Monatshefte für Chemie 134, 1195–1206 (2003)
DOI 10.1007/s00706-003-0046-6

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Synthesis of Side Chain Substituted 3-Butylisocoumarins and Absolute Configurations of Natural Isocoumarins from *Artemisia dracunculus*

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Received March 17, 2003; accepted March 19, 2003
Published online August 18, 2003

Summary. A series of 3-hydroxy- and 3-bromobutyl-substituted isocoumarins was synthesized. The absolute configurations of three isocoumarin derivatives from *Artemisia dracunculus*, namely (−)-epoxyartemidin, (−)-2′-methoxydihydroartemidin, and (+)-3′-hydroxyartemidin were determined by chemical means *via* derivatization, kinetic racemate resolution (*Horeau* method), and comparison of the circular dichroism (CD) spectra.

Keywords. Epoxyartemidin; 2′-Methoxydihydroartemidin; 3′-Hydroxyartemidin; Circular dichroism; Chiral resolution; *Horeau* method.

Introduction

Isocoumarins are metabolites of limited distribution. However, the about 200 until now known compounds have been isolated from a remarkable manifold of sources from bacteria, fungi, lichen, and to a less extent also from higher plants and insects [1, 2]. The biological activities of some isocoumarins [2] have drawn increased attention on some of the derivatives, *e.g.*, the phytoalexine 6-methoxymellein (8-hydroxy-6-methoxy-3-methylisocoumarin) from carrots [3–5].

In the course of an investigation of natural constituents of the genus *Artemisia* (*Compositae*, *Asteraceae*) [6–10] we have now focussed our attention on *A. dracunculus*, a plant which is not only used as a spice (tarragon) but also well known for several biological activities, *e.g.*, against worms in the intestinal [11] or as an

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insect repellent [12]. Tarragon has always been used in folk medicine, *e.g.*, in case of stomache troubles [13] or for treatment of rheumatism, gout [13], or toothache [13, 14].

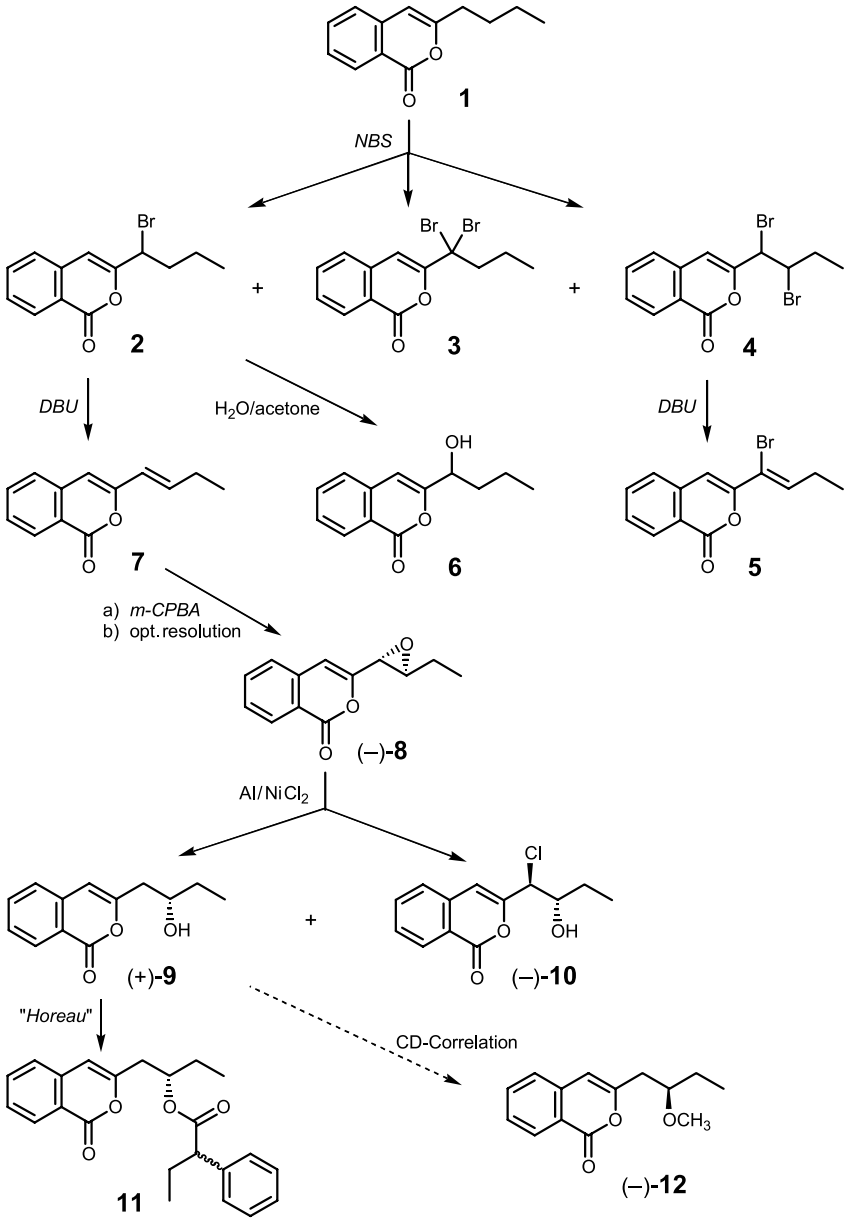
The genus *Artemisia* is characterized by polyacetylenes, sesquiterpene lactones, coumarins, flavanoids, lignans, and terpenoid essential oils [15, 16]. However, especially isocoumarin derivatives represent unique chemical characters of the *A. dracunculus* group (*A. dracunculus* s. str. and closely related species) [17]. Bioassays with several isocoumarins of *A. dracunculus* showed remarkable antifungal activities. Based on these preliminary results it was of interest to synthesize a series of isocoumarins, either natural or closely related compounds, for a more detailed antifungal testing followed by an eventual study of structure-activity relationship and also for the elucidation of the absolute stereochemistries of some of the novel compounds.

Results and Discussion

Since (*E*)-artemidin (**7**) was the central compound of our synthetic efforts, some time was expended to optimize the synthetic route to this compound. The methods for syntheses of isocoumarin derivatives have been reviewed 1997 by *Napolitano* [20]. For the synthesis of dihydroartemidin (**1**) as the starting isocoumarin we followed generally the method of *Batu* and *Stevenson* [21, 22] in the modification of *Liao* and *Cheng* [23]. The former authors reacted the copper acetylide of 1-hexine with 2-iodobenzoic acid and obtained a mixture of 5-ring lactone (phthalide) and the desired 6-ring lactone 3-butylisocoumarin. In the modification of *Liao* and *Cheng* the copper salt for the C–C-coupling reaction was substituted by a zinc salt with $Pd(PPh_3)_4$ as catalyst. We obtained yields between 78 and 91% for the coupling/annelation reaction (Ref. [23] 84%), the amount of the phthalide side product was small (ca. 5%) and did not disturb the crystallization of dihydroartemidin (**1**). In this reaction we could reduce the amount of catalyst by 50% without any decrease of the observed yields (2.5 mol%, Ref. [23] 5 mol%).

