ChemInform Abstract: Marine Metabolites: The Sterols of Soft Coral

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Marine Metabolites: The Sterols of Soft Coral†

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† Dedicated to the memory of the mentors of the first author: Late Professors L. Ramachandra Row and David Lavie worked at Andhra University and the Weizmann Institute of Science, Rehovot, Israel, respectively.

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1. Introduction

Steroids are a highly diverse group of metabolically active compounds. Inborn errors in sterol biosynthesis in humans are now known to cause several disorders, including congenital disorders due to the impairment of the function of embryonic signaling proteins.[1] For example, a deficiency of 7-dehydrocholesterol (**A7.01e$_1$**) is discovered to be at the root of Smith−Lemli−Opitz syndrome (SLOS), one of the best known autosomal recessive malformation syndromes.[2,3]

Among the various classes of secondary metabolites that are produced by soft corals, sesqui- and diterpenes are a major division.[4] Steroids come next as a major group of metabolites characterizing corals. The "usual" sterols have a 3β-hydroxy-Δ^5- (or Δ^0-) cholestane nucleus and a C_8−C_{10} side chain.[5] There are over 200 such sterols, occurring in marine organisms as complex inseparable mixtures, and their identification is usually done by GC-MS. The "unusual" sterols[6] have either or both of the characteristics of (i) side chains ranging from C_0 to C_{12}, involving loss of carbon atoms or their addition at positions other than C-24, and (ii) (multiple) oxygenation of the nucleus and/or the side chain. These sterols, by virtue of their greater spread on the polarity scale, can be isolated in pure condition by liquid chromatography. But many of them are unstable and need careful handling under mild conditions to prevent artifact formation.

Steroidal hormones, bile acids, and signaling compounds such as oxysterols are oxygenated derivatives of cholesterol. Oxysterols exhibit many biological activities that are of potential physiological, pathological, or pharmacological importance. Many of them have been found to be potent inhibitors of cholesterol biosynthesis, and one or more oxysterols may play a role as the physiologic feedback regulator of cholesterol synthesis. Oxysterols also inhibit cell replication and have cytotoxic properties—effects which suggest that these sterols may participate in the regulation of cell proliferation and may be potentially useful as therapeutic agents for cancer. There is also considerable evidence that oxysterols may be involved in the pathogenesis of atherosclerosis.[7] The biological activity of these steroids has often been investigated but not their biosynthesis.[8] A knowledge of the steroid pathway in corals could provide additional clues to understanding their role in reproduction,

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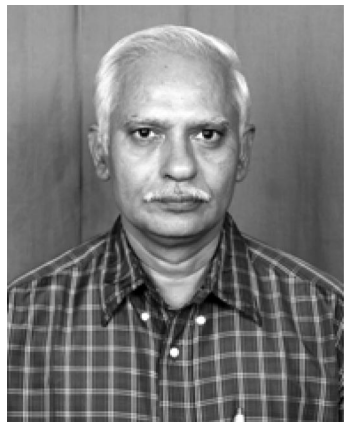

Nittala S. Sarma, a Professor of Marine Chemistry at Andhra University, was born in 1950 in Andhra Pradesh, India. He obtained his M.Sc. (1970) and Ph.D. (1976) degrees from the same university. His research mentors were Professor L. Ramachandra Row initially and later Professor David Lavie at the Weizmann Institute of Science, Israel, where he worked as a DAAD Fellow (1979−81), and Professor Teruo Matsuura (1981-82) at Kyoto University, Japan, where he worked as a JSPS Visiting Scientist. He pioneered the then virgin field of marine natural products at Andhra University in the late seventies and published several papers on the isolation and structural elucidation of bioactive compounds from algae, sponges, and soft corals. In parallel, he developed an interest in marine organic geochemistry and biomarkers that are of paleoceanographic interest. For the benefit of students, he has recently published papers explaining science concepts from the etymology of technical terms. He served on the Editorial Boards of the *Indian Journal of Marine Science* (2000−2002) and *Seaweed Research and Utilization* (2000−2006), and he is now on the editorial Board of the *Journal of Marine and Atmospheric Research*. He received two awards from Andhra University: Best Researcher Award (2003) and Dr. Sarvepalli Radhakrishnan Best Academician Award (2007).

Moturi S. Krishna was born in 1978 (Ethakota, India). He received his B.Sc. in 1999, his M.Sc. in Chemistry in 2001, and his Ph.D. in 2006 from Andhra University, Visakhapatnam, India. His Ph.D. supervisor was Professor Nittala S. Sarma, and his work dealt with the organic geochemical proxies of paleoceanogrpahic processes embedded in the Indian Ocean sediments. He is currently positioned as a Fast Track Young Scientist of the Department of Science and Technology (DST), Government of India. His current research interests include lipid biomarkers with application in climate research. He has coauthored four papers and two chapters in a monograph.

in chemical signaling, or as defensive metabolites and in providing enzyme systems that could be used for *in vitro* synthesis.

Due to the biological activities associated with oxysterols, there is considerable interest in marine organisms when compared to land plants, as the former are a prolific source. Polyhydroxy sterols have been found in various phyla of marine organisms, e.g. algae, porifera, coelenterata, bryozoa,

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mollusca, echinodermata, arthropoda, tunicata, and chordata; among them, the phylum Coelenterata (Cnidaria) and especially its subclass Octocorallia (class: Anthozoa), commonly called "soft corals", occupy a preeminent position as the contributor of the largest number of polar steroids. A comprehensive review of the marine polyhydroxy steroids (of all sources) was published in 1993 (in this journal).[9] The subsequent reviews that appeared briefly touch upon coral sterols.[10−12] The purpose of the present review is, apart from giving the account as of the year 2007, to describe the biogenetic relationships that possibly exist in the elaboration of the oxidation pattern of the sterol ring system.

A holistic biogenetic approach is presented in the review that could be helpful in chemotaxonomy. Success on this front has so far been of limited value, since corals identified as belonging to a particular species in terms of taxonomy produce different sets of sterols in the hands of different groups of workers and in the hands of the same group when the collections are at different times or from different locations. Even so, the sterol chemistry of octocorals, as shown in the present review, appears to follow a pattern. In

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general, in one particular "species" (i.e., a homogeneous collection), the co-occurring sterols all belong to a particular group (only) among the five biogenetic groups "A" to "E" identified. The occurrence of sterols across the groups is rare; whenever it happens in a particular species, the phenomenon is explained in terms of a uniqueness of the organism.

2. Biosynthesis

Extensive studies are available of the general biosynthesis of steroids as a group of compounds.[13,14] But in the case of marine sterols, biosynthetic studies are mainly directed so far to alkylations and not so well on how oxidation proceeds. Much of it is still in the realm of "speculation". What has, however, been realized well in the case of octocorals is that *de novo* biosynthesis is an important mechanism,[15] with the rudimentary process being assimilation or modification of dietary metabolites or those produced by symbiont organisms in the coral polyps.[16] In support of the latter mechanism, it has for example been found that from the metabolites of a microalga, e.g., *Symbiodynium microadriaticum* constituting the diet, the coral is able to perform its share of biosynthesis.[17] It has also been found that axenic cultures of algae living symbiotically in coral polyps produce a set of sterols different from that produced by the host coral.[18] Thus, both the host and guest stand to gain in terms of enriched variety of evolved secondary metabolites. Zooxanthellae are present endosymbiotically in the polyps of most octocorals; recently, zooxanthellae are discovered in octocoral genera that were assumed to be azooxanthellate[19] and it is likely that algal/bacterial endosymbionts may increasingly be realized to be the backbone of octocoral's chemical richness. It should also be mentioned that Scleractinian (hard, i.e., hexa) corals have a much greater trophic contribution of zooxanthellae to their energy budget than octocorals[20] but host less chemical richness. Since, in the biosynthetic ability of a coral, the symbionts (or diet) play a rudimentary role, there is enough ground for the coral's steroid composition to vary with ecological factors, as can be seen in the present review.

The soft corals of Antarctica experience little varying environmental conditions—the sea surface temperature that is near the freezing point changes only a little more than 0.1−0.5 °C throughout the year,[21] and the endemic fauna which are thought to be extremely old, ca. 30 million years, are potentially subject to little seasonal acclimatization.[22] The steroidogenic enzymes present in the Antarctic corals *Alcyonium paessleri* and *Clavularia frankliniana*, viz., 5α-reductase, 3β-hydroxysteroid dehydrogenase (HSD), 17β-HSD, and acyl transferase,[23] are stenothermal, i.e., active at >10 °C above the ambient encountered by these species, as in the case of warm water species.[24] The metabolic rates are, however, much less than those observed for tropical invertebrates.[5,24,25] From the biogeographically isolated corals through species of the extremely cosmopolitan tropical environments such as the Caribbean and Great Barrier reef, the great diversity that exists for enzyme systems and metabolic rates should answer the bewildering variety in sterol oxidation pattern.

The starting material for the production of cholest-5-en-3β-ol is the 30-carbon lanosterol reacting in a series of dehydrogenations, reductions, and demethylations. For the biosynthesis of lanosterol, higher plants use the classical acetate/MVA pathway of IPP (isopentenyl diphosphate) production. Until the early 1990s, this pathway was the only pathway known to be operating in all organisms for terpenoid/steroid synthesis; then, a second pathway, a nonmevalonate pathway, *viz.*, the DOXP/MEP (1-deoxy-D-xylulose-5-phosphate/methyl-D-erythritol) pathway, was detected and found operating in bacteria.[26] Ever since then, more and more discoveries of DOXP/MEP involvement are being reported, and often the two mechanisms exist simultaneously, each for different classes of metabolites. Green plants possess both MVA and DOXP/MEP mechanisms, the former for sterols (such as ergosterol) and the latter for isoprenoid constituents (e.g., carotenoids and phytol). This applies to several algal groups. But in Chlorophyta, the nearest algal group to green plants, the MVA pathway is totally missing. In general, the DOXP/MEP pathway operates in most bacteria; however,

Table 1. Genera That Yielded Polar Sterols

			I. Order: Alcyonaceae			
family	Alcyoniidae	Nephtheidae	Xeniidae	Asterospiculariidae	Nidaliidae	Anthothelidae
genera	*Alcyonium*	*Nephthea*	*Anthelia*	*Asterospicularia*	*Pieterfaurea*	*Tripalea*
	Anthomastus	*Dendronephthya*	*Heteroxenia*	*Scleronephthya*[b]		
	Cespitularia	*Gersemia*[a]	*Xenia*			
	Cladiella	*Capnella*				
	Eleutherobia	*Litophyton*				
	Lobophytum	*Scleronephthya*[b]				
	Minabea	*Spongodes*				
	Sarcophyton	*Stereonephthya*				
	Sclerophytum					
	Sinularia					
			II. Order: Gorgonaceae			
family	Plexauridae	Gorgoniidae	Acanthogorgiidae	Melithaeidae		
genera	*Anthoplexaura*	*Eunicella*	*Acalcygorgia*	*Acabaria*		
	Astrogorgia	*Gorgonella*	*Acanthogorgia*	*Melithaea*		
	Bebryce	*Leptogorgia*	*Anthogorgia*	*Pieterfaurea*		
	Echinogorgia	*Lophogorgia*	*Calcigorgia*			
	Eunicea		*Muricella*[c]			
	Euplexaura					
	Menella					
	Muricea					
	Plexaurella					
	Psudoplelxaura					
family	Subergorgiidae	Ellisellidae	Isiididae	Primnoidae		
genera	*Subergorgia*	*Ctenocella*	*Isis*	*Dasystenella*		
		Junceella				
			III. Order: Stolonifera			
family	Clavulariidae					
genera	*Clavularia*					
	Pachyclavularia					
	Telesto[d]					
			IV. Order: Pennatulaceae			
family	Pteroeididae	Pennatulidae				
genus	*Pteroides*	*Ptilosarcus*				
			V. Order: Telestaceae			
family	Telestiidae					
genera	*Telesto*[d]					

[a] Also referred to as *Eunephthya*. [b] Classified under both families. [c] Classified under the family Paramuriceidae also. [d] Referred to as *Carijoa* also; classified under Telestidae also.

exceptions do occur, e.g., the photosynthesizing *Euglena* and the green nonsulfur bacteria *Chloroflexus*, which do not possess the DOXP/MEP pathway.[27] Human pathogens, e.g., *Mycobacterium tuberculosis*, which causes teberculosis, *Plasmodium falciparum*, causing malaria, and *Helicobacter pylori*, causing gastritis and related health problems that are responsible for a majority of deaths each year globally and particularly in developing countries, operate through the DOXP/MEP pathway. The emergence of their newer strains with multidrug resistance indeed poses a therapeutic challenge. A novel approach for meeting this challenge would be a selective interference of the metabolic pathway of these pathogens, the common nonmevalonate (DOXP/MEP) pathway.[28]

3. Coral Taxonomy

Cnidaria, formerly known as Coelenterata, is one of the largest among the phyla.[29,30] The phylum contains three classes: Anthozoa, Scyphozoa, and Hydrozoa. The largest class is Anthozoa. In the animals of this class, the stomach is divided into various compartments; they have no medusoid stage and are exemplified by sea anemones, corals, and sea pens. The animals of the Scyphozoa class also have no medusoid stage, e.g., jellyfish. The third class, Hydrozoa, are exemplified by hydroids and hydromedusae. There are two subclasses in Anthozoa, viz., Hexacorallia (= zoantharia) and Octocorallia. The sea anemones, including the Antipathiidae, of which the *Antipathes* black coral has received a lot of attention of chemists, and the stony or "true" (hexa) reef building corals, e.g., Scleractinian corals, fall into the former subclass. Unlike these hard corals that contain less than 1% by weight of organic matter, the octocorals are mostly soft bodied with >60% of organic matter on a dry weight basis. A lot of attention has been paid to the chemistry of soft corals. The organisms of the subclass Octocorallia are divided between six orders. Among these, Alcyonacea, which are fleshy soft corals, and Gorgonaceae, which are referred to by the common names of sea fans and sea whips, are by far the most widely distributed and studied. The sea pens and sea pansies of the order Pennatulaceae, which are matlike corals, the members of the order Stolonifera, e.g., the red organ-pipe coral, and the common fouling organisms that constitute the order Telestaceae, due to their limited geographic occurrence, are studied less. Their chemistry is also included in this review. The sixth order, viz., Heliporaceae, are indeed stony corals, e.g., blue coral, and do not figure in this review, as no polar steroids are so far reported from them.

In Alcyonaceae, Alcyoniidae and Nephtheidae are the largest families, containing several commonly occurring genera (Table 1). Xeniidae and Asterospiculariidae corals are less represented. In Gorgonaceae, the important families are Gorgonidae, Plexauridae, and Isiididae, and the less numerously represented families are Acanthogorgiidae, Subergorgidae, Melilthaeidae, and Ellisellidae.

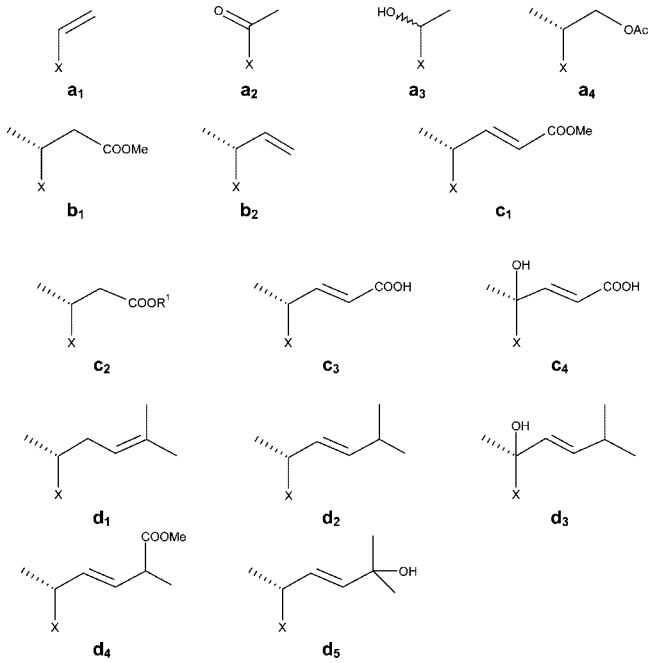


Figure 1. C_2, C_3, C_4, C_5, and C_7 side chains (X = sterol nucleus).

4. Polar Sterols from Corals

The corals subjected to chemical examination by different research groups have been collected from the sprawling Indo Pacific bordering Japan, China, Taiwan, Indonesia, Australia, etc., the Caribbean, Mediterranean, Red Sea, etc. regions, and at locations of the Indian seas, e.g., the Andaman & Nicobar and Lakshadweep Islands and the Gulf of Mannar.

From the available knowledge (literature up to the year 2007), it would not be possible to draw any definitive conclusions on the chemotaxonomy of corals, due to limitations, namely (i) the complete sterol composition is not always available/reported, (ii) chemistry changes in response to geographic (ecological) variations, and (iii) the inchoative, often improper taxonomic identification. Even so, chemical composition seems to have internal order for each "species" reported.

In order to propose biosynthetic relationships that exist between various sterols at the "species" level, as polar sterol biosynthetic studies on corals are rare, clues are taken from the pathways operating in the terrestrial plants and animals, which are documented quite well, and since the pathways operating in corals are perhaps similar to those operating in terrestrial organisms.[24] Recently, we have brought out the possible biogenetic relationships that exist among polar sterols of marine sponges.[31] The oxidation of the sterol ABCD ring system that may be taking place in a sequential manner, as part of biogenesis within the soft corals, appears to be distinct from that operating in sponges. While, for sponges, the presence of unsaturation seems to be providing active sites for oxygenation, for corals, oxygenation seems to proceed, as presented in this review, mostly independent of activation *via* unsaturation.

4.1. Oxidation of Side Chain

Polar sterols can arise by oxidation of the "usual" 3β-hydroxy-Δ^5 nuclear structure or of the "usual" C_8 or C_9 side chain. The side chains of corals can have from nil to eleven carbons. Their structures are given in Figures 1−5 in the sequence of increasing number of carbon atoms—two, three, four, five, and seven carbon side chains in Figure 1, eight carbon side chains in Figure 2, nine carbon side chains in Figure 3, ten carbon side chains in Figure 4, and eleven carbon side chains in Figure 5. The nine and eight carbon side chains are more common, themselves varying in as many as 35 and 27 ways, respectively, in acyclic side chains. The 24-methylene group containing nine carbon side chain (**f$_3$**) is by far the most prolific in coral sterols. Others are the nine carbon containing ergostane (**f$_1$**), two carbon pregnene (**a$_1$**), and eight carbon cholestane (**e$_1$**) side chains followed by the eleven carbon gorgostane (**h$_1$**) side chain. Among polar side chains, the nine carbon side chain **f$_{10}$** is relatively more common. Member sterols with other side chain combinations are fewer; in quite a few cases, a single sterol stands out. Although side chains are predominantly acyclic, in quite a few of the C_8 and C_9 side chains, internal cyclization is prevalent, e.g., **e$_{28}$** and **e$_{29}$** (C_8; Figure 2) and **f$_{31}$** and **f$_{33}$** (C_9; Figure 3) side chains. Oxidation in side chains leading to cyclization between nucleus and side chain carbons is a unique feature of coral sterols. Upon C(18) functionalization as COOH or CHO, C(20) and C(22) are seen producing lactones or lactols, and as a further step, C(22) spiroketals by involvement of 25-OH. A C(16) OH also gives place to formation of new cycles by involvement of C(22) and to formation of ketals by involvement of C(24). A second type of C(22) spiroketals is formed in a unique fashion in

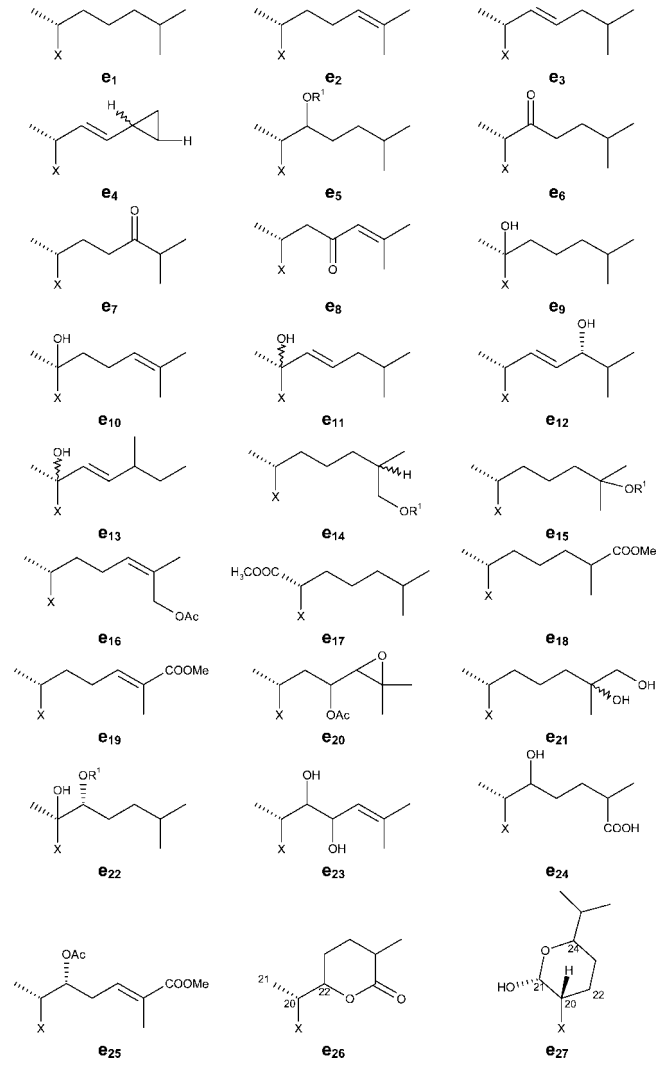


Figure 2. C_8 side chains (X = sterol nucleus).

