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Gold-catalyzed glycosylation in the synthesis of complex carbohydrate-containing natural products

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The methodological developments in gold(I)- and gold(III)-catalyzed glycosylation reactions are fully surveyed, which exploit the special alkynophilicity or the Lewis acidity of the gold cationic complexes. The application of the new methods in the total synthesis of naturally occurring glycoconjugates and glycans is comprehensively reviewed, with a focus on glycosylation of various complex aglycones.

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1. Introduction

The last decade has witnessed groundbreaking development in the glycosylation methodology that employs cationic gold(I) and gold(III) complexes as catalysts. Thus, a number of new types of glycosyl donors have been introduced, which bear various alkyne-containing aglycones as the anomeric leaving groups and can be activated by the alkynophilic gold species. In addition, the weak Lewis acidity of the cationic gold species has also been exploited to catalyze glycosylation reactions with conventional glycosyl donors, such as glycosyl trichloroacetimidates, sugar 1,2-epoxides, and glycals. These methodological developments have been constantly updated in review articles relevant to the glycosylation chemistry.[1–8] Very recently, the evolution and mechanistic elucidation of gold(I)-catalyzed glycosylation with glycosyl *o*-alkynylbenzoates as donors have been thoroughly accounted.[9] The activation mode and reaction conditions of gold-catalyzed glycosylations are different from those of the classical glycosylation reactions, and thus have provided new alternatives to tackle the challenging tasks still occurring in synthetic carbohydrate chemistry. Indeed, a rapidly growing number of naturally occurring glycoconjugates and glycans have been successfully synthesized with the gold-catalyzed glycosylation methods. These syntheses have also been highlighted in recent review articles relevant to gold catalysis or total synthesis of natural glycoconjugates.[9–16] Herein, we provide a full survey of the literature on gold(I)- and gold(III)-catalyzed

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glycosylation reactions through March 2018, with a major focus on the merits of gold-catalyzed glycosylation reactions in the context of total synthesis of complex naturally occurring glycoconjugates and glycans.

2. Methodological developments of gold-catalyzed glycosylation reactions

2.1 Gold(III)-catalyzed glycosylations

In 2006, Hotha *et al.* first reported a gold-catalyzed glycosylation reaction, which involved a Ferrier-type glycosylation of 3-*O*-propargyl glycals (*i.e.*, **A**, Fig. 1) under the promotion of $AuCl_3$.[17] Shortly thereafter they reported that propargyl glycosides (*i.e.*, **B**) could be used as glycosylation donors under the catalysis of $AuCl_3$.[18] This protocol which used stable glycosides as donors and a catalytic amount of the gold(III) complex as promoter was inspiring. However, this glycosylation proceeded under relatively strong conditions (CH_3CN, 60 °C) and the substrates were limited to reactive donors and acceptors. Under similar conditions, it was later found that methyl glycosides (*i.e.*, **I**),[19] including 2-*C*-branched methyl glycosides (*i.e.*, **P**),[20,21] could also undergo effective glycosylation. Evidently, it was the Lewis acidity rather than the alkynophilicity of the gold(III) catalyst that played a role in the promotion of these glycosylation reactions. In 2012, Hotha *et al.* disclosed a careful study of gold(III)-catalyzed glycosylation reactions with a series of substituted propargyl glycosides as donors; the *gem*-disubstituted ones, such as 1-ethynylcyclohexanyl glycosides (*i.e.*, **C**), were found to be much reactive than propargyl glycosides (due to the Thorpe–Ingold effect) and addition of a Ag(I) salt (*i.e.*, $AgSbF_6$ and AgOTf) as co-catalyst was beneficial for the reaction to proceed at room temperature.[22,23] Under the catalysis of $AuCl_3/AgSbF_6$, Balamurugan *et al.* found that dipropargyl-substituted cyanoacetyl glycosides (*i.e.*, **D**) could also undergo glycosylation at room temperature.[24] The application of these glycosylation protocols to the preparation of 1,6-anhydro saccharides,[25] furanosides,[26] and thioglycosides[27] was recorded. Finn *et al.* reported that the gold(III)-catalyzed glycosylation proceeded with unprotected propargyl glycosides.[28]

In 2007, Hotha *et al.* reported that propargyl 1,2-orthoesters (*i.e.*, **E**) could undergo glycosylation under the catalysis of $AuBr_3$ under mild conditions.[29] In fact, these donors could be selectively activated in the presence of propargyl and *n*-pentenyl glycosides.[30,31] The mild reaction conditions and the 1,2-*trans*-glycosylation manner allowed the application of this protocol to the preparation of furanosides,[32] pyrimidine nucleosides,[33] thioglycosides,[34] glycosyl carbamates,[35] aminooxy glycosides,[36] as well as glycosyl acrylate/acrylamides.[37–39]

In 2015, Vankar *et al.* reported a $AuCl_3$-catalyzed glycosylation with trichloroacetimidates as donors (*i.e.*, **J**),[40] wherein the

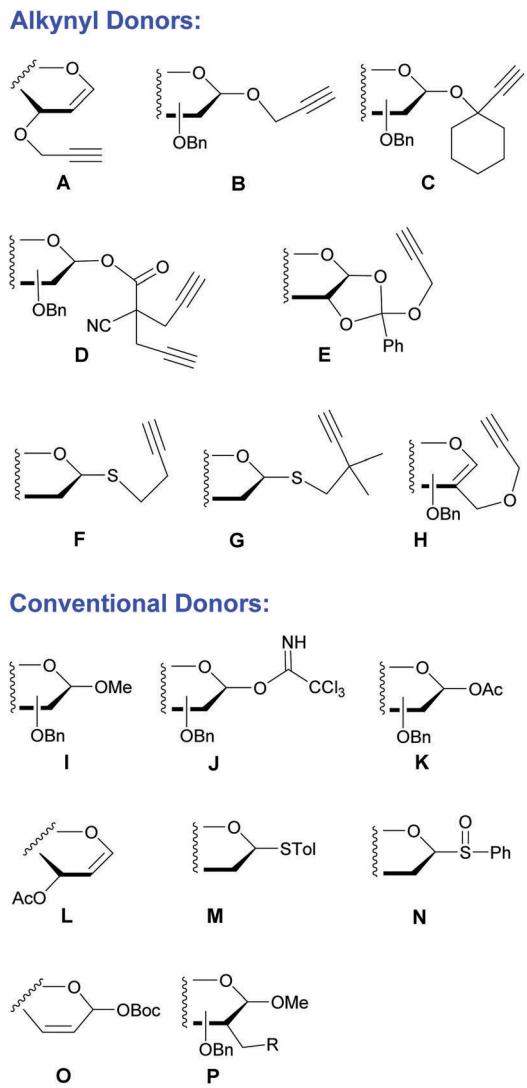

Fig. 1 Representative glycosyl donors which can be activated by a gold(III) catalyst. Those bearing OBn (*O*-benzyl group) represent the necessity of reactive donors (armed donors).

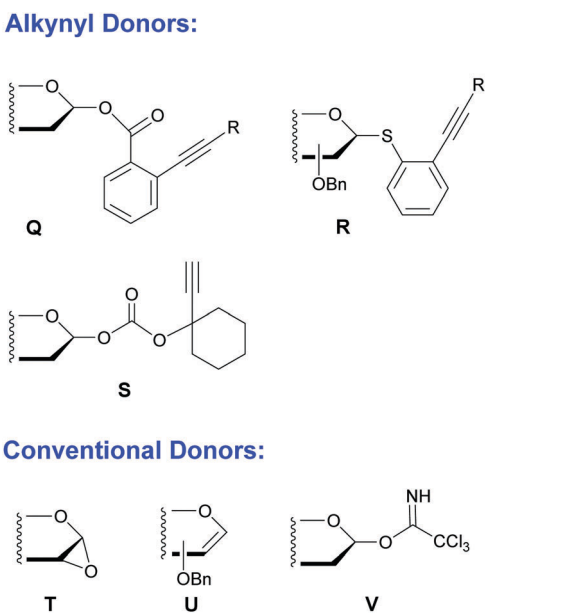

Fig. 2 Representative glycosyl donors which can be activated by a gold(I) catalyst.

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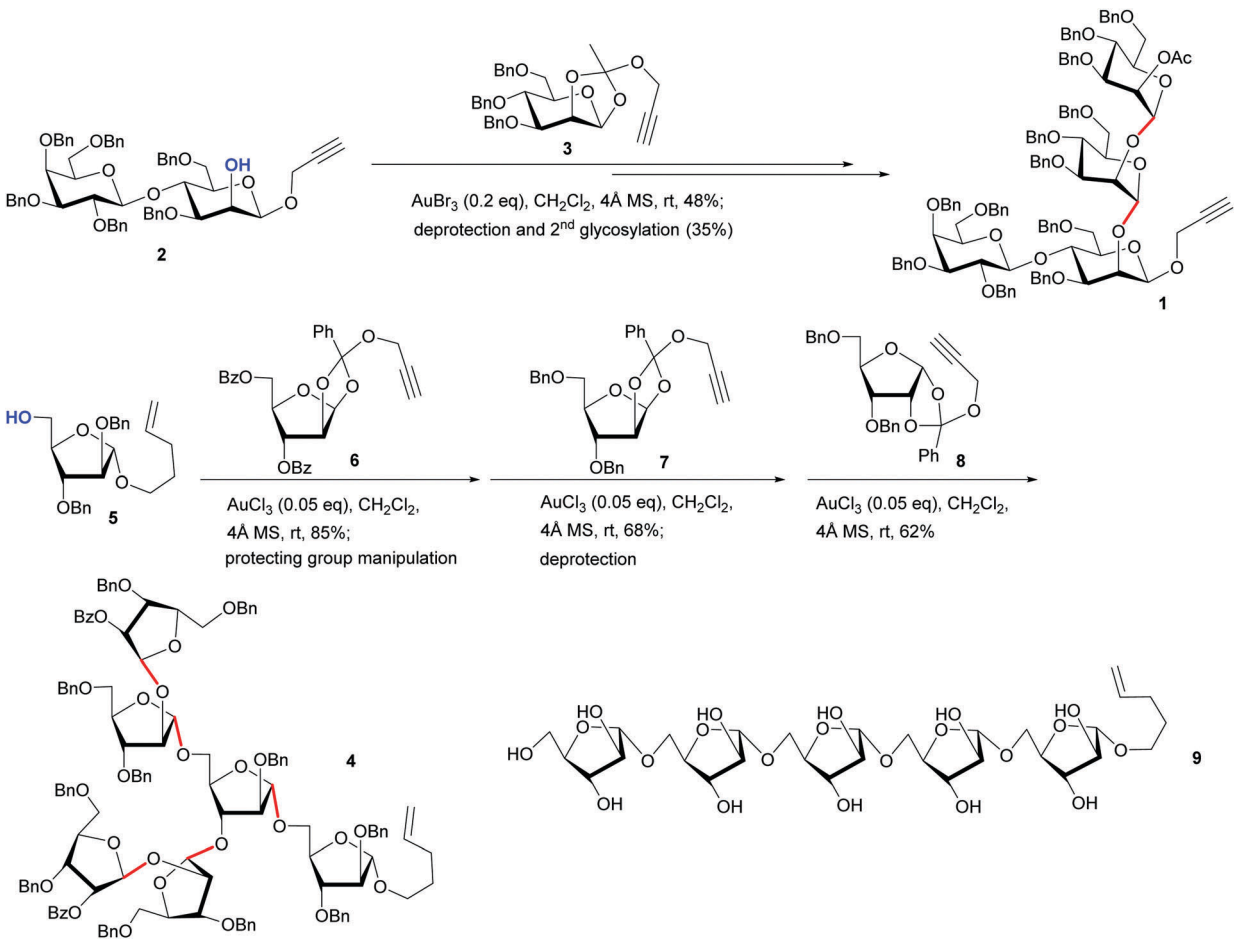
addition of phenylacetylene improved greatly the glycosylation yield. The combination of $AuCl_3$ (or $AuBr_3$) and phenylacetylene was also found to be effective in the activation of propargyl 1,2-orthoester donors (*i.e.*, **E**),[41] 1-*O*-acetyl donors (*i.e.*, **K**),[41,42] and 3-*O*-acetyl glycals (*i.e.*, **L**).[42,43] Schmidt and Peng disclosed that the Lewis acidic gold salts, such as $AuCl_3$, could selectively activate the alcoholic acceptors instead of glycosyl trichloroacetimidate donors at low temperature (−60 °C or −70 °C); the resultant catalyst–acceptor adducts could then facilitate the activation of trichloroacetimidates *via* intramolecular hydrogen-bonding and lead to S_N2-type glycosylation in a stereoselective manner.[44,45] Recently, Sasaki *et al.* reported stereoselective β-mannosylations by using α-trichloroacetimidates bearing a 2,6-lactone scaffold under the combined catalysis of $AuCl_3$ and 3,5-bis(trifluoromethyl)phenyl thiourea.[46,47]

Additionally, *S*-but-3-ynyl and *gem*-dimethyl *S*-but-3-ynyl thioglycosides (*i.e.*, **F** and **G**) were reported by Zhu *et al.* in 2013 as glycosylation donors under the activation of $AuCl_3$ and AgOTf.[48] In 2016, Sureshan *et al.* claimed that tolyl thioglycosides (*i.e.*, **M**) could be catalyzed by $AuCl_3$ for effective glycosylation;[49] unfortunately, it was later found that a stoichiometric amount of $AuCl_3$ was required.[50] Vankar *et al.* demonstrated that glycosyl sulfoxides (*i.e.*, **N**) could be used as glycosylation donors under the catalysis of $AuCl_3$ and AgOTf.[51] Chen *et al.* applied 1-*O*-Boc pyranones (*i.e.*, **O**) in the gold(III)-catalyzed glycosylations.[52] Hotha *et al.* reported the synthesis of C-2 methylene glycosides from C-2 propargyloxymethyl glycals (*i.e.*, **H**) under the catalysis of $AuCl_3$.[53]

2.2 Gold(I)-catalyzed glycosylations

In early 2008, Yu *et al.* reported the gold(I)-catalyzed glycosylation using easily accessible and shelf-stable glycosyl *o*-hexynylbenzoates as donors (*i.e.*, **Q**; Fig. 2) and $Ph_3PAuOTf$ or $Ph_3PAuNTf_2$ (most conveniently) as catalyst.[54] This reaction can proceed under mild conditions and accommodate an extremely wide scope of substrates.[9,55] Extensive studies have since been conducted pertaining to the activation mechanism,[56–58] catalyst development,[59–65] and modification of the *o*-alkynylbenzoyl leaving groups.[66–68] A number of unsuccessful or less effective donors, such as *o*-alkynylphenyl thioglycosides (*i.e.*, **R**),[60] were reported.[9] Some special issues in the glycosylation chemistry have been tackled with this new method, which include β-mannosylation,[63,64] β-rhamnosylation,[67] heparin synthesis,[69] β-Kdo (3-deoxy-D-manno-oct-2-ulsonic acid) glycoside synthesis,[70] 3-aminopyranoside synthesis,[71,72] and glycosyl poly-THF synthesis.[73] Besides glycosylation with regular alcoholic acceptors,



Scheme 1 Synthesis of oligosaccharides (**1**, **4**, and **9**).

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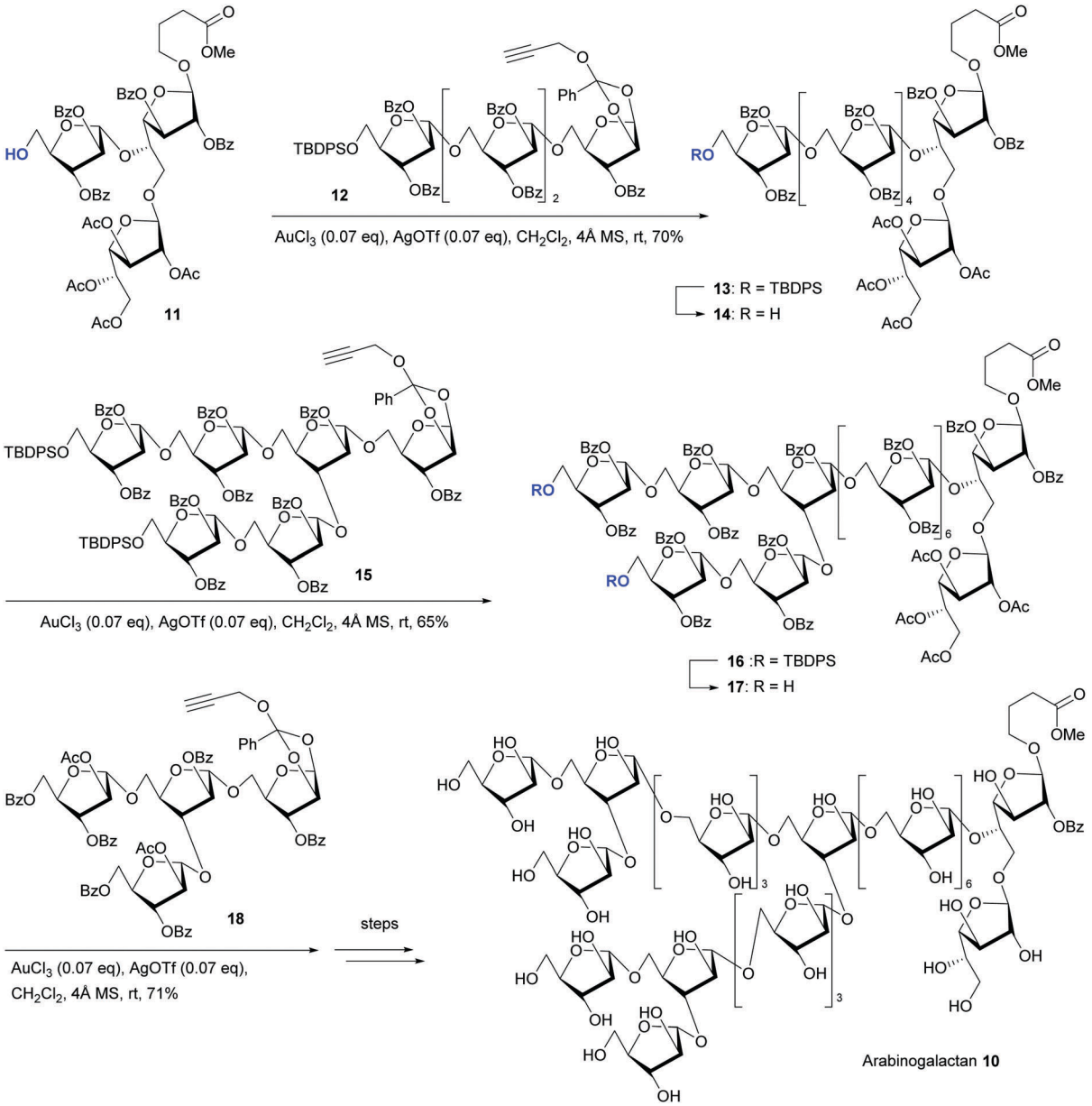
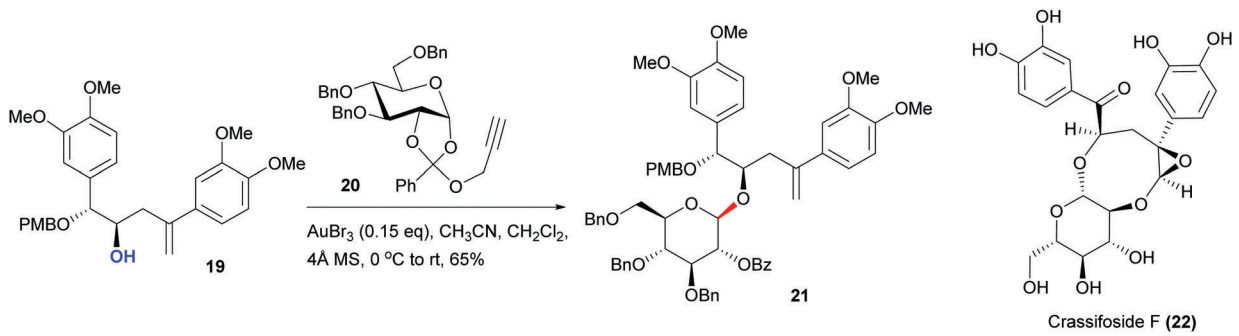


Scheme 2 Synthesis of heneicosafuranosyl arabinogalactan **10**.



