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Synthesis and Stereocontrolled Equatorially Selective Glycosylation Reactions of a Pseudaminic Acid Donor: Importance of the Side Chain Conformation, and Regioselective Reduction of Azide Protecting Groups

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Abstract

Pseudaminic acid is an amino deoxy sialic acid whose glycosides are essential components of many pathogenic Gram-negative bacterial cell walls including those from *Pseudomonas aeruginosa*, *Vibrio cholerae*, *Campylobacter jejuni*, *Campylobacter coli*, *Vibrio vulnificus*, and *Pseudoalteromonas distincta*. The study of pseudaminic acid glycosides is however hampered by poor availability from nature, the paucity of good synthetic methods, and limited to no understanding of the factors controlling stereoselectivity. Conformational analysis of the side chains of various stereoisomeric sialic acids suggested that the side chain of pseudaminic acid would take up the most electron-withdrawing *trans*,*gauche*-conformation, as opposed to the *gauche*,*gauche* conformation of *N*-acetyl neuraminic acid and the *gauche*,*trans*-conformtion of 7-*epi N*-acetyl neuraminic acid, leading to the prediction of high equatorial selectivity. This prediction is borne out by the synthesis of a suitably protected pseudaminic acid donor from *N*-acetyl neuraminic acid in 20 steps and 5% overall yield, and by the exquisite equatorial selectivity it displays in coupling reactions with typical glycosyl acceptors. The selectivity of the glycosylation reactions is further buttressed by the development and implementation of conditions for the regioselective release of the two amines from the corresponding azides, such as required for the preparation of the lipopolysaccharides. These findings open the way to the synthesis and study of pseudaminic acid-based bacterial lipopolysaccharides and, importantly in the broader context of glycosylation reactions in general, underline the significant role played by side chain conformation in the control of reactivity and selectivity.

Graphical Abstract

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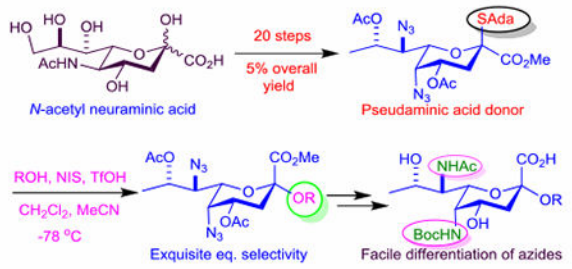
Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs8b09654.

Full experimental details and copies of the ^{1}H and ^{13}C NMR spectra of all new compounds (PDF)



Introduction

In spite of the many advances in chemical and enzymatic glycosidation, whether automated or classical, in recent years,[1–16] the stereocontrolled synthesis of many classes of glycosidic bond continues to be a significant challenge that retards the preparation of saccharides, oligosaccharides and their conjugates for biomedical research. The problem arises because of the location of typical glycosylation reactions at the interface between S_N1 and S_N2 reactions where minor changes in structure and conditions cause major shifts in mechanism,[17–19] is compounded by the iterative nature of oligosaccharide synthesis, and is particularly significant in the preparation of the microbial glycans with their great structural diversity and complexity.[20–24] Indeed, notwithstanding the several spectacular syntheses published in recent years,[25–35] the surface of the microbial glycan problem has barely been scratched leaving many challenges for the ingenuity of the organic chemist.

The bacterial sialic acids legionaminic (Leg) **1** and pseudaminic acid (Pse) **2** and their glycosides, congeners of the ubiquitous *N*-acetyl neuraminic acid (NeuAc) **3** glycosides, are a case in point (Figure 1).[36] Leg and Pse are found in a diverse range of bacterial capsular and lipopolysaccharides in the form of both axial and equatorial glycosides,[23,24] and offer broad opportunities for the development of antibacterial therapeutics and/or vaccines.[37–39] NeuAc on the other hand is found exclusively in the form of its equatorial glycosides,[40–44] for whose preparation a number of effective chemical methods are now available.[45–51] Leg differs from NeuAc, with whom it shares the D-*glycero*-D-*galacto* configuration only by the absence of a C-O bond at the 9-position and by replacement of a C-O by a C-N bond at the 7-position, whereas Pse with the L-*glycero*-L-*manno* configuration differs from NeuAc in configuration at both the 5- and 7-positions in addition to the deoxygenation at C9 and the N for O substitution at C7 (Figure 1). Other members of the class include acinetaminic acid **4** and fusaminic acid **5** (Figure 1), and the 4- and 8-epimers of legionaminic acid (not shown).[23,24,52–55]

Investigations of the glycosylation reactions of Leg and Pse are necessarily preceded by the synthesis of suitable donors as neither substance is presently available from nature in sufficient quantities. Tsvetkov and coworkers described syntheses of both Leg and Pse and their stereoisomers by homologation of hexose sugars,[56,57] while Ito and coworkers adopted an analogous approach to a Pse donor **6** that was found to be axially selective in a single glycosylation reaction conducted with a primary acceptor in acetonitrile at 0 °C.[58] Seeberger and co-workers reported the synthesis of the Leg donor **7** from D-threonine and found it to be axially selective in a single glycosylation with a primary acceptor at −78 °C in

dichloromethane.[38] Subsequently, Li and coworkers adopted an analogous approach to the Pse donors **8**-**10** from L-threonine, each of which showed modest to excellent axial selectivity in dichloromethane at −78 °C (Figure 2).[59] Payne, Kiefel and coworkers reported the synthesis of *N*,*N*-diacetyl Pse from NeuAc but did not describe its conversion into a glycosyl donor and use in glycosylation reactions.[60,61] Biosynthetic and chemoenzymatic approaches to legionaminic acid and its equatorial glycosides have been described.[62,63]

