O-Glycosylation Methods in the Total Synthesis of Complex Natural Glycosides

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O-Glycosylation Methods in the Total Synthesis of Complex Natural Glycosides

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The total syntheses of 33 complex natural *O*-glycosides, such as the glycosides of macrocyclic lactones/lactams, enediynes, anthracyclines, angucyclines, and anthracycline, are highlighted, with a major focus being placed on the *O*-glycosylation reactions which connect the saccharides and the aglycones. These successful *O*-glycosylation reactions employ such donors as glycosyl bromides, fluorides, iodides, trichloroacetimidates, *N*-phenyl trifluoroacetimidates, thioglycosides, sulfoxides, heteroaryl thioglycosides, 1-hydroxyl sugars, 1-*O*-acetates, and *ortho*-alkynylbenzoates. Each synthesis is depicted starting from the *O*-glycosylation of the aglycone (or its precursor); the glycosylation conditions and outcomes (yields and stereoselectivities) are discussed, and the subsequent transformations toward the

final target, including the elongation of the glycan, the elaboration of the aglycone, and the protecting group manipulations are also given in detail.

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1 Introduction

Glycosides occur widely in plants, microorganisms, and low animals as secondary metabolites, and function mainly as signal and defense chemicals.[1-3] The aglycones comprise all types of the natural products, and the sugar moieties are usually added onto the aglycones at the post-modification stage via stepwise glycosylation with various glycosyltransferases.[4,5] Thus, the saccharide parts are highly characteristic and conservative in the monosaccharide composition and the glycosidic linkages, which are dependent on the type of the aglycones. Nevertheless, microheterogeneity occurs due to the tolerance of the glycosyltransferases for a slight variation of the monosaccharide units, the incompleteness of the enzymatic reactions, and the subsequent modifications. In fact, such microheterogeneity is a hallmark of those complex glycosides bearing relatively long saccharides, and this makes isolation of a homogenous congener, especially in a large quantity, an extremely difficult task. On the other hand, numerous glycosides have shown a wide variety of pharmacological activities, especially the antitumor, anti-infective, and immunomodulatory effects.[6] The saccharide residues can affect the pharmacokinetic and pharmacodynamic properties of the glycosides, and can also be part of the pharmacophore.[7,8] These findings constitute a powerful impetus for the advance of chemical synthesis of complex natural glycosides.

Chemical synthesis of a glycoside requires integration of the synthetic chemistry of the particular aglycone and the saccharide, involving especially a condensation of the two distinct parts and an overall protecting-group arrangement. Focusing on the *O*-glycosylation reactions which condense the saccharides and the aglycones, we provide here a comprehensive review on the total synthesis of complex natural *O*-glycosides. An excellent review relevant to this topic was published in 1993 by Toshima and Tatsuta.[9] Besides, the total synthesis of complex natural glycosides has been included in other review articles on the synthetic carbohydrate chemistry.[10-13] However, none of these previous reviews focus on the construction of the

glycosidic linkages between the saccharides and the complex aglycones in the realm of total synthesis.

The present review surveys literatures from 1994 (after the Toshima-Tatsuta article)[9] up to date, the selection of examples is arbitrary but confines to the following scopes: (1) Only the successful total synthesis is included, so that bypassing a challenging step by adjusting the target structures is not possible. (2) Only complex glycosides bearing complicated scaffold and multiple functional groups on the aglycones are considered, thus the glycosylation reactions are challenged beyond the realm of the classical synthesis of glycans. In this sense, the excellent synthesis of glycosides bearing complex glycans, such as glycolipids[14] and glycopeptides[15] is excluded. Moreover, the total synthesis of complex glycopeptide antibiotics such as vancomycin[16] and arylomycin[17] is also excluded. (3) Only *O*-glycosides are covered. The synthesis of *C*-glycosides could also employ classical glycosylation reactions (with *C*-nucleophiles as acceptors), nevertheless, the *C*-glycosidic linkage is stable and can usually be constructed at an early stage of the synthesis.[18] Complex *N*-glycosides are mainly nucleoside antibiotics, wherein the *N*-glycosylation involves only pyrimidine and purine derivatives as acceptors.[19] (4) The glycosides of triterpenoids and steroids are excluded, which have been exhaustively reviewed recently.[20-22] So is the synthesis of glycosides of flavonoids.[23-25]

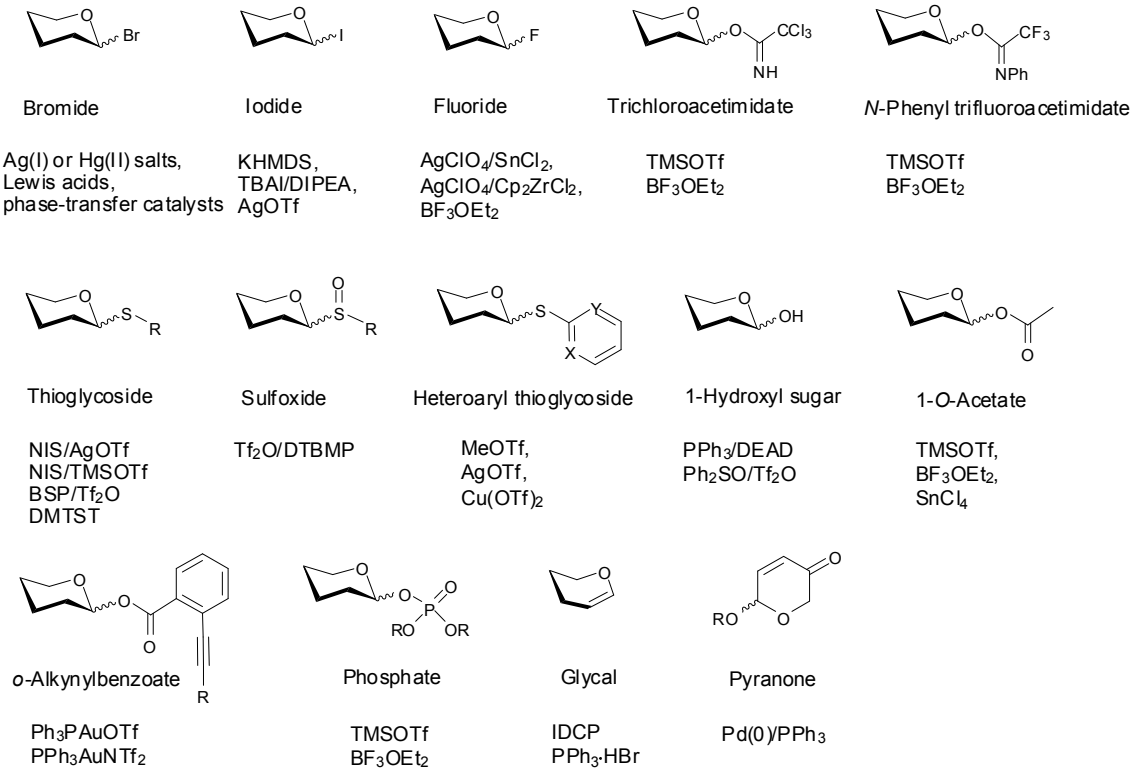
The strategic consideration of the total synthesis of glycosides has been described in our preceding account,[26] so that all the synthesis can be classified into four categories based on the stage at which the glycosidic linkage between the saccharide and the aglycone is constructed. In the present review, we discuss each total synthesis starting from the *O*-glycosylation step which connects the saccharide and the aglycone, and categorize the synthesis based on the glycosyl donors employed in this step. The subsequent transformations toward the final targets are depicted and discussed, those include elongation of the glycans,

elaboration of the aglycone, and/or manipulation of the protecting groups. The late-stage synthesis demonstrates the compatibility of the chemical transformations demanded in the presence of the complex aglycone and the *O*-linked saccharide residues. Before entering into the total synthesis, a brief introduction on the major *O*-glycosylation methods used in the total synthesis and the general mechanism of the *O*-glycosylation reaction is provided.

2 Major *O*-glycosylation methods in the total synthesis and the general mechanistic consideration

Since the first chemical glycosylation reaction was reported by Michael in 1879,[27] numerous methods have been developed for the formation of the *O*-glycosidic linkages.[28,29] The majority of these methods involves the condensation of an alcohol with a glycosyl donor under the action of a promoter which facilitates the departure of the leaving group installed at the anomeric carbon of the donor. The major types of glycosyl donors which have been employed in the total synthesis of complex *O*-glycosides during the past two decades are listed in Scheme 1. Those include glycosyl bromides,[30] fluorides,[31] iodides,[32] trichloroacetimidates,[33,34] *N*-phenyl trifluoroacetimidates,[35,36] thioglycosides,[37-39] sulfoxides,[40] heteroaryl thioglycosides,[41,42] 1-hydroxyl sugars,[43,44] 1-*O*-acetates,[45] and *ortho*-alkynylbenzoates.[46,47] Listed are also the commonly used promoters for each type of the donors, which are demanded by the nature of the leaving groups. Glycosyl phosphates,[48] glycals[49] and pyranones[50,51] have been successfully used in the synthesis of complex glycopeptides[52] and saponins,[53,54] which are not discussed in the present article.

Scheme 1. The major types of glycosyl donors and their promoters employed in the total synthesis of complex *O*-glycosides.

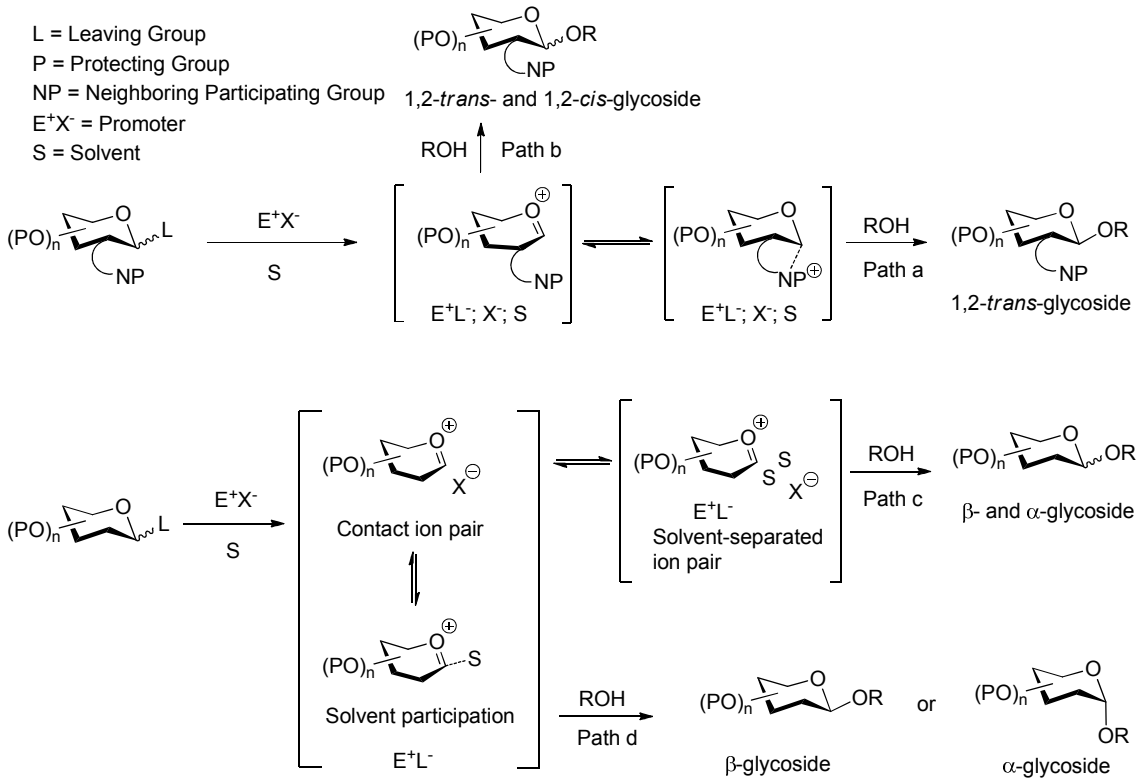


In general, activation of a glycosyl donor by a promoter yields a continuum of the species relevant to the sugar oxocarbenium intermediate (Scheme 2).[55-59] Each of these interconvertible nucleophilic species can react with an alcoholic acceptor to give the *O*-glycoside, but in a different stereo-preference. Thus, the relative abundance of these transient species and their kinetic preference for the glycosylation determine the overall outcome of the stereoselectivity. Accordingly, the stereoselectivity of a glycosylation reaction is affected by the nature of the donor sugar (including its protecting group pattern) and the reaction conditions (i.e., promoter, solvent, temperature, additive, as well as the sequence of mixing the reactants/reagents). Usually, 1,2-*trans*-glycosides can be confidently synthesized with donors installed with a neighboring participating group (path a). This also constitutes a reliable approach to the stereoselective synthesis of 2-deoxy-glycosides, in which the neighboring participating groups need to be removed afterwards.[60-62] Glycosylation through path b (via the oxocarbenium species) erodes the stereoselectivity. Direct stereoselective

synthesis of the 1,2-*cis*-glycosides and the 2-deoxy-glycosides must resort to fine tuning of the reaction parameters, so as to force the glycosylation to proceed via a contact ion pair or a solvent participating intermediate (path d).[63,64] Glycosylation through path c (via the solvent-separated ion pair) usually leads to a mixture of α/β glycosides, however, controlling the conformation of the sugar oxocarbenium intermediate (mainly by the protecting groups) could also lead to stereoselective glycosylation.[65-68]

In the context of synthesis of complex glycosides, one shall bear in mind that all the nucleophilic and electrophilic species derived from the donor and the promoter could react with the functional groups present in the aglycone, leading ultimately to failure of the glycosylation. Additionally, the inherent stereochemistry of the aglycone acceptor, especially when it is of topological prominence, would influence strongly the stereoselectivity of the glycosylation reaction. The last point to emphasize here is that the *O*-glycosidic linkages, especially the abundantly occurring deoxy-glycosides, might undergo anomerization or cleavage in the mild acidic conditions during the synthesis.

Scheme 2. A general mechanistic scheme for the chemical *O*-glycosylation reactions.

