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Syntheses of bis(indolyl)-piperazine alkaloids, dragmacidin B and C, and dihydrohamacanthin A

Tomomi Kawasaki,* Kohsuke Ohno, Hidetaka Enoki, Yasuko Umemoto and Masanori Sakamoto

Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, Japan

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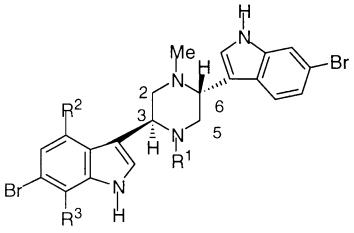
Abstract—The syntheses of *trans*- and *cis*-isomers of dragmacidin C and 3,4-dihydrohamacanthin A, and dragmacidin B have been accomplished by condensation of two indolylglycines followed by cyclization and reduction. The relative stereochemistry of dragmacidin C was confirmed to be *cis*, which is distinct from that of other dragmacidins.

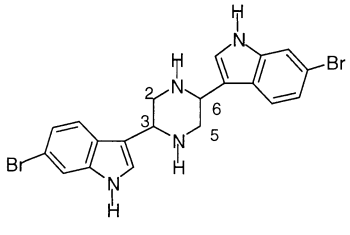
A variety of biologically active metabolites containing the brominated indole ring have been found from marine organisms.[1] Among them, a number of cytotoxic bisindole alkaloids have been discovered in several marine sponges. Dragmacidins and hamacanthins, which have a pyrazine linker between the two indole residues, represent an emerging structural class of marine alkaloids based upon their high degree of biological activities. These central pyrazine units are in various oxidization states: piperazinein dragmacidin **1**[2] and dragmacidin A–C **2**–**4**,[3,4] piperazine-2-one in 3,4-dihydrohamacanthin A **5**,[5] 5,6-dihydropyrazin-2-one in hamacanthin A,[6] and pyrazine-2-one in dragmacidin D–F.[7–9] Dragmacidin **1** and dragmacidin A **2** and B **3** have piperazine rings with *trans* configuration, and *trans*- and *cis*-isomers of dihydrohamacanthin A **5**[8] were isolated. The relative stereochemistry of dragmacidin C **4**,[4] however, has remained obscure.

Interest in the synthesis of this family of bisindole alkaloids has grown over the past few years. Several groups have accomplished total syntheses of dragmacidins **1**,[10] **3**,[11] and hamacanthin A.[12] We also reported the synthesis of dragmacidin A **2** via condensation of two indolylglycines followed by cyclization and reduction.[13] *trans*-2,5-Bis(3′-indoly)piperazine **4a** was recently synthesized to assign the stereochemistry of natural dragmacidin C **4** to a *trans* relationship,[14] but the ^{1}H NMR spectrum of this synthetic *trans*-product **4a** is different from that of the natural product **4**. Namely the coupling pattern in ^{1}H NMR spectrum of natural **4**[4] bears no resemblance to that of the *trans*-products **1**–**3**.[2,3] To further examine this point, we attempted the synthesis of both *trans*- and *cis*-isomers of **4** and dihydrohamacanthin A **5**, and dragmacidin B **3**.[15] In this letter, we describe the syntheses of these bisindole alkaloids **3**–**5**, and report that the relative stereochemistry of dragmacidin C **4** is *cis* rather than *trans*.

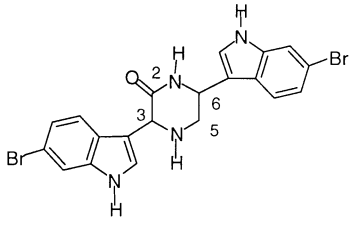
Indolyl-α-azidoacetate **6**, which was readily prepared using our previously reported method,[13] was reduced



1. R^1= H, R^2= OH, R^3 = Br : Dragmacidin
2. R^1= R^2 = R^3= H : Dragmacidin A
3. R^1= Me, R^2 = R^3= H : Dragmacidin B



4a.*trans*-isomer
4b. *cis*-isomer (Dragmacidin C)



5a. *trans*-Dihydrohamacanthin A
5b. *cis*-Dihydrohamacanthin A

* Corresponding author.

