ORGANIC LETTERS

2006
Vol. 8, No. 15
3179−3182

Total Synthesis of Clavepictines A and B and Pictamine

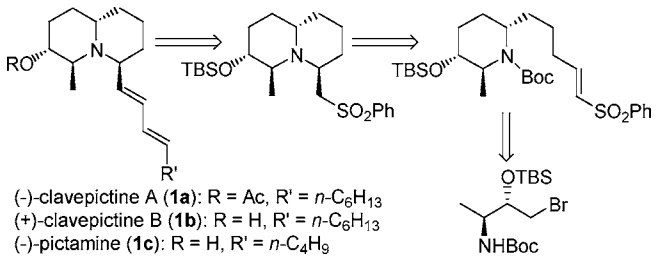
Shanghai Yu, Xiaotao Pu, Tiejun Cheng, Renxiao Wang, and Dawei Ma*

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

madw@pub.sioc.ac.cn

Received April 21, 2006

ABSTRACT



A short route for assembling clavepictines A and B and pictamine is described, which features elaboration of its trisubstituted piperidine moiety via condensation of a β-keto sulfone with an L-alanine-derived bromide and subsequent alkylative cyclization and construction of its quinolizidine skeleton via a diastereoselective intramolecular conjugate addition. The possible stereochemical course for this conjugate addition is discussed.

Clavepictines A and B (**1a** and **1b**) and pictamine (**1c**) are three quinolizidine alkaloids that were isolated from the tunicate *Clavelina picta* in 1991 by the Cardellina and Faulkner groups, respectively (Figure 1).[1] Preliminary biological studies on clavepictines A and B indicated that these two compounds possessed significant cytotoxicity against murine leukemia and human solid tumor cell lines (P-388, A-549, U-251, and SN12K1) at concentrations lower than 9 μg/mL.[1a] A recent study on the structure−activity relationship (SAR) revealed that their cytotoxicity was primarily determined by the side chain connected with C10, as no activity was observed when this unsaturated side chain was replaced with some substituents.[2] Although there have not been any reports on cytotoxicity of pictamine, this alkaloid was recently found to be a potent blocker for two neuronal nicotinic acetylcholine receptors with IC_{50} values of 1.5 and 1.3 μM, respectively.[3]

After the structures of **1a**−**c** were resolved, synthetic studies toward these natural products were immediately

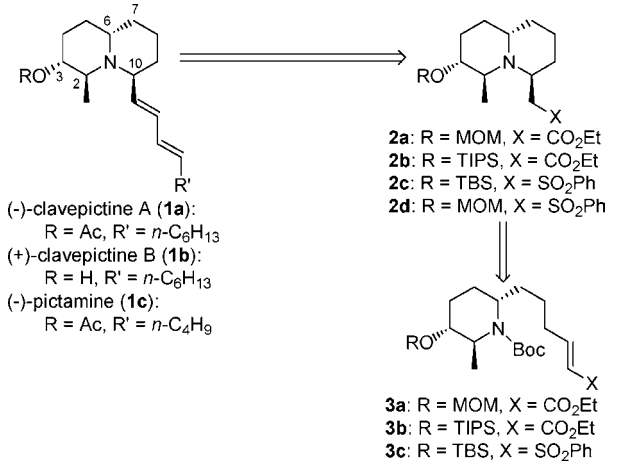


Figure 1. Structures and retrosynthetic analysis of clavepictines and pictamine.

(1) (a) Raub, M. F.; Cardellina, J. H.; Choudhary, M. I.; Ni, C.-Z.; Clardy, J.; Alley, M. C. *J. Am. Chem. Soc.* **1991**, *113*, 3178. (b) Kong, F.; Faulkner, D. J. *Tetrahedron Lett.* **1991**, *32*, 3667.

(2) Agami, C.; Couty, F.; Evano, G.; Darro, F.; Kiss, R. *Eur. J. Org. Chem.* **2003**, 2062.

