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ACYCLIC TETRAPRENYLTOLUQUINOLS FROM *CYSTOSEIRA SAUVAGEUANA* AND THEIR POSSIBLE ROLE AS BIOGENETIC PRECURSORS OF THE CYCLIC *CYSTOSEIRA* METABOLITES

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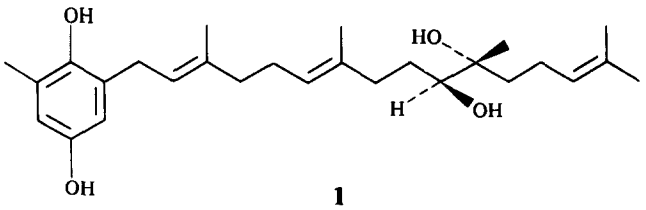
Key Word Index—*Cystoseira sauvageana*; Cystoseiraceae; brown algae; tetraprenyltoluquinols.

Abstract—From the brown alga *Cystoseira sauvageuana* two novel tetraprenyltoluquinols with an acyclic terpenoid side chain have been isolated. Their chemical transformation into compounds containing a cyclopentane ring provides a clue to the biogenesis of the cyclic *Cystoseira* metabolites.

INTRODUCTION

The marine genus *Cystoseira*, consisting of some 40 species, is widespread in the Mediterranean Sea where no less than 30 species rich in subspecies, varieties and forms are reported to occur [1].

In previous work concerned with the isolation of bioactive secondary metabolites from brown algae belonging to this genus, we described the structures of a number of tetraprenylhydroquinol derivatives in which the terpenoid component had an acyclic, a monocyclic or a bicarbocyclic nature [2–8]. Structures 1–4 (with relative stereochemistry only) exemplify the major categories of *Cystoseira* metabolites encountered until now. While compounds of the acyclic and monocyclic types have also been isolated from Atlantic, Pacific and Australian mem-



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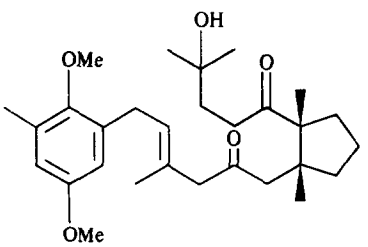

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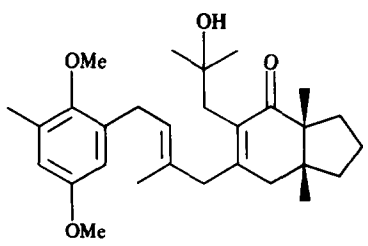

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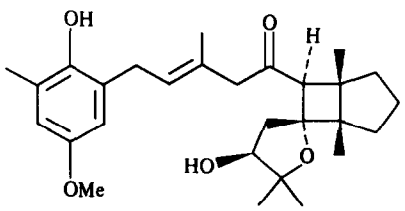

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bers of the families Cystoseiraceae and Sargassaceae [9–13], the bicyclic versions are known only from Mediterranean species.

This paper describes the structural work on two novel phenolic compounds with acyclic terpenoid side chains, isolated from *Cystoseira sauvageuana* Hamel, which appear to be likely candidates as biosynthetic precursors of the monocyclic and bicyclic tetraprenylhydroquinols.

RESULTS AND DISCUSSION

An ether extract of the freeze-dried alga, collected in October 1983 at Aci Castello, near Catania, Sicily, Italy, was chromatographed on a silica gel column to give a mixture of **5** and **7**. Separation of the isomers was achieved by HPLC.

