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Total Synthesis of Deoxy-solomonamide B by Mimicking Biogenesis

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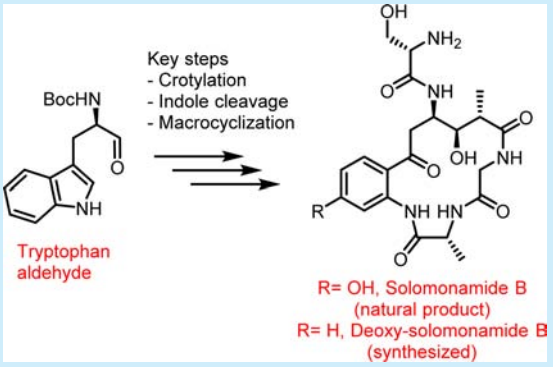
Supporting Information

ABSTRACT: A total synthesis of Deoxy-solomonamide B was accomplished starting from tryptophan in an efficient manner by mimicking the proposed biogenetic route. The present synthesis utilizes a crotylation, oxidative cleavage of the indole moiety, and macrolactamization as key steps. The use of the indole nucleus as a masked anthranilic acid unit paves the way for the easy synthesis of related macrocycles and natural products where the *ortho*-acyl aniline moiety is embedded into them, which otherwise is difficult to synthesize.



Macrocycles are becoming more interesting as scaffolds in medicinal chemistry, as they offer a suitable balance between rigidity due to preorganization and sufficient flexibility that could facilitate interactions with dynamic/flexible protein targets. As a consequence, interest in this field keeps growing.[1] Along these lines, in the year 2011, Zampella's group[2a] isolated two cyclic peptides called Solomonamide A (**1**) and Solomonamide B (**2**) with an unprecedented structure from the marine sponge *Theonella swinhoei*, which is considered an abundant source for highly bioactive natural products (Figure 1).[2b] The gross structures

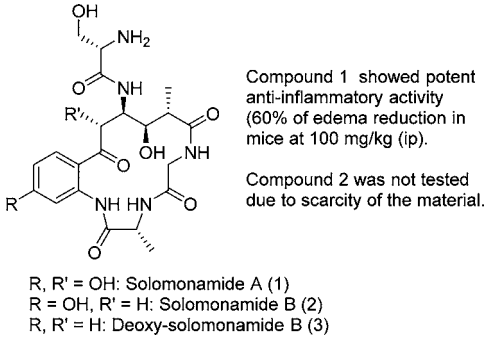


Figure 1. Structures of natural products and the present target.

of **1** and **2** were elucidated with the help of modern analytical techniques (NMR and HRMS), and the absolute stereochemistry was determined with the help of Marfey's method,[2c] QM *J* based analysis, and DFT $J/^{13}C$ calculations. The potent biological profile with a novel chemotype, scarcity of the material, and the increasing interest in macrocycle-based drug discovery recently attracted us to set up a medicinal chemistry program around these natural products toward developing anti-inflammatory agents.[3,4]To date, no total synthesis of Solomonamides has been reported. However, two synthetic approaches were disclosed in the literature including one from our group (Figure 2).[5,6] We have reported the synthesis of AHMOA (4-amino-6-(2-amino-4-hydroxyphenyl)-3-hydroxy-2-methyl-6-oxohexanoic acid), a key fragment of Solo-

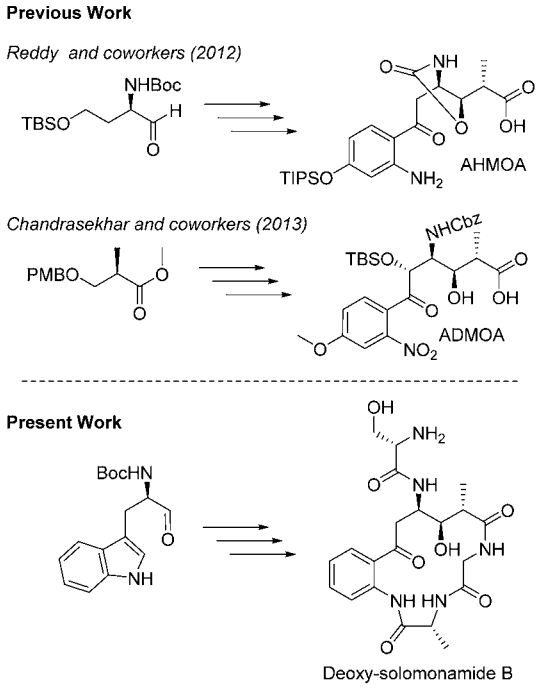


Figure 2. Approaches toward synthesis of Solomonamides.

