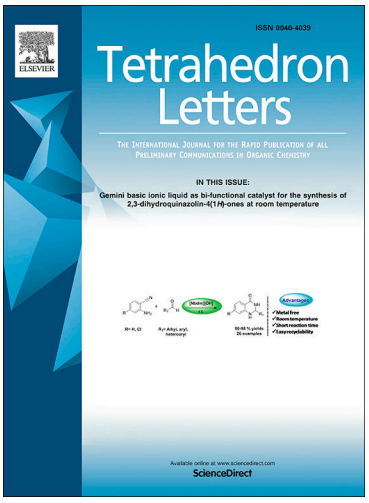

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Total Synthesis of Enhygrolide A and analogs

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Keywords: alkylidene butenolides, natural product, cross-coupling, total synthesis

Abstract: The total synthesis of enhygrolide A, a γ-alkylidene butenolide natural product which exhibits antibacterial activities, is reported. The synthetic route features several key transformations, including a copper mediated Sonogashira/oxacyclization 5-*exo*-dig process to generate the alkylidene butenolide system and a Suzuki cross-coupling to introduce the benzylic unit. The methodology employed for this total synthesis represents a sufficiently flexible route to allow the synthesis of numerous analogs of these enhygrolides.

Introduction

Based on the literature of the last thirty years, γ-alkylidene butenolides are important structures in the areas of heterocyclic chemistry and natural lactones.[1] Because this planar oxygenated heterocycle constitutes the skeleton of many natural products, various strategies have been developed to prepare these γ-lactones with wide diversity on the α, β and γ positions.[2] Representative examples of natural compounds include aspergon isolated from a marine sponge,[3] aruncin B extracted from a variety of the plant *Aruncuns dioicus*,[4] maculalactone B and the nostoclides identified as metabolites of two different cyanobacteria (Fig. 1).[5,6]

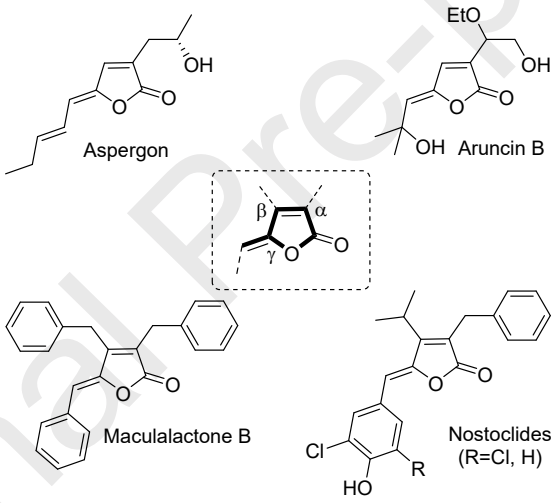
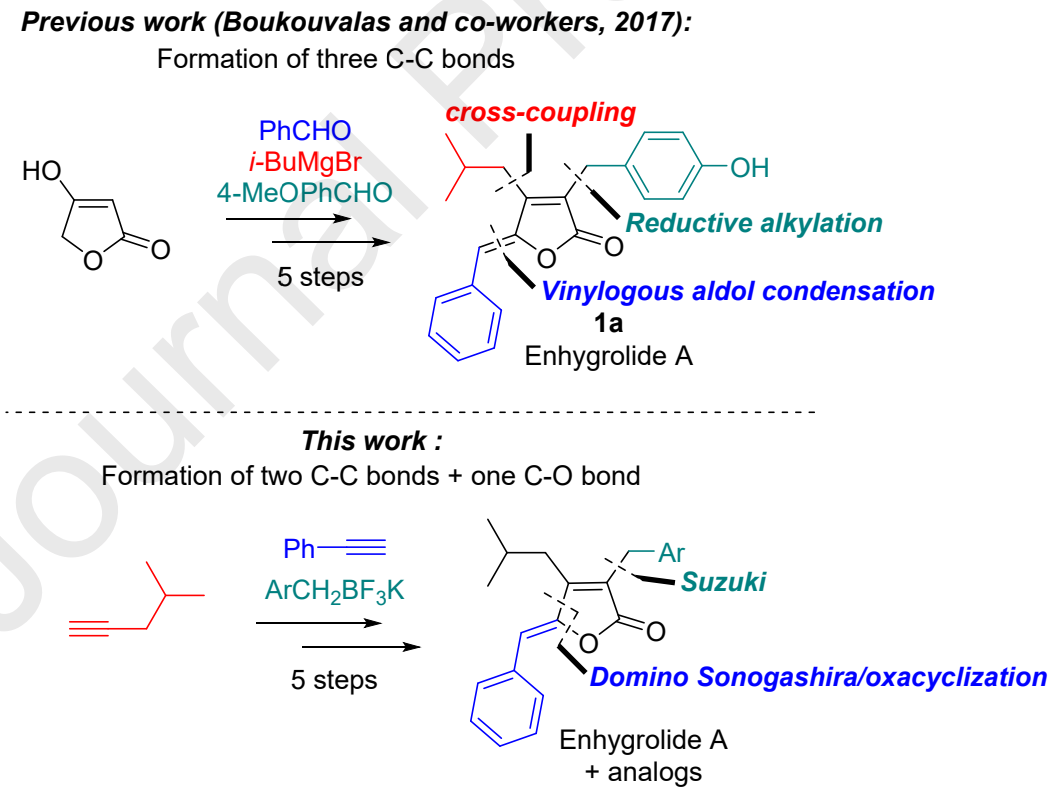


