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Efficient Synthesis of (–)-Hanishin, (–)-Longamide B, and (–)-Longamide B Methyl Ester through Piperazinone Formation from 1,2-Cyclic Sulfamidates

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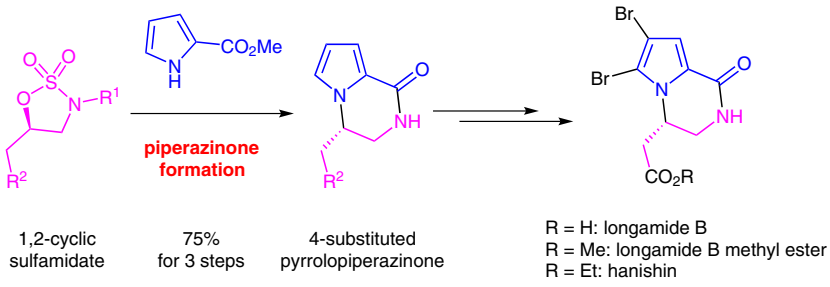

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Abstract We describe a simple chiral-pool synthesis of (–)-longamide B, (–)-longamide B methyl ester, and (–)-hanishin. The key feature of the total synthesis is the formation of a piperazinone from a 1,2-cyclic sulfamidate and methyl 2-pyrrolecarboxylate, which permits efficient construction of the pyrrolopiperazinone core scaffold.

Key words heterocycles, hanishin, longamide B, asymmetric synthesis, piperazinones, sulfamidates

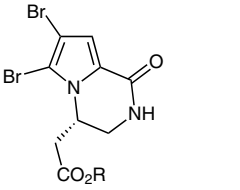


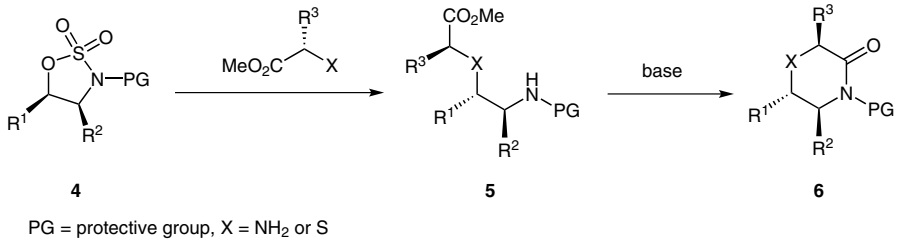
Figure 1 Structures of the bromopyrrole alkaloids

Longamide B (**1**),[1] longamide B methyl ester (**2**),[2] and hanishin (**3**)[3] are bromopyrrole alkaloids isolated from *Agelas dispar*, *Homaxinella* sp., and *Acdanthella carteri*, respectively (Figure 1). Each of these alkaloids has a broad range of interesting biological activities. For example, longamide B exhibits antibiotic activity against Gram-positive bacteria,[1] longamide B methyl ester exhibits cytotoxic activity against P388 lymphocytic leukemia cells,[2] and hanishin exhibits cytotoxicity against NSCLC-N6 human non-small-cell lung carcinoma.[3] Because of their biological importance, several enantioselective syntheses have been described for these three compounds.[4] Patel et al. reported a chiral-pool synthesis of these alkaloids from L-aspartic acid methyl ester.[4a] Trost and co-workers have completed an enantioselective total synthesis of longamide B, based on the construction of the core structure by a palladium-catalyzed asymmetric annulation.[4b,c] Cheng et al. also reported a total synthesis of these alkaloids through construction of an N-substituted pyrrole-2-carboxylate.[4d]

