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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]

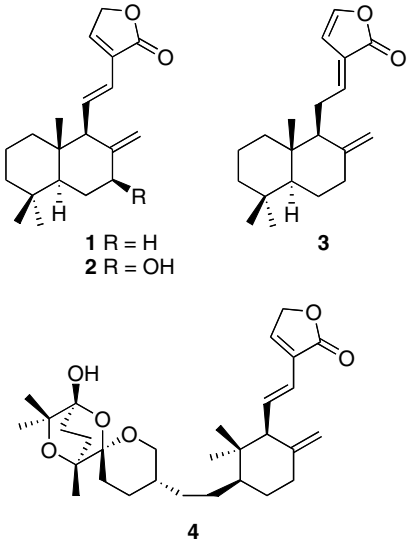

Figure 1.

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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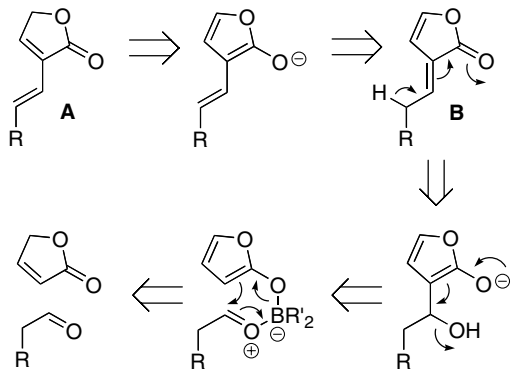


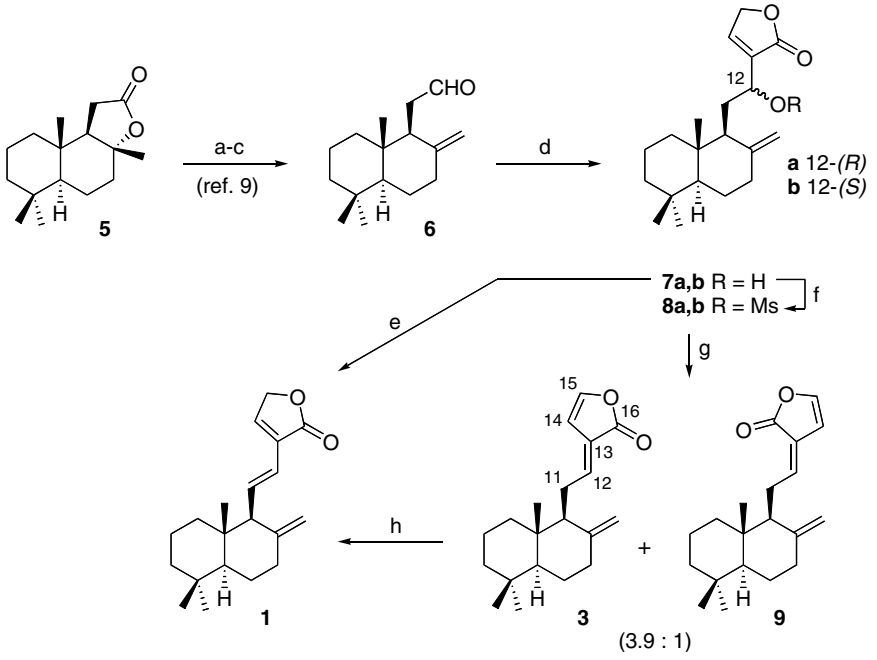
Scheme 1. Retrosynthetic analysis for **A** and **B**.

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%).

