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Carbohydrate Research 343 (2008) 1540–1552
Carbohydrate RESEARCH

Review

C-5 Modifications in *N*-acetyl-neuraminic acid: scope and limitations

Cristina De Meo* and Uvege Priyadarshani

Department of Chemistry, Southern Illinois University Edwardsville, Edwardsville, IL 62026, USA

Received 21 February 2008; received in revised form 2 April 2008; accepted 6 April 2008
Available online 10 April 2008

Abstract—Glycoconjugates containing sialic acid are involved in a large variety of biological phenomena, including cell–cell adhesion, recognition by viruses and bacteria, and oncogenesis. Therefore, they are important synthetic targets for the design of drugs and vaccines. In the last decades, different methodologies that improve yield and stereoselectivity in sialylation reactions have been investigated. This review summarizes the latest developments in the synthesis of C-5 modified sialic acid glycosyl donors and glycosyl acceptors and their application in the synthesis of α-sialosides.

Keywords: Sialylation; Amino protecting groups; Glycosylation; Stereoselectivity

Contents

1. Introduction

Glycoconjugates containing sialic acid are important synthetic targets due to their active participation in a wide variety of biological phenomena, ranging from cell–cell adhesion and recognition, to pathogen attack and oncogenesis.[1–4] The most widespread sialic acid is *N*-acetyl-neuraminic acid (Neu5Ac, Fig. 1), which is naturally found α-(2→3) or α-(2→6)-linked to galactose and α-(2→6)-linked to *N*-acetyl-galactosamine (e.g., α-Neu5Ac-(2→3)-Gal, α-Neu5Ac-(2→6)-Gal, and α-Neu5Ac-(2→6)-GalNAc). The disialosyl structures α-Neu5Ac-(2→8)-Neu5Ac and α-Neu5Ac-(2→9)-Neu5Ac have also been found as constituents of glycoproteins and glycolipids (Fig. 1).[2]

The stereoselective synthesis of α-sialosides in high yield is extremely challenging mainly due to the destabilizing presence of the C-1 carboxylic group and to the lack of a hydroxyl group at C-3. Thus, upon the departure of the leaving group, the resulting carbocation is not assisted by a stereocontrolling neighboring group and therefore an anomeric mixture is often produced.

* Corresponding author. Tel.: +1 618 650 3170; e-mail: cdemeo@siue.edu

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doi:10.1016/j.carres.2008.04.007

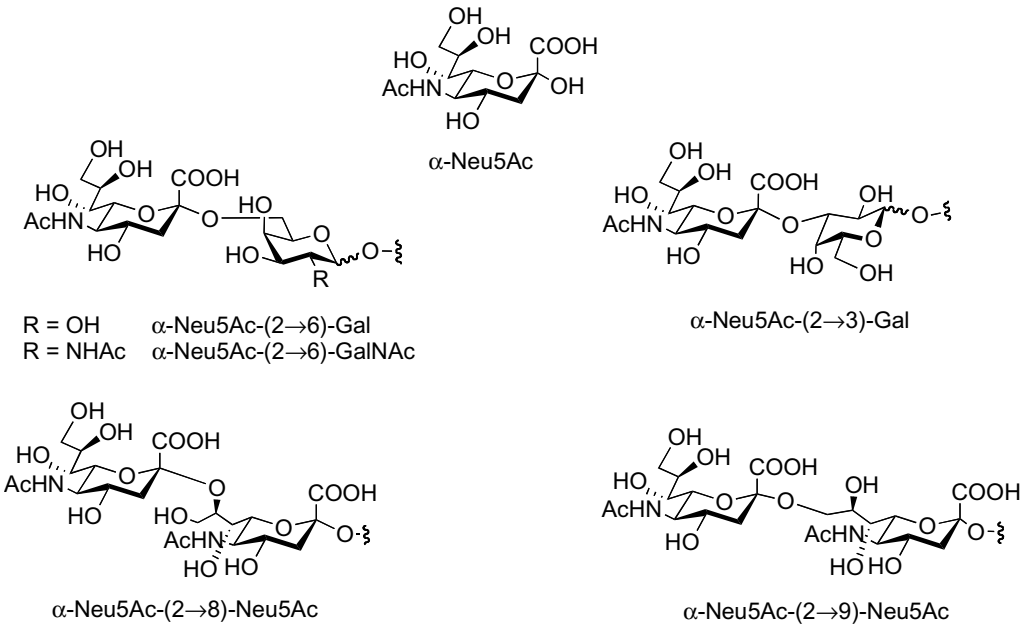
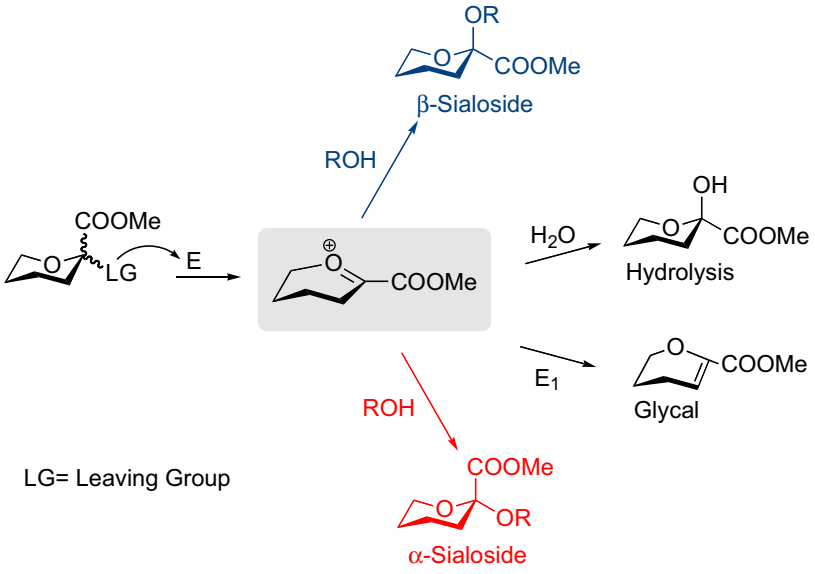


Figure 1. *N*-Acetyl-neuraminic acid and its natural linkages.



Scheme 1. General mechanism of sialylation reactions.

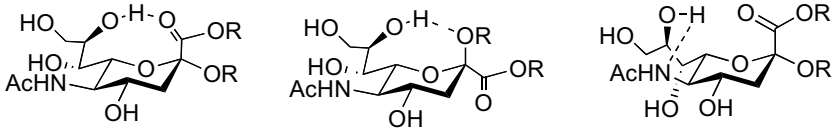
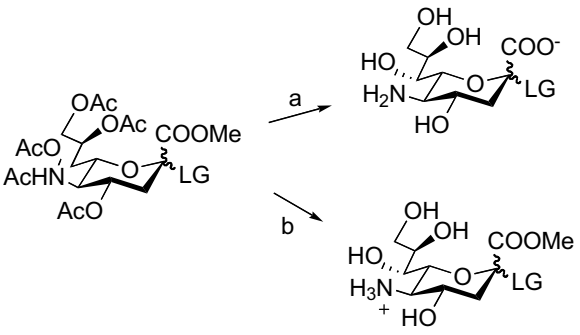


Figure 2. Proposed H-bonds of 8-OH.

In addition, competition with E1 elimination and nucleophilic attack of water (hydrolysis) are other factors that decrease the overall yield (Scheme 1). The synthesis of the disialosyl structure α-Neu5Ac-(2→8)-Neu5Ac linkages is further complicated by the low reactivity of the hydroxyl group at C-8 in the sialosyl acceptor, which has been related to its involvement in H-bonds (Fig. 2).[5–8]

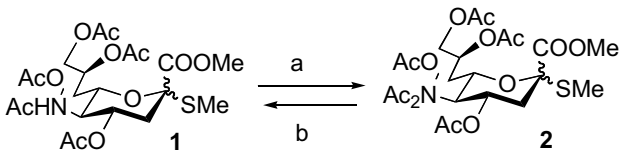


Scheme 2. Reagents and conditions: (a) $Ba(OH)_2$, H_2O, 90 °C, 19 h or NaOH, 100 °C, 48 h; (b) MsOH, MeOH, 65 °C, 24 h.