In this study, we used a cyclic sulfamidate as a key intermediate to synthesize the target bromopyrrole alkaloids. Cyclic sulfamidates have recently become recognized as important precursors for substituted heterocycles.[5] Various nucleophiles can attack the oxygen-bearing carbon in cyclic sulfamidates, causing the ring to open to form esters **5** (Scheme 1). When the resulting intermediate contains an ester or other electrophilic functional group, intramolecular cyclization proceeds smoothly under basic conditions to give the functionalized heterocycle **6**. The advantage of this heterocycle formation is that all reactions proceed in a stereocontrolled manner. Consequently, this strategy has been applied within the last decade in syntheses of various substituted stereodefined heterocycles,[6] including biologically active natural products[7] and drug leads.[8]

Here, we report the first example of the formation of a pyrrolopiperazinone moiety of a natural product that uses a cyclic sulfamidate as the key intermediate. We had expected that this type of piperazinone-formation reaction from a 1,2-cyclic sulfamidate might provide ready access to the pyrrolopiperazinone core structure of bromopyrrole alkaloids, and we describe a novel and efficient total synthesis of longamide B (**1**), longamide B methyl ester (**2**), and hanishin (**3**) by using the piperazinone-formation reaction of a 1,2-cyclic sulfamidate derivative.

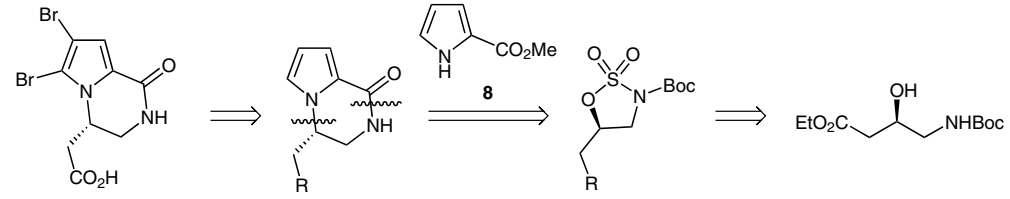
Our retrosynthetic analysis of longamide B is shown in Scheme 2. Nucleophilic substitution of pyrrole **8** to give the 1,2-cyclic sulfamidate **9** is followed by intramolecular lac-



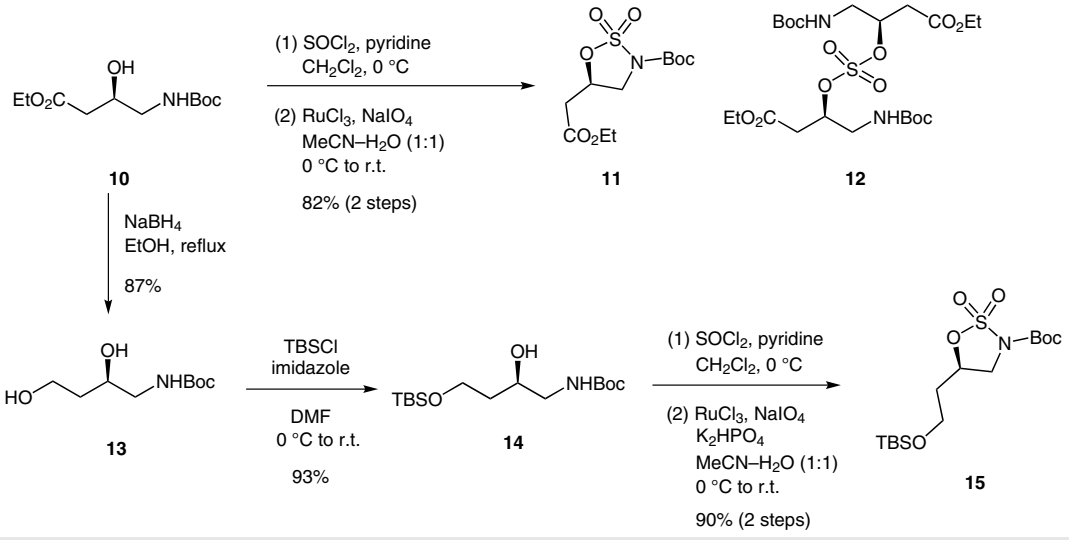
Scheme 1 Heterocycle-formation reactions using 1,2-cyclic sulfamidates

tamization to generate the pyrrolopiperazinone scaffold **7**. The 1,2-cyclic sulfamidate **9** can, in turn, be prepared from the amino alcohol derivative **10**. This synthetic route might also be applicable to divergent syntheses of other derivatives by using various nitrogen-containing heterocycles.

