Recent Progress in the Synthesis of Naturally Occurring Triterpenoid Saponins

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Abstract: This short review describes the recently reported semi- and total syntheses of naturally occurring triterpenoid saponins. Accent is placed on natural monodesmosidic and bidesmosidic saponins of the oleanane- and lupane-type that possess potent pharmacological properties including cytotoxic and antitumor activities.

Keywords: Natural products, Saponins, Triterpenes, Chemical synthesis, Cytotoxic, Anticancer.

1. INTRODUCTION

Saponins are a specific class of secondary metabolites widely distributed in the plant kingdom, which consist of a triterpenoid or steroid skeleton bearing one (monodesmoside) or more (bidesmoside, tridesmoside) sugar chains. Sugar moieties found in naturally occurring saponins are quite diversified, but usually consist of D-glucose, D-galactose, D-xylose, D-fucose, L-rhamnose, L-arabinose and D-glucuronic acid [1]. Historically, the name "saponin" comes from the Latin word *sapo*, which means "soap" since these natural products usually form soapy lathers when mixed with water [2]. The great structural diversity of saponins may be explained by their various biosynthetic origins. Indeed, the biosynthesis of saponins starts with the cyclization of the C-30 oxidosqualene followed by linkage with diverse sugar moieties catalyzed by enzymes such as glycosyltransferases and glycosidases. Subsequently, further biosynthetic modifications such as minor rearrangements, degradations, oxidations, methylations and/or esterifications greatly increase structural diversity [3]. Since the development of high field NMR allowing the elucidation of complex chemical structures [4-6], thousands of saponins have been isolated and identified [7]. It is estimated that more than half of terrestrial plants may contain saponins. Several species widely used in traditional Chinese medicine such as ginseng (*Panax ginseng*) and liquorice (*Glycyrrhiza glabra*) are rich in saponins, especially those having a triterpenoid aglycone [8]. Thus, some authors consider them responsible, along with polyphenols, for the majority of medicinal effects observed in Chinese medical literature [9].

The biological and pharmacological properties exhibited by saponins are quite diversified (haemolytic, cytotoxic, antitumor, anti-inflammatory, molluscicidal, etc.) and have been extensively reviewed over the past few years [10-15]. However, the haemolytic activity of most of the saponins is a major drawback for their clinical development. The exact mechanism of the rupture of red blood cell membranes (hemolysis) induced by saponins is not yet clearly understood, but found to be linked to their amphiphilic and surfactant properties [12]. In the domain of cancer research, saponins have attracted increased attention since several naturally occurring saponins have been shown to induce both cycle arrest and apoptosis within cancerous cells via the mitochondrial pathway, and to exhibit promising *in vivo* antitumor activity [15-18].

The isolation of saponins from plant or animal extracts is often a long and fastidious process involving many purification steps and usually only small amounts of products are obtained in a pure and homogeneous form [1]. Therefore, chemical syntheses appear to be a rational way to gain access to adequate amounts of saponins in order to promote further pharmaceutical studies. In the past few years, two excellent reviews have been published dealing with the synthesis of saponins with an emphasis on the glycosylation of steroids [19,20]. However, to our knowledge, this is the first review devoted to the synthesis of naturally occurring triterpenoid saponins. Hence, this paper summarizes, in the following sections, the recent advances in the field of the semi- and total synthesis of biologically active oleanane- and lupane-type triterpenoid saponins with a major accent regarding saponins that possess cytotoxic and/or antitumor properties.

2. SYNTHESIS OF MONODESMOSIDIC SAPONINS

In the early 1980's, the scientific community demonstrated a renewal of interest toward the synthesis of monodesmosidic saponins. At this time, most of the syntheses involved the use of peracetylated sugars activated through the formation of glycosyl halides such as bromides [21,22] or fluorides [23]. The generally low yields and the use of expensive and toxic silver or mercury salts as promoters of the coupling reaction are the major inconveniences of this so-called Koenigs-Knorr [24] glycosylation method. Alternatively, towards the end of the 1990's, Professor Biao Yu and his coworkers [25] reported a highly efficient procedure to prepare steroid and triterpenoid saponins via Schmidt's trichloroacetimidate (TCA) activated sugars [26]. Interestingly, the authors showed that perbenzoylated TCA sugar donors can react in high yields with diverse sapogenins such as diosgenin, cholesterol, dehydroisoandrosterone, pregnadiene and allyl oleanate (**1**) under the catalytic promotion of the Lewis acid trimethylsilyl trifluoromethanesulfonate (TMSOTf); the use of boron trifluoride diethyletherate ($BF_3.OEt_2$) instead of TMSOTf led to a complex mixture of products. For example, coupling of allyl oleanate (**1**) with 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate (**2**) in the presence of 0.05 equiv of TMSOTf led to the formation of the desired protected glycoside **3** in a pure β-anomeric linkage (Scheme **1**). Indeed, it is worth noting that the C-2 neighboring participating benzoyl group of the TCA sugar donor resulted in the exclusive formation of a 1,2-*trans* glycosidic bond [19]. Since the publication of this important paper, the TCA mediated glycosylation method has been used extensively. Today, it appears to be one of the most ideal procedures for the synthesis of triterpenoid saponins [20], as shown in the examples below.

2.1. Arabinose-Containing Monodesmosidic Saponins

2.1.1. Hederagenin Saponins

δ-Hederin (**7**), also known as koelreuteria saponin A, is a naturally occurring triterpenoid saponin having hederagenin as the aglycone and containing an α-L-arabinose sugar moiety. This molecule is widely distributed in nature [27] and exhibits potent molluscicidal [28], cytotoxic [29] and haemolytic [30] activities. Hederagenin cellobioside (**8**), namely hederagenin 3-*O*-β-D-glucopyranosyl-(1→4)-β-D-glucopyranoside, is another similar but less

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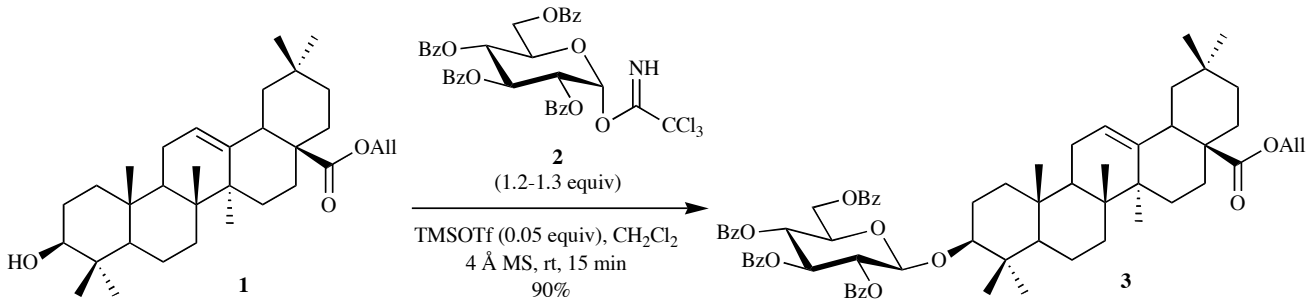
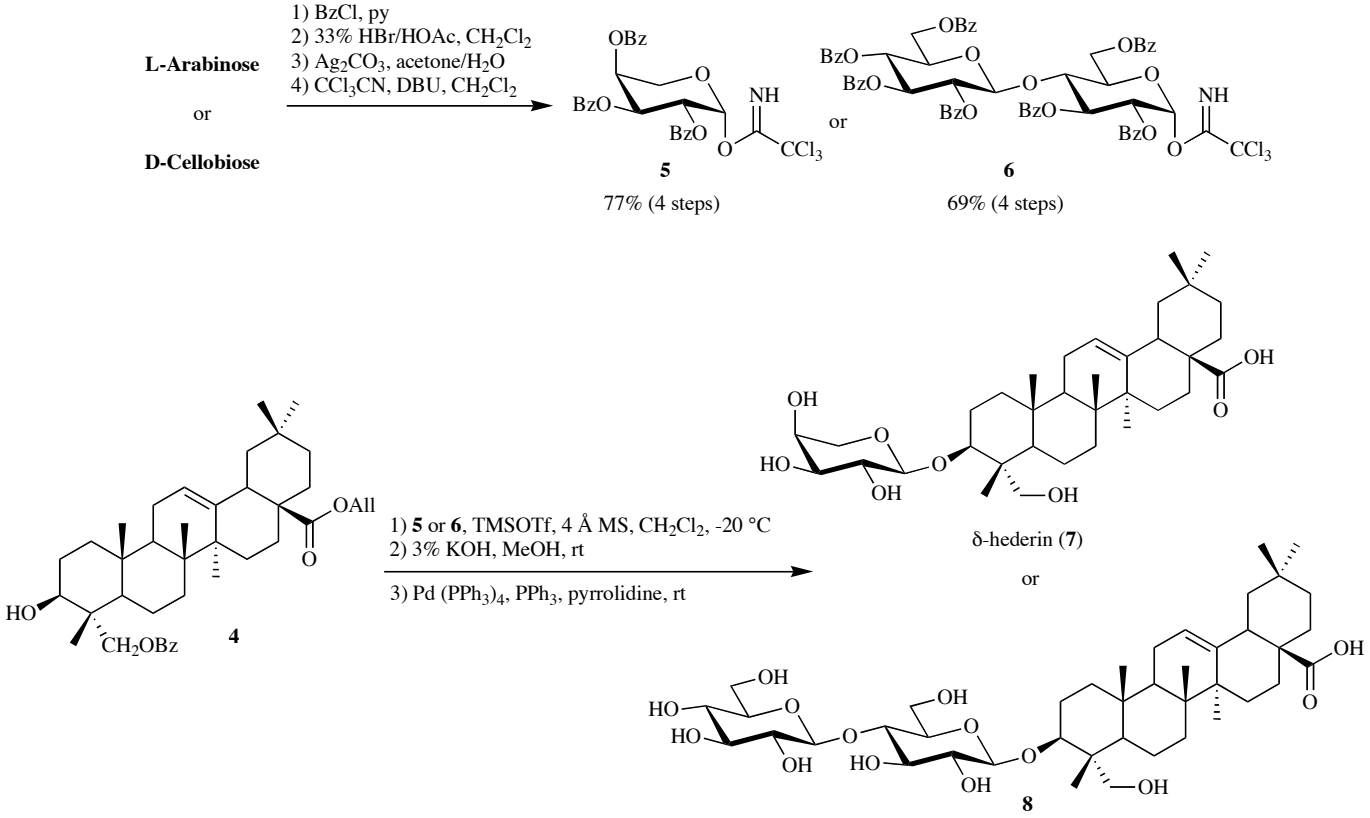


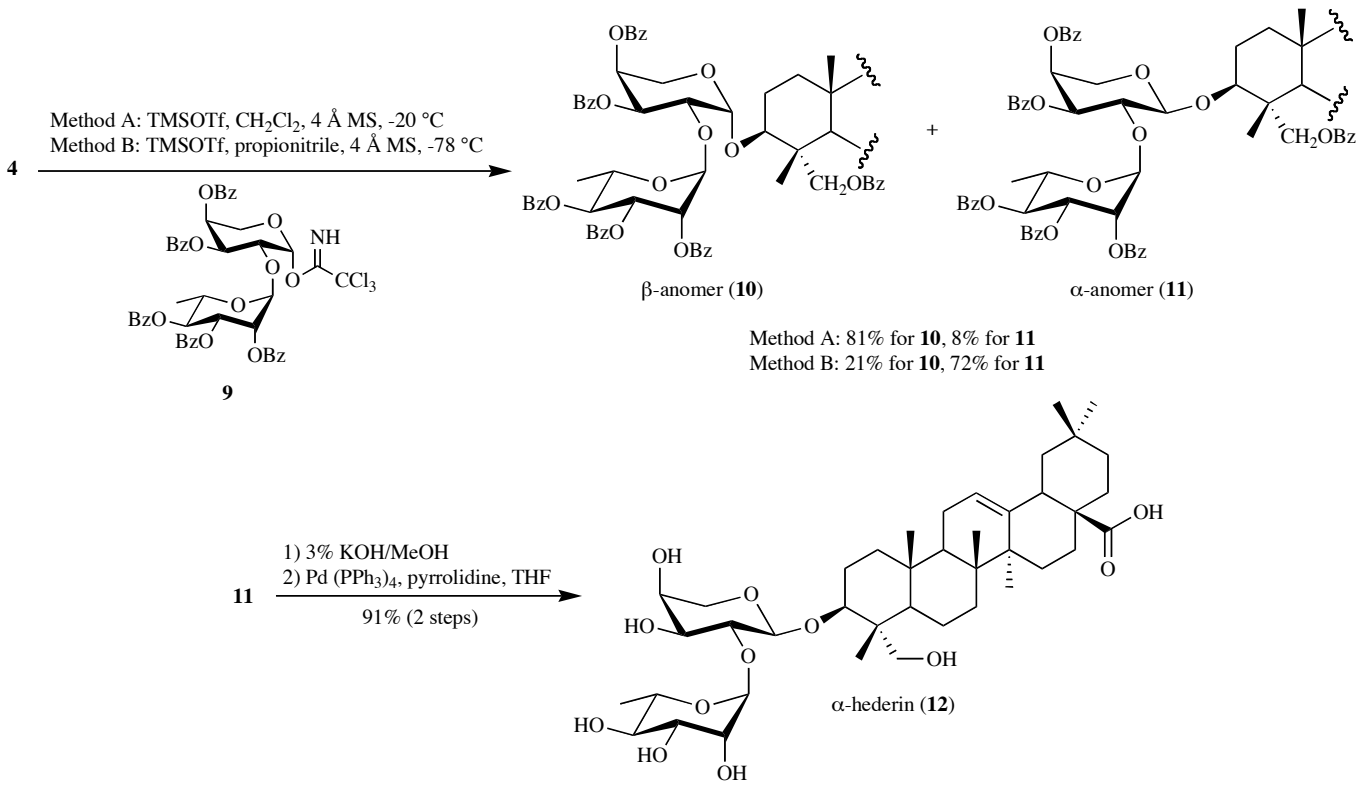
Scheme 1. Synthesis of a benzoylated oleanolic acid saponin (**3**) via Schmidt's glycosylation [25].



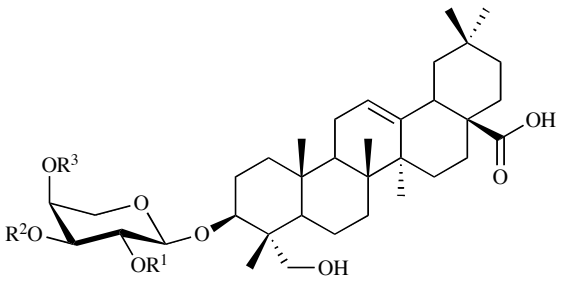
Scheme 2. Synthesis of δ-hederin (**7**) and cellobioside hederagenin saponin (**8**) [33,34].

frequent triterpenoid saponin isolated from *Fatsia japonica* and *Barbarea vulgaris* [31]. The latter possesses feeding deterrent activity against the larvae of *Plutella xylostella* [32]. The synthesis of these two natural bioactive saponins was reported in 2004 by the group of Voutquenne-Nazabadioko and co-workers [33,34]. As depicted in Scheme **2**, the commercially available L-arabinose and D-cellobiose were converted into the corresponding perbenzoylated TCA sugar donors **5** and **6** in 77% and 69% overall yields, respectively, and coupled with the acceptor **4** in the presence of TMSOTf at low temperatures (-20 °C). The further deprotection of benzoyl and allyl groups led to the formation of the target hederagenin saponins **7** and **8**.

α-Hederin (**12**), namely hederagenin 3-*O*-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside and also known as kalopanaxsaponin A or sapindoside A, is a naturally occurring triterpenoid saponin recognized as the active principle of several plant species [35-37]. Recent antitumor *in vivo* studies demonstrated that treatments with α-hederin (**12**) may significantly increase the life expectancy of tumour-bearing mice [38-40]. The antimutagenic activity of α-hederin (**12**) was also confirmed against aflatoxin-, doxorubicin- and carbendazime-induced clastogenesis in mice [41,42]. Moreover, α-hederin (**12**) possesses a hemolytic activity stronger than the commercial saponin mixture sold by Sigma® [30]. In 2004, Plé *et al*. [34] reported the preparation of α-hederin (**12**) starting from hederagenin. The convergent synthetic route of this natural compound is outlined in Scheme **3**. The synthesis started by reacting the fully benzoylated TCA disaccharide donor **9** with the acceptor **4** in the presence of TMSOTf at low temperature (-20 °C). Unfortunately, since the disaccharide donor lacking a participating ester group at the C-2 position, an α,β-anomeric mixture (**10** and **11**) was obtained with the non-natural β-anomer (**10**) as the major compound (81%, method A). The use of propionitrile, which is known to promote the formation of an equatorial glycosidic bond [43], at a cryogenic temperature (-78 °C) instead of dichloromethane (CH_2Cl_2) as the solvent of the reaction led to the desired α-anomer (**11**) as the major compound of the glycosylation reaction (72%, method B). Finally, the glycoside **11** was subjected to deprotection to furnish α-hederin (**12**) in excellent yield (91%) after two



Scheme 3. Synthesis of α-hederin (**12**) by a convergent glycosylation approach [34].



