

# Studies toward the Synthesis of Potent Anti-inflammatory Peptides Solomonamides A and B: Synthesis of a Macrocyclic Skeleton and Key Fragment 4-Amino-6-(2'-amino-4'-hydroxyphenyl)-3-hydroxy-2-methyl-6-oxohexanoic Acid (AHMOA)

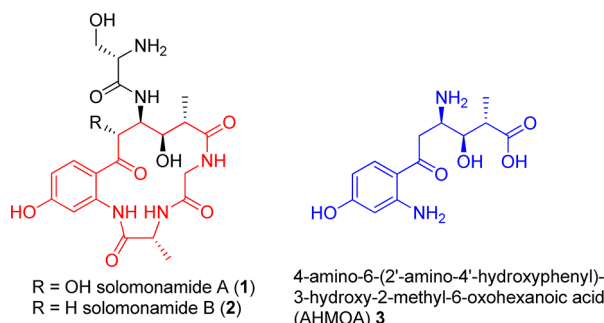
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## ABSTRACT



A first synthetic effort toward total synthesis of highly potent solomonamides is disclosed. An efficient strategy to synthesize this class of compounds, along with the synthesis of a core macrocycle (shown in red) and the key fragment AHMOA, is described.

In early 2011, two cyclic peptides solomonamide A (**1**) and solomonamide B (**2**) with an unprecedented chemotype were isolated from the marine sponge *Theonella swinhoei* by Zampella's group from Italy.<sup>1</sup> The gross structures of these cyclic peptides were established on the basis of detailed NMR analysis and HRMS. The Marfey method,<sup>2</sup> QM J based analysis, and DFT J/<sup>13</sup>C calculations were used in combination to determine the absolute configuration of the molecules. Solomonamide A (**1**) showed significant reduction (~60%) of inflammation in the carrageenan induced paw edema model.<sup>1</sup>

Interestingly, this compound **1** exhibits its anti-inflammatory potential at a very low concentration of 100  $\mu\text{g/kg}$  in animal models. The scarcity of the material has hampered further profiling of these compounds. Because of potent *in vivo* biological activity, novel chemotype, and scarcity of the material, it is expected that many synthetic and medicinal chemists across the globe are in a race to synthesize this target.<sup>3</sup> We have initiated a program to access these important class of molecules by means of chemical synthesis in sufficient quantities for further biological evaluation. We have plans to perform systematic SAR

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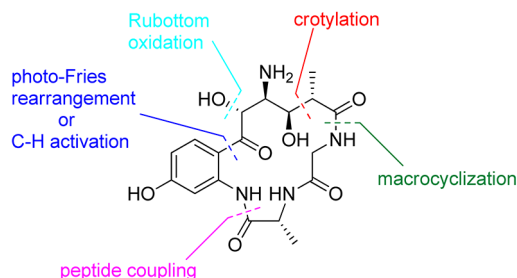
(2) Marfey, P. *Carlsberg Res. Commun.* **1984**, *49*, 591.

(3) Solomonamides A and B were highlighted as part of a "Hot off the press" natural products review published May, 2011. See: Hill, R. A.; Sutherland, A. *Nat. Prod. Rep.* **2011**, *28*, 1031.

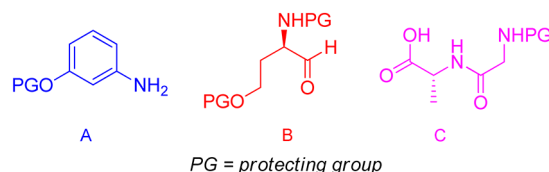
monitoring around this scaffold (including the simplification of structural complexity)<sup>4</sup> to come up with optimized lead(s) which may potentially bring forth a novel compound to be developed as an anti-inflammatory agent.<sup>5</sup> Herein, we report an efficient strategy to synthesize this class of compounds, the synthesis of a macrocyclic core, and the synthesis of a key fragment AHMOA (3).

The key disconnections toward the total synthesis of the target compounds are shown in Figure 1. The macrolactamization was chosen as a final step to assemble cyclic peptides. The fragment AHMOA (3) could be prepared starting from known compound **B** in which diastereoselective crotylation and Photo-Fries rearrangement/palladium catalyzed C–H activation would be the key steps. Other building blocks **A** and **C** could be used for assembling the southern part of the target molecules. Rubottom oxidation<sup>6</sup> could be used for the stereoselective installation of  $\alpha$ -hydroxylation of ketone in the final stages of synthesis to obtain solomonamide **A**.

