Eight-Step Total Synthesis of the Cyclopeptide Alkaloid Mucronine E

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Abstract: An eight-step total synthesis of the 15-membered ring cyclopeptide alkaloid mucronine E is reported. Key steps include the formation of the highly substituted aromatic core using an asymmetric hydrogenation–Vilsmeier formylation sequence. Central to our approach was a macroamidation protocol using a copper-catalyzed coupling reaction to install the enamide with a concomitant straightforward macrocyclization. This synthesis also allowed for the assignment of both relative and absolute configurations of mucronine E.

Key words: alkaloids, copper-catalysis, macrocycles, peptides, total synthesis

Cyclopeptide alkaloids are a group of closely related polyamide bases of plant origin. Although they were mentioned in the literature as early as 1884,[1] the isolation and structural elucidation of pandamine in 1966[2] marks the beginning of a growing interest in these natural products which nowadays encompass over 200 compounds. Structurally speaking, they possess a 13-, 14-, or 15-membered cycle containing a peptide unit connected to an aromatic ring in either a 1,4- or a 1,3-orientation by enamide and alkyl-aryl ether (or methylene) linkages (Figure 1).[3]

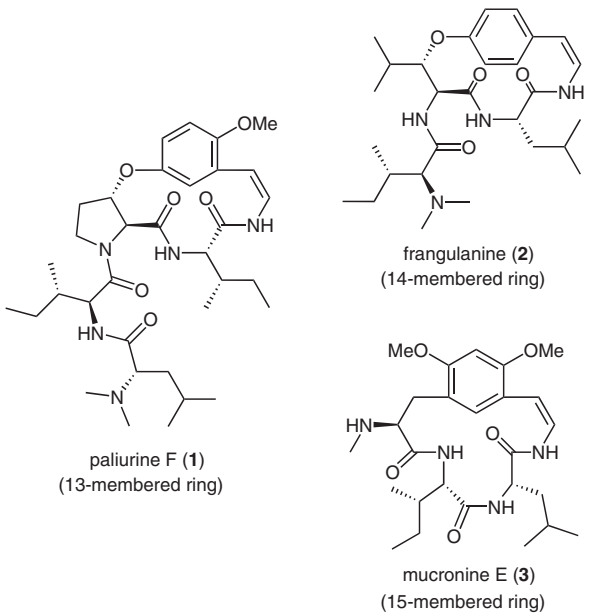

Figure 1 Representative cyclopeptide alkaloids

Cyclopeptide alkaloids are usually present as complex mixtures isolated from various parts of the plant. Yields from dried plants vary from 0.0002–1% depending on the plant source, location, method of isolation, and the plant maturity. Therefore, the biological profile of this class of natural products is not well defined. Some cyclopeptides have been reported to show activity against Gram-positive bacteria and some fungi,[3] others have been found to inhibit energy transfer in plants by interrupting photophosphorylation.[4] Frangulanine, a 14-membered cyclopeptide, has exhibited selective ionophoric properties[5] and sanjoinine, a cyclopeptide isolated from the seeds of a plant used in Chinese medicine for the treatment of insomnia,[6] as well as paliurines[7] have been recently reported to display sedative or hypnotic properties. Recent studies report antiplasmodial properties for ziziphines.[8] However, the limited supplies of cyclopeptide alkaloids have not been sufficient for extensive pharmacological investigations of this class of compounds, and the lack of an efficient synthetic strategy has limited structure–activity relationship studies.

Their biological properties together with their intriguing structures have caused a steady stream of studies directed toward synthesis of these natural products during the past decades. These studies have revealed that the synthetic challenges for these targets include formation of the strained macrocycles and introduction of their enamide unit. The initial report by Schmidt utilized the macrolactamization of a pentafluorophenyl ester,[9] which was later on used in the total syntheses of Joullié[10] and Han,[11] while Zhu's synthesis incorporated an intramolecular S_NAr reaction as macrocyclization protocol.[12] However, all these protocols chose elaboration of the enamide moiety via different stepwise elimination methods after macrocyclization, which somehow decreased the overall synthetic efficiency. Recently, we have developed an alternative cyclization strategy based on an intramolecular amidation reaction and have successfully implemented it in efficient asymmetric syntheses of paliurine F[13] and abyssenine A.[14,15] We now report on the extension of this synthetic route to a straightforward total synthesis of mucronine E (**3**), a 15-membered cyclopeptide alkaloid whose stereochemistry is still unknown, even though this macrocycle was isolated 30 years ago from *Zizyphus mucronata* Willd.[16] We assumed that the configuration of its four stereocenters was *S*,*S*,*S*,*S* as depicted in Figure 1, since the same stereochemistry was assigned for mucronine B, a