13 R^1 = Xyl, R^2 = R^3 = H
14 R^1 = Glc, R^2 = R^3 = H
15 R^1 = H, R^2 = Xyl, R^3 = H
16 R^1 = H, R^2 = Glc, R^3 = H
17 R^1 = R^2 = H, R^3 = Glc

Fig. (1).

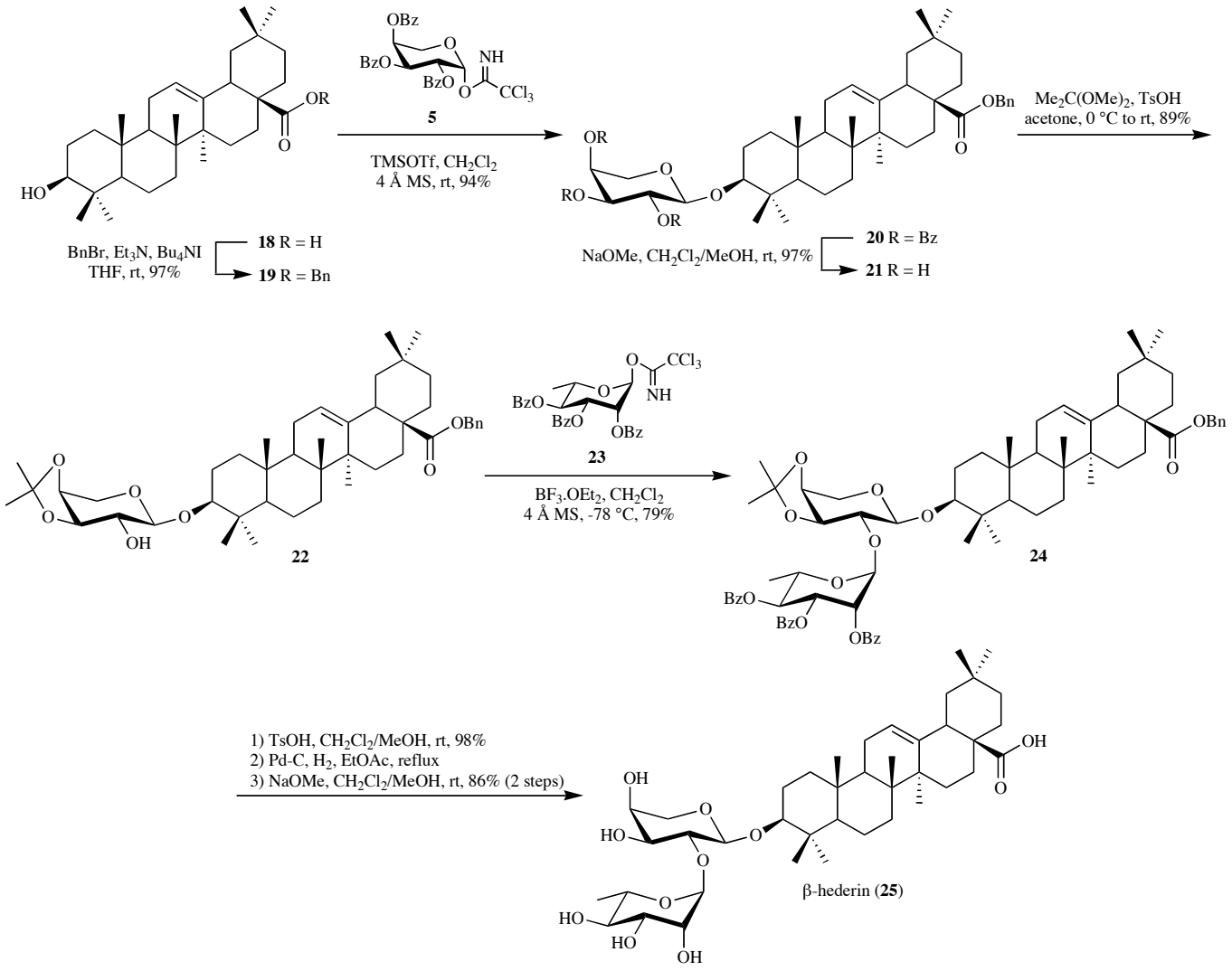
steps. It is noteworthy that a similar glycosylation method has been successfully applied by Plé *et al*. [44] to the synthesis of natural and unnatural L-arabinopyranose containing hederagenin saponins (**13**-**17**, Fig. **1**).

2.1.2. Oleanolic Acid Saponins

In 2006, Cheng *et al*. reported the synthesis of β-hederin (**25**), a naturally occurring oleanolic acid saponin, via a linear glycosylation approach [45]. This saponin is an attractive target in view of its strong cytotoxic activity against various human cancer cell lines [36,46]. Structurally, β-hederin (**25**), namely oleanolic acid 3-*O*-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside, is similar to α-hederin (**12**), the only difference being the C-23 hydroxyl group not present in β-hederin (**25**). As shown in Scheme **4**, the synthesis of β-hederin (**25**) started with the benzyl ester **19** obtained in excellent yield (97%) after the protection of the C-28 carboxylic acid function of oleanolic acid (**18**). Thereafter, the tion of oleanolic acid (**18**). Thereafter, the glycosylation of the L-arabinosyl TCA donor **5** with the benzyl ester **19** under the promotion of TMSOTf led to the formation of the fully protected arabinoside **20** (94%). Deprotection of the benzoyl groups followed by regioselective protection of C-3 and C-4 hydroxyl groups of the arabinose moiety afforded **22**, which was then coupled with the rhamnosyl TCA donor **23** using $BF_3.OEt_2$ as promoter at a cryogenic temperature (-78 °C) to give the branched diglycoside **24** in good yield (79%). Finally, the cleavage of the isopropylidene, benzyl and benzoyl protecting groups afforded β-hederin (**25**).

The same group undertook the synthesis of hederacolchiside A_1 (**29**) since this saponin and β-hederin (**25**) have similar structures consisting of an additional D-glucose moiety at the C-4 position of the arabinose residue. Hederacolchiside A_1 (**29**) is a natural triterpenoid saponin known for its capacity to permeabilize and to form pores within biological membranes [47,48], which is related to its strong antitumor activity both *in vitro* and *in vivo* [36,40]. Moreover, another study highlighted the apoptosis inducing activity of saponin **29** in HL-60 cells [49]. As depicted in Scheme **5** [45], the synthesis of hederacolchiside A_1 (**29**) began with the cleavage of the isopropylidene group of the fully protected saponin **24** to give **26** in an almost quantitative yield. Afterwards, a series of protection-deprotection reactions led to the derivative **27** bearing a free hydroxyl group at the C-4 position of the arabinose moiety. The glycoside **27** was then coupled with the glucosyl TCA donor **2** under the standard TMSOTf promotion to furnish **28** (71%) in which the protecting groups were finally cleaved to afford pure hederacolchiside A_1 (**29**).

Recently, Yan *et al*. have described a shorter route to the synthesis of saponin **29** [50]. As depicted in Scheme **6**, the diol **26** was directly coupled with the TCA donor **2** under standard glycosylation conditions at room temperature to give **30** in good yield (65%). The regioselectivity of the reaction was confirmed by 2D NMR. It is noteworthy that the $^1C_4$ chair conformation instead of the $^4C_1$ one was observed for the protected saponins **26** and **30** as revealed by



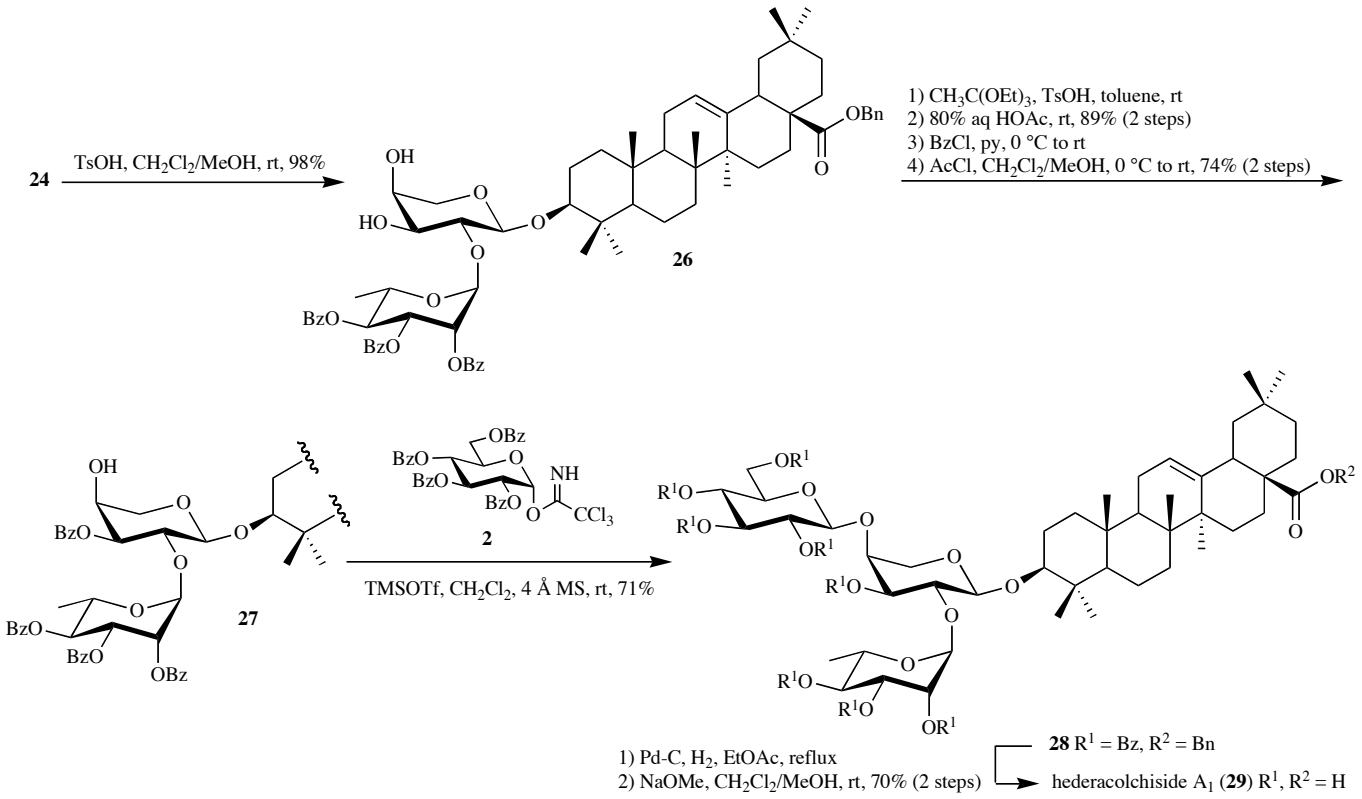
Scheme 4. Synthesis of β-hederin (**25**) by a linear glycosylation approach [45].

the unusual coupling constants of the anomeric protons ($J_{1,2}$ = 1.3 and 3.5 Hz, respectively). After the deprotection of the benzoyl and benzyl groups, hederacolchiside A_1 (**29**) was obtained in excellent yield (89%, two steps) and the arabinose residue returned to the normal $^4C_1$ chair conformation.

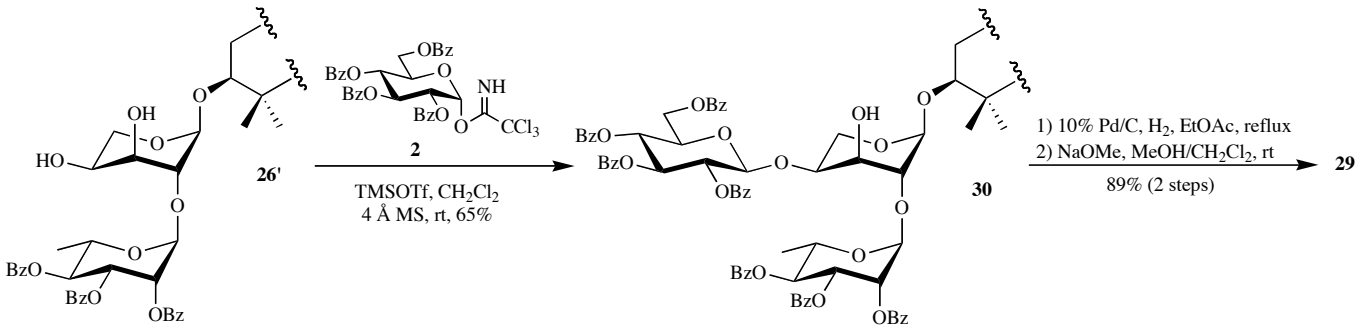
The trisaccharide chain at the C-3 position of hederacolchiside A_1 (**29**), namely α-L-rhamnopyranosyl-(1→2)-[β-D-glucopyranosyl -(1→4)]-α-L-arabinopyranose, is considered to be a unique sugar moiety increasing both the antitumor activity and the water solubility of oleanolic acid saponins [40]. For these reasons, Bang *et al.* undertook the synthesis of both the sugar moiety (**31**) of hederacolchiside A_1 (**29**) [51] and the disaccharide section (**32**) of α-hederin (**12**) [52] (Fig. **2**). These sugar moieties could be further converted into TCA donors and coupled with various bioactive compounds in order to increase their activity and water solubility.

2.2. *N*-Acetylglucosamine-Containing Saponins

Triterpenoid saponins containing an *N*-acetylglucosamine moiety are very scarce in nature. However, quite a number of these saponins were found to exhibit highly potent cytotoxic activity. Saponin **33** (Fig. **3**), namely oleanolic acid 3-*O*-α-L-arabinopyranosyl-(1→2)-α-L-arabinopyranosyl-(1→6)-2-acetamido-2-deoxy-β-D-glucopyranoside, represents a typical example of this particular class of naturally occurring glycosides. This saponin isolated from the rainforest plants *Acacia tenuifolia* and *Albizia subdimidiata* exhibits strong cytotoxic activity against A2780 and M109 lung cancer cell lines (IC_{50} 0.9 and 1.1 μM, respectively) [53,54]. In 2003, Sun and co-workers reported the first synthesis of this structurally unique saponin (**33**) [55]. As depicted in Scheme **7**, the synthesis started with the glycosylation between allyl oleanate (**1**) and 2-deoxy-2-phthalimido-D-glucopyranosyl trifluorophenylacetimidate (TFPA) (**34**) in the presence of the Lewis acid TMSOTf to afford quantitatively the desired glycoside **35**. Cleavage of the acetates using 3% HCl in MeOH (**36**, 91%) followed by regioselective tritylation of the C-7 hydroxyl group and acetylation of other alcohols led to the formation of the protected glycoside **37** (90%). The latter was then coupled to the C-6 position with the activated thioglycoside **38** under the simultaneous promotion of *N*-iodosuccinimide (NIS) and TMSOTf to afford **39** (76%) in which the levulinoyl (Lev) group was selectively removed using hydrazine acetate (NH_2NH_2-HOAc). Thereafter, the glycoside **40** bearing a free hydroxyl group at the C-2 position of the arabinose moiety was glycosylated with the TFPA sugar donor **41** in the presence of TMSOTf to furnish **42** in good yield (76%). Finally, the cleavage of all protecting groups led to the formation of the natural saponin **33**. It is worth noting that the same synthetic route was recently used by Wang *et al.* to prepare a non-natural derivative of ursolic acid bearing this particular trisaccharide residue [56].



Scheme 5. First synthesis of hederacolchiside A_1 (**29**) [45].



Scheme 6. Second synthesis of hederacolchiside A_1 (**29**) [50].

