Review

Sterol Ring System Oxidation Pattern in Marine Sponges

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Abstract: The marine sponges (Porifera) are a unique group of sedentary organisms from which several novel natural products are reported, many of which have useful biological activities. In producing unusual sterols, they occupy a preeminent position among the various groups of organisms. The polar sterols of sponges reported as at the end of the year 2002 number about 250; their ring structure changing a hundred times. The oxidation pattern in the sterol ring system, from the point of view of biogenesis seems to be mainly of four types. Each sponge species is able to produce sterols fitting into one of the four main biogenetic pathways viz., (i) 3β-hydroxy-Δ5-sterol pathway, (ii) 3β-hydroxy-Δ7-sterol pathway, (iii) 3β-hydroxy-Δ5,7-sterol pathway, and (iv) 3α-hydroxy sterol pathway.

Keywords: Marine sponges, Polar sterols, Unusual sterols, Ring system, Oxidation pattern

Introduction

The ‘usual’ sterols have the 3β-hydroxy-Δ5 (or Δ0)-cholestan (I) nucleus and a C8-C10 side chain [1]. 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 [2] have either or both of the characteristics of: (i) side chains ranging from C0 to C12 involving loss or addition of carbon atoms 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 very unstable and should be handled at very mild conditions so that artifacts are not mistaken as natural products.

The polar sterols of sponges, particularly the sulfate esters (Schemes 12-14) have interesting and useful biological activities that make them targets of biological evaluation and synthesis.

Although polyhydroxy sterols have been found in various groups of marine organisms e.g., algae, porifera, coelenterata, bryozoa, molluska, echinodermata, arthropoda, tunicata and chordata, a preeminent position is occupied by porifera, i.e., sponges. A full review of the marine polyhydroxy steroids was published in 1993 [3]. The reviews that appeared since [4,5] discuss briefly on sponge sterols. The present review’s purpose is besides giving the account as of date, to describe for the first time the biogenetic relationships that possibly exist in the sterol nuclear structure. This aspect may have a bearing on sponge classification, and the geographic occurrence of the organism, and be of great utility in chemotaxonomic studies. For brevity, the structures of sterols are presented as part structures, focusing on the oxidation pattern occurring in the sterol ABCD ring system (alone). A single sterol nucleus, as shown in various schemes (Schemes 3-14) may stand for a number of individual steroids with structural changes occurring in the side chain that are, however, not shown.

In order to propose biosynthetic relationships, as marine biosynthetic studies are few [6,7], clues are taken from the pathways operating in the terrestrial plants and animals, which are documented quite well, and since the pathways operating in marine organisms should essentially be similar to those operating in terrestrial organisms [8]. In Schemes 1-14 are presented sequential oxidations within the sterol ABCD ring system that should be taking place as part of biogenesis within marine sponges. In each product structure, the center where the structural change has resulted compared to the precursor is shown in red color. The biogenic connectivity between various sterol ring structures although hypothetical is depicted with the arrow (→) sign for clarity although this sign is usually reserved for chemical conversions that actually take place. Most often, each sponge species contains a particular group of polar sterols dominated by a set of closely related biogenetic mechanisms as presented in each scheme. However, since the schemes are formulated basing on the ‘reported’ sterol composition, and since there is occasionally a lack of information on the total sterol composition of the sponge (often, it is only the new compounds that are described), the schemes are subject to refinement.

Several novel sterols containing extra oxygen substitution and side chain modified by alkylations/dealkylations have been reported from marine sponges. In quite a few species, novel sterols are the (single) major components of their extracts. Typical examples are aplysterol (II) and 24(28)-didehydro aplysterol (III), the first sterols [9] with a methyl group at C-26, which have been found as the major sterols of the sponges of the genus Aplysia (Verongia), calysterol (IV), the major sterol (90% of the sterol mixture) of the sponge Calyx nicaensis [10], petrosterol (V) of the sponge Petrosia ficiformis [11,12], strongylosterol (VI), the sole sterol of Strongylophora durissima [13], and xestosterol (VII) and sutinasterol (VIII) isolated as the predominant sterols of Xestospongia muta [14], and Xestospongia sp. [15] respectively.
General biosynthetic Reactions in marine sponges

Working on the usual cholesterol skeleton, sponges are capable of performing enzymatic oxidation around the active sites, 3β-OH and Δ^5 functionalities.

