Studies on the Syntheses of Sesquiterpene Lactones. 11.[1] The Syntheses of 3-Epizaluzanin C, Zaluzanin C, Zaluzanin D, and Related Compounds 3α-Hydroxyguaia-1(10),4(15),11(13)-trieno-12,6α-lactone and 3α-Hydroxyguaia-4(15),9,11(13)-trieno-12,6α-lactone[2]

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3-Epizaluzanin C (**10**), 3α-hydroxyguaia-1(10),4(15),11(13)-trieno-12,6α-lactone (**36**), and 3α-hydroxyguaia-4(15),9,11(13)-trieno-12,6α-lactone (**37**) have been synthesized in 4.0%, 3.0%, and 1.7% overall yields, respectively, from α-santonine (**13**) in 14 steps. Zaluzanin C (**11**) and zaluzanin D (**12**) have also been synthesized in 2.4% and 2.5% overall yields from α-santonin (**13**) in 16 steps and 15 steps, respectively. The key step involves the solvolytic rearrangement of (11*S*)-3α,4α-epoxy-1β-(mesyloxy)eudesmano-13,6α-lactone (**27**). The stereochemistry of 3-epizaluzanin C (**10**), zaluzanin C (**11**), and zaluzanin D (**12**) have been established by these stereospecific syntheses.

The guaianolides represent one of the largest groups of sesquiterpene lactones with over 200 known naturally occurring compounds.[3] Some of them have been shown to possess high biological activities as antitumor agents,[4,5] allergenic agents,[4,6] and regulators of plant growth.[4,7] Because of their high biological activities and highly functionalized structures, their efficient syntheses are a challenge that has received much attention during the past few years.[8]

With only a few exceptions guaianolides possess a cis-fused (α-H) hydroazulene skeleton as well as the γ-lactone moiety closed in a trans manner toward C_6 (6α-lactone). For these structural requirements we envisioned a general synthetic approach to the guaianolides that consisted of the solvolytic rearrangement of the appropriately functionalized eudesmanolides as shown in a general structure **1**. It is interesting that guaianolide cations (**2**) that are expected to be produced by the solvolytic rearrangement of **1** are the same as the proposed cationic intermediate in the guaianolide biosynthesis from germacranolides (Chart I).[3]

Sovolytic rearrangement of *cis*- and *trans*-decalin derivatives, **3–6**, have been applied to the syntheses of guaiane-type sesquiterpenes with rather simple structures, such as bulnesene (**7**), bulnesol (**8**), and kessane (**9**) (Chart II).[9] Recently we have applied the solvolytic rearrangement of the 1-(mesyloxy)eudesmanolide derivative (**14**) as a key step in the synthesis of arborescin.[8e,l] It is noteworthy that in the solvolytic rearrangement of **14** the guaianolide (**16**), possessing a disubstituted double bond, was formed in addition to the corresponding tetrasubstituted olefin (**15**).

In the present paper we report the efficient syntheses of 3-epizaluzanin C (**10**) (Schemes II and III), zaluzanin C (**11**) (Schemes IV and VI), zaluzanin D (**12**) (Scheme V) (Chart III), and related compounds 3α-hydroxyguaia-1-(10),4(15),11(13)-trieno-12,6α-lactone (**36**) and 3α-hydroxyguaia-4(15),9,11(13)-trieno-12,6α-lactone (**37**) to demonstrate the utility of the solvolytic rearrangement of the 1-(mesyloxy)eudesmanolide derivatives, **14** and **27**, for the syntheses of the naturally occurring guaianolides.

Zaluzanin C (**11**) and zaluzanin D (**12**) were originally isolated from *Zaluzania augusta* and *Zaluzania triloba*, and their structures were proposed by Romo de Vivar et al. as **11** and **12**, except the stereochemistry at C_3.[10] The stereochemistry at C_3 of **11** was later deduced to be the *S* configuration by Nagumo et al. on the basis of Horeau's

Chart I

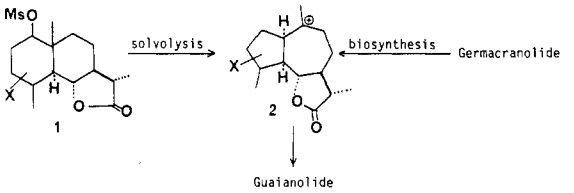


Chart II

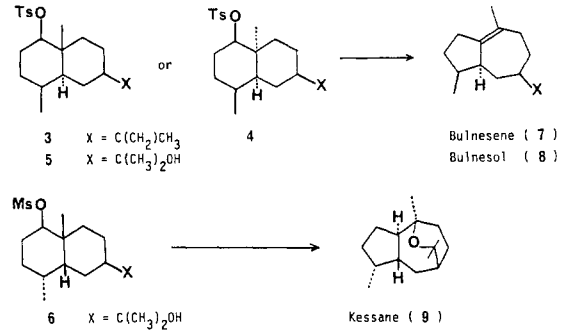
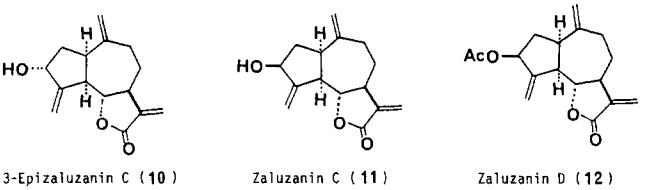


Chart III



† Sumito Pharmaceutical Co., Ltd.

(1) Part 10 of this series: Ando, M.; Wada, T.; Kusaka, H.; Takase, K.; Hirata, N.; Yanagi, Y. *J. Org. Chem.* **1987**, *52*, 4792.

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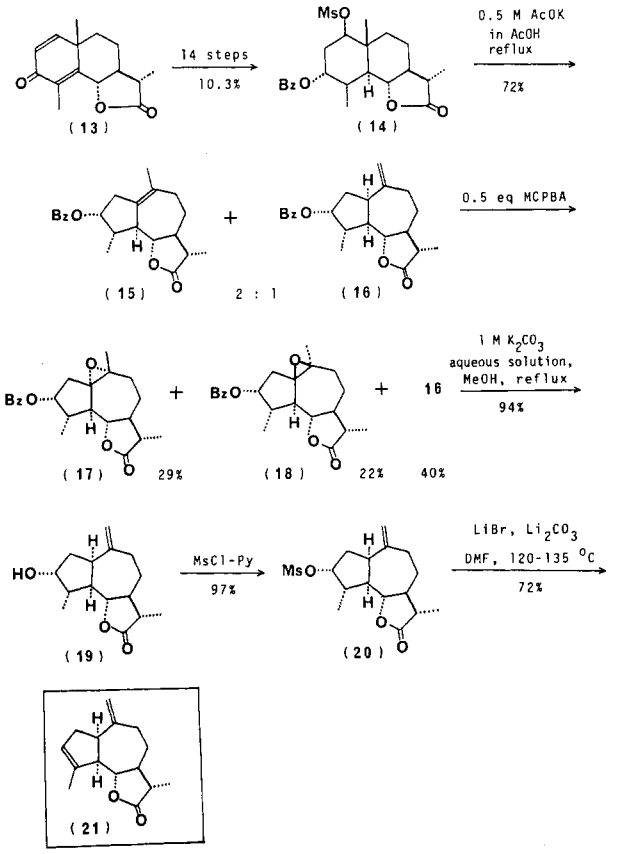
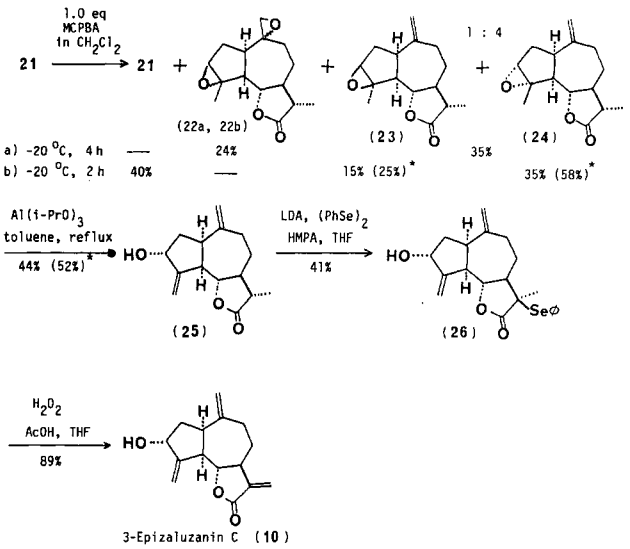
0022-3263/89/1954-1952$01.50/0

Scheme I



method.[11] Recently 3-epizaluzanin C (**10**) were also isolated from *Vernonia anisochoetoides* Sonder by Bohlmann et al.[12] It is interesting that **11** and **12** show high biological activities. Thus **11** shows tumor inhibitory activity in vivo[5e] and **11** and **12** show the inhibitory activity toward germination and root elongation of rice in the husk.[7c]

Scheme II



*The yields in parentheses are based on the recovered starting materials.

Results and Discussion

Syntheses of 3-Epizaluzanin C (10), 3α-Hydroxyguaia-1(10),4(15),11(13)-trieno-12,6α-lactone (36), and 3α-Hydroxyguaia-4(15),9,11(13)-trieno-12,6α-lactone (37). We chose (11*S*)-guaia-3,10(14)-dieno-12,6α-lactone (**21**) as a starting material for our synthesis of 3-epizaluzanin C (**10**). As had been reported in our previous paper,[8e,l] the solvolytic rearrangement of a mesylate (**14**) gave a 2:1 mixture of a tetrasubstituted olefin (**15**) and a disubstituted olefin (**16**). Since the direct separation of the mixture was difficult, **16** was isolated from the mixture in 40% yield by means of the selective epoxidation of **15**. The three-step conversion of **16** gave the desired diene (**21**) (Scheme I).

