Saponins

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Abbreviations

api: β-D-apiose
ara: α-L-arabinose
drib: β-D-2′-deoxyribose
f: furanoside
fuc: β-D-fucose
fru: β-D-fructose
gal: β-D-galactose
galA: β-D-galacturonic acid
glc: β-D-glucose
glcA: β-D-glucuronic acid
qui: β-D-quinovose
rha: α-L-rhamnose
xyl: β-D-xylose

1. Introduction

Saponins are glycosides (see → Carbohydrates: Occurrence, Structures and Chemistry) occurring primarily in plants but also in starfish (*Asteroidea*) and sea cucumbers (*Holothuridea*). Properties generally considered to be shared by this group of natural products are surfactant activity, hemolytic action, steroid- complexing ability, and biocidal capability.

The characteristic soapy lather formed when saponin- containing plant extracts are agitated in water provides this group of secondary metabolites with its common name (Latin *sapo* = soap), although this property is shared with structurally related compounds (→ Cardiac Glycosides and Synthetic Cardiotonic Drugs). Other properties are characteristic of particular types of saponins rather than all members of the class.

Saponins are categorized according to the structure of the aglycone moiety (*sapogenin*) and the number of linked sugar chains. Aglycones can be divided into triterpenoid and steroid sapogenins. Steroid saponins with basic properties are termed glycoalkaloids.

Hexoses common in all saponins are β-D-glucose (glc), β-D-galactose (gal), and α-L-rhamnose (rha); pentoses are α-L-arabinose (ara) and β-D-xylose (xyl). Pentoses occur primarily as pyranosides, less frequently as furanosides (f).

Saponins linked to one or two sugar chains are called *monodesmosides* and *bisdesmosides*, respectively (Greek *desmos* = chain). Trisdesmosidic saponins are rare [1], [2]. Mild hydrolysis of saponins yields *prosapogenins*, neutral glycosides with less than three sugar units, or acidic or basic glycosides with one sugar unit.

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Prosapogenins are less soluble than saponins and do not have typical saponin properties.

1.1. General Properties

Surfactant Activity. The well-known ability of saponins to cause frothing has long been used to detect these materials in plants or plant extracts. The combination of a hydrophobic aglycone and hydrophilic substituents accounts for the amphiphilic nature of saponins. Increased length and branching of the sugar chain correlate with enhanced surfactant power. Hence, triterpenoidal bisdesmosides are more active in this sense than monodesmosides [3].

Hemolytic Activity. Saponins vary considerably in their ability to lyse erythrocytes. Different glycosides of the same sapogenin differ in activity as a function of the type and structure of substituents [4], [5]. Bisdesmosides are generally less potent than monodesmosides. Introducing polar hydroxyl groups into the aglycone decreases activity, whereas esterification restores it. The linkage position of the sugar chain in triterpenoids also influences reactivity; thus, C-3 glycosides are more reactive than saponins with a C-28 glycosidic substituent.

Steroid-Complexing Ability. Saponins form insoluble complexes with cholesterol [6] and other sterols. This affinity is more pronounced with steroid saponins and glycoalkaloids than with triterpenoids.

Biocidal Activity. Monodesmosidic saponins exhibit fungitoxic or fungistatic and weak antimicrobial activity [7]. Examples include the specific action of α-tomatine [8] and the oat (*Avena sativa*) root saponin avenacin [9]. Steroid saponins and glycoalkaloids generally demonstrate more pronounced action, whereas triterpenes exhibit a broader spectrum of effectiveness.

The permeabilization of crucial cell membranes probably explains the toxicity of saponins to mollusks [10] and other invertebrates [11]. Ecdysterone-like activity [12] and the repellent or antifeedant action of saponins against termites [13], leaf-cutting ants [14], and the potato beetle [15] have been reported. Aquatic vertebrates such as fish and tadpoles are affected through permeabilization of their gills [16], resulting in a rapid loss of physiological function.

1.2. Distribution

Saponins occur mainly in plants of the subdivision *Angiospermae* of the division *Spermatophytae*. Steroid saponins are restricted mostly to the class *Monocotyledoneae*, a known exception being the saponins of foxglove (*Digitalis* sp.). Triterpene and glycoalkaloid saponins are found primarily in plants of the class *Dicotyledoneae*, a more recently discovered exception being saponins isolated from montbretia (*Crocosmia crocosmiiflora*) [17]. Certain families of the class *Dicotyledoneae* (e.g., *Solanaceae, Hippocastanaceae, Primulaceae, Rosaceae*, and *Caryophyllaceae*) are especially rich in saponin-containing genera.

Monodesmosides are concentrated in the outer tissues of seeds, roots, and bark, consistent with their function as a barrier against microorganisms, whereas bisdesmosides are more abundant in leaves and stems. Secretion of proteolytic enzymes by fungal hyphae triggers conversion of the more soluble (and, therefore, transportable) bisdesmosides by specific glycosidases [18] into the more active monodesmosidic saponins.

Animal saponins are restricted to representatives of the phylum *Echinodermata*. Species of the class Holothuridea (sea cucumbers) contain triterpene saponins, whereas saponins from species of the class *Asteroidea* (starfish) contain steroids. These saponins induce avoidance responses in susceptible predator species [19].

1.3. Isolation

Methods for saponin isolation and purification are covered in several reviews [20–22]. Ground dried or fresh specimens are extracted after optional defatting with solvents such as methanol, ethanol, their aqueous mixtures, or, in the case of glycoalkaloids, slightly acidified water. Formation of artifacts due to enzymatic or solvolytic cleavage of glycosidic bonds or acid-catalyzed elimination and rearrangement of the

aglycone must be prevented by suitable choice of conditions.

Distribution of a crude extract between water and butanol separates the saponins from such water-soluble compounds as oligosaccharides. Precipitation with organic solvents (e.g., ether or acetone) or complexing agents (e.g., cholesterol) permits further concentration.

Saponins with free carboxylic acid groups can be purified by ion-exchange chromatography. For cases in which further enrichment by crystallization is not possible, chromatographic techniques are used for the separation of crude saponin mixtures. Methods such as high-performance thin-layer chromatography (HPTLC), high-performance liquid chromatography (HPLC), and droplet countercurrent chromatography (DCCC) [23] have gained wide acceptance. Methods have been reported for isolating saponins from roots of ginseng (*Panax schinseng*) [24] and *Bupleurum falcatum* [25] by preparative HPLC of crude extracts.

1.4. Structure Elucidation

Historically, saponin structures were deduced after methylation and acid hydrolysis to aglycones and partially methylated sugars. However, this method leads to artifacts, so milder hydrolysis methods have been developed. Relatively large amounts of purified material are still needed for classical structural analysis.

