Synlett K. Dong Letter

The Total Synthesis of Spermine Alkaloid Kukoamine Bimesylate

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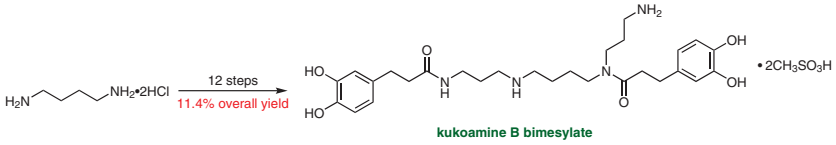

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Abstract The first total synthesis of kukoamine B bimesylate was completed from 1,4-diaminobutane dihydrochloride in 12 steps with a 11.4% overall yield, and all the steps could be carried out at a kilogram scale. The cyano groups were used as the precursor of amino groups to avoid the competitive reaction delicately. The aza-Michael addition reaction, amidation and hydrogenation of the cyano group sequence was streamlined as a general approach towards the synthesis of polyamine structures.

Key words total synthesis, kilogram scale, aza-Michael addition, amidation, hydrogenation

The nature products kukoamines belong to spermine alkaloids, which possess a polyamine backbone and phenolic moieties (Figure 1). The kukoamine A was firstly isolated from dried root bark of Lycium Chinese by Shinji Funayana in 1980,[1] which showed inhibitory activity against angiotensin I-converting enzyme (ACE).[2–4] Ten years later, a new spermine alkaloid kukoamine B was isolated from Lycium Chinese by Shinji Funayana too,[5] which exhibited anti-inflammatory and neuroprotective activities and was considered as a valuable candidate for the antisepsis drug.[6–9] Indeed, several research work on synthesis of kukoamine A had already appeared in literatures.[10–12] In contrast, there were few reports on the synthesis of kukoamine B, probably due to the complex polyamine structures. As part of our long-term efforts on efficient synthetic strategies for potential pharmaceutical molecules, we present herein the further explore on the total synthesis of kukoamine B bimesylate, which exhibited better solubility in water and could be served as a valuable drug candidate.

The retrosynthetic analysis is outlined in Scheme 1. We envisioned that the kukoamine B bimesylate could be obtained from the deprotection of the diamide **1** and subsequent mesylation of the resulting amine with methanesulfonic acid in one-pot.

The compound **1** could be constructed through amidation of amine **2** with acyl chloride **3**. Compound **2** could be derived from the amine **4** through aza-Michael addition reaction. Disconnection of **4** at the amide linkage leads to triamine **6** and acyl chloride **3**. Compound **6** could be traced back to the commercially available diamine **7** and vinyl cyanide **5** via aza-Michael addition reaction.

