Syntheses of Four Possible Diastereoisomers of Bohlmann's Structure of Isoepoxyestafiatin. The Stereochemical Assignment of Isoepoxyestafiatin[1,2]

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The stereochemistry of isoepoxyestafiatin was determined to be 1β,10β:3α,4α-diepoxyguaia-11(13)-eno-12,6α-lactone by the syntheses of the four possible diastereoisomers **23–26**.

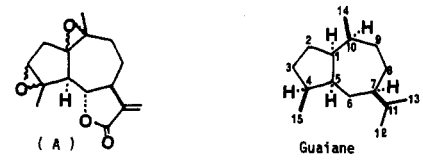
Isoepoxyestafiatin was isolated by Bohlmann and Zdero from *Pentazia elegans*.[3] The structure of this compound was proposed as shown in structure A (Chart I) by them, but the stereochemistry of the epoxide rings at $C_{1,10}$ and $C_{3,4}$ and the absolute configuration were not presented in their paper. This paper gives results of the syntheses of the four possible diastereoisomers **23–26** of Bohlmann's structure of isoepoxyestafiatin with the object of establishing the structure of isoepoxyestafiatin.

The starting material was the β,γ-unsaturated ketone **2**, which can be prepared from α-santonin (**1**) in 23% yield in 10 steps (Scheme I).[4] Selective reduction of the C_1-carbonyl group of **2** with $LiAl(t\text{-}BuO)_3H$ gave 1α-alcohol **3a** and 1β-alcohol **3b** in 9% and 86% yields, respectively. Mesylation of **3b** with methanesulfonyl chloride in pyridine gave a mesylate **4** in 97% yield. Solvolytic rearrangement of **4** in refluxing 0.5 M acetic acid solution of potassium acetate gave dienes **5** and **6** and an inseparable mixture of dienes **7** and **8** (1:8) in 2%, 24%, and 36% yields, respectively (Scheme II). Epoxidation of the mixture of **7** and **8** with 1 molar equiv of *m*-CPBA gave monoepoxides **9**, **10**, **11**, **12**, and **13** in 5%, 22%, 36%, 7%, and 5% yields, respectively.

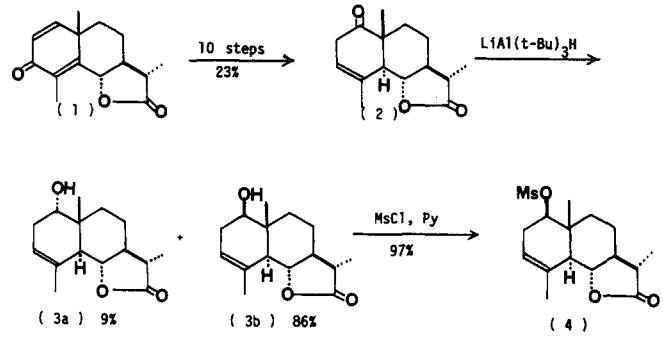
Compounds **9** and **11** were identical with (11*S*)-1β,10β-epoxyguai-3-eno-12,6α-lactone (arborescin) and (11*S*)-1α,-10α-epoxyguai-3-eno-12,6α-lactone (1,10-epiarborescin), respectively, whose structures had already been determined by us unambiguously.[5]

The stereochemistry of 3,4-epoxides **10** and **12** was deduced from the following observation in their ^1H NMR spectra (Chart II). The C_6-H resonance of **10** appeared at 0.23 ppm lower field than that of **12**. On the contrary, the C_5-H resonance of **12** appeared at 0.25 ppm lower field than that of **10**. Since it has been reported that the epoxide function deshields protons that are situated on the same side of oxygen atom,[5,6] the above-mentioned result strongly suggests a cis relationship between the $C_{3,4}$-epoxide ring and the C_6 proton in **10**. An NOE experiment also supports the β and α orientation of the epoxide ring in **10** and **12**, respectively.

Chart I



Scheme I



Further epoxidation of the remaining $C_{3,4}$-double bond of **9** gave two stereoisomeric diepoxides **14** and **15** in 14% and 86% yields, respectively. Since the cis relationship between the $C_{3,4}$-epoxide ring and C_6-H in **15** was clearly demonstrated by the comparison of their ^1H NMR spectra[5,6] in which the signal of the C_6-H of **15** appeared at 0.14 ppm lower field than that of **14**, the stereochemistry of **14** and **15** was depicted as shown in Scheme II.

Epoxidation of the $C_{3,4}$-double bond of **11** also gave two stereoisomeric diepoxides **16** and **17** in 29% and 66% yields, respectively. The stereochemistry of **16** and **17** was depicted as shown in Scheme II by the analogous discussion of ^1H NMR spectra[5,6] in which the signal of C_6-H of **16** appeared at 0.32 ppm lower field than that of **17**.

The stereochemical assignment of diepoxide **14**, **15**, **16**, and **17** based on the analysis of ^1H NMR spectra was also supported by the following independent consideration.

Epoxidation of 3β,4β-monoepoxide **10** gave two stereoisomeric diepoxides **15** and **16** in 32% and 46% yields, respectively. The compound **15** which was the common product in epoxidation of **9** and **10** must be 1β,10β:3β,4β-diepoxide considering the stereochemistry of **9** and **10**. The compound **16** which was the common product in epoxidation of **10** and **11** must be 1α,10α:3β,4β-epoxide considering the stereochemistry of **10** and **11**. This stereochemical assignment is in agreement with that based on the analysis of the above-mentioned ^1H NMR spectra.

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(1) Studies on the Syntheses of Sesquiterpene Lactones. 15.

(2) The preliminary form of this work has appeared as a part of review: Ando, M. The Studies on the Syntheses of Biologically Active Sesquiterpene Lactones. *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem., Jpn)* **1992**, *50*, 858.

(3) Bohlman, F.; Zdero, C. *Tetrahedron Lett.* **1972**, 621.

(4) Ando, M.; Tajima, K.; Takase, K. *J. Org. Chem.* **1983**, *48*, 1210.

(5) Ando, M.; Akahane, A.; Yamaoka, H.; Takase, K. *J. Org. Chem.* **1982**, *47*, 3909.

