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STUDIES ON THE SYNTHESIS OF SESQUITERPENE LACTONES, 16.[1] THE SYNTHESES OF 11β,13-DIHYDROKAUNIOLIDE, ESTAFIATIN, ISODEHYDROCOSTUSLACTONE, 2-OXODESOXYLIGUSTRIN, ARBORESCIN, 1,10-EPIARBORESCIN, 11β,13-DIHYDROLUDARTIN, 8-DEOXY-11β,13-DIHYDRORUPICOLIN B, 8-DEOXYRUPICOLIN B, 3,4-EPILUDARTIN, LUDARTIN, KAUNIOLIDE, DEHYDROLEUCODIN, AND LEUCODIN

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ABSTRACT.—A total of eleven naturally occurring guaianolides, 11β,13-dihydrokauniolide, estafiatin, isodehydrocostuslactone, 2-oxodesoxyligustrin, arborescin, 11β,13-dihydroludartin, 8-deoxy-11β,13-dihydrorupicolin B, ludartin, kauniolide, dehydroleucodin, and leucodin, and three related compounds, 1,10-epiarborescin, 8-deoxyrupicolin B, and 3,4-epiludartin, were synthesized through a common cationic intermediate **A**, which was derived from (11*S*)-1β-(mesyloxy)eudesm-3-eno-12,6α-lactone [**2**] by solvolytic rearrangement.

The guaianolides represent one of the largest groups of sesquiterpene lactones with over 500 known naturally occurring compounds (2). Some of them have been shown to possess high antitumor (3–15), antishistosomal (3,16,17), anthelmintic (18), contraceptive (19,20), root-growth stimulatory (3,21,22), root-growth and germination inhibitory activities (3, 4, 13–15, 23, 24), and preventive or curative activities for crop diseases (4,15). Because of the diverse biological activities of the guaianolides and since they are available from natural sources often in only small quantities, their efficient and systematic synthesis from easily available compounds is very important.

In the present paper, we report on the syntheses of eleven naturally occurring guaianolides, 11β,13-dihydrokauniolide [**4**] (25), estafiatin [**8**] (18), isodehydrocostuslactone [**10**] (26), 2-oxodesoxyligustrin [**11**] (27), arborescin [**13**] (19,20,28,29), 11β,13-dihydroludartin [**16**] (30), 8-deoxy-11β,13-dihydrorupicolin B [**17**] (31), ludartin [**23**] (30), kauniolide [**25**] (25), dehydroleucodin [**26**] (32), and leucodin [**27**] (33,34), through a common cationic intermediate **A**, which was derived from a mesylate [**2**] by solvolytic rearrangement. The cationic intermediate **A** is also presumed to be an intermediate during biosynthesis of these naturally occurring guaianolides from dihydrocostunolide (35) (Figure 1).

RESULTS AND DISCUSSION

We chose the solvolytic rearrangement of 11(*S*)-1β-(mesyloxy)eudesm-3-eno-12,6α-lactone [**2**] as a key reaction in the syntheses of the naturally occurring guaianolides, **4**, **8**, **10**, **11**, **13**, **16**, **17**, **23**, and **25–27**. The starting material **2** can be prepared from α-santonin [**1**] in 19% overall yield in 12 steps (1,36). Solvolytic rearrangement of **2** in a refluxed 0.5 M HOAc solution of potassium acetate gave (11*S*)-guaia-3,10(14)-dieno-12,6α-lactone [**3**] and (11*S*)-guaia-1(10),3-dieno-12,6α-lactone

[1]For Part 15, see Ando *et al.* (1).

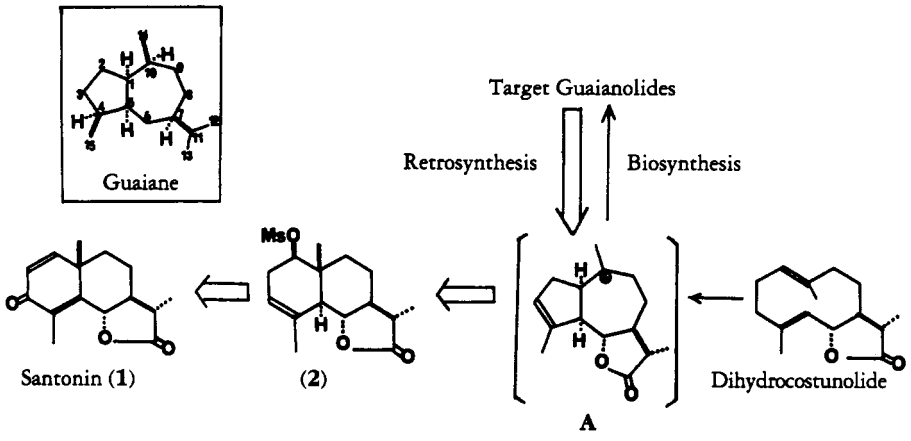
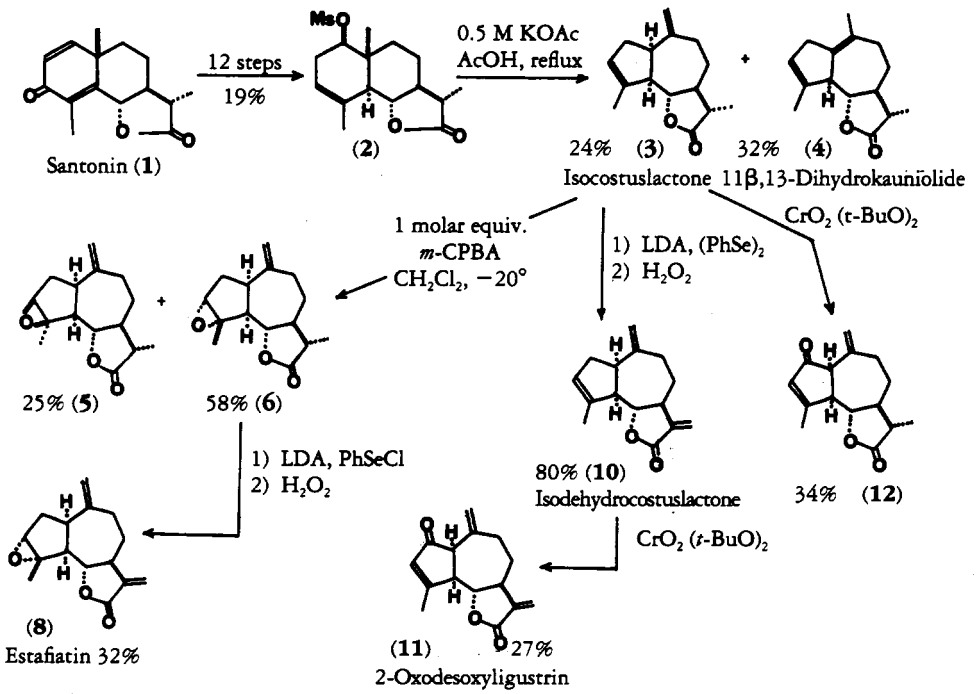


FIGURE 1

[4] in 24% and 32% yields, respectively (Scheme 1). Compound **4** was identical with naturally occurring 11β,13-dihydrokauniolide by comparison of their ^{1}H-nmr spectra and [α]D values (25). Compounds **3** and **4** are considered to be convenient synthetic intermediates of $\Delta^{3,4}$-12,6α-guaianolides and their derivatives, such as **8**, **10**, **11**, **13**, **16**, **17**, **23**, and **25–27**.

Our attention turned next to the synthesis of estafiatin [**8**] (37,38), which is a constituent of *Artemisia mexicana*, whose extracts have been used as an anthelmintic in Mexico (18). The starting material for our synthesis of **8** was diene **3**. Epoxidation of **3**



SCHEME 1

with 1 molar equivalent of *m*-CPBA at −20° in CH_2Cl_2 gave the monoepoxides **5** and **6**, in 25% and 58% yield based on recovered starting material at 60% conversion.

The stereochemical assignments for **5** and **6** are based on the consideration that the reagent attacks **3** preferentially from the less hindered, or convex face. The assignments are also supported by analysis of the ^{1}H-nmr spectra of **5** and **6**. The H-6 signal of **5** (δ 4.23) appears at 0.26 ppm lower field than that of **6** (δ 3.97) due to the deshielding effect of the syn-epoxide oxygen (39).

Phenylselenenylation of **6** gave a phenylseleno lactone [**7**] in 40% yield. The oxidative syn elimination of **7** using H_2O_2 afforded an α-methylene-γ-lactone [**8**] in 80% yield. The ^{1}H-nmr spectrum and [α]D value of **8** were identical with those of naturally occurring estafiatin (18).

We next considered the syntheses of isodehydrocostus lactone [**10**] and 2-oxodesoxyligustrin [**11**]. Isodehydrocostus lactone [**10**] has been isolated from costus root oil (*Saussurea lappa*) (26) as a minor constituent, and 2-oxodesoxyligustrin [**11**] is a constituent of *Stevia sarensis* (27).

The starting material for the syntheses of **10** and **11** is diene **3**. Phenylselenenylation of **3** with diisopropyl amide and diphenyl diselenide gave a phenylseleno lactone [**9**] in 80% yield. Treatment of **9** with H_2O_2 gave **10** in quantitative yield. The structure of **10** shown in Scheme 1 is fully supported by its synthetic path and analysis of its ^{1}H-nmr spectrum.

