

# Facile Access to Optically Active Labdane-Type Diterpenes from (+)-Manool. Synthesis of (+)-Coronarin E, (+)-15,16-Epoxy-8(17),13(16),14-labdatriene, and (+)-Labda-8(17),13(Z)-diene-15,16-diol

José Villamizar,\* Juan Fuentes, Franklin Salazar, Eleonora Tropper, and Randolph Alonso

Centro de Química, Instituto Venezolano de Investigaciones Científicas (IVIC), Apartado 21827, Caracas, 1020-A, Venezuela

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An efficient method for the synthesis of (+)-coronarin E (**1**), (+)-15,16-epoxy-8(17),13(16),14-labdatriene (**2**), and (+)-labda-8(17),13(Z)-diene-15,16-diol (**3**) from (+)-manool is described.

A large number of labdane-type diterpenoids have been isolated from terrestrial plants and sponges.<sup>1</sup> They have been reported to exhibit interesting biological properties such as cytotoxic, antifungal, antiinflammatory, and analgesic.<sup>2</sup> In 1988 Itokawa et al.<sup>3</sup> isolated the furanolabdane coronarin E (**1**) from the rhizomes of the Brazilian medicinal plant *Hedychium coronarium*, but this compound did not show cytotoxic activity against Chinese hamster V-79 cells. This compound has also been isolated from other plants.<sup>4</sup> In 2000 Tasdemir et al.<sup>5</sup> isolated a furanolabdane from *Cacospongia* sp. and assigned it structure **2**, with the A/B ring juncture of normal labdane diterpenes. Only this compound was tested against *Staphylococcus aureus* and methicillin-sensitive *S. aureus*, but was inactive. In 1991 Zdero et al.<sup>6</sup> reported the isolation of compound *ent-2*, with antipodal stereochemistry of **2**, and *ent*-labda-8(17),13(Z)-diene-15,16-diol (*ent-3*) from the terrestrial plant *Blepharispermum zanguebaricum* (Scheme 1).

To date, a number of semisyntheses of these biologically active labdane-type diterpenoids have been reported by employing (–)-sclareol as a starting material.<sup>7a,b</sup>

(+)-Manool (**4**) is a readily available natural diterpene with established absolute stereochemistry. In 1982 Nakano et al.<sup>8</sup> reported the synthesis of some labdane-type diterpenes such as labdafuran (**2**) from (+)-manool (**4**), but with poor yield. Previously Nakano et al.<sup>9</sup> reported the oxidative cleavage of (+)-manool (**4**) to ketone **5** in good yield (Scheme 2). The present work aims to demonstrate the utility of our strategy for the synthesis of optically active labdane-type diterpenes and to confirm the structure proposed for furanolabdane (*ent-2*) and diol (*ent-3*).

Oxidative cleavage of ketone **5** with potassium *tert*-butoxide in the presence of oxygen gave the acid **6a** with only small amounts of *tert*-butyl ester of acid **6b**.<sup>10</sup> Reduction of acid **6a** with LiAlH<sub>4</sub> afforded the alcohol **7**.<sup>10</sup> Subsequent oxidation of alcohol **7** with tetra-*n*-propylammonium perruthenate (TPAP)<sup>11</sup> or pyridinium chlorochromate afforded the aldehyde **8** (Scheme 2).

The nucleophilic addition of the organolithium compound, derived from 3-bromofuran, to the aldehyde **8** afforded a mixture of isomeric furanolabdane alcohols **9a** and **9b**, whose physical and spectroscopic properties were identical to those reported.<sup>7a</sup> The mixture of isomers **9a** and **9b** was dehydrated with 2,6-lutidine in the presence of benzenesulfonyl chloride to afford exclusively coronarin E (**1**), whose physical and spectroscopic properties were identical with those reported.<sup>3,4</sup>

To synthesize compound **2**, we first tried to reduce the hydroxyl group of the furanolabdane hydroxides **9** with the chlorotrimethylsilane/NaI/zinc system.<sup>12</sup> However, this method failed to reduce the alcohol. Reduction with Li/NH<sub>3</sub>/NH<sub>4</sub>Cl<sup>13</sup> gave a good result, yielding the desired compound **2**. This compound gave spectroscopic data identical with those reported,<sup>5,6</sup> except for the optical rotation, which we observed as [α]<sub>D</sub> +23 (c 2.0, CHCl<sub>3</sub>), but Tasdemir et al.<sup>5</sup> reported an opposite sign, [α]<sub>D</sub> –22 (c 0.14, CHCl<sub>3</sub>). The foregoing results indicate that the structure published by Tasdemir et al.<sup>5</sup> for furanolabdane (**2**) needs to be reinvestigated. Probably the compound isolated is impure and needs to be properly purified, and this should possess structure *ent-2*.

