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# Asymmetric Synthesis of Ramariolides A and C through Bimetallic Cascade Cyclization and *Z*–*E* Isomerization Reaction

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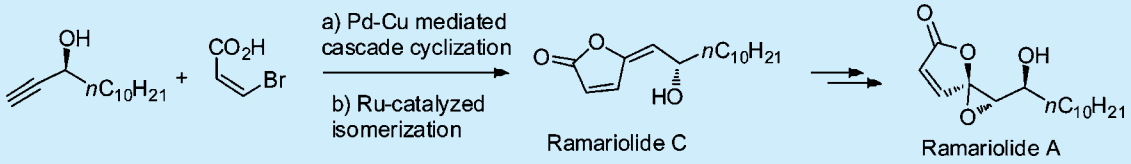
Supporting Information




**ABSTRACT:** A short and flexible asymmetric synthesis of ramariolides A and C was accomplished. A bimetallic catalytic system consisting of Pd–Cu-mediated cascade cyclization, unprecedented *Z*–*E* isomerization by a Ru-based metathesis catalyst, and late-stage stereoselective epoxidation are the key steps involved in the synthesis.

Ramariolides A–D (**1**–**4**), structurally unique butenolides, have recently been isolated from the fruiting bodies of the coral mushroom, *Ramaria cystidiophora*, found in the southern British Columbia region.[1] Ramariolide A (**1**), containing a spiro-oxiranebutenolide core moiety, exhibits significant in vitro antimicrobial activity against *Mycobacterium smegmatis* and *Mycobacterium tuberculosis*. The structure of **1** was established through extensive NMR spectroscopy and X-ray diffraction analysis.

Ramariolide B (**2**), the other butenolide isolated from the same species, containing novel spiro-oxetanebutenolide functionality, was observed only the second time in the nature after sesquiterpenoid parthexetine.[2] The most structurally similar compounds to the ramariolides reported in the literature are the goniobutenolides (A and B)[3a] and hygrophorones (F and G),[3b] which closely resemble ramariolide C and D (containing the γ-(*Z*)-alkylidenebutenolides moiety; Figure 1) in structure but contain additional functional units in the alkyl chain. Owing to their unique structural features and significant biological profile, we pursued the total synthesis of ramariolides in asymmetric fashion. In the majority of natural products containing the γ-alkylidenebutenolide framework, the presence of a thermodynamically more favorable *Z*-isomer was preferred mainly due to steric and electronic reasons, where the notable exceptions are **3** and **4**, goniobutenolide B, and hygrophorone F (all containing the γ-(*E*)-butenolide moiety).

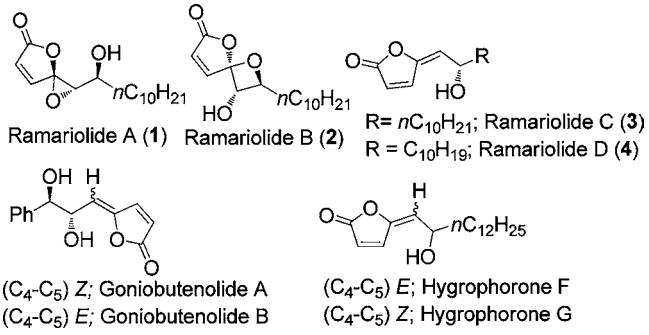
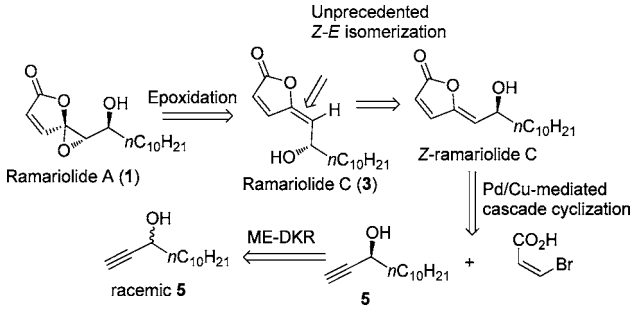



**Figure 1.** Ramariolides A–D (**1**–**4**), goniobutenolides, and hygrophorones.

Ramariolide A was accessed through a stereoselective epoxidation of the exocyclic *E*-olefinic appendage at C4 of **3**. **3** with the required γ-(*E*)-butenolide core was assembled through a novel Pd/Cu-mediated cyclization of an enatiopure alkyne fragment (**5**) and (*Z*)-3-bromoacrylic acid (Scheme 1). This type of cascade cyclization for the synthesis of γ-(*Z*)-butenolide was first reported by Lu et al.[4a] and seemed to be operative through a tandem Sonogashira-type cross-coupling reaction (yne-ene) followed by 5-*exo*-dig cyclization (Pd-catalyzed lactonization followed by reductive elimination).

