OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

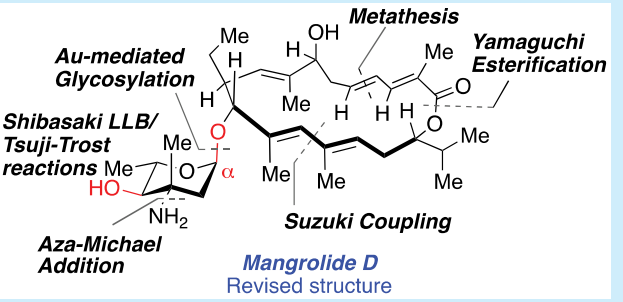
Total Synthesis and Structural Revision of Mangrolide D

Hiromu Hattori, Lukas V. Hoff, and Karl Gademann*

Department of Chemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland

Supporting Information

ABSTRACT: The unique 18-membered macrocyclic natural product mangrolide D was prepared in totally synthetic form. Key steps feature an Au-catalyzed glycosylation, aza-Michael addition, and $LaLi_3$tris(binaphthoxide) catalyzed epoxidation. Detailed analysis of the constitution and configuration of the carbohydrate segment and the total synthesis of the revised structure led to structural revision of the originally proposed structure.



The lack of effective antibiotics for the treatment of bacterial infections remains a global concern.[1] However, due to the diminished economic incentives by the pharmaceutical industry, novel classes of antibiotics approved over the last decades remain few.[2] To address the emergence of resistant microbial strains, the discovery of novel antibiotics via total chemical synthesis can provide an orthogonal solution to fermentation and isolation.[3] Intrigued by the diverse alley of their carbohydrate decoration of the 18-membered antibiotic natural products and their interesting biological activities,[4] we were attracted by a novel antibiotic candidate, mangrolide D (**1**), with an unprecedented vancosamine moiety attached to the 18-membered macrocycle (Figure 1).

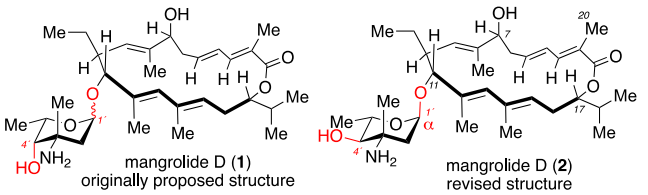


Figure 1. Structure of mangrolide D.

Mangrolide D (**1**) is a bacterial secondary metabolite found in a modified strain of *Actinoalloteichus* sp. (SNA18-M5), of which the wild type was isolated from mangrove sediment samples collected in the Bahamas.[5] The structure of mangrolide D (**1**) was originally deduced by spectroscopic means[5] (mainly NMR spectroscopy) and is characterized by a high degree of unsaturation of the 18-membered macrocyclic scaffold and, particularly, vancosamine as a carbohydrate segment attached at the C11 position of the macrocycle. Impressively, mangrolide D (**1**) is the first example among macrocyclic lactone natural products bearing vancosamine, while few other classes of natural products with similar sugars are well-known (such as vancomycin, nocardicyclin, etc.).

Together with the strong activity of vancomycin, vancosamine and its unique structure have attracted the attention of many synthetic chemists.[6] However, many existing synthetic strategies are either unselective or require lengthy routes, and most importantly, there are only a few such examples applicable to total synthesis of the glycosylated natural product target.[7] The main challenge in the mangrolide D synthesis is associated with the lack of a directing group at the C2′ position, which impedes efficient glycosylation.[8] In addition, the exact configuration of **1** at the anomeric position remained elusive at the start of our work due to minute quantities of material and the impurities stemming from contamination during the isolation work.[5] While this manuscript was finished, a report by De Brabander and coworkers appeared, reporting on the isolation and synthesis of mangrolide D.[9] In this study, we report (1) the selective synthesis of the putative vancosamine segment, (2) comparison of spectral data and subsequent structural revision of the proposed structure **1**, and (3) the total synthesis of the revised structure **2** of mangrolide D.

