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Synthesis of marine bisindole alkaloids, hamacanthins A and B through intramolecular transamidation–cyclization

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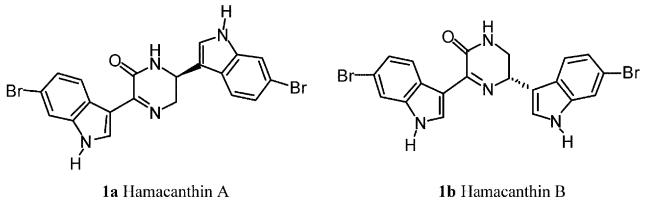
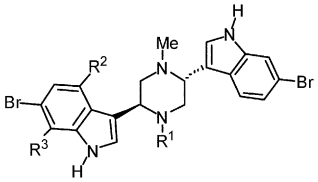
Abstract—The total syntheses of the marine bisindole alkaloids, hamacanthins were achieved by a novel transamidation–cyclization of *N*-(2-aminoethyl)-2-oxoethanamides to 3,5- and 3,6-disubstituted piperazinones.

Bisindole alkaloids possessing either 3,5- or 3,6-linked piperazine unit such as hamacanthins **1**[1] and dragmacidins **2**[2] have been isolated from various genera of marine sponges. These compounds have received considerable attention due to their potent biological activities as antitumor, antifungal, antiviral, and antiinflammatory agents. Several groups have accomplished the total syntheses of hamacanthins **1**[3] and dragmacidins **2**.[3c,4] Recently, we also reported the synthesis of dragmacidins A–C (**2b–d**) via condensation of indolylglycines followed by cyclization and reduction.[5] However, there are few biomimetic approaches except for Horne's method[4c] as the divergent syntheses of both 3,5- and 3,6-isomers of debromodihydro-derivatives of hamacanthins **1** from oxotryptamine. Herein, we describe total syntheses of hamacanthins A (**1a**) and B (**1b**) via regio-controlled cyclization of *N*-(2-aminoethyl)-2-oxoethanamide **10** involving a novel intramolecular transamidation.[6]

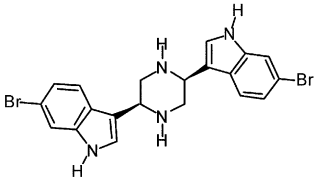


1a Hamacanthin A

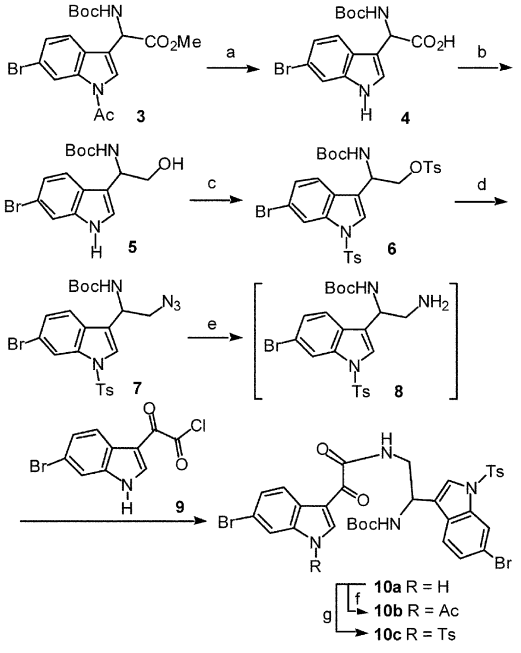
1b Hamacanthin B



2a R^1= H, R^2= OH, R^3 = Br: Dragmacidin
2b R^1= R^2 = R^3= H : Dragmacidin A
2c R^1= Me, R^2 = R^3= H: Dragmacidin B



2d Dragmacidin C



Scheme 1. *Reagents and conditions*: (a) 10% LiOH, THF–MeOH (1:1), rt, quant. yeild; (b) *i*-BuO_2CCl, *N*-methylmorpholine, DME, −15°C, then $NaBH_4$, rt, 91%; (c) TsCl, DMAP, Et_3N, CH_2Cl_2, −20°C, 84%; (d) NaN_3, DMF, 80°C, 81%; (e) Ph_3P, H_2O, THF, reflux, then **9**, Et_3N, THF, 0°C–rt, 93%; (f) Ac_2O, DMAP, Na_2CO_3, THF, rt, 98%; (g) TsCl, DMAP, Et_3N, THF, rt, 99%.

