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Spiro[3.5]nonenyl Meroterpenoid Lactones, Cryptolaevilactones G−L, an Ionone Derivative, and Total Synthesis of Cryptolaevilactone M from *Cryptocarya laevigata*

Fumika Tsurumi,[†] Yuta Miura,[†,#] Misaki Nakano,[†,#] Yohei Saito,[†] Shuichi Fukuyoshi,[†] Katsunori Miyake,[‡] David J. Newman,[§] Barry R. O'Keefe,[⊥] Kuo-Hsiung Lee,[∥,¶] and Kyoko Nakagawa-Goto*[,†,∥]

[†]School of Pharmaceutical Sciences, College of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, 920-1192, Japan

[‡]Tokyo University of Pharmacy and Life Sciences, Hachioji, Tokyo 192-0392, Japan

[§]NIH Special Volunteer, Wayne, Pennsylvania 19087, United States

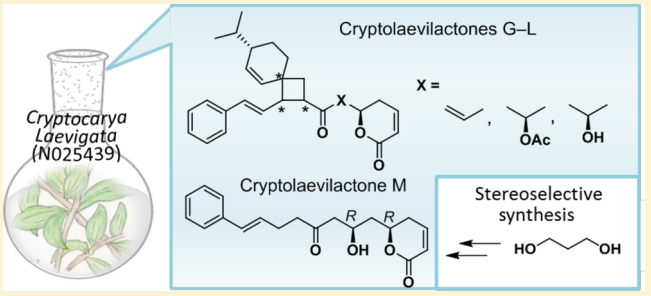
[⊥]Natural Products Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, and Molecular Targets Program, Center for Cancer Research, National Cancer Institute, NCI at Frederick, Frederick, Maryland 21702-1201, United States

[∥]Natural Products Research Laboratories, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-7568, United States

[¶]Chinese Medicine Research and Development Center, China Medical University and Hospital, 2 Yuh-Der Road, Taichung, 40447, Taiwan

Supporting Information

ABSTRACT: A $CH_3OH-CH_2Cl_2$ (1:1) extract (N025439) of the leaves and twigs of *Cryptocarya laevigata* furnished eight new compounds, **1**−**8**. Based on extensive 1D and 2D NMR spectroscopic data examination, the new δ-lactone derivatives **1**−**6** are monoterpene−polyketide hybrids containing a unique spiro[3.5]nonenyl moiety. Their trivial names, cryptolaevilactones G−L, follow those of the related known meroterpenoids cryptolaevilactones A−F. Cryptolaevilactone L (**6**) contains 11,12-*cis*-oriented substituents, while the other cryptolaevilactones contain *trans*-oriented groups. The structure of the linear δ-lactone **7**, cryptolaevilactone M, was characterized from various spectroscopic data analysis, and the absolute configuration was determined by total synthesis through stereoselective allylation and Grubbs olefin metathesis. Compound **8** was elucidated to be an ionone derivative with a 3,4-*syn*-diol functionality.



Plant derived δ-lactones with an alkyl or arylalkyl group at C-6 are produced by a limited number of genera, including *Aniba* (Lauraceae),[1] *Goniothalamus* (Annonaceae), *Piper* (Piperaceae), and *Psilotum* and *Tmesipteris* (Psilotaceae).[2] The genus *Cryptocarya* (Lauraceae) is also known to produce δ-lactone derivatives such as cryptocaryone,[3,4] obolactone,[5] cryptolatifolione,[6,7] cryptomoscatones,[8] rugulactone,[9] cryptocaryols,[10] and cryptoconcatones.[11] These lactones exhibit a wide range of bioactivities such as antitumor,[5] antitrypanosomal,[12] antimalarial,[13] and inhibitory effects on NF-κB activation.[9]

During a phytochemical study on rainforest plants,[14,15] a 50% $MeOH-CH_2Cl_2$ extract of the leaves and twigs of *Cryptocarya laevigata* (Lauraceae), provided by the U.S. National Cancer Institute (code # N025439), was investigated. The characteristic secondary metabolites of *Cryptocarya* include not only 6-alkyl-δ-lactones[3−11,14] but also tetrahydroflavanones[16−19] and their dimers,[5,18,20] as well as pavine alkaloids.[21−23] Our previous study of *C. laevigata* disclosed the unique monoterpene−polyketide hybridized δ-lactones, named cryptolaevilactones A−F.[14] Although the biosynthetic pathway is not clear, their spiro[3.5]nonene moiety is probably biosynthesized through hetero [2 + 2] cycloaddition of a monoterpene, β-phellandrene, and a polyketide δ-lactone containing a double bond. Our continuing research has now furnished six new spiro[3.5]nonenyl meroterpenoid lactones (**1**−**6**), a new linear lactone (**7**), and an ionone derivative (**8**) with a 3,4-*syn*-diol functionality (Figure 1), together with eight known compounds, caryophyllene oxide,[24] (−)-boscialin,[25]

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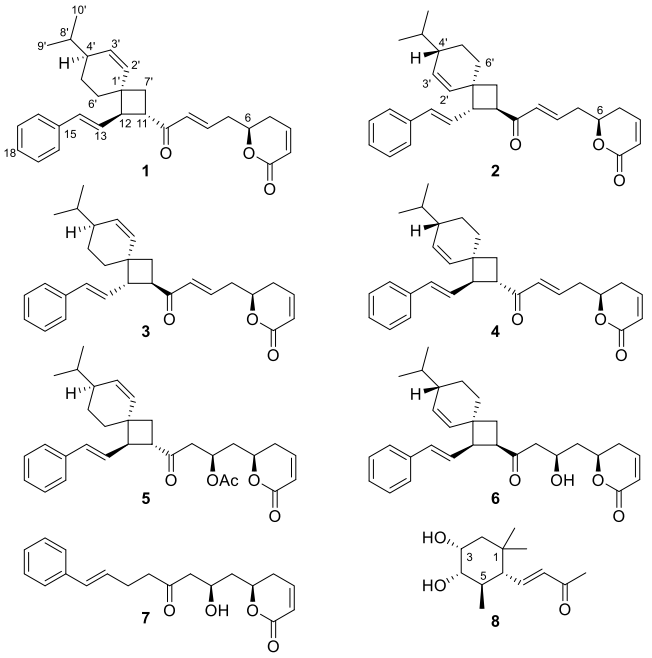

Figure 1. Structures of compounds **1**−**8** from the leaves and twigs of *C. laevigata*. The absolute configuration of compound **6** was proposed from other cryptolaevilactones.

(−)-13aα-antofine,[26] (−)-crychine,[27] *N*-*trans*-feruloyl 3′-*O*-methyldopamine,[28] epicatechin,[29] quercitrin,[30] and lutein.[31,32]

RESULTS AND DISCUSSION

The EtOAc-soluble portion of the 50% MeOH−CH_2Cl_2 extract of the leaves and twigs of *C. laevigata* (N025439) was separated by a combination of column chromatography and preparative HPLC methods, using silica gel, octadecylsilyl (ODS), and chiral-phase columns (CHIRAL ART Cellulose-SC).

Compound **1** was obtained as an optically active colorless, amorphous solid, $[\alpha]^{24}_D$ +208 (*c* 0.05, $CHCl_3$). The ^{1}H NMR data of **1** (Table 1) indicated the presence of a mono-substituted phenyl moiety [δ_H 7.34 (2H, brd, *J* = 7.6 Hz), 7.29 (2H, dd, *J* = 7.6, 7.2 Hz), 7.20 (1H, tt, *J* = 7.2, 1.0 Hz)], two sets of *Z*-olefinic protons [6.70 (1H, ddd, *J* = 9.6, 5.5, 3.1 Hz) and 5.94 (1H, ddd, *J* = 9.6, 2.6, 1.4 Hz); 5.57 (1H, brd, *J* = 10.1 Hz) and 5.53 (1H, brd, *J* = 10.1 Hz)], two sets of *E*-olefinic protons [δ_H 6.75 (1H, ddd, *J* = 16.2, 7.9, 6.9 Hz) and 6.17 (1H, ddd, *J* = 16.2, 1.4, 1.0 Hz); 6.35 (1H, d, *J* = 15.8 Hz) and 6.29 (1H, dd, *J* = 15.8, 7.9 Hz)], and an oxymethine proton [δ_H 4.42 (1H, m)]. Other assignable aliphatic protons, including 14 methylenes or methines and two methyls [δ_H 0.84 (3H, d, *J* = 6.5 Hz), 0.87 (3H, d, *J* = 6.9 Hz)], were also observed. The ^{13}C NMR data of **1** (Table 2) included signals for 27 carbons (two overlapped), including those for a carbonyl carbon (δ_C 200.0), a lactone carbonyl carbon (δ_C 163.7), 14 sp^2 carbons, and an oxymethine carbon (δ_C 76.0). The proton and carbon signals were similar to those of cryptolaevilactone B, which also contains a unique spiro[3.5]-nonenyl moiety.[14]

However, the spectra of **1** did not show signals for an OH group at C-8 and methylene at C-9 but did contain olefinic signals at δ_H 6.75 (1H, ddd, *J* = 16.2, 7.9, 6.9 Hz) and 6.17 (1H, ddd, *J* = 16.2, 1.4, 1.0 Hz) as well as carbons at δ_C 140.6 and 132.7. The observed upfield shift of the C-10 carbonyl (δ_C 212.0 to δ_C 200.0) was likely due to conjugation with a neighboring double bond. Based on these data, a *trans*-$\Delta^{8(9)}$ olefinic moiety was assigned in **1**. HMQC, ^{1}H−^{1}H COSY, and HMBC data (Figure 2) provided support for the C-8−C-10 α,β-unsaturated carbonyl moiety, which might be produced by dehydration at C-8−C-9 of cryptolaevilactone B.[14] The molecular formula of $C_{29}H_{34}O_3$ (HRFABMS *m*/*z* 431.2598 $[M + H]^+$) also suggested a dehydrated molecule relative to cryptolaevilactone B. The two compounds were assigned the same relative configuration on the bases of the NOESY correlations between H-11/H-13, H-12/H-7′α, H-12/H-2′, H-13/H-6′β, H-5′α/H-6′α, and H-5′α/H-4′α (Figure 2), as well as the ^{1}H NMR coupling constants of a pseudoaxial H-5′β [δ_H 1.31 (1H, dddd, *J* = 13.4, 13.4, 10.7, 2.1 Hz)] in **1**. The ECD spectrum of **1** displayed a curve similar to that of the (11*S*, 12*R*, 1′*S*, 4′*S*) isomer based on time-dependent density functional theory/electronic circular dichroism (TDDFT-ECD) calculations.[33] As shown in Figure 3, the experimental ECD curve was slightly closer to the curve calculated for (6*S*) (α-orientation of H-6) than the one computed for (6*R*) (β-orientation of H-6); however, the similarity was not sufficient for an unequivocal assignment. Finally, the (6*S*) configuration was suggested based upon the absolute configuration of **7**, the likely biosynthetic precursor of **1**. Accordingly, the absolute configuration of **1** was postulated to be (6*S*, 11*S*, 12*R*, 1′*S*, 4′*S*). Because the shapes of the ECD spectra of **1** and cryptolaevilactone B were similar, the absolute configuration of cryptolaevilactone B might be (6*R*, 8*R*, 11*S*, 12*R*, 1′*S*, 4′*S*), of which only a relative configuration was proposed in the previous paper.[14] Thus, cryptolaevilactone G (**1**) is the 8,9-dehydrated analogue of cryptocaryalactone B.

