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Polyoxygenated Steroids of Marine Origin

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I. Introduction

Sterols of marine organisms have been found to be comprised of most complex mixtures. Over 200 new monohydroxysterols have so far been identified from marine sources, and evidence has been presented for the occurrence of over 70 sterols from a single marine species.[1] Sterol patterns in marine invertebrates reflect the complexity of sterols arising through food chains. The capability of further biochemical modification of dietary sterols makes the sterol mixtures even more complex. The symbiotic relationship between organisms also complicates the sterol compositions.[2]

In the last 20 years many sterols with unprecedented structures have been isolated from marine sources. For many years the known carbon skeleton of sterols ranged from C_{27} to C_{29}, and the carbon variation occurred exclusively in the side chain at C_{24}.[3] After the discovery of the C26-sterols, first detected in 1970 from the mollusk *Placopecten Magellanicus*[4] and later found widespread in marine invertebrates and also in a marine phytoplankton,[5] thus suggesting that all the marine C26-sterols originate from phytoplankton, a number of "nonconventional" sterols have been reported. These include sterols having side chains modified by the apparent loss of carbon atoms or by the addition of extra carbon atoms at biogenetically unprecedented positions of a normal C_8 side chain, as well sterols with unusual nuclei. The discovery of novel sterols as major components of the extracts of marine organisms is not the rule, although there have been many exceptions, especially from sponges. Typical examples are aplysterol (**9**) and 24(28)-didehydroaplysterol (**10**), the first sterols found[6] with a methyl group at C-26, which have been found as the major sterols of the sponges of the genus *Aplysina* (*Verongia*); calysterol (**51**), the major sterol (90% of the sterol mixture) of the sponge *Calyx nicaensis*;[7] petrosterol (**48**), isolated from the sponge *Petrosia ficiformis*;[8,9] strongylosterol (**27**), the sole sterol of *Strongylophora durissima*;[10] and xestosterol (**15**) and sutinasterol (**37**), apparently the result of four biomethylation, isolated as the predominant sterols of *Xestospongia muta*[11] and a *Xestospongia* sp.,[12] respectively. A series of 19-nor-5α-stanols and A-norstanols, both with conventional and nonconventional side chains, again from marine sponges, have been firstly isolated as the major sterol components from *Axinella polypoides*[13] and *A. verrucosa*,[14] respectively. One more interesting case of discovery of a novel sterol as major component of a mixture is dinosterol (**11**) from *Gonyaulax tamarensis*,[15] which is the most characteristic sterol of dinoflagellates and possibly the biological precursor of the cyclopropyl sterol gorgosterol (**45**) found in zooxanthellae-containing hosts.[16] Structures of the nonconventional side chains of marine monohydroxysterols are shown in Figure 1.

Several excellent reviews on the structures, biosynthesis and distribution of marine sterols are available.[2,55,–62] A paper dedicated to the biosynthesis of marine sterols side chain is published in this issue. This review focuses on polyoxygenated steroids from marine organisms, which are a growing group of metabolites with potential interesting biological and pharmacological activities and is intended to be all inclusive with respect to its coverage. Polyhydroxysteroids have been found in algae, and virtually in every marine invertebrata phyla, *i.e.* Porifera, Coelenterata, Bryozoa, Mollusca, Echinodermata, Arthropoda, and Tunicata as well as in fish.

II. Polyoxygenated Steroids of Marine Algae

Polyoxygenated sterols have been occasionally isolated from red (Rhodophyta) and brown (Phoeophyta) algae, but have not yet been reported from the green (Chlorophyta) ones (Figure 2).

A. Red Algae

Dihydroxy steroids **57** and **58** along with 24,25-epoxycholesterol **59** have been isolated as minor components of *Asparagopsis armata*[63] and *Rissoella verruculosa*;[64] **57** and **58** have been also isolated from *Rhodymenia palmata*[65] and the diol **58** has been found

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Maria Valeria D'Auria was born in Naples, Italy, in 1958. She received her degree (Laurea) in chemistry in 1981 from the Università di Napoli. In 1983 she was appointed as Ricercatore at the Dipartimento di Chimica delle Sostanze Naturali, Università di Napoli Federico II. Her research interests include the echinoderm chemistry and, recently, the study of antitumor macrolides from sponges.

Luigi Minale was born in Tripoli, Libia, in 1936 and obtained his Laurea in Chemistry (1960) and Libera Docenza (1967) from the University of Naples. From 1961 to 1969 he was at the Institute of Organic Chemistry of the University of Naples with Professors R. A. Nicolaus and M. Piattelli. In 1969, he moved to the Institute for the Chemistry of Molecules of Biological Interest, C.N.R., Arco Felice and became Director of this institute in 1973 (until 1981) as well as, almost at the same time, Professor of Organic Chemistry at the University of Catania (1975). In the 1977 he moved to the University of Napoli Federico II, Faculty of Pharmacy, and became Director of Department of the Chemistry of Natural Products in 1984 (until 1990). He has been visiting Professor at the University of Aberdeen (Scotland, U.K.; 1973) and at the Tohoku University, Sendai (Japan; 1986). Professor Minale has published more than 200 papers in the chemistry of natural products and organic chemistry. He is member of the Advisory Board of the Gazzetta Chimica Italiana.

Raffaele Riccio was born in Napoli, Italy, in 1948. He obtained his degree (Laurea) in Chemistry in 1972 from the University of Napoli and in 1973 was appointed as Ricercatore of the Consiglio Nazionale delle Ricerche at the Istituto per la Chimica di Molecole di Interesse Biologico, Arco Felice, where he began his research activity in the field of marine natural products working on the chemistry and sterol biogenesis of Mediterranean sponges. From 1976 to 1977 he spent one year in a post-doctoral position with Paul J. Scheuer at the University of Hawaii. In Napoli again he became interested in the chemistry of polyhydroxylated steroidal glycosides from echinoderms. In 1987 he moved at the Faculty of Pharmacy of the Università di Napoli Federico II as Associated Professor of Organic Chemistry. He has spent research leaves with Koji Nakanishi at Columbia University, in 1981, and with Bill Fenical at Scripps Institution of Oceanography, in 1990. He has published more than 100 papers in the field of natural products and organic chemistry.

in *Liagora distenta*[66] and *Scinaia furcellata*.[66] It has been suggested that these side chain oxygenated sterols may be artifacts caused by autoxidation during the isolation process. Francisco *et al.*[63] have shown that **57** and **58** can indeed be produced by the autoxidation of desmosterol (cholesta-5,24-dien-3β-ol); they are nevertheless present in the fresh red alga *A. armata*.

Two ecdysone-like sterols, pinnasterol (**60**) and acetylpinnasterol (**61**), both showing biological activity as molting hormones, have been isolated from *Laurencia pinnata*.[67] The structures were secured by X-ray crystallography of the acetylpinnasterol (**61**). In contrast with ecdysone and the many ecdysteroids isolated from arthropods and certain plant species, all having the 22*R* configuration, which is very important for high activity, the algal pinnasterol and acetylpinnasterol possess the 22*S* configuration. The same configuration has been found in (20*R*,22*S*)-5α-cholesta-9(11),24(25)-diene-3β,6α,20,22-tetrol, the aglycon of the asterosaponin protoreasteroside (**497**) isolated from the starfish *Protoreaster nodosus* and *Pentaceraster alveolatus*.[68]

5α-Cholestane-3,6-dione (**62**) has been reported from some red algae species,[69] and recently the novel 11α-hydroxy-5α-cholestane-3,6-dione (**63**), of potential utility as corticosteroid intermediate, has been isolated from *Acanthophora spicifera*.[70] Another diketosteroid, 5β-cholest-3-ene-7,11-dione (**64**) was isolated from *Hypnea musciformis*.[71] Recently 2α-oxa-2-oxo-5α-hydroxy-3,4-dinorcholestane (**65**), the first example of a ring A-dinorsteroid from a natural source, has been isolated from *Laurencia obtusa*[72] as a minor component. The structure was confirmed by synthesis from 2-(hydroxymethylene)cholest-4-en-3-one and the 5α-hydroxy stereochemistry was determined by NMR experiments.

B. Brown Algae

The first dihydroxysteroid isolated from a marine source was saringosterol (**66**) identified by Ikekawa *et al.*[73] in two brown algae. Since then **66** and 24-oxocholestane (**67**) have been isolated[74-76] from a number of brown algae. Recently the presence of **66** and **67** along with 24,28-epoxyfucosterol (**68**) in the brown alga *Hizikia fusiformis* has been reported.[77] Their origin was considered as doubtful: they could have been *bona fide* constituents of the algae or be artifacts caused by oxidation during the isolation process. Knights[74] showed that the presence of saringosterol (**66**) and the 24-ketosterol **67** in the brown alga *Ascophyllum nodosum* were artifacts arising from autoxidation during the air-drying of the alga, the fresh material containing only fucosterol. An intriguing steroid diol with a novel side chain **69** was isolated from *Desmarestia aculeata*.[78] An unusual sterol with a 24-(vinyloxy) 23-ene side chain **70** was isolated from *Sargassum thumbergii*[79] as a minor component, the predominant sterol of the mixture being fucosterol. Artifactual formation of **70** appears very unlikely and the authors have suggested a biogenetically possible process involving the removal of some leaving group at C-23 of fucosterol 24,28-epoxide, with simultaneous cleavage of the C-24,28 bond.

Steroids containing a 3,5-dien-7-one and 3,5-diene 7α-hydroxycholestane nucleus were isolated from *Fucus evanescens*.[75] Ikekawa and colleagues have suggested that the 3,5-dien-7-ones are probably formed during the isolation procedure from the 3β-hydroxy-5-en-7-one counterparts.[75] We would note that the steroid Δ^5-3β,7α- and Δ^5-3β,7β-diols, along with the Δ^5-3β-hydroxy 7-ones, are well recognized autoxidation products of Δ^5-sterols,[80] thus leaving the origin of the nuclear oxygenated sterols of *F. evanescens* as doubtful.

C. Microalgae

The Haptophyceae are microscopic unicellular algae, which are widely distributed in the ocean and often constitute a major proportion of marine phytoplankton. A novel sterol sulfate, with the dinosterol side chain, hymenosulfate, **71** has been recently isolated from the cultured marine haptophyte *Hymenomonas* sp.[81] Sulfation is typical in the biosynthesis of secondary metabolites in many marine invertebrates, especially echinoderms, but hymenosulfate is the first report of a sterol sulfate from marine microalgae. This steroid has a potent SR (sarcoplasmic reticulum) Ca-releasing activity.

III. Polyoxygenated Steroids of Porifera (Sponges)

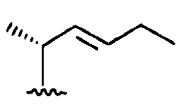
The sponges have yielded the most varied and biogenetically unprecedented array of sterols found among the invertebrate phyla. Most of the 200 new monohydroxysterols found in marine organisms have been isolated from the sponges.[62] The uniqueness of sterols in the cell membranes of sponges is probably related to the presence of unusual fatty acids in their phospholipids.[82-85]

In addition to the monohydroxylated sterols, a number of polyoxygenated sterols have been isolated from sponges; most of them have appeared in the literature in the last two years.

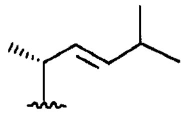
Halistanol sulfate (**72**) isolated from *Halichondria moorei*[86] is the first example of the growing list of sulfated polyhydroxysteroids from sponges (Figure 3), which are very attractive because of their potential activity against HIV virus.[87,88] Both the *tert*-butyl moiety at the end of side chain and the 2β,3α,6α-trihydroxy functions in halistanol are biosynthetically intriguing. Another trisulfated steroid, sokotrosterol sulfate (**73**), has been isolated together with the previous **72** from two Halichondriidae species.[89] The side chain of **73** is unprecedented and involves a "normal" alkylation at C-24 of a standard C_8 side chain and the addition of two extra methyl groups at C-26 and one extra methyl group at C-25. Halistanol and sokotrosterol belong to an unusual class of steroids which possess side chains with quaternary carbons. The side chain of **73** is related to that of mutasterol (**26**), and the authors[89] have proposed a biosynthesis *via* three consecutive SAM biomethylations of codisterol (24*S*-methyl-5,25-cholestadien-3β-ol) or epicodisterol (24*R*). Recently in a continuing search for the biosynthesis of marine lipids, Djerassi and his group[90] have elucidated the biosynthesis of mutasterol in the Caribbean sponge *Xestospongia muta* by feeding selected radioactive precursors and have shown that codisterol is efficiently transformed (10 times faster than its epimer) into mutasterol (**26**). Interestingly, the isolation of the 26-norsokotrasterol sulfate (**74**) with the side chain very similar with that of mutasterol (**26**), the difference being in the position of the double bond, from the sponge *Trachyopsis halichondroides* (family Halichondriidae) has been reported.[91] Very recently Fusetani and his group[92] reported the isolation of four more steroids (**75-78**) with the halistanol sulfate nucleus from the sponge *Epipolasis* sp. The unusual side chain of halistanol sulfate B (**76**) is unprecedented for naturally occurring sterols.[62] A fifth new sulfate steroid isolated from the same sponge, halistanol sulfate E (**79**) is related to **72** by the introduction of an additional hydroxyl group at C-15.[92] Two more steroids with the halistanol sulfate nucleus (**80** and **81**), showing anti-HIV activity, have been isolated from the sponge *Pseudoaxinissa digitata* (order Axinellida, family Axinellidae).[93]

Three novel sterol sulfates (**82-84**), sharing the same tetracyclic nucleus with a sulfate at C-3 and the 19-methyl group oxidized to a carboxyl group, have been isolated from the sponge *Toxadocia zumi*.[94] Antimicrobial, antifeedant, and cytotoxic properties were reported for these steroid sulfates, and the authors suggest that they might be in part responsible for the lack of fouling organisms on *Toxadocia zumi*.[94] A 3β-sulfoxy-4β-hydroxypregnane (**85**) has been isolated from the sponge *Stylopus australis*.[95] A novel group of sterol sulfates (**86-90**) was discovered as antiviral substances in the sponge *Petrosia weinbergi*.[87,88] The structure of the major weinbersterol disulfate A (**86**) was determined by a 2D INADEQUATE NMR experiment performed on a 150-mg sample in conjunction with its HMBC, HETCOR, COLOC, and COSY data, which established the complete connectivity for the molecule.[87] Weibersterol disulfate B (**87**) is related to A (**86**), but lacks the hydroxyl group at C-20 and a further hydroxyl group is located at C-18. Both compounds possess an unprecedented cyclopropane-containing side chain, showing one more examples for the diversity in the side-chain structures of sponge sterols, and exhibited *in vitro* activity against the feline leukemia virus. Weinbersterol disulfate A (**86**) also showed activity against the human immunodeficiency virus. Three minor sterol sulfates (ortho ester disulfates A-C, **88-90**) in the same sponge were isolated, and their structures were found to have an ortho ester functionality.[88] They appear the first reported examples in the steroid class of this particular combination of functionalities. It is of interest to note that the trans diaxial disulfate (2β,3α) and the trans AB ring juncture (5α-H) have been previously encountered in the 5α-cholestane 2β,3α,26-triol sulfates (**530**) isolated from an echinoderm, the ophiuroid *Ophiaracna incrassata*.[96]

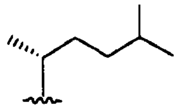
An array of polyoxygenated sterols have been isolated from sponges of the genus *Dysidea* (Figure 4). The



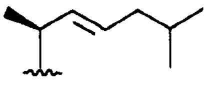
1, *Damiriana hawaiana*[17]
(sponge)



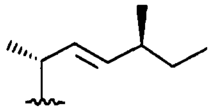
2, *Placopecten magellanicus*[18]
(scallop)



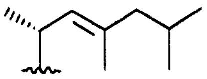
3, *Placopecten magellanicus*[18]
(scallop)



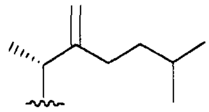
4, *Placopecten magellanicus*[18]
(scallop)



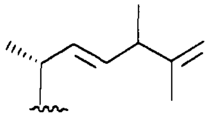
5, occelasterol
Pseudoptamilla occelata[19]
(anellid)



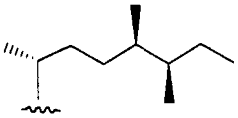
6, dinoflagellates[20]



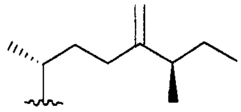
7, *Halichondria panicea*[21]
(sponge)



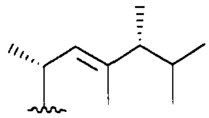
8, *Pseudoaxinella lunacharta*[22]
(sponge)



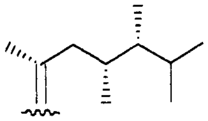
9, aplysterol
Aplysina aerophoba[6]
(sponge)



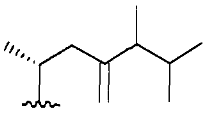
10, *Aplysina aerophoba*[6]
(sponge)



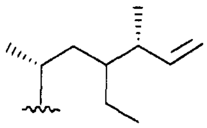
11, dinosterol
Gonyaulax tamarensis[15]
(dinoflagellate)



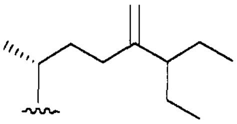
12, peridinosterol
Peridinium foliaceum[23]
(dinoflagellate)



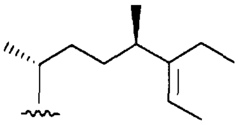
13, *Gonyaulax monilata*[24]
(dinoflagellate)



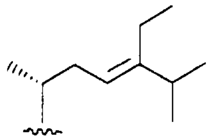
14, ficisterol
Petrosia ficiformis[25]
(sponge)



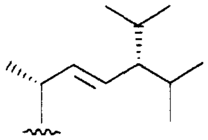
15, xestosterol
Xestospongia muta[11]
(sponge)



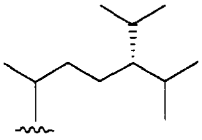
16, verongulasterol
Verongula cauliformis[26]
(sponge)



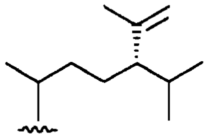
17, *Eutreptia viridis*[27]
(euglenid)



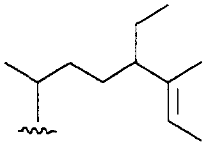
18, *Pseudoaxinissa* sp.[28]
(sponge)



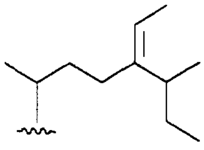
19, *Pseudoaxinissa* sp.[28]
(sponge)



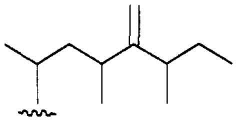
20, *Verongula cauliformis*[29]
(sponge)



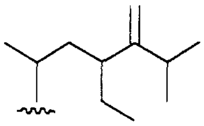
21, stelliferasterol
Jaspis stellifera[30]
(sponge)



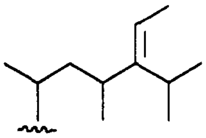
22, isostelliferasterol
Jaspis stellifera[30]
(sponge)



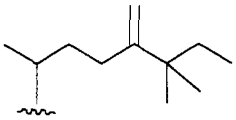
23, reimersterol
Sinularia remei[31]
(soft coral)



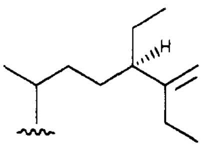
24, siapalosterol
Sinularia siapalosa[32]
(soft coral)



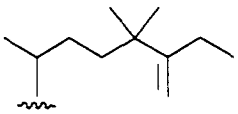
25, *Sinularia ramulosa*[33]
(soft coral)



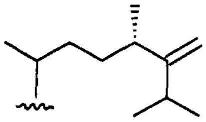
26, mutasterol
Xestospongia muta[34]
(sponge)



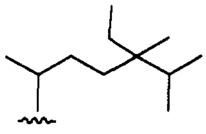
27, strongylosterol
Strongylophora durissima[10]
(sponge)



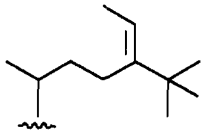
28, durissimasterol
Strongylophora durissima[35]
(sponge)



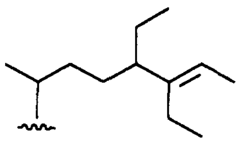
29, pulchrasterol
Aciculites pulchra[36] (sponge)



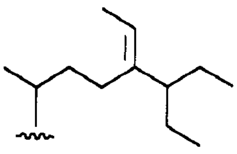
30, *Pseudoaxinissa* sp.[37]
(sponge)



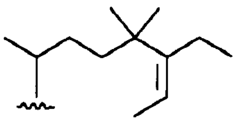
31, *Pseudoaxinissa* sp.[37]
(sponge)



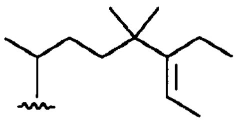
32, *Strongylophora durissima*[35]
(sponge)



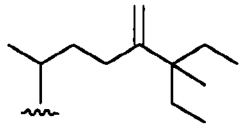
33, *Strongylophora durissima*[35] (sponge)



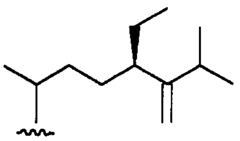
34, xestospongesterol *Strongylophora durissima*[38] (sponge)



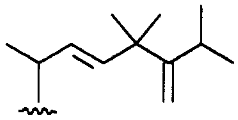
35, *Strongylophora durissima*[39] (sponge)



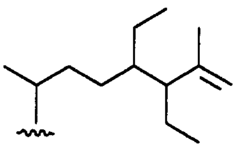
36, *Xestospongia* sp.[39] (sponge)



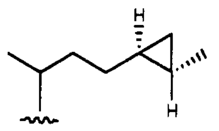
37, sutinasterol *Xestospongia* sp.[12] (sponge)



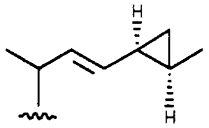
38, Halichondriidae sponges[40]



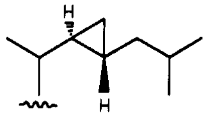
39, *Xestospongia* sp.[12] (sponge)



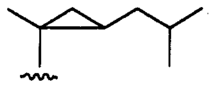
40, *Spheciospongia* sp.[41] (sponge)



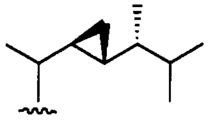
41, glaucasterol *Sarcophytum glaucum*[42] (soft coral)



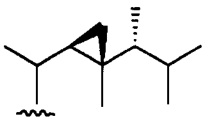
42, *Siphonoborgia* sp.[43] (soft coral)



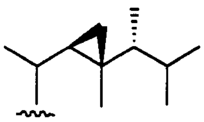
43, *Cystoseira* sp.[44] (algae)



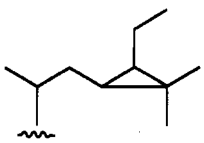
44, *Gorgonia flabellum*[45] (gorgonian)



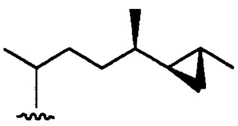
45, gorgosterol zooxanthellae[46,47]



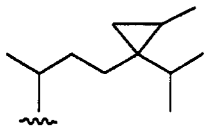
46, *Calyx nicaensis*[48] (sponge)



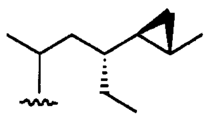
47, nicasterol *Calyx nicaensis*[49] (sponge)



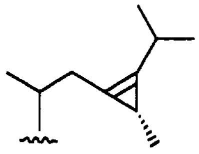
48, petrosterol *Petrosia ficiformis*[8,9] (sponge)



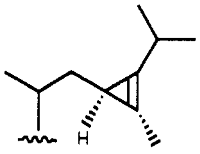
49, Crysophyta sp.[50] (algae)



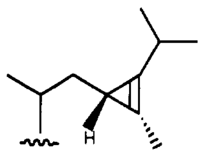
50, hebesterol *Petrosia hebes*[51] (sponge)



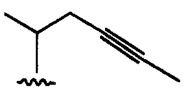
51, calysterol *Calyx nicaensis*[7] (sponge)



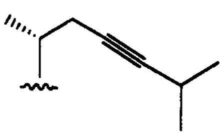
52, *Calyx nicaensis*[48] (sponge)



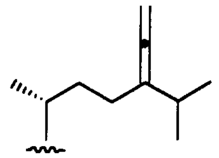
53, *Calyx podatypa*[52] (sponge)



54, *Calyx nicaensis*[53] (sponge)



55, *Calyx nicaensis*[53] (sponge)



56, *Callyspongia diffusa*[54] (sponge)

Figure 1. Nonconventional side chains of marine monohydroxysterols. All compounds possess the cholest-5-ene tetracyclic nucleus except 12 and 13 (4α-methylcholestane nucleus), 14 (5α-cholestane nucleus), 17 (cholesta-5,7-diene nucleus), and 29 (cholest-7-ene nucleus).

first example of this group of steroids is 9α,11α-epoxycholest-7-ene-3β,5α,6β,19-tetrol 6-acetate (**91**) isolated from an unidentified species of *Dysidea* collected in Guam.[97] The 19-hydroxyl group was previously found in one sterol from the soft coral *Lithophyton viridis*[98] and later in many sterols from

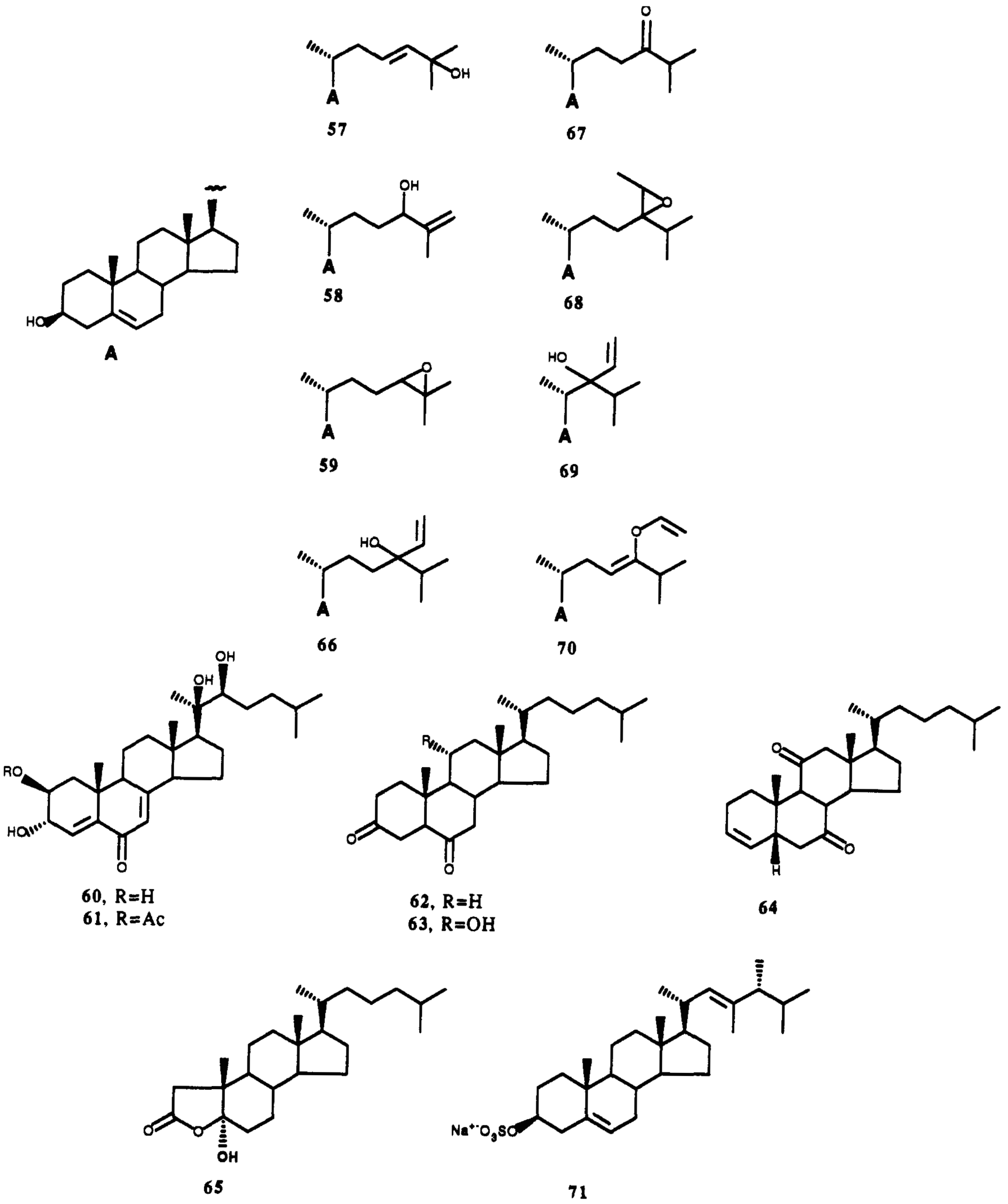


Figure 2. Polyoxygenated sterols from marine algae.

Dysidea. The 9,11-epoxide is the most novel aspect of this sterol. The shape of the 11-H proton signal (doublet with $J = 4.7$ Hz) in the ^1H NMR of **91** was the key argument supporting the 9α,11α stereochemistry, as the 3.5-Hz coupling between H-6 and H-7 was considered by the authors[97] more compatible with a 6β-acetoxy than with a 6α-acetoxy stereochemistry. The stereochemistry at C-6 has subsequently been revised by Fujimoto *et al.*[99] as the 6α-isomer through further NMR measurements involving the evaluation of the pyridine-induced shifts of the protons at C-4 of the corresponding 6-ol.