Oxidation of **10** with *t*-butyl chromate in a mixture of HOAc and CCl_4 in the presence of Ac_2O gave α,β-unsaturated ketone **11** in 27% yield. The ^{1}H-nmr spectrum and [α]D value of **11** were identical with those of naturally occurring 2-oxodesoxyligustrin reported in the literature (27). Analogous oxidation of **3** with *t*-butyl chromate gave α,β-unsaturated ketone **12**, which is an intermediate of leucodin [**27**] (see Scheme 3).

We then examined the epoxidation of **4** and the stereochemistry of the products, leading to the syntheses of arborescin [**13**], 1,10-epiarborescin [**14**], and 11β,13-dihydroludartin [**16**]. Epoxidation of **4** with 1 molar equivalent of *m*-CPBA gave four possible monoepoxides, **13**, **14**, **15**, and **16** in 5%, 36%, 22%, and 8% yield, respectively (Scheme 2). Compounds **13** and **14**[2] were identical with arborescin and 1,10-epiarborescin, the structures of which we have already unambiguously determined (28).

The stereochemistry of the 3,4-epoxides, **15** and **16**, was deduced from the following observation in their ^{1}H-nmr spectra. The H-6 resonance of **15** appeared at 0.23 ppm lower field than that of **16** due to the deshielding effect of the syn-epoxide oxygen (39). An nOe experiment also supported the β and α orientation of the epoxide ring in **15** and **16**. Epoxide **16** was identical with naturally occurring 11β,13-dihydroludartin by comparison of the ^{1}H-nmr spectral data of **16** and those of 11β,13-dihydroludartin reported in the literature (30).

The starting material for the syntheses of 8-deoxy-11β,13-dihydrorupicolin B [**17**] and 8-deoxyrupicolin B [**19**] was 1,10-epiarborescin [**14**] [(11*S*)-1α,10α-epoxyguaia-3-eno-12,6α-lactone]. Treatment of **14** with aluminum isopropoxide in refluxing toluene gave allylic alcohol **17** in 50% yield as the sole product. Compound **17** was identical with naturally occurring 8-deoxy-11β,13-dihydrorupicolin B, which was isolated from *Artemisia adamsii* (31), by comparison of their ^{1}H-nmr spectral data.

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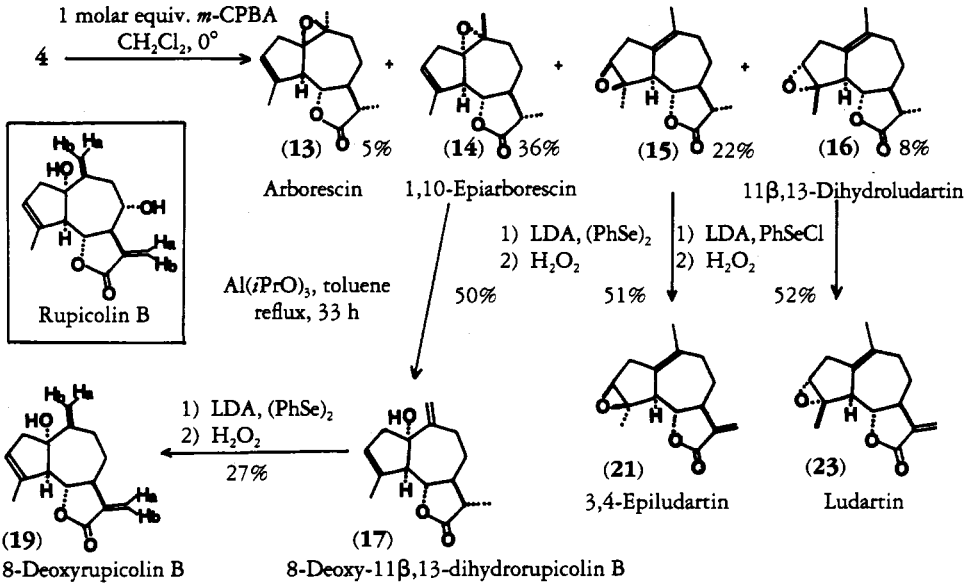
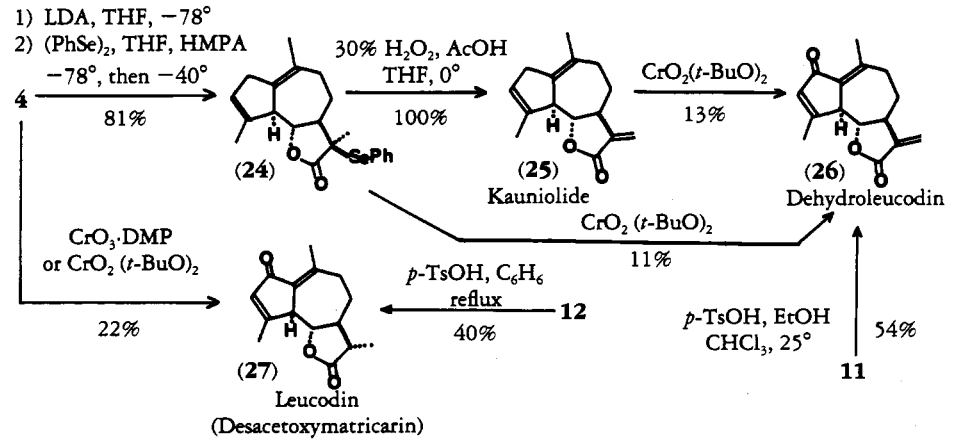
[2]Although Bohlmann *et al.* reported structure **14** as arborescin (31), their ^{1}H-nmr data of arborescin is in good agreement with those of **13**. Because we have already established unambiguously the stereochemistry of arborescin [**13**], their stereochemical assignment of 1,10-epoxide ring of arborescin is incorrect. Reference 2 (p. 494) also shows the wrong 1α,10α-form as arborescin.



SCHEME 2

Phenylselenenylation of **17** and successive treatment of the resulting phenylseleno lactone **18** with H_2O_2 gave 8-deoxyrupicolin B [**19**], which is the 8-deoxy derivative of naturally occurring rupicolin B (40). The structure of **19** was fully supported by the analysis of ir and ^{1}H-nmr spectra as well as by a consideration of the stereochemistry of the starting material, **14**. The ^{1}H-nmr spectral data of **19** and rupicolin B are shown in Table 1. The downfield shifts of the H-7 (−0.20 ppm), H_a-14 (−0.45 ppm), and H_a-13 (−1.11 ppm) resonances of rupicolin B compared with those of **19** could be explained reasonably by the influence of the α-hydroxyl group at C_8 of rupicolin B.

Ludartin [**23**] and its 11β,13-, and 11α,13-dihydro derivatives are constituents of *Artemisia carruthii* (30). The structure elucidation of these natural products was reported by Geissman and Griffin on the basis of an analysis of the ^{1}H-nmr spectra of a mixture of these compounds. Here we report the syntheses of ludartin [**23**] and 3,4-epiludartin [**21**] for the purpose of confirmation of their unambiguous structures.



SCHEME 3

TABLE 1. Comparison of ^{1}H-Nmr Spectral Data of 8-Deoxyrupicolin B (**19**) and Natural Rupicolin B.

Position	8-Deoxyrupicolin B	Rupicolin B
	^{1}H Nmr (pyridine-d_5) (J in Hz)	
	200 MHz	60 MHz[a]
CH_3-4	1.91 (s)	1.94 (s)
H-2	2.75 (d, J=15.7)	
	2.94 (d, J=15.7)	
H-5	3.11 (d, J=9.5)	
H-7	3.28 (m)	3.48
H-6	3.97 (dd, J=9.5, 9.5)	4.02 (dd, J=10, 9)
H-8		4.05 (m)
H_a-14	5.01 (s)	5.46 (d, J=1.8)
H_b-14	5.16 (s)	5.21 (d, J=1.8)
H_a-13	5.42 (d, J=3.0)	6.53 (d, J=3.1)
H_b-13	6.26 (d, J=3.5)	6.38 (d, J=3.3)
H-3	5.54 (br s)	5.55 (br s)

[a]Data taken from Yoshioka *et al.* (43).

Phenylselenenylation of **15** and oxidation of the resulting phenylseleno lactone [**20**] with H_2O_2 gave 3β,4β-epoxy-α-methylene-γ-lactone **21** in 51% overall yield. Compound **21** was completely different from ludartin by comparison of their ^{1}H-nmr spectra (30). By analogy, **16** gave the corresponding α-methylene-γ-lactone **23** in 52% overall yield in two steps. Compound **23**, with a 3α,4α-epoxide, was identical to naturally occurring ludartin by comparison of their ^{1}H-nmr spectra (30).

It was also determined that the major component of naturally occurring 11,13-dihydroludartin is 11β,12-dihydroisomer **16**, by comparison of their ^{1}H-nmr spectral data reported in the literature (30) with those of **15** and **16**.

