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Marine polar steroids

V A Stonik

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Abstract. Structures, taxonomic distribution and biological activities of polar steroids isolated from various marine organisms over the last 8 – 10 years are considered. The peculiarities of steroid biogenesis in the marine biota and their possible biological functions are discussed. Syntheses of some highly active marine polar steroids are described. The bibliography includes 254 references.

I. Introduction

The marine biota differs essentially from the terrestrial one in taxonomic composition and extreme diversity. This includes representatives of much more numerous large animal and plant taxa (*i.e.*, animal phyla and plant divisions) in comparison with those dwelling on land. Many of these taxa contain exclusively marine organisms (*e.g.*, echinoderms, bryozoans, ascidians, nearly all divisions of algae) or comprise very small groups of terrestrial species. For example, only one sponge family inhabits freshwater reservoirs, whereas all other sponges are exclusively sea and ocean dwellers. Taxonomic peculiarities of various producers and their unusual dwelling habitat provide the rationale for the non-coincidence of structures of the absolute majority of marine secondary metabolites and natural products found in terrestrial organisms.

The uniqueness and structural diversity of natural compounds isolated from marine organisms draw the attention of chemists to this particular field. Published material devoted to this problem can now be found in virtually every issue of the majority of international chemical journals. Chemical investigations of marine organisms are making rapid strides. Of $\sim$12 000 newly discovered compounds, 1400 are marine steroids.

It is well known that steroids play an important biological role. They represent constituents of biomembranes and hormones, fulfil protective functions, stimulate plant growth, *etc.* Many representatives of this group are widely used in medicine as essentials of antiinflammatory, anabolic and contraceptive drugs. Steroids isolated from various marine organisms (marine steroids) manifest diverse biological activities. Some of them are extremely toxic against tumour cells and show antimicrobial and other effects. It is therefore not surprising that marine steroids arouse considerable interest in not only chemists, but also in pharmacologists and physicians. Besides, these compounds fall under the scope of biology and biochemistry. Studies on taxonomic distribution of marine steroids make it possible to detect compounds which can be used as chemotaxonomic markers able to resolve many moot points in systematics of marine organisms and phylogenetic relationships in the marine biota. Since marine organisms comprise a large number of the so-called living fossils, comparison of their metabolisms with those of representatives of younger taxa sheds additional light on the evolution of secondary metabolic processes.

Polar (often, water-soluble) steroids constitute an abundant group of marine steroids;† many highly active and structurally unique compounds belong to this group. Studies of marine (including polar) steroids carried out before 1987 are reviewed in a monograph.[1] Some problems related to marine polar steroids are also discussed in the reviews [2, 3] published in the early 1990's. This review is an attempt to generalise the experimental data on marine polar steroids published over the last 8 – 10 years.

II. Polyhydroxysteroids and related compounds

Marine organisms contain a great number of oxygenated sterol derivatives; the majority of these secondary metabolites are related to polyhydroxylated derivatives. These compounds were found in algae and marine invertebrates, particularly in sponges, echinoderms and octocorals (one of the orders of the Anthozoa class which in turn belongs to the phylum Coelenterata). In this section, we shall consider those oxygenated marine steroids and related compounds which have been discovered very recently, namely, after 1993 when Minale *et al.*[2] published a review devoted to polyhydroxylated marine steroids.

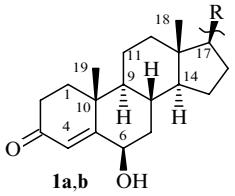
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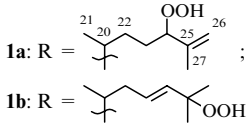
† Steroid compounds which contain three or more oxygen atoms as well as steroid alkaloids, sulfates, phosphates and glycosides of steroid aglycons are usually referred to as polar steroids.

1. Polyhydroxysteroids from algae

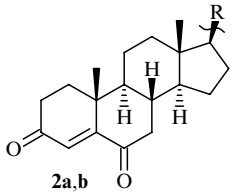
A series of steroid hydroperoxides **1a**,**b** and **2a**,**b** were isolated from the red alga *Galaxaura marginata* collected near the coasts of Taiwan.[4] These compounds manifest high cytotoxic activities against tumour cells P-388, KB, A-549, HT-29 (their semi-inhibiting concentrations, IC_{50}, lie within the range 0.2–1.0 μg ml^{-1}).



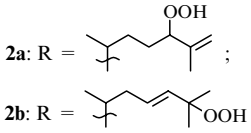
1a,**b**



1a: R = ; **1b**: R = .

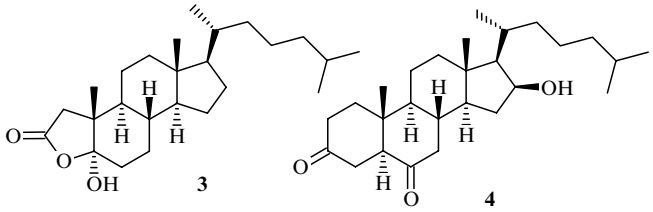


2a,**b**

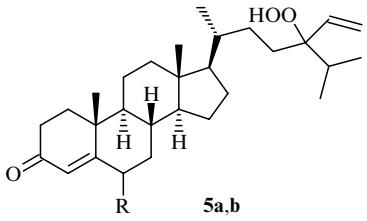


2a: R = ; **2b**: R = .

The oxygenated 3,4-dinorcholestane derivative **3** was isolated from extracts of the red alga *Laurencia obtusa*.[5] The steroidal 3,6-diketone **4** oxygenated at C(16) was isolated from the alga *Jania rubens*, it exhibited high toxicity against some tumour cells ($IC_{50} \approx 0.5$ μg ml^{-1}) (see Ref. 6). The hydroperoxides **5a**,**b** isolated from the brown alga *Turbinaria conoides* also possessed cytotoxic properties.[7]



3 **4**



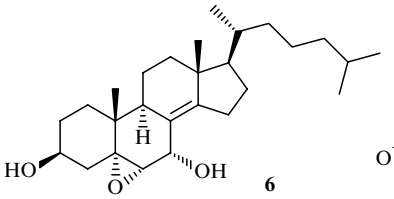
5a,**b**

5a: R = O;
5b: R = β-OH.

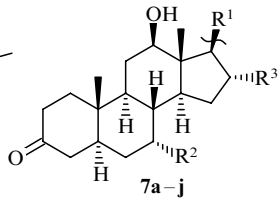
However, highly oxygenated sterols are not very common in algae. These metabolites are much more widely distributed in marine invertebrates.

2. Polyhydroxysteroids from sponges

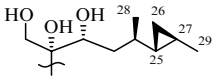
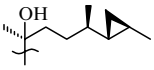
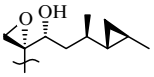
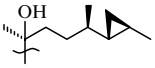
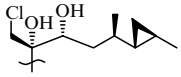
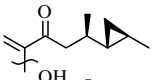
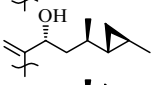
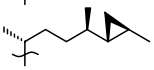
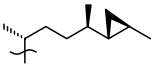
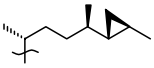
The 5,6-epoxide **6** isolated from the sponge *Ircinia fasciculata* collected near the coasts of India [8] and a series of steroids isolated from the Taiwanese sponge *Xestospongia* sp., *viz*., aragusterols A–D (**7c**–**f**),[9–11] xestokerols A, B (**7a**,**b**) and aragusterols E–H (**7g**–**j**), relate to sponge polyhydroxysteroids.[12] Aragusterols and related compounds have unusual side chains, which contain cyclopropane fragments, while aragusterol C (**7e**) contains a chlorine atom in the side chain, which is a unique structural feature of natural steroids.



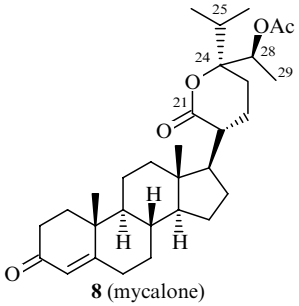
6



7a–**j**

Compound **7**	Name	R^1	R^2	R^3
a	xestokerol A		H	H
b	xestokerol B		OH	H
c	aragusterol A		H	H
d	aragusterol B		H	H
e	aragusterol C		H	H
f	aragusterol D		H	H
g	aragusterol E		H	H
h	aragusterol F		H	OH
i	aragusterol G (3α-OH)		H	H
j	aragusterol H (3β-OH)		H	H

It should be noted that the presence of unusual side chains in sponge polar steroids is due to the presence in the sponges of their precursors (sterols) having identical side chains. In contrast to higher plants where sterols represent minor components, some representatives of sponges and cnidarians (coelenterates) contain unusual sterols as predominant, and sometimes single components of steroid fractions. The side chain of the steroid ketone mycalone **8** from the Australian sponge *Mycale* sp. contains a lactone fragment formed upon oxidation of the ketone precursor at C(21) and C(24).[13]

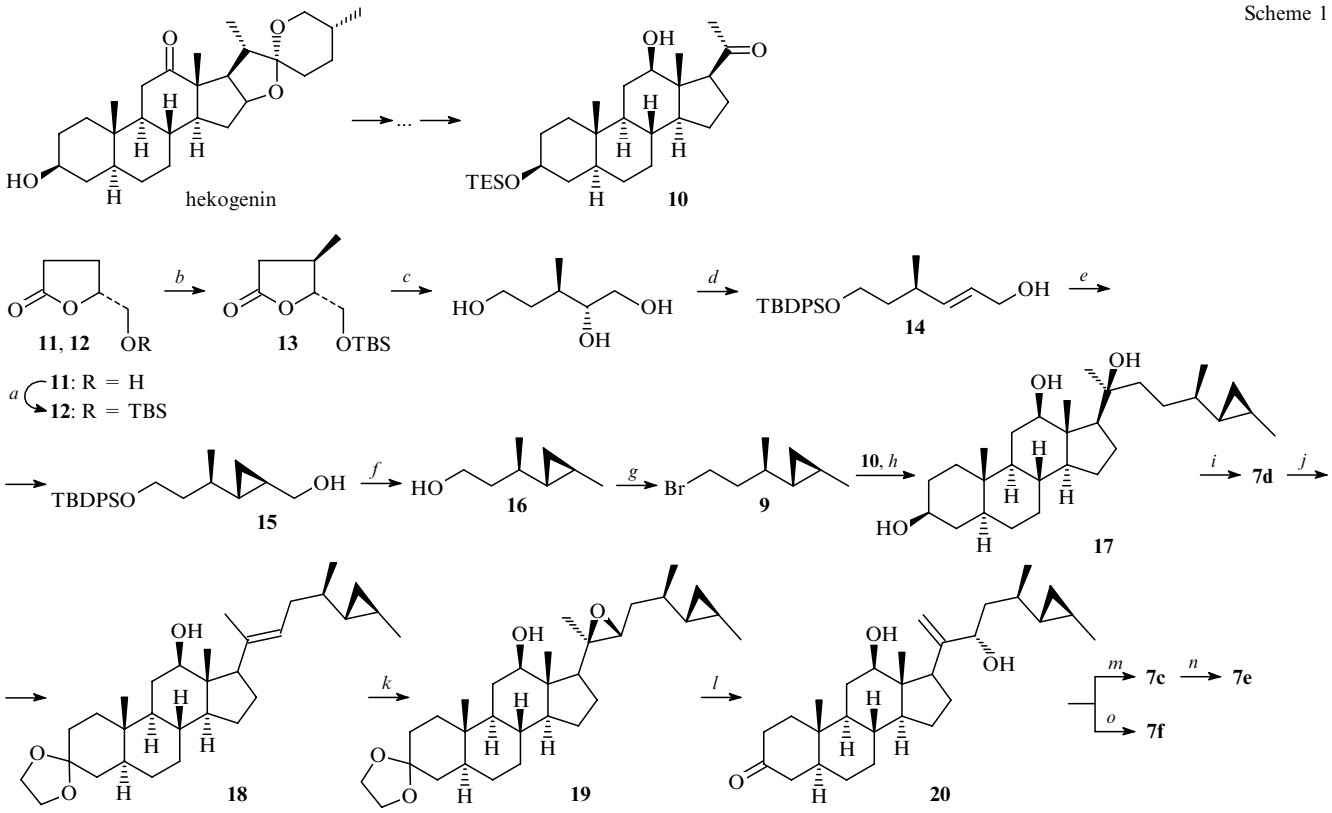


8 (mycalone)

Among the compounds mentioned above, aragusterols manifesting strong cytotoxic and antitumour activities present special interest. The IC_{50} values of aragusterols **7c** and **7d** against tumour cells (KB) are 0.042 and 0.041 μg ml^{-1}, respectively. These steroids (1.6 mg kg^{-1}) increase the lifespan of mice with leukemia L-1210 *in vivo* by 220% and 257%, respectively.

5-Epiaragusterol A synthesised from deoxycholic acid possessed cytotoxic properties comparable to those of aragusterol A (**7c**).[14] The synthesis of aragusterols from (+)-hekogenin[15] included stereoselective formation of side chains, the addition of the corresponding fragment **9** to the 20-ketosteroid **10** prepared from hekogenin and preparation of aragusterol B (**7d**) *via* the intermediate **17** with subsequent transformation of **7d** into **7c**, **7e** and **8f** (Scheme 1). The triethylsilyl (TES) derivative **10** was synthesised in six steps from the readily available hekogenin. The fragment **9**, which is structurally similar to the side chain of

Scheme 1

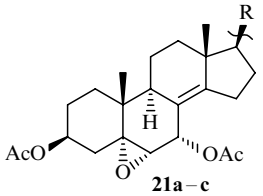


(*a*) $Bu^{t}_{3}SiCl$ (TBSCl), imidazole, DMF (92%); (*b*) Me_2CuLi, Et_2O, −78 °C (90%); (*c*) $LiAlH_4$, THF; 80% AcOH (89%); (*d*) $Pb(OAc)_4$, K_2CO_3, benzene; $Ph_3P{=}CHCO_2Me$, benzene (67%); $Bu^{t}Ph_2SiCl$ (TBDPSCl), imidazole, DMF; $Bu^{i}_{2}AlH$ (DIBAH), CH_2Cl_2, −78 °C (91%); (*e*) CH_2I_2, Et_2Zn + $BuBO_2(CH)_2(CONMe_2)_2$, CH_2Cl_2 (99%); (*f*) Ph_3P, CBr_4, CH_2Cl_2; $LiAlH_4$, THF–Et_2O; $Bu^{n}_{4}NF$, THF (88%); (*g*) Ph_3P, *N*-bromosuccinimide (NBS), CH_2Cl_2 (75%); (*h*) lithium naphthalenide, THF, 0 °C; Bu_4NF, THF (93%); (*i*) $Al(OBu^{t})_3$, cyclohexanone, toluene (66%); (*j*) ethylene glycol, TsOH, boiling benzene (79%); (*k*) $Bu^{t}O_2H$, $VO(acac)_2$, CH_2Cl_2 (78%); (*l*) $Pr^{i}_{2}NMgBr$, THF (93%); 80% AcOH (98%); (*m*) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, 0 °C (54%); (*n*) Li_2CuCl_4, THF (90%); (*o*) pyridinium dichromate (PDC), molecular sieves (4 Å), CH_2Cl_2 (100%).

aragusterols, was synthesised from (5*R*)-hydroxymethyl-2(5*H*)-furanone (**11**) which in its turn was prepared from L-ascorbic acid. Protection of the hydroxy group (as the tris-*tert*-butylsilyl ether) and subsequent reaction of the derivative **12** with lithium dimethylcuprate yielded the lactone **13** with high stereoselectivity. The latter was reduced, and the protective group was removed by treatment with acetic acid. The intermediate triol was converted into the allylic alcohol **14** in four steps, which included oxidation with lead tetraacetate, the Wittig reaction, protection of the hydroxy group as a silyl ether and subsequent reduction of the ester with diisobutylaluminium hydride. The key step in the synthesis of compound **9** was the conversion of the alcohol **14** into the cyclopropane derivative **15** by treatment with diiodomethane in the presence of diethylzinc and *N*,*N*,*N*′,*N*′-tetramethyl-(*S*,*S*)-tartarodiamide n-butylboronate. This reaction proceeded with high stereospecificity (yield 99%). Compound **15** was first converted into the alcohol **16** and then into the bromide **9**.

The stereoselective reaction of the 20-ketosteroid **10** with the alkyllithium derivative prepared from the bromide **9** and subsequent removal of the protective group at C(3) with tetrabutylammonium fluoride resulted in the alcohol **17** with high stereoselectivity. Its Oppenhauer oxidation gave aragusterol B (**7d**) which was further used for the synthesis of the other three aragusterols **7c**,**e**,**f** by chemical modification of the side chain *via* the intermediates **18**–**20**. The oxidation of the steroid alkene **18** to the epoxide **19** was carried out stereoselectively with *tert*-butyl hydroperoxide in the presence of vanadyl bisacetylacetonate.

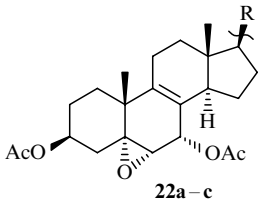
The sponge *Spongia officinalis* represents the source of a series of novel 5,6-epoxysteroids **21a**–**c** and **22a**–**c** which were isolated as acetates and differed in the structures of side chains and the positions of double bonds in the steroid nuclei.[16] Compound **21a** was also isolated from *Ircinia fasciculata*.[8]



21a: R = ;

21b: R = ;

21c: R = .

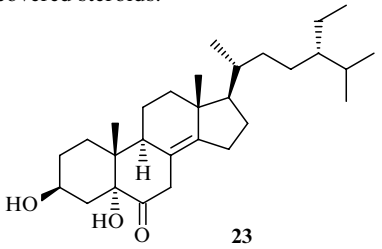


22a: R = ;

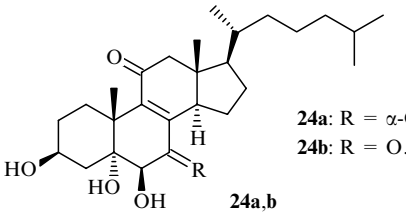
22b: R = ;

22c: R = .

Steroids oxidised in positions 5 and 6 were repeatedly found in sponges where they were apparently formed from Δ^5-sterols.[17] The ketone **23** from *Spirostrella inconstans* is one of such newly discovered steroids.[18]



Incrustasterols A and B (**24a**,**b**) from the Mediterranean sponge *Dysidea incrustans* differ from other polar sponge steroids in the presence of $\Delta^{8(9)}$-7-hydroxy-9-keto- and $\Delta^{8(9)}$-7,9-diketo-fragments, which are uncommon for marine steroids.

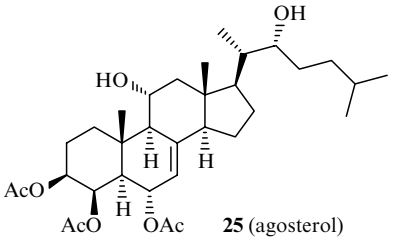


24a: R = α-OH, H;
24b: R = O.

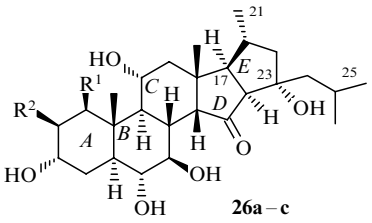
24a,**b**

Compounds **24a**,**b** are toxic for tumour cells (lung and kidney carcinomata, melanoma).[19] These compounds were synthesised from the readily available cholest-7-enol.[20]

The so-called agosterol **25** from *Spongia* sp. abrogates drug resistance of carcinoma cells, conditioned by enhanced expression of membrane glycoproteins.[21] Xestobergsterols A–C (**26a**–**c**), which contain five carbocycles with the *cis*-fused rings *C* and *D*, were found in *Xestospongia bergquistia* and *Ircinia* sp.[22,23] Presumably, the presence of an additional ring in these steroids is due to intramolecular aldol condensation of the yet non-isolated 23-keto derivative. Compounds **26a** and **26b** manifest cytotoxic activities and inhibit the anti-IgE-induced release of histamine from mast cells when used in small doses. Thus these compounds present considerable interest as potential active substances of novel antihistamine drugs. Their activities are closely related to strong inhibition of phosphatidylinositol phospholipase C.



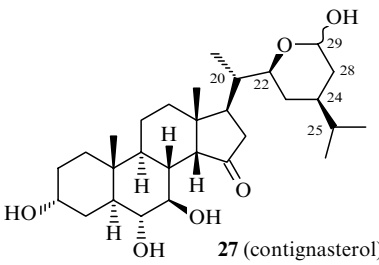
25 (agosterol)



26a–**c**

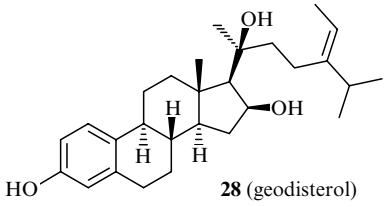
26a: $R^1 = R^2 = H$;
26b: $R^1 = H$, $R^2 = OH$;
26c: $R^1 = R^2 = OH$.

Yet another polar sponge steroid with the *cis*-fused rings *C* and *D*, *viz*., contignasterol (**27**) from *Petrosia contignata*, discovered simultaneously with xestobergsterols[24] produces strong antihistamine effect. Although contignasterol is inferior to compounds **26a** and **26b** in the activity, it is far more active than antihistamine drugs routinely used in clinical practice and is the subject of intense pharmacological studies as a promising candidate for antiallergic and antiasthmatic drugs.



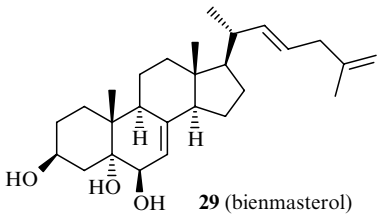
27 (contignasterol)

Geodisterol (**28**), the first marine steroid containing an aromatic ring *A*, was isolated from extracts of *Geodia* sp.[25]



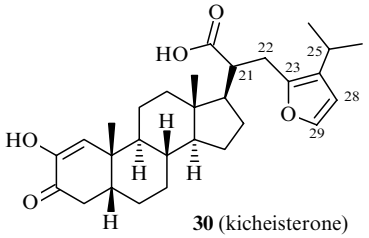
28 (geodisterol)

Previously, such compounds were referred to as hormones; however, in contrast to the latter, geodisterol (**28**) has a ten-carbon side chain characteristic of sterols. Bienmasterol (**29**) from *Bienma* sp.,[26] which is toxic against tumour cells (L-1210 and KB), contains a 22,25-diene fragment in the side chain, which is uncommon for natural steroids. An analogous fragment has been detected by us previously in baicalosterol isolated from the sponge *Baicalospongia bacilifera*.[27]

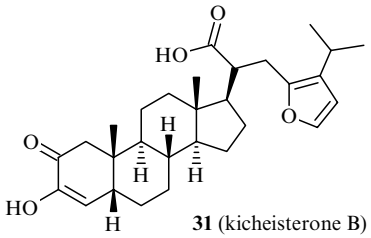


29 (bienmasterol)

Cytotoxic kicheisterones A and B (compounds **30** and **31**) with the *cis*-fused rings *A* and *B*, which contain carboxy groups in position 21 and furan fragments in the side chains, were isolated from an unidentified Hawaiian sponge of the Poecilosclerida order. These compounds are rather stable in acidic media but are easily interconverted in alkaline media to form 1 : 1 mixtures.[28]

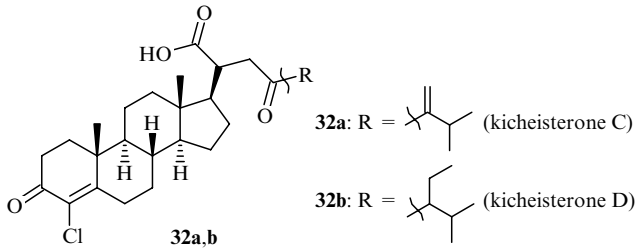


30 (kicheisterone)

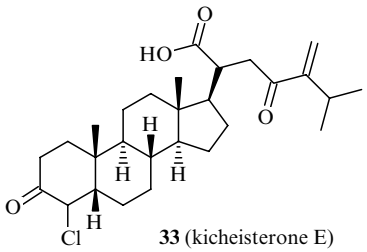


31 (kicheisterone B)

Steroids **30** and **31** were found in the sponge *Strongylacidon* sp. together with kicheisterones C–E (compounds **32a**,**b**, **33**). The latter contain chlorine atoms and belong to the group of extremely rare halogenated steroids.[29]



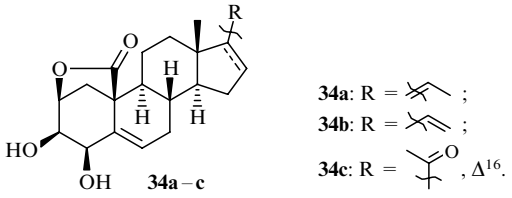
32a,**b**



33 (kicheisterone E)

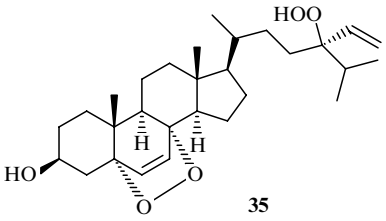
It is of note that no bromine-containing steroids have been isolated so far despite the wide occurrence of brominated metabolites in marine organisms.

Three pregnane derivatives **34a–c** from *Strongylophora* sp. were found to contain unusual (19 → 2)-lactone rings; their structures were established by X-ray diffraction analysis.[30] Hydroperoxides and related peroxides are more common for algal steroids; however, the novel biofouling inhibitor steroid **35** containing a peroxy group has recently been isolated from the sponge *Lendenfeldia chondrodes*.[31] Peroxides similar to compound **35** are readily formed by oxidation of $\Delta^{5,7}$-sterols, which are abundant in fungi, but scarce in sponges.



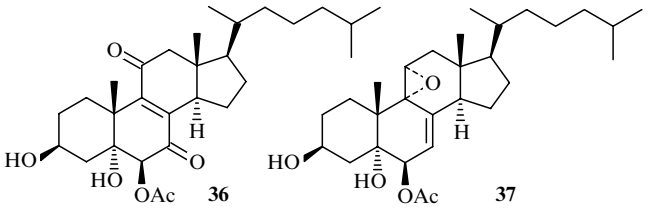
34a–c

34a: R = ;
34b: R = ;
34c: R = , Δ^{16}.

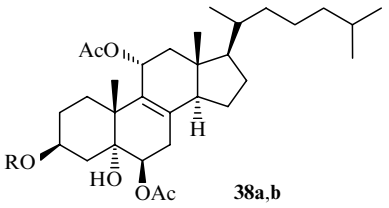


35

The novel acetylated polyhydroxysteroids **36**, **37**, **38a**,**b**[32] and related steroids[33] were detected in some sponges of the *Dysidea* genus. The steroid **37** and, to a lesser degree, steroids **38a**,**b** inhibit the binding of interleukin-8 to its specific receptor of the type A.



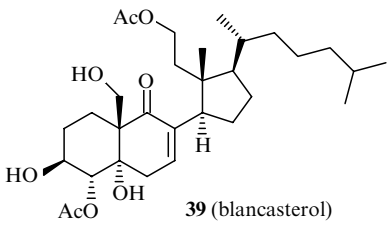
36 **37**



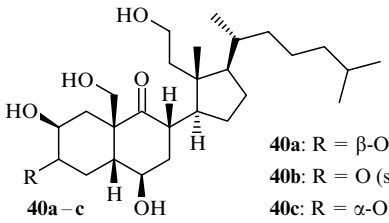
38a,**b**

38a: R = H;
38b: R = Ac.

Secosteroids occur widely in sponges. The most common of them are 9,11-secosteroids, such as blancasterol (**39**), a cytotoxic diacetate from the Northern Pacific sponge *Pleraplysilla* sp., which inhibits the growth of various tumour cells including drug-resistant cell cultures of human mammary carcinoma MCF-7.[34] Stelletasterol (**40a**), the antifungal secosteroid from *Stelletta* sp. isolated simultaneously with stelletasterone (**40b**),[35] differs from the previously known herbasterol (**40c**) from *Dysidea herbacea* only in the stereochemistry of the hydroxy group at the C(3) atom.



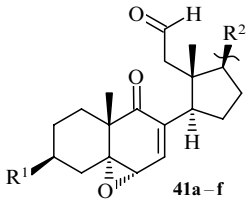
39 (blancasterol)



40a–c

40a: R = β-OH, H (stelletasterol);
40b: R = O (stelletasterone);
40c: R = α-OH, H (herbasterol).

