served at H-6; H-15 and H-6 are clearly on the same molecular face. The observed $J_{5,6} = 9.6$ Hz requires that H-5 and H-6 be *trans* to one another; this completed the proof that stizolicin is, indeed, a *trans,trans* germacranolide. A complex analysis of the coupling constants for H-3, H-2, and H-1 also demonstrated that both methyl groups are oriented in the energetically-favored β-orientations[10].

Trans lactone closure follows from the observed $J_{7,13} > 3.0$[11,12] and closure to C-6 is evident in the negative Cotton Effect ($\theta = -3780$ at λ_{max}^{MeOH} 250 nm) for the n→π* transition[13]. The stereochemistry at C-8 can be assigned based on chemical shift analysis. The β-esters have H-8 resonating around δ 5.7 due to location within the plane of the C-11,13 double bond, while α-esters show H-8 near δ 4.5[14]. Stizolicin has an α-ester in consonance with all other esterified sesquiterpene lactones from this tribe. The structural proof of stizolicin was concluded by hydrolysis in sodium hydroxide-aqueous dioxane to give the rearranged lactone, isospiciformin (**3**). The NMR of this product was identical with that obtained from an authentic sample[15] prepared from desacetyllaurenobiolide epoxidation.

Several other compounds are also known from *S. balsamitus*. The related balsamin (**4**)[16] and stizolin (**5**)[17] are spectroscopically similar to stizolicin, and, thus, are probably also *trans,trans* and not *cis,cis* germacranolides. In addition, the flavonoid 5-O-β-D-glucosyl-3-O-methylquercitin[18] and an alkaloid, stizolophin ($C_{15}H_{23}NO_5$), have been isolated[19].

Stizolicin (NSC 301458) showed cytotoxicity ($LD_{50} = 9.4 \times 10^{-1}$ µg/ml and 4.7 µg/ml in the P388 and KB tumor cell cultures, respectively) and marginal in vivo antitumor activity against P388 murine leukemia (T/C = 123% at 16 mg/kg). A similar compound, eupatoriopicrin, lacking an epoxy and with the same ester beta, has shown slightly better activity in P388 (T/C = 140% at 30 mg/kg)[20].

1 To whom correspondence should be addressed. The authors acknowledge the use of the Purdue University Biomedical Magnetic Resonance Laboratory (NIH grant No. RR01077). Support of contract No. N01-CM-97296 and Grant No. CA-33326 from the National Cancer Institute, HHS is gratefully acknowledged. This is paper 18 in the series 'Potential Antitumor Agents'.

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12-Hydroxy-*E*-γ-bisabolene, a new sesquiterpene alcohol from a Caribbean sea whip of the genus *Pseudopterogorgia* (Gorgonacea, Cnidaria)

S.A. Look, K. Buchholz and W. Fenical[1,2]

Institute of Marine Resources, Scripps Institution of Oceanography, La Jolla (California 92093, USA), 1 December 1983

Summary. A new sesquiterpene alcohol, 12-hydroxy-*E*-γ-bisabolene, is reported from an undescribed Caribbean sea whip of the genus *Pseudopterogorgia*. The structure of this new alcohol was established based upon spectral analyses and through chemical interconversions.

Key words. Caribbean sea whip; sesquiterpene alcohol; *Pseudopterogorgia*; 12-hydroxy-*E*-γ-bisabolene.

Sea whips (gorgonians) of the genus *Pseudopterogorgia* are particularly abundant in the Caribbean Sea and several new terpenoid metabolites have been recently isolated from this source[3,4]. In our studies of these chemically rich marine invertebrates we have found the secondary metabolite composition to be consistent within discrete species, and hence secondary metabolites appear to be potentially useful taxonomic markers. Two of our collections of *Pseudopterogorgia* (voucher specimens: F-24, Belize, 1979, Florida Keys, 1980) were distinct in their physical features from other common species encountered, but anatomical investigations (spicule analyses) placed this animal as closely related to the abundant Caribbean sea whip *P. acerosa*[5]. In previous chemical studies we showed that *P. acerosa* produces the diterpenoid molecule pseudopterolide (**1**). In this paper we wish to show that this gorgonian (F-24) produces exclusively the new sesquiterpene alcohol **2**, identified here as 12-hydroxy-*E*-γ-bisabolene.