Herbasterol (**92**), a polyhydroxylated 9,11-secosterol, is responsible for the ichthyotoxic and antimicrobial activities observed in the methanol extract of *Dysidea herbacea*.[100] The structure of **92** was elucidated by interpretation of spectral data and conversion, on either acid or basic treatment, into 19-norherbasterol (**93**). During the retroaldol reaction, the stereochemistry at C-6 undergoes inversion, and the authors[100] explained this phenomenon by assuming an A/B cis ring junction in herbasterol (**92**), the inversion occurring a C-10 during the retroaldol reaction. A further toxic polyoxygenated steroid **94** has been isolated from the Mediterranean *Dysidea tupha*.[101] A group of eight new polyhydroxysterols, all showing a common 5α-cholest-7-ene-2α,3β,5,6β,9α,11α,19-heptol framework **95** and various conventional side chains, have been isolated

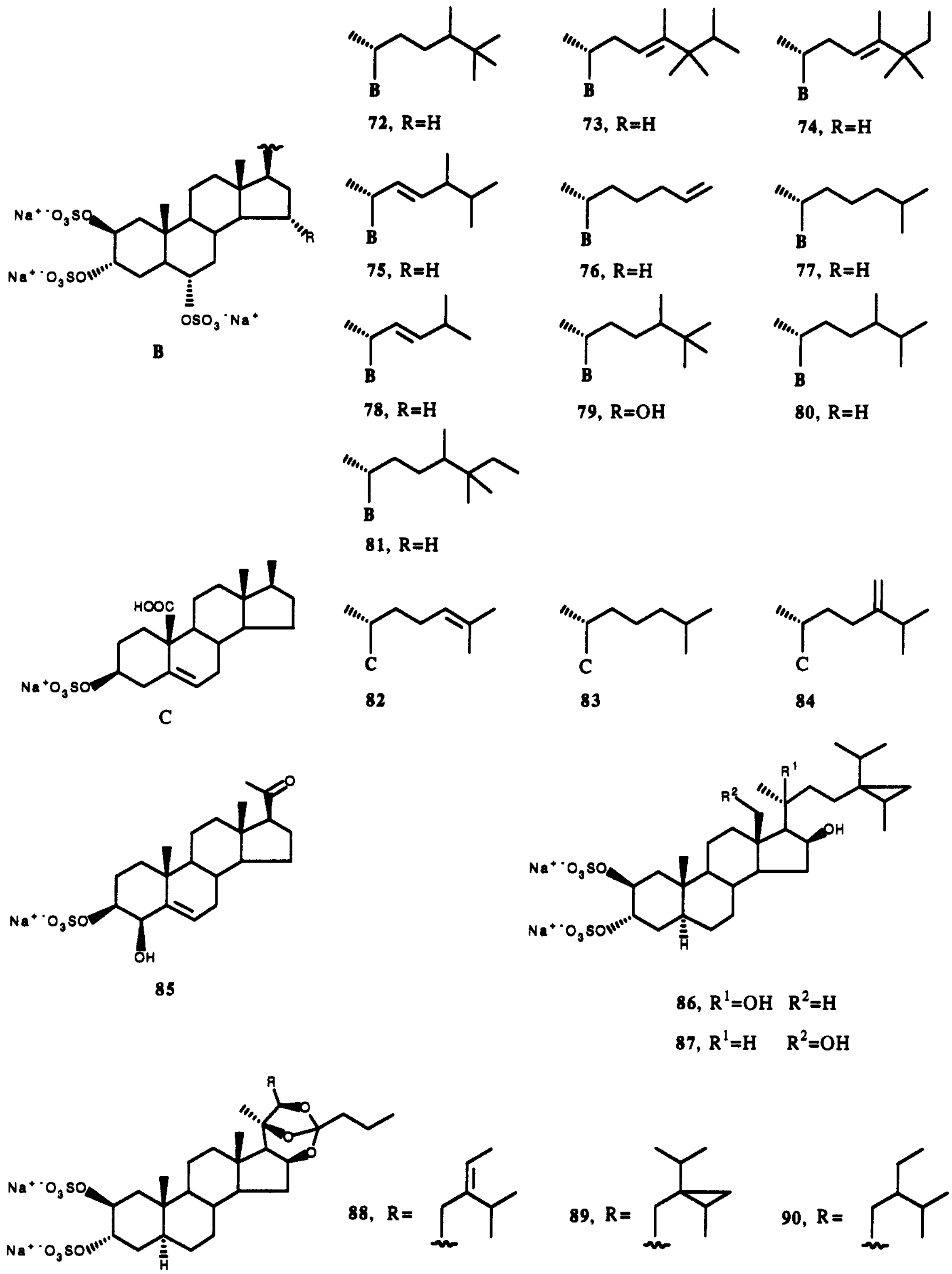
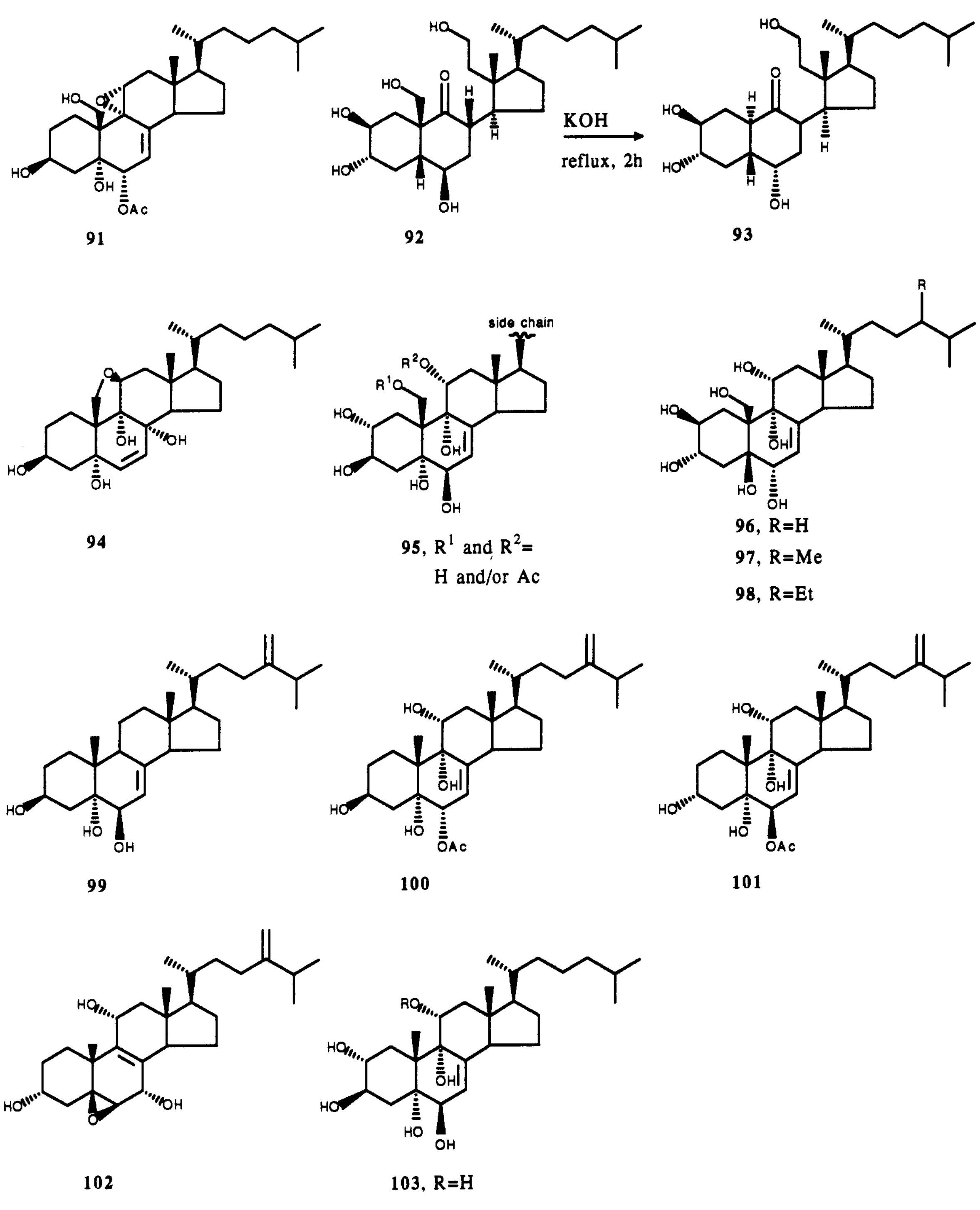


Figure 3. Steroid sulfates from sponge.

from *Dysidea etheria*,[102] collected in Bermuda. The 6β-hydroxy stereochemistry has been confirmed by evaluating the pyridine-induced shifts of the protons at C-4 according to the method suggested by Fujimoto *et al.*[99,103] Specifically, the chemical shift of the 4β-proton at δ 3.12 requires the hydroxyl group at C-6 to be in the β-configuration. The major sterol of this group **95** with $R_1 = R_2 =$ Ac and the cholesterol side chain was active in the cytotoxic KB assay.[102] Three minor polyhydroxylated sterols **96–98** in the same sponge were isolated and their structures were found to be analogous to those discovered earlier **95**, but distinguished by a 5β-skeleton,[104] which is a rare feature among sterols from sponges. Herbasterol (**92**) from *Dysidea herbacea*[100] and a series of coprostanols from *Petrosia ficiformis*[105] are the only other examples of 5β-sterols from Porifera. The authors[104] have suggested that both the 5α,6β- and 5β,6α-hydroxylated series cooccurring in the same sponge could arise from a 5α,6α-epoxide common precursor. More recently another group of polar sterols **99–102** have been discovered in a specimen of *Dysidea herbacea*,[106] collected near Massawa, Ethiopia. Strong support for the assignment of configurations at C-6 of the two epimers **100** and **101** was



91 **92** **93**

94

95, R^1 and R^2= H and/or Ac

96, R=H

97, R=Me

98, R=Et

99 **100** **101**

102

103, R=H

104, R=Ac

Figure 4. Polyhydroxysteroids from sponges of the genus *Dysidea*.

derived from the comparison of the ^1H NMR data. The small coupling constant between H-6 and H-7 (<1 Hz) in **100**, when compared with *J* of 5.5 Hz observed in the spectrum of **101**, determined the configuration 6α-OAc in **100** and the 6β-OAc in **101**. The NOE observed between 19-Me and H-6 in **100** reinforced these assignments. Extensive NOE measurements also yielded data that allow the stereochemistry of **102** to be determined.[106] Two other polyhydroxysteroids **103** and **104** were reported from the sponge *Dysidea fragilis*[107] collected in the Black Sea and their structures were found to be related to **95** earlier isolated from *D. etheria*,[102] but lacking the 19-hydroxyl group.

Several other polyoxygenated sterols were isolated from sponges (Figure 5). Three pregnane steroids **105**–**107** were isolated from *Haliclona rubens*.[108] They appeared to be the first example of pregnane derivatives isolated from marine sources. Two novel unusual pregnanes, agnatasterone A (**108**) and B (**109**), pregnatrienolones without much relationship on reference steroids, have recently been discovered in *Axinella agnata*[109] collected off Roscoff, France, and in Northern area of Ile de Batz. The pregnane structures of **105**–**109** immediately suggest steroid hormones, but the biogenesis and the role of these sponge-derived pregnane steroids have yet to be elucidated.

Sterols with the Δ^7-$3\beta,5\alpha,6\beta$-triol nucleus of **99** have previously been described from *Spongionella gracilis*,[110] *Hippospongia communis*,[111] *Spongia officinalis*,[111] and *Ircinia variabilis*.[111] Sterols with this nucleus have also been isolated from the bryozoan *Myriapora truncata*[112] and from the scallop *Patinopecten yessoensis*.[113] Very recently the 24-ethylcholestane-$3\beta,5\alpha,6\beta$-triol and its 6-keto derivative have been isolated from the sponge *Spirastrella incostans*.[114] The 6β-hydroxy stereochemistry in the Δ^7 derivatives was deduced from spectral data and supported by comparison with synthetic model compounds.[113] *Spongionella gracilis*[115] also gave Δ^7-$3\beta,6\alpha$-dihydroxysterols (**110**), *Spongia officinalis*[116] gave Δ^7-$3\beta,5\alpha,6\beta,9\alpha$-tetrahydroxysterols (**111**) and *Hippospongia communis*[117,118] has yielded 5,6-secosterols (**112**) with various conventional side chains. The Δ^7-$3\beta,5\alpha,6\beta$-trihydroxysterols have been isolated from sponges which contain $\Delta^{5,7}$-sterols as main sterol components and it has been suggested[110] that they could arise from $\Delta^{5,7}$-sterols. The 5,6-secosterols could be in turn derived from the cleavage of the C-5/C-6 bond of the Δ^7-$3\beta,5\alpha,6\beta$-trihydroxysterols.[117] We note that the polyoxygenated derivatives of ergosterol characterized by Δ^7-$3\beta,5\alpha,6\beta$-triol and Δ^7-$3\beta,5\alpha,6\beta,9\alpha$-tetrol partial structures were previously isolated from the terrestial fungus *Polyporus versicolor*.[119]

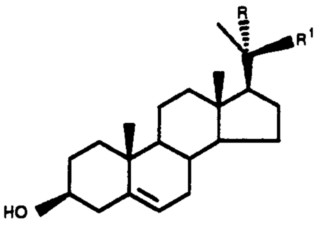
More recently a group of norsterols, incisterols (**113** and conventional Δ^{22} side chains), with an unprecedented highly degraded skeleton have been isolated from the Mediterranean sponge *Dictyonella incisa*.[120] The authors have proposed that they could arise from $\Delta^{5,7}$-sterols, through the formation of $3\beta,5\alpha,6\beta$-triols, both of which are present in *D. incisa*, followed by a successive cleavage of the C-5/C-6 linkage to give 5,6-secosteroids related to **112**. Subsequent cleavage of the C-9/C-10 linkage would result in the removal of the entire ring A including the 19-methyl group. The incisterols, by the authors own admission, are probably artifacts of methanol incorporation, since methanol was used in the extraction. An endoperoxide or a keto acid are suggested as the possible natural products.[120]

Recently a few more secosterols have been recovered from sponges. A new 9,11-secosterol **114** has been isolated from the Mediterranean sponge *Spongia officinalis*.[121] 9,11-Secosterols were earlier found in a gorgonian[122] and in a soft coral of the genus *Sinularia*[123,124] and later in the sponge *Dysidea herbacea*.[100] A 8,9-secosteroid, jereisterol A (**115**), and an 8,14-secosteroid, jereisterol B (**116**), have been isolated from the Pacific sponge *Jereicopsis graphidiophora*.[125] Jereisterol A and B combine the unique 3β-methoxy group with a rare secostructure. Surprisingly this sponge lacks the usual 3β-hydroxysterols, but contains, 3β-methoxysteroids with normal Δ^5,Δ^0 and the rare $\Delta^{8,14},\Delta^8$ and $\Delta^{7,9(11)}$ nuclei; some others have further oxygenation in the nucleus (**117**–**121**).[126]

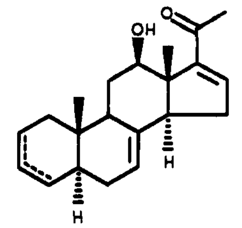
Anthosterones A (**122**) and B (**123**), which represent the first examples of a new type of ring A contraction in a steroid nucleus, have been isolated from the sponge *Anthoracuata graceae*.[127] The structure of anthosterone A (**122**) was verified by single-crystal X-ray diffraction analysis.[127] The authors suggested a possible biosynthesis of the anthosterone nucleus through a benzilic acid rearrangement of a 2,3-diketosteroid precursor as a ring contraction step. Δ^4-3,6-Diketosteroids **124** were also isolated in the same sponge.[127] Steroidal Δ^4-3,6-diketones have been then found in the sponge *Geodia cydonium*[128] and *Cinachyra tarentina*,[129] where they cooccur with the more common steroidal Δ^4-3-ketones. $\Delta^{4,7}$-3,6-Diketones **125** with the conventional 24-methyl-24-ethyl and cholesterol side chains were isolated from *Raphidostila incisa*,[130] where they cooccur with a major amount of 5,8-epidioxy-Δ^6-sterols. Three unusual steroidal $\Delta^{5,8(9)}$-3β-hydroxy 7-ketones (**126**) have been isolated from the sponge *Clathrina clathrus*.[131] Contignasterol (**127**), a highly oxygenated steroid with the "unnatural" 14β-proton configuration and cyclic hemiacetal functionality in its side chain, has been isolated from the sponge *Petrosia contignata*,[132] collected in Papua New Guinea. The authors acknowledge than the 14β-epimers of a number of semisynthetic 15-ketosteroids were found to be more stable that the corresponding 14α-epimers, and they attempted to epimerize contignasterol (**127**) with base in order to determine the relative stability of its 14α- and 14β-epimers. Unfortunately all attempts failed. The extraction and chromatography conditions are unlikely to have caused epimerization, and the authors have assumed that **127** exists exclusively as the 14β-epimer in the sponge. Thus, contignasterol (**127**) represents the first naturally occurring steroid with the 14β-configuration, although steroids with a 14β-hydroxyl group (*e.g.* digitoxin) are well known from nature. A few months later Shoji *et al.*[133] reported the isolation of xestobergsterol A (**128**) and B (**129**), which are the second examples of steroids with the 14β-H proton configuration, from the sponge *Xestospongia bergquistia* collected in Okinawa. The structures of xestobergsterol A (**128**) and B (**129**) are unique also in that they are pentacyclic steroids with the fifth ring linking C-16 to C-23. Extensive NOE measurements indicated a boat conformation of ring C. Both **128** and **129** strongly inhibited histamine release from rat mast cells induced by anti-IgE.

New $\Delta^{8(14)}$-$3\beta,7\alpha$-dihydroxysterols (**130**) have been isolated from the Mediterranean *Pellina semitubulosa*.[134] Rare D-ring unsaturated steroid $3\beta,16\alpha$-diols (**131**) have been isolated from the Mediterranean sponge *Topsentia aurantiaca*.[135] Sterols with a D-ring unsaturation are rare, having been until now discovered only in the sponge *Homaxinella trachys*[136] and from cultured marine dinoflagellates.[137] A series of Δ^5-$3\beta,7\beta$- and Δ^5-$3\beta,7\alpha$-diols, along with the 3β-hydroxy Δ^5-7-ones, well-recognized autoxidation products of Δ^5-sterols, have been isolated from *Haliclona oculata*[138] from the bay of Funds, Canada, and *Stelodoryx chlorophylla*[139] from New Caledonia. They were accompanied by side chain oxygenated sterols, such as 24-oxo-, Δ^{22}-24-oxo-, $\Delta^{24(28)}$-25-hydroxysteroids,[138,139] and short side chain ketones, such as the pregnane derived 20-ketones and the 26,27-bisnor Δ^{22}-24-ketones,[139] also found in a sponge of genus *Hirtio*[140] and in *Damiriana hawaiana*,[17] *Haliclona rubens*,[108] and *Psammaplysilla purpurea*.[141] Also these side chain oxygenated steroids could be of abiotic origin, deriving through oxidation.

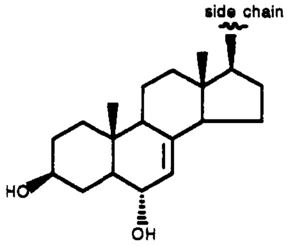
In the echinoderms, sea cucumber and starfish are known to produce saponins. Besides these echinoderms, only a limited number of marine organisms have been shown to contain steroidal or triterpenoid glycosides. Recently, glycosides with cholestane- and



105, R,R^1= ═O
106, R=H R^1=OH
107, R=OH R^1=H



108, Δ^2
109, Δ^3



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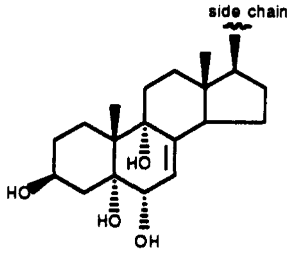

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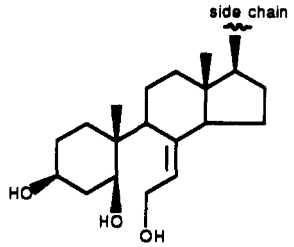

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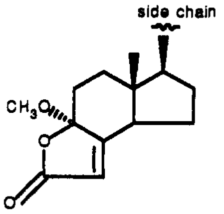

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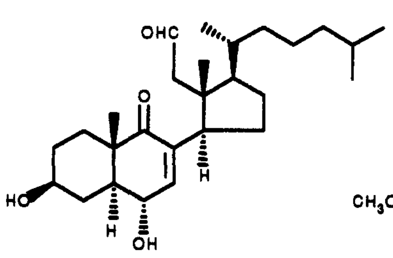

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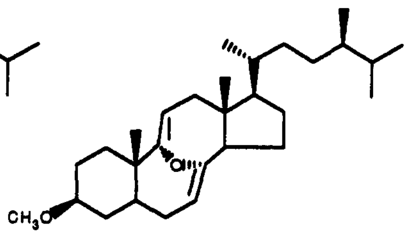

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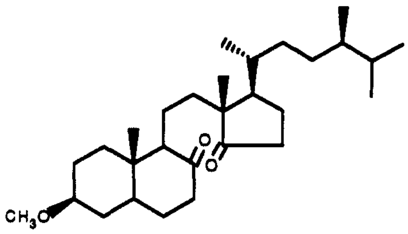

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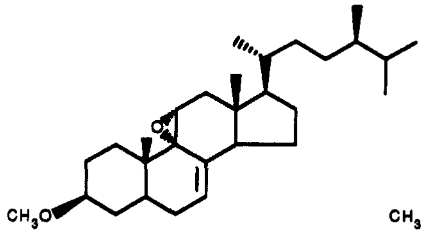

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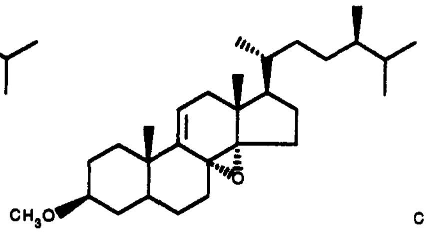

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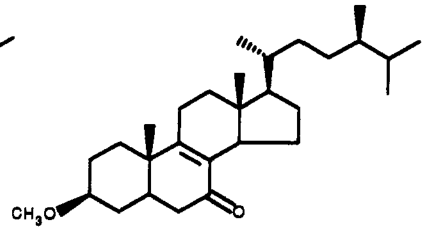

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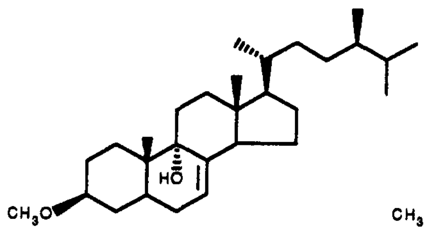

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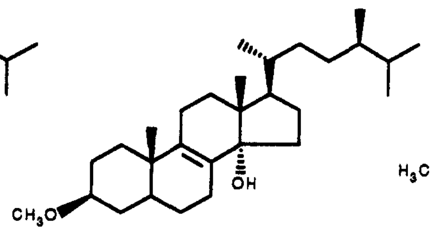

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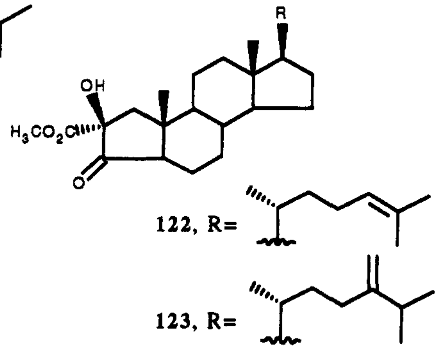
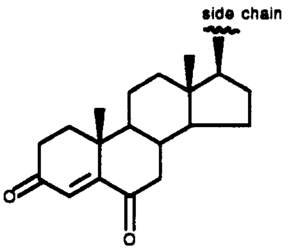


122, R=
123, R=



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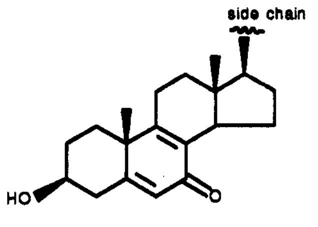
125, Δ^7



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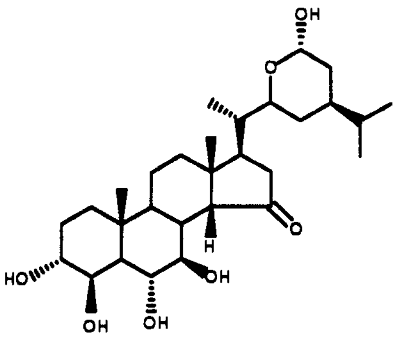

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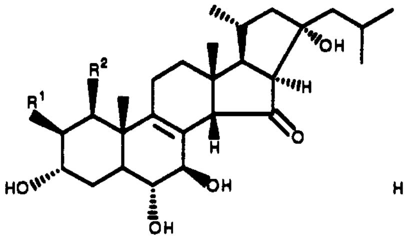
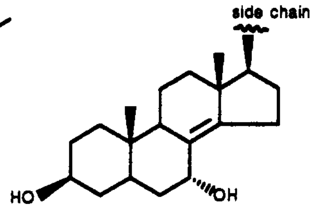


128, $R^1=R^2=H$

129, $R^1=R^2=OH$



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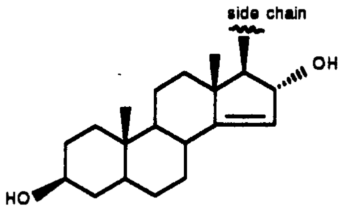


131

Figure 5. Polyoxygenated steroids from other sponge species.

lanostane-type aglycons have also been isolated from some sponges (Figure 6). Several norlanostane triterpenoid glycosides, sarasinosides A_1, B_1, C_1 (**132**) have been isolated from *Asteropus sarasinosum*.[142,143] They are penta- (A_1, B_1) and tetraglycosides (C_1) containing two amino sugars (NAcGlc and NAcGal) each and have been reported to be ichthyotoxic and to inhibit cell division of fertilized starfish eggs.[142] A 4-methyl steroidal diglycoside **133** has been isolated from *Erylus lendenfeldi*,[144] collected in the Red Sea. More recently two novel glycosides eryloside C (**134**) and D (**135**) have been isolated from a sponge of the genus *Erylus*[145] collected at depth of 500 m in south of New Caledonia. The novel lanostane derived aglycon of **134** and **135** features a rare 14-carboxyl group and a 24-methylene-25-methyl side chain. It appears closely related to penasterol, a lanostane-derived metabolite with the 14-carboxy group and the cholestane side chain, isolated from the Okinawan sponge *Penares* sp.[146] Both penasterol and erylosides C and D may have biosynthetic implications concerning the synthesis of sterols in the sponges, in which the loss of the 14-methyl group could involve the intermediacy of a carboxylic acid rather than an aldehyde. A novel steroidal saponin, pachastrelloside A (**136**), has been isolated from the sponge *Pachastrella* sp.[147] This glycoside inhibits cell division of fertilized starfish eggs.

IV. Polyoxygenated Steroids of Coelenterata

The phylum Coelenterata is subdivided into the classes Hydrozoa, Cubozoa, Scyphozoa, and Anthozoa. The latter class is subdivided into Hexacorallia and Octocorallia.

Polyhydroxysteroids have been found in Hydrozoa and Anthozoa.

A. Hydrozoa

Marine hydroids are the simplest Cnidarians, generally characterized by an alternation of generation; they occur in most habitats from the shore to the deep sea. The sessile animals (polyps) grow as bushlike colonies on stones, shells, or seaweeds. Only a few reports on their chemical constituents, including sterols, have appeared, due largely to the difficulties of collection and identifying the biological material. Cholesterol is usually the predominant sterol in hydroids[2,148] and polyhydroxysteroids have been discovered in species of the genus *Eudendrium* sp. (Figure 7). Cimino *et al.*[149] first found 3-oxocholest-4-ene-4,16β,18,22(R)-tetrol 16,18-diacetate (**137**) in Mediterranean hydroids of the genus *Eudendrium* (sp. *rameum*, *racemosus*, and *ramosum*) as well in their predators, several species of nudibranchs (*e.g. Hervia peregrina*, *Flabellina affinis*, *Coryphella lineata*). Other C-18 oxygenated sterols **138**–**141**, containing the rare 2α,3α-diol functionality, have been isolated from *Eudendrium glomeratum*,[150–152] collected in the Bay of Napoli. The 2α-deoxy analog **142** has been isolated from the same organism.[152]

B. Anthozoa

1. Hexacorallia

The subclass Hexacorallia comprises organisms such as sea anemones (order Actinaria) and zoanthids (order Zoanthidea), which are characterized by the production

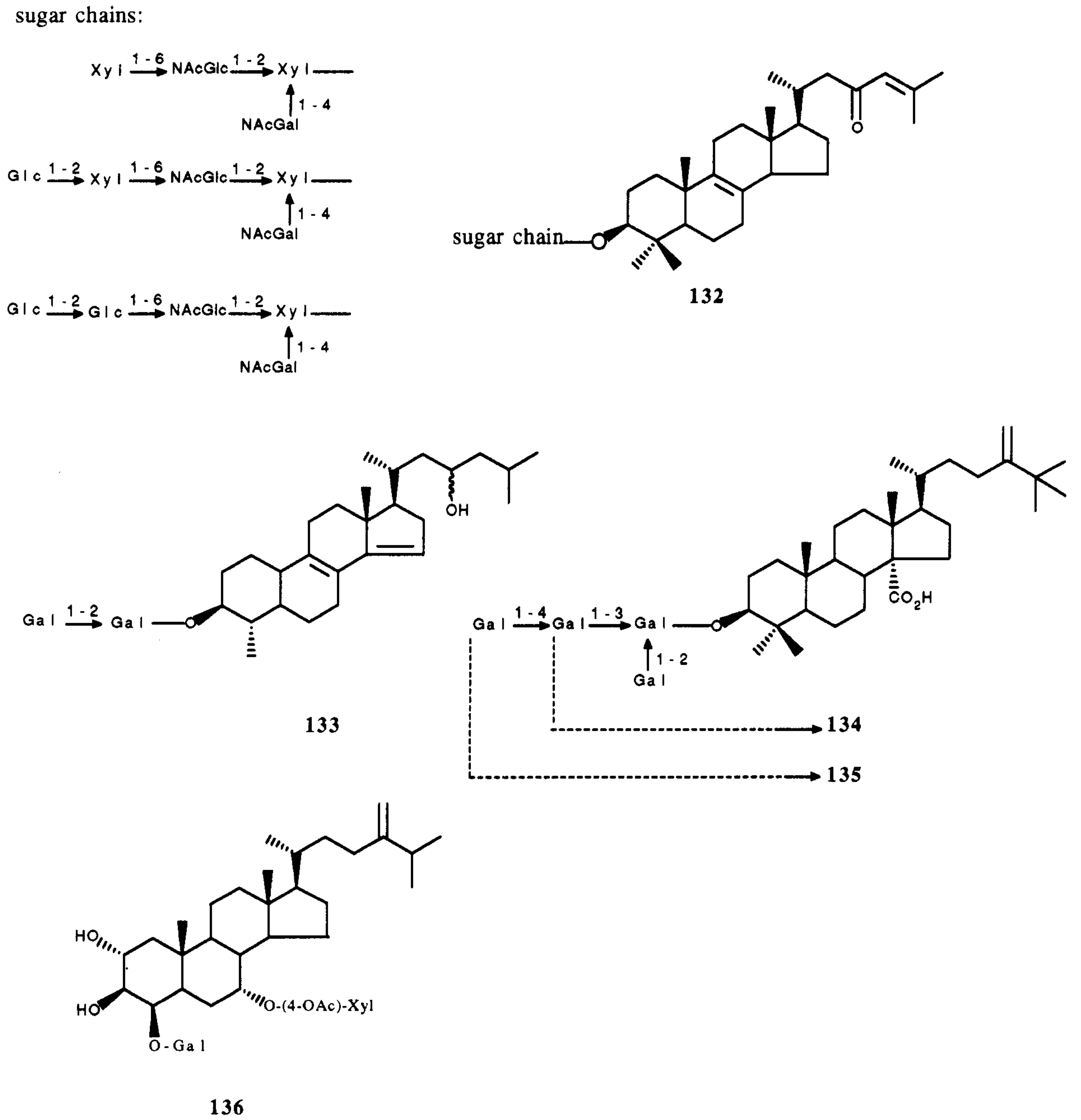
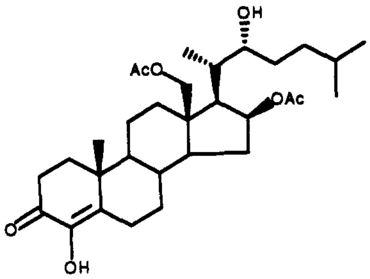


Figure 6. Polyoxygenated steroid glycosides of sponges.

of very powerful toxins.[153] Sea anemone toxins are polypeptides or proteins whose amino acid sequences exhibit a high degree of homology and have become very useful tools for studying the voltage-dependent Na^+ channel in nerve, cardiac, and muscle cells. Toxins isolated from several *Palythoa* spp. were the most toxic marine natural products before the discovery of maitotoxin,[154] one of the causative agent of ciguatera, a poisoning caused by ingestion of coral reef fishes. Palytoxin is uniquely distinct from other molecules with which organic chemists have previously dealt in terms of molecular size and of structural complexity; it has molecular weight of about 3000 Da but totally lacks repeating units, such as amino acid, sugar, and fatty acid residues, commonly found in molecules of that size.[155]

Publications on sterols from Hexacorallia are quite limited and report on the occurrence of conventional Δ^5-sterols.[2] Recent papers from Pietra and colleagues[156-158] account for the discovery of the zoanthid *Gerardia savaglia* as an unexpected marine source of moulting hormones (Figure 8). The authors first reported the isolation of ecysterone (**143**),[156] and then of ecdysone (**144**) and ajugasterone C (**145**),[157] the latter an ecdysteroid previously thought to be an exclusive and rare plant product. All three compounds were obtained in large amounts. The fourth ecdysteroid isolated as minor component from *Gerardia savaglia* is the new gerardiasterone **146**.[158] Ecdysteroids have been identified, in trace amounts, in arthropods,[159] nematodes and anellids,[160] mollusks,[161] and, in relative large amounts, in terrestrial plants.[159] The occurrence of ecdysteroids in such large amounts in the zoanthid *G. savaglia* poses a number of intriguing questions about their origin and role. The authors have noted that *G. savaglia*, after it had been kept for 15 months in an aquarium, still gave ecdysteroids in roughly the same large amounts as immediately after its collection,[157,158] and they suggested that ecdysteroids can be, at least in part, synthesized within the zoanthid from, possibly,



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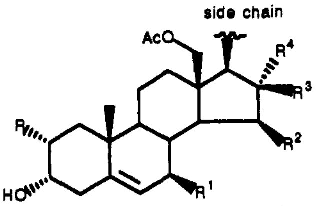


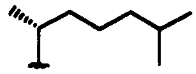
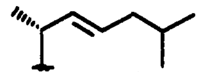
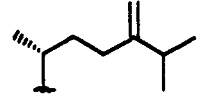
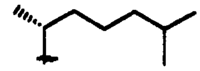
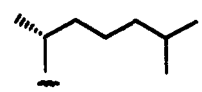
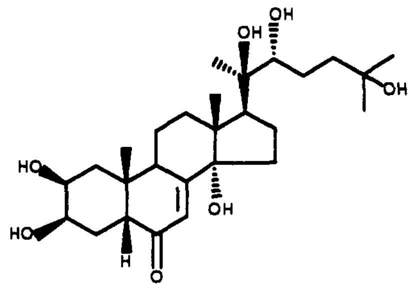
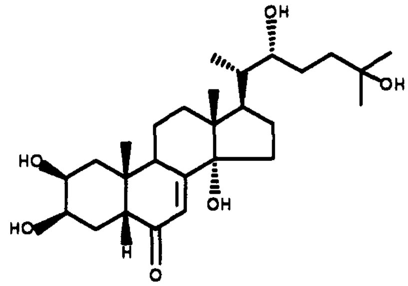
	R	R¹	R²	R³	R⁴	side chain
138,	OAc	OAc	OAc	H	H	
139,	OAc	H	H	H	OAc	
140,	OAc	H	OAc	H	H	
141,	OAc	H	H	OAc	H	
142,	H	OAc	OAc	H	H	

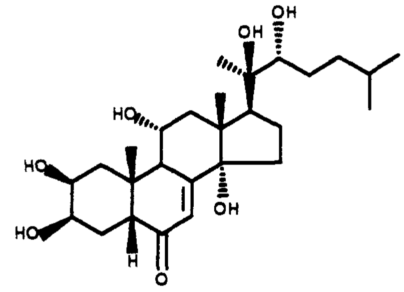
Figure 7. Polyhydroxysteroids from hydroids of genus *Eudendrium*.



