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Asteriscane-Type Sesquiterpenoids from the Soft Coral *Sinularia capillosa*

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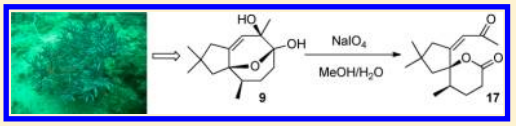
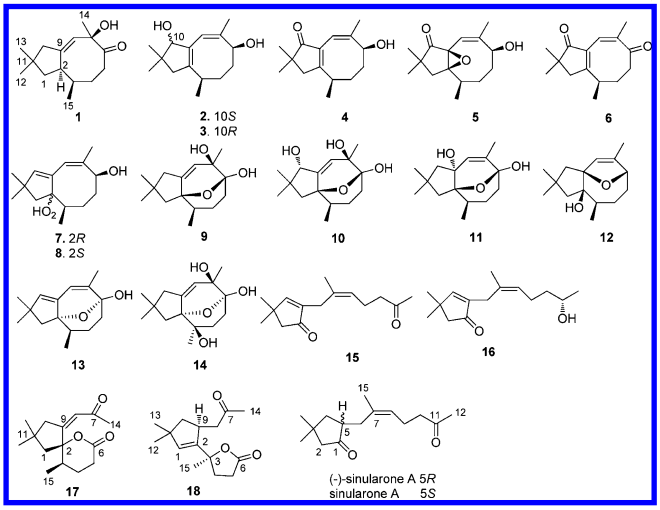
Supporting Information

ABSTRACT: Chemical examination of the soft coral *Sinularia capillosa* collected from the South China Sea resulted in the isolation of 14 new asteriscane-type sesquiterpenoids, namely, capillosananes A–N (**1**–**14**), four new *seco*-asteriscanes, capillosananes O–R (**15**–**18**), and (−)-sinularone A and sinularone A. Their structures were determined on the basis of extensive spectroscopic analyses, while the absolute configurations were determined by CD and ECD calculation, Mosher's method, and chemical conversion. This is the first report of asteriscane-type sesquiterpenoids from soft corals, and capillosananes Q (**17**) and R (**18**) represent new *seco*-asteriscane skeletons. Capillosanane A exhibited potent antifouling activity against *Balanus amphitrite*, with an IC_{50} value of 9.70 μM, while capillosananes B and I and (−)-sinularone A inhibited inflammation-related TNF-α in vitro.



Asteriscane-type sesquiterpenoids feature a bicyclo[6.3.0]-undecane skeleton and are rarely found in nature.[1−5] Asteriscanolide from the plant *Asteriscus aquaticus*[1] was the first asteriscane-type sesquiterpenoid, while an asteriscane from the aeolid nudibranch *Phyllodesmium magnum* is the only one isolated from marine organisms and was proposed to originate from a *Sinularia* sp. soft coral, a prey of this nudibranch.[5] The soft coral genus *Sinularia* is recognized as a rich source of terpenoids, of which cembranoids are commonly regarded as the typical type of secondary metabolites used for chemical taxonomy. Sesquiterpenoids often co-occur with cembranoids in *Sinularia* species, but the number of sesquiterpenoids from the *Sinularia* genus is much less in comparison with cembranoid metabolites. The structural patterns of sesquiterpenoids derived from *Sinularia* species consist of cadinane-type,[6] oppositane-type,[7,8] africane-type,[9−12] and others.[13−15] In order to examine the chemical diversity and the structural variation of soft coral species inhabiting different geographic locations, we collected the specimen *Sinularia capillosa* from the coral reef near Hainan Island. Chromatographic (HPLC) and ^{1}H NMR spectroscopic analyses revealed that the EtOAc extract of this specimen featured numerous terpenoids, differing from those reported in the literature.[16−19] This paper reports the structure elucidation of the new asteriscane-type sesquiterpenoids **1**–**18**. The antifouling and anti-TNF-α activities of selected compounds were evaluated.



RESULTS AND DISCUSSION

The EtOAc-soluble fraction of the soft coral *S. capillosa* was examined by ^{1}H NMR spectroscopy and HPLC, which indicated the presence of diverse terpenoid analogues. Repeated column chromatography including reversed-phase HPLC separation of the EtOAc fraction led to the isolation of 18 new asteriscane-based sesquiterpenoids, named capillosananes A–R (**1**–**18**).

Capillosanane A (**1**) had a molecular formula of $C_{15}H_{24}O_2$, as determined on the basis of the HRESIMS data, requiring four degrees of unsaturation. The IR absorptions suggested the presence of hydroxy (3488 cm^{-1}) and carbonyl (1700 cm^{-1}) functionalities. The APT spectrum displayed a total of 15 resonances involving four methyl, four methylene, three methine, and four quaternary carbons, of which a ketone and a vinyl group were characterized. Thus, a bicyclic nucleus is required from the molecular unsaturation. The COSY cross-

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peaks established an alkyl spin system from C-1 to C-5 and extended to H_3-15 (δ_H 0.85, d, J = 6.9 Hz), whereas the HMBC correlations observed from H_3-12 (δ_H 1.03, s) and H_3-13 (δ_H 0.73, s) to C-1 (δ_C 47.1), C-10 (δ_C 53.1), and C-11 (δ_C 36.9) in addition to the correlations from the geminal protons H_2-10 (δ_H 2.12, 1.75) to C-1, C-2 (δ_C 40.1), C-9 (δ_C 142.5), and C-8 (δ_C 128.8) revealed a dimethylcyclopentane ring. Further HMBC correlations from the olefinic proton H-8 (δ_H 5.42, s) to C-2, C-7 (δ_C 76.5) and C-6 (δ_C 216.6) and from H_2-4 (δ_H 1.89, m) and H_2-5 (δ_H 3.14, 1.96) to C-6 resulted in a cyclooctenone substructure, which was fused to the cyclopentane ring across C-2 and C-9. The positions C-3 and C-7 were methylated. A D_2O exchangeable proton at δ_H 5.57 (s) showed HMBC correlations to C-6, C-7, and C-8, indicating that C-7 is hydroxylated. Accordingly, the gross structure of **1** was determined as 7-hydroxyasterisca-8-en-6-one. The NOE correlations from H_3-15 to H-10b (δ_H 2.12) and H-1b (δ_H 1.61) in addition to the correlation between H-2 (δ_H 2.43) and H-1a (δ_H 1.29) indicated the opposite orientation of H-2 and H_3-15. Additional cross-peaks from H-5b (δ_H 3.16) to H_3-15 and OH-7 (δ_H 5.57) assigned OH-7 the same face as H_3-15 (Figure 1). The absolute configuration of **1** was determined using the modified Mosher's method.[20] First, reduction of **1** by $NaBH_4$ yielded **1a** (Figure 2). The NOE interaction between H-6 (δ_H 3.49, dd, J = 2.5, 10.5 Hz) and H_3-15 (δ_H 0.83, d, J = 6.8 Hz) in association with the absence of NOE interaction between H_3-14 (δ_H 1.36, s) and H-6 indicated H-6 of **1a** had the same orientation as that of H_3-15 and was on the opposite face compared to H_3-14. By a standard procedure, the (*R*)- and (*S*)-MPA (methoxyphenylacetic acid) esters of **1a** were synthesized. Analysis of the $\Delta\delta^{RS}$ ($\delta_R - \delta_S$) values (Figure 3) resulted in a 6*R* configuration. Thus, the remaining stereogenic centers in **1** were defined as 2*R*, 3*R*, and 7*R*.

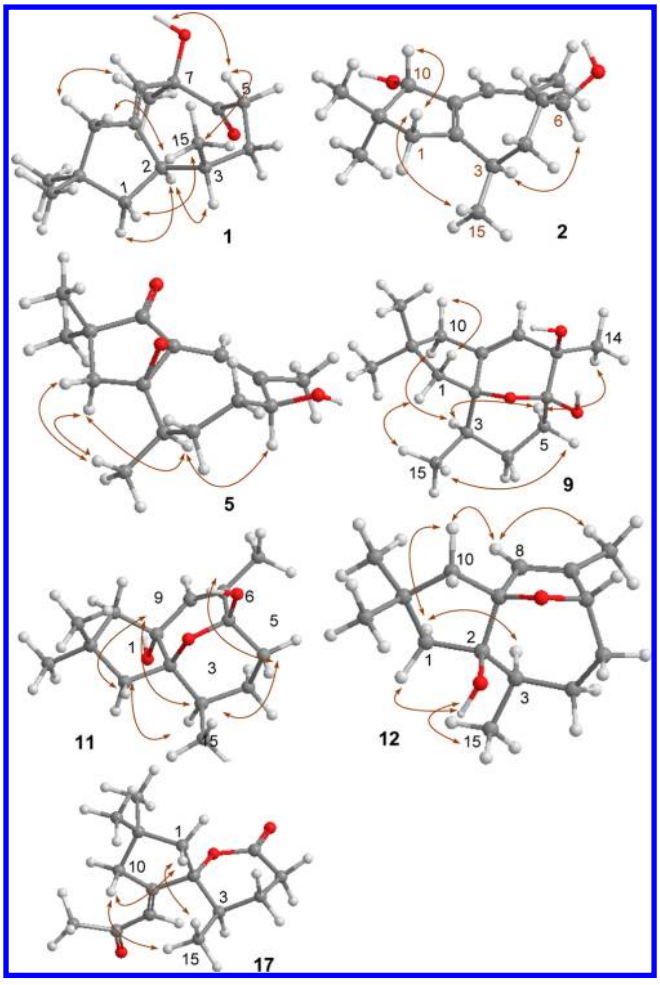

Figure 1. Key NOE correlations of **1**, **2**, **5**, **9**, **11**, **12**, and **17**.

