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SHORT COMMUNICATION

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High-Yielding Total Synthesis of Sexually Deceptive Chiloglottones and Antimicrobial Dialkylresorcinols through an Organocatalytic Reductive Coupling Reaction

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Dedicated to the memory of Professor Carlos F. Barbas III (1964–2014)

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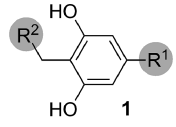
Biologically important, less-explored natural products of sexually deceptive chiloglottones, antimicrobial dialkylresorcinols, and their many analogues were synthesized in very good yields in a sequential two-pot manner by using an "organocatalytic reductive coupling reaction" as the key step.

Introduction

The efforts of the synthetic chemistry community over the last 200 years must be appreciated for the intellectual design of the synthesis of the most complex molecules, but lengthy processing times, wasteful and expensive routes, and environmental issues were often part of it. Thus, the synthesis of the useful molecules that can be used, for example, as natural products, drugs, drug intermediates, and ingredients can be challenging even if they are only moderately complex. In this context, we believe that organic synthesis can be made as perfect as similar cellular reactions by designing multidomino processes in which multicatalysts operate sequentially in one pot with multicomponents. Basically, this sequential one-pot combination of multidomino processes should reduce the cost and waste associated with the synthesis of all kinds of molecules.

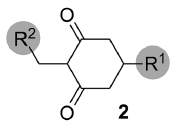
The increasing demands for environmentally and economical friendly synthetic processes have promoted the development of sequential one/two-pot combinations of multidomino processes to provide the desired products in the most efficient ways.[1] The early discovery of amino acid and/or amine-catalyzed double domino,[2] triple domino,[3] and quadruple domino[4] asymmetric reactions initiated a new era in the high-yielding total synthesis of natural products, drugs, and druglike molecules through a sequential one/two-pot combination of multidomino processes.[5] There has been a considerable range of multidomino processes effectively utilized by chemists for the high-yielding total synthesis of natural products/drugs over the last few years.[5] Although the sequential one/two-pot combination of multidomino processes is evolving as a better protocol,[5] whatever is known of the few domino processes is not enough for the synthesis of the vast library of natural products/drugs, and we need to develop different, better combinations of multidomino processes in a one/two-pot manner.



1

Antimicrobial dialkylresorcinols

RMC-2-47: R^1 = Me and R^2 = *n*-pentyl
DB-2073: R^1 = *n*Pr and R^2 = *n*-pentyl
RMC-2-55: R^1 = *n*Pr and R^2 = *n*Pr
Resorstatin: R^1 = *n*-pentyl and R^2 = *n*-pentyl
2-Ethyl Olivetol: R^1 = *n*-pentyl and R^2 = Me
Stemphol: R^1 = *n*-pentyl and R^2 = *n*Pr
Resorcinin: R^1 = isohexyl and R^2 = isodecyl



2

Sexually deceptive chiloglottones

Chiloglottone 1: R^1 = *n*Pr and R^2 = Me
Chiloglottone 2: R^1 = *n*-pentyl and R^2 = Me
Chiloglottone 3: R^1 = Me and R^2 = *n*Pr
Chiloglottone 4: R^1 = allyl and R^2 = Me
Chiloglottone 5: R^1 = *n*Pr and R^2 = *n*Pr
Chiloglottone 6: R^1 = Me and R^2 = *n*-pentyl