The next step towards (*E*)-artemidin (**7**) was the allylic bromination of **1** with *N*-bromosuccinimide (*NBS*) [21, 24, 25] to 1′-bromodihydroartemidin (**2**) (Scheme 1). Compared to Ref. [21], the use of dibenzoylperoxide (*DBPO*) allowed to reduce the reaction time drastically (to about 1/3). The yield of 1′-bromodihydroartemidin depended to a high degree on the purity of **1** and could be increased from 47% to 92% using recrystallized dihydroartemidin (**1**). Two side products, 1′,1′-dibromodihydroartemidin (**3**) and 1′,2′-dibromodihydroartemidin (**4**) (3% each) were also of interest for our biological testing programme. A further derivative, (*E*)-1′-bromoartemidin (**5**) could be obtained in 36% yield by dehydrohalogenation of compound **4** with *DBU* [26, 27]. 1′- Hydroxydihydroartemidin (**6**), which was also needed for the bioassays, was obtained in 100% yield by hydrolysis of the 1′-bromo compound **2** with water/acetone (1 h, 90°C) [28, 29].

The dehydrohalogenation of **2** to artemidin (**7**) by the method described by *Batu* and *Stevenson* [21] gave yields between 35 and 40% (no comments on the yields were given in Ref. [21]). Absolute tetrahydrofuran instead of benzene or toluene as solvent, the slow addition of *DBU* at room temperature, shortening of



Scheme 1

the reaction time from 10 to 2.5 hours, and a modified workup (see Exp.) raised the yields finally to about 60%. Only the (*E*) configured product **7** was obtained, in the ^{1}H NMR spectra not even traces of the (*Z*) product could be detected.

(*E*)-Artemidin (**7**) was oxidized to epoxyartemidin (**8**) by means of 3-chloroperbenzoic acid (*m-CPBA*) [30, 31]. The optical resolution of the resulting racemate was achieved by chiral MPLC on triacetyl cellulose [32, 33], giving the natural (−)-epoxyartemidin ((−)-**8**) [10, 18] and its optical antipode ((+)-**8**) in 100% enantiomeric purity.

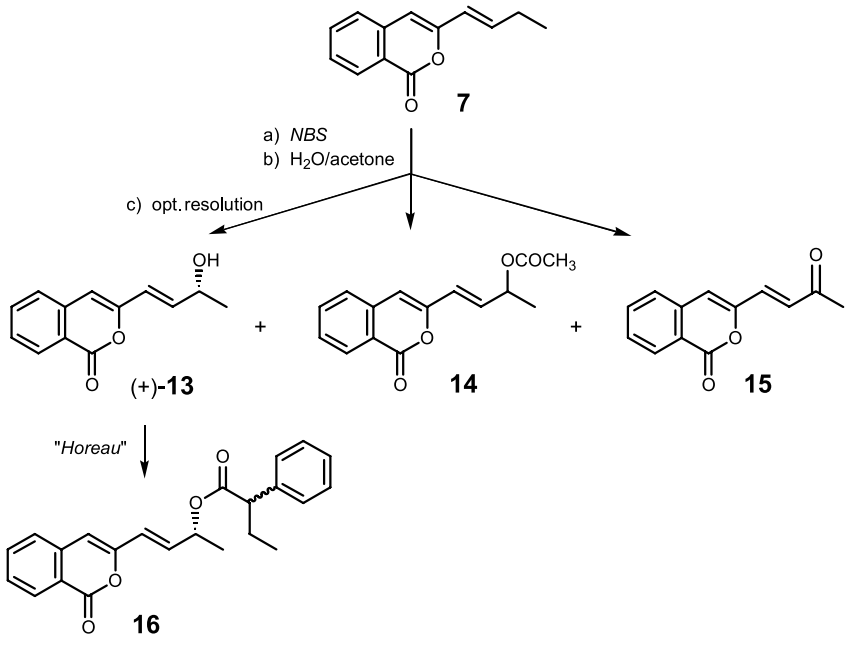
Reduction of epoxides to the corresponding optically active secondary alcohols allowed the determination of absolute configurations using the empirical method of *Horeau via* kinetic racemate resolution of racemic 2-phenylbutanoic acid anhydride [34]. For the reduction of the epoxide function of the lactonic isocoumarin (−)-**8** a relatively mild reducing agent was necessary. $NaBH_4$ failed, however, the method of *Sarmah* and *Barua* [35] using a system of aluminum powder and nickel chloride in tetrahydrofuran was successful. The yield of the resulting alcohol was rather low (14%), but 60% of the starting epoxide could be recovered. Pure (+)-2′-hydroxydihydroartemidin ((+)-**9**) was obtained and no 1′-hydroxy compound was present in the reaction product. The expected retention of configuration was in agreement with the CD spectra showing identical maxima for (−)-**8** and (+)-**9** (see Exp.). Comparison of the optical rotations of (−)-**8** and (+)-**9** at different wave lenghts showed that the small negative $[\alpha]_D$ value (at $\lambda = 589$ nm) of (−)-**8** changes to positive values at lower wavelenghts (365 nm), corresponding to a positive *Cotton* effect in the long wave ORD region, which is again in agreement with the CD data (see Exp.).

A side product of the $Al/NiCl_2$ reduction of (−)-**8**, also of interest for the antifungal testing, was 1′-chloro-2′-hydroxydihydroartemidin ((−)-**10**). This is presumably the product of a nucleophilic substitution with a chloride ion (from the $NiCl_2$ reagent) leading to an inversion of configuration at C-1′ (S_N2-reaction). Since the CD of (−)-**10** is influenced predominantly by the 1′-chloro substituent which is closer to the isocoumarin chromophore, the CD curve for (−)-**10** shows almost a mirror image of the corresponding curve for (+)-**9** (and (−)-**8**).

Following the procedure of *Horeau* [36, 37] the secondary alcohol (+)-**9** was reacted with the anhydride of racemic 2-phenylbutanoic acid. After 20 hours at room temperature the excessive anhydride was hydrolyzed and the remaining 2-phenylbutanoic acid separated from the *Horeau* ester **11**. The optical rotation of the acid had a negative sign, indicating that (+)-2-phenylbutane acid had reacted preferentially. This is indicative for an (*S*) configuration of (+)-**9** and (*R,S*) configuration for (−)-**8**. The ^1H NMR spectrum of the diastereomeric ester mixture **8** showed a diastereomeric ratio of 65:35 corresponding to an optical yield of 30% for the kinetic racemate resolution. This is significantly above the reliability minimum of 20% given by *Horeau* [36, 37].