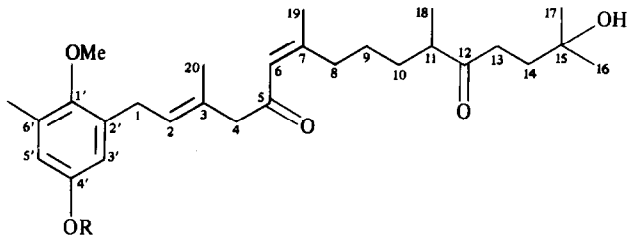
Combustion analysis and ^{13}C NMR spectroscopy revealed that the molecular formula of **5** was $C_{28}H_{42}O_5$ containing eight degrees of unsaturation. In the EI mass spectrum the molecular ion was not discernible; the highest M_r ion was observed at m/z 440 and corresponded to the loss of H_2O from the parent ion. The UV spectrum was consistent with the presence of a hydroquinol [λ_{max} 280 (ε = 3100) and 218 (ε = 13900)] and an enone [λ_{max} 243 (ε = 11400)] chromophore. The IR and ^{13}C NMR spectra of **5** showed the presence of an unconjugated carbonyl (1705 cm^{-1}; δ216.1, *s*) and a conjugated carbonyl (1680 cm^{-1}; δ199.4, *s*), while the ^1H NMR spectrum exhibited a methoxyl resonance at δ3.65. Since acetylation gave a phenolic monoacetate (**6**) (m/z 500 $[M]^+$ (barely detectable); intense peaks at 482 $[M-H_2O]^+$ and 440 $[M-H_2O-CH_2CO]^+$) which still showed hydroxyl absorption in the IR spectrum, the remaining two oxygen atoms were assigned to a phenolic and a tertiary alcohol group.

The ^{13}C NMR data (Table 1) supported the presence of

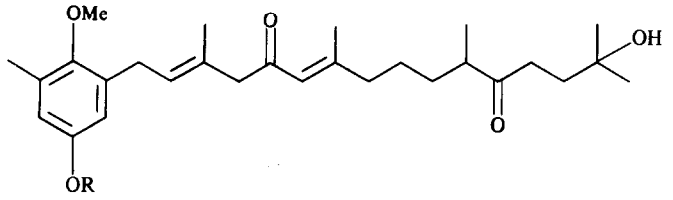
Table 1. ^{13}C NMR of compounds **5** and **7** (75.5 MHz, $CDCl_3$, TMS as int. standard)

C	5	7
12	216.1 *s*	216.4 *s*
5	199.4 *s*	200.3 *s*
7	159.8 *s*	159.2 *s*
4′	152.4 *s*	152.2 *s*
1′	149.9 *s*	150.2 *s*
2′, 6′ and 3	134.3 *s* 131.7 *s* 130.7 *s*	134.8 *s* 132.1 *s* 131.0 *s*
2 and 6	127.7 *d* 123.6 d	128.2 *d* 122.6 d
3′ and 5′	115.5 *d* 113.8 *d*	115.8 *d* 114.7 *d*
15	70.5 *s*	70.7 *s*
OMe	60.4 *q*	60.6 *q*
4	55.1 *t*	55.7 *t*
11	46.2 *d*	46.2 *d*
8, 9, 10, 13 and 14	36.7 *t* 35.7 *t* 33.6 *t* 33.0 *t* 25.6 *t*	41.2 *t* 36.6 *t* 36.2 *t* 32.5 *t* 25.1 *t*
16 and 17	29.3 *q* 29.0 *q*	29.5 *q* 29.3 *q*
1	27.9 *t*	28.2 *t*
19	25.4 *q*	19.4 *q*
18, 20 and 6′-Me	16.6 *q* 16.6 *q* 16.1 *q*	16.5 *q* 16.5 *q* 16.3 *q*

*Multiplicities were obtained by off-resonance decoupling experiments.



