Further Labdane and Kaurane Diterpenoids and Other Constituents from *Plectranthus fruticosus*

Cristina Gaspar-Marques,[†] M. Fátima Simões,*[,†] and Benjamín Rodríguez*[,‡]

Faculdade de Farmácia da Universidade de Lisboa, Centro de Estudos de Ciências Farmacêuticas (CECF), Avenida das Forças Armadas, 1649-019 Lisboa, Portugal, and Instituto de Química Orgánica, Consejo Superior de Investigaciones Científicas (CSIC), Juan de la Cierva 3, E-28006 Madrid, Spain

Received November 13, 2003

Eight new diterpenoids, one labdane and seven kaurane derivatives, and a new aromadendrane-type sesquiterpenoid have been isolated from the most polar chromatographic fractions of an acetone extract of *Plectranthus fruticosus*. The structures of the new compounds (**1**−**9**) were established mainly by 1D and 2D NMR studies and by some chemical transformations. Compounds **6** and **8** were characterized as their methyl ester derivatives (**13** and **14**, respectively). Most of the isolated compounds and some of their derivatives were tested as antimicrobial agents, but only **19** showed moderate inhibitory activity against *Staphylococcus aureus*.

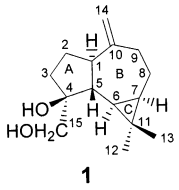
Recently,[1] we reported the isolation of six new diterpenoids from the less polar chromatographic fractions (eluted with petroleum ether, and 9:1 and 3:1 petroleum ether−EtOAc) of an acetone extract of the aerial parts of *Plectranthus fruticosus* L'Hérit. (Labiatae). In this paper, we report on the isolation and structure elucidation of a new aromadendrane-type sesquiterpenoid (**1**) and eight additional new diterpenoids, one labdane (**2**) and seven kaurane derivatives (**3**−**9**), all of them found in the more polar chromatographic fractions (eluted with 1:1 petroleum ether−EtOAc and EtOAc) of the acetone extract of the plant. Labdane **10**[1,2] and kaurane **11**,[3−6] five flavones, and the triterpenoids ursolic and oleanolic acids have also been isolated from the same chromatographic fractions. We also report antimicrobial test results on the isolated compounds and some of their derivatives.

Results and Discussion

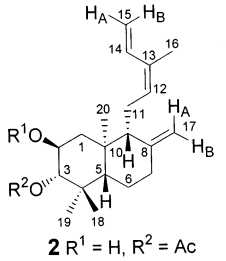
Repeated chromatographic processes on the fractions from the initial chromatography eluted with 1:1 petroleum ether−EtOAc and EtOAc of the acetone extract of *P. fruticosus*[1] (see Experimental Section) yielded compounds **1**−**11**. Compounds **6**, **8**, and **11** were purified and characterized as their methyl ester derivatives. Apigenin-7,4′-dimethyl ether,[7] genkwanin,[8,9] salvigenin,[10,11] cirsimaritin,[12] and eupatorin,[13,14] and ursolic acid and oleanolic acid[15] (characterized as a 2:1 mixture, respectively, of their methyl ester derivatives) were also isolated from the most polar chromatographic fractions of the plant extract.

Combustion analysis and low-resolution mass spectrometry indicated a molecular formula $C_{15}H_{24}O_2$ for **1**, and its IR spectrum showed hydroxyl (3429 cm^{-1}) and exocyclic methylene (3076, 1637, 897 cm^{-1}) absorptions. The ^1H and ^{13}C NMR spectra of **1** (Experimental Section) were very similar to those reported[16,17] for spathulenol [10(14)-aromadendren-4β-ol],[18] and the observed differences were consistent with the presence in **1** of a hydroxymethylene group instead of one of the three C-Me groups of spathulenol. The primary alcohol of **1** at the C-15 position[18] was in agreement with the diamagnetic shifts observed for its C-3 and C-5 γ-carbons with respect to those of spathulenol[16] ($\Delta\delta$ −4.3 and −2.0 ppm, respectively), as well as with the HMBC connectivities between the H_2-15 protons and the C-3, C-4, and C-5 carbons of **1**.

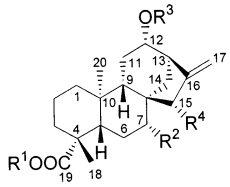
The relative stereochemistry of the H-1α, H-5β, H-6α, and H-7α hydrogens of **1** was supported by the coupling constant values, which were almost identical with those reported[19] for 10(14)-aromadendrene. In particular, the observed coupling between the H-1α and H-5β protons (J = 10.7 Hz) precluded a rings A/B *cis* junction for **1**, because in 10(14)-alloaromadendrene and its derivatives, which



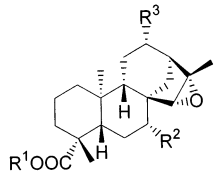
1



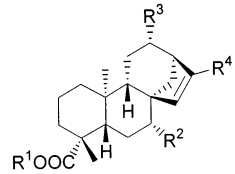
2 R^1 = H, R^2 = Ac
10 R^1 = R^2 = H
15 R^1 = Ac, R^2 = H
16 R^1 = R^2 = COC_6H_5



3 R^1 = R^2 = H, R^3 = Ac, R^4 = OH
4 R^1 = R^4 = H, R^2 = OH, R^3 = Ac
11 R^1 = R^2 = R^3 = R^4 = H
12 R^1 = Me, R^2 = R^3 = R^4 = H
17 R^1 = Me, R^2 = H, R^3 = Ac, R^4 = OH
18 R^1 = Me, R^2 = R^4 = H, R^3 = Ac



8 R^1 = R^2 = H, R^3 = OAc
9 R^1 = R^3 = H, R^2 = OH
14 R^1 = Me, R^2 = H, R^3 = OAc
20 R^1 = Me, R^2 = R^3 = H



5 R^1 = R^3 = H, R^2 = OH, R^4 = Me
6 R^1 = H, R^2 = OH, R^3 = OAc, R^4 = Me
7 R^1 = R^2 = H, R^3 = OAc, R^4 = CHO
13 R^1 = R^4 = Me, R^2 = OH, R^3 = OAc
19 R^1 = Me, R^2 = H, R^3 = OAc, R^4 = CHO

* To whom inquiries should be addressed. (M.F.S.) Tel: +351 217946400. Fax: +352 217946470. E-mail: fasimoes@ff.ul.pt. (B.R.) Tel: +34 915622900. Fax: +34 915644853. E-mail: iqor107@iqog.csic.es.
[†] Faculdade de Farmácia da Universidade de Lisboa, CECF.
[‡] Instituto de Química Orgánica, CSIC.

