# Isolation and Characterization of Diastereomers of Discorhabdins H and K and Assignment of Absolute Configuration to Discorhabdins D, N, Q, S, T, and U

Tanja Grkovic,[†,‡] A. Norrie Pearce,[†] Murray H. G. Munro,[§] John W. Blunt,[§] Michael T. Davies-Coleman,[⊥] and Brent R. Copp*[,†]

*Department of Chemistry, The University of Auckland, Private Bag 92019, Auckland, New Zealand, Department of Chemistry, University of Canterbury, Private Bag 4800, Christchurch, New Zealand, and Department of Chemistry, Rhodes University, PO Box 94, Grahamstown, South Africa*

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Investigations of four different sponge populations of *Latrunculia* species collected in New Zealand waters has led to the characterization of a new diastereomer of discorhabdin H, named discorhabdin $H_2$, confirmation of the structure of discorhabdin K ((+)-**7**), and presentation of a new diastereomer, discorhabdin $K_2$ ((−)-**8**). In each case the structures were established by extensive NMR and MS studies and the absolute configurations interrogated by electronic circular dichroism (ECD). Absolute configurations were assigned to the known metabolites discorhabdins H, D, 2-hydroxy-D, N, and Q by comparison of ECD spectra with those recorded for discorhabdin alkaloids of defined absolute configuration, while the configurations of discorhabdins S, T, and U were assigned by semisynthesis from (+)-(6*S*,8*S*)-discorhabdin B.

Over 40 examples of pyrroloiminoquinone alkaloids belonging to the discorhabdin/prianosin/epinardin family have been reported from marine sponges (Figure 1).[1−21] The alkaloids typically exhibit wide-ranging biological activities, including antiproliferative, antibacterial, and antimalarial properties, the mechanism(s) of which are currently undefined.[22−24] Unfortunately the literature concerning this family of alkaloids contains trivial name duplications, inconsistencies in name assignments, and occurrences of incorrect structures being presented (in reviews).[22,24] In addition, the isolation of enantiomeric pairs of several discorhabdin alkaloids from New Zealand-sourced *Latrunculia* spp. sponges has further compounded uncertainty regarding the absolute configuration assigned to members of the series.[21] The same study reported the application of time-dependent density functional theory (TDDFT) calculations of electronic circular dichroism (ECD) spectra to yield a data set affording the ability to assign the core skeleton absolute configuration of discorhabdin A (**1**)-, B (**2**)-, G*/I (**3**)-, D (**4**)-, and W-type alkaloids.[21] Similar methodology has been used recently to present new discorhabdin alkaloid structures with defined absolute configuration.[18,19]

As part of our collective ongoing studies of the biologically active marine natural products isolated from *Latrunculia* species sponges, we now report the structure of a new diastereomer of discorhabdin H ((−)-**5**), which was been assigned the trivial name discorhabdin $H_2$ ((+)-**6**), confirm the structure of discorhabdin K ((+)-**7**), and present a new diastereomer, discorhabdin $K_2$ ((−)-**8**). In addition, direct comparison of experimental ECD spectra observed for a number of previously reported discorhabdin alkaloids has led to the establishment of absolute configurations for discorhabdin D ((+)-**4**), (+)-2-hydroxydiscorhabdin D (**16**), and discorhabdins N ((−)-**9**) and Q ((−)-**10**), while semisynthesis from (+)-(6*S*,8*S*)-discorhabdin B established the 6*S* configuration of discorhabdins S (**11**), T (**12**), and U (**13**).

* To whom correspondence should be addressed. Fax: 64-9-373-7422. E-mail: b.copp@auckland.ac.nz.
† The University of Auckland.
‡ Current address: Molecular Targets Laboratory, NCI-Frederick, Frederick, MD 21702.
§ University of Canterbury.
⊥ Rhodes University.

## Results and Discussion

Previous studies of the pyrroloiminoquinone chemistry of New Zealand *Latrunculia* spp. sponges have identified the existence of two distinct chemotypes: sponges collected in the remote SW corner of the country (Doubtful and Milford Sounds) yield discorhabdin alkaloids that are enantiomers of those isolated from sponges collected in other regions of New Zealand.[17,21] In an effort to isolate larger quantities of pyrroloiminoquinone alkaloids for biological evaluation and to examine the biosynthetic diversity of the local sponges, we have focused efforts upon four sponge populations, collected in Wellington Harbor, Kaikoura Coast, Doubtful Sound, and Milford Sound (see Supporting Information for locations). The Wellington Harbor (Barrett Reef) specimen of *Latrunculia (Biannulata) wellingtonesis*[25] yielded the previously reported metabolites (+)-discorhabdin A ((+)-**1**),[1,3] (+)-discorhabdin B ((+)-**2**),[3] (+)-discorhabdin D ((+)-**4**),[5] (+)-discorhabdin G*/I ((+)-**3**),[9,10a] (−)-discorhabdin L ((−)-**14**),[9] (−)-discorhabdin N ((−)-**9**),[10] (+)-discorhabdin Q ((+)-**10**),[12] (+)-1-thiomethyldiscorhabdin G*/I ((+)-**15**),[17] and (−)-discorhabdin H ((−)-**5**).[10a] Two Kaikoura Coast-sourced phenotypes[25] were examined, including a red-brown sponge, *Latrunculia (Latrunculia) trivetricillata*, which yielded discorhabdin C,[2,3] 3-dihydrodiscorhabdin C,[6,10a] (+)-discorhabdin D ((+)-**4**), and (+)-2-hydroxydiscorhabdin D ((+)-**16**),[4,7] while a single green specimen of *Latrunculia (Biannulata) kaikoura* yielded (+)-discorhabdin K ((+)-**7**).[24,26] As expected, collections of sponge specimens from Milford and Doubtful Sounds yielded the enantiomeric alkaloid series. Thus, a single specimen of Milford Sound-collected freeze-dried sponge *Latrunculia (Latrunculia) fiordensis*[25] yielded (−)-discorhabdin B ((−)-**2**), (−)-discorhabdin G*/I ((−)-**3**), (+)-discorhabdin $H_2$ ((+)-**6**), (+)-discorhabdin L ((+)-**14**), and (+)-discorhabdin W, while a Doubtful Sound-sourced specimen of *L. (Latrunculia) fiordensis* yielded discorhabdin C, (−)-discorhabdin B ((−)-**2**), (−)-discorhabdin G*/I ((−)-**3**), (+)-discorhabdin L ((+)-**14**), (−)-discorhabdin $K_2$ ((−)-**8**), (+)-discorhabdin W, and (+)-16a,17a-dehydrodiscorhabdin W.

(−)-Discorhabdin H ((−)-**5**) isolated from the Wellington-sourced *L. (Biannulata) wellingtonesis* exhibited $^1$H and $^{13}$C NMR and ECD data that were a close match to the data reported by Antunes et al. for the same alkaloid isolated from a South African collection of *Strongylodesma algoaensis*.[10a] Consistent with the South African study, NOESY correlations observed between proton resonances assigned to H-1 ($\delta_H$ 4.16), H-2 ($\delta_H$ 4.42), and H-7α ($\delta_H$ 2.82)

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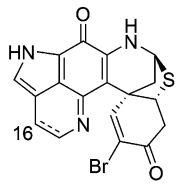
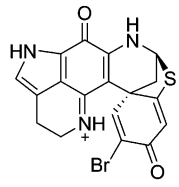
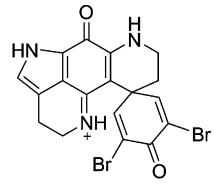


Prianosin A
Discorhabdin A
(+)-(5*R*,6*S*,8*S*) (**1**)

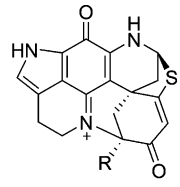
Prianosin B $\Delta^{16}$
(+)-(5*R*,6*S*,8*S*)



Discorhabdin B
(+)-(6*S*,8*S*) (**2**)
(-)-(6*R*,8*R*)

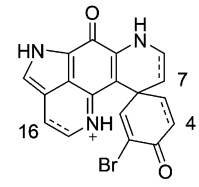


Discorhabdin C

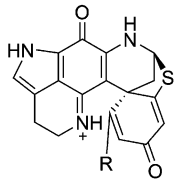


Prianosin C (corrected)
2-Hydroxydiscorhabdin D
(+)-(2*R*,6*R*,8*S*) R=OH (**16**)

Prianosin D (corrected)
Discorhabdin D
(+)-(2*S*,6*R*,8*S*) R=H (**4**)



Discorhabdin E $\Delta^4$
Discorhabdin F $\Delta^4$, $\Delta^{16}$
Discorhabdin G $\Delta^7$

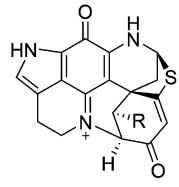


Discorhabdin G* / I
(+)-(6*S*,8*S*) R=H (**3**)
(-)-(6*R*,8*R*) R = H

Discorhabdin K
(+)-(6*S*,8*S*,7'*S**) R=thiomethylhistidine (**7**)

Discorhabdin $K_2$
(-)-(6*R*,8*R*,7'*S**) R=thiomethylhistidine (**8**)

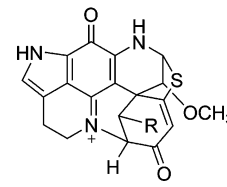
1-Thiomethyldiscorhabdin G* / I
(+)-(6*R*,8*S*) R=SMe (**15**)



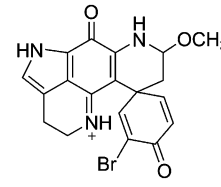
Discorhabdin H / J
(-)-(1*R*,2*R*,6*R*,8*S*,7'*S*)
R=thiomethylhistidine (**5**)