5 R = H
6 R = Ac
8 R = Me



7 R = H
9 R = Me

a tetrasubstituted benzene ring and a methoxyl and also indicated seven methylenes, a methine, an oxygen-bearing quaternary carbon and six methyls, two of them on oxygen-bearing carbon. In addition, four olefinic carbons (two singlets and two doublets) were present, demanding that the diterpene portion be acyclic. Most structural detail was obtained from a ^{1}H NMR analysis of **5** involving extensive double resonance experiments (Table 2). Signals pertaining to the aromatic ring substituents were, in addition to that of the methoxyl group, a methyl singlet at δ2.22 and a 2H doublet (J = 7.5 Hz) at 3.36 associated with the benzylic methylene. The aromatic protons at δ6.50 and 6.55 forming an AB system with J = 3 Hz indicated a 1,2,3,5-tetrasubstituted benzene ring. Definite placement of the substituents followed from nuclear Overhauser enhancement experiments and consideration of the ^{13}C NMR data. Irradiation of the aromatic methyl singlet caused a 15% enhancement of the proton at δ6.55 while irradiation of the benzylic methylene resulted in a 12% enhancement of the second aromatic proton (δ6.50), thus proving that there was only one proton *ortho* to each of the groups irradiated. This result was compatible with only two structures for the aromatic moiety, namely that illustrated by partial structure **A** or the alternative one in which the hydroxyl and the methoxyl groups are interchanged. This second possibility was ruled out on the basis of the value of the chemical shift (60.4 ppm) of the methoxyl in the ^{13}C NMR spectrum; indeed, in a number of closely related compounds typical values for the resonance of a methoxyl group in position 1′ or 4′ are *ca* 60 and 55 ppm, respectively [6, 14]. Part structure **A** could be further expanded to give fragment **B** considering that the benzylic methylene is vicinally coupled to the vinyl proton at δ5.34 (t, J = 7.5 Hz) which is in turn allylically coupled with both the methyl singlet at 1.69 and the methylene singlet at 3.12. Failure of **5** to cyclize to the relevant chromane or chromene further proved the location of the OH group at 4′ rather than 1′.

The following considerations allowed the structure of the remainder of the molecule to be clarified. The 1H singlet at δ6.08 was associated with the vinyl proton α to the carbonyl. One of the β substituents of the conjugated double bond is necessarily the vinyl methyl at δ1.69, while the second one must be the methylene associated with the resonance at 2.49 (C-8), the unusual deshielding being attributable to steric compression with the carbonyl group [15]. Irradiation of the signal at δ2.49 simplified the multiplet at 1.37 and conversely irradiation at 1.37 affected the multiplet at 2.49, but at the same time perturbed complex signals centred at 1.73 and 1.43 where the C-10 methylene protons resonated. Irradiation of each of these signals effected a change in the signal of the C-9 methylene and also collapsed the methine multiplet at δ2.60 (C-11). Finally, irradiation at the methine frequency likewise affected the protons at C-10 and reduced the doublet at 1.06 for the C-18 methyl protons to a singlet. To rationalize the chemical shift of the C-11 methine, the unconjugated carbonyl group had to be placed at C-12. The C-13 and C-14 methylenes appeared as triplets coupled to each other (J = 7.5 Hz) at δ2.66 and 1.75, respectively. Thus, the partial structure involving C-5–C-14 was firmly established, the remaining groups being only two methyls bonded to a hydroxyl-bearing carbon. This led unavoidably to structure **5** for the algal metabolite. The ^{1}H NMR spectrum in C_6D_6 (Table 2) confirmed the above assignments and showed the expected shifts for the signals of the protons in the vicinity of the carbonyl groups.