10.1021/np030490j CCC: $27.50
Published on Web 03/12/2004

possess a H-1β stereochemistry, this coupling value is 6.6−7.0 Hz.[17,19,20] The aromadendrane-type backbone arrangement of **1** was also in agreement with its ^{13}C NMR spectrum because the C-7, C-8, C-9, and C-14 carbon atom resonances were almost identical with those of spathulenol[16] and 10(14)-aromadendrene,[19] but very different from those reported for alloaromadendrane-type derivatives, such as in 10(14)-alloaromadendrene.[19] An α-configuration for the C-15 hydroxymethylene group of **1** was supported by NOE experiments. Irradiation at δ 0.46 (H-6α proton of **1**) caused NOE enhancement in the signals of the H_2-15, H-1α, H-7α, and Me-12 protons, thus establishing that all these hydrogens are on the same side of the plane of the molecule. This result not only substantiated an α-configuration for the hydroxymethylene group of **1** but also confirmed the above established backbone arrangement and allowed the unambiguous assignment of the Me-12 group of this sesquiterpenoid.[21,22] Moreover, comparison of the chemical shift of the C-6 and C-12 carbons of **1** [δ 28.46 (CH) and 28.54 (CH_3), respectively] with those of spathulenol (δ 30.0 and 26.1, respectively)[16] also suggested a 4β-hydroxy-4α-hydroxymethylene arrangement, because a diamagnetic shift of the C-6 carbon ($\Delta\delta \cong -1.5$ ppm) and a downfield shift of the C-12 carbon ($\Delta\delta \cong +2.4$ ppm) with respect to spathulenol have been observed in 4β-hydroxyaromadendrane derivatives possessing an acetoxyl or hydroxyl substituent at the α-side of the molecule, e.g., at the 3α- or 10α-position.[22,23]

Thus, structure **1** (15-hydroxyspathulenol[18]) was assigned to the new sesquiterpenoid. The absolute stereochemistry of **1** was not ascertained, although we suppose that it belongs to the *normal* series like other aromadendranes isolated from higher plants.[24] On the contrary, *ent*-aromadendranes (and exceptionally *normal* enantiomers) have been found in red algae, soft corals, marine sponges, and liverworts.[24] Several aromadendrane derivatives have been reported among the constituents of the essential oils of *Plectranthus* species,[25] and the hydrocarbon 10(14)-aromadendrene occurs in the essential oil of *P. fruticosus*.[26,27]

Compound **2** ($C_{22}H_{34}O_3$) showed ^{1}H and ^{13}C NMR spectra almost identical with those of **15**, an *ent*-labdane derivative[28] previously found[1] in the plant extract. The observed differences between these spectra were consistent with the presence of the acetoxyl group of **2** at the 3β-equatorial position ($\delta_{H-2\beta}$ 3.81, 1H, ddd, J = 11.7, 10.4, 4.3 Hz, $\delta_{H-3\alpha}$ 4.53, 1H, d, J = 10.4 Hz) instead of the equatorial 2α-acetate of **15**.[1,28] The connectivity between the carbonyl carbon of the acetate (δ 172.5) and the proton doublet at δ 4.53 (H-3α), observed in the HMBC spectrum of **2**, further supported that **2** and **15**[1] were regioisomers. Alkaline hydrolysis of **2** yielded **10** ($C_{20}H_{32}O_2$), another diterpenoid now isolated in large amounts from *P. fruticosus* and previously known[1] as a synthetic derivative of **15**. In fact, **10** had been found for the first time in *Croton joufra* Roxb. (Euphorbiaceae),[2] but its structure had been erroneously established.[1,2] An *ent*-labdane absolute stereochemistry for **10** and **15** has been suggested previously[1] on the basis of the change of the molecular rotations. Now, the absolute configuration of all these chemically correlated diterpenoids (**2**, **10**, and **15**) was established by using the CD exciton chirality method.[29] Benzoylation of **10** yielded **16**, the 2α,3β-dibenzoyloxy binary system of which showed a positive first and a negative second Cotton effect ($\Delta\epsilon_{235}$ +12.5, $\Delta\epsilon_{224}$ −10.3),[30] thus defining a positive chirality[29] and, consequently, an *ent*-labdane absolute configuration for **16**, and therefore for **2**, **10**, and **15**.

Another diterpenoid isolated from *P. fruticosus* (**11**) was purified as its methyl ester derivative **12**, which showed physical and spectroscopic data identical to those reported previously[3−6] for methyl *ent*-12β-hydroxykaur-16-en-19-oate.[28] Compound **11** has been found in several Compositae species,[3,5,6] and it was also obtained[4] from grandiflorenic acid.

Compound **3** ($C_{22}H_{32}O_5$) and its methyl ester derivative (**17**, $C_{23}H_{34}O_5$) showed ^{1}H and ^{13}C NMR spectra very similar to those of methyl *ent*-12β-acetoxykaur-16-en-19-oate (**18**), found as the free acid in the same plant.[1] The observed differences in the chemical shifts of the C-7−C−9 and C-13−C-17 carbons of **17** and **18** were in agreement[31] with the presence in **17**, and hence in **3**, of an additional hydroxyl group at the C-15 position. The HMBC spectrum of **3** showed connectivities between the H-15 proton and the C-8, C-9, C-13, C-14, and C-17 carbons, thus confirming the C-15 position for the secondary hydroxyl group. Irradiation at the H-15 proton of **3** and **17** (δ 4.19 and 3.83, respectively) caused NOE enhancements in the signals of the H-9α[28] (+11.6 and +9.1%, respectively) protons, thus establishing an α-configuration for the H-15 proton. This NOE experiment not only established the configuration of the C-15 stereogenic center in **3** but also distinguished both methylene protons at C-17 and, more important, precluded the possibility of a phyllocladane (13β-kaurane)[32] hydrocarbon skeleton for **3**, because the observed NOE between the H-15α and H-9α[28] protons is compatible only with a kaurane stereochemistry and not with that of the diastereoisomer phyllocladane, in which the H_2-15 and H-9 protons are on opposite sides of the plane of the molecule.[32] From all of the above data, it was evident that structure **3** (*ent*-12β-acetoxy-15β-hydroxykaur-16-en-19-oic acid[28]) must be assigned to this diterpenoid. The absolute configuration of **3**, as well as that of the other new kauranes quoted below (**4**−**9**), was not ascertained by direct methods. However, we suppose that **3**−**9** belong to the *enantio* series like **11** and other kaurane derivatives found in *Plectranthus* species.[1,25] Moreover, the vast majority of the kaurane-type diterpenoids until now isolated from natural sources belong to the *enantio* series.[32,33]

Phyllocladane-type diterpenoids are rare in nature, and they have been isolated predominantly from plants of the *Plectranthus* (Labiatae)[32−35] and *Callicarpa* (Verbenaceae)[36] genera.[37] Although several criteria, based on ^{1}H and ^{13}C NMR chemical shifts,[32,38] have been used successfully for distinguishing phyllocladanes from kauranes, in this work NOE experiments have shown to be a reliable and easy method for establishing a kaurane hydrocarbon skeleton for **3** (see above) and **4**−**9** (see below).

The ^{1}H and ^{13}C NMR spectra of **4** ($C_{22}H_{32}O_5$) were in agreement with a structure nearly identical with that of **18**,[1] but possessing a carboxyl function at C-19 instead of the carbomethoxyl group of **18** and an additional secondary alcohol equatorially oriented at the 7β-position.[28] The cross-peaks observed in the HMBC spectrum of **4** between the H-7α proton and the C-6, C-8, C-14, and C-15 carbons further confirmed the presence of a 7-hydroxyl substituent in this diterpenoid. Irradiation at δ 3.72 (H-7α proton of **4**)[28] produced, among others, NOE enhancements in the signals of the H-9α (+15.1%), H-15α (+2.2%), and H-15β (+4.1%) protons. In this compound (**4**), the NOE observed between the H-7α and H-9α protons does not preclude a phyllocladane-type structure, because these two axial protons are on the same side of the plane of the molecule in both kaurane and phyllocladane stereoisomers. However, the NOEs observed between H-7α and both H_2-15

