Discorhabdins from the Korean Marine Sponge *Sceptrella* sp.

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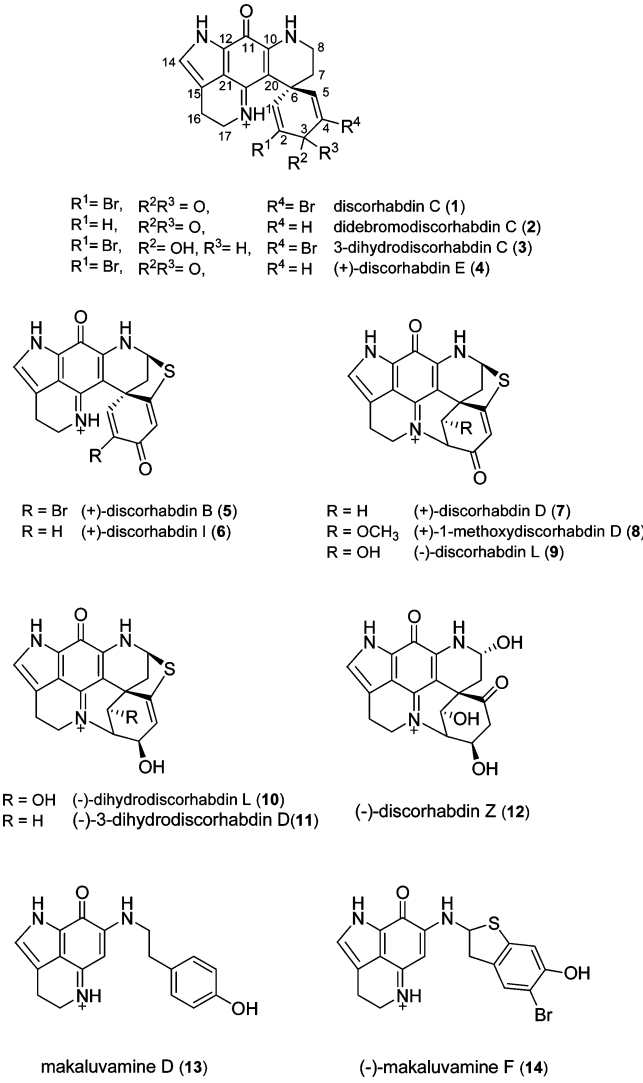
Two new pyrroloiminoquinone alkaloids of the discorhabdin class, along with 12 compounds including one previously described synthetic derivative of the same and related skeletal classes, were isolated from the sponge *Sceptrella* sp., collected from Gageodo, Korea. The structures of these new compounds, designated as (−)-3-dihydrodiscorhabdin D (**11**) and (−)-discorhabdin Z (**12**), were determined by combined spectroscopic analyses. Compound **12** possesses an unusual hemiaminal group among the discorhabdin alkaloids. These compounds exhibited moderate to significant cytotoxicity, antibacterial activity, and inhibitory activity against sortase A.

Pyrroloiminoquinone alkaloids, based on tryptamine, are widely distributed among marine sponges.[1] The most notable examples of this structural class of molecules are the discorhabdins (prianosins) from the family Latrunculiidae, which are composed of a pyrroloiminoquinone and a tyramine moiety.[1,2] These compounds exhibit significant cytotoxic and antibacterial activities against a wide range of cell lines and microbial species, respectively. Due to the structural diversity and potent bioactivity of these compounds, there have been a number of chemical investigations of latrunculid sponges from around the world.[3−18]

During the course of our search for bioactive metabolites from sponges from Korean waters, we encountered the dark green sponge *Sceptrella* sp., previously categorized as belonging to the genus *Latrunculia*, the organic extract of which exhibited significant toxicity (LD_{50} 2.24 ppm) toward brine shrimp larvae. Bioactivity-guided separation of the highly polar fractions from the crude extract yielded several pyrroloiminoquinone alkaloids. Here, we report the isolation and structure determination of two new discorhabdin derivatives, along with 12 known compounds from the same and related structural classes. These compounds exhibited moderate to significant cytotoxicity toward the K562 leukemia cell line, antibacterial activity toward a broad spectrum of microbial species, and significant inhibitory activity against sortase A, a key enzyme in microbial metabolism.