To improve the glycosylation outcome toward the desired α-anomer, different strategies have been proposed in the past decades, including varying the nature of the leaving group, solvent, and promoters. Structurally modified derivatives at C-1, C-3, and C-5 have been also investigated.[9–13] This review summarizes the most recent developments in the C-5 modification strategies for the synthesis of α-sialosides, and discusses their advantages and disadvantages. A detailed description of the following C-5 structural modifications is provided: *N*-acetylacetamido (NAc_2), azido (N_3), *N*-trifluoroacetyl (NHTFA); *N*-trichloroethoxycarbonyl (NHTroc), 5-*N*,4-*O*-oxazolidinone and its N-acetylated version. The last part of the review is dedicated to very recent or less exploited developments: the use of 1,5-lactams, 5-*N*-*t*-butoxycarbonylacetamido (NAcBoc), phthalimido (NPhth) and 5-*N*,7-*O*-oxazinone groups.

2. Acetamido deprotection methods: an overview

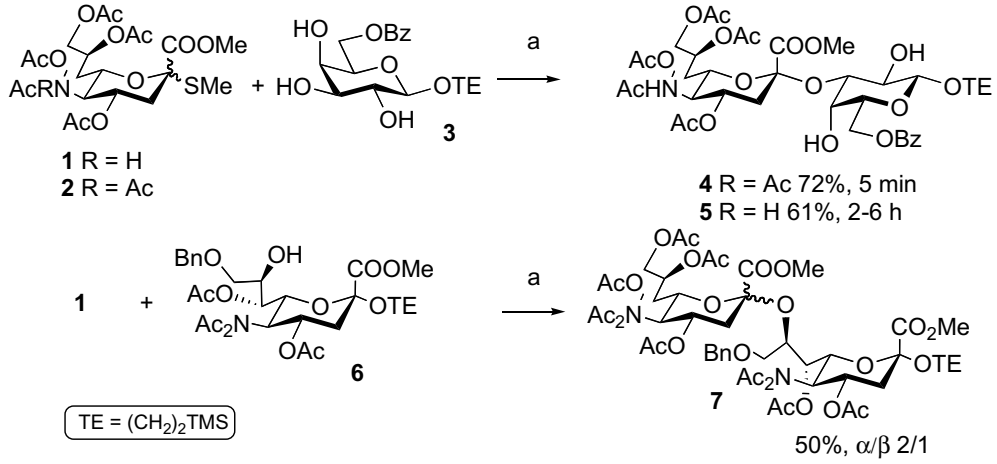
The majority of the N-modifications investigated requires a complete deprotection of the natural acetamido group to yield a free amine. The removal of the 5-*N* acetyl group can be accomplished under basic (hydrazine[14,15] sodium[16] or barium[17] hydroxide) or acidic conditions (methanesulfonic acid).[18] In general, both conditions offer high yields of the deprotected product (~70–90%); however, deprotection in acidic media offers the advantage of maintaining the methyl ester functionality (if present), which is otherwise lost in the presence of a base (Scheme 2).



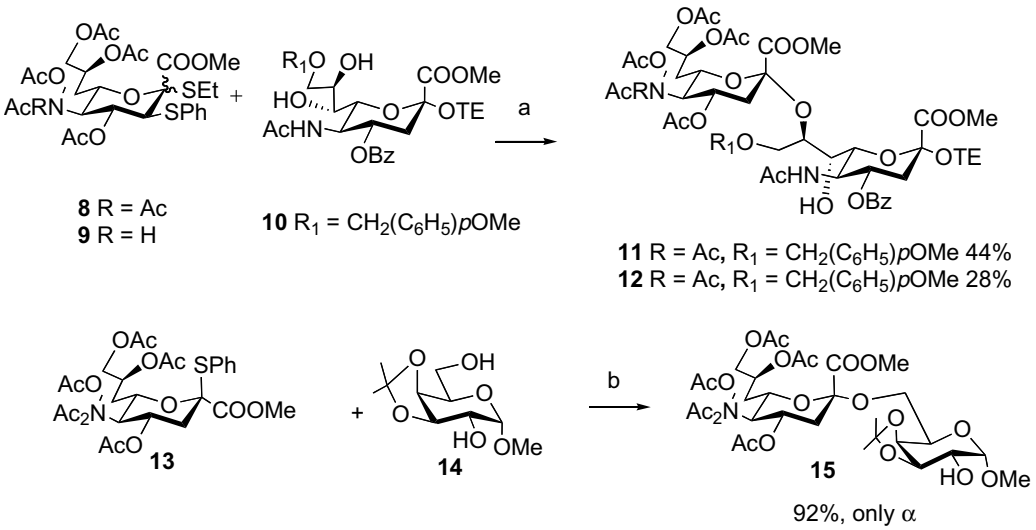
Scheme 3. Reagents and conditions: (a) $CH_2{=}C(CH_3)OAc$, TsOH, 65 °C, 99%; (b) (i) MeONa, MeOH; (ii) Ac_2O, pyridine.

3. *N*-Acetylacetamido (NAc_2)

The introduction of an additional acetyl group is undoubtedly the most straightforward and simple procedure of all investigated C-5 modifications, as neither N-acetylation nor N-deacetylation requires additional synthetic steps for protecting group manipulations. The additional acetyl group at the C-5 position can, in fact, be easily introduced directly from the fully deprotected Neu5Ac with concomitant O-acetylation (or from the N-monoacetylated donor **1**). It is removed under Zémplen deacetylation conditions with concomitant *O*-acetyl group removal (Scheme 3). The higher reactivity of methylthio 5-*N*-acetylacetamido derivative **2**, in comparison to the corresponding mono-N-acetylated donor **1**, was initially reported by Boons and Demchenko for the synthesis of α-(2→3)-linked disaccharides and α-(2→8)-linked dimers.[19,20]



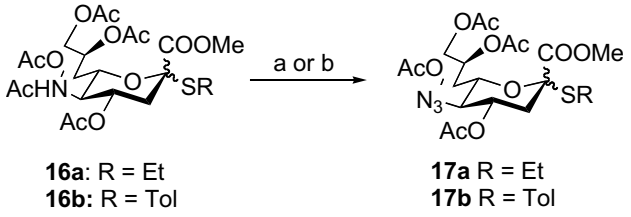
Scheme 4. Reagents and conditions: (a) NIS, TfOH, MS 3 Å, MeCN, −40 °C.



Scheme 5. Reagents and conditions: (a) AgOTf, MeSBr, MS 3 Å, MeCN, CH_2Cl_2, −45 °C; (b) Ph_2SO, TTBP, Tf_2O, CH_2Cl_2, −78 °C.

