MARINE NATURAL PRODUCTS : CHEMICAL CONSTITUENTS FROM NEW CALEDONIAN DEEP-WATER SPECIES

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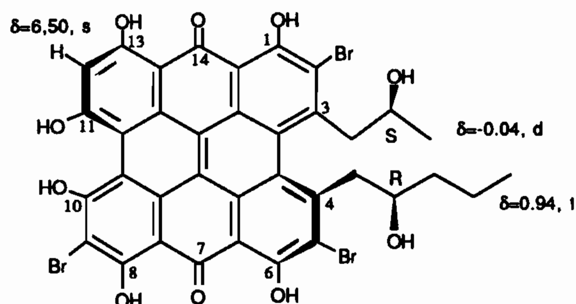
Résumé *: lors de cette conférence, nous présentons les résultats les plus récents obtenus en collaboration avec l'ORSTOM et le CNRS, dans le cadre du programme SMIB; en particulier quelques aspects de la chimie de quatre organismes marins récoltés au large de la Nouvelle Calédonie sont discutés :* Gymnocrinus richeri, *un crinoïde fossile vivant découvert par Bertrand Richer de Forges à 520m de profondeur ; l'étoile de mer* Tremaster novaecaledoniae, *aussi un fossile vivant, récolté à 530m ; deux éponges profondes,* Erylus *sp. and* Jereicopsis graphidiophora, *cette dernière étant d'un nouveau genre découvert par Claude Lévi du Museum National d'Histoire Naturelle de Paris.*

Abstract *: in this paper we present the more recent results obtained in collaboration with ORSTOM and CNRS in the frame of the programme SMIB. In particular some aspects of the chemistry of four marine organisms collected off New Caledonia :* Gymnocrinus richeri, *a living fossil crinoid discovered by Bertrand Richer de Forges at 520 m depth ; the starfish* Tremaster novaecaledoniae, *a living fossil species too, collected at 530 m depth ; and two deep water sponges,* Erylus *sp. and* Jereicopsis graphidiophora, *this latter a new genus discovered by Claude Lévi of the Museum National d'Histoire Naturelle de Paris, are discussed.*

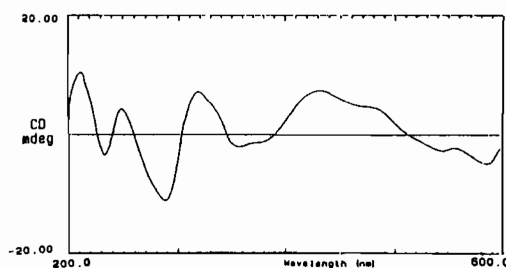
In the first part of the paper I will discuss on the gymnochromes, novel brominated quinonoid pigments from ***Gymnocrinus richeri*** (1) which is one of the best examples to which is appropriate to apply the concept of "living fossil" (2). *In vivo*, this crinoid is saffron yellow with the stalk darker and the tentacles dark yellow-green inside. A few minutes after collecting, outside the water, it turns readily dark green.

Extraction with methanol gave a dark green solution, which on very mild acidification turned violet. The violet pigments were isolated by chromatography on a column of Sephadex LH-20.

The major pigment **gymnochrome B 1** (Fig. 1) showed and IR carbonyl stretching band at low frequency (ν_{max} 1634 cm^{-1}) characteristic of hydrogen bonded quinones and UV-visible (MeOH) maxima very close to those of hypericin and related phenanthroperylenequinones. In basic media (NH_3) the pigment is converted into a bright green one with UV-visible maxima characteristic of chelated extended quinones. The FAB mass spectrum gives a quartet between m/z 853 and 859 suggestive of three bromine atoms. The 500 MHz ^1H NMR spectrum and decoupling experiments identified two separate spin systems ascribed to 2-hydroxypropyl and 2-hydroxypentyl side chains. The remaining signal in the spectrum is an aromatic upfield shifted singlet at δ 6.50 indicating an aromatic proton between two phenolic groups. in addition to the signals for the side chains, the ^{13}C NMR spectrum contains a lowfield CH signal at 106.9 ppm and further twenty seven lowfield quaternary carbon atom signals, with chemical shifts in agreement with an hexahydroxy phenanthroperylenequinone system. Overlap of the substituents of C-3/C-4 and C-10/C-11



1 Gymnochrome B



CD spectrum

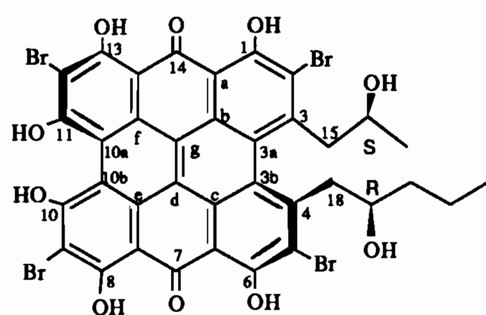
UV : λmax (CH_3OH) = 216(ε=48000),233(51500),295 (32000), 329(27200), 485(13800), 553(19800), 596(39300) nm

IR : νmax (KBr) = 1630 cm^{-1} (C=O).