(6) Paquette, L. A.; Fristad, W. E.; Schuman, C. A.; Beno, M. A.; Cristoph, G. G. *J. Am. Chem. Soc.* **1979**, *101*, 4645.

0022-3263/93/1958-4127$04.00/0

Scheme II

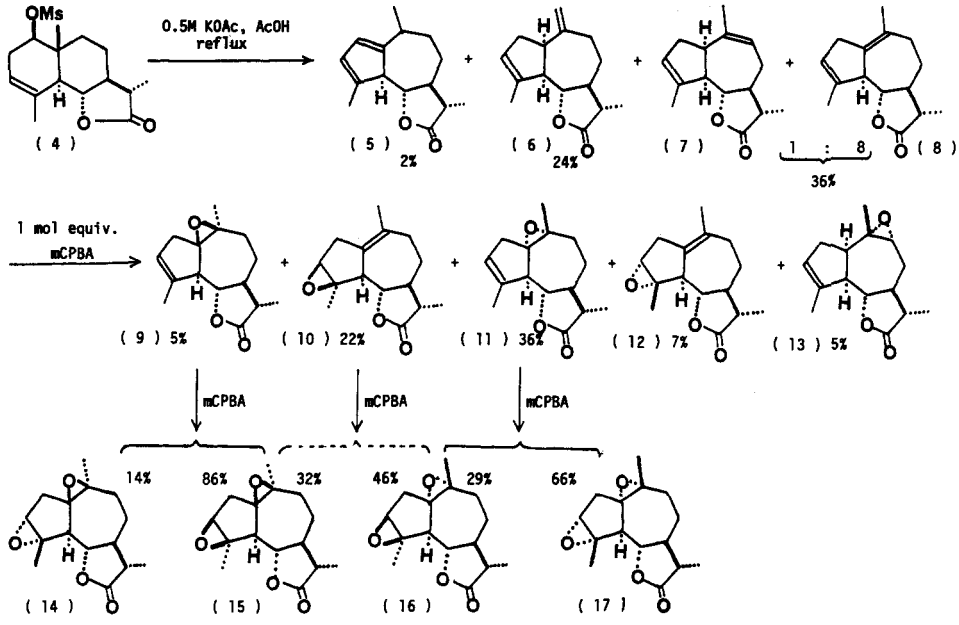
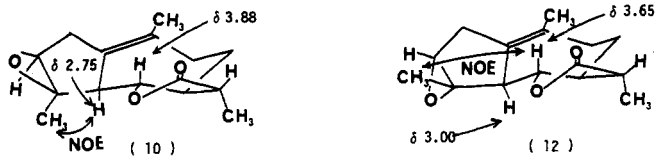
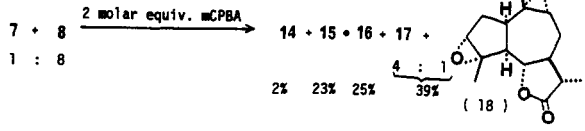


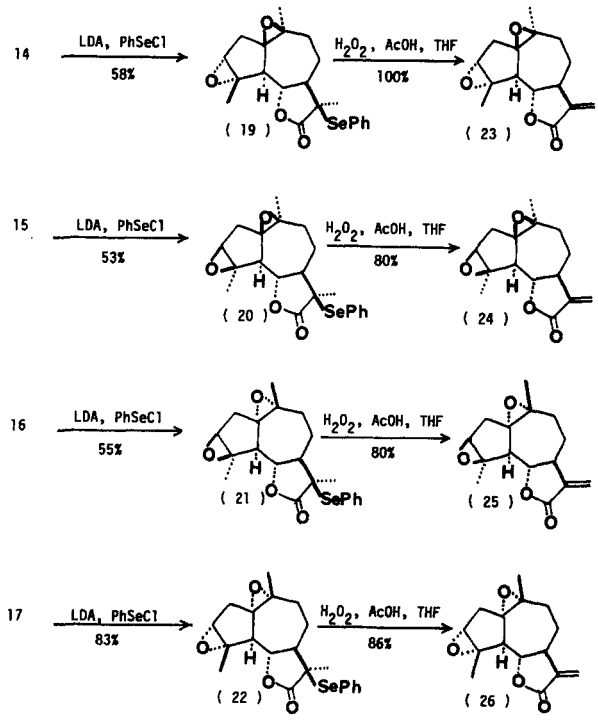
Chart II



Scheme III



Scheme IV



Diepoxides **14**–**18** were obtained directly from the mixture of dienes **7** and **8** (Scheme III). Thus, epoxidation of a 1:8 mixture of **7** and **8** with 2 molar equiv of *m*-CPBA gave **14**, **15**, **16**, and an inseparable mixture of **17** and **18** (4:1) in 2%, 23%, 25%, and 39% yields, respectively. The structure of **18** was tentatively assigned as shown in Scheme III by the analysis of ^{1}H NMR of **18** presented in the Experimental Section.

Phenylselenylation of diepoxides **14**–**17** with phenylselenyl chloride gave the corresponding phenyl selenides **19**, **20**, **21**, and **22** in 58%, 53%, 55%, and 83% yields, respectively (Scheme IV). Successive treatment of phenyl selenides **19**, **20**, **21**, and **22** with 30% H_2O_2 gave the corresponding α-methylene γ-lactones **23**, **24**, **25**, and **26** in 100%, 80%, 80%, and 86% yields, respectively.

Since **23** was identical with natural isoepoxyestafiatin in ^{1}H NMR, $[\alpha]_D$, and melting point (Table I),[3] the structure of isoepoxyestafiatin was assigned to be 1β,10β:3α,4α-diepoxyguai-11(13)-eno-12,6α-lactone (**23**) as depicted in Scheme IV including absolute configuration.

Experimental Section[7]

(11*S*)-1β-Hydroxyeudesm-3-eno-12,6α-lactone (3b). To a stirred solution of **2** (637 mg, 1.21 mmol) in THF (30 mL) at 0 °C was added lithium tri-*tert*-butoxyaluminum hydride (1.96 g, 7.68 mmol). The solution was stirred for 2 h at 0 °C and then quenched by the addition of 2 M HCl (13 mL). The mixture was worked up as usual to give a 1:9 mixture of **3a** (t_R 4.4 min) and **3b** (t_R 6.2 min) as a crystalline material (655 mg) by the analysis of HPLC [column, A; solvent, EtOAc–hexane (3:7); flow rate, 3.1 mL/min].