Compound **3** was synthesized via the naturally occurring sclarene (**10**),<sup>14</sup> which was also obtained from (+)-manool (**4**). In 1967 Carman et al.<sup>15</sup> synthesized a mixture of the *cis/trans* isomers of biformene and sclarene (**10**) by dehydration of manool (**4**) with glacial acetic acid. However, this method produces a mixture of at least seven compounds. Dehydration of manool (**4**) with *p*-toluenesulfonic acid in THF at reflux gave a mixture of double-bonded isomers. Chromatography of the mixture over silica gel impregnated with 20% silver nitrate gave a two-component mixture of the *cis/trans*-biformene and sclarene (**10**), which had physical and spectroscopic properties identical with those reported (Scheme 4).<sup>15</sup>

Turner et al.<sup>16</sup> obtained peroxide **11**, in relatively poor yield, from irradiation of sclarene (**10**) in the presence of oxygen and Rose Bengal. In an attempt to increase the yield of the photooxidation reaction, we irradiated sclarene (**10**) (external 150 W halogen–tungsten lamp) in the presence of oxygen and a catalytic amount of *meso*-tetraphenylporphine and obtained peroxide **11** in good yield. The spectroscopic properties of this peroxide **11** are identical to those reported.<sup>16</sup> Peroxide **11** was reduced with LiAlH<sub>4</sub> to afford the labda-8(17),13(Z)-diene-15,16-diol (**3**), which had spectroscopic data identical with those reported<sup>6</sup> except that the opposite sign for the optical rotation was observed ([α]<sub>D</sub> +40 (c 1.0, CHCl<sub>3</sub>), lit.<sup>6</sup> [α]<sub>D</sub> –42 (c 0.39, CHCl<sub>3</sub>)) (Scheme 4). Thus, the absolute configuration of the natural diol (*ent-3*) is 5*R*, 9*R*, 10*R*.

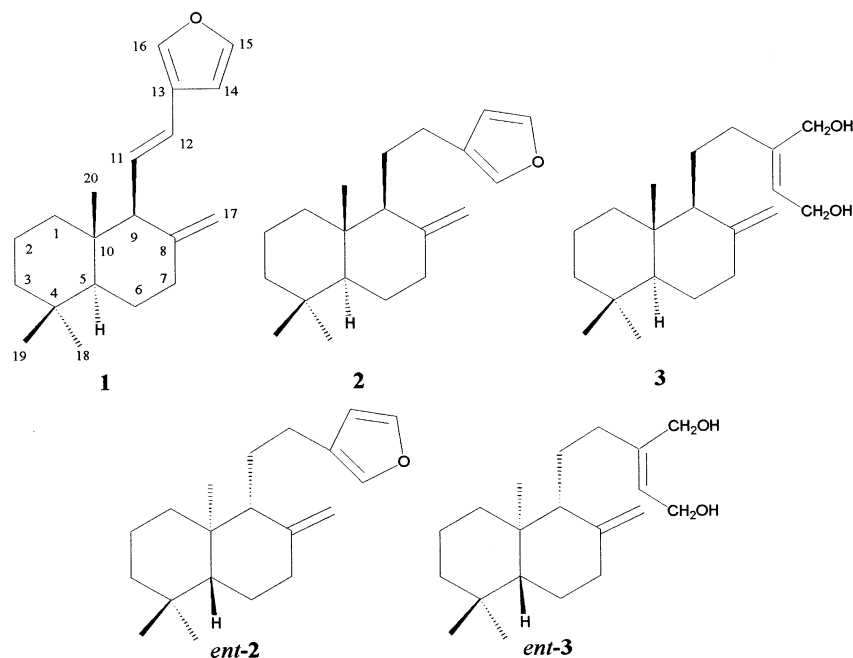
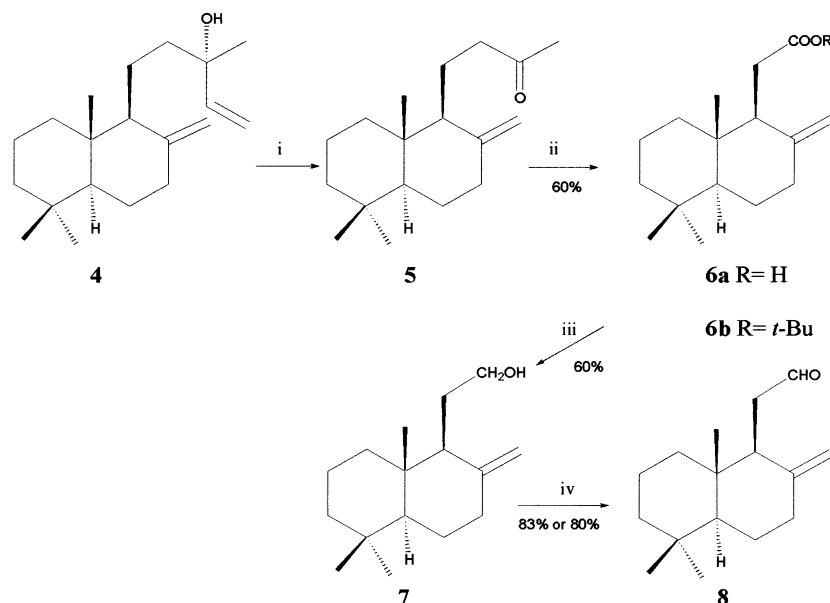
We also synthesized the furanolabdane **2** from diol **3** by use of pyridinium chlorochromate (Scheme 4).