Scheme 3 Synthesis of crassifoside F (**22**).

this method also demonstrated high efficiency in *O*-glycosylation of carboxylic acids,[74] phosphates,[75] and oximes,[76] *N*-glycosylation of nucleobases,[77,78] and *C*-glycosylation of allyltrimethylsilane or silyl enol ethers.[79] Seeberger *et al.* examined the glycosylation

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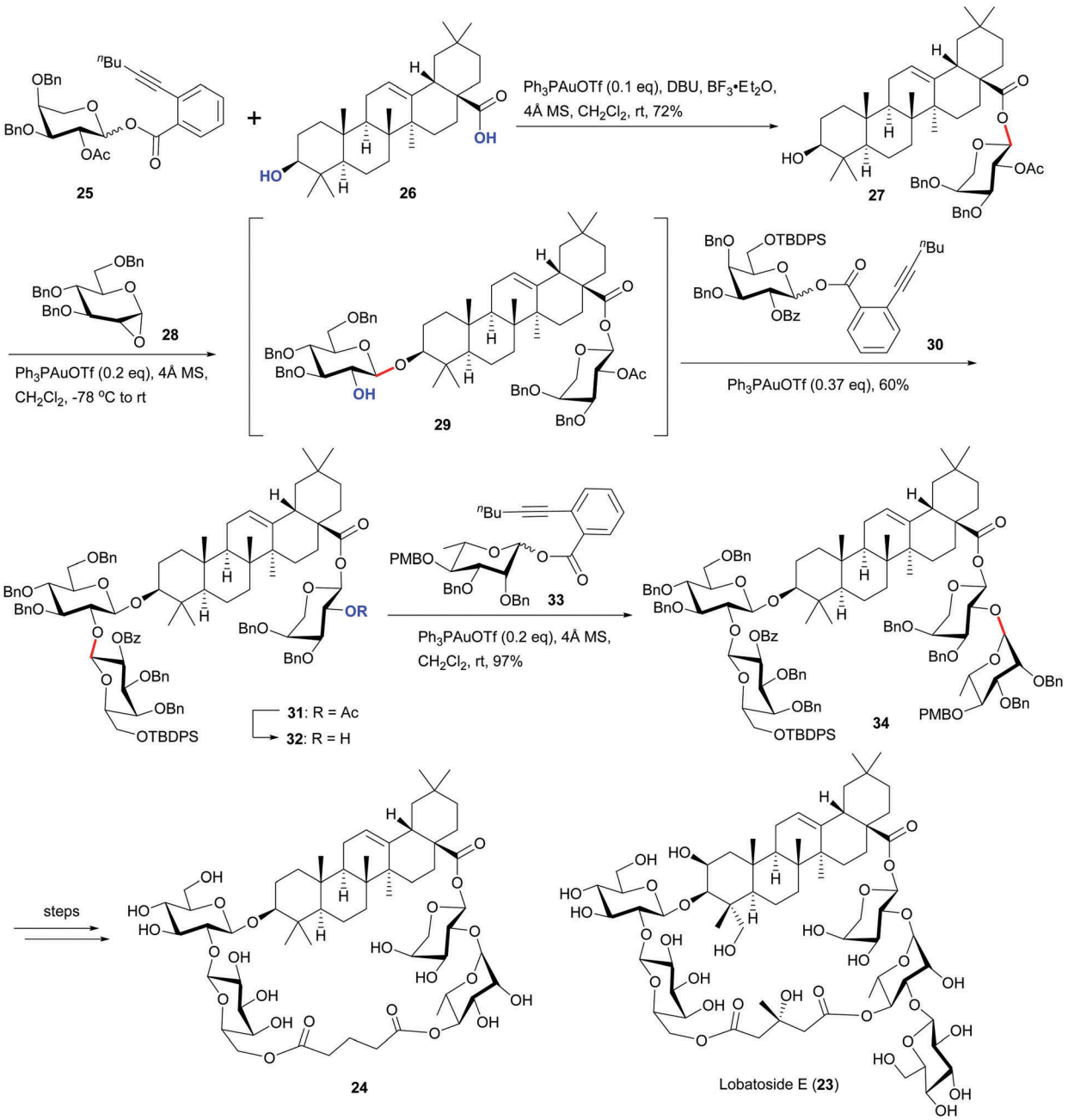
potential of this method under flow conditions.[80] In 2012, Zhu *et al.* reported that *S*-but-3-ynyl 2-deoxy thioglycosides (*e.g.*, **F**) could be used as glycosylation donors under the catalysis of $(p\text{-}CF_3Ph)_3PAuCl/AgOTf$.[81] In 2016, Hotha *et al.* reported glycosyl alkynyl carbonates (*e.g.*, **S**) as effective glycosylation donors under the catalysis of $(2,4\text{-di-}t\text{BuPh})_3PAuCl/AgOTf$.[82]

Several types of classical donors have also been found to be effective under the catalysis of gold(I). In 2008, Yu *et al.* disclosed that sugar 1,2-epoxides (*e.g.*, **T**) could be activated more effectively by $Ph_3PAuOTf$ than by the conventional promoters such as $ZnCl_2$.[83] In 2009, Kunz *et al.* reported that glycosyl trichloroacetimidates could be utilized for effective glycosylation under the catalysis of AuCl.[84] Recently, Galan *et al.* demonstrated that glycals (*e.g.*, **U**) could undergo α-selective glycosylation under the catalysis of $(p\text{-}CF_3Ph)_3PAuCl/AgOTf$.[85]

Although some types of the aforementioned donors could be effectively activated by either a gold(I) or a gold(III) catalyst, in most of the reactions, the catalytic efficiency of gold(I) and gold(III) catalysts has been found to be dramatically different. This difference can always be attributed to the much higher alkynophilicity and lower Lewis acidity of gold(I) catalysts as compared to gold(III) catalysts. In addition, the counter anions of gold catalysts could also play an important role in the glycosylation reactions.[63]



Scheme 4 Synthesis of cyclic oleanane glycoside **24** relevant to lobatoside E (**23**).

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3. Gold(III)-catalyzed glycosylation in the synthesis of natural glycans and glycoconjugates

Using the gold(III)-catalyzed glycosylation method with propargyl 1,2-orthoesters as donors, Hotha *et al.* synthesized several glycans relevant to the cell wall polysaccharides of bacteria (Schemes 1 and 2). Thus, a fully protected tetrasaccharide **1** relevant to the lipophosphoglycan of *Leishmania donovani*[86,87] was prepared from disaccharide **2** *via* glycosylation with mannosyl propargyl 1,2-orthoester donor **3** under the catalysis of $AuBr_3$ (0.2 equiv.).[88] The glycosylation gave the coupled products in ~40% yield, nevertheless, in a complete 1,2-*trans* manner and with the product bearing a 2-*O*-acetyl group suitable for selective removal and further elongation. With furanosyl donors (*e.g.*, **6–8**), the gold(III)-catalyzed glycosylation turned out to be much effective, and a fully protected hexasaccharide **4** relevant to the polysaccharides of *Mycobacterium tuberculosis*[89,90] was efficiently synthesized.[91] Likewise, penta-arabinofuranoside **9** was synthesized,[92] wherein the combination of $AuCl_3$ and AgOTf was found to be a more effective catalyst for the corresponding glycosylation.

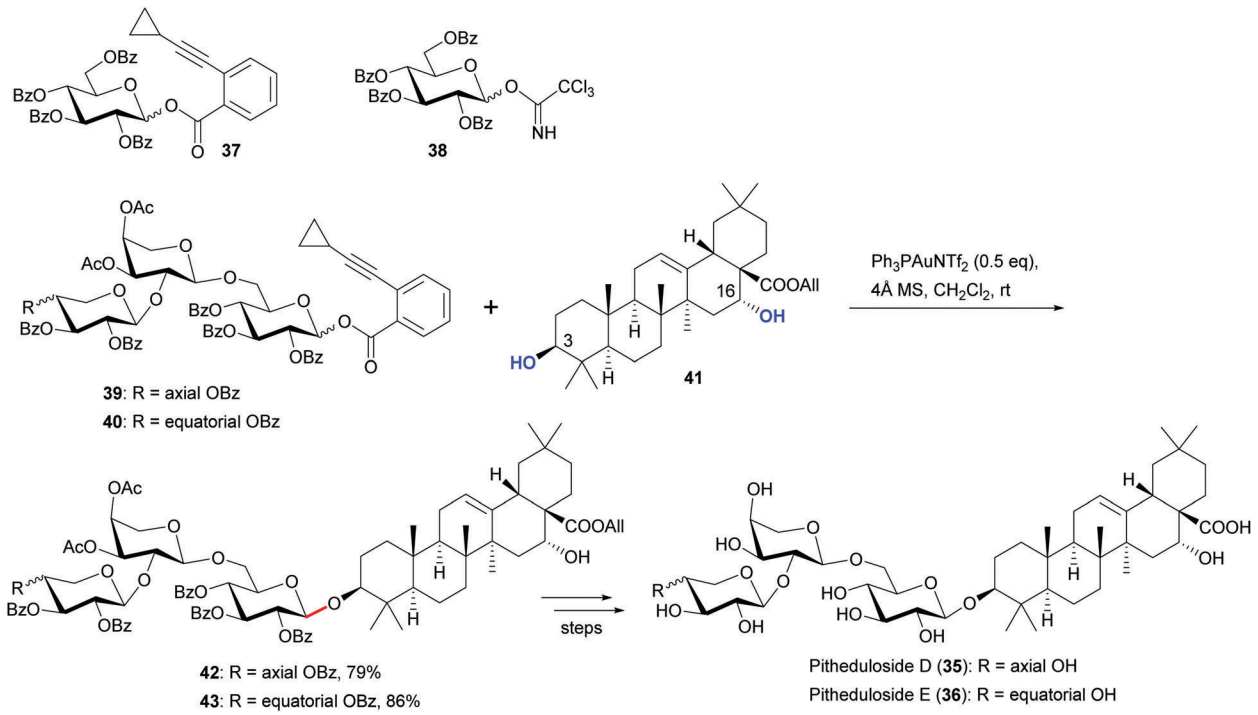
An impressive synthesis of a branched heneicosafuranosyl arabinogalactan **10** relevant to *M. tuberculosis* cell wall polysaccharides was reported in 2017 by Hotha *et al.*, utilizing the $AuCl_3$/AgOTf-catalyzed glycosylation with propargyl 1,2-orthoester donors (Scheme 2).[93] The assembling stage commenced with a [4+3] condensation of tetrasaccharide 1,2-orthoester **12** and trisaccharide alcohol **11** in the presence of $AuCl_3$ (0.07 equiv.) and AgOTf (0.07 equiv.) in CH_2Cl_2 at r.t., giving heptasaccharide **13** in 70% yield. Removal of the TBDPS group and coupling of the resultant **14** with hexasaccharide orthoester **15** led to tridecasaccharide **16** in 65% yield, whereas glycosylation with the corresponding hexasaccharide *n*-pentenyl donor in the presence of NIS and TfOH gave **16** in only 24% yield. The two terminal TBDPS on **16** was removed and the resulting diol **17** was subjected to the final glycosylation with tetrasaccharide orthoester **18** to give the coupled product in 71% yield. Global deprotection furnished arabinogalactan **10**.

Crassifoside F (**22**), isolated from *Curculigo crassifolia* and with angiotensin-converting enzyme inhibitory activity, possesses a glucose residue which is *trans*-fused into an eight-membered ring.[94] In 2017, Maurya reported a synthetic study, wherein an advanced precursor **21** was prepared in 65% yield *via* glycosylation of alcohol **19** with propargyl 1,2-orthoester **20** under the action of $AuBr_3$ (0.15 equiv.) (Scheme 3).[95]

4. Gold(I)-catalyzed glycosylation in the synthesis of natural glycans and glycoconjugates

4.1 Synthesis of saponins

4.1.1 Oleanane and ursane-type triterpene saponins. Lobatoside E (**23**) is a prototypical oleanane-type cyclic triterpene saponin with potent antitumor activities.[96] Yu *et al.* reported the first synthesis in 2008, utilizing conventional glycosylation methods with the relevant glycosyl trichloroacetimidate, bromide, and thioglycoside as donors.[97] With the newly developed gold(I)-catalyzed glycosylation methods with *o*-alkynylbenzoates and



Scheme 5 Synthesis of pithedulosides D and E (**35** and **36**).

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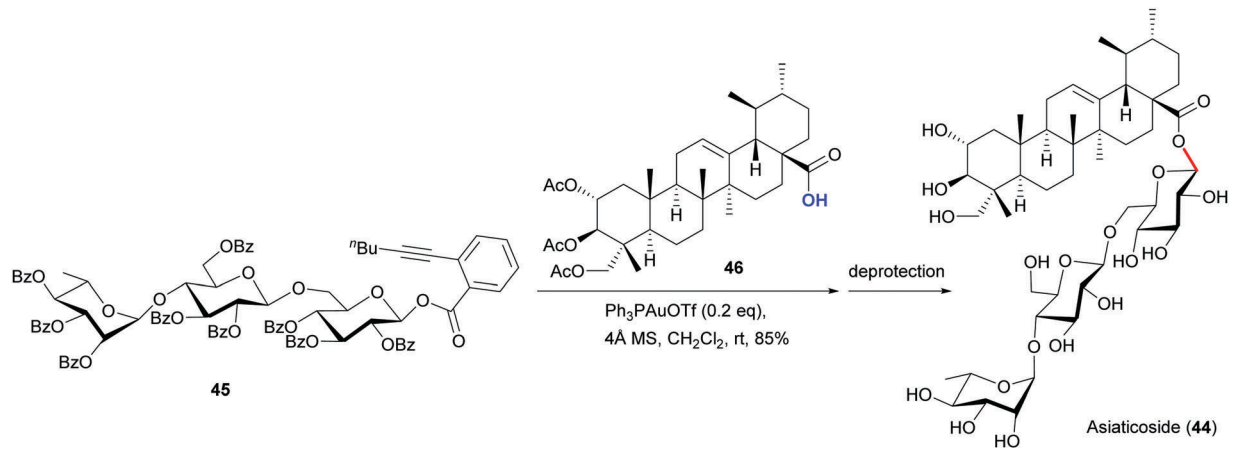
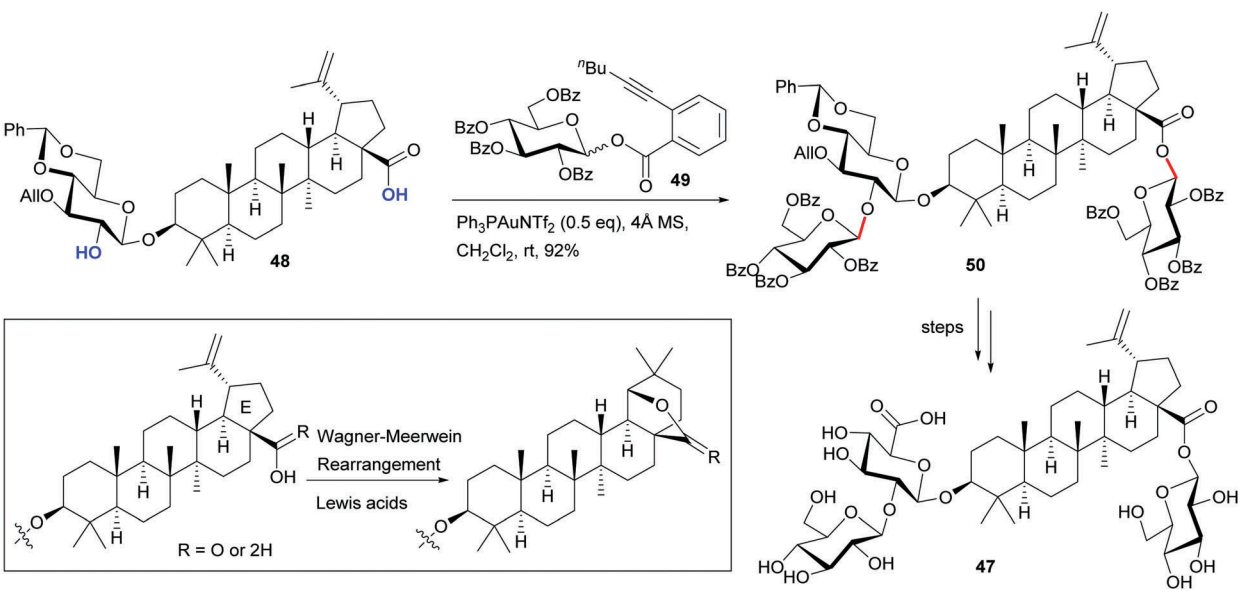
1,2-epoxides as donors, they developed a streamlined approach toward the preparation of this type of glycosides.[98] The synthesis of a simple congener **24** is depicted in Scheme 4.[55] The assembly commenced with the chemoselective glycosylation of oleanolic acid **26** with arabinopyranosyl *o*-hexynylbenzoate **25** (in the presence of DBU and $BF_3{\cdot}Et_2O$),[74] leading to ester glycoside **27** in 72% yield. Then a gold(I)-catalyzed one-pot reaction involving two steps of sequential glycosylations was performed, wherein the remaining 3-OH was glycosylated with 1,2-anhydro-glucoside **28** under the action of $Ph_3PAuOTf$ (0.2 equiv.) in CH_2Cl_2 at −78 °C[83] and subsequent addition of galactosyl *o*-hexynylbenzoate **30** and another portion of $Ph_3PAuOTf$ (0.37 equiv.) promoted the glycosylation of the nascent glucoside 2-OH on intermediate **29**, giving the desired trisaccharide **31** in 60% yield. After removal of the acetyl group on the arabinose residue, the last glycosylation was carried out between the resulting alcohol **32** and rhamnosyl *o*-hexynylbenzoate **33** under the catalysis of $Ph_3PAuOTf$ (0.2 equiv.) at r.t. to provide the desired tetrasaccharide **34** in nearly quantitative yield. Further elaboration furnished **24**.