This crude product was purified by preparative HPLC [column, C; solvent, EtOAc–hexane (2:8); flow rate, 36 mL/min].

The first peak (t_R 14.4 min) gave **3a** (60 mg, 9%).

(7) All melting points are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz in $CDCl_3$ unless otherwise stated. ^{13}C NMR spectra were recorded at 50.3 MHz in $CDCl_3$. Reaction run under an atmosphere of nitrogen. THF was distilled from sodium benzophenone ketyl. $CHCl_3$ was dried over $CaCl_2$ and distilled. HMPA, LDA, and pyridine were distilled from CaH_2. HPLC was monitored with a RI detector. To describe HPLC conditions, we designate column, solvent, flow rate (mL/min), and retention time (t_R in min) in this order. The column codes are as follows: A, 250- × 4-mm i.d. stainless column packed with 10-μm silica gel; B, 250- × 8-mm i.d. stainless column packed with 10-μm silica gel; C, 300- × 20-mm i.d. packed with 15–25-μm silica gel.

Table I. Comparison of Physical and ^1H NMR Spectral Data of Natural Isoepoxyestafiatin Reported in the Literature and Compounds 23–26

	isoepoxyestafiatin	23	24	25	26
mp	168 °C	168 °C	155 °C	107 °C	204 °C
$[\alpha]^{22}_D$ ($CHCl_3$)	+76°	+70°	+77°	+4.7°	+45°
^1H NMR δ (Hz)		600 MHz	200 MHz	200 MHz	200 MHz
10-Me	1.32 (s)	1.30 (s)	1.30 (s)	1.27 (s)	1.30 (s)
4-Me	1.70 (s)	1.67 (s)	1.69 (s)	1.66 (s)	1.72 (s)
7-H	2.1 (m)	2.16 (m)	2.28 (m)	2.70 (m)	2.65 (m)
5-H	2.53 (d, 11)	2.50 (d, 11.2)	2.49 (d, 10.5)	2.44 (d, 11.0)	2.40 (d, 11.2)
3-H	3.46 (d, 3.6)	3.44 (d, 3.6)	3.31 (br s)	3.44 (d, 2.5)	3.44 (s)
6-H	4.01 (dd, 9, 11)	3.98 (dd, 9.9, 11.2)	4.12 (t, 10.5)	4.14 (t, 11.0)	3.76 (dd, 10.1, 11.2)
13-H	5.45 (d, 3)	5.43 (d, 3.0)	5.42 (d, 3.0)	5.44 (d, 3.5)	5.48 (d, 3.1)
	6.21 (d, 3)	6.17 (d, 3.5)	6.16 (d, 3.0)	6.17 (d, 3.5)	6.20 (d, 3.4)

The second peak (t_R 17.2 min) gave **3b** (552 mg, 86%) as colorless needles: mp 132 °C; IR (KBr) 3525, 1750 cm^{-1}; ^1H NMR (60 MHz) δ 0.89 (3 H, s, C_{10}-Me), 1.21 (3 H, d, J = 6.5 Hz, C_{11}-Me), 1.82 (3 H, br s, C_4-Me), 3.63 (1 H, dd, J = 10.0, 7.0 Hz, C_1-H), 3.97 (1 H, br t, J = 10.0 Hz, C_6-H), 5.33 (1 H, m, $W_{h/2}$ = 8.0 Hz); ^{13}C NMR δ 11.08 (q), 12.47 (q), 22.87 (t), 22.29 (q), 32.84 (t), 34.65 (t), 40.69 (d), 40.83 (s), 50.65 (d), 53.71 (d), 75.31 (d), 81.30 (d), 121.16 (d), 133.62 (s), 179.55 (s). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.70; H, 8.82.

(11*S*)-1β-(Mesyloxy)eudesm-3-eno-12,6α-lactone (4). To a stirred solution of **3b** (625 mg, 2.50 mmol) in pyridine (20 mL) was added methanesulfonyl chloride (870 μL, 8.65 mmol). The mixture was allowed to stand at 0 °C for 20 h, poured into a saturated aqueous solution of NaCl (150 mL), and stirred for 30 min. The mixture was worked up as usual to give an oil. This was then chromatographed over silica gel (40 g) and eluted with a mixture of hexane and ethyl acetate (7:3) to give spectroscopically pure **4** (795 mg, 97%) as a colorless oil: IR ($CHCl_3$) 1769, 1170 cm^{-1}; ^1H NMR δ 1.00 (3 H, s, C_{10}-Me), 1.23 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.83 (3 H, br s, C_4-Me), 3.03 (3 H, s, Ms), 3.95 (1 H, dd, J = 10.0, 10.0 Hz, C_2-H), 4.69 (1 H, dd, J = 9.5, 7.0 Hz, C_6-H), 5.34 (1 H, br s, C_3-H). $[\alpha]^{25}_D$ +41.7° (*c* 1.53, $CHCl_3$). Anal. Calcd for $C_{16}H_{24}O_5S$: C, 58.52; H, 7.37. Found: C, 58.35, H, 7.29.

Solvolysis Reaction of 4. Formation of (11*S*)-Guaia-1,3-dieno-12,6α-lactone (5), (11*S*)-Guaia-3,10(14)-dieno-12,6α-lactone (6), (11*S*)-Guaia-3,9-dieno-12,6α-lactone (7), and (11*S*)-Guaia-1(10),3-dieno-12,6α-lactone (8). A mixture of **4** (748 mg, 2.28 mmol) and 0.5 M potassium acetate in acetic acid (35 mL) was stirred at the refluxing temperature for 25 h and cooled. The mixture was worked up as usual to give an oily crude material. This was passed through a short column of silica gel [25 g, EtOAc–hexane (1:9)] and then separated by HPLC [column, B; solvent, EtOAc–hexane (5:95); flow rate, 9.9 mL/min].