A combination of mass and NMR spectroscopy in conjunction with a comparison of spectroscopic data with those published in the literature readily identified compounds **1**−**10** as discorhabdin C, didebromodiscorhabdin C, 3-dihydrodiscorhabdin C, (+)-discorhabdin E, (+)-discorhabdin B, (+)-discorhabdin I, (+)-discorhabdin D, (+)-1-methoxydiscorhabdin D, (−)-discorhabdin L, and (−)-dihydrodiscorhabdin L, respectively.[3−6,11,12,16] Didebromodiscorhabdin C (**2**), previously reported as a synthetic derivative, was isolated here for the first time as a natural product.[9] The absolute configurations of these compounds were also assigned by comparison of optical rotations (**4**, **6**−**8**, **10**, **14**) with those in the literature, as well as CD measurements (**5**, **9**) based on the recent findings of Copp and colleagues.[17] In addition to discorhabdins,



two congeners, **13** and **14**, were identified as makaluvamines D and F, respectively.[20−23]

(−)-3-Dihydrodiscorhabdin D (**11**) was isolated as a dark green solid, the molecular formula of which was identified as $C_{18}H_{16}N_3O_2S$ by combined HRFABMS and ^{13}C NMR analyses. The NMR

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Table 1. NMR Assignments for the Compounds **11** and **12** (^{13}C 150 MHz, ^{1}H 600 MHz)

	11		**12**		
no.	δ_C[a]	δ_H[a]	δ_C[a]	δ_H[a]	δ_H[b]
1	30.3, CH_2	2.50, m 2.35, dd (13.2, 3.7)	72.4, CH	4.11, m[c]	4.18, m[c]
2	60.6, CH	4.29, m	64.0, CH	4.11, m[c]	4.18, m[c]
3	67.1, CH	4.67, dd (5.4, 2.2)	69.4, CH	4.57, m	4.76, m
4	111.3, CH	5.21, d (2.2)	43.5, CH_2	2.55, dd (13.0, 3.2) 2.42, dd (13.0, 5.5)	2.61, m
5	145.1, C		205.5, C		
6	40.4, C		47.9, C		
7	40.2, CH_2	2.54, dd (11.4, 2.4) 2.50, m	33.4, CH_2	2.52, dd (12.3, 4.5) 1.26, dd (12.3, 10.3)	2.76, dd (12.6, 4.2) 1.36, dd (12.6, 9.6)
8	61.0, CH	5.46, d (2.4)	75.0, CH	5.16, m	5.35, dd (9.6, 4.2)
10	146.3, C		146.8, C		
11	167.6, C		166.3, C		
12	123.3, C		123.1, C		
14	126.4, CH	7.28, s	126.4, CH	7.33, s	7.16, s
15	117.8, C		118.0, C		
16	19.6, CH_2	3.00, m	19.0, CH_2	3.16, m 3.01, m	3.16, ddd (16.8, 12.0, 7.2) 3.06, ddd (16.8, 6.0, 4.2)
17	53.7, CH_2	4.27, dt (14.6, 7.3) 4.07, dt (14.6, 7.3)	52.7, CH_2	4.11, m 4.11, m	4.28, ddd (13.8, 7.2, 4.2) 4.15, m
19	150.4, C		152.0, C		
20	104.6, C		90.4, C		
21	121.5, C		121.9, C		
1-OH				6.36, br s	
3-OH		5.71, d (7.2)		5.80, br s	
8-OH				6.65, d (7.3)	
9-NH		9.89, br s		9.22, br s	
13-NH		13.10, br s		13.09, br s	

[a] Measured in DMSO-d_6. [b] Measured in MeOH-d_4. [c] Due to the signal overlapping, coupling constants were not measured.

