= 2.3 Hz C_{10} H), 4.15 (dq, 4 H), 3.52 (m, 1 H, $J_{12,8}$ = 2.7 Hz, $J_{12,11}$ = 2.7 Hz, $J_{12,10}$ = 2.3 Hz C_{12} H), 2.68 (m, 1 H, C_8 H), 2.28 (t, 2 H, C_2 H), 2-1.1 (m 16 H); MS, *m/e* 310 (M), 265 (M - OCH_2CH_3). Anal. Calcd for $C_{17}H_{26}O_5$: C, 67.01; H, 8.40. Found: C, 66.74; H, 8.43.

2,3-*trans*:3,4-*trans*:4,5-*cis*-2-[6-(Ethoxycarbonyl)hexyl]-3-(ethoxycarbonyl)-4,5-epoxycyclopentanone (8). To a solution of **7** (1.55 g, 5 mmol) dissolved in 100 mL of methanol at -45 °C were added 30 mL of 2 N NaOH and 10 mL (40 mmol) of 30% H_2O_2. After the mixture was stirred for 12 h at -45 °C, 30 mL of 2 N NaOH and 10 mL of 30% H_2O_2 were added, and then the solution was stirred for 24 h at -45 °C. The solution was added to 100 mL of saturated ammonium chloride, and the methanol was evaporated under reduced pressure. The aqueous residue was extracted with methylene chloride. The organic layers were washed with saturated sodium chloride solution. After the organic layers were dried and the solvent evaporated, the epoxide (1.3 g, 79%) was obtained as a mixture of α and β epimeric isomers (85/15). A portion of the mixture (0.100 g) was purified by using preparative TLC with 1:3 ethyl acetate-hexane as the solvent to give pure α isomer (0.05 g). The spectral data were as follows: IR (neat) 1740; NMR 4.15 (m, 5 H, 2 CH_2, C_{10} H), 3.4 (m, 1 H, C_{11} H), 3.1 (d, 1 H, C_{12} H, $J_{8,12}$ = 3 Hz), 2.5 (m, 1 H, C_8 H), 2.2 (t, 2 H), 1.9-1 (m, 16 H); MS, *m/e* 326 (M), 281 (M - OCH_2CH_3). Anal. Calcd for $C_{17}H_{26}O_6$: C, 61.76; H, 8.09. Found: C, 62.00; H, 8.06.

***trans,trans*-2-[6-(Ethoxycarbonyl)hexyl]-3-(ethoxycarbonyl)-4-hydroxycyclopentanone (1).** Aluminum amalgam (12.5 g of Al) prepared according to Corey[11] was added to a solution of the epimeric mixture of the epoxides (0.7 g, 2.15 mmol) in THF-H_2O (2:1, 100 mL), and the mixture was stirred at room temperature for 1 h and then filtered. The solid phase was washed with THF. Most of the solvent was removed in vacuo, ethyl acetate (50 mL) was added, the aqueous phase was separated, and the organic phase was dried (Na_2SO_4) and concentrated in vacuo at room temperature to give **1** (0.510 g, 72%) with a good purity degree after chromatography on a short column on silica gel (ethyl acetate-methylene chloride, 1:4): IR (neat) 3500 (w), 1736 (s); NMR 4.15 (m, 5 H, 2 CH_2, C_{11} H), 3.75 (s, 1 H, OH), 2.8 (m, 1 H, C_8 H), 2.6-2.1 (m, 5 H), 1.8-1 (m, 16 H); MS, *m/e* 328 (M), 310 (M - H_2O), 283 (M - OCH_2CH_3). Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.27; H, 8.60. Found: C, 62.19; H, 8.63.

Registry No. **1**, 83693-21-4; **2**, 141-97-9; **3**, 83693-22-5; **4**, 760-95-2; **5**, 83693-23-6; **6**, 83693-24-7; **7**, 83693-25-8; **8** (isomer 1), 83693-26-9; **8** (isomer 2), 83730-10-3.