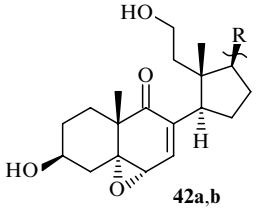
Like many other marine secosteroids, luffasterols A–C (**41a–c**) from *Luffariella* sp.[36] and the related secosteroid **41d** from *Spongia matamata*[37] contain 5,6-epoxy rings. 3-Deacetylluffasterol B (**41e**) and the related compound **41f** were isolated from *Spongia agaricina*. Both compounds manifest highly toxic activities against tumour cells.[38]



41a–f

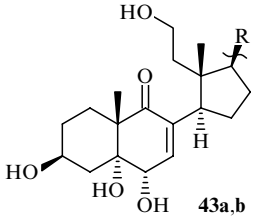
41a: R^1 = OAc, R^2 = (luffasterol A);
41b: R^1 = OAc, R^2 = (luffasterol B);
41c: R^1 = OAc, R^2 = (luffasterol C);
41d: R^1 = OH, R^2 = ; **41e**: R^1 = OH, R^2 = ;
41f: R^1 = OH, R^2 = .

Secosteroids **42a**,**b** and **43a**,**b** along with biogenetically related oxygenated sterols **44** and **45** were found in the Mediterranean sponge *Dysidea fragilis*.[39]



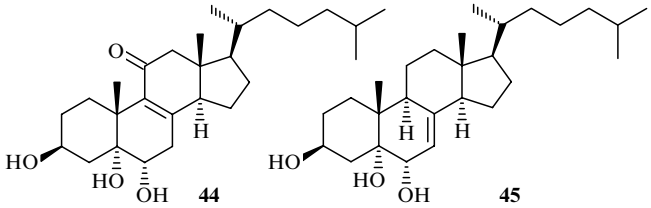
42a,**b**

42a: R = ;
42b: R = .



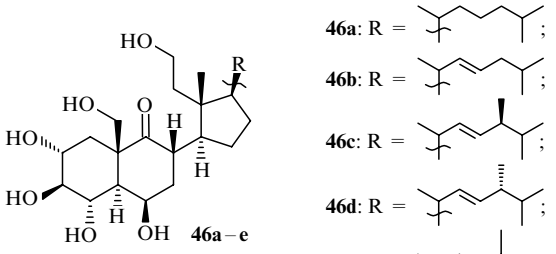
43a,**b**

43a: R = ;
43b: R = .

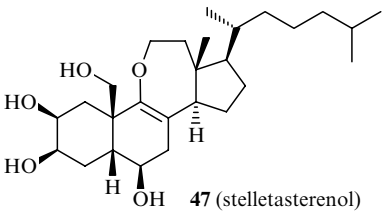


44 **45**

A series of euryspongiols **46a**–**e** and the epimeric 3α-hydroxy analogues possessing antihistamine properties were isolated from the sponge *Euryspongia* sp.[40] These compounds are the most strongly oxygenated sponge secosteroids known so far. The strong inhibiting effect of these and some other secosteroids on histamine release from mast cells during stimulation of the latter with anti-IgE suggests that marine secosteroids are promising candidates for antiallergic and antiasthmatic drugs.



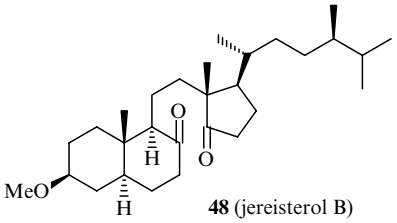
46a–**e**



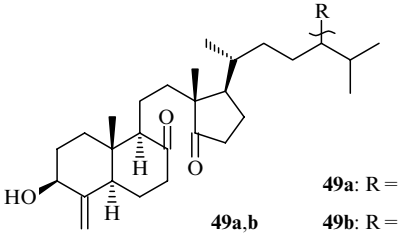
47 (stelletasterenol)

The unusual cyclic 9(11)-secosterenol, *viz*., stelletasterenol (**47**) from *Euryspongia arenaria,* contains an oxygen atom between the C(9) and C(11) atoms and manifests the properties of a PAF (platelet activation factor) agonist.[41]

In addition to 9,11-secosteroids common for marine invertebrates, sponges contain less abundant groups of compounds, which comprise 8,14- and 8,9-secosteroids. The former include jereisterol B (**48**) from *Jereicopsis graphidiophora*[42] and swinhosterols A and B (**49a**,**b**) from *Theonella swinhoe*.[43] Sponge 8,9-secosteroids are represented by unique 8α,9α-epoxy compounds, *e.g*., jereisterol A (**50a**) from *J. graphidiophora*[42] and its homologue **50b** isolated from the Senegalese sponge *Microscleroderma spirophora* together with the isomeric $\Delta^{8(14),9(11)}$ steroid **51**.[44] These compounds contain *O*-methyl groups, which occur rarely in natural steroids. Their structural analogues, *viz*., tilopiols A (**52**) and B (**53**), have recently been found in the microscopic fungus *Tilopilus plumbeoviolaceus*.[45] This finding suggests that microorganisms can be involved in the biosynthesis of sponge steroids **50a**,**b** and **51**.

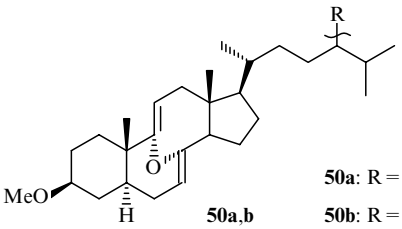


48 (jereisterol B)



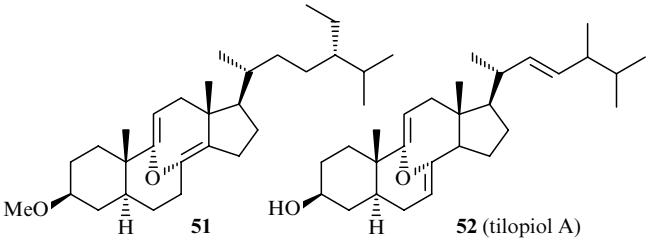
49a,**b**

49a: R = (swinhosterol A);
49b: R = (swinhosterol B).

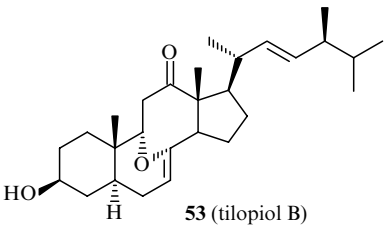


50a,**b**

50a: R = (jereisterol A);
50b: R = .



51 **52** (tilopiol A)



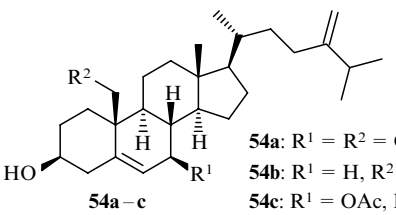
53 (tilopiol B)

It is not excluded that the great diversity of polar sponge steroids and the unique structures of many of them are due to biochemical conversions of the original sterols of both the sponge cells and microbial endosymbionts which are present in some sponges in amounts comparable to the populations of host cells. However, this hypothesis needs further verification and experiment in each particular case.

Although not a single sterol-oxidising enzyme has been isolated from sponges, symbiont bacteria, fungi or microalgae so far, such enzymes obviously differ from analogous enzymes of higher animals and terrestrial microorganisms in those sites in their sterol systems which oxidise the respective substrates. Thus some sponges were found to contain various secosteroids which are absent in terrestrial animals.

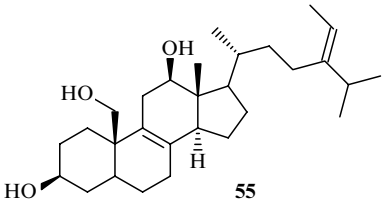
3. Polyhydroxysteroids from cnidarians

Polyhydroxysteroids are even more abundant in cnidarians (Coelenterata), particularly octocorals (soft corals) and gorgonian corals than in sponges. A great number of polyhydroxysteroids and secosteroids were detected in these marine invertebrates as long ago as 1970–1980. In the recent years, the list of these compounds was supplemented with many new names. Thus nephalsterol B (**54a**) found in *Nephthea erecta*,[46] *N. chabroli*[47] and *Litophyton arboreum*[48] [the latter contains additionally the $\Delta^{8(9)}$-triol **55** and related compounds, *e.g*., litosterol (**54b**) and nephalsterol C (**54c**)] are characteristic components of soft corals of the *Nephthea* genus. Compounds **54b**,**c** manifest strong antimicrobial activities, *viz*., they inhibit *Mycobacterium tuberculosis* by 90% and 96% when used in the doses of 3.13 and 12.5 μg ml^{-1}, respectively. The antituberculotic activity of nephalsterol B (**54a**) is less pronounced.[49]



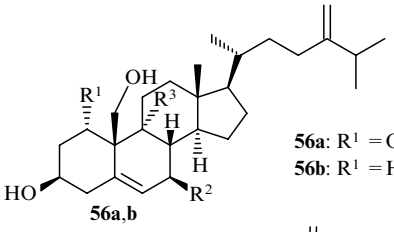
54a–**c**

54a: $R^1 = R^2 =$ OH (nephalsterol B);
54b: $R^1 =$ H, $R^2 =$ OH (litosterol);
54c: $R^1 =$ OAc, $R^2 =$ OH (nephalsterol C).



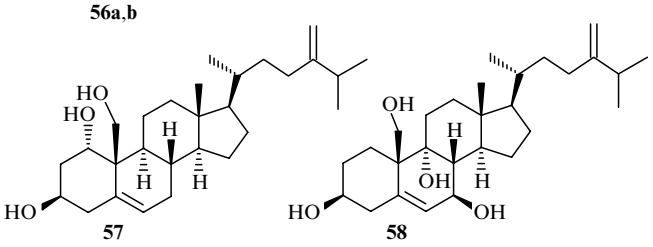
55

Some novel steroids of this series, *viz*., polyols **56a**,**b**, the triol **57** and the tetrol **58** from *Nephthea chabroli*, have recently been described.[47] Their structurally related analogues, *viz*., the triol **59** and the dihydroxy ketone **60**, were isolated from *Nephthea erecta* collected near the coasts of Taiwan.[46]

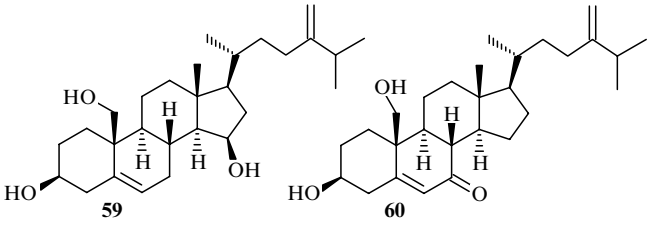


56a,**b**

56a: R^1 = OH, R^2 = R^3 = H;
56b: R^1 = H, R^2 = R^3 = OH.

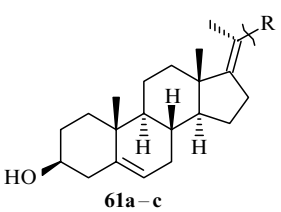


57 **58**

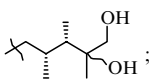


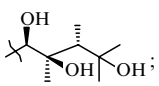
59 **60**

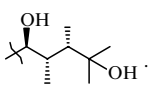
Triols **61a**,**c** and the tetrol **61b** from *Sinularia mayi* contain several hydroxy groups in their side chains.[50] The novel steroidal polyol **62** oxygenated at C(3), C(6), C(9) and C(11) was found in *S. hirta*.[51] The triol **63** and the corresponding glycosides were isolated from extracts of *S. gibbrosa*,[52] whereas the novel steroid pentol **64a** and its acetate **64b** were isolated from *S. dissecta*.[53] The pentol **65a** and the ketone **65b** from *Sinularia* sp.[54] and *S. microclavulata*,[55] respectively, contain oxygen atoms in the same positions, *viz*., at C(1), C(3), C(5), C(6) and C(16). The steroidal peroxide **66** from *Sinularia* sp.[56] proved to be highly toxic for tumour cells (IC_{50} = 0.4–2.7 μg ml^{-1}). This compound was isolated together with pregnenolone earlier detected in the sponge *Haliclona rubens*.[57] The stereochemistry of the C(22), C(23) and C(24) asymmetric centres of the peroxide **66** was established by comparison of its spectra with those of some synthetic model compounds.

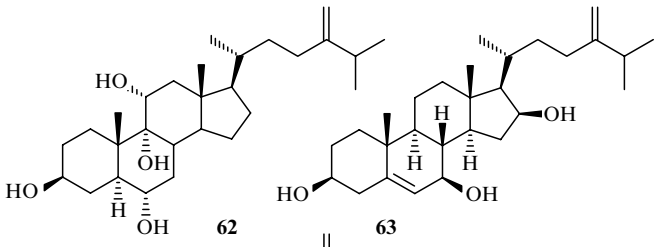


61a–**c**

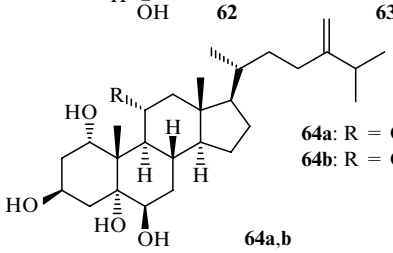
61a: R = ;

61b: R = ;

61c: R = .

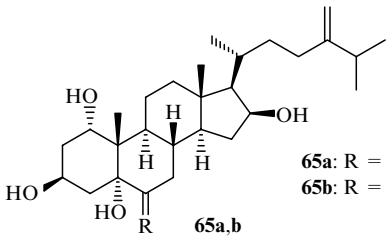


62 **63**



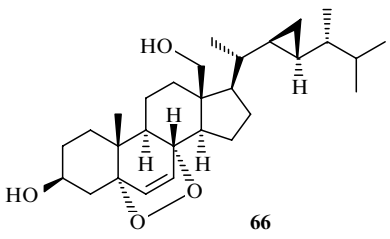
64a: R = OH;
64b: R = OAc.

64a,**b**



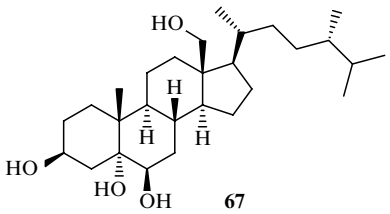
65a: R = β-OH, H;
65b: R = O.

65a,**b**

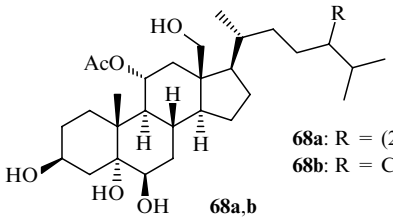


66

Several novel polar steroids were discovered in soft corals of the *Lobophyton* genus. For example, the tetrol **67** was isolated from *L. crassum*,[58] whereas two monoacetates **68a**,**b** were isolated from *L. cf. pauciflorum*.[59] These steroids contain 5α,6β-diol fragments similar to those present in oxygenated steroids isolated from soft corals of the *Sarcophyton* genus. For example, sarcoaldesterol B (**69a**) represents a deacetylated derivative of the steroid **68a**. It was isolated from the Okinawian soft coral *Sarcophyton* sp.

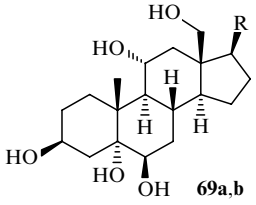


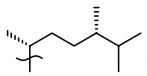
67

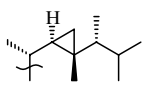


68a: R = (24*S*)-CH_3;
68b: R = CH_2=.

68a,**b**



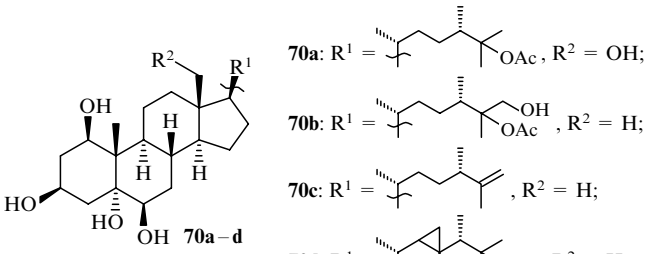
69a: R = ;

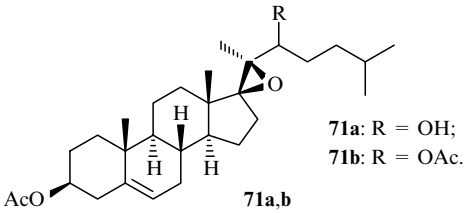
69b: R = .

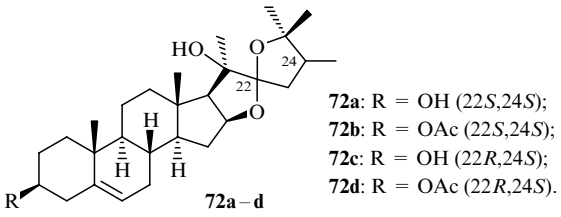
69a,**b**

together with sarcoaldesterol A (**69b**), which contains a side chain similar to that of gorgosterol, the well-known sterol of cnidarians.[60]

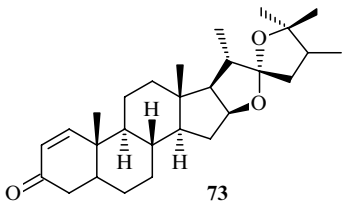
Steroids **70a**–**d** from the soft coral *S. subviride* collected near the coasts of the Andaman Islands are oxygenated to a greater degree. Some of them contain an acetate group at C(25) characteristic of polar steroids of Coelenterata.[61] Two novel polar steroids **71a**,**b** containing unique 17,20-epoxy fragments, two hippurin derivatives **72a**,**c** differing in stereochemistry at C(22) (hippurin is a well-known polar steroid of Coelenterata) and their acetates **72b**,**d**, were isolated from extracts of *S. crassocaule*.[62]

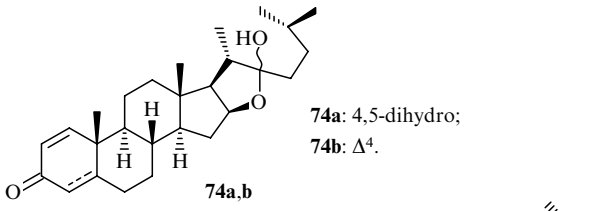


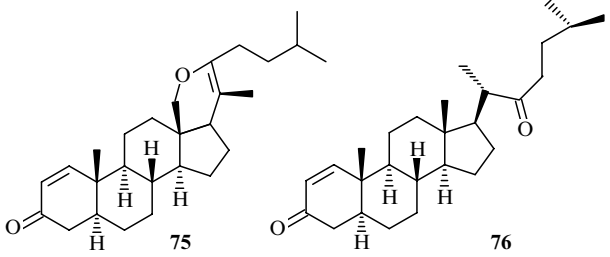




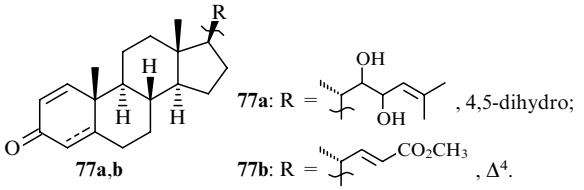
A series of polar steroids including the hippurin analogue, *viz*., compound **73**, as well as derivatives **74a**,**b**, **75** and **76** were detected in the soft coral *Alcyonium gracilum* by Shin *et al*.[63] Presumably, compound **76** is a biosynthetic precursor of all this group of secondary metabolites.



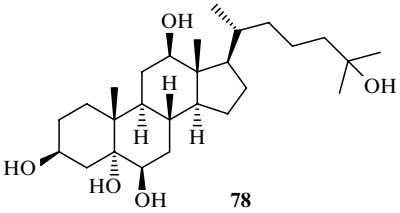


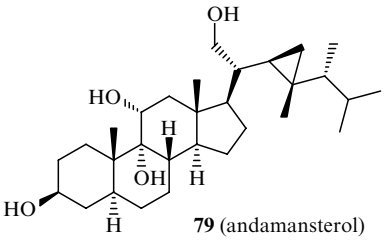


Yet another species of this genus, *viz*., *Alcyonium gracilum* (its mixture with *Dendronephthea* sp. has been studied), contains related steroids **77a**,**b**,[64] which are toxic for barnacle (*Balanus amphitrite*) larvae (LD_{100} = 100 μg ml^{-1}).

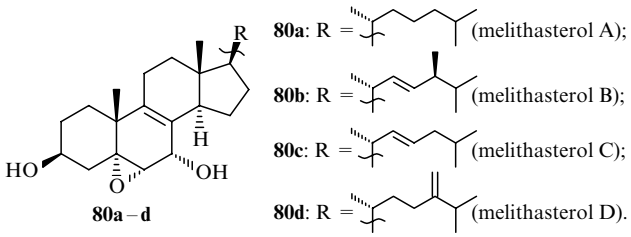


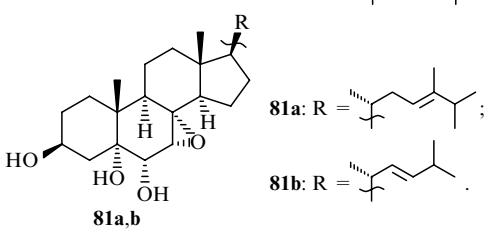
The steroidal pentol **78** was found in the soft coral *Sclerophytum* sp. together with several previously known steroids.[65] Andamansterol (**79**) [66] containing hydroxy groups in positions 9 and 11, which takes its name after the place where it was first collected (Andaman Islands), was detected in another unidentified species of the same genus. Such oxidation can precede the formation of 9,11-secosteroids widely distributed in marine invertebrates. An interesting feature of andamansterol (**79**) is the presence of a hydroxy group at C(21), which is uncommon for polar steroids of Coelenterata, but is common for steroids of some echinoderms, particularly, for ophiuroid metabolites.

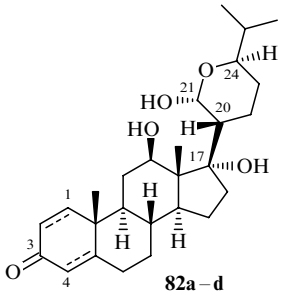




Gorgonian corals are distinguished for a great diversity of oxygenated steroids containing from 2–3 to 5–6 oxygen atoms. Thus melithasterols A–D (**80a**–**d**), each containing an 5,6-epoxy ring and an additional OH-group in position 7, were found in *Melithaea ocracea*.[67] Melithasterol A (**80a**) has recently been synthesised.[68] Steroids **81a**,**b** from *Acabaria undulata* also contain epoxide rings, however, in positions 7 and 8.[69] Anastomosacetals A–D (**82a**–**d**) from *Euplexaura anastomosans* collected near the coasts of Korea contain oxygen atoms in positions 17, 21 and 24.[70]



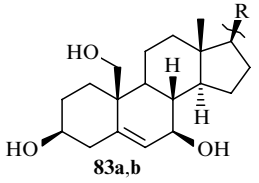




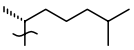
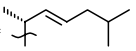
82a–**d**

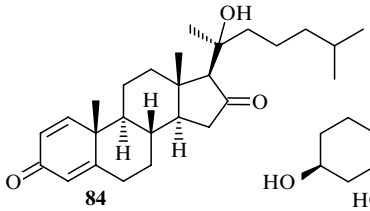
82a: $\Delta^{1,4}$ (anastomosacetal A);
82b: Δ^{4} (anastomosacetal B);
82c: Δ^{1} (anastomosacetal C);
82d: 1,2,4,5-tetrahydro (anastomosacetal D).

The so-called black coral *Anthiphates subpina* related to the Antipatharia order contains steroid triols **83a**,**b** and diketone **84**, which are toxic for crustaceans.[71] The tetrol monoacetate **85a** and the corresponding tetrol **85b** were isolated from *Telesto viisei*.[72]

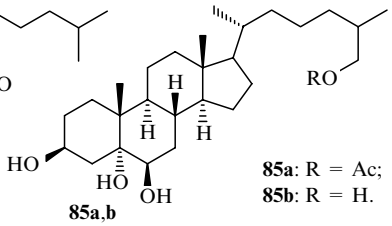


83a,**b**

83a: R = ;
83b: R = .



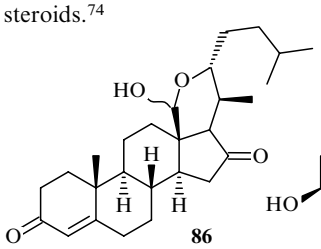
84



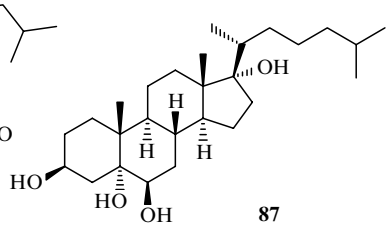
85a,**b**

85a: R = Ac;
85b: R = H.

The steroidal hemiacetal **86** possessing antimicrobial, antiviral and antitumour properties was isolated from the gorgonian coral *Ctenocella* sp.[73] Punacine (**87**) from the gorgonian coral *Lophogorgia punicea* dwelling near the coasts of Brazil contains a hydroxy group at C(17), which is uncommon for cnidarian steroids.[74]

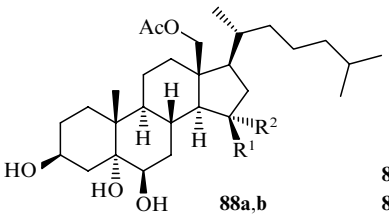


86



87

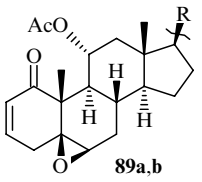
Polyhydroxylated steroids **88a**,**b** from the octocoral *Dendronephthea gigantea*[75] manifested moderate cytotoxic activities against tumour cells (L-1210).



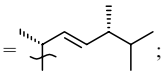
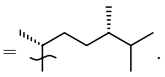
88a,**b**

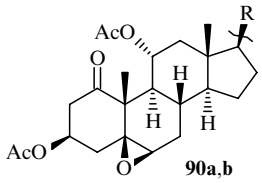
88a: $R^1 = R^2 = H$;
88b: $R^1 = OH$, $R^2 = H$.

A series of steroids oxygenated in positions 1, 5, 6 and 11 (compounds **89a**,**b**, **90a**,**b**, **91a**–**d** and **92**) were isolated from the Okinawian coral *Clavularia viridis*.[76] Compounds **89a**,**b** manifest cytotoxic properties and are similar to vitanolides, the higher terrestrial plant metabolites, in the structures of their polycyclic fragments.

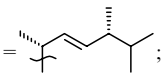
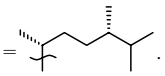


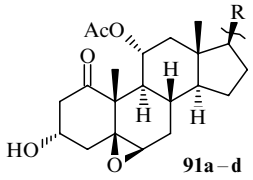
89a,**b**

89a: R = ;
89b: R = .

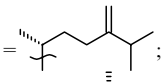
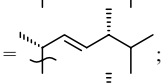
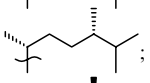
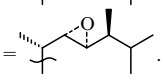


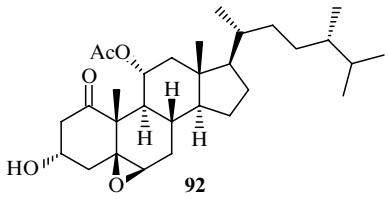
90a,**b**

90a: R = ;
90b: R = .



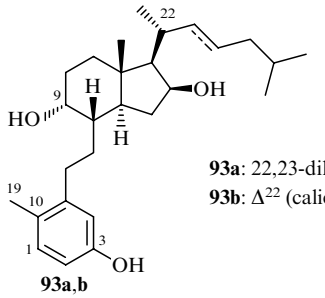
91a–**d**

91a: R = ;
91b: R = ;
91c: R = ;
91d: R = .



92

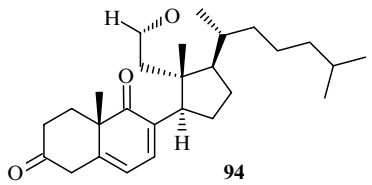
Secosteroids are common metabolic products of octocorals. The 9,10-secosteroids, *viz*., calicopherols A and B (**93a**,**b**), which are toxic for shrimps, were isolated from the gorgonian coral *Caligorgia* sp. collected near the coasts of Japan.[77] A series of novel calicopherols differing structurally from compounds **93a,b** have recently been isolated from the gorgonian coral *Muricella* sp. These compounds manifest high cytotoxic activities against tumour cells and inhibit phospholipase A_2.[78]



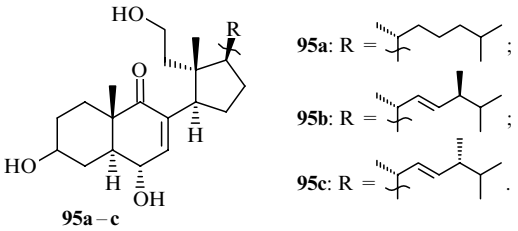
93a,**b**

93a: 22,23-dihydro (calicopherol A);
93b: Δ^{22} (calicopherol B).

9,11-Secosteroids are much more abundant in soft and gorgonian corals. Among the most recent findings, we should make reference to dioxoaldehyde **94** from *Subergorgia suberosa* collected near the coasts of India;[79] steroids **95a**–**c** from the same species collected near the coasts of the Comores Islands;[80] the epoxide **96** from the Indonesian coral *Lobophytum* sp.[81] and 4α-methylsecosteroids **97** and **98** from *Pseudopterogorgia* sp.[82] manifest moderate inhibitory activities with respect to protein kinase C and possess antiinflammatory and cytotoxic properties.