First of all we examined the regioselective epoxidation of the trisubstituted 3,4-double bond of **21** (Scheme II). The epoxidation of **21** with 1.0 molar equiv of *m*-chloroperoxybenzoic acid at −20 °C for 4 h gave the undesired diepoxide (**22**) in 24% yield in addition to the desired 3,4-epoxides, **23** and **24**. On the contrary, the epoxidation of **21** with 1.0 molar equiv of *m*-chloroperoxybenzoic acid at −20 °C for 2 h gave the desired 3,4-epoxides, **23** and **24**, in 15% and 35% yields, respectively, accompanied by a 40% yield of recovered **21**. The stereochemical assignments of **23** and **24** are based on the consideration that the reagent attacks **21** preferentially from the less hindered α or convex face. The assignments are also supported by the analysis of ^1H NMR spectrum of **23** and **24**. The C_6-H of **23** (δ 4.23) appears at 0.26 ppm lower field than that of **24** (δ 3.97) due to the deshielding effect of the syn epoxide oxygen.[8e,13]

Treatment of **24** with aluminum isopropoxide in boiling toluene[8e,l] for 23 h gave an α-allylic alcohol (**25**) in 44% yield accompanied by the recovered epoxide **24**, in 16% yield. The phenylselenenylation[14] of **25** gave a phenylseleno lactone (**26**) in 41% yield. Treatment of **26** with hydrogen peroxide in tetrahydrofuran in the presence of acetic acid[14] gave an α-methylene-γ-lactone (**10**) in 89%

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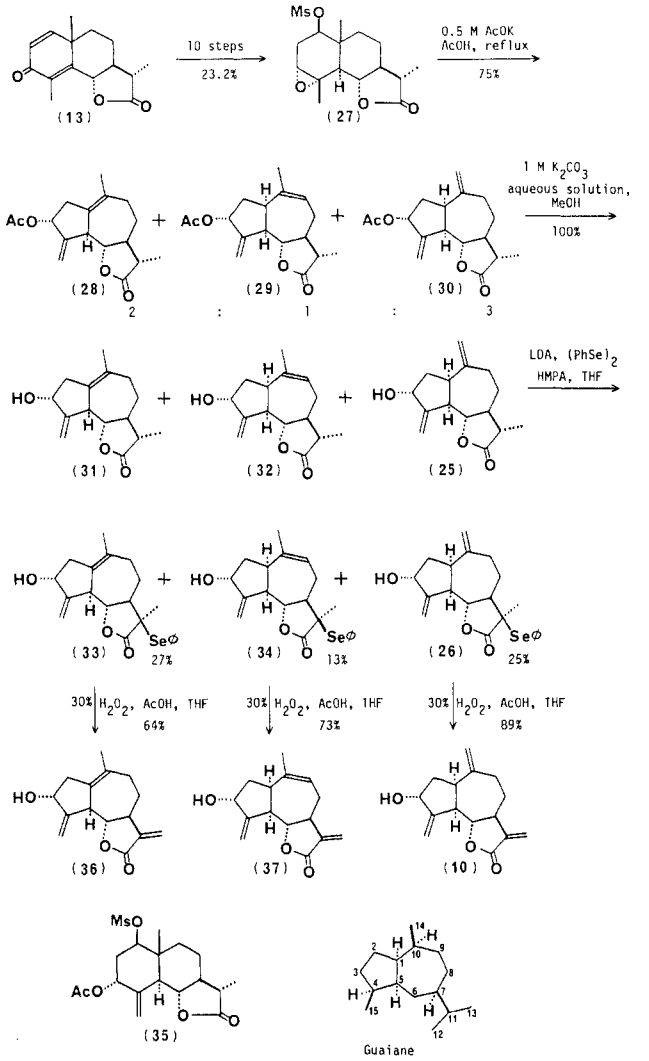
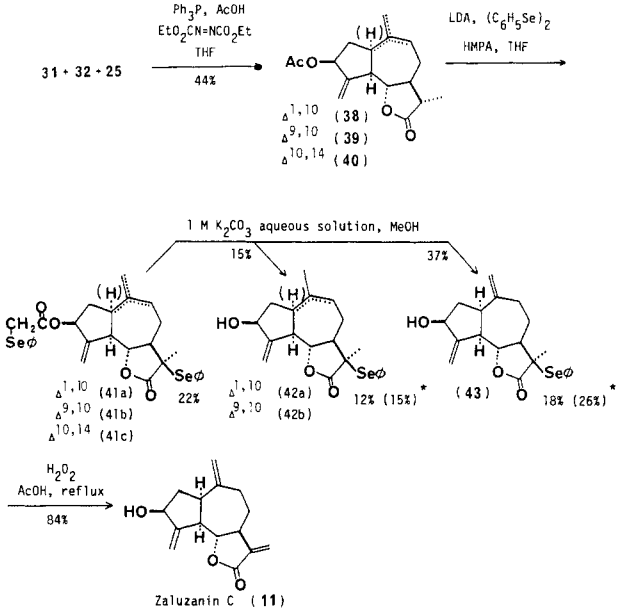
Scheme III



yield. The NMR (C_6D_6) and IR ($CHCl_3$) spectra of **10** were identical with those of natural occurring 3-epizaluzanin C.[15] The optical rotation of **10** [$[\alpha]^{20}_D$ −46.4° (*c* 1.23, $CHCl_3$)] was in good agreement with the reported value[12] of 3-epizaluzanin C [$[\alpha]^{29}_D$ −55.6° (*c* 0.24, $CHCl_3$)]. The stereochemistry of 3-epizaluzanin C (**10**) at C_3 was established to be the *R* configuration by this synthesis. Since the overall yield of **10** from α-santonin (**13**) in this synthesis was poor (0.21% in 23 steps), we examined the more efficient synthesis of **10**.

The starting material is the epoxymesylate (**27**),[16] which can be prepared from α-santonin (**13**) in 23.2% overall yield in 10 steps (Scheme III). Solvolytic rearrangement of **27** in a refluxing 0.5 M acetic acid solution of potassium acetate gave a 2:1:3 mixture of guaianolides **28**, **29**, and **30**, possessing tetra-, tri-, and disubstituted double bonds in 75% yield accompanied by an acetoxy mesylate (**35**) in 8% yield. Treatment of **35** under the same reaction conditions also gave a 2:1:3 mixture of **28**, **29**, and **30**. These results strongly suggest that the solvolytic rearrangement of **27** proceed via **35**. The ratios of **28**, **29**, and **30** were determined by the analyses of the ^1H NMR spectrum and HPLC. Hydrolysis of this mixture gave the corresponding mixture of alcohols **31**, **32**, and **25** in a quantitative yield.

Scheme IV



* The yields of 42 and 43 in parentheses are based on those after the hydrolysis of 41.

Since the complete separation of **31**, **32**, and **25** by HPLC in preparative scale was impossible, this mixture was employed in the next step.

Phenylselenenylation of the mixture of alcohols **31**, **32**, and **25** with lithium diisopropylamide and diphenyl diselenide afforded a mixture of phenylseleno lactones, which was separated by HPLC to give **33**, **34**, and **26** in 27%, 13%, and 25% yields, respectively.

The oxidative syn elimination[14] of **33** and **34** gave 3α-hydroxyguaia-1(10),4(15),11(13)-trieno-12,6α-lactone (**36**) and 3α-hydroxyguaia-4(15),9,11(13)-trieno-12,6α-lactone (**37**) in 64% and 73% yields (3.0% and 1.7% overall yields from α-santonin in 14 steps), respectively, as unstable oils. The spectral data shown in the Experimental Section was in complete agreement with the structures **36** and **37**.

Since we have already mentioned that the oxitative syn elimination of **26** gave 3-epizaluzanin C (**10**) in 89% yield, the overall yield of 3-epizaluzanin C (**10**) from α-santonin (**13**) via the epoxymesylate (**27**) was 3.9% in 14 steps.

Syntheses of Zaluzanin C (11) and Zaluzanin D (12). For the syntheses of zaluzanin C (**11**) and zaluzanin D (**12**) the inversion of the hydroxyl group at C_3 is necessary at the stage of **25** or **26**. The first entry is the inversion of the hydroxyl group in the stage of **25** (Scheme IV). For practical purposes we employed the 2:1:3 mixture of **31**, **32**, and **25** that was obtained by the method shown in Scheme III. Treatment of the mixture with acetic acid in the presence of triphenylphosphine and diethyl azodicarboxylate[17] gave acetates **38**, **39**, and **40**. Phenylselenylation[14] of this mixture gave diselenides (**41a–c**) as a mixture of the three possible regioisomers of the double bond, seleno lactones (**42a,b**) as a 1:1 mixture of the regioisomers possessing tri- and tetrasubstituted double bonds, and a seleno lactone (**43**) possessing a disubstituted double bond in 22%, 12%, and 18% yields, respectively. The hydrolysis of **41** gave **42** and **43** in 15% and 37% yields, respectively. The oxidative syn elimination[14] of **43** gave an α-methylene-γ-lactone (**11**), whose melting point

(15) The ^1H NMR spectrum (270 MHz, C_6D_6) and the IR spectrum ($CHCl_3$) of 3-epizaluzanin C were kindly supplied by Prof. F. Bohlmann.

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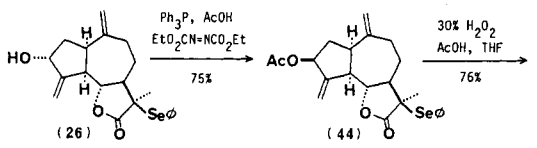
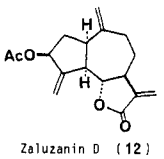
(17) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427. We employed acetic acid instead of benzoic acid for the convenience of the hydrolysis of the product.

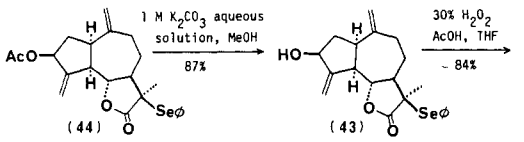
Scheme V

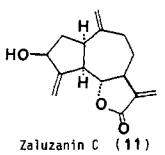




Zaluzanin D (12)

Scheme VI





Zaluzanin C (11)

(106–108 °C) and $[\alpha]^{20}_D$ value (+35.4°; *c* 1.53, $CHCl_3$) were in good agreement with those of zaluzanin C [mp 95–96 °C,[7c,10a] 94–95 °C,[5e] 101–102 °C;[11] $[\alpha]_D$ +37° ($CHCl_3$),[10a] $[\alpha]^{27}_D$ +38° (*c* 1, $CHCl_3$),[5e] $[\alpha]_D$ +33° (*c* 2.5),[7c] $[\alpha]^{15}_D$ +35.4° (*c* 0.8, $CHCl_3$)[11]]. The ^1H NMR (60 MHz, $CDCl_3$) and IR (CHC_3) spectra of **11** were superimposable on those of zaluzanin C recorded under the same conditions.[3b,18] The δ value of the ^{13}C NMR spectrum of **11** was identical with those of zaluzanin C reported by Nagumo et al.[11] The stereochemistry of zaluzanin C at C_3 was established to be the *S* configuration by this synthesis. The overall yield of **11** by this procedure was 1.7% from α-santonin (**13**) in 15 steps.

The second entry to the syntheses of zaluzanin C and zaluzanin D is the inversion of the hydroxyl group at C_3 of **26** (Scheme V). The advantage of this method is that **26** is easily available in a pure form. Treatment of **26** with acetic acid in the precence of triphenylphosphine and diethyl azodicarboxylate[17] gave the desired 3β-acetoxy phenylseleno lactone (**44**) in 75% yield (Scheme V). The oxidative syn elimination[14] of **44** gave an α-methylene-γ-lactone (**12**) in 76% yield. The ^1H NMR (60 MHz, $CDCl_3$) and IR ($CHCl_3$) spectra of **12** were superimposable on those of zaluzanin D recorded under the same conditions.[3b,18] The optical rotation of **12** $[[\alpha]^{20}_D$ +21.7° (*c* 1.35, $CHCl_3$)] was in good agreement with the reported value of zaluzanin C acetate $[[\alpha]^{20}_D$ +24° (*c* 1, $CHCl_3$)].[19] The overall yield of **12** was 2.5% from α-santonin (**13**) in 15 steps.

Hydrolysis of **44** and successive oxidative syn elimination[14] of the resulting 3β-hydroxy phenylseleno lactone (**43**) gave zaluzanin C (**11**) in 73% yield. The overall yield of **11** was 2.4% in 16 steps (Scheme VI).

The Biological Activities. The compounds **36**, **37**, 3-epizaluzanin C (**10**), zaluzanin C (**11**), and zaluzanin D (**12**) showed the significant cell growth inhibitory activity against murin lymphocytic leukemia (P388) in vitro. The results were shown in Table I.

