Jaspolides A—F, Six New Isomalabricane-Type Terpenoids from the Sponge *Jaspis* sp.

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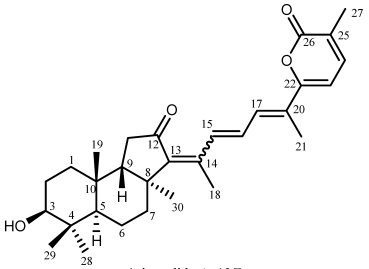
A chemical investigation of *Jaspis* sp., the marine sponge collected from the South China Sea led to the isolation of six new isomalabaricane-type compounds, jaspolides A—F (1—6). The structures of those compounds were elucidated by extensive spectroscopic methods. The structure-types of 1 to 6 could be classified into triterpenes (1, 2), sesterterpene (6), diterpenes (3, 4), and nortriterpene (5). The biogenetic transformation of the isolated compounds was also speculated.

Key words Marine sponge; *Jaspis* sp.; isomalabaricanes; terpenoids; structural elucidation

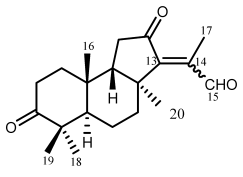
Marine sponges of the genus *Jaspis* (Coppatiidae) have been investigated extensively, and have shown a rich source of biologically active and structurally novel natural products.[1—14] Thus far at least 11 species of *Jaspis* species have been examined chemically and biologically, and hitherto more than 100 compounds involving various type skeletons have been published. The malabaricane skeleton which showed promising anti-cancer activity is one type of remarkable marine natural products from the sponge *Jaspis*.[11—14] Macrolides such as jaspisamide derivatives are another type of the secondary metabolites showing potential antifungal, antiproliferative anthelminthic, cytotoxic, selective antimicrobial, insecticidal and ichthytoxic activities.[3—5] Bengamides are a group of unusual structures containing nitrogen elements which showed interesting antiparasitic, antimicrobial, and cytotoxic activity,[6,7] while the cytotoxity of shingosine derivatives was evaluated against the A549 lung tumor cell line,[8] and bengazole alkaloids have shown in vitro potency against two human tumor cell lines, colon and COLO-205.[9] However, the sponge *Jaspis* sp. distributed off the reef of the South China Sea has not yet been examined. In a continuation of our study on the chemical diversity and the bioactivity of novel structural metabolites from marine organisms, this sponge was collected from a coral reef off Hainan Island. From the MeOH extract, six new isomalabaricane-type derivatives, jaspolides A—F (**1**—**6**) were isolated. Their structures were determined using extensive spectroscopic data analyses.

Results and Discussion

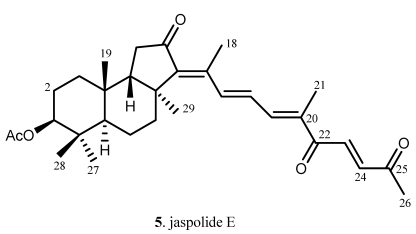
Jaspolide A (**1**) has a formula $C_{30}H_{40}O_4$ as determined by HR-FAB-MS and ^{1}H- and ^{13}C-NMR data. The ^{1}H- and ^{13}C-NMR spectra (Tables 1, 2) exhibited signals characteristic of an isomalabaricane-type triterpene, and closely resembled those of stellettin D.[15,16] ^{13}C-NMR and DEPT spectra exhibited thirty carbons in the molecule, involving seven methyls, five methylenes, eight methines, and ten quaternary carbons. An ABX coupling system of olefinic protons at δ 8.26 (d, J=15.0 Hz), 6.93 (dd, J=11.5, 15.0 Hz), and 7.25 (d, J=11.4 Hz) were attributable to the proton signals at H-15, H-16,



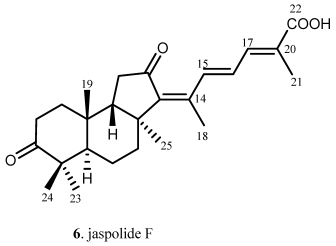
1. jaspolide A, 13*Z*
2. jaspolide B, 13*E*



3. jaspolide C, 13*E*
4. jaspolide D, 13*Z*



5. jaspolide E



6. jaspolide F

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Table 1. ^{13}C-NMR Data of **1** to **6**

