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An Olefin Metathesis Approach towards the Solomonamides

Iván Cheng-Sánchez[a], Cristina García-Ruíz[a,b] and Francisco Sarabia[a]*

[a] Department of Organic Chemistry, Faculty of Sciences, University of Málaga, Campus de Teatinos s/n, 29071 Málaga, Spain
[b] Current address: School of Chemistry, University of Bristol, Cantock´s Close, Bristol BS8 1TS, UK

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ABSTRACT

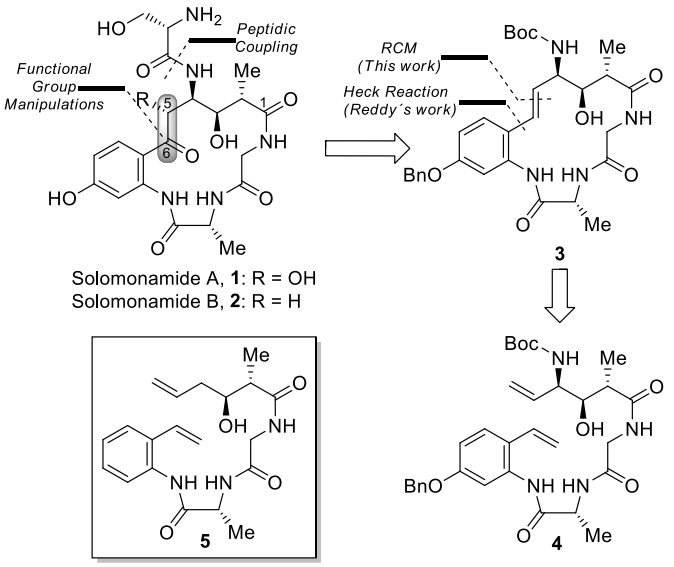
A new synthetic strategy directed towards the solomonamides, a novel class of cyclopeptides of marine origin, has been developed utilizing an olefin metathesis reaction to form the [15]-membered ring contained in these natural products. We demonstrated the efficiency and validity of this synthetic approach for the construction of the macrocyclic core of the solomonamides in a minimally oxidized system. In fact, the olefin metathesis cyclization proceeded in a stereoselective manner to provide exclusively the *Z*-isomer in high yield. The described synthetic strategy for the solomonamides allows for access to the natural products, as well as offering the opportunity for the generation of a diverse set of analogues in the subsequent oxidation phase

The discovery of new natural products offers significant opportunities for the identification and development of new leads and scaffolds in medicinal chemistry. In addition, natural products represent a great deal of fascination for organic chemists by virtue of their structural diversity and challenging molecular frameworks that many of them exhibit.[1] Among the myriad of sources for natural products, particularly prolific is the marine sponge *Theonella swinhoei*, which has proven to be an impressive source of secondary metabolites.[2] In fact, this sponge provides at least nine different classes of natural products, including the very well-known and important polyketide swinholide,[3] together with a wide range of bioactive peptidic-type natural products. Among the peptidic-type natural products, it highlights acyclic peptides (polytheonamides and koshikamides), cyclic peptides (kombamide, orbiculamide, barangamide, cupolamide, perthamides, etc..), large-ring bicyclic peptides such as the theonellamides, depsipeptides (koshikamides, papuamides, nagahamide or theopapuamide) and glycopeptides.[4] As further proof of the value of the genus Theonella as an outstanding and bountiful source of new peptides, Zampella and coworkers recently isolated two new cyclopeptides termed the solomonamides A (**1**) and B (**2**) (Scheme 1), from a Solomon islands collection. The cyclopeptides possessed unique molecular structures and potent anti-inflammatory activities.[5] An exhaustive spectroscopic analysis of both compounds facilitated the elucidation of their intricate cyclic structures, revealing the presence of three conventional amino acids (D-Ala, Gly and L-Ser) and an unprecedented 4-amino(2'-amino-4'-hydroxyphenyl)-3,5-dihydroxy-2-methyl-6-oxohexanoic acid (ADMOA) and the corresponding 5-deoxy derivative (AHMOA) for solomonamides A and B, respectively. The absolute configurations were tentatively established by a combination of spectroscopic and theoretical methods, which must be confirmed, especially for the ADMOA and AHMOA residues. Not surprisingly, these interesting and novel cyclopeptides were found to possess interesting biological properties. For example, solomonamide A (**1**) displayed anti-inflammatory activity, causing a significant 60% reduction of inflammation of edema in an animal model at the dose of 100 μg/Kg. Unfortunately, the extreme scarcity of the isolated solomonamides has hampered further biological evaluations and, indeed, in the case of solomonamide B (**2**) it was not possible to evaluate its anti-inflammatory activity. As a consequence, the solomonamides have been the subject of several synthetic efforts, notably by the Reddy group,[6] who recently reported a total synthesis of a deoxy analogue of solomonamide B[7] together with an array of simple unfunctionalized analogues.[8]

