EDGE ARTICLE

An orthogonal and reactivity-based one-pot glycosylation strategy for both glycan and nucleoside synthesis: access to TMG-chitotriomycin, lipochitooligosaccharides and capuramycin†

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Both glycans (*O*-glycosides) and nucleosides (*N*-glycosides) play important roles in numerous biological processes. Chemical synthesis is a reliable and effective means to solve the attainability issues of these essential biomolecules. However, due to the stereo- and regiochemical issues during glycan assembly, together with problems including the poor solubility and nucleophilicity of nucleobases in nucleoside synthesis, the development of one-pot glycosylation strategies toward efficient synthesis of both glycans and nucleosides remains poor and challenging. Here, we report the first orthogonal and reactivity-based one-pot glycosylation strategy suitable for both glycan and nucleoside synthesis on the basis of glycosyl *ortho*-(1-phenylvinyl)benzoates. This one-pot glycosylation strategy not only inherits the advantages including no aglycon transfers, no undesired interference of departing species, and no unpleasant odors associated with the previously developed orthogonal one-pot glycosylation strategy based on glycosyl *ortho*-alkynylbenzoates, but also highly expands the scope (glycans and nucleosides) and increases the number of leaving groups that could be employed for the multistep one-pot synthesis (up to the formation of four different glycosidic bonds). In particular, the current one-pot glycosylation strategy is successfully applied to the total synthesis of a promising tuberculosis drug lead capuramycin and the divergent and formal synthesis of TMG-chitotriomycin with potent and specific inhibition activities toward β-*N*-acetylglucosaminidases and important endosymbiotic lipochitooligosaccharides including the Nod factor and the Myc factor, which represents one of the most efficient and straightforward synthetic routes toward these biologically salient molecules.

Introduction

Both glycans (*O*-glycosides) and nucleosides (*N*-glycosides) are essential biomolecules with a variety of important roles in numerous biological processes such as viral and bacterial infection, DNA and RNA synthesis, cell growth, proliferation and signaling, immune response, as well as enzyme metabolism and regulation.[1–3] Due to the issues of the micro-heterogeneity, it is extremely difficult to isolate pure and homogeneous glycans and nucleosides from natural resources. Chemical synthesis of both glycans and nucleosides is an effective, reliable and scalable method to solve the issues of the attainability, which can highly facilitate the development of new therapeutic agents and the decipherment of their functions.[3–11] During the past three decades, many strategies including automated chemical synthesis,[12] one-pot glycosylation strategies,[13] orthogonal glycosylation[14] and latent-active synthesis[15] have been developed to achieve the efficient construction of glycosidic bonds (C–O bonds), among which one-pot glycosylation strategies are highly efficient and attractive. In comparison with traditional glycosylation methods, which need tedious deprotection and protection manipulations during glycan assembly, one-pot glycosylation strategies not only avoid the purifications of intermediates and workups of the glycosylation interval, but also highly accelerate glycan synthesis and reduce chemical wastes. However, one-pot glycosylation strategies for nucleoside synthesis (C–N bonds) are much less investigated. The development of one-pot glycosylation strategies suitable for both glycan and nucleoside synthesis remain poor and challenging due to the stereo- and regiochemical issues during glycan assembly,[13,16] together with other problems including the poor

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solubility and nucleophilicity of nucleobases in nucleoside synthesis.[3,11]

In 2019, we reported that the orthogonal one-pot glycosylation strategy based on glycosyl *ortho*-alkynylbenzoates[6b] (ABz) can be applied to the efficient synthesis of a variety of glycans, which solves the shortcomings including aglycon transfers, the interference of departing species and unpleasant odor inherent to orthogonal one-pot glycosylation based on thioglycosides[13b] (Scheme 1). This orthogonal one-pot glycosylation strategy has recently been successfully used in the modular synthesis of a nona-decasaccharide motif from *Psidium guajava* polysaccharides with potent α-glucosidase inhibitory activity.[13c] Notwithstanding these advances, challenges still remain in this field. For instance, the number of leaving groups that can be utilized in multi-step orthogonal one-pot synthesis is still limited.[12b,13] Furthermore, one-pot glycosylation strategies suitable for the construction of both C–O and C–N bonds remain undeveloped. Recently, we developed a new, versatile and efficient glycosylation method for both glycan and nucleoside synthesis, which uses glycosyl *ortho*-(1-phenylvinyl)benzoates (PVB) as novel glycosyl donors.[11a] We wondered whether the utilization of orthogonalities and reactivities of glycosyl PVB could be explored to achieve the efficient one-pot synthesis of both glycans and nucleosides.

Herein, we report the first orthogonal and reactivity-based one-pot glycosylation strategy suitable for both glycan and nucleoside synthesis on the basis of glycosyl PVB. This one-pot glycosylation strategy not only inherits advantages including no

aglycon transfers, no undesired interference of departing species, and no unpleasant odors associated with the previously developed orthogonal one-pot glycosylation strategy based on glycosyl ABz, but also highly expands the scope (glycans and nucleosides) and increases the number of leaving groups that could be employed for the multistep one-pot synthesis (up to the formation of four different glycosidic bonds). A wide range of nucleosides and glycans including α-Gal epitope, isoGb$_3$ trisaccharide and phytoalexin elicitor β-glucan heptasaccharide have been efficiently synthesized with this strategy. Furthermore, the synthetic advantages and utilities of this strategy have been successfully demonstrated by the divergent and formal synthesis of TMG-chitotriomycin with potent and specific inhibition activities toward β-*N*-acetylglucosaminidases and important endosymbiotic lipochitooligosaccharides including the Nod factor and the Myc factor, as well as the total synthesis of nucleoside antibiotic capuramycin with promising anti-tuberculosis activities (Scheme 1).

