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The Junceellolides, New Anti-Inflammatory Diterpenoids of the Briarane Class from the Chinese Gorgonian *Junceella fragilis*

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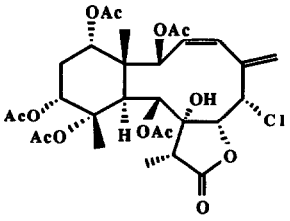
Abstract: Four new diterpenoids, junceellolides A-D (**1-4**), have been isolated from the gorgonian *Junceella fragilis* collected in the South China Sea. The known metabolites praelolide (**5**) and junceellin (**6**) were also isolated from the same organism. The structures of the new compounds were assigned on the basis of extensive NMR analyses and by comparison with analogous spectral data from other briarane diterpenoids.

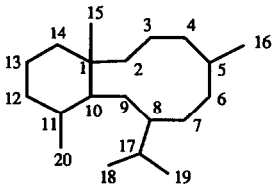
As part of a program to develop the biomedical potential of marine secondary metabolites, we have focussed our recent attention on compounds which possess anti-inflammatory and analgesic properties.[1] Recently, we had the opportunity to explore collections of marine invertebrates from the South China Sea near the island of Hainan in the People's Republic of China. In this region of southern China, many marine invertebrates were used as traditional medicines for a variety of diseases including those producing inflammation and pain.[2] On the basis of the reported medicinal use of gorgonian corals in this region, we made collections of several marine invertebrates, including the abundant white sea whip *Junceella fragilis* Ridley, which was a major inhabitant of the subtropical waters of this region.[3] In this paper we report the isolation and structure determination of four new diterpenoids, junceellolides A-D (**1-4**), from this latter source. The new compounds possess well-known briarane carbon skeletons and most of the metabolites possess significant anti-inflammatory properties. Diterpenoids of the briarane class have been investigated extensively because of their relatively complex structures and potent biological activities. Since the isolation of briarein-A from the Caribbean gorgonian *Briareum asbestinum* [4], briarane diterpenoids have been isolated from the related gorgonians *B. polyanthes* [5-7], *B. steckei* [8], *Erythropodium caribaeorum* [9] and *Solenopodium* sp.[10]. Diterpenoids of this class are also commonly encountered in related orders of octocorals such as the true soft-corals (Alcyonacea) of the genus *Minabea* [11], the sea pansy *Renilla* [12] and several sea pens (Pennatulacea) of the genera *Ptilosarcus* [13,14], *Stylatula* [15,16], *Scytalium* [17], *Pteroides* [18] and *Cavernulia*. [19]

The natural products chemistry of octocorals from the South China Sea is poorly known. Recently however, the structures of two new briarane diterpenoids, praelolide (**5**) and junceellin (**6**), were reported from the related gorgonians *Plexaureides praelonga* [20,21] and *Junceella squamata* [22]. Our collections of *Junceella fragilis* also contain these previously reported diterpenoids.

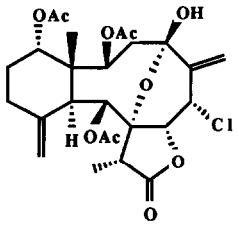
Specimens of the white sea whip *Junceella fragilis* were collected at the southernmost tip of Hainan Island. The animals were stored in isopropanol and later extracted with dichloromethane. Compounds **1-6** were isolated by silica flash chromatography of the condensed extract, followed by successive silica and reversed phase HPLC separation of the relatively polar fractions. Junceellolides A-D composed, in total, approximately 1.5% of the dry weight of the animal and were isolated in roughly equal amounts.

Junceellolide A (**1**) analyzed for $C_{26}H_{33}ClO_{10}$ by high resolution mass and ^{13}C NMR spectrometry. Analyses of ^{1}H and ^{13}C NMR data, combined with infrared spectral features, illustrated **1** to possess three acetyl groups, one additional ester and two double bonds. On the basis of overall unsaturation data, junceellolide A was concluded to be a diterpenoid molecule possessing four rings. The infrared spectrum of **1** showed strong carbonyl absorption at 1790 cm^{-1} indicating that the additional ester was a γ-lactone. Another strong infrared absorption was observed at 3400 cm^{-1}. This observation, in combination with a D_2O exchangeable proton singlet at δ 6.81 in the ^{1}H NMR spectrum (Table 1), showed **1** to possess a hydroxyl functionality. The hydroxyl group was concluded to be part of a hemiketal constellation on the basis of a characteristic carbon signal at δ 97.2 (a quaternary hemiketal carbon) in the ^{13}C NMR spectrum (Table 2). These data, in combination with ^{1}H NMR, COSY and direct $^{1}H/^{13}C$ correlation (XHCORR) NMR experiments, revealed **1** to possess six structural units as in (a) -(f), (Figure 1).

