Chemical Science

EDGE ARTICLE

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Cite this: *Chem. Sci.*, 2014, **5**, 3634

A facile synthesis of sialylated oligolactosamine glycans from lactose *via* the Lafont intermediate†

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Received 7th April 2014
Accepted 17th May 2014

DOI: 10.1039/c4sc01013b

www.rsc.org/chemicalscience

The 2-aminophosphonium iodide lactosamine glycoside (Lafont intermediate) readily obtained from lactose has been previously shown not to be amenable to derivatization for oligosaccharide synthesis, but has now been successfully converted *via* the salicylaldehyde imine into suitably protected lactosamine building blocks (**13–16**) for glycosylation. The titled strategy has enabled us to rapidly synthesize the 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 for the synthesis of other 2-amino sugars (*e.g.*, **23–27**), which provides a useful method for the preparation of 2-amino sugar 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 influenza infection.[5] Recent glycomic analysis of human respiratory tract tissues has revealed the presence of N-glycans with various length of sialylated α-2,3 oligoLacNAc extension in the human lung.[6] Regarding the novel H7N9 outbreaks, investigation of H7 receptor preference using biologically relevant glycans found in the human respiratory tract will provide important implications for 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 large amounts is challenging.

The past decades have witnessed great advances in the construction of complex oligosaccharides, and thus it is fair to state that almost any glycan could be synthesized now if given enough time and resources.[8] 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 glycans of biological interest.[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] (Fig. 1). Thus, a facile synthesis of the lactosamine building block serving as a universal building block will be of

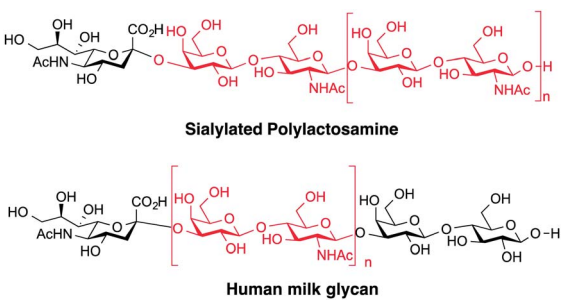

Fig. 1 Glycans containing LacNAc.

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† Electronic supplementary information (ESI) available: Experimental procedures, spectral and other characterization data. See DOI: 10.1039/c4sc01013b

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great importance in the assembly of the above-mentioned glycans.

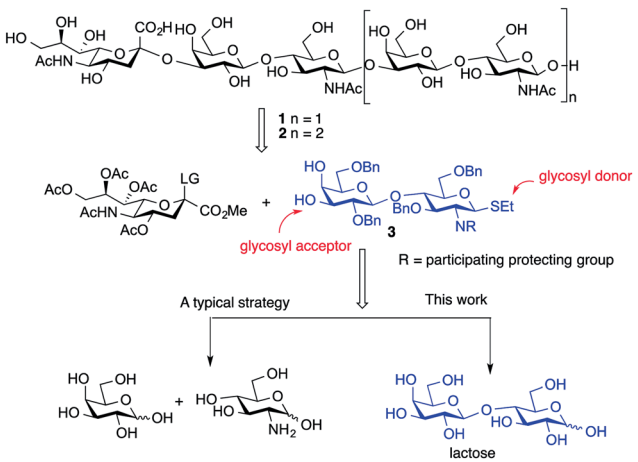
The conventional strategy for synthesis of the lactosamine building block involves coupling a suitable galactopyranosyl donor and a suitable glucosamine acceptor (commercially available *N*-acetyl lactosamine, 100 mg, 765$, Aldrich).[14] In this regard, a lengthy and laborious synthetic route is necessary 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 the synthesis of each building block). 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-workers have applied the Heyns rearrangement to convert lactulose into a lactosamine.[16]

We wished to seek an alternative, robust and easy-handling method to convert inexpensive lactose (1 kg, 147$, Aldrich) into a suitably protected lactosamine building block (*i.e.* **3**, Scheme 1), which could serve effectively 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 thioglycosides are convenient in the preparation and are 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.

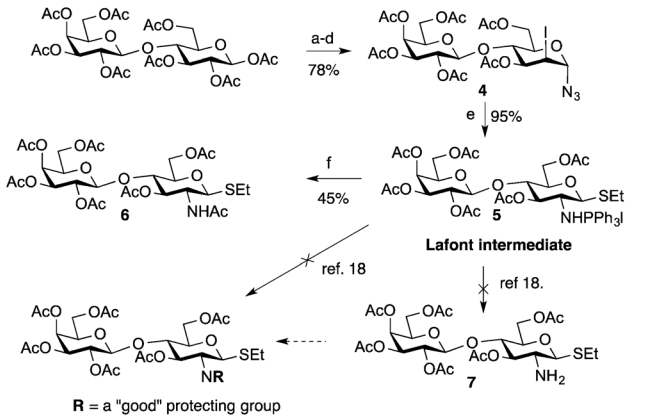
Results and discussion

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



Scheme 1 Retrosynthesis of sialylated oligolactosamine glycans.