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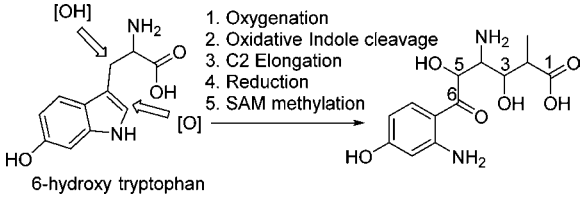
monamide B from a known D-homoserine aldehyde utilizing photo-Fries rearrangement as a key reaction.[5a] Chandrasekhar's group prepared ADMOA (4-amino(2-amino-4-hydroxyphenyl)-3,5-dihydroxy-2-ethyl-6-oxohexanoic acid), a key component of Solomonamide A in an elegant manner.[6]

While still pursuing our first approach, we initiated a parallel approach which is close to the proposed biogenesis. Herein, we disclose the synthesis of Deoxy-solomonamide B using a novel synthetic sequence.

Inspired by the biogenesis of Solomonamides proposed by Zampella's group (Scheme 1),[2] we have designed a new

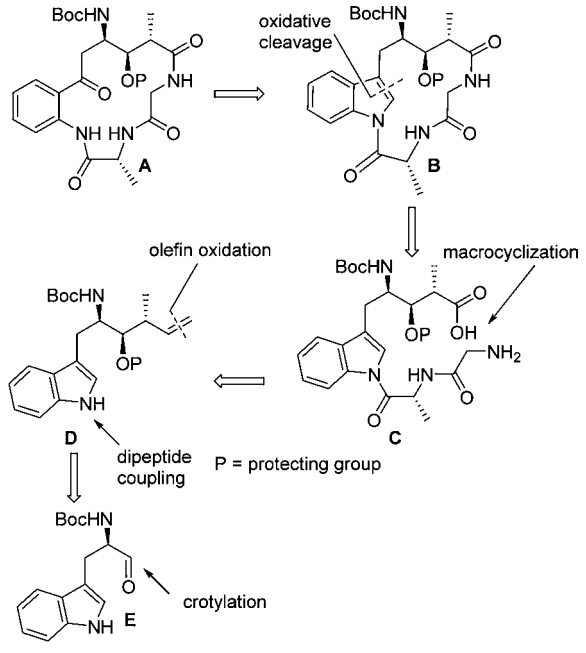
Scheme 1. Proposed Biosynthesis by Zampella's Group



strategy to access target compounds starting from an appropriate tryptophan derivative. In the proposed biosynthesis, 5-hydroxy tryptophan could undergo β-hydroxylation and oxidative scission of the indole ring to afford a kynurenine derivative which on chain elongation using a polyketide synthesis (PKS) pathway could provide the key component of the target. Accordingly, the retrosynthetic analysis of the target macrocycle **A** highlighting the key steps is shown in Scheme 2 through the intermediacy of **B**, **C**, **D**, and **E**, in which we are mimicking tryptophan metabolism through indole cleavage and the PKS process through crotylation followed by oxidation.

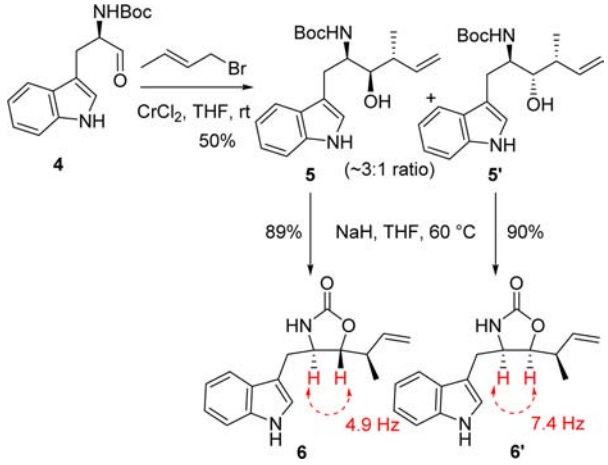
We began our synthesis with a known reaction[7a,b] on Boc-protected tryptophan aldehyde **4**[7c] to afford diastereomeric compounds **5** and **5′** with a 3:1 ratio in 50% isolated yield. Both compounds were cleanly separated on a silica gel

Scheme 2. Retrosynthetic Analysis



column and well characterized by spectral data.[7a] The stereochemistry was assigned by conversion into their corresponding carbamates. The significant difference in coupling constants of vicinal protons on oxazolidinone helped us in assigning the structures as drawn (Scheme 3).[8] In