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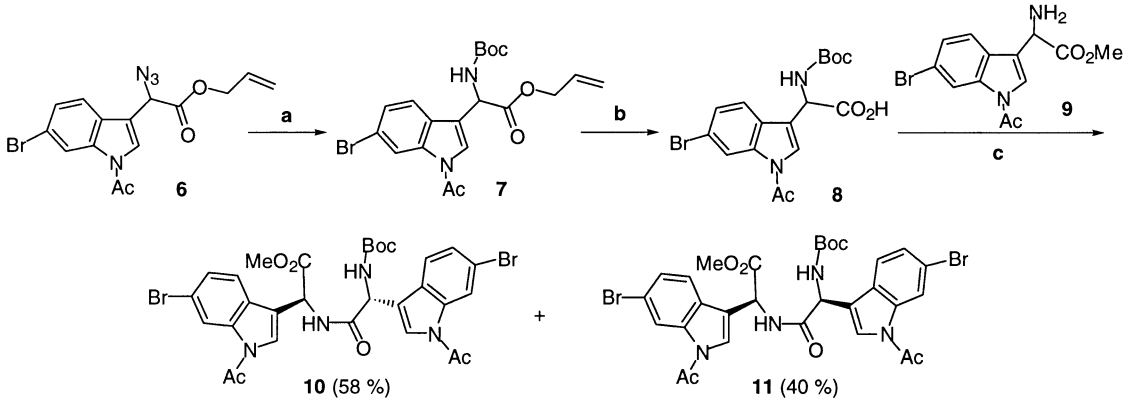
with triphenylphosphine in the presence of water followed by treatment with Boc_2O to give *N*-Boc-indolylglycine **7** in 99% yield (Scheme 1). Selective deprotection of the allyl group of **7** with $RhCl(Ph_3P)_3$ in EtOH–H_2O afforded the indolylglycine **8** in 74% yield. Condensation of **8** and methyl indolylglycinate **9** using BOP[16] and DIEA proceeded smoothly to produce the dipeptide **10**[17] and its diastereomer **11** in 58% and 40% yields, respectively. Successive treatment of **10** with formic acid at room temperature and with ammonium hydroxide at 0°C followed by warming to room temperature took place with deprotection of the *N*-Boc and *N*-acetyl groups of **10** and cyclization to give the piperazine-2,5-dione **12** (82%) (Scheme 2).[18] Reduction of **12** with BH_3·THF at room temperature for 5 days afforded bisindolylpiperazine **4a** in 42% yield. When the reaction was stopped for 70 h, **4a** and dihydrohamacanthin A **5a** were obtained in 16% and 35% yields, respectively. The spectral data of the synthetic product **5a** were identified to those of the natural *trans*-material **5a**.[19] The coupling pattern in the ^1H NMR spectrum of **4a** is similar to that of other dragmacidins **1**–**3**, which have a *trans* relationship as shown in Table 1. The reductive methylation of **4a** with