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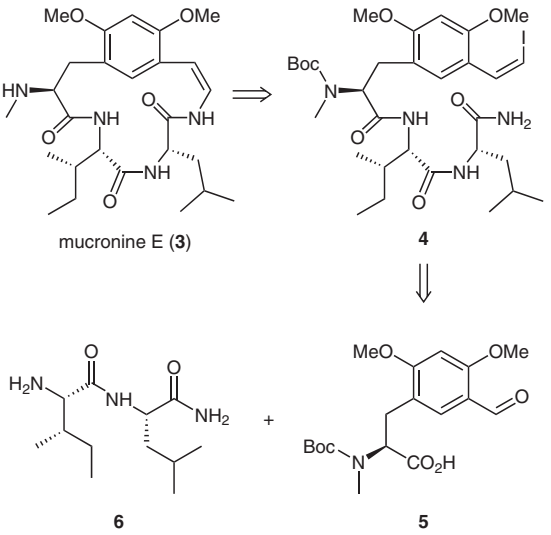
structurally related cyclopeptide alkaloid isolated from the same plant, through total synthesis.[9c]

Our strategy for the synthesis of mucronine E (**3**) is outlined in Scheme 1. Facile generation of the fully elaborated macrocyclic core relies on a challenging copper-mediated intramolecular amidation reaction using amidovinyl iodide **4** as the enamide precursor. The synthesis of this acyclic intermediate **4** would then just require an efficient preparation of the highly functionalized, suitably protected, amino acid **5**. The presence of an aldehyde moiety in **5** would finally allow for the installation of the *Z*-vinyl iodide after coupling of fragments **5** and **6**.

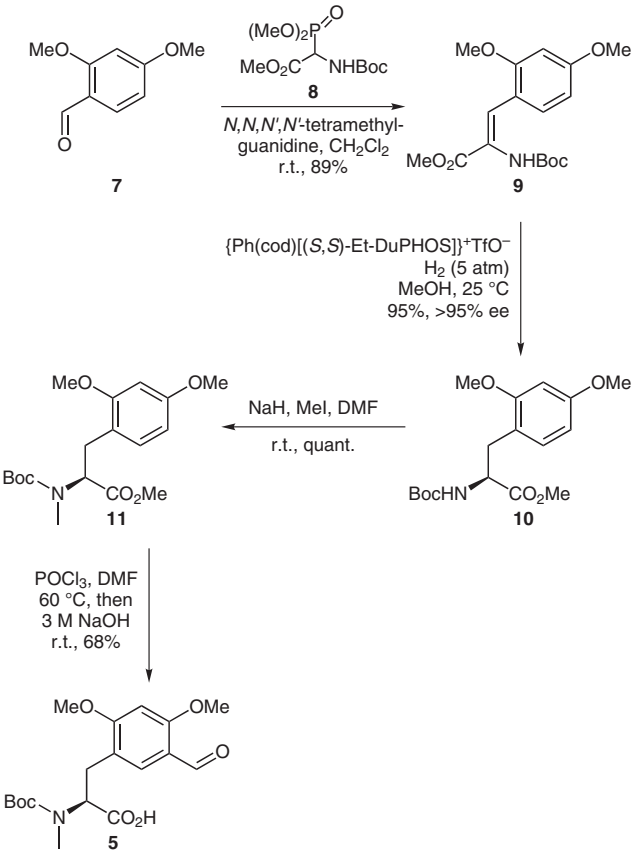


Scheme 1 Retrosynthetic analysis of mucronine E

Compared to our synthesis of abyssenine A,[14] the presence of two methoxy groups on the aromatic core of mucronine E allowed for the design of an especially straightforward preparation of its aminoacid fragment **5** (Scheme 2).