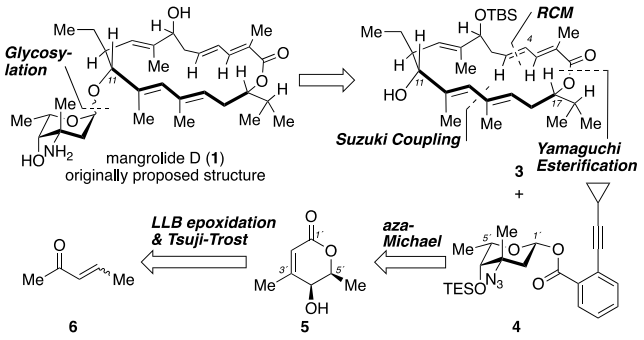
To approach the synthesis, we assumed the absolute configuration for the vancosamine segment to be L based on the biosynthetic proposal of 4′-*epi*-vancosamine.[10] Considering the antibiotic structure−activity relationship (SAR) studies of the compounds potentially produced through the collective synthesis and the unambiguous structure elucidation of mangrolide D, we envisaged the retrosynthetic analysis as described below (Scheme 1).

Retrosynthetically, we envisioned to employ a modular approach to perform a late-stage glycosylation of the macrocycle **3** and the glycosyl donor **4** using Au catalysis.[11] The introduction of the key C3′ stereogenic center could be constructed by an aza-Michael addition reaction from alcohol **5**. The enantiopure alcohol **5** was thought to be accessible

Received: April 10, 2019

DOI: 10.1021/acs.orglett.9b01256
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Retrosynthetic Analysis of Mangrolide D (1)[a]

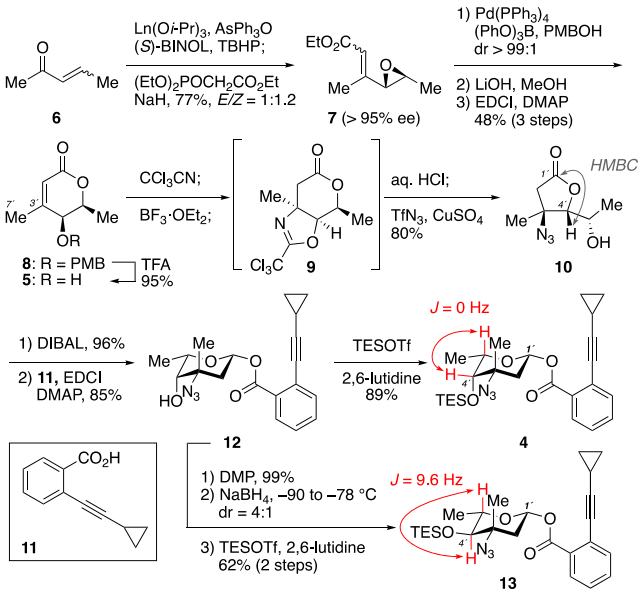


[a]TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, RCM = ring-closing metathesis, LLB = $LaLi_3$tris(binaphthoxide).

through Shibasaki's $LaLi_3$tris(binaphthoxide) (LLB) catalysis[12] and lactonization.

The synthesis of vancosamine segment **4** commenced with the enantioselective epoxidation of commercially available enone **6** employing LLB catalysis developed by Shibasaki (Scheme 2).[12] The obtained epoxyketone intermediate was

Scheme 2. Synthesis of Vancosamine Donor 4 and 4′-*epi*-Vancosamine Donor 13[a]



[a]TBHP = *tert*-butyl hydroperoxide, PMB = *para*-methoxybenzyl, EDCI = 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride, DMAP = 4-dimethylaminopyridine, DIBAL = diisobutylaluminum hydride, OTf = trifluoromethanesulfonate, DMP = Dess–Martin periodinane.

