# 5-Lipoxygenase and Cyclooxygenase-1 Inhibitory Active Compounds from *Atractylodes lancea*

Marion Resch,† Alois Steigel,‡ Zhong-liang Chen,§ and Rudolf Bauer*,†

*Institut für Pharmazeutische Biologie der Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, D-40225 Düsseldorf, Germany, Institut für Organische Chemie und Makromolekulare Chemie der Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, D-40225 Düsseldorf, Germany, and Institute of Materia Medica, Academia Sinica, Yue-yang Road 319, Shanghai, People's Republic of China*

*Received September 19, 1997*

Lipophilic extracts of *Atractylodes lancea* rhizomes exhibited potent inhibitory activities in 5-lipoxygenase [$IC_{50}$ (5-LOX) = 2.9 $\mu$g/mL (*n*-hexane extract)] and cyclooxygenase-1 [$IC_{50}$ (COX-1) = 30.5 $\mu$g/mL (*n*-hexane extract)] enzymatic assays. Bioactivity-guided fractionation of the *n*-hexane extract led to the isolation of a new compound atractylochromene (**1**), a potent inhibitor in both test systems [$IC_{50}$ (5-LOX) = 0.6 $\mu$M, $IC_{50}$ (COX-1) = 3.3 $\mu$M]. Also obtained was 2-[(2*E*)-3,7-dimethyl-2,6-octadienyl]-6-methyl-2,5-cyclohexadiene-1,4-dione (**2**), which showed a selective inhibitory activity against 5-LOX [$IC_{50}$ (5-LOX) 0.2 $\mu$M, $IC_{50}$ (COX-1) 64.3 $\mu$M]. The sesquiterpene atractylon (**3**) and the coumarin osthol (**4**) turned out to be moderate but selective 5-lipoxygenase inhibitors. Atractylenolides I (**5**), II (**6**), and III (**7**) showed no significant inhibitory effects for either enzyme. Structures were established by spectral data interpretation.

In traditional Chinese medicine, "Cangzhu" [the rhizomes of *Atractylodes lancea* (Thunb.) DC. and *Atractylodes chinensis* (Bunge) Koidz., Compositae] is used for the treatment of rheumatic diseases, digestive disorders, mild diarrhea, and influenza and is said to be a diaphoretic, whereas "Baizhu" (*Atractylodes macrocephala* Koidz. rhizomes) has been recommended as a digestive, diuretic, and anhidrotic medication.[1] The rhizomes of *A. lancea* are rich in essential oil compounds and acetylenes such as atractylodin, atractylodinol, and acetylatractylodinol.[2−6] For Baizhu, sesquiterpenes (with the furosesquiterpene atractylon as the main compound) and acetylenic compounds have been described.[4,5,7] The antiinflammatory activity of this genus has been investigated previously when Yamahara et al. found no significant analgesic activity in *A. lancea*, *A. macrocephala*, or *A. japonica*.[8] Endo et al. fractionated a preparation from *A. japonica* rhizomes to afford the sesquiterpenes (+)-eudesma-4(14),7(11)-dien-8-one and atractylenolide I as active compounds in different antiinflammatory assays.[9] Examination of *A. koreana* confirmed the pharmacological property of atractylenolide I and demonstrated the activity of atractylon (being also the major component of *A. koreana* and *A. japonica*) in the rat cotton-pellet-granuloma assay.[10] Atractylon further inhibited 12-*O*-tetradecanoylphorbol 13-acetate (TPA)-induced ear inflammation in mice.[11]

Recently, we published the isolation and structure elucidation of six new polyacetylenes from *A. lancea*, which, however, turned out to be unrelated to antiinflammatory effects.[12] We now report the inhibitory effect of *A. lancea* constituents in 5-lipoxygenase (5-LOX) and cyclooxygenase (COX) bioassays. These are the two key enzymes for the metabolism of arachidonic acid, either to prostaglandins and thromboxanes or to leukotrienes, which play a central role in the regulation of different physiological processes, but also cause pain, inflammation, and hypersensitivity.[13,14] Abnormal amounts of these mediators can be found in patients suffering from rheumatoid arthritis, asthma, psoriasis, anaphylactic shock, and ulcerative colitis.[13,14]

