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Leptogorgolide, a biogenetically interesting 1,4-diketo-cembranoid that reinforces the oxidation profile of C-18 as taxonomical marker for octocorals

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ABSTRACT

The cembranoid **1** and the furanocembranolides **2**–**4** along with the known pukalide were isolated from *Leptogorgia* sp. and their structures determined spectroscopically. The 1,4-diketo-cembranoid **1** follows an oxidation pattern of C-18 that reinforces the concept of oxidation profile of C-18 as taxonomical marker for octocorals. The co-occurrence within a species of furanocembranolide/1,4-diketo-cembranoid congeners **1**/**2**–**4** raises the question about which one is the biogenetic precursor. A biogenetic pathway is proposed.

1. Introduction

Octocorals of the genera *Pseudopterogorgia*, *Alcyonium*, *Gersemia*, *Lophogorgia*, *Leptogorgia*, and *Sinularia* have the ability to biosynthesize highly oxygenated diterpenoids based on a 14-membered carbocyclic cembrane skeleton[1] into which a substituted furan ring and a γ-lactone subunit are embedded. The oxidative cleavage of the furan ring may lead to a 1,4-diketo-derivative and naturally occurring metabolites with this feature are frequently found, mainly in species of genera *Pseudopterogorgia*, *Alcyonium*, *Gersemia*, and *Sinularia*. However, the co-occurrence of both furanocembranolides and their 1,4-diketo-cembranoid equivalents within a species raises the question about which one is the biogenetic precursor.

The search for marine natural products produced by benthic organisms from both sides of the Isthmus of Panama[2] prompted us to study the eastern Pacific octocoral *Leptogorgia* sp. In this paper we report on the structures of four new cembranoids **1**–**4** along with the known compound pukalide,[3] isolated from this species. In a previous paper, based on a survey on marine furanocembranolides, we introduced the concept of *genus-specific oxidation* by which these metabolites could be divided into four classes according to the oxidation degree of their C-18: class A (Me), class B (CHO), class C (COOH), and class D (COOMe).[4] This classification provides a criterion as taxonomical marker for octocorals. In this work, for the first time a 1,4-diketo-cembranoid **1** with an oxidized C-18 as a methyl ester has been discovered in *Leptogorgia*. Thus, the occurrence in *Leptogorgia* of compound **1** and the related furanocembranolide equivalents **2**–**4** suggested that the 1,4-diketo-cembranoid congeners may follow a parallel genus-dependent C-18 specific oxidation.

A new analysis of furanocembranoids and 1,4-diketo-cembranoids isolated from species of the aforementioned six genus are summarized in Table 1. The following features were observable: (1) species of genus *Pseudopterogorgia* biosynthesize furanocembranolides of classes A, C, and D as well as 1,4-diketo-cembranoid congeners of class A (i.e., bipinnatin P) and class D (bipinnatin Q, **1a**)[5] and a 1,4-diketo-nor-C-18-cembranoid (gorgiacerolide);[6] (2) species of genus *Alcyonium* and *Gersemia* exclusively biosynthesize 1,4-diketo-cembranoids and furanocembranolides of class A; (3) no 1,4-diketo-cembranoids of class B, which are to be expected for species of genus *Lophogorgia* and *Leptogorgia*, have been described; (4) species of genus *Sinularia* biosynthesize furanocembranolides and 1,4-diketo-cembranoids of class D. This genus is also specially rich in 1,4-diketo-nor-C-18-cembranolides. Table 1 indicates that C-18 of 1,4-diketo-cembranoids, as well as their furanocembranoid

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Table 1
Correlation genus/class A–D[a] of cembranoids and nor-C-18-cembranoids

Genus	Furanocembranoids	1,4-Diketo-cembranoids
Pseudopterogorgia	A, C, D	A, D, nor-C-18
Alcyonium	A	A
Gersemia	A	A
Lophogorgia	B	Unknown
Leptogorgia	B, D	D
Sinularia	D	D, nor-C-18

[a] Class indicates the type of functionality of C-18: class A (Me); class B (CHO); class C (COOH); class D (COOMe).

congeners follow an identical oxidation pattern, which reinforces the concept of *genus-specific oxidation* as taxonomical marker for octocorals.