10.1021/ol060960b CCC: $33.50
Published on Web 06/21/2006

conducted. In 1995, Hart and Leroy disclosed their unsuccessful attempts.[4] One year later, the first enantioselective total synthesis of clavepictines was accomplished by the Momose group, in which 32 linear steps were required.[5] Soon after, Ha and Cha demonstrated their alternative route (in 27 linear steps) to these two target molecules.[6] Interestingly, in their initial investigations, both the Momose and Cha groups chose an intramolecular conjugate addition of an amine liberated from α,β-unsaturated ester **3a** or **3b** to elaborate the desired bicyclic intermediate **2a** or **2b**.[5a,6b] Unfortunately, this process gave rise to undesired 10-epimer **4a** or **4b** as the major or exclusive product (Figure 2), which

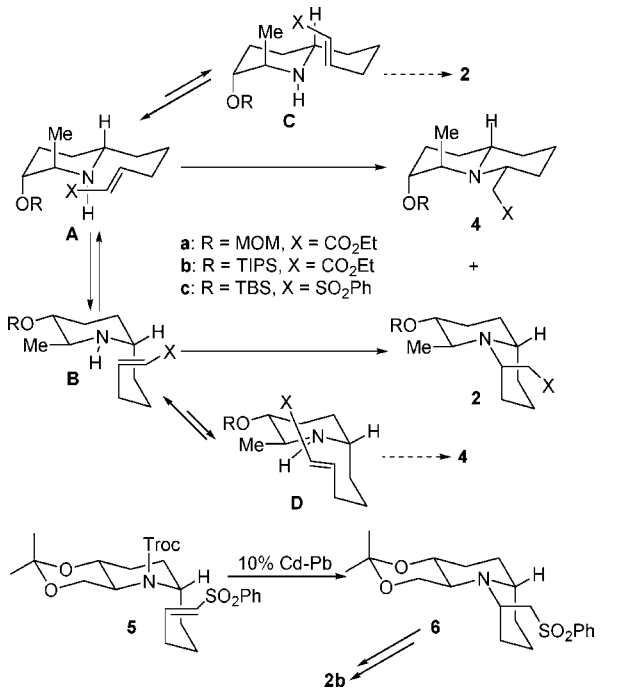


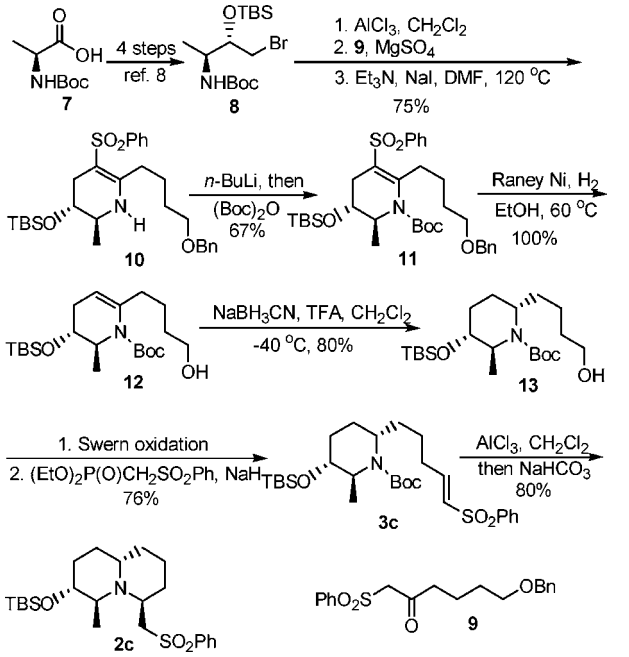
Figure 2. Possible stereochemical courses for formation of quinolizidines **2**, **4**, and **6**.

forced them to give up this obviously short protocol, and completed the total synthesis via another intramolecular conjugate addition (from **5** to **6**), or a silver(I)-promoted cyclization of δ-amino allenes, as the key steps. Notable drawbacks in these two known routes are that the former one required long steps to manipulate the substituents at C2 and C3[5] while the latter one suffered from unsatisfactory diastereoselectivity at the cyclization step.[6]

