A Concise Conversion of (−)-Sclareol into (+)-Coronarin E and (−)-7-*epi*-Coronarin A

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The first synthesis of natural (+)-coronarin E (**1**) and (−)-7-*epi*-coronarin A (**8**) was achieved from (−)-sclareol in four and five steps, respectively.

Labdane terpenes are of special biological interest due to their significant insect antifeedant, antitumor, and antifungal activities, as shown in polygodial,[1] coronarin A,[2] warburganal,[3] and galanolactone.[4] Coronarin E (**1**) was isolated from the chloroform extract of the rhizomes of the Brazilian medicinal plant *Hedychium coronarium*[5] (Zingiberaceae) and *Alpinia javanica*,[6] and from the CH_2Cl_2 extracts of the aerial parts of *Alpinia chinensis*.[7] Labdienedial (**2**) and coronarin A are biogenetically related to **1**. The furanolabdane coronarin E (**1**) could be derived by dehydration of **2**, while allylic oxidation of **1** could provide coronarin A. There was only one case in which both **1** and **2** had been isolated from the same plant.[6] Consequently, it is likely that **1** is not an artifact, and its presence could be useful as a taxonomic marker.[8] Recently, the cytotoxic agent (**2**) was prepared by Jung et al.[9] No information is available on the synthesis of **1** and coronarin A. Coronarin A, isolated from the rhizomes of *H. coronarium*, showed significant cytotoxic activity (IC_{50} = 1.65 μg/mL) against Chinese hamster V-79 cells.[2] The interesting biological activities, natural scarcity (0.002% yield), and furanolabdane-type structure of **1** prompted us to synthesize **1** and its related compound **8**. In this note, we report the first synthesis of optically active coronarin E (**1**) and 7-*epi*-coronarin A (**8**).

(−)-Sclareol (**3**) is a readily available natural product whose structure and absolute stereochemistry make it a suitable chiral synthon for the semisynthesis of **1** and **8**.[9,10] Thus, oxidative degradation of **3** with osmium tetroxide and sodium periodate in aqueous *tert*-butyl alcohol cleanly afforded the acetoxyaldehyde **4**[9,10] in one step (65%) (Scheme 1). The acetoxy group at C-8 of compound **4** was derived from the original CH_3 at C-16 of **3**.[9] Compound **4** could serve as a versatile intermediate for the synthesis of a variety of biologically active natural products, including galanal A,[4] warburganal,[3] and galanolactone.[9] Deacetylation of **4** was regiospecifically achieved with collidine to give **5** (68% yield).[10] Coupling of **5** with 3-bromofuran in the presence of *n*-butyllithium in anhydrous ether at −78 °C for 2 h provided the two diastereoisomeric furanolabdane hydroxides **6** in a 3:1 ratio, respectively (yield 71%). Without isomer separation, dehydration of **6** with 2,6-lutidine in the presence of methanesulfonyl chloride afforded exclusively **1** (70%). However, dehydration with triethylamine in the presence of methanesulfonyl chloride gave exclusively the cis form (**7**) (68%). Allylic oxidation of **1** with selenium oxide and *tert*-butyl peroxide in methylene chloride cleanly provided (−)-7-*epi*-coronarin A (**8**) (73% yield). No natural coronarin A was generated in this oxidation. These syntheses make it possible to solve the problem of natural scarcity of coronarin E (**1**) and (−)-7-*epi*-coronarin A (**8**).