1. epoxidation (generally αα and rarely ββ) followed by its opening in different pathways,
2. oxidation of the allylic C-7 and C-4 carbons to give simple alcohols of the preferred configuration, and
3. isomerisation of the double bond(s).

The reactions that take place on the 3β-OH and the new OH groups that are introduced (Scheme 2) are:

1. oxidation to a carbonyl,
2. dehydration producing unsaturation which will create new active allylic positions for further oxidation,
3. retro Diels-Alder reaction in the case of vicinal diols, and
4. condensation reactions involving OH, CH₂OH, CHO, and COOH groups at appropriate locations.

These reactions centering the Δ^5 and the 3β-OH are shown in Schemes 1 and 2 respectively.
Scheme 1. Significant biosynthetic reactions caused by Δ⁵ (S = side chain; see also scheme 10)
Scheme 2. Significant biosynthetic reactions caused around 3β-OH; [ ] intermediate.

(i) The 6β-OH substituent present in a cis 1,3–dialxial manner to the C-10 Me group can oxidize it in a step-wise fashion.

(ii) Epimerisation of the 3β-OH can occur if activated by migration of Δ⁵ to Δ⁴.

(iii) The Δ⁴ is amenable for alkylation.

In the following account, the progression of biosynthetic oxidative reactions that should be operating on the sterol ring system is presented. The pathways shown in the Schemes and discussed in text refer only to the ring system and not the complete structure of the steroid, as the structure of the side chain is not considered due to space constraint.

I. Δ⁵-3β-Hydroxy Steroids

Polar sterols in which the parent sterol nucleus is retained are 1 and 2 from Calyx nicaensis [16] and C. podatypa [17], and 3 recently from an Indian sample of Petrosia testudinaria [18].

1. Oxidation at C-7 (Scheme 3): The epimeric alcohols 4 and 5 and their ketone 6 are from Corallistes undulatus [19] and Cliona copiosa [20] by the allylic C-7 oxidation. It was for some time suspected that the C-7 oxidation might be resulting from auto-oxidation during isolation procedure. Hence, the isolation of the 7α-glycoside 7 (paschastrelloside A) from Paschastrella sp. confirms a biotic origin of the 7α oxygen [21]. The novel feature of 7 is its 2α-OH; the sterol inhibits cell division of fertilized starfish eggs. The presence of the
7α-OH and 7-keto group naturally in the sponge has received further proof from the recent isolation of a number of steroids 8-11 (gellusters A-D) from *Gellius sp.* of the Panaman Caribbean coast [22]. Sterol 12 was isolated from *Polymastia sobustia* from South China Sea [23], as well as 14 [24], 13 from *Geodia japonica* also from South China Sea [25]. Sterols 15 and 16 are from a Japanese specimen of *Strongylophora corticata* [26], and 17 (polysterol A) from *Epipolasis sp.* [27], and 18-27 topsentinols A to J from an Okinawan species of *Topsentia* [28]. The sterol containing the nucleus 28 (polysterol B belonging to another sterol subclass, the 3α-hydroxy sterol sulfates: Scheme 13) co-occurs with 29 (polysterol A). Although for the 3α-oxygenated sterols also, the parent is the 3β-∆⁵-sterol nucleus, the biogenetic pathway is somewhat different. The isolation of sterols belonging to different biogenetic pathways may be due to symbionts causing species heterogeneity or artifact formation on preservation and the subsequent isolation procedure. Hence, it is necessary to know these factors well for rationalizing the co-occurrence of sterols belonging to different biogenetic classes. The *Strongylophora corticata* sterols may exemplify this dimension.

**Scheme 3.** Oxidations at C-7 of ∆⁵-3β-hydroxy steroid skeleton

1,2,3 → 4

5,8,16,18,19, 20,21,22,23, 24,25,26,27

4 → 6,9,10,11,12, 13,14,15,17, 29

2. Oxidation confined to Ring A (Scheme 4): The alcoholic C-3 and allylic C-4 are active sites for oxidation. The formation of 3-ketone can facilitate migration of the ∆⁵ to the conjugated ∆⁴ position, as found in 30, mycalone from *Mycale sp.* of Southern Australia [29]. The chloroketones 31 and 32, kiheisterones C and E present in *Strongylacedon sp.* from Maui along with the chlorohydrin D 33 are the only halogenated sterols isolated from sponges even though halogenated, particularly brominated natural products are common in marine sponges being derived from red algal symbionts. The products of C-2 activation are the diosphenols 34 (kiheisterone A) and 35 (kiheisterone B) of the same sponge [30]. A hydroxylation of the allylic C-4 is demonstrated by the 3β-sulfoxypregnane 36 isolated
**Scheme 4.** $\Delta^5$ sterols: Oxidations in the ring A/B system; [ ] : not isolated