spectroscopic data of this compound were very similar to those of other discorhabdins; chemical shifts of protons and carbons for the pyrroloiminoquinone and thioether moieties were almost identical to those of (−)-dihydrodiscorhabdin L (**10**).[16] Detailed examination of the NMR data showed that a hydroxy group was removed from the dihydroxyhexene ring of **10** (Table 1). A combination of ^{1}H COSY and HSQC analyses for the signals at this ring showed that the C-1 oxymethine carbon (δ_C 68.2, δ_H 4.51) was replaced with a methylene carbon (δ_C 30.3, δ_H 2.50 and 2.35). This observation and the remaining structure of **11**, including the linkage between the imine nitrogen and cyclohexene, were confirmed by the results of HMBC experiments. Comparison of the ^{1}H and ^{13}C NMR data with those of other discorhabdins, in particular compound **7**,[5] revealed that **11** has the same relative configurations at C-1 and C-8. In addition the relative orientations at C-2 and C-3 were determined to be *cis*, on the basis of the small coupling constant ($J_{2,3}$ = 5.4 Hz) and the mutual NOESY correlations at H-1 (δ_H 2.50 and 2.35)/H-2, H-1 (δ_H 2.50)/H-3, and H-2/H-3.

The absolute configuration was determined by the comparison of an experimental CD spectrum of (−)-3-dihydrodiscorhabdin D (**11**) with a quantum chemically simulated electronic circular dichroism (ECD) spectrum calculated by time-dependent density functional theory (TDDFT). The calculated ECD spectrum of **11** matched well with the experimental CD data. Molecular orbital analysis indicated that the observed negative Cotton effects (CEs) near 420, 310, 266, and 210 nm correspond to n→π* (408 nm, MO83→MO89(LUMO)), π→π* (329 nm, MO84→MO89), σ→π* (270 nm, MO81→MO89), and π→π* (217 nm, MO88(HOMO)→MO92) transitions, repectively. The positive CEs near 365, 280, and 250 nm corresponded to π→π* (386 and 370 nm, MO86→MO89 and MO85→MO89), π→π* (265 nm, MO88→MO91), and π→π* (250 nm, MO80→MO89) transitions, respectively (Supporting Information). Thus, the absolute configuration of (−)-3-dihydrodiscorhabdin D (**11**) was determined to be 2*S*, 3*R*, 6*R*, 8*S*.

The molecular formula of (−)-discorhabdin Z (**12**) was deduced to be $C_{18}H_{18}N_3O_5$, indicating the disappearance of the sulfur atom common to compounds **5**−**11**. The NMR spectroscopic data of this compound were reminiscent of other discorhabdins, with the presence of proton and carbon signals for the pyrroloiminoquinone moiety. However, examination of the NMR data indicated that signals for the didehydropiperidine moiety were significantly shifted. ^{1}H COSY experiments traced a spin system consisting of four protons at δ 6.65 (1H, d, J = 7.3 Hz), 5.16 (1H, m), 2.52 (1H, dd, J = 12.3, 4.5 Hz), and 1.26 (1H, dd, J = 12.3, 10.3 Hz). These were determined to be attached at an oxygen, a methine carbon at δ 75.0, and a methylene carbon at δ 33.4, respectively, on the basis of HSQC analysis. HMBC correlations of these protons with neighboring carbons at C-10, C-11, and C-20 of the iminoquinone moiety, as well as a quaternary carbon at δ 47.9 (C-6), assigned these carbons to C-7 and C-8 of the didehydropiperidine ring, indicating the attachment of a hydroxy group at C-8, thus forming a hemiaminal group. Among the discorhabdin alkaloids, this functional group is preceded only by epinardin D, which possesses a methylaminal group at this position.[8]

The remaining part of the molecule was also determined by 2-D NMR analyses. The proton and carbon NMR data in conjunction with the molecular formula indicated the presence of a ketone, three heteroatom-bearing methines, and a methylene (Table 1). The linear array of these groups was determined by ^{1}H COSY, and the ketone was placed next to the methylene carbon, on the basis of the chemical shifts of methylene protons at δ 2.55 and 2.42. The presence of a six-membered ring accommodating all of these groups, in addition to the C-6 quaternary carbon, was revealed by a series of long-range HMBC correlations between these protons and neighboring carbons, in particular those at H-1/C-7, H-1/C-20, H-2/C-6, H-4/C-6, H-7/C-1, and H-7/C-5 in the HMBC data. Additionally, the imminium linkage between N-17 and C-2 was confirmed by a long-range correlation between H-2 and C-16.