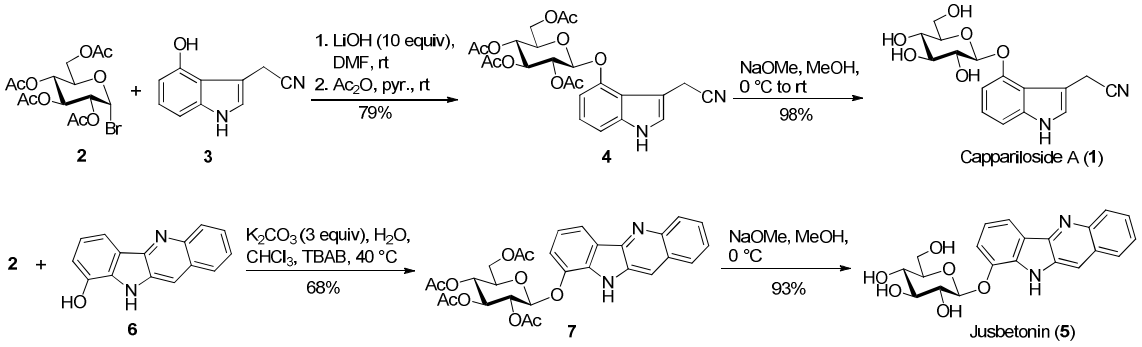


3 Syntheses with glycosyl bromides

The classical Koenigs-Knorr reaction requires an excess amount of the heavy metal salts for activation of the glycosyl bromides for glycosylation.[30] A late extension of this method is the use of basic conditions, especially the phase-transfer catalysis conditions, for coupling of the glycosyl bromides with acidic nucleophiles.[56] These mild conditions are especially applicable to the synthesis of phenolic *O*-glycosides. Thus, cappariloside A (**1**), an indole glycoside isolated from the fruits of *Capparis spinosa* that was used as a diuretic in the folk medicine of Turkey, was readily synthesized (Scheme 3).[69] Lithium hydroxide (10 equiv) was found to be an optimal base for the coupling of glucosyl α-bromide **2** and 4-hydroxyindole **3**. Subsequent acetylation provided the β-glycoside **4** in 79% yield (for two steps). Removal of the acetyl groups in **4** gave cappariloside A (98%).

Jusbetonin (**5**), which was isolated from *Justicia betonica* as the first natural glycoside of indolo[3,2-b]quinolone, was synthesized in 2009 (Scheme 3).[70] Under the phase-transfer catalysis conditions, coupling of bromide **2** with phenol **6** led to the desired β-*O*-glycoside **7** in 68% yield. Saponification of compound **7** with sodium methoxide afforded jusbetonin.

Scheme 3. Synthesis of cappariloside A (**1**) and jusbetonin (**5**).



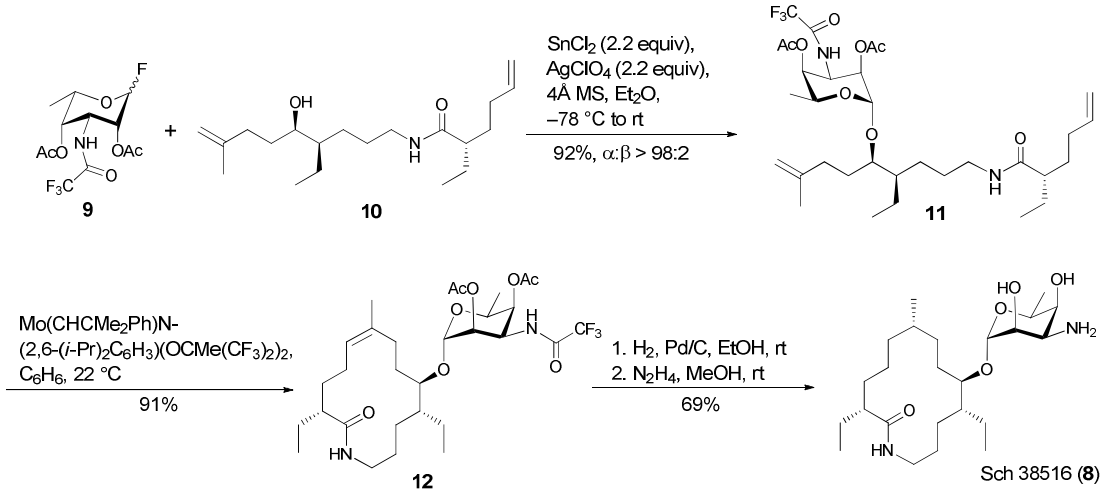
4 Syntheses with glycosyl fluorides

Compared to glycosyl bromides, glycosyl fluorides are much later to be exploited as the glycosylation donors. Nevertheless, since the first report by Mukaiyama *et al.* in 1981,[31] glycosyl fluorides have become one of the most favorably used donors in the synthesis of complex glycosides. Not only are these donors more stable (thus easier for handling), but also their activation is much milder, requiring such fluorophiles as $AgClO_4/SnCl_2$, $AgClO_4/Cp_2ZrCl_2$, and BF_3OEt_2 as the promoter.

In 1996, Hoveyda *et al*. reported the total synthesis of the antifungal agent Sch 38516 (**8**) using glycosyl fluoride in the glycosylation (Scheme 4).[71,72] Thus, under the promotion of $SnCl_2$ (2.2 equiv) and $AgClO_4$ (2.2 equiv), the glycosylation of diene carbinol **10** with fluoride **9** proceeded smoothly to give glycoside **11** in 92% yield with the α-anomer as the predominant isomer (α:β > 98:2). After ring closure of **11** using the Mo-catalyzed olefin

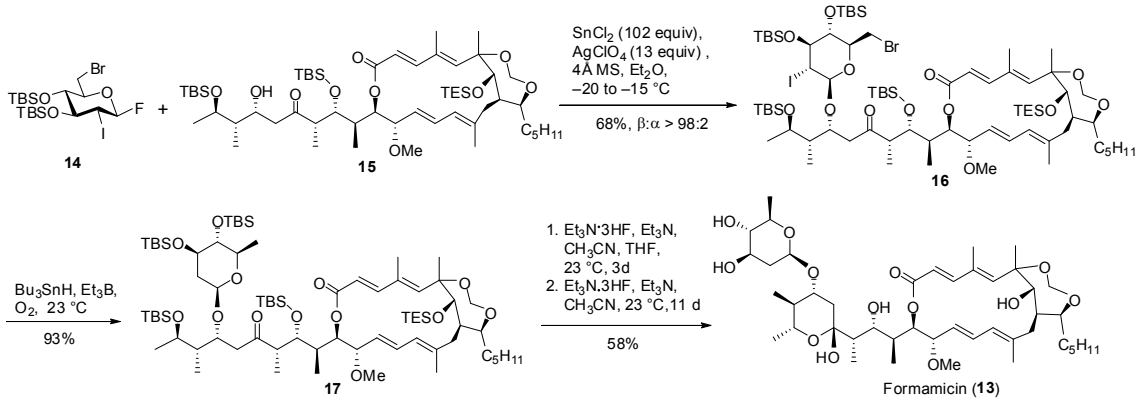
metathesis,[73] the resultant cyclolactam **12** was subjected to a stereocontrolled hydrogenation. Subsequent cleavage of the acetyl and trifluoroacetyl groups with hydrazine at room temperature afforded Sch 38516 (**8**) in 63% yield (for three steps).

Scheme 4. Total synthesis of Sch38516 (**8**).



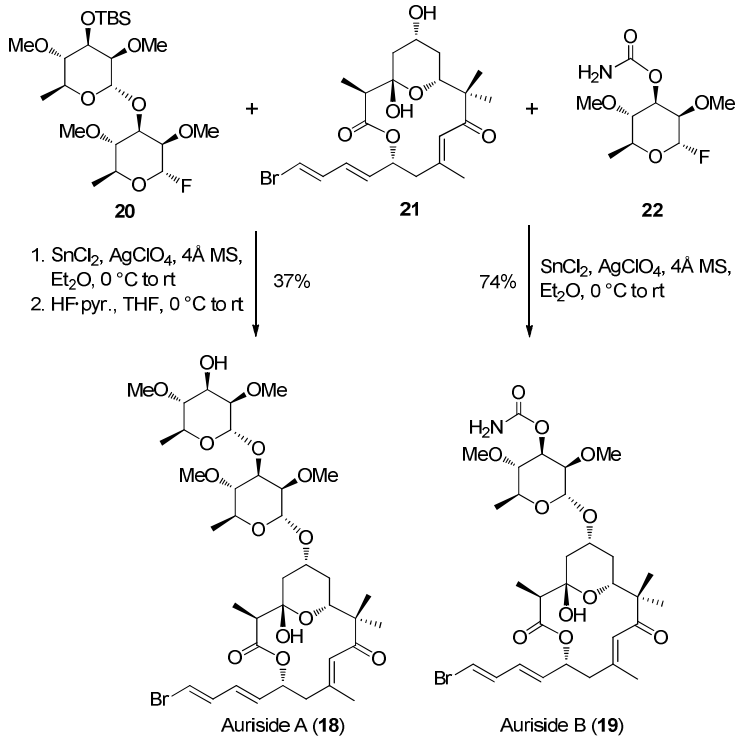
In 2004, Roush *et al.* achieved the total synthesis of formamicin **13**, a plecomacrolide isolated from the culture broth of *Saccharothrix* sp. MK27-91F2 (Scheme 5).[74] This glycoside showed potent cytotoxicity against a panel of cancer cell lines with the IC_{50} values ranging from 0.15–0.13 ng/mL.[75] The coupling of 2-iodo-glycosyl fluoride **14** with the intricate macrolide **15** was effected in the presence of $SnCl_2$ (102 equiv) and $AgClO_4$ (13 equiv), leading to the desired β-glycoside **16** in 68% yield with an excellent stereoselectivity (β:α > 98:2). Reduction of the iodide and bromide groups in the sugar residue was realized with $Bu_3SnH/Et_3B/O_2$[76] to give 2,6-dideoxy-glycoside **17** (93%). Finally, the *O*-TBS and *O*-TES groups were carefully removed with *in situ* generated $Et_3N{\cdot}2HF$[77] in CH_3CN/THF and CH_3CN, respectively; simultaneous hemiacetal formation provided formamicin (**13**) in 58% yield (for two steps).

Scheme 5. Total synthesis of formamicin (**13**).



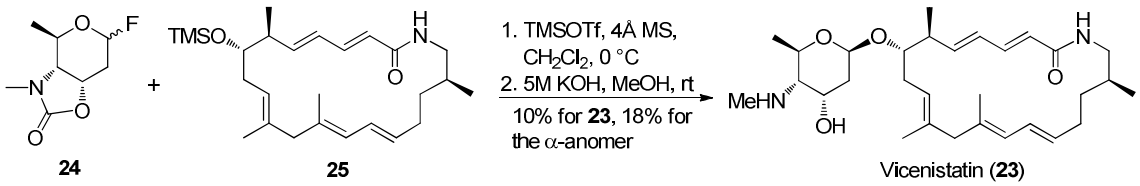
Paterson *et al*. reported the total synthesis of aurisides A (**18**) and B (**19**) in 2005, which were isolated from the Japanese sea hare *Dolabella auricularia* and displayed significant cytotoxicity against HeLa S_3 cervical cancer cell lines (Scheme 6).[78] Under the action of $SnCl_2/AgClO_4$, the coupling of disaccharide fluoride **20** with macrolide **21** proceeded, and subsequent removal of the silyl group with HF·pyridine gave the α-glycoside auriside A (**18**) in a moderate yield of 37% (for two steps). In comparison, the coupling of monosaccharide fluoride **22** with **21** led to the desired α-glycoside auriside B **(19**) in a high 74% yield. Note that, an enantioselective synthesis of aurisides A and B was achieved by Kigoshi *et al.* in 2006 using a similar glycosylation method.[79] Additionally, total synthesis and stereochemical reassignment of (–)-lyngbyaloside B, a structure analogue of aurisides, were recently reported by Fuwa *et al.*, wherein a glycosyl trichloroacetimidate was used as the key glycosylation step.[80]

Scheme 6. Total synthesis of aurisides A (**18**) and B (**19**).



Vicenistatin (**23**), a cytotoxic glycoside of macrocyclic lactam isolated from *Streptomyces halstedii* HC-34, was synthesized by Kakinuma *et al.* in 2002 and Kanoh *et al.* in 2010, respectively (Scheme 7).[81,82] In Kanoh's synthesis, the Mukaiyama protocol (with $SnCl_2/AgClO_4$ as the promoter) was found not reproducible, therefore, the glycosylation of polyene lactam **25** with 2-deoxy-glycosyl fluoride **24** was performed in the presence of TMSOTf;[83] subsequent cleavage of the carbamate under basic conditions delivered vicenistatin (**23**) and its α-anomer in 10% and 18% yield (for two steps), respectively.