Our approach began with the preparation of the cyclic sulfamidates **11** and **15** (Scheme 3). The amino alcohol **10** was easily prepared by a reported procedure.[9] Next, we attempted to convert **10** into the corresponding sulfamidate **11** by the usual method. When thionyl chloride was added to a mixture of alcohol **10** and pyridine in the sulfamidite-formation step, a significant amount of the undesired dimer **12** was obtained after oxidation. To prevent the formation of this dimer, we added a dilute solution of **10** in dichloromethane dropwise to a mixture of thionyl chloride and pyridine in dichloromethane to produce the desired sulfamidate **11** in high yield (82%) after the oxidation. We also prepared the other cyclic sulfamidate **15**. The ester derivative **10** was reduced with sodium borohydride; subsequent protection of the resulting primary alcohol as the corresponding *tert*-butyl(dimethyl)silyl ether gave the intermediate **14** in 81% yield (two steps). Formation of the cyclic sulfamidate from **14** in the same manner as for **11** gave compound **15** in low yield. However, the addition of saturated aqueous K_2HPO_4 to the mixture in the oxidation step improved the yield to give **15** in 90% yield (two steps).

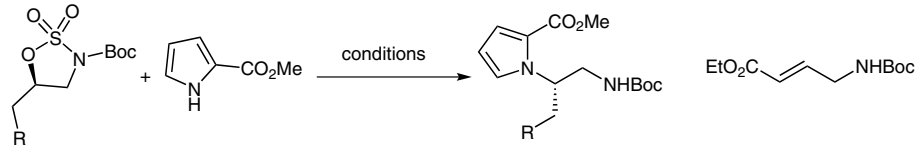


Scheme 2 Retrosynthesis of longamide B



Scheme 3 Synthesis of the key 1,2-cyclic sulfamidates **11** and **15**

Table 1 Optimization of the Nucleophilic Substitution Reaction of Pyrrole **8** with 1,2-Cyclic Sulfamidates **11** and **15**[a]



11 (R = CO_2Et)
15 (R = CH_2OTBS)

8

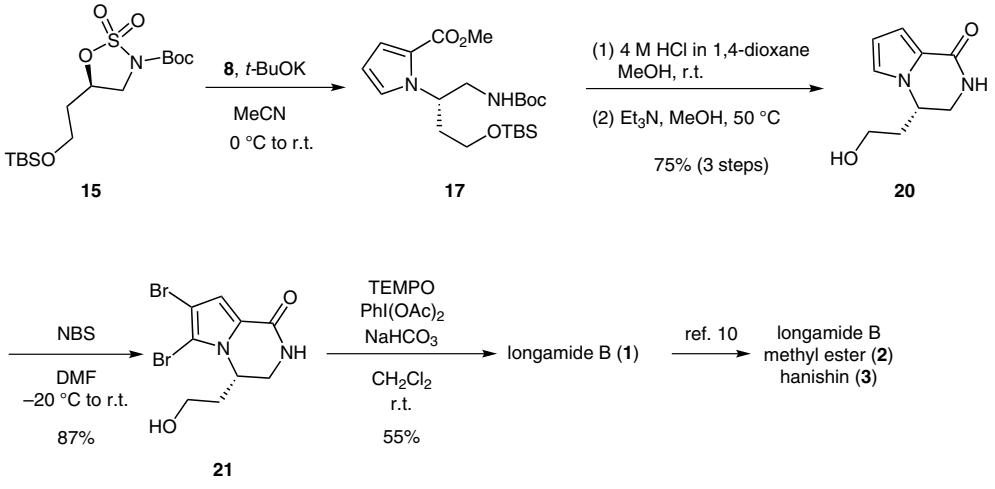
16 (R = CO_2Et)
17 (R = CH_2OTBS)
18 (R = CH_2OH)