Two antitumor oleanane-type saponins, namely pithedulosides D (**35**) and E (**36**), isolated from *Pithecellobium dulce*,[99] were synthesized by Sun *et al.* in 2017 (Scheme 5).[100] A late-stage regioselective glycosylation of the 3-OH on triterpene diol **41** with trisaccharide donors was envisioned. Model reactions were conducted with glucosyl *o*-cyclopropylethynylbenzoate **37** and trichloroacetimidate **38** as donors; the glycosylation of diol **41** with donor **37** under the catalysis of $Ph_3PAuNTf_2$ gave the desired 3-*O*-glycoside in an excellent 90% yield, whereas the glycosylation with donor **38** led to a mixture of 3-*O*-, 16-*O*-, and 3,16-di-*O*-glycoside. Thus, trisaccharide *o*-cyclopropylethynylbenzoates **39** and **40** were prepared and subjected to glycosylation with diol **41**, providing the desired products **42** and **43** in 79% and 86% yield, respectively. Subsequent deacylation and deallylation furnished pithedulosides D (**35**) and E (**36**).



Scheme 6 Synthesis of asiaticoside (**44**).



Scheme 7 Synthesis of the proposed structure of betulinic acid trisaccharide **47** from *Bersama engleriana*.

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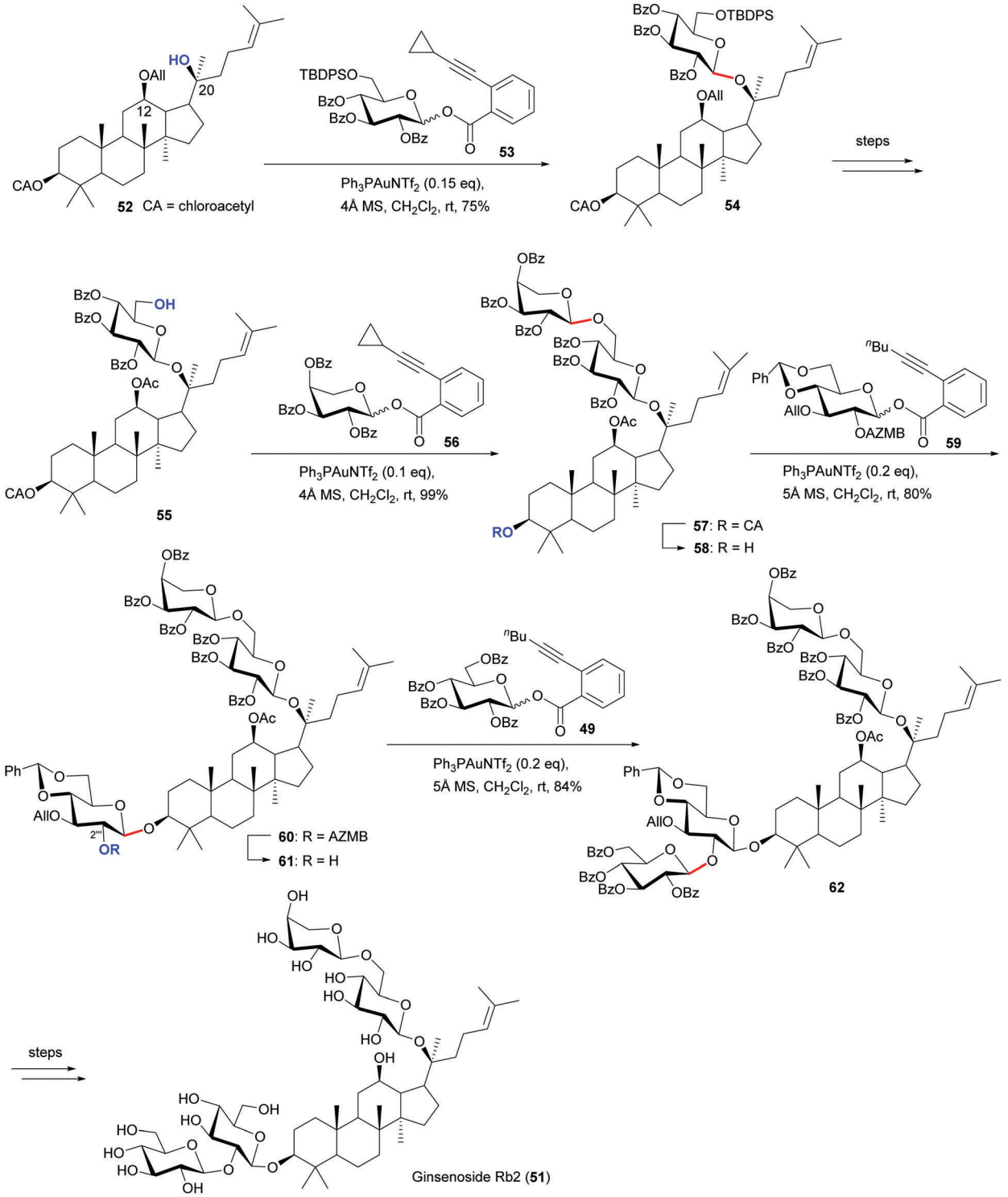
Asiaticoside (**44**), a ursane-type triterpene saponin, is one of the earliest saponins being isolated from nature (Scheme 6).[101,102] It is the major active component of *Centella asiatica*, a herbal medicine that has been used for the treatment of dermatoses and skin lesions.[103–105] Yu *et al.* reported its synthesis in 2017, employing a late-stage gold(I)-catalyzed glycosylation as the key step.[106] Thus, ursane acid **46** was glycosylated with trisaccharide *o*-hexynylbenzoate **45** in the presence of $Ph_3PAuOTf$ in CH_2Cl_2 at r.t. to give the desired ester glycoside in 85% yield. Subsequent removal of the acyl protecting groups accomplished the synthesis.

4.1.2 Lupane-type triterpene saponins. Betulinic acid and betulin are two common aglycones in the lupane-type triterpene



Scheme 8 Synthesis of ginsenoside Rb2 (**51**).

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saponins. The glycosylation of 28-COOH or 28-OH on betulinic acid or betulin, respectively, was found to be problematic due to the potential Wagner–Meerwein rearrangement of the E ring under acidic conditions (Scheme 7).[107,108] This problem was addressed by gold(I)-catalyzed glycosylation with *o*-alkynylbenzoate donors,[109] as exemplified by the synthesis of the proposed structure of betulinic acid trisaccharide **47**, a minor component isolated from *Bersama engleriana*.[110] The glycosylation of 28-COOH and 2′-OH on **48** took place simultaneously with *o*-hexynylbenzoate **49** in the presence of $Ph_3PAuNTf_2$ in CH_2Cl_2 at r.t., providing the desired trisaccharide **50** in an excellent 92% yield. In this case, the amount of $Ph_3PAuNTf_2$ was raised

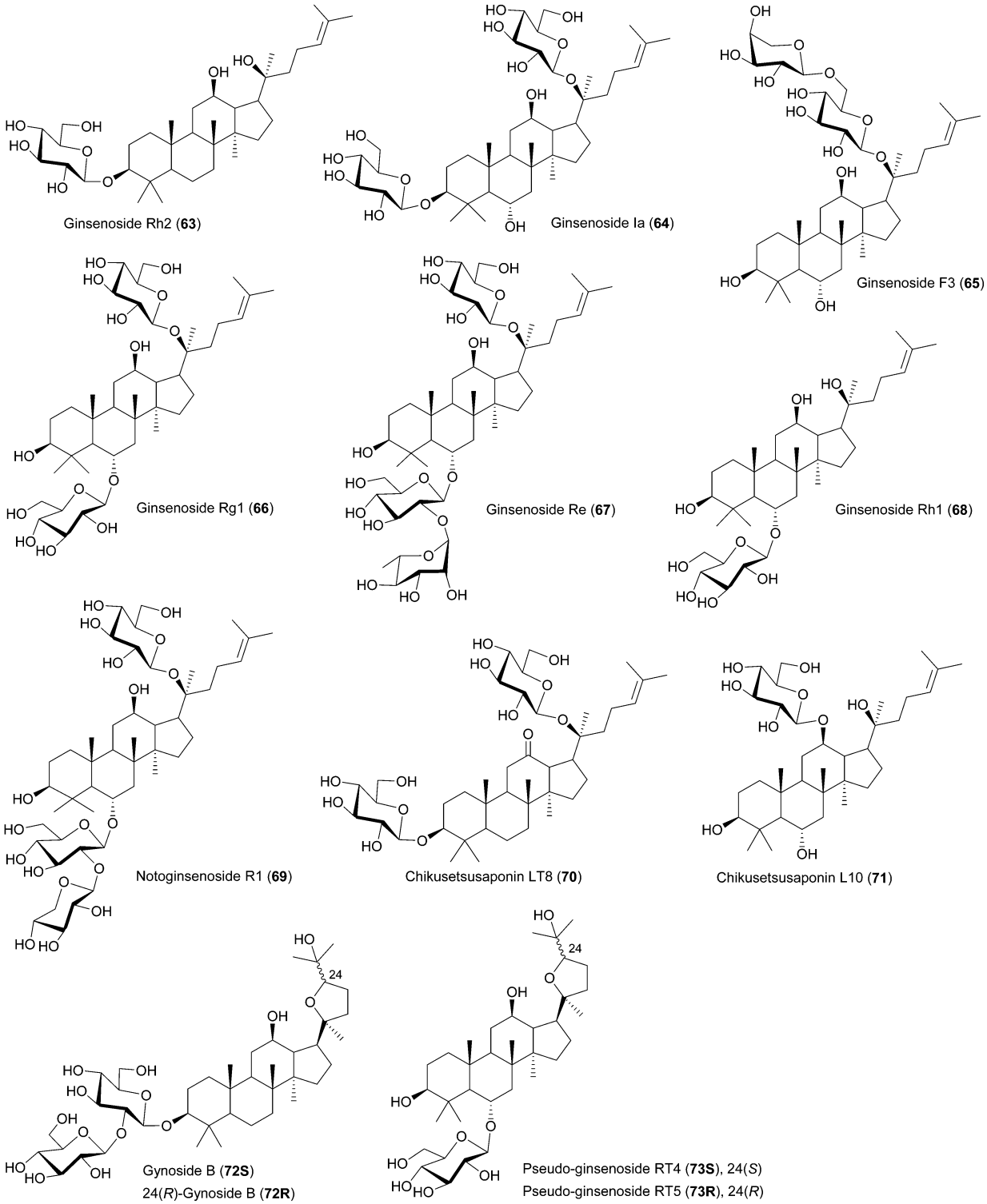

Fig. 3 Ginsenosides (**63–73**) synthesized by the gold(I)-catalyzed glycosylation with *o*-alkynylbenzoate donors.

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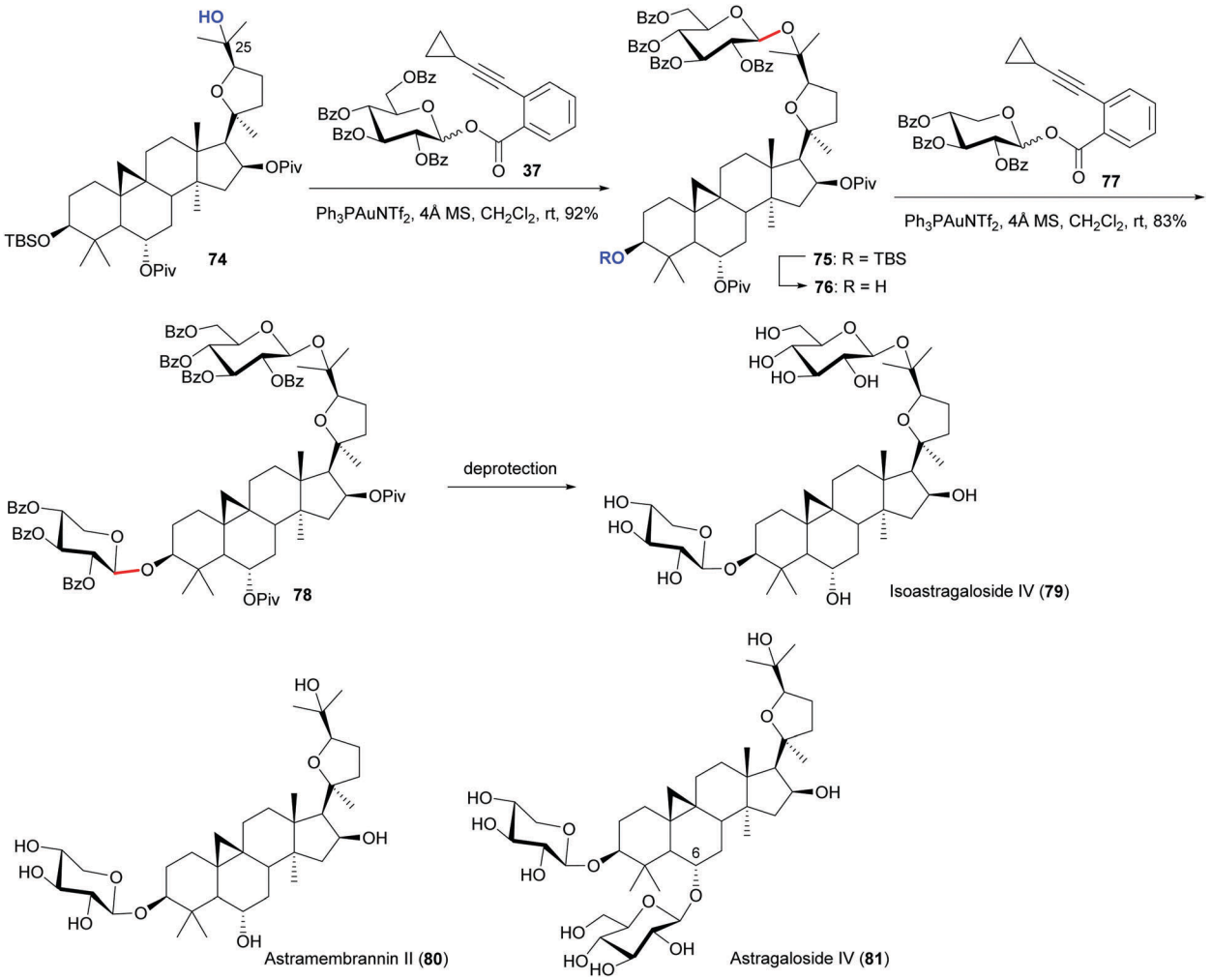
to 0.5 equiv. to avoid formation of the corresponding orthoester by-products.

4.1.3 Dammarane and cycloartane-type triterpene saponins. Ginsenosides, showing numerous pharmacological activities, constitute a large family of triterpene saponins, and most of them share dammarane-type protopanaxadiol or protopanaxatriol as the aglycones. The glycosylation of the tertiary dammarane 20-OH is difficult because of its steric hindrance and vulnerability toward acids and electrophiles.[111] The glycosylation conditions with trifluoroacetimidate, bromide, and sulfoxide donors could lead to dehydration or addition of 20-OH to the C24(25) olefin.[112] Gratifyingly, the gold(I)-catalyzed glycosylation method with *o*-alkynylbenzoate donors has been applied effectively in the synthesis of ginsenosides.[112,113] The synthesis of ginsenoside Rb2 (**51**),[114,115] a complex protopanaxadiol ginsenoside with potent immunosuppressive and antidiabetic activities,[116,117] is shown as an example in Scheme 8.[112] Thus, the tertiary 20-OH on protopanaxadiol **52** was glycosylated with glucosyl *o*-cyclopropylethynylbenzoate **53** to give 20-*O*-glycoside **54** in 75% yield (0.15 equiv. $Ph_3PAuNTf_2$, CH_2Cl_2, r.t.). It was found that the 12-*O*-allyl group greatly enhanced the nucleophilicity of 20-OH through hydrogen bonding, whereas the corresponding 12-*O*-acetyl protopanaxadiol derivative could not be glycosylated under similar conditions. The second gold(I)-catalyzed glycosylation was performed between arabinopyranosyl *o*-cyclopropylethynylbenzoate **56** and glycoside acceptor **55** under similar conditions, leading to disaccharide **57** in quantitative yield. In the third glycosylation step, *o*-hexynylbenzoate **59** bearing a neighbouring participating and selectively removable AZMB [2-(azidomethyl)-benzoyl] group at O2 was condensed with acceptor **58**, giving bis-*O*-glycoside **60** in 80% yield. Similarly, the fourth glycosylation step between acceptor **61** and donor **49** led to tetrasaccharide **62** (84%).

By the same token, a number of ginsenosides have been synthesized (Fig. 3),[112,113,118–120] which include ginsenosides Rh2 (**63**),[121,122] Ia (**64**),[123] F3 (**65**),[124] Rg1 (**66**),[125] Re (**67**),[126] Rh1 (**68**),[127] notoginsenoside R1 (**69**),[128] chikusetsusaponin LT8 (**70**)[129] and L10 (**71**),[130] as well as ocotillol-type pseudoginsenoside gynoside B (**72S**)/24(*R*)-gynoside B (**72R**)[131,132] and RT4 (**73S**)/RT5 (**73R**).[133]

Applying the same methodology, Sun *et al.* achieved the synthesis of cycloartane-type cycloastragenol glycosides (**79–81**)



Scheme 9 Synthesis of isoastragaloside IV (**79**), astramembrannin II (**80**), and astragaloside IV (**81**).