from *Stylopus australis* [31], and the glycoside 37 from *Mycale laxissima* [32]. The C-1 is activated via the $\Delta^2$ formation by dehydration of the 3$\beta$-OH. The $\Delta^2$, not so far observed in sponge sterols is a routine feature in the highly oxygenated sterol classes of withanolides and physalins from land plants belonging to the Solanaceae family [33]. The intermediate $\Delta^2$ can then indulge in vicinal 2$\alpha$,3$\beta$-diol and 2$\beta$,3$\beta$-diol formation, e.g., the glycosides 38-40, the wondosterols A, B and C isolated from a two sponge association of *Poecillastra*
wondoensis and Japsis wondoensis [34]. With the ring A becoming oxygen rich, the 19β-Me becomes amenable for oxidation to −COOH group and consequent lactonisation with the 2β-OH, as seen in the pregnane γ-carbolactones 41-43 isolated from the Hawaiian sponge Strongylophora sp. [35]. The free COOH group can also disappear by loss of CO₂ leading to ring-A aromatisation found in the sterols 44 geodisterol isolated from Geodia sp. from Papua New Guinea [36], and the 19-nor pregnane glycoside 45 from Cribrachalina olemda from Pohnpei, Micronesia [37]. Oxidative elimination of the 19-Me takes place rather easily in sponges belonging to Axinellideae, e.g., Axinella polypoides, which contains 46 as the important sterol [38-40]. Its precursor A/B ring structure containing the 19-COOH group is present in the sterols 47-49 isolated from Toxadocia zumi [41].

3. Oxidations and rearrangements in the A/B ring system (Scheme 5): In sponges, ring A-rearranged sterols cooccur with 3-keto sterols, and 3,6-diones, a phenomenon that is particularly unique in sponges belonging to the families Axinellideae and Hymeniacidonidae. This is attributed to an efficient enzyme system due to which the A/B ring reaction precedes oxidation at other centres, e.g., Δ₁₅ introduction in 50, and Δ₁₄-16α-OH system in 51 found in the sterols of Axinella proliferans from Reunion island in the Indian Ocean [42]. The biosynthesis of the unique 52 and 53 (anthosterones A and B respectively) of Anthoracurata gracia is suggested to take place by a benzilic acid rearrangement of a 2,3-diketo precursor as a new type of ring A contraction step [43].

Scheme 5. Δ⁵ sterols: 3- Ketosterols and rearranged sterols; [ ] : not isolated; S : side chain
The $\Delta^4$-3,6-diketosterols 54, with several conventional side chains are also from *Anthoracurata gracica*, the sponge from which anthosterones 52 and 53 are isolated [43]. The 3,6-diketones of *Geodia cydonium* [44] and *Cinachyra tarentina* [45] co-occur with the more common 3-ketones [46]. The 6-oximino-3-ketones 55 and 56 were obtained from a mixture of *Cinchyrella alloclada* and *C. apion* [47]. The $5\alpha,6\alpha$-dihydroxylation is seen in 57 from *Spirastrella inconstans* from India [48], and the $6\alpha,7\beta$-dihydroxylation is seen in 58 clathriol from *Clathria lissosclera* [49] of New Zealand. The former seems to be the precursor of ring B rearranged 59 orostanal isolated from *Stellata hiwasaensis* of Japan [50]. The sterol 59 is cytotoxic and apoptosis-inducing.

4. **Ring C oxidation (Scheme 6):** The ring C site of oxidation at C-12 may not be requiring activation offered by a $\Delta^\ddagger$, a $\Delta^7$ or a $3\beta$-OH. The saturated sterol 60 is in fact isolated in this group from *Rhizochalina incrustata* [51]. The activation seems to be coming from the heavily oxygenated (cyclopropane ring containing) side chains, c.f., the potent antitumour 61 [52], and 62-64 [53] from *Xestospongia sp.*, which are named aragusterols A to D, and 65 and 66 [54] and 67 [55] named as xestosterol A, xestosterol B and aragusteral E respectively, from another *Xestospongia sp.* collected from Okinawa. In rare cases, a further hydroxylation occurs at C-7, e.g., 68 xestokerol B; [54] isolated along with xestokerols A, B and D and C-16, e.g., 69 [55], another aragusterol (aragusterol F) of the *Xestospongia sp* from Okinawa. The skeletons 70 and 71 are of aragusterols G and H respectively, also isolated from this collection [55]. The sterols 72, and 73 are aragustokeretals A and C respectively that are also from the same sponge [56], and perhaps artifacts of the isolation procedure.

