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Expedient synthesis of villosin and its isomer (*E*)-labda-8(17),12,14-trien-15(16)-olide

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Abstract—The synthesis of the title compounds has been achieved in concise, highly regiocontrolled fashion from commercially available (+)-sclareolide. In addition, we offer evidence that the structure of a newly reported natural product from *Zingiber ottensii* is incorrect.

Villosin (**1**) is a labdane diterpenoid originally obtained from *Hedychium coronarium* (Zingiberaceae),[1a] a medicinal plant used in many countries for treating ailments such as headache, fever, and rheumatism.[2] Subsequently, the same compound was isolated from the related herbs *Hedychium villosum* (hence the name villosin)[1b] and *Hedychium forrestii*.[1c] There is strong evidence that the anti-inflammatory properties of these natural medicines stem from the suppressive effects of their diterpene constituents on vascular permeability and/or NO production.[2a] In addition, the labdanes extracted from *H. coronarium* have attracted much attention due to other potentially useful biological properties, including antitumor and antiallergic activities.[2b,c]

A notable structural feature of **1** is the (*E*)-3-(1-alkenyl)-2(5*H*)-furanone unit, which is encountered in a rapidly expanding group of natural products[3] and bioactive derivatives,[4] that also includes hedyforrestin *B* (**2**)[5] and saponaceolide *G* (**4**, Fig. 1).[6] Recently, the villosin isomer (*E*)-labda-8(17),12,14-trien-15(16)-olide (**3**),[7] featuring a less common (*E*)-3-alkylidene-2(3*H*)-furanone moiety,[8] was reported by Kikuzaki as a new phytochemical constituent of the Malaysian medicinal plant *Zingiber ottensii* (Zingiberaceae).[7]

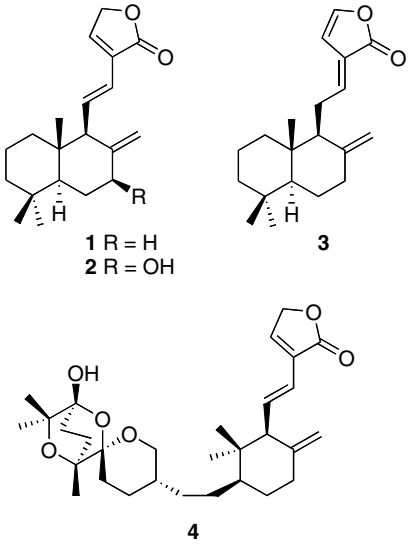

Figure 1.

Our interest in the development of useful methods for the regio and stereocontrolled construction of lactone containing terpenes,[8–10] prompted us to explore a new pathway to alkenylfuranones **A**, based entirely on the judicious use of 2-furanolate chemistry (Scheme 1). In a departure from traditional approaches,[11] access to **A** was envisioned via its alkylidene counterpart **B**, which would arise by C3-regioselective aldol reaction of a boron 2-furanolate with the appropriate aldehyde and ensuing E1cb elimination. Reported herein is the successful implementation of this strategy to a concise synthesis of villosin (**1**) and its isomer **3**, along with

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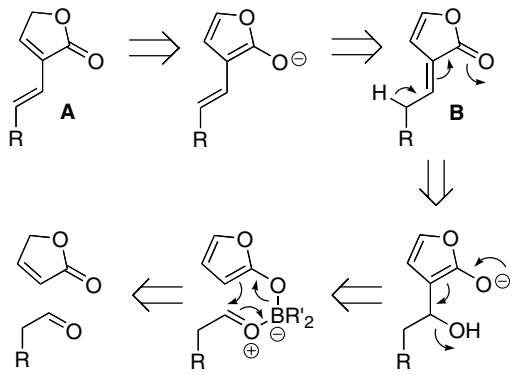