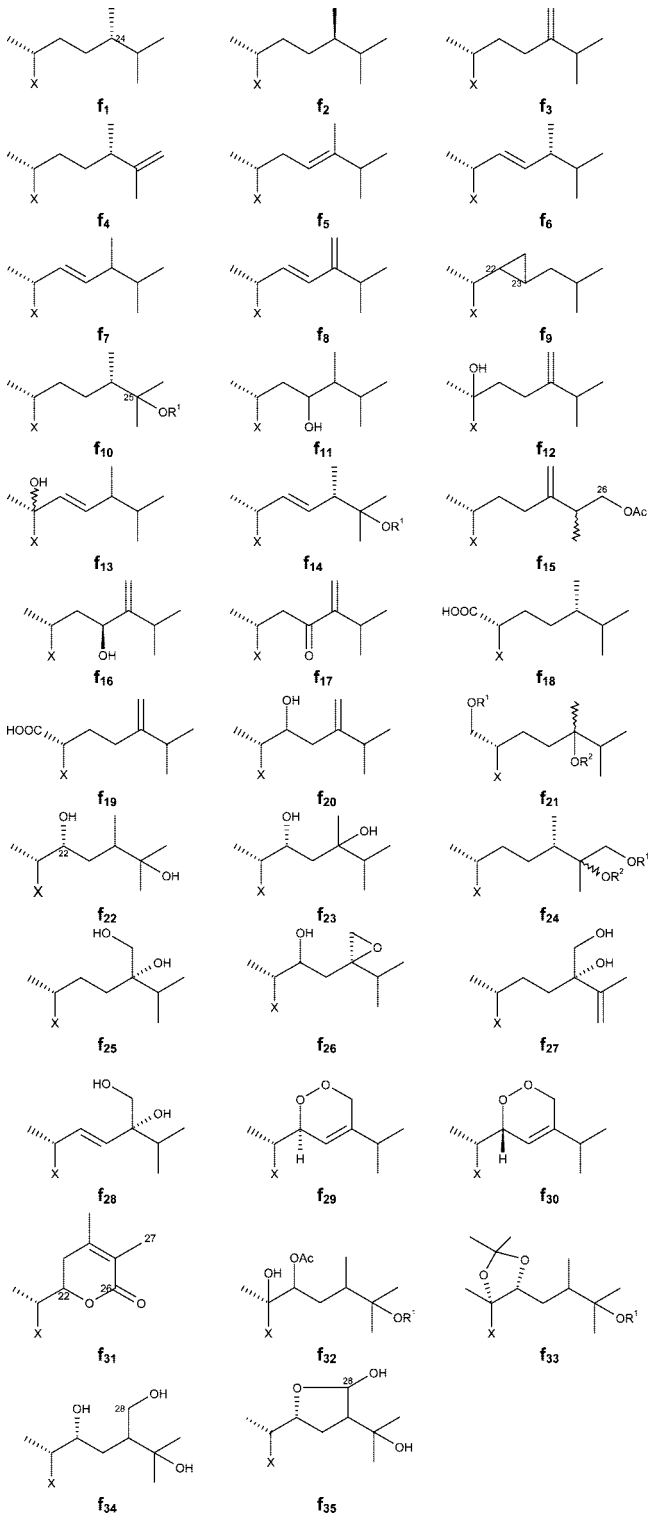


Figure 3. C_9 side chains (X = sterol nucleus).

hippurins and related sterols of the gorgonian *Isis hippuris* by involvement of 16β-OH. Indeed, these were once postulated as chemotaxonomic markers. But with more and more studies performed, the proposals seem to become unsustainable. Except in hippurins and pregnane glycosides, also of gorgonians, side chain oxidations do not, in general, seem to conform to any recognizable pattern. Hence, for this review, side chain oxidation pattern is not examined further. Oxygenation indicated as OR^1 and OR^2 in Figures 1−5 is for carbons of side chains and that given as OR_1, OR_2, and OR_3 in Figures 6−24 is for carbons of the ring system.

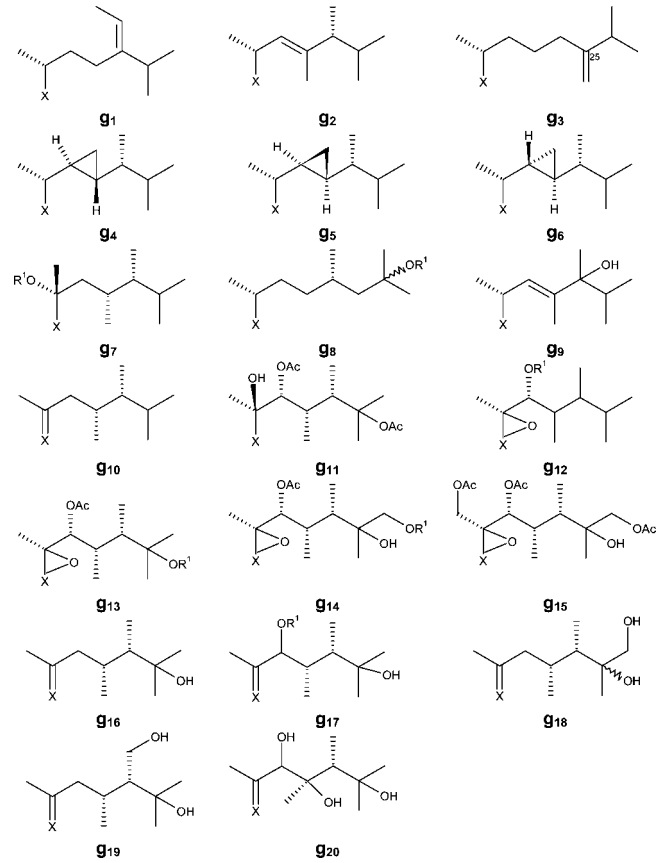


Figure 4. C_{10} side chains (X = sterol nucleus).

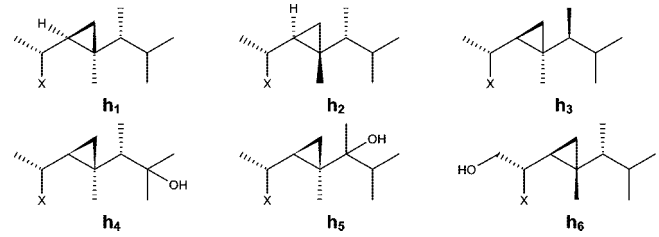


Figure 5. C_{11} side chains (X = sterol nucleus).

4.2. Oxidation of the Ring System

For the oxidation of the regular sterol (i.e., cholesterol) ring nucleus to produce polar sterols, some interesting generalizations can be made. What generally happens is a sequential oxidation usually starts around the 3β-hydroxy-Δ^5 structural moiety of the A/B ring system and proceeds to the other end (rings C/D system). Activation by Δ^5 of the allylic positions generally provides one major pathway in the production of polar steroids. Subsequent dehydration and the progression of activation of new allylic positions in a cascading manner enables oxidation to spread to the remaining part of the molecule. This mechanism is found extensively in marine sponges[31] but only to a lesser extent in corals. In corals, a major phenomenon is that polar sterols form by oxidation of carbons remotely away from Δ^5 or any other activation site. Indeed, even when the Δ^5 is saturated or oxidized to epoxides or diols, oxidation of the rest of the carbons in the nucleus can proceed further. In the account that follows, Δ^5 sterols and sterols in which allylic, i.e., C(7) or C(4), activation by Δ^5 is seen are only few in number and classified as class A sterols (section 5). The large number of polar sterols that are formed independent of Δ^5 activation are grouped into classes B to E (sections 6−10).

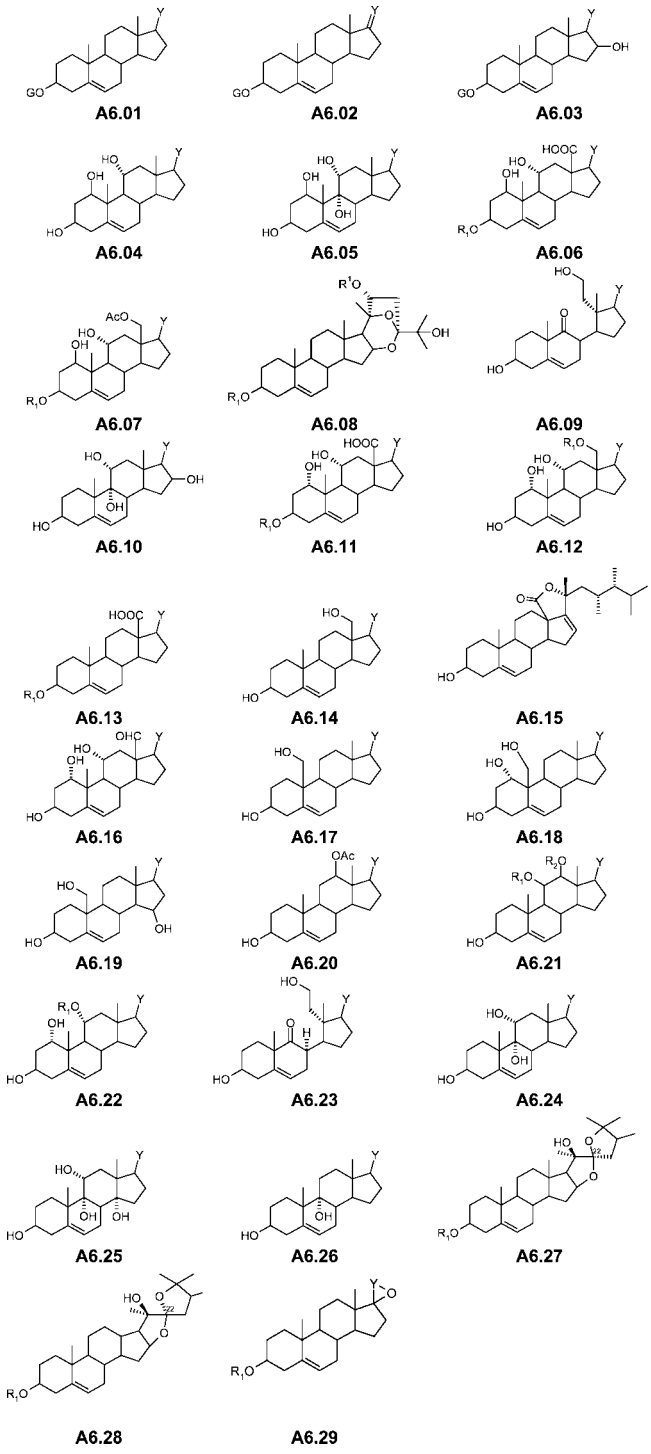


Figure 6. Δ^5-Sterols (Y = side chain).

5. Δ^5 Sterols (Class A Sterols)

5.1. Sterols Lacking Allylic Oxidation (Figure 6)

Sterols containing "usual" (nonpolar) ring structure (and the "usual"/"unusual" nonpolar side chain) would become polar when the regular 3β-OH group is involved in glycoside formation. Two new glycosides that differ only in the sugar part are **A6.01f$_{10}$** (G = α-fucose) from *Sinularia gravis*[32] and **A6.01f$_{10}$** (G = β-arabinose) from *S. grandilobata*;[33] both species from the Andaman & Nicobar Is. (India) are thus polar. These two sugars are quite commonly involved in glycosidating the 3β-OH. *Cladiella krempfi* gave the pregnene glycoside **A6.01a$_1$** (G = arabinose) from the Panaman

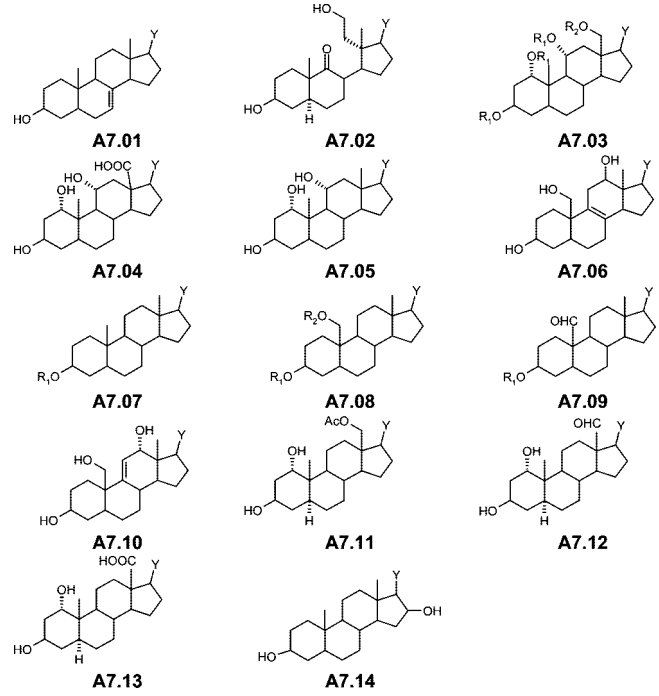


Figure 7. 5,6-Dihydro sterols (Y = side chain).

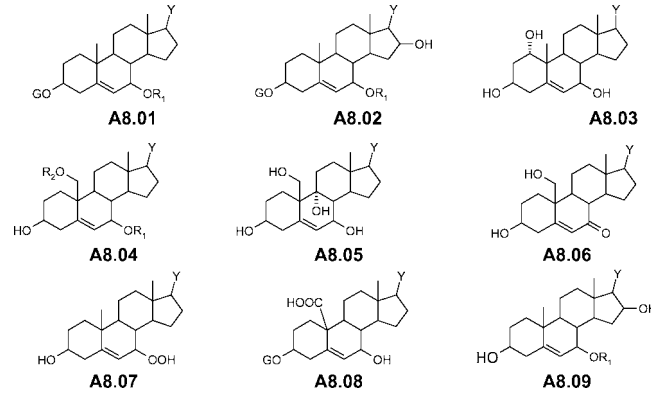


Figure 8. 7β-Activation (Y = side chain).

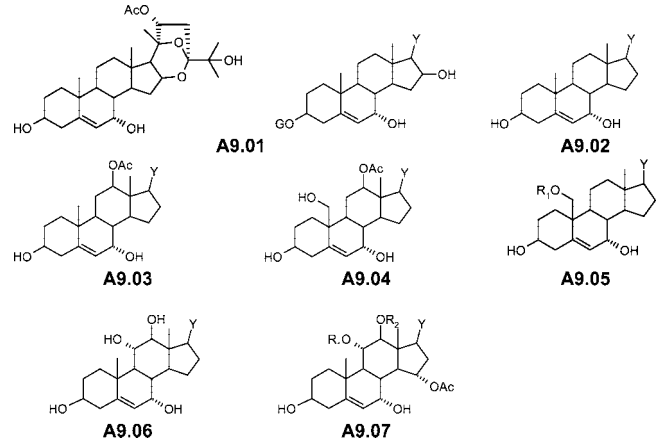


Figure 9. 7α-Activation (Y = side chain).

collection[34] as well as a Chinese collection.[35] Two α-fucosides **A6.01a$_1$** (G = α-L-fucose) and the dihydro compound **A7.07a$_1$** (R$_1$ = α-L-fucose) are also reported in the Chinese collection,[36] while yet another collection from Minicoy Is. (India) gave the regular sterol **A6.03f$_2$** with the 16β-OH.[37] An unidentified *Cladiella sp.* from Sanya Bay (China) gave

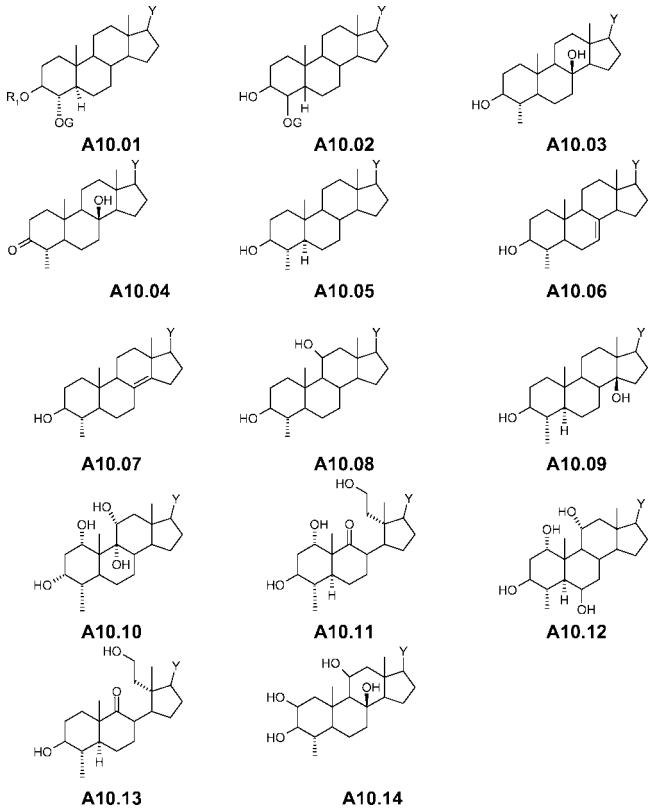


Figure 10. C(4)-Activation (Y = side chain).

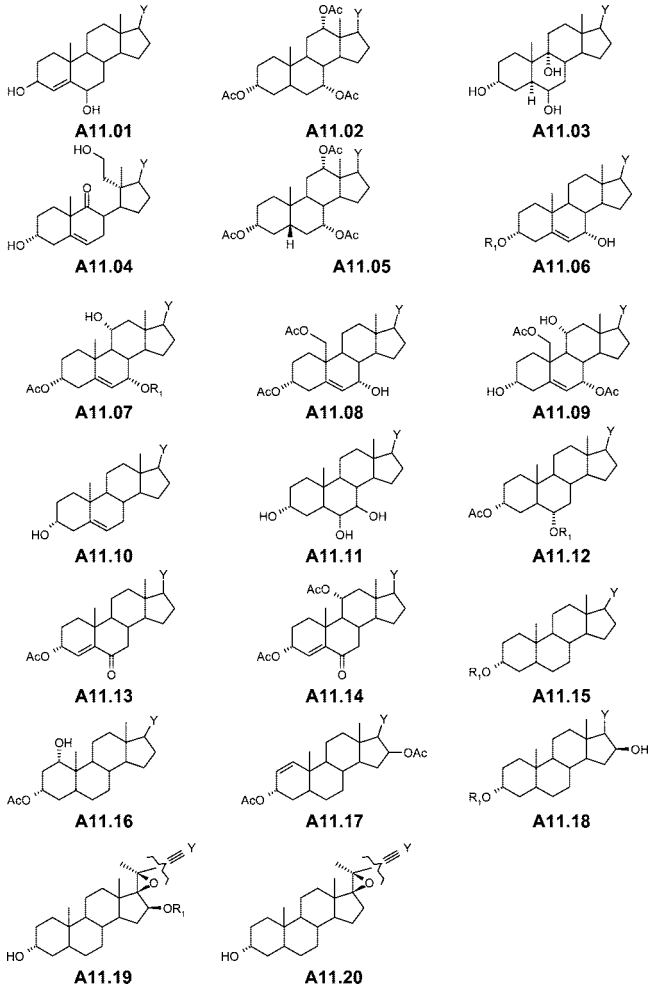


Figure 11. 3α-OH formation (Y = side chain).

