth, Troc, and TFA, were fruitless. Thus, despite the easy and efficient preparation of *N*-acetyl lactosamine from lactose, the Lafont intermediate does not serve to lead to a useful building block for the usage of oligosaccharide synthesis.



Scheme 2 Synthesis of the Lafont intermediate from lactose.[18] (a) HBr, AcOH, CH_2Cl_2 ; (b) Zn, $CuSO_4$•$5H_2O$, AcOH, H_2O; (c) $Cu(OAc)_2$, I_2, AcOH, 80°C; (d) $TMSN_3$, TMSOTf, CH_2Cl_2, 78% over 4 steps; (e) EtSH, PPh_3, CH_2Cl_2, 4 Å MS, 95%; (f) (1) Dowex 2X8 (OH^-), column filtration; (2) NaOMe, MeOH; (3) Ac_2O, pyridine, 45% over 3 steps.

These results have indeed discouraged us. Instead of abandoning this route, we decided to seek the condition enabling the transformation of the Lafont intermediate into its free-amino counterpart **7**. In our initial efforts, various conditions, including acidic[20] and basic conditions, oxidation with H_2O_2, reduction with $LiAlH_4$, failed to give any promising result (Table 1, entry 1-5).

Interestingly, when the Lafont intemediate was treated with $KHCO_3$, the urea **8** was formed (Figure 2). We have tried many conditions (entries 8-10), but compound **8** was always the major product. Although the mechanism is not clear, it is very likely that the iminophosphorane reacted with CO_2 present in $KHCO_3$ solution to generate an isocyanate derivative, which reacted with the liberated amine to form the urea **8**.[21] We next pursued the possibility of the direct protection of **5** with a Boc group with Boc_2O/NEt_3 (Table, entry 7). Instead, a disaccharide linked with a carbodiimide bond (**9**, Figure 2) was obtained. It seems likely that CO_2 resulting from the decomposition of Boc_2O again reacted with the iminophosphorane to give the isocyanate, which underwent an aza Wittig-type reaction with a second molecule of the iminophosphorane to afford the obtained carbodiimide compound.[22] Although these efforts were not fruitful towards the desired product, the formation of compounds **8** and **9** has indicated that this stable N-P bond of the Lafont intermediate could still be amenable to the oxidative electrophilic attack.

Next, we turned our attention to see whether the Lafont intermediate could likely react with an aldehyde to form an imine, which then could be converted to the free-amino derivative easily. To our delight, anisaldehyde could react with compound **5** affording compound **10,** albeit in low yield (18%) (Table 1, entry 12). Nevertheless, after optimizing the reaction conditions, the highest yield obtained was only 30% (entry 17). After we took note of the unusually large rate and equilibrium

constant for the imine formation with salicylaldehyde resulting from the hydrogen bonding,[23] we tried to use salicylaldehyde to react with compound **5**. Gratifyingly, this time compound **11** was obtained in 53% yield (entry 18). Further optimizations revealed that the microwave condition can shorten the reaction time dramatically (from 8 h to 30 min) with a much higher yield (80%).

Table 1. Our studies to convert the Lafont intermediate to a lactosamine derivative.

Entry	Reagent	Temp.& Time	Product (%)
1	0.2 N HCl	rt. 4 d	none
2	50% H_2O_2	rt, 2 d	none
3	$KHCO_3$ (aq), EtOH	rt, 2 d	none
4	NEt_3	rt, 2 d	none
5	$LiAlH_4$	reflux, 12 h	none
6	TrocCl, NEt_3	rt, 12 h	none
7	Boc_2O, NEt_3	rt, 12 h	**9** (52)
8	$KHCO_3$ (aq), THF	40 °C, 1 d	**8** (35)
9	$KHCO_3$ (aq), Acetone	rt, 1 d	**8** (45)
10	$KHCO_3$ (aq), MeCN	rt, 1 d	**8** (40)
11	anisaldehyde, Et_3N, toluene	rt, 3 d	none
12	anisaldehyde, Et_3N, toluene	80 °C, 12 h	**10** (18)
13	anisaldehyde, Et_3N, MeCN	reflux, 12 h	**10** (0)
14	anisaldehyde, Et_3N, xylene	reflux, 12 h	**10** (10)
15	anisaldehyde, Et_3N, xylene	MW, 120 °C, 30 min	**10** (8)
16	anisaldehyde, Et_3N, xylene	MW, 140 °C, 1 h	**10** (10)
17	anisaldehyde, Et_3N, chlorobenzene	MW, 150 °C, 30 min	**10** (30)
18	salicylaldehyde, Et_3N, toluene	reflux, 8 h	**11** (53)
19	salicylaldehyde, Et_3N, chlorobenzene	reflux, 4 h	**11** (57)
20	salicylaldehyde, Et_3N, chlorobenzene	MW, 130 °C, 1 h	**11** (61)
21	salicylaldehyde, Et_3N, chlorobenzene	MW, 140 °C, 30 min	**11** (65)
22	salicylaldehyde, Et_3N, chlorobenzene (1: 2: 2)	MW, 140 °C, 30 min	**11** (80)