We have also dealt with the syntheses of kauniolide [**25**] and dehydroleucodin [**26**]. Kauniolide is a constituent of *Kaunia arbuscularis* and structure **25** was suggested for this compound by Bohlmann *et al.* on the basis of an analysis of the ^{1}H-nmr spectrum of the mixture of kauniolide and 11β,13-dihydrokauniolide (25). Dehydroleucodin was isolated from *Lidkeekia pectinata* by Bohlmann and Zdero and the structure was proposed as **26** on the basis of spectral data (32).

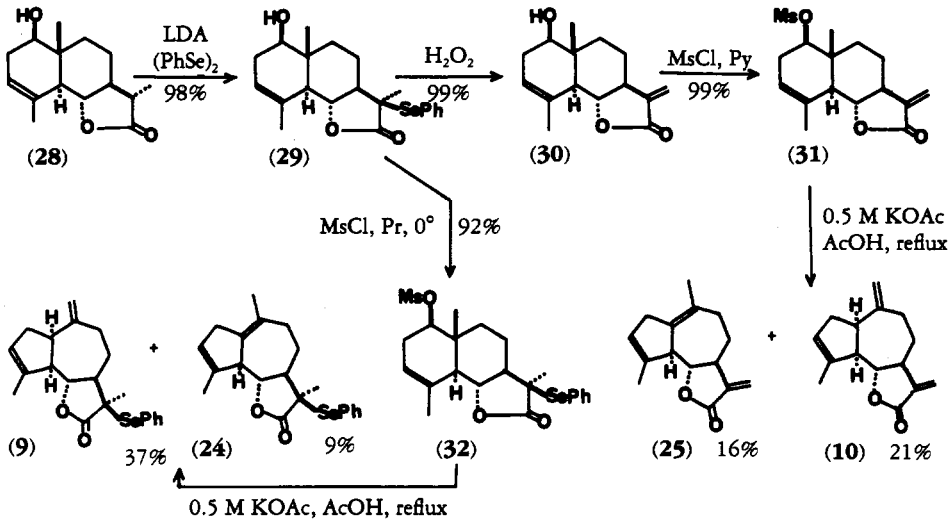
The starting material for the syntheses of **25** and **26** was **4**. Phenylselenenylation of **4** followed by treatment with H_2O_2 gave α-methylene-γ-lactone **25** in 81% yield (Scheme 3). The ^{1}H-nmr spectral data of **25** is in good agreement with those of kauniolide reported in the literature (25).

Oxidation of **25** with *t*-butyl chromate gave unsaturated ketone **26** in 13% yield. Oxidation of **24** in the same reaction conditions gave also **26** in 11% yield. The direct formation of **26** from **24** is rationalized by oxidation of the phenylselenyl group and successive syn-elimination of the resulting phenylselenoxide and subsequent oxidation of the C_1-methylene. Treatment of 2-oxodesoxyligustrin [**11**] with *p*-toluenesulfonic acid in a mixture of $CHCl_3$ and EtOH at 25° gave **26** in 54% yield. Compound **26** was identical with naturally occurring dehydroleucodin by comparison of its ^{1}H-nmr spectral data and [α]D value (32).

We have also synthesized leucodin (desacetoxymatricarin, **27**). Leucodin was isolated from *Artemisia tridentata* (33), *Artemisia leucodes* (41), and *Stevia pilosa* (34) and the synthesis of this compound from *O*-acetyl isophotosantonic lactone has already been reported (42).

Oxidation of **4** with CrO_3·3,5-dimethylpyrazole complex or *t*-butyl chromate gave unsaturated ketone **27** in 22% yield. Compound **27** was also prepared from **12** in 40% yield by treatment with *p*-toluenesulfonic acid in refluxing C_6H_6. The ^{1}H-nmr spectral data, [α]D value, and mp of **27** are in good agreement with those of leucodin reported in the literature (33,34,41).

Finally, we have investigated the syntheses of 1β-mesyloxyeudesm-3,11(13)-dieno-12,6α-lactone [**31**] and 1β-mesyloxy-11β-(phenylseleno)eudesm-3-eno-12,6α-lactone [**32**] as well as their solvolytic rearrangement. Phenylselenenylation of **28** with lithium diisopropyl amide and diphenyl diselenide gave phenylseleno lactone **29** in 98% yield. Treatment of **29** with H_2O_2 gave α-methylene-γ-lactone (santamarin, **30**) in 99% yield. Mesylation of **30** with mesyl chloride in pyridine gave mesylate **31** in 99% yield. Solvolytic rearrangement of **31** with 0.5 M potassium acetate in refluxing HOAc gave exo-olefin **10** and endo-olefin **25** in 21% and 16% yield, respectively (Scheme 4). Mesylation of phenylseleno lactone **29** gave the corresponding mesylate **32** in 92% yield. Solvolytic rearrangement of **32** with 0.5 M potassium acetate in refluxing HOAc gave exo-olefin **9** and endo-olefin **24** in 37% and 9% yield, respectively. The results are summarized in Table 2, which shows that the exo/endo ratio of products is remarkably influenced by the change of substituent at C_{11} of eudesmanolide.



SCHEME 4

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All mps 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 $CDCl_3$. Reactions were run under an atmosphere of N_2. THF was distilled from sodium benzophenone ketyl. $CHCl_3$ was dried over $CaCl_2$ and distilled. HMPA, diisopropylamine and pyridine were distilled from CaH_2. Hplc

TABLE 2. Ratio of Products in Solvolytic Rearrangements of Compounds **2**, **31**, and **32**.

Compound	Substituent(s) at C_{11}	Product Ratio (exo:endo)	Yield (%)
2	−Me, β-H	1:1.3	56
31	$=CH_2$	1:0.76	37
32	−Me, β-PhSe	1:0.24	46

was monitored with a refractive index detector. To describe hplc conditions, the column, solvent, flow rate (ml/min), and retention time (R_t) are designated in order. The column codes are as follows: A, 250×4 mm i.d. stainless column packed with 10 μm Si gel; B, 250×8 mm i.d. stainless column packed with 10 μm Si gel; C, 300×20 mm i.d. stainless column packed with 15–25 μm Si gel.

(11*S*)-1β-(MESYLOXY)EUDESM-3-ENO-12,6α-LACTONE [**2**].—To a stirred solution of **28** (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° 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 Si gel (40 g) and eluted with a mixture of hexane and EtOAc (7:3) to give spectroscopically pure **2** (795 mg, 97%) as a colorless oil: ir ν max ($CHCl_3$) 1769, 1170 cm^{-1}; ^1H nmr δ 1.00 (3H, s, CH_3-10), 1.23 (3H, d, J=7.0 Hz, CH_3-11), 1.83 (3H, br s, CH_3-4), 3.03 (3H, s, $-SO_2CH_3$), 3.95 (1H, dd, J=10.0 and 10.0 Hz, H-6), 4.69 (1H, dd, J=9.5 and 7.0 Hz, H-1), 5.34 (1H, br s, H-3); $[\alpha]^{25}D$ +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.

(11*S*)-GUAIA-3,10(14)-DIENO-12,6α-LACTONE (ISOCOSTUSLACTONE [**3**]) AND (11*S*)-GUAIA-1(10),3-DIENO-12,6α-LACTONE (11β,13-DIHYDROKAUNIOLIDE [**4**]).—A mixture of **2** (748 mg, 2.28 mmol) and 0.5 M KOAc in AcOH (35 ml) was stirred at reflux 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 Si 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].

Compound **3** (R_t 5.0 min, 129 mg, 24%): pale yellow oil; ir ($CHCl_3$) ν max 1760, 1640, 902 cm^{-1}; ^1H nmr δ 1.23 (3H, d, J=7.0 Hz, CH_3-11), 1.83 (3H, br s, CH_3-4), 2.21 (1H, dq, J=11.9 and 7.0 Hz, H-11), 2.79 (1H, dd, J=9.6 and 7.6 Hz, H-5), 3.10 (1H, ddd, J=7.6, 7.6, and 6.0 Hz, H-1), 3.99 (1H, dd, J=9.6 and 9.6 Hz, H-6), 4.83 (1H, br s, H-14), 4.88 (1H, br s, H-14), 5.53 (1H, m, H-3); $[\alpha]^{25}D$ +71.4° (c=0.64, $CHCl_3$); hreims *m/z* 232.1450 ($C_{15}H_{20}O_2$ requires 232.1463).

Compound **4** (R_t 4.4 min, 172 mg, 32%): colorless crystals; mp 80°; ir ν max ($CHCl_3$) 1762 cm^{-1}; ^1H nmr δ 1.21 (3H, d, J=7.0 Hz, CH_3-11), 1.71 (3H, d, J=1.0 Hz, CH_3-10), 1.90 (3H, br s, CH_3-4), 2.95 (2H, m, H-2), 3.29 (1H, d, J=10.0 Hz, H-5), 3.65 (1H, dd, J=10.0 and 10.0 Hz, H-6), 5.50 (1H, m, H-3); $[\alpha]^{25}D$ +8.9° (c=0.41, $CHCl_3$); *anal.* calcd for $C_{15}H_{20}O_2$, C 77.55, H 8.68; found C 77.03, H 8.65.