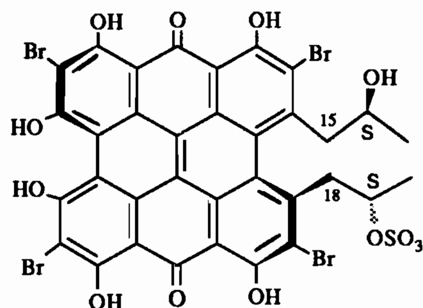
FAB MS (-ve ion), m/z = 853, 855, 857, 859 $[M-H]^-$

^{13}**C NMR : side chains** = 48.4, 68.4, 21.4, 48.1, 73.0, 41.3, 19.9, 14.3., **aromatics** =C-H : 106.9; C-Br: 103.4, 116.1; 116.2; -OH: 160.4 (x2)165.8, 169.4, 171.0, 172.0, C-CH_2-: 143.9, 145.9, C=O: 184.7, 186.4 ; others: 103.2, 104.6, 110.9, 111.0, 119.7, 118.7, 122.7, 122.9, 123.5, 123.7, 126.5, 127.0, 127.0, 128.6

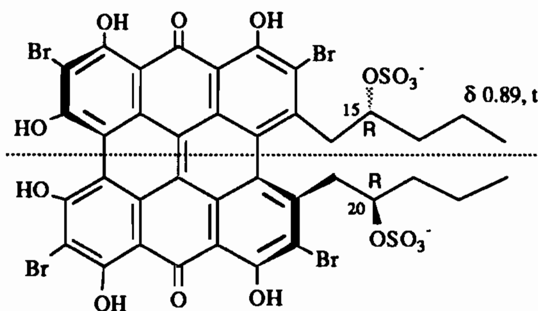
Figure 1 : Major violet pigment from the "living fossil" *Gymnocrinus richeri*



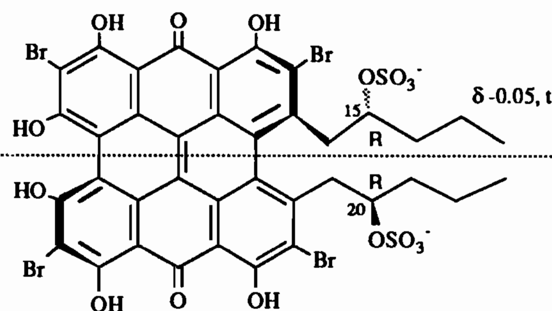
2 Gymnochrome A



3 Gymnochrome C

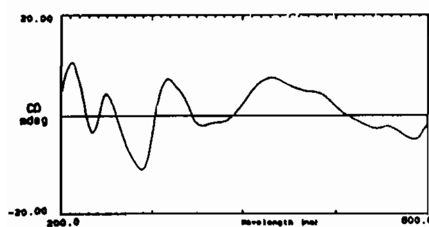


4 Gymnochrome D



5 Isogymnochrome D

CD curve of 4



CD curve of 5

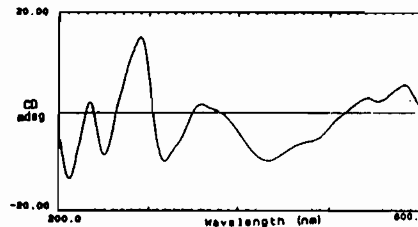


Figure 2 : Gymnochromes from the stalked crinoid " living fossil" *Gymnocrinus richeri*

results in twisting of the ring system, revealed by the circular dichroism spectrum, whose strong peaks are evidently due to the inherently dissymetric chromophore of the phenanthroperylenequinone system, with the consequence that it possesses helicity and hence axial chirality. The strong upfield shift (δ-0.04 ppm) of the methyl doublet of the C_3 side chain in gymnochrome B indicates that this group lies above the phenanthroperylenequinones system enough to undergo a strong shielding effect, whereas the C_7 side chain, whose protons resonate at "downfield" shift values, is outside of the area of the ring current.

Gymnochrome A 2 is related to Gymnochrome B by introduction of a further bromine atom at position 12. The CD spectrum is equal in sign with that of Gymnochrome B, thus implying that both pigments have the same helicity of their phenanthroperylenequinone chromophores.

Gymnochrome C 3 is a very minor phenanthroperylenequinone pigment extracted from the crinoid. The ^1H NMR spectrum identified two separate proton spin systems due to two C_3 side chains, with one of the side chain hydroxyl groups sulfated. On solvolysis, gymnochrome C afforded a desulfated derivative which showed in its ^1H NMR spectrum only half of the expected signals, indicating a symmetric molecule. The CD spectrum of gymnochrome C is equal in sign with those of gymnochromes A and B, thus implying that it has the same helicity as the previous ones. The upfield shift to δ-0.07 and 0.01 ppm of the two methyl doublets in the ^1H NMR spectrum requires both the side chains to be oriented above the phenanthroperylenequinones system.