Our laboratory has a long-standing interest in the stereoselective synthesis of the equatorial sialic acid glycosides,[46–48,64,65] and, following the seminal work of Bols,[66] in the role played by side chain conformation in anomeric reactivity and selectivity.[50,67–71] We viewed Leg and especially Pse as proving grounds for our hypotheses on the manner in which side chain conformation influences the reactivity and selectivity of glycosyl donors and, with Pse in mind first investigated the influence of configuration at the 7-position with the NeuAc and 7-*epi*-NeuAc donors **11** and **12**, respectively (Figure 3).[68] We found, consistent with the earlier NMR studies of Zbiral,[72,73] that the 7-*epi*-NeuAc donor **12** showed a change in predominant side chain conformation from the *gg*-conformer[74] observed in **11** and in NeuAc derivatives in general,[72,75–79] to the *gt*-conformation so as to avoid unfavorable dipolar and steric interactions with the C5-N5 bond (Figure 3). We also found, consistent with the work of Bols and ourselves using rigid bicyclic systems,[66,67] that the change in predominant side chain conformation from *gg* to *gt* was accompanied by a considerable loss of reactivity. Subsequently, working with the NeuAc donor **13** and its C5 epimer **14**, we found that inversion of configuration at C5 was accompanied by a change of side chain conformation from the *gg* to the *gt* conformer, again to minimize dipolar and steric interaction with the C5-N5 bond (Figure 3).[50] We found that the anticipated[80–83] increase in reactivity on replacement of an equatorial C-N bond at the C5 position in **13** by an axial one in **14** was offset by the change in side chain conformation such that **13** and **14** displayed similar selectivity in glycosylation reactions. Extrapolating from these results we predicted that inversion of configuration at C7 of the 5-*epi*-donor **14** would again result in unfavorable dipolar and steric interactions in the hypothetical 5,7-bis-*epi* system **15**, minimization of which would result in a change in side conformation from the *gt* to the most-disarming[66,67] *tg* conformer. This analysis of side chain conformation is consistent with the ^{3}J coupling constant of 10.5 Hz for the H6,H7 spin system in a glycoside of **6** reported by Ito and coworkers,[58] and in both epimers of Pse itself by Tsvetkov and coworkers[57] and by Payne and coworkers,[61] albeit no predictions of reactivity were offered by those workers.

On the basis of this analysis of the influence of configuration at the C5 and C7 on side chain configuration, drawing on experience from our synthesis of the 5-*epi*-NeuAc donor **14**[50] and of moderately equatorially selective Leg donor **16**,[69] we designed the Pse donor **17** in the expectation that its side chain would adopt the *tg*-conformation very predominantly and consequently afford excellent equatorial selectivity in its glycosylation reactions (Figure 4). We report here on the synthesis of **17** from NeuAc, the analysis of its side chain conformation, its highly equatorially selective glycosylation reactions, and on the selective functionalization of the two azido groups in the coupled products such as will be required for the synthesis of many natural Pse oligosaccharides.

Results and Discussion

Donor Synthesis

Our strategy for the synthesis of **17** sought to make use of the readily available NeuAc as starting material taking advantage of the lessons learnt in the previous synthesis of **16**.[69] However, in addition to the operations of deoxygenation at the 9-position and replacement of the C-O by a C-N bond at the 7-position executed in the synthesis of **16**, the preparation of **17** necessitates inversion of configuration at positions 5, 7, and 8. Analogously to Kiefel, Payne and coworkers in their synthesis of *N,N*-diacetyl Pse from NeuAc (Scheme 1), we anticipated that displacement of suitably activated alcohols from the 5- and 7-positions by the azide anion would afford the two C-N bonds both with inversion of configuration. This approach in turn requires initial replacement of the equatorial acetamide at C5 by a hydroxyl group with retention of configuration, for which we anticipated using the Zbiral oxidative deamination[84–86] as in our earlier synthesis of a 3-deoxy-D-*glycero*-D-*galacto*-nonulosonic acid (KDN) donor, our synthesis of the 5-*epi*-NeuAc donor **14**,[50] and the Kiefel-Payne synthesis of *N,N*-diacetyl-Pse.[60,61] However, distinct from the Kiefel-Payne synthesis which employed acetic acid as nucleophile in the deamination step thereby necessitating extra steps to isolate the 5-position for inversion (Scheme 1), we planned to employ levulinic acid as nucleophile as in our synthesis of **14** to facilitate selective manipulation of the ensuing ester at the 5-position. Tactically, in view of the generally modest yields of the Zbiral reaction which rarely exceed 55–60%, we initially elected to conduct the oxidative deamination of the 5-position at a late stage of the synthesis. We also selected the 1-adamantanyl thioglycoside for the glycosyl donor in view of its ready activation at the low temperatures envisaged for the eventual glycosylation reactions.[47]

Thus, NeuAc was converted by a sequence of three well-established literature steps to the known thioglycoside **23** on a 20 g scale in 70% overall yield.[47,87] Global Zemplen deacetylation was followed by installation of an 8,9-*O*-acetonide in the usual manner to give **24** in 93% yield. Regioselective monoacetylation followed the established pattern[88] and afforded the 4-*O*-acetate **25**, which on silylation gave **26** cleanly. Removal of the acetonide was followed by selective sulfonylation of the primary hydroxyl group with 2,4,6-tri-isopropylbenzenesulfonyl chloride to give **27**. Oxidation with the Dess-Martin periodinane[89] was followed by Luche reduction[90] giving the ketone **28** and the inverted alcohol **29**, respectively. Displacement of the sulfonate group from **29** with sodium iodide afforded **30** which, on hydrogenolysis in a mixture of ethyl acetate and triethylamine, gave the 9-deoxy derivative **31**. It is noteworthy that these conditions, with the incorporation of triethylamine, enabled selective hydrogenolysis of the C-I bond without detriment to the thioglycoside moiety, something that we had previously been unable to accomplish cleanly in our synthesis of the Leg donor **16**.[69] Reaction with acetic anhydride and DMAP then gave **32**, the substrate for the deamination step. Adopting thermal conditions for the oxidative deamination similar to the ones employed in the Kiefel-Payne synthesis (Scheme 1), treatment of **32** with nitrosyl tetrafluoroborate and pyridine gave the corresponding *N*-nitrosoacetamide, that on warming to 50 °C in levulinic acid resulted in the formation of the oxidative deamination product **33** as a mixture of diastereomers. Heating was required in this step as the intermediate *N*-nitroso amide did not undergo reaction with levulinic acid at

lower temperatures under standard conditions. To facilitate purification the crude reaction mixture containing **33** was treated with hydrazine hydrate, acetic acid and pyridine resulting in removal of the levulinate ester and the isolation of **34** in 38% overall yield from **32** in the form of an approximately 1:1 mixture of stereoisomers (Scheme 2). Based on our previous studies of substituent effects in the Zbiral oxidative deamination reaction,[86] the poor stereoselectivity in the final deamination reaction presumably arises from the absence of a C-O bond at the 9-position, which reduces the need for stereodirecting participation by the ring oxygen and supports a more carbenium ion-like intermediate at the 5-position. Whatever the reason, the modest yield and unacceptably poor selectivity at this late stage of the synthesis caused us to abandon this route and adopt a sequence in which the deamination reaction was conducted before deoxygenation at the 9-position.