Canin from *Artemisia cana* Pursh ssp. *cana*. Crystal Structure and Identification of Chrysartemin A

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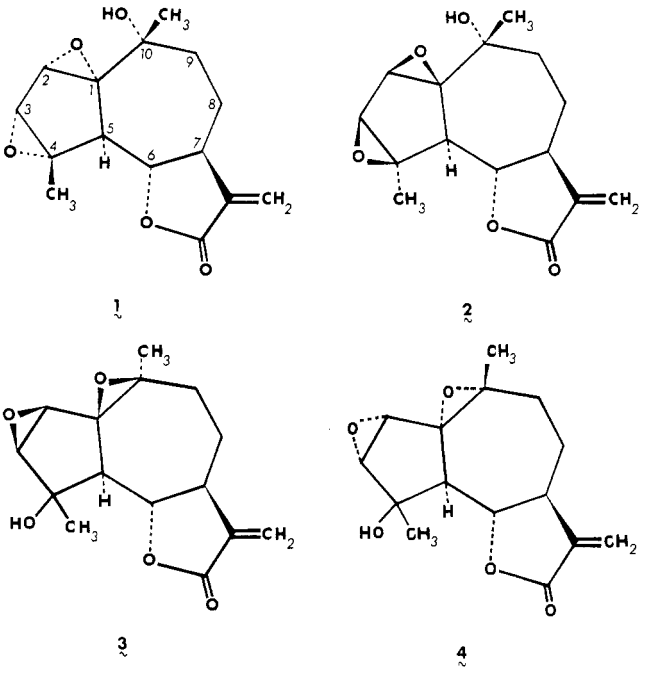
A number of stereoisomeric guaianolides having the molecular formula $C_{15}H_{18}O_5$ have been reported in the literature. Canin, originally isolated from *Artemisia cana* Pursh ssp. *cana* by Lee,[1a] is widely distributed in different species of this genus:[2] *Artemisia caucasica* Willd.,[3] *Artemisia rutifolia* Steph. et Spring.,[4] *Artemisia tripartita* Rydb. ssp. *tripartita*,[5] and *Artemisia frigida* Willd.[6] Artecanin, sometimes occurring with canin, has been isolated from *A. cana* ssp. *cana*[1] and *Artemisia ludoviciana* var. *ludoviciana* Nutt.[7] Chrysartemin A and B were both present in *Chrysanthemum parthenium* (L.) Sch. Bip.[8] whereas only the former occurred in *Artemisia klotzchiana* Bess.[8] and *Artemisia mexicana* Willd.[8] Chrysartemin B is a constituent of *Handelia trichophylla*[9] and *Chrysanthemum morifolium* Ram.[10]

The original structure of canin (1) was reported in 1969[1a] and was subsequently revised to **2**[1b] in 1975 on the basis



of chemical and spectral properties. At this later date artecanin was assigned structure **1**.[1b] In 1970 chrysartemin A and B were isolated and assigned structures **3** and **4**, respectively. As a consequence of a single X-ray crystallographic analysis in 1977, the structure of chrysartemin B was changed to **2**.[10] Subsequent spectral comparison confirmed the identity of chrysartemin B (**2**) as artecanin,[7] necessitating the revision of canin (recently equated with chrysartemin A[6]) back to the original structure of Lee (**1**).[1a]

Hence, a single X-ray crystallographic analysis of canin was undertaken for the following reasons: (1) to unambiguously establish the structure and stereochemistry of canin and verify its relationship to artecanin, chrysartemin A, and chrysartemin B (this information is part of a continuing effort to clarify duplication of literature compounds isolated from different natural sources)[11] and (2) to study

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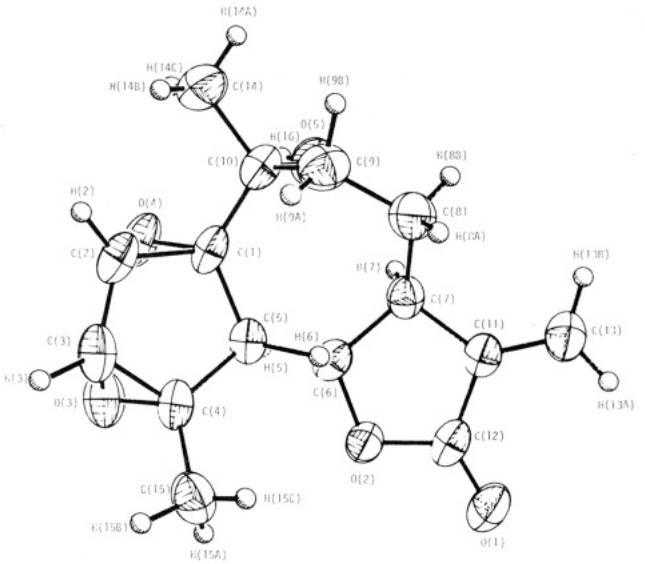