Capillosanane B (**2**) exhibited a pseudomolecular ion peak at m/z 259.1666 $[M + Na]^+$ by HRESIMS, consistent with a molecular formula of $C_{15}H_{24}O_2$. Analyses of 1D and 2D NMR data revealed an asteriscane skeleton, structurally related to **1**. The APT spectrum displayed four olefinic carbons for two double bonds and two oxygenated methines. The HMBC correlations observed from H_3-12 (δ_H 1.00, s) and H_3-13 (δ_H 0.84, s) to C-10 (δ_C 85.4), H_3-14 (δ_H 1.67, s) to C-6 (δ_C 69.6), C-7 (δ_C 140.0), and C-8 (δ_C 120.9), and H_3-15 (δ_H 0.91, d, J = 6.9 Hz) to C-2 (δ_C 141.5) established conjugated double bonds at $\Delta^{2,9}$ and $\Delta^{7,8}$. The COSY correlations of the D_2O exchangeable protons at δ_H 4.63 and 5.42 with H-6 and H-10, respectively, showed C-6 and C-10 to be hydroxylated. The NOE relationships between H-3 (δ_H 2.21, m) and H-6 (δ_H 4.63, br d, J = 9.6 Hz) and from H-1b (δ_H 2.10, d, J = 15.4 Hz) to H_3-15 and H-10 (δ_H 3.98, d, J = 5.5 Hz) were evident from the spatial proximity of H-1b to H-10 and H_3-15, indicating the same orientation of H-10, OH-6, and H_3-15. On the basis of Mosher's method,[20] the absolute configuration of C-6 was assigned as *S* (Figure 3). Accordingly, the configurations of the remaining asymmetric centers were assigned as 3*R* and 10*S*.

The structure of capillosanane C (**3**) was determined as the C-10 epimer of **2** based on the close similarity of NMR spectroscopic data with the exception of an upfield shifted H-10 (δ_H 3.60) and a downfield shifted C-10 (δ_C 87.3) of **3** in comparison with those of **2**. The NOE correlations of H-1b (δ_H 2.31) to H_3-15 (δ_H 0.96) and OH-10 (δ_H 4.50) supported the structural assignment.

A comparison of the NMR data (Tables 1 and 3) in association with analyses of 2D NMR spectra established capillosanane D (**4**) to be a 10-ketone analogue of **2**. The similar NOE interactions and coupling constants of the two compounds indicated **4** had the same relative configuration as that of **2**. Adding $Rh_2(OCOCF_3)_4$ to a solution of **4** in $CHCl_3$ formed a metal complex as an auxiliary chromophore. The sign of the E band reflected the absolute configuration of the secondary alcohol by applying the bulkiness rule.[21,22] The positive E band sign at 350 nm observed in the CD spectrum (Figure 4) was in agreement with a 6*S* configuration. Transformation of **4** to **2** and **3** with $NaBH_4$ further supported the configurational assignment.

Capillosanane E (**5**) had a molecular formula of $C_{15}H_{22}O_3$, as deduced from the HRESIMS data, requiring five degrees of unsaturation. The ^1H and ^{13}C NMR resonances of **5** were closely similar to those of **4**, expect for the presence of two oxygenated carbons at δ_C 76.7 (C-2) and 67.1 (C-9) that replaced the olefinic carbons at C-2 and C-9 of **4**. These findings in addition to **5** possessing an extra oxygen atom compared to **4** assigned an epoxy group across C-2 and C-9. The olefin geometry was identified as *Z* on the basis of the NOE correlation between H-8 (δ_H 5.59, s) and H_3-14 (δ_H 1.69, s). The absolute configuration of C-6 in **5** was assigned as 6*S* by the modified Mosher's method (Figure 3). Thus, the NOE correlations from H-3 (δ_H 2.09, m) to H-6 (δ_H 4.34, dt, J = 12.0, 4.2, 3.6 Hz) assigned a 3*R* configuration. There are two possibilities for the epoxy orientation. The observation of NOE

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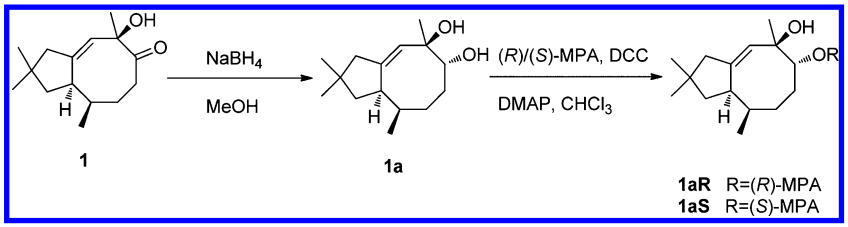

Figure 2. Chemical conversion of **1** to **1a** and the formation of MPA esters of **1a**.

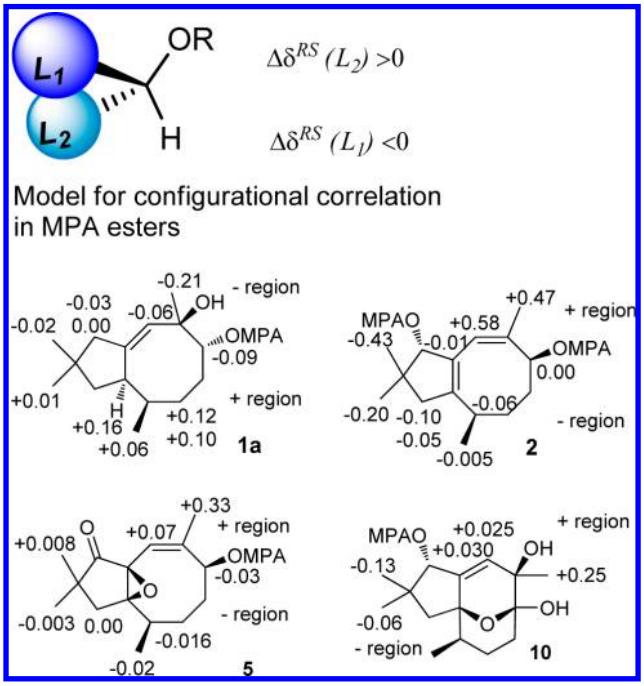

Figure 3. $\Delta\delta^{RS}$ ($\Delta(\delta_R - \delta_S)$) data for the MPA esters.

interactions between H-3 and H-1α (δ_H 1.90, d, J = 14.4 Hz), and between H_3-15 (δ_H 1.08, d, J = 6.0 Hz) and H-1β (δ_H 2.22, d, J = 14.4 Hz) (Figure 1), as well as the absence of NOE interaction between H_2-1 and H_2-4, indicated H-3 was spatially proximal to H-1α. These findings indicated the epoxy group to be β-oriented. Accordingly, the remaining stereogenic centers were determined as 2*R* and 9*S*.

Capillosanane F (**6**) was determined to be the 6-ketone analogue of **4** on the basis of 1D and 2D NMR data. The configuration of the C-3 stereogenic center was assumed to be the same as that of **4** based on biogenetic considerations.

The molecular formula of capillosanane G (**7**) was determined as $C_{15}H_{24}O_3$ on the basis of its HRESIMS and NMR data. Analyses of 1D and 2D NMR data led to the establishment of an asteriscane-type sesquiterpene, structurally related to **2**. The major distinction was attributed to the presence of two conjugated double bonds at $\Delta^{7,8}$ and $\Delta^{9,10}$ instead of $\Delta^{7,8}$ and $\Delta^{2,9}$, which were evident from the HMBC correlations from H_3-12/H_3-13 (δ_H 1.05, s) to C-10 (δ_C 140.8) and from H_3-14 (δ_H 1.60, s) to C-7 (δ_C 140.7) and C-8 (δ_C 120.8). Because an OH at C-6 was recognized by the COSY relationship between H-6 (δ_H 4.42, dd, J = 5.2, 11.5 Hz) and OH (δ_H 4.67) and the HMBC interaction between H_3-14 and C-6 (δ_C 68.8), the remaining O_2H unit was assigned as a

Table 1. ^{1}H NMR Data for Capillosananes A–H (1–8)[a]

no.	1	2	3	4	5	6	7	8
1	1.61, dd (12.8, 8.5)	2.10, d (15.4)	2.31, d (15.9)	2.54, d (18.2)	2.22, d (14.4)	2.71, d (19.6)	2.06, d (14.1)	1.65, br d (5.5)
	1.29, dd (12.8, 7.5)	1.89, d (15.4)	1.79, d (15.9)	2.35, d (18.2)	1.90, d (14.4)	2.57, d (19.6)	1.76, d (14.1)	
2	2.43, dd (8.5, 7.5)							
3	1.58, m	2.21, m	2.19, m	2.59, m	2.09, m	2.75, m	1.65, m	1.96, m
4	1.89, m	1.70, m	1.74, m	1.82, m	1.20, m	2.21, m	1.91, m	1.57, m
		1.34, m	1.33, m	1.51, m	1.03, m	1.89, m	0.93, m	1.29, m
5	3.14, m	1.66, m	1.65, m	1.73, m	1.59, tt (12.4, 5.2)	2.65, m	1.57, m	2.31, m
	1.96, dd (11.6, 5.6)	1.45, m	1.44, m	1.48, m	1.28, m	2.11, ddd (11.3, 4.3, 2.3)	1.33, br t (12.6)	1.46, m
6		4.63, br d (9.6)	4.56, br d (9.6)	4.37, dt (10.0, 4.2, 3.6)	4.34, dt (12.0, 4.2, 3.6)		4.42, dd (11.5, 5.2)	3.92, dd (10.5, 6.1)
8	5.42, s	5.63, s	5.80, s	5.80, s	5.59, s	6.68, s	5.80, s	5.81, s
10	2.12, d (13.3)	3.98, d (5.5)	3.60, d (6.7)				5.23, d (1.3)	5.36, d (1.7)
	1.75, d (13.3)							
12	1.03, s	1.00, s	0.94, s	1.00, s	1.04, s	1.08, s	1.05, s	1.03, s
13	0.73, s	0.84, s	0.91, s	0.98, s	0.98, s	1.09, s	1.05, s	1.11, s
14	1.20, s	1.67, s	1.65, s	1.72, s	1.69, s	1.90, s	1.60, s	1.77, s
15	0.85, d (6.9)	0.91, d (6.9)	0.96, d (6.8)	1.12, d (6.9)	1.08, d (6.9)	1.11, d (6.9)	0.95, d (6.9)	0.77, s
2-OOH							10.71, s	10.58, s
6-OH		4.63, br s	4.63, d (4.2)	4.80, d (4.3)	4.91, d (3.6)	6.27, s	4.67, s	4.61, d (6.1)
7-OH	5.57, s							
10-OH		4.52, d (5.8)	4.50, d (6.7)					

[a]Recorded in DMSO-d_6, at 500 MHz.

