Tetrahedron Letters,Vol.26,No.40,pp 4919-4922,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

CYSTOSEIROL A, A NOVEL REARRANGED DITERPENE OF MIXED BIOSYNTHESIS FROM THE BROWN ALGA *CYSTOSEIRA MEDITERRANEA*

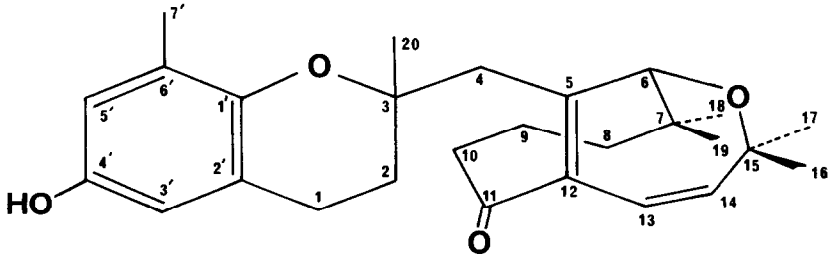
C. FRANCISCO*, B. BANAIGS*, L. CODOMIER* and A. CAVE+

*Groupe de recherches en biologie et chimie des végétaux marins
Université de Perpignan 66025 France
+Centre CNRS-INSERM de Pharmacologie-Endocrinologie, Rue de la Cardoille, 34033 Montpellier France

Summary: The skeleton of a novel class of rearranged meroditerpenoids was established by chemical and spectral methods, including heteronuclear shift correlations ^{1}H-^{13}C 2D-NMR with long range coupling correlation.

We recently described[1-2] from the brown alga *Cystoseira mediterranea* a novel class of rearranged metabolites, mediterraneols, which posses an hitherto unknown bicyclo [4:2:1] nonane ring. In this report, we will present another class of rearranged diterpenoids, representing minor compounds (0.9% from the ether extract) from the same alga.

Collection, extraction and purification of the diterpenoid fraction have already been described[1-2]. The natural metabolite, Cystoseirol A, was isolated from *Cystoseira mediterranea*, *Cystoseira stricta* and *Cystoseira tamariscifolia* by HPLC on μ-Porasil (20% EtOAc/isooctane). Cystoseirol A 1 showed $[\alpha]_D$ = +15° (1.6, CCl_4) and analysed for $C_{27}H_{36}O_4$ by HRMS [M^+ m/z obs. 424.2215; calc. 424.2204]. The infrared spectrum (film) established the presence of an alcohol functionality (ν_{OH} 3450 cm^{-1}), an α,β-unsatured ketone ($\nu_{C=O}$ 1680 cm^{-1}) and a conjugated double bond ($\nu_{C=C}$ 1610 cm^{-1}). In the UV spectrum ($CHCl_3$), an absorption at 296 nm (ε= 4400) indicated a chromanol chromopnore[3] and one at 241 nm the presence of conjugated double bonds or of an α,β-unsatured carbonyl group with steric inhibition of resonance (ε = 4600)[4].



Results from ^{1}H NMR and ^{13}C NMR with decoupling experiments, and ^{1}H - ^{13}C shift correlation 2D-NMR with long range coupling studies[5] are resumed in table 1. These data have permited to identify all the carbons and to obtain the first structural informations.

n° C	^{1}H NMR (360 MHz) δ (ppm) J(Hz)	^{13}C NMR (100 MHz) δ (ppm) off Res	n° C	^{1}H NMR (360 MHz) δ (ppm) J(Hz)	^{13}C NMR (100 MHz) δ(ppm) off Res
1	2.70 m	22.6 t	14	6.04 d 6	139.9 d
2	1.7-1.9 m	31.1 t	15		83.9 s
3		75.3 s	16	1.33 s	26.4 q
4	2.20 m	44.4 t	17	1.29 s	22.6 q
5		145.4 s	18	1.14 s	22.8 q
6	4.34 s	111.1 d	19	0.88 s	20.0 q
7		43.1 s	20	1.36 s	24.9 q
8	1.83;1.31 m	36.2 t	1'		146.3 s
9	1.68;1.43 m	40.7 t	2'		121.2 s
10	1.54 m	20.3 t	3'	6.41 d 3	112.5 d
11		201.3 s	4'		152.6 s
12		139.6 s	5'	6.54 d 3	115.6 d
13	5.56 d 6	126.5 d	6'		127.4 s
			7'	2.08 S	16.1 q

Table 1: NMR DATA of CYSTOSEIROL A

Acetylation (Ac_2O/Pyr) gave, after HPLC purification, a monoacetate [HRMS $C_{29}H_{38}O_5$ M^{+} m/z obs. 466.2713; calc. 466.2709] in agreement with the presence of a chromane moiety. The ^{1}H NMR of the HPLC-purified product of the reduction of 1 by $NaBH_4$ exhibits one allylic proton (δ =4.41 ppm, broad t), shown by spin decoupling to be coupled to a high field methylene group (δ = 1.65-1.5 ppm). Its IR ($\nu_{C=C}$ 1620 cm^{-1}) and UV (λ = 240 nm, ε = 4700) spectra established the presence of conjugated double bonds with steric hindrance (confirmed by Dreiding models) in the structure.

Long range coupling studies and heteronuclear shift correlations ^{1}H - ^{13}C 2D-NMR enabled us to establish the structure of this rearranged diterpene (fig.1). At this point, only one methylene group and the oxygen junction remained to be localized in the molecule. Considering partial structure in fig.1, the ketone was bound obviously to the quaternary double bond. As H-6 gave a singlet in the ^{1}H NMR spectrum, the last methylene group [C-9] must be localized between C-8 and C-10 (proved by careful decoupling experiments), thus establishing the sequence C-7,C-8,C-9,C-10,C-11,C-12.