**Scheme 1. Retrosynthetic Analysis of 1 and 3 through Exploitation of Pd/Cu-Mediated Cascade Cyclization**




Though few sporadic reports[5] for the synthesis of the γ-(*Z*)-butenolide scaffolds are known, Lu's procedure was superior and extremely versatile in terms of its selectivity (regio- and

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diastereoselectivity) and atom economy. Stereochemical information present in the precursor (existing stereocenter in the alkyne fragment) was unaffected by this tandem cross-coupling/lactonization method. The major challenge in our synthetic strategy will be the unprecedented isomerization of γ-(*Z*)-butenolide to the required γ-(*E*)-butenolide (theromodynamically less stable) core in ramariolides. During our investigation, the first total synthesis of all the four ramariolides (racemic) was reported,[6] involving intermolecular chemoselective Wittig olefination as the key step (Figure 2).

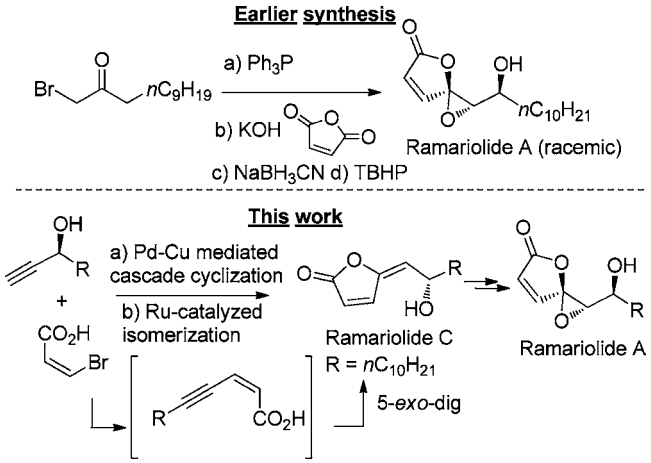
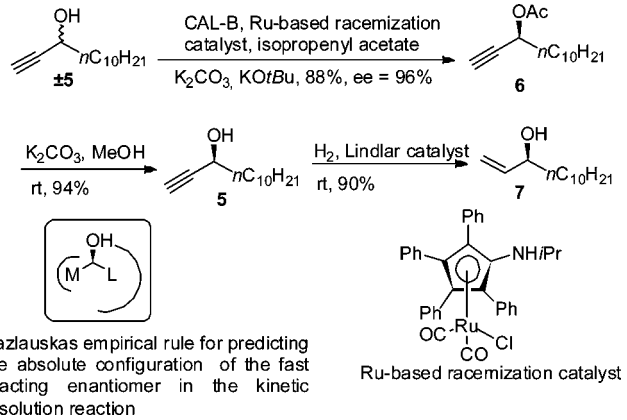