Compounds **2** and **4**−**6** were isolated as mixtures of diastereomers. The small amounts of **2** (0.4 mg), **4** (0.8 mg), **5** (0.5 mg), and **6** (0.4 mg) from the limited plant extract (10.5 g) caused difficulty in further purifications of these interesting secondary metabolites. However, individual structure elucidations could be made based on the intensities of the signals in the NMR spectra.

Compound **2** showed a protonated molecular ion at *m*/*z* 431.2588 in the HRFABMS, corresponding to the same molecular formula, $C_{29}H_{35}O_3$, as **1**. Although the compound was isolated as a mixture with a small amount of a diastereomer and, thus, purification was difficult, its ^{1}H and ^{13}C NMR data (Tables 1 and 2) were quite close to those of **1**. NOESY correlations of H-11 with H-7′α/H-14 and H-12 with H-7′β/H-2′ indicated that H-11 and H-12 were α- and β-oriented, respectively (Figure 2). The coupling constants of H-5′α (dddd, *J* = 12.7, 12.7, 8.9, 3.8 Hz) and H-6′α (ddd, *J* = 14.1, 5.2, 3.8 Hz) suggested a half-chair conformation of the cyclohexene portion of the spiro moiety with H-4′β, 5′α, and 6′β in pseudoaxial and H-5′β and 6′α in pseudoequatorial positions. Additionally, a β-orientation was assigned to H-4′ based on a NOESY correlation between H-13 and H-5′α/6′α. These results indicated that compound **2** has the opposite configurations at C-11, C-12, and C′-1 as **1**, and its spiro moiety has the same relative configuration as in cryptolaevilactone A.[14] The absolute configuration of **2** was concluded as (6*S*, 11*R*, 12*S*, 1′*R*, 4′*S*) based on comparison of experimental and calculated[33] ECD data (Figure 3). Accordingly, the structure of cryptolaevilactone H (**2**) was defined as the 8,9-dehydrated analogue of cryptolaevilactone A. This also permitted assignment of the (6*R*,8*R*,11*R*,12*S*,1′*R*,4′*S*) absolute configuration of cryptolaevilactone A.[14]

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Table 1. ^{1}H NMR Spectroscopic Data of Compounds 1−7 (600 MHz, $CDCl_3$)

	1	2	3	4	5	6	7
position	δ_H (J in Hz)	δ_H (J in Hz)	δ_H (J in Hz)	δ_H (J in Hz)	δ_H (J in Hz)	δ_H (J in Hz)	δ_H (J in Hz)
3	5.94, ddd (9.6, 2.6, 1.4)	5.92, ddd (9.6, 2.4, 1.0)	5.92, 9.6, 2.4, 1.0)	5.93, ddd (9.8, 2.1, 1.4)	5.97, ddd (9.8, 2.7, 1.0)	5.91, ddd (9.6, 2.7, 0.9)	6.03, dt (9.8, 1.7)
4	6.70, ddd (9.6, 5.5, 3.1)	6.65, ddd (9.6, 5.2, 3.1)	6.66, ddd (9.6, 5.5, 3.1)	6.67, ddd (9.8, 5.2, 3.4)	6.81, ddd (9.8, 6.0, 2.4)	6.67, ddd (9.6, 6.2, 2.4)	6.89, dt (9.8, 4.3)
5	2.25, m	2.23, m	2.25, m	2.23, m	2.30, dddd (18.2, 11.7, 2.7, 2.4)	1.84, dddd (18.4, 11.9, 2.7, 2.4)	2.42, m
					2.44, dddd (18.2, 6.0, 3.8, 1.0)	2.08, dddd (18.4, 6.2, 3.6, 0.9)	
6	4.42, m	4.47, m	4.47, m	4.38, m	4.49, m	4.58, dddd (11.9, 6.2, 6.2, 3.6)	4.71, m
7	2.55, dddd (15.1, 7.9, 5.8, 1.0)	2.61, dd (7.2, 6.2)	2.61, dddd (15.9, 7.2, 1.7, 1.7)	2.53, dddd (15.0, 7.9, 5.8, 1.0)	1.94, ddd (14.8, 6.2, 3.8)	1.56, m[h]	1.81, ddd (14.5, 5.8, 3.8)
	2.67, dddd (15.1, 6.9, 6.2, 1.4)		2.63, dddd (15.9, 7.6, 2.1, 1.4)	2.67, dddd (15.0, 6.5, 6.5, 1.4)	2.12, ddd (14.8, 7.9, 6.9)	1.78, m[i]	2.02, ddd (14.5, 8.1, 6.9)
8	6.75, ddd (16.2, 7.9, 6.9)	6.76, dt (15.8, 7.2)	6.77, ddd (16.0, 7.6, 7.2)	6.73, ddd (15.8, 7.9, 6.2)	5.41, m	4.03, m	4.32, m
9	6.17, ddd (16.2, 1.4, 1.0)	6.17, brd (15.8)	6.19, brd (16.0)	6.16, ddd (15.8, 1.4, 1.0)	2.71, dd (17.2, 6.9)	2.45, dd (17.9, 8.6)	2.70, m
					2.77, dd (17.2, 6.5)	2.55, dd (17.6, 3.1)	
11	3.45, ddd (9.7, 9.3, 8.6)	3.46, ddd (9.6, 9.1, 8.2)	3.51, ddd (9.6, 9.3, 8.9)	3.46, ddd (10.0, 8.9, 8.6)	3.21, ddd (9.8, 8.9, 8.8)	3.57, ddd (10.0, 9.3, 8.2)	2.65, t (7.1)
12	3.02, dd (9.3, 7.9)	2.94, dd (9.1, 8.2)	2.91, dd (9.3, 7.2)	2.90, dd (8.9, 8.2)	2.96, dd (8.8, 8.2)	3.20, dd (11.0, 10.0)	2.51, tdd (7.1, 6.9, 1.4)
13	6.29, dd (15.8, 7.9)	6.31, dd (15.8, 8.2)	6.31, dd (15.8, 7.2)	6.27, dd (15.8, 8.2)	6.28, dd (15.8, 8.2)	6.15, dd (15.7, 11.0)	6.18, dt (15.8, 6.9)
14	6.35, d (15.8)	6.36, d (15.8)	6.34, d (15.8)	6.31, d (15.8)	6.41, d (15.8)	6.35, d (15.7)	6.41, brd (15.8)
16	7.34, brd (7.6)	7.34, brd (7.4)	7.34, brd (7.8)	7.27−7.33, m[e]	7.37, d (7.8)	7.28, d (4.1)	7.33, dd (7.6, 1.4)
17	7.29, dd (7.6, 7.2)	7.30, dd (7.4, 7.4)	7.29, dd (7.8, 7.2)	7.27−7.33, m[e]	7.31, dd (7.8, 7.6)	7.28, d (4.1)	7.29, dd (7.6, 7.2)
18	7.20, tt (7.2, 1.0)	7.22, tt (7.4, 1.4)	7.20, tt (7.2, 1.0)	7.19, tt (6.9, 1.7)	7.22, tt (7.6, 1.0)	7.26, m[j]	7.21, tt (7.2, 1.4)
19	7.29, dd (7.6, 7.2)	7.30, dd (7.4, 7.4)	7.29, dd (7.8, 7.2)	7.27−7.33, m[e]	7.31, dd (7.8, 7.6)	7.28, d (4.1)	7.29, dd (7.6, 7.2)
20	7.34, brd (7.6)	7.34, brd (7.4)	7.34, brd (7.8)	7.27−7.33, m[e]	7.37, d (7.8)	7.28, d (4.1)	7.33, dd (7.6, 1.4)
2′	5.57, brd (10.1)	5.58, d (11.2)	6.00, dd (10.3, 1.4)	5.90, brd (10.5)	5.55, d (10.9)	5.63, brd (10.0)	
3′	5.53, brd (10.1)	5.56, d (11.2)	5.66, dd (10.3, 1.7)	5.71, brd (10.5)	5.53, d (10.9)	5.54, brd (10.0)	
4′	1.86, m[a]	1.85, m	1.86, m	1.94, m	1.87, m	1.93, m	
5′α	1.68, m[b]	1.30, dddd (12.7, 12.7, 8.9, 3.8)	1.55, m[c]	1.31, dddd (13.4, 13.1, 10.7, 2.4)	1.66, m[g]	1.29, dddd (13.1, 12.9, 10.0, 2.7)	
5′β	1.31, dddd (13.4, 13.4, 10.7, 2.1)	1.51, m overlap	1.28, dddd (12.7, 12.4, 9.3, 3.3)	1.50, m[f]	1.29, dddd (12.0, 12.0, 10.3, 1.9)	1.62, m[k]	
6′α	1.68, m[b]	2.20, ddd (14.1, 5.2, 3.8)	1.61, ddd (13.1, 12.4, 2.7)	1.79, brd (13.1)	1.65, m[g]	1.98, brd (12.7)	
6′β	1.86, m[a]	1.51, m[d]	1.70, ddd (13.1, 5.2, 3.3)	1.61, ddd (13.4, 13.1, 3.1)	1.80, ddd (12.0, 4.5, 1.9)	1.65, ddd (12.9, 12.7, 2.7)[k]	
7′α	2.15, ddd (11.3, 9.7, 1.0)	1.84, dd (11.5, 8.2)	2.15, dd (11.0, 9.6)	2.18, dd (11.2, 10.0)	2.15, dd (11.3, 9.8)	1.77, dd (13.4, 8.2)[i]	
7′β	1.89, dd (11.3, 8.6)	2.25, dd (11.5, 9.6)	1.97, dd (11.0, 8.9)	1.89, dd (11.2, 8.6)	1.87, dd (11.3, 8.9)	2.64, dd (13.4, 9.3)	
8′	1.54, m	1.51, m[d]	1.55, m[c]	1.50, m[f]	1.53, m	1.53, m[h]	
9	0.84, d (6.5)	0.78, d (6.9)	0.85, d (6.5)	0.75, d (6.9)	0.84, d (6.5)	0.76, d (6.5)	
10	0.87, d (6.9)	0.80, d (6.9)	0.88, d (6.5)	0.78, d (6.9)	0.86, d (6.9)	0.80, d (6.9)	
OH						3.52, d (1.7)	3.28, brs
OAc					2.02, s		