Scheme 3. Key Crotylation and Assignment of Stereochemistry



addition, 2D NMR analysis of these intermediates further confirmed the assigned structures and the details are provided in the Supporting Information. The free hydroxyl group present in compound **5** was protected to give compound **7** in 89% yield (Scheme 4). Dipeptide (Cbz-Gly-D-Ala-OH) coupling to the indole nitrogen would have produced the advanced intermediate toward total synthesis, but all our efforts resulted in either very poor yields or no desired compound. However, we were able to couple the single amino acid Cbz-D-Ala-OH after a few attempts with **7** by using its benzotriazole derivative (Cbz-D-Ala-Bt)[9] in the presence of DBU in CH_3CN to give compound **8** in excellent yield.[10] The terminal olefin present in **8** was transformed to the corresponding ester **9** via a four-step sequence (dihydroxylation; cleavage of diol; oxidation and esterification) with a 78% yield in four steps.[11] Removal of the Cbz group[12] in **9** followed by coupling of Cbz-Gly-OH using EDC·HCl and HOBt gave the desired dipeptide **10**. At this stage, hydrolysis of the ester group did not result in the desired carboxylic acid; instead, compound **11** was isolated, which can probably be explained by the simple base mediated *N*-deacylation[13] of indole.

To overcome this problem, we have altered the originally proposed sequence to indole cleavage followed by macrocylization. The key reaction of the present strategy (oxidative cleavage of indole moiety) was achieved through ozonolysis of compound **10** to furnish the desired product **12** in quantitative yield.[14] This high yielding and practical method is very useful in organic synthesis, and it can be considered as the demasking of the *ortho*-acyl aniline moiety. Hydrolysis of ester (LiOH)[15] followed by Cbz deprotection ($Pd(OAc)_2$, Et_3SiH)[12] in compound **12** resulted in a macrocyclic precursor. After several unsuccessful attempts under various conditions, the desired macrolactamization[16] was achieved by using a combination of multiple peptide coupling reagents (HATU, TBTU, FDPP) in CH_2Cl_2/CH_3CN as solvent (2:1, 0.007 M) to give the product in moderate yields.[17] We have

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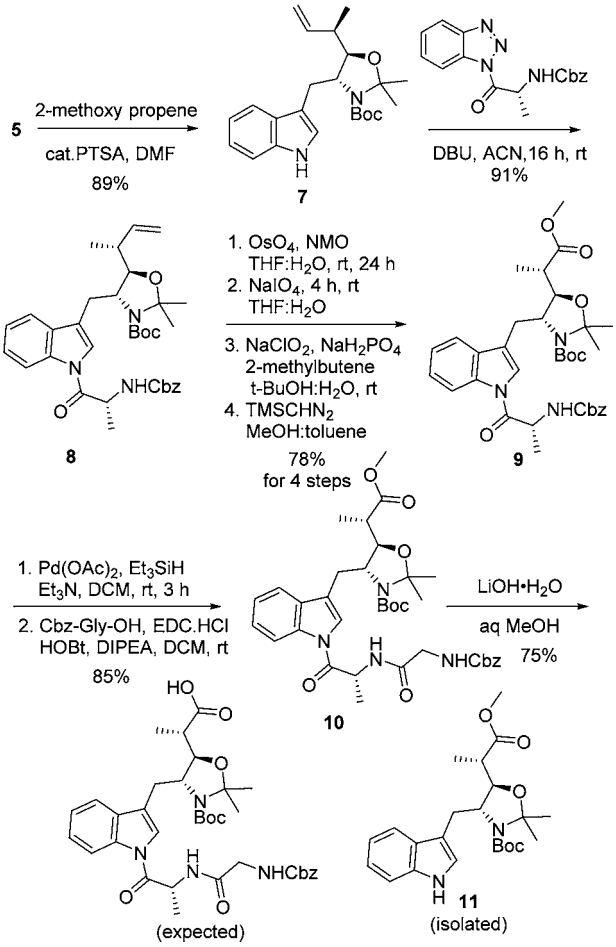
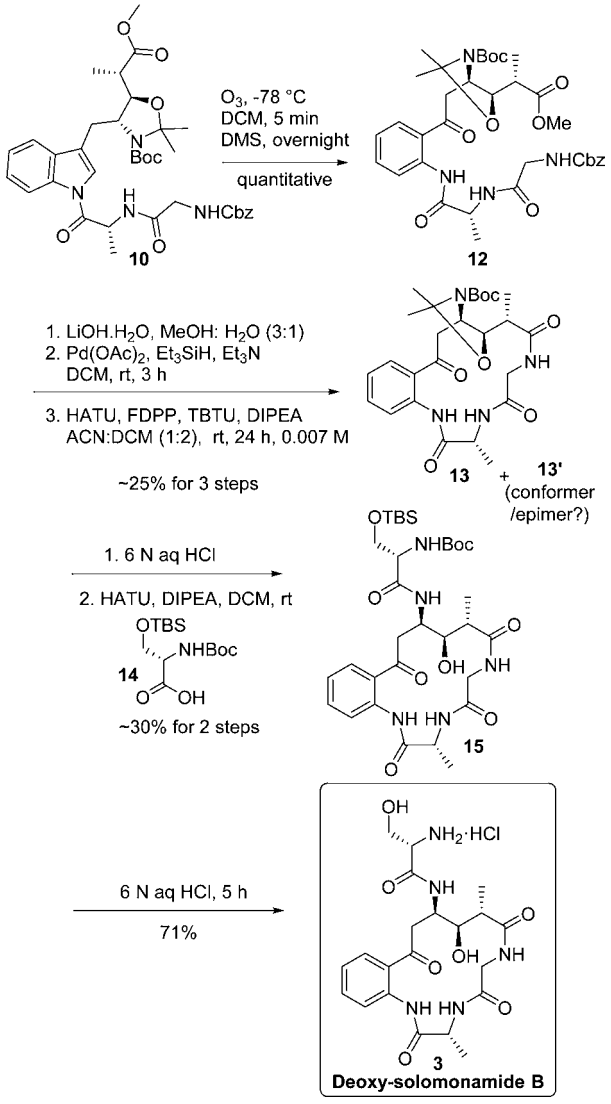
Scheme 4. Attempt towards Target Macrocycle



