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Structure Revision and Synthesis of a Novel Labdane Diterpenoid from *Zingiber ottensii*

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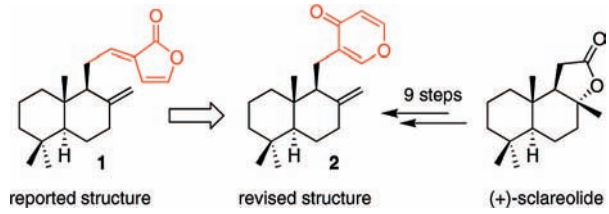
ABSTRACT



The structure of ottensinin, a recently reported constituent of the medicinal plant *Zingiber ottensii*, was revised by re-evaluation of available NMR data from α-ylidenebutenolide 1 to γ-pyrone 2, whose rearranged labdane skeleton is unprecedented. Structure 2 was proven by synthesis from (+)-sclareolide (nine steps, 27% overall yield) and was further validated by X-ray diffraction analysis of our synthetic sample. A plausible biosynthesis of 2 is proposed.

Small molecule natural products continue to provide an unparalleled source of inspiration for advances in organic chemistry and disease treatment.[1] In 2006, Kikuzaki and co-workers reported the isolation of a new $C_{20}H_{28}O_2$ diterpenoid, that we now name ottensinin, from the rhizome of *Zingiber ottensii* Val. (Zingiberaceae).[2] This plant, known in Malaysia as "lempoyang hitam", is reputed to possess sedative properties, and its rhizome has long been used in traditional medicine for treating convulsions and lumbago.[3] Ottensinin was assigned structure **1** (Figure 1) on the basis of extensive spectroscopic studies using 1D and 2D NMR, IR and HREIMS.[2]

Recently, we reported the synthesis of **1** along with evidence that the purported structure of ottensinin is incorrect.[4] In particular, we noted that while the NMR data of the decalin core of **1** were fairly close to those of ottensinin, a significant departure in both the ^{1}H and ^{13}C chemical shifts was apparent for the C11−16 region.[4] Nonetheless, the actual structure of the natural product remained an unsolved mystery.[5]

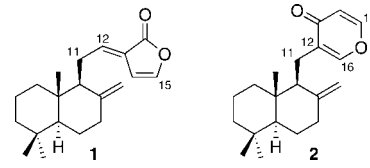


Figure 1. Originally proposed and revised structure of ottensinin.

Our interest in solving this puzzle was piqued by the presence of two distinctly downfield protons (δ 7.52 and

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(2) Akiyama, K.; Kikuzaki, H.; Aoki, T.; Okuda, A.; Lajis, N. H.; Nakatani, N. *J. Nat. Prod.* **2006**, *69*, 1637.

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(5) (a) For an excellent review on missasigned natural product structures, see: Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012. (b) For an unusual case involving misassignment of a natural product structure by total synthesis, see: Boukouvalas, J.; Pouliot, M.; Robichaud, J.; MacNeil, S.; Snieckus, V. *Org. Lett.* **2006**, *8*, 3597.

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7.67), originally assigned as C12-H and C14-H of **1**.[2] These signals are not only inconsonant with an α-alkylidene-butenolide, whose protons absorb below 7 ppm,[4,6] but also with various relatives thereof including γ-ylidenebutenolides[7] and 2-ylidenefuran-3-ones.[8] Careful analysis of available NMR data for this triad[6–8] suggested that each of the two downfield protons is probably attached to a β-carbon atom of an oxygenated enone (cf. O−CH═C−C═O). Accordingly, we reformulated ottensinin as a β-substituted γ-pyrone (**2**, Figure 1). A literature search established that there are no known terpenoids containing a monosubstituted γ-pyrone moiety. In fact, only two compounds were found to share substructure **3**; the fungal metabolite xylaric acid (L-741,494; **4**), which is also a selective and irreversible inhibitor of interleukin-1β converting enzyme (ICE),[9] and its congener **5** (Figure 2).[10] Significantly, the ^{1}H and ^{13}C NMR data of

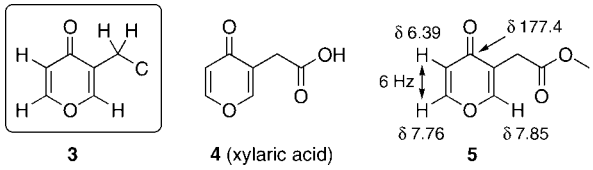


Figure 2. Known compounds with substructure **3**.

the γ-pyrone ring of **5**[10] were consistent with those of ottensinin's C12−16 fragment,[2] aside from the expected variation in the chemical shifts of the substituted β-carbon and the adjacent α-proton.