Accordingly, intermediate **25** was converted to the 7-*O*-naphthylmethyl ether **35** by treatment with sodium hydride and 2-naphthylmethyl bromide in the usual manner[91] on a multigram scale in 82% yield. Reverting to conditions for the Zbiral reaction previously developed in our laboratories,[92] reaction of **35** with nitrosyl tetrafluoroborate and pyridine gave a crude *N*-nitrosoacetamide derivative that was treated with preformed sodium trifluoroethoxide and 18-crown-6 in dichloromethane at −10 °C, with addition of levulinic acid after minutes followed by warming to 0 °C before quenching. In this manner, working with >5 g of **35**, we isolated 21% of the alkene **36**, which is the typical byproduct for this class of reaction,[86] and 55% of the desired levulinate **37** in the form of a single equatorial diastereomer. Removal of the acetonide with aqueous trifluoroacetic acid followed by installation of the triisopropylbenzenesulfonyl group on the primary alcohol with triisopropylbenzenesulfonyl chloride, pyridine and dibutyltin oxide[93,94] gave **38** in 83% yield. Application of the Lattrell-Dax protocol[95–97] then gave the 8-*epi*-isomer **39** in 72% yield. It is noteworthy in this sequence that a secondary triflate is displaced in preference to a primary arenesulfonate ester, testifying to the power of the trifloxy group as a nucleofuge in substitution reactions.[98] Subsequently, the triisopropylbenzenesulfonyl group was displaced with sodium iodide in hot acetone to give an 81% yield of **40**, which on hydrogenolysis over palladium on carbon in ethyl acetate and triethylamine afforded 91% of the 9-deoxy compound **41**. Standard acetylation then gave the triester **42** in excellent yield, from which the naphthylmethyl ether and the levulinate ester were removed sequentially with DDQ and hydrazine hydrate giving **43** and **44**, respectively, in good yields. Finally, triflation of the diol **44** followed by reaction with sodium azide in DMF gave the desired Pse donor **17** in 70% yield (Scheme 3). Overall, we describe a practical synthesis of donor **17** that, with the possible exception of the Zbiral deamination employs well-established, simple and scalable reactions and affords the product on the scale of multiple hundreds of milligrams, suitable for the investigation of the glycosylation reaction.

Glycosylation

Turning to glycosylation we employed the widely used combination of *N*-iodosuccinimide and triflic acid for activation of the thioglycoside and conducted all reactions in a 2:1 mixture of acetonitrile and dichloromethane at −78 °C for ease of comparison with our earlier work. In the event activation of **17** in the presence of benzyl alcohol as acceptor under these conditions afforded the equatorial glycoside **45** as a single anomer in 89% isolated

yield (Scheme 4). Similarly, use of methyl 2,3,4-tri-*O*-benzyl-β-D-galactoside and methyl 2,4,6-tri-*O*-benzyl-β-D-galactoside as acceptor alcohols afforded the equatorial glycosides **46** and **47**, as single anomers in 83 and 77% isolated yield. Finally, use of the highly sterically hindered methyl 2,3,6-tri-*O*-benzyl-β-D-galactoside as acceptor gave 53% of the equatorial glycoside **48**, without competing formation of the axial isomer (Scheme 4). The anomeric configuration of **45-48** was determined by measurement of the $^{3}J_{\text{C1-H3axial}}$ heteronuclear coupling constant which in each case fell in the range 6.8–7.5 Hz that is diagnostic of the equatorial glycoside, as opposed to the ~0 Hz expected for the opposite anomer.[68,99–102] We selected galactopyranosyl 3- and 6-alcohols as acceptors for this study as they afford what are by far the most common types of linkage in the realm of sialic acid glycosides. The highly hindered galactopyranosyl 4-alcohol leading to the glycoside **48** was selected as a model study for the very demanding Pse-β-(2→4)-6-deoxy-*N*-acetylgalactosaminide linkage found in the repeating unit from the *Pseudomonas aeruginosa* O10 lipopolysaccharide.[103]

The results presented in Scheme 4 validate our design hypothesis (Figure 3) particularly in so far the selectivities observed, with the exception of the benzyl glycoside, are superior to those seen with the Leg donor **16** under the same conditions and with the same alcohols.[69] We conclude that donor side chain conformation is an important control element in the preparation of glycosidic bonds, whether the donor is a simple monocyclic pyranosyl system as presented here or the more familiar 4,6-*O*-benzylidene-protected and related donors from the synthesis of β-mannosides and related systems. The contrast between the excellent equatorial selectivity observed here with Pse donor **17** and the mostly unselective or axially selective donors Pse donors **8-10** reported by Li and coworkers[59] is striking, especially as the conditions employed are similar (solvent, temperature, and triflate-based activating systems). Inspection of the spectral data for **8–10** reveals each of them to display a 10.0 Hz $^{3}J_{\text{H6,H7}}$ coupling constant and so the *tg* conformation, indicating that the difference in selectivity must arise from the difference in amine protecting groups, perhaps for steric or hydrogen bonding/association reasons,[19,104–106] or from the use of the more bulky isopropyl ester that is less easily accommodated in the axial position. The Ito study with donor **6** was performed under different conditions (acetonitrile, 0 °C) that do not permit meaningful comparison with the present work.