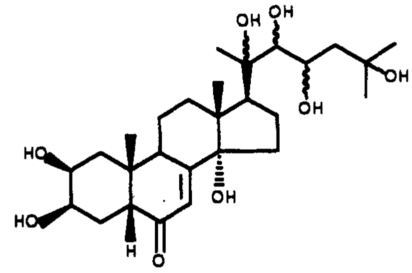
143, ecdysterone



144, ecdysone



145, ajugasterone - C



146, gerardiasterone

Figure 8. Ecdysteroids from the zoanthid *Gerardia savaglia* (Anthozoa, Hexacorallia).

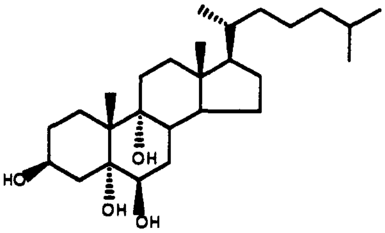
dietary cholesterols. The role of ecdysteroids as hormones in the zoanthid is ruled out because of the high concentration of the steroid, and a possible defensive role has been suggested. Finally, the authors conclude that it is likely that ecdysteroids will prove to be much more widely distributed in the marine environment than was thought.[156,157] The finding that pinnasterol (**60**), an ecdysteroid-like sterol, is a constituent of the red alga *Laurencia pinnata*[67] might support the hypothesis.

2. Octocorallia

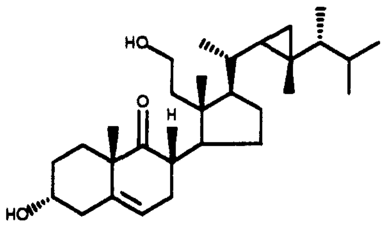
The subclass of Octocorallia comprises different orders among which Gorgonaceae and Alcyonacea are distinguished by their high content of polyhydroxylated sterols, which often are the major steroids. The structures of the polyoxygenated steroids from Gorgonaceae are shown in Figure 9.

5α-Cholestane-3β,5,6β,9-tetrol (**147**) one of first polyhydroxysteroids isolated from marine species was obtained from *Pseudopterogorgia elisabethae*.[162] After the isolation of **147** it was suggested[56] that a more detailed examination of the polar constituents of gorgonians will result in the isolation of others oxygenated sterols.

The first unique 9,11-secocholestane system was 3β,11-dihydroxy-9,11-secogorgost-5-en-9-one (**148**), which was isolated from the gorgonian *Pseudopterogorgia americana* together with the known gorgosterol **45**.[122] The structure and the absolute configuration was established by X-ray analysis. Hippurin-1 (**149**), with a unique oxygenation pattern and a spiroketal ring structure on the side chain of a 24-methylcholestane skeleton, was isolated from *Isis hippuris*,[163] a common gorgonian found on the Great Barrier Reef. A single-crystal X-ray analysis of the monoacetate secured the structure and relative stereochemistry of hippurin-1. ORD studies of the 11-keto and 3,11-diketo derivatives established the absolute configuration shown in **149**, which is the normal configuration found in sterols. Two related steroids of further complex structural features in the same gorgonian were isolated, and their structures



147



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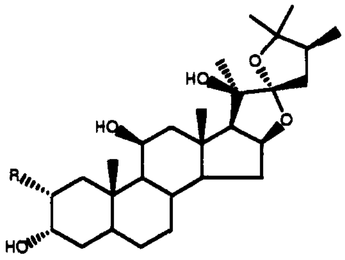
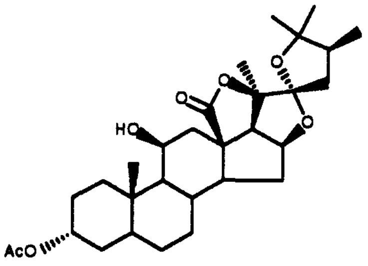


149, R=OAc

152, R=H



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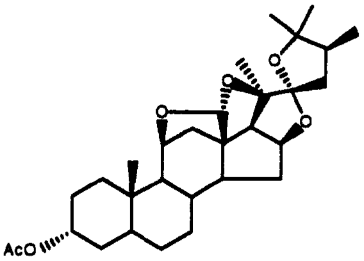

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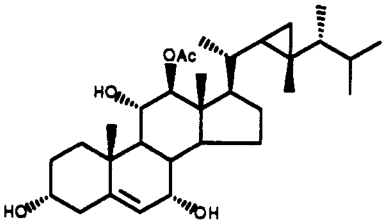

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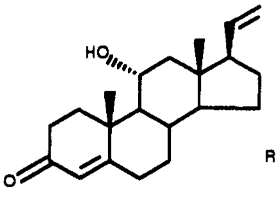

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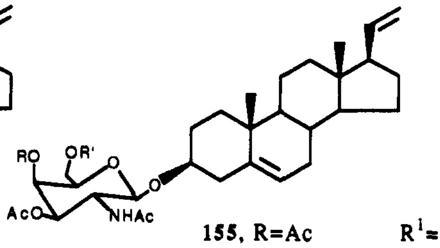
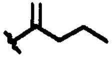
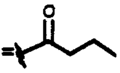
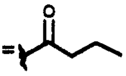
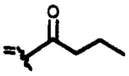
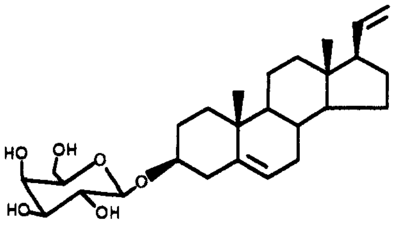


155, R=Ac R^1=Ac

156, R=Ac R^1= 

157, R=  R^1=Ac

158, R=  R^1= 



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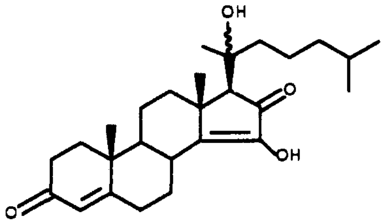

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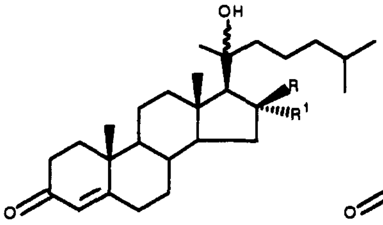
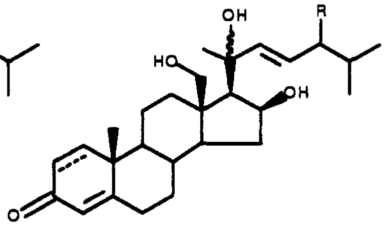


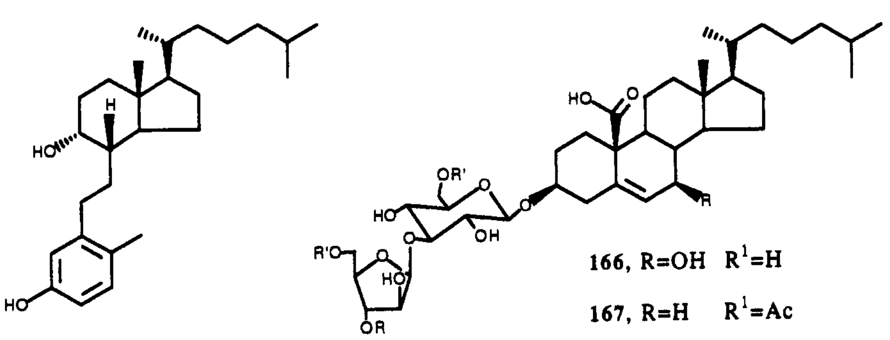
161, R=OH R^1=H

162, R,R^1= =O

163, R=H R^1=OH



164, R=H or Me or Me, 26-nor



165

166, R=OH R^1=H

167, R=H R^1=Ac

Figure 9. Polyoxygenated steroids of Gorgonaceae (Anthozoa, Octocorallia).

were determined as 3α-acetoxy-11β-hydroxy-24-methyl-22,25-epoxy-5α-furostan-18,20β-lactone (**150**) and 3α-acetoxy-11β,18:18,20:22,25-triepoxy-5α-furostan (**151**).[164] The eptacyclic steroid **150** was converted to the octacyclic one **151** on reduction with $LiAlH_4$ at reflux followed by acetylation. A minor compound, presumably the 18-epimer was also formed. The 18*R*-anomer, which requires less strained *cis* junction of the two five-membered rings composed of the bicyclic acetal, is the most stable epimer, as confirmed by treatment of 151 with *p*-toluenesulfonic acid in THF at room temperature for 30 h, which showed no signs of epimerization.[164] The authors remark that naturally occurring 18-substituted steroids are uncommon. They were only found in the aglycons of holothurins,[165] glycosides of sea cucumbers with an 18,20 lactone functionality on the lanostane skeleton, and in the highly active hormone aldosterone and in its metabolic products.[166] More recently C-18 oxygenated sterols have been isolated from hydroids (Figure 7), sponges of the genus *Dysidea* (Figure 4), gorgonians (Figure 9) and soft corals of the genus *Sinularia* (Figure 10). Several related desacetoxy hippurins (*e.g.* **152**) have also been described;[167] five more hippurins closely related to **149** were found in speciments of *Isis hippuris* collected in the Andaman Islands, India.[168] The same species also yielded a tetrahydroxylated steroid, which was identified as gorgost-5-ene-3β,7α,11α-12β-tetrol 12-monoacetate (**153**).[169]

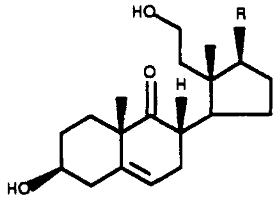
A pregnane derivative **154** has been isolated from the Mediterranean gorgonian *Eunicella cavolini*.[170] Four new metabolites, muricin-1 through muricin-4 (**155**–**158**) which are unique aminogalactose saponins containing pregnane-derived aglycons have been isolated from the Pacific gorgonian *Muricea fruticosa*.[171] They were supposed to be responsible in reducing fouling on *M. fruticosa*, possibly through effective growth inhibition of the pennate diatom *Phaeodactylum tricornutum*. The ecologies and life hystories of *M. fruticosa* in comparison with those of *M. californica*, the two major *Muricea* in California, give support to the potential role of these compounds in contributing to the reduced fouling of *M. fruticosa*. *M. californica*, which is found growing together with the morphologically very similar *M. fruticosa*, was consistently overgrown with typical encrusting plants and animals such as red algae, hydroids, ectoprocts, zoanthids, ascidians, mollusks, and bryozoans. In contrast *M. fruticosa* was found virtually free of surface fouling organisms. While each contained mixtures of triglycerides, sterols, and fatty acids, only the extracts of *M. fruticosa* were found to contain muricin-1 to muricin-4.[171] Another pregnane glycoside, 3β-pregna-5,20-dienyl β-D-galactopyranoside (**159**) has been isolated from the gorgonian *Pseudoplexaura wagenaari*.[172] The pregna-1,4,20-trien-3-one was previously isolated from an alcyonacean coral *Gersemia rubiformis*.[173]

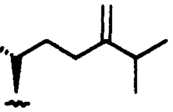
A reactive sterol, 3,16-dioxocholesta-4,14-diene-15,-20-diol (**160**) has been isolated from the Mediterranean gorgonian *Leptogorgia sarmentosa*.[174] On treatment with acetic anhydride and pyridine **160** suffers the loss of the entire side chain through a retro-aldol cleavage. Three polyoxygenated steroids, one being guggulsterol III (**161**) so far thought to be a plant product, the remaining **162** and **163** being closely related to **161**, have been discovered in the same species, *L. sarmentosa*.[175] The unusual upfield resonance of C-17 in guggulsterol III (**161**) (δ_C 60.1 ppm) when compared with its acetate derivative weakly downshifted at δ_C 60.4 ppm and of its 16-epimer **163** at δ_C 68.1 ppm is explained as due to the hydrogen linkage between the hydroxyl groups at C-20 and C-16 in **161**. A series of five C-18 hydroxylated homologues (**164**) of guggulsterol III (**161**) have been isolated from the same organism, *L. sarmentosa*.[176]

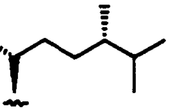
A novel secosterol, astrogorgiadiol (**165**) has been isolated from a gorgonian *Astrogorgia* sp.,[177] as an inhibitor of cell division in fertilized starfish eggs. The authors suggested that **165** is likely biosynthesized from cholestanol via dienol–phenol rearrangement and cleavage of the 9,10-bond. Two more secosterols, closely related to astrogorgiadiol (**165**) have been reported from the gorgonian *Caligorgia* sp.[178]

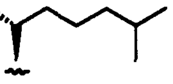
Two novel glycosides named dimorphoside A (**166**) and B (**167**) have been isolated from the gorgonian *Anthoplexaura dimorpha*,[179] widely distributed along the southern coast of Japan, as the major active constituents (inhibition of the development of fertilized sea urchin eggs) of that organism. The oxidation of the C-19 methyl group to carboxylate is a rare feature, although related steroid sulfates have been isolated from a sponge.[94]

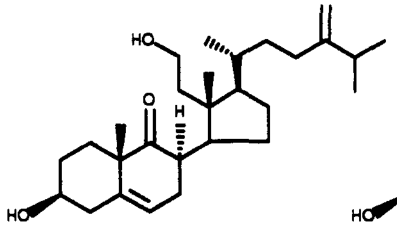
Sinularia sp. (Alcyonacea) has given three new 9,-11-secosterols with the same 9,11-seconucleus as **148** and conventional 24-methylene, 24-methyl, and cholestanol side chains (**168**–**170**).[123,124] The same species also yielded a very minor component, which proved to be the C-8 epimer of 3β,11-dihydroxy-24-methylene-9,11-secocholest-5-en-9-one (**171**).[124] According to the authors it is unlikely that the less stable 8α-H epimer is an artifact of the isolation procedure. The fact that a group of 9,11-secosterols with a variety of side chains has been discovered suggest that *Sinularia* species probably cleaves ring C of exogenous sterols similar



168, R=


169, R=


170, R=




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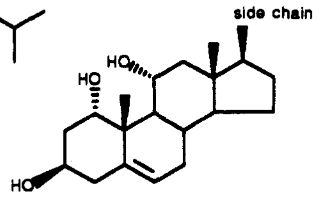

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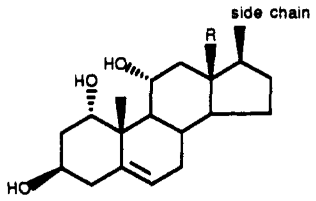
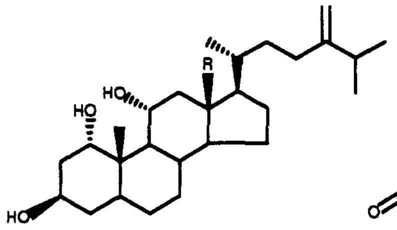


173, R=CH_2OAc

174, R=CHO

175, R=COOH

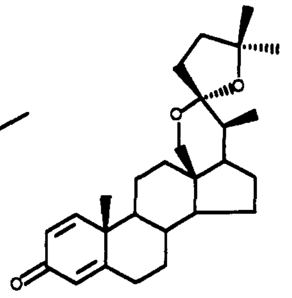


176, R=CH_3

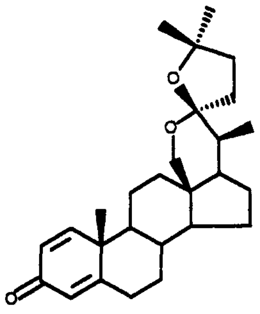
177, R=CH_2OAc

178, R=CHO

179, R=COOH



180



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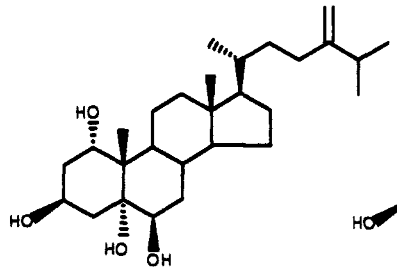

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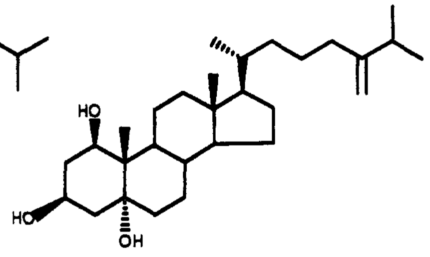

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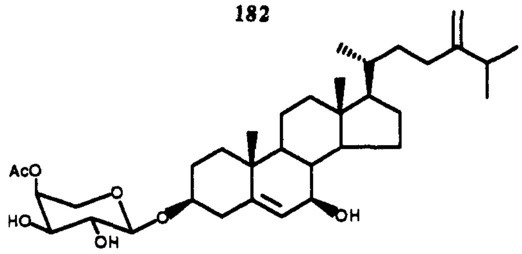

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Figure 10. Polyoxygenated steroids from Alcyonacea (Anthozoa, Octocorallia) of genus *Sinularia*.

to the situation observed in some sponges, *e.g.* 5,6-secosterols in *Hippospongia communis*,[117] incisterols from *Dictyonella incisa*[120] and the ring A contraction of *Achantella acuta* sterols.[180]

In addition to the 9,11-secosterols, the soft corals of the genus *Sinularia* have been shown to produce a series of new polyhydroxylated sterols (Figure 10). The common 3β,5α,6β-trihydroxy sterols were isolated from

Sinularia dissecta.[181] A novel group of eight polyhydroxylated sterols, all of them possessing an 11α-hydroxy substituent of potential utility as corticosteroid intermediates have been then isolated from the same specie.[182] Seven of these compounds possessed identical $1\alpha,3\beta,11\alpha$-trihydroxycholest-5-ene nuclei (**172**), but differed in the side chains, which, in addition to the conventional C_8 and C_9 side chains, include those of gorgosterol (**45**) and 23-demethylgorgosterol (**44**).[183] In continuation with the examination of the extracts of *S. dissecta* the same authors isolated a major group of five sterols with the same $1\alpha,3\beta,11\alpha$-hydroxylation pattern as well as an acetylated group located at C-18, **173**.[183] In addition the same organism also yielded the analogous 13-formyl, **174**, and 13-carboxyl, **175**, derivatives.[183] The corresponding 5α,6-dihydro derivatives of the major 24-methylene side chain sterols have also be found **176–179**. The isolation of three groups of C-18 functionalized sterols from the same organism is so far unprecedented. The authors remark that the fact that similar nuclei possessing diverse side chains are encountered suggests the existence of enzyme systems—either in the coral or in some symbiont—that introduce the 1α- and 11α-hydroxyl groups into a dietary precursor and that may also functionalize the C-18 angular methyl group.[183] Eventual isolation of the enzyme systems may provide a possible practical route to otherwise rare sterols—notably those with oxygenated C-11 and C-18 positions.

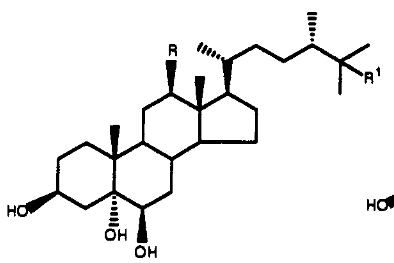
Two new cholestadienone derivatives, **180** and **181**, which possess epimeric cyclic ketals of the C-22 side chain position involving the oxidation of the C-18 methyl group, have been isolated from an apparently undescribed species of *Sinularia* genus.[184] Accurate ^{1}H NMR studies indicated the conformations of the six-membered ketal rings to be a twist boat in **180** and a chair in **181**. The variation in the ring conformation was then related to the stereochemistry of the ketal carbon C-22. Similar sterols were described from the gorgonian *Isis hippuris.*[163,164]

Two novel polyhydroxysterols, numersterols A and B, have been isolated from the South China Sea *Sinularia numerosa*, and their structures were determined as 24-methylenecholestane-$1\alpha,3\beta,5\alpha,6\beta$-tetrol (**182**) and 25-methylene-22-homocholestane-$1\beta,3\beta,5\alpha$-triol (**183**).[185] The structure of numersterol A (**182**) with nuclear hydroxylation pattern differing from that encountered in many polyoxygenated steroids from soft coral (*e.g. Sarcophyton glaucum,*[186–188] *Lobophytum pauciflorum,*[189] and *Sclerophytum* sp.[190]) only in the stereochemistry at C-1, was confirmed by X-ray analysis.[185] The side chain of numersterol B (**183**) is apparently the result of two biomethylations at C-27 of normal cholesterol side chain. The corresponding 6-keto derivative of numersterol A (**182**) has been recently isolated from *Sinularia microclavata,*[191] one of the most typical species found in Indo-Pacific coral reefs, collected at Ishigaki Islands, Okinawa. *Sinularia crispa* from the East coast of Sri Lanka has been shown to contain a novel steroid glycoside (**184**), showing spermatostatic activity.[192]

Figure 11 shows the structures of polyoxygenated steroids found in Alcyonaceans other than those found in the genus *Sinularia.*

A common feature of many polyhydroxysterols from soft corals is the $3\beta,5\alpha,6\beta$-trihydroxy moiety. The first of the soft coral sterols found to have this pattern was **185** isolated from *Sarcophyton elegans,*[193] then found as 25-hydroxy analog **186** also in *Sclerophytum* sp.[190] *Sclerophytum* sp. have been shown to contain also the rare (24*S*)-24-methylcholestane-$3\beta,5\beta,6\alpha$,25-tetrol (**187**),[190] isomeric with the common **186** and differing from that in the stereochemistry at C-5 and C-6. On pyridinium chlorochromate (PCC) oxidation followed by dehydration with thionyl chloride in pyridine, both **186** and **187** afforded the same Δ^4-3,6-diketo derivative.[190] The polyhydroxysteroid **188** was isolated from the same soft coral *Sarcophyton elegans.*[194] After that a series of $1\beta,3\beta,5\alpha,6\beta$-tetrahydroxysteroids (**189–194**) have been isolated from *Sarcophyton glaucum,*[186–188] one of the most common species found in Indo-Pacific coral reefs, collected at Ishigaki Islands, Okinawa, and *Lobophytum pauciflorum,*[189] from the same Ishigaki Islands, and from a species of the genus *Sclerophytum,*[190] collected in the Andaman and Nicobar Seas of the Indian Ocean. Except for some of the 5β-sapogenols and for the Δ^5-ruscogenin,[195] 1β-hydroxysteroids are rare in nature. It is also to be noted that **194** is the first report on the isolation of a polyoxygenated androstane derivative from marine invertebrates.[187] Among the complex mixture of polyhydroxysteroids of *S. glaucum* Kobayashi and Mitsuhashi[196] also isolated a minor polyhydroxysteroid and determined the structure of (24*S*)-24-methyl-5α-cholestane-$3\beta,5,6\beta,25\xi$,26-pentol (**195**). Hydroxylation at C-26 is common among polyhydroxysteroids from starfish[197] and the 24-methyl 25,-26-diol side chain of **195** have been found in a steroidal nonaol from the starfish *Archaster typicus,*[198] but never found before in Anthozoa. More recently new additions to the group of $1\beta,3\beta,5\alpha,6\beta$-tetrahydroxysterols have been found in *Sarcophyton subviride,*[199] soft coral collected from the Katchal Islands of Andaman and Nicobar Coasts. These include the $\Delta^{25(26)}$-analog of **192**, the C-18 hydroxy analog of **189** (**196**), the 25-*O*-acetyl derivative of **195**, and **197** with the gorgostane skeleton. A new $3\beta,5\alpha,6\beta$-trihydroxy steroid with further hydroxylation at C-22 and C-24 (**198**) have been isolated from the soft coral *Asterospicularia randalli*[200] collected at Guam Island. Hydroxylation at C-22 was also found in lobophytosterol (**199**), depresosterol (**200**), and three other closely related sterols, $5\beta,6\beta$-epoxysterols **201–203** from the Red Sea soft coral *Lobophytum depressum.*[201] The occurrence of C-28 oxygenated sterols, which may be intermediate in the demethylation pathway, might be of biogenetic interest.