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Experimental Section

General Experimental Procedures. Melting points were determined in open capillary tubes with a MEL-TEMP II and are uncorrected. IR spectra were obtained as KBr pellets or neat on a NaCl plate, using a Nicolet Impact 400 FT-IR spectrophotometer. The NMR spectra were measured on a Bruker AC 250 NMR spectrometer operating at 250 MHz for ^{1}H NMR and 63 MHz for ^{13}C NMR. All spectra were recorded in $CDCl_3$ as solvent, and chemical shifts were reported in parts per million (δ) relative to TMS. GC/MS spectra were obtained on a Shimadzu GC/MS-QP 2000A. Specific rotations were determined in $CHCl_3$ using a RUDOLPH Research AUTOPOL III. Analytical TLC was performed on Merck precoated Si gel glass plates (Si gel 60, F_{254}, 0.25 mm), and flash column chromatography was performed on Merck 230−400 mesh Si gel. Visualization was achieved with UV (254 nm), solution of molybdic acid (1%) and cerium sulfate (1%) in H_2SO_4, anisaldehyde (1%), and H_2SO_4 (1%) solution in HOAc or $KMnO_4$ (2%) and $NaHCO_3$ (4%) solution. Sclareol (**3**) was purchased from Aldrich Chemical Co., (Milwaukee, WI).

15,16-Epoxy-12-hydroxy-labda-8(17),13(16),14-triene (6). A 1.6-M solution of *n*-butyllithium in hexane (1.2 mL, 1.86 mmol) was added dropwise with stirring to 3-bromofuran (219 mg, 1.49 mmol) in dry ether (10 mL) at −78 °C under nitrogen atmosphere. After 10 min, a solution of **5** (288.3 mg, 1.24 mmol) in dry ether (10 mL) was added into the above reaction mixture. After this mixture had been stirred for 2 h at −78 °C, excess H_2O was added at room temparature with additional stirring for 30 min. The product was extracted with ether (20 mL × 3), and the organic layer was dried over $MgSO_4$ and evaporated. Diastereomers (**6a**: R_f 0.5 and **6b**: R_f 0.3) were separated by Si gel flash column chromatography with eluents (hexane−EtOAc, 5:1) in a 1:3 ratio (**6a**: 69 mg, 18% and **6b**: 205 mg, 54%).

Compound 6a: colorless oil; $[\alpha]_D$ +18.54°(*c* 0.47, $CHCl_3$); IR (neat) ν_{max} 3403, 2933, 2369, 1631, 1469, 1127, 880 cm^{-1}; ^{1}H NMR($CDCl_3$, 250 MHz) δ 7.38, 7.39 (each 1H, s, H-15, H-16), 6.41 (1H, br s, H-14), 4.86 (1H, s, H-17), 4.69 (1H, dd, J = 8.9, 3.1 Hz, H-12), 4.47 (1H, s, H-17), 0.89, 0.81, 0.68 (each 3H, each s, H-18, 19, 20); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 149.0 (C-8), 143.2 (C-16), 138.4 (C-15), 130.2 (C-13), 108.5 (C-17), 106.4 (C-14), 65.2 (C-12), 55.3 (C-5), 52.3 (C-9), 42.0 (C-3), 39.2 (C-10), 39.0 (C-1), 38.2 (C-7), 33.6 (C-4), 32.7 (C-11), 24.3 (C-6), 21.7 (C-19), 19.3 (C-2), 14.6 (C-20), 14.1 (C-18); GC/MS *m*/*z* 302 (M^+, 3), 284 (4), 206 (15), 191 (33), 177 (13), 150 (13), 137 (50), 110 (25), 97 (100), 69 (45).

