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Total synthesis of a novel oxa-bowl natural product paracaseolide A via a 'putative' biomimetic pathway

Laxmaiah Vasamsetty [a], Faiz Ahmed Khan [a,*], Goverdhan Mehta [b,*]

[a] Department of Chemistry, Indian Institute of Technology, Hyderabad 502 205, India
[b] School of Chemistry, University of Hyderabad, Hyderabad 500 046, India

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ABSTRACT

A total synthesis of bioactive tetracyclic natural product paracaseolide A, embodying an architecturally unusual oxa-bowl framework, has been accomplished from commercially available 5-methyl-2-furfural. The key step involving a thermal [4+2]-dimerization of an appropriately crafted 5-methyl-3-alkenylbutenolide is shown to proceed in a stepwise manner.

In 2011, Guo and co-workers reported[1] the isolation and structure determination of a novel natural product, paracaseolide A **1** from the stem bark of *Sonneratia paracaseolaris,* an endemic mangrove species found in China. In structural terms, tetracyclic **1** is an unusual construct that features oxa-bowl architecture and embodies a 3-alkenylbutenolide substructure reminiscent of many bioactive natural products.[2] The five oxygen atoms present in **1** essentially dot the rim of its bowl-like framework and the additional presence of two long linear hydrophobic chains on its convex surface imparts the natural product a dipolarofacial character. Indeed, **1** can be formally derived through a [4+2]-type dimerization of a 3-alkenylbutenolide precursor **2**.

Paracaseolide **1** has been shown to exhibit impressive inhibitory activity against dual-specificity phosphatase CDC25B with an IC_{50} value of 6.44 μM. This is a potentially significant bioactivity attribute as CDC25B is a proto-oncogene in humans and shown to be over expressed in a number of cancers and is implicated in cell cycle progression in tumors.[3]

Both, on account of its complex and unusual molecular structure and its bioactivity profile, natural product **1** presents a challenging and interesting target for total synthesis. We were instantly drawn to a synthesis of **1** in view of our long standing interest in the oxa-bowl like constructs.[4] While our own efforts towards **1** were underway, two total syntheses of **1** from the groups of Vassilikogiannakis[5] and Kraus[6] have appeared in the very recent past. Herein we report a total synthesis of **1**, essentially along the proposed biosynthetic route[1,5] involving the [4+2]-dimerization of a butenolide precursor **2**. Such a biomimetically patterned approach to **1** involving the [4+2]-dimerization was successfully implemented in the first synthesis of the natural product by Noutsias and Vassilikogiannakis[5] However, our access to the key precursor **2** is shorter, well differentiated and the outcome of the dimerization protocol is somewhat different, which in turn sheds some light on the nature of the [4+2]-type dimerization leading to the natural product.

In our quest for **1**, we initially carried out a model study in which a sibling 3-alkenylbutenolide **3** was deployed to probe the key dimerization process. Commercially available furfural **4** was elaborated to butenolide **5** via a known[7] protocol involving dye sensitized photo-oxygenation as the key step, Scheme 1. Bromine addition[8] to **5** and in situ dehydrobromination led to 3-bromo-butenolide **6**. Pd-mediated Suzuki cross-coupling[9] between **6** and vinylic boronate **7** delivered 3-alkenylbutenolide **8** and further 5-methoxy deprotection[10] led to the requisite 3-alkenylbutenolide **3**.[11] Heating (neat, sealed tube, 100 °C) **3** triggered the tandem [4+2]-type dimerization and concomitant dehydration to furnish a mixture (40:60) of two diastereomeric dimers **9** and **10** in 52% isolated yield. Stereo-structures of **9** and **10** were derived through incisive analyses of their 2D NMR (COSY, HMBC and ROESY) studies and the key connectivities are displayed in Figure 1. In addition, structure of one of the diastereomers **10** was further verified by a single crystal X-ray structure determination and an ORTEP[12] is

* Corresponding authors. Tel.: +91 40 23016084 (F.A.K.); tel.: +91 40 23134848; fax: +91 40 23010785 (G.M.).
E-mail addresses: faiz@iith.ac.in (F.A. Khan), gmehta43@gmail.com (G. Mehta).

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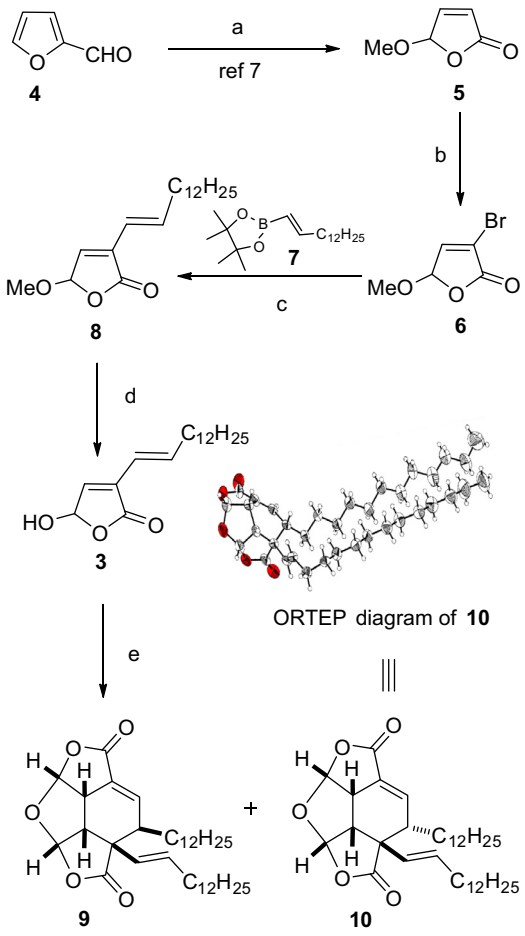