directly homologated with the phosphonate to provide conjugated ester **7** in 77% yield (*E*/*Z* = 1:1.2, >95% ee). The subsequent Pd-catalyzed Tsuji–Trost substitution reaction[13] proceeded smoothly to deliver the *syn*-alcohol with perfect selectivity. Hydrolysis of the ethylester followed by lactonization under Steglich conditions[14] furnished the *δ*-lactone **8** in 48% yield over three steps. Cleavage of the PMB group of **8** was carried out under acidic conditions, and the following addition of trichloroacetonitrile provided the desired trichloroacetimidate intermediate. The direct *in situ* conversion of this intermediate to the oxazoline **9** was attempted using strong bases with heating (excess DBU, reflux).[15] However, all the attempts using basic conditions turned out to be unsuccessful, probably due to the electron-rich nature of the lactone and the larger steric requirements of the C7′ methyl group as compared to literature known examples. Surprisingly, to our delight, we found out that the intended aza-Michael cyclization could be promoted by the addition of stoichiometric amount of Lewis acids to give **9** with perfect diastereoselectivity. It is worth noting that neither epimerization at C4′ nor Overman rearrangement[16] were observed. After the stereoselective introduction of the nitrogen atom at the C3′ position, we next hydrolyzed the oxazoline, and the formed primary amine was transformed to the azide via treatment with TfN_3.[17] Interestingly, we observed a rearrangement from *δ*-lactone to *γ*-lactone **10** during the hydrolysis,[18] which was confirmed by HMBC correlations between C1′and H4′. Selective reduction of **10** using DIBAL provided the desired lactol in an excellent yield (96%), which was selectively acylated at the C1′ position using a known carboxylic acid **11**.[19] The obtained ester **12** was next subjected to TES protection to give **4** in 89% yield.

At this point, we noticed that the coupling constant between H4′ and H5′ of **4** (J = 0 Hz) is completely different from the one reported originally for the natural product (J = 9.5 Hz).[5,20] As the large coupling constant reported for natural product suggested an axial–axial coupling between these two protons, the configuration required for the matching glycosyl donor was proposed to be the 4′-epimer **13** for the total synthesis. The transformation from alcohol **12** to **13** was achieved by the Dess–Martin oxidation, followed by selective reduction as well as TES protection. Corroborating our earlier configurational hypothesis, ^{1}H NMR analysis of **13** revealed the coupling constant between H4′ and H5′ to be J = 9.6 Hz, suggesting that the carbohydrate segment of mangrolide D is not vancosamine but 4′-*epi*-vancosamine instead.[21]

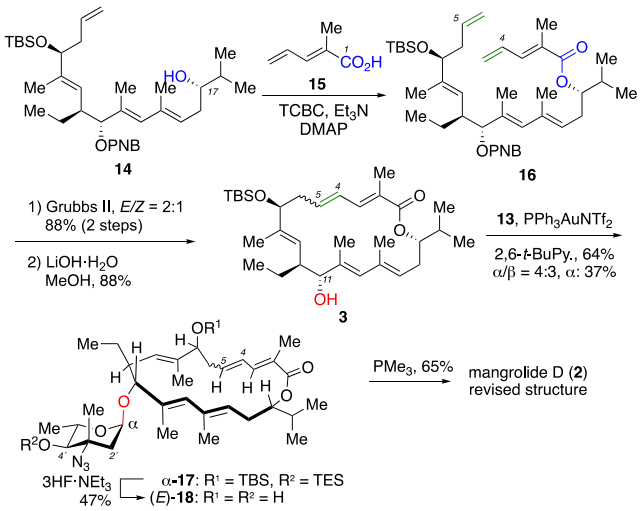
To further elucidate the anomeric configuration of the vancosamine moiety and to gain further evidence for the revised C4′ stereogenic center, we derivatized two donors, **4** and **13**, into all four possible model vancosamine derivatives. The collective synthesis and detailed ^{1}H NMR analysis provided evidence that the carbohydrate segment present on mangrolide D refers to the configuration of *α*-4′-*epi*-vancosamine (see Supporting Information for details).

The synthesis of macrocycle **3** started out with Yamaguchi esterification of the previously synthesized alcohol **14**[4a] and the known carboxylic acid **15**[4c] (Scheme 3). Subsequent ring-closing metathesis using second-generation Grubbs catalyst furnished the macrocycle in an excellent yield (88%). Hydrolysis of the nitrobenzoyl group in the presence of the lactone moiety was selectively achieved in good yield (88%) to give alcohol **3** ready for glycosylation.