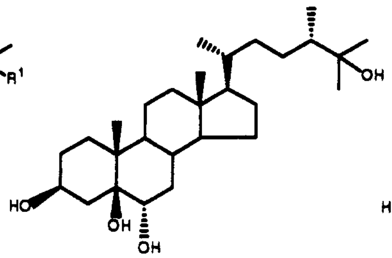
The soft coral *Minabea* sp. contains sterol lactones of the withanolide class, three are new C_{28} compounds, minabeolides 1-3 (**204–206**), and five are C_{27} derivatives, minabeolides 4-8 (**207–211**).[202] Instead of the Δ^2-1-keto ring A, very common in plant withanolides, the marine-derived withanolides have a Δ^4-3-keto ring A. Further sterols with the common $3\beta,5\alpha,6\beta$-trihydroxy moiety feature and a fourth hydroxyl group found in the 7β-position have been isolated in the soft coral *Anthelia glauca*[203] (**212**) collected at Laing Island, Papua, New Guinea, and also as 7β-acetate analogs **213–215** in a species of the genus *Xenia* collected at Zamamijima, Okinawa.[204] Gorgosta-$3\beta,5\alpha,6\beta$-triol has been also isolated from the same species.[204] The mixture con-



185, R=H R^1=OAc

186, R=OH R^1=OH

188, R=OH R^1=OAc



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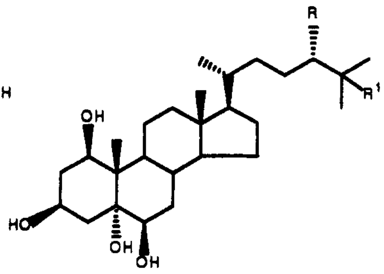
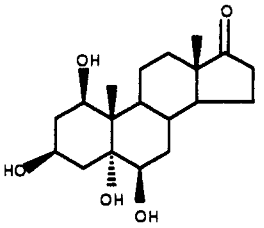


189, R=Me R^1=OAc

190, R=Me R^1=OH

191, R=Me R^1=H

192, R=$=CH_2$ R^1=H



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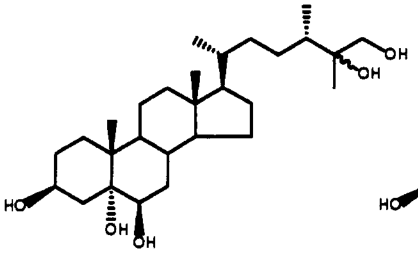

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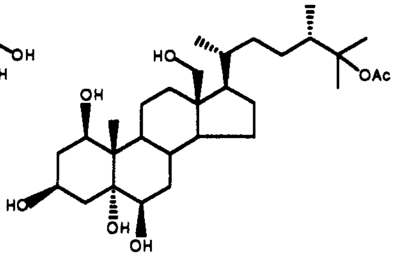

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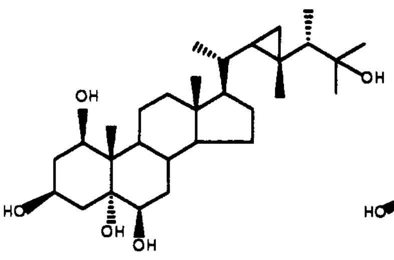

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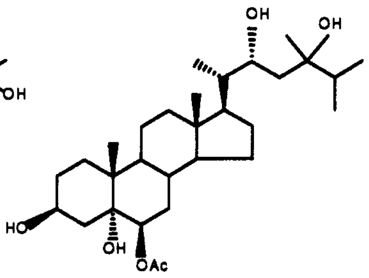

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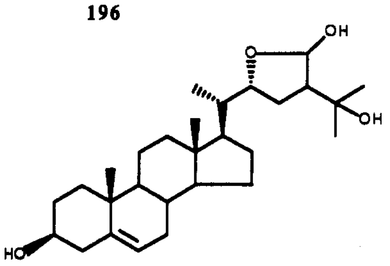

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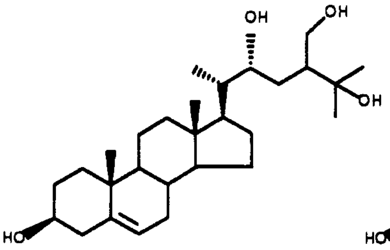

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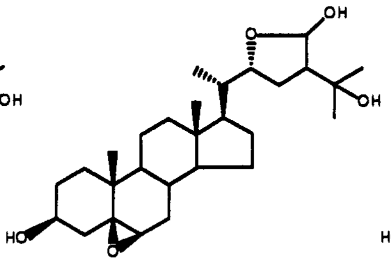

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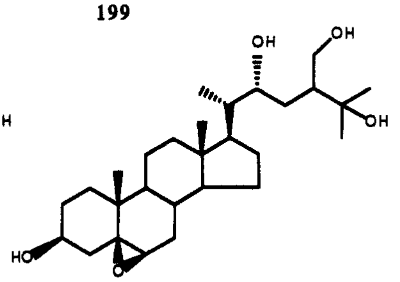

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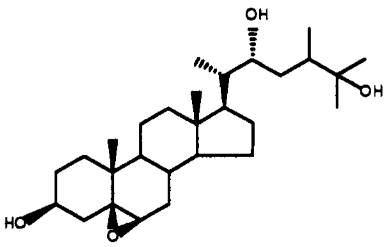

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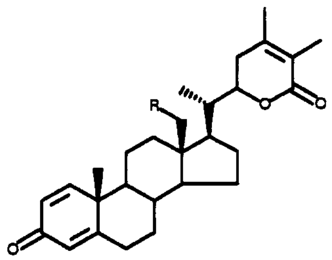
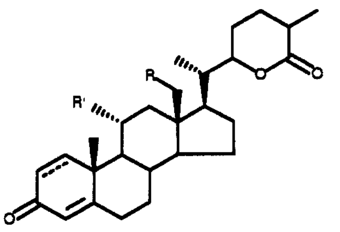


204, R=H

205, R=OAc

206, R=H 1,2-dihydro



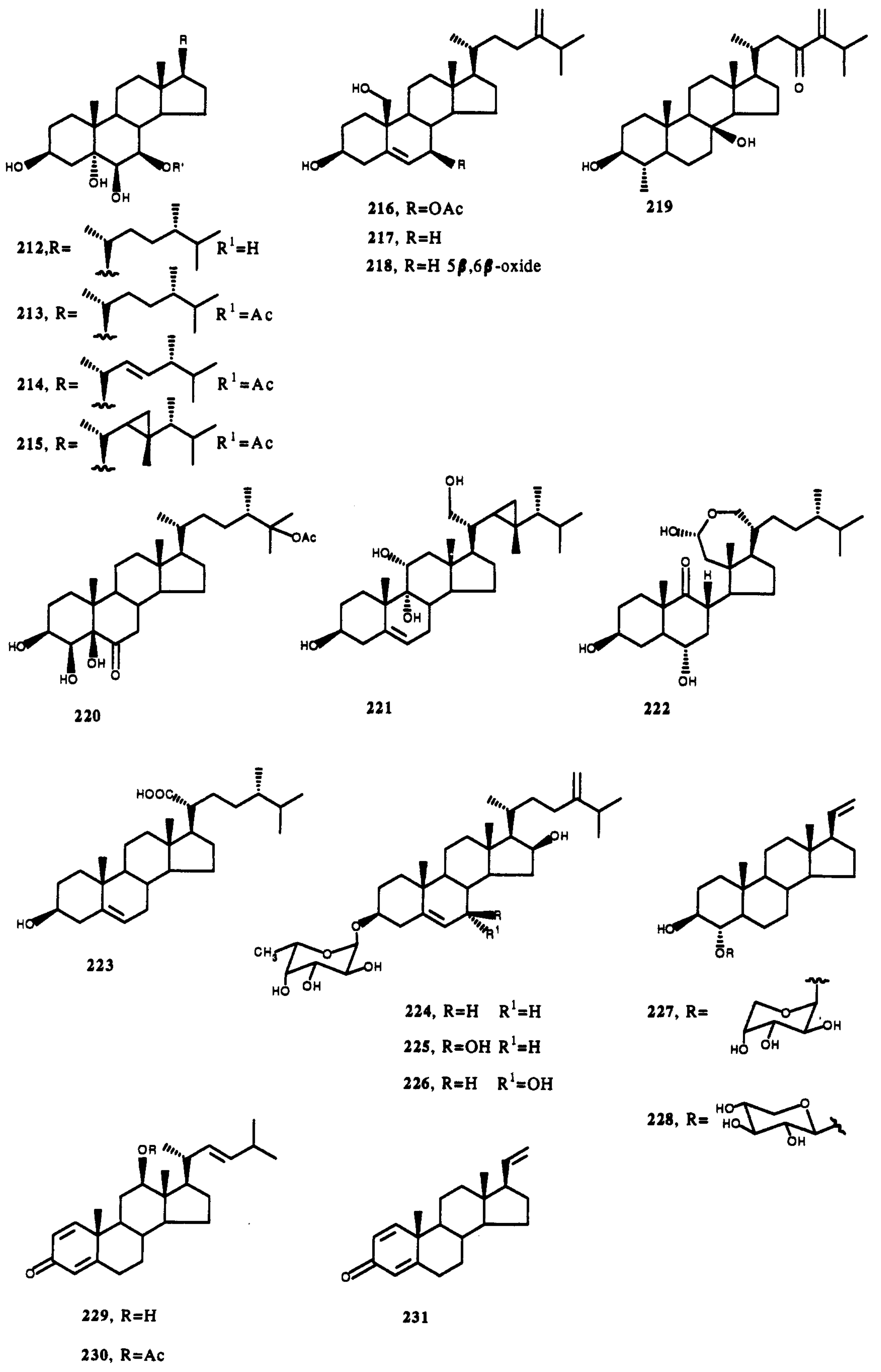
207, R=H R^1=H

208, R=OAc R^1=H

209, R=H R^1=H 1,2-dihydro

210, R=OAc R^1=H 1,2-dihydro

211, R=H R^1=OAc 1,2-dihydro



212, R= R^1=H

213, R= R^1=Ac

214, R= R^1=Ac

215, R= R^1=Ac

216, R=OAc

217, R=H

218, R=H 5β,6β-oxide

219

220

221

222

223

224, R=H R^1=H

225, R=OH R^1=H

226, R=H R^1=OH

227, R=

228, R=

229, R=H

230, R=Ac

231

Figure 11. Polyhydroxysteroids from Alcyonacea (Anthozoa, Octocorallia) other than genus *Sinularia*.

taining the above four sterols exhibited a growth-inhibitory activity against B-16 melanoma cells.[204]

Litophyton viridis is the source of the rare 19-oxygenated sterols **216**–**218**.[98,205] Compound **216** with the 7β-acetoxy functionality appeared to be the first report of a naturally occurring 19-hydroxy steroid.[98] The 5β,6β-epoxide **218** showed antileukemic activity (IC_{50} 0.5 μg/mL) against P_{388} leukemia cells *in vitro*.[205]

The 19-hydroxylated sterols are very rare in nature only found in a sponge[97] and in the soft coral *L. viridis*[98,205] and are of interest as a possible intermediate in the biosynthesis of 19-norsterols. Examination of less polar fractions of the extract of *L. viridis* led Bortolotto *et al.*[206] to isolate 4α-methyl-3β,8β-dihydroxy-5α-ergost-24(28)-en-23-one (**219**). The structure was secured by X-ray of the *p*-bromobenzoate derivative. At that time the 8β-hydroxy function appeared unique in marine sterols; several polyhydroxysteroids have been later isolated from starfish and the majority of them possess the 8β-hydroxy substituent.[197]

The 3,4,5,6-oxygenated pattern discovered in lobosterol (**220**), isolated first from *Lobophytum pauciflorum*[207] and later in species of the genus *Sclerophytum*,[208,209] is unprecedented in natural sterols. This was also the first marine sterol reported to have an A/B *cis* ring fusion. The available amount of lobosterol was *insufficient for a complete chemical elucidation of the* structure, and this determination was obtained by X-ray diffraction analysis of the 4-*O*-*p*-bromobenzoate.[207] In addition to lobosterol (**220**) another *Sclerophytum* sp. of soft coral collected off the Andaman and Nicobar coasts has been shown to contain two new polyhydroxysterols, andamansterol (**221**) and nicobarsterol (**222**).[209] Both compounds **221** and **222** bear an oxygenated C-21, which is rare in marine sterols except for those found in echinoderm ophiuroids and one starfish. The structure of andamansterol (**221**) was secured by X-ray analysis, thus confirming the conventional C-20 configuration. Nicobarsterol (**222**) is a new type of 9,11-secosterol with the C-11 oxidized at a carboxyaldehyde level and forms a seven-membered hemiacetal ring with the C-21 hydroxy group. A sterol with the 9,11-glycolated structure like **221** could likely be a precursor of **222**. Lead tetraacetate treatment of andamansterol (**221**) gave a 9,11-seco derivative having the same seven-membered hemiacetal ring as **222**, including the 11*R* configuration.[209] Examination of another *Sclerophytum* sp. resulted in the isolation of a new steroid **223**, which is the first example to have C-21 oxidized to carboxylate.[210]

In a continuing investigation of the soft corals of the Andaman and Nicobar coasts of the Indian Ocean by Kobayashi and colleagues, three new polyhydroxysterol glycosides were isolated from one sample identified as *Alcyonium* sp.,[211] and their structures were determined as 24-methylenecholest-5-ene-3β,16β-diol 3-*O*-α-L-fucoside (**224**) and its 7β- (**225**) and 7α-hydroxy (**226**) derivatives. From the chemotaxonomic viewpoint it may be of interest that this is the second example of *Alcyonium* sp. containing steroidal glycosides, which are rare in soft corals. Pregnene-type steroidal glycosides were previously isolated from an Okinawan coral-reef *Alcyonium* sp. by Kobayashi *et al.*[212] Two of these glycosides, pregnediosides A and B, were characterized as 4-*O*-β-D-arabinopyranosyl (**227**) and 4-*O*-β-D-xylopyranosyl (**228**) of 3β,4α-dihydroxy-5α-pregn-20-ene, respectively, the remaining three being their monoacetates.[212] The role of the *Alcyonium* sp. steroidal glycosides is still obscure.

Kingston and Fallis[213] have reported the isolation of two unusual C_{26} steroids, 12β-hydroxy-24-norcholesta-1,4,22-trien-3-one (**229**) and its acetate **230** from the sea raspberry *Gersemia rubiformis*, an alcyonacean coral from the cold waters off Newfoundland and Labrador. A $\Delta^{1,4}$-3-ketopregnane **231** was also found in the same organism.[214]

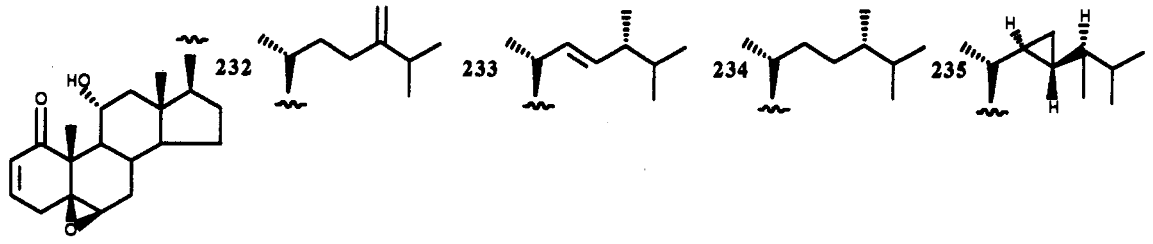
Very few polyhydroxysteroids have been found in species of the class Anthozoa other those found in the order Gorgonaceae and Alcyonacea and are shown in Figure 12. Four new cytotoxic steroids, named stoloniferones were isolated from the stoloniferan Okinawan soft coral *Clavularia viridis*[215] (order Stolonifera). They possess the same 11α-hydroxy-5β,6β-epoxy 2-en-1-one steroidal skeleton, but differ in their side-chain structures. A X-ray crystallographic analysis of stonoliferone D (**235**) confirmed the structures and the relative stereochemistries derived from spectroscopic studies, and CD measurements of the 2,3-dihydrostoloniferone C (**234**) secured the absolute stereostructures. Stoloniferones exhibited growth inhibition against P_{388} leukemia cells. Unusual 20-epicholanic acid derivatives **236**–**239** were isolated from the sea pen *Ptilosarcus guerneyi*[216] (order Pennatulaceae). Characteristic properties of these compounds are (a) the shorter retention time than those of their natural C-20 isomer (20α-H) on GLC analysis and (b) the C-21 methyl protons resonance at 0.1 ppm higher field in the NMR spectra than the 20α-H compounds. The isolated steroids, as methyl esters, were identical with the synthetic 20-epicholanic methyl esters.[217] The authors analyzed also the sea pen's free sterols and found them to possess the "normal" C-20 stereochemistry.[217] Thus the free sterols are not the immediate biosynthetic precursor of the 20-episteroids, and their origin is still an open question. Cholestane-3β,5α,6β-triol has been isolated from the sea pen *Pteroides esperi*[218] (order Pennatulaceae) and found to have steatotic and cytotoxic activity. A series of highly oxygenated sterols **240**–**246** have been isolated from *Anthipathes subpinnata* (order Antipatharia) commonly named black coral.[219,220] The Δ^5-3β,7β,19-hydroxylation pattern of **246** has been previously found in **216** from the soft coral *Litophyton viridis*.[98] Interesting *A. subpinnata* produces both 18- and 19-hydroxylated steroids; the hydroxylation at C-20 is rare in marine steroids except for the aglycons of the asterosaponins found in starfishes.[197]

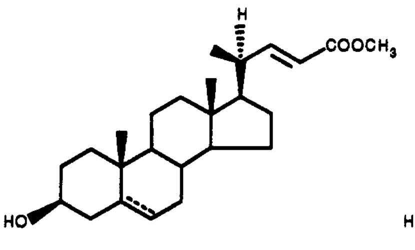
V. Polyoxygenated Steroids of Bryozoa

Bryozoa are minute filter feeders animals which contain biological active alkaloids and macrolides. Despite the considerable interest in anticancer activities of bryostatins from *Bugula neritina*,[221] the chemical studies of bryozoans are proceeding slowly, probably because of the difficulties experienced in collecting sufficient material for analysis. Only two papers on sterols of bryozoans have appeared in the literature, one of which describes the isolation of five polyhydroxysterols, all possessing a common Δ^7-3β,5α,6β-trihydroxy steroidal skeleton and saturated and Δ^{22}-unsaturated conventional C_8, C_9, and C_{10} side chains from *Myriapora truncata*.[112] These sterols have also been found in a sponge[110] and in a mollusk.[113]

VI. Polyoxygenated Steroids of Marine Mollusca

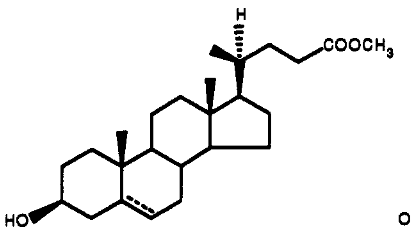
More species of Mollusca have been analyzed for their sterol content and composition than have those of any other phylum, in part because of their nutritional





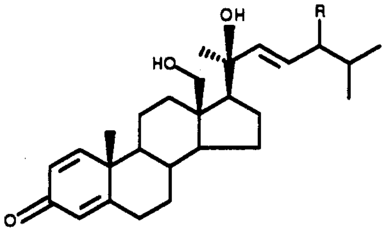
236, Δ^5

237, 5α-H



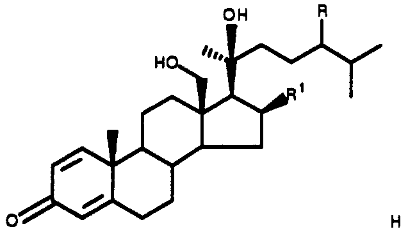
238, Δ^5

239, 5α-H



240, R=H

241, R=Me

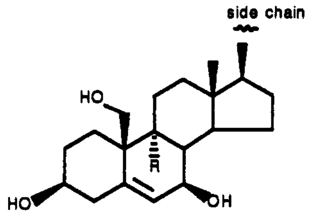


242, R=H R^1=OH

243, R=H Δ^{22} R^1=OH

244, R=Me Δ^{22} R^1=OH

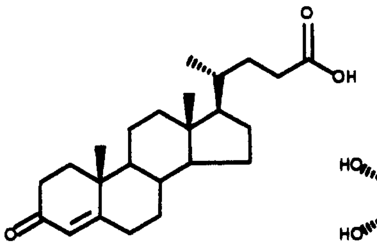
245, R=H R^1= O



246, R=H or OH

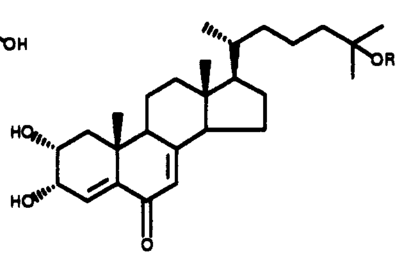
Figure 12. Polyhydroxysteroids from Octocorallia (Anthozoa) other than Gorgonacea and Alcyonacea.

value.[2,60,62] Even so, the occurrence of polyoxygenated sterols in mollusks (Figure 13) is relatively rare. The highly oxygenated steroid 137, isolated from three species of the hydroids of the genus *Eudendrium*, was also found in their predators, the nudibranchs (class Gastropoda) *Hervia peregrina*, *Flabellina affinis*, and *Coryphella lineata*.[149] Recent studies have shown that most dorid nudibranchs utilize organic metabolites obtained from their diets as chemical defences against predation.[222] The steroid 137 seems to be one of the nudibranch metabolites to which no defensive role is ascribed. Two cholanic acid derivatives 247 and 248, with significant antifeedant activity, were isolated from the dorid nudibranch *Aldisa sanguinea cooperi*,[223] but were not found in the sponge *Anthoarcuata graceae* on which it feeds. This nudibranch is apparently obtaining inactive metabolites from its diet and chemically modifying them to produce an active antifeedant.[223] Two new steroids, diaulusterols A (249) and B (250) were isolated from the skin extracts of the dorid nudibranch *Diaulula sandiegensis* and were identified by interpretation of spectral data.[224] Diaulusterols are related to pinnasterol (60) and acetylpinnasterol (61), which were isolated from the red alga *Laurencia pinnata*.[67] All four steroids share structural features with ecdysones. The 2α,3α-diol array of diaulusterols are not commonly encountered in naturally occurring steroids. They have only been isolated from the hydroid *Eudendrium glomeratum*.[150–152] A new cytotoxic epoxysterol 251, active against the L_{1210} cell line, was isolated from the marine gastropod *Planaxis sulcatus*.[225] This is very similar to the 9,11α-epoxysterol 91 isolated from a sponge of *Dysidea* sp. and therefore 251 is suspected to be the precursor of 91.[225] Δ^7-3β,5α,6β-Trihydroxysteroids have also been found in the scallop *Patinopecten yessoensis* (class Bivalvia), including one, 252, with the rare 9α-hydroxylation.[113] The occurrence of Δ^5-3β-hydroxy-7-ketosterols 253 in the prosobranch mollusk *Patingera magellanica* has been reported.[226] The possible abiotic origin of Δ^5-7-ketones, well-recognized autooxidation products of Δ^5-sterols, can be suspected. A series of highly degraded steroids,



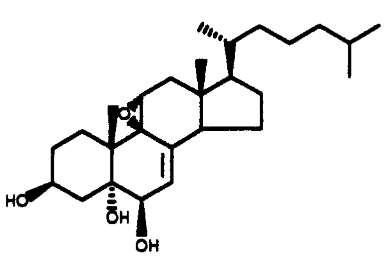
247

248, Δ^{22}

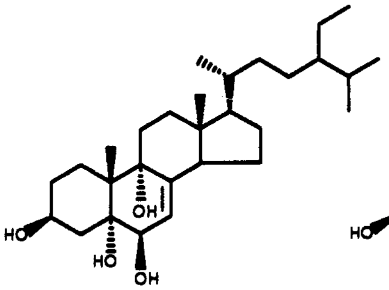


249, R=$COCH_2CHOHCH_3$

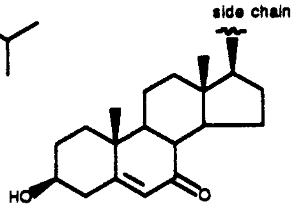
250, R=H



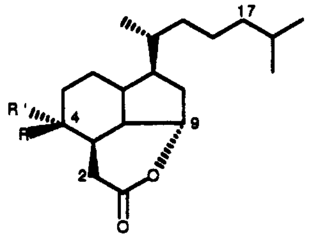
251



252



253



254, R=OH	R^1=H
255, R=OH	R^1=H $\Delta^{17(18)}$
256, R=OAc	R^1=H $\Delta^{17(18)}$
257, R=R^1= ═O	$\Delta^{17(18)}$

Figure 13. Polyhydroxysteroids of marine Mollusca.

named aplykurodins, has been isolated from two ophistobranchs of the genus *Aplysia* (class Gastropoda). The 4β-hydroxy lactones **254** and **255** have been isolated from *A. kurodai*;[227] the 4β-acetoxy derivative **256** and the 4-keto analog **257** have been then isolated from the Mediterranean *A. fasciata*.[228] The relative stereostructure of aplykurodine A (**255**) was deduced by X-ray crystallography, whereas the absolute configuration was determined by application of CD data.[227] The interconversion of the 1–9 δ-lactones, aplykurodines, and their isomeric 1–4 γ-lactones has been investigated[227,228] and the authors concluded that the δ-lactones are the kinetic products, whereas the γ-lactones are the thermodynamic ones.[228] Aplykurodin B (**256**) and aplykurodinone (**257**) which were isolated from the external parts of the body of the animals and showed icthyotoxicity and antifeedant activity (feeding deterrence) were considered by the authors to be the defense allomones of *A. fasciata* against predators.[228]

The endocrine system of steroid hormones in mollusks has been established, and many reports on the biosynthesis and metabolism of progesterone, estrogens, and androgens have been published.[229] *Mytilus edulis* (class Bivalvia), the mussel, had been reported to contain 0.2 pg g^{-1} by weight of a substance, which showed ecdysone activity.[230] The probable role of ecdysteroids in relation to calcification of the shell in mollusk has been suggested.[161,231]

VII. Polyoxygenated Steroids of Echinodermata

The phylum Echinodermata, which comprises about 6000 living species, is divided in five classes: Crinoidea (sea lilies and feather stars), Holothuroidea (sea cucumbers or holothurians), Echinoidea (sea urchins), Asteroidea (sea stars or starfish), and Ophiuroidea (brittle stars).

Among the echinoderms, starfish and sea cucumbers invariably contain saponins, which are responsible of their general toxicity. Chemically, saponins derived from sea cucumbers are triterpenoid glycosides whereas those from starfish are steroidal glycosides. The presence of oligoglycosides in both Holothuroidea and Asteroidea classes gives support to the opinion that sea cucumbers and starfish are phylogenetically closely related. In starfish and sea cucumbers, Δ^7-sterols, which are probably a consequence of the presence of haemolytic saponins, are also predominant, whereas the other three classes contain the usual Δ^5-sterols.[2] Haemolysis is a consequence of the abstraction of membrane cholesterol by the saponins and saponins are known to show a much lower affinity for Δ^7-sterols, thus the presence of Δ^7-sterols might explain the apparent immunity of starfish and sea cucumbers to their own saponins.[232] Ophiuroids, which have received moderate attention by chemists as compared to the above classes, have been reported to contain a series of sulfated polyhydroxysteroids and two steroidal glycosides. In the past few years a large number of metabolites have been isolated from echinoderms, mainly steroidal glycosides and polyhydroxylated steroids from starfish and triterpene glycosides from sea cucumbers, with cytotoxic, antifungal, and antineoplastic activity. The interest in these compounds has resulted in a number of monographs entirely or in part devoted to this subject.

We should mention the works by Hashimoto (1979),[233] Burnell and ApSimon (1983),[232] Krebs (1986),[153] Minale, Riccio, Pizza, and Zollo (1986),[234] Quinn (1988),[235] Stonik and Elyakov (1988),[165] Habermehl and Krebs (1990),[236] and Minale, Riccio, and Zollo (1993).[197,237] The present paper focuses on free and sulfated polyhydroxysteroids and on their oligoglycosides occurring in starfish and ophiuroids.

A. Asteroidea (Starfish)

Most of the work on chemical constituents of starfish has been initially prompted by the discovery of their toxic saponins and interest in their biological properties. In the recent years the structural studies of these molecules has grown up rapidly, largely exceeding the biological studies on individual compounds and almost 250 steroidal constituents, which include free and sulfated polyhydroxysteroids and steroidal glycosides, have been isolated from *ca.* 50 different starfish species, belonging to 14 families and representative of the three major orders (Paxillosida, Valvatida, and Forcipulata) of the class Asteroidea. According to their chemical structures, the steroidal glycosides from starfish have been subdivided into three main groups: the asterosaponins, which are sulfated steroidal penta- and hexaglycosides; the cyclic glycosides, so far only found in two species of the genus *Echinaster*; and the glycosides of polyhydroxysteroids, which, although unnoticed for a long time, are as widespread as asterosaponins among starfish.[238] These molecules, which usually occur in minute amounts, consist of a polyhydroxylated steroidal aglycon linked to one or two sugar units and can be found in both sulfated and nonsulfated forms. Analysis of the polar extractives of the starfish *Tremaster novaecaledoniae* has recently led to the discovery of a new class of steroidal glycosides, in which the polyhydroxylated steroidal aglycon present also a phosphate conjugation to which the sugars are glycosidically attached.[239]

In the present paper we will discuss polyhydroxysteroids, glycosides of polyhydroxysteroids, asterosaponins, and cyclic glycosides, in that order.

1. Polyhydroxysteroids

Starfish appear as the richest source of polyhydroxysteroids. In contrast with other marine phyla, in which polyhydroxysteroids have been isolated from only a limited number of species sometime belonging to the same genus, polyhydroxysteroids are widespread in starfish, where they have been found, usually as complex mixtures, in almost all species examined. More than 80 polyhydroxysteroids from starfish have been reported so far **258–343**. The large majority of them possess a 3β,6α(or β),8,15α(or β),16β-pentahydroxycholestane nucleus, sometimes with additional hydroxyl groups at one or more of positions 4β,5α,7α(or β) and occasionally 14α. A 26-hydroxyl function with 25*S*-configuration is usually present in the side chain; less commonly the side chain is hydroxylated at C-24 with 24*S*-configuration or functionalized in various ways. All hydroxyl groups are disposed on one side of the tetracyclic nucleus inducing an amphiphilic character in the molecules. Up to nine hydroxyl groups have been found in the nonols **310–312**, **315**, and **316**, that to the best of our knowledge represent the most highly hydroxylated sterols isolated from a natural source. Polyhydroxysteroids occur sometimes in sulfated forms, with the sulfate group located at position 3β, 6α, 15α, or 24, and rare examples of phosphated derivatives have been recently isolated from the deep-water starfish *Tremaster novaecaledoniae*.[240]

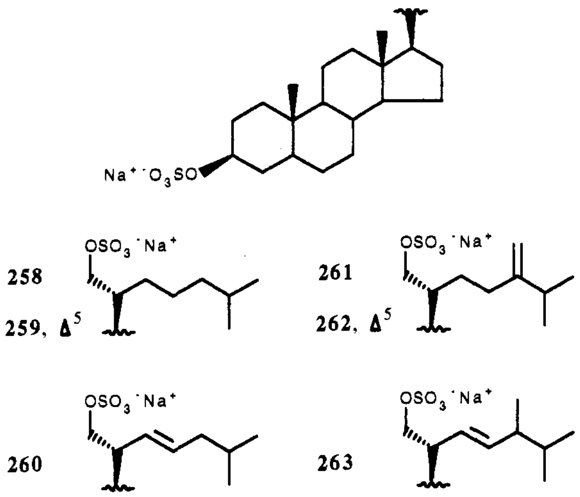


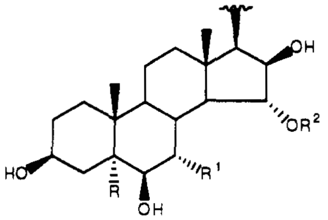
Figure 14. 3,21-Dihydroxysteroids 3,21-disulfates from the starfish *Euretaster insignis*.