The absolute configuration of a further natural isocoumarin derivative, namely 2′-methoxydihydroartemidin ((−)-**12**) [38] could be correlated with (+)-**9** *via* their CD spectra. The entire CD curve of natural (−)-**12** is opposite to the one of (*S*)-(+)-**9** (see Exp.) and is therefore only compatible with the (*R*) configuration. The optical rotation of (*R*)-(−)-**12** is rather small and not really significant, however, the CD spectrum allowed a clear decision.

A further target molecule was the natural (+)-3′-hydroxyartemidin ((+)-**13**) (Scheme 2). To this end, artemidin (**7**) was reacted with *NBS* for allylic bromination to 3′-bromoartemidin [24, 25]. The reaction proceeded not very smooth and the isolation of 3′-bromoartemidin was not possible. Dibenzoyl peroxide as a radical starter and irradiation with a 1000 W halogene lamp was needed to start the reaction. Chromatography of the raw bromination product on Al_2O_3 with petrol ether:ethyl acetate = 1:1 did not yield pure fractions containing the desired



Scheme 2

halogenation product, but already some hydrolized product **13**, its acetate **14** as a result of ester exchange with the eluent ethyl acetate, the α,β-unsaturated ketone **15** as oxidation product, and the 1′,2′-bromo addition product **4**; the latter compound has already been isolated as a side product of the *NBS* bromination of **1** (see above). Due to the obvious instability of 3′-bromoartemidin we resigned on further attempts to purify this compound. To increase the amount of the mainly desired 3′-hydroxyartemidin (**13**), the crude bromination product was subjected directly to hydrolysis with acetone/water at room temperature [28, 29]. The resulting reaction product was chromatographed carefully to give 5% of 3′-hydroxyartemidin (**13**), 3% of 3′-acetoxyartemidin (**14**), 4% of 3′-oxoartemidin (**15**), and finally 3% of 1′,2′-dibromodihydroartemidin (**4**). The unsaturated alcohol **13** was degrading slowly at room temperature but proved to be fairly stable in the freezer. All side products (**14**, **15**, **4**) were also isolated and characterized because they were of interest for antifungal screening.

The optical resolution of racemic **13** on triacetyl cellulose [32, 33] gave the two optically pure enantiomers. Comparison of the CD spectra proved that the (+)-**13** enantiomer was identical with the natural product (+)-3′-hydroxyartemidin obtained from *A. dracunculus* in a very small amount [38, 10]. For determination of the absolute configuration, synthetic (+)-**13** was reacted with racemic 2-phenylbutanoic acid according to the *Horeau* method [36, 37]. The reaction that proceeded very slowly (TLC) was interrupted after *ca*. 50% of (+)-**13** had reacted (48 hours). After workup, the remaining acid showed a positive rotation, the absolute configuration at C-3′ of (+)-**13** was therefore (*R*). The ratio of the diastereomeric esters **16** was 76:24 corresponding to an unusual high optical yield of 52%.

Experimental

Optical rotation, Perkin-Elmer polarimeter 241; CD, Jobin Yvon Dichrograph CD 6; UV, Hewlett-Packard 8452A diode array spectrophotometer; IR, Perkin-Elmer 16PC FT-IR; NMR, Bruker AC-250 and Bruker DPX 250, standard pulse sequence programs provided by the spectrometer manufacturer were used, the HMBC experiments were optimized for a long range coupling constant of 8 Hz, the spectra were either referenced to internal TMS or to the solvent signal ($CDCl_3$ ^1H $\delta = 7.26$ ppm, ^{13}C $\delta = 77.0$ ppm, the chemical shifts depended to some degree on the concentrations of the NMR solutions, therefore the concentrations are included in the NMR data); MS, Finnigan MAT 900 S; *PE* = petrol ether, *EE* = ethyl acetate.

3-Butyl-1H-2-benzopyran-1-one (*Dihydroartemidin*, **1**, $C_{13}H_{14}O_2$)

$Pd(PPh_3)_4$ (5.0 g, 4.33 mmol, 2.5 mol%) and 23.6 g (0.173 mol) of $ZnCl_2$ were added under a flow of N_2 to a solution/dispersion of 43.6 g (0.173 mol) of 2-iodobenzoic acid, 42.6 g (0.519 mol) of 1-hexine, and 87.5 g (0.865 mol) of triethylamine in 180 cm^3 of *DMF*. After 24 h reflux in N_2 atmosphere the clear brown solution was cooled and the solvent was removed at *ca.* 60°C *in vacuo*. The remaining material was prefractionated over Al_2O_3 (column with 300 g Al_2O_3, *PE*:*EE* = 90:10) and the seven fractions of *ca.* 10 g each were chromatographed over silica gel (160 g SiO_2, *PE*:*EE* = 95:5). The yellow crystals (30.5 g, 87%) were recrystallized twice from *PE*:*EE* = 95:5 yielding 20.9 g of colourless crystals. From the deeply orange colored mother liquors another 6.4 g of **1** could be isolated by chromatography and recrystallization. Total yield 27.3 g (78%); mp 45–47°C (Ref. [21] 49.5–50.5°C); ^1H NMR ($CDCl_3$, $c = 10$ mg cm^{-3}): $\delta = 8.23$ (br.d, $J = 8.0$ Hz, 8-H), 7.65 (ddd, $J = 7.8$, ~7.5, 1.3 Hz, 6-H), 7.42 (ddd, $J = 8.0$, ~7.5, 1.0 Hz, 7-H), 7.33 (br.d, $J = 7.8$ Hz, 5-H), 6.24 (s, 4-H), 2.51 (t, $J = 7.6$ Hz, 1′-H_2), 1.68 (br.tt, $J = 7.6$, 7.5 Hz, 2′-H_2), 1.39 (tq, $J = 7.5$, 7.3 Hz, 3′-H_2), 0.93 (t, $J = 7.3$ Hz, 4′-H_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 163.1$ (s, C-1), 158.3 (s, C-3), 137.6 (s, C-4a), 134.6 (d, C-6), 129.4 (d, C-8), 127.5 (d, C-7), 125.0 (d, C-5), 120.1 (s, C-8a), 102.8 (d, C-4), 33.2 (t, C-2′), 28.9 (t, C-1′), 22.1 (t, C-3′), 13.7 (q, C-4′) ppm.