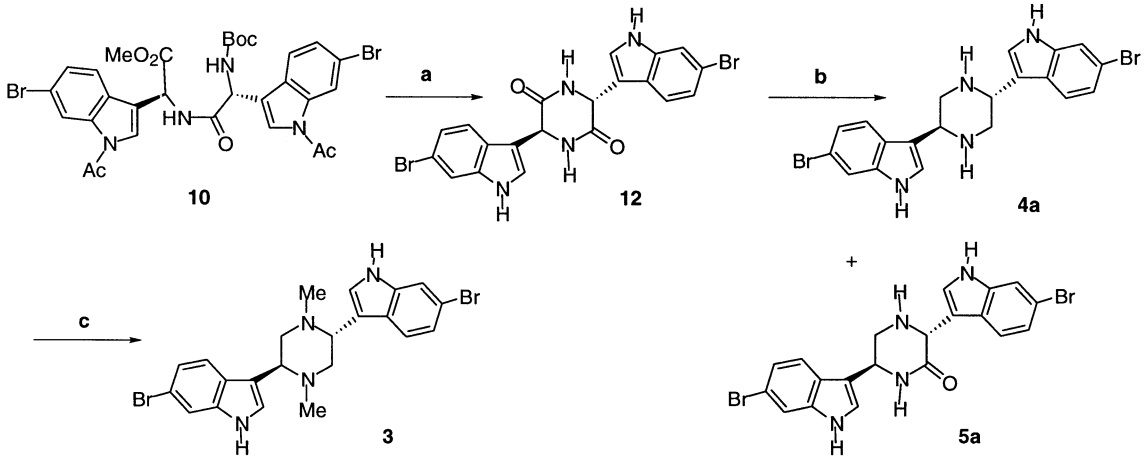
Table 1. ^1H NMR spectral data (acetone-d_6) for the piperazine moiety in dragmacidins **1**–**4**[a]

	H-2 (H-5)	H-3 (H-6)
Synthetic *trans*-**4a**[b]	2.84 (11.6, 10.8), 3.13 (11.6, 2.6)	4.03 (10.8, 2.6)
Synthetic *cis*-**4b**	3.14 (11.7, 3.0), 3.25 (11.7, 6.0)	4.29 (6.0, 3.0)
Natural **4**[4]	3.16 (12.0, 3.0), 3.26 (12.0, 6.0)	4.30 (6.0, 3.0)
Synthetic **3**	2.62 (11.1, 10.8), 2.92 (11.1, 3.0)	3.59 (10.8, 3.0)
Natural **3** (*trans*)[3]	2.64 (11.0, 10.9), 2.93 (11.0, 2.9)	3.60 (10.6, 2.9)
Natural **1** (*trans*)[2]	2.39 (11.9, 10.3), 3.05 (br m)	4.35 (10.3, 2.3)
	3.13 (11.9, 3.9), 3.33 (11.9, 11.3)	3.46 (11.3, 3.9)
Natural **2** (*trans*)[3]	2.38 (11.0, 10.4), 3.18 (11.0, 2.6)	4.43 (10.4, 2.6)
	3.07 (11.0, 3.0), 3.29 (11.0, 10.5)	3.41 (10.5, 3.0)

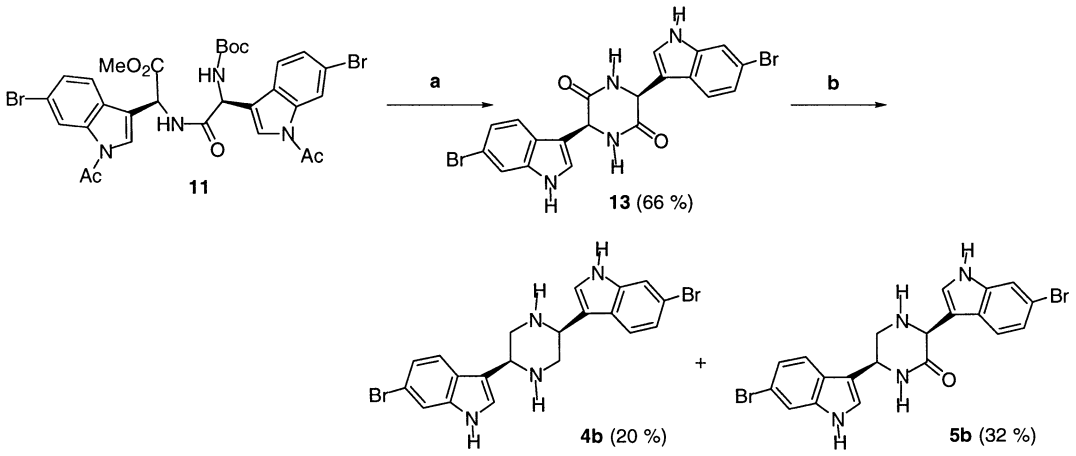
[a] *J* values are given in Hz reported in parentheses.
[b] DMSO-d_6.