Table 2. ^{1}H NMR of compounds **5** and **7** (300 MHz, TMS as int. standard)*

	5		**7**	
H	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
3′	6.50 } AB (3)	6.87 } AB (3)	6.49 *br*	6.83 } AB (3)
5′	6.55 }	6.76 }		6.75 }
1	3.36 *d* (7.5)	3.47 *d* (7.5)	3.36 *d* (7.5)	3.45 *d* (7.5)
2	5.34 *t* (7.5)	5.39 *t* (7.5)	5.42 *t* (7.5)	5.48 *t* (7.5)
4	3.12 *s*	2.90 *s*	3.08 *s*	3.03 *s*
6	6.08 *s*	5.82 *s*	6.11 *s*	6.13 *s*
8	2.49†	2.55†	2.06†	1.87†
9	1.37†	1.31†	1.39†	1.26†
10	1.73†	1.70†	1.60†	1.65†
	1.43†	1.30†	1.30†	1.16†
11	2.60 *m*	2.42 *m*	2.57 *m*	2.29 *m*
13	2.66 *t* (7.5)	2.60 *t* (7.5)	2.59 *t* (7)	2.44 *t* (7)
14	1.75 *t* (7.5)	1.75 *t* (7.5)	1.76 *t* (7)	1.75 *t* (7)
16	1.21 *s*	1.15 *s*	1.22 *s*	1.09 *s*
17	1.21 *s*	1.16 *s*	1.23 *s*	1.11 *s*
18	1.06 *d* (7)	0.95 *d* (7)	1.07 *d* (7)	0.93 *d* (7)
19	1.84 *s*	1.51 *s*	2.09 *s*	2.17 *s*
20	1.69 *s*	1.67 *s*	1.71 *s*	1.70 *s*
OMe	3.65 *s*	3.44 *s*	3.66 *s*	3.44 *s*
6′-Me	2.22 *s*	2.20 *s*	2.22 *s*	2.22 *s*

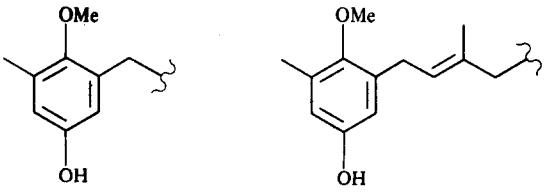
*Coupling constants (J in parentheses) are given in Hz.
†Overlapped with other signals.

The second compound (7) isolated from *C. sauvageuana* was an isomer of **5** and had very similar IR (ν_{max} 3430, 1700, 1682 and 1610 cm^{-1}) and UV [λ_{max} 281 (ε = 2700), 242 (ε = 12 300) and 224 (ε = 13 600)] properties. The ^1H NMR spectral characteristic of **7** were essentially identical to those of **5**, except in the region influenced by the stereochemistry of the C-6 double bond. As expected for a change from *Z* to *E* geometry, the resonance of the C-7 methyl shifted down-field from δ 1.84 in **5** to 2.09 in **7**, while that of the C-8 methylene suffered an upfield shift from 2.49 to 2.06. A comparison of the ^{13}C NMR spectra of the two isomeric compounds confirmed this inference, as the vinyl methyl, in agreement with the literature for similar compounds [16] resonated at δ 25.4 and 19.4 in the *Z* and *E* isomer, respectively. Configuration at the C-11 chiral centre has not been established.

The *C. sauvageuana* metabolites are closely related to a pair of geometrical isomers isolated from *Halidrys siliquosa* (order Fucales, family Fucaceae) which are reported to isomerise rapidly around the C-6 double bond in $CDCl_3$ or on silica gel to give on equilibrium mixture (1:9) with the *E* isomer predominating [10]. In the case in hand we did not observe such a ready isomerization, which could only be obtained photochemically, and therefore we believe that both isomers are naturally occurring compounds.

Simple inspection of the structural characteristics of the new acyclic *Cystoseira* metabolites suggests that they could be intermediates in the biosynthesis of the mono- and bi-carbocyclic versions isolated from brown algae belonging to the same genus. Indeed, C-11 to C-7 bond formation through a Michael reaction would lead to the cyclopentane ring system as in **2**. This monocyclic diterpenoid by an aldol condensation could in turn ring-close from C-5 to C-13 to yield the bicyclo[4.3.0]nonane system present in **3** (the feasibility of this reaction by chemical means has been demonstrated previously), while C-6 to C-12 bonding would give the bicyclo[3.2.0]heptane skeleton found in **4**.

