results comparing the localization of a responsive *versus* a nonresponsive tumor were published elsewhere (29).

The present study also models the observations made by a nuclear medicine scan, where visual differences of film contrast (scales of gray) are the bases for clinical diagnosis. Thus, because visual differences are observable, it is expected that similar visual differences may be observable in the human. In addition, the use of ^{18}F-fluorouracil-labeled material in conjunction with tomographic cuts obtained with the new positron emission tomographic scanners is likely to produce scans whose interpretation can be correlated closely to the present work.

Although the question of whether localization and utilization of chemotherapeutic agents are an indication of their pharmacological activity is a matter of controversy, studies correlating these factors will help in predicting a more appropriate fluorouracil chemotherapeutic regimen.

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Isolation and Characterization of the Sesquiterpene Lactones Costunolide, Parthenolide, Costunolide Diepoxide, Santamarine, and Reynosin from *Magnolia grandiflora* L.

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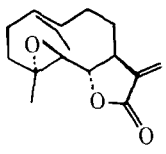
Received February 7, 1977, from the *Pharmacognosy Department, School of Pharmacy, University of Mississippi, University, MS 38677.* Accepted for publication June 27, 1977.

Abstract □ The germacranolide sesquiterpene lactones costunolide, parthenolide, and costunolide diepoxide were isolated from the leaves of *Magnolia grandiflora* L. Costunolide diepoxide might be, at least in part, an artifact derived from air oxidation of parthenolide. The root bark yielded only costunolide together with the two eudesmanolides, santamarine and reynosin. In an attempt to synthesize costunolide diepoxide, the action of *m*-chloroperbenzoic acid on parthenolide and on costunolide was studied. The products were costunolide diepoxide from parthenolide and the two cyclized derivatives, santamarine and reynosin, from costunolide. The elusive costunolide 1,10-epoxide was obtained by epoxidizing costunolide using a biphasic system containing sodium bicarbonate. Under these conditions, epoxidation of costunolide took place without cyclization.

Keyphrases □ *Magnolia grandiflora* L.—leaves, isolation and characterization of various sesquiterpene lactones □ Lactones, various sesquiterpene—isolated and characterized from leaves of *Magnolia grandiflora* L.

Numerous cytotoxic sesquiterpene lactones have been isolated from plants belonging to the Magnoliaceae family (1–4). *Magnolia grandiflora* L., a member of this family, is commonly known as Southern Magnolia (5). This large evergreen ornamental tree is widespread throughout the United States (5).

Only the sesquiterpene parthenolide (I) was reported to occur in this plant (4). The present studies revealed the presence of additional sesquiterpenes in the leaves and root bark. These studies were carried out as a part of a random screening program of local flora for biologically active compounds.



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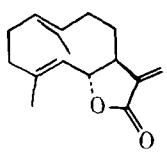

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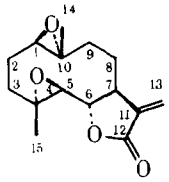
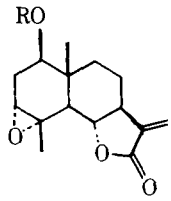


III



IV: R = H
V: R = CCH_3 (=O)

EXPERIMENTAL[1]

Isolation of Parthenolide (I), Costunolide (II), and Costunolide Diepoxide (III)—The dried and powdered leaves[2] (2.25 kg) were exhaustively extracted by percolation with 95% ethanol. The residue (438 g) remaining after solvent evaporation *in vacuo* at 40° was partitioned between chloroform and water. The chloroform residue (161 g) was partitioned between hexane and 10% aqueous methanol to give methanol-soluble material (74 g). Chromatography of the methanol fraction (22 g) on silica gel 60 (1.2 kg), with chloroform as the eluting solvent, gave 2.19 g of the first band, which crystallized spontaneously, and showed one major spot (R_f 0.80) when subjected to TLC.