The first peak (t_R 3.8 min) gave **5** (9 mg, 2%) as colorless crystals: mp 87 °C; IR ($CHCl_3$) 1760 cm^{-1}; ^1H NMR δ 1.09 (3 H, d, J = 6.2 Hz, C_{10}-Me), 1.26 (3 H, d, J = 6.8 Hz, C_{11}-Me), 1.85 (3 H, br s, C_4-Me), 3.00 (1 H, br d, J = 10.0 Hz, C_5-H), 3.80 (1 H, dd, J = 10.0, 10.0 Hz, C_6-H), 5.50 (2 H, m, C_2-H, C_3-H); $[\alpha]^{25}_D$ −88.4° (*c* 0.73, $CHCl_3$); HREIMS *m/e* calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1457.

The second peak (t_R 4.4 min) gave an 8:1 mixture of **8** and **7** as a white powder (193 mg, 36%): mp 77–80 °C; IR ($CHCl_3$) 1762 cm^{-1}; ^1H NMR δ 1.21 (3 H, d, J = 7.0, C_{11}-Me of **8**), 1.23 (3/8 H, d, J = 7.0 Hz, C_{11}-Me of **7**), 1.71 (3 H, d, J = 1.0 Hz, C_{10}-Me of **8**), 1.90 (3 H, br s, C_4-Me of **8**), 2.95 (2 H, m, C_2-H of **8**), 3.29 (1 H, d, J = 10.0 Hz, C_5-H of **8**), 3.65 (1 H, dd, J = 10.0, 10.0 Hz, C_6-H), 4.02 (1/8 H, dd, J = 10.5, 9.5 Hz, C_6-H of **7**), 5.43 (1/8 H, m, C_9-H of **7**), 5.50 (1+1/8 H, m, C_3-H of **7** and **8**); $[\alpha]^{25}_D$ +8.9° (*c* 0.41, $CHCl_3$); EIMS (75 eV, 90 °C), *m/e* (relative intensity) 232 (100, M^+). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.03, H, 8.65.

The third peak (t_R 5.0 min) gave **6** (129 mg, 24%) as a pale yellow oil: IR ($CHCl_3$) 1760, 1640, 902 cm^{-1}; ^1H NMR δ 1.23 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.83 (3 H, br s, C_4-Me), 2.21 (1 H, dq, J = 11.9, 7.0 Hz, C_{11}-H), 2.79 (1 H, dd, J = 9.6, 7.6 Hz, C_5-H), 3.10 (1 H, ddd, J = 7.6, 7.6, 6.0 Hz, C_1-H), 3.99 (1 H, dd, J = 9.6, 9.6 Hz, C_6-H), 4.83 (1 H, br s, C_{14}-H), 4.88 (1 H, br s, C_{14}-H), 5.53 (1 H, m, C_3-H); $[\alpha]^{25}_D$ +71.4° (*c* 0.64, $CHCl_3$); HREIMS *m/e* calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1450.

Epoxidation of 8 with 1 Molar Equiv of *m*-CPBA. The Formation of (11*S*)-1β,10β-Epoxyguai-3-eno-12,6α-lactone (Arborescin, 9), (11*S*)-3β,4β-Epoxyguai-1(10)-eno-12,6α-lactone (10), (11*S*)-1α,10α-Epoxyguai-3-eno-12,6α-lactone (11), (11*S*)-3α,4α-Epoxyguai-1(10)-eno-12,6α-lactone (12), and (11*S*)-9α,10α-Epoxyguai-3-eno-12,6α-lactone (13). A 1:8 mixture of **7** and **8** (171 mg, 0.74 mmol), 80% *m*-CPBA (159 mg, 0.74 mmol), and $CHCl_3$ (2 mL) was allowed to stand at −20 °C for 18 h. The mixture was poured into a mixture of 0.1 M aqueous KI (7.5 mL) and saturated aqueous NaCl (20 mL) and extracted with $CHCl_3$. The combined extracts were washed successively with 0.1 M aqueous $Na_2S_2O_3$ (30 mL), saturated aqueous $NaHCO_3$ (2 × 35 mL), and saturated aqueous NaCl (50 mL), dried (Na_2SO_4), and concentrated to give a mixture (1.2:4.7:1.5:7.9:1) of **9** (t_R 3.2 min), **10** (t_R 3.6 min), **12** (t_R 4.3 min), **11** (t_R 7.8 min), and **13** (t_R 5.8 min) by the analysis of HPLC [column, A; solvent, EtOAc–hexane (2:8); flow rate, 3.10 mL/min] as an oily crude product, which was passed through a short column of silica gel [10 g, EtOAc–hexane (1:9)]. The eluent was then separated by HPLC [column, B; solvent, EtOAc–hexane (1:9); flow rate, 9.9 mL/min]. The first peak (t_R 6.6 min) gave **9** (9.9 mg, 5%) as colorless crystals: mp 140 °C; IR ($CHCl_3$) 1767 cm^{-1}; ^1H NMR δ 1.19 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.35 (3 H, s, C_{10}-Me), 1.93 (3 H, m, C_4-Me), 2.82 (1 H, dm, J = 11.0, Hz, C_5-H), 4.01 (1 H, dd, J = 11.0, 9.5 Hz, C_6-H), 5.56 (1 H, m, C_3-H); ^{13}C NMR δ 12.44 (q), 18.26 (q), 22.74 (q), 22.87 (t), 33.62 (t), 39.62 (t), 41.01 (d), 52.40 (d), 54.65 (d), 62.58 (s), 72.50 (s), 82.70 (d), 124.67 (d), 140.76 (s), 178.90 (s); $[\alpha]^{25}_D$ +60° (*c* 0.09, $CHCl_3$); HREIMS *m/e* calcd for $C_{15}H_{20}O_3$ 248.1413, found 248.1401.