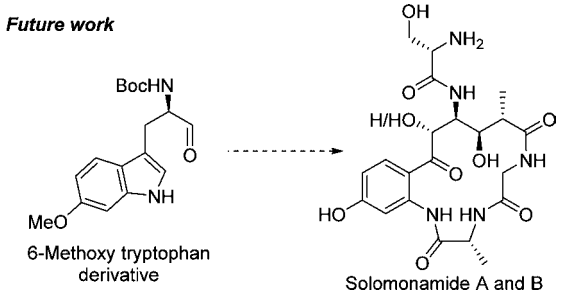
Scheme 5. Synthesis of Deoxy-solomonamide B



observed a mixture of two macrocycles **13** and **13′**, which we could separate in small amounts for the characterization. Although the spectral data for both compounds fit well with the macrocycle, we could not distinguish and completely identify the individual products, because of complications in the NMR spectra. We, then, decided to attempt the coupling of a serine moiety with the mixture as such. To our delight, the deprotection[18] using 6 N aq. HCl followed by coupling with protected L-Serine **14**[19] led us to the complete total synthesis of orthogonally protected Deoxy-solomonamide B (**15**) as a single compound.[20] We could purify the compound **15** by repetitive column chromatography followed by a preparative TLC method (3.2 mg). All the spectral data of the compound **15** are in agreement with the drawn structure (Scheme 5). We have also recorded various 2D NMR spectra using high field NMR (700 MHz), and all of them support our assignments and are provided in the Supporting Information. Finally, simultaneous deprotection of both the TBS and Boc groups using aq HCl furnished the target compound **3**, and it was characterized using ^{1}H NMR and HRMS data.[21]

In summary, we have developed the first, concise, and biomimetic route for the total synthesis of Deoxy-solomonamide B. The present route is potentially useful in preparing the actual natural products Solomonamide A and B and is suitable for producing analogues around the skeleton (Scheme 6). We do have plans to perform systematic SAR around this scaffold (including the simplification of the

Scheme 6. Plan towards Solomonamides



structural complexity) to generate optimized lead(s), which may become potential anti-inflammatory agents. Besides, the present method can be used for the synthesis of biologically active natural/unnatural compounds which contain an *ortho*-acyl aniline moiety. The total synthesis of natural products and their analogues are the current focus of the project and will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details and copies of NMR spectra of all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) After the first step (deprotection of Boc and acetonide), the crude material of both the macrocycles **13** and **13′** showed the same profile in HPLC (individual and coinjection) which indicates that probably they are conformers.

(21) Although we have recorded ^{1}H NMR, ROESY, and HRMS data for compound **3**, we could not purify cleanly and characterize completely with additional data due to the small quantity.