[a−k]Overlapping signals.

The HRFABMS protonated molecular ion of cryptolaevilactone I (**3**) was observed at m/z 431.2596 $[M + H]^+$; thus, the molecular formula of $C_{29}H_{35}O_3$ is the same as those of **1** and **2**. The ^{1}H and ^{13}C NMR data of **3** showed similar, but slightly shifted, signal patterns compared to those of **1**, consistent with **3** being a diastereomer (Tables 1 and 2). The relative configuration of **3** was determined from the NOESY correlations between H-11/H-7′α, H-12/H-7′β, H-12/H-6′β, H-7′α/H-2′, H-5′α/H-6′α, and H-4′α/H-5′α (Figure 2), as well as the following ^{1}H NMR coupling constants [δ_H 1.70 (1H, ddd, J = 13.1, 5.2, 3.3 Hz, H-6′β), 1.61 (1H, ddd, J = 13.1, 12.4, 2.7 Hz, H-6′α), 1.28 (1H, dddd, J = 12.7, 12.4, 9.3, 3.3 Hz, H-5′β)]. Comparison of the experimental and

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Table 2. ^{13}C NMR Spectroscopic Data of Compounds 1−7 (150 MHz, $CDCl_3$)

	1	2	3	4	5	6	7
position	δ_C	δ_C	δ_C	δ_C	δ_C	δ_C	δ_C
2	163.7	163.8	163.8	163.7	no data	164.1	no data
3	121.3	121.2	121.3	121.3	121.2	121.0	121.3
4	144.4	144.5	144.5	144.4	144.9	145.1	145.5
5	28.9	28.8	28.8	28.9	29.1	28.5	26.8
6	76.0	76.0	76.0	76.0	74.8	75.6	75.5
7	37.7	37.6	37.7	37.7	38.9	40.7	40.5
8	140.6	140.4	140.5	140.8	66.9	64.6	64.4
9	132.7	132.9	132.9	132.7	45.2	48.3	48.8
10	200.0	200.0	199.9	199.8	207.9	212.2	211.0
11	43.7	43.7	43.6	43.5	46.3	45.2	43.0
12	52.0	51.2	51.7	54.3	52.0	54.4	29.1
13	128.3	128.1	129.0	131.0	128.0	127.8	128.3
14	131.9	132.0	131.6	131.3	132.0	132.3	131.1
15	137.0	137.1	137.1	137.1	137.0	136.9	137.2
16	126.2	126.2	126.3	126.1	126.3	126.2	126.0
17	128.6	128.7	128.6	128.6	128.6	128.6	128.6
18	127.4	127.4	127.3	127.2	127.5	127.4	127.2
19	128.6	128.7	128.6	128.6	128.6	128.6	128.6
20	126.2	126.2	126.3	126.1	126.3	126.2	126.0
1′	40.8	40.5	41.5	41.3	40.6	40.0	
2′	136.0	135.8	131.2	131.8	135.8	133.1	
3′	131.4	131.2	131.5	132.4	131.6	132.5	
4	42.1	41.3	41.7	41.8	42.1	41.7	
5′	22.4	22.9	22.4	21.9	22.3	22.1	
6	30.0	30.3	36.6	37.8	29.8	36.6	
7	33.9	34.7	35.1	33.1	33.4	31.3	
8	31.9	31.7	31.9	31.8	31.9	31.8	
9	19.3	19.4	19.4	19.1	19.3	19.0	
10	19.6	19.6	19.7	19.4	19.6	19.5	
OAc					21.1		
					170.5		

calculated[33] ECD data supported the (6*S*, 11*R*, 12*S*, 1′*S*, 4′*S*) absolute configuration (Figure 3).

The ^1H NMR data of **4** and **3** (Table 1) were quite similar; however, the signals related to the spiro moiety, H-2′−H-4′ as well as H-5′$_{\alpha,\beta}$ and H-6′$_{\alpha,\beta}$, were shifted, suggesting a different configuration at C-1′. Other NMR spectroscopic data, including 2D, coupled with the HRFABMS ion peak at *m*/*z* 431.2585 $[M + H]^+$ suggested that compound **4** was the C-4′ epimer of **3**. The β-orientation of H-4′ was determined from the NOESY correlations between H-4′/H-5′β, H-4′/H-6′β, H-5′α/H-12, and H-6′α/H-12 (Figure 2), as well as the coupling constants for H-5′α (dddd, *J* = 13.4, 13.1, 10.7, 2.4 Hz), H-6′α (brd, *J* = 13.1 Hz), and H-6′β (ddd, *J* = 13.4, 13.1, 3.1 Hz). Based on these results, cryptolaevilactone J (**4**) has the same 2D structure as **1**−**3** but a different relative configuration. The ECD spectra of compounds **1** and **4** showed highly similar Cotton effects, while those of compounds **2** and **3** displayed similar shapes (Figure 3). The (6*S*, 11*S*, 12*R*, 1′*R*, 4′*S*) absolute configuration was confirmed by the calculated ECD data[33] (Figure 3).

The HRFABMS ion, *m*/*z* 491.2798 $[M + H]^+$, of **5** was different from those of **1**−**4**. The presence of an acetoxy group was supported by the molecular formula, $C_{31}H_{38}O_5$, and an acetoxy methyl resonance at δ_H 2.02 (3H, s) in the ^1H NMR data of **5** (Table 1). Proton signals for a methylene group at δ_H 2.71 and 2.77 and a low field shifted oxymethine at δ_H 5.41 indicated that the acetoxy group was located at C-8. This assignment was supported by the COSY and HMBC analyses (Figure 2). The relative configuration of the spiro portion was identical to that of **1**, by comparison of the NMR spectra and NOESY correlations. The orientation of the styrenyl unit at C-12 and carbonyl chromophore at C-11 could be expected to dominate the ECD spectrum. Thus, the ECD is governed mainly by the C-11 and C-12 stereogenic centers and might be sensitive to the populations of rotamers along the σ-bonds between C-12 and C-13 as well as C-10 and C-11. Accordingly, the absolute configuration of **5** was postulated as (6*R*, 8*R*, 11*S*, 12*R*, 1′*S*, 4′*S*) based on the similarities of the ECD spectra of **5** and cryptolaevilactone B[14] (Figure 4). Cryptolaevilactone K (**5**) was concluded to be the 8-*O*-acetyl derivative of cryptolaevilactone B and was isolated as a mixture with a small amount of a diastereomer.

Compound **6** was isolated as a mixture of diasteromers in a ca. 4:1 ratio. The HRFABMS ion at *m*/*z* 449.2695 $[M + H]^+$ was consistent with the molecular formula $C_{29}H_{36}O_4$ found for cryptolaevilactones A−C.[14] The ^1H and ^{13}C NMR data of **6** were highly similar to those of cryptolaevilactones A−C (Tables 1 and 2). Thus, compound **6** is likely a diastereomer of cryptolaevilactones A−C. The (11*R**, 12*R**, 1′*R**, 4′*S**) relative configuration of the spiro moiety was established from NOESY correlations (H-11/H-12, H-11/H-7′α, H-13/H-7′β, H-13/H-2′, H-7′β/H-2′, H-12/H-5′α, H-12/H-6′α, H-11/H-6′α, Figure 2) and ^1H NMR coupling constants [H-5′α (dddd, *J* = 13.1, 12.9, 10.0, 2.7 Hz), H-6′α (brd, *J* = 12.7 Hz), and H-