Intrigued by the enticing unique molecular structures of the solomonamides, together with their promising biological properties, we initiated a program directed toward the total synthesis of this novel class of cyclopeptides. This synthetic program pursues the consecution of the following objectives: 1) Confirmation of their proposed structures; 2) address the scarcity issue in order to supply enough material for further biological evaluations; and 3) establishment of a flexible synthetic strategy capable of generating analogues for structure-activity relationship studies. To this aim, we designed a retrosynthetic analysis of the targeted molecules based on an olefin metathesis reaction as the key step for the construction of the macrocycle,[9] which could potentially satisfy the established objectives. Thus, as depicted in scheme 1, our analysis began with a straightforward amide disconnection of the L-serine residue and functional group

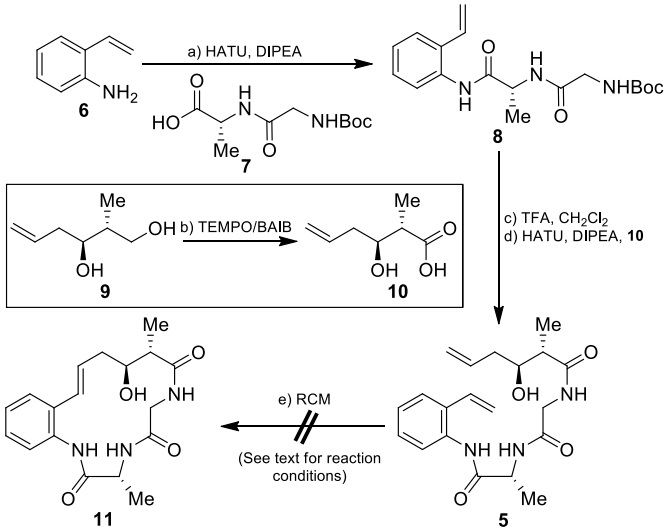
* Corresponding author. Tel.: +34 952 134 258; fax: +34 952 131 941; e-mail: frsarabia@uma.es

manipulations at the C5 and C6 positions to generate the cyclic derivative **3**, which represents a common precursor for both solomonamides. Cyclopeptide **3**, in turn, could be obtained from the acyclic diolefin **4** via a ring-closing metathesis (RCM) process. In order to demonstrate the viability and efficiency of the planned olefin metathesis approach to the synthesis of the solomonamides, we decided to commence this synthetic study with a model system represented by the diolefin **5** (Scheme 1).



Scheme 1. Molecular Structures of the Solomonamides and Retrosynthetic Analysis.

