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Asymmetric Total Syntheses of Ansamacrolactams (+)-Q-1047H-A-A and (+)-Q-1047H-R-A

Shouliang Yang, Yumeng Xi, Rong Zhu, Lin Wang, Jiahua Chen,* and Zhen Yang*

Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education and Beijing National Laboratory for Molecular Science (BNLMS), and Peking-Tsinghua Center for Life Sciences, Peking University, Beijing 100871, China, and Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Shenzhen 518055, China

jhchen@pku.edu.cn; zyang@pku.edu.cn

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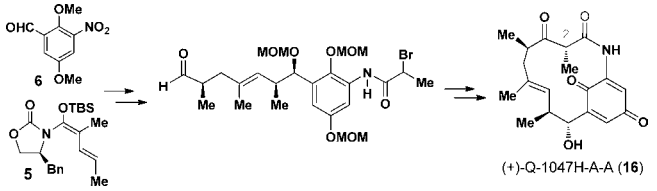
ABSTRACT



The total syntheses of ansamacrolactams (+)-Q-1047H-A-A (16) and (+)-Q-1047H-R-A (17) have been achieved for the first time in 17 steps, leading to the reassignment of the relative stereochemistries and absolute configurations of their natural counterparts. The key steps in the synthetic work included an asymmetric chelation-controlled vinylogous Mukaiyama aldol reaction for the stereoselective synthesis of the *syn*-aldol adduct 7b and an intramolecular SmI_2-mediated Reformatsky reaction for the formation of the macrocyclic lactam 14.

The identification of new chemical entities is of paramount importance to the biomedical sciences for the development of novel therapeutic agents, and natural products have recently been the subject of renewed and considerable attention in this particular context.[1] Of the many different types of natural products, macrolactams represent an important family of natural products and have served as extremely valuable tools for probing a variety of different biological and pharmacological phenomena.[2]

One emerging class of macrolactam bacterial metabolites includes Q-1047H-A-A (**1**) and Q-1047H-R-A (**2**) (Figure 1), which were isolated from a culture of *Pseudonocardia* sp Q-1047 (type strain deposited under FERM-2331) by Saito et al. in 1989, and their structures were elucidated by NMR.[3] Both molecules possess 13-membered lactams with *trans*-substituted olefin units connecting the benzoquinone to the highly functionalized polyketide-derived carbon chains, along with four stereogenic centers (Figure 1).

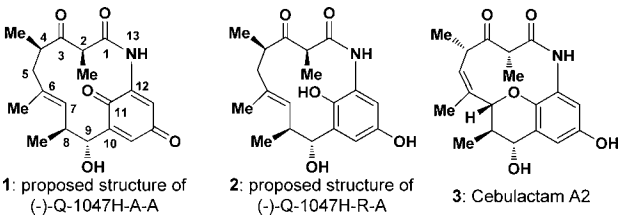


Figure 1. Naturally occurring biologically active lactams.

Q-1047H-A-A **1** holds a special place in this group of natural products, as it possesses the general structural scaffold **C** that could be used as a platform for the syntheses of other natural products, such as cebulactam A2 (**3**)[4] and

(1) (a) Clardy, J.; Walsh, C. *Nature* **2004**, *432*, 829. (b) Koehn, F. E.; Carter, G. T. *Nat. Rev. Drug Discovery* **2005**, *4*, 206. (c) Paterson, I.; Anderson, E. A. *Science* **2005**, *310*, 451.

(2) (a) Floss, H. G.; Yu, T.-W. *Chem. Rev.* **2005**, *105*, 621. (b) Hara, M.; Asano, K.; Kawamoto, I.; Takiguchi, T.; Katsumata, S.; Takahashi, K.; Nakano, H. *J. Antibiot.* **1989**, *42*, 1768. (c) Deboer, C.; Meulman, P. A.; Wnuk, R. J.; Peterson, D. H. *J. Antibiot.* **1970**, *23*, 442.

(3) (a) Yazawa, H.; Imai, H.; Suzuki, K.; Kadota, S.; Saito, T. U.S. Patent 4,912,215, 1990. (b) Imai, Y.; Yazawa, S.; Saito, T. Japanese Patent JP01168671, 1989. (c) Imai, Y.; Yazawa, S.; Suzuki, K.; Yamaguchi, Y. Shibazaki, M. Saito, T. Japanese Patent JP01106884, 1989.