Table I. Cell Growth Inhibitory Activity against Murine Lymphocytic Leukemia (P388) in Vitro[a]

compound	inhibition ratio, % 10 μg/mL	1 μg/mL	10^{-1} μg/mL	10^{-2} μg/mL
36	108	96	2	–
37	108	98	16	–
10	105	109	12	–
11	105	84	6	–
12	104	41	−2	–
adriamycin (control substance)	107	103	104	35

[a] **In Vitro Cell Growth Inhibitory Activities.** Murine lymphocytic leukemia cells (P-388) were incubated with compounds at 37 °C in humidified atmosphere of 5% CO_2 for 48 h. After incubation, the cell number was counted with a Coulter counter (Model ZBI, Coulter Electronics, Inc., Hialeah, Flo.), and the cell growth inhibition ratio (%) was calculated according to the following formula:

$$\text{cell growth inhibition ratio (\%)} = \left(1 - \frac{T - C_0}{C - C_0}\right) \times 100$$

where T is the cell count after culture with compound, C is the cell count after culture without compound, and C_0 is the cell count at the start of culture.

Experimental Section

All melting points are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrometer. NMR spectra were recorded on a Varian XL-200 (200 MHz) spectrometer in $CDCl_3$, and the assignments are based on decoupling experiments. Mass spectra were recorded on JEOL JMS-01SG-2 and JEOL DX303 spectrometers, and the experimental conditions such as ionization method (EI or FD) ionization voltage, and sample temperatures are shown in parentheses. High-resolution mass spectra were recorded on JEOL JMS-01SG-2 and JEOL DX303 spectrometers. Optical rotations were determined on a Perkin-Elmer 241 polarimeter.

Reactions were run under an atmosphere of nitrogen. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Hexamethylphosphoric triamide (HMPA), methylene chloride, and pyridine were distilled from calcium hydride; *N*,*N*-dimethylformamide was dried by removing the benzene–water azeotrope. Toluene was dried over sodium wire. Kieselgel 60 (Merck 70–200 mesh) was employed for column chromatography, and kieselgel GF_{254} (Merck) was used for TLC or preparative TLC (thickness 0.25 mm) unless otherwise stated.

High-pressure liquid chromatography (HPLC) was performed on a Kyowa-Seimitsu high quality pump (Model KHP-011) equipped with a syringe-loading sample-injection valve. The effluent was monitored with a RI detector (Shodex RI SE-11). To describe HPLC conditions, we designate column, solvent, flow rate (mL/min), and retention time (t_R) in minutes. The column codes are as follows: A, 250 × 4 mm i.d. stainless column packed with 10-μm silica gel (kyowa gel MIC-SI-10); B, 250 × 8 mm i.d. stainless column packed with 10-μm silica gel (kyowa gel MIC-SI-10); 300 × 10 mm i.d. glass column paked with 10-μm silica gel (Kyowa gel MIC-SI-10).

(11*S*)-Guaia-3,10(14)-dieno-13,6α-lactone (21): colorless oil; HPLC A, EtOAc–hexane (5:95), 3.1, t_R 6; IR ($CHCl_3$) 1760, 1640 cm^{-1}; ^1H NMR δ 1.23 (3 H, d, *J* = 7.0 Hz, C_{11}-Me), 1.83 (3 H, broad s), 2.21 (1 H, dq, *J* = 11.9, 7.0 Hz, C_{11}-H), 2.79 (1 H, dd, *J* = 9.6, 8.3 Hz, C_5-H), 3.10 (1 H, ddd, *J* = 8.3, 8.3, 6.0 Hz, C_1-H), 3.99 (1 H, dd, *J* = 9.6, 9.6 Hz, C_6-H), 4.83 (1 H, m, $W_{h/2}$ = 4.0 Hz, C_{14}-H), 4.88 (1 H, m, $W_{h/2}$ = 3.5 Hz, C_{14}-H), 5.53 (1 H, m, $W_{h/2}$ = 7.0 Hz, C_3-H); $[\alpha]^{25}_D$ +71.4° (*c* 0.64, $CHCl_3$); MS (EI, 70 eV, 80 °C) *m*/*e* (relative intensity) 232 (61, M^+), 159 (81), 158 (100), 153 (8 9), 107 (87), 93 (99), 80 (70), 78 (60); HRMS *m*/*e* calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1450.

Epoxidation of 21. The Formation of (11*S*)-3α,4α-Epoxy-10(14)-eno-12,6α-lactone (24) and (11*S*)-3β,4β-Epoxy-10(14)-eno-12,6α-lactone (23). A mixture of **21** (117 mg, 0.50

(18) The IR spectra ($CHCl_3$) of zaluzanin C and zaluzanin D were kindly supplied by Prof. Y. Asakawa.

(19) $[\alpha]_D$ values of zaluzanin D were reported ±0° by two groups; see ref 10 and 7c.

mmol) and 98% *m*-chloroperoxybenzoic acid (88 mg, 0.50 mmol) in dichloromethane (2 mL) was allowed to stand at −20 °C for 2 h. The mixture was poured into 0.2 M aqueous solution of KI and extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed successively with a 0.1 M aqueous solution of $Na_2S_2O_3$ (20 mL), a saturated aqueous solution of $NaHCO_3$ (3 × 30 mL), and a saturated aqueous solution of NaCl (30 mL), dried (Na_2SO_4), and concentrated to give an oily crude product, which was purified by HPLC [B, EtOAc–hexane (1:9), 9].

The first peak (t_R 2.8) gave recovered **21** (47 mg, 40%).

The second peak (t_R 10.4) gave **23** (19 mg, 15%) as colorless crystals: mp 106 °C; IR (KBr) 1768, 1640 cm^{-1}; ^1H NMR δ 1.24 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.37 (1 H, dd, J = 13.0, 4.5 Hz, C_8-H), 1.53 (3 H, s, C_4-Me), 2.31 (1 H, dd, J = 10.0, 9.5 Hz, C_5-H), 2.55 (1 H, ddd, J = 12.5, 4.5, 3.5 Hz, C_9-H), 2.81 (1 H, ddd, J = 9.5, 9.5, 2.5 Hz, C_1-H), 3.31 (1 H, broad s, $W_{h/2}$ = 3.0 Hz, C_3-H), 4.23 (1 H, dd, J = 10.0, 10.0 Hz, C_6-H), 5.00 (2 H, broad s, C_{14}-H); $[\alpha]^{25}_D$ +19.8° (*c* 0.20, $CHCl_3$); MS (EI, 75 eV, 100 °C), *m/e* (relative intensity) 248 (100, M^+), 233 (46), 97 (69), 95 (84), 91 (42), 80 (94), 55 (49). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.31; H, 8.19.

The third peak (t_R 14.6) gave **24** (44 mg, 35%) as colorless crystals; mp 91 °C; IR (KBr) 1755, 1640 cm^{-1}; ^1H NMR δ 1.22 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.59 (3 H, s, C_4-Me), 1.80 (1 H, ddd, J = 14.0, 10.5, 1.5 Hz, C_2-H), 2.29 (1 H, dd, J = 10.5, 8.5 Hz, C_5-H), 2.90 (1 H, ddd, J = 10.5, 8.5, 7.5 Hz, C_1-H), 3.37 (1 H, broad s, $W_{h/2}$ = 3.0 Hz, C_3-H), 3.97 (1 H, dd, J = 10.5, 9.5 Hz, C_6-H), 4.84 (1 H, broad s, $W_{h/2}$ = 4.0 Hz, C_{14}-H), 4.88 (1 H, dd, J = 1.5, 1.5 Hz, C_{14}-H); $[\alpha]^{25}_D$ +2.9° (*c* 0.62, $CHCl_3$); MS (EI, 75 eV, 100 °C) *m/e* (relative intensity) 248 (10, M^+), 233 (59), 131 (22), 124 (22), 97 (100), 95 (42), 93 (25), 91 (28), 67 (20), 55 (20). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.38; H, 8.04.

In another experiment, a mixture of **21** (29 mg, 0.12 mmol) and 80% *m*-chloroperoxybenzoic acid (26 mg, 0.12 mmol) in dichloromethane (1 mL) was allowed to stand at −20 °C for 4 h and treated as usual manner to give an oily crude product, which was separated by TLC [EtOAc–$CHCl_3$ (1:9)].

The first band gave a 1:9 mixture of **23** and **24** (11 mg, 35%) by the analysis of HPLC.

The second band gave a 3:4 mixture of diepoxides **22a** and **22b** (8 mg, 24%), which was further separated by HPLC [A, EtOAc–hexane (4:6), 3.1].

The first peak (t_R 3) gave a diepoxide **22a** (3 mg, 9%) as colorless crystals: mp 197 °C; IR (KBr) 3400, 1764 cm^{-1}; ^1H NMR δ 1.26 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.54 (3 H, s, C_4-Me), 2.44 (1 H, dd, J = 10.0 Hz, C_5-H), 2.52 (1 H, d, J = 4.5 Hz, C_{14}-H), 2.82 (1 H, m, C_1-H), 3.02 (1 H, dd, J = 4.5, 1.5 Hz, C_{14}-H), 3.18 (1 H, broad s, $W_{h/2}$ = 4.0 Hz, C_3-H), 4.29 (1 H, dd, J = 10.0, 10.0 Hz, C_6-H); $[\alpha]^{25}_D$ +21.1° (*c* 0.17, $CHCl_3$). Anal. Calcd for $C_{15}H_{18}O_4 \cdot {}^1/_2H_2O$: C, 66.40; H, 7.06. Found: C, 67.02; H, 7.32.

The second peak (t_R 4) gave another stereoisomeric diepoxide **22b** (4 mg, 12%) as colorless crystals: mp 83 °C; IR (KBr) 3450, 1765 cm^{-1}; ^1H NMR δ 1.25 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.61 (3 H, s, C_4-Me), 2.55 (1 H, d, J = 5.0 Hz, C_{14}-H), 2.65 (1 H, d, J = 5.0 Hz, C_{14}-H), 3.34 (1 H, broad s, $W_{h/2}$ = 2.5 Hz, C_3-H), 4.10 (1 H, dd, J = 10.0, 9.0 Hz, C_6-H); $[\alpha]^{25}_D$ +21.0° (*c* 0.095, $CHCl_3$). Anal. Calcd for $C_{15}H_{18}O_4 \cdot {}^1/_2H_2O$: C, 66.40; H, 7.06. Found: C, 66.10; H, 7.88.

(11*S*)-3α-Hydroxyguaia-4(15),10(14)-dieno-12,6α-lactone (25). A solution of **24** (46 mg, 0.185 mmol) in anhydrous toluene (3 mL) was refluxed under stirring with aluminum isopropoxide (378 mg, 1.85 mmol) for 23 h. The mixture was poured into the cold mixture of ethyl acetate (50 mL) and 2 M HCl (15 mL) and stirred for 15 min. The organic layer was separated, and the aqueous layer was further extracted with ethyl acetate (4 × 20 mL). The combined organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 40 mL) and a saturated aqueous solution of NaCl (2 × 40 mL), dried, and concentrated to give an oily crude product (49 mg), which was purified by HPLC [B, EtOAc–hexane (4:6), 6].

The first peak (t_R 1.6) gave recovered **24** (7.5 mg, 16%).

The second peak (t_R 4.6) gave **25** (20.2 mg, 44%) as an oil: IR ($CHCl_3$) 3600, 1762, 1640 cm^{-1}; ^1H NMR δ 1.25 (3 H, d, J = 7.0 Hz, C_{11}-Me), 2.95–3.15 (2 H, m, C_1- and C_5-H), 3.88 (1 H, dd, J = 9.0, 9.0 Hz, C_6-H), 4.70 (1 H, broad dd, J = 6.5, 6.5 Hz, C_3-H), 4.76 (1 H, broad s, C_{14}-H), 4.92 (1 H, broad s, C_{14}-H), 5.36 (1 H, dd, J = 1.5, 1.5 Hz, C_{15}-H), 5.46 (1 H, dd, J = 1.5, 1.5 Hz, C_{15}-H); $[\alpha]^{25}_D$ −7.1° (*c* 0.81, $CHCl_3$); MS (EI, 25 eV, 80 °C) *m/e* (relative intensity) 248 (60, M^+), 175 (71), 174 (87), 157 (45), 95 (44), 85 (66), 83 (100), 43 (46); HRMS *m/e* calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1397.

