CHEMICAL REVIEWS

REVIEW

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Discorhabdins and Pyrroloiminoquinone-Related Alkaloids

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1. INTRODUCTION

Alkaloids, such as lamellarins[1] and manzamines,[2] with complex structures and promising biological activities produced by marine plants, invertebrates and microbes have greatly stimulated interdisciplinary studies by chemists and biologists worldwide. During the past 25 years, the number of alkaloids isolated from marine organisms has grown rapidly. Among them, the discorhabdins and structurally related alkaloids (**1**−**58**, Figures 1−6 and Table 1)[3−32] are a unique class of nitrogenous pigments belonging to the family of pyrroloiminoquinone-type alkaloids. This group of natural products (except a benzene derivative **41**[30]) possesses a characteristic core pyrrolo[4,3,2-*de*]-quinoline tetracyclic skeleton bound to a spiro-substituent at the C-6 position. A few discorhabdins and related alkaloids have an additional sulfur bridge or contain a sulfur-containing substituent, and bromine was often found to incorporate into the skeleton.

The first representative of discorhabdins was discorhabdin C **3**. It was primarily isolated from a red-brown sponge of the genus *Latrunculia* du Bocage (family Latrunculiidae, order Hadromerida) collected in New Zealand by Munro and co-workers in 1986.[3] The structure of **3** was established by a combination of single-crystal X-ray diffraction analysis and interpretation of spectroscopic data. It contains an unprecedented framework consisting of a tetracyclic iminoquinone chromophore with a spiro

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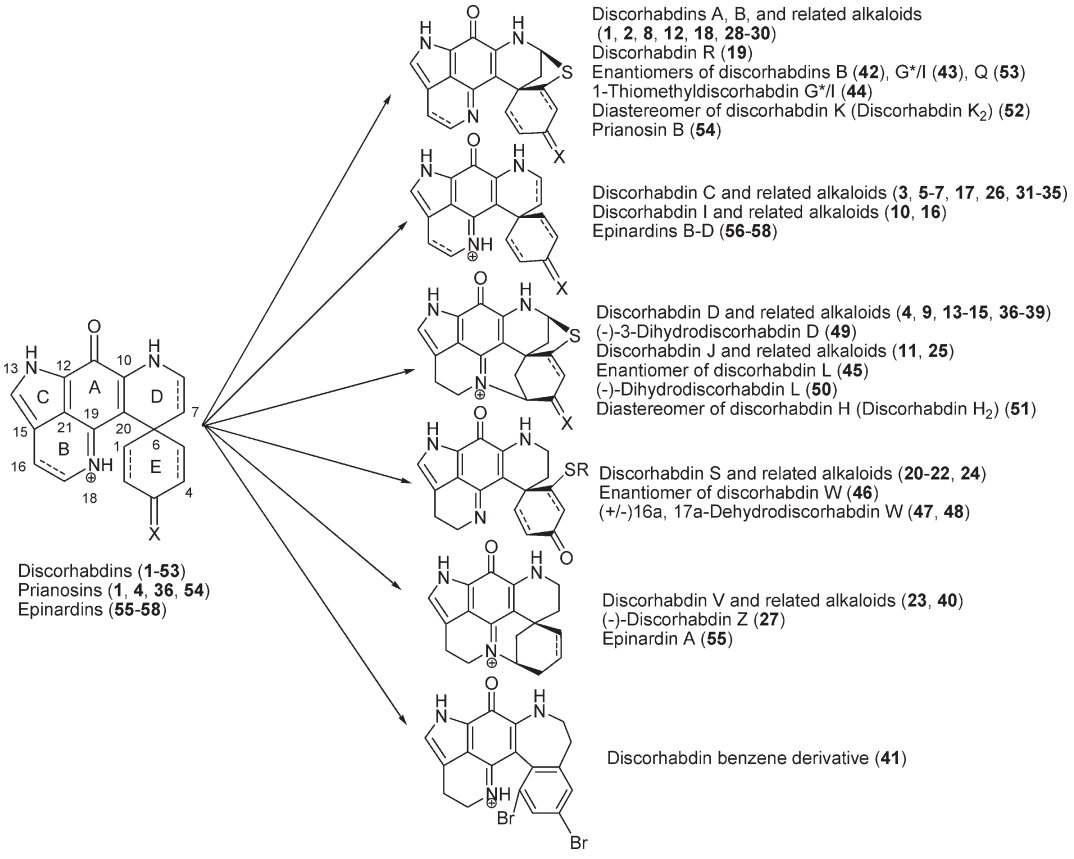

Figure 1. Discorhabdins and related naturally occurring alkaloids.

2,6-dibromocyclohexadienone.[3,5,6] The trivial name of the compound was originally derived from the characteristic discorhabd spicules used to identify *Latrunculia* sponges in the family of Latrunculiidae.[3,25] The atom numbering (Figure 1) in the skeleton of discorhabdin C **3** was initially established by Munro et al.[3] Since then, a number of discorhabdins and structurally related alkaloids have been obtained from various marine organisms (Figures 1−6 and Table 1); these alkaloids include prianosins A **1**, B **54**, C **36**, and D **4** isolated from the Okinawan marine sponge *Prianos melanos* (family Hymeniacidonidae, order Halichondrida)[4,8−10,12] and epinardins A−D (**55**−**58**) found in an undetermined deep-water green demosponge collected near the Crozet Islands in the South Indian Ocean.[16]

The fused tetracyclic iminoquinone fragment in discorhabdins might be biosynthesized from tyrosine (or tyramine) and tryptophan (or tryptamine) derivatives, or might be derived from relatively less cyclized pyrroloiminoquinone intermediates (precursors) (Scheme 1).[3,4,6,25,33,34] As indirect evidence of the latter hypothesis, discorhabdins often co-occur with pyrroloiminoquinone-related alkaloids such as makaluvic acids (**59**−**62**),[35,36] makaluvone (**63**),[37] makaluvamines (**64**−**81**),[37−46] batzellines (**82**−**86**),[46−49] isobatzellines (**87**−**91**),[48,49] secobatzellines (**92**, **93**),[50] damirones (**94**−**97**),[39,44,51] tsitsikammamines (**98**−**101**),[15,23] veiutamine (**102**),[52] wakayin (**103**),[53] and zyzzyanones (**104**−**107**).[54,55] In fact, the pyrrolo[4,3,2-*de*]quinoline ring system was first recognized in the toad poisons dehydrobufotenine (**108**) and bufothionine (**109**).[56−60] Naturally occurring pyrrolo[4,3,2-*de*]quinoline-containing alkaloids have also been isolated from fungi [makaluvamine A (**64**),[61] sanguinolentaquinone (**110**),[62] sanguinones (**111**, **112**),[62] haematopodins (**113**, **114**),[63,64] and mycenarubins (**115**−**119**)[64,65]] (Figures 7−9 and Table 2).

The discorhabdins and related alkaloids (**1**−**58**) were found to have potent biological activities such as cytotoxicity and antitumor,[3−13,16−18,21−24,26−29,31,32,37,66−76] antimicrobial,[6,13−15,19,30,32,67−70,76] antiviral,[30,66] antimalarial,[30] caspase inhibition,[17,73] immunomodulatory,[17,73] and feeding deterrence.[14,77−83] The remarkable biological activities and intriguing structures of discorhabdin-type alkaloids have attracted great interest from synthetic chemists (Table 3).[74,76,84−125] Some earlier findings regarding the chemistry, pharmacology, and ecology of the pyrroloiminoquinone-related alkaloids have been briefly reviewed.[11,20,25,46,66,126−149]

In this survey, we extensively focus on the isolation, structure determination, biological activities, biogenesis and synthetic studies of the discorhabdins and related alkaloids (**1**−**58**) from different marine organisms since the first report of discorhabdin C **3** in 1986 until January 2011. The simple cyclized pyrroloiminoquinone-related alkaloids (**59**−**119**) are, however, only briefly presented herein with their origins of the first reported biomasses.[15,23,35−66]

2. ISOLATION AND STRUCTURE DETERMINATION OF DISCORHABDINS/PRIANOSINS/EPINARDINS FROM MARINE ORGANISMS

Discorhabdins are a class of pyrroloiminoquinone-type alkaloids, which have been isolated from numerous marine sponges.[3−32] In 1986, discorhabdin C **3** was reported as a cytotoxic pigment from a sponge of the genus *Latrunculia* du Bocage collected in

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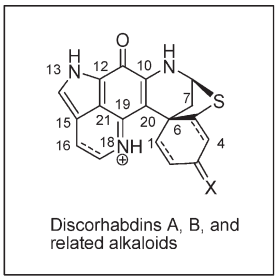
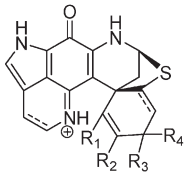
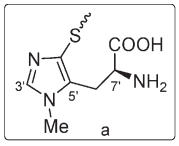


1 (+)-(5*R*, 6*S*, 8*S*)-Discorhabdin A (= Prianosin A): R_1 = H, R_2 = Br, $R_3 + R_4$ = O
28 (+)-(3*R*, 5*R*, 6*S*, 8*S*)-3-Dihydrodiscorhabdin A: $R_1 = R_3$ = H, R_2 = Br, R_4 = OH
29 (+)-Debromodiscorhabdin A: $R_1 = R_2$ = H, $R_3 + R_4$ = O



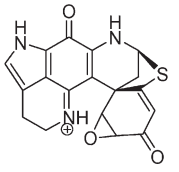
2 (+)-(6*S*, 8*S*)-Discorhabdin B: R_1 = H, R_2 = Br, $R_3 + R_4$ = O, Δ^4
30 3-Dihydrodiscorhabdin B: $R_1 = R_3$ = H, R_2 = Br, R_4 = OH, Δ^4
42 (-)-(6*R*, 8*R*)-Discorhabdin B: R_1 = H, R_2 = Br, $R_3 + R_4$ = O, Δ^4



8 (+)-(6*S*, 8*S*)-Discorhabdin G*/I (or G*): $R_1 = R_2$ = H, $R_3 + R_4$ = O, Δ^4
12 (+)-(6*S*,8*S*,7'*S*)-Discorhabdin K: R_1 = a, R_2 = H, $R_3 + R_4$ = O, Δ^4
43 (-)-(6*R*, 8*R*)-Discorhabdin G*/I: $R_1 = R_2$ = H, $R_3 + R_4$ = O, Δ^4
44 (+)-(6*R*, 8*S*)-1-Thiomethyldiscorhabdin G*/I: R_1 = SMe, R_2 = H, $R_3 + R_4$ = O, Δ^4
52 (-)-(6*R*,8*R*,7'*S*)-Discorhabdin K_2: R_1 = a, R_2 = H, $R_3 + R_4$ = O, Δ^4

18 (-)-(6*R*, 8*R*)-Discorhabdin Q : R_1 = H, R_2 = Br, $R_3 + R_4$ = O, Δ^4, Δ^{16}
53 (+)-(6*S*, 8*S*)-Discorhabdin Q : R_1 = H, R_2 = Br, $R_3 + R_4$ = O, Δ^4, Δ^{16}

54 Prianosin B: R_1 = H, R_2 = Br, $R_3 + R_4$ = O, Δ^{16}



19 Discorhabdin R

Figure 2. Naturally occurring pyrroloiminoquinone-related discorhabdins (I).

New Zealand.[3] Since then, a series of structurally related alkaloids have been isolated and characterized. These include discorhabdins A (= prianosin A) **1**,[4,6−8,11,22,23,27,30,37] B **2**,[6,11,19,22,24,26,28,32] C **3**,[3,5,6,11,13,14,26,28−30,32] D (= prianosin D) **4**,[7,9,11,12,23,24,27,29,32] E **5**,[11,13,30,32] F **6**,[11] G **7**,[14] G*/I **8**,[22−26,28,32] H **9**,[23] I **10**,[20,25,32] J **11**,[20,25] K **12**,[20,25,29] L **13**,[20,22,24−26,28−30] M **14**,[20,25] N **15**,[20,23,25] O **16**,[20,25] P **17**,[17] Q (= 16,17-dehydrodiscorhabdin B) **18**,[18] R **19**,[19] S **20**,[21] T **21**,[21] U **22**,[21] V **23**,[23] W **24**,[24,26,28,29] X **25**,[27] Y **26**,[30] Z **27**,[32] (+)-3-dihydrodiscorhabdin A **28**,[26−28] (+)-debromodiscorhabdin A **29**,[27] dihydrodiscorhabdin B **30**,[30] 3-dihydrodiscorhabdin C **31**,[23,29,30,32] 14-bromodiscorhabdin C **32**,[15,23] 14-bromo-3-dihydrodiscorhabdin C **33**,[15,23] 14-bromo-3- dihydro-7,8-dehydrodiscorhabdin C **34**,[23] 3-dihydro-7,8-dehydrodiscorhabdin C **35**,[23] 2-hydroxy-discorhabdin D (= prianosin C) **36**,[9,12] 1-aminodiscorhabdin D **37**,[23] 1-methoxydiscorhabdin D **38**,[23,32] (+)-3-dihydrodiscorhabdin L **39**,[27] 14-bromo-1-hydroxydiscorhabdin V **40**,[23] discorhabdin benzene derivative **41**,[30] (−)-discorhabdin B **42**,[26] (−)-discorhabdin G*/I **43**,[26] (+)-1-thiomethyl-discorhabdin G*/I **44**,[28] (+)-discorhabdin L **45**,[26] (−)-discorhabdin W **46**,[26] (−)-16a,17a- dehydrodiscorhabdin W **47**,[28] (+)-16a,17a-dehydrodiscorhabdin W **48**,[28] (−)-3-dihydrodiscorhabdin D **49**,[32] (−)-3-dihydrodiscorhabdin L **50**,[32] (+)-discorhabdin H_2 **51**,[29] (−)-discorhabdin K_2 **52**,[29] (+)-discorhabdin Q **53**,[29] prianosin B **54**,[9,10] and epinardins A−D **55**−**58**[16] (Figures 1−6 and Table 1).

2.1. Discorhabdins A−Z and Related Alkaloids

2.1.1. Discorhabdins A−D. From 1986 to 1988, discorhabdins A−D **1**−**4** were reported as the major pigments from sponges of the genus *Latrunculia* (family Latrunculiidae, order Hadromerida) and the genus *Prianos* (family Hymeniacidonidae, order Halichondrida) by Munro and co-workers.[3,5−7,66−69]

Discorhabdin A **1**, characterized as an optically active dark-green hydrochloride, was isolated from the sponge *L. brevis* harvested from depths of 110 to 145 m off the Otago Peninsula in Dunedin (New Zealand).[6] Discorhabdin B **2** was obtained from an undescribed *Latrunculia* species collected from depth of 25 m, off the Kaikoura Peninsula in Canterbury (New Zealand).[6] In fact, discorhabdin C **3**, the first alkaloid with the characteristic core pyrrolo[4,3,2-*de*]quinoline tetracyclic skeleton bound to a spiro-substituent at the C-6 position, was reported two years earlier than discorhabdins A **1** and B **2**. Discorhabdin C **3** was isolated from a red-brown sponge of the genus *Latrunculia* collected in New Zealand.[3] The structure of **3** was established by X-ray diffraction analysis and NMR studies.[3,6] The structures of **1** and **2**, both containing an additional sulfur ring formed by a tetrahydrothiophene bridge between C-5 and C-8, were determined by comparing their NMR data with those of **3**. Compound **1** lacks a Δ^4 double bond, while **1** and **2** both lack a bromine substituent at C-4 when comparing their structural features with **3**.[6]

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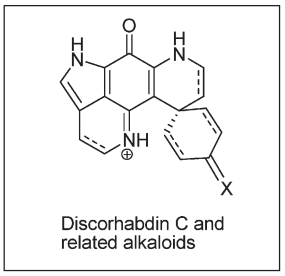

3 Discorhabdin C: $R_1 = R_4 = Br$, $R_2 + R_3 = O$, $R_5 = R_6 = H$, Δ^4
31 3-Dihydrodiscorhabdin C: $R_1 = R_4 = Br$, $R_2 = R_5 = R_6 = H$, $R_3 = OH$, Δ^4
32 14-Bromodiscorhabdin C: $R_1 = R_4 = R_6 = Br$, $R_2 + R_3 = O$, $R_5 = H$, Δ^4
33 14-Bromo-3-dihydrodiscorhabdin C: $R_1 = R_4 = R_6 = Br$, $R_2 = R_5 = H$, $R_3 = OH$, Δ^4
34 14-Bromo-3-dihydro-7,8-dehydrodiscorhabdin C: $R_1 = R_4 = R_6 = Br$, $R_2 = R_5 = H$, $R_3 = OH$, Δ^4, Δ^7
35 3-Dihydro-7,8-dehydrodiscorhabdin C: $R_1 = R_4 = Br$, $R_2 = R_5 = R_6 = H$, $R_3 = OH$, Δ^4, Δ^7

5 Discorhabdin E: $R_1 = Br$, $R_2 + R_3 = O$, $R_4 = R_5 = R_6 = H$, Δ^4
6 Discorhabdin F: $R_1 = Br$, $R_2 + R_3 = O$, $R_4 = R_5 = R_6 = H$, Δ^4, Δ^{16}
7 Discorhabdin G: $R_1 = Br$, $R_2 + R_3 = O$, $R_4 = R_5 = R_6 = H$, Δ^7
17 Discorhabdin P: $R_1 = R_4 = Br$, $R_2 + R_3 = O$, $R_5 = Me$, $R_6 = H$, Δ^4
26 (+)-(6*R*)-Discorhabdin Y: $R_1 = Br$, $R_2 + R_3 = O$, $R_4 = R_5 = R_6 = H$

10 Discorhabdin I: $R_1 = R_2 = H$
16 Discorhabdin O: $R_1 = Br$, $R_2 = OMe$

56 Epinardin B: R = H
57 Epinardin C: R = H, Δ^7
58 Epinardin D: R = OMe

Figure 3. Naturally occurring pyrroloiminoquinone-related discorhabdins (II).