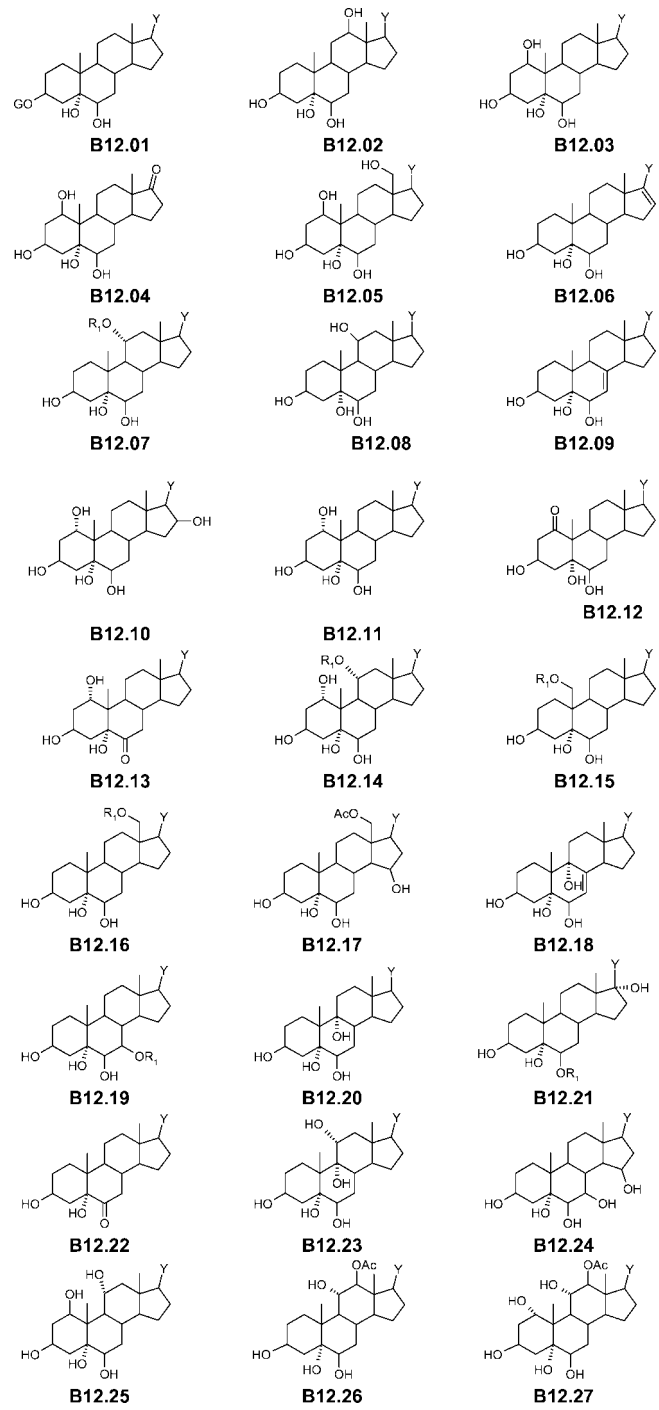


Figure 12. 3β,5α,6β-Trihydroxy sterols (Y = side chain).

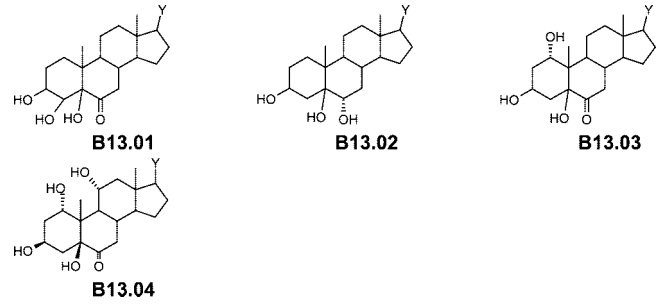


Figure 13. 5β-Hydroxy sterols (Y = side chain).

the pregnene glycosides **A6.01a$_1$** (G = α-L-fucose) and **A6.01a$_1$** (G = β-D-xylose).[38]

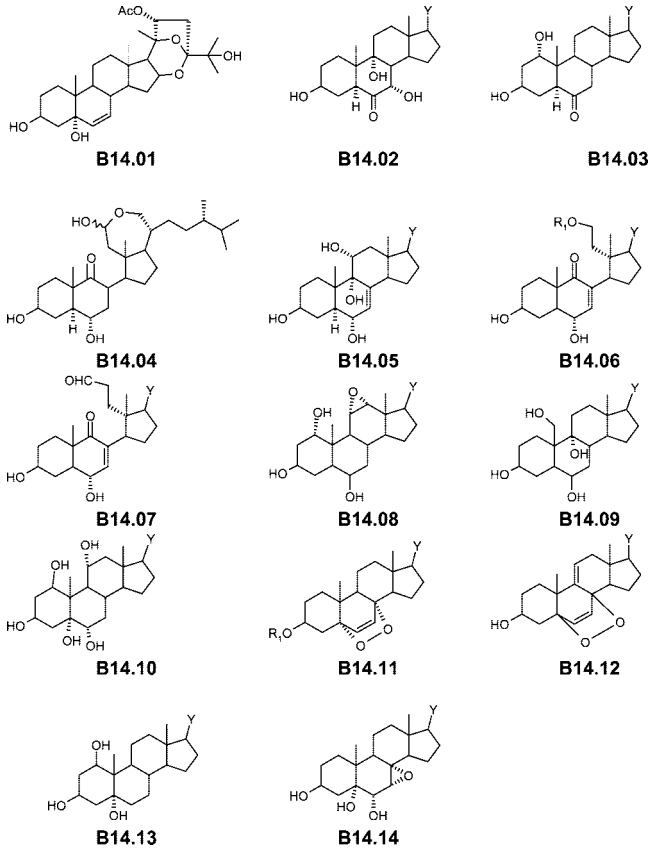


Figure 14. 5α(H)- and 5α-oxy sterols (Y = side chain).

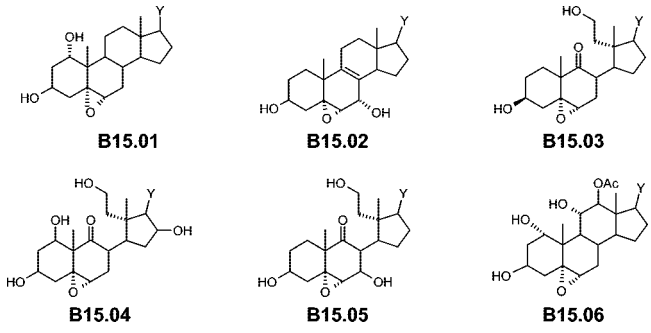


Figure 15. 5α,6α-Epoxides (Y = side chain).

The gorgonians produce pregnene glycosides in large yields, a feature once postulated as a chemotaxonomic marker. The pregene **A6.01a$_1$** (G = 6′-acetyl-β-D-galactose) is from the gorgonian *Eunicea lacinata* from Barbados,[39] while the same glycoside **A6.01a$_1$** (G = 6′-acetyl-α-L-galactose) with the less usual α-glycoside linkage attached to the 3β-OH is from *Muricea purpurea* from Panama.[40] Pregnene glycosides based on arabinosyl acetate are **A6.01a$_1$** (G = 3′-acetyl arabinose) and **A6.01a$_1$** (G = 4′-acetyl arabinose) from *Muricia austere*, also of the Pacific coast off Panama.[34] Muricins 1 to 4 from *Muricia fruticosa*[41] are all based on **A6.01a$_1$** but have different sugar units (G) based on α-glucosamine-2,3-diacetate on the 3β-oxygen. Different muricins arise by esterification of the sugar C(4) and C(6) alcohol groups as Ac and COPr″ (muricin 2), COPr″ and Ac (muricin 3), and COPr″ and COPr″ (muricin 4), respectively. A further variety of the sugar moiety is seen in the pregnene (**A6.01a$_1$**) glycosides of *Eunicea sp*. (G = 4′-*O*-acetyl-α-L-fucopyranose)[42] and *E. pinta* (G = β-D-xylopyranose), both from Columbia.[43] The species of *Eunicea* are among the most abundant octocorals of the Caribbean.

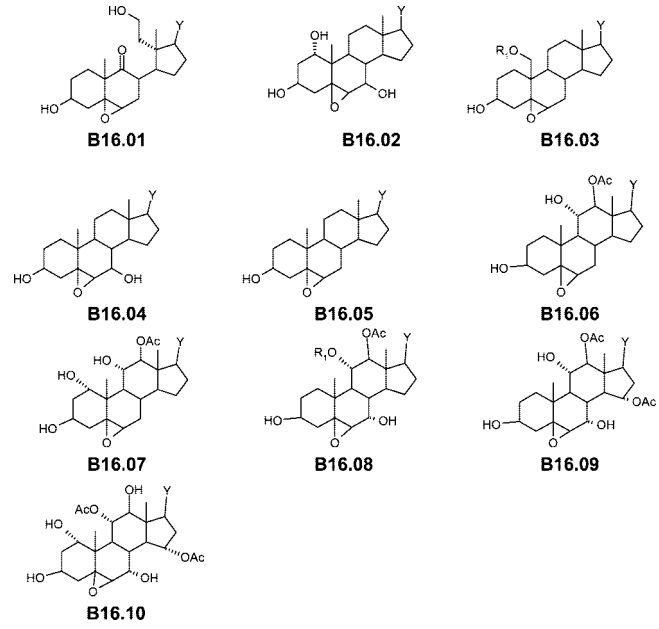


Figure 16. 5β,6β-Epoxides (Y = side chain).

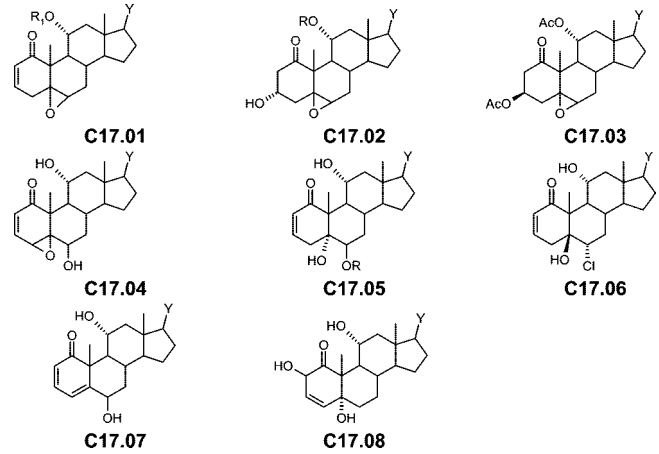


Figure 17. C(1) ketones (Y = side chain).

Pregnene glycosides should no longer be considered as chemotaxonomic markers for gorgonians, as they have since been isolated, although in lower yields, from some Alcyonacean corals too (see above). Glycosides of regular sterols are also isolated from gorgonians, e.g., the β-D-galactopyranoside of **A6.01** from *Pseudoplexaura wagenaari* collected from Key Biscayne, Florida.[44] The differently acetylated arabinosides **A6.17e$_{16}$** (G = 4-*O*-acetyl arabinose, R^1 = H), **A6.17e$_{16}$** (G = 3-*O*-acetyl arabinose, R^1 = H), **A6.17e$_{16}$** (G = arabinose, R^1 = Ac), and **A6.17e$_{16}$** (G = arabinose, R^1 = H) are from the gorgonian *Junceella juncea* of China.[45]

Glaucasterol **A6.01e$_4$** is a nonpolar sterol unique for its cyclopropane ring in the side chain isolated from the Ishigaki Is. (Southern Japan) collection of *Sarcophyton glaucum*.[46] Also unique is sarcosterol **A6.02g$_{10}$**, considered as the first example of a genuine marine sterol having a 17(20)E double bond from the same organism.[47] Its side chain hydroxylated steroid, 25-hydroxysarcosterol (**A6.02g$_{16}$**), is from *S. mayi* from Japan.[48] Steroids **A6.02g$_{17}$**, **A6.02g$_{18}$**, **A6.02g$_{19}$**, and **A6.02g$_{20}$**, in which a more extensive side chain oxidation is present, are from a collection of the same species from an unspecified location.[49] *S. digitatum* from China gave **A6.01f$_{34}$** (G = Ac), named as sardisterol, which also contains three

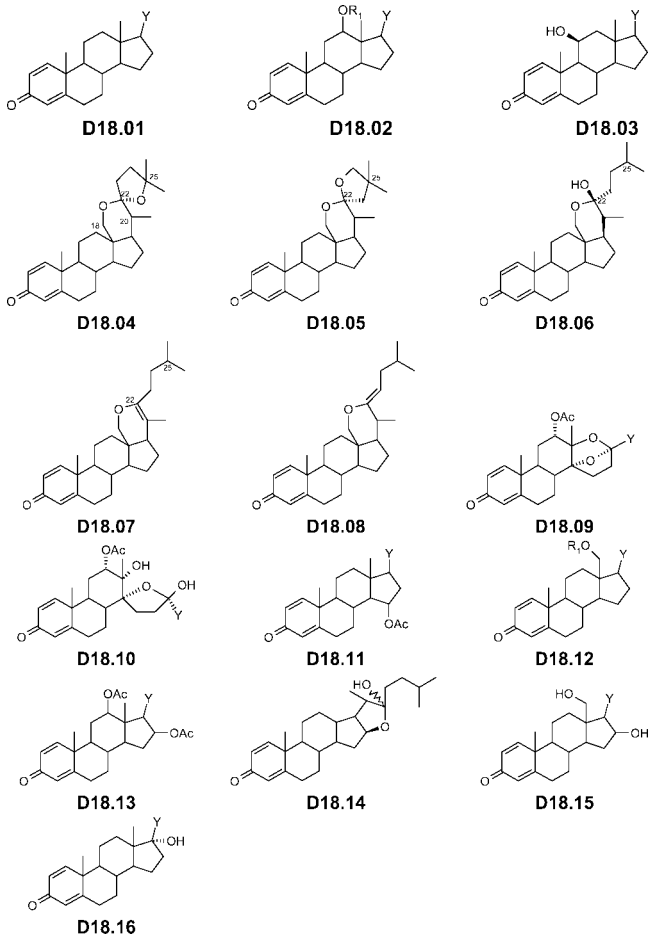


Figure 18. C(3) ketones/dienones (Y = side chain).

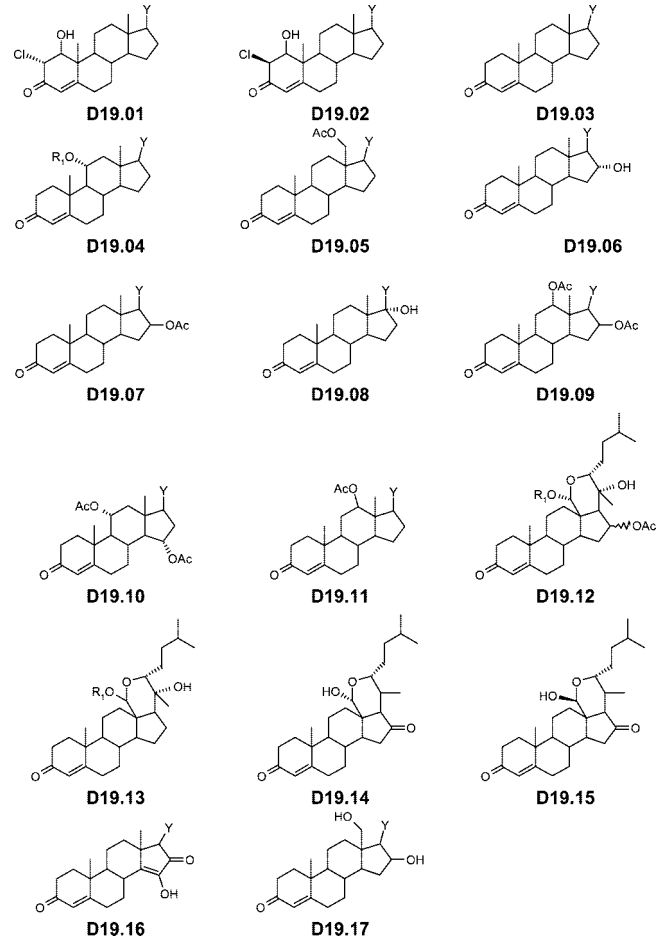


Figure 19. C(3) ketones: Δ^4-enones (Y = side chain).

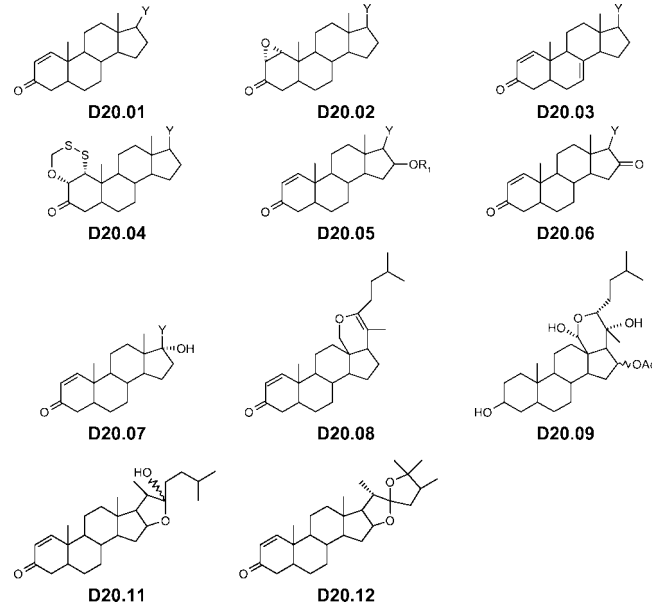


Figure 20. C(3) ketones: Δ^1-enones (Y = side chain).

OH groups in the side chain.[50] Its alcohol **A6.01f$_{34}$** (G = H) is recently reported from *S. crassocaule* of the Sanya Bay.[51]

Cladiella australis produces the carboxylic acid **A6.01f$_{18}$** (G = Ac).[52] Sinulabosterol **A6.06f$_3$** (R_1 = Ac) and its 3-desacetate **A6.06f$_3$** (R_1 = H) of *Sinularia abrupta* from Okinawa have oxygen substitution similar to that in **A6.05 h$_6$**, but uniquely the 18-CH_3 is oxidized to a COOH group. The precursors of 18-COOH compounds, namely the 18-CH_2OAc and 18-CH_3 steroids **A6.07f$_3$** and **A6.04f$_3$**, respectively, have also been isolated as known compounds.[53] In tests for antihistamine activity, sinulabosterol showed an inhibitory effect that was 6500 times stronger than that of disodium cromoglycate, a known antiallergic drug.[53]

Extensive side chain modification is seen in the sterols of gorgonians, e.g., *Gorgonella umbraculum* of the South West Bay of Bengal (India), yielding the C(24) ketal **A6.08** (R_1 = H, R^1 = Ac)[54] and its 22-desacetate **A6.08** (R_1 = R^1 = H).[55] The C(24) ketal structure in the side chain was unprecedented. A recent report on *Subergorgia reticulata* of Hainan Is. (South China Sea) yielded five sterols named suberoretisteroids A through E that also contain this C(24) ketal structure in the side chain. Steroids A **A6.08** (R_1 = Ac; R^1 = H), B **A6.08** (R_1 = H; R^1 = Ac), and C **A6.08** (R_1 = R^1 = Ac) among them have the unactivated ring A/B system. In D **A9.01** (full structure), the C(7) is functionalized with α-OH, and in E **B14.01**, the A/B structural moiety is 5α-OH-Δ^6 (Figure 14).[56] The stereochemistry of C(16) that is involved in the ketal formation, originally given as α,[54,55] is recently revised to β.[56] Suberoretisteroid A was given the name "reticulatin" by another group, who also reported from the same species collected in China, reticulatic acid (**A6.01c$_4$**; R_1 = Ac) with a degraded side chain.[57] A *Muricea sp.* from off the Panaman coast yielded **A6.01f$_{26}$** (G = H), together with the pregnane **A7.07a$_1$** (R_1 = H).[58] The genus *Pseudopterogorgia* was considered as one of the most chemically defended among gorgonians. This ability seems to derive from 9(11)-seco steroids present in these gorgonians at high concentrations. *P. americana* has an enzyme that leads to 9(11)-seco steroids from regular sterols in the coral in such

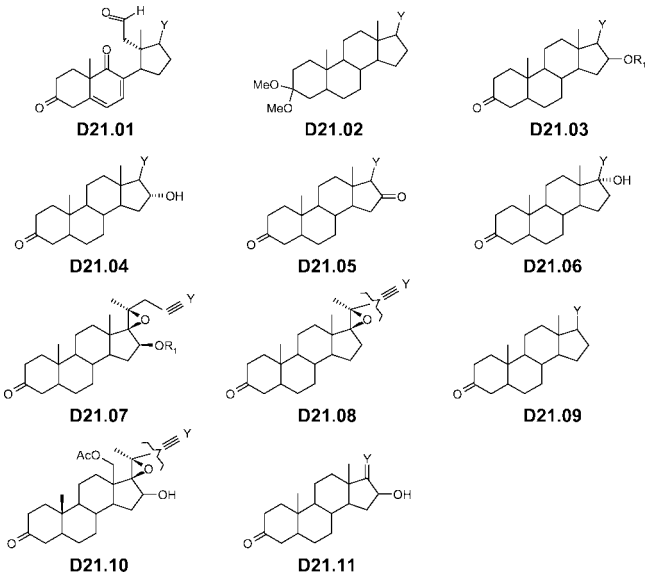


Figure 21. Saturated ketones (Y = side chain).