Table 1. ^{13}C NMR Spectral (δ) Data for Compounds **3**−**5**, **8**, **9**, **13**, **17**, and **19**[a]

carbon	**3**[b]	**4**[b]	**5**[c]	**8**[d]	**9**[b]	**13**[d]	**17**[d]	**19**[d]
C-1	41.2 (CH_2)	40.9 (CH_2)	41.4 (CH_2)	40.6 (CH_2)	40.9 (CH_2)	40.2 (CH_2)	40.6 (CH_2)	40.4 (CH_2)
C-2	19.8 (CH_2)	19.7 (CH_2)	19.9 (CH_2)	18.8 (CH_2)	19.8 (CH_2)	18.8 (CH_2)	18.9 (CH_2)	18.8 (CH_2)
C-3	38.6 (CH_2)	38.5 (CH_2)	38.7 (CH_2)	37.9 (CH_2)	38.5 (CH_2)	37.8 (CH_2)	37.8 (CH_2)	37.78 (CH_2)
C-4	44.1 (C)	43.83 (C)	43.8 (C)	43.8 (C)	43.8 (C)	43.6 (C)	43.8 (C)	43.8 (C)
C-5	57.0 (CH)	53.8 (CH)	54.3 (CH)	56.4 (CH)	53.7 (CH)	53.2 (CH)	56.7 (CH)	56.2 (CH)
C-6	22.0 (CH_2)	32.3 (CH_2)	31.2 (CH_2)	20.5 (CH_2)	31.4 (CH_2)	29.5 (CH_2)	20.8 (CH_2)	20.1 (CH_2)
C-7	36.1 (CH_2)	74.55 (CH)	75.4 (CH)	35.4 (CH_2)	75.1 (CH)	75.2 (CH)	34.9 (CH_2)	37.78 (CH_2)
C-8	47.5 (C)	49.8 (C)	56.2 (C)	42.6 (C)	49.7 (C)	54.2 (C)	46.7 (C)	49.7 (C)
C-9	54.2 (CH)	55.1 (CH)	48.1 (CH)	49.4 (CH)	49.0 (CH)	47.3 (CH)	53.4 (CH)	46.2 (CH)
C-10	39.2 (C)	39.2 (C)	40.1 (C)	38.0 (C)	39.6 (C)	37.9 (C)	38.4 (C)	38.4 (C)
C-11	23.5 (CH_2)	23.5 (CH_2)	19.5 (CH_2)	24.1 (CH_2)	18.3 (CH_2)	24.9 (CH_2)	23.0 (CH_2)	24.6 (CH_2)
C-12	74.1 (CH)	74.58 (CH)	26.0 (CH_2)	69.7 (CH)	27.7 (CH_2)	69.2 (CH)	73.3 (CH)	68.0 (CH)
C-13	46.9 (CH)	48.4 (CH)	44.7 (CH)	44.3 (CH)	39.0 (CH)	48.5 (CH)	46.1 (CH)	42.3 (CH)
C-14	30.8 (CH_2)	25.9 (CH_2)	35.7 (CH_2)	25.7 (CH_2)	24.9 (CH_2)	28.8 (CH_2)	30.1 (CH_2)	36.6 (CH_2)
C-15	83.1 (CH)	43.83 (CH_2)	134.6 (CH)	67.6 (CH)	67.0 (CH)	135.1 (CH)	83.0 (CH)	163.4 (CH)
C-16	157.3 (C)	152.3 (C)	143.0 (C)	59.7 (C)	59.5 (C)	144.2 (C)	155.5 (C)	147.1 (C)
C-17	110.7 (CH_2)	106.4 (CH_2)	15.5 (CH_3)	14.9 (CH_3)	14.8 (CH_3)	15.8 (CH_3)	111.7 (CH_2)	188.4 (CH)
C-18	29.5 (CH_3)	29.4 (CH_3)	29.2 (CH_3)	28.7 (CH_3)	29.3 (CH_3)	28.6 (CH_3)	28.8 (CH_3)	28.7 (CH_3)
C-19	180.2 (C)	180.1 (C)	178.7 (C)	177.8 (C)	180.0 (C)	177.7 (C)	178.0 (C)	177.7 (C)
C-20	14.9 (CH_3)	14.8 (CH_3)	16.1 (CH_3)	13.9 (CH_3)	15.9 (CH_3)	13.3 (CH_3)	13.9 (CH_3)	13.3 (CH_3)
$-OCOCH_3$	170.1 (C)	170.1 (C)		170.3 (C)		170.6 (C)	170.4 (C)	170.1 (C)
$-OCOCH_3$	21.3 (CH_3)	21.4 (CH_3)		21.4 (CH_3)		21.6 (CH_3)	21.5 (CH_3)	21.4 (CH_3)
$-COOCH_3$				51.2 (CH_3)		51.2 (CH_3)	51.2 (CH_3)	51.3 (CH_3)

[a] At 100 MHz. All these assignments were in agreement with HSQC and HMBC spectra. [b] In pyridine-d_5 solution. [c] In acetone-d_6 solution. [d] In $CDCl_3$ solution.

protons clearly established that **4** possessed a kaurane-type structure, in which these hydrogens are on the same side of the molecule, whereas they are on opposite sides in the phyllocladane hydrocarbon skeleton.[32] In addition, irradiation at δ 3.30 (H-15β proton of **4**) caused a strong NOE enhancement (+4.4%) in the signal of H_A-17. Consequently, compound **4** was formulated as *ent*-12β-acetoxy-7β-hydroxykaur-16-en-19-oic acid.[28]

The ^1H and ^{13}C NMR spectra of compound **5** ($C_{20}H_{30}O_3$) showed signals for a C-19 carboxyl group and a 7β-hydroxyl substituent oriented equatorially as in **4**. This conclusion was supported by the HMBC spectrum of **5**, which displayed connectivities compatible only with the proposed structure (e.g., between the H-7α proton and the C-14 and C-15 carbons, and between the C-7 carbon and the H-5α, H_2-6, and H_2-14 protons, as well as between the carboxyl carbon at C-19 and the H_2-3, H-5α, and Me-18 protons). Irradiation at the olefinic proton of **5** (δ 5.14, H-15) caused NOE enhancements in the signals of the H-9α (+2.0%) and H-7α (+5.0%) protons, thus confirming a kaurane-type structure for **5** and located its secondary hydroxyl group at the 7β-position. Therefore, compound **5** is *ent*-7β-hydroxykaur-15-en-19-oic acid.[28]

The kaur-15-ene derivative **6** was also found in the acetone extract of *P. fruticosus*, and it was purified as its methyl ester derivative **13** ($C_{23}H_{34}O_5$). The ^1H and ^{13}C NMR spectra of this substance (**13**: methyl *ent*-12β-acetoxy-7β-hydroxykaur-15-en-19-oate)[28] were similar to those of **4**, showing characteristic signals for a kaur-15-ene derivative instead of the kaur-16-ene structure of **4**. Moreover, the observed differences in the chemical shifts of the C-6−C-9, C-12, and C-14 carbons of **13** and **4** (Table 1) further supported[31] the structure of the former. The kaurane-type structure of **13** was also in agreement with the NOE observed for the H-9α signal[28] (+2.1% NOE enhancement) when the signal of the H-15 proton (δ 5.19) was irradiated.

