

Structurally Similar Natural Products in Phylogenetically Distant Marine Organisms, and a Comparison with Terrestrial Species

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1 Background

Technologies that allow us to get direct information on the genome of living organisms have opened a new window through which to look at evolutionary relationships. What portion of the genome is examined depends on the scope of the investigation. Universal phylogenetic trees, such as the one displayed in Figure 1, encompass all organisms from bacteria to mammals and thus their construction requires examination of genes that, although intrinsically variable, are highly conserved. This is commonly achieved, from prokaryotes to diploblastic animal phyla, by comparing sequence similarities of genes encoding for rRNAs.^{1a} At the other extreme of the evolutionary time scale are problems of population structure and dynamics of morphospecies. Widely used in these fields of investigation are the polymorphic enzymes of primary metabolism, which can be analysed by electrophoresis, searching for diagnostic alleles between any pair of populations.²

What is the place of secondary metabolites in this context? The distribution among living organisms of a restricted variety of compound types, grouped together according to functions (e.g. pheromones, neurotransmitters, and hormones) has been frequently examined by biologists from the evolutionary viewpoint but these compounds have failed to prove of wide utility in constructing phylogenies. This is not surprising since secondary metabolites, though having their enzymes encoded in fundamentally the same way as primary metabolites,^{3a} are twofold limited in this respect. First, because they have typically restricted distribution among living organisms. Secondly, because they play adaptive roles and are thus subjected to variability in response to environmental selective pressure. It is just these properties that turn out to be useful, however, when short evolutionary distances are considered. Thus, comparative examination of the distribution of secondary metabolites may provide phylogenetic clues that would be difficult to obtain otherwise from groups of organisms which differ more in the selective expression of genes than in the genome.^{3b}

Secondary metabolites may also characterize higher level taxonomic categories such as families or orders, although the

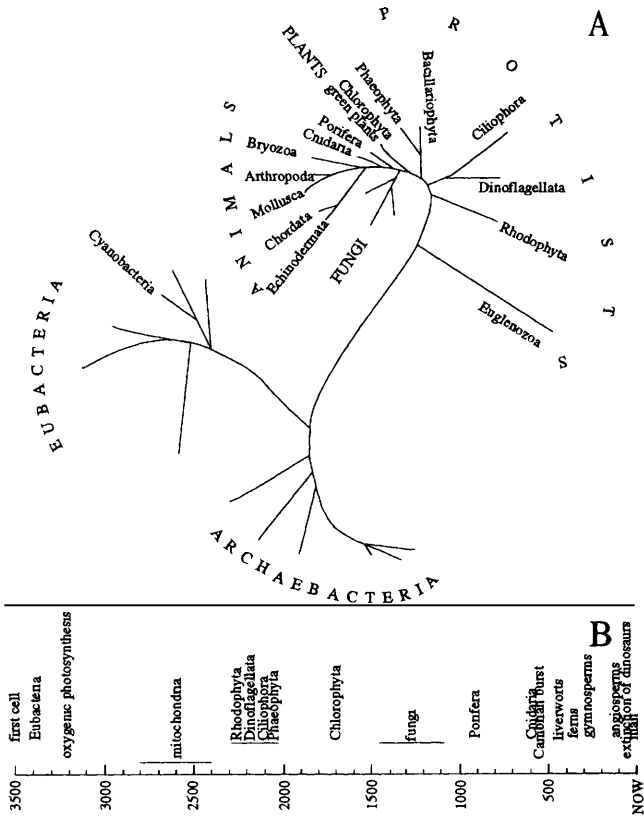
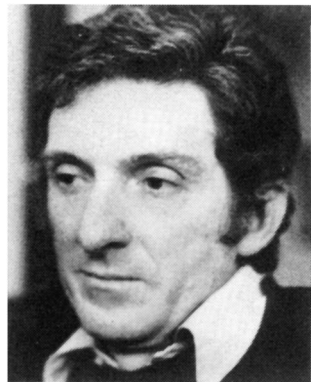


Figure 1 (A) Unrooted multikingdom tree where prokaryotic and organellar eukaryotic phylogenies, from bacteria to diploblastic animals, were inferred from small subunit (16S-like) rRNA sequence similarities.^{1a} For triploblastic animal phyla, classical phylogenetic inferences were used.^{1b} Only groups of organisms discussed in this paper are included. (B) Highly hypothetical geological scale for key events and radiation of the organisms. Dating is in millions of years before present.