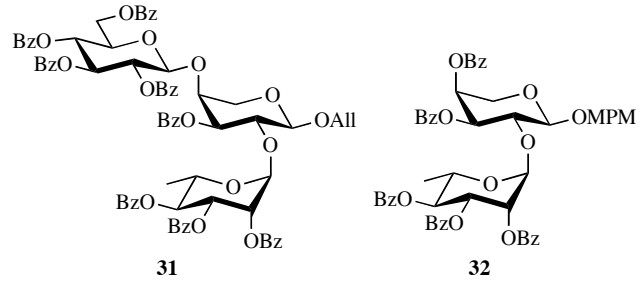


Fig. (2).

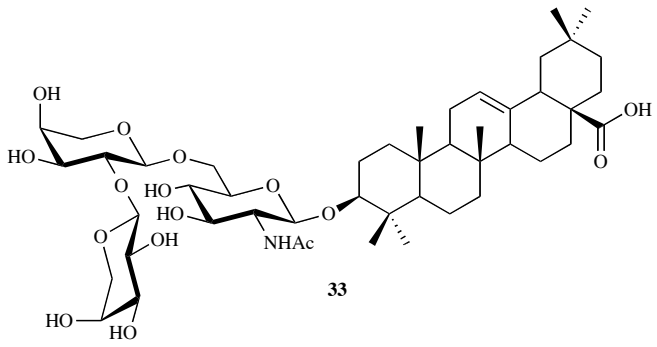
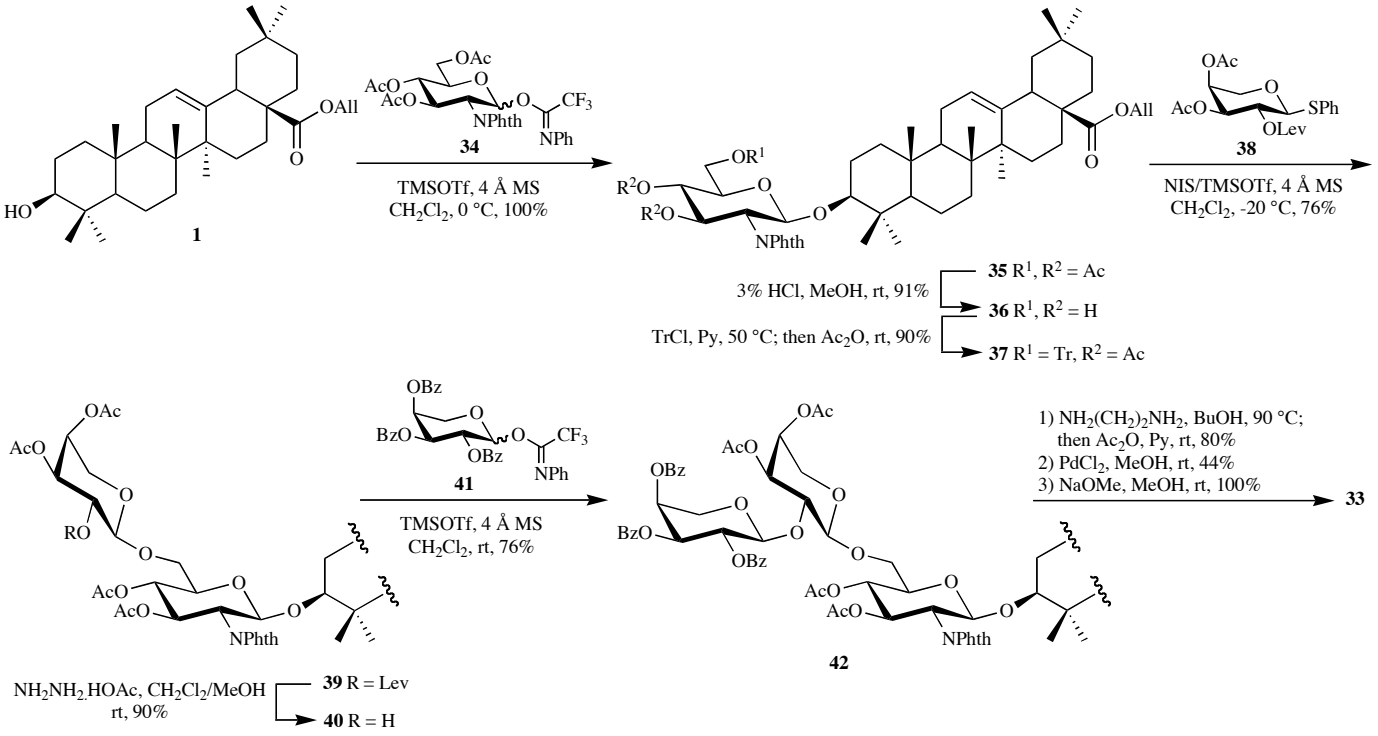


Fig. (3).

Lotoidoside D (**43**) and E (**44**) (Fig. **4**) are two other examples of *N*-acetylglucosamine-containing saponins. These saponins were isolated in very low yields from the roots of the medicinal plant *Glinus lotoides* growing in Egyptian desert [57]. In view of their highly potent anticancer activity against murine fibrosarcoma cell lines (WEHI-164) [57], Yan *et al*. achieved the synthesis of these naturally occurring saponins as outlined in Scheme **8** [58]. Thus, glycosylation of the C-28 benzyl ester **19** of oleanolic acid (**18**) with 2-phthalimido-2-deoxyglucosyl TCA donor **45** under the promotion of TMSOTf led to the formation of **46** in excellent yield



Scheme 7. Synthesis of a *N*-acetylglucosamine containing oleanolic acid saponin (**33**) [55].

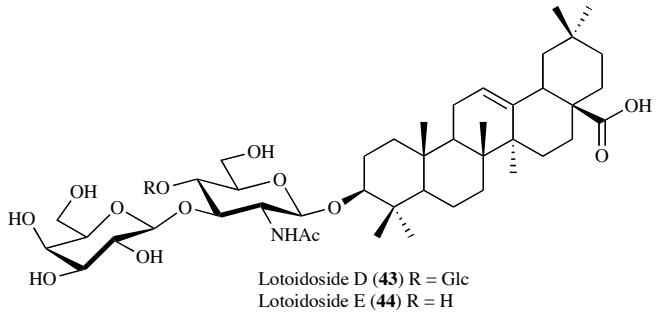


Fig. (4).

(96%). The latter was then treated with hot ethylenediamine/butanol and Ac_2O followed by NaOMe/MeOH to furnish **47** in which the C-2, C-3 and C-4 hydroxyl groups of the glucose moiety were unprotected. The glycoside **47** was converted to the corresponding benzylidene **48** using $PhCH(OMe)_2$ and DL-camphorsulfonic acid (CSA), which was coupled with the galactose TCA donor **49** under standard glycosylation conditions to afford **50** (69%). Deprotection of the benzyl, benzylidene and benzoyl groups finally led to the formation of lotoidoside E (**44**). In another experiment, the benzylidene of the fully protected glycoside **50** was cleaved using Et_3SiH-BF_3.OEt_2 to give **51**, which was then coupled with the glucosyl TCA donor **52** in the presence of TMSOTf to afford **53** (66%). Lotoidoside D (**43**) was obtained after cleavage of all the protecting groups of the derivative **53**.

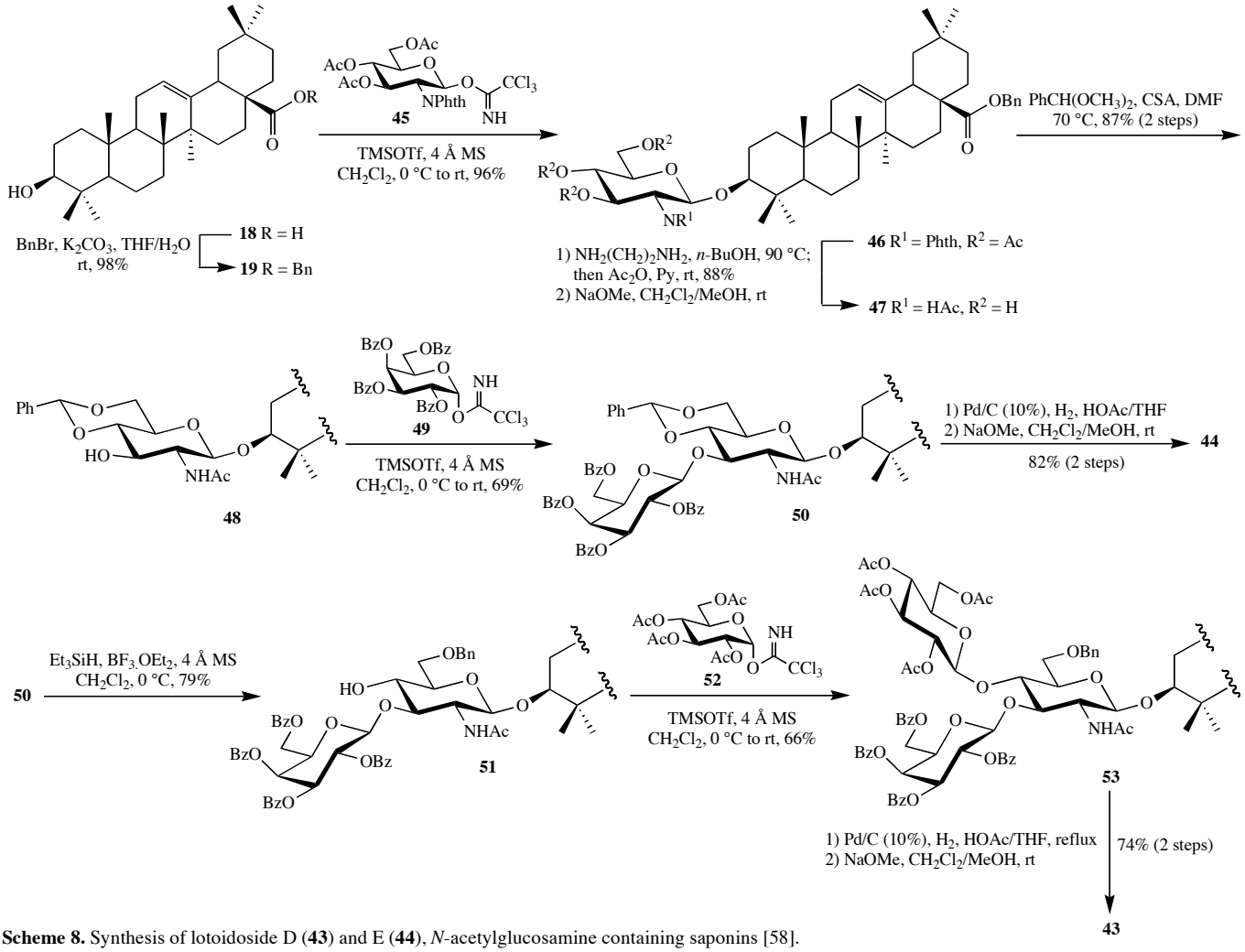
3. SYNTHESIS OF BIDESMOSIDIC SAPONINS

3.1. Arabinose-Containing Bidesmosidic Saponins

Bidesmosidic saponins, that is, triterpenoids or steroids bearing two distinct sugar chains, are pharmacologically quite attractive compounds since they are known to exhibit weaker haemolytic activity than corresponding monodesmosidic saponins [59]. The first synthesis of a bidesmosidic saponin having a triterpenoid aglycone was reported in the late 1990's by Yu and co-workers [60]. By the use of one-pot successive glycosylations, the preparation of the naturally occurring bidesmoside **62** isolated from the leaves of *Acanthopanax senticosus* [61], a Chinese medicinal herb, was straightforward and gave high yields. As shown in Scheme **9**, glycosylation at low temperatures (-60 °C) of trityl oleanate (**54**) and the arabinosyl TCA donor **5** promoted by TMSOTf followed by a 20 minutes elevation of temperature led to the derivative **55**, which was immediately treated with the glucosyl TCA donor **56** to afford the protected bidesmoside **57**. In another flask, the phenyl thiodisaccharide **59** as acceptor was glycosylated with the TCA donor **58** in the presence of TMSOTf to give **60**, which was subsequently coupled with **57** by dropwise addition to the first flask. The resulting bidesmoside **61** bearing a particular α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl at the C-28 position was then deprotected to give the natural saponin **62** in excellent yield (45%) after only two silica gel chromatographic separations.

In 2005, Wang *et al*. reported the synthesis of two naturally occurring bidesmosidic saponins (**63** and **64**) both containing an arabinose moiety (Fig. **5**) [62]. These compounds isolated from the medicinal plants *Fagonia indica* [63] and *F. arabica* [64] featured ursolic acid (**65**) as the aglycone, which is well known for its anticancer and anti-inflammatory properties [65]. The synthesis of saponin **64** (Scheme **10**) began by coupling ursolic acid (**65**) with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**66**) under modified phase-transfer conditions to afford almost quantitatively the acyl glycoside **67** (99%). Thereafter, glycosylation of **67** with the particular TCA disaccharide **68** in the presence of TMSOTf led to the bidesmoside **69** in excellent yield (88%). Regioselective deprotection of the Lev group using NH_2NH_2-HOAc furnished **70**, which was coupled with the xylosyl TCA donor **71** (97%) under standard glycosylation conditions. The target natural saponin **64** was then obtained in excellent yield (98%) after the cleavage of all protecting groups. It is noteworthy that a similar glycosylation protocol was used to achieve the synthesis of saponin **63** [62].

Bidesmosidic saponins **72** and **73** (Fig. **6**) are two other natural products having oleanolic acid as the aglycone, which were isolated



Scheme 8. Synthesis of lotoidoside D (**43**) and E (**44**), *N*-acetylglucosamine containing saponins [58].

from the spiny shrub *F. indica*, a folk medicine widely distributed in Egypt and Pakistan [63]. Recently, Li *et al*. reported the preparation of these two natural saponins [66]. The synthetic route of saponin **73**, namely 28-*O*-β-D-glucopyranosyl oleanolic acid 3-*O*-β-D-glucopyranosyl-(1→2)-[α-L-arabinopyranosyl-(1→3)]-α-L-arabinopyranoside, is outlined in Scheme **11**. Firstly, trityl oleanate (**54**) was coupled with the TCA sugar donor **5** under the promotion of TMSOTf from -60 °C to room temperature to provide the monodesmoside **55** (89%). After the deprotection of benzoyl groups (→**74**) and isopropylidenation of C-3' and C-4' alcohols, the acceptor **75** was simultaneously glycosylated with the TCA sugar donor **2** at both C-28 and C-2' positions to afford **76** in excellent yield (88%). Afterwards, the deisopropylidenation of derivative **76** was achieved followed by the regioselective acetylation of the C-4' hydroxyl group. The resulting acceptor **77** was then coupled with the TCA sugar donor **5** in the presence of $BF_3.OEt_2$ to give **78** (95%), which was subsequently deprotected in good yield (83%). Interestingly, the authors pointed out that the terminal arabinose residue in natural saponin **73** took the $^1C_4$ chair conformation instead of the typical $^4C_1$ form even after treatment with high temperature. It is worth noting that such a phenomenon was recently observed for natural saponins isolated from *Stryphnodendron fissuratum* bearing a terminal arabinose moiety [67].