This fraction was purified by recrystallization from ether–hexane to give II (0.371 g), mp 105–106°, $[\alpha]_D^{22}$ +117° (*c*, 0.200 in $CHCl_3$); UV: end absorbance 210 nm, log ϵ = 4.05; IR ($CHCl_3$): ν_{max} 1765, 1667, 1285, 1136, 995, and 930 cm^{-1}; PMR ($CDCl_3$): δ 1.70 and 1.42 (each 3H, br s, C_4CH_3 and $C_{10}CH_3$), 4.57 (1H, t, J = 10 Hz, C_6H), 4.79 (1H, m, C_5H), 4.9 (1H, m, C_1H), 5.54 (1H, d, J = 3 Hz, $C_{13}H$), and 6.27 (1H, d, J = 4 Hz, $C_{13}H$) ppm; mass spectrum: M^+ at *m/e* 232 (57%).

Anal.—Calc. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.39; H, 8.45.

The IR and PMR spectra were superimposable on those of II (6).

The band following the II fraction from the silica gel 60 column provided 5.7 g of crude I and gave one major spot on TLC (R_f 0.65). The material was crystallized twice from absolute ethanol–ether to give prisms or plates of I (4.11 g), mp 115–116°, $[\alpha]_D^{22}$ −71.4° (*c*, 0.220 in CH_2Cl_2); UV: end absorbance 210 nm, log ϵ = 3.97; IR ($CHCl_3$): ν_{max} 1777, 1670, 1287, 1137, and 982 cm^{-1}; PMR ($CDCl_3$): δ 1.30 (3H, s, C_4CH_3), 1.73 (3H, s, $C_{10}CH_3$), 2.78 (1H, d, J = 9 Hz, C_5H), 3.88 (1H, t, J = 8 Hz, C_6H), 5.25 (1H, m, C_1H), 5.65 (1H, d, J = 3 Hz, $C_{13}H$), and 6.33 (1H, d, J = 3.5 Hz, $C_{13}H$) ppm; mass spectrum: M^+ at *m/e* 248 (11%).

Anal.—Calc. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.38; H, 8.19.

The compound was identical in all regards to an authentic sample of parthenolide[3] (R_f, melting point, mixed melting point, and superimposable IR and PMR spectra).

The band following the parthenolide fraction was much less colored than the preceding band and gave one spot (R_f 0.50) on TLC. It was crystallized from absolute ethanol–ether to give needles (0.91 g) of III, mp 168–169°, $[\alpha]_D^{22}$ −30° (*c*, 0.200 in CH_2Cl_2); UV: end absorbance 210 nm, log ϵ = 3.89; IR ($CHCl_3$): ν_{max} 1777, 1670, 1386, 1287, and 1132 cm^{-1}; PMR ($CDCl_3$): δ 1.32 and 1.38 (each 3H, s, C_4CH_3 and $C_{10}CH_3$), 2.85 (1H, d, J = 8.0 Hz, C_5H), 3.87 (1H, t, J = 8.5 Hz, C_6H), 5.47 (1H, d, J = 3.0 Hz, $C_{13}H$), and 6.18 (1H, d, J = 3.5 Hz, $C_{13}H$) ppm; mass spectrum: M^+ at *m/e* 264 (less than 1%).

Anal.—Calc. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.37; H, 7.69.

Epoxidation of I—Compound I (100 mg) was dissolved in 10 ml of chloroform. Then 1.0 equivalent (82 mg) of *m*-chloroperbenzoic acid (85%) was added, and the solution was allowed to stand at 5° for 2 hr. The reaction mixture was diluted with 100 ml of chloroform and was then washed with 5% Na_2SO_3 (30 ml), 5% $NaHCO_3$ (30 ml), and then water (10 ml). The chloroform phase was dried over anhydrous sodium sulfate and evaporated to leave 120 mg of a crystalline residue. This residue was recrystallized from absolute ethanol–ether to give 100 mg of a product identical in all respects to the isolated material (same R_f, melting point, mixed melting point, specific rotation, and superimposable IR and PMR spectra).