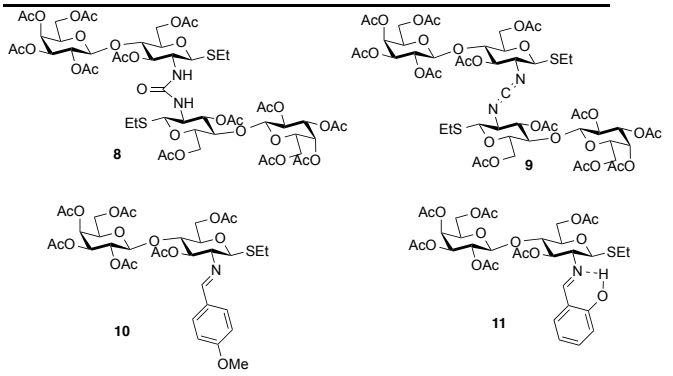
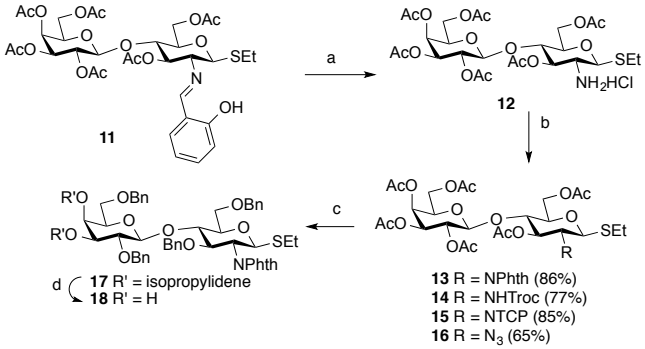


Fig. 2 The resultant products from the reactions of the Lafont intermediate under the conditions in Table 1.

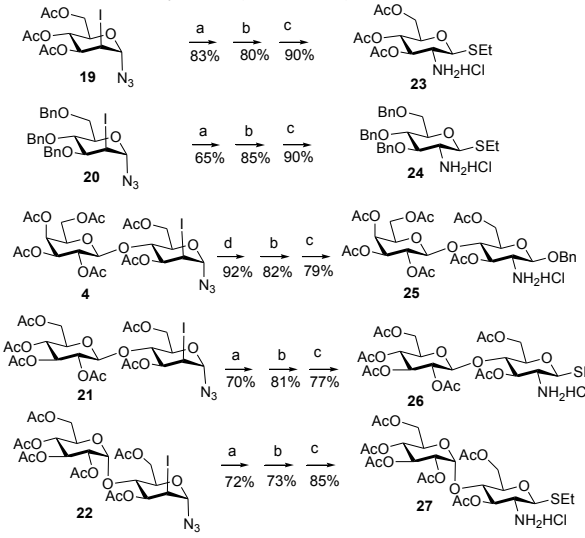


Scheme 3. Synthesis of lactosamine glycan building blocks. (a) 3 N HCl (aq), acetone/CH_2Cl_2 (8 : 1), 76%; (b) for **13**: phthalic anhydride, Et_3N, pyridine, then, Ac_2O, 95 °C; for **14**: TrocCl, CH_2Cl_2/H_2O (1 : 1), Et_3N, rt; for **15**: tetrachlorophthalic anhydride, Et_3N, pyridine, then, Ac_2O, 95 °C; for **16**: imidazole-1-sulfonyl azide hydrochloride, $NaHCO_3$, $CuSO_4{\cdot}5H_2O$, MeOH/H_2O (1:1); (c) (1) K_2CO_3, THF/MeOH (1 : 2), then H^+ resin; (2) $Me_2C(OMe)_2$, camphorsulfonic acid (3) BnBr, NaH, 4Å MS, dry DMF, 54% over 3 steps; (d) $KHSO_4{\cdot}SiO_2$, MeOH/ CH_2Cl_2 (1 : 1), 92%.