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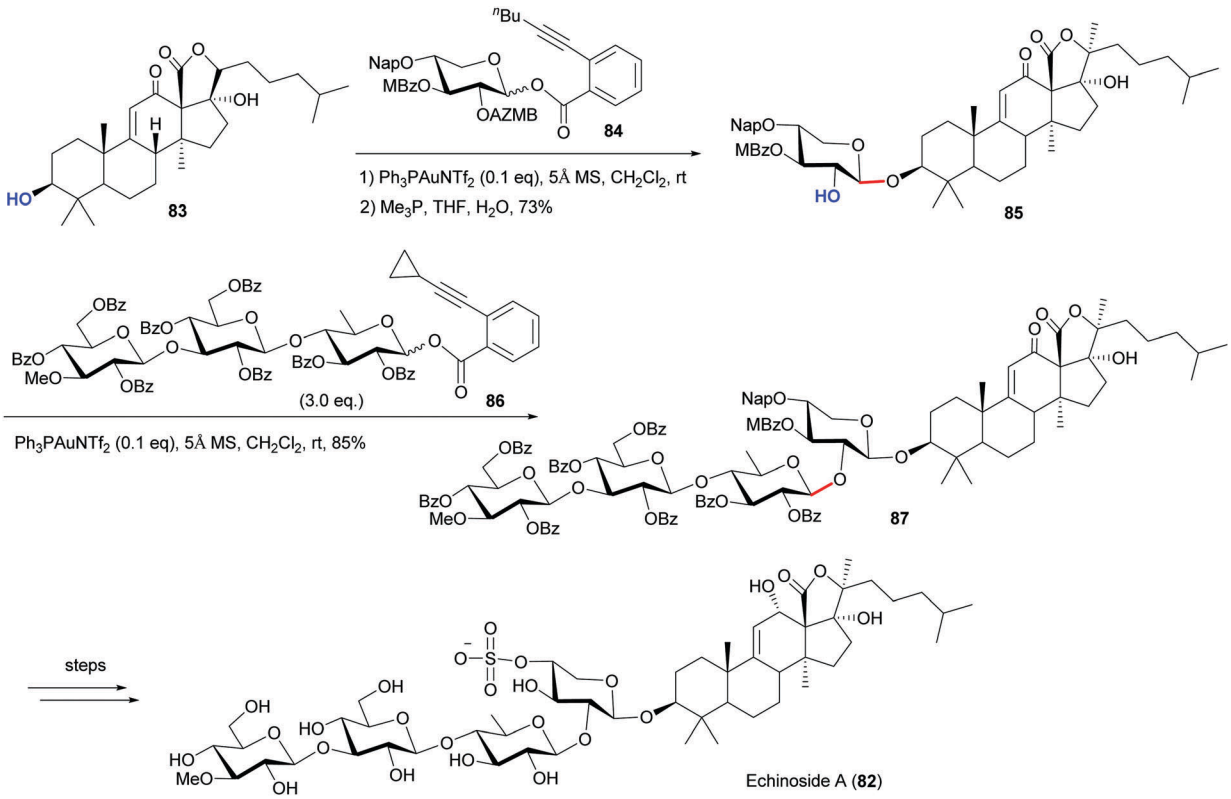
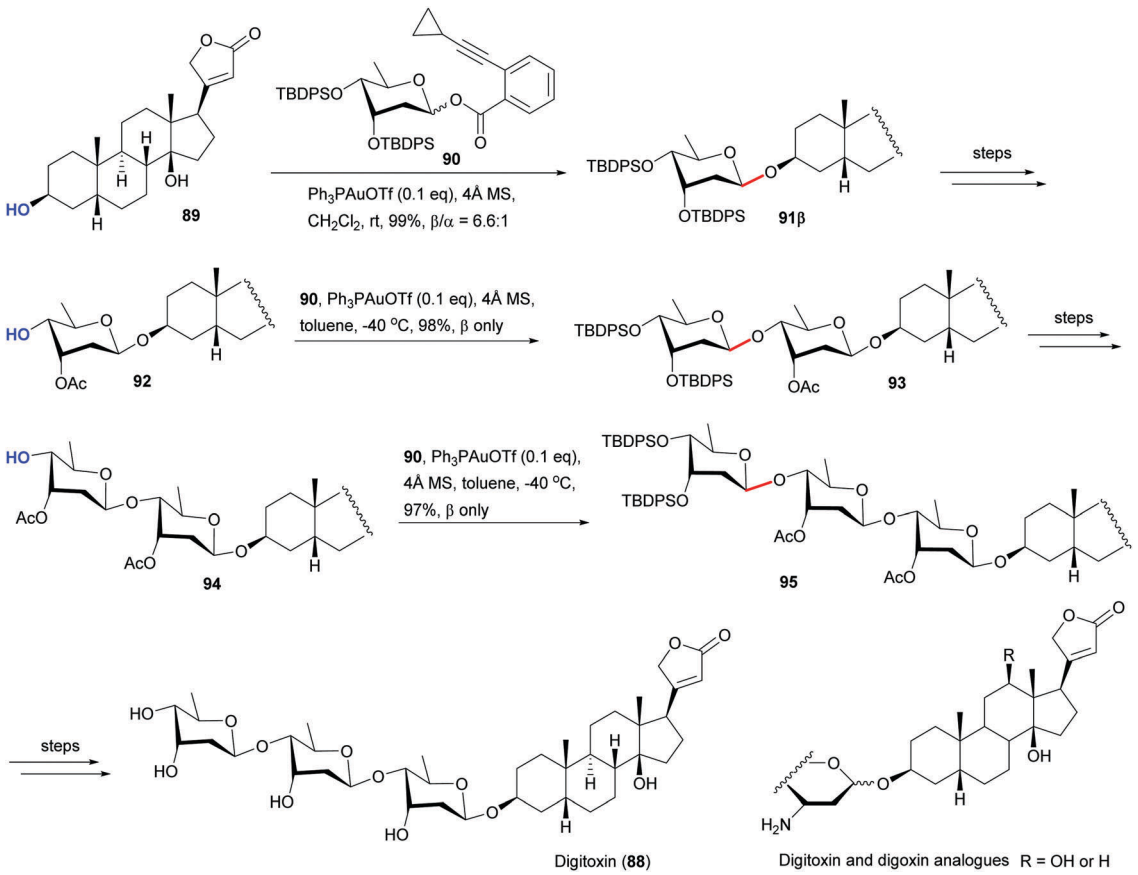


Scheme 10 Synthesis of echinoside A (**82**).



Scheme 11 Synthesis of digitoxin (**88**) and the synthetic digitoxin/digoxin analogues bearing 2,3-deoxy-3-amino sugars.

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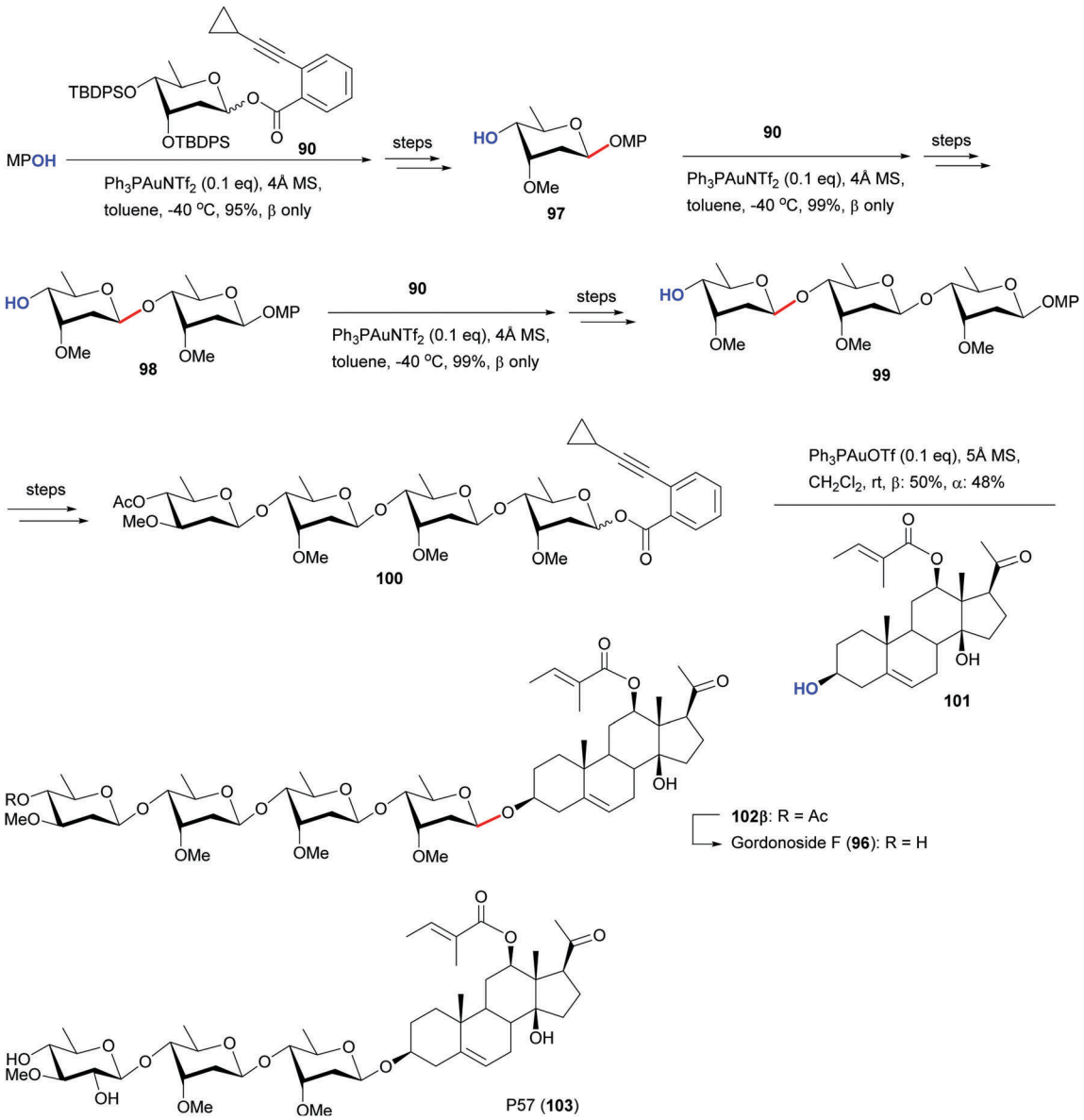
isolated from *Astragali Radix* (Scheme 9).[134] Thus, glycosylation of cycloartane tertiary alcohol **74** with glucosyl *o*-cyclopropylethynylbenzoate **37** gave 25-*O*-glycoside **75** in 92% yield (0.2 equiv. $Ph_3PAuNTf_2$, CH_2Cl_2, r.t.). After cleavage of the 3-*O*-TBS group, the resulting **76** was subjected to glycosylation with xylopyranosyl *o*-cyclopropylethynylbenzoate **77** under similar conditions to provide 3,25-*O*-bisglycoside **78** (83%). The final removal of the acyl protecting groups furnished isoastragaloside IV (**79**).[135] Similarly, astramembrannin II (**80**)[136] and astragaloside IV (**81**)[137] were synthesized. During the synthesis of astragaloside IV (**81**), $Ph_3PAuOTf$ was found to be more effective than $Ph_3PAuNTf_2$ in catalyzing glycosylation of the hindered cycloartane 6-OH. In addition, the subsequent glycosylation of 3-OH was hampered by the presence of the 6-*O*-glucose residue and thus one equivalent of $Ph_3PAuOTf$ was used to achieve a good 80% yield of the glycosylation reaction.

4.1.4 Lanostane-type triterpene saponin (echinoside A). Echinoside A (**82**), a lanostane-type triterpene glycoside with potent antifungal and anticancer activities,[138–142] belongs to a family of saponins occurring characteristically in sea cucumbers. Yu *et al.* achieved its synthesis in 2017, wherein gold(I)-catalyzed glycosylations were employed at a late assembly stage (Scheme 10).[143] Thus, β-selective glycosylation of holostanol derivative **83** with xylosyl *o*-hexynylbenzoate **84** proceeded smoothly in the presence of $Ph_3PAuNTf_2$ (0.1 equiv.) at r.t.; subsequent removal of the 2′-*O*-AZMB group with Me_3P led to glycoside **85** in 73% yield. The resulting 2′-OH on **85** was then glycosylated with trisaccharide *o*-cyclopropylethynylbenzoate **86** (3 equiv.) under similar conditions to furnish tetrasaccharide **87** in a satisfactory 85% yield. Further modification of the aglycone and the glycan residues led to echinoside A (**82**).

4.1.5 Cardenolide and pregnane-type steroidal saponins. Digitoxin (**88**), a representative cardenolide-type saponin, is well



Scheme 12 Synthesis of gordonoside F (**96**) and the previously synthesized congener P57 (**103**).

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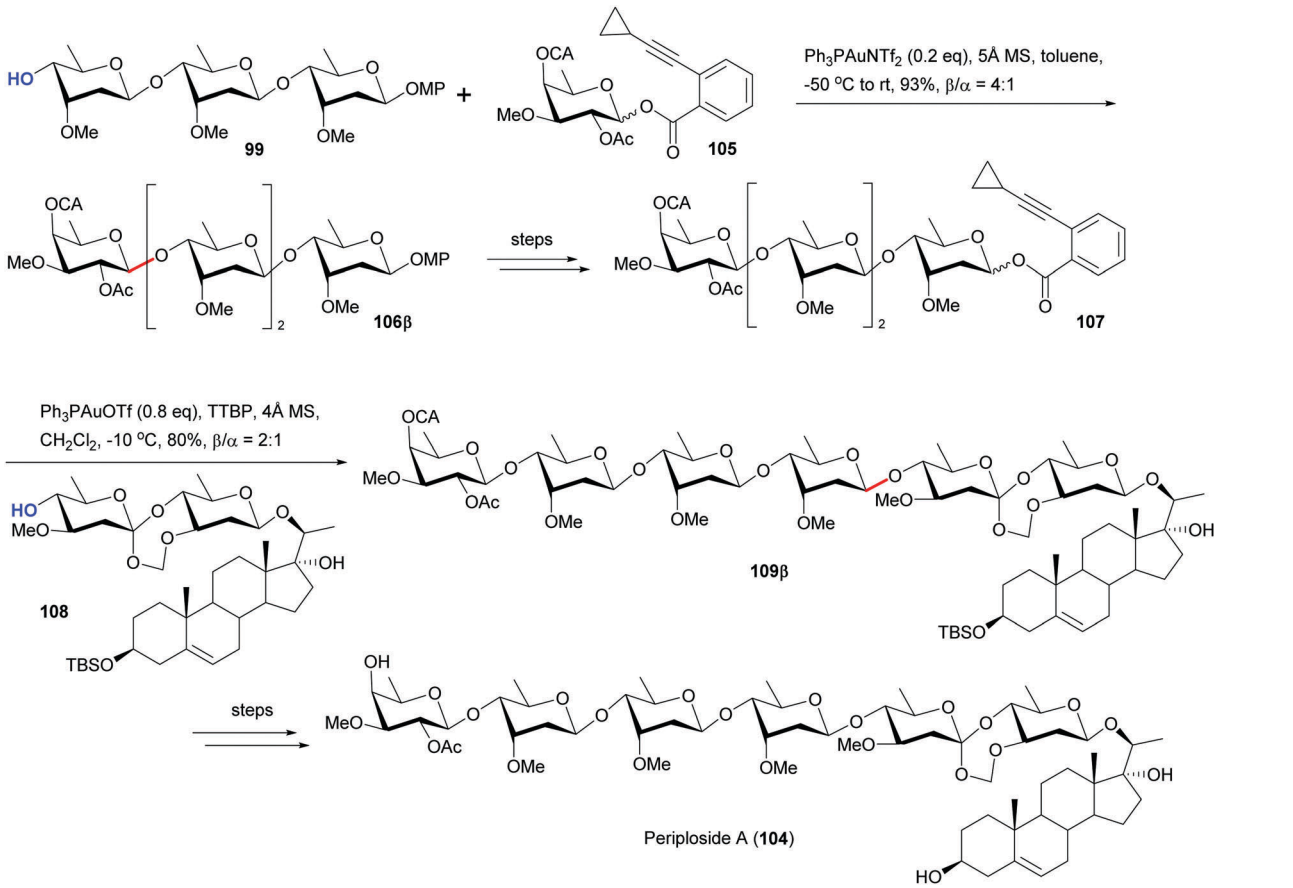
prescribed for the treatment of congestive heart failure and cardiac arrhythmia (Scheme 11).[144,145] Its chemical synthesis has attracted great attention,[146–150] with the construction of the 2-deoxy-β-glycosidic linkages being a persistent challenge.[146–148,151,152] Employing digitoxosyl *o*-cyclopropylethynylbenzoate **90** as donor, Yu *et al.* developed an efficient approach toward the synthesis of this molecule.[153] Given the bulkiness of the 3,4-di-*O*-TBDPS groups blocking the α face in donor **90**, the glycosylation of digitoxigenin **89** (0.1 equiv. $Ph_3PAuOTf$, CH_2Cl_2, r.t.) led to 2-deoxy-β-glycoside **91** with an excellent β-selectivity (β/α = 6.6 : 1) and in nearly quantitative yield. The second glycosylation between alcohol **92** and donor **90** (0.1 equiv. $Ph_3PAuOTf$, toluene, −40 °C) provided β-disaccharide **93** in 98% yield, without detection of the α-anomer. Similarly, the third glycosylation between disaccharide acceptor **94** and donor **90** resulted in β-trisaccharide **95** as the only anomer in excellent yield. Thus, digitoxin was prepared from digitoxigenin **89** and digitoxosyl *o*-cyclopropylethynylbenzoate **90** in 9 steps and 52% overall yield. Recently, Wan *et al.* applied this glycosylation method to the effective synthesis of a series of digitoxin and digoxin analogues bearing 2,3-deoxy-3-amino sugar residues.[72]

The di-*O*-TBDPS protected *o*-alkynylbenzoate **90** was also used effectively in the synthesis of gordonoside F (Scheme 12),[154] an appetite-suppressant pregnane saponin occurring in *Hoodia gordonii*.[155] The synthesis commenced with three iterative glycosylations under the catalysis of $Ph_3PAuNTf_2$ (0.1 equiv.) in toluene at −40 °C, wherein donor **90** was coupled with *p*-methoxyphenol, cymaroside acceptor **97**, and disaccharide acceptor **98**, respectively, in >95% yield and with complete β-selectivity, affording trisaccharide **99**.[152] Trisaccharide **99** was then converted into tetrasaccharide *o*-cyclopropylethynylbenzoate **100**, which was coupled with hoodigogenin **101** (0.1 equiv. $Ph_3PAuOTf$, CH_2Cl_2, r.t.). Although the yield of the coupled tetrasaccharide **102** was high (98%) and the acid-labile 14-OH remained unaffected, the stereoselectivity of this step is yet to improve (β/α = 1 : 1). Selective removal of the terminal acetyl group of the β-anomer (**102β**) furnished gordonoside F (**96**). Previously, Yu *et al.* have reported the synthesis of a trisaccharide congener, namely P57 (**103**),[156] wherein the stereoselectivity of the gold(I)-catalyzed glycosylation with 2-deoxy glycosyl donors was recorded as an unsolved problem.[151]

Similar gold(I)-catalyzed glycosylations were applied in the synthesis of periploside A (**104**, Scheme 13),[152] a unique pregnane saponin occurring in *Periploca sepium* with potent immunosuppressive activities.[157–160] Thus, the aforementioned deoxytrisaccharide **99** was employed as acceptor to couple with digitalosyl *o*-cyclopropylethynylbenzoate **105**. Given the acid lability of the cymarosyl β-(1→4)-linkage, the less acidic $Ph_3PAuNTf_2$ (0.2 equiv.) was utilized (toluene, −50 °C to r.t.) to catalyze the glycosylation, leading to tetrasaccharide **106** in 93% yield as a



Scheme 13 Synthesis of periploside A (**104**).