Francesco Pietra was educated in chemistry at the University of Padova and, although uninvolved in the renowned lobbies of Italian university chemistry, has held research and teaching positions (in chronological order) at the Universities of Camerino, Padova, Perugia, Pisa, Catania, and Trento, where he is at present. He also



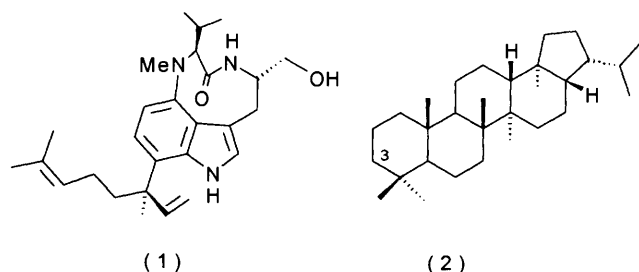
carried out research at the Gorlaeus Laboratories, Leiden (E. Havinga), and at Imperial College, London (D. H. R. Barton). Starting out as a physical organic chemist, he moved to classical organic chemistry, and then chose marine organic chemistry as his main theme, turning leisure diving to professional use in leading marine institutions throughout the world, where he has received informal education in marine biology.

norm is that phylogenetically distant organisms produce structurally unrelated secondary metabolites. This is particularly evident from a comparison of marine with land organisms, and reflects the scarcity (or total absence) of certain groups of marine organisms on land, apart from different lifestyles. However, when a large range of structural types – and not only structures related to certain biological functions – is considered, identical secondary metabolites may exceptionally be found in phylogenetically distant organisms, even when any metabolite exchange among them is prevented. Examples of such a break in the normal distribution of secondary metabolites appear from time to time in the literature in marginal notes where the cause is sought in the diet, symbionts, chemical propensity towards certain structural types, if not chance. While in some cases these explanations may be true, I attach a deeper significance to such abnormal distribution of secondary metabolites, although our present understanding of the enzymology of the secondary metabolism drastically limits attempts at a comprehensive rationalization. Since, however, any broad assessment of this area of enzymology lies far in the future, even a mere documen-

tation of facts should have heuristic value. I have gone even further, however, by drawing conclusions, albeit well aware that some of them will be heavily modified, or even disproven, by future research. Let me thus start with the most ancient organisms.

2 Bacteria

Bacteria have successfully penetrated all eukaryotic organisms. As such they may be involved in the production of metabolites that either accumulate in the host or enter the host's secondary metabolic pathways.^{4a} The former is probably the case for the well known neurotoxic alkaloids tetrodotoxin and saxitoxin, found not only in pure (axenic) cultures of marine bacteria but also in various marine and terrestrial eukaryotes.^{4b} But the presence of the tumour promoter lyngbyatoxin A (1) in a marine cyanobacterium and a land actinobacterium^{4c} is likely to reflect phyletic lineage, *i.e.* the occurrence of a common ancestor. In contrast, views on diketopiperazines are changing: formerly thought to be exclusive bacterial products released to the sponges, these peptides are now recognized to be widely distributed among living organisms.



Derivatives of hopane (2) – hopanes and geohopanes – are the most abundant elaborated biogenic compounds in sediments. They are produced from squalene by ferns and, as sterol substitutes, by freshwater ciliates.⁵ Genes for hopanes date, however, from the eubacteria, although most of the bacterial hopanes also bear a D-pentose chain at the isopropyl group.⁵ The open genome of the bacteria might have allowed horizontal transfer of gene blocks to protists through either a plasmid or a virus in a process of natural genetic engineering. Only marine bacteria from standard collections have been examined for hopane production however;⁵ typical wild strains are scarce biomass producers. Thus, if extant marine bacteria are representative of their ancestors, I believe that the hopanes present in huge amounts in sediments⁵ derive more from protists than from bacteria. Anyway, production of 3-hydroxyhopanes required squalene 2,3-epoxide as an intermediate and must have started as late as with the radiation of the angiosperms (see Figure 1).

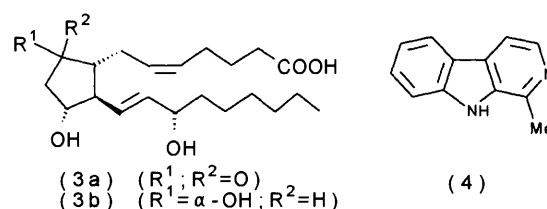
At this primitive stage of the studies we are thus left with only a handful of secondary metabolites from marine bacteria that may also be synthesized *de novo* by other organisms. This suggests that, in contributing to the construction of metabolic machineries, marine bacteria are responsible more for cytoplasmic growth than for secondary metabolism of the eukaryotes. The biosynthesis of isoprenoid building blocks by bacteria along routes different from those used by eukaryotes⁵ is in line with these conclusions.

3 Euglenozoa and Dinoflagellata (Euglenids and Dinoflagellates)

The euglenids are the most primitive eukaryotes (Figure 1) for which problems of structural relatedness of secondary metabolites with other organisms arise: they biosynthesize 4-methylsterols like certain methane-oxidizing bacteria and the dinoflagellates.^{1b} This may be considered as an evolutionary transition from the primitive synthesis of triterpenes by early bacteria to that of typical sterols by later eukaryotes.