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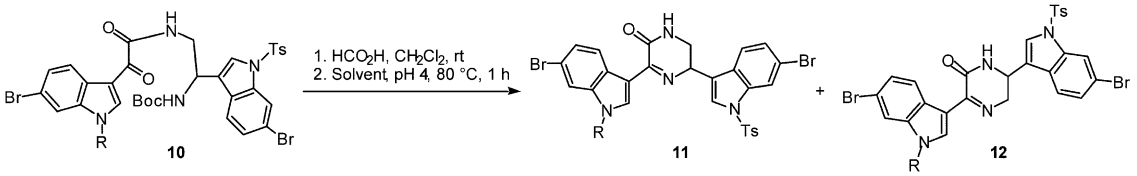
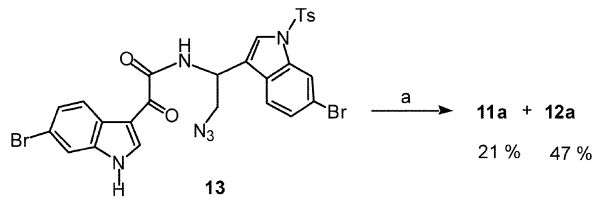


Table 1. Transamidation–cyclization of **10**

Entry	**10**	R	Solvent	Yield (%)		Ratio
				11	**12**	**11**:**12**
1	**a**	H	$ClCH_2CH_2Cl$	35	42	1:1.2
2	**a**	H	1,4-Dioxane	38	30	1.3:1
3	**a**	H	EtOH	75	15	5.4:1
4	**a**	H	DMF	46	7	6.6:1
5	**b**	Ac	$ClCH_2CH_2Cl$	55	42	1.4:1
6	**c**	Ts	$ClCH_2CH_2Cl$	68	18	3.8:1

2-Oxoethanamides **10** were prepared from readily available indolylglycine **3** using our synthetic method[5a] (Scheme 1). Indolylglycine **3** was hydrolyzed with LiOH to afford deacetylated carboxylic acid **4**, which was reacted with isobutyl chloroformate followed by $NaBH_4$-reduction of the mixed-anhydride to alcohol **5**. Treatment of **5** with excess tosyl chloride afforded ditosylate **6**, which was displaced with NaN_3 leading in azide **7**.[3a,7] After reduction of azide **7** with triphenylphosphine–H_2O, condensation of **8** with 2-oxoacyl chloride **9**[8] gave 2-oxoethanamide **10a** in an excellent yield. Ordinary acetylation and tosylation of **10a** gave **10b** (98%) and **10c** (99%), respectively.

Successive treatment of **10a** with HCO_2H and heating in dichloroethane for 1 h took place with cyclization to give 3,5-bisindolyl-2-piperazinone **11a**[3b] and its corresponding isomer, 3,6-bisindole **12a**[3a] in a 35% yield and 42% (Table 1, entry 1).[9,10] Formation of 3,6-isomer **12a** is explained in terms of transamidation of amine **14a** to its regioisomer **15a** (Scheme 3, path b) followed by cyclization to **12a**. This transamidation–cyclization was also observed in the same treatment of the regio-isomer **13**[3a] to result in production of both **11a** (21%) and **12a** (47%) (Scheme 2). This illustrates that the transamidation between **14** and **15** is in equilibrium and that cyclization of **15a** to **12a** is predominant over that of **14a** to **11a** under the reaction conditions (Scheme 3).



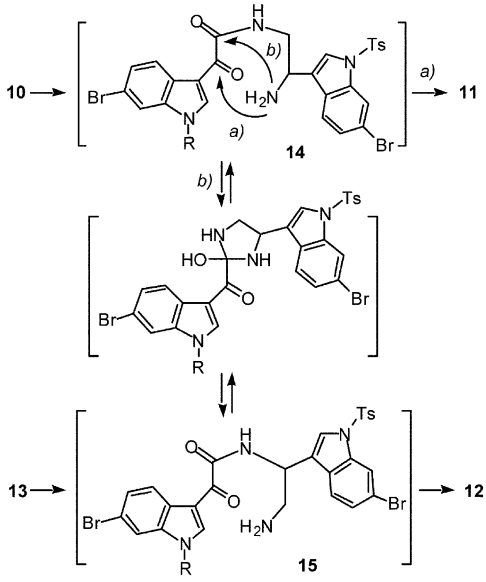
Scheme 2. *Reagents and conditions*: Ph_3P, H_2O, THF, 40°C, then $ClCH_2CH_2Cl$, pH 4, reflux, 1 h.

To explore the effect of reaction solvent on the transamidation–cyclization, after removal of the Boc group from **10a** with HCO_2H, amine **14a** was heated at 80°C in various solvents (Table 1, entries 2–4). When 1,4-dioxane was used instead of dichloroethane, **11a** was obtained over **12a**. On heating in either ethanol or DMF, the more selective formation of **11a** was observed. These results indicate that the transamidation–cyclization is significantly affected by the solvent used, namely, more polar solvents accelerate cyclization of **14a** to **11a** (Scheme 3, path a).