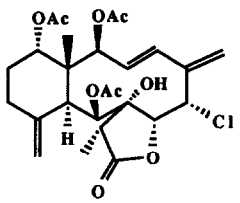




briarein-A



1



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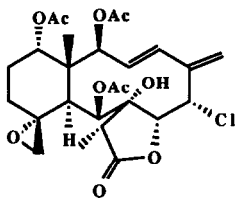

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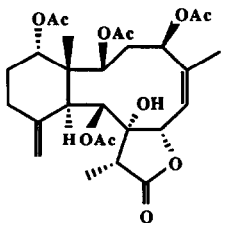

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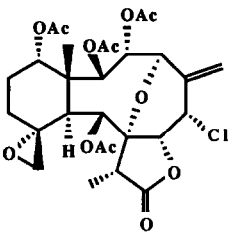
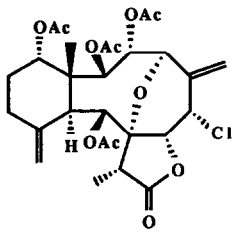


5

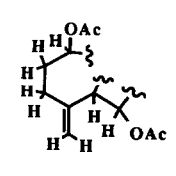


6

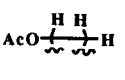
Combination of these structural units was made possible by long range ^{1}H-^{13}C NMR correlation experiments (COLOC, 6 and 8 Hz, Table 3). Carbon signals at δ 74.4, 72.9, 47.6 and 43.7 (C-14, 2, 1 and 10, respectively) showed correlations with a common methyl signal at δ 1.12 , assigned as C-15. Therefore, units (a), (b) and (e) must be connected to a quaternary carbon, (d). Several carbon-proton couplings between (a) and (c) also indicated that they were directly connected. A carbon signal at δ 81.2 showed two- and three-bond couplings with protons at δ 5.97, 4.45, 3.07 and 1.28 (H-9, 7, 10 and 18, respectively). This is the only carbon resonance from the γ-lactone functionality which could not be directly assigned by NMR COSY and XHCORR experiments. The downfield shift of this carbon (C-8) implied that it is derived from the ether carbon of the hemiketal group, (f). Another linkage of (f) was determined by long-range couplings between the hemiketal carbon (δ 97.2) with the terminal methylene protons at δ 5.94 and 5.65, assigned at C-16. In addition, coupling between the carbon at δ 137.8 (C-5) and the hemiketal hydroxyl proton at δ 6.81 was observed. The only connectivity which could not be determined by COLOC experiments was that between (b) and (f).

Junceellolide A possesses a hemiketal group at C-4 which is connected to C-8 by an ether linkage. To the best of our knowledge, this is the second example of a compound possessing this functionality within the Briarane class of marine diterpenoids. The previous example is pteroidine, isolated from the sea-pen *Pteroides laboutei* [18]. Junceellolide A (**1**) has several asymmetric carbon centers which have been assigned as in several common briarian diterpenoids. The only unusual asymmetric center in **1** is the hemiketal carbon (C-4) The configuration at this carbon center was determined by Nuclear Overhauser Enhancement Difference Spectroscopy (NOEDS). Irradiation of the hydroxyl proton at δ 6.81 (C-4 OH) resulted in a 12.5% of enhancement of the proton at δ 5.34 (C-2), indicating that

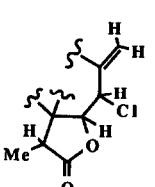
Figure 1 Structural Components of Junceellolide A



(a)



(b)



(c)

(d)

(e)

(f)

they are in close proximity. Consideration of a 3-dimensional model of junceellolide A revealed that the additional ketal linkage between C-4 and C-8 creates an overall ring conformation very different from that of the other briarane diterpenoids. Drawing C-4 closer to C-8 radically alters the bond angles in the vicinity of C-4, and as a result, the hydroxyl group which is β-oriented to the C-3-5 plane, is drawn in proximity to the α-proton at C-2. Thus, the configuration of C-4 was assigned as **S***. The overall relative stereochemistry for **1** is thus proposed as: **1R*, 2S*, 4S*, 6S*, 7R*, 8R*, 9S*, 10S*, 14S*** and **17R***. This conclusion was further supported by the subsequent isolation of praelolide (**5**), which possesses most of the same configurations as determined by X-ray analysis.

