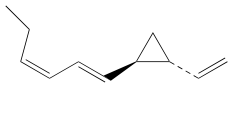
Structural Types

1. ALIPHATIC NATURAL PRODUCTS (VA)

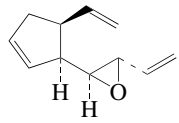
A wide variety of small aliphatic and alicyclic compounds occur in nature. Because they are diverse, no attempt will be made here to give a general account; for information on specific aliphatics, their individual entries should be consulted. In the Type of Compound Index, the aliphatic compounds included in the Dictionary are simply classified by functional group and ring/chain structure.

1.1 Semiochemicals

Semiochemicals are defined as chemicals that mediate communication between individual organisms. When semiochemicals act between members of the same species they are known as pheromones. Pheromonal systems are usually the most highly developed semiochemical systems because the species directly benefits from any improvement. The phrase 'highly developed', in this context means that release of the pheromone is efficient and timely and that the receiver has a sensitive and selective detection system. Because most pheromones are involved in reproductive functions (mate attraction, courtship and copulation), increased efficacy is immediately apparent in higher fecundity. The most widely known semiochemicals in the marine environment are the pheromones of the brown algae which are described in more detail below (section ZH1000). Examples are **Dictyopterene B** and **Caudoxirene**.



Dictyopterene B
(Hormosirene)



Caudoxirene

Pohnert, G. *et al, Nat. Prod. Rep*., 2002, **19**, 108–122 (*algal pheromones*)

1.2 Lipids

Lipids have been defined in different ways at different times and there is still no agreed definition of the term. A simple definition is fatty acids and their derivatives, and substances related biosynthetically or functionally to them.

1.2.1 **Fatty acids** (VA0300, VA0600, VA1100, VA1500, VA1750)

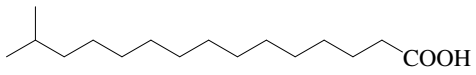
A wide variety of fatty acids are found in marine organisms. These include the common ones found in virtually all organisms, to rare types, typically polyunsaturated, which may be unique to certain phyla or classes of marine animal. No attempt will be made here to give an account of their distribution. Useful searches can be done on the CD-ROM version of this Dictionary by combining one or more codes for fatty acid type as given above (e.g. VA1100, with a code for organism type, e.g. ZE0001, green algae. A more detailed treatment is given in Kornprobst (2005) (various locations), Berge (2005), Rezanka (1989), Dalsgaard (2003) and Ackman (2006). The best general reference for lipids is Gunstone *et al*.

Fatty acids are given in this Dictionary under their systematic chemical names, and their trivial names (e.g. **Palmitic**, **Linoleic**) are given as synonyms and can readily be found in the CD-ROM version. The carbon chain is numbered from the carboxy group (COOH=1). The position of a double bond is sometimes denoted by Δ. Hence a Δ^9 indicates a double bond between the carbons 9 and carbon 10 and a Δ^9-desaturase inserts this unsaturation. An internationally accepted nomenclature uses abbreviations of the form A: B(C). A indicates the number of

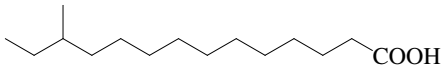
carbon atoms in the molecule, B represents the number of unsaturated centres which are usually *cis*-(*Z*-)-alkenic, and C indicates the position and configuration of the unsaturation counted from the *terminal* methyl of the carbon chain. Symbols such as ω3 or *n*-3 indicate the position of the unsaturated centre closest to the terminal CH_3 group. In this case it is assumed that all unsaturation is methylene-interrupted and has *cis*-(*Z*-) configuration.

Trivial	**Systematic**	**Abbreviation**
Palmitic acid	Hexadecanoic acid	16:0
Oleic acid	*cis*-9-Octadecenoic acid	18:1 (9*Z*)
Arachidonic acid	all-*cis*-5,8,11,14-Eicosatetraenoic acid	20:4 (*n*-6)

Acids with a single methyl substituent, most commonly have this at the penultimate position of the chain, and are named **isoacids**. If the methyl substituent is located on the antepenultimate carbon from the end of the chain the acids are named **anteiso** acids.



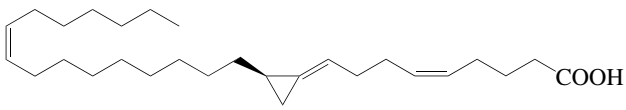
Isopalmitic acid
(14-Methylpentadecanoic acid)



Anteisopentadecanoic acid
(12-Methyltetradecanoic acid, Sarcinic acid)

The number of natural fatty acids known exceeds 1000 though only 20–50 are ubiquitous. From a survey of all these structures it is possible to make a number of generalisations, although there are significant exceptions to each statement. These statements were first based on chemical structure but it is clear that they also reflect underlying biosynthetic pathways.

(i) Natural fatty acids – both saturated and unsaturated – are mostly straight-chain compounds with an even number of carbon atoms. Chain lengths range from two to more than eighty carbon atoms but are most commonly between C_{12} and C_{22}. Odd-carbon acids (e.g. Hentriacontanoic acid) occur and are widespread in marine sources. Acids with branched structures (e.g. **Isopalmitic**, **Anteisononadecanoic**) or with carbocyclic units (e.g. **Amphimic acids**) also occur.



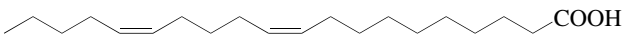
Amphimic acid B

(ii) Acids with one unsaturated centre are usually alkenic compounds with *cis*-(*Z*-) configuration and with the double bond in one of a limited number of preferred positions. This is most commonly Δ^9 (e.g. **Oleic acid**) or *n*-9 (e.g. **Erucic acid**) but the double bond can occur in other positions (e.g. **Petroselinic acid**) and monoacetylenic acids are also known (e.g. **7-Hexadecynoic acid**).

$$H_3C(CH_2)_7C{\equiv}C(CH_2)_5COOH$$

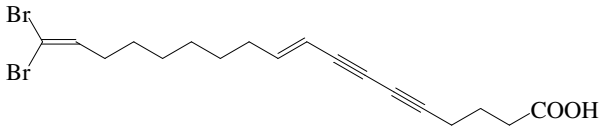
7-Hexadecynoic acid

(iii) Polyunsaturated acids are mainly polyalkenic (*cis*-/*Z*-configuration) with a methylene-interrupted arrangement of double bonds, i.e. double bonds are separated from each other by one CH_2 group. The pattern of 1,4-unsaturation is characteristic of fatty acids and differs from that in isoprenoids which are usually 1,3- or 1,5- conjugated. Polyunsaturated fatty acids occur in biochemically related families and the two most important are the *n*-6 family based on **Linoleic acid** and the *n*-3 family based on **α-Linolenic acid**. Some acids have conjugated unsaturation which is both *cis* and *trans* (e.g. **5,7,9,14,17-Eicosapentaenoic acid**), some have mixed ene/yne unsaturation both conjugated (e.g. **7,9,12-Octadecatrien-5-ynoic acid**) and non-conjugated (e.g. **16,16-Dibromo-15-hexadecen-5-ynoic acid**), and there is a group of acids in which unsaturation is not methylene-interrupted (e.g. **10,15-Eicosadienoic acid**).



10*Z*,15*Z*-Eicosadienoic acid

(iv) Fatty acids having additional functionality apart from the carboxyl group and unsaturation and are widespread. Acids are known with chloro, bromo, hydroxy, methoxy, oxo, and epoxy groups. Examples are **10-Chloro-9-hydroxy-hexadecanoic acid, 2-Methoxy-6-tetradecenoic acid, 18,18-Dibromo-9,17-octodecadiene-5,7-diynoic acid**.



(9*E*)-18,18-Dibromo-9,17-octadecadiene-5,7-diynoic acid

The major biosynthetic pathways leading to fatty acids are summarised in Figure 1. In the *de novo* pathway leading to saturated fatty acids, acetate (the primer) condenses with malonate (the extender) to produce a C_4 oxo acid which is reduced in three steps to butanoate. This cycle of condensation and reduction continues until, most commonly, palmitate has been obtained. The malonate is itself derived from acetate by carboxylation in the presence of a biotin enzyme and the carbon dioxide lost during condensation is that derived during carboxylation so that the carbon atoms in butanoate and in the longer chain acids are entirely acetate-derived. If the acetate is replaced by a different primer then other fatty acids are produced. This can be propanoate (major product: heptadecanoate), 2-methylpropionate (*iso* acids), or 2-methylbutanoate (*anteiso* acids).

The chain-elongation process is similar in outline to the *de novo* process but differs in some significant details. It operates with both saturated and unsaturated acids and occurs with either acetate or malonate. **Erucic acid** is made from Oleic acid by two chain-elongation steps:

$$18:1(9Z) \rightarrow 20:1(11Z) \rightarrow 22:1(13Z)$$

The most common route to monoene acids involves Δ^9 desaturation. This oxygen-requiring process occurs in plants, animals and microorganisms and furnishes acids with a *cis*-double bond between carbon atoms 9 and 10, e.g. **9-hexadecenoic**, **9-octadecenoic acids** (**Oleic acid**).

Further desaturation of **Oleic acid** to the 9,12-diene (**Linoleic acid**) and 9,12,15-triene (**α-Linolenic acid**) occurs only in plants. The additional double bonds assume a methylene interrupted pattern and lie between the existing double bond and the methyl group. Generally only plants are capable of biosynthesising *de novo* *n*-3 and *n*-6 polyunsaturated acids. Animals requiring these acids for the production of *n*-6 and *n*-3 polyene acids must obtain them through their dietary intake. Figure 1 shows the major pathways in marine algae and herbivorous calanoid copepods.

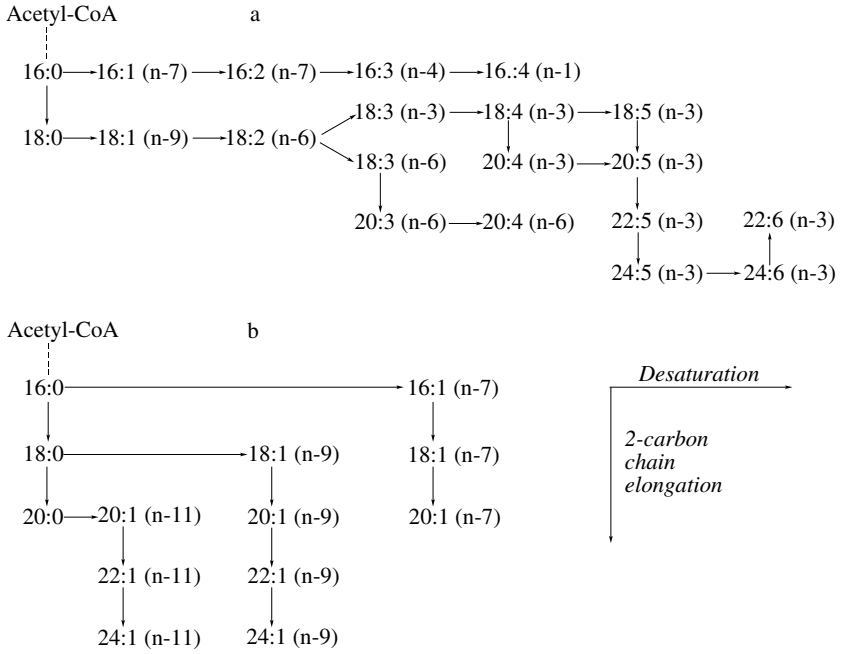


FIGURE 1. Major pathways of fatty acid biosynthesis in (a) marine algae and (b) herbivorous calanoid copepods (Dalsgaard et al)

Desaturation between an existing double bond and the carboxyl group occurs only rarely in plants (e.g. γ-Linolenic acid) but readily in animals. The additional double bonds have *cis*- configuration and are introduced in a methylene-interrupted pattern.

A wide variety of unusual fatty acids and phospholipids are found in sponges, and these arise by totally different biosynthetic pathways (Djerassi (1991). The fatty acids are derived by homologation of short chain fatty acid precursors largely derived from exogenous sources, most likely bacteria and plankton. Fatty acid desaturation in sponges has characteristics of both animal and plant processes. There is no conclusive evidence that sponges are incapable of *de novo* fatty acid biosynthesis, but so far the formation of short-chain acids from radiolabelled acetate had not been observed to any significant extent. Examples are 5*Z*,9*Z*,19*Z*-hexacosatrienoic acid and 6-bromo-5E,9Z-hexacosatrienoic acid.

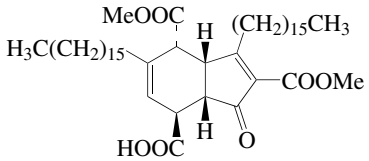
Rezanka, T., *Prog. Lipids Res*., 1989, **28**, 147–1879 (*very long fatty acids*)
Djerassi, C. *et al, Acc. Chem. Res*., 1991, **24**, 69–75 (*sponge fatty acids*)
Jie, M.S.F.L.K. *et al*, *Nat. Prod. Rep*., 1997, **14**, 163–189 (*rev*)
Debitsky, V.M. *et al, Prog. Lipid Research*, 2002, **41**, 315–367 (*halogenated fatty acids*)
Dalsgaard, J. *et al, Adv. Marine Biology*, 2003, **46**, 225–340 (*marine fatty acids, rev*)
Christie, W.W., *Lipid Analysis*, Oily Press, Bridgwater, U.K., 2003 (*analysis*)
Berge, J.-P. *et al*, *Adv. Biochem. Engin. Biotech*., 2005, **96**, 49–125 (*marine fatty acids, rev*)
Kornprobst, J.-M., *Substances Naturelles d'Origine Marine*, Lavoisier, Paris, 2005
Ackman, R.G., *Handbook of Functional Lipids*, (ed. Akoh, C.C.), CRC/Taylor & Francis, Boca Raton, 2006, 311–324 (*marine lipids, nutrition*)
Gunstone, F.D. *et al*, *The Lipid Handbook with CD-ROM*, 3rd edn, Chapman & Hall/CRC Press, Boca Raton, 2007

1.2.2 **Oxylipins** (VA6150)

Three C_{20} acids, 20:3 (*n*-6), 20:4 (*n*-6), and 20:5 (*n*-3) are precursors of prostaglandins and of many other C_{20} metabolites. These are known collectively as eicosanoids and are products of the eicosanoid cascade.

The term oxylipin has been coined relatively recently to describe the class of natural product, of which prostaglandins are the most widespread. They are produced from C_{20} and in some cases C_{18} fatty acid precursors in at least one stage of mono- or dioxygenase-dependent oxidation. Since it is now known that C_{20} precursors are not universal, the term oxylipin is to be preferred to the previous term eicosanoid.

A wide variety of structural types is found in marine organisms where ring formation may produce three, (e.g. **Constanolactones**), five (e.g. **Ecklonialactone A**) or six- (e.g. **Manzamenone A**) membered rings.

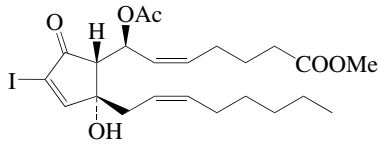


Manzamenone A

Gerwick, W.H., *Chem. Rev*., 1993, **93**, 1807–1823 (*marine oxylipins*)
Gerwick, W.H., *Adv. Exp. Med. Biol*., 1999, **447**, 211 (*biosynth*)
Pohnert, G. *et al, Nat. Prod. Rep*., 2002, **19**, 108–122 (*brown algal oxylipins*)

1.2.3 **Prostaglandins** (VA6100)

The eicosanoid or arachidonic acid cascade produces prostaglandins. **Prostaglandins $F_{2\alpha}$** and **E_2** are encountered in marine algae and invertebrates. In corals, it has been demonstrated that these arise via the cyclooxygenase from the arachidonic acid pathway involved in arachidonic acid metabolism. Other compounds in this group are the **Clavulones** and the **Punaglandins**. An example is **Iodopunaglandin 8**.



Iodopunaglandin 8

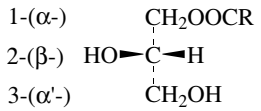
Bentley, P.H., *Chem. Soc. Rev*., 1973, **2**, 29–48 (*synth*)
Lai, S.M.F. *et al*, *Nat. Prod. Rep*., 1984, **1**, 409–441(*rev*)
Newton, R.F. *et al*, *Synthesis*, 1984, 449–478 (*synth*)
Hart, T.W., *Nat. Prod. Rep*., 1988, **5**, 1–45 (*synth*)
Lands, W.E.M., *Annu. Rev. Nutr*., 1991, **11**, 41–60 (*biosynth*)
Smith, W.L., *Am. J. Physiol*., 1992, **263**, F181 (*biosynth, action*)
Collins, P.W. *et al*, *Chem. Rev*., 1993, **93**, 1533–1564 (*synth*)
Moore, B.S. *et al*, *Nat. Prod. Rep*., 2006, **23**, 615–629 (*biosynth*)

1.2.4 **Glycerides** (VA6700, VA6800, VA6900)

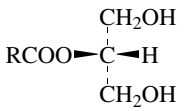
Fatty acids occur naturally as esters of **Glycerol** or of some other hydroxy compound or as amides of long-chain amines such as **Sphingenine**. The less common long-chain alcohols occur as esters or as ethers. Triacylglycerols are major storage lipids whilst phospholipids (see below) are important membrane constituents.

Acylglycerols are esters of glycerol and fatty acids. Partial glycerides are important intermediates in metabolism and triacylglycerols are the major constituents of natural fats and oils. In this Dictionary, glycerides are named as glycerol triesters, e.g. entry name = **Glycerol tri-9-octadecenoate**.

Monoacylglycerols (monoglycerides) (VA6700) are fatty acid monoesters. See the major Dictionary entries for **Glycerol 1-alkanoates** and **Glycerol 2-alkanoates**.



1-Monoacyl-*sn*-glycerol
(chiral)



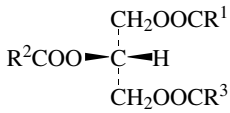
2-Monoacyl-*sn*-glycerol
(achiral)

Diacylglycerols (diglycerides) (VA6800) are fatty acid diesters of glycerol. See the major Dictionary entries for **Glycerol 1,2-dialkanoates** and **Glycerol 2,3-dialkanoates**.

1,2-Diacyl-*sn*-glycerol (α,β-isomer)

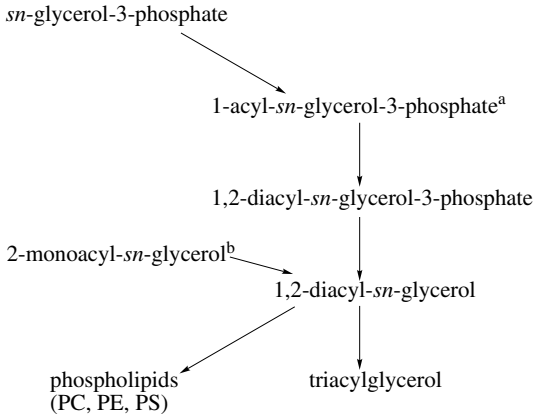
1,3-Diacyl-*sn*-glycerol (α,α'-isomer)

Triacylglycerols (triglycerides) (VA6900) are fatty acid triesters of glycerol. The fatty acids may be all different, two different, or all alike. See the major Dictionary entries for **Glycerol trialkanoates (diacid**, **symmetrical)**, **Glycerol trialkanoates (diacid**, **unsymmetrical)** and **Glycerol trialkanoates (triacid)**. The common monoacid triesters have separate entries.



Triacyl-*sn*-glycerol

Particular fatty acids may be concentrated in or excluded from particular positions in the glycerol ester.



a = also produced from dihydroxyacetone phosphate
b = produced from exogenous (dietary) triacylglycerols by lipolysis

FIGURE 2. Biosynthesis of the major lipid classes

In plants glycerolipids are produced by wholly endogenous pathways but in animals there are additional routes by which dietary lipids are modified. The lipid composition of animals is influenced by dietary intake but is not completely defined by it.

1,2-Diacyl-*sn*-glycerols (Figure 2) are key intermediates in the biosynthesis of both triacylglycerols and phospholipids and are produced mainly from *sn*-glycerol-3-phosphate (a product of carbohydrate metabolism) by acylation of both free hydroxyl groups in separate stages followed by dephosphorylation. Further acylation of the *sn*-3 hydroxyl group gives triacylglycerols.

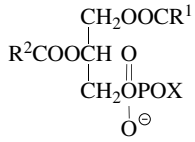
Gunstone, F.D. *et al*, *The Lipid Handbook with CD-ROM*, 3rd edn, Chapman & Hall/CRC Press, Boca Raton, 2007

1.2.5 Phospholipids and sphingolipids (VA7000, VA7200)

Phospholipids and sphingolipids are constituents of cell membranes and they play an essential role in the synthesis of plasma lipoproteins and in the transduction of messages from cell surfaces to second messengers that control cellular processes. **Phosphatidylcholine** (Lecithin) is the most abundant phospholipid (see Figure 3).

Sphingosine (4-Sphingenine) – the most common of the long-chain bases – is produced from Palmitic acid (as its CoA derivative) and Serine as shown in Figure 4. Such compounds are then acylated at the NH_2 group to give

ceramides and further modified at the primary hydroxyl group to give sphingolipids (Figure 5). In this Dictionary, most ceramides are reported as acyl derivatives of the various amino bases. A variety of unusual odd-carbon and branched-chain amines have been reported from marine organisms.



X	Name of class	Abbreviation
H	phosphatidic acid	PA
$CH_2CH_2N^{\oplus}H_3$	phosphatidylethanolamine	PE
$CH_2CH_2N^{\oplus}Me_3$	phosphatidylcholine	PC
$CH_2CH(N^{\oplus}H_3)COOH$	phosphatidylserine	PS
$CH_2CH(OH)CH_2OH$	phosphatidylglycerol	PG
$C_6H_{11}O_6$	phosphatidylinositol	PI

FIGURE 3. Structures of the major phospholipids

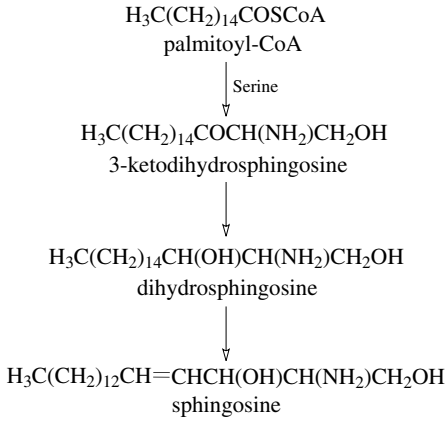


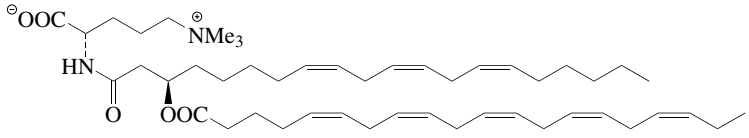
FIGURE 4. Biosynthesis of Sphingosine

sphingosine	($R^1 = R^2 = H$)
ceramides	($R^1 = COR$, $R^2 = H$)
cerebrosides	($R^1 = COR$, R^2 = sugar residue)
sphingomyelin	($R^1 = COR$, $R^2 = PO_3^{\ominus}CH_2CH_2N^{\oplus}Me_3$)

FIGURE 5. Structures of sphingolipids

Alternatively the free hydroxyl group is converted to an appropriate phosphate ester to produce a phospholipid. Dietary triacylglycerols can be hydrolysed to 2-monoacyl-*sn*-glycerols and then reacylated to diacylglycerols and triacylglycerols.

Typical compounds in these classes are the **Acanthacerebrosides**, **Plakosides**, **Stellettacholine A** and **Yendolipin**.



Yendolipin

Djerassi, C. *et al, Acc. Chem. Res*., 1991, **24**, 69–75 (*sponge phospholipids*)
Gunstone, F.D., *Fatty Acid and Lipid Chemistry*, Blackie, London, 1996
Carballeira, N.M. *et al, Recent Res. Dev. Lipids Res*., 1997, **1**, 9–17 (*brominated phospholipids*)
Fattorusso, E. *et al, Progress in the Chemistry of Organic Natural Products*, (eds. Hertz, W. *et al*), SpringerWien, New York, 1997, **72**, 215–301 (*rev, glycolipids*)
Jie, M.S.F.L.K. *et al*, *Nat. Prod*. Rep., 1997, **14**, 163–189 (*rev*)
Carbohydr. Res., 1998, **312**, 167–175 (*glycolipid nomenclature*)
Tan, R.X. *et al*, *Nat. Prod. Rep*., 2003, **20**, 509–534 (*cerebrosides*)
Gunstone, F.D. *et al*, *The Lipid Handbook with CD-ROM*, 3rd edn, Chapman & Hall/CRC Press, Boca Raton, 2007

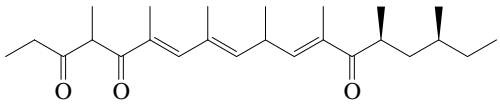
2. POLYKETIDES (VC)

Many organisms have the ability to produce a very wide range of structural types of metabolite which are derived from a poly-β-ketomethylene chain. This chain is formed by condensation of an acetyl unit (or other acyl unit) with malonyl or methylmalonyl units, with concomitant decarboxylation as in fatty acid biosynthesis but without the reduction of the intermediate β-dicarbonyl system. The resulting polyketide chain can take part in internal aldol-type condensations to give aromatic systems characterised by an alternating oxygenation pattern. Alternatively reduction or partial reduction of the carbonyls during biosynthesis can give rise to nonaromatic metabolites. One method of classifying polyketides is by the number of acetate (or propionate) units in a metabolite; however, this has the disadvantage of separating structurally similar types. The vast array of polyketides is treated in DMNP according to a mixture of structural, biosynthetic and functional criteria. The advantage of this approach is that related compounds are listed together. Aromatic polyketides are classified under the appropriate aromatic grouping (see section VG below).

Simpson, T.J., *Nat. Prod. Rep*., 1985, **2**, 321–347; 1987 **4**, 339–376; 1991, **8**, 573–602 (*biosynth*)
Herbert, R.B., *The Biosynthesis of Secondary Metabolites*, 2nd edn, Chapman & Hall, London, 1989
O'Hagan, D., *The Polyketide Metabolites*, Ellis Horwood, New York, 1991
O'Hagan, D., *Nat. Prod. Rep*., 1992, **9**, 447–479; 1995, **12**, 1–32 (*biosynth*)
Hopwood, D.A., *Chem. Rev*., 1997, **97**, 2465–2498 and refs therein (*biosynth*)
Davies-Coleman, M.T. *et al*, *Nat. Prod. Rep*., 1998, **15**, 477–493 (*marine polypropionates*)
Rawlings, B.J., *Nat. Prod. Rep*., 2001, **18**, 231–281 (*bacterial polyketides*)
Staunton, J. *et al*, *Nat. Prod. Rep*., 2001, **18**, 380–416 (*biosynth*)
Moore, B.S. *et al*, *Nat. Prod. Rep*., 2002, **19**, 70–99 (*bacterial starter units*)

2.1.1 Linear polyketides (VC0050)

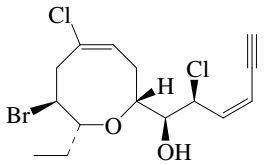
This section contains polyketides that do not contain carbocyclic or macrolide ring systems but may contain tetrahydrofuran or tetrahydropyran rings. An example is **Aglajne 1**.



Aglajne 1

2.1.2 Marine halogenated acetogenins (VC0070)

Marine metabolites include a series of halogenated polyketides particularly from red algae (*Laurencia* spp.). The metabolites contain, along with bromine and chlorine substituents, oxygen heterocycles, acetylenes and allenes. A typical example is **Bermudenynol**.

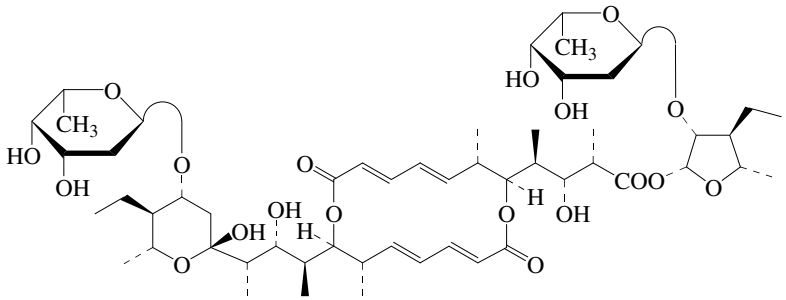


Bermudenynol

Faulkner, D.J., *Nat. Prod. Rep*., 1996, **13**, 75–125 (*rev*)
Butler, A. *et al*, *Nat. Prod. Rep*., 2004, **21**, 180–188 (*biosynth*)

2.1.3 Macrolides and lactone polyketides (VC0100, VC0150)

Structurally, macrolides are a class of complex lactones; normally containing a 12–16 membered macrocyclic ring, often with ether bridges forming further 3-, 4-, 5-, or 6-membered rings, and one to three neutral or aminosugar residues that are linked to the macrocycle via ether linkages. Examples in this class are the **Bryostatins**, **Amphidinolides**, **Macrolactins**, **Oscillatoxins** and **Halichoblelide**.