The configurations at the asymmetric carbon centers of **12** were determined by NOESY experiments and a 3-D model study (Figure 1a). The presence of an iminium bridge between C-2 and N-17 placed an α-oriented H-2 in the cyclohexanone ring. Although signals of the H-1 and H-2 protons overlapped precisely with each other in various NMR solvents, a prominent NOESY cross-peak with H-3 revealed that either one or both of these protons were spatially proximal to the H-3 oxymethine proton. The configuration was further clarified and the *trans* 1,3-dihydroxy orientation was assigned, on the basis of a NOESY cross-peak at H-3/1-OH in

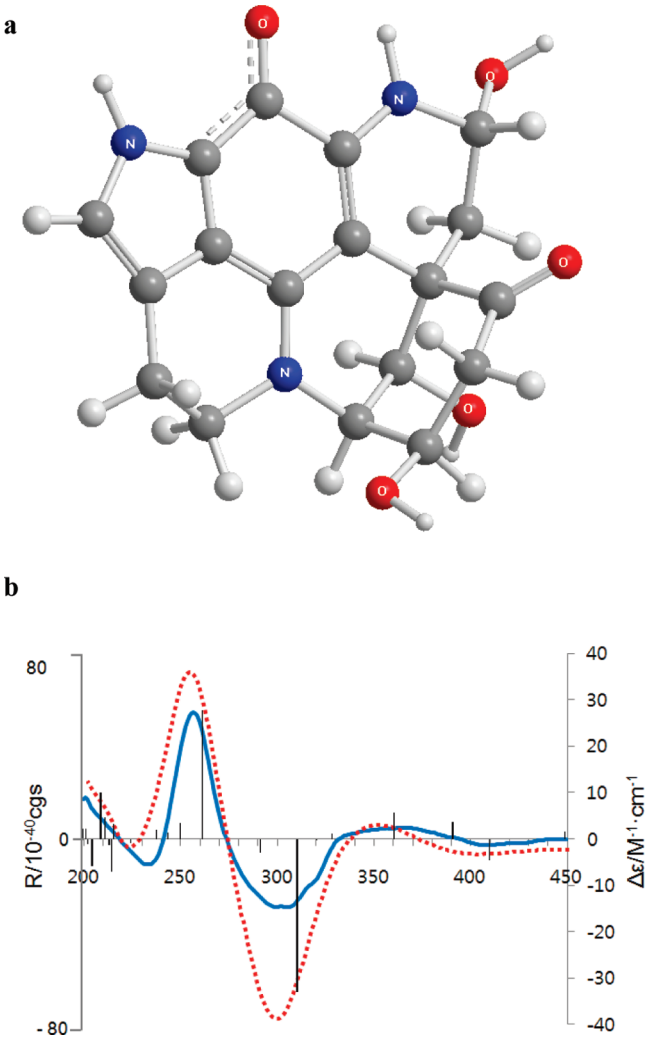

Figure 1. (a) Optimized geometry of discorhabdin Z (**12**) cation at the B3LYP/6-31G (d,p) level in the gas phase. (Each heteroatom is labeled.) (b) Calculated and experimental ECD spectra of (−)-discorhabdin Z (**12**) (dotted line, at the B3LYP/6-31G (d,p) level in the gas phase; solid line, experimental in MeOH). For computational calculation, see Supporting Information, page S20.

DMSO-d_6 (Table 1). Similarly, an α-orientation was assigned for the 8-OH by NOESY cross-peaks at H-1/H-7α (δ 1.36) and H-8/H-7β (δ 2.76) in conjunction with a large vicinal coupling constant ($J_{7,8}$ = 9.6 Hz). Thus, the relative configurations were assigned as 1*R**, 2*R**, 3*R**, 6*R**, 8*R** for (−)-discorhabdin Z (**12**).

As for **11**, the absolute configuration of **12** was determined by CD and ECD data, which matched well with each other (Figure 1b). Detailed molecular orbital analysis revealed that the observed negative Cotton effects (CEs) near 412, 306, and 234 nm correspond to n→π* (389 nm, MO89→MO94(LUMO)), π→π* (299 nm, MO93(HOMO)→MO95), and π→π* (214, 205 nm, MO92→MO96, MO91→MO96) transitions, respectively. Additionally the positive CEs near 368, 257, and 210 nm correspond to π→π* (344 nm, MO90→MO94), π→π* (255 nm, MO92→MO95), and π→π* (208 nm, MO93→MO97, and other transitions). Thus, the absolute configuration of (−)-discorhabdin Z (**12**) was determined to be 1*R*, 2*R*, 3*R*, 6*R*, 8*R*.