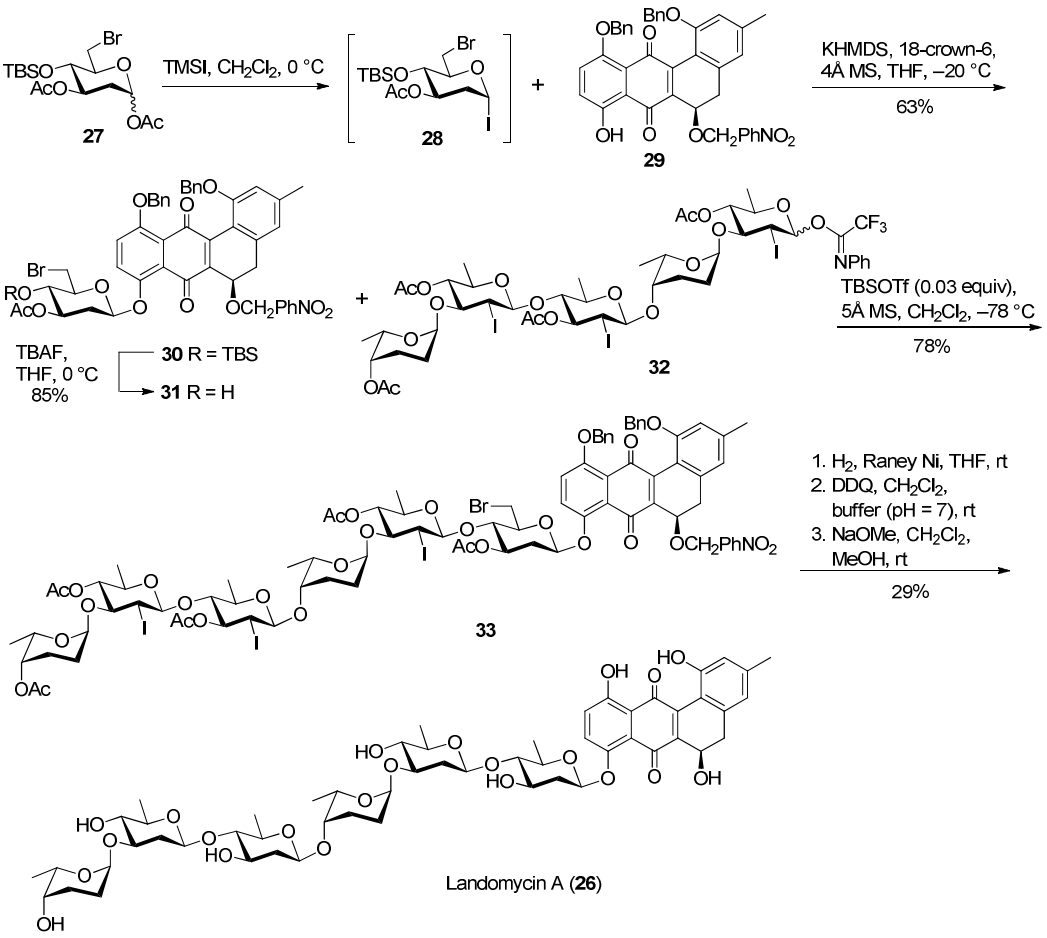
Scheme 7. Total synthesis of vicenistatin (**23**).



5 Synthesis with glycosyl iodides

Glycosyl iodides, although were recognized as early as in 1929,[32] have never been a popular type of glycosyl donors because of their vulnerability. Nevertheless, recent findings that the glycosyl iodides could be generated stereoselectively and undergo *in situ* glycosylation under basic conditions[84-86] offered them a chance to be applied in the total synthesis of peculiar targets. An example in point is the total synthesis of landomycin A (**26**), which represents the largest congener of the angucycline antibiotics (Scheme 8).[87] Thus, in the presence of KHMDS and 18-crown-6,[88] α-glycosyl iodide **28** that was formed from treatment of glycosyl acetate **27** with TMSI, was reacted with landomycinone **29**, affording the desired β-glycoside **30** in 63% yield, along with the corresponding $\Delta^{5,6}$ elimination derivative (14%). The *O*-TBS group in the sugar residue of **30** was then removed, subsequent coupling with pentasaccharide *N*-phenyl trifluoroacetimidate **32** under the catalysis of TBSOTf (0.03 equiv) furnished hexasacharide **33** (78%). Finally, hydrogenolysis of **33** with Raney–Ni (to remove the iodides, bromide, and benzyl groups), DDQ oxidation (of the resultant hydroquinone), and saponification (to remove the acetyl groups) furnished landomycin A (29% for three steps).

Scheme 8. Total synthesis of landomycin A (**26**).

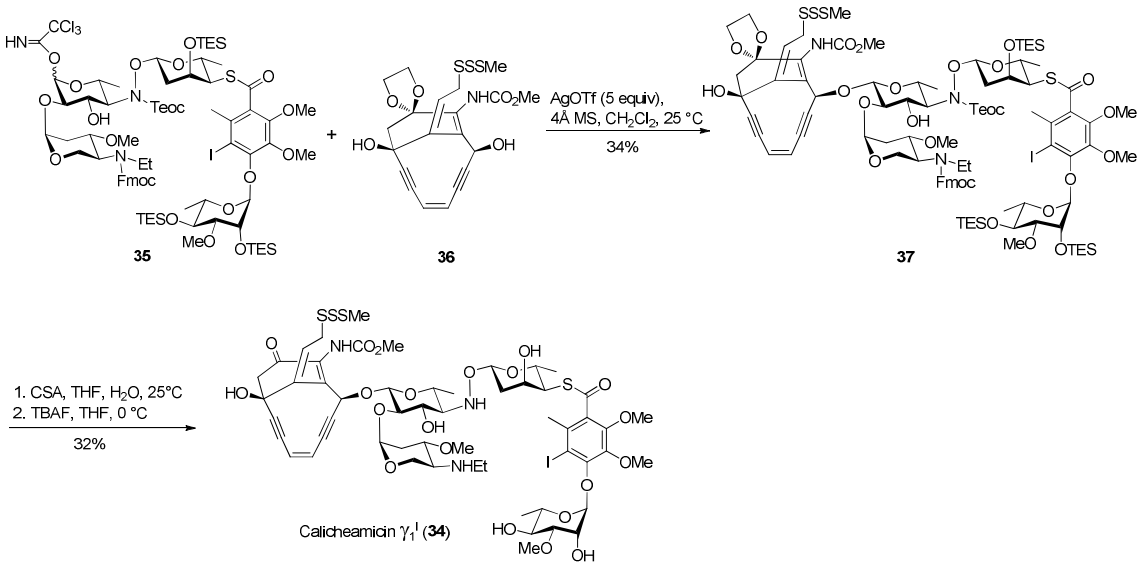


6 Syntheses with glycosyl trichloroacetimidates

Given the extremely mild glycosylation conditions that require only a catalytic amount of Lewis acid (e.g., TMSOTf or BF_3OEt_2), glycosyl trichloroacetimidates (the Schmidt donors)[33,34] stand out as the most popular type of glycosyl donors for the total synthesis of complex glycosides. In fact, some of the most complicated glycosides were synthesized employing glycosylation with glycosyl trichloroacetimidates. A remarkable example is the total synthesis of the enediyne antitumor agent calicheamicin γ_1^I (**34**), achieved by Nicolaou *et al.* in 1992[89] and Danishefsky *et al.* in 1995[90]. Both syntheses condense the aglycone and the saccharide with the trichloroacetimidate method. As in the Danishefsky synthesis shown in Scheme 9, the coupling between glycosyl trichloroacetimidate **35** and enediyne **36** was

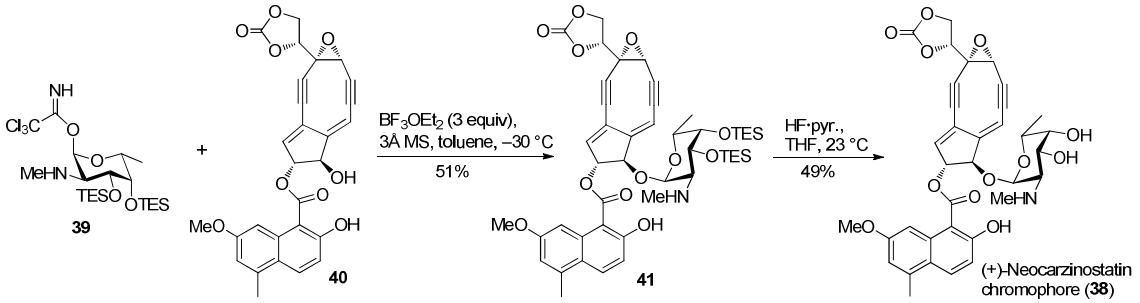
achieved under the action of AgOTf (5 equiv), providing the desired β-glycoside **37** in a decent 34% yield. The α-glycoside was not detected, this is attributable to the play of the double stereodifferentiation effect[91] in the glycosylation. Removal of the ketal in **37** (with CSA) followed by cleavage of the silyl groups (with TBAF) furnished calicheamicin γ_1^I in 32% yield (for two steps).

Scheme 9. Total synthesis of calicheamicin γ_1^I (**34**).



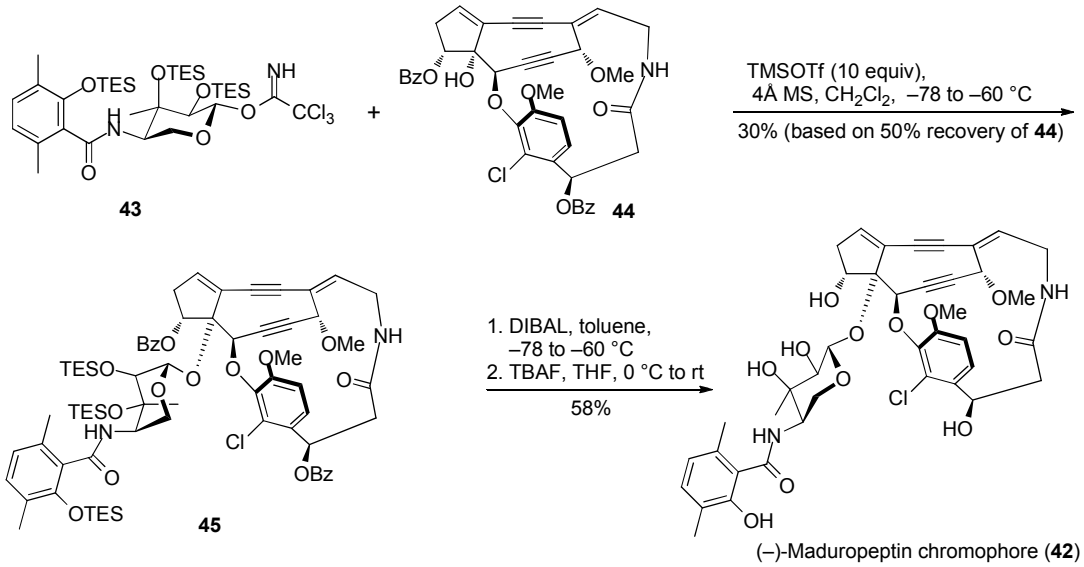
In 1998, Myers *et al.* reported the total synthesis of (+)-neocarzinostatin chromophore (**38**), which was the first identified enediyne antibiotics (Scheme 10).[92,93] Based on a model study on the glycosylation of a simple alcohol with glycosyl trichloroacetimidate **39**, the optimal conditions employing BF_3OEt_2 (3 equiv) as the promoter and toluene as the solvent were applied to the coupling of imidate **39** with aglycone **40**; the desired α-glycoside **41** was obtained in 51% yield. Removal of the *O*-TES groups in **41** (with HF·pyridine) furnished (+)-neocarzinostatin chromophore in 49% yield.

Scheme 10. Total synthesis of (+)-neocarzinostatin chromophore (**38**).



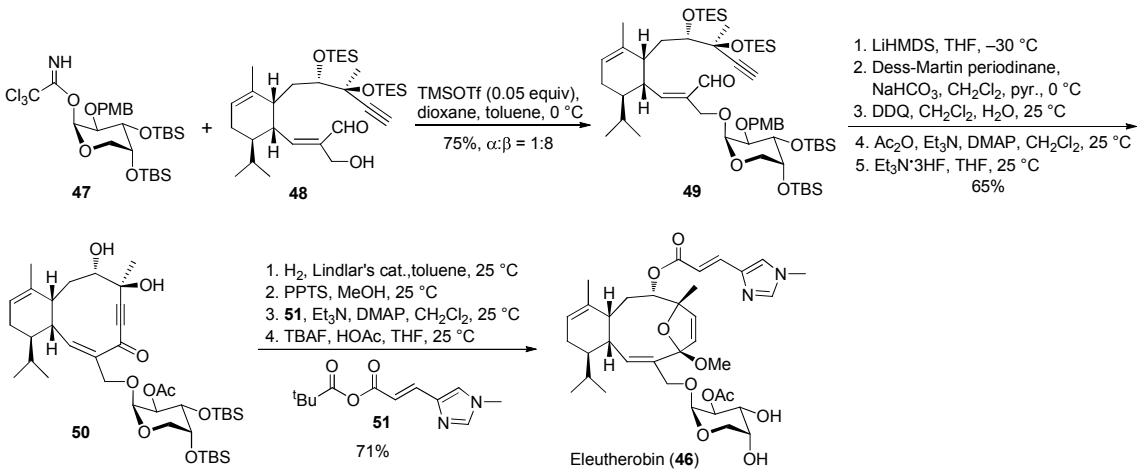
In 2009, Hirama *et al.* achieved a remarkable total synthesis of (–)-maduropeptin chromophore (**42**), the synthesis led to structure revision of this enediyne antibiotic isolated from the broth filtrate of *Actinomadura madurae* (Scheme 11).[94] The glycosylation of the tertiary hydroxyl group in the enediyne derivative **44** was achieved with glycosyl trichloroacetimidate **43** under the promotion of an excess amount of TMSOTf (10 equiv) at low temperature (–78 to –60 °C), leading to the desired glycoside **45** in a decent 30% yield based on 50% recovery of the acceptor **44**. Removal of the benzoyl groups in **45** with DIBAL-H and subsequent cleavage of the *O*-TES groups with TBAF furnished (–)-maduropeptin chromophore (58% yield for two steps).

Scheme 11. Total synthesis of the revised structure of (–)-maduropeptin chromophore (**42**).



Total synthesis of eleutherobin **46**, which is an antitumor agent isolated from an *Eleutherobia* species of soft coral, has been achieved by Nicolaou *et al.* and Danishefsky *et al.* (Scheme 12).[95,96] In Nicolaou's synthesis, it was found that, after screening various solvents, such as CH_2Cl_2, Et_2O, hexane, and CH_3CN, the coupling of arabinosyl trichloroacetimidate **47** with hydroxyaldehyde **48** under the catalysis of TMSOTf (0.05 equiv) proceeded best in a mixture of dioxane/toluene, leading to β-glycoside **49** predominantly (β:α = 8:1) in a combined yield of 75%. Glycoside **49** was then subjected to further elaboration. Aglycone cyclization via an acetylide-ketone addition (mediated by LiHMDS), Dess-Martin oxidation,[97] replacement of the PMB group with acetyl group, and selective removal of the *O*-TES groups (with $Et_3N{\cdot}3HF$), afforded acetylene **50** (65% yield for five steps). Finally, the advanced precursor **50** was converted into eleutherobin (**46**) in four steps (71% yield), those included: 1) selective hydrogenation of the acetylene with Lindlar catalyst, 2) formation of the five-membered methoxy ketal unit, 3) esterification of the remaining hydroxyl group with mixed anhydride **51**, and 4) cleavage of the *O*-TBS groups (with TBAF and acetic acid).

