ORGANIC LETTERS

2007
Vol. 9, No. 12
2357−2359

Asymmetric Annulation toward Pyrrolopiperazinones: Concise Enantioselective Syntheses of Pyrrole Alkaloid Natural Products

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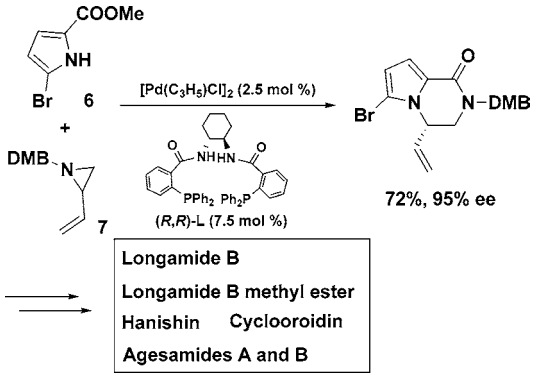
Received March 26, 2007

ABSTRACT



A novel Pd-catalyzed asymmetric annulation between 5-bromopyrrole-2-carboxylate esters and vinyl aziridines has been developed to efficiently construct pyrrolopiperazinones, which can serve as key intermediates in the enantioselective syntheses of pyrrole alkaloid natural products. In this paper, the total synthesis of (–)-longamide B in five steps and the first total syntheses of agesamides A and B in six steps from 6 and 7 are reported.

Bromopyrrole alkaloids represent a large class of marine natural products with various interesting biological properties.[1] Pyrrolopiperazinone skeletons have been found in numerous bromopyrrole alkaloids, such as longamide B (**1**), longamide B methyl ester (**2**), hanishin (**3**), cyclooroidin (**4**), and the agesamides (**5**). Longamide B, isolated from *Agelas dispar* in racemic form, exibits antibiotic activity against several strains of Gram-positive bacteria (MIC 50 μg/mL).[2] Longamide B methyl ester, originally obtained from *Homaxinella* and recently from *Agelas* ceylonica, displays cytotoxic activity against P388 lymphocytic leukemia cells (ED_{50} 30 μg/mL).[3] Hanishin, the ethyl ester of longamide B, was isolated from *Acanthella carteri* and shows cytotoxic activity against NSCLC-N6 human non-small-cell-lung carcinoma (IC_{50} 9.7 μg/mL).[4] No bioactivity has been found in (−)-cyclooroidin from marine sponge *Agelas oroides*[5] and no activity study has been conducted on the newly isolated agesamides A and B from *Agelas* species.[6]

Despite their interesting biological activities and chemical structures, limited enantioselective syntheses of the above

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10.1021/ol070742y CCC: $37.00
Published on Web 05/12/2007

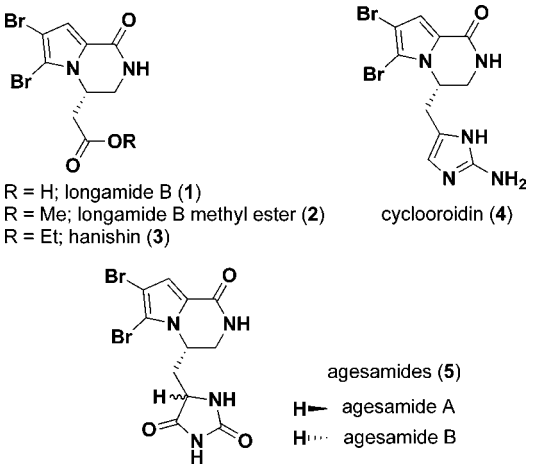
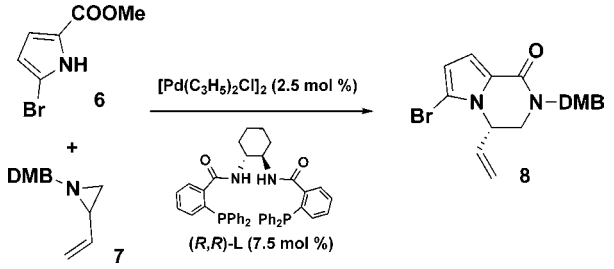


Figure 1. Structures of longamide B (**1**), longamide B methyl ester (**2**), hanishin (**3**), cyclooroidin (**4**), and agesamides (**5**).

Table 1. Selected Optimization Studies[a]



entry	additives	yield,[b] %	ee,[c] %
1	10 mol % HOAc	19 (28)[d]	71
2	50 mol % Cs_2CO_3	41	89
3	none	72	95

[a] All reactions were performed with 1.05 equiv of **6** and 1.0 equiv of **7** at ambient temperature in DCM (0.1 M); DMB = 2,4-dimethoxybenzyl. [b] Isolated yield. [c] ee determined by chiral HPLC. [d] Parentheses indicate yield based on recovered starting material (brsm).

bromopyrrole alkaloids have been reported.[7] In this paper, we report a new Pd-catalyzed asymmetric annulation between 5-bromopyrrole-2-carboxylate esters and vinyl aziridines to give pyrrolopiperazinones, which serve as key intermediates in the enantioselective syntheses of longamide B, longamide B methyl ester, hanishin, cyclooroidin, and agesamides.