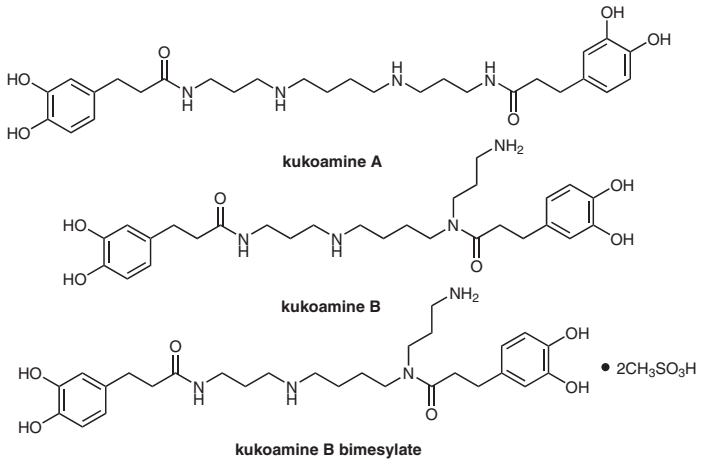
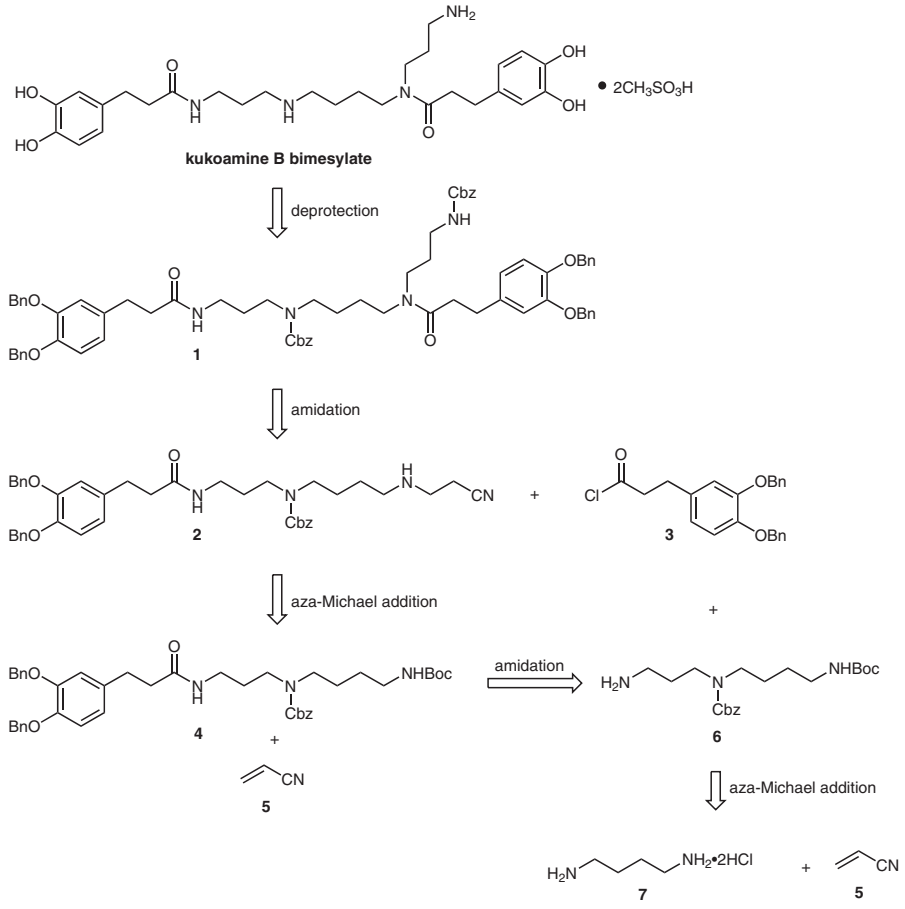


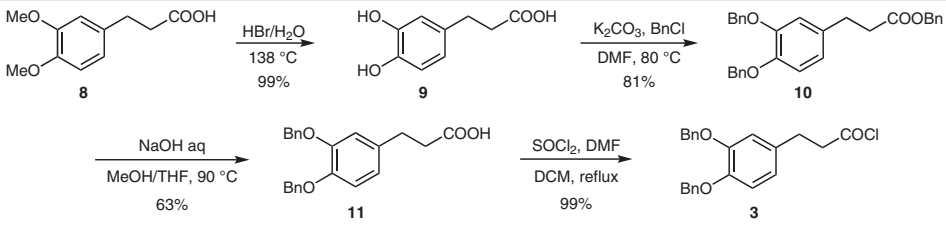
Figure 1 Structures of kukoamine A, kukoamine B, and kukoamine B bimesylate

The synthesis was commenced with preparation of the acyl chloride **3** (Scheme 2). Demethylation of **8** with aqueous hydrogen bromide at 138 °C afforded acid **9** quantitively, which was subjected to potassium carbonate and benzylic chloride in *N*,*N*′-dimethyl formamide (DMF) to generate the compound **10** in 81% yield.[13] Subsequent hydrolysis of ester **10** with aqueous sodium hydroxide furnished acid **11** in 63% yield. Finally, treatment of **11** with thionyl dichloride under the catalyst of DMF delivered the corresponding acyl chloride **3** quantitively which was prepared freshly. Notably, all the manipulation could be carried out successfully at a kilogram scale.

