Organic LETTERS

Letter

pubs.acs.org/OrgLett

Total Synthesis and Determination of the Absolute Configuration of Vinylamycin

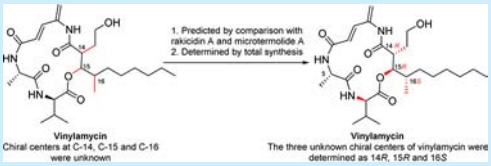
Zhantao Yang,[†] Guang Yang,*[,†] Meiyan Ma,[†] Jiangnan Li,[‡] Jianwei Liu,[†] Jinghan Wang,[†] Shende Jiang,[‡] Quan Zhang,[†] and Yue Chen*[,†]

[†]The State Key Laboratory of Medicinal Chemical Biology, College of Pharmacy, Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), and Tianjin Key Laboratory of Molecular Drug Research, Nankai University, Tianjin 300071, People's Republic of China

[‡]School of Pharmaceutical Science and Technology, Tianjin University, Tianjin, 300072, People's Republic of China

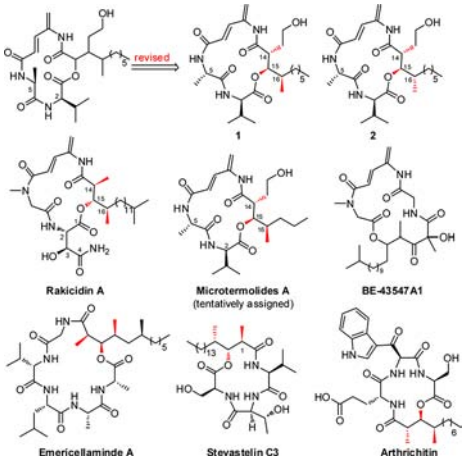
Supporting Information

ABSTRACT: The absolute configurations of the three unknown chiral centers in vinylamycin were predicted according to the structural comparison with microtermolide A and rakicidin A, and then total syntheses of vinylamycin were applied to determine the three unknown chiral centers as 14*R*, 15*R*, and 16*S*.



The antimicrobial natural product, vinylamycin, was discovered as a metabolite of *Streptomyces sp.* and was initially proposed to be a 14-membered ring with five chiral centers (Scheme 1).[1] Vinylamycin belongs to a family of cyclic depsipeptides, which possess a unique 4-amino-2,4-pentadienolate structure, and include rakidicins,[2] microtermolide A,[3] and BE43547A1.[4] Using degradation and chiral HPLC analysis, the amino acids of vinylamycin at C-2 and C-5 were identified as D-valine (2*R*) and L-alanine (5*S*);[1] however, its three consecutive chiral centers, C-14, C-15, and C-16 in the polyketide fragment, have remained unknown. In 2012, another similar natural product, microtermolide A, was isolated and extensively studied with NMR.[3] As a result, the three absolute configurations of microtermolide A were tentatively assigned as 14*R*, 15*R*, and 16*R*,[3] thereby representing an *anti*−*anti* relative relationship among the chiral centers. Based on this analysis of microtermolide A and prediction with calculation, the structure of vinylamycin was revised to a 15-member ring,[3] and then the absolute configuration of vinylamycin could also be tentatively assigned as 14*R*, 15*R*, and 16*R* (compound **1**).

Scheme 1. Structure of Cyclic Despipeptides Natural Products



Recently, *anti*-cancer stem cell natural product rakicidin A was prepared through total synthesis in our group. The absolute configuration of rakicidin A was determined to be 2*S*, 3*S*, 14*S*, 15*S*, and 16*R*; thus, the three consecutive chiral centers exhibited an *anti*−*syn* relative relationship.[5a] This result was further approved by degradation and HPLC analysis.[5b] Furthermore, many other depsipeptides with three consecutive chiral centers and long lipophilic side chains, including emericellaminde A,[6] stevastelin C3,[7] and arthrichitin,[8] have an *anti*−*syn* polyketide carbon framework. Therefore, it was also possible that vinylamycin exhibited *anti*−*syn* relative stereochemistry, i.e., 14*R*, 15*R*, and 16*S* for its three consecutive chiral centers (compound **2**).