Results and discussion

In order to develop one-pot glycosylation strategies (Scheme 1), two criteria should be met: (1) when the leaving group LG_n is activated, the next leaving group LG_{n+1} must be stable and unaffected; (2) sideproducts produced during the glycosylation should not interfere with the next glycosylations. To this end, we commenced with the investigation of the orthogonalities of glycosyl PVB with the other glycosyl donors. First, glycosyl PVB was fixed as the bifunctional acceptor with the activatable leaving group and the free hydroxyl group. Several different glycosyl donors were studied, including glycosyl trichloroacetimidate (TCAI),[17] glycosyl *N*-phenyltrifluoroacetimidate (PTFAI),[18] *S*-benzoxazolyl (SBox) glycoside,[19] *S*-thiazolinyl (STaz) glycoside[20] and glycosyl *ortho*-alkynylbenzoate (ABz).[6b] The screening results showed that the bifunctional acceptor glycosyl PVB **2** could be successfully coupled with a variety of glycosyl donors under the activation conditions for TCAI **1a** and PTFAI **1b** (cat. TMSOTf, −20 °C), SBox **1c** (AgOTf, rt), STaz **1d** (MeOTf, rt) and ABz **1e** (PPh$_3$AuOTf, rt), affording the corresponding PVB disaccharides **3a–3b** in excellent yields (Scheme 2). Self-condensation products were not detected.

Next, we went on to study whether glycosyl PVB could be selectively coupled with other bifunctional acceptors in the activation of NIS and TMSOTf. Due to the much higher reactivities of glycosyl PVB than thioglycosides,[11a] the desired disaccharide **6a** was indeed obtained in an excellent yield (90%) during glycosylation between the disarmed glucosyl PVB **4** and the disarmed thioglycoside[21] **5a** in the presence of NIS and TMSOTf at −15 °C. Similarly, PVB **4** was selectively coupled with the disarmed acceptor *n*-Pen[22] **5b**, providing the desired disaccharide **6b** in 90% yield (Scheme 3).

Having investigated orthogonalities and reactivities of glycosyl PVB with other glycosyl donors, we next focused on the one-pot synthesis of glycans (Scheme 4). For the glycosyl TCAI and PVB pair, TCAI **1a** (1.2 equiv.) was glycosylated with PVB **2** (1.0 equiv.) in the catalysis of TMSOTf at −20 °C, furnishing the
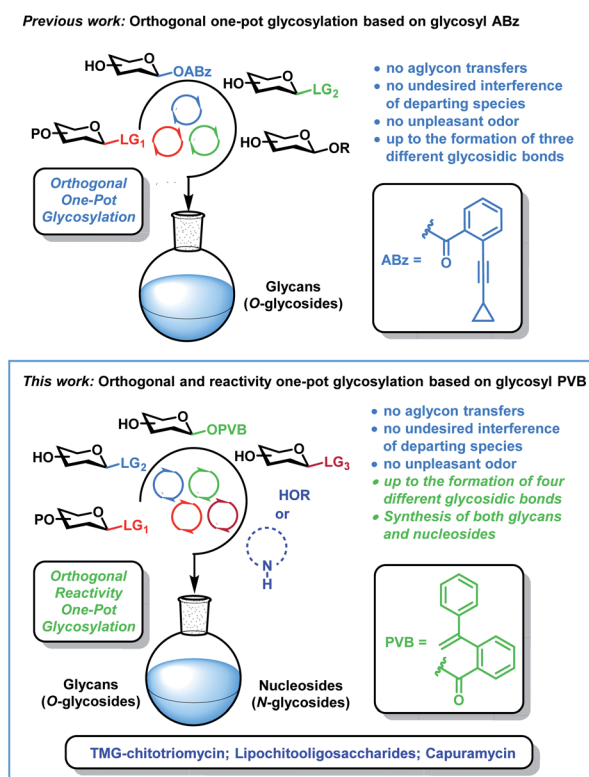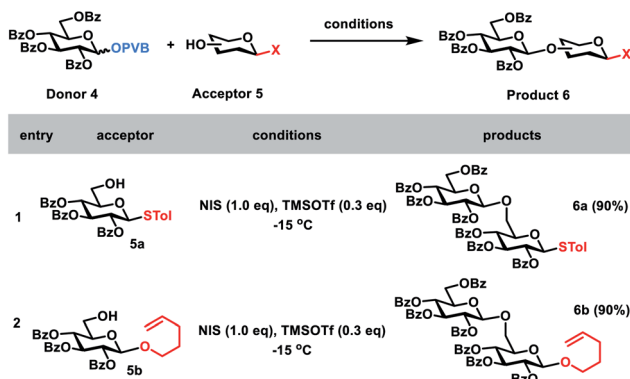

Scheme 1 Strategies of one-pot glycosylation based on glycosyl ABz and glycosyl PVB.
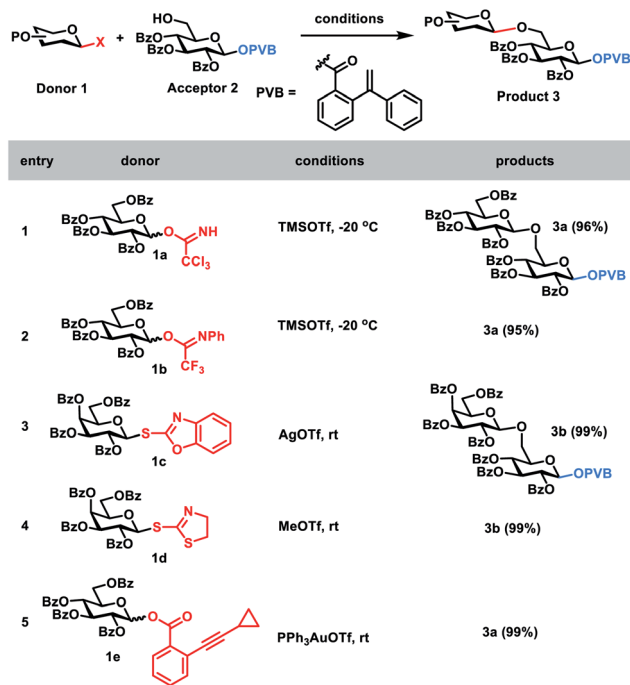
Scheme 2 The investigation of the orthogonalities of glycosyl PVB with other glycosyl donors.