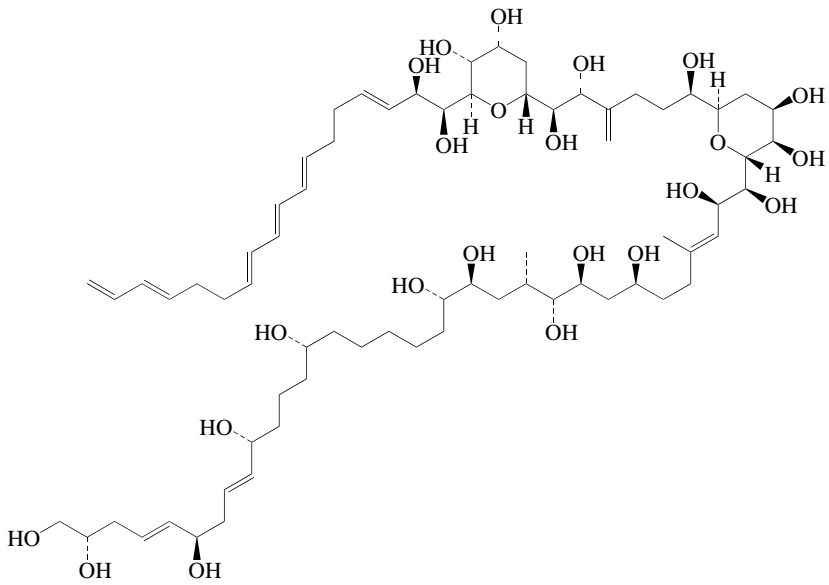


Halichoblelide

Omura, S., *Macrolide Antibiotics, Chemistry, Biology and Practice*, Academic Press, London, 1984 (*general*)
Paterson, I. *et al*, *Tetrahedron*, 1985, **41**, 3569–3624 (*synth*)
Omura, S., *Biotechnology*, (ed. Page, H.), VCH, Weinheim, 1986, **Vol. 4**, 359 (*general*)
Tatsuta, K., *Recent Prog. Chem. Synth. Antibiot*., 1990, 1–38 (*synth, rev*)
Nakata, M. *et al*, *Studies in Natural Product Chemistry*, (ed. Atta-ur-Rahman), Amsterdam, Elsevier, 1993, **Vol. 12**, 35 (*synth*)
O'Hagan, D., *Nat. Prod. Rep*., 1989, **6**, 205–219 (*biosynth*)
Hale, K.J. *et al*, *Nat. Prod. Rep*., 2002, **19**, 413–453 (*Bryostatins*)

2.1.4 Polyenes (VC0300)

The group of compounds, known collectively as polyenes, are compounds containing a series of conjugated double bonds. This leads to the sub-division of the group into trienes, tetraenes etc. The **Amphidinols** are built up with five regular C2-elongation sequences, which are separated by continuous acetate-methyl derived carbons. An example of this group is **Amphidinol 3**.



Amphidinol 3

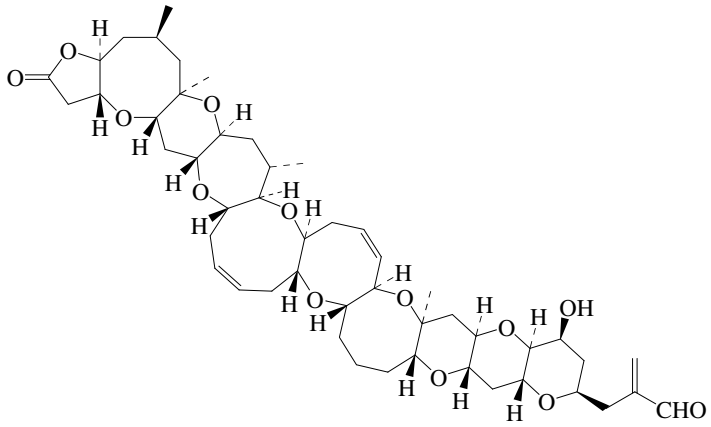
Rinehart, K.L., *Bio/Technology*, 1983, **1**, 581–588 (*ms*)
Omura, S., *Macrolide Antibiotics, Chemistry, Biology and Practice*, Academic Press, London, 1984
Thomas, A.H., *J. Antimicrob. Chemother*., 1986, **17**, 269–279 (*action*)
Rychnovsky, S.D., *Acta Pharm. Nord*., 1990, **2**, 155–160 (*synth, rev*)
Beau, J.M., *Recent Prog. Chem. Synth. Antibiot*., 1990, 135–182 (*synth, rev*)
Houdai, T. *et al*, *Tetrahedron*, 2001, **57**, 5551–5557 (*biosynth*)

2.1.5 Polyether antibiotics (VC0500)

The majority of polyethers are characterised by a linear series of tetrahydrofuran and tetrahydropyran residues, frequently linked by spiroketal systems. They are metabolites of marine microoganisms that are often symbiotic with sponges. Polyethers are generally produced as a series of closely related compounds, e.g. the major component may possess methyl substituents on each of the cyclic ether units, but in addition small amounts of ethyl homologues may also be present. Chemical subdivision can be based on the number of spiroketal functionalities, and the presence or absence of a sugar residue.

Polyethers possess the ability to bind and transport certain ions, and each antibiotic has its own ion specificity. The antibiotics show a wide range of activities, being active against gram-positive organisms and mycobacteria, fungi and yeasts, but because of their toxicity, these properties have found little application. Polyether compounds of this type, however, are now much more than antibiotics, e.g. **Halichondrins** are potent antimitotic agents, analogues of which are being developed through clinical trials.

Biosynthetically, the polyethers are polyketide in origin. The major building blocks are acetate, propanoate, and butyrate. There is evidence to suggest the intermediacy of an epoxide in the formation of the tetrahydrofuran and tetrahydropyran systems. **Brevetoxin** A is a typical polyether compound.



Brevetoxin A

Wieranga, W., *Total Synthesis of Natural Products* (ed. Ap'Simon, J.), Wiley, New York, 1981
Westley, J.W. (ed.), *Polyether Antibiotics*, Marcel Dekker, NY, 1982
Westley, J.W., *J. Nat. Prod*., 1986, **49**, 35–47 (*biosynth*)
Berdy, J., *Biotechnology*, (ed. Page, H.) VCH, Weinheim, Ger., 1986, **Vol 4**, 494
Crandall, L.W. *et al*, *The Bacteria*, (eds. Queener, S.W. *et al*.), Academic Press, Orlando, 1986, **Vol IX**, 385
Siegel, M.M. *et al, Biomed. Environ. Mass Spectrom*., 1987, **14**, 29–38 (*ms*)
Yonemitsu, O. *et al, Recent Prog. Chem. Synth. Antibiot*., 1990, 447–466 (*synth*)
Robinson, J.A., *Progress in the Chemistry of Organic Natural Products*, (eds. Herz, W. *et al*), SpringerWien, New York, 1991, **Vol. 58**, 1–81 (*biosynth*)
Dutton, C.J. *et al*, *Nat. Prod. Rep*., 1995, **12**, 165–181 (*rev*)
Rein, K.S. *et al, Comp. Biochem. Physiol., B: Comp. Biochem. Mol. Biol*., 1999, **124**, 117–131 (*dinoflagellate metabolites, pharmacol, biosynth*)
Fernandez, J.J. *et al, Recent Res. Dev. Org. Chem*., 2000, **4**, 188–189 (*diarrhetic shellfish poisons, biosynth*)
Nicholson, G.M. *et al*, *Mar. Drugs*, 2006, **4**, 82–118 (*Ciguatoxins, activity*)
Satake, M., *Top. Heterocyclic Chem*., (ed. Kiyota, H.), Springer, Berlin, 2006, **Vol. 5**, 21–51 (*rev*)

3. CARBOHYDRATES (VE)

This is an abbreviated account dealing only with aspects of carbohydrate chemistry relevant to marine natural products. Although carbohydrates are important components of the tissues of marine bacteria and algae, and of marine animal tissues (e.g. **chitin**), their marine chemistry presents few aspects that have not already been documented among terrestrial organisms. For a fuller coverage including synthetic carbohydrates, see the companion publication *Dictionary of Carbohydrates*.

Carbohydrates comprise a family of polyhydroxy aldehydes, ketones and acids, together with linear and cyclic polyols. They are diverse because they exist as a wide range of stereoisomers. These compounds are the most abundant and widespread organic substances in nature and are essential constituents of all living matter. Of the 36 possible stereoisomeric pentoses, pentuloses, hexoses and hexuloses only D-glucose, D-fructose, D-galactose, D-mannose and L-arabinose occur naturally in the free state, and only the first two are found in large amounts. However, modified sugar residues belonging to many of the stereoisomeric series are crucial components of, and precursors to, a wide range of important biologically active molecules.

Photosynthesis is the means by which plants produce sugars from carbon dioxide and water. In brief, it occurs by carbon dioxide being transferred to D-*erythro*-pentulose-1,5-diphosphate to give, via an unstable β-keto-6-carbon acid, two molecules of D-glyceric acid-3-phosphate, from which hexoses, for example, D-fructose 1,6-diphosphate and D-glucose 1-phosphate can be formed. Animals, on the other hand, use the reverse of the glycolysis metabolic pathway to produce glucose from proteins and fats utilising phosphoenolpyruvate as an intermediate. Most of the routes used by nature to interconvert sugars occur by way of enzymic reactions on nucleoside diphosphate sugars, particularly **Uridine diphosphate glucose** (UDPG) which gives D-galactose on epimerisation at *C*-4, D-glucuronic acid by oxidation at *C*-6 and D-xylose by decarboxylation of this acid. Deoxygenation at *C*-6 and configuration changes at *C*-4 and *C*-5 give L-rhamnose and by similar means the commonly occurring D-sugars may be transformed into members of the L-series.

3.1.1 Fundamental aldoses and ketoses (VE0100–VE2200)

In the Type of Compound classification the simple sugars are classified into their various stereoisomeric subgroups.

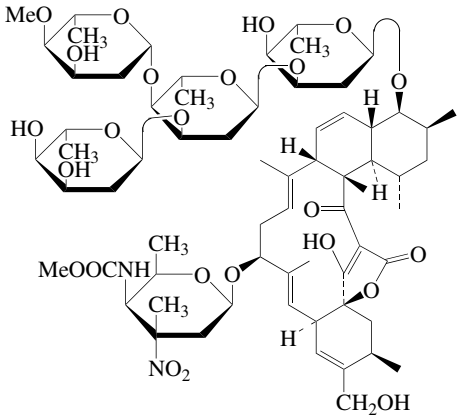
3.1.2 Modified aldoses and ketoses (VE2600–VE8400)

The number of natural sugars increases when modified forms of the 36 fundamental sugars are considered. Thus in addition to the common occurrence of combined forms of the five sugars mentioned above, D-allose, D-talose, D-arabinose, D-ribose, D-xylose, L-lyxose, D-psicose, L-sorbose and D-tagatose are also found as their derivatives in varying quantities. It is rather surprising that the vast number of naturally occurring carbohydrate compounds is derived from so few sugars in this pool. The shortfall is made up by the occurrence of so called modified sugars such as deoxy-, amino-, thio-, branched chain, and higher sugars in addition to various alditols, cyclitols and sugar acids.

Bacteria contain several sugars that are unique to their constitution. **Muramic acid**, glycosidically linked to ***N*-Acetylglucosamine**, is the disaccharide repeating unit that forms the peptidoglycan of gram-negative bacterial cell walls. In gram-positive bacteria, teichoic acids, which are large polymers of the phosphates of D-ribitol or glycerol, form up to 50% of the cell wall.

3.1.3 Branched-chain sugars (VE7200)

Carbon chain branching in sugars can arise biogenetically in two ways; either *C*-bonded hydrogen atoms are replaced to give *C*-substituted derivatives of the normal straight-chain compounds (CHOH → CROH), or else hydroxyl functions are replaced (CHOH →CHR). In the naming of the latter class, the 'deoxy' prefix is included to denote the absence of the hydroxyl substituent at the branching carbon atom, and members can be described as belonging to the 'deoxy' group of branched chain sugars (e.g. 3-*C*-methyl-D-glucose and 3-deoxy-3-*C*-methyl-D-glucose are the respective names of compounds obtained by replacing in glucose either the hydrogen at *C*-3 or the hydroxyl at *C*-3 by methyl). **Kijanimicin** produced by an actinomycete isolated from the alga *Lobophora variegata* contains a 3-*C*-methyl sugar residue.



Kijanimicin

3.1.4 Carbohydrate acids (VE7900, VE8000, VE8100, VE8200)

The following four types of carbohydrate acids occur in nature for which named examples are given for compounds derived from glucose: aldonic acids (VE7900) (**D-Gluconic acid**) which are formed when the aldehydic function in an aldose is oxidised; aldaric acids (VE8100) (**D-Glucaric acid**) which are dicarboxylic acids formed by oxidation of the aldehydic groups and hydroxymethyl groups in aldoses; uronic acids (VE8000) (**D-Glucuronic acid**) and ketoaldonic acids (VE8200) (**D-*arabino*-Hex-2-ulosonic acid**) which are formed by oxidation of the hydroxymethyl groups in aldoses and ketoses respectively.

3.1.5 Alditols (VE8600–VE8900)

The polyols, obtained by reduction of the aldehyde function of an aldose, are known as alditols. An example is **Mannitol**. They are named by a straightforward extension of the rules used for aldoses. The alditol corresponding to a chiral sugar may be *meso*-, e.g. **Galactitol**.

3.1.6 Cyclitols (VE9000)

The polyhydroxycycloalkanes, known as cyclitols, are a group of natural products closely related to the carbohydrates proper, of which the most important are the inositols (1,2,3,4,5,6-cyclohexanehexols). Trivial names are often used but systematic rules have been introduced to assign configurations at each enumerated ring carbon atom and this requires the application of a recommended numbering convention. Further information on the various descriptions of stereochemistry for these compounds can be obtained by the inspection of the individual Dictionary entries. It should be noted that some *meso*-isomers in the series can have optically active derivatives.

Angyal, S.J. *et al*, *Adv. Carbohydr. Chem*., 1959, **14**, 135–212 (*rev*)
Posternak, T., *The Cyclitols*, Holden-Day, San Francisco, 1965
Percival, E., *Oceanography and Marine Biology: An Annual Review*, CRC Press, Boca Raton, FL, 1968, **6**, 137–161 (*marine algal carbohydrates*)
Anderson, L., *The Carbohydrates*, (eds. Pigman, W. and Horton, D.), Academic Press, 1972, **IA**, 519
Pure Appl. Chem., 1974, **37**, 285–297 (*cyclitol nomenclature*)
Reitz, A.B., *Inositol Phosphates and Derivatives*, ACS Symposium Series, Washington, DC, 1991
Trefzer, A. *et al, Nat. Prod. Rep*., 1999, **16**, 283–314 (*deoxy sugars, biosynth*)
Collins, P.M., *Dictionary of Carbohydrates*, 2nd edn, Chapman & Hall/CRC, Boca Raton, 2006

3.1.7 Oligosaccharides and polysaccharides (VE9300, VE9400)

Oligosaccharides are most often found as glycosides in, for example, plants, antibiotics and some glycoproteins. Polysaccharides are the most abundant form of carbohydrates. **Cellulose** is the principal constituent of plant cell walls providing their structural strength. **Starch** and **Glycogen** are found preponderantly in plants and animals respectively where they serve as energy reserves. Whereas glucose is the building unit for the previous three polymers, **Chitin**, which is found in the shells of arthropods, is a polymer of 2-acetamido-2-deoxyglucose. **Carrageenan** and **Agar** are structural polysaccharides of the red algae. These polymers are derivatives of linear galactans.

Glycosidic bonds in naturally occurring oligosaccharides and glycosides are formed in natural glycosylations which take place primarily by way of the nucleoside diphosphate sugars as follows:

$$\text{nucleoside} - \text{DP} - \text{ sugar} + \text{ROH} \rightarrow \text{sugar} - \text{OR} + \text{nucleoside} - \text{DPH}$$

Disaccharides or their phosphates are produced when ROH is a sugar or a sugar phosphate. Polysaccharide biosynthesis is basically similar but requires an oligomer primer as an acceptor; glycogen synthesis follows the course:

$$\text{primer} + \text{UDPG} \rightarrow \text{G}\alpha\text{-primer} + \text{UDP}$$

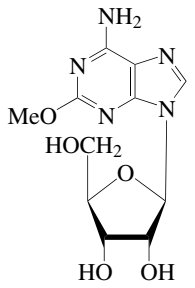
there being one enzyme present which catalyses the formation of 1,4-bonds and another responsible for glycosylations at position 6. The biosynthesis of cellulose and other polysaccharides is basically similar, UDP being the nucleoside diphosphate used predominantly. However, starch synthesis depends rather on adenosine diphosphate.

Guiry, M.D., *Trop. Sci.* 1979, **21**, 183–185 (*red algal polysaccharides*)
Ziener, M. *et al, Carbohydr. Res*., 2000, **328**, 209–216 (*polysaccharides, sponges*)
Duarte, M.E.R. *et al, Carbohydr. Res*., 2001, **333**, 281–293 (*sulfated polysaccharides*)
Aquino, R.S. *et al*, *Glycobiology*, 2005, **15**, 11–20 (*sulfated galactans*)
Nichols, C.A.M. *et al, Mar. Biotech*., 2005, **7**, 253–271 (*marine microbial exopolysaccharides*)

3.1.8 Nucleosides (VE9900)

These are glycosides of purines, pyrimidines and other heterocyclic bases. The well-known quartet of **Adenosine**, **Guanosine**, **Cytidine** and **Thymidine** are fundamental biomolecules essential to life through their participation in the structure of DNA and RNA. A number of 'hypermodified' nucleosides occur in bacterial nucleic acids.

Another group of nucleosides consist of a sugar linked to a base either via a ring nitrogen or through a ring C atom (the latter are designated *C*-nucleosides). Structurally they are rather diverse but a subclassification is given by Isono. A typical example is **Spongosine**.



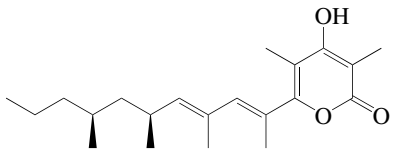
Spongosine

Suhadolnik, R.J., *Nucleosides as Biological Probes*, Wiley, New York, 1979
Suhadolnik, R.J., *Antibiotics* (N.Y.), 1981, **4**, 353–370 (*biosynth*)
Buchanan, J.G., *Progress in the Chemistry of Organic Natural Products*, (eds. Herz, W. *et al*), SpringerWien, New York, 1983, **Vol. 44**, 243–299 (*C-nucleosides*)
Isono, K., *J. Antibiot*., 1988, **41**, 1711–1739 (*biosynth, struct, rev*)
Townsend, L.B., *Chem. of Nucleosides and Nucleotides*, Plenum Press, New York, 1988, **Vol. 1**
Garner, P., *Studies in Natural Products Chemistry*, (ed. Atta-ur-Rahman), Elsevier, Amsterdam, 1988, **Vol. 1**, 397–434 (*synth, rev*)
Secrist, J.A. *et al* (eds.), *Nucleosides Nucleotides*, 1989, **8**, parts 5 and 6 (*rev*)
Brown, E.G., *Methods in Plant Biochemistry*, (ed. Roger, L.J.), Academic Press, New York, 1991, **5**, 53–90 (*rev*)
McCloskey, J.A., *Methods in Enzymology: Mass Spectrometry*, (ed. McCloskey, J.A.), Academic Press, San Diego, 1990, **Vol. 193**, 771–781 (*anal, ms*)
Hobbs, J.B., *The Chemistry of Natural Products*, 2nd edn (ed. Thomson, R.H.), Blackie, Glasgow, 1993, 259

4. OXYGEN HETEROCYCLES (VF)

Many simple natural products contain basic oxygen heterocycles - although most can be seen to be derived from polyketides or carbohydrates, some have unknown biosynthetic origins. The oxygen heterocycles are listed under

the headings: β-Lactones (VF1000), Furans (VF2000), Butanolides (VF3000), Pyrans (VF4000), Pentanolides (VF5000), 2-Pyrones (VF6000) and 4-Pyrones (VF7000). Natural products that contain these substructures in terpenoid, steroid or alkaloid skeletons are not listed here. An example of this group is **Diemenensin A**, which is clearly a polyketide and also coded as such.



Diemenensin A

Turner, W.B. *et al*, *Fungal Metabolites II*, Academic Press, London, 1983
Davies-Coleman, M.T. *et al*, *Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SpringerWien, New York, 1989, **Vol. 55**, 1–98 (*rev*)
Ley, S.V., *Heterocycles in Bioorganic Chemistry*, (eds. J. Bergman *et al*), RSC, London, 1991
Dickinson, J.M., *Nat. Prod. Rep*., 1993, **10**, 71–98 (*microbial 2-pyrones*)
Davies-Coleman, M.T. *et al*, *Nat. Prod. Rep*., 1998, **15**, 477–493 (*2- and 4-pyrones, biosynth*)
McGlacken, G.P. *et al, Nat. Prod. Rep*., 2005, **22**, 369–385 (*2-pyrones*)

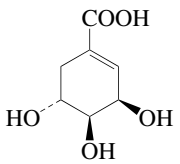
5. SIMPLE AROMATIC NATURAL PRODUCTS (VG)

5.1.1 Simple benzene derivatives (VG0005)

These may be of terpenoid, polyketide or shikimate origin. Those of terpenoid origin, such as the aromatic *p*-menthanes are coded as such and are described below. Fungi are a prolific source of simple benzoquinones which in the main arise by the polyketide route.

Thomson, R.H., *Naturally Occurring Quinones*, 2nd edn, Academic Press, London, 1971
Tyman, J.H.P., *Chem. Soc. Rev*., 1979, **8**, 499–537 (*long chain phenols*)
Turner, W.B. *et al*, *Fungal Metabolites II*, Academic Press, London, 1983
Simpson, T.J., *The Chemistry of Natural Products*, (ed. Thomson, R.H.), Blackie, Glasgow, 1985, 107
Thomson, R.H., *Naturally Occurring Quinones III*, Chapman & Hall, London, 1987
Herbert, R.B., *The Biosynthesis of Secondary Metabolites*, 2nd edn, Chapman & Hall, London, 1989
Simpson, T.J., *Nat. Prod. Rep*., 1991, **8**, 573–602 (*biosynth*)
Gill, M., *The Chemistry of Natural Products*, 2nd edn (ed. Thomson, R.H.), Blackie, Glasgow, 1993, 60

Shikimic acid is derived from glucose in plants *via* the shikimate pathway, which feeds many biosynthetic pathways including those involving the aromatic amino acids **Phenylalanine**, **Tyrosine**, **Tryptophan** and also **p-Aminobenzoic acid**, **Anthranilic acid**, **Cinnamic acid** and other phenylpropanoids. **4-Hydroxybenzoic acid** is the precursor of **2,4,6-Tribromophenol** in the green alga *Ulva lactuca*.

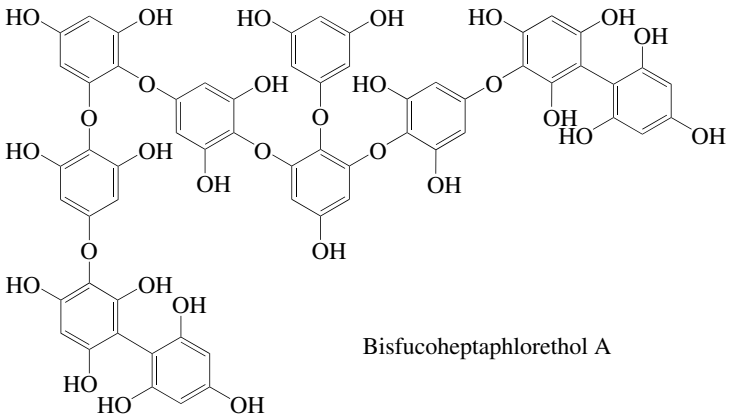


Shikimic acid

Floss, H.G., *Recent Adv. Phytochem*., 1979, **12**, 59–89 (*shikimate pathway*)
Bentley, R., *Crit. Rev. Biochem. Mol. Biol*., 1990, **25**, 307–384 (*shikimate pathway*)
Dewick, P.M., *Nat. Prod. Rep*., 1992, **9**, 153–181 (*biosynth*)
Haslam, E., *Shikimic Acid*, Wiley, Chichester, 1993
Campbell, M.M. *et al*, *Synthesis*, 1993, 179–193 (*shikimate derivs, synth*)
Dewick, P.M., *Nat. Prod. Rep*., 1995, **12**, 101–133; 579–607 (*shikimate metabolites*)
Flodin, C. *et al, Phytochemistry*, 1999, **51**, 249–255 (*tribromophenol biosynth*)
Knaggs, A.R., *Nat. Prod. Rep*., 2001, **18**, 334–355; 2003, **20**, 119–136 (*shikimate metabolites*)

5.1.2 Diphenyl ethers, biphenyls, dibenzyls and phlorotannins (VG1000, VG2000, VG3000, VG2500)

Diphenyl ethers and biphenyls probably arise by radical coupling mechanisms whereas dibenzyl derivatives may be derived from a mixed shikimate-polyketide pathway. Phlorotannins from brown algae are produced by the polymerisation of **Phloroglucinol**. An example is **Bisfucoheptaphlorethol A**.



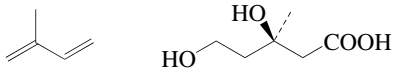
Bisfucoheptaphlorethol A

Turner, W.B. *et al*, *Fungal Metabolites II*, Academic Press, London, 1983
Ragan, M.A. *et al*, *Prog. Phycol. Res*., 1986, **4**, 129–241 (*phlorotannins*)
Gill, M. *et al*, *Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SpringerWien, New York, 1987, **Vol. 51**, 1–286 (*fungal phenolics*)
Bringmann, G. *et al, Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SpringerWien, New York, 2001, **Vol. 82**, 1–249 (*biaryls*)
Singh, I.P. *et al, Nat. Prod. Rep*., 2006, **23**, 558–591 (*phloroglucinols, phlorotannins*)

6. TERPENOIDS (VS)

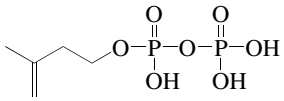
6.1 Classification of terpenoids

The immense variety of structural types found in the terpenoids was rationalised by the isoprene rule of Ruzicka. However, the number of exceptions to the regular arrangement of isoprene units led to the biogenetic isoprene rule which encompassed the possibility of rearrangements during biosynthesis. Terpenoids are thus seen as being formed from linear arrangements of isoprene units followed by various cyclisations and rearrangements of the carbon skeleton. They can also be biosynthetically modified by the loss or addition of carbon atoms. It is useful to classify terpenoids according to the number of isoprene units from which they are biogenetically derived, even though some carbons may have been added or lost. (This sometimes causes some uncertainty if it is believed that more than five carbons have been lost; only a biosynthetic study can resolve this issue). The biogenetic isoprene rule implies the involvement of a branched five-carbon unit in the biosynthesis of terpenoids. The biosynthetic origin of this five-carbon unit is well established; isoprene iself, although a natural product, is not a precursor of the terpenoids. There are two pathways to the common precursors, isopentenyl diphosphate and dimethylallyl diphosphate. One pathway involves mevalonic acid whereas the more recently discovered pathway involves 1-deoxyxylulose 5-phosphate and is known as the non-mevalonate pathway. The mevalonate pathway is found in animals, the cytoplasm of higher plants, fungi and some bacteria whereas the deoxyxylulose phosphate pathway is found in chloroplasts, algae, cyanobacteria, eubacteria and apicomplexan parasites.