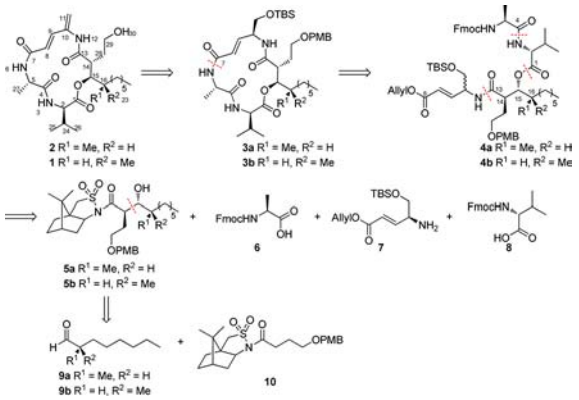
In contrast to the total synthesis of rakicidin A,[5a] the synthetic strategy of vinylamycin was modified such that lactamization was performed at C-7, which involved a less hindered carboxylic acid. Compound **4a**/**4b** could be prepared from the aldol product **5a**/**5b**, which may be obtained from the L-camphorsultam derivative **10** and the chiral aldehyde **9a**/**9b**. Due to the liability of the conjugated diene group, it was necessary to produce it in the final steps of the synthesis. Fragment **7** was prepared in prior steps using D-serine to overcome the low yield and low selectivity of the HWE reaction in this complex system[5a] (Scheme 2).

The compound **15** with the desired configuration was synthesized with high diastereoselectivity via a Mukaiyama aldol reaction, and the configuration was confirmed by X-ray analysis

Received: September 28, 2015
Published: November 2, 2015

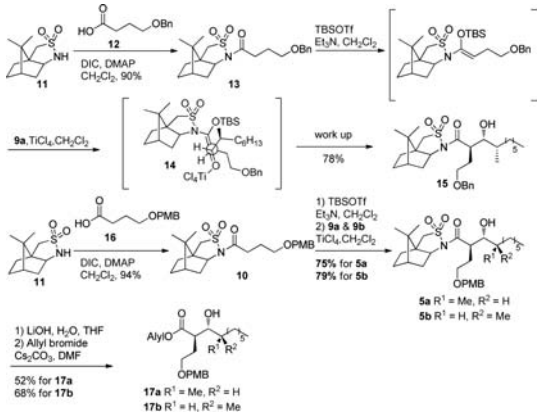
DOI: 10.1021/acs.orglett.5b02809
Org. Lett. 2015, 17, 5725−5727

Scheme 2. Retrosynthetic Analysis



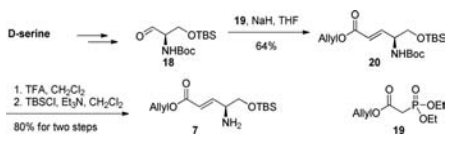
of the single crystal of **15** (refer to the Supporting Information). The high *dr* may be explained by the fact that the process underwent the proposed transition state **14**. Thus, the desired products **5a**/**5b** were synthesized with good selectivity (*dr* > 10:1) and moderate yields following the same route (Scheme 3). Hydrolysis of **5a**/**5b** followed by treatment with Cs_2CO_3 and allyl bromide achieved the allyl ester **17a**/**17b**.

Scheme 3. Aldol Reaction To Form Polyketide Fragments



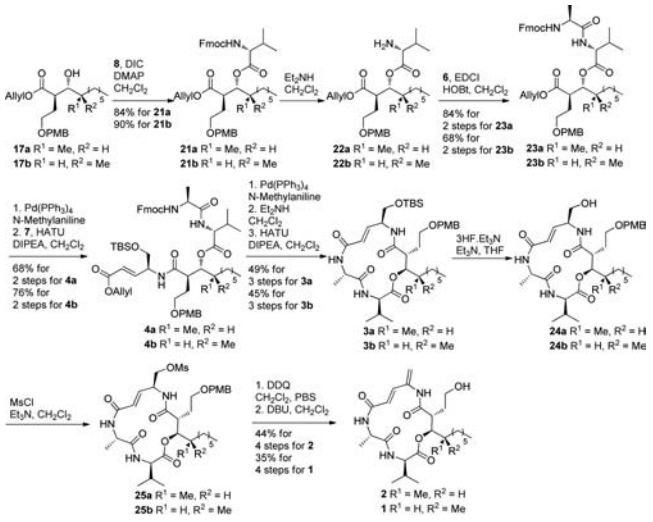
For the synthesis of the required serine derivative **7**, aldehyde **18**[12] was subjected to the highly selective HWE reaction (*E*:*Z* > 25:1) to provide the conjugated alkene **20** (Scheme 4).[13] Deprotection of both Boc and TBS groups in compound **20** was followed by reprotection of the OH group with TBS to obtain compound **7**.[14]