To rationalize the stereochemical outcome for the intramolecular conjugate addition, two possible conformers **A** and **B** were proposed (Figure 2).[5,6] The amine generated from **3a** or **3b** may prefer the conformer **A** to deliver the undesired isomer **4a** or **4b**, because in the conformer **B** the long carbon side chain must be axial. To inhibit the formation of the conformer **A**, Momose and co-workers employed sulfone **5** as a substrate, in which an additional ring was introduced to fix the conformation of the piperidine ring into *trans*-decalin type. As expected, compound **5** underwent a deprotection/conjugate addition process to provide the desired quinolizidine **6** exclusively, which was subsequently transformed into the advanced intermediate **2d**.[5]

During the studies on the synthesis of bicyclic alkaloids,[7,8b,9a] we became interested in development of a more efficient protocol for assembling clavepictines A and B and pictamine. We envisaged that revising the balance from the conformer **A** to the conformer **B** could also be achieved by replacing the MOM protecting group and α,β-unsaturated ester moiety with larger TBS and α,β-unsaturated sulfone, respectively. These measurements would make the conformer **A** less stable because of its axially disposed bulky silyloxy group and severe repulsive interaction between the benzenesulfonmethyl, methyl and silyloxy groups, thereby giving **2c** predominantly through cyclization of the conformer **B**. The investigations thus undertaken are detailed here.

Scheme 1



As depicted in Scheme 1, the required piperidine ring was constructed from Boc-protected γ-amino bromide **8**, which was prepared from *N*-Boc-L-alanine via Arndt−Eistert

(3) Tsuneki, H.; You, Y.; Toyooka, N.; Sasaoka, T.; Nemoto, H.; Dani, J. A.; Kimura, I. *Biol. Pharm. Bull.* **2005**, *28*, 611.
(4) Hart, D. J.; Leroy, V. *Tetrahedron* **1995**, *51*, 5757.
(5) (a) Toyooka, N.; Yotsui, Y.; Yoshida, Y.; Momose, T. *J. Org. Chem.* **1996**, *61*, 4882. (b) Toyooka, N.; Yotsui, Y.; Yoshida, Y.; Momose, T.; Nemoto, H. *Tetrahedron* **1999**, *55*, 15209.
(6) (a) Ha, J. D.; Lee, D.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 4550. (b) Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012.
(7) (a) Zhu, W.; Cai, G.; Ma, D. *Org. Lett.* **2005**, *7*, 5545. (b) Zhu, W.; Dong, D.; Pu, X.; Ma, D. *Org. Lett.* **2005**, *7*, 705. (c) Pu, X.; Ma, D. *J. Org. Chem.* **2003**, *68*, 4400. (d) Zhu, W.; Ma, D. *Org. Lett.* **2003**, *5*, 5063. (e) Ma, D.; Zhu, W. *Org. Lett.* **2001**, *3*, 3927. (f) Ma, D.; Sun, H. *Org. Lett.* **2000**, *2*, 2503. (g) Ma, D.; Zhang, J. *Tetrahedron Lett.* **1998**, *39*, 9067.
(8) (a) Rotella, P. D. *Tetrahedron Lett.* **1995**, *36*, 5453. (b) Pu, X.; Ma, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4222.

synthesis and subsequent transformations, and has been successfully utilized in the total synthesis of lepadins.[8b] After cleavage of the Boc group in **8** with $AlCl_3$, the liberated amine was immediately condensed with β-keto sulfone **9** under solvent free conditions to provide an enamine sulfone, which was then treated with triethylamine and sodium iodide at 120 °C to produce the alkylative cyclization product **10** in 75% overall yield.[8b,9]