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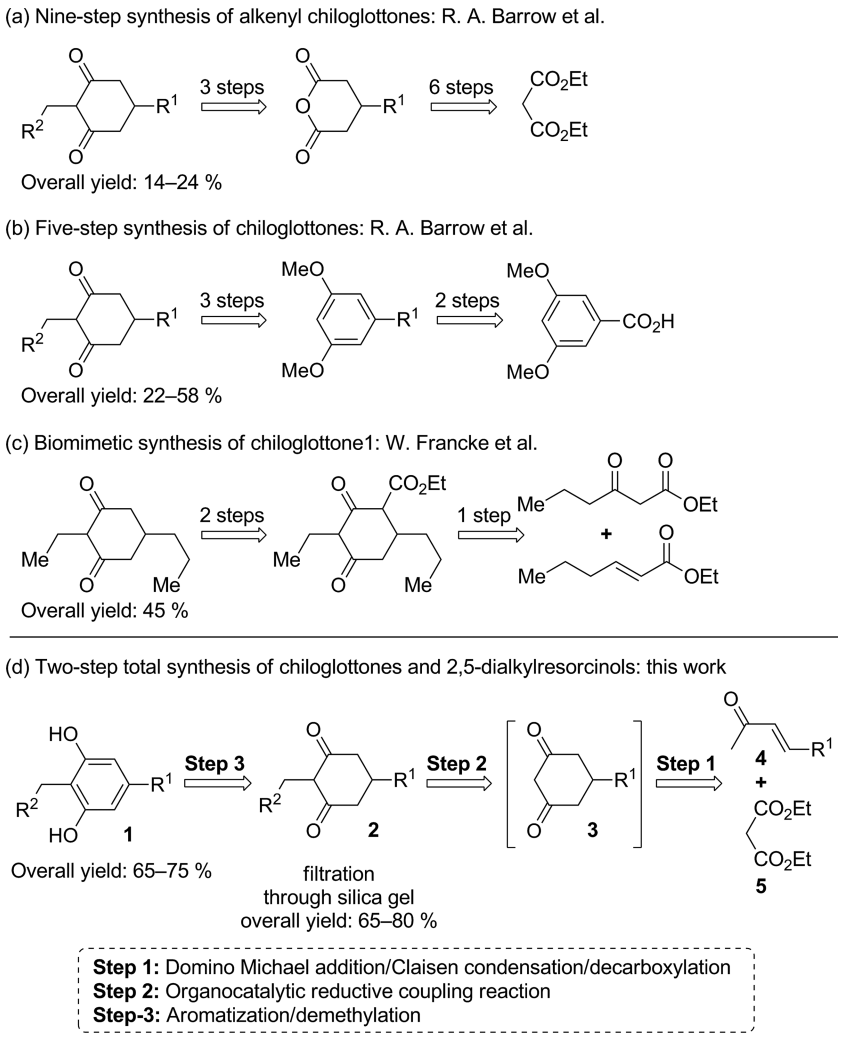
Herein, we designed a new multidomino process for the sequential two-pot high-yielding total synthesis of sexually deceptive chiloglottones **2**[6] and antimicrobial dialkylresorcinols **1**.[7]

Results and Discussion

Chiloglottones **2** and dialkylresorcinols **1** can be regarded as an unexplored class of natural products. Thus far, the only examples of 2,5-dialkylcyclohexane-1,3-dione natural products are chiloglottones 1–6 (**2**); they were identified in orchids of the genus *Chiloglottis*, in which they act as pheromones to fool its pollinator, the male wasp *Neozeleboria cryptoides*.[6] Interestingly, chiloglottones 1–6 can be easily transformed into other kinds of natural products, that is, 2,5-dialkylresorcinols **1**, by oxidative aromatization, and the only known examples of dialkylresorcinols **1** are RMC-2-47 (**1e**), RMC-2-55 (**1i**), DB-2073 (**1k**), 2-ethyl olivetol (**1m**), stemphol (**1o**), resorstatin (**1q**), resorcinin (**1x**), and their analogues, which show very good antibacterial and anticancer activities.[7]