Table 1. Proton NMR Data for Compounds **1** - **6**

#	1	2	3	4	5	6
2	5.34 d(7.2)	5.52 d(9.2)	5.61 d(9.2)	4.77 brd(5.3)	4.48 d(10.9)	4.48 d(10.9)
3	3.34 dd(16.3, 7.2)	6.05 dd(16.0, 9.2)	6.10 dd(15.9, 9.2)	2.77 dd(14.0, 12.7)	6.17 dd(10.9, 7.0)	6.14 dd(10.9, 6.5)
	1.58 d(16.3)			1.9 m		
4	----	6.77 brd(16.0)	6.80 brd(15.9)	5.19 dd(12.7, 5.7)	5.41 brd(7.0)	5.43 d(6.5)
6	4 94 brd(1.9)	5.13 d(3.4)	5.09 d(3.5)	5.78 dd(10.2, 0.6)	5.00 brd(3.2)	5.02 brd(2.8)
7	4.45 brd(2.3)	4.26 d(3.4)	4.17 d(3.5)	5.59 brd(10.4)	4.40 d(3.2)	4.51 d(2.8)
9	5.97 brs	5.67 d(4.3)	5.16 d(1.5)	5.26 d(5.0)	5.59 brs	5.94 brs
10	3.07 brs	3.48 brd(3.4)	3.28 brs	3.31 d(5.0)	2.80 brs	3 11 brs
12	2.3 m(2H)	2.2 m(2H)	2.2 m	2.3 m	2.2 m	2.3 m(2H)
			1.2 m	2.1 m	1.3 m	
13	1.8 m	1.8 m(2H)	1.8 m(2H)	2.0 m	1.9 m(2H)	1.8 m(2H)
	1.7 m			1.7 m		
14	5.03 brs	4.84 brd(2.6)	4.97 brs	4.70 brd(4.9)	4.99 brs	4.97 brs
15	1.12 s	1.09 s	1.15 s	1.11 s	1.26 s	1.12 s
16	5.94 brs	5.40 brs	5.34 brs	2.23 d(0.6,3H)	5.37 d(1.9)	5.56 d(1.9)
	5.65 brs	5.31 brs	5.32 brs		5.59 d(1.9)	5.36 brd(1.9)
17	2.75 q(7.0)	2.79 q(7.1)	2.86 q(7.2)	2.49 q(7.2)	2.79 q(7.0)	2.79 q(7.0)
18	1.28 d(7.0)	1.11 d(7.1)	1.26 d(7.2)	1.12 d(7.2)	1.33 d(7.0)	1.29 d(7.0)
20	5.09 brs	5.05 brs	2.63 brd(2.9)	5.04 brs	2.68 brd(3.8)	5.10 brs
	4.75 brs	4.97 brs	2.58 dd(2.9, 1.6)	4.88 brs	2.44 brd(3.8)	4.76 brs
OAc	2.25 s	2.12 s	2.16 s	2.25 s	2.32 s	2.32 s
	2.09 s	2.09 s	2.12 s	2.05 s	2.09 s	2.07 s
	2.08 s	2.04 s	2.04 s	2.00 s	2.04 s	2.05 s
				1.90 s	1.98 s	2.00 s
OH	6.81 s	3.38 s	3.04 s	2.00 s	----	----

Proton NMR data were obtained at 360 MHz in $CDCl_3$ solution. Assignments were made by COSY experiments.