(11*S*)-3α-Hydroxy-11β-(phenylseleno)guaia-4(15),10-(14)-dieno-12,6α-lactone (26). A solution of **25** (15 mg, 0.06 mmol) in THF (2 mL) was slowly added over an 8-min period to a cooled (−70 °C) solution of lithium diisopropylamide [prepared from diisopropylamine (29 μL, 0.21 mmol) and 1.62 M butyllithium in hexane (131 μL, 0.21 mmol)] in THF (1 mL) under stirring. After 1 h a solution of diphenyl diselenide (66 mg, 0.21 mmol) in THF (1 mL) containing HMPA (37 μL, 0.21 mmol) was added at −70 °C. The reaction mixture was stirred at −70 °C for 30 min and then warmed at −30 °C where stirring was continued for an additional 1 h. The reaction was quenched by the addition of 0.4 M aqueous solution of HCl. The mixture was extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with a saturated aqueous solution of NaCl, dried (Na_2SO_4), and concentrated to give an oily crude product, which was purified by preparative TLC (EtOAc–$CHCl_3$, 1:9).

The first band gave diphenyl diselenide.

The second band (R_f 0.16) gave spectroscopically pure **26** (10 mg, 41%) as a colorless crystalline material, which was recrystallized from a mixture of ethyl acetate and hexane to give colorless needles: mp 166–167 °C; HPLC [A, EtOAc–hexane (3:7), 3.1] t_R 8.2; IR (KBr) 3480, 3075, 3010, 1755, 1648, 922, 902, 758, 702 cm^{-1}; ^1H NMR δ 1.55 (3 H, s, C_{11}-Me), 1.58 (1 H, ddd, J = 12.5, 12.0, 5.0 Hz, C_8-H), ca. 1.9 (1 H, C_2-H), ca. 2.1 (1 H, C_7-H), 2.15 (1 H, C_2-H), 2.62 (1 H, ddd, J = 12.0, 4.0, 3.0 Hz, C_9-H), 3.05 (1 H, C_5-H), 3.07 (1 H, C_1-H), 4.02 (1 H, dd, J = 9.5, 9.0 Hz, C_6-H), 4.64 (1 H, dddd, J = 6.0, 6.0, 1.9, 1.5 Hz, C_3-H), 4.80 (1 H, broad s, $W_{h/2}$ = 3.0 Hz, C_{14}-H), 4.96 (1 H, broad s, $W_{h/2}$ = 2.5 Hz, C_{14}-H), 5.36 (1 H, dd, J = 1.9, 1.9 Hz, C_{15}-H), 5.42 (1 H, dd, J = 1.5, 1.5 Hz, C_{15}-H), 7.25–7.65 (5 H, C_6H_5); $[\alpha]^{20}_D$ +56.5° (*c* 2.43, $CHCl_3$); MS (EI, 25 eV, 140 °C) *m/e* (relative intensity) 406 [9, M^+ (^{82}Se)], 404 [63, M^+ (^{80}Se)], 402 [25, M^+ (^{78}Se)], 401 [8, M^+ (^{77}Se)], 400 [12, M^+ (^{76}Se)], 173 (31), 158 (50), 157 (33), 78 (100). Anal. Calcd for $C_{21}H_{24}O_3Se$: C, 62.53; H, 6.00. Found: C, 62.30; H, 5.98.

3-Epizaluzanin C (10). A solution of **26** (33 mg, 0.082 mmol) in THF (4.1 mL) containing acetic acid (55 μL, 0.96 mmol) was treated at 0 °C with 30% H_2O_2 (275 μL, 2.70 mmol). After the addition was complete, stirring was continued for additional 1.5 h at this temperature. The reaction mixture was poured into a cold saturated aqueous solution of $NaHCO_3$ (41 mL) and extracted with ethyl acetate (5 × 50 mL). The combined extracts were washed with a saturated aqueous solution of NaCl (2 × 80 mL), dried (Na_2SO_4), and concentrated to give an oily crude product (32 mg), which was chromatographed over a short column of silica gel (500 mg) and eluted with a mixture of ethyl acetate and hexane (1:1). The eluent was further purified by HPLC [C, EtOAc–hexane (3:7), 2.7, t_R 55] to give 3-epizaluzanin C (18 mg, 89%) as a colorless oil: IR ($CHCl_3$) 3600, 3460, 3090, 3015, 1760, 1642, 1310, 1263, 1150, 1000 cm^{-1}; IR (neat) 3420, 3090, 1765, 1662, 1642, 1310, 1262, 1145, 995, 902, 816, 755 cm^{-1}; ^1H NMR (C_6D_6) δ 3.36 (1 H, t, J = 9.0 Hz, C_6-H), 4.40 (1 H, dd, J = 6.2, 6.2 Hz, C_3-H), 4.52 (1 H, broad s, $W_{h/2}$ = 3.2 Hz, C_{14}-H), 4.62 (1 H, broad s, $W_{h/2}$ = 3.2 Hz, C_{14}-H), 4.87 (1 H, d, J = 3.4 Hz, C_{13}-H), 5.22 (1 H, broad s, $W_{h/2}$ = 5.2 Hz, C_{15}-H), 5.56 (1 H, broad s, $W_{h/2}$ = 4.8 Hz, C_{15}-H), 6.14 (1 H, d, J = 3.4 Hz, C_{13}-H); ^1H NMR ($CDCl_3$) δ 1.43 (1 H, m, C_8-H), 1.90 (1 H, m, C_2-H), 2.55 (1 H, m, C_9-H), 2.89 (1 H, m, C_7-H), 3.02–3.22 (2 H, m, C_1-H, C_5-H), 3.95 (1 H, dd, J = 10.0, 9.0 Hz, C_6-H), 4.73 (1 H, t, J = 6.0 Hz, C_3-H), 4.83 (1 H, s, C_{14}-H), 4.97 (1 H, d, J = 0.8 Hz, C_{14}-H), 5.40 (1 H, dd, J = 1.7, 1.5 Hz, C_{15}-H), 5.53 (1 H, d, J = 3.0 Hz, C_{13}-H), 5.54 (1 H, dd, J = 1.7, 1.7 Hz, C_{15}-H), 6.27 (1 H, d, J = 3.5 Hz, C_{13}-H); ^{13}C NMR (50.309 MHz) δ 31.0 (t), 36.7 (t), 39.9 (t), 44.2 (d), 45.6 (d), 49.6 (d), 74.6 (d), 84.9 (d, C_6), 113.2 (t), 113.3 (t), 120.5 (t), 139.4 (s), 148.5 (s), 154.1 (s), 170.1 (s, C_{12}); MS (EI, 25 eV, 80 °C) *m/e* (relative intensity) 246 (46, M^+), 228 (84), 200 (58), 150 (56), 143 (56), 131 (77), 122 (68), 117 (68), 107 (71), 96 (82), 91 (100), 87 (70); $[\alpha]^{20}_D$ −46.4° (*c* 1.23, $CHCl_3$).

Solvolysis Reaction of 27. Formation of (11*S*)-3α-Acetoxyguaia-1(10),4(15)-dieno-12,6α-lactone (28), (11*S*)-3α-Acetoxyguaia-4(15),9-dieno-12,6α-lactone (29), and (11*S*)-3α-Acetoxyguaia-4(15),10(14)-dieno-12,6α-lactone (30). A

mixture of **27** (429 mg, 1.25 mmol) and 0.5 M potassium acetate in acetic acid (20 mL) was stirred at the refluxing temperature for 24 h, cooled, poured into a saturated aqueous solution of NaCl (65 mL), and extracted with ethyl acetate (4 × 50 mL). The combined extracts were washed successively with a saturated aqueous solution of $NaHCO_3$ (5 × 40 mL) and a saturated aqueous solution of NaCl, dried (Na_2SO_4), and concentrated to give an oily crude material (400 mg). This was then chromatographed over silica gel (20 g, 2.5 cm i.d. column) and eluted with a mixture of ethyl acetate and hexane (1:9) to give a mixture of **28**, **29**, and **30** (a 2:1:3 mixture based on the analyses of ^1H NMR and HPLC), as an oily material (273 mg, 75%), which was employed in the next step without further purification. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.09; H, 7.70.

A part of the mixture of **28**, **29**, and **30** was separated by HPLC [A, EtOAc–hexane (1:9), 2.6].

The first peak (t_R 12.2) gave **28** as colorless crystals: mp 106 °C; IR ($CHCl_3$) 3030, 1770, 1735, 905 cm^{-1}; ^1H NMR δ 1.23 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.75 (3 H, broad s, C_{10}-Me), 1.88 (1 H, ddd, J = 12.5, 9.8, 3.8 Hz, C_7-H), 2.10 (1 H, s, CH_3CO), 2.28 (1 H, dq, J = 12.5, 7.0 Hz, C_{11}-H), 2.92 (1 H, broad dd, J = 16.0, 7.0 Hz, C_2-H), 3.42 (1 H, broad d, J = 9.8 Hz, C_5-H), 3.63 (1 H, dd, J = 9.8, 9.8 Hz, C_6-H), 5.31 (1 H, dd, J = 1.5, 1.5 Hz, C_{15}-H), 5.43 (1 H, dd, J = 1.5, 1.5 Hz, C_{15}-H), 5.49 (1 H, broad dd, J = 7.0, 7.0 Hz, C_3-H); $[\alpha]^{25}_D$ −77.9° (*c* 0.60, $CHCl_3$); MS (EI, 42 eV, 120 °C) *m/e* (relative intensity) 290 (0.1, M^+), 248 (1.4, $M^+ - CH_3CO + 1$), 247 (0.8, $M^+ - CH_3CO$), 231 (18), 230 (100, $M^+ - CH_3CO_2H$), 215 (11), 173 (11), 157 (15), 131 (10), 119 (21), 118 (13), 117 (11), 105 (11), 91 (13); HRMS *m/e* calcd for $C_{17}H_{22}O_4$ 290.1518, found 290.1526; *m/e* calcd for $C_{15}H_{18}O_2$ ($M^+ - CH_3CO_2H$) 230.1306, found 230.1305. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.07; H, 7.92.

The first half of the second peak (t_R 13.4) gave **30** as a colorless oil: IR ($CHCl_3$) 1765, 1730 cm^{-1}; ^1H NMR δ 1.25 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.33 (1 H, J = 11.0, 11.0, 5.5 Hz, C_8-H), 2.07 (3 H, s, CH_3CO), 2.52 (1 H, C_9-H), 2.96–3.08 (2 H, m, C_1-H, C_5-H), 3.88 (1 H, dd, J = 9.3, 9.3 Hz, C_6-H), 4.78 (1 H, broad s, $W_{h/2}$ = 2.5 Hz, C_{14}-H), 4.93 (1 H, broad s, $W_{h/2}$ = 2.5 Hz, C_{14}-H), 5.39 (1 H, dd, J = 1.5, 1.5 Hz, C_{15}-H), 5.49 (1 H, dd, J = 1.5, 1.5 Hz, C_{15}-H), 5.67 (1 H, dddd, J = 6.0, 6.0, 1.5, 1.5 Hz, C_3-H); $[\alpha]^{25}_D$ +21.5° (*c* 0.41, $CHCl_3$); MS (EI, 40 eV, 150 °C) *m/e* (relative intensity) 290 (3, M^+), 248 (93), 247 (100), 230 (57), 157 (61), 156 (48), 91 (56); HRMS *m/e* calcd for $C_{17}H_{22}O_4$ 290.1518, found 290.1524; *m/e* calcd for $C_{15}H_{19}O_3$ ($M^+ - CH_3CO$), 247.1334, found 247.1332; *m/e* calcd for $C_{15}H_{18}O_2$ ($M^+ - CH_3CO_2H$), 230.1308, found 230.1279.