Epoxidation of II—Compound II (100 mg) was epoxidized with 2.0 equivalents of *m*-chloroperbenzoic acid (180 mg), as described for I, and yielded 154 mg of a crystalline residue. This residue was recrystallized from absolute ethanol–ether to give needles (53 mg) of IV, mp 243–246°, $[\alpha]_D^{22}$ +73° (*c*, 0.140 in C_2H_5OH); UV: end absorbance 210 nm, log ϵ = 4.16; IR (KBr): ν_{max} 3430, 1767, 1677, 1131, and 994 cm^{-1}; PMR (dimethyl sulfoxide-d_6): δ 0.80 (3H, s, $C_{10}CH_3$), 1.35 (3H, s, C_4CH_3), 2.96 (1H, d, J = 3.5 Hz, C_5H), 3.24 (1H, m, CH), 4.08 (1H, t, J = 11.0 Hz, C_6H), 4.64 (1H, exchangeable, d, J = 5.0 Hz, C_1OH), 5.53 (1H, d, J = 3.0 Hz, $C_{13}H$), and 5.96 (1H, d, J = 3.5 Hz, $C_{13}H$) ppm; mass spectrum: M^+ at *m/e* 264 (15%).

Anal.—Calc. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.05; H, 7.64.

This compound was characterized as epoxysantamarine (IV) by comparing its physical and spectral data to those published (7). Acetylation of IV following the previously reported procedure (7) gave needles of V, mp 183–185°; $[\alpha]_D^{22}$ +64° (*c*, 0.14 in absolute ethanol); UV: end absorbance 210 nm, log ϵ = 3.92; IR ($CHCl_3$): ν_{max} 1772, 1734, 1674, 1127, 997, and 957 cm^{-1}; PMR ($CDCl_3$): δ 1.02 (3H, s, $C_{10}CH_3$), 1.50 (3H, s, C_4CH_3), 2.06 (3H, s, $CH_3C{=}O$), 3.00 (1H, d, J = 3.5 Hz, C_5H), 3.93 (1H, dd, J = 10 and 11 Hz, C_6H), 4.75 (1H, dd, J = 9.5 and 6.0 Hz, C_1H), 5.45 (1H, d, J = 3.0 Hz, $C_{13}H$), and 6.14 (1H, d, J = 3.0 Hz, $C_{13}H$) ppm; mass spectrum: M^+ at *m/e* 306 (11%).

Anal.—Calc. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.47; H, 7.26.

The physical and spectral characteristics of V were identical to those reported for acetylepoxysantamarine (7).

In another run, 300 mg of II was dissolved in 20 ml of chloroform, and 1 equivalent (263 mg) of *m*-chloroperbenzoic acid was added. The reaction mixture was worked up as already described to yield 320 mg of a residue. This residue, when treated with a chloroform–ether mixture, deposited 81 mg of pure santamarine (VII), mp 134–135°, $[\alpha]_D^{22}$ +72.8° (*c*, 0.180 in absolute ethanol); UV: end absorbance 210 nm, log ϵ = 4.30; IR (KBr): ν_{max} 3380, 1773, 1673, 1128, and 995 cm^{-1}; PMR ($CDCl_3$): δ 0.86 (3H, s, $C_{10}CH_3$), 1.85 (3H, s, C_4CH_3), 3.70 (1H, dd, J = 6.0 and 9.5 Hz, C_1H), 3.98 (1H, t, J = 10 Hz, C_6H), 5.43 (1H, d, J = 3.0 Hz, $C_{13}H$), and 6.10 (1H, d, J = 3.0 Hz, $C_{13}H$) ppm; mass spectrum: M^+ at *m/e* 248 (64%).

Anal.—Calc. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.45; H, 8.22.

The identity of VII was further confirmed by comparison with an authentic sample of santamarine[4]; the two compounds proved to be identical in all respects.