Figure 1. Selected natural compounds containing the γ-alkylidene butenolide core.

Among them, enhygrolide A **1a**, a structure close to the nostoclides, was found to inhibit the growth of the Gram-positive bacterium *Arthobacter crystallopoietes* with an MIC of 4 μg/mL. This metabolite was isolated by König and co-workers from the marine myxobacterium *Enhygromyxa salina* in 2013.[7] Four years later, Boukouvalas and co-workers published the first synthesis of **1a** using tetronic acid as the starting material.[8] In this elegant five-step sequence, the

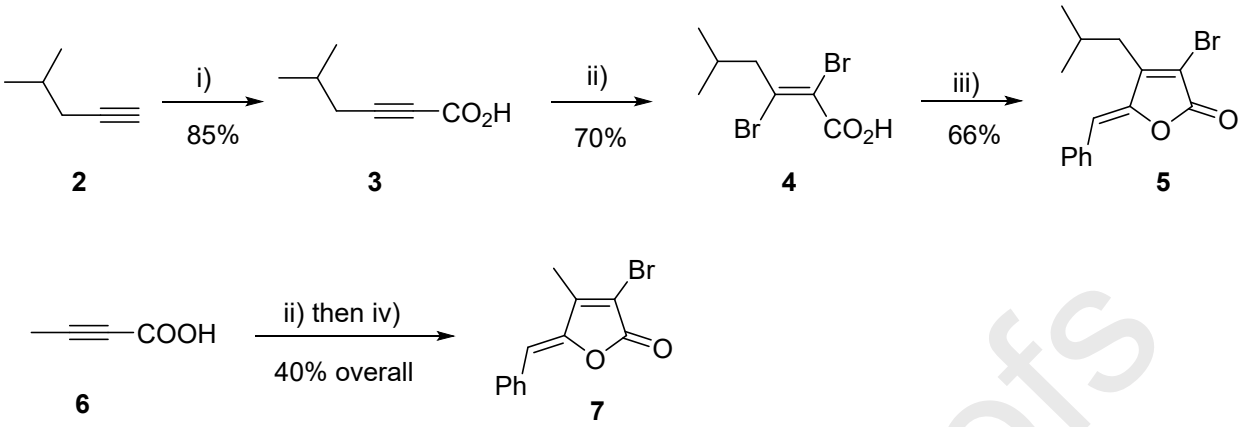
α, β and γ substituents of the lactone ring were respectively introduced *via* a reductive alkylation of an aldehyde, an iron-catalyzed cross-coupling reaction with a Grignard reagent, and a vinylogous aldol condensation with another aldehyde. To the best of our knowledge, no other synthesis of **1a** has been reported in the literature until now. In the current context of bacteria resistance to antibiotics, new antibacterial compounds such as **1a** have a potential interest in this field of research.[9] Herein, we report a five step-synthesis of enhydrolide A **1a** and analogs on the α and β position of the lactone, using 4-methylpent-1-yne **2** as the starting material. This approach relies on a strategy previously developed in our group, based on a regioselective domino Sonogashira/oxacyclization 5-*exo*-dig process[2i, 10] followed by a Suzuki-Miyaura cross-coupling, which has already been used as a key-step for the total synthesis of the nostoclides (Scheme 1).[2j]



Scheme 1. Approaches for the preparation of enhygrolide A **1a**.