Discorhabdin $H_2$
(+)-(1*S*,2*S*,6*S*,8*R*,7'*S*)
R=thiomethylhistidine (**6**)

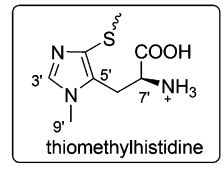
Discorhabdin L
(-)-(1*R*,2*S*,6*R*,8*S*) R=OH
(+)-(1*S*,2*R*,6*S*,8*R*) R=OH (**14**)

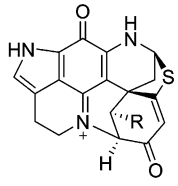


Discorhabdin M
(1?,2*R**,6*R**,7?,8*S**)
R =thiomethylhistidine



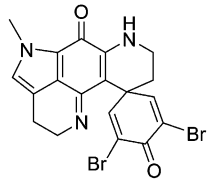
Discorhabdin O



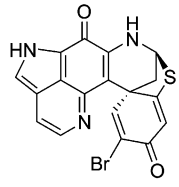



Discorhabdin N
(-)-(1*R*,2*S*,6*R*,8*S*) (**9**)
R=$NHCH_2COOH$

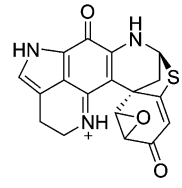
1-Aminodiscorhabdin D R=$NH_2$
1-Methoxydiscorhabdin D R=$OCH_3$



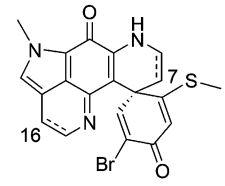
Discorhabdin P



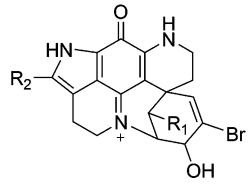
Discorhabdin Q
(+)-(6*S*,8*S*)
(-)-(6*R*,8*R*) (**10**)



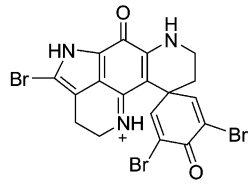
Discorhabdin R
(1?,2?,6*R**,8*S**)



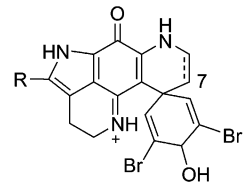
Discorhabdin S (6*S*) $\Delta^{16}$ (**11**)
Discorhabdin T (6*S*) $\Delta^7$, $\Delta^{16}$ (**12**)
Discorhabdin U (6*S*) $\Delta^7$ (**13**)



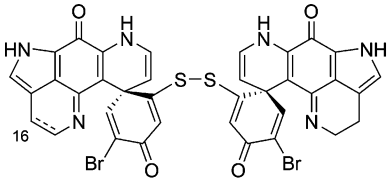
Discorhabdin V $R_1$=$R_2$=H
1-Hydroxy-14-bromodiscorhabdin V
$R_1$=OH, $R_2$=Br



14-Bromodiscorhabdin C

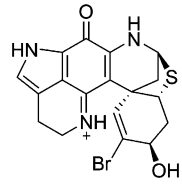


3-Dihydrodiscorhabdin C R=H
3-Dihydro-14-bromodiscorhabdin C R=Br
3-Dihydro-7,8-dehydrodiscorhabdin C R=H, $\Delta^7$
3-Dihydro-7,8-dehydro-14-bromodiscorhabdin C R=Br, $\Delta^7$

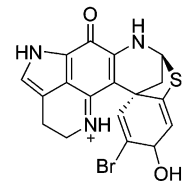


Discorhabdin W
(-)-(6*S*,6'*S*)
(+)-(6*R*,6'*R*)

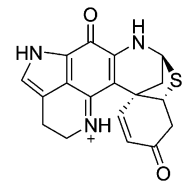
16a,17a-Dehydrodiscorhabdin W, $\Delta^{16}$
(-)-(6*S*,6'*S*)
(+)-(6*R*,6'*R*)



3-Dihydrodiscorhabdin A
(+)-(3*R*,5*R*,6*S*,8*S*)



3-Dihydrodiscorhabdin B



Debromodiscorhabdin A
(5*R**,6*S**,8*S**)

**Figure 1.** Continued.

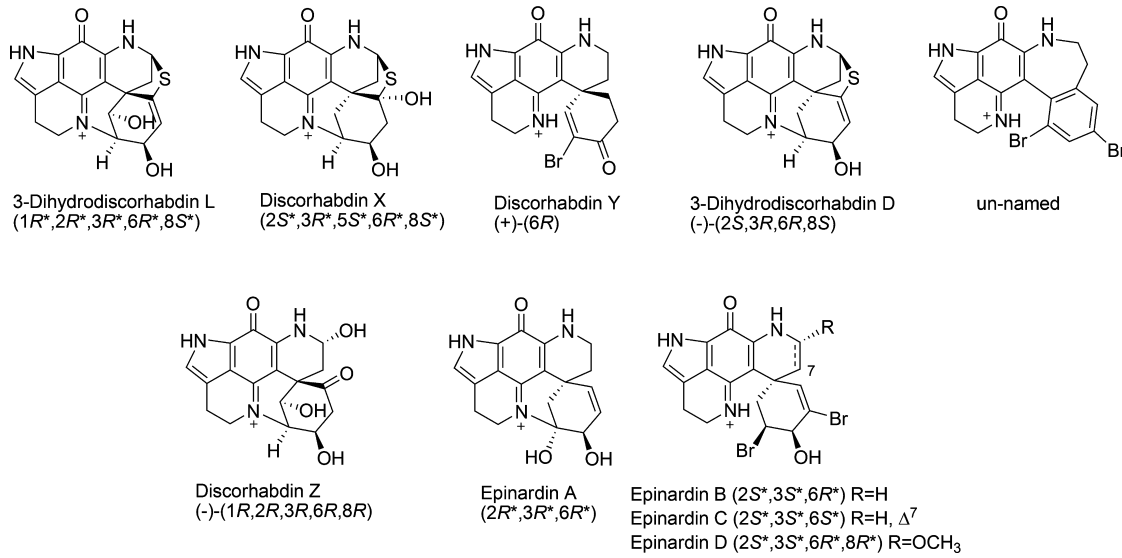



**Figure 1.** Structures of marine pyrroloiminoquinone alkaloids belonging to the discorhabdin, prianosin, and epinardin families.

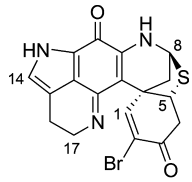



**Figure 2.** Numbering scheme of discorhabdin alkaloids.

established the relative configuration of the alkaloid as 1*R**,2*R**,6*R**,8*S** (for discorhabdin numbering see Figures 1 and 2).

Antunes et al. applied degradative techniques to establish the 7′*S* absolute configuration of the C-1 thiomethylhistidine substituent in **5**; however they were unable to assign absolute configurations to any of the remaining stereogenic centers. In order to complete the stereochemical assignment of (−)-discorhabdin H, the experimental ECD spectrum of the compound was compared to that of a structurally related discorhabdin alkaloid of previously defined configuration. An example of such a model compound is (−)-(1*R*,2*S*,6*R*,8*S*)-discorhabdin L, (−)-**14**, for which TDDFT calculations of ECD spectra were used to establish the absolute configuration.[21] The experimental ECD spectrum of (−)-discorhabdin H ((−)-**5**) was essentially identical to that observed for (−)-(1*R*,2*S*,6*R*,8*S*)-discorhabdin L ((−)-**14**) (Figure 3), thereby establishing that (−)-discorhabdin H has the 1*R*,2*R*,6*R*,8*S*,7′*S* configuration. It is relevant to note the negligible effect of the presence of a thiomethylhistidine residue on the ECD spectrum of (−)-**5**.

A Milford Sound-sourced specimen of *Latrunculia (Latrunculia) fiordensis* yielded a dextrorotary ($[\alpha]_D$ +40) alkaloid. The HRFAB mass spectrometric data confirmed that the alkaloid was isobaric with (−)-(1*R*,2*R*,6*R*,8*S*,7′*S*)-discorhabdin H ((−)-**5**), while the $^1$H and $^{13}$C NMR chemical shifts observed for (+)-**6** (Table 1) were similar, *but not identical*, to those observed for (−)-**5**. The differences were centered upon the resonances assigned to H-1 and Ha-17 (see Supporting Information). Extensive analysis of the HSQC and HMBC NMR data established that both alkaloids shared a common carbon skeleton, while interpretation of a NOESY NMR experiment also established that both alkaloids shared the same relative configuration at C-1/C-2/C-6/C-8. The observation of opposite sign of specific rotation and essentially equal and opposite experimental ECD spectra observed for both alkaloids (see Experimental Section and Supporting Information) led to the conclusion that (−)-(1*R*,2*R*,6*R*,8*S*,7′*S*)-**5** and (+)-**6** were in fact diastereomers, possessing enantiomeric configurations associated with the pyrroloiminoquinone skeleton (C-1/C-2/C-6/C-8), but with the same (7′*S*) configuration of the pendant thiomethylhistidine residue. The natural product (+)-**6** was assigned the trivial name (+)-(1*S*,2*S*,6*S*,8*R*,7′*S*)-discorhabdin $H_2$.

