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Breaking and Making of Olefins Simultaneously Using Ozonolysis: Application to the Synthesis of Useful Building Blocks and Macrocyclic Core of Solomonamides

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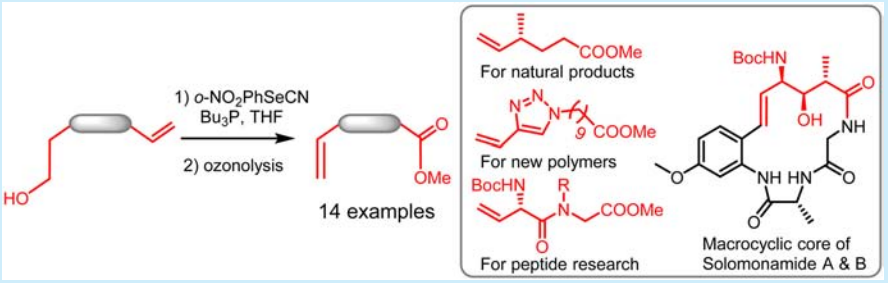
Supporting Information

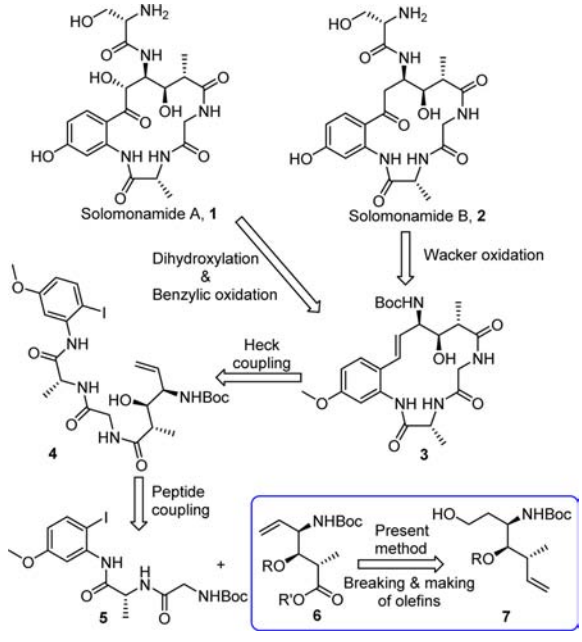


ABSTRACT: A simple and practical one-pot, two-directional approach to access olefinic esters through simultaneous breaking and making of olefins using ozonolysis of alkenyl aryl selenides is disclosed. The scope of the method with a variety of examples is demonstrated, and the end products obtained here are useful building blocks. As a direct application of the present method, the macrocyclic core of potent anti-inflammatory natural cyclic peptides, solomonamides, is synthesized.

Solomonamide A, **1**, and solomonamide B, **2**, are the two cyclic peptides isolated by Zampella's group in early 2011 (Scheme 1).[1] Solomonamide A, **1**, was reported to have shown very potent anti-inflammatory activity in mouse model at a very low concentration of 100 μg/kg and solomonamide B, **2**, could not be tested due to scarcity of the material.[1] Because of its interesting biological potential, it is now one of the major research projects in our group, and we have already made significant contributions to this project.[2,3] As of today, no total synthesis of solomonamides has been reported. However, three synthetic approaches have been disclosed in the literature including two from our group.[2−4] Chandrasekhar's group prepared the nonpeptide key component of solomonamide A, **1**, starting from a readily available chiral building block.[4] In our group, we have taken up parallel approaches to expedite the project timelines. The photo-Fries rearrangement[2] and biomimetic indole ring cleavage[3] were the key steps, respectively, in the previous two approaches from this group. We are disclosing here the third approach toward the total synthesis of solomonamides. During this process, we have developed an interesting one-pot method to generate olefinic esters through a simultaneous breaking and making of olefins using ozonolysis. The scope of the method is demonstrated with various examples.

In this new approach, we have designed a key macrocyclic intermediate **3** to access both the target natural products **1** and **2**. Solomonamide A, **1**, was planned from **3** through a dihydroxylation followed by a chemoselective oxidation of benzylic alcohol. Solomonamide B, **2**, could be accessed from **3** using Wacker-type oxidation.[5] The key compound **3** was visualized from its acyclic precursor **4** using an intramolecular Heck coupling which was hardly utilized in macrocyclizations.