## Experimental Section

Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded with Bruker Avance-300 and Avance-500 spectrometers. IR spectra were recorded using a Nicolet Magna 560 FT-IR

\* Corresponding author. Fax: 58-212-5041350. E-mail: jvillami@ivic.ve.

Scheme 1

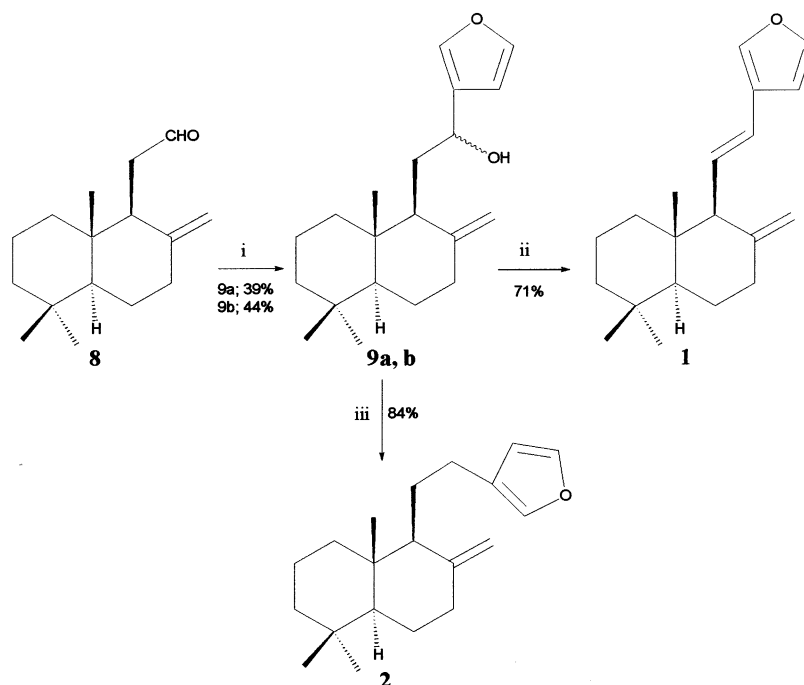
Scheme 2<sup>a</sup>

<sup>a</sup> (i)  $\text{KMnO}_4$ ,  $\text{MgSO}_4$ , acetone, 20 °C; (ii) potassium *tert*-butoxide,  $\text{O}_2$ , DME, rt; (iii)  $\text{LiAlH}_4$ , THF, reflux; (iv) TPAP, *N*-methylmorpholine *N*-oxide,  $\text{CH}_2\text{Cl}_2$ , or pyridinium chlorochromate,  $\text{CH}_2\text{Cl}_2$ , rt.