Deprotection

Reaction of the benzyl glycoside **45** with excess thioacetic acid in pyridine[107] for 40 h at room temperature afforded 73% of the bisacetamide **49** (Scheme 5). Heating of this bisamide to 60 °C with aqueous barium hydroxide in 1,4-dioxane followed after workup by hydrogenolysis also in aqueous 1,4-dioxane over palladium charcoal afforded *N,N*-diacetyl Pse **22**, whose spectral data were consistent with those provided by Tsvetkov and by Kiefel and Payne.[57,61]

Many Pse glycosides,[23] including the axially-linked *Pseudomonas aeruginosa* 1244 pilin glycoside prepared by Li and coworkers[59] and the Pse-β-(2→4)-6-deoxy-*N*-acetylgalactosaminide linkage found in the repeating unit from the *Pseudomonas aeruginosa* O10 lipopolysaccharide,[103] are characterized by the presence of two different amides at

positions 5 and 7. This requires either the synthesis of donors with differentially protected amines at the 5- and 7-positions, with all the associated complexity, as in **8**-**10**, or the regioselective unmasking of one of two identically protected amines. We anticipated that the differing steric environments of the two azides in glycosides **45**-**48** would permit the latter option and were encouraged by the work of Kiefel and coworkers who showed in a model system, albeit one with the incorrect configuration at the 8-position and so a different steric environment, that the side chain azide was more reactive than the axial azide in the pyranose ring toward Staudinger reaction with triphenylphosphine.[60] In the event, heating of **47** with thioacetic acid and lutidine in chloroform at reflux for 10 h yielded 68% of a single monoamide **50** arising from conversion of the side chain azide (Scheme 6). Subsequent treatment with 1,3-propanedithiol and triethylamine in wet pyridine[108] at room temperature followed by installation of a Boc group afforded the amido carbamate **51** in 72% yield. Finally, heating with aqueous barium hydroxide in dioxane followed by hydrogenolysis afforded the Pse glycoside **52** with the two amines differentially protected, one in the form of a *tert*-butylcarbamate suitable for selective cleavage and further elaboration (Scheme 6).

Finally, the sequence of azide cleavage reactions was reversed providing first the 5-azido-7-*N*-Boc derivative **53**, then the 5-*N*-acetyl-7-*N*-Boc derivative **54**, and ultimately the Pse glycoside **55** in which the amino group at the 7-position is poised for use in further steps following cleavage of the Boc group (Scheme 7).

Conclusion.

Readily available *N*-acetylneuraminic acid is shown to be a suitable starting material for the synthesis of a pseudaminic acid donor, in which both amines are protected in the form of azides. The synthesis employs operationally simple chemistry and proceeds in 20 steps and 5% overall yield on such as scale as to afford multi-hundred milligram quantities for the study of glycosylation reactions. The thioglycoside serves as an effective donor for coupling to a range of primary and hindered secondary alcohols and affords the corresponding equatorial glycosides with exquisite selectivity. Conformational analysis of the side chain reveals this selectivity to be a function of the *trans,gauche* conformation of the side chain, with its maximal electron-withdrawing capacity, which is a function of the 5,7-bis-*epi*-configuration when compared to the prototypical *N*-acetylneuraminic acid and the *gauche,gauche* conformation of its side chain. This study underlines the role played by side chain conformation in the reactivity and selectivity of glycosyl donors and further enables the mechanism-based development of stereoselective glycosylation reactions. The development of two different modes of regioselective deprotection sequence enables conversion of the azide-protected glycosides to differently substituted amine functionality in the final pseudaminic acid glycosides, suitable for further elaboration to bacterial lipopolysaccharides.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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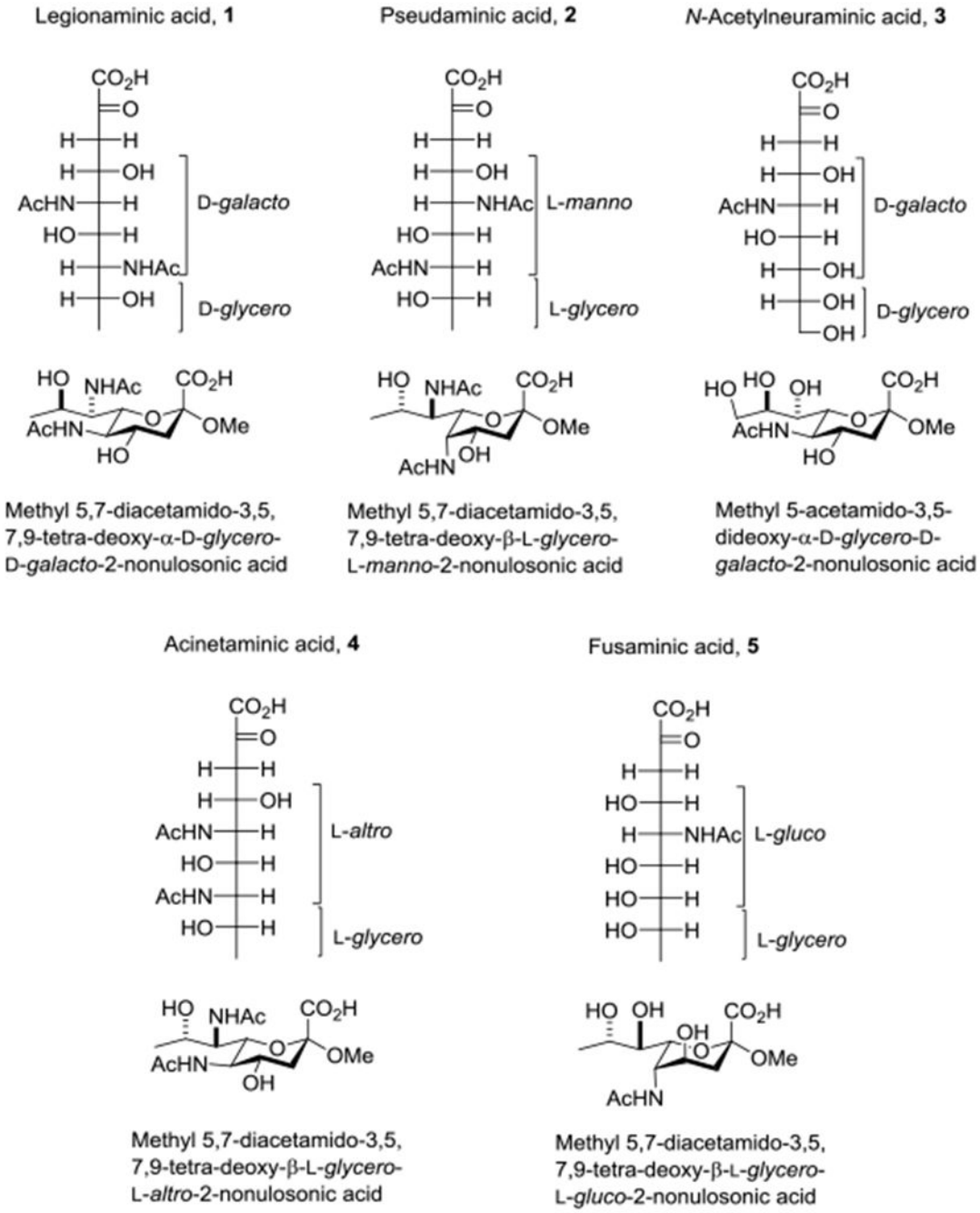


Figure 1.