**Table 1.** 5-LOX and COX-1 Inhibitory Activities of Different *Atractylodes* Extracts

| extract | 5-LOX $IC_{50}$ [$\mu$g/mL] | COX-1 $IC_{50}$ [$\mu$g/mL] |
|---|---|---|
| *Atractylodes lancea* rhizomes | | |
| *n*-hexane | 2.9 | 30.5 |
| $CH_2Cl_2$ | 2.8 | 21.5 |
| MeOH | 9.1 | 72.3 |
| *Atractylodes macrocephala* rhizomes | | |
| *n*-hexane | 11.8 | 49.8 |
| $CH_2Cl_2$ | 10.5 | 52.0 |
| MeOH | 78.8 | 144.5 |

## Results and Discussion

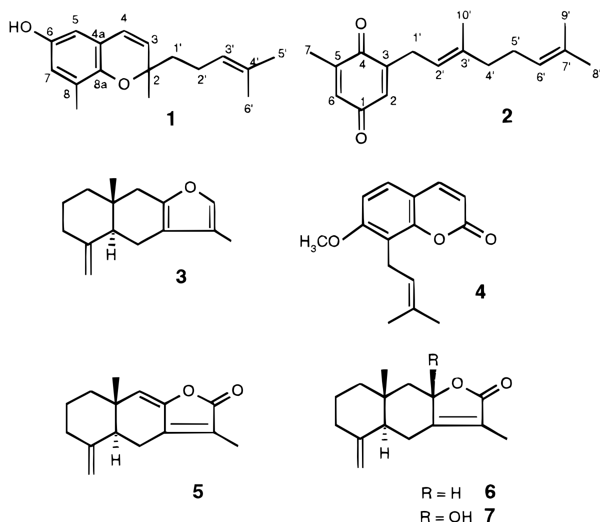
Traditionally, Cangzhu and Baizhu are used as decoctions. When tested undiluted, the inhibition of *A. lancea* and *A. macrocephala* decoctions in both the 5-LOX and the COX-1 assay was 50−60%, except the decoction of *A. lancea* which showed 100% inhibition in the 5-LOX assay (60% inhibition after dilution 1:10); however, the actual test concentrations—ranging from 1500 $\mu$g/mL up to 5000 $\mu$g/mL (1:10-diluted decoction of *A. lancea* about 150 $\mu$g/mL)—were much higher than those of the less polar Soxhlet extracts (from the two drugs) with comparable antiinflammatory effects (Table 1). Among these, the inhibitory activity of lipophilic extracts from *A. lancea* against both enzymes was superior to MeOH extracts of the same drug and to *n*-hexane, $CH_2Cl_2$, and MeOH extracts from rhizomes of *A. macrocephala*. All Soxhlet extracts exhibited inhibition against 5-LOX at

* To whom correspondence should be addressed. Tel: ++49-211-811-4180. Fax: ++49-211-811-1923. E-mail: bauerr@uni-duesseldorf.de.
† Institut für Pharmazeutische Biologie.
‡ Institut für Organische und Makromolekulare Chemie.
§ Institute of Materia Medica, Academia Sinica.

S0163-3864(97)00430-8 CCC: $15.00 © 1998 American Chemical Society and American Society of Pharmacognosy
Published on Web 02/28/1998

2–10 times lower concentrations than against COX-1. Because TLC and HPLC chromatograms of the lipophilic extracts of *A. lancea* showed the same pattern of constituents, for toxicological reasons, workup of the *n*-hexane extract was given precedence over the $CH_2Cl_2$ extract.