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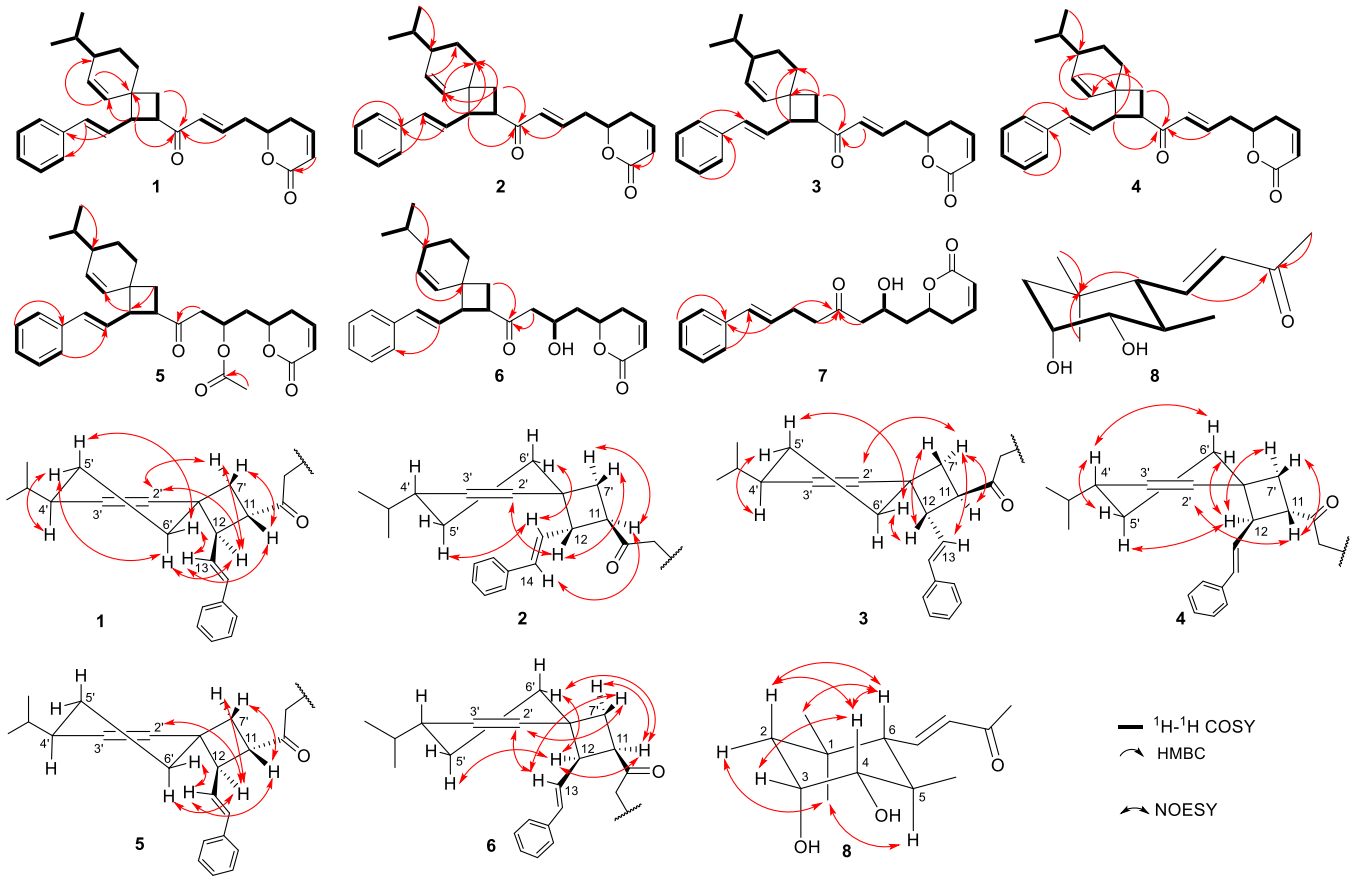

Figure 2. Selected HMBC correlations (arrows), COSY connectivities (bold line), and key NOESY correlations for **1**−**8**.

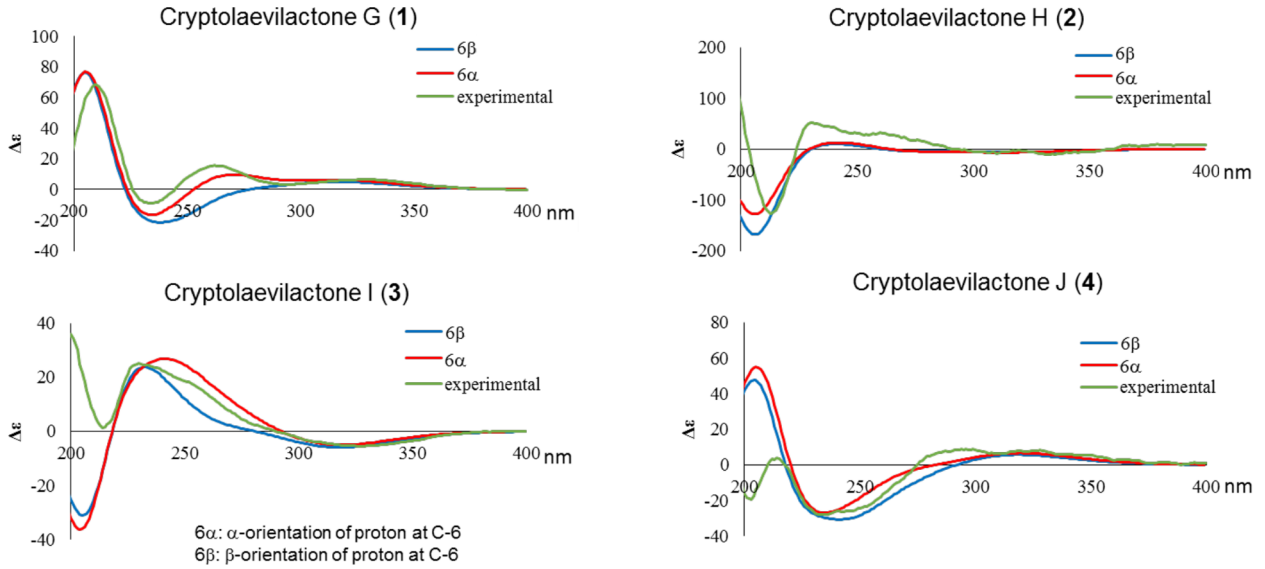

Figure 3. Experimental and calculated ECD spectra of compounds **1**−**4** in MeCN.

6′*β* (ddd, *J* = 12.9, 12.7, 2.7 Hz)]. The (11*R*, 12*R*, 1′*R*, 4′*S*) absolute configuration of the spiro moiety was defined by comparison of experimental and calculated ECD data (Figure 5). Thus, the C-11 and C-12 substituents are *cis* in compound **6** (cryptolaevilactone L), but *trans* in all related spiro[3.5]-nonenyl meroterpenoid lactones (cryptolaevilactones A−K). Because the two stereogenic centers at C-6 and C-8 contribute less to the overall shape of the ECD curve, their absolute configurations at C-6 and C-8 could not be determined from the TDDFT-ECD calculation (Figure 5) but are most likely (6*R*, 8*R*) based on the absolute configurations of other cryptolaevilactones.

Compound **7** showed a protonated molecular ion at *m*/*z* 315.1590 in the HRFABMS, corresponding to the molecular formula $C_{19}H_{22}O_4$. The ^{1}H NMR data displayed similar signals to those of cryptolaevilactone A;[14] however, the 18 proton signals for the spiro moiety were not observed (Table 1). Instead, four aliphatic hydrogens were detected at δ_H 2.65 (2H,

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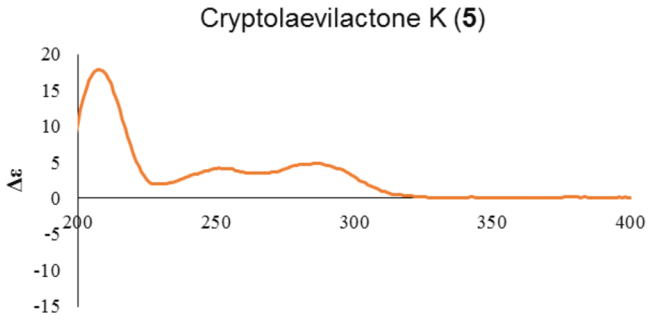


Figure 4. Experimental ECD spectrum of compound **5** in MeCN.

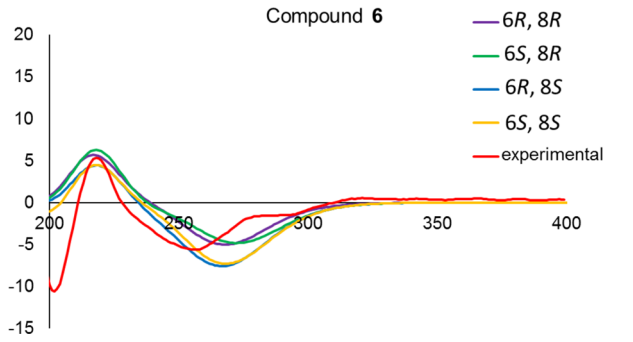
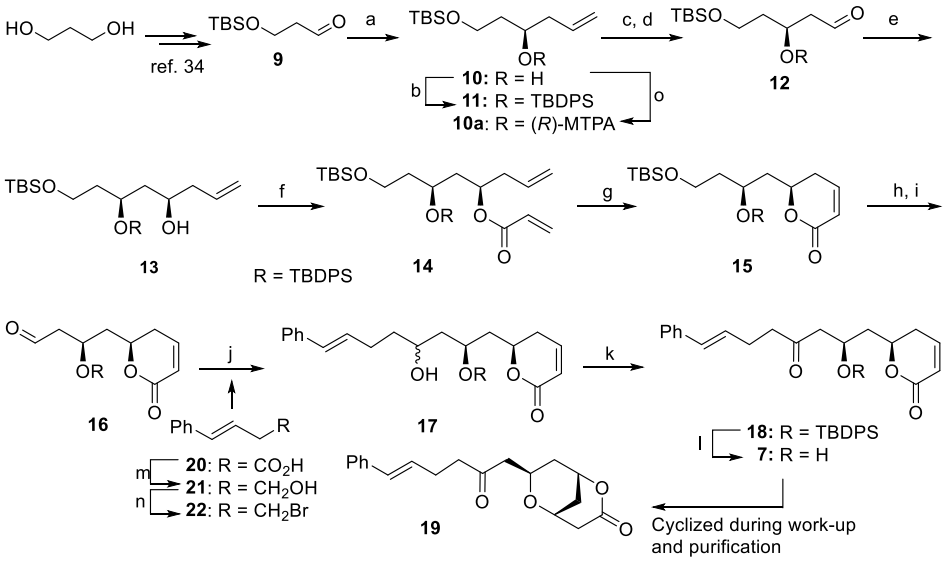


Figure 5. Experimental and calculated ECD spectra of compound **6** (11*R*, 12*R*, 1′*R*, 4′*S*) in MeCN.