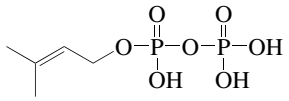


Isoprene

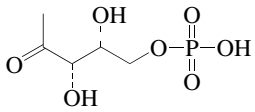
Mevalonic acid



Isopentenyl diphosphate



Dimethylallyl diphosphate



1-Deoxyxylulose 5-phosphate

Ruzicka, L. *et al*, *Experientia*, 1953, **9**, 357–367 (*Isoprene rule*)
Ruzicka, L., *Proc. Chem. Soc.*, 1959, 341–360 (*Isoprene rule)*
Loomis, W.D. *et al*, *Recent Adv. Phytochem.*, 1973, **6**, 147–185 (*biochem*)
Chappell, J., *Ann. Rev. Plant Physiol. Plant Mol. Biol*., 1995, **46**, 521–547 (*biosynth*)
Ramos-Valdivia, A.C. *et al, Nat. Prod. Rep*., 1997, **14**, 591–603 (*Isopentenyl diphosphate isomerase*)
Dewick, P.M., *Nat. Prod. Rep.*, 2002, **19**, 181–222 (*biosynth*)
Hunter, W.N. *et al, Biochem. Soc. Trans*., 2003, **31**, 537–542 (*non-mevalonate pathway*)
Dubey, V.S. *et al*, *J. Biosci*., 2003, **28**, 637–646 (*non-mevalonate pathway*)
Tomohisa, K. *et al*, *Nat. Prod. Rep*., 2003, **20**, 171–183 (*biosynth*)
Eisenreich, W. *et al, Cell. Mol. Life Sci*., 2004, **61**, 1401–1426 (*non-mevalonate pathway*)
Kashman, Y. *et al*, *Phytochem. Rev*., 2004, **3**, 309–323 (*biosynth*)

6.1.1 Nomenclature

The systems used for the nomenclature of terpenoids have evolved over a long period. For many terpenoid classes more than one name has been proposed for the carbon skeleton and in a large number of cases, including many recently discovered marine terpenoid skeletons, several numbering systems are in use. This Dictionary has used the most accepted numbering system for most skeletal types. In cases for which no numbering system has been proposed or where several are in use, preference has been given to the biogenetic system. Many higher terpenoids are named as formal variants of steroid structures and their nomenclature and numbering therefore follows on from that of steroids, which is described more fully in section VT below.

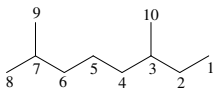
6.2 Monoterpenoids (VS0100–VS1200)

Monoterpenoids are found in many marine organisms, where they are generally halogenated, and as insect pheromones and defence secretions. The biosynthetic pathways of the main classes of monoterpenes have been well studied.

Banthorpe, D.V. *et al*, *Chem. Rev*., 1972, **72**, 115–155 (*monoterpene biosynth*)
Naylor, S. *et al, Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SpringerWien, New York, 1983, **Vol. 44**, 189–241 (*marine monoterpenoids*)
Croteau, R., *Chem. Rev*., 1987, **87**, 929–954 (*monoterpene biosynthesis*)
Grayson, D.H. *et al*, *Nat. Prod. Rep*., 2000, **17**, 385–419 (*monoterpenoids*)

6.2.1 Acyclic monoterpenoids (VS0100)

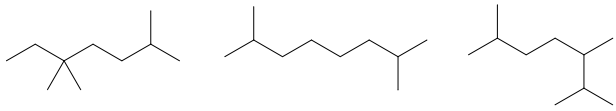
In this section are grouped the regular linear monoterpenoids, that is those formed by a head to tail arrangement of the isoprene units. No semisystematic name has been ascribed to this carbon skeleton because the systematic 2,6-dimethyloctane naming is straightforward. The numbering system shown below is in line with that used with other acyclic terpenoids.



Regular acyclic monoterpenoid skeleton
2,6-Dimethyloctane, 9Cl, 8Cl

6.2.2 Irregular acyclic monoterpenoids (VS0150)

Some acyclic monoterpenoids arise from other arrangements of the isoprene units. These may arise by alternative linkages of the units, e.g. head to head, by rearrangement of regular acyclic monoterpenoids or by cleavage of cyclic monoterpenoids.



Irregular acylic monoterpenoid skeletons

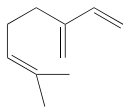
6.2.3 Halogenated dimethyloctane monoterpenoids (VS0200)

This group is obtained principally from marine organisms. They are all regular acyclic monoterpenoids and the numbering system follows the accepted pattern.

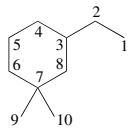
Naylor, S. *et al, Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SpringerWien, New York, 1983, **Vol. 44**, 189–241 (*marine terpenoids*)

6.2.4 Ochtodane monoterpenoids (VS0220)

The ochtodanes are also principally from marine organisms particularly *Ochtodes* spp. and presumably arise by cyclisation of myrcene.



Myrcene

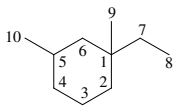


Ochtodane
3-Ethyl-1,1-dimethylcyclohexane, 9Cl

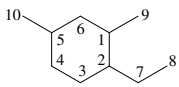
Naylor, S. *et al, Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SpringerWien, New York, 1983, **Vol. 44**, 189–241 (*marine terpenoids*)

6.2.5 1-Ethyl-1,3-dimethylcyclohexane and 1-ethyl-2,4-dimethylcyclohexane monoterpenoids (VS0240, VS0260)

These two terpenoid skeletons are only found in marine organisms and presumably arise by cyclisation of a regular acyclic monoterpene skeleton followed in the latter case by an ethyl migration. The numbering systems reflect their probable biogenetic relationship.



1-Ethyl-1,3-dimethyl-
cyclohexane



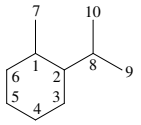
1-Ethyl-2,4-dimethyl-
cyclohexane

Naylor, S. *et al, Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SpringerWien, New York, 1983, **Vol. 44**, 189–241 (*marine terpenoids*)

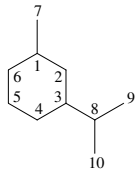
6.2.6 Menthane monoterpenoids (VS0500, VS0520, VS0540)

The menthane group comprises three isomeric types, *o*-, *m*- and *p*-menthanes. The *p*-menthanes are the most widespread and arise by a cyclisation of a regular acyclic monoterpenoid. The *o*- and *m*-menthanes are much rarer, and presumably arise by alkyl migration of *p*-menthanes. The numbering systems of the menthanes reflect

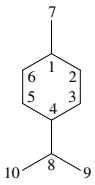
their biogenetic relationship. Since *p*-menthane has a plane of symmetry the numbering of ring substituents is chosen to give the lowest numbers consistent with the avoidance of compound locants for double bonds when possible. For example the name *p*-menth-1-en-6-one is preferred to *p*-menth-1(6)-en-2-one. They are mostly plant products and are thinly scattered in the marine environment.



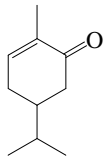
o-Menthane



m-Menthane



p-Menthane, 8Cl
1-Methyl-4-(1-methylethyl)-cyclohexane, 9Cl



p-Menth-1-en-6-one

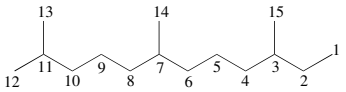
6.3 Sesquiterpenoids (VS1300–VS5320)

The sesquiterpenoids are C_{15} compounds formed by the assembly of three isoprenoid units. There is a large number of sesquiterpenoid carbon skeletons, which all however arise from the common precursor, farnesyl pyrophosphate, by various modes of cyclisations followed, in many cases, by skeletal rearrangement.

Cordell, G.A., *Chem. Rev*., 1976, **76**, 425–460 (*biosynth*)
Dewick, P.M., *Nat. Prod. Rep*., 2002, **19**, 181–222 (*biosynth*)
Fraga, B.M., *Nat. Prod. Rep*., 2004, **21**, 669–693 (*sesquiterpenoids*)

6.3.1 Simple farnesane sesquiterpenoids (VS1300)

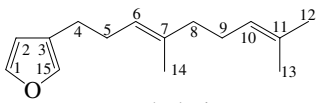
The simple farnesanes are named semi-systematically in this Dictionary although the systematic trimethyldodecane naming is also used extensively in the literature and often leads to numbering from the other end of the chain. The farnesane numbering system is used as a biogenetic numbering system for many sesquiterpenoid skeletons.



Farnesane
2,6,10-Trimethyldodecane, 9Cl

6.3.2 Furanoid farnesane sesquiterpenoids (VS1320)

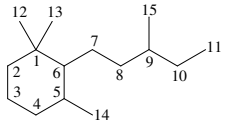
Although many numbering systems have been used for furanoid farnesanes, such as **Dendrolasin**, it is logical to use the farnesane numbering system for this group.



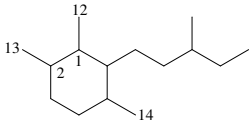
Dendrolasin

6.3.3 Cyclofarnesane and rearranged cyclofarnesane sesquiterpenoids (VS1450, VS1460, VS1470)

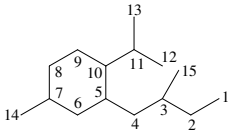
Cyclofarnesanes arise by formation of a six-membered ring between carbons 6 and 11 of farnesane, e.g. Aplysistatin. Methyl group migration gives the rearranged cyclofarnesane skeleton. The herbertianes, included in this group, (not to be confused with herbertanes) are 5,10-cyclofarnesanes.



Cyclofarnesane
1,1,3-Trimethyl-2-(3-methyl-pentyl)cyclohexane



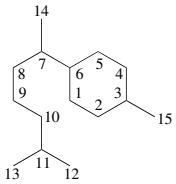
Rearranged cyclofarnesane skeleton
1,2,4-Trimethyl-3-(3-methyl-pentyl)cyclohexane



Herbertiane
4-Methyl-2-(2-methylbutyl)-1-(1-methylethyl)cyclohexane

6.3.4 Bisabolane sesquiterpenoids (VS1500)

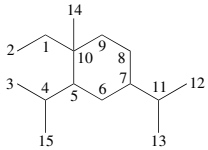
The bisabolanes are a fairly large group mainly found as constituents of higher plants, with some marine occurrences. The numbering system used for bisabolanes is the same as the farnesane system. Since the cyclohexane ring has a plane of symmetry, substituents in this ring should be numbered where possible avoiding the compound locant, 1(6), for a double bond and keeping the numbers for the substituents in the cyclohexane ring as low as possible.



Bisabolane
1-(1,5-Dimethylhexyl)-4-methylcyclohexane, 9Cl

6.3.5 Elemane sesquiterpenoids (VS1600)

Elemanes are numbered consistently with eudesmanes (see below) and germacranes. They are rapidly formed *in vitro* by Cope rearrangement of the corresponding 1(10),4-germacradienes and it is possible that they are artifacts produced during the isolation procedures.

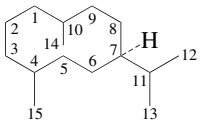


Elemane
1-Ethyl-1-methyl-2,4-bis-(1-methylethyl)cyclohexane, 9CI

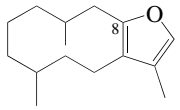
6.3.6 Germacranes (VS1650–VS1700)

These are extremely common as higher plant products but are scarce among marine algae. The numbering of the germacrane skeleton poses a problem since there is a plane of symmetry through carbons 2 and 7. Germacranes are normally drawn in a conventional way as shown below with *H*-7 in the α-configuration. Care should be taken with the small number of germacranes with a double bond at *C*-7 as the ring can be numbered in either direction. Germacranes frequently have double bonds in the 1(10) and 4 positions. A further problem with the representation of germacranes arises from substituents at carbons drawn as reentrant angles. Wherever possible germacranes should be drawn without substituents at reentrant centres as in this Dictionary, and care should be exercised when reading the literature.

The germacrane group is divided into simple germacranes, which is those without a lactone or furan ring (VS1650), 12,6-germacranolides (VS1660), 12,8-germacranolides and furanogermacranes (VS1670), nor- and homo-germacranes (VS1680), secogermacranes (VS1690) and cyclogermacranes (VS1700).



Germacrane
1,7-Dimethyl-4-(1-methyl-ethyl)cyclodecane, 9Cl

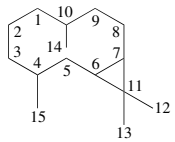


Furanogermacrane
4,5,6,7,8,9,10,11-Octahydro-3,6,10-trimethylcyclodeca[*b*]-furan, 9Cl

Fischer, N.H. *et al, Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SpringerWien, New York, 1979, **Vol. 38**, 47–390 (*sesquiterpene lactones*)
Fischer, N.H., *Recent Adv. Phytochem*., 1990, **24**, 161–201 (*biogenesis*)
Tashkhodzhaev, B. *et al*, *Chem. Nat. Compd*., 1997, **33**, 382–388 (*germacranes*)

6.3.7 Lepidozanes and bicyclogermacrane sesquiterpenoids (VS1710)

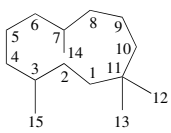
Bicyclogermacranes, found largely in higher plants, have a *cis*-fused cyclopropane ring junction whereas the stereoisomeric lepidozanes from liverworts and marine organisms have a *trans*-fused ring junction.



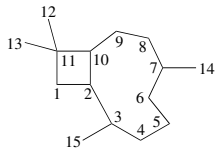
Bicyclogermacrane
3,7,11,11-Tetramethylbicyclo[8.1.0]undecane, 9Cl

6.3.8 Caryophyllane sesquiterpenoids (VS1730)

Cyclisation of the humulane skeleton between carbons 2 and 10 produces the caryophyllane skeleton. Several numbering systems are in use for caryophyllanes; the one chosen for this Dictionary is that based on farnesane.



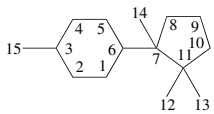
Humulane
1,1,4,8-Tetramethylcycloundecane, 9Cl



Caryophyllane
2,6,10,10-Tetramethylbicyclo[7.2.0]undecane, 9Cl

6.3.9 Cuparane sesquiterpenoids (VS1750)

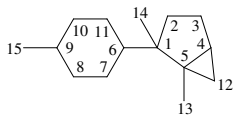
Cuparane is formed by cyclisation between carbons 6 and 11 of the bisabolane skeleton and the numbering system used here takes account of this fact. Cuparanes are found in liverworts, higher plants and marine organisms.



Cuparane
(Most have an aromatic ring and are named in CA as substituted benzenes)

6.3.10 Cyclolaurane sesquiterpenoids (VS1760)

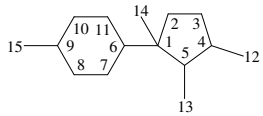
Cyclolauranes found in marine organisms may be considered as cyclocuparanes but as they co-occur with lauranes, the numbering system has been chosen to agree with the accepted laurane system.



Cyclolaurane
1,2-Dimethyl-2-(4-methylcyclohexyl)bicyclo[3.1.0]hexane, 9Cl

6.3.11 Laurane sesquiterpenoids (VS1850)

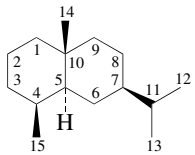
Lauranes are found in marine organisms, particularly *Laurencia* spp.



Laurane
(Mostly named as substituted benzenes in 9Cl)

6.3.12 Eudesmane sesquiterpenoids (VS1950–VS2000)

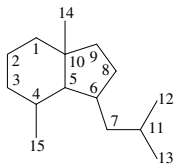
Eudesmanes are called selinanes in the older literature. As with the germacrane group, the eudesmanes are divided into groups comprising simple eudesmanes (VS1950), eudesman-12,6-olides (VS1970), eudesman-12,8-olides and furanoeudesmanes (VS1975), secoeudesmanes (VS1990), and noreudesmanes (VS2000). Within the eudesmane group there is some confusion concerning the numbering of carbons 14 and 15. The numbering given here should be adopted. Like the germacranes, they are common as higher plant products but only a few have been characterised from marine sources.



Eudesmane
Decahydro-1,4*a*-dimethyl-
7-(1-methylethyl)-
naphthalene, 9Cl

6.3.13 Oppositane sesquiterpenoids (VS2020)

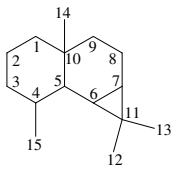
The oppositanes are 8(7 → 6)-abeoeudesmanes and are found in plants and marine organisms.



Oppositane
Octahydro-3*a*,7-dimethyl-1-(2-methylpropyl)-1*H*-indene, 9Cl

6.3.14 Cycloeudesmane sesquiterpenoids (VS2050)

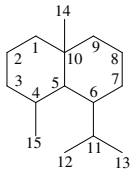
Various cycloeudesmanes are included in this section including the maalianes from marine organisms.



Maaliane
Decahydro-1,1,3*a*,7-tetramethyl-
1*H*-cyclopropa[*a*]naphthalene, 9CI

6.3.15 Gorgonane sesquiterpenoids (VS2060)

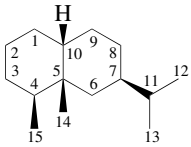
The gorgonanes are derived from eudesmanes by isopropyl group migration to C-6.



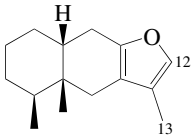
Gorgonane
Decahydro-1,4*a*-dimethyl-8-(1-methylethyl)naphthalene, 9Cl

6.3.16 Eremophilane sesquiterpenoids (VS2100–VS2130)

The eremophilanes have been shown to be derived from eudesmanes by migration of the methyl group at *C*-10 to *C*-5. There is confusion in the literature about the numbering of carbons 14 and 15; the biogenetic numbering given below should be used. The normal stereochemistry is shown, although there are several exceptions to this.



Eremophilane
Decahydro-1,8*a*-dimethyl-
7-(1-methylethyl)-
naphthalene, 9Cl

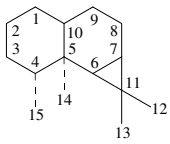


Furanoeremophilane
4,4*a*,5,6,7,8,8*a*,9-Octahydro-
3,4*a*,5-trimethylnaphtho-
[2,3-*b*]furan, 9Cl

Pinder, A.R., *Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SpringerWien, New York, 1977, **Vol. 34**, 81–186 (*eremophilanes*)

6.3.17 Aristolane sesquiterpenoids (VS2150)

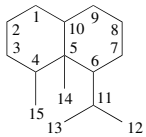
The aristolanes are 6,11-cycloeremophilanes.



Aristolane
Decahydro-1,1,7,7*a*-tetramethyl-1*H*-cyclopropa-
[*a*]naphthalene, 9Cl

6.3.18 Nardosinane sesquiterpenoids (VS2160)

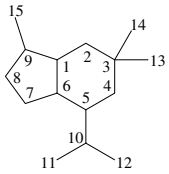
The nardosinanes, isolated from marine organisms, are eremophilanes in which the isopropyl group has migrated to carbon 6.



Nardosinane
Decahydro-1,8*a*-dimethyl-8-(1-methylethyl)naphthalene

6.3.19 Brasilane sesquiterpenoids (VS2170)

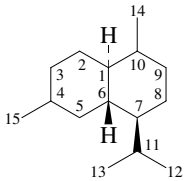
The brasilanes are rearranged sesquiterpenoids largely from *Laurencia* and *Aplysia* species.



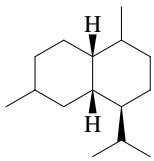
Brasilane
Octahydro-1,6,6-trimethyl-4-(1-methylethyl)-1*H*-indene

6.3.20 Cadinane sesquiterpenoids (VS2250, VS2260)

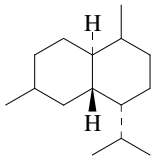
The nomenclature, numbering and absolute stereochemistry of this group is somewhat confused. Biogenetic (germacrane) numbering is used here, but many other numbering systems have been used in the literature. Historically, the names of the skeletons depended on the relative stereochemistries at carbons 1, 6 and 7 as indicated, but in this Dictionary the various stereoisomeric forms are merged into the same entry with these obsolescent names given as synonyms. The aromatised skeletons have also in the past been given different names, calamenene and cadalene, and these have often been given different numbering systems. Nor-and seco-cadinanes are grouped separately (VS2260).



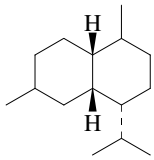
Cadinane
Decahydro-1,6-dimethyl-
4-(1-methylethyl)naphthalene, 9Cl



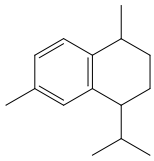
Muurolane



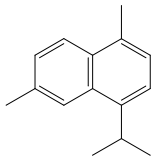
Bulgarane



Amorphane



Calamenene

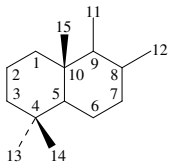


Cadalene

Bordoloi, M. *et al*, *Phytochemistry*, 1989, **28**, 2007–2037 (*cadinanes*)

6.3.21 Drimane sesquiterpenoids (VS2300)

The drimanes, mainly from terrestrial fungi and higher plants but also from marine organisms, arise by direct cyclisation of a farnesane derivative. The accepted numbering system is shown.

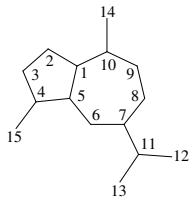


Drimane
Decahydro-1,1,4*a*,5,6-pentamethylnaphthalene

Vlad, P.F. *et al*, *Russ. Chem. Bull*., 1997, **46**, 855–873 (*synth*)

6.3.22 Guaiane sesquiterpenoids (VS2400–VS2440)

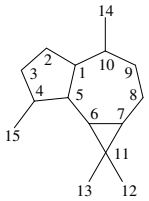
This large group is divided into simple guaianes (VS2400), 12,6-guaianolides (VS2410), 12,8-guaianolides (VS2420), guaiane dimers (VS2430), and seco-, cyclo- and abeo- and norguaianes (VS2440). They are very common in higher plants but are also found in marine organisms.



Guaiane
Decahydro-1,4-dimethyl-7-(1-methylethyl)azulene, 9Cl

6.3.23 Aromadendrane sesquiterpenoids (VS2500)

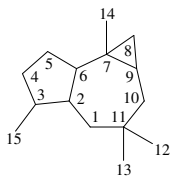
The aromadendranes are 6,11-cycloguaianes.



Aromadendrane
Decahydro-1,1,4,7-tetramethyl-1*H*-cycloprop[*e*]azulene, 9Cl

6.3.24 Africanane sesquiterpenoids (VS2750)

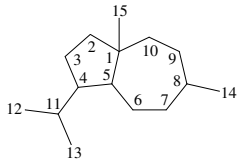
The farnesane numbering system is used for the africanane skeleton although the biosynthesis has not been established conclusively. Some compounds (e.g. **Africanone**) have been named as africananes but have since been shown to have a different skeleton.



Africanane
Decahydro-3,3,5,7*b*-tetramethyl-1*H*-cycloprop[*e*]azulene

6.3.25 Daucane sesquiterpenoids (VS3180)

Many numbering systems have been used for the daucanes; that chosen here is related to the guaiane system. They are mostly from terrestrial organisms but some are from marine sources.

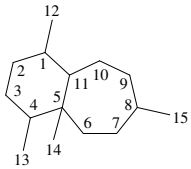


Daucane
Decahydro-3*a*,6-dimethyl-1-(1-methylethyl)azulene

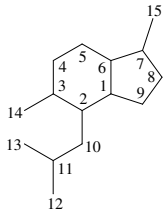
Ghisalberti, E.L., *Phytochemistry*, 1994, **37**, 597–623 (*daucanes*)

6.3.26 Perforane and pacifigorgiane sesquiterpenoids (VS3200, VS3350)

The perforanes form a small group found in *Laurencia* spp. Pacifigorgianes are found in liverworts, higher plants and marine organisms.



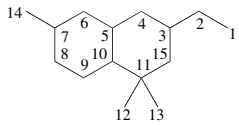
Perforane
Decahydro-1,4,7,9*a*-tetra-methyl-1*H*-benzocyclo-heptane



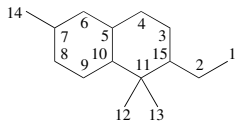
Pacifigorgiane
Octahydro-1,5-dimethyl-4-(2-methylpropyl)-1*H*-indene

6.3.27 Furodysin and furodysinin sesquiterpenoids (VS3550, VS3560)

A farnesane numbering system is used for the furodysin and the rearranged furodysinin groups from *Dysidea* spp.



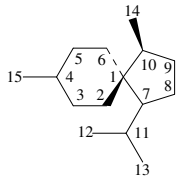
Furodysin skeleton
3-Ethyldecahydro-1,1,6-trimethylnaphthalene



Furodysinin skeleton
2-Ethyldecahydro-1,1,6-trimethylnaphthalene

6.3.28 Acorane sesquiterpenoids (VS3750)

The acoranes and the enantiomeric alaskanes have a symmetrical six-membered ring. It has been suggested that *C*-2 should be chosen to be *syn*- to *C*-14.

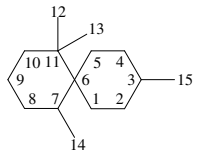


Acorane
1,8-Dimethyl-4-(1-methylethyl)spiro[4.5]decane, 9Cl

Marshall, J.A. *et al*, *Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SpringerWien, New York, 1974, **Vol. 31**, 283–376 (*acoranes*)

6.3.29 Chamigrane sesquiterpenoids (VS3800)

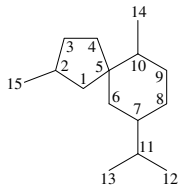
The chamigranes are a group of mainly marine natural products, mostly from *Laurencia* and *Aplysia* spp. The numbering system is based on farnesane. There are also some secochamigranes known (VS3810).



Chamigrane
1,1,5,9-Tetramethylspiro[5.5]undecane, 9Cl

6.3.30 Spiroaxane sesquiterpenoids (VS3820)

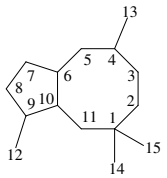
The spiroaxanes are marine natural products that appear to be rearranged cadinane derivatives.



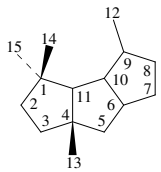
Spiroaxane
2,6-Dimethyl-9-(1-methylethyl)spiro[4.5]decane

6.3.31 Precapnellane and capnellane sesquiterpenoids (VS4200, VS4250)

Precapnellanes and capnellanes are of marine origin. Capnellanes are 4,11-cycloprecapnellanes.



Precapnellane
Decahydro-1,5,8,8-tetramethyl-1*H*-cyclopentacyclooctene



Capnellane
Decahydro-3,3,4,7*a*-tetramethyl-1*H*-cyclopenta[*a*]pentalene, 9Cl

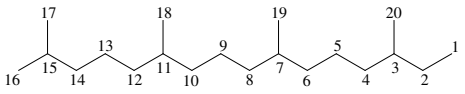
6.4 Diterpenoids (VS5350–VS7340)

The diterpenoids constitute a large group of compounds derived from geranylgeranyl pyrophosphate. They are found in higher plants, fungi, insects and marine organisms.

Hanson, J.R., *Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SpringerWien, New York, 1971, **Vol. 29**, 395–419 (*biosynth*)
West, C.A., *Biosynthesis of Isoprenoid Compounds*, (eds. Porter, J.W. *et al*), Wiley, New York, 1981, **Vol. 1**, 375
Dewick, P.M., *Nat. Prod. Rep*., 2002, **19**, 181–222 (*biosynth*)
Hanson, J.R., *Nat. Prod. Rep*., 2005, **22**, 594–602 (*diterpenoids*)

6.4.1 Phytane diterpenoids (VS5350)

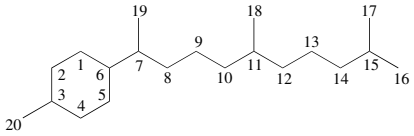
Phytanes are regular acyclic diterpenoids. The phytane numbering system is shown here.



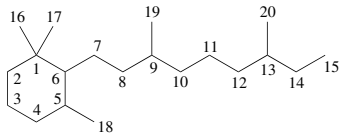
Phytane
2,6,10,14-Tetramethylhexadecane

6.4.2 Prenylbisabolane and 10,15-cyclophytane diterpenoids (VS5380, VS5390)

The prenylbisabolanes arise by cyclisation between carbons 1 and 6 of the phytane skeleton. They retain their phytane numbering system. The 10,15-cyclophytanes are important compounds including the retinal group. Since 10,15-cyclophytanes resemble carotenoids, a carotenoid-like numbering system has usually been adopted. It is possible to view 10,15-cyclophytanes as 9,10-secolabdanes and some are named and numbered as such in the literature.



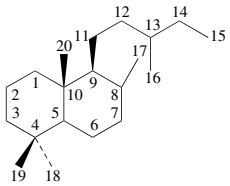
Prenylbisabolane
1-Methyl-4-(1,5,9-trimethyldecyl)cyclohexane



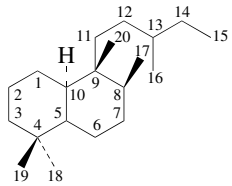
10,15-Cyclophytane
1,1,3-Trimethyl-2-(3,7-dimethylnonyl)cyclohexane

6.4.3 Labdane and halimane diterpenoids (VS5400–VS5470)

Labdanes form a large group and occur in both enantiomeric series. The halimanes are derived from labdanes by migration of the *C*-20 methyl group to *C*-9. Nor-, seco- and rearranged labdanes are given separate codes.