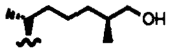
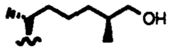
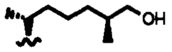
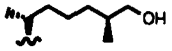
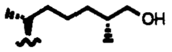
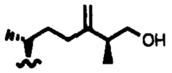
Euretaster insignis is a unique example among the many starfish species examined, it is apparently devoid of both common asterosaponins and glycosides of polyhydroxysteroids and also lacks the type of polyhydroxysteroids occurring in all other species. The analysis of its polar extract yielded instead the 3β,21-dihydroxysteroid 3,21-disulfates **258–263** (Figure 14) as a mixture resistant to further attempts of separation. After solvolysis to remove the sulfate groups, the mixture was fractionated by HPLC to afford pure desulfated **259** and two more fractions, still containing mixed dihydroxysteroids, that were resolved in the individual components by acetylation followed by argentic silica gel column chromatography.[241]

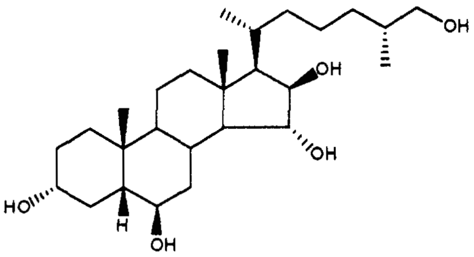
Although the large majority of polyhydroxysteroids from starfish (Table 1) possess a 8β-hydroxyl group, the compounds **264–272** lack this distinctive feature. These simpler polyhydroxylated nuclei are easily identifiable by their characteristic ^{1}H NMR spectral data (Tables 2 and 3). The 3β,5,6β-trihydroxy moiety in **265** is a common element in marine polyhydroxysteroids and is encountered in a large number of polyhydroxysteroids from starfish. Besides the relatively low field shifts of the 19-methyl protons, the occurrence of a 5α-hydroxyl group in 3β-hydroxy-5α-steroidal nuclei is well evidenced by an *ca.* 0.5 ppm downfield shift experienced by the 3α-H resonance. Hydroxylation of C-26 is a further common feature in the large majority of polyhydroxysteroids from starfish. ^{1}H and ^{13}C NMR spectral data of epimeric 26-hydroxysteroids show such small differences[248] that direct comparison of both stereoisomer is required for uniequivocal assignment of configuration at C-25. For instance in the 500-MHz ^{1}H NMR spectra of **265** and **269** the signals of the 27-methyl protons are observed at δ 0.934 (25*S*-isomer) and 0.925 (25*R*-isomer) ppm, respectively and equally small differences are observed for carbon signals C-24, C-26, and C-27 in the ^{13}C NMR spectra [δ_C 34.1, 68.4, and 17.3 for the 25*S*-isomer **265** and 34.7, 68.6, and 17.1 for the 25*R*-isomer **269**].[240] Since it was observed that

Table 1. Polyhydroxysterols from Starfish

Basic Nuclear Hydroxylation Pattern: 3β,6β,15α,16β

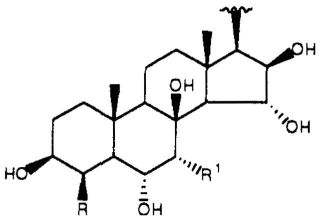


no.	side chain	R	R¹	R²	sources and references
264		H	H	H	*Hacelia attenuata*[242]
265		OH	H	H	*Luidia maculata*,[243] *Solaster borealis*,[244] *Myxoderma platyacanthum*[245]
266		OH	H	$SO_3^-Na^+$	*Myxoderma platyacanthum*,[245] *Rosaster* sp.[246]
267		H	OH	H	*Luidia maculata*[243]
268		OH	OH	H	*Luidia maculata*[243]
269		OH	H	H	*Tremaster novaecaledoniae*[240]
270		OH	H	$SO_3^-Na^+$	*Tremaster novaecaledoniae*[240]
271		H	H	H	*Sphaerodiscus placenta*[247]



272, from *Tremaster novaecaledoniae*[240]

Basic Nuclear Hydroxylation Pattern: 3β,6α,8,15α,16β



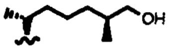
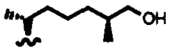
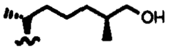
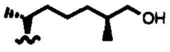
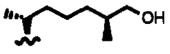
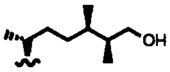
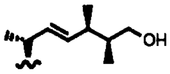
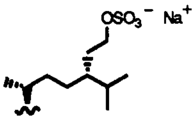
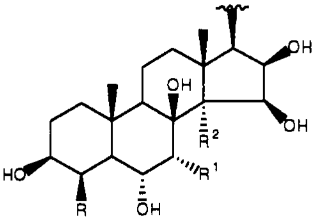
no.	side chain	R	R¹	sources and references
273		H	H	*Protoreaster nodosus*,[250] *Poraster superbus*,[251] *Pentaceraster alveolatus*,[252] *Asterina pectinifera*,[253,254] *Patiria pectinifera*,[255] *Patiria miniata*,[256] *Rosaster* sp.[246]
274		OH	H	*Protoreaster nodosus*,[257] *Patiria moniata*,[256] *Pentaceraster alveolatus*,[252] *Solaster borealis*[244]
275		H	OH	as **273**, *Pycnopodia helianthoides*,[258] *Solaster borealis*[244]
276		OH	OH	as **273**, *Pycnopodia helianthoides*,[258] *Solaster borealis*[244]
277	 6-O-sulfate	OH	OH	*Oreaster reticulatus*[259]

Table 1 (Continued)

no.	side chain	R	R^1	sources and references
278		H	H	*Protoreaster nodosus*[257]
279		OH	H	*Protoreaster nodosus*[257]
280		H	H	*Poraster superbus*[251]

Basic Nuclear Hydroxylation Pattern: 3β,6α,8,15β,16β



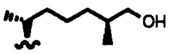
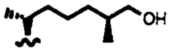
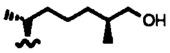
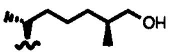
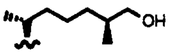
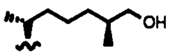
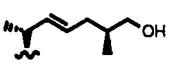
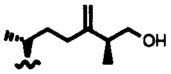
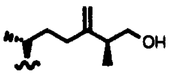
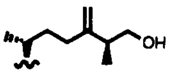
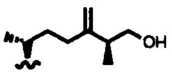
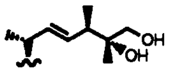
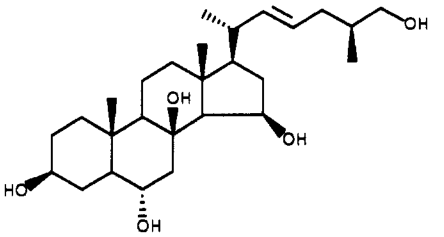
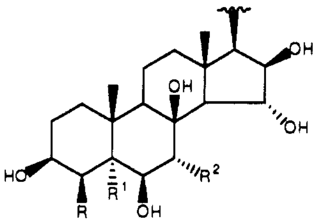
no.	side chain	R	R^1	R^2	sources and references
281		H	H	H	*Halityle regularis*,[264] *Nardoa gomophia*,[265] *Pycnopodia helianthoides*,[258] *Dermasterias inbricata*,[266] *Astropecten scoparius*[267]
282		OH	H	H	*Halityle regularis*[264]
283	 3-O-sulfate	OH	H	H	*Coscinasterias tenuispina*[268]
284		H	OH	H	*Pycnopodia helianthoides*,[258] *Asterina pectinifera*,[254] *Astropecten scoparius*[267]
285		H	H	OH	*Dermasterias imbricata*[266]
286		OH	OH	H	*Asterina pectinifera*,[253,254] *Patiria miniata*,[256] *Solaster borealis*,[244] *Astropecten scoparius*[267]
287	 6-O-sulfate	OH	OH	H	*Asterina pectinifera*[253]
288		H	H	H	*Dermasterias imbricata*[266]
289		H	H	H	*Dermasterias imbricata*[266]
290		OH	H	H	*Culcita novaeguineae*[269]
291		H	H	OH	*Dermasterias imbricata*[266]
292		OH	OH	H	*Patiria miniata*,[256] *Astropecten scoparius*,[267] *Solaster borealis*[244]
293	 6-O-sulfate	OH	OH	H	*Patiria miniata*[256]

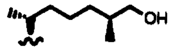
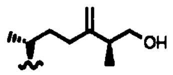
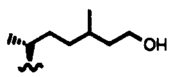
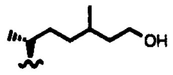
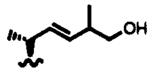
Table 1 (Continued)



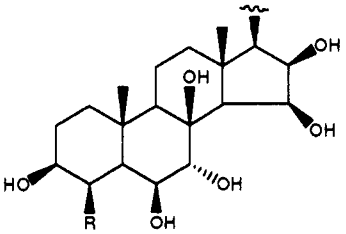
294 from *Dermasterias imbricata*[266]

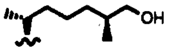
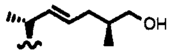
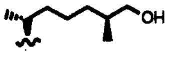
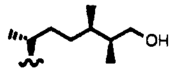
Basic Nuclear Hydroxylation Pattern: 3β,6β,8,15α,16β



no.	side chain	R	R¹	R²	sources and references
295		H	H	H	*Sphaerodiscus placenta*,[247] *Crossaster papposus*,[270] *Culcita novaeguineae*[269]
296		H	H	OH	*Rosaster* sp.,[246] *Culcita novaeguinea*[269]
297		OH	H	OH	*Rosaster* sp.[246]
298		H	H	H	*Sphaerodiscus placenta*[247]
299		H	H	H	*Hacelia attenuata*[271]
300		OH	H	H	*Hacelia attenuata*[271]
301		OH	H	H	*Hacelia attenuata*[271]

Basic Nuclear Hydroxylation Pattern: 3β,6β,8,15β,16β



no.	R	side chain	no.	R	side chain	sources and references
302	H		**304**	OH		*Solaster borealis*[244]
303	OH		**305**	OH		*Solaster borealis*[244]

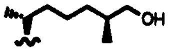
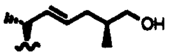
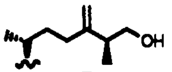
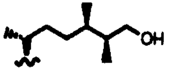
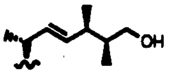
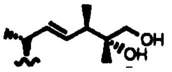
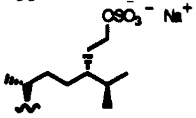
26-O derivatization of a signal natural stereoisomer with chlorides of (*R*)-(+)- and (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA, the Mosher's reagent) results in significant differences in the ^1H NMR spectra of the two diastereomeric derivatives,[249] the assignment of configuration at C-25 has been systematically made by comparison of the diastereotopic 26-H_2 signals in the spectra of the (*R*)-(+)- and (*S*)-(−)-MTPA esters.[197] As exemplified by **265** and **269**, in the spectra of the MTPA esters of the 25*S*-isomer **265** the 26-methylene proton signals appear much closer in the spectrum of the (*R*)-(+)-MTPA ester (δ 4.21 ppm, bd) than in that of the (*S*)-(−)-MTPA derivative (δ 4.13–4.29 ppm, dd), while the reverse occurs for MTPA esters

Table 2. ^{1}H NMR Data of Representative Polyhydroxysterols from Starfish

no.	hydroxylation pattern	3-H	4-H	6-H	7β-H	15-H	16-H	18-H$_3$	19-H$_3$	others
264	3β,6β,15α,16β	3.57 m		3.76 br s		3.80 dd (10.5, 3.0)	4.00 dd (8.5, 3.0)	0.95 s	1.07 s	
265	3β,5,6β,15α,16β	4.04 m		3.50 br s		3.76 dd (10.5, 3.0)	4.00 dd (8.5, 3.0)	0.94 s	1.21 s	
266	3β,5,6β,15α,16β 15-*O*-sulfate	4.08 m		3.50 br s		4.38 dd	4.33 dd	1.00 s	1.20 s	
267	3β,6β,7α,15α,16β	3.60 m		3.62 t (3.5)	3.91 t (3.5)	3.89 dd (10.5, 3.0)	4.04 dd (7.5, 3.0)	0.96 s	1.04 s	
268	3β,5,6β,7α,15α,16β	4.05 m		3.55 d (3.0)	4.02 t (3.0)	3.88 dd (10.5, 3.0)	4.04 dd (7.5, 3.0)	0.96 s	1.17 s	
273	3β,6α,8,15α,16β	3.59 m		3.66 dd (10.0, 3.0)	2.43 dd (12.0, 3.0)	4.06 dd (11.5, 2.5)	4.00 dd (8.5, 2.5)	1.15 s	1.03 s	
274	3β,4β,6α,8,15α,16β	3.46 m	4.28 br s	4.24 m	2.50 dd (12.0, 3.0)	4.09 dd (10.5, 3.0)	4.01 dd (7.5, 3.0)	1.15 s	1.21 s	
275	3β,6α,7α,8,15α,16β	3.58 m		3.81 m	3.81 m	4.16 dd (11.5, 2.5)	4.03 dd (8.5, 2.5)	1.15 s	1.03 s	
276	3β,4β,6α,7α,8,15α,16β	3.46 m	4.22 m	4.25 dd (11.5, 2.5)	3.88 d (2.5)	4.18 dd (10.5, 2.5)	4.03 dd (8.5, 2.5)	1.15 s	1.21 s	
277	3β,4β,6α,7α,8,15α,16β 6-*O*-sulfate	3.52 m	4.26 br s	5.03 dd (11.5, 2.5)	4.18 d (2.5)	4.18 dd (10.0, 2.5)	4.02 dd (7.0, 2.5)	1.15 s	1.30 s	
281	3β,6α,8,15β,16β	3.62 m		3.74 td (10.5, 4.0)	2.42 dd (12.5, 4.0)	4.40 dd (6.8, 5.6)	4.25 t (6.8)	1.27 s	1.02 s	
282	3β,4β,6α,8,15β,16β	3.50 m	4.29 br s	4.22 td (10.5, 4.0)	2.49 dd (12.5, 4.0)	4.40 dd (6.8, 5.6)	4.25 t (6.8)	1.27 s	1.19 s	
284	3β,6α,7α,8,15β,16β	3.53 m		3.87 td (12.5, 2.5)	3.90 d (2.5)	4.50 dd (6.5, 5.5)	4.25 t (6.5)	1.28 s	1.02 s	14-H: 1.43 d (5.5)
285	3β,6α,8,14α,15β,16β	3.50 m		3.77 td (10.5, 4.0)	2.14 dd (12.5, 4.0)	4.00 d (6.5)	4.37 t (6.5)	1.35 s	1.04 s	
286	3β,4β,6α,7α,8,15β,16β	3.47 m	4.22 br s	4.32 td (11.0, 2.5)	3.98 d (2.5)	4.51 dd (6.5, 5.5)	4.26 t (6.5)	1.27 s	1.19 s	5-H: 1.52 dd (11,2, 3.0) 14-H: 1.42 d (5.5)
295	3β,6β,8,15α,16β	3.43 m		3.89 br s	2.46 dd (15.0, 2.5)	4.17 dd (11.2, 7.5)	4.02 dd (7.5, 2.5)	1.15 s	1.20 s	
296	3β,6β,7α,8,15α,16β			3.72 dd (3.1, 2.9)	3.87 d (3.1)	4.21 dd (10.0, 2.5)	4.000 dd (7.5, 2.5)	1.15 s	1.15 s	
297	3β,4β,6β,7α,8,15α,16β	3.50 m	4.10 br s	4.04 dd (3.1, 2.9)	3.85 d (3.0)	4.21 dd (10.0, 2.5)	4.000 dd (7.5, 2.5)	1.15 s	1.43 s	
302	3β,6β,8,15β,16β	3.60 m		3.60 dd (3.0, 2.9)	4.03 d (3.0)	4.50 dd (5.0, 6.2)	4.25 t (6.2)	1.30 s	1.18 s	
303	3β,4β,6β,8,15β,16β	3.55 m	4.08 br s	4.00 dd	4.02 d (3.0)	4.50 dd (5.0, 6.2)	4.23 t (6.2)	1.30 s	1.45 s	

[a] Data (δ, ppm) were mostly obtained at 250 MHz from solution in CD$_3$OD and are referred to the central line of the CHD$_2$OD signal (δ 3.34 ppm).

Table 3. Selected ^{1}H NMR Data of Side Chains of Polyhydroxysterols from Starfish

	no.	21-H	22, 23-H's	26-H$_2$	27-H$_3$	28-H's	other
	**273**	0.96 d (7.0)		3.46 dd (10.5, 6.0) *ca.* 3.32[b]	0.94 d (7.0)		
	**288**	1.06 d (6.5) 5.51 dt (16.0, 6.5)	5.60 dd (6.5, 16.0)	3.46 dd (10.5, 6.0) *ca.* 3.32[b]	0.92 d (7.0)		
	**289**	1.00 d (7.5)		3.41 dd (11.0, 7.5) 3.63 dd (11.0, 6.0)	1.10 d (7.5)	4.78 br s 4.85 br s	
	**278**	0.95 d (7.0)		3.40 dd (10.5, 6.0) *ca.* 3.32[b]	0.82 d (6.5)	0.84 d (6.5)	
	**279**	1.04 (7.0)	5.45 m	3.41 dd (11.0, 6.0) 3.56 dd (11.0, 6.0)	0.91 d (7.0)	0.99 d (7.0)	20-H: 2.55 m 24-H: 2.10 m
	**293**	1.07 (7.0)	5.54 m	3.42 d (11.0) 3.50 d (11.0)	1.10 s	1.01 d (7.0)	
	**280**	0.96 d (7.0)		0.89 d (7.0)	0.92 d (7.0)		29-H$_2$: 4.06 m (desulfated: 3.60 m)

[a] Data (δ, ppm) were mostly obtained at 250 MHz from solution in CD$_3$OD and are referred to the central line of the CHD$_2$OD signal (δ 3.34 ppm). [b] Partially overlapping with solvent signal.

of the 25*R*-isomer **269**, the resonance being closer in the (*S*)-(−)-MTPA ester (δ 4.19–4.23 ppm, dd) and more separated in the (*R*)-(+)-MTPA (δ 4.14–4.28 dd). It has also been observed that derivatization on ring D, as sulfate group at C-15 in **266** and **270**, can affect the extent of the separation of the 26-methylene proton signals, thus it is always advisable to assign the configuration by direct comparison of both (*R*)-(+)- and (*S*)-(−)-MTPA derivatives.[240,245]

Compounds **269**, **270**, and **272**, all isolated from the deep-water starfish *Tremaster novaecaledoniae*, represent the only examples of 26-hydroxysteroids from starfish with 25*R* configuration. **272** is also the only one to exhibit a 3α-hydroxy-5β-steroidal nucleus, as indicated by the low field signal of the angular methyl carbon-19 at 26.1 ppm and by the multiplet at δ 3.54 ppm, having the typical shape for a 3β-hydroxymethine signal in a 5β-steroid.

Compounds **273**, **275**, and **276**, with the basic 3β,6α,8,15α,16β-hydroxylation pattern, were the first polyhydroxysteroids to be isolated from a starfish, the Pacific Ocean species *Protoreaster nodosus*;[250] they were later shown to be the most common polyhydroxysteroids from starfish. They exhibited moderate cytotoxic and anticancer activities.[253,260] The structures of these first steroids were determined on the results of NMR and mass spectral analysis, chemical transformations and related spectroscopic data. Acetylation of **273** followed by oxidation with Jones reagent afforded 3β,6α,15α,26-tetrakis(acetyloxy)-8-hydroxy-5α-cholestan-16-

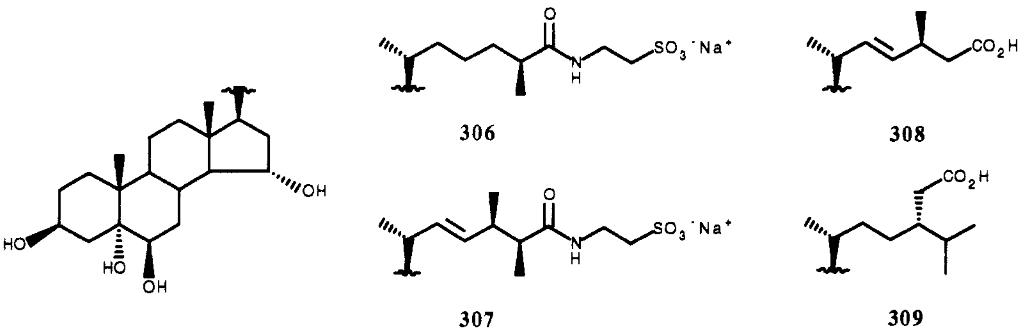


Figure 15. Unusual polyhydroxysteroids with a side-chain methyl group oxidized to carboxyl group from the starfish *Myxoderma platyacanthum*.

one. The elimination of the side chain with migration of one hydrogen (*m/z* 464, McLafferty rearrangement) followed by 18-methyl fission (*m/z* 449) in the mass spectrum was diagnostic of a 16-ketosteroid. Acetylation of **275** and **276** afforded likewise the corresponding tetraacetates [3β,6α,15α,26-tetrakis(acetyloxy)], which, on oxidation with Jones reagent, gave the 3β,6α,15α,-26-tetrakis(acetyloxy)-7α,8-dihydroxy-5α-cholestan-16-one and 3β,6α,15α,26-tetrakis(acetyloxy)-7α,8-dihydroxy-5α-cholestane-4,16-dione, respectively. Treatment of **273**, **275**, and **276** with *p*-bromobenzoyl chloride in pyridine led to the formation of the corresponding 3β,6α,15α,26-tetrakis(*p*-bromobenzoates) with CD curves displaying strong positive first and negative second Cotton effects ($\Delta_{\epsilon\ 252}$ +37.2/$\Delta_{\epsilon\ 235}$ −20.0) in agreement with the expected positive chirality of the three major dibenzoates interactions (3β/6α, 3β/15α, 6α/15α) in a cholestane skeleton with 5α-H absolute configuration. The 25*S* configuration was assigned, as described before, by ^{1}H NMR pattern of the 26-H_2 signals of the (*R*)-(+)- and (*S*)-(−)-MTPA derivatives.[249]

Steroids **274**, **278**, and **279** were later isolated from the same starfish species, *Protoreaster nodosus*;[257] has since been isolated also from other species. The stereochemistry of the side chains of **278** and **279** is suggested after the stereoselective synthesis of the 24-methyl-26-hydroxysteroid models.[261] Compound **280** is a quite rare example of non-glycosylated C-29 polyhydroxysteroid, these compounds have been more commonly found as aglycons in several glycosides of polyhydroxysteroids (see section VII.A.2). The 24*R* configuration is suggested on the basis of the reported chemical shifts of the isopropyl methyls in both ^{1}H and ^{13}C NMR spectra and comparison with model compounds.[262,263]

Steroids **281–293** share the common 3β,6α,8,15β,16β-hydroxylation pattern, while **294** is a rare example of a 26-hydroxysteroid missing the 16β-hydroxyl function. The inversion of stereochemistry at C-15, with respect to the previous ones, is connected with a slight downfield shift of the 18-methyl proton signal and with major changes of the 7-, 15-, and 16-proton signals, whose shapes and chemical shifts become distinctive features of this structural subgroup. The *cis*-15,16-dihydroxy stereochemistry was supported by the formation of a 15,16-monoacetonide on treatment of the hexol **281** with Me_2CO and TsOH and by the formation of a 3,4:15,-16-bisacetonide on similar treatment of the heptol **282**.[264] The chemical shift differences of the 26-methylene protons in the 26-*O*-(*R*)-(+)- and 26-*O*-(*S*)-(−)-MTPA esters (δ 4.26–4.31 dd and 4.20–4.41 dd, respectively) were used to establish the 25*S* configuration of **292**.[256] The 14α-hydroxyl group in **285** and **291** induces substantial modifications in both ^{1}H and ^{13}C NMR spectra *vs* their 14-deoxy analogs **281** and **289**, most significant in the ^{13}C NMR spectrum are the large γ-upfield shifts observed for the C-7 (−4.6 ppm), C-9 (−8.9 ppm), C-12 (−5.4 ppm), and C-17 (−10.0 ppm) signals. The absolute configuration of the side chain in **291** has been suggested by comparison of ^{1}H and ^{13}C NMR data with those of the steroid **315** from *Archaster tipicus*.

The steroids **295–301** originate the structural group having the 3β,6β,8,15α,16β-hydroxylation pattern. Most significant modifications of ^{1}H NMR signals *vs* their 6α-counterparts refer to the shape and chemical shift of the 6-H signal and to the 19-methyl proton signal, downfield shifted by *ca.* 0.17 ppm. Compounds **299–301** are very minor components of the Mediterranean starfish *Hacelia attenuata* and their structures with truncated side chains were mainly deduced by interpretation of NMR spectra. The occurrence of these truncated steroids may be of some interest as indicators of the capability of the starfish to oxidize dietary sterols.

Steroids **302–305**, all isolated recently from the starfish *Solaster borealis*,[244] represent a further and minor variation in the stereochemical disposition of the nuclear hydroxyl groups. Compounds **302** and **303** are epimeric with the previous **284**, **286**, **296** and **297** from which they differ alternatively for the stereochemistry at C-6 or at C-15. The relative *threo* configuration at C-24 and C-25 of **305** was assigned by comparison of the NMR spectral data of the side chain with those of synthetic model compounds, while the absolute (24*R*,25*S*) configuration followed from derivatization with (*R*)-(+)-MTPA chloride and comparison of the ^{1}H NMR spectrum with those of the 26-*O*-(*R*)-(+)-MTPA esters of the two *threo* synthetic models (*i.e.* the 24*R*,25*S*- and 24*S*,25*R*-isomeric pair).

Polyhydroxysteroids **306–309** (Figure 15), isolated from the starfish *Myxoderma platyacanthum*[245] together with **265** and **266**, have the same 3β,5,6β,15α-tetrahydroxycholestane nucleus with different side chains: 26-acid; Δ^{22}-24-methyl 26-acid; Δ^{22}-27-nor-24-methyl 26-acid; and 24-carboxymethyl. In **306** and **307** the carboxylic acid function is found as the amide derivative of taurine. They are examples of the structural variety of steroids cooccurring in the same organism and also constitute the first reported isolation from starfish of steroids with a methyl group oxidized to carboxyl. The absolute configuration of the side chain stereogenic centers in **307–309** was determined

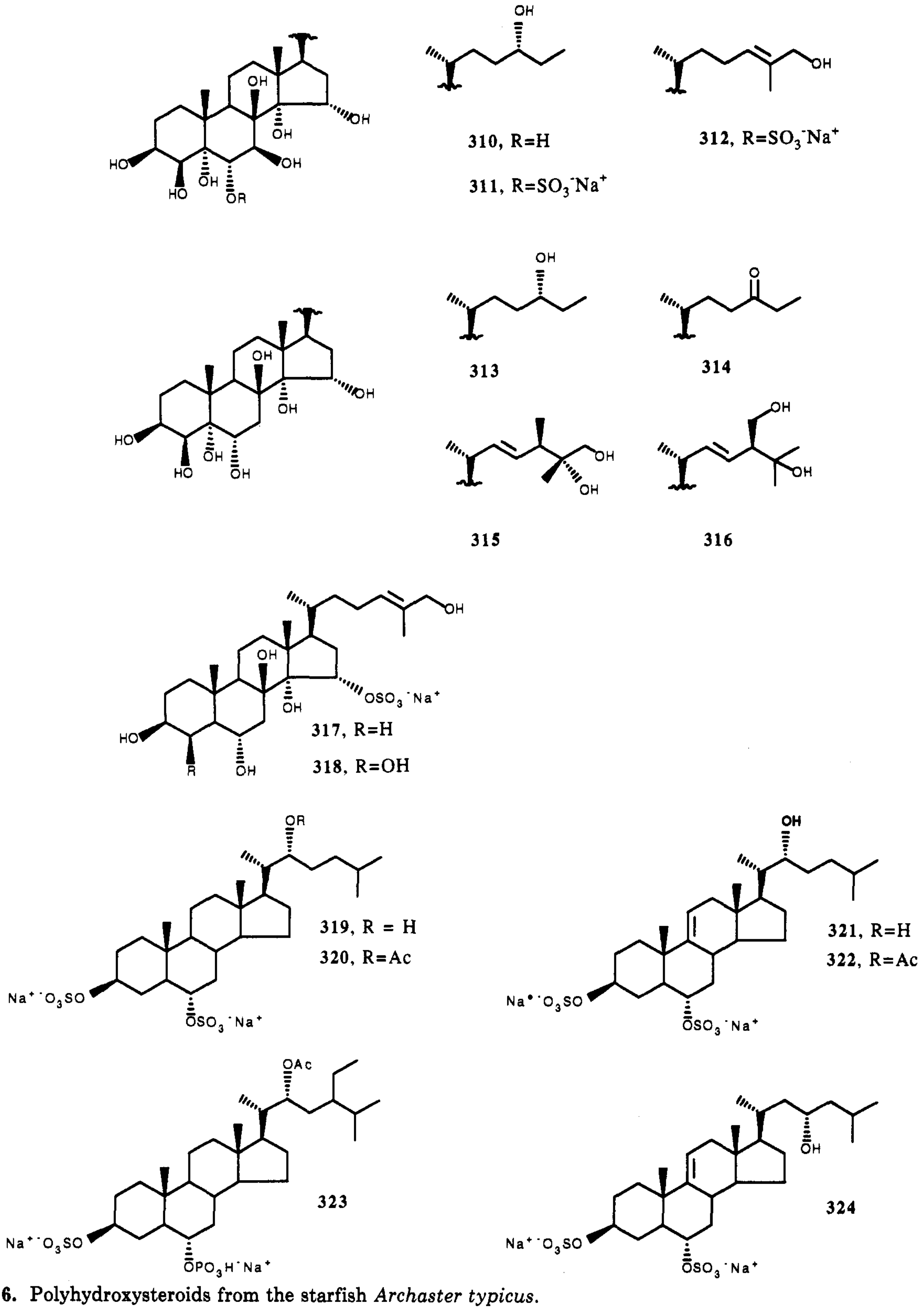
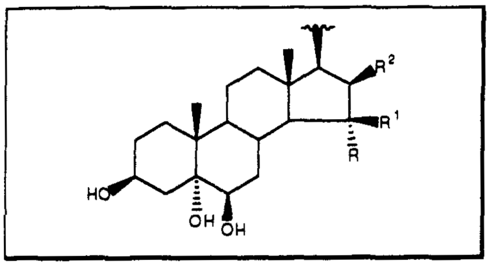
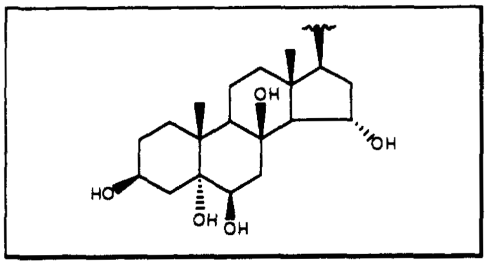


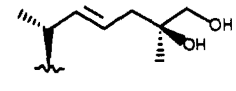
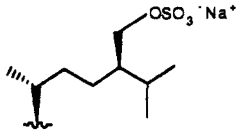
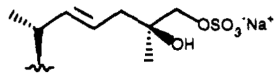
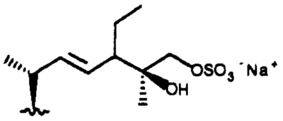
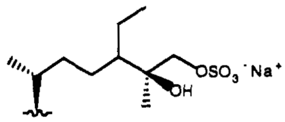
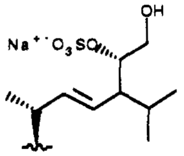
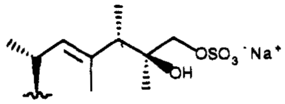
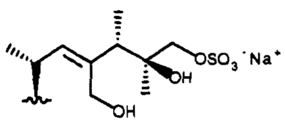
Figure 16. Polyhydroxysteroids from the starfish *Archaster typicus*.

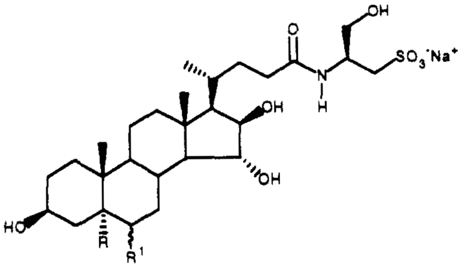
by spectral comparison with stereoisomeric $\Delta^{22(E)}$-24-methyl 26-acid,[261] 24-methyl-27-nor 26-acid,[245] and 24-carboxymethyl[263] steroidal models obtained by stereoselective synthesis. Only very small differences were observed in the ^{1}H NMR spectra of the two epimeric 24-methyl-27-nor 26-acid synthetic models, mainly dealing with the shifts of the olefinic protons: double doublets centered at δ 5.32 with the internal lines coincident in the 24*S*-isomer and separated by 1 Hz in the 24*R*-isomer. The olefinic pattern in the spectrum of the natural **308** was coincident with that of the 24*S*-model, thus suggesting the reported absolute configuration.

Figure 16 illustrates the variety of highly hydroxylated steroids encountered in *Archaster typicus*;[198,272] these steroids have been isolated in relatively large amounts as compared to the very limited fraction of steroidal glycosides in this starfish. Compounds **313** and **318** were shown to be moderately cytotoxic and to cause inhibition of growth of human lymphoma cells at a dose of 0.05 μg/mL.[260] The structures of the nonols **310**–**312**, **315**, and **316**, the most highly hydroxylated





#	side chain	R	R¹	R²	#	side chain
325		H	OH	H	330	
326		OH	H	H	331	
327		OH	H	OH	332	
328		OH	H	H		
329		OH	H	H		

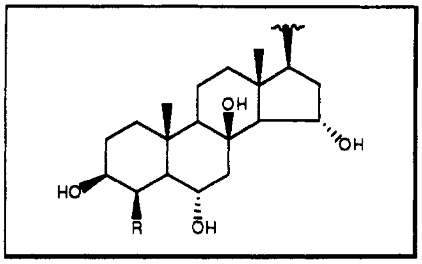


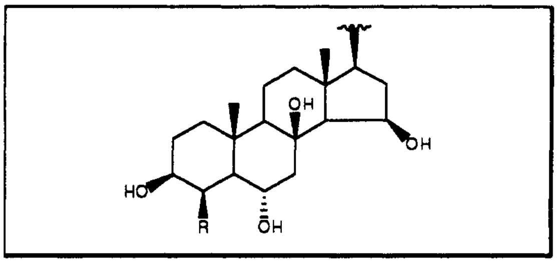
#	R	R¹
333	OH	◀OH
334	OH	═O
335	H	⋯OH

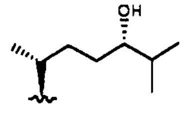
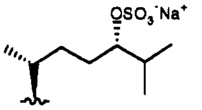
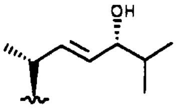
Figure 17. Polyoxygenated steroids from the starfish *Styracaster caroli*.