3.2. Synthesis of Flaccidoside II

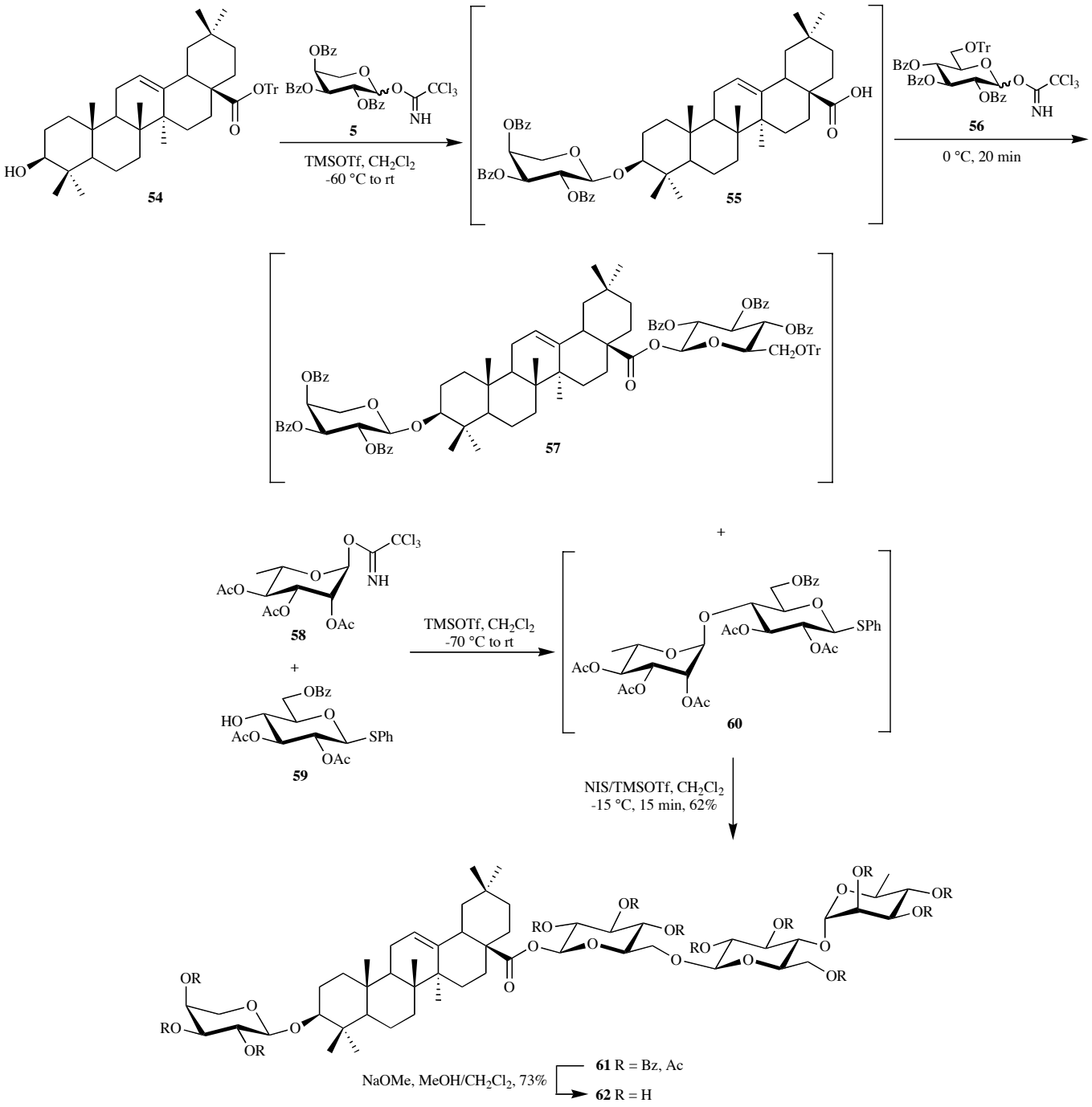
The dry rhizome of *Anemone flaccida* called "Di Wu" is used in China as a folk medicine for detoxication [68]. Studies have revealed that triterpenoid saponins are the main active principles of "Di Wu". Flaccidoside II (**85**) is a bioactive bidesmosidic saponin, which was isolated from the alcohol extracts of *A. flaccida* [69]. Recently, Cheng *et al*. reported the synthesis of flaccidoside II (**85**) by using a partially protected thioglycosyl donor (**79**) that significantly improved the synthetic route [70]. As depicted in Scheme **12**, trityl oleanate (**54**) was glycosylated with the thioglycosyl donor **79** under the simultaneous promotion of NIS and TMSOTf in good yield (70%). The resulting glycoside **80** was then coupled with the TCA sugar donor **23** to afford **81** (75%), which was treated with 80% aqueous HOAc in order to cleave the trityl ester group. Coupling of the acceptor **82** with the trisaccharide TCA donor **83** formed the protected bidesmosidic saponin **84** (78%). Finally, deprotection of **84** using alkaline hydrolysis led to the formation of pure flaccidoside II (**85**).

3.3. Glucuronide-Containing Saponins

The isolation of saponins bearing a glucuronide moiety directly linked to the C-3 position of the aglycone has been frequently reported in the literature [71]. In this section, the following examples are exclusively devoted to the total synthesis of these natural products, which exhibited diverse pharmacological properties.

3.3.1. Synthesis of Ginsenoside Ro

Ginsenoside Ro (**87**), namely 28-*O*-β-D-glucopyranosyl oleanolic acid 3-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucuronopyranoside, and the structurally similar bidesmoside **86** are two typical examples of the family of naturally occurring glucuronide-containing saponins (Fig. **7**). Although saponin **86** demonstrated highly cyto-



Scheme 9. First synthesis of a bidesmosidic triterpenoid saponin (**62**) by one-pot glycosylation [60].

toxic activity against KB and Hela-S_3 human cancer cell lines [72], ginsenoside Ro (**87**) showed no haemolytic or cytotoxic activities [73]. However, ginsenoside Ro (**87**), which has been isolated principally from plants of the *Panax* species [74], demonstrated significant anti-thrombic, anti-inflammatory and anti-hepatitis activities [75-77]. In 2004, Peng *et al*. reported the straightforward preparation of both of these natural saponins via a synthetic route that featured the elaboration of the glucuronide residue at a later stage of the synthesis using the TEMPO-mediated selective oxidation [78,79]. Scheme **13** presents the synthetic route leading to the preparation of ginsenoside Ro (**87**) [79]. Thus, 28-*O*-*tert*-butyldiphenylsilyl oleanolic acid (**88**) was easily converted to glycoside **90** (87%) by coupling with the TPFA sugar donor **89** in which the 2-*O*-2-(azidomethyl)benzoyl (AZMB) group was present at the C-2 position. Removal of *tert*-butyldiphenylsilyl (TBDPS) ester and AZMB protecting groups led to the formation of the partially protected monodesmoside **91**, which was then simultaneously glycosylated at both the C-28 and C-2' positions to give bidesmoside **93**. Thereafter, selective cleavage of acetyl groups in **93** was achieved in the presence acetyl chloride (AcCl). The C-6' primary alcohol in the resulting **94** was subsequently regioselectively oxidated using the TEMPO-KBr-$Ca(ClO)_2$ oxidative system [80]. Deprotection of pivaloyl and benzoyl groups finally provided the target ginsenoside Ro (**87**).

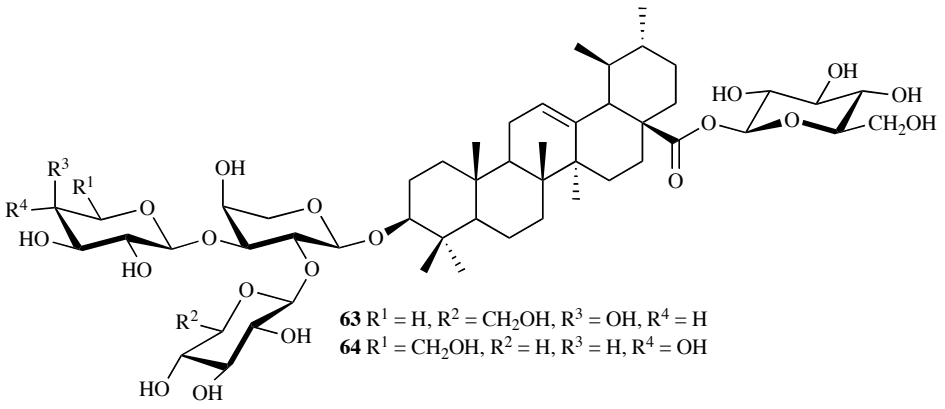
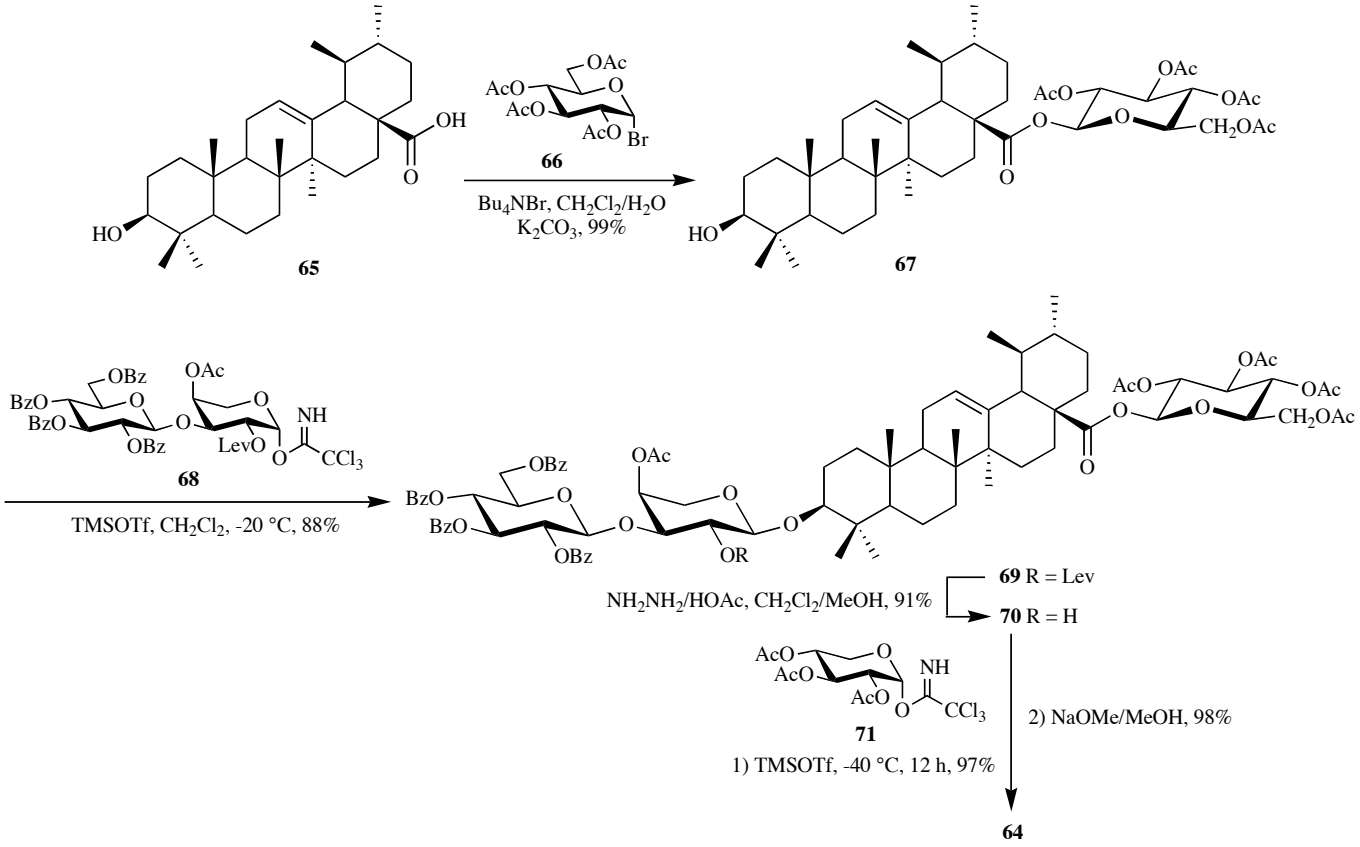


Fig. (5).



Scheme 10. Synthesis of a bidesmosidic ursolic acid saponin (**64**) [62].

3.3.2. Synthesis of Betavulgaroside III

Betavulgaroside III (**98**) is a rare member of the triterpene *seco*-glycosides family, which feature an oxidative fragmentation of the terminal monosaccharide moiety. It is interesting to note that this natural saponin firstly isolated from the sugar beet *Beta vulgaris* [81] is able to mimic the sialyl Lewis X (sLe^x) structure, a tetrasaccharide playing a vital role in cell-cell recognition processes [82]. Recently, the preparation of betavulgaroside III (**98**) was achieved by Zhu *et al.* via a convergent glycosylation approach [83]. As shown in Scheme **14**, the first step of the synthetic route consisted in reacting oleanolic acid (**18**) with the glucosyl bromide **66** under phase-transfer conditions. The resulting acyl glycoside **95** (78%) was then coupled with the particular TCA sugar donor **96** in the presence of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf). It is noteworthy that the sugar derivative **96** was synthesized in several steps from the commercially available D-glucose and L-arabinose. The principal steps of these transformations were the oxidative cleavage of the terminal arabinose residue by treatment with sodium periodate ($NaIO_4$) followed by further oxidation using sodium chlorite ($NaClO_2$) and sulfamic acid (NH_2SO_3H). Finally, after the cleavage of all protecting groups in **97**, betavulgaroside III (**98**) was obtained in excellent yield (85%, two steps).

3.3.3. Total Synthesis of QS-21-Api

QS-21-Api (**99**) and QS-21-Xyl (**100**) were identified in the semi-purified extract of the South American tree *Quillaja saponaria* (Fig. **8**) [84]. These complex bidesmosidic glucuronide-containing saponins are the principal constituents found in the adjuvant-active fraction of *Q. saponaria* (the 21st fraction from RP-HPLC) [85]. Early clinical studies revealed that saponins **99** and **100** are the most promising adjuvants for immune response poten-