Next, we attempted reactions of 2-oxoethanamides **10b**,**c** having an additional electron-withdrawing group at the indole nitrogen to examine the effect of substituents on the transamidation–cyclization (Table 1, entries 5 and 6). After the Boc group of acetyl derivative **10b** was removed with HCO_2H, the reaction mixture was heated in dichloroethane to afford **11b** and **12b** in 55 and 42% yields, respectively. Similar treatment of the tosyl derivative **10c** produced **11c** (68%) and **12c** (18%). The stronger electron-withdrawing group at the indole nitrogen led to the predominant formation of **11** over that of **12** through transamidation to **15**. This is due to the increase in electrophilicity of the carbonyl group adjacent to the indole ring in **14** by the additional electron-withdrawing group, consequently cyclization of **14** to **11** proceeded in preference to the transamidation to **15** (path a versus b, Scheme 3).

As an example of a secondary rather than a primary amine, the reaction of *N*-benzyl derivative **16** was carried out under the same conditions. The amine **16** was easily obtained by Boc-deprotection of **10a** followed by reductive alkylation with benzaldehyde and $NaBH_3CN$. On heating of **16**, transamidation–cyclization smoothly occurred to give 3,6-bisindole-piperazinone **17** in 59% yield without formation of the corresponding 3,5-isomer (Scheme 4).

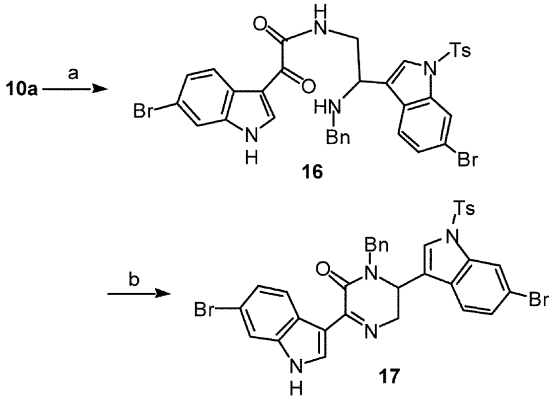
Finally, we attempted the transformation of **11** and **12** to hamacanthins A (**1a**) and B (**1b**), respectively. Although the alkaline hydrolysis of **12a** to **1a** was achieved,[3a] our attempts to remove the tosyl group from **11** were troublesome.[11] Since deacetylation at the indole nitrogen is generally easier than desulfonylation, we used *N*,*N*′-diacetyl derivative **10d** for the synthesis of hamacanthins A and B (Scheme 5). Hydrolysis of 2-oxoethanamide **10a** with KOH followed by acetylation afforded *N*,*N*′-diacetyl derivative **10d** in 72% yield (two steps). Removal of the Boc group in **10d** followed by heating in dichloroethane provided 3,5-bisindole-piperazinone **11d** and 3,6-isomer **12d** in 63 and 31%



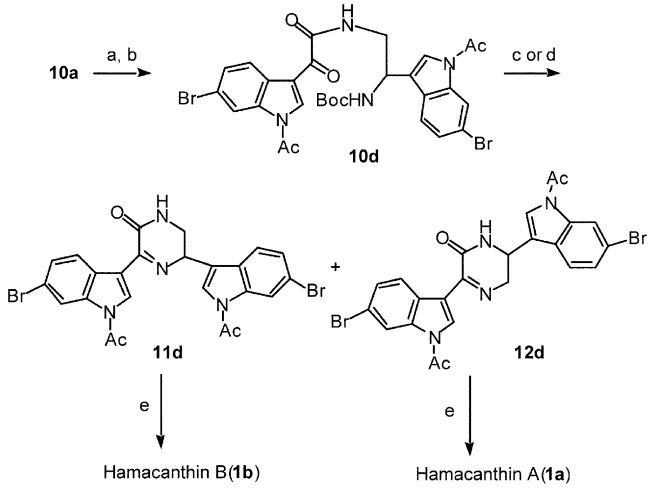
Scheme 3. Transamidation of **10** and **13** to **11** and **12**.

yields, respectively. When reacted in ethanol, the cyclization proceeded regioselectively to yield only **11d** (74%) without formation of **12d**. Deacetylation of **12d** and **11d** with ammonium hydroxide proceeded smoothly to afford hamacanthins A (**1a**) and B (**1b**) in 93 and 98% yields, respectively. The spectral data of synthetic products **1a** and **1b** are identical to those of natural hamacanthins A and B, respectively.[1a,12]

In summary, we have demonstrated the biomimetically divergent synthesis of hamacanthins A (**1a**) and B (**1b**) from 2-oxoethanamides **10** through a new type of transamidation–cyclization,[13] which was controlled by altering the reaction conditions (solvent and additive) and the substituent on **10**. Further work involving the synthesis of optically active hamacanthins A and B is in progress.