**Scheme 6.** $\Delta^\ddagger$ sterols: Ring C oxidation in saturated sterols ; [ ] : not isolated; S : side chain
II. $\Delta^7$-Sterols

The parent $3\beta$-hydroxy-$\Delta^2$-sterol nucleus is present in 74 thymosiosterol and 75 (24,27-didehydrothymosiosterol) isolated from *Thymosiopsis* sp. from France [57], and 76 isolated from a Caribbean sponge *Scleritoderma* sp. cf. *paccardi* [58].

1. Oxidation involving C-7, C-8, C-9, C-11, and C-14 (Scheme 7): The $3\beta$-hydroxy-5,6-dihydro-$\Delta^7$ sterol nucleus seems to be undergoing allylic C-9 and C-14 (of the isomerised $\Delta^8$ nucleus) oxidation pathways. The C-9 oxidized 77 from *Jericopsis graphidiophora* [59] co-occurs with the C-14 oxidized 78 and 79 [60].

**Scheme 7.** $\Delta^7$ sterols: Oxidation involving C-7, C-8, C-9, C-11, and C-14; [ ]: not isolated; S : side chain
The $\Delta^8$ migrated to $\Delta^{8(14)}$ while 8$\alpha$-OH is formed in 80 isolated from *Pellina semitubulosa* [20]. The $\Delta^8$-7-ketone 81 is from *Jereicopsis graphidiophora* [59]. The $\Delta^{14}$-16-$\alpha$-hydroxy sterol 82 is from the Mediterranean sponge *Topsentia aurantiaca* [61]. Extension of unsaturation to $\Delta^{8(11)}$ followed by epoxidation is behind 83 and 84 [62]. The products of retro Diels-Alder reaction followed by cyclic ether formation, viz., 85-87, and their 3-methyl ethers 88, and 89 are from *Microscleroderma spirophora* from Senegal [60] that co-occur with the 8,14-seco-8,14-dione 90.

2. Sterol amines (Scheme 8): The steroidal alkaloids, plakinamines 91-95 are $\alpha$-amino ketones that are significantly cytotoxic from a *Corticium sp.* from Vanuatu [63]. Recently, it is found that the aminoketones (e.g., 96 plakinamine F) cooccur with the aminohydrins, e.g., 97 (plakinamine E) in the *Corticium sp.* of Guam [64], and 98 in a Vanuatuan collection of the same sponge [65]. The amines 96 and 97 have moderate cytotoxicity and antifungal activity, and nucleic acid-cleaving property. These aminohydrins probably formed via the addition of the elements of (CH$_3$)$_2$NOH across a $\Delta^3$ which may be responsible for the aminoketones cited above. The 3-amino steroids 99 and 100 that result from the addition of NH$_3$ across $\Delta^3$ are also isolated from the Vanuatuan collection [65].

**Scheme 8.** $\Delta^7$ sterols: Sterol amines; [ ] : not isolated
III. Δ⁵,⁷-Sterols

Many sponge sterols are derived by oxidation of the Δ⁵,⁷-sterol nucleus. An intact 3β-hydroxy-Δ⁵,⁷ nucleus is present in the recently isolated 101 from the Jamaican sample of Agelas sceptrum [66].

1. Epidioxides (Scheme 9): Endoperoxides are routinely prepared in the laboratory by the action of singlet oxygen on cyclic conjugated dienes. Hence, when the endoperoxides 102-106 were isolated from Tethya aurantia [67] and 102, 107 and 108 from Axinella cannabina [68], it was suspected that they might be artifacts. However, such epidioxides continue to be isolated even when extreme care is taken to prevent their possible formation during extraction and isolation procedure. Thus, the Okinawan sponge Axinyssa sp. gave 109 axinysterol [69], and Lendenfeldia chondroides from Palau gave the antifouling sterols 110 and 111 [70]. The sponge species Luffariella cf. variabilis of Japan gave a mixture of the sterol epidioxides 112-120, accompanied with the cytotoxic 121, possessing extra Δ⁹(11) double bond [71], which system is also present in 122, recently isolated [72] from the same Axinyssa sp. that earlier gave 109 axinysterol [69] and which inhibits the growth of several human cancer cell lines.

