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# Carbohydrate Chemistry in the Total Synthesis of Saponins

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**Keywords:** Saponins / Carbohydrates / Glycosylation / Protecting groups / Steroids / Triterpenes

Significant examples relating to the total synthesis of natural saponins with potent biological activities are discussed, with major emphasis on the applicability of contemporary glycosylation and protecting group manipulation protocols to the sophisticated scaffolds of steroids/triterpenes.



## 1. Introduction

Saponins are conventionally (long before the full characterization of any single saponin structure) and literally (from the Latin word *sapo*) defined as any of various plant glycosides that form soapy lathers when mixed and agitated with water. Most of these plant surfactants were later found to be glycosides of steroids and triterpenes, and the concept of 'saponins' then came to be confined to those compounds that have such structural characters.[1,2] However, the steroidal cardiac glycosides and steroidal alkaloid glycosides are conventionally (and also in this review) excluded, being assigned to their own categories. Thus far, thousands of homogeneous saponins have been characterized, not only from terrestrial plants but also from marine species. The tremendous structural diversity of these natural metabolites can be explained by their biogenesis,[3] which includes the synthesis of the steroids and triterpenes from the 30-carbon oxidosqualene by a variety of pathways, the assembly of 'glycoforms' by an array of the glycosyltransferases and glycosidases, and the various post-modifications, such as oxidation, rearrangement, and acylation.

Saponins, as natural surfactants, have been used routinely as detergents, foaming agents, and emulsifiers. With surprising correctness, many plant saponin extracts have also been used as significant folk medicines to treat various human ailments.[1,2] The prominent ones include those from ginseng, liquorice, horse chestnuts (aescine), ivy leaves, quillaia barks, primula roots, senega roots, and sarsaparilla roots, to name but a few. Continuous isolation and bioassay of the components have led to the disclosure of many homogeneous saponins possessing significant biological activities. However, little is known of the structure/activity relationships and the mechanisms of action of saponins, due to the poor accessibility to homogeneous saponins of various structures in appreciable amounts. This situation calls for chemical synthesis of saponins.

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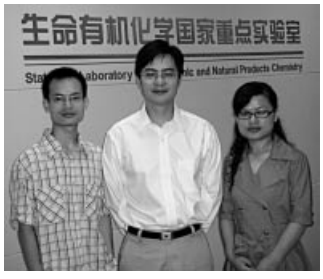



*Biao Yu (middle) was born in 1967 in Huzhou (Zhejiang province), a town about 200 km west of Shanghai. He received his B.A. in radiochemistry from Beijing University in 1989, and his M.S and Ph.D (with Prof. Y. Hui) from Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (CAS), in 1992 and 1995, respectively. After a one-year postdoctoral stay at New York University, Dr. Yu returned to SIOC as an assistant Professor, and became an associate Professor in 1997 and Professor at the end of the last century. His research interests include total synthesis, synthetic methodology, and chemical biology of biologically significant oligosaccharides and glycoconjugates, such as the glycosides of plants and marine species, the antibiotics of microbes, and the glycosaminoglycans of mammals.*

*Yichun Zhang (right) was born in 1977 in Kashi (Xinjiang province), a town roughly 5600 km northwest of Shanghai. She received her B.A. in chemistry from the Ocean University of China in 2000, and her Ph.D from the same University in 2005, working on the synthesis of steroid saponins. She then joined Prof. Yu's group in the SIOC as a postdoc to continue the saponin synthesis.*

*Pingping Tang (left) was born in 1980 in Anhua (Hunan province), a town roughly 1500 km west of Shanghai. He received his B.A. in chemistry from Nankai University in 2002, and then entered the SIOC as a graduate student (with Prof. B. Yu). After completing the total synthesis of candicanoside A and a series of the OSW-1 saponin analogues (mentioned in this review), he received his PhD in July 2007.*

The synthesis of saponins requires the integration of two disparate disciplines of synthetic chemistry: the synthetic chemistry of steroids/triterpenes and that of carbohydrates.[4] Both disciplines have represented intensive research themes since very early in the history of organic chemistry, but it was not until the 1990s that the synthesis of the complex natural saponins became a feasible objective and started to attract attention. An exhaustive review on the glycosylation of steroids/triterpenes was provided by Pellissier in 2004.[5] Here we discuss the total synthesis of natural saponins with a major emphasis on the applicability of the contemporary glycosylation and protecting group manipulation protocols to the sophisticated scaffolds of steroids and triterpenes. The steroid/triterpene aglycons can either be obtained by degradation of the "glycoforms" from the natural saponin extracts or synthesized from commercially available steroid/triterpene materials, which are in fact also derived from the natural sources by various degradation processes.

## 2. Synthesis of Saponins Bearing One Sugar Moiety (Monodesmosides)

### 2.1 Basic Tactics

For tactical consideration, saponins bearing one sugar moiety (monodesmosides) are much simpler synthetic targets than those with two or more sugar moieties. Convergent synthesis can be achieved through direct glycosylation of the aglycon with a prefabricated sugar donor. Alternatively, the sugar moiety can be attached to the aglycon in a linear manner (Scheme 1).[4]

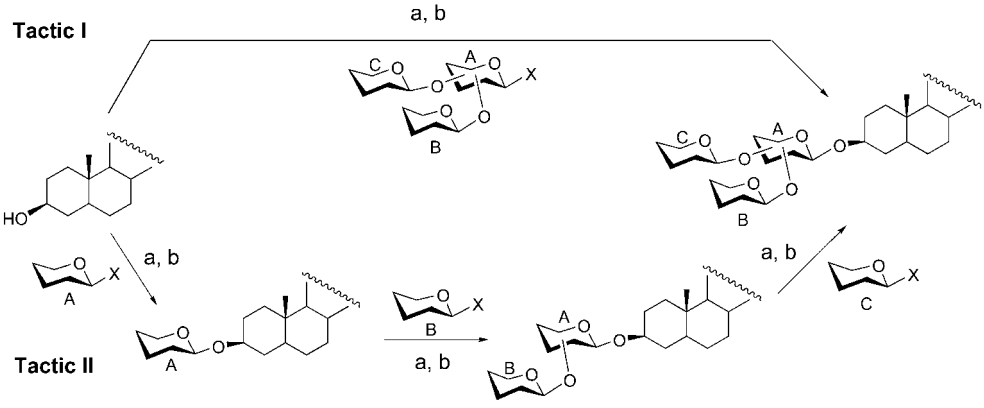
The convergent tactic is advantageous when the aglycon is precious or contains functional groups labile to the conditions used for linear sugar extension. However, glycosylation of the aglycon with an oligosaccharide donor might be problematic. Especially when the required donor contains a (1→2)-linkage at the reducing end, where no neighboring-group participation can be exploited, the glycosylation would lead to a pair of α and β anomers. In fact, such types of oligosaccharides are common in natural saponins. The linear tactic could be warranted for a stereospecific and high-yielding formation of the glycosidic bond to the aglycon, in which the natural linkage is always 1,2-*trans* and could be controlled by means of a temporary participating group installed at the 2-OH group of a monosaccharide donor, but subsequent elongation of the sugar chain in the presence of a multifunctional aglycon would require additional consideration.

### 2.2 Convergent Attachment of the Sugar Moiety to the Aglycone

#### *2.2.1 Glycosylation in the Presence of a Neighboring Participating Group*

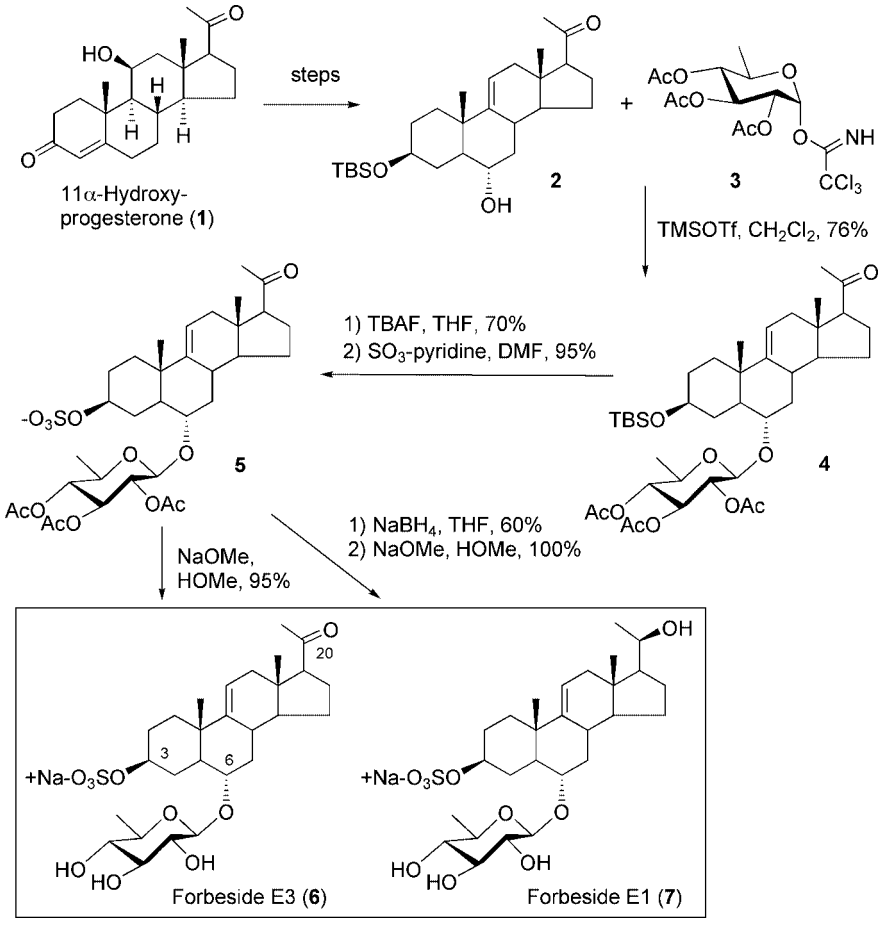
*A) Synthesis of the Starfish Saponin Forbesides E3 and E1*

Sulfated steroid glycosides are found as predominant secondary metabolites in starfish, and are responsible for the general toxicity of these species. The synthesis of the starfish glycosides forbesides E3 (**6**) and E1 (**7**) by Jiang, Han, and Schmidt in 1993 represents an early example of the total synthesis of natural saponins (Scheme 2).[6] Starting from the commercially available 11α-hydroxyprogesterone (**1**), the aglycon diol derivative **2** was prepared, with the more active 3-OH blocked with a *tert*-butyldimethylsilyl (TBS) ether. Glycosylation of the 6-α-OH group of **2** with 2,3,4-tri-*O*-acetyl-α-D-quinovopyranosyl trichloroacetimidate (**3**) with promotion by TMSOTf provided the desired β-glycoside **4** in 76% isolated yield. The presence of the 2-*O*-acetyl group on donor **3** ensured the exclusive formation of the β-anomer; a model reaction using a 2-*O*-benzyl-protected quinovosyl imidate led to a pair of the corresponding α- and β-anomers in nearly equal amounts. Treatment of **4** with tetrabutylammonium fluoride (TBAF) (to remove the 3-*O*-TBS group), followed with the sulfur trioxide/pyridine complex gave the 3-*O*-sulfate **5** as its pyridinium salt. Ion exchange of the pyridinium salt provided the corresponding sodium salt, which was readily characterized. Final removal of the acetyl groups on the sugar residue on **5** furnished forbeside E3 (**6**). Reduction of the 20-ketone on the sodium




Scheme 1. Two basic tactics for the synthesis of monodesmosides (a: glycosylation; b: protective group manipulation).