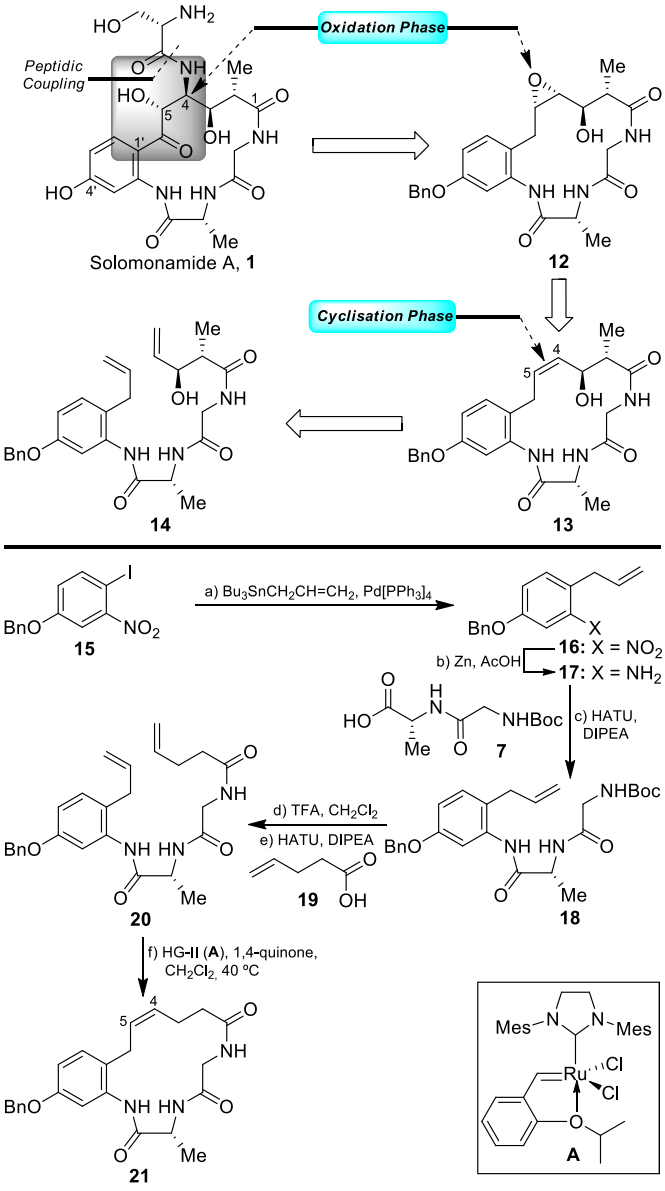
For the synthesis of the model compound **5**, we started from the simple aniline **6**,[10] which was coupled with dipeptide **7**[11] to obtain derivative **8** in 78% yield. The coupling with the hydroxy acid **10**, obtained from the known diol **9**[12] by selective oxidation with TEMPO/BAIB,[13] was achieved by conventional amide bond synthesis to provide the model olefin metathesis precursor **5** in excellent yield (92% over two steps). With the dialkene **5** in hand, we proceeded with the olefin metathesis reaction utilizing the Hoveyda-Grubbs 2nd generation catalyst (HG-II, **A**) in refluxing dichloromethane. However, after 24 h the reaction failed to afford any macrocyclic product, leading instead to decomposition and/or polymerization, together with the recovery of some starting material (~12%). In an effort to obtain the ring-closing metathesis product, more forcing conditions (toluene at 65 ºC or 100 ºC) and other catalysts (Grubbs 1st and 2nd generations, Hoveyda-Grubbs, 1st generation) were used, but the results were similarly unsuccessful in all the cases, with no detection of the formation of the desired macrocyclic product **11** (Scheme 2). Shortly after the execution of these synthetic studies carried out by us in this direction, Reddy et al published a synthetic variant, based on an intramolecular Heck reaction, that provided a synthetic precursor closely related to compound **3**[6c] (See Scheme 1).