Next, the conversion of the imine **11** into the free-amino sugar **12** was uneventful with 3 N HCl aq. (Scheme 3) in 76% yield (72% for 7 gram scale). Having obtained compound **12**, we were poised to synthesize a suitable lactosamine glycosyl donor. To further exemplify the efficiency of this method, compound **12** was protected with the commonly-used Phth, Troc, TCP and azide. All the conversions were in good yields with the common preparation conditions (Scheme 3). These disaccharides could be further applied to form the β or α glycosides easily.

Extension of the strategy to other sugars to synthesize 2-aminosaccharides

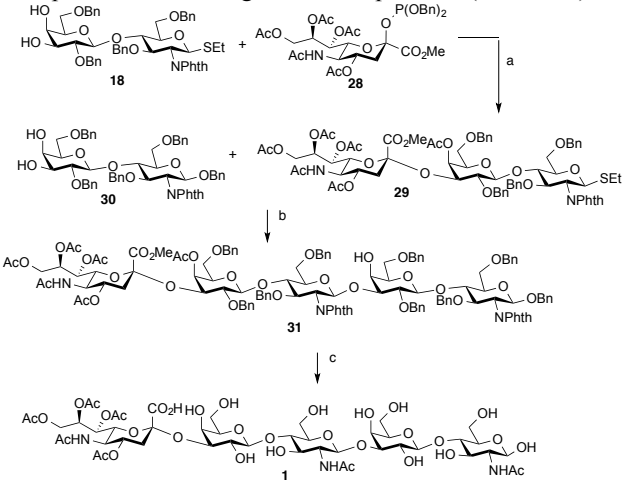
Thus, we have developed a two-step strategy to transform the Lafont intermediate into a derivatizable compound **12** (7 steps from lactose). Having established the validity of this approach, we continued to extend the principle of this strategy to prepare other types of 2-amino sugars from the corresponding compounds **19**-**22**, which were readily obtained from glycals. To our delight, various saccharides with different protecting groups could also proceed smoothly using this protocol to form corresponding 2-aminosaccharides (**23**-**27**) in overall 44-60% yields (Scheme 4).



Scheme 4 Extension of the strategy to other types of sugars. (a) EtSH, PPh_3, dry CH_2Cl_2, 4 Å MS; (b) salicylaldehyde, Et_3N, chlorobenzene; (c) 3 N HCl (aq.), acetone/CH_2Cl_2 (8 : 1); (d) BnOH, PPh_3, dry CH_2Cl_2, 4 Å MS. Compounds **19**-**22** were obtained according to the literature.[18,24,25]

Synthesis of Neu5Ac-α-2,3LacNAc-β-1,3LacNAc (3'SLN-LN) and Neu5Ac-α-2,3LacNAc-β-1,3LacNAc-β-1,3LacNAc (3'SLN-LN-LN)

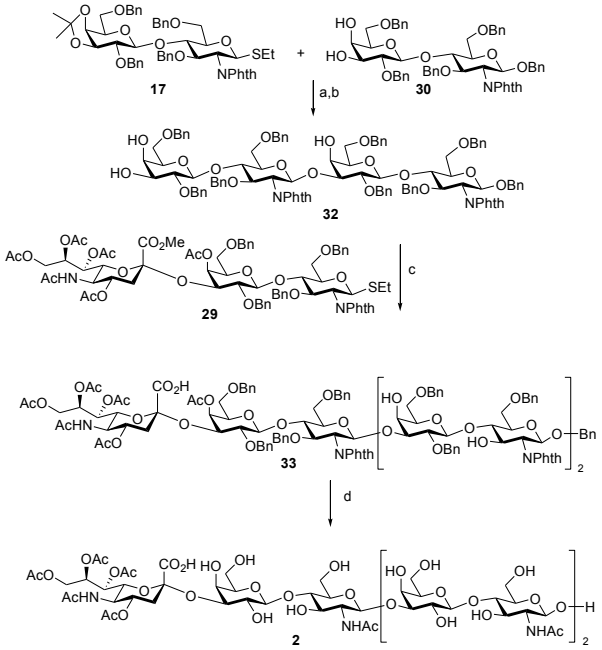
We selected Phth protected compound (i.e., **13**) as our key intermediate to advance towards the targeted sialylated oligolactosamine glycans. Compound **13** could be transformed into **17** as a suitable glycosyl donor and **18** as a suitable glycosyl acceptor, through a series of protecting group manipulations following the known protocol (Scheme 3).[26]