Discorhabdin D **4** was isolated from the sponges *L. brevis*, collected in New Zealand, and *P.* spp., collected in Okinawa.[7] This compound was found to co-occur with discorhabdin A **1**, and these two were successfully separated either by preparative RP-HPLC or by centrifugal counter current chromatography (CCCC). The structure of **4** was elucidated based on spectral comparisons (especially NMR, IR, and UV) with discorhabdins A−C **1**−**3**, which revealed the presence of an additional ring formed by the C_2-N_{18} bond in **4**. The relative configuration of discorhabdin D **4** was determined by difference NOE NMR experiments,[7] and the absolute configuration was successfully assigned most recently (in 2010) by direct comparison of experimental electronic circular dichroism (ECD) spectra.[29]

Interestingly, prianosin A **1** from the Okinawan sponge *P. melanos* was reported shortly before discorhabdin A **1**, and the two were later shown to be identical.[4,8] Just one year later, the same group isolated prianosins B **54**, C (= 2-hydroxydiscorhabdin D) **36**, and D (= discorhabdin D) **4** from the same sponge species.[9,12] The structure of prianosin A **1** was confirmed by X-ray diffraction analysis,[4] while comparison of the CD spectra of prianosins B−D with that of prianosin A (= discorhabdinA) **1** provided the same (6*R*,8*S*) absolute configuration in the latter three compounds.[9,25] Recently, the absolute configuration of prianosins C (2*R*,6*R*,8*S*) and D (2*S*,6*R*,8*S*) was reconfirmed by Copp's group.[29] Similar to prianosin A, prianosins B−D were also structurally related to discorhabdins A−D, and prianosins C and D were later revised to 2-hydroxydiscorhabdin D and discorhabdin D, respectively.[11,12]

In the following two decades, there have been extensive reports (Table 1) about the occurrence of discorhabdins A−D **1**−**4** from the genus *Latrunculia*.[22−24,26,28−30] Noticeably, discorhabdin A **1**, together with a series of less cyclized pyrroloiminoquinones (e.g., makaluvone **63**, makaluvamines A-F **64**−**69**, and damirone B **95**), was isolated from the Fijian sponge *Zyzzya* cf. *marsailis* in 1993.[37] In 2009, discorhabdins A **1** and D **4** were purified from the southern Australian marine sponge of the genus *Higginsia* by Capon and Ei-Naggar.[27] Capon et al. pointed out that the measured $[\alpha]_D$ values of discorhabdins featuring a ring G (such as discorhabdin D **4**) might particularly depend on the concentration.[27] Recently, discorhabdins B **2**, C **3**, and D **4** were also isolated from the sponge *Sceptrella* spp. collected from the shore of Gageodo, West Sea, Korea.[32]

2.1.2. Discorhabdins E−O. Discorhabdin E **5**, a red-colored 4-debromo derivative of discorhabdin C **3**, was discovered during reisolaton of discorhabdin C from the sponge *Latrunculia* cf. bocagei, collected in Auckland Islands, New Zealand.[13] Although there is a chiral center at C-6, discorhabdin E **5** was found to be a racemic mixture due to the rapid conformational inversion of rings B and D.[13] Recently, this compound was also obtained from an undescribed deep-water sponge species of the genus *Latrunculia* harvested from the Aleutian Island (Alaska)[30] and a sponge *Sceptrella* spp. collected off the shore of Gageodo,

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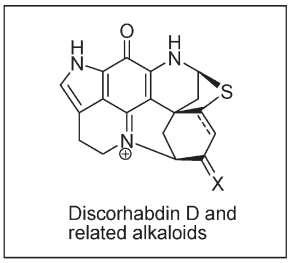
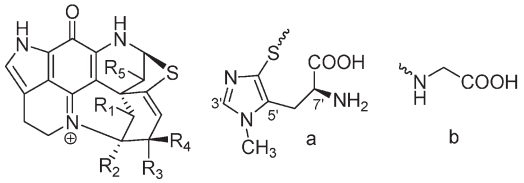


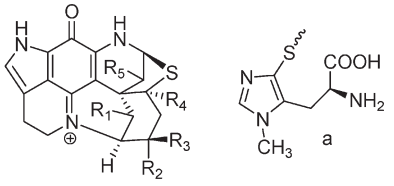


4 (+)-(2*S*,6*R*,8*S*)-Discorhabdin D (= Prianosin D): $R_1 = R_2 = R_5 = H$, $R_3 + R_4 = O$
36 (+)-(2*R*,6*R*,8*S*)-2-Hydroxydiscorhabdin D (= Prianosin C): $R_1 = R_5 = H$, $R_2 = OH$, $R_3 + R_4 = O$
37 1-Aminodiscorhabdin D: $R_1 = NH_2$, $R_2 = R_5 = H$, $R_3 + R_4 = O$
38 (+)-1-Methoxydiscorhabdin D: $R_1 = OMe$, $R_2 = R_5 = H$, $R_3 + R_4 = O$
49 (-)-(2*S*,3*R*,6*R*,8*S*)-3-Dihydrodiscorhabdin D: $R_1 = R_2 = R_3 = R_5 = H$, $R_4 = OH$

9 (-)-(1*R*,2*R*,6*R*,8*S*,7'*S*)-Discorhabdin H (Δ^4-discorhabdin J): $R_1 = a$, $R_2 = R_5 = H$, $R_3 + R_4 = O$
51 (+)-(1*S*,2*S*,6*S*,8*R*,7'*S*)-Discorhabdin H_2: $R_1 = a$, $R_2 = R_5 = H$, $R_3 + R_4 = O$

13 (-)-(1*R*, 2*S*, 6*R*, 8*S*)-Discorhabdin L: $R_1 = OH$, $R_2 = R_5 = H$, $R_3 + R_4 = O$
39 (+)-3-Dihydrodiscorhabdin L: $R_1 = R_4 = OH$, $R_2 = R_3 = R_5 = H$
45 (+)-(1*S*, 2*R*, 6*S*, 8*R*)-Discorhabdin L: $R_1 = OH$, $R_2 = R_5 = H$, $R_3 + R_4 = O$
50 (-)-3-Dihydrodiscorhabdin L: $R_1 = R_4 = OH$, $R_2 = R_3 = R_5 = H$

14 Discorhabdin M: $R_1 = a$, $R_2 = H$, $R_3 + R_4 = O$, $R_5 = OMe$
15 (-)-(1*R*,2*S*,6*R*,8*S*)-Discorhabdin N: $R_1 = b$, $R_2 = R_5 = H$, $R_3 + R_4 = O$



11 Discorhabdin J: $R_1 = a$, $R_2 + R_3 = O$, $R_4 = R_5 = H$
25 (+)-Discorhabdin X: $R_1 = R_2 = R_5 = H$, $R_3 = R_4 = OH$

Figure 4. Naturally occurring pyrroloiminoquinone-related discorhabdins (III).

West Sea, Korea.[32] In fact, the structures of discorhabdins E **5** and F **6** were first presented in a review article regarding marine natural products by Blunt et al. However, no spectral data were reported therein.[11]

Discorhabdin G **7**, the first Δ^7 derivative in the discorhabdin series, was obtained as an optically active green solid from specimens of the sponge *L. apicalis* collected in 1995 from Hut Point, Danger Slopes, and Cape Evans on Ross Island, Antarctica.[14] Its structure was characterized by extensive 1D and 2D NMR data and by comparison of the spectral data with those of discorhabdin C **3**.[14]

Compound **8** was originally called discorhabdin G by Munro et al. in a presentation of the 1996 American Society of Pharmacognosy (ASP) meeting.[25] This compound was first isolated together with discorhabdins I−M.[25] Later, it was isolated from *L. brevis* (sponge samples were collected from Patagonia, Argentina) with a name of discorhabdin I.[22] At almost the same time, it was also obtained from the South African latrunculid sponge *L. bellae* and referred to discorhabdin G*[23] in order to avoid a confusion with Baker et al.'s nomenclature for discorhabdin G **7**.[14] In 2009, an enantiomeric pair (**8** and **43**) of discorhabdins G*/I was isolated from Wellington Harbor-sourced and Doubtful Sound-sourced *Latrunculia* sponges in New Zealand, respectively, and their absolute configuration was established (see discussion in section 2.2).[26]

The original structures and spectral data of discorhabdins H−O **9**−**16**, isolated from the New Zealand sponges of *Latrunculia* by Munro et al., were first presented at the 37th Annual ASP Meeting in 1996.[20,25] In 2000, the structures of discorhabdins I−O **10**−**16** were listed in a review of bioactive marine alkaloids by Munro et al., however, discorhabdin H was paradoxically omitted by the authors.[20] The ^1H and ^{13}C NMR data for discorhabdins H−O were relatively inaccessible, which led to some ambiguities in the nomenclature of new discorhabdins discovered later.[23,25] In 2004, discorhabdin H (= Δ^4-discorhabdin J) **9**, was isolated from the South African latrunculid

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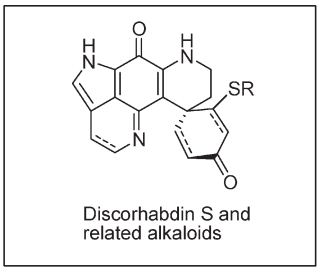
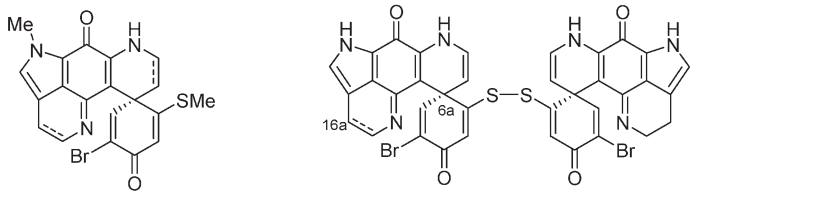
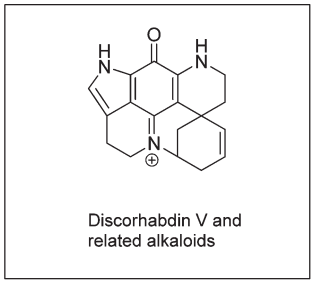
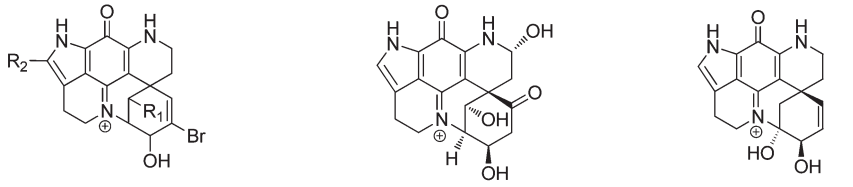




20 (6*S*)-Discorhabdin S: Δ^{16}
21 (+)-(6*S*)-Discorhabdin T: Δ^{7}, Δ^{16}
22 (+)-(6*S*)-Discorhabdin U: Δ^{7}
46 (-)-(6*S*, 6a*S*)-Discorhabdin W
24 (+)-(6*R*, 6a*R*)-Discorhabdin W
47 (-)-(6*S*, 6a*S*)-16a, 17a-Dehydrodiscorhabdin W: Δ^{16a}
48 (+)-(6*R*, 6a*R*)-16a, 17a-Dehydrodiscorhabdin W: Δ^{16a}

Figure 5. Naturally occurring pyrroloiminoquinone-related discorhabdins (IV).





23 Discorhabdin V: R_1 = R_2 = H
40 14-Bromo-1-hydroxydiscorhabdin V: R_1 = OH, R_2 = Br
27 (-)-(1*R*,2*R*,3*R*,6*R*,8*R*)-Discorhabdin Z
55 Epinardin A

Figure 6. Naturally occurring pyrroloiminoquinone-related discorhabdins (V).

sponge *Strongylodesma algoaensis* and its spectral data were completely assigned by Davies-Coleman and his co-workers.[23]

The fully assigned spectral data of discorhabdin L **13**, isolated from the sponge *L. brevis* collected in Tierra del Fuego, Patagonia, Argentina, was first reported by Reyes et al. in 2002.[22] Recently, it was also obtained from *L.* species collected at different locations in New Zealand,[24,26] and also found from a new deep-water Alaskan sponge species of the genus *Latrunculia* by Hamann et al. in 2010.[30]

A Δ^4 olefin was inadvertently omitted from the original structure drawing of discorhabdin N **15** presented in the Munro's review.[20,23] As a result, a confusion had surrounded the accurate structure of discorhabdin N, which was finally clarified by Davies-Coleman et al. in 2004.[23] The complete assignment of the spectral data of **15**, a minor metabolite in the South African sponge *L. bellae*, was presented by Davies-Coleman et al.[23] However, the relative configuration at the four stereocenters in discorhabdin N **15** was ambiguous at that time. Just recently, its absolute configuration was established as 1*R*,2*S*,6*R*,8*S* by a combination of NOESY correlations, *J*-based configuration analysis and the calculated ECD spectra data.[29]

2.1.3. Discorhabdins P−Z. Discorhabdin P (*N*-13-methyl discorhabdin C) **17**, was isolated from a deep-water Caribbean sponge of the genus *Batzella* collected from a depth of 141 m off the Great Bahama Bank by Gunasekera et al. in 1999.[17] The structure was confirmed by single-crystal X-ray diffraction.[17] Discorhabdin P **17** was the first *N*-methylated discorhabdin isolated from a sponge of *Batzella* spp., and *N*-methylation was a feature of the pyrroloiminoquinones found in the genus of *Batzella*.[21,47,49,50,76] This discovery could establish a