Table 1. ^{1}H and ^{13}C NMR Data for the C11–16 fragment of **3**[a]

C	Synthetic **3**		Data from Ref. 7	
	δ_H[b]	δ_C	δ_H[c]	δ_C
11	2.55 (ddd, 16, 7, 3) 2.42 (dd, 16, 8)	25.9	2.69 (ddd, 16, 2, 1) 2.45 (ddd, 16, 2, 1)	19.5
12	6.74 (dddd, 8, 7, 2, 1)	145.3	7.52 (ddd, 1, 1, 1)	153.0
13		125.5		129.8
14	6.18 (dd, 4, 1)	105.1	7.67 (dd, 6, 1)	154.6
15	6.98 (ddt, 4, 2, 1)	145.1	6.31 (d, 6)	116.4
16		168.0		178.8

[a] All spectra were recorded in $CDCl_3$.
[b] 400 MHz.
[c] 500 MHz.

In summary, a new and efficient pathway to (*E*)-3-(1-alkenyl)-2(5*H*)-furanones from aldehydes, as demonstrated by the straightforward synthesis of villosin (**1**),[22] has been established. In addition, the villosin isomer (*E*)-labda-8(17),12,14-trien-15(16)-olide (**3**), corresponding to the putative structure of a newly isolated constituent of *Z. ottensii*,[7] was synthesized for the first time and shown to exhibit significantly different NMR data from those of the natural product. Efforts to uncover the correct structure of the latter, and apply the foregoing methodology to the synthesis of more complex natural products, are underway.

Acknowledgments

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Supplementary data

NMR spectra of compounds **1**, **3** and **9**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2007.09.033.

