Organic LETTERS

Letter

pubs.acs.org/OrgLett

Total Synthesis of the Marine Natural Product Solomonamide B Necessitates Stereochemical Revision

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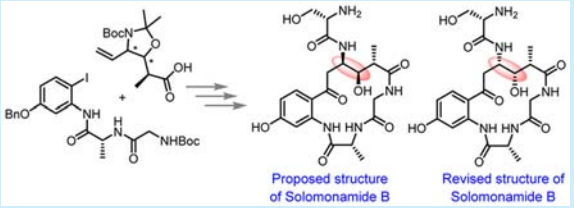
Supporting Information

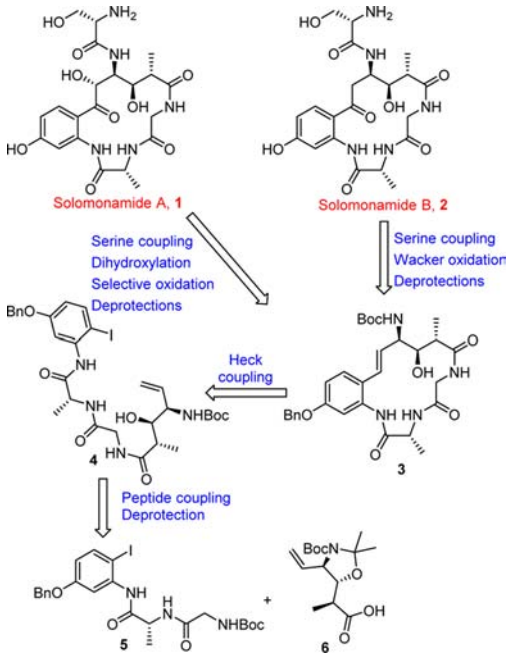
ABSTRACT: The first total synthesis of the proposed structure of solomonamide B has been achieved. However, the ^{1}H and ^{13}C NMR spectral data of the synthesized compound was not exactly matching with that of the natural solomonamide B. This prompted us to revise the originally proposed structure, in particular, the stereochemistry of the nonpeptide part, which was confirmed by its total synthesis. During the course of the synthesis, we have developed an interesting hydroxy group directed Wacker oxidation of internal olefins in a macrocyclic setting.



The two cyclic peptides called solomonamide A and solomonamide B were isolated from marine sponge by Zampella's group.[1] The most challenging task of stereochemical assignment of the nonpeptide unit of solomonamide A was carried out by QM *J* based analysis and DFT $J/^{13}C$ calculations by her group.[1] Consequently, the same was derived for solomonamide B on biogenetical consideration. Solomonamide A (**1**) was reported to have shown very potent anti-inflammatory activity (~60% paw edema reduction) in mouse model at as low as 100 μg/kg dose. However, the closely related solomonamide B (**2**) could not be tested due to the scarcity of the material.[1] Because of the tremendous potential of solomonamides in treating inflammatory diseases, their synthesis as well as biological evaluation is one of the ongoing major research projects in our group for the past few years.[2] Other research groups led by Chandrasekhar and Butler are also independently working toward the synthesis of these target molecules.[3] After crossing several hurdles in our program,[2] we have finally achieved the total synthesis of the proposed structure of solomonamide B. However, the NMR spectroscopic data of the synthesized compound was found to be different from that of the natural product. Hence, the veracity of the original structural assignment had to be questioned, and we decided to change the stereochemistry at two centers of the nonamino acid portion of the proposed structure. Total synthesis of a new structure having 2*S*, 3*S*, 4*S* configuration on nonamino acid portion had matching NMR to the reported data and therefore resulted in the structural revision of solomonamide B.

As outlined retrosynthetically in Scheme 1, both the natural products solomonamide A (**1**) and solomonamide B (**2**) can be accessed from a common intermediate macrolide **3** via installation of serine moiety in **3** with an appropriate protecting group, Wacker-type oxidation of the double bond in the macrolide ring and the removal of all the protecting groups to access solomonamide B (**2**). For the total synthesis of solomonamide A (**1**) we planned a stereoselective dihydroxylation of the double bond in **3** by taking advantage of the adjacent chiral center followed by a chemoselective oxidation of the benzylic alcohol.

