Organic LETTERS

Letter

pubs.acs.org/OrgLett

Practical Asymmetric Synthesis of Amathaspiramides B, D, and F

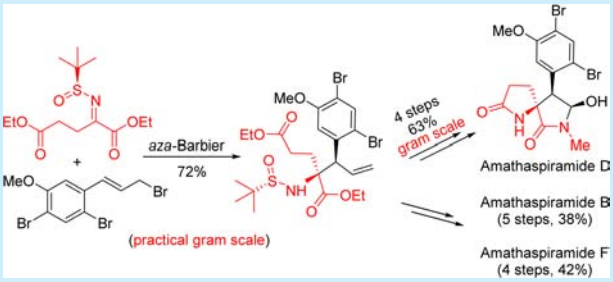
Sen-Lin Cai,[†,§] Ran Song,[†,§] Han-Qing Dong,[‡] Guo-Qiang Lin,[†,‡] and Xing-Wen Sun*[,†]

[†]Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China

[‡]Shanghai Institute of Organic Chemistry, CAS, 345 Lingling Road, Shanghai 200032, China

Supporting Information

ABSTRACT: The practical asymmetric synthesis of amathaspiramides B, D, and F has been accomplished by utilizing an aza-Barbier allylation as the key step to construct the common intermediate with two adjacent stereocenters. A kinetically controlled cyclization to build the challenging thermodynamically less stable 8*R*-hemiaminal moiety is also important in the synthesis of amathaspiramide D. The route is readily scalable, and gram quantity of the final product D has been prepared.



Amathaspiramides A–F (Figure 1) were isolated by Prinsep and Morris from a collection of the marine bryozoans

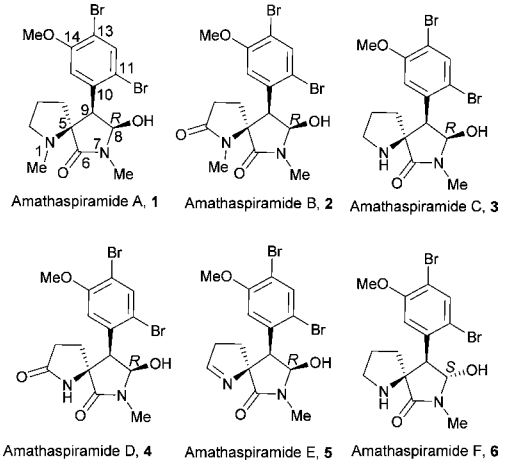


Figure 1. Amathaspiramides A–F.

Amathia wilsoni.[1] The family members share a densely functionalized aza-spirobicyclic core possessing three contiguous stereocenters, including a *tert*-alkylamino carbon center and a hemiaminal center. Due to their attractive bioactivities and chemical structure,[1] significant efforts have been devoted to the development of their total syntheses.[2,3] Previous synthetic studies suggest that the 8*R*-hemiaminal moiety, which was found in amathaspiramides A–E (**1**–**5**), is thermodynamically less stable than the corresponding 8*S*-isomer (e.g., amathaspiramide F).[2] The first total synthesis of the 8*R* series was reported by Fukuyama and co-workers.[3a] They were able to obtain amathaspiramide D from a spiroimide by selective reduction, from which amathaspiramides A–C, E, and F were synthesized. Very recently, Lee reported a rapid access to amathaspiramides utilizing a similar reduction.[3b] As five compounds out of six amathaspiramide family members contain an 8*R*-hemiaminal unit, a highly efficient synthetic approach is desirable to access them. In the meantime, we have reported several practical approaches[4] for Zn-mediated allylation of *N*-*tert*-butanesulfinyl imines[5] under mild conditions, with which a series of homoallylic amines, especially *β*-substituted homoallylic amines, could be constructed in high efficiency. Noticeably, ketimines are also suitable substrates in these allylations and generated homoallylic amines with quaternary stereocenters in high yields and diastereoselectivities. Herein, we report an approach to prepare amathaspiramides B, D, and F utilizing this allylation.

As shown in the retrosynthetic analysis (Scheme 1), amathaspiramide D, a versatile precursor to the other amathaspiramide family members in Fukuyama's work, can be prepared from aldehyde **7** through cyclization. Although the 8*R*-isomer is thermodynamically less stable, the nucleophilic attack of N7 to the aldehyde is likely to occur from the side of *Si* face as the hydrogen bond N1–H–O fixed the comformation. Thus, it is possible to access the 8*R*-isomer under kinetically controlled reaction conditions. Aldehyde **7** can be prepared from alkene **8** through aminolysis and ozonolysis, while the corresponding *β*-aryl-substituted homoallylic amine framework in **8** can be derived by applying the *tert*-butanesulfinyl ketimine based aza-Barbier-type allylation to construct C5 and C9 stereocenters.