94

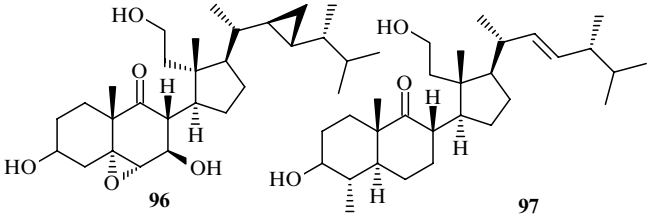


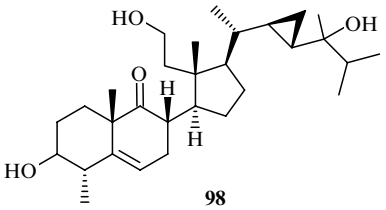
95a: R = ;

95b: R = ;

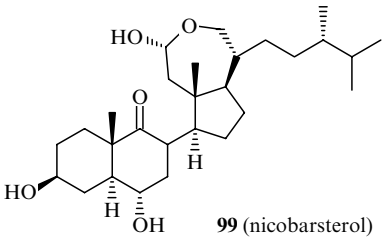
95c: R = .

95a – c



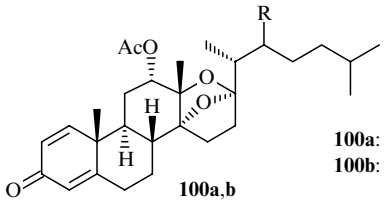


The unusual hemiacetal **99** (nicobarsterol) from *Sclerophytum* sp. was named after the place where it was first collected (the Nicobar Islands in the Indian Ocean).[66]



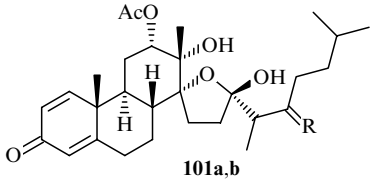
99 (nicobarsterol)

A search for novel compounds able to prevent biofouling of ship bottoms and submerged structures undertaken by the Fusetani group [93] resulted in the isolation of four novel unprecedented 13,17-secosteroids **100a**,**b** and **101a**,**b** (isogosterols A – D) from *Dendronephthea* sp. They manifested much higher antifouling activities in comparison with steroids **77a**,**b** and inhibited the settlement of barnacle (*Balanus amphitrite*) larvae when used in concentrations of ~ 2 μg ml^{-1} (see Ref. 83).



100a,**b**

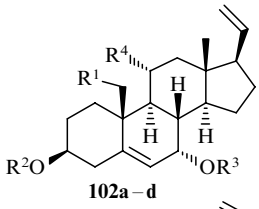
100a: R = H (isogosterol A);
100b: R = OAc (isogosterol D).



101a,**b**

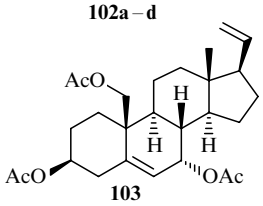
101a: R = O (isogosterol B);
101b: R = OAc, H (isogosterol C).

Oxygenated steroids with the pregnane skeleton were often found in various representatives of Coelenterata; in particular, acetylated pregnanes **102a – d** and **103** have recently been found in the South African population of *Pieterfaura inilobata*.[84]



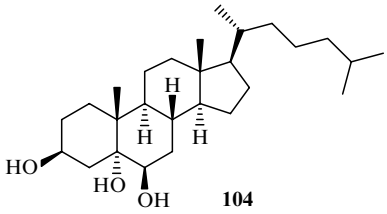
102a – d

102a: $R^1 = R^3 = H$, $R^2 = Ac$, $R^4 = OH$;
102b: $R^1 = H$, $R^2 = R^3 = Ac$, $R^4 = OH$;
102c: $R^1 = OAc$, $R^2 = Ac$, $R^3 = R^4 = H$;
102d: $R^1 = OAc$, $R^2 = R^3 = Ac$, $R^4 = OH$.



103

The detection of polar steroids in the sea pens of the Pennatulaceae order is the most uncommon case. Thus the triol **104**, the simplest oxygenated steroid formed upon oxidation of cholesterol at the 5(6)-double bond, was isolated from *Pteroides esperi*.[85]



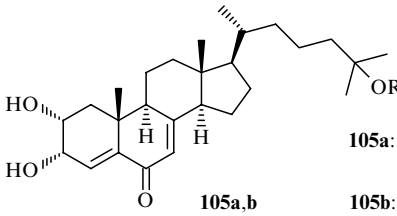
104

It should be said in conclusion that hydroxylation in Coelenterata predominantly occurs in positions 3, 5, 6, 22 and 25 and less frequently in positions 1, 2, 11, 16, *etc*. Steroids containing angular hydroxymethyl groups are widespread in these invertebrates; the oxygenation of the 19-methyl group occurs most often. In these animals, sterols can be oxidised to pregnane derivatives. 9,11-Seco compounds are as widely occurring in cnidarians as in sponges. It is noteworthy that polar steroids are seldom found in other taxa of Coelenterata, with the exception of octocorals.

4. Polyhydroxylated steroids from molluscs

Polar steroids are seldom found in molluscs, usually these are of exogenous origin, *viz*., they are consumed with food and accumulated in either an unchanged or a modified form. In most cases, the steroids accumulated in molluscs play the protective role.

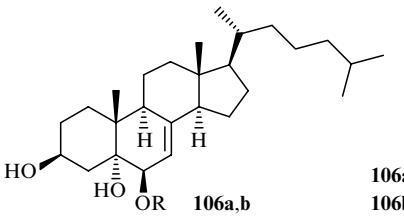
For example, unusual 2α,3α-dihydroxy cross-conjugated ketones, such as diaulusterols A and B (**105a**,**b**), one of which containing a hydroxybutyrate substituent in the side chain, were detected in the nudibranch mollusc *Diaula sandiegensis*.[86] Recent *in vitro* studies of 1,2-^{13}C-acetate as a biosynthetic precursor showed that the steroid **105a** is not biosynthesised by these molluscs but is modified by addition of a substituent to the hydroxy group at C(25); this substituent is biosynthesised from acetate.[87] It is of note that nudibranch molluscs are devoid of shells and other mechanical protective means, they readily absorb toxic and deterrent metabolites from the sponges they feed on.



105a,**b**

105a: R = $COCH_2CH(OH)CH_3$ (diaulusterol A);
105b: R = H (diaulusterol B).

The triol **106a** and its 6-*O*-methyl derivative **106b** widely occurring in sponges were isolated from fertilised eggs of the mollusc *Aplysia juliana*.[88]



106a,**b**

106a: R = H;
106b: R = CH_3.

5. Polyhydroxysteroids of echinoderms

Echinoderms, particularly starfishes, are the source of the most oxygenated steroids. A great number of polyhydroxy derivatives have been discovered in these organisms since 1974. More than 20 novel compounds, (compounds **107**–**128**)[89–95] have been isolated recently (Table 1). The hydroxy groups in positions 3β, 6α or 6β, 8β, 15α or 15β, 16β and 26 are especially abundant in starfish steroids, while polyhydroxysteroids containing hydroxy groups in positions 4α or 4β, 7α, 14α, 24, 28 and 29 are isolated less often. Some starfish polar steroids contain eight or nine hydroxy groups,

Table 1. The structures of polyhydroxysteroids isolated from starfishes.

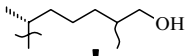
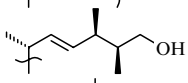
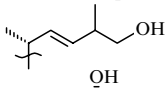
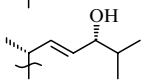
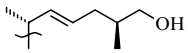
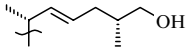
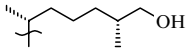
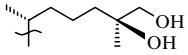
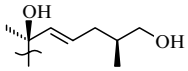
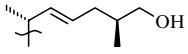
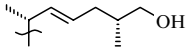
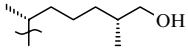
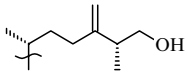
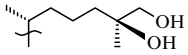
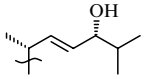
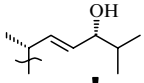
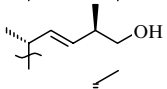
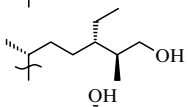
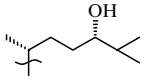
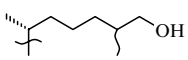
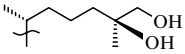
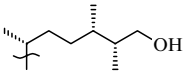
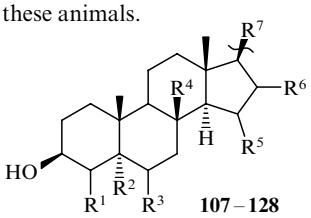
Compound	Unsaturation type	R^1	R^2	R^3	R^4	R^5	R^6	The side chain (R^7)	The biological source	Ref.
107	–	H	H	α-OH	H	β-OH	β-OH		*Ceramaster patagonicus*	89
108	$\Delta^{8(14)}$	H	H	α-OH	H	β-OH	H		*Acodontaster conspicuus*	90
109	$\Delta^{8(14)}$	H	H	α-OH	H	β-OH	H		*Acodontaster conspicuus*	90
110	–	H	H	α-OH	OH	α-OH	H		*Ceramaster patagonicus*	89
111	–	H	H	β-OH	H	α-OH	β-OH		Echinasteridae gen. sp.	91
112	–	H	H	β-OH	H	α-OH	β-OH		Echinasteridae gen. sp.	91
113	–	H	H	β-OH	H	α-OH	β-OH		Echinasteridae gen. sp.	91
114	–	H	H	β-OH	H	α-OH	β-OH		Echinasteridae gen. sp.	91
115	–	H	H	β-OH	H	α-OH	β-OH		Echinasteridae gen. sp.	91
116	–	H	H	β-OH	OH	α-OH	β-OH		Echinasteridae gen. sp.	91
117	–	H	H	β-OH	OH	α-OH	β-OH		Echinasteridae gen. sp.	91
118	–	H	H	β-OH	OH	α-OH	β-OH		Echinasteridae gen. sp.	91
119	–	H	H	β-OH	OH	α-OH	β-OH		Echinasteridae gen. sp.	91
120	–	H	H	β-OH	OH	α-OH	β-OH		Echinasteridae gen. sp.	91
121	–	H	H	β-OH	OH	α-OH	H		Echinasteridae gen. sp.	91
122	–	β-OH	H	α-OH	OH	β-OH	H		Echinasteridae gen. sp.	91
123	–	β-OH	H	α-OH	OH	β-OH	H		*Acodontaster conspicuus*	90
124	–	β-OH	H	α-OH	OH	β-OH	β-OH		*Acodontaster conspicuus*	90
125	–	β-OH	H	β-OH	OH	β-OH	H		*Henricia derjugini*	93
126	–	H	α-OH	β-OH	H	α-OH	β-OH		*Ctenodiscus crispatus*	94

Table 1 (continued).

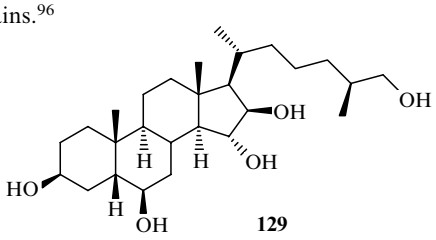
Compound	Unsaturation type	R^1	R^2	R^3	R^4	R^5	R^6	The side chain (R^7)	The biological source	Ref.
127	–	H	α-OH	β-OH	H	α-OH	β-OH		*Ctenodiscus crispatus*	94
128	–	H	α-OH	β-OH	H	α-OH	β-OH		*Luidiaster dawsoni*	95

although the corresponding pentols and hexols are more common for these animals.

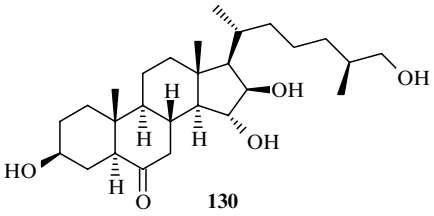


107 – 128

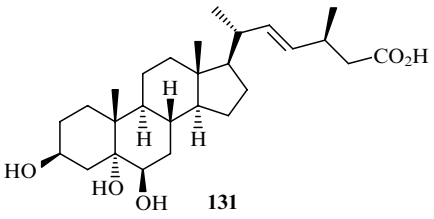
Sometimes starfish metabolites contain other functional groups or manifest other structural features. For example, the pentol **129** from *Luidia clathrata*[92] is a 5β-cholestane derivative in contrast to other polar steroids of this series. One of the hydroxy groups in compound **130** from Echinasteridae gen sp. is oxidised to the keto group,[91] whereas steroids **131** and **132** from *Myxoderma platyacanthus* contain carboxy groups in their side chains.[96]



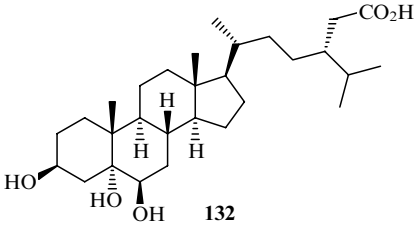
129



130



131



132

Recent studies on the distribution of polyhydroxy compounds in various body components and organs and structures of starfishes[97] prompted several conclusions concerning their biological roles. Since polyhydroxysteroids and related mono- and biosides were found only in digestive organs and solubilise lipid suspensions like bile acids, their role in starfishes can be similar to that of bile acids and bile alcohols in vertebrates.

Some starfish polyhydroxysteroids manifested antimicrobial activities against the gram-positive bacterium *Staphylococcus aureus* but did not inhibit the gram-negative bacterium *Escherichia coli*. A series of octols and nonols containing hydroxy groups in positions 4, 7, and 8 manifested high cytotoxic activities against human lymphoma cells JURCAT.[98]

It is interesting to note that polyhydroxysteroids are not common in other classes of echinoderms. Related sulfated polyols were found only in ophiuroids, whereas in holothurians and sea urchins polar steroids have not been identified yet. Recently, steroidal 3β,5α,6β-triols of the Δ^7-series were found in one representative of sea lilies (Crinoidea).[99]

Not all groups of marine invertebrates are rich in polyhydroxysteroids. The latter are not common for bryazoans and ascidians, but occur predominantly as ecdysteroids in crustaceans; however this group of polar steroids fall beyond the scope of the present review. In sponges, cnidarians and echinoderms, they are represented by only very few orders or classes. Notwithstanding, the immense diversity of marine polyhydroxysteroids is amazing and seems to reflect the intense evolutional search characteristic of taxa located in the basements of phylogenetic trees. Obviously, cnidarians and sponges are the most ancient animal organisms that have come down to us.

The biological roles of oxygenated sterol derivatives and related pregnane and other steroids are different in vertebrates and marine invertebrates. Whereas in the former they predominantly act as hormones and take part in digestion as bile acids, in sponges and cnidarians they usually perform protective functions, *e.g.*, they frighten away predators, inhibit the growth of pathogenic microorganisms, protect producers from fouling with algae, barnacles, molluscs, *etc.*

It is interesting to note that there are such biochemical transformations of sterols in some primitive marine invertebrates, which as happy findings of the Nature are repeated many time in other types of organisms and become to be of considerable importance in more advanced animal taxa and in higher plants. For example, as it was mentioned above, sponges and cnidarians contain pregnenolone, a biosynthetic precursor of steroid hormones of higher animals. Compounds of the spirostane series, which are analogous to aglycons of steroid saponins of higher plants, were repeatedly found in cnidarians and some other marine invertebrates. C_{28}-Steroid lactones, which are structurally similar to some witanolides (metabolites of terrestrial higher plants of the *Solanaceae* family), were found in the soft coral *Minabea* sp.[100] These biochemical parallelisms presumably testify to some degree of determinism in evolution of secondary metabolic processes occurring in living organisms.

III. Steroid sulfates

Sulfated compounds are extensively distributed in marine organisms. They were found in micro- and macroalgae, marine invertebrates (*e.g.*, sponges, echinoderms, molluscs), hemichordates and fishes. Sulfation is an essential mechanism of biosynthetic conversions occurring in the marine biota. This is not surprising, since sulfur (in the form of a sulfate ion) is the fourth most abundant

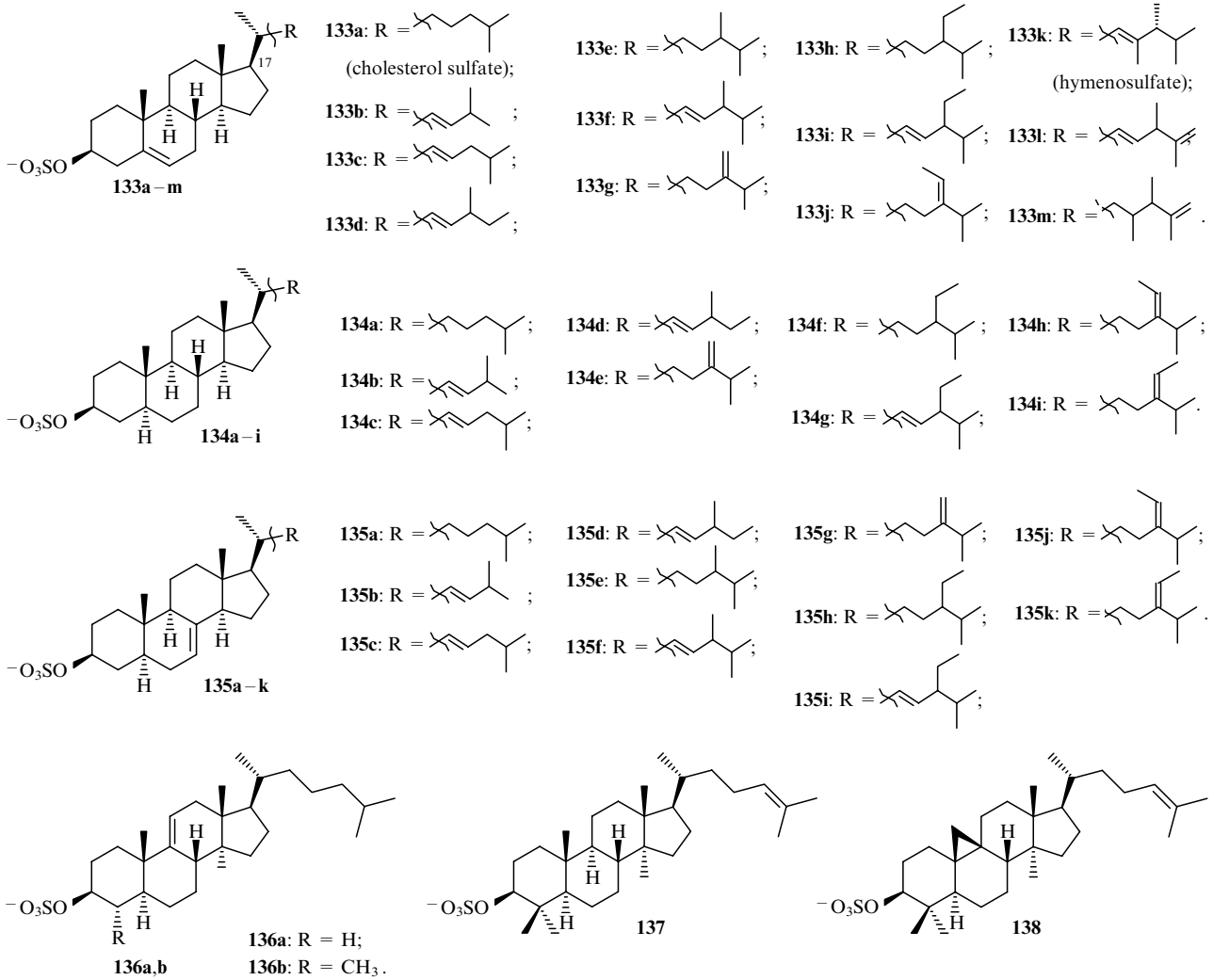
element in sea water after chlorine, sodium and magnesium. The introduction of a sulfate group increases the solubility of marine natural products and makes them biphilic, which is especially important for manifestation of their detergent and toxic activities and signal functions in various inter- and intraspecies interactions. The presence of sulfate groups ensures efficient transport of the corresponding compounds in water, while the presence of hydrophobic fragments in their molecules facilitates their binding to hydrophobic receptors of recipient organisms.

In macroalgae and some microalgae, sulfated compounds are largely represented by polysaccharides, while those in marine animals are represented by low-molecular-weight bioregulators. Over 500 sulfated secondary metabolites of different chemical groups (*e.g.*, terpenoids, carotenoids, steroids, alkaloids, aromatic metabolites, *etc.*) have been identified.[101]

Sulfated steroids constitute one of the most numerous groups of these compounds. They were mostly isolated from animals related to two large phyla of marine invertebrates, *viz.*, echinoderms (Echinodermata) and sponges (Porifera), although sulfated steroids were also found in other marine organisms. The biological functions of compounds related to this group are still poorly understood, although the facts that the least polar of them are essential components of biomembranes, while other representatives of this group are used for chemical protection against predators and pathogenic or fouling microorganisms leave no doubts.

1. Sterol sulfates

Structurally, sterol sulfates are the simplest sulfated steroids. In echinoderms, they occur as common metabolites; their concentrations in starfishes (Asteroidea), holothurians (Holothurioidea), ophiuroids (Ophiuroidea) and sea lilies (Crinoidea) amount to 4–5 mg per gram of dry tissue, those in sea urchins (Echinoidea) are somewhat lower.[1] The predominant component in the respective fractions is cholesterol sulfate **133a**. In addition, these fractions always contain sulfates of other Δ^5-sterols. Toxic representatives of holothurians and starfishes contain small amounts of sulfated stanols and sulfates of Δ^7-sterols along with sulfates of the Δ^5 series. For example, the Far Eastern holothurian *Eupentacta* (= *Cucumaria*) *fraudatrix* was found to contain polar steroids **133a**–**i**, **134a**–**k** and **135a**–**l**. Moreover, the same holothurian species contain trace amounts of sulfates of 14α-methyl-$\Delta^{9(11)}$-sterols **136a**,**b** and of triterpenoids **137** and **138**.[102] Practically all free sterols from *E. fraudatrix* are subject to sulfation, however, in different degrees. Δ^5-Sterols (in the first place, cholesterol), which are consumed with food, are sulfated in the greatest degree. In contrast with sulfates, free sterols of the Δ^5 series are present in toxic holothurians in small amounts; they can be transformed into sulfates, stanols and Δ^7-sterols. Stanols and Δ^7-sterols, contrariwise, predominate in fractions of free sterols, but are sulfated in a very low degree. These peculiarities of steroid metabolism in holothurians and starfishes are explained by the presence of toxic glycosides, which react with the membrane cholesterol and other Δ^5-sterols resulting in the formation of membrane pores. This is why cholesterol and its homologues are highly toxic for holothurian cells; their substitution by $\Delta^{9(11)}$- and Δ^7-sterols, stanols and sulfates of the type **133**, which are less capable to form membrane complexes with holothurian toxins, protects these animal cells from deleterious effects of their intrinsic glycosides.[103]



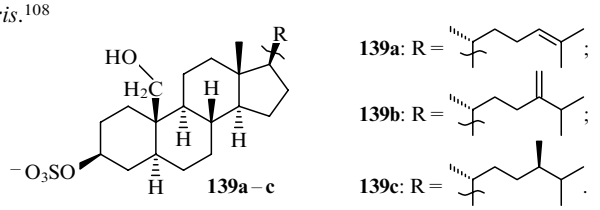
These data suggest that sulfation of free cholesterol in echinoderms is a result of their adaptation to the effects of intrinsic membranolytic toxins and that sterol sulfates fulfil a membrane-protective function by preventing the effects of these toxins on cell membranes.

Recently, Indian and Italian scientists have isolated two novel sulfated sterols **133l**,**m** from the tropical sea cucumber *Holothuria* sp.[104]

Sterol sulfates were detected not only in echinoderms but also in some other marine organisms. For example, 24-methylidene-cholesterol sulfate **133g** was detected in the diatomic microalga *Nitzchia alba* as long as 35 years ago,[105] whereas the so-called hymenosulfate **133k**, which contains an unusual side chain similar to those of some free microalgal (dynoflagellate) sterols, was found in the haptophytic microalga *Hymenomonas* sp.[106]

2. Polyhydroxysteroid monosulfates

Polyhydroxysteroid monosulfates from sponges and echinoderms contain sulfate groups in 3β- or other positions. Thus compounds **139a**–**c** containing additional hydroxy groups at C(19) were isolated from the sponge *Toxadocia zumi*.[107] A new β-1,3-glucanase inhibitor, *viz*., annasterol sulfate **140**, was isolated in our laboratory from the Pacific deep-water sponge *Poecilastra laminaris*.[108]

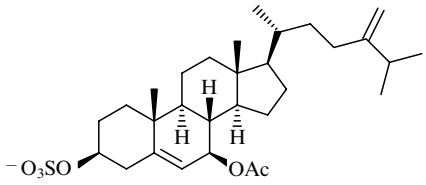


139a–**c**

139a: R = ;

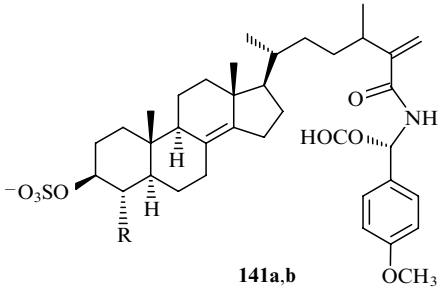
139b: R = ;

139c: R = .



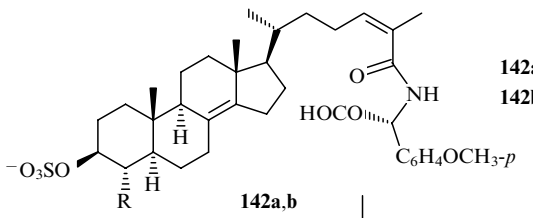
140 (annasterol sulfate)

The unusual steroid polymastiamide A (**141a**) was isolated from the sponge *Polymastia boletiformis* collected near the coasts of Norway.[109] This is the amide of a rarely occurring amino acid, *viz*., *p*-methoxyphenylglycine, and its steroidal fragment is a $\Delta^{8(14)}$-derivative methylated in position 4. Earlier, 4α-methyl-$\Delta^{8(14)}$-sterols were detected in some archaebacteria of the *Methylococcus* genus. This points to participation of symbiont bacteria in biosynthesis of compound **141a**, since archaebacteria have recently been identified as symbionts in some sponges. Polymastiamides B–F (**141b**, **142a**,**b**, **143a**,**b**) isolated from the same sponge are structurally close to polymastiamide A (**141a**). Their treatment with CH_3OH/HCl is accompanied by both migration of the double bond and aromatisation of the ring C resulting in the artificial products **144** and **145**.[110]



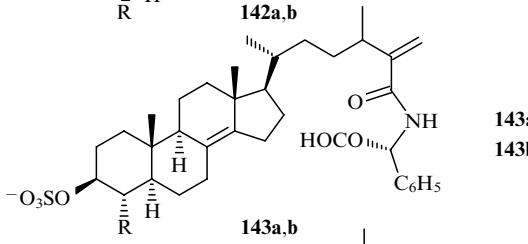
141a,**b**

141a: R = CH_3;
141b: R = H.



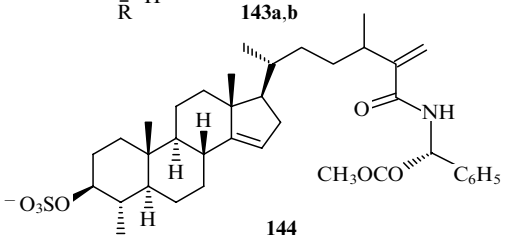
142a,**b**

142a: R = CH_3;
142b: R = H.

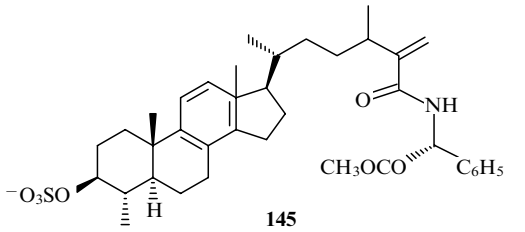


143a,**b**

143a: R = CH_3;
143b: R = H.

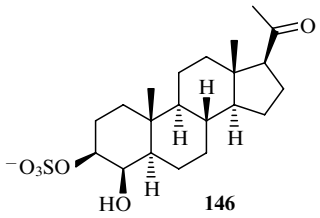


144



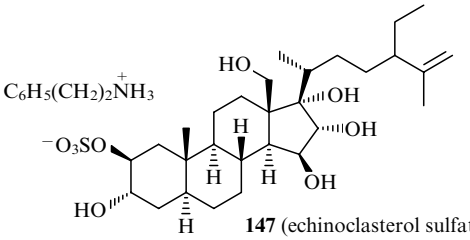
145

The steroid **146** from the sponge *Stilopus australis*[111] is unrelated to sterol derivatives, this rather resembles steroid hormones because of the presence of the pregnane skeleton.