Scheme 5 Synthesis of 3S'LN-LN. (a) (1) TMSOTf, 4 Å MS, -40 °C to rt; (2) Ac_2O, pyridine, DMAP, 39% over 2 steps; (b) *p*-$NO_2C_6H_4SCl$/AgOTf, CH_2Cl_2, AW 300 MS, 75%; (c) (1) NaOMe, MeOH; (2) H_2O, Dowex 50; (3) $NH_2NH_2{\cdot}H_2O$, PhMe, *n*-BuOH, 90 °C; (4) Ac_2O, Et_3N, MeOH; (5) $Pd(OH)_2/C$, H_2, 3 d, 47% over 5 steps.

Compound **18** was then subjected to the glycosylation with the sialyl donor **28** to form trisaccharide **29** as the only isomer in a simlar yield as that reported.[26] Disaccharide glycosyl acceptor **30** was synthesized from **25** in a similar strategy with compound **18** and could be reacted with trisaccharide **29** to obtain the pentasaccharide **31** in 75% yield (Scheme 5). Among NIS/AgOTf[27], NIS/TfOH[28], *p*-$NO_2C_6H_4SCl$/AgOTf[29] promoting systems, the latter gave the best yield. All the acetate groups of compound **31** were removed by NaOMe in MeOH, followed by subsequent addition of water in the same flask to convert the methyl ester of the sialic acid to a carboxylic acid. Then the Phth protecting group was deprotected with hydrazine hydrate and the liberated free amine group was selectively protected with the acetate group. After removal of all the Bn groups under hydrogenation with $Pd(OH)_2/C$, compound **1** was obtained with an overall yield of 47%.

Next, we continued to synthesize 3'SLN-LN-LN. Firstly, the glycosylation between donor **17** and acceptor **30** using *p*-$NO_2C_6H_4SCl$/AgOTf promoting system afforded the tetrasaccharide in 70% yield. After deprotecting the isopropylidene group of the obtained tetrasaccharide, compound **32** was obtained in 91% yield, which was subjected to the glycosylation with trisaccharide **29**. Under the *p*-$NO_2C_6H_4SCl$/AgOTf promoted glycosylation condition, the fully protected heptasaccharide **33** was isolated in 72% yield. Following the same deprotecting procedure as that of pentasaccharide **31**, compound **2** was obtained in 41% yield over 5 steps (Scheme 6).



Scheme 6 Synthesis of 3S'LN-LN-LN. (a) *p*-$NO_2C_6H_4SCl$/AgOTf, CH_2Cl_2, AW 300 MS, 70%; (b) $KHSO_4{\cdot}SiO_2$, MeOH/DCM, 91%; (c) *p*-$NO_2C_6H_4SCl$/AgOTf, CH_2Cl_2, AW 300 MS, 72%; (d) (1) NaOMe, MeOH; (2) H_2O, Dowex 50; (3) $NH_2NH_2{\cdot}H_2O$, PhMe, *n*-

BuOH, 90 ^{o}C; (4) Ac_2O, Et_3N, MeOH; (5) $Pd(OH)_2/C$, H_2, 3 d, 41% over 5 steps.

Conclusions

In summary, we have developed a facile synthesis of the sialylated oligolactosamine glycans, including Neu5Ac-α-2,3LacNAc-β-1,3LacNAc (3'SLN-LN) and Neu5Ac-α-2,3LacNAc-β-1,3LacNAc-β-1,3LacNAc (3'SLN-LN-LN). The key feature of the current study includes a rapid and robust synthesis of a suitably protected lactosamine building block (i.e., **3**) from inexpensive lactose via the Lafont intermediate. The stable 2-aminophosphonium iodide lactosamine glycoside has been shown not amenable to transform into a useful glycosyl building block previously, while we found herein that it could react with salicylaldehyde under microwave conditions, affording an imine derivative, which upon mild acidolysis gave rise to the 2-amino lactosamine. This strategy could be extended to convert other types of sugars to form corresponding 2-aminosaccharide (**23**-**27**). The whole process can be completed in a multi-gram scale over a short time (~ 2 weeks), which provides rapid access to the necessary building blocking used in the automated glycan synthesis technology[30] for the synthesis of the 2-amino sugar containing glycans.