Gymnochrom D 4 and Isogymnochrome D 5 were the key pigments, which shed light on the stereochemical features of this group of compounds. The FAB MS spectrum (negative ion mode) of Gymnochrome D gives molecular ion peaks at m/z 1119, 1121, 1123, 1125, 1127 ($[M-H]^{-\cdot}$ quintet) indicating four bromine atoms. Gymnochrome D is a chiral molecule but symmetric by virtue of a C_2 axis of symmetry in its structure, as revealed by the symmetry of its NMR spectra, showing only half of the signals. The ^1H NMR spectrum identified only one proton spin system assigned to a 2-oxygenated pentyl side chain, whereas the ^{13}C NMR spectrum contains only 19 carbon resonances. The helicity of gymnochrome D must be the same as that of the previous gymnochromes, being its CD spectrum equal in sign with those of the previous ones. Moreover the existence of the C_2 axis of symmetry requires that the chiral carbon atoms of the chains must have the same absolute configuration. The 2-sulfoxypentyl chains adopt a preferred orientation outside the area of the ring current, because the chemical shift of the terminal methyl protons is observed ar "downfield" chemical shift value.

Isogymnochrome D 5 is isomeric with gymnochrome D. They give identical FAB mass spectra and virtually identical UV-visible and IR spectra. On the contrary, the ^1H NMR spectrum of isogymnochrome D is substantially different from that of gymnochrome D. The major difference deals with the chemical shift values of the terminal methyls, strongly upfield shifted to δ-0.05 in the spectrum of isogymnochrome D. The presence of only half of the expected resonance signals in both ^1H and ^{13}C NMR spectra indicates that isogymnochrome D also possesses a symmetric structure, with a C_2 axis of symmetry. The CD spectrum of isogymnochrome D is however opposite in sign to that of gymnochrome D and from these findings isogymnochrome D is suggested to be a diastereomer of gymnochrome D, with an out-of-plane distorded phenanthroperylenequinone chromophore of opposite helicity. On solvolysis isogymnochrome D afforded the desulfated derivative, which, on heating in pyridine at 160°C, gave a mixture with the desulfated gymnochrome D. Analogously this latter, on heating in pyridine at 160°C, gave a mixture with desulfated isogymnochrome D. As the configuration of the side chain centers cannot be modified by thermal isomerization process, this finding definitively established isogymnochrome D as a diastereomer of gymnochrome D, the difference between the two consisting only in the opposite helicity of the

phenanthroperylenequinone ring. Since this process interconverts two diastereomers, the two chiral carbons of the side chain gymnochrome D and isogymnochrome D must have the same configuration. We note that the inversion of the helicity is accompained by a change in the orientation of the side chain, as evidenced ^1H NMR.

Stereochemistry : recently, a group of natural pigments, produced by a wide variety of moulds, has been intensively studied with regard to their intriguing stereochemical features, *i.e.* the axial chirality generated by the perylenequinone system forced into a nonplanar helical shape. By heating in various solvents, cercosporin isomerizes into almost equimolecular equilibrium with the diastereomer isocercosporin with opposite helicity (Fig. 3). Inversion of the helix is accompained by a change in orientation of the side chains as evidenced by the chemical shift values of the methyl doublets upfield shifted to δ 0.60 in cercosporin and downfield shifted to 0.96 ppm in isocercosporin. X-Ray analysis of a natural ester of cercosporin gave the helicity of the ring [axial chirality R (or helicity M)] and confirmed the R configuration for the carbons of the side chain (3).