The mother liquor (239 mg) gave two spots with R_f values of 0.52 (santamarine; major) and 0.40 (reynosin; minor) when chromatographed on silver nitrate-impregnated silica gel G plates[5]. Separation of the two compounds of the mother liquor was achieved by chromatography on a column of 10 g of silver nitrate-impregnated silica gel G[6] with ether as a solvent. The separation was monitored by TLC. A mixture of unreacted

[1] Melting points were determined on a Thomas-Hoover Uni-Melt melting-point apparatus and are uncorrected. Elemental analyses were performed by Scandinavian Microanalytical Laboratories, Herlev, Denmark. IR spectra were run in potassium bromide or chloroform using a Perkin-Elmer 257 or Beckman IR-33 IR spectrometer. ^{1}H-NMR (PMR) spectra were recorded on a Jeolco C-60-HL spectrometer using deuterated chloroform as the solvent (unless otherwise specified) and tetramethylsilane as the internal standard; chemical shifts were reported in δ (parts per million) units. UV spectra were obtained in methanol on a Beckman Acta III spectrophotometer. Optical rotations were determined on a Perkin-Elmer 141 automatic polarimeter. Mass spectral data were obtained on a DuPont CEC 492 spectrometer. TLC was performed on Merck silica gel G plates using absolute ethanol–chloroform (6:94) as the eluent. The spots were visualized by spraying with 0.3% aqueous potassium permanganate.

[2] The plant material was collected at Tupelo, Miss., in June 1976; a voucher specimen has been deposited in the Herbarium, Department of Pharmacognosy, School of Pharmacy, University of Mississippi.

[3] Provided by Dr. G. Cordell, Department of Pharmacognosy and Pharmacology, University of Illinois.

[4] Provided by Dr. T. Mabry, Department of Botany, University of Texas.

[5] Silver nitrate impregnation was done by spraying silica gel G precoated plates with a 5% aqueous solution of silver nitrate and then drying the plates at 110° for 30 min. The plates were then spotted and developed with ether.

[6] Silver nitrate silica gel G for column separations was prepared by suspending 50 g of the TLC-grade silica gel G in 100 ml of 5% aqueous silver nitrate. The mixture was dried at 110° for 6 hr, passed through a 60–80-mesh sieve, and stored in amber-colored jars.

II and VII was obtained first, followed by 64 mg of pure VII and then 33 mg of reynosin (VIII), mp 145–146°, $[\alpha]_D^{22}$ +122° (*c*, 0.100 in absolute ethanol); UV: end absorbance at 210 nm, log ϵ = 3.96; IR ($CHCl_3$): ν_{max} 3610, 1772, 1653, 1410, 1127, and 1082 cm^{-1}; PMR ($CDCl_3$): δ 0.83 (3H, s, $C_{10}CH_3$), 3.55 (1H, dd, J = 4 and 10.5 Hz, C_1H), 4.06 (1H, t, J = 11.0 Hz, C_6H), 4.90 and 5.03 (1H each, br s, $C_4{=}CH_2$), 5.45 (1H, d, J = 3.0 Hz, $C_{13}H$), and 6.12 (1H, d, J = 3.5 Hz, $C_{13}H$) ppm; mass spectrum: M^+ at *m/e* 248 (4.7%).

Anal.– Calc. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.51; H, 8.02.

The physical and spectral properties were identical to those reported for reynosin (7).

Controlled Epoxidation of II to Costunolide 1,10-Epoxide (VI)—Compound II (100 mg) was dissolved in 30 ml of methylene chloride, and the solution was stirred with 30 ml of 0.5 *M* aqueous sodium bicarbonate. One equivalent of *m*-chloroperbenzoic acid (96 mg) was then added slowly, and the two-phase system was stirred for 1 hr. The organic phase was separated and washed successively with 30 ml of 1.0 *M* sodium sulfite, 60 ml of 1.0 *M* NaOH, and finally with 30 ml of water. The methylene chloride layer was dried over anhydrous sodium sulfate and then evaporated under reduced pressure to leave a residue.