Labdane
Decahydro-1,1,4*a*,6-tetra-methyl-5-(3-methyl-pentyl)naphthalene, 9Cl

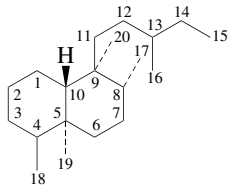


Halimane
Decahydro-1,1,5,6-tetra-methyl-5-(3-methyl-pentyl)naphthalene

Singh, M. *et al*, *Planta Med*., 1999, **65**, 2–8 (*activity*)

6.4.4 Clerodane diterpenoids (VS5500–VS5530)

Clerodanes arise from labdanes by two methyl migrations. They are abundant in terrestrial plants, particularly in *Teucrium* spp., but are also found in marine species. In the past *ent*-clerodanes have been named as neoclerodanes and kolavanes but these names are not widely used. There is some confusion in the literature concerning the numbering of *C*-18 and *C*-19 in clerodanes.

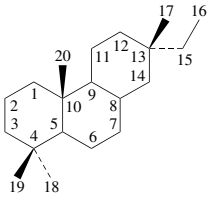


ent-Clerodane
Decahydro-1,2,4*a*,5-tetramethyl-1-(3-methylpentyl)naphthalene, 9Cl

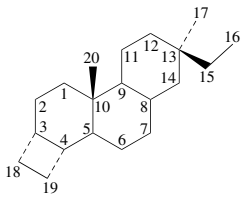
Merritt, A.T. *et al*, *Nat. Prod. Rep*., 1992, **9**, 243–287 (*clerodanes*)
Tokoroyama, T., *Synthesis*, 2000, 611–633 (*synth*)

6.4.5 Parguerane, isoparguerane and isopimarane diterpenoids (VS5730–VS5750)

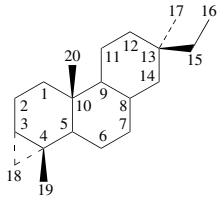
The isopimaranes (VS5750) (formerly called sandaracopimaranes) arise by further cyclisation of the labdane skeleton. The isopimaranes are largely of terrestrial origin but do occur in some marine species. Pargueranes (VS5730) and Isopargueranes (VS5735), mainly from *Laurencia* and *Aplysia* species, are derived from the isomeric pimarane skeleton.



Isopimarane
7-Ethyltetradecahydro-1,1,4*a*,7-tetramethylphenanthrene



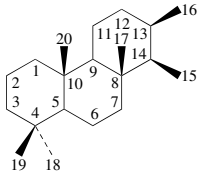
Isoparguerane
6-Ethyltetradecahydro-6,8*b*-dimethylcyclobuta[*a*]-phenanthrene



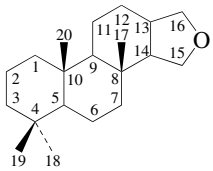
Parguerane
5-Ethyltetradecahydro-1*a*,5,7*b*-trimethyl-1*H*-cyclopropa[*a*]phenanthrene

6.4.6 Isocopalane and spongiane diterpenoids (VS5950)

Isocopalanes and spongianes are of marine origin and both have the same carbon skeleton. A spongiane or spongian is a 15,16-epoxyisocopalane.



Isocopalane
Tetradecahydro-1,1,4*a*,7,8,8*a*-hexamethylphenanthrene

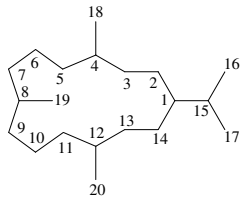


Spongiane skeleton

Keyzers, R.A. *et al*, *Nat. Prod. Rep*., 2006, **23**, 321–334 (*spongianes*)

6.4.7 Cembrane diterpenoids (VS6400–VS6410)

The cembranes form a large group of diterpenoids found in higher plants, insects and marine organisms. The cembrane nucleus has a plane of symmetry and is conventionally drawn with *C*-7 at the top as defined by the *C*-1, *C*-8 axis, *C*-7 being chosen as bearing a double bond or equivalent. The numbering system shown is generally accepted. Many polycyclic diterpenoids can be regarded as formally arising by cyclisation of the cembrane skeleton. Care is necessary in interpreting published configurations at centres involving reentrant angles.

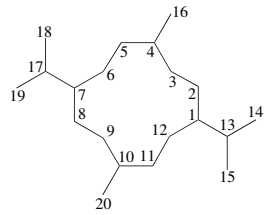


Cembrane
1,7,11-Trimethyl-4-(1-methylethyl)cyclotetradecane, 9Cl

Weinheimer, A.J. *et al*, *Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SpringerWien, New York, 1979, **Vol. 36**, 285–387 (*cembranoids*)
Tius, M.A., *Chem. Rev*., 1988, **88**, 719–732 (*synth*)
Marshall, J.A., *Studies in Natural Products Chemistry*, (ed. Atta-ur-Rahman), Elsevier, Amsterdam, 1992, **Vol. 10**, 3–42 (*synth*)
Wahlberg, I. *et al*, *Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SpringerWien, New York, 1992, **Vol. 59**, 141–294; **Vol. 60**, 1–141 (*cembranoids*)
Bernardelli, P. *et al*, *Heterocycles*, 1998, **49**, 531–556 (*marine cembranoids*)
Sung, P.-J. *et al*, *Heterocycles*, 2002, **57**, 1705–1715 (*gorgonian cembranoids*)

6.4.8 Rearranged cembrane diterpenoids (VS6420) and pseudopterane diterpenoids (VS6425)

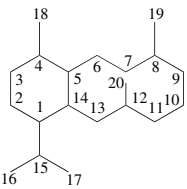
Various rearranged cembranes are found in marine organisms including the pseudopteranes from *Pseudopterogorgia* species.



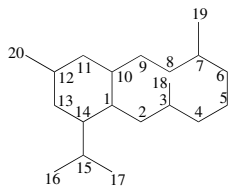
Pseudopterane
1,7-Dimethyl-4,10-bis(1-methylethyl)-
cyclododecane

6.4.9 Eunicellane and asbestinane diterpenoids (VS6440, VS6450)

These are marine natural products. The eunicellane (cladiellane) skeleton is formally a 5,14-cyclocembrane and the cembrane numbering system is preferred. The closely related asbestinane group has been assigned a different numbering system.



Eunicellane
Tetradecahydro-4,7,11-
trimethyl-1-(1-methylethyl)-
benzocyclodecene, 9CI

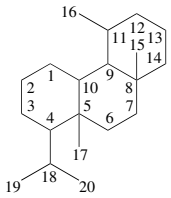


Asbestinane
Tetradecahydro-3,7,11-
trimethyl-1-(1-methylethyl)-
benzocyclodecene

Sung, P.-J. *et al, Heterocycles*, 2002, **57**, 1705–1715 (*eunicellanes, asbestinanes*)

6.4.10 Sphaerane diterpenoids (VS6460)

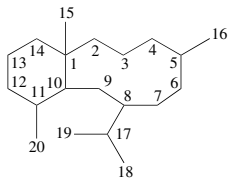
The bromosphaerol group of marine natural products contains an unusual carbon skeleton. The numbering system is as shown. Bicyclic (lacking the 1,10-bond) and tetracyclic (with a 2,17-bond) derivatives are known. (N.B. Sphaeranes are not to be confused with sphaeroanes, see below).



Sphaerane
Tetradecahydro-5,8*a*,10*a*-trimethyl-1-(1-methylethyl)-
phenanthrene

6.4.11 Briarane diterpenoids (VS6470)

The briaranes are a large group of marine diterpenoids with the numbering system as shown. The carbon skeleton is formerly a 3,8-cyclocembrane.

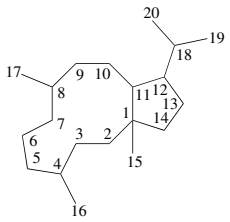


Briarane
Tetradecahydro-1,4*a*,8-trimethyl-
11-(1-methylethyl)benzocyclodecene

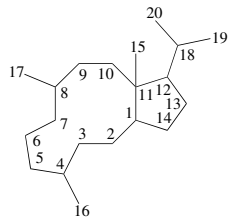
Sung, P.-J. *et al*, *Heterocycles*, 2002, **57**, 535–579; 2005, **65**, 195–204 (*briaranes*)

6.4.12 Dolabellane and modified dolabellane diterpenoids (VS6500, VS6510)

Dolabellanes are found in marine organisms and in liverworts. Several numbering systems have been used in the literature. We have used the one shown. The modified dolabellane group includes the neodolabellanes in which a methyl has migrated from *C*-1 to *C*-11.



Dolabellane
Tetradecahydro-3*a*,6,10-
trimethyl-1-(1-methylethyl)-
cyclopentacycloundecene

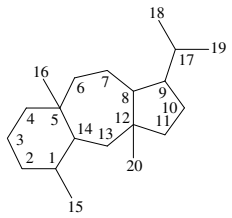


Neodolabellane
Tetradecahydro-6,10,12*a*-
trimethyl-1-(1-methylethyl)-
cyclopentacycloundecene

Rodriguez, A.D. *et al*, *Tetrahedron*, 1998, **54**, 11683–11729 (*dolabellanes*)
Hiersemann, M. *et al*, *Topics in Current Chemistry*, (ed. Mulzer, J.), Springer, Berlin, 2005, **Vol. 243**, 73–136 (*synth*)

6.4.13 Dolastane and modified dolastane diterpenoids (VS6540, VS6550)

The name clavularane was originally used for this group of marine natural products but now dolastane appears to be widely accepted. Dolastane is a 3,8-cyclodolabellane but a different numbering system is used. The modified dolastane group contains 8,9-secodolastanes and a chromophycane, a skeletal type related to dolastane by migration of the methyl *C*-20 to *C*-13.

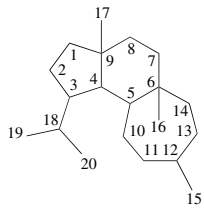


Dolastane
Tetradecahydro-3*a*,5,8*a*-trimethyl-1-(1-methylethyl)-
benz[*f*]azulene, 9Cl

Hiersemann, M. *et al*, *Topics in Current Chemistry*, (ed. Mulzer, J.), Springer, Berlin, 2005, **Vol. 243**, 73–136 (*synth*)

6.4.14 Cyathane diterpenoids (VS6560)

The cyathanes found in marine sponges are also fungal metabolites. The biosynthesis of this unusual skeleton has been studied. The accepted numbering system is as shown.

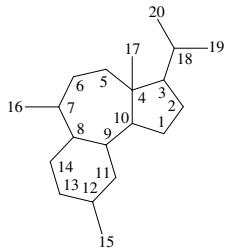


Cyathane
Tetradecahydro-3*a*,5*a*,8-trimethyl-1-(1-methylethyl)-
cyclohept[*e*]indene

Turner, W.B. *et al*, *Fungal Metabolites II*, Academic Press, London, 1983

6.4.15 Sphaeroane diterpenoids (VS6570)

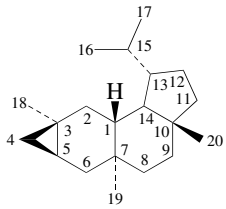
The sphaeroanes are marine algal products with a skeleton which is formally a 2,7-cyclodolabellane though the numbering system is different from that of dolabellanes.



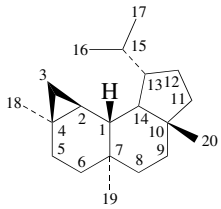
Sphaeroane
Dodecahydro-3*a*,6,9-trimethyl-3-(1-methylethyl)-
benz[*e*]azulene, 9Cl

6.4.16 Verrucosane and modified verrucosane diterpenoids (VS6580, VS6590)

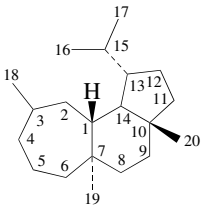
Verrucosanes and their modifications, including neoverrucosanes and 3,5-secoverrucanes, are constituents of marine sponges. The tetracyclic verrucosane skeleton is formally related to dolabellane by 4,10- and 6,8-bond formation. A different numbering system from that of dolabellane is used. The isomeric neoverrucosane has the cyclopropane bridging *C*-2 and *C*-3.



Verrucosane
Tetradecahydro-3*a*,5*a*,7*a*-trimethyl-
1-(1-methylethyl)cyclopenta-
[*a*]cyclopropa[*g*]naphthalene, 9Cl



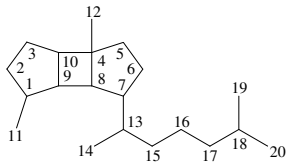
Neoverrucosane
Tetradecahydro-1*a*,3*a*,5*a*-trimethyl-
8-(1-methylethyl)cyclopenta-
[*a*]cyclopropa[*h*]naphthalene



3,5-Secoverrucane
Tetradecahydro-3*a*,5*a*,9-trimethyl-
1-(1-methylethyl)cyclohept[*e*]indene

6.4.17 Spatane diterpenoids (VS6800, VS6810)

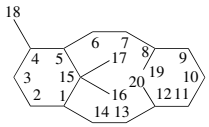
The spatane skeleton is formally derived from a prenylgermacrane by 1,5- and 6,10-cyclisation. The numbering system unfortunately does not reflect this derivation. Spatanes and the related 4,10-secospatanes are marine natural products.



Spatane
Decahydro-3*a*,6-dimethyl-1-(1,5-dimethylhexyl)cyclo-
buta[1,2:3,4]dicyclopentene, 9Cl

6.4.18 Verticillane diterpenoids (VS6880)

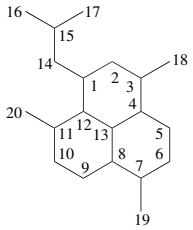
The verticillane group is formally derivable from cembrane by an 11,15-cyclisation. A non-cembrane numbering system is used. The Cespitularins from a soft coral are verticillane derivatives.



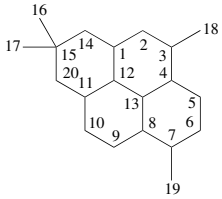
Verticillane
4,8,12,15,15-Pentamethylbicyclo[9.3.1]pentadecane, 9Cl

6.4.19 Amphilectane, cycloamphilectane, adociane and neoamphilectane diterpenoids (VS7020, VS7030, VS7040)

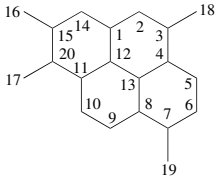
The amphilectanes (including the pseudopterosins), the cycloamphilectanes and adocianes (also called is isocycloamphilectanes) and neoamphilectanes are marine products. They are found with serrulatane derivatives from which amphilectanes are derived by cyclisation. Cycloamphilectanes represent a further cyclisation and adocianes have undergone a methyl migration. Neoamphilectanes are 2(1→12)-abeoamphilectanes. Many marine natural products from these groups contain isocyanate, isothiocyanate and isonitrile functional groups.



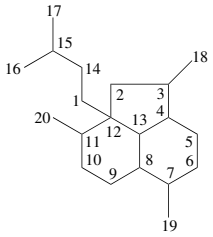
Amphilectane
Dodecahydro-1,4,7-trimethyl-3-(2-methylpropyl)-1*H*-phenalene, 9Cl



Cycloamphilectane
Hexadecahydro-1,4,7,7-tetramethylpyrene



Adociane
Hexadecahydro-1,2,5,8-tetramethylpyrene, 9Cl

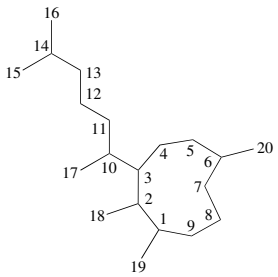


Neoamphilectane
Dodecahydro-1,3,6-trimethyl-2*a*-(3-methylbutyl)-acenaphthylene

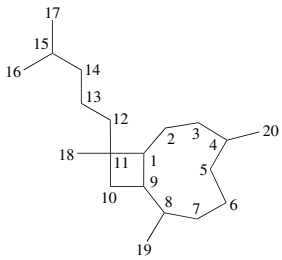
König, G.M., *J. Org. Chem*, 1996, **61**, 3259–3267 (*isocyanates, isothiocyanates, isonitriles*)
Kohl, A.C. *et al, J. Ind. Microbiol. Biotechnol*., 2003, **30**, 495–499 (*biosynth*)
Gross, H. *et al*, *Phytochem. Rev*., 2006, **5**, 115–141 (*rev*)

6.4.20 Xenicane and xeniaphyllane diterpenoids (VS7100, VS7110, VS7150)

Xenicanes and xeniaphyllanes are marine natural products. Xeniaphyllanes are the diterpenoid equivalent of the caryophyllane skeleton. Xenicanes are cleaved xeniaphyllanes.



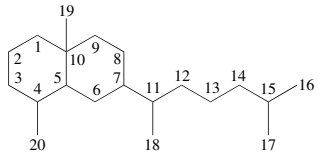
Xenicane
1,2,6-Trimethyl-3-(1,5-dimethylhexyl)-cyclononane



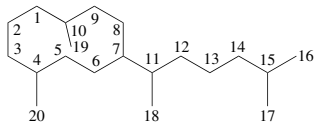
Xeniaphyllane
2,6,10-Trimethyl-10-(4-methylpentyl)-bicyclo[7.2.0]undecane

6.4.21 Prenyleudesmane, prenylgermacrane and prenylbicyclogermacrane diterpenoids (VS7190, VS7200, VS7210)

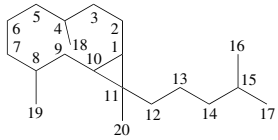
These three groups of 'extended' sesquiterpenoid skeletons are largely of marine origin.



Prenyleudesmane
Decahydro-7-(1,5-dimethylhexyl)-1,4*a*-dimethylnaphthalene



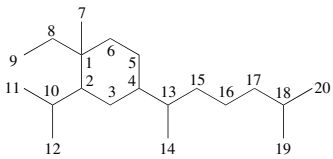
Prenylgermacrane
4-(1,5-Dimethylhexyl)-1,7-dimethylcyclodecane



Prenylbicyclogermacrane
3,7,11-Trimethyl-11-(4-methylpentyl)bicyclo-
[8.1.0]undecane

6.4.22 Lobane diterpenoids (VS7220)

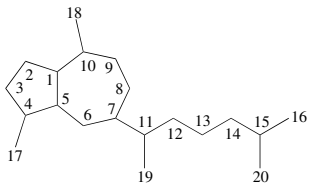
Lobanes are of marine origin and are 'extended' elemanes. A most unusual non-standard numbering system is used in the literature.



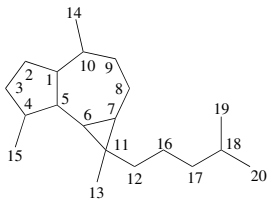
Lobane
4-(1,5-Dimethylhexyl)-1-ethyl-1-methyl-2-
(1-methylethyl)cyclohexane

6.4.23 Pachydictyane and cneorubine diterpenoids (VS7230, VS7240)

These two groups are also 'extended' sesquiterpenoids. The pachydictyanes are prenylguaianes from marine organisms and the cneorubine group are prenylaromadendranes found in marine species as well as leaves of *Cneorum tricoccon*.



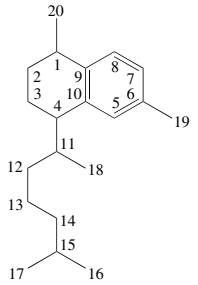
Pachydictyane
Decahydro-7-(1,5-dimethyl-
hexyl)-1,4-dimethyl-
azulene



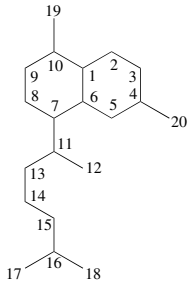
Cneorubine skeleton
Decahydro-1,4,7-trimethyl-1-
(4-methylpentyl)-1*H*-
cycloprop[*e*]azulene

6.4.24 Serrulatane and biflorane diterpenoids (VS7250)

The biflorane skeleton is found in marine organisms, insects and *Eremophila* spp. The skeleton is an 'extended' cadinane. The serrulatane name is given to the aromatic analogue. Unfortunately different numbering systems have been given to serrulatanes and bifloranes.



Serrulatane
4-(1,5-Dimethylhexyl-
1,2,3,4-tetrahydro-1,6-
dimethylnaphthalene

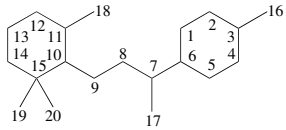


Biflorane
Decahydro-4-(1,5-dimethyl-
hexyl)-1,6-dimethyl-
naphthalene

Hechrodt, T.J. *et al*, *Topics in Current Chemistry*, (ed. Mulzer, J.), Springer, Berlin, 2005, **Vol. 244**, 1–41 (*serrulatanes*)

6.4.25 Obtusane diterpenoids (VS7280)

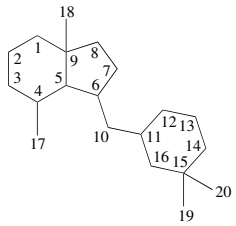
The obtusanes, of marine origin, are bicyclic phytanes. The numbering system is almost the same as for phytane (Note that the terpenoid **Obtusane** itself is a chamigrane).



Obtusane
1,1,3-Trimethyl-2-[3-(4-methylcyclohexyl)butyl]-
cyclohexane

6.4.26 Irieol diterpenoids (VS7290)

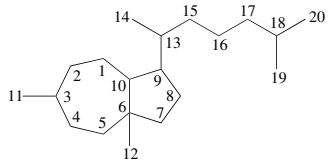
The irieol group, also of marine origin, represents an unusual diterpenoid skeleton.



Irieol skeleton
Octahydro-1-[(3,3-dimethylcyclohexyl)methyl]-
3*a*,7-dimethyl-1*H*-indene

6.4.27 Sphenolobane diterpenoids (VS7300)

The sphenolobane skeleton is an 'extended' daucane skeleton.



Sphenolobane
Decahydro-1-(1,5-dimethylhexyl)-3*a*,6-dimethylazulene

6.4.28 Miscellaneous diterpenoids (VS7310–VS7340)

Diterpenoids that do not easily fit into the other categories are collected here. Mono-, bi-, tri- and tetracyclic diterpenoids are given separate codes.

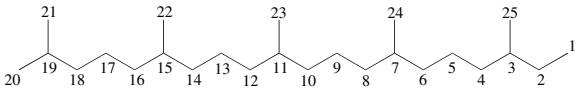
6.5 Sesterterpenoids (VS7400–VS7580)

Sesterterpenoids are a group of natural products that arise from five isoprene units. Although sesterterpenoids strictly have 25 carbons, there are many nor- and alkylated members. Also included here are the C_{21} acyclic terpenoids although their biosynthetic relationship with the sesterterpenoids has not been established with certainty. Sesterterpenoids are found in fungi, higher plants, insects and particularly in marine organisms.

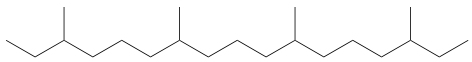
Cordell, G.A., *Progress in Phytochemistry*, (eds. Reinhold, L. *et al*), Pergamon Press, Oxford, 1977, **Vol. 4**, 209–256 (*sesterterpenoids*)
Crews, P. *et al, Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SprigerWien, New York, 1985, **Vol. 48**, 203–269 (*sesterterpenoids*)
Hanson, J.R. *et al*, *Nat. Prod. Rep*., 1996, **13**, 529–535 (*sesterterpenoids*)
Dewick, P.M., *Nat. Prod. Rep*., 2002, **19**, 181–222 (*biosynth*)

6.5.1 Acyclic and noracyclic sesterterpenoids (VS7400, VS7410)

The acyclic sesterterpenoids arise by a head to tail fusion of isoprene units. The accepted numbering system is used here. The noracyclic sesterterpenoids (VS7410) are numbered in a similar way; however, a problem arises with the symmetry of the C_{21} compounds as they may be numbered from either end. The acyclic sesterterpenoids frequently contain furanoid rings.



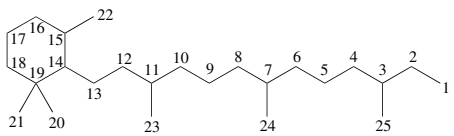
Acyclic sesterterpenoid skeleton
2,6,10,14,18-Pentamethyleicosane



C_{21} sesterterpenoid skeleton
3,7,11,15-Tetramethylheptadecane

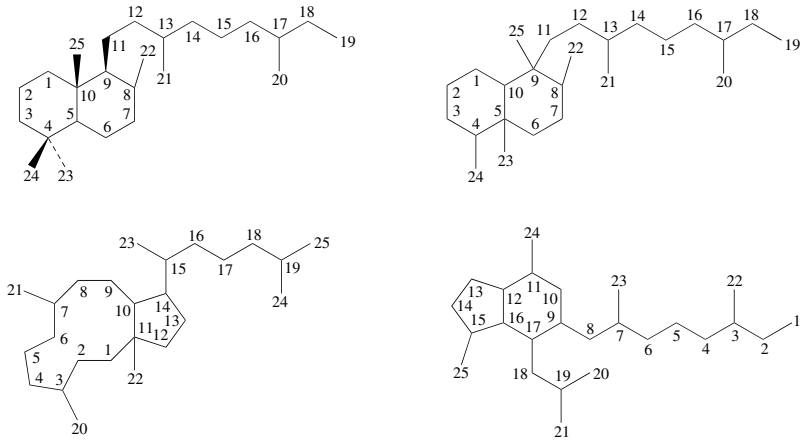
6.5.2 Cyclohexane sesterterpenoids (VS7420)

Most of the cyclohexane sesterterpenoids arise by cyclisation of the acyclic skeleton between carbons 14 and 19.



6.5.3 Bicyclic sesterterpenoids (VS7460)

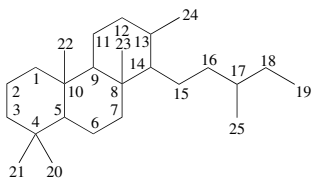
Various bicyclic sesterterpenoids are known. Some are prenylated analogues of diterpene skeletons and the numbering systems are related to the corresponding diterpenoid systems. Others have biogenetic numbering systems.



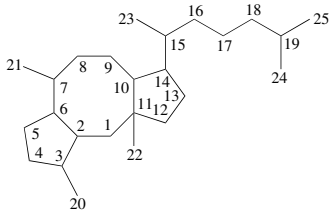
Some bicyclic sesterterpenoid skeletons

6.5.4 Cheilanthane and ophiobolane sesterterpenoids (VS7500, VS7520)

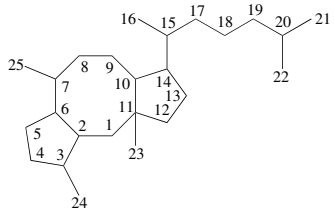
The accepted numbering systems for the cheilanthanes and ophiobolanes are shown here. *Chemical Abstracts* uses ophiobolane as a stereoparent; however it uses a different numbering system for the non-ring carbons.



Cheilanthane
4,4,8-Trimethyl-*D*(15),24-dinor-13,17-secocholane, 9Cl



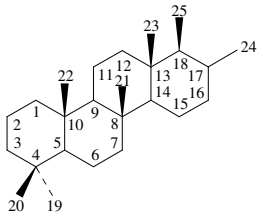
Ophiobolane



Ophiobolane, CA numbering

6.5.5 Scalarane sesterterpenoids (VS7540, VS7550)

The scalarane numbering system is shown here. Carbons 12, 24 and 25 are generally oxygenated in this skeleton. Several methyl and dimethylscalaranes are found in marine organisms. The additional methyl groups attached to *C*-24 and *C*-20 are numbered 26 and 27 respectively.

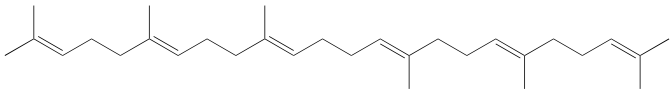


Scalarane
4,4,8,17,17*a*-Pentamethyl-*D*-homoandrostane, 9Cl

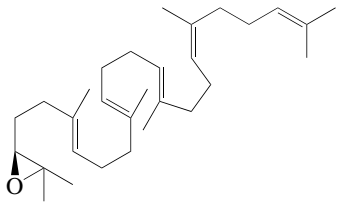
Ungur, N. *et al, Recent Res. Dev. Org. Chem*., 2003, **7**, 241–258 (*synth*)

6.6 Triterpenoids (VS7600–VS9450)

The triterpenoids constitute a large diverse group of natural products derived from squalene or, in the case of 3β-hydroxytriterpenoids, the 3*S*-isomer of squalene 2,3-epoxide. The conformation that *all-trans*-squalene 2,3-epoxide adopts when the initial cyclisation takes place determines the stereochemistry of the ring junctions in the triterpenoid produced. Thus cyclisation of the chair-boat-chair-boat conformation gives the protostane cation and cyclisation of the chair-chair-chair-boat conformation leads to the dammarane cation. The initially formed cation intermediate may undergo a series of 1,2-hydride and methyl migrations, commonly called backbone rearrangements, to give a variety of skeletal types.