Compound **7** was transformed into its methyl ester derivative **19** ($C_{23}H_{32}O_5$) by treatment with an ethereal solution of diazomethane. The IR and UV spectra of **19** showed absorptions typical for an α,β-unsaturated aldehyde function, and its kaur-15-en-17-al partial structure was supported[39−42] by the ^1H and ^{13}C NMR data. In addition, the ^1H NMR spectra of **7** and **19**, as well as the ^{13}C NMR spectrum of **19** (Table 1), revealed the presence of a 12β-acetoxyl substituent in both compounds, identical with that found in **13**, and a carbomethoxyl group at the C-19 position, which is a carboxylic acid in **7**. The HMBC spectrum and other spectroscopic data of **19** were in agreement with a structure of *ent*-12β-acetoxy-17-oxokaur-15-en-19-oic acid[28] for this new diterpenoid (**7**).

Compound **8** was characterized as its methyl ester derivative **14** ($C_{23}H_{34}O_5$). The ^1H and ^{13}C NMR spectra of **14** were very similar to those reported[1] for **20**. The observed differences between the ^1H and ^{13}C NMR spectra of **14** and **20** were consistent with the presence in the former of a 12β-acetoxyl substituent instead of the C-12 methylene of the later. This was strongly supported by the HMBC spectrum of **14** (connectivities between the C-12 carbon and the H-9α, H_2-11, H-13β, and H-14α protons) and by the observed downfield shifts of the C-11−C-13 ($\Delta\delta$ +5.9, +42.7, and +5.3 ppm, respectively) and upfield shifts of the C-14 and C-16 ($\Delta\delta$ −6.3 and −1.7) carbons of **14** (Table 1) with respect to those of **20**.[1] In addition, irradiation at δ 4.97 (H-12α of **14**) produced strong NOE enhancements in the signals of the H-11α (+4.8%) and Me-17 (+4.7%) protons, whereas on irradiating at δ 2.63 (H-15α of **14**) the signals of the H-7α, H-9α, H-11α, and Me-17 protons were enhanced (+1.8, +4.1, +1.1, and +3.3%, respectively). These NOE results established 15β,16β-stereochemistry for the oxirane and confirmed a kaurane-type structure for **14**, which must be methyl *ent*-12β-acetoxy-15β,16β-epoxykauran-19-oate.[28]

Compound **9** ($C_{20}H_{30}O_4$) possessed a 15,16-epoxyde [δ_H 2.91 (1H, s, H-15α) and 1.41 (3H, s, Me-17); δ_C 67.0 (CH, C-15), 59.5 (C, C-16), and 14.8 (CH_3, C-17)] as in **14** (see above) and **20**.[1] The ^1H and ^{13}C NMR spectra of **9** were in agreement with the presence of a C-19 carboxyl group and a secondary hydroxyl group at the C-7β equatorial position such as in **4**, **5**, and **13**. The *ent*-7β-hydroxy-15β,16β-epoxykauran-19-oic acid[28] structure for **9** was also supported by the observed HMBC cross-peaks between the H-7α proton and the C-5, C-6, C-8, C-9, C-14, and C-15 carbons and by the NOE caused on the H-7α, H-9α, and Me-17 proton signals (+4.1, +3.9, and +2.3% NOE en-

hancement, respectively) when the H-15α proton of **9** (δ 2.91) was irradiated.

Compounds **1**, **3**−**5**, **7**, **9**, **10**, **12**−**14**, **17**, and **19** were tested for antimicrobial activity against Gram-positive and Gram-negative bacteria and yeast strains (see Experimental Section). None of the compounds showed activity against *Pseudomonas aeruginosa*, *Escherischia coli*, and *Candida albicans* strains. Against *Staphylococcus aureus* only the kaurane **19** showed moderate activity (MIC value 62.5 μg/mL).

Experimental Section

General Experimental Procedures. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. UV spectra were recorded on a Perkin-Elmer Lambda 2 UV/vis spectrophotometer. IR spectra were obtained on a Perkin-Elmer Spectrum One spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (**1**, **2**, **7**, **10**, **12**−**14**, **16**, **17**, and **19**), pyridine-d_5 (**3**, **4**, and **9**), or acetone-d_6 (**5**) solution on a Varian INOVA 400 apparatus at 400 and 100 MHz, respectively, except for **7** (^{1}H NMR at 300 MHz, Varian INOVA 300 apparatus). Chemical shifts are reported with respect to residual $CHCl_3$ (δ 7.25) or pyridine-d_5 (δ 8.71, 7.55, 7.19) or acetone-d_6 (δ 2.04) signals for protons and to the solvent signals (δ_{CDCl_3} 77.00, $\delta_{pyridine-d_5}$ 149.9, 135.5, 123.5, $\delta_{acetone-d_6}$ 206.1, 29.8) for carbons. All the assignments for protons and carbons were in agreement with 2D COSY, TOCSY, gHSQC, gHMBC, and 1D NOESY spectra. Mass spectra were registered in the positive EI mode on a Hewlett-Packard 5973 instrument (70 eV). Elemental analyses were conducted on a Carlo Erba EA 1108 apparatus. Merck Si gel (70−230 mesh and 230−400 mesh, for gravity flow and flash chromatograpy, respectively) was used for column chromatography. Merck 5554 Kieselgel 60 F254 sheets were used for TLC analysis. Petroleum ether (bp 50−70 °C) was used for column chromatography.

Plant Material. *Plectranthus fruticosus* was cultivated in the Faculty of Pharmacy Hortum, Lisbon University, from seeds provided by the Herbarium of the Botanical Garden of Lisbon, Portugal. Aerial parts of this species were collected in June 1999, and voucher specimens were deposited in the Herbarium of the Botanical Center of the "Instituto de Investigação Científica Tropical", Lisbon (ref C. Marques, S/N° LISC).

Extraction and Isolation. Dried and powdered *P. fruticosus* aerial parts (3.58 kg) were extracted with Me_2CO as described previously.[1] A part (100 g) of the total extract (444 g) was subjected to column chromatography (Si gel 70−230 mesh, 960 g) eluting successively with petroleum ether, petroleum ether−EtOAc (9:1, 3:1, and 1:1), and EtOAc. The constituents of the chromatographic fractions eluted with 9:1 and 3:1 petroleum ether−EtOAc have previously been reported,[1] and those eluted with 1:1 petroleum ether−EtOAc and EtOAc were isolated as follows.