Alcohol **2** was isolated by repetitive chromatography as 20% of the organic extracts of *Pseudopterogorgia* species conforming morphologically to voucher F-24. High-resolution mass spectrometry and ^{13}C NMR data (table) confirmed a molecular formula of $C_{15}H_{24}O$ for the compound[6]. Infrared absorption at 3350 cm^{-1}, coupled with appropriate ^{13}C NMR bands showed that the oxygen atom in **2** was in the form of a primary alco-

hol. Acetylation (Ac_2O, py, RT) cleanly yielded the corresponding acetate **3** which confirmed these aforementioned conclusions[7].

Further consideration of both the ^1H and ^{13}C NMR features of **2** yielded considerable insight into the structure of this alcohol. By ^{13}C NMR analysis, 3 olefinic bonds were present. Since the molecular formula of **2** contained 4 degrees of unsaturation, the new alcohol was determined to be monocarbocyclic.

Two reactions fully established the nature of the ring and hence the final structure proof of alcohol **2**. Treatment of acetate **3** with 10% Pd on carbon in refluxing xylene for 50 h yielded the aromatized curcumene derivative **4** as the major reaction product. Comparison of the spectral characteristics of **4**[8] with several other curcumene derivatives showed close similarities. In the ^1H NMR spectrum of **4**, the presence of an aromatic methyl group (δ 2.09, 3 H, s) and 4 aromatic protons (δ 7.11, 4 H, m) as well as a newly formed methyl doublet (δ 1.22, 3 H, d, J = 6.9 Hz) fully supported the final assignment of **4** as 12-acetoxycurcumene.

Further information on the structure of alcohol **2**, and in particular, data to define the side chain, was gained by selective cleavage of the compound at the tetrasubstituted (Δ^5) double bond. Treatment of **2** with stoichiometric amounts of m-chloroperbenzoic acid in Na_2HPO_4-buffered CH_2Cl_2 solution yielded the epoxide **5** (93%)[9]. Cleavage of epoxide **5** with periodic acid in diethyl ether yielded a complex mixture from which the ketoalcohol **6**[10] was isolated by silica HPLC.

These latter transformations established that alcohol **2** possessed a disubstituted 6-membered ring and a C_8 isoprenoid side chain. These data, and the presence of a tetrasubstituted double bond, strongly suggested that the alcohol was a derivative of γ-bisabolene. What remained to be established were the stereochemistry of the Δ^5 olefin (as defined by its spatial arrangement to the Δ^8 olefin) and the position of the hydroxyl functionality at either C12 or C13. Comparison of the ^{13}C NMR bands for **2** with those from both *E* and *Z*-γ-bisabolene[11] showed a very close correlation with the *E* geometrical isomer. A particularly close correlation was observed for the C7, C14 and C11 carbons which vary between the *E* and *Z*-γ-bisabolene isomers by 1.5 to 3.0 ppm. Since the values for **2** were within 0.2 ppm of those reported for the *E* isomer, alcohol **2** was also assigned the *E* configuration.

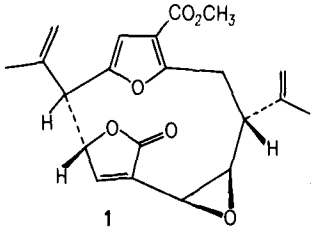
Data to confidently assign the position of the hydroxyl group were obtained by ^1H NMR studies of the natural product and several derivatives. In the ^1H NMR spectrum of epoxide **5**, for example, the Δ^1 olefin proton was clearly observed as a broad singlet at δ 5.36 and the hydroxyl methylene group as a broad 2-proton singlet at δ4.00. Measurement of the enhancement observed by nuclear Overhauser enhancement difference spectroscopy (NOEDS), when either of these bands was irradiated,

^1H and ^{13}C NMR assignments for alcohol **2**[a,b]

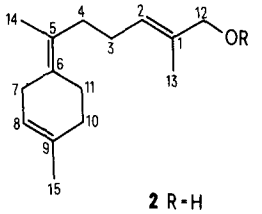
C	^1H	^{13}C	C	^1H	^{13}C
1	–	133.8[c]	9	–	135.2[c]
2	5.42 (1H, bs)	125.4	10	2.11 (2H, bs)	31.9
3	2.32 (2H, bt)	26.8	11	2.11 (2H, bs)	27.2
4	1.99 (2H, bt)	34.1	12	3.99 (2H, bs)	68.3
5	–	125.4	13	1.67 (3H, s)	13.6
6	–	128.7	14	1.67 (3H, s)	18.4
7	2.72 (2H, bs)	29.9	15	1.67 (3H, s)	23.5
8	5.37 (1H, bs)	121.0			