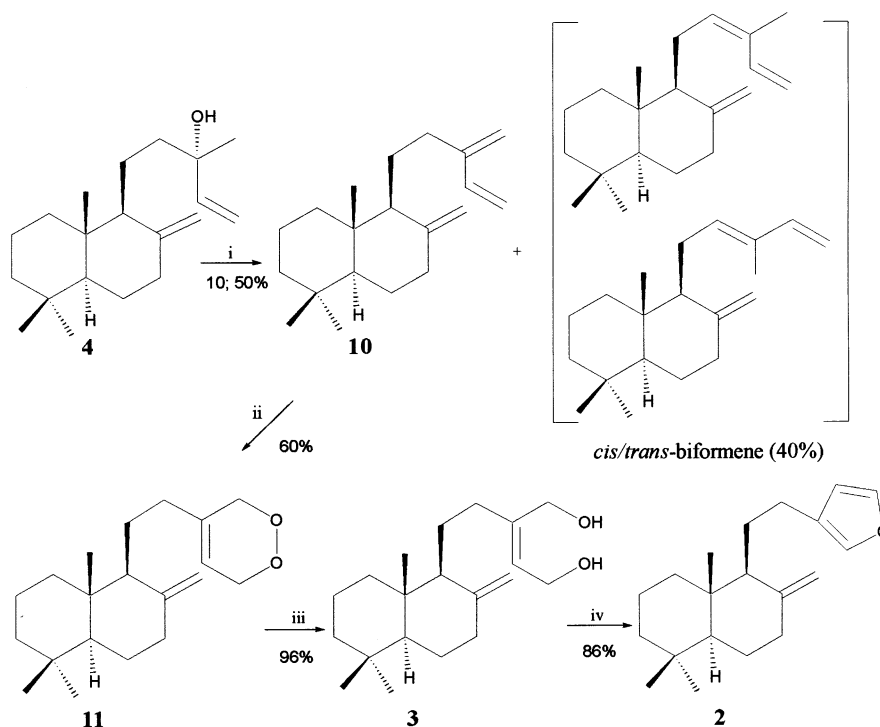
spectrometer. High-resolution mass spectra (HRMS) were obtained on a ZAB HS or Nermag R 10-10 mass spectrometer and Kratos MS25RFA. GC/MS spectra were obtained on a Varian Saturn GC/MS 2000. The intensity of each peak in the mass spectrum relative to the base peak is reported in parentheses. Optical rotations were obtained for  $\text{CHCl}_3$  solutions on a Perkin-Elmer 341 polarimeter, and their concentrations are expressed in g/100 mL. Manool resin was purchased from Westchem Industries, Ltd. and purified to obtain (+)-manool,  $[\alpha]^{24}_{\text{D}} +28$  (*c* 1.5,  $\text{CHCl}_3$ ). THF, ether, DME, and benzene were freshly distilled from Na-benzophenone before use. All other solvents and reagents were obtained from commercial suppliers and used without further purification. Merck silica gel (70–230 mesh ASTM) was used for column chromatography. TLC was performed on Analtech silica gel 60 G<sub>254</sub>, and the spots were observed by exposure to either

iodine or UV light. All organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and evaporated under reduced pressure below 60 °C.

**Oxidative Cleavage of Ketone 5.** To a solution of ketone 5 (2.32 g, 8.85 mmol) in dry DME (10 mL) was added potassium *tert*-butoxide (1.49 g, 13.27 mmol) at room temperature. Oxygen was bubbled through the mixture for 4 h and then diluted with brine, and the product was extracted with ether. The solvent was evaporated under reduced pressure, and the product was chromatographed over silica gel. Elution with 5% ether in hexane yielded only small amounts of *tert*-butyl ester 6b. Elution with 40% ether in hexane afforded the acid 6a as an oil (1.34 g, 60%);  $[\alpha]^{24}_{\text{D}} -24$  (*c* 1.9,  $\text{CHCl}_3$ ); IR (neat)  $\nu_{\text{max}}$  2900, 1705, 1650, 890  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.66, 0.78, 0.86 (3H each, s,  $\text{CH}_3$ -14,  $\text{CH}_3$ -15,  $\text{CH}_3$ -16), 4.51 (1H, s, H-13), 4.75 (1H, s, H-13);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.45 MHz)  $\delta$  14.37, 19.21, 21.69, 23.89, 29.67, 30.68, 33.53, 37.46, 38.84, 38.92, 41.95, 52.34, 55.01, 106.47, 148.78, 180.01; GC/

Scheme 3<sup>a</sup>

<sup>a</sup> (i) 3-Bromofuran, *n*-BuLi, THF,  $-78^{\circ}\text{C}$ ; (ii) benzenesulfonyl chloride, 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ ,  $0^{\circ}\text{C}$ –rt; (iii)  $\text{Li}/\text{NH}_3/\text{NH}_4\text{Cl}$ , THF,  $-78^{\circ}\text{C}$ .

Scheme 4<sup>a</sup>

<sup>a</sup> (i) *p*-Toluenesulfonic acid, THF, reflux; (ii)  $\text{O}_2$ , *meso*-tetraphenylporphyrine,  $\text{CCl}_4$ /5% MeOH,  $15^{\circ}\text{C}$ ; (iii)  $\text{LiAlH}_4$ , THF, reflux; (iv) pyridinium chlorochromate,  $\text{CH}_2\text{Cl}_2$ , rt.

MS  $m/z$  250 ( $\text{M}^+$ , 52), 235 (100), 233 (19), 191 (30), 153 (34), 137 (79), 95 (55), 81 (50); HRMS  $m/z$  250.1935 (calcd for  $\text{C}_{16}\text{H}_{26}\text{O}_2$ , 250.2064).