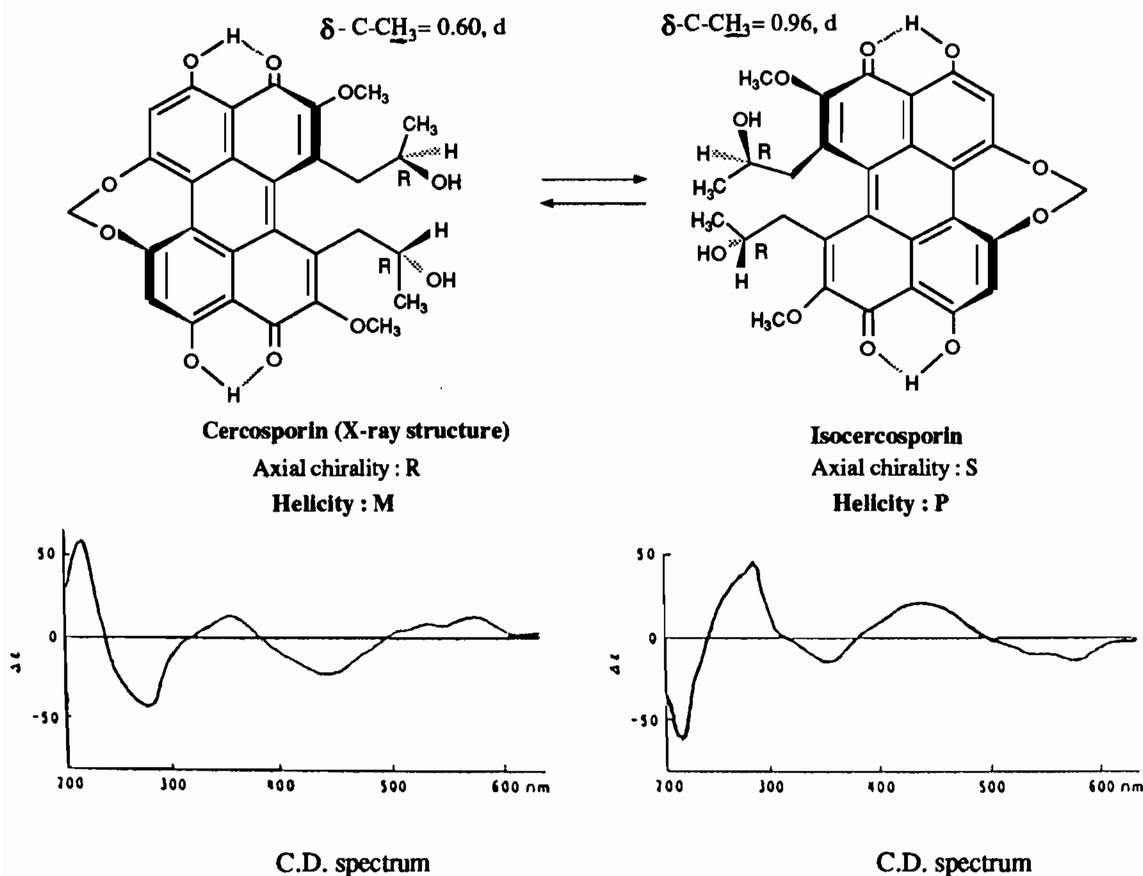


Figure 3 : Isomerization of cercosporin

These results enabled the Authors (4) to obtain the axial chirality of some other perylenequinones, by correlating the CD spectra with those of cercosporin. Inspection of the configuration and the NMR data of the pairs of isomers led the Authors to the conclusion that the orientation of the side chains is regulated by both the sense of the helicity and the configuration of the stereogenic centers in the side chains [*i.e.* when the helicity and the configuration at the side chain chiral carbon is M, R (or P, S), the side chain is oriented above the ring system (shielded zone) ; when the helicity and configuration at the side chain stereogenic carbons are M, S (or P, R), the side chain is located outside of the aromatic ring (deshielded zone)].

Since the CD curves of gymnochromes show close similarity in the shape of the curves and positions of most peaks and throughs with those of cercosporin or isocercosporin, we have assumed a possible CD correlation with cercosporin-isocercosporin to give the helicity of the ring of phenanthroperylenequinone pigments. Thus gymnochromes A, B, C and D, which have CD spectra opposite in sign to cercosporin, are suggested to have helicity P (axial chirality S), opposite to that of cercosporin, while isogymnochrome D, which has a CD spectrum equal in sign to cercosporin, is suggested to have helicity M (or axial chirality R) like cercosporin. Furthermore, on the basis of the correlation between the conformation of the side chains and ^1H NMR and CD data and by analogy with cercosporin, the configurations of the stereogenic carbons of the side chains have been suggested as reported in Fig. 1 and 2.

As our next step, we have tried to obtain evidence confirming the configuration at the side chains. As it was said above, in gymnochrome D as well as in isogymnochrome D the two chiral carbons of the C_3 side chains must have the same absolute configuration. Thus we decided to determine the configurations of the side chain carbons of gymnochrome D and isogymnochrome D, by applying the empirical approach of Horeau to appropriate derivatives in which all the phenolic groups were protected. Thus the absolute configuration of both carbons of gymnochrome D desulfated was determined as R, in agreement with the above assignments based on CD and ^1H NMR data and analogy with the perylenequinone pigments. The same procedure was then applied to the desulfated isogymnochrome D and the absolute configuration of the side chain carbon was again determined as R, as expected.

The green color of the animals suggests that the pigments are present as salts with ionized phenolic groups probably in the form of metal complexes. Indeed, an analysis by atomic absorption spectroscopy of a partially purified sample of gymnochromes A and B in the green form has revealed the presence of significant amounts of zinc. The yellow color of the *in vivo* animals suggests that the phenanthroperylenequinone system of the gymnochromes is possible formed in part by oxidation and sunlight exposure of the related bianthrones or other dimeric precursors. The eventual relationship between the stereochemistry of the bianthrones or related dimeric precursors and the helicity of the derived phenanthroperylenequinones is also an interesting matter of investigation.