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Table 2. ^{1}H NMR Data for Capillosananes I–N (9–14)[a]

no.	9	10	11	12	13	14
1	1.72, d (13.6)	1.76, d (13.6)	1.70, d (14.0)	1.71, d (13.3)	1.83, d (14.1)	1.99, d (14.0)
	1.38, d (13.6)	1.35, d (13.6)	1.50, d (14.0)	1.24, d (13.3)	1.73, d (14.1)	1.22, d (14.0)
3	1.50, m	1.78, m	1.93, m	1.48, m	1.61, m	
4	1.70, m	1.79, m	1.97, m	1.61, m	1.58, br d (13.6)	1.68, m
	1.31, br d (11.2)	1.28, dd (12.3, 4.0)	1.16, dt (13.4, 4.0, 3.5)	1.21, m	1.32, qd (13.6, 3.6)	1.39, m
5	1.66, ddd (14.0, 12.8, 4.5)	1.65, ddd (14.0, 13.5, 4.5)	1.50, ddd (14.0, 12.5, 3.5)	1.82, m	1.58, dd (12.1, 3.6)	1.71, m
	1.49, m	1.50, dt (12.9, 4.1, 2.5)	1.31, ddd (13.3, 4.2, 2.9)	1.47, m	1.46, dt (3.6, 12.9)	1.69, m
6				4.45, d (8.8)		
8	5.46, d (1.5)	5.65, s	5.54, s	5.38, s	6.14, br s	5.51, d (1.7)
10	2.13, dd (14.2, 1.7)	3.61, d (2.0)	1.95, d (13.3)	2.13, d (13.2)	5.25, s	2.39, dd (12.5, 1.6)
	1.88, d (14.2)		1.68, d (13.3)	1.39, d (13.2)		1.72, d (12.5)
12	1.05, s	0.88, s	1.04, s	1.12, s	1.10, s	1.05, s
13	0.99, s	0.96, s	1.06, s	1.08, s	1.08, s	0.95, s
14	1.05, s	1.11, s	1.52, d (1.0)	1.72, s	1.63, s	1.10, s
15	1.03, d (6.9)	0.98, d (6.9)	0.93, d (6.9)	0.83, d (6.9)	0.80, d (6.5)	1.19, s
2-OH				3.92, s		
3-OH						4.44, s
6-OH	5.07, s	5.10, s	5.96, s		6.27, s	5.08, s
7-OH	4.88, s	4.88, s				4.85, s
9-OH			4.54, s			
10-OH		4.84, d (2.5)				

[a]Recorded in DMSO-d_6, at 500 MHz.

hydroperoxy group, which was characterized by the presence of a hydroperoxy proton (OOH) at δ_H 10.71 (s).[23] This group was located at C-2 (δ_C 100.7) on the basis of the HMBC correlations from the OOH proton and H-10 (δ_H 5.23, d, J = 1.3 Hz) to C-2. The NOE correlation between H-3 and H-6 indicated both protons are oriented on the same face, while the NOE relationship between H-3 (δ_H 1.65, m) and H-1a (δ_H 1.76, d, J = 14.1 Hz) suggested that the hydroperoxy group is oriented opposite H-3.

The gross structure of capillosanane H (**8**) was determined to be the same as that of **7** on the basis of HRESIMS data and 1D and 2D NMR data analyses. The NOE correlation between H-3 (δ_H 1.96, m) and H-6 (δ_H 3.92, dd, J = 11. 5, 6.1 Hz) in the NOESY spectrum indicated their spatial proximity. However, the presence of an NOE interaction from H_3-15 to H_2-1 and the absence of an interaction between H-3 and the protons at C-1 were indicative of a C-2 epimer. The absolute configuration at C-2 of **8** was established by Cotton effects in the CD spectrum. On the basis of the Beecham rule for allylic oxygen-containing dienes,[24,25] the positive sign at 220 nm in **8** follows from the right-handed helix with the allylic oxygen and the first double bond of diene, indicating a 2*S* configuration. Accordingly, the negative sign at 220 nm in **7** reflected a 2*R* configuration. These assignments were confirmed by the calculated ECD data of **8** at the B3LYP-SCRF/6-311++G(d,2p) level (Figure 5).

Capillosanane I (**9**) had a molecular formula of $C_{15}H_{24}O_3$, as determined from the HRESIMS and NMR data, requiring four degrees of unsaturation. The ^{1}H and ^{13}C NMR data were closely related to those of **1**, indicating an asteriscane-type analogue. Differences included an oxygenated quaternary carbon at δ_C 84.8 (C-2) of **9** in place of a methine in **1**, whereas C-6 of **9** presented as a hemiacetal carbon (δ_C 98.2) based on a hydroxy proton at δ_H 5.07 (s) correlated to C-7 (δ_C 68.2), C-6, and C-5 (δ_C 26.6) in the HMBC spectrum. On the basis of the molecular formula, the remaining site of unsaturation was attributed to an ether bridge across C-2 and C-6. The NOE interaction between H-3 (δ_H 1.50, m) and H-10a (δ_H 2.13, dd, J = 1.7, 14.2 Hz) (Figure 1) indicated that the oxygen bridge was oriented on the same face as H_3-15. Additional NOE interactions between H_3-14 (δ_H 1.05, s)/H-5a (δ_H 1.50) and H_3-15 (δ_H 1.03, d, J = 6.9 Hz)/H-5b (δ_H 1.66) clarified the orientation of H_3-14 as opposite of H_3-15. Upon addition of dimolybdenum tetraacteate [$Mo_2(OAc)_4$] to a solution of **9** in DMSO, a metal complex was generated. The sign of the induced CD bands at 310, 350, and 400 nm reflected the O–C–C–O torsion angle on the basis of the in situ dimolybdenum CD method.[26,27] The negative CD effects observed at 300 and 380 nm (Figure 6) permitted assignment of the 6*S* and 7*R* configurations. Accordingly, the configurations of remaining asymmetric centers of **9** were assigned as 2*R*, 3*R*, 6*S*, and 7*R*.

Interpretation of 1D and 2D NMR data disclosed the structure of capillosanane J (**10**) as a 10-hydroxylated analogue of **9**. The closely similar NOE interactions confirmed that **10** shares the same relative configuration as that of **9**, while the NOE correlation between H-3 (δ_H 1.78, m) and 10-OH (δ_H 4.84, d, J = 2.5 Hz) revealed H-10 to be oriented on the same face as H_3-15. The absolute configuration of **10** was determined by the modified Mosher's method.[20] Analysis of the $\Delta\delta^{RS}$ ($\delta_R - \delta_S$) values (Figure 3) resulted in a 10*S* assignment. Thus, the other stereogenic centers in **10** were assigned as 2*R*, 3*R*, 6*S*, and 7*R*.

Capillosanane K (**11**) and **9** possessed the same molecular formula, while the ^{1}H NMR and APT data of **11** were mostly similar to those of **9**. An obvious distinction was recognized for the double bond in **11** residing at C-7/C-8 instead of C-8/C-9, whereas C-9 (δ_C 79.6) of **11** was hydroxylated. These assignments were confirmed through HMBC correlations of the olefinic methyl protons H_3-14 (δ_H 1.52, d, J = 1.0 Hz) to C-6 (δ_C 97.0), C-7 (δ_C 132.1), and C-8 (δ_C 132.0), in addition to the correlations of OH-9 (δ_{OH} 4.54, s) to C-2 (δ_C 91.3), C-8, C-9, and C-10 (δ_C 57.9). The NOE correlations indicated the relative configurations of the stereogenic centers at C-2, C-3,

Table 3. ^{13}C NMR Data for Capillosananes A–N (1–14)[a]

no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	47.1, CH_2	49.2, CH_2	49.7, CH_2	46.4, CH_2	42.6, CH_2	43.3, CH_2	48.5, CH_2	43.0, CH_2	49.4, CH_2	48.6, CH_2	52.7, CH_2	45.9, CH_2	52.4, CH_2	46.8, CH_2
2	40.1, CH	141.5, C	144.7, C	175.0, C	76.7, C	180.5, C	100.7, C	99.7, C	84.8, C	84.7, C	91.3, C	89.8, C	91.2, C	87.0, C
3	36.9, CH	37.3, CH	37.3, CH	38.6, CH	35.8, CH	35.0, CH	43.9, CH	32.3, CH	31.0, CH	33.3, CH	28.4, CH	39.2, CH	38.8, CH	70.6, C
4	33.8, CH_2	31.3, CH_2	31.0, CH_2	30.8, CH_2	26.0, CH_2	39.9, CH_2	27.2, CH_2	31.3, CH_2	25.9, CH_2	25.6, CH_2	26.7, CH_2	29.9, CH_2	29.8, CH_2	34.0, CH_2
5	35.3, CH_2	33.9, CH_2	33.9, CH_2	32.9, CH_2	34.8, CH_2	38.7, CH_2	36.0, CH_2	32.7, CH_2	26.6, CH_2	26.8, CH_2	28.3, CH_2	30.8, CH_2	33.6, CH_2	31.3, CH_2
6	216.6, C	69.6, CH	69.4, CH	69.5, CH	68.6, CH	205.6, C	68.8, CH	72.8, CH	98.2, C	98.2, C	97.0, C	82.7, CH	98.8, C	98.0, C
7	76.5, C	140.0, C	139.3, C	143.4, C	146.8, C	138.8, C	140.7, C	141.2, C	68.2, C	68.4, C	132.1, C	143.4, C	138.8, C	68.5, C
8	128.8, CH	120.9, CH	120.8, CH	115.7, CH	112.5, CH	129.0, CH	120.8, CH	120.2, CH	125.1, CH	128.6, CH	132.0, CH	124.6, CH	121.3, CH	126.8, CH
9	141.5, C	133.8, C	133.1, C	131.3, C	67.1, C	135.0, C	140.3, C	140.3, C	145.6, C	147.1, C	79.6, C	102.5, C	136.4, C	145.7, C
10	53.1, CH_2	85.4, CH	87.3, CH	212.7, C	214.9, C	210.7, C	140.8, CH	141.7, CH	44.6, CH_2	81.4, CH	57.9, CH_2	49.9, CH_2	134.5, CH	48.0, CH_2
11	36.9, C	41.2, C	39.8, C	42.5, C	42.0, C	42.7, C	41.5, C	42.4, C	35.4, C	40.8, C	35.9, C	35.5, C	43.6, C	36.4, C
12	28.8, CH_3	27.5, CH_3	28.6, CH_3	25.7, CH_3	27.8, CH_3	25.9, CH_3	30.9, CH_3	29.7, CH_3	31.3, CH_3	29.3, CH_3	33.3, CH_3	33.3, CH_3	28.1, CH_3	30.1, CH_3
13	27.3, CH_3	23.2, CH_3	23.0, CH_3	25.1, CH_3	26.5, CH_3	24.6, CH_3	29.1, CH_3	28.8, CH_3	31.3, CH_3	24.3, CH_3	33.4, CH_3	33.1, CH_3	33.4, CH_3	29.8, CH_3
14	26.2, CH_3	18.2, CH_3	18.5, CH_3	18.5, CH_3	17.4, CH_3	20.3, CH_3	16.7, CH_3	23.4, CH_3	23.8, CH_3	23.7, CH_3	17.5, CH_3	12.6, CH_3	18.5, CH_3	24.0, CH_3
15	14.8, CH_3	23.2, CH_3	23.0, CH_3	22.7, CH_3	20.1, CH_3	17.3, CH_3	19.9, CH_3	17.1, CH_3	12.7, CH_3	12.7, CH_3	16.0, CH_3	18.8, CH_3	18.0, CH_3	22.0, CH_3

[a]Recorded in DMSO-d_6, at 125 MHz.