That physiologically active PGE₂ (3a) and PGF_{2a} (3b) are also of old design is revealed by their presence in both euglenids and red algae, accompanied by their biosynthetic precursor, arachidonic acid, which also occurs in dinoflagellates.^{6a} While it is established that prostaglandins are formed in mammals *via* a cyclooxygenase route, it has been proposed that in octocorals (and presumably also in euglenids and red algae) an 8-lipoxygenase route is followed instead,^{6a} although this has been recently challenged.^{6b} This contrast, if genuine recalls several examples of primitive protists where similar biochemical steps are catalysed by non-homologous enzymes, suggesting lateral transfer, if not endosymbiotic events, which have brought in new sets of genes in one step⁷ rather than by an accumulation of mutations.

The dinoflagellates also produce harman (4), a simple β -carboline alkaloid,^{6c} as do bryozoans and terrestrial angiosperms.

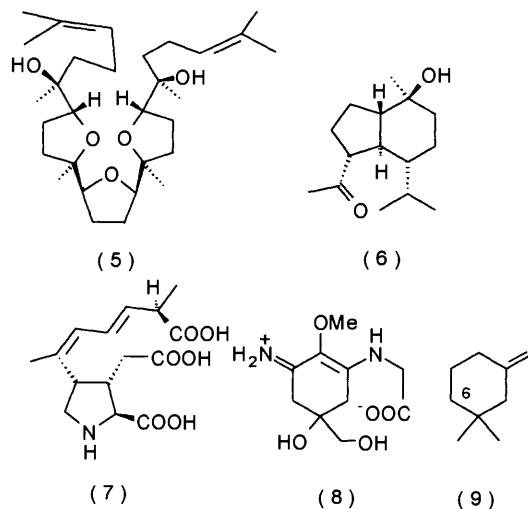


4 Rhodophyta (Red Algae)

Teurilene (5), a cytotoxic oxidized squalene derivative, has been found in both the red seaweed *Laurencia obtusa* of Teuri Island and in a land angiosperm.^{8a} The cases of a larvae-settling factor, the simple quinol jacaranone, and the sesquiterpene *ent*-oplopanone (6) are similar, although marine and terrestrial oplopanone are enantiomeric. The hypothesis of horizontal transfer would account for the fact that each of these seaweeds is atypical of its division, each one resembling instead an angiosperm. But the different lifestyles of seaweeds and land plants are an obstacle to this conclusion. Lateral transfer can be more plainly accepted for the production of domoic acid (7) by a red seaweed and a marine diatom.^{4b}

Transfer of the whole genome in an endosymbiotic event has been suggested to rationalize production of phycoerythrobili-proteins by both cyanobacteria and red algae. This position is today widely accepted.^{1b}

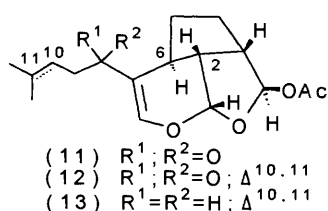
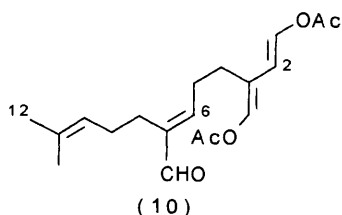
Palythine (8) functions as a UV filter for marine invertebrates and seaweeds, protecting them from the strong solar radiation of the tropics. Adaptively, production of this amino acid is elicited by light. Close structural analogues of palythine occur in land fungi, from which the class name of mycosporines was derived for these substances.



The driving force of chemical propensity towards strain-free, stabilized structures may also be responsible for production of similar compounds in phylogenetically distant organisms. This might be the case for six-membered carbocyclics like ochtodenones (9), which occur as such in insects or, in C-6 brominated form, in red seaweeds, apparently from geraniol as precursor, triggered by H^+ in insects or Br^+ in seaweeds. The low specificity of these cyclases,^{3a} which accept large variations in substrate structure, may have favoured such events. The presence of jasmonates in both red algae and terrestrial plants may be similarly rationalized in view of the facile autoxidation of polyunsaturated fatty acids to give prostanoid-like compounds.