Scheme 9. Δ⁵,⁷ sterols: Epidioxides

2. Epoxy derivatives of Δ⁵,⁷ system (Scheme 10): The 1,2-oxides of the Δ⁵,⁷ sterols are predominantly α,α. The intact epoxide 123 and 124 its Δ⁷(14) isomer, both having cytotoxicity to a range of human and murine cell lines are isolated recently [73] from Polymastia tenax. These 7α-alcohols are associated with the dienone 125 in the sponge. This typical dienone structure containing steroids were earlier isolated as 126, 127 and 128 from Clathrina clathrus [74]. The 5α,6α-epoxy-7α-hydroxy-Δ⁷(14) system is also present in 129 isolated from an Indian specimen of Ircinia fasciculata [75] which should be the biogenetic precursor of 130 [76]. The 5α,6α-epoxy group opens up in a number of possible ways (see also Scheme 1), producing 5α,6α-dihydroxy system, 5α,6β-dihydroxy system, and the 5α-H,6α-hydroxy system. The 5β,6β-epoxide system also occurs in which the 3β-OH had epimerised to 3α-OH. The opening of this epoxide also proceeds in a number of ways, e.g., 5α,6β-dihydroxy system, 5β,6α-dihydroxy system and 5β-H,6β-hydroxy sterols. In each case, the Δ⁹ causes activation of sites for further modification of the sterol structure.
Scheme 10. $\Delta^{5,7}$ sterols: Epoxides and derivatives; [ ] : not isolated
The 5α,6α-dihydroxy system is evidenced in sterols 131 [77], 132 [78], and 133 [79] which are products of oxidation at extended sites. The sterol 131 is from Dysidea sp. from Northern Australia, and contains the additional 9α,11α-epoxide of a Δ⁹(11), itself made possible by action from Δ⁸. The sterols that co-occur with 131 in the sponge are 134 and 135, in which the C-11 activation is in evidence. The sterols 134 and 135 inhibit the binding of IL-8 to the human recombinant IL-8 receptor type A. The sterol 132, also containing the 9α,11α-epoxide is from an unidentified species of Dysidea collected from Guam [78]. In this sterol, the 19-Me is additionally hydroxylated. The sterol 133 is from D. herbaceae [79] from Ethiopia. This sponge is unique since each of the four sterols 136, 133, 137 and 138 isolated from it represents one type of 5,6-epoxide (or its opening), viz., a trans opening of the 5α,6α-epoxide, a cis opening of the 5α,6α-epoxide, a trans opening of the 5β,6β-epoxide of the 3α-hydroxy sterol and the 5β,6β-epoxy-4α-hydroxy sterol itself respectively.

The 5α,6β-dihydroxy system is shown in addition to 136, in 139-148. The sterol 139 and 140 are from D. fragilis [80] collected in the Black Sea. The eight sterols 141-148 are from D. etheria from Bermuda [81]. The 5α-H,6α-hydroxy system is present in 149 [82] and 150 [83]. It is also present in 151 obtained from a Japanese Spongia sp. [84] which also gave 152-157 [85]. The unique feature of these six sterols is the presence of 4β-oxygen function. Further products of the 5β,6β-epoxide opening, in addition to 137 of Dysidea herbaceae [79] are the A/B cis 158-160 obtained from the same species of D. etheria that gave the A/B trans 141-148; hence, the unique ability of the two species of Dysidea. D. herbaceae is further unique for its 161 herbasterol [86], a 5β-H-9(11)-seco steroid, which is ichthyotoxic and antimicrobial. The cyclic ether 162 is from D. tupha of the Mediterranean [87].