#### Key disconnections



#### Building blocks



**Figure 1.** Key disconnections and building blocks.

Before embarking on the synthesis of an actual molecule, we wanted to explore the model synthesis to test the designed strategy, in particular, oxidative coupling of aldehyde to *N*-acyl-*m*-anisidine through C–H activation, less reactive aniline peptide coupling, and key macrocyclization. Accordingly, the model synthesis of a macrocycle was achieved and the results are compiled in Scheme 1. The model synthesis

commenced with the key C–H activation step starting from known *N*-acyl-*m*-anisidine **4**<sup>7</sup> and aldehyde **5**.<sup>8</sup> After a few attempts, we were successful in obtaining compound **6** by employing the recently reported Li and Kwong method (Pd(TFA)<sub>2</sub> catalyst, TBHP in toluene) in 65% yield.<sup>9</sup> Deacetylation was carried out by acidic hydrolysis to release free amine **7** in 92% yield.<sup>10</sup> As anticipated the peptide coupling was not smooth because of the weak nucleophilicity of the aryl-NH<sub>2</sub> which was in an extended conjugation with the carbonyl group (such as vinylogous amide).<sup>11</sup> As we were not successful in the coupling of dipeptide Boc-Gly-Ala-OH despite several attempts, Fmoc-protected alanine was coupled through the corresponding acid chloride, Fmoc-D-Ala-Cl,<sup>12</sup> to provide compound **8** in good yield. Next, deprotection of the Fmoc group in **8** was carried out using standard conditions (piperidine). However, we could not isolate the desired compound **9'**; instead benzodiazepinone **9** was isolated in 93% yield. It is interesting to note that compound **9** and its derivatives can be explored further, as this skeleton is a privileged structure in medicinal chemistry.<sup>13,14</sup>

To circumvent the problem of benzodiazepinone formation, the ketone present in **6** was protected with propane-1,2-dithiol in the presence of BF<sub>3</sub>·Et<sub>2</sub>O to give dithioketal **10** in 89% yield. At this stage, coupling of dipeptide Boc-Gly-Ala-OH was attempted considering that the protection of ketone removed the vinylogous amide functionality. However, the coupling of dipeptide was not successful. Hence, the compound **10** was transformed to compound **11** in a two-step sequence (deacetylation followed by *N*-acylation with Fmoc-D-Ala-Cl). Fmoc deprotection (piperidine) gave the desired free amine **12**, which was coupled with Boc-Gly-OH to produce **13** which on further hydrolysis furnished the acyclic precursor **14** in good yields. The crude acyclic amino acid resulting from Boc deprotection was subjected to key macrolactamization<sup>15</sup> using HATU followed by thioketal deprotection under standard conditions resulted in the formation of key macrocyclic core **15**<sup>16</sup> of solomonamides.