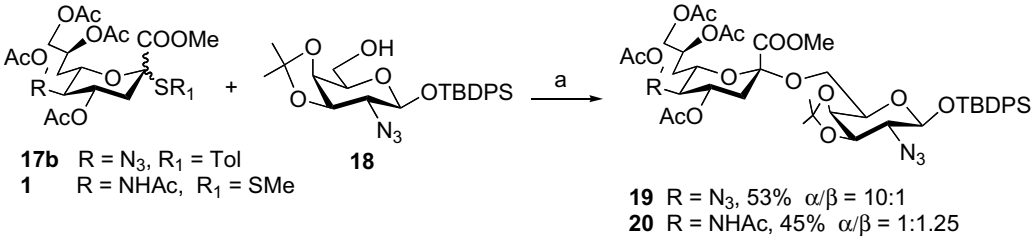
Thus, when sialosyl donor **2** was coupled with galactosyl acceptor **3**, the desired disaccharide **4** was obtained in less than 5 min in 72% yield, whereas the monoacetylated donor **1** gave the corresponding disaccharide **5** in 61% yield after a much longer reaction time (2–6 h, Scheme 4). Acetylation of the acetamido group at C-5 has been also used for the synthesis of α-(2→8) dimeric linkages, which are complicated by the low reactivity of the acceptor, as mentioned above. Thus, when sialosyl donor **1** was coupled with sialosyl acceptor **6**, also bearing an acetylacetamido group at C-5, the desired dimer **7** was obtained in 50% yield as 2:1 α/β anomeric mixture. Similar glycosylations using common 5-acetamido donors and acceptors gave low yield of the product,[21] suggesting an important role of the C-5 protecting group also in the reactivity of sialosyl acceptors. In this respect, it has been proposed that the reactivity of the C-8 hydroxyl is inversely correlated to the basicity of nitrogen at C-5. Thus, electron withdrawing substituents at the C-5 amino group would weaken the H-bond with 8-OH, increasing therefore its nucleophilicity (Fig. 2).[22]

Modification at C-5 such as NAc_2 has been used in combination with other synthetic strategies such as C-3 modifications (indirect sialylation) and promoter investigations.[23–25] For example, ethylthio-3-thio-

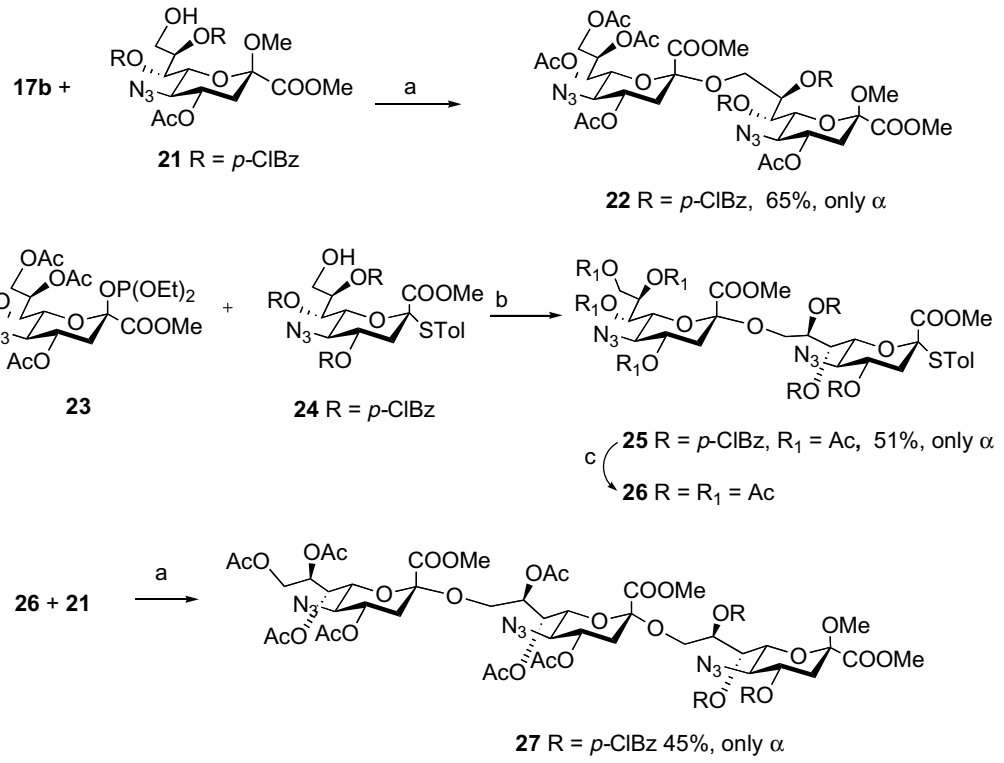


Scheme 6. Reagents and conditions: (a) (**16a**) (i) KOH, EtOH; (ii) TfN_3, DMAP; (iii) Ac_2O, pyridine; (iv) CH_2N_2, 63% overall yield; (b) (**16b**): (i) MsOH, MeOH, 55%; (ii) TfN_3, $CuSO_4{\cdot}5H_2O$, MeOH; (iii) Ac_2O, pyridine, 66% over two steps.

phenyl-5-*N*-acetylacetamido donor **8** gave higher yields than the corresponding monoacetylated donor **9** with a series of different glycosyl acceptors. In particular, sialylation of **8** with glycosyl acceptor **10** gave the α dimer **11** in 44% yield, whereas the corresponding monoacetylated counterpart **9** gave the α-linked dimer **12** in 28% yield (Scheme 5).[23,24] More recently, high yields were reported when sialosyl donor **13** was coupled with different acceptors using the Ph_2SO–TTBP–Tf_2O promoter system. For example, coupling of **13** with galactosyl acceptor **14** gave the desired disaccharide **15** in 92% yield as the α-anomer only.[25]



Scheme 7. Reagents and conditions: NIS, TfOH, MS 3 Å, MeCN, −40 °C.



Scheme 8. Reagents and conditions: (a) NIS, TfOH, MS 3 Å, MeCN, −40 °C; (b) TMSOTf, MS 3 Å, MeCN, −40 °C; (c) (i) NaOMe, MeOH; (ii) Ac_2O, Py.

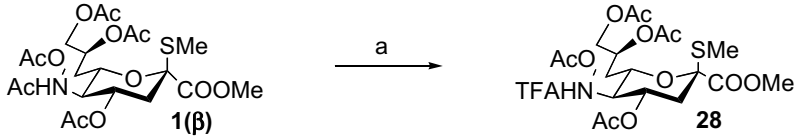
4. Azido (N_3)

Conversion of the C-5 position of *N*-acetyl-neuraminic acid into an azido (N_3) group has been accomplished by enzymatic[26–30] and chemical methods.[31–34] In general, enzymatic synthesis of 5-azido sialic acid can be accomplished by treatment of the 2-azido-2-deoxy mannose precursor in the presence of sodium pyruvate and *N*-acetyl-neuraminic acid aldolase. As example of chemical methods, it is possible to convert thiosialosyl donors **16a**,**b** in azido-bearing donors **17a**,**b** using trifluoromethanesulfonyl azide (triflic azide, TfN_3) as the diazo transfer reagent (Scheme 6).[32,33,35] Removal of the azido group can be accomplished by catalytic hydrogenolysis to give a free amine that can be further derivatized.[36,37]

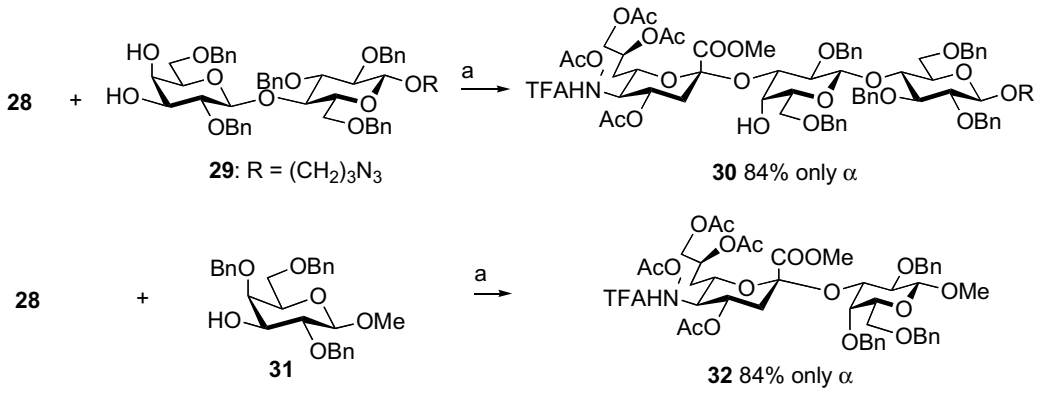
The higher stereocontrol of azido-bearing sialyl donor **17b** has been demonstrated by coupling with glycosyl acceptor **18** for the synthesis of α-(2→6) linkages, obtaining the desired disaccharide **19** in 53% yield as 10:1 α/β mixture. Similar glycosylation using C-5 acetamido thiomethyl donor **1** gave the corresponding disaccharide **20** as 1:1.25 α/β mixture (Scheme 7).