Tremaster novaecaledoniae is a living fossil starfish species, which was collected at a depth of 530 m off New Caledonia. During the last ten years and intensive collaboration with ORSTOM and CNRS firstly in the frame of the programme SNOM (Substances Naturelles d'Origine Marine) and then in the frame of the programme SMIB (Substances Marines d'Intérêts Biologiques) has led, *inter alia*, to the chemical and pharmacological study about 30 different starfish species belonging to 10 families, all collected off New Caledonia. This study along with that on more other starfish species collected in Mediterranean Sea and Pacific Ocean along the coasts of Japan and in the Bay of California, by our group and the investigation of other groups such as Komori (5) at Fukoka and Elyakov and Stonik (6) at Vladivostok, has led to the isolation of a large variety of highly oxygenated steroidal glycosides (*ca* two hundred compounds) which were grouped into three major groups (7). Besides the so-called "asterosaponins" which are sulfated steroidal penta- and hexa-glycosides, whose structural features are well represented by thorasteroside A from *Acanthaster planci*, steroidal glycosides belonging to at least two more structural groups are present in starfish ; the cyclic steroidal glycosides here exemplified by sepositoside A from *Echinaster sepositus* and the glycosides of polyhydroxysteroids here exemplified by nodososide from the Pacific *Protoreaster nodosus* (Fig. 4). While the cyclic compounds have only been found in starfish of the genus *Echinaster*, compounds of the last group, although unnoticed for a long time, are as much widespread as "asterosaponins" among starfishes. They are mono and diglycosides of polyhydroxysteroids, usually occur in minute amounts and are present in both sulfated and non-sulfated forms. Sulfation is typical in the biosynthesis of secondary metabolites in many marine invertebrates, and especially in echinoderms.

Tomasteroside A

Sepositoside A

Nodososide

Figure 4 : Examples of oligoglycosides from starfish

The so-called glycosides of polyhydroxysteroids are often accompained by varied polyhydroxylated sterols. Polyhydroxysteroids are not uncommon in marine species. They have been isolated from soft corals, gorgonians, nudibranches and sponges. However it appears that starfishes are the richest source for the discovery of polyhydroxylated steroids with new structures. The 3β, 6α (or β), 8β, 15α (or β), 16β 26-hexahydroxy moiety is a common feature ; additional hydroxyl groups are in position 4β, 5α, 7α (or β) and some time 14α, all grouped on one side of the molecule, giving an amphiphlic character to the molecules with an hydrophilic and an hydrophobic region (8).

Analysis of the polar extractives of *Tremaster novaecaledoniae* has now led to the discovery of a further group of steroid constituents, in which the polyhydroxysteroids have both sulfate and phosphate conjugation, as shown in Fig. 5.

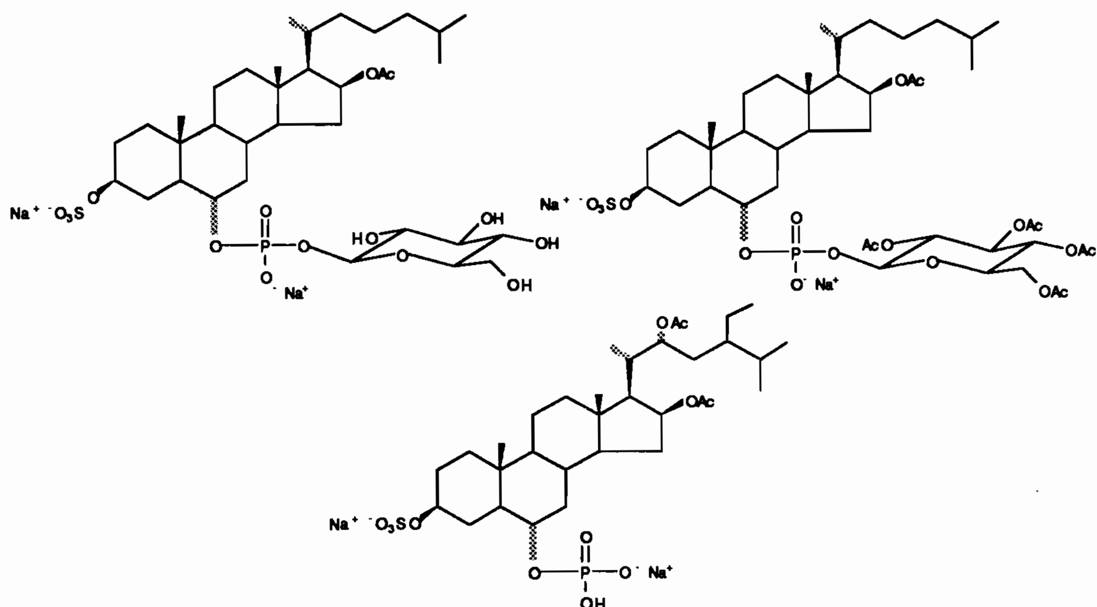


Figure 5 : Phosphated steroids from *Tremaster novaecaledoniae*

In the first two compounds the monophosphate residue is further linked to glucose and glucose tetracetate, respectively. To the best of our knowledge this is the first reported isolation of marine steroids with both sulfate and phosphate conjugation.