The latter half of the second peak (t_R 16.3) gave **29** as a colorless oil: ^1H NMR δ 1.24 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.82 (3 H, broad s, C_{10}-Me), 2.09 (3 H, s, CH_3CO), 2.72 (1 H, dd, J = 10.0, 6.5 Hz, C_5-H), 2.86 (1 H, ddd, J = 12.0, 6.5, 6.5 Hz, C_1-H), 3.87 (1 H, dd, J = 10.0, 10.0 Hz, C_6-H), 5.40 (1 H, broad s, C_{15}-H), 5.53 (1 H, broad s, C_{15}-H), 5.5–5.65 (2 H, C_9-H, C_3-H).

The oily material (50 mg) eluted with a mixture of ethyl acetate and hexane (3:7) from column chromatography was further purified by HPLC [A, EtOAc–hexane (3:7), 3.1, t_R 13.4] to give **35** (38 mg, 8%) as a colorless oil; IR ($CHCl_3$) 1770, 1730 cm^{-1}; ^1H NMR δ 0.92 (3 H, s, C_{10}-Me), 1.25 (3 H, d, J = 7.0 Hz, C_{11}-Me), 2.08 (3 H, s, CH_3CO), ca. 2.1 (1 H, C_2-H), 2.25 (1 H, dd, J = 5.0, 2.5 Hz, C_2-H), 2.36 (1 H, dq, J = 12.0, 7.0 Hz, C_{11}-H), 2.55 (1 H, d, J = 10.5 Hz, C_5-H), 3.03 (3 H, s, CH_3SO_2–), 4.01 (1 H, dd, J = 10.5, 10.5 Hz, C_6-H), 4.84 (1 H, dd, J = 11.5, 5.0 Hz, C_1-H), 5.16 (1 H, broad s, $W_{h/2}$ = 4.0 Hz, C_{15}-H), 5.35 (1 H, broad s, $W_{h/2}$ = 3.0 Hz, C_{15}-H), 5.50 (1 H, dd, J = 2.5, 2.5 Hz, C_3-H); $[\alpha]^{25}_D$ +49.6° (*c* 0.28, $CHCl_3$); MS (FD) *m/e* (relative intensity) 386 (100, M^+), 345 (20), 308 (23), 79 (21), 43 (29); MS (EI, 40 eV, 120 °C) 343 (31, $M^+ - CH_3CO$), 231 (47), 230 (100), 175 (41), 157 (63); HRMS *m/e* calcd for $C_{16}H_{23}O_6S$ ($M^+ - CH_3CO$) 343.1215, found 343.1206.

Solvolysis Reaction of 35. A mixture of **35** (9 mg) and 0.5 M potassium acetate in acetic acid (2 mL) was refluxed for 24 h and worked up in the usual manner to give oily crude products, which were separated by HPLC [A, EtOAc–hexane (1:9), 1.9]. The eluent (t_R 21.6–30) gave a 2:1:3 mixture of **28**, **29**, and **30** (5 mg, 74%).

The Hydrolysis of the Mixture of 28, 29, and 30. To a mixture of **28**, **29**, and **30** (168 mg, 0.58 mmol) in methanol (7.5 mL) was added 1 M aqueous solution of K_2CO_3 (2.7 mL). The mixture was allowed to stand at room temperature for 23 h, poured into a mixture of a saturated aqueous solution of NaCl (30 mL) and 2 M HCl (15 mL), and extracted with ethyl acetate (2 × 45 mL). The combined extracts were washed successively with a saturated aqueous solution of $NaHCO_3$ (2 × 45 mL) and a saturated solution of NaCl (30 mL), dried (Na_2SO_4), and concentrated to give an oily product (a mixture of **31**, **32**, and **25**, 150 mg, 100%), which was employed in the next step without further purification. This crude product showed two peaks by HPLC [A, EtOAc–hexane (3:7), 2.1, t_R 9.6 and t_R 11.6].

A part of the crude product (92 mg) was separated by HPLC [C, EtOAc–hexane (2:8), 2.7].

The first peak (t_R 82–98) gave **31** (20 mg, 22%) as colorless crystals: mp 113 °C; IR (KBr) 3480, 3100, 1740, 1682, 898 cm^{-1}; ^1H NMR δ 1.23 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.31 (1 H, broad dd, J = 12.0, 12.0 Hz, C_8-H), 1.76 (3 H, broad s, C_{10}-Me), 1.87 (1 H, dddd, J = 12.0, 9.5, 2.5, 2.0 Hz, C_7-H), ca. 2.2 (C_{11}-H), ca. 2.28 (C_2-H), 2.82 (1 H, broad dd, J = 15.0, 7.5 Hz, C_2-H), 3.42 (1 H, broad d, J = 10.0 Hz, C_5-H), 3.61 (1 H, dd, J = 10.0, 9.5 Hz, C_6-H), 4.56 (1 H, broad m, $W_{h/2}$ = 18.0 Hz, C_3-H), 5.30 (1 H, dd, J = 1.8, 1.8 Hz, C_{15}-H), 5.36 (1 H, dd, J = 1.8, 1.8 Hz, C_{15}-H); $[\alpha]^{20}_D$ −80.2° (*c* 0.09, $CHCl_3$); MS (EI, 75 eV, 120 °C) *m/e* (relative intensity) 248 (100, M^+), 230 (74), 175 (34), 119 (36), 91 (42), 55 (52); HRMS *m/e* calcd for $C_{15}H_{20}O_3$ 248.1413, found 248.1393.

The second peak (t_R 82–98) gave a mixture of **32** and **25**. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.80; H, 8.36.

^1H NMR signals of **32** were assigned from those of this mixture: δ 1.23 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.83 (3 H, broad s, C_{10}-Me), 2.70 (1 H, dd, J = 10.5, 6.5 Hz, C_5-H), 2.94 (1 H, ddd, J = 13.0, 6.5, 6.5 Hz, C_1-H), 3.85 (1 H, dd, J = 10.5, 9.5 Hz, C_6-H), 4.65 (1 H, broad dd, J = 8.0, 8.0 Hz, C_3-H), 5.42 (1 H, dd, J = 1.0, 1.0 Hz, C_{15}-H), 5.49 (1 H, dd, J = 1.3, 1.3 Hz, C_{15}-H), 5.54 (1 H, broad d, J = 8.0 Hz, C_9-H).

3α-Hydroxy-11β-(phenylseleno)guaia-1(10),4(15)-dieno-12,6α-lactone (33), 3α-Hydroxy-11β-(phenylseleno)guaia-4(15),9-dieno-12,6α-lactone (34), and 3α-Hydroxy-11β-(phenylseleno)guaia-4(15),10(14)-dieno-12,6α-lactone (26). A solution of the mixture of **31**, **32**, and **25** (213 mg, 0.86 mmol) in THF (13 mL) was slowly added over a 20-min period to a cooled (−76 °C) solution of lithium diisopropylamide [prepared from diisopropylamine (300 μL, 2.14 mmol) and 1.50 M butyllithium in hexane (1.43 mL, 2.15 mmol)] in THF (8.5 ml) under stirring. After 1 h a solution of diphenyl diselenide (680 mg, 2.18 mmol) in THF (5.5 mL) containing HMPA (375 μL, 2.20 mmol) was added over a 10-min period at −76 °C. The reaction mixture was stirred at −76 °C for 30 min and warmed to −30 °C during 30 min where stirring was continued for additional 1.5 h. The reaction was quenched by addition of 0.4 M aqueous solution of HCl (70 mL) at −10 °C. The mixture was extracted with ethyl acetate (5 × 75 mL). The combined extracts were washed with a saturated aqueous solution of NaCl (3 × 120 mL), dried (Na_2SO_4), and concentrated to give an oily crude product (939 mg), which was chromatographed over silica gel (30 g, 14 × 2.5 cm i.d.).

The fraction eluted with hexane gave diphenyl diselenide.

The fraction eluted with a mixture of ethyl acetate and hexane (1:1) gave an oily crude product (315 mg), which showed three peaks (t_R 6.6, t_R 8.2, and t_R 11.8) by the analysis of HPLC [A, EtOAc–hexane (3:7), 2.1].

This crude product was separated by HPLC [B, EtOAc–hexane (2:8), 7.8].

The first peak (t_R 15) gave **33** (92 mg, 27%) as a colorless oil: IR (neat) 3440, 1765 cm^{-1}; ^1H NMR δ 1.53 (3 H, s, C_{11}-Me), 1.78 (3 H, broad s, C_{10}-Me), 2.04 (1 H, s, J = 12.0, 10.0, 2.5 Hz, C_7-H), ca. 2.25 (1 H, C_2-H), 2.83 (1 H, broad dd, J = 16.0, 7.0 Hz, C_2-H), 3.39 (1 H, broad d, J = 10.0 Hz, C_5-H), 4.03 (1 H, dd, J = 10.0, 10.0 Hz, C_6-H), 4.60 (1 H, broad dd, J = 7.5, 7.0 Hz, C_3-H), 5.32 (1 H, dd, J = 2.0, 2.0 Hz, C_{15}-H), 5.37 (1 H, dd, J = 1.5, 1.5 Hz, C_{15}-H), 7.25–7.65 (5 H, C_6H_5); $[\alpha]^{20}_D$ −30.5° (*c* 1.36, $CHCl_3$); MS (EI, 13.5 eV, 100 °C) 406 [31, M^+ (^{82}Se)], 404 [100, M^+ (^{80}Se)], 402 [49, M^+ (^{78}Se)], 401 [28, M^+ (^{77}Se)], 400 [27, M^+ (^{76}Se)], 246 (100), 228 (85), 158 (50). Anal. Calcd for $C_{21}H_{24}O_3Se$: C, 62.53; H, 6.00. Found: C, 62.64; H, 6.06.