The residue (20.3 g) of the fractions eluted with 1:1 petroleum ether−EtOAc was rechromatographed (Si gel 230−400 mesh column, 800 g, eluted with a petroleum ether−EtOAc gradient from 8.5:1.5 to 3:7). The fraction eluted with 8.5:1.5 petroleum ether−EtOAc yielded impure **2** (30 mg), which was rechromatographed (Si gel 230−400 mesh, 20 g, 7:1 petroleum ether−EtOAc as eluent), affording pure **2** (12 mg, 0.0015% on dry plant material). The fraction eluted with 8.2:1.8 petroleum ether−EtOAc yielded apigenin-7,4′-dimethyl ether[7] (5-hydroxy-7,4′-dimethoxyflavone, 3 mg, 0.00037%). The residue (4 g) of the fractions eluted with 4:1 petroleum ether−EtOAc was treated with an excess of an ethereal solution of CH_2N_2 at room temperature for 3 h and then subjected to column chromatography (Si gel 230−400 mesh, 200 g, 9:1 CH_2Cl_2−EtOAc as eluent), giving the following compounds in order of increasing polarity: **14** (methyl ester of **8**, 197 mg, 0.024%), a 2:1 mixture of the methyl esters of ursolic and oleanolic acids[15] (255 mg, 0.032%), the aromadendrene derivative **1** (4 mg, 0.0005%), and **10**[1,2] (590 mg, 0.073%). The residue (1.1 g) of the fractions eluted with 3:1 petroleum ether−EtOAc was rechromatographed (Si gel 230−400 mesh column, 120 g, eluted with 8.2:1.5 CH_2Cl_2−EtOAc), yielding, in order of increasing polarity, genkwanin[8,9] (5,4′-dihydroxy-7-methoxyflavone, 3 mg, 0.00037%), **7** (28 mg, 0.0034%), and a mixture of **7** and **11**. This mixture was methylated with an ethereal solution of CH_2N_2 and then subjected to column chromatography (Si gel 230−400 mesh, 40 g, eluted with 3:1 petroleum ether−EtOAc), affording the methyl ester of **7** (**19**, 26 mg, 0.0032%) and the previously known[3−6] kaurane derivative **12** (7 mg, 0.0009%). The fractions eluted with 7:3 petroleum ether−EtOAc contained 630 mg of a complex mixture of compounds. This mixture was rechromatographed (Si gel 230−400 mesh column, 140 g, eluted with 3:1 CH_2Cl_2−EtOAc), yielding the following compounds in order of increasing polarity: salvigenin[10,11] (5-hydroxy-6,7,4′-trimethoxyflavone, 188 mg, 0.023%), **5** (3 mg, 0.00037%), **3** (68 mg, 0.0084%), cirsimaritin[12] (5,4′-dihydroxy-6,7-dimethoxyflavone, 7 mg, 0.0009%), and **4** (37 mg, 0.0046%). Finally, the fractions eluted with 3:7 petroleum ether−EtOAc (720 mg) yielded, after rechromatography (Si gel 230−400 mesh column, 80 g, 97:3 CH_2Cl_2−MeOH as eluent), 30 mg of an impure compound (**6**), which was treated with an excess of an ethereal solution of CH_2N_2 for 3 h and then chromatographed (Si gel 230−400 mesh column, 20 g, 3:1 petroleum ether−EtOAc as eluent), giving pure **13** (25 mg, 0.0031%).

The fractions from the initial chromatography eluted with EtOAc gave a residue (21.5 g). Rechromatography of this residue (Si gel 230−400 mesh column, 350 g, 1:1 CH_2Cl_2−EtOAc as eluent) successively afforded eupatorin[13,14] (5,3′-dihydroxy-6,7,4′-trimethoxyflavone, 19 mg, 0.0024%) and **9** (100 mg, 0.012%).

The previously known flavones (apigenin-7,4′-dimethyl ether,[7] genkwanin,[8,9] salvigenin,[10,11] cirsimaritin,[12] and eupatorin[13,14]) were identified by their mp and ^{1}H NMR spectra, and the mixture of ursolic and oleanolic acid methyl esters was characterized by a careful study[15] of the ^{1}H NMR spectrum and by comparison (TLC) with authentic samples.

10(14)-Aromadendrene-4*β*,15-diol (1): colorless needles (spontaneously on cooling), mp 73−75 °C; $[\alpha]_D^{18}$ +9.3° (*c* 0.215, $CHCl_3$); IR (KBr) ν_{max} 3429, 3076, 2922, 2862, 1637, 1456, 1375, 1090, 1026, 897 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.70 (1H, t, $J_{14B,14A} = J_{14B,1\alpha} = 1.8$ Hz, H_B-14), 4.67 (1H, dd, $J_{14A,14B} = 1.8$ Hz, $J_{14A,9\alpha} = 0.8$ Hz, H_A-14), 3.70 (1H, d, $J_{15B,15A} = 11.2$ Hz, H_B-15), 3.57 (1H, d, $J_{15A,15B} = 11.2$ Hz, H_A-15), 2.41 (1H, ddd, $J_{9\beta,9\alpha} = 13.6$ Hz, $J_{9\beta,8\alpha} = 6.4$ Hz, $J_{9\beta,8\beta} = 1.2$ Hz, H-9*β*), 2.18 (1H, dddd, $J_{1\alpha,2\alpha} = 6.0$ Hz, $J_{1\alpha,2\beta} = 12.0$ Hz, $J_{1\alpha,5\beta} = 10.7$ Hz, $J_{1\alpha,14B} = 1.8$ Hz, H-1α), 2.00 (1H, dddd, $J_{9\alpha,9\beta} = 13.6$ Hz, $J_{9\alpha,8\alpha} = 1.1$ Hz, $J_{9\alpha,8\beta} = 12.3$ Hz, $J_{9\alpha,14A} = 0.8$ Hz, H-9α), 1.96 (1H, dddd, $J_{8\alpha,8\beta} = 13.6$ Hz, $J_{8\alpha,7\alpha} = 6.0$ Hz, $J_{8\alpha,9\alpha} = 1.1$ Hz, $J_{8\alpha,9\beta} = 6.4$ Hz, H-8α), 1.91 (1H, dddd, $J_{2\beta,2\alpha} = 13.1$ Hz, $J_{2\beta,1\alpha} = 12.0$ Hz, $J_{2\beta,3\alpha} = 13.0$ Hz, $J_{2\beta,3\beta} = 6.0$ Hz, H-2*β*), 1.90 (1H, br s, 15-OH), 1.81 (1H, ddd, $J_{3\beta,3\alpha} = 13.0$ Hz, $J_{3\beta,2\alpha} = 1.2$ Hz, $J_{3\beta,2\beta} = 6.0$ Hz, H-3*β*), 1.69 (1H, dddd, $J_{2\alpha,2\beta} = 13.1$ Hz, $J_{2\alpha,1\alpha} = 6.0$ Hz, $J_{2\alpha,3\alpha} = 6.0$ Hz, $J_{2\alpha,3\beta} = 1.2$ Hz, H-2α), 1.58 (1H, br s, 4*β*-OH), 1.51 (1H, td, $J_{3\alpha,3\beta} = J_{3\alpha,2\beta} = 13.0$ Hz, $J_{3\alpha,2\alpha} = 6.0$ Hz, H-3α), 1.36 (1H, dd, $J_{5\beta,1\alpha} = 10.7$ Hz, $J_{5\beta,6\alpha} = 11.2$ Hz, H-5*β*), 1.05 (3H, s, Me-12), 1.04 (3H, s, Me-13), 0.98 (1H, dddd, $J_{8\beta,8\alpha} = 13.6$ Hz, $J_{8\beta,7\alpha} = 11.3$ Hz, $J_{8\beta,9\alpha} = 12.3$ Hz, $J_{8\beta,9\beta} = 1.2$ Hz, H-8*β*), 0.73 (1H, ddd, $J_{7\alpha,6\alpha} = 9.5$ Hz, $J_{7\alpha,8\alpha} = 6.0$ Hz, $J_{7\alpha,8\beta} = 11.3$ Hz, H-7α), 0.46 (1H, dd, $J_{6\alpha,5\beta} = 11.2$ Hz, $J_{6\alpha,7\alpha} = 9.5$ Hz, H-6α); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.7 (C, C-10), 107.0 (CH_2, C-14), 82.9 (C, C-4), 68.3 (CH_2, C-15), 53.9 (CH, C-1), 52.4 (CH, C-5), 38.6 (CH_2, C-9), 37.5 (CH_2, C-3), 28.54 (CH_3, C-12), 28.46 (CH, C-6), 27.6 (CH, C-7), 27.2 (CH_2, C-2), 24.4 (CH_2, C-8), 20.5 (C, C-11), 16.1 (CH_3, C-13); EIMS *m*/*z* 236 $[M]^+$ (1), 218 (29), 205 (100), 203 (52), 187 (61), 175 (25), 162 (30), 149 (44), 147 (44), 145 (39), 133 (44), 131 (52), 119 (55), 107 (55), 105 (61), 93 (58); *anal.* C 76.34%, H 10.28%, calcd for $C_{15}H_{24}O_2$, C 76.23%, H 10.23%.