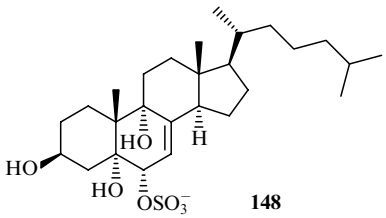
146

One of a few steroid monosulfates **147** with the sulfate group in position 2β was isolated from *Echinoclathria suhispida* collected near the coasts of Japan. Echinoclasterol sulfate **147** is a salt in which protonated tyramine is the counter-ion.[112]

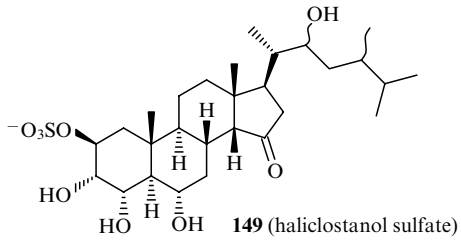


147 (echinoclasterol sulfate)

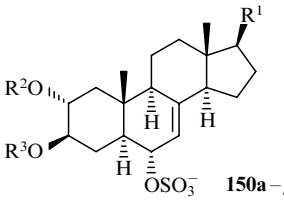
The unique cytotoxic steroid **148** containing a sulfate group in position 6α was found in the sponge *Dysidea fragilis* collected from the lagoon of Venice.[39] Haliclostanone sulfate (**149**) from the Malaysian sponge *Haliclona* still remains the only sulfated sponge steroid with an uncommon *cis*-fusion of rings *C* and *D*.[113] Sulfates of acanthosterols A–J (**150a**–**j**) from the sponge *Acanthodendrilla* sp. contain sulfate groups in position 6.[114] Thus, sponges contain various steroid metabolites, mostly those sulfated in positions 3, 2 or 6.



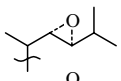
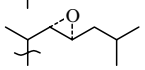
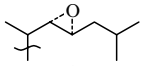
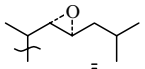
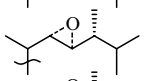
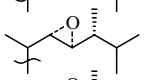
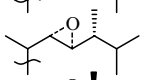
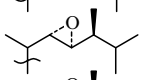
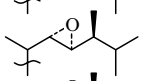
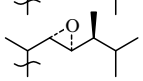
148



149 (haliclostanol sulfate)

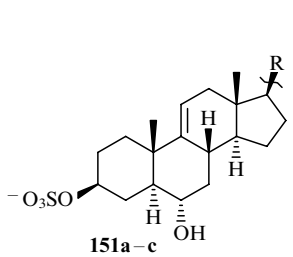


150a–**j**

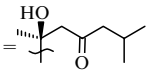
Compound **150**	R^1	R^2	R^3
a		H	H
b		H	Ac
c		H	H
d		Ac	H
e		H	Ac
f		H	H
g		Ac	H
h		H	Ac
i		H	H
j		Ac	H

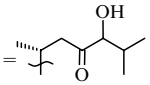
Non-glycosylated polyhydroxysteroid sulfates are abundant in starfishes and usually contain sulfate groups in the side chains. If sulfation takes place in the steroid nucleus, the sulfate group is bound to C(3), C(6), C(15) or C(16). Thus different starfish species contained steroids of the general formula **151**. Steroids **151a**,**c** are genuine algycons of many asterosaponins.[3, 115] Presumably, these compounds are biosynthetic precursors of asterosaponins, which are converted into them after the attachment of the carbohydrate chain. The related compound apheloketotriol (**151b**) was isolated from *Aphelasterias japonica*.[116]

The novel steroid **152** sulfated at C(6) was detected in the starfish *Oreaster reticulatus* together with 16 steroid glycosides and several polyhydroxysteroids.[117]

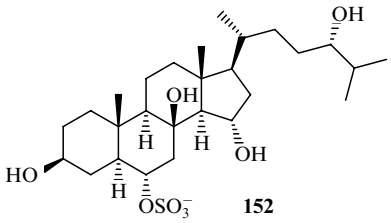


151a–**c**

151a: R =  (tornasterol A sulfate);

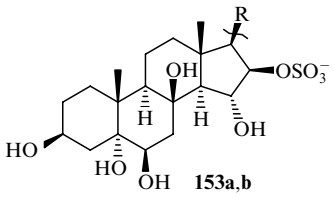
151b: R =  (apheloketotriol);

151c: R =  (asterone sulfate).

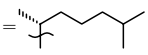


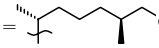
152

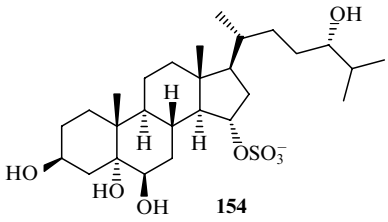
The monosulfates **153a**,**b** and **154** containing sulfate groups in position 15 or 16 were isolated from *Luidia clathrata*,[92] whereas the 3-monosulfate **155** was isolated from *L. quinaria*.[118]



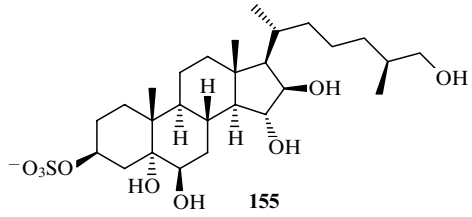
153a,**b**

153a: R = ;

153b: R = OH.



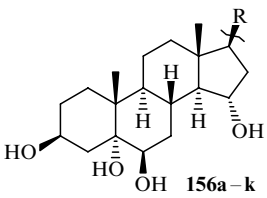
154



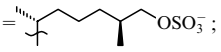
155

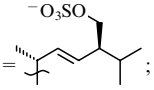
A large series of compounds **156b**–**e** containing sulfate groups in different positions of their side chains were found in *L. clathrata*.[92] The structurally related monosulfate **156a** was isolated from extracts of *Luidia ludwigi*.[119] The related sulfates **156f**–**i** from the starfish *Styracaster caroli*[120] collected at 2-km depth near the coasts of New Caledonia have highly oxygenated side chains. Sulfates **156j** and **156k** were isolated from the starfish *Ctenodiscus crispatus*.[94] Steroids **157a**–**c** sulfated in side chains and hydroxylated at C(16) of the side chains were found in *L. clathrata* [92] and *Styracaster caroli* (**157c**).[120]

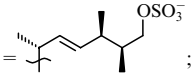
The unusual steroidal ketones, *viz*., asterosterols B and C (**158a**,**b**) containing saturated ketone fragments in rings *B* characteristic of ecdysteroids, were isolated from antarctic starfishes belonging to the Asteriidae family.[121] These animals also contained a unique sulfate **159** with a seven-membered unsaturated lactone ring. Regioisomeric lactone rings are present in brassinosteroids, the higher-plant growth stimulants.

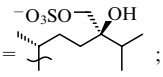


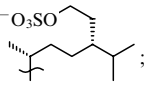
156a–**k**

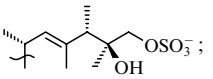
156a: R = ;

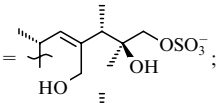
156b: R = ;

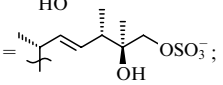
156c: R = ;

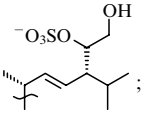
156d: R = ;

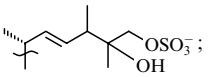
156e: R = ;

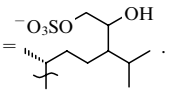
156f: R = ;

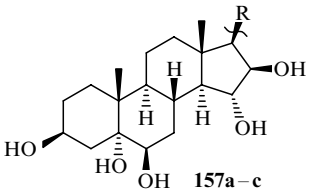
156g: R = ;

156h: R = ;

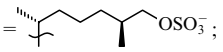
156i: R = ;

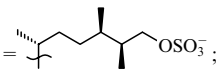
156j: R = ;

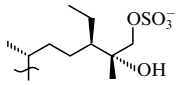
156k: R = .

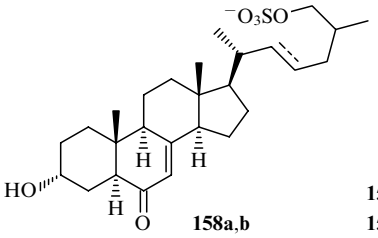


157a–**c**

157a: R = ;

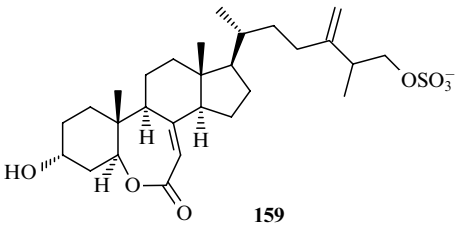
157b: R = ;

157c: R = .



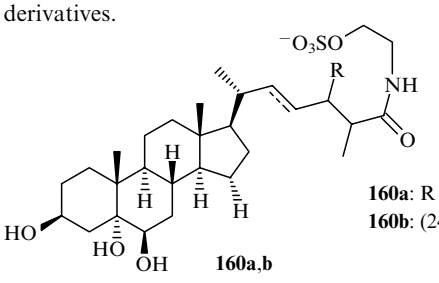
158a,**b**

158: 22,23-dihydro;
158b: Δ^{22}.



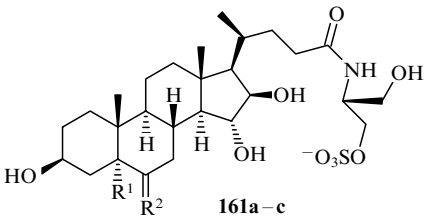
159

Finally, a group of steroid sulfates containing sulfate groups in the taurine fragments or in other sulfated amino alcohol fragments, which represent the corresponding amides, have been isolated recently from *Myxoderma platyacanthum* (compounds **160a**,**b**)[96] and *Styracaster caroli* (compounds **161a**–**c**).[122] In contrast to other starfish steroids, the latter are cholanic acid derivatives.



160a,**b**

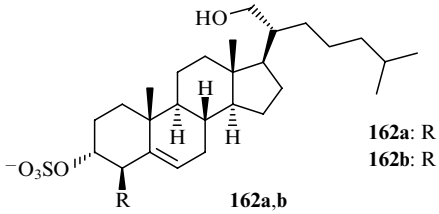
160a: R = H;
160b: (24*R*)-CH_3, Δ^{22}.



161a–**c**

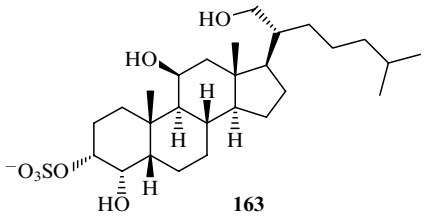
161a: R^1 = OH;
R^2 = β-OH, H;
161b: R^1 = OH;
R^2 = O;
161c: R^1 = H;
R^2 = α-OH, H.

In ophiuroids (brittle stars) belonging to yet another class of echinoderms, polyhydroxysteroid sulfates are represented predominantly by 3α-derivatives. Monosulfates are less widely distributed in these animals in comparison with di- and trisulfates, although several compounds of this type have been isolated from different representatives of the class Ophiuroidea. Thus compounds **162a**,**b** were found in Far Eastern brittle stars *Ophiura leptoctenia* and *O. sarsi*.[123, 124] The monosulfated steroid **163** was isolated from *Ophiarachna incrassata* collected near the coasts of New Caledonia.[125] Later, it was found that this compound inhibits protein kinase pp $60^{v\text{-}src}$ responsible for regulation of cell growth and intercellular signalling.[126]



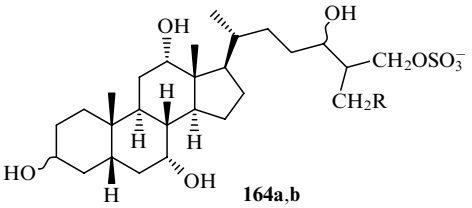
162a,**b**

162a: R = H;
162b: R = OH.



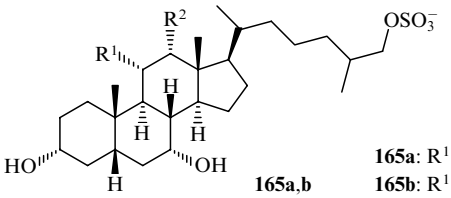
163

Sulfated bile alcohols from fishes (for an early review, see Ref. 1) are also related to polyhydroxysteroid monosulfates. Among those, scymnol sulfate **164a** isolated from the shark *Scymnus borealis* as long ago as in 1898 is the most widely known one. Recently, both C(24) epimers of this compound have been isolated from the shark *Lamna ditropis*.[127] The related bile alcohol, chymaerol sulfate **164b**, was found in the bile of two shark species, *viz*., *Lamna ditropis* and *Rhizoprionodon acutis*.[128] Three novel steroid sulfates **165a**,**b** and **166** were found in the bile of the sunfish *Mola mola*.[129] Compounds **165a**,**b** represent 25*R*- and 25*S*-isomers, whereas compound **166** represents a taurine conjugate of an acid, which differs from cholic acid in that one of its hydroxy groups occupies position 11 rather than 12. The novel sulfated pregnane derivative **167** was isolated from the urine of

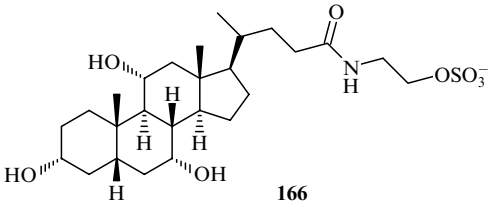


164a,**b**

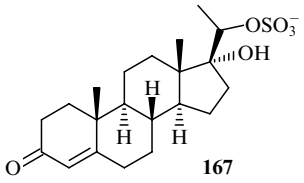
164a: R = OH, 3β-OH, 24*S* and 24*R* (scymnol sulfate);
164b: R = H, 3α-OH, 24*R* and 25*S* (chymaerol sulfate).



165a,**b** **165a**: R^1 = OH, R^2 = H; **165b**: R^1 = H, R^2 = OH.



166

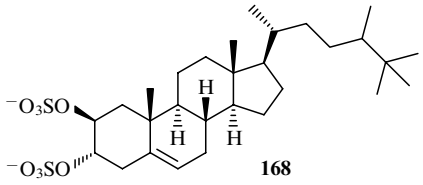


167

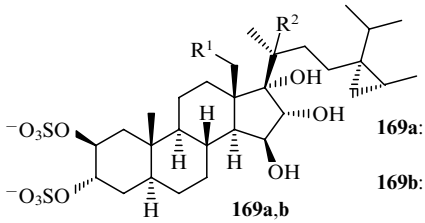
female salmon *Salmo solar*.[130] The most recent findings and the data obtained previously testify to the fact that sulfated steroids are extensively distributed in fishes.

3. Steroid disulfates

Some sponge steroids contain sulfate groups in positions 3α and 2β. This series of compounds includes compound **168**, a possible biogenetic precursor of halistanol sulfate,[131] which is the most widely occurring trisulfate of sponges, and weinbersterols A and B (**169a**,**b**) from the sponge *Petrosia weinbergi*. The latter have unique side chains containing cyclopropane fragments, which makes them different from other polysulfated sponge steroids. Steroids **169a**,**b** manifest antiviral activities against cat leukemia and mouse influenza viruses.[132] The absolute configurations (24*S*,28*S*) of weinbersterols A and B were established by comparing them with those of the free sterols, which represent biogenetic precursors of steroids **169a**,**b** isolated from the same sponge.[133]



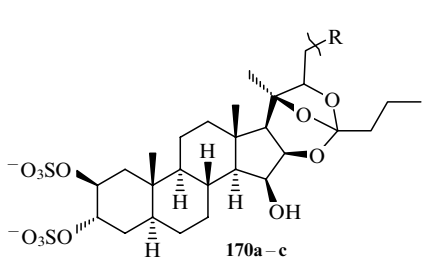
168



169a,**b** **169a**: R^1 = H, R^2 = OH (weinbersterol A); **169b**: R^1 = OH, R^2 = H (weinbersterol B).

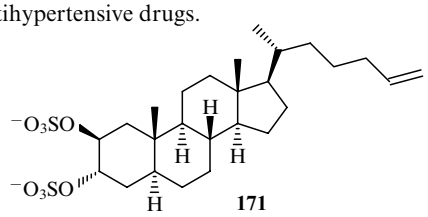
Yet another group of antiviral disulfates, the so-called orthoestrols A–C from the Caribbean sponge *P. weinbergi*,[134] comprises derivatives of orthobutyric acids. The stereochemistry of orthoestrol B (**170b**) appears as 24*R*,28*S*; that of orthoestrol C (**170c**) is 24*R*.

Halistanol B disulfate (**171**) from the South African sponge *Pachastrella* sp.[135] presents interest with regard to both its structure (its side chain contains no methyl group in position 27, which makes this compound different from cholesterol) and biological activity. It inhibits the activity of the enzyme catalysing the conversion of the protein precursor of endothelin into endothelin-1 (IC_{50} = 1.3 μg ml^{-1}). Endothelin induces vascular



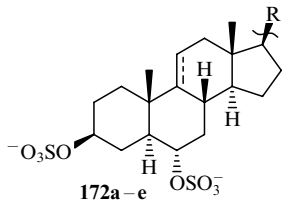
170a–**c** **170a**: R = (orthoestrol A); **170b**: R = (orthoestrol B); **170c**: R = (orthoestrol C).

spasms and is abundant in patients with hypertension and renal insufficiency. Compound **171** as an inhibitor of endothelin synthesis is a promising model substance for development of new antihypertensive drugs.



171

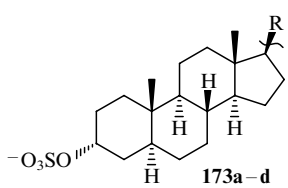
A series of steroid disulfates were found in starfishes and ophiuroids. Thus compounds **172a**–**d** were isolated from the starfish *Tremaster novaecaledonia*[136] and compound **172e**, from *Aphelasterias japonica*.[137]



172a–**e**

172a: R = , Δ^0; **172b**: R = , Δ^0; **172c**: R = , $\Delta^{9(11)}$; **172d**: R = , $\Delta^{9(11)}$; **172e**: R = , $\Delta^{9(11)}$.

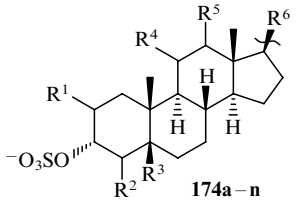
In contrast to their starfish counterparts, steroid disulfates isolated from ophiuroids have a number of specific structural features. In nearly all of them, one sulfate group is in position 3α and the second one is in the side chain at C(21). These steroids comprise stanol derivatives as well as 5(6)-unsaturated derivatives. For example, sulfated stanols of the general formulas **173** and **174** are widely distributed in various representatives of this class, *e.g.*, in more than 30 species of Ophiuroidea.[3,99] Disulfate **173a**, which was first discovered together with compound **173b**,**c** in *Ophioderma longicaudum*[138] and later in different species of Ophiuridae, Gorgonocephalidae and Asteronychnidae families,[99] is the most widespread disulfate of the general formula **173**. The steroid **173d** was isolated from the antarctic brittle star *Astrotoma agassizii*.[139]



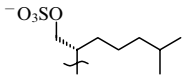
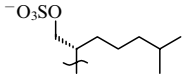
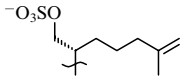
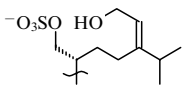
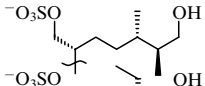
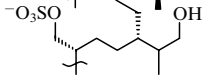
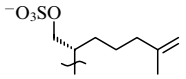
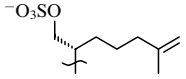
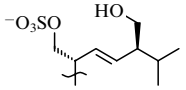
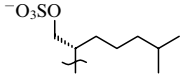
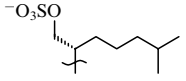
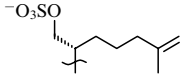
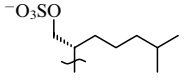
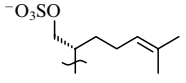
173a–**d**

173a: R = ; **173b**: R = ; **173c**: R = ; **173d**: R = , 2β-OH.

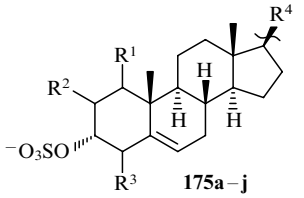
Steroid disulfates of many ophiuroids are characterised by *cis*-fusion of rings *A* and *B*. For example, compound **174a** first described by Italian scientists in 1985[140] was later discovered in various representatives of the *Ophiocoma*, *Ophioarthrum*, *Ophiolepis*, *Ophionereis* and *Ophiozona* genera.[3,99] The steroid **174b** was found in *Ophiocoma dentata*, *Ophioarthrum elegans*, *Ophiorachna incrassata*, *Ophiolepis superba* and *Ophiomastix annulosa*.[3] The steroid **174c**, which differs from the latter in the structure of its side chain, was first discovered in *Ophiocoma dentata*,[3] whereas compounds **174d**–**f** were found in *Ophiolepis superba*, which also contains additionally oxygenated derivatives **174g**,**h**,**i**.[141] The steroid **174j** containing an additional hydroxy group at C(12) was isolated from *Ophioderma longicaudum*,[138] whereas steroids **174k**,**l** were isolated from *Ophiomastix annulosa*[142] and *Ophiopholis superba*.[141] The steroid **174m** containing an unusual 5,9-epoxy fragment was found in *Ophiomastix annulosa*[142] and compound **174n** was detected in the antarctic ophiura *Astrotoma agassizi*.[139]



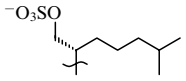
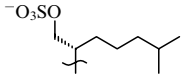
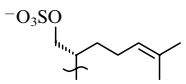
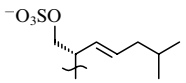
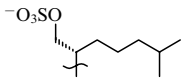
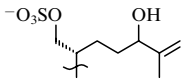
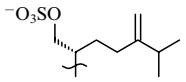
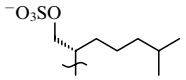
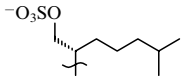
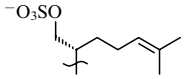
174a–**n**

Compound **174**	R^1	R^2	R^3	R^4	R^5	R^6
a	H	α-OH	H	β-OH	H	
b	H	α-OH	H	H	H	
c	H	α-OH	H	H	H	
d	H	α-OH	H	H	H	
e	H	α-OH	H	H	H	
f	H	α-OH	H	H	H	
g	H	α-OH	β-OH	H	H	
h	β-OH	α-OH	H	H	H	
i	β-OH	α-OH	H	H	H	
j	H	α-OH	H	β-OH	β-OH	
k [$\Delta^{9(11)}$]	H	α-OH	H	H	H	
l	H	α-OH	α-OH	H	H	
m	H	4α,9α-epoxy	H	H	H	
n	β-OH	H	H	H	H	

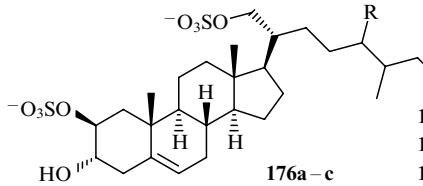
5(6)-Unsaturated steroids of the general formula **175** are often present in ophiuroids. Thus compounds **175a** and **175b** were isolated from the Far Eastern brittle star *Ophiura sarsi*[124] and steroids **175c-f** were isolated from *Ophiopholis aculeata*.[143] The steroid **175a** was also isolated from *Ophiura texturata*,[144] *Gorgonocephalus caryi*,[145] *Ophiotrix fragilis*[2] and some other species. The steroid **175g** was found in *O. texturata*,[144] the steroid **175h** was detected in *Ophiarachna incrassata*.[140] The disulfate **175i** containing three functional groups in the ring *A* was isolated from the antarctic brittle star *Ophiosparte gigas*[146] as well as from *Astroclades exiguus* and *Amphiophiura ponderosa*.[147]



175a–**j**

Compound **175**	R^1	R^2	R^3	R^4
a	H	H	β-OH	
b	H	β-OH	H	
c	H	H	β-OH	
d	H	H	β-OH	
e	H	β-OH	H	
f (24*S* and 24*R*)	H	β-OH	H	
g	H	H	β-OH	
h	β-OH	H	H	
i	H	β-OH	β-OH	
j	H	β-OH	H	

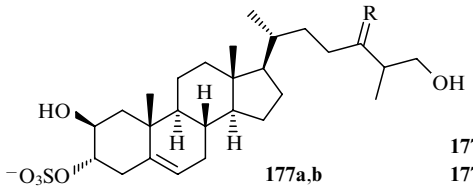
The unusual steroid disulfate **176a** was detected in the brittle star *Ophiosparte gigas*.[146] It contains a sulfate group in position 2β but not in position 3α, like other sulfates of this series. Later, this disulfate was isolated from several other representatives of this class.[99] Its 24(25)-unsaturated derivative **176b** and related ophiuroid disulfates **175j** and **174n** from *Astrotoma agassizii*[139] and their acetates manifested strong antiviral activities against the pathogenic virus HSV-2, which evokes meningitis and other severe infections in humans.[147]



176a–**c**

176a: R = H, X = H;
176b: R = H, X = H, Δ^{24};
176c: R = H, X = OH.

The typical ophiuroid steroids **175a**,**b** and **176a** were unexpectedly found in the starfishes of the *Pteraster* genus.[148] These compounds differ from steroids of the majority of other starfish species in the stereochemistry of substituents at C(3) (3α instead of more common 3β) and oxygenation at C(21). A detailed analysis of steroids isolated from this group of starfishes led to the discovery of a compound earlier identified in ophiuroids (compound **175g**) and novel compounds **176c** and **177a**,**b** which combine structural features of steroids from brittle stars (*e.g.*, oxygenation in positions 3α and 21) and starfish (*e.g.*, oxygenation in position 26).[149] The presence of the same or structurally related secondary metabolites in brittle stars and starfishes corroborates the viewpoint of some taxonomists that these two classes of echinoderms are phylogenetically more closely related in comparison with other classes of Echinodermata.



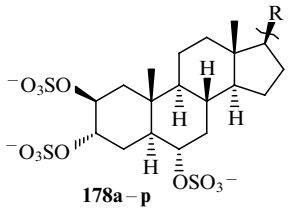
177a,**b**

177a: R = CH_2;
177b: R = H_2.

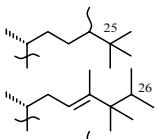
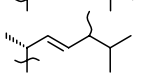
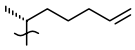
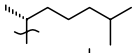
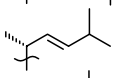
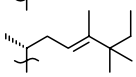
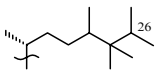
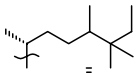
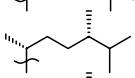
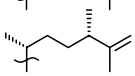
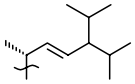
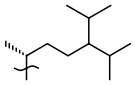
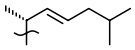
Disulfates from ophiuroids manifest the properties of activators of some enzymes, particularly glucanases.[150] Steroids of the Δ^5-series isolated from *Ophiopholis aculeata* activate the transport of calcium ions into different cells without disturbing the integrity of biomembranes.[151]

4. Steroid trisulfates

Trisulfated polyhydroxysteroids are typical representatives of marine metabolites. They were found in sponges and echinoderms.[1, 17, 99, 152] Halistanol sulfate (**178a**), the most widespread sponge steroid sulfate, was isolated from the sponge *Halichondria moori* in 1981 by Fusetani *et al.*[153] It contains three sulfate groups in rings *A* and *B* of the steroid tetracyclic nucleus. The structure of socotrasterol sulfate (**178b**) isolated repeatedly from different sponges was established in our laboratory.[154] Both compounds have unusual side chains, which are additionally alkylated (compared with those of terrestrial sterols). The side chain of socotrasterol sulfate is unique in that it contains two 'extra' methyl groups at C(26) and a 23(24) double bond uncommon for natural steroids. A large series of analogous natural compounds have been isolated from different sponges. These include halistanol sulfates A–D (**178c**–**f**) from *Epipolasis* sp.,[155] norsocotrasterol sulfate (**178g**) from sponges of the *Halichondridae* family,[156] dihydrosocotrasterol sulfate (ophirapstanol sulfate) **178h** from *Topsentia ophiraphidites*,[157] halistanol sulfates F–H (**178i**–**k**) from *Pseudaxinyssa digitata*,[158] compound **178l** from *Trachiopsis halichondroides*[159] and steroids **178m**–**p** from *T. halichondroides* and *Cymbastella coralliophila*.[160]

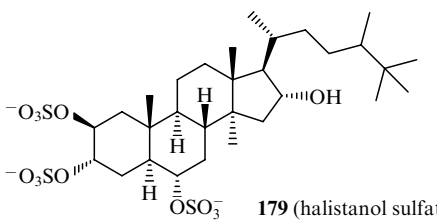


178a–**p**

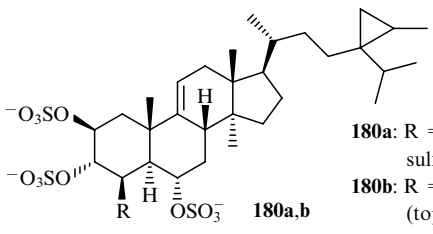
Compound **178**	Name	R
a	halistanol sulfate	
b	socotrasterol sulfate	
c	halistanol sulfate A	
d	halistanol sulfate B	
e	halistanol sulfate C	
f	halistanol sulfate D	
g	26-norsocotrasterol sulfate	
h	ophirapstanol sulfate	
i	halistanol sulfate F	
j	halistanol sulfate G	
k	halistanol sulfate H	
l	–	
m	–	
n	–	
o	–	
p	–	

The sulfated steroids of this series manifest a broad range of biological activities (*e.g.*, antimicrobial, hemolytic, ichthyotoxic, *etc.*), inhibit HIV-1-induced infection,[161] suppress the activities of some enzymes including that of β-1,3-glucanase[162] and interact with the thrombin receptor.[155]

Several related trisulfates have recently been identified in sponges. These include halistanol sulfate E (**179**) from *Epipolasis* sp.,[155] which contains an additional hydroxy group at C(16), ibisterol sulfate **180a** from the sponge *Topsentia* sp., which inhibits HIV-1 and, in contrast to related steroids, possesses a 9(11)-double bond and an unusual side chain with a cyclopropane fragment.[163] Topsentiasterols **180b** and **181a**–**d** from an unidentified sponge of the *Topsentia* genus carry hydroxy groups at C(4) and in the majority of cases contain oxygenated side chains. These compounds possess antimicrobial properties.[164]

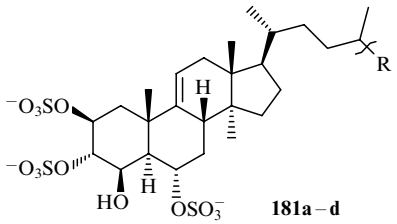


179 (halistanol sulfate E)

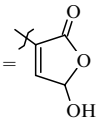


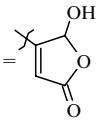
180a,**b**

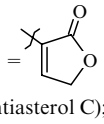
180a: R = H (ibisterol sulfate);
180b: R = OH (topsentiasterol E).