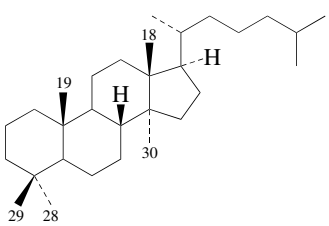


Squalene

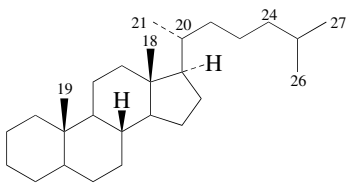


Squalene 2,3-epoxide

Backbone rearrangement of the protostane cation gives the lanostane skeleton; **Lanosterol** is the biogenetic precursor of the steroids in animals. The methyl groups at carbons 4 and 14 are removed during steroid biosynthesis. The steroid numbering system is adopted for lanostane and related tetracyclic triterpenoids. The three methyl groups that were removed during the biosynthesis of steroids are currently numbered 28, 29 and 30 as shown. However, older literature uses the numbers 31, 30 and 32, respectively. This was based on the assignment of carbon numbers 28 and 29 to the stigmastane ethyl group, even though most lanostanes do not have such an ethyl group. The numbering used here follows the currently accepted convention. (See also Steroid section following).



Lanostane numbering



Steroid numbering

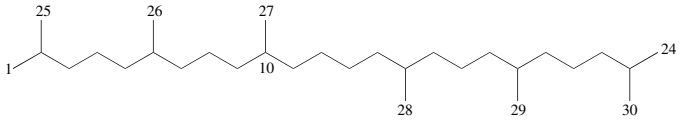
Abe, I. *et al*, *Chem. Rev*., 1993, **93**, 2189–2206 (*biosynth*)
Spencer, T.A., *Acc. Chem. Res*., 1994, **27**, 83–90 (*biosynth*)
Mahato, S.B., *Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SpringerWien, New York, 1998, **Vol. 74**, 1–96 (*saponins*)
Brown, G.D., *Nat. Prod. Rep*., 1998, **15**, 653–696 (*biosynth*)
Connolly, J.D. *et al*, *Nat. Prod. Rep*., 2005, **22**, 487–503 (*triterpenoids*)

The main tetracyclic triterpenoid skeletons have the steroid numbering for the skeleton including the side chain and only the methyl groups will be numbered in the structures that follow. As a general rule the methyls which migrate during terpenoid biosynthesis retain their numbering.

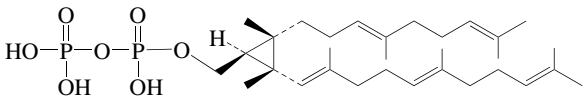
CA names most tetracyclic triterpenoids as derivatives of the steroid stereoparents. This has the disadvantage that some are assigned different names from those commonly used.

6.6.1 Linear triterpenoids (VS7600)

This group contains simple derivatives of squalene. The preferred numbering system is shown and is used for the related polyether derivatives found in marine algae, e.g. *Laurencia* spp. Also included are C_{30} polyprenols, and some homo- and nor-squalenes. Squalene is formed biosynthetically from farnesyl pyrophosphate *via* presqualene pyrophosphate.



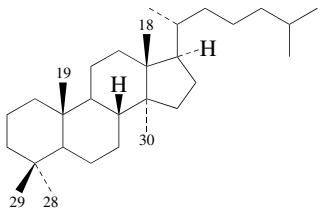
Squalane
2,6,10,15,19,23-Hexamethyltetracosane, 9Cl



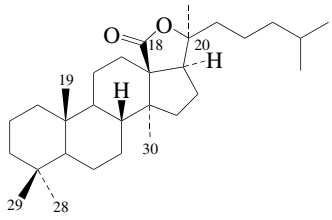
Presqualene pyrophosphate

6.6.2 Lanostane triterpenoids (VS7750)

The lanostanes are very common in higher plants and fungi. **Lanosterol** is a key intermediate in steroid biosynthesis. The metabolites of sea cucumbers or holothurians are characterised by lanostane glycosides with most aglycones possessing the 18,20-lactone of the holostane skeleton. Many of the glycosides of these metabolites are sulfated.



Lanostane

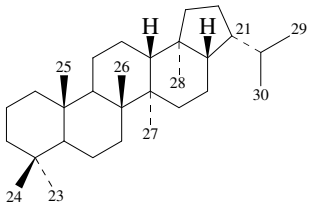


Holostane

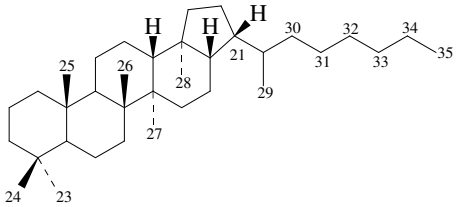
Stonik, V.A. *et al*, *J. Nat. Toxins*, 1999, **8**, 235–248 (*holothuroids*)
Chludil, H.G. *et al, Studies in Natural Products Chemistry*, (ed. Atta-ur-Rahman), Elsevier, Amsterdam, 2003, **Vol. 28**, 587–616 (*holothurian glycosides*)
Kalinin, V.I. *et al, Phytochem. Rev*., 2005, **4**, 221–236 (*holothurian glycosides*)

6.6.3 Hopane triterpenoids (VS8720, VS8730)

Cyclisation of squalene in the chair-chair-chair-chair-chair conformation affords the hopane skeleton. Degraded and extended hopanes, the bacteriohopanoids, occur widely in natural sediments and the latter are important components of archaeal lipid membranes and have been identified in marine sponges.



Hopane
A' -Neogammacerane, 9Cl

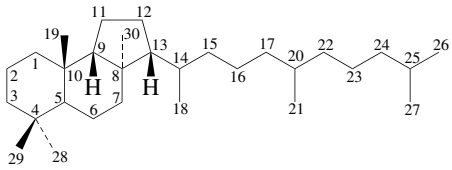


Bacteriohopane

Ourisson, G. *et al*, *Acc. Chem. Res*., 1992, **25**, 398–402 (*geohopanoids*)
Ourisson, G. *et al*, *Acc. Chem. Res*., 1992, **25**, 403–408 (*bacteriohopanoids*)
Kannenberg, E.L. *et al*, *Naturwissenschaften*, 1999, **86**, 168–176 (*biosynth*)
Costantino, V. *et al, Tetrahedron*, 2001, **57**, 4045–4048 (*sponge bacteriohopanoids*)

6.6.4 Isomalabaricane triterpenoids (VS9100)

Partial cyclisation of squalene 2,3-epoxide from one end leads to the isomalabaricane skeleton of marine triterpenoids. The 8,9-diepimeric malabaricane skeleton is found in terrestrial triterpenoids.

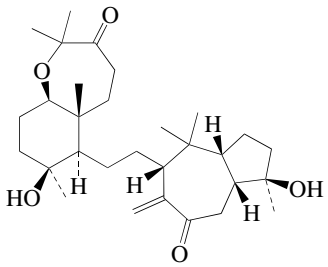


Isomalabaricane
Dodecahydro-3*a*,6,6,9*a*-tetramethyl-
3-(1,5,9-trimethyldecyl)-
1*H*-benz[*e*]indene

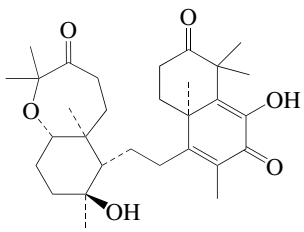
Fouad, M. *et al*, *J. Nat. Prod*., 2006, **69**, 211–218 (*bibl*)

6.6.5 Miscellaneous triterpenoids (VS9300)

This group contains assorted triterpenoid skeletons which are less easily classified. It includes intriguing group of compounds, such as **Sipholenone C**, from the sponge *Siphochalina siphonella* and **Sodwanone A** from *Axinella weltneri*.



Sipholenone C

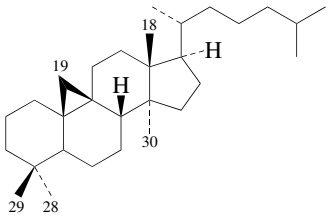


Sodwanone A

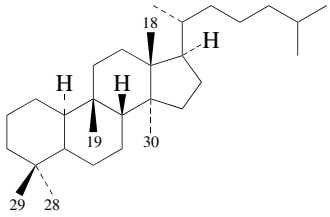
Kashman, Y. *et al Phytochem. Rev*., 2004, **3**, 309–323 (*bibl*)

6.6.6 Other marine triterpenoids

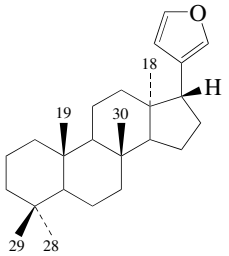
Triterpenoids are characteristic metabolites of terrestrial higher plants and are rare in the marine environment apart from the groups listed above. Many triterpenoids are important biomarkers in marine sediments. The triterpenoid groups are listed below for reference.



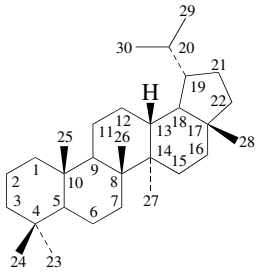
Cycloartane



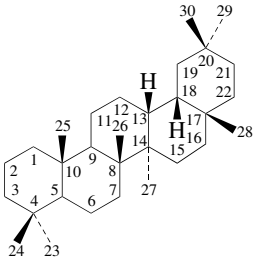
Cucurbitane



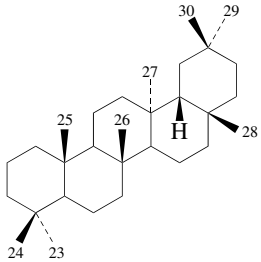
Tetranortriterpenoid skeleton



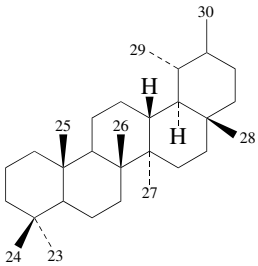
Lupane, 9Cl
(23/24 substituents specified in CA as (4α)23- and (4β)23- respectively)



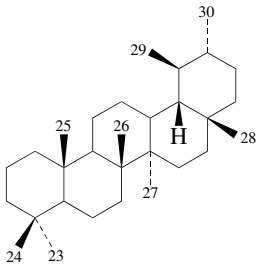
Oleanane, 9Cl
(23/24 substituents specified in CA as (4α)23- and (4β)23- respectively; and 29/30 substituents as (20α)29- and (20β)29- respectively)



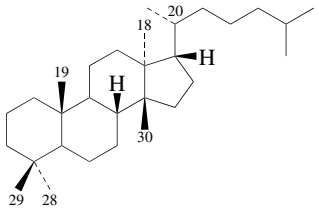
Taraxerane
D -Friedooleanane, 9Cl



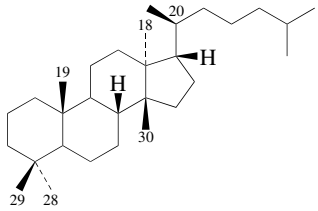
Taraxastane



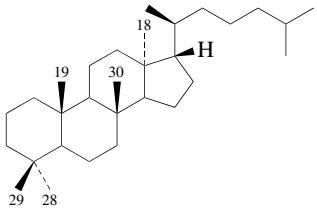
Ursane, 9Cl



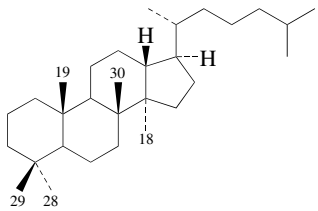
Euphane



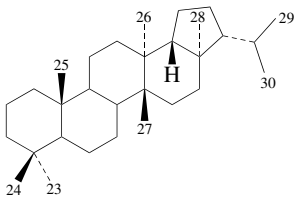
Tirucallane



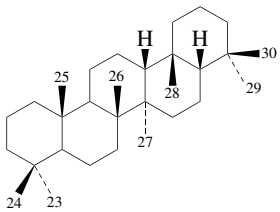
Apotirucallane



Dammarane



Fernane
D : *C* -Friedo-*B*' : *A*'-neogammacerane, 9Cl

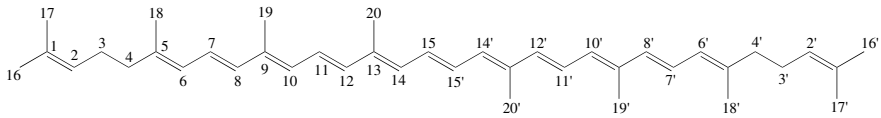


Gammacerane, 9Cl

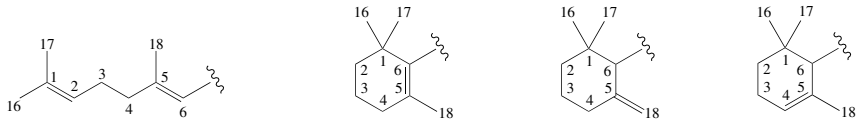
Minale, L. *et al, Advances in Experimental Medicine and Biology*, (eds, Waller, G.R. *et al*) Springer, 1996, **Vol. 404**, 335–356 (*marine triterpenoids*)

6.7 Tetraterpenoids (VS9400)

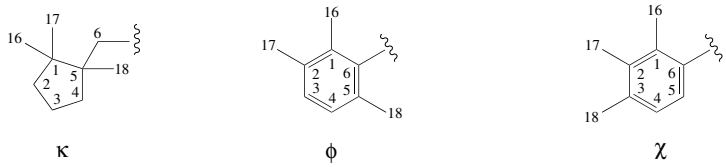
The tetraterpenes arise by head to head coupling of two geranylgeranyl diphosphate molecules.



ψψ-Carotene



ψ β γ ε



κ ϕ χ

Carotenoid end-groups

Spurgeon, S.L. *et al*, *Biosynthesis of Isoprenoid Compounds*, (eds. Porter, J.W. *et al*), Wiley, New York, 1981, **Vol. 2**, 1

6.7.1 Carotenoids

These include the hydrocarbons (carotenes) and their oxygenated derivatives (xanthophylls). Carotenoid nomenclature is based on a stem name, carotene, and two Greek letters as prefixes to define the two end groups. The numbering system and end groups are given below.

IUPAC treats 'hydro' prefixes in carotenoid names as non-detachable. This Dictionary follows IUPAC recommendations for nomenclature except that the 'hydro' prefix is treated as detachable and is placed alphabetically with the other prefixes. CA also uses a detachable 'hydro' prefix but it does not use hypothetical parents such as β-caroten-6-ols which are incapable of existence (see current *Chemical Abstracts Index Guide*). The following examples illustrate this point.

IUPAC name	**Chemical Abstracts name**
5,6-Dihydro-β,β-caroten-3-ol	5,6-Dihydro-β,β-caroten-3-ol
5,6-Dihydro-β,β-caroten-6-ol	5,6-Dihydro-6-hydroxy-β,β-carotene

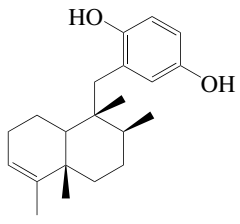
IUPAC, *Pure Appl. Chem*., 1975, **41**, 407–431 (*nomenclature*)
Goodwin, T.W., *Biochemistry of the Carotenoids*, 2nd edn, Chapman & Hall, London, 1980
Matsuno, T., *Pure Appl. Chem*., 1985, **57**, 659–666 (*marine animal carotenoids*)
Britton, G., *Nat. Prod. Rep*., 1991, **8**, 223–249 (*carotenoids*)
Liaaen-Jensen, S., *Pure Appl. Chem*., 1991, **63**, 1–12 (*marine carotenoids*)
Sandmann, G., *Eur. J. Biochem*., 1994, **223**, 7–24 (*biosynth*)
Mercadante, A.Z., *Pure Appl. Chem*., 1999, **71**, 2263–2272 (*carotenoids*)
Miki, W., *Food Style* 21, 2000, **4**, 67–70 (*marine carotenoids in food*)
Matsuno, T., *Fish. Sci*., 2001, **67**, 771–783 (*aquatic animal carotenoids*)
Carotenoids Handbook, (eds. Britton, G. *et al*) Birkhäuser, Basel, 2004

6.7.2 Apocarotenoids (VS9700)

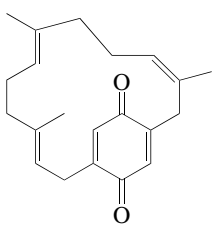
Apocarotenoids are carotenoids in which the carbon skeleton has been shortened by the formal removal of fragments from one or both ends. A locant is used to indicate that all of the molecule beyond the carbon with that locant has been removed. It is not necessary to give a Greek-letter end group designation if the apo-locant is greater than 5.

6.8 Meroterpenoids (VS9900)

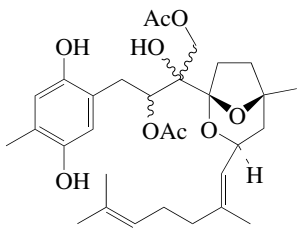
Meroterpenoids are of mixed biogenesis containing terpenoid and non-terpenoid derived fragments. This broad definition could include the vast number of simple prenylated phenolics but is normally reserved for compounds where the terpenoid fragment comprises a large part of the molecule. Many marine meroterpenoids have interesting biological activities such as **Avarol**, with a rearranged drimane terpenoid moiety, from the sponge *Dysidea avara*. The tunicate *Aplidium longithorax* contains a range of meroterpenoids such as **Longithorone B** with a sesquiterpenoid chain in paracyclophane arrangement. Meroditerpenoid and merotriterpenoid representatives include the tetraprenyltoluquinol **Sindurol** from the soft coral *Sinularia dura* and **Toxiusol** from the sponge *Toxiclona toxius*.



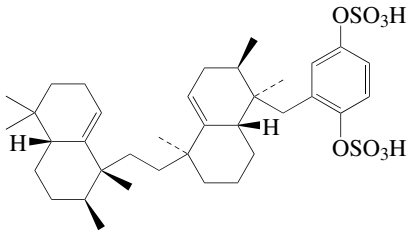
Avarol



Longithorone B



Sindurol



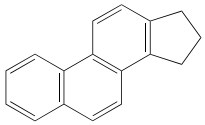
Toxiusol

Koren-Goldshlager, G. *et al*, *J. Nat. Prod*., 1996, **59**, 262–266 (*tetraprenyltoluquinols*)
Braekman, J.-C. *et al*, *Phytochem. Rev*., 2004, **3**, 275–283 (*sponge meroterpenoids*)
Zubia, E. *et al, Mini-Rev. Org. Chem*., 2005, **2**, 389–399 (*Aplidium meroterpenoids*)
Sladic, D. *et al*, *Molecules*, 2006, **11**, 1–33 (*avarol group*)

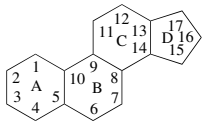
7. STEROIDS (VT)

For general information on the biogenesis of steroids, see the preceding terpenoid section.

The steroid structure is based on four carbocyclic rings arranged as in cyclopenta[*a*]phenanthrene, which is normally fully or partially reduced so that only limited unsaturation, if any, is present. The four steroid rings are labelled, and their carbon atoms are numbered according to the universal convention illustrated.

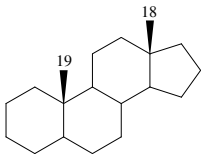


Cyclopenta[*a*]phenanthrene



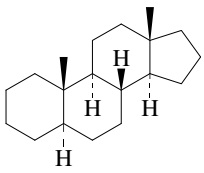
Basic steroid structure

The great majority of steroids also have one or two methyl groups present at the bridgehead positions *C*-10 and *C*-13; the methyl carbon atoms are numbered *C*-19 and *C*-18, respectively.



Methyl groups, hydrogen atoms, or substituents at the bridgehead positions *C*-8, 9, 10, 13, and 14 are assumed to have the 8β, 9α, 10β, 13β, 14α configurations unless otherwise specified. *C*-5 is a special case, as there are many steroids of each of the 5α and 5β configurations, and it is therefore necessary to specify the *C*-5 configuration for any steroid which is saturated at *C*-5 (e.g. 5α-Androstane or 5β-Androstane).

It is worth noting here some changes in *Chemical Abstracts* indexing policy. Prior to the 8th Collective Index (1967), the indexing of steroid stereoisomers gave priority to the *C*-5 configuration which effectively led to a separation of 5α- and 5β-steroids. Users should be alert to this when searching the literature before 1967.

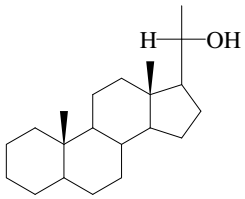


5α-Androstane

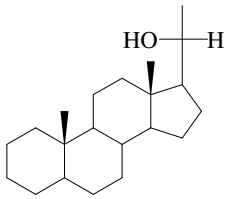
The hydrogen atoms at *C*-8, 9 and 14 are generally omitted from formulae if they have the natural configurations shown here.

Any side-chain at *C*-17 is assumed to have the 17β-configuration unless otherwise indicated. This is shown either by using a wedge bond or, where there is any possibility of uncertainty owing to substitution at *C*-20, by drawing in the *C*-17 α-hydrogen atom.

Configurations of substituents in the side chain were formerly also indicated by α or β, (Fieser convention), whereby the side-chain is drawn in Fischer projection, with the highest numbered locant at the top.



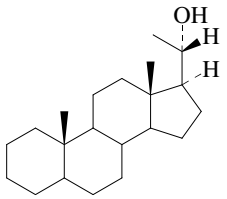
20α-form



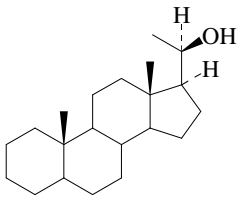
20β-form

The Fieser convention for pregnan-20-ols

The unambiguous Cahn-Ingold-Prelog sequence rule descriptors (*R* or *S*) are now recommended for side-chain configurations.

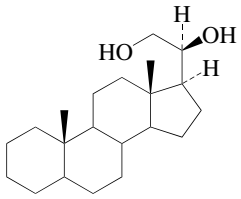


20*S* (= 20α)

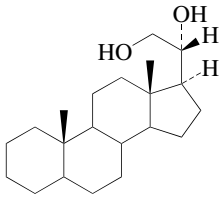


20*R* (= 20β)

The presence of substituents at *C*-17 or *C*-21 may change the priority of groups so that 20*S* is no longer equivalent to 20α. This happens for example in the pregnane-20,21-diols.

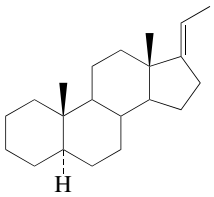


20*S* (= 20β)

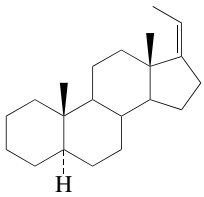


20*R* (= 20α)

The sequence rule descriptors (*E*-) and (*Z*-) are required for defining side-chain double bond configurations. The configuration of additional side-chain methyl or other alkyl groups, which are common in steroids produced by sponges and other marine organisms, are denoted by *R*- and *S*- (or ξ if unknown).



5α-Pregn-17(20)*E*-ene



5α-Pregn-17(20)*Z*-ene

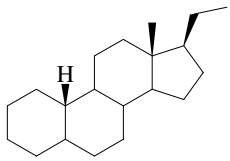
(Note that both locants for unsaturation are required when the numbers are non-consecutive)

Steroids, (eds. Fieser, L.F. *et al*) Reinhold, New York, 1959
Bernstein, S. *et al*, *Physical Properties of Steroid Conjugates*, Springer-Verlag, Berlin, 1968
Atlas of Steroid Structure, (eds. Duax, W.L. *et al*) Plenum, New York, 1975, **Vol. 1**; 1984, **Vol. 2**
Biochemistry of Steroid Hormones, 2nd edn, (ed. Makin, H.L.J.), Blackwell, Oxford, 1984
Danielsson, H. and Sjövall, J., *Sterols and Bile Acids*, Elsevier, Amsterdam, 1985
Zeelen, F.J., *Medicinal Chemistry of Steroids*, Elsevier, Amsterdam, 1990
Dictionary of Steroids, (eds. Hill, R.A. *et al*) Chapman & Hall, London, 1991
Zeelen, F.J., *Nat. Prod. Rep*., 1994, **11**, 607–612 (*total synth*)
Analysis of Sterols, (eds. Goad, L.J. *et al*), Blackie, London, 1997
Brown G.D., *Nat. Prod. Rep*., 1998, **15**, 653–696 (*biosynth*)
Hanson, J.R., *Nat. Prod. Rep*., 2006, **23**, 100–107 (*synth*)

7.1 Steroid classes

7.1.1 C_{20} steroids (VT0400)

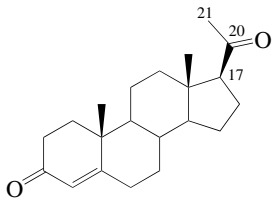
These are scarce among natural products. A few 19-norpregnanes, with the pregnane skeleton (see below) but lacking the bridgehead methyl group (*C*-19) occur in marine organisms. Alternative names based upon 17-ethylestrane are also often used for this series of compounds (see pregnanes).



19-Norpregnane

7.1.2 Pregnane steroids (C_{21}) (VT0450)

Pregnane is the parent hydrocarbon of the pregnancy hormone progesterone (pregn-4-ene-3,20-dione), and of the great majority of the corticosteroids and many other natural products, which together make the pregnanes the largest single group of steroids. Many pregnane derivatives have hydroxyl or a related group at *C*-17. To avoid any ambiguity as to the configuration, epimeric forms of 17-substituted pregnanes are specified as 17αOH or 17βOH.



Pregn-4-ene-3,20-dione (Progesterone)

7.2 The sterols

The sterols comprise several major groups of steroids characterised by having a hydroxyl group at *C*-3, normally in the β-configuration, and branching side chains of from eight to ten or more carbon atoms at *C*-17. They occur widely throughout the animal and particularly the plant kingdoms. They have both structural roles, as membrane constituents, and a key place in the biosynthetic sequences which lead to the steroid hormones and other biologically active steroidal species.

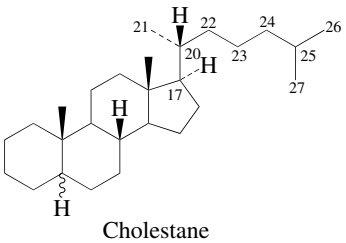
The following sections detail the main features of the various parent hydrocarbons which provide the structural basis and classification of the sterols.

Kerr, R.G. *et al*, *Nat. Prod. Rep*., 1991, **8**, 465–497 (*marine sterols*)
Baker, B.J. *et al*, *Topics in Current Chemistry*, (ed. Scheuer, P.J.), Springer, Berlin, 1993, **Vol. 167**, 1–31 (*biosynth*)
D'Auria, M.V. *et al*, *Chem. Rev*., 1993, **93**, 1839–1895 (*marine steroids*)
Giner, J.L. *et al*, *Chem. Rev*., 1993, **93**, 1735–1752 (*biosynth*)

Minale, L., *Progress in the Chemistry of Organic Natural Products*, (eds, Herz, W. *et al*), SpringerWien, New York, 1993, **Vol. 62**, 75–308 (*echinoderm sterols*)
Stonik, V.A., *Russ. Chem. Rev*., 2001, **70**, 673–715 (*marine steroids*)
Sica, D. *et al*, *Steroids*, 2004, **69**, 743–756 (*marine secosteroids*)
Sarma, N.S. *et al*, *Mar. Drugs*, 2005, **3**, 84–111 (*sponge sterols*)

7.2.1 Cholestane steroids (C_{27}) (VT1050, VT1100)

The cholestane skeleton, which derives its name from the longest-known and most familiar compound of its class, **Cholesterol**, can be regarded as the parent from which almost all other sterols are derived. This is true structurally, if not necessarily in terms of the detailed biosynthetic pathway.



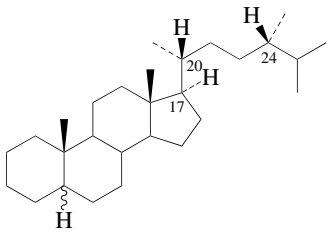
Cholestane

Other classes of sterols are derived from cholestane by the addition of one or more carbon atoms at side-chain positions, most commonly *C*-24 (see ergostanes, stigmastanes, etc, below).