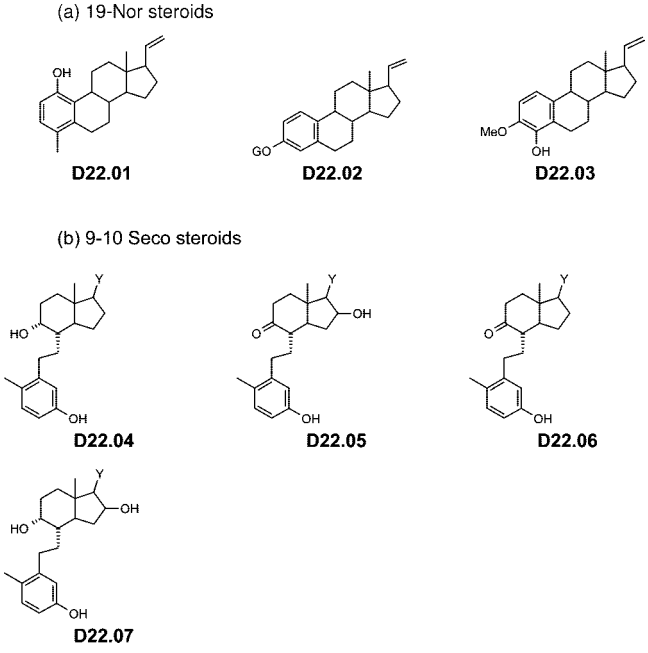


Figure 22. Ring A aromatization (Y = side chain).

a high concentration that the enzyme preparation has been patented for synthetic applications.[59] In *P. hummelinkii* of the Caribbean, the 9,11-seco sterol with the intact Δ^5, viz., **A6.09h$_1$**, is noticed.[60] The side chain **h$_1$** was first noticed in gorgosterol **A6.01h$_1$**. It was the first sterol shown to have alkyl substitution at C(22) and C(23) and also the first sterol shown to have a cyclopropane ring in the side chain. Biosynthetically, the cyclopropane ring has been suggested to originate from methionine. Seven new 9,11-seco sterols with intact Δ^5 are recently reported from another gorgonian *Tripalea clavaria* collected from off Argentina. They are **A6.09e$_5$** (R′ = H) and **A6.09e$_{25}$** and their 3-acetates, **A6.09e$_{11}$**, **A6.09f$_{20}$**, and **A6.09d$_2$**.[61]

The same secosterol nuclear structure is present in **A6.09f$_3$** and **A6.09f$_2$** isolated first from a *Sinularia sp*. of the Great Barrier Reef[62] and several other species subsequently. Recently, the new epoxy sterol **B16.01f$_3$** (Figure 16) has been reported along with these two sterols from *Sinularia lochmodes* off the Taiwanese coast.[63] The sterol nucleus **A6.09**

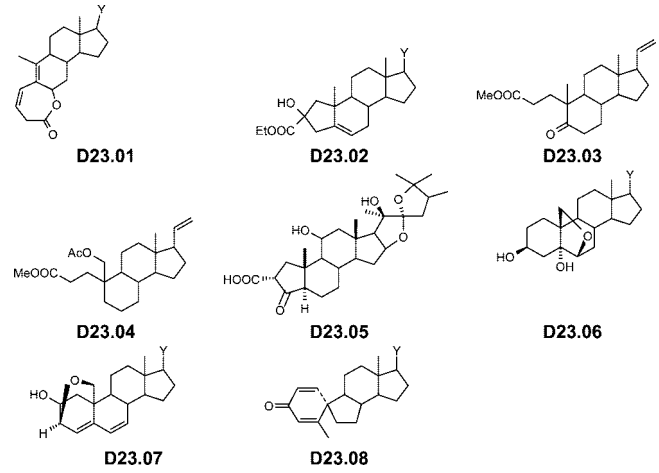


Figure 23. Ring A opened/contracted steroids (Y = side chain).

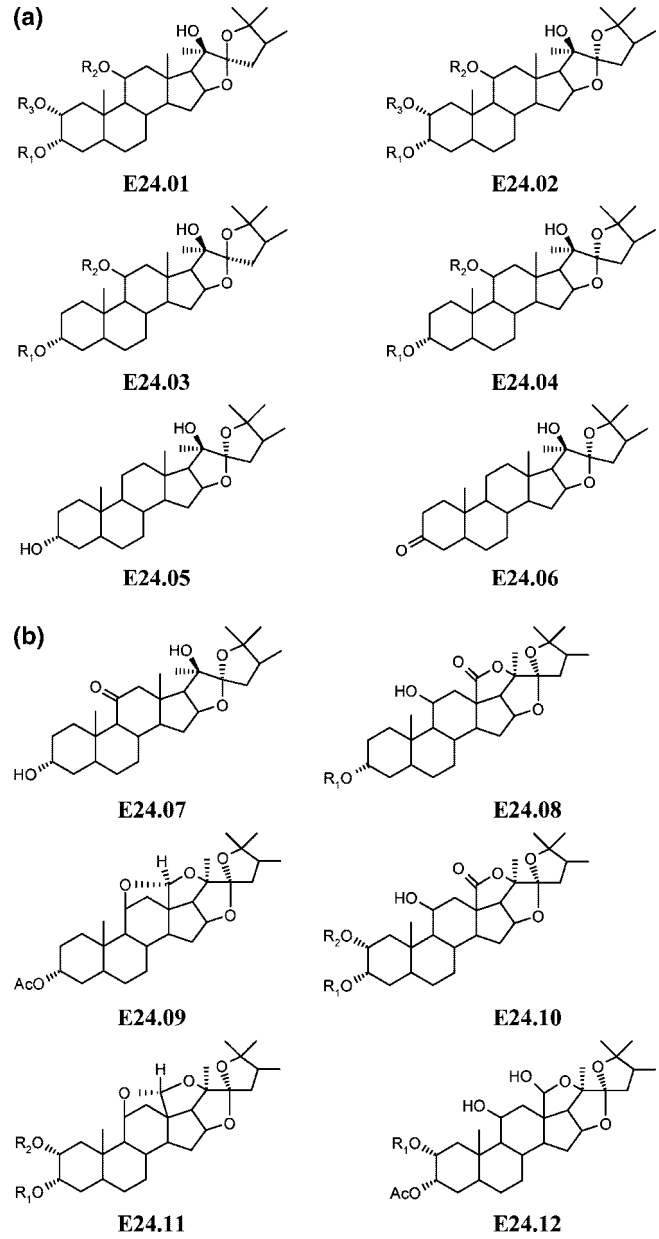
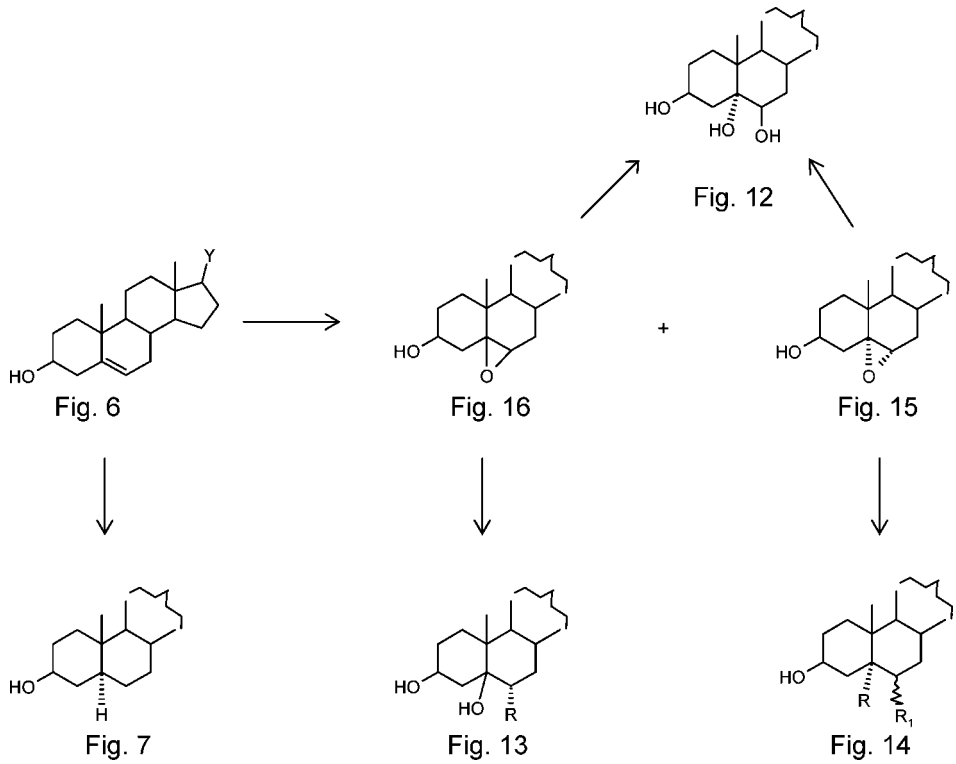


Figure 24. Hippuristanols.

contributes as much as 73% to the sterol mixture of the coral extract, giving an indication of the ease with which secosterol

Scheme 1. Oxidation[a] Routes of Δ^5 (R and R′ Can Be H or OH)



[a] Figure 7 sterols are by reduction.

biogenesis takes place in the coral, even as Δ^5 remains intact. The sterol **A6.09f$_3$** is the most major (55% of the sterol mixture) and was also found to be the most potent of the three against the MCF-7 cancer cell line.[63] The coral *Sinularia leptoclados* from the same region as *S. lochmodes* gave the 5,6-dihydro steroid **A7.02f$_3$**[63] (Figure 7), which is rare in this group of steroids but more common with steroids associated with hippurins in *Isis hippuris* (section 9).

5.2. Oxidation of Allylic Carbons: C(7)

The allylic oxidation route is preferred in a few "species" of both the alcyonacean and gorgonian orders. The carbons undergoing oxidation are C(7) and C(4). Formation of anhydro intermediates from the oxygenated sterols would activate the newly created allylic positions, and thus, the oxidation of the sterol nucleus progresses. Oxidation of carbons remotely away from the intact remaining Δ^5 is a special characteristic of corals.

5.2.1. 7β-Activation (Figure 8)

Both 7β and 7α hydroxylations are possible (Scheme 1); the former is more prevalent though. *Sinularia crispa* of the east coast of Sri Lanka gave 3β-*O*-glycoside **A8.01f$_3$** (R_1 = H, G = 4-acetyl fucose), which contains a free 7β-OH. It is vested with spermatostatic activity.[64] *S. conferta* also gave this glycoside accompanied with the glycoside **A6.01f$_3$** (G = α-L-fucose) without 7β-OH (Figure 6).[65] It was thought that steroidal glycosides are unique to the *Sinularia* genus in the Bay of Bengal, cf., *S. gravis*[32] and *S. grandilobata*[33] referred to above. *S. gibberosa* gave the sterol **A8.02f$_3$**, having 7β-OH. This sterol is accompanied with glycosides **A6.03f$_{10}$** (G = α-L-fucopyranose) and **A6.10e$_1$** (G = α-L-fucopyranose)[66] (Figure 6), which have no C(7) oxygen. *S. grandilobata* from off the Taiwanese coast gave the **7**β-hydroxy steroids **A8.03f$_3$** and **A8.03f$_8$** together with their respective 5β,6β-epoxides **B16.02f$_3$** and **B16.02f$_8$**. The four new sterols were named as sinugrandisterols A to D, respectively.[67] A *Sinularia* sp. also of the Andaman & Nicobar Is. claimed by the authors as a new species gave the 7β-acetoxy sterol glycoside **A8.01f$_3$** (G = H, R_1 = Ac)[68] while a *Sinularia sp*. collected from Hainan Is. (South China Sea) gave 19-*O*-acetate **A8.04f$_3$** (R_1 = H, R_2 = Ac) and **A8.04f$_3$** (R_1 = Ac, R_2 = H) and the known **A8.04f$_3$** (R_1 = Ac, R_2 = H).[69] *S. dissecta* also from Hainan Is. gave as many as 15 polyhydroxy steroids with functionalization of 18(CH_3) as p-alcohol, aldehyde, and carboxylic acid or its lactone; all are Δ^5 (or 5,6-dihydro) sterols and lack activation of allylic carbons.[70] Of these, new sterols are as follows: **A6.11** (R_1 = Ac), **A6.12** (R_1 = H), **A6.12** (R_1 = Ac), **A6.13** (R_1 = Ac), **A6.14**, and **A6.15** (Figure 6). In particular, **A6.15**, named dissectolide, has a unique lactone between the COOH group of erstwhile 18-CH_3 and 21-OH of the side chain. Known steroids from this source have the Δ^5 containing **A6.11** (R_1 = H), **A6.16**, and **A6.13** (R_1 = H) (Figure 6) and the 5,6-dihydro compounds (Figure 7) **A7.03** (R_1 = R_2 = Ac), **A7.03** (R_1 = H, R_2 = Ac), **A7.03** (R_1 = R_2 = H), **A7.04** (R_1 = H), **A7.04** (R_1 = Ac), and **A7.05** (Figure 7). *Litophyton viridis* gave 19-hydroxy sterols with the 7β-OAc function (**A6.10f$_3$**; Figure 6)[71,72] and without it (**A6.17f$_3$**; litosterol) as well as its 5β,6β-epoxide (**B16.03f$_3$**; Figure 16), which showed antileukemic activity.[73] The C(19) hydroxylation was later noticed in several marine sponges.[31] *L. arboreum* from the South China Sea gave 19-OH sterols **A8.04f$_3$** (R_1 = H) and the 5,6-dihydro-Δ^8 sterol **A7.06 g$_1$** (Figure 7) in addition to litosterol.[74] In the mass spectrum of **A7.06 g$_1$**, a fragment *via* McLafferty rearrangement involving the transfer of H to C(8) and loss of the neutral CH_2O occurs. The 19-hydroxylated Δ^5 sterols are also isolated from *Nephthea chabroli* (India) with and without 7β-OH substitution, viz.,

A8.05f$_3$ and **A6.18f$_3$**, respectively.[75] The known sterols reported from this organism also have Δ^5 and 19-OH groups, cf., **A6.17f$_3$** (litosterol), later also isolated from *Nephthea erecta*,[76] and, additionally, 7β-OH, **A8.04e$_1$** (R_1 = H), and the known **A8.04f$_3$** (R_1 = H). *N. erecta* sterols included the C(7) sterone **A8.06f$_3$** and **A6.19f$_3$** without C-7 functionalization but with an extra 15β-OH that were shown to be cytotoxic. Known sterols isolated included **B12.18f$_3$** (Figure 12), containing a 3β,5α,6β-trihydroxy system.[76] Significant cytotoxicity was shown against the growth of cell lines P-388 and HT-29 for the sterone **A8.06f$_3$** and additionally of A549 and KB cell lines for **A6.19f$_3$**, and the known steroids **A6.17f$_3$**, **A8.04f$_3$** (R_1 = Ac), **A8.04f$_3$** (R_1 = H), and **B12.18f$_3$**.[76] Recently, from *Stereonephthya crystallina* of Formosa, nine new pregnenes named as stereonsterols A through I are isolated. All of them except stereonsterol H (**A6.01a$_1$**) (G = 3′-acetyl-α-L-fucose) are 5,6-dihydro steroids (Figure 7). Seven (C through I) are glycosides: C (**A7.08a$_1$**), D (**A7.08a$_1$**), E (**A7.09a$_1$**), and F (**A7.07a$_1$**) of 4′-acetyl-α-L-fucose, G (**A7.07a$_1$**) and H (**A6.01a$_1$**) of 3′-acetyl-α-L-fucose, and I (**A7.07a$_1$**) of β-xylopyranose. The remaining two, A (**A7.07a$_1$**) and B (**A7.09a$_1$**), are genins. Of the nine steroids, four (F through I) are 19-Me steroids while three (A, C, and D) have C(19) oxidized to the p-alcohol stage and two (B and E) have it further oxidized to the aldehyde group.[77] The 7β position activated with a unique peroxide substitution is noticed in **A8.07f$_3$** from *Sinularia sp*. from Taiwan.[78]

Although 19-hydroxy sterols have been reported widely [from soft corals, from the hard coral commonly known as black coral (*Antipathes subpinnata*, a scleractinian coral whose chemistry is not included in this review),[79] and from marine sponges[31]], their occurrence in gorgonians has been encountered only recently. From *Acanthogorgia vagae* Aurivillius of the South China Sea, six 19-hydroxy sterols [two of them known, namely litosterol (**A6.17f$_3$**) and **A6.17e$_1$**] are isolated.[80] The new sterols are named acanthovagasteroids A through D, **A6.17e$_3$**, **A6.17e$_2$**, **A6.17f$_7$**, and **A6.17f$_6$**, respectively.[81] The 19-hydroxy sterols were first used to explain the biogenesis of 19-nor steroids.[71] In fact, in the MS of 19-hydroxy steroids, major fragments are produced by the loss of 10-CH_2OH after the loss of 3-OH.[80] In the gorgonian *Anthoplexaura dimorpha*, the 10-CH_2OH is further oxidized to a 10-COOH group in the glycosides, namely dimorphoside A (**A8.08e$_1$**), with 7β-OH, and dimorphoside B (**A8.09e$_1$**), without 7β-OH.[82] The sugar part was shown to be a disaccharide—arabinosyl galactose in **A8.08e$_1$** and 2′-acetylarabinosyl galactose in **A8.09e$_1$**. The dimorphosides inhibit the development of fertilized sea urchin eggs. *Junceella juncea* from the South China Sea is another gorgonian that is reported to yield a 19-hydroxy steroid in the form of the glycoside **A7.08** (G = 4′-*O*-acetyl-β-D-arabinopyranose)[83] (Figure 7). The sterols that co-occur are the known ones, namely **B12.09f$_6$**, **B12.01f$_6$**, and **B12.01f$_{10}$** (R^1 = Ac), which have the 3β,5α,6β-trihydroxy system in common (Figure 12) and the "usual" Δ^5 sterol, **A6.01f$_6$**. In corals, 3β,5α,6β-trihydroxy systems containing steroids, when present, are usually the sole or predominant products. Hence, it is interesting that, in the gorgonian, the Δ^5 sterols constituted as much as 40% of the (polar) sterol mixture, even as the remaining is made up of the 3β,5α,6β-trihydroxy system containing sterols.