Fischer Projections of Legionaminic, Pseudaminic, *N*-Acetyl Neuraminic, *N*-Acetylacinetaminic and Fusaminic Acid, and Structures and Formal Names of their Equatorial Methyl Pyranosides.

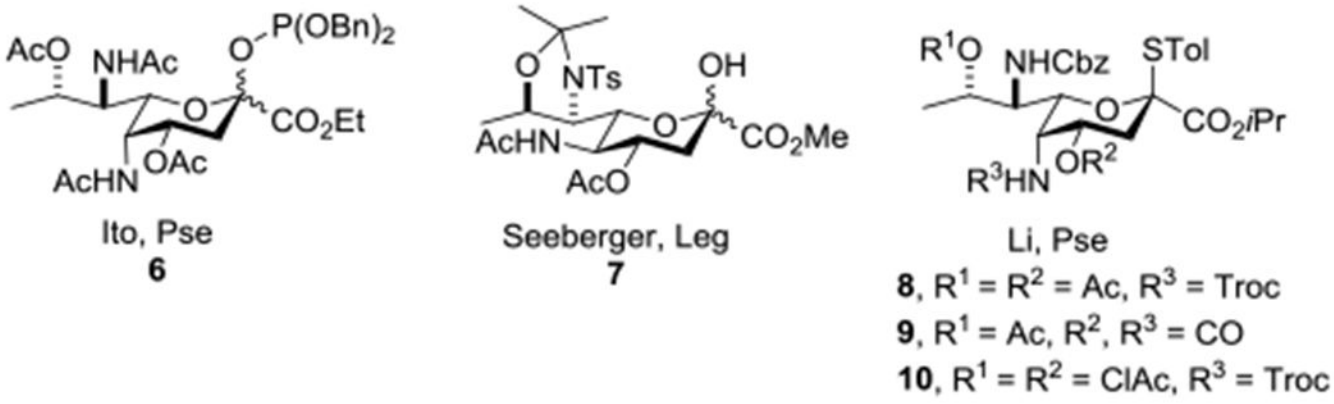


Figure 2.
Axially Selective Leg and Pse Donors

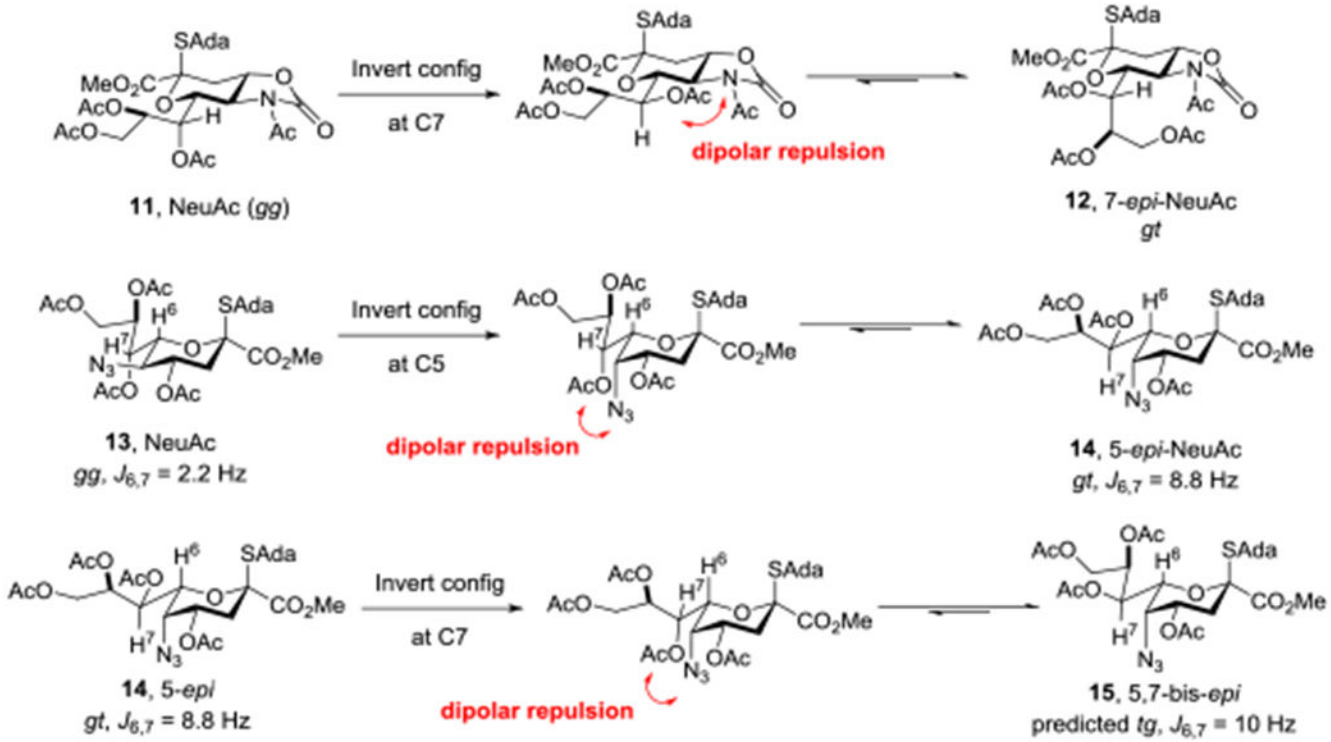
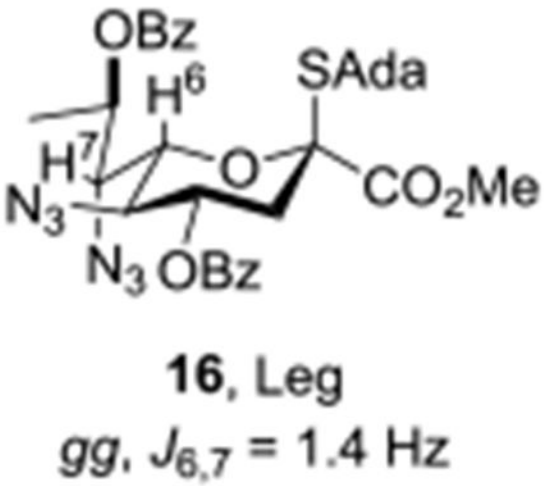
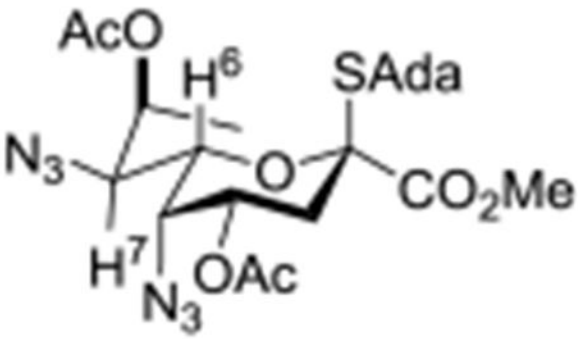