At this point, we assumed that **2** represented the true structure of ottensinin and sought to prove this by the synthesis of compound **2**. Since none of the existing γ-pyrone syntheses[11] were deemed suitable for the task at hand, we designed a new approach based on the retrosynthetic analysis shown in Figure 3. We envisioned regiodefined access to the β-alkyl-γ-pyrone structure **A** by *6-endo-dig* cyclization[12,13] of enolate-ynone **B**, which would in turn arise by Claisen formylation of ynone **C**.

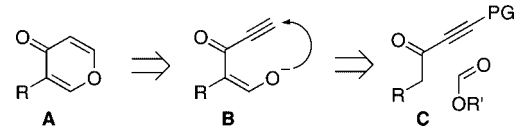
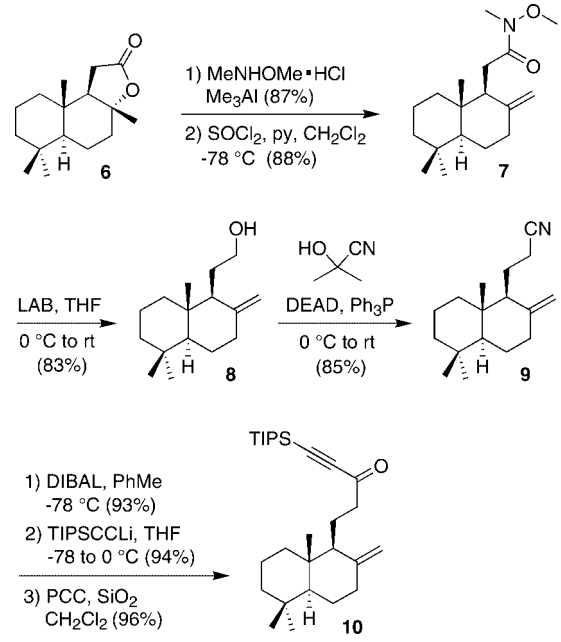


Figure 3. Plan for regiodefined access to β-alkyl-γ-pyrones.

The synthesis began with the two-step conversion of commercially available (+)-sclareolide (**6**) to Weinreb amide **7** according to recently established methodology[14] (Scheme 1). In contrast to α-oxygenated Weinreb amides, which

Scheme 1. Synthesis of Ynone **10**



undergo smooth reduction with $NaBH_4$/MeOH,[15] **7** proved unresponsive to these conditions and was fully recovered. The desired reduction was ultimately achieved by recourse to Meyer's in situ generated lithium amidotrihydroborate (LiH_2NBH_3, LAB)[16] to afford alcohol **8** in 83% yield.

Submission of **8** to the Mitsunobu−Wilk procedure[17] led to one-carbon chain extension to furnish nitrile **9** in high yield (85%).[18] We had hoped to transform **9** directly to ynone **10** by addition of TIPSCCLi, but after several unavailing attempts, which included the use of Lewis acids such as

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(10) Edwards, R. L.; Maitland, D. J.; Pittayakhajonwut, P.; Whalley, A. J. S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1296.
(11) See for example: (a) Li, C.-S.; Lacasse, E. *Tetrahedron Lett.* **2002**, *43*, 3565. (b) Kamino, T.; Kuramochi, K.; Kobayashi, S. *Tetrahedron Lett.* **2003**, *44*, 7349. (c) Crimmins, M. T.; Washburn, D. G.; Zawacki, F. J. *Org. Synth.* **2004**, *10*, 355. (d) Luo, S.; Mi, X.; Xu, H.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2004**, *69*, 8413. (e) Hobuss, D.; Laschat, S.; Baro, A. *Synlett* **2005**, 123. (f) Sibi, M. P.; Zimmerman, J. *J. Am. Chem. Soc.* **2006**, *128*, 13346. (g) Clawson, R. W., Jr.; Söderberg, B. C. G. *Tetrahedron Lett.* **2007**, *48*, 6019. (h) Yan, Y.-L.; Cohen, S. M. *Org. Lett.* **2007**, *9*, 2517.
(12) For the use of *6-endo-dig* cyclization in chromone synthesis, see: (a) Tietze, L. F.; Singidi, R. R.; Gericke, K. M. *Org. Lett.* **2006**, *8*, 5873. (b) Macklin, T. K.; Panteleev, J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2008**, *47*, 2097.
(13) Zhu, J.; Porco, J. A., Jr. *Org. Lett.* **2006**, *8*, 5169.
(14) Boukouvalas, J.; Wang, J.-X.; Marion, O.; Ndzi, B. *J. Org. Chem.* **2006**, *71*, 6670.
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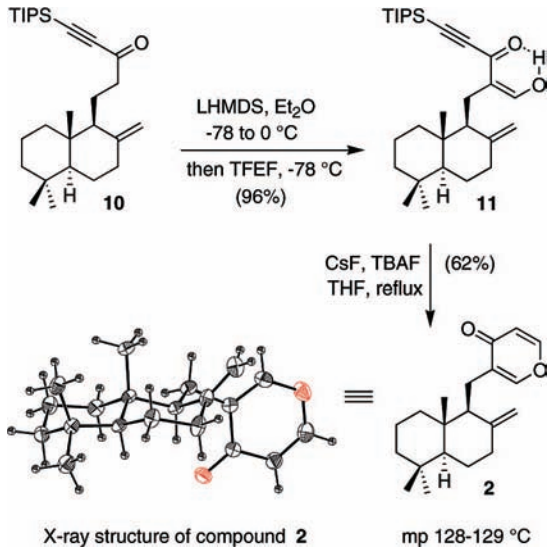
BF_3•Et_2O,[19,20] we settled for a more conventional but reliable sequence involving DIBAL reduction to the aldehyde, acetylide addition and oxidation of the resulting alcohol epimers (84% yield over three steps, Scheme 1).