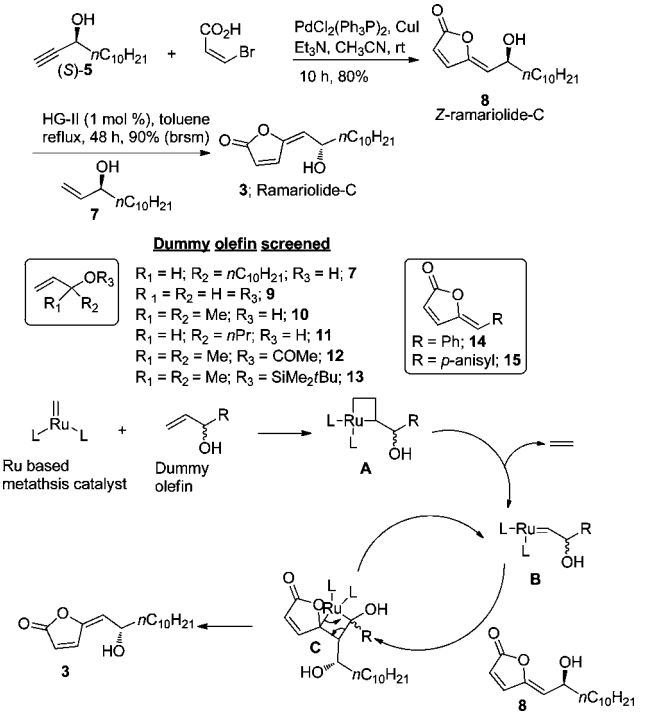

**Figure 2.** Earlier synthesis of racemic ramariolides and proposed plan of action.

Our synthesis was initiated from known racemic alcohol **5**,[7] which was subjected to metal enzyme combined dynamic kinetic resolution (ME-DKR) reaction using CAL-B as the enzyme and the Ru-based racemization catalyst[8] to afford (*S*)-acetate **6** in 88% yield (Scheme 2). Compound **6** after treatment with $K_2CO_3$ in MeOH afforded enantiopure (*S*)-**5** (96% ee). The absolute configuration of (*S*)-**5** was predicted based on the Kazlauskas empirical model.[9] Alkyne **5** on partial hydrogenation with Lindlar catalyst furnished alkene **7** in 90% yield, which was required for our next step. When alkyne (*S*)-**5** was reacted with (*Z*)-3-bromoacrylic acid[10] in the presence of $PdCl_2(Ph_3P)_2$ and CuI in acetonitrile, γ-(*Z*)-butenolide **8** (*Z*-ramariolide C) was obtained in 80% yield as an exclusive product (Scheme 3). The *Z* geometry in **8** was confirmed by NOESY analysis (see the Supporting Information for details). As construction of γ-(*E*)-alkylidenebutenolide present in **3** and **4** remains elusive by the above method, we searched for an alternative method. We speculate that a CM (cross-metathesis) reaction between **8** and a suitable olefinic partner may lead to the thermodynamically less stable **3**, though the chemical yield will be a major issue. The CM reaction of **8** with olefin **7** (generated by partial reduction from alkynol (*S*)-**5**) in the presence of 1 mol % of HG-II (Hoveyda–Grubbs second generation) catalyst[11] in refluxing toluene afforded **3** in 90% yield (brsm; 35% conversion from **8**, overall yield = 59% from racemic **5**). The spectral data of our synthesized **3** ($^1H/^{13}C$ NMR) matches perfectly with those reported.[1]

**Scheme 2. Preparation of Compound 5**




**Scheme 3. Mechanistic Rationale for Unprecedented *Z*–*E* Isomerization for the Synthesis of Ramariolide C**




To further investigate mechanical aspects of this *Z*–*E* isomerization reaction, after exposure of **8** with HG-II catalyst in refluxing toluene for 2 days, only the starting material was recovered, which suggested that the presence of an external olefin (dummy olefin) is necessary. Several olefins (**7**, **9**–**13**) were screened as a dummy olefin for the isomerization reaction, and it was found that successful *Z*–*E* isomerization of **8** to **3** took place in the presence of olefins **7** and **9**–**11**. **3** was always isolated as a major product in the isomerization, which also nullifies the possibility of a CM reaction as anticipated earlier. The presence of a dummy olefin with a free –OH group is essential to enforce the *Z*–*E* isomerization in the presence of HG-II catalyst (in the case of olefins **12** and **13**, isomerization did not occur due to the absence of a free allylic –OH moiety). Starting substrates γ-(*Z*)-butenolides should also contain an allylic –OH moiety for this isomerization, as γ-(*Z*)-butenolides **14** and **15**[4,5c] did not undergo the isomerization in the presence of dummy olefin **7** and HG-II catalyst. A series of Ru-based metathesis catalysts were screened (C1–C7; Scheme 3), and it was found that HG-II worked best in the presence of a dummy olefin (Table 1) containing an allylic alcohol moiety (compounds **7**, **9**–**11**). It was demonstrated earlier that the presence of a free 2° allylic alcohol moiety has a rate-enhancing effect in RCM and CM reactions.[12] The reason for that high activity was not very clear,