Scheme 3 The investigation of the reactivities of glycosyl PVB with other glycosyl donors.

PVB disaccharide intermediate. The above intermediate was further coupled with the disarmed thioglycoside **5a** (0.9 equiv.) under the activation of NIS and TMSOTf at −15 °C, providing the trisaccharide **25** in 87% yield in one pot. Similarly, for the glycosyl PTFAI and PVB pair, the successive coupling of Gla PTFAI **7**, Gla PVB **8** and the poor 4-OH glucosaminyl thioglycoside acceptor **9** produced the trisaccharide **26** in 54% yield in a one-pot manner. This trisaccharide motif was discovered as an α-Gal epitope that could induce xenograft rejection.[23] Replacing the above acceptor **9** with the poor 4-OH glucosyl acceptor **10a** also generated trisaccharide **27** in the same flask in 81% yield, the motif of which is the glycosphingolipid analogue of isoGb₃ that could serve as a key endogenous human NKT cell antigen.[24] It is noted that the 4,6-di-*tert*-butylsilyene group

ensures the highly stereoselective α-galactosylation during the synthesis of **26–27**.[25] For the SBox glycoside and glycosyl PVB pair, coupling of SBox **1c** (1.3 equiv.) with PVB **2** (1.0 equiv.) in the activation of AgOTf at room temperature produced the disaccharide intermediate, which was further glycosylated with the acceptor **11** (0.8 equiv.) in the promotion of NIS and TMSOTf, efficiently generating trisaccharide **28** in 91% yield in one pot. Similarly, for the STaz glycoside and glycosyl PVB pair, MeOTf was used to activate STaz **1d** over PVB **2**, followed by the addition of acceptor **10b** and the activators NIS and TMSOTf, successfully furnishing trisaccharide **29** in 90% yield in one pot. For the glycosyl ABz and PVB pair, Yu glycosylation of ABz **12** (1.3 equiv.) with 3-OH glucosyl PVB **13** (1.0 equiv.) under the catalysis of PPh₃AuOTf afforded the PVB disaccharide, which was followed by coupling with the acceptor **11** (1.0 equiv.) in the presence of NIS and TMSOTf, generating trisaccharide **30** in a one-pot manner in 88% yield. Using the above similar procedures, sequential glycosylation of ABz **1e**, PVB **2** and 3-OH glucosyl acceptor **14** provided trisaccharide **32** in the same flask in 89% yield. For the glycosyl PVB and thioglycoside pair, the disarmed PVB **4** (1.0 equiv.) was coupled with the disarmed STol **5a** (1.0 equiv.) in the presence of NIS (1.0 equiv.) and TMSOTf (0.3 equiv.) at −15 °C, generating the STol disaccharide intermediate. The above intermediate was further glycosylated with acceptor **15** (0.8 equiv.) under the activation of NIS and TMSOTf at a higher temperature (−15 °C to rt), producing trisaccharide **33** efficiently in 88% yield *via* reactivity-based one-pot glycosylation. For the glycosyl PVB and *n*-Pen glycoside pair, reactivity-based one-pot glycosylation of PVB **4** (1.1 equiv.), *n*-Pen **5b** (1.0 equiv.) and acceptor **16** (0.8 equiv.) using the above similar procedures also successfully afforded trisaccharide **34** in 81% yield.