To check whether the postulated internal Michael reaction was practicable *in vitro*, the isomeric mixture of the acyclic diketones **5** and **7** (more readily available than the individual compounds) was methylated with methyl iodide in the presence of potassium carbonate to yield an approximately equimolar mixture of **8** and **9**. When this mixture was treated with potassium ethoxide in ethanol* four products were obtained after chromatographic separation. One of them, $C_{29}H_{42}O_4$, had spectral properties (UV, IR, ^1H NMR) identical to those of **3**, but was optically inactive; from this it was concluded that the compound in question was a racemic mixture of the enantiomers with the angular methyls *cis*. None of the remaining three compounds, which were optically inactive, could be identified with known *Cystoseira* metabolites. On the basis of the spectral data (see Experimental), a second product (**10**) was recognized as the *Z* isomer of **3**. Compounds **11** and **12** both had molecular formula $C_{29}H_{44}O_5$; the IR and UV spectra of each showed the presence of an unconjugated carbonyl (**11**: ν_{max} 1712 cm^{-1}; **12**: ν_{max} 1695 cm^{-1}) and a conjugated carbonyl [**11**: ν_{max} 1690 cm^{-1}, λ_{max} 243 nm (ε = 7300); **12**: ν_{max} 1680 cm^{-1}, λ_{max} 243 nm (ε = 10 100)]. These data and the ^1H NMR spectra (see Experimental) provided evidence that they were geometrical isomers formed from **2** by C-2 to C-3 double-bond migration. To confirm this structural assignment we reinvestigated the previously reported [6] base-induced cyclization of **2** into **3**. The by-products formed in this reaction have now been isolated and found to be optically active **10**, **11** and **12**, in which the relative stereochemistry of the chiral centres is obviously the same as in **2**. The identity of the proton spectra of these compounds with those of their optically



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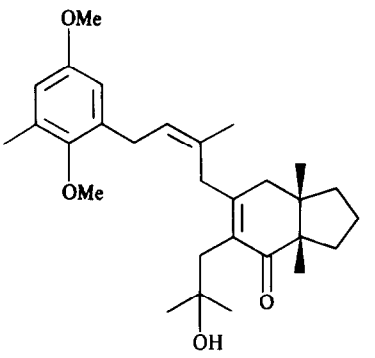

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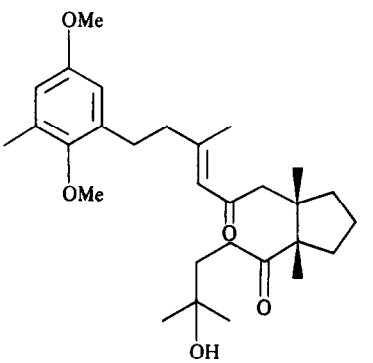

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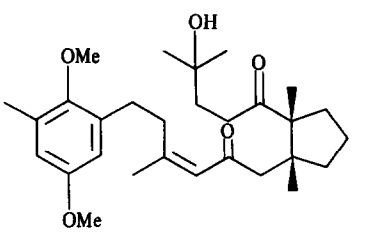

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*Since in these conditions an equilibrium between **8** and **9** could be anticipated, it was considered useless to carry out the reaction on the individual isomers.

inactive counterparts, obtained by cyclization of **8** and **9**, indicates that these last are all racemic mixtures of the stereoisomers with the bridgehead methyl groups in a *cis*-disposition.

The chemical transformation of open-chain metabolites into compounds containing the cyclopentane ring lend support the hypothesis that the biological process takes place in a similar way.

EXPERIMENTAL

EIMS: 70 eV (Kratos MS-50); ^{1}H NMR: 300 and 80 MHz; ^{13}C NMR: 75.5 MHz. Chemical shifts are quoted in ppm (δ) relative to TMS. Prep. LC and HPLC: were carried out on a Jobin–Yvon LC Miniprep and a Varian 5020 equipped with Varian UV-50 detector instruments, respectively.