3-(1-Bromobutyl)-1H-2-benzopyran-1-one (*1′-Bromodihydroartemidin*, **2**, $C_{13}H_{13}BrO_2$)

20.4 g (101 mmol) of Dihydroartemidin (**1**) and 20.8 g (117 mmol) of *NBS* were dissolved in 400 cm^3 of absolute CCl_4 and after adding *ca.* 0.2 g of dibenzoylperoxide (*DBPO*) the mixture was heated under reflux. After 1.5 h and 2.5 h further portions of 0.1 g of *DBPO* were added until a change of color to orange indicated that the reaction had started. After another 1.5 h the reaction was complete. The white precipitate of succinimide was filtered from the yellow solution and the solvent was removed in vacuum. The dark yellow viscous crude product (35 g) was chromatographed over silica gel (column $d = 10$ cm, 1 kg SiO_2, *PE*:*EE* = 90:10). The yellowish crystals obtained were recrystallized from *PE*:*EE* = 90:10 and a second time from *PE*:*EE* = 75:25. Yield 26 g (92%); mp 67–69°C (Ref. [21] 69.5–70°C); ^1H NMR ($CDCl_3$, $c = 10$ mg cm^{-3}): $\delta = 8.27$ (br.d, $J = 8.0$ Hz, 8-H), 7.71 (ddd, $J = 8.0$, 7.8, 1.4 Hz, 6-H), 7.51 (ddd, $J = 8.0$, 7.8, 1.2 Hz, 7-H), 7.42 (br.d, $J = 8.0$ Hz, 5-H), 6.54 (s, 4-H), 4.70 (t, $J = 7.6$ Hz, 1′-H), 2.20 (dt, $J = 7.6$, ~7.8 Hz, 2′-H_2), 1.48 (m, 3′-H_2), 0.96 (t, $J = 7.3$ Hz, 4′-H_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 161.7$ (s, C-1), 154.7 (s, C-3), 136.4 (s, C-4a), 134.9 (d, C-6), 129.7 (d, C-8), 128.8 (d, C-7), 126.0 (d, C-5), 120.9 (s, C-8a), 104.1 (d, C-4), 49.0 (d, C-1′), 37.8 (t, C-2′), 21.0 (t, C-3′), 13.2 (q, C-4′) ppm.

3-(1,1-Dibromobutyl)-1H-2-benzopyran-1-one (*1′,1′-Dibromodihydroartemidin*, **3**, $C_{13}H_{12}Br_2O_2$)

This side product of the *NBS* bromination above crystallized from earlier chromatographic fractions and was recrystallized from ether. Yield 0.93 g (3%); mp 124–126°C; ^1H NMR ($CDCl_3$,

$c = 20\,mg\,cm^{-3}$): $\delta = 8.30$ (dm, $J = 7.9$ Hz, 8-H), 7.76 (ddd, $J = 7.8$, ~7.5, 1.4 Hz, 6-H), 7.58 (ddd, $J = 7.9$, ~7.5, 1.2 Hz, 7-H), 7.53 (br.d, $J = 7.8$ Hz, 5-H), 7.15 (d, $J = 0.5$ Hz, 4-H), 2.77 (m, 2′-H_2), 1.63 (m, 3′-H_2), 1.02 (t, $J = 7.4$ Hz, 4′-H_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 160.8$ (s, C-1), 153.8 (s, C-3), 136.0 (s, C-4a), 135.1 (d, C-6), 129.8, 129.5 (2d, C-7, C-8), 127.0 (d, C-5), 120.5 (s, C-8a), 105.2 (d, C-4), 61.7 (s, C-l′), 49.8 (t, C-2′), 21.1 (t, C-3′), 13.1 (q, C-4′) ppm; EIMS (70 eV): m/z (%) = 360 (6, M^+), 281/279 (100), 199 (70), 171 (49), 159 (35), 145 (93), 89 (96), 86 (50).

3-(1,2-Dibromobutyl)-1H-2-benzopyran-1-one (*1′,2′-Dibromodihydroartemidin*, **4**, $C_{13}H_{12}Br_2O_2$)

In the bromination reaction of **1**, with 1.82 g (9 mmol) of **1** and 1.86 g of *NBS*, but without addition of *DBPO* and l0 h reaction time, the l′,2′-bromination product was formed as a side product of the 1′-bromo derivative **2** in the ratio 1:10. The retention time was only a little different from that of **2**, but **4** could be crystallized from the earlier (still unpure) fractions of the chromatography (*PE*:*EE* = 75:25, see above) and recrystallized from *PE*:*EE* = 80:20. Yield 83 mg (3%); mp 141–143°C; ^{1}H NMR ($CDCl_3$, $c = 4\,mg\,cm^{-3}$): $\delta = 8.31$ (br.d, $J = 8.1$ Hz, 8-H), 7.73 (ddd, $J = 7.8$, ~7.5, 1.2 Hz, 6-H), 7.51 (ddd, $J = 8.1$, ~7.5, 1.1 Hz, 7-H), 7.45 (br.d, $J = 7.8$ Hz, 5-H), 6.55 (s, 4-H), 4.84 (d, $J =$ 11.3 Hz, 1′-H), 4.66 (ddd, $J = 11.3$, 8.0, 2.6 Hz, 2′-H), 2.43 (ddq, $J = 14.6$, 7.3, 2.6 Hz, 3′-H_a), 2.00 (ddq, $J = 14.6$, 8.0, 7.3 Hz, 3′-H_b), 1.15 (t, $J = 7.3$ Hz, 4′-H_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 152.5$ (s, C-3), 135.0 (d, C-6), 129.9 (d, C-8), 129.1 (d, C-7), 126.2 (d, C-5), 121.2 (s, C-8a), 105.8 (d, C-4), 54.8 (d, C-l′), 51.5 (d, C-2′), 29.5 (t, C-3′), 10.6 (q, C-4′) ppm, signals of C-l and C-4a are too weak for detection; EIMS (70 eV): m/z (%) = 360 (5, M^+), 281/279 (25), 201 (49), 200 (54), 189 (100), 159 (43), 131 (31), 89 (46).

(E)-3-(1-Bromo-1-butenyl)-1H-2-benzopyran-1-one (*(E)-1′-Bromoartemidin*, **5**, $C_{13}H_{11}BrO_2$)

38 mg (0.25 mmol) of *DBU* were added to a solution of 18 mg of **4** in 0.5 cm^3 of anhydrous *THF* under a flow of N_2. After 2.5 h at room temperature the reaction mixture was acidified with 0.5 cm^3 of 2 *M* HCl, saturated with NH_4Cl, and extracted with 3×2 cm^3 of ether. The combined ether layers were washed neutral with a solution of saturated aqu. NaCl and dried over $MgSO_4$. After evaporation of the solvent the remaining yellow oil (15 mg) was purified by repeated preparative TLC (silica gel, *PE*:*EE* = 90:10). Yield 5 mg (36%); colourless oil; ^{1}H NMR ($CDCl_3$, $c = 2\,mg\,cm^{-3}$): $\delta = 8.30$ (br.d, $J = 8.0$ Hz, 8-H), 7.73 (ddd, $J = 7.8$, ~7.5, 1.4 Hz, 6-H), 7.53 (ddd, $J = 8.0$, ~7.5, 1.2 Hz, 7-H), 7.46 (br.d, $J = 7.8$ Hz, 5-H), 6.74 (s, 4-H), 6.39 (t, $J = 7.8$ Hz, 2′-H), 2.46 (dq, $J = 7.8$, 7.5 Hz, 3′-H_2), 1.11 (t, $J = 7.5$ Hz, 4′-H_3) ppm; EIMS (70 eV): m/z (%) = 280/278 (54, M^+), 199 (100), 171 (54), 153 (21), 128 (37), 89 (33).