3. 9(11)-Seco Steroids: A Δ⁹(11) activation produces the 9α,11α-vicinal diol system which in turn appears to be responsible for the producion by retro-Diels Alder reaction, the 9,11-seco ketoaldehydes 163-165 luffasterols A, B and C present in Luffariella sp. from Palau [88], 166 [45] and 167 [89] isolated from the Mediterranean sponge Spongia officinalis. The keto aldehyde 166 goes to the keto alcohols 168 and 169 [45] in the sponge. The epoxy keto alcohol 170 glaciasterol B-3-acetate of Fasciospongia cavernosa which is toxic to brine shrimp, also from the Mediterranean [90], is however not associated with its corresponding aldehyde as also in the case of 171 blanasterol from the NE Pacific sponge Pleraplysilla sp. [91] from Vancouver and 172 from a Japanese species of Stelletta [92]. In the antihistaminic secosterols 173-182 of Euryspongia sp. from New Caledonia [93]; the 2-OH which is usually β in this series is epimerised to α-OH.
4. Oxidation not involving 5α,6α-epoxide (Scheme 11): The reactions of the Δ⁵,7 system without the mediation of the 5α,6α-epoxide come under this group, e.g., 183 from an Indian specimen of Suberites carnosus [94]. Of particular significance is the methylation at C-4, activated by Δ⁵, as indicated by the occurrence of 184 polymastiamides A [95], and 185-189 polymastiamides B to F in Polymastia baletiformis from Norway, of which A, C, D and F have the 4α-Me substituent and B and E do not have substitution at C-4 [96]. The mildly cytotoxic 190 from Theonella swinhoei from Phillipines, has instead a C-4 methylene group, a group that also occurs in the sterols 191-193 from T. swinhoei from Okinawa [97]. In 191 and 193, the Δ⁸(14) underwent oxidation to give the 8-14 seco-8,14-dione. The C-4 activation leading to a 4α-oxysulfate substitution is noticed in the ten sterols 194-203 acanthosterol sulfates A to J from Acanthodendrilla sp. from Japan [98]. Of these, 202 (acanthosterol sulfate I) and 203 (acanthosterol sulfate J) showed antifungal activity and cytotoxicity.
IV. 3α-Hydroxy Steroids

The mandatory configuration of the 3-OH is β\textsubscript{eq} for the basic sterol skeleton. However, the shifting of Δ\textsuperscript{5} to Δ\textsuperscript{4} can induce epimerization of the 3-OH to α\textsubscript{ax}, a configuration that gets stabilized by sulfate ester formation and Δ\textsuperscript{4} reduction in the sponge sterols.

1. Δ\textsuperscript{5}-Origin (Scheme 12): The ring system of the sulfated steroids has a lone representative containing unsaturation in 204 [99]; all others are saturated, cf., 205 halistanol B sulfate from Pachastrella sp. [100] that inhibits endothelium converting enzyme. Weinbergsterols 206 (A) and 207 (C), have hydroxylation at C-16 while weinbergsterol B 208 has further hydroxylation at C-18; they are isolated from Petrosia weinbergii [101,102]. The disulfates 209, 210 and 207 are sterol orthoesters involving 16β-OH (and 20-OH and 22-O-butyrate of the regular side chain), isolated from the same sponge. In this group, the 15α,16β-dihydroxylation is seen in 211 clathsterol with
anti HIV-1 reverse transcriptase activity from an Eritrean sponge of genus *Clathria* [103]. The cytotoxic and antifungal *212* echinoclasterol with heavily oxygenated ring E is from the south Australian sponge *Echinoclathria subhispida* [104].

**Scheme 12.** 3α-oxysteroids: Δ⁵ origin; [ ]: not isolated, S = side chain

3. **Δ⁵⁻⁷-Origin (Scheme 13):** The 3α-sulfate esterification is more prolific when the genesis is from the Δ⁵⁻⁷ sterol skeleton. The activation of ring carbons by Δ⁷ seems to extend to C-15α by migration of Δ⁷ to Δ⁸(14). In this group, *213* is halistanol sulfate from *Halichondria moorei* [99] which has potential activity against HIV virus. It is the forerunner of several halistanol sulfates, e.g., *214-217* halistanol A to D from *Epipolasis sp.* [105], and *218* to *220*, *in vitro* HIV inhibiting halistanol sulfates F to H from *Pseudoaxynissa digitata* [106]. The sterol *221* which showed inhibition in guanosine diphosphate/G protein RAS exchange assay is ophirapstanol trisulfate from *Topsentia ophiraphidites* [107]. The sterol *222* is sokotrasterol sulfate isolated from two Halichondriidea species [108], and *223* is norsokotrasterol sulfate from *Trachyposis halichondroides* [109]. The sterol *224* is from a Japanese specimen of *Topsentia sp.* [110]. The trioxysulfate *29* polysterol B sulfate of a
Japanese specimen of *Epipolasis* sp. is accompanied in the sponge with 28 polysterol A[27], a sterol that belongs to group 1 as mentioned earlier (Scheme 3).