**Reduction of Acid 6a with Lithium Aluminum Hydride.** To a suspension of  $\text{LiAlH}_4$  (0.305 g, 8.0 mmol) in dry THF (5 mL) was added dropwise acid 6a (0.99 g, 4.8 mmol) in THF (4 mL) at  $0^{\circ}\text{C}$ . This mixture was refluxed for 2 h, then water was added and extracted with ether. The solvent was evaporated under reduced pressure, and the product was chromatographed over silica gel. Elution with 40% ether in hexane afforded alcohol 7 as an oil (0.84 g, 90%);  $[\alpha]_D^{24} +28$  (c

2.0,  $\text{CHCl}_3$ ), lit.<sup>10</sup>  $[\alpha]_D^{25} +27$  (c 2.1,  $\text{CHCl}_3$ ); IR (neat)  $\nu_{\text{max}}$  3400, 2930, 2850, 1450, 880  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.65, 0.77, 0.84 (3H each, s,  $\text{CH}_3$ -14,  $\text{CH}_3$ -15,  $\text{CH}_3$ -16), 3.48 (1H, m, H-12), 3.68 (1H, m, H-12), 4.50 (1H, bs, H-13), 4.79 (1H, bs, H-13);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.45 MHz)  $\delta$  14.42, 19.32, 21.64, 24.32, 27.02, 33.53, 33.53, 37.50, 38.19, 39.35, 42.09, 52.80, 55.46, 62.44, 106.33, 148.79; GC/MS  $m/z$  236 ( $\text{M}^+$ , 67), 221 (57), 203 (43), 177 (94), 137 (100), 95 (98), 81 (73); HRMS  $m/z$  236.2141 (calcd for  $\text{C}_{16}\text{H}_{28}\text{O}$ , 236.2190).

**Oxidation of Alcohol 7 with Tetra-*n*-propylammonium Perruthenate.** Alcohol 7 (85 mg, 0.36 mmol) was dissolved

in dichloromethane (3 mL) containing both 4 Å molecular sieves (0.200 g) and *N*-methylmorpholine *N*-oxide (63.27 mg, 0.54 mmol). After stirring the mixture for 10 min, tetra-*n*-propylammonium perruthenate (6.3 mg, 0.018 mmol) was added and the reaction was followed by TLC until complete. The reaction mixture was filtered through silica gel and eluted with hexane, affording aldehyde **8** (70 mg, 83%) as a oil;  $[\alpha]_D^{24} +25$  (c 1.5, CHCl<sub>3</sub>), lit.<sup>10</sup>  $[\alpha]_D +24$  (c 1.9, CHCl<sub>3</sub>); IR (neat)  $\nu_{\max}$  1724, 1641, 880 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  0.67, 0.78, 0.86 (3H each, s, CH<sub>3</sub>), 4.35 (1H, bs, H-13), 4.78 (1H, bs, H-13), 9.60 (1H, m, H-12); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.45 MHz)  $\delta$  14.53, 19.16, 21.66, 23.83, 33.48, 37.42, 38.84, 39.29, 39.77, 41.93, 50.89, 55.16, 107.96, 148.47, 203.50; GC/MS *m/z* 234 (M<sup>+</sup>, 15), 217 (77), 190 (100), 137 (96), 95 (64), 81 (53); HRMS *m/z* 234.1985 (calcd for C<sub>16</sub>H<sub>26</sub>O, 234.2010).

**Oxidation of Alcohol 7 with Pyridinium Chlorochromate.** Alcohol **7** (0.108 g, 0.45 mmol) was dissolved in dichloromethane (3 mL) and oxidized with pyridinium chlorochromate (0.197 g, 0.91 mmol) at room temperature for 30 min. The reaction mixture was filtered through silica gel, and the filtrate was evaporated. The resulting crude product was chromatographed over silica gel, and elution with 1% diethyl ether in hexane afforded aldehyde **8** (86 mg, 80%) as an oil.

**Coupling of Aldehyde 8 with 3-Furyllithium.** To a cooled solution of the 3-bromofuran (0.163 g, 0.6 mmol) in dry THF (3 mL) at -78 °C was added *n*-butyllithium (0.6 mL, 1.6 M in hexane). The resulting brown solution was stirred for 10 min at -78 °C, and then a solution of aldehyde **8** (0.121 g, 0.51 mmol) in THF (2 mL) was added dropwise. After this mixture had been stirred for 2 h at -78 °C, excess H<sub>2</sub>O was added at room temperature with additional stirring for 30 min. The product was extracted with ether and dried, and the solvent was evaporated under reduced pressure. The product was chromatographed over silica gel, and elution with 40% ether in hexane afforded isomeric furanolabdane alcohols **9a** (61.3 mg, 39.2%) and **9b** (68.3 mg, 43.7%).