Scheme 2. Synthesis of forbesides E3 (**6**) and E1 (**7**).

salt of **5** with $NaBH_4$ provided a pair of the epimeric 20-ols with the natural (20*R*) isomer predominating (60% isolated yield). This was then deacetylated to furnish forbeside E1 (**7**).

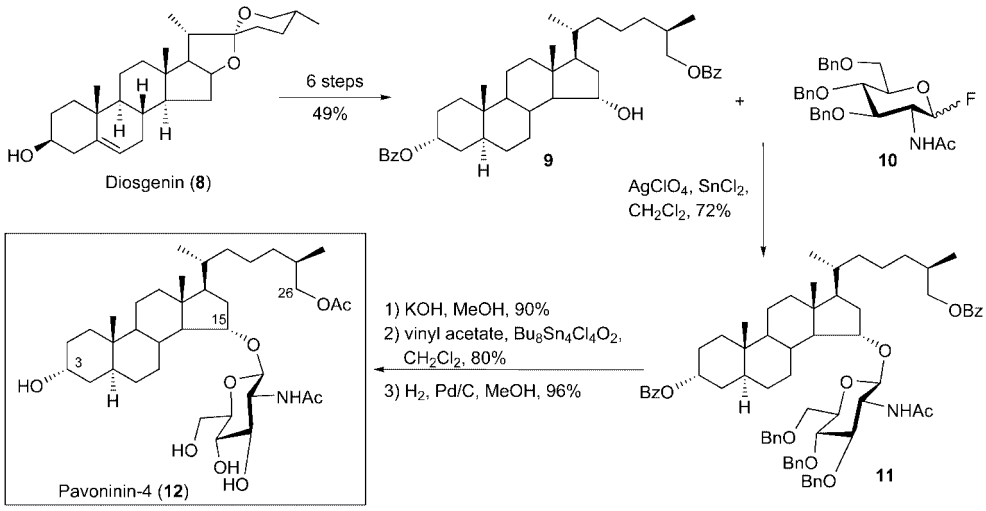
### *B) Synthesis of the Shark Repellent Pavoninin-4*

Fish of the sole species *Pardachirus pavoninus* excrete a mixture of the steroidal β-D-*N*-acetylglucosaminides, known as pavoninins, which show potent shark repellent activities.[7a] The total synthesis of pavoninin-4 (**12**) was recently achieved by Williams et al. (Scheme 3).[7b] The aglycon triol derivative **9**, prepared from the industrial material diosgenin (**8**), with only the least reactive 15-α-OH free, was coupled with 2-acetamido-2-deoxy-3,4,6-tri-*O*-benzyl-D-glucopyranosyl fluoride (**10**) with promotion by $AgClO_4$ and $SnCl_2$. The desired β-glycoside **11** was obtained stereoselectively in 72% yield. After removal of the 3- and 26-*O*-benzoyl groups, selective acetylation of the primary 26-OH group was successful only with vinyl acetate in the presence of 1,3-dichlorodistannoxane. Finally, hydrogenolysis of the three *O*-benzyl groups on the sugar moiety furnished pavoninin-4 (**12**).

### *C) Synthesis of the Exceptionally Potent Antitumor Saponin OSW-1*

Some twenty saponins, each featuring a 16β,17α-dihydroxycholest-22-one aglycon and an acylated sugar residue attached to the 16β-hydroxy group, have been isolated from the bulbs of *Ornithogalum saudersiae* and its taxonomically related plants since 1992.[8] The earliest (and the most abundant) member to be identified was OSW-1 (**17**), which showed a mean $IC_{50}$ value of 0.78 nM against the growth of 60 NCI (US National Cancer Institute) cell lines, 10–100 times lower than those of clinically used anticancer agents such as cisplatin, camptothecin, and taxol.[8b] The first total synthesis of OSW-1 was achieved by Deng et al. in 1999 (Scheme 4).[9] The aglycon triol derivative **14** was prepared from dehydroisoandrosterone (**13**), a common steroid degradation product, with the most active 3-OH protected with a TBS group. Glycosylation of **14** with the disaccharide trichloroacetimidate donor **15** in the presence of 0.05 equiv. of TMSOTf afforded the desired 16-*O*-glycoside **16** in 69% yield. The α configuration of the nascent L-arabinosidic linkage was ensured by the neighboring-group participation of the 2-*O*-acetyl group on donor **15**. Finally, the 3-*O*-TBS group, the three *O*-triethylsilyl (TES) groups on



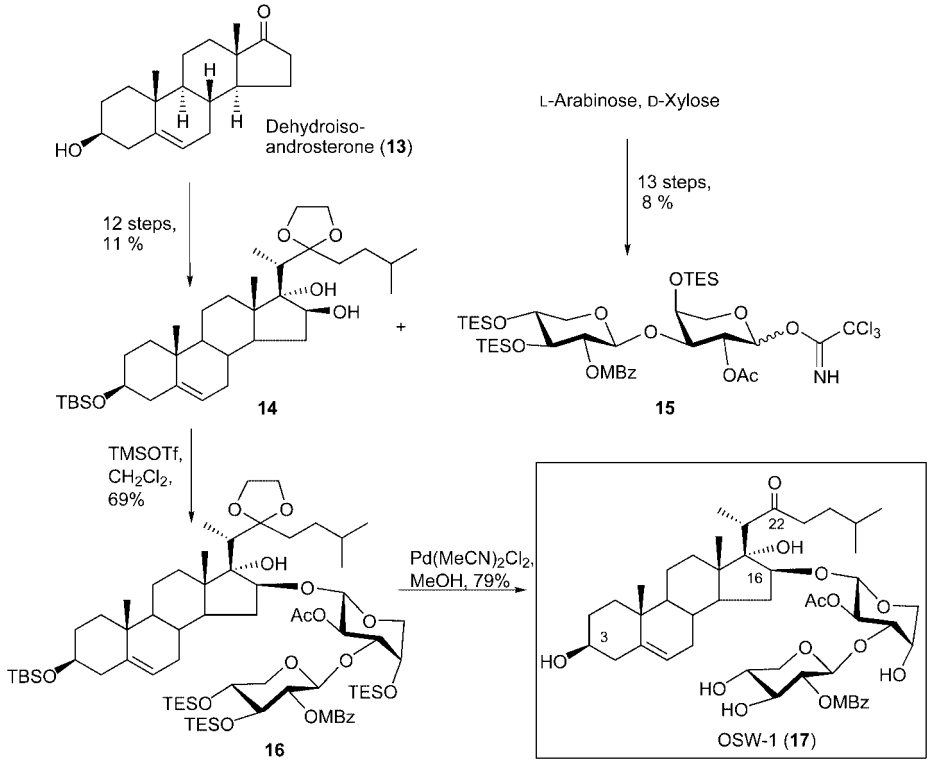

Scheme 3. Synthesis of pavoninin-4 (**12**).

the sugar moiety, and the 22-ethylene glycol ketal were taken off with $Pd(CN)_2Cl_2$ under neutral conditions without affecting the acetyl and *p*-methoxylbenzoyl (MBz) groups, affording OSW-1 (**17**) cleanly in 79% yield. Similar glycosylation protocols have been applied successfully to a later synthesis of OSW-1[10] and its analogues with variations on the aglycon.[11]

### *2.2.2 Glycosylation in the Absence of a Neighboring Participating Group*

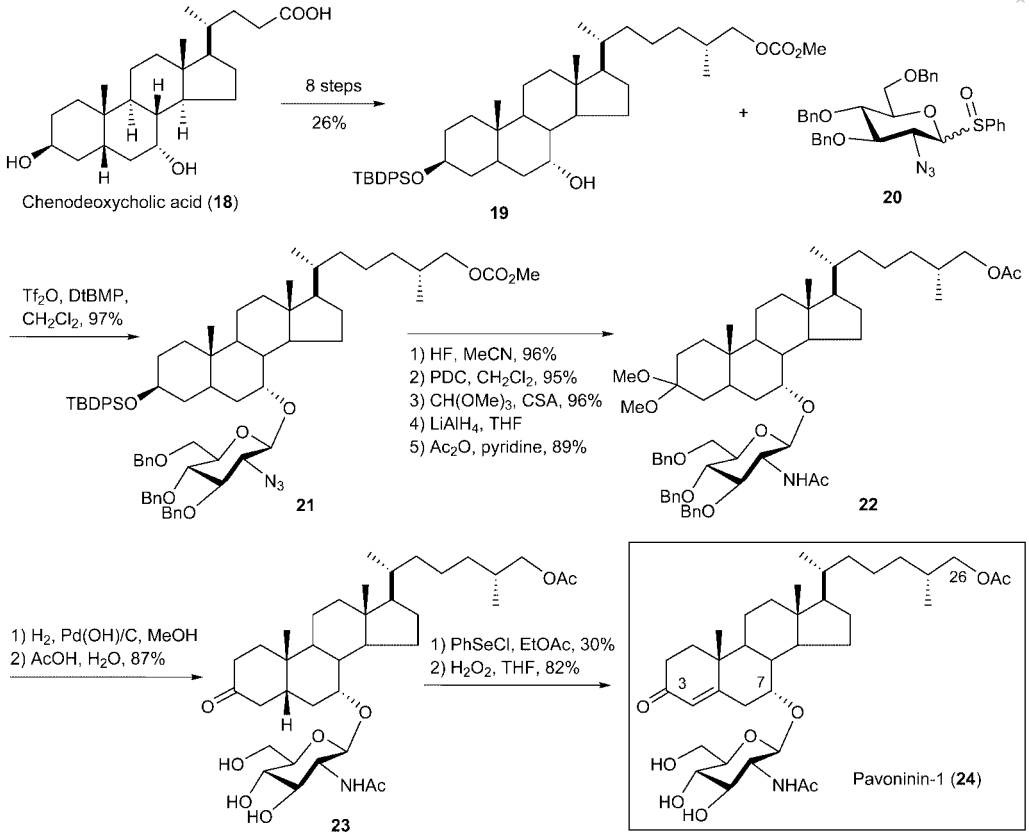
*A) Synthesis of the Shark Repellent Pavoninin-1*