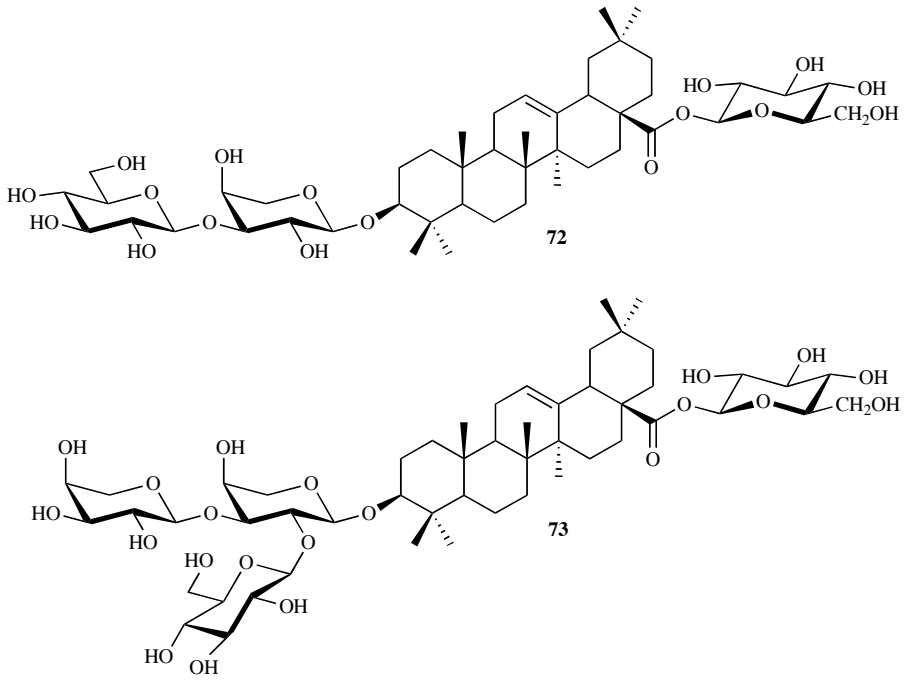
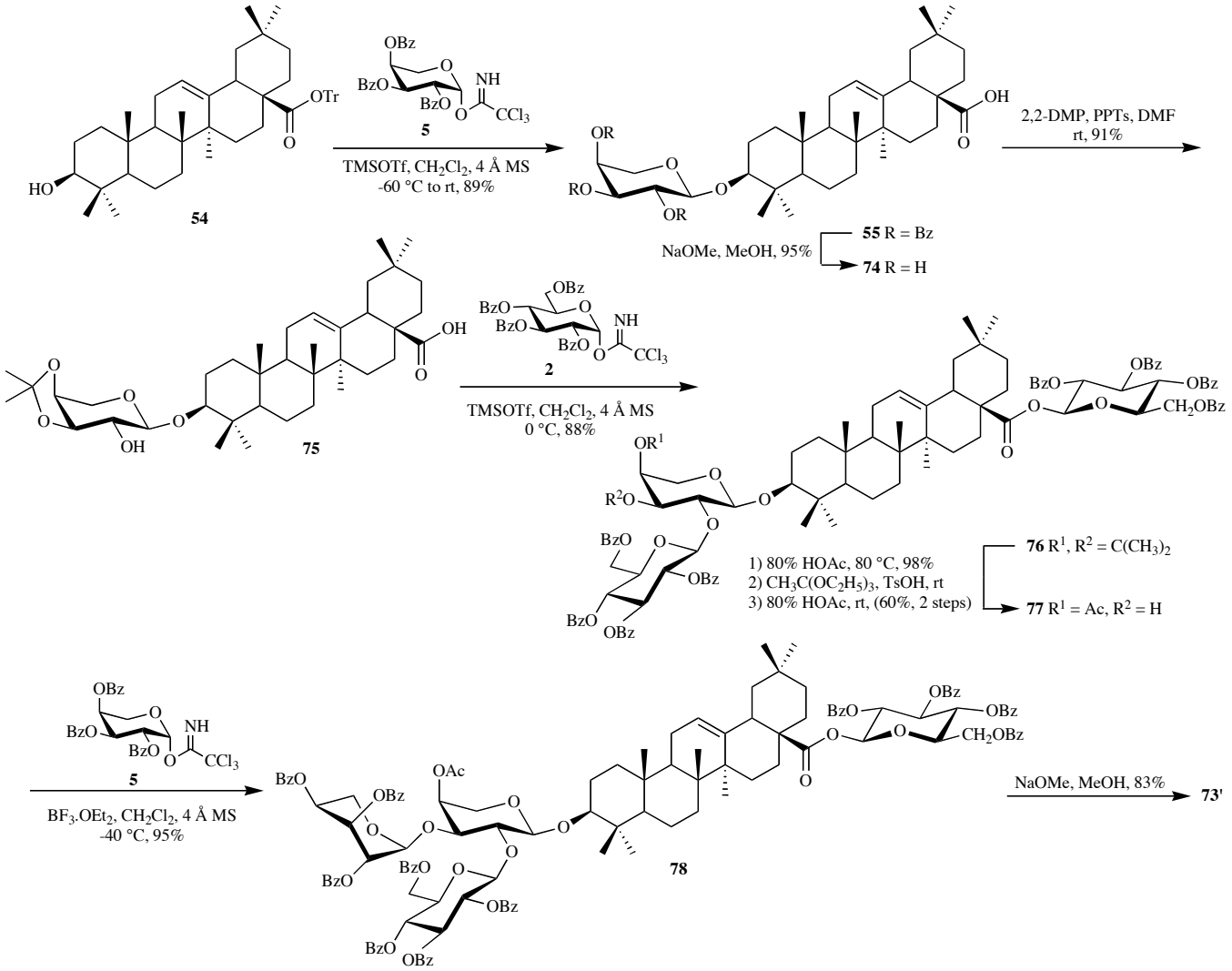
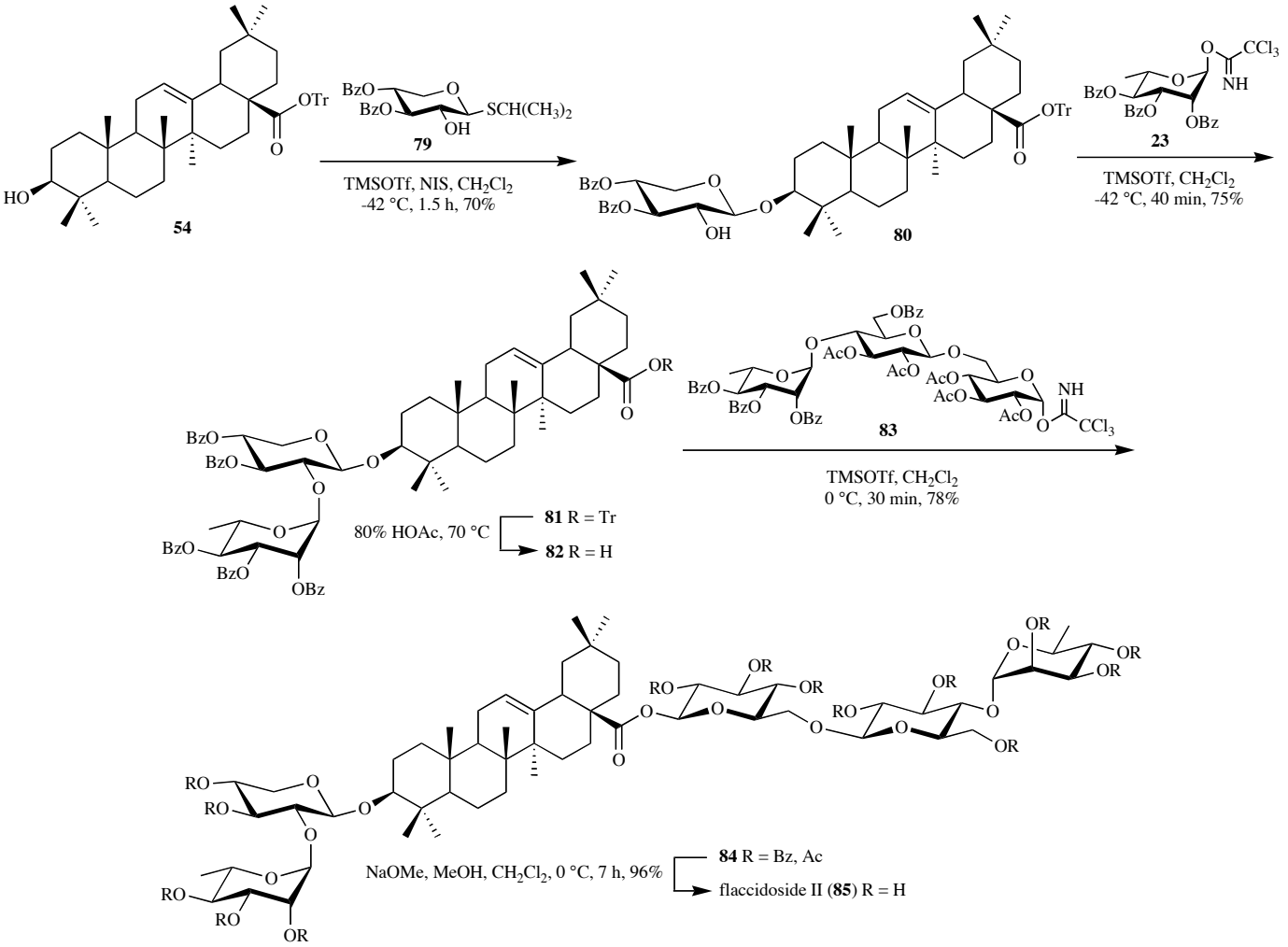


Fig. (6).



Scheme 11. Synthesis of a bidesmosidic saponin containing a terminal arabinopyranose in the $^1C_4$ chair conformation (**73′**) [66].



Scheme 12. Synthesis of flaccidoside II (**85**) [70].

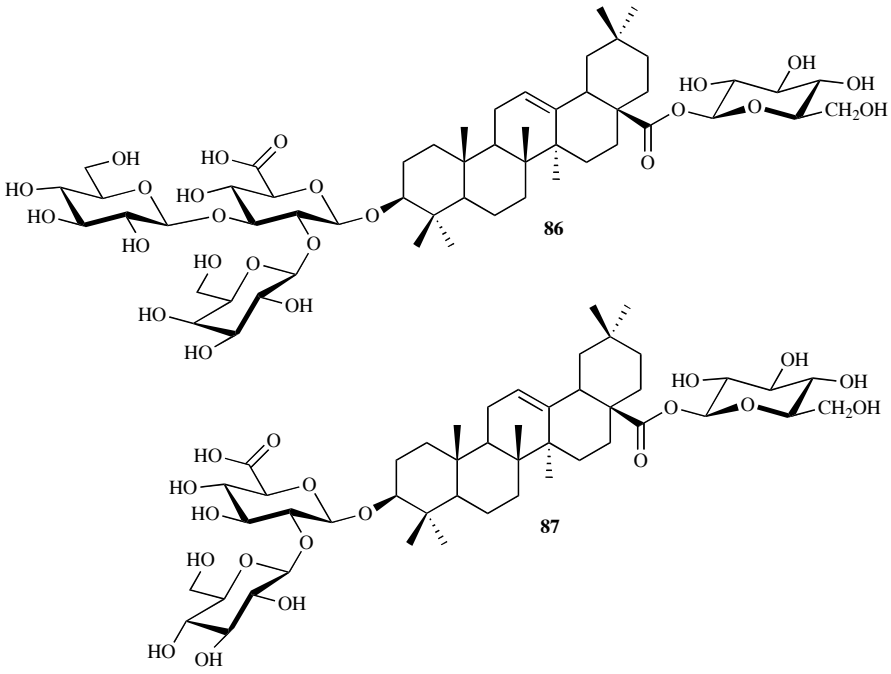
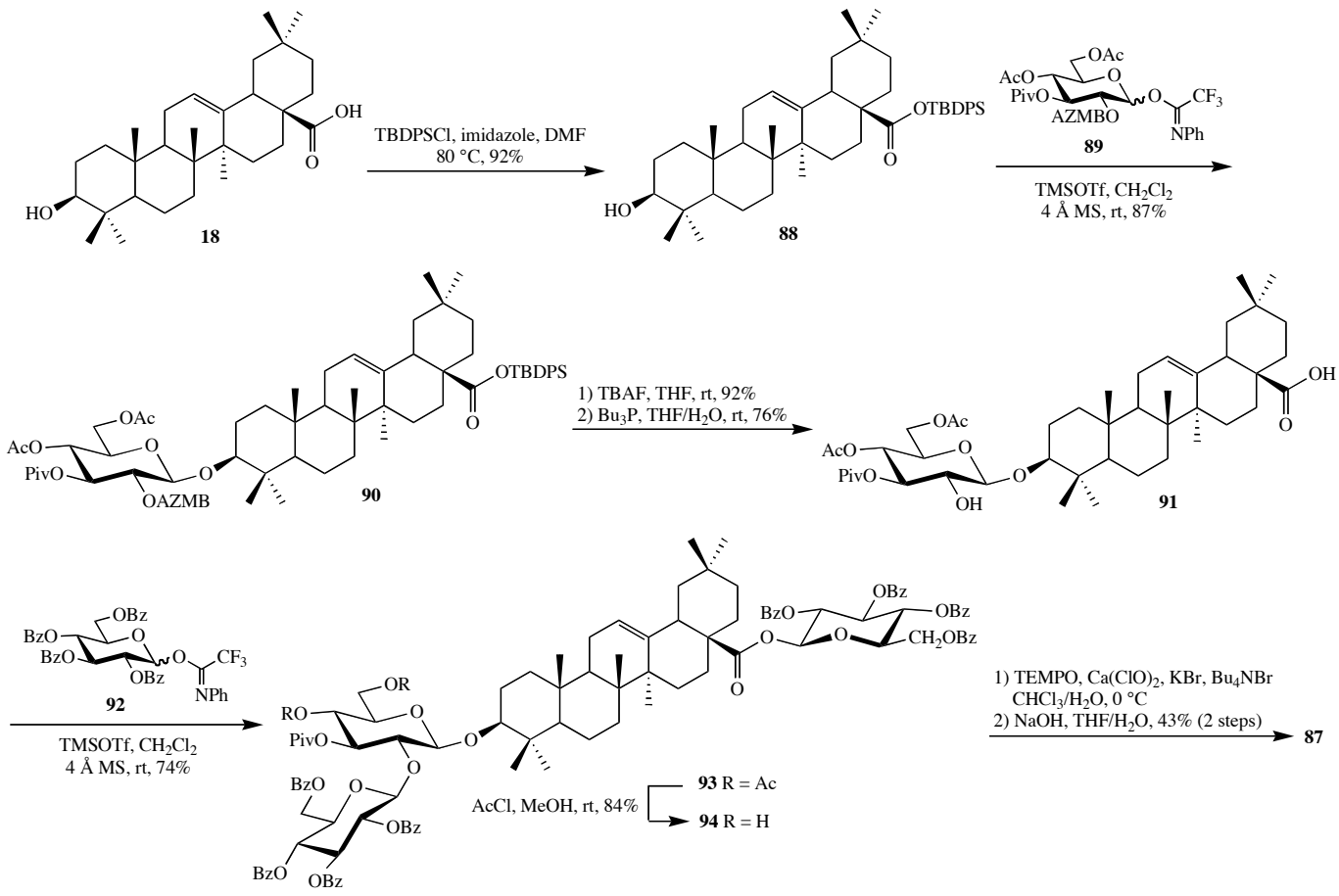


Fig. (7).

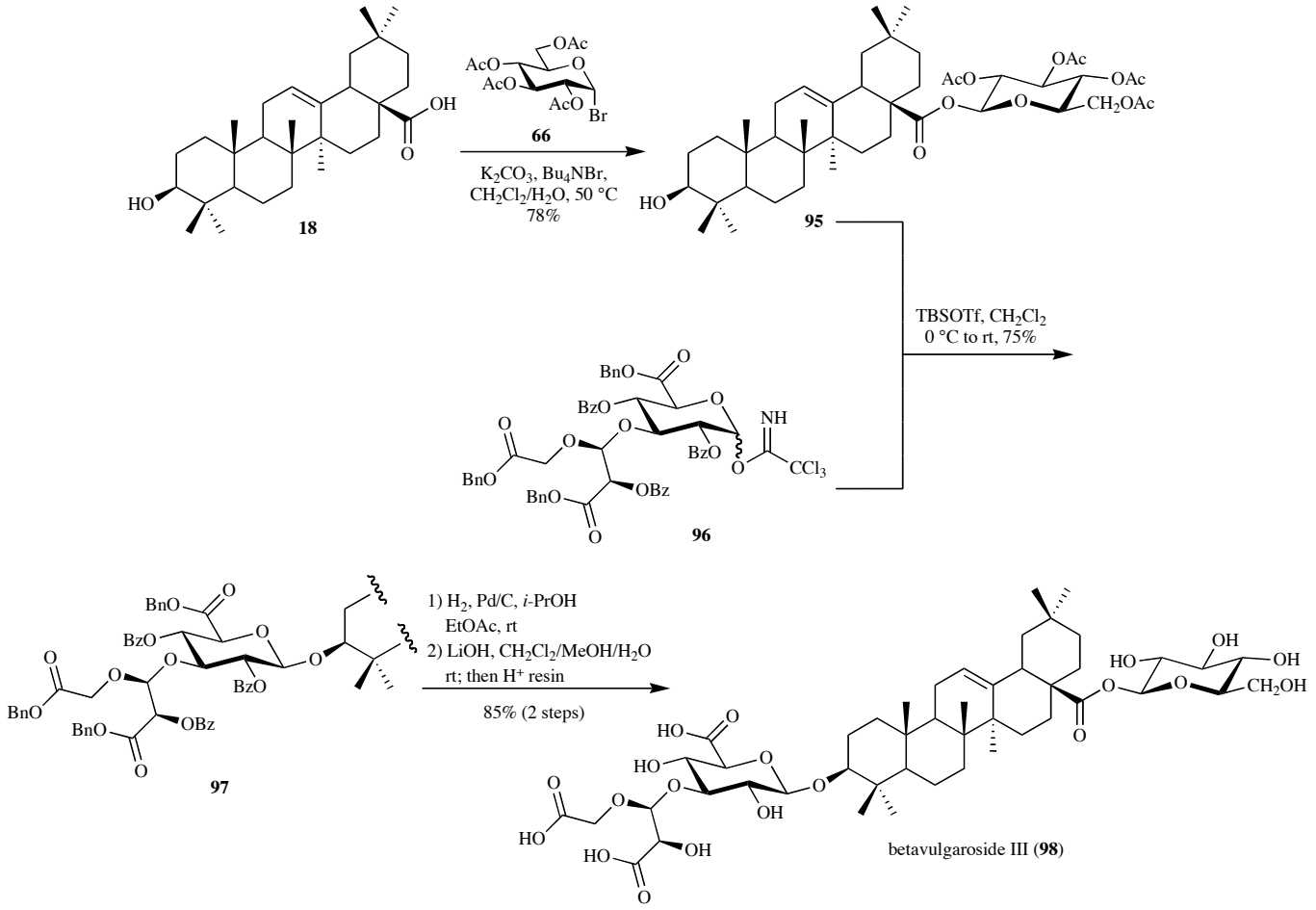


Scheme 13. Synthesis of ginsenoside Ro (**87**), a glucuronide containing bidesmosidic saponin [79].

tiation and dose-sparing in vaccine therapy [86]. Recently, in order to expand their availability for clinical trials, the synthesis of both QS-21-Api (**99**) [87] and QS-21-Xyl (**100**) [88] was achieved by the group of David Y. Gin and co-workers. The final steps in the total synthesis of the immunostimulant QS-21-Api (**99**), the major component of the QS-21 active fraction, are outlined in Scheme **15** [87]. Structurally, natural saponin **99** features a quillaic acid triterpenoid aglycone bearing two complex oligosaccharide moieties, one branched trisaccharide and one linear tetrasaccharide linked to a glycosylated fatty acyl chain. Briefly, condensation between tetrasaccharide **102** and the linear carboxylic acid **101** under Yamaguchi conditions [89] furnished the glycosylated ester **103** (90%), which was converted into the TCA donor **104**. In another experiment, coupling between the allylic acceptor **105** and the trisaccharide TCA glucuronide donor **106** catalyzed by tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] led to the formation of the protected monodesmoside **107** in good yield and anomeric selectivity (59%, α/β 1:7). Afterwards, a series of protection-deprotection reactions was able to form the derivative **108** bearing a free carboxylic group, which was glycosylated with the TCA **104** under the promotion of $BF_3.OEt_2$ to give the protected bidesmosidic saponin **109** in good yield (70%). The highly potent immunostimulant QS-21-Api (**99**) was then obtained in a pure and homogeneous form as revealed by HPLC after the cleavage of all protecting groups (Bn, TES, TBS, benzylidene and isopropylidene).