The second peak (t_R 18) gave **34** (46 mg, 13%) as a crystalline material, which was recrystallized from a mixture of ethyl acetate and hexane to give colorless needles: mp 185 °C; IR (KBr) 3480, 1750 cm^{-1}; ^1H NMR δ 1.53 (3 H, s, C_{11}-Me), 1.72 (1 H, dd, J = 13.5, 6.5 Hz, C_2-H), 1.83 (3 H, broad s, C_{10}-Me), 1.97 (1 H, ddd,

J = 10.0, 10.0, 4.0 Hz, C_7-H), 2.10 (1 H, dd, J = 13.5, 6.5 Hz, C_2-H), 2.36 (1 H, dd, J = 7.5, 4.0 Hz, C_8-H), 2.62 (1 H, dd, J = 10.5, 6.5 Hz, C_5-H), 2.88 (1 H, ddd, J = 13.0, 6.5, 6.0 Hz, C_1-H), 4.05 (1 H, dd, J = 10.5, 10.0 Hz, C_6-H), 4.60 (1 H, d, J = 6.5 Hz, C_3-H), 5.41 (1 H, dd, J = 1.0, 1.0 Hz, C_{15}-H), 5.49 (1 H, broad s, $W_{h/2}$ = 4.0 Hz, C_{15}-H), 5.60 (1 H, dq, J = 7.5, 1.5 Hz, C_9-H), 7.26–7.65 (5 H, C_6H_5); $[\alpha]^{21}_D$ +20.5° (c 1.34, $CHCl_3$); MS (EI, 13.5eV, 120 °C) m/e (relative intensity) 406 [7, M^+ (^{82}Se)], 404 [100, M^+ (^{80}Se)], 402 [38, M^+ (^{78}Se)], 401 [8, M^+ (^{77}Se)], 400 [15, M^+ (^{76}Se)], 314 (39), 248 (54), 247 (50), 246 (47), 230 (77), 229 (73), 211 (40), 173 (30), 157 (34), 83 (70); HRMS m/e calcd for $C_{21}H_{24}O_3{}^{80}Se$ 404.0890, found 404.0884; m/e calcd for $C_{21}H_{24}O_3{}^{78}Se$ 402.0898, found 402.0901; m/e calcd for $C_{21}H_{24}O_3{}^{77}Se$ 401.0924, found 401.0944; m/e calcd 400.0917; $C_{21}H_{24}O_3{}^{76}Se$ 400.0917, found 400.0914.

The third peak (t_R 25) gave **26** (88 mg, 25%).

3α-Hydroxyguaia-1(10),4(15),11(13)-trieno-12,6α-lactone (36). A solution of **33** (61 mg, 0.15 mmol) in THF (7.5 mL) containing acetic acid (95 μL, 0.17 mmol) was treated at 0 °C with 30% H_2O_2 (525 μL, 5.14 mmol). After the addition was complete, stirring was continued for additional 1.5 h at this temperature. The reaction mixture was poured into a cold saturated aqueous solution of $NaHCO_3$ (70 mL) and extracted with ethyl acetate (5 × 60 mL). The combined extracts were washed with a saturated aqueous solution of NaCl (2 × 80 mL), dried (Na_2SO_4), and concentrated to give an oily crude product (29 mg), which was purified by HPLC [A, EtOAc–hexane (4:6), 2.5, t_R 4.3] to give **36** (24 mg, 64%) as a colorless oil: IR ($CHCl_3$) 3700, 3610, 3020, 1768, 1675, 1605, 1258, 1142, 1000, 968, 948, 918 cm^{-1}; ^1H NMR δ 1.78 (3 H, s, C_{10}-Me), 3.54 (1 H, broad d, J = 10.1 Hz, C_5-H), 3.63 (1 H, dd, J = 10.1, 10.1 Hz, C_6-H), 4.58 (1 H, broad dd, J = 7.5, 7.5 Hz, C_3-H), 5.36 (1 H, broad s, C_{15}-H), 5.42 (1 H, broad s, C_{15}-H), 5.43 (1 H, d, J = 3.7 Hz, C_{13}-H), 6.17 (1 H, d, J = 3.2 Hz, C_{13}-H); $[\alpha]^{20}_D$ −86.6° (c 0.97, $CHCl_3$); MS (EI, 25 eV, 80 °C) m/e (relative intensity) 246 (100, $^+$M), 231 (29), 228 (60), 199 (29), 171 (26), 131 (46), 123 (37), 105 (36), 95 (35), 83 (38), 43 (36); HRMS m/e calcd for $C_{15}H_{18}O_3$ 246.1255, found 246.1234.

3α-Hydroxyguaia-4(15),9,11(13)-trieno-12,6α-lactone (37). A solution of **34** (18.3 mg, 0.045 mmol) in THF (2.3 mL) containing acetic acid (30 μL, 0.52 mmol) was treated at 0 °C with 30% H_2O_2 (150 μL, 1.47 mmol). After the addition was complete, stirring was continued for additional 1.5 h at this temperature. The reaction mixture was worked up as usual to give an oily crude product (13 mg), which was purified by HPLC [A, EtOAc–hexane (3:7), 2.1, t_R 10.6] to give **37** (8.2 mg, 73%) as a colorless oil: IR ($CHCl_3$) 3600, 3005, 1760, 1660, 1625, 1256, 1138, 997 cm^{-1}; ^1H NMR δ 1.80 (1 H, ddd, J = 13.5, 12.5, 6.5 Hz, C_2-H), 1.86 (3 H, broad s, C_{10}-Me), 2.02 (1 H, ddm, J = 17.0, 13.0 Hz, C_8-H), 2.17 (1 H, dd, J = 13.5, 6.5 Hz, C_2-H), 2.62 (1 H, ddd, J = 17.0, 7.0, 3.5 Hz, C_8-H), 2.73 (1 H, ddddd, J = 13.0, 9.0, 3.5, 3.5, 3.0 Hz, C_7-H), 2.86 (1 H, broad dd, J = 10.5, 7.0 Hz, C_5-H), 3.04 (1 H, ddd, J = 12.5, 7.0, 6.5 Hz, C_1-H), 3.88 (1 H, dd, J = 10.5, 9.0 Hz, C_6-H), 4.64 (1 H, broad d, J = 6.5 Hz, C_3-H), 5.48 (1 H, dd, J = 1.3, 1.3 Hz, C_{15}-H), 5.52 (1 H, d, J = 3.0 Hz, C_{13}-H), 5.55 (1 H, dd, J = 1.3, 1.3 Hz, C_{15}-H), 5.58 (1 H, broad d, J = 7.0 Hz, C_9-H), 6.24 (1 H, d, J = 3.5 Hz, C_{13}-H); $[\alpha]^{20}_D$ −113° (c 1.22, $CHCl_3$); MS m/e (relative intensity) 246 (25, M^+), 228 (18) 161 (22), 150 (100), 131 (22), 122 (47), 105 (25), 96 (25), 79 (25); HRMS m/e calcd for $C_{15}H_{18}O_3$ 246.1255, found 246.1252.

Mitsunobu Reaction of the Olefinic Mixture of 25, 31, and 32. Into a THF solution (1 mL) of a mixture of **25**, **31**, and **32** (64 mg, 0.26 mmol), which was obtained by the solvolysis of **27** and the successive hydrolysis of the resulting mixture of acetates **28**, **29**, and **30**, were added triphenylphosphine (174 mg, 0.66 mmol), acetic acid (100 μL, 1.75 mmol), and diethyl azodicarboxylate (130 μL, 0.83 mmol). The solution was stirred for 23 h at room temperature, poured into a saturated aqueous solution of NaCl (30 mL), and extracted with ethyl acetate (4 × 20 mL). The combined extracts were washed successively with a saturated aqueous solution of $NaHCO_3$ (40 mL) and a saturated aqueous solution of NaCl (40 mL), dried (Na_2SO_4), and concentrated to give an oily crude product, which was purified by preparative TLC [AcOEt–$CHCl_3$ (1:9)].

The first band (R_f 0.35) gave an olefinic mixture of acetates (**38**, **39**, and **40**, 33 mg, 44%) as an oily material, which was employed as the starting material of the next step without separation.

The second band (R_f 0.08) gave a inseparable mixture of the starting material (**25**, **31**, and **32**) and phosphine derivatives (327 mg).

The mixture of **38**, **39**, and **40** (9 mg) was separated by HPLC [A, EtOAc–hexane (1:9), 3.1] for the identification.

The first peak (t_R 11.6) gave **39** (1.5 mg) as colorless cyrstals: mp 102 °C; IR ($CHCl_3$) 1765, 1730 cm^{-1}; ^1H NMR δ 1.24 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.80 (3 H, broad s, C_{10}-Me), ca. 1.8 (1 H, C_7-H), 2.03 (3 H, s, CH_3CO), 2.32 (1 H, dq, J = 12.0, 7.0 Hz, C_{11}-H), ca. 2.53 (1 H, C_5-H), 4.08 (1 H, dd, J = 10.0, 9.3 Hz, C_6-H), 5.35 (1 H, broad s, $W_{h/2}$ = 3.5 Hz, C_{15}-H), 5.45 (1 H, broad s, $W_{h/2}$ = 4.0 Hz, C_{15}-H), 5.51 (1 H, dddd, J = 7.5, 7.5, 1.8, 1.8 Hz, C_3-H), 5.56 (1 H, broad d, J = 7.5 Hz, C_9-H); $[\alpha]^{25}_D$ +29.0° (c 0.15, $CHCl_3$); MS (EI, 60 eV, 100 °C) m/e (relative intensity) 290 (13, M^+), 248 (40), 247 (88), 230 (100), 157 (51), 152 (52), 91 (53); HRMS m/e calcd for $C_{17}H_{22}O_4$ 290.1518, found 290.1504.

Repeated purification of the second peak (t_R 12) gave **38** (1.8 mg) as a colorless oil: IR ($CHCl_3$) 1760, 1725 cm^{-1}; ^1H NMR δ 1.24 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.76 (3 H, broad s, C_{10}-Me), 1.86 (1 H, C_7-H), 2.02 (3 H, s, CH_3CO), 2.30 (1 H, dd, J = 12.5, 7.0 Hz, C_{11}-H), 2.45 (1 H, broad d, J = 17.0 Hz, C_2-H), 2.66 (1 H, broad d, J = 17.0 Hz, C_2-H), 3.28 (1 H, broad d, J = 10.0 Hz, C_5-H), 3.71 (1 H, dd, J = 10.0, 10.0 Hz, C_6-H), 5.40 (1 H, dd, J = 0.7 Hz, C_{15}-H), 5.45 (1 H, dd, J = 0.8 Hz, C_{15}-H), 5.49 (1 H, dd, J = 5.5, 2.0 Hz, C_3-H); $[\alpha]^{25}_D$ −16.5° (c 0.18, $CHCl_3$); MS (EI, 60 eV, 100 °C) m/e (relative intensity) 290 (5, M^+), 248 (28), 247 (42), 230 (100), 157 (34), 119 (26), 105 (26) 91 (32), 55 (26); HRMS m/e calcd for $C_{17}H_{22}O_4$ 290.1518, found 290.1513.

The third peak (t_R 13.6) gave **40** (4.8 mg) as a colorless prisms: mp 104 °C; IR (KBr) 1762, 1745 cm^{-1}; ^1H NMR δ 1.24 (3 H, d, J = 7.0 Hz, C_{11}-Me), 1.80 (1 H, ddd, J = 14.0, 6.5, 6.5 Hz, C_2-H), 2.11 (3 H, s, CH_3CO), 2.47 (1 H, dd, J = 14.0, 7.5, 7.5 Hz, C_2-H), 2.80 (1 H, dddd, J = 9.5, 7.5, 2.0, 2.0 Hz, C_5-H), 2.91 (1 H, ddd, J = 7.5, 7.5, 6.5 Hz, C_1-H), 4.00 (1 H, dd, J = 9.5, 9.0 Hz, C_6-H), 4.92 (1 H, broad s, C_{14}-H), 4.94 (1 H, broad s, C_{14}-H), 5.28 (1 H, dd, J = 2.0, 2.0 Hz, C_{15}-H), 5.42 (1 H, dd, J = 2.0, 2.0 Hz, C_{15}-H), 5.55 (1 H, dddd, J = 7.5, 6.5, 2.0, 2.0 Hz, C_3-H); $[\alpha]^{25}_D$ +56.8° (c 0.48, $CHCl_3$); MS (EI, 60 eV, 100 °C) m/e (relative intensity) 290 (7, M^+), 248 (89), 247 (100), 230 (62), 157 (57), 156 (47), 91 (33); HRMS m/e calcd for $C_{17}H_{22}O_4$ 290.1518, found 290.1526.