Scheme 4. Synthesis of Serine Derivative 7



Using compounds **17a**/**17b** and **7**, an efficient synthetic approach for fragment coupling was investigated (Scheme 5). Esterification of alcohol **17a**/**17b** with the D-Fmoc-valine **8** produced compounds **21a** and **21b**. Deprotection of the Fmoc group and coupling with L-Fmoc-alanine **6** provided compounds **23a**/**23b**. Thus, deprotection of the allyl groups,

Scheme 5. Forward Synthesis of Vinylamycin



followed by coupling with the D-serine derivative **7**, resulted in the cyclization precursors, **4a**/**4b**. Following cleavage of the allyl ester and Fmoc protecting group, the resulting intermediates were used directly in the next lactamization with the previously optimized conditions to produce lactam **3a** and **3b** in 49% and 45% yield, respectively.[5a] Exposure of cyclic compounds **3a** and **3b** to HF provided free alcohols **24a**/**24b**. With subsequent mesylation, the intermediates **25a**/**25b** were achieved. Deprotection of PMB with DDQ and final elimination of the Ms group with DBU furnished compounds **2** and **1**, respectively. Of note, both compounds were not very stable at room temperature.

NMR analytic data of the compounds **1** and **2** were compared with those of natural vinylamycin reported in the literature,[1] including both the ^{1}H and ^{13}C NMR data (Supporting Information). The ^{1}H NMR analytic data of reported vinylamycin, compound **1**, and compound **2** were very similar, suggesting that prediction of stereochemistry outside the macrocyclic ring using calculation was difficult. However, the data for compound **2** and natural vinylamycin matched perfectly, while the data for compound **1** clearly differed at C-15, C-16, C-17, C-20, C-22, and C-23 in the ^{13}C NMR. These results indicated that the structure of compound **2** represented the real structure of natural vinylamycin. Consequently, the three previously unknown consecutive chiral centers of vinylamycin were assigned as 14*R*, 15*R*, and 16*S*, thereby representing *anti*−*syn* relative stereochemistry.

In conclusion, the structure of the natural cyclic depsipeptide, vinylamycin, was recently revised to a 15-member ring. However, three consecutive chiral centers in vinylamycin remained unknown,[1,3] and vinylamycin possibly represented one of eight possible diastereoisomers. Here, a structural comparison of microtermolide A[3] and rakicidin A[5] with vinylamycin performed respectively to predict the stereochemistry of three consecutive chiral centers. The difference between the two predictions is an *anti*−*anti* or *anti*−*syn* relative stereochemistry in the three consecutive chiral centers, respectively. Therefore, both predicted compound **1** (*anti*−*anti*) and compound **2** (*anti*−*syn*) underwent total syntheses. Both compounds **1** and **2** were synthesized in a highly efficient manner in 16 linear steps with a 3.7% overall yield, which is significantly higher than the overall yield (0.17%) of total synthesis of rakicidin A.[5a] When the analytic data for

DOI: 10.1021/acs.orglett.5b02809
Org. Lett. 2015, 17, 5725−5727

compounds **1** and **2** were compared with those for natural vinylamycin,[1] only the analytic data for compound **2** perfectly matched those reported for vinylamycin. Therefore, the remaining three unknown consecutive chiral centers of vinylamycin should be assigned as 14*R*, 15*R*, and 16*S*, thereby identifying vinylamycin as another example of *anti*−*syn* relative stereochemistry in a cyclic depsipeptide with three consecutive chiral centers and long lipophilic side chains. The determination of three unknown consecutive chiral centers and the highly efficient synthetic sequence of vinylamycin provide the opportunity for further investigation of vinylaymycin and similar depsipeptides as interesting biologically active natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02809.

Experimental details and characterization of all new compounds, including ^{1}H, ^{13}C, and selected X-ray crystal structure, 2D-HMQC, and HMBC data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yuechen@nankai.edu.cn.
*E-mail: Guang.Yang@nankai.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (NSFC) (No. 21372129 to Y.C. and No. 81370086 to Q.Z.), Program for New Century Excellent Talents in University to Y.C., and Hundred Young Academic Leaders Program of Nankai University. General Financial Grant from the China Postdoctoral Science Foundation (No. 2015M571261) to G.Y.