3.4. Total Synthesis of the Cyclic Bidesmoside Lobatoside E

The isolation of cyclic bidesmosidic saponins such as lobatoside E (**127**) has been rarely reported in the literature. To this date, only 10 compounds of this family have been isolated from the two Chinese medicinal plants *Bolbostemma paniculatum* and *Actinostemma lobatum* [90]. Lobatoside E (**127**), which is a typical example of this class of natural products, was shown to exhibit strong cytotoxic activity (GI_{50} = 0.14-0.36 μM) against lung adenocarcinoma (A549), colon adenocarcinoma (SW-620) and melanoma (SK-MEL-5) human cancer cell lines [91]. Recently, Zhu *et al.* achieved the total synthesis of lobatoside E (**127**), which is outlined in Scheme **16** [90]. Briefly, the triterpene **110** was obtained after the functionalization of the C-2 and C-23 positions of oleanolic acid (**18**) via a linear approach involving the Baldwin's cyclopalladation [92]. Glycosylation of the acceptor **110** with the sugar bromide **111** under phase-transfer conditions provided the acyl glycoside **112** (80%). The latter was subsequently coupled with the glucosyl TCA donor **113** in the presence of TMSOTf to afford **114** (96%). The branched bidesmoside **117** was then obtained after the selective cleavage of the chloroacetyl (CA) group followed by condensation with the galactose TCA donor **116** under standard glycosylation conditions. Once the acetyl removed, the acceptor **118** was coupled with the thiodisaccharide **119** providing **120** in good yield (81%). Interconversion of the benzoyl group for a benzyl group in the terminal galactose residue led to derivative **121**, which was condensed with the carboxylic acid in **122** under Yamaguchi conditions [89] after the cleavage of the TBDPS group. Once the *para*-methoxybenzyl (PMB) group of **123** was removed, the resulting bidesmoside **124** was then macrocyclized via the Yamaguchi conditions [93] providing two C-3' epimeric cyclic bidesmosides (**125** and **126**), which were separated by silica gel column chromatography. The total synthesis of lobatoside E (**127**) was then completed after the hydrogenolysis of all benzyl groups in derivative **125**, the overall yield being 1.2% after 73 synthetic steps.



Scheme 14. Synthesis of betavulgaroside III (**98**) [83].

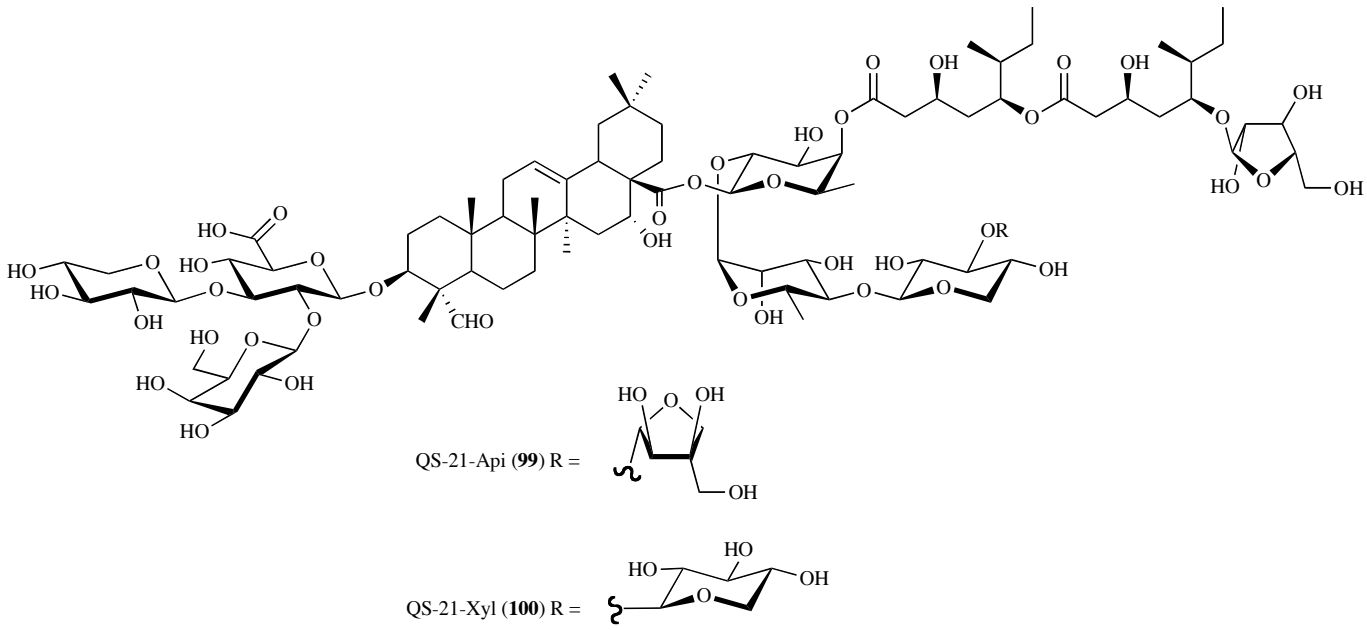
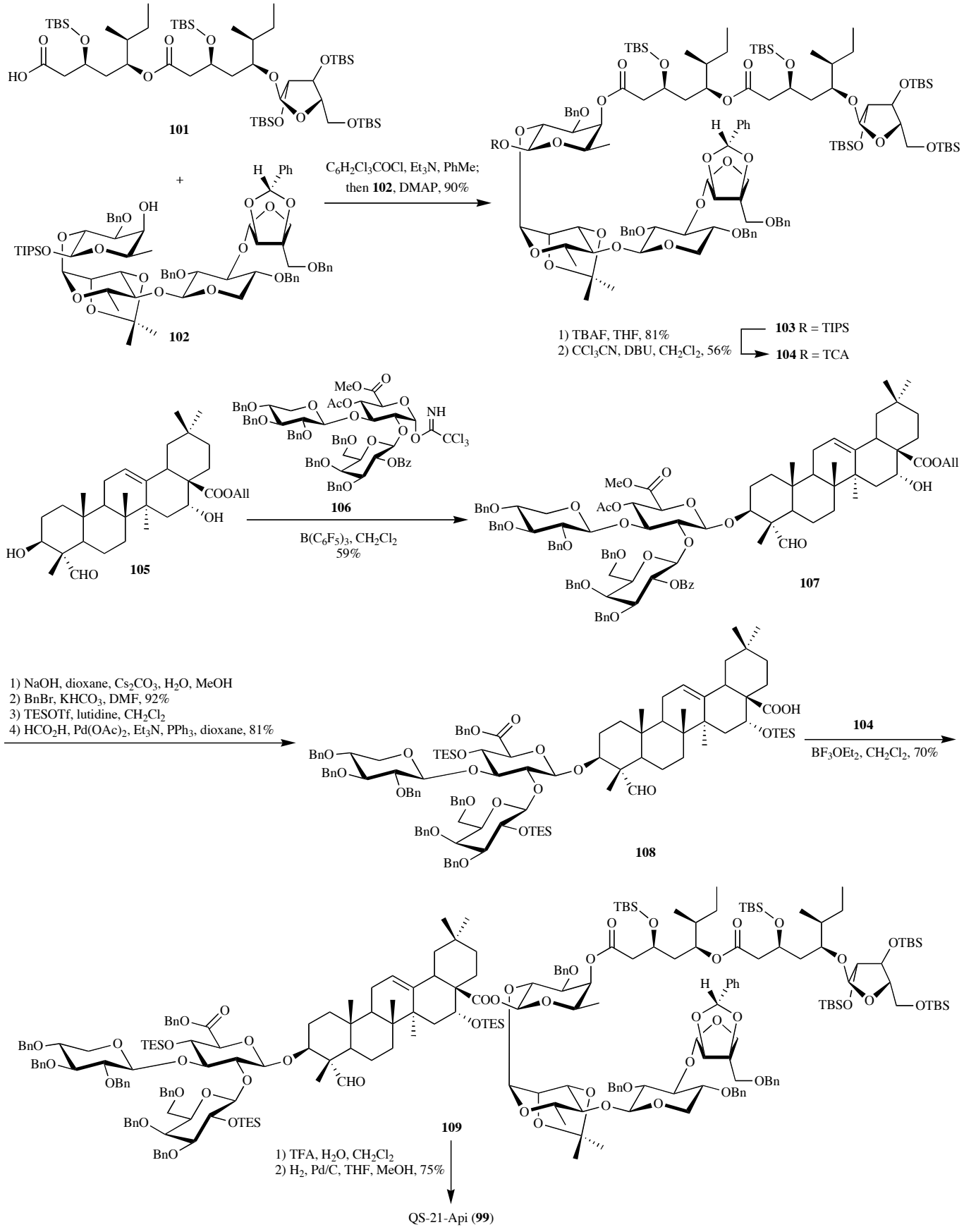
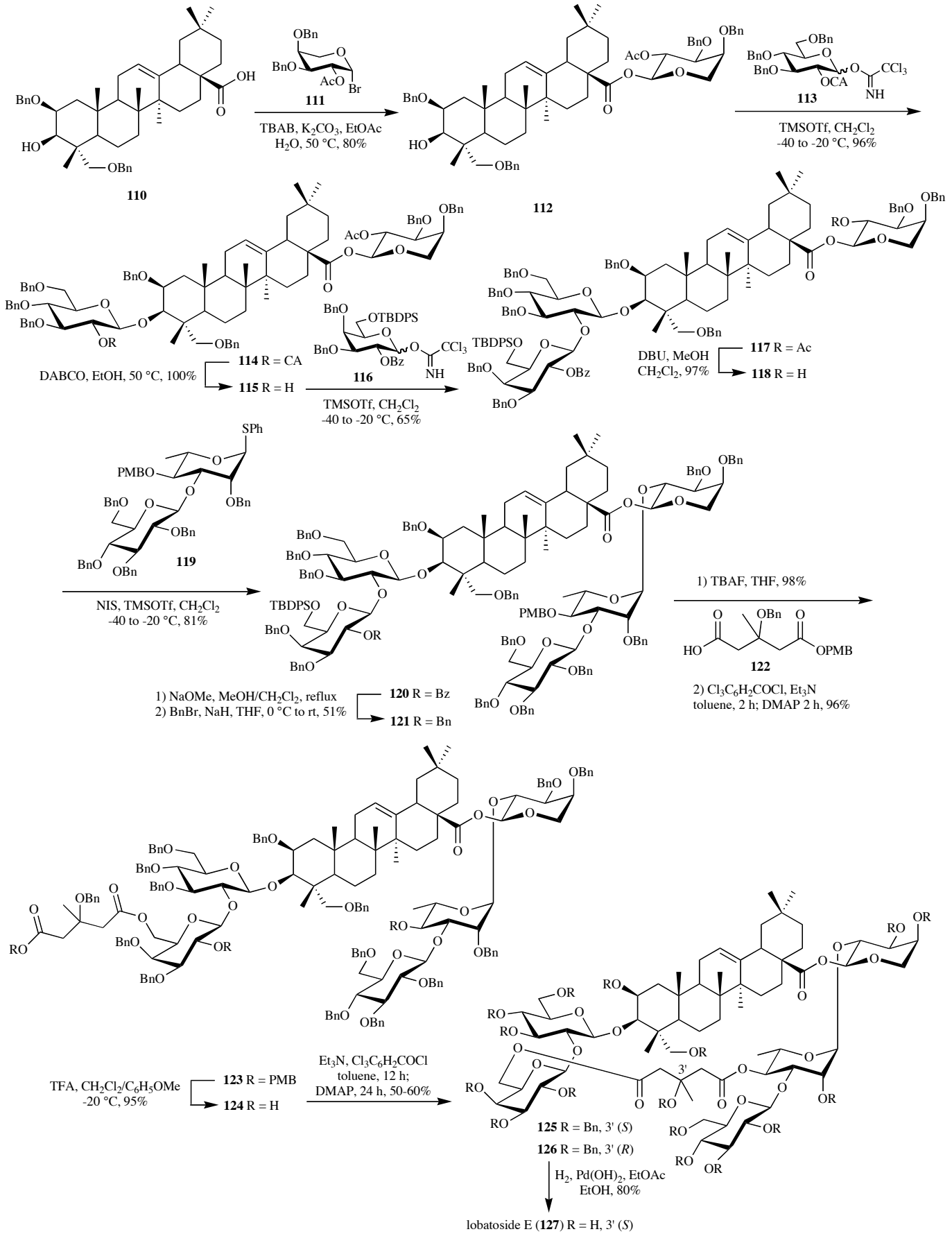


Fig. (8).



Scheme 15. Final stage in the total synthesis of the immunostimulant QS-21-Api (**99**) [87].



Scheme 16. Total synthesis of lobatoside E (**127**), a cyclic bidesmosidic saponin [90].

4. LUPANE-TYPE SAPONINS

4.1. Isolation of Lupane-Type Saponins

Naturally occurring pentacyclic lupane-type triterpenoids such as betulinic acid (**128**), betulin (**129**) and lupeol (**130**) have attracted increased attention over the past decades since they possess multiple pharmacological activities (anti-inflammatory, cytotoxic, anticancer, anti-HIV, antibacterial, etc.) [94,95]. For example, betulinic acid (**128**), which is the most studied member of this family, has the ability to inhibit the growth of various cancerous cell lines without affecting normal cells [96]. Thus, due to the selective cytotoxicity and favourable therapeutic index, natural triterpenoid **128** is considered as a promising anticancer agent [97]. It is known that triterpenoid saponins having a lupane-type aglycone such as betulinic acid (**128**) are less frequent in nature than those having an oleanane-type aglycone [98]. In order to find publications reporting the isolation and identification of lupane-type saponins, a number of computer-databases including STN Easy®, Web of Science® and SCOPUS® were used. The results of our literature search are shown in Table **1**, which presents the latin names of the plant species containing saponins and the nature of sugar moieties linked to both C-3 and C-28 positions. Fig. (**9**) shows the chemical structures of all lupane-type aglycones (**128**-**146**) found within these natural saponins.