181a–d

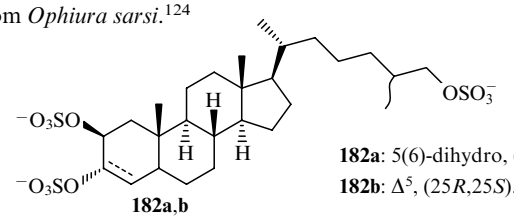
181a: R =  (topsentiasterol A);

181b: R =  (topsentiasterol B);

181c: R =  (topsentiasterol C);

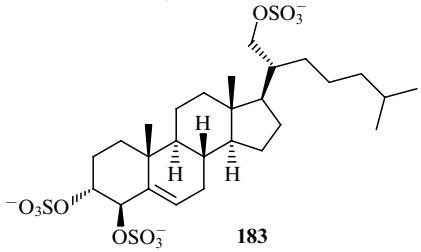
181d: R =  (topsentiasterol D).

Several trisulfated steroids were found in echinoderms, particularly in ophiuroids. Thus steroids **182a**,**b** were isolated from *Ophiorachna incrassata* extracts[3] and the steroid **183** was isolated from *Ophiura sarsi*.[124]



182a,**b**

182a: 5(6)-dihydro, (25*R*,25*S*);
182b: Δ^5, (25*R*,25*S*).



183

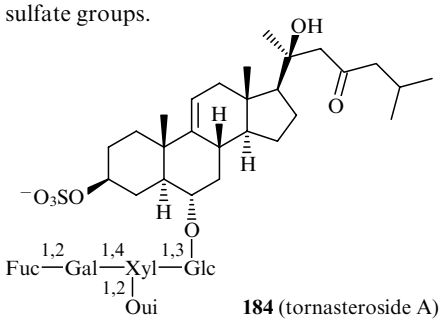
On the whole, sulfated steroids present substantial interest owing to their unusual chemical structures and biological activities. Some of them are attractive objects for synthetic modelling aimed at the design of novel antimicrobial, antiviral and other drugs. It is of note that sulfated steroids seem to be absent in Coelenterata. In any case, none has been isolated from these invertebrates so far.

IV. Steroid glycosides

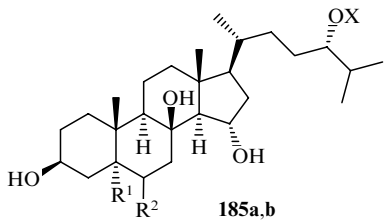
Over a long time, steroid glycosides were considered to be typical metabolites of higher plants; however, in the last 25–30 years they were isolated from starfishes along with the corresponding polyols and sulfates.[1,3] Later, they were found in sponges, cnidarians and fishes of the *Pardachiras* genus. A small review devoted to marine steroid glycosides was published in 1996.[165] Therefore, in this section we shall consider the results of the most recent studies published 4–6 years ago and those data which have not been discussed in this review.

Marine steroid glycosides, like any other marine polar steroids, have original structures, no one of them coincides with the structures of glycosides isolated from taxonomically remote biological sources, such as terrestrial plants.

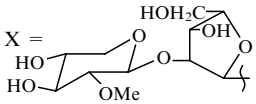
Starfish glycosides are conventionally divided into several large groups,[3] *viz*., (i) steroid glycosides, which are sulfated at C(3) [their carbohydrate chains are attached at O(6) (classical asterosaponins)]; (ii) mono- and biosides of polyhydroxylated steroid, containing as a rule carbohydrate residues in their side chains and (iii) glycosides containing carbohydrate fragments attached to C(3) and C(6) of the aglycons to form macrocycles. The structures of individual representatives of these groups are given below. Glycosides related to the first structural type, *e.g*., tornasteroside A (**184**)[166] from *Acanthaster planci* (a starfish commonly referred to as the 'crown of thorns'), differ from each other in both the structures of their carbohydrate chains which usually contain from four to six monosaccharide residues and in the structures of the aglycon side chains. Glycosides related to yet another structural type, *e.g*., nodososide (**185a**) from *Protoreaster nodosus*[167] and asterosaponin P_1 (**185b**) from *Asterina* (= *Patiria*) *pectinifera*[168]), are structurally very diverse and may contain sulfate groups.

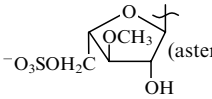


184 (tornasteroside A)

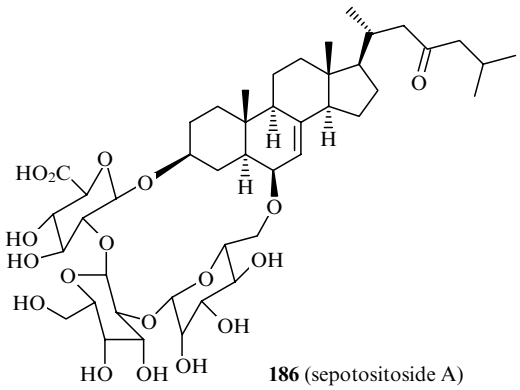


185a,**b**

185a: R^1 = OH, R^2 = β-OH, X =  (nodososide);

185b: R^1 = H, R^2 = α-OH, X =  (asterosaponin P_1).

Glycosides containing carbohydrate chains involved in a macrocycle exemplified in sepositoside A (**186**)[169] were detected only in a few species of starfishes of the *Echinaster* genus.



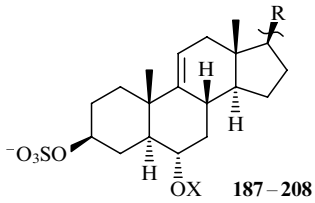
186 (sepotositoside A)

Classical asterosaponins are usually present in starfishes as complex mixtures; they are toxic to fishes, manifest cytotoxic and hemolytic activities, are predominantly accumulated in animal body walls and probably fulfil protective functions. All these compounds contain aglycons of the same structural type with a 9(11) double bond and a sulfate group at C(3), the aglycon of tornasteroside A being the most common fragment.

Tetraosides usually possess linear carbohydrate chains, whereas the carbohydrate chains of penta- and hexaosides have one or (more seldom) two branch points, predominantly at the second monosaccharide of the chain. Monosaccharides are represented mostly by pyranose forms of D-fucose, D-quinovose, D-glucose, D-galactose, D-xylose and 6-deoxy-D-*xylo*-hexos-4-

ulose (the latter contains the hydrated keto group in position 4). The glycosidic bonds have usually β-configurations.

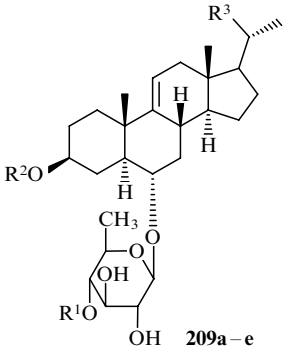
Quite a lot of novel asterosaponin oligoglycosides have recently been isolated from starfishes (Table 2). For example, the so-called nipoglycosides A – D (**187** – **190**) were isolated from the starfish *Distolasterias nipon*[170] and brasiliensoside (**191**) was isolated from *Echinaster brasiliensis*.[171] In contrast with the glycosides from the other two species of this genus, these glycosides are devoid of carbohydrate chains incorporated in a macrocycle. Cosmasterosides A – D (**192** – **195**) containing two xylose residues each in their carbohydrate chains were isolated from the starfish *Cosmasterias lurida*.[172]



187 – **208**

In contrast to most asterosaponins containing five to six sugar residues, compounds **194** and **195** have only four monosaccharide residues. Reticulatosides A and B (**196**, **197**) and asterosaponin (**198**) containing a pregnane aglycon were found in *Oreaster reticulatus*.[117] About 20 steroid glycosides including the novel asterosaponins **199** – **203** were isolated from a non-identified starfish species belonging to the Echinasteriidae family collected near Antarctic coasts by Italian scientists,[173] whereas asteriidosides A – E (**204** – **208**) were isolated from a non-identified Antarctic species belonging to the Asteriidae family.[174]

Asterosaponin-like glycosides with 'shortened' carbohydrate chains were first isolated from *Asterias forbesi*[175, 176] and *Lethasterias nanimensis chelifera*.[115] Forbesides E, E_1, E_2 and E_3 (**209a** – **d**) and cheliferoside L_1 (**209e**) represent pregnane mono-

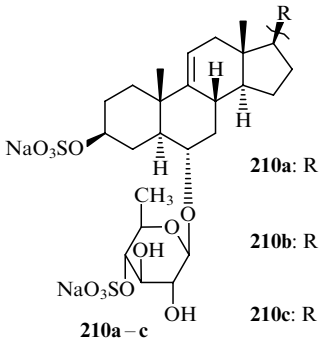


209a – **e**

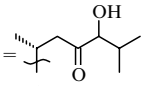
Compound **209**	Name	R^1	R^2	R^3
a	forbeside E	SO_3Na	SO_3Na	OH
b	forbeside E_1	H	SO_3Na	OH
c	forbeside E_2	SO_3Na	H	OH
d	forbeside E_3	H	SO_3Na	O
e	cheliferoside L_1	SO_3Na	SO_3Na	O

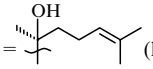
quinovosides; most of them contain additional sulfate groups in their monosaccharide residues.

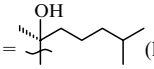
Aphelasteroside C (**210a**) from *Aphelasterias japonica* differs from cheliferoside L_1 (**209e**) in its relatedness to cholestane, rather than to pregnane derivatives; its side chain contains a 23-keto-24-hydroxy fragment uncommon for asterosaponins.[116] Latespinosides A – D (**210b**,**c**, **211**, **212**) from *Asteropecten latespinus* differ from aphelasteroside C (**210a**) exclusively in the structures of their side chains, compound **212** being the first androstane steroid isolated from starfishes.[177]

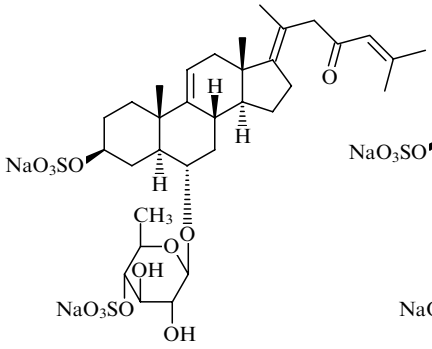


210a – **c**

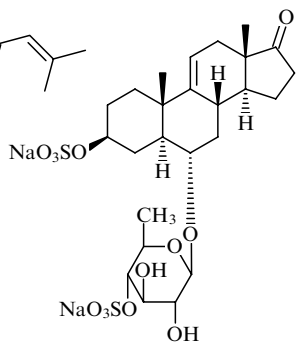
210a: R =  (aphelasteroside C);

210b: R =  (latespinoside A);

210c: R =  (latespinoside B).

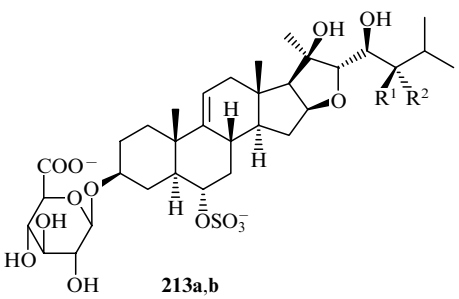


211 (latespinoside C)



212 (latespinoside D)

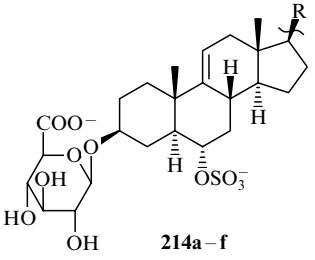
Yet another recently discovered group of asterosaponins with shortened carbohydrate chains includes downeosides (**213** – **216**) from *Henricia downeyae*.[178, 179] These compounds contain one or two monosaccharide residues in their carbohydrate fragments; their high polarities are due to the presence of glucuronic acid residues, which are not common in 'classical' asterosaponins, but are present in cyclic asterosaponins. In contrast to other asterosaponins, the carbohydrate fragments in these glycosides are bound to C(3) atoms, whereas their sulfate groups are bound to C(6). Downeyosides A and B (**213a**,**b**) possess additional tetrahydrofuran rings and side chains containing three contiguous hydroxy groups at C(20), C(22) and C(23), which is uncommon for natural steroids. Downeyosides C – G and J (**214a** – **f**) resemble 'classical' asterosaponins in the structures of their side chains, whereas downeyosides K and L (**215a**,**b**) contain additional hydroxy groups at C(16). And, finally, downeyosides H and I



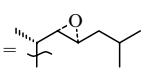
213a,**b**

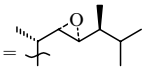
213a: $R^1 = CH_3$, $R^2 = H$ (downeyoside A);

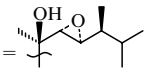
213b: $R^1 = H$, $R^2 = CH_3$ (downeyoside B).

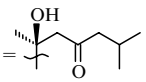


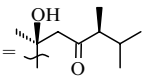
214a – **f**

214a: R =  (downeyoside C);

214b: R =  (downeyoside D);

214c: R =  (downeyoside E);

214d: R =  (downeyoside F);

214e: R =  (downeyoside G);

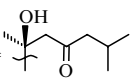
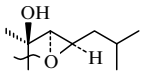
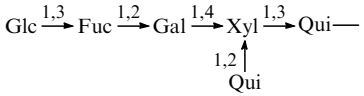
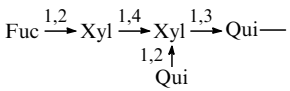
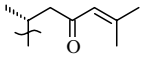
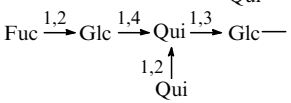
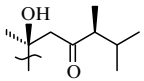
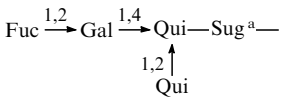
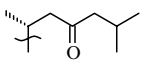
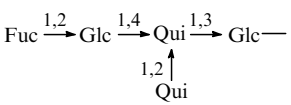
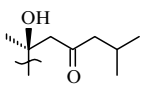
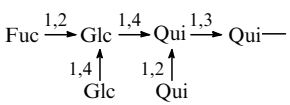
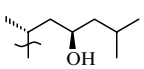
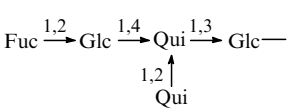
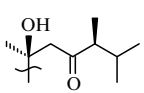
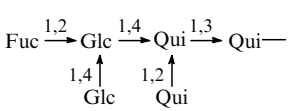
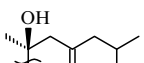
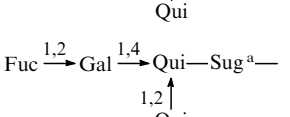
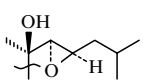
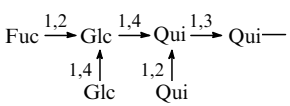
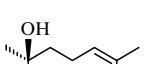
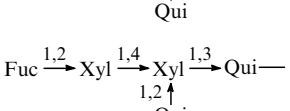
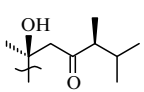
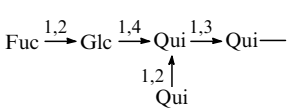
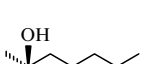
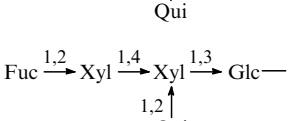
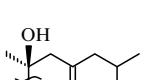
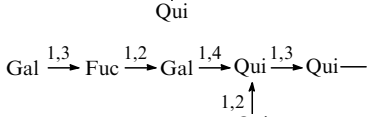
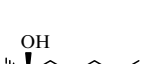
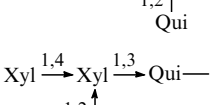
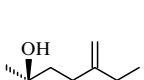
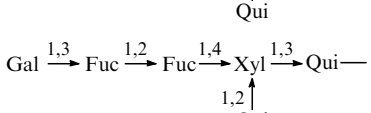
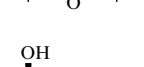
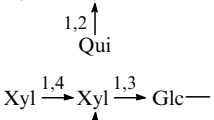
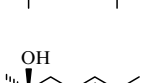
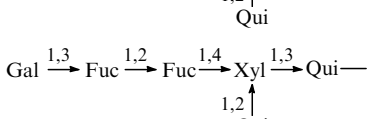
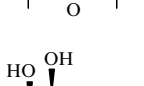
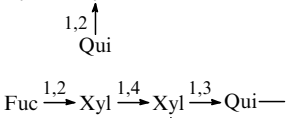
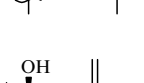
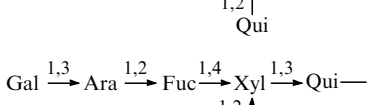
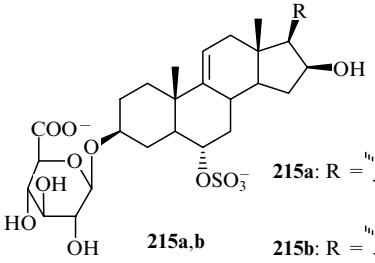
214f: R =  9(11)-dihydro, (downeyoside J) .

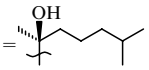
Table 2. Asterosaponins isolated from starfishes.

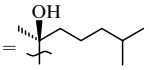
Compound	Name	The structure of the side chain (R)	The structure of the carbohydrate chain (X)	Ref.	Compound	Name	The structure of the side chain (R)	The structure of the carbohydrate chain (X)	Ref.
187	nipoglycoside A			170	**198**	–			117
188	nipoglycoside B			170	**199**	24-methylbrasiliensoside			173
189	nipoglycoside C			170	**200**	antarcticoside A			173
190	nipoglycoside D			170	**201**	antarcticoside B			173
191	brasiliensoside			171	**202**	antarcticoside C			173
192	cosmasteroside A			172	**203**	24-methylpectenoside A			173
193	cosmasteroside B			172	**204**	asteriidoside A			174
194	cosmasteroside C			172	**205**	asteriidoside B			174
195	cosmasteroside D			172	**206**	asteriidoside C			174
196	reticulatoside A			117	**207**	asteriidoside D			174
197	reticulatoside B			117	**208**	asteriidoside E			174

[a] Sug is 6-deoxy-*xylo*-hexos-4-ulose.

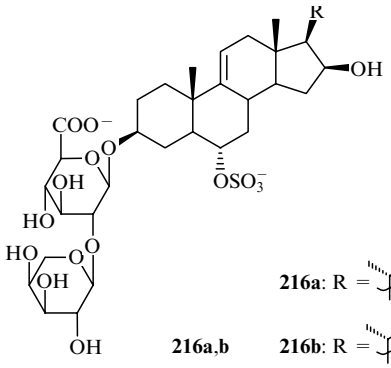


215a,**b**

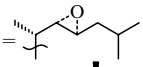
215a: R =  (downeyoside K);

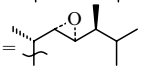
215b: R = ,

9(11)-dihydro (downeyoside L).



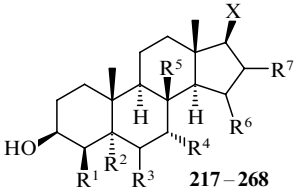
216a,**b**

216a: R =  (downeyoside H);

216b: R =  (downeyoside I).

(**216a**,**b**) are biosides, each containing an additional L-arabinose residue bound to glucuronic acid by α-glycosidic bond.

In recent years, the list of newly discovered mono- and biosides of polyhydroxysteroids has been supplemented with more than 50 new names (Table 3).

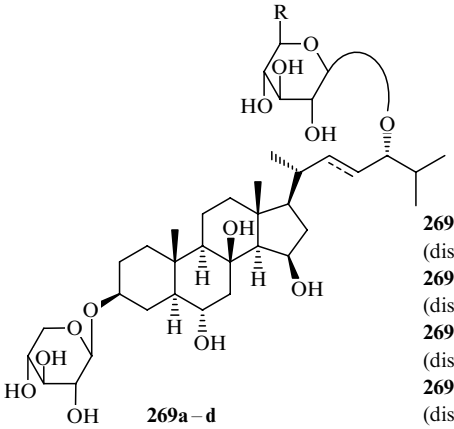


217–**268**

As a rule, the carbohydrate fragments of these compounds are bound to C(24) or C(26) (cholestane series), to C(28) or C(26) (ergostane series) and to C(29) or C(26) (stigmastane series). Xylose, its various methylated derivatives (in a pyranose form), arabinose and 3-*O*-methylarabinose (in a furanose form) are the monosaccharide components. Glucopyranose, arabinopyranose, xylofuranose, galactofuranose and fucofuranose are found less often. The glycosides of this series contain sometimes one or several sulfate groups in the carbohydrate part and the aglycons. In biosides, the monosaccharides are linked by 1,2-bonds or, less frequently, by 1,5- and 1,6-bonds (the author's data), *e.g.*, as in compounds **262**, **264**–**267**.[184–186]

Novel structural series of glycosides recently discovered in starfishes include compounds containing two monosaccharide fragments, *viz*., one at C(3) and the other in the side chain. Some representatives of this class, *viz*., distolasterosides D_1–D_3 (**269a**–**c**) were found in *Distolasterias nipon*.[187] Reinvestigations of polar steroids from the same species collected near the coasts of Japan led to the isolation of yet another steroid bisglycoside, *viz*., distolasteroside D_4 (**269d**) and distolasteroside D_5 (**270**), which contains a sulfate group instead of a monosaccharide residue at C(3).[170]

In the most recent times, this group of compounds was further expanded owing to asteriidosides F–I (**271a**,**b** and **272a**,**b**)

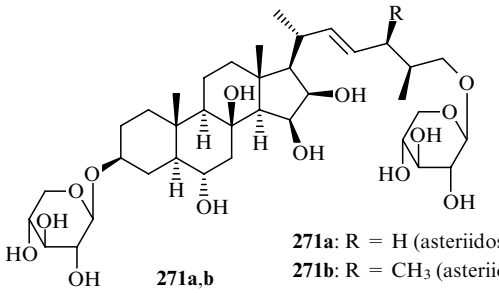


269a–**d**

269a: R = H (distolasteroside D_1);
269b: R = H, Δ^{22} (distolasteroside D_2);
269c: R = CH_2OH (distolasteroside D_3);
269d: R = $CH_2OSO_3^-$ (distolasteroside D_4).

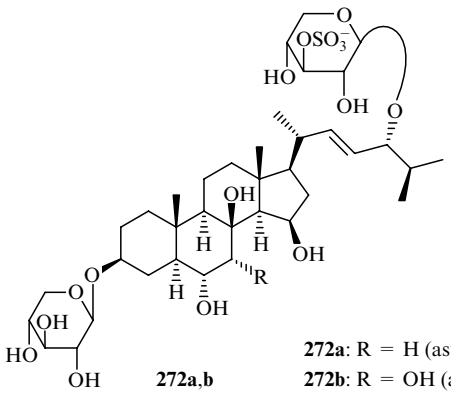
270 (distolasteroside D_5)

isolated from the Antarctic starfish belonging to Asteriidae gen. sp.[174] and echinasterosides B_1 (**273**) and F (**274**) from *Echinaster sepositus*[188] and *E. brasiliensis*,[171] respectively.



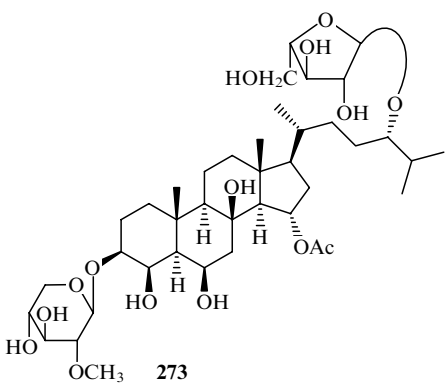
271a,**b**

271a: R = H (asteriidoside F);
271b: R = CH_3 (asteriidoside G).



272a,**b**

272a: R = H (asteriidoside H);
272b: R = OH (asteriidoside I).



273

Table 3. Some novel polyhydroxysteroid glycosides isolated from starfishes.

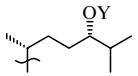
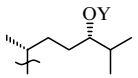
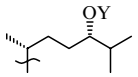
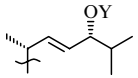
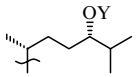
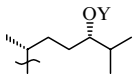
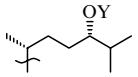
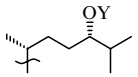
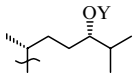
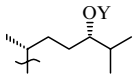
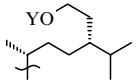
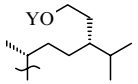
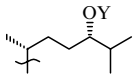
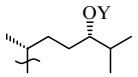
Compound	Name	R^1	R^2	R^3	R^4	R^5	R^6	R^7	The side chain (X) (the double bond)	The carbohydrate fragment (Y)	The source	Ref.
217	validoside A	OH	H	6α-SO_3^-	H	OH	β-OH	H		2,4-$(OCH_3)_2$-Xyl_p-(1→2)-Ara_f	*Odontaster validus*	180
218	validoside B	H	H	α-OH	H	OH	β-OH	H		2-SO_3-3-OCH_3-Xyl_p	*Odontaster validus*	180
219	luridoside A	H	H	α-OH	H	OH	β-OH	H		4-SO_3-Xyl_p	*Cosmasterias lurida*	181
220	luridoside B	H	H	α-OH	H	OH	β-OH	H		4-SO_3-Xyl_p	*Cosmasterias lurida*	181
221	helianthoside	H	H	α-OH	H	OH	α-OH	H		3-SO_3-Xyl_p	*Heliaster helianthus*	182
222	oreasteroside A	H	H	α-OH	H	OH	α-OH	H		3-OCH_3-Ara_f	*Oreaster reticulatus*	117
223	oreasteroside B	H	H	α-OH	H	OH	α-OH	H		Xyl_p-(1→2)-3-OCH_3-Ara_f	*Oreaster reticulatus*	117
224	oreasteroside C	H	H	α-OH	H	OH	α-OH	H		2-OCH_3-Xyl_p-(1→2)-Ara_f	*Oreaster reticulatus*	117
225	oreasteroside D	H	H	α-OH	H	OH	α-OH	H		2-OCH_3-Xyl_p-(1→2)-3-OCH_3-Ara_f	*Oreaster reticulatus*	117
226	oreasteroside E	H	H	α-OH	H	OH	β-OH	H		Xyl_p-(1 → 2)-3-OCH_3-Ara_f	*Oreaster reticulatus*	117
227	oreasteroside F	H	H	α-OH	H	OH	α-OH	β-OH		5-OCH_3-Gal_f	*Oreaster reticulatus*	117
228	oreasteroside G	H	H	6α-SO_3^-	H	OH	α-OH	β-OH		5-OCH_3-Gal_f	*Oreaster reticulatus*	117
229	oreasteroside H	H	H	6α-SO_3^-	H	OH	α-OH	H		3-OCH_3-Ara_f	*Oreaster reticulatus*	117
230	oreasteroside I	H	H	6α-SO_3^-	H	OH	α-OH	H		Ara_f	*Oreaster reticulatus*	117

Table 3 (continued).