Position	**1**[a)]	**2**[a)]	**3**[a)]	**4**[a)]	**5**[b)]	**6**[a)]
1	33.6 (t)	33.4 (t)	31.4 (t)	31.4 (t)	33.2 (t)	31.4 (t)
2	29.0 (t)	29.0 (t)	33.3 (t)	33.3 (t)	25.6 (t)	33.4 (t)
3	79.3 (d)	79.2 (d)	218.0 (s)	218.1 (s)	80.8 (d)	219.0 (s)
4	39.7 (s)	39.7 (s)	46.9 (s)	46.8 (s)	38.5 (s)	46.9 (s)
5	46.5 (d)	46.6 (d)	45.4 (d)	45.4 (d)	47.0 (d)	45.4 (d)
6	18.4 (t)	18.4 (t)	19.8 (t)	19.8 (t)	18.7 (t)	19.6 (t)
7	38.3 (t)	39.2 (t)	40.3 (t)	40.3 (t)	39.8 (t)	37.1 (t)
8	44.7 (s)	45.0 (s)	45.4 (s)	45.3 (s)	45.2 (s)	44.9 (s)
9	50.1 (d)	50.1 (d)	47.5 (d)	47.5 (d)	50.0 (d)	47.9 (d)
10	35.4 (s)	35.6 (s)	35.0 (s)	35.0 (s)	35.7 (s)	34.8 (s)
11	36.7 (t)	36.7 (t)	36.0 (t)	36.0 (t)	36.7 (t)	36.7 (t)
12	206.4 (s)	207.9 (s)	208.0 (s)	208.3 (s)	206.4 (s)	206.0 (s)
13	147.9 (s)	148.6 (s)	157.5 (s)	157.4 (s)	150.6 (s)	148.0 (s)
14	141.1 (s)	140.3 (s)	138.0 (s)	138.0 (s)	138.8 (s)	142.0 (s)
15	137.0 (d)	137.3 (d)	194.2 (d)	194.2 (d)	140.4 (d)	139.4 (d)
16	129.2 (d)	130.5 (d)	23.6 (q)	23.6 (q)	130.5 (d)	128.7 (d)
17	131.6 (d)	130.7 (d)	11.3 (q)	11.3 (q)	139.4 (d)	140.7 (d)
18	15.9 (q)	15.9 (q)	29.2 (q)	29.2 (q)	14.7 (q)	15.9 (q)
19	22.3 (q)	22.3 (q)	19.4 (q)	19.4 (q)	22.4 (q)	23.5 (q)
20	128.1 (s)	128.1 (s)	27.9 (q)	27.9 (q)	139.4 (s)	127.8 (s)
21	12.8 (q)	12.8 (q)			12.6 (q)	12.8 (q)
22	159.5 (s)	158.9 (s)			190.5 (s)	171.0 (s)
23	102.4 (d)	103.0 (d)			133.0 (d)	29.2 (q)
24	139.7 (d)	139.7 (d)			137.7 (d)	19.4 (q)
25	124.0 (s)	124.5 (s)			196.6 (s)	24.5 (q)
26	163.1 (s)	163.1 (s)			28.8 (q)	
27	16.4 (q)	16.8 (q)			29.4 (q)	
28	29.1 (q)	29.1 (q)			17.4 (q)	
29	15.9 (q)	15.9 (q)			26.4 (q)	
30	24.7 (q)	26.0 (q)				
Ac					170.2 (s)	
					21.0 (q)	

a) Measured in $CDCl_3$. *b*) Measured in C_6D_6.