The advent of modern spectroscopic methods has simplified the task. Fast-atom bombardment mass spectrometry (FAB – MS) facilitates the sequencing of sugar chains, while ^{1}H and ^{13}C NMR [27] techniques are used to establish specific linkages and resolve ambiguities. Structures of saponins from the starfish *Asterias forbesii* [28], *Astragalus ernestii* [29], and *Allium giganteum* [30] were elucidated by modern two-dimensional NMR methods.

1.5. Analysis

Analytical procedures must be adapted to the particular application in question. Crude estimates of saponin content are obtained via gravimetric methods [31]. Most technical-grade saponins are mixtures rather than single substances. Quantitative estimation of their makeup is accomplished by measuring the surface tension of solutions, their foaming power, and their hemolytic activity [32].

Saponins or saponin mixtures for pharmaceutical applications require analytical methods more specific to particular active compounds, such as spectrophotometric quantitation of a saponin color reaction [33], [34]. Combinations of methods including thin-layer chromatography – densitometry (TLC – DM) [35], gas chromatography – mass spectrometry (GC – MS) [36], LC – MS [37], HPLC [38], and radioimmunoassay (RIA) [39], have been reported for ginseng saponins and other compounds.

2. Pharmacology

Toxicology. In contrast to poikilothermic animals, saponin toxicity to homeothermic species by oral intake is quite low (50 – 100 mg/kg). The significance of saponins as components of the human diet or of animal feeds has been reviewed extensively [20]. Saponins exhibit different spectra of toxicity on parenteral or intravenous application (LD_{50} 0.7 – 50 mg/kg). The hemolytic action of many saponins prevents their intravenous administration, although detoxification by complex formation with serum cholesterol, albumin, or other plasma constituents reduces this effect.

Membranolytic saponins combine irreversibly with cell membrane systems and produce lesions [40] with a pore diameter of about 8 nm. Various structural models for the complex have been proposed [40], [41]. The role of cholesterol as the primary binding site for saponins in cell membranes has been challenged [42], and various saponins have been shown to interact in different ways with erythrocytes and liposomal membranes with respect to cholesterol, phosphatidylcholine, and distearoyllecithin [43]. The theory that β-glucosidase-induced hydrolysis of the glycosidic bond is an essential step in membranolysis [4] cannot explain changes induced by saponins in the osmotic behavior of liposomes devoid of β-glucosidase [44]. A unifying theory of saponin action on membranes has still to be developed.

Pharmacology. Claims of therapeutic activity for saponins are numerous, with the result that saponins have been denounced by some as panaceas [45].

Resorption of saponins by the small intestine is generally low [46], but enzymatic or bacterial decomposition in the large intestine [47] has been demonstrated. Permeabilization of cells of the small intestinal mucosa [48] reduces their capacity to transport nutrients and increases secretion. A therapeutic benefit is increased secretion in the nasal pharyngeal cavity after administration of cough syrup containing extracts of roots from *Primula officinalis*, *Glycyrrhiza glabra*, and *Gala senega*.

Anti-inflammatory activity has been reported for saponins from the seed of the horse chestnut (*Aesculus hippocastanum*) [49] and *Panax inseng* (Greek *pan* = all, *axos* = cure) [50], [51]. In the former case, pharmacological action was blocked by adrenalectomy, hypophysectomy, or sympatholytic drugs. Antiexudative and antigranulomatous action was explained in terms of activation of corticosterone secretion.

The saponin from *Glycyrrhiza glabra* and the hemisuccinate of the corresponding aglycone (carbenoxolone) are used to treat gastric ulcers [52]. Chemical modifications of the aglycone have been reported to reduce side effects [53]. The ammonium salt of the aglycone is used as an antiallergic agent, and the same effect is reported for saponins from *Ilex crenata* [54].

Hypocholesterolemic effects of saponins might be due to a reduction in the uptake of dietary cholesterol by complex formation, increasing bile salt excretion, or direct interaction with sterols in the membranes of mucosal cells [20]. Active saponins have been found in soybean (*Glycine max*) [55] and *Quillaja saponaria* [56].

Psychotropic effects are reported for ginseng saponins [57], and patents have been filed for analgesic, sedative, and cardiovascular-activating effects [58] as well as antitumor activity [59].

Antiviral activity of saponins has been reported against the herpes- and poliovirus [60], Epstein – Barr virus [61], and human immunodeficiency virus (HIV-1) [62].

Bisdesmosidic saponins solubilize monodesmosides [63], an adjuvant effect that seems to increase immune response to vaccines [64] and the uptake of β-lactam antibiotics [65] after oral administration.

3. Plant Saponins

3.1. Steroid Saponins

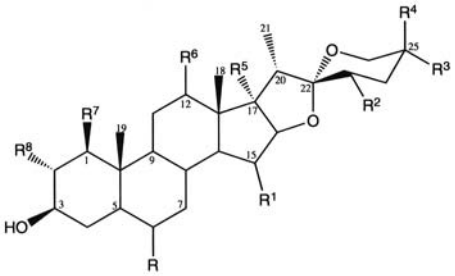
Aglycones of monodesmosidic steroid saponins from plants consist of a hexacyclic spirostanol system, whereas bisdesmosides are derived from the pentacyclic furostanol system or a hexacyclic structure such as that in nuatigenin. Hydrolysis of C-26 glycosidic linkages of furostanol sapogenins results in cyclization to spirostanols. Therefore, furostanol saponins carry the designation "proto-" prefixed to the name of the corresponding spirostanol saponin. Especially in the older literature, the suffix "-oside" provides another indication of a furostanol saponin. Nuatigenin saponins rearrange to the spirostanol derivative isonuatigenin on acid hydrolysis [66].

Aglycones are named after the plant sources from which they were first isolated. C-25 (*S*)-epimers of known C-25 (*R*)-sapogenins are assigned the prefix "neo-", whereas C-25 (*R*)-epimers of known C-25 (*S*)-sapogenins are given the prefix "iso-". Epimers with a C-3 α-OH instead of a C-3 β-OH are designated by the prefix "epi-".

Monodesmosides have linear or branched sugar chains linked in most cases to the C-3 β-OH group, whereas furostanol bisdesmosides display an additional glycosidic linkage at C-26. Besides the common sugars listed previously, less prevalent sugars include D-fucose (fuc), β-D-2′-deoxyribose (drib), and β-D-apiose [api (f)]. For a review of steroid saponins, see [67].