Table 1. Naturally Occurring Lupane-Type Triterpenoid Saponins

Species	Name/Aglycone (see Fig. 9)	Sugar Moieties		Ref.
		C-3	C-28	
Acacia leucophloea	(**128**)	Mal	-	[99]
Acanthopanax koreanum	(**133**)	-	Rha(1-4)Glc(1-6)Glc	[100]
	Acankoreoside C (**133**)	Glc	Rha(1-4)Glc(1-6)Glc	[101]
Acanthopanax gracilistylus	Wujiapioside B (**137**)	-	Rha(1-4)Glc(1-6)Glc	[102]
	Acankoreoside C (**133**)	Glc	Rha(1-4)Glc(1-6)Glc	[102]
	Acantrifoside A (**133**)	-	Rha(1-4)Glc(1-6)Glc	[102]
	(**131**)	-	Rha(1-4)Glc(1-6)Glc	[102]
	Acankoreoside D (**141**)	-	Rha(1-4)Glc(1-6)Glc	[101]
Acanthopanax sessiliflorus	Sessiloside (**146**)	-	Rha(1-4)Glc(1-6)Glc	[103]
Acanthopanax trifoliatus	(**133**)	-	Rha(1-4)Glc(1-6)Glc	[100]
Acanthus illicifolius	(**130**)	Ara*f*(1-4)Glc	-	[104]
Amoora rohituka	(**129**)	Xyl	-	[105]
Anomospermum grandifolium	(**135**)	-	Glc(1-2)[Xyl(1-3)]Xyl(1-2)Glc	[106]
Bersama engleriana	(**128**)	Glc(1-2)GlcA	Glc	[107]
Bupleurum fruticescens	Fruticesaponin A (**138**)	Rha(1-4)Glc(1-6)Glc	-	[108]
	Fruticesaponin B (**138**)	Rha(1-4)Glc	Glc	[108]
	Fruticesaponin C (**138**)	Rha(1-4)Glc(1-6)Glc	Glc	[108]
Campsiandra guayanensis	(**128**)	Xyl(1-2)Xyl	3(IsoVal)Rha	[109]
	(**128**)	Xyl(1-2)Glc	3(IsoVal)Rha	[109]
	(**134**)	Xyl(1-2)Xyl	3(IsoVal)Rha	[109]
Cordia obliqua	(**128**)	Rha	-	[110]
Cussonia racemosa	(**128**)	Glc	Glc(1-2)Glc	[111]
	Cussosaponin A (**128**)	Glc	Ara(1-2)Glc	[111]
	Cussosaponin B (**128**)	Gal(1-2)Ara	Rha(1-4)Glc(1-6)Glc	[111]
	Cussosaponin C (**128**)	Rha(1-2)Ara	Rha(1-4)Glc(1-6)Glc	[111]
Dillenia pentagyna	(**128**)	Rha	-	[112]
Oplopanax elatus	(**128**)	Glc	Rha(1-4)Glc(1-6)Glc	[113]
Oreopanax guatemalensis	(**128**)	Glc	Glc(1-6)Glc	[114]
	(**128**)	Glc	Rha(1-4)Glc(1-6)Glc	[114]
Pavonia zeylanica	(**128**)	Ara*f*(1-2)Rha(1-4)Glc	-	[115]
Pulsatilla chinensis	Pulsatilloside C (**136**)	-	Rha(1-4)Glc(1-6)Glc	[116]
	(**128**)	Rha(1-2)Ara	Rha(1-4)Glc(1-6)Glc	[117]
	(**136**)	Rha(1-2)[Glc(1-4)]Ara	Rha(1-4)Glc(1-6)Glc	[117]
	(**136**)	Rha(1-2)[Glc(1-4)Glc(1-4)]Ara	Rha(1-4)Glc(1-6)Glc	[117]
	(**144**)	Rha(1-2)Ara	Rha(1-4)Glc(1-6)Glc	[117]
	Chinensioside A (**136**)	Rha(1-2)Ara	-	[118]
	Chinensioside B (**136**)	Rha(1-2)[Glc(1-4)]Ara	Rha(1-4)Glc(1-6)Glc	[118]
	Pulsatilloside A (**136**)	Ara	-	[119]
	Pulsatilloside B (**136**)	Rha(1-2)Ara	-	[119]
	Pulsatilloside D (**136**)	Glc(1-3)Ara	Rha(1-4)Glc(1-6)Glc	[119]

Table 1. contd…

Species	Name/Aglycone (see Fig. 9)	Sugar Moieties		Ref.
		C-3	C-28	
	Pulsatilloside E (**136**)	Rha(1-2)[Glc(1-4)]Ara	Rha(1-4)Glc(1-6)Glc	[119]
	Anemoside B_4 (**136**)	Rha(1-2)Ara	Rha(1-4)Glc(1-6)Glc	[119]
Pulsatilla koreana	(**136**)	Rha(1-2)[Glc(1-4)]Ara	-	[120]
	(**136**)	Glc(1-3)Rha(1-2)Ara	-	[120]
	(**136**)	Glc(1-4)Ara	-	[120]
	(**128**)	Glc(1-4)Ara	-	[120]
	(**128**)	Glc(1-3)Rha(1-2)Ara	-	[120]
Schefflera divaricata	(**128**)	Xyl(1-2)GlcA	-	[121]
	(**136**)	Xyl(1-2)[Glc(1-3)]GlcA	-	[121]
	(**136**)	Xyl(1-2)GlcA	-	[121]
	(**136**)	GlcA	-	[121]
	(**136**)	Glc(1-3)GlcA	-	[121]
	(**140**)	Xyl(1-2)GlcA	-	[121]
	(**140**)	Glc(1-3)GlcA	-	[121]
	(**140**)	GlcA	-	[121]
Schefflera fagueti	(**142**)	Glc(1-3)Rha(1-2)Ara	Rha(1-4)Glc(1-6)Gal	[122]
	(**142**)	Rha(1-2)Ara	Rha(1-4)Glc(1-6)Gal	[122]
	(**143**)	Glc(1-3)Rha(1-2)Ara	Rha(1-4)Glc(1-6)Gal	[122]
	(**143**)	Rha(1-2)Ara	Rha(1-4)Glc(1-6)Gal	[122]
Schefflera lucantha	(**128**)	Rha(1-2)Glc(1-2)GlcA	-	[123]
	(**128**)	Rha(1-2)Xyl(1-2)GlcA	-	[123]
Schefflera octophylla	(**131**)	Glc	-	[124]
	(**139**)	-	Rha(1-4)Glc(1-6)Glc	[124]
	(**131**)	Glc	-	[125]
	(**131**)	Glc	Rha(1-4)Glc(1-6)Glc	[125]
Schefflera rotundifolia	(**128**)	Rha(1-2)Ara	Glc	[126]
	(**128**)	Ara	Glc	[126]
Schefflera venulosa	(**128**)	Glc(1-2)Glc	-	[127]
Stenocereus eruca	Erucasaponin A (**128**)	Rha(1-2)[Rha(1-3)]MeGlcA	Rha	[128]
	Stellatoside B (**145**)	Xyl(1-2)Glc(1-2)MeGlcA	-	[128]

Some general statements may be drawn following the analysis of data presented in Table **1**:

- Betulinic acid (**128**) is the most frequent aglycone (n = 23) followed by 23α-hydroxybetulinic acid (**136**, n = 17), 3α,11α-hydroxybetulinic acid (**133**, n = 5) and 3α-betulinic acid or *epi*-betulinic acid (**131**, n = 4);
- Only one natural betulin saponin was reported [105], namely 3β-*O*-β-D-xylopyranoside betulin (**150**);
- Monodesmosidic lupane-type saponins usually bear the sugar moiety at the C-3 position (n = 29) rather than the C-28 position (n = 9);
- The sugar moiety found at the C-28 position of bidesmosidic lupane-type saponins (n = 31) is generally of the type α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranosyl-(1→6)-β-D-glucopyranose (n = 24) whereas the sugar moieties found at the C-3 position are more diversified.
- Natural lupane-type saponins are principally found in plant species of the *Schefflera* (n = 23) and *Pulsatilla* (n = 17) genera. Within these genera, the α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranose moiety is frequently found at the C-3 position.

4.2. Synthesis of Naturally Occurring Lupane-Type Saponins

To our knowledge, the synthesis of naturally occurring lupane-type saponins has only been achieved by our laboratory although the preparation of unnatural betulin and betulinic acid glycosides has already been reported [129-131]. As shown in Scheme **17**, three natural monodesmosidic lupane-type saponins (**149**, **150** and **152**) having, respectively, lupeol (**130**), betulin (**129**) and betulinic acid (**128**) as aglycones were easily synthesized by us [132,133] in a one-pot procedure using Schmidt's TCA activated sugars catalyzed by TMSOTf. It is worth noting that saponin **152**, namely 3β-*O*-α-L-rhamnopyranoside betulinic acid, exhibits a strongly potent cytotoxic activity against several human cancer cell lines and is up to four fold more active than the parent triterpenoid betulinic acid (**128**). Moreover, this glycoside (**152**) showed a selectivity on human lung carcinoma (A549, IC_{50} 2.6 μM) up to 12-fold higher than on human normal skin fibroblasts (WS1, IC_{50} 31 μM) [132].

Betulinic acid 3β-*O*-α-L-rhamnopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→4)-]-α-L-arabinopyranoside (**158**) was isolated from the roots of *Pulsatilla koreana* [120], which is a Chinese medicinal plant widely used for the treatment of malaria, amoebic dysentery and various cancers. This monodesmosidic saponin (**158**) exhibited moderate *in vitro* anticancer activity and significant *in vivo* anticancer activity against BDF1 mice bearing Lewis lung carcinoma (LLC) [40]. Recently, we reported the straightforward

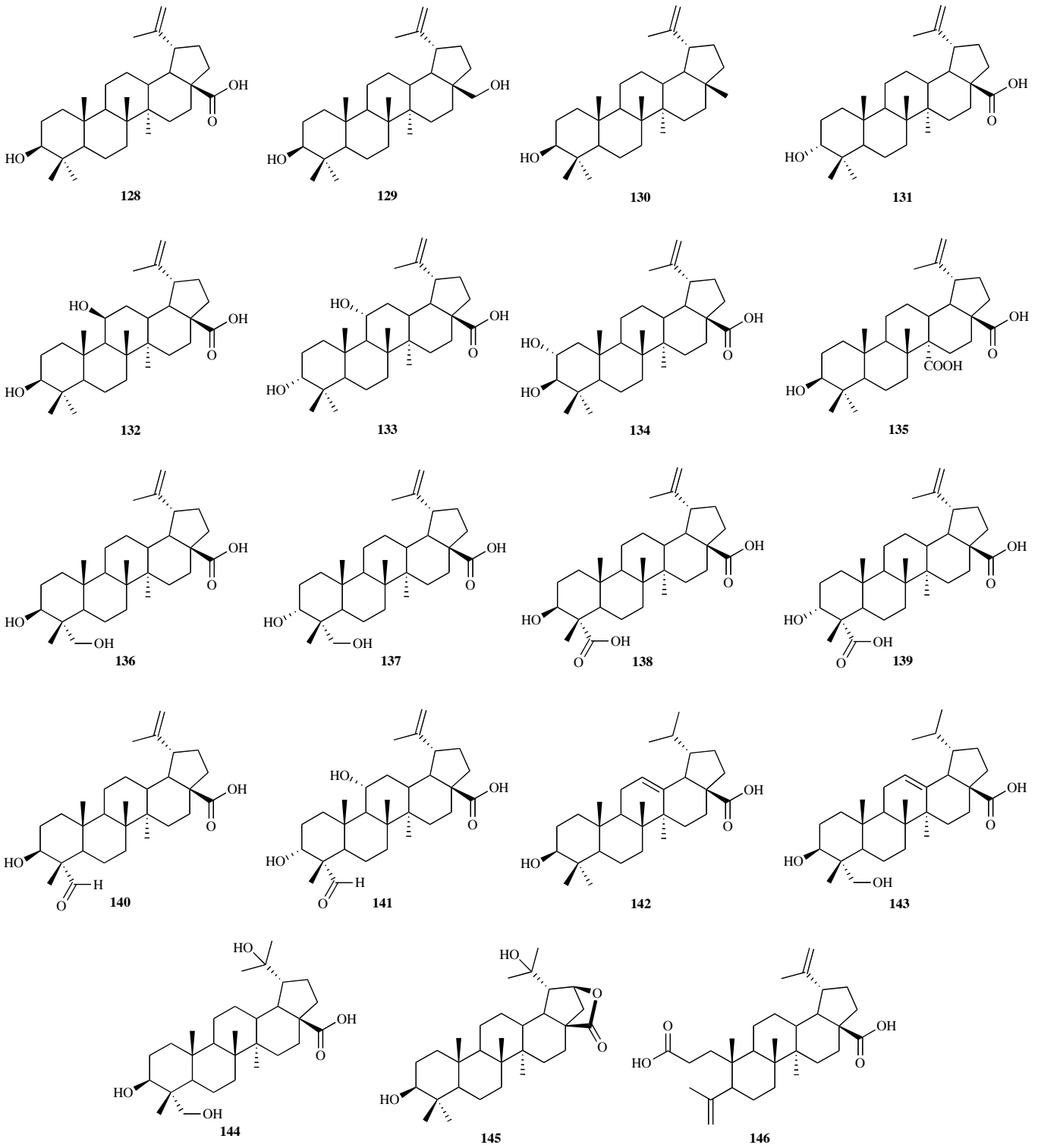
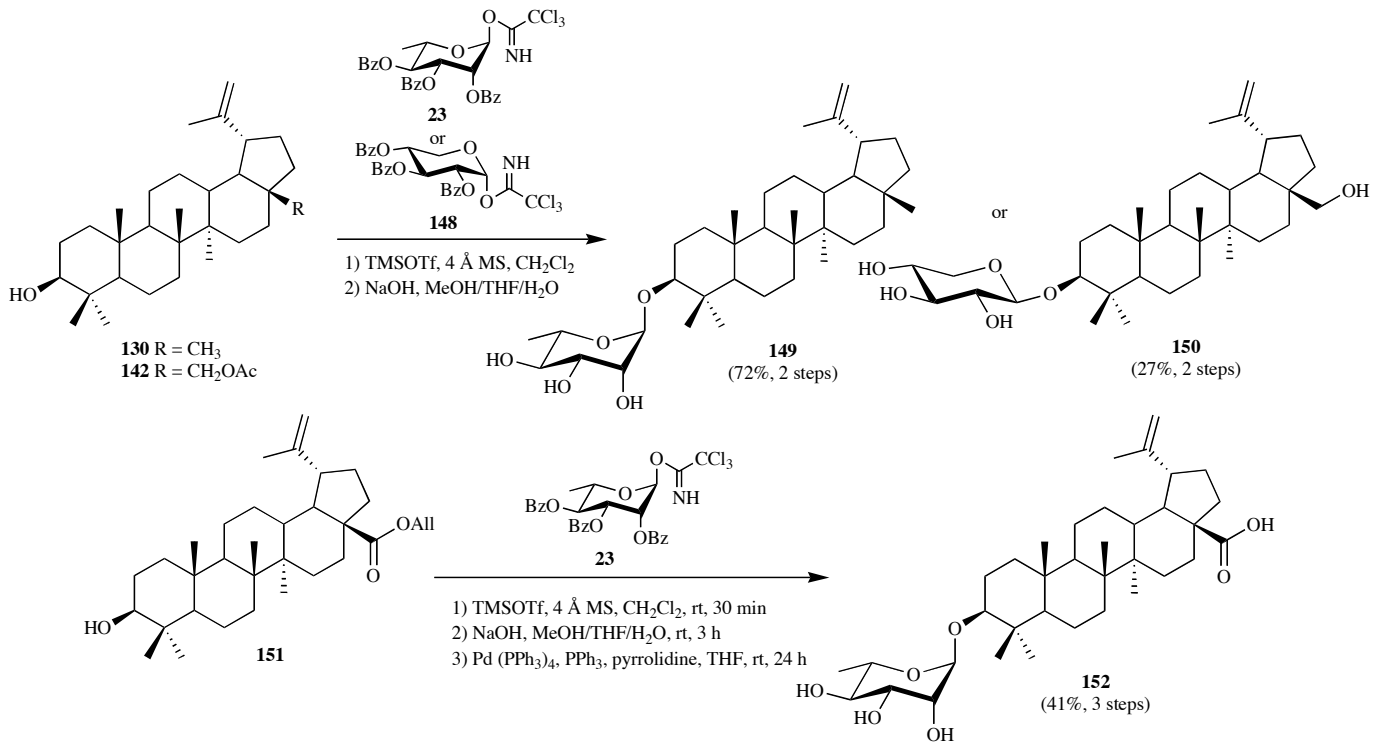
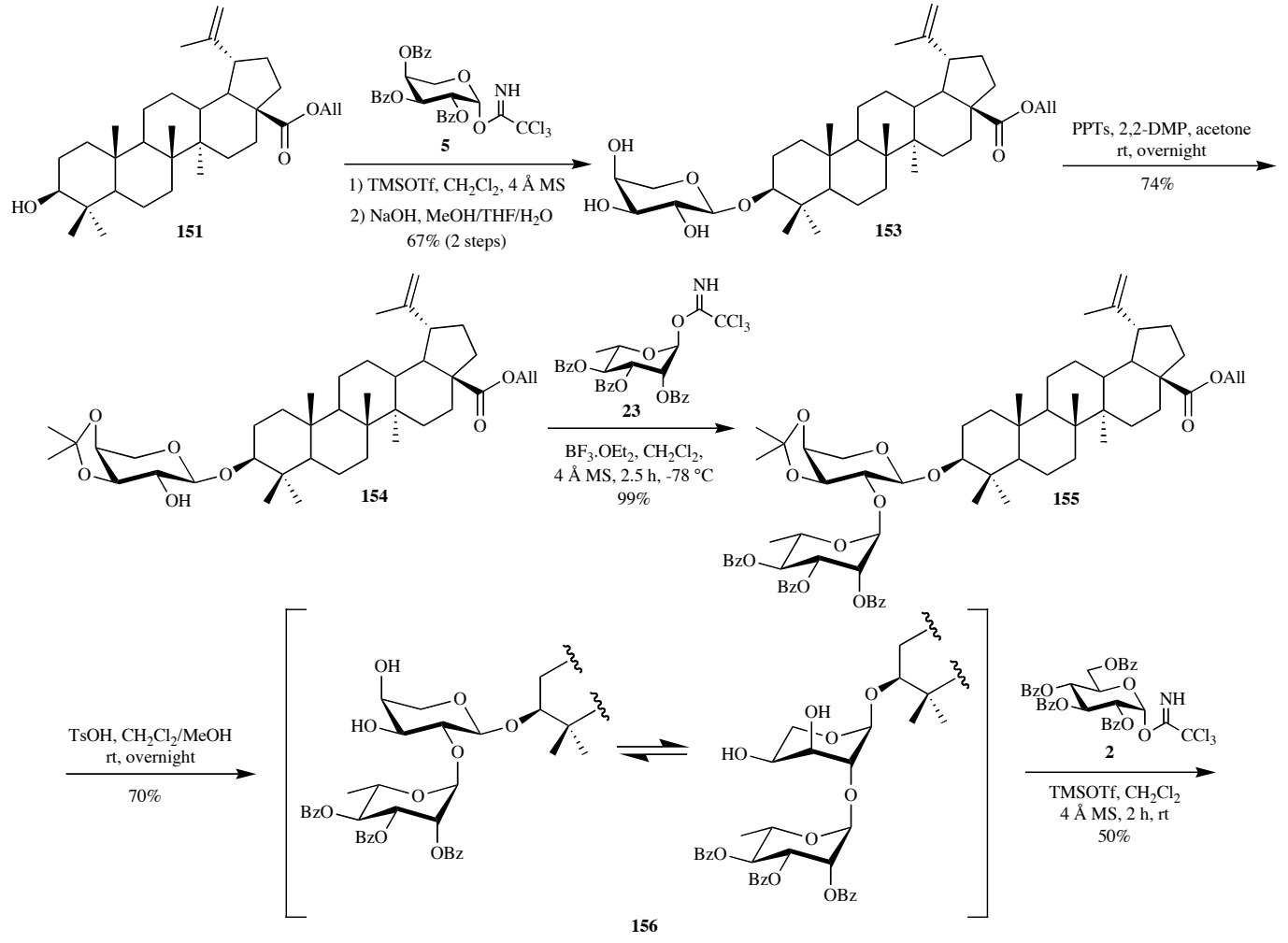