With the key macrocycle **3** and glycosyl donor **13** in hand, we set forward to attempt the late-stage glycosylation. The initial attempt using literature known Au catalysis (PPh_3AuOTf) turned out to be unproductive due to the decomposition of macrocycle **3**. Therefore, we screened various activation conditions and finally found that the addition of 2,6-di-*tert*-butylpyridine was essential for the reaction to proceed smoothly and provide the desired *α*-**17** in 37% together with the epimeric *β*-**17** in 27%. At this point, we did not try to increase the selectivity to maximize the scope of successive derivatives available for antibiotic testing. Having

DOI: 10.1021/acs.orglett.9b01256
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 3. Total Synthesis of the Revised Structure of Mangrolide D (2)[a]



[a]TCBC = 2,4,6-trichlorobenzoyl chloride, 2,6-*t*-BuPy = 2,6-di-*tert*-butylpyridine.

obtained the α-isomer α-**17**, we attempted the final transformations to the revised structure **2** of mangrolide D . Deprotections of the silyl protecting groups were achieved using $3HF{\cdot}NEt_3$ to give diol **18**. At this point, we were surprised to find that the (*E*)-**18** could be separated from the undesired (*Z*)-isomer.[22] The pure azide (*E*)-**18** was finally reduced under Staudinger conditions, and the subsequent purification by reversed-phase HPLC furnished the targeted product **2**. Analysis of ^1H and ^{13}C NMR spectra revealed that the chemical shift and coupling constants of the revised compound **2** completely match those reported for natural sample as well as the recently reported data for revised mangrolide D.[9] Other spectroscopic data, including 2D NMR results, also supported the identity between the synthetic **2** and the natural **2**.[5]

In conclusion, the total synthesis of the revised structure **2** of mangrolide D is presented. The synthesis of the carbohydrate segment is enabled by an enantioselective LLB catalyzed epoxidation, Lewis acid promoted intramolecular aza-Michael addition, and careful selection of leaving groups and the respective activation conditions for the key glycosylation. The differences in ^1H NMR spectra of the key sugar segment **4** led us to revise the structure to its epimer **13** as an intermediate. Finally, the successful glycosylation with the sterically demanding macrocyclic alcohol provided the revised structure **2** after a series of deprotections.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01256.

Experimental procedures, characterization data, and copies of ^1H, ^{13}C, and 2D NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: karl.gademann@uzh.ch.

ORCID

Karl Gademann: 0000-0003-3053-0689

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is dedicated to the memory of Prof. Dr. Kenji Mori. We gratefully acknowledge financial support from the Swiss National Science Foundation (182043) and thank Simon Jurt (University of Zurich) for assistance with NMR spectroscopy.

■ REFERENCES

(1) Luepke, K. H.; Suda, K. J.; Boucher, H.; Russo, R. L.; Bonney, M. W.; Hunt, T. D.; Mohr, J. F. *Pharmacotherapy* **2017**, *37*, 71.

(2) (a) Simpkin, V. L.; Renwick, M. J.; Kelly, R.; Mossialos, E. *J. Antibiot.* **2017**, *70*, 1087. (b) Fischbach, M. A.; Walsh, C. T. *Science* **2009**, *325*, 1089. (c) Cooper, M. A.; Shlaes, D. *Nature* **2011**, *472*, 32.

(3) Liu, F.; Myers, A. G. *Curr. Opin. Chem. Biol.* **2016**, *32*, 48.

(4) Totally synthetic mangrolide A: (a) Hattori, H.; Roesslein, J.; Caspers, P.; Zerbe, K.; Miyatake-Ondozabal, H.; Ritz, D.; Rueedi, G.; Gademann, K. *Angew. Chem., Int. Ed.* **2018**, *130*, 11020. Totally synthetic fidaxomicin: (b) Kaufmann, E.; Hattori, H.; Miyatake-Ondozabal, H.; Gademann, K. *Org. Lett.* **2015**, *17*, 3514. (c) Hattori, H.; Kaufmann, E.; Miyatake-Ondozabal, H.; Berg, R.; Gademann, K. *J. Org. Chem.* **2018**, *83*, 7180. Syntheses of the fidaxomicin aglycon : (d) Jeanne-Julien, L.; Masson, G.; Astier, E.; Genta-Jouve, G.; Servajean, V.; Beau, J. M.; Norsikian, S.; Roulland, E. *Org. Lett.* **2017**, *19*, 4006. (e) Glaus, F.; Altmann, K. H. *Angew. Chem., Int. Ed.* **2015**, *54*, 1937. (f) Erb, W.; Grassot, J. M.; Linder, D.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 1929. (g) Miyatake-Ondozabal, H.; Kaufmann, E.; Gademann, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 1933–1936.