3-(1-Hydroxybutyl)-1H-2-benzopyran-1-one (*1′-Hydroxydihydroartemidin*, **6**, $C_{13}H_{14}O_3$)

To a solution of 86 mg of **2** in 5 cm^3 of acetone 10 cm^3 of H_2O were added under vigorous stirring. The turbid solution was heated to 90°C for 1 h. Then the reaction mixture was diluted with 10 cm^3 of saturated aqu. NaCl solution and extracted with 5×5 cm^3 of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and after evaporation practically pure **6** was obtained. Yield 67 mg (100%); colorless oil; ^{1}H NMR ($CDCl_3$, $c = 20\,mg\,cm^{-3}$): $\delta = 8.18$ (br.d, $J = 8.0$ Hz, 8-H), 7.64 (br.dd, $J = 7.8$, ~7.5 Hz, 6-H), 7.42 (br.dd, $J = 8.0$, ~7.5 Hz, 7-H), 7.34 (br.d, 1H, $J = 7.8$ Hz, 5-H), 6.53 (s 4-H), 4.45 (br.t, $J = 5.1$ Hz, l′-H), 1.78 (m, 2′-H_{a+b}), 1.44 (m, 3′-H_2), 0.92 (t, $J = 7.3$ Hz, 4′-H_3), 3.12 (br.s, 1′-OH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 162.5$ (s, C-1), 158.5 (s, C-3), 136.9 (s, C-4a), 134.8 (d, C-6), 129.4 (d, C-8), 128.0 (d, C-7), 125.6 (d, C-5), 120.3 (s, C-8a), 102.0 (d, C-4), 70.6 (d, C-l′), 37.1 (t, C-2′), 18.5 (t, C-3′), 13.7 (q, C-4′) ppm; EIMS (70 eV): m/z (%) = 218 (15, M^+), 200 (14), 175 (100), 147 (79), 89 (37).

(E)-3-(1-Butenyl)-1H-2-benzopyran-1-one (*(E)-Artemidin*, **7**, $C_{13}H_{12}O_2$)

To 10.0 g (35.6 mmol) of **2** in 100 cm^3 of anhydrous *THF* a solution of 17.2 g of 1,8-diazabicyclo[5.4.0]undec-7-en (*DBU*) in 85 cm^3 of anhydrous *THF* was added slowly under a stream of N_2. The solution changed its color from yellow to green and later to reddish brown. The combined solutions were heated at reflux in N_2 atmosphere for additional 2.5 h. Then the reaction mixture was cooled in the refrigerator and acidified with a cold (*ca.* 4°C) buffer of 150 cm^3 of saturated aqu. NH_4Cl solution and 25 cm^3 of conc. HCl. After dilution with 50 cm^3 of saturated aqu. NaCl solution this mixture was extracted with 3×50 cm^3 of ether. The combined ether phases were washed neutral with 3×50 cm^3 of NaCl solution and dried over $MgSO_4$. Then the dry ether phase was filtered over 20 g Al_2O_3 and the solvent was evaporated. The remaining crude reddish-yellow crystalline material was chromatographed over silica gel (600 g SiO_2, *PE*:*EE* = 90:10) to give colourless crystals of racemic **7**. Yield 4.1 g (58%); mp 48–50°C (Ref. [21] 49.5–50.5°C); ^{1}H NMR ($CDCl_3$, $c = 20$ mg cm^{-3}): $\delta = 8.18$ (br.d, $J = 8.0$ Hz, 8-H), 7.59 (ddd, $J = 7.9$, ~7.5, 1.0 Hz, 6-H), 7.36 (br.dd, $J = 8.0$, ~7.5 Hz, 7-H), 7.30 (br.d, $J = 7.9$ Hz, 5-H), 6.20 (s, 4-H), 6.62 (dt, $J = 15.6$, 6.7 Hz, 2′-H), 5.97 (dt, $J = 15.6$, 1.3 Hz, 1′-H), 2.20 (qdd, $J = 7.4$, 6.7, 1.3 Hz, 3-H_2), 1.05 (t, $J = 7.4$ Hz, 4′-H_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 162.1$ (s, C-1), 152.5 (s, C-3), 137.6 (s, C-4a), 134.5 (d, C-6), 129.4 (d, C-8), 127.5 (d, C-7), 125.4 (d, C-5), 120.4 (s, C-8a), 103.4 (d, C-4), 120.8 (d, C-l′), 138.1 (d, C-2′), 25.6 (t, C-3′), 12.8 (q, C-4′) ppm.

3-(1,2-Epoxybutyl)-1H-2-benzopyran-1-one (*Epoxyartemidin*, **8**, $C_{13}H_{12}O_3$)

A solution of 1.36 g of 3-chloroperbenzoic acid (*ca.* 5.5 mmol of *ca.* 70% *m-CPBA*) in 60 cm^3 of $CHCl_3$ was dropped slowly to a solution of 1.01 g (5.05 mmol) of **5** in 50 cm^3 of $CHCl_3$. After 2 h the resulting solution was heated to reflux for 4 h. Then further 0.25 g of *m-CPBA* in 10 cm^3 of $CHCl_3$ were added and the solution was kept at reflux for further 5 h. After cooling, the acidic products were removed by extraction with 10% aqu. $NaHCO_3$ and washed neutral with 2 × 25 cm^3 of aqu. NaCl solution. The aqueous phases were reextracted with 10 cm^3 of $CHCl_3$, the combined organic extracts were dried over $MgSO_4$, and the solvent was removed. The remaining yellow oily product was purified by chromatography over silica gel (100 g SiO_2, *PE*:*EE* = 80:20) to give racemic **8**. Yield 0.345 g (32%); colourless oil; ^{1}H NMR ($CDCl_3$, $c = 10$ mg cm^{-3}): $\delta = 8.25$ (br.d, $J = 8.0$ Hz, 8-H), 7.70 (ddd, $J = 7.9$, ~7.5, 1.3 Hz, 6-H), 7.49 (ddd, $J = 8.0$, ~7.5, 1.1 Hz, 7-H), 7.40 (br.d, $J = 7.9$ Hz, 5-H), 6.53 (s, 4-H), 3.46 (d, $J = 2.1$ Hz, 1′-H), 3.29 (td, $J = 5.4$, 2.1 Hz, 2′-H), 1.71 (m, 3′-H_2), 1.06 (t, $J = 7.5$ Hz, 4′-H_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 161.8$ (C-l), 152.8 (s, C-3), 136.5 (s, C-4a), 134.9 (d, C-6), 129.6 (d, C-8), 128.4 (d, C-7), 125.5 (d, C-5), 120.8 (s, C-8a), 103.8 (d, C-4), 54.4 (d, C-l′), 61.5 (d, C-2′), 24.7 (t, C-3′), 9.5 (q, C-4′) ppm.