Higher stereoselectivities have also been reported for the synthesis of α-(2→9) dimers. Thus, coupling of sialosyl donor **17b** with sialosyl acceptor **21** also bearing N_3 at C-5 gave the desired (2→9) linked dimer **22** in 65% yield as the α-anomer only (Scheme 8). Similarly, selective activation of phosphite donor **23** over thioglycoside acceptor **24** gave disaccharide **25** in 51% yield as the α anomer only.[33] Protecting group manipulations converted **25** into the fully acetylated glycosyl donor **26**, which was coupled with glycosyl acceptor **21** to give trimer **27** in 45% yield with complete stereoselectivity.

Similar results have been reported using 5-azido sialyl fluoride donor.[38] Unfortunately, the azido group's higher control on stereoselectivity in glycosylation reactions is also associated with a deactivating effect when compared to the acetamido counterpart. This effect becomes more prominent for the coupling with sterically hindered and/or less reactive secondary acceptors, such as



Scheme 9. Reagents and conditions: (a) (i) MsOH, MeOH, 65 °C; (ii) CF_3COOMe, Et_3N, MeOH; (iii) Ac_2O, pyridine.



Scheme 10. Reagents and conditions: (a) NIS, TfOH, MS3 Å, MeCN, −35 °C.

the synthesis of α-(2→3) galactosyl derivatives and α-(2→8) dimers. For the latter, the coupling between a 5-azido perbenzylated thioglycoside donor and a 5-azido sialyl acceptor did not give any dimeric product.[39]

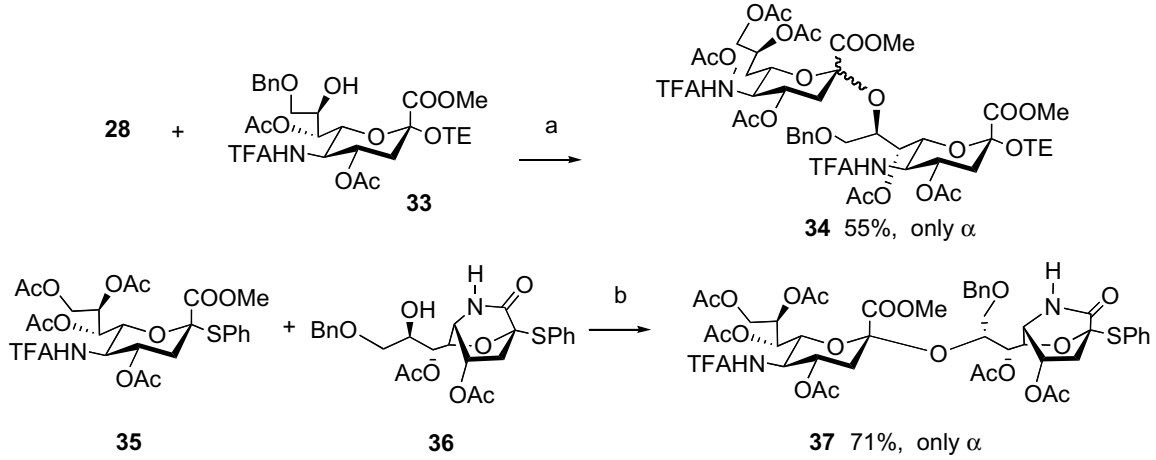
5. Trifluoroacetamido (NHTFA)

The introduction of a trifluoroacetyl group can be accomplished by complete deprotection in acidic conditions followed by selective N-acylation with methyl trifluoroacetate in the presence of triethylamine and O-acetylation.[18,40] Thus, conversion of sialosyl donor **1** into 5-trifluoroacetamido donor **28** was accomplished in three steps in 73% yield (Scheme 9).[22] The removal of the TFA group can be performed under basic conditions in the presence of sodium hydroxide.[22]

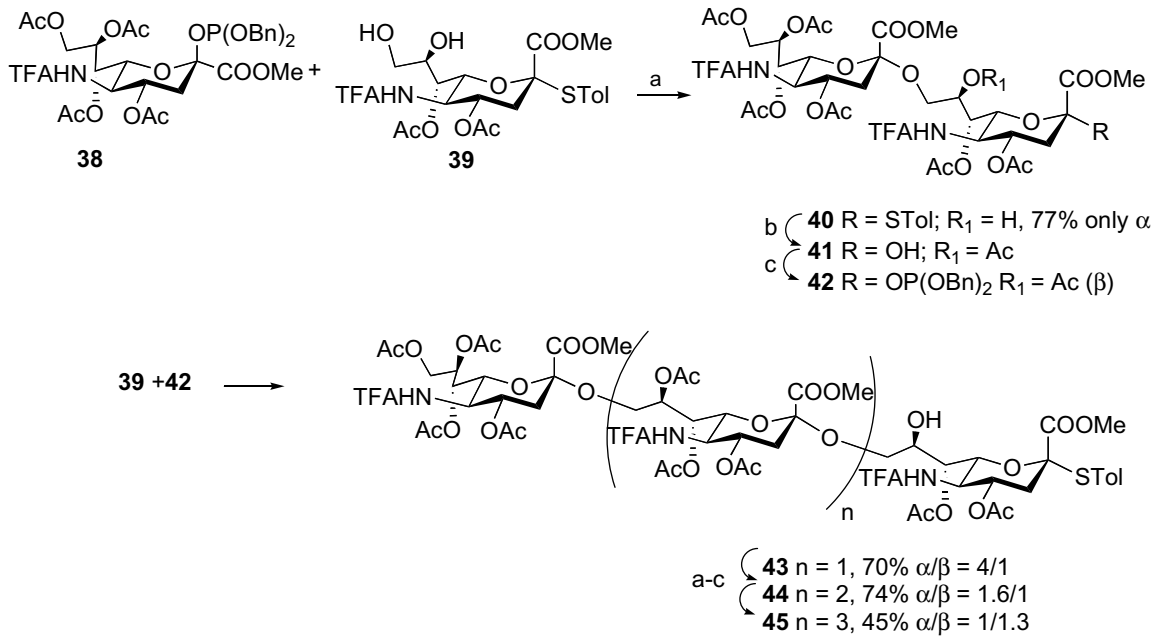
For the synthesis of an α-(2→3) glycosyl linkage, trifluoroacetyl-modified sialyl donors gave high yields and stereoselectivities when coupled with hindered glycosyl acceptors. For example, sialosyl donor **28** was coupled with glycosyl acceptor **29** to give the desired disaccharide **30** in 84% yield as the α-anomer. Similar results were obtained by coupling **28** with galactosyl acceptor **31** (Scheme 10). On the other hand, when **28** was coupled with more reactive/less hindered secondary acceptors or primary acceptors, a decrease in regioselectivity and stereoselectivity was also observed.[41]

Perhaps the most efficient application of trifluoroacetamido modification is to the synthesis of α-(2→8) and α-(2→9) linked dimers.[22,42–44] Thus, coupling of sialosyl donor **28** with sialosyl acceptor **33** also bearing at C-5 a trifluoroacetamido group, gave dimer **34** as only the α-anomer in 55% yield.[22] Additional improvement was observed when 1,5-lactam acceptor **36** was coupled with thiophenyl donor **35**. As a result, the corresponding α-anomer **37** was obtained with a remarkable yield of 71% (Scheme 11).[44]

TFA-modification has been also applied to the selective coupling of phosphite donor **38** with thiosialosyl acceptor **39** for the synthesis of α-(2→9) oligomers (Scheme 12).[45] Also in this case, higher degree of α-anomeric selectivity as compared to conventional sialyl donors was detected. Thus, *N*-TFA phosphite donor **38** was coupled with *N*-TFA thioglycoside acceptor **39** thereby leading to the α-linked dimer **40** with 77% yield.