5 Ciliophora (Ciliates)

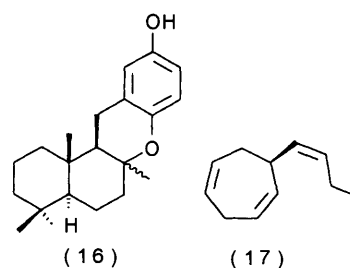
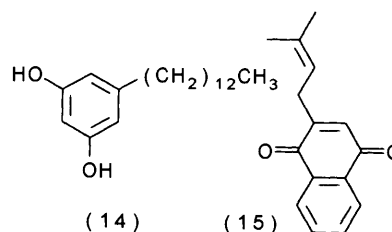
Seaweeds in the families Caulerpaceae and Udoteaceae, some of the latter of which contribute to the structure of coral reefs, were thought until recently to be unique producers of 1,4-diacetoxybutadiene-bearing sesqui- and diterpenes. That these compounds cannot be taken as taxonomic markers of these algae, however, became clear with the discovery that marine ciliates of the genus *Euplotes* produce compounds of the same class, like preuplotin (10), which is the C-12 deprenyl analogue of udoteal, a diterpenoid isolated from tropical seaweeds of the genus *Udotea*.⁹ Moreover, euplotin A (11), B (12), and C (13), which are also produced by these ciliates, likely through (10), are structurally analogous to 2,6-*cis*-cyclized products isolated from *Udotea* spp.⁹



The ciliates radiated before the green algae (Figure 1) and could thus have furnished genes for these terpenoids, *via* lateral transfer, to an ancient member of these seaweeds. In this hypothesis it must be admitted that the terpenoid cyclases of green algae have lost the ability of ciliate enzymes to 2,6-*trans*-cyclize a farnesyl-type precursor. Thus, these terpenoids have evolved from adjuvant factors of the radiation of ciliates, exploiting in cell-to-cell contacts the quick response of the highly strained 2,6-*trans*-cyclized unit, to less strained, 2,6-*cis*-cyclized agents which less hurriedly develop their distasteful properties in the grazing apparatus of herbivorous predators.⁹ Both strategies anyway fulfil the economy of avoiding the release of bioactive compounds into the environment.

6 Phaeophyta (Brown Algae)

Brown algae, particularly in the order Fucales, are rich in phenolic compounds, often of mixed biogenesis, which also occur in other organisms. Thus, grevillol (14) also occurs in a haplosclerid sponge, land angiosperms, and the more primitive ginkgos as a vesicant principle,¹⁰ the cytotoxic deoxylapachol (15) also in land angiosperms, and (+)-chromazonarol (16) also in a dictyoceratid sponge, albeit in enantiomeric form.



Several cosmopolitan brown seaweeds produce ectocarpene (17) as a lure for conspecific male gametes. The biosynthesis involves a 9-lipoxygenase on icosapentaenoic acid, followed presumptively by, a hydroperoxide lyase.¹¹ Ectocarpene is also produced on land by the composite *Senecio isatideus* for no known purpose, and the biosynthesis follows a different route involving unsaturated C_{12} fatty acids, while icosanoids are refused.¹¹ *S. isatideus*, lacking arachidonic acid,¹¹ could not have used a 9-lipoxygenase. This may be explained as above for the proposed biosynthesis of prostaglandins along different pathways in octocorals and mammals.

Bioactive terpenoids of the prenylated guaiane, dolabellane, and xenicane classes commonly occur both in brown seaweeds of the order Dictyotales and in alcyonarian corals.¹² Fusicocanes have been found both in these seaweeds and terrestrial phytopathogenic fungi, while dolabellanes also occur in liverworts. However, since these structural similarities are restricted to the skeletal type, which can only have a few varieties, these distributions probably merely reflect chemical bias in organisms where terpenoid cyclases are very active.

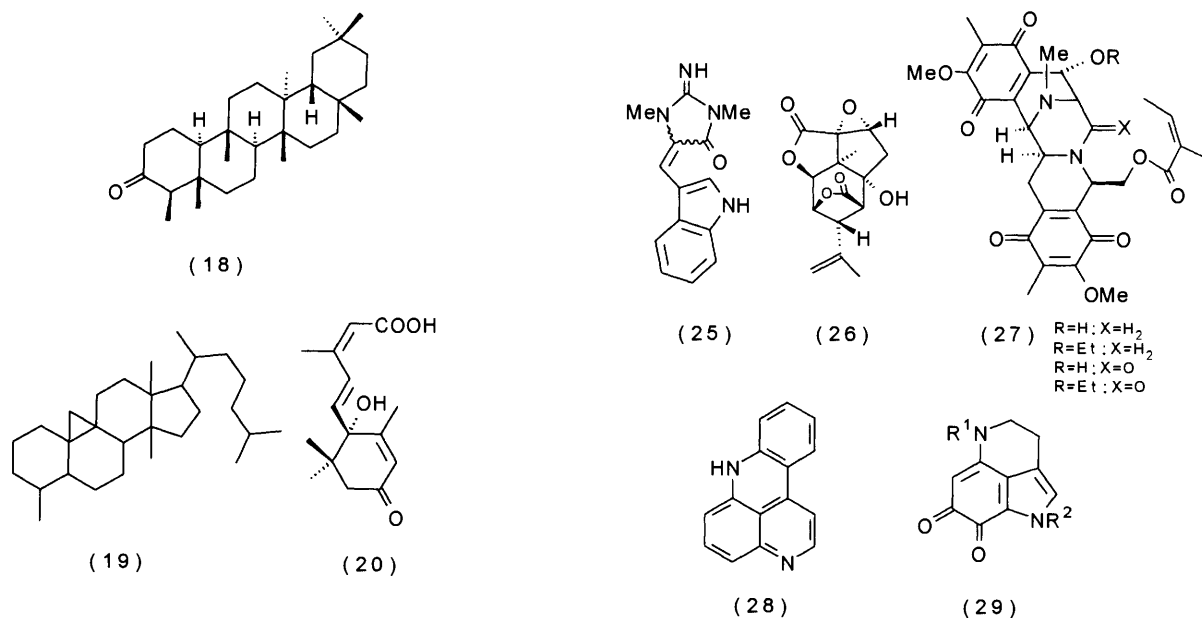
7 Chlorophyta (Green Algae)