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Notes and references

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Electronic Supplementary Information (ESI) available: [Experimental procedures, spectral and other characterization data]. See DOI: 10.1039/b000000x/

1 (a) N. M. Ferguson, C. Fraser, C. A. Donnelly, A. C. Ghani and R. M. Anderson, *Science,* 2004, **304**, 968; (b) J. S. Peiris, W. C. Yu, C. W. Leung, C. Y. Cheung, W. F. Ng, J. M. Nicholls, T. K. Ng, K. H. Chan, S. T. Lai, W. L. Lim, K. Y. Yuen and Y. Guan, *Lancet*, 2004, **363**, 617.
2 (a) R. J. Garten, C. T. Davis, C. A. Russell, B. Shu, S. Lindstrom, A. Balish, W. M. Sessions, X. Xu, E. Skepner, V. Deyde, et al *Science,* 2009, **325**, 197; (b) G. J. D. Smith, D. Vijaykrishna, J. Bahl, S. J. Lycett, M. Worobey, O. G. Pybus, S. K. Ma, C. L. Cheung, J. Raghwani, S. Bhatt, et al *Nature,* 2009, **459**, 1122.
3 R. Gao, B. Cao, Y. Hu, Z. Feng, D. Wang, W. Hu, J. Chen, Z. Jie, H. Qiu, K. Xu, et al *N. Engl. J. Med.,* 2013, **368**, 1888.
4 J. J. Skehel and D. C. Wiley, *Annu. Rev. Biochem.,* 2000, **69**, 531.
5 (a) A. S. Gambaryan, V. E. Piskarev, I. A. Yamskov, A. M. Sakharov, A. B. Tuzikov, N. V. Bovin, N. E. Nifant'ev and M. N. Matrosovich, *FEBS Lett.,* 1995, **366**, 57; (b) A. Chandrasekaran, A. Srinivasan, R. Raman, K. Viswanathan, S. Raguram, T. M. Tumpey, V. Sasisekharan and R. Sasisekharan, *Nat. Biotechnol.*, 2008, **26**, 107.
6 T. Walther, R. Karamanska, R. W. Y. Chan, M. C. W. Chan, N. Jia, G. Air, C. Hopton, M. P. Wong, A. Dell, J. S. M. Peiris, S. M. Haslam and J. M. Nicholls, *Plos Pathog*., 2013, e1003223.
7 T. Haselhorst, J.-M. Garcia, T. Islam, J. C. C. Lai, F. J. Rose, J. M. Nicholls, J. S. M. Peiris and M. von Itzstein, *Angew. Chem. Int. Ed.,* 2008, **47**, 1910.
8 (a) A. V. Demchenko, *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*, Wiley-VCH, Weinheim, 2008; (b)Y. Wang, X.-S. Ye and L.-H. Zhang, *Org. Biomol. Chem.,* 2007, **5**, 2189; (c) X. Zhu and R. R. Schmidt, *Angew. Chem. Int. Ed.,* 2009, **48**, 1900; (d) T. J. Boltje, T. Buskas and G.-J. Boons, *Nat. Chem.,* 2009, **1**, 611; (e) P . H. Seeberger, *Chem. Soc. Rev.,* 2008, **37**, 19; (f) D. Crich, *Acc. Chem. Res.,* 2010, **43**, 1144; (g) C.-H. Hsu, S.-C. Hung, C.-Y. Wu and C.-H. Wong, *Angew. Chem. Int. Ed.,* 2011, **50**, 11872; (h) R. M. Schmaltz, S. R. Hanson and C.-H. Wong, *Chem. Rev.,* 2011, **111**, 4259; (i) Y. Li and X. Chen, *Appl. Microbiol. Biotechnol.,* 2012, **94**, 887; (j) B. Yu, J. Sun and X. Yang, *Acc. Chem. Res.,* 2012, **45**, 1227.
9 *Transforming Glycoscience: A Road Map for the Future*, Washington: National Academies Press (US), 2012.
10 C. Kunz, S. Rudloff, W. Baier, N. Klein and S. Strobel, *Annu. Rev. Nutr.,* 2000, **20**, 699.
11 P.-C. Pang, P. C. N. Chiu, C.-L. Lee, L.-Y. Chang, M. Panico, H. R. Morris, S. M. Haslam, K.-H. Khoo, G. F. Clark, W. S. B. Yeung and A. Dell, *Science,* 2011, **333**, 1761.
12 Y. Wang, X. Huang, L.-H. Zhang and X-S. Ye, *Org. Lett*., 2004, **6**, 4415.
13 R. Cummings, *Mol. BioSyst*., 2009, **5**, 1087.
14 (a) G. Srivastava and O. Hindsgaul, *J. Carbohydr. Chem.,* 1991, **10**, 927; (b) T. K. K. Mong, C.-Y. Huang and C.-H. Wong, *J. Org. Chem.,* 2003, **68**, 2135; (c) T. Buskas, P. Konradsson and S. Oscarson, *J. Carbohydr. Chem.,* 2001, **20**, 569; (d) H.-Y. Liao, C.-H. Hsu, S.-C. Wang, C.-H. Liang, H.-Y. Yen, C.-Y. Su, C.-H. Chen, J.-T. Jan, C.-T. Ren, C.-H. Chen, et al *J. Am. Chem. Soc.,* 2010, **132**, 14849; (e) Z. Tu, H.-W. Hsieh, C.-M. Tsai, C.-W. Hsu, S.-G. Wang, K.-J. Wu, K.-I. Lin and C.-H. Lin, *Chem. Asian J.,* 2013, **8**, 1536.
15 P. P. Deshpande, H. M. Kim, A. Zatorski, T.-K. Park, G. Ragupathi, P. O. Livingston, D. Live and S. J. Danishefsky, *J. Am. Chem. Soc.,* 1998, **120**, 1600.
16 (a) T. M. Wrodnigg and A. E. Stütz, *Angew. Chem. Int. Ed.,* 1999, **38**, 827; (b) A. E. Stütz, G. Dekany, B. Eder, C. Illaszewicz and T. M. Wrodnigg, *J. Carbohydr. Chem.,* 2003, **22**, 253; (c) Y. Shan, F. Oulaidi and M. Lahmann, *Tetrahedron Lett.,* 2013, **54**, 3960.

