SHORT PAPER

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Synthesis of (+)-coronarin E, (-)-7-*epi*-coronarin A and (+)-15, 16-epoxy-8(17), 13(16), 14-labdatriene from (+)-manool†

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An efficient method for the synthesis of (+)-coronarin E **1**, (+)-*epi*-coronarin A **2** and (+)-15, 16-epoxy-8(17), 13(16), 14-labdatriene **3** *via* the homodrimane **9**, obtained in four steps from (+)-manool **5**, is described.

Keywords: labdane diterpene, furanolabdane, diterpene, homodrimane

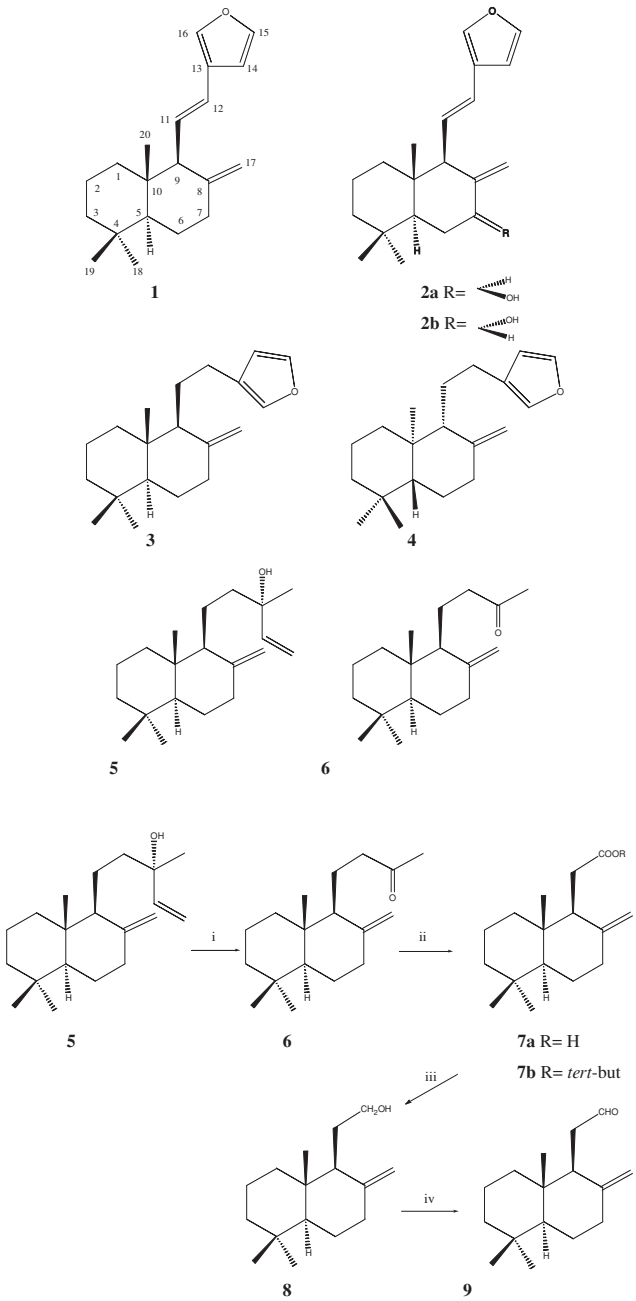
A large number of labdane-type diterpenoids have been isolated from terrestrial plants and sponges.[1] They exhibit interesting biological properties such as cytotoxic, antifungal, anti-inflamatory and analgesic activity.[2] In 1988 Itokawa *et al*.[3] isolated the furanolabdane coronarin E **1** from the rhizomes of the Brazilian medicinal plant *Hedychium coronarium*. This compound was also isolated from other plants.[4] In 1988 Itokawa *et al*.[5] isolated the furanolabdane coronarin A **2a** from the rhizomes *Hedychium coronarium*, which exhibited significant biological activity. In 2000, Tasdemir *et al*.[6] isolated a furanolabdane from *Cacospongia* sp. and assigned to it configuration **3** with the A/B ring junction of normal labdane diterpenes. In 1991, Zdero *et al*.[7] reported the isolation of compound **4** with the antipodal stereochemistry of **3** from terrestrial plant *Blepharispermum zanguebaricum*.

So far, a number of semi-synthesis[8] of these biologically active labdane-type diterpenoids have been reported by employing (–)-sclareol as a starting material.

(+)-Manool **5** is a readily available natural diterpene with established absolute stereochemistry. In 1982 Nakano *et al*.[9] reported the synthesis of some labdane type diterpenes such as labdafuran **3** from (+)-manool **5** but in poor yield. Previously Nakano *et al*. [10] reported the oxidative cleavage of (+)-manool **5** to ketone **6** in good yield. In this paper we report the synthesis of (+)-coronarin E **1**, (+)-*epi*-7-coronarin A **2b** and (+)-furanolabdane **3** from (+)-manool **5**.