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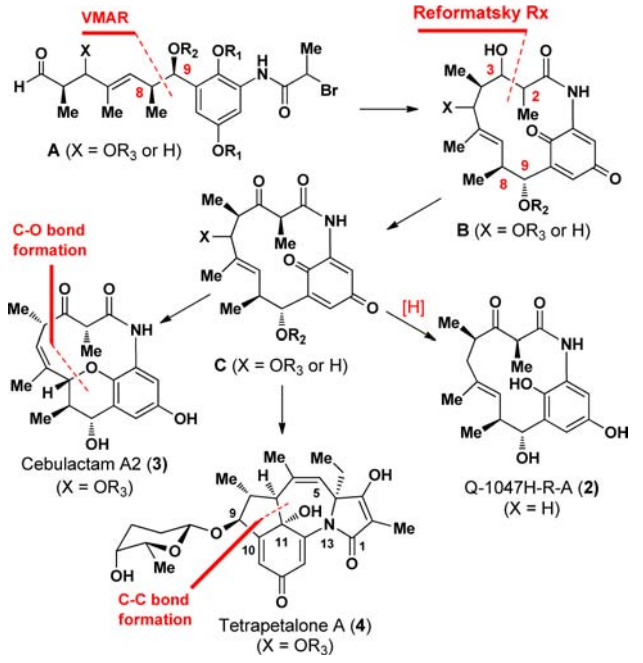
tetrapetalone A (**4**),[5] with C−O and C−C bond formations being involved as the key steps, respectively (Scheme 1). To date and to the best of our knowledge, there have been no reports describing the successful total syntheses of these natural products.[6]

Scheme 1. Synthetic Analysis



During the planning of our total synthesis of Q-1047H-A-A (**1**), we realized the challenges associated with the formation of its medium-sized macrolactam[7] because of the transoid conformation resulting from the existing amide and double bonds and the phenyl ring, which could make it difficult for the two terminal ends of the molecule to meet each other.[8] Cognizant of this challenge, our initial mission focused on identifying the efficient methods for the formation of this medium-sized macrolactam ring.

Samarium diiodide (SmI_2) is a useful reagent for promoting reductive couplings, leading to the formation of structurally diverse carbocycles.[9] In this context, the SmI_2-mediated Reformatsky reaction[10] for syntheses of macrocyclic lactams is particularly attractive since many functionalized complex molecules could be synthesized using this method as a key step[11] because they operate under extremely mild reaction conditions and are tolerant of a wide degree of different functional groups.[12]

With this in mind, the decision was taken to use a SmI_2-mediated Reformatsky reaction for the formation of the lactam ring of **1**. Herein, we report an expedient synthetic strategy for assembling the elaborate structural scaffold of **1**, which culminated in the annulation of its macrolactam ring, and thus led to the reassignment of the stereochemistry and the absolute configuration of **1**.

Central to our synthetic strategy was the decision to introduce the chiral center at the C_2-position during the later stages of the synthesis. This decision was taken because of the known tendency of the C_2-position to undergo epimerization under acidic, basic, or even neutral conditions. We envisaged that this chiral center in intermediate **C** (Scheme 1) could be generated naturally following the oxidation of the C_3 hydroxyl group in intermediate **B** to the corresponding ketone.

Our synthesis started with the synthesis of **7b** (Scheme 2). The use of the chelation-controlled vinylogous Mukaiyama aldol reaction (VMAR) process represented an attractive strategy in this particular instance since the selective synthesis of *syn*-aldol subunits is typically challenging.[13]

We recently reported a method for the stereoselective synthesis of *syn*-aldol subunits via chelation-controlled VMAR.[14] Thus, under our optimized conditions,[14a] reaction of *N*,*O*-acetal **5**[14a] with benzaldehyde **6** in the presence

(4) (a) Pimentel-Elardo, S. M.; Gulder, T. A. M.; Hentschel, U.; Bringgman, G. *Tetrahedron Lett*. **2008**, *49*, 6889. (b) Clardy, J.; Walsh, C. *Nature* **2004**, *432*, 829. (c) Koehn, F. E.; Carter, G. T. *Nat. Rev. Drug Discovery* **2005**, *4*, 206. (d) Paterson, I.; Anderson, E. A. *Science* **2005**, *310*, 451. (e) Fenical, W.; Jensen, P. R. *Nat. Chem. Biol*. **2006**, *2*, 666.