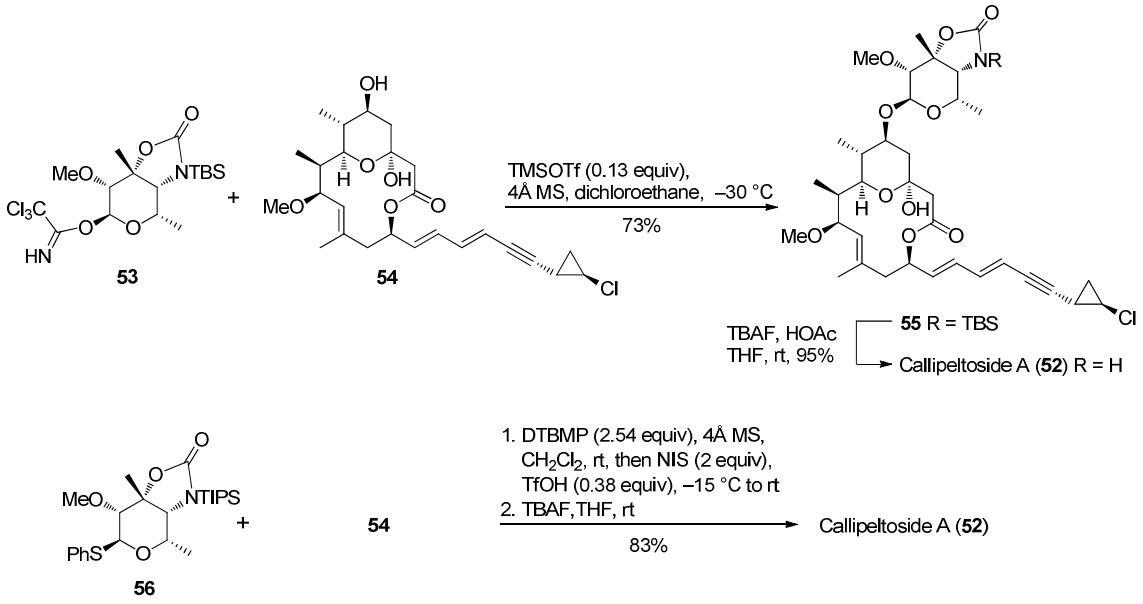
Scheme 12. Total synthesis of eleutherobin (**46**).



Total synthesis of callipeltoside A (**52**), which is an antitumor agent isolated from the sponge *callipelta* sp., has been reported by several research groups.[98-103] The synthesis

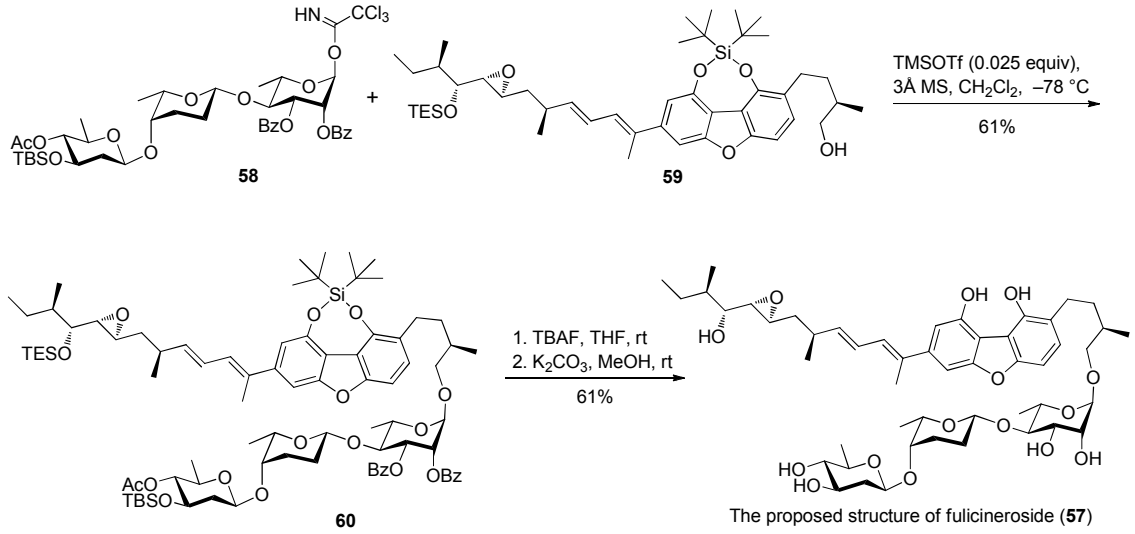
reported by Trost *et al.* in 2002 was depicted in Scheme 13. The glycosylation of enyne lactone **54** with glycosyl trichloroacetimidate **53** was achieved under the catalysis of TMSOTf (0.13 equiv) at –30 °C, subsequent removal of the *N*-TBS group with TBAF and acetic acid provided callipeltoside A (**52**) in 69% yield (for two steps).[98] A recent synthesis by Ley *et al.* realized the glycosylation of **54** with thioglycoside **56** as donor in the presence of DTBMP (2.54 equiv), NIS (2 equiv) and TfOH (0.38 equiv); subsequent removal of the *N*-TIPS group with TBAF furnished callipeltoside A (**52**) in a higher 83% yield (for two steps).[103]

Scheme 13. Total synthesis of callipeltoside A (**52**).



In 2013, Koert *et al.* described a total synthesis of the proposed structure of fulicineroside (**57**), which was isolated from the slime mold *Fuligo cinerea* and exhibited inhibitory activity against *Staphylococcus aureus* and *Bacillus subtilis* (Scheme 14).[104] Convergent coupling of trisaccharide trichloroacetimidate **58** with aglycone derivative **59** in the presence of TMSOTf (0.025 equiv) afforded the α-anomer **60** exclusively in 61% yield. Removal of the silyl groups in **60** with TBAF followed by methanolysis of the esters furnished the proposed structure of fulicineroside (**57**) (61% yield for two steps).

Scheme 14. Total synthesis of the proposed structure of fulicineroside (**57**).

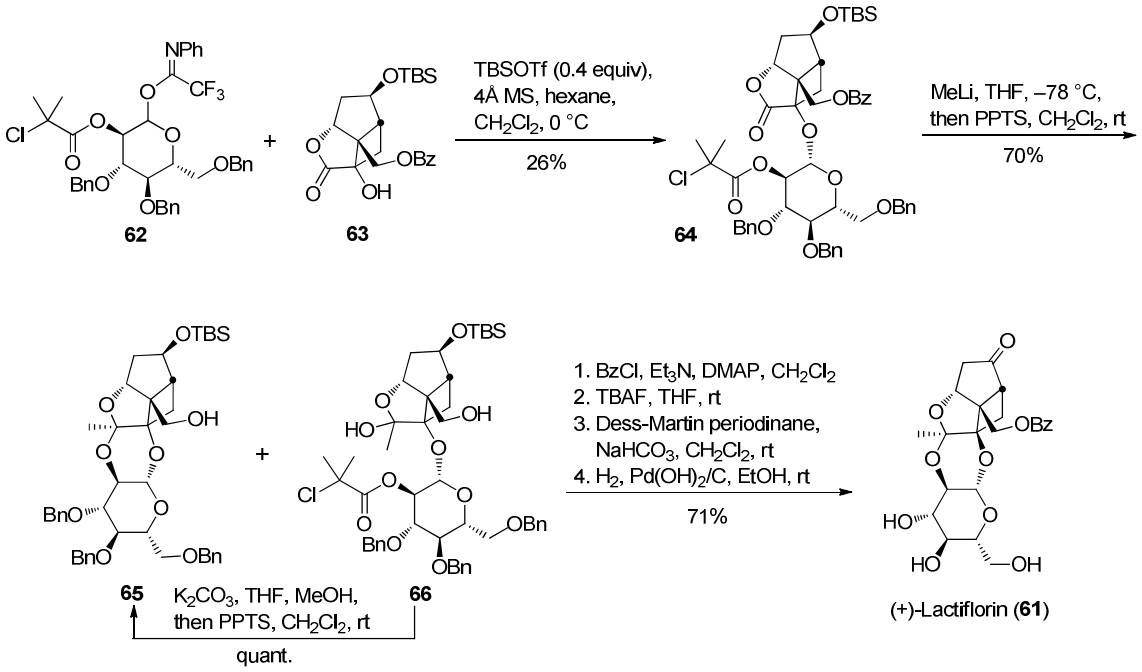


7 Syntheses with glycosyl *N*-phenyl trifluoroacetimidates

When the hydroxyl group to be glycosylated is poorly nucleophilic or highly steric hindered, the leaving entity from the trichloroacetimidate donors, that is trichloroacetamide, could compete and lead to the *N*-glycosyl trichloroacetamide as the byproduct. To address this problem, Yu and Tao reported glycosyl *N*-phenyl trifluoroacetimidates (PTFAI) as alternative imidate donors,[35] which have since been extensively utilized for the synthesis of glycans and complex glycosides.[36] As a recent example, Lu and Bach applied this method to the total synthesis of (+)-lactiflorin **61**, which was isolated from the roots of *Paeonia lactiflora* Pall (Scheme 15).[105] In fact, a range of the glycosyl donors (e.g., trichloroacetimidates and thioglycosides), various promoters (e.g., TMSOTf, TBSOTf, TfOH, BF_3OEt_2, PPTS, NIS/AgOTf, and NIS/TfOH), as well as solvents (e.g., CH_2Cl_2, hexane, CH_2Cl_2/hexane, CH_3CN, and toluene) were screened for the coupling of the glucosyl residue with the poorly reactive aglycone acceptor; the optimal outcomes were attained with a glucosyl *N*-phenyl trifluoroacetimidate as donor. Thus, tertiary alcohol **63** was glycosylated with donor **62** in the

presence of TBSOTf (0.4 equiv) in CH_2Cl_2/hexane at 0 °C to provide the desired β-*O*-glycoside **64** in 26% yield; the corresponding α-anomer was isolated in 44% yield. Treatment of compound **64** with excess methyl lithium followed by addition of PPTS gave ketal **65** and in some batches also alcohol **66**, which could be converted quantitatively into ketal **65** under basic conditions followed by treatment with PPTS. Compound **65** was then transformed into (+)-lactiflorin (**61**) in four steps (71% yield), those included benzoylation, desilylation, Dess-Martin oxidation, and hydrogenolysis.

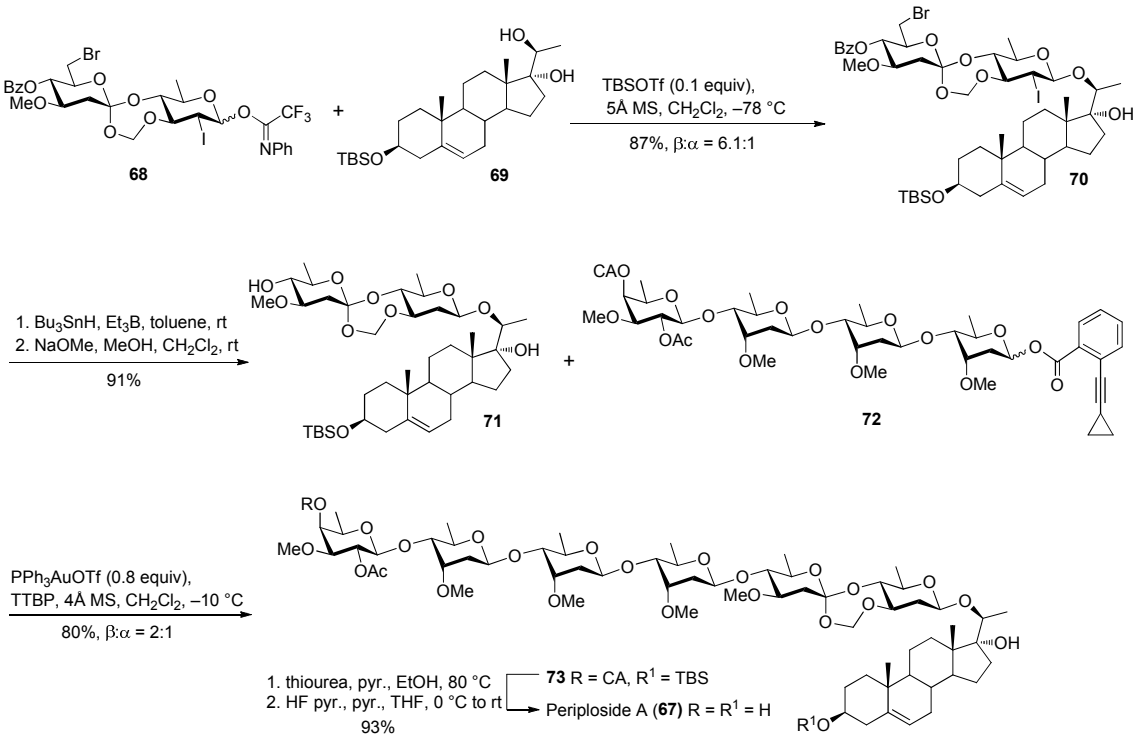
Scheme 15. Total synthesis of (+)-lactiflorin (**61**).