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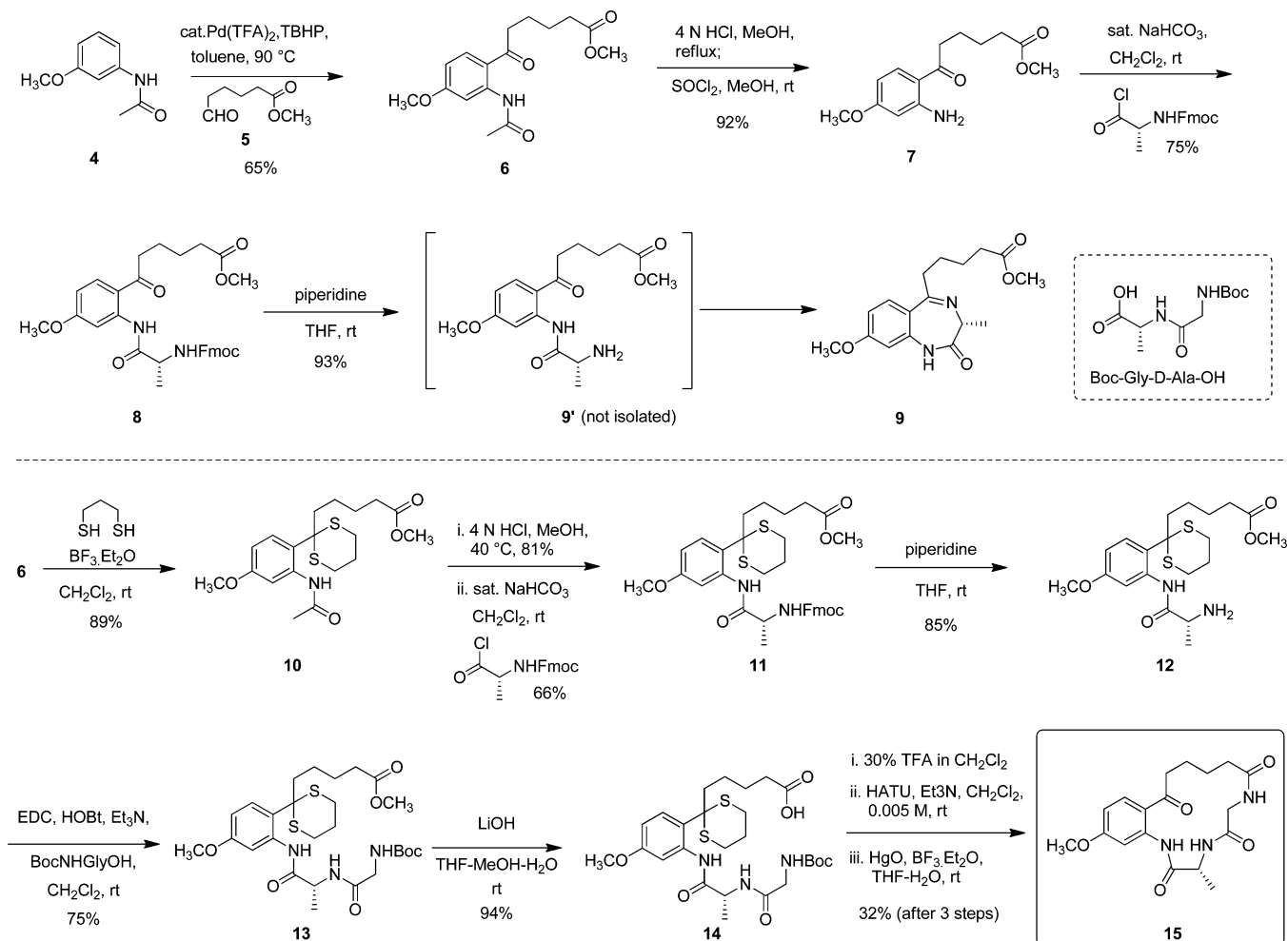
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**Scheme 1.** Synthesis of Macrocyclic Skeleton of Solomonamides



After the successful synthesis of the macrocyclic core, we turned our attention toward the synthesis of key fragment AHMOA (**3**). The known aldehyde **16**<sup>17</sup> was subjected to a key crotylation reaction to introduce the new chiral centers present in the target molecule. Freshly activated  $\text{CrCl}_2$  gave a 1:2 ratio of diastereomers **17a** and **17b** in which the desired **17b** was the major compound.<sup>18</sup> The stereochemistry of more deshielded chiral protons was established by comparing their proton coupling constants in the corresponding cyclic carbamates **18a** and **18b**.<sup>18a</sup> It is worth mentioning that undesired isomer **17a** can be converted to **17b** via an inversion reaction.<sup>19</sup> The complete stereostructure

of **18b** as drawn was further confirmed by the single X-ray crystal structure (Scheme 2). The carboxylic acid **19** prepared from cyclic carbamate **18b** (TBS deprotection followed by Jones oxidation) was coupled with TIPS protected *m*-amino-phenol **20**<sup>20</sup> to provide compound **21**. Attempts to form  $\text{sp}^2\text{--sp}^2$  C–C bond formation through C–H activation in a similar way to that of the model substrate resulted in very poor yields of the desired product. Photolysis of the amide **21** using a Hg lamp (254 nm) under dilute conditions in acetonitrile furnished the photo-Fries rearranged product **22** in a highly regioselective manner.<sup>21,22</sup> This reaction needs further optimization to improve the yield. Oxidative cleavage of olefin in **22** followed by further oxidation furnished carboxylic acid **23** in good yield. Thus, we have prepared the key fragment AHMOA in a protected form which will be carried forward to the total synthesis of natural solomonamides.

(16) All the spectral data are in agreement with the assigned structure. See details in the Supporting Information.

(17) Compound **16** was prepared by following modified and economical procedures starting from D-methionine. Alewi, B. A.; Schneider, C. M.; Kurosu, M. *J. Org. Chem.* **2012**, *77*, 3859.