Leptogorgolide **1** is oxidized at C-18 (class D) as expected for *Leptogorgia* cembranoids. This and the above facts suggested that 1,4-diketo-cembranoids may follow an oxidation pattern at C-18 like their related furanocembranoids, thus reinforcing the concept of *genus-specific oxidation* as taxonomical marker for octocorals.

2. Results and discussion

Leptogorgolide **1** was an unstable colorless oil $[\alpha]_D^{20}$ −61 (*c* 0.23, CH_2Cl_2). Its EIMS showed a peak at 404.1457, which corresponds to the empirical formula $C_{21}H_{24}O_8$ $[M-CH_3COOH]^+$ (HREIMS). Absorption for carbonyl groups at 1785, 1765, and 1740 cm^{-1} were observed in the IR spectrum. The ^{13}C NMR and DEPT spectra of **1** (Table 2) showed the presence of 23 carbon signals assigned to 4×CH_3 (one methoxy group, and one from an acetyl group), 5×CH_2 (one olefinic), 6×CH and eight quaternary carbons (two ketones, three carboxyls and one olefinic). ^1H and ^{13}C NMR data were very similar to those of bipinnatin Q,[5] particularly the chemical shifts for the carbons implied in the 1,4-dicarbonyl moiety of the molecule. Connectivity information obtained from COSY, HSQC, and HMBC experiments unambiguously determined the planar structure of compound **1** as a 1,4-diketo cembranoid containing a C5-C8-oxane ring, a C10-C20-epoxylactone, and an acetate group at C-13.

The relative stereochemistry of compound **1** was deduced by the study of NOESY experiments and coupling constants. NOE correlations of H_3-19 with H-5 as well as the correlation of H-5 with H-4 indicated that H-4, H-5, and Me-19 are on the same face of the molecule. A dihedral angle of 95° for H-10/H-11 calculated for the energy-minimized[7] conformation of **1**, Figure 2, proved to be in good agreement with the absence of coupling constant for H-11 (*δ* 4.25, s) (Table 2), and confirms the relative stereochemistry of C-10 and C-11 as represented in **1**. On the other hand, the NOE observed between H-11 and H-13 and between H-13 and H-1 as well as the *J* values of H-13 (dd, 9.1 and 5.4 Hz) fixed the relative configuration of the acetyl group and the epoxide ring as shown, thus establishing the whole relative stereochemistry of **1**.

Leptodiol **2** was a colorless oil $[\alpha]_D^{20}$ +44 (*c* 0.41, CH_2Cl_2) with a mass of 464.1666 corresponding to an elemental composition of $C_{23}H_{28}O_{10}$. The NMR data of **2** (Table 2) resemble those of lophodiol A,[8] **2a**, Figure 1, with the primary difference being an methyl ester substituent at C-4 (δ_H 3.78 s, δ_C 51.5 and δ_C 163.8 ppm) instead of the aldehyde group of compound **2a**. The planar structure of compound **2** was confirmed by, COSY, HSQC, and HMBC experiments.

Acetate of leptodiol **3** was isolated as an oil $[\alpha]_D^{20}$ +27 (*c* 0.49, CH_2Cl_2). NMR data coupled with a molecular ion at *m/z* 506.1809 (HREIMS) suggested a molecular formula of $C_{25}H_{30}O_{11}$ indicating 11 degrees of unsaturation. Compound **3** was verified as the acetate derivative of leptodiol **2**, as was corroborated via chemical transformation. Acetylation of **2** produced a compound whose ^1H NMR spectrum displays signals that exactly reproduce those obtained for the natural product.