Recently, Yu *et al.* accomplished the total synthesis of periploside A (**67**), a pregnane hexasaccharide with potent immunosuppressive activities (Scheme 16).[106] This complex glycoside, isolated from the Chinese medicinal plants *Periploca sepium* and *P. forrestii*, carries a unique seven-membered formyl acetal bridged orthoester (FABO) linkage between two sugar moieties.[107] The fabricated FABO disaccharide was elaborated as an *N*-phenyl trifluoroacetimidate **68**, which was condensed with pregnane diol **69** in the presence of

TBSOTf (0.1 equiv), leading to the desired β-*O*-glycoside **70** with a satisfactory yield and stereoselectivity (87%, α:β = 6.1:1). The bromide and iodide which facilitated the β-selective glycosylation in **70** were then removed with Bu_3SnH and Et_3B; subsequent removal of the benzoyl group with NaOMe afforded disaccharide acceptor **71** (91% for two steps). The condensation of disaccharide **71** with tetrasaccharide *ortho*-alkynylbenzoate **72** was achieved under the action of PPh_3AuOTf (0.8 equiv) in the presence of TTBP, providing the coupled hexasaccharide in 80% yield, albeit in a moderate stereoselectivity (β:α = 2.1:1). Finally, cleavage of the *O*-CA and *O*-TBS groups in **73** with thiourea[108] and pyridine-buffered HF·pyridine, respectively, furnished periploside A (**67**) (93% for two steps).

Scheme 16. Total synthesis of periploside A (**67**).

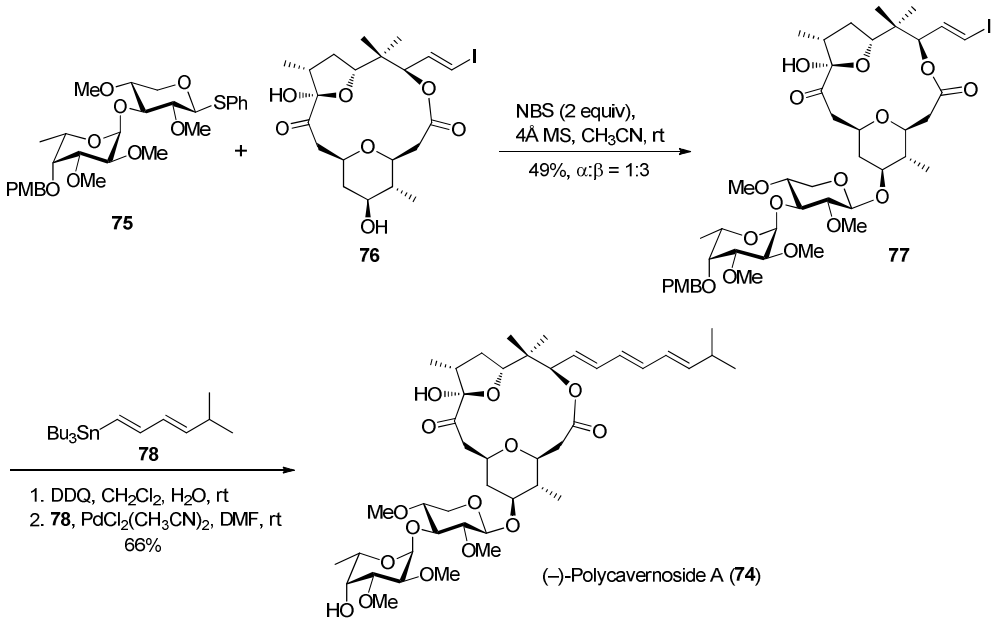


8 Syntheses with thioglycosides

Thioglycosides have been widely used as glycosyl donors in the synthetic carbohydrate chemistry because of their ease of preparation, shelf stability, and versatility in glycosylation. A wide variety of the thiophilic agents, such as NIS/AgOTf, NIS/TMSOTf, BSP/Tf_2O, MeOTf, IDCP (iodonium dicollidine perchlorate), and DMTST (dimethyl(methylthio)sulfonium triflate), have been developed to activate different thioglycosides selectively under mild conditions.[38,39] In the synthesis of complex glycosides, however, one should keep alert that the thiophilic promoters which are used stoichiometrically in the glycosylation might cause serious side reactions on the multifunctional aglycones.

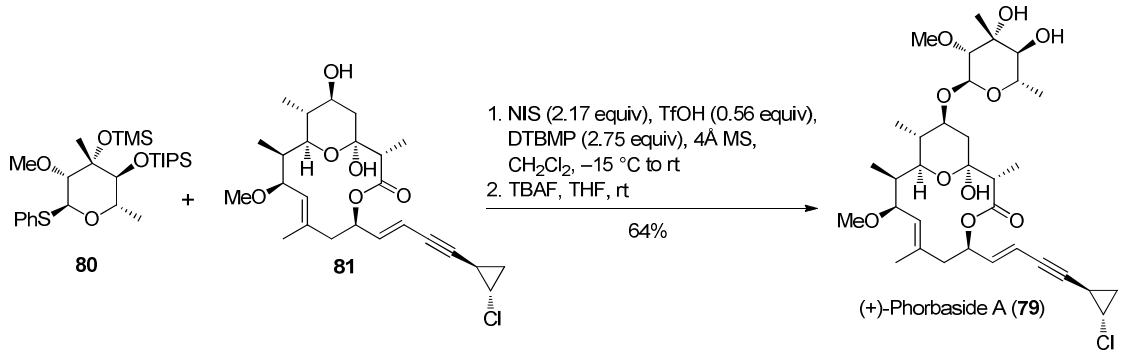
Total synthesis of (–)-polycavernoside A (**74**), a toxic metabolite from the red alga *Polycavernosa tsudai*, has been achieved by several research groups via a similar thioglycoside glycosylation method.[109-114] In Paquette's synthesis,[110] coupling of the advanced aglycone precursor **76** with thiodisaccharide **75** in the presence of NBS (2 equiv)[115] provided the desired β-*O*-glycoside **77** along with its α-anomer in a moderate yield of 49% and α/β selectivity of 1:3 (Scheme 17). The *O*-PMB protecting group in **77** was removed with DDQ; installation of the diene residue via a Stille coupling[116] with dienylstannane **78** completed the total synthesis (66% for two steps).

Scheme 17. Total synthesis of (–)-polycavernoside A (**74**).



In 2010, Paterson and Paquet reported the total synthesis of (+)-phorbaside A (**79**), a cytotoxic glycoside of macrolide from the sponge *Phorbas* sp. (Scheme 18).[117] Wherein, glycosylation of the intact aglycone **81** with thioglycoside **80** was achieved under the promotion of NIS (2.17 equiv)/HOTf (0.56 equiv) in the presence of DTBMP (2.75 equiv);[118] subsequent removal of the silyl protecting groups with TBAF furnished the target α-glycoside **79** in a good 64% yield (for two steps).

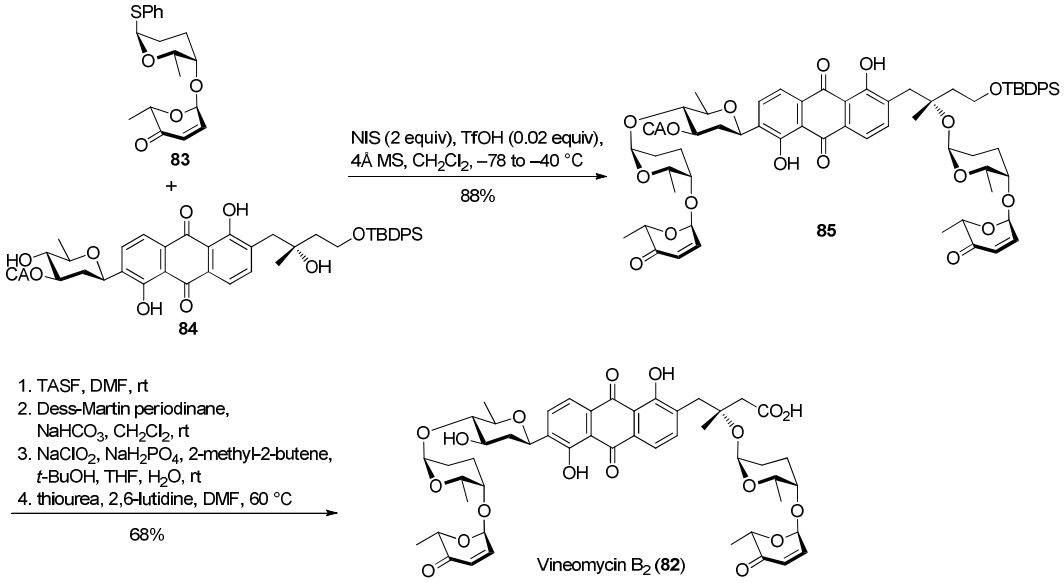
Scheme 18. Total synthesis of (+)-phorbaside A (**79**).



In 2013, Toshima *et al.* accomplished the total synthesis of vineomycin B_2 (**82**), which is an anthracycline antibiotic isolated from the culture broth of *Streptomyces matensis* subsp.

vineus and inhibited Gram-positive bacteria and solid tumors (Scheme 19).[119] The coupling of aglycone *C*-glycoside **84** with thiodisaccharide **83** in the presence of NIS (2 equiv to **83**) and TfOH (0.02 equiv to **83**) was controlled by the concentration[120] to afford selectively the bis-glycosylated product **85** in a high 88% yield and complete α-selectivity. Finally, cleavage of the *O*-TBDPS group in **85** with TASF, oxidation of the resulting primary alcohol into the carboxylic acid, and deprotection of the chloroacetyl group, furnished the target glycoside **82** in 68% yield over four steps.

Scheme 19. Total synthesis of vineomycin B_2 (**82**).

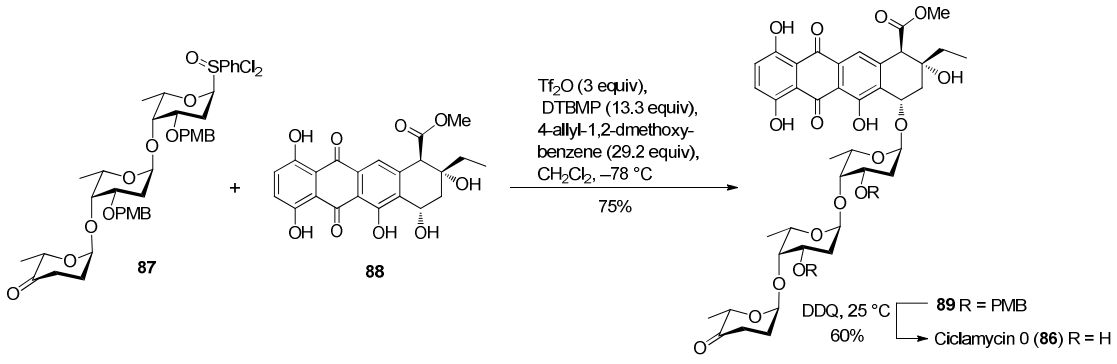


9 Syntheses with glycosyl sulfoxides

Glycosyl sulfoxides are prepared from the corresponding thioglycosides via controlled oxidation (to avoid the generation of sulfone), which can undergo glycosylation upon activation with triflic anhydride in the presence of DTBMP (2,6-di-*tert*-butyl-4-methylpyridine) at very low temperature.[40] Due to the mild reaction conditions, glycosyl sulfoxides have gained recognition in the total synthesis of complex glycosides. Employing

this method, Kahne *et al*. completed the total synthesis of ciclamycin 0 (**86**) in 1999, which is an anthracycline antibiotic isolated from *Streptomyces capoamus* (Scheme 20).[121] Thus, the condensation of the intact aglycone **88** with trisaccharide sulfoxide **87** was performed in the presence of Tf_2O (3 equiv), DTBMP (13.3 equiv), and 4-allyl-1,2-dimethoxybenzene (29.2 equiv, as a scavenger of phenylsulfenyl triflate) at –78 °C, leading regio- and stereoselectively to the desired α-glycoside **89** in a high 75% yield. Subsequent removal of the *O*-PMB protecting groups in **89** with DDQ provided the target glycoside **86** in 60% yield. Note that, the first synthesis of ciclamycin 0 was reported by Danishefsky *et al.* using a trisaccharide glycal as donor in 1990.[122]

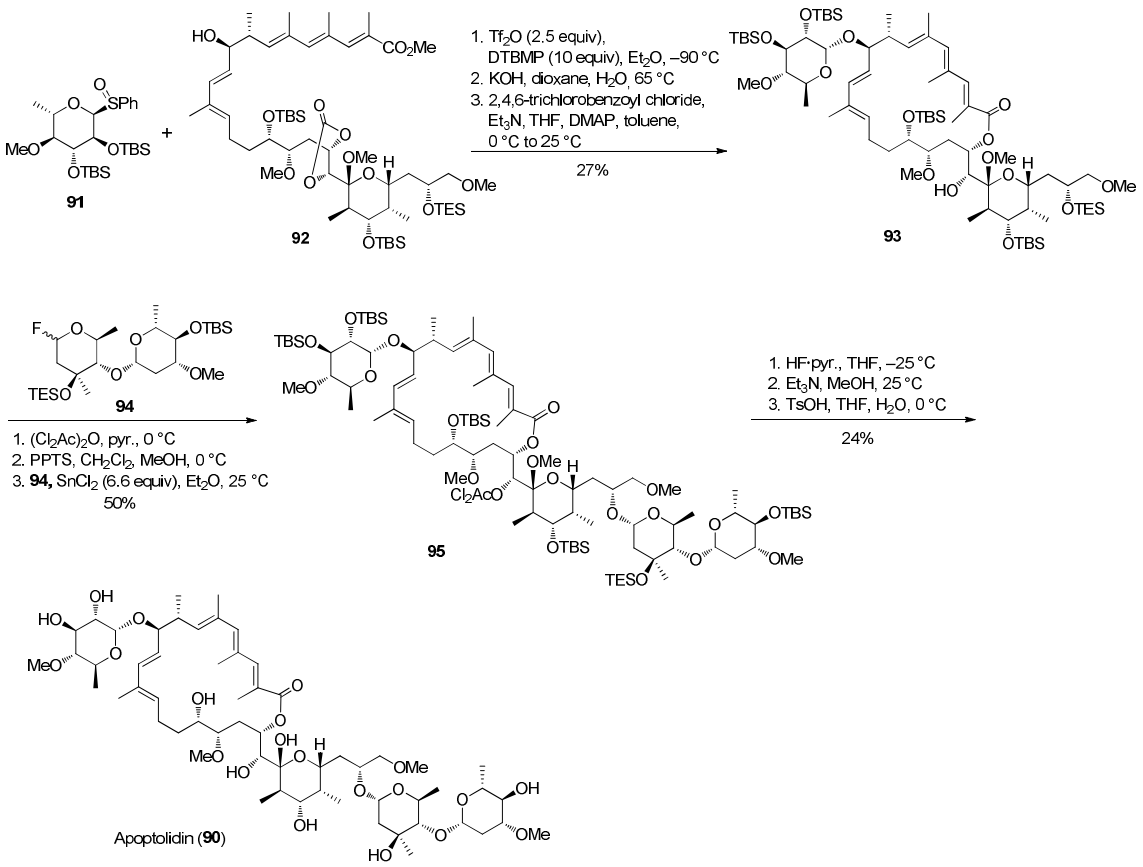
Scheme 20. Total synthesis of ciclamycin 0 (**86**).