**Furanolabdane alcohol 9a:** colorless oil;  $[\alpha]_D^{24} +19$  (c 1.0, CHCl<sub>3</sub>), lit.<sup>7a</sup>  $[\alpha]_D +18.54$  (c 0.47, CHCl<sub>3</sub>); IR (neat)  $\nu_{\max}$  3400, 2935, 2368, 1630, 1469, 880 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  0.64, 0.77, 0.84 (3H each, s, CH<sub>3</sub>), 4.64 (1H, dd, *J* = 8.8, 2.4 Hz, H-12), 4.48 (1H, bs, H-17), 4.83 (1H, s, H-17), 6.38 (1H, bs, H-14), 7.34, 7.35 (1H each, s, H-15, H-16); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.45 MHz)  $\delta$  14.39 (C-20), 19.30 (C-2), 21.64 (C-19), 24.31 (C-6), 31.73 (C-11), 33.52 (C-4), 33.52 (C-18), 38.26 (C-7), 38.97 (C-1), 39.65 (C-10), 42.06 (C-3), 53.80 (C-9), 55.54 (C-5), 65.14 (C-12), 106.88 (C-14), 108.48 (C-17), 130.23 (C-13), 138.36 (C-15), 143.19 (C-16), 149.70 (C-8); GC/MS *m/z* 302 (M<sup>+</sup>, 19), 284 (44), 191 (69), 177 (68), 137 (86), 97 (87), 95 (100), 69 (84), 41 (54); HRMS *m/z* 302.2248 (calcd for C<sub>20</sub>H<sub>30</sub>O<sub>2</sub>, 302.2291).

**Furanolabdane alcohol 9b:** colorless oil;  $[\alpha]_D^{24} +13$  (c 1.2, CHCl<sub>3</sub>), lit.<sup>7a</sup>  $[\alpha]_D +12.73$  (c 1.5, CHCl<sub>3</sub>); IR (neat)  $\nu_{\max}$  3388, 2936, 1650, 1126, 889 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  0.65, 0.74, 0.79 (3H each, s, CH<sub>3</sub>), 4.64 (1H, dd, *J* = 9.6, 5.1 Hz, H-12), 4.67 (1H, bs, H-17), 4.84 (1H, bs, H-17), 6.36 (1H, bs, H-14), 7.27 (1H, bs, H-16), 7.34 (1H, t, H-15); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.45 MHz)  $\delta$  14.50 (C-20), 19.20 (C-2), 21.59 (C-19), 24.19 (C-6), 31.73 (C-11), 33.40 (C-4), 33.40 (C-18), 38.08 (C-7), 38.62 (C-1), 39.35 (C-10), 41.85 (C-3), 52.70 (C-9), 55.16 (C-5), 65.76 (C-12), 106.55 (C-14), 108.16 (C-17), 128.63 (C-13), 139.58 (C-15), 143.28 (C-16), and 148.71 (C-8); GC/MS *m/z* 302 (M<sup>+</sup>, 29), 284 (77), 191 (58), 177 (53), 137 (80), 97 (100), 69 (85), 41 (50); HRMS *m/z* 302.2250 (calcd for C<sub>20</sub>H<sub>30</sub>O<sub>2</sub>, 302.2291).

**Dehydration of Furanolabdane Alcohols 9.** 2,6-Lutidine (108.9 mg, 1.01 mmol) was added to a solution of **9** (61 mg, 0.2 mmol) in dry dichloromethane (3 mL) under N<sub>2</sub> atmosphere at 0 °C with stirring for 30 min. To the stirred reaction mixture was added benzenesulfonyl chloride (178.3 mg, 1.01 mmol), and then it was stirred at 0 °C for an additional 30 min and then at room temperature overnight. An excess of dichloromethane was added to the reaction mixture, which was washed with 10% HCl solution, saturated NaHCO<sub>3</sub>, and brine. The solvent was evaporated under reduced pressure, and the product was chromatographed over silica gel. Elution with 30% ether in hexane afforded coronarin E (**1**) (41 mg, 71%) as a colorless oil;  $[\alpha]_D^{24} +25$  (c 1.7, CHCl<sub>3</sub>),