(5) (a) Komoda, T.; Sugiyama, Y.; Abe, N.; Imachi, M.; Hirota, H.; Hirota, A. *Tetrahedron Lett*. **2003**, *44*, 1659. (b) Komoda, T.; Sugiyama, Y.; Abe, N.; Imachi, M.; Hirota, H.; Koshino, H.; Hirota, A. *Tetrahedron Lett*. **2003**, *44*, 7417. (c) Komoda, T.; Yoshida, K.; Abe, N.; Sugiyama, Y.; Imachi, M.; Hirota, H.; Koshino, H.; Hirota, A. *Biosci. Biotechnol. Biochem*. **2004**, *68*, 104. (d) Komoda, T.; Kishi, M.; Abe, N.; Sugiyama, Y.; Hirota, A. *Biosci. Biotechnol. Biochem*. **2004**, *68*, 903.

(6) (a) Wang, X.; Porco, J. A., Jr. *Angew. Chem., Int. Ed*. **2005**, *44*, 3067. (b) Wang, X.; Porco, J. A., Jr. *Angew. Chem., Int. Ed*. **2006**, *45*, 6607. (c) Li, C.; Li, X.; Hong, R. *Org. Lett*. **2009**, *11*, 4036. (d) Marcus, A. P.; Sarpong, R. *Org. Lett*. **2010**, *12*, 4560.

(7) For review articles, see: (a) Nubbemeyer, U. *Top. Curr. Chem*. **2001**, *216*, 125. (b) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131. (c) Illuminati, G.; Mandolini, L. *Acc. Chem. Res*. **1981**, *14*, 9.

(8) (a) Schmidt, U.; Langner, J. *J. Pept. Res*. **1997**, *49*, 67. (b) Pastuszak, J.; Gardner, J. H.; Singh, J.; Rich, D. H. *J. Org. Chem*. **1982**, *47*, 2982. (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *J. Comput.-Aided Mol. Des*. **2002**, *16*, 415.

(9) (a) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573. (b) Kagan, H. B.; Sasaki, M.; Collin, J. *Pure Appl. Chem*. **1988**, *60*, 1725. (c) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc*. **1989**, *111*, 8236.

(10) (a) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem*. **2009**, *121*, 7276. *Angew. Chem., Int. Ed*. **2009**, *48*, 7140. (b) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev*. **2004**, *104*, 3371. (c) Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325. (d) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (e) Krief, A.; Laval, A.-M. *Chem. Rev*. **1999**, *99*, 745. (f) Molander, G. A. *Chem. Rev*. **1992**, *92*, 29. (g) Molander, G. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 1, pp 251.

(11) (a) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Haseqawa, M.; Yamada, K.; Saitoh, K. *Chem.—Eur. J*. **1999**, *5*, 121. (b) Shiina, I.; Shibata, J.; Ibuka, R.; Imai, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **2001**, *74*, 113. (c) Tatsuta, K.; Narazaki, F.; Kashiki, N.; Yamamoto, J.-I.; Nakano, S. *J. Antibiot*. **2003**, *56*, 584. (d) Sammakia, T.; Johns, D. M.; Kim, G.; Berliner, M. A. *J. Am. Chem. Soc*. **2005**, *127*, 6504. (e) Nagamitsu, T.; Takano, D.; Marumoto, K.; Fukuda, T.; Furuya, K.; Otoguro, K.; Takeda, K.; Kuwaijima, I.; Harigaya, Y.; Ohmura, S. *J. Org. Chem*. **2007**, *72*, 2744. (f) Zi, W.; Yu, S.; Ma, D. *Angew. Chem., Int. Ed*. **2010**, *49*, 5887. (g) Zi, W.; Yu, S.; Ma, D. *Chem. Asian J*. **2011**, *6*, 573.

(12) Molander, G. A.; Hahn, G. *J. Org. Chem*. **1986**, *51*, 1135.