Then, we investigated the multistep one-pot synthesis of oligosaccharides. For the SBox glycoside, glycosyl ABz and PVB triplet, the orthogonal one-pot glycosylation of SBox **17** (1.2 equiv.), ABz **18** (1.0 equiv.), PVB **2** (0.9 equiv.) and the acceptor **19** (0.8 equiv.) successfully provided the tetrasaccharide **35** in 65% yield. For the glycosyl PTFAI, ABz and PVB triplet, the sequential glycosylation of PTFAI **1b** (1.3 equiv.), ABz **20** (1.1 equiv.), PVB **21** (1.0 equiv.), and the acceptor **5b** (1.2 equiv.) also proceeded smoothly, generating the tetrasaccharide **36** in the same flask with 62% yield, whose sulfated derivatives exhibit strong proangiogenic activity.[26] Fungal β-glucan oligosaccharides possess the structure of the branched heptasaccharide motif **37**, which could elicit phytoalexin production in soybean plant.[27] Orthogonal double glycosylation of PTFAI **22a** (2.5 equiv.) with 3-OH, 6-OH-glucosyl ABz **23** (1.0 equiv.) in the catalysis of HOTf provided the ABz trisaccharide, which was further coupled with PVB **21** (0.9 equiv.) *via* Yu glycosylation, generating the PVB tetrasaccharide. The above intermediate was further glycosylated with the trisaccharide acceptor **31** (0.9 equiv.) derived from **30**, producing the branched heptasaccharide **37** with the formation of four new glycosidic linkages in the same flask in 72% yield. For a group of glycosyl PTFAI, ABz, PVB and thioglycoside, orthogonal one-pot glycosylation of PTFAI **1b** (1.3 equiv.), ABz **20** (1.1 equiv.) and PVB **21** (1.0 equiv.) efficiently furnished the PVB trisaccharide
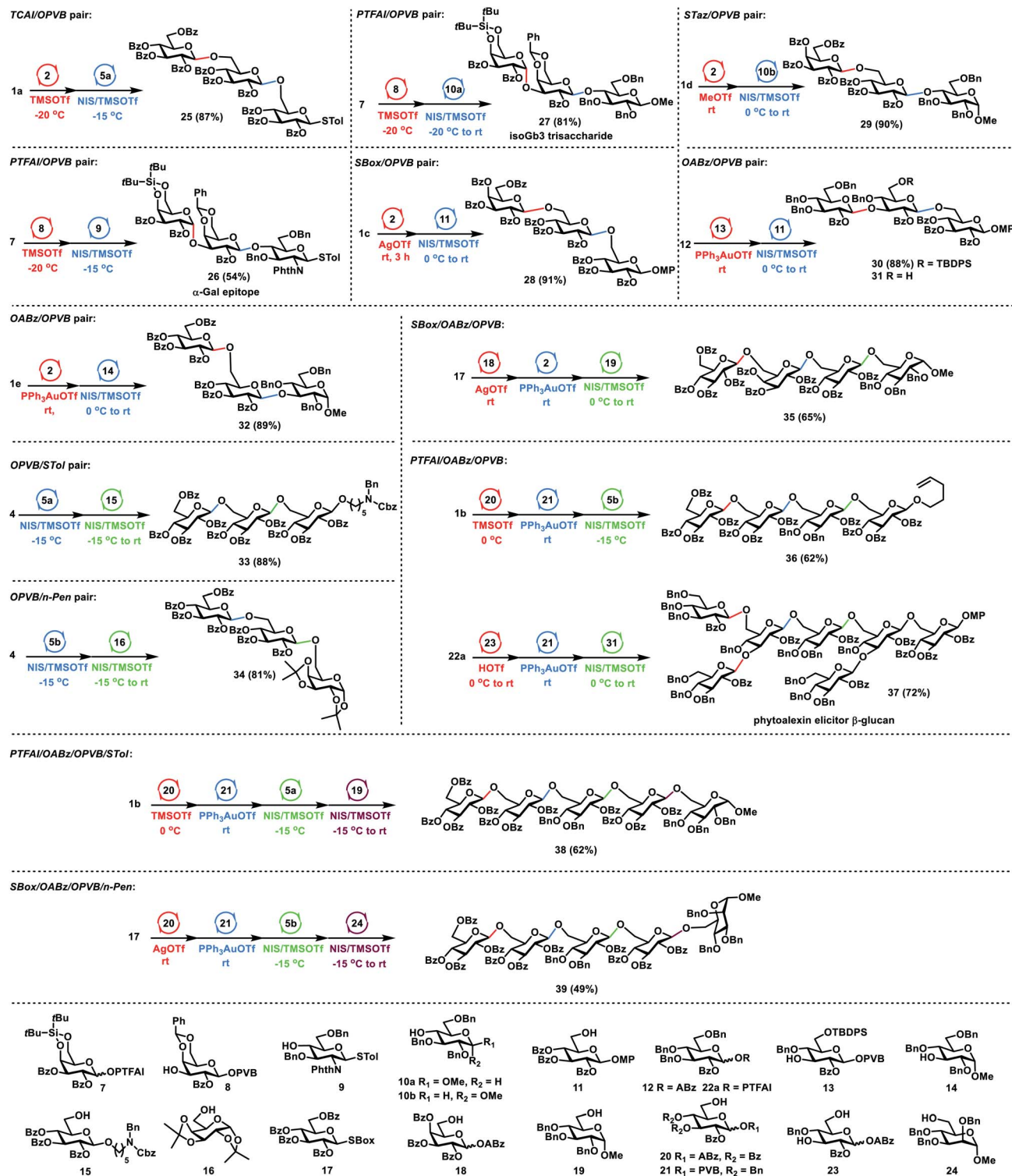
Scheme 4 The orthogonal and reactivity-based one-pot glycosylation strategy for glycan synthesis.

intermediate, which was further coupled with the disarmed STol **5a** (1.0 equiv.) in the presence of NIS and TMSOTf at −15 °C, producing the tetrasaccharide. The above tetrasaccharide intermediate was further coupled with acceptor **19** (0.9 equiv.) in the activation of NIS and TMSOTf at a higher reaction temperature (−15 °C to rt), affording the

pentasaccharide **38** in 62% yield with the production of four new linkages via an orthogonal and reactivity-based one-pot glycosylation strategy. For a group of SBox glycoside, glycosyl ABz and PVB, as well as *n*-Pen glycoside, the orthogonal and reactivity-based one-pot glycosylation of SBox **17** (1.3 equiv.), ABz **20** (1.1 equiv.), PVB **21** (1.0 equiv.), *n*-Pen **5b** (1.2 equiv.) and
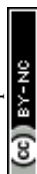
the acceptor **24** (0.9 equiv.) also successfully provided the desired pentasaccharide **39** in 49% yield with the formation of four new different glycosidic bonds.