This synthesis started from commercially available 2,4-dimethoxybenzaldehyde (**7**). In order to install the amino acid group of the target fragment, **7** was first reacted with phosphonate **8**[17] and gave the (*Z*)-dimethoxydehydrophenylalanine derivative **9**. Catalytic asymmetric hydrogenation of **9** then proceeded smoothly in the presence of {Rh(cod)[(*S*,*S*)-Et-DuPHOS]}$^+$TfO$^-$[18] to afford the corresponding amino ester **10** with excellent yield and enantioselectivity (95%, >95% ee) and the exocyclic *N*-methyl group of mucronine E was next installed by methylation of **10** using Benoiton's racemization-free conditions.[19] Vilsmeier formylation of **11** was then carried out using $POCl_3$ and DMF at 60 °C followed by in situ hydrolysis of the intermediate chloroamine with sodium hydroxide which proceeded with concomitant cleavage of the methyl ester to give **5**, therefore saving us an additional saponification step (Scheme 2).

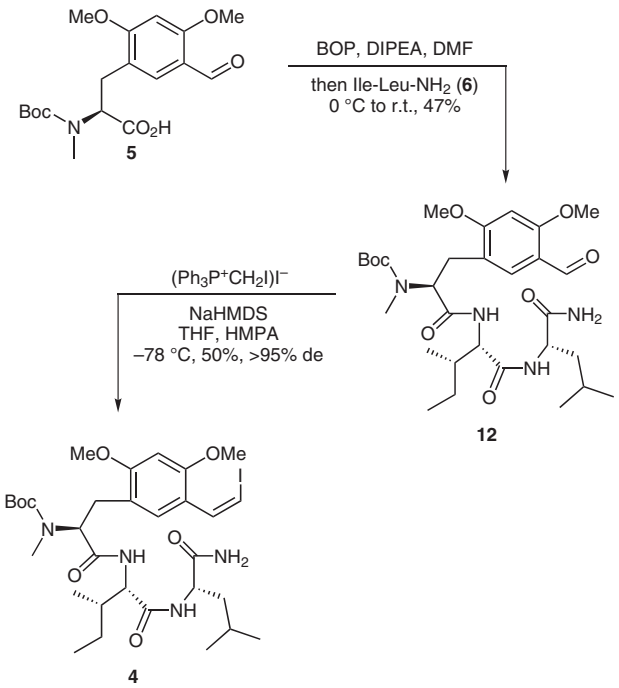
Having in hand useful quantities of the amino acid fragment **5**, the assembly of the acyclic skeleton of mucronine E was next undertaken. To avoid a stepwise installation of



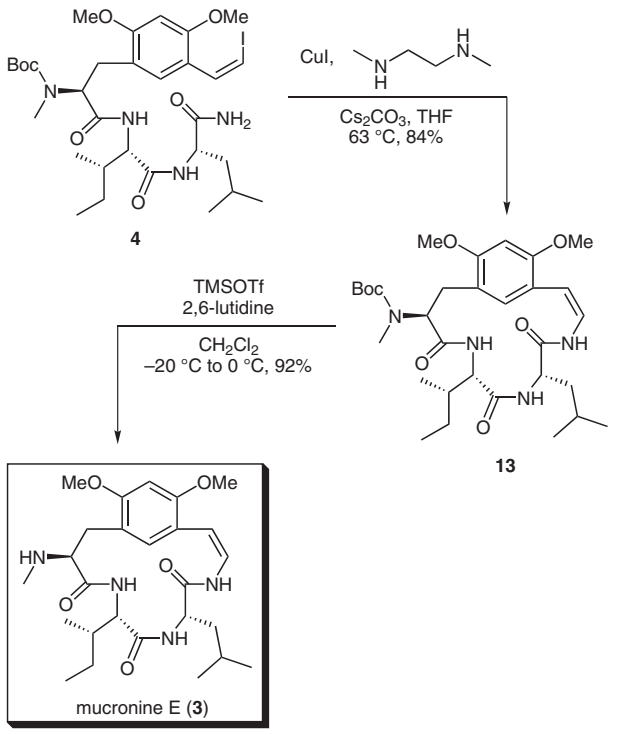
Scheme 2 Asymmetric synthesis of the aminoacid fragment **5**

