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Synthesis of hedychenone, yunnancoronarins and aframodial derivatives

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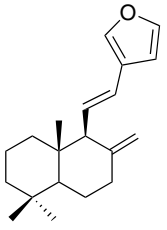
This paper is dedicated to the memory of F. Aslaoui

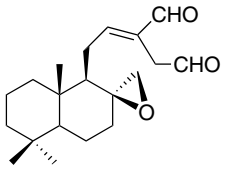
Abstract—Starting with larixol, syntheses of furan and 1,4-enedial labdane-type diterpenes are presented, which has enabled a preparation of hedychenone (20% yield).

Extracts of Zingiberacaea, one of the major tropical plant families, have long been used in traditional medicine[1] and their examination has resulted in the isolation of labdanes such as the biogenetically-related coronarin E (**1**) and aframodial (**2**).[2,3] In particular, the rhyzomes[4] of *Hedychium spicatum, H. yunnanense, H. coronarium* and *H. forrestii* were found to contain bioactive hedychenone (**3**) yunnancoronarins A (**4**) and D (**5**);[5–7] the structures of these labdanes have been established by spectroscopic methods[8] and that of hedychenone confirmed by radiocrystallographic analysis;[9] in this work we disclose the synthesis of **3**–**5** as well as a compound related to **2**.

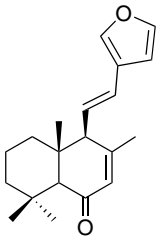
At first larixol (**6**), a labdane which is readily available from larch oleoresin,[10] was converted into the aldehyde **7**[11] by a three-steps transformation based on an osmium tetroxide/sodium periodate oxidation sequence;[12] protection of the hydroxyl group as a silyl ether was



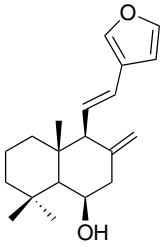
coronarin E (**1**)



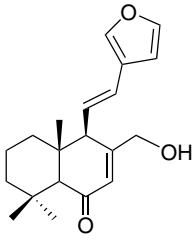
aframodial (**2**)



hedychenone (**3**)



yunnancoronarin A (**4**)



yunnacoronarin D (**5**)