Figure 3.
Influence of Configuration at C5 and C7 on the Side Chain Conformation of NeuAc Donors.

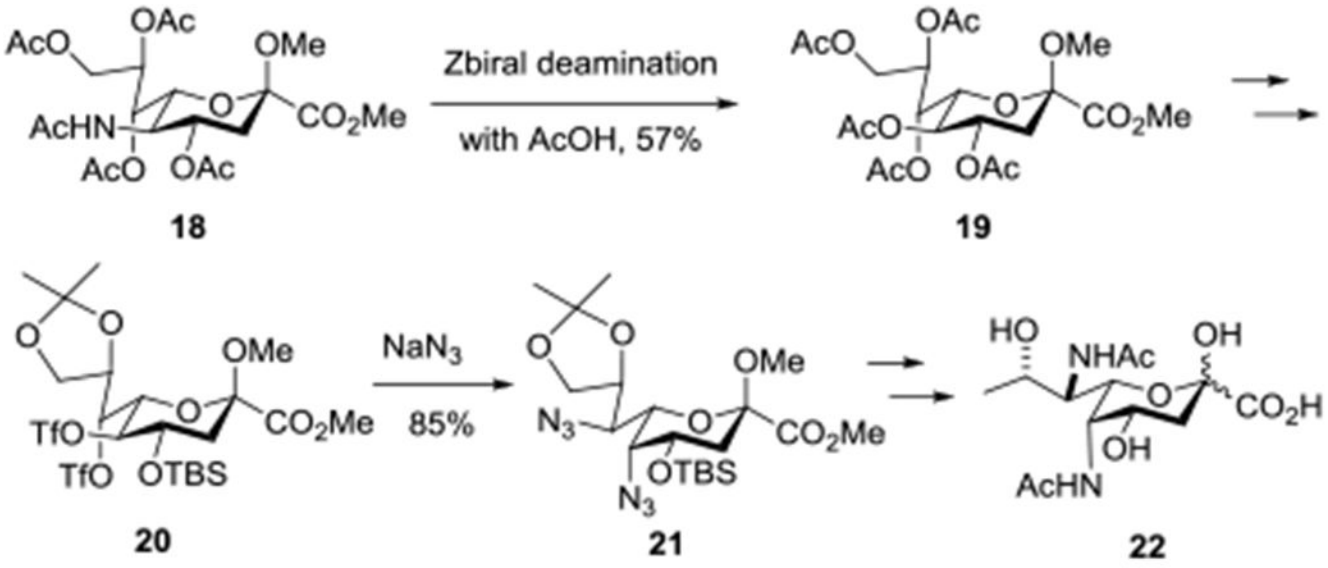


16, Leg
gg, $J_{6,7}$ = 1.4 Hz

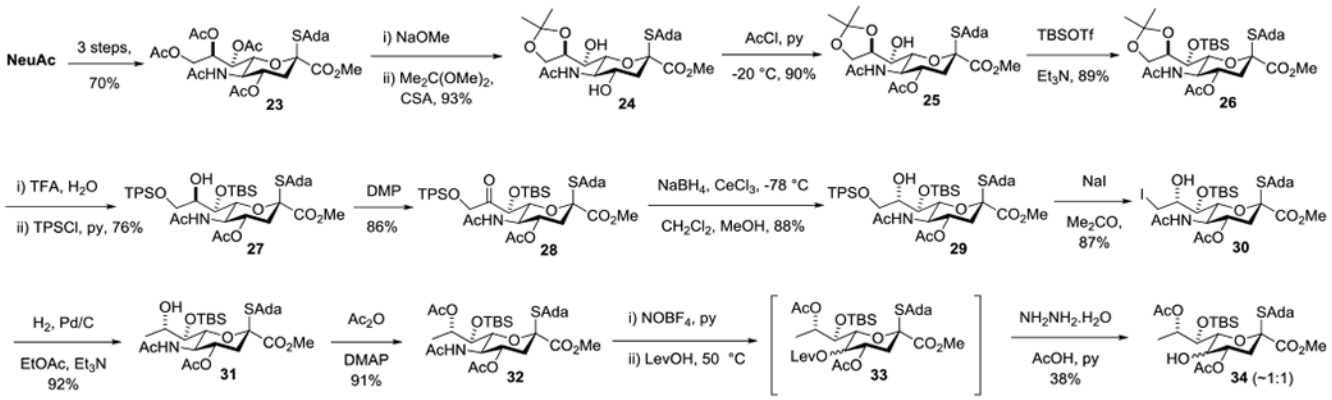


17, Pse, (5,7,8-tris-*epi*)