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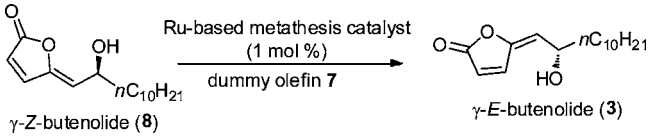
**Table 1. Catalyst Screening for *Z*−*E* Isomerization of γ-Butenolides**




| entry | catalyst[a] | solvent | isolated yield (%)[b] |
|---|---|---|---|
| 1 | G-I (C1) | $CH_2Cl_2$ | <5 |
| 2 | G-I (C1) | toluene | 10 |
| 3 | G-II (C2) | $CH_2Cl_2$ | <5 |
| 4 | G-II (C2) | toluene | 10 |
| 5 | HG-I (C3) | $CH_2Cl_2$ | <5 |
| 6 | HG-II (C4) | $CH_2Cl_2$ | <5 |
| 7 | HG-II (C4) | toluene | 35 |
| 8 | HG-II (C4) | xylene | 20 |
| 9 | Stewart−Grubbs (C5) | toluene | 8 |
| 10 | C6 | toluene | <5 |
| 11 | C7 | toluene | <5 |

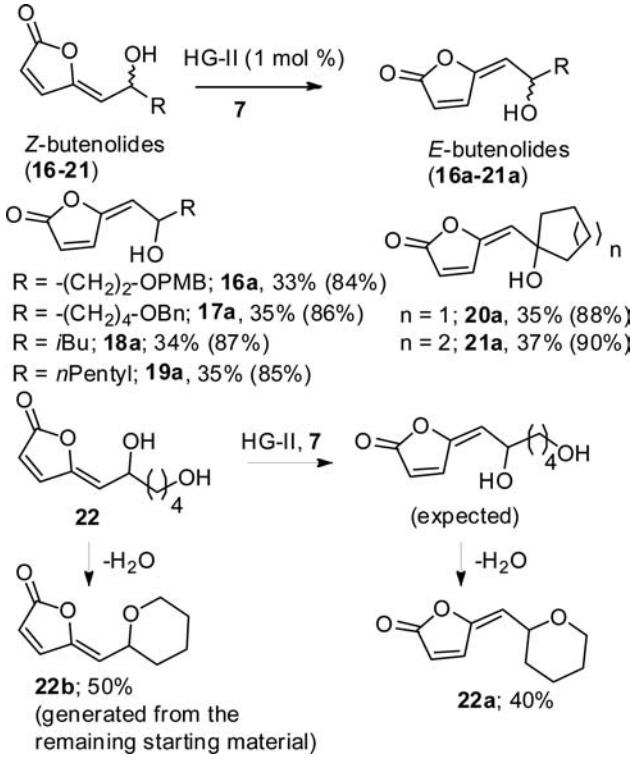
[a]Structures of the catalyst are provided in the SI. [b]Isolated yields after chromatographic separation.

but the possibility of rapid and reversible ligand exchange (alkoxy group replaces the Cl) and hydrogen bonding between a hydroxyl group and one of the chloride ligands cannot be ruled out. The proposed mechanism for this *Z*−*E* isomerization is outlined in Scheme 3, which involves formation of initial metallacyclobutane species A between the dummy olefin and the metathesis catalyst. Expulsion of ethylene from A will then lead to intermediate B, which on reaction with (*Z*)-**8** afforded another metallacyclobutane C, which collapses to generate thermodynamically less stable (*E*)-**3** and B. Thus, the catalytic cycle continues. This further proves that a *Z*−*E* isomerization occurs through an associative and dissociative pathway with a Ru-based metathesis catalyst. Note that **8** is very stable and never isomerized to its *E* counterpart (without the catalyst and dummy olefin). On the contrary, upon exposure of pure **3** in the presence of HG-II catalyst (1 mol %) and dummy olefin **7**, formation of a substantial amount of thermodynamically more stable *Z*-isomer **8** was detected. This also confirms the reversible nature of this isomerization process (Scheme 3). All attempts to increase the conversion % of **8** to **3** by changing the catalyst loading and using high boiling solvent (entry 8, Table 1) were not successful.

To explore the synthetic utility of such a thermal isomerization reaction, we synthesized a few γ-(*Z*)-butenolides (**16**−**22**; see the SI for details). These compounds were subjected to the above reaction in the presence of HG-II and olefin **7** (as a dummy olefin) under similar reaction conditions. We found that in all cases corresponding γ-(*E*)-butenolides (**16a**−**21a** and **22a**) were obtained from corresponding γ-(*Z*)-butenolides (**16**−**22**) in substantial amounts (Scheme 4). Eventually, 30−40% conversion was observed and starting γ-(*Z*)-butenolides were separated from γ-(*E*)-butenolides through chromatographic separation. In Scheme 4, subsequent conversion and isolated yields (provided in the parentheses; brsm) were provided for all compounds. Although the conversion of *Z* to *E* isomer is lower, no other side product formed under the reaction conditions and the reaction is very high yielding (based on recovery of starting material).