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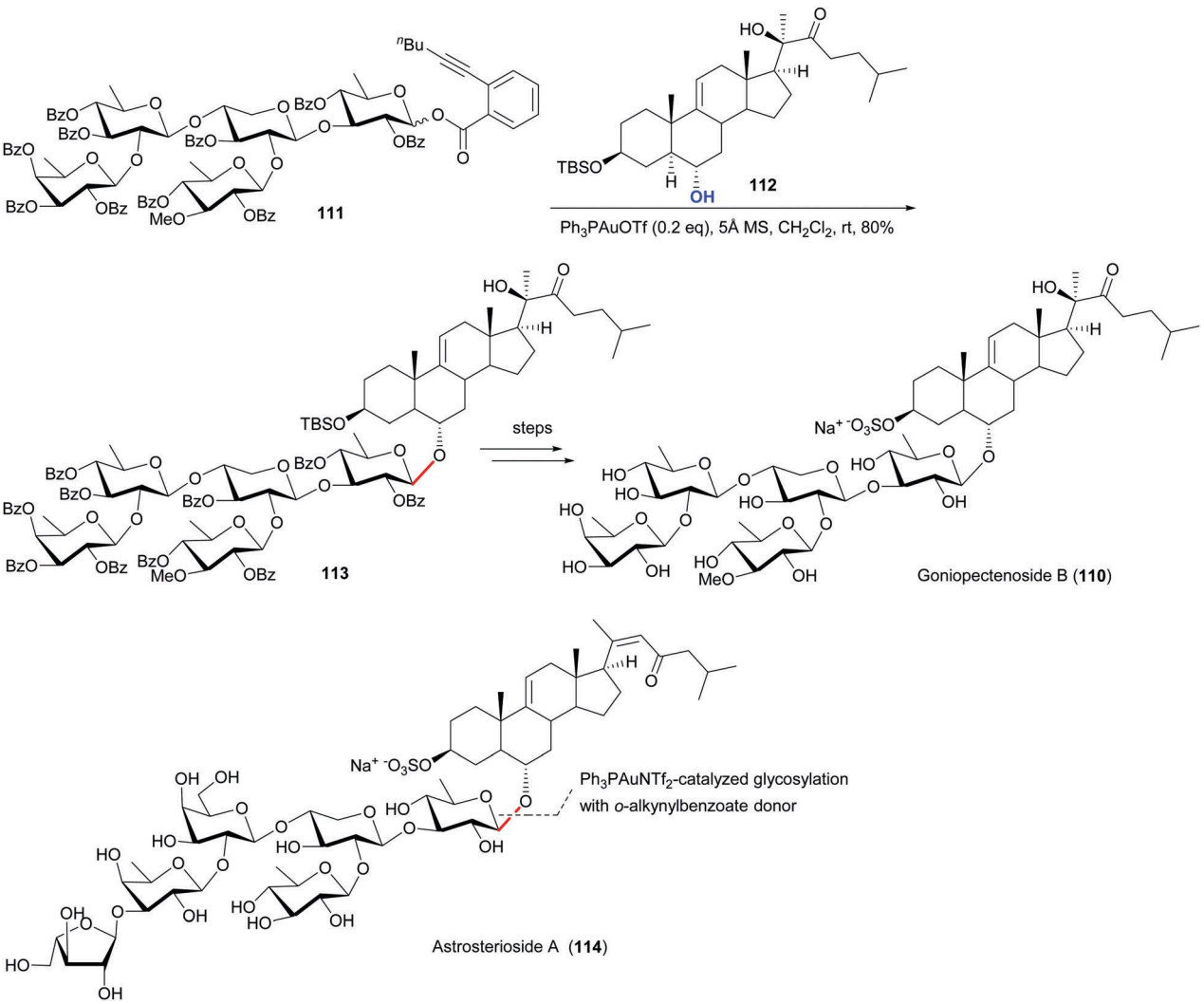
mixture of anomers (β/α = 4 : 1). The β anomer was converted into *o*-cyclopropylethynylbenzoate donor **107** to couple with disaccharide acceptor **108**. The formyl acetal bridged orthoester motif in disaccharide **108** and the coupled hexasaccharide **109** was found to be vulnerable to the transient proton generated in the glycosylation process, and therefore a hindered base TTBP (2,4,6-tri-*tert*-butylpyrimidine, 1.5 equiv.) was added in the reaction. The interception of the proton hampered the gold(I) catalytic cycle, and therefore 0.8 equivalent of $Ph_3PAuOTf$ was required to drive the reaction to completion, furnishing hexasaccharides **109** in 80% yield with a β/α ratio of ~2 : 1. Subsequent removal of the terminal CA (chloroacetyl) and TBS groups on **109β** furnished periploside A (**104**).

4.1.6 Cholestan-type steroidal saponins. Goniopectenoside B (**110**), a representative asterosaponin of starfishes, was isolated from starfish *Goniopecten demonstrans* and was found to possess antifouling activity.[161] Yu *et al.* reported its synthesis in 2013 (Scheme 14).[162] A pentasaccharide *o*-hexynylbenzoate (**111**) was prepared and attached to the 6-OH of cholestane derivative **112** (0.2 equiv. $Ph_3PAuOTf$, CH_2Cl_2, r.t.), giving rise to the desired β-*O*-glycoside **113** in 80% yield. Another asterosaponin, namely astrosterioside A (**114**) with anti-inflammatory activity,[163] was assembled in a similar manner,[164] wherein the late-stage gold(I)-catalyzed glycosylation of the corresponding aglycone with a hexasaccharide *o*-cyclopropylethynylbenzoate donor led to the desired glycoside in 83% yield.

Apart from the aforementioned asterosaponins, polyhydroxysteroid glycosides constitute another major type of starfish saponins. Linckosides A (**115**) and B (**116**), two such congeners isolated from starfish *Linckia laevigata* with neuritogenic activities,[165] were synthesized by Yu *et al.* in 2015 (Scheme 15).[166] Thus, glycosylation of 29-OH on aglycone **117** with arabinofuranosyl *o*-hexynylbenzoate **118** proceeded smoothly under the catalysis of $Ph_3PAuNTf_2$ (0.2 equiv.); subsequent cleavage of the 3-*O*-MOM group gave β-glycoside **119** in 72% yield. Selective elimination of 5-OH resulted in **120**, which was then subjected to glycosylation with 2-*O*-methyl-β-D-xylosyl *o*-hexynylbenzoate **121**. Gratifyingly, this glycosylation (0.2 equiv. $Ph_3PAuNTf_2$, CH_2Cl_2, −10 °C) led to the coupled glycoside **122** in a high 93% yield with an extraordinary β-selectivity (β/α > 20 : 1).



Scheme 14 Synthesis of goniopectenoside B (**110**) and astrosterioside A (**114**).

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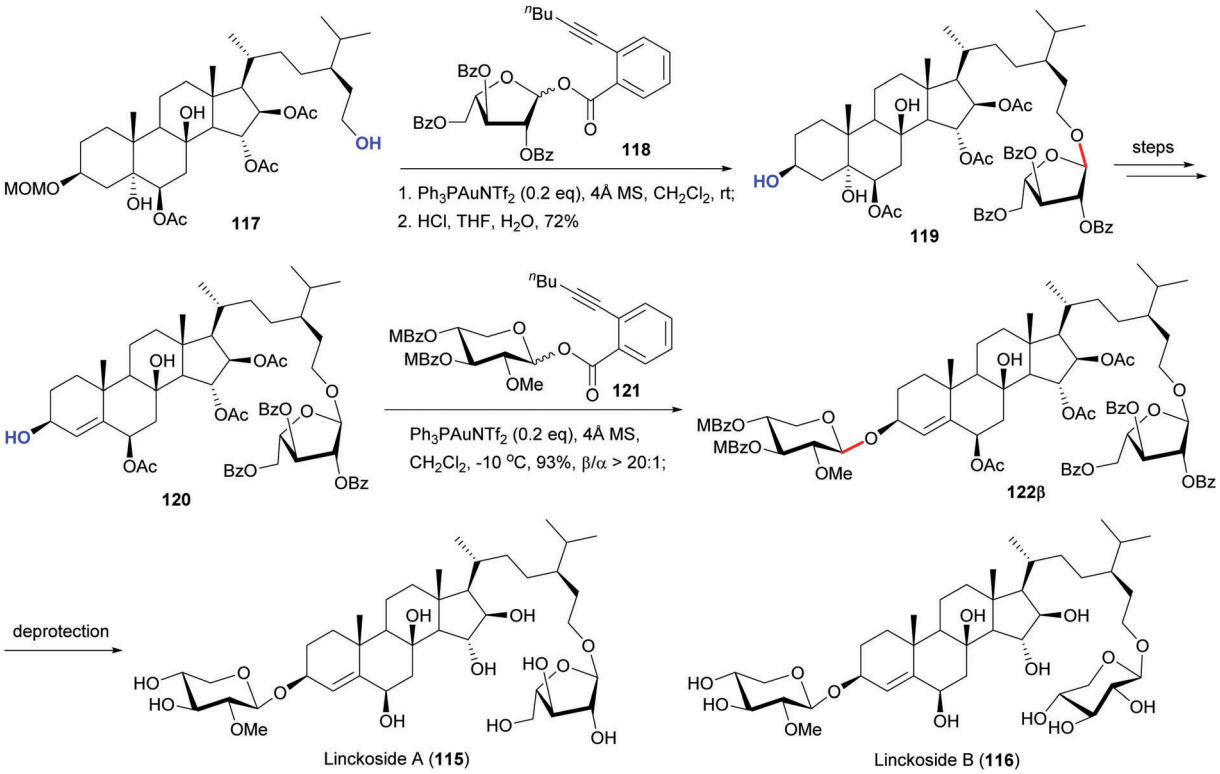
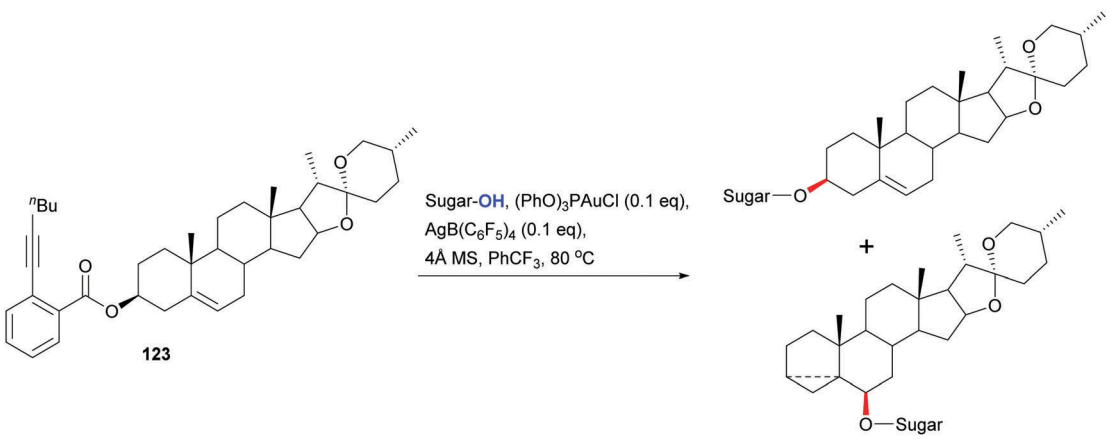


Scheme 15 Synthesis of linckoside A and B (**115** and **116**).



Scheme 16 Synthesis of diosgenin-3-yl or i-diosgenin-6-yl glycoconjugates.

The matched geometries of the coupling partners might account for this unusual stereoselectivity. Removal of the acyl protecting groups furnished linckoside A (**115**). Similarly, linckoside B (**116**) was prepared by replacement of the arabinofuranosyl donor (**118**) with a xylopyranosyl counterpart in the first glycosylation step.

In 2016, Li *et al.* reported an effective approach to the synthesis of diosgenin glycoconjugates, in which diosgenin-3-yl *o*-hexynylbenzoate **123** was employed as a "donor" to couple with sugar alcohols (Scheme 16).[167] The combination of $(PhO)_3PAuCl$ (0.1 equiv.) and $AgB(C_6F_5)_4$ (0.1 equiv.) in $PhCF_3$ at 80 °C was found to be the optimal condition for this reaction, leading to the corresponding diosgenin-3-yl or i-diosgenin-6-yl glycoconjugates in 38–99% yields. This transformation is reminiscent of the gold(I)-catalyzed alkylation reactions firstly reported by Asao *et al.*[168,169]

4.2 Synthesis of flavonoid glycosides

4.2.1 Flavonoid 3-*O*-glycosides. Kaempferol 3-*O*-(3″,6″-di-*O*-*E*-*p*-coumaroyl)-β-D-glucopyranoside **124** was isolated from the needles of *Picea obovata*[170] and the leaves of *Stenochlaena palustris*,[171] which could protect the deep-lying tissue from the harmful UV-B radiation.[172] In 2010, Yu *et al.* reported its synthesis with glucosyl bromide **126** and *o*-alkynylbenzoate **129**

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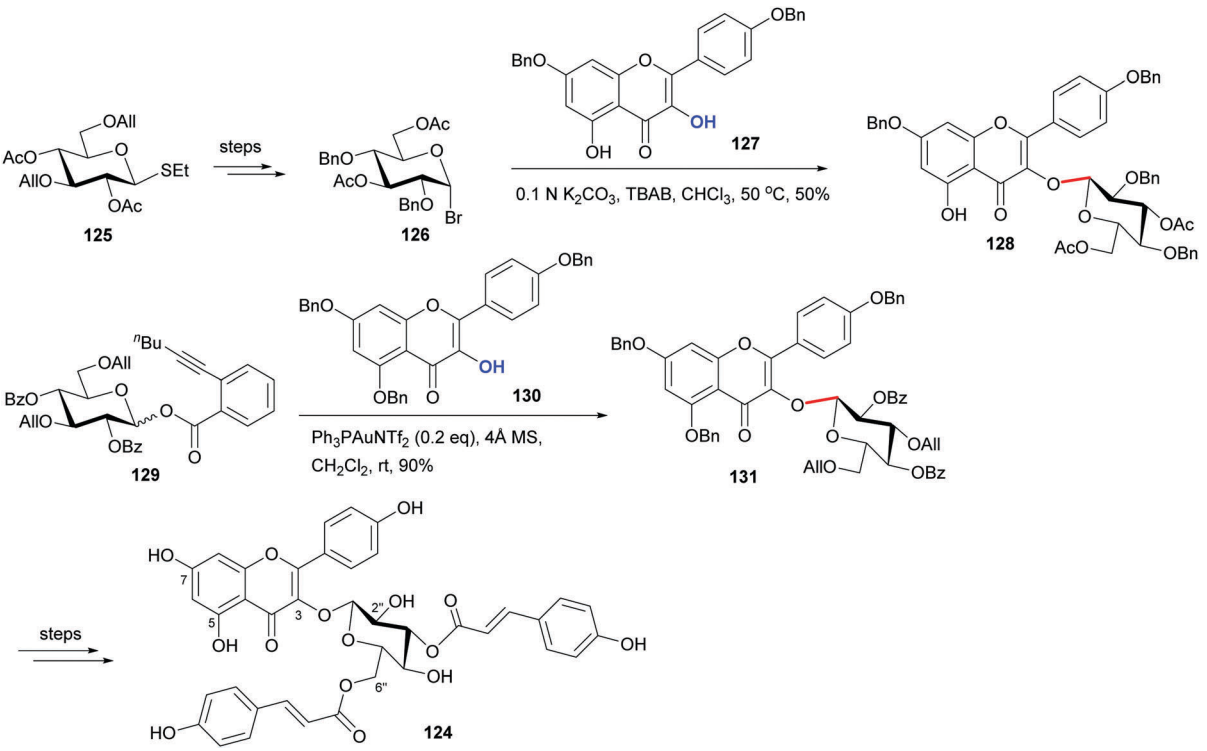
as the donors, respectively (Scheme 17).[173] The bromide, prepared from thioglycoside **125** in multi-steps, was successfully coupled to kaempferol derivative **127** under phase-transfer conditions to give 3-*O*-glycoside **128** in 50% yield. The *o*-hexynylbenzoate **129** bearing allyl groups was much easily prepared, and its glycosylation of kaempferol derivative **130** under the catalysis of $Ph_3PAuOTf$ (0.2 equiv.) provided the desired 3-*O*-glycoside **131** in a high 90% yield. Further elaborations afforded the target kaempferol glycoside **124**. Similar gold(I)-catalyzed glycosylations with *o*-alkynylbenzoate donors were used in the synthesis of a series of flavonoid 3-*O*-glycosides (Fig. 4),[66,174] including kaempferol 3-*O*-α-rhamnosides (**132** and **133**)[175,176] and 3,7-*O*-bisglycosides (**134** and **135**).[177,178] In a later synthesis,[174] the regioselective glycosylation of 3-OH on 3,7-diol substrates was realized.

4.2.2 Flavonoid 5-*O*-glycosides. The poor nucleophilicity of 5-OH on flavone derivatives has been proven by the unsuccessful



Scheme 17 Synthesis of kaempferol glycoside **124**.

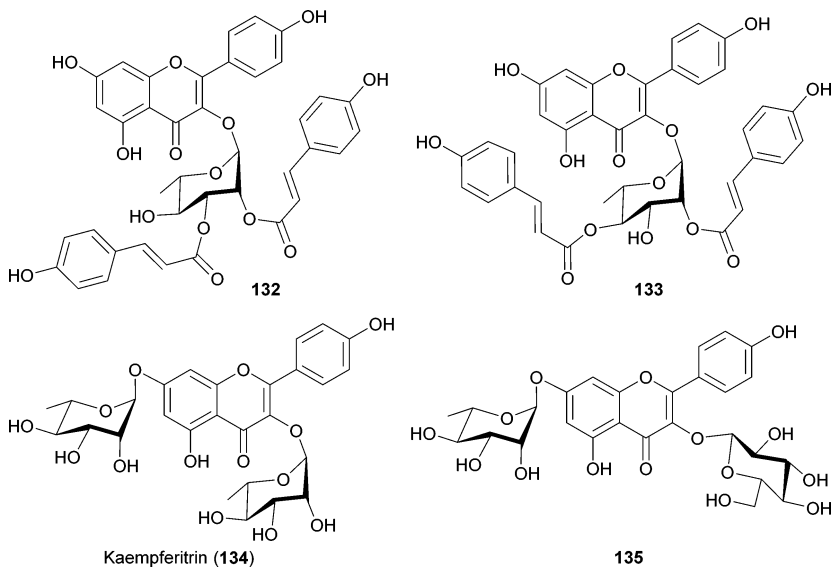


Fig. 4 Kaempferol glycosides **132**, **133**, **134** (kaempferitrin), and **135** synthesized by the gold(I)-catalyzed glycosylation.