Discorhabdins and related alkaloids are widely recognized for their cytotoxicity and antibacterial activity.[6,12−15,18,19,22] In the present study, several compounds displayed moderate activity against a wide range of bacteria (Table 2). These compounds also showed significant cytotoxicity against the K562 cell line, comparable to doxorubicin. Additionally, our measurements indicated that discorhabdins were remarkably active against sortase A, a pivotal enzyme for bacterial adhesion and invasion of host cells.[24] It is noteworthy that (−)-discorhabdin Z (**12**), possessing a unique hemiaminal group, exhibited inhibition of sortase A that was 10-fold more potent than that of *p*-HMB, as a positive control.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a JASCO P-1020 polarimeter using a 1 cm cell. CD spectra were obtained on a JASCO J-715 using a 0.2 mm cell. UV spectra were recorded on a Hitachi U-3010 spectrophotometer, and IR spectra were recorded on a JASCO 300E FT-IR spectrometer. NMR spectra were recorded in MeOH-d_4 and DMSO-d_6 solutions containing Me_4Si as an internal standard on a Bruker Avance 600 spectrometer. Proton and carbon NMR spectra were measured at 600 and 150 MHz, respectively. Mass spectrometric data were obtained from the Korea Basic Science Institute (Daegu) on a Jeol JMS 700 mass spectrometer, Korea. All solvents used were spectral grade or distilled from glass prior to use.

Animal Materials. The specimens of *Sceptrella* sp. (voucher number 07SH-1) were collected by hand using scuba off the shore of Gageodo (Gukhuldo), West Sea, Korea, at a depth of 20 m on June 18, 2007. The sponge was oval in shape, measured 45 × 38 mm, and was 25 mm thick. The surface was smooth and the texture was elastic in alcohol. The color in life was dark green. The megascleres are styles (255−310 × 5−8 μm), and microscleres were isoconicodiscorhabds (28−40 μm). A voucher specimen (registry No. Spo. 53) was deposited at the Natural History Museum, Hannam University, Korea, under the curatorship of C.J.S.

Extraction and Isolation. Freshly collected specimens were immediately frozen and kept at −25 °C until chemical investigation. The combined specimens were lyophilized (dry wt 970 g), macerated, and repeatedly extracted with CH_2Cl_2 (3 L × 3) and MeOH (3 L × 3). The combined extracts were successively partitioned between H_2O and *n*-BuOH, and then the latter was repartitioned between 15% aqueous MeOH (14.51 g) and *n*-hexane (40.63 g). The aqueous MeOH layer was separated by C_{18} reversed-phase vacuum flash chromatography, using a sequential mixture of MeOH and H_2O as eluents (elution order: 50%, 40%, 30%, 20%, 10% MeOH(aq), and 100% MeOH), acetone, and finally EtOAc.

On the basis of the results of ^{1}H NMR analysis, the fractions eluted with 50% MeOH(aq) (2.31 g) from flash chromatography were separated by semipreparative reversed-phase HPLC (YMC-ODS-A column, 1 × 25 cm, 50% MeOH(aq)) to yield four peaks rich in secondary metabolites. Separation and purification of the first peak by reversed-phase HPLC (90% MeOH(aq)) afforded, in order of elution, compounds **6**, **9**, **7**, **10**, and **11** as amorphous solids. Separation of the second peak under the same HPLC conditions afforded compounds **8** and **4**.

Separation and purification of the other peaks were accomplished by reversed-phase HPLC (80% MeOH(aq) for the third peak, 70% MeOH(aq) for the fourth and fifth peaks) to afford, in order of elution, compounds **5**, **1**, **3**, **13**, **14**, **2**, and **12** as pure compounds, with **5** and **12** from the third peak, **1**, **13**, and **14** from the fourth peak, and **2** and **3** from the fifth peak. The purified metabolites were isolated in the following amounts: 2.2, 2.0, 2.0, 4.6, 35.4, 8.7, 29.9, 5.7, 79.8, 20.7, 117.9, 3.8, 50.9, and 4.4 mg for **1**−**14**, respectively.