Scheme 11. Reagents and conditions: (a) NIS, TfOH, MS3 Å, MeCN, −35 °C; (b) NIS, TfOH, MS 3 Å, EtCN, −80 °C.



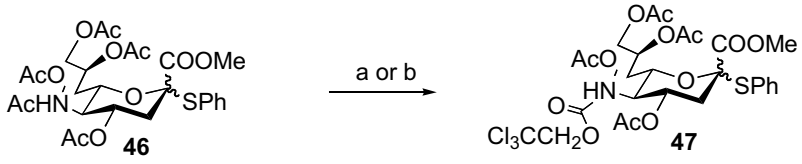
Scheme 12. Reagents and conditions: (a) TMSOTf, MS 3 Å, MeCN, −40 °C; (b) (i) Ac_2O, pyridine; (ii) NBS, acetone, H_2O; (c) 1*H*-tetrazole, dibenzyl *N*,*N*-diisopropylphosphoramidite, MeCN.

The STol moiety of **40** was then replaced with phosphite. By iterating these coupling-reprotection steps, higher-order oligomeric sialosides were obtained in high yields (Scheme 12).

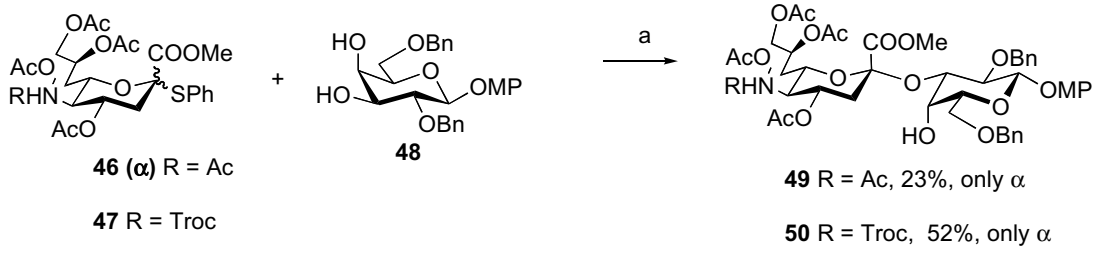
6. Trichloroethoxycarbonyl (NHTroc)

The introduction of trichloroethoxycarbonyl group at C-5 has been described by Wu and co-workers[46] and Kiso and co-workers[47] via deprotection of the *N*-acetyl phenylthioglycoside derivative **46** under acidic conditions and selective N-protection using succinimidyl 2,2,2-trichloroethyl carbonate or trichloroethylchloroformate, respectively (Scheme 13). Conversion of *N*-Troc derivatives into the corresponding free amine can be easily accomplished in the presence of zinc in acetic acid.[47]

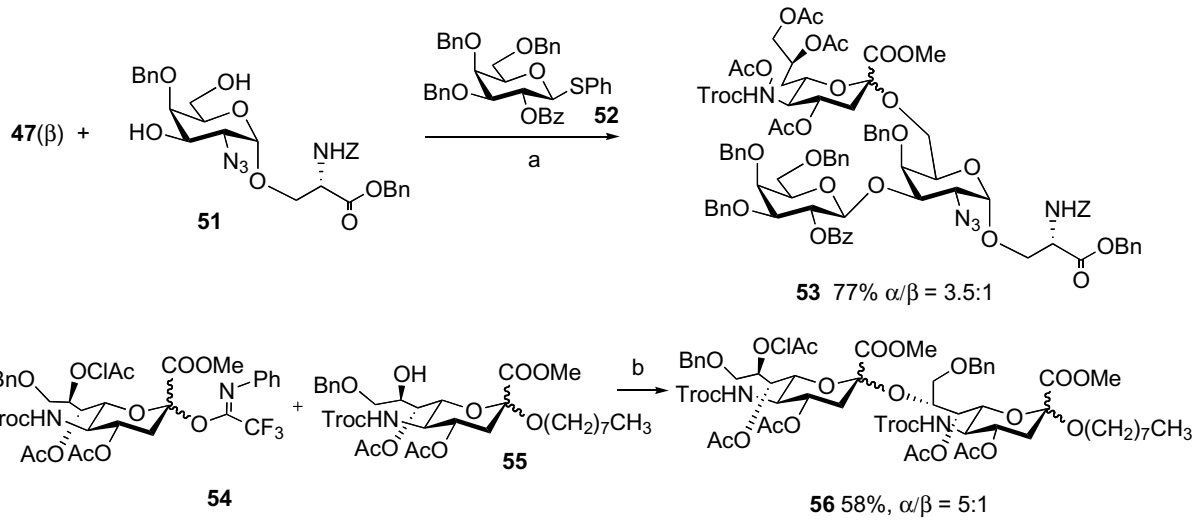
The higher reactivity of **47** in comparison with C-5 acetamido donor **46** was first noticed by Kiso and co-workers[47] in the coupling with galactosyl acceptor **48**, obtaining initially a decrease in stereoselectivity



Scheme 13. Reagents and conditions: (a) (i) MsOH, MeOH; (ii) TrocSu, $NaHCO_3$, 77% (2 steps); (iii) Ac_2O, pyridine, 94%;[46] (b) (i) MsOH, MeOH; (ii) TrocCl, Et_3N, MeOH; (iii)Ac_2O, pyridine, 68% (three steps).[47]

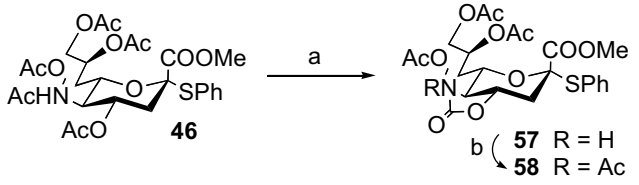


Scheme 14. Reagents and conditions: (a) NIS, TfOH, MS3 Å, for **46** (α): MeCN–CH_2Cl_2, −25 °C; for **47**, EtCN, −50 °C.