Another member of the pavoninins that has been synthesized is pavoninin-1 (**24**; Scheme 5).[12] Unlike pavoninin-4 (**12**), pavoninin-1 (**24**) has a β-D-*N*-acetylglucosaminide

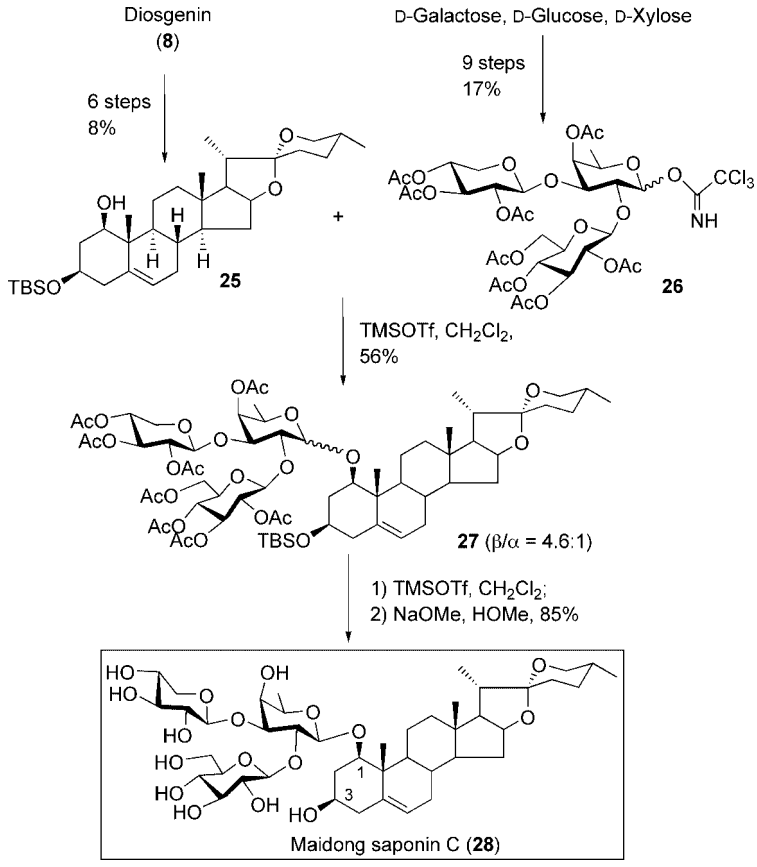



Scheme 4. The first total synthesis of OSW-1 (**17**).




Scheme 5. Synthesis of pavoninin-1 (**24**).




Scheme 6. Synthesis of Maidong saponin C (**28**).

system at the 7-α-OH group and an enone function in ring A. The 7-α-OH group in a cholate-type steroid is highly hindered, due to 1,3-diaxial positioning of the C4-methylene in the A-ring and two angular hydrogens. However, glycosylation of the cholate derivative **19**, prepared in eight steps from the commercially available chenodeoxycholic acid (**18**), with 2-azido-2-deoxy-3,4,6-tri-*O*-benzyl-D-glucopyranosyl phenyl sulfoxide (**20**) with sulfonic anhydride promotion in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DtBMP) at –20 °C in $CH_2Cl_2$ fortunately afforded the desired β-glycoside **21** in an excellent 97% yield. The 3-*O*-TBDPS group was then removed, and the resulting hydroxy group was oxidized to furnish the 3-carbonyl function, which was temporarily protected as a dimethyl ketal. Subsequent treatment with $LiAlH_4$ in THF removed the 26-*O*-methyoxycarbonyl group and converted the 2′-azido group into an amine moiety, and diacetylation provided **22** in high yield. The three *O*-benzyl groups in the sugar moiety were removed by hydrogenolysis before final elaboration of the enone function. Treatment of ketone **23** with PhSeCl in EtOAc gave the desired 4β-selenenylated ketone as the major product, albeit in a moderate 30% yield, and this was subjected to *cis*-elimination with hydrogen peroxide in aqueous THF to afford pavoninin-1 (**24**) in 82% yield.

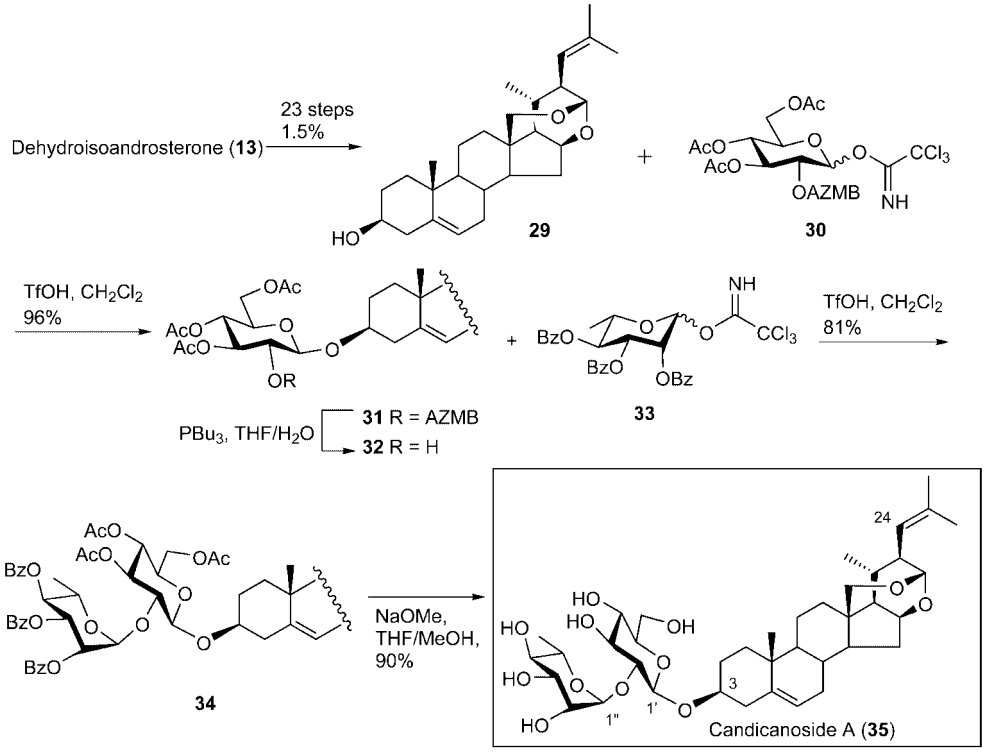
*B) Synthesis of the Anti-inflammatory Maidong Saponin C*

The tubers of some *Ophiopogon* and *Liriope* plants are commonly used in traditional Chinese medicine under the name of Maidong, which contains a large variety of steroid saponins. Maidong saponin C (**28**), a minor component, was shown to have potent anti-inflammatory activity in a rat edema model.[13] The synthetic route to this compound is shown in Scheme 6.[14] The aglycon diol derivative **25**, with the more active 3-OH masked with a TBS group, prepared from diosgenin in a short six steps, was subjected to glycosylation with the trisaccharide trichloroacetimidate donor **26**. Because of the powerful hindrance of the 1-β-OH group on steroid **25**, however, only small amounts of coupling products were formed prior to the decomposition of the labile trisaccharide donor. Because of this, the "inverse procedure"[15] was used, donor **26** being slowly added at around 0 °C to a solution of the steroid **25** containing a catalytic amount of the promoter TMSOTf. The resulting glycosides were α/β mixtures, with the total yields no higher than 56% in favor of the β-anomer. Separation of the anomeric mixtures was achieved by careful chromatography. Finally, the β-anomer was subjected to deprotection with TMSOTf (1 equiv., –78 °C) to remove the 3-*O*-TBS group, and subsequently with NaOMe in methanol to remove the acetyl groups, affording the target saponin **28**.

### 2.3 Linear Assembly of the Sugar Moiety on the Aglycone

*A) Synthesis of the Antitumor Saponin Candicanoside A*

During the exhaustive isolation of OSW saponins,[8] a group of minor saponins with arranged steroidal side chains was identified from the same plants. Candicanoside A (**35**), isolated from the bulbs of *Galtonia candicans*, represents such a member.[16] This compound showed potent antitumor activities (e.g., $IC_{50}$ = 32 nM against HL-60 human promyelocytic leukemia cells) comparable to those of the clini-



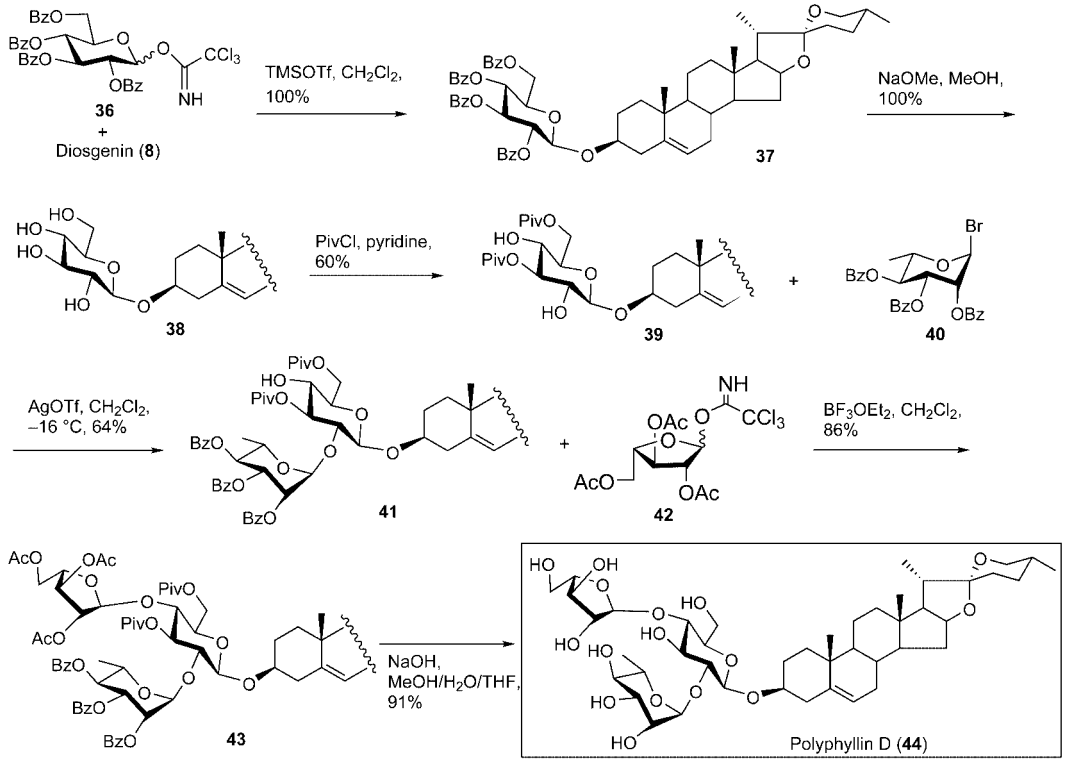

Scheme 7. Synthesis of candicanoside A (**35**).