***ent*-3*β*-Acetoxylabda-8(17),12*Z*,14-trien-2α-ol (2):**[28] amorphous white solid, mp 105−115 °C; $[\alpha]_D^{18}$ −16.5° (*c* 0.291, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 234 (3.82) nm; IR (KBr) ν_{max}

3437, 3082, 2939, 2851, 1736, 1643, 1439, 1371, 1246, 1057, 1030, 958, 890 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.76 (1H, ddd, $J_{14,15A} = 10.8$ Hz, $J_{14,15B} = 17.2$ Hz, $J_{14,12} = 0.8$ Hz, H-14), 5.28 (1H, br t, $J_{12,11A} = J_{12,11B} = 6.5$ Hz, H-12), 5.18 (1H, ddd, $J_{15B,15A} = 1.6$ Hz, $J_{15B,14} = 17.2$ Hz, $J_{15B,12} = 0.8$ Hz, pro-*Z* H_B-15), 5.09 (1H, dt, $J_{15A,15B} = J_{15A,12} = 1.6$ Hz, $J_{15A,14} = 10.8$ Hz, pro-*E* H_A-15), 4.87 (1H, q, $J_{17B,17A} = J_{17B,7\alpha} = J_{17B,9\alpha} = 1.6$ Hz, pro-*E* H_B-17), 4.53 (1H, d, $J_{3\alpha,2\beta} = 10.4$ Hz, H-3α), 4.52 (1H, q, $J_{17A,17B} = J_{17A,7\alpha} = J_{17A,9\alpha} = 1.6$ Hz, pro-*Z* H_A-17), 3.81 (1H, ddd, $J_{2\beta,1\alpha} = 11.7$ Hz, $J_{2\beta,1\beta} = 4.3$ Hz, $J_{2\beta,3\alpha} = 10.4$ Hz, H-2*β*), 2.42 (1H, m*, H_B-11), 2.40 (1H, ddd, $J_{7\beta,7\alpha} = 13.2$ Hz, $J_{7\beta,6\alpha} = 2.4$ Hz, $J_{7\beta,6\beta} = 4.2$ Hz, H-7*β*), 2.21 (1H, dd, $J_{1\beta,1\alpha} = 12.6$ Hz, $J_{1\beta,2\beta} = 4.3$ Hz, H-1*β*), 2.19 (1H, ddd, $J_{11A,11B} = 17.5$ Hz, $J_{11A,9\alpha} = 11.0$ Hz, $J_{11A,12} = 6.5$ Hz, H_A-11), 2.14 (3H, s, 3*β*-OAc), 2.00 (1H, br ddd, $J_{7\alpha,7\beta} = 13.2$ Hz, $J_{7\alpha,6\alpha} = 5.2$ Hz, $J_{7\alpha,6\beta} = 12.7$ Hz, H-7α), 1.76 (3H, d, $J_{16,12} = 1.2$ Hz, Me-16), 1.74 (1H, br dd, $J_{9\alpha,11A} = 11.0$ Hz, $J_{9\alpha,11B} = 3.3$ Hz, H-9α), 1.70 (1H, m*, H-6α), 1.58 (1H, br, 2α-OH), 1.38 (1H, m*, H-6*β*), 1.26 (2H, m*, H-1α and H-5α), 0.89 (3H, s, Me-18), 0.86 (3H, s, Me-19), 0.79 (3H, s, Me-20);[43] ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.5 (C, O*C*OCH$_3$), 146.9 (C, C-8), 133.7 (CH, C-14), 132.0 (C, C-13), 130.7 (CH, C-12), 113.6 (CH_2, C-15), 108.9 (CH_2, C-17), 84.5 (CH, C-3), 67.9 (CH, C-2), 56.9 (CH, C-9), 54.4 (CH, C-5), 46.3 (CH_2, C-1), 40.1 (C, C-10), 39.3 (C, C-4), 37.6 (CH_2, C-7), 28.7 (CH_3, C-18), 23.5 (CH_2, C-6), 22.3 (CH_2, C-11), 21.2 (CH_3, OCO*C*H$_3$), 19.7 (CH_3, C-16), 17.5 (CH_3, C-19), 15.4 (CH_3, C-20); EIMS *m/z* 346 $[M]^+$ (0.5), 331 (1), 286 (1), 271 (3), 253 (2), 187 (8), 149 (14), 137 (14), 135 (16), 133 (23), 109 (27), 107 (23), 43 (100); *anal.* C 76.41%, H 9.69%, calcd for $C_{22}H_{34}O_3$, C 76.26%, H 9.89%.

***ent*-12*β*-Acetoxy-15*β*-hydroxykaur-16-en-19-oic acid (3):**[28] colorless hexagonal plates (EtOAc−*n*-pentane), mp 244−246 °C; $[\alpha]_D^{20}$ −58.5° (*c* 0.301, MeOH); IR (KBr) ν_{max} 3415, 3065, 2950, 2850, 1740, 1703, 1636, 1449, 1371, 1228, 1014, 999, 964, 906 cm^{-1}; ^1H NMR (pyridine-d_5, 400 MHz) δ 14.70 (1H, br, 19-COOH), 5.90 (1H, br, 15*β*-OH), 5.52 (1H, dd, $J_{17B,17A} = 1.2$ Hz, $J_{17B,15\alpha} = 0.8$ Hz, H_B-17, *cis* hydrogen with respect to C-15), 5.28 (1H, dd, $J_{17A,17B} = 1.2$ Hz, $J_{17A,15\alpha} = 1.6$ Hz, H_A-17, *trans* hydrogen with respect to C-15), 4.97 (1H, br t, $J_{12\alpha,11\alpha} = 4.5$ Hz, $J_{12\alpha,11\beta} < 0.5$ Hz, $J_{12\alpha,13\beta} = 4.6$ Hz, H-12α), 4.19 (1H, br s, H-15α), 2.97 (1H, ddd, $J_{13\beta,12\alpha} = 4.6$ Hz, $J_{13\beta,14\alpha} = 5.0$ Hz, $J_{13\beta14\beta} = 0.5$ Hz, H-13*β*), 2.50 (1H, dddd, $J_{3\beta,3\alpha} = 13.2$ Hz, $J_{3\beta,2\alpha} = 4.1$ Hz, $J_{3\beta,2\beta} = 3.6$ Hz, $J_{3\beta,1\beta} = 0.8$ Hz, H-3*β*), 2.32 (1H, br dd, $J_{14\beta,14\alpha} = 11.4$ Hz, $J_{14\beta,13\beta} = 0.5$ Hz, $J_{14\beta,15\alpha} = 1.0$ Hz, H-14*β*), 2.26 (4H, m*, H-2*β*, H-6α, H-6*β*, and H-7*β*), 1.98 (3H, s, 12*β*-OAc), 1.85 (2H, m*, H-7α and H-11α), 1.81 (1H, m*, H-1*β*), 1.78 (1H, br d, $J_{11\beta,11\alpha} = 16.8$ Hz, $J_{11\beta,9\alpha} \cong J_{11\beta,12\alpha} < 0.5$ Hz, H-11*β*), 1.57 (1H, dd, $J_{14\alpha,14\beta} = 11.4$ Hz, $J_{14\alpha,13\beta} = 5.0$ Hz, H-14α), 1.49 (1H, ddddd, $J_{2\alpha,2\beta} = 14.0$ Hz, $J_{2\alpha,1\alpha} = 4.1$ Hz, $J_{2\alpha,1\beta} = 3.2$ Hz, $J_{2\alpha,3\alpha} = 4.4$ Hz, $J_{2\alpha,3\beta} = 4.1$ Hz, H-2α), 1.40 (3H, s, Me-20), 1.38 (3H, s, Me-18), 1.31 (1H, br d, $J_{9\alpha,11\alpha} = 8.8$ Hz, $J_{9\alpha,11\beta} < 0.5$ Hz, H-9α), 1.18 (1H, dd, $J_{5\alpha,6\alpha} = 3.8$ Hz, $J_{5\alpha,6\beta} = 10.2$ Hz, H-5α), 1.08 (1H, td, $J_{3\alpha,3\beta} = J_{3\alpha,2\beta} = 13.2$ Hz, $J_{3\alpha,2\alpha} = 4.4$ Hz, H-3α), 0.82 (1H, ddd, $J_{1\alpha,1\beta} = 13.2$ Hz, $J_{1\alpha,2\alpha} = 4.1$ Hz, $J_{1\alpha,2\beta} = 12.8$ Hz, H-1α);[43] ^{13}C NMR (pyridine-d_5, 100 MHz), see Table 1; EIMS *m/z* 376 $[M]^+$ (1), 334 (1), 316 (100), 301 (38), 298 (20), 283 (17), 270 (30), 255 (19), 243 (12), 237 (15), 199 (11), 197 (13), 183 (10), 173 (14), 161 (25), 160 (20), 148 (30), 145 (25), 133 (24), 131 (29), 123 (27), 121 (34), 109 (34), 105 (40); *anal.* C 70.39%, H 8.61%, calcd for $C_{22}H_{32}O_5$, C 70.18%, H 8.57%.