5.2.2. 7α-Activation (Figure 9)

Capnella genus was first noted to be dominated by sesquiterpenes and a few diterpenes; sterols are reported from them rarely.[84−86] *Capnella lacertiliensis* of the Great Barrier reef yielded the Δ^5-7α-OH sterols **A9.02h$_1$** and **A9.03h$_1$**, which are gorgosterol derivatives, and the Δ^5 sterols (Figure 9) **A6.20f$_{11}$** (R_1 = R_2 = H) and **A6.20f$_{11}$** (R_1 = H, R_2 = Ac) and **A6.20f$_{11}$** (R_1 = Ac, R_2 = H), lacking C(7) activation and which are ergosterol derivatives.[84] Sterols with the ring structure **A6.20** are unique for their 11β (as opposed to the usual 11α) oxygenation and exhibit weak inhibition of tyrosine kinase $p56^{lck}$, while all the five sterols exhibited weak antifungal activity.[84]

In *Sinularia gibberosa* (wrongly referred to as *Alcyonium sp*. in ref 87 and corrected later[88]) from India, the Δ^5 sterol 3β-*O*-α-L-fucopyranosides with 7β activation (**A8.02f$_3$**, R_1 = H; Figure 8), 7α activation (**A9.04f$_3$**; Figure 9), and no activation of C-7, viz., **A6.03f$_3$** (G = H) (Figure 6), are all reported. The steroids **A6.03f$_3$** (G = H) and **A8.02f$_3$** (G = α-L-fucopyranose, R_1 = H) have 5α-reductase inhibitory activity on testosterone (to dihydrotestosterone).[89]

5.3. Activation of Allylic Carbons: C(4) (Figure 10)

Activation of C(4) by Δ^5 is usually followed by reduction of Δ^5 to yield the 5,6-dihydro compounds. Four 4α-glycosides (pregnediosides) of pregnene that are based on **A10.01a$_1$** (R_1 = H) and **A10.01a$_1$** (R_1 = Ac) have for their sugar (G) either xylose or arabinose in *Alcyonium sp*. of Okinawa (Japan). They are accompanied by the genin **A10.01a$_1$** (G = R_1 = H).[90] Recently from *Lobophytum sp*. from Hainan Is. also, a similar glycoside **A10.01a$_1$** (G = 3-acetyl xylose, R_1 = H) is reported.[91] From *Sclerophytum sp.*, the known glycoside **A10.01a$_1$** (G = arabinose, R_1 = H) was isolated along with the Δ^5 sterol **A6.01f$_{18}$**, which contains a 20-COOH function in the side chain.[92] The gorgonian *Eunicella verrucosa* from Spain gave the cytotoxic verrucoside **A10.02a$_1$**, a 4β-*O*-glycoside (G = 2-*O*′-acetyl-3-*O*-methyl-6-deoxyglucose) with 5β(H) configuration.[93]

In other examples of C(4) activation, the carbon undergoes methylation. 4α-Methylation was noticed quite early in *Litophyton viridis*. Its sterol **A10.03f$_{15}$** in addition contains a unique 8β-OH. This sterol is accompanied with the Δ^5 sterols **A8.04f$_3$** (Figure 8) and **A6.17f$_3$** (litosterol; Figure 6) and the 5,6-epoxide **B16.03f$_3$** (Figure 16), as mentioned earlier.[71,72] More recently, *Cladiella sp.* off Andaman and Nicobar Islands is reported to contain the nonpolar 4α-methyl sterol **A10.05h$_7$**, whose side chain is unique in that it is the only C_{11} side chain that does not contain a cyclopropane ring.[94] A *Sinularia sp.* from China is unique in that it contains **A10.14f$_3$** as the new 4α-methyl steroid along with **B12.15f$_3$** (R = H) of the class B steroids. Six more known sterols are also reported.[95] Among soft corals, species of *Nephthea* are a better source of 4α-methyl sterols, e.g., **A10.03f$_3$**, another 8β-OH containing sterol isolated from *Nephthea brassica* from India.[96] *Nephthea erecta* from Formosa also produced a 8β-hydroxy steroid **A10.04f$_{17}$** (erectasteroid B), the only example of a 3-ketone in this group of steroids. Another 4α-methyl steroid from this coral is erectasteroid A, i.e., **A10.05f$_{17}$**. The organism further produces six more new and two known polar steroids, all formed by C(7) activation. Erectasteroids C to E and H are by β-activation. They are **A8.04e$_1$** (R_1 = Ac, R_2 = H), **A8.04e$_3$** (R_1 = Ac, R_2 = H),

A8.04f$_8$ (R_1 = Ac, R_2 = H), and **A8.04f$_8$** (R_1 = R_2 = H). F and G are α-activated: **A9.05e$_3$** (R_1 = H) and **A9.05e$_1$** (R_1 = Ac).[97] A *Nephthea sp.* from China gave three new 4α-methyl steroids, **A10.06f$_{17}$**, **A10.07f$_{17}$**, and **A10.08f$_{17}$**, and three new Δ^5 sterols, **A6.01f$_{27}$** (R_1 = H), **A6.01f$_{16}$**, (R_1 = H) and **A6.01f$_3$** (R_1 = H).[98] The 8β-OH is perhaps the precursor of Δ^8 in *Litophyton arboreum* sterol **A7.06g$_1$** (Figure 7), mentioned above.[74] The coral *N. chabroli* from South China Sea produces **A10.09f$_{15}$**, which contains another unique oxidation, the 14β-OH co-occurring with the 5,6-dihydrosterol **A7.10f$_3$** (Figure 7) possessing the $\Delta^{9(11)}$-12α-OH system.[99] The Δ^5 sterol **A6.17f$_3$** (Figure 6), its 7β-activated sterols (Figure 8) **A8.04f$_3$** (R_1 = H), **A8.04f$_3$** (R_1 = Ac), and **A8.06f$_3$**, as well as the 5α,6β-dihydroxy sterol **B12.15f$_3$** (R_1 = H; Figure 12) were also isolated as known steroids from this coral. In some species of *Pseudopterogorgia* gorgonians also, sterols incorporate a 4α-methylation feature; in some, a 9,11-seco structure is additionally present. *P. americana* from Puerto Rico gave the 4α-methyl sterols **A10.10g$_2$** and the 9,11-seco product **A10.11g$_2$**.[100] A Δ^5 sterol, the known secogorgosterol **A6.09h$_1$** (Figure 6), was isolated as the major sterol.[100] From *P. acerosa*, **A10.12g$_2$**, named as acerosterol, is reported.[101] From *Pseudopterogorgia sp.* of Florida, the 9,11-seco sterols with Δ^5 intact, **A6.09h$_5$** (Figure 6), which lacks 4α-methylation, and the 4α-methyl containing sterols **A10.13g$_9$** and **A10.13g$_2$** were isolated by a bioassay guided scheme. The three sterols have moderate inhibitory activity against protein kinase C.[102] Shortly afterward, the Caribbean *P. americana* from off Barbados also gave **A10.13g$_9$**.[103] The secosterols of *P. americana* are found to deter fish feeding in aquarium tanks.[104]

5.3.1. 3α-Hydroxy Sterols (Figure 11)

This section should be read along with section 9, which discusses hippurins, many of which are also 3α-oxygenated steroids. The precursor step in the generation of 3α-OH is seen in the A/B ring structure of **A11.01f$_3$**, a cytotoxic sterol from *Alcyonium patagonicum* from the South China Sea[105] and *Sinularia ovispiculata* from Andaman & Nicobar Is. (India),[106] and **A11.01f$_1$** from the gorgonian *Rumphella aggregata*.[107] *S. ovispiculata* also yielded[106] several known glycosides in large yields, viz., **A6.03** (G = α-L-fucose; Figure 6), **A9.04** (G = α-L-fucose; Figure 9), and **A8.02** (G = α-L-fucose, R = H; Figure 8), as in the case of other *Sinularia* species.[32,33,64,66,68,108] *Sinularia* is a versatile genus, species of which also yield group B sterols (section 6, see below). In *Sarcophyton tortuosum* from the South China Sea, sartortuosterol A **A11.03f$_{10}$** (R^1 = Ac) having 3α-OH was reported.[109] *Alcyonium sp.* of Formosa yielded the triacetoxy sterol **A11.02c$_2$**.[110]

The gorgonian *Pseudopterogorgia americana* contains gorgosterol **A6.01h$_1$** (Figure 6) with the unique gorgosterol side chain as major sterol. Accompanying it is the 3α-hydroxy-9,11-seco sterol **A11.04h$_1$**.[111] This sterol was indeed the first instance of a 9,11-secosterol from natural sources, and more have been added since then from species of both Alcyonaceae and Gorgonacea orders. The 9,11-secosterols are more common in marine sponges, e.g., *Spongia officinalis*.[31] In the 3,12-diacetates of *Junceella fragilis* **A11.05c$_2$** (R^1 = H) and **A11.05c$_2$** (R^1 = Ac), the ring A/B fusion is *cis*.[112] In pregndienes of *Pieterfaurea unilobata* from South Africa, the 3β oxygen is involved in epimerization (Figure 11), as demonstrated in **A11.06a$_1$** (R_1 = Ac), **A11.07a$_1$** (R_1 = H), **A11.07a$_1$** (R_1 = Ac), **A11.08a$_1$**, and **A11.09a$_1$**.[113] The yield ratio of 3α-oxy sterols to the 3β-oxysterols, not taking into account the "usual" sterols, is as large as 6:1.

6. Δ^5 Oxidized Sterols (Class B Sterols)

In this major group, steroids formed *via* initial epoxidation of Δ^5 are included. Since these steroids are sometimes accompanied with Δ^5 precursors in the coral, it is reasonable to assume that Δ^5 oxidation is the starting precursor for these sterols, as shown in Scheme 1.

6.1. 3β,5α,6β-Trihydroxy Sterols (Figure 12)

The 3β,5α,6β-trihydroxy system is extensively present in corals; in fact, "unusual sterols" containing this system are the only products of a large number of coral species, particularly the Alcyonarian corals of the genera *Sarcophyton, Sinularia*, and *Lobophytum*. These sterols can be readily recognized in the ^{1}H NMR spectra. In pyridine-d_5, the 4β-H is strongly deshielded and appears at a basic value of δ2.94 (dd, J = 12.5.12 Hz). The 19-Me protons also show moderate deshielding to ca. δ1.61.[114]

Sarcophyton elegans was the earliest in this category with the trihydroxy system reported in the sterol **B12.01f$_{10}$** (G = H, R^1 = Ac).[115] Sterols that have 5α-reductase inhibitory activity are usually Δ^5 sterols. However, **B12.01f$_{11}$** (R^1 = H) from *Lobophytum sp.* of Andaman & Nicobar Is. and **B12.19f$_1$** (described later from *Anthelia glauca* from Papua New Guinea[116]), although saturated, showed 5α-reductase inhibitory activity similar to that of the Δ^5 sterols **A6.03f$_3$** (Figure 6) and **A8.02f$_3$** (G = R_1 = H) (Figure 8,; see above).[89] The further 12β-hydroxylated **B12.02f$_{10}$** (R^1 = Ac) was also reported later[117] from the same species (*S. elegans*). From *S. crassocaule*, more famous for hippurins from Indian collections of the organism (see section 9.3), **B12.01f$_1$** (G = H) and **B12.01f$_{10}$** (G = H, R^1 = Ac), known sterols by then, have been reported from the Formosan collection.[118] Earlier, in *S. glaucum* of Okinawa (Japan), the trihydroxy sterol ring system containing **B12.01f$_{24}$** (R^1 = H), which contains two more oxygens in the side chain,[119] is accompanied with **B12.01f$_{10}$** (R^1 = Ac) and its free alcohol **B12.01f$_{10}$** (R^1 = H) and the 1β-hydroxy sterols **B12.03e$_1$**, **B12.03f$_1$**, and **B12.03f$_{10}$** (R^1 = Ac) and **B12.03f$_3$** as well as the side chain lacking androstane **B12.04**. The C(21) oxidized **B12.01f$_{21}$** (R^1 = $C_{10}H_{21}$, R^2 = H) and **B12.01f$_{21}$** (R^1 = R^2 = Ac) were also isolated.[120−122] The monoacetoxy sterol **B12.03f$_{10}$** (R^1 = Ac) of the pentahydroxy sterol showed significant activity against the HT-29 cell line. The same species (*S. glaucum*) from Taiwan has yielded the decanoate **B12.01f$_{24}$** (R^1 = H, R^2 = $CO(CH_2)_8CH_3$) and diacetate **B12.01f$_{24}$** (R^1 = R^2 = Ac).[123] Three more known sterols are also isolated. From *S. subviridae* of India,[124] in addition to five known polyhydroxy sterols, four new sterols were reported. The new sterol **B12.01f$_{24}$** (R^1 = H, R^2 = Ac) with the 3β,5α,6β-trihydroxy ring system has a similar oxidation pattern to that in the sterols of *S. glaucum*. Two sterols have an additional 1β-OH, cf., **B12.03f$_4$** and **B12.03h$_4$**. The fourth sterol, **B12.05f$_{10}$** (R^1 = Ac), has a further 18-OH group. The sterol **B12.06g$_7$** from *S. trocheliophorum* of Singapore has 20α-OH in the ten carbon side chain (R = H), and uniquely a Δ^{16} in ring D.[125] This new sterol is accompanied by a known sterol **B12.01e$_{16}$** (R^1 = Ac) of the series and the Δ^5 sterol **A6.01h$_1$** (gorgosterol) in the coral. The new sterol **B12.06g$_7$** showed potent growth inhibitory activity against several human cancer cell lines. An unidentified *Sarcophyton*

sp. from Okinawa (Japan) is the source of the 11α-hydroxy sterols sarcoaldesterols A (**B12.07h$_1$**; R_1 = H) and B (**B12.07f$_1$**; R_1 = H).[126] The sterol **B12.01f$_{23}$**-C(6) monoacetate with two oxygens in the side chain is from *Asterospicularia randalli* from Guam Is.[127]

In the gorgonian *Menella verrucosa* (family: Plexauridae), the steroids **B12.08e$_1$** and **B12.08e$_3$**, named menella steroids A and B, respectively, have the alternate but rare 11*β*-OH group.[128] In another gorgonian, *Echinogorgia aurantiaca*, of the same family, from the South China Sea, the steroid **B12.08e$_1$** is accompanied with two keto steroids, **B14.02** (6-keto) and **B12.12e$_1$** (1-keto). New steroids having a 6-keto group are not unusual; the group occurs in combination with 5*β*-OH (**B13.01**, **B13.03**, and **B13.04** in Figure 13), 5α-OH (**B12.13** and **B12.22** in Figure 12), Δ^4 (**A11.13** and **A11.14** in Figure 11), and now 5α-H (**B14.02**).[129] But, C(1)-keto steroids are extremely rare. They are confined to only *Clavularia* (Figure 17), a genus that belongs to Clavulariidae of Gorgonaceae.

Sinularia is a genus that shows a large variation in chemical elaboration. *Sinularia sp*. from Andaman & Nicobar Is. (India) gave the Δ^7-sterol **B12.09g$_5$** with a demethyl gorgosterol side chain along with the known **B12.01f$_3$**.[114] In *Sinularia sp*. also from the Andaman & Nicobar islands, a pentahydroxy nucleus with the unique 1α-OH is present in the new sterol **B12.10f$_3$**. Also isolated were another 1α-OH containing numersterol A, **B12.11f$_3$**, which was previously isolated from *S. numerosa,*[130] and **B12.09f$_6$**.[131] Two known Δ^5 steroids, **A6.01f$_3$** (G = H) and **A6.01f$_3$** (G = fucose), have also been isolated. From *S. microclavata* and *S. dissecta*, both also from the same islands, 1α-hydroxy sterols were isolated: numersterol A **B12.11f$_3$** and its 6-ketone **B12.13f$_3$** from the former[132] and the 11α-hydroxy **B12.14f$_3$** (R_1 = H) and its 11α-acetate **B12.14f$_3$** (R_1 = Ac) from the latter.[133]

Sinularia dissecta is a coral species investigated extensively. In addition to polyhydroxysteroids, cembrane diterpenoids and sesquiterpenoids have also been reported from it. Very early, *S. dissecta* was reported[134,135] to produce hydroxylations at the 1α and 11α positions. Eight new sterols in which the Δ^5 remains intact (Figure 6), e.g., **A6.22f$_3$** (R_1 = H), **A6.22f$_3$** (R_1 = Ac), **A6.22e$_1$** (R_1 = H), **A6.22f$_2$**, and **A6.22f$_6$** (R_1 = H), or is reduced to the 5,6-dihydro sterols (Figure 7), e.g., **A7.05h$_3$**, **A7.05h$_1$**, and **A7.05f$_3$**, were reported.[134] An additional fourteen sterols reported[135] had the then unique C(18) functionalization. Eight of them were new. The Δ^5 is reduced in as many as 12 of these sterols, perhaps because of the strong reducing (5,6-dihydrogenase) activity of the two remaining Δ^5 sterols. The sterol **A7.11f$_3$** and four others with varying alkyl side chains are primary alcohols, all Δ^5-saturated (Figure 7). The sterol **A7.12f$_3$** (Figure 7) and three others with varying side chains are aldehydes, one of them with Δ^5. The sterol **A7.13f$_3$** (Figure 7) and four others also with varying side chains are carboxylic acids, one of them with Δ^5. In *Sinularia sp.*, 9,11-seco sterols were reported.[136−138] The new compounds, both Δ^5 sterols (Figure 6) with the secosterol nucleus (and a primary alcohol group) that were characterized, are **A6.09e$_1$** and the trace **A6.23f$_3$** in which the usual 8*β*(H) is epimerized to 8α(H). *S. gibberosa* yielded the known 5,6-dihydro secosterols **A7.02f$_3$** and **A7.02f$_1$** and the former's C(11) acetate **A7.02f$_3$**[139] (Figure 7).

From a few Nephtheidae (Alcyonaria) corals also, 3*β*,5α,6*β*-trihydroxy sterols (only) were reported, cf., nephalsterol A **B12.15f$_3$** (R_1 = H) from a mixed collection of *Nephthea allida* and *N. tiexera* from China.[140] The steroid **B12.15f$_3$** (R_1 = H), isolated from *Nephthea erecta* off the Taiwanese coast, undergoes a slow dehydration reaction within the NMR tube *in situ*, producing **D23.06f$_3$**. A second case of internal cyclization is also noticed with the congener **A8.04e$_1$** (R_1 = R_2 = H) when it transformed to **D23.07e$_1$**,[141] attesting the vulnerability of oxidized moieties in the steroidal structure to a trace concentration of acid associated with $CDCl_3$. The 19-*O*-acetate of the sterol, viz., **B12.15f$_3$** (R_1 = Ac) designated as armatinol B, has been reported from *Nephthea armata* of Taiwan recently together with armatinol A **B16.03f$_3$**, a 5*β*,6*β*-epoxide (Figure 16). Armatinols A and B showed cytotoxicity of nearly equal magnitude.[142] Dendronesterol A **B12.16e$_1$** (R_1 = Ac) and its 15*β*-hydroxy analogue dendronesterol B **B12.17e$_1$** (R_1 = Ac) are both C(19)-*O*-acetates shown to be mildly cytotoxic and were from *Dendronephthya gigantia* of Japan,[143] associated with three sterols having this triol system plus the common $\Delta^{7,22}$ diunsaturation, viz., **B12.18f$_6$**, **B12.18e$_3$**, and the 24-nor sterol **B12.09b$_2$** known earlier from sponges.[144,145]

In three of the four Xeniidae corals from which steroids are reported so far, sterol oxidation is limited to the A/B ring system, cf., xeniasterol C, **B12.01h$_1$**, with the 3*β*,5α,6*β*-trihydroxy system and xeniasterols A, **B12.19f$_6$** (R_1 = Ac), B, **B12.19f$_1$** (R_1 = Ac), and D, **B12.19h$_1$** (R_1 = Ac), with an additional 7*β*-acetoxy function isolated from *Xenia sp.* of Okinawa (Japan). The known sterol gorgosta-3*β*,5α,6*β*-triol (**B12.01h$_1$**) belonging to this group was also isolated from this species.[146] The 3*β*,5α,6*β*,7*β*-tetrahydroxy system is also contained in **B12.19f$_1$** from *Anthelia glauca* from Papua New Guinea.[116] The 11α-OH containing sarcoaldosterol A **B12.07h$_1$**, shown to be an antifungal, is obtained from *Heteroxenia sp*. from the Philippines.[147] In the fourth Xeniidae coral *Cespitularia hypotentaculata*, the 5,6-epoxy-9,11-seco steroids **B16.01e$_1$** and **B16.01h$_2$** have recently been reported.[148]

Among the gorgonians in which new sterols with a 3*β*,5α,6*β*-trihydroxy system are reported, *Pseudopterogorgia elisabethae* was the earliest, whose **B12.20e$_1$** contains the extra 9α-OH and an absent side chain oxidation.[149] In punicin **B12.21e$_1$** (R_1 = Ac) of *Lophogorgia punicea* from Brazil, a unique 17α-OH is present that is also with no side chain oxygenation.[150] The *Acalycygorgia inermis* (from Korea) sterols **B12.22e$_{15}$** (25*R*, R^1 = Ac) and **B12.22e$_{15}$** (25*S*, R^1 = Ac), which are a C(25) epimeric pair, are accompanied by additional steroids **B12.22e$_{17}$** and **B12.22e$_{19}$**.[151] In *Eunicea lacinata* of the Caribbean (Venezuela), the 9α,11α-vicinal diol system containing sterol **B12.23h$_3$** is associated with **A6.24h$_3$** (Figure 6), a Δ^5 precursor sterol[152] and the known **B12.01e$_1$** having steatotic activity that was previously characterized from *Pteroides esperi*, a sea pen.[153] *Plexaurella grisea*, also of the Caribbean (Dominican Republic), also produces the sterol containing 9α,11α-dihydroxy system **A6.25h$_1$** (6) with an intact Δ^5 unsaturation. Another new steroid reported, **A6.26h$_1$** (6), contains only the 9α-OH group. The other four new sterols are the 5,6-epoxide **B16.04f$_3$** (16), **B12.19f$_3$** (R_1 = H), and the C(6)-ketones **B12.22f$_{15}$** (25*R*) and **B12.22f$_{15}$** (25*S*), which are an epimeric pair at C(25).[154] Several known sterols are also isolated with 5,6-epoxide and C(7)-OH functionalities. The sterols possess significant anticancer activity. A *Plexaura sp.* of Bahamas has also produced the Δ^5 sterol **A6.24h$_3$** along with sterols containing the 3*β*,5α,6*β*-trihydroxy system, viz., **B12.19f$_3$**