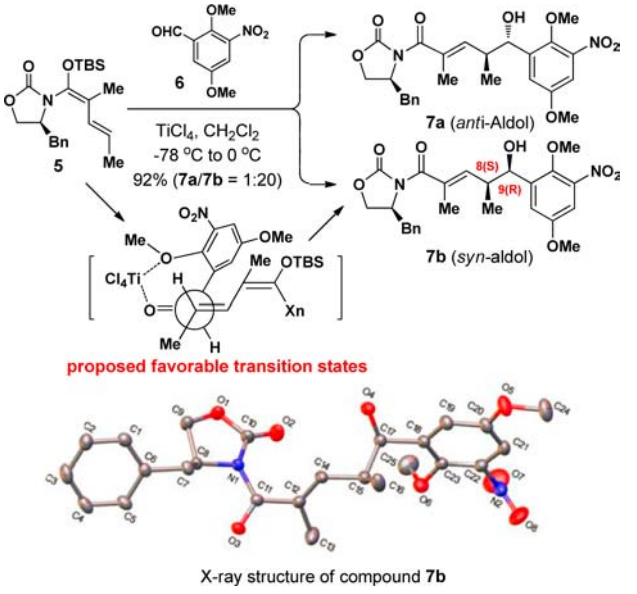
(13) Selected examples: (a) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc*. **1997**, *119*, 7883. (b) Crimmins, M. T.; Chaudhary, K. *Org. Lett*. **2000**, *2*, 775. (c) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem*. **2001**, *66*, 894. (d) Hong, Y.-S.; Lee, D.; Kim, W.; Jeong, J.-K.; Kim, C.-G.; Sohng, J. K.; Lee, J.-H.; Paik, S.-G.; Lee, J. J. *J. Am. Chem. Soc*. **2004**, *126*, 11142. (e) Aldrich, C. C.; Venkatraman, L.; Sherman, D. H.; Fecik, R. A. *J. Am. Chem. Soc*. **2005**, *127*, 8910. (f) Crimmins, M. T.; Dechert, A.-M. R. *Org. Lett*. **2009**, *11*, 1635.

(14) (a) Liang, Y.; Wang, L.; Zhu, R.; Deng, L.; Yang, Y.; Quan, J.; Chen, J.; Yang, Z. *Adv. Synth. Catal*. **2010**, *352*, 2387. (b) Wang, L.; Xi, Y.; Yang, S.; Zhu, R.; Liang, Y.; Chen, J.; Yang, Z. *Org. Lett*. **2011**, *13*, 74.

of $TiCl_4$ (1.1 equiv) in CH_2Cl_2 afforded a 92% yield of the *syn*-aldol adducts **7a** and **7b** as an inseparable mixture of diastereomers (1:20) at the C_9-position. The favored formation of **7b** can be rationalized according to the formation of the chelation complex **A** (Scheme 2), in which a six-membered chelation complex of $TiCl_4$ was favorably formed, leading to the formation of the *syn*-aldol **7b** as a major product.

The structure of **7b** was confirmed by X-ray crystallographic analysis, and its absolute stereochemistry was determined via NMR analysis of its corresponding Mosher's ester (see Supporting Information for further details).

Scheme 2. Asymmetric Synthesis of Intermediate **7b**

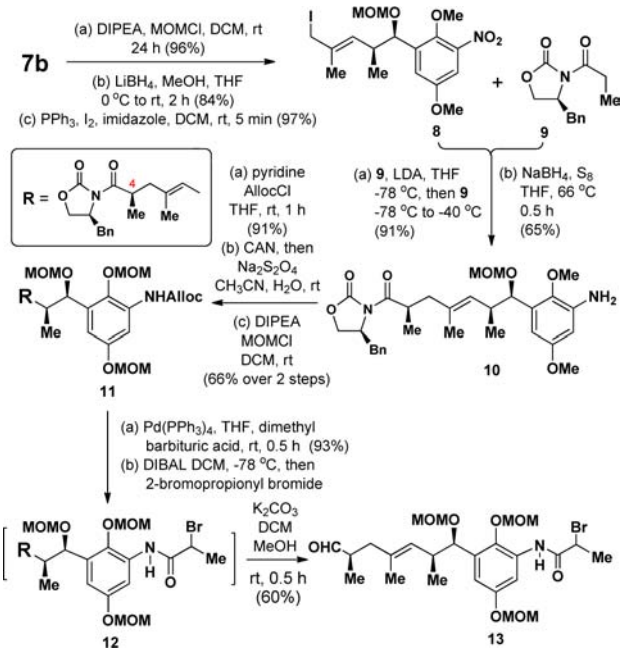


We proceeded with the straightforward elaboration of compound **7b** to produce **13** (Scheme 3). **7b** was initially protected as the corresponding MOM ether and reduced with $LiBH_4$ to afford a primary alcohol, which was converted to the corresponding iodide **8** by the treatment with a mixture of I_2, PPh_3, and imidazole.