Phenylselenylation of the Olefinic Mixture of Acetates 38, 39, and 40. A solution of the olefinic mixture of acetates **38**, **39**, and **40** (48 mg, 0.165 mmol) in THF (3 mL) was slowly added over a 12-min period to a cooled (−70 °C) solution of lithium diisopropylamide [prepared from diisopropylamine (138 μL, 0.98 mmol) and 1.50 M butyllithium in hexane (600 μL, 0.90 mmol)] in THF (2 mL) with stirring. After 1 h a solution of diphenyl diselenide (246 mg, 0.79 mmol) in THF (2 mL) containing HMPA (140 mg, 0.80 mmol) was added over a 5-min period at −70 °C. The reaction mixture was stirred at −70 °C for 30 min and then warmed to −10 °C during 40 min where stirring was continued for additional 1.5 h. The reaction was quenched by addition of 0.4 M aqueous solution of HCl (20 mL) at −10 °C. The mixture was extracted with ethyl acetate (4 × 20 mL). The combined extracts were washed with a saturated aqueous solution of NaCl (2 × 20 mL), dried (Na_2SO_4), and concentrated to give an oily crude product (282 mg), which was separated by TLC [AcOEt–$CHCl_3$ (1:9)].

The first band gave diphenyl diselenide.

The second band (R_f 0.46) gave an olefinic mixture of diphenylselenyl derivatives (**41a**, **41b**, and **41c**, 22 mg, 22%) as a pale yellow oil, which was further purified by HPLC [A, EtOAc–hexane (1:9), 3.1]. The first peak (t_R 9.4) gave **41b** (3.4 mg) as a colorless oil: IR ($CHCl_3$) 1755, 1725, cm^{-1}; ^1H NMR δ 1.52 (3 H, s, C_{11}-Me), 1.79 (3 H, broad s, C_{10}-Me), ca. 2.0 (C_7-H), ca. 2.5 (C_5-H), 3.52 (1 H, d, J = 13.0 Hz, $SeCH_2CO$), 3.60 (1 H, d, J = 13.0 Hz, $SeCH_2CO$), 4.37 (1 H, dd, J = 10.0, 10.0 Hz, C_6-H), 5.30 (1 H, broad s, C_{15}-H), 5.46 (1 H, broad s, C_{15}-H), 5.50 (1 H, broad dd, J = 8.5, 8.5 Hz, C_3-H), 5.60 (1 H, ddq, J = 8.5, 4.0, 1.5 Hz, C_9-H), 7.20–7.70 (10 H, C_6H_5); $[\alpha]^{20}_D$ +83.4° (c 0.34, $CHCl_3$); MS (EI, 45 eV, 200 °C) m/e (relative intensity) 602 [31, M^+ ($^{80}Se_2$)], 600 [28, M^+ (^{78}Se,^{80}Se)], 229 (71), 183 (60), 157 (80), 91 (100), 78 (73), 77 (96); HRMS m/e calcd for $C_{29}H_{30}O_4{}^{80}Se_2$ 602.0474, found 602.0475.

The second peak (t_R 11) gave **41a** (6.9 mg) as a colorless oil: IR ($CHCl_3$) 1755, 1725 cm^{-1}; ^1H NMR δ 1.51 (3 H, s, C_{11}-Me), 1.75

(3 H, broad s, C_{10}-Me), 2.03 (1 H, broad dd, J = 10.0, 10.0 Hz, C_7-H), 2.47 (1 H, broad d, J = 17.0 Hz, C_2-H), 2.63 (1 H, broad d, J = 17.0 Hz, C_2-H), 3.26 (1 H, broad d, J = 10.0 Hz, C_5-H), 3.53 (2 H, s, $SeCH_2CO$), 4.29 (1 H, dd, J = 10.0, 10.0 Hz, C_6-H), 5.43 (1 H, broad s, C_{15}-H), 5.46 (1 H, broad s, C_{15}-H), 5.49 (1 H, dd, J = 5.0, 1.5 Hz, C_3-H), 7.20–7.65 (10 H, C_6H_5); $[\alpha]^{20}_D$ +8.7° (c 0.69, $CHCl_3$); MS (45 eV, 150 °C) m/e (relative intensity) 602 [16, M^+ ($^{80}Se_2$)], 600 [14, M^+ (^{78}Se,^{80}Se)], 446 (32), 333 (68), 229 (31), 216 (48), 171 (42), 157 (51), 105 (34), 91 (100), 83 (43), 79 (30), 78 (46), 77 (62), 55 (42); HRMS m/e calcd for $C_{29}H_{30}O_4{}^{80}Se_2$ 602.0475, found 602.0488.

The third peak (t_R 21) gave **41c** (11.9 mg) as a colorless oil: IR ($CHCl_3$) 1755, 1725 cm^{-1}; ^1H NMR δ 1.55 (3 H, s, C_{11}-Me), ca. 1.6 (C_2-H), 2.08 (C_7-H), 2.40 (1 H, dd, J = 7.0, 15.0 Hz, C_2-H), ca. 2.8 (C_5-H), 2.84 (C_1-H), 3.56 (2 H, s, $SeCH_2CO$), 4.13 (1 H, dd, J = 9.5, 9.5 Hz, C_6-H), 4.85 (1 H, s, C_{14}-H), 4.95 (1 H, s, C_{14}-H), 5.23 (1 H, dd, J = 1.5, 1.5 Hz, C_{15}-H), 5.38 (1 H, dd, J = 1.5, 1.5 Hz, C_{15}-H), 5.51 (1 H, dddd, J = 7.0, 7.0, 1.5, 1.5 Hz, C_3-H), 7.20–7.70 (10 H, C_6H_5); $[\alpha]^{20}_D$ +73.3° (c 1.18, $CHCl_3$); MS (EI, 45 eV, 180 °C) m/e (relative intensity) 602 [24, M^+ ($^{80}Se_2$)], 600 [22, M^+ (^{78}Se,^{80}S)], 386 (66), 229 (45), 157 (58), 119 (60), 111 (41), 91 (100), 83 (75), 77 (65), 55 (31), 51 (32); HRMS m/e calcd for $C_{29}H_{30}O_4{}^{80}Se_2$ 602.0474, found 602.0477; m/e calcd for $C_{29}H_{30}O_4{}^{78}Se^{80}Se$ 600.0482, found 600.0522.

The third band (R_f 0.13) gave an olefinic mixture of 11-phenylselenyl derivatives (**42a** and **42b**, 8 mg, 12%) as a pale yellow oil: IR ($CHCl_3$) 3500, 1765 cm^{-1}; ^1H NMR (60 MHz) δ 1.53 (C_{11}-Me), 1.80 (broad s, C_{10}-Me), 3.90–4.80 (C_3-H, C_6-H), 4.97, 5.17, 5.34, 5.45 (m, olefinic protons), 7.20–7.80 (C_6H_5).

The fourth band (R_f 0.08) gave 3β-hydroxy-11β-(phenylseleno)guaia-4(15),10(14)-dieno-12,6α-lactone (**43**, 12 mg, 18%) as a colorless crystalline material, which was recrystallized from a mixture of ethyl acetate and hexane to give colorless needles: mp 176–177.5 °C; IR (KBr) 3470, 1750 cm^{-1}; ^1H NMR δ 1.55 (3 H, s, C_{11}-Me), ca. 2.1 (C_7-H), 2.35 (1 H, ddd, J = 13.0, 7.5, 7.5 Hz, C_2-H), 2.70–2.90 (2 H, m, C_1-H, C_5-H), 4.14 (1 H, dd, J = 9.2, 9.2 Hz, C_6-H), 4.52 (1 H, dddd, J = 7.5, 7.5, 2.0, 1.6 Hz, C_3-H), 4.98 (2 H, broad s, $W_{h/2}$ = 4.5 Hz, C_{14}-H), 5.32 (1 H, dd, J = 2.0, 2.0 Hz, C_{15}-H), 5.38 (1 H, dd, J = 1.6, 1.6 Hz, C_{15}-H), 7.30–7.70 (5 H, C_6H_5); $[\alpha]^{21}_D$ +110° (c 1.29, $CHCl_3$); MS (EI, 25 eV, 80 °C) m/e (relative intensity) 406 [15, M^+ (^{82}Se)], 404 [87, M^+ (^{80}Se)], 402 [39, M^+ (^{78}Se)], 401 [21, M^+ (^{77}Se)], 229 (100), 228 (40), 201 (79), 173 (79), 158 (58), 78 (86); HRMS m/e calcd for $C_{21}H_{24}O_3{}^{82}Se$ 406.0892, found 406.0872; m/e calcd for $C_{21}H_{24}O3{}^{80}Se$ 404.0890, found 404.0883; m/e calcd for $C_{21}H_{24}O_3{}^{78}Se$ 402.0898, found 402.0870; m/e calcd for $C_{21}H_{24}O_3{}^{77}Se$ 401.0924, found 401.0908; m/e calcd for $C_{21}H_{24}O_3{}^{76}Se$ 400.0917, found 400.0885.

The Hydrolysis of the Olefinic Mixture of Diphenylselenyl Derivatives (41). A mixture of **41** (20 mg, 0.033 mmol), methanol (3 mL), and 1 M aqueous solution of K_2CO_3 (1 mL) was allowed to stand at room temperature for 23 h and then poured into a mixture of a saturated aqueous solution of NaCl (20 mL) and 2 M HCl (10 mL), and the resulting mixture was extracted with ethyl acetate (5 × 20 mL). The combined extracts were treated as usual to give an oily crude product (14 mg), which was separately by TLC [AcOEt–$CHCl_3$ (1:9)].

The first band gave **42** (2 mg, 15%).

The second band gave **43** (5 mg, 37%).

Zaluzanin C (11). A solution of **43** (14 mg, 0.035 mmol) in THF (1.8 mL) containing acetic acid (24 μL, 0.42 mmol) was treated at 0 °C with 30% H_2O_2 (120 μL, 1.17 mmol). After the addition was complete, stirring was continued for additional 1.5 h at this temperature. The reaction mixture was poured into a cold saturated aqueous solution of $NaHCO_3$ (18 mL) and extracted with ethyl acetate (5 × 25 mL). The combined extracts were washed with a saturated aqueous solution of NaCl (2 × 80 mL), dried (Na_2SO_4), and concentrated to give an oily crude product (12 mg), which was purified by HPLC [A, EtOAc–hexane (4:6), 2.6, t_R 4.5]. The eluent was concentrated and crystallized from a mixture of EtOAc–hexane (4:6) to give zaluzanin C (7 mg, 84%) as colorless needles: mp 106–108 °C; IR (KBr) 3460, 3095, 1758, 1664, 1640, 1300, 1258, 1158, 1096, 998, 915, 822 cm^{-1}; IR ($CHCl_3$) 3585, 3500, 3075, 1762, 1662, 1640, 1263, 1148, 1008, 947, 908 cm^{-1}; ^1H NMR δ 1.48 (1 H, m, C_8-H), 1.78 (1 H, m, C_2-H), 2.17 (1 H, m, C_9-H), 2.27–2.42 (2 H, m, C_2-H, C_8-H), 2.52 (1 H, m, C_9-H), 2.74–3.02 (3 H, m, C_1-H, C_5-H, C_7-H), 4.13 (1 H, dd, J = 9.0, 9.0 Hz, C_6-H), 4.60 (1 H, broad dd, J = 6.0, 6.0 Hz, C_3-H), 4.98 (1 H, d, J = 0.5 Hz, C_{14}-H), 5.04 (1 H, s, C_{14}-H), 5.36 (1 H, dd, J = 2.0, 2.0 Hz, C_{15}-H), 5.49 (1 H, dd, J = 2.0, 2.0 Hz, C_{15}-H), 5.53 (1 H, d, J = 3.0 Hz, C_{13}-H), 6.25 (1 H, d, J = 3.5 Hz, C_{13}-H); ^{13}C NMR (50.309 MHz) δ 30.6 (t), 34.2 (t), 39.0 (t), 44.2 (d), 45.6 (d), 50.0 (d), 73.6 (d, C_3), 83.9 (d, C_6), 111.3 (t), 114.4 (t), 120.2 (t), 139.7 (s), 148.0 (s), 153.1 (s), 170.1 (s, C_{12}); $[\alpha]^{20}_D$ +35.4° (c 1.53, $CHCl_3$); MS (EI, 25 eV, 100 °C) m/e (relative intensity) 246 (100, M^+), 228 (88), 200 (77), 150 (66), 148 (84), 122 (80), 121 (66), 119 (65), 105 (100), 96 (100), 95 (77), 93 (89), 81 (77); HRMS m/e calcd for $C_{15}H_{18}O_3$ 246.1255, found 246.1244.