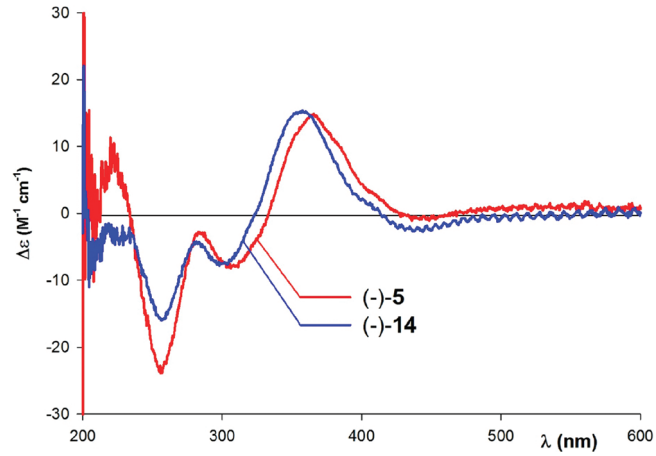



**Figure 3.** Experimental ECD spectra (MeOH) of the TFA salts of (−)-(1*R*,2*S*,6*R*,8*S*)-discorhabdin L ((−)-**14**) (blue) and Wellington-sourced (−)-diastereomer of discorhabdin H ((−)-**5**) (red).

Compound **8** was isolated as an optically active ($[\alpha]_D$ −260) dark purple-brown oil trifluoroacetate salt from a single specimen of a Doubtful Sound-sourced *Latrunculia (Latrunculia) fiordensis* sponge. HRFABMS established a molecular formula for **8** of $C_{25}H_{23}N_6O_4S_2$. The $^1$H and $^{13}$C NMR data observed for **8** (Table 2) were similar to those observed for discorhabdin H (**5**), indicating the presence of a pyrroloiminoquinone skeleton and a thiomethylhistidine fragment. Differences in the NMR spectra between **8** and **5** corresponded to those resonances assigned to C-1 and C-2. The $sp^3$ methine resonances of C-1 ($\delta_C$ 50.7, $\delta_H$ 4.16) and C-2 ($\delta_C$ 66.8, $\delta_H$ 4.42) observed for **5** were absent in **8**, and new resonances attributable to an $sp^2$ quaternary carbon ($\delta_C$ 163.3, C-1) and an $sp^2$ methine ($\delta_C$ 126.3, $\delta_H$ 5.94 (d, $J$ = 1.3 Hz), C-2) were observed. Direct comparison of $^1$H and $^{13}$C NMR data reported for 1-thiomethyldiscorhabdin G*/I (**15**)[17] supported the conclusion that **8** represented a ring-opened, oxidized analogue of discorhabdin H. This structure has previously been assigned the trivial name discorhabdin K,[26] although fully assigned spectroscopic data have not been published before now.

The original source of discorhabdin K was a Kaikoura Coast-sourced *Latrunculia (Biannulata) kaikoura*.[25] Re-examination of

**Table 1.** NMR Data for Milford Sound-Sourced (+)-Discorhabdin $H_2$ ((+)-**6**) TFA Salt ($CD_3OD$)

| no. | $\delta_C$ | $\delta_H$ (*J* in Hz) | HMBC[a] |
|---|---|---|---|
| 1 | 51.2 | 4.01, d (3.1) | 4′, 2, 3, 5, 6, 20 |
| 2 | 67.0 | 4.46, d (3.1) | 1, 3, 6, 17, 19 |
| 3 | 183.7 | | |
| 4 | 114.5 | 6.19, s | 2, 5, 6, 20 |
| 5 | 171.8 | | |
| 6 | 47.3 | | |
| 7A | 39.4 | 3.34, dd (12.0, 3.6) | 1, 5, 6, 8, 20 |
| 7B | | 2.76, br d (12.0) | 5, 6, 8, 20 |
| 8 | 64.1 | 5.67, dd (3.6, 1.1) | 5, 6, 10 |
| 10 | 148.4 | | |
| 11 | 167.3 | | |
| 12 | 125.6 | | |
| 14 | 127.4 | 7.09, s | 12, 15, 21 |
| 15 | 119.4 | | |
| 16A | 20.7 | 3.16, m | 15, 21 |
| 16B | | 3.03, ddd (16.8, 7.0, 2.7) | |
| 17A | 52.8 | 4.07, ddd (14.0, 7.3, 2.7) | 15, 16, 19 |
| 17B | | 3.88, td (14.0, 7.0) | 15, 16, 19 |
| 19 | 150.4 | | |
| 20 | 101.7 | | |
| 21 | 122.8 | | |
| 2′ | 141.3 | 7.90, s | 4′, 5′, 9′ |
| 4′ | 128.7 | | |
| 5′ | 132.9 | | |
| 6′A | 26.3 | 3.43, dd (15.3, 8.3) | 4′, 5′, 7′, 8′ |
| 6′B | | 3.23, dd (15.3, 7.5) | 4′, 5′, 7′, 8′ |
| 7′ | 53.4 | 4.10, br t (7.9) | 5′, 6′, 8′ |
| 8′ | 171.2 | | |
| 9′ | 33.2 | 3.75, s | 2′, 5′ |

[a] HMBC correlations, optimized for 8.3 Hz, are from proton(s) stated to the indicated carbon.

**Table 2.** NMR Data for Doubtful Sound-Sourced (−)-Discorhabdin $K_2$ ((−)-**8**) TFA Salt ($CD_3OD$)

| no. | $\delta_C$ | $\delta_H$ (*J* in Hz) | COSY | HMBC[a] |
|---|---|---|---|---|
| 1 | 163.3 | | | |
| 2 | 126.3 | 5.94, d (1.3) | H-4 | 1, 4, 6 |
| 3 | not observed | | | |
| 4 | 119.2 | 6.09, d (1.3) | H-2 | 2, 6 |
| 5 | 171.3 | | | |
| 6 | 52.8 | | | |
| 7A | 44.3 | 3.11, br d (12.0) | H-8 | 6, 8, 20 |
| 7B | | 2.75, dd (12.0, 3.9) | H-8 | 6, 8, 20 |
| 8 | 60.8 | 5.64, dd (3.9, 1.1) | H-7A, H-7B | 5, 6, 10 |
| 10 | 153.6[b] | | | |
| 11 | not observed | | | |
| 12 | 125.5[b] | | | |
| 14 | 128.1 | 7.22, s | | 12, 15, 21 |
| 15 | 122.2 | | | |
| 16 | 19.0 | 2.96, m | | 14, 15, 17, 21 |
| 17A | 46.2 | 4.09, m | H-16, H-17B | 15, 16, 19 |
| 17B | | 3.90, m | H-16, H-17A | 15, 16, 19 |
| 19 | 156.5 | | | |
| 20 | 99.1[b] | | | |
| 21 | 124.0[b] | | | |
| 2′ | 142.8 | 7.94, s | H-9′ | 4′, 5′ |
| 4′ | 124.7 | | | |
| 5′ | 134.7 | | | |
| 6′A | 26.2 | 3.44, dd (15.6, 7.8) | H-6′B, H-7′ | 5′, 7′, 8′ |
| 6′B | | 3.19, m | H-6′A, H-7′ | 5′, 7′, 8′ |
| 7′ | 53.5[b] | 4.06, t (7.8) | H-6′A, H-6′B | 5′, 6′, 8′ |
| 8′ | 171.0[b] | | | |
| 9′ | 33.1 | 3.79, s | H-2′ | 2′, 5′ |

[a] HMBC correlations, optimized for 8.3 Hz, are from proton(s) stated to the indicated carbon. [b] Denotes values were taken from correlations observed in a $^1H-^{13}C$ HMBC NMR experiment.

the chemistry of the original collection voucher specimen of this sponge species afforded (+)-discorhabdin K ((+)-**7**) as a trifluoroacetate salt. The Doubtful Sound-sourced and Kaikoura-sourced discorhabdin K samples exhibited subtle differences in $^1H$ and $^{13}C$ NMR data centered upon resonances of the spiro-ring and the thiohistidine moiety (Tables 2 and 3), suggesting the alkaloids were related as diastereomers rather than being enantiomeric. The two compounds exhibited opposite signed specific rotation values of −260 and +340 for samples originating from Doubtful Sound and the Kaikoura Coast, respectively, and the experimental ECD spectra of (+)-**7** and (−)-**8** were equal and opposite (see Experimental Section and Supporting Information). These chiroptical results indicated that, just as for discorhabdin H (**5**), the induced circular dichroism properties of this molecule were due to the core discorhabdin structure only. The absolute configurations of the discorhabdin chromophore of (+)-**7** and (−)-**8** were assigned by comparison of ECD spectra with that observed for discorhabdin G*/I (**3**)[21] and 1-thiomethyldiscorhabdin G*/I (**15**).[17] The ECD spectrum of the (+)-**7** diastereomer was in close agreement with that of (+)-(6*S*,8*S*)-discorhabdin G*/I ((+)-**3**) and (+)-(6*R*,8*S*)-1-thiomethyldiscorhabdin G*/I ((+)-**15**),[17] thereby establishing the absolute configuration of the C-6 and C-8 stereogenic centers as 6*S*,8*S* (Figure 4).