predicted *tg* conformation

Figure 4.
Equatorially Selective Leg and Pse Donors

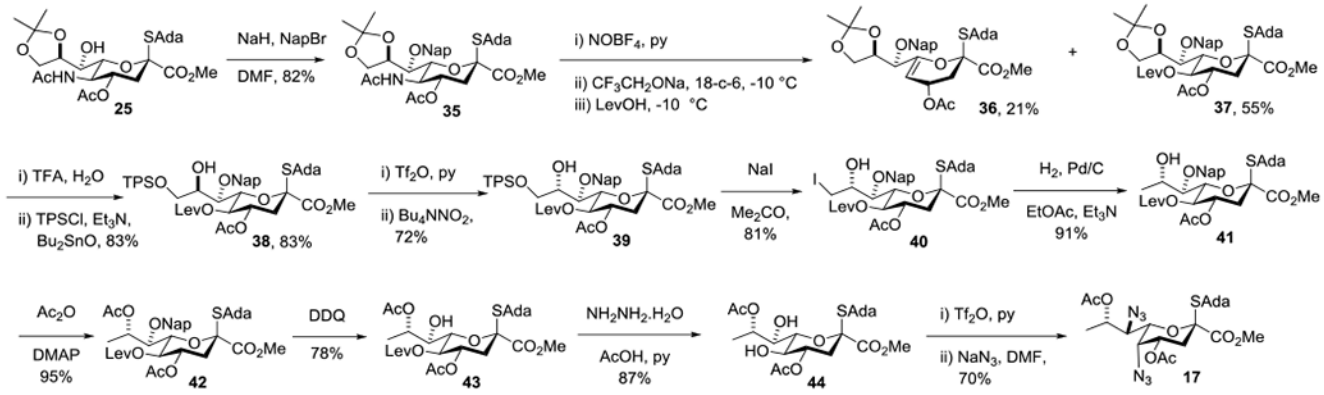


Scheme 1.
Key Steps in the Kiefel-Payne Synthesis of *N,N*-diacetyl-Pse **22**.

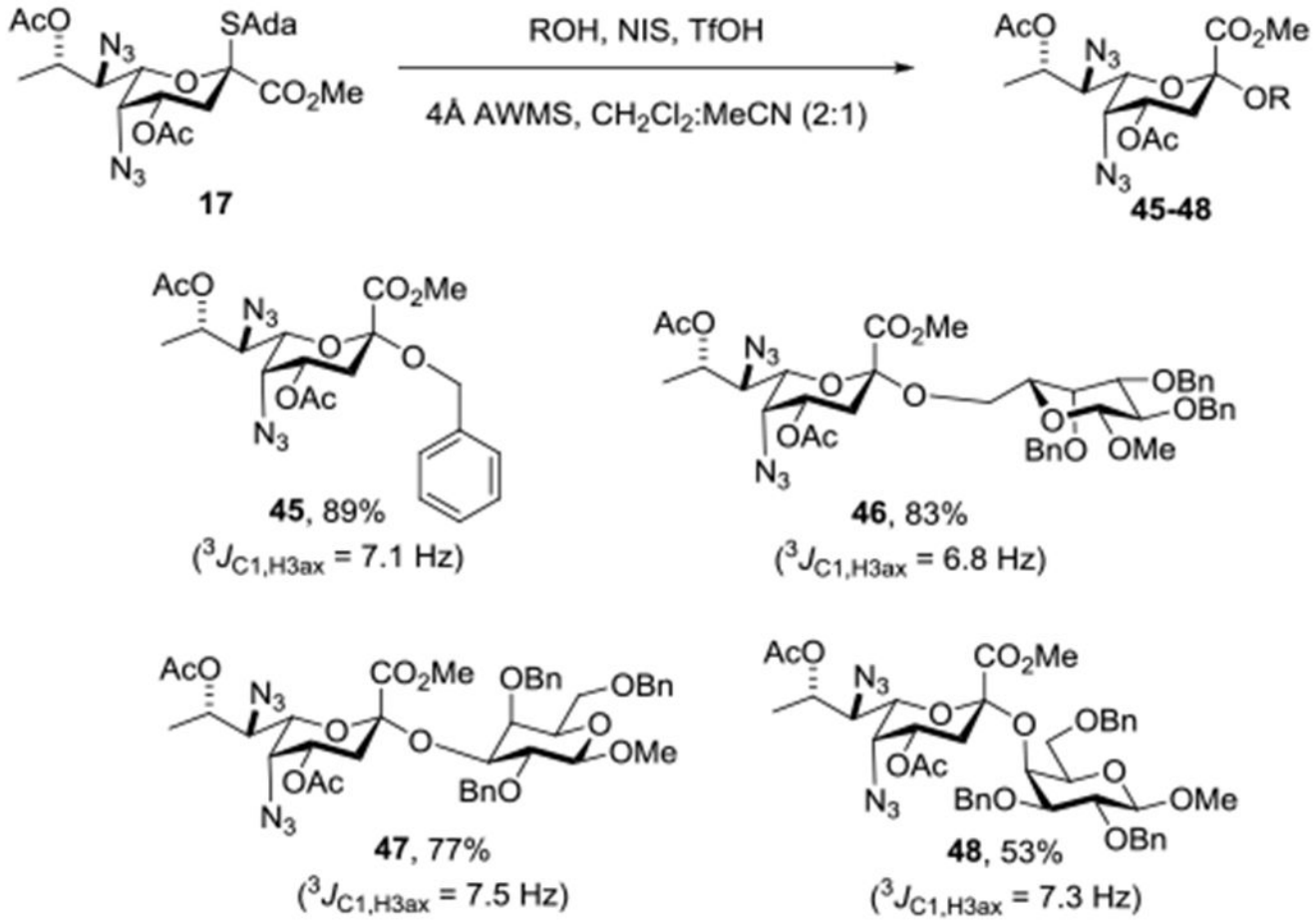


Scheme 2.