(R_1 = H) and **B12.23h$_3$** as known sterols.[155] In the binding assay, the sterols containing the gorgostane side chain, namely **B12.23h$_3$** and **A6.24h$_3$** (6), are found to be potent and specific agonists of LXR_α (and not LXR_β) receptors. In particular, **B12.23h$_3$** exhibits a 13-fold induction of the α-receptor in a trans activation assay in HEX-293 cells.[155]

Telesto (synonym: *Carijoa*) is an octocoral about which the taxonomists are divided about its classification. According to one classification, the genus is included in Clavulariidae (order: Stolonifera).[12] According to the classification adopted for this review,[29,30] the genus is included as a separate family Telestiidae in the order Telestaceae. Geographically diverse collections of *Carijoa* (*Telesto) riisei* produce a diversity of natural products. The Hawaiian specimens yielded a series of nineteen prostanoids—the famed punaglandins with antiviral and anticancer activities. Sterols are reported in Micronesian (SW Pacific) collections from the Chuuk Atoll[156] and Marshall Is.[157] Sterols reported in the former collection are **B12.01e$_{15}$** (R^1 = H) and its acetate **B12.01e$_{15}$** (R^1 = Ac), which are significantly cytotoxic to p388 cells; the 25-*O*-acetate is twice as active as the free alcohol.[156] Steroids of the latter collection are C_{21} pregn-trien-3-ketone **D18.03a$_1$** (R_1 = H) and its 18-acetate **D18.03a$_1$** (R_1 = Ac; see section 8.1.1).[157] The species collected from the Brazilian coast showed an oxygenation pattern similar to that of **B12.01e$_{15}$**, but with the 3β-OH involved in a glycoside linkage. Its riisein A **B12.01e$_{15}$** (G = 3′-*O*-acetyl-β-D-arabinopyranose; R^1 = Ac) and riisein B **B12.01e$_{15}$** (G = 4′-*O*-acetyl-β-D-arabinopyranose, R^1 = Ac) are isomeric monoacetates in the sugar part.[158]

Sterols **A6.01f$_{22}$** (G = H)[159] and **A6.01f$_{14}$** (G = H, R^1 = H)[160] of *Lobophytum sp.* collected four years apart from the Andaman & Nicobar islands do not have extra oxygen(s) in the ring system but have them in the side chain that make them polar. The known Δ^5 sterols pregnanes **A6.01a$_2$** and **A6.01f$_{10}$** (R^1 = H) accompany the former. The pregnane **A6.01a$_2$** has been found to stimulate the 5α-reductase reaction of testosterone to dihydrotestosterone, unlike congener sterols, which were found to have the opposite activity.[89] Steroidal derivatives having a nonconjugated double bond are generally found to have this type of activity.[89,161] Sterols other than these 3β-hydroxy-Δ^5 sterols were not reported from the earlier collection. In the later collection, known nonpolar sterols, cf., 4α-methyl-5,6-dihydro gorgostanes (Figure 10) **A10.05f$_{10}$** (R^1 = H) and **A10.05f$_{14}$** (R^1 = H) and the known polyhydroxy sterols **B12.01f$_{10}$** (R^1 = Ac), **B12.03f$_{10}$** (R^1 = Ac), and **B12.03f$_{10}$** (R^1 = H) are also present,[160] with the yield ratio of Δ^5:4α-methyl:3β,5α,6β-trihydroxy patterns being 3:1:4. The 4α-methyl steroids might have been derived from (dinoflagellate) symbiotic organisms. In another *Lobophytum sp.*, also of the Andaman & Nicobar Is., the new sterol **B12.01f$_{10}$** (G = H, R^1 = Ac) isolated as 3,6-diacetate was associated with two known glycosides: the pregnene **A10.01a$_1$** (G = β-D-arabinopyranose; Figure 10) and **A8.02f$_3$** (G = α-L-fucopyranose; Figure 8).[162] In yet another *Lobophytum sp*. from Andaman & Nicobar Is.,[114] the sterol **B12.24f$_1$** lacks side chain oxygenation, although as many as 5-OH groups are present in the ring system. In the known tetrahydroxy **B12.19f$_1$** (R_1 = H) and trihydroxy **B12.01f$_6$** also of the same species, oxygen is absent in the side chain. The 11α-acetoxy sterols **B12.07f$_3$** (R_1 = Ac) and **B12.07f$_1$** (R_1 = Ac) lacking side chain oxygenation are also reported from *Lobophytum cf. pauciflorum* of Palau (Micronesia, SW Pacific).[163] In *Lobophytum crassum* of the Gulf of Mannar of India,[164] **B12.16f$_1$** (R_1 = H) is the new sterol. Eight known sterols co-occur with it; they are the Δ^5 sterols (Figure 6) **A6.01f$_9$**, **A6.01f$_3$**, **A6.01f$_6$**, and **A6.01f$_4$** and tetra oxygenated sterols **B12.01f$_{10}$** (R^1 = H), **B12.01f$_{10}$** (R^1 = Ac), **B12.01f$_1$**, and **B12.01f$_3$**. The Δ^5 sterols and 3β,5α,6β-trihydroxy steroids are yieldwise distributed in the ratio of 3:5. *Lobophytum crassum* was originally known for its cembranoid diterpenes.[165,166] The organism was from the Red Sea. Much later, its Indian collections gave the sterol **A9.01g$_2$** with 7α activation isolated as the diacetate[167] and several Δ^5 (Figure 6) and 5α,6β-vicinal dihydroxy sterols (Figure 12).[164] *Lobophytum* sp. from Andaman & Nicobar Is. (India) gave **A8.01f$_1$** (G = H, R_1 = H).[168] The monohydroxy sterol mixture of *Lobophytum sp.* of Andaman & Nicobar Is. (India) purified *via* acetylation of the 3β-OH contains the new sterols **A6.01f$_4$** and **A6.01f$_6$**, which are Δ^5, and **A7.01f$_3$** (Figure 7), which is a Δ^7 sterol.[169] *Lobophytum strictum* gave the 1β- and 11α-hydroxy sterols **A6.04h$_6$** and the further 9α-hydroxylated **A6.05h$_6$**.[170] *Lobophytum depressum* of the Red Sea is among the earliest corals studied.[171] It produces the Δ^5 sterols (Figure 6) lobophytosterol **A6.01f$_{35}$** and depressosterol **A6.01f$_{34}$**, and the 5β,6β-epoxides (Figure 16) **B16.05f$_{22}$**, **B16.05f$_{34}$**, and **B16.05f$_{35}$** with the common 22α-OH (or oxygen) and 25-OH. The ability to produce the 3β,5α,6β-trihydroxy system is perhaps withdrawn since the Δ^5 is preferably reduced to the 5,6-dihydrosterols **A7.07f$_{34}$** (R_1 = H) and **A7.07f$_{35}$** (R_1 = H), which are the major sterols of this coral.[172]

6.2. 5β-Hydroxy Sterols (Figure 13)

Continuing with *Lobophytum* sterols, lobosterol **B13.01f$_{10}$** (R^1 = Ac) of *L. pauciflorum* is a unique 3β,4β,5β-trihydroxy-6-oxo steroid in which the 25-oxyacetate is also present.[173] The 5β-hydroxy sterols are relatively rare. In *Lobophytum sp*. from Andaman & Nicobar Is. (India), claimed as a new species by the authors, the A/B cis sterol **B13.02f$_{10}$** (R^1 = H), isolated first from a *Sclerophytum sp.* of the same islands (see below), is accompanied with a number of known A/B trans sterols **B12.01f$_{10}$** (R^1 = H), **B12.01f$_{10}$** (R^1 = Ac), **B12.03f$_{10}$** (R^1 = Ac), **B12.03f$_1$**, and the known **B12.03e$_1$**.[174] The yield ratio of 5α-OH:5β-OH sterols is 1:60 in the species.[174] Gibberoketosterol **B13.03f$_3$**, having 1α-OH, is from *Sinularia gibberosa* of Taiwan.[175] This was the first instance of 1α,3β,5β-trihydroxy-6-oxosteroids from natural sources. Gibberoketosterol was shown to significantly inhibit the up-regulation of the pro-inflammatory I Nos and COX-2 proteins of LPS-stimulated RAW 264.7 macrophage cells.[176] The same school later reported its Δ^{22} analogue **B13.03f$_8$** (gibberoketosterol B) as well as rings of A/B *trans* fused sterols **14.03f$_8$** (gibberoketosterol C) and the 5,6-epoxide **B15.01f$_3$** (gibberoepoxysterol).[176] The yield ratio of the 5α and 5β sterols is 1:4, much less than in *Lobophytum pauciflorum*, but still significant. The first report of co-occurrence of a 3β,5β,6α-trihydroxy system and a 3β,5α,6β-trihydroxy system is of **B13.02f$_{10}$** (R^1 = H) and **B12.02f$_{10}$** (R^1 = H) in a *Sclerophytum sp*.[177] In another *Sclerophytum sp.* of Andaman & Nicobar Is. also, **B13.02f$_{10}$** (R^1 = H) occurs accompanied with the known 3β,5α,6β-trihydroxy sterols **B12.01e$_{16}$** (R^1 = H) and its 25-*O*-acetate **B12.01e$_{16}$** (R^1 = Ac), **B12.03e$_{22}$**, and the 1β-hydroxy analogues **B12.03f$_1$** and **B12.03f$_{10}$** (R^1 = H) and **B12.03f$_{10}$** (R^1 = Ac).[177] 24-Methyl cholesterol **A6.01f$_1$** also accompanies them. Eight "species" of *Sclerophytum* from Andaman & Nicobar Is. that were examined[178] commonly contain **B12.01e$_{16}$** (R^1 = H)

or its 25-*O*-acetate **B12.01e$_{16}$** (R^1 = Ac), or both.[178] In addition, one of these "species" contained 25-desacetyl lobosterol **B13.01f$_{10}$** (R^1 = H), along with lobosterol (**B13.01f$_{10}$**, R^1 = Ac) of the 5β-OH category and the known sterols that contain the common 3β,5α,6β-trihydroxy system, viz., **B12.02f$_{10}$** (R^1 = Ac), **B12.01f$_{14}$** (R^1 = H), and the Δ^5 intact **A6.01f$_{10}$** (R^1 = H).

6.3. 5α(H)- and 5α-Oxy Sterols (Figure 14)

Sclerophytum sp. of Andaman & Nicobar Is. (India), examined by the same group of workers as above but of different collections, gave the Δ^5 sterol andamansterol **A6.24h$_6$** (Figure 6) co-occurring with the known sterols containing the common 3β,5α,6β-trihydroxy systems (Figure 12) **B12.01f$_{10}$** (R^1 = H), **B12.01f$_{10}$** (R^1 = Ac), and **B12.01f$_{24}$** (R^1 = H) and the 5β-hydroxy derivative lobosterol **B13.01f$_{10}$** (R^1 = Ac; Figure 13). The unique sterol, however, is nicobarsterol **B14.04** with the Δ^5 modified into a 5α(H),6α-hydroxy system and a 9,11-seco intermediate containing either a 11-CHO or a 11-CH_2OH group involved in lactolization with 20-CH_2OH or 20-CHO, respectively.[179]

Sinularia hirta contains the Δ^5 sterol fucoside **A6.03f$_3$** (G = α-L-fucose; Figure 6) along with the 5α(H),6α-hydroxy steroid **B14.05f$_3$**.[108] The 9,11-seco structural formation is sometimes found in soft corals. Recently, **B14.06f$_1$** (R_1 = H) with this structure is reported from *Sarcophyton mililatensis* collected from off Vietnam, and the compound is found to stimulate growth of preosteoblastic MC3T3-E1 cells, which suggests the compound to be a potential cure for osteoporosis.[180] Polar sterols of cold water species were studied for the first time in *Gersemia fruticosa* of the White Sea (Arctic Ocean), and the same biosynthetic reactions as happening in the warm water species were observed. The sterols **B14.06d$_1$** (R_1 = Ac),[181] **B14.06e$_3$** (R_1 = Ac), and **B14.07d$_1$**[182] have the 9−11 seco structural feature. Among them, **B14.06d$_1$** (R_1 = Ac) was found endowed with cytotoxicity[181] and **B14.07d$_1$** was highly antiproliferative.[182] Proir to **B14.06d$_1$** (R_1 = Ac), only herbasterol, a sponge metabolilte with unique 3α-OH, was the known 9−11 secosteroid. From the coral, more sterols in which 3β-OH is epimerized to 3α-OH are isolated, cf., **A11.10e$_8$** (similar to hippuristerols, see section 9.2.1), **A11.11e$_2$**, and **A11.12e$_8$** (Figure 11), and the 5β,6β-epoxide **B16.04e$_2$** (Figure 16) is also isolated.[182] This species seems to be unique for its mixed biogenesis.

Subergorgia suberosa, a gorgonian, also seems to be unique, producing sterols by both 5β,6β-epoxide and 5α,6α-epoxide as well as Δ^5 routes. The 9,11-seco sterols **B14.06e$_1$** (R_1 = H), **B14.06f$_6$** (R_1 = Ac, 24*S*), and **B14.06f$_6$** (R_1 = Ac, 24*R*) with a 6α-OH were isolated from the Comoros Is. (Madagascar) collection.[183] Occurrence of both *R* and *S* conformers is rare in coral sterols, even though it is a common phenomenon in sterols of marine sponges. Even here, the fact that 24*S* dominates over 24*R* (ratio = 3:1) attests the enantiomeric selectivity of 24-alkylation in coral sterols.[4] The collection from the Gulf of Mannar (India) gave the new $\Delta^{5,7}$-3-sterone **D21.01e$_1$** (Figure 21) with the 9,11-seco moiety. Known sterols isolated from this collection were the 3β,5α,6β-trihydroxy sterol **B12.09f$_6$** (Figure 12), which originates from the 5β,6β-epoxide, and the 5α(H),6α-hydroxy sterol, **B14.07e$_1$**, which originates from the 5α,6α-epoxide. Pregnenes, viz., the Δ^5 sterol **A6.01a$_1$** and the 5,6-dihydro sterol **A7.07a$_1$** (Figure 7)[184] and the 3-(dimethyl)acetal **D21.02a$_2$** (Figure 21)[185] that originate through the Δ^5 route have also been reported from this gorgonian. Recently, **B14.06g$_{11}$** (R_1 = H), **B14.15f$_7$**, and **B12.09f$_{14}$** are reported from this species collected in the Sanya Bay (Japan).[186]

An alternative 5α(H),6β-hydroxy system is present in a few sterols. *Sinularia sp.* from India gave the sterol **B14.08f$_3$** with a unique of 11α,12α-epoxide.[187] *S. inexplicata*[188] and *Nephthea brassica*,[189] both from the South China Sea, gave **B14.09f$_3$** with 9α-OH. In *S. dissecta* from India, 5α(H),6β-hydroxy sterol **B14.08f$_2$** is associated with the 3β,5α,6β-trihydroxy system containing **B12.25f$_2$** and **B12.25f$_3$** (Figure 12) and the latter's 6α-OH analogue **B14.10f$_3$**.[190]

Epidioxides are quite common in marine sponges, cf., *Tethya aurantia*, *Axinella cannabina*, *Lendenfeldia chondroides*, *Luffariella variabilis*, and *Axinyssa sp*.[31] They are rarely found in corals, e.g., *Sinularia* species. From *S. maxima* of the Andaman & Nicobar Is. (India), the Δ^6-5α,8α-epidioxide **B14.11f$_9$** (R_1 = H) and its 24-methyl analogue **B14.11g$_4$** (R_1 = Ac), a 3β-*O*-acetate were isolated.[191] *S. gibberosa*, also of the same islands, yielded the epidioxide **B14.11f$_9$** and the Δ^5 sterol **A6.03f$_1$** (Figure 6). Several known sterols, cf., the 3β,5α,6β-trihydroxy sterols (Figure 12) **B12.01g$_8$** (R^1 = Ac) and **B12.01g$_8$** (R^1 = H) and the Δ^5 sterols (Figure 6) **A6.01f$_1$** (G = H,24*S*-methylcholesterol), **A6.03f$_3$** (G = α-L-fucose), and **A8.02f$_3$** (G = α-L-fucose) (Figure 8), co-occur with them.[192] The Δ^5 sterols pregnenolone, **A6.01a$_2$** (Figure 6), and the 3β,5α,6β-trihydroxy system containing sterol numersterol A, **B12.11f$_3$**, are known sterols, and the epidioxide **B14.11g$_4$** is a new sterol from *Sinularia sp.* from Taiwan.[193] Two new epidioxides, **B14.11g$_5$** and the Δ^9 containing **B14.12g$_5$**, were isolated from *S. flexibilis* of Hainan Is. of the South China Sea, along with two new Δ^5 sterols, **A6.01f$_{29}$** (G = H) and **A6.01f$_{30}$** (G = H), which are an epimeric pair at C(22).[194] Known epidioxides with the nuclear strucure **B14.11** have **f$_3$**, **f$_6$**, **f$_1$**, **g$_6$**, and **g$_2$** side chains), and those with the nuclear structure **B14.12** have **f$_3$** and **f$_6$** side chains. The epidioxide formation in the source coral (*S. flexibilis*) is quite efficient, as the yield ratio of Δ^5 sterols to the epidioxides is 2:3. Numersterol A (**B12.11f$_3$**) gets its name from *S. numerosa*, from which it was originally isolated.[195] It was later also found in *S. maxima*.[191] In *S. numerosa*, numersterol A is associated with numersterol B, **B14.13g$_3$**, in which the 6β-OH is absent and the C(1)-OH takes the alternative β-configuration.[195] A *Lobophytum sp.* of the Andaman & Nicobar Is. (India) also gave the epidioxy sterol of the nuclear structure **B14.11**. Its side chain was not distinguished between **f$_1$** and **f$_2$**.[196]

6.4. 5α,6α-Epoxides (Figure 15)

In the gorgonians, product sterols that are formed appear to be formed *via* the 5α,6α-epoxide route. The epoxide itself has been encountered rarely. Melithasterols A (**B15.02e$_1$**), B (**B15.02f$_6$**), C (**B15.02e$_3$**), and D (**B15.02f$_3$**), all having a common nuclear structure but only varying in the side chain (unsaturation/alkylation), are from *Melithaea ocracea* of Okinawa in Japan.[197] The 9,11-seco sterols **B15.03h$_1$** and its 1β,16β-dihydroxy analogue **B15.04h$_1$** are from *Pseudopterogorgia americana*.[198] *P. americana*, called by the common name "sea plume", is abundant off Florida and in the Caribbean. The first novel 9,11-secosterol system containing the gorgosterol side chain (**h$_1$**) in Octocorallia is noticed in *P. americana*,[111] which led to the belief that the side chain oxygenation pattern is indicative of the producing organism. The gorgosterol side chain has since been noticed in *Sarcophyton sp.*[126] The 7β-hydroxy sterol **B15.05h$_1$**, active

against human ovarian tumor and human leukemia cell lines, was isolated from a *Lobophytum sp.* from Indonesia.[199] The 5α,6α-diols **B14.14e$_1$**, **B14.14f$_5$**, **B14.14d$_1$**, and **B14.14e$_2$** are from *Acabaria undulata* of Keomum Is. (Korea). Of these, the first three sterols exhibit moderate cytotoxicity, while two among them, **B14.14f$_5$** and **B14.14e$_2$**, inhibited phospholipase A_2.[200]

7. C(1)-Ketones (Class C Sterols; Figure 17)

Clavularia viridis is a common western Pacific coral (order: Stolonifera), which produces a number of steroids with a C(1)-ketone function. The steroids of this group contain, in addition, a Δ^2 or its precursor structure and a 11α-OH or 11α-OAc group. The earliest report on this coral was by Kitagawa's group, describing new cytotoxic sterols named stoloniferones a−d (**C17.01f$_3$**, **C17.01f$_6$**, **C17.01f$_1$**, and **C17.01g$_5$**) (R_1 = H in all structures) with the Δ^2-5β,6β-epoxy-11α-hydroxy-1-ketone nuclear structure in common.[201] Interest in this organism was renewed in further collections from Ishigaki Is. (Okinawa, Japan) when eight more sterones of this group, all 11α-*O*-acetates with the same set of side chains, were reported.[202] Two of them, **C17.02f$_6$** and **C17.02f$_1$**, which are 3α-hydroxy sterones, showed growth inhibition activity toward HeLa $3 cells and human diploid cells *in vitro*. More similar sterones, e.g., **C17.02f$_3$** and **C17.02g$_5$**, were also isolated. These sterones indicate that migration of Δ^5 to Δ^4 is involved as an intermediate step. Other sterols isolated, e.g., **C17.03f$_6$** and **C17.03f$_1$**, which have the 3β-oxygen intact, give an inkling of the precursor requirement for the Δ^2 formation of this group of sterones. From the relative yields of the three groups of sterols, the 3β-acetoxy steroids are 2.5 times less abundant than either the Δ^2 sterols or the 3α-hydroxy sterols. Epimerization at C(3) makes the A/B structural moiety more stable in C(1) ketones. In another study of Okinawan collections, a total of nine yonarasterols are isolated to date,[203,204] which conform to the biogenetic scheme. Yonarasterols were so named from the habitat name, viz., the Yonara channel near Ishigaki island from where the organism was collected. Yonarasterols D, E, and F (**C17.04f$_6$**, **C17.04f$_1$**, and **C17.04g$_5$**, respectively) are 4,5-epoxides (with an additional 6β-OH group).[203] Yonarasterols A, B, and C are 5α,6β-acetoxy sterones **C17.05f$_6$**, **C17.05f$_1$**, and **C17.05 g$_5$** with an A/B trans junction.[203] Yonarasterols A, B, C, and E showed cytotoxic activity against human colorectal denocarcinoma cells (DLD-1, IC_{50}: 3, 3, 50, and 0.02 mg/mL, respectively) and also against human T lymphocyte leukemia cells (MOLT-4, IC_{50}: 2.5, 3, 10, and 0.01 mg/mL, respectively). Yonarasterols G, H, and I are the chlorohydrins **C17.06f$_6$**, **C17.06f$_1$**, and **C17.06 g$_5$** with an A/B cis junction.[204] Isolation of chlorohydrins was the first of its kind from among corals. Previous reports were of kiheisterones and aragusterol C from marine sponges[31] *Strongylacidon sp.* from Maui (Hawaii Is.)[205] and *Xestospongia sp.* from Okinawa,[206] respectively. The latter was shown to possess potent antitumor activity.

