Absolute Structures of New Briarane Diterpenoids from *Junceella fragilis*

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Four new diterpenoids with the briarane skeleton, (−)-4-deacetyljunceellolide D (**2**), (+)-11α,20α-epoxyjunceellolide D (**3**), (−)-11α,20α-epoxy-4-deacetyljunceellolide D (**4**), and (−)-11α,20α-epoxy-4-deacetoxyjunceellolide D (**5**), (+)-junceellolide A (**6**) [the antipodal derivative of the known (−)-junceellolide A], along with three known briaranes, (−)-junceellolide D (**1**), (−)-junceellin (**7**), and (−)-praelolide (**8**), were isolated from the Indonesian gorgonian *Junceella fragilis*. The structures of the new compounds were established on the basis of extensive NMR studies and by comparison with the spectral data from other briarane compounds. The absolute configurations for four of the compounds were determined by the modified Mosher method and by unambiguous chemical interconversions.

Gorgonians belonging to the genus *Junceella* (Gorgonacea) are known to produce highly oxidized diterpenoids of the briarane class (3,8-cyclized cembranoids). About 24 briaranes have been isolated from the four species of *Junceella* studied so far.[1,2] Most of these compounds are characterized by the presence of a chloro-substituent at C-6 (19 compounds), an 11,20-epoxide group (17 compounds), or by a $\Delta^{(11),20}$ double bond (six compounds). Although several briaranes showed potent biological activities (cytotoxic, antiinflammatory, ichthyotoxic, antiviral, etc.), the absolute configuration is known in very few of them (nine compounds).[3]

Results and Discussion

The gorgonian *Junceella fragilis* Ridley, collected along the coast of Halmahera Island (Indonesia), was extracted with MeOH to give a crude extract that was fractionated by a previously described partition procedure.[4] The CH_2-Cl_2 partition gave a diterpene mixture that was chromatographed on a Si gel flash column (CH_2Cl_2 mixtures with MeOH) and HPLC [normal-phase with EtOAc−hexane mixtures and reversed-phase with MeOH−H_2O (1:1)] to give pure compounds **1**−**8**. The properties of the known junceellolide D [(−)-**1**], the major briarane isolated from this gorgonian, were very useful in the characterization of the new derivatives[5] (see Scheme 1).

A new briarane, compound **2**, was isolated as a colorless oil. The FABMS (positive ion) displayed a pseudomolecular ion at *m*/*z* 509 $[M + H]^+$ corresponding to the molecular formula $C_{26}H_{36}O_{10}$. The carbon and proton NMR chemical shifts of **2** were very similar to those of (−)-**1**, but they showed that one of the acetate groups in (−)-**1** had been replaced by a hydroxyl group in (−)-**2**. The upfield shift of the signal for H-4 by 0.85 ppm in the ^{1}H NMR spectrum of **2** in relation to the corresponding proton in **1** allowed us to assign the hydroxyl group to the C-4 position and indicated that **2** is the 4-deacetyl derivative of **1** (Table 1). The relative configuration of (−)-**2** was shown to be the same as that of (−)-**1** by the analysis of proton−proton coupling constants in the ^{1}H NMR spectrum of **2** and by comparison of its NMR data with those of (−)-junceelloide D (**1**).[5] Furthermore, acetylation of (−)-**2** with Ac_2O−pyridine gave exclusively a compound whose NMR data and optical rotation were identical to those of (−)-junceelloide D [(−)-**1**]. Thus, we assigned compound (−)-**2** as (−)-4-deacetyljunceellolide D.