To install the required chirality at the C_4-position, **8** was reacted with the Evans' oxazolidinone **9**[15] to afford **10** as a single diastereoisomer in 91% yield. To synthesize **11**, the nitro group in **10** was reduced to its corresponding amine, which was then protected with an allyloxycarbonyl (Alloc) group by reaction with AllocCl/pyridine. The protected amine was subjected to an oxidative demethylation/reduction/protection process to afford **11**. Deprotection of the Alloc group in **11** was achieved by the treatment with $Pd(PPh_3)_4$ in the presence of 1,3-dimethylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)trione, and the resulting amine was then subjected to DIBAl-H reduction, followed by acylation with 2-bromopropionyl bromide to afford *N*,*O*-acetal **12**, which

(15) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

Scheme 3. Asymmetric Synthesis of Intermediate **13**

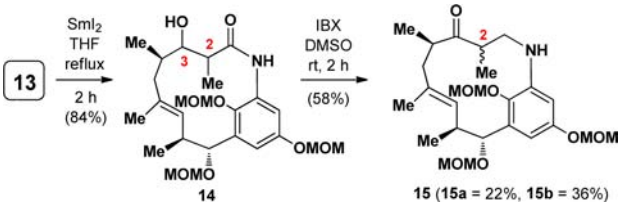


without purification was hydrolyzed to afford aldehyde **13** in 60% overall yield.

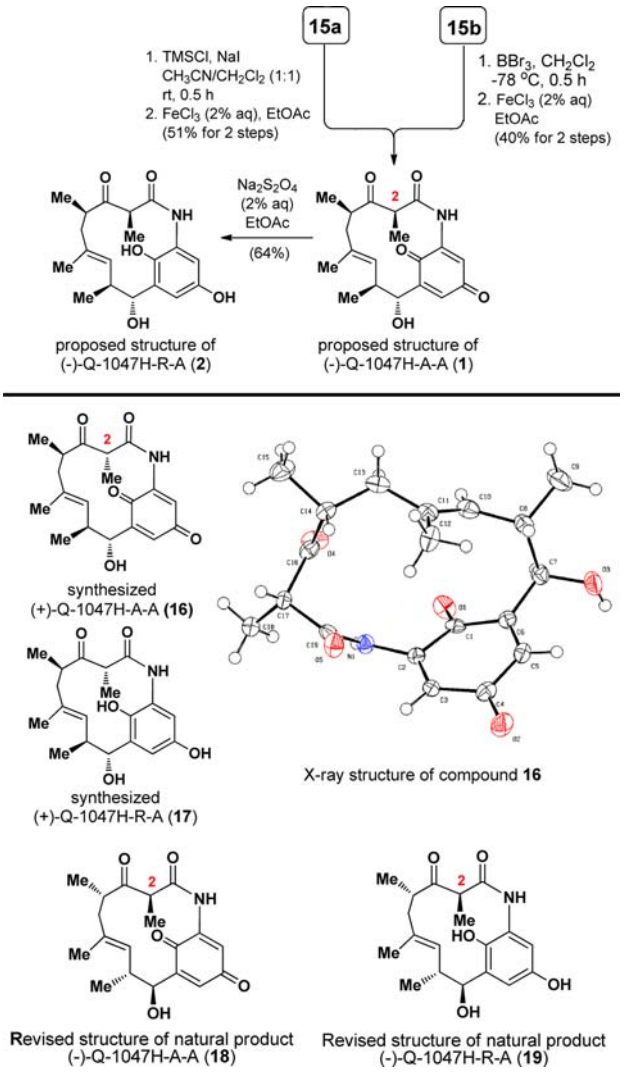
With **13** in hand, the stage was set for the crucial SmI_2 induced Reformatsky reaction (Scheme 4). Given that there is inherent competition in **13** between the simple reduction of the aldehyde or dehalogenation and the reductive cyclization process, our initial study focused on the evaluation of different solvent systems (such as SmI_2/HMPA/*t*-BuOH,[11a] SmI_2/HMPA,[11b] and SmI_2/THF) in high dilution (0.002 M) at temperatures ranging from −78 °C to room temperature. Unfortunately, however, none of the desired annulated product **14** was obtained, and in most cases, the simple reduction of the aldehyde to the alcohol and the dehalogenation of the α-bromoester were observed.