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Table 1. Discorhabdins and Their Analogues from Marine Organisms

discorhabdins and related analogues	marine sources	collection localities	ref
discorhabdin C (**3**)	sponge of the genus *Latrunculia* du Bocage (= *L.* sp., family Latrunculiidae)	New Zealand	3, 5
prianosins A (= discorhabdin A) (**1**), B (**54**), C (= 2-hydroxydiscorhabdin D) (**36**), D (= discorhabdin D) (**4**)	the sponge *Prianos melanos* (later reidentified as a species of *Strongylodesma* later, family Latrunculiidae)[25]	Motobu Peninsula (−2 to −3 m), Okinawa Island	4, 8−10, 12
discorhabdin A (**1**)	the sponge of *L. brevis*	from depths of 110−145 m off the Otago Peninsula, New Zealand	6
discorhabdin B (**2**)	an undescribed *Latrunculia* species	from the Kaikoura Peninsula, New Zealand	6
discorhabdin A (**1**)	the Fijian sponge *Zyzzya* cf. *marsailis.* (= *Z. fuliginosa*)	Makaluva Island and Mbengga harbor both in the Fiji islands	37
ethanol solvated discorhabdin A	the new sponge species *L.oparinae*	near the shores of Kuril Islands (Ushishir Island, Rikord Straits, 49°22.10′N, 154°09.5′E), Russia	31
discorhabdins A (**1**), D (**4**)	the sponges *L. brevis* and *P.* sp.	*L.brevis*: from the Sugar Loaf Islands (−30 m), Taranaki, New Zealand; *P.* sp.: from the legs of Aquapolice, a floating building at Ocean EXPO Park, Okinawa	7
discorhabdins E (**5**), F (**6**), 2-hydroxydiscorhabdin D (**36**)	sponge of the genus *Latrunculia*	from the Antarctic to the subtropical waters to the NE of New Zealand	11
discorhabdin E (**5**)	the New Zealand sponge *L.* cf. bocagei (= *L.* sp.)	Auckland Islands, New Zealand	13
discorhabdins C (**3**), G (**7**)	*the sponge* L. apicalis	between 6 and 40 m depth from Hut Point, Danger Slopes, and Cape Evans on Ross Island, Antarctica (77°51.5′S, 166°39′E)	14
discorhabdins A (**1**), B (**2**), G*/ I (**8**), L (**13**)	the sponge *L. brevis* Ridley and Dendy (family Latrunculiidae)	from Tierra del Fuego (−72−76 m), Patagonia, Argentina (49°18.1′S, 65°33.9′W)	22
discorhabdins A (**1**), D (**4**), H (**9**), 3-dihydrodiscorhabdin C (**31**)	the South African latrunculid sponge *Strongylodesma algoaensis*	from Algoa Bay (−15 m), South Africa (33°50′S, 25°45′ E)	23
discorhabdins I (**10**), J (**11**), K (**12**), L (**13**), M (**14**), N (**15**), O (**16**)	New Zealand *Latrunculia* sponges	New Zealand	20,25
discorhabdins G*/ I (**8**), N (**15**)	the South African latrunculid sponge *L. bellae*	from Riy Banks (−22 m), Algoa Bay, South Africa (33°59′S, 25°51′ E)	23
discorhabdin P (**17**)	a deep-water Caribbean sponge of the genus *Batzella* (class Demospongia, order Poecilosclerida, family Desmacididae)	from the western Great Bahama Bank (−141 m), Bahamas (25°15.56′N, 79° 11.10′W)	17
(−)-discorhabdin Q (= 16,17-dehydrodiscorhabdin B) (**18**)	sponges of *L. purpurea* and numerous collections of *Z. fuliginosa*, and *Z.* spp.	*L. purpurea*: on Horseshoe Reef west northwest of Margaret Brock Lighthouse, Australia; *Z. fuliginosa*: in the bay south of Sphinx Head, Wessell Island, Australia; and Bega Lagoon, Fiji; *Z.* spp.: at Assail Bank, between North Island and the Wallab Group, Australia.	18
discorhabdins R (**19**), B (**2**)	an Antarctic *L.* sp. and a southern Australian *Negombata* sp.	the central Prydz channel of Prydz Bay, Antarctica, and Port Campbell, Victoria	19
discorhabdins S (**20**), T (**21**), U (**22**)	a deep-water marine sponge of the genus *Batzella*	a depth of 141 m, from the Ocean Cay, approximately 20 nautical miles south of Bimini, Bahamas (25°23.9′ N, 79°14.3′W)	21
discorhabdin V (**23**)	the South African sponge *Tsitsikamma pedunculata*	from Thunderbolt Reef (−40 m), Algoa Bay, South Africa (34°03′S, 25°41′ E)	23
discorhabdins W (**24**), B (**2**), D (**4**), G*/ I (**8**), L (**13**)	a sponge of *L.* sp.	at Anita Bay (−22 m), in Milford Sound, Fiordland, New Zealand	24
(+)-discorhabdins X (**25**), A (**1**), D (**4**), (+)-3-dihydrodiscorhabdin A (**28**), (+)-debromodiscorhabdin A (**29**), (+)-dihydrodiscorhabdin L (**39**)	southern Australian marine sponges of the genera *Higginsia* and *Spongosorites* (class Demospongiae, order Halichondirda)	at Deal Island (147°21.1′ E, 39°29.3′S) at a depth of 8−12 m and Port Campbell (142°49.8′ E, 38°38.0′S) at a depth of 15−20 m	27

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Table 1. Continued

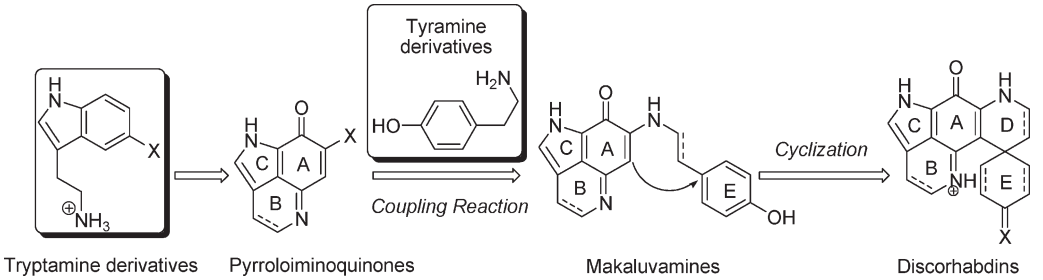
discorhabdins and related analogues	marine sources	collection localities	ref
discorhabdins Y (**26**), A (**1**), C (**3**), E (**5**), L (**13**), dihydrodiscorhabdin B (**30**), 3-dihydrodiscorhabdin C (**31**), discorhabdin benzene derivative (**41**)	a new deep-water Alaskan sponge species of the genus *Latrunculia*	from the Aleutian Islands (53.06264 N, −169.0872) at a depth of 230 m, Alaska	30
(−)-discorhabdins Z (**27**), L (**13**), discorhabdins B (**2**), C (**3**), D (**4**), discorhabdins E (**5**), G*/I (**8**), I (**10**), 3-dihydrodiscorhabdin C (**31**), (+)-1-methoxydiscorhabdin D (**38**), (−)-3-dihydrodiscorhabdin D (**49**), (−)-3-dihydrodiscorhabdin L (**50**)	sponges of *Sceptrella* sp.	from the shore of Gageodo (Gukhuldo) (−20 m), West Sea, Korea	32
14-bromodiscorhabdin C (**32**), 14-bromo-3-dihydrodiscorhabdin C (**33**)	an undescribed latrunculid sponge (later identified as *Tsitsikamma favus*)	in the Tsitsikamma Marine Reserve, off the southeastern South African coast	15
3-dihydrodiscorhabdin C (**31**), 14-bromodiscorhabdin C (**32**), 14-bromo-3-dihydrodiscorhabdin C (**33**), 14-bromo-3-dihydro-7,8-dehydrodiscorhabdin C (**34**), 3-dihydro-7,8-dehydrodiscorhabdin C (**35**), 14-bromo-1-hydroxydiscorhabdin V (**40**)	the South African sponge *T. pedunculata*	from Thunderbolt Reef (−40 m), Algoa Bay, South Africa (34°03́S, 25°41́ E)	23
14-bromo-3-dihydrodiscorhabdin C (**33**), 3-dihydro-7,8-dehydrodiscorhabd -in C (**35**), 14-bromo-1-hydroxydiscorh -abdin V (**40**)	the South African sponge *T. favus*	from Rheeders Reef (−22 m), Tsitsikamma National Park (34°16́S, 25°34́ E), southeast coast of South Africa	23
1-aminodiscorhabdin D (**37**), 1-methoxydiscorhabdin D (**38**)	the South African latrunculid sponge *L. bellae*	from Riy Bank (−22 m), Algoa Bay, South Africa (33°59́S, 25°51́E)	23
(−)-discorhabdins B (**42**), G*/I (**43**), (+)-discorhabdins W (**24**), L (**45**), (+)-discorhabdin H_2 (**51**)	Milford Sound-sourced freeze-dried sponge *L. (Lautrunculia) fiordensis.*	New Zealand	26, 29
(+)-discorhabdins B (**2**), G*/I (**8**), Q (**53**), (−)-discorhabdins L (**13**), W (**46**), (+)-3-dihydrodiscorhabdin A (**28**), (+)-1-thiomethyldiscorhabdin G*/I (**44**), (−)-16a,17a-dehydrodiscorhabdin W (**47**)	*L. (Biannulata) wellingtonesis*	New Zealand	26, 28
discorhabdin C (**3**), (+)-discorhabdins W (**24**), L (**45**), (−)-discorhabdins B (**42**), G*/I (**43**), K_2 (**52**), (+)-16a,17a-dehydrodiscorhabdin W(**48**)	doubtful sound-sourced freeze-dried *L. (Lautrunculia) fiordensis*	New Zealand	26, 28, 29
(+)-discorhabdin K (**12**)	freeze-dried *L. (Biannulata) kaikoura*	New Zealand	29
(+)-discorhabdin D (**4**), 3-dihydrodiscorhabdin C (**31**), (+)-2-hydroxydiscorhabdin D (**36**)	freeze-dried *L. (Lautrunculia) trivetricillata*	New Zealand	29
epinardins A (**55**), B (**56**), C (**57**), D (**58**)	undetermined deep-water green demosponges	pre-Antarctic waters near the Crozet Islands in South Indian Ocean	16

chemotaxonomic link among the sponges *Batzella*, *Zyzzya*, *Latrunculia* and *Strongylodesma*.[17]

Subsequently, discorhabdins Q **18** and R **19** were isolated.[18,19] Investigation of cytotoxic extracts of the sponge *L. purpurea*, and numerous species of *Z. massalis*, *Z. fuliginosa*, and an unidentified sponge *Z.* spp, afforded disocrhabdin Q (16,17-dehydrodiscorhabdin B or Δ^{16}-discorhabdin B) **18**. It was considered to be the most prevalent discorhabdin in the genus of *Zyzzya*. Its ^{1}H NMR spectrum revealed the presence of a pair of mutually coupled olefinic methines (H_2-16 and H_2-17). The structure was assigned by comparison of spectral data with discorhabdin B **2**. The absolute configuration of (−)-discorhabdin Q **18** was assigned as 6*R*,8*R*, which was directly deduced by the observation of an opposite optical rotation differing from that of (+)-(6*S*,8*S*)-discorhabdin Q **53**.[29]

Discorhabdin R **19** was isolated together with discorhabdin B **2** from two latrunculid sponges (Antarctic *L.* sp. and Australian *Negombata* spp).[19] The structure was determined by analysis of spectroscopic data including 1D and 2D NMR data and comparison of the spectral data with those of discorhabdin B **2**. The ^{1}H NMR spectrum revealed that discorhabdin R **19** contained two mutually coupled epoxy methine signals, but lacked a bromine substituent at C-2 and a Δ^1 olefin.[19] So far, compound **19** is the sole *cis*-1,2-epoxy-discorhabdin, and the relative configuration of

Scheme 1. Possible Biosynthesis Pathways of Pyrroloiminoquinone-Related Alkaloids and Discorhabdins.[20,25,33,109]



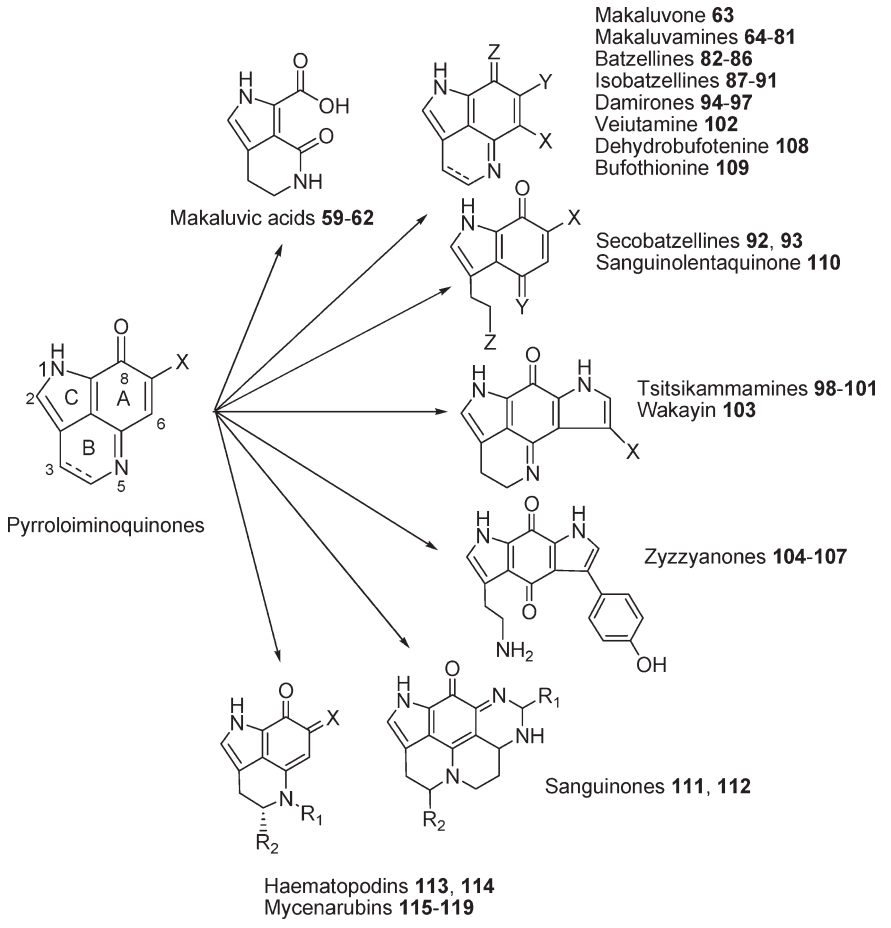


Figure 7. Naturally occurring pyrroloiminoquinone-related alkaloids.

the epoxide was not assigned by either 1D NOE difference or 2D NOESY NMR experiments.

Discorhabdins S−U (**20**−**22**) were isolated from a deep-water marine sponge of the genus *Batzella* collected from a depth of 141 m off the coast of the Bahamas by Gunasekera et al. in 2003.[21] Discorhabdins S **20**, T (= Δ^7-discorhabdin S) **21**, and U (= 16,17-dihydrodiscorhabdin S) **22** were all C-5 *S*-methyl derivatives of discorhabdin P. The structures were assigned by analyses of HR-MS and extensive NMR data and by comparison of the spectral data with related known compounds.[21] Recently, the 6*S* configuration in discorhabdins S, T, and U was established by semisynthetic conversion from (+)-discorhabdin B **2**,[29] in which the 6*S*,8*S* configuration was previously well-defined.[26]

Discorhabdin V **23** and 14-bromo-1-hydroxydiscorhabdin V **40** were isolated from the South African sponge *Tsitsikamma pedunculata*.[23] The configurations at C-2, C-3, and C-6 were not established in either compound. Discorhabdin W **24**, a discorhabdin dimer, was isolated together with the known discorhabdins B **2**, D **4**, G*/I **8**, and L **13** from a New Zealand *L.* sp. by Munro et al. in 2005.[24] The presence of the disulfide bond was confirmed by reduction of discorhabdin W **24** with dithiothreitol, which yielded a product identical to the naturally occurring discorhabdin B **2**. Conversely, **2** could be dimerized to **24** under exposure to light.[24]

In 2009, discorhabdin X **25** was isolated from southern Australian marine sponges of the genera *Higginsia* and *Spongosorites*.[27]

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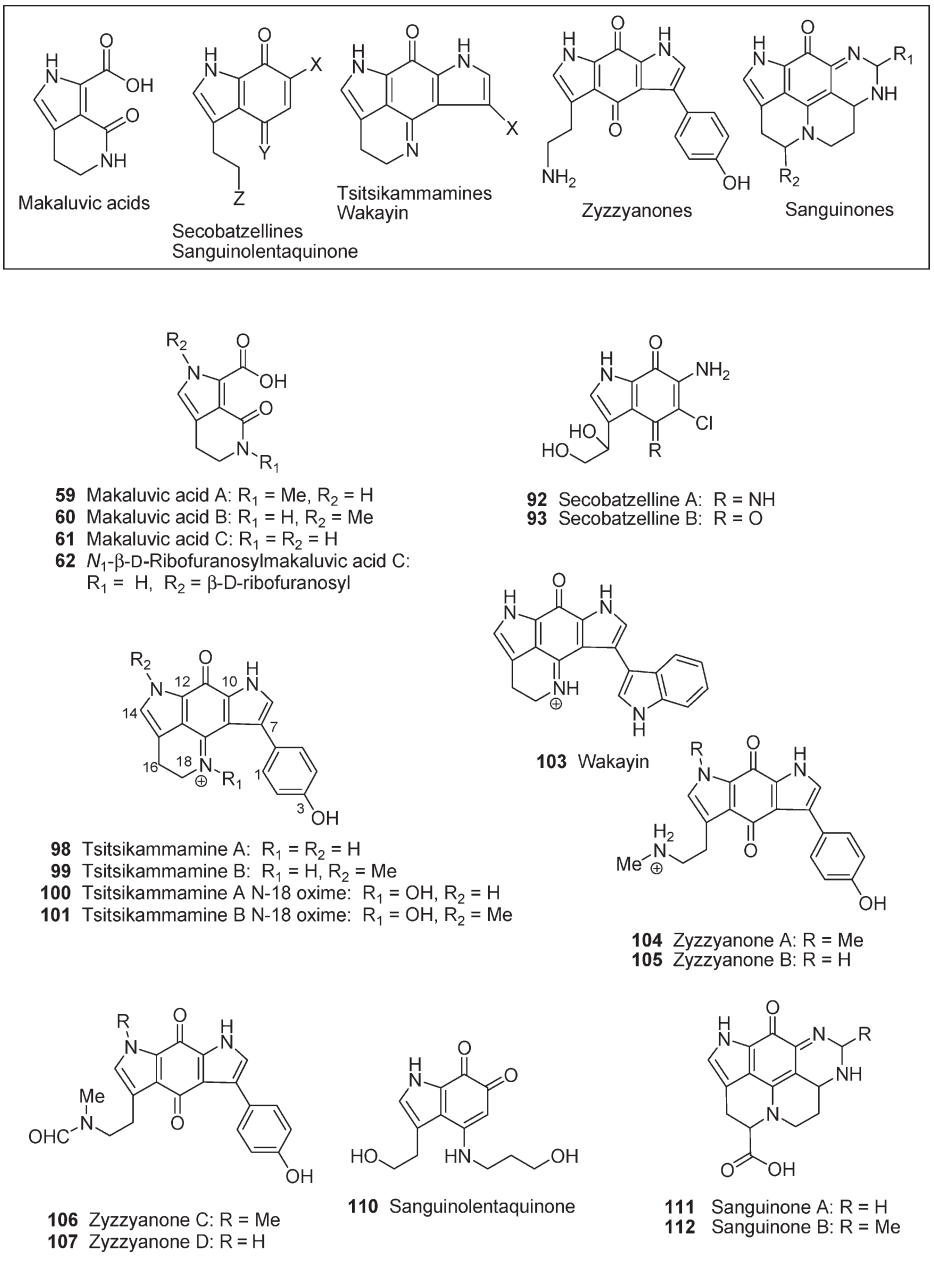

Figure 8. Naturally occurring pyrroloiminoquinone-related alkaloids (I).