the amide group required for the macrocyclization step after introduction of the other two constitutive amino acids of the macrocycle, a direct peptide bond formation between **5** and isoleucine-leucinamide **6**[14] was envisioned. Therefore, condensation of the acid **5** with dipeptide **6** was conducted under the action of BOP to provide tripeptide **12** without any noticeable epimerization (Scheme 3). Finally, and to install the *Z*-vinyl iodide required for the final macroamidation step, aldehyde **12** was treated with Stork–Zhao reagent[20] and gave the fully elaborated acyclic skeleton **4** in moderate yield but with complete diastereoselectivity.

This set the stage for the crucial macrocyclization step:[13,14] Subjection of iodoamide **4** to catalytic copper(I) iodide and *N*,*N*′-dimethylethylenediamine[21] in THF under high dilution conditions at 63 °C smoothly provided the 15-membered ring **13** in 84% yield (Scheme 4). The most striking feature of this approach is that this mild intramolecular amidation protocol proceeds with complete regioselectivity for the terminal amide, without any epimerization at the three amino acid stereocenters or isomerization of the *Z*-vinyl iodide and without dimerization or formation of higher oligomers. Finally, careful removal of the Boc group using TMSOTf and 2,6-lutidine provided synthetic mucronine E (**3**) which was identical in all respects {Mp, NMR $[\alpha]_D^{20}$, IR, UV, and MS} to the natural product,[16,22] therefore establishing both its relative and absolute configurations.[23]



Scheme 3 Synthesis of the acyclic skeleton



Scheme 4 Completion of the synthesis of mucronine E

In summary, we have developed an efficient and straightforward total synthesis of mucronine E, which implements the general and unified route to cyclopeptide we designed. Mucronine E could be obtained in only eight steps and 10% overall yield from commercially available starting materials. The key step of our synthesis relies on installation of enamide concomitant with macrocyclization using a copper-mediated macroamidation reaction. This new strategy clearly renders the elaboration of this class of natural products much easier than previously and should therefore facilitate the synthesis of analogues for their further pharmacological evaluation and structure–activity studies.