**Table 3.** NMR Data for Kaikoura-Sourced (+)-Discorhabdin K ((+)-**7**) TFA Salt ($CD_3OD$)

| no. | $\delta_C$ | $\delta_H$ (*J* in Hz) | COSY | HMBC[a] |
|---|---|---|---|---|
| 1 | 163.5 | | | |
| 2 | 126.0 | 5.90, d (1.1) | H-4 | 1, 4, 6 |
| 3 | 181.9 | | | |
| 4 | 119.3 | 6.09, br s | H-2 | 2, 6 |
| 5 | 171.2 | | | |
| 6 | 52.8 | | | |
| 7A | 44.4 | 3.10, br d (11.9) | H-8 | 5, 6, 8, 20 |
| 7B | | 2.74, dd (11.9, 3.7) | H-8 | 6, 8, 20 |
| 8 | 60.8 | 5.64, dd (3.7, 0.9) | H-7A, H-7B | 5, 6, 10 |
| 10 | 153.5 | | | |
| 11 | 166.1 | | | |
| 12 | 125.6 | | | |
| 14 | 128.1 | 7.23, s | | 12, 15, 21 |
| 15 | 122.2 | | | |
| 16 | 19.1 | 2.96, m | | 15, 17, 21 |
| 17A | 46.2 | 4.10, m | H-16, H-17B | 15, 16, 19 |
| 17B | | 3.89, m | H-16, H-17A | 15, 16, 19 |
| 19 | 156.5 | | | |
| 20 | 99.3 | | | |
| 21 | 124.3 | | | |
| 2′ | 142.9 | 7.94, s | H-9′ | 4′, 5′ |
| 4′ | 124.9 | | | |
| 5′ | 134.7 | | | |
| 6′A | 26.1 | 3.37, dd (15.3, 8.1) | H-6′B, H-7′ | 5′, 7′, 8′ |
| 6′B | | 3.24, dd (15.3, 7.3) | H-6′A, H-7′ | 5′, 7′, 8′ |
| 7′ | 53.3 | 4.05, m | H-6′A, H-6′B | 4′, 5′, 6′, 8′ |
| 8′ | 171.1 | | | |
| 9′ | 33.1 | 3.79, s | H-2′ | 2′, 5′ |

[a] HMBC correlations, optimized for 8.3 Hz, are from proton(s) stated to the indicated carbon.

The absolute configuration of the discorhabdin core of Doubtful Sound-sourced (−)-**8** was assigned as 6*R*,8*R* by virtue of the fact that the circular dichroism Cotton effects observed in the ECD spectrum were of equal wavelength but opposite magnitude to those observed for (+)-(6*S*,8*S*)-**7** (see Supporting Information). The natural product (−)-**8** was assigned the trivial name discorhabdin $K_2$. The absolute configuration at 7′ for both diastereomers remains unresolved but is assumed to be *S* by analogy with discorhabdin H.

During the course of this and previous studies of *Latrunculia* sp. a number of known pyrroloiminoquinone alkaloids, with currently undefined absolute configuration, were purified. Included among these metabolites were discorhabdins D (**4**),[4,5] N (**9**),[10a] and Q (**10**).[12] Structurally, **4** and **9** are related to discorhabdin L (**14**), being examples of C-2−N-18 ring-closed congeners, while discorhabdin Q is $\Delta^{16}$ discorhabdin B (**2**). As the absolute configurations of both **14** and **2** are known,[21] comparison of ECD spectra was again used to aid in the assignment of absolute configurations of **4**, **9**, and **10**.

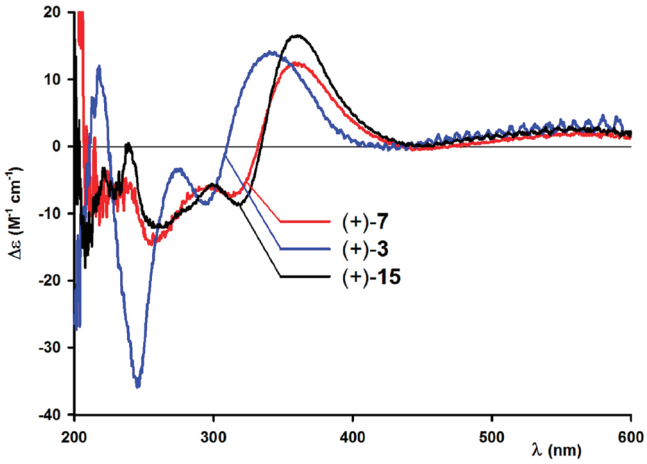



**Figure 4.** Experimental ECD spectra (MeOH) of the TFA salts of (+)-(6*S*,8*S*)-discorhabdin G*/I ((+)-**3**) (blue), (+)-(6*R*,8*S*)-1-thiomethyldiscorhabdin G*/I ((+)-**15**) (black), and Kaikoura-sourced (+)-diastereomer of discorhabdin K ((+)-**7**) (red).

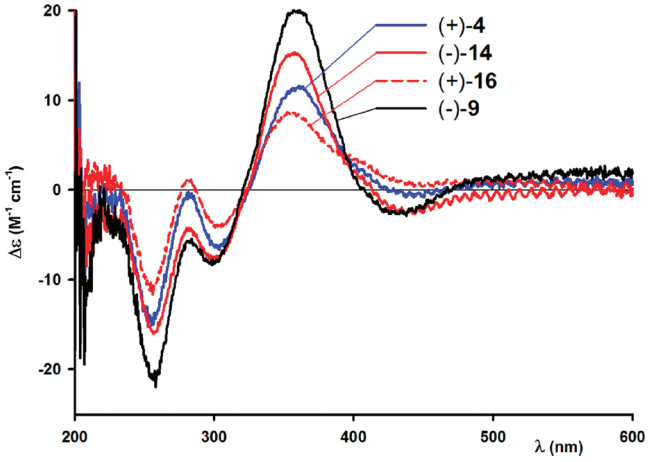



**Figure 5.** Experimental ECD spectra (MeOH) of the TFA salts of Wellington Harbor-sourced (−)-(1*R*,2*S*,6*R*,8*S*)-discorhabdin L ((−)-**14**) (red), (+)-discorhabdin D ((+)-**4**) (blue), (+)-2-hydroxydiscorhabdin D ((+)-**16**) (dashed), and (−)-discorhabdin N ((−)-**9**) (black).

The ECD spectrum of Wellington-sourced (+)-discorhabdin D (**4**) was found to be in close agreement with that of Wellington-sourced (−)-(1*R*,2*S*,6*R*,8*S*)-discorhabdin L (**14**) (Figure 5), thereby confirming the absolute configuration of (+)-**4** as 2*S*,6*R*,8*S*. This agrees with the absolute configuration assigned to the alkaloid previously characterized as (+)-prianosin D.[4a,b] The related metabolite (+)-2-hydroxydiscorhabdin D (prianosin C) ((+)-**16**) was originally reported from Japanese collections of *Prianos melanos*[4a,b] and subsequently from New Zealand specimens of *Latrunculia* sp.[7] In their publication, Kobayashi et al. established the absolute configuration of (+)-prianosin C free base to be 2*R*,6*R*,8*S* by comparison of ECD data with that observed for prianosin A (discorhabdin A), the 5*R*,6*S*,8*S* configuration of which had been secured by an X-ray crystal study.[1] In this current study, it was observed that the ECD spectrum of the Kaikoura-sourced (+)-2-hydroxydiscorhabdin D ((+)-**16**) was similar to that of the Wellington-sourced (−)-(1*R*,2*S*,6*R*,8*S*)-discorhabdin L ((−)-**14**) (Figure 5), further confirming the absolute configuration of (+)-2-hydroxydiscorhabdin D as 2*R*,6*R*,8*S*.

The $^{1}$H and $^{13}$C NMR data ($d_6$-DMSO) observed for the Wellington-sourced (−)-discorhabdin N ((−)-**9**) were identical to those reported by Antunes et al. for the same alkaloid isolated from a South African collection of *Latrunculia bellae*.[10a] The South African group did not specify the relative configuration of **9**. In the current study, a combination of NOESY dipolar coupling correlations and *J*-based configurational analysis was used to establish a 1*R**,2*S**,6*R**,8*S** relative configuration for (−)-**9**. NOESY correlations were observed between the H-1 ($\delta_H$ 3.60) resonance and both H-2 ($\delta_H$ 4.33) and one of the diastereotopic H-7 methylene proton resonances ($\delta_H$ 2.47) (Figure 6). The α-face orientation of this specific methylene proton was confirmed by interpretation of a heteronuclear long-range coupling *J*-HMBC NMR experiment,[27] which detected a large $^{3}J_{CH}$ coupling constant (10.5 Hz) between the proton H-7α ($\delta_H$ 2.47) and C-5 ($\delta_C$ 168.7). This result required an antiperiplanar geometrical relationship between H-7α and C-5 (Figure 6), confirming a relative configuration of 1*R**,2*S**,6*R**,8*S**.[28] The ECD spectrum of (−)-**9** was essentially identical to that of (−)-(1*R*,2*S*,6*R*,8*S*)-discorhabdin L ((−)-**14**) (Figure 5), thereby establishing the absolute configuration of (−)-discorhabdin N as 1*R*,2*S*,6*R*,8*S*.

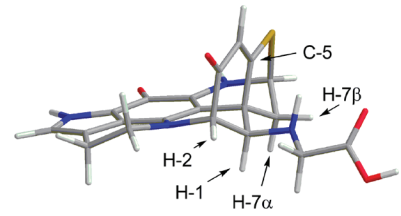



**Figure 6.** A $^{3}J_{CH}$ coupling constant of 10.5 Hz requires an antiperiplanar geometrical relationship between H-7α and C-5, defining the relative configuration of discorhabdin N (**9**) as 1*R**,2*S**,6*R**,8*S**.