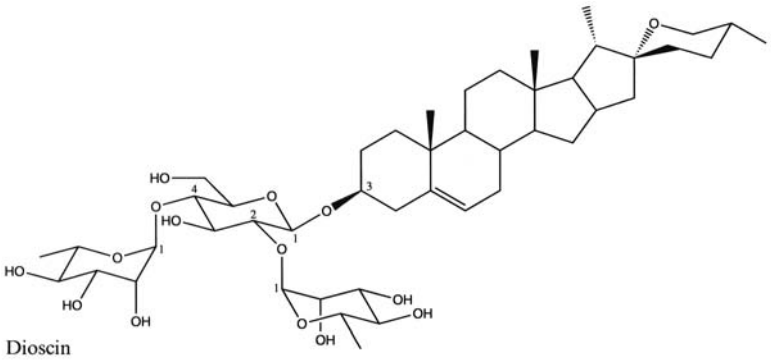
Spirostanol Saponins. Figure 1 provides the structures for a number of spirostanol aglycones. Most spirostanol saponins are monodesmosides with a single glycosidic bond at the C-3 β-OH. This is also true of hydroxylated sapogenins such as digitogenin (**15**) and paniculogenin (**14**). Monodesmosidic steroid saponins exhibit typical saponin properties, such as strong hemolytic activity.

Important saponins derived from diosgenin (**1**; → Hormones) and its C-25 (*S*)-epimer yamogenin (**2**) are dioscin [rha1 → 2(rha1 → 4glc)-**1**] (see Fig. 2 for an example of the signifance of the abbreviated notation used here and elsewhere) and gracillin [rha1 → 2(glc1 →3glc)-**1**], two glycosides first isolated from wild yam (*Dioscorea* sp.). Dioscin has been reported in



Sapogenin	CAS registry no.	Δ	C-5 H	R	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
Diosgenin (**1**)	[*512-04-9*]	5		H	H	H	CH_3	H	H	H	H	H
Yamogenin (**2**)	[*512-06-1*]	5		H	H	H	H	CH_3	H	H	H	H
Pennogenin (**3**)	[*507-89-1*]	5		H	H	H	CH_3	H	OH	H	H	H
Ruscogenin (**4**)	[*472-11-7*]	5		H	H	H	CH_3	H	H	H	OH	H
Yuccagenin (**5**)	[*511-97-7*]	5		H	H	H	CH_3	H	H	H	H	OH
Kammagenin (**6**)	[*564-44-3*]	5		H	H	H	CH_3	H	H	O=	H	OH
Isonuatigenin (**7**)	[*7050-41-1*]	5		H	H	H	OH	CH_3	H	H	H	H
Tigogenin (**8**)	[*77-60-1*]		α	H	H	H	CH_3	H	H	H	H	H
Neotigogenin (**9**)	[*470-01-9*]		α	H	H	H	H	CH_3	H	H	H	H
Chlorogenin (**10**)	[*562-34-5*]		α	α-OH	H	H	CH_3	H	H	H	H	H
Neochlorogenin (**11**)	[*511-91-1*]		α	α-OH	H	H	H	CH_3	H	H	H	H
Hecogenin (**12**)	[*467-55-0*]		α	H	H	H	CH_3	H	H	O=	H	H
Gitogenin (**13**)	[*511-96-6*]		α	H	H	H	CH_3	H	H	H	H	OH
Paniculogenin (**14**)	[*16750-37-1*]		α	α-OH	H	OH	H	CH_3	H	H	H	H
Digitogenin (**15**)	[*511-34-2*]		α	H	β-OH	H	CH_3	H	H	H	H	OH
Smilagenin (**16**)	[*126-18-1*]		β	H	H	H	CH_3	H	H	H	H	H
Sarsasapogenin (**17**)	[*126-19-2*]		β	H	H	H	H	CH_3	H	H	H	H

Figure 1. Spirostanol-type sapogenins



Dioscin

rha1 → 2(rha1 → 4g1c)−3−O−diosgenin

rha1 → 2(rha1 → 4g1c)−**1**

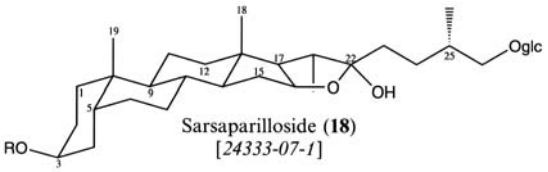
rha1

$^{4}_{2}$g1c → diosgenin

rha1

Figure 2. Alternative notational schemes for saponins, using dioscin as an example

a number of plant sources, including palms [68]. The aglycones are important sources for steroid synthesis, as are hecogenin (**12**), smilagenin (**16**), and its epimer sarsasapogenin (**17**). The latter were first isolated from *Agave* sp. and *Smilax crenata*, respectively. Sarsasapogenin (**17**) yields the monodesmoside parillin, glc1 → 2[rha1 → 4 (glc1 → 6glc)]-**17**, and the bisdesmoside sarsaparilloside (**18**).



Sarsaparilloside (**18**)
[*24333-07-1*]

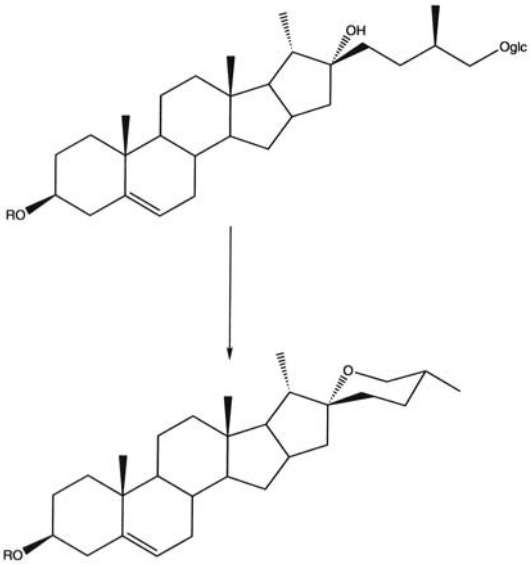
A number of steroid saponins have been isolated from foxglove (*Digitalis purpurea, D. lanata*), of which digitonin, glc1 → 3gal1 → 2 (xyl1 → 3glc)1 → 4gal-**15**, and its aglycone digitogenin (**15**) are the most important. Digitonin forms very insoluble complexes with cholesterol, and has been used as a reagent for the determination of this sterol. Minor sapogenins in *Digitalis* sp. are gitogenin (**13**), tigogenin (**8**), and its epimer neotigogenin (**9**). The saponin glc1 → 3glc-**13** was isolated from Agave cantala [69].