Next, we focused on the one-pot synthesis of nucleosides (Scheme 5). For the glycosyl TCAI and PVB pair, coupling of Glc TCAI **22b** (1.2 equiv.) with Rib PVB **40** (1.0 equiv.) in the activation of TMSOTf at −20 °C generated the disaccharide PVB intermediate, which underwent further *N*-glycosylation with the silylated uracil intermediate derived from silylating uracil **41** (2.0 equiv.) with *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) in CH$_3$CN, providing the desired nucleoside **50** in 80% yield in a one-pot manner. Under similar reaction conditions, a catalytic amount of TMSOTf was used to couple Man TCAI **42** with Rib PVB **43**, affording the disaccharide PVB intermediate. The above PVB intermediate was further glycosylated with silylated nucleobases derived from 5-fluorouridine **44**, trifluorothymine **45**, *N*4-benzoylcytosine **46** and 5-fluorocytosine derivative **47** with BSTFA in CH$_3$CN, furnishing the desired nucleosides **51–54** in 85%, 90%, 88%, and 71% yields respectively in one-pot. It is noteworthy that the current protocol of *N*-glycosylation of pyrimidines with glycosyl PVB tolerates the carbamate functionality in pyrimidines. When a famous Vorbrüggen type reaction[28] was utilized to couple the silylated 5-fluorocytosine derivative **47** under the action of pyridinium triflate salts,[29] significant decomposition of the carbamate

functionality and moderate coupling yield (50% yield) were observed.[30] Besides pyrimidines, purines are also viable substrates. It was noted that *N*-glycosylation of purines was a challenging task due to the *N*9/*N*7 regioselectivity issues of purines in the glycosylation reactions. Nevertheless, nucleoside **55** was prepared successfully in an excellent 87% yield in one-pot by successive coupling of TCAI **42**, PVB **43**, and *N*6-bis(*tert*-butoxycarbonyl)adenine **48**. It was noted that the *tert*-butoxycarbonyl (Boc) group installed in purine **48** served two purposes, namely, solving the solubility issues of purine nucleobases and blocking the glycosylation of *N*7 position. Similarly, sequential glycosylation of TCAI **42**, PVB **43**, and *N*2-*tert*-butoxycarbonyl-2-amino-6-iodopurine **49** gave the desired nucleoside **56** in 82% yield in a one-pot manner, which is a useful intermediate to the guanine nucleoside or 6-substituted analogs. For the SBox glycoside and glycosyl PVB pair, the coupling of Gla SBox **1c** (1.3 equiv.) with Glc PVB **2** (1.0 equiv.) in the activation of AgOTf produced the disaccharide intermediate, which was further glycosylated with the silylated nucleobase derived from 5-fluorouridine **44** (2.0 equiv.), furnishing the desired nucleoside **57** in a one-pot manner with 80% yield. For the STaz glycoside and glycosyl PVB pair, MeOTf was used to activate Gla STaz **1d** (1.3 equiv.) over Rib PVB **40** (1.0 equiv.), followed by *N*-glycosylation with silylated *N*4-benzoylcytosine **46** (2.0 equiv.) in the presence of NIS and TMSOTf,
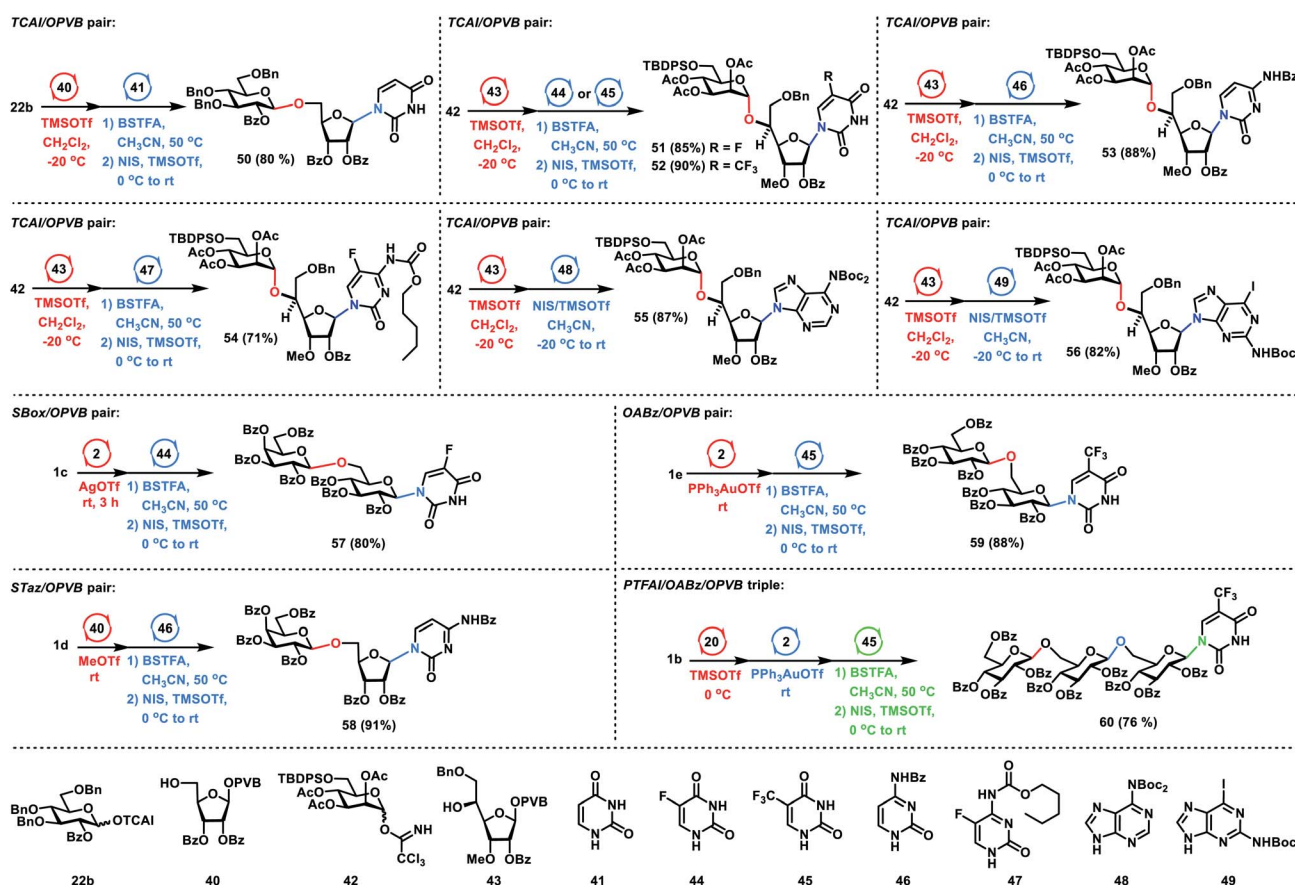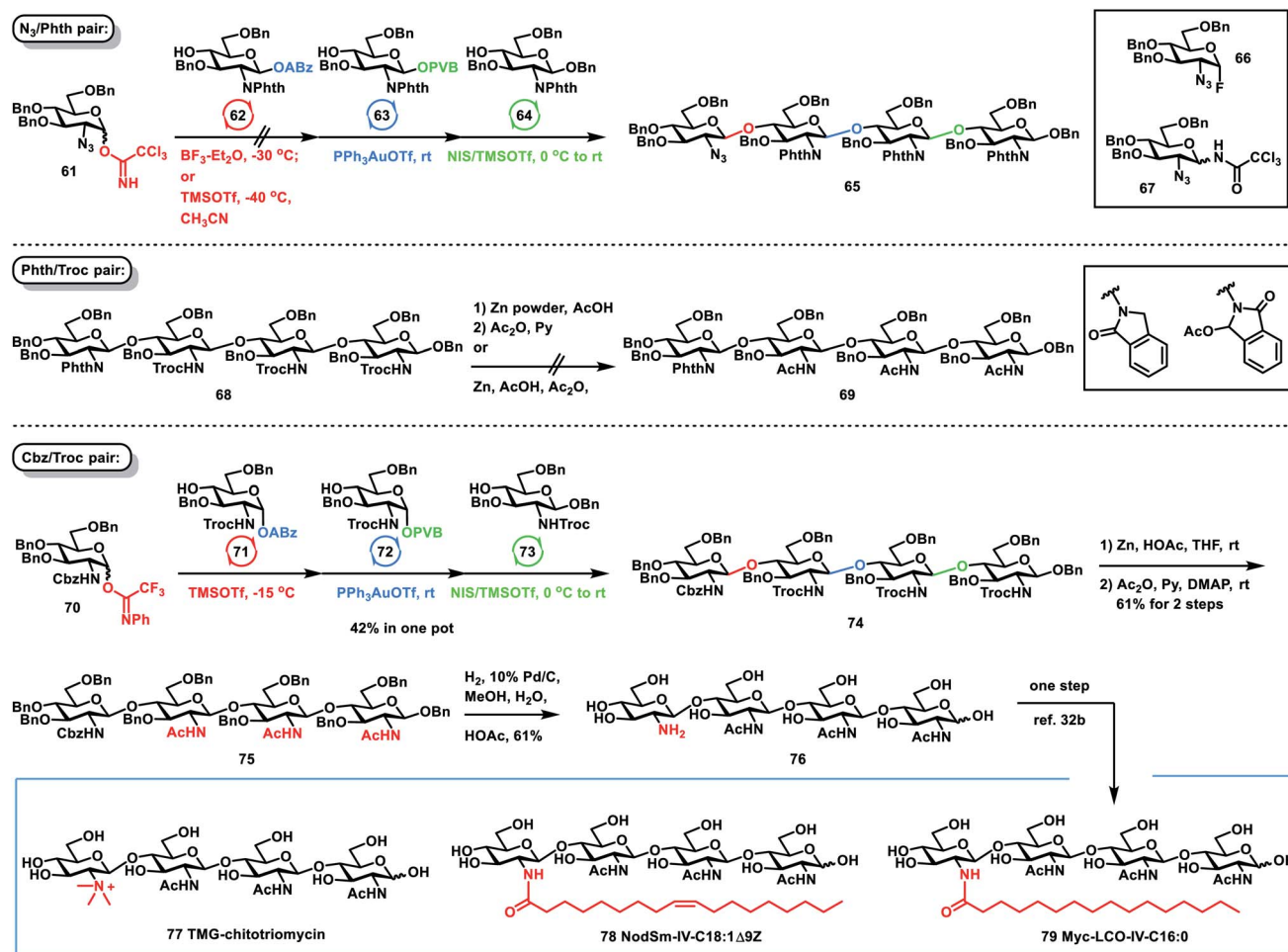