Table 2. ^{1}H-NMR Data of **1**—**6**

	1[a)]	**2**[a)]	**3**[a)]	**4**[a)]	**5**[b)]	**6**[a)]
1	1.42 (m), 1.60 (m)	1.43 (m), 1.60 (m)	1.55 (m), 1.60 (m)	1.54 (m), 1.61 (m)	1.05 (m), 1.30 (m)	1.52 (m), 2.22 (m)
2	1.70 (m), 1.87 (m)	1.74 (m), 1.82 (m)	2.42 (m), 2.80 (ddd 5.5, 10.5, 11.5)	2.45 (m), 2.77 (ddd 6.5, 10.5, 12.0)	1.67 (m), 1.96 (m)	2.42 (m)
3	3.33 (dd 5.0, 11.5)	3.37 (dd 4.9, 11.5)			4.84 (dd 5.0, 12.0)	
5	1.67 (m)	1.77 (m)	2.48 (dd 2.5, 13.0)	2.45 (dd 3.0, 11.5)	1.63 (m)	2.41 (m)
6	1.42 (m), 1.70 (m)	1.44 (m), 1.68 (m)	1.55, 1.61 (m)	1.53, 1.62 (m)	1.48 (m), 1.68 (m)	1.50 (m), 1.62 (m)
7	2.10 (m), 2.20 (m)	1.90 (m), 2.00 (m)	2.30 (m), 2.33 (m)	2.26 (m), 2.28 (m)	1.97 (m), 2.03 (m)	2.28 (m)
9	1.85 (dd 7.0, 11.0)	1.89 (dd 6.8, 11.5)	2.01 (dd 8.5, 13.5)	1.96 (m)	1.50 (dd 7.0, 13.0)	1.91 (m)
11	2.22 (d 11.5), 2.13 (m)	2.32 (m)	2.34 (m), 2.38 (m)	2.25 (m), 2.36 (m)	2.13 (dd, 7.0, 14.0) 2.04 (dd 13.0, 14.0)	2.30 (m)
15	8.26 (d 15.0)	6.96 (d 15.3)	10.25 (s)	10.55 (s)	7.02 (d 15.5)	8.34 (d 15.2)
16	6.93 (dd 11.5, 15.0)	6.98 (dd 11.4, 15.3)	0.92 (s)	0.92 (s)	6.93 (dd 11.0, 15.5)	6.87 (dd 13.0, 15.2)
17	7.25 (d 11.4)	7.28 (d 11.4)	2.15 (s)	1.96 (s)	7.32 (d 11.0)	7.49 (d 13.0)
18	2.06 (s)	2.34 (s)	1.09 (s)	1.10 (s)	2.63 (s)	2.10 (s)
19	1.02 (s)	1.01 (s)	1.16 (s)	1.16 (s)	0.75 (s)	0.89 (s)
20			1.60 (s)	1.44 (s)		
21	2.04 (s)	2.04 (s)			2.04 (s)	2.03 (s)
23	6.23 (d 7.0)	6.26 (d 6.9)			7.57 (d 15.5)	1.08 (s)
24	7.16 (d 7.0)	7.20 (d 6.9)			7.06 (d 15.5)	1.14 (s)
25						1.43 (s)
26					1.71 (s)	
27	2.13 (s)	2.15 (s)			1.03 (s)	
28	0.84 (s)	1.09 (s)			0.98 (s)	
29	1.06 (s)	1.09 (s)			1.11 (s)	
30	1.38 (s)	1.43 (s)				
Ac					1.88 (s)	

a) Measured in $CDCl_3$. *b*) Measured in C_6D_6.

and H-17 of the side chain, respectively, while an AB coupling system at δ 7.16 (d, J=7.0 Hz) and 6.23 (d, J=7.0 Hz) were due to the olefinic protons of H-24 and H-23 at the terminal unsaturated δ-lactone. There were seven methyl singlets in the ^{1}H-NMR spectrum, of which three vinyl methyls were assigned to positions at C-14 (δ 2.06, s, Me-18), C-20 (δ 2.04, s Me-21), and C-25 (δ 2.13, s, Me-27), and the remaining four were located at the tricyclic unit (δ 1.38, 1.06, 1.02, 0.84) on the basis of HMQC and HMBC analysis. Compound **1** differed from stellettin D solely at C-3 where an acetyl unit of latter to be replaced by a hydroxyl group of **1** due to NMR spectra. This evidence was also supported by the molecular weight of **1** showing 42 amu less than that of stellettin D, and the ^{1}H-NMR signal of H-3 in **1** resonated at δ 3.33 (dd, J=5.0, 11.5 Hz) rather than at δ 4.73, dd, J=4.9, 11.7 Hz) in stellettin D. The similar coupling constants of H-3 in both compounds indicated a β-configuration of the hydroxyl group. The remaining stereochemistry of **1** was in agreement with that of stellettin D due to the comparable NMR data and the NOESY correlations.

HR-FAB-MS of jaspolide B (**2**) showed the same molecular formula as that of **1**. Comparison of the ^{1}H- and ^{13}C-NMR spectra with **2** and **1** verified that the gross structure of **2** was the same as that of **1**, except for the signals at the side chain where H-15 (δ 8.26, d) in **1** shifted to highfield at δ 6.96 (d, J=15.3 Hz, H-15) in **2**, whereas Me-18 of **2** shifted to downfield at δ 2.34 (s) under the deshielding zone of the C-12 ketone group. This evidence in association with the comparison of its NMR data with those of stellettin C[15,16] indicated that the double bond C_{13}–C_{14} of **2** adopted a 13*E*-orientation instead of 13*Z* of **1**. Accordingly, the structure of **2** was determined to be a C-13 geometric isomer of **1**.