Scheme 1. Retrosynthetic Analysis



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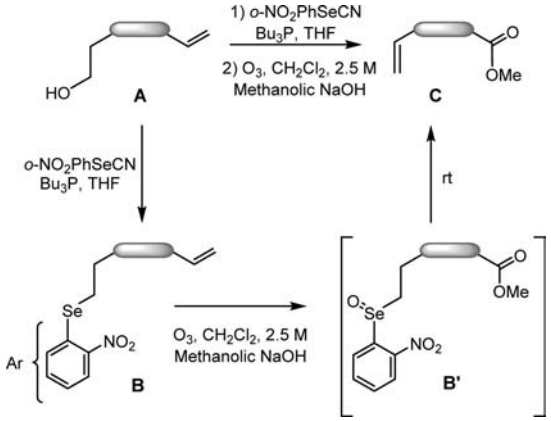
Compound **4** could be readily prepared from the appropriate intermediates, dipeptide derivative **5**, and nonpeptide component **6**. The olefinic ester **6** could be prepared using the title method starting from **7**, which was prepared earlier in our group.

The Grieco elimination[6] of an alcohol which proceeds through an organoselenium intermediate requires comparatively milder conditions with respect to classical drastic conditions such as strong acids, pyrolysis, etc.[7] In this reaction, the alcohol is first converted to selenide followed by oxidation to selenoxide using H_2O_2 or *m*-CPBA, which then undergoes *syn* elimination to afford olefin with the expulsion of selenol. The literature reports on oxidation of selenides to selenoxides using ozonolysis are very few and underexplored. Zaidi's group used ozonolysis as a handle to convert selenide to selenoxide followed by conversion of alkene in the synthesis of a 4-acylcyclohexa-2,5-dienone.[8] Clive's group performed ozonolysis on olefinic phenyl selenides with preservation of the selenium unit, where the selenoxide formed was reduced back to selenide.[9] Ozonolysis of terminal alkenes in the presence of methanolic NaOH will convert them to corresponding methyl esters.[10] By considering the multiutility of ozonolysis in various functional group transformations[11] and the present requirement for the total synthesis of solomonamides, we have combined these two operations for the first time to produce olefinic esters using a two-directional approach.

A general outline for the present method is shown in Scheme 2. First, conversion of olefinic alcohol **A** to the corresponding

Scheme 2. General Synthetic Approach



arylselenide **B** followed by ozonolysis of alkenyl selenide **B** in methanolic NaOH solution to produce the desired olefinic ester **C**, which goes through the intermediate selenoxide **B′**.

After a few optimizations, alcohol was reacted with 2-nitrophenyl selenocyanate in the presence of tributylphosphine to give alkenyl 2-nitrophenyl selenide. Aryl selenide on ozonolysis at −78 °C in CH_2Cl_2 and 5 equiv of 2.5 M methanolic NaOH followed by stirring the reaction mixture at room temperature for 3−4 h furnished the desired olefinic ester in very good yield. Having an interesting and practically simple transformation (simultaneous cleavage and formation of double bonds) in hand, we decided to expand the scope of the method, which we believe is beneficial for the synthetic organic community. Accordingly, we have transformed a variety of examples, and all the results are compiled in Table 1. In the first example, *β*-citronellol **1a** was transformed into olefinic ester **1c**, a known intermediate in the synthesis of myxobacterial pheromone, reported by Mori et al. where they prepared the same intermediate in six steps.[12] It is noteworthy to mention that corresponding carboxylic acid of **1c** was used in natural product synthesis by different groups.[13] Undecenol **2a** was converted to the corresponding selenide **2b** followed by ozonolysis to afford olefinic ester **2c** in good yield. Alkenol **3a** was synthesized by *O*-alkylation on ethylene glycol with decenyl bromide and converted to selenide **3b**, followed by ozonolysis, to afford *O*-vinyl ester **3c**. It is worth highlighting that vinyl ethers are difficult to prepare under mild conditions.[14] Triazole compound **4a**, obtained by click reaction between 3-butynol and the corresponding azide, was converted to 4-vinyl-1,2,3-triazole derivative **4c**, an important and highly useful building block in the new class of polymers.[15] Similarly, aromatic alkenol **5a** and (−)-nopol **6a** were converted to **5c** and **6c**, respectively, in good yields. The cyclobutyl derivative **6c** with fixed stereochemistry, obtained from **6a**, can be a useful building block in organic synthesis. Alkenols **7a**, **8a**, and **9a** were synthesized by opening *N*-Boc-L-homoserine lactone[16] with allylamine, *N*-methylallylamine, and diallylamine, respectively. These compounds on conversion to the corresponding selenides followed by ozonolysis afforded the desired dipeptide vinyl Gly-Gly derivatives. These can be potenial components in peptide research. Further, to increase the scope, we have chosen compound **10a**[17] and compound **11a** having an electron-donating group (methyl) and -withdrawing group (ester) at the *β* position, respectively, which were converted to corresponding olefinic esters **10c** and **11c** in good yields via **10b** and **11b**. It was observed that reaction was faster in the later example. Interestingly, compound **11a** is a secondary alcohol, which also works well in the present method. As can be seen from the literature, vinylglycine derivatives are generally prepared from methionine derivatives using high temperatures, and they often suffer from the side products formation due to migration of the double bond.[18] Toward the total synthesis of solomonamides, the compound **12a**,[2] previously prepared in our laboratory, starting from D-methionine, was converted to compound **12b** in 95% yield. However, on ozonolysis under the same conditions, the desired olefin ester **12c** was obtained in low yield. Protection of free NH group (DMAP, $(Boc)_2O$) gave compound **13b**, which on ozonolysis afforded the olefinic ester **13c** with an improved yield of 75%. In a similar manner, amino alcohol **14b** obtained after hydrolysis of carbamate in **13b**, when subjected to ozonolysis reaction, afforded compound **14c** in 46% yield. Because of problems (elimination of secondary alcohol in compound **13c**) associated with follow-up reactions toward total synthesis, the later compound **14c** was used for the synthesis of solomonamides.