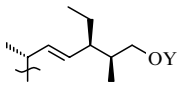
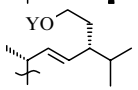
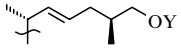
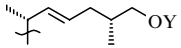
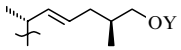
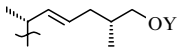
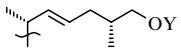
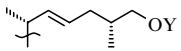
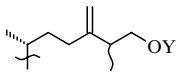
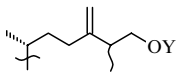
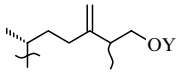
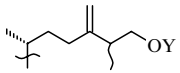
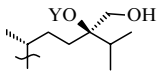
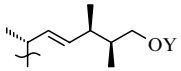
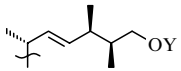
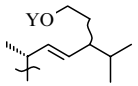
Compound	Name	R^1	R^2	R^3	R^4	R^5	R^6	R^7	The side chain (X) (the double bond)	The carbohydrate fragment (Y)	The source	Ref.
231	oreasteroside J	H	H	α-OH	OH	OH	β-OH	β-OH		2-SO_3-3-OCH_3-Xyl_p	*Oreaster reticulatus*	117
232	oreasteroside K	H	H	α-OH	OH	OH	β-OH	β-OH		2-SO_3-3-OCH_3-Xyl_p	*Oreaster reticulatus*	117
233	antarcticoside D	OH	H	α-OH	H	OH	β-OH	H		3-OCH_3-Xyl_p	Echinasteridae gen. sp.	91
234	antarcticoside E	OH	H	α-OH	H	OH	β-OH	H		3-OCH_3-Xyl_p	Echinasteridae gen. sp.	91
235	antarcticoside F	OH	H	α-OH	H	OH	β-OH	H		2,4-$(OCH_3)_2$-Xyl_p-(1→2)-Ara_f	Echinasteridae gen. sp.	91
236	antarcticoside G	OH	H	α-OH	H	OH	β-OH	H		Xyl_p-(1→2)-Ara_f	Echinasteridae gen. sp.	91
237	antarcticoside H	OH	H	α-OH	H	OH	β-OH	H		Ara_f	Echinasteridae gen. sp.	91
238	antarcticoside I	OH	H	α-OH	H	OH	β-OH	H		Gal_f	Echinasteridae gen. sp.	91
239	antarcticoside J	OH	H	α-OH	H	OH	β-OH	H		4-SO_3-3-OCH_3-Xyl_p	Echinasteridae gen. sp.	91
240	antarcticoside K	OH	H	α-OH	H	OH	β-OH	H		3-OCH_3-Xyl_p	Echinasteridae gen. sp.	91
241	antarcticoside L	OH	H	α-OH	H	OH	β-OH	H		4-OCH_3-Xyl_p-(1→2)-Gal_f	Echinasteridae gen. sp.	91
242	antarcticoside M	OH	H	α-OH	H	OH	β-OH	H		4-OCH_3-Xyl_p-(1→2)-Ara_f	Echinasteridae gen. sp.	91
243	antarcticoside N	OH	H	α-OH	H	OH	β-OH	H		Ara_f	Echinasteridae gen. sp.	91
244	antartcicoside O	OH	H	6α-SO_3^-	H	OH	β-OH	H		3-OCH_3-Glc_p	Echinasteridae gen. sp.	91
245	antarcticoside P	OH	H	6α-SO_3^-	H	OH	β-OH	H		2,4-$(OCH_3)_2$-Xyl_p-(1→2)-Gal_f	Echinasteridae gen. sp.	91
246	ceramasteroside C_1	OH	H	α-OH	H	OH	β-OH	β-OH		2-OCH_3-Xyl_p-(1→2)-Gal_f	*Ceramaster patagonicus*	89

Table 3 (continued).

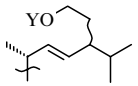
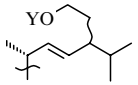
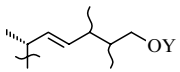
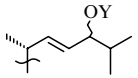
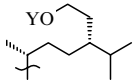
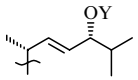
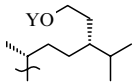
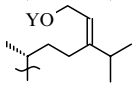
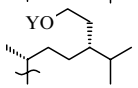
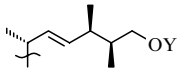
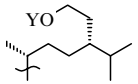
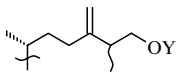
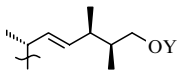
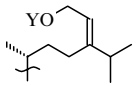
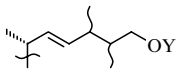
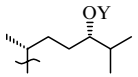
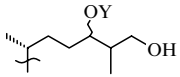
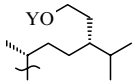
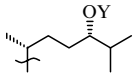
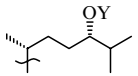
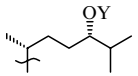
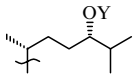
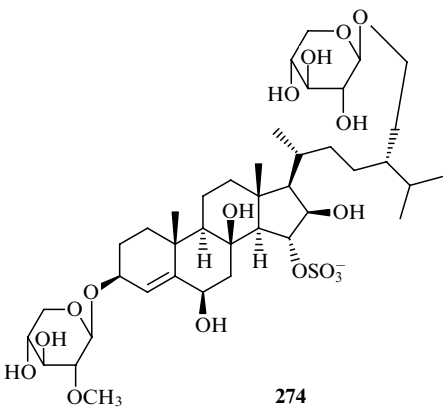
Com-pound	Name	R^1	R^2	R^3	R^4	R^5	R^6	R^7	The side chain (X) (the double bond)	The carbohydrate fragment (Y)	The source	Ref.
247	ceramasteroside C_2	H	H	α-OH	H	OH	β-OH	β-OH		2,4-$(OCH_3)_2$-Xyl_p-(1→2)-Gal_f	*Ceramaster patagonicus*	89
248	ceramasteroside C_3	H	H	α-OH	H	OH	β-OH	β-OH		2-OCH_3-Xyl_p-(1→2)-Gal_f	*Ceramaster patagonicus*	89
249	ceramasteroside C_4	OH	H	α-OH	H	OH	β-OH	H		2-OCH_3-Xyl_p-(1→2)-Gal_f	*Ceramaster patagonicus*	89
250	ceramasteroside C_5	H	H	α-OH	H	OH	β-OH	H		2-OCH_3-Xyl_p-(1→2)-Xyl_p	*Ceramaster patagonicus*	89
251	leptasteroside L	H	OH	β-OH	H	OH	α-OH	H		Glc_p	*Leptasterias polaris acervata*	183
252	acodontasteroside A	OH	H	6α-SO_3^-	H	OH	β-OH	H		2-OCH_3-Xyl_p-(1→2)-Gal_f	*Acodontaster conspicuus*	90
253	acodontasteroside B	OH	H	6α-SO_3^-	H	OH	β-OH	H		2-OCH_3-Xyl_p-(1→2)-Xyl_p	*Acodontaster conspicuus*	90
254	acodontasteroside C	OH	H	6α-SO_3^-	H	OH	β-OH	H		2-OCH_3-Xyl_p-(1→2)-Xyl_p	*Acodontaster conspicuus*	90
255	acodontasteroside D	OH	H	α-H	H	OH	β-OH	H		Xyl_p-(1→2)-Xyl_p	*Acodontaster conspicuus*	90
256	acodontasteroside E	OH	H	α-H	H	OH	β-OH	H		2-OCH_3-Xyl_p-(1→2)-Xyl_p	*Acodontaster conspicuus*	90
257	acodontasteroside F	OH	H	α-H	H	OH	β-OH	H		2-OCH_3-Xyl_p-(1→2)-Xyl_p	*Acodontaster conspicuus*	90
258	acodontasteroside G	OH	H	α-H	H	OH	β-OH	H		2-OCH_3-Xyl_p-(1→2)-Xyl_p	*Acodontaster conspicuus*	90
259	acodontasteroside H	H	H	α-H	H	H	β-OH	H	 ($\Delta^{8(14)}$)	2-OCH_3-Xyl_p-(1→2)-Xyl_p	*Acodontaster conspicuus*	90

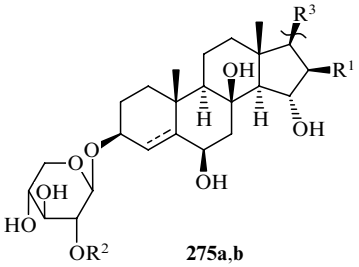
Table 3 (continued).

Compound	Name	R^1	R^2	R^3	R^4	R^5	R^6	R^7	The side chain (X) (the double bond)	The carbohydrate fragment (Y)	The source	Ref.
260	acodontasteroside I	H	H	α-H	H	H	β-OH	H	 ($\Delta^{8(14)}$)	Xyl_p	*Acodontaster conspicuus*	90
261	crossasteroside P_3	H	H	α-H	H	OH	H	H	 ($\Delta^{14(15)}$)	3-OCH_3-Glc_p	*Crossaster papposus*	184
262	crossasteroside P_4	OH	H	α-H	H	OH	β-OH	H		2,4-$(OCH_3)_2$-Xyl_p-(1→5)-Ara_f	*Crossaster papposus*	184
263	solasteroside S_1	H	H	β-OH	H	H	α-H	H		Xyl_p	*Solaster dawsoni*	185
264	solasteroside S_2	H	H	α-H	H	OH	β-OH	β-OH		Gal_f-(1→6)-Gal_f	*Solaster dawsoni*	185
265	mediasteroside M_1	H	H	α-H	H	OH	β-OH	H		2-OCH_3-Xyl_p-(1→5)-Ara_f	*Mediaster murrayi*	186
266	mediasteroside M_2	H	H	α-H	H	OH	β-OH	H		Xyl_p-(1→5)-Ara_f	*Mediaster murrayi*	186
267	mediasteroside M_3	H	H	α-H	H	OH	β-OH	H		2,4-$(OCH_3)_2$-Xyl_p-(1→5)-Ara_f	*Mediaster murrayi*	186
268	mediasteroside M_4	H	H	α-H	H	OH	β-OH	H		2,3-$(OCH_3)_2$-Xyl_p-(1→2)-Ara_f	*Mediaster murrayi*	186

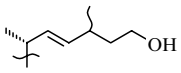
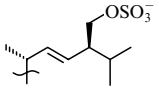


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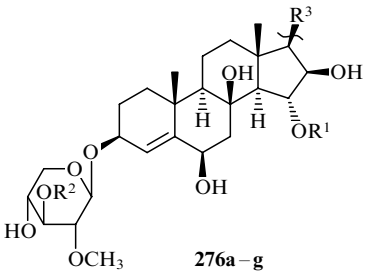
Yet another group of recently discovered glycosides contains only one carbohydrate fragment linked to the C(3) atom. These compounds include desulfated 26-norechinasteroside A (**275a**)



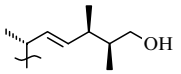
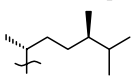
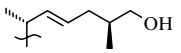
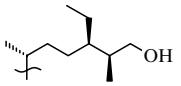
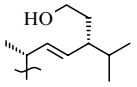
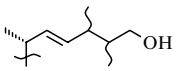
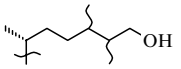
275a,**b**

Compound **275**	Name	R^1	R^2	R^3
a (Δ^4)		OH	CH_3	
b	asteriidoside L	H	H	

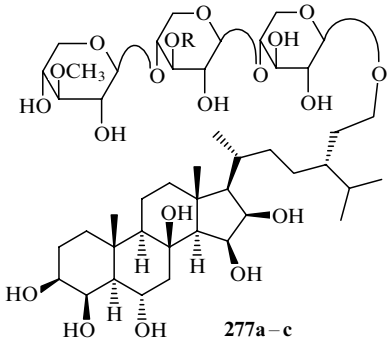
from *Henricia downeyae*,[179] compounds **276a**–**e** from *Echinaster brasiliensis*,[171] henriciosides H_2 and H_3 (**276f**,**g**) from *H. derjugini*[93] and asteriidoside L (**275b**) from Asteriidae gen sp.[174]



276a–**g**

Compound **276**	Name	R^1	R^2	R^3
a		SO_3^-	H	
b		H	H	
c	echinasteroside C	SO_3^-	H	
d	echinasteroside D	SO_3^-	H	
e	echinasteroside E	H	H	
f	henricioside H_2	H	CH_3	
g	henricioside H_3	H	CH_3	

In contrast to all other polyhydroxysteroid glycosides containing one or two monosaccharide residues, cytotoxic compounds **277a**–**c** from *Fromia monilis*[189] contain three monosaccharides.



277a: R = CH_3;
277b: R = CH_3, Δ^{22};
277c: R = H.

277a–**c**

The impressive diversity of glycosides of polyhydroxysteroids and other polar steroids found in starfishes reflects the immense variety of oxidising and glycosylating enzymes present in these animals, which is comparable only to the wide occurrence of steroid-oxidising enzymes in microorganisms and glycosyl transferases in terrestrial higher plants. Several newly discovered groups of glycosides not mentioned in previous reviews[2,3] include monoquinovosides related to classical asterosaponins as well as mono- and biosides sulfated at C(6) and containing carbohydrate chains in position 3.

It should be stressed that starfish enzymes differ from known enzymes of terrestrial origin in the specificities of hydroxylation and ability to transfer mono- or oligoside residues into definite positions of sterol substrates. Sulfation of metabolites in different positions is a distinguishing feature of biogenesis of steroid glycosides in starfishes.

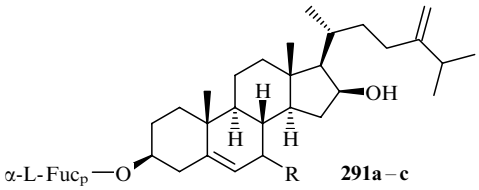
In other phyla of marine invertebrates, such as sponges, glycosides have been discovered much later than in starfishes. Sponge glycosides usually contain mono-, di- or trimethylsterol aglycons and carbohydrate chains linked to C(3). These metabolites were first isolated from *Asteropus sarasinosum* by Kitagawa *et al.*[190,191] Sarasinosides represent oligoglycosides of hitherto unknown dimethylsterol aglycons. They manifest high ichthyotoxic activities and moderate cytostatic activities in tests with fertilised eggs of the starfish *Asterina pectinifera*. Compounds **278a**–**c**, **279a**–**c** and **280a**–**c** were found in the starfish *A. sarasinosum* collected near the Palau Island in the Pacific Ocean,[191] whereas compounds **281**, **282a**–**b** and **283** were isolated from the same sponge species dwelling in the region of the Solomon Islands.[192] The aglycons of sarasinoside D (**281**) contain a rarely occurring 4,4,8-trimethylsterane skeleton system similar to that of scalarane sesterterpenoids, but differing from that of dammarane triterpenoids in a 1,2-shift of the methyl group from C(14) to C(13).

The so-called pachastrelloside A (**284**), which inhibits cell division in fertilised sea urchin eggs without affecting cell nuclei resulting in the formation of multinuclear unicellular embryos, was isolated from *Pachastrella* sp. Unlike other steroid glycosides, pachastrelloside A (**284**) contains monosaccharide residues in unusual positions. Thus, one of them, *viz*., galactose, is linked to C(4), whereas the other one, *viz*., xylose, is bound to C(7) of the aglycon.[193] Comparison of the aglycon structures of eryloside A (**285**) from *Erylus lendenfeldi*,[194] erylosides C and D (**286a**,**b**) from

Erylus sp.,[195] eryloside E (**287**) from *E. goffrileri*[196] and ulososides (**288**, **289**) isolated by us from *Ulosa* sp.[197,198] showed that stepwise demethylation of the lanostane or the related terpene precursor in sponges resembles the conversion of lanosterol into cholesterol in higher animals. This process consists in oxidative removal of the methyl group from position 14 and subsequent elimination of the methyl groups linked to C(4) (Table 4).

The hopaioside **290** isolated from the Micronesian sponge *Cribrochalina olemda* differs significantly from other sponge steroid glycosides.[199] This compound is related to 19-norpregnane rather than to sterol or norlanostane derivatives.

Interesting steroid glycosides were also detected in some octocorals. Most of them are monosides of the pregnane series and contain one or several acetate or propionate groups. Several novel glycosylated sterol derivatives and novel pregnane glycosides have recently been isolated from these animals. Thus α-L-fucosides containing aglycons of the 24-methylcholesterol series **291a**–**c** were found in some soft corals (*e.g.*, *Alcyonium* sp.) and some representatives of the *Sinularia* and *Lobophytum* genera.[200] The related glycosides **292a**,**b** and **293** were isolated from *Sinularia gibberosa*[52,201] and *S. grandilobata*.[202]



291a–**c**

291a: R = H;
291b: R = β-OH;
291c: R = α-OH.

Table 4. Sponge glycosides.

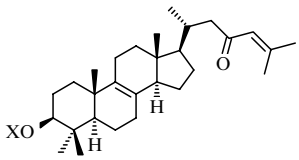
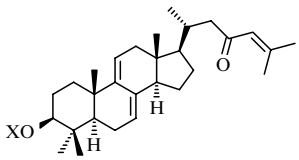
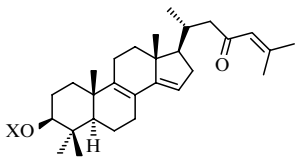
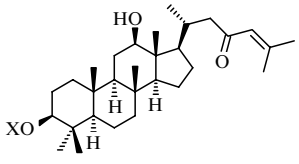
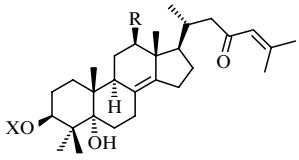
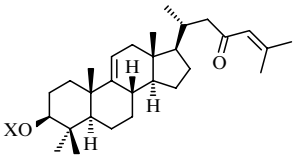
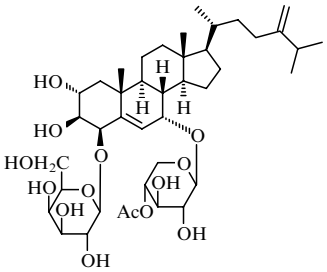
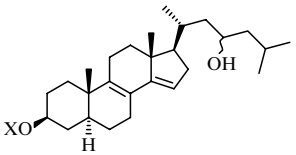
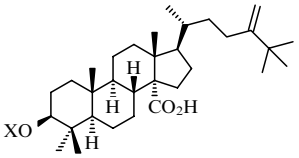
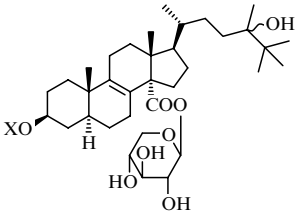
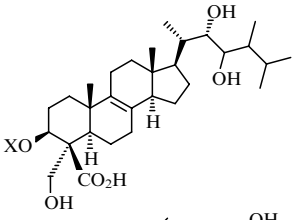
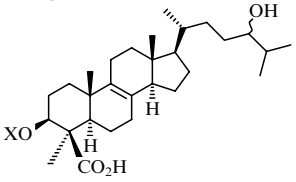
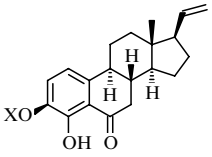
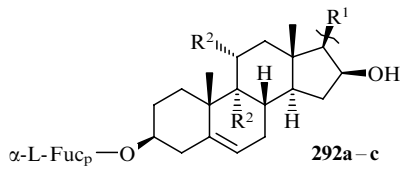
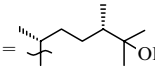
Structural formula	Compound	Structure of the carbohydrate chain (X)	Name
	**278a**	β-1,2 β-1,6 β-1,2 Glc$_p$—Glc$_p$—NAcGlc$_p$—Xyl$_p$— β-1,4 | NAcGal$_p$	sarasinoside A$_1$
	278b	β-1,2 β-1,6 β-1,2 Glc$_p$—Xyl$_p$—NAcGlc$_p$—Xyl$_p$— β-1,4 | NAcGal$_p$	sarasinoside B$_1$
	278c	β-1,6 β-1,2 Xyl$_p$— NAcGlc$_p$—Xyl$_p$— β-1,4 | NAcGal$_p$	sarasinoside C$_1$
	**279a**	β-1,2 β-1,6 β-1,2 Glc$_p$—Glc$_p$—NAcGlc$_p$—Xyl$_p$— β-1,4 | NAcGal$_p$	sarasinoside A$_2$
	279b	β-1,2 β-1,6 β-1,2 Glc$_p$—Xyl$_p$—NAcGlc$_p$—Xyl$_p$— β-1,4 | NAcGal$_p$	sarasinoside B$_2$
	279c	β-1,6 β-1,2 Xyl$_p$— NAcGlc$_p$—Xyl$_p$— β-1,4 | NAcGal$_p$	sarasinoside C$_2$
	**280a**	β-1,2 β-1,6 β-1,2 Glc$_p$—Glc$_p$—NAcGlc$_p$—Xyl$_p$— β-1,4 | NAcGal$_p$	sarasinoside A$_3$
	280b	β-1,2 β-1,6 β-1,2 Glc$_p$—Xyl$_p$—NAcGlc$_p$—Xyl$_p$— β-1,4 | NAcGal$_p$	sarasinoside B$_3$
	280c	β-1,6 β-1,2 Xyl$_p$— NAcGlc$_p$—Xyl$_p$— β-1,4 | NAcGal$_p$	sarasinoside C$_3$
	**281**	β-1,2 β-1,6 β-1,2 Glc$_p$—Xyl$_p$—NAcGlc$_p$—Xyl$_p$— β-1,4 | NAcGal$_p$	sarasinoside D
	**282a** (R = H)	β-1,2 β-1,6 β-1,2 Glc$_p$—Xyl$_p$—NAcGlc$_p$—Xyl$_p$— β-1,4 | NAcGal$_p$	sarasinoside E
	282b (R = OCH$_3$)	β-1,2 β-1,6 β-1,2 Glc$_p$—Xyl$_p$—NAcGlc$_p$—Xyl$_p$— β-1,4 | NAcGal$_p$	sarasinoside F

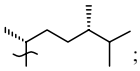
Table 4 (continued).

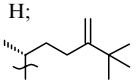
Structural formula	Compound	Structure of the carbohydrate chain (X)	Name
	**283**	Glc_p(β-1,2)—Xyl_p(β-1,6)—NAcGlc$_p$(β-1,2)—Xyl_p— NAcGlc$_p$(β-1,4)	sarasinoside G
	**284**	–	pachastrelloside A
	**285**	Gal_p(β-1,2)—Gal_p—	eryloside A
	**286a**	Gal_p(1,4)—Gal_p(1,3)—Gal_p— Gal_p(1,2)	eryloside C
	286b	Gal_p(1,3)—Gal_p— Gal_p(1,2)	eryloside D
	**287**	Gal_p(1,2)—NAcGlc$_p$—	eryloside E
	**288**	Glc_pA(β-1,6)—Glc_p—	ulososide A
	**289**	NAcGlc$_p$–	ulososide B
	**290**	4-OAc-L-Fuc–	chopaioside

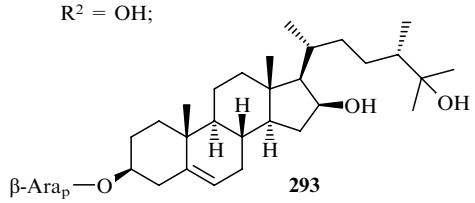


292a–c

292a: R^1 =  ; R^2 = H;

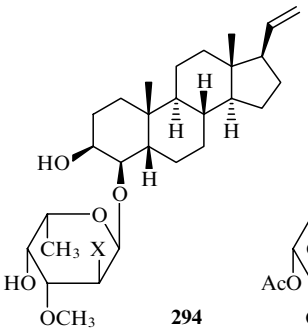
292c: R^1 =  ; R^2 = H.

292b: R^1 =  ; R^2 = OH;



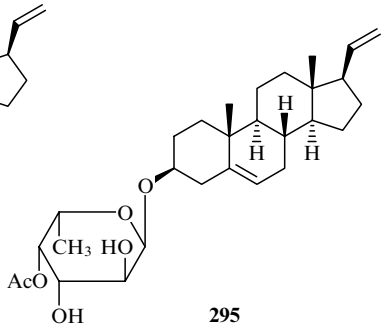
293

The cytotoxic pregnane glycoside verrucoside (**294**) from *Eunicella verrucosa*[203] contains L-digitalose as a carbohydrate component, enantiomeric with the corresponding 6-deoxyhexose occurring in terrestrial plants. This compound inhibits tumour cells P-388, A-549 and HT-29 (IC_{50} = 5.9, 7.2 and 6.3 μg ml^{-1}, respectively). The glycoside **295** from the gorgonian coral *Eunicea* sp. is its structural analogue.[204] Glycosides **296** and **297** from the soft corals *Scleronephthya palida*[205] and *Alcyonium* sp.[64] collected near the coasts of Thailand represent 19-norpregnane derivatives.

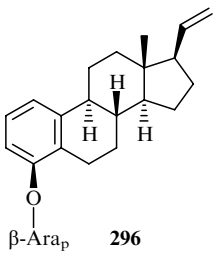


294

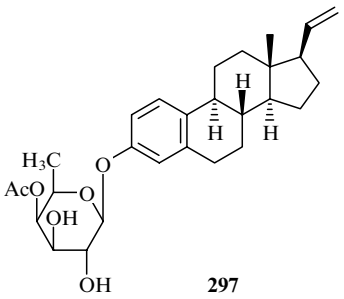
X = $OCOCH_3$.



295

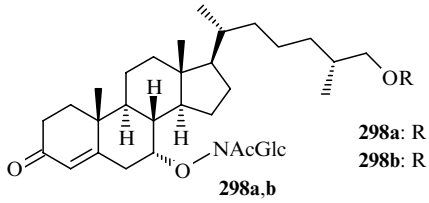


296



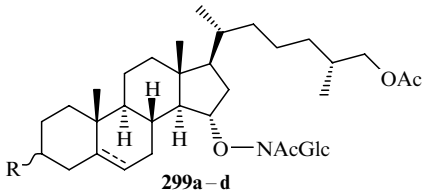
297

Some fish species also contain steroid glycosides. This fact is surprising in that glycosides are not common for terrestrial vertebrates. Among other known secondary marine glycoside metabolites, special mention should be made of shark reppelant compounds isolated from the corresponding glands of the sole *Pardachirus marmoratus* and the peacock fish *Pardachirus pavoninus*. Although these fishes swim extremely slowly, they successfully withstand the attacks of predatory fishes in their vehement struggle for existence under conditions of coral reefs. Both fish species belong to the same genus and secrete toxic substances at the moment of danger. These substances contain the peptides pardaxins causing paralysis of shark's gnathic muscles and two groups of toxic glycosides endowed with hemolytic activities, *viz*., pavonins **298a**,**b** and **299a–d** from *P. pavoninus*[206,207] and mosesines **300a–d** and **301** from *P. marmoratus*.[208]



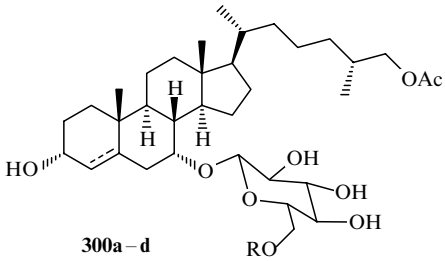
298a: R = Ac;
298b: R = H.

298a,**b**



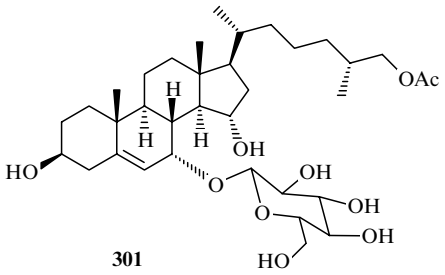
299a: Δ^5, R = α-OH;
299b: Δ^5, R = β-OH;
299c: 5(6)-dihydro, R = α-OH;
299d: 5(6)-dihydro, R = β-OH;

299a–d



300a: Δ^4, R = Ac;
300b: 4(5)-dihydro, R = Ac;
300c: Δ^4, R = H;
300d: 4(5)-dihydro, R = H.

300a–d



301

These data suggest that steroid glycosides can be synthesised by taxonomically very distant and diverse groups of marine animals (from invertebrates to fishes). As regards the diversity of their constituent biologically active steroid glycosides, starfishes resemble other well-known sources of these compounds, *viz*., higher terrestrial plants.