Computational Chemistry. The ground-state geometries were optimized with density functional theory (DFT) calculations, using Gaussian 03, at 298 K in the gas phase at the B3LYP/6-31G(d,p) level, and the ground states were further confirmed by the harmonic frequency calculation. The calculated ECD data corresponding to the optimized structures were obtained with TDDFT at the B3LYP/6-31G(d,p) level in the gas phase. The CD spectra were simulated by overlapping Gaussian functions[25]

$$\Delta\varepsilon(E) = \frac{1}{2.297 \times 10^{-39}} \frac{1}{\sqrt{2\pi}\sigma} \sum_{i}^{A} \Delta E_i R_i e^{[-(E - \Delta E_i)^2/(2\sigma)^2]}$$

for each transition, where σ is the width of the band at 1/e height and ΔE_i and R_i are the excitation energies and rotatory strengths for transition i, respectively. In the current work a value of σ was 0.40 eV.

Table 2. Results of Bioactivity Tests[a]

	MIC (μg/mL)							
	Gram (+) bacteria			Gram (−) bacteria			K562	sortase A
compound	A	B	C	D	E	F	IC_{50} (μM)	IC_{50} (μM)
1	25	12.5	>100	>100	50	>100	25.2	164.8
2	>100	>100	>100	>100	>100	>100	21.0	127.4
3	100	100	>100	>100	>100	>100	20.2	>300
4	50	50	100	>100	25	50	1.3	186.1
5	12.5	25	50	>100	3.125	100	7.2	131.7
6	12.5	25	25	>100	50	50	25.0	159.9
7	25	6.25	100	>100	>100	>100	6.1	
8	50	12.5	50	>100	100	100	2.5	146.3
9	25	12.5	50	>100	100	100	4.5	129.7
10	100	25	>100	>100	50	>100	2.5	192.2
11	25	25	>100	>100	50	>100	2.1	75.7
12	>100	50	>100	>100	>100	>100	2.2	6.5
13	25	50	>100	>100	>100	100	24.6	148.5
14	12.5	3.125	50	>100	25	100	8.9	174.7
ampicillin	1.56	1.56	1.56	12.5	3.12	3.12		
doxorubicin							8.5	
*p*HMB[b]								110.9

[a] A: *Bacillus subtilis* (ATCC 6633), B: *Micrococcus luteus* (IFO 12708), C: *Staphylococcus aureus* (ATCC 65389), D: *Escherichia coli* (ATCC 25922), E: *Proteus vulgaris* (ATCC 3851), F: *Salmonella typhimurium* (ATCC 14028). [b] *para*-(Hydroxymercury)benzoic acid sodium salt.

Discorhabdin C (1): dark yellow, amorphous solid; $[\alpha]_D^{25}$ 0 (*c* 0.009, MeOH){lit. 0};[3] NMR, UV, IR, and MS data are consistent with those in the literature.[3]

Didebromodiscorhabdin C (2): green, amorphous solid; $[\alpha]_D^{25}$ 0 (*c* 0.009, MeOH); UV (MeOH) λ_{max} (log ϵ) 285 (3.38), 368 (3.40) nm; NMR, IR, and MS data are consistent with those in the literature.[9]

3-Dihydrodiscorhabdin C (3): dark yellow, amorphous solid; $[\alpha]_D^{25}$ 0 (*c* 0.009, MeOH); NMR, UV, IR, and MS data are consistent with those in the literature.[6]

(+)-Discorhabdin E (4): red, amorphous solid; $[\alpha]_D^{25}$ +700 (*c* 0.009, MeOH), +94 (*c* 0.01, MeOH) {lit. 0 (*c* 0.003, MeOH)};[6] NMR, UV, IR, and MS data are consistent with those in the literature.[6]

(+)-Discorhabdin B (5): green, amorphous solid; $[\alpha]_D^{25}$ +344 (*c* 0.009, MeOH), +276 (*c* 0.12, MeOH) {lit. +400 (*c* 0.17, MeOH)};[4] NMR, UV, IR, and MS data are consistent with those in the literature.[4]