In continuation toward the total synthesis, the dipeptide derivative **5** was synthesized by coupling of Boc-Gly-D-Ala-OH to known compound 2-iodo-5-methoxyaniline **15**[19] in 63% yield. The crude carboxylic acid **14c′** prepared from **14c** was coupled with the amine obtained from **5** to yield macrocycle precursor **4** in good yield. Compound **4** on intramolecular Heck reaction, using $Pd(OAc)_2$, Et_3N under dilute conditions, furnished the macrocycle **3** in 42% yield (Scheme 3). It is worth highlighting that macrocylizations using Heck reactions are very rare,[20] and we are pleased to find that the macrocyclization reaction worked very well in the present case. The synthesized compound **3** represents the complete macrocyclic core of the solomonamides with the desired functionalities and stereochemistry pattern.

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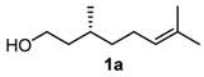
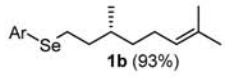
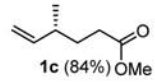
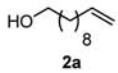
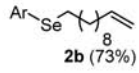
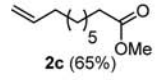
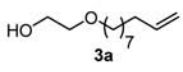
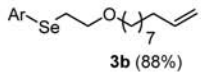
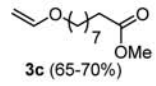
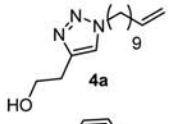
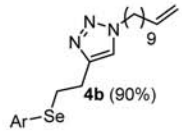
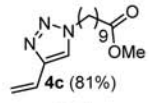
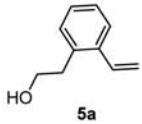
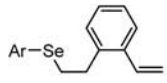
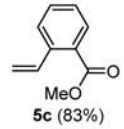
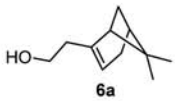
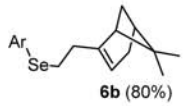
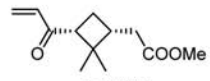
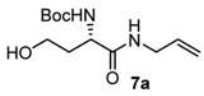
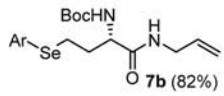
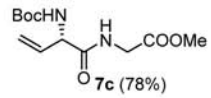
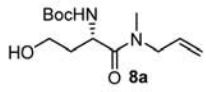
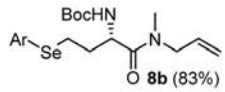
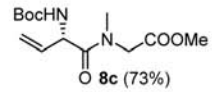
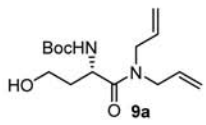
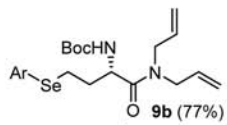
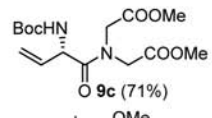
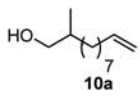
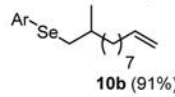
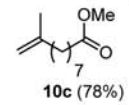
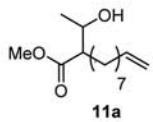
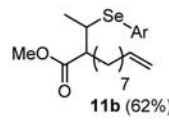
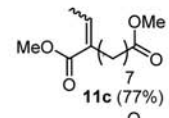
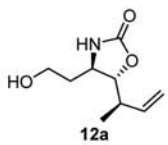
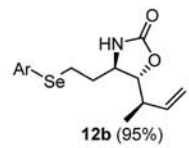
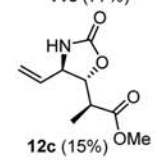
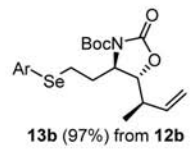
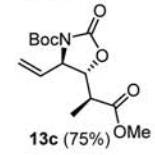
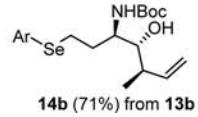
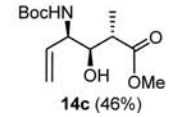
Table 1. Scope of the Method