Fig. 6 summarize some remarks on the structure elucidation of those metabolites. Next to the molecular anion peak, the FAB mass spectrum displayed intensed fragments at m/z 641 and 619, which correspond to the loss of an hexosyl residue, while the peaks at m/z 539 and 521 were interpreted as losses of SO_3 from m/z 619 and $NaHSO_4$ from m/z 641, respectively. The presence of a steroid skeleton was deduced from ^1H NMR methyl signals, and one sugar unit (identified as glucose) would be also considered from the signals in the 3.3 - 4.0 ppm region and the anomeric one at δ ca 5.0. The multiplet at δ 4.24 has the complexity normally seen for a 3β-oxygenated group in a steroid skeleton, and its downfield shift suggested a sulfate to be located there. The signal assigned to H-6β of the steroid has the shape of an apparent quartet, with one more large coupling (~8Hz) than expected, and this firstly suggested the presence of a phosphate group, to which the glucose residue should be glycosidally attached. This was supported by the proton noise decoupled ^{13}C NMR spectrum, in which carbons 1' and 2' of glucose and carbon 5 and 6 of the steroid appeared as doublets because of the coupling P-O-C and P-O-C-C. The presence of the phosphate was definitively confirmed by the ^{31}P NMR spectrum, which showed a triplet signal at 3.53 ppm downfield from external standard H_3PO_4 85% in D_2O, converted into doublets on irradiation at δH 4.06 (H-6) and 4.90 (H-1'). The structure was confirmed by very mild acid treatment which removed glucose followed by solvolysis in pyridine-dioxane which removed sulfate at C-3. The third oxygenated function, which was an acetoxy grouping, was located at C-16β.

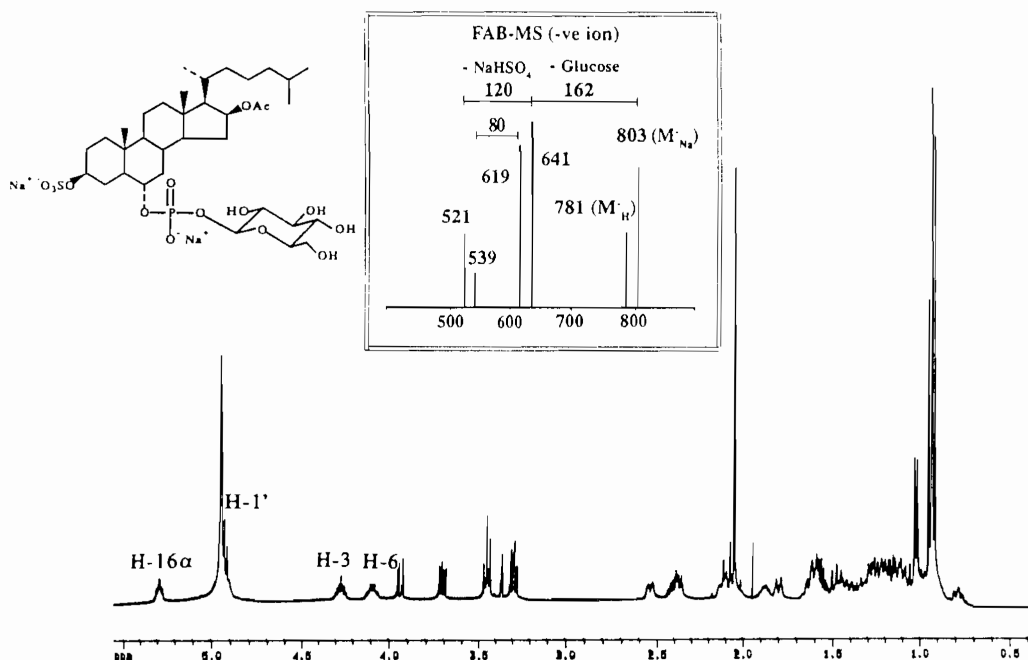


Figure 6

Steroidal and triterpene oligoglicosides are the predominant metabolites of starfishes and sea cucumbers, respectively. Besides echinoderms, only a limited number of marine organisms have been shown to contain glycosides. Recently some glycosides have been isolated from sponges (9). We have now isolated a new lanostane derived triterpene tetra-galactoside from a sponge of the genus *Erylus sp.* (Fig. 7) collected at a depth of 500 m in the South of New Caledonia. What may be of interest in the structure analysis of the oligosaccharide chain, made up of four D-galactose units, achieved exclusively by a combination of 2D-NMR techniques, and very difficult, it is not impossible, to determine by using traditional chemical methods.

The structure of the aglycone, which features a rare 14-carbonyl group in a lanostane skeleton was derived by ^{1}H and ^{13}C NMR data and comparison with penasterol, recently isolated from a sponge of the genus *Penares* (10). The four galactopyranosyl residues are connected by β-glycosidic linkages, as immediately indicated by the doublets with J~7Hz for the anomenic H's observed in the monodimensional ^{1}H NMR spectrum.

