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SPECIALIA

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Sesquiterpenes based on the cadalane skeleton from the brown alga *Dilophus fasciola*[1]

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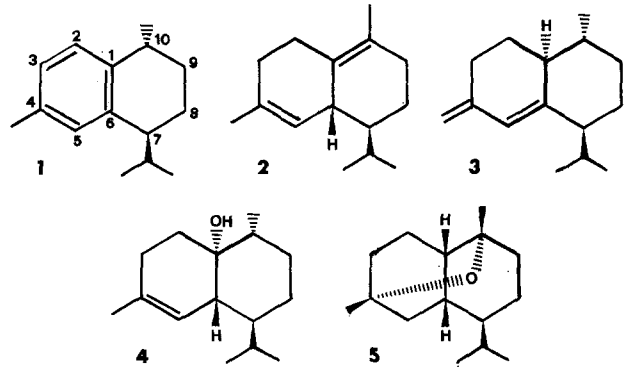
Summary. From the brown alga *Dilophus fasciola* (Dictyotaceae) the new sesquiterpene ether 4,10-epoxymuurolane has been isolated, along with known sesquiterpenes based on the cadalane skeleton, and its structure determined by spectroscopic methods.

The algal family Dictyotaceae is a rich source of terpenoids and other metabolites[2]. In a recent paper[3] we reported the isolation of a compound of mixed biogenesis, namely geranylgeranyl glycerol, from the more polar fractions of the chloroform extract of *Dilophus fasciola* (Roth) Howe, a brown alga belonging to this family. An investigation of the less polar fractions of the same extract has now led to the isolation of 5 sesquiterpenoids based on the cadalane skeleton, the hydrocarbons **1**–**3**, the alcohol **4** and the novel cyclic ether **5**.

Material and methods. D. fasciola (2.5 kg fresh weight) was collected near Catania, Sicily, during the spring of 1977. The chloroform extract of the freeze-dried alga was subjected to a gross fractionation on silica gel using increasing concentrations of ether in hexane as the eluent. From the early fractions of the hexane eluent, a hydrocarbon mixture was obtained, wherefrom isolation of individual components in pure form required extensive use of chromatography over $AgNO_3$ impregnated silica gel. Later eluates, which emerged from the column with 10% ether, on further chromatography over silica gel using benzene as eluent, gave the alcohol **4** and the ether **5**, and in addition 2 further oxygenated sesquiterpenoids currently under investigation. Aromatization was performed by heating at 250 °C for 3 h the pertinent compound (100 mg) with 10% Pd/C (100 mg). The crude product was chromatographed on silica gel (hexane as eluent) to give cadalene, identified by comparison of physical properties (UV, IR and NMR) with those of a reference sample. Partial aromatization of 1-epibicyclosesquiphellandrene was carried out with trifluoroacetic acid in the condition described by Andersen et al.[4].

Results and discussion. For all the isolated compounds the cadalane skeleton was established by dehydrogenation to cadalene. Compound **1** (0.1% dry weight of the alga) $C_{15}H_{22}$, and compound **2** (0.02%), $C_{15}H_{24}$, were identified, respectively as (1S-trans)-(−)-calamenene and δ-cadinene by comparison of their physical data ($[\alpha]_D$, MS, UV, IR and NMR) with those reported in the literature[4,5]. The 3rd hydrocarbon (0.25%), $C_{15}H_{24}$, $[\alpha]_D = +4.1°$ (c 1 in EtOH), was a conjugated diene that had spectral properties which matched those reported for 1-epibicyclosequiphellandrene[6]. However, since the OR of this compound, recently isolated from *Ocimum basilicum*[6], has not been recorded, the possibility that the algal metabolite could be its enantiomer was taken into consideration but definitely ruled out in view of the formation of (1S-trans-)-(−)calamenene by partial aromatization of **3**.