The *n*-hexane extract of *A. lancea* was subjected to vacuum–liquid column chromatography (VLCC) on Si gel, and all fractions were tested in both the 5-LOX and the COX-1 assay to lead to a potent, active fraction (with 100% inhibition at 5 $\mu$g/mL in the 5-LOX assay) containing compounds **1** and **2**. Further bioactivity-guided fractionation on Si gel columns afforded **2** in pure state. Additional purification steps on RP-18 material (MPLC) and on Sephadex LH-20 were carried out to isolate **1** and, using the same procedure, atractylenolide II (**6**). Atractylon (**3**), osthol (**4**), and atractylenolide III (**7**) were isolated by Si gel column chromatography from less active fractions.




The EIMS data of **1** and **2** revealed similarities, with a $[M]^+$ at *m/z* 258 in each case. While the EIMS of **1** possessed a dominant base peak at *m/z* 175 and minor fragments at *m/z* 41 and 69, the base peak of **2** could be found at *m/z* 41, with, in addition, abundant fragments at *m/z* 69 and 175. The diagnostic base peak at *m/z* 175 in the EIMS of **1** pointed to a stable, probably conjugated system that remained after an isoprenyl moiety fragmented from the molecule; however, the UV spectrum of **1** differed significantly from that of **2**. Instead of a single maximum at about 255 nm as in **2**, **1** exhibited five UV absorption maxima at 220, 231, 265, 275 and 333 nm, indicating the presence of an extended chromophore. The $^1$H NMR spectrum of **1** was consistent with the presence of an isohexenyl side chain. An olefinic signal at $\delta$ 5.10 (1H, t sept, $J = 7.2$, 1.4 Hz) coupled with a broad quartet at $\delta$ 2.09 (2H, br q, $J = 7.2$ Hz) that itself coupled with a further signal at $\delta$ 1.67 (2H, t, $J = 7.2$ Hz). Close to this triplet, one of the two methyls belonging to this isohexenyl group appeared as a broad singlet ($\delta$ 1.66, 3H), with the other occurring at $\delta$ 1.57 (3H, br s). Furthermore, the $^1$H NMR spectrum of **1** contained two pairs of doublets that were observed downfield (1H each, $\delta$ 6.48, 6.32, $J = 2.9$ Hz; $\delta$ 6.25, 5.58, $J = 9.8$ Hz) and two singlets at $\delta$ 2.14 and 1.36 (3H each) indicating the presence of either a 2,2,5,7- or a 2,2,6,8-tetrasubstituted chromene. Calculation of the $^{13}$C NMR chemical shifts of the aromatic carbon atoms via substituent increments applied to simple chromenes and comparison of the NMR data of **1** with reference data of similar structures in the literature,[15,16] as well as the use of COSY, DEPT and HETCOR experiments, led to the elucidation of **1** as 2,8-dimethyl-6-hydroxy-2-(4-methyl-3-pentenyl)-2H-chromene, a new natural product, for which we propose the name atractylochromene.

**Table 2.** $IC_{50}$ Values of Compounds **1**–**7** and Positive Controls

| compound | 5-LOX $IC_{50}$ [$\mu$M] | COX-1 $IC_{50}$ [$\mu$M] |
|---|---|---|
| **1** (atractylochromene) | 0.6 | 3.3 |
| **2** (quinone) | 0.2 | 64.3 |
| **3** (atractylon) | 25.1 | >200 |
| **4** (osthol) | 36.2 | >200 |
| **5** (atractylenolide I) | >200 | >200 |
| **6** (atractylenolide II) | >200 | >200 |
| **7** (atractylenolide III) | >200 | >200 |
| positive controls | | |
| indomethacin | | 1.2 |
| nordihydroguaiaretic acid | 0.5 | |

From its MS and UV data as well as from its IR, $^1$H NMR, and $^{13}$C NMR spectra, **2** corresponded closely with those data reported for the known compound 2-[(2*E*)-3,7-dimethyl-2,6-octadienyl]-6-methyl-2,5-cyclohexadiene-1,4-dione, originally isolated from a brown alga, *Cystophora* sp.,[17] and later from *A. koreana*.[18]

Being one of the main compounds in the *n*-hexane extract of *A. lancea*, **3** was identified as the known sesquiterpene atractylon.[19,20] Spectral data of **4** matched very well those of osthol, a coumarin isolated for the first time from this genus.[21] Compounds **6** and **7** were elucidated as atractylenolides II and III and were compared with authentic samples from *A. macrocephala*.[22] This is the first report of their isolation from *A. lancea* rhizomes.