Scheme 4. *Reagents and conditions*: (a) HCO_2H, CH_2Cl_2, rt, then PhCHO, $NaBH_3CN$, HCl, THF–MeOH (2:1), 74%; (b) $ClCH_2CH_2Cl$, pH 4, reflux, 4 h, 59%.



Scheme 5. *Reagents and conditions*: (a) 10% KOH, EtOH, reflux, 82%; (b) Ac_2O, DMAP, Na_2CO_3, THF, rt, 88%; (c) HCO_2H, CH_2Cl_2, rt, then $ClCH_2CH_2Cl$, pH 4, reflux, **11d** and **12d** (63 and 31%, respectively); (d) HCO_2H, CH_2Cl_2, rt, then EtOH, pH 4, reflux, **11d** (74%); (e) NH_4OH, THF–MeOH (3–1:1), rt, hamacanthin B (**1b**) 98%, hamacanthin A (**1a**) 93%.

Acknowledgements

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7. Since some attempts to react *O*-monotosylate of **5** with NaN_3 were unsuccessful to result in a complex mixture, protection of the indole nitrogen using an electron-withdrawing group in the substitution reaction was required.
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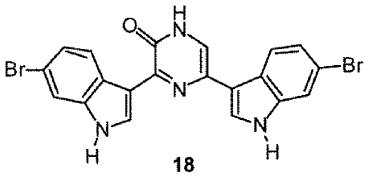
9. *General experimental procedure*: A solution of 2-oxoethanamide **10** (1 mmol) in CH_2Cl_2–HCO_2H (1: 1, 75 mL) was kept at room temperature for 4.5 h. The resulted mixture was concentrated under reduced pressure to give a residue, which was dissolved in 1,2-dichloroethane (55 mL) and the pH was adjusted to 4 with HCO_2H. After heating at 80°C for 1 h, the mixture was concentrated under reduced pressure to yield a residue, which was purified by column chromatography on a silica-gel with hexane–ethyl acetate as an eluent to afford **11** and **12**.
10. After complete removal of HCO_2H, the reaction under neutral conditions required prolonged heating (5 h) to give **11a** and **12a** in 55 and 26% yields, respectively.
11. For example, when **11c** was heated with KOH in refluxing methanol, dehydrohamacanthin B **18** was obtained in 90% yield through elimination of toluene sulfinic acid followed by isomerization.



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12. Hamacanthin A (**1a**): mp 289°C (acetone–hexane) [lit. yellow powder[1a] and mp 275°C[3a]]. IR (KBr) *v*: 1669, 1586, 1445 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 4.05 (1H, dd, $J=16.2$, 8.2 Hz), 4.13 (1H, dd, $J=16.2$, 5.0 Hz), 4.98 (1H, ddd, $J=8.2$, 5.0, 2.0 Hz), 7.14 (1H, dd, $J=8.4$, 1.8 Hz), 7.20 (1H, dd, $J=8.6$, 1.8 Hz), 7.31 (1H, d, $J=2.4$ Hz), 7.56 (1H, d, $J=1.8$ Hz), 7.62 (1H, d, $J=1.8$ Hz), 7.66 (1H, d, $J=8.4$ Hz), 8.29 (1H, d, $J=8.6$ Hz), 8.41 (1H, d, $J=2.8$ Hz), 8.79 (1H, br), 11.16 (1H, br), 11.59 (1H, br). HRMS (EI): Calcd for $C_{20}H_{14}Br_2N_4O$: 483.9534; Found: 483.9529.
Hamacanthin B (**1b**): mp 167–169°C (diethyl ether–hexane) [lit.[1a,3b] yellow powder]. IR (KBr) *v*: 1672, 1580, 1447 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 3.46 (1H, ddd, $J=12.4$, 9.5, 1.9 Hz), 3.61 (1H, dt, $J=12.4$, 4.8 Hz), 5.25 (1H, dd, $J=9.5$, 4.8 Hz), 7.12 (1H, dd, $J=8.4$, 1.5 Hz), 7.17 (1H, dd, $J=8.6$, 1.5 Hz), 7.27 (1H, d, $J=2.4$ Hz), 7.58 (1H, d, $J=1.7$ Hz), 7.62 (1H, d, $J=1.7$ Hz), 7.65 (1H, d, $J=8.6$ Hz), 8.29 (1H, d, $J=8.4$ Hz), 8.41 (1H, d, $J=2.6$ Hz), 8.51 (1H, br), 11.14 (1H, br), 11.63 (1H, br). HRMS (EI): Calcd for $C_{20}H_{14}Br_2N_4O$: 483.9534; Found: 483.9540.
13. Although intramolecular transamidations are well known as ring-transformation of either lactam[6a–c] or cyclic imide,[6d–f] to our knowledge, no intramolecular transamidation of acyclic amide to another acyclic amide followed by cyclization to lactam has been recognized other than Dinsmore's report[6g–h] and the pathway described in this report.