Scheme 2. RCM Approach to the Solomonamides: First Generation. Reagents and conditions: a) 1.5 equiv HATU, 1.0 equiv DIPEA, DMF, 25 ºC, 12 h, 78%; b) 0.5 equiv TEMPO, 5.0 equiv BAIB, CH_3CN/H_2O 1/1, 25 ºC, 7 h, 65%; c) 8% TFA in CH_2Cl_2, 0 ºC→ 25 ºC, 3 h; d) 1.0 equiv **10**, 1.0 equiv HATU, 3.0 equiv DIPEA, DMF, 25 ºC, 12 h, 92% over 2 steps; e) See text for different reaction conditions. BAIB = (diacetoxyiodo)benzene, DIPEA = *N*,*N*-diisopropylethylamine, HATU = *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridine-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical.

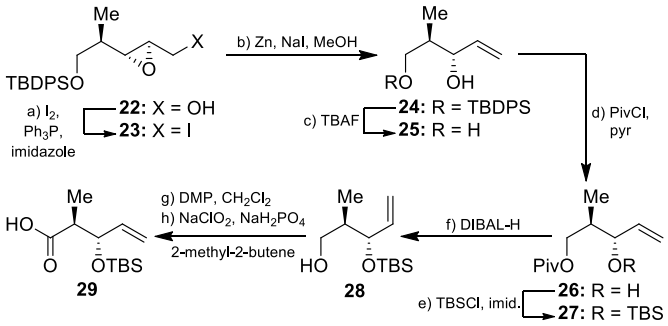
In reevaluating our approach to the solomonamides, we decided to maintain the olefin metathesis reaction as a key step for the construction of the macrocyclic structure. However, in this new retrosynthetic scenario, we envisaged the C4-C5 bond of the natural product for bond disconnection, which would require the removal of functional groups present at these positions. This retrosynthetic action would then lead to epoxy alcohol **12** as a potential precursor for solomonamide A (**1**), which, in turn, can be traced back to the olefin **13**. At this stage, the preparation of the macrocyclic olefin **13** was envisioned to proceed without difficulties from its acyclic precursor, diene **14**, given the favourable reactivity effected by the hydroxyl group at the allylic position in facilitating the ring closing metathesis reaction of olefins[14] (Scheme 3). Thus, we designed a synthetic plan to be executed in two phases, the first initiated with a cyclisation phase, via a ring closing metathesis, and the second, an oxidation phase of the resulting macrocyclic product to install the functional groups in order to obtain the final compound. It is noteworthy to point out the advantages of this new synthetic strategy in that utilizes simple starting materials and avoids the preparation of the complex ADMOA residue, which would be constructed at the later stages of the synthesis. In addition, the relatively simple macrocyclic intermediate **13** may represent an interesting scaffold that could provide access to the generation of analogues from late stage intermediates, allowing the divergent entry to numerous scaffolds. Encouraged by these appealing features, we initiated the synthetic route with the preparation of the readily accessible dipeptide **18** from the known iodonitrobenzene derivative **15**[15] according to the synthetic sequence depicted in Scheme 3. Thus, the introduction of the allylic group in **15**, via a Stille reaction, was followed by the reduction of the nitro group to produce aniline **17**. Coupling of **17** with dipeptide **7** was carried out under the same conditions as those described before for **8** to obtain in good yield dipeptide **18**. Prior to the synthesis of the acyclic precursor **14**, we decided to check the olefin metathesis reaction by use of the model

compound **20**, which was prepared by coupling of the amine derived from the Boc derivative **18** with commercial acid **19**. Thus, when **20** was treated with 10 mol% of HG-II catalyst (**A**) in refluxing dichloromethane in the presence of *p*-benzoquinone,[16] the macrocycle **21** was obtained as the sole product in an excellent 79% yield. To our delight, the newly formed double bond ($\Delta^{4,5}$) of **21** was present exclusively as the *Z*-isomer, as demonstrated by the coupling constant J =12.9 Hz.