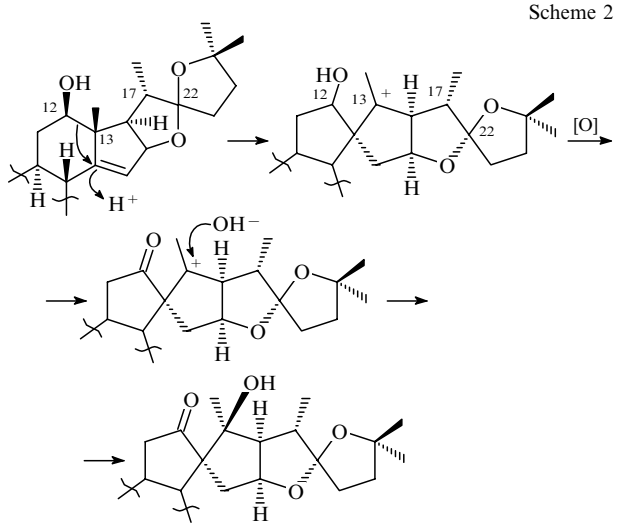
V. Steroidal alkaloids

Bissteroidal pyrazines constitute a special group among other natural compounds, which are supertoxic for tumour cells. The structure of cephalostatin 1 (**302a**), the first compound of this series isolated from the marine tubular worm *Cephalodiscus gilchristi* by Pettit *et al*. (USA),[209] was established by X-ray diffraction analysis. This compound in extremely low concentration was toxic for tumour cells P-388 (IC_{50} = 10^{-7}–10^{-9} μg ml^{-1}). Later, about 20 cephalostatins of this series, *e.g*., compounds **302b–g**, **303**, **304a**,**b**, **305**, **306a**,**b** and **307**, were isolated from this animal.[210–215]

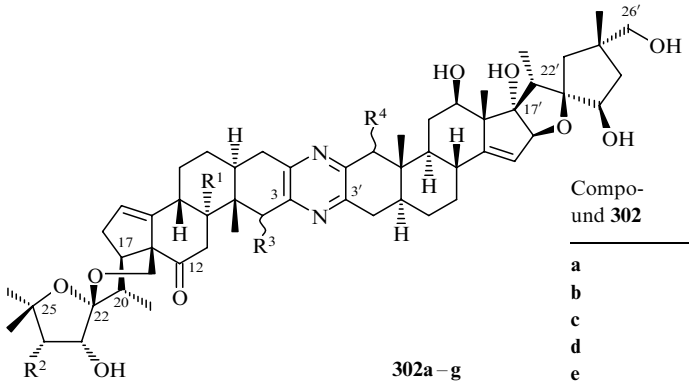
Structurally close dimeric steroid alkaloids were unexpectedly found in the sea squirt *Ritterella tokioka* by Fusetani *et al*.[216–219] Ritterasine A (**308a**), the first compound in this series, is highly toxic for P-388 cells ($IC_{50} = 3.5 \times 10^{-3}$ μg ml^{-1}) (see Ref. 216). The origin of the unusual fragment containing four five-membered rings in ritterazine A and related compounds was explained by the rearrangement of the 12-hydroxy-Δ^{14}-steroid system of their precursor (Scheme 2).

Later, this group of Japanese chemists isolated more than twenty ritterazines, *e.g*., compounds **308b**, **309a**,**b**, **310**, **311**, **312a**,**b** and **313**, differing in the structures of rings *C*, *D*, *E* and *F* in one or both steroid fragments.[217–219] The majority of ritterazines appeared to be highly toxic for tumour cells; some of them manifested superhigh activities (Table 5).[218]

Scheme 2

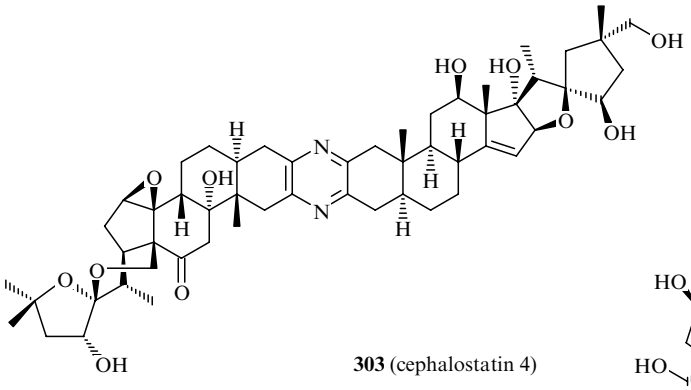


The isolation of two closely related groups of compounds from phylogenetically distant taxa, such as sea worms and ascidians, prompted a suggestion that their biosynthesis is carried out by symbiont microorganisms rather than by the host organism. Cephalostatin 7 (**305**) is the most active compound of this series. Studies carried out at the National Cancer Institute (USA) showed that its average IC_{50} for 60 strains of tumour cells was equal to 10^{-9} mol litre^{-1}. Later, this and some other dimeric steroidal alkaloids were synthesised. According to Pettit,[209] these compounds are formed by dimerisation and subsequent oxidation of steroidal α-amino ketones. Fuchs *et al.*[220] described the biomimetic synthesis of cephalostatins 7 (**305**), 12 (**307**) and ritterazin K (**311**). The starting compound in this synthesis was steroid pentacyclic aldehyde **314** prepared from readily available hekogenin acetate. This was converted *via* the intermediate ketones **315**, **316** and bromo ketones **317** and **318** into azido ketones **319** and **320** (Scheme 3). Treatment of the azido ketone mixture (1 : 1) with 6 equiv. of NaHTe in ethanol for 1 h and subsequent addition of silica gel as a mild catalyst yielded a mixture of **321** (14%), **322** (35%) and **323** (23%). Compounds

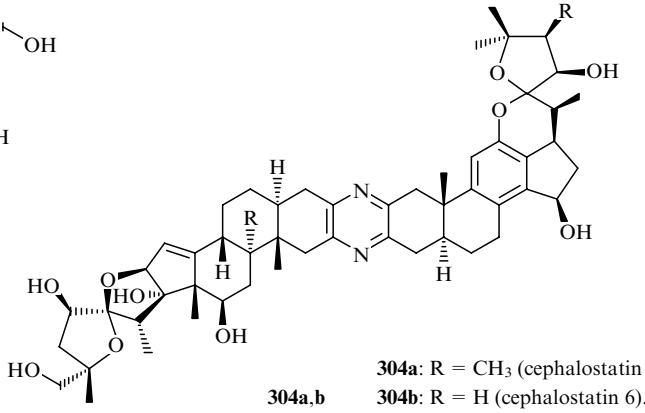


302a–**g**

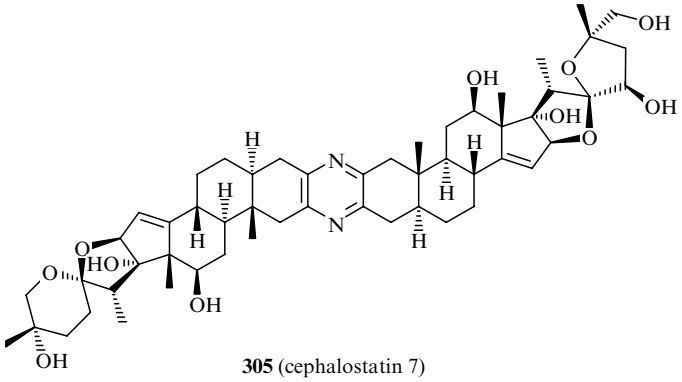
Compound **302**	Name	R^1	R^2	R^3	R^4
a	cephalostatin 1	H	H	H	H
b	cephalostatin 2	OH	H	H	H
c	cephalostatin 3	OH	CH_3	H	H
d	cephalostatin 10	OH	H	H	α-OCH_3
e	cephalostatin 11	OH	H	α-OCH_3	H
f	cephalostatin 18 (22′epimer)	H	H	H	α-OCH_3
g	cephalostatin 19 (22′epimer)	H	H	α-OCH_3	H



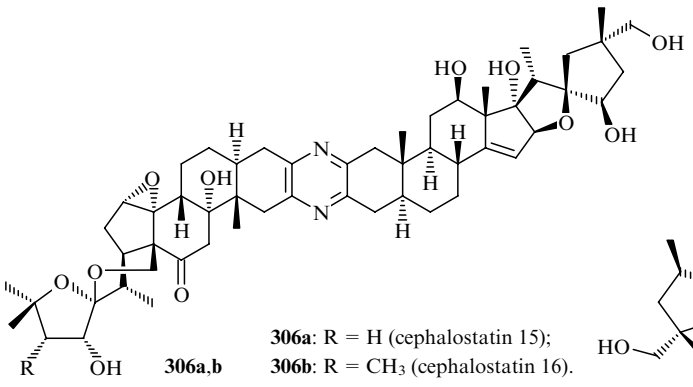
303 (cephalostatin 4)



304a,**b** **304a**: R = CH_3 (cephalostatin 5); **304b**: R = H (cephalostatin 6).

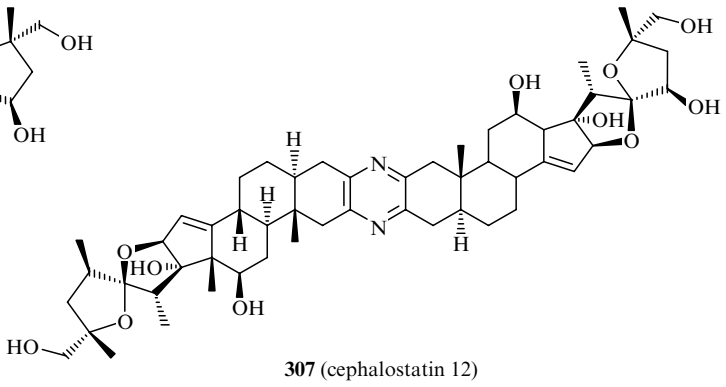


305 (cephalostatin 7)

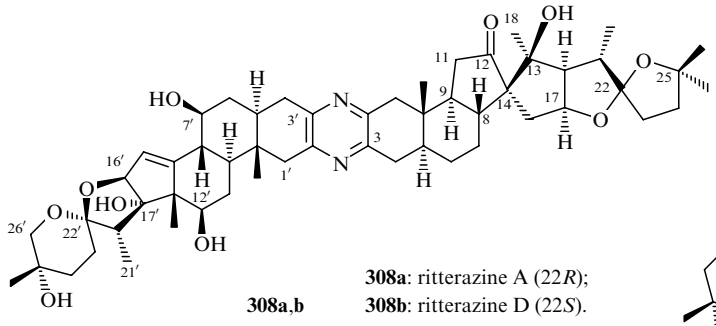


306a: R = H (cephalostatin 15);
306b: R = CH_3 (cephalostatin 16).

306a,**b**

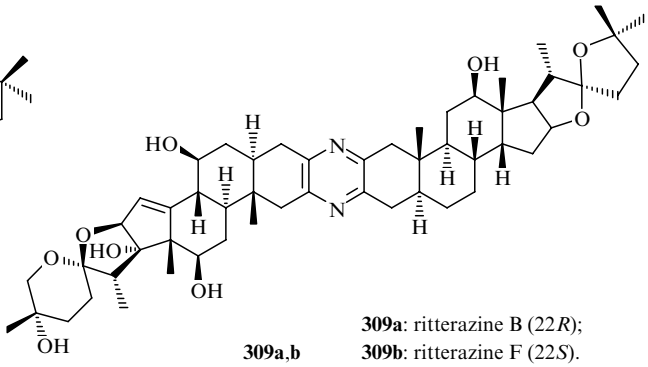


307 (cephalostatin 12)



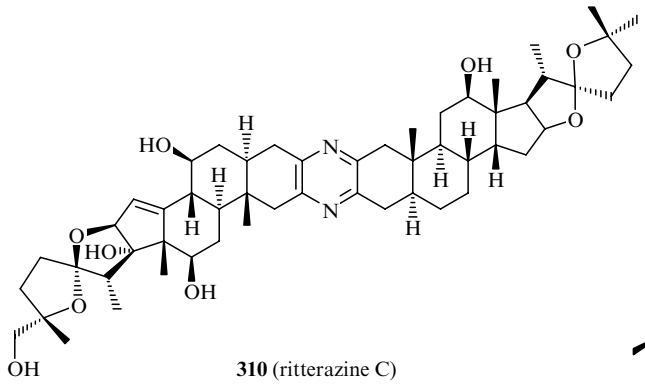
308a: ritterazine A (22*R*);
308b: ritterazine D (22*S*).

308a,**b**

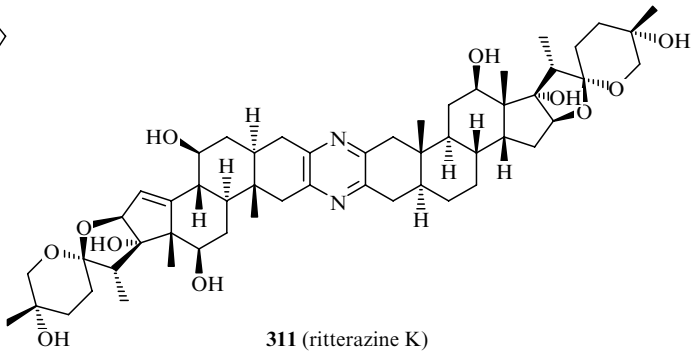


309a: ritterazine B (22*R*);
309b: ritterazine F (22*S*).

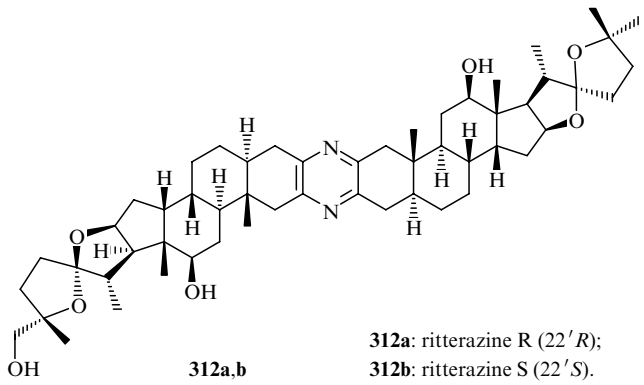
309a,**b**



310 (ritterazine C)

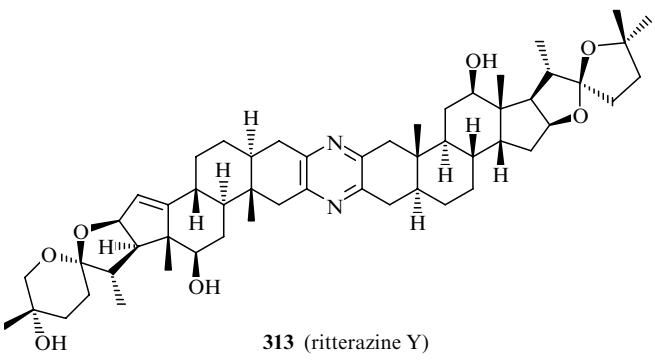


311 (ritterazine K)



312a: ritterazine R (22′*R*);
312b: ritterazine S (22′*S*).

312a,**b**



313 (ritterazine Y)

321–**323** were purified by chromatography; their subsequent deprotection gave products identical with natural cephalostatins 7 (**305**) and 12 (**307**) and ritterazine K (**311**), respectively.

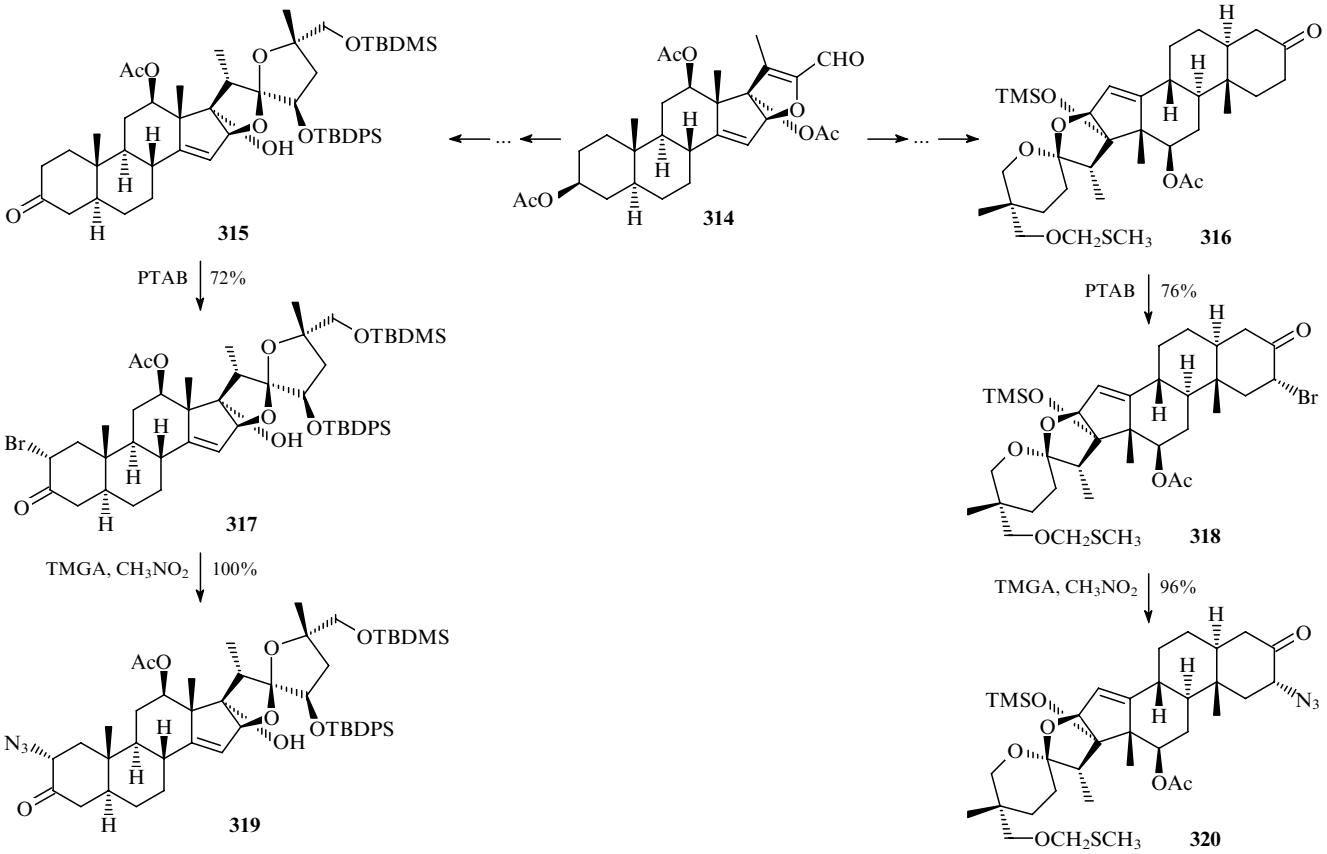
Pyrazine steroidal dimeric alkaloids belong to the most toxic natural products for tumour cells presently known. The synthesis of some of them has opened new opportunities for their further pharmacological and clinical investigations.

Squalamine (**324a**), an unusual sulfated derivative of spermidine, was isolated from the shark *Squalus acanthis*.[221, 222] Its structure was determined by spectroscopic methods; the stereo-

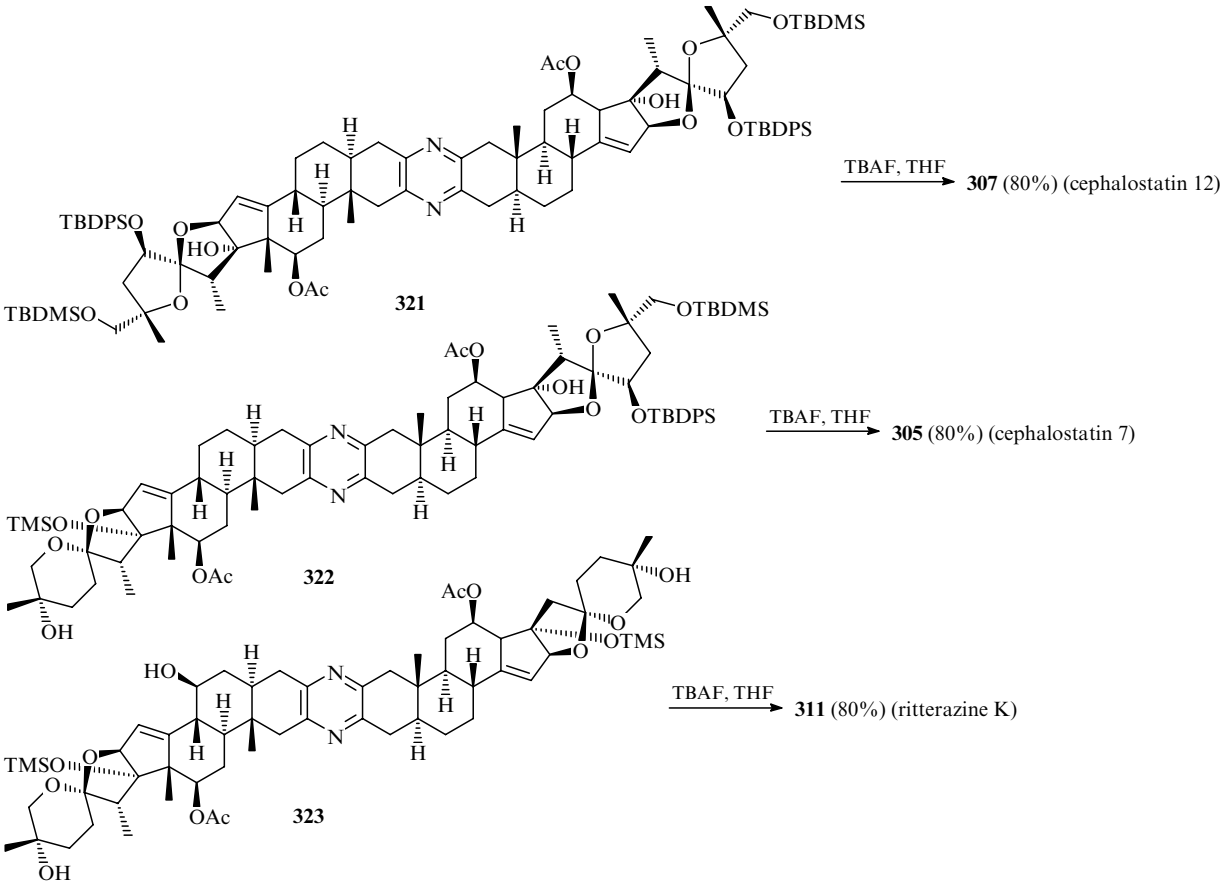
Table 5. The cytotoxic activities of ritterazines against tumour cells P-388.[218]

Compound	IC_{50} /μg ml^{-1}	Compound	IC_{50} /μg ml^{-1}
ritterazine A	0.0035	ritterazine F	0.00073
ritterazine B	0.00015	ritterazine K	0.0095
ritterazine C	0.092	ritterazine S	0.46
ritterazine D	0.016	ritterazine Y	0.0035

Scheme 3

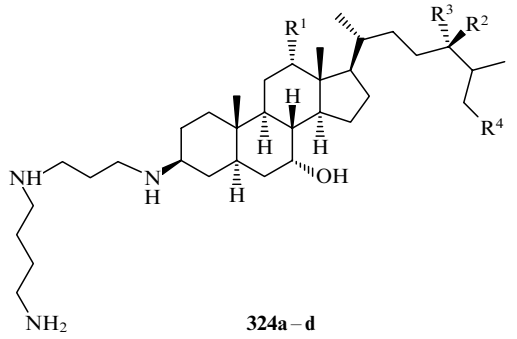


TBDMS, *tert*-butyldimethylsilyl; PTAB, phenyltrimethylammonium tribromide; TMGA, tetramethylguanidinium azide.



TBAF, tetrabutylammonium fluoride.

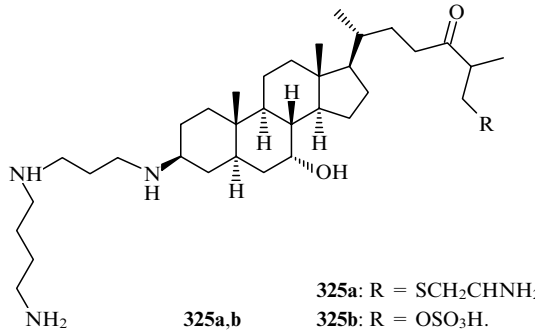
chemistry of the asymmetric centre C(24), (24*R*), was established based on the synthesis of desulfosqualamine and its (24*S*) isomer starting from stigmasterol.[223] In contrast to bile alcohols of fishes, squalamine (**324a**) is present not only in the liver and the gallbladder but also in other shark organs, *e.g.*, in the spleen and ovaries. Squalamine (**324a**) manifests interesting properties, *viz.*, its antibacterial activity is comparable to that of the broad-spectrum antibiotic ampicillin (see Table 6), but its antifungal and antiprotozoan effects are stronger.



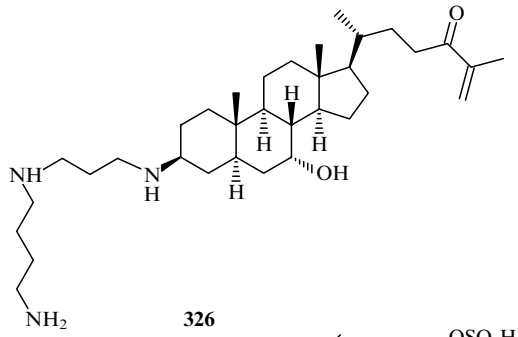
324a–d

Compound **324**	R^1	R^2	R^3	R^4
a	H	OSO_3H	H	H
b	H	OH	H	OSO_3H
c	OH	OSO_3H	H	H
d	H	OSO_3H	CH_2OH	H

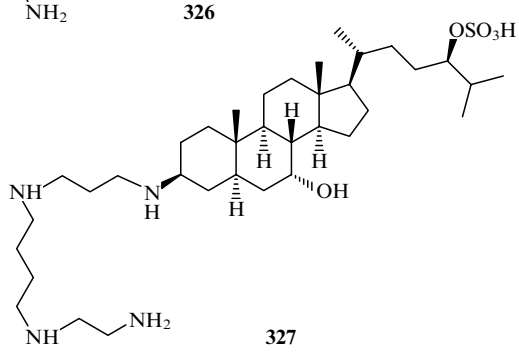
Some novel alkaloids of this series, *viz.*, compounds **324b–d**, **325a**,**b**, **326** and **327**, have been isolated recently. Noteworthy, the antimicrobial activity of compound **327** is comparable to that of squalamine.[234] Compounds of this series suppress the appetite in mice and other animals, which prompted a conclusion about their role in sporadic alimentary behaviour of the shark *S. acanthis*, which eats only once in two weeks.



325a,**b** **325a**: R = $SCH_2CHNH_2CO_2H$; **325b**: R = OSO_3H.



326

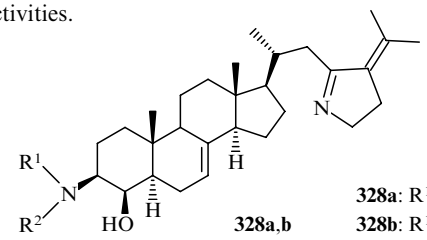


327

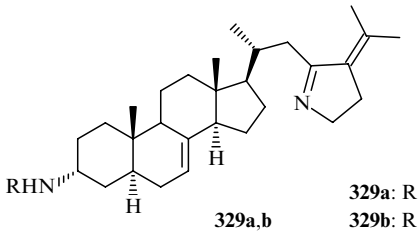
Table 6. Comparison of the antimicrobial activities of squalamine (minimum IC /mg ml^{-1}) and the antibiotic ampicillin.

Microorganism	Squalamine	Ampicillin
E.coli	1–2	2–4
Pseudomonas aeruginosa	4–8	62–125
Staphylococcus aureus	1–2	<1
Streptococcus faecalis	1–2	<0.25
Proteus vulgaris	4–8	8–16
Serratia marcescens	>125	4–62
Candida albicans	4–8	>125
Paramecium caudarum	4–8	>65

Two novel alkaloids **328a**,**b**[225] related to the previously known antimicrobial metabolites, plakinamides A and B (**329a**,**b**) from the sponge *Plakina* sp.,[226] were isolated from extracts of the sponge *Corticum* sp. collected near the coasts of Indonesia. Compounds **328a**,**b** are highly toxic for tumour cells and manifest moderate immunomodulating and antimicrobial activities.

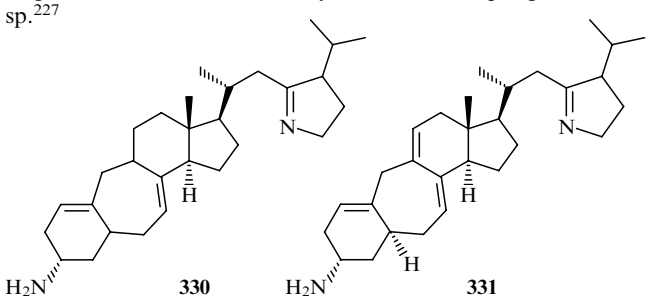


328a,**b** **328a**: $R^1 = R^2 = CH_3$; **328b**: $R^1 = COCH_3$, R^2 = H.