lit.<sup>3</sup>  $[\alpha]_D +22.3$  (c 0.44, CHCl<sub>3</sub>); IR (neat)  $\nu_{\max}$  2927, 1603, 1470, 1218, 1050, 759 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  0.82, 0.83, 0.87 (3H each, s, CH<sub>3</sub>), 4.52 (1H, bs, H-17), 4.74 (1H, bs, H-17), 5.96 (1H, dd, *J* = 15.9, 9.9 Hz, H-11), 6.18 (1H, d, *J* = 15.9, H-12), 6.53 (1H, bs, H-14), 7.34 (2H, bs, H-15, H-16); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.45 MHz)  $\delta$  14.99 (C-20), 19.09 (C-2), 21.94 (C-19), 23.35 (C-6), 33.54 (C-4), 33.54 (C-18), 36.74 (C-7), 39.13 (C-10), 40.74 (C-1), 42.27 (C-3), 54.77 (C-5), 61.44 (C-9), 107.61 (C-14), 107.94 (C-17), 121.71 (C-11), 124.47 (C-13), 128.26 (C-12), 139.59 (C-15), 143.25 (C-16), 150.22 (C-8); GC/MS *m/z* 284 (M<sup>+</sup>, 100), 269 (9), 241 (3), 199 (5), 147 (36), 137 (9), 105 (6), 95 (14), 81 (7); HRMS *m/z* 284.2146 (calcd for C<sub>20</sub>H<sub>28</sub>O, 284.2157).

**Deoxygenation of Furanolabdane Alcohols 9 with Li/NH<sub>3</sub>/NH<sub>4</sub>Cl.** A stirred mixture of Li (44 mg, 15 equiv) in NH<sub>3</sub> (15 mL) and THF (5 mL) at -78 °C was added (5 min) to a solution of furanolabdane alcohols **9** (68 mg, 0.22 mmol) in THF (2 mL) during 5 min. After stirring for an additional 20 min at -78 °C, NH<sub>4</sub>Cl (0.4 g) was cautiously added to discharge the blue color, and the NH<sub>3</sub> was allowed to evaporate. After brine was added, the product was extracted with ether. The solvent was evaporated under reduced pressure, and the product was chromatographed over silica gel and eluted with 5% ether in hexane to afford compound **2** (54 mg, 84%) as a colorless oil;  $[\alpha]_D^{24} +23$  (c 2.0, CHCl<sub>3</sub>), lit.<sup>5</sup>  $[\alpha]_D -22$  (c 0.14, CHCl<sub>3</sub>); IR (neat)  $\nu_{\max}$  3050, 1635, 1495, 870 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  0.67, 0.78, 0.85 (3H, s, CH<sub>3</sub>), 2.23 (1H, m, H-12), 2.39 (1H, m, H-7), 2.54 (1H, m, H-17), 4.55 (1H, bs, H-17), 4.84 (1H, bs, H-17), 6.25 (1H, bs, H-14), 7.18 (1H, bs, H-16), 7.33 (1H, t, H-15); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.45 MHz)  $\delta$  14.47 (C-20), 19.36 (C-11), 21.70 (C-19), 23.59 (C-12), 24.05 (C-2), 24.42 (C-6), 33.55 (C-4), 33.55 (C-18), 38.30 (C-7), 38.98 (C-1), 39.56 (C-10), 42.10 (C-3), 55.42 (C-5), 56.05 (C-9), 106.23 (C-17), 110.94 (C-14), 125.59 (C-13), 138.62 (C-16), 142.58 (C-15), 148.51 (C-8); GC/MS *m/z* 286 (M<sup>+</sup>, 31), 271 (9), 253 (3), 191 (27), 135 (26), 95 (100), 67 (18), 41 (13); HRMS *m/z* 286.2290 (calcd for C<sub>20</sub>H<sub>30</sub>O, 286.2299).

**Dehydration of Manool (4) with *p*-Toluenesulfonic Acid.** To a solution of manool (**4**) (3.29 g, 11.3 mmol) in dry THF (25 mL) was added *p*-toluenesulfonic acid (5.83 g, 33.89 mmol) at room temperature. This mixture was refluxed for 2 h, then water was added and extracted with ether. The solvent was evaporated under reduced pressure, and the product was chromatographed over silica gel and eluted with hexane to afford a colorless oil (2.01 g). Further elution with 40% ether in hexane afforded unchanged manool (**4**) (0.98 g). The initial fraction (2.01 g) was rechromatographed over silica gel impregnated with 20% silver nitrate. Elution with 15% ether in hexane afforded a colorless oil (0.85 g, 40%). The NMR spectrum indicated that it consisted of a mixture of *cis/trans*-biformene.<sup>15</sup> Elution with 20% ether in hexane gave sclarene (**10**) (1.07 g, 50%) as a colorless oil;  $[\alpha]_D^{24} +45$  (c 1.0, CHCl<sub>3</sub>); IR (neat)  $\nu_{\max}$  3050, 1626, 900; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  0.66, 0.78, 0.86 (3H, s, CH<sub>3</sub>), 4.53 (1H, bs, H-17), 4.82 (1H, bs, H-17), 4.96 (1H, bs, H-16), 4.97 (1H, bs, H-16), 5.02 (1H, d, *J* = 10.9 Hz, H-15), 5.20 (1H, d, *J* = 17.5 Hz, H-15), 6.35 (1H, dd, *J* = 17.5, 10.9, H-14); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.45 MHz)  $\delta$  16.15, 18.50, 22.40, 22.90, 24.60, 29.90, 33.55, 34.40, 37.60, 39.70, 39.85, 41.80, 52.35, 54.20, 95.90, 102.21, 111.55, 138.90, 144.89, 146.73; GC/MS *m/z* 272 (10), 257 (100), 229 (11), 175 (19), 137 (15), 123 (18), 95 (31), 81 (13); HRMS *m/z* 272.2581 (calcd for C<sub>20</sub>H<sub>32</sub>, 272.2508).