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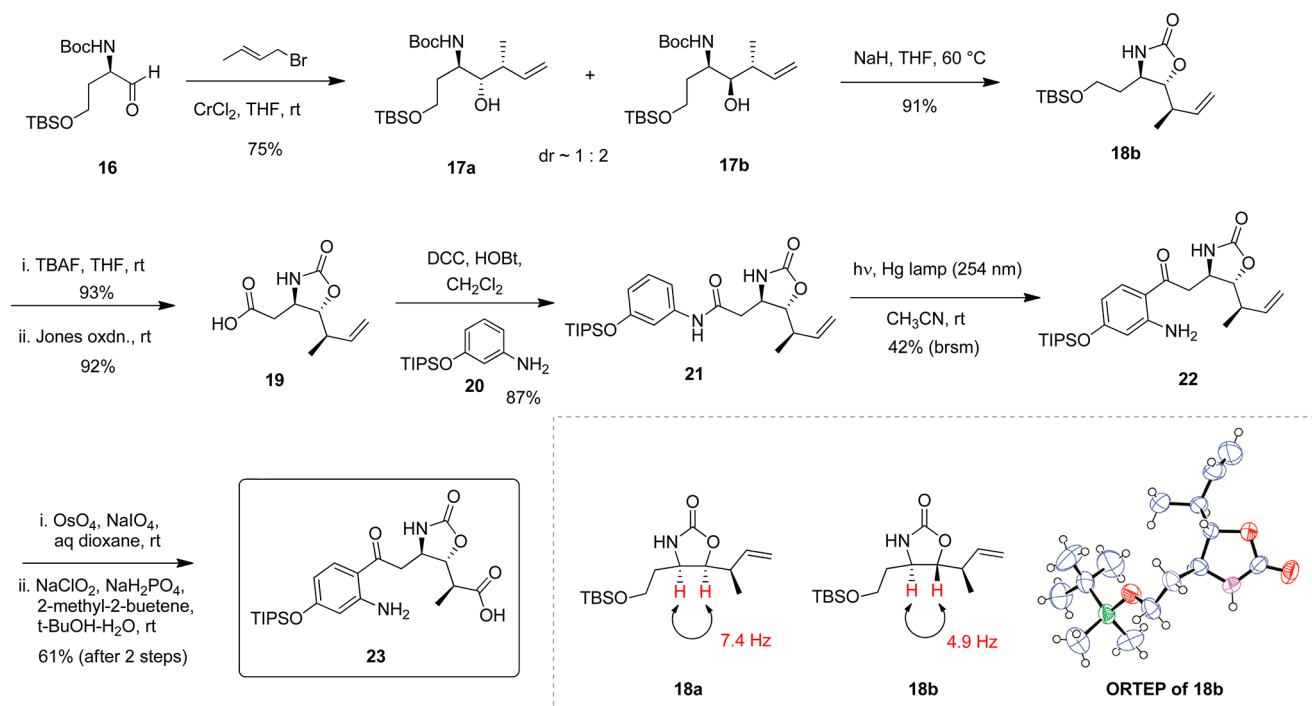
(19) **17a** was transformed to **17b** via a Mitsunobu reaction followed by ester hydrolysis in modest yield. This inversion reaction needs further optimization which is ongoing experimentation in the lab.

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(22) Photo-Fries rearrangement of the *m*-methoxy aniline derivative resulted in a mixture of regioisomers. Introduction of bulky TIPS protection solved the problem. Details will be reported in a full paper.

**Scheme 2.** Synthesis of 4-Amino-6-(2'-amino-4'-hydroxyphenyl)-3-hydroxy-2-methyl-6-oxohexanoic Acid Residue (AHMOA)



In short, we have designed a feasible strategy and executed key steps toward the total synthesis of highly attractive and potent anti-inflammatory cyclic peptides. Synthesis of the macrocyclic core and a key fragment in an orthogonally protected form are the highlights of the present work. Having tested the feasibility of key reactions and established a synthetically viable route, the total synthesis, synthesis of analogues, and their biological evaluation will constitute our future publications.

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MLP022126) for financial support; Dr. Nithyanandhan, NCL for helpful discussions on photolysis reactions; Mr. Santoshkumar S. Dange, NCL for his help in scale up of intermediates; and Mr. Bishnu Biswal, NCL for helping in X-ray analysis. K.K. and N.V. thank CSIR and UGC for the award of research fellowships, respectively.

**Supporting Information Available.** Characterization data, NMR spectra, detailed experimental procedures, and CIF file of X-ray crystal structure. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.