Oxidative cleavage of ketone **6** with potassium *tert*-butoxide in the presence of oxygen gave an acid **7a** (60 % yield) with only small amounts of *tert*-butyl ester of acid **7b**.[10] Reduction of acid **7a** with $LiAlH_4$ afforded the alcohol **8** (90 % yield).[11] Subsequent oxidation of this alcohol **8** with tetra-*n*-propylammonium perruthenate TPAP [12] or pyridinium chlorochromate yielded the aldehyde **9** in 83 % and 80 % yield respectively.

The nucleophilic addition of the organolithium compound derived from 3-bromofuran, to the aldehyde **9** afforded a mixture of isomeric furanolabdane hydroxides **10a** (39.2 % yield) and **10b** (43.7 % yield), whose physical and spectroscopic properties were identical to those reported.[8a] Elimination of the hydroxyl group to the exclusively *E*-configurated side chain succeeded by using a modified procedure according to Jung *et al*.[8a] This mixture of isomers, without separation, was dehydrated with 2,6-lutidine in the presence of benzenesulfonyl chloride to afford coronarin E **1** (71 % yield), whose physical and spectroscopic properties were



Scheme 1 (i) $KMnO_4$, $MgSO_4$, acetone, 20°C; (ii) Potassium *tert*-butoxide, O_2, DME, r.t.; (iii) $LiAlH_4$, THF, refl.; (iv) TPAP, N-methylmorpholine N-oxide, CH_2Cl_2, or PCC, CH_2Cl_2, r.t.

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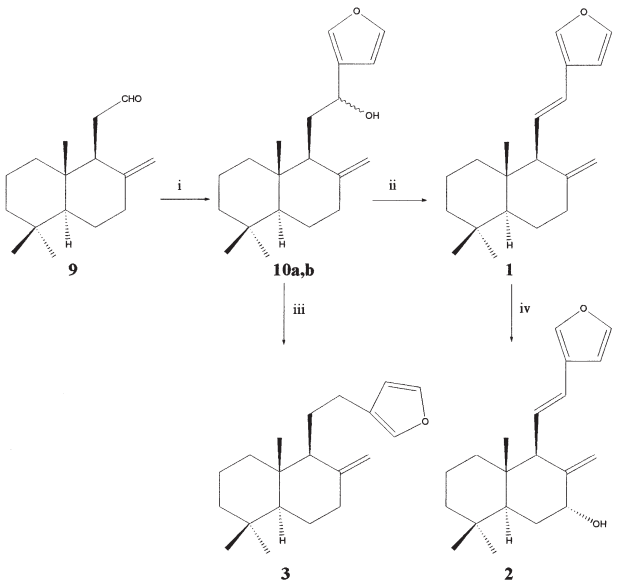
identical to those reported.[3, 4] Allylic oxidation of **1** with selenium oxide and *tert*-butyl peroxide in methylene chloride provided (–)-*epi*-coronarin A **2b** (73 % yield).[8a]



Scheme 2 (i) 3-bromofuran, *n*-BuLi, THF, -78 °C (ii); benzenesulfonyl chloride, 2,6-lutidine, CH_2Cl_2, 0 °C- r.t.;(iii) Li/NH_3/NH_4Cl, THF, -78°C; (iv) SeO_2, *tert*-BuOOH, CH_2Cl_2, r.t.

To synthesise the compound **3**, we first tried to reduce the hydroxyl group of the furanolabdane hydroxides **10** with a chlorotrimetylsilane/NaI/zinc system.[13] However, this method failed to reduce the alcohol. Reduction with Li/NH_3/NH_4Cl[14] gave a good result, yielding the desired compound **3** in 84 % yield. This compound had spectroscopic data identical to those reported,[6, 7] but it showed $[\alpha]_D$ + 45° (*ca* 2.0, $CHCl_3$). Tasdemir *et al*.[6] reported for this compound the optical rotation of the opposite sign, $[\alpha]_D$ -22 (*ca* 0.14, $CHCl_3$). This indicates that the structure **3** which he assigned to his furanolabdane is not correct and the compound should possess structure **4**, the enantiomer of **3**.

Experimental

Mps were measured with a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded with a Bruker Advance-300 and Advance-500 spectrometers for solutions in $CDCl_3$. IR spectra were recorded using a Nicolet Magna 560 FT-IR 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. Specific rotations were measured at 24 °C with a Perkin-Elmer 341 polarimeter. THF, ether, DME and benzene were freshly distilled from sodium 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 G254 and the spots were observed either by exposure to iodine or by UV light. All organic extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure below 60°C.