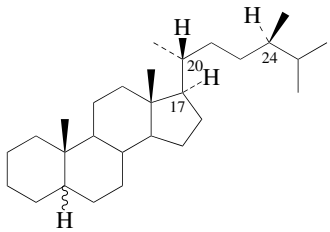
Alkylated cholestanes of many types occur widely in plants, fungi, and marine organisms. The very large classes of 24-methylcholestanes (ergostanes and campestanes) and 24-ethylcholestanes (stigmastanes and poriferastanes) are sufficiently important that their parent hydrocarbons have been assigned these special systematic names (not used in *Chemical Abstracts* however). They are treated in separate sections below. The 4,4,14-trimethylcholestanes (lanostanes) are covered in the preceding terpenoid section. Many alkylcholestane derivatives, however, fall outside these major groups, and have not been signified by special class names. They can be named as derivatives of cholestane, or alternatively if they contain a 24-methyl or 24-ethyl group can be named as substituted ergostanes or stigmastanes respectively. Both forms are usually given in the Dictionary to aid location. Others are homocholestanes, in which additional carbon atoms lengthen the side-chain, rather than branching off it. Many of these unusual sterols are best known by trivial names that reflect their biological origins.

7.2.2 Ergostane steroids (VT1300)

The 24-methylcholestane structure is termed ergostane. While the saturated and Δ^{25}-unsaturated ergostane side-chains have the 24*S* configuration, the altered priorities of groups around *C*-24 give ergost-22-ene the 24*R* configuration.

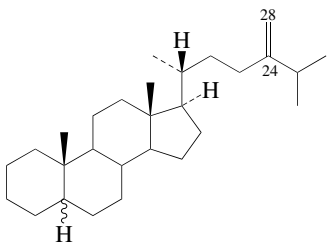


Ergostane

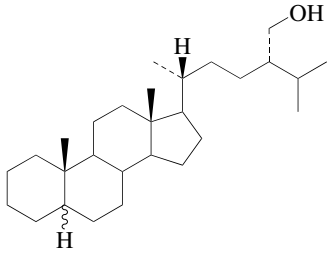


Campestane

A further complication, firmly rooted in historical precedent, is the use of the locant *C*-28 for the carbon atom of the 24-methyl group. The latest IUPAC-IUB recommendation is that the locant *C*-28 be reserved for the 4α-methyl group in lanostanes, and in other 4,4-dimethylsterols of terpenoid type, with *C*-29 and *C*-30 allocated, respectively, to the 4β- and 14α-methyl groups. The locant *C*-28 has therefore acquired two distinct meanings, according to context. In this Dictionary the *C*-24 methyl group in ergostanes and campestanes retains its original locant as *C*-28, allowing the use of derivative names containing such expressions as ergost-24(28)-ene (for 24-methylenecholestanes) or ergostan-28-ol (for 24-hydroxymethylcholestanes). The cholestane-based synonyms favoured by IUPAC-IUB are also given, where necessary, for clarity.



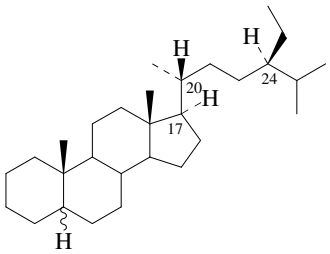
24-Methylenecholestane
[Ergost-24(28)-ene]



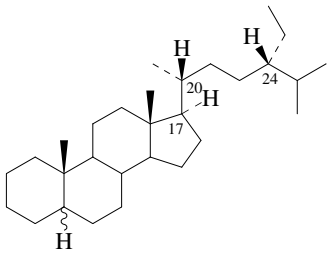
24-Hydroxymethylcholestane
(Ergostan-28-ol)

7.2.3 Stigmastane steroids (C_{29}) (VT1550)

These are the 24-ethylcholestanes, stigmastanes and poriferastanes being epimeric at *C*-24. The long history of stigmastane-based nomenclature, derived from the common plant sterol Stigmasterol, has ensured that this is by far the more widely used of the two names. In the Fieser system, stigmastanes have the 24α configuration, and poriferastanes are 24β. Again the sequence rule is now preferred, with 24*R* or 24*S* depending upon local substitution and/or unsaturation.

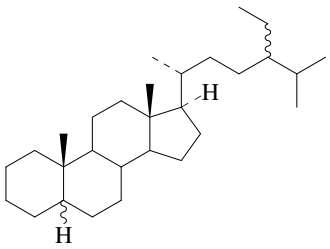


Stigmastane

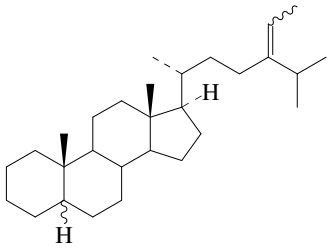


Poriferastane

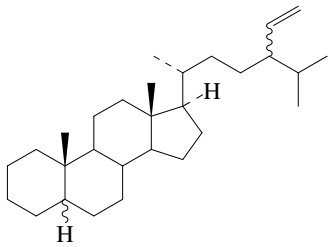
As with ergostanes, common usage over several decades has favoured the locants *C*-28 and *C*-29 for the two ethyl carbon atoms, and these are used here. The IUPAC-IUB recommendation is that the two ethyl carbon atoms be designated 24^1 and 24^2 whenever locants are needed. Synonyms based upon 24-ethylcholestane, 24-ethylidenecholestane, or 24-vinylcholestane are given in the Dictionary where suitable.



24-Ethylcholestane



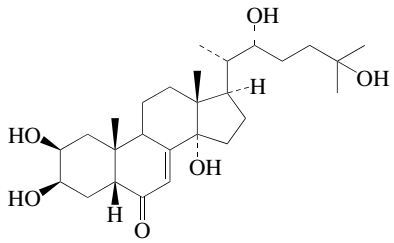
24-Ethylidenecholestane



24-Vinylcholestane

7.2.4 Ecdysteroids (C_{27}) (VT1150)

Ecdysteroids or ecdysones are moulting hormones of insects and crustaceans. They have also been isolated from many plants. The first ecdysone to be isolated was α-Ecdysone from the silkworm (*Bombyx mori*). Most ecdysteroids have a 2β,3β,14α,20,22-pentahydroxy-5β-cholest-7-en-6-one skeleton with further hydroxylation.

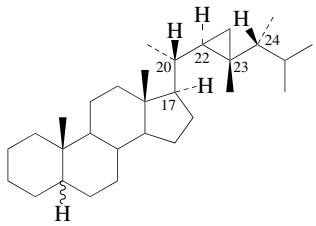


α-Ecdysone

Dauphin-Villemant, C., *Ann. NY Acad. Sci*., 1998, **839**, 306–310 (*biosynth*)
Subramoniam, T., *Comp. Biochem. Physiol*., 2000, **125C**, 135–156 (*crustacean ecdysteroids*)
Suksamrarn, A. *et al*, *J. Nat. Prod*., 2002, **65**, 1194–1197 (*bibl*)
Hopkins, P.M., *Recent Advances in Marine Biotechnology*, (eds. Fingerman, N. *et al*), Science Publishers, USA, 2003, **Vol. 10**, 263–278 (*crustacean ecdysteroids*)
Lafont, R. *et al*, *Comprehensive Molecular Insect Science*, (eds. Gilbert. L. *et al*), Elsevier, 2005, **Vol. 3**, 125–195 (*ecdysteroids*)

7.2.5 Gorgostane and other cyclopropacholestane steroids (C_{30}) (VT1700)

Gorgostane is the parent hydrocarbon of a widely-occurring group of sterols in marine organisms. Its skeleton comprises ergostane with an additional methyl group at *C*-23, and a methylene bridge between *C*-22 and *C*-23, forming a cyclopropane ring. Configurations in the side chain are as illustrated unless otherwise specified.



Gorgostane

A wide variety of at least 100 diverse C_{30} and C_{31} marine sterols in the gorgostane and related structural classes are known. Sponges are the most prolific source. Sponge sterols are characterised by multiply alkylated side chains, frequent presence of cyclopropane/cyclopropene functionality in the side chain, and wide variation in the steroid A-D ring skeleton, including many examples of A-nor and 19-nor variants.

Djerassi, C. *et al*, *Acc. Chem. Res*., 1991, **24**, 371–378 (*biosynth*)
Djerassi, C., *Studies in Natural Products Chemistry*, (ed. Atta-ur-Rahman), Elsevier, Amsterdam, 1991, **Vol. 9**, 25–50 (*marine cyclopropane sterols*)

8. AMINO ACIDS AND PEPTIDES (VV)

8.1 Amino acids (VV0050–VV0140)

8.1.1 Protein α-amino acids (VV0050)

The common α-amino acids are characterised by the structure $RCH(NH_2)COOH$, where R is an aliphatic (including hydrogen), aromatic or heterocyclic group. The exception is **Proline**, strictly an iminoacid, in which the N atom is incorporated into a 5-membered pyrrolidine ring.

They are the primary products of nitrogen anabolism in plants, where they are produced from ammonia (derived *ab initio* by nitrate reduction or nitrogen fixation) by a process called the glutamate synthetase cycle. This produces glutamate which is then transformed into the other amino acids by a variety of processes.

The amino acids thus represent the most important nitrogenous component (in terms of volume and accessibility) of the chiral pool produced by living organisms and are of great importance in chiral synthesis.

Several hundred natural amino acids are known. Of these, only 20 (known as the primary protein amino acids) are incorporated by all organisms into peptides and proteins (not all of these 20 amino acids can be biosynthesised by animals). This protein synthesis occurs in the ribosomes by a process involving ribonucleic acid (RNA), the nucleoside chain of which transmits the template instructions of the DNA genetic material to the protein sequences, each primary amino acid in the chain being coded for by one or more nucleoside base triplets or codons.

There is an IUPAC-IUB standard 3-letter code for each of the protein amino acids (as well as for the common non-protein amino acids). For ease of computerised documentation of large peptide structures, one-letter codes have more recently been introduced.

8.1.2 IUPAC-IUB abbreviations

Amino acids and their corresponding 3-letter and 1-letter codes

1.	Alanine	Ala	A
2.	Arginine	Arg	R
3.	Asparagine	Asn	N
4.	Aspartic acid	Asp	D
5.	Cysteine	Cys	C
6.	Glutamic acid	Glu	E
7.	Glutamine	Gln	Q
8.	Glycine	Gly	G
9.	Histidine	His	H
10.	Isoleucine	Ile	I
11.	Leucine	Leu	L
12.	Lysine	Lys	K
13.	Methionine	Met	M
14.	Phenylalanine	Phe	F
15.	Proline	Pro	P
16.	Serine	Ser	S
17.	Threonine	Thr	T
18.	Tryptophan	Trp	W
19.	Tyrosine	Tyr	Y
20.	Valine	Val	V

Various posttranslational protein amino acids, known as secondary amino acids, may then arise in the protein by various processes such as conjugation of OH, SH or NH groups, *N*-methylation or hydroxylation (especially to produce **4-Hydroxyproline**). A special case of posttranslational change is the reversible oxidation of cysteine residues to produce the disulfide, **Cystine**, thus linking different parts of the peptide chain by disulfide bridges as part of the secondary structure of the protein.

With the exception of **Glycine**, all of the genetically coded protein amino acids are chiral and belong to the L-series. In all cases, except Cysteine, this corresponds to the *S*-form according to the Cahn-Ingold-Prelog convention. In Cysteine, the higher priority of the CH_2SH group over the COOH group means that L- corresponds to the *R*-form.

Amino acids of the opposite D-series can be detected in hydrolysates of aged proteins in which they arise by slow racemisation (they are also produced as artifacts of racemisation during acid or especially alkaline hydrolysis of polypeptides). D-Amino acids are common constituents of antibiotics and bacterial proteins.

Chemistry and Biochemistry of the Amino Acids, (ed. Barrett, G.C.) Chapman & Hall, London, 1985
Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids, (ed. Coppola, G.M. *et al*) Wiley, New York, 1987
Synthesis of Optically Active α-Amino Acids, (ed. Williams, R.M.), Pergamon, Oxford, 1989
Hunt, S., *Methods in Plant Biochemistry*, (ed. Rogers, L.J.), Academic Press, New York, 1991, **Vol. 5**, 1–52

8.1.2 Non-protein α-amino acids (VV0100)

In addition to the proteinaceous amino acids, there are several hundred known natural non-protein amino acids which arise by a variety of metabolic routes. Some of these have demonstrated functions, for example as defence chemicals; the plant amino acids probably perform a generalised nitrogen storage function.

A considerable number of atypical α-amino acids have been isolated from microbial sources. They inhibit the growth of a range of microorganisms but their effects can be readily reversed by supplementing the growth medium by the requisite principal amino acid.

Atypical amino acids are encountered in the hydrolysates of microbial peptide antibiotics. These do not always occur in the free state but a number have been included in DMNP since a given amino acid may be present in a range of different peptides.

Scannell, J.P. *et al*, *Chemistry and Biochemistry of Amino Acids Peptides and Proteins*, Dekker, New York, 1974 (*antimetabolites*)
Hatanaka, S.I. *et al*, *Progress in the Chemistry of Organic Natural Products*, (eds. Hertz, W. *et al*), SpringerWien, New York, 1992, **59**, 1 (*fungi amino acids*)

8.1.3 β-Amino acids (VV0120)

A small number of β-amino acids occur in the marine environment, especially in sponges. Of these the most widespread is 2-(aminomethyl)-2-propenoic acid and associated amides.

Drey, C.N.C., *Chemistry and Biochemistry of the α-Amino Acids*, (ed. Barrett, G.C.), Chapman & Hall, London, 1985

8.2 Peptides (VV0150–VV0500)

Peptides are oligomers and polymers notionally derived from amino acids by condensation to produce amide linkages. The boundary between oligopeptides and polypeptides is arbitrary and in DMNP has been set at 10 amino acid residues. The configuration of amino acid residues in polypeptides is assumed to be L- when not indicated otherwise.

There is evidence that in higher organisms small peptides (hormones) can arise only by cleavage of protein prohormones.

A large number of biologically-active atypical peptides have been isolated from bacteria, actinomycetes, cyanobacteria, fungi and higher animals. Structurally they represent an extremely diverse group, encompassing those metabolites containing two or more amino acid residues linked by a peptide bond, but possessing some additional features not characteristic of proteins. These may include unusual amino acid residues, protein amino acids with D-configuration or increased to a higher oxidation level, or non-peptide linkages between residues (e.g. ester, lactone or a γ-glutamyl amide). In addition, the molecules may be linear or cyclic, contain one or a combination of the above mentioned features, be modified by further interactions between the side chains of amino acid units within the peptide, or conjugated with either lipids or sugar units. They can possess a wide range of biological activities, e.g. the neuropeptides **Carcinustatins**, the hormone **Salcatonin**, and the enzyme inhibitor **Cyclotheonamide A**. Also worthy of note are the **Conotoxins**, a group of marine venoms isolated from snails with interesting biological properties, as well as many other toxins isolated from higher marine animals.

8.2.1 Diketopiperazines (dipeptide anhydrides) (VV0150)

These are among the most numerous of all naturally occurring peptides. They range from simple cyclic dipeptides, e.g. **Dysamide A**, to highly complex fused ring systems such as the cytotoxic **Leptosins** and related compounds. Nomenclature of the simple diketopiperazines is complicated by the proliferation of different ways of naming them. In this Dictionary, systematic *Chemical Abstracts* names are usually used as their entry names, but the entries contain a full range of possible synonyms.

8.2.2 Cyclic oligo- and polypeptides (VV0500)

No cyclic homodetic tripeptides with or without biological activity have been observed to date. Cyclic peptides derived from 4–11 amino acid residues linked by peptide bonds have been isolated from a variety of microorganisms, particularly those associated with sponges and algae, e.g. **Phakellistatins**. Their biological properties are diverse, ranging from antitumour/cytotoxic activities and antifungal and antibacterial properties.

8.2.3 Depsipeptides (VV0600, VV0610)

Cyclic heterodetic peptides or peptide lactones are those in which one or more of the peptide bonds have been replaced by ester linkages, examples include **Dolastatin 11** and **Aplidine** which has been used in clinical trials.

8.2.4 Large peptides and proteins (VV1000, VV2000)

Entries are given in DMNP for the majority of bioactive peptides secreted by marine plants and animals for which reasonable structural information exists, including many neuropeptides which are an active field of research. Entries are presented for the most important non-enzyme proteins and for some enzymes (VV1000), but full structures are not given in individual entries, the structures where known can be assessed *via* the cited references.

The Peptides, (ed. Gross, E.), Academic Press, New York, 1983 (*general*)
Bladon, C., *The Chemistry of Natural Products*, 2nd edn (ed. Thomson, R.H.), Blackie, Glasgow, 1993, 183 (*rev*)
Fusetani, N. *et al*, *Chem. Rev*., 1993, **93**, 1793–1806 (*sponge peptides*)

8.3 Glycopeptides and glycoproteins (VV3000)

This is a relatively small and structurally self-evident category of peptides predominantly consisting of proteinaceous toxins such as **Dolabellanins** and **Verrucotoxin**.

Fattorusso, E. *et al, Marine Natural Products: Chemical and Biological Perspectives*, (ed. Scheuer, P.J.), Academic Press, New York, 1980, **Vol. 3**, 95–140 (*amino acids from algae*)
Ireland, C.M. *et al, Bioorganic Marine Chemistry*, (ed. Scheuer, P.J.), Springer-Verlag, New York, 1989, **Vol. 3**, 1–46 (*peptides from marine organisms*)
Suzuki, N., *Bioorganic Marine Chemistry*, (ed. Scheuer, P.J.), Springer-Verlag, New York, 1989, **Vol. 3**, 47–70 (*peptides from sea urchins*)
Bernheimer, A.W., *ACS Symp. Ser*., 1990, **418**, 304–311 (*marine toxins*)
Sharma, G.M. *et al, Mar. Technol*., 1993, **1**, 153–180 (*marine proteins in clinical chem*)
Wipf, P., *Chem. Rev*., 1995, **95**, 2115–2134 (*cyclic peptides, synth*)
Gulavita, N.K. *et al, J. Nat. Toxins*, 1996, **5**, 225–234 (*peptides from sponges*)
Norton, R.S., *J. Toxicol. Toxin Rev*., 1998, **17**, 99–130 (*toxins in marine organisms*)
Fields, P.A., *Comp. Biochem. Physiol., A: Mol. Integr. Physiol*., 2001, **129**, 417–431 (*proteins in marine environment*)
O'Keefe, B.R., *J. Nat. Prod*., 2001, **64**, 1373–1381 (*proteins; activity*)
Anderluh, G. *et al, Toxicon*, 2002, **40**, 111–124 (*toxins from sea anemones*)
Massilia, G.R. *et al, Recent Res. Dev. Biochem*., 2002, **3**, 113–128 (*conopeptides*)
Matsunaga, S. *et al, Curr. Org. Chem*., 2003, **7**, 945–966 (*non-ribosomal peptides from sponges*)
Lehrer, R.I. *et al, Integr. Comp. Biol*., 2003, **43**, 313–322 (*peptide antibiotics from tunicates*)
Aneiros, A. *et al, J. Chromatogr. B*, 2004, **803**, 41–53 (*bioactive peptides, isol, pharmacol*)
Terlau, H. *et al, Physiol. Rev*., 2004, **84**, 41–68 (*Conus venoms*)
Tincu, J.A. *et al, Antimicrob. Agents Chemother*., 2004, **48**, 3645–3654 (*antimicrobial peptides from invertebrates*)
Gowd, K.H. *et al*, *Ann. NY Acad. Sci*., 2005, **1056**, 462–473 (*Conus peptides*)
Ma, D. *et al, Pept. Sci*., 2004, **41**, 71–74 (*cyclic peptides, synth*)
Hamada, Y. *et al*, *Chem. Rev*., 2005, **105**, 4441–4482 (*cyclic peptides, synth*)
Honma, T. *et al, Mar. Biotechnol*., 2006, **8**, 1–10 (*sea anemone toxins*)
Rawat, D.S. *et al, Anti-Cancer Agents Med. Chem*., 2006, **6**, 33–40 (*peptides in clinical trials*)
Layer, R.T. *et al*, *Mar. Drugs*, 2006, **4**, 119–142 (*Conotoxins*)

9. ALKALOIDS (VX)

Alkaloids are a large group of nitrogen-containing secondary metabolites of plant, microbial or animal origin. Biogenetically and structurally the alkaloids are diverse, and because of the structural complexity of many marine alkaloids, some of them are classified here under more than one heading.

In general, less is known about the biogenesis of marine alkaloids than their terrestrial counterparts because of experimental difficulties and the complexity of the ecosystems. There are many synthetic studies, but comparatively few biosynthetic ones. Few characteristic key intermediates have been identified in the later stages of marine alkaloid biosynthesis; an exception is Oroidine. Some types of marine alkaloid are of mixed biogenesis, different stages of the biosynthesis being affected by different organisms.

Where structural similarities exist between certain marine alkaloids and their terrestrial counterparts, this is frequently indicated in the following sections, but this should not be taken to imply that their biosynthesis takes place by identical routes. There may be cases of biochemical parallelism arising from convergent evolution. In many cases the relevant information is just not available for the marine alkaloids.

The order of the following sections, and the accompanying Type of Compound codes that can be used for searching the electronic version of the database, follows that of the parent *Dictionary of Natural Products* database, which is loosely based on biogenetic considerations (for example, ornithine-derived alkaloids precede those derived from lysine). However, in considering marine alkaloids, these considerations may not necessarily apply and the order is more arbitrary. Sections dealing with structurally related types of alkaloid are, though, usually close together. Some types have been extensively studied biosynthetically, for others there is currently no, or only fragmentary, information. In addition, details are now being uncovered about formerly unsuspected enzyme systems present in marine organisms, which superpose new biosynthetic possibilities on top of the traditional routes, thus blurring the traditional alkaloid subtypes. Foremost among these are the 'Diels-Alderases' (not confined to alkaloids) which are capable of catalysing the formation of new carbon skeletons from known types. The Type of Compound categories in the database are therefore subject to future revision in the light of new research results.

The term alkaloid originally implied pharmacologically active bases, but the definition has subsequently been broadened so that it is now generally considered to include the majority of nitrogen-containing natural products with the exception of the simple amino acids, proteins and nitrogen-containing substances of polyketide origin such as aminoglycosides. Basic properties may be weak or absent as in the various types of amide alkaloids. The term 'imperfect alkaloid' has been used for miscellaneous nitrogenous natural products, including amides that do not fall into one of the well-defined traditional alkaloid types. Nitrogenous compounds of novel structural type are of obvious medicinal interest.

Garson, M.J., *Chem. Rev*., 1993, **93**, 1699–1733 (*rev, biosynth*)
Oikawa, H. *et al, Nat. Prod. Rep*., 2004, **21**, 321–352 (*rev, Diels-Alder enzymes*)
Newman, D.J. *et al, J. Nat. Prod*., 2004, **67**, 1216–1238 (*rev, marine compounds in clinical trial*)
Moore, B.S., *Nat. Prod. Rep*., 2005, **22**, 580–593; 2006, **23**, 615–629 (*rev, biosynth*)

The following codes occur at the beginning of the sequence and refer to simple and miscellaneous amines, amides and related compounds;

9.1.1 Simple acyclic amine alkaloids with one N (VX0100)

These include simple amines of mostly widespread biological occurrence such as choline and ethylamine.

9.1.2 Simple acyclic amine alkaloids with two N (VX0120)

These include a variety of linear diamines such as the **Clathculines** and **Calyxoside**.

9.1.3 Simple guanidines (VX0150)

This heading covers low MW guanidinoid bases. The guanidine or modified guanidine group is common as a structural component of higher MW alkaloids, including hybrid polyketide alkaloids and peptide-alkaloids which have been classified elsewhere as polyketides or peptides.

Berlinck, R.G.S. *et al, Nat. Prod. Rep*., 2002, **19**, 617–649; 2005, **22**, 516–550 (*rev*)
Nagasawa, K. *et al, Chem. Rec*., 2003, **3**, 201–211 (*rev, synth*)

9.1.4 Nitriles, isonitriles and related compounds (VX0200)

Compounds containing the -NC, -NCS and -NHCHO groups frequently occur together and are biogenetically related. They are usually included in the same entry. It now appears that the thiocyanates are central in their biosynthesis.

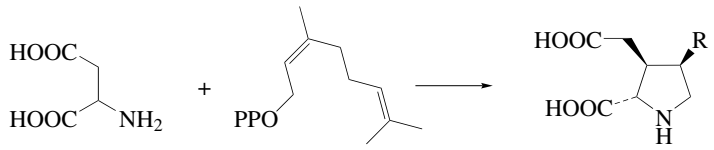
Garson, M.J. *et al, Nat. Prod. Rep*., 2004, **21**, 164–179 (*rev*)

9.1.5 Simple amide alkaloids (VX0250)

These include a variety of simple amides such as the **Variceramides**.

9.1.6 Pyrrolidine alkaloids (VX0300, VX0380)

These may arise by different biosynthetic pathways. The kainoids, e.g. **α-Kainic acid**, **Domoic acid**, are a group of non-proteinogenic pyrrolidinedicarboxylic acids. α-Kainic acid was first isolated from a rhodophyte alga but has since been found in terrestrial organisms. The kainoids are biosynthesised from glutamate and geranyl pyrophosphate. Other marine pyrrolidines such as the **Sarcotrines** are degraded pyrrolosesterterpenes, while many others are presumably proline-derived.



e.g. Domoic acid, R = $C(CH_3)$=CHCH=CHCH(CH_3)COOH

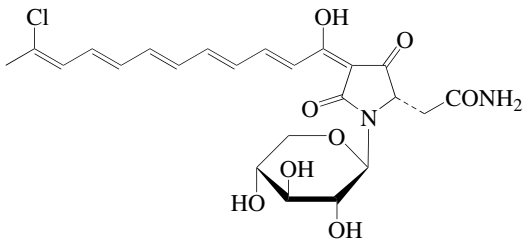
Parsons, A.F., *Tetrahedron*, 1996, **52**, 4149–4174 (*kainoids, rev*)

9.1.7 Chromone alkaloids (VX0340)

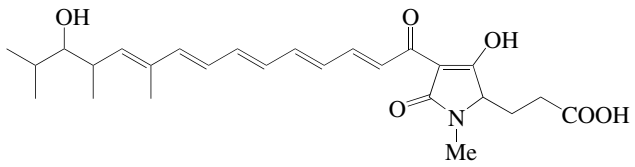
Chromone alkaloids, moderately common in higher plants, are currently represented only by **Tubastraine**, which appears doubtful.

9.1.8 Tetramic acids (VX0390)

These are longer-chain pyrrolidines exemplified among marine examples by the halogenated **Aurantosides** and **Rubrosides** from sponges (microbial products). They are polyketide in origin and are most closely related to nonhalogenated tetramic acids from terrestrial microorganisms such as Erythroskyrin and the Lipomycins.



Aurantoside G

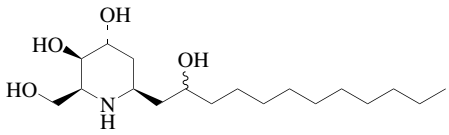


β-Lipomycin
(terrestrial)

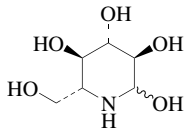
9.1.9 Piperidine alkaloids (VX0620, VX0680, VX0700)

The majority of the alkaloids in this group are plant-derived, but **Anabaseine** and several related alkaloids have been isolated from a hoplonemertean worm. Like the pyrrolidines, these alkaloids may arise by different biosynthetic routes, so the class is structural rather than biosynthetic. They may be derived from lysine, acetate, acetoacetate, etc. but the longer-chain **Batzellasides**, present in sponges, are iminoglycosides structurally related to the intensively-studied terrestrial iminosugars such as **Nojirimycin**, evidently with the incorporation of a fatty-acid derived fragment.

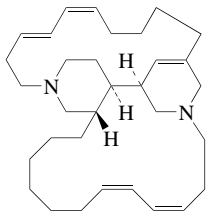
Other piperidine alkaloids included here include the **Halicyclamines** and relations, which are classified under miscellaneous piperidine alkaloids (VX0700), but which are the first of several types of alkaloids including the Xestospongins and the Manzamines below, which appear to be closely related and are based on elaboration of a macrocycle-linked 1,3-linked bispiperidine theme.



Batzellaside A



Nojirimycin
(terrestrial)

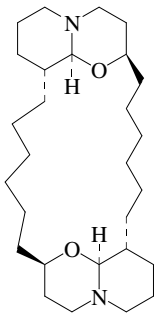


Halicyclamine A

Jaspars, M. *et al, J. Org. Chem*., 1994, **59**, 3253–3255 (*Halicyclamines, biosynth*)
Andersen, R.J. *et al, Alkaloids: Chemical and Biological Perspectives*, (ed. Pelletier, S.W.), Elsevier, Amsterdam, 1996, **10**, 301 (*rev, 3-alkylpiperidines*)

9.1.10 **Xestospongins** (VX0690)

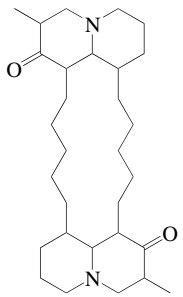
These are a group of exclusively marine elaborated piperidines. Their biosynthesis would appear to imply the involvement of a C_{10} dialdehyde equivalent as hypothesised for the Manzamine group (VX2250) below, and they appear closely related to intermediates postulated in the Baldwin scheme.