Figure 1. Perspective view (SHELXTL)[13] of canin showing atom numbering and 50% thermal ellipsoids for the anisotropic atoms.

conformations of different classes of sesquiterpene lactones possessing the α-methylene γ-lactone moiety with the ultimate goal of relating structure with observed biological activity.

Results and Discussion

The perspective view of canin or its mirror image is represented by Figure 1. The structure of canin shows trans fusion at C-6 and C-7 of the α-methylene γ-lactone moiety characteristic of a guaianolide in which the C-7 side chain is β oriented. The two epoxide groupings are cis within the cyclopentane framework. The C-14 and C-15 methyl groups are trans to the 3,4-epoxide and 2,3-epoxide, respectively, which unequivocally designates canin as possessing structure **1**.

The four carbons C(1)–C(2)–C(3)–C(4) of the cyclopentane ring containing the epoxide rings all have shorter C–C single bond lengths (≤1.48 Å) than the standard 1.54 Å of the sp^3 C–C bond. The net result is a planar cyclopentane ring. The lactone ring moiety is also planar, with the C(11)–C(12) bond being somewhat shortened. The cycloheptane ring is in a "boatlike" conformation in order to compensate for the planarity of the two five-membered rings.

As previously mentioned, conformational comparison of sesquiterpene lactones such as canin (**1**) and chrysartemin B (**2**) may contribute to a better understanding of the three-dimensional arrangement of functional groups such as epoxides and α-methylene lactones, required to confer biological activity.

Both canin (**1**) and chrysartemin B (**2**) crystallize in the orthorhombic space group $P2_12_12_1$ with four molecules per unit cell. The unit cell parameters are close with a = 6.438, b = 13.274, and c = 15.646 Å for canin (**1**) and a = 14.371, b = 16.049, and c = 5.853 Å for chrysartemin B (**2**). On examination of the bond length and bond angle data (supplementary Tables I and II, respectively) some interesting similarities and differences are revealed. All of the bond lengths in both compounds are extremely close. For consideration of bond angles, the structural segments of the cyclopentane–diepoxide ring, the cycloheptane ring, the lactone ring, and the C(14) and C(15) methyl groups may be inspected. With only minor bond angle differences, the cyclopentane–diepoxide ring region is similar in both structures, the cyclopentane ring being held in a planar conformation by the two epoxide rings. Major differences occur in the conformations of the seven-membered ring and the lactone moiety. In canin (**1**) the lactone ring is planar while in chrysartemin B (**2**) it assumes a "twisted or envelope" conformation, giving rise to markedly different bond angles. The C(7)–C(6)–O(2) angle in chrysartemin B (**2**) is 6° larger than that in canin (**1**).

Conversely, the cycloheptane ring is more "puckered" in canin (**1**) with relatively large bond angle differences. The seven-membered ring in chrysartemin B (**2**) appears to be in a "twist-chairlike" conformation. The C(1)–C(5)–C(6) and the C(5)–C(1)–C(10) angles were 5° and 6° larger, respectively, in canin (**1**) than in chrysartemin B (**2**). This effect may result from the steric interaction of the H(6) with the C(15) methyl group which in canin (**1**) is directed toward the lactone ring, whereas in chrysartemin B (**2**) it is directed outward, away from the balance of the molecule. The C(14) methyl and the hydroxyl groups do not appear to be sterically crowded in either structure.

The more highly puckered nature of canin (**1**) in the cycloheptane ring manifests itself in more severe 1,2-, 1,3-, and 1,4-diaxial hydrogen interactions. The H(9A) and H(6) 1,4 interaction is the most stringent. Overall canin (**1**) projects a less favorable structure energywise because of steric strain. Its molecular packing (supplementary material Figure 1) in the unit cell is such that there may be hydrogen bonding between the hydroxyl [O(5)–H(16)] of molecule A and the O(3) epoxide of a second molecule B and between the hydroxyl of molecule B and the O(3) epoxide of molecule A.