Compounds **1**–**7** were tested for inhibitory activity against 5-LOX and COX-1, and the $IC_{50}$ values obtained are listed in Table 2. Atractylochromene (**1**) turned out to be a potent inhibitor on both enzymes [$IC_{50}$ (5-LOX) 0.6 $\mu$M, $IC_{50}$ (COX-1) 3.3 $\mu$M]. Synthetic chromenes have previously been described as orally active 5-LOX inhibitors;[23] however, this is the first report of a naturally occurring chromene having this pharmacological property. Quinone **2**, showing an even lower $IC_{50}$ value of 0.2 $\mu$M against 5-LOX, but less activity on COX-1 ($IC_{50}$ 64.3 $\mu$M), can be regarded as a strong and selective inhibitor of 5-LOX. Atractylon (**3**) and osthol (**4**) also turned out to be selective 5-LOX inhibitors, but were found to be about 100 times less potent than **2** ($IC_{50}$/5-LOX (**3**) 25.1 $\mu$M, $IC_{50}$/5-LOX (**4**) 36.2 $\mu$M). Atractylenolides I (**5**), II (**6**), and III (**7**) showed no remarkable effects against either enzyme, in contrast to earlier literature reports.[9,10]

Many of 5-LOX inhibitors act as antioxidants.[14] For atractylon (**3**), radical-scavenging properties have already been described in connection with its antihepatotoxic activity.[24,25] From its chemical structure (similar to vitamin E), it is probable that atractylochromene (**1**) is an antioxidant as well. As there is a chemical relation between compound **1** and the quinone **2** (when heated strongly on a TLC plate, **2** was partially decomposed to **1**), radical-scavenging activity of **2** might also be a factor.

Compared to the $IC_{50}$ values of **1** and **2** (Table 2), moderate inhibition of 5-LOX ($IC_{50}$ > 5 $\mu$M) by different tocopherol derivatives has been reported previously. Interestingly, this effect was proposed to be due to a strong interaction between the investigated tocopherols and the enzyme, instead of being related to the antioxidant function of these compounds.[26]

## Experimental Section

**General Experimental Procedures.** NMR spectra were recorded at 300 MHz ($^1$H) and 75 MHz ($^{13}$C) on a Varian VXR-300 spectrometer (**1**, **2**, **6**) or at 500 MHz ($^1$H) and 125 MHz ($^{13}$C) on a Bruker DRX 500 (**3**–**5**) in $CDCl_3$. Chemical shifts are expressed in $\delta$ values from TMS as internal standard, and coupling constants are given in Hertz. EIMS were recorded at 70 eV using a Finnigan 1020 GC/EIMS instrument; GC/CIMS (atractylochromene, **1**) was carried out on an INCOS 50 mass spectrometer (Finnigan) attached to a Varian 3400 GC. UV spectra were obtained on-line by an HP1040M photodiode array detector attached to an HP 1050 liquid chromatograph (Hewlett–Packard). IR spectra were measured with a Perkin–Elmer 297 IR spectrometer. The optical rotation of **1** was obtained with a Perkin–Elmer polarimeter 241 MC (20 °C, absolute EtOH). Column chromatography was carried out on Si gel (230–400 mesh, Merck) and on Sephadex LH-20 (Pharmacia), and MPLC columns were filled with RP-18 Si gel (25–40 $\mu$m, Merck). After every evaporation step, the residue was flushed with nitrogen.