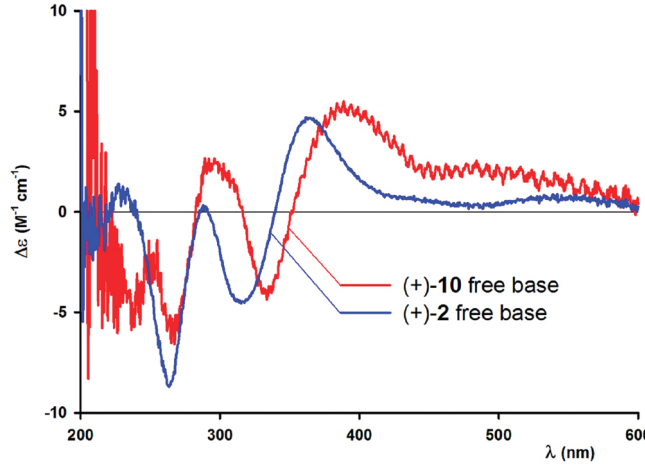
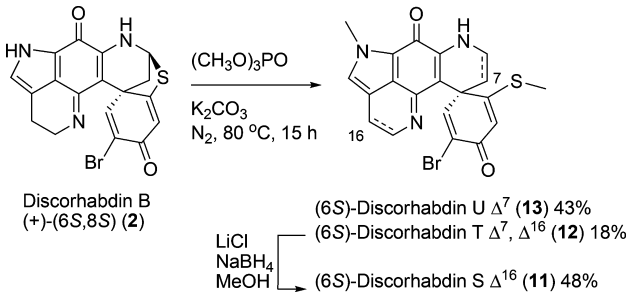



**Figure 7.** Experimental ECD spectra (MeOH) of the free base forms of (+)-(6*S*,8*S*)-discorhabdin B ((+)-**2**) (blue) and Wellington-sourced (+)-discorhabdin Q ((+)-**10**) (red).

The ECD spectrum of the free base form of Wellington Harbor-sourced (+)-discorhabdin Q ((+)-**10**) showed similarities of the sign of the Cotton effect maxima to that of the free base form of Wellington-sourced (+)-(6*S*,8*S*)-discorhabdin B ((+)-**2**) (Figure 7), thereby establishing the absolute configuration of (+)-**10** as 6*S*,8*S*. Further confirmation of this stereochemical assignment was achieved by semisynthesis, whereby heating (+)-(6*S*,8*S*)-discorhabdin B ((+)-**2**) at reflux in aqueous acetone with an excess of $K_2CO_3$ yielded (+)-**10**, which exhibited identical chiroptical properties to those observed for the isolated natural product.

In the original report of the isolation of discorhabdin Q (**10**) from Australian and South Pacific collections of *Latrunculia* and *Zyzzya* spp. sponges, it was observed that the alkaloid exhibited a specific rotation of $[\alpha]_D = -904$.[12] Since this value is equal in magnitude but opposite in sign to the $[\alpha]_D$ value observed for (+)-(6*S*,8*S*)-**10** (+720), we concluded that the Australian and South Pacific sponge samples contained the 6*R*,8*R* enantiomer of discorhabdin Q.[29]

**Scheme 1.** Semisynthesis of Discorhabdins S, T, and U from Discorhabdin B




Discorhabdins S (**11**), T (**12**), and U (**13**) are chiral alkaloids isolated from a deep sea collection of *Batzella* sp., but for which no specific rotation or ECD data have been reported.[14] In an effort to assign absolute configuration to **12** and **13**, we have made use of the previously reported semisynthetic conversion of discorhabdin B to discorhabdin U.[30] Thus, reaction of (+)-(6*S*,8*S*)-discorhabdin B ((+)-**2**) in trimethylphosphate with $K_2CO_3$ afforded discorhabdin U with an observed $[\alpha]_D$ of +222, which, assuming the resolute nature of the configuration at C-6 under these mild reaction conditions, assigned a 6*S* absolute configuration to (+)-**13** (Scheme 1). As expected, the same reaction with enantiomeric (−)-(6*R*,8*R*)-discorhabdin B yielded (−)-(6*R*)-discorhabdin U ($[\alpha]_D$ −220). Further exposure of (+)-(6*S*)-discorhabdin U to $K_2CO_3$ in DMF yielded (+)-(6*S*)-discorhabdin T (**12**) ($[\alpha]_D$ +280), the $^1$H NMR spectrum of which was identical to that reported for the natural product.[14] Reduction of the enamine $\Delta^7$ present in (6*S*)-**12** with LiCl−$NaBH_4$ yielded (6*S*)-discorhabdin S (**11**), which was found to be dextrorotary (+80) as the free base, but levorotary (−120) as the trifluoroacetate salt.

Cytotoxicity toward murine and human tumor cell lines associated with the pyrroloiminoquinone alkaloids has been a driving force in the isolation of this wide range of structural types. Of those reported to date, discorhabdins A, B, C, U, and W represent the more potent examples, with $IC_{50}$ values of approximately 0.1 $\mu$M.[1−3,11,15] Those alkaloids that embody ring closure between N-18 and C-2, e.g., discorhabdins D, L, and N, typically exhibit more modest activity, with $IC_{50}$ values of 1−15 $\mu$M.[5,9,10a] In the present study, diastereomers of both discorhabdin H ((−)-**5** and (+)-**6**) and discorhabdin K ((+)-**7** and (−)-**8**) were essentially inactive against the murine leukemia P388 cell line, with $IC_{50}$ values of >8.2 $\mu$M. These results suggest that the presence of bulky substituents on the spirodienone ring and N-18 and C-2 ring closure are detrimental to the cytotoxic action of the discorhabdin alkaloids.

In summary, our studies of the chemical diversity of *Latrunculia* species sponges have led to the characterization of two new discorhabdin metabolites, discorhabdins $H_2$ and $K_2$, the clarification of the structure of discorhabdin K, and either the confirmation or establishment of the absolute configurations of 2-hydroxydiscorhabdin D and discorhabdins D, H, N, Q, S, T, and U.

## Experimental Section

**General Experimental Procedures.** Optical rotations were measured with a Perkin-Elmer 341 polarimeter. Infrared spectra were recorded using a Perkin-Elmer Spectrum One Fourier-transform IR spectrometer as a dry film. Ultraviolet−visible spectra were run as methanol solutions on a UV-2102 PC Shimadzu UV−vis scanning spectrophotometer. ECD spectra were recorded on an Applied Photophysics Pi Star spectrophotometer. NMR spectra were recorded on either a Bruker Avance DRX-600 spectrometer operating at 600 MHz for $^1$H nuclei and 150 MHz for $^{13}$C nuclei, a Bruker Avance DRX-400 spectrometer operating at 400 MHz for $^1$H nuclei and 100 MHz for $^{13}$C nuclei, or a Bruker Avance DRX-300 spectrometer operating at 300 MHz for $^1$H nuclei and 75 MHz for $^{13}$C nuclei. Residual solvent signals and the solvent carbons were used as internal references (DMSO-$d_6$: $\delta_H$ 2.50, $\delta_C$ 39.43; $CD_3OD$: $\delta_H$ 3.30, $\delta_C$ 49.05; $CDCl_3$: $\delta_H$ 7.25, $\delta_C$ 77.0). Standard Bruker pulse sequences were utilized. HRMS were acquired on either a VG-7070 or a Bruker micrOTOF Q II mass spectrometer. Analytical reversed-phase HPLC was run on a Waters 600 HPLC photodiode array system using either an Alltech $C_{18}$ or $C_8$ column (3 $\mu$m Econosphere Rocket, 7 × 33 mm) and eluting with a linear gradient of $H_2O$ (0.05% TFA) to MeCN over 13.5 min at 2 mL/min. Reversed-phase flash column chromatography was carried out on $C_{18}$, $C_8$, and CN LiChroprep stationary support with a pore size of 40−63 $\mu$m. Gel filtration flash chromatography was carried out using Sephadex LH-20 (Pharmacia). Cytotoxicity against the P388 D1 murine leukemia cell line was measured using a standard protocol.[31]

**Sponge Material.** All sponge specimens used in this study were from either the National Institute of Water and Atmospheric (NIWA) Research or University of Canterbury collections and have been previously described.[25]

**Extraction and Isolation.** A single specimen of wet *Latrunculia* (*Biannulata*) *wellingtonesis* (code 98BR1-1) was extracted with MeOH. The solvent was filtered and then removed in vacuo to give a dark brown extract (4.43 g), which was subjected to $C_{18}$, $C_8$, and CN flash (MeOH, $H_2O$−TFA (0.05%)) and Sephadex LH-20 (MeOH−TFA (0.05%)) column chromatography. The following discorhabdin alkaloids were isolated: (+)-discorhabdin A (**1**) trifluoroacetate salt (6.6 mg, 0.15% wet weight), (+)-discorhabdin B (**2**) trifluoroacetate salt (80.6 mg, 1.82% wet weight), (+)-discorhabdin D (**4**) trifluoroacetate salt (12.7 mg, 0.29% wet weight), (+)-discorhabdin G*/I (**3**) trifluoroacetate salt (24.6 mg, 0.56% wet weight), (−)-discorhabdin H (**5**) trifluoroacetate salt (52.9 mg, 1.19% wet weight), (−)-discorhabdin L (**14**) trifluoroacetate salt (39.0 mg, 0.88% wet weight), (−)-discorhabdin N (**9**) trifluoroacetate salt (20.0 mg, 0.45% wet weight), (+)-discorhabdin Q (**10**) trifluoroacetate salt (4.8 mg, 0.11% wet weight), and (+)-1-thiomethyldiscorhabdin G*/I (**15**) trifluoroacetate salt (3.2 mg, 0.072% wet weight).

A single specimen of the freeze-dried green sponge *Latrunculia (Biannulata) kaikoura* (code 91K1-1) (25.84 g) was extracted with MeOH (4 × 200 mL). The solvent was filtered and then removed in vacuo to give a dark brown extract (5.94 g). A portion of the extract (310 mg) was subjected to Sephadex LH-20 and $C_{18}$ flash (MeOH, $H_2O$−TFA (0.05%)) chromatography, yielding (+)-discorhabdin K (**7**) trifluoroacetate salt (1.10 mg, 0.08% dry weight).