Scheme 2 Synthesis of the Lafont intermediate from lactose.[18] *Reagents and conditions*: (a) HBr, AcOH, CH_2Cl_2; (b) Zn, $CuSO_4 \cdot 5H_2O$, 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.

the hexa-acylated lactal obtained from lactose in overall 3 steps, followed by 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 rearrangement with the 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 on 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 to be 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 the stable 1,2-oxazoline intermediate under the glycosylation conditions.[19] However, the direct installation of suitable N-protecting groups on 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 usage in oligosaccharide synthesis.

These results have indeed discouraged us. Instead of abandoning this route, we decided to seek the conditions 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, and reduction with $LiAlH_4$, failed to give any promising results (Table 1, entry 1–5).

Interestingly, when the Lafont intermediate was treated with $KHCO_3$, the urea **8** was formed (Fig. 2). We have tried many

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

Entry	Reagents	Temperature and time	Product (%)
1	0.2 M HCl	rt, 4 days	None
2	50% H_2O_2	rt, 2 days	None
3	$KHCO_3$ (aq), EtOH	rt, 2 days	None
4	NEt_3	rt, 2 days	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 day	**8** (35)
9	$KHCO_3$ (aq), acetone	rt, 1 day	**8** (45)
10	$KHCO_3$ (aq), MeCN	rt, 1 day	**8** (40)
11	Anisaldehyde, Et_3N, toluene	rt, 3 days	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)

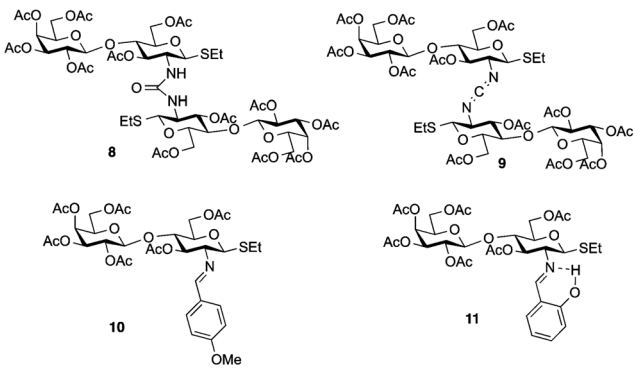
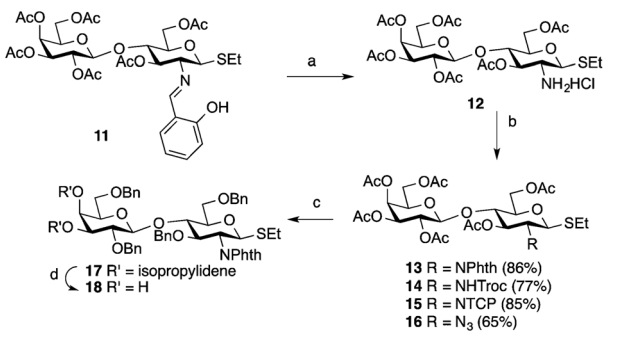


Fig. 2 The resultant products from the reactions of the Lafont intermediate under the conditions in Table 1.

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 using Boc_2O/NEt_3 (Table 1, entry 7). Instead, a disaccharide linked with a carbodiimide bond (**9**, Fig. 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 the stable N–P bond of the Lafont intermediate could still be amenable to 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 could then be converted easily to the free-amino derivative. 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 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



Scheme 3 Synthesis of lactosamine glycan building blocks. *Reagents and conditions*: (a) 3 M 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, 4 Å MS, dry DMF, 54% over 3 steps; (d) $KHSO_4 \cdot SiO_2$, MeOH–CH_2Cl_2 (1 : 1), 92%.

revealed that the microwave condition can shorten the reaction time dramatically (from 8 h to 30 min) with a much higher yield (80%).

Next, the conversion of the imine **11** into the free-amino sugar **12** was uneventful with 3 M HCl aq. (Scheme 3) in 76% yield (72% for the 7-g 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 using 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

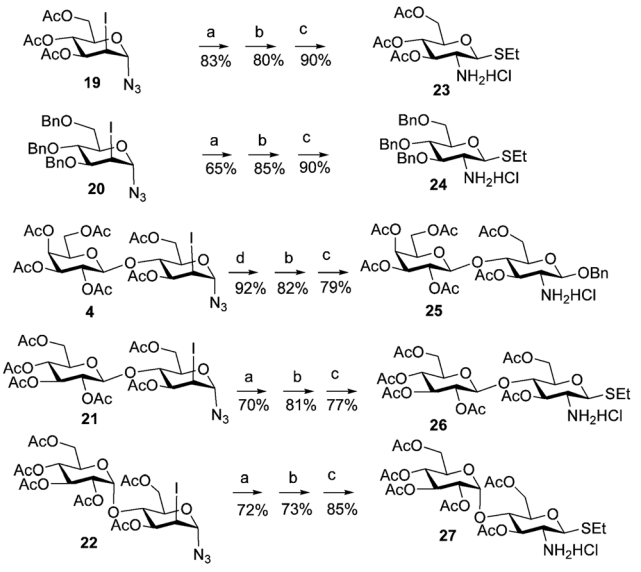
Thus, we have developed a two-step strategy to transform the Lafont intermediate into a derivatizable compound **12** (7 steps from lactose). Having established the validity of this approach, we continued to extend the principle of this strategy to prepare other types of 2-amino sugars from the corresponding 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 the corresponding 2-aminosaccharides (**23–27**) in 44–60% overall yields (Scheme 4).