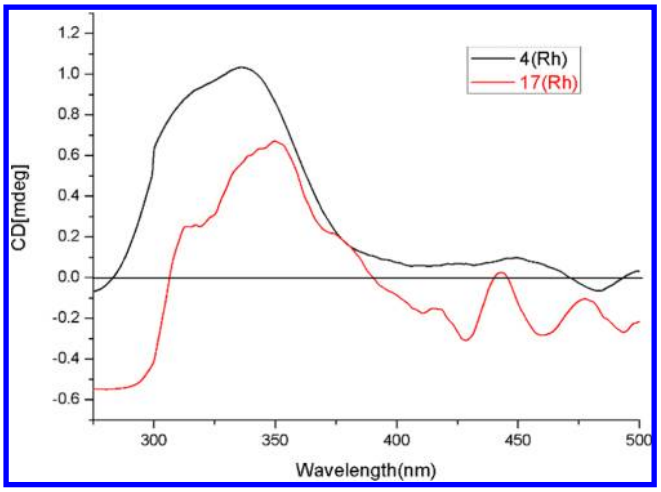

Figure 4. CD spectra for $Rh_2(OCOCF_3)_4$ complexes of **4** and **16**.

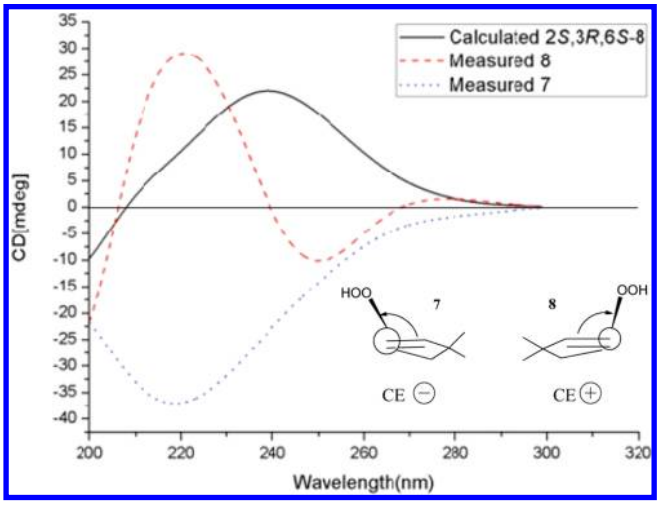

Figure 5. CD curves of **7** and **8** and the calculated CD spectrum of the 2*S*, 3*R*, 6*S* isomer of **8**.

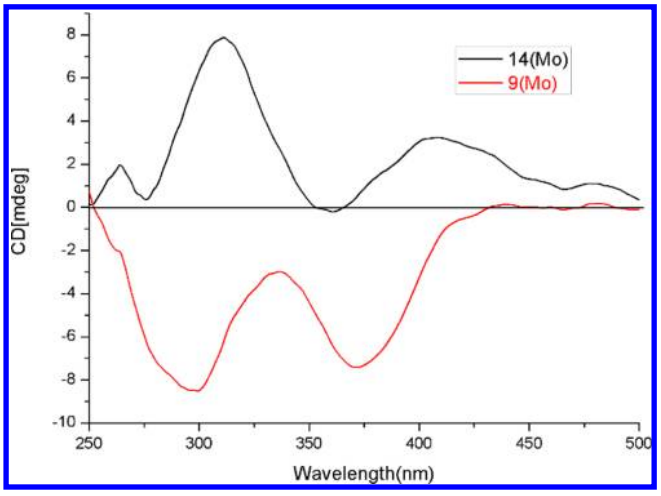

Figure 6. ICD curves of **9** and **14** induced by $Mo_2(OAc)_4$ in DMSO-d_6.

and C-6 to be the same as those of **9** (Figure 1). Additional NOE correlations from 9-OH to H-3 (δ_H 1.93, m) and H-10α (δ_H 1.68, d, J = 13.3 Hz) assigned 9-OH to the same face as H-3.

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Capillosanane L (**12**) had a molecular formula of $C_{15}H_{24}O_2$, as determined through HRESIMS and NMR data. Analysis of the ^{1}H NMR and ^{13}C NMR data disclosed **12** to be an asteriscane-type sesquiterpenoid, structurally related to **11**. The HMBC correlations from H_3-14 (δ_H 1.72, s) to C-6 (δ_C 82.7), C-7 (δ_C 143.4), and C-8 (δ_C 124.6) ascertained a double bond at $\Delta^{7,8}$, whereas C-6 was oxygenated. In addition the quaternary carbons C-2 (δ_C 89.8) and C-9 (δ_C 102.5) were distinguished through HMBC correlations from H_3-15 (δ_H 0.83, d, J = 6.9 Hz) to C-2. An additional HMBC correlation from H-6 (δ_H 4.45, d, J = 8.8 Hz) to C-9 confirmed the formation of an ether bridge across C-6 and C-9. Thus, a D_2O exchangeable proton at δ_{OH} 3.92 (s) was derived from a hydroxy group at C-2. The NOE correlations between H-8 (δ_H 5.38, s)/H-10a (δ_H 2.14), H-10b/H-1b (δ_H 1.24, d, J = 13.3 Hz), H-10b/OH-2, and H-1a (δ_H 1.71, d, J = 13.3 Hz)/H-3 (δ_H 1.48, m) located the bridging oxygen on the same face as that of OH-2.

The molecular formula of capillosanane M (**13**) was determined as $C_{15}H_{22}O_2$ according to the HRESIMS and NMR data. Interpretation of the 1D and 2D NMR data revealed the gross structure of **13** to be a $\Delta^{7,8}$, $\Delta^{9,10}$ analogue of **9**. The NOE observed from H_3-15 to H_3-12 (δ_H 1.10, s) and H-1b (δ_H 1.83, d, J = 14.1 Hz) and between H-1a (δ_H 1.74, d, J = 14.1 Hz) and H-3 (δ_H 1.61, m) established that the ether oxygen was oriented on the same face as H-3. In order to determine the absolute configuration of **13**, compound **9** was converted to **9a** and **9b** in an acidic solution (Figure 7). The

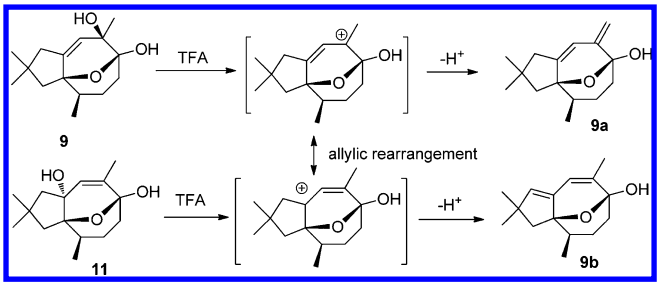

Figure 7. Acidic transformation of **9** and **11** to **9a** and **9b**.

absolute configurations of the stereogenic centers in **9b** were the same as those of **9**. The opposite CD effects of **13** and **9b** (Figure 8) led to the assignment of the configuration of **13** as 2*S*, 3*R*, and 6*R*.

Analyses of 1D and 2D NMR data and comparison of the NMR data revealed capillosanane N (**14**) to be a 3-hydroxylated analogue of **9**, which was supported by the methyl singlet H_3-15 (δ_H 1.19, s) and an OH proton (δ_{OH} 4.44, s) correlated to C-3 (δ_C 70.6) and to C-2 (δ_C 87.0) and C-4 (δ_C 34.0). The ROESY spectrum showed NOE correlations from OH-3 to H-10β (δ_H 2.39, dd, J = 12.5, 1.6 Hz) and H-1β (δ_H 1.99, d, J = 14.0 Hz), enabling assignment of the same orientation of the ether oxygen as for that of **13**, whereas OH-3 was β-oriented. Based on the in situ dimolybdenum CD method, the positive Cotton effects around 310 and 400 nm (Figure 6) were in agreement with 6*R* and 7*R* configurations. Accordingly, the remaining asymmetric centers were assigned the 2*R* and 3*R* configurations.

Capillosanane O (**15**) was determined as a $\Delta^{9,10}$ analogue of (−)-sinularone A on the basis of the similar NMR data, except for the presence of two additional olefinic carbons at δ_C 168.3 (C-10, CH) and 140.2 (C-9, C) as well as the HMBC

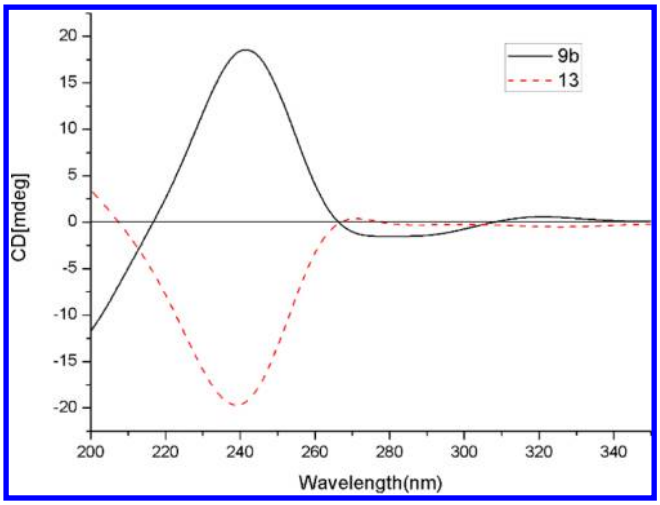

Figure 8. CD curves of **9b** and **13**.

correlations of H-10 (δ_H 7.10, s) to C-1, C-2, C-11, C-12, and C-13.