Freeze-dried specimens of the red sponge *Latrunculia (Latrunculia) trivetricillata* (code MNP 6116) (12.36 g) were extracted with MeOH (4 × 200 mL). The solvent was filtered and then removed in vacuo to give a purple-brown extract (2.74 g). A portion of the extract (506 mg) was subjected to Sephadex LH-20 (MeOH (0.05% TFA)) and $C_{18}$ flash (MeOH, $H_2O$−TFA (0.05%)) chromatography, yielding discorhabdin C trifluoroacetate salt (48.9 mg, 2.13% dry weight), (+)-2-hydroxydiscorhabdin D ((+)-**16**) trifluoroacetate salt (0.6 mg, 0.026% dry weight), (+)-discorhabdin D ((+)-**4**) trifluoroacetate salt (3.7 mg, 0.16% dry weight), and 3-dihydodiscorhabdin C trifluoroacetate salt (11.0 mg, 0.48% dry weight).

A single specimen of Milford Sound-collected freeze-dried sponge *Latrunculia (Latrunculia) fiordensis* (code 95MS1-(1-10)) was extracted with MeOH (4 × 200 mL). The solvent was filtered and then removed in vacuo to give a dark brown extract (2.79 g). A portion of the extract (370 mg) was subjected to Sephadex LH-20 and $C_{18}$ flash (MeOH, $H_2O$−TFA (0.05%)) chromatography, yielding (−)-discorhabdin B ((−)-**2**) trifluoroacetate salt (1.12 mg, 0.06% dry weight), (−)-discorhabdin G*/I ((−)-**3**) trifluoroacetate salt (0.71 mg, 0.039% dry weight), (+)-discorhabdin $H_2$ ((+)-**6**) trifluoroacetate salt (3.50 mg, 0.19% dry weight), (+)-discorhabdin L ((+)-**14**) trifluoroacetate salt (1.35 mg, 0.073% dry weight), and (+)-discorhabdin W trifluoroacetate salt (6.77 mg, 0.37% dry weight).

A single specimen of freeze-dried Doubtful Sound-sourced *Latrunculia (Latrunculia) fiordensis* sponge (code 95DS1-(1-10)) (4.78 g) was extracted with MeOH (4 × 200 mL). The solvent was filtered and then removed in vacuo to give a dark brown extract (1.290 g). A portion of the extract (420 mg) was subjected to combinations of Sephadex LH-20 (MeOH) and $C_{18}$ flash (MeOH, $H_2O$−TFA (0.05%)) chromatography, yielding discorhabdin C trifluoroacetate salt (0.1 mg, 0.006% dry weight), (−)-discorhabdin B ((−)-**2**) trifluoroacetate salt (2.49 mg, 0.16% dry weight), (−)-discorhabdin G*/I ((−)-**3**) trifluoroacetate salt (1.50 mg, 0.096% dry weight), (+)-discorhabdin L ((+)-**14**) trifluoroacetate salt (1.80 mg, 0.12% dry weight), (−)-discorhabdin $K_2$ ((−)-**8**) trifluoroacetate salt (2.14 mg, 0.14% dry weight), (+)-discorhabdin W (2.13 mg as free base, 0.13% dry weight; and 5.53 mg converted to

a TFA salt, 0.36% dry weight), and (+)−16a,17a-dehydrodiscorhabdin W (converted to a TFA salt, 0.6 mg, 0.04% dry weight).

**(+)-(2*S*,6*R*,8*S*)-Discorhabdin D ((+)-4):** TFA salt, green oil, $[\alpha]^{20}_D$ = +80 (*c* 0.025, MeOH); $[\alpha]_D$ = 0, $[\alpha]_{578}$ = 0, $[\alpha]_{546}$ = −58 (*c* 0.05, MeOH); UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 203 (4.22) 249 (4.24), 283 (4.05), 321 (3.84), 397 (3.82), 584 (2.89) nm; ECD (MeOH) $\lambda_{max}$ ($\Delta\varepsilon$) 256 (−14.8), 281 (−0.3), 303 (−6.5), 325 (0), 360 (+11.5), 420 (0) nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 13.16 (1H, br s, *N*H-13), 10.71 (1H, br s, *N*H-9), 7.28 (1H, br s, H-14), 6.13 (1H, s, H-4), 5.67 (1H, br s, H-8), 4.37 (1H, br s, H-2), 4.04 (1H, m, H-17A), 3.83 (1H, m, H-17B), 3.03 (2H, m, H-16), 2.91 (1H, d, *J* = 13.0 Hz, H-1A), 2.70 (1H, d, *J* = 12.1 Hz, H-7A), 2.56 (1H, d, *J* = 12.1 Hz, H-7B) 2.44 (1H, d, *J* = 13.0 Hz, H-1B); (+)-HRFABMS *m*/*z* [M + H]$^+$ 336.08051 (calcd for $C_{18}H_{14}N_3O_2S$, 336.08067).

**(−)-(1*R*,2*R*,6*R*,8*S*,7′*S*)-Discorhabdin H ((−)-5):** TFA salt, green oil, $[\alpha]^{20}_D$ = −77, $[\alpha]_{578}$ = −210, $[\alpha]_{546}$ = −330 (*c* 0.05, MeOH); UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 246 (4.31), 288 (4.08), 322 (3.91), 397 (3.92), 585 (2.90) nm; ECD (MeOH) $\lambda$ ($\Delta\varepsilon$) 212 (0), 220 (+11.0), 233 (0), 255 (−23.6), 283 (−2.9), 305 (−8.11), 333 (0), 366 (+14.9) 427 (0) nm; $^1$H NMR ($CD_3OD$, 600 MHz) $\delta$ 8.14 (1H, s, H-2′), 7.09 (1H, s, H-14), 6.19 (1H, s, H-4), 5.67 (1H, dd, *J* = 3.5, 1.0 Hz, H-8), 4.42 (1H, d, *J* = 3.2 Hz, H-2), 4.18 (1H, dd, *J* = 9.4, 6.6 Hz, H-7′), 4.16 (1H, d, *J* = 3.2 Hz, H-1), 3.98 (1H, ddd, *J* = 14.2, 7.3, 2.8 Hz, H-17A), 3.87 (1H, m, H-17B), 3.79 (3H, s, H-9′), 3.39 (1H, m, H-6′A), 3.32 (1H, m, H-6′B), 3.24 (1H, dd, *J* = 12.2, 3.5 Hz, H-7$\beta$), 3.13 (1H, m, H-16A), 3.02 (1H, ddd, *J* = 16.3, 6.8, 2.8 Hz, H-16B), 2.82 (1H, br d, *J* = 12.2 Hz, H-7$\alpha$); $^{13}$C NMR ($CD_3OD$, 150 MHz) $\delta$ 183.7 (C-3), 171.2 (C-5), 170.7 (C-8′), 167.2 (C-11), 150.4 (C-19), 148.4 (C-10), 141.0 (C-2′), 133.5 (C-4′), 127.4 (C-14), 127.2 (C-5′), 125.5 (C-12), 122.8 (C-21), 119.4 (C-15), 114.5 (C-4), 101.7 (C-20), 66.8 (C-2), 64.0 (C-8), 52.9 (C-17), 52.7 (C-7′), 50.7 (C-1), 47.0 (C-6), 39.3 (C-7), 33.6 (C-9′), 26.0 (C-6′), 20.7 (C-16); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 13.22 (1H, br s, *N*H-13), 10.99 (1H, br s, *N*H-9), 8.58 (3H, br s, *N*H-10′), 8.11 (1H, s, H-2′), 7.29 (1H, s, H-14), 6.31 (1H, s, H-4), 5.75 (1H, d, *J* = 2.4 Hz, H-8), 4.43 (1H, d, *J* = 3.2 Hz, H-2), 4.02 (1H, d, *J* = 3.2 Hz, H-1), 3.98 (1H, m, H-7′), 3.76 (2H, m, H-17), 3.68 (3H, s, H-9′), 3.16 (2H, m, H-6′), 3.02 (3H, m, H-7A/16), 2.71 (1H, br d, *J* = 11.6 Hz, H-7B); (+)-HRFABMS *m*/*z* [M + H]$^+$ 535.12218 (calcd for $C_{25}H_{23}N_6O_4S_2$, 535.12222).

**(+)-(1*S*,2*S*,6*S*,8*R*,7′*S*)-Discorhabdin B$_2$ ((+)-6):** TFA salt, green oil; $[\alpha]^{20}_D$ = +40, $[\alpha]_{578}$ = +80, $[\alpha]_{546}$ = +180 (*c* 0.05, MeOH); UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 247 (4.33), 288 (4.12), 322 (3.95), 395 (3.93), 585 (2.94) nm; ECD (MeOH) $\lambda$ ($\Delta\varepsilon$) 256 (+22.2), 282 (+4.1), 305 (+9.2), 334 (0), 365 (−13.1) 417 (0) nm; $^1$H NMR ($CD_3OD$, 600 MHz) and $^{13}$C NMR ($CD_3OD$, 150 MHz) data, see Table 1; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 13.18 (1H, br s, *N*H-13), 10.95 (1H, br s, *N*H-9), 8.49 (3H, br s, *N*H-10′), 7.87 (1H, s, H-2′), 7.30 (1H, s, H-14), 6.31 (1H, s, H-4), 5.75 (1H, br s, H-8), 4.50 (1H, d, *J* = 3.1 Hz, H-2), 4.01 (1H, m, H-7′), 3.93 (1H, d, *J* = 3.1 Hz, H-1), 3.75 (2H, m, H-17), 3.64 (3H, s, H-9′), 3.25 (2H, m, H-6′), 3.06 (3H, m, H-7A/16), 2.64 (1H, br d, *J* = 11.7 Hz, H-7B); (+)-HRFABMS *m*/*z* [M + H]$^+$ 535.12372 (calcd for $C_{25}H_{23}N_6O_4S_2$, 535.12222).