EPOXIDATION OF **3**. (11*S*)-3β,4β-EPOXY-10(14)-ENO-12,6α-LACTONE [**5**] AND (11*S*)-3α,4α-EPOXY-10(14)-ENO-12,6α-LACTONE [**6**].—A mixture of **3** (117 mg, 0.50 mmol) and 98% *m*-CPBA (88 mg, 0.50 mmol) in CH_2Cl_2 (2 ml) was allowed to stand at −20° for 2 h. The product was poured into a mixture of 0.2 M aqueous solution of KI (2.5 ml) and saturated aqueous NaCl (50 ml) and extracted with EtOAc (3×25 ml). The combined extracts were washed successively with 0.1 M aqueous $Na_2S_2O_3$ (20 ml), saturated aqueous $NaHCO_3$ (3×30 ml), and saturated aqueous NaCl (30 ml), dried (Na_2SO_4), and concentrated to give an oily crude product, which was purified by hplc [column; B, solvent; EtOAc-hexane (1:9), flow rate; 9 ml/min].

The first peak (R_t 2.8 min) gave recovered **3** (47 mg, 40%).

The second peak (R_t 10.4 min) gave **5** (19 mg, 15%) as colorless crystals: mp 106°; ir (KBr) ν max 1768, 1640 cm^{-1}; ^1H nmr δ 1.24 (3H, d, J=7.0 Hz, CH_3-11), 1.37 (1H, dd, J=13.0 and 4.5 Hz, H-8), 1.53 (3H, s, CH_3-4), 2.31 (1H, dd, J=10.0 and 9.5 Hz, H-5), 2.55 (1H, ddd, J=12.5, 4.5, and 3.5 Hz, H-9), 2.81 (1H, ddd, J=9.5, 9.5, and 2.5 Hz, H-1), 3.31 (1H, br s, $W_{h/2}$=3.0 Hz, H-3), 4.23 (1H, dd, J=10.0 and 10.0 Hz, H-6), 5.00 (2H, br s, H_2-14); $[\alpha]^{25}D$ +24.0° (c=0.21, $CHCl_3$); hreims *m/z* 248.1392 ($C_{15}H_{20}O_3$ requires 248.1413); *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 (R_t 14.6 min) gave **6** (44 mg, 35%) as colorless crystals: mp 91°; ir (KBr) ν max 1755, 1640 cm^{-1}; ^1H nmr δ 1.22 (3H, d, J=7.0 Hz, CH_3-11), 1.59 (3H, s, CH_3-4), 1.80 (1H, ddd, J=14.0, 10.5, and 1.5 Hz, H-2), 2.29 (1H, dd, J=10.5 and 8.5 Hz, H-5), 2.90 (1H, ddd, J=10.5, 8.5, and 7.5 Hz, H-1), 3.37 (1H, br s, $W_{h/2}$=3.0 Hz, H-3), 3.97 (1H, dd, J=10.5 and 9.5 Hz, H-6), 4.84 (1H, br s, $W_{h/2}$=4.0 Hz, H-14), 4.88 (1H, dd, J=1.5 and 1.5 Hz, H-14); $[\alpha]^{25}D$ +8.3° (c=0.71, $CHCl_3$); hreims *m/z* 248.1400 ($C_{15}H_{20}O_3$: requires 248.1413); *anal.* calcd for $C_{15}H_{20}O_3$, C 72.55, H 8.12; found C 72.38, H 8.04.

3α,4α-EPOXY-11β-(PHENYLSELENO)GUAIA-10(14)-ENO-12,6α-LACTONE [**7**].—A solution of **6** (8 mg, 32 μmol) in THF (0.6 ml) was slowly added to a cooled (−78°) solution of LDA prepared from diisopropylamine (14 μl, 96 μmol) and 1.59 M BuLi in hexane (60 μl, 96 μmol) in THF (0.4 ml). After 40 min, a solution of PhSeCl (19 mg, 96 μmol) containing HMPA (17 μl, 96 μmol) in THF (0.4 ml) was added at −78°. The reaction mixture was stirred at −78° for 40 min, warmed to −40° and stirred for an additional 1 h. The reaction was quenched by the addition of AcOH (6 μl). The mixture was poured into saturated aqueous NaCl (20 ml) and extracted with EtOAc (3×10 ml). The combined extracts were washed with saturated aqueous NaCl (2×20 ml), dried (Na_2SO_4), and concentrated to give an oily crude product, which was separated by hplc [column; A, solvent; EtOAc-hexane (2:8), 3.1 ml/min].

The peak (R_t 2.8 min) gave **7** (5 mg, 40%) as a pale yellow oil: ir ν max ($CHCl_3$) 1763, 1440 cm^{-1};

^{1}H nmr δ 1.53 (3H, s, CH_3-11), 1.58 (3H, s, CH_3-4), 2.47 (1H, dd, J=10.5 and 8.0 Hz, H-5), 2.85 (1H, br ddd, J=9.5, 8.5, and 8.0 Hz, H-1), 3.35 (1H, br s, H-3), 4.02 (1H, dd, J=10.5 and 9.5 Hz, H-6), 4.81 (1H, br s, H-14), 4.88 (1H, br s, H-14), 7.26–7.48 (3H, m), 7.56–7.66 (2H, m); $[\alpha]^{24}$D +106° (c=0.51, $CHCl_3$), hreims m/z 404.00857 ($C_{21}H_{24}O_3Se$ requires 404.0890).

ESTAFIATIN [**8**].—A solution of **7** (4 mg, 0.01 mmol) in THF (0.2 ml) containing AcOH (6 μl, 0.10 mmol) was treated at 0° with 30% H_2O_2 (30 μl, 0.24 mmol). After the addition was complete, stirring was continued for an additional 2 h at this temperature. The reaction mixture was poured into cold saturated aqueous $NaHCO_3$ (10 ml) and extracted with $CHCl_3$ (3×5 ml). The combined extracts were worked up as usual to give a crystalline crude material, which was purified by hplc [column; A, solvent; EtOAc-hexane (2:8), flow rate; 3.1 ml/min] to give **8** (R_t 4.6 min, 2 mg, 80%) as colorless crystals: mp 112°; ir ν max ($CHCl_3$) 1760, 1640 cm^{-1}; ^{1}H nmr δ 1.62 (3H, s, CH_3-4), 2.31 (1H, dd, J=11.0 and 8.0 Hz, H-5), 2.85 (1H, m, H-7), 2.98 (1H, ddd, J=10.5, 10.0, and 8.0 Hz, H-1), 3.38 (1H, s, H-3), 4.08 (1H, dd, J=11.0 and 8.6 Hz, H-6), 4.86 (1H, d, J=2.0 Hz, H-14), 4.95 (1H, br s, H-14), 5.48 (1H, d, J=3.0 Hz, H-13), 6.21 (1H, d, J=3.5 Hz, H-13); $[\alpha]^{25}$D −11° (c=0.10, $CHCl_3$); hreims m/z 246.1259 ($C_{15}H_{18}O_3$ requires 246.1256).

11β-(PHENYLSELENO)GUAIA-3,10(14)-DIENO-12,6α-LACTONE [**9**].—A solution of **3** (19.2 mg, 0.083 mmol) in THF (0.8 ml) was slowly added to a cooled (−78°) solution of LDA prepared from diisopropylamine (35 μl, 0.25 mmol) and 1.6 M BuLi in hexane (155 μl, 0.25 mmol) in THF (0.8 ml). After 1 h a solution of $(PhSe)_2$ (77 mg, 0.25 mmol) containing HMPA (44 μl, 0.25 mmol) in THF (0.8 ml) was added in 1 h. The reaction mixture was stirred at −78° for 1 h and then warmed to −40° where stirring was continued for an additional 1 h. The mixture was poured into 0.2 M aqueous HCl (15 ml) and extracted with EtOAc (3×10 ml). The combined extracts were worked up as usual to give an oily crude product (94 mg), which was separated by hplc [column; B, solvent; EtOAc-hexane (5:95), flow rate; 6.0 ml/min].

The major peak (R_t 9.0 min) gave **9** (25.6 mg, 80%) as a pale yellow oil: ir ν max ($CHCl_3$) 1762, 1642 cm^{-1}; ^{1}H nmr δ 1.54 (3H, s, CH_3-11), 1.82 (3H, br s, $W_{h/2}$=5.0 Hz, CH_3-4), 2.43 (2H, m, $W_{h/2}$=14.0 Hz, CH_2-2), 2.73 [1H, ddd, J=9.7, 7.5, and 1.3 Hz (irr. at 1.82), H-5], 3.11 (1H, ddd, J=7.5, 7.5, and 7.5 Hz, H-1), 4.15 (1H, dd, J=9.7, 9.7 Hz, H-6), 4.84 (1H, s, H-14), 4.93 (1H, s, H-14), 5.53 (1H, br s, $W_{h/2}$=6.5 Hz, H-3), 7.2–7.5 (3H, m), 7.60 (2H, dd, J=6.9 and 1.0 Hz).