Though allylic double bond isomerization through migration (double bond shifting) was explored with the help of a Ru-based

**Scheme 4. Substrate Scope for the *Z*−*E* Isomerization for the Synthesis of γ-(*E*)-Butenolides from γ-(*Z*)-Butenolides[a]**




[a]Numbers before parentheses are isolated yield, and the numbers in the parentheses denote yield based on starting material recovery (brsm).

metathesis catalyst,[13] such unfavorable *Z*−*E* isomerization remains unexplored. By considering the importance of several naturally occurring γ-butenolides[14] in medicinal chemistry, we do believe that such adventitious *Z*−*E* isomerization reactions can serve as a potential route for the synthesis of enantiopure γ-(*E*)-butenolide scaffolds. A detailed literature search also reveals that such a reliable and efficient synthetic protocol of γ-(*E*)-butenolides is virtually unknown. So the reported method of accessing such an important molecular framework through Ru-catalyzed thermal isomerization is of significant importance. The only potential limitation is that the substrate and the dummy olefin must bear a free allylic −OH group, which facilitates the smooth *Z*−*E* isomerization. In the case of diol **22** (which is exclusively *Z* at the beginning), after 40% conversion (after the isomerization), cyclic products **22b** (from *Z*-diol) and **22a** (from *E*-diol) were isolated as major products, which originated from dehydrative cyclization (Scheme 4). The structures of all γ-(*E*)-butenolides (**16a**−**21a** and **22a**) were confirmed by $^1$H NMR analysis and 2D-NOESY analysis (in all cases, the C3 proton for (*E*)-butenolide appeared at a reasonably downfield region compared to its *Z* counterpart[4a]).

With enantiopure **3** in hand, we proceeded to the total synthesis of **1**. The free hydroxyl group was protected as its corresponding TBS ether **23** (in 85% yield), which upon epoxidation with *m*CPBA through a steric control approach[15] furnished epoxide **24** as a sole product in 78% yield. Desilylation of **24** with HF-pyridine[16] afforded **1** in excellent yield (34% overall yield from racemic **5**). Spectral data (NMR and optical rotation) of synthesized **1** are in good agreement with those of the natural one.[1] Several stereoisomers of ramariolide A (**25**, **26**,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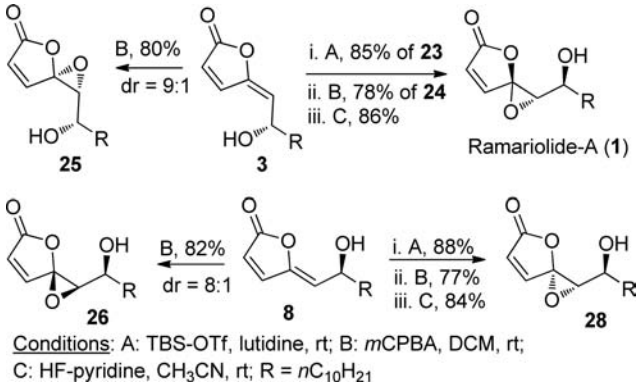
and **28**) was also synthesized starting from **3** and **8** by substrate-directed epoxidation, as presented in Scheme 5. The synthetic

**Scheme 5. Completion of the Synthesis of Ramariolide A and Its Stereoisomers**




steps outlined in Scheme 5 should also constitute a formal synthesis of oxetane-based **2**, as exposure of ramariolide A with (±)-CSA afforded the target as recently reported,[6] albeit in relatively lower yield.

In conclusion, asymmetric total synthesis of naturally occurring γ-(*E*)-butenolides **1** and **3** was accomplished by adopting a linear strategy for the first time. ME-DKR and Pd−Cu-mediated cascade cyclization was employed to construct the core butenolide framework. Finally, an unprecedented *Z*−*E* isomerization with a HG-II catalyst and substrate-directed epoxidation was enforced to complete the total synthesis in a short and elegant way. The synthetic strategy delineated here can be regarded as protection-group-free, as the synthesis of ramariolides C (**3** and **8**) and stereoisomers of ramariolide A (**25** and **26**) does not require any protecting group in the overall synthetic pathway.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00202.

Full experimental details, spectral data, and HPLC chromatogram (PDF)

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### Notes

The authors declare no competing financial interest.

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