We established the absolute configuration at carbon C-4 of compound (−)-**2** by applying the modified Mosher methodology to the free hydroxyl group at that position.[6,7] Thus, (−)-4-deacetyljunceellolide D [(−)-**2**] was esterified separately with the (*R*) and (*S*) enantiomers of 2-methoxyphenylacetic acid (MPA),[8,9] and each of the resulting pair of diastereomers, **2a** and **2b**, was analyzed for differential ^{1}H NMR resonances (Figure 1). For a given proton we consider $\Delta\delta^{SR}$ as the difference between the chemical shift in the (*S*)-MPA derivative minus that of the same proton in the (*R*)-MPA derivative (**2a** and **2b**, respectively). In this way, we obtained $\Delta\delta^{SR}$ signs and values (Table 2) for key signals (H-2, H-3, H-6, and Me-16) indicating that the absolute stereochemistry of the secondary alcohol at C-4 is *R*. This requirement led us to complete the absolute structure of (−)-**2**, which was determined to be (1*R*,2*S*,4*R*,-5*Z*,7*S*,8*R*,9*S*,10*S*,14*S*,17*R*)-2,9,14-triacetoxy-4,8-dihydroxybriara-5,11(20)-dien-18-one. Chemical interconversion of (−)-**2** into (−)-junceellolide D [(−)-**1**] fixed the absolute stereochemistry of the latter. Thus, the absolute structure for (−)-junceellolide D is (1*R*,2*S*,4*R*,5*Z*,7*S*,8*R*,9*S*,10*S*,14*S*,-17*R*)-2,4,9,14-tetraacetoxy-8-hydroxybriara-5,11(20)-dien-18-one.

Compound **3** was isolated as a colorless solid. The FABMS (positive ion) displayed two pseudomolecular ions at *m*/*z* 589 $[M + Na]^+$ and *m*/*z* 567 $[M + H]^+$ suggesting a molecular formula of $C_{28}H_{38}O_{12}$, which was confirmed by HRFABMS. ^{1}H NMR, ^{13}C NMR, ^{1}H−^{1}H COSY, and HMQC experiments allowed us to assign all the protons to their corresponding carbons as shown in Table 1. A ^{13}C−^{1}H HMBC experiment permitted determination of the connectivity of the isolated spin systems. The carbon resonances of C-11 and C-20 at δ 62.3 (s) and 59.1 (t), respectively, indicated the presence of an epoxy group between these positions. The proton chemical shifts of H-20 at δ 2.94 and 2.85 (1H each, br d, J = 3.4 Hz) confirmed the presence of this functionality. Comparison of the spectral data obtained for (+)-**3** with those of (−)-**1** indicated that the two compounds are very similar, differing only in that the $\Delta^{11(20)}$ double bond in (−)-**1** is epoxidized in (+)-**3**. The relative configuration of compound (+)-**3** was determined by a NOESY experiment. NOESY correlations between H-10 to H-9 and H-2 and this, in turn, to H-4 and also between Me-18 to H-9, indicated that these protons are on the same side of the cyclodecene ring. Additional

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Scheme 1

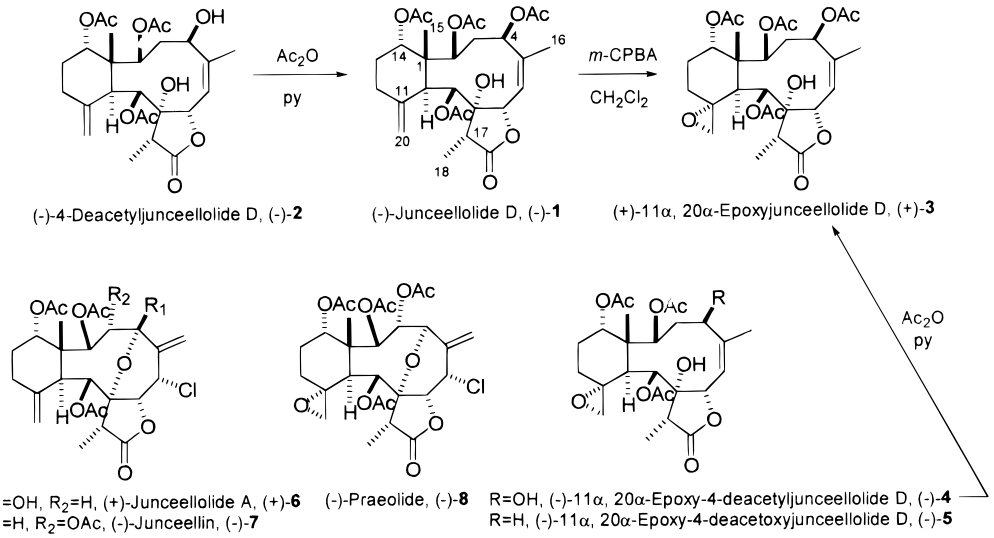

Table 1. ^{13}C and ^{1}H NMR ($CDCl_3$) Data for Compounds **2**−**5**[a]