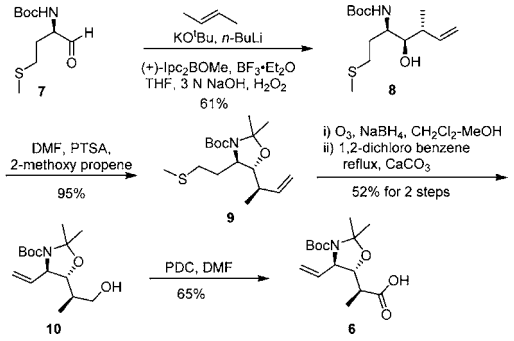
Scheme 1. Retrosynthetic Analysis of Solomonamides



Received: May 12, 2016
Published: June 22, 2016

DOI: 10.1021/acs.orglett.6b01395
Org. Lett. 2016, 18, 3178–3181

Scheme 2. Synthesis of the Key Component 6

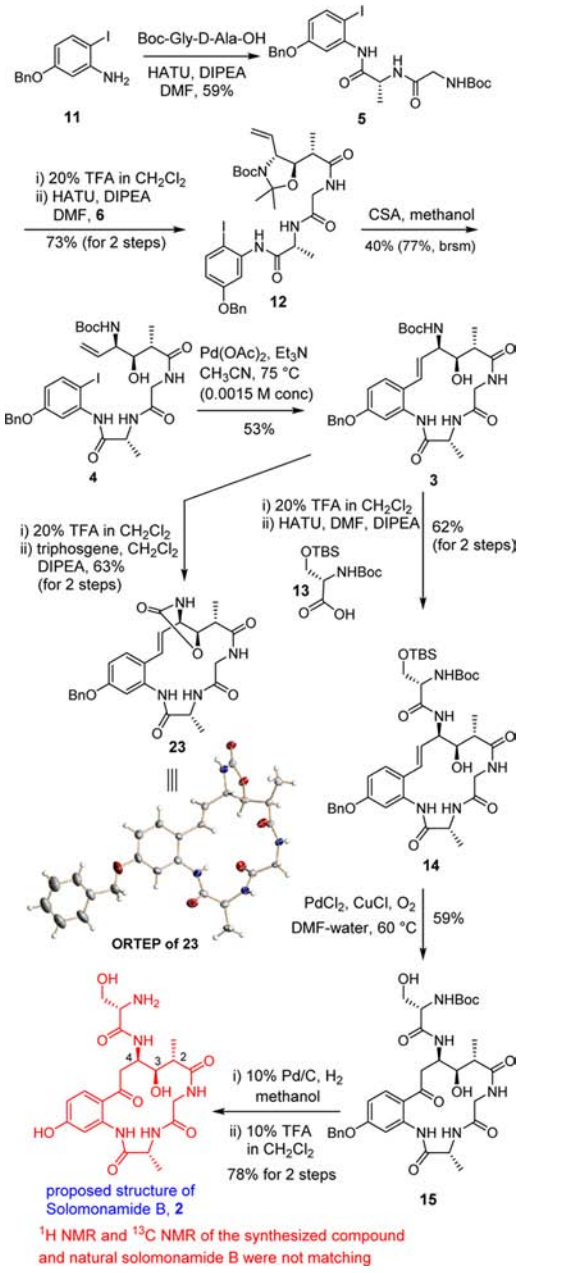


Macrolide **3** can be obtained from an intramolecular Heck reaction (key step) on **4**, which can be obtained from coupling of the free amine of the dipeptide fragment **5** and the unnatural amino acid component **6**.

The synthesis commenced with Brown crotylation reaction on the known D-methionine aldehyde **7**[4] using (+)-(*E*)-B-crotyldiisopinocamphenylborane[5] to afford compound **8** with desired stereochemistry in 61% yield. The amino alcohol in compound **8** was protected as an acetonide to give compound **9** in very good yield. The compound **9** on reductive ozonolysis (O_3/$NaBH_4$)[6] followed by refluxing in 1,2-dichloro benzene[7] with $CaCO_3$ afforded alkenol **10** in 52% yield for 2 steps. The alcohol **10** was converted to the desired key unnatural amino acid component **6** under Corey−Schmidt condition (PDC/DMF).[8] Earlier, the similar intermediate was prepared in our previous approach[2a,d] using 8 steps from a known intermediate, which suffered from poor yields and stereoselectivity (Scheme 2). Therefore, the present route to access the nonpeptide fragment is significantly improved.