GUAIA-3,10(14),11(13)-TRIENO-12,6α-LACTONE (ISODEHYDROCOSTUSLACTONE) [**10**].—A solution of **9** (105 mg, 0.27 mmol) in THF (1 ml) containing AcOH (46.5 μl, 0.81 mmol) was treated at 0° with H_2O_2 (179 μl, 1.75 mmol). After the addition was complete, stirring was continued for an additional 40 min at this temperature and at room temperature (26°) for 10 min. The reaction mixture was worked up as usual to give spectroscopically pure **10** (62 mg, 100%) as a pale yellow oil; ir ν max ($CHCl_3$) 1760, 1666, 1642 cm^{-1}; ^{1}H nmr δ 1.85 (3H, m, $W_{h/2}$=5.0 Hz, CH_3-4), 2.85 (2H, m, H-5, H-7), 3.14 (1H, ddd, J=7.5, 7.5, and 5.5 Hz, H-1), 4.05 (1H, dd, J=10.0 and 9.0 Hz, H-6), 4.88 (2H, m, $W_{h/2}$=6.0 Hz, H-14), 5.49 (1H, d, J=3.0 Hz, H-13), 5.55 (1H, m, H-3), 6.21 (1H, d, J=3.5 Hz, H-13); ^{13}C nmr δ 16.82 (q), 31.23 (t), 35.49 (t), 37.27 (t), 45.91 (d), 47.54 (d), 56.11 (d), 85.22 (d), 113.03 (t), 119.86 (t), 126.63 (d), 139.79 (s), 140.09 (s), 149.24 (s), 170.33 (s); hreims m/z 230.1310 ($C_{15}H_{18}O_2$, requires 230.1307).

2-OXOGUAIA-3,10(14),11(13)-TRIENO-12,6α-LACTONE [**11**].—Into a stirred solution of **10** (17 mg, 0.075 mmol) in a mixture of CCl_4 (0.68 ml), Ac_2O (52 μl, 0.55 mmol) and AcOH (1.0 ml), was added 0.48 M t-butyl chromate (0.29 ml, 0.14 mmol) in CCl_4. The reaction mixture was stirred for 3 h at room temperature and an aqueous solution of oxalic acid (13 mg, 0.14 mmol/0.68 ml H_2O) was added. After the solution was stirred for 1 h, the mixture was worked up as usual to give a crude product. This material was passed through a column (Si gel; 0.5 g), eluted with a mixture of EtOAc and hexane (3:7) and the eluent was concentrated and purified by hplc [column; B, solvent; EtOAc-hexane (3:7), flow rate; 6.0 ml/min]. The major peak (R_t 16.4 min) gave **11** (5.0 mg, 27%) as colorless crystals: mp 150°; ir ν max ($CHCl_3$) 3008, 1772, 1702, 1624 cm^{-1}; ^{1}H nmr δ 2.32 (3H, s, CH_3-4), 3.18 (1H, dd, J=10.0 and 7.7 Hz, H-5), 3.32 (1H, d, J=7.7 Hz, H-1), 4.12 (1H, dd, J=10.0 and 8.5 Hz, H-6), 4.83 (1H, br s, $W_{h/2}$=2.5 Hz, H-14), 5.10 (1H, br s, $W_{h/2}$=2.5 Hz, H-14), 5.57 (1H, d, J=3.1 Hz, H-13), 6.14 (1H, m, $W_{h/2}$=4.5 Hz, H-3), 6.28 (1H, d, J=3.5 Hz, H-13); ^{13}C nmr δ 19.93 (q), 31.16 (t), 36.48 (t), 46.11 (d), 53.19 (d), 56.13 (d), 83.30 (d), 117.29 (t), 121.21 (t), 132.60 (d), 138.36 (s), 144.10 (s), 169.42 (s), 177.72 (s), 206.65 (s); hreims m/z 244.1099 ($C_{15}H_{16}O_3$ requires 244.1099); $[\alpha]^{22}\ \underset{589,\ 578,\ 546,\ 436}{+216°,\ +223°,\ +258°,\ +460°}$ (nm) (c=0.18, $CHCl_3$).

(11*S*)-2-OXOGUAIA-3,10(14)-DIENO-12,6α-LACTONE [**12**].—Into a solution of **3** (54 mg, 0.23 mmol) in a mixture of CCl_4 (2.2 ml), Ac_2O (0.16 ml, 1.66 mmol) and AcOH (3.30 ml), was added 1.79 M t-butyl chromate (0.90 ml, 1.61 mmol) in CCl_4 under stirring. The solution was stirred for 3 h at room temperature and aqueous oxalic acid (38 mg, 0.42 mmol/2.1 ml H_2O) was added. The solution was stirred for 1 h and worked up as usual to give a crude product, which was passed through a short column of Si gel (2 g). The eluent was then separated with hplc [column; B, solvent; EtOAc-hexane (3:7), flow rate; 6.0 ml/min]. The

most prominent peak (R_f 9.9 min) gave **12** (19.4 mg, 34%) as colorless crystals: mp 131°; ir ν max ($CHCl_3$) 1774, 1702, 1622 cm^{-1}; ^1H nmr δ 1.26 (3H, d, J=7.0 Hz, CH_3-11), 2.28 (3H, s, CH_3-4), 3.07 (1H, br dd, J=10.0 and 7.5 Hz, H-5), 3.25 (1H, br d, J=7.5 Hz, H-1), 4.08 (1H, dd, J=10.0 and 10.0 Hz, H-6), 4.79 (1H, s, H-14), 5.06 (1H, s, H-14), 6.12 (1H, m, H-3); ^{13}C nmr δ 13.31 (q), 19.85 (q), 32.80 (t), 37.65 (t), 41.43 (d), 50.85 (d), 53.27 (d), 55.58 (d), 83.12 (d), 116.38 (t), 132.65 (d), 144.62 (s), 177.76 (s), 177.93 (s), 206.65 (s); hreims *m/z* 246.1258 ($C_{15}H_{18}O_3$ requires 246.1256).

Arborescin [**13**].— Mp 140°; ir ν max ($CHCl_3$) 1767 cm^{-1}; ^1H nmr δ 1.19 (3H, d, J=7.0 Hz, CH_3-11), 1.35 (3H, s, CH_3-10), 1.93 (3H, m, CH_3-4), 2.82 (1H, dm, J=9.5 Hz, H-5), 4.01 (1H, dd, J=10.5 and 9.5 Hz, H-6), 5.56 (1H, m, H-3); ^{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/z* 248.1401 ($C_{15}H_{20}O_3$ requires 248.1413).

1,10-Epiarborescin [**14**].— Mp 108°; ir ν max ($CHCl_3$) 1770 cm^{-1}; ^1H nmr δ 1.22 (3H, d, J=7.0 Hz, CH_3-11), 1.33 (3H, s, CH_3-10), 1.94 (3H, d, J=1.0 Hz, CH_3-4), 2.54 (1H, d, J=11.0 Hz, H-5), 2.86 (1H, br d, J=18.0 Hz, H-2), 3.78 (1H, dd, J=11.0 and 10.0 Hz, H-6), 5.57 (1H, m, H-3); ^{13}C nmr δ 12.40 (q, C-13), 17.88 (q, C-15), 20.63 (q, C-14), 25.10 (t, C-8), 37.63 (t, C-9), 38.21 (t, C-2), 41.40 (d, C-11), 55.27 (d, C-7), 56.75 (d, C-5), 62.61 (s, C-10), 71.95 (s, C-1), 84.40 (d, C-6), 124.30 (d, C-3), 141.07 (s, C-4), 177.94 (s, C-12); $[\alpha]^{25}D$ +36.5° (c=0.65, $CHCl_3$); hreims *m/z* 248.1402 ($C_{15}H_{20}O_3$ requires 248.1413); *anal.* calcd for $C_{15}H_{20}O_3$, C 72.55, H 8.12; found: C 72.29, H 8.19.

(11S)-3β,4β-Epoxyguaia-1(10)-eno-12,6α-lactone [**15**].— Mp 102°; ir ν max ($CHCl_3$) 1768 cm^{-1}; ^1H nmr δ 1.21 (3H, d, J=7.0 Hz, CH_3-11), 1.62 (3H, s, CH_3-4), 1.66 (3H, d, J=1.0 Hz, CH_3-10), 2.75 (1H, d, J=10.0 Hz, H-5), 3.31 (1H, d, J=2.0 Hz, H-3), 3.88 (1H, dd, J=10.0 and 10.0 Hz, H-6); ^{13}C nmr 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, $CHCl_3$); hreims *m/z* 248.1405 ($C_{15}H_{20}O_3$ requires 248.1413); *anal.* calcd for $C_{15}H_{20}O_3$, C 72.55, H 8.12; found C 72.29, H 8.18.

(11S)-3α,4α-Epoxyguaia-1(10)-eno-12,6α-lactone [**16**].—Colorless oil; ir ν max ($CHCl_3$) 1769 cm^{-1}; ^1H nmr δ 1.22 (3H, d, J=7.0 Hz, CH_3-11), 1.64 (3H, s, CH_3-4), 1.67 (3H, d, J=1.0 Hz, CH_3-10), 3.00 (1H, br d, J=10.5 Hz, H-5), 3.38 (1H, s, H-3), 3.65 (1H, dd, J=10.5 and 9.5 Hz, H-6); ^{13}C nmr 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/z* 248.1405 ($C_{15}H_{20}O_3$ requires 248.1413).