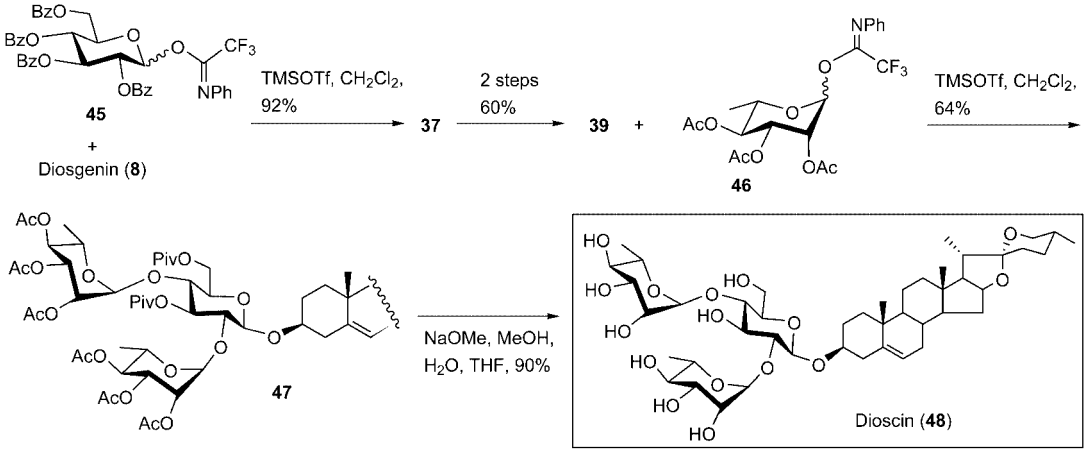
cally applied anticancer agents etoposide and methotrexate. In addition, its antitumor profile was found not to correlate with those shown by any of the other antitumor compounds. In the content of linear assembly of saponins, synthesis of this disaccharide is a simple task (Scheme 7).[17] Glycosylation of steroid **29**, prepared from dehydroisoandrosterone (**13**) in 23 steps, with glucosyl imidate **30** bearing the neighboring participating 2-*O*-2-(azidomethyl)benzoyl (AZMB) group afforded the desired β-glycoside **31** in an excellent 96% yield in the presence of 0.2 equiv. of trifluoromethanesulfonic acid (TfOH). The 2′-*O*-AZMB group in **31** was then selectively removed in the presence of acetyl groups by treatment with $PBu_3$, providing **32**. The resulting 2-OH group was sterically hindered, nonetheless, coupling with the benzoyl-protected rhamnosyl imidate **33** in the presence of TfOH (0.2 equiv.) was able to form the desired disaccharide **34** in 81% yield (for two steps). Finally, removal of the acetyl and benzoyl groups on the sugar residue with NaOMe in MeOH/THF furnished the target candicanoside A (**35**) in 90% yield.

### *B) Synthesis of the Antitumor Saponin Polyphyllin D and Its Congeners*

Spirostan saponins constitute the largest group of the steroidal saponins in plants. Many members of this group have the oligosaccharide chain at the steroidal 3-OH with

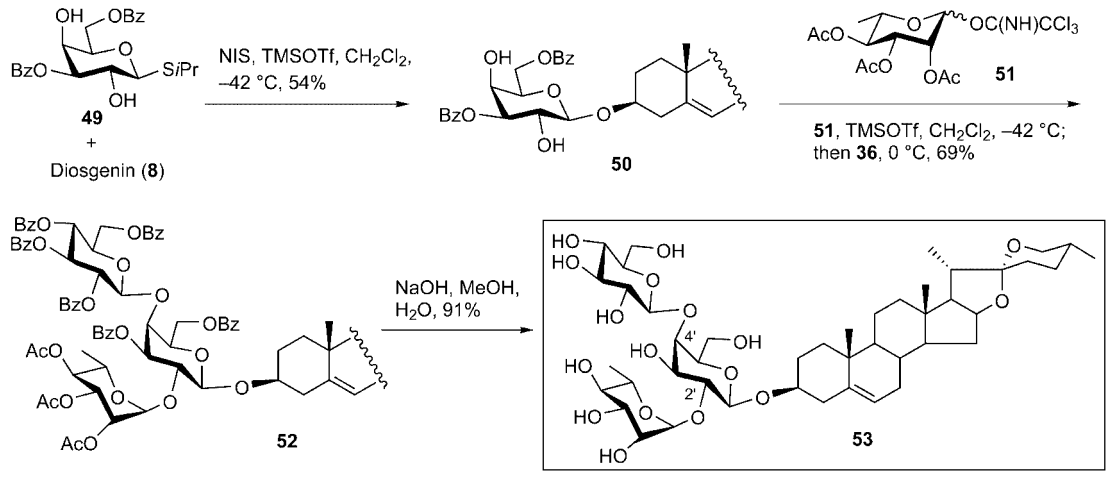



Scheme 8. Practical synthesis of polyphyllin D (**44**).




Scheme 9. Synthesis of dioscin (**48**) using trifluoroacetimidate donors.

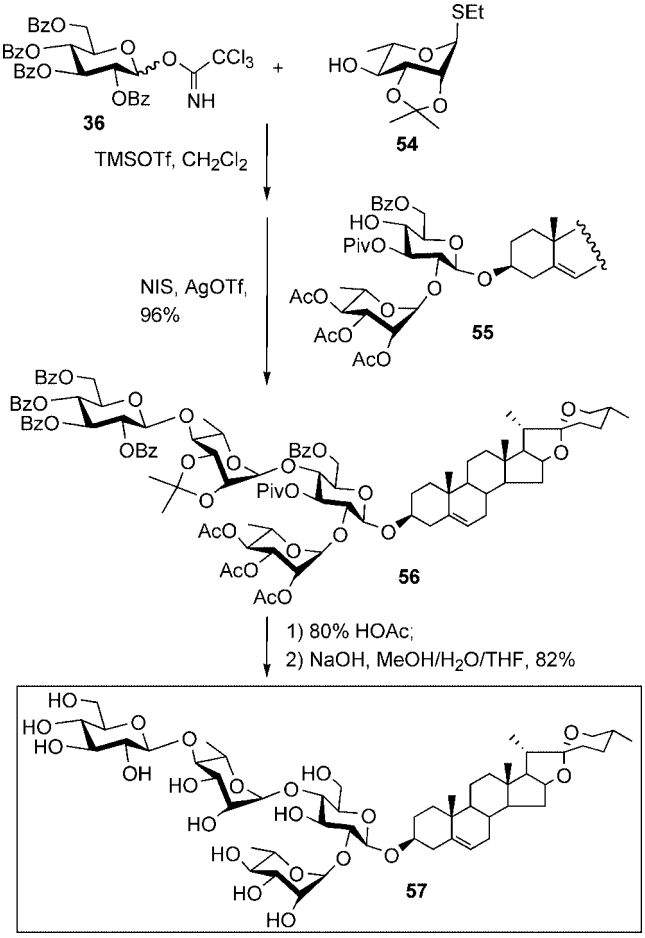



Scheme 10. Synthesis of saponin **53** employing a partially protected glycosyl donor.

β-D-glucopyranose as the first sugar unit, with this in turn having an α-L-rhamnose substituted at the 2-*O*-position and another sugar or sugar chain at the 3- or 4-*O*-position. Polyphyllin D (**44**), isolated from various *Paris* species with medicinal applications, represents such a saponin and shows the most potent antitumor activities among the spirostan saponins.[18] The synthetic route to this trisaccharide has been improved and is readily scalable (Scheme 8).[19] Glycosylation of diosgenin (**8**) with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl trichloroacetimidate (**36**) in the presence of 0.05 equiv. of TMSOTf provided the β-glycoside **37** quantitatively. Removal of the *O*-benzoyl groups, followed by selective protection of the resulting 3- and 6-OH functions with pivaloyl groups, gave the 2,4-diol **39** in 60% yield. Selective rhamnosylation at 2-OH with a variety of donors was briefly examined; favorable results were obtained with 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (**40**) with promotion by AgOTf at –16 °C, affording the 2-*O*-rhamnoside **41** in 64% yield; the 2,4-di-*O*-rhamnoside was also isolated in 8% yield and 24% of the diol **39** was recovered. Coupling of the disaccharide **41** with 2,3,5-tri-*O*-acetyl-L-arabinofuranosyl trichloroacetimidate (**42**) in the presence of $BF_3{\cdot}OEt_2$ provided the desired trisaccharide derivative **43** in a good 86% yield. Finally, removal of the acetyl, benzoyl, and pivaloyl groups with NaOH furnished polyphillin D (**44**) in 91% yield.

Application of the above linear assembly approach to the synthesis of dioscin (**48**), one of the most abundant plant spirostan saponins, by using the recently available glycosyl trifluoroacetimidate donors succeeded in a linear five steps and in 32% overall yield (Scheme 9).[20]

Interestingly, glycosylation of diosgenin (**8**) with partially protected glycosyl donors was also found to be feasible, as illustrated by the synthesis of the trisaccharide **53**,[21] a natural saponin with cholesterol-lowering activity (Scheme 10).[22] Thioglycoside **49**, with its 2,4-OHs unprotected, was condensed with diosgenin (**8**; NIS/TMSOTf, –42 °C) to afford the desired β-glycoside **50** in a good 54% isolated yield. Selective glycosylation of the equatorial 2′-OH group in **50** with rhamnosyl imidate **51** at low temperature, followed by glycosylation of the remaining axial 4′-OH group with glucosyl imidate **36** at 0 °C, provided the desired trisaccharide **52** in 69% isolated yield. Final re-




Scheme 11. Synthesis of a spirostan tetrasaccharide (**57**) by an orthogonal "one-pot" glycosylation protocol.