COSY experiments allowed the sequential assignment of most of the resonances for each glactosyl ring, starting from the anomeric signals. Cross peaks displayed full coupling informations, which helped assignements and allowed identification of multiplet patterns and measurement of coupling constants. Nevertheless not all proton resonances could be successfully assigned with confidence, because of the overelapping of some signals in the one dimensional spectrum. Complete assignements were then achieved by combination of COSY and 2D-Hartmann-Hann coherence transfer experiments (11), which clearly showed correlation signals for the H1 to H4 spin system of every glactosyl residue. The coherence transfer to H5 was not obtained because of the small coupling H4-H5 ($J_{4,5}$<1.5Hz), but the H5 signals were clearly visible in the COSY spectrum. Thus, having assigned all proton resonances of each galactosyl residue, an one bond H-C correlation experiment correlated all proton resonances with those of their correponding carbons, which allowed the determination of the position of

interglycosidic linkages. Two galactosyl residues are terminal because of the absence of any ^{13}C glicosidation shift for these sugars. The shift observed on C-2 and C-3 of Gal I (δ_c 77.3 and 85.2 ppm) established the presence of one branching unit glycosidated at C-2 and C-3, while the shift observed on C-4 galactose II (d_c 79.8 ppm) established a C-4 glycosidated galactopyranosyl unit. These data could be accomodated into three possible structures; a multiple bond H-C correlation experiment allowed us to differentiate between the three hypothesis. Key correlation peaks through the glycosidic linkages were observed between the terminal Gal III unit and C-4 of the inner Gal II unit, which in turn proved to be linked at C-3 of the nodal galactose I moiety. Significative cross peaks were also observed between the terminal Gal IV and C-2 of Gal I, which in turn proved to be linked to the aglycone (Fig. 8). Thus the structure of the oligogalactoside chain is as shown in Fig. 7

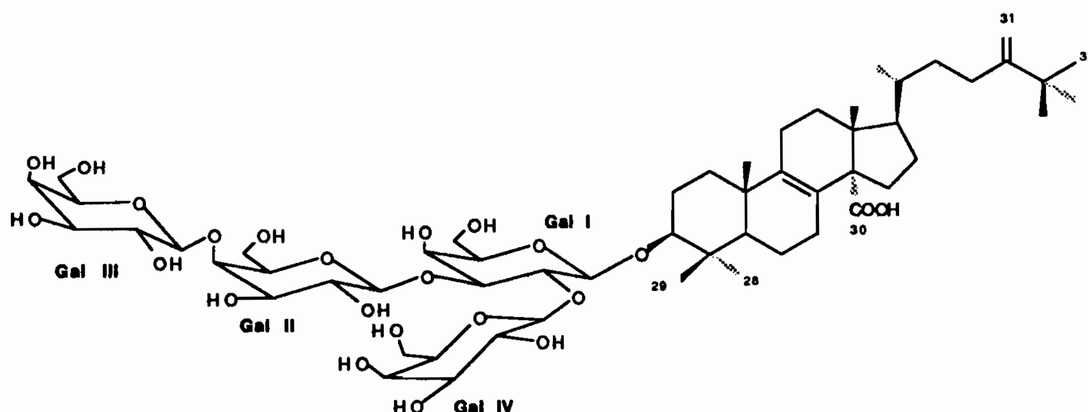


Figure 7 : Structure of Eryloside D, a triterpene oligoglycoside from the Pacific sponge *Erylus* sp.