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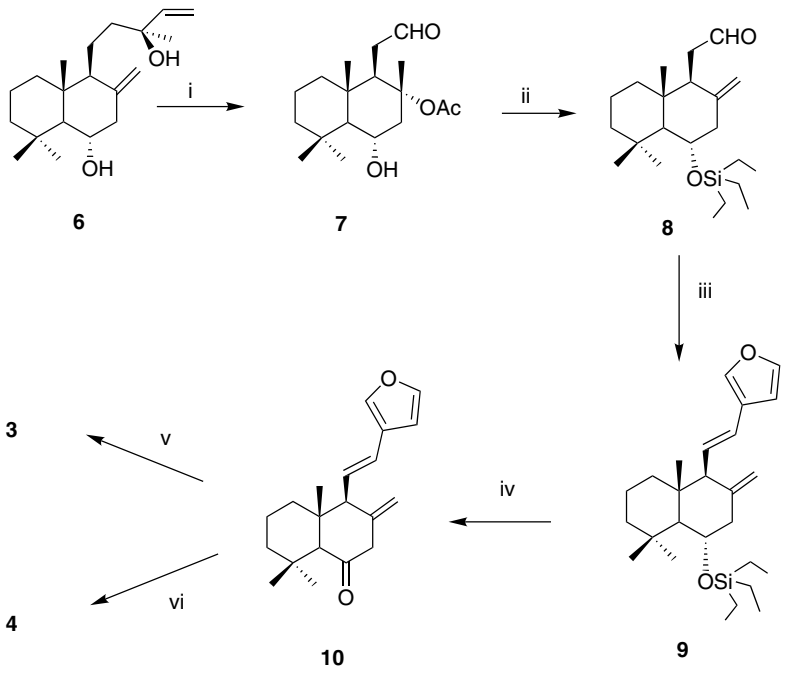
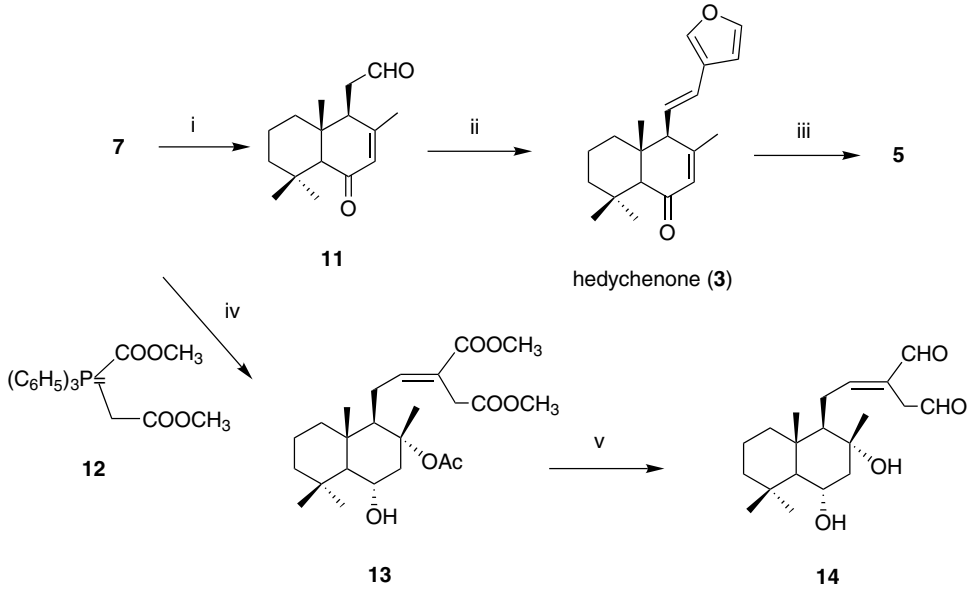
followed by elimination of the tertiary acetate by use of 2,4,6-collidine;[13] that the double bond was *exo* was revealed by the presence of two vinylic protons (singlets at 4.8 and 4.55 ppm). Then, addition of 3-furyl lithium[14] to the aldehydic group of **8** afforded a ca. 1:1 mixture of epimeric alcohols, which without separation, were mesylated in the presence of 2,6-lutidine; this gave the elimination product **9** with the desired *trans*-configuration ($J = 16$ Hz). Cleavage of the silyl ether followed by oxidation then afforded **10**. This intermediate gives access to both hedychenone (**3**), after isomerization, and yunnancoronarin A (**4**) after reduction with diisobutylaluminum hydride which, for steric reasons, occurs from the alpha side (Scheme 1).

With a preparation of hedychenone in hand, a shorter route based on the preferential reaction of an aldehyde group (over a ketone) was explored (Scheme 2); after



Scheme 1. Reagents and conditions: (i) Ref. 11 (50%); (ii) (1) Et_3SiCl, DMAP cat, py, 8 h (94%), (2) 2,4,6-collidine as solvent, 170 °C, 12 h (79%); (iii) (1) 3-furyllithium, −78 °C, 2 h (68%), (2) 2,6-lutidine (7 equiv), CH_2Cl_2, add MsCl (3 equiv), rt, 18 h (68%); (iv) (1) AcOH, THF–H_2O (5:1:3), rt, overnight (95%), (2) IBX (3 equiv) AcOEt, 60 °C, 3 h (85%); (v) MeONa (0.2 M in MeOH), 2 h (quant); (vi) THF, −78 °C, Dibal-H (6 equiv), 2 h (95%).