Scheme 5 The orthogonal one-pot glycosylation for nucleoside synthesis.

providing nucleoside **58** in 91% yield in the same flask. For the glycosyl ABz and PVB pair, Yu glycosylation[6b] between ABz **1e** (1.2 equiv.) and PVB **2** (1.0 equiv.) produced the disaccharide intermediate, which further underwent *N*-glycosylation with silylated trifluorothymine **45** (2.0 equiv.), affording the desired nucleoside **59** in 88% yield in a one-pot manner. For a group of glycosyl PTFAI, ABz and PVB, orthogonal one-pot glycosylation of PTFAI **1b** (1.3 equiv.), ABz **20** (1.1 equiv.), PVB **2** (1.0 equiv.) and silylated trifluorothymine **45** (2.0 equiv.) generated the desired nucleoside **60** in 76% yield.

After the orthogonal and reactivity-based one-pot synthesis of both glycans and nucleosides was successfully investigated, we further applied this one-pot glycosylation strategy to the formal synthesis of TMG-chitotriomycin and lipochitooligosaccharides (Scheme 6). TMG-chitotriomycin is an enzyme inhibitor specific for insect and fungal β-*N*-acetylglucosaminidases (GlcNAcase) with no inhibition of mammalian and plant GlcNAcases.[31] Especially because the unique inhibitory character of TMG-chitotriomycin can be very useful for the development of selective pesticides or fungicides and chitinolytic systems studies, TMG-chitotriomycin has stimulated broad synthetic interest.[32] Structurally, TMG-chitotriomycin is very

close to important glycolipids and lipochitooligosaccharides including the Nod factors[33] and the Myc factors.[34] They are important signal molecules involved in two ecologically crucial endosymbioses, nitrogen-fixing rhizobia and legume endosymbiosis and arbuscular mycorrhiza endosymbiosis between fungi and terrestrial plants. Due to their important actions and natural scarcity, these molecules also intrigued chemists for chemical synthesis.[35] However, because of the poor solubility of glucosamine units and the notoriously poor nucleophilicity of the 4-hydroxyl group of glucosamine derivatives, the efficient and stereoselective one-pot synthesis of these bioactive molecules still remains challenging.