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)

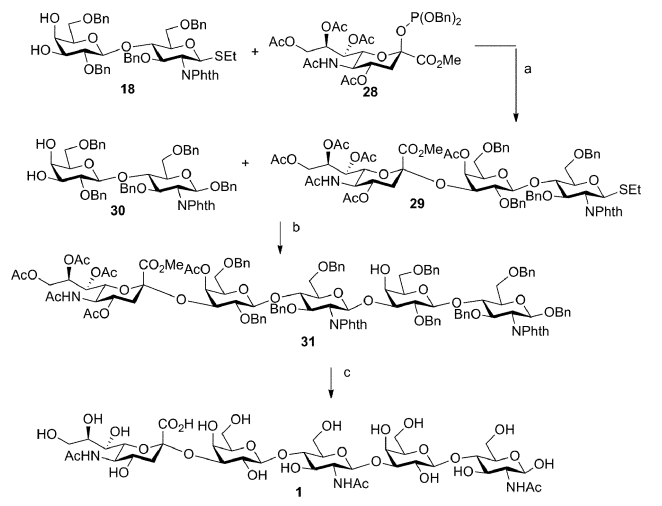
We selected the Phth-protected compound (*i.e.*, **13**) as our key intermediate to advance towards the targeted sialylated oligolactosamine glycans. Compound **13** could be transformed into **17** as a suitable glycosyl donor and **18** as a suitable glycosyl acceptor, through a series of protecting-group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

Compound **18** was then subjected to glycosylation with the sialyl donor **28** to form trisaccharide **29** as the only isomer in a similar yield as that reported.[26] Disaccharide glycosyl acceptor **30** was synthesized from **25** through 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] and *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 the subsequent addition of water to 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%.

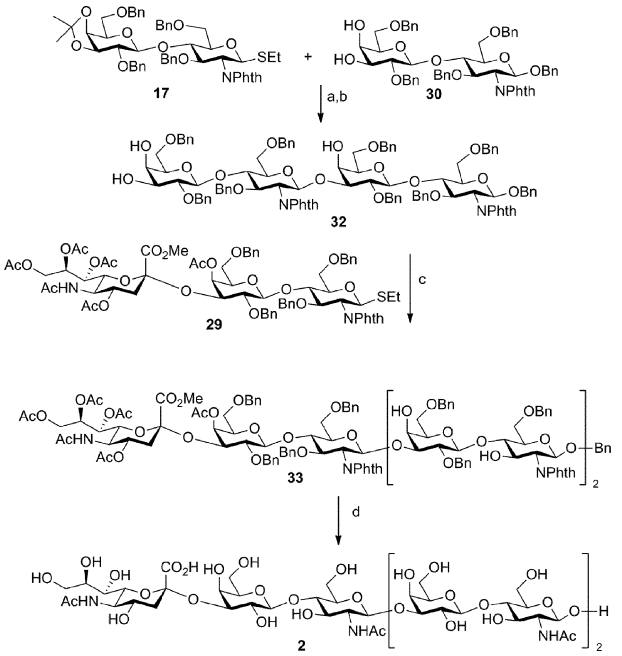
Next, we continued to synthesize 3′SLN-LN-LN. Firstly, the glycosylation between donor **17** and acceptor **30** using the *p*-$NO_2C_6H_4SCl$/AgOTf-promoting system afforded the tetrasaccharide in 70% yield. After deprotecting the isopropylidene group of the obtained tetrasaccharide, compound **32**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



Scheme 4 Extension of the strategy to other types of sugars. *Reagents and conditions*: (a) EtSH, PPh_3, dry CH_2Cl_2, 4 Å MS; (b) salicylaldehyde, Et_3N, chlorobenzene; (c) 3 M 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]



Scheme 5 Synthesis of 3S′LN–LN. *Reagents and conditions*: (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 days, 47% over 5 steps.



Scheme 6 Synthesis of 3S′LN-LN-LN. *Reagents and conditions*: (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 °C; (4) Ac_2O, Et_3N, MeOH; (5) $Pd(OH)_2/C$, H_2, 3 days, 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 previously been shown not to be amenable to transformation into a useful glycosyl building block; however, 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 the corresponding 2-aminosaccharides (**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 automated glycan synthesis technology[30] for the synthesis of the 2-amino sugar-containing glycans.

Acknowledgements

The work was supported by the National Basic Research Program of China (973 Program, 2013CB836900) and the Area of Excellence Scheme of the University Grants Committee (AoE/M-12/06).

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