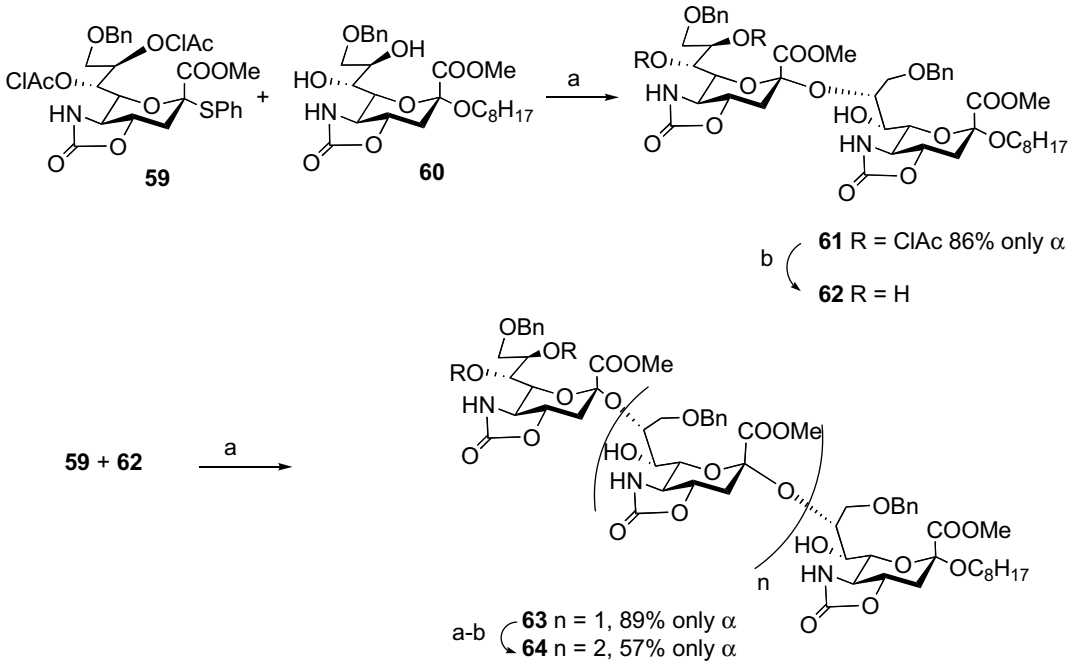
Scheme 15. Reagents and conditions: (a) **47**, **51**, NIS, TfOH, MS 3 Å, MeCN, −35 °C; then **52** , NIS, TfOH, CH_2Cl_2, −30 °C; (b) TMSOTf, MS 3 Å, CH_2Cl_2–MeCN (2:3), −78 °C.

(α:β 5.4:1 for **50** in 20 min vs only α for **49** after 16 h). However, an improvement in the stereoselectivity was recently reported and the desired disaccharide **50** was obtained as the α-anomer in 52% yield (Scheme 14).[48]



Scheme 16. Reagents and conditions: (a) MsOH, MeOH, 65 °C, 80%; (b) NPCC, $NaHCO_3$, MeCN, H_2O, 3 h, 80%; (c) Ac_2O, pyridine, 16 h, 90%; (d) DIPEA, AcCl, CH_2Cl_2, 0 °C, 94%.

The applicability of the *N*-Troc modification for a different class of sialyl donors has been reported by Takahashi and co-workers for the synthesis of the α-(2→6)-sialyl T antigen by one-pot glycosylation and the synthesis of α-(2→8)-linked dimers using *N*-phenyl trifluoroacetimidate as a leaving group (Scheme 15).[49,50] Thus, coupling of sialosyl donor **47** with glycosyl acceptor **51** and in situ addition of donor **52** gave 2,6-sialyl T antigen trisaccharide **53** in 77% overall yield (Scheme 15).[51] Similarly, coupling of *N*-phenyl trifluoro-



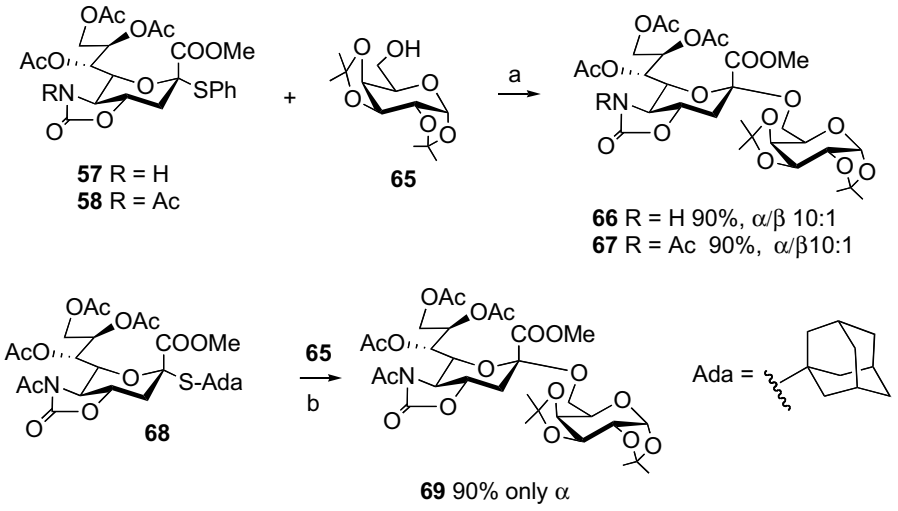
Scheme 17. Reagents and conditions: (a) NIS, TfOH, MS 3 Å CH_2Cl_2, −78 °C; (b) thiourea, 2,6-lutidine, DMF, 70 °C.

acetimidoyl donor **54** with glycosyl acceptor **55** for the synthesis of α-(2→8) linkages gave the dimeric product **56** in 55% yield as a 5:1 α/β anomeric mixture.[50] More recently, Seeberger and co-workers. described the synthesis of sialyl Lewis X and sialylated glycans having α-(2→3) and α-(2→6) linkages, using *N*-Troc modified thiophenyl and phosphite sialosyl donors.[52,53]

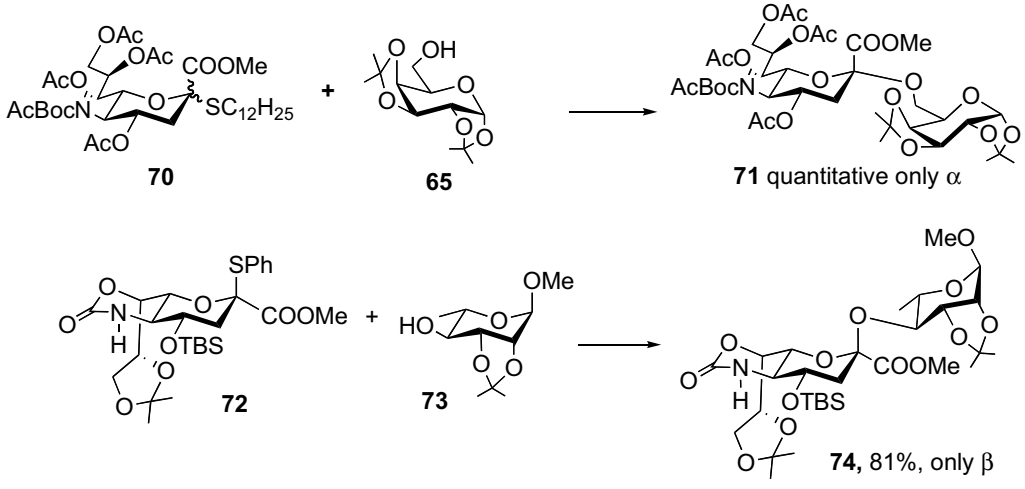
7. 5-*N*,4-*O*-oxazolidinone group and its N-acetylated version

Modification at C-5 of thiophenyl sialosyl donor **46** by introduction of a trans-fused oxazolidinone ring can be accomplished by deprotection in acidic medium followed by N-functionalization by treatment with *p*-nitrophenylchloroformate (NPCC), and then O-acetylation to afford glycosyl donor **57**.[54] Additionally N-acetylation of **57** with acetyl chloride in diisopropylethylamine (DIPEA) leads to compound **58** in 94% yield (Scheme 16).[55] Removal of oxazolidinone in **57** can be performed in the presence of a strong base, such as barium or lithium hydroxide, to yield a free amine.[54,56] On the other hand, the N-acetylated version 58 offers the advantage of removal under milder basic conditions in the presence of sodium methoxide in methanol.[55]

The first to evaluate the proprieties of oxazolidinone protecting group in sialylations were Takahashi and co-workers[56] for the synthesis of α-(2→8)-sialic acid oligomers. Thus, coupling of oxazolidinone protected sialosyl donor **59** with sialosyl acceptor **60**, also bearing a C-5 oxazolidinone protection, gave the desired dimer **61** with a remarkable yield of 86% as the α anomer. Selective deprotection to afford the free 8-OH gave **62** as glycosyl acceptor, which was coupled with glycosyl donor **59** to allow trimer **63** in 89% yield with complete



Scheme 18. Reagents and conditions: (a) NIS, TfOH, MS 3 Å, MeCN, −40 °C; (b) NIS, TfOH, MS 3 Å, CH_2Cl_2–MeCN (1:1), −78 °C.