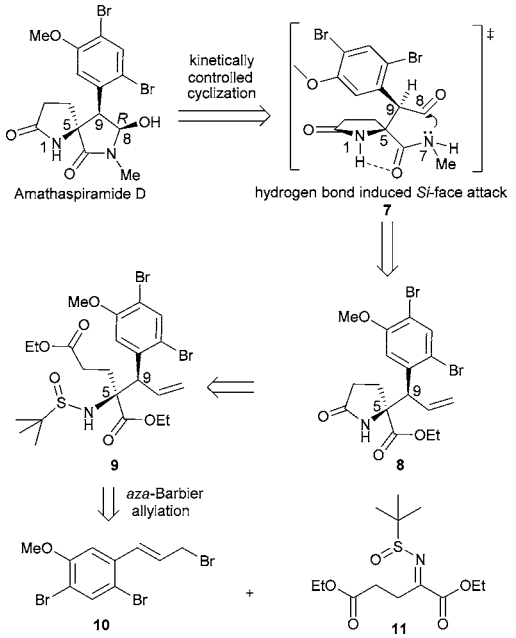
Our synthesis began with the preparation of aza-Barbier allylation partners allyl bromide **10** and ketimine **11**. Compound **10** could be synthesized from known compound **12**[6] (Scheme 2), and **11** was prepared from the condensation between diester **14** and chiral sulfinamine **15** (Scheme 3).[7]

With both allylation partners in hand, the aza-Barbier reaction was evaluated (Table 1). The allylation between (S_s)-ketimine **11** and the in situ generated organozinc reagent from allyl bromide **10** and Zn dust in *N*,*N*-dimethylformamide (DMF) afforded two

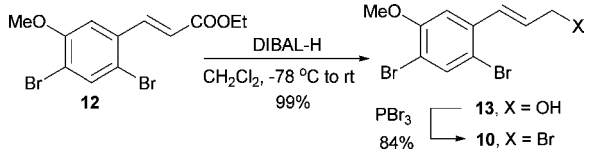
Received: March 1, 2016
Published: April 11, 2016

DOI: 10.1021/acs.orglett.6b00588
Org. Lett. 2016, 18, 1996–1999

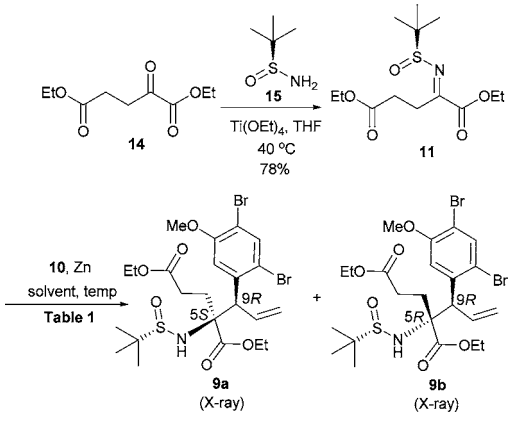
Scheme 1. Retrosynthetic Analysis of Amathaspiramide D



Scheme 2. Synthesis of Allylbromide 10



Scheme 3. Construction of C5 and C9 Stereocenters



diastereoisomers (dr = **9a**/**9b** = 2:1) in 66% yield (Table 1, entry 1). Compounds **9a** and **9b** could be separated by silica gel chromatography. X-ray single-crystal diffraction unambiguously assigned their absolute configurations as (5*S*,9*R*)-**9a** and (5*R*,9*R*)-**9b**.[8] When *N*,*N*-diethylformamide (DEF) was employed as solvent, the dr increased to 4:1 (Table 1, entry 2). The diastereoselectivity could be further improved by lowering the reaction temperature, and the best dr (10:1) was obtained at −40 °C (Table 1, entry 4). The selectivity did not improve further at −60 °C (Table 1, entry 5) because the reaction mixture became very viscous at −50 °C (the melting point of DEF is −61 °C).