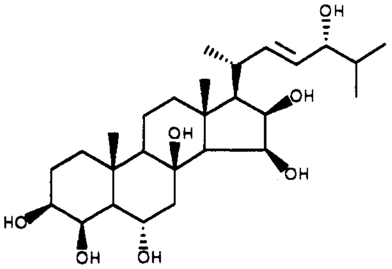
steroids isolated from natural sources, were determined essentially upon accurate spectral analysis. Major support in the elucidation of structures 310–312 came from 2D ^{1}H-^{13}C NMR heterocorrelation experiments

Chart I

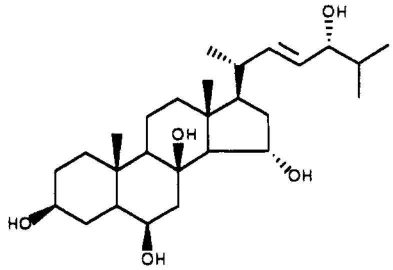




#	R	sources and references	side chain	#	R	sources and references
336	H	*Asterina pectinifera*[253]		338	H	*Gomophia watsoni*[276], *Nardoa gomophia*[265], *Dermasterias imbricata*[266], *Culcita novaeguineae*[269]
				339	OH	*G. watsoni*[276], *C. novaeguineae*[269]
337	H	*Aphelasterias japonica*[274]		340	H	*Astropecten scoparius*[267]
				341	H	*Dermasterias imbricata*[266]



342



343

source
Coscinasterias tenuispina[268]

(HETCOR and COLOC) that, through the long-range correlations with quaternary carbons C-5 and C-14, allowed firm location of tertiary hydroxyl groups and consequent build up of the tetracyclic framework. Stereochemical arrangement of hydroxyl groups was deduced by NOEDS experiments showing through-space interactions between 6-H and 19-Me, 9-H and 7-H, 15-H and 18-Me. Furthermore, on treatment with acetone and TsOH, compound **310** afforded a 3β,4β:14α,15α-bisacetonide, thus supporting the 14α-hydroxy stereochemistry. The application of the Horeau's method of kinetic resolution to this bisacetonide allowed the assignment of the 24*R* configuration to C-24. The assignment of the stereochemistry at C-24 and C-25 in **315** and **316** required NMR spectral comparison with synthetic model compounds.[198] The structure **310**, which has the remarkable feature of eight sequential hydroxyl groups protruding from the same side of the molecule, has been confirmed by a single-crystal X-ray diffraction study.[273] The crystal packing of molecules was shown to be a consequence of the amphiphilic character; the hydroxyl groups develop an intricate and extensive network of hydrogen bonds connecting the molecules through their hydrophilic moieties and giving rise to double layers, which interact through the hydrophobic surfaces.

A group of 3β,6α-disulfated steroids **319**–**322** has been more recently isolated from the "living fossile" species *Tremaster novaecaledoniae* collected at a depth of 530 m during exploration of the bathyal zone off New Caledonia.[240] Furthermore, analysis of polar extracts led to the isolation of the steroid **323** and of a new group of glycosides of polyhydroxysteroids, the tremasterols A–C (**459**–**461**), all possessing both phosphate and sulfate conjugation.[239,240] To the best of our knowledge they constitute the first reported isolation of phosphated steroids from a natural source. The presence of the phosphate group at C-6, at first indicated by the shape of the 6-proton signal, was confirmed by the proton noise-decoupled ^{13}C NMR spectrum in which the C-5 and C-6 signals appeared as doublets due to the ^{31}P–^{13}C couplings through two and three linkages and finally by ^{31}P NMR. *Tremaster novaecaledoniae* contains also the uncommon polyhydroxysteroids with 25*R* stereochemistry **269**, **270**, and **272**.

A further 3β,6α-disulfated steroid **324**, closely related to the aglycons of the asterosaponins also by the presence of an oxygenated function at C-23, has been isolated from the starfish *Aphelasterias japonica*.[274]

The very recent investigation of *Styracaster caroli*, a deep-water starfish collected between Thio and Lifou (New Caledonia) at a depth of 2000 m, revealed the occurrence of a very complex mixture of unprecedented polyhydroxysteroids (Figure 17) with unusual side chains.[275] Compounds **327** and **331** show a unique 24-ethyl-25-hydroxy-26-sulfoxycholestane skeleton, while compound **328** presents a Δ^{22}-23,24-dimethyl substitution pattern typical of dinosterol (**11**) and **329** is its 29-hydroxy derivative. An unusual oxygenation pattern is found in the C_{29} side chain of **332**, with a sulfoxy group at C-28 and a hydroxyl group at C-29. Compounds **333**–**335** are further examples of polyhydroxysteroids possessing an amido function in the side chain, with a D-(−)-cysteinolic acid (2*S*-amino-3-hydroxypropanesulfonic acid) linked to a C-24 carboxyl group.

In a more limited number of cases polyhydroxysteroids with hydroxyl or sulfate groups at C-24 have been isolated, **336**–**343** (Chart I). The hydroxylation at C-24 is a structural feature commonly encountered in the aglycons of the many steroidal glycosides isolated from starfish and indeed **336** is the aglycon of the glycosides **351**–**359**, while **338** and **339** have been found as the native aglycons in the glycosides **369**–**383** and **384**–**388**, respectively. The unsaturated **341** is the aglycon of **391**–**393** and the 15-*O*-sulfated of **343** has been found in **434**. The isomeric relationship at C-15 between **336** and **338** was confirmed by formation of an 8,15-phenylboronate in **338**. The 24*S* configuration was suggested in **338** by ^{13}C NMR data in comparison with those reported for 24(*S*)- and 24(*R*)-hydroxycholestanol. In fact differences observed between the spectra of the two epimers are very small[277,278] and in the desulfated **340** the 24*S* configuration was later confirmed, upon derivatization with (*R*)-(+)- and (*S*)-(−)-MTPA, by the Mosher's method for determination of absolute configuration of chiral secondary carbinols.[279,280] The steroid **341** was only isolated in admixture, with its 22,-23-dihydro congeners **338** resistant to further attempts of separation.

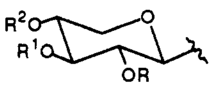
2. Glycosides of Polyhydroxysteroids

This group of steroidal glycosides from starfish shows a large degree of structural variability. Most of these compounds usually occur in minute amounts and are also widespread among starfish, having been found, usually as complex mixtures, in almost all the species investigated. They are composed of a polyhydroxylated steroidal aglycon and a carbohydrate portion mostly made up from one or two monosaccharide units (Figure 18) often linked to each other and glycosidically attached at C-3 or C-24 of the aglycon. Only very recently cytotoxic triglycosides (**418**, **419**, and **421**) were isolated from the New Caledonian species *Fromia monilis*.[281] They constitute the only examples of triglycosides among more than 100 different mono and diglycosides of polyhydroxysteroids isolated so far. The most common monosaccharides are D-xylopyranose, often methylated at position 2 and/or 4 and occasionally at position 3, and L-arabinose, found in its furanose form. Rare examples of xylofuranosides (**371**, **372**, and **403**), galactofuranosides (**400**, **441**, and **444**), fucofuranosides (**389** and **390**), and arabinopyranosides (**417** and **420**) have also been found.

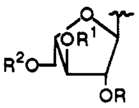
The first representative of such compounds, the cytotoxic nodososide **431**, was first isolated from Pacific *Protoreaster nodosus*[282] and later from other Valvatida species. This was followed by the structures of more than 100 different glycosides of polyhydroxysteroids. Structural variations originate from the hydroxylation pattern of the steroidal tetracyclic nucleus, the functionalization of the side chain, the presence of sulfate, and the nature and location of the saccharide moiety. Beside the invariable 3β-hydroxylation, hydroxyl groups are commonly found at the positions 6α(or β), 8, 15α(or β), and 24 of the aglycon with additional hydroxyl group(s) at one or more of the positions 4β, 5α, 7α, and 16β. The glycosides of polyhydroxysteroids often occur as complex mixtures with free and sulfated polyhydroxysteroids and asterosaponins; for example the polar steroids from *Coscinasterias tenuispina* have been resolved into 19 constituents.[268] Illustrative examples of the structural variety of steroidal glycosides cooccurring in the same organism are the 11 glycosides of polyhydroxysteroids isolated from the starfish *Henricia laeviuscola*,[283] the eight steroidal diglycosides, the halitylosides, isolated from the starfish *Halityle regularis*[264] along with two polyhydroxysteroids and four asterosaponins, and the 11 glycosides and five polyhydroxysteroids isolated during a recent reinvestigation of the polar extractives from the starfish *Culcita novaeguineae*.[269]

The structures of the currently known glycosides of polyhydroxysteroids are listed in Table 4 with their sources and references. Compounds **344**–**350** are uncommon examples of steroidal glycosides lacking the hydroxyl group at C-8 of the aglycon, a structural feature present in all other glycosides. Glycosides **351**–**363** are characterized by the steroidal aglycons with the basic 3β,6α,8,15α-hydroxylation pattern, while in **364**–**368** the tetracyclic nucleus also bears a 16β-OH. The largest group of compounds presents aglycons with the basic 3β,6α,8,15β-hydroxylation pattern, **369**–**402**, with a single case of Δ^4-unsaturation in **402**. The (24*S*)-5α-cholestane-3β,6α,8,15β,24-pentol aglycon, first encountered in attenuatoside A II (**369**) from *Hacelia attenuata*, is the most common steroidal aglycon found in the glycosides from starfish. In the aglycons with the 3β,6α,8,15β,16β-hydroxylation pattern **403**–**422** the oxygenated C-28 and C-29 side chains prevail on the common 24-hydroxyl side chain only found in indicoside C (**403**). Compounds **423**–**436** constitute the group of glycosides whose aglycons possess the basic 3β,6β,8,-15α-hydroxylation pattern; this group of compounds comprises several examples of those glycosides in which the two monosaccharides are not linked to each other but at positions 3 and 24 of the aglycon. Also in the group with 3β,6β,8,15α,16β-hydroxylation pattern **437**–**452** the C-28 and C-29 aglycons are predominant; moreover in the Δ^4-unsaturated compounds **447**–**452** the xylosyl unit in constantly found linked at C-3 of the aglycon. The smallest group comprising compounds **453**–**455** has the basic 3β,6β,8,15β-hydroxylation pattern.

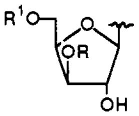
Compounds **456**–**458** cannot be classified in any of the above structural groups; they contain aglycons with



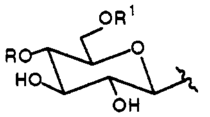
	R	R^1	R^2
X_1	H	H	H
X_2	CH_3	H	H
X_3	H	CH_3	H
X_4	CH_3	H	CH_3
X_5	H	H	$SO_3^-Na^+$
X_6	H	CH_3	$SO_3^-Na^+$



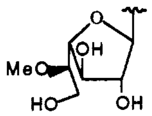
	R	R^1	R^2
A_1	H	H	H
A_2	H	CH_3	$SO_3^-Na^+$
A_3	H	$SO_3^-Na^+$	H
A_4	$SO_3^-Na^+$	H	CH_3
A_5	H	H	$SO_3^-Na^+$



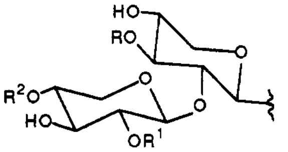
	R	R^1
Xf_1	H	$SO_3^-Na^+$
Xf_2	CH_3	$SO_3^-Na^+$



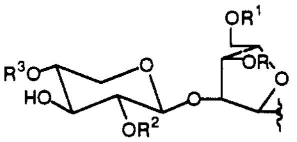
	R	R^1
Glc_1	H	H
Glc_2	H	$SO_3^-Na^+$
Glc_3	$SO_3^-Na^+$	H



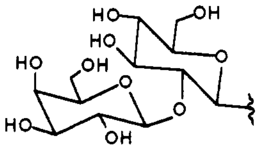
Gal*f*



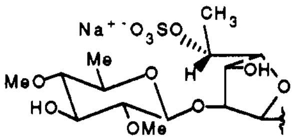
	R	R^1	R^2
XX_1	H	H	H
XX_2	CH_3	H	H
XX_3	CH_3	H	CH_3
XX_4	H	CH_3	H



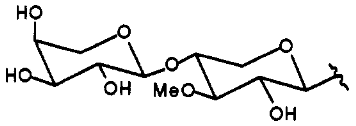
	R	R^1	R^2	R^3
XA_1	$SO_3^-Na^+$	H	H	H
XA_2	H	$SO_3^-Na^+$	H	H
XA_3	H	$SO_3^-Na^+$	CH_3	H
XA_4	H	H	H	CH_3
XA_5	H	H	CH_3	H
XA_6	H	H	CH_3	CH_3



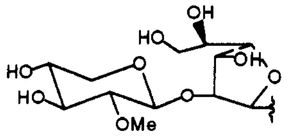
GalGlc



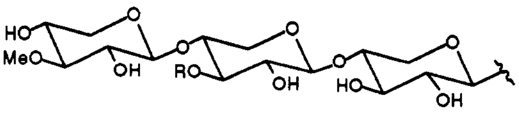
QuiFuc*f*



AX



XGal*f*



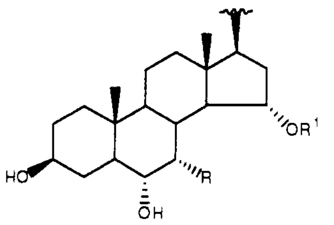
XXX_1 R = H
XXX_2 R = OH

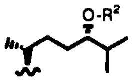
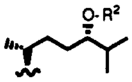
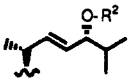
Figure 18. Saccharide chains found in glycosides of polyhydroxysterols from starfish.

unsaturated tetracyclic nuclei, a quite unusual feature among glycosides of polyhydroxysteroids from starfish, only found in the above mentioned compounds with Δ^4-steroidal skeleton.

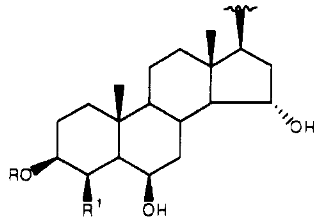
Table 4. Glycosides of Polyhydroxysteroids[a]

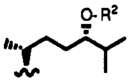
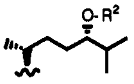
Basic Nuclear Hydroxylation Pattern: 3β,6α,15α



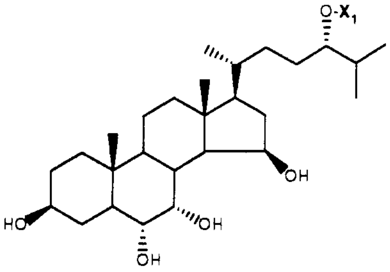
name	no.	side chain	R	R^1	R^2	sources and references
amurensoside A	**344**		H	$SO_3^-Na^+$	X_1	*Asterias amurensis*[284]
amurensoside B	**345**		OH	$SO_3^-Na^+$	X_1	*Asterias amurensis*[284]
amurensoside C	**346**		H	H	X_5	*Asterias amurensis*[284]

Basic Nuclear Hydroxylation Pattern: 3β,6β,15α



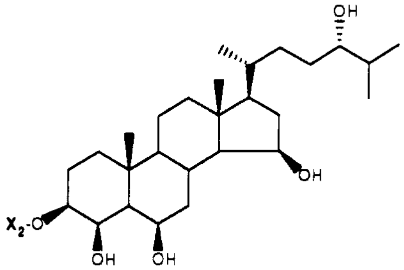
name	no.	side chain	R	R^1	R^2	sources and references
granulatoside B	**347**		X_2	H	A_1	*Choriaster granulatus*[285]
laeviuscoloside F	**348**		X_4	OH	A_1	*Henricia laeviuscola*[283]

3β,6α,15β



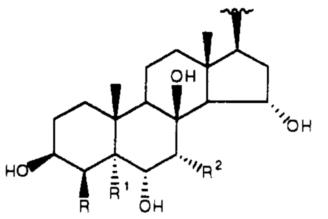
amurensoside D **349** *Asterias amurensis*[284]

3β,6β,15β



moniloside C **350** *Fromia monilis*[281]

Basic Nuclear Hydroxylation Pattern: 3β,6α,8,15α



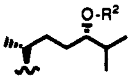
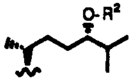
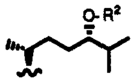
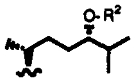
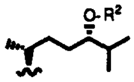
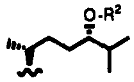
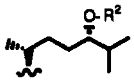
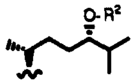
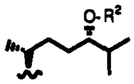
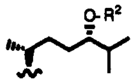
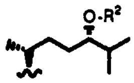
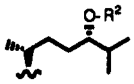
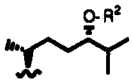
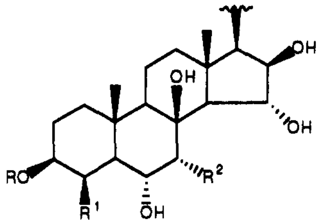
name	no.	side chains	R	R^1	R^2	R^3	sources and references
asterosaponin P-1	**351**		H	H	H	A_2	*Patiria pectinifera*,[286] *Oreaster reticulatus*,[259] *Patiria miniata*[256]

Table 4 (Continued)

name	no.	side chains	R	R¹	R²	R³	sources and references
	352		H	H	H	A_3	*Oreaster reticulatus*,[259] *Patiria miniata*[256]
miniatoside B	353		H	H	H	XA_1	*Patiria miniata*[256]
crossasteroside B	354		H	H	H	XX_3	*Crossaster papposus*[287]
crossasteroside C	355		H	H	H	XA_4	*Crossaster papposus*[287]
borealoside A	356		H	H	H	XA_3	*Solaster borealis*[244]
borealoside B	357		H	H	H	XA_2	*Solaster borealis*[244]
borealoside C	358		H	H	H	X_3	*Solaster borealis*[244]
crossasteroside A	359		H	H	OH	XX_3	*Crossaster papposus*[288]
crossasteroside D	360		H	H	OH	XX_2	*Crossaster papposus*[288]
attenuatoside C	361		OH	H	H	A_1	*Hacelia attenuata*[289]
borealoside D	362		OH	H	H	X_3	*Solaster borealis*[244]
6-*epi*-nodososide	363		H	OH	H	XA_5	*Pentaceraster alveolatus*[252]

Basic Nuclear Hydroxylation Pattern: 3β,6α,8,15α,16β



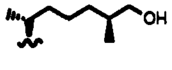
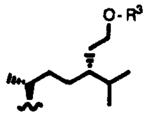
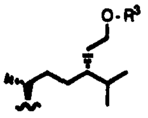
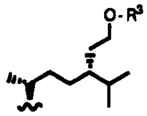
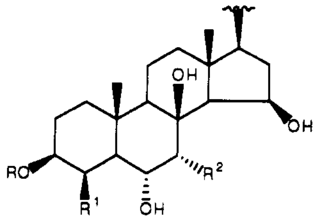
name	no.	side chains	R	R¹	R²	R³	sources and references
	364		X_2	H	H		*Poraster superbus*[251]
	365		X_2	H	OH		*Poraster superbus*[251]
	366		H	H	H	A_1	*Patiria pectinifera*[290]
miniatoside A	367		H	H	H	A_4	*Patiria miniata*[256]

Table 4 (Continued)

name	no.	side chains	R	R¹	R²	R³	sources and references
asterosaponin P-2	**368**		H	OH	H	A_2	*Patiria pectinifera*[291]

Basic Nuclear Hydroxylation Pattern: 3β,6α,8,15β



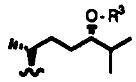
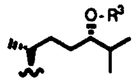
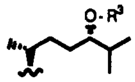
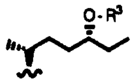
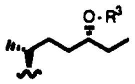
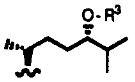
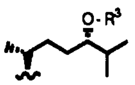
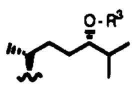
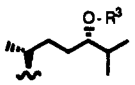
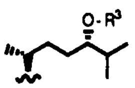
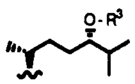
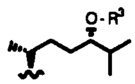
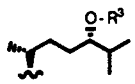
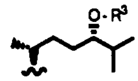
name	no.	side chain	R	R¹	R²	R³	sources and references
attenuatoside A-II	**369**		H	H	H	A_1	*Hacelia attenuata*[271]
scoparioside A	**370**		H	H	H	A_5	*Astropecten scoparius*[267]
scoparioside B	**371**		H	H	H	Xf_1	*Astropecten scoparius*[267]
indicoside B	**372**		H	H	H	Xf_2	*Astrospecten indicus*[292]
pycnopodioside A	**373**		H	H	H	X_1	*Pycnopodia helianthoides*[258]
pycnopodioside B	**374**		$So_3^-Na^+$	H	H	X_1	*Pycnopodia helianthoides*[258]
pycnopodioside C	**375**		H	H	H	Glc_2	*Pycnopodia helianthoides*[258]
luridoside A	**376**		H	H	H	X_5	*Comasterias lurida*[293]
scoparioside C	**377**		H	H	H	X_6	*Astropecten scoparius*[267]
attenuatoside A-I	**378**		H	H	H	XA_5	*Hacelia attenuata*[294]
culcitoside C_4	**379**		H	H	H	XA_4	*Culcita novaeguineae*[269]
halityloside E	**380**		H	H	H	XA_6	*Halityle regularis*,[264] *Nardoa gomophia*,[265] *Sphaerodiscus placenta*,[247] *Culcita novaeguineae*[269]
glacialoside A	**381**		X_1	H	H	$SO_3^-Na^+$	*Marthasterias glacialia*[295]
distolasteroside D_1	**382**		X_1	H	H	X_1	*Distolasterias nippon*[296]

Table 4 (Continued)

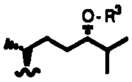
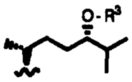
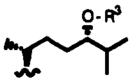
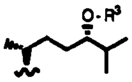
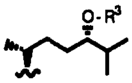
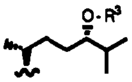
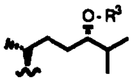
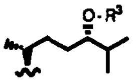
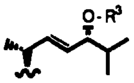
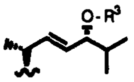
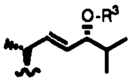
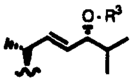
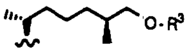
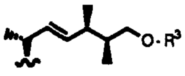
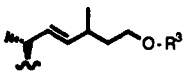
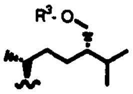
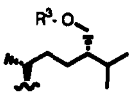
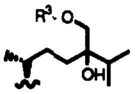
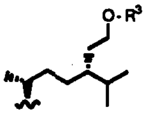
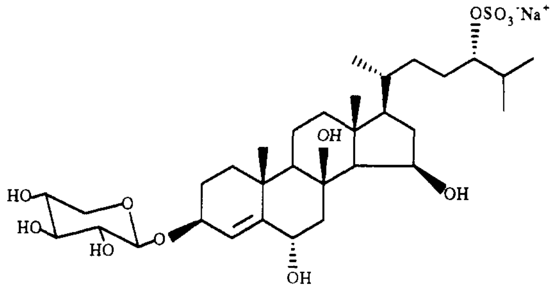
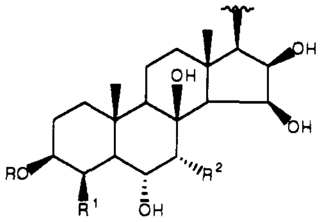
name	no.	side chain	R	R¹	R²	R³	sources and references
distolasteroside D_3	383		S_1	H	H	**Glc**$_1$	*Distolasterias nippon*[296]
attenuatoside B-2	384		H	OH	H	**A**$_1$	*Hacelia attenuata*[289]
attenuatoside B-1	385		H	OH	H	**XA**$_5$	*Hacelia attenuata*[289]
culcitoside C_5	386		H	OH	H	**XA**$_4$	*Culcita novaeguineae*[269]
halytiloside D (culcitoside C_1)	387		H	OH	H	**XA**$_6$	*Halityle regularis,*[264] *C. novaeguineae,*[269,297] *N. gomophia, N. novaecaledoniae,*[265] *Linkia guildingi*[297]
glacialoside B	388		$SO_3^-Na^+$	OH	H	**X**$_1$	*Marthasterias glacialis*[295]
imbricatoside B	389		H	H	OH	**QuiFuc*f***	*Dermasterias imbricata*[266]
imbricatoside A	390		H	OH	OH	**QuiFuc*f***	*Dermasterias imbricata*[266]
luridoside B	391		H	H	H	**X**$_5$	*Comasterias lurida*[293]
22-dehydrohalityloside E (poranoside A)	392		H	H	H	**XA**$_6$	*Sphaerodiscus placenta,*[247] *Porania pulvillus*[298]
distolasteroside D_2	393		X_1	H	H	**X**$_1$	*Distolasterias nippon*[296]
22-dehydrohalytilodside D	394		H	OH	H	**XA**$_6$	*Sphaerodiscus placenta*[247]
coscinasteroside F	395		H	OH	H	**X**$_1$	*Coscinasterias tenuispina*[268]
halityloside I (6-O-sulphate)	396		H	OH	H	**XX**$_4$	*Halityle regularis,*[264] *Nardoa gomophia*[265]
placentoside A	397		H	OH	H	**XX**$_4$	*Sphaerodiscus placenta*[247]
culcitoside C_6	398		H	OH	H	**XA**$_6$	*Coscinasterias tenuispina*[268]
culcitoside C_7 6-sulfate	399		H	OH	H	**XA**$_6$	*Coscinasterias tenuispina*[268]
indicoside A	400		H	H	OH	**Gal*f***	*Astropecten indicus*[299]
gomophioside B	401		H	OH	H	**XA**$_6$	*Gomophia watsoni*[276]

Table 4 (Continued)



pisasteroside E **402** *Pisaster giganteus*[300]

Basic Nuclear Hydroxylation Pattern; 3β,6α,8,15β,16β



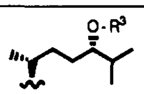
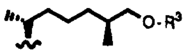
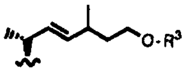
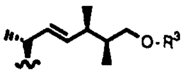
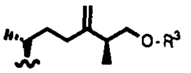
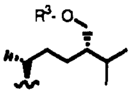
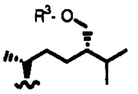
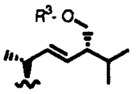
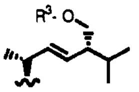
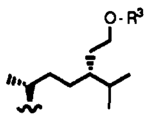
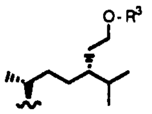
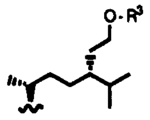
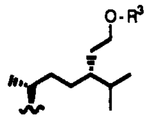
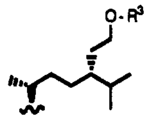
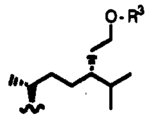
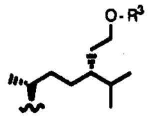
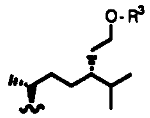
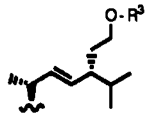
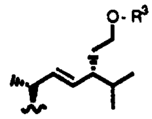
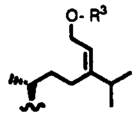
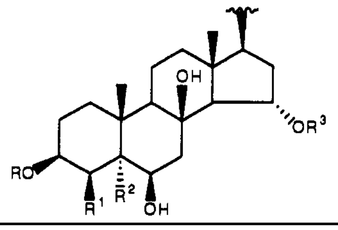
name	no.	side chain	R	R^1	R^2	R^3	sources and references
indicoside C	**403**	 O-R^3	H	H	H	**Xf_2**	*Astropecten indicus*[292]
coscinasteroside E	**404**	 O-R^3	H	OH	H	**X$_1$**	*Coscinasterias tenuispina*[268]
coscinasteroside D	**405**	 O-R^3	H	H	H	**Glc$_2$**	*Coscinasterias tenuispina*[268]
coscinasteroside A	**406**	 O-R^3	**X$_1$**	H	OH	SO$_3^-$Na$^+$	*Coscinasterias tenuispina*[268]
culcitoside C$_8$	**407**	 O-R^3	H	H	H	**XX$_4$**	*Culcita novaeguineae*[269]
culcitoside C$_3$	**408**	 R^3-O	H	H	H	**XA$_6$**	*Culcita novaeguineae*[301]
culcitoside C$_2$	**409**	 R^3-O	H	OH	H	**XA$_6$**	*Culcita novaeguineae*[301]
coscinasteroside C	**410**	 R^3-O	H	H	H	**Glc$_3$**	*Coscinasterias tenuispina*[268]
pisasteroside A	**411**	 R^3-O	H	H	H	**Glc$_2$**	*Pisaster ochraceus* and *Pisaster brevispinus*[302]
pisasteroside F	**412**	 O-R^3	H	H	H	**Glc$_2$**	*Pisaster giganteus*[300]
halityloside B	**413**	 O-R^3	H	H	H	**XX$_4$**	*Halityle regularis*,[264] *Nardoa novaecaledoniae* and *N. gomophia*,[265] *Sphaerodiscus placenta*,[247] *Culcita novaeguineae*[269]

Table 4 (Continued)

name	no.	side chain	R	R^1	R^2	R^3	sources and references
halityloside A	414		H	OH	H	XX$_4$	*Halityle regularis,*[264] *Nardoa novaecaledoniae* and *N. gomophia,*[265] *Sphaerodiscus placenta,*[247] *Culcita novaeguineae*[269]
halityloside H	415		H	OH	H	XA$_6$	*Halityle regularis,*[264] *N. gomophia*[265]
halityloside H 6-*O*-sulfate	416		H	OH	H	XA$_6$	*Halityle regularis,*[264] *N. gomophia*[265]
moniloside E	417		H	OH	H	AX	*Fromia monilis*[284]
moniloside I	418		H	OH	H	XXX$_1$	*Fromia monilis*[284]
moniloside G	419		H	OH	H	XXX$_2$	*Fromia monilis*[284]
moniloside F	420		H	OH	H	AX	*Fromia monilis*[284]
moniloside H	421		H	OH	H	XXX$_2$	*Fromia monilis*[284]
pisasteroside C	422		H	H	H	X$_5$	*Pisaster brevispinus*[302]

Basic Nuclear Hydroxylation Pattern: 3β,6β,8,15α



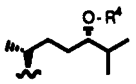
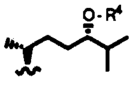
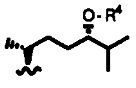
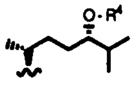
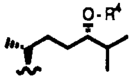
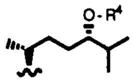
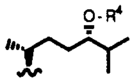
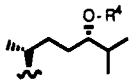
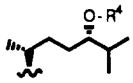
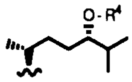
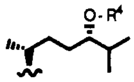
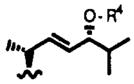
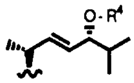
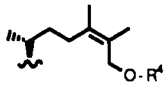
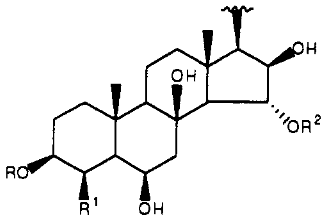
name	no.	side chain	R	R^1	R^2	R^3	R^4	sources and references
coscinasteroside B	423		H	H	H	$SO_3^-NA^+$	X$_1$	*Coscinasterias tenuispina,*[268] *Pycnopodia helianthoides*[258]
pisasteroside B	424		X$_1$	H	H	H	$SO_3^-Na^+$	*Pisaster ochraceus*[302]
aphelasteroside A	425		$SO_3^-NA^+$	H	H	H	X$_1$	*Aphelasterias japonica*[274]
5-deoxyisonodososide	426		X$_2$	H	H	H	A$_1$	*Acanthaster planci,*[303] *Choriaster granulatus*[285]