Together with diosgenin (**1**) derivatives, the pennogenin (**3**) saponin dioscinin, rha1 → 4rha1 → 4(rha1 → 2glc)-**3** was isolated from the palm *Trachycarpus wagnerianus* [70]. Another saponin was isolated from *Dracaena mannii* [71] and characterized as rha1 → 2rha1 → 3glc-**3**, showing antimicrobial activity.

Saponins of ruscogenin (**4**) were isolated from *Ophiopogon* sp. [72] and identified as ophiopogonin B (rha1 → 2fuc-1-O-**4**) and D [rha1 → 2 (xyl1 → 3fuc)-1-*O*-**4**]. In both cases the sugar chain is attached to the C-1-hydroxyl group.

Chlorogenin (**10**) was first isolated from *Chlorogalum pomeridianum*. Its saponins were used historically as a poison to stun fish, while at the same time leaving them edible by humans.

Furostanol Saponins. As already mentioned, furostanol saponins are readily converted to spirostanol saponins by dilute acid or β-glucosidases.



Leaves and stems often yield the protosaponins of spirostanols isolated from other parts of the plant.

The hydroxyl group at C-22 can be displaced by alkyl alcohols to yield alkylprotosaponins [73], or eliminated with acetic acid. The resulting $\Delta^{20,22}$-furostene saponins are termed pseudoprotosaponins. The isolation of furostene bisdesmosides [69] represents the first report of a genuine pseudoprotosaponin in nature.

Furostanols are easily distinguished from spirostanol saponins with Ehrlich's reagent [74], and also by IR spectroscopy, since furostanols lack the characteristic absorption bands of a C-22 spiroketal moiety.

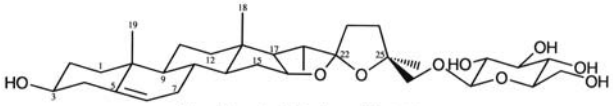
The best known example of a bisdesmosidic steroid saponin is sarsaparilloside (**18**) (R = glc1 → 2[rha1 → 4(glc1 → 6glc)] –) from sarsaparilla, the dried root of *Smilax aristolochiaefolia*, used as a flavoring in beverages.

Furostanol glycosides isolated from garlic (*Allium sativum*) [75] were shown to be derived from chlorogenin (**10**). Mild hydrolysis yields antifungal spirostanol saponins.

Furostanols of tigogenin (**8**) were isolated from *Nicotiana tabacum* [76], of sarsasapogenin (**17**) from *Asparagus sp*. [77], of diosgenin (**1**) from *Balanites aegyptiaca* [78], and of gitogenin (**13**) from *Trigonella foenum-graecum* [79].

Trisdesmosidic furostanol glycosides have been reported for ruscogenin (**4**) saponins [72].

Avenacosides A and B were isolated from oat seeds [80] and identified as glc1 → 2(rha1 → 4glc)- and glc1 → 3glc1 → 2(rha1 → 4glc)-glycosides of nuatigenin-26-glucopyranoside (**19**), respectively. A highly specific β-glucosidase (avenacosidase) [81] yields the antifungal 26-desglucoavenacosides. Nuatigenin saponins from *Solanum aculeatissimum* have recently been proposed as a starting material for steroid synthesis [82].



Nuatigenin-26-glucoside (**19**)

Other Steroid Systems. Saponins from *Polypodium vulgare* are derived from a rare type of cholestanone system with a hydroxytetrahydropyran ring at C-17 [83].

Uses. Spirostanol and furostanol saponins of diosgenin (**1**) and its epimer yamogenin (**2**) were the first natural starting materials for the industrial synthesis of pregnenolone and progesterone (→ Hormones, Section 3.2.). Hecogenin (**12**), smilagenin (**16**), and sarsasapogenin (**17**) are also used as educts for steroid hormones. However, the growth in demand could not be satisfied by saponins alone, so the microbiological conversion of sterols such as stigmasterol to steroid precursors and total synthesis have both become important alternatives.

3.2. Glycoalkaloids (→ Alkaloids, Section 9.23.)

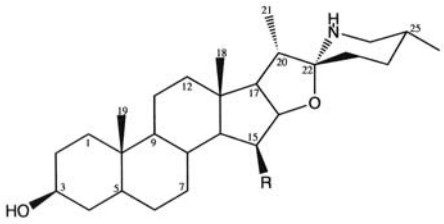
Glycoalkaloids are limited principally to the genera *Solanum, Lycopersicum, Cestrum*, and *Veratrum* of the family Solanaceae. They share a common C_{27} cholestane structure but differ in the structures of their side chains. Because of the presence of these materials in cultivated plants [84], [85], the corresponding structures have been known for some time.

Nitrogen analogues of the spirostanol steroid saponins, with nitrogen replacing an oxygen in the spiroketal ring, are called spirosolanes. Depending on the stereochemistry at C-22 they belong to either the solasodane (22*R*) or the tomatidane (22*S*) group. Analogues in which the 3-β-hydroxyl group has been replaced by an amino group are called aminospirostanes.

Solanidanes and *solanocapsines* have contiguous six-ring systems, whereas epinitrilocholestanes have a tetrahydropyridine ring bound to C-20 of a cholestane structure. Glycosides of the spirosolane and solanidane types are bound exclusively through the C-3 β-OH group.

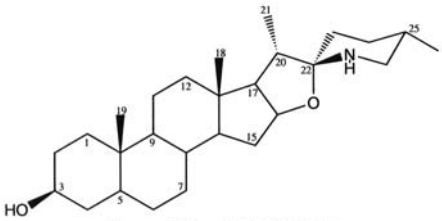
The spirosolane-type aglycone solasodine (**20**) and its saponin α-solamargine (rha1 → 2 (rha1 → 4glc)-**20**) are analogues of diosgenin (**1**) and dioscin, respectively. Soladulcidine (**21**) and 15-hydroxysoladulcidine (**22**) correspond to tigogenin (**8**) and chlorogenin (**10**), respectively (cf. Fig. 3).

Solasodine (**20**) can be converted by *N*-acetylation and subsequent rearrangement to a $\Delta^{20,22}$-furostene, useful as a precursor in steroid synthesis [86]. This reaction is also feasible with the C-22 epimers tomatidine (**23**) and tomatidenol (**24**). Saponins such as α-tomatine (gal1 → 2(xyl1 → 3glc)1 → 4gal-**23**) can be used as natural sources for steroid precursors. The distribution of α-tomatine and its significance have been reviewed [87].