In conclusion, the molecular structure of canin (**1**) or its mirror image is represented by Figure 1; the absolute stereochemistry has not been established. It has the original structure proposed by Lee[1a] and is identical with chrysartemin A. Further evidence for this result is provided by recent spectral studies.[6] Chrysartemin B (**2**) and artecanin are the same compound as verified previously.[7]

Experimental Section

X-ray analysis was performed on a Nicolet R3m/E crystallographic system at Nicolet XRD in Cupertino, CA. IR spectra were obtained of KBr pellets from a Sargent-Welch Pye Unicam Model 3-300, and proton spectra were recorded on a 60-MHz Hitachi Perkin-Elmer Model R-24B at Kalamazoo College, Kalamazoo, MI.

X-ray Structural Determination of Canin. A single crystal of canin, $C_{15}H_{18}O_5$, was obtained by slow evaporation of an acetone solution of a sample of the original canin isolated from *Artemisia cana* Pursh. ssp. *cana* by Bhadane and Shafizadeh.[1b] X-ray data collection was carried out on a Nicolet R3m automated diffractometer equipped with a Cu target X-ray tube (λ = 1.5418 Å) and a graphite crystal monochromator.[12] Canin crystallized in the orthorhombic space group $P2_12_12_1$ and possessed unit cell constants of a = 6.438 (2), b = 13.274 (3), and c = 15.646 (3) Å with Z = 4. X-ray intensity data were measured for a total of 905 independent observed reflections with $I \geq 3\sigma(I)$. The structure was solved by direct methods which revealed the locations of all nonhydrogen atoms on the initial E map. The structure was refined down to a final value of R_1 = 4.5% and R_2 = 4.8% by full-matrix least-squares techniques with anisotropic thermal parameters for all nonhydrogen atoms. Hydrogen atoms were placed in idealized positions with isotropic thermal parameters.

(11) Unpublished results of the current authors for the X-ray structure of tatridin A diacetate which substantiates its identity with tulirinol acetate.

(12) Programs used for centering of reflections, autoindexing, refinement of cell parameters, axial photographs, and data collection were those described in: Calabrese, J. C., Ed. "Nicolet P3/R3 Data Collection Manual"; Nicolet XRD Corp: Cupertino, CA, 1980.

All structural determinations and refinement calculations were carried out with the SHELXTL package on the Nicolet R3m/E crystallographic system.[13] On the basis of four molecules of $C_{15}H_{18}O_5$ in a unit cell with a volume of 1337.08 Å^3, the calculated density was 1.337 g/cm^3. The experimental density measurement was 1.393 g/cm^3. The final difference map revealed no abnormal features.

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Registry No. 1, 24959-84-0; 2, 29431-84-3.

Supplementary Material Available: Figure 1 showing the packing diagram of the unit cell of canin and Tables I–V listing bond distances and bond angles for canin and chrysartemin B, final atomic parameters, and final anisotropic thermal parameters (8 pages). Ordering information is given on any currrent masthead page.

(13) Programs used for data reduction, Fourier syntheses, direct method structure solution, least-squares refinement, error analysis, least-squares planes calculation, and calculation of hydrogen positions are those described in: Sheldreck, G. M., Ed. "Nicolet SHELXTL Structure Determination Manual"; Nicolet XRD Corp: Cupertino, CA, 1980.

Synthesis of Acamelin

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Australian blackwood (*Acacia melanoxylon* R. Brown) is one of the commercial timbers exhibiting a potential for human health injury.[1] Cases of contact dermatitis and bronchial asthma have been reported since 1925 among workers exposed to wood dust and shavings.[2] Hausen and his co-workers have demonstrated a sensitizing capacity of crude extracts of the heartwood. At least two quinone constituents having contact allergenic activity were isolated and identified by X-ray crystallographic analysis as 2,6-dimethoxy-1,4-benzoquinone (1)[3] and 2-methyl-6-methoxy-4,7-benzofurandione (2).[4] For the latter, which exhibited the stronger and longer lasting skin response in sensitized guinea pigs, the name acamelin was proposed. We report here a synthesis of this product, which had been obtained only in minute amounts from the natural source.