17 For a review, see: J. D. C. Codee, R. E. J. N. Litjens, L. J. van den Bos, H. S. Overkleeft and G. A. van der Marel, *Chem. Soc. Rev.,* 2005, **34**, 769.
18 (a) D. Lafont, P. Boullanger, F. Carvalho and P. Vottero, *Carbohydr. Res.,* 1997, **297**, 117; (b) D. Lafont, P. Guilloux and G. Descotes, *Carbohydr. Res*., 1989, **193**, 61.
19 A. F. G. Bongat and A. V. Demchenko, *Carbohydr. Res*., 2007, **342**, 374.
20 X. Wang, X. Wang, X. Tan, J. Lu, K. W. Cormier, Z. Ma and C. Chen, *J. Am. Chem. Soc.,* 2012, **134**, 18834.
21 (a) P. Molina, M. Alajarin and A. Arques, *Synthesis,* 1982, 596; (b) E. W. van Tilburg, A. D. Windhorst, M. van der Mey and J. D. M. Herscheid, *J. Labelled Compd. Radiopharm.,* 2006, **49**, 321.
22 P. Molina, M. Alajarín, P. Sánchez-Andrada, J. Elguero, and M. L. Jimeno, *J. Org. Chem.,* 1994, **59**, 7306.
23 P. George, C. W. Bock and M. Trachtman, *J. Mol. Struct.(THEOCHEM),* 1985, **133**, 11.
24 D. Lafont, B. Gross, R. Kleinegesse, F. Dumoulin and P. Boullanger, *Carbohydr. Res.,* 2001, **331**, 107.
25 D. W. Gammon, H. H. Kinfe, D. E. De Vos, P. A. Jacobs and B. F. Sels, *J. Carbohydr. Chem.,* 2007, **26**, 141.
26 P. Nagorny, B. Fasching, X. Li, G. Chen, B. Aussedat and S. J. Danishefsky, *J. Am. Chem. Soc.,* 2009, **131**, 5792.
27 P. Konradsson, U. E. Udodong and B. Fraser-Reid, *Tetrahedron Lett.,* 1990, **31**, 4313.
28 G. H. Veeneman, S. H. van Leeuwen and J. H. van Boom, *Tetrahedron Lett.,* 1990, **31**, 1331.
29 D. Crich, F. Cai and F. Yang, *Carbohydr. Res.,* 2008, **343**, 1858.
30 O. J. Plante, E. R. Palmacci and P. H. Seeberger, *Science,* 2001, **291**, 1523.