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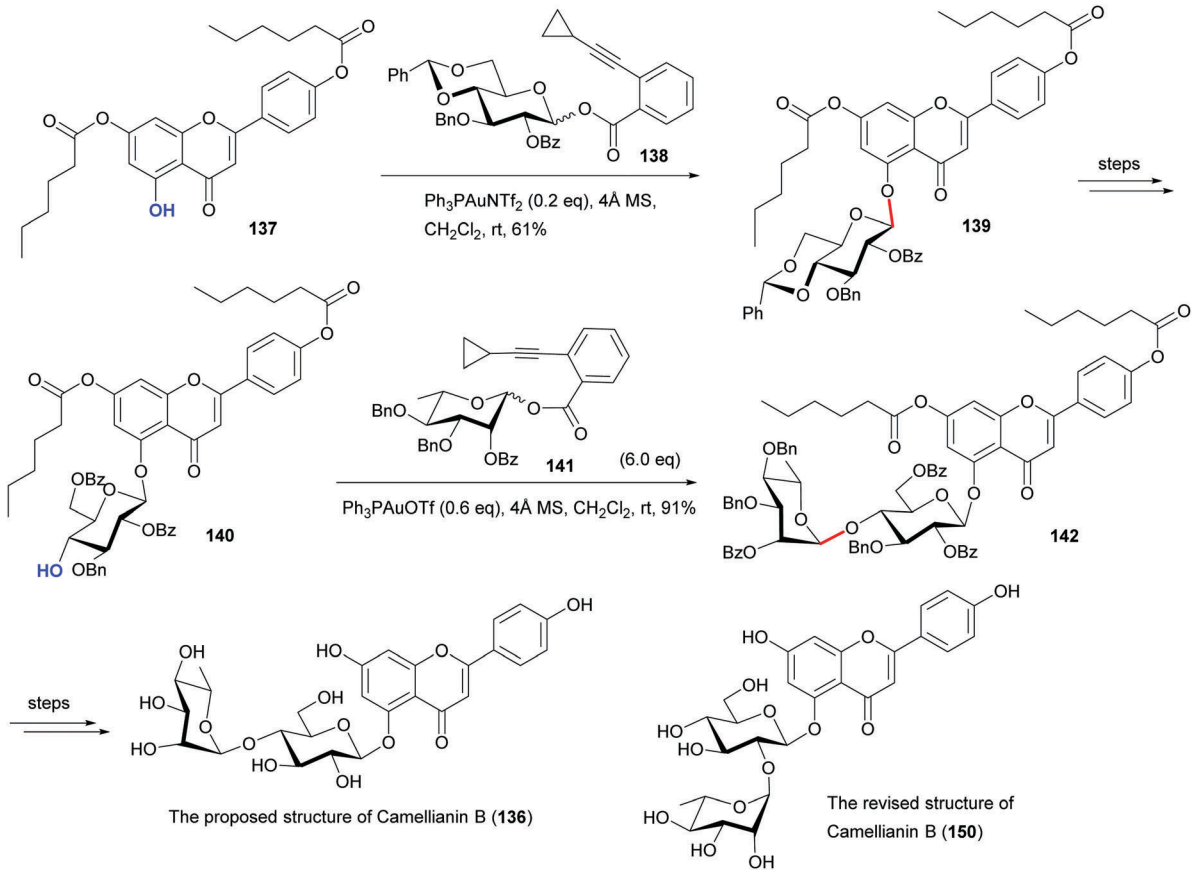
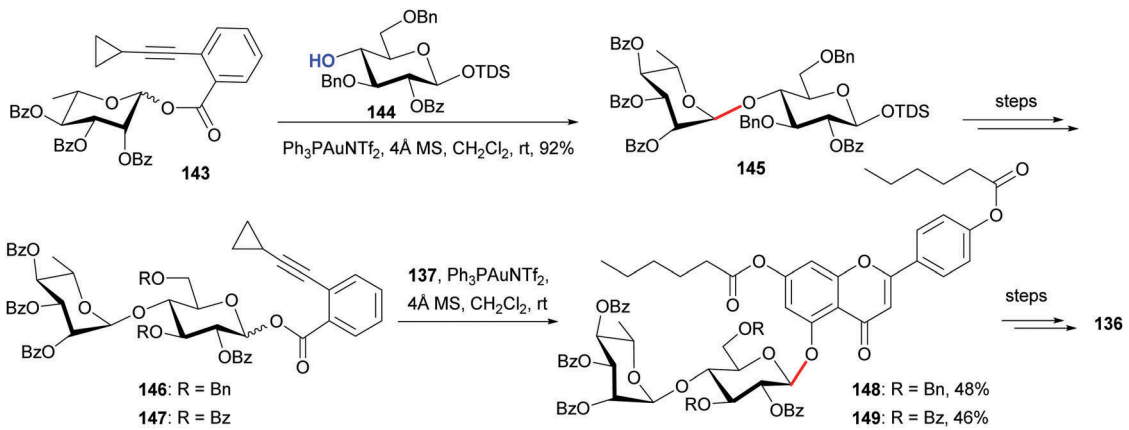


Scheme 18 A linear synthesis of the originally proposed structure of camellianin B (**136**) and its revised structure (**150**).



Scheme 19 A convergent synthesis of the proposed structure of camellianin B (**136**).

benzylation of the relevant substrates;[179] it makes glycosylation of this type of phenol substrates a difficult task.[180,181] Sun *et al.* applied *o*-hexynylbenzoate donors in the successful synthesis of a series of natural flavonoid 5-*O*-glycosides,[182] such as camellianin B (**136**) (Scheme 18).[183–185] In a linear synthesis, the 5-OH of apigenin derivative **137** was glycosylated with glucosyl *o*-cyclopropylethynylbenzoate **138** under the catalysis of $Ph_3PAuNTf_2$ (0.2 equiv.) in a decent 61% yield. The resultant **139** was then converted into acceptor **140**, which was subjected to the next glycosylation. Given the inertness of the alcoholic acceptor **140**, 6.0 equivalents of the donor **141** and 0.6 equivalent of $Ph_3PAuOTf$ were used to drive the glycosylation to completion, giving disaccharide **142** in 91% yield.

In a convergent synthesis, the assembly commenced with glycosylation of glucoside acceptor **144** with rhamnosyl *o*-cyclopropylethynylbenzoate **143** (Scheme 19). The resulting disaccharide **145** was then converted into *o*-cyclopropylethynylbenzoate **146** and **147**, both of which were used effectively in the condensation

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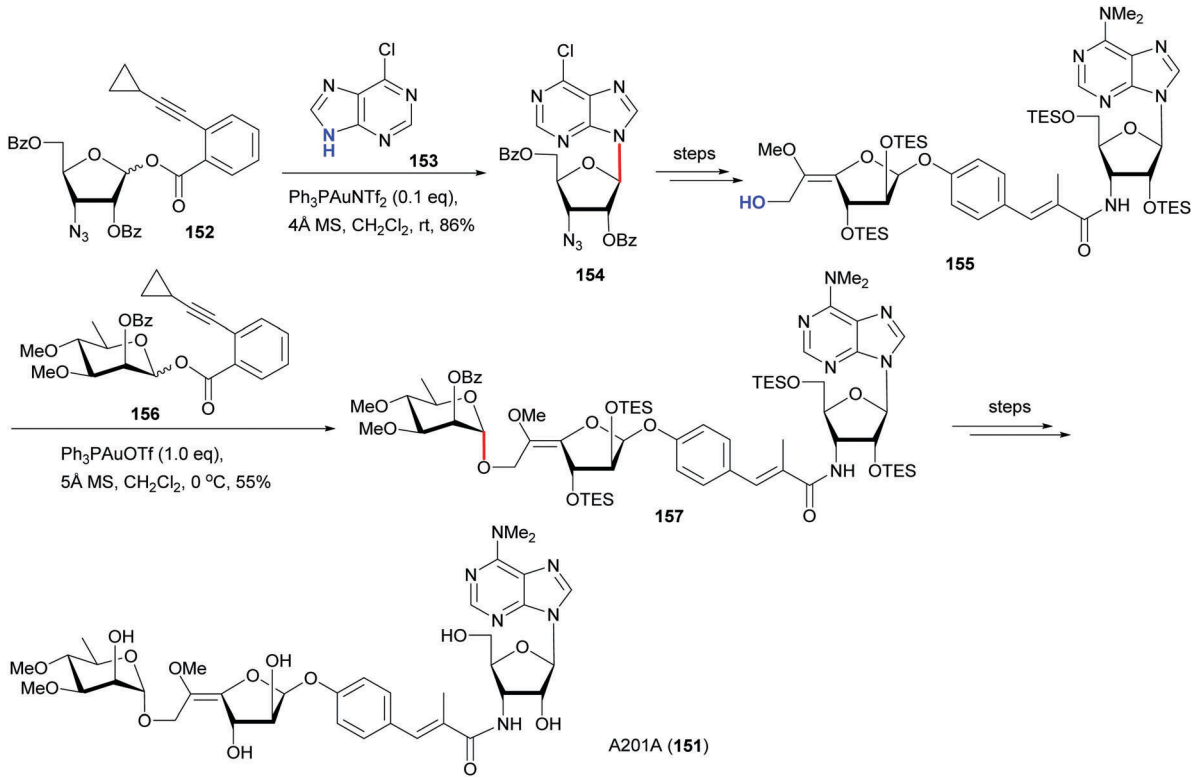
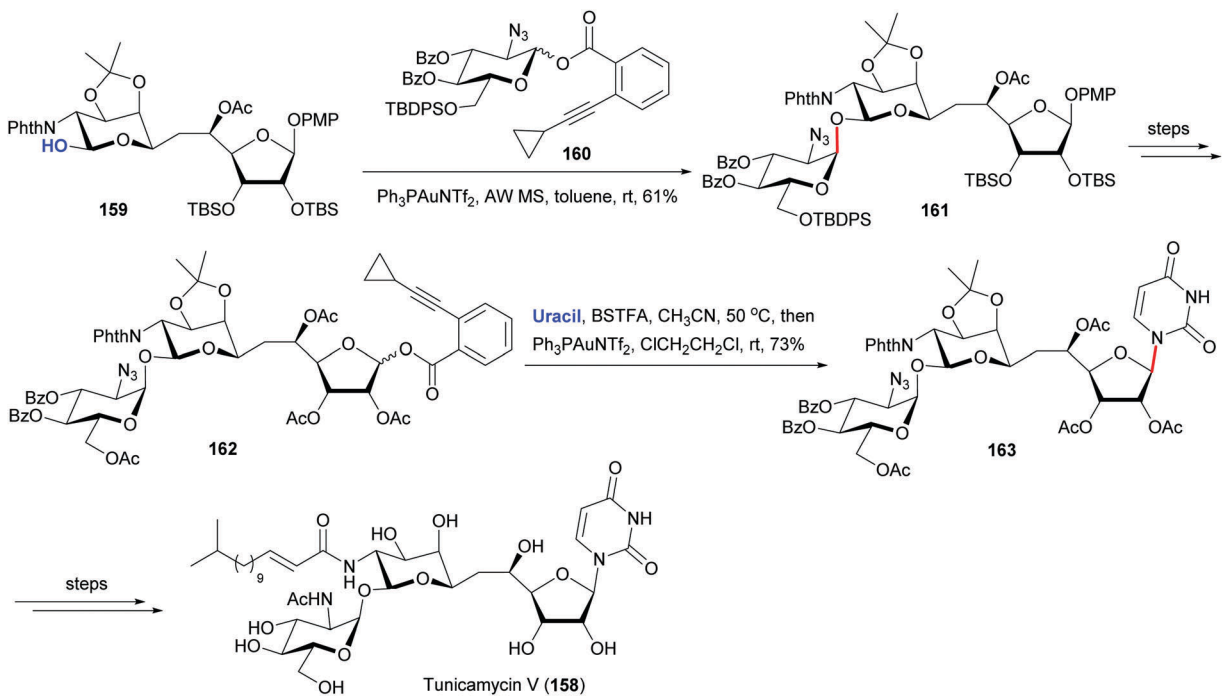
with apigenin derivative **137**, leading to disaccharides **148** and **149** in ~50% yield under the catalysis of $Ph_3PAuNTf_2$. Structural analysis of the synthetic camellianin B (**136**) led to revision of its structure to the (1→2)-linked disaccharide **150** (Scheme 18).

4.3 Synthesis of nucleosides

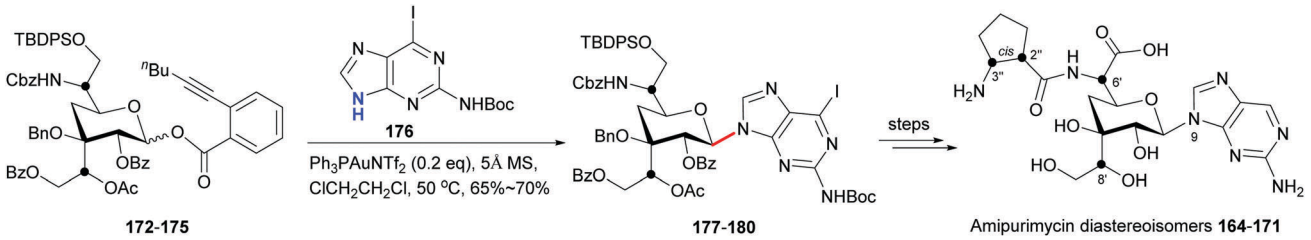
A201A (**151**, Scheme 20), a nucleoside antibiotic originally isolated from *Streptomyces capreolus* in the 1970s,[186,187] was synthesized by Yu *et al.* in 2014.[188] Thus, 6-chloro-purine **153** was glycosylated



Scheme 20 Synthesis of A201A (**151**).



Scheme 21 A recent synthesis of tunicamycin V (**158**).



Scheme 22 Synthesis of amipurimycin diastereoisomers **164–171**.

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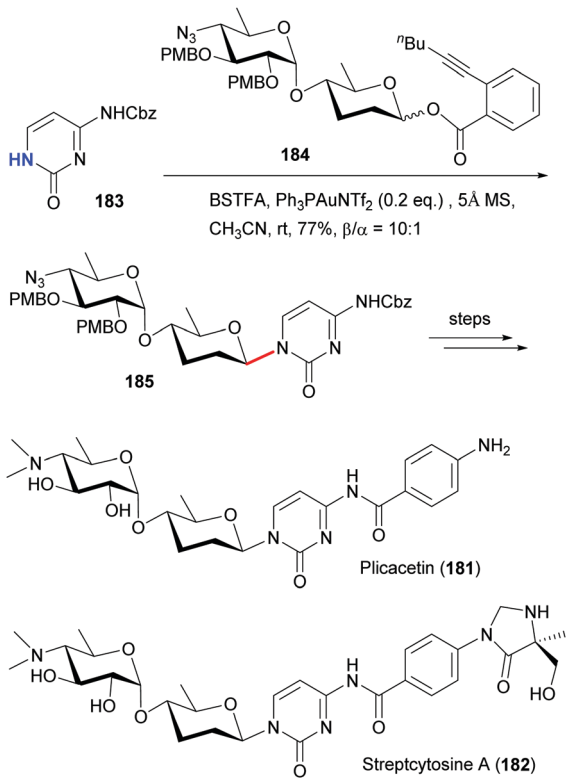
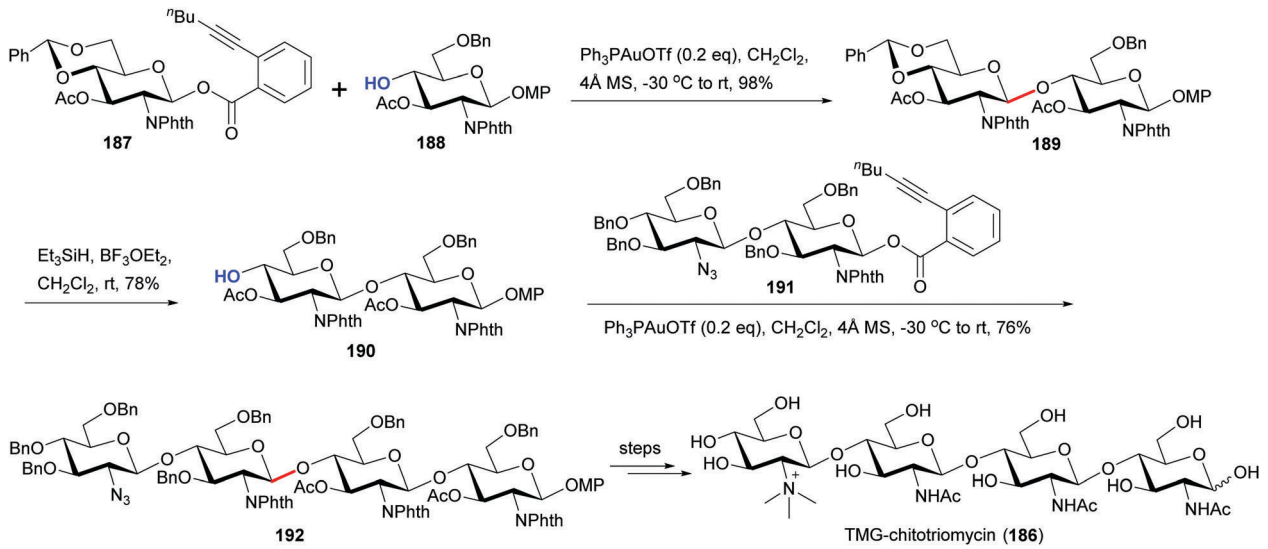


Scheme 23 Synthesis of plicacetin (**181**) and streptcytosine A (**182**).

with *o*-cyclopropylethynylbenzoate **152** (0.1 equiv. $Ph_3PAuNTf_2$, CH_2Cl_2, r.t.) to give nucleoside **154** (86%). Subsequent transformations led to **155**, which bears an acid labile exocyclic enol ether moiety. The mild gold(I)-catalyzed glycosylation method was proven to be effective for the glycosylation of **155**; a satisfactory 55% yield of the coupled product **157** was obtained with D-rhamnosyl *o*-cyclopropylethynylbenzoate **156** as the donor ($Ph_3PAuNTf_2$, CH_2Cl_2, 0 °C). A stoichiometric amount of $Ph_3PAuNTf_2$ (1.0 equiv.) was required because the basic nitrogen atoms in the purine moiety could capture the incipient protons so as to prevent the release of the gold(I) species from the isochromen-4-yl gold(I) intermediate.[56] Finally, removal of the acyl and silyl groups on **157** furnished A201A (**151**).

Tunicamycins constitute a family of nucleoside antibiotics, which possess potent inhibitory activities against the bacterial translocase and eukaryotic GlcNAc-1-P transferase.[189–192] Studies have been devoted to the head-to-head coupling of the GlcN and GalN residues, which is critical for the synthesis of tunicamycins.[193–198] The installation of a bulky *N*-protecting group on the GalN hemiacetal acceptor could enhance the β-selectivity on its side, while the GlcN donor should be masked with N3 to secure α-selective glycosylation.[195–198] One of the best results for the construction of this head-to-head disaccharide moiety was reported by Myers *et al.*, utilizing a $GlcN_3$ trichloroacetimidate donor and a *N*-Phth-GalN acceptor at an early stage of the total synthesis.[195,196] In a recent synthesis reported



Scheme 24 Synthesis of TMG-chitotriomycin (**186**).