It represents the first example of pyrroloiminoquinone bearing a thio heterocycle flanked by oxo-thio-acetal and azo-thio-acetal functionalities.[27] In 2010, Hamann et al. reported a new brominated pyrroloiminoquinone, discorhabdin Y **26**, together with the known discorhabdins A **1**, C **3**, E **5**, L **13**, 3-dihydrodiscorhabdin C **31**, and a discorhabdin benzene derivative **41** from an undescribed deep-water Alaskan sponge species of the genus *Latrunculia*.[30] The configuration at C-6 in discorhabdin Y **26** was established as *R* by comparison of the experimental CD spectrum with ECD spectra calculated by time-dependent density functional theory (TDDFT). Almost at the same time, (−)-discorhabdin Z **27** was isolated from a sponge *Sceptrella* spp. collected from Gageodo, West Sea, Korea.[32] Compound **27** possesses a unique hemiaminal functionality among the discorhabdin alkaloids. The absolute configuration in **27** was determined as 1*R*,2*R*,3*R*,6*R*,8*R* by comparison of calculated and experimental ECD data.

2.1.4. Derivatives of Discorhabdins A−D, L, G*/I, V, and W. In 2009, two new derivatives of discorhabdin A, (+)-3-dihydrodiscorhabdin A **28** and (+)-debromodiscorhabdin A **29** together with discorhabdins A **1**, D **4**, X **25** were isolated from a southern Australian marine sponge of the genus *Higginsia*.[27] The absolute configuration of **28** and **29** was attributed to be the same as (+)-discorhabdin A **1** based on a biogenetic consideration.[27] However, the putative 3*S* configuration reported for compound **28** was immediately revised as 3*R* according to conformational analysis and a semisynthetic study by Copp's group, who also isolated **28** from the New Zealand-sourced sponge *L. (Biannulata) wellingtonesis*.[28] A discorhabdin L derivative, (+)-3-dihydrodiscorhabdin L **39**, was also obtained from a southern Australian sponge of the genus *Higginsia*.[27] Most recently, (−)-3-dihydrodiscorhabdin L **50** was reported from sponges *Sceptrella* spp.[32] However, the absolute configuration in both **39** and **50** remains unknown.

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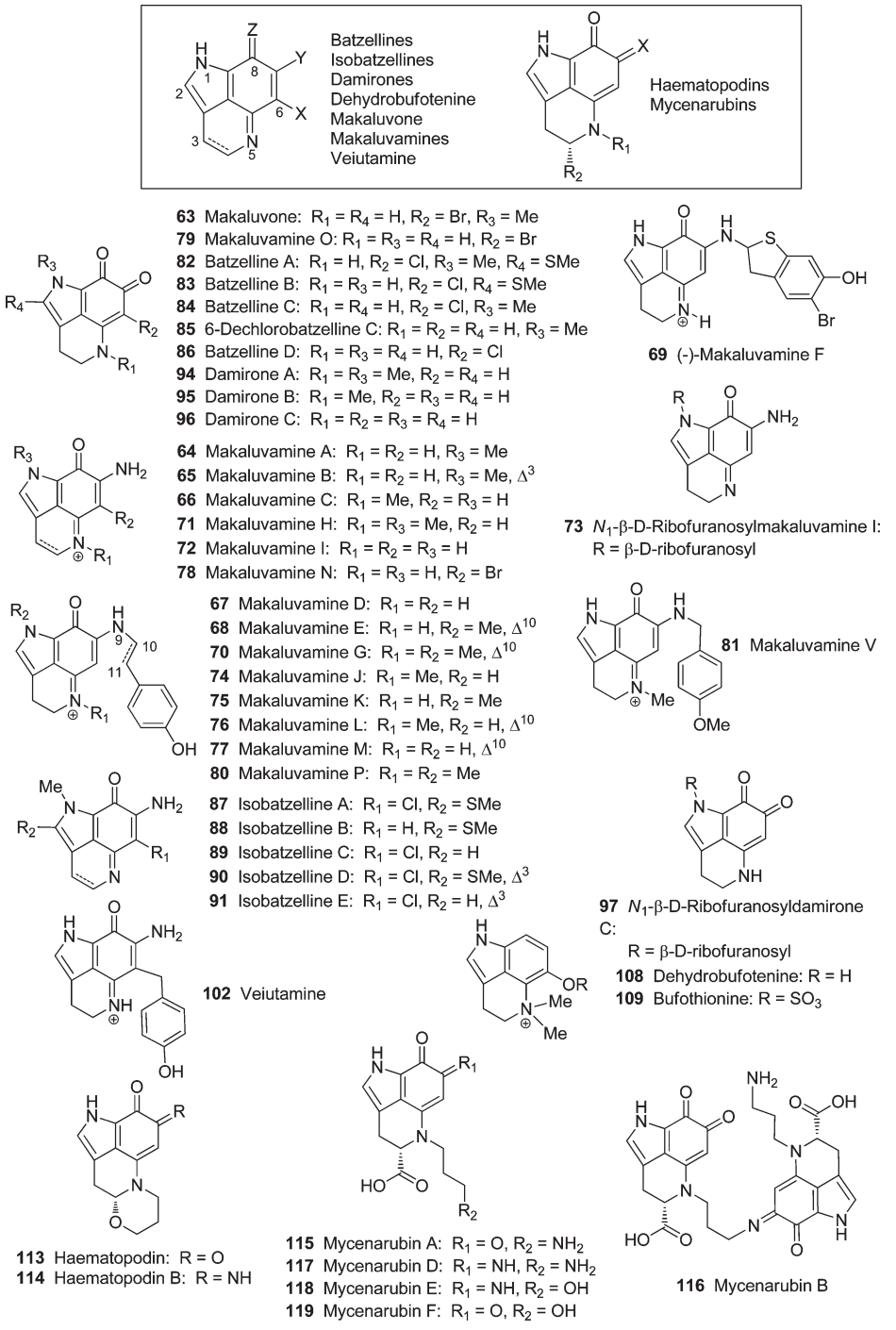

Figure 9. Naturally occurring pyrroloiminoquinone-related alkaloids (II).

A new discorhabdin B derivative, dihydrodiscorhabdin B **30**, was obtained from an Alaskan sponge of the genus *Latrunculia*.[30] However, the absolute configuration of **30** was not assigned due to decomposition of the sample.[30] Two brominated discorhabdin C derivatives, 14-bromodiscorhabdin C **32** and 14-bromo-3-dihydrodiscorhabdin C **33**, were first reported from the sponge *Tsitsikamma favus* collected in South African in 1996.[15] These two compounds were later also isolated in 2004 from *T. pedunculata* together with 3-dihydrodiscorhabdin C **31**, 14-bromo-3-dihydro-7,8-dehydro-discorhabdin C **34**, and 3-dihydro-7,8-dehydro-discorhabdin C **35**.[23] Interestingly, compound **31** was previously semisynthesized via a reduction of discorhabdin C **3**.[13]

2-Hydroxydiscorhabdin D **36**, originally assigned as prianosin C, was isolated from the Okinawan sponge *P. melanos* by a Japanese group in 1988[9] and later reisolated from the New Zealand sponge *L. brevis* in 1990.[11] Another two derivatives of discorhabdin D, 1-aminodiscorhabdin D **37** and 1-methoxydiscorhabdin D **38**, were subsequently isolated from the South African latrunculid sponge *L. bellae* in 2004.[23] The configuration of compounds **37** and **38** was not established yet.[23] Meanwhile, 14-bromo-1-hydroxydiscorhabdin V **40** was also reported from

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Table 2. Naturally Occurring Pyrroloiminoquinone-Related Alkaloids

alkaloids	marine/fungi sources	collection localities	ref
makaluvic acids A (**59**), B (**60**)	the marine sponge *Zyzzya fuliginosa* (order Poecilosclerida)	within the lagoon of Kuop atoll (−20 m) and the Northeast pass of Chuuk lagoon (−20 m), Chuuk State, Federated States of Micronesia	35
makaluvic acid C (**61**), N_1-β-D-ribofuranosyl makaluvic acid C (**62**)	the sponge *Strongylodesma aliwaliensis* (class Demospongia, order Poecilosclerida, family Latrunculiidae)	from the Aliwal Shoal (−15−18 m) off the KwaZulu-Natal coast, South Africa	36
makaluvone (**63**), makaluvamines A (**64**), B (**65**), C (**66**), D (**67**), E (**68**), F (**69**), damirone B (**95**)	the Fijian sponge *Z.* cf. *massalis* (later reidentified as *Z. fuliginosa*)[25,46]	at Makaluva Island and Mbengga harbor in the Fiji island group	37
makaluvamine G (**70**)	sponge of the genus *Histodermella* (later reidentified as *Z. fuliginosa*)[25,39,46]	Indonesia	38
makaluvamines H (**71**), I (**72**), J (**74**), K (**75**), L (**76**), M (**77**), damirone C (**96**)	the sponge *Z. fuliginosa*	Nahpali Island (−13 m), Pohnpei, Federated States of Micronesia	39
makaluvamine N (**78**)	the Philippine sponge *Z. fuliginosa*	from Cape S. Ildefonso, The Philippines	40
makaluvamine O (**79**)	the Jamaican sponge *Smenospongia aurea* (Hyatt)	from "LTS-1" Discovery Bay (−16−30 m), Jamaica	41
makaluvamine P (**80**)	the sponge *Z.* cf. *fuliginosa*	from the coasts of Vanuatu Islands	43
makaluvamine V (**81**)	the sponge *Z. Massalis* (reclassified as *Z. fuliginosa*)	from a Fijian collection	46
N-1-β-D-ribofuranosylmakaluvamine I (**73**), *N*-1-β-D-ribofuranosyl damirone C (**97**)	the South African latrunculid sponge, *S. aliwaliensis*	from the Aliwal Shoal off the coast of KwaZulu-Natal, South Africa.	44
batzellines A (**82**), B (**83**), C (**84**)	the deep water Bahamas sponge *Batzella* sp.	Bahamas	47
6-dechlorobatzelline C (**85**)	the sponge *Z. massalis* (reclassified as *Z. fuliginosa*)	Marchinbar Island	46
batzelline D (**86**), isobatzelline E (**91**)	the sponge *Z. fuliginosa*	from Abrohlos Island in the Indo-West Pacific	48
isobatzellines A (**87**), B (**88**), C (**89**), D (**90**)	a sponge of *B.* sp.	one from between Freeport and West End in the Grand Bahamas Islands(−120 m); one from Mangrove Island off West End (−130 m), Grand Bahamas Islands	49
secobatzellines A (**92**), B (**93**)	two sponges of the genus *Batzella* (class Demospongia, order Poecilosclerida, family Desmacididae)	one from the western Great Bahama Bank (−152 m), Bahamas (25° 23.921′N, 79° 14.104′ W); one from North Bimini west of Alice Town (−138 m), Bahamas (25° 44.288′ N, 79° 18.981′ W)	50
damirones A (**94**), B (**95**)	the Palauan sponge *Damiria* sp. (reidentified as *Z. fuliginosa*)[39]	Ngemelis drop-off (−20 m), Republic of Palau	51
tsitsikammamines A (**98**), B (**99**)	the undescribed latrunculid sponge (later identified as *Tsitsikamma. favus*)	in the Tsitsikamma Marine Reserve, off the southeastern South African coast	15
tsitsikammamine A N-18 oxime (**100**), tsitsikammamine B N-18 oxime (**101**)	the South African sponge *T. favus*	from Rheeders Reef (−22 m), Tsitsikamma National Park (34°10́S, 25°34́ E), southeast coast of South Africa	23
veiutamine (**102**)	the Fijian sponge *Z. fuliginosa*	from Suva Harbor, Fiji islands	52
wakayin (**103**)	the ascidian *Clavelina* species (Chordata, Aplousobranchia, Clavelinidae)	from shallow reef waters off Wakaya Island in the Fiji Group	53
zyzzyanone A (**104**)	the sponge *Z. fuliginosa*	from a depth of −10 m off Mid Island, Australian Great Barrier Reef	54
zyzzyanones B (**105**), C (**106**), D (**107**)	the sponge *Z. fuliginosa*	from a depth of −10 m off Mid Islet, Eastern Australia	55
dehydrobufotenine (**108**)	from the parotid glands of the South American toad *(Bufo marinus)*	South America	56, 57
bufothionine (**109**)	toad (the skin of *Bufo bufo gargarizans*)	South America	56, 60
sanguinolentaquinone (**110**), sanguinones A (**111**), B (**112**)	frozen fruiting bodies of the mushroom *Mycena sanguinolenta*	beech forests near Starnberg, 20 km south of Munich (Bavaria), Germany	62
haematopodin (**113**)	fruiting bodies of the toadstool *M. haematopus* (Pers.ex Fr.) Kummer		63

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Table 2. Continued

alkaloids	marine/fungi sources	collection localities	ref
haematopodin B (**114**), mycenarubins D (**117**), E (**118**), F (**119**)	fruiting bodies of *M. haematopus* (leg. et det. S. Peters and P. Spiteller)	in beech forest mear Kelheim	64
mycenarubins A (**115**), B (**116**)	fruiting bodies of the mushroom *M. rosea* (leg. et det. S. Peters and P. Spiteller)	beech forests 20 km south of Munich (Bavaria), Germany	65

Table 3. Syntheses of Discorhabdins and Related Analogues

discorhabdins and related analogues	research group	ref
(±)-discorhabdin A	Kita	113
(+)-discorhabdin A (**1**)	Kita	118
(+)-discorhabdin A (**1**), (−)-discorhabdin A	Kita	122
discorhabdin A (**1**)	Fukuyama	115
discorhabdin A oxa analogues	Kita	125
discorhabdin C (**3**)	Yamamura	94
discorhabdin C (**3**)	Kita	89, 91
discorhabdins C (**3**), E (**5**), I (**10**), dethiadiscorhabdin D	Heathcock	109
3-dihydrodiscorhabdin C (**30**), discorhabdin C 1H-azepine derivatives	Munro	11
N-benzyl discorhabdin C	Yamamura	88
discorhabdins P (**17**), S (**20**), T (**21**), U (**22**), (+)-disocorhabdin Q (**53**), discorhabdins U analogues	Copp	29, 76
prianosin B (**54**)	Kita	124

the specimens of *Tsitsikamma pedunculata* and *T. favus*.[23] In 2010, (+)-1-methoxydiscorhabdin D **38** along with (−)-3-dihydrodiscorhabdin D **49** and (−)-3-dihydrodiscorhabdin L **50** was obtained from a Korean marine sponge *Sceptrella* spp.[32] The absolute configuration of compound **49** was determined to be 2*S*,3*R*,6*R*,8*S* by comparison of the experimental CD spectrum with a quantum chemically simulated ECD spectrum calculated by time-dependent density functional theory (TDDFT).[32]

In 2009, (+)-(6*R*,8*S*)-1-thiomethyldiscorhabdin G*/I **44** and both enantiomers (**47**, **48**) of 16a,17a-dehydrodiscorhabdin W were isolated from New Zealand *L.* spp. sponges.[28] The absolute configurations of these three discorhabdin derivatives were assigned by comparison of their experimental ECD spectra with those of closely related discorhabdin alkaloids [e.g., (+)-discorhabdin G*/I **8** and (−)-discorhabdin W **46**].[28]

2.2. Stereoisomers of Discorhabdins B, G*/I, H, K, L, Q, and W

In 2009, the enantiomeric pairs of discorhabdins B (**2**, **42**), G*/I (**8**, **43**), L (**13**, **45**), and W (**24**, **46**) were isolated for the first time from a number of different marine sponges of *Latrunculia* species collected at different regions along the New Zealand coast by Copp et al.[26] The absolute configurations of the above enantiomeric discorhabdins were determined by comparison of the experimental CD spectra with ECD spectra calculated by TDDFT.[26] In the following studies carried out by Copp et al., both enantiomers (**47**, **48**) of 16a,17a-dehydrodiscorhabdin W,[28] a diastereomer of discorhabdin H [(+)-discorhabdin H_2 **51**],[29] a diastereomer of discorhabdin K [(−)-discorhabdin K_2 **52**][29] and enantiomeric (+)-discorhabdin Q **53**[29] were identified by direct comparison of experimental CD spectra with those of structurally related discorhabdins with defined configuration [e.g., (+)-discorhabdin G*/I **8** and (−)-discorhabdin L **13**].