Both 16S-like rRNA sequence similarities (Figure 1) and classical evolutionary evidence suggest that green plants are descended phyletically from green algae. This is reflected in the similarity of secondary metabolites in these two groups of organisms. Thus, the triterpenoids friedelin (18),^{13a} taraxerol, and 31-norcycloartanes (19) occur in both green seaweeds and land angiosperms, and the last named compound also in ferns. Moreover, the evolutionary transition from the green algae to the green plants is suggested by the presence of a flavonoid (a taxonomic marker for the angiosperms) in a brackish-water member of the stoneworts^{13b} whose biological characters are intermediate between the green algae and the green plants.

But the case of abscisic acid (20), a regulatory agent of humidity loss through the stomata in land angiosperms, is curious indeed: this metabolite also occurs in freshwater green algae and perhaps in brown seaweeds,^{13c} although the algae lack stomata.

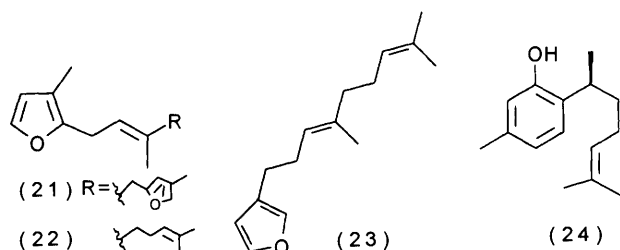
8 Fungi

Marine fungi are often encountered which give the same secondary metabolites as terrestrial fungi, such as the aromatic, cytotoxic siccayne,^{14a} the diketopiperazine alkaloid gliovictin,^{14b} and the phenolic lactone ochracin.^{14c} This may often – though not always – result from the fungi examined being marine-adapted rather than truly marine fungi. Anyway, synthesis of hydroxyproline and chitin is carried out by both fungi and animals, in line with rRNA-inferred lineage.^{1a}



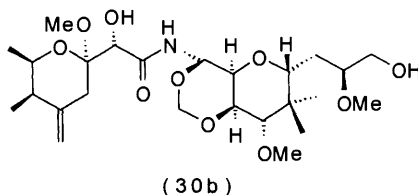
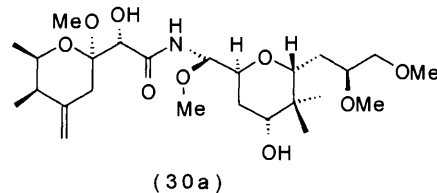
9 Porifera (Sponges)

Demosponges often contain the same terpenoids as are found in phylogenetically distant organisms. Thus, longifolin (21), sesquiosfuran (22), and dendrolasin (23) commonly occur in both dictyoceratid sponges and in land angiosperms, and (23) also occurs in an ant.¹⁵ Dextrorotatory curcuphenol (24), which is a H,K-ATPase inhibitor, occurs in poecilosclerid sponges and as the antipode in gorgonian corals. Furanic and aromatic sesquiterpenes, in particular bisabolanes, are common in sponges, gorgonians, and angiosperms. Other, same-skeleton terpenoids found in both sponges and land angiosperms include β -gorgonenes, penlanfurans, luffalactones, atisanes, and bifloranes, the last mentioned occurring also in insects, while cyathanes have been found in both sponges and land fungi.