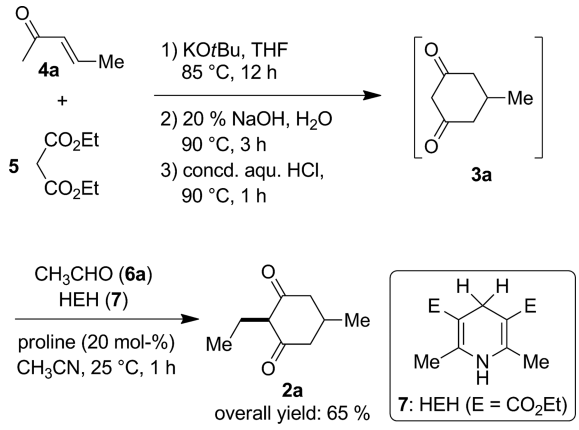
On the basis of their many applications, the development of an efficient and environmentally friendly two-pot protocol from simple substrates to synthesize natural products **1** and **2** is a challenging task. The first total synthesis of chiloglottone 1 was reported in 2008 by Barrow et al., for which the product was obtained in nine steps in 14–24% overall yield (Scheme 1, a).[8] In 2009, the same group developed a five-step protocol for the total synthesis of chiloglottone 1 in 22–58% overall yield (Scheme 1, b).[8] In 2009, Francke et al. developed a three-step protocol for the total synthesis of chiloglottone 1 in 45% overall yield (Scheme 1, c).[9] In the above three methods, the Barrow group utilized five to nine linear synthetic steps and longer reaction times to furnish only natural product chiloglottone 1 and its analogues in poor overall yields. The Francke group used three steps to furnish chiloglottone 1 and its analogues in moderate overall yields from designed substrates, but by using this



Scheme 1. Previous multistep approaches and the present two-pot/two-step approach for the total synthesis of chiloglottones **2** and dialkylresorcinols **1**.

method, they also synthesized only one natural product (Scheme 1a–c). These three methods required harsh reaction conditions with purification for each step or highly functionalized designed starting materials to furnish chiloglottone 1 out of the six chiloglottones (Scheme 1). With these limitations in mind, herein we describe the total synthesis of a library of chiloglottones **2**, 2,5-dialkylresorcinols **1**, and their many analogues from alkylideneacetones **4** and diethyl malonate (**5**) by using a triple domino Michael addition/Claisen condensation/hydrolysis/decarboxylation[10] sequence followed by metal-free reductive coupling[11–13] in a sequential two-pot manner. Chiloglottones 1–6 and their analogues were transformed into 2,5-dialkylresorcinols **1** by using oxidative aromatization followed by metal-free demethylation in a sequential two-pot manner (Scheme 1, d).

Our high-yielding two-pot strategy for the synthesis of chiloglottones **2** began with the facile in situ construction of 5-alkylcyclohexane-1,3-diones **3**, which are the starting materials for the reductive coupling with **6** and **7** under proline catalysis.[11] For this purpose, we utilized domino Michael addition/Claisen condensation of alkylideneacetones **4** with diethyl malonate (**5**) to furnish the β,δ-diketo ester, which upon one-pot hydrolysis/decarboxylation[10] delivered required 5-alkylcyclohexane-1,3-diones **3** in very good yields. Removal of the water layer from the reaction mixture and further treatment with **6** and **7** under proline catalysis delivered chiloglottones **2** and their analogues in very good yields (Schemes 1 and 2). Recently, we developed a novel three-component reductive alkylation protocol for the selective C-alkylation of highly reactive cyclic-1,3-diones with a variety of aldehydes and Hantzsch ester (hydrogen source) through olefination followed by transfer hydrogenation under proline catalysis.[11] Soon after the discovery of this reductive coupling reaction in 2006, many chemists realized the importance of this reaction in the total synthesis of natural products, drugs, and druglike molecules.[12,13] Herein, we utilized this three-component reductive coupling protocol as a main reaction in the one-pot synthesis of chiloglottones through C–C bond formation.



Scheme 2. High-yielding total synthesis of chiloglottone 3 analogue **2a** through an organocatalytic two-pot/two-step reaction sequence; HEH = Hantzsch ester.