2.3. Prianosins A−D and Epinardins A−D

Discorhabdins, prianosins, and epinardins are structurally very close or identical to each other. Although prianosins A-D were reported at almost the same time as the discorhabdins, the latter trivial name has subsequently taken precedence in the literature. To avoid confusion, prianosins A, C, and D were accordingly renamed as discorhabdin A **1**, 2-hydroxydiscorhabdin D **36** and discorhabdin D **4**, respectively, while prianosin B (= Δ^{16}-discorhabdin A) **54** has remained unchanged in the literature.[25]

Epinardins A−D (**55**−**58**) were isolated from undetermined deep-water green demosponges collected in pre-Antarctic waters near the Crozet Islands in the South Indian Ocean.[16] These four alkaloids contained an allylic alcohol functionality in place of the enone system in the discorhabdins/prianosins. Relative configuration of the epinardins was assigned from NOE correlations and *J*-value based configuration analysis.[16]

As shown above, fifty-eight (**1**−**58**) amazing pyrroloiminoquinone alkaloids classified as discorhabdin/prianosin/epinardin have been so far reported from marine sponges. In this review, some duplications and inconsistencies of the trivial names and occurrences of incorrect structures in previous literature have been clarified. The determination of the absolute configuration for this class of compounds has been challenging; however, X-ray diffraction (e.g., discorhabdins A **1**, C **3**, P **17**),[3,4,17] semisynthetic transformation (e.g., discorhabdins S **20**, T **21**, U **22**, W **24**),[26,29] and especially ECD spectra[26−30,32] have proven to be powerful tools. The TDDFT calculations of ECD spectra were first undertaken by Copp's group for reconfirmation of discorhabdin A **1**, the absolute configuration of which was previously secured by X-ray crystal analysis.[26] Later, the same procedure was successfully applied to configurational assignment for discorhabdins Y **26**,[30] Z **27**,[32] (−)-3-dihydrodiscorhabdin D **49**,[32] and enantiomeric pairs of discorhabdins B (**2**, **42**), G*/I (**8**, **43**), L (**13**, **45**), W (**24**, **46**).[26] In addition, direct comparison of experimental ECD spectra with those of previously well-defined discorhabdins was used to aid in the assignment of absolute configurations for discorhabdins D **4**,[29] H **9**,[29] K **12**,[29] N **15**,[29] (+)-3-dihydrodiscorhabdin A **28**,[28] (+)-2-hydroxydiscorhabdin D (= prianosin C) **36**,[29] (+)-1-thiomethyldiscorhabdin G*/I **44**,[28] (±)-16a,17a-dehydrodiscorhabdins W **47**,[28] **48**,[28] discorhabdins H_2 **51**,[29] K_2 **52**,[29] and (+)-discorhabdin Q **53**.[29]

3. SIMPLE CYCLIZED NATURALLY OCCURRING PYRROLOIMINOQUINONE-RELATED ALKALOIDS

During the past decades, there has been great interest in pyrroloiminoquinone alkaloids. In general, the pyrroloiminoquinone family consists of discorhabdins/prianosins, epinardins, batzellines/isobatzellines/secobatzellines, damirones, makaluvic acids/makaluvone/makaluvamines, tsitsikammamines, veiutamine, wakayin, zyzzyanones, hematopodins, mycenarubins, and

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sanguinones.[25,132] From a structure point of view, the discorhabdins are biosynthetically related to the simple cyclized pyrroloiminoquinone alkaloids such as makaluvic acids/makaluvamines (**59**−**81**),[35−46] batzellines/isobatzellines/secobatzellines (**82**−**93**),[47−50] or damirones (**94**−**97**).[39,44,51] On the basis of their structural similarities, it is tempting to propose that makaluvamines could occupy an intermediate position in the biosynthetic network of more complex pyrroloiminoquinone alkaloids.[20,25,34]

3.1. Pyrroloiminoquinone-Related Alkaloids from Marine Organisms

3.1.1. Makaluvic acids/Makaluvone/Makaluvamines. In 1996, two pyrrolecarboxylic acids, makaluvic acids A **59** and B **60**, were isolated from the sponge *Zyzzya fuliginosus* (corrected as *Z. fuliginosa*[25]) collected in the Federated States of Micronesia.[35] Around nine years later, makaluvic acid C **61** and *N*-1-β-D-ribofuranosylmakaluvic acid C **62** were isolated from the sponge *Strongylodesma aliwaliensis* collected off the east coast of South Africa.[36]

The makaluvamines, a class of alkaloids containing a 7-amino substituted pyrroloiminoquinone skeleton, received attention due to their significant cytotoxicity in a cell-based mechanism screen.[37] The first reported examples of this series, makaluvamines A−F **64**−**69**, were isolated in 1993 from the Fijian sponge *Z.* cf. *marsailis* (reidentified as *Z. fuliginosa*[25]) together with makaluvone **63**.[37] Shortly thereafter, makaluvamine G **70** was isolated from the sponge *Histodermella* sp. (reidentified as *Z. fuliginosa*[25,39,46]) collected in Indonesia.[38] In 1995, makaluvamines H−M **71**, **72**, **74**−**77** were purified from the sponge *Z. fuliginosa* collected from a reef at Nahpali Island, Pohnpei, Micronesia.[39] The same species collected in the Philippines (in 1997) and Vanuatu Islands (in 2001) afforded makaluvamines N **78**[40] and P **80**,[43] respectively. A makaluvamine-type riboside, *N*-1-β-D-ribofuranosyl-makaluvamine I **73**, was isolated from the latrunculid sponge of *S. aliwaliensis* collected from the Aliwal Shoal off the coast of KwaZulu-Natal, South Africa.[44]

In 2002, makaluvamine O **79** was first isolated by one of the authors (J.-F. Hu) from the Jamaican sponge *Smenospongia aurea*.[41] Almost at the same time, this compound was reported from a Philippine marine sponge *Smenospongia* sp.[42] The structure of makaluvamine V **81** had been originally presented in a U.S. patent describing the secondary metabolites and structurally related compounds sourced from a Fijian collection of the sponge *Z. fuliginosa*.[45,46]

3.1.2. Batzellines/Isobatzellines/Secobatzellines. Three similar pyrroloiminoquinone alkaloids, batzellines A−C **82**−**84**, were isolated from the deep water Bahamas sponge *Batzella* sp. (Family Esperiopsidae, order Poecilosclerida) in 1989 by a research group at Harbor Branch Oceanographic Institute (Florida, U.S.A.).[47] One year later, a further investigation on bioactive compounds from *Batzella* by the same group afforded four structurally related pyrroloiminoquinones, isobatzellines A−D **87**−**90**.[49] The isobatzellines possess the same pyrrolo[4,3,2-*de*]quinoline ring system. The presence of *S*-methyl, *N*-methyl, *N*-methylene, and an allylic methylene group including eight nonprotonated sp^2 carbons in isobatzelline A **87** is consistent with the structural features of batzelline A **82**, but **87** contains one more nitrogen and one less oxygen atom. 6-Dechlorobatzelline C **85** was previously reported in a patent,[45] but it was first shown in 2005 as a natural product from the sponge of *Z. fuliginosa* collected off Marchinbar Island, southeast of Cape Wessel, Australia.[46] Batzelline D **86** and isobatzelline E **91** were isolated from an Indopacific sponge *Z. fuliginosa* in 2002.[48] Secobatzellines A **92** and B **93** (a likely artifact formed during the isolation) were isolated from a deep-water Caribbean sponge of the genus *Batzella* in 1999. However, the absolute configuration of the secondary hydroxyl group in both compounds **92** and **93** has so far not been determined.[50]

3.1.3. Damirones. In 1991, damirones A **94** and B **95** were isolated from the Palauan sponge *Damiria* sp. by Faulkner and coworkers.[51] Four years later, damirone C **96** was obtained from the Micronesian sponge *Z. fuliginosa* by the same group.[39] *N*-1-β-D-ribofuranosyldamirone C **97** along with compound **73** were obtained from the South African latrunculid sponge *S. aliwaliensis*.[44]

3.1.4. Tsitsikammamines/Veiutamine/Wakayin/Zyzzyanones. In 1996, two bispyrroloiminoquinone alkaloids, tsitsikammamines A **98** and B **99**, were isolated from an undescribed latrunculid sponge collected from the Tsitsikamma Marine Reserve, South Africa.[15] Their corresponding N-18 oxime derivatives **100** and **101** were obtained from *T. favus* in 2004.[23] Veiutamine **102** was isolated from the Fijian sponge *Z. fuliginosa* in 1997. It was the first pyrroloiminoquinone alkaloid bearing a characteristic C-6 *p*-oxy benzyl group in **102**.[52] As the first example of a pyrroloiminoquinone alkaloid to be isolated from the ascidian *Clavelina* species, wakayin **103** was reported by Ireland and Copp's group in 1991.[53] Zyzzyanone A **104**, a dipyrroloquinone, was isolated along with a few makaluvamines and damirones from the Australian marine sponge *Z. fuliginosa* by Utkina's group in 2004.[54] One year later, continuous investigation on the same sponge yielded the similar compounds zyzzyanones B **105**, C **106**, and D **107**.[55]

3.2. Miscellaneous

In addition to marine organisms, pyrroloiminoquinone-related alkaloids were also detectable from other natural sources (e.g., toad and fungi). For example, the plasmodium of the myxomycete *Didymium bahiense* was cultured on a medium containing oatmeal agar, and the marine pyrroloiminoquinone alkaloid makaluvamine A **64** was isolated from the cultured organisms in 2001.[61]

Dehydrobufotenine **108** was the major indole constituent isolated from the parotid glands of the South American toad (*Bufo marinus*),[57] whose pyrrolo[4,3,2-*de*]quinoline ring system was first recognized in a natural product.[57−59] Bufothionine **109** was isolated from the dried skin of toads, which has been widely used as a traditional Chinese medicine (TCM) for the treatment of hepatoma, lung and colon cancer, etc.[56,60]

Similar pigments with a pyrrolo[4,3,2-*de*]quinoline ring were also found from mushrooms. Sanguinolentaquinone **110**, and sanguinones A **111** and B **112**, were purified from *Mycena sanguinolenta* fruiting bodies in 2007.[62] In the same year, mycenarubin A **115** and the dimeric mycenarubin B **116** were isolated from fruiting bodies of the mushroom *M. rosea*.[65]

The unusual pyrroloiminoquinone derivative haematopodin **113** was isolated from the fungus *M. haematopus* in 1993.[63] Almost 15 years later, haematopodin B **114** and mycenarubins D **117**, E **118**, F **119**, were isolated from fruiting bodies of *M. haematopus* by Spiteller et al.[64] Surprisingly, so far there has been no report of a mycenarubin C, which may have inadvertently been skipped and not used in the nomenclature of mycenarubin family.

4. CHEMOTAXONOMIC MARKERS OF DISCORHABDINS

On the basis of the chemotaxonomic and morphological studies of the marine sponge family Latrunculiidae, a pattern of

occurrence of certain secondary metabolites in specific genera within this family has become evident.[15] For example, the genera *Latrunculia* and *Zyzzya* are predominant reservoirs of discorhabdin-type and makaluvamine-type metabolites, respectively. In 2001, Miller et al. undertook a comprehensive study of the relationship between taxonomic, environmental, and chemical variation within the sponge genus of *Latrunculia* in New Zealand.[134] Results of chemical investigations on *Latrunculia* showed that the amounts of five discorhabdins A **1**, B **2**, C **3**, D **4**, and J **11** varied predictably among several different sponge species of the genus *Latrunculia* collected from five locations around New Zealand, which suggested that the discorhabdin variation was due to species specificity rather than phenotypic plasticity.[134] In 2004, Davies-Coleman et al. proposed that C-14 brominated discorhabdins and the hexacyclic discorhabdin V template may be more suitable chemotaxonomic markers than bis-pyrroloiminoquinone alkaloids for the genus *Tsitsikamma*.[23] However, it may be tenuous that the discorhabdins or other related metabolites could be utilized as definitive chemotaxonomic markers within the family Latrunculiidae because of the proposed closely biogenetic relationships among the pyrroloiminoquinone alkaloids.

5. BIOLOGICAL AND ECOLOGICAL ACTIVITIES OF DISCORHABDINS AND RELATED ALKALOIDS

The discorhabdins have attracted considerable attention in the past two decades not only because of the intriguing structures but also due to their promising pharmacological and ecological bioactivities, including cytotoxicity and antitumor activity,[3−13,16−18,21−24,26−29,31,32,37,66−76] antimicrobial effect,[6,13−15,19,30,32,67−70,76] antiviral activity,[30,66] antimalarial activity,[30] immunomodulatory,[17,73] caspase inhibition,[17,73] and feeding deterrence.[14,77−83]

5.1. Cytotoxicity and Antitumor Activity

The discorhabdins represent a novel class of potential antitumor agents, and most exhibited significant cytotoxicities in vitro against multiple cancer cell lines, including P-388, L-1210, L-5178Y, HCT-116, A-549, HT-29, KB, MDA-MB-231, K562, and PANC-1.[3−13,16−18,21−24,26−29,31,32,37,66−76]

Discorhabdin C **3** showed significant cytotoxic effect (ED_{50} < 100 ng/mL) against L-1210 mouse leukemia cells in 1986.[3] Two years later, the same research group reported that discorhabdins A **1**, B **2**, and C **3** were highly cytotoxic against P-388 murine leukemia cells *in vitro*, with ED_{50} values of 0.05, 0.1, and 0.03 μg/mL, respectively.[6] Discorhabdin B **2** was found to exhibit *in vivo* antitumor activity against the P-388 leukemia system in mice, with a T/C (life expectancy of treated animals vs life expectancy of control animals) value of 117% (but did not reach the significance level of 120%) at a dose of 0.25 mg/kg. Neither discorhabdin A **1** nor C **3** was active in the same in vivo assays; these two compounds were toxic to mice at about 2 mg/kg of body weight.[6] It was interesting that discorhabdin D **4** exhibited significant in vivo activity against P-388 with a T/C value of 132% at 20 mg/kg, but in contrast, it had a lower in vitro activity against the P-388 leukemia system (IC_{50} = 6 μg/mL).[7]

Prianosin A (= discorhabdin A) **1**, isolated independently by Kobayashi's group, exhibited similar cytotoxicity data to those reported for discorhabdins A−C **1**−**3**, with IC_{50} values of 37 and 14 ng/mL against murine lymphoma cell lines L-1210 and L-5178Y, respectively.[4,8] Subsequently, prianosins B **54**, C **36**, and D **4** reported by the same group were also cytotoxic against L-1210 (IC_{50} 0.15−2.0 μg/mL), L-5178Y (IC_{50} 0.024−1.8 μg/mL) and human epidermoid carcinoma KB cells (IC_{50} 0.46−5 μg/mL).[9] Kobayashi's group also reported that **1** and **4** could induce Ca^{2+} release from the sarcoplasmic reticulum 10 times more potently than caffeine in the same assay. Interestingly, this effect was not observed for prianosins B **54** and C (= 2-hydroxydiscorhabdin D) **36**.[4,9]

Chemical modification of discorhabdin C **3** provided its 1*H*-azepine derivatives by acid-catalyzed rearrangement.[11] However, none of the derivatives were more potent than the naturally occurring precusor. Discorhabdin C **3** and the 1*H*-azepine ring system of dienol, phenol and benzene derivatives were further evaluated by NCI in their antitumor screen. Only discorhabdin C **3** and the dienol met the criteria for further evaluation by exhibiting differential cytotoxicity, but no further action was reported.[13]

Discorhabdins A **1** and C **3** also exhibited significant cytotoxicity against two human tumor cell lines, nonsmall cell lung carcinoma A-549 (IC_{50} 0.04 and 0.3 μg/mL, respectively) and colon adenocarcinoma HT-29 (IC_{50} 0.01 and 0.1 μg/mL, respectively).[71] Noticeably, in a cytotoxicity assay against the human colon tumor cell line HCT-116, discorhabdin A **1** was the most cytotoxic (IC_{50} = 0.08 μM) among several pyrroloiminoquinones including makaluvone **63**, makaluvamines A−F **64**−**69**, and damirone B **95**.[37] In 2009, among the cytotoxic metabolites from southern Australian sponges of the genera *Higginsia* and *Spongosorites*, discorhabdin A **1** also showed the most cytotoxic effect (IC_{50} 0.05−0.1 μg/mL) against the human colon (HT-29), lung (A-549), and breast (MDA-MB-231) cancer cell lines, followed by 3-dihydrodiscorhabdin A **28** and (+)-3-dihydrodiscorhabdin L **39** (both possessed IC_{50} values of 0.1−0.5 μg/mL).[27]