Comparison of the coupling constants of H_2-9, H-10, H-11, and H-13 of **2** and **3** with those of lophodiol A **2a** and its acetate **3a**,

Table 2
NMR data of compounds **1**–**4** [500 MHz, *δ* ppm, (*J*) Hz, $CDCl_3$]

No.	Leptogorgolide **1**		Leptodiol **2**		Leptodiol acetate **3**		8-*epi*-Lopholide **4**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	3.06 m	38.9	3.20 br s	37.6	3.26 br s	37.8	2.60 (overlapped)	40.8
2	2.58 m	45.4	3.00 m	32.7	3.09 dd (17.0, 10.4)	32.6	3.32 dd (14.8, 11.7)	30.9
	2.67 dd (12.9, 8.2)				3.01 dd (17.0, 4.1)		3.09 dd (14.8, 3.2)	
3		202.4		159.8		160.1		161.5
4	3.92 d (2.5)	60.8		115.0		115.5		115.3
5	4.26 d (2.5)	76.4	6.62 s	108.9	6.63 s	109.8	6.78 s	112.7
6	—	211.1		152.6		149.0		147.4
7	2.64 d (18.0)	50.4	5.12 br s	73.5	6.14 s	74.3	3.76 s	57.3
	2.51 d (18.3)							
8		80.0		73.9		73.5		59.4
9	2.27 m	41.8	1.61 dd (14.5, 8.8)	41.1	1.61 dd (14.8, 9.2)	41.4	2.60 dd (14.5, 4.7)	35.8
	2.56 m		1.68 dd (14.5, 6,9)		1.75 dd (14.8, 6.9)		1.71 m (overlapped)	
10	4.76 dd (6.0,2.2)	77.5	4.78 dd (8.7, 7.2)	74.7	4.78 dd (8.8, 6.9)	74.6	4.55 dd (12.6, 4.7)	75.0
11	4.25 s	66.6	4.24 br s	63.3	4.09 m	63.0	3.66 br s	62.9
12	—	60.3		59.0		59.0		58.6
13	5.16 dd (9.1,5.4)	67.9	4.94 dd (6.6, 2.8)	69.2	4.95 dd (7.3, 2.8)	69.2	4.95 dd (6.9, 6.6)	65.8
14	2.04 m	34.5	1.76 d (14.8)	33.0	1.70 m	33.0	2.22 ddd (14.8, 7.6, 7.6)	34.3
	2.29 m		2.32 m		2.37 m		1.71 m (overlapped)	
15		147.0		147.3		147.2		146.3
16	4.63 br s	111.6	4.81 s	110.9	4.83 br s	111.1	4.80 s	110.5
	4.74 dd (1.3, 1.3)		4.79 s				4.73 s	
17	1.72 s	19.2	1.80 s	20.7	1.82 s	20.6	1.80 s	21.6
18		167.5		163.8		163.5		163.1
19	1.48 s	26.0	1.38 s	22.7	1.40 s	23.2	1.52 s	21.7
20		168.7		168.8		167.9		167.6
21	3.75 s	52.7	3.78 s	51.5	3.79 s	51.6	3.83 s	51.7
22		169.8		170.6		170.4		169.7
23	2.08 s	20.9	2.05 s	20.6	2.06 s	20.6	2.01 s	20.7
24						169.7		
25					2.16 s	20.9		

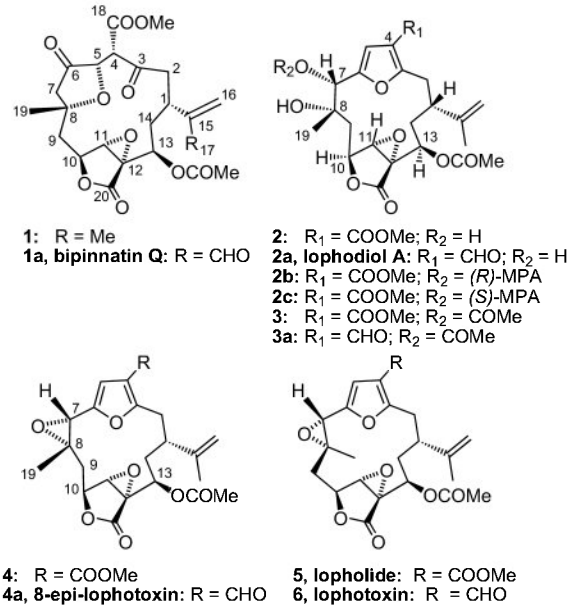

Figure 1. Cembranolides **1**–**4** and related known cembranoids.

respectively, indicates that **2** and **3** must possess the same relative sterochemistry as lophodiol A, Table S1 (Supplementary data). The relative configuration at C-7 and C-8 of **2** and **3** was corroborated by the NOE observed between H-7 with H_3-19 and H-5, Figure 2.