Inspired by Prof. Ma's synthesis of GB-13,[11f] a variation of the Reformatsky reaction was also attempted involving the slow addition of the precursor **13** (0.005 M in THF) to a solution of SmI_2 at reflux in THF (Scheme 4). Pleasingly, the desired annulated product **14** was isolated in 80% yield as a mixture of two pairs of diastereoisomers corresponding to the C_2 and C_3 carbon centers in a ratio of

Scheme 4. Synthesis of Intermedaite **15**



Scheme 5. Completion of the Total Synthesis



3.9:1:4.0:3.3 according to the results of HPLC analysis (see Supporting Information for further details).

Having developed a method for the cyclization of this highly strained lactam ring, we proceeded to explore the total synthesis. The annulated mixture of **14** was oxidized with IBX to afford **15** as a pair of diastereoisomers, which could be separated by flash chromatography on silica gel to give **15a** and **15b** in 22 and 36%, respectively.

To complete the total synthesis, substrate **15a** was deprotected with TMSI in CH_3CN/DCM (1:1) (Scheme 5). The resulting diol was not isolated from the reaction mixture because of the instability of the hydroquinone moiety under the reaction conditions, and the material was instead further oxidized with $FeCl_3$ (2% aq) to give Q-1047H-A-A (**1**) in 51% yield over two steps. Thus, Q-1047H-R-A (**2**) was eventually obtained in 64% yield via the reduction of Q-1047H-A-A (**1**) with $Na_2S_2O_4$.

Interestingly, our attempts to convert another diastereoisomer **15b** to Q-1047H-A-A (**1**) using an identical protocol to that used to convert **15a** to Q-1047H-A-A (**1**) failed. Other conditions were also tested but suffered the same failure. Eventually, **15b** was converted to **1** using an alternative approach involving the treatment of **15b** with BBr_3 at −78 °C to remove its methoxymethyl ether (MOM) group, followed by oxidation of the resulting hydroquinone with $FeCl_3$ (2% aq) to give product Q-1047H-A-A (**1**) in 40% yield over the two steps.

Although the ^1H and ^{13}C NMR spectral data for the synthesized Q-1047H-A-A were in good agreement with those reported for the natural material,[3] the sign of its optical rotation was the opposite of the natural material [synthetic: $[\alpha]_D^{25} = +67°$ (*c* 1 in $CHCl_3$); natural: $[\alpha]_D^{25} = -68°$ (*c* 1 in $CHCl_3$)]. Furthermore, its X-ray crystallographic analysis indicated that the original assignment of the stereochemistry at the C_2-position in the proposed structure of Q-1047H-A-A (**1**) was incorrect. Thus, the structures of natural products Q-1047H-A-A and Q-1047H-R-A have been reassigned as compounds **18** and **19** (Scheme 5), and the molecules (+)-Q-1047H-A-A (**16**) and (+)-Q-1047H-R-A (**17**) that we synthesized are actually the enantiomers of natural products.

In conclusion, (+)-Q-1047H-A-A (**16**) and (+)-Q-1047H-R-A (**17**) have been synthesized for the first time via an asymmetric chelation-controlled vinylogous Mukaiyama aldol reaction for the stereoselective synthesis of the *syn*-aldol adduct **7b** and an intramolecular SmI_2-mediated Reformatsky reaction for the formation of the macrocyclic lactam **14** as key steps. On the basis of our synthetic results, the relative stereochemistry and absolute configuration of the natural products (−)-Q-1047H-A-A and (−)-Q-1047H-R-A have been assigned as compound **18** and **19**. The developed synthetic chemistries should pave the way for the syntheses of other structurally and biologically related products, as well as analogues based on (−)-Q-1047H-A-A and, therefore, facilitate the exploration of the chemical biology of these compounds.

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Supporting Information Available. Experimental procedure and ^1H and ^{13}C NMRs spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.