19

Entry	Substrate	Base	Solvent	Product	Yield (%)
1	**11**	*t*-BuOK	DMF	**16** **19**	5[b] 24[b]
2	**15**	*t*-BuOK	DMF	**18**	46
3	**15**	K_2CO_3[c]	DMF	ND[d]	ND
4	**15**	DIPEA[c]	DMF	ND	ND
5	**15**	*t*-BuOK	CH_2Cl_2	ND	ND
6	**15**	*t*-BuOK	MeCN	**17** **18**	74 13[b]
7	**15**	*t*-BuOK	THF	ND	ND

[a] Reaction conditions: **8** (1.2–1.5 equiv), base (1.1–1.5 equiv), solvent, r.t., 1–1.5 h.
[b] Isolated yield.
[c] 2.0 equiv.
[d] ND = not detected.

With the desired sulfamidates in hand, we next investigated the nucleophilic substitution reaction of pyrrole **8** with the 1,2-cyclic sulfamidates **11** and **15** (Table 1). The reaction of sulfamidate **11** with pyrrole **8** in the presence of potassium *tert*-butoxide in *N*,*N*-dimethylformamide produced the desired compound **16** in 5% yield, and the undesired side-product **19** was mainly formed (entry 1). Formation of **19** can be rationalized in terms of an elimination reaction resulting from the relatively high acidity of the α-proton adjacent to the carbonyl group. To suppress this elimination reaction, we performed the reaction by using substrate **15**, which has a protected hydroxy group instead of an ester group. As predicted, the reaction of pyrrole **8** with sulfamidate **15** produced the desired product **18** in moderate yield; the *tert*-butyl(dimethyl)silyl group was removed in the workup operation. This result encouraged us to optimize the base and solvent to improve the yield. The reaction failed to proceed when a weaker base such as potassium carbonate or *N*,*N*-diisopropylethylamine was used instead of potassium *tert*-butoxide (Table 1, entries 3 and 4). Among the solvents tested (entries 5–7), acetonitrile was the most effective (74% yield, entry 6).



15 **17** **20** **21**

Scheme 4 Synthesis of the target bromopyrrole alkaloids **1**–**3**

Having optimized the conditions for the nucleophilic substitution reaction, we next investigated the intramolecular lactamization (Scheme 4). Removal of the *tert*-butoxycarbonyl and *tert*-butyl(dimethyl)silyl groups from **17** by using a 4 M solution of hydrogen chloride in 1,4-dioxane, followed by intramolecular cyclization of the resulting amino ester with triethylamine, gave the pyrrolopiperazinone derivative **20** (75% yield, three steps).[11] Bromination of compound **20** produced compound **21**. Finally, the hydroxy group of compound **21** was oxidized to a carboxylic acid with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and (diacetoxyiodo)benzene to give longamide B.[4c] Longamide B was converted into longamide B methyl ester and hanishin by the reported procedures.[10] Physical data were in agreement with the reported values for the natural products.

In conclusion, we have achieved a short synthesis of longamide B, longamide B methyl ester, and hanishin that highlights the utility of 1,2-cyclic sulfamidates in forming complex piperazinones. This approach should be applicable to divergent syntheses of pyrrolopiperazinone derivatives with various substituents on the ring system.