With supplies of **10** in hand, attention was turned to the Claisen reaction. Initial attempts to install the formyl group under classical equilibrating conditions[21] (e.g., HCOOEt/NaOEt) led to complex mixtures containing only traces of the desired product. Much to our delight, however, it was discovered that modification of Zayia's procedure[22] provided a highly effective solution. Thus, sequential treatment of **10** with LHMDS and 2,2,2-trifluoroethyl formate (TFEF) at −78 °C delivered enol **11** as a single isomer in nearly quantitative yield (Scheme 2).

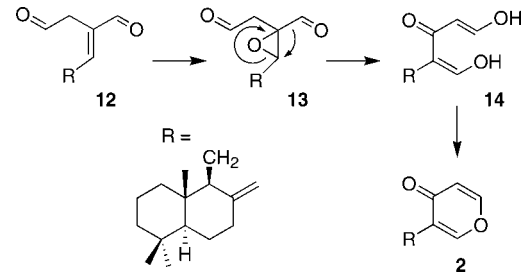
Scheme 2. Construction of the γ-Pyrone Ring



Heating **11** with a mixture of CsF and TBAF in THF accomplished both desilylation and cyclization to afford pyrone **2** in an unoptimized yield of 62%. Unlike naturally derived ottensinin, which was obtained as an oil,[2,23] compound **2** was highly crystalline, thereby allowing its structure to be confirmed by X-ray diffraction analysis (Scheme 2). The ^1H and ^{13}C NMR and IR spectra of **2** were indistinguishable from those of natural ottensinin, and the specific rotation values ($[\alpha]^{24}_D$ +31.3, *c* 0.42, $CHCl_3$ [lit.[2] $[\alpha]^{25}_D$ +21.4, *c* 0.17, $CHCl_3$)] were the same in sign and reasonably close in magnitude.[23] It is therefore beyond doubt that **2** depicts the correct structure of ottensinin, including absolute stereochemistry.

Notwithstanding over 5000 known labdane natural products,[24] the rearranged carbon skeleton of **2** is unprecedented. Biosynthetically, it is conceivable that **2** arises from the 20-fold more abundant co-metabolite labdienedial (**12**)[2,25] by means of oxidation, epoxide rearrangement with concomitant 1,2-formyl migration,[26] and dehydrative cyclization (Scheme 3).

Scheme 3. Postulated Biogenesis of Ottensinin



Besides corroborating the revised structure of ottensinin, the foregoing synthesis of **2** from (+)-sclareolide (nine steps, 27% overall yield) unveils new methodology for γ-pyrone construction that should allow access to other members of this class, including the ICE inhibitor xylaric acid (**4**)[9] and related natural products of biomedical importance.[27] Such applications along with studies aimed at establishing a biomimetic approach, based on the putative biogenesis of **2** from **12**, are currently underway.

Acknowledgment. We thank NSERC of Canada for financial support and Professor Hiroe Kikuzaki (Osaka City University) for the NMR and IR spectra of natural ottensinin.

Supporting Information Available: Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Traces of other compounds, including acetone, could be detected in the NMR and IR spectra of the natural product, kindly provided to us by Prof. Hiroe Kikuzaki; see the Supporting Information for details.

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