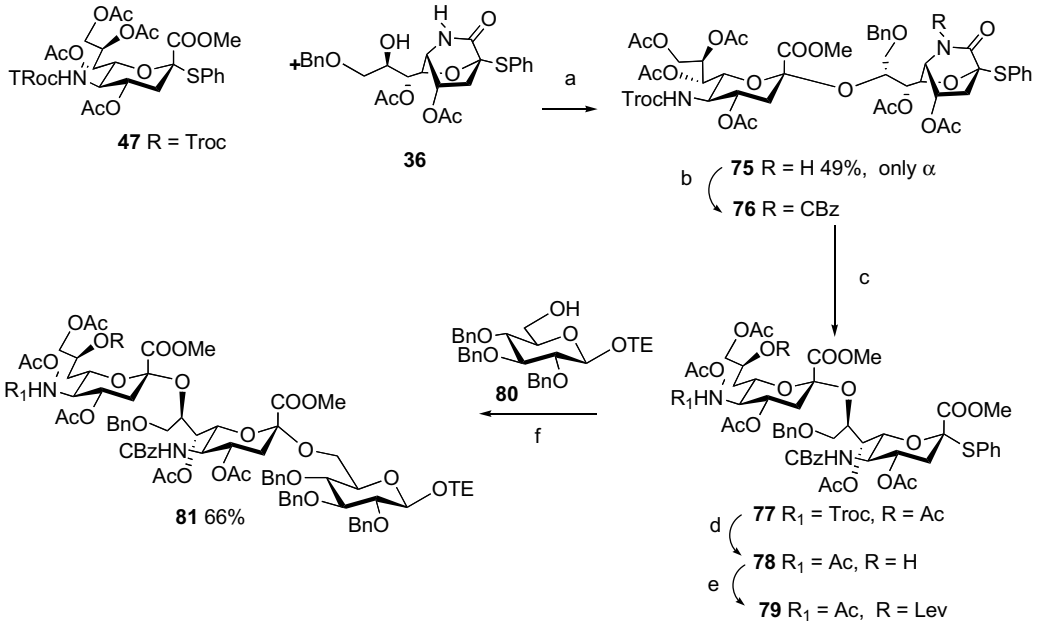
Scheme 19. Reagents and conditions: (a) NIS, TfOH, MS 3 Å, CPME, −40 °C; (b) Ph_2SO, Tf_2O, TTBP, MS 4 Å, CH_2Cl_2, −78 °C.

stereoselectivity. The iterative deprotection and coupling gave tetrasaccharide **64** as α-anomer only in 57% yield (Scheme 17). Similar results were also obtained for the synthesis of α-(2→9) dimers.[56]

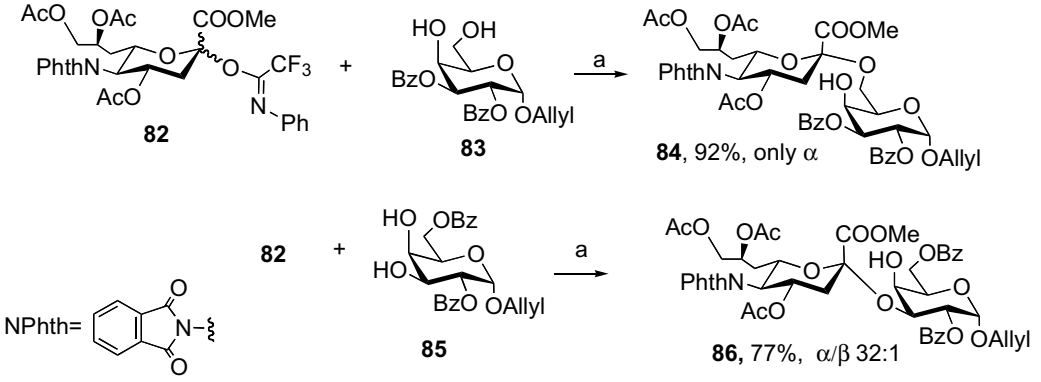
For the synthesis of α-(2→3) and α-(2→6) linkages to galactose, sialosyl donors **57**[54] and **58**[55] were coupled with a wide range of glycosyl acceptors. Thus, for the coupling of primary acceptors and alcohols high yields and stereoselectivities were observed for both donors. For example, coupling of **57** with galactosyl acceptor **65** gave the desired disaccharide **66** as a 10:1 α:β anomeric mixture in 90% yield (Scheme 18). Similar results were observed for the N-acetylated donor **58**, suggesting that in this case the additional acetyl group does not influence the glycosylation outcome. An improvement of the methodology has been reported by Crich with the use of 1-adamantyl thiosialosyl donor **68**, and disaccharide **69** was obtained in this case as only the α anomer.[57]

8. Miscellaneous substituents

Modifications of the C-5 acetyl group into other conventional protecting groups, such as *N*-*t*-butyloxycarbonyl (Boc),[17] *N*-benzyloxycarbonyl (Cbz,Z),[58] phthalimido (NPhth),[59–61] and *N*-*t*-butyloxycarbonylacetamido (NAcBoc)[62,63] as well as into less conventional polycyclic compounds, such as 1,5 lactam[44] (as sialosyl acceptor) and 5,7-*N*,*O* oxazinanone protected sialosyl donor[64] have been recently reported. For example, combination of NAcBoc modification and laurylthiol leaving group as in sialosyl donor **70** gave quantitative yield when cou-



Scheme 20. Reagents and conditions: (a) NIS, TfOH, MS 3 Å, EtCN, -80 °C; (b) CbzOSu, DMAP, pyridine, 79%; (c) (i) Et_3N, H_2O, MeCN, 40 °C; (ii) MeI, K_2CO_3, DMF, 79%; (d) Zn, AcOH, THF, 94%; (e) LevOH, DCC, DMAP, CH_2Cl_2, 95%; (f) NIS, TfOH, MS 3 Å, EtCN, −80→−60 °C.



Scheme 21. Reagents and conditions: (a) TMOTf, MS 4 Å, EtCN, −78 °C.

pled with acceptor **65** (Scheme 19).[63] A dramatic decrease in stereoselectivity has been reported in the case of C-5 modification as 5,7-*N*,*O* oxazinanone group. For example, coupling of sialosyl donor **72** with acceptor **73** gave compound **74** in 81% yield as the unnatural β-anomer (Scheme 19).

Activation of the 8-OH in a sialosyl acceptor has been reported by modification into 1,5-lactam **36** (Scheme 11 and 20). Thus, thiophenyl sialosyl donor **47** gave 49% of the α-anomer when coupled with glycosyl acceptor **36**, while only traces of the desired dimer were observed without the conformational strain of the lactam. Conversion of compound **75** into *N*-Cbz protected and lactam ring opening gave dimer **77** as glycosyl donor. Subsequent protecting group manipulations and glycosylation of glycosyl donor **79** with glucosyl acceptor **80** gave trisaccharide **81** in 66% overall yield.

High yields and stereoselectivities have been reported by Fukase and co-workers [60,61] when *N*-phthaloyl protected sialosyl donor **82** was coupled with acceptor **83** for the synthesis of α-(2→6) linkages. Thus, disaccharide **84** was obtained in 92% yield as the α-anomer only. Similar results were obtained for the synthesis of α-(2→3) linkages by coupling **82** with acceptor **85** (Scheme 21).