Acknowledgment

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References and Notes

(1) Cafieri, F.; Fattorusso, E.; Taglialatela-Scafati, O. *J. Nat. Prod.* **1998**, *61*, 122.
(2) Umeyama, A.; Ito, S.; Yuasa, E.; Arihara, S.; Yamada, T. *J. Nat. Prod.* **1998**, *61*, 1433.
(3) Mancini, I.; Guella, G.; Amade, P.; Roussakis, C.; Pietra, F. *Tetrahedron Lett.* **1997**, *38*, 6271.
(4) (a) Patel, J.; Pelloux-Léon, N.; Minassian, F.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 9081. (b) Trost, B. M.; Osipov, M.; Dong, G. *J. Am. Chem. Soc.* **2010**, *132*, 15800. (c) Trost, B. M.; Dong, G. *Org. Lett.* **2007**, *9*, 2357. (d) Cheng, G.; Wang, X.; Bao, H.; Cheng, C.; Liu, N.; Hu, Y. *Org. Lett.* **2012**, *14*, 1062. (e) Adhikary, N. D.; Kwon, S.; Chung, W.-J.; Koo, S. *J. Org. Chem.* **2015**, *80*, 7693.
(5) Bower, J. F.; Rujirawanich, J.; Gallagher, T. *Org. Biomol. Chem.* **2010**, *8*, 1505.
(6) (a) Williams, A. J.; Chakthong, S.; Gray, D.; Lawrence, R. M.; Gallagher, T. *Org. Lett.* **2003**, *5*, 811. (b) Bower, J. F.; Švenda, J.; Williams, A. J.; Charmant, J. P.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Lett.* **2004**, *6*, 4727. (c) So, S. M.; Yeom, C.-E.; Cho, S. M.; Choi, S. Y.; Chung, Y. K.; Kim, B. M. *Synlett* **2008**, 702. (d) Hirschhäuser, C.; Parker, J. S.; Perry, M. W.; Haddow, M. F.; Gallagher, T. *Org. Lett.* **2012**, *14*, 4846. (e) Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 3238.
(7) (a) Bower, J. F.; Szeto, P.; Gallagher, T. *Chem. Commun.* **2005**, 793. (b) Bower, J. F.; Riis-Johannessen, T.; Szeto, P.; Whitehead, A. J.; Gallagher, T. *Chem. Commun.* **2007**, 728.
(8) (a) Richter, H. G. F.; Adams, D. R.; Benardeau, A.; Bickerdike, M. J.; Bentley, J. M.; Blench, T. J.; Cliffe, I. A.; Dourish, C.; Hebeisen, P.; Kennett, G. A.; Knight, A. R.; Malcolm, C. S.; Mattei, P.; Misra, A.; Mizrahi, J.; Monck, N. J. T.; Plancher, J. M.; Roever, S.; Roffey, J. R. A.; Taylor, S.; Vickers, S. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1207. (b) Boyer, S. J.; Burke, J.; Guo, X.; Kirrane, T. M.; Snow, R. J.; Zhang, Y.; Sarko, C.; Soleymanzadeh, L.; Swinamer, A.; Westbrook, J.; DiCapua, F.; Padyana, A.; Kugler, S.; O'Neill, M. M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 733. (c) Shiokawa, Z.; Hashimoto, K.; Saito, B.; Oguro, Y.; Sumi, H.; Yabuki, M.; Yoshimatsu, M.; Kosugi, Y.; Debori, Y.; Morishita, N.; Dougan, D. R.; Snell, G. P.; Yoshida, S.; Ishikawa, T. *Bioorg. Med. Chem.* **2013**, *21*, 7938.
(9) Nishiguchi, S.; Sydnes, M. O.; Taguchi, A.; Regnier, T.; Kajimoto, T.; Node, M.; Yamazaki, Y.; Yakushiji, F.; Kiso, Y.; Hayashi, Y. *Tetrahedron* **2010**, *66*, 314.
(10) Banwell, M. G.; Bray, A. M.; Willis, A. C.; Wong, D. J. *New J. Chem.* **1999**, *23*, 687.
(11) **(4*S*)-4-(2-Hydroxyethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (20)**
t-BuOK (33 mg, 0.29 mmol) was added to a mixture of sulfamidate **15** (101 mg, 0.27 mmol) and methyl pyrrole-2-carboxylate (**8**) (33 mg, 0.32 mmol) in MeCN (5.0 mL) at 0 °C, and the mixture was stirred at r.t. for 1.5 h. The reaction was quenched with 10% aq citric acid, and the mixture was extracted with EtOAc. The extracts were washed with sat. aq $NaHCO_3$ and brine, then dried ($MgSO_4$) and concentrated under reduced pressure. To a mixture of the residue in MeOH (2.0 mL) was added 4 M HCl in 1,4-dioxane (2.0 mL) at r.t., and the mixture was stirred at r.t. for 1 h. The mixture was evaporated under reduced pressure and the residue was washed with Et_2O and dried under reduced pressure. A mixture of the residue and Et_3N (0.22 mL, 1.6 mmol) in MeOH (7.0 mL) was stirred at r.t. for 1.5 h and then overnight at 50 °C. The mixture was the concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 10% MeOH–EtOAc) to give **20** as an off-white solid. Yield: 36 mg (75%); mp 130–134 °C; $[\alpha]_D^{27}$ –76.8 (*c* 0.59, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 6.93 (dd, *J* = 2.8, 1.6 Hz, 1 H), 6.75 (dd, *J* = 4.0, 1.2 Hz, 1 H), 6.11 (dd, *J* = 3.6, 2.4 Hz, 1 H), 4.34–4.38 (m, 1 H), 3.72 (dd, *J* = 13.2, 4.4 Hz, 1 H), 3.51–3.57 (m, 1 H), 3.35–3.42 (m, 2 H), 1.81–1.94 (m, 2 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 163.38, 125.33, 123.94, 114.84, 110.27, 59.06, 52.47, 45.43, 36.43. HRMS-ESI: *m*/*z* [M + Na] calcd for $C_9H_{12}N_2NaO_2$: 203.0791; found: 203.0794.
(4*S*)-6,7-Dibromo-4-(2-hydroxyethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (21)
NBS (87 mg, 0.49 mmol) was added to a solution of **20** (44 mg, 0.24 mmol) in DMF (4.0 mL) at –20 °C, and the mixture was stirred at the 20 °C for 15 min then at r.t. overnight. The reaction was then quenched with sat. aq $NaHCO_3$ and extracted with EtOAc. The extracts were washed with H_2O and brine then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 5% MeOH–EtOAc) to give a colorless solid. Yield: 72 mg (87%); mp 139–142 °C; $[\alpha]_D^{27}$ –25.6 (*c* 0.23, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 6.91 (s, 1 H), 4.57–4.60 (m, 1 H), 3.80 (ddd, *J* = 13.8, 4.4, 0.8 Hz, 1 H), 3.63–3.69 (m, 3 H), 1.94–2.02 (m, 1 H), 1.80–1.87 (m, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 159.72, 124.63,