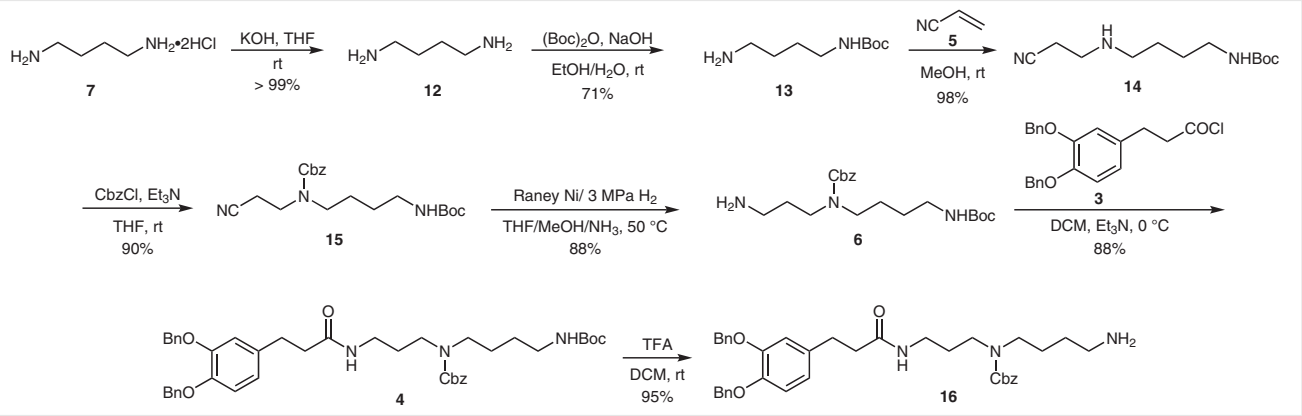
With the acyl chloride **3** in hand, an efficient synthetic approach to complete the kukoamine B bimesylate was conducted (Scheme 3). The commercial 1,4-diaminobutane dihydrochloride underwent dissociation upon exposure to potassium hydroxide to generate dissociative 1,4-diaminobutane **12** quantitively. Then the diamine was treated with *t*-butyloxy carbonyl ($(Boc)_2O$) to give the monoprotected amine **13** in 71% yield. Exposure of compound **13** to vinyl nitrile **5** resulted in an aza-Michael addition reaction to afford amine **14** in 98% yield,[14] and then the remained amino group of **14** was subjected to benzyl chloroformate to furnish compound **15** in 90% yield, which underwent hydro-



Scheme 1 The retrosynthetic analysis of kukoamine B bimesylate



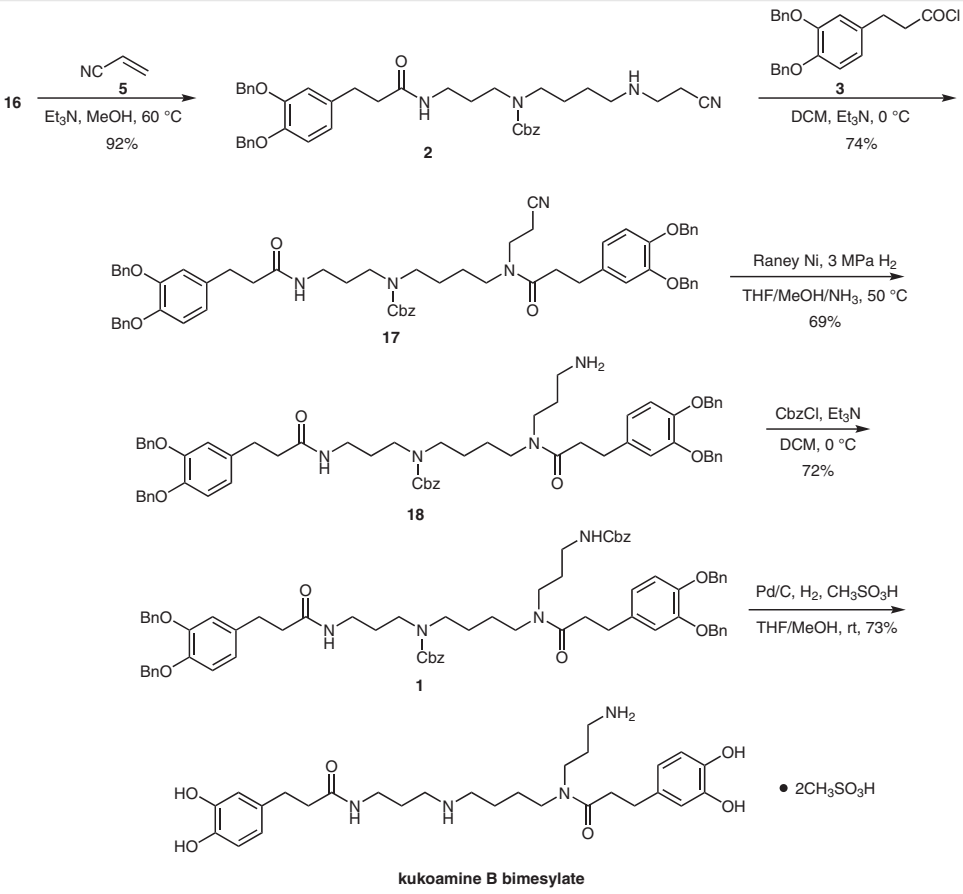
Scheme 2 The synthesis of fragment **3**