Certain alkaloids and amino acid derivatives occur in sponges and other organisms as well. Apart from the ubiquitous neuroactive serotonin, cytotoxic aplysinopsin (25) was found in dictyoceratid and choristid sponges, as well as in dendrophylliid scleractinian corals.^{16a} Picrotoxinin (26), the active principle of terrestrial angiosperms used in India as a fish poison, also occurs in the haplosclerid sponge *Spirastrella inconstans*.^{16b} Same-skeleton alkaloids found in sponges and other organisms comprise: the renieramycins (27) (which are found in haplosclerid sponges, sea anemones, and in ascidians and are closely related to the saframycins of terrestrial actinobacteria); the (28)-type pyridoacridines (in petrosiid, haplosclerid, and choristid sponges and ascidians, biosynthesized, at least in the latter, from tryptophan, dopa, and cysteinic precursors^{16b}); and the batzellines (29) (in poecilosclerid sponges, toadstools, and toads). The comment (Section 6) regarding chemical bias in terpenoids of the brown algae may be extended to these terpenoids and alkaloids also.

But a case apart is that of pederin (30a), isolated from the blister beetle (*Paederus fuscipes*), and the structurally quite similar antiviral and antitumoral mycalamide B (30b) and

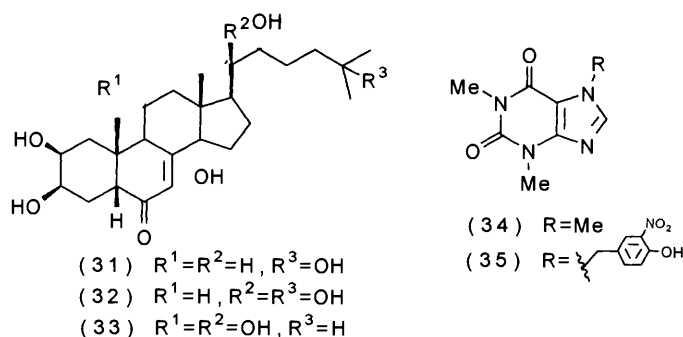


onnamide A, isolated from two phylogenetically unrelated marine sponges.¹⁷ It is attractive to imagine that genes for these impressively similar, stereochemically complex compounds were first expressed in demosponges during the Cambrian burst and then this metabolic capability was conveyed by lateral transfer to another organism.

10 Cnidaria (Coelenterates)

Ecdysone (31) and the crustacean and insect molting hormone 20-hydroxyecdysone (32), as well as the phytoecdysteroid ajugasterone C (33) and exclusive ecdysteroids,^{18a} were found in the erect zoanthid coral *Gerardia savaglia*. The large accumulation of these substances in the coral rules out any hormonal role for them and suggests instead a protective role.^{18a} This finding lay dormant (although we had provided evidence against any dietary source of these ecdysteroids as a unique example in non-moulting animals) until recently when ecdysteroids were found in large amounts in flat zoanthids,^{18b} which are far more common than erect zoanthids like *G. savaglia*. This suggests that ecdysteroids are characteristic of zoanthids as an order and that they mark the start (Figure 1) of genes, or gene expression, for these special steroids. This seems to constitute a further case of evolution of functions for secondary metabolites, from protective agents in zoanthids to hormones in crustaceans and insects.

The case of xanthine alkaloids is another area of overlap. Thus, caffeine (34), the active principle of *Coffea* and other land



angiosperms, was also found in a Mediterranean gorgonian,^{19a} and a close analogue, phidolopin (35), in a marine bryozoan.^{19b}

But the most impressive of all series of structurally identical secondary metabolites was encountered with terpenoids from anthozoans and land gymnosperms and angiosperms.²⁰ A selected series comprises linderazulene (36), guaiazulene (37), (+)-ledol (38), (–)-germacrene A (39), thunbergol (40), smilagenin (42) and glycyrrhetic acid (43), while (–)-cembrene A (41) and (38) also occur in insects. Moreover, many sesquiterpenoids from anthozoans, such as α -cubebene, β -copaene, palustrol, viridiflorol, γ -maaliene, α -muurolene, and 1(10)-aristolene, are antipodal to those found in land angiosperms. Other sesquiterpenoids from anthozoans, like α -curcumene, α -copaene, 9-aristolene, β -bisabolene, and δ -cadinene, occur as both enantiomers in land angiosperms.

Many same-skeleton terpenoids have also been found in both anthozoans and terrestrial plants, viz sterpurane, paciforgiane, nardosinane, spirobicyclo[5.4]decane, and lepidozene sesquiterpenoids as well as cubitane and serrulatane diterpenoids.

The origin of these terpenoids in cnidarians is poorly known although motile forms of symbiotic zooxanthellae proved unproductive, it has long been suggested that symbiotic zooxanthellae furnish terpenoids to their cnidarian host.^{21a} Actually, what is going on in associations with these aspecific, genetically-undifferentiated^{21b} symbionts is only fragmentarily known. Similar difficulties are met anytime that symbiosis is involved, as

the integrated biont forms a new whole, the holobiont, where the secondary metabolic pathways of the partners may merge to a large extent. In any event, that of anthozoans is a world of terpenoid enzymes, which allies them to terrestrial green plants and some insects. The metabolic cost of biosynthesizing terpenoids is as high as for the fatty acids, which implies a strict need of terpenoids by anthozoans, terrestrial plants, and insects.