Comparison of the NMR data between capillosanane P (**16**) and **15** and analyses of the 2D NMR data indicated the structure of **16** to be a 3-hydroxylated analogue of **15**, as evident by the presence of a hydroxymethine (δ_H 3.56, m; δ_C 65.8) replacing the ketone carbon at C-3 of **15**, in addition to the COSY relationship between H-3 and H_3-15 (δ_H 1.03, d, J = 6.0 Hz). On the basis of the bulkiness rule, the $Rh_2(CF_3COO)_4$ complex of **16** presenting a positive CD effect at 350 nm was in agreement with a 3*S* configuration (Figure 4).

Capillosanane Q (**17**) had a molecular formula of $C_{15}H_{22}O_3$, as determined by HRESIMS data, requiring five degrees of unsaturation. The APT spectrum displayed four methyl, four methylene, two methine, and five quaternary carbons, including the resonances for two olefinic carbons, a ketone, and a lactone carbonyl. Thus, the structure of **17** should be a bicyclic nucleus. A dimethylcyclopentane ring was established on the basis of the HMBC interactions from the methyl singlets at δ_H 1.09 (s, H_3-12) and 1.01 (s, H_3-13) to C-10 (δ_C 51.3), C-1 (δ_C 47.8), and C-11 (δ_C 36.7) in addition to the methylene protons H_2-1 (δ_H 1.97, 1.59) and H_2-10 (δ_H 2.22, 2.18) to C-11, C-2 (δ_C 92.7) and C-9 (δ_C 159.5). An olefinic proton at δ_H 6.41 (1H, s, H-8) correlating to C-2 and C-10, as well as a ketone (δ_C 198.4, C-7) and a methyl carbon C-14, and correlations from H_3-14 (δ_H 2.17, s) to C-7 and C-8 (δ_C 125.8) in the HMBC spectrum supported an ylidenepropan-2-one unit fused to C-9. Additional HMBC and COSY correlations established a spirocyclic 3-methyl-δ-lactone linked to C-2, which was evidenced by the HMBC interactions from H_2-1 to C-3 and from H-3 (δ_H 2.84, m) to C-2 and C-1 in association with the molecular unsaturation. The NOE interaction between H_2-10 and H-8 was indicative of an 8*Z* geometry, while the NOE correlations from H_3-15 (δ_H 0.85, d, J = 6.9 Hz) to H-1a (δ_H 1.97) and H-10a (δ_H 2.18) clarified C-1 to be oriented on the same face as H_3-15. The absolute configuration of C-2 was determined as *R* according to the chemical conversion of **9** to **17** by $NaIO_4$ oxidation (Figure 9). This assignment was also supported by the computed ECD data of the 2*R* cognate at the B3LYP/aug-cc-pVDZ+6-31+G(d) level using a TD-DFT/B3LYP calculation, which showed a similar CD curve as compared to the measured CD spectrum (Figure 10).

Capillosanane R (**18**) had the same molecular formula as that of **17** based on HRESIMS data. The ^{1}H and ^{13}C NMR features

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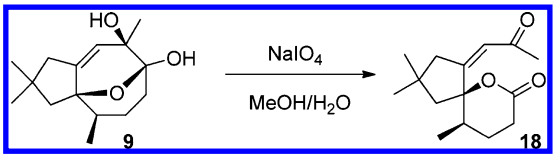

Figure 9. Transformation from **9** to **17**.

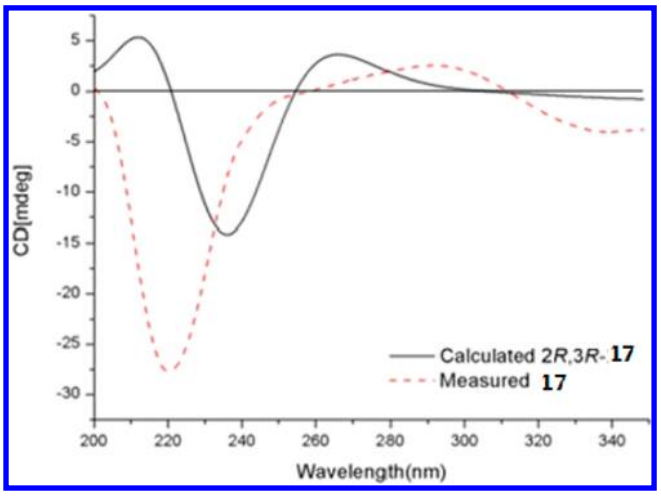

Figure 10. CD and computed ECD spectra of **17**.

were very similar to those of **17**, implying **18** to be structurally related to **17**. However, 2D NMR data distingushed different structural patterns. The HMBC correlations established a dimethyl cyclopentene. The olefinic doublet H-1 (δ_H 5.56, d, J = 1.5 Hz) was attributed to a long-range coupling with H-9 (δ_H 3.27, m), indicating C-2 to be substituted. COSY correlations gave rise to a segment from H_2-8 to H_2-10, while H-9, H_2-8, and H_3-14 (δ_H 2.10, s) correlated to a ketone carbon at δ_C 208.0 (C-7) in the HMBC spectrum, revealing a propanone unit linked to C-9. A γ-methyl-γ-lactone ring was assembled based on the COSY coupling between H_2-4 and H_2-5 and the HMBC correlations from a carbonyl carbon at δ_C 176.6 and a oxygenated sp^3 quaternary carbon at δ_C 85.7 (C-3) to H_2-4 and H_2-5 in addition to the correlation between H_3-15 (δ_H 1.43, s) and C-3. The linkage of the γ-lactone to the cyclopentene ring through a C-2/C-3 bond was deduced by the HMBC interaction from H_3-15 to C-2 (δ_C 144.5). The presence of an NOE interaction between H-9 and H_3-15 and the absence of an interaction between H_3-15 and H_2-8 supported the same orientation for H-9 and H_3-15. The measured CD curve of **18** was in accordance with that calculated for the 3*S*,9*S*-cognate at the TD-DFT/B3LYP-6-31+G(d) level using the B3LYP/aug-cc-pVDZ method and opposite of that calculated for the 3*R*,9*R*-cognate (Figure 11).

In addition, (−)-sinularone A and sinularone A[27] were separated on a chiral-phase column by semipreparative HPLC. The structure of (−)-sinularone A was identified on the basis of the identical NMR data compared to those of sinularone A, except for the specific rotation [$[\alpha]^{15}_D$ −23.4 (c 0.2, MeOH)] and CD effects (see SI) opposite those of sinularone A [$[\alpha]^{15}_D$ +7.3 (c 0.27, MeOH)].[27] Because C-5 of sinularone A has the *S* configuration, the same stereogenic center in (−)-sinularone A has the 5*R* configuration.

During the separation and storage of the new compounds, degradation and/or rearrangement of some of the compounds occurred. Capillosanane I (**9**) was partially converted to **9a** and

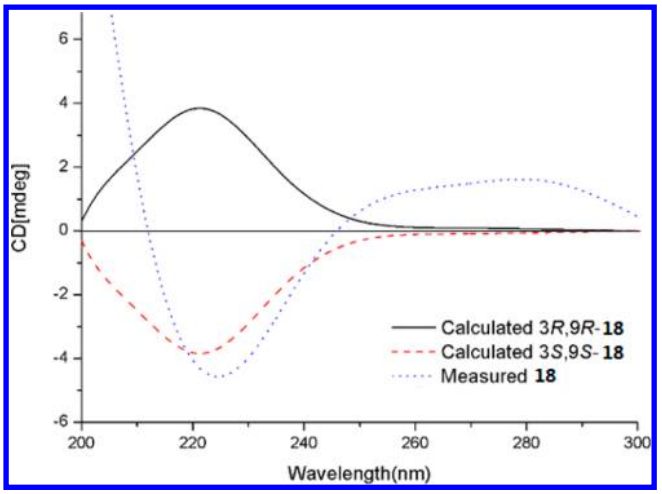

Figure 11. CD spectrum of **18** and calculated CD spectra of 3*R*,9*R* and 3*S*,9*S* isomers.

9b during storage in $CDCl_3$ solution for two weeks (Figure 7). HRESIMS and 2D NMR data established the structures of **9a** and **9b**, which are the dehydrated analogues of **9**. Adding a trace of TFA to a solution of **9** rapidly induced the conversion. The absolute configuration of C-6 in **9b** was determined via the CD data of the in situ formed [$Rh_2(OCOCF_3)_4$] complex, where the negative E band (363 nm) sign in the CD spectrum determined a 6*S* configuration (see SI). The remaining asymmetric centers were determined as 2*R* and 3*R*, accordingly. Treatment of **11** with a trace of TFA also produced **9a** and **9b** (Figure 7). Thus the absolute configuration of **11** was determined to be 2*R*, 3*R*, 6*S*, and 9*R*. Capillosanane G (**7**) was partially converted to derivative **7a** during HPLC separation using MeCN/H_2O (Figure 12). Compound **7a**

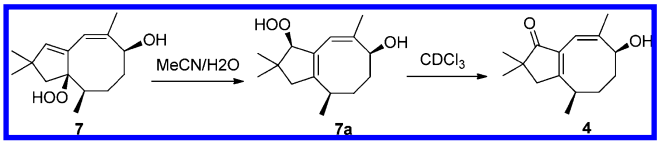

Figure 12. Autotransformation of **7** to **7a** and **4**.

had the same molecular formula as that of **7** as determined by HRESIMS data, while the ^{1}H NMR resonances in **7a** were mostly similar to those of **7** with the exception of H-10 in **7a** being shifted upfield to δ_H 3.96 (s). This finding suggested **7a** to be a 10-hydroperoxy-$\Delta^{2(9)}$-analogue of **7**. The pathway is depicted as an allylic rearrangement to give the isomeric hydroperoxide.[28,29] Further conversion of **7a** to **4** during ^{13}C NMR measurement in $CDCl_3$ confirmed the structural assignment (Figure 12).

All compounds were inactive against human tumor cell lines HCT-8, HePG2, BGC-823, A549, and SKOV3 with IC_{50} values of >10 μ/mL. Compounds **2**, **9**, and (−)-sinularone A, representing different structural patterns, were selected for a bioassay to inhibit inflammation-related TNF-α. They showed weak activity with inhibitory rates of 16%, 21%, and 23% at 10 μM, respectively. Nevertheless, compound **1** showed potent activity for antifouling against *Balanus amphitrite*, with an IC_{50} value of 9.7 μM, whereas the IC_{50} values of **9** and (−)-sinularone A were 54 and 74 μM. In addition, sinularone A was previously reported to potently inhibit *B. amphitrite* with the EC_{50} of 13.9 μg/mL,[27] indicating the configuration at C-9

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plays a key role in the inhibitory activity. These results suggest that asteriscane-based sesquiterpenoids in *S. capillosa* play a chemoecological role such as antifouling without toxicity to higher organisms.