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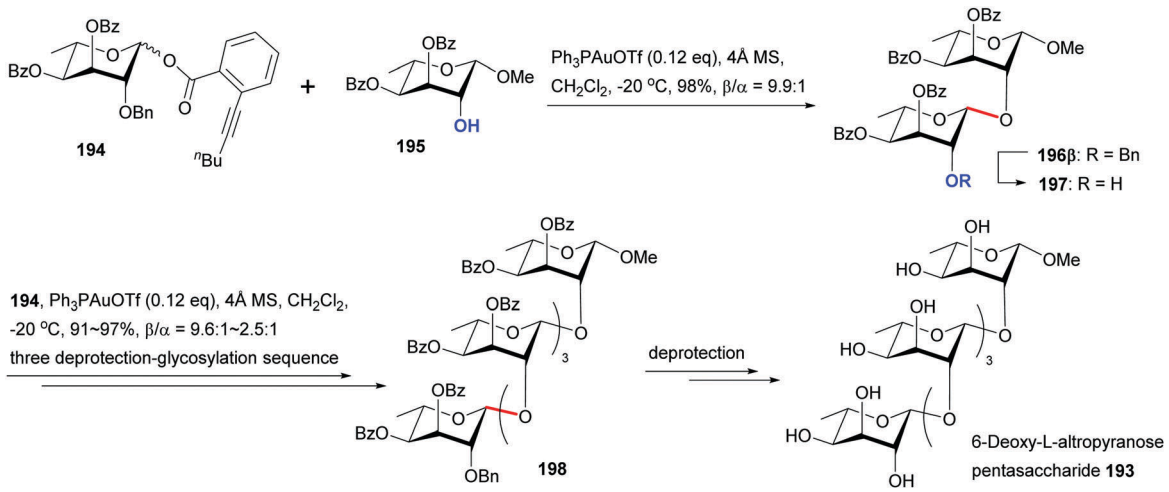
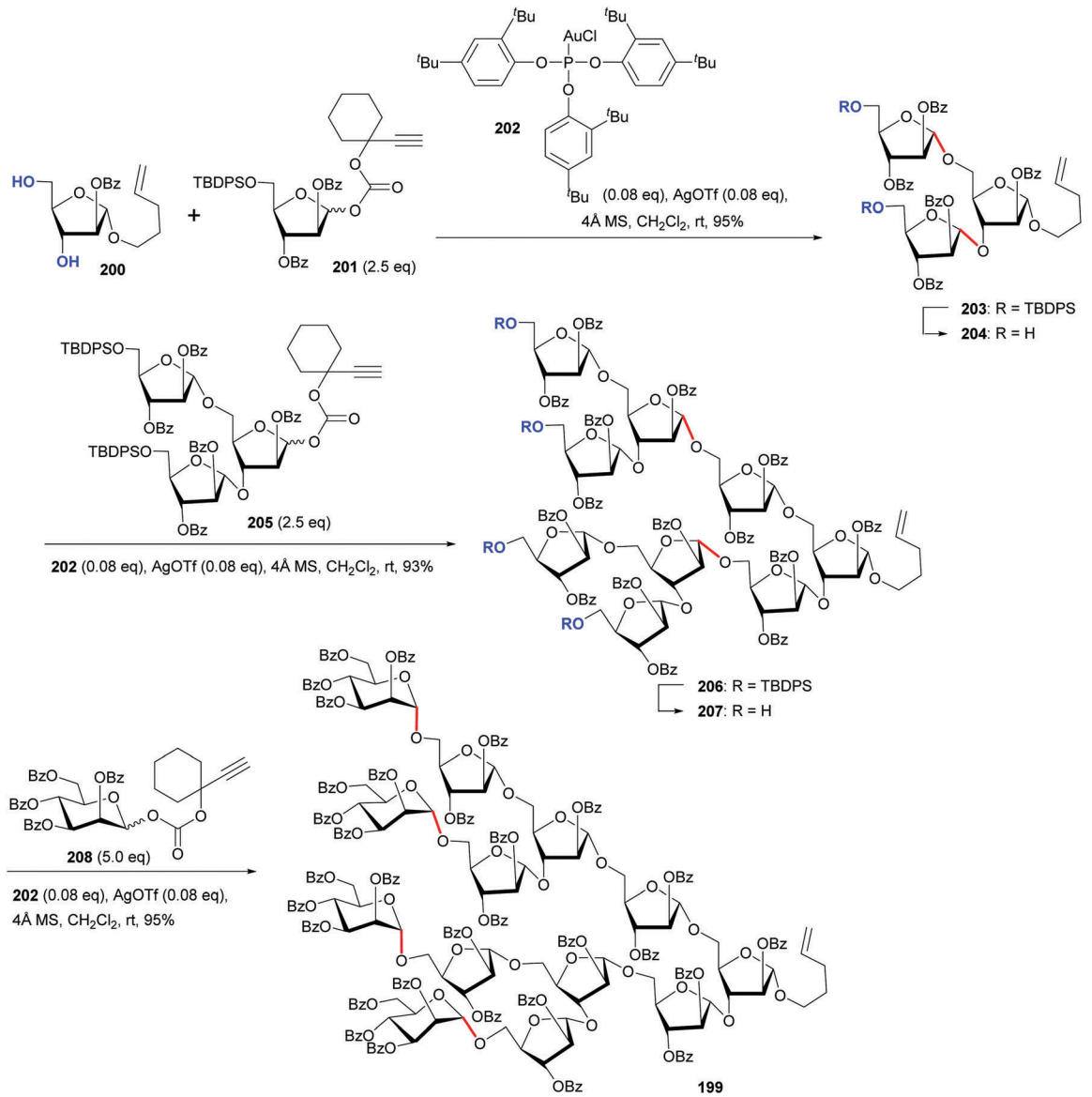


Scheme 25 Synthesis of β-(1→2)-linked 6-deoxy-L-altropyranose pentasaccharide **193**.



Scheme 26 Synthesis of the fully protected mannose-capped arabinan 13 mer **199**.

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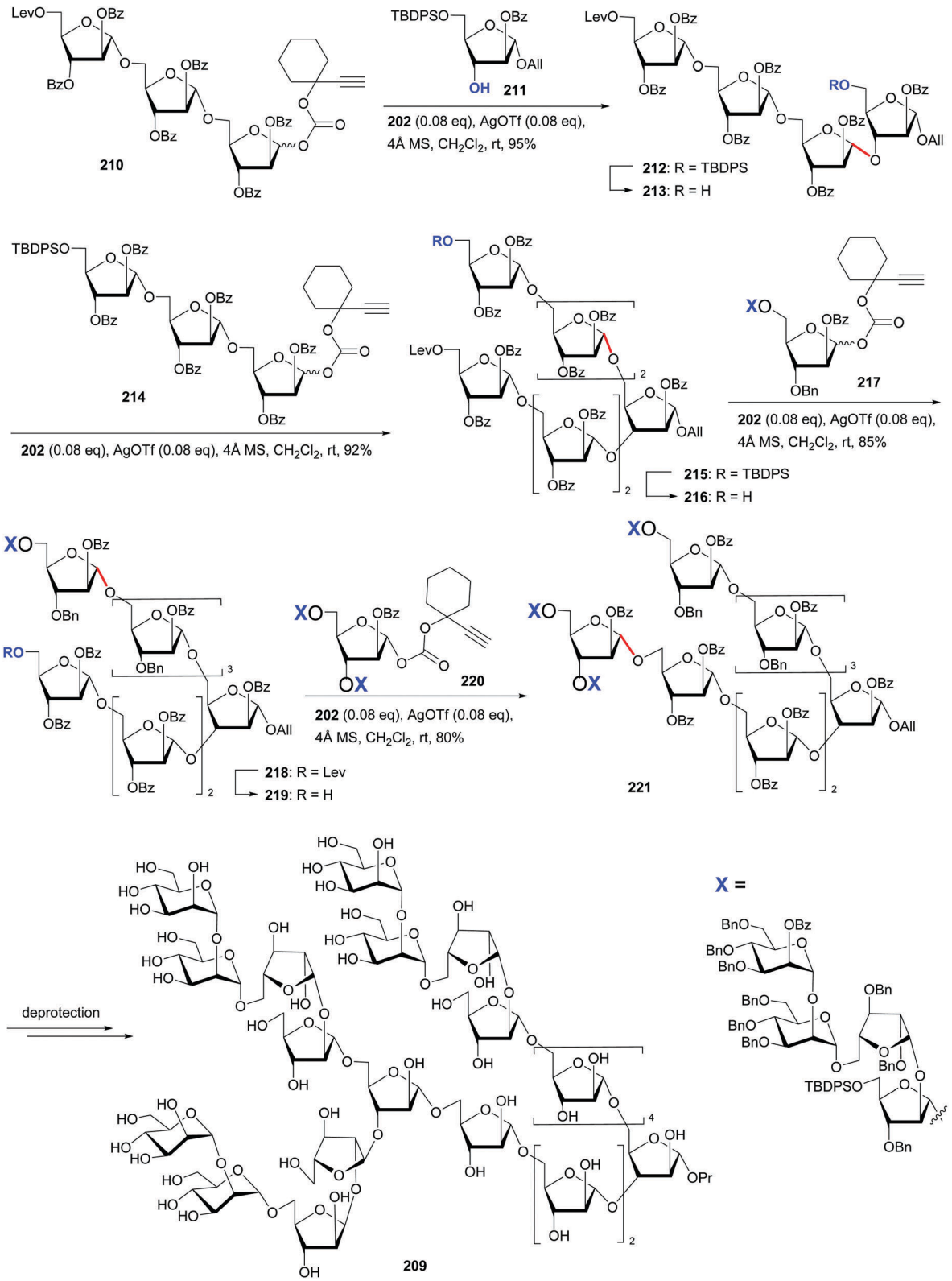
by Yu *et al.* (Scheme 21),[199,200] the construction of this peculiar glycosidic linkage was achieved by glycosylation of saccharide hemiacetal **159** with $GlcN_3$ *o*-cyclopropylethynylbenzoate **160** (0.4 equiv. $Ph_3PAuNTf_2$, acid-washed molecular sieves, toluene, r.t.); the desired coupled saccharide **161** was isolated in 61% yield with excellent stereoselectivity. Saccharide



Scheme 27 Synthesis of heneicosasaccharide **209** relevant to the cell wall glycans of *Mycobacterium tuberculosis*.

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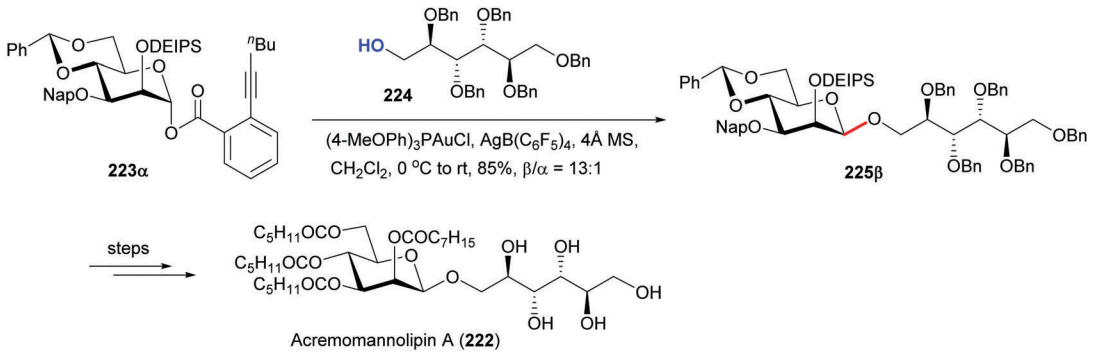


Scheme 28 Synthesis of acremomannolipin A (**222**).

o-cyclopropylethynylbenzoate **162**, prepared from **161**, was subjected to glycosylation with the silylated uracil (prepared *in situ* by stirring uracil and BSTFA [*N*,*O*-bis(trimethylsilyl)trifluoroacetamide] in CH_3CN at 50 °C for 30 min). Under optimized conditions (0.2 equiv. $Ph_3PAuNTf_2$, $ClCH_2CH_2Cl$, r.t.), the desired nucleoside **163** was obtained in a good 73% yield. Further elaboration led to the synthesis of tunicamycin V (**158**).

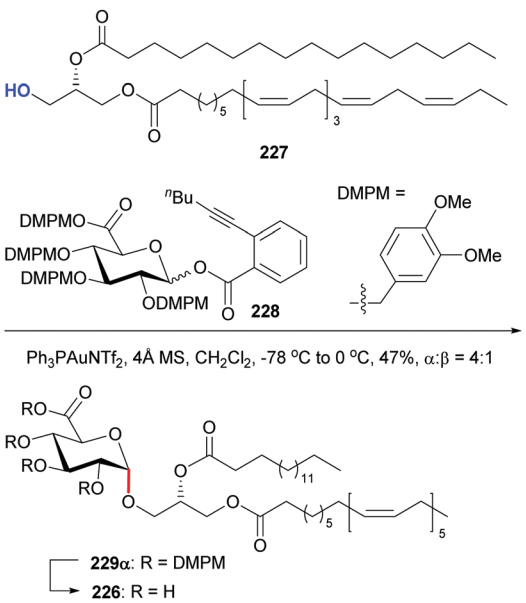
Amipurimycin, isolated from *Streptomyces novoguineensis* with curative effects on rice blast disease,[201,202] was proposed to contain a C3-branched pyranosyl amino acid core attached β-glycosidically with a 2-aminopurine moiety (Scheme 22).[203] Previous studies have shown the difficulty in installation of 2-aminopurine onto the pyranose core at a later stage.[204] Recently, Yu *et al.* achieved the total synthesis of the eight proposed possible diastereoisomers (**164–171**) of amipurimycin.[205] Thus, four *o*-hexynylbenzoate diastereoisomers (**172–175**) were prepared, which bear a neighbouring participating benzoyl group at O2. The glycosylation of 6-iodopurine **176** with these donors proceeded smoothly under the action of $Ph_3PAuNTf_2$ (0.2 equiv.) in $ClCH_2CH_2Cl$ at 50 °C, leading to the corresponding nucleosides **177–180** in 65–70% yield. Further elaboration furnished the target molecules.

Plicacetin (**181**) and streptcytosine A (**182**) are two members of the amicetin family antibiotics, which show potent antibacterial and antiviral activities (Scheme 23).[206–209] In previous synthetic studies, this *N*-glycosidic linkage was constructed with monosaccharide donors and cytosine in moderate yields and stereoselectivity.[210,211] Recently, Yu *et al.* achieved the condensation of disaccharide *o*-hexynylbenzoate **184** with silylated cytosine acceptor (prepared *in situ* from **183** with BSTFA) under the catalysis of $Ph_3PAuNTf_2$ (0.2 equiv.) in CH_3CN at r.t.[212] The desired β-linked nucleoside **185** was obtained in 70% yield, and the α-anomer was separated in 7% yield. The high β-selectivity could be attributed to the putative 1-α-glycosyloxy-isochromenylium-4-gold(I) intermediate[57,63] as well as the cooperative solvent effect of CH_3CN.[213,214] Further elaboration furnished the target molecules.

4.4 Synthesis of glycans

Tetrasaccharide TMG-chitotriomycin (**186**) is a β-*N*-acetylglucosaminidase inhibitor isolated from *Streptomyces anulatus* NBRC13369 (Scheme 24).[215] In the chemical synthesis of the revised structure of TMG-chitotriomycin (**186**),[216,217] *o*-hexynylbenzoate donor **187** was coupled with GlcN acceptor **188** (1.3 equiv.) in the presence of $Ph_3PAuOTf$ (0.2 equiv.) in CH_2Cl_2 to give the desired β-(1→4)-linked disaccharide **189** in an excellent 98% yield. Regioselective opening of the benzylidene acetal on **189** resulted in alcohol **190**, which was subjected to the subsequent [2+2] coupling with disaccharide *o*-hexynylbenzoate **191** to provide β-(1→4)-linked tetrasaccharide **192** in 76% yield. Further conversion accomplished the synthesis of TMG-chitotriomycin (**186**).

Pentasaccharide **193** consisting of β-(1→2)-linked 6-deoxy-L-altropyranose represents a fragment of the *O*-antigen of *Yersinia enterocolitica* O:3 (Scheme 25).[218–220] The 1,2-*cis*-β-glycosidic linkages were successfully synthesized *via* gold(I)-catalyzed glycosylation with altropyranosyl *o*-hexynylbenzoate **194** as donor,[221] which bears two benzoyl groups at O3 and O4 to enhance the β-selectivity *via* a putative remote participation. Thus, glycosylation of altropyranoside acceptor **195** with donor **194** (0.12 equiv. $Ph_3PAuOTf$, CH_2Cl_2, −20 °C) gave disaccharide **196** in 98% yield with an excellent β selectivity (β/α = 9.9 : 1). Hydrogenolysis of



Scheme 29 Synthesis of glucuronosyldiacylglycerol **226**.

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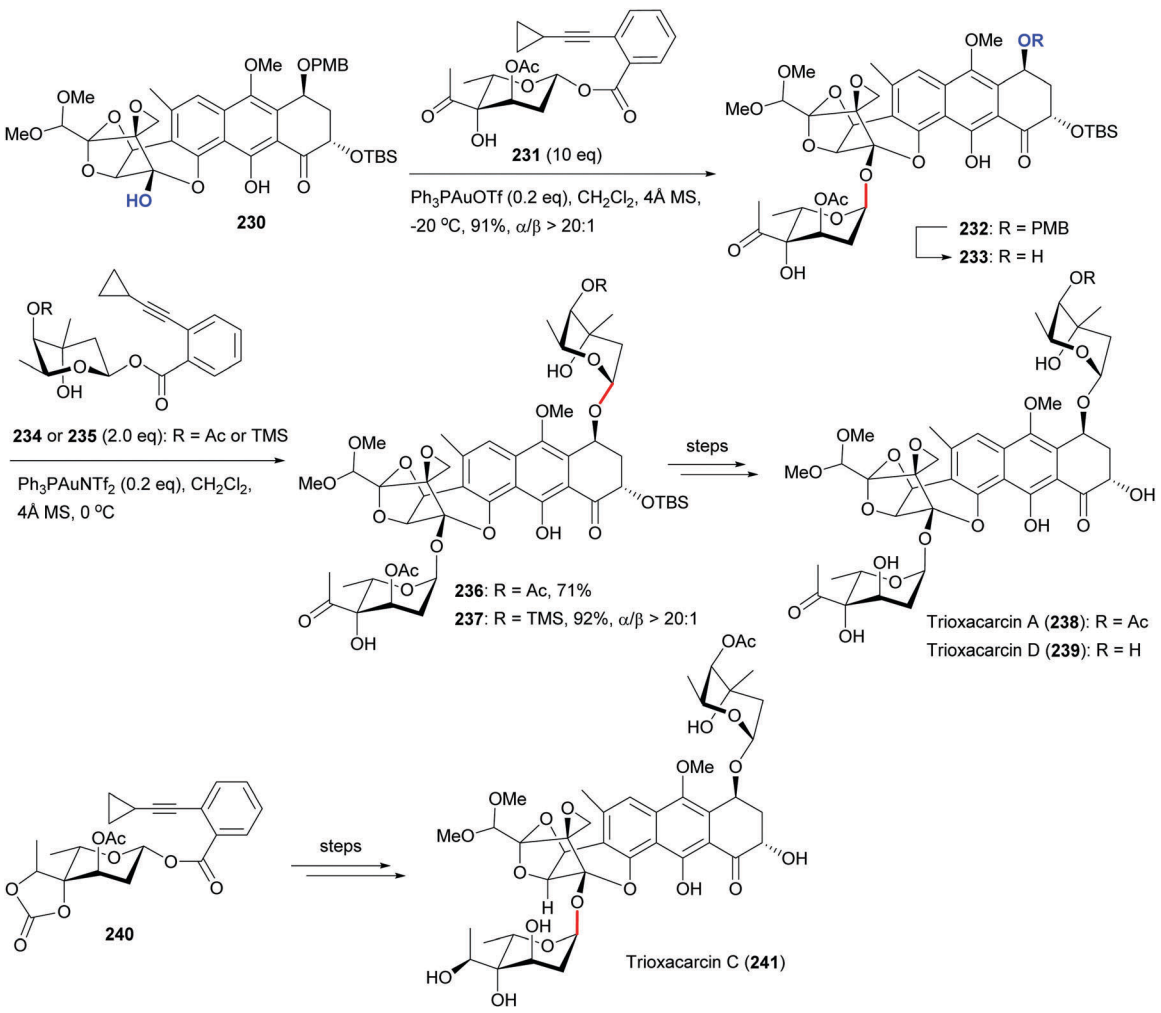
the 2-*O*-benzyl group resulted in disaccharide alcohol **197**, which was used as the next acceptor for glycan elongation. Iterative glycosylation–deprotection–glycosylation with donor **194** led to pentasaccharide **198**, in which the three glycosylation reactions proceeded under similar conditions with excellent yields (>90%) but decreased β selectivity (β/α = 9.6 : 1 to 2.5 : 1). Global deprotection of **198** led to pentasaccharide **193**.