The correct selection of protecting groups for the differentiation of the amino groups between the nonreducing units and reducing unit is required to achieve the successful, efficient and stereoselective one-pot synthesis of TMG-chitotriomycin **77**, the Nod factor **78** and the Myc factor **79**. At first, we chose a pair of azido (N₃) and phthalimido (Phth) groups as amino protecting groups. However, it was unsuccessful in preparing tetrasaccharide **65** *via* orthogonal one-pot glycosylation of 2-N₃ GlcN TCAI **61**, 2-*N*-Phth GlcN ABz **62**, 2-*N*-Phth GlcN PVB **63** and GlcN **64**. The issue is the first glycosylation between **61** and **62**. When

Scheme 6 Divergent and formal synthesis of TMG-chitotriomycin and lipochitooligosaccharides *via* the orthogonal one-pot glycosylation strategy based on glycosyl PVB.
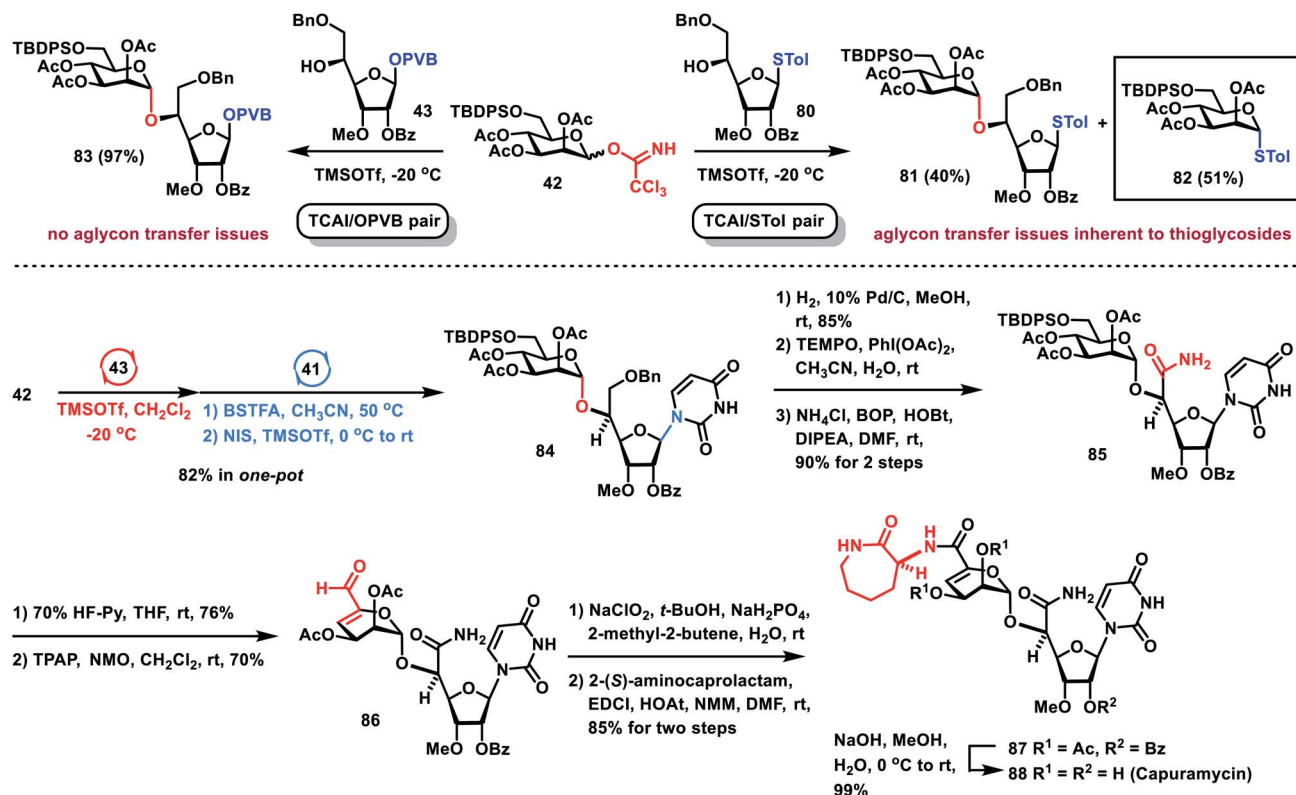
Scheme 7 Total synthesis of capuramycin *via* the orthogonal one-pot glycosylation strategy based on glycosyl PVB.