The soft coral *S. capillosa* has been reported to contain various terpenoids with unique skeletons. Furanosesquiterpenes are a group of typical sesquiterpenes isolated from this specimen collected from an Australian coral reef.[30] The unprecedented sesquiterpenoid capillosanol,[16] the furanosesquiterpenoid capillofuranocarboxylate, the furanobenzosesquiterpenoids capillobenzopyranol and capillobenzofuranol, and other sesquiterpenoids were isolated from the same species inhabiting Dongsha Atoll.[18] However, the same species from Sanya Bay of Hainan Island produced cembranoids.[19] The present work dramatically enriches the numbers of the asteriscane-type family, while it represents the first isolation of asteriscane-based sesquiterpenoids from soft corals. These findings support the depiction that an asteriscane-type sesquiterpenoid from the aeolid nudibranch *Phyllodesmium magnum* originates in the *Sinularia* soft coral, which is the prey for this organism. The *seco*-derivatives (**15**–**18**) are derived from asteriscane-type sesquiterpenoids through oxidation, while compounds **17** and **18** present an unusual carbon skeleton.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured using an Autopol III automatic polarimeter (Rudolph Research Co.). UV spectra were detected by a UVIS-205 detector (Alltech). CD spectra were measured on a JASCO J-810/J-815 spectropolarimeter. IR spectra were recorded on a Thermo Nicolet Nexus 470 FT-IR spectrometer. NMR spectra were measured on a Bruker Avance-500 FT NMR spectrometer (500 MHz) using TMS as the internal standard. HRESIMS spectra were obtained on a PEQ-STAR ESI-TOF-MS/MS spectrometer. Column chromatography was performed on silica gel (200–300 mesh). The HF_{254} silica gel for TLC was provided by Sigma Co. Ltd. Sephadex LH-20 (18–110 μm) was obtained from Pharmacia Co., and ODS (50 μm) was provided by YMC Co. HPLC was performed on an Alltech 426 apparatus with a UV detector. A YMC-Pack C8 column (ODS, 10 mm × 250 mm, for reversed phase) and a chiral-phase column (OD-RH, 4.6 mm × 150 mm) were used in the HPLC separation.

Animal Material. The fresh soft coral *Sinularia capillosa* was collected from the inner coral reef at a depth of around 10 m in Sanya Bay, Hainan Province, People's Republic of China, in May 2004, and the sample was immediately frozen after collection. The specimen was identified by one of the authors (L.v.O.). A voucher specimen (HSE-14) was deposited at the State Key Laboratory of Natural and Biomimetic Drugs, Peking University.

Extraction and Isolation. The frozen soft coral was homogenized and extracted with EtOH. The concentrated extract was desalted by dissolving in MeOH to obtain a residue that was further partitioned between H_2O and EtOAc. The EtOAc fraction (20.0 g) was subjected to VLC (vacuum liquid chromatography) using 200–300 mesh Si gel and eluted with a gradient of petroleum ether/acetone (50:1, 20:1, 10:1, 5:1, 3:1, 1:1) to get six fractions (F1–F6). Each fraction was examined by ^{1}H NMR spectroscopy, and sesquiterpenoids were recognized to exist in fractions F3–F-5. F3 was further fractionated on an ODS column with a gradient of MeOH/H_2O (from 53% to 93%) followed by preparative RP-C8 HPLC to give **3** (0.7 mg), **4** (0.8 mg), **6** (0.9 mg), **7** (5.2 mg), and **8** (1.1 mg). F4 was subjected to flash chromatography on an ODS column with a gradient of MeOH/H_2O (from 60% to 80%) followed by semipreparative RP-C8 HPLC to give **1** (9.0 mg), **2** (4.6 mg), **5** (1.7 mg), **9** (10.6 mg), **13** (4.8 mg), **11** (6.4 mg), **12** (1.6 mg), **15** (0.7 mg), **16** (0.8 mg), **17** (4.5 mg), **18** (2.2 mg), and racemic sinularone A (9.6 mg). The enantiomers were separated on an OD-RH chiral-phase column using a mobile phase of H_2O/MeOH (2:8) to yield (−)-sinularone A (4.6 mg) and sinularone A (5.0 mg). F5 was fractionated by repeated ODS column chromatography and preparative HPLC to give **10** (1.4 mg) and **14** (2.6 mg).

*Capillosanane A (**1**):* colorless oil; $[\alpha]^{26}_D$ −39 (*c* 0.5, MeOH); UV (MeOH) λ_{max} (log ε) 204 (3.81), 289 (2.64) nm; IR (KBr) ν_{max} 3488, 1700, 1470, 1432, 1361 cm^{-1}; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Tables 1 and 3; HRESIMS *m*/*z* 259.1666 [M + Na]$^+$ (calcd for $C_{15}H_{24}O_2Na$, 259.1674).

*Capillosanane B (**2**):* colorless oil; $[\alpha]^{24}_D$ −160 (*c* 0.8, MeOH); UV (MeOH) λ_{max} (log ε) 214 (3.17), 236 (3.94) nm; IR (KBr) ν_{max} 3330, 1652, 1458, 1370 cm^{-1}; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Tables 1 and 3; HRESIMS *m*/*z* 259.1666 [M + Na]$^+$ (calcd for $C_{15}H_{24}O_2Na$, 259.1674).

*Capillosanane C (**3**):* colorless oil; $[\alpha]^{27}_D$ −120 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 217 (3.28), 234 (3.75) nm; IR (KBr) ν_{max} 3427, 1635, 1457, 1380 cm^{-1}; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Tables 1 and 3; HRESIMS *m*/*z* 259.1669 [M + Na]$^+$ (calcd for $C_{15}H_{24}O_2Na$, 259.1674).

*Capillosanane D (**4**):* colorless oil; $[\alpha]^{27}_D$ −44 (*c* 0.2, MeOH); UV (MeOH) λ_{max} (log ε) 213 (3.91), 265 (2.94) nm; IR (KBr) ν_{max} 3437, 1694, 1655, 1460, 1370 cm^{-1}; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Tables 1 and 3; HRESIMS *m*/*z* 257.1512 [M + Na]$^+$ (calcd for $C_{15}H_{22}O_2Na$, 257.1518).

*Capillosanane E (**5**):* colorless oil; $[\alpha]^{26}_D$ −31 (*c* 0.3, MeOH); UV (MeOH) λ_{max} (log ε) 206 (4.21) nm, 303 (2.78); IR (KBr) ν_{max} 3262, 1736, 1593, 1457, 1371 cm^{-1}; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Tables 1 and 3; HRESIMS *m*/*z* 273.1460 [M + Na]$^+$ (calcd for $C_{15}H_{22}O_3Na$, 273.1467).

*Capillosanane F (**6**):* colorless oil; $[\alpha]^{27}_D$ −10 (*c* 0.02, MeOH); UV (MeOH) λ_{max} (log ε) 217 (3.89), 243 (3.34), 287 (3.16), 322 (2.42) nm; IR (KBr) ν_{max} 3449, 1717, 1691, 1453, 1377, 1282 cm^{-1}; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Tables 1 and 3; HRESIMS *m*/*z* 233.1535 [M + H]$^+$ (calcd for $C_{15}H_{21}O_2$, 233.1541).

*Capillosanane G (**7**):* colorless oil; $[\alpha]^{18}_D$ −76 (*c* 0.5, MeOH); UV (MeOH) λ_{max} (log ε) 219 (3.61) nm; IR (KBr) ν_{max} 3450, 1642, 1457, 1378, 1043 cm^{-1}; CD (MeOH) λ (mdeg) 220 (−37) nm; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Tables 1 and 3; HRESIMS *m*/*z* 275.1618 [M + Na]$^+$ (calcd for $C_{15}H_{24}O_3Na$, 275.1623).

*Capillosanane H (**8**):* colorless oil; $[\alpha]^{27}_D$ −9 (*c* 0.2, MeOH); UV (MeOH) λ_{max} (log ε) 217 (3.86) nm; IR (KBr) ν_{max} 3446, 1653, 1459, 1369, 1163 cm^{-1}; CD (MeOH) λ (mdeg) 220(+30), 250(−10) nm; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Tables 1 and 3; HRESIMS *m*/*z* 275.1618 [M + Na]$^+$ (calcd for $C_{15}H_{24}O_3Na$, 275.1623).

*Capillosanane I (**9**):* colorless oil; $[\alpha]_D^{26}$ −55 (*c* 0.6, MeOH); UV (MeOH) λ_{max} (log ε) 206 (4.21) nm; IR (KBr) ν_{max} 3431, 1635, 1385, 1164 cm^{-1}; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Tables 2 and 3; HRESIMS *m*/*z* 275.1612 [M + Na]$^+$ (calcd for $C_{15}H_{24}O_3Na$, 275.1623).

*Capillosanane J (**10**):* colorless oil; $[\alpha]^{24}_D$ −51 (*c* 0.3, MeOH); UV (MeOH) λ_{max} (log ε) 206 (3.81) nm; IR (KBr) ν_{max} 3440,1653, 1464, 1360, 1064 cm^{-1}; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Tables 2 and 3; HRESIMS *m*/*z* 291.1564 [M + Na]$^+$ (calcd for $C_{15}H_{24}O_4Na$, 291.1573).

*Capillosanane K (**11**):* colorless oil; $[\alpha]^{22}_D$ +20 (*c* 1.0, MeOH); UV (MeOH) λ_{max} (log ε) 205 (3.94) nm; IR (KBr) ν_{max} 3421, 1647, 1454, 1376 cm^{-1}; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Tables 2 and 3; HRESIMS *m*/*z* 275.1615 [M + Na]$^+$ (calcd for $C_{15}H_{24}O_3$ Na, 275.1623).

*Capillosanane L (**12**):* colorless oil; $[\alpha]^{21}_D$ −2 (*c* 0.16, MeOH); UV (MeOH) λ_{max} (log ε) 206 (4.24) nm; IR (KBr) ν_{max} 3418, 1639, 1475, 1387 cm^{-1}; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Tables 2 and 3; HRESIMS *m*/*z* 259.1668 [M + Na]$^+$ (calcd for $C_{15}H_{24}O_2Na$, 259.1674).