Oxidative cleavage of ketone **6**: To a solution of ketone **6** (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 by 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 **7b**. Elution with 40 % ether in hexane afforded the acid **7a** as an oil (1.34 g, 60 %); HRMS *m/z* 250.1935 (M^+, $C_{16}H_{26}O_2$ requires 250.2064); GC/MS *m/z* 250 (M^+, 52), 235 (100), 233 (19), 191 (30), 153 (34), 137 (79), 95 (55), and 81 (50); δ_H (300 MHz) 0.66, 0.78, 0.86 (3H each, s, CH_3-14, CH_3-15, CH_3-16), 4.51 (1H, s, H-13), 4.75 (1H, s, H-13); δ_C (75.45 MHz) 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, and 180.01.

Reduction of acid **7a** *with lithium aluminium hydride:* To a suspension of $LiAlH_4$ (0.305 g, 8.0 mmol) in dry THF (5 ml) was added dropwise acid **7a** (0.99 g, 4.8 mmol) in THF (4 ml) at 0°C. This mixture was refluxed for 2 h. then water was added and the product was 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 **8** (0.84 g, 90 %); HRMS *m/z* 236.2141 (M^+, $C_{16}H_{28}O$ requires 236.2190); GC/MS *m/z* 236 (M^+, 67), 221 (57), 203 (43), 177 (94), 137 (100), 95 (98), and 81 (73); δ_H (300 MHz) 0.65, 0.77, 0.84 (3H each, s, CH_3-14, CH_3-15, CH_3-16), 3.48 (1H, m, H-12), 3.68 (1H, m, H-12), 4.50 (1H, bs, H-13) and 4.79 (1H, bs, H-13); δ_C (75.45 MHz) 14.25, 19.30, 21.64, 24.29, 26.98, 33.54, 33.54, 38.17, 38.97, 39.34, 42.05, 52.74, 55.41, 62.46, 106.33, and 148.78.

Oxidation of alcohol **8** *with tetra-n-propylammonium perruthenate*: Alcohol **8** (85 mg, 0.36 mmol) was dissolved in dichloromethane (3 ml) containing both 4Å 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 followed by TLC until complete. The reaction mixture was filtered through silica gel and elution with hexane afforded aldehyde **9** (70 mg, 83 %) as a oil; HRMS *m/z* 234.1985 (M^+, $C_{16}H_{26}O$ requires 234.2010); GC/MS *m/z* 234 (M^+, 15), 217 (77), 190 (100), 137 (96), 95 (64), and 81 (53); δ_H (300 MHz) 0.67, 0.78, 0.86 (3H each, s, CH3), 4.35 (1H, bs, H-13), 4.78 (1H, bs, H-13) and 9.60 (1H, m, H-12); δ_C (75.45 MHz) 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, and 203.50.

Oxidation of alcohol **8** *with PCC*: Alcohol **8** (0.108 g, 0.45 mmol) was dissolved in dichloromethane (3 ml) and oxidised 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. Elution with 1 % diethyl ether in hexane afforded aldehyde **9** (86 mg, 80 %) as an oil.

Coupling of the aldehyde **9** *with 3-furyllithium:* To a cooled solution of the 3-bromofuran (0.163 g, 0. mmol) in dry THF (3 ml) at –78 °C, was added *n*-butyllithium (0.6 ml, 1.6M in hexane). The resulting brown solution was stirred for 10 min. at –78 °C and then a solution of aldehyde **9** (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_2O was added at room temperature with additional stirring for 30 minutes. The product was 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 isomeric furanolabdane hydroxides **10a** (61.3 mg, 39.2 %) and **10b** (68.3 mg, 43.7 %).

Furanolabdane hydroxide **10a**: HRMS *m/z* 302.2248 (M^+, $C_{20}H_{30}O_2$ requires 302.2291); GC/MS *m/z* 302 (M^+, 19), 284 (44), 191 (69), 177 (68), 137 (86), 97 (87), 95 (100), 69 (84), and 41 (54); δ_H (300 MHz) 0.64, 0.77, 0.84 (3H each, s, CH_3), 4.64 (1H, dd, *J*= 8.8, 2.4 Hz, H-12), 4.48 (1H, s, H-17), 4.83 (1H, s, H-17), 6.38 (1H, bs, H-14), and 7.34, 7.35 (1H each, s, H-15, H-16); δ_C (75.45 MHz) 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), and 149.70 (C-8).

Furanolabdane hydroxides **10b**: HRMS *m/z* 302.2250 (M^+, $C_{20}H_{30}O_2$ requires 302.2291); GC/MS *m/z* 302 (M^+, 29), 284 (77), 191 (58), 177 (53), 137 (80), 97 (100), 69 (85), and 41 (50); δ_H (300 MHz) 0.65, 0.74, 0.79 (3H each, s, CH_3), 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), and 7.34 (1H, t, H-15); δ_C (75.45 MHz) 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).