	2		**3**		**4**		**5**	
position	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	47.3 s		47.1 s		47.1 s		47.4 s	
2	72.8 d	4.70 (br d, 4.9)	71.8 d	4.67 (br d, 4.7)	72.7 d	4.60 (d, 4.9)	73.4 d	4.71 (br d, 4.9)
3	40.5 t	2.70 (t, 13.7), 2.00 (m)	37.7 t	2.75 (t, 14), 1.93 (m)	40.3 t	2.67 (t, 13.9), 2.02 (m)	31.9 t	2.51 (m), 1.71 (m)
4	71.3 d	4.38 (dd, 12.2, 5.9)	72.4 d	5.12 (dd, 12.7, 5.7)	71.1 d	4.32 (dd, 11.9, 5.7)	28.7 t	2.01 (m), 1.05 (m)
5	147.2 s		143.1 s		145.8 s		135.6 s	
6	123.3d	5.89 (d, 10.2)	124.8 d	5.70 (d, 10.3)	124.5 d	5.77 (d, 10.0)	120.7 d	5.60 (br d,10.2)
7	76.8 d	5.79 (d, 10.2)	77.1 d	5.48 (d, 10.3)	76.8 d	5.72 (d, 10.0)	77.9 d	5.13 (d, 10.2)
8	82.9 s		80.1 s		80.1 s		80.1 s	
9	71.1 d	5.24 (d, 5.4)	73.2 d	4.85 (d, 5.1)	73.3 d	4.86 (d, 5.2)	77.6 d	4.84 (d, 4.9)
10	42.2 d	3.31 (d, 5.4)	39.8 d	2.38 (s)	39.8 d	2.37 (s)	39.6 d	2.17 (s)
11	151.1 s		62.3 s		62.3 s		62.6 s	
12	25.7 t	1.8 (m), 1.1 (m)	23.6 t	1.90 (m), 1.14 (m)	23.7 t	1.78 (m), 1.09 (m)	23.6 t	1.81 (m), 1.05 (m)
13	27.5 t	2.2 (m), 2.1 (m)	24.3 t	2.40 (m), 2.24 (m)	24.3 t	2.38 (m), 2.12 (m)	24.3 t	2.4 (m), 2.1 (m)
14	73.7 d	4.70 (br d, 4.9)	67.4 d	5.65 (d, 5.6)	67.4 d	5.65 (d, 5.6)	67.4 d	5.63 (br d, 5.4)
15	15.1 q	1.11 (s)	14.7 q	1.12 (s)	14.7 q	1.13 (s)	14.5 q	1.10 (s)
16	26.2 q	2.15 (d, 0.5)	25.9 q	2.17 (s)	26.1 q	2.09 (d, 1.0)	28.1 q	2.02 (s)
17	42.4 d	2.47 (q, 7.1)	42.2 d	2.36 (q, 7.0)	42.2 d	2.34 (q, 7.0)	42.3 d	2.37 (q, 7.1)
18	6.4 q	1.10 (d, 7.1)	6.6 q	1.15 (d, 7.0)	6.6 q	1.16 (d, 7.0)	6.5 q	1.15 (d, 7.1)
19	176.0 s		176.5 s		176.4 s		176.8 s	
20	112.9 t	5.03 (br s),	59.1 t	2.94 (d, 3.4),	59.1 t	2.95 (d, 3.3),	59.1 t	2.98 (br d, 4.1),
		4.87 (br s)		2.85 (d, 3.4)		2.85 (d, 3.3)		2.86 (br d, 4.1)
COMe	170.7 s		170.4 s		169.7 s		170.6 s	
	170.6 s		170.1 s		169.8 s		170.2 s	
	169.9 s		169.8 s		170.6 s		169.9 s	
			169.5 s					
CO**Me**	20.9 q	2.23 ($2CH_3$, s)	20.7 q	2.25 (s)	20.9 q	2.24 (s)	20.8 q	2.23 (s)
	21.1 q	1.99 (s)	20.9 q	2.13 (s)	21.1 q	2.01 (s)	20.9 q	2.02 (s)
	21.8 q		21.1 q	2.07 (s)	21.7 q	1.95 (s)	21.7 q	1.97 (s)
OH			21.8 q	1.98 (s)				
				4.82 (s)		4.84 (s)		