t, J = 7.1 Hz) and 2.51 (2H, tdd, J = 7.1, 6.9, 1.4 Hz), suggesting the presence of a 1,2-disubstituted 11,12-ethyl unit. The ^{1}H−^{1}H COSY and HMBC data of **7** (Figure 2) supported the 2D structure shown in Figure 1. The absolute configuration was proved by total synthesis (Scheme 1). Aldehyde **9**, which was prepared from ethylene glycol,[34] was converted to allyl alcohol **10** through a stereoselective Keck allylation. An enantiomeric excess (ee) of >99% was confirmed by the ^{1}H NMR spectrum of its Mosher ester **10a** (Figure S59, Supporting Information). Silyl protection of the hydroxy group, followed by oxidative cleavage of the terminal olefinic group, afforded aldehyde **12**, which was transformed under Brown conditions into **13**[34] in 91% de. After removal of the unwanted diastereomer, compound **13** was treated with acryloyl chloride and cyclized by Grubbs olefin metathesis. The resulting lactone **15** was converted to aldehyde **16** through deprotection of the primary alcohol and 2-iodobenzoic acid (IBX) oxidation. Treatment of **16** with phenylbutenyl-MgBr prepared from (*E*)-4-phenylbut-3-enoic acid (**20**) in three steps gave alcohol **17** as a diastereomer mixture, which was oxidized to generate ketone **18**. Careful reaction, workup, and purification conditions were required to remove the *tert*-butyldiphenylsilyl (TBDPS) protecting group, because the target compound **7** cyclizes readily to form **19**. Finally, deprotection was achieved successfully by treatment with tetra-*n*-butylammonium fluoride (TBAF) and purification without the use of acidic silica gel to furnish compound **7** with (6*R*, 8*R*) configuration. Because the ^{1}H NMR (Figure S60, Supporting Information) and ECD (Figure 6) spectra of synthesized **7** were identical with those of isolated **7**, the structure of cryptolaevilactone M (**7**) was elucidated as (*R*)-6-[(*R*,*E*)-2-hydroxy-4-oxo-8-phenyloct-7-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one.

Compound **8** was isolated as a colorless oil with an HRFABMS ion at m/z 227.1631 $[M + H]^+$, indicating a molecular formula of $C_{13}H_{22}O_3$. The ^{1}H NMR data (Table 3) revealed four methyl groups (three singlets at δ_H 0.85, 1.11, and 2.28; a doublet at δ_H 0.92), two *trans* olefinic protons (δ_H

Scheme 1. Stereoselective Total Synthesis of 7[a]



[a]Reagents and conditions: (a) (*R*)-BINOL, Ti(O*i*Pr)$_4$, 4 Å MS, allylSnBu$_3$, anhydrous toluene, −20 °C, 70%; (b) TBDPSCl, imidazole, anhydrous CH_2Cl_2, rt, 4 h, 97%; (c) OsO_4, NMO, *t*BuOH−H_2O (3:1), rt, 2 h, 99%; (d) $NaIO_4$, THF−H_2O (3:1), rt, 2 h, 99% for 2 steps; (e) (+)-IPc$_2$B(allyl), anhydrous Et_2O, −78 °C, 4 h; (f) acryloyl chloride, Et_3N, anhydrous CH_2Cl_2, 0 °C, 2 h, 76% for 2 steps; (g) second Grubbs catalyst, anhydrous CH_2Cl_2, reflux, 3 h, 93%; (h) p-TsOH·H_2O, THF−H_2O (3:1), rt, 21 h, 99%; (i) IBX, anhydrous CH_2Cl_2, anhydrous DMSO, rt, 11 h, 96%; (j) **22**, Mg, anhydrous THF, −40 °C to rt, 4 h, 42%; (k) IBX, anhydrous CH_2Cl_2, anhydrous DMSO, rt, 4 h, 82%; (l) TBAF, anhydrous THF, rt, 19 h, 61%; (m) LAH, anhydrous THF, 0 °C to rt, 1 h, 87%; (n) CBr_4, PPh_3, imidazole, anhydrous CH_2Cl_2, rt, 1 h, 83%; (o) (*S*)-MTPA-Cl, Et_3N, DMAP, CH_2Cl_2, 40 °C, 1 h, 88%.

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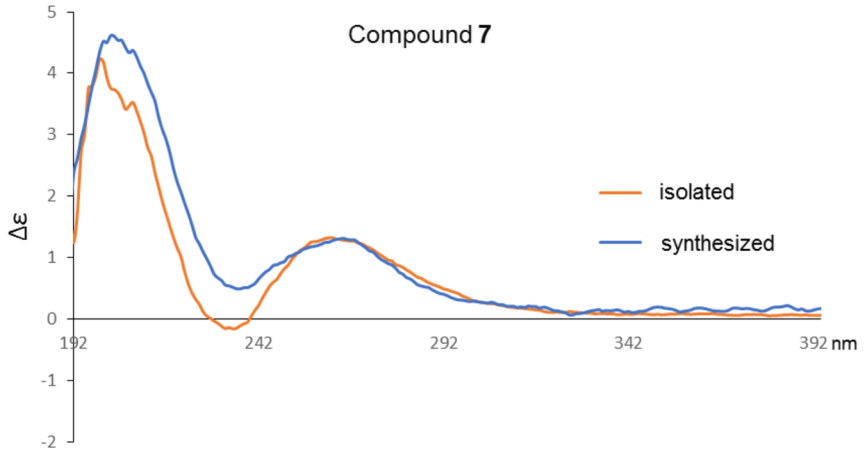

Figure 6. Experimental ECD spectra of isolated and synthesized **7** in MeCN.

Table 3. ^{1}H and ^{13}C NMR Spectroscopic Data of Compound 8 ($CDCl_3$)

	δ_H (J in Hz)	δ_C
position	600 MHz	150 MHz
1		33.5
2_{ax}	1.46, dd (15.0, 3.1)	44.7
2_{eq}	1.85, dd (15.0, 3.1)	
3	4.03, q (3.1)	69.8
4	3.18, dd (10.3, 3.1)	76.7
5	1.92, ddd (10.3, 10.7, 6.5)	32.5
6	1.66, dd (10.7, 10.3)	56.7
7	6.56, dd (16.0, 10.3)	148.2
8	6.03, d (16.0)	133.6
9		198.2
10	2.28, s	27.1
1_{ax}-Me	1.11	23.6
1_{eq}-Me	0.85	31.8
5-Me	0.92, d (6.5)	16.6
OH	2.03, br s	
OH	2.12, br s	

6.03, d, J = 16.0 Hz and δ_H 6.56, dd, J = 16.0, 10.3 Hz), and two oxymethine protons (δ_H 3.18, dd, J = 10.3, 3.1 Hz and δ_H 4.03, q, J = 3.1 Hz). The ^{13}C NMR data (Table 3) suggested the presence of a conjugated carbonyl carbon at δ_C 198.2 in addition to the aforementioned groups. Based on the HMQC and COSY analyses (Figure 2), the 2D structure of **8** was assigned to be an ionone derivative; its 4-epimer was derived artificially from natural (3*S*,4*S*,5*S*,6*S*,9*R*)-3,4-dihydroxy-5,6-dihydro-β-ionol.[35] A NOESY correlation between H-3 and H-4 suggested that the two hydroxy groups were *syn*-oriented, which was supported by the coupling constant of 3.1 Hz. Additional correlations of H-4 with H-2β and H-6, H-2β, with H-6 and of 1α-Me with H-5 and H-2α established the (3*S**, 4*R**, 5*S**, 6*S**) configuration. Subsequently, the (3*R*, 4*S*, 5*R*, 6*R*) absolute configuration was defined via the ECD spectrum, which agreed with the calculated spectrum (Figure 7).

In conclusion, six monoterpene−polyketide hybrids containing a unique spiro[3.5]nonane moiety, cryptolaevilactones G−L, were found in a CH_3OH−CH_2Cl_2 (1:1) extract (N025439) of the leaves and twigs of *C. laevigata*. Although some analytical difficulty precluded complete structure elucidation, extensive spectroscopic and spectrometric experiments, including ^{1}H/^{13}C NMR, HMBC, COSY, NOESY,

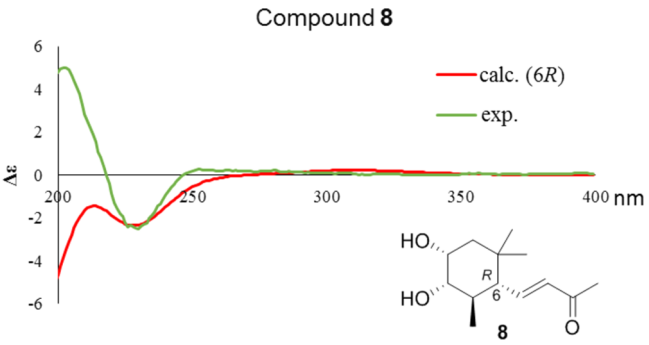

Figure 7. Calculated and experimental ECD spectra of compound **8** in MeCN.

HRFABMS, and ECD, revealed the structures of the new compounds **1**−**6**. While the new cryptolaevilactones G−K (**1**−**5**) and the known analogues[14] contain *trans*-oriented cyclobutane rings, the new cryptolaevilactone L (**6**) contains a *cis* moiety. Cryptolaevilactone M (**7**) was characterized as a related δ-lactone without a spiro[3.5]nonane moiety. The absolute configuration was defined by total synthesis through stereoselective allylation and Grubbs olefin metathesis. Compound **8** was defined as an ionone derivative with a 3,4-*syn*-diol moiety.

In our previous paper,[14] the absolute configurations of the pyrone moiety of cryptolaevilactones A−C were proposed based on their ECD Cotton effects. However, the recent TDDFT-ECD calculations clearly indicated that the chirality of the pyrone moiety results in a minor contribution to the ECD spectrum. Accordingly, cryptolaevilactones A−F[14] are likely to have an identical absolute configuration at C-6, namely, 6*R* for cryptolaevilactones A−C and 6*S* for cryptolaevilactones D−F.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured on a JASCO P-2200 digital polarimeter. ECD spectra were recorded on a JASCO J-820 spectrometer. Infrared spectra (IR) were recorded on a Thermo Fisher Scientific NICOLET iS5 FT-TR spectrometer with samples in CH_2Cl_2. NMR spectra were obtained on JEOL JMN-ECA600 and JMN-ECS400 NMR spectrometers with tetramethylsilane as an internal standard, and chemical shifts are indicated as δ values. HRMS data were recorded on a JEOL JMS-700 (FAB) mass spectrometer. MPLC was performed with C_{18} cartridges (ODS-25, YMC-DispoPack). Preparative HPLC was conducted on a GL Science recycling system using an InertSustain C_{18} column (5 μm,

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20 × 250 mm) and a CHIRAL ART Cellulose-SC column (5 μm, 10 × 250 mm, YMC).