The alcohol **4**, $C_{15}H_{26}O$ (0.03%), was identified as cubenol by comparison of $[\alpha]_D$ and spectral data with those reported in the literature[5,7]. Compound **5** was isolated as an oil (0.08%), $[\alpha]_D = +15.4°$ (c 1 in EtOH). High resolution mass spectrometry established the elemental composition as $C_{15}H_{26}O$. The IR- and UV-spectra indicated the absence of hydroxyl or carbonyl group in the molecule. The single oxygen atom must be part of an ether bridge connecting 2 fully substituted carbon atoms; the IR-spectrum exhibited strong absorption at 1090 cm^{-1}, while the ^{13}C-NMR showed 2 singlets at 72.45 and 69.65 ppm. This spectrum also comprised 4 methines (47.27, 32.36, 30.89, 28.04), 5 methylenes (39.33, 34.80, 33.96, 27.31, 18.86) and 4 methyls (25.91, 22.29, 22.29, 21.34). The ^1H-NMR spectrum (270 MHz, $CDCl_3$) displayed singlets at δ 1.12 and 1.14 assignable to tertiary methyls attached to oxygen-bearing carbons. Other diagnostically valuable signals appeared at δ 0.69 (3H, d, J = 6.7 Hz) and 0.93 (3H, d, J = 6.7 Hz) and were assigned to methyls of an isopropyl group, since they collapsed to singlets by irradiation at frequency of an 1H multiplet at δ 1.73. From the above data it was established that **5** possessed the cadalane skeleton bearing an ether bridge connecting position 4 and 10. Closure of the oxane ring requires a cis relationship between H-1, H-6, Me-4 and Me-10. The relative stereochemistry of the remaining chiral centre at C-7 was established by the following criteria. a) Irradiation at δ 0.91 caused the isopropyl methine multiplet to collapse into a slightly broadened singlet; this revealed that the 1H signal masked by methyl groups, but evidenced by integration, was due to H-7. b) The signal of this proton and those of the isopropyl group remained almost unaffected by the addition of $Eu(fod)_3$ and thus the isopropyl-bearing ring must have, as expected, a chair conformation. c) In the ^1H-NMR spectrum a signal (dddd, J = 13.5, 13.5, 4.5, 4.5) is seen at δ 1.98, partially obscured by other protons, but well separated in C_6D_6; this signal, which suffers a remarkable europium shift, is simplified to a double-double doublet (J = 13.5, 13.5, 4.5) by irradiation at the frequency of H-7 (0.91); this result can only be explained assuming that the signal at δ 1.98 is due to the axial proton attached to C-8 and that H-7 is equatorial. Therefore, the new ether is 4,10-epoxymuurolane possessing the relative stereochemistry depicted in **5**. It is worth noting that *D. fasciola* accumulates sesquiterpenoids based on the cadalane skeleton, whereas the congener species *D. ligulatus* synthesizes perhydroazulene diterpenes[8].

Cadalane sesquiterpenes have been previously isolated from algae of the related genus *Dictyopteris* (cadalene, (−)-γ_1-cadinene and (−)-δ-cadinol from *D. divaricata*[9] and zonarene from *D. zonaroides*)[10].

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Synthesis of 5'-deoxypyridoxal derivatives

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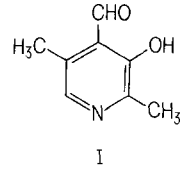
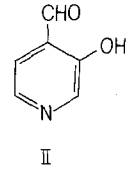
Summary. A convenient synthesis of 5'-deoxypyridoxal derivatives is described. The method involves catalytic hydrogenolysis of the corresponding 5'-phosphorylated derivatives; products are obtained in high yields.

5'-Deoxypyridoxal (**I**) and 3-hydroxypyridine-4-carboxaldehyde (**II**) are the best compounds available for the study of the mechanism of vitamin B_6 catalysis in model systems and have been used extensively for that purpose[3-11]. These vitamin analogs have the functional groups essential for pyridoxal phosphate-like catalysis and at the same time avoid the complications associated with pyridoxal phosphate and pyridoxal. In the case of pyridoxal phosphate, kinetic and equilibrium studies as a function of pH become more difficult owing to ionizations of the 5'-phosphate group. In the case of pyridoxal, internal hemiacetal formation between the 5-hydroxymethyl group and the 4-carboxyaldehyde group creates a condition that does not exist in the enzymically active, phosphorylated form of the vitamin[12]. Consequently, the vitamin analogs **I** and **II** are better in vitro model compounds than the naturally occuring forms of vitamin B_6. In addition to model system studies, compounds of this type have been used in the study of structure-activity relationships in vitamin B_6-dependent enzymes[13-16].



I



II

Several schemes for the synthesis of 5'-deoxypyridoxal, **I**[17-19], and 3-hydroxypyridine-4-carboxaldehyde, **II**[4, 20-22], have been reported. However, even the best synthetic approach for the preparation of 5'-deoxypyridoxal requires 5 steps[23], starting from commercially available pyridoxine. We report in this communication a general synthetic method that conveniently leads, in high yields, to the