The second peak (t_R 8.6 min) gave **10** (39.5 mg, 22%) as colorless crystals: mp 102 °C; IR ($CHCl_3$) 1768 cm^{-1}; ^1H NMR δ 1.21 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.62 (3 H, s, C_4-Me), 1.65 (3 H, d, J = 1.0 Hz, C_{10}-Me), 2.75 (1 H, d, J = 10.0 Hz, C_5-H), 3.31 (1 H, d, J = 2.0 Hz, C_3-H), 3.88 (1 H, t, J = 10.0 Hz, C_6-H); ^{13}C NMR (150 MHz) δ 12.22 (q), 19.04 (q), 23.83 (q), 27.06 (t), 34.73 (t), 34.78 (t), 41.62 (d), 51.72 (d), 55.22 (d), 64.35 (d), 67.64 (s), 82.24 (d), 133.69 (s), 134.11 (s), 178.33 (s); $[\alpha]^{25}_D$ −5.8° (*c* 0.29, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.29; H, 8.18.

The third peak (t_R 10.6 min) gave **12** (12.4 mg, 7%) as a colorless oil: IR ($CHCl_3$) 1769 cm^{-1}; ^1H NMR δ 1.22 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.64 (3 H, s, C_4-Me), 1.67 (3 H, d, J = 1.0 Hz, C_{10}-Me), 3.00 (1 H, br d, J = 10.5 Hz, C_5-H), 3.38 (1 H, s, C_3-H), 3.65 (1 H, dd, J = 10.5, 9.5 Hz, C_6-H); ^{13}C NMR (150 MHz) δ 12.26 (q), 19.09 (q), 22.56 (q), 27.47 (t), 33.54 (t), 34.30 (t), 41.34 (d), 51.91 (d), 57.70 (d), 63.83 (d), 67.20 (s) 80.45 (d), 133.52 (s), 135.29 (s), 178.10 (s); $[\alpha]^{25}_D$ +11° (*c* 0.52, $CHCl_3$); HREIMS *m/e* calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1405.

The fourth peak (t_R 11.4 min) gave **11** (66.1 mg, 36%) as colorless crystals: mp 108 °C; IR ($CHCl_3$) 1770 cm^{-1}; ^1H NMR δ 1.22 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.33 (3 H, s, C_{10}-Me), 1.94 (3 H, d, J = 1.0 Hz, C_4-Me), 2.54 (1 H, d, J = 11.0 Hz, C_5-H), 2.86 (1 H, br d, J = 18.0 Hz, C_2-H), 3.78 (1 H, dd, J = 11.0, 10.0 Hz, C_6-H), 5.57 (1 H, m, C_3-H); ^{13}C NMR δ 12.40 (C_{13}), 17.88 (C_{15}), 20.63 (C_{14}), 25.10 (C_8), 37.63 (C_9), 38.21 (C_2), 41.40 (C_{11}), 55.27 (C_7), 56.75 (C_5), 62.61 (C_{10}), 71.95 (C_1), 84.40 (C_6), 124.30 (C_3), 141.07 (C_4), 177.94 (C_{12}); $[\alpha]^{25}_D$ +36.5° (*c* 0.65, $CHCl_3$). HREIMS *m/e* calcd for $C_{15}H_{20}O_3$ 248.1413, found 248.1402. Anal. Calcd for $C_{15}H_{20}O_3$ C, 72.55; H, 8.12. Found: C, 72.29; H, 8.19.

The fifth peak (t_R 15.2 min) gave **13** (8.4 mg, 5%) as a colorless

crystals: mp 143 °C; IR ($CHCl_3$) 1769 cm^{-1}; ^1H NMR δ 1.22 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.34 (3 H, s, C_{10}-Me), 1.89 (3 H, m, C_4-Me), 3.04 (1 H, d, J = 5.0 Hz, C_9-H), 3.71 (1 H, dd, J = 9.5, 10.5 Hz, C_6-H), 5.57 (1 H, m, C_3-H); $[\alpha]^{25}_D$ +25.3° (c 0.34, $CHCl_3$); HREIMs m/e calcd for $C_{15}H_{20}O_3$ 248.1413, found 248.1406.

Epoxidation of 9. Formation of (11*S*)-1β,10β;3α,4α-Diepoxiguaiano-12,6α-lactone (14) and (11*S*)-1β,10β;3β,4β-Diepoxyguaiano-12,6α-lactone (15). A solution of **9** (6 mg, 0.024 mmol) and 80% m-CPBA (8 mg, 0.036 mmol) in $CHCl_3$ (0.2 mL) was allowed to stand at room temperature for 18 h. The mixture was treated as mentioned above to give a crystalline crude product (1:6 mixture of **14** and **15**) which was purified by HPLC [column, A; solvent, EtOAc–hexane (3:7); flow rate, 3.0 mL/min].

The first peak (t_R 4.6 min) gave **14** (0.9 mg, 14%): mp 143 °C; IR ($CHCl_3$) 1774 cm^{-1}; ^1H NMR δ 1.19 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.27 (3 H, s, C_{10}-Me), 1.62 (3 H, s, C_4-Me), *ca.* 1.8 (1 H, C_2-H), 2.30 (1 H, d, J = 15.9 Hz, C_2-H), 2.38 (1 H, d, J = 11.5 Hz, C_5-H), 3.43 (1 H, d, J = 3.8 Hz, C_3-H), 3.98 (1 H, dd, J = 11.5, 8.2 Hz, C_6-H); $[\alpha]^{22}_D$ +40° (c 0.13, $CHCl_3$); HREIMS m/e calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1361.

The second peak (t_R 7.8 min) gave **15** (5.5 mg, 86%): mp 167 °C; $[\alpha]^{25}_D$ +35° (c 0.44, $CHCl_3$); ^1H NMR δ 1.18 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.28 (3 H, s, C_{10}-Me), 1.63 (3 H, s, C_4-Me), 2.34 (1 H, dd, J = 15.3, 1.4 Hz, C_2-H), 2.37 (1 H, d, J = 10.0 Hz, C_5-H), 3.30 (1 H, br s, C_3-H), 4.12 (1 H, dd, J = 10.0, 10.0 Hz, C_6-H); ^{13}C NMR δ 12.32 (q), 18.58 (q), 22.56 (t), 22.70 (q), 33.45 (t), 36.45 (t), 41.08 (d), 49.88 (d), 54.27 (d), 59.14 (s), 62.05 (d), 65.28 (s), 69.14 (s), 80.35 (d), 178.79 (s); $[\alpha]^{25}_D$ +35° (c 0.44, $CHCl_3$); HREIMS m/e calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1364. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.62. Found: C, 67.95; H, 7.79.