Recently, we have developed the use of pyrroles as nucleophiles in the Pd-catalyzed AAA (asymmetric allylic alkylation) reactions, and have successfully applied this methodology in the total synthesis of agelastatin A.[8] The Pd-catalyzed dynamic kinetic asymmetric transformation (DYKAT) of vinyl aziridines has been established with isocyanates[9] and several other nucleophiles.[10] Aziridines are usually less reactive toward nucleophilic additions, thus in this scenario isocyanates not only act as nucleophiles but also activate the aziridines to make it a better leaving group. The extension of the DYKAT methodologies with the combination of pyrroles and vinyl aziridines would potentially provide valuable building blocks for the syntheses of pyrrole alkaloids, and we envisioned that by using a 5-bromopyrrole-2-carboxylate: the nitrogen on the pyrrole would behave as a good nucleophile to regioselectively open the aziridine ring during the AAA, while the ester group on the pyrrole would act as a nitrogen acceptor to form a 6-membered lactam. Therefore, the pyrrolopiperazinone skeleton can be formed in one step.

Initial studies examined the reaction between methyl 5-bromopyrrole-2-carboxylate **6** and vinyl aziridine **7**[11] (Table 1) in the presence of 2.5 mol % of $[Pd(C_3H_5)Cl]_2$ and 7.5 mol % of (*R*,*R*)-L. A catalytic amount of HOAc has been shown to greatly increase the enantioselectivity in the Pd-catalyzed cycloadditions of isocyanates to vinyl aziridines.[9] By using 10 mol % of HOAc we obtained the desired pyrrolopiperazinone **8** in 71% ee but very low yield due to the decomposition of starting materials. Addition of 50 mol % of Cs_2CO_3 gave much higher ee (89%) but slightly improved yield (41%). However, to our surprise, without any additives, the annulation product **8** was obtained in 72% yield and 95% ee. The absolute configuration was assigned by analogy to other reactions of substrate **7**.[11]

With pyrrolopiperazinone **8** in hand, longamide B could be synthesized in four steps (Scheme 1). Hydroboration of **8** with 9-BBN followed by oxidation with sodium perborate gave primary alcohol **9** in high yield and excellent regioselectivity. Under optimized conditions, the DMB group was cleaved by treating **9** with 5 equiv of tetrahydrothiophene in TFA/DCM (1:1). Although the deprotection product was contaminated with its protiodebrominated counterpart product, the following NBS-mediated bromination afforded dibromo alcohol **10** in 96% yield over two steps. Conditions for oxidizing primary alcohol **10** to the carboxylic acid have been screened, and the PCC-catalyzed oxidation with H_5IO_6[12] gave (*S*)-(−)-longamide B (**1**) in 63% (brsm 90%) yield. A more effective oxidation was found later in an attempt to oxidize **10** to the corresponding aldehyde. Surprisingly, the treatment of **10** with 10 mol % of TEMPO and 2.5 equiv of $PhI(OAc)_2$ in DCM[13] produced carboxylic acid **1** instead of the aldehyde in 95% yield. The total synthesis of (*S*)-(−)-longamide B also confirmed the absolute configuration of the Pd-catalyzed asymmetric annulation reaction. According to Banwell et al.,[7c] longamide B methyl ester and hanishin can be respectively accessed from longamide B in

(7) For the asymmetric syntheses of **1**−**4**, see: (a) Patel, J.; Pelloux-Léon, N.; Minassian, F.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 9081. (b) Patel, J.; Pelloux-Léon, N.; Minassian, F.; Vallée, Y. *Tetrahedron Lett.* **2006**, *47*, 5561. For racemic syntheses of **1**−**4**, see: (c) Banwell, M. G.; Bray, A. M.; Willis, A. C.; Wong, D. J. *New J. Chem.* **1999**, *23*, 687. (d) Papeo, G.; Gómez-Zurita Frau, M. A.; Borghi, D.; Varasi, M. *Tetrahedron Lett.* **2005**, *46*, 8635. (e) Põverlein, C.; Breckle, G.; Lindel, T. *Org. Lett.* **2006**, *8*, 819.