Plant Material. A crude CH_2Cl_2−CH_3OH (1:1) extract (N025439) of *C. laevigata* leaves and twigs was provided by the NCI Natural Products Branch (Developmental Therapeutics Branch, Frederick, MD, USA). The plants were collected in The Philippines by D. D. Soejarto, E. Reynoso, E. Sagcal, and R. Edrada in March 1990. The taxonomic determination of the plant material was confirmed by J. C. Regalado in 1994. A voucher specimen (#U44Z.1628) was deposited at the Smithsonian Institution (Washington, DC, USA), and reference samples of N025439 were deposited at NCI-Frederick and Kanazawa University (Kanazawa, Japan).

Extraction and Isolation. The extract, N025439 (10.5 g), was partitioned between EtOAc and H_2O. The EtOAc-soluble fraction (5.0 g) was chromatographed on silica gel using *n*-hexane−EtOAc (1:0−0:1) and MeOH as eluents to give six fractions, F1−F6. F2 (1.37 g) was separated by silica gel column chromatography (CC) eluted with *n*-hexane−acetone (5:1−0:1) to furnish five subfractions, SF2a−e. SF2a was purified by recycling preparative HPLC with MeOH−H_2O (9.5:0.5) to provide caryophyllene oxide (1.2 mg). F4 (620 mg) was separated by silica gel CC eluted with CH_2Cl_2−acetone (1:0−0:1) to provide four subfractions, SF4a−d. SF4a (70.5 mg) was subjected to silica gel CC eluted with *n*-hexane−EtOAc (5:1−0:1) and MeOH to yield seven subfractions, SF4a1−4a7. SF4a6 (7.0 mg) was purified by MPLC on ODS-25 (YMC-DispoPack AT 12 g) with MeOH−H_2O (9:1−1:0), followed by repeated recycling preparative HPLC with MeOH−H_2O (9:1) and CHIRAL column HPLC with *n*-hexane−*i*PrOH (1:2) to provide compounds **1** (0.9 mg), **2** (1.2 mg), **3** (0.4 mg), **4** (0.8 mg), and **5** (0.5 mg). SF4b (72.6 mg) was separated by repeated recycling preparative HPLC with MeCN−H_2O (7:3−0:1) to provide (−)-crychine (3.0 mg). SF4d was subjected to recycling preparative HPLC with MeCN−H_2O (8.5:1.5−0:1) to give lutein (2.1 mg). F5 (448 mg) was chromatographed on silica gel eluted with CH_2Cl_2−MeOH (40:1−0:1), leading to seven subfractions, SF5a−g. SF5c (64.3 mg) was subjected to MPLC with MeCN−acetone−MeOH−H_2O (1:2:1:2), followed by repeated recycling preparative HPLC with acetone−H_2O (3:1), to afford compound **6** (0.4 mg). SF5d (65.9 mg) was separated by MPLC with acetone−H_2O (4:1−1:0), followed by repeated recycling preparative HPLC with MeOH−H_2O (1:1), to afford compound **8** (1.3 mg). SF5f (225.3 mg) was subjected to MPLC with MeCN−H_2O (1:4−0:1), followed by repeated recycling preparative HPLC with MeOH−H_2O (1:1−0:1), to afford (−)-boscialin (1.2 mg), *N-trans*-feruloyl 3′-*O*-methyldopamine (1.5 mg), and epicatechin (2.4 mg). F6 (1.78 g) was chromatographed on silica gel using *n*-hexane−acetone (3:1−0:1) and MeOH as eluents to yield seven subfractions, SF6a−g. SF6d (97.1 mg) was subjected to MPLC with MeCN−H_2O (2:3−0:1) to give five subfractions, SF6d1−6d5. SF6d1 was purified by recycling preparative HPLC with MeOH−H_2O (13:7) to furnish compound **7** (0.4 mg).

*Cryptolaevilactone G (**1**):* colorless, amorphous solid; $[\alpha]^{28}_D$ +208 (*c* 0.1, $CHCl_3$); IR ν_{max} (CH_2Cl_2) 2955, 2929, 2864, 1724, 1691, 1664, 1385, 1245, 1145, 1044, 969, 815, 758, 743, 696 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; HRFABMS *m*/*z* 431.2598 $[M + H]^+$ (calcd for $C_{29}H_{35}O_3$, 431.2586).

*Cryptolaevilactone H (**2**):* colorless, amorphous solid; $[\alpha]^{27}_D$ +43 (*c* 0.02, $CHCl_3$); IR ν_{max} (CH_2Cl_2) 2955, 2927, 2870, 1725, 1664, 1632, 1388, 1247, 1047, 965, 820, 747, 698 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; HRFABMS *m*/*z* 431.2596 $[M + H]^+$ (calcd for $C_{29}H_{35}O_3$, 431.2586).

*Cryptolaevilactone I (**3**):* pale yellow oil; ^1H and ^{13}C NMR, see Tables 1 and 2; HRFABMS *m*/*z* 431.2588 $[M + H]^+$ (calcd for $C_{29}H_{35}O_3$, 431.2586).

*Cryptolaevilactone J (**4**):* pale yellow oil; ^1H and ^{13}C NMR, see Tables 1 and 2; HRFABMS *m*/*z* 431.2585 $[M + H]^+$ (calcd for $C_{29}H_{35}O_3$, 431.2586).

*Cryptolaevilactone K (**5**):* colorless oil; ^1H and ^{13}C NMR, see Tables 1 and 2; HRFABMS *m*/*z* 491.2798 $[M + H]^+$ (calcd for $C_{31}H_{39}O_5$, 491.2797).

*Cryptolaevilactone L (**6**):* colorless oil; ^1H and ^{13}C NMR, see Tables 1 and 2; HRFABMS *m*/*z* 449.2695 $[M + H]^+$ (calcd for $C_{29}H_{37}O_4$, 449.2692).

*Cryptolaevilactone M (**7**):* colorless oil; ^1H and ^{13}C NMR, see Tables 1 and 2; HRFABMS *m*/*z* 315.1590 $[M + H]^+$ (calcd for $C_{19}H_{23}O_4$, 315.1596).

*(3R,4S,5R,6R)-3,4-Dihydroxy-4,5-dihydro-α-ionone (**8**):* colorless oil; $[\alpha]^{27}_D$ +12 (*c* 0.1, $CHCl_3$); ^1H and ^{13}C NMR, see Table 3; HRFABMS *m*/*z* 227.1631 $[M + H]^+$ (calcd for $C_{13}H_{23}O_3$, 227.1647).

Stereoselective Total Synthesis of Cryptolaevilactone M (7). *3-[(tert-Butyldimethylsilyl)oxy]propanal (**9**).* To a suspension of NaH (60%, 508 mg, 12.7 mmol) in anhydrous tetrahydrofuran (THF, 12.5 mL) was added dropwise 1,3-propanediol (899 mg, 11.8 mmol) in anhydrous THF (12.5 mL) at 0 °C. The suspension was stirred for 45 min at room temperature (rt), *tert*-butyldimethylsilyl chloride (1.87 g, 12.4 mmol) in anhydrous THF (5.0 mL) was added dropwise at 0 °C, and the resulting mixture was stirred at rt for 2 h. The mixture was quenched with saturated $NaHCO_3$ at 0 °C and extracted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with column chromatography to afford 3-(*tert*-butyldimethylsilanyloxy)propan-1-ol (1.82 g, 81%) as a colorless oil.

To a solution of 3-(*tert*-butyldimethylsilanyloxy)propan-1-ol (432 mg, 2.27 mmol) in EtOAc (4.0 mL) was added IBX (1.51 g 5.39 mmol), and the mixture was refluxed at 80 °C for 3.5 h. Subsequently, the mixture was cooled to rt and filtered. The organic phase was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The title aldehyde (**9**, 399 mg, 2.12 mmol) was obtained as a colorless oil without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.88 (s, 9H), 2.60 (dt, *J* = 2.0 Hz, 2H), 3.99 (t, *J* = 6.0 Hz, 2H), 9.81 (t, *J* = 2.4 Hz, 1H).

*(R)-1-[(tert-Butyldimethylsilyl)oxy]hex-5-en-3-ol (**10**).* A mixture of (*R*)-1,1′-bi-2-naphthol (BINOL) (388 mg, 1.36 mmol) and Ti(O*i*-Pr)$_4$ (0.19 mL, 0.65 mmol) in anhydrous toluene (6.0 mL) in the presence of 4 Å molecular sieves (600 mg) was stirred at rt. After 3 h, a solution of aldehyde **9** (499 mg, 2.66 mmol) in anhydrous toluene (1.0 mL) was added, and the resulting mixture was stirred for 10 min. The mixture was cooled to −78 °C, and allyltributyltin (2.4 mL, 7.8 mmol) was added. The stirring was continued at −20 °C for 35 h. After completion of the reaction (detected by TLC), the reaction was quenched with saturated $NaHCO_3$ and stirred for an additional 30 min. The solution was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (*n*-hexane−EtOAc, 10:1) to afford **10** (431 mg, 70%, > 99% ee by ^1H NMR spectroscopy of its MTPA ester; see Supporting Information) as a colorless oil: ^1H NMR (600 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.69−1.65 (m, 2H), 3.37 (d, *J* = 2.4 Hz, 1H), 3.84−3.78 (m, 1H), 3.93−3.88 (m, 2H), 5.13−5.08 (m, 2H), 5.90−5.80 (m, 1H).