In a screen of 20 pyrroloiminoquinones against the human colon tumor cell line HCT-116, the ubiquitous discorhabdin A **1** demonstrated the highest cytotoxicity (IC_{50} = 0.007 μM), followed by 14-bromodiscorhabdin C **32** (IC_{50} = 0.077 μM), 1-aminodiscorhabdin D **37** (IC_{50} = 0.119 μM), 3-dihydro-7,8-dehydro-discorhabdin C **35** (IC_{50} = 0.197 μM), 14-bromo-3-dihydro-7,8-dehydro-discorhabdin C **34** (IC_{50} = 0.222 μM), 1-methoxydiscorhabdin D **38** (IC_{50} = 0.232 μM), and 3-dihydrodiscorhabdin C **31** (IC_{50} = 0.323 μM).[23] However, discorhabdin V **23**, and the closely related 14-bromo-1-hydroxydiscorhabidn V **40**, exhibited much lower potencies (IC_{50} 1.2 and 12.5 μM, respectively). Makaluvic acid A **59**, damirone B **95**, tsitsikammamine A *N*-18 oxime **100** and B *N*-18 oxime **101** were also relatively inactive.[23]

A series of discorhabdin A oxa derivatives with the oxygen cross-linked spiro-fused ring system were synthesized and evaluated for their activity against several tumor cell lines in vitro. Some of them were found to exhibit the same level of cytotoxicity as discorhabdin A **1**.[125] In addition, similar to its unsolvated form, the ethanol-solvated discorhabdin A was also a strong cytotoxin against tumor cells and inhibited murine Erlich carcinoma cells (ED_{50} = 0.055 μg/mL).[31]

Discorhabdins G*/I **8** and L **13** demonstrated submicromolar cytotoxicity against a panel of 14 tumor cell lines. In this assay, they exhibited the highest potency against HT-29 colon cell line with GI_{50} values of 0.35 and 0.12 μg/mL, respectively.[22] Discorhabdin P **17** exhibited cytotoxicity against the P-388 and A-549 cell lines with IC_{50} values of 0.025 and 0.41 μg/mL, respectively.[17] In the NCI's 60 cell line antitumor screen,

(−)-discorhabdin Q **18** showed moderate cytotoxicity (mean panel GI_{50} = 0.5 μg/mL) without differential cytotoxicity profile.[18] The 13-*N*-methyl-*S*-methyl discorhabdins S−U **20**−**22** exhibited cytotoxicity against P-388 murine leukemia cells (IC_{50} 3.08, > 5 and 0.17 μM, respectively), A-549 human lung adenocarcinoma cells (IC_{50} > 5, > 5 and 0.17 μM, respectively) and PANC-1 human pancreatic tumor cells (IC_{50} 2.6, 0.7, and 0.069 μM, respectively).[21] Discorhabdin W **24**, a symmetrical dimer, was found to be strongly cytotoxic against the P-388 cell line with an IC_{50} value of 0.084 μM, comparable to discorhabdin B **2** (IC_{50} = 0.087 μM) and much more potent than discorhabdins D **4**, G*/I **8** and L **13** (IC_{50} 0.51−1.6 μM).[24] Recently, (−)-discorhabdin Z **27** in parallel with discorhabdins B−E **2**−**5**, G*/I **8**, I **10**, L **13** and the closely related derivatives **31**, **38**, **49**, and **50** were evaluated for their cytotoxicity against K562 leukemia cells. These compounds only exhibited moderate potency with IC_{50} values ranging from 1.3 to 25.2 μM.[32]

Significantly, enantiomeric discorhabdins exhibit almost equipotent antiproliferative activity against P-388 cells, with IC_{50} values of 0.2/0.17 μM [for **2** (+)- and **42** (−)-discorhabdin B, respectively], 0.6/0.53 μM [for **8** (+)- and **43** (−)-discorhabdin G*/I], 0.78/1.08 μM [for **45** (+)- and **13** (−)- discorhabdin L], 0.1/0.13 μM [for **24** (+)- and **46** (−)-discorhabdin W] and 0.45 μM for both enantiomers (**47**, **48**) of 16a,17a-dehydrodiscorhabdin W.[26,28] However, diastereomers of both discorhabdins H (**9**, **51**) and K (**12**, **52**) were less active against P-388 cell line, with IC_{50} values of >8.2 μM.[29]

Epinardins A **55** and C **57** were evaluated against L-1210 and doxorubicin-resistant L-1210/DX murine lymphocytic leukemia cells in vitro. Epinardin C **57** was significantly equipotent against both doxorubicin-sensitive and doxorubicin-resistant cell lines with IC_{50} values of 0.32 and 0.36 μg/mL, respectively, while epinardin A **55** showed only moderate cytotoxicities with IC_{50} values of 1.7 and 6.8 μg/mL, respectively.[16]

So far, the exact mechanism of antiproliferative effect for discorhabdins remains unknown. Previous research indicated that many compounds containing a core of a planar iminoquinone moiety could intercalate into DNA and cleave the DNA double helix or inhibit the action of topoisomerases.[13,23,132] For example, makaluvamines are potent inhibitors of topoisomerase II.[37] However, even though discorhabdins A **1** and C **3** also contained the same core iminoquinone skeleton, they exhibited no inhibition of topoisomerase II in contrast of their significant cytotoxicity.[37,132] The inability of discorhabdins A **1** and C **3** to inhibit topoisomerase II suggested that cytotoxicity of discorhabdin-type alkaloids most probably arose by a different mechanism.[37]

Thus, discorhabdin alkaloids exhibited broad-spectrum antiproliferative effect. Discorhabdins A **1** and C **3** demonstrated the highest cytotoxicities against several tumor cell lines. Enantiomeric pairs were found to demonstrate similar cytotoxic potency. However, the nonselective cytotoxicity of discorhabdins has thus far precluded their further development as anticancer drugs.[137]

5.2. Antimicrobial Activity

Strong antimicrobial activity is regarded as a characteristic of discorhabdin alkaloids. In 1988, Munro et al. first reported that discorhabdins A−C **1**−**3** were all active against *Escherichia* coli (gram-negative) and *Bacillus subtilis* (gram-positive), but not against *Pseudomonas aeruginosa* (gram-negative). Meanwhile, both discorhabdins A **1** and C **3** were active against *Candida albicans* (fungus), but discorhabdin B **2** was not.[6] Later, discorhabdins D **4** and E **5** were also reported to show strong inhibitory effects against *E. coli* and *C. albicans* by the same group.[13,68]

In 1995, discorhabdin G **7** was found to demonstrate equipotent activity with discorhabdin C **3** against both gram-positive and gram-negative bacteria.[14] Two C-14 brominated derivatives of discorhabdin C, 14-bromodiscorhabdin C **32** and 14-bromo-3-dihydrodiscorhabdin C **33**, exhibited antimicrobial activity against *Bacillus subtilis* comparable with that of wakayin **103**.[15] The ethanol extracts of a southern Australian sponge *Negombata* sp. and an Antarctic sponge *Latrunculia* sp. demonstrated antibacterial activity against both gram-positive (*Straphylococcus aureus*, *Micrococcus luteus*) and gram-negative (*Serratia marcescens*, *E. coli*) bacteria. Discorhabdins B **2** and R **19** isolated from the EtOH extracts of two sponges were proven to be responsible for the antibacterial effect.[19] In 2006, Copp et al. reported that discorhabdins P **17** and U **22** were inhibitory against *B. subtilis*, but not active against *E. coli*.[76] Recently, discorhabdins A **1**, C **3**, and 3-dihydrodiscorhabdin C **31** also showed selective antimicrobial activity against AIDS opportunistic pathogens methicillin-resistant *S. aureus* (MRSA), *Mycobacterium intracellulare*, and *M. tuberculosis*.[30]

In 2010, a variety of discorhabdins (**2**−**5**, **8**, **13**, **27**, **38**, **39**, **49**) were evaluated for their activities against a wide range of gram-positive (*B. subtillis*, *M. luteus*, *S. aureus*) and gram-negative (*E. coli*, *Proteus vulgaris*, *Salmonella typhimurium*) bacteria.[32] Several compounds displayed only moderate activity. Among them, discorhabdin D **4** was most active against *M. luteus* (MIC 6.25 μg/mL), while discorhabdin B **2** showed the highest inhibitory potency against *P. vulgaris* (MIC 3.125 μg/mL). Additionally, these discorhabdins proved to be remarkably active against sortase A, a pivotal enzyme for bacterial adherial adhesion and invasion of host cells. Significantly, (−)-discorhabdin Z **27**, possessing a unique hemiaminal moiety, exhibited the most potent inhibitory effect on sortase A with an IC_{50} value of 6.5 μM, which was 10-fold more potent than the positive control (p-HMB).[32]

5.3. Anti-HCV and Antimalarial Activities

In 2010, discorhabdins A **1** and C **3** and 3-dihydrodiscorhabdin C **31** were reported by Hamann et al. to have anti-HCV activity with EC_{50} values less than 10 μM, and displayed potent and selective in vitro antimalarial activity against both the chloroquine-susceptible (D6) and chloroquine−resistant (W2) clones of *Plasmodium falciparum*, with IC_{50} values ranging from 53 to 2800 nM.[30] However, in further investigation of in vivo antimalarial activity for discorhabdin A **1** and 3-dihydrodiscorhabdin C **31**, *P. berghei*-infected mice did not respond to these discorhabdin-type alkaloids because of their toxicity in vivo.

5.4. Immunomodulation and Caspase Inhibition

In mechanism-based assays, discorhabdin P **17** was the first discorhabdin-type alkaloid to be screened for inhibition of the phosphatase activity of calcineurin (CaN) (an immune system signal transduction enzyme) and the peptidase activity of CPP32 (caspase-3, a member of a pivotal group of enzymes involved in apoptosis) with IC_{50} values of 0.55 and 0.37 μg/mL, respectively, whereas discorhabdin C **3** was inactive against both enzymes at the highest concentration of 5 μg/mL.[17,73] CaN is recognized as a principal signaling molecule that regulates immune response. Therefore, inhibitors of CaN, such as discorhabdin P **17**, could be used to inhibit immune response for the treatment of systemic autoimmune disease, immunodeficiency diseases,

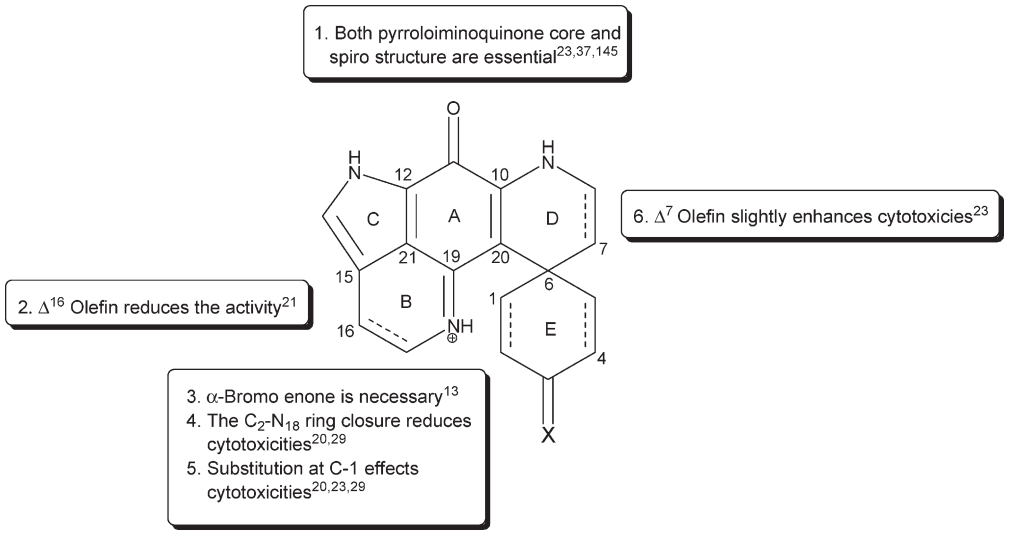

Figure 10. Structure−activity (cytotoxicity and antitumor) relationships of discorhabdins.

immunotherapy of cancer or to prevent rejections of foreign organs or other tissues in transplants.[73]

5.5. Feeding Deterrence

Discorhabdins can serve as chemical defense agents in marine sponges. Extracts from the dark green sponge *Latrunculia apicalis* elicited a significant tube-foot retraction response in the major predator of Antarctic sponges, the sea star *Perknaster fuscus*.[79,80] Further study indicated that discorhabdin G **7** isolated from *L. apicalis* was responsible for the feeding deterrence behavior in *P. fuscus* and the inhibition effect on two common water column microorganisms isolated from the surrounding water.[14] In 2003, Baker and co-workers confirmed the role of discorhabdin G **7** as a chemical deterrent to predation in *L. apicalis* by a series of sea star tube foot retraction response experiments.[83] Research on the content of discorhabdin G in different layers revealed that the outermost sponge layer (0−2 mm) contained significantly more discorhabdin G than any other layer (mean 52%, range 35−78%).[83] These results supported the predictions of the optimal defense theory, as *L. apicalis* sequesters its chemical feeding deterrent (discorhabdin G) against *P. fuscus* in its most vulnerable surface tissues.[83]

6. STRUCTURE−ACTIVITY RELATIONSHIP (SAR) STUDIES OF DISCORHABDINS

The isolation and biological activities of discorhabdins and related derivatives stimulated great interest in structure−activity relationship (*SAR*) studies. In this review, discussion on the *SARs* of discorhabdins is focused on their cytotoxicity and antitumor activity (Figure 10).

Kita's group evaluated the biological activities of natural and synthesized discorhabdin derivatives.[145] The compounds with both the pyrroloiminoquinone unit and the tyrosine unit exhibited much weaker activity than the spiro compounds. However, the naphthoquinone derivative was inactive. From these results, it can be concluded that both the pyrroloiminoquinone core and spiro structure are essential to anticancer activity for discorhabdins, which was also confirmed by both Davies-Coleman's group[23] and Ireland's group.[37] The enhanced activity was also observed in the presence of a additional bromine atom in the dienone moiety.[145]

To explore the structural features responsible for the biological activities of the discorhabdins, several discorhabdin C derivatives were semisynthesized and evaluated for their antiproliferative and antimicrobial properties.[13] The 1*H*-azepine derivatives of discorhabdin C, which did not contain an α-bromo enone moiety, were much less active than the compounds bearing an α-bromo enone. This result implied that cytotoxicities against P-388 cells and activity against *E. coli* seemed to correlate with the presence of the α-bromo-unsaturated ketone moiety, which might contribute to some cytotoxicity of the discorhabdins by acting as Michael acceptor.[13]

In 2000, Munro et al. concluded that generation of an additional ring system formed by a C_2-N_{18} bond (e.g., discorhabdin D **4**) and substitution at C-1 lead to significant loss of cytotoxicity (e.g., discorhabdin I **10** is about 50-fold more potent than discorhabdin K **12**),[20] which was recently further confirmed by Copp et al. in 2010.[29] Interestingly, a contrary result about the effect of substitution at C-1 on cytotoxicity was obtained by Davies-Coleman's group in 2004.[23] In the HCT-116 assay, the cytotoxicities of discorhabdin D analogues appeared to be enhanced by the presence of a C-1 substituent. It was also concluded that the cytotoxicity was slightly improved in the presence of a Δ^7 olefin.[23]

In 1999, Boyd et al. postulated that Δ^{16} unsaturation reduces cytotoxicity relative to the more common 16,17-saturated members of the discorhabdin series.[18] The relatively enhanced cytotoxicity of discorhabdin U **22** compared with discorhabdins S **20** and T **21** against three tumor cell lines further supported the hypothesis of cytotoxicity was diminished by Δ^{16}-unsaturation in discorhabdins.[21]

7. BIOGENESIS OF DISCORHABDINS AND RELATED ALKALOIDS

Due to the slow growth rate of sponges, low incorporation rates and the presence of symbiotic microorganisms, biosynthetic studies of metabolites from marine sponges are very complicated. In 1995, Munro and co-workers presented a putative biogenesis of the discorhabdin-type compounds based on the