Inspection of the oxygen substitution pattern of acamelin indicated that the benzofuranoid skeleton might be readily constructed from phloroglucinol or phloroglucinol dimethyl ether by attachment of an appropriate three-carbon chain. To this end, phloroglucinol (3) was acylated with 2-chloropropionitrile under Houben–Hoesch conditions[5,6] to yield, after cyclization with potassium acetate solution, the dihydroxydihydrobenzofuranone 5 (Scheme I). This was readily converted to the dimethyl ether 6 by treatment with dimethyl sulfate in dimethoxyethane. Alternatively, the dimethyl ether 6 could be isolated directly as one of two major products obtained by the same acylation–cyclization sequence on 3,5-dimethoxyphenol (4).

Selective partial demethylation of 6 was achieved in excellent yield to give the monomethyl ether 7 by the action of aluminium chloride in dichloromethane at room temperature. At reflux temperature, further demethylation to the dihydroxydihydrobenzofuranone 5 occurred. The conversion of 7 to the desired intermediate benzofuran 8 by the action of lithium aluminium hydride was examined.[7] When the reduction was carried out in the usual way by heating the reactants under reflux in diethyl ether or tetrahydrofuran solution, there was obtained a mixture of the benzofuran 8 and dihydrobenzofuran 9, with the latter predominating. This difficulty was overcome, however, and the benzofuran 8 was cleanly obtained by conducting the reduction in tetrahydrofuran at room temperature.

Conventional oxidation of this phenolic benzofuran with Fremy's salt yielded in bright orange-red crystalline form 6-methoxy-2-methyl-4,7-benzofurandione (2), i.e., the structure attributed to acamelin, with spectroscopic data (^{1}H NMR, UV, IR) fully concordant with expectations for that structure. Since paucity of the natural specimen prevented direct comparison, identification was sought by determination of the unit cell dimensions of the synthetic specimen, measured by least-squares analysis of 15 X-ray reflections by using Mo Kα X-rays on a Nicolet diffractometer. They are in complete agreement with those reported for the crystal of the natural specimen.[8]

The second product obtained from phloroglucinol dimethyl ether (4) by the action of 2-chloropropionitrile followed by potassium acetate gave empirical analytical data corresponding to $C_{11}H_{13}O_4Cl$ and a ^{1}H NMR spectrum consistent with the structure of α-chloroethyl 4-hydroxy-2,6-dimethoxyphenyl ketone (10). Cleavage of one methyl ether function was effected by aluminium chloride treatment to give the dihydroxymethoxyphenyl ketone 11, which by potassium acetate cyclization yielded a product differing from but isomeric with the dihydrobenzofuranone 7. This product can accordingly be formulated as 6-hydroxy-4-methoxy-2-methyl-2,3-dihydrobenzofuran-3-one (12). It yielded, as expected, the same dimethyl ether (6) from which 7 had been obtained.

Experimental Section

Melting points were determined with a Gallenkamp or Fisher-Johns apparatus. NMR spectra were obtained with a Varian EM-390 spectrometer with Me_4Si as an internal standard. Infrared spectra were recorded with a Perkin-Elmer 683 spectrophotometer and ultraviolet spectra with a Perkin-Elmer 323 spectrophotometer.

4,6-Dihydroxy-2-methyl-2,3-dihydrobenzofuran-3-one (5). Dry hydrogen chloride gas was passed through a stirred mixture of phloroglucinol (4.58 g), anhydrous zinc chloride (9 g), and 2-chloropropionitrile (2.24 g) in diethyl ether (200 mL) for 3 h at room temperature, with continued stirring overnight. The resultant red lower layer was separated from the upper ether (yellow) layer and added carefully to water (100 mL) at ice-bath temperature. After it had dissolved, the solution was heated under reflux for 1.5 h, cooled, and extracted with ethyl acetate (3 × 100 mL). The extract was washed with saturated brine, and the solvent removed under reduced pressure to yield a yellow solid residue (8 g) to which was added a solution of potassium acetate

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