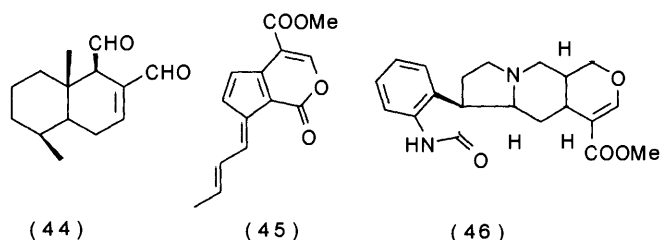
11 Bryozoa (Moss Animals)

Geraniol, nerol, citronellol, and *cis*- and *trans*-citral, which constitute a pheromonal mixture in land insects, occur also (but for no known purpose) in marine bryozoans.²² Likewise, physostigmine alkaloids, which are poisons of seeds of the Calabar bean, have also been found in terrestrial fungi of the genus *Penicillium*, in a bromine-containing hemiprenylated form in the bryozoan *Flustra foliacea*, and, bearing a pteridine derivative, in sea squirts (ascidians).

12 Mollusca

Polygodial (44), a long-known antifeedant metabolite of land angiosperms, has been recently found, stored in a protected form, in dendrodid sea slugs. Unusually for secondary metabolites from opisthobranchs, polygodial results from *de novo* synthesis.^{23a}

Also remarkable is the occurrence of the terrestrial plant metabolites fulvoplumierin (45) and isopteropodine (46) in the archeogastropod *Nerita albicilla*.^{23b} Because of the different lifestyles of terrestrial plants and marine molluscs, the suggestion of dietary uptake of these metabolites by the mollusc^{23b} is difficult to accept.

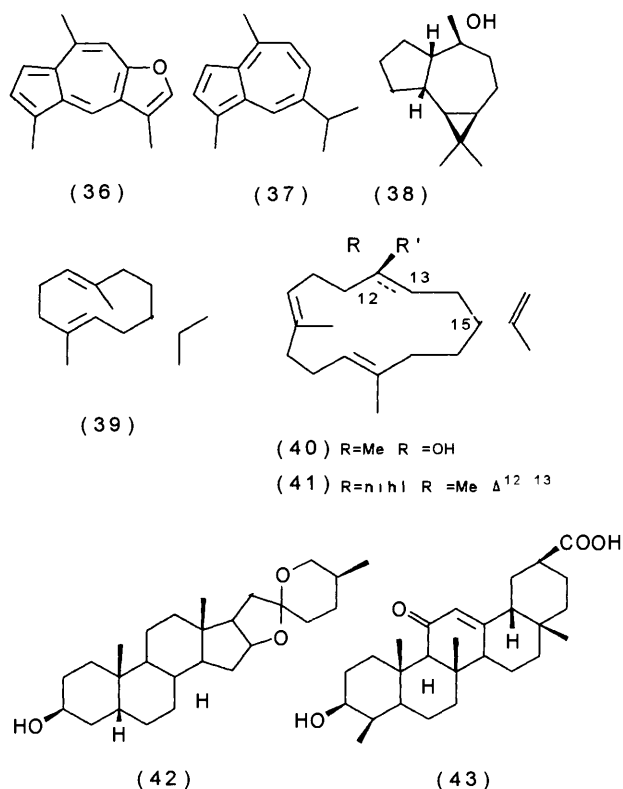


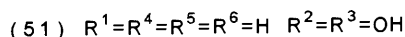
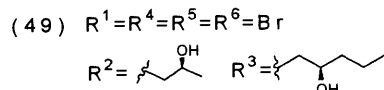
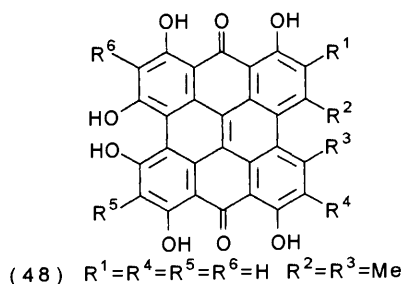
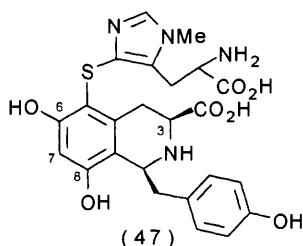
But the most famous case of secondary metabolite identity in molluscs and terrestrial organisms is that of indigo. This compound occurs as a glucoside in terrestrial plants from the East in the genera *Indigofera*, *Isatis*, *Marsdenia*, and *Polygonum* and, accompanied by 6,6'-dibromoindigo, also in the prosobranch snail *Murex trunculus*, as the components of Tyrian purple, a dye which was at the basis of the first chemical industry in the city of Tyre as early as 1600 years BC.