[a] ^{13}C NMR multiplicities were assigned from the DEPT spectrum.

NOESY correlations between Me-15 to H-14 and H-17 indicated that these are on the other side of the cyclodecene ring. The carbon and proton chemical shifts at positions C-11 and C-20 were coincident with those of known briaranes bearing an epoxy group between these positions where C-20 is pseudoaxial and β-oriented to the cyclohexane ring.[5]

The absolute configuration of compound (+)-**3** was determined by its chemical interconversion from (−)-**1**. Thus, (−)-junceellolide D [(−)-**1**] was submitted to epoxidation with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 to give a mixture of epoxides. HPLC of the resulting mixture allowed the isolation of a compound whose NMR data and optical rotation were coincident with those of compound (+)-**3**. Therefore, we assigned compound (+)-**3** as (+)-11α,20α-epoxyjunceelloide D, and its absolute structure is (1*R*,2*S*,4*R*,5*Z*,7*S*,8*R*,9*S*,10*S*,11*R*,14*S*,17*R*)-2,4,9,14-tetraacetoxy-11,20-epoxy-8-hydroxybriara-5-en-18-one.

Diterpene **4** was also isolated as a colorless solid, and its LREIMS showed a molecular ion at *m*/*z* 524, suggesting the molecular formula $C_{26}H_{36}O_{11}$. The spectral data of **4** are very similar to those of compound **3** but differ in the absence of an acetate group. The H-4 chemical shift value at δ 4.32 (1H, dd, J = 11.9, 5.7 Hz) of compound (−)-**4** is shifted upfield by 0.80 ppm in relation to the corresponding proton in (+)-**3**, and this indicates that the free hydroxyl group must be placed at C-4. Acetylation of compound (−)-**4** with Ac_2O in pyridine gave exclusively a compound whose ^{1}H NMR data and optical rotation showed it to be (+)-**3**. Consequently, we assigned compound (−)-**4** as (−)-

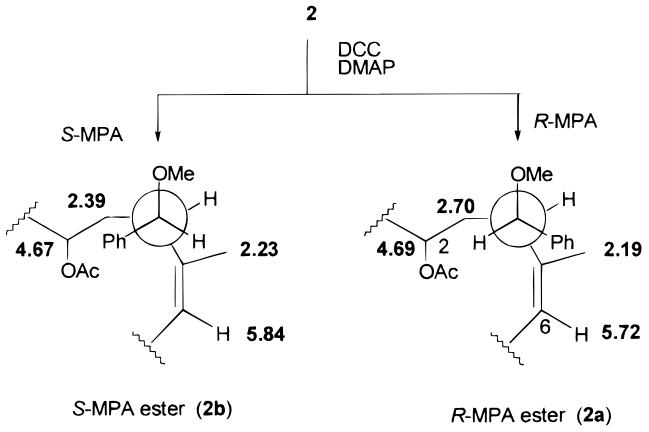

Figure 1. $\Delta\delta^{SR}$ values (in ppm) obtained from the MPA esters of 2.