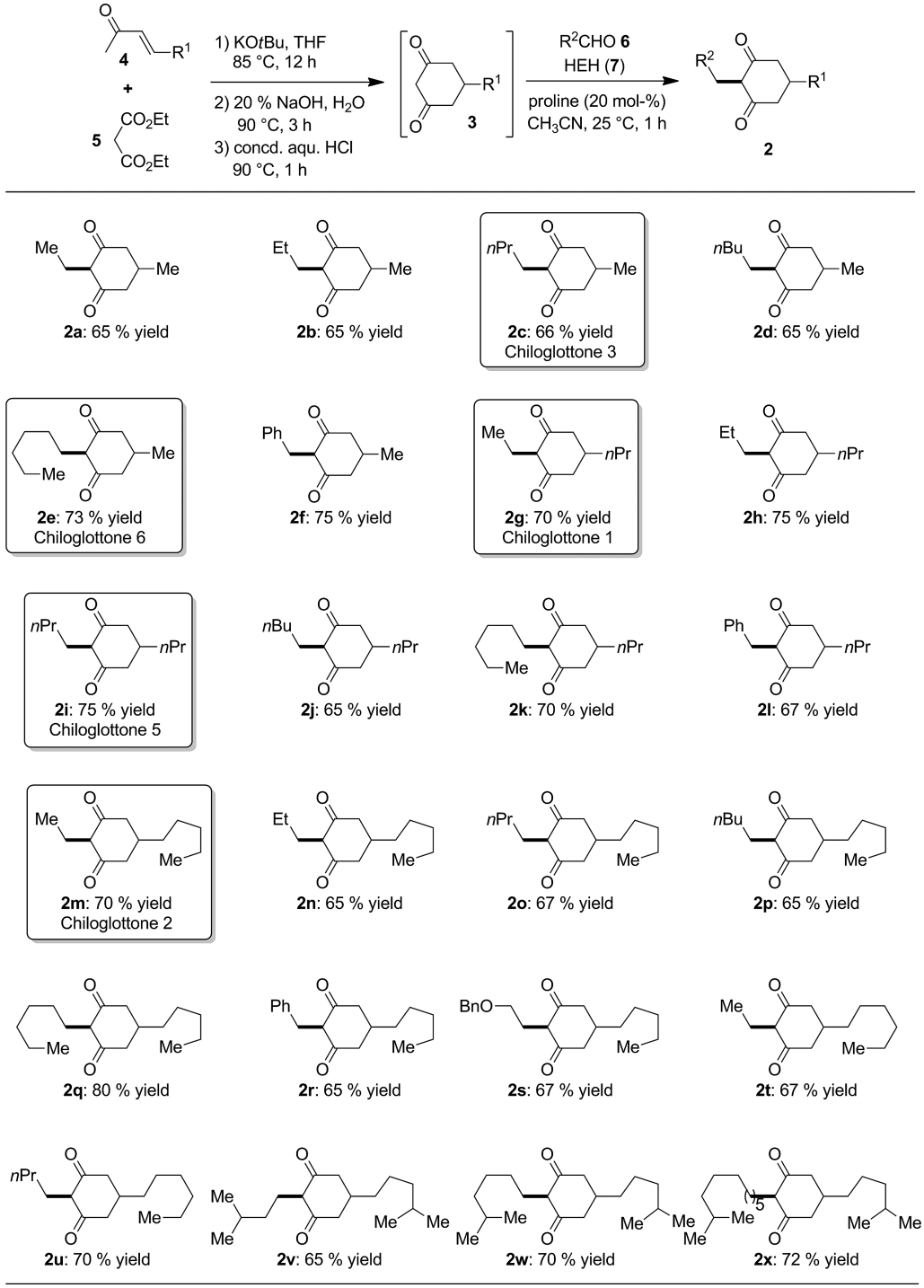
This design was first demonstrated with model substrates of **4a**, **5**, **6a**, and **7** under proline catalysis (Scheme 2). Base-induced domino Michael addition/Claisen condensation of **5** with **4a** in refluxing THF for 12 h followed by one-pot hydrolysis with 20% aqueous NaOH at 90 °C for 3 h and in situ decarboxylation with concentrated HCl at 90 °C for 1 h furnished the basic skeleton, 5-methylcyclohexane-1,3-dione (**3a**), with an active functional group in very good conversion. Quick removal of the aqueous layer from the reaction mixture followed by reductive coupling of crude product **3a** with acetaldehyde (**6a**, 5 equiv.) and Hantzsch ester (**7**, 1 equiv.) in the presence of proline (20 mol-%) in CH_3CN at 25 °C for 1 h furnished chiloglottone 3 analogue **2a** in 65% yield (Scheme 2). The overall yield obtained from this two-pot method was very good relative to that obtained in the previous multipot methods (Scheme 1).