Scheme 1. *Reagents and conditions*: (a) Ph_3P, H_2O, THF, rt; then Boc_2O, $NaHCO_3$, rt, 99%. (b) $RhCl(PPh_3)_3$, EtOH, H_2O, 70°C, 74%. (c) BOP, DIEA, THF, 0°C–rt.



Scheme 2. *Reagents and conditions*: (a) HCO_2H, rt, and then NH_3, MeOH, 0°C–rt, 82%. (b) BH_3–THF (30 equiv.), 0°C–rt, 5 days, 42%. (c) HCO_2H, $NaBH_3CN$, 70°C, 22%.



Scheme 3. *Reagents and conditions*: (a) HCO_2H, rt, and then NH_3, MeOH, 0°C–rt, 66%. (b) BH_3–THF, 0°C–rt.

$NaBH_3CN$ in formic acid according to the reported method[14] gave dragmacidin B **3**. On the basis of these chemical transformations and comparison of the NMR spectral data, the relative stereochemistries of **4a** and **12** were confirmed to be *trans*. The ^1H NMR spectrum of the natural product **4**, however, is obviously different from that of the synthetic material **4a** (Table 1). This suggests that natural dragmacidin C **4** has the *cis* configuration.

We next attempted the synthesis of *cis*-piperazine **4b** in a similar manner as shown in Scheme 3. Another dipeptidic diastereomer **11** was successively treated with formic acid and with ammonium hydroxide[18] followed by BH_3-reduction of **13** to give bisindolypiperazine **4b** and dihydrohamacanthin A **5b** in 20% and 32% yields, respectively. The spectral data of synthetic products **4b** and **5b** were identical to those of natural dragmacidin C (Table 1) and *cis*-dihydrohamacanthin A,[19] respectively. These results indicate that the relative stereochemistries of **13b** and the natural dragmacidin C **4b** are *cis*. The ^1H NMR spectrum of **4b** demonstrates that the dominant conformation of **4b** in $CDCl_3$ is a symmetrical boat-like form rather than a chair form.

In summary, we have described the general method for syntheses of bisindolylpiperazine alkaloids, *trans*- and *cis*-isomers of dragmacidin C **4** and 3,4-dihydrohamacanthin A **5**, and dragmacidin B **3**. The naturally obtained dragmacidin C was determined to be *cis*-**4b**, not *trans*-**4a**.

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15. See the coupling constants of **1**–**4** in Table 1.

16. BOP: benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate.
17. The stereochemistry was confirmed by its conversion to the corresponding piperazines **3** or **5**, whose stereochemistry was previously established.
18. When the cyclization was performed above room temperature or using a large excess of ammonium hydroxide, epimerization occurred to produce a mixture of **12** and **13** from either **10** or **11**, respectively.
19. ^{1}H NMR spectral data (δ, acetone-d_6) of dihydrohamacanthin A: Synthetic *trans*-**5a**, 3.20 (dd, $J=12.3$, 9.0 Hz, H-5), 3.43 (dd, $J=12.3$, 4.4, H-5), 4.88 (s, H-3), 5.15 (dd, $J=9.0$, 4.4, H-6); Natural *trans*-**5a**, 3.23 (dd, $J=12.3$, 8.8, H-5), 3.45 (dd, $J=12.3$, 4.4, H-5), 4.91 (s), 5.19 (dd, $J=8.8$, 4.4, H-6); Synthetic *cis*-**5b**, 3.17 (dd, $J=13.2$, 7.3, H-5), 3.26 (dd, $J=13.0$, 4.8, H-5), 4.89 (s), 5.07 (dd, $J=6.6$, 4.8, H-6); Natural *cis*-**5b**, 3.20 (dd, $J=13.2$, 7.0, H-5), 3.29 (dd, $J=13.2$, 4.8, H-5), 4.93 (s), 5.10 (dd, $J=7.0$, 4.8, H-6).