This residue readily crystallized from ether–absolute ethanol to give 66 mg of colorless needles, mp 123–125°, $[\alpha]_D^{22}$ +14° (*c*, 0.15 in methylene chloride); UV: end absorbance at 210 nm, log ϵ = 4.07; IR ($CHCl_3$): ν_{max} 1767, 1667, 1437, 1379, 1278, 1236, 1066, and 948 cm^{-1}; PMR ($CDCl_3$): δ 1.15 (3H, s, $C_{10}CH_3$), 1.85 (3H, s, C_4CH_3), 4.63 (1H, t, J = 10 Hz, C_6H), 5.32 (1H, br d, J = 10.0 Hz, C_5H), 5.48 (1H, d, J = 3.5 Hz, $C_{13}H$), and 6.25 (1H, d, J = 3.5 Hz, $C_{13}H$) ppm; mass spectrum: M^+ at *m/e* 248 (19%).

Since the compound started to cyclize within a few hours after it had been prepared, no attempts were made to submit it for elemental analysis.

Epoxidation of II using the two-phase system described, but in the presence of excess *m*-chloroperbenzoic acid for several days, produced III.

Cyclization of VI—Compound VI (80 mg) was dissolved in 15 ml of chloroform, which was preshaken with 1 ml of concentrated hydrochloric acid. The reaction was monitored by TLC; after 20 min, all of the VI was converted to a mixture of reynosin and santamarine. The solvent was then removed by evaporation, and the residue was chromatographed on a 1.0 × 10.0-cm column packed with 7 g of 5% silver nitrate-impregnated silica gel. The column was eluted with ether, and the separation was monitored by TLC. The first band yielded 59 mg of VII, followed by another band which provided 15 mg of VIII; the identity of these compounds was established by comparison with the compounds described earlier.

Compound VI underwent facile cyclization to VII and VIII upon storage, even in the solid form.

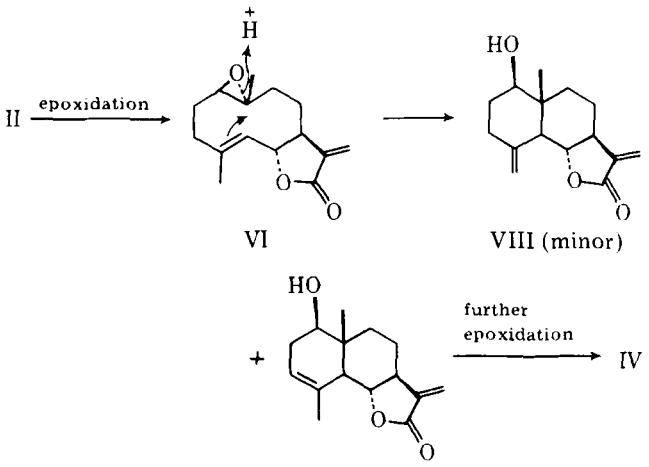
Air Oxidation of I—Parthenolide (I; 20 mg) was dissolved in three drops of chloroform, and the solution was allowed to stand at room temperature for 4 weeks. Evaporated solvent was replaced as needed, and the composition of the solution was monitored daily by TLC. After 4 weeks, most I was oxidized to II, but some of it underwent polymerization. The reaction mixture was dissolved in chloroform and filtered. The oily material obtained (10 mg) was crystallized from an absolute ethanol–ether mixture, and the product was identical in all regards to III.

Isolation of II, VII, and VIII from Root Bark—The root bark (1.0 kg) was exhaustively extracted by percolation with chloroform at room temperature. Then the solvent was evaporated *in vacuo* to leave 61 g of a crystalline residue, which was partitioned between 10% aqueous methanol (100 ml) and hexane (3 × 100 ml). The methanol solubles (43 g) were chromatographed on 1200 g of silica gel 60 with chloroform as a solvent. Costunolide (II; 29 g) was eluted first, followed by an orange band (200 mg) which deposited crystals (74 mg) of santamarine (VII) upon standing.