Table 2. $\Delta\delta^{SR}$ Values Obtained from the MPA Esters of **2**

H	**2**	**3a**	**6**	**16**
$\Delta\delta^{SR} = \delta_S - \delta_R$ (ppm)	−0.02	−0.31	+0.12	+0.04

11α,20α-epoxy-4-deacetyl junceelloide D, and thus its absolute structure is (1*R*,2*S*,4*R*,5*Z*,7*S*,8*R*,9*S*,10*S*,11*R*,14*S*,-17*R*)-2,9,14-triacetoxy-11,20-epoxy-4,8-dihydroxybriara-5-en-18-one.

Compound **5** was isolated as a colorless solid. The molecular formula $C_{26}H_{36}O_{10}$ was established by (+)-HRFABMS, which displayed a pseudomolecular ion at *m/z* 509.2386 $[M + H]^+$ (Δ 1.3 mmu). The ^1H NMR and ^{13}C NMR spectra indicated the presence of three acetate groups in **5**. Comparison of the NMR spectral data for compound (−)-**5** with those of (+)-**3** and (−)-**4** suggested that these compounds have very similar structures. However, the proton and carbon chemical shifts of H-4 [δ_H 2.01 and 1.05 (1H each, m)] and C-4 (δ_C 28.7, t) in **5** indicated the absence of an acetate group, or a hydroxyl group at this location. Therefore, compound (−)-**5** must be (−)-11α,20α-epoxy-4-deacetoxyjunceellolide D. As the relative stereochemistry of **2** was generally the same as **3** and **4**, we propose the following relative stereochemistry for this compound: (1*R**,2*S**,7*S**,8*R**,9*S**,10*S**,11*R**,14*S**,17*R**).

Compound (+)-**6** was isolated as a yellow solid. The FABMS (positive ion) showed pseudomolecular ions at *m/z* 541/543 $[M + H]^+$ and 563/565 $[M + Na]^+$, corresponding to the molecular formula $C_{26}H_{33}ClO_{10}$. This molecular formula was corroborated by HREIMS, which showed the $[M]^+$ as a cluster at *m/z* 540.1755/542.1732. The NMR spectral data were found to be identical with those reported by Fenical et al. for (−)-junceelloide A isolated from *Junceella fragilis*.[5] However, these compounds differed in the sign of specific rotation: $[\alpha]_D$ +3.1° (*c* 0.6, CH_2Cl_2) for compound **6** versus $[\alpha]_D$ −7.9° (*c* 0.6, $CHCl_3$) for (−)-junceelloide A. On the basis of this fact, compound **6** must be the enantiomer of (−)-junceelloide A, and thus we assigned (+)-**6** as (+)-junceelloide A. Additional examples of antipodal isolation within this class of compounds include gemmacolides B and C, which were isolated in both enantiomeric forms from two different *Junceella* species.[2,10] Moreover, the spectral data of compounds **7** and **8** matched those reported by Fenical et al. for (−)-junceellin and (−)-praelolide, both isolated from *Junceella fragilis*.[5]

Compounds **1**−**8** showed no cytotoxic activity against several tumor cells (P-388, A-549, HT-29, MEL-28).

Experimental Section

General Experimental Procedures. Optical rotations were measured in CH_2Cl_2 using a JASCO DIP-1000 polarimeter with a sodium lamp operating at 598 nm. The NMR spectra were recorded on a Brucker AC 200 F and AMX 500 instruments, using $CDCl_3$ as solvent and internal standard. Multiplicities were obtained by DEPT. Semipreparative HPLC was carried out using μ-Bondapack C_{18} reversed-phase columns (300 × 8 mm) and a μ-Porasil normal-phase column (300 × 7.8 mm) using a differential refractometer detector. Fast-atom bombardment mass spectra (FABMS and HRFABMS) were obtained using VG QUATTRO and Autospec-M mass spectrometers employing Xe atoms in a thioglycerol matrix. HREIMS and LREIMS were obtained on those spectrometers operating at 70 eV. (*R*)- and (*S*)-MPAs were obtained from Aldrich.