For further conversion, we had to protect the enamine in **10** with a Boc group, which was proven a challenging task owing to its poor reactivity and sterically hindered environment. After some trials, we found that this goal was reached by treatment of **10** with *n*-BuLi and subsequent trapping the anion with di-*tert*-butyl dicarbonate. Next, Raney-Ni-catalyzed hydrogenolysis of **11** was carried out at 60 °C to afford alcohol **12**, which was reduced with $NaBH_3CN$ in the presence of TFA to yield 2,6-trans-substituted piperidine **13**.[10] After Swern oxidation of **13**, olefination of the resultant aldehyde via a Wittig reaction provided α,β-unsaturated sulfone **3c**. Then it was time to check our hypothesis about the stereochemistry of cyclization step. To our delight, removal of the Boc group in **3c** with $AlCl_3$ followed by exposure of the liberated amine to aqueous $NaHCO_3$ delivered **2c** as a single isomer. Its stereochemistry was determined by NOESY studies and was further confirmed by X-ray diffraction analysis (Figure 3). Importantly, the

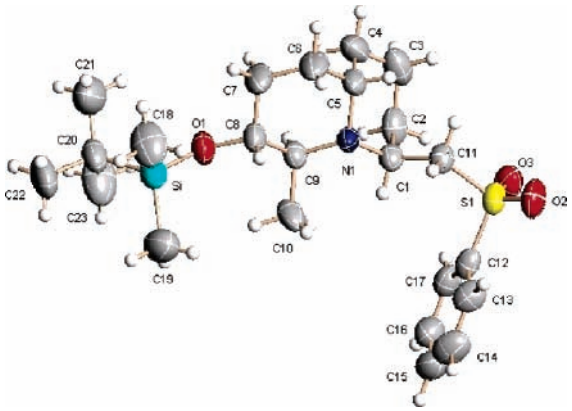


Figure 3. X-ray structure of **2c**.

X-ray structure clearly showed that **2c** has an exact conformation as indicated in Figure 2, in which the quinolizidine has a cis ring junction, both silyloxy and methyl groups are in equatorial orientations, and benzenesulfonmethyl group is disposed at an axial position. This result serves as a strong evidence for the mechanism proposed in Figure 2.

To obtain an in-depth understanding of the stereoselectivity exhibited in our intramolecular conjugate addition reaction, we are currently exploring each possible reaction pathway in Figure 2 through high-level density function theory calculations. Nevertheless, a comparison of the electronic energies of the products given by cyclization of conformers **A**−**D** may already provide some insights into the probability of each reaction pathway. For this purpose, molecular models of the four possible products were built by using the Gaussian 03 program.[11] The geometry of each molecule was fully optimized at the B3LYP 6-31++G(d,p) level, and the single-point electronic energy of each molecule was computed at the same level (Table 1). We noticed that Ha and Cha[6] reported a similar reaction before showing different stereochemistry. Their reactant was different from ours only by R and X (R = TIPS, X = CO_2Et). To make a comparison, we studied their reaction with the same computational method above. The results are also summarized in Table 1.

Table 1. Electronic Energies of the Direct Products by Cyclization of Conformers A−D

product given by cyclization of	electronic energy[a] (kcal/mol)	
	R = TBS, X = SO_2Ph	R = TIPS, X = CO_2Et
A	0.25	−0.78
B	0	0
C	2.43	2.44
D	4.52	3.95

[a] The product by cyclization of conformer **B** is chosen as the reference in both reactions.