(5) Jamison, M. T. Mangrolide A, A Novel Marine Derived Polyketide with Selective Antibiotic Activity. Ph.D. thesis, The University of Texas Southwestern Medical Center (US), May 2013. http://hdl.handle.net/2152.5/1576.

(6) (a) Bylsma, M.; Bennett, C. S. *Org. Lett.* **2018**, *20*, 4695. (b) Parker, K. A.; Chang, W. *Org. Lett.* **2003**, *5*, 3891 and references therein .

(7) For the few successful applications, see: (a) Nicolaou, K. C.; Mitchell, H. J.; Jain, N. F.; Bando, T.; Hughes, R.; Winssinger, N.; Natarajan, S.; Koumbis, A. E. *Chem. - Eur. J.* **1999**, *5*, 2648. (b) Kitamura, K.; Maezawa, Y.; Ando, Y.; Kusumi, T.; Matsumoto, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 1262.

(8) Review for glycosylation of 2-deoxy sugars: Bennett, C. S.; Galan, M. C. *Chem. Rev.* **2018**, *118*, 7931.

(9) Gong, J.; Li, W.; Fu, P.; MacMillan, J.; De Brabander, J. K. *Org. Lett.* **2019**, *21*, 2957.

(10) Chen, H.; Thomas, M. G.; Hubbard, B. K.; Losey, H. C.; Walsh, C. T.; Burkart, M. D. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 11942.

(11) (a) Yu, B. *Acc. Chem. Res.* **2018**, *51*, 507. (b) Li, W.; Yu, B. *Chem. Soc. Rev.* **2018**, *47*, 7954.

(12) Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2725.

(13) (a) Yu, X.-Q.; Yoshimura, F.; Ito, F.; Sasaki, M.; Hirai, A.; Tanino, K.; Miyashita, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 750. (b) Yu, X. Q.; Yoshimura, F.; Tanino, K.; Miyashita, M. *Tetrahedron Lett.* **2008**, *49*, 7442.

(14) A mixture of (*E*)- and (*Z*)-isomers was used for the lactonization. We found that separation of the isomers was unnecessary as both could be converted to the desired lactone **8** under the given conditions. We assume the reduction in yield is

DOI: 10.1021/acs.orglett.9b01256
Org. Lett. XXXX, XXX, XXX−XXX

attributed to the partial deprotection of the PMB group during acidic work-up of the carboxylic acid intermediate. Ono, M.; Zhao, X. Y.; Shida, Y.; Akita, H. *Tetrahedron* **2007**, *63*, 10140.
(15) (a) Matsushima, Y.; Kino, J. *Tetrahedron* **2008**, *64*, 3943. (b) Matsushima, Y.; Kino, J. *Eur. J. Org. Chem.* **2010**, *2010*, 2206.
(16) Tsuzaki, S.; Usui, S.; Oishi, H.; Yasushima, D.; Fukuyasu, T.; Oishi, T.; Sato, T.; Chida, N. *Org. Lett.* **2015**, *17*, 1704.
(17) Use of PhMe as a solvent: Conrow, R. E.; Dean, W. D. *Org. Process Res. Dev.* **2008**, *12*, 1285.
(18) Fortunately, no epimerization at C4′ nor C5′ was observed.
(19) Hashmi, A. S. K.; Lothschütz, C.; Döpp, R.; Ackermann, M.; De Buck Becker, J.; Rudolph, M.; Scholz, C.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 133.
(20) Indeed, the vancosamine segment of vancomycin displays a coupling constant value of J = 3.2 (*s*, DMSO-d_6) between H4′ and H5′. Pearce, C. M.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 2* **1995**, *2*, 153.
(21) (a) Chhetri, B. K.; Lavoie, S.; Sweeney-Jones, A. M.; Kubanek, J. *Nat. Prod. Rep.* **2018**, *35*, 514. (b) Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012. (c) Scherer, M.; Gademann, K. *Org. Lett.* **2017**, *19*, 3915.
(22) Usually, the separation of the (*E*)- and (*Z*)-isomers at $\Delta^{4,5}$ of 18-membered macrocyclic natural product lactones is very difficult. See reference 4 for details.

DOI: 10.1021/acs.orglett.9b01256
Org. Lett. XXXX, XXX, XXX−XXX