(+)-Discorhabdin I (6): green, amorphous solid; $[\alpha]_D^{25}$ +500 (*c* 0.009, MeOH), +358 (*c* 0.07, MeOH) {lit. −562.8 (*c* 0.13, MeOH)};[11] NMR, UV, IR, and MS data are consistent with those in the literature.[11]

(+)-Discorhabdin D (7): green, amorphous solid; $[\alpha]_D^{25}$ +411 (*c* 0.009, MeOH), +247 (*c* 0.07, MeOH) {lit. 0 (*c* 0.15, MeOH)};[5] NMR, UV, IR, and MS data are consistent with those in the literature.[5]

(+)-1-Methoxydiscorhabdin D (8): dark green, amorphous solid; $[\alpha]_D^{25}$ +677 (*c* 0.009, MeOH), +42 (*c* 0.067, MeOH); UV (MeOH) λ_{max} (log ϵ) 293 (3.76), 321 (3.68), 386 (3.62) nm; IR (ZnSe) ν_{max} 3376, 1620, 1559, 1526, 1411 cm^{-1}; NMR and MS data are consistent with those in the literature.[12]

(−)-Discorhabdin L (9): dark green, amorphous solid; $[\alpha]_D^{25}$ −333 (*c* 0.009, MeOH), −561 (*c* 0.018, MeOH) {lit. 0 (*c* 0.1, MeOH)};[11] NMR, UV, IR, and MS data are consistent with those in the literature.[11]

(−)-Dihydrodiscorhabdin L (10): green, amorphous solid; $[\alpha]_D^{25}$ −100 (*c* 0.12, MeOH), −190 (*c* 0.022, MeOH) {lit. +256 (*c* 0.002, MeOH)};[16] IR (ZnSe) ν_{max} 3289, 1667, 1622, 1586, 1536, 1412, 1346 cm^{-1}; NMR, UV, and MS data are consistent with those in the literature.[16]

(−)-3-Dihydrodiscorhabdin D (11): dark green, amorphous solid; $[\alpha]_D^{25}$ −188 (*c* 0.009, MeOH), −94 (*c* 0.018, MeOH); CD (MeOH) $\Delta\epsilon$ 266.0 nm (−3.91), 365.0 nm (+6.78); UV (MeOH) λ_{max} (log ϵ) 203 (3.89), 231 (4.06), 261 (3.74), 367 (3.74) nm; IR (ZnSe) ν_{max} 3334, 1622, 1539, 1490, 1412, 1326 cm^{-1}; ^1H NMR (600 MHz) and ^{13}C NMR (150 MHz) data, see Table 1; HRFABMS *m*/*z* 338.0959 $[M]^+$ (calcd. for $C_{18}H_{16}N_3O_2S$, 338.0963).

(−)-Discorhabdin Z (12): dark purple, amorphous solid; $[\alpha]_D^{25}$ −188 (*c* 0.009, MeOH), −150 (*c* 0.018, MeOH); CD (MeOH) $\Delta\epsilon$ 257.0 nm (+27.32), 306.0 nm (−14.74); UV (MeOH) λ_{max} (log ϵ) 369 (3.87) nm; IR (ZnSe) ν_{max} 3334, 2923, 1619, 1591, 1540, 1415, 1318 cm^{-1}; ^1H NMR (600 MHz) and ^{13}C NMR (150 MHz) data, see Table 1; HRFABMS *m*/*z* 356.1244 $[M]^+$ (calcd. for $C_{18}H_{18}N_3O_5$, 356.1246).

Makaluvamine D (13): dark red, amorphous solid; $[\alpha]_D^{25}$ 0 (*c* 0.009, MeOH); NMR, UV, IR, and MS data are consistent with those in the literature.[20]

(−)-Makaluvamine F (14): dark orange, amorphous solid; $[\alpha]_D^{25}$ −111 (*c* 0.009, MeOH), −39 (*c* 0.018, MeOH) {lit. −475 (*c* 0.0248, MeOH)};[20] NMR, UV, IR, and MS data are consistent with those in the literature.[20]