After the successful high-yielding synthesis of **2a**, the principle of the "sequential two-pot reactions" was further extended by treating a library of functionalized alkylideneacetones **4a**–**e** with diethyl malonate (**5**) under basic and acidic conditions to afford 5-alkylcyclohexane-1,3-diones **3a**–**e**, which were treated with a variety of aldehydes **6a**–**j** and Hantzsch ester (**7**) catalyzed by proline (20 mol-%) at 25 °C in CH_3CN for 1 h (Table 1). Substrates **4a**–**e**, **5**, **6a**–**j**, and **7** furnished the huge library of expected 2,5-dialkylcyclohexane-1,3-diones **2a**–**x** in overall yields of 65–80%, irrespective of the electronic and steric effects of the substituents. From this two-pot method, for the first time we synthesized the total chiloglottone family of sexually deceptive natural products, that is, chiloglottone 3 (**2c**), chiloglottone 6 (**2e**), chiloglottone 1 (**2g**), chiloglottone 5 (**2i**), and chiloglottone 2 (**2m**), in overall yields of 66–75% (Table 1). We also prepared 19 chiloglottone analogues in overall yields of 65–80%, as shown in Table 1.

After demonstrating the two-pot high-yielding synthesis of chiloglottones and analogues **2a**–**x**, the same protocol was further extended to benzylideneacetone (**4f**) with diethyl malonate (**5**) under basic/acidic conditions to afford 5-phenylcyclohexane-1,3-dione (**3f**), which was treated with aldehydes **6a**, **6c**, **6e**, and **7** in the presence of proline (20 mol-%) at 25 °C in CH_3CN for 1 h (Scheme 3). Surprisingly, expected 2-alkyl-5-phenylcyclohexane-1,3-diones **2y**–**a′** were furnished in overall yields of 50–65%, irrespective of the electronic/steric effects (Scheme 3).

After synthesizing the library of chiloglottones **2** in a sequential two-pot manner, we further transformed them into medicinally important 2,5-dialkylresorcinols **1** through a two-step sequence involving oxidative aromatization followed by demethylation.[14] Thorough investigation of **2**→**1** through the two-step sequence of oxidative aromatization/demethylation proved that I_2/MeOH-BBr_3/CH_2Cl_2 were suitable conditions to synthesize 2,5-dialkylresorcinols **1** in good yields with high purity (Table 2).[14] Reaction of chiloglottone 6 (**2e**) with I_2 (2 equiv.) in MeOH at 65 °C for 8 h furnished aromatized dimethoxy compound **8e** as the major isomer. Quick filtration of **8e** through silica gel followed by demethylation with BBr_3 (3 equiv.) in CH_2Cl_2 at 0–25 °C for 4 h furnished the natural product 2-hexyl-5-