Interestingly, when THF was employed as the solvent, the percentage of **9b** was increased to 60% (Table 1, entry 8). These stereochemical outcomes could be explained by the proposed

Table 1. Optimization for the Aza-Barbier Allylation

entry[a]	solvent	temp (°C)	time (h)	yield[b] (%)	dr (**9a**/**9b**)[c]
1	DMF	RT	0.5	66	2:1
2	DEF	RT	0.5	72	4:1
3	DEF	−20	12	67	7:1
4	DEF	−40	24	68	10:1
5	DEF	−60	30	60	9:1
6[d,e]	DEF	−40	24	72 of **9a** 6 of **9b**	10:1
7[d,f]	DEF	−40	24	82	10:1
8	THF	RT	2	60	2:3

[a]Unless otherwise noted, the reaction was performed with **11** (1.0 equiv, 0.25 mmol), **10** (1.5 equiv), and Zn (2.0 equiv). [b]Isolated yield for the mixture of **9a** and **9b**. [c]Determined by crude ^{1}HNMR. [d]With **10** (3.0 equiv) and Zn (4.0 equiv). [e]The reaction was conducted with 1.0 mmol of **11**. [f]The reaction was conducted with 1.0 g (3.3 mmol) of **11**.

reaction transition states (TSs) (Figure 2). In polar aprotic solvent, the organozinc reagent was solvated and formed a bulky

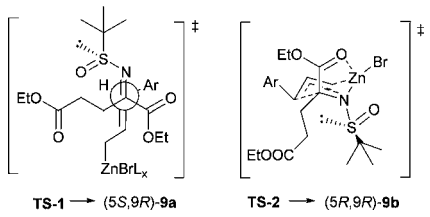


Figure 2. Proposed transition states for the aza-Barbier allylation.

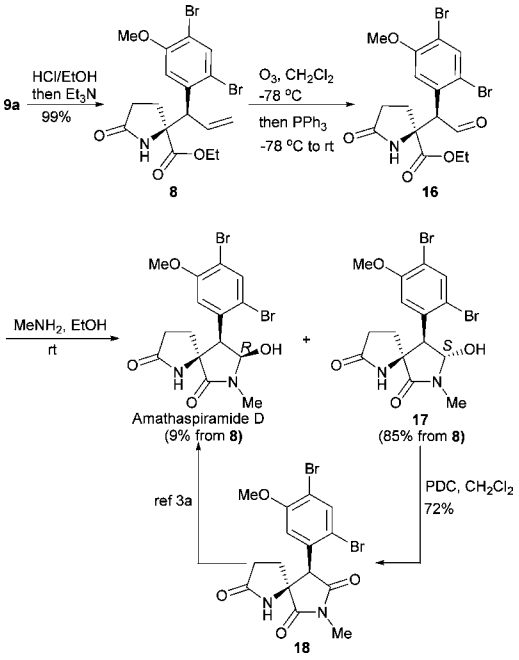
R-ZnBrL$_x$ complex. The reaction mostly proceeded through open-chain **TS-1** and gave (5*S*,9*R*)-**9a** as the major product. The coordinate capability of THF was weaker than that of the polar aprotic solvent; therefore, the reaction mainly proceeded through six-membered cyclic **TS-2** and gave more (5*R*,9*R*)-**9b** in THF. The yield of the reaction could be increased without sacrificing the diastereoselectivity when more equivalents of **10** and Zn were used (Table 1, entry 6), and this result was maintained even if the reaction was performed in gram scale (Table 1, entry 7).

With a scalable route to highly functionalized sulfinamide **9a** established, we turned our attention to the construction of the pyrrolidinone moiety (Scheme 4). Upon removal of the *N*-*tert*-butanesulfinyl group in **9a** under acidic condition, the resulting hydrochloride salt was treated with Et_3N to afford pyrrolidinone **8** in nearly quantitative yield. Interestingly, the two pyrrolidinone isomers from compounds **9a** and **9b** showed quite different physical properties. The desired isomer (5*S*,9*R*)-**8** is a fine solid, with poor solubility in EtOAc, while the (5*R*,9*R*)-isomer derived from **9b** is a semisolid, with excellent solubility in EtOAc. Such significant solubility difference could be utilized to simplify the purification process. For a multigram scale preparation, a mixture of **9a** and **9b** from the aza-Barbier reaction could be subjected to the above sequence to form pyrrolidinones, and the desired isomer of **8** was conveniently obtained by recrystallization.