13 Echinodermata (Starfish, Sea Urchins, Sea Cucumbers, and Crinoids)

Recently the benzyltetrahydroisoquinoline alkaloid imbricatine (47) has been found in the starfish *Dermasterias imbricata*.²⁴ However, (47) has little to do with the taxonomic markers of the angiosperms: the biogenesis of benzyltetrahydroisoquinoline alkaloids must follow different routes in starfish and plants. In fact, imbricatine bears hydroxyl groups at C-6 and C-8 and has D-configuration at C-3, suggesting biogenesis from D-3-(3,5-dihydroxyphenyl)alanine, while plant 1-benzyltetrahydroisoquinoline alkaloids, deriving from L-dopa, are hydroxylated at C-6 and C-7 and have L-configuration at C-3.

Phenanthroperylenequinones have wide distribution. Thus, hypericin (48) was found in St John's wort, gymnochrome A (49), in the 'living fossil' crinoid *Gymnocrinus richeri*,^{25a} and stentorin (50) exerts photoreceptor functions in the freshwater ciliate *Stentor coeruleus*.^{25b} The extraordinary stability of this highly conserved structural unit is attested by the isolation of





fringelite D (51) from the fossil crinoid *Apiochrinus* sp from Jurassic sediments^{25c}

Genes of the sea urchin *Strongylocentrotus purpuratus* encode a protein that is homologous to the epidermal growth factor of land insects and mammals,^{26a} suggesting that the epidermal-growth-factor peptide domain dates back at least to the protostomes, before radiation of the deuterostomes^{26a} On this basis, these genes are expected to occur widely in metazoans

S. purpuratus also possesses cannabinoid receptors remarkably similar to those of mammalian brain and non-neural tissues This indicates that cannabinoid binding properties have been highly conserved during evolution^{26b}

14 Fish

The pardaxins, small peptides of 33 amino acid residues, are found in soles of the genus *Parolachurus* from both the Red Sea and the Ryukyu Archipelago, where they exert shark-repelling properties In structure these peptides resemble melittin, the toxic principle of the honeybee²⁷ Thus, similar peptides, implying similar genes that derive from primordial ancestors, have acquired different functions during the course of evolution This recalls the evolution of the functions of insulin, which arose in insects, and of prostaglandins and other eicosanoids, which arose in euglenids, and then became mammalian hormones Evolution of pathways has already been discussed for the proposed lipoxygenase route in octocorals *versus* an endoperoxide route in mammals to prostaglandins These examples, and that above of ecdysteroids, suggest that evolution of secondary metabolites has to be seen in parallel with that of their receptors Lack of strict specificity by these receptors conforms to their need of interacting with families of compounds, as secondary metabolites usually occur

15 Concluding Remarks

There are three main messages from this comparative perusal of marine secondary metabolites The first is that the highest

frequency of secondary-metabolite structural similarities occurs for terpenoids from anthozoans *versus* those from land plants This suggests that the major diversification of the terpenoid enzymes occurred in parallel with the radiation of the invertebrates during the bare 5–10 million years of the Cambrian burst²⁸ Ancestral anthozoans were already there (Figure 1) and took the opportunity of making much of what terpene chemistry allows This capability was later conveyed to the plants by lateral transfer

The second message concerns the evolution of the functions for secondary metabolites, such as from defensive agents to hormones While the latter serve in only trace amounts, so as to be rapidly switchable on and off, defensive compounds are needed in massive amounts No wonder therefore that different biosynthetic routes were selected for the two classes of agents Perhaps it may be a general consequence of the different organization of phylogenetically distant organisms that in biosynthesizing identical secondary metabolites phylogenetically close organisms use the same pathways, while phylogenetically distant organisms use different pathways

The last message concerns the scarce contribution of marine bacteria to genetic information for secondary metabolites in eukaryotes This fits the slowness of phenotypic evolution before the Cambrian period but is in contrast with the emphasis that horizontal transfer²⁹ and endosymbiotic events^{1b,7} are currently receiving Clarification is awaited from progress in the studies of marine bacteria

This general pattern of distribution of secondary metabolites in marine organisms is unlikely to change drastically in the future since, judging from current reports, the explosion of discoveries of new structural types of marine natural products is already away It lasted only a few millionths of the time that nature, in the Cambrian burst, took to invent the bulk of the structural diversities It is sad that this bright period is over, but other challenges emerge, such as understanding how things happened and exploiting the new molecular architectures that have been found Though less open to the enchantment of serendipity, an even brighter period may be foreseen

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