^{13}C NMR chemical shifts in connection with identification by ^{1}H - ^{13}C correlations (J_{CH}), allowed us to place a supplementary oxygen bridge between C-6 (δ = 111.1 ppm) and the sp^3 quaternary carbon C-15 (δ = 83.9 ppm).

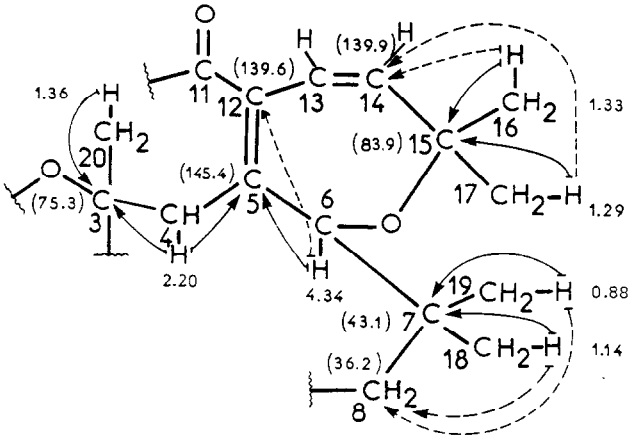
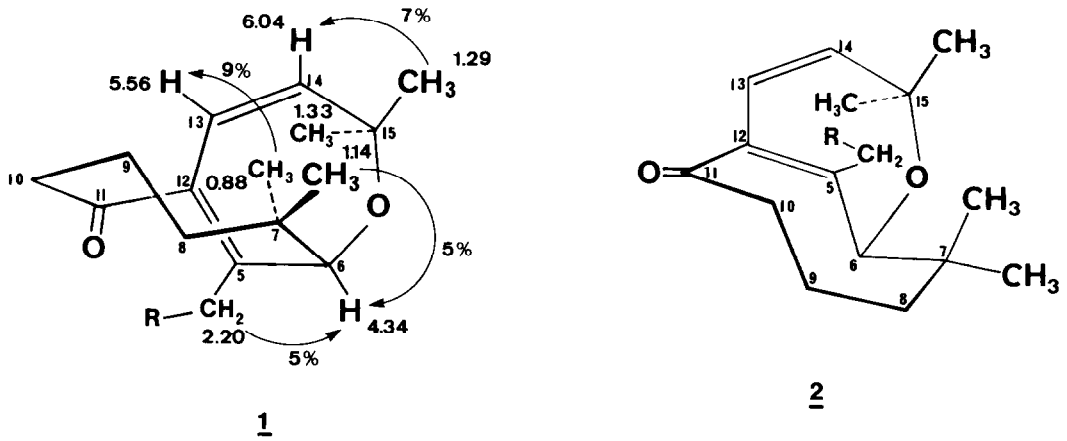


Fig: 1 $^{2}J_{CCH}$ ⟶ ; $^{3}J_{CCH}$ ⟶

Two different skeletons can be built from the set of found elements, confidently defined by enhancements between C-4 and C-6 during NOE irradiations and by $^{1}H - ^{13}C$ long range coupling results. However, structure 2 (fig.2) was found to contain a trans double bond in a seven-membered ring. As NOE experiments were in complete agreement with structure 1, this proposal was chosen for Cystoseirol A. Structure 1 contains a bridge-head, anti-Bredt, double bond but it is localized in a large enough system to be accomodated.



1 2

Fig: 2 H (irradiated) ⟶ H (enhanced)

Mediterraneols and Cystoseirols can be hypothetically derived from a linear regular precursor by an unusual cyclisation, with a trans-cyclooctene ring as initial product. In this way Bifurcarenone[6], already described in *Cystoseira mediterranea*[2] and also found in *Cystoseira strita* and *Cystoseira tamariscifolia*, will be biosynthetically related to such compounds via this former intermediate. Single methyl group displacement, supplementary bridges and ring fission would occur latter by appropriate metabolic pathways. Other related compounds with the same oxabicyclo [5:4:1] dodecane ring will be reported soon in a more detailed paper[7].

Acknowledgements

We thank Dr J. M. LHOSTE (Institut Curie) for ^{13}C NMR measurements. We are greatly indebted to Prof. W. FENICAL for reading and commenting upon the whole work made on *Cystoseira mediterranea*.

References

1.C. FRANCISCO, B. BANAIGS, R. VALLS and L. CODOMIER, *Tetrahedron Lett.*, 26, 2629 (1985).
2.C. FRANCISCO, B. BANAIGS, J. TESTE, A. CAVE and W. FENICAL, *J. Org. Chem.* (submitted).
3.A. G. GONZALEZ, J. DARIAS, J. D. MARTIN and C. PASCUAL, *Tetrahedron*, 29, 1605 (1973).
4.W. M.SCHUBERT and W. A. SWEENEY, *J. Am. Chem. Soc.*, 77, 2297 (1955).
5.A. BAX "Two dimensional NMR in liquids" D. Reidel Publishing Co, DORDRECHT, Holland(1982)
6.H. H. SUN, N. M. FERRARE, O. J. McCONNELL and W. FENICAL, *Tetrahedron Lett.*, 21, 3123 (1980)
7.C. FRANCISCO, B. BANAIGS, M. RAKBA, J. TESTE and A. CAVE, *Tetrahedron* (submitted).

(Received in France 4 July 1985)