■ REFERENCES

(1) Igarashi, M.; Shida, T.; Sasaki, Y.; Kinoshita, N.; Naganawa, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1999**, *52*, 873−879.

(2) (a) McBrien, K. D.; Berry, R. L.; Lowe, S. E.; Neddermann, K. M.; Bursuker, I.; Huang, S.; Klohr, S. E.; Leet, J. E. *J. Antibiot.* **1995**, *48*, 1446−1452. (b) Hu, J. F.; Wunderlich, D.; Sattler, I.; Feng, X. Z.; Grabley, S.; Thiericke, R. *Eur. J. Org. Chem.* **2000**, *2000*, 3353−3356. (c) Igarashi, Y.; Shimasaki, R.; Miyanaga, S.; Oku, N.; Onaka, H.; Sakurai, H.; Saiki, I.; Kitani, S.; Nihira, T.; Wimonsiravude, W.; Panbangred, W. *J. Antibiot.* **2010**, *63*, 563−565.

(3) Carr, G.; Poulsen, M.; Klassen, J. L.; Hou, Y. P.; Wyche, T. P.; Bugni, T. S.; Currie, C. R.; Clardy, J. *Org. Lett.* **2012**, *14*, 2822−2825.

(4) Nishioka, H.; Nakajima, S.; Nagashima, M.; Ojiri, K.; Suda, H. JP10147594-A, 1998.

(5) (a) Sang, F.; Li, D. M.; Sun, X. L.; Cao, X. Q.; Wang, L.; Sun, J. L.; Sun, B. X.; Wu, L. L.; Yang, G.; Chu, X. Q.; Wang, J. H.; Dong, C. M.; Geng, Y.; Jiang, H.; Long, H. B.; Chen, S. J.; Wang, G. Y.; Zhang, S. Z.; Zhang, Q.; Chen, Y. *J. Am. Chem. Soc.* **2014**, *136*, 15787−15791. (b) Oku, N.; Matoba, S.; Yamazaki, Y. M.; Shimasaki, R.; Miyanaga, S.; Igarashi, Y. *J. Nat. Prod.* **2014**, *77*, 2561−2565.

(6) Oh, D. C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Nat. Prod.* **2007**, *70*, 515−520.

(7) Kurosawa, K.; Matsuura, K.; Nagase, T.; Chida, N. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 921−937.

(8) Schlingmann, G.; Milne, L.; Williams, D. R.; Carter, G. T. *J. Antibiot.* **1998**, *51*, 303−316.

(9) Prantz, K.; Mulzer, J. *Chem. - Eur. J.* **2010**, *16*, 485−506.

(10) Sedrani, R.; Kallen, J.; Cabrejas, L. M. M.; Papageorgiou, C. D.; Senia, F.; Rohrbach, S.; Wagner, D.; Thai, B.; Eme, A. M. J.; France, J.; Oberer, L.; Rihs, G.; Zenke, G.; Wagner, J. *J. Am. Chem. Soc.* **2003**, *125*, 3849−3859.

(11) Poulsen, T. B. *Chem. Commun.* **2011**, *47*, 12837−12839.

(12) Cook, G. R.; Shanker, P. S. *J. Org. Chem.* **2001**, *66*, 6818−6822.

(13) Wadsworth, J. M.; Clarke, D. J.; McMahon, S. A.; Lowther, J. P.; Beattie, A. E.; Langridge-Smith, P. R. R.; Broughton, H. B.; Dunn, T. M.; Naismith, J. H.; Campopiano, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 14276−14285.

(14) Palomo, C.; Aizpurua, J. M.; Balentova, E.; Jimenez, A.; Oyarbide, J.; Fratila, R. M.; Miranda, J. I. *Org. Lett.* **2007**, *9*, 101−104.

(15) Takeuchi, M.; Ashihara, E.; Yamazaki, Y.; Kimura, S.; Nakagawa, Y.; Tanaka, R.; Yao, H.; Nagao, R.; Hayashi, Y.; Hirai, H.; Maekawa, T. *Cancer Sci.* **2011**, *102*, 591−596.

DOI: 10.1021/acs.orglett.5b02809
Org. Lett. 2015, 17, 5725−5727