*(R)-1-[(tert-Butyldimethylsilyl)oxy]hex-5-en-3-yl-(R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**10a**).* To a solution of (*R*)-1-[(*tert*-butyldimethylsilyl)oxy]hex-5-en-3-ol (**10**, 1.8 mg, 6.4 μmol) in CH_2Cl_2 (0.4 mL) were added Et_3N (3.1 μL, 23 μmol), 4-dimethylaminopyridine (DMAP) (3.3 mg, 27 μmol), and (*S*)-(+)-MTPA-Cl (4.1 μL, 23 μmol). The reaction mixture was stirred for 1 h at 40 °C, and the reaction was quenched with water. The aqueous phase was extracted with EtOAc, the combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane−EtOAc, 5:1) to afford Mosher ester **10a** as a colorless oil (2.8 mg, 88%): ^1H NMR (600 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.89 (s, 6H), 1.81−1.90 (m, 2H), 2.36−2.46 (m, 2H), 3.54 (s, 3H), 3.61−3.68 (m, 2H), 5.02−5.04 (m, 2H), 5.29−5.33 (m, 2H), 5.62−5.69 (m, 1H), 7.38−7.41 (m, 3H), 7.53−7.54 (m, 2H).

*(3R)-1-[(tert-Butyldimethylsilyl)oxyl]-3-[(tert-butyldiphenyl)oxyl]-hex-5-ene (**11**).* To a stirred solution of alcohol **10** (386 mg, 1.68 mmol) in anhydrous CH_2Cl_2 (6.0 mL) was added imidazole (348 mg, 5.12 mmol) followed by TBDPSCl (0.86 mL, 3.3 mmol) at rt. After

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stirring for 4 h, the reaction was quenched with water. The aqueous phase was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane−EtOAc, 30:1) to give silyl ether **11** (759 mg, 97%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.03 (d, J = 3.6 Hz, 6H), 0.83 (s, 9H), 1.68−1.72 (m, 2H), 2.14−2.23 (m, 2H), 3.57−3.67 (m, 2H), 3.91−3.94 (m, 1H), 4.88−4.96 (m, 2H), 5.69−5.73 (m, 1H), 7.35−7.42 (m, 6H), 7.67 (d, J = 6.0 Hz, 4H).

*(S)-5-[(tert-Butyldimethylsilyl)oxy]-3-[(tert-butyldiphenylsilyl)-oxy]pentanal (**12**).* To a solution of silyl ether **11** (351 mg, 0.750 mmol) in ^{t}BuOH−H_2O (3:1, 12.0 mL) were added *N*-methylmorpholine-*N*-oxide (NMO) (50% in water, 0.48 mL, 0.23 mmol) and microencapsulated OsO_4 (ca. 10%, 93.0 mg, 0.037 mmol). The resulting solution was stirred at rt for 33 h; then excess solid Na_2SO_3 was added. The mixture was diluted with EtOAc, and the layers were separated. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was dissolved in THF−H_2O (3:1, 12.0 mL), to which $NaIO_4$ (470 mg, 2.20 mmol) was added. The reaction mixture was stirred at rt for 2 h and diluted with H_2O. The whole solution was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane−EtOAc, 10:1) to obtain **12** (348 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (d, J = 5.2 Hz, 6H), 0.81 (s, 9H), 1.04 (s, 9H), 1.73−1.83 (m, 2H), 2.48 (ddd, J = 3.2, 6.0, 16 Hz, 1H), 2.58 (ddd, J = 2.4, 5.6, 16 Hz, 1H), 3.53−3.63 (m, 2H), 4.36−4.42 (m, 1H), 7.36−7.45 (m, 6H), 7.66 (d, J = 6.0 Hz, 4H), 9.67 (t, J = 2.4 Hz, 1H).

*(4R,6S)-8-[(tert-Butyldimethylsilyl)oxy]-6-[(tert-butyldiphenylsilyl)oxy]oct-1-en-4-ol (**13**).* To a solution of (+)-Ipc_2B(allyl) (1.0 M, 0.82 mL, 0.82 mmol) in anhydrous Et_2O (6.0 mL) was added dropwise aldehyde **12** (277 mg, 0.589 mmol) in anhydrous Et_2O (4.0 mL) at −78 °C under Ar. The reaction mixture was stirred for 4 h at −78 °C and quenched with 3N aqueous NaOH (0.70 mL) and 30 wt % aq H_2O_2 (0.35 mL). The resulting mixture was stirred overnight at rt. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product (304 mg) was used without further purification.

*(3S,5R)-1-[(tert-Butyldimethylsilyl)oxyl]-3-[(tert-butyldiphenyl)-oxyl]oct-7-ene-5-yl Acrylate (**14**).* To a solution of alcohol **13** (304 mg, 0.594 mmol) in anhydrous CH_2Cl_2 (4.0 mL) at 0 °C were added Et_3N (0.42 mL, 3.0 mmol) and acroylyl chloride (0.20 mL, 2.5 mmol). The reaction mixture was stirred at 0 °C for 2 h and diluted with CH_2Cl_2 and saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane−Et_2O, 10:1) to give ester **14** (246 mg, 74% in 2 steps) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ −0.04 (d, J = 4.2 Hz, 6H), 0.83 (s, 9H), 1.05 (s, 9H), 1.69−1.83 (m, 4H), 2.08−2.21 (m, 2H), 3.63 (ddt, J = 17.2, 6.8, 3.2 Hz, 2H), 3.93−3.97 (m, 1H), 4.91−4.97 (m, 2H), 5.06−5.10 (m, 1H), 5.54−5.63 (m, 1H), 5.73 (d, J = 10.8 Hz, 1H), 5.93 (dd, J = 10.8, 17.6 Hz, 1H), 6.23 (d, J = 17.2 Hz, 1H), 7.35−7.44 (m, 6H), 7.65−7.69 (m, 4H).

*(4R,6S)-8-[(tert-Butyldimethylsilyl)oxy]-6-[(tert-butyldiphenylsilyl)oxy]oct-1-en-4-yl Acrylate (**15**).* To a solution of **14** (99 mg, 0.18 mmol) in degassed CH_2Cl_2 (25 mL) at rt was added the second-generation Grubbs catalyst (13 mg, 0.017 mmol). The reaction mixture was refluxed for 3 h. The solvent was evaporated and the residue was purified by silica gel column chromatography (*n*-hexane−EtOAc, 10:1) to give **15** (93 mg, 96%) as a pale, yellow oil: $[\alpha]^{25}_D$ +47 (*c* 2.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ −0.03 (d, J = 2.0, 6H), 0.82 (s, 9H), 1.05 (s, 9H), 1.71−1.91 (m, 4H), 1.95−2.05 (m, 2H), 3.45−3.51 (m, 2H), 3.58−3.59 (m, 2H), 4.11−4.17 (m, 1H), 4.51−4.58 (m, 1H), 5.90−5.93 (m, 1H), 6.64−6.68 (m, 1H), 7.37−7.45 (m, 6H), 7.63−7.67 (m, 4H); ^{13}C NMR (600 MHz, $CDCl_3$) δ −5.45, −5.42, 18.2, 19.4, 25.9, 27.0, 29.1, 39.4, 41.2 59.4, 67.5, 75.2, 121.2, 127.6, 127.7, 129.72, 129.75, 133.94, 133.98, 135.8, 135.9, 144.9, 164.4; HRMS-FAB (*m*/*z*) [M + H]$^+$ calcd for $C_{31}H_{47}O_4Si_2$, 539.3013; found, 539.3002.

(3S,5R)-3-[(tert-Butyldiphenyl)oxyl]oct-7-ene-1-ol-5-yl Acrylate. To a solution of **15** (152 mg, 0.283 mmol) in 20:1 THF−H_2O (2.0 mL) was added $TsOH·H_2O$ (7.1 mg, 0.037 mmol). The resulting solution was stirred at rt for 21 h. Saturated $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane−EtOAc, 5:1) to give the title compound (118 mg, 99%) as a colorless oil: $[\alpha]^{25}_D$ +44 (*c* 0.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.07 (s, 1H), 1.76−1.81 (m, 2H), 1.91−2.44 (m, 4H), 3.66−3.73 (m, 2H) 4.18−4.24 (m, 1H), 4.48−4.55 (m, 1H), 4.37 (s, 1H), 5.92 (d, J = 9.6 Hz, 1H), 6.68−6.73 (m, 1H), 7.38−7.47 (m, 6H), 7.67 (d, J = 7.2 Hz, 4H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 19.3, 26.9, 29.2, 41.5, 50.2, 65.6, 74.3, 121.2, 127.9, 130.04, 130.08, 133.2, 133.3, 135.79, 135.83, 144.9, 163.9, 201.2; HRMS (*m*/*z*) [M + H]$^+$ calcd for $C_{25}H_{33}O_4Si$, 425.2148; found, 425.2136.

*(R)-3-[(tert-Butyldiphenylsilyl)oxy]-4-[(R)-6-oxo-3,6-dihydro-2H-pyran-2-yl]butanal (**16**).* A solution of (3*S*,5*R*)-3-[(*tert*-butyldiphenyl)oxyl]oct-7-ene-1-ol-5-yl acrylate (83 mg, 0.28 mmol) in anhydrous CH_2Cl_2 (4.0 mL) was added to 2-iodoxybenzoic acid (83 mg, 0.30 mmol) in anhydrous dimethyl sulfoxide (DMSO) (2.0 mL). The mixture was stirred at rt for 11 h and filtered through a pad of Celite. The organic filtrates were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane−EtOAc, 3:1) to give **16** (77 mg, 96%) as a colorless oil: $[\alpha]^{25}_D$ +46 (*c* 2.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.73−1.79 (m, 1H), 1.89−1.96 (m, 1H), 2.01−2.10 (m, 2H), 2.63−2.68 (m, 1H), 2.78−2.84 (m, 1H), 4.45−4.50 (m, 1H), 4.53−4.60 (m, 1H), 5.93−5.96 (m, 1H), 6.70−6.75 (m, 1H), 7.38−7.47 (m, 6H), 7.63−7.66 (m, 4H), 9.71 (s 1H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 19.2, 27.0, 29.3, 38.3, 41.2, 59.4, 68.2, 74.8, 121.2, 127.78, 127.81, 129.9, 133.4, 133.6, 135.9, 144.8, 164.1.