The alkynyl carbonate donors developed recently by Hotha *et al.* have been successfully applied in the synthesis of a series of complex glycans.[82] A fully protected mannose-capped arabinan 13 mer **199** reminiscent of the cell wall lipoarabinomannan of *Mycobacterium tuberculosis*[222–224] was synthesized as shown in Scheme 26. Glycosylation of arabinofuranoside diol **200** with arabinofuranosyl alkynyl carbonate **201** (2.5 equiv.) led to trisaccharide **203** in 95% yield under the action of $(ArO)_3PAuCl$ **202** (0.08 equiv.) and AgOTf (0.08 equiv.) in CH_2Cl_2 at r.t. Deprotection of the two terminal TBDPS groups gave diol **204**, which was used in the second glycosylation with trisaccharide carbonate **205** under similar gold(I)-catalyzed conditions to provide nonasaccharide **206** (93%). The four terminal TBDPS was then removed to afford **207**, which was applied to the final glycosylation with mannosyl alkynyl carbonate **208** to furnish tridecasaccharide **199** (95%).

A more complex heneicosasaccharide **209**[90,225] was assembled *via* four steps of glycosylation under similar conditions (0.08 equiv. $(ArO)_3PAuCl$ **202**, 0.08 equiv. AgOTf, CH_2Cl_2, r.t.; Scheme 27).[226] Thus, glycosylation of arabinoside acceptor **211** with trisaccharide alkynyl carbonate **210** led to tetrasaccharide **212**. Removal of the TBDPS group provided alcohol **213**, which was glycosylated with trisaccharide alkynyl carbonate **214** to give heptasaccharide **215**. A [5+7] glycosylation was then carried out between heptasaccharide acceptor **216** and pentasaccharide alkynyl carbonate **217** to afford dodecasaccharide **218**. The Lev group was then removed and the final [9+12] glycosylation of the resulting dodecasaccharide acceptor **219** with the complex nonasaccharide alkynyl carbonate **220** led to heneicosasaccharide **221**. Remarkably, all these glycosylation steps displayed excellent yields and β-selectivity (due to the neighbouring group participation).

4.5 Synthesis of glycolipids

Glycolipid acremomannolipin A (**222**), a calcium signal modulator isolated from *Acremonium strictum*, is composed of a β-linked



Scheme 30 Synthesis of trioxacarcin A, D, and C (**238**, **239**, and **241**).

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peracyl mannopyranose and mannitol.[227] In 2015, Li *et al.* reported its synthesis based on a gold(I)-catalyzed β-selective mannopyranosylation (Scheme 28).[64] Thus, mannosyl *o*-hexynylbenzoate **223** (α/β = 4 : 1) was prepared, which bears a 4,6-*O*-benzylidene acetal to enhance the β-selective glycosylation.[228–231] The α-anomer **223α** was then coupled with mannitol derivative **224** under optimized conditions [(4-MeOPh)$_3$PAuCl, AgB(C$_6$F$_5$)$_4$, CH_2Cl_2, 0 °C to r.t.] to give β-mannopyranoside **225** in 85% yield with an excellent β-selectivity (β/α = 13 : 1). In comparison, the previous glycosylation with a relevant sulfoxide donor gave the corresponding β-mannopyranoside in 71% yield.[232,233]

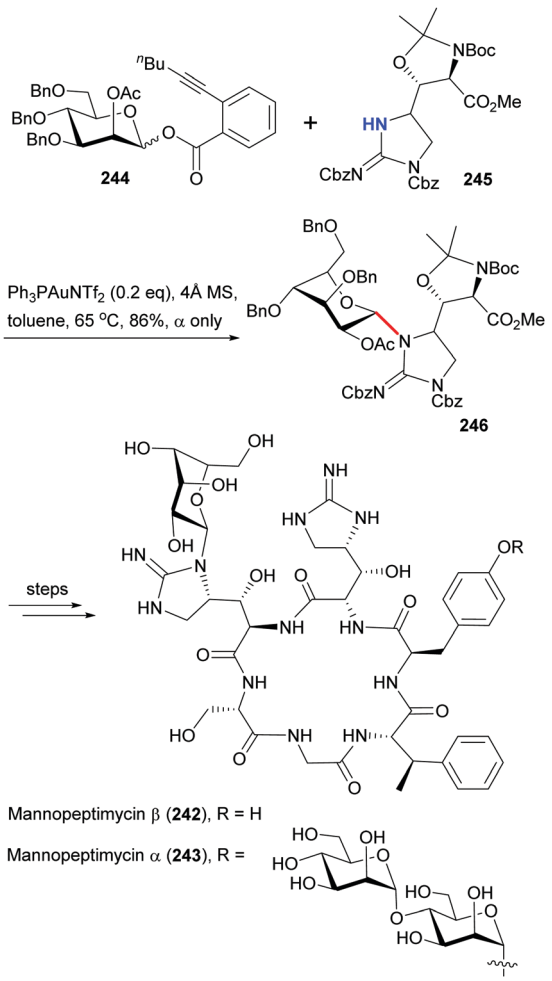
Glucuronosyldiacylglycerol **226** consists of a glucuronic acid α-linked to a diacylglycerol aglycone (Scheme 29).[234] Recently, Sodeoka *et al.* reported a direct glycosylation reaction of the lipid aglycone **227** with glucuronic *o*-hexynylbenzoate **228**, which bears acid-labile DMPM (dimethoxybenzyl) protecting groups.[235] The glycosylation (0.05 equiv. $Ph_3PAuNTf_2$, CH_2Cl_2, −78 °C to 0 °C) led to the desired glycolipid **229** in 47% yield with a stereoselectivity of α/β = 4 : 1. In contrast, the relevant glycosylation with a thioglycoside donor (MeOTf, DTBMP) gave **229** in 31% yield with an α/β ratio of 1.5 : 1. Selective removal of the DMPM groups on **229α** furnished glucuronosyldiacylglycerol **226**.

4.6 Synthesis of anthraquinone glycosides (trioxacarcins)

Trioxacarcins, showing potent cytotoxicity, constitute a small group of complex anthraquinone glycosides isolated from *Streptomyces bottropensis* (Scheme 30).[236–239] The challenging task of construction of the acid labile glycosidic linkages occurring in trioxacarcins was well addressed by Nicolaou *et al.* recently with the gold(I)-catalyzed glycosylation with *o*-alkynylbenzoate donors.[240,241] Thus, trioxacarcinose B *o*-cyclopropylethynylbenzoate **231** was used to glycosylate aglycone **230**. With excess **231** (10 equiv.) under the action of $Ph_3PAuNTf_2$ (0.2 equiv.) in CH_2Cl_2 at −20 °C for 5 min, the desired acetal glycoside **232** was obtained in an excellent 91% yield and α-selectivity (α/β > 20 : 1). In comparison, the highest yield reported by Myers *et al.* was 78% upon utilizing 30 equivalents of a relevant 1-*O*-acetyl donor in the presence of 20 equivalents of TMSOTf at −78 °C,[242] and other donors such as fluoride, thioglycoside, and pentenyl glycoside failed to give the desired products under various conditions. The PMB protecting group in **232** was then removed and the resulting **233** was subjected to second glycosylation. With trioxacarcinose A *o*-cyclopropylethynybenzoate **234** (2.0 equiv.) as donor under the action of $Ph_3PAuNTf_2$ (0.2 equiv.) in CH_2Cl_2 at 0 °C, the desired glycoside **236** was obtained in 71% yield. In fact, the pre-attached trioxacarbinoside B residue was prone to cleavage in acidic conditions, so a hindered base (*i.e.*, DTBMP, 8.0 equiv.) was required in Myers' synthesis using a thioglycoside as donor and $AgPF_6$ (6.0 equiv.) as promoter. The resultant **236** was finally subjected to global deprotection to furnish trioxacarcin A (**238**). Replacing the 4-*O*-acetyl donor **234** with the 4-*O*-TMS donor **235** in the second glycosylation step led to glycoside **237** (92%, α/β > 20 : 1), which was transformed to trioxacarcin D (**239**). Additionally, replacement of donor **231** in the first glycosylation step with carbonate-fixed donor **240** also gave excellent yield and α-selectivity, and thus trioxacarcin C (**241**) was synthesized. Similarly, other trioxacarcin congeners and artificial analogues could be effectively prepared.[240,241]

4.7 Synthesis of glycopeptides (mannopeptimycins)

Mannopeptimycin α (**242**) and β (**243**), cyclic glycopeptides isolated from *Streptomyces hygroscopicus*, show potent antibiotic activities against multidrug-resistant pathogens (Scheme 31).[243] In 2016, Chen *et al.* achieved the first total synthesis of these complex glycosides.[244] The construction of the characteristic *N*-mannosyl-D-β-hydroxyenduracididine unit turned out to be a formidable task, owing to the Lewis basicity and steric hindrance of the guanidine NH and the instability of the β-hydroxyenduracididine moiety. Model glycosylation reactions with di-Cbz-protected cyclic guanidine as acceptor were examined. In fact, the attempted glycosylation with mannosyl imidate and thioglycoside as donors failed to give any *N*-glycoside under various conditions (*e.g.*, TMSOTf, $BF_3{\cdot}OEt_2$, and NIS); with a relevant bromide donor in the presence of Ag_2CO_3 the glycosylation led to only 12% yield of the desired *N*-glycoside, and the yield decreased to <5% when β-hydroxyenduracididine **245** was used as the acceptor. Gratifyingly, the glycosylation of **245**



Scheme 31 Synthesis of mannopeptimycin α and β (**242** and **243**).

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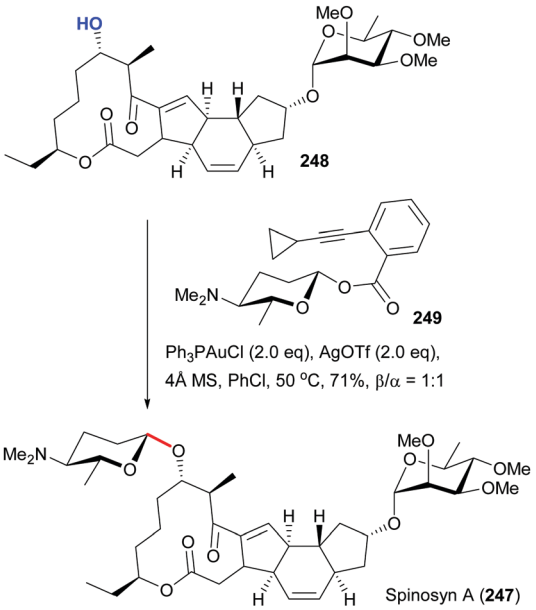


Scheme 32 Synthesis of spinosyn A (**247**).

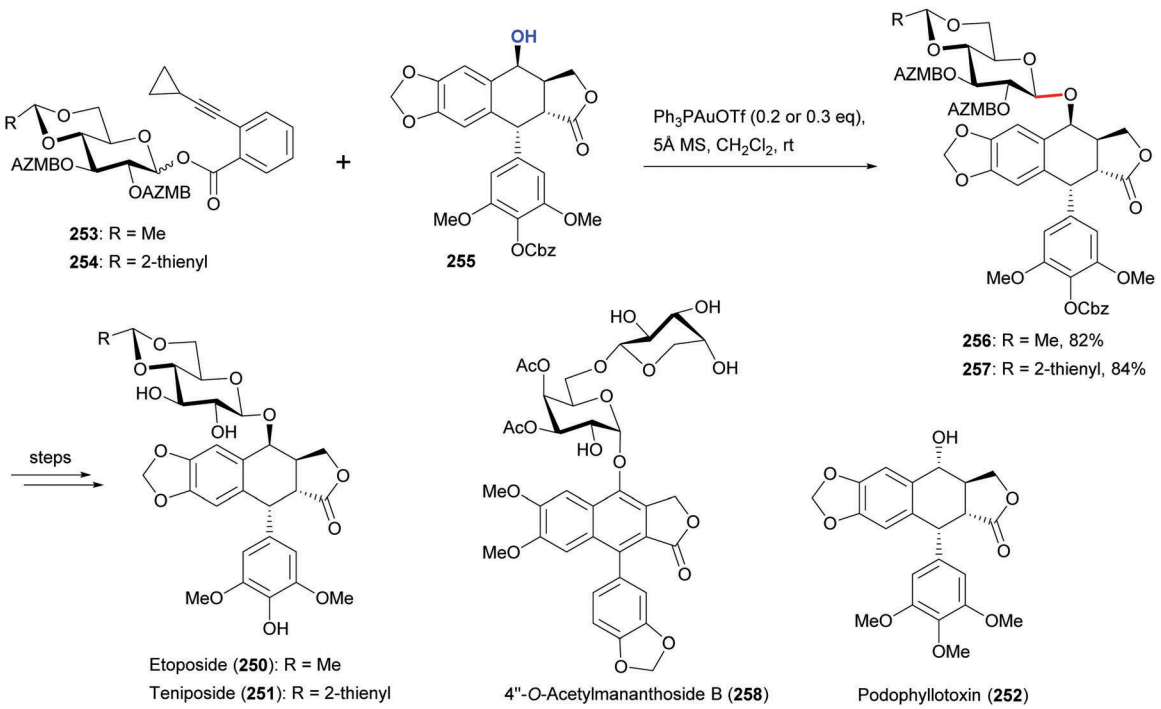
with 2-*O*-acetyl *o*-hexynylbenzoate **244** as donor in the presence of $Ph_3PAuNTf_2$ (0.2 equiv.) in toluene led to the desired *N*-α-glycoside **246** in an excellent 86% yield. Notably, the reaction temperature here was raised to 65 °C to shorten the reaction time.

4.8 Synthesis of macrolide glycoside (spinosyn A)

Spinosyn A (**247**) is a major component of the FDA-approved insecticide spinosad, which is produced by *Saccharopolyspora spinose* (Scheme 32).[245] Its chemical synthesis involves a challenging β-selective glycosylation for installation of a rare deoxy sugar, namely D-forosamine, on the aglycone. In the previous synthesis, the glycosylation with forosamine bromide and thioglycoside donors gave the desired β-glycoside in only ~10% yield.[246–248] Thus, Roush *et al.* employed 2-*O*-acetyl glycosyl imidate as donor to build the required glycosidic linkage; however, multi-steps were required for conversion of the installed sugar moiety into forosamine.[249] A recent total synthesis by Dai *et al.* successfully applied the gold(I)-catalyzed glycosylation to the attachment of forosamine to the aglycone.[250] Thus, glycosylation of macrolide aglycone **248** with forosamine *o*-cyclopropylethynylbenzoate **249** under the catalysis of Ph_3PAuCl (2.0 equiv.)/AgOTf (2.0 equiv.) in PhCl at 50 °C afforded spinosyn A (**247**) and its α-anomer in 71% yield (β/α = 1 : 1).

4.9 Synthesis of lignin glycosides

Etoposide (**250**) and teniposide (**251**) are first-line anticancer drugs derived from the natural lignin podophyllotoxin (**252**) and its 4-*O*-glycosides (Scheme 33).[251–254] Glycosylation of the 4-OH of podophyllotoxin was found to be problematic due to its vulnerability under both acidic and basic conditions. In addition, the axial orientation of 4-OH on (*eip*)-podophyllotoxin makes it even more difficult to be glycosylated. Recently, Sun *et al.* disclosed that gold(I)-catalyzed glycosylation with glycosyl *o*-alkynylbenzoate donors could be effectively applied to the glycosylation of both podophyllotoxin and (*eip*)-podophyllotoxin.[255] The corresponding 4-*O*-glycosides were obtained in high yields (80–90%), as exemplified by the depicted preparation of **256**/**257** from **253**/**254** and **255** en route toward the synthesis of etoposide (**250**) and teniposide (**251**). Similar glycosylation was also applied



Scheme 33 Synthesis of etoposide (**250**), teniposide (**251**), and 4''-*O*-acetylmananthoside B (**258**).

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to the synthesis of 4″-*O*-acetylmananthoside B (**258**),[256] a relevant lignin disaccharide occurring in *Justicia patentiflora* with potent anticancer activities.[257]

5. Conclusion and outlook

A wide variety of gold-catalyzed glycosylation protocols have been reported, which employ either conventional glycosyl donors (*e.g.*, trichloroacetimidates, 1,2-epoxides, and glycals) or new ones bearing various alkyne-containing leaving groups. All these reactions rely on either the high alkynophilicity (π acidity) or low oxophilicity (Lewis acidity) of the cationic gold catalysts for selective activation of the donors. However, the catalytic mechanisms proposed in the literature are largely speculative lacking experimental evidence. Most of the reactions are still at the phase of methodological studies, and their practical applications, which hold promise, are yet to be explored.

To apply a glycosylation protocol to the synthesis of complex glycans and glycoconjugates, mild reaction conditions capable of accommodating various functional groups and chemical scaffolds are required. Thus, the gold(III)-catalyzed glycosylation method with propargyl 1,2-orthoesters as donors, which can proceed effectively at room temperature, has been used successfully in the synthesis of a branched heneicosafuranoside.

The gold(I)-catalyzed glycosylation method with glycosyl *o*-alkynylbenzoates as donors has been proven to be generally applicable for the synthesis of glycans and glycoconjugates and especially advantageous for the synthesis of complex glycoconjugates bearing vulnerable scaffolds and functional groups. Its merits are prominent, including (1) the easy preparation and shelf-stability of the donors, even those of the di- and trideoxy sugars; (2) the catalytic promotion with a gold (I) complex, which possesses little oxophilic character or Lewis acidity; (3) the extremely wide substrate scope, due to the absence of nucleophilic, electrophilic, and acidic species from the leaving group and the promoter; (4) the convenient operation, with most reactions being performed at r.t. and with no need for quenching before workup. Importantly, the gold(I)-catalytic mechanism of this reaction has been thoroughly elucidated, with the key gold(I)-intermediates being experimentally characterized.[9] This mechanistic knowledge provides a foundation for the application and further development of the gold-catalyzed glycosylation reactions.

Conflicts of interest

There are no conflicts to declare.

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