**Plant Material.** The dried rhizomes of *A. lancea* and *A. macrocephala* were provided by the TCM-Klinik (Hospital for Traditional Chinese Medicine) in Kötzting, Germany, in May and September 1994. Voucher specimens are deposited at the Institute of Pharmaceutical Biology, Düsseldorf, Germany.

**5-LOX Assay.** The 5-LOX antiinflammatory screening bioassay used was originally developed by Kuhl[27] and later modified by Wagner and Fessler.[28] Intact porcine leukocytes ($1.5 \times 10^7$ cells/mL) were incubated with 17.6 $\mu$M Ionophore A 23187 (Boehringer Mannheim), 2 mM $CaCl_2$, 10 $\mu$M 5,8,11,14-eicosatetraynoic acid (Sigma), 50 $\mu$L test solution (extract or compound, dissolved in absolute EtOH) or 50 $\mu$L absolute EtOH (controls), respectively, and 9 $\mu$M 1-[$^{14}$C]-arachidonic acid (Amersham) for 8 min at 37 °C. After extraction by EtOAc, arachidonic acid and its radiolabeled metabolites were separated and quantified by reversed-phase HPLC using the following instruments and methods: liquid chromatograph HP 1050; Berthold HPLC radioactivity monitor LB 507 B; column LiChroCART 125–4 with LiChrospher 100 RP-18, 5 $\mu$m (Merck); mobile phase [A = $H_2O$ with 0.1% (v/v) 10 N phosphoric acid; B = MeCN with 0.1% (v/v) 10 N phosphoric acid]; solvent gradient, 50% B to 90% B linear in 20 min, 90% B isocratic for 6 min; flow 1.0 mL/min.

**Cox-1 Assay.** This assay was performed after the preparation of microsomal COX-1 from sheep seminal vesicles on a microtiter scale,[29] containing an incubation mixture of the microsomal fraction, 1 mM reduced glutathione, 1 mM L-adrenaline-D-hydrogen tartrate, and 0.05 mM $Na_2EDTA$ in 180 $\mu$L 0.1 M Tris buffer (pH 8.0). An aliquot (10 $\mu$L) of test solution (extract/compound dissolved in absolute EtOH) or control (absolute EtOH) was added and preincubated for 5 min at room temperature. After the reaction was started by adding 10 $\mu$L of 4.5 $\mu$M 1-[$^{14}$C]-arachidonic acid (0.05 $\mu$Ci absolute), the mixture was incubated for 20 min at 37 °C. In this assay, arachidonic acid and $PGE_2$ could be determined by reversed-phase HPLC directly from the incubation mixture. For instrumentation, columns, and mobile phase, see 5-LOX assay; gradient: 64% B isocratic for 7 min, 64% B to 80% B linear in 1 min, 80% B isocratic for 12 min; flow, 1 mL/min. Inhibition refers to reduction of 5-HETE (5-LOX) and $PGE_2$ (COX-1) peak areas compared to those of the controls. Results were the means of at least three experiments. $IC_{50}$ values were determined by regression analysis of the results at three different concentrations of the inhibitor. The maximum observed standard deviation (absolute) was about 20% for the 5-LOX assay and 10% for the COX-1 assay. Positive control measurements were performed with nordihydroguaiaretic acid ($IC_{50}$ = 0.5 $\mu$M) for 5-LOX inhibition and with indomethacin ($IC_{50}$ 1.5 $\mu$M) for COX-1 inhibition.