Next, we focused on the formation of the challenging C8 hemiaminal center. Alkene **8** was first subjected under ozonolysis conditions to provide aldehyde **16**, which was subsequently treated with methylamine at room temperature (Scheme 4). Not surprisingly, in accord with previous reports about direct cyclization from aldehyde,[2] the major product turned out to be

DOI: 10.1021/acs.orglett.6b00588
Org. Lett. 2016, 18, 1996−1999

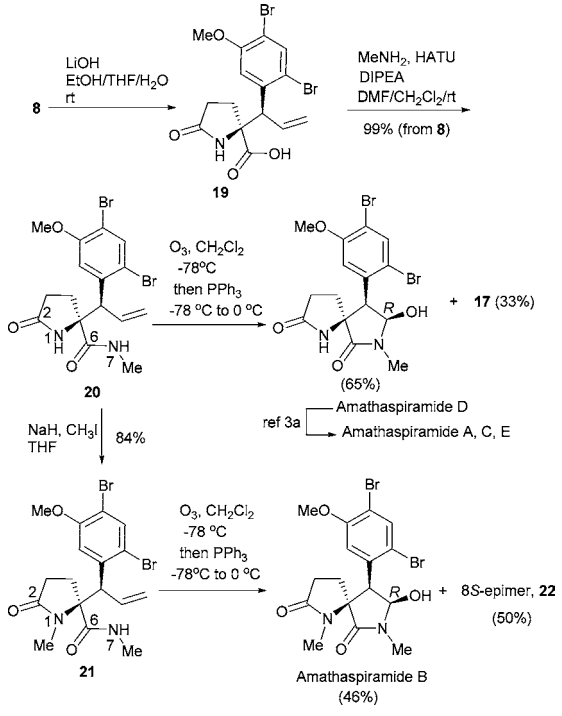
Scheme 4. Initial Approach to Amathaspiramide D



8*S*-hemiaminal **17**, while the desired product D was isolated only in 9% yield.

Although **17** can be transformed into amathaspiramide D by a protocol of oxidation and subsequent selective reduction,[3a] a straightforword and efficient method to obtain a *R*-hemiaminal moiety is highly desirable. Based on the analysis mentioned before, we assumed that the reaction might favor the kinetically controlled product if conducted at lower temperature and under nonbasic conditions. Thus, we converted the ester **8** to *N*-methyl amide **20** prior to the ozonolysis (Scheme 5). As expected,

Scheme 5. Final Approach to D and B

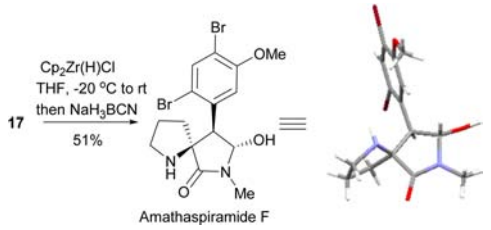


treatment of **20** with O_3 in dichloromethane at −78 °C and subsequent quenching with PPh_3 successfully gave the kinetically controlled 8*R*-amathaspiramide D in moderate 65% yield and decreased the 8*S*-epimer **17** to 33% yield.

Amathaspiramide B could be synthesized in a manner similar to that of amathaspiramide D. As shown in Scheme 5, selective N-methylation was achieved for the lactam N−H by using 1 equiv of NaH in dry THF, resulting in compound **21** in 84% yield. Following the established ozonolysis and cyclization procedures, 46% yield of amathaspiramide B and 50% yield of its 8*S*-epimer **22** were obtained, respectively.

Alternatively, the correctly established three stereocenters in **17** could allow for rapid preparation of amathaspiramide F (Scheme 6). Upon the treatment with Schwartz's reagent,[3,9] the

Scheme 6. Synthesis of Amathaspiramide F



secondary amide was selectively reduced to an imine intermediate, which was further reduced by $NaBH_3CN$ in one pot to afford amathaspiramide F in 51% yield. The structure of F was further comfirmed by X-ray single-crystal diffraction.[8]

In summary, the practical asymmetric synthesis of amathaspiramides B, D, and F was achieved. The key feature of this route is the construction and regulation of two adjacent stereocenters, including a *tert*-alkylamino carbon center, through an aza-Barbier-type allylation. In addition, the thermodynamically less stable 8*R*-hemiaminal unit was first achieved by a direct kinetically controlled cyclization under nonbasic conditions at low temperature. The choice of prefunctionalized allyl bromide **10** significantly streamlined the synthetic work. The longest linear route, 10 steps from 3-hydroxybenzaldehyde to amathaspiramide D, could be operated in gram scale and achieved in 27% overall yield. Benefiting from the inexpensive materials and the efficient transformations, our stereoselective diversity-oriented synthesis strategy readily affords a library of amathaspiramide derivatives for biological studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00588.