Scheme 3. RCM Approach to Solomonamides: Second Generation. Reagents and conditions: a) 1.2 equiv allylSnBu$_3$, 0.15 equiv Pd[PPh$_3$]$_4$, DMF, 60 ºC, 12 h, 73%; b) Zn dust, AcOH, 25 ºC, 1 h, 65%; c) 1.0 equiv **7**, 1.5 equiv HATU, 1.0 equiv DIPEA, CH_2Cl_2, 25 ºC, 12 h, 81%; d) 8% TFA in CH_2Cl_2, 0 ºC→ 25 ºC, 3 h; e) 1.0 equiv **19**, 1.0 equiv HATU, 3.0 equiv DIPEA, CH_2Cl_2, 25 ºC, 12 h, 97% over 2 steps; f) 0.10 equiv Hoveyda-Grubbs 2nd Generation (**A**), 0.10 equiv 1,4-benzoquinone, CH_2Cl_2, 40 ºC, 12 h, 79%.

With the formation of the macrocyclic system demonstrated in an efficient manner, we then proceeded to extend this reaction to the desired system. To this aim, olefinic acid **29** was previously prepared from the described epoxy alcohol **22**,[17] according to the methodology reported in the literature for related compounds.[18] Thus, after the transformation of **22** into the iodide **23**, a reductive opening process was accomplished by treatment with Zn/NaI to obtain allylic alcohol **24**. After treatment of **24** with TBAF, all attempts to directly oxidize the primary alcohol to the corresponding acid of the resulting diol **25** met with no success. These disappointing results forced us to manipulate the primary and secondary hydroxyl groups of **25**, via selective protection and deprotection steps, to obtain alcohol **28** without difficulty. Olefinic alcohol **28** was then oxidized in two steps, Dess-Martin periodinane (DMP) oxidation[19] followed by final treatment of the aldehyde with sodium chlorite under Pinnick conditions[20] to furnish acid **29** in good overall yield (Scheme 4).