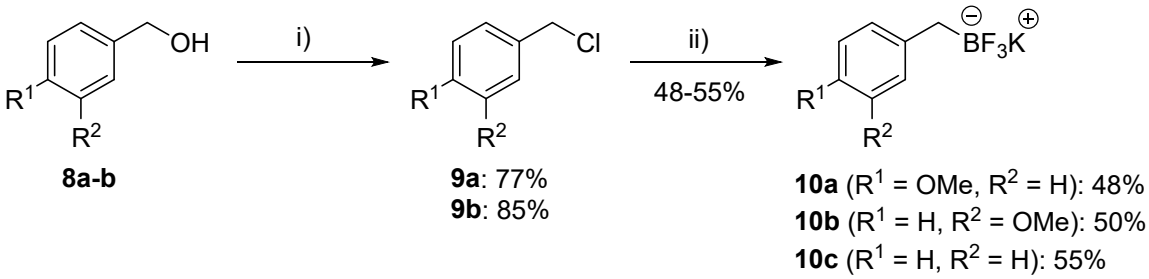
Results and Discussion

First, the α-brominated butenolide **5** was prepared according to the sequence described in Scheme 2. Briefly, the sequence started with commercially available **2** which was transformed into the corresponding ynoic acid **3** using a stoichiometric amount of a freshly prepared solution of EtMgBr in THF, followed by bubbling carbon dioxide into the reaction mixture. The dibromination of **3** was performed in the presence of bromine in methanol according to a reported method[11] and afforded **4** with good yield and excellent stereoselectivity in favor of the (*E*)- isomer. Finally, **5** was obtained through a domino reaction involving a regioselective copper(I) promoted Sonogashira-like cross-coupling between **4** and phenylacetylene, followed by a 5-*exo*-dig cyclization. It is noteworthy that the reaction conditions (stoichiometric amount of copper iodide and diisopropylamine) were modified compared to those described in the original paper (catalytic amount of copper iodide and potassium carbonate),[2i] in order to obtain **5** with a satisfactory yield of 66%. With the aim of preparing analogs in the β-position, we also performed the last two steps of this sequence starting from commercially available 2-butynoic acid **6**, which afford the α-brominated butenolide **7** with an overall yield of 40% (see ESI for details).



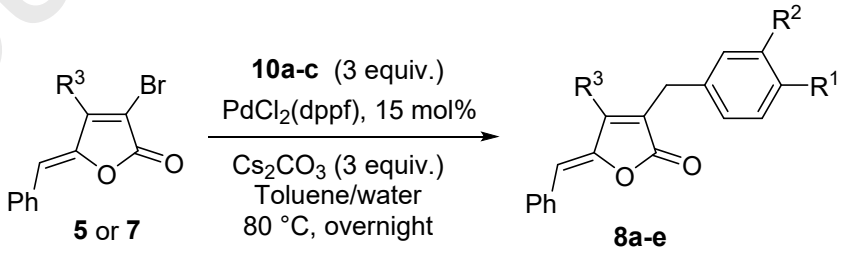
Scheme 2. Synthesis of **5** and **7**. Reagents and conditions: i) EtMgBr in THF (1M, 1 equiv.), THF, −10 °C to reflux, 1 h then CO_2 (gas), −10 °C; ii) Br_2 (2 equiv.), MeOH, −10 °C, 40 minutes; iii) phenylacetylene (2 equiv.), CuI (1 equiv.), *i*Pr_2NH (DMF, 80 °C, overnight; iv) phenylacetylene (2 equiv.), CuI (0.2 equiv.), K_2CO_3 (2 equiv.), DMF, 50 °C, overnight

We envisaged introducing the benzylic subunit on the α-position through a Suzuki-Miyaura coupling with various potassium benzyltrifluoroborates **10a-c**. Indeed, these stable and easy to handle boronate salts were found to be better coupling partners than boronic acids.[2j] Benzyltrifluoroborates **10a-b** were therefore prepared through a two-step procedure starting from the corresponding benzylic alcohols **8a-b**. Classical chlorination of **8a-b** in the presence of thionyl chloride afforded the corresponding benzylic chloride **9a-b** (benzyl chloride **9c** is commercially available). These benzylic chlorides were transformed into their corresponding Grignard reagents and **10a-c** were prepared according to a modified literature procedure (Scheme 3).[12]



Scheme 3. Synthesis of **5** and **7**. Reagents and conditions: i) $SOCl_2$ (1.5 equiv.), CH_2Cl_2, 0 ° to rt., overnight ; ii) Mg (1 equiv.), Et_2O, reflux, then $B(OMe)_3$ (1.5 equiv.), THF, −78 °C to rt., 2 h, then KHF_2 (6 equiv.), H_2O, 0 °C, 1 h.