X-ray data for amathaspiramide F (CIF)
X-ray data for **8** (CIF)
X-ray data for **9a** (CIF)
X-ray data for **9b** (CIF)
X-ray data for **20** (CIF)
Detailed experimental procedures and full spectroscopic data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sunxingwen@fudan.edu.cn.

DOI: 10.1021/acs.orglett.6b00588
Org. Lett. 2016, 18, 1996−1999

Author Contributions

[§]S.-L.C. and R.S. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge financial support from the National Natural Science Foundation of China (21342009 and 21472019). We also thank Prof. Ran Hong (SIOC), Dr. Yiyang Liu (Caltech), and Dr. Haoxuan Wang (MIT) for their valuable advice.

■ REFERENCES

(1) Morris, B. D.; Prinsep, M. R. *J. Nat. Prod.* **1999**, *62*, 688.

(2) (a) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4556. (b) Sakaguchi, K.; Ayabe, M.; Watanabe, Y.; Okada, T.; Kawamura, K.; Shiada, T.; Ohfune, Y. *Org. Lett.* **2008**, *10*, 5449. (c) Sakaguchi, K.; Ayabe, M.; Watanabe, Y.; Okada, T.; Kawamura, K.; Shinada, T.; Ohfune, Y. *Tetrahedron* **2009**, *65*, 10355. (d) Soheili, A.; Tambar, U. K. *Org. Lett.* **2013**, *15*, 5138.

(3) (a) Chiyoda, K.; Shimokawa, J.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 2505. (b) O'Connor, M.; Sun, C.; Lee, D. *Angew. Chem., Int. Ed.* **2015**, *54*, 9963.

(4) (a) Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979. (b) Sun, X.-W.; Liu, M.; Xu, M.-H.; Lin, G. Q. *Org. Lett.* **2008**, *10*, 1259. (c) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831. (d) Liu, M.; Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Chem. - Eur. J.* **2009**, *15*, 10217. (e) Liu, M.; Shen, A.; Sun, X.-W.; Deng, F.; Xu, M.-H.; Lin, G.-Q. *Chem. Commun.* **2010**, *46*, 8460. (f) Liu, W.-J.; Zhao, Y.-H.; Sun, X.-W. *Tetrahedron Lett.* **2013**, *54*, 3586. (g) Guo, T.; Song, R.; Yuan, B.-H.; Chen, X.-Y.; Sun, X.-W.; Lin, G.-Q. *Chem. Commun.* **2013**, *49*, 5402. (h) Tan, Y.; Yang, X.-D.; Liu, W.-J.; Sun, X.-W. *Tetrahedron Lett.* **2014**, *55*, 6105. (i) Dong, H.-Q.; Xu, M.-H.; Feng, C.-G.; Sun, X.-W.; Lin, G.-Q. *Org. Chem. Front.* **2015**, *2*, 73.

(5) For selected reviews on the chemistry of *N-tert*-butanesulfinyl imine, see: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallon, E. *Aldrichimica Acta* **2005**, *38*, 93−104. (c) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162. (d) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600. (e) Yus, M.; Gonzalez-Gomez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595.

(6) Compound **12** could be synthesized from inexpensive 3-hydroxybenzaldehyde: (a) Ramírez Osuna, M.; Aguirre, G.; Somanathan, R.; Molins, E. *Tetrahedron: Asymmetry* **2002**, *13*, 2261. (b) Khan, F. A.; Ahmad, S.; Kodipelli, N.; Shivange, G.; Anindya, R. *Org. Biomol. Chem.* **2014**, *12*, 3847.

(7) (a) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278. (b) Datta, G. K.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 6283.

(8) CCDC 1055098 (intermediate **9a**), CCDC 1055028 (**9b**), CCDC 1055029 (**8**), CCDC 1055030 (**20**), and CCDC 1055031 ((−)-amathaspiramide **F**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

(9) (a) Schedler, D. J. A.; Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1993**, *34*, 5035. (b) Schedler, D. J.; Li, J.; Ganem, B. *J. Org. Chem.* **1996**, *61*, 4115. (c) Xia, Q.; Ganem, B. *Tetrahedron Lett.* **2002**, *43*, 1597. (d) Arnold, M. A.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2005**, *127*, 6924. (e) Arnold, M. A.; Day, K. A.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 13255.

DOI: 10.1021/acs.orglett.6b00588
Org. Lett. 2016, 18, 1996−1999