**(+)-(6*S*,8*S*,7′*S**)-Discorhabdin K ((+)-7):** TFA salt, brown oil; $[\alpha]^{20}_D$ = +340, $[\alpha]_{578}$ = +200, $[\alpha]_{546}$ = −200 (*c* 0.05, MeOH); UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 240 (4.28), 280 (shoulder, 4.05), 328 (3.97), 399 (3.77) 565 (2.87) nm; ECD (MeOH) $\lambda$ ($\Delta\varepsilon$) 236 (−4.9), 256 (−14.7), 298 (−5.9), 312 (−7.6), 332 (0), 358 (+12.5), 433 (0) nm; $^1$H NMR ($CD_3OD$, 600 MHz) and $^{13}$C NMR ($CD_3OD$, 150 MHz) data, see Table 3; (+)-HRFABMS *m*/*z* [M + H]$^+$ 535.12221 (calcd for $C_{25}H_{23}N_6O_4S_2$, 535.12222).

**(−)-(6*R*,8*R*,7′*S**)-Discorhabdin K$_2$ ((−)-8):** TFA salt, brown oil; $[\alpha]^{20}_D$ = −260, $[\alpha]_{578}$ = −180, $[\alpha]_{546}$ = +80 (*c* 0.05, MeOH); IR (smear) $\nu_{max}$ 2932, 1664, 1616, 1523, 1411, 1327, 1178, 1120 cm$^{-1}$; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 230 (4.31), 241 (4.30), 280 (4.10), 327 (4.00), 392 (shoulder, 3.84) nm; ECD (MeOH) $\lambda_{max}$ ($\Delta\varepsilon$) 255 (+17.2), 305 (+7.9), 313 (+8.7), 333 (0), 359 (−12.3), 415 (0) nm; $^1$H NMR ($CD_3OD$, 600 MHz) and $^{13}$C NMR ($CD_3OD$, 150 MHz) data, see Table 2; (+)-HRFABMS *m*/*z* [M + H]$^+$ 535.12262 (calcd for $C_{25}H_{23}N_6O_4S_2$, 535.12222).

**(−)-(1*R*,2*S*,6*R*,8*S*)-Discorhabdin N ((−)-9):** TFA salt, dark green oil; $[\alpha]^{20}_D$ = −160, $[\alpha]_{578}$ = −260, $[\alpha]_{546}$ = −520 (*c* 0.05, MeOH); UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 203 (4.53), 249 (4.32), 285 (4.10), 323 (3.96), 399 (3.93), 580 (3.03) nm; ECD (MeOH) $\lambda_{max}$ ($\Delta\varepsilon$) 258 (−21.9), 284 (−5.4), 299 (−8.7), 321 (0), 360 (+20.0), 407 (0), 430 (−2.7), 467 (0) nm; $^1$H NMR (DMSO-$d_6$, 600 MHz) $\delta$ 13.18 (1H, br s, *N*H-13), 10.76 (1H, br s, *N*H-9), 7.28 (1H, s, H-14), 6.18 (1H, s, H-4), 5.68 (1H, d, *J* = 2.5 Hz, H-8), 4.34 (1H, d, *J* = 3.2 Hz, H-2), 4.01 (1H, ddd, *J* = 14.3, 7.1, 3.2 Hz, H-17A), 3.78 (1H, m, H-17B), 3.62 (1H, d, *J* = 3.2 Hz, H-1), 3.47 (1H, d, *J* = 18.0 Hz, H-23A), 3.40 (1H, d, *J* = 18.0 Hz, H-23B), 3.07 (1H, dd, *J* = 12.4, 2.5 Hz, H-7A), 3.03 (2H, m, H-16), 2.47 (1H, under solvent peak, H-7B); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 183.1 (C-3), 173.6 (C-24), 168.7 (C-5), 166.4 (C-11), 147.2 (C-19), 146.5 (C-10), 126.8 (C-14), 123.6 (C-12), 121.2 (C-21), 117.6 (C-15), 113.2 (C-4), 100.5 (C-20), 63.7 (C-2), 62.3 (C-8), 56.5 (C-1), 51.1 (C-17), 47.8 (C-23), 45.9 (C-6), 36.3 (C-7), 19.2 (C-16); (+)-HRFABMS *m*/*z* [M + H]$^+$ 409.09880 (calcd for $C_{20}H_{17}N_4O_4S$, 409.09705).

**(+)-(6*S*,8*S*)-Discorhabdin Q ((+)-10):** free base, orange solid; $[\alpha]^{20}_D$ = +720 (*c* 0.025, MeOH); UV (MeOH) $\lambda$ (log $\varepsilon$) 224 (3.78), 288 (3.54), 408 (3.34), 418 (3.32), 428 (3.33), 666 (2.18) nm; ECD (MeOH) $\lambda$ ($\Delta\varepsilon$) 255 (−1.4), 268 (−6.5), 283 (0), 296 (+2.6), 315 (0), 334 (−4.4), 350 (0), 389 (+5.5) nm; $^1$H NMR (acetone-$d_6$, 400 MHz) $\delta$ 8.27 (1H, d, *J* = 5.8 Hz, H-17), 8.23 (1H, s, H-14), 7.75 (1H, s, H-1), 7.51 (1H, d, *J* = 5.8 Hz, H-16), 7.34 (1H, br s, *N*H-9), 5.94 (1H, s, H-4), 5.92 (1H, d, *J* = 4.1 Hz, H-8), 3.03 (1H, d, *J* = 11.4 Hz, H-7A), 2.60 (1H, dd, *J* = 11.4, 4.1 Hz, H-7B); (−)-HRESIMS *m*/*z* [M − H]$^-$ 409.9607 (calcd for $C_{18}H_9{}^{79}BrN_3O_2S$, 409.9604), 411.9594 (calcd for $C_{18}H_9{}^{81}BrN_3O_2S$, 411.9585).

**Semisynthesis of (+)-(6*S*,8*S*)-Discorhabdin Q ((+)-10).** (+)-(6*S*,8*S*)-Discorhabdin B ((+)-**2**) TFA salt (6.0 mg, 11.4 $\mu$mol) was dissolved in aqueous acetone (5% $H_2O$) (6 mL), to which an excess of $K_2CO_3$ (20 mg) was added. The reaction mixture was kept at reflux at 75 °C for 1 h under $N_2$, at which time analytical HPLC indicated complete consumption of starting material. The solvent was removed in vacuo and the solid purified by $C_8$ flash (MeOH, $H_2O$−TFA (0.05%)) chromatography and then washed with $CH_2Cl_2$ to yield (+)-(6*S*,8*S*)-discorhabdin Q ((+)-**10**) free base (1.3 mg, 3.2 $\mu$mol, 28% yield): free base orange solid; $[\alpha]_D$ = +400 (*c* 0.025, MeOH); ECD (MeOH) $\lambda$ ($\Delta\varepsilon$) 237 (−5.0) 249 (−1.2), 268 (−5.5), 283 (0), 296 (+2.3), 314 (0), 336 (−3.7), 352 (0), 389 (+4.6) nm; $^1$H NMR (acetone-$d_6$, 400 MHz) $\delta$ 8.27 (1H, d, *J* = 5.8 Hz, H-17), 8.23 (1H, s, H-1), 7.75 (1H, s, H-14), 7.51 (1H, d, *J* = 5.8 Hz, H-16), 5.94 (1H, s, H-4), 5.92 (1H, d, *J* = 4.1 Hz, H-8), 3.03 (1H, d, *J* = 11.5 Hz, H-7A), 2.60 (1H, dd, *J* = 11.4, 4.1 Hz, H-7B).

**Semisynthesis of (6*S*)-Discorhabdin S (11).** (+)-(6*S*)-Discorhabdin T trifluoroacetate salt (3.1 mg, 7.0 $\mu$mol) was dissolved in dry MeOH (2 mL). An excess of LiCl (5 mg) and $NaBH_4$ (5 mg) were added, and the mixture was stirred overnight. The reaction was quenched with water−TFA (5%, 5 mL) and subjected to $C_{18}$ column chromatography, a red oil eluting with 40% MeOH and 60% $H_2O$−TFA (0.05%), yielding (6*S*)-discorhabdin S (**11**) as the trifluoroacetate salt (1.5 mg, 3.4 $\mu$mol, 48%): red oil; $[\alpha]^{20}_D$ = −120, $[\alpha]_{365}$ = −600 (*c* 0.025, MeOH); $^1$H NMR ($CD_3OD$, 400 MHz) 8.17 (1H, s), 7.79 (1H, s), 7.72 (1H, d, *J* = 7.0 Hz), 7.56 (1H, d, *J* = 7.0 Hz), 6.45 (1H, s), 4.35 (3H, s), 3.94 (1H, m), 3.73 (1H, m), 2.44 (1H, m), 2.41 (3H, s), 2.25 (1H, m); (+)-HRESIMS *m*/*z* [M + H]$^+$ 442.0228 (calcd for $C_{20}H_{17}{}^{79}BrN_3O_2S$ 442.0219), 444. 0218 (calcd for $C_{20}H_{17}{}^{81}BrN_3O_2S$ 444.0199).