The unique sterols in this category are the 1,10 secosterols containing a new seven membered ring lactone (Figure 23), viz., stolonolide I (**D23.01f$_6$**) and stolonolide II (**D23.01f$_1$**) isolated from the same Japanese collection.[207] Stolonolides I and II were the first examples of steroids of the 1,10-secoergostane skeleton. Their biosynthesis was thought to be by an initial nucleophilic attack at the C(1) ketone of stoloniferones that coexisted with stolonolides in *C. viridis*. The Taiwanese collection of this organism also yielded C(1)-ketone stoloniferones E (**C17.07f$_1$**), F (**C17.08f$_1$**), and G (**C17.08f$_3$**).[208] Ten more stoloniferones, H−Q, are recently reported from the same species: **C17.05f$_6$**, **C17.05f$_2$**, **C17.05 g$_5$**, **C17.05f$_1$**, **C17.03f$_6$** (R_1 = R_2 = H), **C17.03g$_5$**, **C17.03f$_1$**, **C17.07f$_6$**, **C17.07f$_2$**, and **C17.07g$_5$**.[209]

Pachyclavularia is also a genus of the Stolonifera order. The coral *P. violaceae* from Indonesia did not yield the C(1)-ketones but instead the new 9,11-seco sterol **B16.01e$_1$** (Figure 16). The sterol's biogenetic precursors, however, should have a 9α-OH, a common feature of all the sterones of Stolonifera.[210] The taxonomy of this genus is debated. Alderslade proposes[211] based on morphology that *Pachyclavularia* is the same genus as *Briareum* (order: Gorgonaceae) that the sterol chemistry of this genus seems to suggest a commonality with both.

8. C(3) Ketones and Ring A Aromatized Sterols (Class D Sterols)

8.1. C(3) Ketones

These sterones are present in several species of both Gorgoniidae and Alcyoniidae orders. The earliest report is from an unidentified Pacific species.[212] New sterones continue to be reported to date, cf. the sterones of *Nephthea bayeri* (see below).[213] The biosynthetic origin of the ring A-unsaturated 3-ketones from the Δ^5-3β-hydroxy system of the usual sterols (**A6.01**) involves the migration of Δ^5 to Δ^4, and the consequent activation of the 3β-OH for oxidation to a Δ^4-3-ketone. The activation then proceeds to the remaining part of ring A to produce the other ketones, as shown above, including the dienones. In the oxidation−reduction process, a late Δ^4 reduction of the dienone would produce the Δ^1-3-ketone.

8.1.1. Dienones (Figure 18)

Dienones, i.e., cross-conjugated 3-ketones, were reported as the only products, apart from the regular 3β-hydroxy-Δ^5 sterols reported in quite a few Alcyonacean corals, e.g., the pregnene **D18.01a$_1$** and 12β-hydroxy and 12β-acetoxy dienone steroids **D18.02d$_1$** (R_1 = H) and **D18.02d$_1$** (R_1 = Ac), respectively, of the cold water species *Gersemia rubiformis* (family: Nephtheidae). Their congener is the pregnene **A6.01a$_1$**.[214−216] In the Alcyoniidae family, *Anthomastus bathyproctus* of South Shetland Is. (Antarctica) is reported to yield exclusively as many as seven new dienones. Of these, **D18.01e$_{19}$**, **D18.01e$_{20}$**, **D18.01e$_{27}$**, and **D18.01d$_4$** are methyl carboxylates in the side chain. The last sterone as well as **D18.01d$_5$** and **D18.01d$_3$** are unique 24-nor compounds. The dienone **D18.03f$_{12}$** has a nine carbon side chain.[217] Since corals are more usually common in tropical waters, their occurrence in the cold waters of Antarctica raises issues concerning the biogenesis of their metabolites. It is believed that these cold water corals, in common with the corals of tropical and subtropical waters, share the common mevalonate pathway for the sterol biogenesis.[217] *Sinularia sp*. of Guam Is. yielded no other steroids (as reported), apart from dienones.[218] Its dienones are functionalized at C(18) with oxygen that is involved in pyran ring formation, with the C-22 of the side chain yielding the pair of epimeric C(22) spiroketals **D18.04** and **D18.05**. Recently, another Alcyoniidae coral *Cladiella sp.* yielded a new dienone, the related hemiketal **D18.06**. The sterol, which the authors named as cladiellin A, was isolated using bioassay-guided fractionation.

The hemiketal is highly unstable. In the NMR tube itself, the sterol lost the 22-OH and converted to **D18.07** in $CDCl_3$ and to **D18.08** in py-d_5. Bioassay showed that the parent and the products all possess antioxidant activity.[219]

In *Dendronephthya sp.* (family: Nephtheidae) of Japan also, dienones are reported exclusively. Its sterone **D18.01c$_1$** has a degraded side chain.[220] Other sterones were named as isogosterones A−D by the authors, after Isogo-ku in the Yokohama prefecture, where their laboratory is situated. They are unique in that all four are 13,17-secosterols isolated for the first time from nature. They contain new rings formed without the involvement of the side chain, and all have the 12α-*O*-acetate function in ring C. Among them, isogosterones A (**D18.09e$_1$**) and D (**D18.09e$_5$**) (R^1 = Ac) have a new bicyclic system in a newly formed ring D and isogosterones B (**D18.10e$_6$**) and C (**D18.10e$_5$**) (R^1 = Ac) have a newly formed spirocarbon at C(14).[221] The uniqueness of the antifouling character of these sterones is that they are not toxic even at the high concentrations tested (ca. 100 μg mL^{-1}); yet they inhibit cyprid larvae settlement at low concentration (ca. 2.2 μg mL^{-1}). The compounds appear to be promising nontoxic antifoulants.

In the fouling organism *Carijoa sp.* of the Indo Pacific, two pregnenes with dienone structure in ring A are reported recently.[222] They are **D18.11a$_1$** with a 15-acetoxy function and **D18.12a$_1$** (R_1=Ac) with a 18-acetoxy function. Both sterones are moderately potent inhibitors of the mitochondrial respiratory chain. Two more pregnenes that are isomeric chlorohydrins in ring A, namely **D19.01a$_1$** and **D19.02a$_1$** (Figure 19), are reported also recently from *Carijoa multiflora* of Panama.[223]

8.1.2. Δ^4-Enones (Figure 19)

With the dienones, the Δ^4-3-ketones (Figure 19) co-occur in quite a few cases, e.g., the Alcyonacean corals. In *Eleutherobia sp.* of Pohnpei (Micronesia), a coral with the common name "deadman's fingers", the enone **D19.03c$_2$**, with antifeedant activity, and its side chain analogue **D19.03c$_3$**, previously isolated from the dorid nudibranch *Aldisa sanguinea* cooperi,[224] are associated with a new enone, the former's 11α-acetoxy analogue **D19.04c$_2$**. Among the dienones that co-occur in the coral, **D18.01c$_2$** is known[225] and its Δ^{22} analogue **D18.01c$_3$** is new.[226] Minabeolides are novel sterones of *Minabea sp.* (family: Alcyoniidae) from Turkey[227] containing a unique side chain δ-lactone akin to the steroids named withanolides of land plants of the solanaceae family.[228] Of the new minabeolides 1−8 reported, four have the dienone nuclear structure (Figure 18), cf., minabeolide 1 (**D18.01f$_{31}$**), 2 (**D18.12f$_{31}$**) (R_1 = Ac), 4 (**D18.01e$_{28}$**) (R_1 = H), and 5 (**D18.12e$_{28}$**) (R_1 = Ac), and four have the (Δ^4) enone structure (Figure 18), cf., minabeolides 3 (**D19.03f$_{31}$**), 6 (**D19.03e$_{28}$**), 7 (**D19.05e$_{28}$**) (R_1 = Ac), and 8 (**D19.04e$_{28}$**) (R_1 = Ac). The dienone minabeolides 2 and 5 and the enone minabeolide 7 have additional functionalization of C(18) while the enone minabeolide 8 has an extra 11α-OAc function. The 11α-acetoxylation is also present in the enone **D19.04e$_{26}$**, which appears to be an artifact in the side chain. From the yields reported, the dienone and enone structural moieties are in a 3:1 ratio, giving an indication of the high propensity with which the enone precursors pass on to the dienone. A precursor of the side chain δ-lactone structural moiety of minabeolides involving C(22) and C(26) can be found in **D19.03e$_{30}$** (R′ = β-D-xylose) named bebrycoside reported recently from the gorgonian *Bebryce indica* of the South China Sea.[229] The uniqueness of this glycoside is the side chain glycosidation.

Nephthea chabroli from the south Taiwanese coast is a source of nine new sterones named chabrolosteroids.[230,231] Steroids A, B, and H are dienones **D18.01f$_{25}$**, **D18.01f$_{28}$**, and **D18.16f$_{19}$**, respectively. The enones are D (**D19.06f$_{19}$**), E (**D19.03f$_{19}$**), F (**D19.08f$_{19}$**), and G (**D19.03f$_{20}$**). New sterol with the regular Δ^5 nuclear structure is chabrolosteroid I (**A6.01f$_{19}$**). The ninth steroid (chabrolosteroid C) is a rearranged steroid **D23.08**. The dienones constitute 23% of the sterol mixture, the enones 60%, and the Δ^5 sterol 15%. The rearranged steroid is very minor (<2%) and could be an artifact of isolation procedure, but the authors went on to claim its natural origin and proposed a concerted biosynthetic mechanism involving initial protonation of the 3-ketone and a 1,2-shift of the 19-Me to C(5), followed by a shift of C(6) to C(1).[230] In *Nephthea bayeri* from China, five sterones are reported. The only dienone is **D18.13e$_9$**, which has extra features of 12β,16β-diacetoxylation. The other four are enones **D19.09e$_9$**, **D19.07e$_9$**, **D19.07e$_{10}$**, and **D19.09e$_{10}$**.[213,232] As the coral was collected from off the Nanji Is., the steroids were named as nanjiols A, B, C, D, and E, respectively. In this coral also, the yields of different sterones indicate that the enone moiety is more expressed than the dienone moiety by a factor of over six.

Recently, Δ^4-3-ketones are reported as exclusive principles of two gorgonian species. *Muricella flexuosa* from the South China Sea gave **D19.03e$_{23}$** (R^1 = Ac), named muricisteroid. The vicinal deoxygenated side chain structure is so reactive that it suffers elimination of both H_2O and HOAc in the NMR tube itself.[128] In *Subergorgia mollis* from Taiwan, **D19.03a$_1$**, a synthetic intermediate previously,[233] and **D19.10a$_1$** are reported as the new sterones.[234] *Dasystenella acanthina* of the eastern Weddel Sea was the first Antarctic coral to be reported to contain polyoxygenated steroids.[235] Prior to this, the study of Antarctic corals was confined to exploring the ecological role of the "usual" sterols, e.g., of cholesterol and its 24-methylen-, 22-dehydro-, and 22-dehydro-7β-hydroxy derivatives in *Alcyonium paessleri*.[236] The new sterones reported from *D. acanthina* included **D19.03d$_5$**, which is a norcholestane derivative. With the same nuclear structure are **D19.03e$_{13}$** and **D19.03e$_{21}$**. Two sterones **D19.11e$_7$** and **D19.11e$_{21}$** are 12β-*O*-acetates.[235] Two more sterones isolated have the unique 3α-acetoxy-Δ^4-6-keto system, cf., **A11.13e$_{16}$** (R^1 = H) and its 11α-acetoxy product **A11.14e$_{16}$** (R^1 = H).[235] All compounds showed significant activities as growth inhibitors of several human tumor cell lines. In addition, cytostatic and cytotoxic effects were also observed on selected tumor cell lines.

8.1.3. Δ^1-Enones (Figure 20)

The dienones also co-occur with Δ^1-3-ketones in the Alcyonacean corals usually and gorgonian corals occasionally. The Δ^1-3-ketones (Figure 20) perhaps result by reduction of Δ^4 of the dienones. The earliest in this category is the unidentified Pacific species referred to earlier,[212] in which the pregnene dienone **D18.01a$_1$** is accompanied by the enone **D20.01a$_1$**. The intermediates involved in the evolution of the ring A pattern, **A11.15a$_1$** and **A11.16a$_1$**, with the common 3α-OH, were also isolated. In *Alcyonium gracillimum* of Korea,[237] the dienone **D18.14** is accompanied by four Δ^1-enones, including **D20.01e$_6$**. In the other three, the 16β-oxygen is involved in hemiketal formation with C(22) alone cf., **D20.10**, or a spiroketal formation with C(22) and C(25)

simultaneously, cf., **D20.11**. In **D20.08**, the 18-oxygen forms an ether bridge with C(22). In **D20.11**, the spiroketal structure is reminiscent of the hippurin structure. In **D20.10**, a possible biogenic precursor (of the hippurin side chain) is seen. The reduction of 3-ketone to 3α-OH and an (optionally) additional 2α-OH in ring A would complete the hippurin formation from **D19.07.** Two additional sterols that were reported are known. The hemiketals exhibited moderate cytotoxicity and antiviral activity.

From a few Nephtheidae corals and a gorgonian, new Δ^1−3-ketones (Figure 20) were reported. *Spongodes sp.* from China yielded the cytotoxic **D20.01e$_{18}$** found to have cytotoxicity against BEL-7402 at a fairly low concentration. This is the first example of a C(21)-oate among coral steroids, although among sponges, they (kiheisterones) are known.[238] From *Scleronephthya sp.* of the South China Sea, the side chain degraded **D20.01a$_4$** is also a Δ^1-enone. In the pregnene **D20.02a$_1$**, which co-occurs with it, the Δ^2 is epoxidized.[239] In *Dendronephthya gigantea* from Green Is. (Taiwan), the new enones dendrosterone A (**D20.01e$_3$**), dendrosterone B (**D20.01f$_3$**),[240] and (**D20.01e$_9$**) that were previously isolated from *Alcyonium gracillimum*[237] are accompanied by the new dienone **D18.01e$_3$** (dendrosterone C).[240] *Cladiella krempfi*, in the foregoing, has been shown to be a prolific source of pregnene glycosides. Its collection from Hainan Is. contains the enones **D20.01a$_3$** (krempene C) and **D20.03a$_3$** (krempene D). The more exotic steroids are krempene A (**D20.04**), formed perhaps by the addition of methanol persulfide (HS-S-CH_2OH) across Δ^1, and krempene B, the ring A aromatic **D22.01** (Figure 22).[241] In *Capnella erecta*,[242] the pregnene **D20.01a$_1$** reported was known earlier from an unidentified Pacific species.[212] In *C. thyrsoidea*, a common octocoral of the South African waters[243] that occurs in two color (bright yellow and gray) variants, **D20.05a$_1$** (R_1 = Ac) is also a pregnene but with an additional 16β-OAc; also isolated is the 3α-acetoxy pregnene **A11.17a$_1$**.

The other enone, cf., **D19.04a$_1$** (R_1 = H), is prevalent in the gorgonian *Eunicella cavolini*.[244] Pectinoacetal A (**D19.12**) and its C18-epimer pectinoacetal B (**D19.13**) (and pectinoacetal C (**D20.09**) with saturated ring A) from *Ctenocella pectinata* from New Caledonia are the isomeric hemiacetals at C(18).[245] In the lactolization of 18-CHO with 22-OH (of the side chain) of the precursor aldehyde, of the two epimers **D19.12** with a *re* face and **D19.13** with a *si* face, the former is more favored. Their 16-keto-20-deoxy analogues **D19.14** and **D19.15**, which are cancer cell antiproliferative, are from *Ctenocella sp*. of the same region.[246] These hemiacetals have only been reported in *Ctenocella* and were considered by the authors to be specific markers of this genus.

8.1.4. Ring A Saturated Ketones (Figure 21)

Reduction of both double bonds of ring A appears in gorgonians. In the gorgonian *Leptogorgia sarmentosa* of the Gibralter Strait,[247] the enone **D20.06e$_9$**, a 16β-hydroxy sterone, is accompanied by **D21.03e$_9$** (R_1 = H), also a 16β-hydroxy sterone, and **D21.05e$_9$**, its C(16) keto derivative. All compounds, including the known steroids, showed significant cytotoxicity against several tumor cell lines. Sterones with saturated ring A co-occur with Δ^4- enones and $\Delta^{1,3}$-dienones, cf., the gorgonian *Leptogorgia sarmentosa* referred to above.[247] The Spanish collection gave[248−250] sterols **D21.03e$_9$** (R_1 = H, guggulsterol III) and **D21.04e$_9$**, which are a pair of C-16 epimeric alcohols, and **D21.05e$_9$**, their 16-ketone with saturated ring A. In the ring D diosphenol **D19.16e$_9$** and the 18-functionalized **D19.17f$_{13}$** and **D19.17e$_{12}$**, ring A contains a Δ^4-enone moiety. More 18-functionalized sterols isolated, namely **D18.15e$_{14}$**, **D18.15e$_{12}$**, and **D18.15f$_{13}$**, contain the dienone moiety.[248−250] The gorgonian *Euplexaura anastomosans* of Korea is unique for its anastomosacetals A−D,[251] which have a cyclic acetal function in the side chain reminiscent of δ-lactones in withanolides earlier isolated from *Minabea sp*.[227] The dienone **D18.16e$_{29}$** is A, the two enones are **D20.07e$_{29}$** (Δ^1, B) and **4.50e$_{29}$** (Δ^4, C), and the saturated ketone **D21.06e$_{29}$** is D.[251]

8.2. Ring A Aromatized Sterols (Figure 22)

The dienone structure is highly reactive in the Alcyonarian corals, giving place to ring A aromatization by loss of 19-Me or by C(9)−C(10) bond cleavage.

8.2.1. 19-Nor Steroids

The phenols **D22.02a$_1$** (G = H) and the 3-*O*-methyl ether **D22.03a$_1$** are from a new *Capnella sp*.[242] The phenol **D22.02a$_1$** (G = H) occurs as a known compound in *Scleronephthya pallida* from Thailand[252] accompanied with the new **D22.02a$_1$** (G = fucose) and **D22.02a$_1$** (G = arabinose). In this species, these norpregnenes are associated with the lone pregnene **D20.01a$_1$** (Figure 20), a known steroid having a Δ^1 enone moiety in ring A. The fucoside **D22.02a$_1$** (G = α-fucopyranose) exhibits moderate antimalarial activity and cytotoxicity. The ring A aromatization is very efficient, going by the yields of steroids; the conversion is to an extent of as much as 80%.