**Extraction and Isolation.** For 5-LOX and COX-1 assay screening, 5 g each of *A. lancea* or *A. macrocephala* rhizomes were extracted in a Soxhlet apparatus with *n*-hexane, $CH_2Cl_2$ or MeOH for 2 h. Decoctions were prepared with 10 g of crude drug according to the Pharmacopoeia of the People's Republic of China.[30] To isolate compounds **1**–**4**, **6**, and **7**, the dried rhizomes of *A. lancea* (570 g) were extracted in a Soxhlet apparatus with *n*-hexane for 150 h. The extract was evaporated to produce an oily mass (46 g). Vacuum-liquid column chromatography (VLCC) with *n*-hexane, then *n*-hexane–EtOAc mixtures on Si gel, afforded 10 fractions. Fraction V (*n*-hexane–EtOAc 8:2, 3 g) was further separated by column chromatography on Si gel with the same eluents. In a fraction obtained with *n*-hexane–EtOAc (96:4) (17.5 mg), **2** was contained in almost pure state. In two fractions eluted by *n*-hexane–EtOAc (9:1) (115 and 148 mg), **1** and **6** were obtained in impure form. The first of these fractions was purified once more on Si gel (*n*-hexane, 100%) to give 7.4 mg **2**. Purification of 2.7 mg of compound **1** was carried out on RP-18 material using MPLC with MeOH–$H_2O$ gradients and on Sephadex LH-20 (eluent, MeOH). By the same procedure, **6** was isolated (3.5 mg). Atractylon (**3**) was detected in fraction III of the first vacuum column (*n*-hexane–EtOAc, 9:1; 18.5 g) and was obtained in a pure state after separation on a second Si gel column, with *n*-hexane and *n*-hexane/toluene (95:5) as eluents (57 mg). A total of 1.3 mg of **4** contained in fraction VII (column 1, *n*-hexane–EtOAc 3:1, 620 mg) was also isolated on Si gel (*n*-hexane–EtOAc 92:8). Altogether, 47 mg of atractylenolide III (**7**) crystallized from the same column when eluted by hexane–EtOAc (85:15).

**Atractylochromene [2,8-dimethyl-6-hydroxy-2-(4-methyl-3-pentenyl)-2H-chromene] (1):** obtained as a yellow oil: $[\alpha]^{20}_D$ ca. −10° ($c$ 0.071, EtOH); UV (MeCN–$H_2O$) $\lambda_{max}$ 220, 231, 265, 275, 333 nm; IR (KBr) $\nu_{max}$ 2920, 1590, 1470, 1320, 860, 720 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.48 (1H, br d, $J$ = 2.9 Hz, H-7), 6.32 (1H, br d, $J$ = 2.9 Hz, H-5), 6.25 (1H, d, $J$ = 9.8 Hz, H-4), 5.58 (1H, d, $J$ = 9.8 Hz, H-3), 5.10 (1H, t sept, $J$ = 7.2, 1.4 Hz, H-3′), 2.14 (3H, s, Me-8); 2.09 (2H, br q, $J$ = 7.2 Hz, $H_2$-2′), 1.67 (2H, t, $J$ = 7.2 Hz, $H_2$-1′),

1.66 (3H, br s, $H_3$-5′), 1.57 (3H, br s, $H_3$-6′), 1.36 (3H, s, Me-2); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 148.5 and 144.9 (C-6 and C-8a), 131.6 (C-4′), 130.8 (C-3), 126.4 (C-8), 124.2 (C-3′), 122.8 (C-4), 121.3 (C-4a), 117.0 (C-7), 110.2 (C-5), 77.8 (C-2), 40.8 (C-1′), 25.8 ($CH_3$-2), 25.7 (C-5′), 22.7 (C-2′), 17.6 (C-6′), 15.5 ($CH_3$-8); EIMS *m*/*z* 258 $[M]^+$ (22), 243 (7), 215 (2), 175 $[M - \text{isoprenyl}]^+$ (100), 145 (7), 131 (7), 91 (10), 77 (7), 69 (18), 41 (23); CIMS 175 (43), 259 (86), 261 (48), 276 (100), 293 (25).