(R,S)-(−)-3-(1,2-Epoxybutyl)-1H-2-benzopyran-1-one (*(−)-Epoxyartemidin*, (−)-**8**, $C_{13}H_{12}O_3$)

Optical resolution to enantiomerically pure (+)- and (−)-**8** was achieved by means of cyclic chromatography on triacetyl cellulose [32, 33]. ^{1}H NMR and chiroptical data of (−)-**8** were identical with (−)-epoxyartemidin isolated from *A. dracunculus* [10, 18]. The absolute configurations were determined as (1′*R*,2′*S*) *via* correlation with (+)-**9** (*Horeau* method, see below). Yield 50% (−)-**8** (and 50% of the (+)-enantiomer); colourless oil; $[\alpha]_D^{20} = -10°\ cm^3\ g^{-1}\ dm^{-1}$, $[\alpha]_{365}^{20} = +61°\ cm^3\ g^{-1}\ dm^{-1}$ (*Et*OH, $c = 0.2$); CD (*Et*OH): λ ($\Delta\varepsilon$) = 327 (+0.4), 275 (+0.5), 266 (+0.8) nm; UV (*Et*OH): $\lambda_{max} = 325$, 274 (sh), 267 nm.

(S)-(+)-3-(2-Hydroxybutyl)-1H-2-benzopyran-1-one (*(+)-2′-Hydroxydihydroartemidin*, (+)-**9**, $C_{13}H_{14}O_3$)

Under N_2 3.85 g (16.2 mmol) of $NiCl_2 \cdot 6H_2O$ were mixed with 292 mg (10.82 mmol) of Al powder and a solution of 70 mg (0.324 mmol) of (−)-**8** in 12 cm^3 of anhydrous *THF* was added rapidly. If

the reaction did not start for itself, the mixture was heated to 40–45°C with a hot gun until strong bubbling indicated the start of the reduction. After about 15 min of heating the mixture was stirred for further 18 h at room temperature. Then all solids were filtered off, the solvent was removed in vacuum, and the crude product chromatographed over silica gel (15 g SiO_2, *PE*:*EE* = 80:20). Yield 10 mg (14%, 42 mg of the starting material were also recovered, therefore 35% yield with respect to reacted material); colourless oil; $[\alpha]_D^{20} = +69°\ cm^3\ g^{-1}\ dm^{-1}$, $[\alpha]_{365}^{20} = +565°\ cm^3\ g^{-1}\ dm^{-1}$ (*Et*OH, $c = 0.2$); CD (*Et*OH): λ ($\Delta\varepsilon$) = 325 (+0.8), 273 (+1.0), 263 (+1.5) nm; UV (*Et*OH): λ_{max} = 326, 273 (side max.), 265 (max.), 257 (side max.) nm; ^{1}H NMR ($CDCl_3$, $c = 5\ mg\ cm^{-3}$): δ = 8.25 (br.d, J = 8.1 Hz, 8-H), 7.68 (ddd, J = 7.9, ~7.5, 1.3 Hz, 6-H), 7.47 (dd, J = 8.1, ~7.5, 1.1 Hz, 7-H), 7.37 (br.d, J = 7.9 Hz, 5-H), 6.37 (s, 4-H), 4.04 (m, 2′-H), 2.74 (br.dd, J = 14.6, 3.9 Hz, 1′-H_a), 2.58 (dd, J = 14.6, 8.5 Hz, 1′-H_b), 1.60 (m, 3′-H_{a+b}), 1.01 (t, J = 7.4 Hz, 4′-H_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 162.8 (s, C-1), 155.1 (s, C-3), 137.3 (s, C-4a), 134.8 (d, C-6), 129.6 (d, C-8), 127.9 (d, C-7), 125.2 (d, C-5), 120.3 (s, C-8a), 102.8 (d, C-4), 70.6 (d, C-2′), 41.3 (t, C-l′), 30.1 (t, C-3′), 9.8 (q, C-4′) ppm; EIMS (70 eV): m/z (%) = 218 (6, M^+), 160 (100), 136 (20), 131 (39), 118 (20),89 (50), 59 (33).

(S,S)-(−)-3-(1-Chloro-2-hydroxybutyl)-1H-2-benzopyran-1-one
((−)-1′-Chloro-2′-hydroxydihydroartemidin, (−)-**10**, $C_{13}H_{13}ClO_3$)

This compound was a side product of the reaction above. Further chromatograpy (20 g SiO_2, *PE*:*EE* = 80:20) yielded colorless crystals of (−)-**10**. Yield 8 mg (9% or 25% based on reacted material); mp 122–124°C; $[\alpha]_D^{20} = -40°\ cm^3\ g^{-1}\ dm^{-1}$, $[\alpha]_{365}^{20} = -330°\ cm^3\ g^{-1}\ dm^{-1}$ (*Et*OH, c = 0.1); CD (*Et*OH): λ ($\Delta\varepsilon$) = 318 (−1.2), 278 (−1.7, side min.), 268 (−2.2), 260 (−2.1, sh.), 235 (+5.5) nm; UV (*Et*OH): λ_{max} = 322, 276 (side max.), 268 (max.), 260 (sh.), 233 nm; ^{1}H NMR ($CDCl_3$, $c = 4\ mg\ cm^{-3}$): δ = 8.25 (br.d, J = 8.0 Hz, 8-H), 7.73 (ddd, J = 7.8, ~7.5, 1.4 Hz, 6-H), 7.53 (ddd, J = 8.0, ~7.5, 1.2 Hz, 7-H), 7.45 (br.d, J = 7.8 Hz, 5-H), 6.68 (s, 4-H), 4.57 (d, J = 7.0 Hz, 1′-H), 4.17 (ddd, J = 8.5, 7.0, 3.0 Hz, 2′-H), 2.29 (br.s, 2′-OH), 1.91 (ddq, J = 14.0, 7.3, 3.1 Hz, 3-H_a), 1.61 (m, 3-H_b), 1.06 (t, 3H, J = 7.4 Hz, 4′-H_3) ppm; ^{13}C NMR ($CDCl_3$): δ = (s, C-1 not detected), 152.4 (s, C-3), 136.3 (s, C-4a), 135.0 (d, C-6), 129.8 (d, C-8), 129.0 (d, C-7), 126.1 (d, C-5), 121.1 (s, C-8a), 106.7 (d, C-4), 61.7 (d, C-1′), 73.9 (d, C-2′), 26.2 (t, C-3′), 9. 7 (q, C-4′) ppm; EIMS (70 eV): m/z (%) = 254/252 (2/6, M^+), 281/279 (25), 196 (32), 194 (100), 160 (27), 159 (24).