(11*S*)-1α-HYDROXYGUAIA-3,10(14)-DIENO-12,6α-LACTONE [**17**].—A solution of **14** (10 mg, 0.04 mmol) in toluene (2 ml) was refluxed with Al(*i*-PrO)$_3$ (41 mg, 0.20 mmol) for 13 h. Additional Al(*i*-PrO)$_3$ (82 mg, 0.40 mmol) was added and reflux was continued for 20 h. The solvent was removed under reduced pressure and the residue was stirred with a mixture of EtOAc (5 ml) and 2 M HCl (5 ml) until the residue was dissolved. The organic layer was separated and the aqueous layer was poured into saturated NaCl (5 ml). The aqueous layer was further extracted with EtOAc (3×10 ml). The combined organic layer was worked up as usual to give an oily material, which was purified by hplc [column; A, solvent; EtOAc-hexane (3:7), flow rate; 3.0 ml/min].

Purification of an hplc zone (R_f 4.0 min) gave **17** (5.0 mg, 50%) as a pale yellow oil: ir ν max ($CHCl_3$) 3600, 1770, 1640 cm^{-1}; ^1H nmr δ 1.23 (3H, d, J=6.8 Hz, CH_3-11), 1.89 (3H, m, CH_3-4), ca. 2.0 (1H, H-7), ca. 2.2 (1H, H-11), ca. 2.4 (1H, H-2), 2.67 (1H, d, J=10.0 Hz, H-5), 2.95 (1H, J=17.0 Hz, H-2), 3.81 (1H, dd, J=10.0 and 9.3 Hz, H-6), 5.03 (1H, d, J=1.0 Hz, H-14), 5.12 (1H, s, H-14), 5.52 (1H, br s, H-3); $[\alpha]^{25}D$ +154° (c=0.27, $CHCl_3$) hreims *m/z* 248.1395 ($C_{15}H_{20}O_3$; requires 248.1413).

1α-HYDROXY-11β-(PHENYLSELENO)GUAIA-3,10(14)-DIENO-12,6α-LACTONE [**18**].—Phenylselenylation of **17** (6 mg, 0.024 mmol) with $(PhSe)_2$ (19 mg, 0.06 mmol), LDA (0.06 mmol), and HMPA (10 μl, 0.06 mmol) in THF (0.8 ml) by the method described above and purification of crude product by hplc [column; A, solvent; EtOAc-hexane (3:7), flow rate 3.0 ml/min] gave **18** (R_f 4.4 min, 4 mg, 41%) as a pale yellow oil: ir ν max ($CHCl_3$) 3600, 1760, 990 cm^{-1}; ^1H nmr δ 1.55 (3H, s, CH_3-11), 1.62 (1H, m, H-8), 1.90 (3H, br d, J=1.8 Hz, CH_3-4), 2.15 (1H, m, H-7), 2.40 (1H, br d, J=16.0 Hz, H-2), 2.45 (2H, m, H-9), 2.62 (1H, d, J=10.0 Hz, H-5), 2.97 (1H, br d, J=16.0 Hz, H-2), 4.00 (1H, dd, J=10.0 and 10.0 Hz, H-6), 5.09 (1H, s, H-14), 5.13 (1H, s, H-14), 5.53 (1H, br s, H-3), 7.28–7.45 (3H, m, aromatic H), 7.54–7.63 (2H, m, aromatic H); $[\alpha]^{25}D$ +228° (c=0.43, $CHCl_3$); hreims *m/z* 404.0858 ($C_{21}H_{24}O_3Se$ requires 404.0890).

1α-HYDROXYGUAIA-3,10(14),11(13)-TRIENO-12,6α-LACTONE (8-DEOXYRUPICOLIN B) [**19**].—A solution of **18** (3.6 mg, 9 μmol) in THF (0.1 ml) containing HOAc (3 μl, 52 μmol) was treated at 0° with 30% H_2O_2 (9 μl, 88 μmol). After the addition was complete, stirring was continued for an additional 1 h at this temperature. The reaction mixture was treated in the usual manner to give a colorless oil (2 mg), which was purified by hplc [column; A, solvent; EtOAc-hexane (3:7), flow rate; 3.0 ml/min] to give **19** (R_f 3.8 min; 1.5 mg, 68%) as colorless crystals: mp 102°; ir ν max ($CHCl_3$) 3600, 1762, 1670, 1640 cm^{-1}; ^1H

nmr δ 1.91 (3H, br s, CH_3-4), 2.40 (1H, br d, J=16.0 Hz, H-2), 2.75 (1H, br d, J=10.2 Hz, H-5), 2.93 (1H, br d, J=16.0 Hz, H-2), 3.05 (1H, m, H-7), 3.88 (1H, dd, J=10.2 and 9.1 Hz, H-6), 5.05 (1H, s, H-14), 5.14 (1H, s, H-14), 5.47 (1H, d, J=3.1 Hz, H-13), 5.53 (1H, br s, H-3), 6.19 (1H, d, J=3.5 Hz, H-13); ^{1}H nmr (pyridine-d_5) δ 1.91 (3H, s, CH_3-4), 2.75 (1H, d, J=15.7 Hz, H-2), 2.94 (1H, d, J=15.7 Hz, H-2), 3.11 (1H, d, J=9.5 Hz, H-5), 3.28 (1H, m, $W_{h/2}$=20 Hz, H-7), 3.97 (1H, dd, J=9.5 and 9.5 Hz, H-6), 5.01 (1H, s, H-14), 5.16 (1H, s, H-14), 5.42 (1H, d, J=3.0 Hz, H-13), 5.54 (1H, br s, $W_{h/2}$=6.0 Hz, H-3), 6.26 (1H, d, J=3.5 Hz, H-13); $[\alpha]^{25}D$ +161° (c=0.32, $CHCl_3$); hreims m/z 246.1298 ($C_{15}H_{18}O_3$ requires 246.1256).

3β,4β-EPOXY-11β-(PHENYLSELENO)GUAIA-1(10)-ENO-12,6α-LACTONE [**20**].—Phenylselenenylation of **15** (20 mg, 0.081 mmol) with $(PhSe)_2$ (63 mg, 0.20 mmol) and LDA (0.20 mmol) in THF (1.2 ml) containing HMPA (35 μl, 0.20 mmol) by the method described above and purification of crude product by hplc [column; A, solvent; EtOAc-hexane 2:8, flow rate; 3.0 ml/min], gave **20** (R_t 3.4 min; 20 mg, 62%) as colorless crystals: mp 164°; ir ν max ($CHCl_3$) 1771 cm^{-1}; ^{1}H nmr δ 1.53 (3H, s, CH_3-11), 1.64 (3H, s, CH_3-4), 1.68 (3H, d, J=1.0 Hz, CH_3-10), 2.75 (1H, br d, J=10.0 Hz, H-5), 3.33 (1H, d, J=2.0 Hz, H-3), 4.37 (1H, dd, J=10.0 and 10.0 Hz, H-6), 7.26–7.46 (3H, m, aromatic H), 7.58–7.66 (2H, m, aromatic H); $[\alpha]^{25}D$ +65.3° (c=1.84, $CHCl_3$); hreims m/z 404.0903 ($C_{21}H_{24}O_3Se$ requires 404.0890).

3β,4β-EPOXYGUAIA-1(10),11(13)-DIENO-12,6α-LACTONE [**21**].—A solution of **20** (18 mg, 0.045 mmol) in THF (0.2 ml) containing AcOH (7 μl, 0.12 mmol) was treated at 0° with 30% H_2O_2 (32 μl, 0.313 mmol). After the addition was complete, stirring was continued for 30 min at this temperature. The reaction mixture was treated in the usual manner to give a colorless oil (10 mg), which was purified by hplc [column; A, solvent; EtOAc-hexane (2:8), flow rate 3.0 ml/min] to give **21** (R_t 4.0 min; 9 mg, 82%) as a pale yellow oil; ir ν max ($CHCl_3$) 1761 cm^{-1}; ^{1}H nmr δ 1.66 (3H, s, CH_3-4), 1.68 (3H, br s, CH_3-10), 2.49 (1H, br d, J=17.5 Hz, H-2), 2.69 (1H, br d, J=17.5 Hz, H-2), 2.78 (1H, m, H-7), 2.87 (1H, br d, J=10.0 Hz, H-5), 3.32 (1H, d, J=2.0 Hz, H-3), 3.87 (1H, dd, J=10.0 and 10.0 Hz, H-6), 5.41 (1H, d, J=3.1 Hz, H-13), 6.15 (1H, d, J=3.5 Hz, H-13); $[\alpha]^{25}D$ −14.8° (c=0.80, $CHCl_3$); hreims m/z 246.1247 ($C_{15}H_{18}O_3$ requires 246.1256).