**2-[(2*E*)-3,7-Dimethyl-2,6-octadienyl]-6-methyl-2,5-cyclohexadiene-1,4-dione (2):** yellow-brownish oil; UV and IR data found in accordance with literature;[17] $^1$H NMR and $^{13}$C NMR data, confirmed by COSY and HETCOR experiments, some reassignments were made compared with literature values:[18] $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.55 (1H, dq, $J = 2.7$, 1.6 Hz, H-5), 6.47 (1H, dt, $J = 2.7$, 1.8 Hz, H-3), 5.15 (1H, t sext, $J = 7.3$, 1.2 Hz, H-2′), 5.08 (1H, t sept, $J = 6.8$, 1.4 Hz, H-6′), 3.13 (2H, br d, $J = 7.3$ Hz, $H_2$-1′), 2.08 (1H, m, H-5′), 2.06 (4H, m, H-4′ and $H_3$-7), 1.70 (3H, d, $J = 1.0$ Hz, $H_3$-9′), 1.62 (3H, br s, $H_3$-10′), 1.60 (3H, br s, $H_3$-8′); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 188.1 and 188.0 (C-1 and C-4), 148.5 and 145.9 (C-2 and C-6), 139.9 (C-3′), 133.2 (C-5), 132.3 (C-3), 131.8 (C-7′), 123.9 (C-6′), 118.0 (C-2′), 39.6 (C-4′), 27.5 (C-1′), 26.4 (C-5′), 25.7 (C-9′), 17.7 (C-8′), 16.1 (C-10′), 16.0 (C-7); EIMS *m*/*z* 258 $[M]^+$ (<1), 243 (2), 215 (10), 175 $[M - \text{isoprenyl}]^+$ (29), 69 (60), 41 (100).

Chemical transformation of **2** into **1** was achieved by treating a small amount of **2** on a TLC plate (Merck) with heat (200 °C) and UV light (254 nm) for five minutes each. Then, reference samples of **1** and **2** were applied to the plate. TLC separation was obtained with toluene-EtOAc (93:7), evaluation was done under UV 254 nm. Compound **2** could still be detected in the mixture of products formed under these conditions, as well as a zone at the *Rf* of **1**. To give proof to the identity of this zone, **1** was isolated from it by preparative TLC and injected into the GC/MS.

**Atractylon (3):** isolated as a colorless oil; UV, IR, $^1$H NMR, and $^{13}$C NMR data matched those described in the literature.[19,20]

While Osthol **(4)** and atractylenolide II **(6)** were isolated as yellow oils, atractylenolide III **(7)** was obtained as a crystalline solid. Their identities were confirmed by MS and $^1$H NMR data comparison with literature values,[21,22] and by co-TLC and co-HPLC with authentic samples.

**Atractylenolide I (5):** obtained as a reference sample from *A. macrocephala* rhizomes.[7]

**Acknowledgment.** The authors thank Dr. J.-H. Liu for a reference sample of osthol and Dr. U. Matthiesen for recording the CIMS of compound **1**. They are also grateful to Mrs. S. Borstel, Mrs. A. Seibt, and Mrs. S. Zschocke for assisting in testing the compounds for 5-LOX and COX-1 activity and to Mrs. M. Beuer and Mr. K.-D. Jansen for technical assistance. This paper is part of the Ph.D. thesis of M. Resch.