Determination of the Absolute Configuration of (+)-**9** (*Horeau Esters* **11**, $C_{23}H_{24}O_4$)

Racemic 2-phenylbutanoic acid anhydride (22 mg, 0.07 mmol) was dissolved in 0.6 cm^3 of dry pyridine and poured over 5 mg (0.023 mmol) of (+)-**9**. The mixture was stirred for 20 h at room temperature. Then 1 cm^3 of 10% aqu. $NaHCO_3$ solution was added and stirring was continued for 1 additional h. After adding 4 cm^3 of H_2O, the reaction mixture was extracted with 4 × 2 cm^3 of ether, the combined ether solutions were dried over Na_2SO_4, and the solvent was evaporated *in vacuo* to give the diastereomeric mixture of esters of the alcohol (+)-**9** with (+)- and (−)-2-phenylbutanoic acid. The aqu. phase was acidified with 10 cm^3 of 2*M* HCl and extracted with 3 × 2 cm^3 of benzene. The benzene phases were washed neutral with water, dried over Na_2SO_4, and the solvent was evaporated. The remaining 2-phenylbutanoic acid, dissolved in a minimum amount of benzene, showed a negative optical rotation ($\alpha_D = -0.028°$) indicating (*S*) configuration for (+)-**9**. The ester mixture of the ether phase was analyzed by ^{1}H NMR showing that the ratio of diastereomers was (*S*,*S*):(*S*,*R*) = 65:35 corresponding to an optical yield of 30%. ^{1}H NMR ($CDCl_3$, $c = 2\ mg\ cm^{-3}$): δ (*S*,*S*)/(*S*,*R*) = 8.19/8.24 (8-H), 7.62/7.66 (6-H), 7.44/7.46 (7-H), ~7.2/7.2 (5-H), ~7.2/7.2 (Ph), 5.84/6.12 (4-H), ~5.15/5.15 (2′-H), 3.39/3.40 (2″-H), ~2.7/2.7(1′-H), ~2.05/2.05 (3″-H_a), ~1.7/ 1.7 (3′-H), ~1.7/ 1.7(3″-H_b), ~0.85/0.85 (4′-H), ~0.85/0.85 (4″-H) ppm; FDMS: m/z = 364 (M^+, $C_{23}H_{24}O_4$).

Absolute Configuration of (−)-3-(2-Methoxybutyl)-1H-2-benzopyran-1-one ((−)-2′-Methoxydihydroartemidin, **12**, $C_{14}H_{16}O_3$)

(−)-**12** has been isolated in very low yield from *A. dracunculus* [10, 38]. The CD spectrum of the natural compound was practically a mirror image of the CD spectra of compounds (−)-**8** and (+)-**9**, the absolute configuration at C-2′ was therefore (*R*). $[\alpha]_D^{20} = \sim -15°\ cm^3\ g^{-1}\ dm^{-1}$, $[\alpha]_{365}^{20} = -80°\ cm^3\ g^{-1}\ dm^{-1}$ (*Et*OH, $c = 0.03$); CD (*Et*OH): $\lambda\ (\Delta\varepsilon) = \sim 320\ (-1.0), \sim 270\ (-0.7), \sim 250\ (-0.6$, sh.) nm; UV (*Et*OH): $\lambda_{max} = 327$, 273 (side max.), 264, 257 (sh.) nm; ^{1}H NMR ($CDCl_3$, $c = 2\ mg\ cm^{-3}$): $\delta = 8.26$ (br.d, $J = 8.0$ Hz, 8-H), 7.68 (ddd, $J = 7.8$, ∼7.5, 1.3 Hz, 6-H), 7.46 (ddd, $J = 8.0$, ∼7.5, 1.2 Hz, 7-H), 7.37 (br.d, $J = 7.8$ Hz, 5-H), 6.34 (s, 4-H), 3.62 (tdd, $J = \sim 7.0$, 7.2, 5.7 Hz, 2′-H), 3.35 (s, 2′-OCH_3), 2.71 (dd, $J = 14.7$, 7.2 Hz, 1′-H_a), 2.63 (dd, $J = 14.7$, 5.7 Hz, 1′-H_b), 1.62 (m, 3′-H_2), 0.96 (t, $J = 7.4$ Hz, 4 ′-H_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta =$ (s, C-1 not detected), 155.4 (s, C-3), 140.3 (s, C-4a), 134.7 (d, C-6), 129.5 (d, C-8), 127.7 (d, C-7), 125.2 (d, C-5), (s, C-8a not detected), 104.9 (d, C-4), 79.3 (d, C-2′), 57.2 (q, OCH_3), 38.2 (t, C-1′), 26.3 (t, C-3′), 9.2 (q, C-4′) ppm.

Bromination of (E)-Artemidin (**7**) *with NBS*

NBS (0.6 g) was added to a solution of 0.6 g of **7** in 6 cm^3 of anhydrous CCl_4 and the mixture was heated to reflux. Then *ca.* 5 mg of dibenzoylperoxide (*DBPO*) were added and the mixture was irradiated with a 1000 W halogene lamp. TLC indicated very slow progress of the reaction. Therefore further 5 mg of *DBPO* were added after 1.5 h, and again after 5.5 h. After 10 h of irradiation the lamp was removed and the mixture heated to reflux for further 12 h. Then the mixture was cooled, filtered, and the solvent was removed to leave 0.92 g of crude oily product. Several attempts to obtain the obviously rather instable 3′-bromo derivative were not successful. However, the desired 3′-hydroxy derivative **13** and two further 3′- derivatives, **14** and **15**, were obtained as pure compounds by chromatography. The 1′,2′-dibromo product **4**, also present in the reaction mixture, had already been obtained by *NBS* bromination of **1** (see above).

(E)-3-(3-Hydroxy-1-butenyl)-1H-2-benzopyran-1-one ((E)-3′-Hydroxyartemidin, **13**, $C_{13}H_{12}O_3$)

The crude bromination product (735 mg) was chromatographed on Al_2O_3 (100 g Al_2O_3, gradient *PE*:*EE* = 75:25 → 50:50) and the remaining material (120 mg) was subjected to MPLC with the same gradient. Finally pure racemic **13** could be obtained which proved to be fairly stable in the refrigerator. Yield 27 mg (5%); slightly yellow oil; ^{1}H NMR ($CDCl_3$, $c = 10\ mg\ cm^{-3}$): $\delta = 8.24$ (br.d, $J = 8.0$ Hz, 8-H), 7.66 (ddd, $J = 7.8$, ∼7.5, 1.4 , 6-H), 7.44 (br.dd, $J = 8.0$, ∼7.5 Hz, 7-H), 7.37 (br.d, $J = 7.8$ Hz, 5-H), 6.33 (s, 4-H), 6.66 (dd, $J = 15.6$, 5.0 Hz, 2′-H), 6.28 (dd, $J = 15.6$, 1.5 Hz, 1′-H), 4.53 (qdd, $J = 7.3$, 5.0, 1.5 Hz, 3-H), 1.37 (d, $J = 7.3$ Hz, 4′-H_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 162.0$ (s, C-1), 152.0 (s, C-3), 137.4 (s, C-4a), 134.8 (d, C-6), 129.7 (d, C-8), 128.1 (d, C-7), 25.7 (d, C-5), 120.8 (s, C-8a), 105.2 (d, C-4), 120.4 (d, C-l′), 138.7 (d, C-2′), 67.7 (t, C-3′), 23.4 (q, C-4′) ppm.