*Capillosanane M (**13**):* colorless oil; $[\alpha]^{23}_D$ −49 (*c* 0.3, MeOH); UV (MeOH) λ_{max} (log ε) 212 (2.96), 239 (3.85) nm; CD (*c* 0.3, MeOH) λ ($\Delta\varepsilon$) 242(−2.0) nm; IR (KBr) ν_{max} 3432, 1637, 1454, 1382, 1108 cm^{-1}; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see

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Table 4. ^{1}H and ^{13}C NMR Data for Capillosananes O−R (15−18)[a]

	15		16		17		18	
no.	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
1	50.3, CH_2	2.23, s	50.3, CH_2	2.23, s	47.8, CH_2	1.97, d (14.4)	138.3, CH	5.56, d (1.50)
						1.59, dd (14.4, 2.0)		
2	208.6, C		208.5, C		92.7, C		144.5, C	
3	65.8, CH	3.56, m	208.5, C		34.6, CH	2.84, m	85.7, C	
4	39.7, CH_2	1.33, m	43.2, CH_2	2.46, t (7.3)	24.9, CH_2	1.65, m	32.9, CH_2	2.37, m
						1.50, m		2.06, m
5	24.5, CH_2	2.00, m	22.4, CH_2	2.17, q (7.3)	30.0, CH_2	2.51, m	29.0, CH_2	2.63, ddd (17.0, 9.0, 6.7)
								2.46, ddd (16.9, 9.5, 7.0)
6	127.2, CH	5.23, t (7.1)	125.9, CH	5.17, t (7.2)	170.3, C		176.6, C	
7	131.9, C		132.7, C		198.4, C		208.0, C	
8	26.8, CH_2	2.76, d (15.5)	26.8, CH_2	2.76, s	125.8, CH	6.41, s	49.4, CH_2	2.89, dd (17.0, 4.3)
		2.72, d (15.5)						2.36, dd (17.0, 9.8)
9	140.4, C		140.2, C		159.5, C		39.7, CH	3.27, m
10	168.1, CH	7.10, s	168.3, CH	7.13, s	51.3, CH_2	2.22, br d (15.4)	46.8, CH_2	1.97, dd (13.0, 8.4)
						2.18, br d (15.4)		1.26, dd (13.0, 6.7)
11	38.8, C		38.9, C		36.7, C		43.2, C	
12	28.4, CH_3	1.14, s	28.4, CH_3	1.15, s	28.8, CH_3	1.09, s	29.8, CH_3	1.06, s
13	28.4, CH_3	1.14, s	28.4, CH_3	1.15, s	27.8, CH_3	1.01, s	28.7, CH_3	0.98, s
14	23.8, CH_3	1.60, s	23.7, CH_3	1.58, s	32.1, CH_3	2.17, s	30.6, CH_3	2.10, s
15	24.1, CH_3	1.03, d (6.0)	30.2, CH_3	2.08, s	16.5, CH_3	0.85, d (6.9)	26.8, CH_3	1.43, s
3-OH		4.37, d (4.7)						

[a]Recorded in DMSO-d_6, at 500 MHz.

Tables 2 and 3; HRESIMS m/z 257.1509 $[M + Na]^+$ (calcd for $C_{15}H_{22}O_2Na$, 257.1518).

*Capillosanane N (**14**):* colorless oil; $[\alpha]^{24}_D$ −5 (c 0.5, MeOH); UV (MeOH) λ_{max} (log ε) 202 (3.78) nm; IR (KBr) ν_{max} 3435, 1634, 1461, 1384, 1077 cm^{-1}; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Tables 2 and 3; HRESIMS m/z 291.1563 $[M + Na]^+$ (calcd for $C_{15}H_{24}O_4Na$, 291.1573).

*Capillosanane O (**15**):* colorless oil; UV (MeOH) λ_{max} (log ε) 221 (4.12) nm; IR (KBr) ν_{max} 1709, 1678, 1646, 1474, 1376 cm^{-1}; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Table 4; HRESIMS m/z 257.1511 $[M + Na]^+$ (calcd for $C_{15}H_{22}O_2Na$, 257.1518).

*Capillosanane P (**16**):* colorless oil; $[\alpha]^{21}_D$ −1.8 (c 0.14, MeOH); UV (MeOH) λ_{max} (log ε) 222 (4.32) nm; $Rh_2(CF_3COO)_4$-induced CD (c 0.4, $CHCl_3$) λ ($\Delta\varepsilon$) 353 (+0.7) nm; IR (KBr) ν_{max} 3441, 1704, 1623, 1454, 1383, 1123 cm^{-1}; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Table 4; HRESIMS m/z 259.1669 $[M + Na]^+$ (calcd for $C_{15}H_{24}O_2$ Na, 259.1674).

*Capillosanane Q (**17**):* colorless oil; $[\alpha]^{27}_D$ −6.2 (c 0.4, MeOH); UV (MeOH) λ_{max} (log ε) 211 (3.12), 237 (3.92) nm; IR (KBr) ν_{max} 1737, 1702, 1633, 1461, 1380, 1052 cm^{-1}; CD (c 0.3, MeOH) λ ($\Delta\varepsilon$) 220 (−27) nm; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Table 4; HRESIMS m/z 273.1462 $[M + Na]^+$ (calcd for $C_{15}H_{22}O_3Na$, 273.1467).

*Capillosanane R (**18**):* colorless oil; $[\alpha]^{27}_D$ −8.6 (c 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 208 (3.83) nm; IR (KBr) ν_{max} 1723, 1634, 1440, 1382, 1113 cm^{-1}; CD (c 0.5, MeOH) λ ($\Delta\varepsilon$) 223 (−5) nm; ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data, see Table 4; HRESIMS m/z 273.1461 $[M + Na]^+$ (calcd for $C_{15}H_{22}O_3Na$, 273.1467).

(−)-Sinularone A: colorless oil; $[\alpha]^{15}_D$ −23.4 (c 0.2, MeOH); CD (c 0.3, MeOH) λ ($\Delta\varepsilon$) 300 (−0.56) nm. $[\alpha]^{15}_D$ +25.5 (c 0.2, MeOH) is for the freshly separated sinularone A. The reported $[\alpha]^{23}_D$ +7.26 (c 0.27, MeOH)[27] is attributed to a mixture of enantiomers.

*Compound **7a**:* colorless oil; $[\alpha]^{27}_D$ −70 (c 0.2, MeOH); IR (KBr) ν_{max} 3437, 1642, 1459, 1368, 1160 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 11.31 (1H, s, 10-OOH), 5.80 (1H, s, H-8), 4.70 (1H, d, J = 4.3 Hz, 6-OH), 4.55 (1H, m, H-6), 3.96 (1H, s, H-10), 2.36 (1H, d, J = 16.3 Hz, H-1a), 2.22 (1H, m, H-3), 1.80 (1H, d, J = 16.3 Hz, H-1b), 1.66 (3H, s, H_3-14), 1.09 (3H, s, H_3-12), 0.99 (3H, s, H_3-13), 0.95 (3H, d, J = 6.9 Hz, H_3-15); HRESIMS m/z 275.1616 $[M + Na]^+$ (calcd for $C_{15}H_{24}O_3Na$, 275.1623).

*Compound **9a**:* colorless oil; $[\alpha]^{23}_D$ +8.1 (c 0.1, MeOH); IR (KBr) ν_{max} 3436, 1657, 1464, 1365 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 6.19 (1H, s, 6-OH), 6.10 (1H, s, H-8), 5.00 (1H, s, H-14a), 4.81 (1H, s, H-14b), 2.23 (1H, d, J = 14.4 Hz, H-10a), 1.97 (1H, d, J = 14.4 Hz, H-10b), 1.78 (1H, m, H-4a), 1.77 (1H, m, H-5a), 1.75 (1H, d, J = 14.3 Hz, H-1a), 1.45 (1H, m, H-3), 1.41 (1H, d, J = 14.3 Hz, H-1b), 1.35 (1H, m, H-4b), 1.34 (1H, m, H-5b), 1.07 (3H, s, H_3-12), 1.03 (3H, d, J = 6.9 Hz, H_3-15), 0.94 (3H, s, H_3-13); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C 149.0 (C, C-9), 146.6 (C, C-7), 122.1 (CH, C-8), 109.4 (CH_2, C-14), 97.6 (C, C-6), 85.2 (C, C-2), 50.2 (CH, C-1), 45.5 (CH_2, C-10), 36.4 (C, C-11), 33.4 (CH_2, C-5), 30.9 (CH, C-3), 30.6 (CH_3, C-13), 30.2 (CH_3, C-12), 26.1 (CH_2, C-4), 13.3 (CH_3, C-15); HRESIMS m/z 257.1510 $[M + Na]^+$ (calcd for $C_{15}H_{22}O_2Na$, 257.1518).

*Compound **9b**:* colorless oil; $[\alpha]^{23}_D$ +20 (c 0.1, MeOH); IR (KBr) ν_{max} 3435, 1634, 1436, 1377, 1061 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 6.25 (1H, s, 6-OH), 6.14 (1H, s, H-8), 5.26 (1H, s, H-10), 2.04 (1H, d, J = 13.1 Hz, H-1a), 1.47 (1H, d, J = 13.1 Hz, H-1b), 1.66 (3H, s, H_3-14), 1.62 (1H, m, H-3), 1.07 (3H, s, H_3-12), 1.08 (3H, d, J = 6.9 Hz, H_3-15), 1.05 (3H, s, H_3-13); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C 141.1 (C, C-9), 139.0 (C, C-7), 132.4 (CH, C-10), 121.1 (CH, C-8), 98.8 (C, C-6), 88.3 (C, C-2), 50.3 (CH, C-1), 42.4 (C, C-11), 34.8 (CH, C-3), 31.5 (CH_3, C-13), 28.3 (CH_3, C-12), 27.6 (CH_2, C-4), 27.1 (CH_2, C-5), 18.6 (CH_3, C-14), 16.0 (CH_3, C-15); HRESIMS m/z 257.1510 $[M + Na]^+$ (calcd for $C_{15}H_{22}O_2Na$, 257.1518).

*Conversion of **9** to **18**.* To a MeOH/H_2O (3:2, 3 mL) solution of **9** (5.0 mg) was added $NaIO_4$ (10 mg), and the reaction mixture was stirred for 7 h at room temperature (rt). The solution was then diluted with H_2O (5 mL) and extracted with $CHCl_3$ (10 mL) to yield **18** (1.0 mg) after Si gel column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (1H, s, H-8), 3.09 (1H, m, H-3), 2.75 (1H, m), 2.59 (1H, dd, J = 17.3, 6.2 Hz) 2.24 (3H, s, H_3-14), 1.13 (6H, s, H_3-12, 13), 0.92 (3H, d, J = 6.9 Hz, H_3-15).