The fractions next to the orange band were combined, based on TLC, and evaporated to leave 1.0 g of a colorless residue. A portion of this residue (500 mg) was chromatographed on 40 g of silica gel G with chloroform as a solvent. The separation was monitored by TLC, and the column yielded 56 mg of crystalline reynosin (VIII). The identity of the isolated VII and VIII was established by comparison to those compounds prepared by treatment of II with 1 equivalent of *m*-chloroperbenzoic acid, as described earlier.

RESULTS AND DISCUSSION

An alcoholic extract of the leaves of *M. grandiflora* L. yielded a number of sesquiterpene lactones upon solvent partitioning and chromatography on silica gel with chloroform as a solvent. The two germacranolide sesquiterpenes[7], costunolide (II) and parthenolide (I), were obtained from the first and the second chromatographic bands[8], respectively. They were characterized by direct comparison with authentic samples.



Scheme I

Costunolide diepoxide (III), $C_{15}H_{20}O_4$, was eluted next to the parthenolide band and was crystallized from an absolute ethanol–ether mixture to give needles, mp 168–169°. Its IR spectrum exhibited no hydroxyl absorption and still showed the characteristic α,β-unsaturated-γ-lactone carbonyl band at ν_{max} ($CHCl_3$) 1777 cm^{-1} with the C=C absorption band at 1670 cm^{-1}. This result suggested that the remaining two oxygen atoms must be in the form of ether groups.

The PMR spectrum of III exhibited two three-proton singlets at δ 1.32 and 1.38 ppm, which were assigned to a pair of methyl groups on oxygenated carbon atoms (1). Except for the absence of the signal for the olefinic C-1 proton, other resonances in the spectrum were similar to those of I.

The spectral data obtained for III suggested a 1,10-epoxyparthenolide structure. To confirm this assignment, epoxidation of I was undertaken using 1 equivalent of *m*-chloroperbenzoic acid. The exclusive product was III, so its structure was secured. It followed that the absolute stereochemistry of C-4, C-5, C-6, and C-7 should be the same as for I (8). The chirality at C-1 and C-10 will be discussed later in connection with the structure and stereochemistry of VI.

Chloroform solutions of I were found to contain III when stored at room temperature for a few days. The transformation of I to III became nearly complete in 4 weeks. This finding indicated that III might be, at least in part, an artifact obtained by air oxidation of I. This type of air oxidation was reported previously (9) with other sesquiterpenes.

This is the first report of costunolide diepoxide (III), although compounds of similar type, *e.g.*, epitulipinolide diepoxide (1) and agerol diepoxide (10), were reported previously.

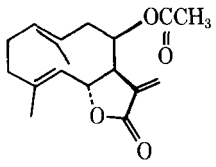
Unexpectedly, epoxidation of II using 2 equivalents of *m*-chloroperbenzoic acid did not yield III. Instead, the major product, mp 243–246°, was identified as the hydroxylated eudesmanolide, epoxysantamarine (IV). The structure of IV was established by comparing its physical and spectral data and those of its acetate derivative (V) to the data reported (7) for epoxysantamarine and acetylepoxysantamarine, respectively.

The formation of IV during the attempted epoxidation of II can be best explained by assuming that epoxidation first involves the less hindered 1,10-double bond of II to produce VI. The latter compound could then cyclize under the acidic conditions of epoxidation to give VII. Further epoxidation of VII by more of the peracid should then produce IV (Scheme I). To confirm this mechanism, II was treated with only 1 equivalent of the peracid. As expected, the major product under these conditions was characterized as VII; a small amount of its β-isomer, VIII, was also obtained.

The role played by VI in the cyclization of II during attempted epoxidation made it both interesting and challenging to try to synthesize it.

[7] Both parthenolide (4) and costunolide (6) were reported to possess cytotoxic activity in KB cells with ED_{50} values of 23 and 0.26 μg/ml, respectively.