3α,4α-EPOXY-11β-(PHENYLSELENO)GUAIA-1(10)-ENO-12,6α-LACTONE [**22**].—Phenylselenylation of **16** (10 mg, 0.04 mmol) with PhSeCl (38 mg, 0.20 mmol) and LDA (0.20 mmol) in THF (1.2 ml) containing HMPA (35 μl, 0.20 mmol) by the method described above and separation of the crude product by hplc [column; A, solvent; EtOAc-hexane (2:8), flow rate; 3.0 ml/min] gave **22** (R_t 3.3 min; 10.6 mg, 65%) as pale yellow crystals: mp 125°; ir ν max ($CHCl_3$) 1764 cm^{-1}; ^{1}H nmr δ 1.52 (3H, s, CH_3-11), 1.65 (3H, s, CH_3-4), 1.72 (3H, d, J=1.0 Hz, CH_3-10), 2.47 (1H, br d, J=17.0 Hz, H-2), 2.73 (1H, br d, J=17.0 Hz, H-2), 2.97 (1H, br d, J=11.0 Hz, H-5), 3.40 (1H, br s, H-3), 4.11 (1H, dd, J=11.0 and 9.5 Hz, H-6), 7.28–7.44 (3H, m, aromatic H), 7.56–7.64 (2H, m, aromatic H); $[\alpha]^{25}D$ +72.6° (c=0.31, $CHCl_3$); hreims 404.0862 ($C_{21}H_{24}O_3Se$ requires 404.0890).

3α,4α-EPOXYGUAIA-1(10),11(13)-DIENO-12,6α-LACTONE (LUDARTIN [**23**]).—A solution of **22** (8.2 mg, 0.02 mmol), in THF (0.2 ml) containing AcOH (8 μl, 0.14 mmol) was treated at 0° with 30% H_2O_2 (41 μl, 0.40 mmol). After the addition was complete, stirring was continued for 30 min at this temperature. The reaction mixture was treated in the usual manner to give colorless crystals, which were purified by hplc [column; A, solvent; EtOAc-hexane (2:8), flow rate; 3.0 ml/min], to give **23** (R_t; 4.48 min, 4.0 mg, 80%) as colorless crystals: mp 116°; ir ν max ($CHCl_3$) 1760 cm^{-1}; ^{1}H nmr (600 MHz) δ 1.30 (1H, ddd, J=12.0, 12.0 and 12.0 Hz, H_{ax}-8), 1.68 (3H, s, CH_3-4), 1.70 (3H, s, CH_3-10), 2.45 (1H, br d, J=17.6 Hz, H-2), 2.72 (1H, d, J=17.6 Hz, H-2), 2.78 (1H, m, H-7), 3.10 (1H, d, J=10.0 Hz, H-5), 3.40 (1H, s, H-3), 3.65 (1H, dd, J=10.0 and 10.0 Hz, H-6), 5.39 (1H, d, J=3.1 Hz, H-13), 6.13 (1H, d, J=3.2 Hz, H-13); $[\alpha]^{25}D$ +49° (c=0.023, $CHCl_3$); hreims m/z 246.1272 ($C_{15}H_{18}O_3$ requires 246.1256).

11β-(PHENYLSELENO)GUAIA-1(10),3-DIENO-12,6α-LACTONE [**24**].—Phenylselenylation of **4** (114.5 mg, 0.493 mmol) with $(PhSe)_2$ (246 mg, 0.788 mmol) and LDA (0.788 mmol) in THF (2 ml) containing HMPA (137 μl, 0.788 mmol) by the method described above and separation of crude product by hplc [column; B, solvent; EtOAc-hexane (5:95), flow rate; 6.0 ml/min] gave **24** (R_t 5.6 min; 155 mg, 81%) as pale yellow crystals: mp 144°; ir ν max ($CHCl_3$) 3056, 1758, 910 cm^{-1}; ^{1}H nmr δ 1.53 (3H, s, CH_3-11), 1.75 (3H, br d, J=1.5 Hz, CH_3-10), 1.95 (3H, br t, J=1.0 Hz, CH_3-4), 2.99 (2H, br s, $W_{h/2}$=8.0 Hz, H-2), 3.28 (1H, br d, J=10.0 Hz, H-5), 4.13 (1H, dd, J=10.0 and 10.0 Hz, H-6), 5.55 (1H, br t, $W_{h/2}$=5.0 Hz, H-3), 7.26–7.47 (3H, m, aromatic H), 7.56–7.65 (2H, m, aromatic H).

GUAIA-1(10),3,11(13)-TRIENO-12,6α-LACTONE (KAUNIOLIDE [**25**]).—A solution of **24** (103.6 mg, 0.267 mmol) in THF (2 ml) containing AcOH (46 μl, 0.80 mmol) was treated at 0° with 30% H_2O_2 (175 μl, 1.71 mmol). After the addition was complete, stirring was continued for 40 min at 0° and then at 17° for 10 min. The reaction mixture was treated in the usual manner to give a colorless oil, which was purified

by hplc [column; B, solvent; EtOAc-hexane (5:95), flow rate; 6.0 ml/min] to give **25** (*R*, 7.0 min; 61.5 mg, 100%) as an unstable colorless oil; ir ν max ($CHCl_3$) 3028, 1770, 1670 cm^{-1}; ^1H nmr δ 1.72 (3H, d, J=1.1 Hz, CH_3-10), 1.94 (3H, br dd, J=2.4 and 2.4 Hz, CH_3-4), 2.79 (1H, m, H-7), 2.97 (2H, br s, $W_{h/2}$=7.0 Hz, H-2), 3.40 (1H, br d, J=10.0 Hz, H-5), 3.64 (1H, dd, J=10.0 and 10.0 Hz, H-6), 5.39 (1H, d, J=3.2 Hz, H-13), 5.53 (1H, br t, J=2.3 Hz, H-3), 6.12 (1H, d, J=3.3 Hz, H-13); ^{13}C nmr δ 17.85 (q), 23.29 (q), 26.00 (t), 34.03 (t), 37.90 (t), 53.24 (d), 56.32 (d), 85.51 (d), 117.67 (t), 126.16 (d), 131.28 (s), 135.59 (s), 139.99 (s), 140.68 (s), 170.21 (s); $[\alpha]^{24}D$ +35° (c=0.86, $CHCl_3$).

2-OXOGUAIA-3,1(10),11(13)-TRIENO-12,6α-LACTONE (DEHYDROLEUCODIN [**26**]).—Into a stirred solution of **25** (61.5 mg, 0.267 mmol) in a mixture of CCl_4 (2.6 ml), Ac_2O (0.24 ml, 2.55 mmol), and AcOH (4.0 ml) was added 2.37 M solution of *t*-butyl chromate, (0.78 ml, 1.85 mmol) in CCl_4. The reaction mixture was stirred for 10 h at room temperature and an aqueous solution of oxalic acid dihydrate (58 mg, 0.46 mmol/3 ml H_2O) was added. After the solution was stirred for 40 min, the mixture was worked up as usual to give an oily crude mixture, which was separated by hplc [column; B, solvent; EtOAc-hexane (3:7), flow rate; 6 ml] to give spectroscopically pure **26** (*R*, 8.8 min; 8.5 mg, 13%). This was recrystallized from a mixture of $CHCl_3$ and Et_2O to give colorless prisms: mp 130°; ir ν max ($CHCl_3$) 3008, 1770, 1686, 1640, 1622 cm^{-1}; ^1H nmr δ 2.33 (3H, br t, J=1.3 Hz, CH_3-4), 2.45 (3H, br s, $W_{h/2}$=2.0 Hz, CH_3-10), 2.89 (1H, m, H-7), 3.51 (1H, br d, J=9.5 Hz, $W_{h/2}$=3.5 Hz, H-5), 3.63 (1H, dd, J=9.9 and 9.9 Hz, H-6), 5.47 (1H, d, J=3.2 Hz, H-13), 6.18 (1H, m, H-3), 6.19 (1H, d, J=3.2 Hz, H-13); ^{13}C nmr δ 19.83 (q), 21.82 (q), 24.43 (t), 37.25 (t), 52.94 (d), 53.08 (d), 84.38 (d), 118.89 (t), 131.96 (s), 135.71 (d), 138.55 (s), 151.86 (s), 169.14 (s), 169.49 (s), 195.81 (s); $[\alpha]^{22}\ \frac{+65.4°,\ +68.4°,\ +77.6°,\ +129.3°}{589\quad 578\quad 546\quad 436}$ (nm) (c=0.34, $CHCl_3$).

DIRECT CONVERSION OF **24** TO DEHYDROLEUCODIN [**26**].—Oxidation of **24** (28 mg, 0.072 mmol) with 1.79 M *t*-butyl chromate (0.28 ml, 0.50 mmol) in CCl_4 by the method described above and purification by hplc [column; A, solvent; EtOAc-hexane (3:7), flow rate; 3.0 ml/min] gave **26** (2.0 mg, 11%).

CONVERSION OF 2-OXODEOXYLIGUSTIN [**11**] TO DEHYDROLEUCODIN [**26**].—Into a solution of **11** (11.4 mg, 0.47 mmol) in $CHCl_3$ (2 ml) was added a solution of *p*-toluenesulfonic acid monohydrate (2 ml) (8.9 mg, 0.047 mmol) in EtOH (0.1 ml). The mixture was stirred at 25° for 28 h and poured into $CHCl_3$ (10 ml). The mixture was worked up as usual to give a crude oily product (11 mg), which was passed through a column [Si gel (70–230 mesh) 0.8 g, 4×0.7 cm i.d. column, solvent; EtOAc-hexane (3:7)]. The eluent was further purified by hplc [column; B, solvent; EtOAc-hexane (3:7), flow rate; 6.0 ml/min] to give **26** (*R*, 8.8 min, 6.2 mg, 54%).