***ent*-12*β*-Acetoxy-7*β*-hydroxykaur-16-en-19-oic acid (4):**[28] colorless fine needles (EtOAc−*n*-pentane), mp 250−252 °C; $[\alpha]_D^{20}$ −52.1° (*c* 0.313, MeOH); IR (KBr) ν_{max} 3419, 3071, 2940, 2873, 1736, 1691, 1635, 1467, 1372, 1238, 1028, 968, 876 cm^{-1}; ^1H NMR (pyridine-d_5, 400 MHz) δ 6.15 (1H, br, 7*β*-OH), 5.05 (1H, ddd, $J_{17B,17A} = 1.2$ Hz, $J_{17B,15\alpha} = 0.5$ Hz, $J_{17B,15\beta} = 2.3$ Hz, H_B-17, *trans* hydrogen with respect to C-15), 5.01 (1H br dd, $J_{12\alpha,11\alpha} = 5.8$ Hz, $J_{12\alpha,11\beta} < 0.5$ Hz, $J_{12\alpha,13\beta} = 5.0$ Hz, H-12α), 4.95 (1H, ddd, $J_{17A,17B} = 1.2$ Hz, $J_{17A,15\alpha} = 0.5$ Hz, $J_{17A,15\beta} = 2.3$ Hz, H_A-17, *cis* hydrogen with respect to C-15), 3.72 (1H, dd, $J_{7\alpha,6\alpha} = 4.5$ Hz, $J_{7\alpha,6\beta} = 11.3$ Hz, H-7α), 3.30 (1H, dt, $J_{15\beta,15\alpha} = 17.0$ Hz, $J_{15\beta,17A} = J_{15\beta,17B} = 2.3$ Hz, H-15*β*), 2.94 (1H, m, $W_{1/2} = 9$ Hz, H-13*β*), 2.62 (1H, ddd, $J_{6\alpha,6\beta} = 13.6$ Hz, $J_{6\alpha,5\alpha} = 2.4$ Hz, $J_{6\alpha,7\alpha} = 4.5$ Hz, H-6α), 2.57 (1H, ddd, $J_{6\beta,6\alpha} = 13.6$ Hz, $J_{6\beta,5\alpha} = 12.0$ Hz, $J_{6\beta,7\alpha} = 11.3$ Hz, H-6*β*), 2.50 (1H, dddd, $J_{3\beta,3\alpha} = 13.5$ Hz, $J_{3\beta,2\alpha} = 2.8$ Hz, $J_{3\beta,2\beta} = 3.5$ Hz, $J_{3\beta,1\beta} = 1.0$ Hz, H-3*β*), 2.26 (1H, dddt, $J_{2\beta,2\alpha} = 13.6$ Hz, $J_{2\beta,1\alpha} = 13.1$ Hz, $J_{2\beta,3\alpha} = 13.5$ Hz, $J_{2\beta,1\beta} = J_{2\beta,3\beta} = 3.5$ Hz, H-2*β*), 2.14 (2H, br s, H-14α and H-14*β*), 2.12 (1H, br d, $J_{15\alpha,15\beta} = 17.0$ Hz, $J_{15\alpha,17A} = J_{15\alpha,17B} = 0.5$ Hz, H-15α), 2.01 (1H, ddd, $J_{11\alpha,11\beta} = 16.9$ Hz, $J_{11\alpha,9\alpha} = 9.2$ Hz, $J_{11\alpha,12\alpha} = 5.8$ Hz, H-11α), 1.95 (3H, s, 12*β*-OAc), 1.83 (1H, br d, $J_{11\beta,11\alpha} = 16.9$ Hz, $J_{11\beta,9\alpha} = J_{11\beta,12\alpha} < 0.5$ Hz, H-11*β*), 1.76 (1H, dddd, $J_{1\beta,1\alpha} = 13.1$ Hz, $J_{1\beta,2\alpha} = 3.0$ Hz, $J_{1\beta,2\beta} = 3.5$ Hz, $J_{1\beta,3\beta} = 1.0$ Hz, H-1*β*), 1.50 (1H, ddddd, $J_{2\alpha,2\beta} = 13.6$ Hz, $J_{2\alpha,1\alpha} = 3.6$ Hz, $J_{2\alpha,1\beta} = 3.0$ Hz, $J_{2\alpha,3\alpha} = 4.2$ Hz, $J_{2\alpha,3\beta} = 2.8$ Hz, H-2α), 1.44 (3H, s, Me-20), 1.38 (3H, s, Me-18), 1.30 (1H, br d, $J_{9\alpha,11\alpha} = 9.2$ Hz, $J_{9\alpha,11\beta} < 0.5$ Hz, H-9α), 1.27 (1H, dd, $J_{5\alpha,6\alpha} = 2.4$ Hz, $J_{5\alpha,6\beta} = 12.0$ Hz, H-5α), 1.09 (1H, td, $J_{3\alpha,3\beta} = J_{3\alpha,2\beta} = 13.5$ Hz, $J_{3\alpha,2\alpha} = 4.2$ Hz, H-3α), 0.82 (1H, td, $J_{1\alpha,1\beta} = J_{1\alpha,2\beta} = 13.1$ Hz, $J_{1\alpha,2\alpha} = 3.6$ Hz, H-1α); ^{13}C NMR (pyridine-d_5, 100 MHz), see Table 1; EIMS *m/z* 376 $[M]^+$ (1), 358 (11), 343 (1), 340 (1), 334 (1), 316 (43), 301 (12), 298 (100), 283 (15), 273 (84), 253 (18), 237 (15), 227 (15), 197 (17), 183 (19), 171 (14), 162 (88), 145 (35), 144 (37), 133 (23), 131 (27), 123 (42), 119 (34), 117 (24), 109 (31), 107 (42), 105 (42); *anal.* C 70.02%, H 8.71%, calcd for $C_{22}H_{32}O_5$, C 70.18%, H 8.57%.