The Suzuki-Miyaura cross-coupling reaction was performed between **5** or **7** and **10a-c**, in presence of $PdCl_2$(dppf) as the catalyst and cesium carbonate as the base (Table 1). Compounds **8a-e** were therefore obtained in average to good yields. Among them, deoxyenhygrolide A **8c**, a natural analog of enhygrolide A,[13] was obtained in 66% yield.



Entry	α-Bromolactone	Benzyltrifluoroborate	Product	Yield

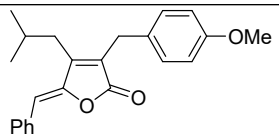
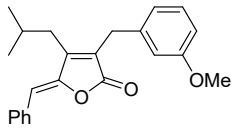
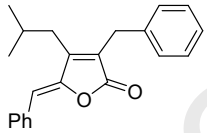
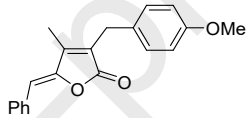
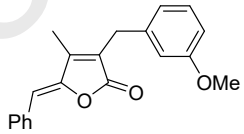
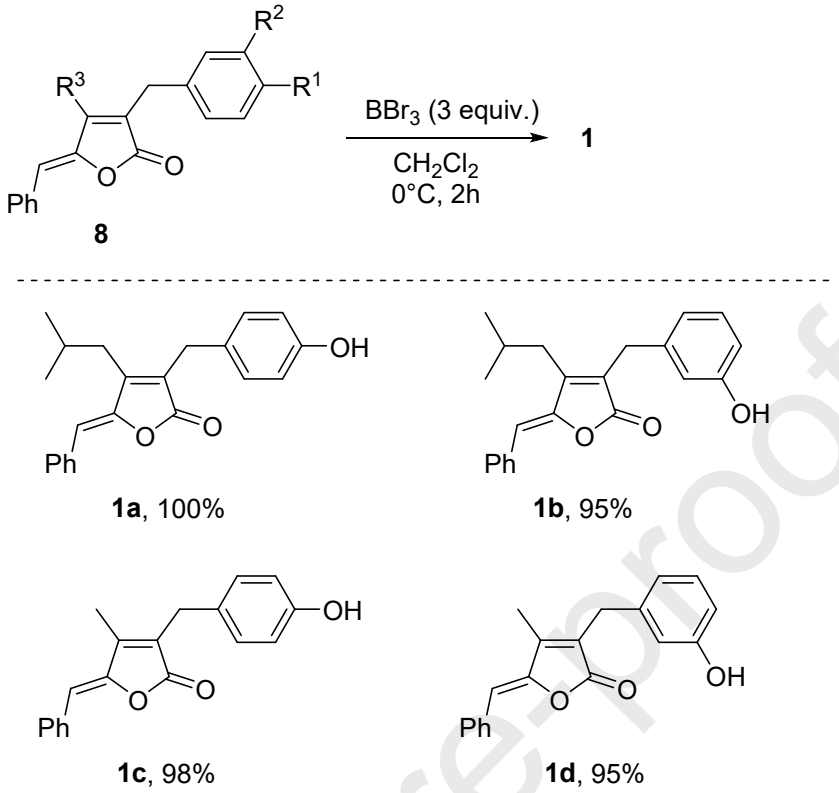
1	**7**	**10a**	 **8a**	44%
2	**7**	**10b**	 **8b**	47%
3	**7**	**10c**	 **8c**	66%
4	**5**	**10a**	 **8d**	41%
5	**5**	**10b**	 **8e**	32%

Table 1. Suzuki-Miyaura cross-coupling reaction between **5**, **7** and **10a-c**.

Demethylation of the aromatic methyl ether of compounds **8** was finally performed in the presence of BBr_3 to achieve the total synthesis of enhygrolide A **1a** and three others analogs **1b-d**, in excellent to quantitative yields.



Scheme 4. Demethylation of compounds **8**.

Conclusion

In this study, we have developed a new route for the preparation of enhygrolide A **1a** in five steps starting from 4-methylpent-1-yne **2** (overall yield = 17%). This synthetic pathway was also exploited to synthesize three new analogs **1b-d** and the natural deoxyenhygrolide A **8c** as new potential antimicrobial agents.

Acknowledgements

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Appendix A: Supplementary data

Supplementary data to this article can be found online at http://

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Highlights

- A concise total synthesis of a natural γ-alkylidene butenolide: the enhygrolide A.
- Sonogashira/oxacyclization copper(I)-mediated reaction to generate the lactone ring.
- Benzylic subunit was introduced *via* a Suzuki-Miyaura coupling.
- Four analogs including the natural deoxyenhygrolide A were synthesized.