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16. *Data for* **1**: Mp 124–125 °C, (lit. 124,[1a] 108.4–108.8,[1b] 118–120[1c]); $[\alpha]_D^{21}$ −6.9 (*c* 0.38, $CHCl_3$), lit.[1a] $[\alpha]_D^{22}$ −45.0 (*c* 0.71, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (tt, $J = 2.1$, 0.6 Hz, 1H, H-14), 6.90 (ddq, $J = 15.8$, 10.0, 0.6 Hz, 1H, H-11), 6.11 (dm, $J = 15.8$ Hz, 1H, H-12), 4.81 (dt, $J = 2.0$, 0.7 Hz, 2H, H-15), 4.76 (q, $J = 1.7$ Hz, 1H, H-17), 4.50 (q, $J = 1.7$ Hz, 1H, H-17), 2.44 (ddd, $J = 13.6$, 4.4, 2.3 Hz, 1H, H-7), 2.37 (br d, $J = 10.0$ Hz, 1H, H-9), 2.08 (tdq, $J = 13.4$, 5.3, 1.0 Hz, 1H, H-7), 1.70 (ddt, $J = 12.9$, 5.2, 2.5 Hz, 1H, H-6), 1.53 (dm, $J = 13.7$ Hz, 1H, H-2), 1.45 (dm, $J = 13.5$ Hz, 1H, H-1), 1.40 (m, 1H, H-2), 1.39 (m, 2H, H-3,6), 1.18 (td, $J = 13.8$, 4.0 Hz, 1H, H-3), 1.09 (dd, $J = 12.6$, 2.8 Hz, 1H, H-5), 1.00 (td, $J = 12.9$, 3.2 Hz, 1H, H-1), 0.89 (s, 3H, H-18), 0.87 (s, 3H, H-20), 0.84 (s, 3H, H-19); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6 (C-16), 149.6 (C-8), 142.7 (C-14), 137.1 (C-11), 129.7 (C-13), 120.8 (C-12), 108.6 (C-17), 69.8 (C-15), 54.9 (C-5), 62.4 (C-9), 42.5 (C-3), 41.0 (C-1), 33.8 (C-4), 39.5 (C-10), 37.0 (C-7), 23.6 (C-6), 33.8 (C-18), 19.3 (C-2), 22.2 (C-19),15.3 (C-20).
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18. *Data for* **3**: Mp 162 °C (dec); $[\alpha]_D^{21}$ +16.0 (*c* 0.55, $CHCl_3$); IR (ν_{max}, neat) 2927, 2848, 1781 (C=O), 1646, 1572, 1460, 1388, 1133, 1043, 890, 801 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.98 (ddt, $J = 3.6$, 1.8, 0.8 Hz, 1H, H-15), 6.74 (dddd, $J = 8.0$, 6.8, 1.8, 1.0 Hz, 1H, H-12), 6.18 (dd, $J = 3.6$, 1.0 Hz, 1H, H-14), 4.83 (m, 1H, 17-H), 4.40 (m, 1H, 17-H), 2.55 (ddd, $J = 16.0$, 6.8, 3.2 Hz, 1H, H-11), 2.42 (dd, $J = 16.0$, 8.0 Hz, 1H, H-11), 2.39 (ddd, $J = 13.2$, 4.5, 2.4 Hz, 1H, H-7), 2.00 (td, $J = 13.0$, 5.1 Hz, 1H, H-7), 1.91 (br d, $J = 10.5$ Hz, 1H, H-9), 1.74 (ddt, $J = 13.0$, 5.2, 2.5 Hz, 1H, H-6), 1.71 (dm, $J = 13.0$ Hz, 1H, H-1), 1.58 (m, 1H, H-2), 1.52 (m, 1H, H-2), 1.42 (dtd, $J = 13.2$, 3.3, 1.7 Hz, 1H, H-3), 1.34 (tdd, $J = 13.0$, 12.8, 4.4 Hz, 1H, H-6), 1.20 (td, $J = 13.2$, 4.4 Hz, 1H, H-3), 1.14 (dd, $J = 12.6$, 2.7 Hz, 1H, H-5), 1.10 (td, $J = 13.0$, 4.4 Hz, 1H, H-1), 0.89 (s, 3H, 18-H), 0.82 (s, 3H, 19-H), 0.74 (s, 3H, 20-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0 (C-16), 147.9 (C-8), 145.3 (C-12), 145.1 (C-15), 125.5 (C-13), 107.9 (C-17), 105.1 (C-14), 33.57 (C-4), 33.55 (C-18), 56.5 (C-9), 55.4 (C-5), 37.8 (C-7), 39.6 (C-10), 39.3 (C-1), 42.0 (C-3), 25.9 (C-11), 21.7 (C-19), 24.1 (C-6), 19.3 (C-2), 14.4 (C-20); HRMS: Calcd for $C_{20}H_{29}O_2$ (*m*/*z*): 301.2168 ($M+H^+$). Found: 301.2160.
19. *Data for* **9**: IR (ν_{max}, neat) 2927, 2867, 2847, 1769 (C=O), 1642, 1581, 1460, 1135, 1050, 893 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.86 (dq, $J = 3.2$, 1.0 Hz, 1H, H-15), 6.48 (t, $J = 7.2$ Hz, 1H, H-12), 5.95 (d, $J = 3.4$ Hz, 1H, H-14), 4.83 (dd, $J = 2.8$, 1.4 Hz, 1H, H-17), 4.46 (dd, $J = 2.6$, 1.2 Hz, 1H, H-17), 2.99 (ddd, $J = 17.8$, 7.0, 3.2 Hz, 1H, H-11), 2.88 (ddd, $J = 17.8$, 11.6, 7.9 Hz, 1H, H-11), 2.40 (ddd, $J = 13.0$, 4.3, 2.4 Hz, 1H), 2.01 (br dt, $J = 13.0$, 5.5 Hz, 2H), 1.87 (br d, $J = 11.5$ Hz, 1H, H-9), 1.80 (dm, $J = 13.0$ Hz, 1H), 1.74 (dm, $J = 13.0$ Hz, 1H), 0.88 (s, 3H, 18-H), 0.82 (s, 3H, 19-H), 0.76 (s, 3H, 20-H).
20. A similar ratio of **3**/**9** (ca. 4.5:1) was obtained by starting with isomerically pure **8a**. Also, exposure of **8a** to 0.05 equiv of DBU in dichloromethane for 5 min at rt led to a mixture containing **3**, **9** and **1**.
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