LEUCODIN (DESACETOXYMATRICARIN [**27**]).—Oxidation of **4** (68 mg, 0.29 mmol) with a 1.80 M solution of *t*-butyl chromate (1.28 ml, 2.30 mmol) in CCl_4 by the method described above gave an oily crude product (53 mg), which was passed through a column [Si gel (70–230 mesh) 2.7 g, solvent; EtOAc-hexane (3:7)]. The eluent was further purified by hplc [column; B, solvent; EtOAc-hexane (3:7), flow rate; 6 ml/min] to give spectroscopically pure **27** (*R*, 8.8 min; 16 mg, 22%) as a crystalline material, which was recrystallized from a mixture of $CHCl_3$ and Et_2O to give prisms: mp 206°; ir ν max (KBr) 1782, 1686, 1640, 1620 cm^{-1}; ^1H nmr δ 1.26 (3H, J=7.0 Hz, CH_3-11), 1.98 (1H, m, H-7), 2.22 (1H, s, H-11), 2.29 (3H, s, CH_3-4), 2.43 (3H, m, CH_3-10), 3.40 (1H, br d, J=10.0 Hz, H-5), 3.62 (1H, dd, J=10.0 and 9.5 Hz, H-6), 6.16 (1H, m, H-3); ^{13}C nmr δ 12.30 (q), 19.81 (q), 21.63 (q), 26.00 (t), 37.58 (t), 41.15 (d), 52.59 (d), 56.40 (d), 84.22 (d), 131.88 (s), 135.54 (d), 152.12 (s), 169.94 (s), 177.53 (s), 195.90 (s); $[\alpha]^{25}D$ +51° (c=0.60, $CHCl_3$); hreims m/z 246.1253 ($C_{15}H_{18}O_3$ requires 246.1256).

CONVERSION OF **12** TO DESACETOXYMATRICARIN [**27**].—A mixture of **12** (10 mg, 0.041 mmol) and *p*-toluenesulfonic acid monohydrate (6 mg, 0.0352 mmol) in C_6H_6 (2 ml) was refluxed for 5 h, and worked up as usual to give an oily crude product (8 mg), which was purified by hplc [column; A, solvent; EtOAc-hexane (3:7); flow rate; 3.0 ml] to give **27** (*R*, 5.7 min; 4 mg, 40%).

PREPARATION OF LEUCODIN [**27**] FROM **4** BY OXIDATION WITH CrO_3·DMP COMPLEX.—Chromic anhydride (862 mg, 8.62 mmol) was added to a mixture of CH_2Cl_2 (4.8 ml) and 3,5-dimethylpyrazole (829 mg, 8.62 mmol) at −20° and the mixture was stirred for 15 min. Then **4** (89 mg, 0.38 mmol) dissolved in CH_2Cl_2 (4.8 ml) was added slowly, and the mixture was stirred at −10° for 2 h and poured into 1 M aqueous NaOH (10.8 ml). The mixture was stirred at 0° for 1 h and extracted with CH_2Cl_2 (3×30 ml). The combined extracts were worked up as usual to give the crude product, which was passed through a short column of Si gel (EtOAc-hexane 3:7). The eluent was further purified by hplc [column; B, solvent; EtOAc-hexane 3:7, flow rate (6 ml)] to give **27** (*R*, 8.8 min; 21 mg, 22%).

(11*S*)-1β-HYDROXY-11β-(PHENYLSELENO)EUDESM-3-ENO-12,6α-LACTONE [**29**].—Phenylselenenylation of **28** (300 mg, 1.20 mmol) with $(PhSe)_2$ (988 mg, 3.17 mmol) and LDA (3.14 mmol) in

THF (2 ml) containing HMPA (553 μl, 3.7 mmol) by the method described above and purification of the crude product by hplc [column; C, solvent; EtOAc-hexane (2:8), flow rate; 17 ml/min] gave **29** (*R*, 33 min, 478 mg, 98%) as crystalline material: mp 87°; ir ν max ($CHCl_3$) 3528, 1774 cm^{-1}; ^1H nmr δ 0.89 (3H, s, CH_3-10), 1.54 (3H, s, CH_3-11), 1.79 (3H, s, CH_3-4), 3.63 (1H, dd, *J*=10.0 and 7.0 Hz, H-1), 4.36 (1H, dd, *J*=10.0 and 10.0 Hz, H-6), 5.33 (1H, br s, H-3), 7.24–7.48 (3H, m, aromatic H), 7.64 (2H, d, *J*=8.5 Hz, aromatic H).

1β-HYDROXYEUDESM-3,11(13)-DIENO-12,6α-LACTONE [**30**].—Compound **29** (250 mg, 0.617 mmol) was treated with 30% H_2O_2 (425 μl, 4.16 mmol) in the usual manner to give **30** (152 mg, 99%) as colorless crystals: mp 136°; ir ν max ($CHCl_3$) 3544, 1774 cm^{-1}; ^1H nmr δ 0.88 (3H, s, CH_3-10), 1.85 (3H, s, CH_3-4), 3.68 (1H, dd, *J*=10.0 and 6.5, H-1), 3.95 (1H, dd, *J*=11.0 and 11.0 Hz, H-6), 5.35 (1H, br s, H-3), 5.41 (1H, d, *J*=3.0 Hz, H-13), 6.08 (1H, d, *J*=3.0 Hz, H-13); hreims *m/z* 248.1410 ($C_{15}H_{20}O_3$ requires 248.1412).

1β-MESYLOXYEUDESM-3,11(13)-DIENO-12,6α-LACTONE [**31**].—To a stirred solution of **30** (114 mg, 0.46 mmol) in pyridine (4.0 ml) was added methanesulfonyl chloride (160 μl, 2.05 mmol). The mixture was allowed to stand at 0° for 20 h, poured into saturated aqueous NaCl (27 ml), and stirred for 30 min. The mixture was worked up as usual to give an oil. This was then chromatographed over Si gel (7 g) and eluted with a mixture of hexane and EtOAc (7:3) to give **31** (148 mg, 99%) as colorless crystals: mp 42°; ir ν max ($CHCl_3$) 1772, 1682 cm^{-1}; ^1H nmr δ 0.99 (3H, s, CH_3-10), 1.85 (3H, s, CH_3-4), 3.04 (3H, s, $-SO_2CH_3$), 3.93 (1H, dd, *J*=11.0 and 11.0 Hz, H-6), 4.72 (1H, dd, *J*=9.5 and 7.0 Hz, H-1), 5.35 (1H, br s, $W_{h/2}$=11.0 Hz, H-3), 5.43 (1H, d, *J*=3.0 Hz, H-13), 6.10 (1H, d, *J*=3.5 Hz, H-13).

SOLVOLYSIS REACTION OF **31**.—A mixture of **31** (174 mg, 0.53 mmol) and 0.5 M KOAc in AcOH (5.5 ml) was stirred at the refluxing temperature for 25 h, and worked up as usual to give an oily crude material. This was passed through a short column of Si gel (7 g) with a mixture of EtOAc and hexane (1:9) and further purified by hplc [column; B, solvent; EtOAc-hexane (5:95), flow rate; 6.0 ml/min].

The first fraction (*R*, 7 min) gave **25** (19.6 mg, 16%).

The second fraction (*R*, 9.1 min) gave **10** (25.8 mg, 21%).

1β-MESYLOXY-11β-(PHENYLSELENO)EUDESM-3-ENO-12,6α-LACTONE [**32**].—To a stirred solution of **29** (580 mg, 1.43 mmol) in pyridine (12.3 ml) was added methanesulfonyl chloride (498 μl, 6.39 mmol). The mixture was stirred at 0° for 5 h and worked up as usual to give a crystalline crude material, which was chromatographed over a short column of Si gel (15 g) and eluted with EtOAc-hexane (3:7) to give **32** (634 mg, 92%) as pale yellow crystals: mp 192°; ir ν max ($CHCl_3$) 1774 cm^{-1}; ^1H nmr δ 1.00 (3H, s, CH_3-10), 1.54 (3H, s, CH_3-11), 1.80 (3H, s, CH_3-4), 3.03 (3H, s, $-SO_2CH_3$), 4.34 (1H, dd, *J*=11.5 and 9.5 Hz, H-6), 4.67 (1H, dd, *J*=9.5 and 7.0 Hz, H-1), 5.33 (1H, br s, H-3), 7.24–7.48 (3H, m, aromatic H), 7.64 (2H, dd, *J*=8.5 and 2.0 Hz, aromatic H); hreims *m/z* 484.0818 ($C_{22}H_{28}O_5SSe$ requires 484.0822).

SOLVOLYSIS REACTION OF **32**.—A mixture of **32** (400 mg, 0.83 mmol) and 0.5 M KOAc in AcOH (8.5 ml) at the refluxing temperature for 25 h was worked up as usual to give oily crude material. This was passed through a short column of Si gel (15 g) with a mixture of EtOAc-hexane (5:95) and further purified by hplc [column; B, solvent; EtOAc-hexane (5:95), flow rate; 6.0 ml/min].

The first peak (*R*, 5.8 min) gave **24** (30 mg, 9%).

The second peak (*R*, 8.6 min) gave **9** (119 mg, 37%).

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