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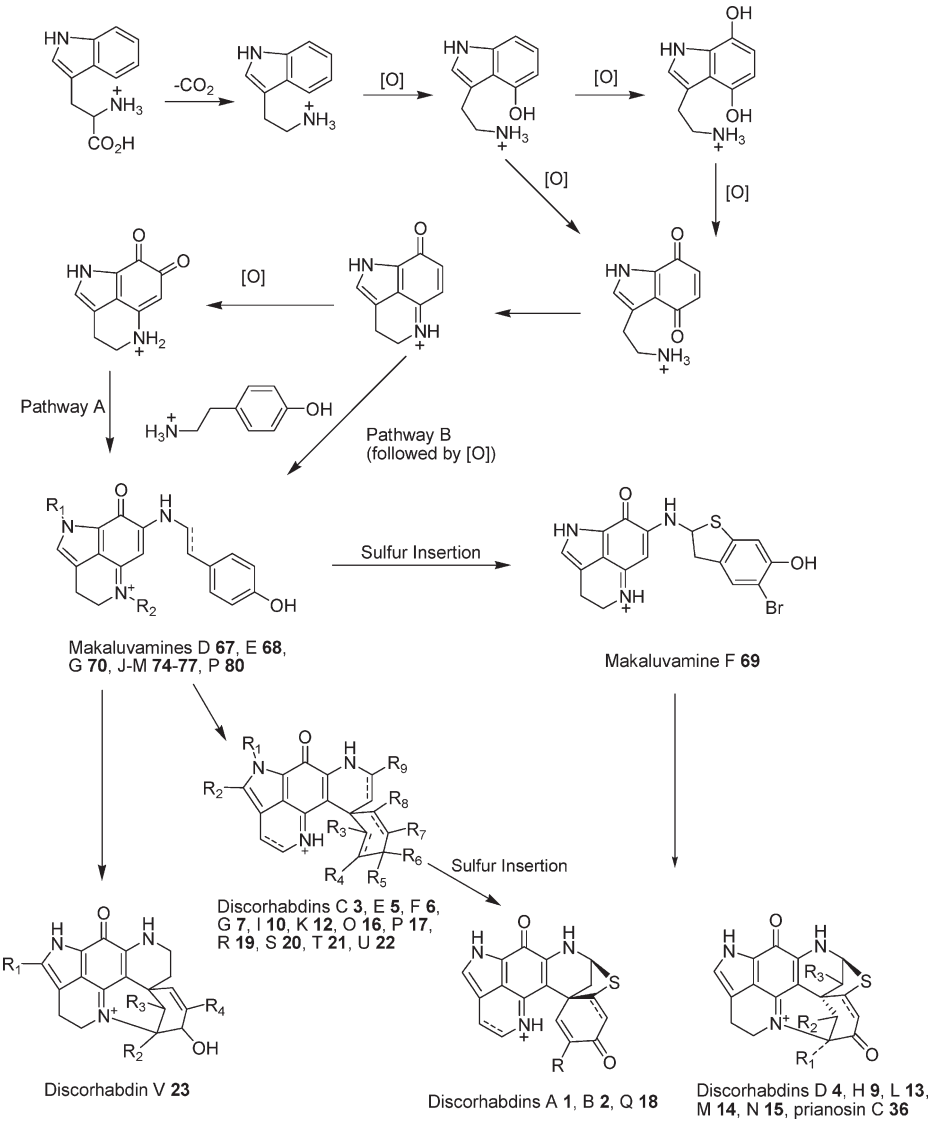
Scheme 2. Postulated Biogenesis of the Discorhabdins[25]



chemotaxonomic relationships and structural similarities among various groups of pyrroloiminoquinones.[34]

From the postulated biogenetic scheme outlined by Munro et al., a reasonable premise was that the amino acids tryptophan and phenylalanine (via tryptamine and tyramine) are considered to be the precursors of the discorhabdin skeleton.[20,33] Appropriate functionalization and oxidation of tryptamine could form the backbone of the pyrroloiminoquinone core of the damirones, batzellines, isobatzellines, and simple makaluvamines.[20,25] The biosynthesis of discorhabdin B **2** utilizing slices of sponge tissue incubated with {U−14C}-L-phenylalanine was carried out by Munro's group. Results showed that ^{14}C from the {U−14C}-L-phenylalanine was incorporated into discorhabdin B **2**, which implied that L-phenylalanine (closely related to tyrosine or tyramine) is also a possible precursor of the discorhabdin skeleton.[34] Thus, Munro et al. proposed that incorporation of a tyramine or a functionalized tyramine derivative into the parent pyrroloiminoquinone core would lead directly to makaluvamine D **67** or closely related derivatives. These makaluvamines could then be the direct precursors of discorhabdins. Four years later (in 1999), this biogenetic pathway suggested by Munro was shown by Heathcock and Aubart based on the successful biomimetic syntheses of discorhabdins C **3**, E **5**, and dethiadiscorhabdin D.[109] Heathcock and Aubart postulated that cyclization of an appropriate makaluvamine produced by an intramolecular Michael addition of the tyramine phenoxide, followed by auto-oxidation back to the quinone, would furnish the discorhabdin C-type skeleton (Schemes 1 and 2).

8. SYNTHESES OF DISCORHABDINS AND RELATED ALKALOIDS

Because of their unusual highly fused structures and prominent biological properties but mass-limited samples in natural sources, the discorhabdins and related alkaloids have attracted great interest for organic synthesis over the past 20 years. So far, several groups have accomplished the total syntheses of the natural discorhabdins A **1**,[113,114,118−120,122,123,144,145,147,148]

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Table 4. Syntheses of Naturally Occurring Simple Cyclized Pyrroloiminoquinone Alkaloids

naturally pyrroloiminoquinone-related alkaloids	research group	ref
makaluvamine A (**64**), batzelline C (**84**), isobatzelline C (**89**), damirone A (**94**)	Somei	158
makaluvamines A-D (**64**−**67**), batzelline C (**84**), isobatzelline C (**89**), damirones A (**94**), B (**95**)	Joule and Alvarez	101
makaluvamines A-E (**64**−**68**)	Yamamura	154
makaluvamines A-D (**64**−**67**)	Yamamura	155
makaluvamine C (**66**)	Kraus	161
makaluvamines A (**64**), D (**67**), I (**72**), K (**75**)	Iwao	107
makaluvamine D (**67**)	White	95
makaluvamine D (**67**)	Cava	96
makaluvamine D (**67**), batzelline C (**84**), isobatzelline C (**89**)	Joule and Alvarez	98
makaluvamine F (**69**)	Kita	111, 112
batzellines A (**82**), B (**83**), isobatzellines A (**87**), B (**88**)	Alvarez and Joule	163
batzelline C (**84**), isobatzelline C (**89**)	Yamamura	152
isobatzelline B (**88**)	Alvarez and Joule	160
damirones A (**94**), B (**95**)	Alvarez and Joule	156
damirones A (**94**), B (**95**)	Cava	153
damirone B (**95**)	Bakare	159
veiutamine (**102**)	Iwao	162
dehydrobufotenine (**108**)	Daly	151
dehydrobufotenine (**108**)	Buchwald	150
secobatzelline B (**93**)	Velu	167
tsitsikammamine A (**98**)	Delfourne	168
tsitsikammamines A (**98**), B (**99**), wakayin (**103**)	Delfourne	165, 166
haematopodin (**113**)	Steglich	100

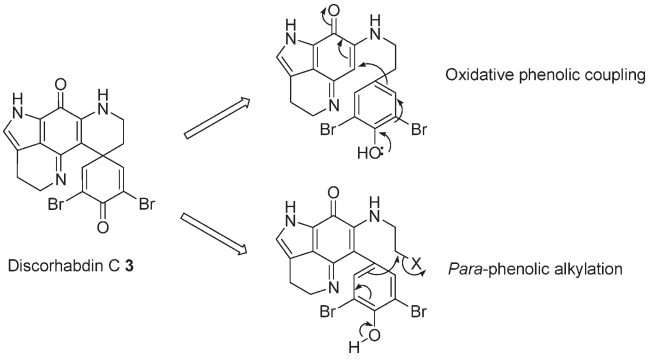
C **3**,[88,89,91−94,109,144−147] E **5**,[109] and prianosin B **54**[124] (Table 3), while extensive synthetic studies were focused on the syntheses of the key intermediates of discorhabdins and related alkaloids.[87−90,95−108,110,115,117,121,150] The key structure of discorhabdin D **4** with a characteristic C_2-N_{18} bond, was synthesized by Heathcock et al. in 1999.[109] Synthetic studies toward the simple marine pyrroloiminoquinone-related alkaloids (**59**−**119**) have also been investigated (Table 4),[150−170] and some approaches have already been reviewed.[20,132,145] Herein, we only focus on the strategies toward the total or semisyntheses of discorhabdin-type alkaloids.

8.1. Syntheses of Discorhabdin C and Its Key Intermediates

As the first example of the discorhabdin-type alkaloids, discorhabdin C **3** possesses an unprecedented framework of a tetracyclic pyrroloiminoquinone system with a spiro 2,6-dibromocyclohexadienone.[3] For the total synthesis of discorhabdin C **3**, construction of the pyrroloiminoquinone core and cylization reaction to form the spirocycle were considered to be the key techniques (see details below).

8.1.1. Approaches to Spirocyclization. Two strategies involving either oxidative phenolic coupling or intramolecular phenolic alkylation were utilized for the spiroclyclization reaction (Scheme 3).[85] The latter procedure was developed by Confalone and co-workers in 1990. In this method, an appropriate phenol is intramolecularly *para*-alkylated under basic conditions to form the spirocycle. This synthetic approach was successfully applied to the preparation of the aza-spirobicyclic system of discorhabdin C **3**,[85,86] but there has not been any further report on the application of this strategy to the total syntheses of the target compound discorhabdin C **3** or any other discorhabdins.

Scheme 3. Retrosynthetic Analysis of Discorhabdin C: Strategies of Spirocylization[85]



The phenolic coupling approach initially developed in the model study toward the preparation of the key spirobicyclic system by Kita et al. in 1989,[84] was successfully applied to the total synthesis of discorhabdin C **3** by several groups. The coupling reaction was accomplished using a hypervalent iodine reagent by Kita's group,[84,89,91,97] or electrochemical oxidation by Yamamura's group,[87,88,94,116] or Michael addition by Heathcock's group.[109] Additionally, an unusual approach to generate the spiro-cyclohexadienone system was iron-mediated spiroannulation developed by Knölker's group, and a tetracyclic spirocyclohexenone, which was considered to be a promising precursor for discorhabdin C **3**, was synthesized.[90,110]

8.1.2. Construction of the Pyrroloiminoquinone Nucleus. As the essential moiety of discorhabdins and related metabolites, the pyrroloiminoquinone system, has been a challenging target for synthetic chemists for years. In general, the

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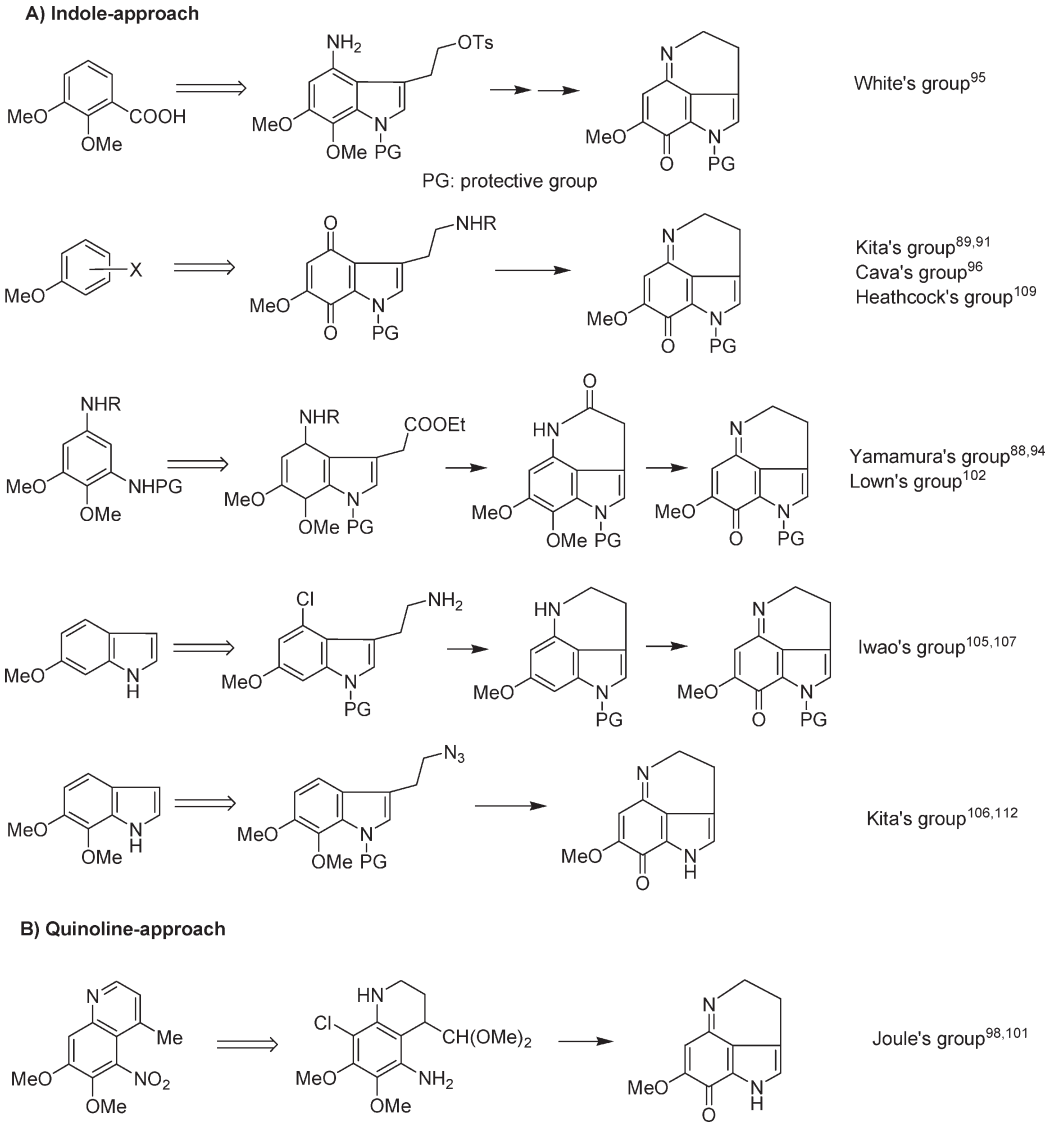
Scheme 4. Typical Procedures to the Syntheses of Pyrroloiminoquinones



following two synthetic approaches have been utilized for the construction of the pyrroloiminoquinones nucleus (Scheme 4):

(A) Indole-approach. The majority of the synthetic work has proceeded via a readily available indole nucleus[105−107,112] or a synthesized indolic skeleton[88,89,91,94−96,102,109] prepared from appropriate benzene derivatives. The newly added six-membered ring is commonly formed by condensation of a tryptamine quinone, or by cyclization of a 4-aminoindole bearing a C_2 unit at the 3-position. Iwao's group reported that pyrroloiminoquinones were prepared by aryne-mediated cyclization of the 4-chloro-tryptamine derivatives.[105,107] In 1998, a novel and efficient route *via* an intromolecular cyclization of 3-(azidoethyl)indole derivatives using a hypervalent iodine(III) reagents was developed by Kita's group.[106,112] (B) Quinoline-approach. Joule's group performed their synthesis starting from a quinoline and accomplished the preparation of pyrroloiminoquinone together with damirones A **94** and B **95**, batzelline C **84**, isobatzelline C **89** and makaluvamines A−D **64**−**67** (Scheme 4).[98,101]

Apart from the above two major synthetic approaches, a route to pyrroloiminoquinones based on a benzene skeleton via various nucleophilic substitution of hydrogen was developed by Makosza et al. in 1997.[103,117]

8.1.3. The Total Synthetic Study in Yamamura Group. The Yamamura group is one of the distinguished research groups devoted to the total syntheses of discorhabdins and related pyrroloiminoquinone metabolites. Yamamura and co-workers successfully extended their approach to the tricyclic pyrroloiminoquinone nucleus for the first total synthesis of *N*-benzyl discorhabdin C, which was initiated from conversion of 3,4-dimethoxy-5-nitro-benzaldehyde into the corresponding amide.[88] The crucial phenolic oxidation of the appropriate phenol carrying no protective group was achieved by electrochemical methodology.[116] Unfortunately, in the last step, all efforts made to remove the benzyl protective group were frustrated (Scheme 5). As an improvement, an unprotected pyrroloiminoquionone core was prepared by hydrogenation under acidic conditions to remove both the benzyl and [2-(trimethylsilyl)ethoxy]carbonyl