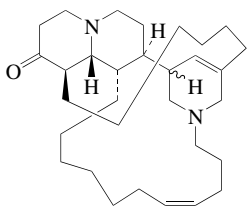
Xestospongin A

9.1.11 **Quinolizidine alkaloids** (VX0900, VX0980)

A few relatively simple marine quinolizidine alkaloids are known such as **Pictamine** and the **Clavepictines**. The **Saraines** are more complex sponge products classified under miscellaneous quinolizidines (VX0980), together with Halichlorine, a popular synthetic target, and the **Petrosines**, further examples of dimeric alkaloids in which the units are linked in a medium-sized aliphatic ring as in the Xestospongins.



Petrosines
(various stereoisomers)

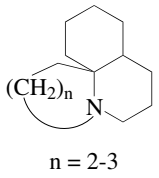


Saraine 1

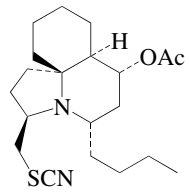
Michael, J.P., *Nat. Prod. Rep*., 2002, **19**, 719–741; 2004, **21**, 625–649 (*revs*)

9.1.12 Cylindricines (VX0960)

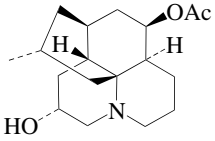
This small group of alkaloids is based on the perhydrobenzo[*i*]quinolizine and perhydrocyclopenta[*i*]quinoline skeletons. There are structural similarities to some of the terrestrial *Lycopodium* alkaloids such as **Paniculine**. The isolation of both thiocyanates and isothiocyanates is noteworthy.



n = 2-3



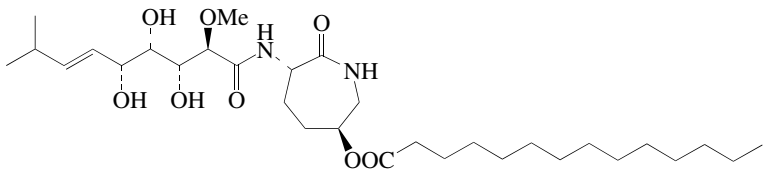
Cylindricine H



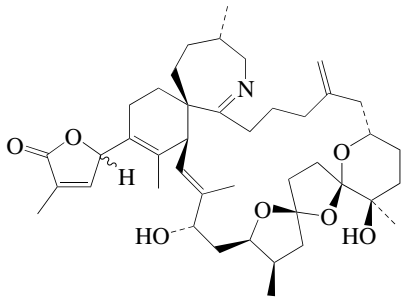
Paniculine (terrestrial)

9.1.13 Azepine alkaloids (VX1000)

These include the **Bengamides** and the **Spirolides**. The former are thought to be symbiotic products deriving from bacterial fatty acids, cyclised lysine and a 4-carbon diketide. The spirolides are shellfish toxins related to the Pinnatoxins (which are classified under VC0550, polyketides; the division is arbitrary) and like them presumably arising by a Diels-Alder process from a long-chain polyketides precursor.



Bengamide A



Spirolide A

9.1.14 Pyridine alkaloids (VX1040)

As well as some simple nicotinic acid-related bases (VX1040), a considerable number of pyridines carrying a long-chain substituent at *C*-3 have been isolated mostly from sponges. Examples include the **Xestamines**, **Ikimines** and **Niphatesines**. Small pyridinium betaine alkaloids such as **Trigonelline** are widespread in marine plants and animals as well as terrestrial organisms.

Almeida, A.M.P. *et al, Quim. Nova, 1997*, **20**, 170 (*rev, alkylpyridines from sponges*)
Sepčić, K., *J. Toxicol., Toxin Rev*., 2000, **19**, 139–160 (*rev, alkylpyridinium compounds from sponges*)

9.1.15 Cytochalasan alkaloids (VX1300)

Cytochalasins are metabolites of several different and unrelated fungi. They are characterised structurally by the presence of a perhydroisoindolone system fused to a macrocyclic ring of 11, 13 or 14 atoms. The macrocycle may be a carbocycle, a lactone or a carbonate. In addition the isoindole ring carries either a phenyl or an indolyl substituent at position 10; the latter group includes the Chaetoglobosins.

Biosynthetically, cytochalasins arise from phenylalanine or tryptophan and a polyketide derived from acetate and methionine. Cytochalasins possess a range of distinctive biological properties. These include inhibition of cytoplasmic cleavage leading to polynucleate cells, nuclear extrusion and the inhibition of cell mobility.

Some members of this important class of metabolites have been obtained from marine ascomycetes. It can be anticipated that other members of the series will be found in marine fungal cultures in future.

9.1.16 Indolizidine alkaloids (VX1360)

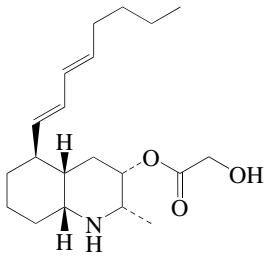
A few simple indolizidines (e.g. the **Stelletamides**) have been isolated from sponges. Indolizidines of a different structural type are commoner in terrestrial animals, esp. as frog toxins.

Michael, J.P., *Nat. Prod. Rep*., 2004, **21**, 625–649; 2005, **22**, 603–626 (*revs*)

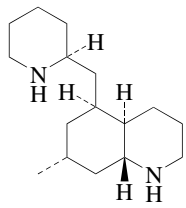
9.1.17 Quinoline alkaloids (VX1480, VX1580)

The majority of these are from higher plants, but a variety of simple heteroaromatic quinolines (VX1480) have been isolated from various marine sources including **2-Heptyl-4-hydroxyquinoline** from a marine pseudomonad, and **4,8-Quinolinediol** from cephalopod ink. There are also more elaborated hydrogenated quinolines (VX1580), especially the **Lepadins** from tunicates and flatworms. Bryozoans contain a number of simple quinolinequinone pigments and there are also the **Trididemnic acids** from ascidians. **Halitulin** from a sponge has been the subject of a recent major collaborative synthesis effort.

Quinoline alkaloids occur across a wide range of organisms and there are some structural similarities between marine octahydroquinolines such as **Lepadin A** and terrestrial alkaloids such as Phlegmarine from *Lycopodium* spp.



Lepadin A

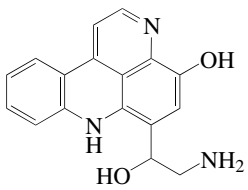


Phlegmarine
(terrestrial)

Michael, J.P., *Nat. Prod. Rep*., 2004, **21**, 650–668; 2005, **22**, 627–646 (*revs*)

9.1.18 Pyrido[2,3,4-*kl*]acridines (VX1700)

This is a group of exclusively marine alkaloids which includes the **Kuanoniamines**, the **Ascididemins**, the **Cystodytins**, the **Styelsamines**, the **Varamines** and others. The isolation of some of them from a variety of organisms argues for a microbial origin, but it could alternatively be a case of convergent evolution. They are biosynthesised from common amino acids.



Styelsamine A

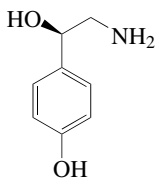
Ding, Q. *et al, Curr. Med. Chem*., 1999, **6**, 1–28 (*rev*)
Salomon, C.E. *et al, Mar. Biol*., 2001, **139**, 313–319 (*biosynth*)
Moore, B.S., *Nat. Prod. Rep*., 2006, **23**, 615–629 (*rev*)

9.1.19 Benzodiazepine alkaloids (VX1760)

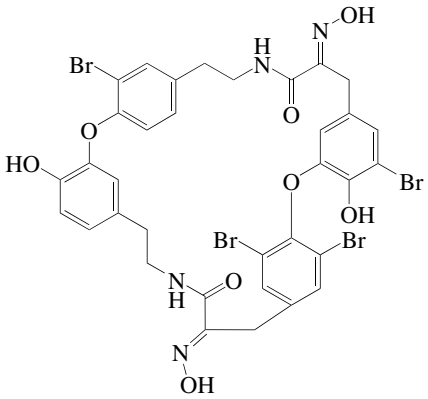
These are rare and among non-microbial products are currently limited to **Aplysepine** and **Diazepinomicin**. They are clearly derived from anthranilic acid and phenylalanine.

9.1.20 Phenethylamine alkaloids (VX2000–VX2015)

The simplest derivatives of phenylalanine or tyrosine are the β-phenylethylamines resulting from decarboxylation and obvious oxidation/alkylation, which are widespread among marine natural products. Compounds showing side-chain hydroxylation (VX2005), common among higher plants, are rare (e.g. **Octopamine**, which is an endometabolic neurotransmitter of molluscs); the majority of marine representatives are brominated compounds (VX2008) such as the **Purpuramines** and the **Bastadins** (including macrocyclic oligomers), produced by Verongid sponges. These are biosynthesised from the simple brominated tyrosines.



Octopamine



Bastadin 9

Bentley, K.W., *Nat. Prod. Rep*., 2004, **21**, 395–424; 2005, **22**, 249–268; 2006, **23**, 444–463 (*revs*)

9.1.21 Cinnamic acid amides (VX2020)

Simple cinnamate residues are scarcer among marine alkaloids than among terrestrial plant products. Examples are found for example in the **Tunichromes**, for which phenylalanine can function as a biosynthetic precursor.

Taylor, S.W. *et al, Chem. Rev*., 1997, **97**, 333–346 (*rev, tunichromes*)

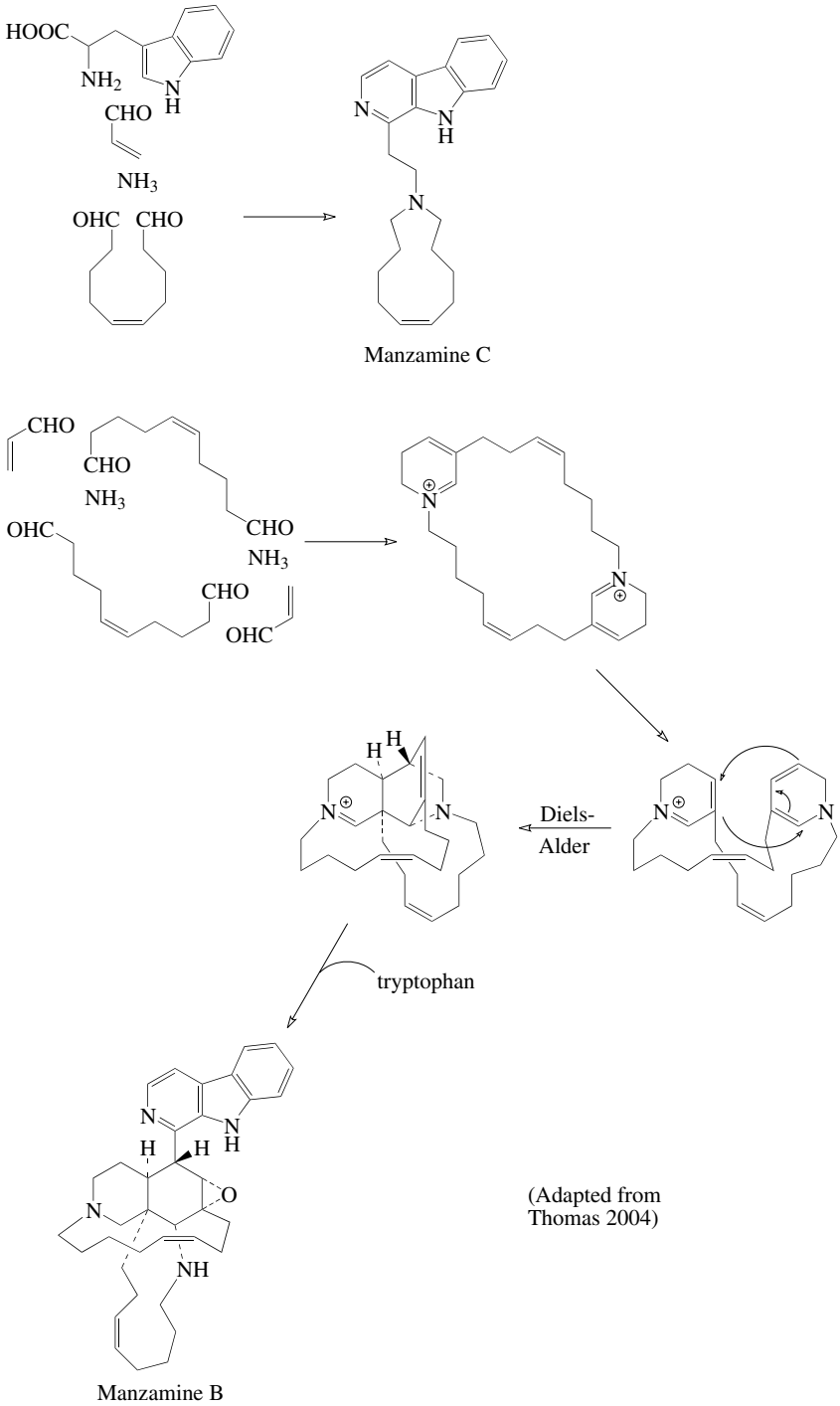
9.1.22 Simple isoquinoline alkaloids (VX2200)

These too are less widespread than in terrestrial sources, and isolated examples are restricted to some bases related to **Reneirol** and the **Cribrostatins**. However the isolation of one or two marine benzylisoquinoline alkaloids (VX2320) (**Imbricatine**; **Theoneberine**) is noteworthy.

Baker, B.J., *Alkaloid: Chemical and Biological Perspectives*, (ed. Pelletier, S.W.), Elsevier, Amsterdam, 1996, **10**, 357 (*rev, marine isoquinolines*)
Bentley, K.W., *Nat. Prod. Rep*., 2004, **21**, 395–424: 2005, **22**, 249–268; 2006, **23**, 444–463 (*revs*)

9.1.23 Manzamine alkaloids (VX2250)

This fairly extensive group is exclusively marine and represents the most structurally complex and characteristic type of marine alkaloid for which a biosynthetic scheme has been proposed. Their biosynthesis has been postulated to involve the condensation of tryptamine with one or more C_3 units and one or more straight-chain C_{10} dialdehyde equivalents, followed by an enzyme-assisted Diels-Alder cyclisation. The origin of the C_3 and C_{10} units is uncertain but it has been suggested that they could arise by oxidative fission of a hydroxylated fatty acid.



Tsuda, M. *et al, Heterocycles*, 1997, **46**, 765–794 (*rev*)
Baldwin, J. *et al*, *Chem. Eur. J.*, 1999, **5**, 3154–3161 (*biosynth*)
Thomas, R., *Nat. Prod. Rep*., 2004, **21**, 224–248 (*rev, biosynth*)

9.1.24 **Indole alkaloids** (VX4000-VX5950)

Indole alkaloids are numerous in marine organisms but the range of structural types differs from those found in terrestrial counterparts, and many of the 'traditional' indole alkaloid types produced by land plants have not been found. Halogenation is common.

Pindur, U. *et al, Curr. Med. Chem*., 2001, **8**, 1681–1698 (*rev*)

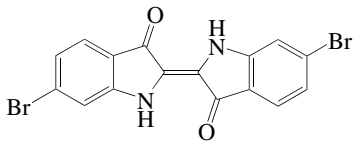
9.1.25 Simple indole alkaloids (VX4000)

Under this heading appear various halogenated indoles together with some higher MW alkaloids containing unsubstituted indole ring systems, such as **Aplysinopsin** and its relatives (which are also imidazoles).

Somei, M. *et al, Nat. Prod. Rep*., 2004, **21**, 278–311; Kawasaki, T. *et al*, *ibid*, 2005, **22**, 761–793 (*revs*)

9.1.26 Simple biindoles (VX4020)

This category includes **Indirubin**, **6,6′-Dibromoindigotin** and other biindoles, mostly polybrominated.

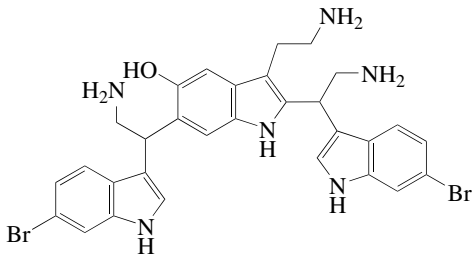


6,6'-Dibromoindigotin

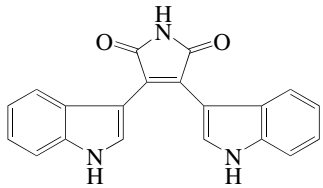
Yang, C.-G. *et al, Curr. Org. Chem*., 2004, **8**, 1691–1720 (rev, bisindole alkaloids from sponges)

9.1.27 Simple tryptamines (VX4040, VX4140, VX4160)

Tryptamine itself and some simple relatives have been isolated from marine tissues, and it noteworthy that **Bufotenine**, long known as an amphibian product, has more recently been detected in a gorgonian. More highly elaborated marine alkaloids containing a (dehydro)tryptamine residue include the **Kottamides**. There are also some simple tryptamine dimers (VX4140) and oligomers (VX4160) such as the **Gelliusines**. The bisindolylmaleimides such as the **Arcyriarubins** listed here are closely related to the indolo[2,3-*a*]carbazoles (VX4350) below.



Gelliusines A-B



Arcyriarubin A

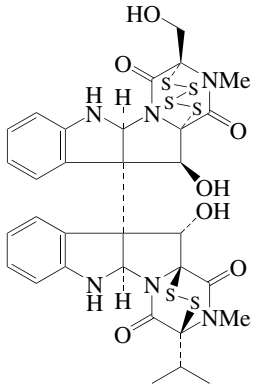
Somei, M. *et al*, *Nat. Prod. Rep*., 2004, **21**, 278–311; Kawasaki, T. *et al*, *ibid*, 2005, **22**, 761–793 (*revs*)

9.1.28 Physostigmine-like alkaloids (VX4100)

Physostigmine itself was originally isolated from a land plant, and has also been isolated from microorganisms. Alkaloids sharing the physostigmine (hexahydropyrrolo[2,3-*b*]indole) nucleus such as the **Flustramines** have however been isolated from marine animals, as well as from land animals, especially amphibians.

9.1.29 Chaetocin-like alkaloids (VX4110)

Also called Epipolythiodioxopiperazines, although some members of the series lack the polysulfur bridge. These are microbial products, but a considerable number, including Chaetocin itself and the extensive series of **Leptosins**, have been isolated from marine sources. They are thought to be biosynthesised from diketopiperazines (VV0150).

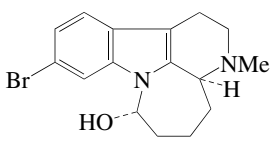


Leptosin A

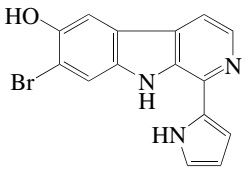
Somei, M. *et al, Nat. Prod. Rep*., 2004, **21**, 278–311; Kawasaki, T. *et al*, *ibid*, 2005, **22**, 761–793 (*revs*)
Gardiner, D.M. *et al*, *Microbiology*, 2005, **151**, 1021–1032 (*biosynth*)

9.1.30 β-Carboline alkaloids (VX4240)

Long known as terrestrial alkaloids, these are also widespread in marine organisms. β-Carboline (Norharman) itself has been found in an ascidian and in dinoflagellates, and examples of simple brominated analogues include the **Eudistomins** and some of the **Arborescidines**. Another group of β-carboline derivatives, presumably derived from tryptophan and cysteine, have been isolated from *Eudistoma olivaceum*, a Caribbean tunicate. The β-carboline nucleus is also found in some of the **Manzamines** and other more complex alkaloids.



Arborescidine C

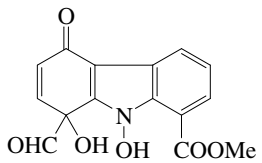


Eudistomin A

Baker, B.J., *Alkaloids: Chemical and Biological Perspective*, (ed. Pelletier, S.W.), Elsevier, Amsterdam, 1996, **Vol. 10**, 357 (*rev, marine* β-*carbolines*)
Somei, M. *et al, Nat. Prod. Rep*., 2004, **21**, 278–311; Kawasaki, T. *et al*, *ibid*, 2005, **22**, 761–793 (*revs*)
Fresneda, P.M. *et al*, *Synlett*, 2004, 1–17 (*rev, synth*)

9.1.31 Carbazole alkaloids (VX4300)

A few simple halogenated carbazoles have been isolated such as **3,6-dibromo-** and **3,6-diiodocarbazoles**. **Coproverdine** exemplifies a small number of unhalogenated carbazoles so far isolated.

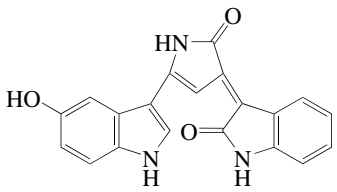


Coproverdine

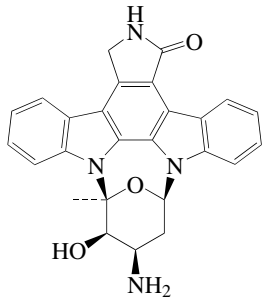
Knölker, H.-J. *et al, Chem. Rev*., 2002, **102**, 4303–4428 (*rev*)
Somei, M. *et al, Nat. Prod. Rep*., 2004, **21**, 278–311; Kawasaki, T. *et al*, *ibid*, 2005, **22**, 761–793 (*revs*)
Knölker, H.-J., *Curr. Org. Synth*, 2004, **1**, 309–331 (*rev, synth*)

9.1.32 Indolo[2,3-*a*]carbazole alkaloids (VX4350)

These are a class of alkaloids exemplified by **Staurosporine**, which was first isolated in 1977 from a terrestrial microorganism but which has since been found to be widely distributed. They are essentially microbial metabolites from a variety of organisms (field-collected or cultured), and show a wide range of biological activities. The isolation of **4′-*N*,*O*-Didemethylstaurosporine** from a flatworm *Pseudoceros* sp. is noteworthy. Their biosynthesis has been intensively studied; they are produced from diindolyl precursors resembling **Violacein**; the indolyl residues are derived from tryptophan *via* 7-chlorotryptophan followed by an oxidative ring closure.



Violacein

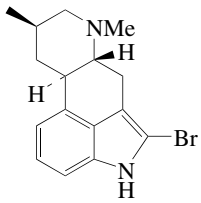


4'-*N*,*O*-Didemethylstaurosporine

Sánchez, C. *et al, Nat. Prod. Rep*., 2006, **23**, 1007–1045 (*rev, biosynth*)
Walsh, C.T. *et al, Nat. Prod. Rep*., 2006, **23**, 517–531 (*rev, biosynth*)

9.1.33 Ergot alkaloids (VX4460)

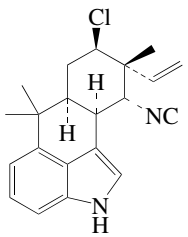
These have been considered exclusively the metabolites of terrestrial fungi and microorganisms, but the recent isolation of the **Pibocines**, simple brominated analogues of Festuclavine, from *Eudistoma* ascidians, have provided a first marine occurrence. In terrestrial fungi these bases are derived from 4-prenyltryptophan by cyclisation. The presence of the bromine substituent in the Pibocines argues for their being genuine ascidian products, and this is presumably a case of biochemical parallelism.



Pibocine A

9.1.34 Hapalindoles (VX5950)

The extensive series of hapalindoles, from *Hapalosiphon* and other cyanophytes, have mostly been characterised from freshwater species but are included in the Dictionary for completeness. They are mostly based on the naphth[1,2,3-*cd*]indole skeleton as shown by **Hapalindole A**.

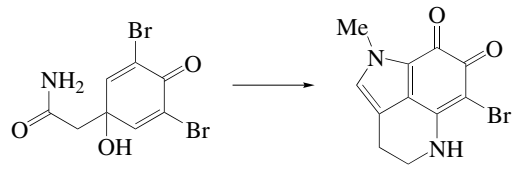


Hapalindole A

Somei, M. *et al, Nat. Prod. Rep*., 2004, **21**, 278–311; Kawasaki, T. *et al*, *ibid*, 2005, **22**, 761–793 (*revs*)

9.1.35 Pyrrolo[4,3,2-*de*]quinoline alkaloids (VX6070)

This skeleton is characteristic of and almost exclusive to marine (sponge) alkaloids. Major subgroups include the simple **Batzellines**, **Makaluvamines** and **Damirones**, and those in which the pyrroloquinoline nucleus forms part of a larger skeleton such as in the **Discorhabdins** and the closely related **Epinardines**. They are thought to be biosynthesised from tyrosine via **3,5-Dibromoverongiaquinol**.



3,5-Dibromoverongiaquinol Makaluvone

Ding, Q. *et al, Curr. Med. Chem*., 1999, **6**, 1–28 (*rev*)

9.1.36 Miscellaneous indole alkaloids (VX6100)

Under this heading are listed a large number of miscellaneous types of marine indole alkaloids for which a classification remains premature, either because they currently belong to a very limited subtype, and/or because there has been no work on their biosynthesis. Many of them probably represent minor branches on the biosynthetic pathways to the larger groups; for example the **Rhopaladins** are probably biosynthetically close to the indolo[2,3-*a*]carbazole alkaloids (VX4350), but this is not yet established experimentally. **Granulatimide** may represent a lower benzologue of these alkaloids incorporating a histamine residue in place of one tryptamine.

Somei, M. *et al, Nat. Prod. Rep*., 2004, **21**, 278–311; Kawasaki, T. *et al*, *ibid*, 2005, **22**, 761–793 (*revs*)

9.1.37 Sesquiterpene alkaloids (VX6300)

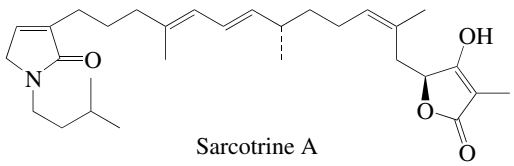
A variety of sesquiterpene alkaloids have been isolated which are nearly all relatively simple amine or amide derivatives of well-known sesquiterpenoid skeletons. These may be acyclic (e.g. **Axinyssimides**), monocyclic (**Siphonodictidine**) or bicyclic (**Nakijiquinones**). The relevant alkaloids are also coded with to the appropriate sesquiterpene (VS) code.

9.1.38 Miscellaneous diterpene alkaloids (VX6480)

There are few reported diterpenoid alkaloids (as opposed to nonalkaloidal diterpenes) reported from marine species. The **Agelasines**, **Agelasimines** and related compounds are a series of guanidinoid- or purinoid-substituted simple acyclic, mono- or bi-cyclic terpenoids, and there are one or two simple amino-substituted cembranoids.

9.1.39 Sesterterpene alkaloids (VX6490)

The number of nitrogen-containing sesterterpenoids so far isolated is relatively low by comparison with the number of nitrogen-free tetracyclic sesterterpenes known. The **Spongidines** and the **Molliorins**, in which a ring-E pyridine or pyrrole ring, respectively, is fused to one of the common tetracyclic skeletons, are the main types. There are also linear pyrrolic compounds including the **Sarcotrines** and **Sarcotragins** which are considered to have a common biosynthetic origin, the latter being degraded norsesterterpenoids.

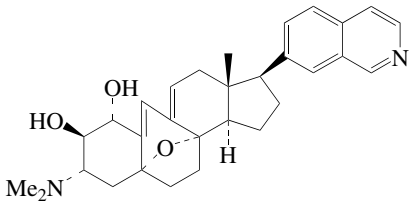


Sarcotrine A

Liu, Y. *et al, Nat. Prod. Rep*., 2006, **23**, 630–651 (*rev*)

9.1.40 Steroidal alkaloids (Buxus type) (VX6760)

Few steroidal alkaloids (as opposed to nitrogen-free steroids) have been isolated from marine organisms. The recent characterisation of the **Cortistatin** alkaloids from a *Corticium* sponge, represent a new development in marine natural products. Structurally their 9(10 →19)-abeosteroid moiety resembles that of one subgroup of the terrestrial *Buxus* alkaloids, but the presence of an isoquinoline ring system at the other end of the molecule is without precedent among terrestrial alkaloids



Cortistatin A

9.1.41 Miscellaneous steroidal alkaloids (VX6790)

This heading covers a small number of marine steroidal alkaloids of novel type such as the **Plakinamines**.

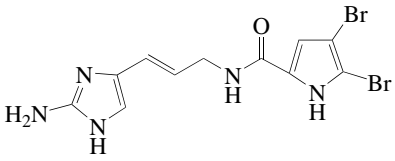
9.1.42 Pyrazole alkaloids (VX6900)

Pyrazole alkaloids are rare in general and there is only one marine example, **1-Methyl-1*H*-pyrazole-5-carboxylic acid**, from a gorgonian.