For the synthesis of the second fragment **5**, the known aniline derivative **11**[9] was coupled with the dipeptide, Boc-Gly-D-Ala-OH,[10] to obtain compound **5** in 59% yield. The unnatural amino acid component **6** was coupled with the free amine prepared from **5** (HATU-DIPEA conditions) to yield compound **12** in 73% yield for 2 steps. Acetonide deprotection in compound **12** afforded the macrocyclic precursor **4** in moderate yields. Having **4** in hand, it was subjected to ligand free intramolecular Heck reaction,[2d] using $Pd(OAc)_2$, Et_3N under dilute conditions to furnish the macrocycle **3** in moderate yields (Scheme 3). Compound **3** represents the complete macrocyclic core of the proposed structure of solomonamides with appropriate functionalities and stereochemistry pattern. Initially, we had targeted solomonamide B (**2**) owing to the fact that it was never tested before for biological activity due to scarcity of the material. As per the plan, removal of the Boc protecting group in macrocycle **3** followed by coupling to the serine derivative **13**[11] gave the desired compound **14** in 62% yield. The next task was to selectively introduce the oxygen functionality at the benzylic carbon in **14**. After a few trials, the double bond present in compound **14** was subjected to Wacker-type oxidation[12] to furnish the macrocyclic ketone **15** in which an exclusive regioselectivity was observed.[13] It is worth mentioning that an oxidation of the double bond in a macrolide ring, to the best of our knowledge, is the first of this kind. As this transformation and the associated regioselectivity is interesting and can find profound application in macrolide chemistry, we wanted to explore the scope of the reaction. Accordingly, we attempted the reaction under the same conditions on six different macrocycles (Scheme 4). Macrocyclic compounds **16**[2d] and **18** that had homoallylic alcohol group like in **14** underwent a smooth

Scheme 3. Synthesis of the Proposed Structure of 2

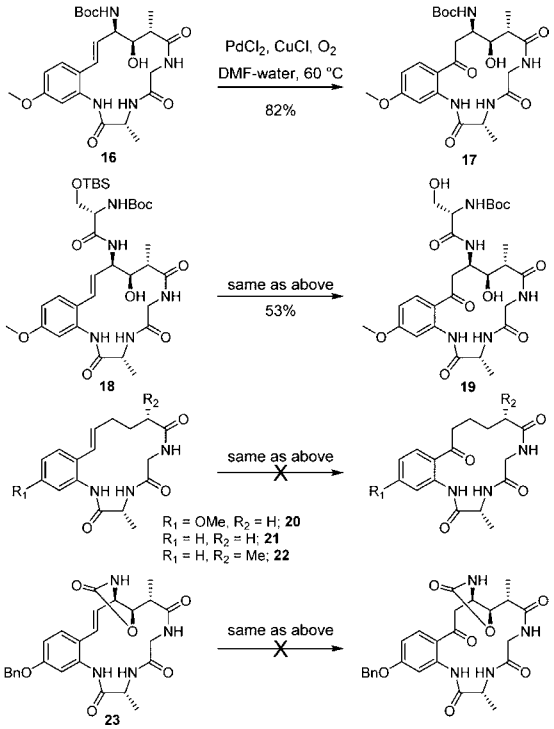


Wacker oxidation with complete regioselectivity and afforded the keto compounds **17** and **19**, respectively, whereas, macrocyclic compounds **20**, **21**, **22**,[2b] and **23**, which lack the homoallylic alcohol group, did not undergo the reaction. These experimental results indicate that the presence of the homoallylic alcohol is essential for the desired transformation. Probably, the success of the reaction on selected macrocycles can be explained by a coordination of the palladium species with the homoallylic OH group and the double bond.[14] Deprotection of the benzyl group in **15** furnished the phenolic compound, which was then treated with 10% TFA in CH_2Cl_2 to remove the Boc protecting group and afford the target compound, **2**. HRMS of the final compound **2** has shown the desired mass as $[M + H]^+$ and the NMR (^{1}H and ^{13}C) data indicated the gross structure as drawn (Scheme 3). NMR spectroscopic data for **2** was obtained in DMSO-d_6 at 300 K on a 500 MHz spectrometer. The complete ^{1}H and ^{13}C chemical shift assignment was achieved by 1D and 2D (DQF-COSY,

DOI: 10.1021/acs.orglett.6b01395
Org. Lett. 2016, 18, 3178−3181

TOCSY, ROESY, HSQC, and HMBC)[15] homo- and heteronuclear experiments. The measured optical rotation for the compound **2** is $[\alpha]_D^{25}$ − 10.89 (*c* 0.34, CH_3OH). The complete details are available in the Supporting Information. However, the chemical shifts data for the synthesized solomonamide B did not match with the reported values.[1] Before going for further interpretation and concluding anything on the original structural assignment of **2**, we wanted to reassure the stereochemistry of the synthesized compound **2** by carrying out further structural characterization studies.