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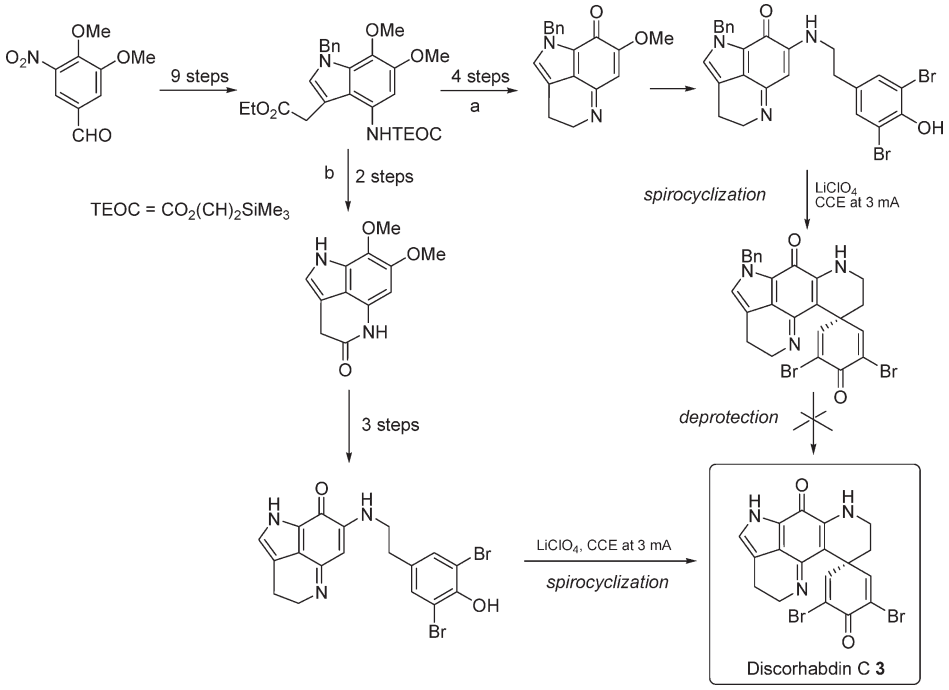
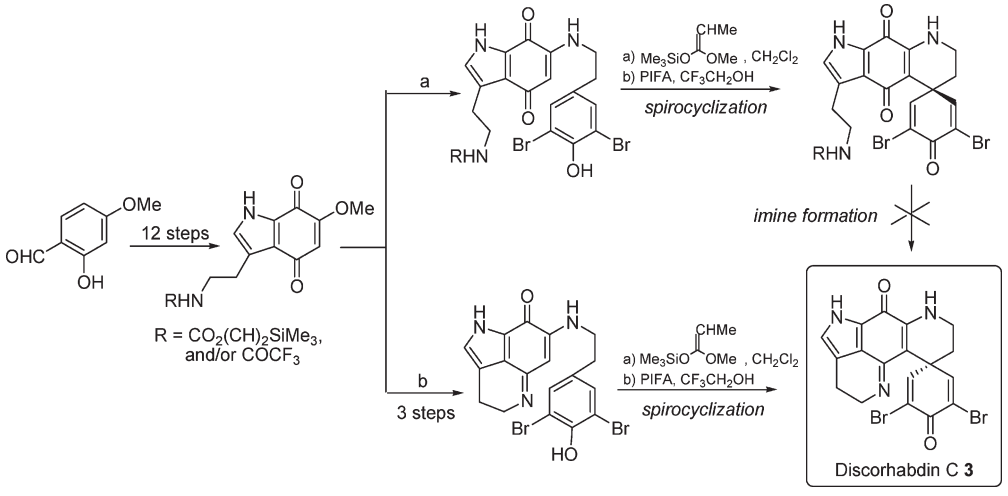
Scheme 5. Total Synthesis of Discorhabdin C 3 by Yamamura et al.[88,94]



Scheme 6. Total Synthesis of Discorhabdin C 3 by Kita et al.[84,89,91]



(TEOC) protective groups. A further nucleophilic substitution reaction with 3,5-dibromotyramine followed by electrochemical oxidation furnished the desired discorhabdin C **3** accompanied by a ring-expanded product.[94]

8.1.4. Total Synthetic Study in Kita Group. Almost at the same time as Yamamura's report,[88] Kita and co-workers carried out another total synthesis of discorhabdin C **3** via spirodienone formation using a hypervalent iodine(III) reagent and phenyliodine bis-(trifluoroacetate) (PIFA).[84,89,91] Attempts to synthesis of **3** by construction of the iminoquione at the final stage (route a, Scheme 6) were unsuccessful, probably owing to an instability of the spirodienone moiety under the reaction conditions. An alternative approach (route b, Scheme 6) in which spirocyclization was employed in the final step after construction of the pyrroloiminoquinone nucleus accomplished the total synthesis of discorhabdin C **3**. The strategy for the construction of the spirocyclic dienone system was similar to Yamamura's, except for a hypervalent iodine reagent utilized for the final oxidative reaction instead of the electrochemical oxidation.

8.1.5. Synthetic Study in Heathcock Group. In 1999, Heathcock and Aubart reported a biomimetic approach to the spirodienone core of the discorhabdin alkaloids, leading to the syntheses of discorhabdins C **3** and E **5** (Scheme 7).[104,109] In this approach, 2-nitroguaiacol was chosen as the starting material. The key spirocyclization reaction was accomplished via an intramolecular Michael addition between the phenoxide of the

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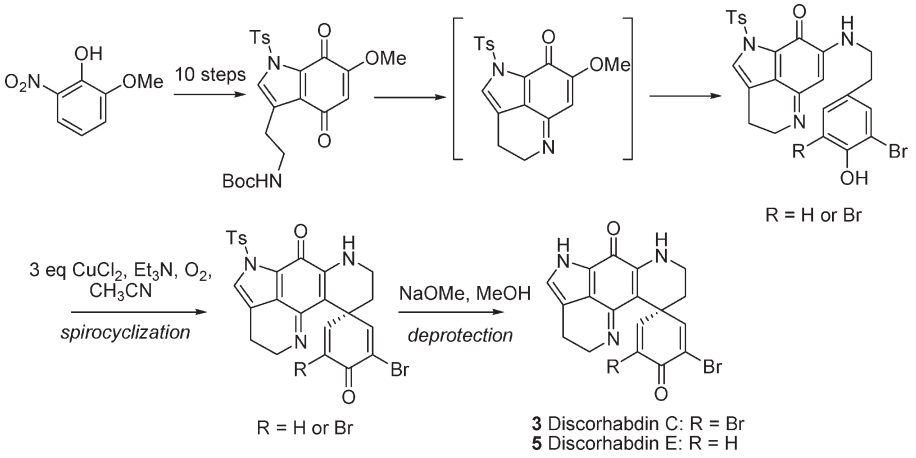
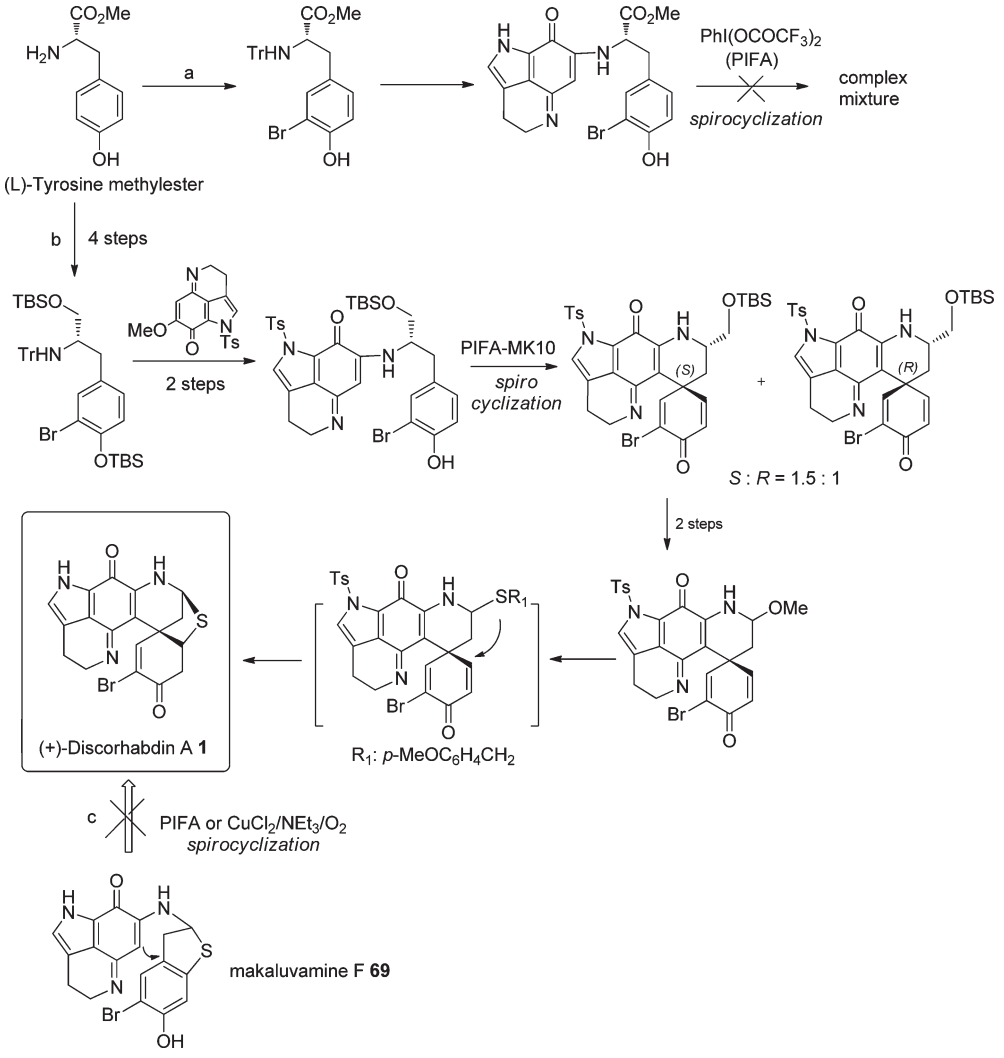
Scheme 7. Total Syntheses of Discorhabdins C 3 and E 5 by Heathcock and Aubart[109]



Scheme 8. Kita Group's Studies toward Total Synthesis of Discorhabdin A 1[118]



tyramine portion and the quinonimine portion of the molecule, followed by a copper(II) catalyzed reoxidation of the resultant aminophenol derivatives into the quinone. Finally, detosylation with NaOMe yielded the expected discorhabdins.

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8.2. Total Syntheses of Discorhabdin A and Prianosin B

Discorhabdin A (= prianosin A) **1** was a challenging synthetic target because of its labile and highly strained sulfur cross-linked core. Kita's group once tried to synthesize discorhabdin A by the biosynthetically plausible route from makaluvamine F **69** using the previously developed spiro-cyclization reaction with PIFA, but failed (Scheme 8).[113]

In 2002, Kita and co-workers described synthetic studies on the sulfur-cross-linked spirodienone core of discorhabdin alkaloids and successfully applied it to the synthesis of discorhabdin A **1** (Scheme 8).[113] This is the first report about the total synthesis of discorhabdin A. The key elements of the synthetic strategy, which employed L-tyrosine methyl ester as the starting material, included the use of the diastereoselective oxidative spirocyclization with PIFA and the introduction of the sulfur group via a nucleophilic addition reaction.[113] However, there were two problems in this synthetic approach. One was the low selectivity of the spirodienone formation (diastereomeric mixture), and the other was the use of the toxic lead tetraacetate [$Pb(OAc)_4$] for the oxidative fragmentation. The stereoselective spiroannulation was further achieved by using PIFA in the presence of Montmorillonite K10 (MK10).[118] In 2004, a novel and efficient synthesis of *N,O*-acetal compounds via an oxidative fragmentation reaction using bis(trifluoroacetoxy)iodo(III) pentafluorobenzene [$C_6F_5I(OCOCF_3)_2$] instead of toxic $Pb(OAc)_4$ were reported by Kita's group.[121]

In 2009, Kita and his colleagues reported the first asymmetric total synthesis of prianosin B **54** from L-tyrosine methyl ester hydrochloride by 10 steps in 1.3% total yield. The key step was the synthesis of the 16,17-dehydropyrroloiminoquinone skeleton from the pyrroloiminoquinone unit.[124] In addition, discorhabdin A oxa derivatives were also achieved by the same group in the same year.[125]

8.3. Total Synthetic Study toward Discorhabdin D

Discorhabdin D **4**, characterized by an additional bond formed between C_2 and N_{18}, is one of the most complex members in the discorhabdin family. The formation of the C_2-N_{18} bond was critical to the preparation of the discorhabdin D skeleton. A unique dethia derivative of discorhabdin D, dethiadiscorhabdin D, was efficiently accomplished by Heathcock and Aubart.[109] This was the first time to generate a discorhabdin D-type alkaloid possessing a C_2-N_{18} bond.

8.4. Semisyntheses of Discorhabdins P, Q, S, T, U, and W

In 2006, Copp's group reported semisyntheses of discorhabdins P **17** and U **22** by one-step methylation reactions of discorhabdins C **3** and B **2**, respectively. Two novel semisynthetic derivatives of discorhabdin U **22** were also prepared, one of which exhibited significant antiproliferative activity.[76] Recently, semisyntheses of discorhabdins S **20**, T **21**, (−)-discorhabdin W **46** and (+)-discorhabdin Q **53** from (+)-discorhabdin B **2** to aid in the assignment of absolute configuration were accomplished by the same group, as well as preparation of enantiomeric (−)-discorhabdin U from (−)-discorhabdin B **42**.[26,29]

9. CONCLUSION

The ocean has proven to be a great natural source of fantastic alkaloids.[1,2,11,20,25,39,126−132,169] Large numbers of pyrroloiminoquinone-related alkaloids have already been isolated from marine organisms, including the simple cyclized batzellines (**82**−**86**) and isobatzellines (**87**−**91**) obtained from the sponges of the genus *Batzella*,[47−49] damirones (**94**−**97**)/makaluvamines (**64**−**81**) from the sponges of the genus *Zyzzya*,[37−40,51] and wakayin (**103**) from a marine ascidian.[53] The most complex pyrroloiminoquinone alkaloids are discorhabdins, which possess a rare pyrrolo[4,3,2-*de*]quinoline tetracyclic skeleton bound to a spiro-substituent at the C-6 position. This class of compounds occurred mainly in marine sponges of the genus *Latrunculia*.[25] Between the first isolation of discorhabdin C **3** in 1986,[3] and January 2011, fifty-eight (**1**−**58**) pyrroloiminoquinone metabolites belonging to the discorhabdin/prianosin/epinardin family have been reported.

Most of the discorhabdin-type compounds have exhibited potent, albeit generally nonspecific and universal cytotoxicities. This nonselective cytotoxicity of discorhabdins has hindered their further development into anticancer drugs.[137] In addition, further investigation on the exact mechanism for their antiproliferative effect is still required and might be beneficial for the ongoing development and lead optimization of this class of compounds.

Because of the prominent biological properties and unusual highly fused ring system, the discorhabdins and related alkaloids have attracted great interest for organic synthesis over the past two decades.[132,145] So far, the total syntheses for discorhabdins A **1**, C **3**, and E **5** have been effectively accomplished by several groups. However, the discorhabdin D-type alkaloids, characterized by an additional ring formed by the C_2-N_{18} bond, will continue to be challenging targets for synthetic chemists in the future. Moreover, modification of the discorhabdin-type metabolites seems to be promising for *SAR* studies and would provide novel potential medicinal agents.

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Jin-Feng Hu, born in Hubei Province (1967), studied organic chemistry at Lanzhou University, where he obtained his B.Sc. (1990) and Ph.D. (1996) degrees in Natural Organic Chemistry under the supervision of Professor Zhong-Jian Jia. He was a postdoctoral fellow (1996-1998) in the Department of Natural Products Chemistry, Institute of Materia Medica (Chinese Academy of Medical Sciences and Peking Union Medical College), with Professor Xiao-Zhang Feng. He joined the Hans-Knoell-Institute for Natural Products Research as a German BMBF & DLR fellow (1998-2000) with Professors Susanne

Grabley and Ralf Thiericke. He moved to the United States as a postdoctoral associate at the Department of Pharmacognosy, the University of Mississippi, with Professor Mark T. Hamann (2000−2001), and at the Genomics Institute of the Novartis Research Foundation and The Scripps Research Institute, with Professor Peter G. Schultz (2001-2002). He left his position as a Principal Scientist in Natural Products Chemistry from Sequoia Sciences, Inc. (U.S.A.), where he worked from 2002 to 2006, and since has been a Full Professor of Natural Products for Chemical Genetic Research at the Key Laboratory of Brain Functional Genomics (Ministry of Education), East China Normal University. Most recently (2011), Dr. Hu joined the Faculty of the Pharmacy School at Fudan University and has been appointed as Chair of the Department of Natural Products Chemistry. His group is actively involved in the isolation, structure elucidation and synthetic optimization of bioactive natural products and chemical biology studies. He has authored over 80 scientific publications.

Hui Fan was born in Hebei Province (China) in 1977. She is currently working toward her Ph.D. degree under the guidance of Professors Jin-Feng Hu and Yinghe Hu. She received her B.Sc. (2000) and M.Sc. (Botany, 2003) degrees from Hebei Agriculture University and Beijing Forestry University, respectively. From 2003 to 2011, she has been working as a research assistant at the Key Laboratory of Brain Functional Genomics (Ministry of Education), East China Normal University. Her research focuses on isolation and structure elucidation of bioactive natural products and the application of mass spectrometry.

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