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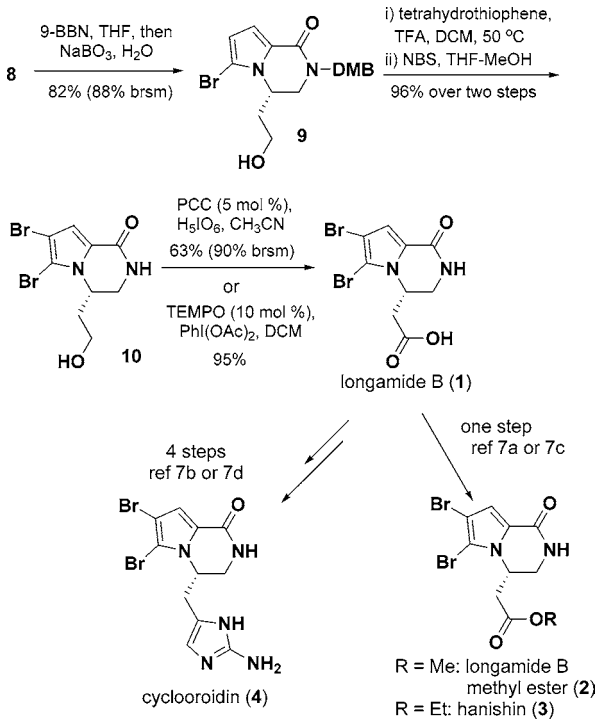
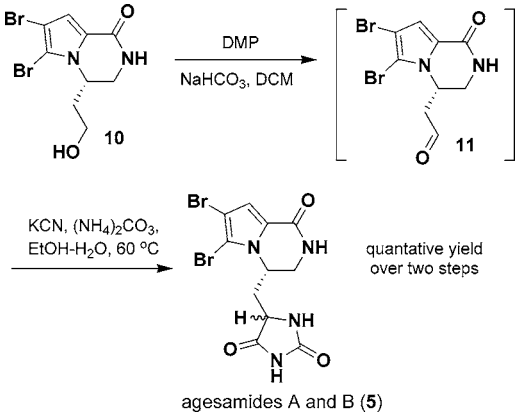
Scheme 1. Syntheses of (*S*)-Longamide B, Hanishin, Longamide B Methyl Ester, and Cyclooroidin



one step, while cyclooroidin can be synthesized in four steps from longamide B based on the work of Papeo et al.[7d] and Pelloux-Léon et al.[7b] Therefore, our route also constitutes formal total syntheses of longamide B methyl ester (**2**), hanishin (**3**), and cyclooroidin (**4**).

Agesamides A and B were isolated as a 1:1 epimeric mixture from marine sponge *Agelas* (SS-1056),[6] and to the best of our knowledge no total synthesis has been reported to date. Treatment of alcohol **10** with Dess−Martin periodane (DMP) under buffered conditions gave the desired aldehyde **11**, which was subsequently subjected to the Bucherer−Bergs hydantoin formation protocol.[14] To our delight, agesamides A and B (**5**) were produced in quantative yield over two

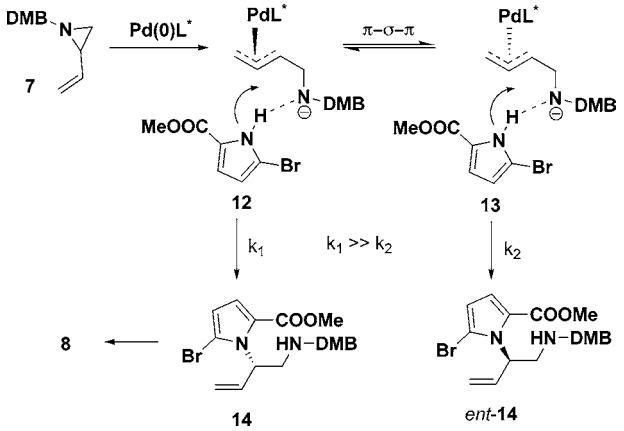
Scheme 2. Synthesis of Agesamides A and B



steps as a 1:1 mixture, and are spectroscopically identical with those previous isolated.[6]

The mechanism of the Pd-catalyzed asymmetric alkylation−annulation between bromopyrrole **6** and vinyl aziridine **7** is outlined in Scheme 3. Both enantiomers of vinyl aziridine

Scheme 3. Mechanism of the Asymmetric Alkylation−Annulation



7 can be ionized by chiral Pd(0)L* and the hydrogen on the pyrrole acts as a mild proton source to facilitate the ring-opening. To obtain the asymmetric induction, the interconversion of the diastereomeric π-allyl palladium intermediates **12** and **13** via a $\pi-\sigma-\pi$ sequence must occur faster than the subsequent nucleophilic addition and be under Curtin−Hammett conditions. The regioselectivity of the addtion can be explained by the directing effect of the N−H−N hydrogen bond.

In conclusion, we have developed an enantioselective, Pd-catalyzed alkylation−annulation reaction to construct a pyrrolopiperazinone from a 5-bromopyrrole-2-carboxylate ester and a vinyl aziridine. Application of this protocol leads to the concise asymmetric synthesis of longamide B in five steps from **6** and **7**. We have also completed the first total synthesis of agesamides A and B, which further demonstrates the value of this methodology in the enantioselective syntheses of pyrrole alkaloid natural products.

Acknowledgment. We thank the National Institutes of Health (GM33049) and the National Science Foundation for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California−San Francisco, supported by the NIH Division of Research Resources. We also thank Dr. Daniel Fandrick for a thoughtful discussion and vinyl aziridine samples. G.D. is a Stanford Graduate Fellow. Palladium salts were generally supplied by Johnson-Matthey.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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