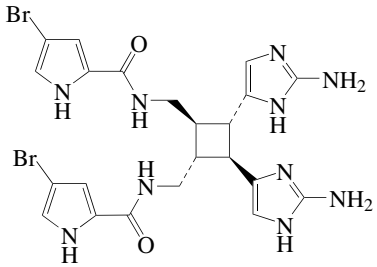
9.1.43 Imidazole alkaloids (VX6920)

This group, obviously derived from histidine, contains many structurally diverse marine examples, for example **Aplysinopsin** and related alkaloids, **Odiline** and the **Rhopaladins**. They show a range of biological activities and considerable pharmaceutical potential.

One of the most important subtypes is the pyrrole-imidazole alkaloids exemplified by **Oroidine** which with various relatives (e.g. the dimeric **Sceptrine**) appears to be a genuine sponge product. A recent biogenetically-based classification (see Hoffmann) recognises a class of nearly 100 pyrrole-imidazole alkaloids arising in various ways from this key intermediate and containing 0-4 further rings, additional to the pyrrole and imidazole rings already present. Future organisation of this database may recognise this category; at present, many of them are placed in the miscellaneous categories VX9000–VX9400.



Oroidine

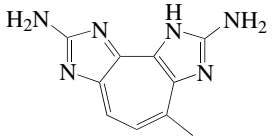


Sceptrine

Hoffmann, H. *et al, Synthesis*, 2003, 1753–1783 (*pyrrole-imidazole alkaloids*)
Jin, Z. *et al, Nat. Prod. Rep*., 2005, **22**, 196–229; 2006, **23**, 464–496 (*revs*)

9.1.44 Cycloheptadiimidazoles (Zoanthoxanthins) (VX6925)

These are a group of marine alkaloids which are condensed imidazoles closely related in structure, and which in this Dictionary are grouped under just two entries; those for **Pseudozoanthoxanthin A** and **Parazoanthoxanthin A**. Their biosynthesis does not appear to have been studied in detail but they are condensed imidazoles presumably derived from histidine.



Pseudozoanthoxanthin A
(one tautomer)

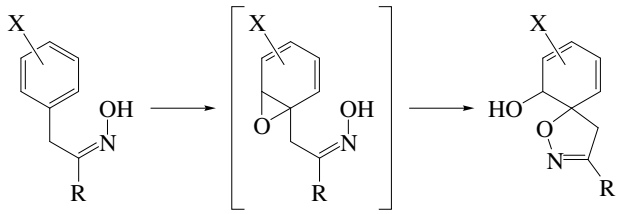
9.1.45 Oxazole and benzoxazole alkaloids (VX6930)

Numerous naturally occurring oxazoles are currently known, isolated from various marine (and terrestrial) sources – nudibranch egg masses (**Ulapualides**), algae and microorganisms. The marine and bacterial oxazoles appear to have been formed from peptides of aliphatic amino acids. Structurally they are diverse and may be open-chain (e.g. **Bengazoles**) or macrocyclic (e.g. **Patellamides**). Like the imidazoles, they show considerable drug potential.

Pattenden, G., *J. Heterocycl. Chem*., 1992, **29**, 607–618 (*rev, synth*)
Yeh, V.S.C., *Tetrahedron*, 2004, **60**, 11995–12042 (*rev, synth*)
Jin, Z. *et al, Nat. Prod. Rep*., 2005, **22**, 196–229; 2006, **23**, 464–496 (*revs*)

9.1.46 Spirobenzoxazoline alkaloids (VX6934)

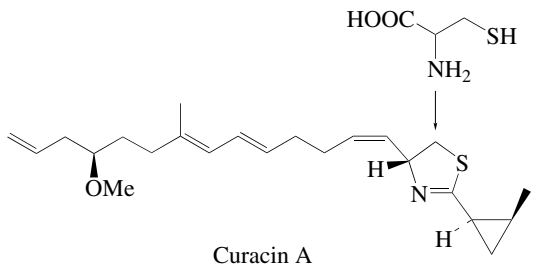
These exclusively marine alkaloids such as the **Psammaplysins** are derived by cyclisation of open-chain halogenated tyrosinoid oxime precursors (see VX2008 above). This is probably via the intermediary of an arene oxide, although attempts to replicate this chemically have given only low yields.



Okamoto, K.T. *et al*, *Tetrahedron Lett*., 1987, **28**, 4969–4972 (*biosynth*)

9.1.47 Thiazole alkaloids (VX6935, VX6937)

More than 100 naturally occurring compounds that incorporate the thiazole ring system have been isolated to date from marine organisms. These alkaloids are a heterogeneous group ranging in complexity from small molecules such as **Herbamide A** (isolated from a sponge) to open-chain or macrocyclic compounds such as the **Lyngbyapeptins**, **Dysidenin** and its relatives. These appear to be essentially microbial products, from cyanobacteria or other microorganisms, although some such as the **Patellamides** were actually isolated from tunicates. The **Latrunculins** (VX6936) are a subclass of mostly macrocyclic tetrahydrothiazoles isolated from sponges. Marine thiazoles show a range of interesting drug activities. The biosynthesis of the thiazole ring in the highly bioactive **Curacin A** has been shown to be from cysteine, with the rest of the carbon chain including the cyclopropane functionality acetate-derived.

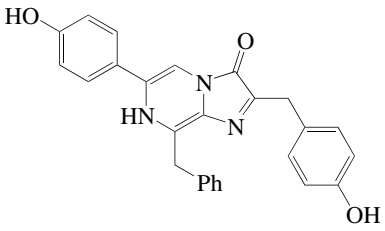


Curacin A

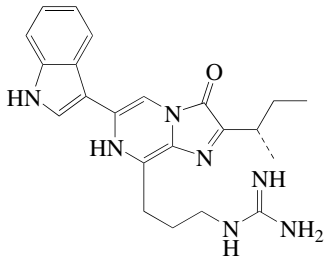
Pattenden, G., *J. Heterocycl. Chem*., 1992, **29**, 607–618 (*rev, synth*)
Jin, Z. *et al*, *Nat. Prod. Rep*., 2005, **22**, 196–229; 2006, **23**, 464–496 (*revs*)

9.1.48 Pyrazine and quinoxaline alkaloids (VX6940)

Pyrazines have been isolated from widely differing biological sources including marine organisms, where some of them are the actual light emitters in bioluminescence processes. Bioluminescence emitters are found scattered throughout different types of organism, which implies multiple independent origins during the course of evolution. The imidazopyrazine **Coelenterazine** and closely related compounds though account for the great majority of observed bioluminescence. There is evidence for Coelenterazine's *de novo* biosynthesis in shrimps. ***Cypridina*** **Luciferin** is biosynthesised from arginine and tryptophan.



Coelenterazine



Cypridina Luciferin

Rees, J.F. *et al, J. Exp. Biol*., 1998, **201**, 1211–1221 (*rev, bioluminescence*)

9.1.49 Morpholines (VX6955)

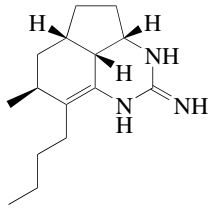
These are relatively few in number, e.g. **Chelonins A**, **B** and **C** and the **Oxazinines**.

9.1.50 Pyrimidines (VX6960)

Simple thymine-derived bases such as **Thyminol** are found in marine organisms together with some more highly elaborated substances such as the **Meridianins**.

9.1.51 Ptilocaulins (VX6970)

This group is based on the (partially hydrogenated) cyclopenta[*de*]quinazoline skeleton, which contains a pyrimidine nucleus. It comprises **Ptilocaulin** and relatives, the **Mirabilins** and a few other related alkaloids, mostly isolated from sponges, but which may be symbiont metabolites. It has been suggested that these arise by a late-stage addition of guanidine to a polyketide precursor.

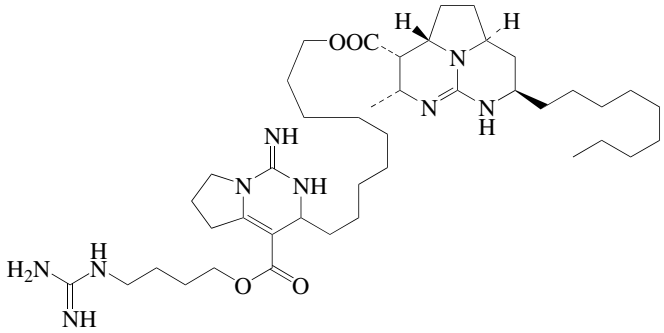


Ptilocaulin

Snider, B.B. *et al, J. Org. Chem*., 1993, **58**, 3828–3839 (*biosynth*)

9.1.52 Triazaacenaphthylene alkaloids (VX6980)

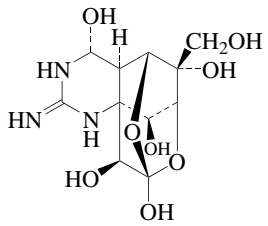
These are another group based on a tricyclic pyrimidine-related nucleus, and include the **Batzelladines** and the **Crambescidins** from sponges and echinoderms. Their biosynthesis does not appear to have been studied in detail, but they are formally composed of a guanidine unit, with which the biological activity is associated, embedded in a linear unbranched perimeter, presumably derived from a lipid precursor.



Batzelladine A

9.1.53 Tetrodotoxins (VX6990)

Tetrodotoxin and its homologues are well-known and important causes of human poisoning and are known principally from certain tissues of the Japanese puffer fish, but also found in other organisms and are thought to be *Pseudomonas* products. They have been extensively reviewed. The carbocycle ring in tetrodotoxins may be of isoprenoid origin.



Tetrodotoxin

Miyazawa, K. *et al, Toxin Rev*., 2001, **20**, 11–33 (*rev*)
Yotsu-Yamashita, M., *Toxin Rev*., 2001, **20**, 51–66 (*rev*)
Daly, J.W., *J. Nat. Prod*., 2004, **67**, 1211–1215 (*rev, occur*)

9.1.54 Phenazine and phenoxazine alkaloids (VX7000, VX7005)

A limited number of simple phenazines and phenoxazines have been reported from microorganisms, some of them from marine sources.

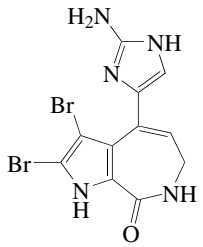
9.1.55 Pyrrole alkaloids (VX7010)

The pyrrole alkaloids are a heterogeneous group ranging in complexity from the very simple brominated pyrroles (e.g. **2,3-Dibromo-1*H*-pyrrole**) and peptides to the lipophilic **Malyngamides**, porphyrins and other tetrapyrrole pigments (see following section). Compounds that incorporate the pyrrole nucleus have been isolated from a variety of marine sources (sponges, microorganisms and algae). Further examples are the dimeric **Tambjamines** and a range of alkaloids in which halogenated pyrrole residues are linked to indolic and other heterocyclic nuclei, e.g. **Ageliferin** and its relatives. The pyrrole nucleus is of course a component of the indole alkaloids, but whereas these are tryptophan-derived, the polypyrroles are biosynthesised from 5-Amino-4-oxopentanoic acid (5-aminolaevulinic acid, ALA). Lower-MW alkaloids may arise from either route, or from proline/ornithine pathways via pyrrolidines (see above under VX0300); in the **Prodigiosins**, each of the three pyrrole residues is biosynthesised differently. The process of biohalogenation differs between Cl and Br. Chlorination takes place oxidatively by a combination of chloride ion, dioxygen and reduced FAD producing a Cl^+ equivalent, whilst bromination is mediated by vanadium bromoperoxidases.

Hoffmann, H. *et al, Synthesis*, 2003, 1753–1783 (*pyrrole-imidazole alkaloids*)
Walsh, C.T. *et al, Nat. Prod. Rep*., 2006, **23**, 517–531 (*rev, biosynth*)

9.1.56 **Pyrroloazepines** (VX7015)

These form a numerically limited but well-defined group consisting of **Hymenialdisine**, **Odiline** and related alkaloids, all with an additional imidazole ring system attached to a pyrrolo[2,3-*c*]azepine residue. Odiline (Stevensine) has been postulated to arise by cyclisation of the open-chain pyrrolic precursor Oroidine (see above).



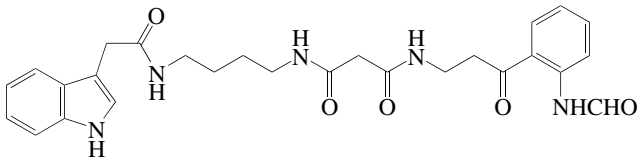
Odiline

Walsh, C.T. *et al*, *Nat. Prod. Rep*., 2006, **23**, 517–531 (*rev, biosynth*)

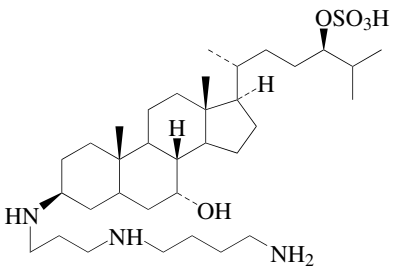
9.1.57 **Polyamine alkaloids** (VX7020, VX7030, VX7040, VX7050, VX7060, VX7070)

These categories cover the various types of alkaloid containing one or more -N$(CH_2)_n$N- groups, with *n* usually 3 or 4, less often 2 or 5. They show markedly different properties (reactivity, basicity, complexing ability, mass spectrometry) from monobasic amines. Alkaloids based on the ornithine-derived putrescine (*n*=4, classified as PA 4 alkaloids) are common in terrestrial plants but only a few have so far been characterised from marine organisms, such as the **Monodontamides** from gastropods. A number of alkaloids are derived from **Spermine** (PA 343) or **Spermidine**, (PA 34) themselves derived (in plants, certainly) from ornithine *via* putrescine, but again, the number currently characterised is much lower than those known from terrestrial organisms. See for example the **Penaramides** and the unusual medium-ring azaaliphatic **Motuporamines**. Classes PA 33, PA 35, PA 44 and PA 33433 have also been found in nature, but less frequently. The largest number is arachnid toxins, not marine alkaloids. In terrestrial plants it is well established that these alkaloids derive from decarboxylation and coupling of amino acids such as ornithine.

PA structures also occur in more complex alkaloids such as **Crambescidin 816** (PA 34 substructure) and as steroidal conjugates, in **Squalamine** and related compounds from fish livers (PA 34 and PA 343 substructures).



Monodontamide D



Squalamine

Bienz, S. *et al*, *Alkaloids* (N.Y.), 2002, **58**, 83–338 (*rev*)
Bienz, S., *Nat. Prod. Rep*., 2005, **22**, 647–658 (*rev*)

9.1.58 Peptide alkaloids (VX7100)

Several hundred peptide alkaloids are known, many macrocyclic, which by definition are composed of a number of amino acids, among which phenylalanine or tyrosine is frequently found. The boundaries between compounds classified under this heading and those classified under peptides (VV) or macrolide polyketides (VC) are vague and subjective, and these categories should also be scanned when browsing. They occur in both terrestrial and marine organisms, but most peptide alkaloids isolated from higher plants form a relatively homogenous group based on a medium-sized ring incorporating an *ansa*- aromatic ring. The marine peptide alkaloids are much more heterogenous, incorporating unusual, often halogenated, amino acid residues (e.g. the **Dysidenins**, **Geodiamolides**) and/or thiazole and oxazole rings, either open-chain or macrocyclic (**Dolastatins**, **Bistratamides**, **Lissoclinamides**, etc). The **Patellamides** are widely distributed in the tissues and are suspected to be of cyanobacterial origin, but this is by no means established. Peptides play an important role in invertebrate defence mechanisms.

Tincu, J.A. *et al, Antimicr. Agents Chemother*., 2004, **48**, 3645–3654 (*rev, biochem*)
Aneiros, A. *et al, J. Chromatog., B*., 2004, **803**, 41–53 (*rev, isol, pharmacol*)

9.1.59 Pyrrolo[2,3-*d*]pyrimidines (VX7200)

This is a numerically limited group consisting of the nucleosides **Tubercidin**, **Mycalisine B** and related bases and some simple halogenated pyrrolopyrimidines as well as the **Rigidins**. These appear to be microbial products. It has been shown that the pyrimidine ring is derived intact from a purine base precursor which undergoes ring opening and reformation with the incorporation of a C_2 fragment to form the pyrrole ring.

9.1.60 Purines (VX7300)

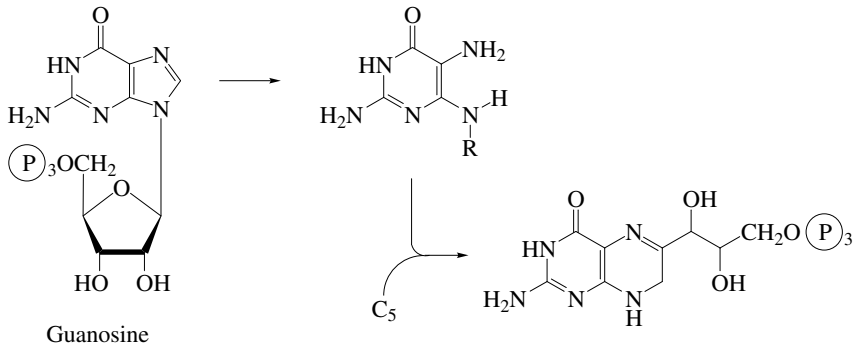
Purines are involved along with pyrimidines as bases in DNA and RNA. The well-known purine bases **Xanthine**, **Inosine**, **Theobromine** and **Theophylline** have been found in marine organisms along with substituted purines (e.g. **Phidolopin**) and terpenoid-purine alkaloid bases (**Agelines** and others).

Rosemeyer, H., *Chem. Biodiversity*, 2004, **1**, 361–401 (*rev*)

9.1.61 Pteridines and analogues (VX7350)

Pteridines are a widely distributed class of naturally occurring compounds. They owe their exceptional position in the field of heterocyclic chemistry mainly to their unusual chemical properties, their conspicuous fluorescence and their importance in metabolism. Pteridine bases were characterised as pigments originally from butterfly wings, but more recently from fish and other marine organisms (see **Isoxanthopterin**). Marine pteridines are also represented by **Leucettidine** and **Urochordamines**, and the pteridine nucleus is also present in the **Pseudoanchynazines**.

The biosynthesis of pteridines pigments has been well studied in terrestrial organisms; as in the case of the pyrrolopyrimidines above, the imidazole ring is derived unchanged from a purine precursor, in this case guanosine triphosphate, and the pyrazine ring is built by ring fission and incorporation of two carbons derived from a ribose fragment. The biosynthesis in marine organisms need not necessarily be the same.

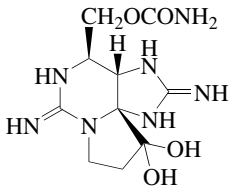


Guanosine triphosphate

Pfleiderer, W., *J. Heterocycl. Chem*., 1992, **29**, 583–605 (*rev*)

9.1.62 Saxitoxins (VX7400)

The saxitoxins are a group of over 30 highly important modified purinoid toxins known as Paralytic Shellfish Toxins or PSTs. Originally characterised as a cause of dangerous shellfish poisoning, they are now known definitely to be biosynthesised only by dinoflagellates (and some freshwater cyanobacteria), although it is possible that the red alga *Jania* does so also. Their presence in shellfish tissues probably results by diffusion according to a yet unknown mechanism. Their exact biosynthesis is not yet known but it appears from radiolabelling experiments that the two guanidine groups derive from arginine and the carbamoyl side-chain from methionine.



Saxitoxin

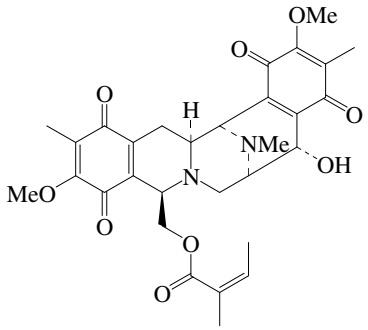
Garson, M.J., *Chem. Rev*., 1993, **93**, 1699–1733 (*rev, biosynth*)
Llewellyn, L.E., *Nat. Prod. Rep*., 2006, **23**, 200–222 (*rev*)

9.1.63 Naphthyridinomycins (VX7700)

These are a class of microbial products. Only a handful, so far, have been isolated from marine bacteria.

9.1.64 Saframycins (VX7800)

These are representative of the group known as the tetrahydroisoquinoline antitumour antibiotics (also including among terrestrial products some having slightly different skeletons, such as Lemonomycin). The saframycins themselves are microbial products produced by *Streptomyces* spp. of terrestrial origin. Close analogues such as the **Renieramycins** and the **Ecteinascidins** were isolated from marine organisms (sponges or tunicates) and are all presumably microbial products. The skeleton (studied for Saframycin A) is derived from two tyrosine molecules and the methyl groups from methionine.



Renieramycin A

Mikami, Y. *et al*, *J. Biol. Chem*., 1985, **260**, 344–348 (*biosynth*)

9.1.65 Miscellaneous alkaloids with 0-4+ rings (VX9000, VX9100, VX9200, VX9300, VX9400)

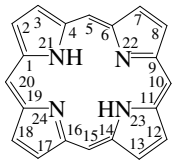
These categories are self-explanatory, and include some fairly well-defined structural groups where the small number of representatives currently known does not appear to justify the creation of individual categories at the present time.

10. POLYPYRROLES (VY)

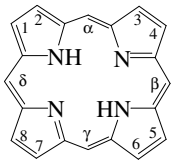
The polypyrroles (tetrapyrroles) are a numerically limited class of natural products that are mostly strictly functional. The main examples are haems, chlorophylls, bilins and Vitamin B_{12}. Only a few polypyrroles included under the miscellaneous category (VY0945) can be considered truly characteristic of marine organisms - the

chlorophylls for example are found in all types of photosynthetic organism, although there are important differences between the chlorophylls present in different phyla of marine plants. For a full description of the different polypyrrole types and their nomenclature and numbering, refer to the *Dictionary of Natural Products on DVD*. All types of organism use tetrapyrroles of one or more of these classes and all the functional tetrapyrroles derive from one common tetrapyrrolic intermediate, Uroporphyrinogen III (Uro'gen III). Uro'gen III is derived entirely from eight molecules of 5-Aminolaevulinic acid (ALA) by the action of three enzymes, *via* Porphobilinogen (PBG) and Hydroxymethylbilane (HMB) as intermediates. A particularly important feature in Uro'gen III is the fact that ring D has been inverted and so the acetate and propionate side-chains are not in the same order as on the other three pyrrolic rings, A to C. This feature can be found in virtually all naturally occurring tetrapyrroles.

The main system of nomenclature used in this Dictionary is that recommended by the IUPAC-IUB Joint Commission on Biochemical Nomenclature. For the cyclic tetrapyrroles this is based on the porphyrin with the carbon atoms numbered 1 to 20 and the nitrogen atoms numbered 21 to 24. This has superseded the older 'Fischer' numbering which numbered only the eight β-positions of the five-membered pyrrole rings and labelled the four bridging *meso*-carbons α, β, γ and δ.

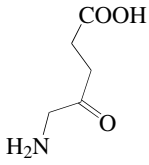


Porphyrin; IUPAC-IUB numbering

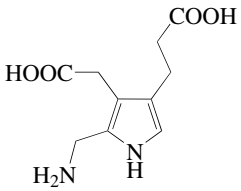


Porphyrin; Fischer numbering

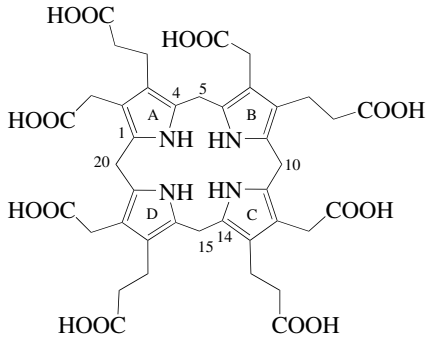
For natural porphyrins the IUPAC-IUB numbering starts on ring A and continues to rings B, C, and D, as shown below for Uro'gen III (ring D is always the inverted ring, see above). *Chemical Abstracts* on the other hand, though it uses the same 1 to 20 numbering for the carbon atoms, starts the numbering at such a position and in such a direction that the propionate side-chains get the lowest possible locants (thus for Uro'gen III the numbering would start at the position shown as 14 and proceed anticlockwise).



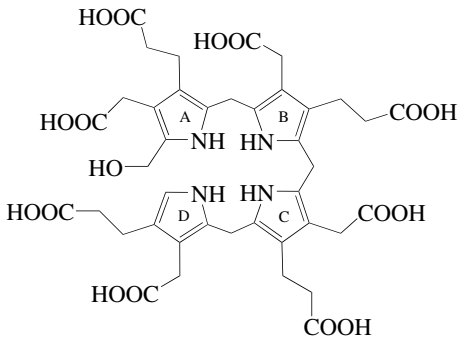
ALA



PBG



Uro'gen III



HMB

10.1.1 Porphyrins and porphyrinogens (VY0905)

The main biosynthetic pathway from Uro'gen III starts with the stepwise decarboxylation of each of the four acetate side-chains to give Coproporphyrinogen III, then oxidative decarboxylation of two of the propionate side-chains to give Protoporphyrinogen. These porphyrinogens and the partly decarboxylated intermediates are always isolated after aerial oxidation to give the corresponding porphyrin which is much more stable. Enzymic oxidation of Protoporphyrinogen gives **Protoporphyrin**, which is the branch point in the pathways to the haems and bilins and to the chlorophylls. Protoporphyrin has been isolated from the cnidarian *Atolla wyvillei*. Other porphyrins that can be found are mostly bacterial degradation products of Protoporphyrin with modification of the vinyl groups, e.g. **Haematoporphyrin**.

10.1.2 Bile pigments (bilins) (VY0915)

In animals the degradative pathway for haem is *via* an oxidative ring cleavage to give **Biliverdin** (Biliverdin IXα). This is then reduced to Bilirubin (10,23-dihydrobiliverdin) and excreted, as a bis-glucuronide ester, through the bile duct into the gut, where further reduction of double bonds by bacteria occurs. The same oxidative cleavage of haem can be affected non-enzymically by the coupled action of oxygen and a reducing agent such as ascorbic acid. In this reaction, cleavage can occur at any one of the four *meso* positions (*C*-5, 10, 15 and 20) and thus four isomeric Biliverdins (IXα, β, γ and δ) are produced.

In plants, the same oxidative cleavage of haem leads to the photoresponsive pigment Phytochromobilin and, in algae, to the light-harvesting pigments such as **Phycocyanobilin**. Both of these are found *in vivo* covalently attached to proteins by thioether links, and their presence or absence is an important taxonomic marker for different types of marine algae (see under the organism descriptions below).

10.1.3 Chlorophylls and derivatives (VY0920)

Insertion of Mg^{2+} is the start of the pathway that leads to the chlorophylls. A key intermediate in this pathway is **Protochlorophyllide**, in which the carbocyclic ring E, found in all chlorophylls and bacteriochlorophylls, has been formed in an oxidative cyclisation reaction. The chlorophyll c family, found in phytoplankton, have a porphyrin skeleton derived from Protochlorophyllide by insertion of a double bond into the propionate side-chain but the plant chlorophylls are all chlorins, having the *C*-17/18 double bond reduced in a photochemical, NADPH-dependent reduction of Protochlorophyllide giving **Chlorophyllide a**. Esterification with phytol gives **Chlorophyll a**.

10.1.4 Bacteriochlorophylls and derivatives (VY0925)

Photosynthetic bacteria rely on a slightly more diverse range of tetrapyrrole pigments. Purple photosynthetic bacteria contain **Bacteriochlorophyll a**, which is a bacteriochlorin, having two opposite pyrrole rings reduced. Green sulfur bacteria on the other hand contain Bacteriochlorophylls c, d and e, which are in fact chlorins, not bacteriochlorins, and are each a family of pigments with varying numbers of extra methyl groups introduced onto the *C*-8 and *C*-12 side-chains.

Bacteriochlorophylls also have a wider range of esterifying groups than do the chlorophylls. Thus, whereas Bacteriochlorophyll a usually has the normal phytyl ester, Bacteriochlorophylls c, d and e commonly have a farnesyl group. Geranylgeranyl and straight-chain hydrocarbon esters are also found in some organisms.

10.1.5 Miscellaneous polypyrroles (VY0945)

Although the majority of tetrapyrroles found in organisms are the ones described above, widely-distributed and having specific well understood catalytic functions, there are a few that are found in individual organisms and have more obscure or unusual functions. Some are present purely as pigments. Among the unusual functions are those of **Bonellin**, produced as a hormone by the females of the annelid worm *Bonella viridis* to determine the ender of the offspring. Other examples, such as **Corallistin A** from a sponge or **Chlorophyllone a** from various molluscs, do not have any recognised function.

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