Sapogenin	CAS registry no.	Δ	C-5 H	R
Solasodine (**20**)	[*126-17-0*]	5		H
Soladulcidine (**21**)	[*511-98-8*]		α	H
Hydroxysoladulcidine (**22**)	[*4912-43-0*]		α	OH

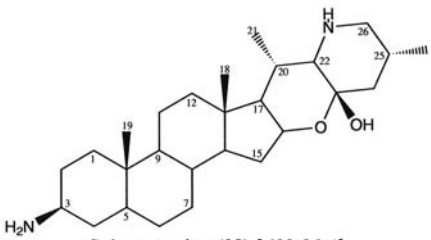
Figure 3. Solasodane-type glycoalkaloids



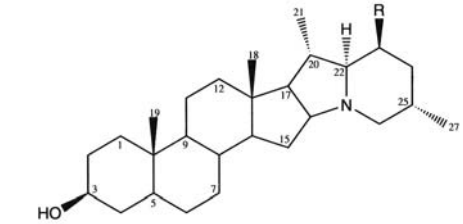
Tomatidine (**23**) [*77-59-8*]
Δ^5, tomatidenol (**24**) [*546-40-7*]

The glycoalkaloid solanine was found in the cultivated potato (*Solanum tuberosum*) and identified as consisting of saponins derived from solanidine (**25**), namely, α-chaconine (rha1 → 2(rha1 → 4glc)-**25**) and α-solanine (rha1 → 2(glc1 → 3gal)-**25**) [88]. Other sapogenins found in *Solanum* sp. (see Fig. 4) are leptinidine (**26**) [89] and demissidine (**27**), with the saponins demissine (glc1 → 2(xyl1 → 3glc)1 → 4gal-**27**) and commersonine [glc1 → 2(glc1 → 3 glc)1 → 4gal-**27**].Chemical degradation of solanidanes to steroids has not been achieved [90].

Solanocapsine (**28**) has been isolated as a sapogenin from *S. pseudicapsicum* [91]; no glycoside has yet been reported.

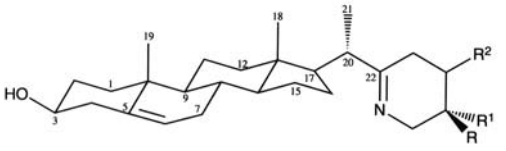


Solanocapsine (**28**) [*639-86-1*]



Sapogenin	CAS registry no.	Δ	C-5 H	R
Solanidine (**25**)	[*80-78-4*]	5		H
Leptinidine (**26**)	[*2448-17-1*]	5		OH
Demissidine (**27**)	[*474-08-8*]		α	OH

Figure 4. Solanidane-type glycoalkaloids

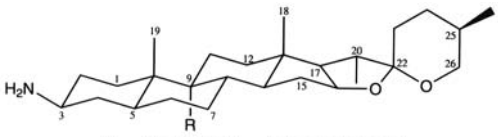


Sapogenin	CAS registry no.	Δ	R	R^1	R^2
Verazine (**29**)	[*14320-81-1*]	5	H	CH_3	H
Tomatillidine (**30**)	[*986-45-8*]	5	CH_3	H	O=

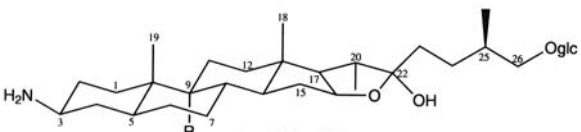
Figure 5. Epinitrilocholestane-type glycoalkaloids

Natural epinitrilocholestanes (Fig. 5) include verazine (**29**) and tomatillidine (**30**). Intermediates in the conversion of spirosolanes to steroids [92] and in the transformation of spirosolanes to solanidanes [93] have similar structures.

The aminospirostanes jurubidine (**31**) and paniculidine (**32**) from *S. paniculatum* [94] are sapogenins of furostane glycosides such as jurubine (**33**).



R = H, jurubidine (**31**) [*6084-44-2*]
R = OH, paniculidine (**32**) [*138464-37-6*]



Jurubine (**33**)

Uses. The spirosolanes solasodine (**20**), tomatidine (**23**), and tomatidenol (**24**) serve as natural sources for steroid synthesis. The use of enzymes [95] for glycolysis of solasodine saponins produced by plant cell cultures has been proposed [96].

Other glycoalkaloids or sapogenins have gained little commercial interest.

3.3. Triterpene Saponins

Triterpene glycosides are the most common saponins in nature, and they have been reviewed extensively [20–22]. A derivative of triterpenoids was found in tertiary sediments [97].

Monodesmosides have linear or branched sugar chains, usually linked to the C-3 β-OH group. The common sugars listed previously are supplemented by such less frequently encountered sugars as β-D-fucose (fuc), β-D-fructose [fru (f)], β-D-quinovose (qui), β-D-glucuronic acid (glcA), and β-D-galacturonic acid (galA).

Oleananes. Saponins derived from β-amyrin (**34**) are the most common triterpene glycosides (cf. Fig. 6).

The variability of substituents is immense. The most frequently hydroxylated carbon centers of the ring system are C-2, C-16, C-21, and C-22. Saponins of hydroxylated aglycones are esterified with organic acids (e.g., acetic, butyric, 2-methylbutyric, tiglic, angelic, and benzoic acids). One example is the principal saponin glc1 → 2(glc1 → 4glcA)-**47** of horse chestnut, which is esterified at C-22 with acetic acid and at C-21 with tiglic or angelic acid. The complete mixture of saponins is called escin.

Of the methyl substituents, C-23, C-24, C-28, C-29, and C-30 are most frequently oxidized to hydroxymethyl, aldehyde, and carboxylic acid groups. Sapogenins with a C-28 carboxylic acid function are present in plant leaves and stems in the form of bisdesmosides with an acyl – glycosidic linkage to a second sugar chain. Enzymatic cleavage of the acyl – glycosidic bond yields the biologically more active monodesmosides. One example is found in a report on the isolation of two oleanolic acid (**54**) saponins from *Momordica cochinchinensis* [98], momordins Id [xyl1 → 2 (xyl1 → 3glcA)-3-*O*-**54**] and IId [xyl1 → 2(xyl1 → 3glcA)-3-*O*-**54**-28-*O*-glc]. Quinoside A from *Chenopodium quinoa* has been reported [2] to be a trisdesmoside of hederagenin (**59**), 3,23-bis (glc)-**59**-28-*O*-ara3 ← 1glc.

Saponins from licorice, the extract of *Glycyrrhiza glabra*, have a keto group at C-11. The resulting enone structure facilitates UV detection during HPLC separation. The composition, uses, and analysis of licorice have been reviewed [99]. The main sapogenin from this source is glycyrrhetic acid (**38**), with the principal saponin being glycyrrhizin (glcA1 → 2glcA-38).