115.85, 106.89, 100.72, 59.12, 52.34, 43.10, 34.39. HRMS-ESI: *m/z* [M + Na] calcd for $C_9H_{10}Br_2N_2NaO_2$: 360.9005; found: 360.8996.

(*S*)-(–)-Longamide B (1)

White solid; yield: 51 mg (74%); mp 225–227 °C; $[\alpha]_D^{28}$ –5.6 (*c* 0.40, MeOH) {Lit.[4a] mp 208–210 °C; $[\alpha]_D^{20}$ –5.51 (*c* 1, MeOH)}. ^{1}H NMR (400 MHz, CD_3OD): δ = 6.93 (s, 1 H), 4.78–4.81 (m, 1 H), 3.88 (ddd, *J* = 13.8, 4.4, 1.6 Hz, 1 H), 3.66 (dd, *J* = 14.0, 0.8 Hz, 1 H), 2.84 (dd, *J* = 16.8, 11.2 Hz, 1 H), 2.53 (ddd, *J* = 16.6, 3.2, 1.2 Hz, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 173.45, 161.08, 126.21, 116.59, 107.98, 101.66, 52.14, 43.76, 36.71. HRMS-ESI: *m/z* [M – H] calcd for $C_9H_7Br_2N_2O_3$: 348.8829; found: 350.8803.