**Photooxygenation of Sclarene (10).** A solution of sclarene (**10**) (0.40 g, 1.47 mmol) in CCl<sub>4</sub>/5% methanol (50 mL) containing *meso*-tetraphenylporphine (3 mg) was irradiated at 15 °C with an external 150 W halogen-tungsten lamp for 24 h, during which time oxygen was bubbled through the reaction mixture. The solvent was evaporated under reduced pressure, and the residue was chromatographed over silica gel and eluted with 5% ether in hexane to afford compound **11** (0.270 g, 60%) as white crystals (hexane): mp 36–38 °C;  $[\alpha]_D^{24} +36$  (c 3.0, CHCl<sub>3</sub>); IR (neat)  $\nu_{\max}$  3069, 1640, 880; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  0.66, 0.77, 0.84 (3H each, s, CH<sub>3</sub>), 4.47 (4H, m, H-15 and H-16), 4.55 (1H, bs, H-17), 4.81 (1H, bs, H-17), 5.61 (1H, m, H-14); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.45 MHz)  $\delta$



14.45, 19.34, 21.26, 21.69, 24.41, 31.24, 33.54, 33.57, 38.28, 39.08, 39.65, 42.10, 55.49, 56.21, 70.00, 72.50, 106.25, 116.85, 136.18, 148.31; HRMS  $m/z$  304.2404 (calcd for  $C_{20}H_{32}O_2$ , 304.2490).

**Reduction of Peroxide 11 with Lithium Aluminum Hydride.** To a suspension of  $LiAlH_4$  (37.43 mg, 0.98 mmol) in dry THF (5 mL) was added dropwise peroxide **11** (0.250 g, 0.82 mmol) in THF (4 mL) at 0 °C. This mixture was refluxed for 2 h, then water was added and extracted with ether. The solvent was evaporated under pressure, and the product was chromatographed over silica gel and eluted with 50% ether in hexane to afford diol **3** (0.241 g, 96%) as white crystals (hexane): mp 119–120 °C;  $[\alpha]_D^{24} +40$  ( $c$  1.0,  $CHCl_3$ ), lit.<sup>6</sup>  $[\alpha]_D -42$  ( $c$  0.39,  $CHCl_3$ ); IR (neat)  $\nu_{max}$  3602, 3079, 1642, 900;  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  0.65, 0.77, 0.84 (3H each, s,  $CH_3$ ), 4.15 (1H, d,  $J = 12.9$  Hz, H-16), 4.17 (1H, d,  $J = 12.9$  Hz, H-16), 4.18 (2H, bd, H-15), 4.49 (1H, bs, H-17), 4.80 (1H, bt, H-17), 5.57 (1H, bt,  $J = 6.9$  Hz, H-14);  $^{13}C$  NMR ( $CDCl_3$ , 75.45 MHz)  $\delta$  14.47 (C-20), 19.34 (C-11), 21.69 (C-19), 22.09 (C-2), 24.41 (C-6), 33.58 (C-4), 33.58 (C-18), 34.63 (C-12), 38.31 (C-7), 39.06 (C-1), 39.67 (C-10), 42.11 (C-3), 55.48 (C-5), 56.39 (C-9), 58.50 (C-16), 60.80 (C-15), 106.29 (C-17), 126.05 (C-14), 144.47 (C-13), 148.56 (C-8); HRMS  $m/z$  306.2558 (calcd for  $C_{20}H_{34}O_2$ , 306.2560).

**Oxidation of Diol 3 with Pyridinium Chlorochromate.** Diol **3** (0.240 g, 0.78 mmol) was dissolved in dichloromethane (3 mL) and oxidized with pyridinium chlorochromate (0.253 g, 1.17 mmol) at room temperature for 30 min. The reaction mixture was filtered through silica gel, and the filtrate was evaporated. The resulting crude product was chromatographed over silica gel. Elution with 5% diethyl ether in hexane afforded furanolabdan (2) (0.192 g, 86%) as a colorless oil.

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## References and Notes

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