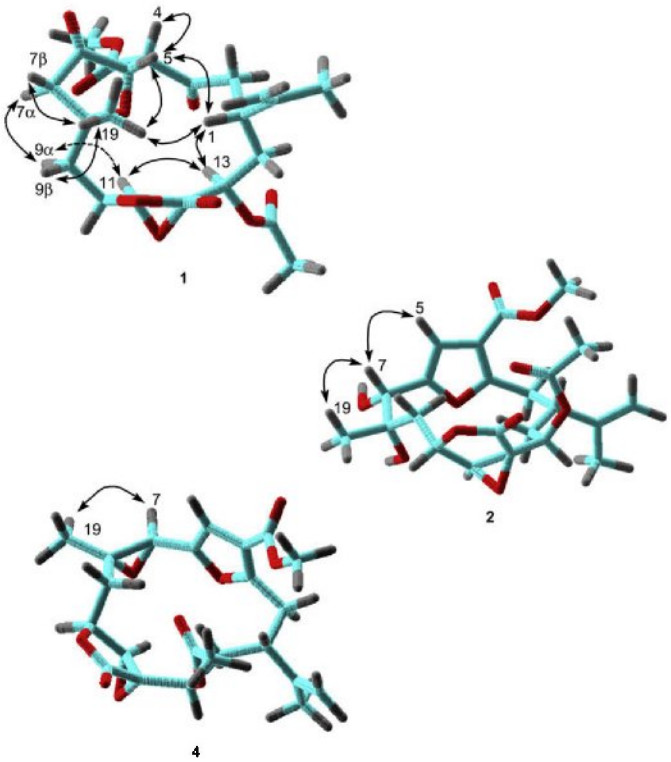

Figure 2. Selected NOEs of compounds **1**–**4**.

The absolute configuration of **2** was established by derivatization with (*R*)- and (*S*)-α-methoxy-α-phenylacetic acids (MPA). NMR analysis[9] of the Δδ values for the two MPA esters **2b** and **2c** gave clear evidence to assign the absolute stereochemistry at C-7 as *S*, Table 3. Thus, this information allowed to establish the absolute configuration of leptodiol **2** as 1*R*,7*S*,8*S*,10*S*,11*S*,12*S*,13*R*.

Table 3
^{1}H NMR Δδ ($\delta_R-\delta_S$) values ($CDCl_3$, ppm, recorded at 500 MHz) of the diastereomeric MPA esters **2b** and **2c**

	δ_R	δ_S	$\Delta\delta^{RS}$
H-5	6.58	6.41	+0.17
Me-19	1.00	1.32	−0.32
H-10	4.38	4.63	−0.25

8-*epi*-Lopholide **4** was isolated as a colorless oil $[\alpha]_D^{20}$ −22 (*c* 0.41, CH_2Cl_2). Its HREIMS exhibited a molecular ion peak at *m*/*z* 446.1546, consistent with the molecular formula $C_{23}H_{26}O_9$. The planar structure of **4** determined on the basis of spectroscopic data, Table 2, showed to be coincident to that of lopholide **5**,[10] Figure 1. Comparison of the chemical shifts of compound **4** with those of lopholide showed strong differences at H-7, Me-19 and also at C-7, C-8, and C-9, indicative of changes in the stereochemistry of the 7,8-epoxide ring, Table S2 (Supplementary data). The NOE correlation between H_3-19 and H-7, Figure 2, evidences a *cis*-epoxide with an opposite configuration at C-8 to that corresponding to lopholide. On the other hand, comparison of the coupling constants of H_2-9, H-10, H-11, H-13, and H_2-14 with those of synthetic 8-*epi*-lophotoxin **4a**,[5] obtained by epimerization of lophotoxin **6**, Figure 1, revealed that compounds **4** and **4a** possess the same relative configuration, as depicted in Figure 1.