The molecular formula of jaspolide C (**3**) was established as $C_{20}H_{28}O_3$ by HR-FAB-MS, indicating seven degrees of unsaturation in the molecule. The ^{13}C-NMR and DEPT spectra exhibited the signals (Table 1) for five methyls, five methylenes, three methines, and seven quaternary carbons, involving an aldehydic carbon at δ 194.2 (d), two keto carbons at δ 218.0 (s) and 208.0 (s), and two olefinic carbons at δ 138.0 (s) and 157.5 (s). The presence of one aldehyde, two ketones, and one double bond implied that **3** must be a tricyclic nucleus. The ^{1}H-NMR spectrum displayed five methyl singlets at δ 0.92 (s, H_3-16), 1.09 (s, H_3-18), 1.16 (s, H_3-19), 1.60 (s, H_3-20), and 2.15 (s, H_3-17), and HMQC assigned the protons and the protonated carbons. The COSY and HMBC spectral analysis resulted in a partial structure of the tricyclic moiety being an isomalabaricane basic skeleton, identical to that of stellettin A and its analogues.[1,2] The methyl proton H_3-17 exhibited HMBC correlations with olefinic carbons at δ 138.0 (s, C-14) and 157.5 (s, C-13), and the aldehydic carbon, indicating the olefinic carbon C-14 to be substituted by an aldehydic and a methyl group, respectively. The comparable NMR data of both **3** and stellettin A suggested that the ring fusion between A/B and B/C adopted *trans*-form. The presence of NOE correlation observed between H-15 and H_3-20 and the absence of NOE relationship between H_3-17 and H_3-20 allowed the assignment of 13*E* geometry.

The HR-FAB-MS data of jaspolide D (**4**) indicated that its molecular formula was the same as that of **3**. Most of the NMR data recorded for **4** were nearly identical to the data for **3**, except for the highfield shift of methyl protons H_3-17 (δ 1.96, s) and a downfield shift of aldehydic proton

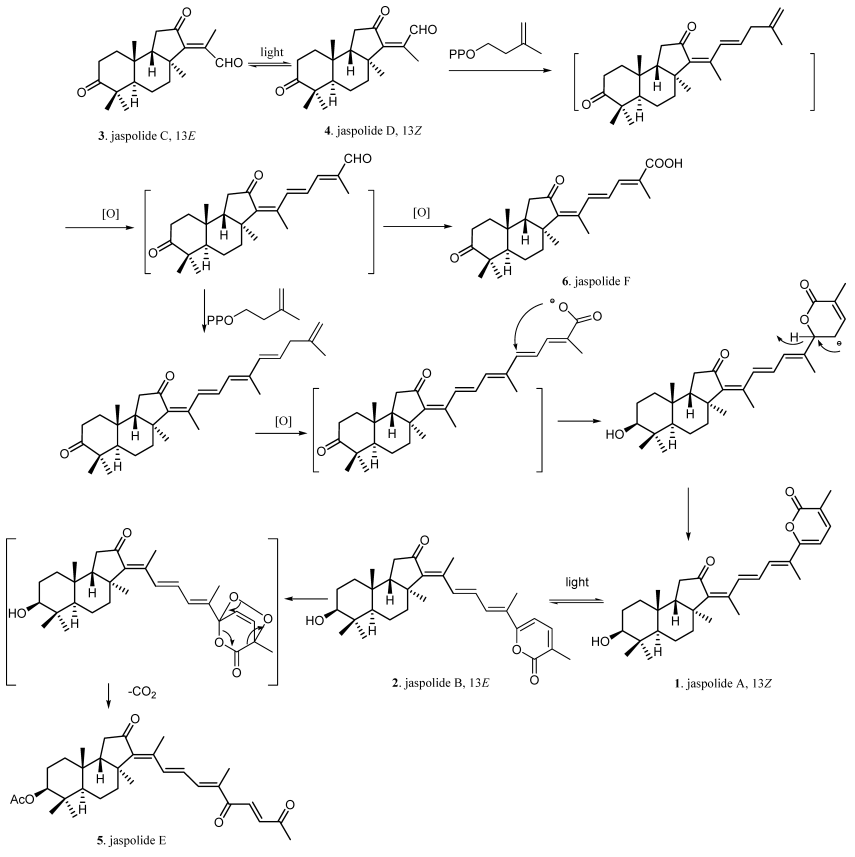

Chart 1. The Proposed Biogenetic Transformation of the Isolated Compounds

(δ 10.55, s) in comparison with those of **3**; thus the structure of **4** was assumed to be a 13*Z* geometric isomer of **3**. The geometry of double bond at C-13 was also supported by NOESY correlation between H_3-17 and H_3-20 (δ 1.44, s).