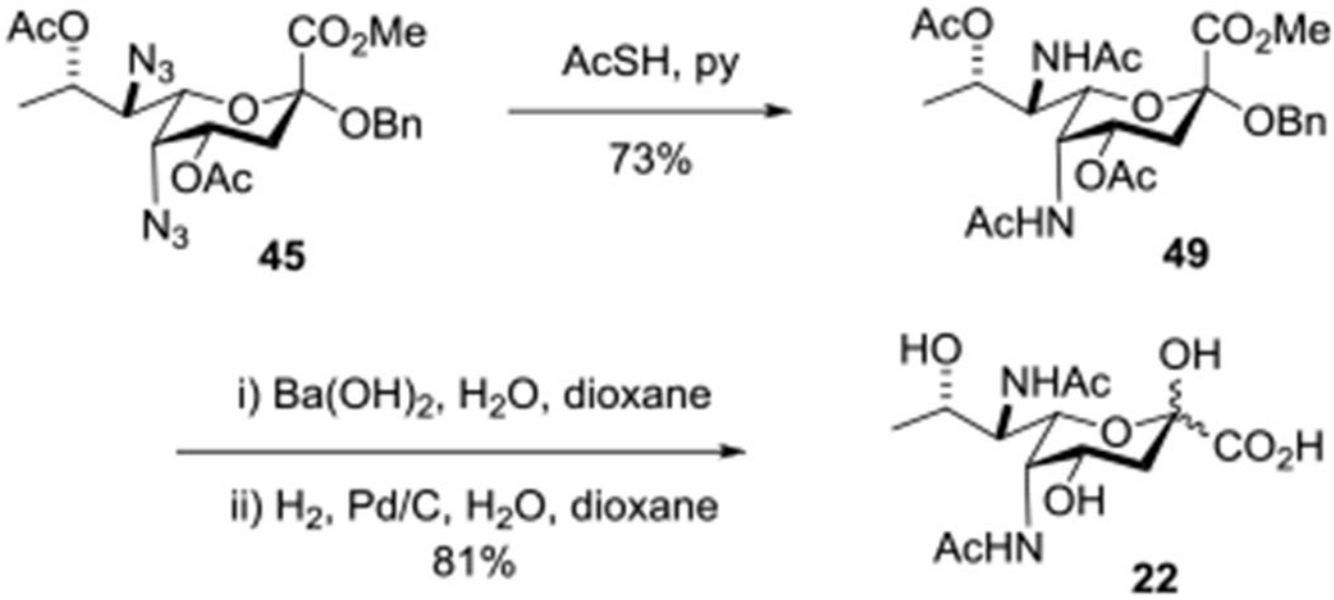
First Approach with Late Stage Oxidative Deamination



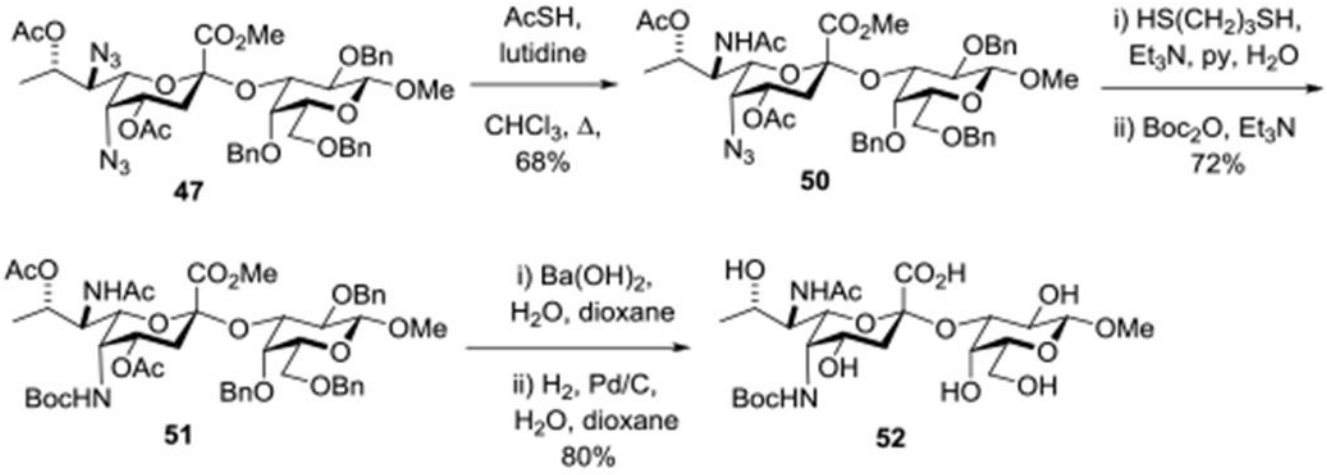
Scheme 3.
Synthesis of Pse Donor **17**.



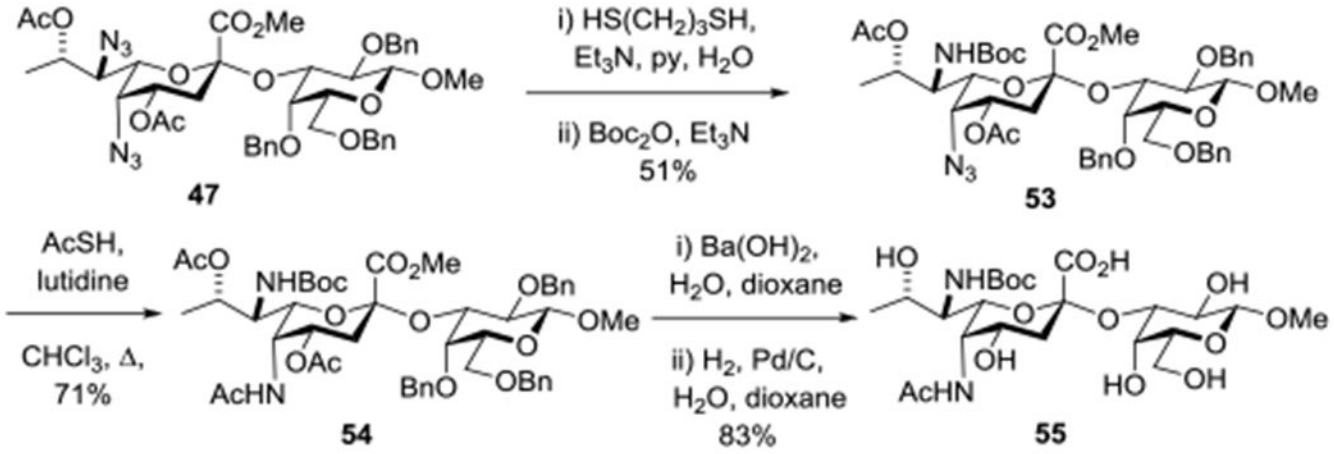
Scheme 4.
Stereoselective Synthesis of Equatorial Pse Glycosides



Scheme 5.
Synthesis of *N,N*-Diacetyl Pse



Scheme 6.
Regioselective Azide Cleavage.



Scheme 7.
Alternative Regioselective Azide Cleavage.