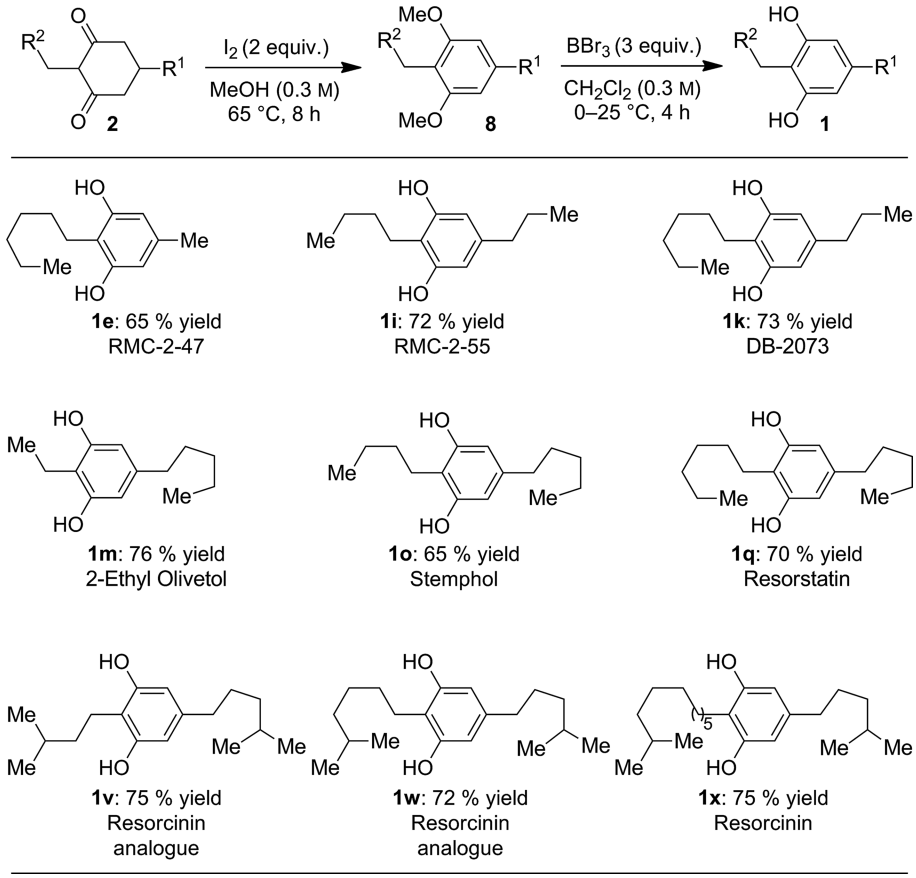
Table 1. Total synthesis of chiloglottones and analogues **2** through a sequential two-pot operation.[a]



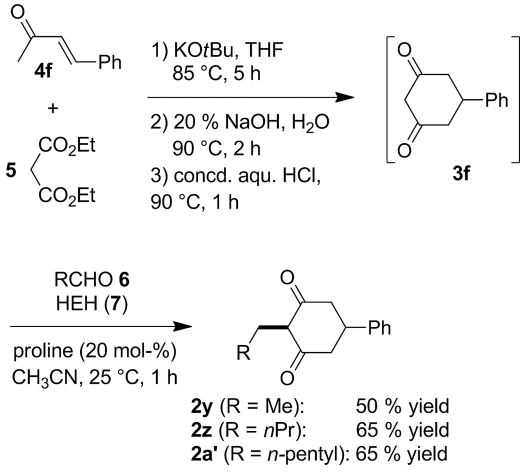
[a] Yield refers to the column-purified product.

methylbenzene-1,3-diol (**1e**) in an overall yield of 65%, which we named RMC-2-47 (Table 2, entry 1).[7] In a similar manner, the selective two-step sequential oxidative aromatization/demethylation strategy was demonstrated with eight more substrates of chiloglottones **2** containing different 2,5-dialkyl groups to furnish medicinally important 2,5-dialkylresorcinol natural products **1** in overall yields of 65–76% with high purity (Table 2, entries 2–9). For the first time, we prepared seven natural products and two analogues of 2,5-dialkylresorcinols **1** in very good yields by using a common protocol. The structure and regiochemistry of **1** and **2** were confirmed by NMR spectroscopy and were also finally confirmed by correlation with the literature data.

Table 2. Total synthesis of dialkylresorcinols **1** from chiloglottones **2** through the two-step process.[a]



[a] Yield refers to the column-purified product.



Scheme 3. Two-pot total synthesis of chiloglottone analogues **2y**–**a′**.

Conclusions

In summary, we developed a common method for the high-yielding total synthesis of a library of important natural products, chiloglottones 1–6 and 2,5-dialkylresorcinols, from readily available simple substrates through a sequential two-pot combination of domino Michael addition/Claisen condensation/hydrolysis/decarboxylation, organocatalytic reductive coupling, and oxidative aromatization/demethylation reactions. This sequential two-pot protocol is an ideal method to synthesize the entire family of chiloglottone natural products.

Supporting Information (see footnote on the first page of this article): Experimental procedures, and characterization data (^{1}H NMR, ^{13}C NMR, and HRMS).

Acknowledgments

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