[a]The ^1H NMR spectrum was recorded at 360 MHz in $CDCl_3$. Assignments were aided by spin-decoupling experiments. Chemical shifts are reported in δ units (ppm downfield from TMS).
[b]The ^{13}C NMR spectrum was recorded in C_6D_6 at 50.3 MHz. Multiplicities were obtained by single frequency off resonance decoupling, and assignments were made based upon comparison to models. The δ values are given in ppm downfield from TMS.
[c]Signals may be reversed.

Structures I

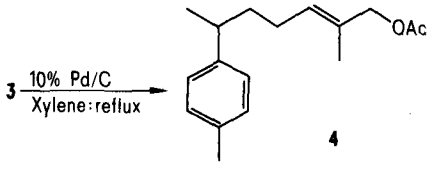


1



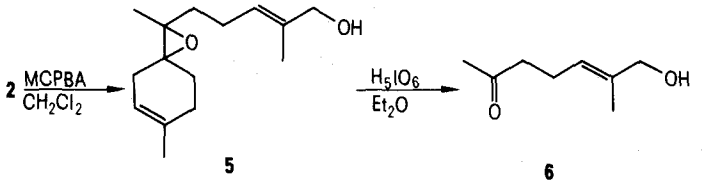
2 R = H
3 R = Ac

Structures II



4

Structures III



5 **6**

confidently established the hydroxyl group on the *cis* side of the olefin at C1. Under these conditions, and as expected, enhancement of the olefin methyl (C13) was not observed.

The discovery of bisabolene derivatives in *Pseudopterogorgia* species is precedented by our earlier report of curcumene derivatives from the related Caribbean gorgonian *P. rigida*[13]. Hydrocarbons possessing this common ring system have also been reported from gorgonians of the genera *Plexaurella* and *Muricea*[14-16]. Despite the widespread occurrence of numerous common carbon skeletons, our observations suggest that specific chemical components characterize discrete species of gorgonian octocorals. The potential use of secondary metabolites in gorgonian taxonomy has recently been reviewed[17], and while more data must be accumulated, this approach to complex problems in taxonomy appears promising.

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6 Other physical and spectral features for alcohol **2** include: oil, UV λ_{max} (MeOH) = 250 nm (ε = 4900), IR ($CHCl_3$): 3350-3450, 2960, 2930, 1715, 1670, 1450, 1380 cm^{-1}, HRMS: M^+ m/z obsd. 219.1746 (M^+-H, 25.5), $C_{15}H_{23}O$ requires 219.1749, 201.1633 M^+-H_3O, $C_{15}H_{21}O$, 13).

7 Compound **3** exhibited the following spectral characteristics: (IR ($CHCl_3$): 2940, 1720, 1670, 1510, 1420, 1380, 1210 cm^{-1}, LRMS: M^+, m/z 262 for $C_{17}H_{26}O_2$; ^1H NMR (360 MHz, CCl_4): δ 5.50 (1 H, bs), 5.37 (1 H, bs), 4.44 (2 H, bs), 2.72 (2 H, bs), 2.30 (2 H, bt), 2.08 (3 H, s), 2.11 (4 H, bs), 2.08 (3 H, s), 1.98 (2 H, bt), 1.67 (9 H, s).

8 Compound **4** exhibited the following spectral characteristics: UV: λ_{max} (MeOH) = 247 nm (ε = 2200), IR ($CHCl_3$): 2960, 1720, 1450, 1360 cm^{-1}, LRMS: M^+, m/z (relative intensity) 260 (0.3) for $C_{17}H_{24}O_2$, 200 (M^+-HOAc, 5), 158 (6), 145 (11), 143 (22), 132 (37), ^1H NMR (360 MHz, $CDCl_3$): δ 7.11 (4 H, m), 5.42 (1 H, bt), 4.43 (2 H, bs), 2.67 (1 H, m), 2.32 (3 H, s), 2.09 (3 H, s), 1.59 (3 H, s), 1.22 (3 H, d, J = 6.9 Hz).