Junceellolide B (**2**) analyzed for $C_{26}H_{33}ClO_9$ by high resolution mass and ^{13}C NMR spectrometry. The infrared spectrum of **2** showed strong absorptions at 3500, 1780 and 1730 cm^{-1} indicating the presence of hydroxyl, γ-lactone and ester functionalities. Proton NMR COSY experiments, and comparison of overall ^1H and ^{13}C NMR data, revealed similarities between **2** and junceellolide A , and showed that partial structures (a), (c), (d) and (e) are also present in this compound. However, there were several significant differences in the spectral data. Although hydroxyl absorption (3500 cm^{-1}) was observed in the infrared spectrum of **2**, the compound lacked the hemiketal carbon found in junceellolide A. The ^{13}C NMR spectrum of junceellolide B showed two additional resonances at δ131.3(d) and 130.9(d). A corresponding difference was also observed in the ^1H NMR spectrum of this compound. Instead of higher field methylene protons, junceellolide B showed two new olefinic protons at δ 6.77 (brd, J=16.0) and 6 05 (dd, J=16.0,9.2). Proton NMR COSY experiments showed couplings between protons at δ 6.77 and 5.40 (C-16). All of these changes were accommodated in junceellolide B by formation of a double bond between C-3 and 4, and positioning the hydroxyl group at C-8. This conclusion was supported by the presence of UV absorption at λ max 230 nm (ε=7000). The large coupling constant (16.0 Hz) between the two olefinic protons suggested the uncommon ***E*** configuration. Overall, the relative stereochemistry of **2** is proposed as: **1R*, 2S*, 6S*, 7R*, 8R*, 9S*, 10S*, 14S***, and **17R***

Junceellolide C (**3**) analyzed for $C_{26}H_{33}ClO_{10}$ by high resolution mass and ^{13}C NMR spectrometry. The spectral data for **3** were very similar with those from junceellolide B However, the ^{13}C NMR spectrum of **3** showed that one of the two terminal vinyl groups in **2** was converted to a terminal epoxide group in this metabolite [δ 57.2 (s) and 50.1 (t)]. This conclusion was supported by ^1H NMR features [δ 2.63, brd (J=2.9) and 2.58, dd (J=2.9, 1.6)] characteristic for this functionality. Proton NMR COSY measurements revealed that the vinyl group identified in (a) had been oxidized. This was supported by the observation of UV absorption at 230 nm (ε 7100) for this metabolite,

Table 2. Carbon NMR Data of Compounds **1-6**

#	1	2	3	4	5	6
1	47.6 s	48.2 s	49.0 s	47.3 s	46.9 s	47.6 s
2	72.9 d	80.9 d*	81.1 d*	73.8 d	78.9 d*	77.0 d*
3	40.5 t	131.3 d^	133.0 d^	37.7 t	73.9 d*	79.0 d*
4	97.2 s	130.9 d^	129.3 d^	72.5 d	64.0 d	63.9 d
5	137.8 s	141.6 s	141.5 s	144.2 s	134.2 s	134.5 s
6	55.3 d	63.6 d	63.5 d	123.6 d	53.9 d	54.0 d
7	78.6 d	76.0 d*	75.8 d*	77.0 d	79.1 d*	79.2 d*
8	81.2 s	83.4 s	82.5 s	82.6 s	82.9 s	82.9 s
9	78.2 d	75.8 d*	74.1 d*	71.3 d	72.9 d*	74.6 d*
10	43.7 d	42.2 d	38.9 d	42.1 d	41.0 d	44.1 d
11	147.1 s	147.5 s	57.2 s	150.4 s	56.2 s	147.4 s
12	27.6 t	27.7 t	24.9 t	25.9 t	24.7 t	27.6 t
13	32.6 t	30.0 t	30.1 t	27.4 t	29.8 t	32.7 t
14	74.4 d	74.3 d*	72.0 d*	73.6 d	70.9 d*	73.0 d
15	14.7 q	15.0 q	14.9 q	16.0 q	15.9 q	15.0 q
16	117.8 t	115.7 t	115.7 t	25.8 q	119.4 t	119.4 t
17	50.3 d	49.7 d	50.1 d	42.4 d	49.5 d	49.9 d
18	7.0 q	6.6 q	7.2 q	6.3 q	7.3 q	7.1 q
19	174.0 s	174.3 s	174.8 s	176.0 s	174.0 s	174.1 s
20	111.8 t	112.8 t	50.1 t	112.9 t	51.3 t	111.8 t
OAc	173.7 s	170.2 s	170.3 s	170.1 s	170.1 s	170.4 s
	169.9 s	170.2 s	170.0 s	170.1 s	170.0 s	170.0 s
	169.4 s	170.0 s	170.0 s	169.9 s	169.7 s	169.8 s
				169.1 s	169.7 s	169.8 s
	21.4 q	21.4 q	21.2 q	21.5 q	21.1 q	21.0 q
	21.2 q	21.2 q	21.1 q	20.8 q	21.0 q	20.9 q
	20.2 q	21.0 q	20.9 q	20.8 q	20.5 q	20.4 q
				20.5 q	20.4 q	20.4 q