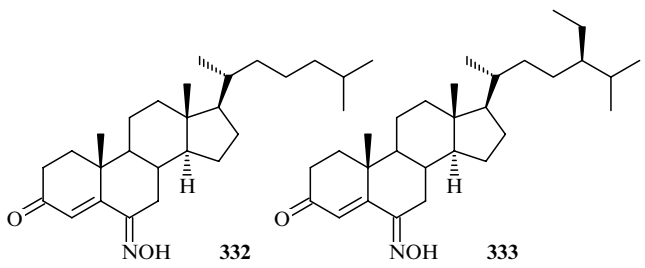
329a,**b** **329a**: R = H; **329b**: R = $COCH_3$.

The unusual steroidal alkaloids **330** and **331** with expanded ring *B* have been found recently in the Pacific sponge *Corticum* sp.[227]



330 **331**

The steroidal oximes **332** and **333** from the sponge *Cinachyrella* sp. inhibit competitively human placental aromatase and are



332 **333**

potential inhibitors of hormone-dependent tumours.[228] The syntheses of these compounds have been described.[229]

Although marine steroid alkaloids known thus far are not numerous, they present substantial interest with regard to their chemical structures and physiological activities.

VI. Miscellaneous marine steroids

In this section, we shall consider those marine steroids which can hardly be related to any of the above-mentioned structural groups.

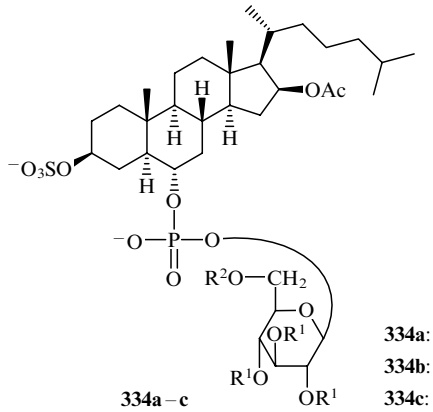
Steroid phosphates were found in the starfish *Tremaster novaecaledoniae*. Tremasterols A–C (**334a–c**) related to glycosides were the first to be described.[230] The monosaccharide residues in these compounds are bound to aglycons by phosphodiester rather than glycosidic bonds. The signals for the protons at C(6) in the ^{1}H NMR spectra of tremasterols represented doublets of doublets of doublets of doublets (J = 9.5, 9.5, 7.5 and 4.5 Hz), *i.e.*, they contained an additional spin coupling constant compared with the corresponding spectra of 6α-hydroxy cholestane derivatives due to the HC–O–P coupling. Their ^{31}P NMR spectra contained triplet signals at δ 3.54, which coalesced into doublets upon irradiation of C<u>H</u>(6) or C<u>H</u>(1′), which suggests the presence of a phosphate group between C(6) and the monosaccharide residue. Chemical shifts of phosphorus atoms for phosphate and other functional groups in the ^{31}P NMR spectra are well established (see, *e.g.*, Ref. 231). Later, the steroid **335** containing sulfate and phosphate groups in positions 3 and 6, respectively, was isolated from the same starfish species.[136]

Some sponges were found to contain dimeric steroids. Thus bistheonellasterone (**336**) and bisconicasterone (**337**) were isolated from the Okinawian sponge *Theonella swinhoei* by Japanese scientists.[232, 233] Compound **338** was prepared in nearly quantitative yield from theonellasterone **338** upon heating and evaporation of the latter in chloroform (50 °C, 2 h). The coupling occurred with excellent regio- and stereospecificity. It is assumed that the dimeric steroids **336** and **337** are formed as a result of the Diels–Alder cycloaddition of theonellasterone **338** to its Δ^4-isomer or, correspondingly, by cycloaddition of two molecules of conicasterone **339** to each other. Ketones **338** and **339**, the possible precursors of compounds **336** and **337**, and related compounds have been isolated from the same sponges where they occur as crystalline inclusion compounds.

Crellastatin A (**340**) was the first sulfated steroid dimer isolated from the sponge *Crella* sp.[234] The related compounds **341, 342**, *etc.*, were isolated later.[235]

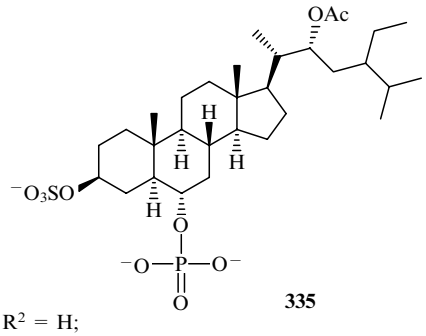
Hymnosterone A (**343**), the unusual cytotoxic steroid derivative of mixed biogenesis, was isolated from the microscopic fungus *Gymnascella dankaliensis* associated with the sponge *Halichondria japonica*.[236] Hymnostatins containing a non-steroid fragment of compound **343**, *e.g.*, hymnostatin A (**344**), were detected in the same microorganism. They manifest high toxicities against tumour cells P-388.[237]

Polar steroids are seldom found in scleroactinian corals. However, steroidal acids **345a** and **346**, the carbon skeletons of which are identical with those of cholic acids, were discovered in deep-water *Deltocyanthus magnificus* by Pietra *et al.*[238]. Some of

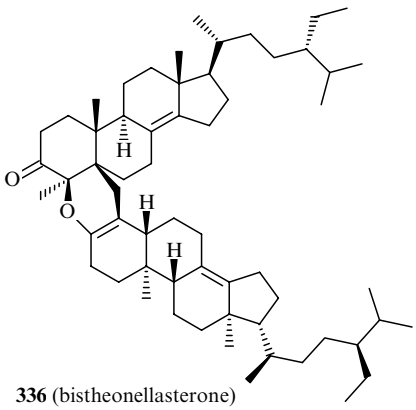


334a–c

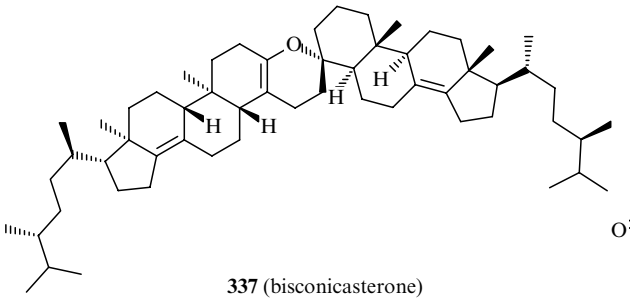
334a: $R^1 = R^2 = H$;
334b: $R^1 = R^2 = Ac$;
334c: $R^1 = H$, $R^2 = Ac$.



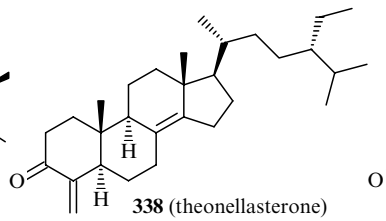
335



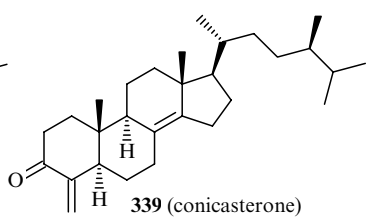
336 (bistheonellasterone)



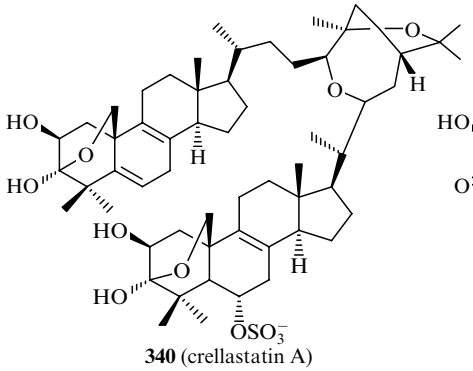
337 (bisconicasterone)



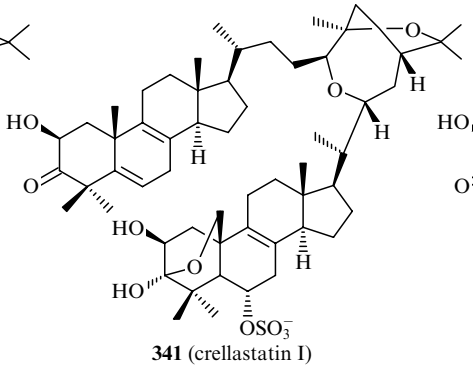
338 (theonellasterone)



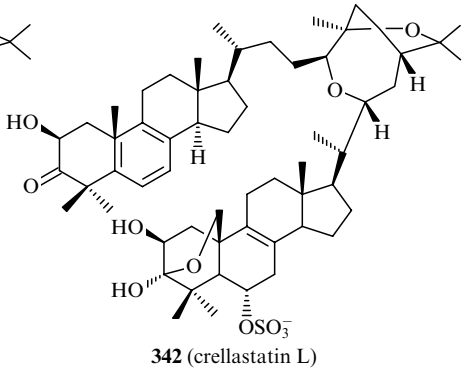
339 (conicasterone)



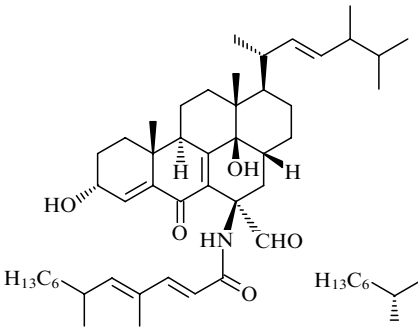
340 (crellastatin A)



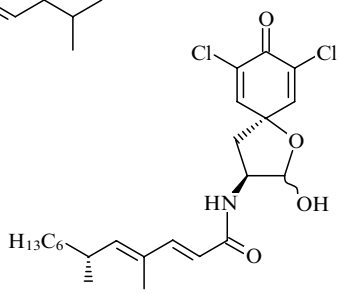
341 (crellastatin I)



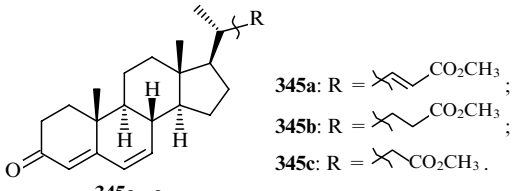
342 (crellastatin L)



343 (hymnosterone A)

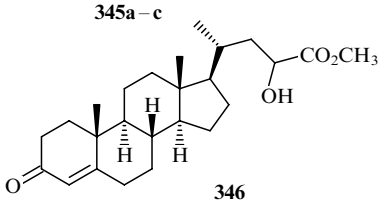


344 (hymnostatin A)



345a: R = CO_2CH_3 ;
345b: R = CO_2CH_3 ;
345c: R = CO_2CH_3 .

345a – c

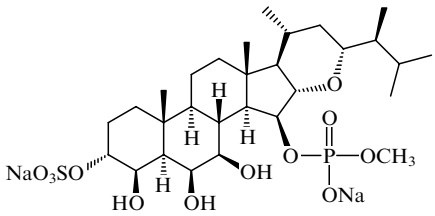


346

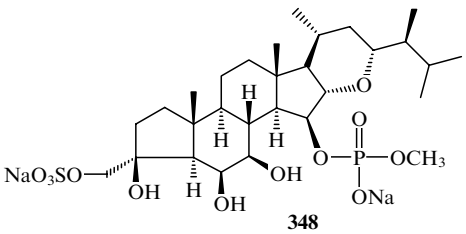
these compounds were isolated as methyl esters by treatment of the corresponding fractions with diazomethane.

* * *

Several interesting papers devoted to marine polar steroids were published after this review had been written. Thus Fujita *et al.*[239] reported on the isolation of two novel unusual polar steroids, *viz.*, haplosamate A (**347**) and the minor steroid **348** from the sponge *Cribrochalina* sp. dwelling near the Western coast of Japan.



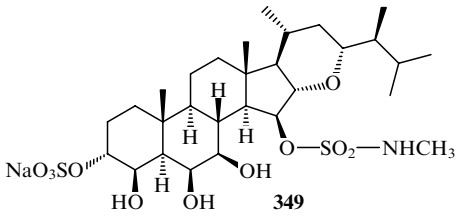
347 (haplosamate A)



348

These compounds were discovered during the search for inhibitors of matrix metalloproteinases of the membrane type (MT-MMPs), the key enzymes in tumour metastasis. These enzymes activate progelatinase A, which causes the degradation of type IV collagen. The latter inhibits invasion of tumour cells in different body organs and tissues. It is suggested that MT-MMPs inhibitors hold considerable promise as antitumour agents. Compounds **347** and **348** inhibited MT-MMPs (IC_{50} = 150 and 160 μg ml^{-1}, respectively).

Haplosamate A was found to be identical with the inhibitor of integrase, a specific enzyme of the human immunodeficiency virus, with a tentative formula **349**, which has earlier been isolated from two Philippine sponges.[240]

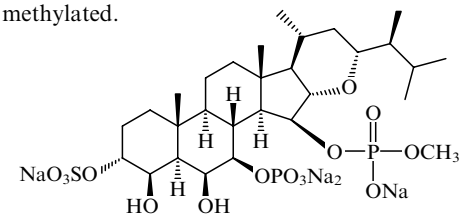


349

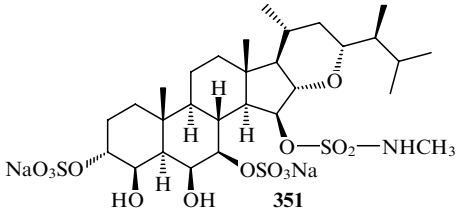
It was suggested that this polyhydroxylated steroid contains one sulfate group and one *N*-methylsulfamate group. However, the NMR spectra of haplosamate A displayed additional splitting of signals for certain protons, which could not be inferred from the formula **349**. Thus the proton signal corresponding to the methoxy group occurred as a doublet, which points to the presence of a phosphorus atom in this steroid. Further structural analysis corroborated the correctness of the structure **347** for haplosamate A and the compound isolated from Philippine sponges.

Haplosamate A (**347**) and the related steroid **348** are the first sponge steroids containing both sulfate and methyl phosphate groups. The absolute stereochemistry of compounds **347** and **348** was established on the basis of their chemical conversions and using a modified Mosher's method.

The structure of haplosamate B (**350**),[239] which was erroneously identified as compound **351**,[240] is even more surprising. Haplosamate B is the first polar steroid containing two phosphate and one sulfate groups; one of the phosphate groups in steroid **350** is methylated.

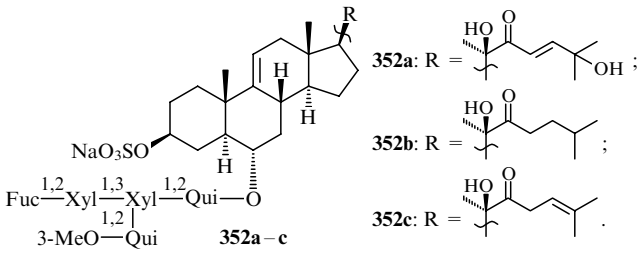


350 (haplosamate B)



351

The number of marine steroid glycosides is rapidly increasing. A recent report is devoted to the isolation of three novel antibacterial asterosaponins, *viz.*, goniopectenosides A – C (**352a – c**), from the starfish *Goniopecten demonstrans*.[241]

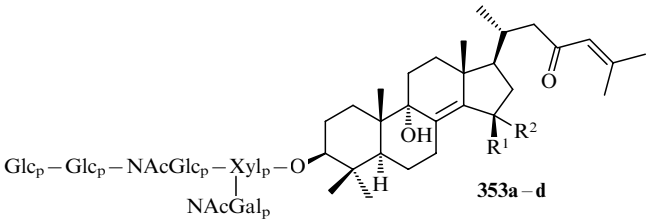


352a: R = ;
352b: R = ;
352c: R = .

352a – c

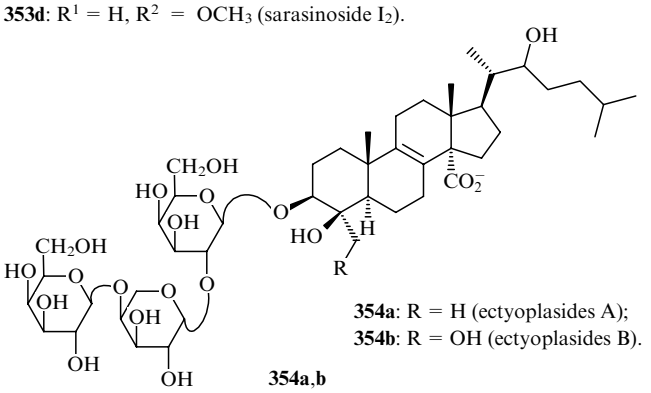
The carbohydrate chains of these compounds contain a rarely occurring monosaccharide, *viz.*, 3-*O*-methylquinovose, whereas their aglycons contain a keto group in position 22 rather than in 23. The use of a new instrumental approach, *viz.*, liquid chromatography combined with NMR and mass-spectroscopic detection (LC-NMR-MS), in the analysis of the well-studied asterosaponin fraction isolated from the starfish *Asterias rubens* revealed five novel steroid glycosides named ruberosides A – D.[242]

Four novel glycosides of this series, *viz*., sarasinosides H_1, H_2, I_1 and I_2 (compounds **353a**–**d**), were isolated from the sponge *Melophlus isis* together with the previously identified sarasinosides A_1 and A_3.[243] In contrast to sarasinosides, the cytotoxic glycosides ectyoplasides A and B (**354a**,**b**) from the Caribbean sponge *Ectyoplasia ferox*,[244] represent oxygenated derivatives of 4,14-dimethylsterols and contain two galactose and one arabinose residues in their carbohydrate chains.



353a–**d**

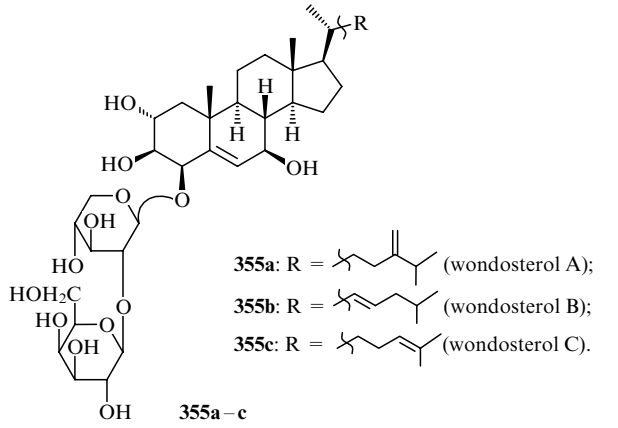
353a: R^1 = OH, R^2 = H (sarasinoside H_1);
353b: R^1 = OCH_3, R^2 = H (sarasinoside H_2);
353c: R^1 = H, R^2 = OH (sarasinoside I_1);
353d: R^1 = H, R^2 = OCH_3 (sarasinoside I_2).



354a: R = H (ectyoplasides A);
354b: R = OH (ectyoplasides B).

354a,**b**

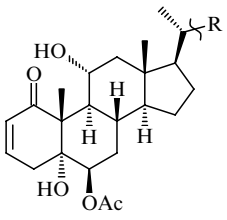
Yet another series of steroid glycosides, *viz*., wondosterols A–C (**355a**–**c**), were detected in a mixture of two different sponge species dwelling near the coasts of Korea.[245] These compounds contain carbohydrate chains linked to C(4) of the aglycons. Wondosterols (**355a**–**c**) belong to the same structural series as the known bioside pachastrelloside A (**284**), but differ from the majority of other sponge glycosides in that they derive from polyhydroxysterols rather than from methylsterols.



355a: R = (wondosterol A);
355b: R = (wondosterol B);
355c: R = (wondosterol C).

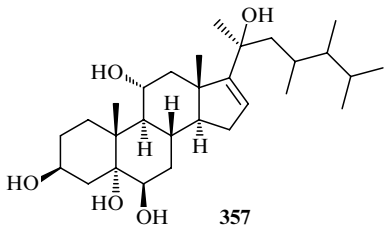
355a–**c**

Among novel steroids isolated from Coelenterata, special mention should be made of a series of compounds similar to witanolides isolated recently from the Okinawian soft coral *Clavularia viridis*, *viz*., the so-called jonarasterols A–C (**356a**–**c**)[246] and the steroidal pentol **357** from the soft coral *Sarcophyton trocheliophorum*,[247] which was weakly toxic against normal human leucocytes, but inhibited leukemia cells HL-60, melanoma cells M-14 and mammary carcinoma cells MCF-7 (IC_{50} = 3–5 μg ml^{-1}).



356a–**c**

356a: R = (jonarasterol A);
356b: R = (jonarasterol B);
356c: R = (jonarasterol C).



357

VII. Problems of isolation and structural analysis of marine polar steroids

Polar steroids are usually present in marine organisms as very complex mixtures of structurally related compounds, which significantly complicates their isolation and separation. These steroids may contain several functional groups or fragments. Thus trisulfated sterol derivatives are widespread in sponges, whereas steroids containing sulfate or phosphate groups in addition to monosaccharide fragments are more common for starfishes. Moreover, many highly active marine steroids are minor components of extracts where their concentrations do not exceed 0.001% of the dry weight of the corresponding organisms. Their isolation and purification present a difficult and not always solvable problem, although these procedures are usually carried out with the use of the most advanced separation techniques.

In our laboratory, we use reversed-phase column chromatography on a PTFE powder (Polychrome-1) in the first step of isolation of polar steroids. This consists in application of aqueous extracts on columns with this sorbent, elution of salts by washing the columns with water and elution of polar steroids with aqueous alcohol.[99,160]

Italian chemists perform this procedure on a column with Amberlite XAD-2.[3,165] Further separation usually requires the use of several separation techniques including gel-permeation chromatography on Sephadexes LH-20 and LH-60, adsorption chromatography on silica gel, reversed-phase HPLC as well as drop counter-current distribution. The isolation of 22 novel polar steroids from the starfish *Oreaster raticulatus*,[117] about 20 cephalostatins from *Cephalodiscus gilchristi*[211–217] and 20 ritterazines from *Ritterella tokioka*[216–219] provide illustrative examples of progress achieved.

NMR spectroscopy including the most updated techniques, *e.g*., HMBC and NOESY experiments, is the most popular structural physicochemical method. The absolute configurations of asymmetric carbon atoms of polyhydroxysteroids are often established by the Mosher's method,[248] which consists in the conversion of the corresponding hydroxy groups into ester groups by treatment with chiral *R*-(+)- and *S*-(−)-α-methoxy-α-trifluoromethylphenylacetyl chlorides (MTPA) with subsequent determination of the chemical shifts of protons at the adjacent carbon atoms of the diastereomeric esters formed. In the case of the 24*R*-configuration of the corresponding asymmetric centres in (+)- and (−)-MTPA esters, the signals corresponding to the $C(26)H_3$ and $C(27)H_3$ groups are observed at δ 0.89–0.91, whereas those for the 24*S*-isomers are found in the higher field, *viz*., at δ 0.83–0.86.

FAB-mass spectrometry is the most popular modern mass spectrometric technique for the determination of molecular masses of polar steroids and establishment of the sequences of

monosaccharide units in carbohydrate chains of steroid glycosides.

Although the chemical properties of many marine polar steroids are still poorly investigated, the use of chemical procedures for the establishment of their chemical structures sometimes demonstrates their unusual or unpredicted chemical behaviour especially in acidic media, *e.g.*, migration of the double bond in the steroid nucleus from position 8(9) to positions 8(14) and 14(15),[110, 191, 197] aromatisation of a ring in the steroid skeleton,[110] *etc*.

VIII. Conclusion

In marine organisms, steroid substrates can be oxygenated at any carbon atom without exceptions (Table 7). Even the products of steroid metabolism formed by oxidative cleavage of the bonds between the quaternary carbon atoms, *e.g.*, C(10) or C(13), and the neighbouring carbon atoms, were found in these organisms. Compounds containing hydroxy groups in methine and methylene groups instead of hydrogen atoms are even more numerous. Some representatives of starfishes, sponges and cnidarians contain steroids with three, four and even more (up to nine) hydroxy groups. Further modifications of polar steroids in marine organisms include sulfation (sponges, starfishes, ophiuroids and fishes), acylation (octocorals and some other cnidarian species and sponges), methylation (sponges), oxidation of hydroxy groups to keto and carboxy groups (sponges, cnidarians and echinoderms), phosphorylation (starfishes and sponges) and glycosylation (starfishes, sponges, fishes, cnidarians, less frequently, ophiuroids). Sometimes, biochemical conversions of polar steroids lead to the formation of nitrogen-containing derivatives, *viz*., alkaloids. All this provides evidence for the wide structural diversity of marine polar steroids.

The analysis of published data suggests that in-depth studies in this area are still in progress. In the last few years, the number of newly discovered marine steroids increases annually by 50 – 100 compounds. Many novel unexpected findings still remain to be made.

Although the biological activities and functions of marine polar steroids have not been adequately investigated yet, many of them have attracted the attention of pharmacologists and physicians. This concerns supercytotoxic antitumour compounds, efficient antimicrobial agents, inflammation inhibitors, *etc*. In-depth studies of antiinflammatory activities of contignasterol, antitumour activities of cephalostatins and specific physiological activities of other marine polar steroids are currently under way. However, the array of activities tested employed in the isolation of novel polar steroids is still rather narrow. Thus the majority of investigators have concentrated on the search for novel antitumour compounds, whereas all other types of activities of marine steroids are neglected.

The experimental data and the unusual structural peculiarities of some polar steroids attract keen attention of synthetic chemists. Recent developments in this field culminated in complete and partial syntheses of these natural compounds, their analogues and derivatives. Thus the syntheses of two novel sponge 9,10-secosteroids,[250] *viz*., calicopherol E and astrogorgiadiol (by the method of Barton [249]); of cytotoxic stolonipherones earlier isolated from the soft coral *Clavularia viridis;*[251] of incrustasterols possessing antitumour activities;[252] of xestobergsterol A obtained in 24 steps from stigmasterol [253] and of 3-epi-6,7-dideoxysestobergsterol A [254] have recently been carried out. Apparently, the synthetic trend in the study of marine polar steroids will be developed in the future.

It is obvious that the vast pool of fundamental knowledge concerning the structure, taxonomic distribution and properties of marine polar steroids created owing to joint efforts of many research groups all over the world will serve as a basis for the development of novel biotechnological approaches to their preparation in sufficiently large amounts. Close cooperation of bioorganic chemistrs and specialists in aquatic, cell and tissue cultures and gene engineering will be a valuable contribution.

In the next few years, significant progress can be anticipated in the study of biogenesis of marine steroids, particularly in isolation and investigation of enzymes responsible for their biosynthesis

Table 7. Examples of marine organisms containing oxygenation polar steroids with oxiden-containing functional groups at different positions.

Carbon atom	Marine organisms	Carbon atom	Marine organisms	Carbon atom	Marine organisms
1	sponges (*Xestospongia*), corals (*Sinularia*), *etc*.	10	gorgonian corals (*Caligorgia*), sponges (*Corticum*)	19	corals (*Nephthea*, *Antiphates*, *Litophyton*), sponges (*Toxadocia*, *Strongylophora*, *Crella*)
2	many ophiuroids, sponges (*Aplyinopsis*, *Echinoclathria*, *Halichondria*, *Topsentia*, *etc*.)	11	many sponges and corals, some ophiuroids, fishes (*Mola*)	20	many starfishes, sponges (*Petrosia*, *Geodia*), corals (*Sarcophyton*, *etc*.)
3	all marine organisms excluding bacteria	12	some fishes, sea worm (*Cephalodiscus gilchristi*), ascidia (*Ritterella tokioka*)	21	many ophiuroids, starfishes (*Pteraster*), some corals and sponges
4	many ophiuroids and starfishes, corals, sponges (*Stilopus*, *Haliclona*)	13	octocorals (*Dendronephthea*)	22	sponges (*Haliclona*, *Petrosia*, *etc*.), corals (*Alcyonium*, *etc*.)
5	many sponges, corals and starfishes, some sea lilies	14	some starfishes, sponges (*Jereicopsis*, *Theonella*)	23	many starfishes, some corals, sponges (*Xestospongia*, *Ircinia*)
6	many sponges, corals and starfishes, some sea lilies	15	many starfishes	24	many starfishes, fishes, sponges (*Crella*)
7	some starfishes and octocorals, fishes, sponges (*Poecilastra*)	16	Many starfishes, corals, sea worm (*Cephalofiscus gilchristi*)	25	some starfishes and octocorals
8	many starfishes, sponges (*Jereicopsis*, *Theonella*), fungi (*Tilopilus*)	17	sponges (*Echinoclathria*, *etc*.), corals (*Dendronephthea*), sea worm (*Cephalofiscus gilchristi*)	26	many starfishes, some fishes, sponges (*Polymastia*)
9	many sponges and corals, fungi (*Tilopilus*)	18	octocorals (*Sinularia*, *etc*.), sponges (*Echinoclathria*)	27	many starfishes, some fishes, sponges (*Polymastia*)
				28 [a]	many starfishes
				29 [b]	many starfishes, sponges (*Petrosia*)

[a] In the side chains of ergostane derivatives. [b] In the side chains of ergostane and stigmastane derivatives.

and the use of these enzymes or competent cells for targeted transformations of steroid substrates.

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