Total synthesis of apoptolidin (**90**), a metabolite of *Nocardiopsis* sp. which displayed potent antitumor activities, was accomplished by several research groups via a similar glycosyl sulfoxide method (Scheme 21).[123-125] In Nicolaou's synthesis, coupling of the complex alcohol **92** with sulfoxide **91** was performed in the presence of Tf_2O (2.5 equiv) and DTBMP (10 equiv); the coupled glycoside was subjected to cleavage of the ester and carbonate (with KOH); subsequent Yamaguchi macrolactonization[126] afforded the desired lactone α-*O*-glycoside **93** in 27% yield over three steps. After protection of the free hydroxyl group in **93** with dichloroacetic anhydride, the *O*-TES group was selectively cleaved with

PPTS; the resulting alcohol was glycosylated with disaccharide fluoride **94** in the presence of $SnCl_2$ (6.6 equiv) to provide α-glycoside **95** exclusively (50% over three steps). Global deprotection of **95** involved desilylation with HF·pyridine, cleavage of the dichloroacetyl group with triethylamine in methanol, and hydrolysis of the methoxy acetal with TsOH, leading to apoptolidin (**90**) in 24% yield (for three steps).

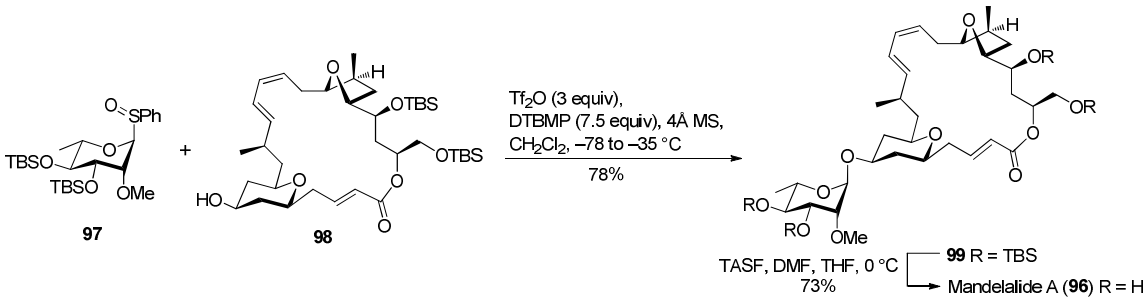
Scheme 21. Total synthesis of apoptolidin (**90**).



Mandelalide A (**96**) is a novel glycoside of macrolide which was isolated from *Lissoclinum* ascidian and showed potent cytotoxicity against human NCI-H460 lung cancer cells (IC_{50} = 12 nm). The proposed structure of Mandelalide A was synthesized by Fürstner *et al.* in 2014,[127] shortly, Ye *et al*. revised the structure via total synthesis (Scheme 22).[128] In Ye's total synthesis, the protected macrolide **98** was glycosylated with sulfoxide **97** under the

activation of Tf_2O (3 equiv) and DTBMP (7.5 equiv), providing the desired α-*O*-glycoside **99** in a good 78% yield as a single anomer. Removal of the *O*-TBS groups in **99** with TASF furnished the authentic natural glycoside **96** in 73% yield.

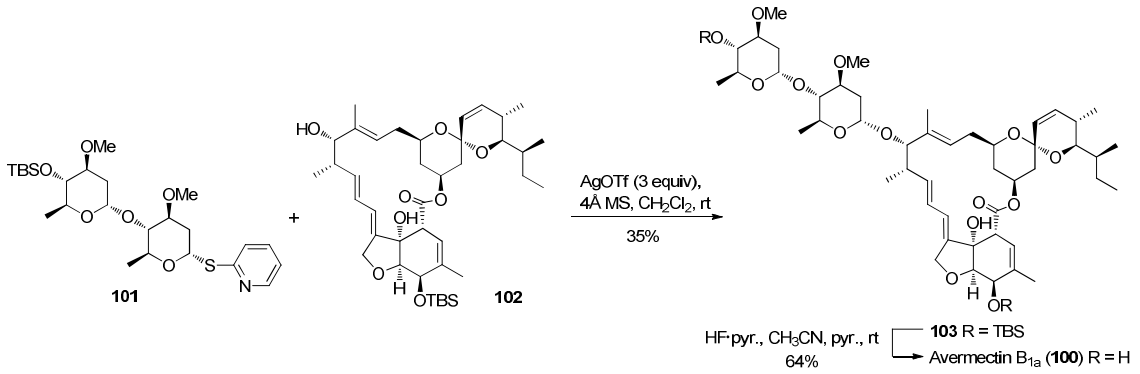
Scheme 22. Total synthesis of the revised structure of mandelalide A (**96**).



10 Syntheses with heteroaryl thioglycosides

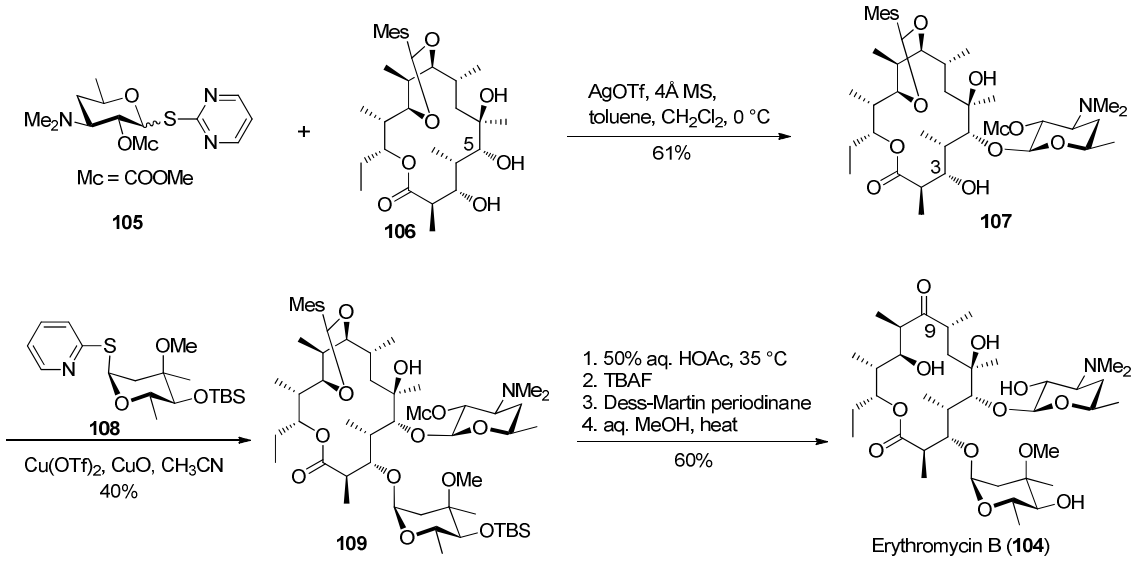
In comparison to the alkyl and aryl thioglycosides, heteroaryl thioglycosides could be activated at the remote heteroatom, thus rendering varied conditions for glycosylation.[41,42] These donors have also found applications in the total synthesis of complex glycosides. Employing a thiopyridyl glycoside as donor, White *et al*. achieved the total synthesis of avermectin B_{1a} (**100**) in 1995, which is an antiprarasitic agent for the treatment of parasitic diseases (Scheme 23).[129] Thus, glycosylation of the aglycone derivative **102** with 2-deoxy-disaccharide donor **101**[130] under the promotion of silver triflate (3 equiv) at room temperature afforded the desired α-*O*-glycoside **103** in 35% yield as a single anomer. Removal of the two *O*-TBS groups in **103** with HF·pyridine furnished the target glycoside **100** in 64% yield. It should be noted that total syntheses of avermectins have been reported by other research groups before 1993.[130-132]

Scheme 23. Total synthesis of avermectin B_{1a} (**100**).



Total syntheses of erythromycins A and B, the macrolide antibiotics which can inhibit the ribosomal-dependent protein biosynthesis, have been achieved by Woodward *et al.* and Martin *et al.*, respectively.[133,134] In Martin's total synthesis, the glycosylation of macrolide **106** with pyrimidyl thioglycoside **105** proceeded smoothly under the promotion of AgOTf,[135] affording the C5-*O*-β-glycoside **107** regio- and stereoselectively (61%; Scheme 24). Glycosylation of the remaining poorly reactive C3 hydroxyl group (in **107**) with a protected L-cladinose donor using the Woodward protocol[133] failed to give the coupled glycosides. Instead, this task was realized with a thiopyridyl donor (i.e., **108**). The coupling of **107** and **108** under the promotion of $Cu(OTf)_2$ and CuO in acetonitrile provided α-glycoside **109** in 40% yield. Finally, the 3,5-*O*-bisglycoside **109** was converted into erythromycin A (**104**) in 60% yield over four steps, those steps included: 1) acidic cleavage of the mesitylene acetal, 2) removal of the *O*-TBS group with TBAF, 3) selective oxidation of the C9 hydroxyl group into ketone with Dess-Martin periodinane, and 4) cleavage of the methyl carbonate moiety using aqueous methanol under heating conditions.

Scheme 24. Total synthesis of erythromycin B (**104**).

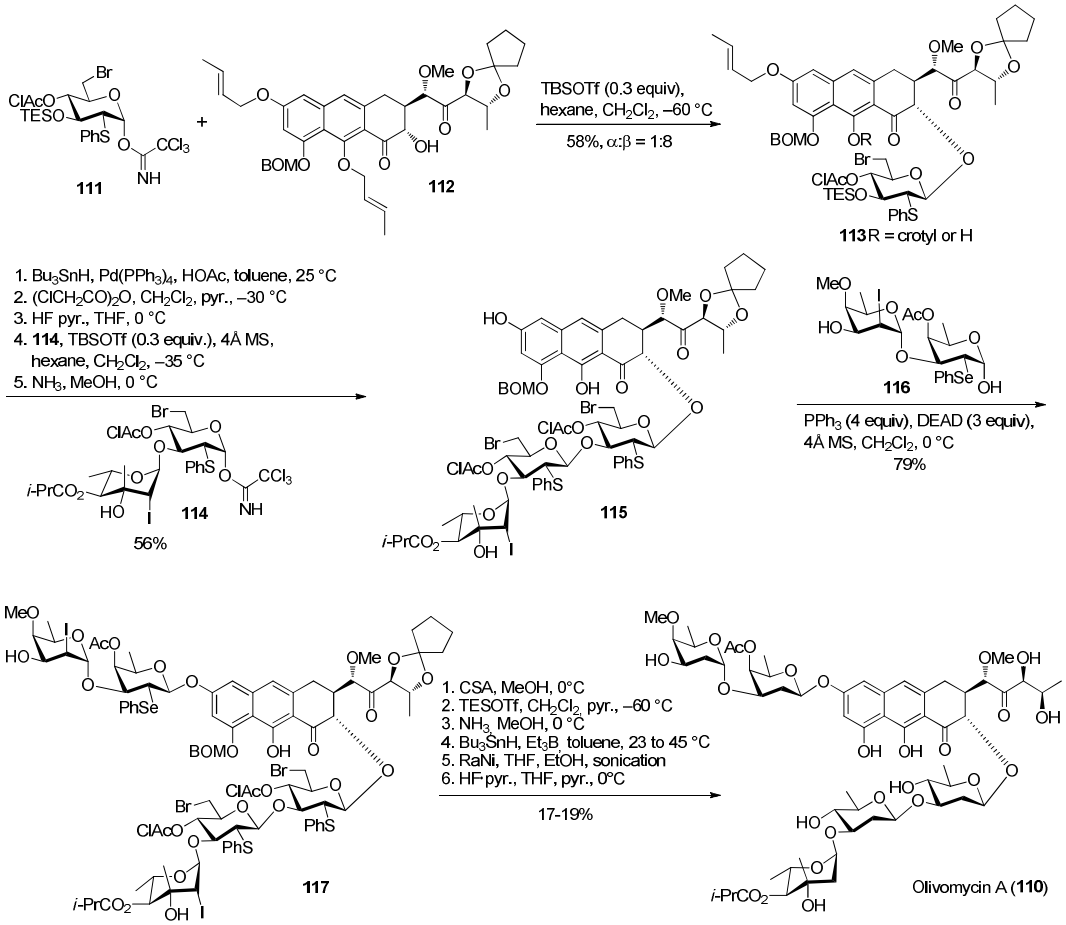


11 Syntheses with 1-hydroxyl sugars

1-Hydroxyl sugars have been employed successfully in the glycosylation of complex phenols under the mild Mitsunobu conditions. In this regard, Roush *et al.* achieved in 1999 a remarkable total synthesis of olivomycin A (**110**), an antitumor antibiotic belonging to the aureolic acid family (Scheme 25).[136] The first glycosylation was performed with 2-phenylthio-glucosyl trichloroacetimidate **111** as donor under the catalysis of TBSOTf (0.3 equiv); the coupling of aglycone **112** with **111** gave β-*O*-glycoside **113** in 58% yield (α:β = 1:8). After a three-step protecting group manipulation, extension of the monosaccharide to the trisaccharide **115** was realized by glycosylation with disaccharide imidate **114** in the presence of TBSOTf (0.3 equiv), that was followed by removal of the phenolic chloroacetate with ammonium (56% for five steps). The phenolic glycosidic linkage was then constructed by a Mitsunobu condensation[137] of **115** with 2-phenylseleno-disaccharide **116** in the presence of PPh_3 (4 equiv) and DEAD (3 equiv) at 0 °C, providing the desired olivomycin A derivative **117** in a satisfactory 79% yield. Finally, replacement of the cyclopentylidene ketal in **117** with

TES groups, cleavage of the chloroacetates (with ammonium in methanol), reductive removal of the iodo-, bromo-, and selenophenyl groups (with Bu_3SnH and Et_3B), removal of the thiophenyl and *O*-BOM groups (with Raney Ni), and cleavage of the *O*-TES groups (with HF·pyridine), furnished olivomycin A (**110**) (~18% for six steps).