BF$_3$–Et$_2$O was used to activate 2-N$_3$ GlcN **61** over 2-*N*-Phth GlcN **62** at −30 °C, considerable amounts of side products glycosyl fluoride **66** and *N*-glycosyl trichloroacetamide **67** *via* rearrangement were formed, which was detrimental to the successful one-pot assembly of **65**. While TMSOTf was employed as a catalyst for coupling of **61** and **62** in the presence of CH$_3$CN at −40 °C, no glycosyl fluoride byproduct **66** was formed, but the stereoselectivity of this glycosylation was low (β/α = 2/1). Later, we switched to Phth and 2,2,2-trichloroethoxycarbonyl (Troc) groups as the pair of amino protecting groups. Although one-pot assembly of tetrasaccharide **68** was successfully carried out on the basis of a group of glycosyl PTFAI, ABz and PVB, the conversion of **68** to the desired tetrasaccharide **69** was not successful *via* selective deprotection of three Troc groups over one Phth group. While zinc powder and acetic acid were used to remove three Troc groups, the Phth group in **68** was also reduced, generating an isoindolin-1-one derivative or a 3-oxoisoindolin-1-yl acetate derivative. Finally, we used a benzyloxycarbonyl (Cbz) amino protecting group instead of the Phth group. To our delight, orthogonal one-pot glycosylation of 2-*N*-Cbz PTFAI **70** (1.4 equiv.), 2-*N*-Troc ABz **71** (1.0 equiv.), 2-*N*-Troc PVB **72** (0.8 equiv.) and the acceptor 2-*N*-Troc GlcN **73** (0.7 equiv.) proceeded smoothly and stereoselectively, affording the desired tetrasaccharide **74** in a satisfactory 42% yield. Furthermore, selective removal of three Troc groups over one Cbz group in **74** was successfully carried out with zinc power and acetic acid, which was followed by acetylation of the resulting amine group, furnishing the desired tetrasaccharide **75** in 61% yield over two steps. Finally, global

hydrogenolysis of 10 Bn groups and one Cbz group in the presence of 10% Pd/C successfully provided the desired tetrasaccharide **76** in 61% yield. The analytical data of synthetic tetrasaccharide **76** are consistent with those reported for **76**, from which the synthesis of TMG-chitotriomycin **77**, the Nod factor **78** and the Myc factor **79** was reported by Jean-Marie Beau and co-workers *via* one-step protocol of methylation and acylation, respectively.[32b] Compared with the previous synthetic approaches toward lipochitooligosaccharides and TMG-chitotriomycin,[32,35] the current one-pot and divergent synthetic strategy represents one of the most efficient and straightforward synthetic routes toward these important and bioactive molecules.

After the one-pot and formal synthesis of TMG-chitotriomycin **77**, the Nod factor **78** and the Myc factor **79** has been successfully carried out, we further demonstrated that the one-pot glycosylation strategy based on glycosyl PVB can be successfully applied to the efficient total synthesis of the nucleoside antibiotic capuramycin **88** (Scheme 7), which is a promising tuberculosis drug lead.[36,37] When Man TCAI **42** was coupled with thioglycoside **80** under the catalysis of TMSOTf, besides the desired disaccharide **81** (40% yield), a significant amount of aglycone transfer byproduct **82** (51% yield) was obtained, which exposed the aglycone transfer issue inherent to one-pot glycosylation based on thioglycosides.[38] Instead, under the same reaction conditions, glycosylation of TCAI **42** and PVB **43** proceeded smoothly, generating the desired disaccharide PVB **83** in an excellent 97% yield, which precludes the aglycone transfer issue. Furthermore, orthogonal one-pot glycosylation

of TCAI **42** (1.2 equiv.), PVB **43** (1.0 equiv.) and silylated uracil **41** (2.0 equiv.) furnished the desired nucleoside **84** in 82% yield. Hydrogenolytic removal of the benzyl group in **84** produced an alcohol, which was oxidized to carboxylic acid under TEMPO oxidation conditions,[39] followed by condensation with NH_4Cl to give the corresponding primary amide **85**. The removal of the TBDPS group in **85** with 70% HF–Py afforded the alcohol intermediate, which was subjected to the same TEMPO oxidation conditions, producing complex mixtures. Modified Parikh–Doering oxidation of the alcohol intermediate also gave unsuccessful results.[40] However, Ley oxidation of the resulting alcohol (TPAP, NMO) resulted in the successful oxidation–elimination reaction, providing the desired α,β-unsaturated aldehyde **86** in 70% yield.[41] Pinnick oxidation of aldehyde **86** ($NaClO_2$, t-BuOH, NaH_2PO_4, 2-methyl-2-butene, H_2O) furnished a carboxylic acid, which was condensed with 2-(S)-amino-caprolactam (EDCI, HOAt, NMM), producing protected capuramycin **87** in 85% yield over two steps. Saponification of **87** by using NaOH in aq. MeOH provided capuramycin **88** in quantitative yield. The analytical data of synthetic capuramycin **88** are in good agreement with those reported for nucleoside antibiotic capuramycin.[37]

Conclusions

In summary, the orthogonalities and reactivities of glycosyl PVB with the other leaving groups have been systematically investigated, and the first orthogonal and reactivity-based one-pot glycosylation strategy suitable for both glycan and nucleoside synthesis based on glycosyl PVB has been successfully developed, which has advantages such as no aglycon transfers, no undesired interference of departing species, and no unpleasant odors. Furthermore, the scope (glycans and nucleosides) and the number of leaving groups that could be employed for the multistep one-pot synthesis has also been highly expanded with this strategy. A variety of nucleoside and glycan motifs including α-Gal epitope, isoGb$_3$ trisaccharide and phytoalexin elicitor β-glucan heptasaccharide had been efficiently prepared with this strategy. In particular, this one-pot glycosylation strategy has been successfully applied to the divergent and formal synthesis of TMG-chitotriomycin with the potent and specific inhibition of GlcNAcase activities and important plant endosymbiotic glycolipids. The correct selection of Cbz and Troc orthogonal amino protecting groups is crucial for the divergent, stereoselective and formal one-pot synthesis of TMG-chitotriomycin and lipochitooligosaccharides, which represents one of the most straightforward synthetic routes toward these biologically salient molecules. Furthermore, the total synthesis of nucleoside antibiotic capuramycin with promising anti-tuberculosis activities has also been successfully demonstrated with the current one-pot glycosylation strategy, which can highly streamline the chemical synthesis of both glycans and nucleosides with important biological functions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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