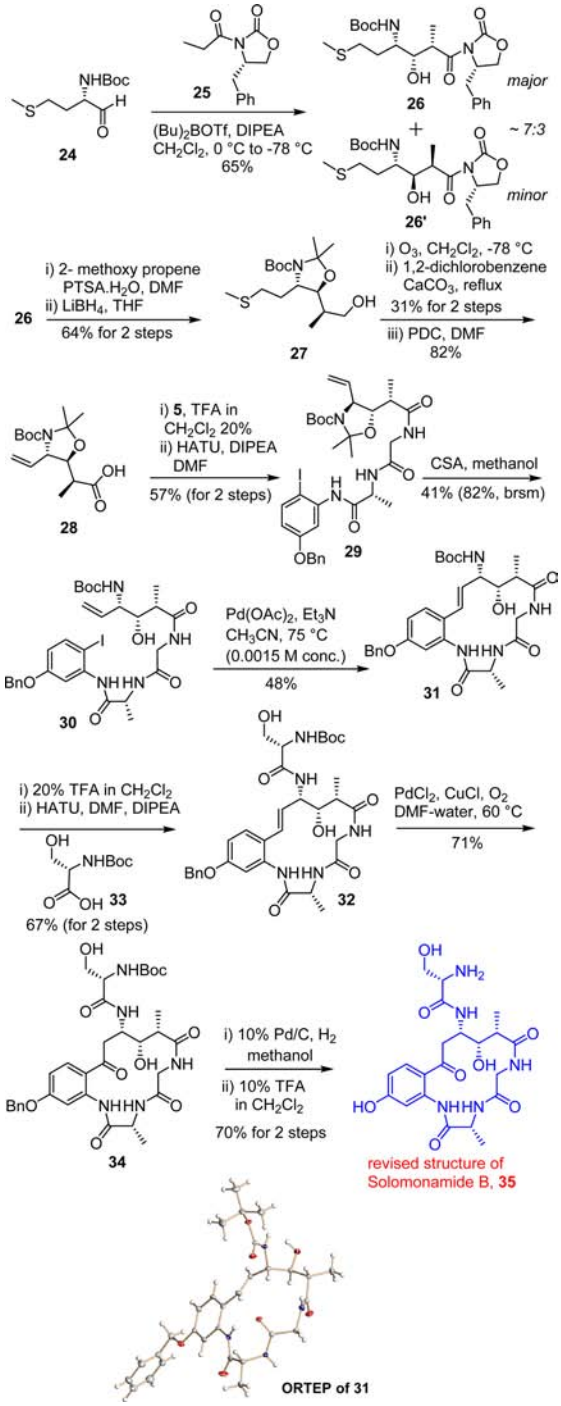
Scheme 4. Scope of Wacker Oxidation on Macrolides



Despite that the relative stereochemistry at two, three, and four carbons of **2** were concretely established from the stereoselective synthetic Schemes 2 and 3, to ensure the same in final stages, we have carried out supporting NMR studies on a derivative of **3**. For this purpose, a five-membered cyclic carbamate derivative **23** has been synthesized from **3** by Boc deprotection followed by treating with triphosgene. This derivatization was necessary so as to induce some conformational rigidity into the macrolide ring of **3**, which otherwise might be flexible. All the NMR data analysis supports the assigned structure, and complete details are available in the Supporting Information. Along with the NMR studies, crystallization on various macrocyclic compounds was also tried simultaneously. Although our attempts to obtain suitable crystals of the macrocyclic intermediates were not successful, fortunately compound **23** had crystallized in the NMR tube upon long-standing and the corresponding crystal structure (Scheme 3) unambiguously confirmed the presence of the required stereochemistry in **23**. Thus, any unlikely and unpredictable modifications during the late stages of the chemical synthesis were ruled out.