Carbon NMR data were obtained in $CDCl_3$ solutions. Multiplicities were obtained by SFORD experiments. Assignments of compounds 1 and 4 are based upon XHCORR and COLOC experiments Assignments of compounds 2, 3, 5 and 6 are based upon comparisons with known compounds. *,^ in the same column indicates the assignments may be interconverted.

Table 3. Long Range Carbon-Proton Correlations of Compounds 1 and 4

carbon	protons	
	compound 1	compound 4
1	9, 10, 15	3, 10, 13, 15
2	3, 10, 15	15
4	16	16
5	6, 7, 16, OH	16
6	16	7, 16
7	----	6, 9, 17
8	7, 9, 10, 18	9, 17, 18
9	----	10, 17
10	15, 20	----
11	9	9, 10, 12
14	15	15
15	10	----
16	6	6
17	9, 18	18
19	18	18
OAc(9)	9	----

Experiments were performed for coupling constants of both 6 and 8 Hz.

which confirmed the presence of the diene. Therefore, junceellolide C was identified as C-11,20-epoxide derivative of **2**.

Compound **3** possesses an additional asymmetric center at C-11. All of the known briarans have the same configuration at this center; C-20 is always axial and β oriented to cyclohexane ring. An observed W coupling (J=1.6) between one of epoxide protons (δ 2.58) and a methine proton at δ 3.28 (H-10) showed that **3** also has the same configuration at C-11. Thus, junceellolide C is proposed to possess the following overall relative stereochemistry: **1R*, 2S*, 6S*, 7R*, 8R*, 9S*, 10S*, 11R*, 14S*** and **17R***.

Junceellolide D (**4**) analyzed for $C_{28}H_{38}O_{11}$ by high resolution mass and ^{13}C NMR spectrometry. The infrared spectrum of **4**, as with the other compounds, showed absorptions at 3500, 1775, and 1740 cm^{-1} indicating the presence of hydroxyl, γ-lactone and ester groups. However, significant differences were found in the NMR spectral data. The ^{13}C NMR features of **4** showed that one of two terminal vinyl groups had been replaced by a

trisubstituted double bond. The lack of diene absorption for **4** indicated that the new double bond must be isolated from the remaining terminal vinyl group. The spectral features (mass spectral and ^{13}C NMR) attributed to the chlorine atoms in **1-3** were conspicuously absent in junceellolide D. Finally, the presence of a new vinyl methyl group (δ 2.23 in the ^{1}H NMR and δ 25.8 in the ^{13}C NMR spectra) was observed. On the basis of COSY and XHCORR NMR experiments, partial structures (a), (d) and (e), were also found in **4** (Figure 1). The modifications clearly illustrated in the spectral data were the formation of an olefinic bond between C-5 and C-6 and concommitant loss of the chlorine atom. Junceellolide D was also modified in the C-2 to C-4 region. NMR experiments (COLOC with J values of 6 to 8 Hz) readily allowed positioning the acetoxyl groups at C-2 and C-4 (Table 3). Junceellolide D possesses an additional asymmetric center at C-4. The relative configuration of this center could also be assigned by NMR NOEDS methods. Irradiation of the proton at δ 4.77 (H-2) enhanced protons at δ 3.31 (H-10) and 5.19 (H-4) by 9.7 and 15.4%, respectively. On the basis of these data, the relative stereochemistry of junceellolide D was concluded as: **1R*, 2S*, 4R*, 7R*, 8R*, 9S*, 10S*, 14S* and 17R*.**

Conclusions regarding the spectral analyses of the junceelolides were strongly supported by the simultaneous isolation of two known briaranes, praelolide (**5**) and junceellin (**6**), from this source. Praelolide, isolated from the Chinese gorgonian coral *Plexaureides praelonga*, was identified by spectral and crystallographic measurements[20,21]. A closely related compound, junceellin, was isolated from another gorgonian coral, *Junceella squamata* [22], and its structure was determined by spectral and crystallographic methods. The NMR and other spectral data for the junceellolides were highly analogous with comparable data from these latter compounds.