Dehydration of furanolabdane hydroxides **10**: 2,6-Lutidine (108.9 mg, 1.01 mmol) was added to a solution of **10** (61 mg, 0.2 mmol) in dry methylene chloride (3 ml) under N_2 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 additional 30 min. and then at room temperature overnight. An excess methylene chloride was added to the reaction mixture, which was washed with 10% HCl solution, saturated $NaHCO_3$, 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 colourless oil; $[\alpha]_D$ +25 (*c* 1.7, $CHCl_3$), lit.[3] $[\alpha]_D$ +22.3 (*c* 0.44, $CHCl_3$); IR (neat) ν_{max} 2927, 1603, 1470, 1218, 1050, 759 cm^{-1}; HRMS *m/z* 284.2146 (M^+, $C_{20}H_{28}O$ requires 284.2157); GC/MS *m/z* 284 (M^+, 100), 269 (9), 241 (3), 199 (5), 147 (36), 131 (8), 105 (6), 95 (14), and 81 (7); δ_H (300 MHz) 0.82, 0.83, 0.87 (3H each, s, CH_3), 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), and 7.34 (2H, bs, H-15, H-16); δ_C (75.45 MHz) 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), and 150.22 (C-8).

Oxidation of coronarin E **1** *with* SeO_2: To a stirred solution of SeO_2 (150 mg, 1.35 mmol) in methylene chloride (2 ml), *tert*-BuOOH (228 mg, 2.53 mmol) was added dropwise under N_2 atmosphere at room temperature. After 10 min, a solution of coronarin E **1** (90 mg, 0.31 mmol) in dry methylene chloride (3 ml) was added. The mixture was stirred for 5 h and then excess of methylene chloride was added and washed with H_2O. The solvent was evaporated under reduced pressure and the product was chromatographed over silica gel. Elution with 40 % ethyl acetate in hexane afforded compound **2b** (70 mg, 73 %) as colourless oil; $[\alpha]_D$ -7.9 (*c* 1.5, $CHCl_3$), (lit.[8a] $[\alpha]_D$ -6.9 (*c* 0.1, $CHCl_3$)); IR (neat) ν_{max} 3435, 2930, 1465, 1370, 1020, 870 cm^{-1}; HRMS *m/z* 300.2089 (M^+, $C_{20}H_{28}O_2$ requires 300.2091); GC/MS *m/z* 300 (M^+, 90), 282 (40), 209 (18), 189 (100), 161 (45), 149 (23), 121 (80) 105 (65), and 94 (89); δ_H (300 MHz) 0.79, 0.81, 0.88 (3H, s, CH_3), 2.87 (1H, d, *J*= 9.6 Hz, H-9), 4.41 (1H, d, *J*= 2.7 Hz, H-7), 4.68 (1H, bs, H-17), 4.97 (1H, bs, H-17), 6.23 (1H, d, *J*= 15.6 Hz, H-12), 6.52 (1H, bs, H-14), and 7.34 (2H, bs, H-15, H-16); δ_C (75.45 MHz) 14.02 (C-20), 19.03 (C-2), 21.73 (C-19), 29.91 (C-6), 33.06 (C-18), 33.22 (C-4), 39.35 (C-10), 40.37 (C-1), 42.17 (C-3), 46.91 (C-5), 55.96 (C-9), 73.37 (C-7), 107.51 (C-17), 111.81 (C-14), 122.36 (C-11), 124.30 (C-13), 127.16 (C-12), 139.77 (C-15), 143.33 (C-16), and 151.26 (C-8);.

Deoxygenation of furanolabdane hydroxides **10** *with* $Li/NH_3/NH_4Cl$: A stirred mixture of Li (44mg, 15 equiv.) in NH_3 (15 ml) and THF (5 ml) at –78°C was added (5 min) a solution of furanolabdane hydroxides **10** (68 mg, 0.22 mmol) in THF (2 ml) during 5 min. After stirring for an additional 20 min. at –78°C, NH_4Cl (0.4 g) was cautiously added to discharge the blue color, and the NH_3 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. Elution with 5 % ether in hexane afforded compound **3** (54 mg, 84 %) as colourless oil; $[\alpha]_D$ + 45 (*c* 2.0, $CHCl_3$), lit.[6] $[\alpha]_D$ –22 (*c* 0.14, $CHCl_3$); IR (neat) ν_{max} 3050, 1635, 1495, 870 cm^{-1}; HRMS *m/z* 286.2290 (M^+, $C_{20}H_{30}O$ requires 286.2299); GC/MS *m/z* 286 (M^+, 31), 271 (9), 253 (3), 191 (27), 135 (26), 95 (100), 67 (18), and 41 (13); δ_H (300 MHz) 0.67, 0.78, 0.85 (3H, s, CH_3), 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), and 7.33 (1H, t, H-15); δ_C (75.45 MHz) 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), and 148.51 (C-8).

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