Biological Material. Specimens of *Junceella fragilis* were collected in October 1996, at Halmahera Island (Indonesia) (1° 41.550′ N, 127° 32.156′ E) at a depth of 27−33 m. Voucher samples are deposited at the Departamento de Química Fundamental e Industrial, Universidade da Coruña, under reference UDC 96026.

Extraction and Isolation. Specimens of the gorgonian (2 kg) were homogenized in MeOH (3 × 2.5 L), and the solvent was evaporated under reduced pressure. The crude extract was partitioned between CH_2Cl_2 and H_2O (1:1). The fraction soluble in CH_2Cl_2 was evaporated under pressure and partitioned between 10% aqueous MeOH (400 mL) and hexane (2 × 400 mL). H_2O was added to the polar fraction until the mixture became 50% aqueous MeOH and then was extracted with CH_2Cl_2 (3 × 400 mL). The H_2O-soluble fraction was extracted with *n*-BuOH saturated with H_2O (3 × 400 mL). After evaporation, the combined organic layers yielded 3.3 g (hexane), 1.5 g (CH_2Cl_2), and 1.3 g (*n*-BuOH) of residues. The viscous oil (3.3 g) obtained from the CH_2Cl_2 fraction was purified by flash column chromatography (Si gel 230−400 mesh, eluting with CH_2Cl_2−MeOH mixtures of increasing polarity) to give a fraction rich in diterpenes. This fraction was separated by reversed-phase HPLC eluting with MeOH−H_2O (1:1) and then by normal-phase HPLC eluting with mixtures of hexane−EtOAc to give several fractions. Purification of the individual fractions was achieved by normal-phase HPLC to give compounds **1** (24 mg) and **5** (10 mg) eluting with hexane−EtOAc (2:3), compounds **2** (15 mg), **4** (8 mg), **7** (5 mg), and **8** (3 mg) eluting with hexane−Me_2CO (65:35), and compound **6** (15 mg) eluting with hexane−EtOAc (1:4). Reversed-phase HPLC eluting with MeOH−H_2O−TFA (50:50:0.1) provided compound **3** (11 mg).

(−)-4-Deacetyljunceellolide D [(−)-2]: colorless powder; $[\alpha]^{22}_D$ −54.1° (*c* 0.3, CH_2Cl_2); ^1H and ^{13}C NMR see Table 1; (+) LRFABMS *m/z* 509 $[M + H]^+$, 391 $[M - 2OAc + H]^+$.

(+)-11α,20α-Epoxyjunceellolide D [(+)-3]: colorless powder; $[\alpha]^{22}_D$ +5.3° (*c* 0.4, CH_2Cl_2); ^1H and ^{13}C NMR see Table 1; (+) LRFABMS *m/z* 589 $[M + Na]^+$, 567 $[M + H]^+$; (+) HRFABMS *m/z* 567. 2441 $[M + H]^+$ (calcd for $C_{28}H_{39}O_{12}$, 567. 2414), and 589.2240 $[M + Na]^+$ (calcd for $C_{28}H_{38}O_{12}Na$ 589.2260).

(−)-11α,20α-Epoxy-4-deacetyljunceellolide D [(−)-4]: colorless powder; $[\alpha]^{22}_D$ −12.6° (*c* 0.15, CH_2Cl_2); ^1H and ^{13}C NMR see Table 1; LREIMS *m/z* 524 $[M]^+$ (4), 506 $[M - H_2O]^+$ (10), 446 $[M - H_2O - AcOH]^+$ (22), 95 (100).

(−)-11α,20α-Epoxy-4-deacetoxyjunceellolide D [(−)-5]: colorless powder; $[\alpha]^{22}_D$ −53.1° (*c* 0.5, CH_2Cl_2); ^1H and ^{13}C NMR see Table 1; (+) LRFABMS *m/z* 509 $[M + H]^+$, 491 $[M - H_2O + H]^+$; (+) HRFABMS *m/z* 509.2373 $[M + H]^+$ (calcd for $C_{26}H_{37}O_{10}$ 509.2386).