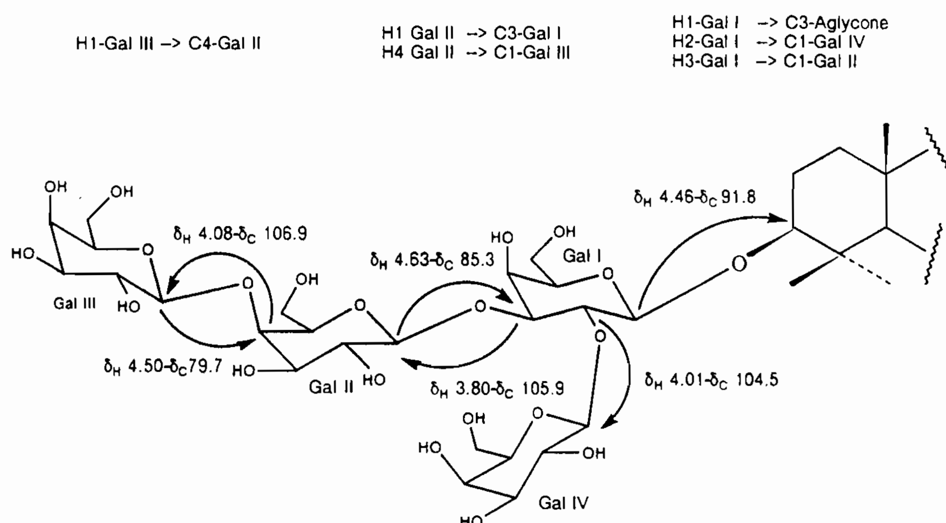


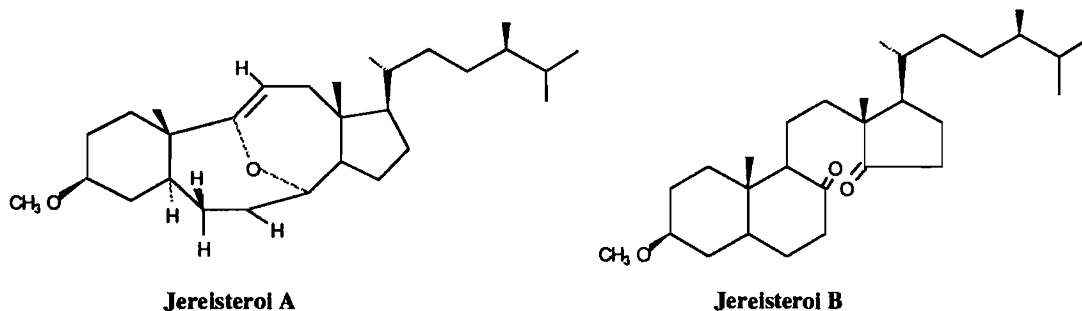
Figure 8 : Sequential analysis of oligosaccharide moiety through heteronuclear multiple bond correlation (CD_3OD, 500 MHz)

Finally we describe the steroidal constituents of the sponge ***Jereicopsis graphidiophora***, also collected in the North of New Caledonia at a depth of 220 m, and

identified by Professor Claude Lévi as a new genus. This sponge contains unique 3β-O-methyl sterols, while the conventional 3β-hydroxysteroids were totally absent. Along with Δ^0, Δ^5, Δ^7, $\Delta^{7,9}(11)$, Δ^8, $\Delta^{8,14}$ - 3β-methoxy sterols, the sponge also contains a series of steroids with further oxygenated functionalities in the nuclei (12) and two ones which combine the unique 3ß-methoxyl group with a rare seco-structure (13) (Fig. 9).

The olefinic signals high field shifted to δ 4.92 and 4.53, along with two sp^2 CH signals are relatively high field at δ 106.8 and 107.2 ppm, were suggestive for the presence of an enol ether structure in the minor jereisterol A. Sequential decoupling experiments identified the sequences C-1 to C-14 and C-9 to C-13 ; thus the oxygen atom, indicated by MS, was fixed between the olefinic carbons C-8 and C-9 giving rise to an unique 8,9-oxido-8,9-secocholesta-7,9 (11) -diene structure. The α-orientation of the oxido function was firstly suggested by the downfield shift of the proton at C-5(δ 2.79) implying the oxygen function and H-5 to be located on the same face of the molecule. Better support comes from the application of computational and molecular modeling methods, which allowed to generate the α- and β- conformations, shown in the slide, by using the MM2 force field method. The dihedral angles of the α-oxido conformations requires the H-7 signal to appear in the ^{1}H NMR spectrum as a triplet with coupling constants with H-6α and H-6β almost identical, while H-11 signal should appear as a dd with larger coupling constants, in agreement with the experimental data. The reverse is to be expected with the β-oxido conformation. It is to be noted that the α-oxido structure is the lowest energy conformer.

The second seco-steroid, jereisterol B, has the 8,14-secoergostane-8,14-doine structure which was confirmed by synthesis, accomplished by oxidation with ruthenium tetroxide of 3β-acetoxy-ergost-8(14)-ene.



Figuere 9 : Structures of jereisterol A and B, 3ß-methoxysteroids from the Pacific sponge *Jereicopsis graphidiophora.*

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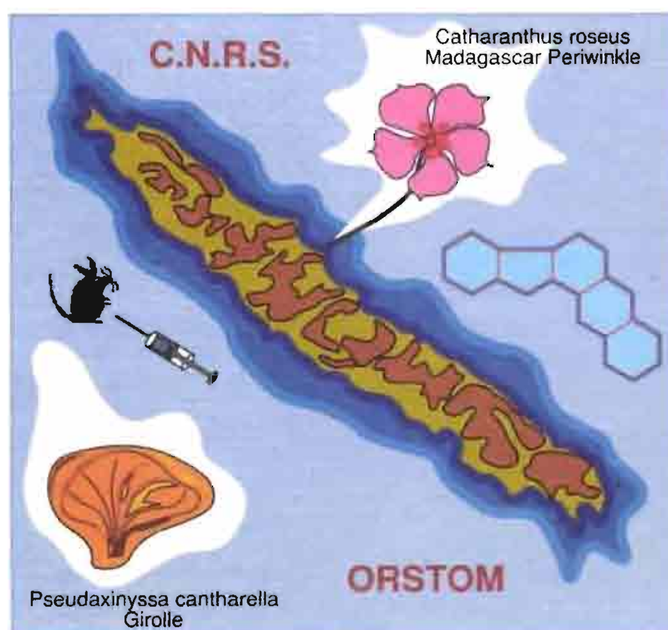

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