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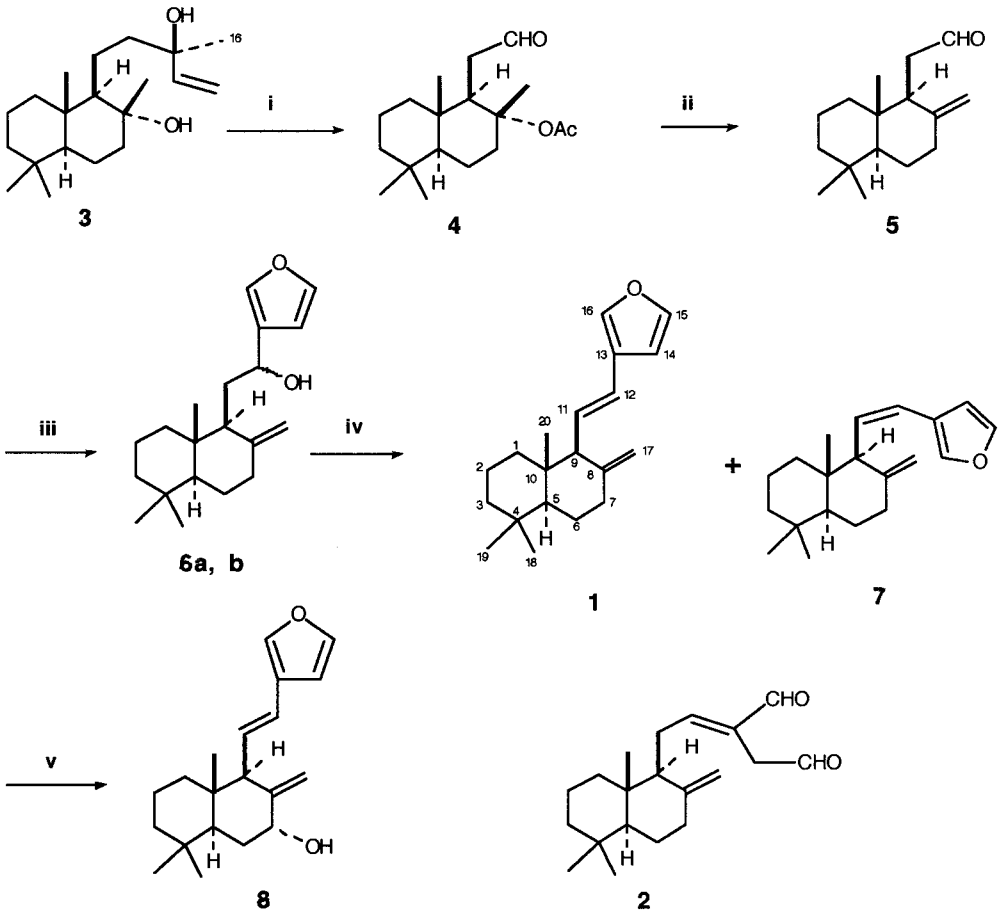
Scheme 1[a]



[a] Reagents and conditions: (i) OsO_4 (cat.)/$NaIO_4$ (1.8 eq.), *tert*-butyl alcohol, THF, 25 °C, 5.5 h (65%); (ii) collidine, reflux, 25 h, (68%); (iii) 3-bromofuran (1.2 eq.), *n*-BuLi (1.5 eq.), ether, −78 °C, 2 h., (71%); (iv) MsCl (5 eq.), 2,6-lutidine (10 eq.), CH_2Cl_2, room temperature, 30 h (70%); (v) SeO_2 (4 eq.), *tert*-BuOOH (8 eq.), CH_2Cl_2, room temperature, 6 h, (73%).

Compound 6b: colorless oil; $[\alpha]_D$ +12.73° (*c* 1.5, $CHCl_3$); IR (neat) ν_{max} 3385, 2933, 1649, 1643, 1125, 890 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.40, 7.34 (each 1H, s, H-15, H-16), 6.42 (1H, br s, H-14), 4.88 (1H, s, H-17), 4.71 (1H, s, H-17), 4.69 (1H, d, J = 5.42 Hz, H-12), 0.82, 0.78, 0.69 (each 3H, each s, H-18, 19, 20); GC/MS *m/z* 302 (M^+, 3), 284 (5), 206 (20), 191 (33), 177 (13), 150 (20), 137 (50), 110 (25), 97 (100), 69 (45).