Plant material. Cystoseira sauvageuana Hamel (voucher specimen deposited at the Herbarium of the Institute of Botany, Catania, Italy) was collected at about 4 m depth in Oct. 1983 at Aci Castello, Sicily.

Extraction and purification. Shade dried and ground alga (1.5 kg) was extracted ×3 with $CHCl_3$ at room temp. with continuous stirring. The extracts were pooled and evaporated to give a dark green oil (18 g). The crude extract was applied to a column (3 × 100 cm) of Florisil and eluted with increasing concentrations of Et_2O in hexane starting with 40% Et_2O in hexane. Fractions of 200 ml were collected and those exhibiting similar TLC profiles combined. Fractions 35–61 were pooled and subjected to prep. LC (LiChroprep Si-60, C_6H_{12}–*i*-PrOH, 19:1) to give an oily residue (400 mg). An aliquot (100 mg) of this oil was subjected to prep. HPLC (Whatman, Partisil M9 10/25, gradient elution from 2 to 3% *i*-PrOH in CH_2Cl_2) to give pure **5** (50 mg, total yield 0.013% dry wt) and **7** (28 mg, total yield 0.008% dry wt).

Compound **5**, oily, $[\alpha]_D^{20}$ +1.07° (*c* 0.8 in EtOH); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3410, 1705, 1680, 1610; UV λ_{max}^{EtOH} nm: 218 (ε = 13 900), 243 (ε = 11 400), 280 (ε = 3100); MS *m/z* (%): 440 (15), 422 (3), 235 (13), 191 (6), 175 (8), 153 (18), 152 (100), 139 (35), 121 (13), 109 (19), 95 (16), 81 (13), 69 (37), 55 (16), 43 (21), 41 (31). (Found: C, 73.15; H, 9.02. $C_{28}H_{42}O_5$ requires C, 73.36; H, 9.17.)

Compound **7**, oily, $[\alpha]_D^{20}$ +1.18° (*c* 1.02 in EtOH); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3430, 1700, 1682, 1610; UV λ_{max}^{EtOH} nm: 224 (ε = 13 600), 242 (ε = 12 300), 281 (ε = 2700); MS *m/z* (%): 440 (8), 422 (3), 235 (13), 191 (9), 175 (11), 153 (13), 152 (100), 139 (16), 121 (10), 109 (21), 95 (22), 81 (17), 69 (35), 55 (14), 43 (16), 41 (47). (Found: C, 73.09; H, 9.00. $C_{28}H_{42}O_5$ requires C, 73.36; H, 9.17.)

Acetylation of **5** *to give* **6**. Compound **5** (5 mg) was acetylated (Ac_2O–pyridine; overnight at room temp.) to give **6** (4 mg); HRMS: $[M]^+$ 500.3130 (calc. for $C_{30}H_{44}O_6$ 500.3137); MS *m/z*: 500 $[M]^+$, 482 $[M-H_2O]^+$, 440 $[M-H_2O-CH_2CO]^+$; IR ν_{max}^{film} cm^{-1}: 3450, 1745, 1705, 1680, 1605.

Attempted cyclization of **5**. When **5** was refluxed in pyridine for 10 hr neither chromane nor chromene could be detected.

Photoisomerization of **5** *to give* **7**. A soln of **5** (10 mg) in EtOH (3 ml) in a quartz cell (1 cm path) was deoxygenated with pure N_2 and irradiated at 280 nm with a Hanau Q 400 mercury vapour lamp by means of an interference filter (Zeiss Jena). The reaction was followed by analytical HPLC (Merck, LiChrosorb Si-100, 10 μm, 2% *i*-PrOH in CH_2Cl_2), and was stopped when more polar by-products began to appear. The constituents of the reaction mixture were separated by prep. HPLC (Whatman, Partisil M9 10/25, gradient elution from 2 to 3% *i*-PrOH in CH_2Cl_2) to give 3 mg of **7** and 6 mg of starting material. The physical properties of the semisynthetic product were identical with those of the natural metabolite.

