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Synthesis of (+)-Coronarin E

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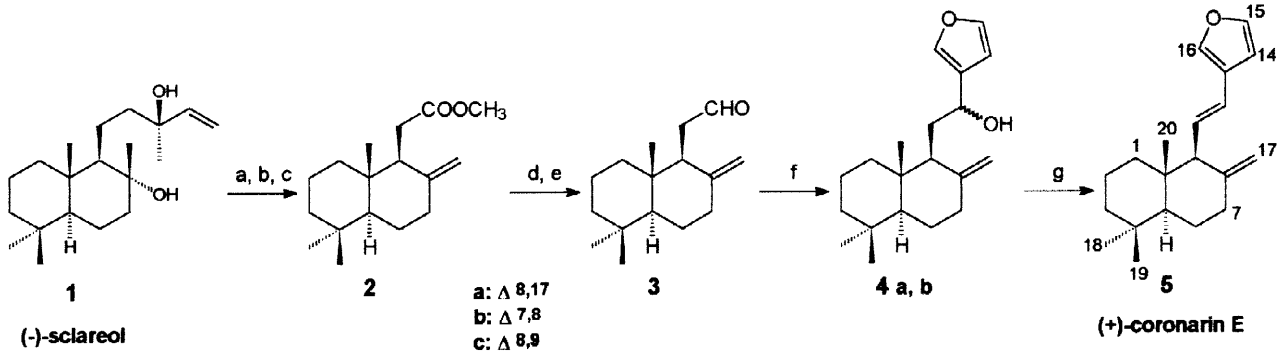
Abstract: The labdane-type diterpenoid (+)-coronarin E (**5**) has been synthesized in 7 steps from (-)-sclareol (**1**) for the first time.

Labdane-type diterpenoids are one of the main groups in terpenoid natural products. Some of these compounds have interesting pharmacological properties such as cytotoxic[1], anti-inflammatory and analgesic activity[2]. (+)-Coronarin E (**5**) has been isolated from the rhizomes of the Brazilian medical plant *Hedychium coronarium* (Zingiberaceae)[3] and 5 other plants.[4] Starting from (-)-sclareol (**1**) we have synthesized (+)-coronarin E (**5**) for the first time.



a) $RuCl_3 H_2O$, $NaIO_4$, H_2O/CH_3CN, CCl_4, r. t. (acetoxyacid: 50 %, sclareolide: 30 %); b) Me_2SO_4, $LiOH H_2O$, DMF, r. t. (99 %); c) $KHCO_3$, DMSO, 150°C (74%, rel. to turnover); d) $LiAlH_4$, THF or diethyl ether, refl. (97 %); e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C - r. t. or PCC/Alox B, CH_2Cl_2, 0°C - r. t. (86 - 96 %); f) 3-furyllithium, THF, -78°C (total 65 %, relation 1:1); g) $Cl_3C\text{-}CO\text{-}CF_3$, pyridinium p-toluenesulphonate, benzene, refl. (50 %, rel. to turnover).

Scheme

The side chain of **1** can effectively be cleaved with loss of 4 carbon atoms by using the reaction described by Martres.[5] The formed (-)-acetoxyacid can be separated from (+)-sclareolide[6] and easily transformed to the methyl ester with Me_2SO_4. Heating this ester the acetoxy group in position 8 was eliminated to produce compound **2a** as the main product. The two isomers with double bonds in positions $\Delta^{7,8}$ **2b** and $\Delta^{8,9}$ **2c** resulted also. The reduction of the isomer mixture with $LiAlH_4$ to the alcohols and the oxidation by Swern

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or with pyridinium chlorochromate (PCC) yielded the corresponding aldehydes (**3a/3b/3c** = 13:1:1). **3a** could be separated by means of MPLC.[7] Coupling reaction of **3a** with freshly prepared 3-furyllithium in absolute THF gave the diastereomers **4a** and **4b**. Elimination of the hydroxy group to the exclusively *E*-configurated side chain succeeded by using a modified procedure according to Abdel-Baky.[8] The reaction of 1,1,1-trichlorotrifluoroacetone with the furanoic alcohol **4a** or **4b** in absolute benzene formed the corresponding hemiketals which eliminate water to produce (+)-coronarin E (**5**).[9] No *Z*-isomer of **5** was detected by NMR-spectroscopy. We substituted p-toluenesulphonic acid which was used by Abdel-Baky in catalytic amounts by pyridinium p-toluenesulphonate. The exocyclic double bond of **4a, 4b** is unstable under the original conditions.