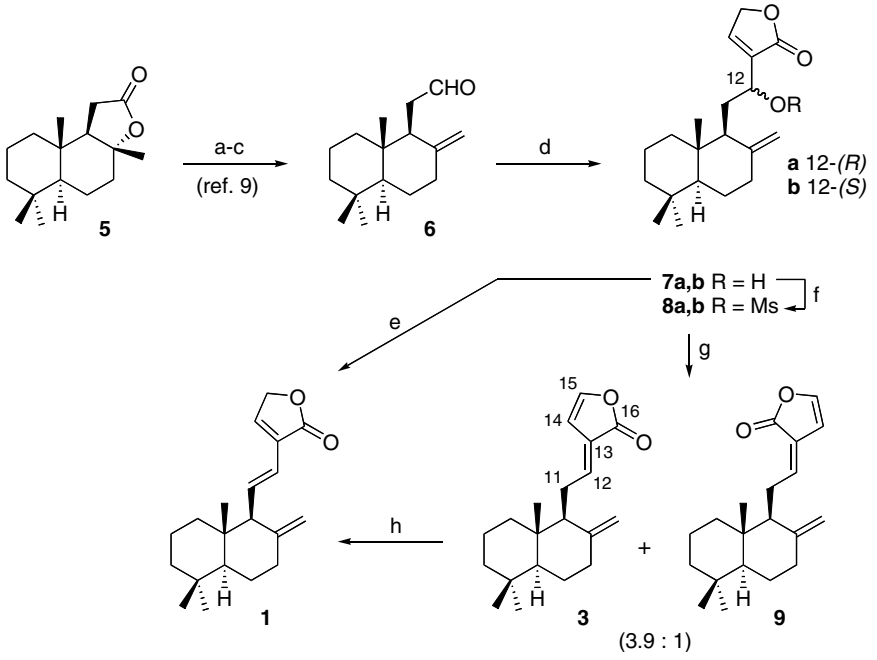
Scheme 1. Retrosynthetic analysis for **A** and **B**.

irrefutable proof that Kikuzaki's structural assignment[7] (vide supra) is incorrect.[12]

The requisite aldehyde **6** was efficiently prepared from commercially available (+)-sclareolide (**5**) according to previously established methodology[9] (Scheme 2). Aldol reaction of **6** with in situ generated dibutylboron 2-furanolate[13] proceeded with complete regioselectivity to furnish the diastereomeric alcohols **7a** and **7b** (3.8:1 ratio) in 95% yield after flash chromatography.[14] These alcohols were initially transformed to (–)-villosin (**1**) by conversion to the corresponding mesylates **8a**,**b** and subsequent treatment with DBU (78% over two steps). While this sequence could be performed in one-pot fashion, the yield of **1** was only about 50%. After trying a number of alternative procedures, we were pleased to find that heating the mixture of alcohols **7a**,**b** with Al_2O_3 in pyridine[15] directly provided **1** in 89% yield. Synthetic **1** exhibited NMR data[16] in full agreement with those of the natural product,[1] and its specific rotation was the same in sign with a sample derived from *Hedychium coronarium*.[1a] Although optical data are unavailable for the samples isolated from *Hedychium villosum*[1b] and *Hedychium forrestii*,[1c] the co-occurrence of villosin with other diterpenoids belonging to the *normal* labdane series,[1] such as isocoronarin *D* or coronarin *E*,[17] suggests that all three plants produce the same enantiomer (cf. **1**).

Further scrutiny of the transformation of mesylates **8a**,**b** to villosin (**1**) provided evidence in support of our working assumption that alkylidenefuranone **3** is involved as an intermediate (cf. **B** in Scheme 1). Thus, when DBU was replaced by Hünig's base, compound **3**[18] was obtained as the main product together with a small amount of its *Z*-isomer **9**[19] (ratio 3.9:1; Scheme 2).[20] Also, exposure of **3** to DBU in dichloromethane at room temperature accomplished rapid isomerization to villosin.

The respective identities of **3** and **9** were unequivocally established by direct comparison of their NMR spectra with those of simple 3-alkylidenefuranones prepared by an alternative, highly stereoselective method.[8] Moreover, the chemical shifts of the olefinic protons of our compounds were identical with the values recorded for a pair of *E*/*Z* 3-alkylidenefuranones derived from saponaceolide A.[21] However, neither the ^1H nor the ^{13}C NMR data of synthetic **3** matched those reported by Kikuzaki.[7] Given the irreconcilable differences in the chemical shifts of the C11–16 fragment (Table 1), it is obvious that Kikuzaki's natural product is not a 3-alkylidene-2(3*H*)-furanone.



Scheme 2. Reagents and conditions: (a) MeNHOMe·HCl, Me_3Al, CH_2Cl_2, 0 °C (87%); (b) $SOCl_2$, py, CH_2Cl_2, −78 °C, (88%); (c) DIBAL, Et_2O, −78 °C (93%); (d) 2(5*H*)-furanone, *n*-Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, then **6**, −78 °C, 2 h (95%); (e) Al_2O_3 (1.5 equiv), pyridine, reflux, 8 h (89%); (f) MsCl (4 equiv), Et_3N or *i*-Pr_2NEt (4 equiv), CH_2Cl_2, −78 to 0 °C, 1 h; (g) *i*-Pr_2NEt (5 equiv), CH_2Cl_2, rt, 2 h (63% for **3**, ca. 8% for **9**, two steps); (h) DBU (ca. 2 equiv), CH_2Cl_2, rt, 15–20 min (90%).