Scheme 3 The synthesis of amine fragment

genation in the presence of Raney Ni and hydrogen (3 MPa) to deliver the corresponding amine **6** in 88% yield.[15] Treatment of compound **6** with freshly prepared acyl chloride **3** followed by deprotection of the Boc group gave amine **16** in 84% yield for two steps.

The further conversion was shown in Scheme 4, Compound **16** underwent the aza-Michael addition reaction with vinyl nitrile **5** to afford the nitrile **2** in 92% yield, and the secondary amine of **2** was amidated with acyl chloride to provide compound **17** in 74% yield. After hydrogenation of the cyano group of **17** under the catalyst of Raney Ni, the



Scheme 4 The total synthesis of kukoamine B bimesylate

resulted amino group was further exposed to benzyl chloroformate to give the key precursor **1** in 72% yield. Finally, exposure of compound **1** to palladium on carbon and hydrogen led to cleavage of benzyl and benzoxycarbonyl simultaneously, and the resulted amine could be mesylated to generate kukoamine B bimesylate through acidification with methanesulfonic acid quantitively in one pot. Notably, all the manipulation could be carried out successfully at a kilogram scale.

In summary, we have developed an efficient strategy to accomplish the total synthesis of kukoamine B bimethylate from 1,4-diaminobutane dihydrochloride in 12 steps with a 11.4% overall yield, and all the steps could be carried out at a kilogram scale.[16] The chemoselective protection of the amino groups and the use of the cyano groups as the precursor of the amino groups were served as the key reactions to avoid the competitive reaction delicately. The aza-Michael addition reaction, amidation and hydrogenation of the cyano group sequence could be streamlined as a general approach towards the synthesis of polyamine structures. The kukoamine B bimesylate exhibited better solubility in water and could be served as a valuable drug candidate. The further exploration of the pharmacological activities of kukoamine B bimesylate and its analogues is underway in our lab.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610326.