Epoxidation of 10. Formation of 15 and (11*S*)-1α,10α;3β,4β-Diepoxyguaiano-13,6α-lactone (16). A solution of **10** (16 mg, 0.06 mmol) and 80% m-CPBA (14 mg, 0.06 mmol) in $CHCl_3$ (0.5 mL) was allowed to stand at room temperature for 17 h. The mixture was treated in the usual manner to give an oily crude product, which was purified by HPLC [column, A; solvent, EtOAc–hexane (3:7); flow rate, 3.0 mL/min].

The first peak (t_R 5.6 min) gave **16** (7.8 mg, 46%) as colorless crystals: mp 166 °C; IR ($CHCl_3$) 1774 cm^{-1}; ^1H NMR δ 1.22 (3 H, d, J = 6.9 Hz, C_{11}-Me), 1.26 (3 H, s, C_{10}-Me), 1.64 (3 H, s, C_4-Me), 1.88 (1 H, ddd, J = 16.0, 3.0, 1.0 Hz, C_2-H), 2.29 (1 H, d, J = 10.5 Hz, C_5-H), 2.34 (1 H, d, J = 16.0 Hz, C_2-H), 3.47 (1 H, d, J = 3.0 Hz, C_3-H), 4.07 (1 H, dd, J = 10.5, 10.5 Hz, C_6-H); ^{13}C NMR δ 12.47, 19.60, 21.60, 24.58, 36.09, 37.27, 41.81, 53.03, 53.52, 63.23, 63.48, 68.06, 73.89, 81.00, 177.88; $[\alpha]^{25}_D$ +8.7° (c 0.43, $CHCl_3$); HREIMS m/e calcd for $C_{15}H_{26}O_4$ 264.1362, found 264.1362. Anal. Calcd for $C_{15}H_{26}O_4$: C, 68.16; H, 7.62. Found: C, 67.57; H, 7.49.

The second peak (t_R 7.8 min) gave **15** (5.5 mg, 32%).

Epoxidation of 11. Formation of 16 and (11*S*)-1α,10α;3α,4α-Diepoxiguaiano-12,6α-lactone (17). A solution of **11** (32 mg, 0.13 mmol) and 80% m-CPBA (28 mg, 0.12 mmol) in $CHCl_3$ (1 mL) was allowed to stand at room temperature for 17 h. The mixture was treated in the usual manner to give an oily crude product, which was purified by HPLC [column, A; solvent, EtOAc–hexane (3:7); flow rate, 3.0 mL/min].

The first peak (t_R 3.0 min) gave recovered starting material (5.7 mg, 18%).

The second peak (t_R 5.6 min) gave **16** (8.5 mg, 24%; 29% based on recovered **11**).

The third peak (t_R 12.4 min) gave **17** (18.4 mg, 54%; 66% based on recovered **11**) as colorless crystals: mp 160 °C; IR ($CHCl_3$) 1775 cm^{-1}; ^1H NMR δ 1.24 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.29 (3 H, s, C_{10}-Me), 1.68 (3 H, s, C_4-Me), *ca.* 1.68 (1 H, C_7-H), *ca.* 2.28 (1 H, C_5-H), 3.42 (1 H, s, C_3-H), 3.75 (1 H, dd, J = 11.2, 9.5 Hz, C_6-H); $[\alpha]^{25}_D$ +24° (c 0.68, $CHCl_3$); HREIMS m/e calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1365. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.62. Found: C, 67.43; H, 7.68.

Epoxidation of a 1:8 Mixture of 7 and 8 with 2 Molar Equiv of *m*-CPBA. Direct Formation of Diepoxides 14–17 and (11*S*)-3α,4α,9α,10α-Diepoxyguaia-12,6α-lactone (18). A 1:8 mixture of **7** and **8** (42 mg, 0.18 mmol), 80% m-CPBA (78 mg, 0.36 mmol), and $CHCl_3$ (1 mL) was allowed to stand at −20 °C for 18 h and then treated in usual manner to give a crude oily product (58 mg), which was separated by HPLC [column, A; solvent, EtOAc-hexane (3:7); flow rate, 3.0 mL/min].

The faster running fraction (t_R 2–4 min) gave a mixture of monoepoxides (5.1 mg, 11%).

The first peak (t_R 4.6 min) gave **14** (0.9 mg, 2%).

The second peak (t_R 5.6 min) gave **16** (11.3 mg, 25%).

The third peak (t_R 7.8 min) gave **15** (10.5 mg, 23%).

The fourth peak (t_R 12.4 min) gave a 4:1 mixture of **17** and **18** (17.6 mg, 39%). Pure **18** was separated from the faster running fraction of the fourth peak by repeated HPLC in the same conditions. **18**, colorless crystals: mp 183 °C; IR ($CHCl_3$) 1772 cm^{-1}; ^1H NMR δ 1.23 (3 H, d, J = 6.7 Hz, C_{11}-Me), 1.32 (3 H, s, C_{10}-Me), 1.59 (3 H, s, C_4-Me), *ca.* 2.05 (1 H, C_7-H), *ca.* 2.25 (1 H, C_5-H), 2.47 (1 H, ddd, J = 15.0, 5.5, 1.8 Hz, C_8-H), 2.69 (1 H, ddd, J = 12.5, 6.5, 6.5 Hz, C_1-H), 2.99 (1 H, d, J = 5.5 Hz, C_9-H), 3.30 (1 H, s, C_3-H), 3.62 (1 H, dd, J = 11.0, 9.5 Hz, C_6-H); $[\alpha]^{25}_D$ +44° (c 0.29, $CHCl_3$); HREIMS m/e calcd for $C_{15}H_{20}O_4$ 264.1362; found 264.1365.