(6*S*)-Discorhabdin S trifluoroacetate salt (**11**) (1.1 mg, 2.4 $\mu$mol) was stirred in dry acetone (1.5 mL) with an excess of $K_2CO_3$ (3 mg) under $N_2$ for 10 min, during which time the solution turned from red to orange. The solvent was removed in vacuo, and the solid was partitioned between ethyl acetate and water, yielding (6*S*)-discorhabdin S as the free base (0.88 mg, 2 $\mu$mol, 80%): orange solid; $[\alpha]_D$ = +80, $[\alpha]_{365}$ = −880, $[\alpha]_{436}$ = +760, $[\alpha]_{546}$ = +200, $[\alpha]_{578}$ = +160 (*c* 0.025, MeOH); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.23 (1H, d, *J* = 5.8 Hz), 7.56 (1H, s), 7.53 (1H, s), 7.23 (1H, d, *J* = 5.8 Hz), 6.26 (1H, s), 4.33 (3H, s), 3.84 (1H, m), 3.56 (1H, m), 2.36 (1H, m), 2.25 (3H, s), 2.15 (1H, m); $^1$H NMR (10% $CD_3OD$−$CDCl_3$) data agreed with published values.[14]

**Semisynthesis of (+)-(6*S*)-Discorhabdin T ((+)-12).** (+)-(6*S*)-Discorhabdin U ((+)-**13**) trifluoroacetate salt (1.4 mg, 2.5 $\mu$mol) was dissolved in dry DMF (2 mL), to which an excess of $K_2CO_3$ (20 mg) was added. The reaction mixture was heated at reflux at 80 °C for 4 h under $N_2$. The crude reaction mixture was loaded onto a $C_8$ flash column and the solid purified eluting with 50% MeOH and 50% $H_2O$ (0.05%), to yield (+)-(6*S*)-discorhabdin T ((+)-**12**) (0.60 mg, 54% yield): free base orange powder; $[\alpha]^{20}_D$ = +280 (*c* 0.025, 10% MeOH in $CH_2Cl_2$)); $^1$H NMR ($CDCl_3$ (+10% $CD_3OD$), 400 MHz) [spectrum referenced on the $CHD_2OD$ resonance at 3.30 ppm] $\delta$ 8.23 (1H, d, *J* = 5.8 Hz, H-17), 7.68 (1H, s, H-1), 7.64 (1H, s, H-14), 7.34 (1H, d, *J* = 5.8 Hz,

H-16), 6.48 (1H, d, $J = 7.5$ Hz, H-8), 5.98 (1H, s, H-4), 4.31 (3H, s, H-22), 4.16 (1H, d, $J = 7.5$ Hz, H-7), 2.21 (3H, s, H-23).[14] Alternatively, (+)-(6*S*,8*S*)-discorhabdin B trifluoroacetate salt (15.8 mg, 38.2 $\mu$mol) was dissolved in trimethylphosphate (2 mL), to which an excess of $K_2CO_3$ (7 mg) was added. The reaction mixture was heated at 80 °C overnight under $N_2$. The crude reaction mixture was cooled and was subjected to $C_{18}$ column chromatography, the products eluting with 35% MeOH and 65% $H_2O$−TFA (0.05%) yielding (+)-(6*S*)-discorhabdin U ((+)-**13**) (7.3 mg, 16.5 $\mu$mol, 43%) and (+)-(6*S*)-discorhabdin T ((+)-**12**) (3.1 mg, 7.0 $\mu$mol, 18%).

**Semisynthesis of (+)- and (−)-Discorhabdin U (13).** Wellington-sourced (+)-(6*S*,8*S*)-discorhabdin B ((+)-**2**) trifluoroacetate salt (2.1 mg, 4.0 $\mu$mol) was dissolved in trimethylphosphate (1 mL), to which an excess of $K_2CO_3$ (6 mg) was added. The reaction mixture was heated at reflux at 90 °C for 3 h under $N_2$. The crude reaction mixture was loaded on a $C_8$ flash column and the product eluted with 50% MeOH and 50% $H_2O$−TFA (0.05%), yielding (+)-(6*S*)-discorhabdin U ((+)-**13**) (1.7 mg, 75% yield): TFA salt, dark green oil; $[\alpha]^{20}_D = +222$, $[\alpha]_{578} = +180$, $[\alpha]_{546} = +220$ (*c* 0.05, MeOH); IR (smear) $\nu_{max}$ 3296, 2923, 1680, 1651, 1489, 1357, 1198, 1129 cm$^{-1}$; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 203 (4.20), 247 (3.87), 309 (3.67), 431 (3.36), 603 (2.85) nm; ECD (MeOH) $\lambda$ ($\Delta\varepsilon$) 215 (0), 228 (−16.4), 242 (0), 250 (+10.4), 265 (0), 267 (−1.3), 272 (0), 289 (+6.1), 306 (+1.8), 328 (+6.6), 353 (0), 384 (+2.7), 429 (0) nm; $^1$H and $^{13}$C NMR and mass spectrometry data have been previously reported.[30]

Doubtful Sound-sourced (−)-(6*R*,8*R*)-discorhabdin B ((−)-**2**) trifluoroacetate salt (1.1 mg, 2.1 $\mu$mol) was dissolved in trimethylphosphate (1 mL), to which an excess of $K_2CO_3$ (5 mg) was added. The reaction mixture was heated at reflux at 90 °C for 3 h under $N_2$. The crude reaction mixture was loaded on a $C_8$ flash column and the product eluted with 50% MeOH and 50% $H_2O$−TFA (0.05%), yielding (−)-(6*R*)-discorhabdin U ((−)-**13**) (0.8 mg, 70% yield): TFA salt dark green oil; $[\alpha]^{20}_D = -220$ (*c* 0.05, MeOH); ECD (MeOH) $\lambda$ ($\Delta\varepsilon$) 215 (0), 228 (+18.1), 242 (0), 251 (−7.5), 260 (0), 267 (+3.8), 275 (0), 288 (−4.8), 307 (−0.3), 327 (−6.8), 353 (−1.4), 377 (−3.6), 436 (0) nm; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 10.70 (1H, br s, *N*H-9), 8.84 (1H, br s, *N*H-18), 7.77 (1H, s, H-1), 7.41 (1H, br s, H-14), 6.54 (1H, dd, $J = 7.5$, 4.8 Hz, H-8), 6.07 (1H, s, H-4), 4.71 (1H, br d, $J = 7.5$ Hz, H-7), 3.94 (3H, s, H-22), 3.77 (2H, t, $J = 7.9$ Hz, H-17), 2.84 (2H, m, H-16), 2.42 (3H, s, H-23); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 174.1 (C-3), 168.3 (C-5), 165.8 (C-11), 156.7 (C-19), 147.8 (C-1), 144.3 (C-10), 131.5 (C-14), 124.7 (C-8), 123.3 (C-2), 122.9 (C-12), 121.6 (C-21), 118.9 (C-15), 117.5 (C-4), 114.4 (C-7), 95.7 (C-20), 48.3 (C-6), 44.4 (C-17), 36.1 (C-22), 17.6 (C-16), 14.6 (C-23); (+)-HRFABMS *m/z* [M + H]$^+$ 442.02209 (calcd for $C_{20}H_{17}{}^{79}BrN_3O_2S$ 442.02248) 444.02064 (calcd for $C_{20}H_{17}{}^{81}BrN_3O_2S$, 444.02044).

**(−)-(1*R*,2*S*,6*R*,8*S*)-Discorhabdin L ((−)-14):** TFA salt, dark green oil; $[\alpha]^{20}_D = -240$, $[\alpha]_{578} = -400$ (*c* 0.0125, MeOH); ECD, $^1$H NMR, and $^{13}$C NMR data were identical with that previously reported;[9,21] HRFABMS *m/z* [M + H]$^+$ 352.07544 (calcd for $C_{18}H_{14}N_3O_3S$, 352.07559).

**(+)-(2*R*,6*R*,8*S*)-2-Hydroxydiscorhabdin D ((+)-16):** TFA salt, green oil; $[\alpha]^{20}_D = +80$ (*c* 0.05, MeOH); UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 249 (4.06), 283 (3.86), 321 (3.66), 396 (3.66), 578 (2.78) nm; ECD (MeOH) $\lambda_{max}$ ($\Delta\varepsilon$) 235 (0), 255 (−11.3), 277 (0), 281 (+1.1), 286 (0), 303 (−4.2), 323 (0), 354 (+8.6), 452 (0) nm; $^1$H NMR ($CD_3OD$, 400 MHz) $\delta$ 7.11 (1H, s, H-14), 6.08 (1H, s, H-4), 5.63 (1H, dd, $J = 3.6$, 1.6 Hz, H-8), 4.04 (2H, m, H-17), 3.50 (1H, m, H-16A), 3.08 (1H, m, H-16B), 2.85 (1H, d, $J = 13.0$ Hz, H-1A), 2.80 (1H, dd, $J = 12.1$, 3.6 Hz, H-7A), 2.62 (2H, m, H-1B/H-7B); (+)-HRFABMS *m/z* [M + H]$^+$ 352.07589 (calcd for $C_{18}H_{14}N_3SO_3$, 352.07559).

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**Supporting Information Available:** Map of location sites of sponge material used in this study, $^1$H and $^{13}$C NMR spectra of (+)-discorhabdin $H_2$ ((+)-**6**) and (−)-discorhabdin H ((−)-**5**), a figure highlighting the differences observed in the $^1$H NMR spectra of (+)-**6** and (−)-**5**, a plot of ECD spectra of (+)-**6** and (−)-**5**, $^1$H and $^{13}$C NMR spectra (+)-discorhabdin K ((+)-**7**) and (−)-discorhabdin $K_2$ ((−)-**8**), and a plot of ECD spectra of (+)-**7** and (−)-**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

## References and Notes

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