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5) Martres, P.; Perfetti, P.; Zahra, J. P.; Waegell, B.; Giraudi, E.; Petrzilka, M. *Tetrahedron Lett.* **1993**, 34, 629-30; Martres, P.; Perfetti, P.; Zahra, J. P.; Waegell, B. *Tetrahedron Lett.* **1993**, 34, 3127-3128.

6) Reaction and separation are practicable in large scale. Usually we started with 15.0 g (-)-sclareol (**1**). Separations were carried out with column chromatography (500 g silica, cyclohexane/ethyl acetate = 9:1, isocratic).

7) MPLC: column 920 x 24 mm (LiChroSpher Si 60, 15 μm), flow 25 ml/min, gradient hexane/ethyl acetate = 100:0 → 15:1 in 30 min.

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9) **(+)-Coronarin E** (**5**): colourless oil, $[\alpha]_D^{23}$ + 23° (c 0.22, $CHCl_3$). Ref. 3: $[\alpha]_D$ + 22.3° ($CHCl_3$). **IR** ν_{max} cm^{-1}: 2930, 1640, 1510, 900, 870. **MS** m/z (%): 284 (M^+, 36), 199 (4), 159 (12), 147 (100), 81 (26). **HRMS**: Calcd. for $C_{20}H_{28}O$ 284.2140. Found: 284.2140. **^{1}H NMR** (500 MHz, $CDCl_3$): 7.35 (br.s, 2H, H-15/16), 6.53 (br.s, 1H, H-14), 6.17 (d, 1H, 15.7 Hz, H-12), 5.96 (dd, 1H, 15.7/9.8 Hz, H-11), 4.74 (d, 1H, 1.7 Hz, H-17), 4.51 (d, 1H, 1.7 Hz, H-17'), 2.43 (ddd, 1H, 13.5/4.3/2.2 Hz, H-7eq), 2.38 (d, 1H, 9.8 Hz, H-9ax), 2.08 (ddd, 1H, 13.5/4.9 Hz, H-7ax), 1.68 (dddd, 1H, 13.0/4.9/2.7 Hz, H-6eq), 1.49 (2H, H-1eq, H-2ax), 1.38 (3H, H-2eq, H-3eq, H-6ax) 1.17 (ddd, 1H, 13.7/4.5 Hz, H-3ax), 1.09 (dd, 1H, 12.6/2.6 Hz, H-5), 1.01 (ddd, 1H, 13.5/3.3, H-1ax), 0.88 (s, 3H, H-18), 0.83 (s, 6H, H-19, H-20). **^{13}C NMR** ($CDCl_3$): 150.2 (C-8), 143.3 (C-15), 139.6 (C-16), 128.3 (C-11), 124.5 (C-13), 121.7 (C-12), 107.9 (C-17), 107.6 (C-14), 61.4 (C-9), 54.8 (C-5), 42.3 (C-3), 40.7 (C-1), 39.1 (C-10), 36.7 (C-7), 33.6 (C-18), 33.6 (C-4), 23.4 (C-6), 22.0 (C-19), 19.1 (C-2), 15.0 (C-20).
The reaction was carried out under argon atmosphere. 114.0 mg (0.265 mmol) 1,1,1-trichlorotrifluoroacetone was cleaned through Alox B and added to a mixture of 1.7 mg (0.006 mmol) pyridinium p-toluenesulphonate in 2 ml benzene. A solution of 80.0 mg **4a** in 3 ml benzene was added and refluxed for 7 h. After cooling at r. t. the mixture was separated between water and diethyl ether. The organic layers were washed with 15% $KHCO_3$ and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded 89.0 mg crude product, which was chromatographed by MPLC to get 19 mg **5** and 35 mg **4a**. (MPLC analogous to ref. 7, gradient hexane/toluene = 100:0 → 15:1 in 15 min.)