A subgroup of the oleanane-type saponins consists of glycosides with an ether bridge between C-13 and C-18 referred to as epoxyoleanane saponins (Fig. 7).

Examples are protoprimulagenin A (**70**), found in *Primula* sp., cyclamiretin A (**72**) and its saponin cyclamin [xyl1 → 2(glc1 → 3glc)1 → 4(glc1 → 2-ara)-**72**] from *Cyclamen europeaum*, and the saikogenins (**75**) – (**77**) from *Bupleurum falcatum*, used in traditional oriental medicine [100].

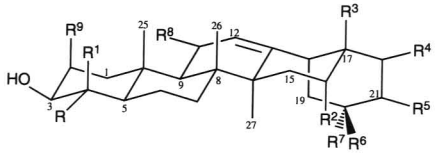
Epoxyoleanane-type saponins are very sensitive to extraction conditions, and they yield artifacts upon acidic cleavage of the ether linkage. Protoprimulagenin A (**70**) yields primulagenin A (**48**), whereas saikogenins (**75**) – (**77**) rearrange to $\Delta^{11,13(18)}$-dienes not found in natural sources.

Ursanes. Aglycones of the ursane type (cf. Fig. 8) are derived from α-amyrin (**78**). Reports describe the isolation of saponins of ursolic acid (**79**) from both maté (*Ilex paraguayensis*) [101] and *Cynara cardunculus* [102]. Ilexgenin A (**82**) was first isolated from *I. pubenscens* [103]. An example of acyl – glycosidic linkages in ursane-type saponins is the asiaticoside rha1 → 4-glc1 → 6glc-28-O-**84**.

Dammaranes. In addition to saponins derived from oleanolic acid (**54**), the roots of *Panax schinseng* contain saponins originating from the tetracyclic dammarane-type aglycones (see Fig. 9). Elucidation of their true structures was complicated by rapid epimerization at C-20 during isolation. Progress in the identification of saponins from *Panax* sp. has been reviewed [104].

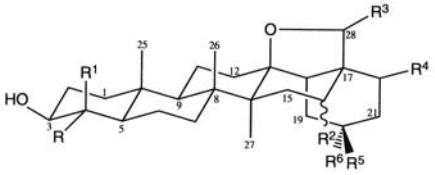
Ginsenosides of protopanaxadiol (**87**) are bisdesmosides with glycosidic linkages at C-3 and C-20, whereas protopanaxatriol (**88**) has glycosides linked to C-6 and C-20. Major saponins are ginsenosides Rb1 (glc1 → 2glc-3-O-87–20-O-glc6 ← 1glc) and Rg1 (glc-3-*O*-**88**-20-*O*-glc).

Lupanes and Hopanes. Sapogenins of the pentacyclic lupane and hopane systems are not very common compared to other triterpenes. Although unsubstituted ring systems are present in fruit waxes and other nonpolar plant materials, saponins are scarce. A saponin from *Asparagus gonocladus* has been isolated and identified as the glc1 → 2rha-glycoside of betulinic acid (90) [105]. Known hopane-type sapogenins include **91** and **92**.



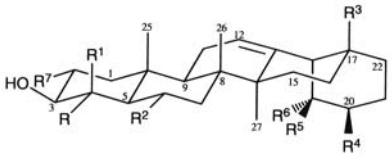
Sapogenin	CAS registry no.	R	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9
β-Amyrin (**34**)	[*559-70-6*]	CH_3	CH_3	H	CH_3	H	H	CH_3	CH_3	H	H
Sophoradiol (**35**)	[*6822-47-5*]	CH_3	CH_3	H	CH_3	α-OH	H	CH_3	CH_3	H	H
Canoniensistriol (**36**)	[*83718-68-7*]	CH_3	CH_3	H	CH_3	α-OH	α-OH	CH_3	CH_3	H	H
Glycyrrhetol (**37**)	[*14226-18-7*]	CH_3	CH_3	H	CH_3	H	H	CH_3	CH_2OH	O=	H
Glycyrrhetic acid (**38**)	[*471-53-4*]	CH_3	CH_3	H	CH_3	H	H	CH_3	COOH	O=	H
Liquiritic acid (**39**)	[*10379-72-3*]	CH_3	CH_3	H	CH_3	H	H	COOH	CH_3	O=	H
Epikatonic acid (**40**)	[*76035-62-6*]	CH_3	CH_3	H	CH_3	H	H	COOH	CH_3	H	H
Liquiridiolic acid (**41**)	[*20528-70-5*]	CH_3	CH_2OH	H	CH_3	H	β-OH	COOH	CH_3	H	H
Melilotigenin (**42**)	[*114702-59-9*]	CH_3	CH_2OH	H	CH_3	O=	H	COOH	CH_3	H	H
Soyasapogenol B (**43**)	[*595-15-3*]	CH_3	CH_2OH	H	CH_3	α-OH	H	CH_3	CH_3	H	H
Soyasapogenol E (**44**)	[*6750-59-0*]	CH_3	CH_2OH	H	CH_3	O=	H	CH_3	CH_3	H	H
Soyasapogenol A (**45**)	[*508-01-0*]	CH_3	CH_2OH	H	CH_3	α-OH	α-OH	CH_3	CH_3	H	H
Azukisapogenol (**46**)	[*86425-21-0*]	CH_3	CH_2OH	H	CH_3	H	H	COOH	CH_3	H	H
Protoescigenin (**47**)	[*20853-07-0*]	CH_3	CH_2OH	OH	CH_2OH	β-OH	α-OH	CH_3	CH_3	H	H
Primulagenin A (**48**)	[*465-95-2*]	CH_3	CH_3	OH	CH_2OH	H	H	CH_3	CH_3	H	H
Theasapogenol D (**49**)	[*53227-91-1*]	CH_3	CH_3	OH	CH_2OH	β-OH	H	CH_3	CH_3	H	H
Theasapogenol B (**50**)	[*13844-01-4*]	CH_3	CH_3	OH	CH_2OH	β-OH	α-OH	CH_3	CH_3	H	H
Theasapogenol C (**51**)	[*14440-27.8*]	CH_2OH	CH_3	OH	CH_2OH	β-OH	H	CH_3	CH_3	H	H
Theasapogenol A (**52**)	[*13844-22-9*]	CH_2OH	CH_3	OH	CH_2OH	β-OH	α-OH	CH_3	CH_3	H	H
Theasapogenol E (**53**)	[*15399-41-4*]	CHO	CH_3	OH	CH_2OH	β-OH	α-OH	CH_3	CH_3	H	H
Oleanolic acid (**54**)	[*508-02-1*]	CH_3	CH_3	H	COOH	H	α-H	CH_3	CH_3	H	H
Echinocystic acid (**55**)	[*510-30-5*]	CH_3	CH_3	OH	COOH	H	H	CH_3	CH_3	H	H
Entagenic acid (**56**)	[*5951-41-7*]	CH_3	CH_3	H	COOH	β-OH	β-OH	CH_3	CH_3	H	H
Serratagenic acid (**57**)	[*6488-64-8*]	CH_3	CH_3	H	COOH	H	H	COOH	CH_3	H	H
Sperculagenic acid (**58**)	[*18671-48-2*]	CH_3	CH_3	H	COOH	H	H	CH_3	COOH	H	H
Hederagenin (**59**)	[*465-99-6*]	CH_2OH	CH_3	H	COOH	H	H	CH_3	CH_3	H	H
Bayogenin (**60**)	[*6989-24-8*]	CH_2OH	CH_3	H	COOH	H	H	CH_3	CH_3	H	OH
Polygalacic acid (**61**)	[*22338-71-2*]	CH_2OH	CH_3	OH	COOH	H	H	CH_3	CH_3	H	OH
Platycodigenin (**62**)	[*22327-82-8*]	CH_2OH	CH_2OH	OH	COOH	H	H	CH_3	CH_3	H	OH
Esculentic acid (**63**)	[*56283-68-2*]	CH_2OH	CH_3	H	COOH	H	H	CH_3	COOH	H	H
Jaligonic acid (**64**)	[*51776-39-7*]	CH_2OH	CH_3	H	COOH	H	H	CH_3	COOH	H	OH
Gypsogenin (**65**)	[*639-14-5*]	CHO	CH_3	H	COOH	H	H	CH_3	CH_3	H	H
Quillaic acid (**66**)	[*631-01-6*]	CHO	CH_3	OH	COOH	H	H	CH_3	CH_3	H	H
Dianic acid (**67**)	[*91652-29-8*]	CHO	CH_3	H	COOH	H	H	CH_2OH	CH_3	H	H
Gypsogenic acid (**68**)	[*5143-05-5*]	COOH	CH_3	H	COOH	H	H	CH_3	CH_3	H	H
Medicagenic acid (**69**)	[*599-07-5*]	COOH	CH_3	H	COOH	H	H	CH_3	CH_3	H	OH