As has been observed with related compounds, the junceellolides possess potent biological activities in several pharmacological assays. Junceellolide B and praelolide (**2** and **5**) show weak antiviral activities against Herpes simplex viruses I and II within concentration ranges of 27 to 52 ug/ml (*in vitro*). As anti-inflammatory agents, the junceellolides possess potencies comparable to commercial standards.[23] Junceellolides A-D show reductions in edema of 88.4, 70.2, 80.0 and 82.3%, repectively, in an assay designed to assess topical efficacy. Although the pharmacological mechanisms of anti-inflammatory action are unstudied, junceellolides B and C (**2** and **3**) were found to inhibit bee venom-derived phospholipase A_2 in *in vitro* testing.[23]

Experimental

General. Infrared spectra were recorded on a Perkin-Elmer model 137 spectrophotometer. Ultraviolet spectra were obtained in methanol using a Beckman Acta XIV spectrophotometer. Proton NMR spectra were recorded in $CDCl_3$ at 360 MHz, using a spectrometer constructed from an Oxford magnet and Nicolet-1180E Fourier transform data system, at UCSD NMR Facility. NOEDS experiments were performed essentially following the experiments outlined by Hall and Sanders[24]. Carbon-13 NMR spectra were recorded in $CDCl_3$ solution at 50 MHz using a Nicolet Wide-Bore spectrometer. Direct(XHCORR) and long range(COLOC) carbon-proton correlation spectra were recorded in $CDCl_3$ solution at 50 MHz on an IBM WP-200SY spectrometer. Mass measurements were supplied by Dr. Richard W. Kondrat, University of California, Riverside. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter with a 10-cm microcell. Melting points were determined on a Fisher-Johns apparatus and are reported uncorrected. All solvents used were either spectral grade or were distilled from glass prior to use.

Collection, Extraction, and Isolation of metabolites. *Junceella fragilis* (specimen number CG-2) was collected by hand using SCUBA at the Sanya Bay, Hainan Island, People's Republic of China, in April, 1986. The animals were stored in isopropanol, returned to the laboratory and extracted exhaustively with dichloromethane. The extracts were chromatographed over TLC grade silica gel using vacuum flash chromatographic methods. Fractions eluted with 40-60% ethyl acetate in isooctane were further purified by silica HPLC using the same solvent mixtures, to obtain the junceellolides A-D, praelolide and junceellin, as 1.5% of the dry weight of the animal.

Junceellolide A (**1**). m.p. 115-116°, $[\alpha]_D$ -7.9° (c 0.6, chloroform); no UV absorption above 200 nm (methanol); IR (chloroform) 3400, 2960, 1790, 1740, 1730, 1645, 1270 cm^{-1}; HRMS M^+ 540.1765 for $C_{26}H_{33}ClO_{10}$ (requires 540.1762).

Junceellolide B (**2**). m.p. 95-96°, $[\alpha]_D$ +9.4° (c 1.3, chloroform); UV (methanol) 230 nm (ε=7000); IR (chloroform) 3500, 2960, 1780, 1730, 1640, 1270 cm^{-1}; HRMS M^+ 524.1814 for $C_{26}H_{33}ClO_9$ (requires 524.1813).

Junceellolide C (**3**). m.p. 120-125° (sublimation); $[\alpha]_D$ +36.1° (c 1.2, chloroform); UV (methanol) 230 nm (ε=7100); IR (chloroform) 3500, 2950, 1780, 1735, 1635, 1245 cm^{-1} ; HRFABMS M^++H 541.1871 for $C_{26}H_{33}ClO_{10}$ (requires 541.1840).

Junceellolide D (**4**). m.p. 208-209°, $[\alpha]_D$ -7.7° (c 2.5, chloroform); no UV absorption above 200 nm (methanol); IR (chloroform) 3500, 2940, 1775, 1740, 1645, 1250 cm^{-1}; HRFABMS M^++H 551.2517 for $C_{28}H_{38}O_{11}$ (requires 551.2492).

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