The molecular formula of jaspolide E (**5**) was established as $C_{31}H_{42}O_5$ by HR-FAB-MS. A detailed ^{1}H- and ^{13}C-NMR spectral analysis and comparison of its NMR data with those reported for geoditin B[17] revealed major similarities, with exception of the side chain where the olefinic proton assigned to H-15 of **5** shifted to highfield at δ 7.02 (1H, d, J=15.5 Hz, H-15), and in turn H_3-18 shifted to downfield at δ 2.63 (s, H_3-18) under the deshielding zone of ketone group at C-12. The NOE correlation between H_3-29 (δ 1.11, s) and H-15 supported the geometry of the double bond at C-13 to be in *E*-orientation. Therefore, the structure of **5** was identified as C-13 isomer of geoditin B.

Jaspolide F (**6**) has a molecular formula $C_{25}H_{34}O_4$ as determined by HR-FAB-MS. Comparison of its ^{1}H- and ^{13}C-NMR spectral data with those of **3** and **4** indicated that they shared the same tricyclic nucleus. In addition, the ^{13}C-NMR and DEPT spectral analyses of the side chain resulted in three double bonds [δ 148.0 (s, C-13), 142.0 (s, C-14), 137.3 (d, C-15), 139.4 (d, C-16), 140.7 (d, C-17), 127.8 (s, C-20)], a carbonyl carbon (δ 171.0, s, C-22), and two vinyl methyls [δ 15.9 (q, C-18) and 12.8 (q, C-21)]. The presence of an ABX spin-system at δ 8.34 (1H, d, J=15.2 Hz, H-15), 6.87 (1H, dd, J=13.0, 15.2 Hz, H-16) and 7.49 (1H, d, J=13.0 Hz, H-17) was similar to those of jaspolide A. The HMBC correlations between H_3-18 (δ 2.10, s) and C-13, C-14, and C-15, and between H_3-21 (δ 2.03, s) and C-17, C-20, and C-22, indicated the three double bonds to be conjugated and allowed positioning of a carboxyl group at C-20. The geometry of the side chain was determined mainly by NOESY spectrum. The NOE correlations between H_3-18/H_3-25 (δ 1.43, s), H_3-18/H-16, and H_3-21/H-16 were in agreement with the geometry of the double bonds to be in 13*Z*, 15*E*, 17*E*.

The speculated biogenetic transformation of the isolated compounds is described in Chart 1. Jaspolide D (**4**) was regarded as a light-induced product of jaspolide C (**3**), and **4** was considered to be a precursor to form jaspolide F (**6**) through condensation with an IPP followed by oxidation at an end methyl group. Jaspolide F followed in the same manner as jaspolide D through condensation of an IPP and oxidation, and then *via* intra-cyclization to yield jaspolide A. Jaspolide B was a light-induced product from jaspolide A. Jaspolide E was generated from jaspolide B *via* oxidation to form a peroxide derivative which loses a CO_2 through a ring rearrangement. When the MeOH solution of jaspolide A was exposed to air and light for more than 2 h, the TLC showed an additional spot of jaspolide B, and a spot of jaspolide E appeared after 2.5 h. This evidence partly supported the supposed transformation route and indicated that jaspolide A is a light-sensitive product.

Experimental

General Procedure Optional rotations were measured on a JASCO DIP-370 polarimeter. The IR spectra were determined on a Perkin-Elmer Nicol FT-50X spectrometer. The ^{1}H- and ^{13}C-NMR as well as 2D NMR spectra were recorded on a Bruker Avance-500 FT 500 MHz NMR spectrometer using TMS as an internal standard. High resolution mass spectra were obtained on a VG Atospec spectrometer, and ESI-MS were recorded on a Q-STAR ESI-TOF$^-$-MS/MS mass spectrometer. Column chromatography was carried out on Merck silica gel (200—400 mesh), and the HF_{254} silica gel for TLC was provided by Sigma Co. Ltd. Sephadex LH-20 (18—110 μm) was obtained from Pharmacia Co. ODS (50 μm) was provided by YMC Co. Higher pressure liquid chromatography (HPLC) was performed on an Alltech 426 apparatus using a Kromasil prepack column (ODS, 10 mm×250 mm, for reverse-phase) and monitored by a UV detector.