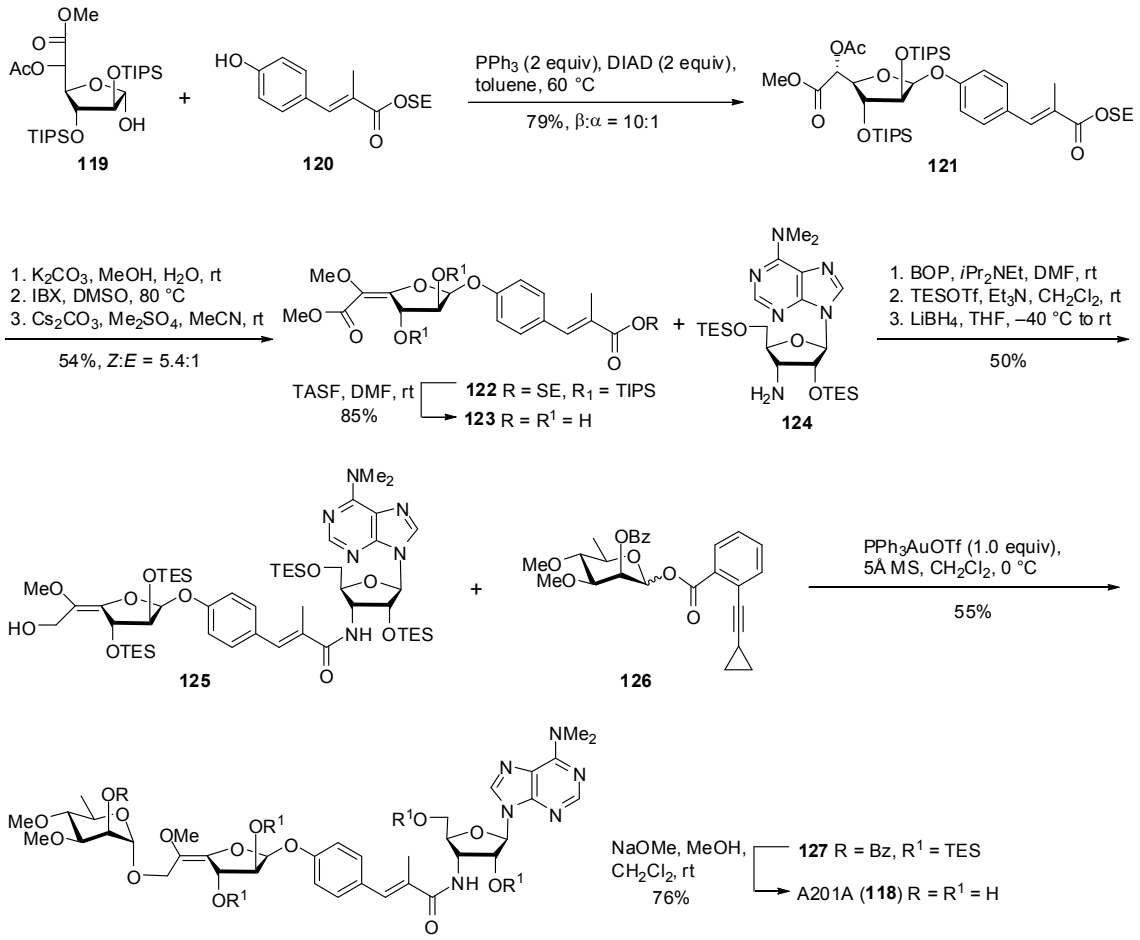
Scheme 25. Total synthesis of olivomycin A (**110**).



Hygromycin A and A201A (**118**) are structurally relevant nucleoside antibiotics, originally isolated from *Streptomyces hygroscopicus* and *S. capreolus*, respectively. Ogawa *et al.* and Donohoe *et al.* reported, respectively, the total synthesis of hygromycin A by utilizing the Mitsunobu glycosylation as the key step for assembly of the phenol and furanose unit.[138,139] Yu *et al*. completed the total synthesis of A201A (**118**) in 2014, which carries a

unique hexofuranose unit containing an exocyclic enol ether (Scheme 26).[140] The phenolic glycoside linkage was realized similarly by a Mitsunobu glycosylation. Thus, phenol **120** was condensed with furanose **119** in the presence of PPh_3 (2 equiv) and DIAD (2 equiv) in toluene at 60 °C to give the desired 1,2-*cis*-*O*-glycoside **121** in 79% yield with a high β-selectivity (β:α = 10:1). Removal of the acetyl group in **121** with K_2CO_3 followed by oxidation with IBX and DMSO provided an α-keto-ester, which was treated with Cs_2CO_3 and Me_2SO_4 to yield enol ether **122** (54% for three steps, *Z*:*E* = 5.4:1). Next, the SE and TIPS groups were unmasked with TASF to afford acid **123** (85%). Condensation of acid **123** with amine derivative **124** (with BOP and $^{i}Pr_2NEt$),[141] installation of *O*-TES groups on the remaining hydroxyl groups, and reduction of the methyl ester (with $LiBH_4$)[142] generated alcohol **125** (50% yield for three steps). Promoted by a stoichiometric amount of PPh_3AuOTf,[51] the last coupling between alcohol **125** and glycosyl *ortho*-alkynylbenzoate **126** provided the desired α-*O*-rhamnoside **127** (55%). Finally, cleavage of the benzoyl and *O*-TES groups in **127** with NaOMe furnished A201A (**118**) in 76% yield.

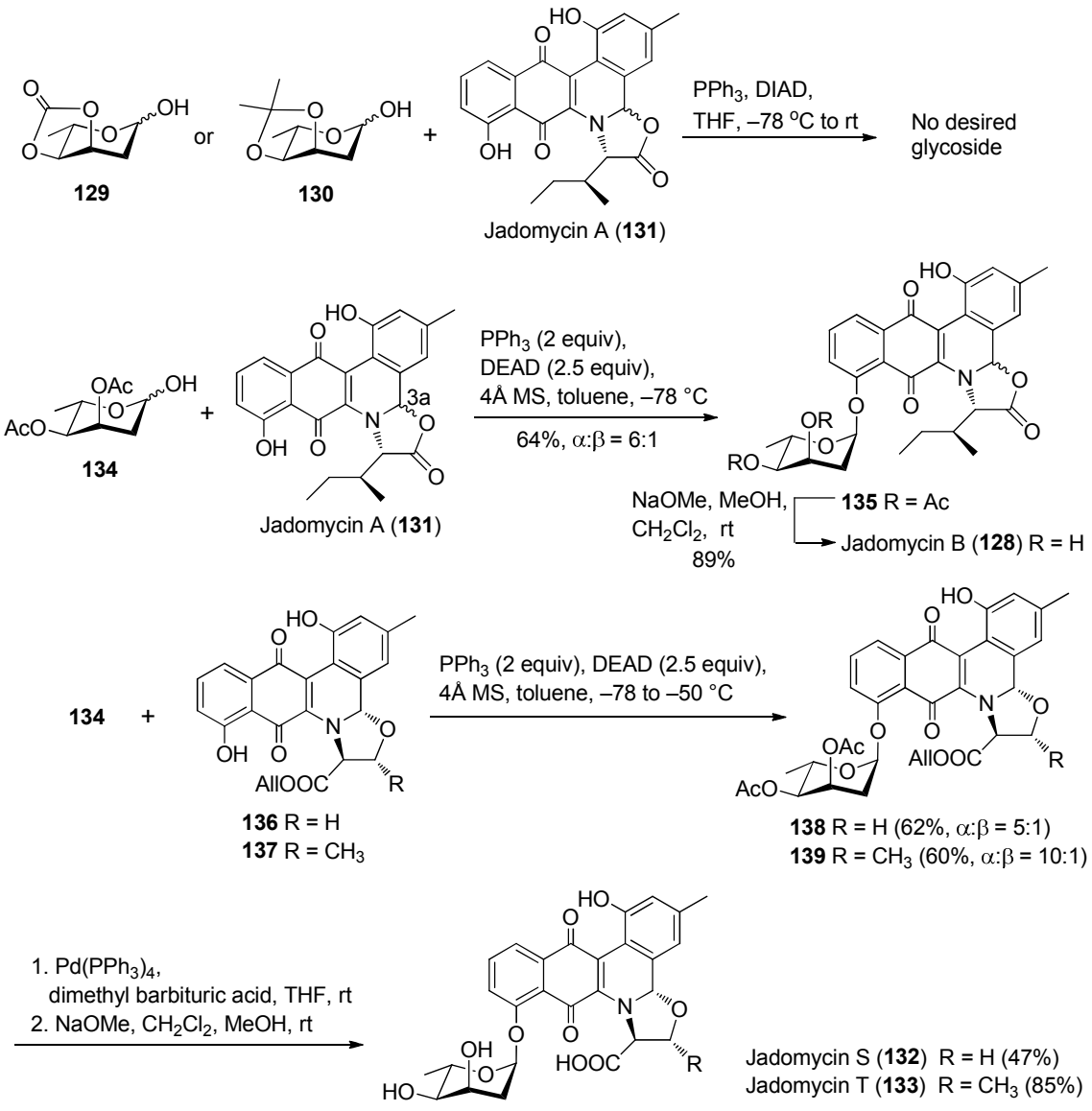
Scheme 26. Total synthesis of A201A (**118**).



Jadomycins (e.g., **128**, **132**, and **133**) are a group of angucycline antibiotics produced upon feeding *Streptomyces venezuelae* with various amino acids. O'Doherty *et al.* found that Mitsunobu condensation of the aglycone **131** with 3,4-*O*-carbonate or 3,4-*O*-isopropylidene-protected L-digitoxoses (**129** or **130**) failed to provide the coupled *O*-glycosides (Scheme 27).[143] Nevertheless, by adjusting the protecting groups on the digitoxose, Yang and Yu realized this challenging glycosylation and succeeded in the total synthesis of Jadomycins.[144] Thus, glycosylation of aglycone **131** with the L-digitoxose **134** in the presence of PPh_3 (2 equiv) and DEAD (2.5 equiv) (4Å MS, toluene, –78 °C) led to the desired *O*-glycoside **135** in 64% yield with a good α-selectivity (α:β = 6:1). It should be noted that other types of the donors, including glycosyl iodides and bromides, have been tried but failed to glycosylate **131**.

Removal of the acetyl groups in **135** with NaOMe afforded jadomycins B (**128**) in 89% yield (3a*S*:3a*R* = 3:2). Similar glycosylations of aglycones **136** and **137** provided glycosides **138** and **139** (62%, α:β = 5:1 for **136**; 60%, α:β = 10:1 for **137**). Removal of the allyl groups in **138** and **139** with $Pd(PPh_3)_4$, followed by saponification, furnished jadomycins S (**132**) and T (**133**) in 47% and 85% yield, respectively.

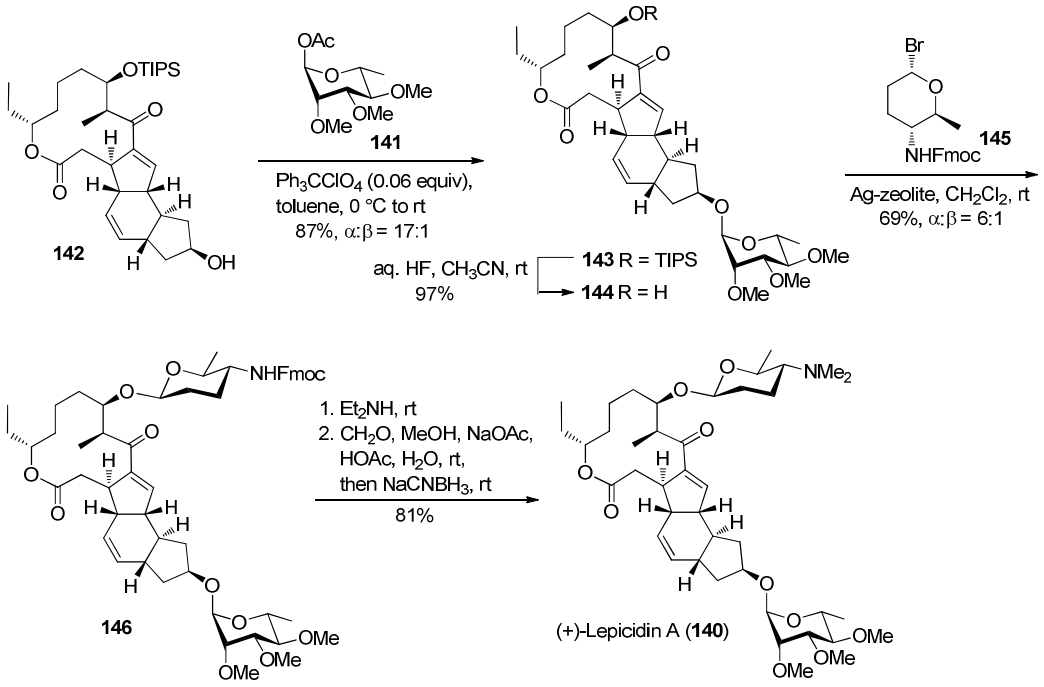
Scheme 27. Total synthesis of jadomycins B (**128**), S (**132**) and T (**133**).