Compounds **1**, **3**, and **4** were isolated from a unique extract of *Leptogorgia*, therefore all of them should belong to the same enantiomeric series as **2**. Thus, the absolute stereochemistry of these compounds have been assigned as follow: leptogorgolide **1**, 1*R*,4*S*,5*S*,8*R*,10*S*,11*S*,12*S*,13*R*; acetate of leptodiol **3**, 1*R*,7*S*,8*S*,10*S*,11*S*,-12*S*,13*R*; 8-*epi*-lopholide **4**, 1*R*,7*S*,8*S*,10*S*,11*S*,12*S*,13*R*.

2.1. Biogenetic pathway

Genus-dependent C-18 specific oxidation model for the tandem furanocembranolide/1,4-diketo-cembranoid provides evidence regarding the mechanism of the biogenesis of the biosynthetic equivalent couples. To the best of our knowledge, all regular naturally occurring furanocembranolide (**11**)/1,4-diketo-cembranoid (**13**) congeners belong to either class A (Me) or class D (COOMe). No 1,4-diketo-cembranoids of class B or class C have been so far described. The genus *Sinularia*, in addition to furanocembranolides of class D, also biosynthesizes a number of related 1,4-diketo-nor-C-18-cembranoids, **14**. From the biosynthetic point of view, and considering that no nor-C-18-furanocembranolides (**12**) from any genus of octocorals have been reported, it appears reasonable to suppose that regular furanocembranolides (**11**) may be considered as precursors of their 1,4-diketo-cembranoid congeners (**13**). Then, they could evolve to their corresponding nor-1,4-dicarbonyl species (**14**) by loss of the methyl group in a decarboxylative step from a Me-18 oxidation cascade (Fig. 3). The discovery of a nor-1,4-diketo-cembranoid, gorgiacerolide,[6] from *Pseudopterogorgia acerosa* supports this hypothesis.

However, from the genus *Lophogorgia*, that exclusively biosynthesize furanocembranolides of class B (CHO), four 1,4-diketo-cembranoid of class A (Me) have been reported: lophodione, isolophodione, and epoxylophodione isolated from *Lophogorgiaalba*,[11] and isoepoxylophodione from *Lophogorgia peruana*[8] (Fig. 4). This finding opposes the aforementioned biogenetic hypothesis since the oxidation degree at C-18 has not been conserved, and leads to question if 1,4-diketocembranoids are, in these two cases, precursors of their furanocembranoid congeners. However, it should be noted that the species *Lophogorgia chilensis*, *Lophogorgia cuspidata*, *Lophogorgia rigida*, and *Lophogorgia*

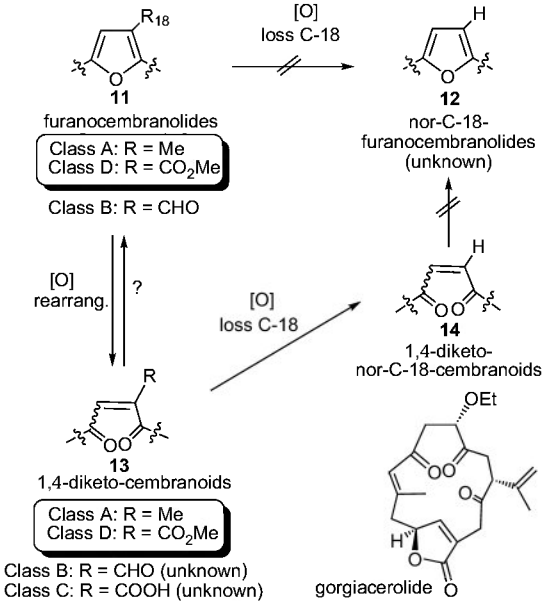

Figure 3. Furanocembranolides as biogenetic precursors of 1,4-diketo- and nor-C-18-cembranoids.

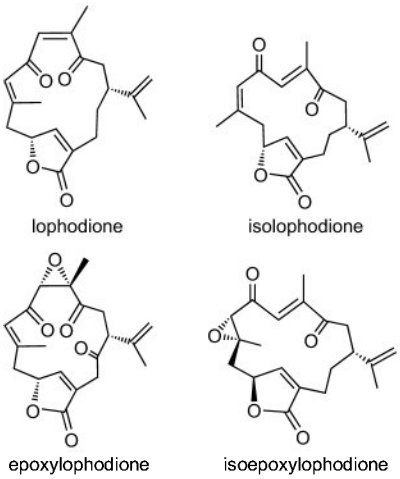

Figure 4. 1,4-Diketo-cembranoids of class A (Me) isolated from *L. alba*[11] and *L. peruana*.[8]

violacea biosynthesize furanocembranolides of class B, as expected, but neither of them has been reported to biosynthesize 1,4-diketo-cembranoids of class A–D.