(E)-3-(3-Acetyloxy-1-butenyl)-1H-2-benzopyran-1-one ((E)-3′-Acetoxyartemidin, **14**, $C_{15}H_{14}O_4$)

The crude bromination product (184 mg) was subjected to chromatography on Al_2O_3 (15 g Al_2O_3, *PE*:*EE* = 95:5). Yield 4 mg (3%); colorless oil; ^{1}H NMR ($CDCl_3$, $c = 3\ mg\ cm^{-3}$): $\delta = 8.27$ (br.d, $J = 8.0$ Hz, 8-H), 7.69 (ddd, $J = 8.0$, ∼7.5, 1.4 Hz, 6-H), 7.48 (ddd, $J = 8.0$, ∼7.5, 1.2 Hz, 7-H), 7.40 (br.d, $J = 8.0$ Hz, 5-H), 6.38 (s, 4-H), 6.56 (dd, $J = 15.6$, 6.2 Hz, 2′-H), 6.23 (dd, $J = 15.6$, 1.3 Hz, 1′-H), 5.53 (qdd, $J = 6.6$, 6.2, 1.3 Hz, 3′-H), 2.09 (s, $COCH_3$), 1.40 (d, $J = 6.6$ Hz, 4′-H_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 134.8$ (d, C-6), 129.8 (d, C-8), 128.3 (d, C-7), 125.8 (d, C-5), 105.9 (d, C-4), 122.6 (d, C-l′), 134.0 (d, C-2′), 70.0 (t, C-3′), 20.2 (q, C-4′), 20.2 (q, $COCH_3$) ppm, no s detected;

EIMS (70 eV): m/z (%) = 258 (64, M^+), 216 (95), 199 (32), 187 (39), 173 (100), 155 (31), 145 (26), 115 (28), 89 (52).

(E)-3-(3-Oxo-1-butenyl)-1H-2-benzopyran-1-one (*(E)-3′-Oxoartemidin*, **15**, $C_{13}H_{10}O_3$)

This oxidation product was obtained during the chromatography for the isolation of **13** from earlier main fractions of the MPLC separation as yellowish crystalline material (18 mg); recrystallized from *PE*:*EE* = 65:35. Yield 12 mg (2%); colourless crystals, mp 173–175°C; ^{1}H NMR ($CDCl_3$, $c = 20\,mg\,cm^{-3}$): $\delta = 8.28$ (dm, $J = 8.0$ Hz, 8-H), 7.72 (ddd, $J = 7.8$, ~7.5, 1.4 Hz, 6-H), 7.54 (ddd, $J = 8.0$, ~7.5, 1.2, 7-H), 7.47 (br.d, $J = 7.8$ Hz, 5-H), 6.68 (s, 4-H), 7.07 (d, $J = 15.5$ Hz, 2′-H), 6.96 (d, $J = 15.5$ Hz, 1′-H), 2.34 (s, 4′-H_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 197.0$ (s, C-3′), 160.8 (s, C-1), 152.3 (s, C-3), 136.2 (s, C-4a), 135.0 (d, C-6), 132.4 (d, C-2′), 130.0 (d, C-8), 129.7 (d, C-7), 126.6 (d, C-5), 121.9 (s, C-8a), 111.7 (d, C-4), 128.5 (d, C-1′), 29.3 (q, C-4′) ppm; EIMS (70 eV): m/z (%) = 214 (78, M^+), 199 (100), 158 (15), 144 (32), 115 (66), 89 (67), 63 (29).

(R)-(+)-3-(3-Hydroxybutyl)-1H-2-benzopyran-1-one (*(+)-3′-Hydroxyartemidin*, (+)-**13**, $C_{13}H_{12}O_3$)

Optical resolution to enantiomerically pure (+)- and (−)-**13** was achieved by cyclic chromatography on triacetyl cellulose [32, 33]. ^{1}H NMR and chiroptical data of (+)-**13** were identical with (+)-3′-hydroxyartemidin isolated from *A. dracunculus* [10, 18]. The absolute configuration was determined as (*R*) by means of the *Horeau* method (see below). Yield 50% (+)-**13** (and 50% of the (−)-enantiomer); colourless oil; $[\alpha]_D^{20} = +18°\,cm^3\,g^{-1}\,dm^{-1}$, $[\alpha]_{436}^{20} = +54°\,cm^3\,g^{-1}\,dm^{-1}$ (*Et*OH, $c = 0.2$); CD (*Et*OH): λ ($\Delta\varepsilon$) = 341 (+0.5), ~300 (−0.1), 227 (−0.8) nm; UV (*Et*OH): $\lambda_{max} = 343$, 302, 288, 283 (sh), 231 nm.

Determination of the Absolute Configuration of (+)-**13** (*Horeau Esters* **16**, $C_{23}H_{22}O_4$)

Procedure in analogy to the *Horeau* esters **11**: 12 mg (0.04 mmol) of racemic 2-phenylbutanoic acid anhydride in 0.5 cm^3 of dry pyridine were poured over 3 mg (0.014 mmol) of (+)-**13**; 48 h at room temperature; after workup, the remaining 2-phenylbutanoic acid, in a minimum amount of benzene, showed an optical rotation of $\alpha_D = +0.030°$ indicating (*R*) configuration for (+)-**13**. The diastereomeric ester mixture was analyzed by ^{1}H NMR showing that the ratio of diastereomers was (*R*,*R*):(*R*,*S*) = 76:24 corresponding to an optical yield of 52%. ^{1}H NMR ($CDCl_3$, $c = 1\,mg\,cm^{-3}$): δ (*R*,*R*)/(*R*,*S*) = 8.24/8.29 (8-H), 7.67/7.76 (6-H), 7.45/~7.47 (7-H), ~7.37/7.37 (5-H), ~7.3/7.3 (Ph), 6.07/6.29 (4-H), 6.46/6.55 (2′-H), 5.75/6.11 (1′-H), 5.54/5.52 (3′-H), ~2.1/2.1 (3′-H_a), ~1.8/1.8 (3″-H_b), ~1.3/1.3 (4′-H), 0.92/0.92 (4″-H_3) ppm; FDMS: $m/z = 362$ (M^+, $C_{23}H_{22}O_4$).

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