3β-Acetoxy-11β-(phenylseleno)guaia-4(15),10(14)-dieno-12,6α-lactone (44). Into a THF solution (1 mL) of **26** (24 mg, 0.060 mmol) were added triphenylphosphine (39 mg, 0.15 mmol), acetic acid (6.9 μL, 0.12 mmol), and diethyl azodicarboxylate (23.5 μL, 0.15 mmol). The solution was stirred for 53 h at 17 °C, poured into a saturated aqueous solution of NaCl (10 mL), and extracted with ethyl acetate (4 × 5 mL). The combined extracts were washed succesively with a saturated aqueous solution of $NaHCO_3$ (10 mL) and a saturated aqueous solution of NaCl (10 mL), dried (Na_2SO_4), and concentrated to give an oily mixture (110 mg), which was chromatographed over silica gel [EtOAc–hexane (2:8)] to give an oily crude product (41 mg). This was further purified by HPLC [A, EtOAc–hexane (2:8), 3.0, t_R 4.5] to give spectroscopically pure **44** (20 mg, 75%), which was recrystallized from a mixture of ethyl acetate and hexane to give colorless needles: mp 102–103.5 °C; IR (KBr) 1760, 1745 cm^{-1}; ^1H NMR δ 1.55 (3 H, s, C_{11}-Me), 1.77 (1 H, ddd, J = 13.5, 7.5, 7.5 Hz, C_2-H), 2.12 (3 H, s, CH_3CO), 2.12 (C_7-H), 2.48 (1 H, ddd, J = 13.5, 7.5, 7.5 Hz, C_2-H), 2.80 (1 H, broad dd, J = 9.3, 7.5 Hz, C_5-H), 2.92 (1 H, broad ddd, J = 7.5, 7.5, 7.5 Hz, C_1-H), 4.15 (1 H, dd, J = 9.3, 9.3 Hz, C_6-H), 4.91 (1 H, broad s, $W_{h/2}$ = 3.0 Hz, C_{14}-H), 4.98 (1 H, broad s, $W_{h/2}$ = 3.0 Hz, C_{14}-H), 5.28 (1 H, dd, J = 2.0, 2.0 Hz, C_{15}-H), 5.40 (1 H, dd, J = 2.0, 2.0 Hz, C_{15}-H), 5.52 (1 H, ddd, J = 7.5, 7.5, 2.0, 2.0 Hz, C_3-H), 7.30–7.65 (5 H, C_6H_5); $[\alpha]^{21}_D$ +84.3° (c 1.97, $CHCl_3$); MS (EI, 25 eV, 140 °C) m/e (relative intensity) 448 [7, M^+ (^{82}Se)], 446 [33, M^+ (^{80}Se)], 444 [17, M^+ (^{78}Se)], 443 [7, M^+ (^{77}Se)], 442 [7, M^+ (^{76}Se)], 247 (50), 229 (100), 201 (57), 157 (64), 145 (50); HRMS m/e calcd for $C_{23}H_{26}O_4{}^{82}Se$ 448.0998, found 448.0998; m/e calcd for $C_{23}H_{26}O_4{}^{80}Se$ 446.0996, found 446.0971; m/e calcd for $C_{23}H_{26}O_4{}^{78}Se$ 444.1004, found 444.1002; m/e calcd for $C_{23}H_{26}O_4{}^{77}Se$ 443.1030, found 443.0985; m/e calcd for $C_{23}H_{26}O_4{}^{76}Se$ 442.1023, found 442.1000.

Zaluzanin D (12). A solution of **44** (25.3 mg, 0.057 mmol) in THF (2.8 mL) containing acetic acid (38 μL, 0.66 mmol) was treated at 0 °C with H_2O_2 (190 μL, 1.86 mmol). After the addition was complete, stirring was continued for additional 1.5 h at this temperature. The reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ (30 mL) and extracted with ethyl acetate (5 × 40 mL). The combined extracts were washed with a saturated aqueous solution of NaCl (2 × 55 mL), dried (Na_2SO_4), and concentrated to give an oily crude product (24 mg), which was purified by HPLC [A, EtOAc–hexane (2:8), 2.6, t_R 6] to give zaluzanin D (**12**) as a colorless oil (12.4 mg, 76%): IR ($CHCl_3$) 3090, 1770, 1745, 1668, 1645, 1377, 1260, 1148, 1023, 920 cm^{-1}; ^1H NMR δ 1.46 (1 H, m, C_8-H), 1.83 (1 H, m, C_2-H), 2.12 (3 H, s, CH_3CO), 2.14–2.36 (2 H, m, C_8-H, C_9-H), 2.36–2.60 (2 H, m, C_2-H, C_9-H), 2.78–2.96 (2 H, m, C_5-H, C_7-H), 2.99 (1 H, dd, J = 8.3, 8.3 Hz, C_1-H), 4.09 (1 H, dd, J = 9.3, 9.3 Hz, C_6-H), 4.98 (2 H, s, C_{14}-H), 5.32 (1 H, t, J = 2.0, 2.0 Hz, C_{15}-H), 5.51 (1 H, t, J = 2.0, 2.0 Hz, C_{15}-H), 5.53 (1 H, d, J = 3.2 Hz, C_{13}-H), 5.59 (1 H, dddd, J = 8.0, 6.0, 2.0, 2.0 Hz, C_3-H), 6.26 (1 H, d, J = 3.5 Hz, C_{13}-H); ^{13}C NMR (50.309 MHz) δ 21.3 (q, CH_3CO), 30.6 (t), 34.5 (t), 36.5 (t), 44.6 (d), 45.3 (d), 50.3 (d), 74.7 (d, C_3), 83.8 (d, C_6), 113.6 (t), 114.4 (t), 120.4 (t), 139.6 (s), 147.6 (s), 148.0 (s), 169.9 (s, C_{12}), 170.8 (s, CH_3CO); $[\alpha]^{20}_D$ +21.7° (c 1.35, $CHCl_3$); MS m/e (relative intensity) 288 (3, M^+), 246 (100), 245 (75), 228 (47), 199 (48), 129 (48), 105 (52), 32 (75); HRMS m/e calcd for $C_{17}H_{20}O_4$ 288.1360, found 288.1355.

3β-Hydroxy-1β-(phenylseleno)guaia-4(15),10(14)-dieno-12,6α-lactone (43). The mixture of **44** (51 mg, 0.11 mmol) and 1 M aqueous solution of K_2CO_3 (0.44 mL) in methanol (1.5 mL) was allowed to stand at room temperature for 2 h, poured into a mixture of a saturated aqueous solution of NaCl (10 mL) and 2 M HCl (5 mL), and extracted with ethyl acetate (5 × 10 mL). The combined extracts were washed successively with a saturated

aqueous solution of $NaHCO_3$ (15 mL) and a saturated aqueous solution of NaCl (20 mL), dried (Na_2SO_4), and concentrated to give a colorless crystalline material (47 mg), which was purified by HPLC [A, EtOAc–hexane (3:7), 3.0].

The major peak (t_R 5.6 min) gave spectroscopically pure **43** (40 mg, 87%) as a colorless crystalline material, which was recrystallized from a mixture of ethyl acetate and hexane to give colorless needles, mp 176–177.5 °C.

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Kinetically Controlled, Stereoselective Formation of Vinylic Sulfones by Conjugate Addition of Lithiated 3-Alkylallylic Sulfones to Cyclic Enones

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Like the corresponding lithiated sulfoxides, lithiated but-2-enyl and oct-2-enyl sulfones undergo kinetically controlled, highly diastereoselective aprotic conjugate addition to five-membered cyclic enones in tetrahydrofuran to deliver vinylic sulfones whose formation and stereochemistry are rationalized in terms of planar or near-planar lithiated reagents reacting through an extended trans-decalyl or trans-fused chair–chair transition state. In contrast to cyclopentenone, 4-*tert*-butoxycyclopent-2-enone gives mixtures of conjugate and carbonyl adducts with the lithiated sulfones at −70 °C. This is ascribed to a steric effect involving the *tert*-butoxy group at C4 of the enone destabilizing the extended transition state. Reactions with cyclohexenone are less stereoselective and are temperature dependent, with lower temperatures (−85 °C) favoring carbonyl addition to generate allylic sulfones as mixtures of diastereomers. At 0 °C rapid conjugate addition takes place to give the vinylic sulfone. The lithiated alkoxides of the carbonyl adducts rearrange to the conjugate vinylic sulfones at 0 °C at a considerably slower rate than that of direct conjugate addition of the lithiated sulfone to the cyclohexenone at 0 °C. The stereoconvergence in the rearrangement excludes an intramolecular Cope rearrangement. Overall the conjugate addition reactions are more sensitive to temperature and steric effects than are the reactions involving the lithiated allylic sulfoxides and, unlike those reactions, are sensitive to the presence of hexamethylphosphoric triamide, which induces formation of allylic sulfones.

Introduction

The structures of carbanions stabilized by an α-sulfonyl group have received considerable scrutiny from both theoretical and experimental standpoints. The impetus for this has largely been provided by the lack of racemization attending the generation and reactions of such carbanions from optically active sulfone precursors.[1,2] Although previously the subject of some controversy, it now appears on the basis of recent MO calculations,[3] NMR spectroscopic[4,5] studies, and X-ray crystallographic studies[6-9] that the structures of such carbanions are planar or near-planar. An NMR study of lithiated methyl phenyl sulfone indicates a carbanion whose hybridization is intermediate between sp^2 and sp^3. By contrast, lithiated methyl phenyl sulfoxide is demonstrated by the NMR technique to be planar. X-ray studies of crystalline complexes of lithiated phenyl alkyl sulfones with either tetramethylethylenediamine (TMEDA) or diglyme reveal that the lithium cation is in the proximity of, but closer to one of, the two oxygen atoms. There are no Li–C bonding contacts, and the C1–S bond is considerably shorter than that in the neutral sulfone. The orbital containing the pair of electrons at the carbanionic center lies in a plane bisecting the O–S–O bond angle. The carbanionic sites in

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