[8] The costunolide band yielded, in addition to costunolide, a novel sesquiterpene hydroperoxide; similarly, the parthenolide band yielded another novel sesquiterpene hydroperoxide. The structures of both compounds were discussed recently by El-Feraly *et al.* (*Tetrahedron Lett.*, 1977, 1973).



IX

This synthesis was accomplished by epoxidizing II in a two-phase system containing sodium bicarbonate (11). The presence of the latter prevented any cyclization and provided VI as the only product. As expected, VI underwent facile acid-catalyzed cyclization to VII and VIII. Moreover, it could be further epoxidized to III in the presence of excess peracid.

Since the absolute stereochemistry of C-1 in VII is *R* (7), it then followed that C-1 in VI must have the same absolute configuration. Also, the epoxide group of VI, being derived from the *trans*-1,10-double bond of II, must also have a *trans*-geometry. Therefore, the absolute stereochemistry of costunolide 1,10-epoxide should be as depicted in Structure VI. Consequently, III, which could be obtained by further epoxidation of VI, as mentioned before, must have similar chirality at C-1 and C-10.

Dihydrocostunolide was reported (12) to undergo epoxidation with perbenzoic acid to dihydrocostunolide diepoxide. In other words, epoxidation of dihydrocostunolide proceeded without cyclization. This behavior can be explained in terms of the poor acidity of perbenzoic acid and its reduction product, benzoic acid, relative to *m*-chloroperbenzoic acid and *m*-chlorobenzoic acid. However, there may be another explanation. The germacranolide sesquiterpene epitulipinolide (IX) can be epoxidized (1) with *m*-chloroperbenzoic acid to epitulipinolide 1,10-epoxide without cyclization. It appears, therefore, that the conformational factors affecting the transannular system of double bonds must play a significant role in deciding whether facile cyclization is to take place or not.

The root bark of *M. grandiflora* L. yielded, in addition to II, the two eudesmanolides VII and VIII. In view of the above discussion, these compounds must have been derived by the cyclization of biogenetically formed VI.

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Sustained Release from Inert Wax Matrixes I: Drug–Wax Combinations

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Abstract □ The melting and energy characteristics of several drug–wax combinations were investigated using differential scanning calorimetry. The phase diagrams of binary mixtures of tripelennamine hydrochloride and tolazoline hydrochloride with carnauba wax and castor wax showed no eutectic formation and gave no indication that a significant interaction was involved. However, in tripelennamine mixtures, a slight depression in the drug melting point was observed at around 50% concentration. For ternary systems, *i.e.*, drug, carnauba wax, and stearyl alcohol, thermograms of samples prepared by a fusion method differed slightly from those obtained with mixtures formulated by dissolving all ingredients in chloroform and evaporating the solvent. However, the location of the peak of each component remained essentially the same. A plot of melting point *versus* concentration of each compound showed insignificant changes in melting point and indicated that no interaction was occurring. The phase diagrams suggested that the combinations are strictly physical and that it is the physical characteristics, such as the hardness and composition of the core and drug particle size, that influence the release or dissolution of the drug from the waxy matrix.

Keyphrases □ Wax matrixes, inert—release of tripelennamine hydrochloride or tolazoline hydrochloride from mixtures with carnauba wax or castor wax □ Tripelennamine hydrochloride—release from inert carnauba or castor wax matrixes □ Tolazoline hydrochloride—release from inert carnauba or castor wax matrixes □ Dosage forms—inert wax matrixes, release of tripelennamine hydrochloride or tolazoline hydrochloride from mixtures with carnauba or castor wax □ Antihistaminics—tripelennamine hydrochloride, release from inert carnauba or castor wax matrixes □ Vasodilators, peripheral—tolazoline hydrochloride, release from inert carnauba or castor wax matrixes

The major factors influencing drug distribution in a sustained-release matrix (core) and drug release from the core include the particle size and drug solubility as well as core hardness and composition. Generally, the drug is physically incorporated into a wax matrix and compressed.