*(6R)-6-{(2S,E)-2-[(tert-Butyldiphenylsilyl)oxy]-4-hydroxy-8-phenyloct-7-en-1-yl}-5,6-dihydro-2H-pyran-2-one (**17**).* To a stirred suspension of Mg (turnings) (493 mg, 20.5 mmol) in anhydrous THF (2.0 mL) was added dropwise a solution of **22** (1.43 g, 6.79 mol) in anhydrous THF (4.0 mL) at rt and refluxed for 1 h. The resulting alkenyl Grignard reagent was added dropwise to **16** (51 mg, 0.12 mmol) dissolved in anhydrous THF (1.5 mL) at −40 °C, and the reaction mixture was stirred at 0 °C for 3 h and at rt for 1 h, then quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane−EtOAc, 4:1) to give **17** (28 mg, 42%) as a colorless oil. Diastereomeric mixture: ^{1}H NMR (600 MHz, $CDCl_3$) major δ 1.06 (s, 9H), 1.50−1.55 (m, 2H), 1.59−1.91 (m, 4H), 1.93−2.03 (m, 2H), 2.19−2.32 (m, 2H), 3.81−3.86 (m, 1H), 4.24−4.30 (m, 1H), 4.51−4.56 (m, 1H), 5.90−5.92 (m, 1H), 6.31−6.21 (m, 1H), 6.37 (t, J = 17.4 Hz, 1H), 6.67−6.70 (m, 1H), 7.19 (t, J = 7.2 Hz 1H), 7.28−7.33 (m, 4H), 7.37−7.47 (m, 6H), 7.65−7.68 (m, 4H): minor δ 1.06 (s, 9H), 1.50−1.55 (m, 2H), 1.59−1.91 (m, 4H), 1.93−2.03 (m, 2H), 2.19−2.32 (m, 2H), 3.81−3.86 (m, 1H), 4.24−4.30 (m, 1H), 4.38−4.42 (m, 1H), 5.87−5.89 (m, 1H), 6.31−6.21 (m, 1H), 6.37 (t, J = 17.4 Hz, 1H), 6.61−6.64 (m, 1H), 7.19 (t, J = 7.2 Hz 1H), 7.28−7.33 (m, 4H), 7.37−7.47 (m, 6H), 7.65−7.68 (m, 4H).

*(R)-6-{(R,E)-2-[(tert-Butyldiphenylsilyl)oxy]-4-oxo-8-phenyloct-7-en-1-yl}-5,6-dihydro-2H-pyran-2-one (**18**).* A solution of alcohol **17** (16 mg, 0.028 mmol) in anhydrous CH_2Cl_2 (4.0 mL) was added to IBX (30 mg, 0.107 mmol) in anhydrous DMSO (2.0 mL). The mixture was stirred at rt for 4 h and filtered through a pad of Celite. The combined organic filtrates were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane−EtOAc, 3:1) to give **18** (13 mg, 96%) as a colorless oil: $[\alpha]^{25}_D$ +44 (*c* 0.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.04 (s,

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1H), 1.69−1.73 (m, 1H), 1.83−1.88 (m, 1H), 1.97−2.07 (m, 2H), 2.36−2.39 (m, 2H), 2.45−2.50 (m, 1H), 2.58−2.64 (m, 1H), 2.67 (dd, J = 4.8, 16.8 Hz, 1H), 2.85 (dd, J = 7.2, 16.2 Hz, 1H), 4.41−4.53 (m, 1H), 4.59−4.64 (m, 1H), 5.91−5.93 (m, 1H), 6.01−6.14 (m, 1H), 6.34 (d, J = 15.6 Hz, 1H), 6.68−6.71 (m, 1H), 7.18−7.21 (m, 1H), 7.28−7.30 (m, 4H), 7.36−7.45 (m, 6H), 7.62−7.65 (m, 4H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 19.3, 26.7, 27.0, 41.0, 43.3, 49.2, 66.4, 74.5, 121.1, 126.0, 127.0, 127.77, 127.82, 128.4,128.9, 129.94, 129.97, 130.6, 133.49, 133.54, 135.8, 145.1, 164.1, 208.5; HRMS (m/z) [M + H]$^+$ calcd for $C_{35}H_{41}O_4Si$, 553.2774; found, 553.2739.

Cryptolaevilactone M (7). To a stirred solution of **18** (4.6 mg, 8.3 μmol) in THF (1.0 mL) was added TBAF (1.0 M in THF) (9 μL, 9 μmol) at 0 °C. The reaction mixture was stirred for 40 min at the same temperature. HOAc (0.4 μL, 7 μmol) was added, and upon stirring for 35 min, additional TBAF (1.0 M in THF) (27 μL, 27 μmol) and HOAc (1.5 μL, 26 μmol) were added. The reaction mixture was warmed to rt over 25 min, stirred for 19 h, and quenched with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by HPLC to give **7** as a colorless solid (1.6 mg, 61%), which cyclized gradually to form compound **19**. **7**: $[\alpha]^{25}_D$ +49 (c 0.03, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.79−1.83 (m, 1H), 2.00−2.05 (m, 1H), 2.41−2.43 (m, 2H), 2.48−2.52 (m, 2H), 2.65 (t, J = 7.2 Hz, 2H), 2.70−2.71 (m, 2H), 3.27 (d, J = 3.0 Hz, 1H), 4.30−4.33 (m, 1H), 4.69−4.73 (m, 1H), 6.02−6.04 (m, 1H), 6.15−6.20 (m, 1H), 6.41 (d, J = 15.6 Hz, 1H), 6.88−6.91 (m, 1H), 7.20−7.22 (m, 1H), 7.28−7.34 (m, 1H); HRMS (m/z) [M + H]$^+$ calcd for $C_{19}H_{23}O_4$, 315.1596; found, 315.1595.

Compound 19: $[\alpha]^{25}_D$ +32 (c 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.61−1.66 (m, 1H), 1.89−1.93 (m, 1H), 1.97−2.01 (m, 1H), 2.05−2.10 (m, 1H), 2.46−2.51 (m, 3H), 2.62 (t, J = 7.2 Hz, 2H), 2.69 (dd, J = 7.8, 15.6 Hz, 1H), 2.77 (dd, J = 5.4, 19.2 Hz, 1H), 2.91 (d, J = 18.6 Hz, 1H), 4.28−4.33 (m, 2H), 4.87−4.90 (m, 1H), 6.18 (dt, J = 6.6, 15.6 Hz, 1H), 6.40 (d, J = 16.2 Hz, 1H), 7.18−7.22 (m, 1H), 7.27−7.34 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 26.8, 29.5, 36.2, 36.3, 43.2, 48.4, 62.6, 65.9, 72.6, 126.0, 127.1, 128.5, 128.7, 130.8, 169.3, 206.8; HRMS (m/z) [M + H]$^+$ calcd for $C_{19}H_{23}O_4$, 315.1596; found, 315.1579.

(E)-4-Phenylbut-3-en-1-ol (21). To a solution of *trans*-styrylacetic acid (**20**, 201 mg, 1.24 mmol) in anhydrous THF (6.0 mL) was added dropwise lithium aluminum hydride (LAH, 1.9 mL, 1.9 mmol, 1 M solution in THF) at 0 °C. The reaction was stirred at 0 °C for 20 min and at rt for 60 min, then quenched with H_2O, followed by a 10% NaOH aqueous solution. The reaction mixture was filtered through Celite, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane−EtOAc, 5:1) to give **21** (160 mg, 87%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.48−2.51 (m, 2H), 3.77 (t, J = 6.0 Hz, 2H), 6.21 (dt, J = 7.2, 15.6 Hz, 1H), 6.51 (d, J = 15.6 Hz, 1H), 7.18−7.23 (m, 1H), 7.30 (t, J = 7.8 Hz, 2H), 7.36 (d, J = 7.2 Hz, 2H).

(E)-(4-Bromobut-1-en-1-yl)benzene (22). To a solution of CBr_4 (5.3 g, 16 mmol) in CH_2Cl_2 (25 mL) was added PPh_3 (4.2 g, 16 mmol) at rt for 10 min. **21** (789 mg, 5.33 mmol) in CH_2Cl_2 was added dropwise over 15 min and stirred for 1 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane−EtOAc, 3:1) to give **22** (930 mg, 83%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.76−2.80 (m, 2H), 3.48 (t, J = 7.2 Hz, 2H), 6.19 (dt, J = 7.2, 15.6 Hz, 1H), 6.49 (d, J = 16.2 Hz, 1H), 7.22−7.24 (m, 1H), 7.31 (t, J = 7.8 Hz, 2H), 7.37 (d, J = 7.8 Hz, 2H).

Calculation of ECD Spectra. Preliminary conformational analysis of each compound was performed by using CONFLEX8 with the MMFF94 force field. The conformers were further optimized in MeCN by the DFT method with the B3LYP functional and 6-31(d) basis set. The ECD spectrum was calculated by the TDDFT method with the CAM-B3LYP functional and TZVP basis set. The calculation was performed using the conformers within 2 kcal/mol predicted in MeCN. The solvent effect was introduced by the conductor-like polarizable continuum model (CPCM). The DFT optimization and TDDFT-ECD calculation were performed using Gaussian09 (Gaussian, Inc., Wallingford, CT, USA). The calculated spectrum was displayed using GaussView 5.0.920 with the peak half-width at half-height being 0.333 eV. The Boltzmann-averaged spectrum at 298.15 K was calculated using Excel 2016 (Microsoft Co., Redmond, WA, USA). The calculations were reoptimized according to the literature.[33]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.8b00732.

NMR spectra for **1**−**8**, experimental details for the synthesis of **7**, and comparison of ^{1}H NMR spectrum for synthesized and isolated **7** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +81-76-264-6305. E-mail: kngoto@p.kanazawa-u.ac.jp.

ORCID

Yohei Saito: 0000-0003-2313-8339
Shuichi Fukuyoshi: 0000-0002-9015-0920
Katsunori Miyake: 0000-0001-6199-8781
David J. Newman: 0000-0002-4959-2428
Barry R. O'Keefe: 0000-0003-0772-4856
Kuo-Hsiung Lee: 0000-0002-6562-0070
Kyoko Nakagawa-Goto: 0000-0002-1642-6538

Author Contributions

#Y.M. and M.N. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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