Therefore, since the concept of genus-specific oxidation of C-18 is applicable to the tandem furanocembranolide/1,4-diketo-cembranoid, with the aforementioned exception, we propose a biogenetic route (Fig. 5) by which 1,4-diketo-cembranoids, for example, **1**, may be originated from an oxidative cleavage of the furan ring[1b] of a furanocembranolide like **7**. Insertion of biologically excited singlet oxygen O_2 ($^1\Delta g$) in the 1,4-diene of **7** leading to **8** in an overall 1,4-addition, followed by an endoperoxide cleavage to **9**, could be an interesting pathway to **1**, since it may represent an evolutionary advantage in quenching damaging reactive oxygen species (ROS), thus enhancing the fitness of *Leptogorgia* sp.

Since the taxonomic work is difficult and time consuming, the rationalization genus/classes A–D correlation of the present study seems a relevant tool to facilitate taxonomic work dealing with several genus of octocorals.

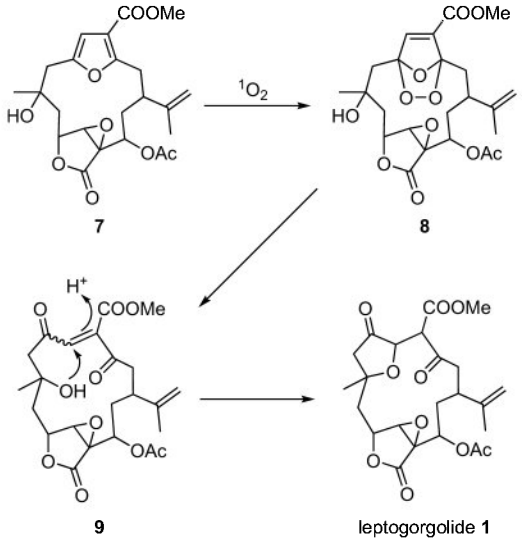

Figure 5. Possible biogenesis of leptogorgolide **1**.

3. Experimental

3.1. General procedures

Optical rotations were measured on a Perkin–Elmer model 343 Plus polarimeter using a Na lamp at 25 °C. IR spectra were obtained with a Perkin–Elmer 1650/FTIR spectrometer. ^{1}H NMR and ^{13}C NMR, HSQC, HMBC, and COSY spectra were measured employing a Bruker AMX 500 instrument operating at 500 MHz for ^{1}H NMR and at 125 MHz for ^{13}C NMR. Two-dimensional NMR spectra were obtained with the standard Bruker software. EIMS and HRMS data were taken on a Micromass Autospec spectrometer. HPLC separations were performed with a Hewlett–Packard 1050 (Jaigel-Sil semipreparative column, 10 μm, 20×250 mm) with hexane/EtOAc mixtures. The gel filtration column (Sephadex LH-20) used hexane/MeOH/CH_2Cl_2 (3:1:1) as eluent. The spray reagent for TLC was H_2SO_4/H_2O/AcOH (1:4:20).

3.2. Biological material

Leptogorgia sp. was collected by SCUBA diving off Jicarita (Panama) at −15 m. A voucher specimen has been deposited at Smithsonian Tropical Research Institute (Panama) with code 200511.

3.3. Extraction and isolation

Specimens of *Leptogorgia* sp. were extracted with acetone at room temperature and were concentrated to give a dark residue (44.2 g). The extract was partitioned between EtOAc (3×100 mL) and water (100 mL). The EtOAc extracts were combined to obtain a brown oil (24.5 g). Vacuum flash chromatography of the organic extract gave three fractions (30–50% hexane/EtOAc) containing cembranolides, as indicated by their ^{1}H NMR spectra. The fractions were further chromatographed by molecular exclusion LH-20 and HPLC to give compounds **1** (9.8 mg), **2** (34.8 mg), **3** (12.6 mg) and **4** (13.8 mg), and the known compounds pukalide (32.5 mg) and *E*-deoxypukalide (4.3 mg).