1β,10β;3α,4α-Diepoxy-11β-(phenylseleno)guaiano-12,6α-lactone (19). A solution of **14** (1.2 mg, 4.5 μmol) in THF (0.2 mL) was slowly added to a cooled (−78 °C) solution of lithium diisopropylamide [prepared from diisopropylamine (6.3 μL, 45 μmol) and 1.57 M butyllithium in hexane (25 μL, 39 μmol)] in THF (0.2 mL). After 40 min a solution of phenylselenyl chloride (8.6 mg, 45 μmol) containing HMPA (7.8 μL, 45 μmol) in THF (0.2 mol) was added at −78 °C. The reaction mixture was stirred at −78 °C for 40 min and then warmed to −40 °C where stirring was continued for an additional 1 h. The reaction was quenched by the addition of acetic acid (2.6 μL). The mixture was worked up as usual to give an oily crude product, which was separated by HPLC [column, A; solvent, EtOAc–hexane (3:7); 3.0 mL/min].

The peak (t_R 3.4 min) gave **19** (1.1 mg, 58%) as a pale yellow oil: IR ($CHCl_3$) 1766 cm^{-1}; ^1H NMR δ 1.29 (3 H, s, C_{10}-Me), 1.48 (3 H, s, C_{11}-Me), 1.59 (3 H, s, C_4-Me), 1.85 (1 H, dd, J = 16.8, 3.5 Hz, C_2-H), 2.29 (1 H, d, J = 16.8 Hz, C_2-H), 2.34 (1 H, d, J = 11.2 Hz, C_5-H), 3.42 (1 H, d, J = 3.5 Hz, C_3-H), 4.29 (1 H, dd, J = 11.2, 9.5 Hz, C_6-H), 7.20–7.48 (3 H, m), 7.59–7.68 (2 H, m); $[\alpha]^{22}_D$ +80° (c 0.09, $CHCl_3$); HREIMS m/e calcd for $C_{21}H_{24}O_4Se$ 420.0840, found 420.0837.

1β,10β;3β,4β-Diepoxy-11β-(phenylseleno)guaiano-12,6α-lactone (20). Phenylselenylation of **15** (12 mg, 0.045 mmol) with phenylselenyl chloride (26 mg, 0.136 mmol), lithium isopropylamide (0.136 mmol), and HMPA (24 μL) by the above-mentioned analogous method and successive separation of crude product by HPLC [column, A; solvent, EtOAc–hexane (3:7); flow rate, 3.0 mL/min] gave **20** (t_R 9 min; 10.1 mg, 53%) as colorless crystals: mp 190 °C; ^1H NMR δ 1.29 (3 H, s, C_{10}-Me), 1.49 (3 H, s, C_{11}-Me), *ca.* 1.52 (1 H, C_7-H), 1.66 (3 H, s, C_4-Me), 2.34 (1 H, d, J = 10.5 Hz, C_5-H), 3.30 (1 H, s, C_3-H), 4.56 (1 H, dd, J = 10.5, 10.5 Hz, C_6-H), 7.26–7.48 (3 H, m), 7.57–7.66 (2 H, m); ^{13}C NMR δ 18.66 (q), 20.68 (t), 21.99 (q), 22.68 (q), 33.58 (t), 36.46 (t), 49.59 (s), 50.15 (d), 58.44 (d), 58.92 (s), 62.09 (d), 65.38 (s), 69.07 (s), 78.65 (d), 128.94 (d), 129.69 (d), 138.42 (d), 138.42 (s), 175.76 (s); $[\alpha]^{25}_D$ +82° (c 0.94, $CHCl_3$); HREIMS m/e calcd for $C_{21}H_{24}O_4Se$ 420.0840, found 420.0843.

1α,10α;3β,4β-Diepoxy-11β-(phenylseleno)guaiano-12,6α-lactone (21). Phenylselenylation of **16** (8 mg, 0.03 mmol) with phenylselenyl chloride (17 mg, 0.09 mmol), lithium diisopropylamide (0.09 mmol), and HMPA (16 μL, 0.09 mmol) by the above-mentioned analogous method and successive separation of crude product by HPLC [column, A; solvent, EtOAc–hexane (3:7); flow rate, 3.0 mL/min] gave **21** (t_R 3.6 min; 7 mg, 55%) as colorless crystals: mp 245 °C; IR ($CHCl_3$) 1767 cm^{-1}; ^1H NMR δ 1.29 (3 H, s, C_{10}-Me), 1.52 (3 H, s, C_{11}-Me), 1.64 (3 H, s, C_4-Me), 2.26 (1 H, d, J = 11.0 Hz, C_5-H), 2.36 (1 H, d, J = 16.0 Hz, C_2-H), 3.47 (1 H, d, J = 3.0 Hz, C_3-H), 4.48 (1 H, dd, J = 11.0, 11.0 Hz, C_6-H), 7.2–7.48 (3 H, m), 7.58–7.68 (2 H, m); $[\alpha]^{25}_D$ +71° (c 0.57, $CHCl_3$); HREIMS m/e calcd for $C_{21}H_{24}O_4Se$ 420.0840, found 420.0842.

1α,10α;3α,4α-Diepoxy-11β-(phenylseleno)guaiano-12,6α-lactone (22). Phenylselenylation of **17** (16 mg, 0.06 mmol) with phenylselenyl chloride (35 mg, 0.18 mmol), lithium diisopropylamide (0.18 mmol), and HMPA (31 μL, 0.18 mmol) by the above-mentioned analogous method and successive separation of crude product by HPLC [column, A; solvent, EtOAc–hexane (3:7); flow rate, 3.0 mL/min] gave **22** (t_R 5 min; 21 mg, 83%) as colorless crystals: mp 239 °C; ^1H NMR δ 1.32 (3 H, s, C_{10}-Me), 1.53 (3 H, s, C_{11}-Me), 1.68 (3 H, s, C_4-Me), 2.23 (1 H, d, J = 11.5 Hz, C_5-H),

3.43 (1 H, s, C_3-H), 4.09 (1 H, dd, J = 11.5, 9.5 Hz, C_6-H), 7.29–7.51 (3 H, m), 7.58–7.69 (2 H, m); $[\alpha]^{25}_D$ +89° (c 0.84, $CHCl_3$); HREIMS m/e calcd for $C_{21}H_{24}O_4Se$ 420.0840, found 420.0839.