Methylation of the mixture of **5** *and* **7**. K_2CO_3 (1 g) and MeI (0.5 ml) where added to a soln of a mixture of **5** and **7** (100 mg) in Me_2CO (5 ml) and the suspension was refluxed for 3 hr. After addition of H_2O the organic material was extracted with Et_2O. Evaporation of the solvent left 90 mg of a mixture of **8** and **9**. An aliquot (10 mg) of this mixture was separated by prep. HPLC (Whatman, Partisil M9 10/25, 1% *i*-PrOH in CH_2Cl_2) to afford analytical samples of **8** (4 mg) and **9** (4 mg).

Compound **8**, oily. (Found: C, 73.55; H, 9.19. $C_{29}H_{44}O_5$ requires C, 73.73; H, 9.32); ^{1}H NMR ($CDCl_3$, 80 MHz, TMS): δ6.40 (2H, *s* (*br*), H-3′ and H-5′), 5.94 (1H, *s*, H-6), 5.29 (1H, *t*, *J* = 7.5 Hz, H-2), 3.65 and 3.59 (3H each, *s*, OMe), 3.30 (2H, *d*, *J* = 7.5 Hz, H-1), 3.01 (2H, *s*, H-4), 2.21 (3H, *s*, 6′-Me), 1.79 (3H, *s*, H-19), 1.69 (3H, *s*, H-20), 1.18 (6H, 2*s*, H-17 and H-16), 1.05 (3H, *d*, *J* = 7 Hz, H-18).

Compound **9**, oily. (Found: C, 73.51; H, 9.22. $C_{29}H_{44}O_5$ requires C, 73.73; H, 9.32); ^{1}H NMR ($CDCl_3$, 80 MHz, TMS): δ6.40 (2H, *s* (*br*), H-3′ and H-5′), 5.95 (1H, *s*, H-6), 5.30 (1H, *t*, *J* = 7.5 Hz, H-2), 3.65 and 3.60 (3H each, *s*, OMe), 3.30 (2H, *d*, *J* = 7.5 Hz, H-1), 3.00 (2H, *s*, H-4), 2.20 (3H, *s*, 6′-Me), 2.05 (3H, *s*, H-19), 1.70 (3H, *s*, H-20), 1.18 (6H, 2*s*, H-17 and H-16), 1.07 (3H, *d*, *J* = 7 Hz, H-18).

Cyclization of **8** *and* **9** *to give* **3**, **10**, **11** *and* **12**. The remainder of the mixture of **8** and **9** (80 mg) was dissolved in EtOH (2 ml) and a 10% soln of EtOK in EtOH (2 ml) was added. After standing overnight at room temp. the soln was diluted with H_2O and extracted with Et_2O. Evaporation of the solvent left a residue which was subjected to prep. LC (LiChroprep Si-60, using as eluent 40% Et_2O in hexane followed by 60% Et_2O in hexane). Three fractions were obtained in order of increasing polarity: the first one was a mixture of **10** and **3**, while the other two were pure **11** and **12**. Prep. HPLC (Whatman, Partisil M9 10/25, *i*-PrOH in C_6H_{14}) of the first fraction yielded 5 mg of **10** and 16 mg of **3**.