12 Syntheses with 1-*O*-acetates

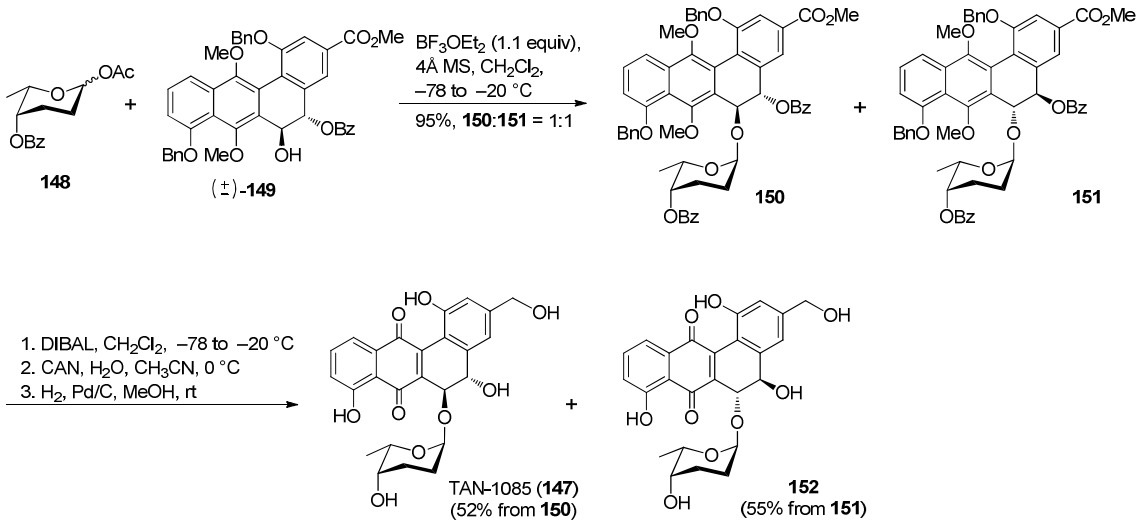
Compared to other types of the glycosyl donors, 1-*O*-acetates (or other 1-*O*-acyl sugars) require relatively stronger acidic conditions for activation, therefore, only those inherently reactive sugars (i.e., the deoxy sugars) can their 1-*O*-acyl derivatives be applied in the synthesis of complex glycosides. In 1993, Evans and Black completed the synthesis of (+)-lepicidin A (**140**), an insecticidal macrolide glycoside isolated from the fermentation broth of *Saccharopolyspora spinosa* (Scheme 28).[145] Glycosylation of the aglycone derivative **142** was achieved with glycosyl acetate **141** as donor under the catalysis of trityl perchlorate (0.06 equiv)[146] to afford the thermodynamically favored α-glycoside **143** in 87% yield (α:β = 17:1). After removal of the *O*-TIPS group in **143** with aqueous HF, the resulting alcohol **144** was coupled with 2-deoxy-glycosyl bromide **145** in the presence of silver zeolite,[147] affording the desired β-glycoside **146** as the minor anomer (69%, α:β = 6:1). Cleavage of the *N*-Fmoc group in **146** with Et_2NH followed by methylation of the resulting amine with formaldehyde and $NaCNBH_3$ furnished (+)-lepicidin A (**140**) in 81% yield (for two steps).

Scheme 28. Total synthesis of (+)-lepicidin A (**140**).



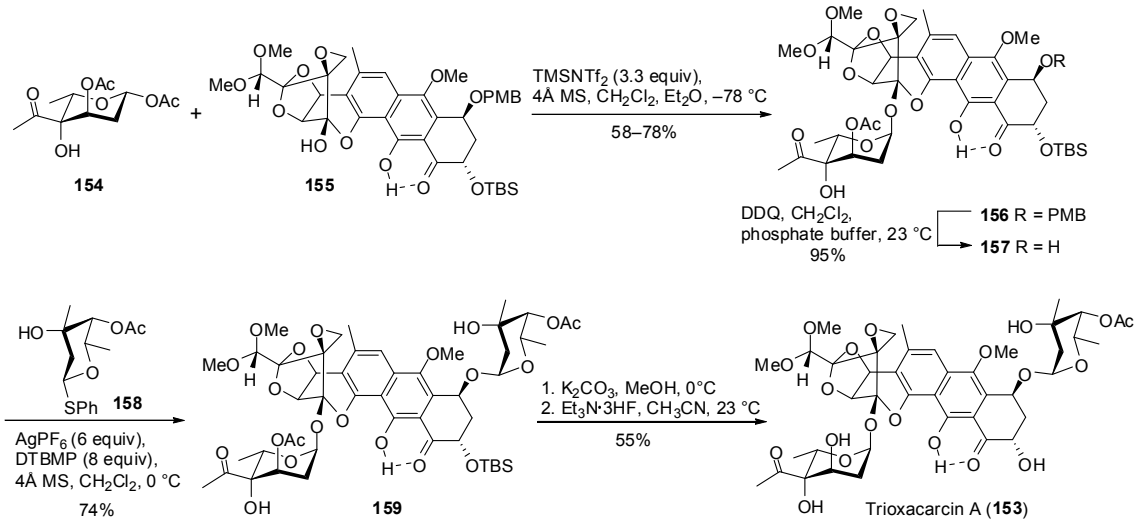
In 2004, Suzuki *et al.* achieved the total synthesis of TAN-1085 (**147**), an angucycline antibiotic excreted by *Streptomyces* sp. S-11106 (Scheme 29).[148,149] Exposure of the racemic angucycline derivative **149** to L-rhodinosyl acetate **148** in the presence of BF_3OEt_2 (1.1 equiv) at –78 to –20 °C afforded a pair of the enantio-pure α-glycosides **150** and **151** in 95% yield. A three-step sequence, involving 1) DIBAL reduction of the methyl ester and simultaneous removal of the benzoyl groups, 2) oxidation with CAN, and 3) hydrogenolysis with Pd/C, was then employed to convert **150** and **151** into TAN-1085 (**147**) and its diastereoisomer **152** in moderate yields, respectively.

Scheme 29. Total synthesis of TAN-1085 (**147**).



In 2013, Myers *et al*. accomplished a remarkable total synthesis of trioxacarcin A (**153**), which is a bacterial metabolite exhibiting extraordinary inhibitory effect against the growth of cancer cells (Scheme 30).[150,151] Attempts to glycosylate the aglycone derivative **155** with a range of trioxacarcinose B donors, including glycosyl fluoride, n-pentenyl, and thioglycoside met with failure. This task was fulfilled with glycosyl acetate **154** as donor and $TMSNTf_2$ (e.g., 3.3 equiv) as promoter,[152] providing the desired α-glycoside **156** in 58–78% yield as a single anomer. Cleavage of the *O*-PMB group in **156** with DDQ gave alcohol **157**. The glycosylation of **157** could be effected with a 1-*O*-acetyl donor, however, was also accompanied with serious decomposition. Instead, the glycosylation with phenylthioglycoside **158** in the presence of silver hexafluorophosphate (6 equiv) and DTBMP (8 equiv) provided the desired α-glycoside **159** in a satisfactory 74% yield.[153] Finally, selective cleavage of the acetyl group on the trioxacarcinose B moiety in **159** with potassium carbonate in ice-cold methanol followed by desilylation with $Et_3N{\cdot}3HF$ furnished trioxacarcin A (**153**) in 55% yield (for two steps).

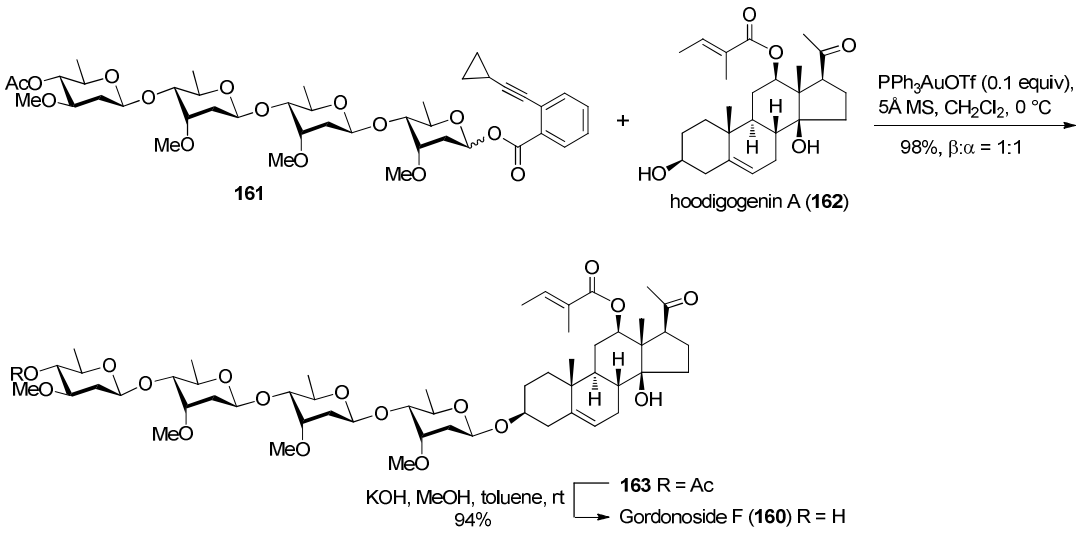
Scheme 30. Total synthesis of trioxacarcin A (**153**).



13 Glycosylation with glycosyl *ortho*-alkynylbenzoates

Glycosyl *ortho*-alkynylbenzoates, the recent addition to the arsenal of glycosyl donors,[50] are as stable as other 1-*O*-acyl sugars, and yet, can undergo glycosylation under extremely mild conditions with the catalysis of a gold(I) complex (such as $Ph_3PAuOTf$ and $Ph_3PAuNTf_2$). The nearly neutral glycosylation conditions ensure their successful application in the syntheses of a number of the highly acid-labile glycosides.[154-156] As a recent example in point, Yu *et al*. accomplished the total synthesis of gordonoside F (**160**), a pregnane tetrasaccharide isolated from *H. gordonii* and found to be a specific agonist of GPR119 (Scheme 31).[157] Thus, the convergent coupling of hoodigogenin A (**162**)[158] with tetrasaccharide *ortho*-alkynylbenzoate **161** under the promotion of PPh_3AuOTf (0.1 equiv) provided the coupled glycoside in an excellent 98% yield, albeit with poor stereoselectivity (α:β = 1:1). It should be noted that the glycosylation with 2-deoxy sugar donors usually led to the thermodynamically favored α-glycosides predominantly. Finally, selective removal of the acetyl group in the β-glycoside **163** with KOH furnished gordonoside F (**160**) in 94% yield.

Scheme 31. Total synthesis of gordonoside F (**160**).



14 Conclusions

The total syntheses of many complex natural *O*-glycosides have been achieved, those include the most formidable enediyne glycosides (calicheamicin γ_1 **34**, (+)-neocarzinostatin chromophore **38**, (–)-maduropeptin chromophore **42**), macrolide glycosides (formamicin **13**, apoptolidin **90**, avermectin B_{1a} **100**, erythromycin A **104**), anthracycline glycosides (vineomycin B_2 **82**, ciclamycin 0 **86**, olivomycin A **110**, and trioxacarcin A **153**), and angucycline glycosides (landomycin A **26**). The vulnerable aglycone, the unusual sugar unit, and the peculiar *O*-glycosidic linkage make the *O*-glycosylation reaction a great challenge in each synthesis. Such a challenge has been addressed by a judicious choice of the donor types (which are categorized by the leaving groups), the protecting group pattern, the promoters, as well as the solvent and temperature of the glycosylation reaction. Among the successful *O*-glycosylation reactions applied in the total synthesis, the glycosyl trichloroacetimidates are the most frequently used, owing to their mild activation conditions requiring only a catalytic amount of Lewis acid. Glycosyl *N*-phenyl trifluoroacetimidates are alternatives to the

trichloroacetimidates, which could avoid the rearrangement of the trichloroacetimidates occurring in the glycosylation of alcohols less nucleophilic than the trichloroacetamide. Glycosyl fluorides can be activated by such fluorophiles as $AgClO_4/SnCl_2$ and $AgClO_4/Cp_2ZrCl_2$, which have found wide application in the synthesis of complex glycosides. The thioglycosides, including alkyl/aryl thioglycosides, sulfoxides, and heteroaryl thioglycosides, are versatile donors, which can be activated under a wide variety of the promoters. The 1-hydroxyl sugars are particularly useful in the synthesis of phenolic glycosides under the Mitsunobu conditions. Other types of donors, such as glycosyl bromides, iodides, and 1-*O*-acyl sugars have also been chosen considering the nature of the coupling partners. Recently, glycosyl *ortho*-alkynylbenzoates, which can be activated by a catalytic amount of gold(I) complex such as $Ph_3PAuOTf$ and $Ph_3PAuNTf_2$, have been proven to be particularly useful donors for the glycosylation of acid vulnerable aglycones.

Notwithstanding these glycosylation methods have allowed the successful total syntheses of complex glycosides, the glycosylation yields and stereoselectivities are generally far from ideal. In fact, a quite number of the glycosylation reactions led to the coupled glycosides in only moderate yields (e.g., **20**+**21**, **24**+**25**, **35**+**36**, **43**+**44**, **62**+**63**, and **101**+**102**) and/or poor stereoselectivities (e.g., **24**+**25**, **62**+**63**, **75**+**76**, 144+145, and **161**+**162**). Under the influence of the coupling aglycone, even the installation of a neighboring participating group in the donor could not ensure a complete 1,2-*trans*-selective glycosylation (e.g., e.g., **9**+**10**, **14**+**15**, **62**+**63**, **68**+**69**, and **111**+**112**). Given the complex mixture resulted from the glycosylation reaction, the desired glycoside might be difficult to purify, thus, the crude product has to be carried out in the subsequent transformations. In addition, excess amounts of the promoters (and the donors) are usually required, thus hampering the large scale synthesis. To address these challenges for the glycosylation reactions in the realm of total

synthesis of complex glycosides, new innovation in the glycosylation chemistry is urgently required.

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