References and Notes

(1) Funayama, S.; Yoshida, K.; Konno, C.; Hikino, H. *Tetrahedron Lett.* **1980**, *21*, 1355.
(2) Zhang, Y.; Gao, L.; Cheng, Z.; Cai, J.; Niu, Y.; Meng, W.; Zhao, Q. *Neurotoxic. Res.* **2017**, *31*, 259.
(3) Hu, X.; Gao, L.; Niu, Y.; Tian, X.; Wang, J.; Meng, W.; Zhang, Q.; Cui, C.; Han, L.; Zhao, Q. *Biochim. Biophys. Acta* **2015**, *1850*, 287.
(4) Hadjipavlou-Litina, D.; Garnelis, T.; Athanassopoulos, C. M.; Papaioannou, D. *J. Enzyme Inhib. Med. Chem.* **2009**, *24*, 1188.
(5) Funayama, S.; Zhang, G.-R.; Nozoe, S. *Phytochemistry* **1995**, *38*, 1529.
(6) Qin, W. T.; Wang, X.; Shen, W. C.; Sun, B. W. *Exp. Ther. Med.* **2015**, *9*, 725.
(7) Hu, X. L.; Guo, L. P.; Song, Q.; Zhang, Q.; Chen, Y.; Wang, J.; Meng, W. H.; Zhao, Q. C. *Neurochem. Int.* **2015**, *87*, 66.
(8) Hu, X. L.; Niu, Y. X.; Zhang, Q.; Tian, X.; Gao, L. Y.; Guo, L. P.; Meng, W. H.; Zhao, Q. C. *Environ. Toxicol. Pharmacol.* **2015**, *40*, 230.
(9) Zheng, X.; Wang, N.; Yang, Y.; Chen, Y.; Liu, X.; Zheng, J. *RSC Adv.* **2016**, *6*, 85756.
(10) Chantrapromma, K.; Ganem, B. *Tetrahedron Lett.* **1985**, *22*, 23.
(11) Moriwake, T.; Saito, S.; Tamai, H.; Mitsuda, H.; Inaba, M. *Heterocycles* **1985**, *23*, 277.
(12) Zhang, Q.; Xu, Y.; Zhang, H.; Zhang, H.; Liu, J.; Zhan, Y.; Yiu, Y.; Chi, M.; Tian, Y.; Ao, J.; Liu, D. CN105906525, **2016**.
(13) Das, S.; Lee, B. H.; Linstadt, R. T. H.; Cunha, K.; Li, Y.; Kaufman, Y.; Levine, Z.; Lipshutz, A. B. H. R.; Lins, D.; Shea, J.-E.; Heeger, A. J.; Ahn, B. K. *Nano. Lett.* **2016**, *16*, 6709.
(14) Corcé, V.; Morin, E.; Guihéneuf, S.; Renault, E.; Renaud, S.; Cannie, I.; Tripier, R.; Lima, L. M.; Julienne, P. K.; Gouin, S. G.; Loréal, O.; Deniaud, D.; Gaboriau, F. *Bioconjugate Chem.* **2012**, *23*, 1952.
(15) Gardner, R. A.; Kinkade, R.; Wang, C.; Phanstiel, O. IV. *J. Org. Chem.* **2004**, *69*, 3530.
(16) **General Procedure**
To a solution of compound **1** (48.2 g, 0.04 mol) in THF (30 mL) was added methanol (700 mL) and methanesulfonic acid (5.9 mL, 0.09 mol). Then, palladium on carbon (4.8 g) was added to the mixture carefully. Air in the flask was exhausted, and the mixture was stirred at ambient temperature for 15 h under hydrogen atmosphere. TLC showed that all the starting materials were consumed (*n*-BuOH/H_2O/HOAc = 4:1:1, UV), the mixture was filtered, and the was residue washed with THF. The filtrate was collected, and the solvent was removed in vacuum to give kukoamine B bimesylate (16.1 g, 73%) as white solid. ^{1}H NMR (400 MHz, D_2O): δ = 6.84–6.80 (m, 2 H), 6.75 (m, 2 H), 6.67–6.66 (m, 2 H), 3.39–3.34 (m, 2 H), 3.27–3.15 (m, 4 H), 2.91–2.79 (m, 2 H), 2.79 (m, 4 H), 2.79 (s, 6 H), 2.75–2.71 (m, 2 H), 2.66 (m, 2 H), 2.53 (m, 4 H), 1.82 (t, *J* = 6.8Hz, 2 H), 1.69 (t, *J* = 6.8 Hz, 2 H), 1.46 (m, 2 H), 1.34 (m, 2 H). ^{13}C NMR (100 MHz, D_2O): δ = 178.5, 178.3, 146.2, 146.1, 144.6, 135.8, 135.6, 135.2, 123.1, 123.0, 118.7, 118.5, 118.4, 49.9, 49.4, 46.8, 44.9, 40.7, 39.1, 39.0, 37.8, 36.3, 33.0, 32.7, 27.8, 27.3, 27.2, 25.1. ESI-HRMS: *m/z* calcd for $C_{28}H_{42}N_4O_6$ + H: 531.3183; found: 531.3185.