Scheme 2. Reagents and conditions: (i) (1) IBX (3 equiv), AcOEt, 70 °C, 3 h (84%); (2) 2,4,6-collidine, 160 °C, 2 h (90%); (ii) (1) 3-furyllithium, −78 °C, (2) 2,6-lutidine, MsCl (59%, two steps); (iii) (1) SeO_2 (1.5 equiv), dioxane, 80 °C—8 h; (2) $NaBH_4$, EtOH, −78 °C (60% two steps); (iv) **12** (65%); (v) LAH, then IBX (56% overall), see Ref. 21.

oxidation of **7** followed by conjugation of the *exo* double bond, enone **11** was obtained.[15] Pleasingly, the addition of 3-furyl lithium occurred preferentially on its aldehyde group to afford **3** after mesylation/elimination.[16] Hedychenone (**3**), identical to that prepared according to Scheme 1, is now obtained in four steps from **7** (22% overall yield from larixol).

Yunnancoronarin D (**5**) could be synthesized from hedychenone in only two steps: oxidation of the allylic methyl group, followed by reduction of the aldehyde group thus formed (Scheme 2); as other yunnancoronarins have been obtained by photooxydation[17] of hedychenone, this work also constitutes their formal preparation. Finally, the availability of **7** led us to consider introduction of the 1,4-enedial (3-formyl-3-butenal) structural unit as this pharmacophore is found in a number of bioactive terpenoids.[18] Reaction of ylide **12**[19] with **7** afforded **13** (only the *E* isomer was obtained);[20] reduction of **13**, followed by selective oxidation[21] then afforded the desired 1,4-enedial **14**[22] (Scheme 2).

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15. This material should be prepared freshly before use; characteristic spectroscopic data: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.89 (s, 1H, CHO), 5.78 (large s, 1H, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.8 (C=O); 199.4 (CHO); 155.9 (C-8); 128.9 (C-7).
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22. Under Ar, to a solution of **7** (167 mg, 0.539 mmol) in dry toluene (3 mL) was added ylide **12**[18] (875 mg, 2.16 mmol, 4 equiv) and the mixture was heated at 115 °C for 72 h. After cooling and evaporation of the volatiles the residue was purified by column chromatography on silica gel (cyclohexane/AcOEt 8:2) to afford **13** (oil, 158 mg, 0.361 mmol, 67%) which was then added as a THF solution (2 mL) to a suspension of $LiAlH_4$ (10 equiv) in dry THF (4 mL) at 4 °C. After 12 h stirring at rt the solution was cooled to 4 °C and 1 M aqueous HCl was added before extractive work-up with ethyl acetate. After evaporation of the volatiles, the residue was taken-up in ethyl acetate (4 mL) and IBX (prepared according to Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022) (4 equiv) added before stirring 4 h at 60 °C. After cooling and evaporation of the volatiles, column chromatography (cyclohexane/AcOEt 6:4) afforded **14** in 56% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.69 (s, 1H, H-16); 9.45 (large s, 1H, H-15); 7.01 (t, J_{14-15} = 7 Hz, 1H,

H-12); 4.10 (m, 1H, H-6); 3.45 and 3.55 (AB system, J_{AB} = 16 Hz, 2H, H-14); 1.53 (s, CH_3-17); 1.21, 0.95, 0.84 (3 s, CH_3-18, -19, -20). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 198.3 (C-16); 193.3 (C-15); 160.4 (C-12); 133.8 (C-13); 76.0 (C-8); 66.4 (C-6); 62.2 (C-9, C-5); 42.5 (C-7); 40.8 (C-3); 39.4 (C-1); 39.0 (C-10); 35.8 (C-14); 32.3 (C-18); 29.6 (C-4); 25.9 (C-11); 22.4, 21.9 (C-19, C-17); 18.0 (C-2); 16.3 (C-20). For data on aframodial: see: Kimbu, S. F.; Njimi, T. K.; Sondengam, L.; Akinniyi, J. A.; Connoly, J. D. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1303–1305.