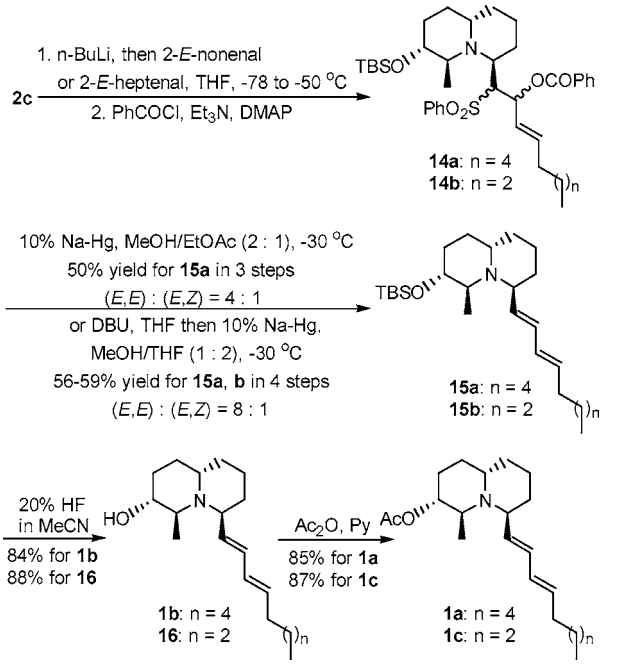
According to our computations, the products of **C** and **D** in both reactions are considerably unfavorable as compared to the ones of **A** and **B**. In these two products, the $-CH_2X$ branch is in fact close to the methyl group in space, which leads to steric repulsions. In contrast, cyclization of **B** or **A** does not result in a molecule with such a problem. It is thus reasonable to expect that these two reaction pathways should govern the stereochemistry in the final product. Our computation indicates that in our reaction the electronic energy of the product of **B** is 0.25 kcal/mol lower than the counterpart of **A**, while in Ha and Cha's reaction, however, the electronic energy of the product of **A** is lower by 0.78 kcal/mol (Table 1). Both results are in agreement with the stereochemistry observed in experiment. Therefore, the preference between these two reaction pathways seems to stem from the relative magnitude of the 1,2-gauche interaction between the methyl group and the −OR branch. As a larger substituent group, TIPS is more sensitive than TBS to the spatial hindrance from the nearby methyl group. Thus, TIPS tends to stay away from the methyl group even on the price of taking an axial orientation, as seen in the product of conformer **A** (Figure 2). In fact, Ha and Cha found by ^1H NMR spectrum that conformer **A** of their reactant was indeed favored over conformer **B**.[6]

With sulfone **2c** in hand, we decided to employ Julia coupling to complete our synthesis.[12] As outlined in Scheme 2, deprotonation of **2c** with *n*-BuLi followed by trapping the resultant anion with 2(*E*)-nonenal or 2(*E*)-heptenal to provide

(9) This strategy has been used for assembling 3-acyl-substituted piperidines; see: (a) Yu, S.; Zhu, W.; Ma, D. *J. Org. Chem.* **2005**, *70*, 7364. Beak and Nakajima have reported an alternative approach to 3-benzenesulfonylpiperidines; see: (b) Back, T. G.; Nakajima, K. *Org. Lett.* **1999**, *1*, 261. (c) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543.

(10) Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1991**, *56*, 2506.

Scheme 2



esters **14**, after esterification with benzoic chloride. Initially, direct treatment of **14** with sodium amalgam was attempted. This approach gave the desired dienes **15** with unsatisfactory stereoselectivity (4:1 for (*E*,*E*)- and (*E*,*Z*)-isomers). Fortunately, Danishefsky's sequential elimination/reduction procedure (DBU then Na/Hg) could improve the selectivity to 8:1.[13] The overall yields for four steps were 56−59%.

Removal of the silyl protectiong group in **15a** with 20% HF in acetonitrile furnished clavepictine B (**1b**), which was acylated with acetic anhydride to afford clavepictines A (**1a**). Similarly, deprotection of **15b** followed by acylation provided pictamine (**1c**). Although these three final products all contain about 12% inseparable (*E*,*Z*)-isomers, analytical data of the major isomers were all identical with those reported.[1]

In conclusion, we have described here a facile protocol to clavepictines A and B and pictamine by using a diastereoselective intramolecular conjugate addition as the key step. The overall yields were about 7.7% for less than 19 linear steps. The stereochemical outcome in formation of quinolizidine **2c** clearly indicated that subtle change in substituents of the piperidine ring could alter the stereochemical course greatly. This work shall be of value to quinolizidine chemistry.

Acknowledgment. The authors are grateful to Chinese Academy of Sciences, National Natural Science Foundation of China (Grant No. 20321202), for their financial support.

Supporting Information Available: Experimental procedures and characterizations for compounds **1**, **2c**, **3c**, and **10**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060960B

(11) Gaussian 03, Revision B.03: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 2003.

(12) (a) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, 4833. For a recent review, see: (b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.

(13) Chen, S.-H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834.