9 Epoxide **5** exhibited the following spectral characteristics: IR ($CHCl_3$): 3410, 2980, 2950, 2920, 1430, 1370 cm^{-1}, LRMS: M^+, m/z 236 for $C_{20}H_{24}O_2$, 218 (M^+-H_2O); ^1H NMR (360 MHz, $CDCl_3$): δ 5.42 (1 H, bt), 5.36 (1 H, bs), 4.00 (2 H, bs), 2.38 (1 H, bs), 2.33 (1 H, bs), 2.16 (2 H, m), 2.04 (2 H, m), 1.76 (2 H, m), 1.70 (3 H, s), 1.68 (3 H, s), 1.62 (2 H, m), 1.33 (3 H, s).

10 Compound **6** exhibited the following spectral characteristics: IR ($CHCl_3$): 3300 (brd), 2920, 1715, 1350 cm^{-1}, LRMS: M^+, m/z 124 for $C_8H_{12}O$ (M^+-H_2O); ^1H NMR (360 MHz, $CDCl_3$): δ 5.37 (1 H, bt), 4.00 (2 H, bs), 2.51 (2 H, t), 2.32 (2 H, t), 2.15 (3 H, s), 1.68 (3 H, s).

11 The reported values for C7, C11 and C14 for *E*-γ-bisabolene are 29.7, 27.4 and 18.4 ppm. The *Z* isomer shows resonances at 26.8, 29.4 and 17.8 ppm[12]. Since **2** shows bands at 29.9, 27.2 and 18.4 ppm it is assumed to be the *E* isomer.

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Fluorinated analogs of insect sex pheromones[1]

F. Camps[2], J. Coll, G. Fabriàs, A. Guerrero and M. Riba

Instituto de Química Bio-Orgánica, Jorge Girona Salgado s/n. Barcelona-34 (Spain), 7 October 1983

Summary. The syntheses of fluorinated mimics of pheromones of *Spodoptera littoralis, Diparopsis castanea, Laspeyresia pomonella, Bombyx mori* and *Thaumetopoea pityocampa* are described. These analogs showed biological activities similar to those of the natural pheromones in laboratory assays (EAG).

Key words. Pheromones, insect sex; *Spodoptera littoralis; Diparopsis castanea; Laspeyresia pomponella; Bombyx mori; Thaumetopoea pityocampa;* pheromone analogs, fluorinated.

In connection with our ongoing interest on the study of bioactive fluorinated compounds in insect biochemistry[3,4], we describe in the present communication the previously unreported synthesis of fluorinated analogs of several insect sex pheromones, along with their biological activity on EAG.

Replacement of hydrogen atoms by fluorine at definite sites of a given pheromone molecule could eventually disrupt the mating communication system by irreversible binding of these fluorinated analogs with specific pheromone receptors. Furthermore, an enhancement of the chemical stability of the pheromone molecule, which might be essential under experimental field conditions, could also be expected.

As shown in scheme 1, synthesis of (Z)-9,(Z)-11,11-fluorotetradecadien-1-yl acetate **3a**, a fluorinated mimic of the sex pheromone of the Egyptian cotton leafworm *Spodoptera littoralis* (Boisd.)[5] was accomplished by Wittig reaction of the tetrahydropyranyl derivative of 9-hydroxy *n*-nonyltriphenylphosphonium ylide **1** with fluoroaldehyde **2a**[6]. The stereochemistry of **3a** was Z/E 92/8 according to GC analysis (glass capillary column OV-1 20 m, 0.30 mm i.d., 0.15 µl).

Analogously, aldehydes **2b**[6] and **2c**[6] were allowed to react with the required Wittig ylides under Schlosser procedure[7] (addition of 1 equivalent of *n*-BuLi. LiBr to the initially formed betaine), to yield the expected dienic alcohols, **3b** and **3c**, with predominantly the desired E stereochemistry of the newly formed double bond (Z/E 4/96 by GC analysis). Alcohol **3c** is a fluorinated mimic of the sex pheromone of the codling moth *Laspeyresia pomonella* L.[8] (Lepidoptera, Tortricidae). Acetylation of **3b** under standard conditions afforded (E)-9,11-fluorododecadien-1-yl acetate, **3'b**, a fluorinated analog of the sex pheromone of the red bollworm moth *Diparopsis castanea* Hampson[5] (Lepidoptera, Noctuidae).