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Supporting Information Available: Images of ^1H, ^{13}C NMR and 2D NMR spectra for (−)-3-dihydrodiscorhabdin D (**11**) and (−)-discorhabdin Z (**12**); the energy-minimized structure and the comparison of experimental and calculated CD data for compound **11** are available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Blunt, J. W.; Copp, B. R.; Hu, W.-P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2008**, *25*, 35–94, and earlier reports in the series.
(2) Antunes, E. M.; Copp, B. R.; Davies-Coleman, M. T.; Samaai, T. *Nat. Prod. Rep.* **2005**, *22*, 62–72.
(3) Perry, N. B.; Blunt, J. W.; McCombs, J. D.; Munro, M. H. G. *J. Org. Chem.* **1986**, *51*, 5476–5478.
(4) Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron* **1988**, *44*, 1727–1734.
(5) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Higa, T.; Sakai, R. *J. Org. Chem.* **1988**, *53*, 4127–4128.
(6) Copp, B. R.; Fulton, K. F.; Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *J. Org. Chem.* **1994**, *59*, 8233–8238.
(7) Yang, A.; Baker, B. J.; Grimwade, J.; Leonard, A.; McClintock, J. B. *J. Nat. Prod.* **1995**, *58*, 1596–1599.
(8) D'Ambrosio, M.; Guerriero, A.; Chiasera, G.; Pietra, F. *Tetrahedron* **1996**, *52*, 8899–8906.
(9) Aubart, K. M.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 16–22.
(10) Ford, J.; Capon, R. J. *J. Nat. Prod.* **2000**, *63*, 1527–1528.
(11) Reyes, F.; Martin, R.; Rueda, A.; Fernandez, R.; Montalvo, D.; Gomez, C.; Sanchez-Puelles, J. M. *J. Nat. Prod.* **2004**, *67*, 463–465.
(12) Antunes, E. M.; Beukes, D. R.; Kelly, M.; Samaai, T.; Barrows, L. R.; Marshall, K. M.; Sincich, C.; Davies-Coleman, M. T. *J. Nat. Prod.* **2004**, *67*, 1268–1276.
(13) Harayama, Y.; Kita, Y. *Curr. Org. Chem.* **2005**, *9*, 1567–1588.
(14) Dijoux, M.-G.; Schnabel, P. C.; Hallock, Y. F.; Boswell, J. L.; Johnson, T. R.; Wilson, J. A.; Ireland, C. M.; van Soest, R.; Boyd, M. R.; Barrows, L. R.; Cardellina, J. H., II *Bioorg. Med. Chem.* **2005**, *13*, 6035–6044.

(15) Grkovic, T.; Kaur, B.; Webb, V. L.; Copp, B. R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1944–1946.
(16) El-Naggar, M.; Capon, R. J. *J. Nat. Prod.* **2009**, *72*, 460–464.
(17) Grkovic, T.; Copp, B. R. *Tetrahedron* **2009**, *65*, 6335–6340.
(18) Na, M.; Ding, Y.; Wang, B.; Tekwani, B. L.; Schinazi, R. F.; Franzblau, S.; Kelly, M.; Stone, R.; Li, X.-C.; Ferreira, D.; Hamann, M. T. *J. Nat. Prod.*, in press.
(19) Grkovic, T.; Ding, Y.; Li, X. -C.; Webb, V. L.; Ferreira, D.; Copp, B. R. *J. Org. Chem.* **2008**, *73*, 9133–9136.
(20) Radisky, D. C.; Radisky, E. S.; Barrows, L. R.; Copp, B. R.; Kramer, R. A.; Ireland, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 1632–1638.
(21) Schmidt, E. W.; Harper, M. K.; Faulkner, D. J. *J. Nat. Prod.* **1995**, *58*, 1861–1867.
(22) Venables, D. A.; Concepcion, G. P.; Matsumoto, S. S.; Barrows, L. R.; Ireland, C. M. *J. Nat. Prod.* **1997**, *60*, 408–410.
(23) Lang, G.; Pinkert, A.; Blunt, J. W.; Munro, M. H. G. *J. Nat. Prod.* **2005**, *68*, 1796–1798.
(24) Jang, K. H.; Chung, S.-C.; Shin, J.; Lee, S.-H.; Kim, T.-I.; Lee, H.-S.; Oh, K.-B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5366–5369.
(25) Diedrich, C.; Grimme, S. *J. Phys. Chem. A* **2003**, *107*, 2524–2539.

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