(+)-Junceellolide A [(+)-6]: colorless powder; $[\alpha]^{22}_D$ +3.1° (*c* 0.6, CH_2Cl_2); LREIMS *m/z* 540/542 $[M]^+$ (8), 480/482 $[M - AcOH]^+$ (100/35), 420/422 $[M - 2AcOH]^+$ (58/17), 360 $[M - 3AcOH]^+$ (49); HREIMS *m/z* $[M]^+$ 540.1755 (calcd for $C_{26}H_{33}O_{10}$-^{35}Cl, 540.1762), 542.1756 (calcd for $C_{26}H_{33}O_{10}{}^{37}Cl$, 542.1732).

Acetylation of 2 and 4. Compound **2** (5 mg) and **4** (2 mg) were each dissolved in a mixture of dry pyridine (1 mL) and Ac_2O (1 mL), and each mixture was left stirring for 8 h at room temperature. The reaction mixtures were then concentrated under reduced pressure to give 7 mg and 4 mg of compound identical in all respects to natural junceellolide D (**1**) and 11α,20α-epoxyjunceellolide D (**3**), respectively.

Reaction of 1 with *m*-CPBA. To a stirred solution of compound **1** (5 mg) in 1 mL of CH_2Cl_2 was added a solution of *m*-CPBA (4 mg in 2 mL of CH_2Cl_2) at room temperature and then a catalytic amount of HNa_2PO_4 at 0 °C. After stirring overnight at that temperature, the mixture was washed with 10% aqueous $NaHCO_3$ and H_2O, and the organic layer was dried (Na_2SO_4) and concentrated. The crude reaction product was purified by reversed-phase HPLC using MeOH−H_2O−TFA (50:50:0.1) as eluent to give 1 mg of a compound identical in all respects with natural (+)-11α,20α-epoxyjunceellolide D (**3**).

Preparation of 2a and 2b. The esters **2a** and **2b** were prepared upon the reaction of **2** (2 mg) with 1 equivalent of the (*R*) and the (*S*) enantiomers of 2-MPAs, respectively, in the presence of DCC and DMAP (catalytic). Purification followed by HPLC (μ-Porasil, hexane−Me_2CO, 7:3).

Compound 2a [(*R*)-MPA ester]: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.69 (d, J = 4.4 Hz, H-2), 2.70 (t, J = 13.7 Hz, H-3), 4.09 (d, J = 6.8 Hz, H-4), 5.72 (d, J = 10.7 Hz, H-6), 5.22 (d, J = 4.4 Hz, H-9), 3.24 (d, J = 5.4 Hz, H-10), 4.70 (d, J = 5.0 Hz, H-14), 1.11 (s, H-15), 2.19 (d, J = 1 Hz, H-16), 2.27 (t, J = 7.6 Hz, H-17), 1.09 (d, J = 7.5 Hz, H-18), 5.02, 4.88 (1H each, s, H-20), 1.98, 1,94, 1.88 (3H each, s, OAc); (+) LRFABMS *m*/*z* 679 $[M + Na]^+$.

Compound 2b [(*S*)-MPA ester]: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.67 (d, J = 5.3 Hz, H-2), 2.39 (t, J = 12.9 Hz, H-3), 4.08 (d, J = 8.3 Hz, H-4), 5.84 (d, J = 10.2 Hz, H-6), 5.24 (d, J = 5.9 Hz, H-9), 3.23 (d, J = 5.1 Hz, H-10), 4.67 (d, J = 5.3 Hz, H-14), 1.13 (s, H-15), 2.23 (d, J = 1 Hz, H-16), 2.22 (t, J = 7.5 Hz, H-17), 1.11 (d, J = 7. Hz, H-18), 5.01, 4.86 (1H each, s, H-20), 2.16, 1,98, 1.83 (3H each, s, OAc); (+) LRFABMS *m*/*z* 695 $[M + K]^+$, 679 [M+Na], 619 $[M + Na - HOAc]^+$.

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