Animal Material The sponge *Jaspis* sp. was collected off a coral reef at a depth of 15 m in Sanya, Hainan Island, the South China Sea of People's Republic of China, in June 2003. The sample was frozen immediately after collection, and was identified by Dr. R. van Soest (Institute of Systematic and Ecology, Amsterdam University) as an unrecorded species belonging to the *Jaspis* genus. A voucher specimen (HSC-39) was deposited at the State Key Laboratory of Natural and Biomimetic Drugs of Peking University, Beijing, People's Republic of China.

Extraction and Isolation The frozen sponge (2.0 kg) was homogenized and extracted with MeOH, and the extract was concentrated under reduced pressure to afford a residue (150 g). The residue was dissolved in water and then partitioned between H_2O and CH_2Cl_2. The concentrated CH_2Cl_2 fraction (40.0 g) was chromatographed on a silica gel column by eluting with petroleum ether–EtOAc (4 : 1, 2 : 1) to obtain ten portions (A—J). Portion G (2.0 g) was further subjected to chromatography over silica gel column eluting with a gradient of CH_2Cl_2 : acetone, and **1** (20.3 mg), **2** (13.8 mg), **3** (5.0 mg), and **4** (0.5 mg) were yielded at a ratio of 20 : 1, while **5** (4.1 mg) and **6** (1.2 mg) were obtained at the ratio of 10 : 1.

Jaspolide A (**1**): Yellow crystal, mp 260—263 °C, $[\alpha]_D^{25}$ −42.9° (c=0.02, acetone). IR (KBr) ν_{max} 3446, 2929, 2870, 1695, 1647, 1557, 1092 cm^{-1}. ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2. HR-FAB-MS *m/z*: $[M+H]^+$ 465.3003 (Calcd for $C_{30}H_{41}O_4$, 465.2999). ESI-MS *m/z*: 465 $[M+H]^+$, 282.

Jaspolide B (**2**): Yellow crystal, mp 259—260 °C, $[\alpha]_D^{25}$ −86.7° (c=0.03, acetone). IR (KBr) ν_{max}: 3433, 2928, 1568, 1419, 1106 cm^{-1}. ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2. HR-FAB-MS *m/z*: $[M+H]^+$ 465.3005 (Calcd for $C_{30}H_{41}O_4$, 465.2999). ESI-MS *m/z*: 465 $[M+H]^+$, 282, 256.

Jaspolide C (**3**): Coless oil, $[\alpha]_D^{25}$ −7.7° (c=0.01, acetone). IR (KBr) ν_{max}: 3433, 2923, 1706, 1650, 1098, 1027 cm^{-1}. ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2. HR-FAB-MS *m/z*: $[M+H]^+$ 317.21107 (Calcd for $C_{20}H_{29}O_3$, 317.2111). ESI-MS *m/z*: 317 $[M+H]^+$, 303, 299.

Jaspolide D (**4**): Colorless oil, $[\alpha]_D^{25}$ −10.1° (c=0.01, acetone). IR (KBr) ν_{max}: 3332, 2923, 2853, 1798, 1759, 1706, 1462, 1029 cm^{-1}. ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2. HR-FAB-MS *m/z*: $[M+H]^+$ 317.2110 (Calcd for $C_{20}H_{29}O_3$, 317.2111).

Jaspolide E (**5**): Yellow solid, $[\alpha]_D^{25}$ −8.6° (c=0.2, acetone). IR (KBr) ν_{max}: 2923, 1732, 1697, 1649, 1596, 1246, 1026 cm^{-1}. ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2. HR-FAB-MS *m/z*: $[M+H]^+$ 495.3098 (Calcd for $C_{31}H_{42}O_5$, 495.3105). ESI-MS *m/z*: 517 $[M+Na]^+$, 495 $[M+H]^+$, 429, 331.

Jaspolide F (**6**): Pale yellow solid, $[\alpha]_D^{25}$ −14.9° (c=0.01, acetone). IR (KBr) ν_{max}: 3349, 2924, 2855, 1699, 1165, 1115 cm^{-1}. ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2. HR-EI-MS *m/z*: $[M]^+$ 398.2458 (Calcd for $C_{25}H_{34}O_4$, 398.2462).

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