Acknowledgment

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References and Notes

(1) Clinch, J. H. M. *Am. J. Pharm.* **1884**, *56*, 131.
(2) Pais, M.; Jarreau, F. X.; Lusinchi, X.; Goutarel, R. *Ann. Chim. (Paris)* **1966**, *14*, 83.
(3) For reviews, see: (a) Gournelif, D. C.; Laskaris, G. G.; Verpoorte, R. *Nat. Prod. Rep.* **1997**, *14*, 75. (b) Joullié, M. M.; Richard, D. J. *Chem. Commun.* **2004**, 2011. (c) Tan, N. H.; Zhou, J. *Chem. Rev.* **2006**, *106*, 840. (d) El-Seedi, H. R.; Zahra, M. H.; Goransson, U.; Verpoorte, R. *Phytochem. Rev.* **2007**, *6*, 143.
(4) Ravizzini, R. A.; Andreo, C. S.; Vallejos, R. H. *Plant Cell Physiol.* **1977**, *18*, 701.
(5) Kawai, K.; Nozawa, Y.; Ogihara, Y. *Experientia* **1977**, *33*, 1454.
(6) Han, B. H.; Park, M. H.; Park, J. H. *Pure Appl. Chem.* **1989**, *61*, 443.
(7) Lee, S. S.; Su, W. C.; Liu, K. C. S. C. *Phytochemistry* **2001**, *58*, 1271.
(8) Suksamrarn, S.; Suwannapoch, N.; Aunchai, N.; Kuno, M.; Ratananukul, P.; Haritakun, R.; Jansakul, C.; Ruchirawat, S. *Tetrahedron* **2005**, *61*, 1175.
(9) (a) Schmidt, U.; Lieberknecht, A.; Bökens, H.; Griesser, H. *J. Org. Chem.* **1983**, *48*, 2680. (b) Schmidt, U.; Schanbacher, U. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 152. (c) Schmidt, U.; Schanbacher, U. *Liebigs Ann. Chem.* **1984**, 1205. (d) Schmidt, U.; Zäh, M.; Lieberknecht, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1002.
(10) (a) Heffner, R. J.; Jiang, J.; Joullié, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 10181. (b) Xiao, D.; East, S. P.; Joullié, M. M. *Tetrahedron Lett.* **1998**, *39*, 9631. (c) East, S. P.; Shao, F.; Williams, L.; Joullié, M. M. *Tetrahedron* **1998**, *54*, 13371.
(11) Han, B. H.; Kim, Y. C.; Park, M. K.; Park, J. H.; Go, H. J.; Yang, H. O.; Suh, D. Y.; Kang, Y. H. *Heterocycles* **1995**, *41*, 1909.
(12) (a) Laïb, T.; Zhu, J. *Tetrahedron Lett.* **1999**, *40*, 83. (b) Laïb, T.; Bois-Choussy, M.; Zhu, J. *Tetrahedron Lett.* **2000**, *41*, 7645. (c) Temal-Laïb, T.; Chastanet, J.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 583. (d) Cristau, P.; Temal-Laïb, T.; Bois-Choussy, M.; Martin, M. T.; Vors, J. P.; Zhu, J. *Chem. Eur. J.* **2005**, *11*, 2668.
(13) Toumi, M.; Couty, F.; Evano, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 572.
(14) Toumi, M.; Couty, F.; Evano, G. *J. Org. Chem.* **2007**, *72*, 9003.
(15) An intermolecular copper-mediated amidation reaction–macrolactamization strategy was reported by Ma for the synthesis of ziziphine N: He, G.; Wang, J.; Ma, D. *Org. Lett.* **2007**, *9*, 1367.
(16) Tschesche, R.; David, S. T.; Zerbes, R.; von Radloff, M.; Kaußmann, E. U.; Eckhardt, G. *Justus Liebigs Ann. Chem.* **1974**, 1915.
(17) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53.
(18) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363.

(19) Coggins, J. R.; Benoiton, N. L. *Can. J. Chem.* **1971**, *49*, 1968.
(20) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173.
(21) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667.
(22) **Selected Data for (–)-Mucronine E (3)**
Mp 230 °C; $[\alpha]_D^{20}$ –87 (*c* 0.4, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.39 (d, *J* = 7.2 Hz, 1 H), 8.42 (d, *J* = 11.4 Hz, 1 H), 8.14 (d, *J* = 6.4 Hz, 1 H), 7.03 (s, 1 H), 6.86 (dd, *J* = 11.4, 9.7 Hz, 1 H), 6.47 (s, 1 H), 5.78 (d, *J* = 9.7 Hz, 1 H), 4.48 (ddd, *J* = 11.2, 8.0, 3.7 Hz, 1 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.35 (dd, *J* = 13.7, 5.8 Hz, 1 H), 3.22–3.30 (m, 2 H), 2.98 (dd, *J* = 13.7, 2.2 Hz, 1 H), 2.45–2.56 (m, 1 H), 2.47 (s, 3 H), 2.21 (br s, 1 H), 1.92–2.04 (m, 1 H), 1.69–1.80 (m, 2 H), 1.51 (dqd, *J* = 13.5, 7.5, 3.3 Hz, 1 H), 1.13 (dqd, *J* = 13.5, 7.5, 7.5 Hz, 1 H), 1.00 (d, *J* = 6.3 Hz, 3 H), 0.94 (d, *J* = 6.3 Hz, 3 H), 0.87 (d, *J* = 6.8 Hz, 3 H), 0.84 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 169.9, 157.4, 157.2, 130.1, 120.2, 117.6, 116.5, 104.7, 95.9, 66.5, 65.7, 55.9, 52.4, 41.2, 36.5, 33.5, 31.1, 25.9, 25.1, 23.5, 21.1, 15.4, 9.7.
(23) After submission of this manuscript, Ma and co-workers reported the synthesis of mucronine *E* using an intermolecular copper-catalyzed amidation. See: Wang, J.; Schaeffer, L.; He, G.; Ma, D. *Tetrahedron Lett.* **2007**, *48*, 6717.