## References and Notes


(1) Tang, W.; Eisenbrand, G. *Chinese Drugs of Plant Origin*; Springer: Berlin, 1992; p 199.
(2) Chow, W. Z.; Motl, O.; Šorm, F. *Collect. Czech. Chem. Commun.* **1962**, *27*, 1914−1926.
(3) Bruns, K.; Dolhaine, H.; Weber, U. *World Crops: Prod., Util., Descr.* **1982**, *7 (Aromat. Plants)*, 207−210.
(4) Yosioka, I.; Nishino, T.; Tani, T.; Kitagawa, I. *Yakugaku Zasshi* **1976**, *96*, 1229−1235.
(5) Nishikawa, Y.; Yasuda, I.; Watanabe; Y., Seto, T. *Yakugaku Zasshi* **1976**, *96*, 1322−1326.
(6) Nishikawa, Y.; Yasuda, I.; Watanabe, Y.; Seto, T. *Shoyakugaku Zasshi* **1976**, *30*, 132−137.
(7) Chen, Z.-L. *Planta Med.* **1987**, *53*, 493−494.
(8) Yamahara, J.; Sawada, T.; Tani, T.; Nishino, T.; Kitagawa, I.; Fujimura, H. *Yakugaku Zasshi* **1977**, *97*, 873−879.
(9) Endo, K.; Taguchi, T.; Taguchi, F.; Hikino, H.; Yamahara, J.; Fujimura, H. *Chem. Pharm. Bull.* **1979**, *27*, 2954−2958.
(10) Sin, K. S.; Kim, H. P.; Lee, W. C.; Pachaly, P. *Arch. Pharm. Res.* **1989**, *12*, 236−238.
(11) Yu, S.; Yasukawa, K.; Takido, M. *Phytomedicine* **1994**, *1*, 55−58.
(12) Lehner, M. S.; Steigel, A.; Bauer, R. *Phytochemistry* **1997**, *46*, 1023−1028.
(13) Samuelsson, B. *Science* **1983**, *220*, 568−575.
(14) Mantri, P.; Witiak, D. T. *Curr. Med. Chem.* **1994**, *1*, 328−355.
(15) Tímár, T.; Sebök, P.; Kövér, K. E.; Jászberényi, J. C., Batta, G. *Magn. Reson. Chem.* **1989**, *27*, 303−4.
(16) Numata, A.; Kanbara, S.; Takahashi, C.; Fujiki, R.; Yoneda, M.; Usami, Y.; Fujita, E. *Phytochemistry* **1992**, *31*, 1209−1213.
(17) Capon, R. J.; Ghisalberti, E. L.; Jefferies, P. R. *Phytochemistry* **1981**, *20*, 2598−2600.
(18) Pachaly, P.; Lansing, A.; Sin, K. S. *Planta Med.* **1989**, *55*, 59−60.
(19) Nishikawa, Y.; Watanabe, Y.; Seto, T.; Yasuda, I. *Yakugaku Zasshi* **1976**, *96*, 1089−1093.
(20) Hikino, H.; Hikino, Y.; Yosioka, I. *Chem. Pharm. Bull.* **1964**, *12*, 755−760.
(21) Harkar, S.; Razdan, T. K.; Waight, E. S. *Phytochemistry* **1984**, *23*, 419−426.
(22) Huang, B.; Sun, J.; Chen, Z. *Acta Bot. Sin.* **1992**, *34*, 614−617.
(23) Satoh, Y.; Stanton, J. L.; Hutchison, A. J.; Libby, A. H.; Kowalski, T. J.; Lee, W. H.; White, D. H.; Kimble, E. F. *J. Med. Chem.* **1993**, *36*, 3580−3594.
(24) Kiso, Y.; Tohkin, M.; Hikino, H. *Planta Med.* **1985**, *51*, 97−100.
(25) Hwang, J.-M.; Tseng, T.-H.; Hsieh, Y.-S.; Chou, F.-P.; Wang, C. J.; Chu, C.-Y. *Arch. Toxicol.* **1996**, *70*, 640−644.
(26) Reddanna, P.; Rao, M. K.; Reddy, C. C. *FEBS Lett.* **1985**, *193*, 39−43.
(27) Kuhl, P.; Shiloh, R.; Jha, H.; Murawski, U.; Zilliken, F. *Prostaglandins* **1984**, *28*, 783−804.
(28) Wagner, H.; Fessler, B. *Planta Med.* **1986**, *52*, 374−377.
(29) Redl, K.; Breu, W.; Davis, B.; Bauer, R. *Planta Med.* **1994**, *60*, 58−62.
(30) *Pharmacopoeia of the People's Republic of China* (English ed.), People's Medical Publishing House: Beijing, China, 1992.


NP970430B