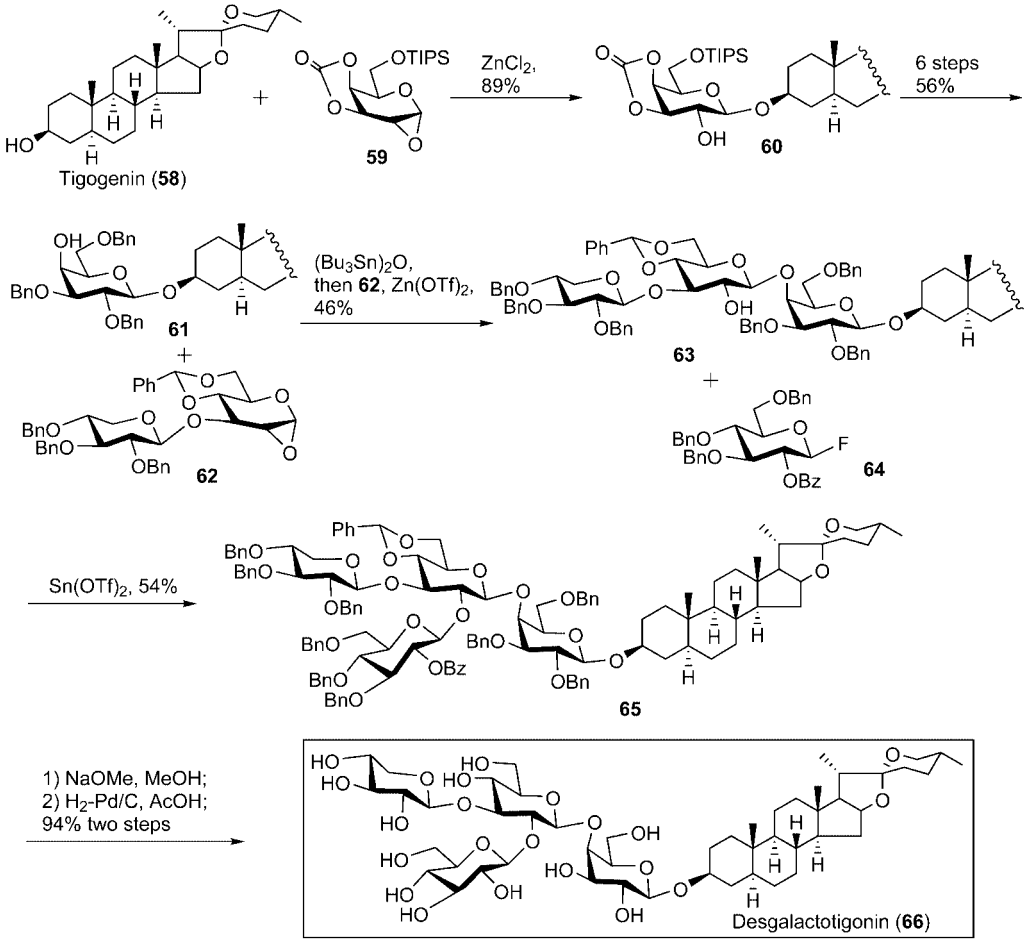
  

moval of the acetyl and benzoyl groups with aqueous NaOH in MeOH cleanly furnished the target saponin **53**.

The orthogonal "one-pot" glycosylation protocol[23] was also successfully applied to the parallel synthesis of the spirostan saponins. Scheme 11 shows such an example.[24] TMSOTf (0.3 equiv.) was added at –78 °C to a mixture of the glucosyl imidate **36** (2.3 equiv.) and thioglycoside **54** (2.0 equiv.), the temperature was then raised to –20 °C, and the diosgenin disaccharide **55** (1.0 equiv.) was added, followed by the addition of *N*-iodosuccinimide (NIS, 2.0 equiv.). The desired tetrasaccharide **56** was isolated in an excellent 96% yield. Removal of the isopropylidene group and acyl groups with HOAc and NaOH subsequently provided the target tetrasaccharide saponin **57** in 82% yield after column chromatography on silica gel.

### *C) Synthesis of Desgalactotigonin*

Desgalactotigonin (**66**), isolated from the purple foxglove *Digitalis purpurea* L., is a component of the heterogeneous digitalis saponins used as biological detergents for the solubilization and isolation of membrane proteins. The total synthesis of desgalactotigonin (**66**) was achieved by Randolph and Danishefsky in 1993 (Scheme 12).[25] Coupling of tigogenin (**58**) with the newly prepared galactose 1,2-epoxide **59** in the presence of $ZnCl_2$ provided the desired β-galactoside **60** in a satisfactory 89% yield. Conventional protecting group manipulation on **60** led to the 2,3,6-tri-*O*-benzyl-β-D-galactoside **61** over six steps. Direct glycosylation of the axial 4-OH of **61** with the disaccharide 1,2-epoxide **62** was not successful. However, the corresponding stannyl ether of **61** coupled with epoxide **62** with promotion by zinc triflate, affording the trisaccharide **63** in 46% yield (94% based upon the recovered **61**). Glycosylation of the resulting 2′′-OH group in **63** was again found to be futile with a glucose 1,2-epoxide donor, but this task was achieved with 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride (**64**) in the presence of stannous triflate, giving the desired tetrasaccharide **65** in 54% yield. Finally, removal of the benzoyl group with NaOMe in methanol followed by hydrogenolysis of the nine *O*-benzyl groups and one benzylidene acetal over palladium black cleanly furnished desgalactotigonin (**66**).




Scheme 12. Synthesis of desgalactotigonin (**66**).

## 3. Synthesis of Saponins Bearing Two Sugar Moieties (Bidesmosides)

*A) Synthesis of the Representative Furostan Saponin Methyl Protodioscin*

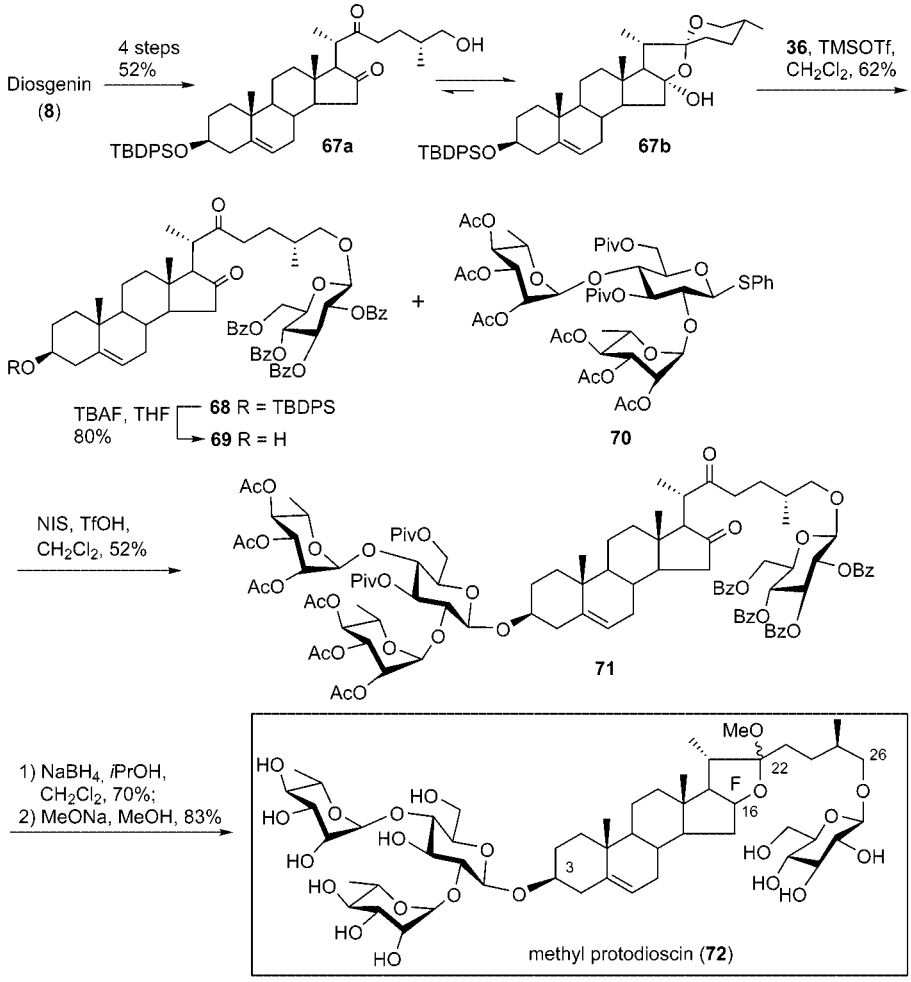
Steroid saponins are usually divided into three classes according to the steroidal aglycons: cholestan saponins (e.g., **12**, **17**, **24**), spirostan saponins (e.g., **28**, **44**, **48**, **53**, **57**, and **66**), and furostan saponins.[1] Furostan saponins have an additional β-D-glucopyranose substituent (with few exceptions) at the 26-OH group. In plants, cleavage of this β-D-glucopyranoside by a specific enzyme leads to the closure of the F ring to produce the corresponding spirostan saponins.[26]

Methyl protodioscin (**72**), the counterpart of the spirostan dioscin (**48**), represents one of the most common furostan saponins, and is claimed to possess antitumor activities as potent as those of dioscin but does not show hemolytic effects.[27] The first synthetic route toward furostan saponins was developed in 2001,[28] and following this protocol, Cheng et al. accomplished the synthesis of methyl protodioscin (**72**; Scheme 13).[29] The 16,22-dione-26-ol **67a**, readily prepared from diosgenin (**8**) in four steps through oxidative opening of the spirostan E and F rings, existed in equilibrium with the prevailing 16-hemiketal **67b**. Glycosylation of the mixture with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl trichloroacetimidate (**36**) provided the 26-*O*-β-glucoside **68** in 62% yield, and selective removal of the 3-*O*-TBDPS group provided 3-ol **69**. Glycosylation of **69** with the trisaccharide thiodonor **70** in the presence of NIS and a catalytic amount of TfOH in $CH_2Cl_2$ fortunately led to the desired β-glycoside **71** in 52% yield, in the absence of a neighboring-group participation. Finally, selective reduction of the 16-carbonyl group with $NaBH_4$ in propan-2-ol, followed by global removal of the acyl protecting groups with NaOMe in methanol, afforded methyl protodioscin (**72**).