Scheme 1. Reagents and conditions: (a) (i) $^1O_2$, MeOH; (ii) MeOH, reflux, 3 d; (b) 1.2 equiv Br_2, 0.08 equiv PBr_3, CCl_4, 0 °C to rt, 12 h; py, 0 °C to rt, 4 h, 65%; (c) 1.5 equiv **7**, 3 mol % $PdCl_2$dppf, 4 equiv CsF, 1 equiv TBAB, THF/H_2O (4:1), μW, 100 °C, 4 min, 41%; (d) TFA/acetone/H_2O (1:1:1), 0 °C to rt, 2 h, 59%; (e) neat, sealed tube, 100 °C, 14.5 h, 52% (9:10 = 2:3).

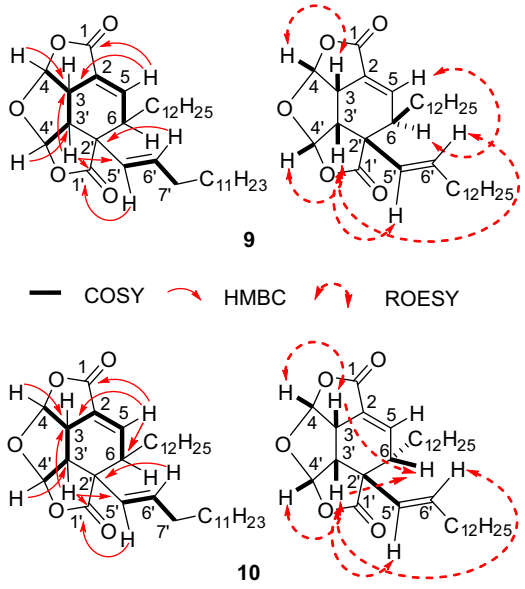
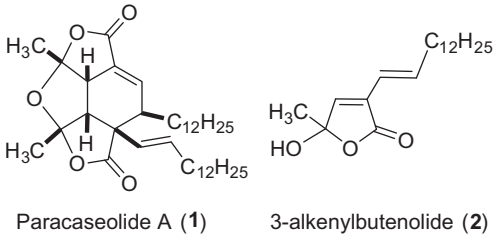
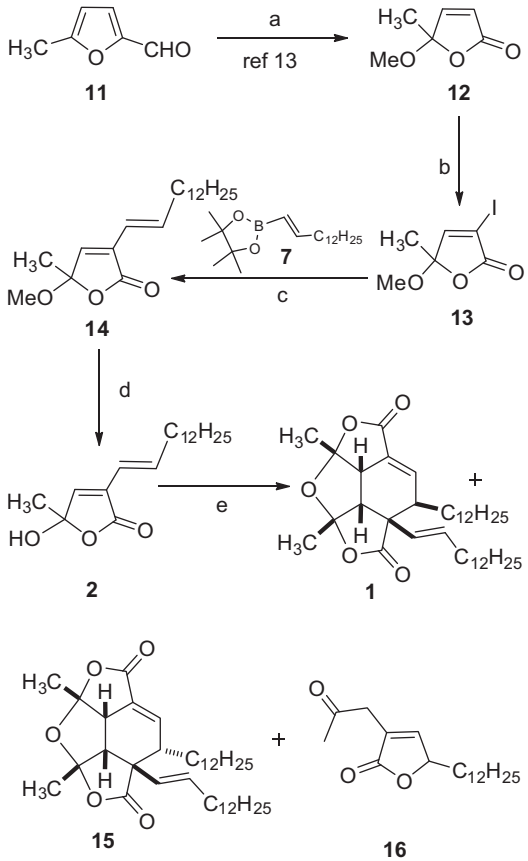


Figure 1. Key HMBC, COSY and ROESY connectivities of compound **9** and **10**.

shown in Scheme 1. Interestingly, in **9** both the alkenyl and the alkyl hydrophobic chains are *cis* disposed and located on the convex surface as present in the natural product **1**, but in the diastereomer **10** the two chains are *trans* with the alkyl chain protruding towards the cavity of the oxa-bowl. In separate experiments, it was shown that under the conditions of thermal activation employed to effect dimerization, both **9** and **10** were stable and did not interconvert. This clearly established that **9** and **10** were independently produced during the [4+2]-dimerization protocol.



Having demonstrated the viability of the 3-alkenylbutenolide dimerization in **3**, it was decided to extend the protocol to 5-methyl-3-alkenylbutenolide **2** to target the natural product **1**. Towards this end, 5-methyl-2-furfural **11** was photooxygenated[13] to 5-methylbutenolide **12** (Scheme 2). Single pot iodination-dehydroiodination in **12** led to 5-methyl-3-iodobutenolide **13**. Pd-medi-



Scheme 2. Synthesis of diastereomeric dimers paracaseolide A (**1**), **15** and **16**. Reagents and conditions: (a) $^1O_2$, MeOH; (b) 4 equiv I_2, py/CCl_4 (1:1), 0 °C to rt, 24 h, 50%; (c) 1.5 equiv **7**, 3 mol % $PdCl_2$dppf, 4 equiv CsF, 1 equiv TBAB, THF/H_2O (4:1), μW, 120 °C, 40 min, 60%; (d) TFA/acetone/H_2O (1:1:1), 0 °C to rt, 13 h, 82%; (e) neat, sealed tube, 110 °C, 12 h, 66% (**1**:**15**:**16** = 4.9:1:2.4).