Compound **10**, $[\alpha]_D^{20}$ 0°; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3430, 1670, 1605; UV λ_{max}^{EtOH} nm: 218 (ε = 12 100), 250 (ε = 10 200), 283 (ε = 3100); HRMS: $[M]^+$ 454.3075 (calc. for $C_{29}H_{42}O_4$ 454.3082); ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ6.59 and 6.56 (2H, AB system, *J* = 3 Hz, H-3′ and H-5′), 5.51 (1H, *t*, *J* = 7.5 Hz, H-2), 3.77 and 3.70 (3H each, *s*, OMe), 3.42 (2H, *d*, *J* = 7.5 Hz, H-1), 3.17 (2H, *s* (*br*), H-4), 2.78 and 2.53 (2H, AB system, *J* = 14 Hz, H-14), 2.42 and 2.17 (2H, AB system, *J* = 18 Hz, H-6), 2.30 (3H, *s*, 6′-Me), 1.64 (3H, *s*, H-20), 1.24 and 1.17 (3H each, *s*, H-16 and H-17), 1.05 (3H, *s*, H-19), 0.84 (3H, *s*, H-18).

Compound **3**, $[\alpha]_D^{20}$ 0°; all the other physical properties were identical to those of the natural product.

Compound **11**, 25 mg, $[\alpha]_D^{20}$ 0°; IR ν_{max}^{film} cm^{-1}; 3450, 1712, 1690, 1600; UV λ_{max}^{EtOH} nm: 220 (ε = 12 200), 243 (ε = 7300), 280 (ε = 2850); HRMS: $[M]^+$ 472.3183 (calc. for $C_{29}H_{44}O_5$ 472.3188); ^{1}H NMR ($CDCl_3$, 80 MHz, TMS): δ6.42 (2H, *s* (*br*), H-3′ and H-5′), 5.96 (1H, *s*, H-4), 3.66 and 3.59 (3H each, *s*, OMe), 2.54 (2H, *t*, *J* = 7 Hz, H-13), 2.21 (3H, *s*, 6′-Me), 1.82 (3H, *s*, H-20), 1.72 (2H, overlapped, H-14), 1.18 (6H, 2*s*, H-16 and H-17), 1.08 (3H, *s*, H-19), 0.91 (3H, *s*, H-18).

Compound **12**, 18 mg, $[\alpha]_D^{20}$ 0°: IR ν_{max}^{film} cm^{-1}: 3450, 1695, 1680, 1610; UV λ_{max}^{EtOH} nm: 224 (ε = 11 900), 242 (ε = 10 100), 280 (ε = 2900); HRMS: $[M]^+$ 472.3180 (calc. for $C_{29}H_{44}O_5$ 472.3188); ^{1}H NMR ($CDCl_3$, 80 MHz, TMS): δ6.47 and 6.39 (2H, AB system, *J* = 3 Hz, H-3′ and H-5′), 5.96 (1H, *s*, H-4), 3.65 and 3.59 (3H each, *s*, OMe), 2.87 and 2.31 (2H, AB system, *J* = 14 Hz, H-6), 2.45 (2H, *t*, *J* = 7 Hz, H-13), 2.20 (3H, *s*, 6′-Me), 2.11 (3H, *s*, H-20), 1.77 (2H, overlapped, H-14), 1.17 (6H, 2*s*, H-16 and H-17), 1.07 (3H, *s*, H-19), 0.89 (3H, *s*, H-18).

Treatment of **2** *with base to give* **3**, **10**, **11** *and* **12**. Compound **2** (100 mg) was treated with base in the conditions reported previously. Chromatographic separation of the products gave **10** (8 mg), **11** (30 mg) and **12** (28 mg), in addition to **3** (25 mg). All physical properties (IR, UV, MS, NMR) of the compounds

obtained were identical to those of the corresponding products formed by cyclization of **8** and **9**, apart from the optical rotations which were as follows: **10** $[\alpha]_D^{20}$ (λ) +48.5° (589), +55.2° (578), +76.5° (546) (c = 0.9 in EtOH); **11** $[\alpha]_D^{20}$ (λ) +19.1° (589), +19.5° (578), +22.6° (546) (c = 0.9 in EtOH); **12** $[\alpha]_D^{20}$ (λ) +10.3° (589), +10.5° (578), +10.8° (546) (c = 0.6 in EtOH).

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