*Reduction of Capillosanane A (**1**) to **1a**.* Compound **1** (5.1 mg) was treated with $NaBH_4$ (10 mg) in MeOH (2 mL) by stirring at rt for 60 min. The reaction was quenched by the addition of H_2O (2 mL), and the mixture was evaporated in vacuo. The residue was purified by

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reversed-phase semipreparative HPLC using MeCN/H_2O (65:35) as the mobile phase to obtain **1a** (3.1 mg).

*Compound **1a**:* colorless oil; $[\alpha]^{23}_D$ +40 (*c* 0.1, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ_H 5.55 (1H, s, H-8), 3.49 (1H, dd, *J* = 10.5, 2.5 Hz, H-6), 3.09 (1H, dd, *J* = 13.5, 6.4 Hz, H-2), 2.20 (1H, d, *J* = 13.4 Hz, H-10a), 1.96 (1H, m, H-4a), 1.89 (1H, t, *J* = 13.4 Hz, H-5a), 1.78 (1H, d, *J* = 13.4 Hz, H-10b),1.66 (1H, m, H-3), 1.65 (1H, m, H-5b), 1.64 (1H, m, H-1a), 1.61 (1H, m, H-1b), 1.36 (3H, s, Me-14), 1.20 (1H, m, H-4b), 1.11 (3H, s, Me-12), 0.92 (3H, s, Me-13), 0.83 (3H, d, *J* = 6.8 Hz, Me-15); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.58 (1H, s, H-8), 3.51 (1H, dd, *J* = 10.5, 2.5 Hz, H-6), 2.96 (1H, m, H-2), 2.17 (1H, d, *J* = 13.4 Hz, H-10a), 1.79 (1H, d, *J* = 13.4 Hz, H-10b), 1.41 (3H, s, Me-14), 1.13 (1H, m, H-4b), 1.11 (3H, s, Me-12), 0.91 (3H, s, Me-13), 0.81 (3H, d, *J* = 6.8 Hz, Me-15); ^{13}C NMR (CD_3OD, 125 MHz) δ_C 143.2 (C, C-9), 130.2 (CH, C-8), 78.7 (CH, C-6), 75.9 (C, C-7), 53.0 (CH_2, C-10), 43.8 (CH_2, C-1), 39.8 (CH, C-2), 36.3 (C, C-11), 35.3 (CH, C-3), 31.9 (CH_2, C-4), 28.2 (CH_2, C-5), 28.0 (CH_3, C-13), 27.9 (CH_3, C-12), 20.4 (CH_3, C-14), 16.6 (CH_3, C-15).

*Preparation of (R)- and (S)-MPA Esters of **1a**.* To a $CDCl_3$ solution (0.5 mL) containing **1a** (1.4 mg, 0.0059 mmol) were added (*R*)-MPA (2.0 mg, 0.012 mmol), DMAP (0.8 mg, 0.006 mmol), and *N*,*N*′-dicyclohexylcarbodiimide (DCC, 2.5 mg, 0.012 mmol). After reacting at rt for 24 h, the crude products were separated by silica gel column chromatography eluting with petroleum ether/acetone (7:1) to afford the (*R*)-MPA ester (1.5 mg). By the same protocol, the (*S*)-MPA ester (1.3 mg) was prepared from (*S*)-MPA.

*(R)-MPA ester of **1a**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.382 (1H, s, H-8), 4.784 (1H, dd, *J* = 9.2, 2.2 Hz, H-6), 2.935 (1H, m, H-2), 2.154 (1H, d, *J* = 13.6 Hz, H-10a), 1.942 (1H, m, H-4a), 1.770 (1H, d, *J* = 13.7 Hz, H-10b), 1.277 (1H, m, H-4b), 1.124 (3H, s, Me-14), 1.086 (3H, s, Me-12), 0.871 (3H, s, Me-13), 0.800 (3H, d, *J* = 6.8 Hz, Me-15); ESIMS *m*/*z* 387.25 $[M + H]^+$.

*(S)-MPA ester of **1a**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.443 (1H, s, H-8), 4.874 (1H, dd, *J* = 9.2, 2.2 Hz, H-6), 2.769 (1H, m, H-2), 2.154 (1H, d, *J* = 13.6 Hz, H-10a), 1.828 (1H, m, H-4a), 1.799 (1H, d, *J* = 13.2 Hz, H-10b), 1.180 (1H, m, H-4b), 1.338 (3H, s, Me-14), 1.077 (3H, s, Me-12), 0.888 (3H, s, Me-13), 0.741 (3H, d, *J* = 6.8 Hz, Me-15); ESIMS *m*/*z* 387.25 $[M + H]^+$.

Preparation of (*R*)- and (*S*)-MPA Esters of 2. Following the same protocol as that for **1a**, the (*R*)-MPA ester (1.3 mg) and the (*S*)-MPA ester (1.2 mg) were obtained from **2** (each 0.8 mg, 0.0032 mmol).

Preparation of (*R*)- and (*S*)-MPA Esters of 5. Following the same protocol as that for **1a**, the (*R*)-MPA ester (0.9 mg) and the (*S*)-MPA ester (0.8 mg) were obtained from **5** (each 0.8 mg, 0.0032 mmol).

*(R)-MPA ester of **2**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.865 (1H, m, H-6), 5.701 (1H, s, H-8), 5.336 (1H, s, H-10), 2.258 (1H, m, H-3), 2.158 (1H, d, *J* = 16.7 Hz, H-1a), 2.097(1H, d, *J* = 16.7 Hz, H-1b), 1.574 (3H, s, Me-14), 0.983 (3H, d, *J* = 6.8 Hz, Me-15), 0.931 (3H, s, Me-12), 0.591 (3H, s, Me-13); ESIMS *m*/*z* 385.23 $[M + H]^+$.

*(S)-MPA ester of **2**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.862 (1H, m, H-6), 5.346 (1H, s, H-10), 5.116 (1H, s, H-8), 2.318 (1H, m, H-3), 2.261 (1H, d, *J* = 15.8 Hz, H-1a), 2.151 (1H, d, *J* = 15.8 Hz, H-1b), 1.129 (3H, s, Me-12), 1.108 (3H, s, Me-14), 1.021 (3H, s, Me-13), 0.976 (3H, d, *J* = 6.8 Hz, Me-15); ESIMS *m*/*z* 385.23 $[M + H]^+$.

*(R)-MPA ester of **5**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.849 (1H, s, H-8), 5.572 (1H, dd, *J* = 12.1, 4.2 Hz, H-6), 2.292 (1H, d, *J* = 14.3 Hz, H-1a), 2.069 (1H, m, H-3),1.835 (1H, d, *J* = 14.3 Hz, H-1b), 1.707 (3H, s, Me-14), 1.161 (3H, d, *J* = 6.8 Hz, Me-15), 1.152 (3H, s, Me-12), 1.104 (3H, s, Me-13); ESIMS *m*/*z* 399.23 $[M + H]^+$.

*(S)-MPA ester of **5**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.775 (1H, s, H-8), 5.603 (1H, dd, *J* = 12.3, 4.7 Hz, H-6), 2.292 (1H, d, *J* = 14.3 Hz, H-1a), 2.086 (1H, m, H-3),1.835 (1H, d, *J* = 14.3 Hz, H-1b), 1.381 (3H, s, Me-14), 1.183 (3H, d, *J* = 6.8 Hz, Me-15), 1.144 (3H, s, Me-12), 1.108 (3H, s, Me-13); ESIMS *m*/*z* 399.23 $[M + H]^+$.

Reduction of Capillosanane D (4) to 2 and 3. Compound **4** (0.6 mg) was stirred with $NaBH_4$ (1.0 mg) in MeOH (2 mL) at rt for 45 min. The reaction was quenched by addition of H_2O (2 mL), and the mixture was evaporated in vacuo. The residue was separated by reversed-phase HPLC using MeCN/H_2O (61:39) as eluent to yield **2** (0.3 mg) and **3** (0.25 mg).

Preparation of (*R*)- and (*S*)-MPA Esters of 10. Following the same protocol as that for **1a**, the (*R*)-MPA ester (2.3 mg) and the (*S*)-MPA ester (2.0 mg) were obtained from **10** (each 1.8 mg).

*(R)-MPA ester of **10**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.072 (1H, s, H-8), 4.944 (1H, s, H-10), 1.254 (3H, s, Me-14), 0.978 (3H, s, Me-12), 0.741 (3H, s, Me-13); ESIMS *m*/*z* 417.22 $[M + H]^+$.

*(S)-MPA ester of **10**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.047 (1H, s, H-8), 4.914 (1H, s, H-10), 1.039 (3H, s, Me-12), 1.009 (3H, s, Me-14), 0.873 (3H, s, Me-13); ESIMS *m*/*z* 417.22 $[M + H]^+$.

Bioassay against Larval Settlement (refs 31, 32). Adults of the barnacle *Balanus amphitrite* Darwin were exposed to air for more than 6 h and then were placed in a container filled with fresh 0.22 μm filtered seawater to release nauplii. The collected nauplii were reared to the cyprid stage according to the method described by Thiyagarajan et al.[26] When kept at 26−28 °C and fed with *Chaetoceros gracilis*, larvae developed to cyprids within four days. Fresh cyprids were used in the tests.

Assay for the Production of Pro-inflammatory Cytokines (TNF-α) (ref 33). Compounds were dissolved in DMSO, and NK-007 was used as a positive control.[28] Suspensions of BALB/c mouse splenocytes were cultured in complete RPMI 1640 medium (Hyclone Laboratories) containing 10% FBS (Gibco). Raw 264.7 cells were grown in DMEM (Hyclone Laboratories) supplemented with 10% FBS. Cultured cells were treated in the presence or absence of NK-007 (100 nM) and tested compounds (10 μM) for 24 h followed by LPS stimulation (1 μg/mL). Supernatants were collected for analysis of cytokine levels. For cytokine determinations in culture supernatants or serum, cytometric bead array kits (BD Biosciences) were used.

Cytotoxic Assay. Cell viability in the presence or absence of tested compounds was determined using the standard MTT assay as described.[34]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectroscopic data for the new compounds (**1**−**18**) including ^{1}H, ^{13}C, and 2D NMR spectra, IR, and ESIMS/MS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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