Recently, a concise protocol for the conversion of spirostan saponins into furostan saponins was established. Thus, methyl protodioscin (**72**) was prepared from the readily available dioscin pivalate **73** in six steps and 21% overall yield (Scheme 14).[30]

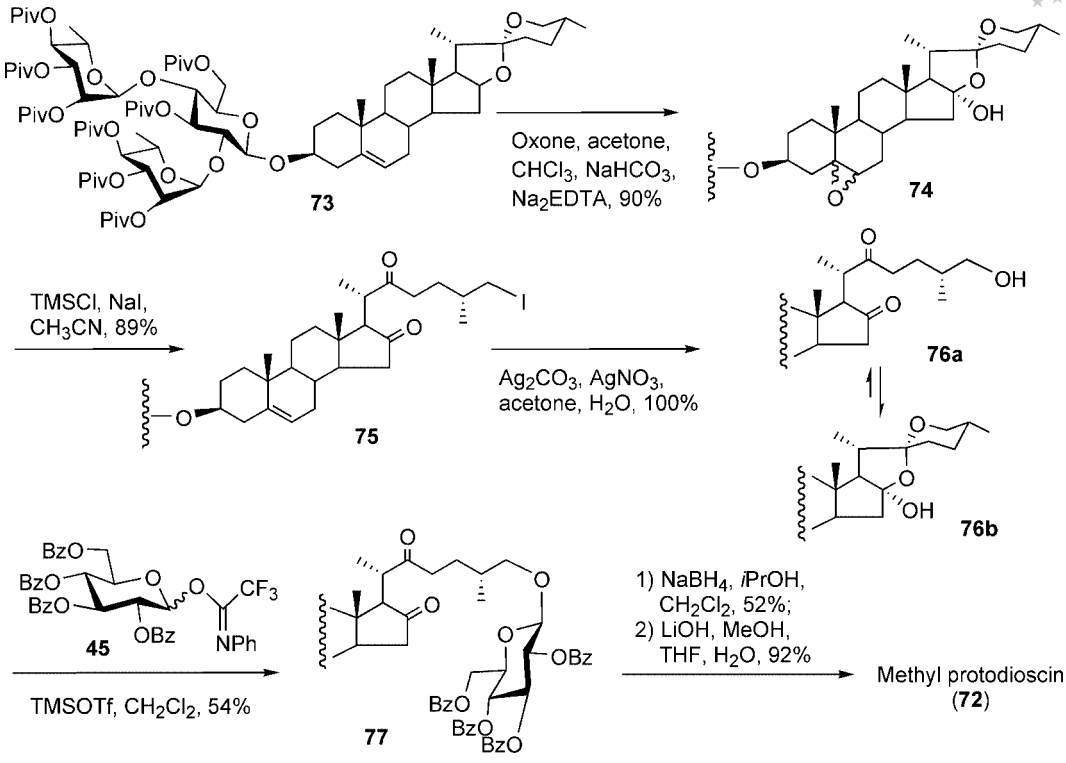
*B) Synthesis of the Intensively Sweet Saponin Osladin*

Osladin (**86**) is a sweet principle of the rhizome of the European fern *Polypodium vulgare*. The initially proposed




Scheme 13. Synthesis of methyl protodioscin (**72**).



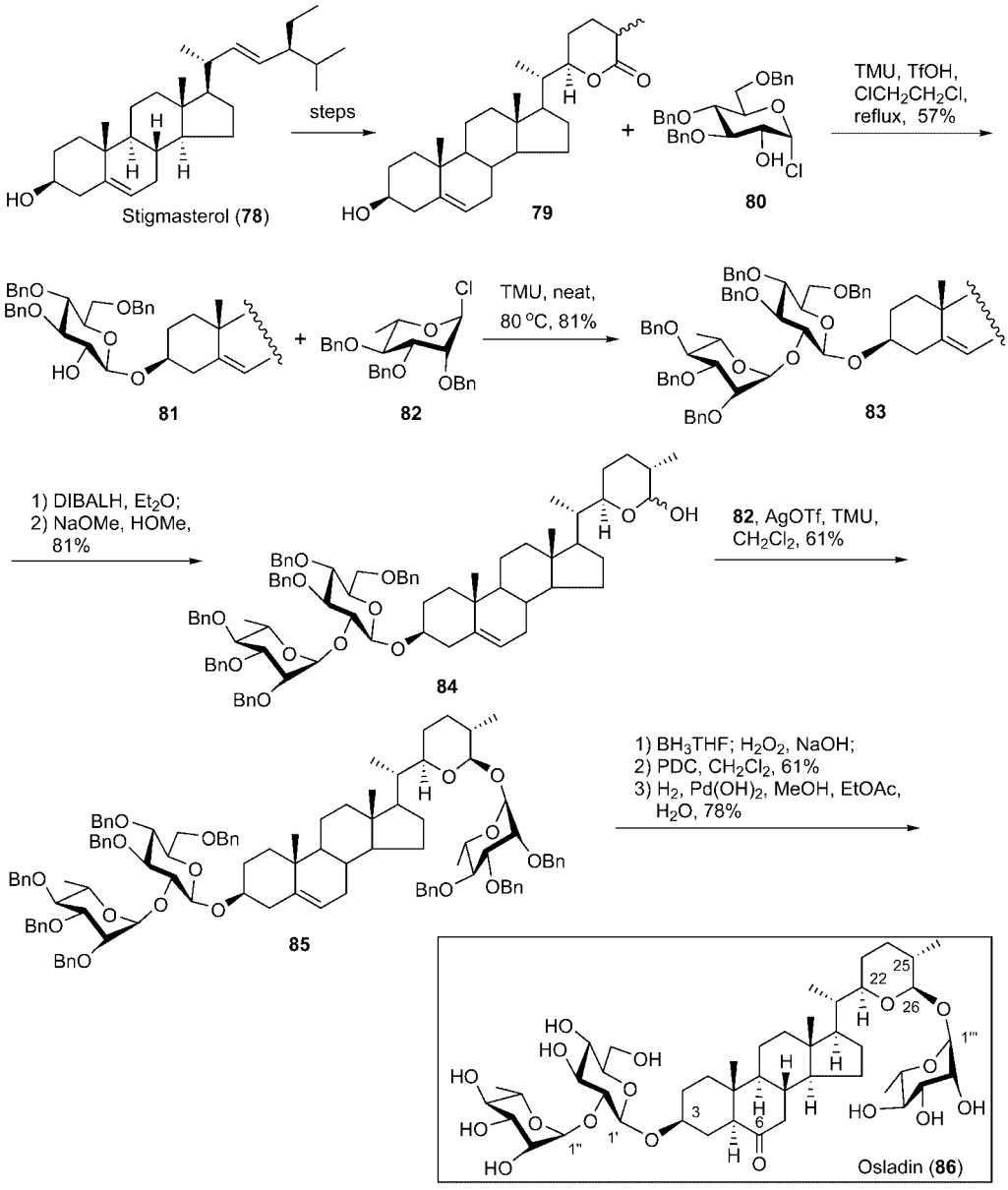

Scheme 14. Simple conversion of dioscin pivalate **73** into methyl protodioscin (**72**).

structure of osladin (the stereoisomer of **86** at C-22, C-25, and C-26) was firstly synthesized by Yamada and Nishizawa in 1993, but turned out not to be sweet at all.[31] The revised structure (**86**) was then synthesized (Scheme 15), and the product tasted 500 times sweeter than sucrose.[32] The total synthesis of osladin (**86**) was achieved by sequential assembly of the disaccharide moiety at the 3-OH group, followed by releasing of the lactol 26-OH and subsequent glycosylation. Thus, starting from the naturally abundant stigmasterol (**78**), the aglycon-3-ol derivative **79** was prepared and subjected to the first glycosylation. By the "thermal glycosylation protocol",[33] condensation of **79** with 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl chloride (**80**) in the presence of tetramethylurea (TMU) and triflic acid in $ClCH_2CH_2Cl$ at reflux gave the β-glucoside **81** in 57% yield. Glycosylation of the free 2′-OH group with 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl chloride (**82**) in neat TMU at 80 °C provided the desired disaccharide **83** in 81% yield. The 26-carbonyl group was then reduced to the corresponding hemiacetal, which upon treatment with a base was converted into the more stable 25-equatorial methyl compound **84**. Treatment of hemiacetal **84** with the α-L-rhamnopyranosyl chloride **82** in the presence of AgOTf and TMU at 25 °C provided the trisaccharide **85** in 61% isolated yield with the corrected stereochemistry at C-26 (25,26-*trans*) and C-1′′′ (α-L-rhamnopyranoside). Finally, elaboration of the 6-carbonyl function from the 5,6-double bond, followed by global hydrogenolysis of the benzyl groups on the sugar moieties, furnished osladin (**86**).

### *C) Synthesis of a Cytotoxic Glucuronide Triterpene Bisdesmoside*

Saponin **95** represents a typical member of the saponin subfamily termed glucuronide oleanane-type triterpene carboxylic acid 3,28-*O*-bisdesmoside (GOTCAB). This compound was isolated from the Chinese folk medicinal plant *Aralia dasyphylla* and was claimed to be highly cytotoxic.[34] In line with the previous efforts on the synthesis of triterpene saponins,[35] 3,28-*O*-bisdesmoside **95** was synthesized in a highly efficient manner (Scheme 16).[36] Selective glycosylation of the 28-COOH group of oleanolic acid (**87**) was successfully accomplished with glucosyl α-bromide **88** under phase-transfer conditions, giving the 28-ester-glycoside **89** in 90% yield. The remaining 3-OH group in **89** was then glycosylated with the disaccharide trifluoroacetimidate donor **90**, possessing a neighboring-participating AZMB group at the 2-OH group, to provide the desired β-glycoside in a stereocontrolled manner in 89% yield. Selective removal of the 2′-*O*-AZMB group with $Bu_3P$ and subsequent glycosylation of the resulting 2′-OH group with the galactosyl trifluoroacetimidate **92** with TBSOTf promotion afforded the tetrasaccharide **93** in 90% yield. Finally, the 4′,6′-*O*-acetyl groups in **93** were removed selectively with HCl in methanol, and the resulting primary 6′-OH group was selectively oxidized into a carboxylic acid with TEMPO/$Ca(ClO)_2$/KBr under phase-transfer conditions,[37] providing (after methyl ester formation to facilitate the isolation and characterization) glucuronate **94** in good yield.