Table 4 (Continued)

name	no.	side chain	R	R^1	R^2	R^3	R^4	sources and references
laeviuscoloside I forbeside I	**427**		X_4	OH	H	H	H	*Henricia laeviuscola*,[283] *Asterias forbesi*[304]
granulatoside A	**428**		X_2	OH	H	H	A_1	*Choriaster granulatus*,[285] *Thromidia catalai*[305]
laeviuscoloside G	**429**		X_4	OH	H	H	A_1	*Henricia laeviuscola*,[283] *Asterias forbesi*[304]
isonodososide	**430**		X_2	H	OH	H	A_1	*Acanthaster planci*[303]
nodososide	**431**		H	H	OH	H	XA_5	*Protoreaster nodosus*,[282] *Pentaceraster alveolatus*,[68] *A. planci*, *Linkia Laevigata*[306]
echinasteroside B_2	**432**		H	OH	H	H	XA_5	*Echinaster sepositus*[307]
echinasteroside B_1	**433**		H	OH	H	$COCH_3$	XA_5	*Eschinaster sepositus*[307]
scoparioside D	**434**		H	H	H	$SO_3^-NA^+$	X_1	*Astropecten scoparius*[267]
laeviuscoloside H	**435**		X_4	OH	H	H	H	*Henricia laeviuscola*[283]
forbeside K	**436**		X_2	OH	H	H	A_1	*Asterias forbesi*[304]

Basic Nuclear Hydroxylation Pattern: 3β,6β,8,15α,16β



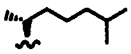
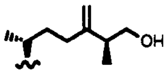
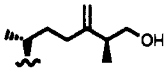
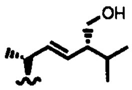
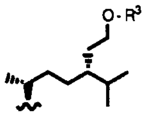
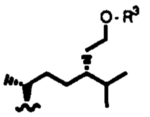
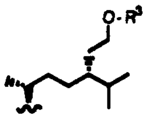
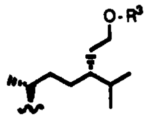
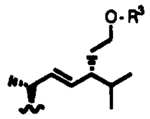
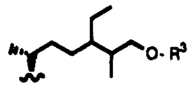
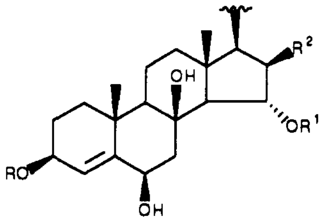
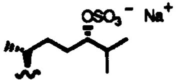
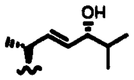
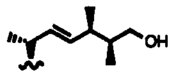
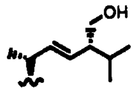
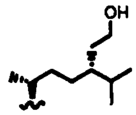
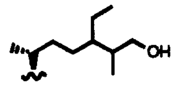
name	no.	side chain	R	R^1	R^2	R^3	sources and references
laeviuscoloside B	**437**		X_4	H	SO_3-Na^+		*Henricia laeviuscola*[283]
	438		X_2	H	H		*Poraster superbus*[251]
thromidioside	**439**		X_2	OH	H		*Thromidia catalai*[305]
laeviuscoloside C	**440**		X_2	H	$SO_3^-NA^+$		*Henricia laeviuscola*[283]
crossasteroside P_1	**441**		H	H	H	**XGal*f***	*Crossaster papposus*[308]
attenuatoside S-I	**442**		H	H	$SO_3^-NA^+$	X_1	*Hacelia attenuata*[309]

Table 4 (Continued)

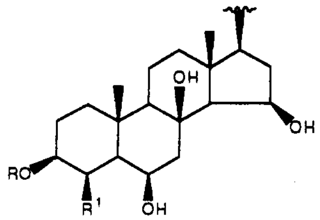
name	no.	side chain	R	R^1	R^2	R^3	sources and references
laeviuscoloside E	**443**		X_2	H	$SO_3^-NA^+$	H	*Henricia laeviuscola*[283]
crossasteroside P_2	**444**		H	OH	H	**XGal*f***	*Crossaster papposus*[308]
attenuatoside S-II	**445**		H	H	$SO_3^-NA^+$	X_1	*Hacelia attenuata*[309]
attenuatoside S-III	**446**		H	H	$SO_3^-NA^+$	X_1	*Hacelia attenuata*[309]

Basic Nuclear Hydroxylation Patterns: Δ^4-3β,6β,8,15α and Δ^4-3β,6β,8,15α,16β



name	no.	side chain	R	R^1	R^2	sources and references
pisasteroside D	447		X_1	H	H	*Pisaster giganteus*[300]
aphelasteroside B	448		X_1	$SO_3^-Na^+$	OH	*Aphelasterias japonica*[274]
echinasteroside A	449		X_2	$SO_3^-Na^+$	OH	*Echinaster sepositus*,[310] *Henricia laeviuscola*[283]
laeviuscoloside D	450		X_2	$SO_3^-Na^+$	OH	*Henricia laeviuscola*[283]
echinasteroside B	451		X_2	$SO_3^-Na^+$	OH	*Eschinaster sepositus*,[310] *Henricia laeviuscola*[283]
forbeside L	452		X_2	H	OH	*Asterias forbesi*[304]

Basic Nuclear Hydroxylation Pattern: 3β,6β,8,15β



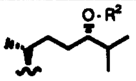
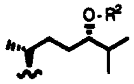
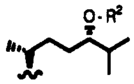
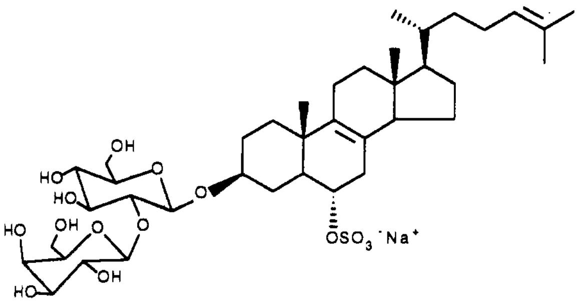
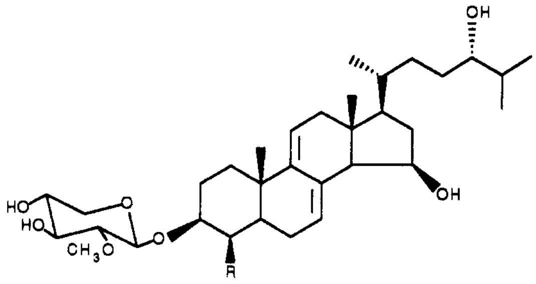
name	no.	side chain	R	R^1	R^2	sources and references
halityloside F	453		H	H	XA_6	*Halityle regularis*,[264] *Gomophia watsoni*,[276] *Nardoa gomophia*,[265] *Culcita novaeguineae*[269]

Table 4 (Continued)

name	no.	side chain	R	R^1	R^2	sources and references
gomophioside A	**454**		H	OH	XA_6	*Gomophia watsoni*,[276] *C. novaeguineae*[269]
moniloside D	**455**		X_2	OH	H	*Fromia monilis*[281]

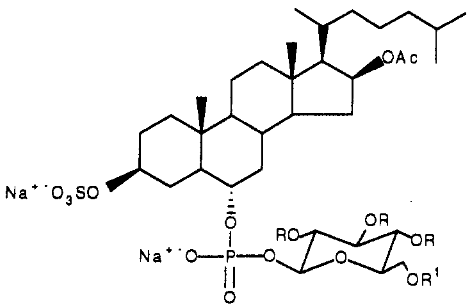


laeviuscoloside A **456** *Henricia laeviuscola*[283]



moniloside A **457** R = H *Fromia monilis*[281]

moniloside B **458** R = OH *Fromia monilis*[281]



name	no.	R	R^1	sources and references
tremasterol A	459	H	H	*Tremaster novaecaledoniae*[239]
tremasterol B	460	$COCH_3$	$COCH_3$	
tremasterol C	461	H	$COCH_3$	

[a] Abbreviations for R groups are defined in Figure 18.

Further recent additions are the phosphated steroids tremasterols A–C (**459**–**461**), isolated from the deep-water species *Tremaster novaecaledoniae*.

3. Asterosaponins

The term asterosaponin was originally coined to generally designate toxic steroidal saponins occurring in starfish, by analogy with the term holothurin used for triterpenoid saponins of holothuroids. Following the elucidation of first structures and the subsequent discovery of different structural type of steroidal glycosides from starfish, the term has been used to indicate those highest molecular weight compounds unified by a number of structural analogies involving both the aglycons and the oligosaccharide chains. The aglycons are $\Delta^{9(11)}$-3β,6α-dihydroxysteroids bearing a sulfate group at C-3 and often a 23-oxo function. The oligosaccharide chains, commonly made up by five or six sugar units, are always glycosidically linked at C-6. A close resemblance is also evident in this saccharide portions: sugars are in their pyranose form with β-anomeric configurations (α for L-arabinose) and linked with a constant pattern of interglycosidic linkages. A branching point is always located on the second monosaccharide (usually xylose or quinovose) starting from the aglycon and a terminal quinovose is always found 2-linked to the branched sugar. The more common sugars are D-fucose, D-quinovose, D-xylose, D-galactose, and D-glucose. Other less common monosaccharides are D-6-deoxy-*xylo*-hex-4-ulose and L-arabinose. The single exception to the general pattern of interglycosidic linkages is represented by the recently isolated santiagoside (**488**),[311] with a 4-substituted glucose unit linked to the aglycon, instead of the 3-substituted unit present in all asterosaponins. We would note that the ^{13}C NMR data of santiagoside (**488**) are very close to those assigned to related asterosaponins [*e.g.* marthasteroide C (**489**)], including the unusually downfield shifted signal at 91.0 ppm, which is a distinctive feature of ^{13}C NMR spectra of all asterosaponins and has been assigned to the glycosylated carbon-3 of the monosaccharide unit (β-glucopyranosyl or β-quinovopyranosyl) directly attached to the aglycon.

Also asterosaponins are widespread among starfish, having been found in the majority of species examined. The toxic properties of starfish have been known for many years, but it was only in 1960 that Hashimoto

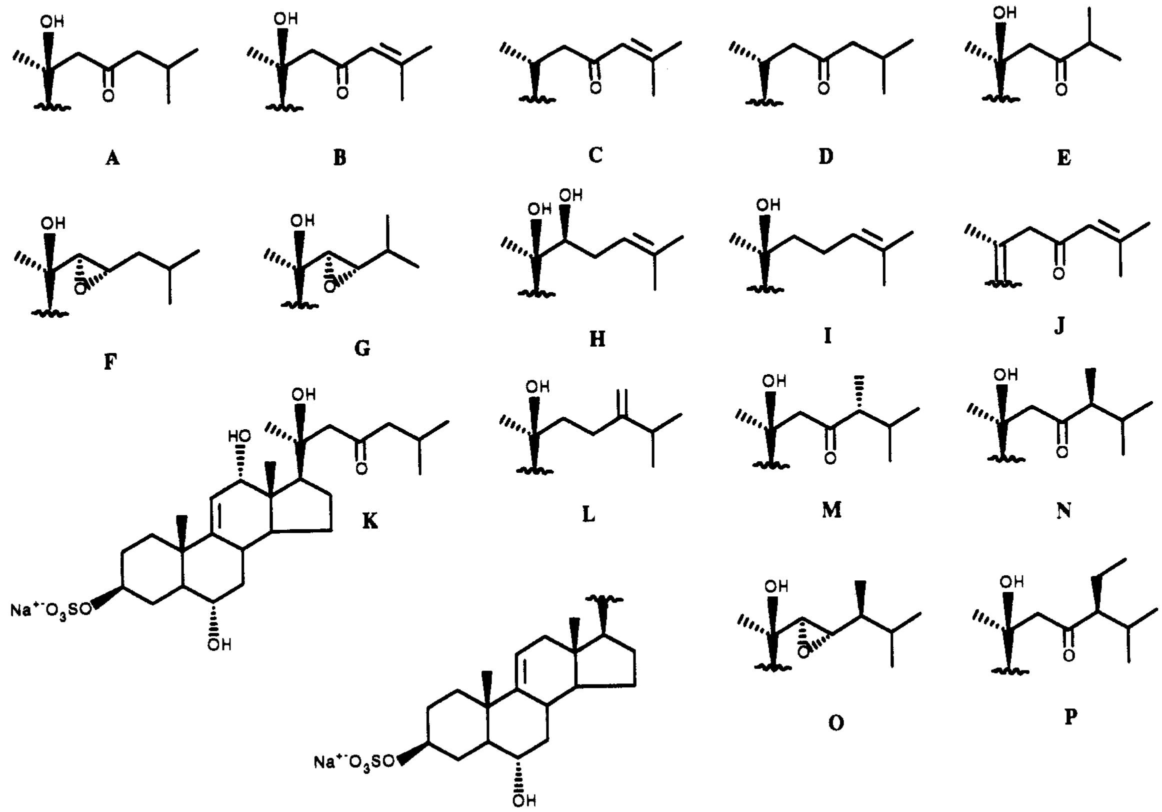
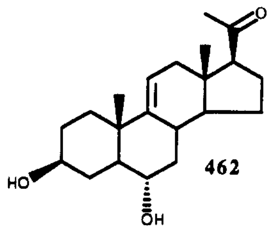


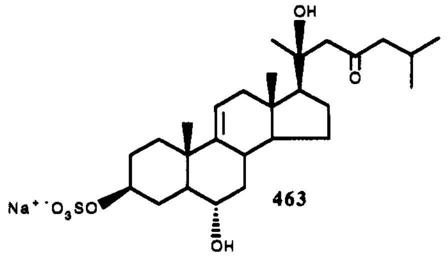
Figure 19. Steroidal aglycons found in astereosaponins from starfish.

and Yasumoto recognized that the toxicity is associated with compounds similar to plant saponins.[312] Asterosaponins also possess ichtyotoxicity,[312,313] and toxicity has also been noted toward anellids, mollusks, arthropods and vertebrates.[314] Because of their general toxicity, it is probable that saponins act primarily as chemical defense agents, rejecting infectious aquatic fungi, protists, parasites, and predators. Makie *et al.* found that asterosaponins are the substances eliciting the escape response in some species of molluscs when in presence of starfishes.[315] In addition, these oligoglycosides, in some species of starfish, participate in reproduction processes. Ikegami *et al.* identified saponins as the spawning inhibitors in the ovaries of *Asterias amurensis*.[316] Fujimoto *et al.* observed that three steroidal saponins, designated Co-ARIS I, II, and III, isolated from the egg jelly of the starfish *Asterias amurensis*, are essential for inducing the acrosome reaction.[317] Starfish extracts and purified saponin fractions have shown a variety of pharmacological activities: hemolytic activity;[314,318] *in vitro* cytotoxicity toward tumor cells;[319–321] antiviral activity;[322] blockage of neuromuscular transmission in mammals;[323] and antiinflammatory, analgesic, and hypotensive activities.[324] Starfish saponins are also known to inhibit development of fertilized sea urchin eggs.[318,325] A more recent study of the biological activity of representative saponins and related steroids from starfish confirmed a high incidence of cytotoxicity and inhibition of Gram-positive bacteria but only weak antiviral activity and no inhibition of Gram-negative bacteria.[260]

Asterosaponins, as do all these polyhydroxysteroids and glycosides from starfish, also occur as complex mixtures that are fairly difficult to separate in the individual components. This has probably been the main reason for which most of the initial papers were concerned with the analysis of aglycons obtained by acid hydrolysis of partially purified saponin mixtures. This procedure resulted in the production of several artifacts, such as asterone (**462**),[326,327] an artifact obtained by retro-aldol cleavage of the genuine thornasterol A sulfate (**463**),[328] which has been the most widely reported steroid obtained by acid hydrolysis of asterosaponins. $\Delta^{20(22)}$- and $\Delta^{17(20)}$-steroids, along with a rearranged $\Delta^{13(14)}$-17-methyl-18-norsteroid, certainly artifacts generated during acid hydrolysis, have also been reported.[329,330] An excellent review of previous work on the aglycons can be found in the work of Burnell and ApSimon.[232]



462



463

The first complete structure of an asterosaponin, thornasteroside A (**464**), was reported in 1978 by

Table 5. Asterosaponins from Starfish[a]

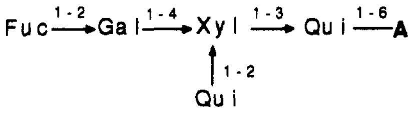
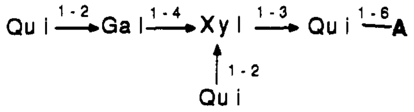
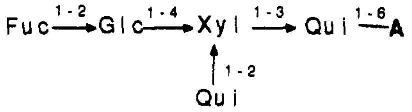
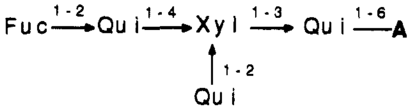
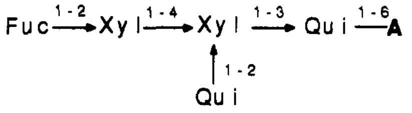
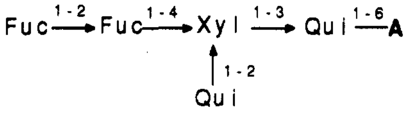
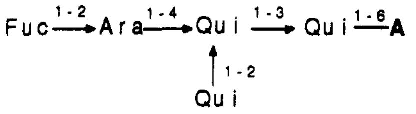
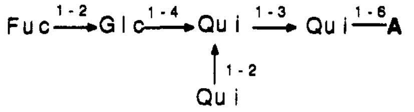
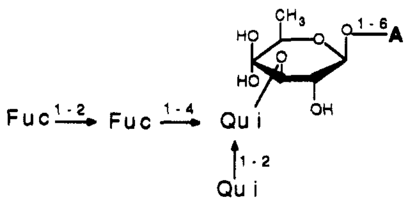
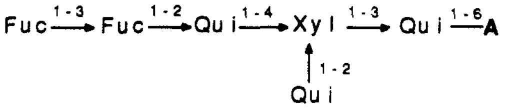
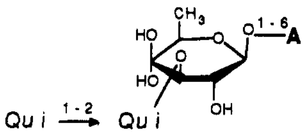
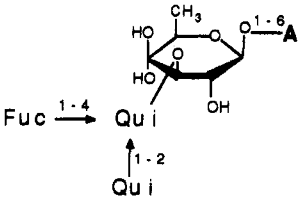
Name	#	oligosaccharide chain	sources and references
Asterosaponins containing thornasterol A, aglycone A			
thornasteroside A	**464**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Gal}\xrightarrow{1-4}\underset{\mathrm{Qui}}{\underset{\uparrow 1-2}{\mathrm{Xyl}}}\xrightarrow{1-3}\mathrm{Qui}\xrightarrow{1-6}\mathrm{A}$	*Acanthaster planci*[331], *Asterias amurensis*[332], *Luidia maculata*[333], *Ophidiaster ophidianus*[334], *Linkia laevigata*[335], *Protoreaster nodosus* and *Pentaceraster alveolatus*[68], *Halityle regularis*[336], *Nordoa gomophia*[265], *Coscinasterias tenuispina*[268], *Thromidia catalai*[305], *Pisaster ochraceus* and *Pisaster brevispinus*[303], *Pisaster giganteus*[300], *Pycnopodia helianthoides*[258]
glycoside B$_2$ = forbeside B	**465**	 $\mathrm{Qui}\xrightarrow{1-2}\mathrm{Gal}\xrightarrow{1-4}\underset{\mathrm{Qui}}{\underset{\uparrow 1-2}{\mathrm{Xyl}}}\xrightarrow{1-3}\mathrm{Qui}\xrightarrow{1-6}\mathrm{A}$	*Asterias amurensis*[284, 337], *Asterias forbesi*[338]
acanthaglycoside C	**466**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Glc}\xrightarrow{1-4}\underset{\mathrm{Qui}}{\underset{\uparrow 1-2}{\mathrm{Xyl}}}\xrightarrow{1-3}\mathrm{Qui}\xrightarrow{1-6}\mathrm{A}$	*Astropecten latespinosus*[339], *Acanthaster planci340*, *Asterina pectinifera*[341], *Patiria miniata*[342]
maculatoside = luidiaglycoside B	**467**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Qui}\xrightarrow{1-4}\underset{\mathrm{Qui}}{\underset{\uparrow 1-2}{\mathrm{Xyl}}}\xrightarrow{1-3}\mathrm{Qui}\xrightarrow{1-6}\mathrm{A}$	*Luidia maculata*[333], *Linkia laevigata*[335]
ophidianoside F	**468**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Xyl}\xrightarrow{1-4}\underset{\mathrm{Qui}}{\underset{\uparrow 1-2}{\mathrm{Xyl}}}\xrightarrow{1-3}\mathrm{Qui}\xrightarrow{1-6}\mathrm{A}$	*Ophidiaster ophidianus*[334], *Linkia laevigata*[335], *Thromidia catalai*[305]
regularoside B	**469**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Fuc}\xrightarrow{1-4}\underset{\mathrm{Qui}}{\underset{\uparrow 1-2}{\mathrm{Xyl}}}\xrightarrow{1-3}\mathrm{Qui}\xrightarrow{1-6}\mathrm{A}$	*Halityle regularis*[336], *Coscinasterias tenuispina*[268], *Thromidia catalai*[305]
laevigatoside	**470**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Ara}\xrightarrow{1-4}\underset{\mathrm{Qui}}{\underset{\uparrow 1-2}{\mathrm{Qui}}}\xrightarrow{1-3}\mathrm{Qui}\xrightarrow{1-6}\mathrm{A}$	*Linkia laevigata*[335]
pectinioside A	**471**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Glc}\xrightarrow{1-4}\underset{\mathrm{Qui}}{\underset{\uparrow 1-2}{\mathrm{Qui}}}\xrightarrow{1-3}\mathrm{Qui}\xrightarrow{1-6}\mathrm{A}$	*Asterina pectinifera*[343]
ovarian asterosaponin I = Co-Aris I = forbeside C	**472**		*Asterias amurensis*[317, 284, 344, 345], *Asterias forbesi*[346], *Asterias vulgaris*[346]
marthasteroside A$_2$ = luidiaglycoside A	**473**	 $\mathrm{Fuc}\xrightarrow{1-3}\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Qui}\xrightarrow{1-4}\underset{\mathrm{Qui}}{\underset{\uparrow 1-2}{\mathrm{Xyl}}}\xrightarrow{1-3}\mathrm{Qui}\xrightarrow{1-6}\mathrm{A}$	*Luidia maculata*[333, 347], *Marthasterias glacialis*[348, 349]

Table 5 (Continued)

Name	#	oligosaccharide chain	sources and references
marthasteroside A$_1$	**474**	$\text{Fuc}\xrightarrow{1-3}\text{Fuc}\xrightarrow{1-2}\text{Gal}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2 \\ \text{Qui}}}{\text{Xyl}}\xrightarrow{1-3}\text{Qui}\overset{1-6}{\text{—}}\mathbf{A}$	*Marthasterias glacialis*[348, 349], *Astropecten latespinosus*[339], *Linkia laevigata*[335], *Nardoa gomophia*[265], *Pisaster brevispinus*[303], *Achantaster planci*[340], *Astropecten scoparius*[267]
versicoside A = forbeside A	**475**	$\text{Gal}\xrightarrow{1-3}\text{Fuc}\xrightarrow{1-2}\text{Gal}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2 \\ \text{Qui}}}{\text{Xyl}}\xrightarrow{1-3}\text{Qui}\overset{1-6}{\text{—}}\mathbf{A}$	*Asterias amurensis versicolor*[332], *Pisaster ochraceus* and *Pisaster brevispinus*[303], *Pisaster giganteus*[300], *Asterias forbesi*[338]
pectinioside F	**476**	$\text{Gal}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2 \\ \text{Fuc}}}{\text{Glc}}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2 \\ \text{Qui}}}{\text{Xyl}}\xrightarrow{1-3}\text{Qui}\overset{1-6}{\text{—}}\mathbf{A}$	*Asterias pectinifera*[321]
pectinioside E	**477**	$\text{Fuc}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2 \\ \text{Xyl}}}{\text{Glc}}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2 \\ \text{Qui}}}{\text{Qui}}\xrightarrow{1-3}\text{Qui}\overset{1-6}{\text{—}}\mathbf{A}$	>>
pectinioside G	**478**	$\text{Ara}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2 \\ \text{Fuc}}}{\text{Glc}}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2 \\ \text{Qui}}}{\text{Qui}}\xrightarrow{1-3}\text{Qui}\overset{1-6}{\text{—}}\mathbf{A}$	*Asterina pectinifera*[254], *Patiria miniata*[342]
forbeside H	**479**	$\text{Qui}\xrightarrow{1-2}\text{Xyl}\xrightarrow{1-3}\text{Qui}\overset{1-6}{\text{—}}\mathbf{A}$	*Asterias forbesi*[350]
forbeside G	**480**		>>
forbeside F	**481**		>>
myxodermoside A	**482**	$\text{Gal}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2 \\ \text{Qui}}}{\text{Xyl}}\xrightarrow{1-3}\text{Qui}\overset{1-6}{\text{—}}\mathbf{A}$	*Myxoderma platyacanthum*[245]

Asterosaponins containing 24,25-dehydro-thornasterol A, aglycone **B**

achantaglycoside A	**483**	$\text{Fuc}\xrightarrow{1-2}\text{Qui}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2 \\ \text{Qui}}}{\text{Xyl}}\xrightarrow{1-3}\text{Qui}\overset{1-6}{\text{—}}\mathbf{B}$	*Achantaster planci*[351]
achantaglycoside B	**484**	$\text{Fuc}\xrightarrow{1-2}\text{Glc}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2 \\ \text{Qui}}}{\text{Xyl}}\xrightarrow{1-3}\text{Qui}\overset{1-6}{\text{—}}\mathbf{B}$	*Achantaster planci*[340]
achantaglycoside D	**485**	$\text{Fuc}\xrightarrow{1-2}\text{Gal}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2 \\ \text{Qui}}}{\text{Xyl}}\xrightarrow{1-3}\text{Qui}\overset{1-6}{\text{—}}\mathbf{B}$	*Achantaster planci*[340]

Table 5 (Continued)

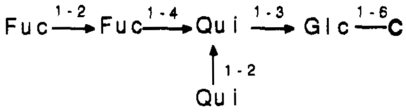
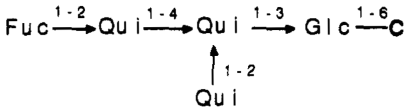
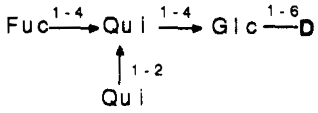
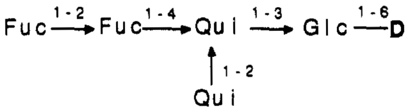
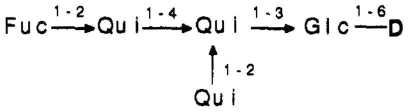
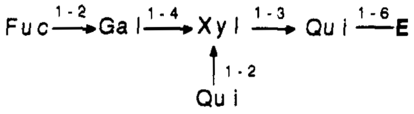
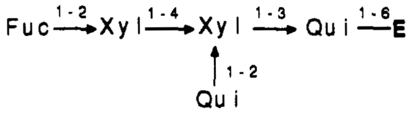
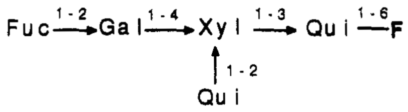
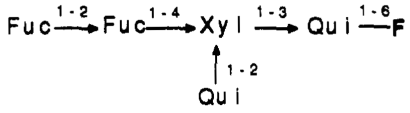
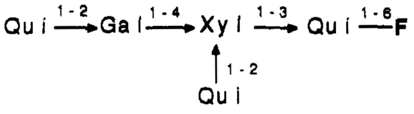
Name	#	oligosaccharide chain	sources and references
Asterosaponins containing marthasterone, aglycone **C**			
marthasteroside B	**486**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Fuc}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Qui}}\xrightarrow{1-3}\mathrm{Glc}\overset{1-6}{\text{—}}\mathbf{C}$	*Marthasterias glacialis*[348, 349], *Luidia maculata*[333], *Coscinasterias tenuispina*[268]
luidiaglycoside C	**487**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Qui}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Qui}}\xrightarrow{1-3}\mathrm{Glc}\overset{1-6}{\text{—}}\mathbf{C}$	*Luidia maculata*[352]
Asterosaponins containing 24,25-dihydromarthasterone, aglycone **D**			
santiagoside	**488**	 $\mathrm{Fuc}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Qui}}\xrightarrow{1-4}\mathrm{Glc}\overset{1-6}{\text{—}}\mathbf{D}$	*Neosmilaster georgianus*[311]
marthasteroside C	**489**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Fuc}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Qui}}\xrightarrow{1-3}\mathrm{Glc}\overset{1-6}{\text{—}}\mathbf{D}$	*Marthasterias glacialis*[348, 349], *Luidia maculata*[333], *Coscinasterias tenuispina*[268]
luidiaglycoside D	**490**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Qui}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Qui}}\xrightarrow{1-3}\mathrm{Glc}\overset{1-6}{\text{—}}\mathbf{D}$	*Luidia maculata*[352]
Asterosaponins containing 24-nor-thornasterol A, aglycone **E**			
ophidianoside B	**491**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Gal}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{—}}\mathbf{E}$	*Ophidiaster ophidianus*and *Hacelia attenuata*[334]
ophidianoside C	**492**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Xyl}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{—}}\mathbf{E}$	>>
asterosaponins containing 22,23-epoxy-aglycone **F**			
tenuispinoside A	**493**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Gal}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{—}}\mathbf{F}$	*Coscinasterias tenuispina*[268]
tenuispinoside B	**494**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Fuc}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{—}}\mathbf{F}$	>>
asteroside A	**495**	 $\mathrm{Qui}\xrightarrow{1-2}\mathrm{Gal}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{—}}\mathbf{F}$	*Asterias amurensis*[284]

Table 5 (Continued)