Figure 6. Oleanane-type sapogenins



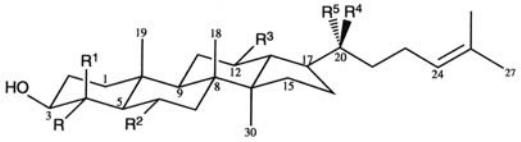
Sapogenin	CAS registry no.	Δ	R	R^1	R^2	R^3	R^4	R^5	R^6
Protoprimulagenin A (**70**)	[*2611-08-7*]		CH_3	CH_3	a-OH	H	H	CH_3	CH_3
Priverogenin B (**71**)	[*20054-97-1*]		CH_3	CH_3	a-OH	H	β-OH	CH_3	CH_3
Cyclamiretin A (**72**	[*5172-34-9*]		CH_3	CH_3	a-OH	H	H	CH_3	CHO
Anagalligenin A (**73**)			CH_3	CH_3	a-OH	OH	β-OH	CH_3	CH_3
Anagalligenin B (**74**)	[*33722-92-8*]		CH_2OH	CH_3	a-OH	H	H	CH_3	CH_3
Saikogenin E (**75**)	[*13715-23-6*]	11	CH_3	CH_3	e-OH	H	H	CH_3	CH_3
Saikogenin F (**76**)	[*14356-59-3*]	11	CH_2OH	CH_3	e-OH	H	H	CH_3	CH_3
Saikogenin G (**77**)	[*18175-79-6*]	11	CH_2OH	CH_3	a-OH	H	H	CH_3	CH_3

Figure 7. Epoxyoleanane-type sapogenins



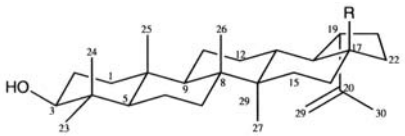
Sapogenin	CAS registry no.	R	R^1	R^2	R^3	R^4	R^5	R^6	R^7
Amyrin (**78**)	[*638-95-9*]	CH_3	CH_3	H	CH_3	CH_3	H	CH_3	H
Ursolic acid (**79**)	[*77-52-1*]	CH_3	CH_3	H	COOH	CH_3	H	CH_3	H
Pomolic acid (**80**)	[*13849-91-7*]	CH_3	CH_3	H	COOH	CH_3	OH	CH_3	H
Cincholic acid (**81**)	[*5948-32-3*]	CH_3	CH_3	H	COOH	CH_3	OH	CH_3	OH
Ilexgenin A (**82**)	[*108524-94-3*]	CH_3	COOH	H	COOH	CH_3	OH	CH_3	H
Rotundic acid (**83**)	[*20137-37-5*]	CH_2OH	CH_3	H	COOH	CH_3	OH	CH_3	H
Asiatic acid (**84**)	[*464-92-6*]	CH_2OH	CH_3	H	COOH	CH_3	H	CH_3	OH
Madecassic acid (**85**)	[*18449-41-7*]	CH_2OH	CH_3	OH	COOH	CH_3	H	CH_3	OH

Figure 8. Ursane-type sapogenins

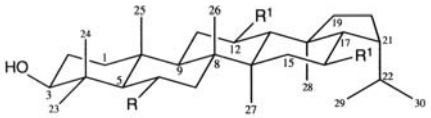


Sapogenin	CAS registry no.	R	R^1	R^2	R^3	R^4	R^5
Dammarenediol (**86**)	[*14351-29-2*]	CH_3	CH_3	H	H	OH	CH_3
Protopanaxadiol (**87**)	[*7755-01-3*]	CH_3	CH_3	H	OH	OH	CH_3
Protopanaxatriol (**88**)	[*1453-93-6*]	CH_3	CH_3	OH	OH	OH	CH_3

Figure 9. Dammarane-type sapogenins



R = CH_3, lupeol (**89**) [*545-47-1*]
R = COOH, betulinic acid (**90**) [*472-15-1*]



$\Delta^{15,17(21)}$, R = OH, R^1 = H, mollugogenol B (**91**) [*22554-64-9*]
$\Delta^{21(22)}$, R = H, R^1 = OH, spergulatriol (**92**) [*61127-09-1*]

Uses. Commercial applications of triterpene saponins are based largely on their surfactant properties and their ability to form oil-in-water emulsions. Formerly used as emulsifiers in X-ray film manufacture (→ Disperse Systems and Dispersants, Section 5.3.7.) and as components of detergents or cosmetics, saponins have been largely replaced in these applications by synthetic compounds.

