

Synthesis of (+)-Coronarin E

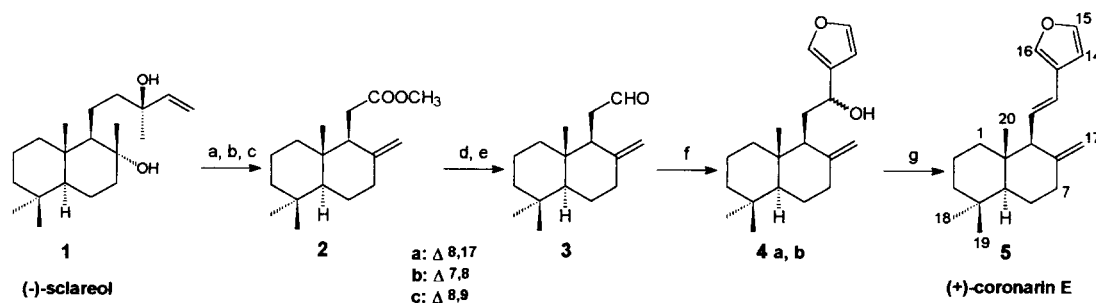
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Abstract: The labdane-type diterpenoid (+)-coronarin E (**5**) has been synthesized in 7 steps from (-)-sclareol (**1**) for the first time. © 1998 Elsevier Science Ltd. All rights reserved.

Labdane-type diterpenoids are one of the main groups in terpenoid natural products. Some of these compounds have interesting pharmacological properties such as cytotoxic¹, anti-inflammatory and analgesic activity². (+)-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) $\text{RuCl}_3 \cdot \text{H}_2\text{O}$, NaIO_4 , $\text{H}_2\text{O}/\text{CH}_3\text{CN}$, CCl_4 , r. t. (acetoxyacid: 50 %, sclareolide: 30 %); b) Me_2SO_4 , $\text{LiOH} \cdot \text{H}_2\text{O}$, 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, $(\text{COCl})_2$, 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) $\text{Cl}_3\text{C-CO-CF}_3$, 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 (+)-sclareolide⁶ 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

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*-configured 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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- 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.
- 8) Abdel-Baky, S.; Moussa, A. *Synth. Commun.* **1988**, *18*, 1795-1800.
- 9) (+)-**Coronarin E (5)**: colourless oil, $[\alpha]_D^{23} + 23^\circ$ (c 0.22, CHCl₃). Ref. 3: $[\alpha]_D^{23} + 22.3^\circ$ (CHCl₃). IR $\nu_{\max}$ cm⁻¹: 2930, 1640, 1510, 900, 870. MS *m/z* (%): 284 (M⁺, 36), 199 (4), 159 (12), 147 (100), 81 (26). HRMS: Calcd. for C₂₀H₂₈O 284.2140. Found: 284.2140. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (CDCl₃): 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% KHCO₃ and brine and dried over anhydrous Na₂SO₄. 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.)