**Scheme 13.** $3\alpha$-oxysteroids; $\Delta^{5,7}$ origin; [ ] : not isolated, S : side chain

\[ \begin{align*}
R=\text{Na}; & \quad 28, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223. \\
R=\text{tris-(2 amino-imidazolium)}; & \quad 224
\end{align*} \]
In *Epipolasis sp.* [105], the trioxysulfates are associated with the product 225 of further hydroxylation at C-15. The 15-ketosterol 226 xestobergsterol A, that inhibits the release of histamine from rat mast cells was isolated from *Xestospongia bergqustii* [111]. It was earlier isolated from *Ircinia sp.* from Okinawa [112]. The simultaneous activation of 6α by Δ⁴ and 7β and 15α by Δ⁸(14) followed by oxidation of the 15-OH to 15-ketone appears to be taking place in 227 contignasterol [113]. In these 15-keto sterols, the configuration at C-14 is 14βH as opposed to the usual 14αH configuration. The same 14βH configuration is noticed in 228 xestobergsterol C and the further 1β-hydroxylated steroid 229 xestobergsterol B from the above *Ircinia sp.* The sterol 230 with an additional 4α-OH from the Malaysian *Haliclona sp.* [114] and 231 from a new species of *Oceanapia* [115] also contain this ring structure. The sterol 231 is in fact accompanied with its 14αH epimer 232 in the sponge. Hence, a switchover of the original 14αH configuration to the more stable 14βH is indicated in these ketones. The reduction thereafter of the 15-ketone to 15β-OH should be responsible for 233 and 234 of two Philippine unidentified Haplosclerid sponges [116].

3. **14α-Methylation (Scheme 14):** The 14α-methylation is more common among tetracyclic triterpenes of land plants, e.g., lanosterol (VIII). This feature, together with the 4,4-dimethylation over the C₁₉ cholesterol nucleus gives the usual C₂₂ tetracyclic triterpene nucleus.

**Scheme 14.** 14α-Methylation; [ ] : not isolated, S : side chain
The 14α-sterols of sponges all possess a $\Delta^{9(11)}$-unsaturation indicating that biological methylation in these sterols by 1,2-addition is facilitated in a homoannular-1,3-diene ring C as shown in the Scheme 14, cf., 235 lembehsterol B with $\Delta^5$ retained from the Indonesian Petrosia strongylata isolated together with the 6-O-sulfate ester viz., 236 lembehsterol A [117]. This steroid ring system was earlier found in 237 ibisterol sulfate (which is cytoprotective against the HIV-1 virus) from Topsentia sp. [118] and later also in 238 and 239, ibisterols B and C of a Phillipine sponge Xestospongia sp. These two sterols are associated with the ketoepoxide 240 [119]. The sterols 238, 239 and 240 are inhibitors of HIV-1 integrase. In 241 to 245, topsentiasterol sulfates A to E isolated from an Okinawan Topsentia sp. have the additional 4β-OH group [120].

Conclusions

As at the end of the year 2002, there are about 250 polar sterols from marine sponges that contain features of oxidation in the ring structure following a set pattern; the ring structure changing a hundred times. From this pattern, the sponges are inferred to follow pathways that appear to be distinct and characteristic of the individual sponge species. The marine sponges, in terms of their ability to produce polar sterols appear to be working on one of the four types of the sterol A/B ring system viz., (i) $\Delta^5$-3β-hydroxy system, (ii) $\Delta^7$-3β-hydroxy system, (iii) $\Delta^{5,7}$-3β-hydroxy system and (iv) 3α-oxy-$\Delta^5$ and 3α-oxy-$\Delta^{5,7}$ sterol systems. In a few exceptional cases, a sponge may, however, contain sterols belonging to different classes, e.g., Dysidea herbaceae. Since the observed chemical composition of a sponge may have been, in addition to the intrinsic nature of the sponge itself, due to symbionts, ecological variations, and isolation procedure, these changes should be carefully considered in trying to infer biogenetic relationships. Once this is done, it may become possible to predict new structures that can perhaps fit into the gaps of the biogenetic sequence of a given sponge, before they are actually isolated as natural products.

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