The extract of *Glycyrrhiza glabra* containing glycyrrhetic acid (**38**) and glycyrrhetin is used by the tobacco and food industries for flavoring purposes [99]. As already mentioned, this sapogenins and saponins also have pharmaceutical value for the treatment of ulcers and gastritis [52]. Saponins used as expectorants are isolated from *G. glabra*, *Gala senega, Primula officinalis*, and *Hedera helix* [106].

A vast number of folk medicines contain saponins, and they are used as tonics and stimulants. The best-known examples are extracts of *Panax schinseng*, containing ginsenosid saponins, and *Bupleurum falcatum*, containing saikosaponins, which are important in traditional oriental medicine.

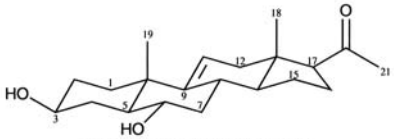
Molluscicidal saponins have been proposed as a means of controlling the spread of schistosomiasis in tropical countries through elimination of the snail vector *Biomphalaria glabrata* [10].

4. Animal Saponins

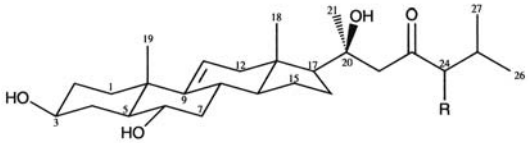
Marine invertebrates of the phylum Echinodermata are categorized into five classes [107]: *Holothuridea* (sea cucumbers), *Asteroidea* (starfish), *Echinoidea* (sea urchins, sand dollars), *Ophiuroidea* (brittle stars, basket stars), and *Crinoidea* (sea lilies, feather stars). Only members of the classes *Holothuridea* and *Asteroidea* produce saponins. Asterosaponins are based on a steroid cholestane system, whereas holothurins have a triterpenoid lanostane framework. 'Besides the common sugars listed previously, less common sugars encountered are the 6-deoxy compounds β-D-quinovose (qui) and β-D-fucose (fuc), both in their pyranose forms.

4.1. Asterosaponins

Hydrolysis of crude saponin isolated from starfish yields the steroid asterone (**93**) [107] together with asterogenol, the corresponding 20*S*-hydroxyl reduction product [108]. A noteworthy feature is the $\Delta^{9(11)}$ double bond. Asterone (**93**) is derived from the genuine sapogenins thornasterol A (**94**) and B (**95**) [109] via retro-aldol cleavage.



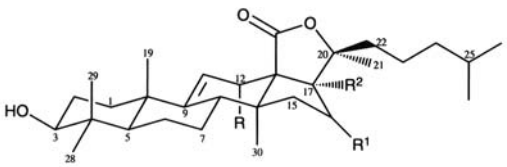
Asterone (**93**) [*37717-02-5*]



R = H, thornasterol A (**94**) [*55897-77-3*]
R = CH_3, thornasterol B (**95**) [*55897-78-4*]

Most saponins from starfish are sulfated at the 3-β-OH group and glycosylated at the 6-α-OH moiety. Their sugar chains consist of five to six monomeric units, with branching at the second sugar. Examples are forbesides A, B, and C, isolated from *Asterias forbesi* and characterized as gal1 → 3fuc1 → 2gal1 → 4(qui1 → 2xyl)1 → 3qui-6-O-**94**-3-O-$SO_3^-Na^+$, qui1 → 2gal1 → 4 (qui1 → 2xyl)1 → 3qui-6-O-**94**-3-O-$SO_3^-Na^+$, and fuc1 → 2gal1 → 4(qui1 → 2qui) 1 → 3(6-deoxy-β-D-xylo-4-hexosulopyranosyl)-6-*O*-**94**-3-*O*-$SO_3^-Na^+$, respectively [28].

Sapogenins with an epoxy function in place of the keto group in the thornasterol side chain [110] or penta- and hexahydroxylated cholestane ring systems [111] have been reported.



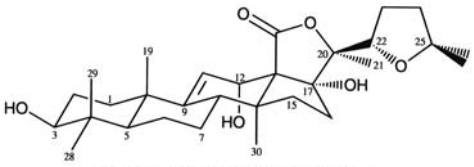
Sapogenin	CAS registry no.	Δ	R	R^1	R^2
Deoxybivittogenin (**97**)	[*77394-02-6*]		H	H	H
Bivittogenin (**98**)	[*67797-17-5*]		OH	H	H
Echinogenol (**99**)			OH	H	OH
Holotoxigenol (**100**)		25	H	O=	H

Figure 10. Holothurinogen-type sapogenins

Uses. Biological activities reported for asterosaponins [112] include cytotoxicity to tumor cells and antiviral activity. However, the high toxicity of these compounds prevents their pharmaceutical use. Use as precursors for steroid synthesis [113] is not technically feasible.

4.2. Holothurins

Holothurins are similar to the asterosaponin glycosides isolated from sea cucumbers. They have a $\Delta^{9(11)}$ double bond, and are prone to yield artifacts. The genuine aglycone holothurigenol (**96**) yields a $\Delta^{7,9(11)}$-diene elimination product on acidic hydrolysis.



Holothurigenol (**96**) [*72244-90-7*]

Aglycones are glycosylated at the 3-β-OH group with sugar chains containing two to six monomer units. In contrast to asterosaponins, hydroxyl groups on the aglycone system are not sulfated. Instead, hydroxyl moieties in the glycoside chain are methylated and sulfated.

Holothurin B, isolated from *Holothuria leucospilata*, was identified as qui1 → 2($Na^+ {}^-O_3S$--*O*-4′-xyl)-3-*O*-**96** [114], whereas holothurin A was shown to be CH_3-*O*-3′-glc1 → 3glc1 → 4-holothurin B [115].

Other examples are saponins derived from aglycones with linear side chains at C-20 (cf. Fig. 10). Bivittosides A through D are derived from **97** and **98** [116], echinosides from **99**, and holotoxins A and B from holotoxigenol (**100**) [117].

Sapogenins with a Δ^7 — instead of $\Delta^{9(11)}$ — double bond have been reported in *Cucumaria frondosa* [118] and *C. echinata* [119].

Uses. Although interesting biological activities have been reported (e.g., cytotoxicity to tumor cells [119] and positive inotropic and chronotropic action on atrial muscle [120]), the pharmaceutical use of holothurins is prevented by their severe toxic effects.

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