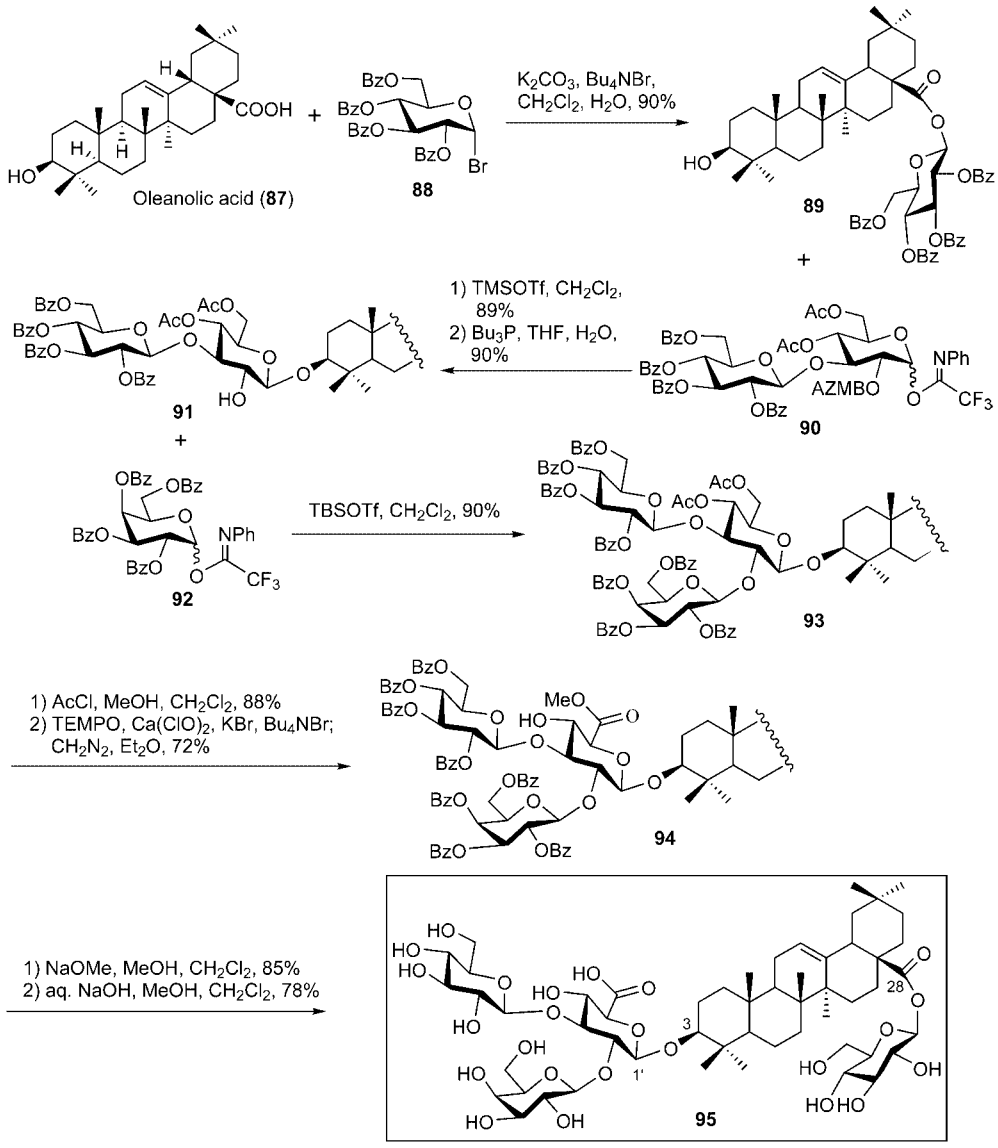

Scheme 15. Synthesis of osladin (**86**).

The 28-sugar-ester survived well in the final alkaline deprotection of the acyl groups, furnishing the glucuronide triterpene bisdesmoside **95** in 78% yield after silica gel column chromatography.

### *D) Synthesis of a Triterpene Bisdesmoside by Successive Glycosylation*

It is noteworthy that over half of the triterpene saponins (including the aforementioned compound **95**) are glycosides of oleanolic acid or its derivatives with one sugar chain glycosidically attached through the hydroxy function at C-3 and another through an ester linkage at C-28.[1] Saponin **105** is such a compound, isolated from the leaves of the commonly used Chinese medicinal herb *Acanthopanax senicosus*.[38] The synthesis of compound **105** in 1999 represents a highly efficient assembly of the glycoconjugates by the contemporary "one-pot" glycosylation protocol (Scheme 17).[39] Assembly of the fully protected oleanane tetrasaccharide **104** was achieved by four successive glycosylation steps. 1) Coupling of oleanolic 28-trityl ester **96** with arabinopyranosyl imidate **97** was completed within 20 min in the presence of a catalytic amount of TMSOTf in $CH_2Cl_2$ at low temperature (–60 °C), after which the 28-COOH was unmasked upon warming the mixture to room temperature for 20 min. 2) Addition of a $CH_2Cl_2$ solution of the glucopyranosyl imidate **100** to the above mixture at 0 °C cleanly afforded disaccharide **101** within 20 min, as monitored by TLC. 3) In a second flask, thio-disaccharide **103** was generated by condensation of thio-glucopyranoside




Scheme 16. Synthesis of the glucuronide triterpene bisdesmoside **95**.

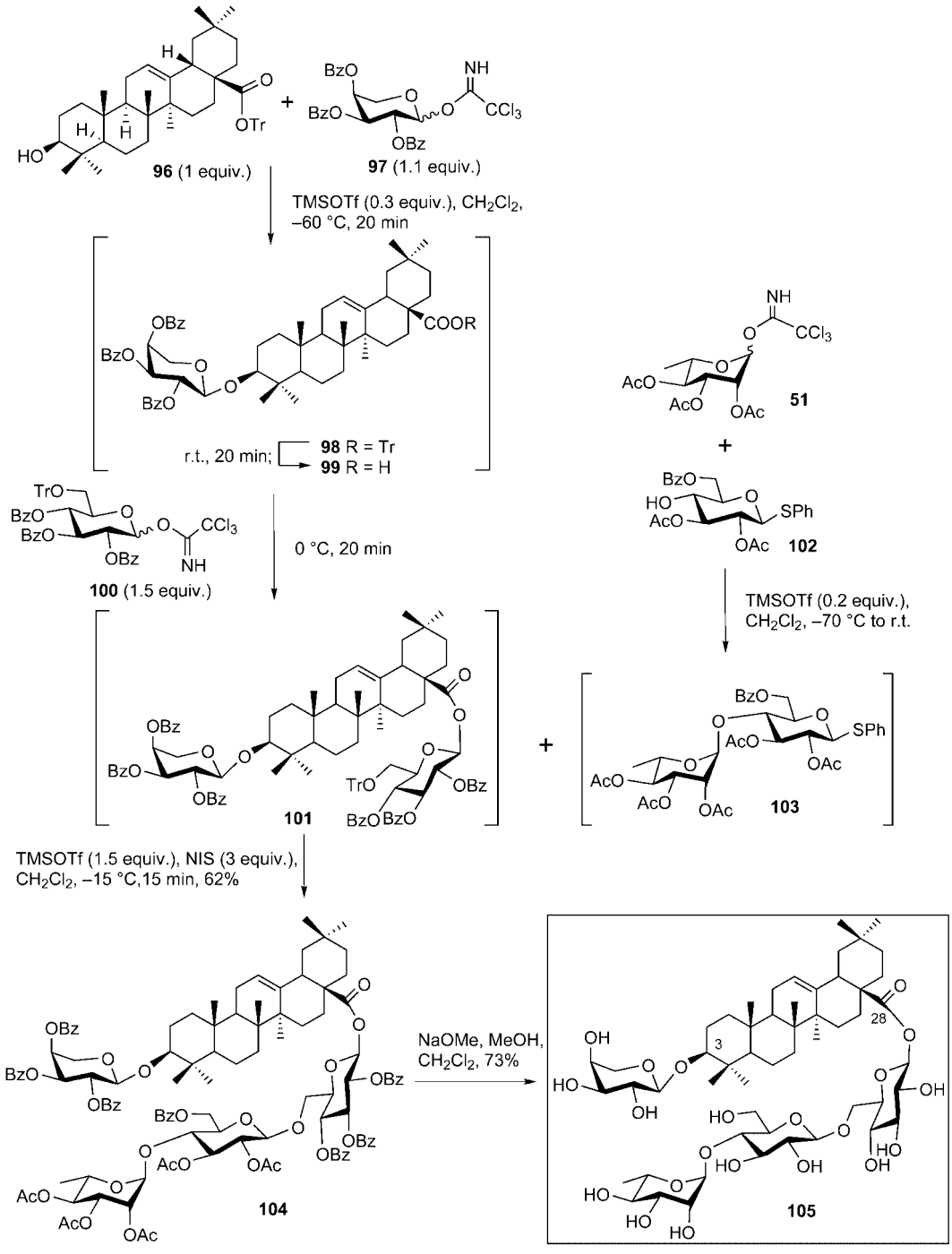
**102** with rhamnosyl imidate **51** in the presence of TMSOTf in $CH_2Cl_2$. 4) Addition of the mixture in the second flask into the first, followed by addition of TMSOTf and NIS, led to the consumption of the trityl ether **101** within 15 min. Flash column chromatographic purification provided **104** in a good 62% yield (based on **96**). Finally, removal of the acetate and benzoate protecting groups afforded the target saponin **105**.

### *E) Synthesis of the Potent Immunoadjuvant QS-21A$_{api}$*

The extracts of the South American tree *Quillaja saponaria* Molina have long been used as commercial saponins: as foaming agents in beverages, for example, or in confectioneries, baked goods, dairy desserts, and cosmetics. Recently, tremendous attention has been given to their immunological adjuvant activities.[40] QS-21A$_{api}$ (**115**) is a minor component from quillajasaponins, which has proven to be a potent compound for immune response potentiation and dose-sparing in vaccine therapy.[41] Representing a typical quillajasaponin structure, QS-21A$_{api}$ (**115**) contains a central quillaic acid triterpene core flanked on either side by complex oligosaccharides. The total synthesis of this complex molecule was achieved recently by Gin et al.[42] A convergent modular assembly of the four pieces [i.e., the branched trisaccharide (part A), the triterpene (part B), the linear tetrasaccharide (part C), and the fatty acyl moiety (part D)] was successfully achieved by judicious choice of the coupling protocols and protecting patterns (Scheme 19).