alkenol, A	alkenyl aryl selenide, B (yield %)	olefinic ester, C (yield %)
 **1a**	 **1b** (93%)	 **1c** (84%)
 **2a**	 **2b** (73%)	 **2c** (65%)
 **3a**	 **3b** (88%)	 **3c** (65-70%)
 **4a**	 **4b** (90%)	 **4c** (81%)
 **5a**	 **5b** (92%)	 **5c** (83%)
 **6a**	 **6b** (80%)	 **6c** (86%)
 **7a**	 **7b** (82%)	 **7c** (78%)
 **8a**	 **8b** (83%)	 **8c** (73%)
 **9a**	 **9b** (77%)	 **9c** (71%)
 **10a**	 **10b** (91%)	 **10c** (78%)
 **11a**	 **11b** (62%)	 **11c** (77%)
 **12a**	 **12b** (95%)	 **12c** (15%)
	 **13b** (97%) from **12b**	 **13c** (75%)
	 **14b** (71%) from **13b**	 **14c** (46%)

In short, we have developed a mild and practical one-pot method to access olefinic esters using ozonolysis in a two-directional approach, and it is overall an oxidation with loss of one carbon. The method was generalized with a variety of

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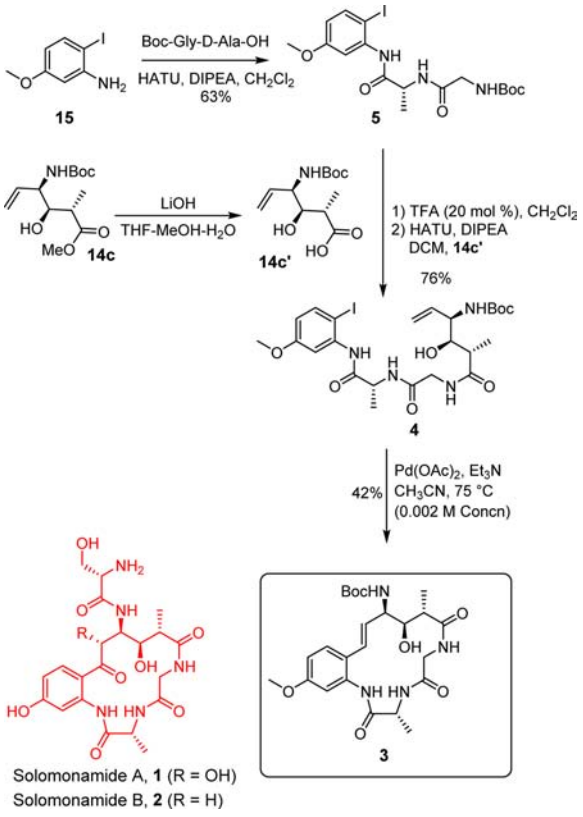
Scheme 3. Synthesis of Macrocyclic Core of Solomonamides



important and useful substrates. The present method is better compared to existing methods as two operations can take place in one pot under mild conditions. In addition, it was successfully applied to the synthesis of key components of solomonamides, which in turn was utilized for the construction of the complete core of solomonamides with desired functionalities.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and NMR spectra. 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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■ DEDICATION

This work is dedicated to Dr. J. S. Yadav, IICT - Hyderabad, on the occasion of his 65th birthday.

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