Isoepoxyestafiatin (23). A solution of **19** (0.8 mg, 1.9 mmol) in THF (0.1 mL) containing acetic acid (1.1 μL, 19 μmol) was treated at 0 °C with 30% H_2O_2 (5.8 μL, 57 μmol). After the addition was complete, stirring was continued for additional 2 h at this temperature. The reaction mixture was worked up as usual to give a crystalline crude material (0.8 mg), which was purified by HPLC [column, A; solvent, EtOAc–hexane (3:7); flow rate, 3.0 mL/min]. The peak (t_R 4.8 min) gave **23** (0.5 mg, 100%) as colorless crystals: mp 168 °C; IR ($CHCl_3$) 1767 cm^{-1}; ^1H NMR (600 MHz) δ 1.30 (3 H, s, C_{10}-Me), 1.67 (3 H, s, C_4-Me), 1.86 (1 H, dd, J = 15.9, 3.6 Hz, C_2-H), 2.16 (1 H, m, C_7-H), 2.31 (1 H, d, J = 15.9 Hz, C_2-H), 2.50 (1 H, d, J = 11.2 Hz, C_5-H), 3.44 (1 H, d, J = 3.6 Hz, C_3-H), 3.98 (1 H, dd, J = 11.2, 9.9 Hz, C_6-H), 5.43 (1 H, d, J = 3.0 Hz, C_{13}-H), 6.17 (1 H, d, J = 3.5 Hz, C_{13}-H); $[\alpha]^{22}_D$ +70° (c 0.05, $CHCl_3$); HREIMS m/e calcd for $C_{15}H_{18}O_4$ 262.1205, found 262.1189.

1β,10β;3β,4β-Diepoxyguaia-11(13)-eno-12,6α-lactone (24). A solution of **20** (7 mg, 0.017 mmol) in THF (0.2 mL) containing acetic acid (7 μL, 0.12 mmol) was treated at 0 °C with 30% H_2O_2 (34 μL, 0.33 mmol). After the addition was complete, stirring was continued for an additional 2 h at this temperature. The reaction mixture was treated in the usual manner to give a colorless oil (4 mg), which was purified by HPLC [column, A; solvent, EtOAc–hexane (3:7); flow rate, 3.0 mL/min]. The peak (t_R 9.6 min) gave **24** (3.5 mg, 80%) as colorless crystals: mp 155 °C; IR ($CHCl_3$) 1768, 1672 cm^{-1}; ^1H NMR δ 1.30 (3 H, s, C_{10}-Me), 1.69 (3 H, s, C_4-Me), *ca.* 2.28 (1 H, m, C_7-H), 2.49 (3 H, d, J = 10.5 Hz, C_5-H), 3.31 (1 H, br s, C_3-H), 4.12 (1 H, dd, J = 10.5, 10.5 Hz, C_6-H), 5.42 (1 H, d, J = 3.0 Hz, C_{13}-H), 6.16 (1 H, d, J = 3.0 Hz, C_{13}-H); $[\alpha]^{25}_D$ +77° (c 0.29, $CHCl_3$); HREIMS m/e calcd for $C_{15}H_{18}O_4$ 262.1205, found 262.1201.

1α,10α;3β,4β-Diepoxyguaia-11(13)-eno-12,6α-lactone (25). A solution of **21** (3.0 mg, 7 μmol) in THF (0.1 mL) containing acetic acid (3 μL, 0.05 mmol) was treated at 0 °C with 30% H_2O_2 (15 μL, 0.14 mmol). After the addition was complete, stirring was continued for 2 h at 0 °C. The reaction mixture was treated in the usual manner to give a colorless oil (2.3 mg), which was purified by HPLC [column, A; solvent, EtOAc–hexane (3:7); flow rate, 3.0 mL/min] to give **25** (1.5 mg, 80%) as colorless crystals: mp 107 °C; IR ($CHCl_3$) 1771, 1670 cm^{-1}; ^1H NMR δ 1.27 (3 H, s, C_{10}-Me), 1.66 (3 H, s, C_4-Me), 2.44 (1 H, d, J = 11.0 Hz, C_5-H), *ca.* 2.70 (1 H, m, C_7-H), 3.44 (1 H, d, J = 2.5 Hz, C_3-H), 4.14 (1 H, t, J = 11.0 Hz, C_6-H), 5.44 (1 H, d, J = 3.5 Hz, C_{13}-H), 6.17 (1 H, d, J = 3.5 Hz, C_{13}-H); $[\alpha]^{25}_D$ +4.7 °C (c 0.23, $CHCl_3$); HREIMS m/e calcd for $C_{15}H_{18}O_4$ 262.1205, found 262.1202.

1α,10α;3α,4α-Diepoxyguaia-11(13)-eno-12,6α-lactone (26). A solution of **22** (7.4 mg, 0.018 mmol) in THF (0.2 mL) containing acetic acid (7 μL, 0.12 mmol) was treated at 0 °C with 30% H_2O_2 (36 μL, 0.35 mmol). After the addition was complete, stirring was continued for an additional 2 h at 0 °C. The reaction mixture was treated in the usual manner to give an oily crude product (4.7 mg), which was purified by HPLC [column, A; solvent, EtOAc–hexane (3:7); flow rate, 3.0 mL/min] to give **26** (4.0 mg, 86%) as colorless crystals: mp 204 °C; IR ($CHCl_3$) 1772, 1672 cm^{-1}; ^1H NMR δ 1.30 (3 H, s, C_{10}-Me), 1.72 (3 H, s, C_4-Me), 1.88 (1 H, d, J = 15.5 Hz, C_2-H), 2.36 (1 H, d, J = 15.5 Hz, C_2-H), 2.40 (1 H, d, J = 11.2 Hz, C_5-H), 2.65 (1 H, m, C_7-H), 3.44 (1 H, s, C_3-H), 3.76 (1 H, dd, J = 11.2, 10.1 Hz, C_6-H), 5.48 (1 H, d, J = 3.1 Hz, C_{13}-H), 6.20 (1 H, d, J = 3.4 Hz, C_{13}-H); $[\alpha]^{25}_D$ +45° (c 0.20, $CHCl_3$); HREIMS m/e calcd for $C_{15}H_{18}O_4$ 262.1205, found 262.1198.

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