(+)-Coronarin E (1). The base 2,6-lutidine (485 mg, 4.5 mmol) was added to a solution of **6** (273 mg, 0.91 mmol) in dry methylene chloride under N_2 atmosphere at 20 °C with stirring for 30 min. To the stirred reaction mixture was added methanesulfonyl chloride (517 mg, 0.14 mL, 4.5 mmol), and then it was stirred at 20 °C for an additional 18 h. An excess methylene chloride was added to the reaction mixture, which was then washed with 10% HCl solution (20 mL × 3), saturated $NaHCO_3$, and brine, then dried over $MgSO_4$. The colorless oily product, **1**, was obtained by Si gel column chromatography in 70% yield (176 mg) (eluents: hexane−EtOAc, 5:1): **1** (R_f 0.73), colorless oil; $[\alpha]_D$ +21.3° (*c* 0.44, $CHCl_3$), lit.[5] $[\alpha]_D$ + 22.3° (*c* 0.44, $CHCl_3$); IR (neat) ν_{max} 2926, 1604, 1472, 1218, 1128, 1056, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.36 (2H, s, H-15, H-16), 6.55 (1H, s, H-14), 6.20 (1H, d, J = 15.7 Hz, H-12), 5.98 (1H, dd, J = 15.7 Hz, 9.7 Hz, H-11), 4.76 (1H, s, H-17), 4.54 (1H, s, H-17), 0.90, 0.85, 0.84 (each 3H, each s, H-18, 19, 20); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 150.4 (C-8), 143.0 (C-16), 139.7 (C-15), 128.0 (C-12), 124.7 (C-13), 121.8 (C-11), 107.8 (C-17), 107.6 (C-14), 62.9 (C-9), 54.7 (C-5), 42.5 (C-3), 40.9 (C-1), 39.4 (C-10), 36.8 (C-7), 33.6 (C-4), 33.5 (C-18), 23.4 (C-6), 22.0 (C-19), 19.0 (C-2), 15.1 (C-20); GC/MS *m/z* 284 (M^+, 53), 269 (5), 241 (3), 199 (5), 173 (5), 160 (13), 147 (100), 131 (20), 105 (15), 81 (35), 77 (20).

***cis*-Coronarin E 7.** (R_f 0.72), colorless oil; IR (neat) ν_{max} 2930, 1594, 1465, 1210, 1132, 1056, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.42, 7.39 (2H, s, H-15, C-16), 6.46 (1H, s, H-14), 4.96 (1H, dd, J = 10.11, 2.15 Hz, H-11), 4.91 (1H, d, J = 10.8 Hz, H-12), 4.86 (1H, s, H-17), 4.37 (1H, s, H-17), 0.89, 0.78, 0.69 (each 3H, each s, H-18, 19, 20).

(−)-7-*epi*-Coronarin A (8). To a stirred solution of SeO_2 (202 mg, 182 mmol) in methylene chloride, *tert*-BuOOH (656 mg, 7.28 mmol) was added dropwise under a N_2 atmosphere at room temperature. After 10 min, a solution of coronarin E(**1**) (273 mg, 0.91 mmol) in dry methylene chloride was added with vigorous stirring for 5 h. Excess CH_2Cl_2 was added to the reaction mixture and washed with H_2O, then dried over $MgSO_4$. A colorless oily product, **8**, was obtained by flash chromatography in 73% yield (eluents: hexane−EtOAc, 5:2): **8** (R_f 0.52), colorless oil; $[\alpha]_D$ −6.9°(*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 3436, 2933, 1468, 1375, 1204, 1026, 873, 768 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.35 (2H, s, H-15, H-16), 6.54 (1H, s, H-14), 6.22 (1H, d, J = 15.6 Hz, H-12), 5.97 (1H, dd, J = 15.7 Hz, 9.8 Hz, H-11), 5.00 (1H, s, H-17) 4.71 (1H, s, H-17) 4.42 (1H, d, J = 2.8 Hz, H-7), 2.89 (1H, d, J = 9.6 Hz, H-9), 0.91, 0.84, 0.82 (each 3H, each s, H-18, 19, 20); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 151.3 (C-8), 143.3 (C-16), 139.8 (C-15), 127.2 (C-12), 124.4 (C-13), 122.4 (C-11), 111.1 (C-14), 107.6 (C-17), 73.4 (C-7), 56.0 (C-9), 47.0 (C-5), 42.2 (C-3), 40.4 (C-1), 39.4 (C-10), 33.3 (C-4), 33.1 (C-18), 30.0 (C-6), 21.8 (C-19), 19.1 (C-2), 14.1 (C-20); GC/MS *m/z* 300 (M^+, 95), 282 (33), 209 (18), 189 (100), 161 (50), 149 (33), 121 (75), 105 (70), 94 (100).

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