Coupling of the quillaic allyl ester **106** with the branched trisaccharide α-imidate **107** was finally achieved through promotion by $B(C_6F_5)_3$, leading to the 3-*O*-glycoside **108**

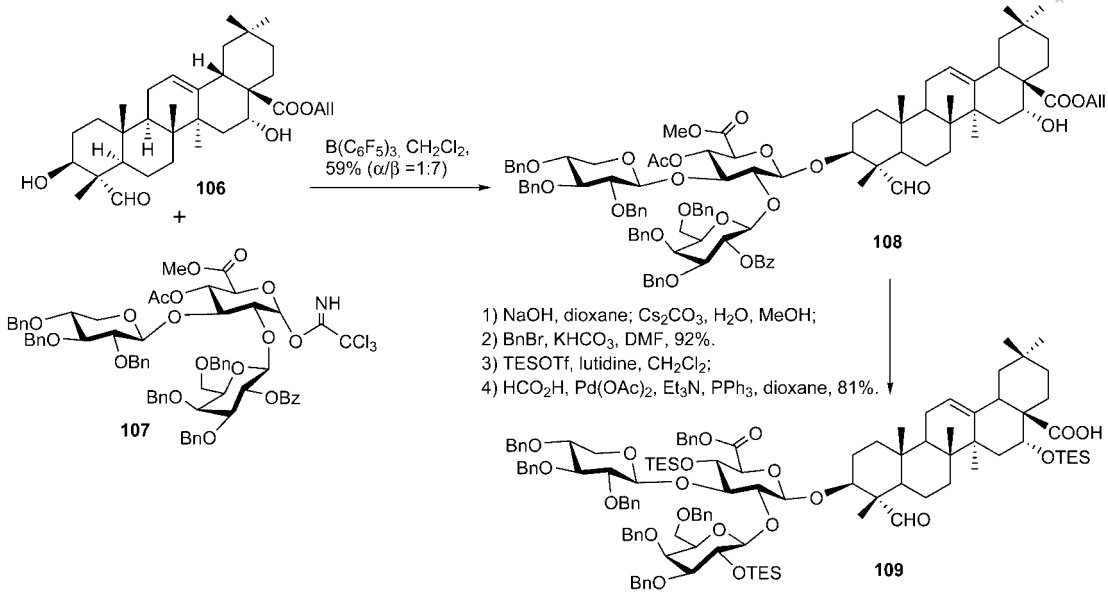



Scheme 17. Synthesis of a triterpene bisdesmoside **105** by successive glycosylation.

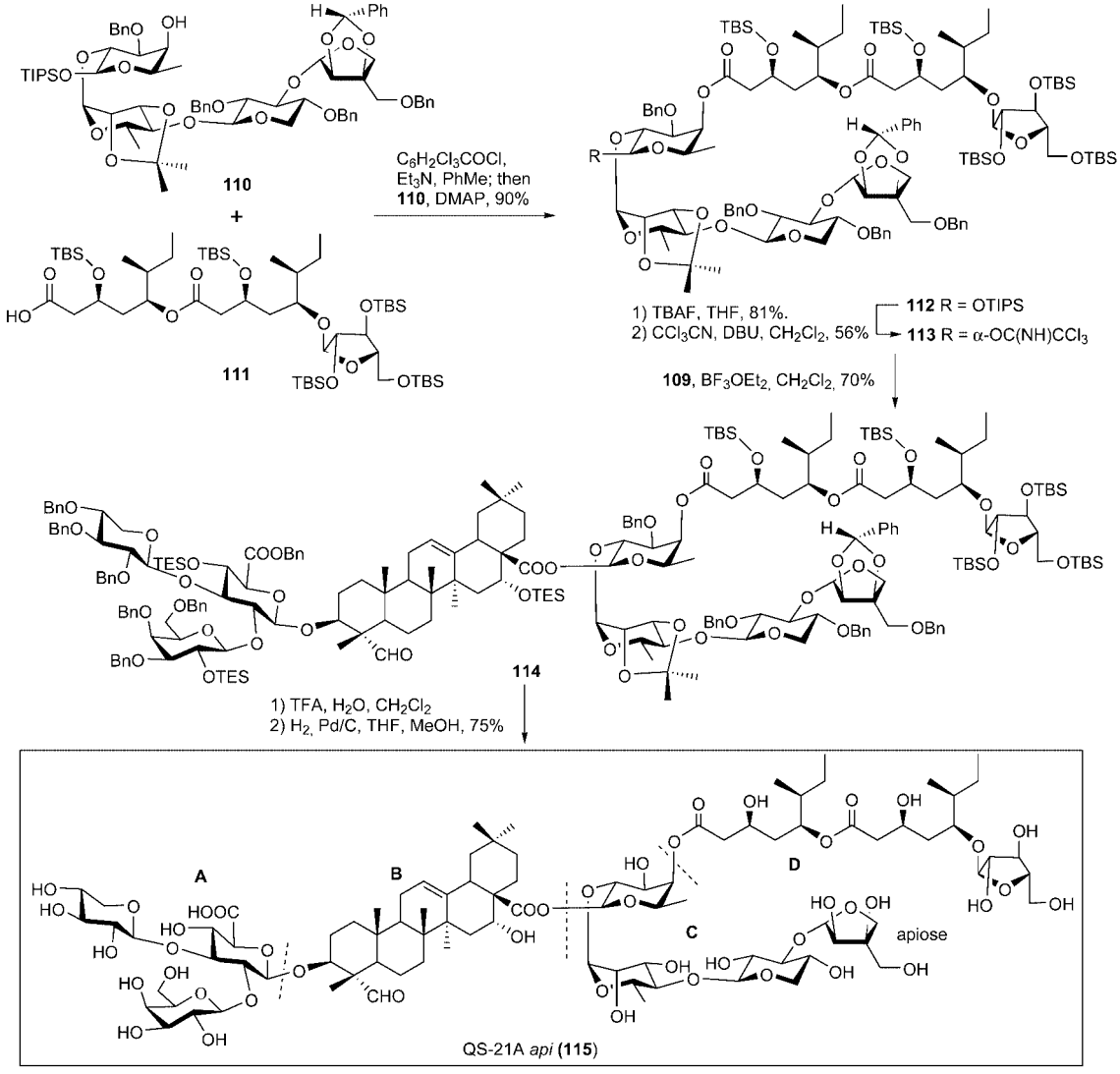
with a satisfactory β selectivity (β/α = 7:1) and in 59% yield (Scheme 18). The ester protecting groups were then converted into groups that are labile either to mild acid or to hydrogenolysis to facilitate the final global deprotection in the presence of the inherent acyl moiety of the target molecule; the 28-allyl ester was cleaved for the subsequent coupling (**108**→**109**).

Condensation of the tetrasaccharide derivative **110** (with only the 4-OH free) with acid **111** under Yamaguchi conditions provided sugar ester **112** in 90% yield (Scheme 19), and this was converted into the trichloroacetimidate **113** by selective removal of the anomeric *O*-TIPS group with TBAF in THF. Glycosylation of the acid **109** with the α-imidate **113** proceeded smoothly with $BF_3{\cdot}Et_2O$ promotion, affording the fully protected QS-$21_{api}$ **114** in a good 70% yield. Finally, the silyl groups (3×TES and 5×TBS) and the rhamnose 2,3-*O*-isopropylidene ketal were successfully cleaved with a 4:1 (v/v) mixture of trifluoroacetic acid




Scheme 18. Synthesis of QS-21A$_{api}$ (part I).




Scheme 19. Synthesis of QS-21A$_{api}$ (part II).

(TFA) and water at 0 °C, without compromising the glycosidic linkages, while the remaining twelve benzylic groups were removed with $H_2$ and Pd/C without reduction of the trisubstituted alkene in the triterpene, providing QS-$21_{api}$ (**115**) in 75% yield.

## 4. Summary and Outlook

Saponins are a structurally and biologically diverse class of glycosides of steroids and triterpenes that are widely distributed in terrestrial plants and in some marine organisms. A number of saponin extracts have long been used as significant folk medicines to treat various human ailments. Many homogeneous saponins with promising pharmaceutical and biological activities have also been identified. However, isolation of homogeneous saponins of various structures in appreciable amounts from the natural sources, where they exist in an extremely heterogeneous state, is, if not impossible, always a formidable task. Alternatively, chemical synthesis could provide a realistic way to determine the availability of homogeneous saponins, thus affording opportunities for understanding and applying this important group of natural products. The latter practice has been proven fruitful recently, as illustrated by the examples described in this article.

The achievements in the synthesis of the complex saponins reflect the advancements of contemporary synthetic carbohydrate chemistry. A variety of glycosylation protocols have been successfully applied to glycosidic couplings with the sophisticated steroid/triterpene substrates, including the use of glycosyl halides (chlorides **80** and **82**, bromide **88**, fluoride **10**), imidates (trichloroacetimidates 3, **15**, **26**, **30**, **36**, **97**, **100**, **107**, and **113**, trifluoroacetimidates **45** and **90**), a sulfoxide (**20**), a 1,2-epoxide (**59**), and thioglycosides (**49** and **70**). Of particular importance is the imidate protocol, which requires only a catalytic amount of the Lewis acid (usually TMSOTf or $BF_3OEt_2$) for promotion under very mild conditions and always leads to superior results than other protocols. Glycosyl donors possessing neighboring participating groups are always a safe choice for construction of the 1,2-*trans*-glycosidic linkages, always the natural linkages in saponins, in a stereocontrolled manner. Benzoyl groups (as in the donors **30**, **36**, **45**, **90**, **97**, and **100**) have proved superior for this purpose while minimizing orthoester formation and without compromising steric hindrance.[43] Glycosylation with a branched oligosaccharide donor (e.g., **26**, **70**, **107**, **113**) devoid of neighboring participation, which is always required in the convergent modular synthesis of saponins, to provide the desired 1,2-*trans*-glycoside with good selectivity is also possible, but judicious choice of the coupling conditions is required and the resulting anomers might be difficult to separate. The global protection/deprotection pattern is always critical for a total synthesis, but the glycosidic linkages (including the triterpene 28-ester linkages) in saponins are always stable enough to tolerate various conditions for common protecting group manipulations.

The synthetic routes toward certain saponins have been developed into practical and flexible processes, as illustrated by the syntheses of the antitumor active spirostan saponins (Scheme 8 and Scheme 9). In fact, a large number of the congeners of the spirostan saponins have been synthesized[44] and, in-depth studies on the structure/activity relationships and the mechanisms of action of saponins have therefore become undergoing projects.[45]

In conclusion, it should be noted that only very limited numbers of the natural saponins have been synthesized; many others, such as the starfish asterosaponins, featuring polyhydroxylated and unstable aglycons,[1,2] are still formidable targets waiting for creative efforts by synthetic chemists. On the other hand, it is the chemist's hope that studies in this direction should lead to the development of clinically approved synthetic saponin drugs.

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