In *Alcyonium gracillimum* collected from Japan,[220] the A ring aromatized nor pregnene **D22.02a$_1$** (G = Me), a 3-*O*-methyl ether, and **D22.02a$_1$** (G = 6-deoxygalactose), its 3-*O*-glycoside, co-occur with the steroidal enone **D20.01e$_{24}$**. The methyl ether is probably an artifact; the glycosidic linkage, however, confirms the 3-oxygen function in the natural product. The glycoside was found to be toxic to the cyprid larvae of *Balanus amphitrite*.

8.2.2. C(1)−C(10) Seco Sterols

The dienone structure undergoes rearrangement involving C(1)−C(10) bond breaking, a reaction unique only in some gorgonians. In this, the major metabolite astrogorgiadiol **D22.04e$_1$** and a series of nine related metabolites named as calicoferols are included. The fertilized starfish egg cell division inhibiting astrogorgiadiol **D22.04e$_1$** is from *Astrogorgia sp*.[253] Calicoferols are its side chain variants, first from *Calicogorgia sp.* of Japan and later *Muricella sp.* of Korea. Calicoferols C (**D22.04f$_3$**),[254] F (**D22.04f$_6$**), G (**D22.04e$_2$**), H (**D22.04d$_2$**), and I (**D22.05e$_1$**)[255] are side chain variants of astrogorgiadiol. Calicoferols D (**D22.06f$_6$**), E (**D22.06e$_1$**), and I (**D22.05e$_1$**) have keto groups at C(9).[254] The calicoferols are accompanied with astrogorgiadiol (**D22.04e$_1$**) as the major metabolite. Calicoferols A and B (**D22.06e$_3$** and **D22.07e$_1$**)[256] were from *Calicogorgia sp*. (Japan). Calicoferols A and B are toxic to brine shrimp, calicoferol D exhibited potent antiviral activity, and calicoferols F, G, H, and I are cytotoxic and PLA_2 inhibitory.

8.3.3. Ring-A Degraded and Contracted Sterols (Figure 23)

Ring A modification resulting in the breaking of the ring at other than the C(1)−C(10) bond or its reappearance as a

contracted (5-membered) ring is included in this group. Ring A-contracted sterols are more common among marine sponges belonging to the families Microcionidae, Phloeodictyidae, and Axinellidae,[31] e.g., *Anthoarcuata graceae*,[257] *Phorbas amaranthus*,[258] and *Axynella proliferans*, respectively.[259]

In *Dendronephthya sp.* (family: Nephtheidae), the driving force for the rearrangement is from an initial formylation of the 3β-OH in the form of formate esters **A6.01e$_3$** (G = CHO) and **A6.01f$_7$** (G = CHO). Another compound, 3-β-formyloxycholest-5-ene (**A6.01e$_1$**) (G = CHO), also isolated, was earlier known as a synthetic product.[260] Along with the formate esters, three ring-A contracted sterones **D23.02e$_1$**, **D23.02e$_3$** and **D23.02f$_7$** were isolated as new steroids. Known steroids that do not belong to the formate pathway, cf., the alcohols **A8.01e$_1$** (G = R$_1$ = H; Figure 8), **A9.01e$_1$**, **A9.01f$_2$**, and **A9.01f$_7$** (Figure 9) and the ketones **D19.03e$_1$**, **D19.03e$_3$**, **D19.03f$_3$**, and **D19.03f$_7$** (Figure 19), are also isolated.[261] The ketones indeed constitute a major two-thirds of the suite of steroids. The remaining one-third is shared equally by the other three groups of steroids: the A-ring contracted, the regular Δ^5, and the formate esters.[261]

A gorgonian *Muricia sp.* of the Bay of Mazaltan (Mexico) yielded ring-A opened pregnanes muricinone A (**D23.03**) and muricinone B (**D23.04**).[262] Hippurins are discussed in section 9 below. Recently, the first A-nor hippurin **D23.05** has been isolated from *Isis hippuris* from Taiwan.[263]

9. Hippurins and Associated Sterols (Class E Sterols)

9.1. Hippuristanols (Figure 24a)

It was nearly three decades ago that hippurin-1 (**E24.01**) (R$_1$ = R$_2$ = H, R$_3$ = Ac) was first isolated as a major metabolite (20% of the partially purified extract) from *Isis hippuris* of the Great Barrier Reef.[264] The polyoxygenated steroid opened up a new class of unique sterols containing a spiro C(22) ketal function in the side chain by involvement of the 16β-oxygen of ring D. A common characteristic of this group of steroids is 3α (instead of 3β)-oxygen and a 11β (not 11α)-oxygen substitution and Δ^5 saturation. Although the structure of the acetyl derivative of hippurin-1 was correctly assigned by XRD by the authors,[264] exact structure assignment for hippurin-1 itself had to wait for 4 years, when Higa et al.,[265] working on *Isis hippuris* of Okinawa, found that the 22-spiroketal function was so unstable that, during acetylation, the ketal epimerized and that the Australians[264] were actually dealing with the 3-acetate of 22-epi hippurin-1 (**E24.02**) (R$_1$ = R$_3$ = Ac, R$_2$ = H). The Japanese[265] indeed isolated both 22*R* and 22*S* epimers of different hippurins from the same organism/collection. The 22*R* and 22*S* epimers can be distinguished in NMR spectra. Both the H-22*S* and C-22*S* appear at lower field (δ values 4.4 and 118, respectively) than H-22*R* and C-22*R* (4.3 and 115). The same is also true for the H-16α. The 22*S* configuration is for the "epi" series.

Hippuristanol (**E24.03**) (R$_1$ = R$_2$ = H), the name introduced by the Japanese,[265] lacks C(2) oxygen substitution. It is 2-desacetoxy hippurin-1. And hippurin-1 is thus 2-acetoxy hippuristanol. The confusion arising out of this referral duality for naming different hippurins should preferably be set in order. It would be better to limit the name "hippurin" to the sterol class and use "hippuristanol" as the referral name for different members that result by substitution with a hydroxy or acetoxy group of the parent skeleton. The Okinawan collection gave, in addition to the known 2α-actoxy hippuristanol (hippurin-1) (**E24.01**) (R$_1$ = R$_2$ = H, R$_3$ = Ac), 2α-hydroxy hippuristanol (**E24.01**) (R$_1$ = R$_2$ = R$_3$ = H), hippuristanol (**E24.03**) (R$_1$ = R$_2$ = H), as well as the C(22) epimers of each, i.e., **E24.02** (R$_1$ = R$_2$ = H, R$_3$ = Ac), **E24.04** (R$_1$ = R$_2$ = H), and **E24.02** (R$_1$ = R$_2$ = R$_3$ = H), respectively. Hippuristanol-3-acetate (**E24.03**) (R$_1$ = Ac, R$_2$ = H) was also isolated as a new compound.[265] Hippuristanol and 2α-hydroxy hippuristanol are potent anticancer agents.[265] From *Isis hippuris* of Andaman & Nicobar Is. (India), five new hippurins of the hippuristanol class in addition to three known ones were reported.[266] Two are the epimeric pair: **E24.01** (R$_1$ = R$_2$ = R$_3$ = Ac) and **E24.02** (R$_1$ = R$_2$ = R$_3$ = Ac). The acetylation of 11β-OH, which is present in these two compounds, has not since been reported. The rest are 22*S* hippuristanols without 22*R* counterparts, viz., **E24.01** (R$_1$ = R$_3$ = Ac, R$_2$ = H), **E24.01** (R$_1$ = Ac, R$_2$ = R$_3$ = H), and **E24.01** (R$_1$ = R$_2$ = R$_3$ = H).[266] The Indonesian collection of the gorgonian yielded 3-acetyl hippuristanol (**E24.03**) (R$_1$ = Ac, R$_2$ = H) and, for the first time, 11-deoxysterol (**E24.05**) and its 3-ketone (**E24.06**) (11-dehydroxy-22-*epi*-hippuristan-3-one).[267] The Green Is. (Taiwan) collection of the gorgonian afforded 2-hydroxy-3-*O*-acetyl-hippuristanol (**E24.01**) (R$_1$ = Ac, R$_2$ = R$_3$ = H) and hippuristanol-11-ketone (**E24.07**).[268]

Epihippuristanol (**E24.04**, R$_1$ = R$_2$ = H) is stated[267] to be in the process of patenting for its cytotoxic properties.[269] Gonzalez and co-workers[267] made some generalizations on structure−activity relationship in *Isis hippuris* steroids. They found that 22-spiroketals are more active than steroids without this function (section 9.2 below) and that, between 22*R* and 22*S* hippuristanols, there is no significant difference in activity. 11-OH substitution, if present in combination with 3-OH (only), imparts activity, while if it is present in combination with 3-OH as well as 2-OH, activity disappears. In the former class of compounds, the authors found that acetylation of C(3) decreases activity but increases cytotoxic selectivity. Diacetylation (of both 3-OH and 11-OH) resulted in complete loss of activity.

9.1.1. 18-Functionalized Hippurins (Figure 24b)

Functionalization of the 13(CH$_3$) of hippuristanols as a COOH group or a CHO group is implied in lactones or lactols, respectively, involving the 21β-OH. A concerted mechanism (with CHO as precursor) also involving the 11β-OH would yield the 18-acetals. Higa et al.[270] observed this phenomenon as early as 1981 in the isolation of **E24.08** (R$_1$ = Ac) and **E24.09**. Hippuristanols in which the 13(CH$_3$) fuctionalization is only up to CH$_2$OH, i.e., 5-membered ring cyclic oxides, have not so far been isolated. The C(22) stereochemistry was not resolved by Higa et al.[270] Its 3-desacetylated product **E24.08** (R$_1$ = H) has also been isolated subsequently by the same group of workers, and its stereochemistry was established by X-ray as 22*S*.[271] Four new hippuristanol lactones, **E24.10** (R$_1$ = R$_2$ = Ac), **E24.10** (R$_1$ = R$_2$ = H), **E24.10** (R$_1$ = H, R$_2$ = Ac), and **E24.10** (R$_1$ = Ac, R$_2$ = H), three new acetals, **E24.11** (R$_1$ = R$_2$ = Ac), **E24.11** (R$_1$ = Ac, R$_2$ = H), and **E24.11** (R$_1$ = H, R$_2$ = Ac), and two lactols, **E24.12** (R$_1$ = H) and **E24.12** (R$_1$ = Ac), isolated for the first time, are among the hippurin class of steroids isolated from the gorgonian from Green Is. (Taiwan).[268]

9.2. Associated Nonhippuristanol Sterols

Bereft of the characteristic spiroketal function of the hippuristanol class, i.e, the steroids with acyclic side chains that co-occur in the gorgonian *Isis hippuris* mainly, some Alcyonacean corals recently fall into three subclasses, viz., (i) hippuristerols, (ii) hippuristerones, both of which are 5,6-dihydro-5α(H)-steroids, and (iii) Δ^5 steroids.

9.2.1. Hippuristerols (Figure 11)

Hippuristerols, in common with hippuristanols, have the 3α-oxygen function. These sterols have side chain oxygenation at appropriate carbons, ca., C(25) and C(22), and should be considered as intermediates that could, with suitable enzymes present, pass on to the (22-spiro) hippuristanols. Spiroketal formation does not proceed due to the rigidity introduced into the side chain and/or the unavailability/inaccessibility of the 16β-OH precursor. They are hippuristerols A−D, i.e., **A11.19g$_{13}$** (R_1 = H, R^1 = Ac), **A11.18g$_{13}$** (R^1 = Ac), **A11.19g$_{13}$** (R_1 = R^1 = Ac), and **A11.15f$_{32}$** (R_1 = R^1 = Ac), respectively.[267] New hippuristerols E **A11.18g$_{13}$** (R_1 = R^1 = H) and F **A11.19g$_{13}$** (R_1 = R^1 = H) have been recently added from the Green Is. collection referred above.[272] The sterol epimeric pair at C(3) named as orthohippuristerol A and orthohippuristerol B are both orthoesters in the side chain—**A7.14f$_{33}$** (R^1 = Ac) (Figure 7), with the rare 3β-OH, and **A11.18f$_{33}$** (R_1 = H, R^1 = Ac) (Figure 11) are from the Indonesian collection.[268] The 3α-hydroxy sterols are usually accompanied by their 3-ketones (hippuristerones). Thus, hippuristerols A−D co-occur with hippuristerones A−D (Figure 20) in the gorgonian.

9.2.2. Hippuristerones (Figure 21)

These are C(3)-ketones of hippuristerols. All these sterones have functionalization of the side chain C(20) as 20β-OH or a 17,20β-epoxide or as $\Delta^{17(20)}$. As many as nine of the hippuristerones are from a single laboratory (of Sheu) in Taiwan,[272−274] including the first of the series, viz., hippuristerone A (**D21.07g$_{13}$**) (R_1 = H, R^1 = Ac).[273] The sterones of the Indonesian collection,[267] in addition to the new epihippuristanone (**E24.06**) (Figure 24) mentioned above and the known hippuristerone A, are hippurinsterones B, C, and D and orthohippurinsterone, which is an orthodiester in the side chain. Their structures are **D21.08 g$_{13}$** (R^1 = Ac), **D21.07g$_{13}$** (R_1 = R^1 = Ac), **D21.09f$_{32}$** (R^1 = Ac), and **D21.03f$_{33}$** (R_1 = H), respectively. The Taiwanese (Green Is.) collection, on further examination, yielded hippuristerone E (**D21.05g$_{13}$**) (R^1 = Ac), which is a 3,16-diketone, hippuristerone F (**D21.10g$_{13}$**) (R^1 = H), and its 25-acetate, hippuristerone G (**D21.10g$_{13}$**, R^1 = Ac), hippuristerone H (**D21.07g$_{13}$**, R_1 = R^1 = H), and hippuristerone I (**D21.08g$_{13}$**, R^1 = H).[274] Three new hippuristerones (J, K, and L) are added more recently;[272] J (**D21.07g$_{15}$**, R_1 = H) and K (**D21.08g$_{14}$**, R^1 = Ac) have new acetoxylations at C(21) and C(27), respectively. Hippuristerone L (**D21.11g$_{17}$**, R^1 = Ac), with a $\Delta^{17(20)}$, seems to be a precursor of 17,20β-epoxides. Formation of the 20α,22α-orthoester functionality of the side chain **f$_{33}$** was proposed by the authors to originate from a 20-hydroxy,22α-*O*-acetyl precursor by nucleophilic attack at the carbonyl carbon. Since the stereochemistry cannot permit it and since the precursor cannot be a 17,20β-oxide either, hippuristerone L appears to be a common intermediate for the orthoester also. The particular feature of these sterols and the sterones is that oxidation does not extend to other carbons.

9.2.3. 3β,11α,12β-Trihydroxy Sterols

On the other hand, a second set of nonhippuristanol sterols, in parallel to the earlier set, co-occur with hippuristanols. In them, the regular 3β-hydroxy-Δ^5-ring system is extensively oxidized, as in the case of group B sterols, but not the side chain. Strikingly, all are 3β,11α,12β-trioxygenated sterols. These sterols are from *Isis hippuris* of Japan. The Δ^5 sterol **A9.06h$_1$** (Figure 9)[275] is the forerunner in this group. **A9.07h$_1$** (R_1 = H, R_2 = Ac) and **A9.07h$_1$** (R_1 = Ac, R_2 = H), which are also Δ^5 sterols (Figure 9), and the 5α,6β-vicinal dihydroxy system containing sterols, cf., **B12.26h$_1$** and **B12.27h$_1$** (Figure 12), were reported later.[271] The latter's nuclear oxidation is also present in isihippurol A (**B12.27h$_3$**), occurring along with isihippurol B (**B15.06h$_3$**) (Figure 15), a 5α,6α-epoxide.[276] The cyclopropane ring containing side chain is present in **B13.04h$_1$** (Figure 13), a 5β-hydroxy-6-ketosteroid that occurs along with hippuristerones in the Green Is. collection.[272]

9.2.4. 5β,6β-Epoxy Sterols (Figure 16)

Barring this lone α-epoxide, **B15.06h$_3$** (Figure 15), the epoxide ring is β in the nonhippuristanol steroids, cf, **B16.06h$_1$**. Its oxygenation at 1α would produce **B16.07**. In parallel, its successive oxygenations at 7α, 15α, and then 1α produce **B16.08h$_1$** (R_1 = H) and its acetates **B16.08h$_1$** (R_1 = Ac), **B16.09h$_1$**, and **B16.10h$_1$**, respectively.[271]

9.3. Hippurin-like Sterols from Alcyonaceae

Sarcophyton crassocaule of the Andaman & Nicobar Islands (India) is an Alcyonacean coral to yield hippurin-like sterol **A6.27** (R_1 = H) and its 22-epimeric **A6.28** (R_1 = H) and their corresponding 3-acetates **A6.27** (R_1 = Ac) and **A6.28** (R_1 = Ac). These steroids are unique in that they contain the cyclic side chains involving 16β-oxygen as in hippurins but do not share their 3α-hydroxy-Δ^5-saturated A/B ring structure.[277] The 3β-hydroxy-Δ^5- structural feature persists in them and in the 17,20-oxides **A6.29g$_{12}$** (R^1 = H) and **A6.29g$_{12}$** (R^1 = Ac) also isolated and the known 9,11-seco sterol **A7.02h$_1$** (Figure 7).[278] This species collected from the Australian coast was reported to contain cembranoid diterpenes,[279] of which sarcophine and sarcophytoxide released into the seawater were reported as allelochemicals.[280] The Indian authors did not notice any diterpenoid in their collections.[278]

10. Conclusions

As many as 561 new polar steroids have been reported from species of 16 octocoral families. The genera to which the species, most of them identified but several unidentified, belong are principally of the families Alcyoniidae (10 genera) and Nephtheidae (8) in the order Alcyonaceae (total genera: 24) and Plexauridae (10), Gorgoniidae (4), and Acanthogorgiidae (6) in Gorgonaceae (total genera: 27). The polar sterols are based on 246 structural types for the ring system and 107 types for the side chain. For the side chain structure, a large variety is for the nine and eight carbon chains, contributing 35 and 30 structural types, respectively, followed by ten carbon side chains (20) and eleven carbon side chains (7).

As more and more polar sterols are added to the literature, a clearer oxidation pattern is noticeable in corals. A conspicuous difference of coral polar sterols from other polar sterols, cf., sponge sterols, is that oxygenation of sterol carbons takes place even in the absence of activating groups such as Δ^5. The coral sterols seem to belong to five groups: (i) Δ^5 sterols that do incorporate, on a limited scale, features of activation of the allylic C(7) and C(4), (ii) Δ^5 oxidized sterols, i.e., sterols in which Δ^5 is directly involved in oxidation, producing epoxides, alcohols, (vicinal) diols, etc., (iii) C(1) ketones specific to species of the Stolonifera order, (iv) C(3) ketones and ring A aromatized sterols, and (v) hippurins and associated sterols. The number of oxygen atoms attaching to ring carbons is between one and seven; for the side chain, the number is between nil and three. Group D sterols have up to three oxygen atoms in the ring system and up to two in the side chain. Groups A and C sterols have up to four oxygen atoms in the ring system; with three and nil oxygenated carbons in the side chain, respectively. The sterols of groups B and E have the highest number of oxygenated carbons, both in the ring system and the side chain. In hippurins where the 3-OH is α_{ax} oriented, C(11)-hydroxylation is β_{ax}, while, in the regular sterols occurring in association with them in which the 3-OH is β_{eq}, the C(11)-OH is α_{eq}. A simultaneous 12β-hydroxylation also takes place in them.

Each "species" (collection) produces, in general, a set of sterols that belong to only one of the identified groups. The sterol composition, as a first approximation, could be of value in chemotaxonomy of corals, cf., gorgonians that produce a specific set of sterols such as pregnene glycosides, ring A aromatized and C(1)−C(10) seco sterols, *etc.*, the stolonifers that produce C(1) ketones and fleshy soft corals that produce 3β,5α,6β-trihydroxy sterols. However, this is of very limited value, since a single "species" examined by different groups of workers and by the same group of workers on collections made at different locations yields different sterols, reflecting the role of symbionts in the sterol biogenesis. However, the wizardry of the corals in evidence should excite chemists and biochemists looking for suitable enzymes that could effect laboratory conversion of inactive sterols to appropriately oxidized sterols of targeted biological activity.

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