Hence, we concluded that the mismatched NMR of **2** with the reported values is more likely due to the mis-assignment of the stereochemistry in the isolated natural product by Zampella's group.[1] It is very unlikely that assignment of serine and alanine

Scheme 5. Synthesis of the Revised Structure of Solomonamide B



was wrong as the reported R_f values[1] in Marfey's method were very clear and distinguishable. This leaves three stereocenters present on the nonpeptide portion, for which the absolute and relative configuration was assigned (from the possible eight stereoisomers) by computational methods.[1] In our endeavor to synthesize the remaining seven possible stereoisomers (a mega task that involves remodelling of the synthetic pathways), we have prioritized beginning with the isomer having 2*S*, 3*S*, 4*S* configuration, based on the analysis of Zampella's group publication[1] and Festa's doctoral thesis.[16]

DOI: 10.1021/acs.orglett.6b01395
Org. Lett. 2016, 18, 3178−3181

The synthesis of the planned isomer began with a diastereoselective *syn*-aldol addition of the boron (*Z*)-enolate derived from (*S*)-4-benzyloxazolidin-2-one **25** with L-methionine aldehyde **24** to afford compounds **26** and **26′** with 7:3 diastereomeric ratio. The stereochemistry of compounds **26** and **26′** was assigned on the basis of the literature precedence.[17] The required diastereomer **26** on acetonide protection followed by treatment with $LiBH_4$ furnished the alcohol **27** in 64% yield over 2 steps. Compound **27** on ozonolysis followed by refluxing in 1,2-dichloro benzene[7] with $CaCO_3$ afforded alkenol in 31% yield for 2 steps, which was converted to the desired key unnatural amino acid **28** using Corey−Schmidt conditions. After having the required nonpeptide fragment **28** in hand, the next task was to complete the total synthesis. For this purpose, it was converted into macrocycle **31** through the intermediacy of **29** and **30** by following the similar reaction sequence used for the synthesis of the proposed structure of solomonamide B (**2**). After a few attempts, the macrocycle was crystallized using ethyl acetate−hexane mixture resulting in suitable crystals for the diffraction. The single crystal X-ray structure analysis of **31** confirmed the assigned stereochemistry without any ambiguity. Removal of the Boc protection in **31** followed by coupling of BocNH-L-Ser-OH (**33**) afforded compound **32** in 67% yield for two steps. In the end game, compound **32** subjected to a Wacker oxidation under the optimized conditions resulted in compound **34** with an excellent regioselectivity and good yield. Removal of both protecting groups (Bn and Boc) similar to the synthetic protocols of **2**, afforded the target compound **35** with 2*S*, 3*S*, 4*S* stereochemistry (Scheme 5). To our delight the ^1H and ^{13}C NMR spectral data of the compound **35** was matching with the natural product. The proton and carbon NMR of both the compounds are compared in a table supplied in the Supporting Information. The measured optical rotation $[\alpha]_D^{26}$ + 9.99 (*c* 0.23, CH_3OH) of the synthetic solomonamide is higher than that of the natural solomonamide ($[\alpha]_D^{25}$ + 4.8 (c 0.28, CH_3OH)) but with the same sign.[1]

In conclusion, we have accomplished the total synthesis of the proposed structure of solomonamide B for the first time. Comparison of the ^1H and ^{13}C NMR spectral data of the synthesized compound and natural solomonamide B suggests discrepancy with the original structure assignment, in particular in the stereochemistry of the nonpeptide portion. Accordingly, the structure was revised, and it was confirmed by total synthesis. As the structure of solomonamide B was derived from solomonamide A, it is likely that the structure of solomonamide A also needs revision. Furthermore, during the journey toward the total synthesis, we have developed and tested the scope of the hydroxyl group directed regioselective Wacker oxidation in different macrocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01395.

Characterization data, NMR spectra, 2D-NMR analysis, and detailed experimental procedures (PDF)

X-ray crystal structure of **23** (CIF)

X-ray crystal structure of **31** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The following are acknowledged for supporting this work: DST, New Delhi (SR/S1/OC-17/2011) for financial support; CSIR, New Delhi for the research fellowship to K.K. and G.R.J.; Mr. Shridhar Thorat and Samir Shaik of Center for Materials Characterization, CSIR-NCL, Pune for X-ray analysis; Professor Angela Zampella of Universitá di Napoli, Italy for providing NMR spectral details.

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DOI: 10.1021/acs.orglett.6b01395
Org. Lett. 2016, 18, 3178−3181