3.3.1. *Compound* ***1***

Colorless oil, $[\alpha]_D^{20}$ −61 (*c* 0.23, CH_2Cl_2); ^{1}H ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 1; EIMS *m/z* 404 (100) $[M-AcOH]^+$, 372 (67) $[M-AcOH-MeOH]^+$, 346 (32); HREIMS

m/z 404.1457 (calcd for $C_{21}H_{24}O_8$, 404.1471); IR (film) ν_{max} 1785, 1765, 1740, 1234, cm^{-1}.

3.3.2. Compound **2**

Colorless oil, $[\alpha]_D^{20}$ +44 (*c* 0.41, CH_2Cl_2); ^1H ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 1; EIMS *m/z* 464 (0.2) $[M]^+$, 446 (0.6) $[M-H_2O]^+$, 355 (1), 237 (13), 168 (100); HREIMS *m/z* 464.1666 (calcd for $C_{23}H_{28}O_{10}$, 464.1682), 446.1598 (calcd for $C_{23}H_{26}O_9$ 464.1577); IR (film) ν_{max} 3480, 2952, 1783, 1716, 1442, 1375, 1232 cm^{-1}.

3.3.3. Compound **3**

Colorless oil, $[\alpha]_D^{20}$ +27 (*c* 0.49, CH_2Cl_2); ^1H ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 1; EIMS *m/z* 506 (0.6) $[M]^+$, 446 (2) $[M-AcOH]^+$, 355 (5), 168 (100); HREIMS *m/z* 506.1809 (calcd for $C_{25}H_{30}O_{11}$, 506.1788), 446.1585 (calcd for $C_{23}H_{26}O_9$ 464.1577); IR (film) ν_{max} 3483, 2952, 1783, 1731, 1440, 1373, 1232 cm^{-1}.

3.3.4. Compound **4**

Colorless oil, $[\alpha]_D^{20}$ −22 (*c* 0.41, CH_2Cl_2); ^1H ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 1; EIMS *m/z* 446 (75) $[M]^+$, 386 (31) $[M-AcOH]^+$, 168 (100); HREIMS *m/z* 446.1546 (calcd for $C_{23}H_{28}O_{10}$, 446.1577); IR (film) ν_{max} 2954, 1788, 1738, 1721, 1715, 1646, 1615, 1578, 1228 cm^{-1}.

3.3.5. *(R)- and (S)-MPA ester derivatives* ***2a*** *and* ***2b***

A solution of compound **2** (2.8 mg, 6.0×10^{-3} mmol) in 1.0 mL of CH_2Cl_2 was treated with *N,N′*-dicyclohexylcarbodiimide (2.5 mg, 1.2×10^{-2} mmol), 4-dimethylaminopyridine (5.0 mg, 4.1×10^{-2} mmol), and (*R*)-α-methoxy-α-phenylacetic acid (6.5 mg, 3.9×10^{-2} mmol) and stirred at room temperature for 1 h. After filtration, the reaction mixture was purified by silica gel chromatography (hexane/EtOAc 1:1) to give the (*R*)-MPA ester derivative **2a** (1.9 mg, 3.1×10^{-3} mmol, 51.7% yield). The same experimental procedure was followed to obtain the (*S*)-MPA ester derivative **2b** (2.1 mg, 3.5×10^{-3} mmol, 58.3% yield).

3.3.6. *Acetylation of* ***2***

A solution of compound **2** (6.4 mg, 1.4×10^{-2} mmol) in dry C_5H_5N (0.5 mL) was treated with Ac_2O (0.3 mL), stirred at room temperature for 12 h, then poured into 5% aqueous HCl, and extracted with CH_2Cl_2. The reaction mixture was purified on HPLC (hexane/EtOAc 1:1) to give a compound (6.0 mg, 1.2×10^{-2} mmol, 85.7% yield) that showed a ^1H NMR spectrum coincident to that for the natural compound **3**.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.05.068.

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