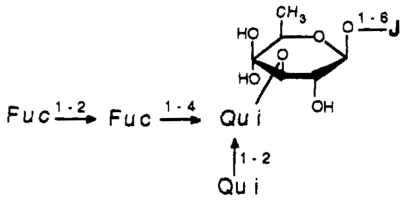
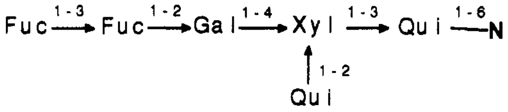
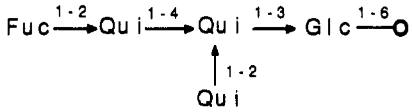
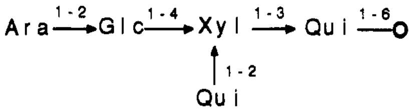
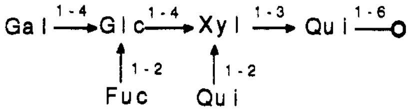
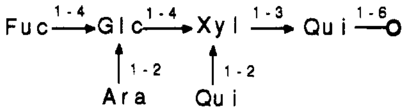
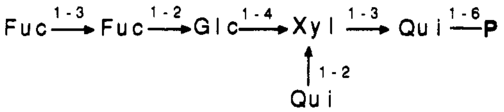
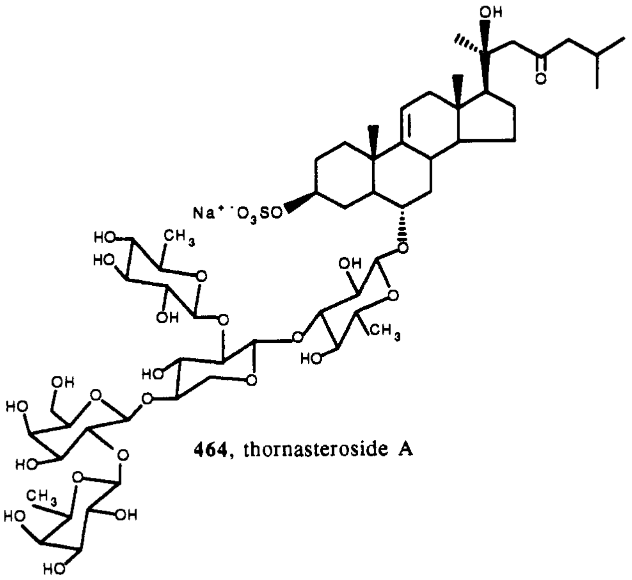
Name	#	oligosaccharide chain	sources and references
asterosaponin containing 22,23-epoxy-24-nor-aglycone **G**			
asteroside B	**496**	$\mathrm{Qui}\xrightarrow{1-2}\mathrm{Gal}\xrightarrow{1-4}\underset{\underset{\mathrm{Qui}}{\uparrow 1-2}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{——}}\mathbf{G}$	*Asterias amurensis*[284]
asterosaponins containing the less common aglycones **H**, **I**, **J**, **K** and **L**			
protoreasteroside	**497**	$\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Qui}\xrightarrow{1-4}\underset{\underset{\mathrm{Qui}}{\uparrow 1-2}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{——}}\mathbf{H}$	*Protoreaster nodosus* and *Pentaceraster alveolatus*[68]
ovarian asterosaponin-4 = Co-Aris III	**498**	$\mathrm{Qui}\xrightarrow{1-2}\mathrm{Glc}\xrightarrow{1-4}\underset{\underset{\mathrm{Qui}}{\uparrow 1-2}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{——}}\mathbf{I}$	*Asterias amurensis*[317, 284, 353]
solasteroside A	**499**	$\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Fuc}\xrightarrow{1-4}\underset{\underset{\mathrm{Qui}}{\uparrow 1-2}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{——}}\mathbf{I}$	*Solaster borealis*[244]
Co-Aris II	**500**		*Asterias amurensis*[317]
tenuispinoside C	**501**	$\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Gal}\xrightarrow{1-4}\underset{\underset{\mathrm{Qui}}{\uparrow 1-2}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{——}}\mathbf{K}$	*Coscinasterias tenuispina*[268]
asteroside D	**502**	$\mathrm{Qui}\xrightarrow{1-2}\mathrm{Glc}\xrightarrow{1-4}\underset{\underset{\mathrm{Qui}}{\uparrow 1-2}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{——}}\mathbf{L}$	*Asterias amurensis*[284]
asterosaponins containing (24R)-24-methylthornasterol A, aglycone **M**			
versicoside C = thornasteroside B	**503**	$\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Gal}\xrightarrow{1-4}\underset{\underset{\mathrm{Qui}}{\uparrow 1-2}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{——}}\mathbf{M}$	*Asterias amurensis* [cf.] *versicolor*[345], *Coscinasterias tenuispina*[268]
asteroside C	**504**	$\mathrm{Qui}\xrightarrow{1-2}\mathrm{Gal}\xrightarrow{1-4}\underset{\underset{\mathrm{Qui}}{\uparrow 1-2}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{——}}\mathbf{M}$	*Asterias amurensis*[284]
versicoside B	**505**	$\mathrm{Gal}\xrightarrow{1-3}\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Gal}\xrightarrow{1-4}\underset{\underset{\mathrm{Qui}}{\uparrow 1-2}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{——}}\mathbf{M}$	*Asterias amurensis* [cf.] *versicolor*[345]

Table 5 (Continued)

Name	#	oligosaccharide chain	sources and references
asterosaponin containing (24S)-24-methylthornasterol A, aglycone **N**			
acanthaglycoside F	**506**	 $\mathrm{Fuc}\xrightarrow{1-3}\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Gal}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{—}}\mathrm{N}$	*Acanthaster planci*[340]
asterosaponins containing (24S)-22,23-epoxy-24-methyl aglycone **O**			
regularoside A	**507**	 $\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Qui}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Qui}}\xrightarrow{1-3}\mathrm{Glc}\overset{1-6}{\text{—}}\mathrm{O}$	*Halityle regularis*[336]
henricioside A	**508**	 $\mathrm{Ara}\xrightarrow{1-2}\mathrm{Glc}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{—}}\mathrm{O}$	*Henricia laeviuscola*[283]
pectinioside B	**509**	 $\mathrm{Gal}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Fuc}}}{\mathrm{Glc}}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{—}}\mathrm{O}$	*Asterina pectinifera*[343]
patirioside A	**510**	 $\mathrm{Fuc}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Ara}}}{\mathrm{Glc}}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{—}}\mathrm{O}$	*Patiria miniata*[342]
asterosaponin containing (24S)-ethylthornasterol A, aglycone **P**			
pectinioside C	**511**	 $\mathrm{Fuc}\xrightarrow{1-3}\mathrm{Fuc}\xrightarrow{1-2}\mathrm{Glc}\xrightarrow{1-4}\underset{\substack{\uparrow 1-2\\ \mathrm{Qui}}}{\mathrm{Xyl}}\xrightarrow{1-3}\mathrm{Qui}\overset{1-6}{\text{—}}\mathrm{P}$	*Asterina pectinifera*[341]

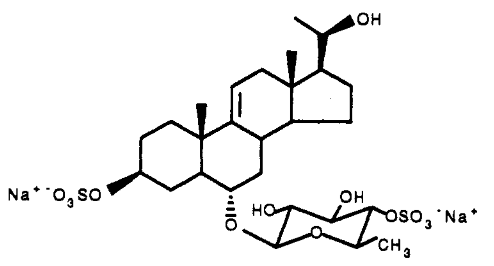
[a] Qui = D-quinovose. Fuc = D-fucose. Xyl = D-xylose. Ara = L-arabinose. Gal = D-galactose. Glc = D-glucose. All monosaccharides are in their pyranose forms and the glycosidic linkages are β (α for L-arabinose).

Kitagawa and Kobayashi.[331] Thornasteroside A (**464**) is the most widely distributed asterosaponin, having been isolated from 15 species representative of the three major orders of Asteroidea, and it is also a good example of the general structure of pentaglycosides, the more common components among asterosaponins. Thornasterol A sulfate (**463**), the aglycon of thornasteroside A (**464**), is by far the more common aglycon, but a number of asterosaponins containing aglycons with different functionalities in the side chain have also been isolated (Figure 19). The aglycon **K** of tenuispinoside C (**501**) is the only one having a different functionalization of the tetracyclic nucleus, with an extra 12α-hydroxyl group. The structures of all reported asterosaponins are listed in Table 5 with sources and references.



464, thornasteroside A

A further minor constituent of *Asterias forbesi*, forbeside E (**512**), was shown to be the 6-*O*-quinovopyranosyl 4′-sulfate of (20*R*)-5α-pregn-9(11)-ene-3β,6α,-20-triol 3-sulfate,[354] an aglycon also isolated as hydrolysis product of saponins from *Asterias vulgaris*.[355] The corresponding asterone **462** analog, cheliferoside LI, has been reported from *Lethasterias nanimensis chelifera*.[356]



forbeside E **512** *Asterias forbesi*

4. Cyclic Steroidal Glycosides

Toxic saponins of a completely different structural type have been discovered in two species of the genus *Echinaster* (Figure 20). They have a number of unusual features when compared to the more common asterosaponins: there is no sulfate group and charge is due to a glucuronic acid unit in the saccharide moiety, the Δ^7-3β,6β-dihydroxysteroidal nucleus is unprecedented, and, the most remarkable feature, the trisaccharide chain is cyclized between C-3 and C-6 of the aglycon, giving rise to a macrocyclic ring reminiscent of a crown ether. Sepositoside A (**513**), the major saponin from the Mediterranean starfish *Echinaster sepositus*,[357] is accompanied by smaller amounts of three related saponins **514–516**, which differ only in the structure of the side chain of the aglycons, all having a 22,23-epoxy functionality.[358] The key step during structural study of sepositoside A (**513**) was the mild acid hydrolysis, which, by cleavage of the allylic ether linkage, gave rise to the opening of the macrocyclic ring and formation of the UV-active glycoside, **517**. A further representative of this class of glycosides was isolated from a Pacific starfish belonging to the same genus, *E. luzonicus*, and accordingly named luzonicoside A (**518**).[359] Sepositoside A (**513**) is moderately toxic (LD_{50} = 43 mg kg^{-1} by ip injection in mouse) and showed cytotoxic activity toward bovine turbinate cells up to a level of 1 μg mL^{-1}.[260] Both sepositoside A (**513**) and luzonicoside A (**518**) were slightly effective in the inhibition of cell division of fertilized sea urchin eggs (*ca.* 30% inhibition at 10^{-5} M) and showed antifungal activity.

B. Ophiuroidea (Brittle Stars)

Until a few years ago brittle stars (ophiuroids) had only received moderate attention as compared to the echinoderm classes of asteroids and holothuroids and only sporadic papers dealing with their sterols content had appeared in the literature. Quite recently we had the occasion to investigate a number of ophiuroid species from which we could isolate several sulfated polyhydroxysteroids and two steroidal glycosides (Figure 21).

The steroid glycosides, longicaudoside A (**519**) and B (**520**) have been isolated from the Mediterranean *Ophioderma longicaudum*.[360] Both have a 5α-cholestane-3α,6β,12β,21-tetrol aglycon bearing a sulfate group at C-3 and a monosaccharide residue at C-12 (β-D-xylopranosyl in **519** and β-D-glucopyranosyl in **520**). In contrast with the hydroxylation at C-26, commonly encountered among polyhydroxysteroids from starfish, the polar steroids from ophiuroids are characterized by the hydroxylation at C-21, only found among

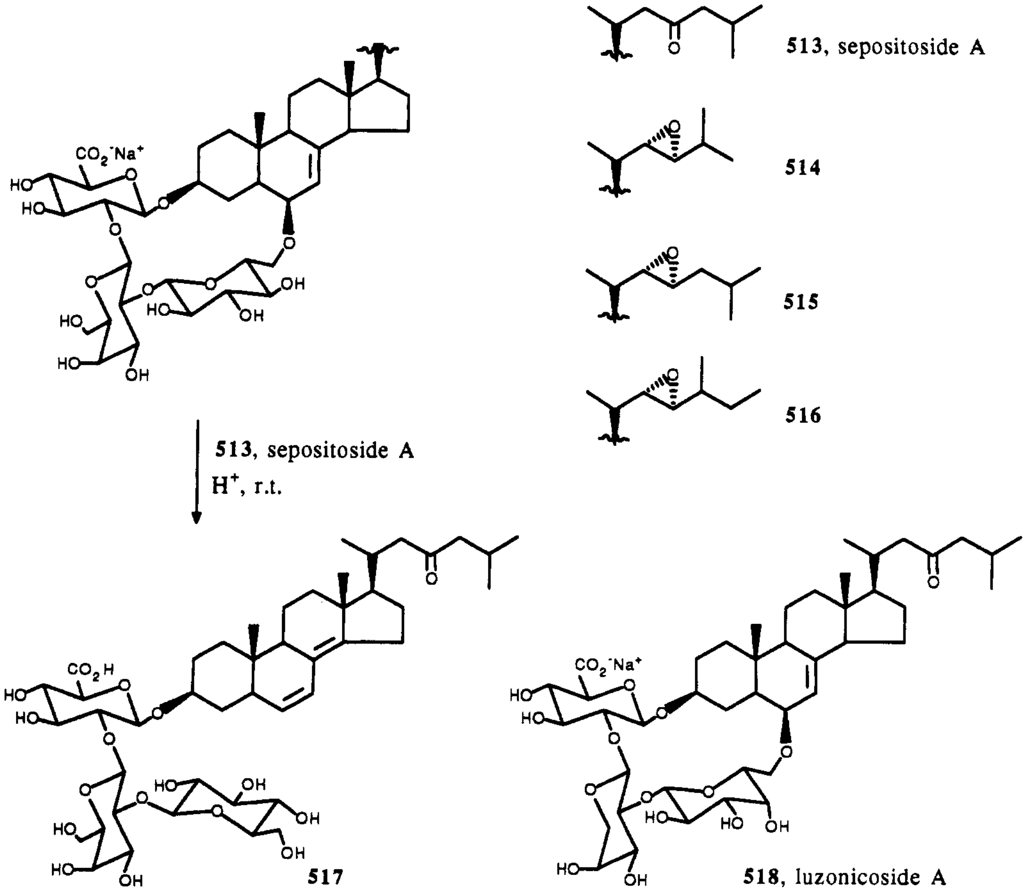


Figure 20. Cyclic steroidal glycosides from starfish of the genus *Echinaster*.

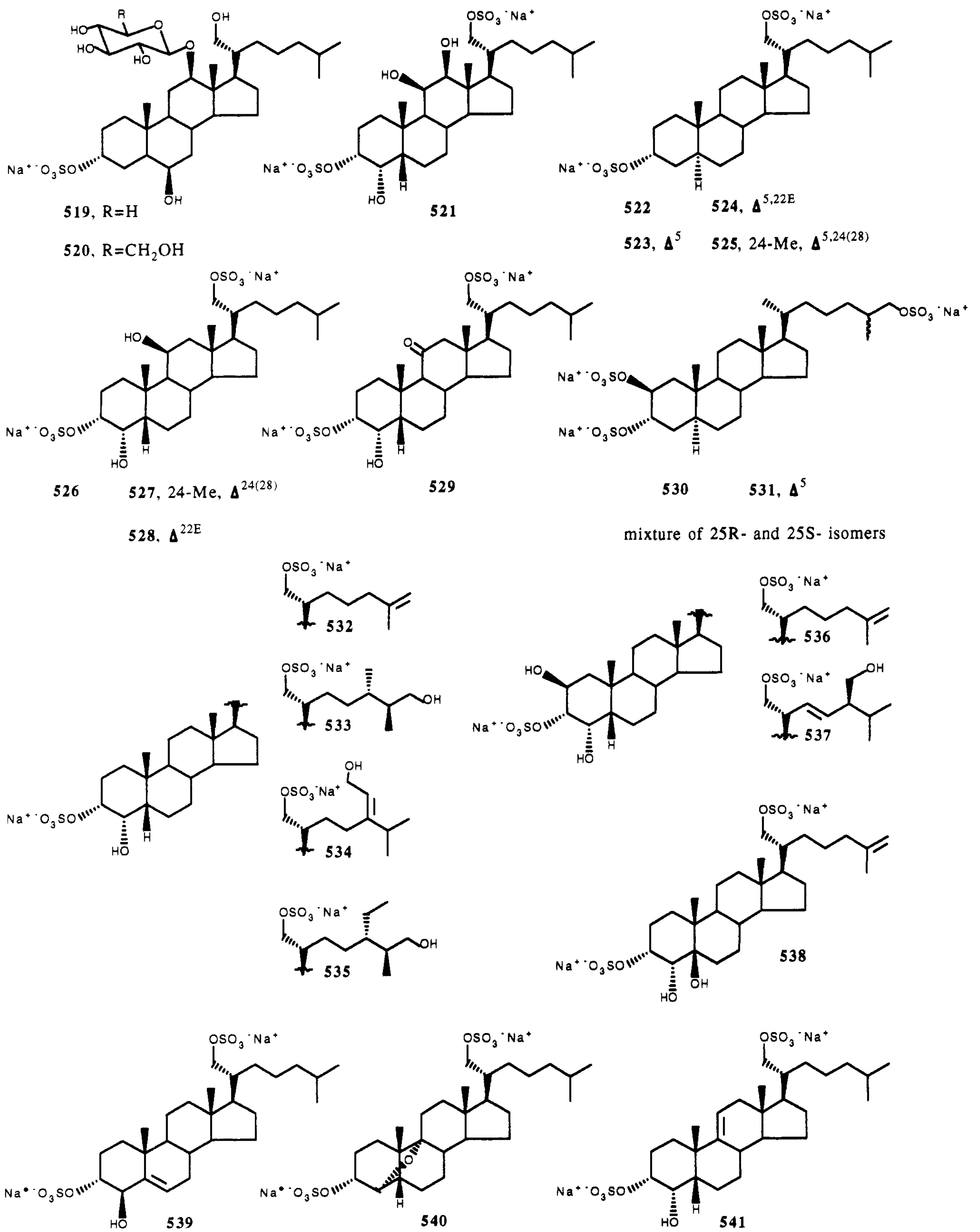


Figure 21. Polyhydroxysteroids from ophiuroids.

starfish metabolites, in steroids from *Euretaster insignis*.[241] ^{13}C NMR spectroscopy proved to be the better tool for differentiation between the two hydroxylated side chains. Noticeable differences are observed in the methyl and hydroxymethyl resonances: the C-21 hydroxylated side chain exhibits the typical signals for C-26 and C-27 at 23.0 and 23.1 ppm and the CH_2OH signal at 63.4 ppm, while the C-26 hydroxylated side chain exhibits methyl carbon signals at 17.3 and 19.2 ppm and the CH_2OH signal at 68.4 ppm. The narrow signal at a rather low field (δ 4.72 ppm, $W_{1/2}$ = 7 Hz) in the ^1H NMR spectra of both **519** and **520**, shifted to δ 4.10 in the spectra of their desulfated derivatives, was indicative of a 3α-sulfato-5α-stanol structure. The alternative 3β-sulfato-5β-stanol structure could be eliminated mainly because of the chemical shift of C-19 at 15.3 ppm. *Ophioderma longicaudum* also furnished unusual sulfated polyhydroxysterols together with a mixture of common Δ^5-3β-hydroxysterols.[361] The more polar sulfated sterol was characterized as 5β-cholestane-$3\alpha,4\alpha,11\beta,12\beta$,21-pentol 3,21-disulfate (**521**), featuring the *cis*-A/B ring fusion, later also found in the polar steroids from the further species analyzed.[96,362] A second group of components consisted in a mixture of disulfated 3α,21-dihydroxysteroids **522–525**, whose composition was established after solvolytic removal of the sulfate groups.[361] Additional sulfated polyhydroxysteroids have been then isolated recently from three further species of ophiuroids, *Ophiocoma dentata*, *Ophiarthrum elegans*, and *Ophiorachna incrassata*, all collected off Noumeà (New Caledonia).[96] The major compound in all three species has been shown to be 5β-cholestane-$3\alpha,4\alpha,11\beta$,21-tetrol 3,21-disulfate (**526**). Two minor components of *Ophiocoma dentata* possess the same nucleus as **526** but differ in the side chain, **527** and **528**. Along with minor amounts of **528** and major amounts of the disulfated tetraol **526**, *Ophiarthrum elegans* also contains the 11-keto derivative **529**. *Ophiorachna incrassata* also contains major amounts of the steroid disulfate **526** along with minor amounts of the two more polar steroids **530** and **531**, bearing three sulfate groups, which represent the first occurrence of 26-hydroxylation in ophiuroids. Major support for the presence of both 25*S*- and 25*R*-epimers is found in the ^{13}C NMR spectra, where every side-chain carbon signal appears split into two peaks separated by 0.04–0.2 ppm. The pentol disulfate **521**, the tetrol disulfate **526**, and the Δ^5-steroidal sulfates **523** and **525** have moderate cytotoxic activity.[260]

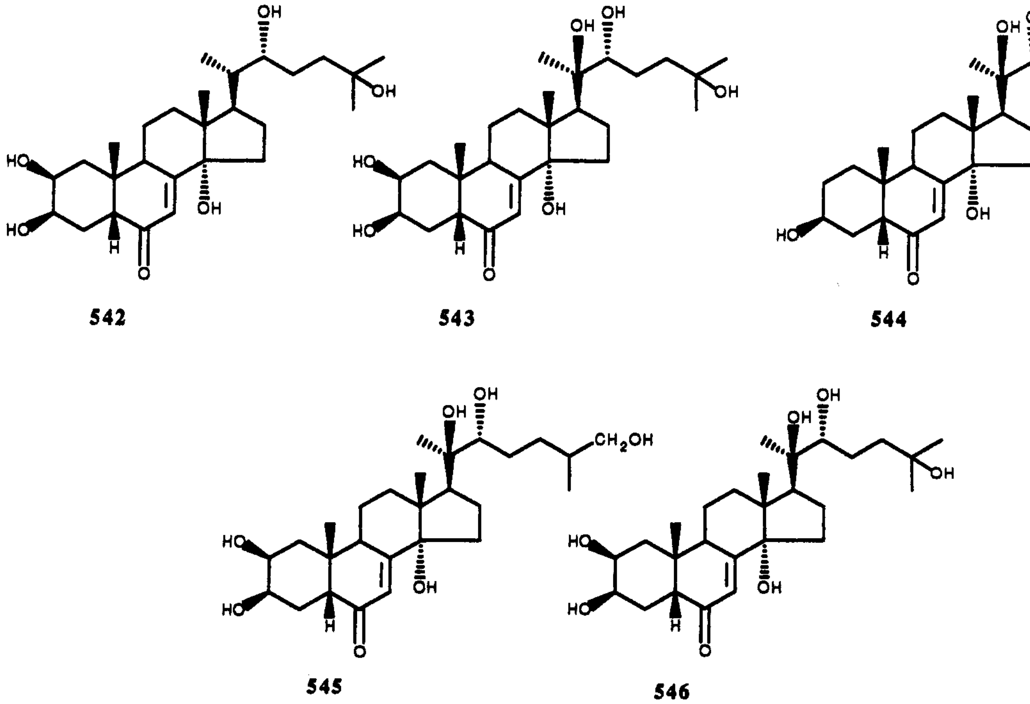
The investigation of the Pacific ophiuroid *Ophiolepis superba*, collected at Okinawa, Japan, has led to the isolation of seven sulfated polyhydroxysteroids (**532–538**), all with 3α,21-disulfoxy-4α-hydroxy substituents and the A/B *cis* ring junction.[362] The stereochemistry at C-24 and C-25 in **533** and **535** have been determined after the synthesis of model compounds.[261,363] The $3\alpha,4\alpha,5\beta$-trihydroxycholestane structure of **538** was derived from analysis of ^{1}H and ^{13}C NMR data and confirmed by the synthesis of 5β-cholestane-$3\alpha,4\alpha$,5-triol and the alternative 5α-cholestane-$3\beta,4\beta$,5-triol models. A comparison of the ^{1}H and ^{13}C NMR spectra of **538** with those of its desulfated derivative allowed the placement of the sulfoxy group at C-3. The introduction of an additional hydroxyl group at C-2β in the 3α-sulfoxy-4α-hydroxy-5β-steroidal nucleus, as in structures **536** and **537**, leads to the appearance in the ^{1}H NMR spectrum of a signal at δ 4.03 overlapping with the 3-H signal. When the spectrum of the desulfated **536** was measured, the three hydroxymethine protons appeared as isolated signals at δ 3.81 (m), 3.23 (dd, J = 9.5, 3.5 Hz) and 3.94 (t, J = 3.5 Hz) ppm. Decoupling experiments proved that they were located in a sequential arrangement and allowed the inference of a $2\beta,3\alpha,4\alpha$-trihydroxy-5β-steroidal structure. The 24*S* configuration was assigned to **537** after the stereoselective synthesis of (24*R*,22*E*)- and (24*S*,22*E*)-24-(hydroxymethyl)cholesta-5,22-dien-3β-ol.[364]

Stonik and Elyakov reported to have isolated cholest-5-ene-$3\alpha,4\beta$,21-triol 3-sulfate (**539**) from *Ophiura sarsi*.[365]

More recent additions to the sulfated polyhydroxysteroids from ophiuroids are a new 5β-steroid, 3β,21-disulfate **540** with a unique $4\alpha,9\alpha$-ether bridge, and a minor related steroid **541** from *Ophiomastix annulosa*.[366] *O. annulosa* also contained the more common tetrol **526** and its keto derivative **529**.

VIII. Polyoxygenated Steroids of Arthropoda

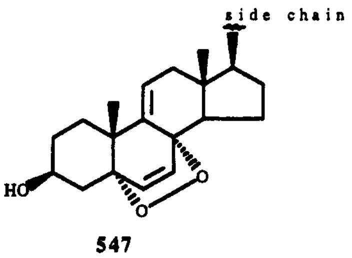
In arthropods, the molting process is under the control of a group of polyhydroxysteroid hormones referred as ecdysones. Although much of the interest of ecdysone biochemistry has centered on Insecta, the role of these steroids in crustaceans has also received considerable attention. The structures of ecdysones reported in crustaceans are shown in Figure 22. In 1960, the



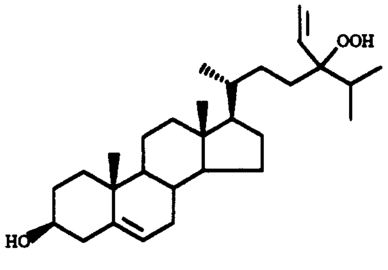
542 **543** **544**

545 **546**

Figure 22. Structures of ecdysones found in Crustacea.



547



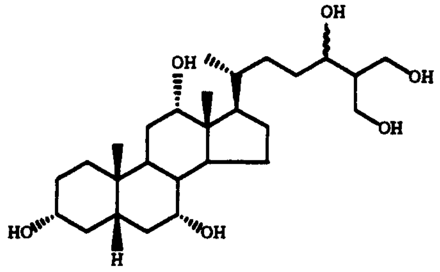
548

Figure 23. Polyhydroxysteroids from Tunicata.

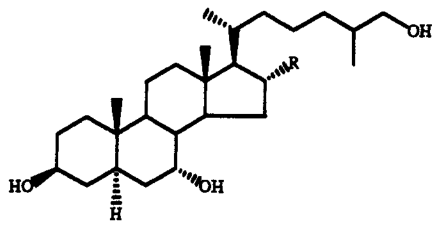
presence of a substance which showed ecdysone (**542**) activity was detected in crabs by Karlson and Skinner.[367] In 1966, crustecdysone (**543**) was first isolated from the crayfish, *Jasus lalandei*, by Horn *et al.*[368] and subsequently 2-deoxycrustecdysone (**544**)[369] was isolated. The 20-hydroxyecdysteroids, callinecdysone A (inokosterone) (**545**) and callinecdysone B (makisterone A) (**546**) were isolated from *Calinectes sapidus*.[370] Ecdysteroids metabolism in crustaceans has been reviewed by Goad[2,229] and Ikekawa.[60]

IX. Polyoxygenated Steroids of Tunicates

Several species of ascidians have been analyzed for their sterol content and were shown to contain typical mixtures of sterols with cholesterol as the major component.[2] Coprostanols along with Δ^4-3-ketosteroids and 4α-methylsterols have been described from *Ascidia nigra*.[371] 5β-Stanols have later been found in *Halocynthia papillosa*, *Microcosmus sulcatus*, *Microcosmus savignyi*, and *Styela plicata*.[372] The tunicates *Phallusia*

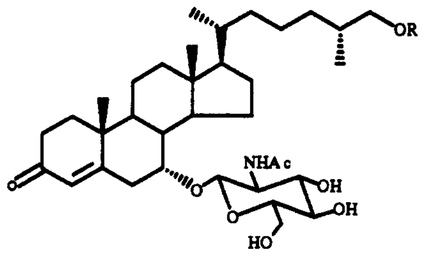


549



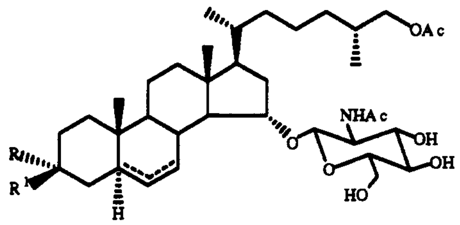
550, R=OH

551, R=H



552, R=H

553, R=Ac

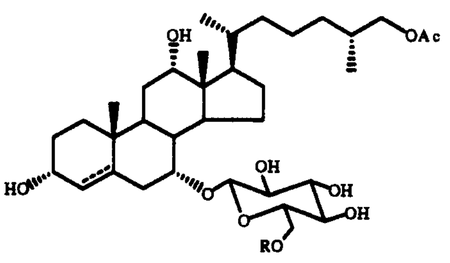


554, Δ^5 R=OH R^1=H

555, R=OH R^1=H

556, Δ^5 R=H R^1=OH

557, Δ^6 R=H R^1=OH



558, Δ^4 R=Ac

559, R=Ac

560, R=H

561, Δ^4 R=H

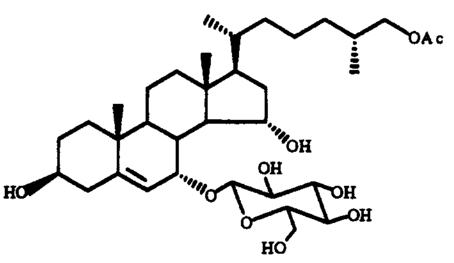


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Figure 24. Polyoxygenated steroids from fish.

mamillata and *Ciona intestinalis* were reported to contain 5,8-endoperoxides of several $\Delta^{5,7,9(11)}$-sterols (**547**)[373] and the 24-hydroperoxy-24-vinylcholesterol (**548**) along with its corresponding 24-hydroxy derivative,[374] this latter previously found in an alga (Figure 23).

X. Polyoxygenated Steroids from Vertebrates (Fish)

The bile of vertebrates characteristically contains bile salts, and in most animals these are largely steroidal C_{24} carboxylic acid derivatives. In the case of some fish the bile salts include C_{27} alcohols present as their sodium sulfate esters.

Scymnol (**549**, Figure 24) is the bile alcohol from shark bile and the first of such alcohols to be isolated.[375] The history of the structure determination of this alcohol has been reviewed by Scheuer.[376] The final structure **549** was deduced by two groups, Cross[377] and Briggs and Haslewood.[378] The two bile alcohols myxinol (**550**) and deoxymyxinol (**551**) were both isolated from hagfish. For myxinol, the first of the two to be isolated,[379] the 5β-structure was initially proposed, but later work established the 5α-structure **550**.[380] Deoxymyxinol was then assigned the structure **551** by the same research group.[381]

Certain fish have a self-defense mechanism consisting of the secretion of toxic substances that repel their predators. Among them are the Red Sea Moses sole *Pardachirus marmoratus* and its congener, the peacock sole *Pardachirus pavoninus*, which repel sharks by emission of their toxic secretion at the moment when they are about to be bitten. The chemical nature of the shark repellents has been shown by Tachibana, Nakanishi, and co-workers to consist of mixture of the peptidic paradaxins and two group of steroid glycosides, pavonins 1–6 (**552**–**557**) from *P. pavoninus*,[382,383] and mosesins 1–5 (**558**–**562**) from *P. marmoratus*.[384] The chemical structure of both pavonins and mosesins has been established by spectroscopic studies and chemical conversions. Mosesin 4 (**560**) has been successfully obtained by synthesis.[385] The biological activity of these toxins is believed to be related to their surfactant properties, that in the case of glycosides arises from a hydrophobic "top" and a hydrophilic "bottom" region. The respective roles of the steroidal glycosides and of the peptidic paradaxins in defense mechanism still remain obscure. It has been suggested that pavonins and mosesins are repellents that act on the shark's olfactory sense, whereas the proteinaceus toxin is possibly an antifeedant that acts on its gustatory sense. A review on chemical defense in fishes, which includes the fascinating history of the shark repellents from *Pardachirus* sp. has been published by Tachibana.[386]

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