Fig. (9).

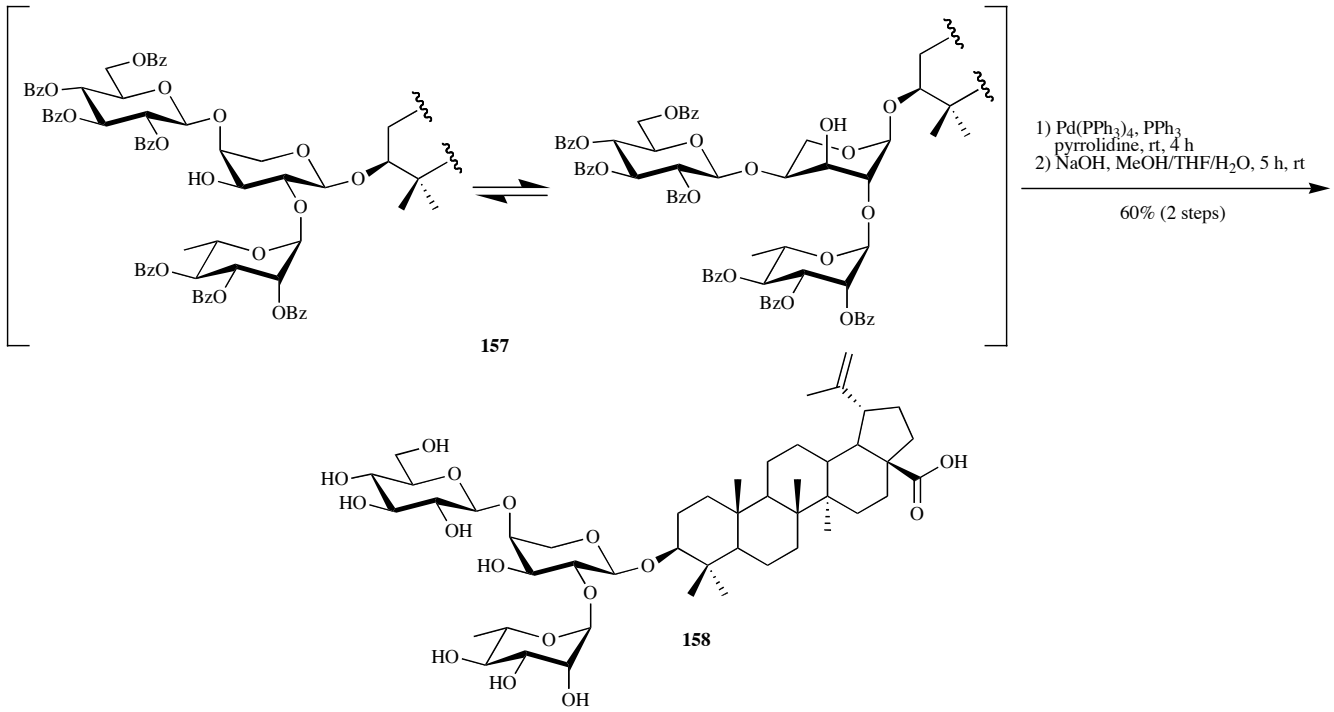
synthesis of this natural saponin (**158**) via a synthetic route featuring three successive glycosylations [134]. As depicted in Scheme **18**, allyl betulinate (**151**) was condensed with the arabinosyl TCA donor **5** under TMSOTf promotion and the benzoyl groups were removed to furnish **153** (67%, two steps). Thereafter, the regioselective isopropylidenation of C-3' and C-4' hydroxyl groups led to the formation of **154**, which was quantitatively glycosylated with the rhamnosyl TCA donor **23** in the presence of $BF_3.OEt_2$ at a cryogenic temperature (-78 °C) providing **155**. After removal of the isopropylidene group, the diol **156** was subjected to glycosylation with the glucosyl TCA donor **2** under standard conditions. The protection groups of the resulting trisaccharidic glycoside **157** (50%) were finally removed to give the natural monodesmosidic saponin **158**. It is interesting to point out that, once the isopropylidene was cleaved, the arabinopyranosyl moiety of derivatives **156** and **157** underwent ring-flipping to adopt preferentially the $^1C_4$ chair conformation rather than the usual $^4C_1$ form.



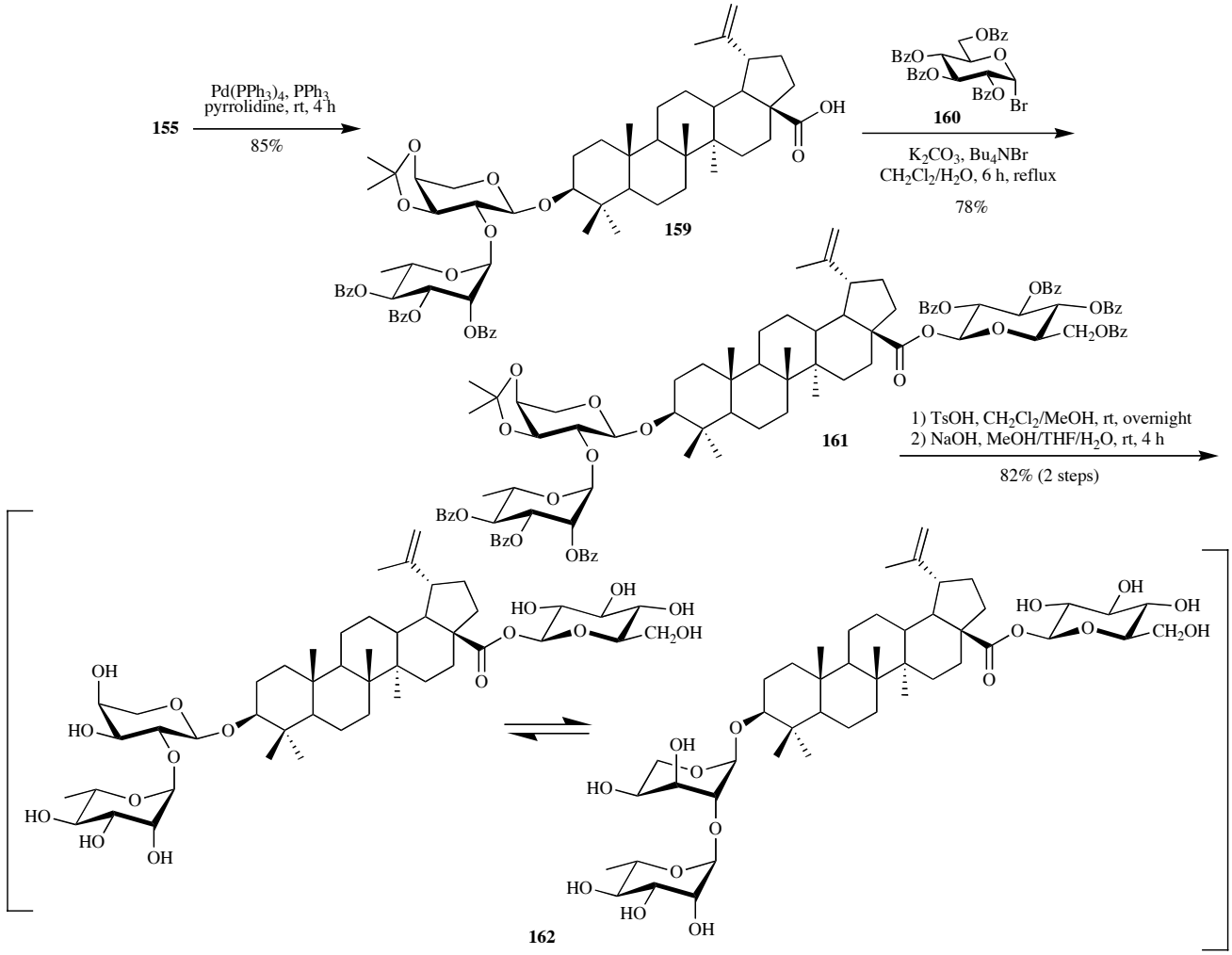
Scheme 17. Synthesis of naturally occurring monodesmosidic lupane-type saponins (**149**, **150**, **152**) [132,133].



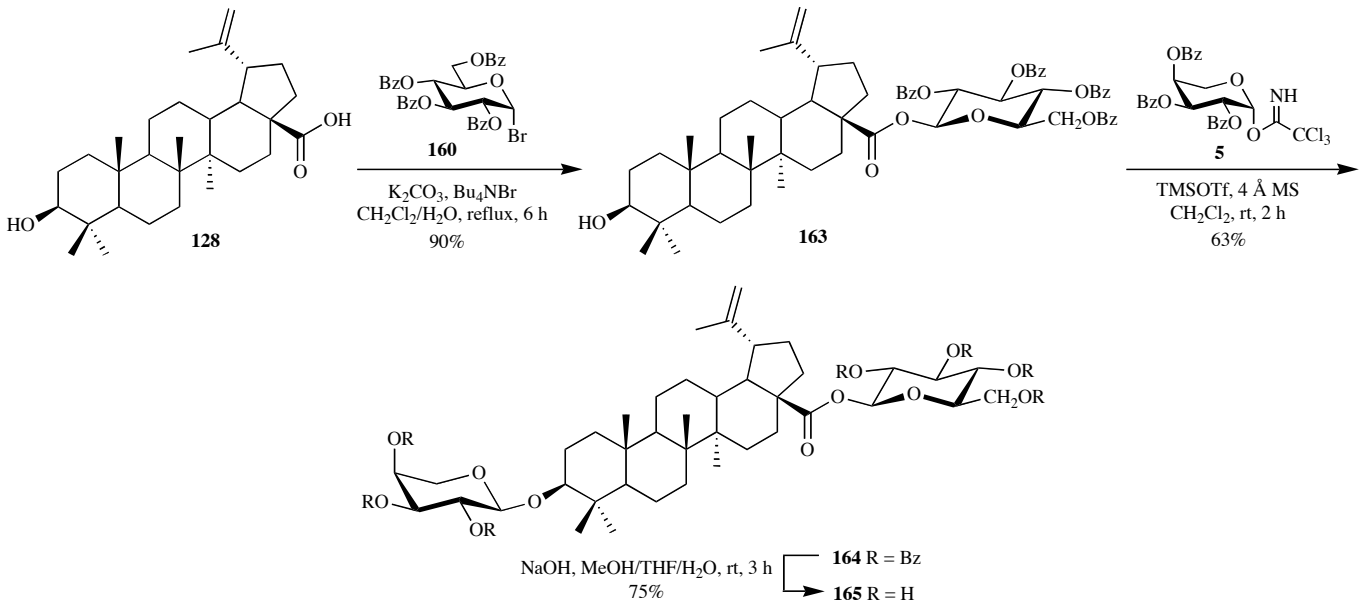
Scheme (18). Contd….



Scheme 18. Synthesis of a monodesmosidic betulinic acid saponin (**158**) isolated from *P. koreana* [134].



Scheme 19. Synthesis of a bidesmosidic betulinic acid saponin (**162**) isolated from *S. rotundifolia* [134].



Scheme 20. Synthesis of a bidesmosidic betulinic acid saponin (**165**) isolated from *S. rotundifolia* [134].

Bidesmosides **162** and **165** are two other betulinic acid saponins that we have recently synthesized [134,135]. They were isolated from the aerial parts of *Schefflera rotundifolia* [126], which is a plant used as folk remedies for the treatment of pain, rheumatic arthritis and lumbago in Asian countries. Saponins **162** and **165** exhibited noticeable antiproliferative activity against J774.A1, WEHI-164 and HEK-298 cell lines (IC_{50} 0.32-0.79 μM) [126]. As shown in Scheme **19** [134], the synthesis of saponin **162** started from the allylic ester removal of the fully protected derivative **155**. Glycosylation between the acceptor **159** and the bromide sugar donor **160** afforded the bidesmoside **161** (78%) in which the isopropylidene and benzoyl groups were removed to provide the natural saponin **162**. Notably, a ^{1}H NMR analysis of saponin **162** in which the temperature was raised from 0 to 100 °C suggested that the arabinose residue was in a high conformational mobility. The synthesis of the structurally similar natural saponin **165** was also realized in a straightforward manner (Scheme **20**) [135]. Thus, betulinic acid (**128**) was condensed with the bromide donor **160** under phase-transfer conditions to give **163** (90%), which was subsequently coupled with the TCA donor **5** in the presence of TMSOTf providing **164** in good yield (63%). Finally, deprotection of the benzoyl groups led to the formation of the bidesmosidic saponin **165**.

5. CONCLUSION

In summary, the present paper reviewed the recent progress in the synthesis of naturally occurring mono- and bidesmosidic triterpenoid saponins. Many of these natural products such as α-hederin (**12**), hederacolchiside A_1 (**29**), lotoidoside D (**43**) and E (**44**), betavulgaroside III (**98**), QS-21-Api (**99**), lobatoside E (**127**) and betulinic acid saponin **152** exhibited promising pharmacological and biological properties. Two general synthetic routes have been reviewed to elaborate the glycosidic chain within the saponin, i.e. the linear glycosylation approach in which the sugar moieties are introduced one after the other into the triterpenoid skeleton, and the convergent glycosylation involving the preparation of the activated sugar residue before coupling with the triterpene acceptor. Generally, the glycosylation reactions were shown to provide high yields and anomeric selectivities when using the perbenzoylated TCA or TFPA sugar donors under the catalytic promotion of the Lewis acids TMSOTf or $BF_3.OEt_2$. Thus, as pure and homogeneous saponins will continue to become more and more available in appreciable amounts by means of chemical synthesis, it is realistic to think that the biopharmaceutical development of this important class of natural products should significantly accelerate in the next few years.

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