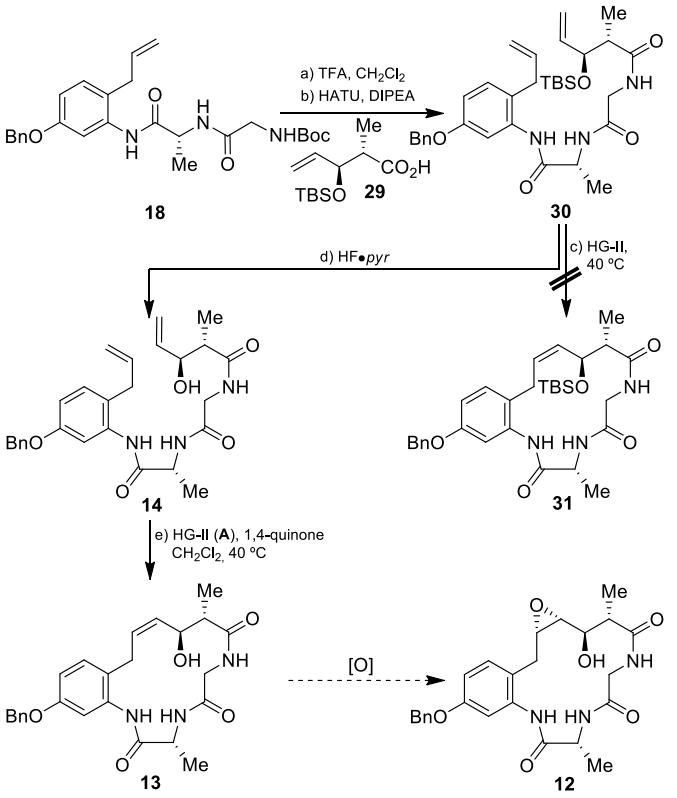


Scheme 4. Synthesis of the Acid **29**. Reagents and conditions: a) 1.5 equiv I_2, 1.5 equiv PPh_3, 3.0 equiv imidazole, THF, 0 ºC→ 25 ºC, 20 min, 84%; b) Zn dust, 1.5 equiv NaI, MeOH, reflux, 2 h, 88%; c) 2.0 equiv TBAF, THF, 0 ºC→ 25 ºC, 3 h, 90%; d) 1.3 equiv PivCl, 20.0 equiv pyridine, CH_2Cl_2, -30 ºC; e) 1.5 equiv TBSCl, 2.0 equiv imidazole, DMF, 25 ºC, 12 h, quant. over 2 steps; f) 2.0 equiv DIBAL-H, CH_2Cl_2, -78 ºC, 1 h; g) 5.0 equiv DMP, CH_2Cl_2, 0 ºC→ 25 ºC, 12 h; h) 7.0 equiv $NaClO_2$, 7.0 equiv NaH_2PO_4, 2.0 equiv 2-methyl-2-butene, *t*-BuOH/H_2O (4:1), 25 ºC, 12 h, 43% over 3 steps. DMP = Dess-Martin periodinane [1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one, PivCl = pivaloyl chloride, TBSCl = *tert*-butyldimethylsilyl chloride, TBAF = tetrabutylammonium fluoride.

The assembly of the key fragments, dipeptide **18** and acid **29**, was achieved in a similar manner as described before for **20**, to obtain **30** in 74% overall yield. In an initial attempt, **30** was subjected to the action of the catalyst HG-II (**A**). Not surprisingly, the reaction failed and no ring-closing metathesis product **31** was detected, only recovered starting material and some decomposition products were observed. Alternatively, when **30** was treated with HF•pyr, to give allylic alcohol **14**, followed by treatment with the HG-II catalyst in dichloromethane at 40 ºC in the presence of *p*-benzoquinone, the expected macrocyclic olefin **13** was obtained in 71% yield with the *Z*-olefin as the only isomer, as observed in the ^{1}H NMR spectra of the resulting crude reaction mixture. With macrocyclic derivative **13** in hand, we can now explore various epoxidation methodologies directed toward the preparation of epoxy alcohol **12** (Scheme 5).

In conclusion, we have established the basis for a new synthetic approach directed towards the solomonamides, a unique and unprecedented class of cyclic peptides that represents a new scaffold of biological and medicinal interest. This new synthetic strategy features an olefin metathesis reaction, which allows for rapid access into the macrocyclic core of the solomonamides in high-yielding and stereoselective manners. In addition, the delineated strategy was conceived to work with minimally oxidized derivatives so as to allow introduction of the remaining functional groups present in the natural products, in a subsequent oxidation phase, as well as the possibility of introducing diverse

structural modifications to rapidly and easyly access analogues. Consequently, this diversity-oriented synthetic approach to the solomonamides represents a novel and advantageous alternative to the synthetic approaches reported thus far, and offers new opportunities for the synthesis of solomonamide analogues as well as new cyclopeptide-type scaffolds based on their structures. The oxidation phase, leading to the final products, is currently in progress and the results will be reported in due course.



Scheme 5. Towards the Total Synthesis of Solomonamides. Reagents and conditions: a) 15% TFA in CH_2Cl_2, 0 ºC→ 25 ºC, 3 h; e) 1.0 equiv **29**, 1.0 equiv HATU, 3.0 equiv DIPEA, CH_2Cl_2, 25 ºC, 12 h, 74% over 2 steps; c) 0.10 equiv Hoveyda-Grubbs 2nd Generation (**A**), 0.10 equiv 1,4-benzoquinone, CH_2Cl_2, 40 ºC, 12 h, no reaction; d) 3.0 equiv HF•pyr, THF, 0 ºC, 12 h, 83%; e) 0.10 equiv Hoveyda-Grubbs 2nd Generation (**A**), 0.10 equiv 1,4-benzoquinone, CH_2Cl_2, 40 ºC, 12 h, 71%.

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Supplementary Material

Supplementary material (experimental details, compound characterization and copies of ^1H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http:…