9. Conclusions

Although it is clear that modifications at the C-5 position of *N*-acetyl-neuraminic acid influences reactivity and stereoselectivity in glycosylation reactions, each protecting group has to be selected based on the nature of the desired glycosidic bond, for example (2→3) and (2→6), as well as the nature of the glycosyl acceptor (e.g., protecting groups). In addition, the glycosylation yields and stereoselectivities have to compensate for the number of added steps required for the protection and deprotection.

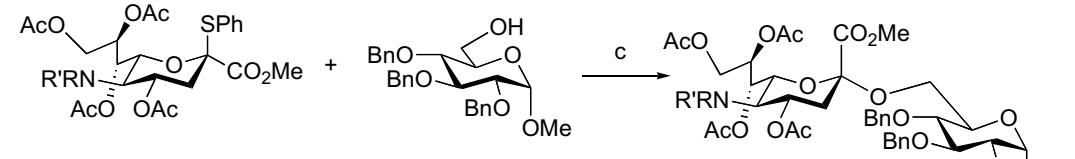
For its easy introduction and removal, *N*-acetylacetamido can be the modification of choice for primary acceptors and some secondary acceptors. High yields and stereoselectivities can be accomplished with less reactive acceptors by using the trifluoroacetamido group, while the azido group can be a suitable choice when the coupling with primary alcohols is desired. Trichloroethoxycarbonyl allows an efficient armed–disarmed approach for the synthesis of (2→9) dimers, but in general gives lower yields and stereoselectivities than the azido and trifluoroacetamido approaches (Table 1). The oxazolidinone protection is clearly one of the best

Table 2. Comparison of glycosidations of different N-protected thioglycosides with **87**[51]

Entry	Donor	Yield	α/β ratio
1	**46**	47	6:1
2	**47**	91	8:1
3	**13**	65	2:1
4	**88**	68	5:1
5	**89**	—	—
6	**90**	44	7:1
7	**91**	91	6:1
8	**35**	92	11:1
9	**92**	83	10:1

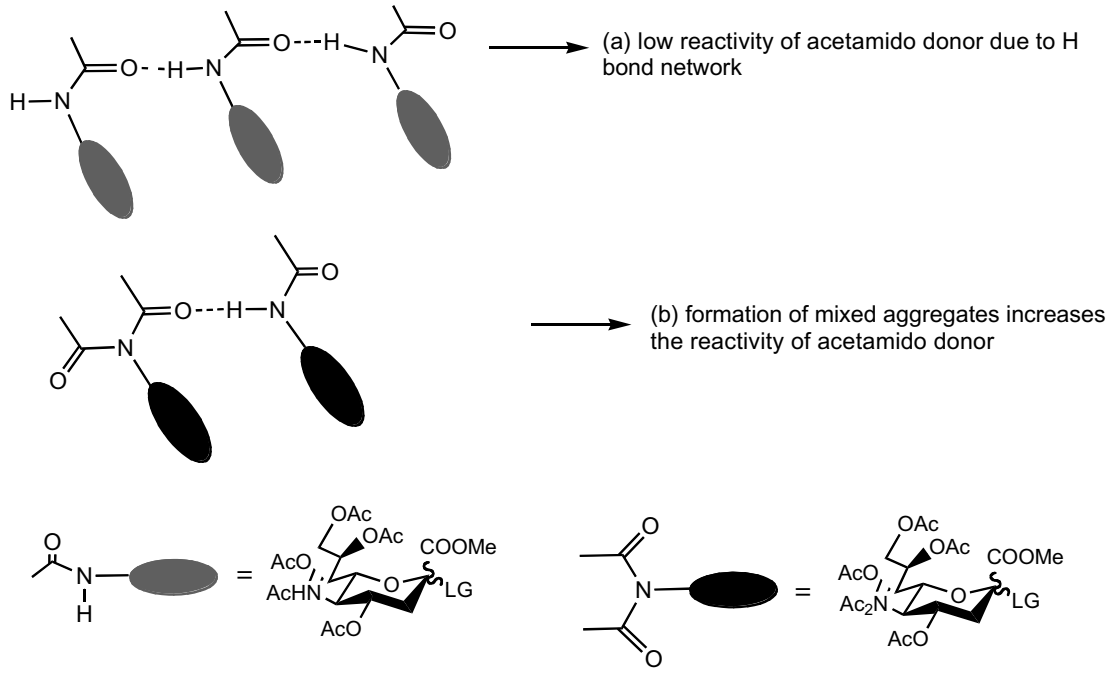
Table 1. Summary of various C-5 modified Neu5Ac donors

C-5 modification	Advantages	Suitable for
Ac_2	Easy introduction and removal by Zemplen deacetylation	Primary alcohols
N_3	Can be removed in the presence of acetyl groups	Primary alcohols
TFA	High yields and stereoselectivities observed with a wide range of acceptors	Hindered, less reactive alcohols
Troc	Can be removed in the presence of acyl groups and acid/base labile groups, such as amino acids	Armed–disarmed approach
5-*N*,4-*O*-oxazolidinone	High yields and stereoselectivities observed with a wide range of acceptors	Primary acceptors, dimers synthesis



46(β) R' = Ac, R = H
47(β) R' = Troc, R = H
13 R' = R = Ac
88 R' = Z, R = H
89 R' = Boc, R = H
90 R' = Alloc, R = H
91 R' = Fmoc, R = H
35 R' = TFA, R = H
92 R' = TCA, R = H

Scheme 22. Reagents: NIS, TfOH, MS3 Å, MeCN.



Scheme 23. Possible explanation of the change of reactivity order observed in competitive glycosylations.

modification for the synthesis of α(2→8) dimers, as well as some primary acceptors, while it is not so activating and stereocontrolling for the secondary galactosyl acceptors (Table 1).

It has been proposed that the reactivity of C-5 modified sialosyl donors is inversely correlated to the nitrogen nucleophilicity, which is decreased when electron withdrawing groups are present. This factor might explain the reactivity increase in the following sequence: acetamido < acetylacetamido < trifluoroacetamido. On the other hand, another set of competitive glycosylation data suggests a different order of reactivity, according to which the acetylacetamido derivative is more reactive than its trifluoroacetamido counterpart.[47] For the azido derivatives, the high stereoselectivity was also attributed to steric and electronic effects, considering the electron-withdrawing and linear character of the azido group. On the other hand, the higher reactivity and its stereocontrol of *N*-phthalimido sialosyl donor has been related to the presence of a fixed dipole stabilizing effect.[61]

Comparative study of the glycosidation of differently N-protected thioglycosides with methyl glucoside 87 was reported by Tahashashi et al. (Scheme 22 and Table 2).[51] Based on these results, sialosyl donors bearing *N*-Troc (**47**, entry 2), *N*-TFA (**35**, entry 8), and *N*-trichloroacetate (**92**, entry 9) gave the best yields and stereoselectivity. Another interesting set of comparison data has been provided by Fukase and co-workers.[61]

Based on the aforesaid, the relative order of reactivity of C-5 modified derivatives is not so straightforward, and a possible explanation for these contradicting data has been offered by Kononov et al.[65] Based on these studies, the low reactivity of acetamido donor was explained by its ability to form H-bond aggregates (Scheme 23a). In a mixture of NAc_2 and NHAc, the reactivity of NHAc donor is now relative to the presence of the other sialyl donor and its ability to make H-bonds (Scheme 23b). According to this scenario, an acetamido donor can be more reactive in the presence of *N*-acetylacetamido donor than alone.

All the groups described herein offer advantages and disadvantages for specific building blocks, and therefore the choice of the C-5 modification to be used is mainly dependent of the nature of the glycosyl acceptor and its protecting groups. It is clear that a better understanding of the influence of the C-5 position in sialic acid chemistry is a key factor for the design of a versatile approach that would give the highest performance regardless of the nature of the glycosyl acceptor, donor, promoter or the type of glycosidic bond to be synthesized.

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