***ent*-7*β*-Hydroxykaur-15-en-19-oic acid (5):**[28] colorless fine needles (EtOAc−*n*-pentane), mp 266−268 °C; $[\alpha]_D^{20}$ −58.2° (*c* 0.146, MeOH); IR (KBr) ν_{max} 3417, 2932, 2872, 1697, 1469, 1295, 1251, 1237, 1193, 1057, 1000, 898, 811 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 5.14 (1H, q, $J_{15,17} = 1.5$ Hz, H-15), 3.48 (1H, dd, $J_{7\alpha,6\alpha} = 3.9$ Hz, $J_{7\alpha,6\beta} = 11.7$ Hz, H-7α), 2.31 (1H, m, $W_{1/2} = 8$ Hz, H-13*β*), 2.12 (1H, dddd, $J_{3\beta,3\alpha} = 13.2$ Hz, $J_{3\beta,2\alpha} = 2.9$ Hz, $J_{3\beta,2\beta} = 3.4$ Hz, $J_{3\beta,1\beta} = 1.3$ Hz, H-3*β*), 2.00 (2H, m*, H-6α and H-14α), 1.91 (1H, dtt, $J_{2\beta,2\alpha} = 13.4$ Hz, $J_{2\beta,1\alpha} = J_{2\beta,3\alpha} = 13.2$ Hz, $J_{2\beta,1\beta} = J_{2\beta,3\beta} = 3.4$ Hz, H-2*β*), 1.84 (1H, m*, H-1*β*), 1.79 (1H, ddd, $J_{6\beta,6\alpha} = 13.1$ Hz, $J_{6\beta,5\alpha} = 12.6$ Hz, $J_{6\beta,7\alpha} = 11.7$ Hz, H-6*β*), 1.67 (3H, d, $J_{17,15} = 1.5$ Hz, Me-17), 1.61 (1H, br d, $J_{14\beta,14\alpha} = 10.2$ Hz, $J_{14\beta,13\beta} < 0.5$ Hz, H-14*β*), 1.56 (2H, m*, H-11α and H-11*β*), 1.50 (2H, m*, H-12α and H-12*β*), 1.38 (1H, ddddd, $J_{2\alpha,2\beta} = 13.4$ Hz, $J_{2\alpha,1\alpha} = 3.9$ Hz, $J_{2\alpha,1\beta} = 3.1$ Hz, $J_{2\alpha,3\alpha} = 4.2$ Hz, $J_{2\alpha,3\beta} = 2.9$ Hz, H-2α), 1.19 (3H, s, Me-18), 1.11 (1H, dd, $J_{5\alpha,6\alpha} = 2.1$ Hz, $J_{5\alpha,6\beta} = 12.6$ Hz, H-5α), 1.00 (1H, td, $J_{3\alpha,3\beta} = J_{3\alpha,2\beta} = 13.2$ Hz, $J_{3\alpha,2\alpha} = 4.2$ Hz, H-3α), 0.98 (3H, s, Me-20), 0.93 (1H, br d, $J_{9\alpha,11\alpha} = 7.8$ Hz, $J_{9\alpha,11\beta} < 0.5$ Hz, H-9α), 0.79 (1H, td, $J_{1\alpha,1\beta} = J_{1\alpha,2\beta} = 13.2$ Hz, $J_{1\alpha,2\alpha} = 3.9$ Hz, H-1α);[43] ^{13}C NMR (acetone-d_6, 100 MHz), see Table 1; EIMS *m/z* 318 $[M]^+$ (65), 303 (15), 300 (14), 290 (3), 285 (5), 272 (22), 229 (11), 223 (11), 207 (10), 164 (21), 157 (11), 147 (26), 131 (21), 123 (61), 121 (54), 118 (43), 109 (51), 107 (52), 105 (40), 94 (100); *anal.* C 75.30%, H 9.64%, calcd for $C_{20}H_{30}O_3$, C 75.43%, H 9.50%.

***ent*-12*β*-Acetoxy-17-oxokaur-15-en-19-oic acid (7):**[28] amorphous white solid, mp 90−100 °C; $[\alpha]_D^{20}$ −37.2° (*c* 0.326, $CHCl_3$); IR (KBr) ν_{max} 3426, 2930, 2851, 2725, 1733, 1693, 1678, 1607, 1445, 1369, 1238, 1209, 1027, 986, 974, 854, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.70 (1H, s, H-17), 6.61 (1H, s, H-15), 4.91 (1H, br dd, $J_{12\alpha,11\alpha} = 6.2$ Hz, $J_{12\alpha,11\beta} < 0.5$ Hz, $J_{12\alpha,13\beta} = 3.4$ Hz, H-12α), 3.08 (1H, br dd, $J_{13\beta,12\alpha} = 3.4$ Hz, $J_{13\beta,14\alpha} = 4.2$ Hz, H-13*β*), 2.50 (1H, br d, $J_{14\beta,14\alpha} = 11.3$ Hz, $J_{14\beta,13\beta} \cong 0$ Hz, H-14*β*), 2.02 (3H, s 12*β*-OAc), 1.26 (3H, s, Me-18), 1.01 (3H, s, Me-20); EIMS *m/z* 374 $[M]^+$ (3), 332 (27), 314 (52), 299 (18), 268 (59), 161 (37), 147 (32), 146 (31), 133 (36), 131 (30), 121 (80), 119 (40), 117 (35), 109 (47), 107 (45), 43 (100).

***ent*-7*β*-Hydroxy-15*β*,16*β*-epoxykauran-19-oic acid (9):**[28] colorless fine needles (EtOAc−*n*-pentane), mp 246−248 °C and 285−290 °C dec; $[\alpha]_D^{20}$ −41.0° (*c* 0.441, MeOH); IR (KBr) ν_{max} 3417, 2928, 2869, 1702, 1470, 1251, 1229, 1198, 1044, 903, 842, 790 cm^{-1}; ^1H NMR (pyridine-d_5, 400 MHz) δ 3.98 (1H, dd, $J_{7\alpha,6\alpha} = 4.0$ Hz, $J_{7\alpha,6\beta} = 11.5$ Hz, H-7α), 2.91 (1H, s, H-15α), 2.52 (1H, ddd, $J_{6\alpha,6\beta} = 13.4$ Hz, $J_{6\alpha,5\alpha} = 2.2$ Hz, $J_{6\alpha,7\alpha} = 4.0$ Hz, H-6α), 2.47 (1H, dddd, $J_{3\beta,3\alpha} = 13.2$ Hz, $J_{3\beta,2\alpha} = 4.1$ Hz, $J_{3\beta,2\beta} = 3.7$ Hz, $J_{3\beta,1\beta} = 1.1$ Hz, H-3*β*), 2.39 (1H, dt, $J_{6\beta,6\alpha} = 13.4$ Hz, $J_{6\beta,5\alpha} = J_{6\beta,7\alpha} = 11.5$ Hz, H-6*β*), 2.26 (1H qt, $J_{2\beta,2\alpha} = J_{2\beta,1\alpha} = J_{2\beta,3\alpha} = 13.2$ Hz, $J_{2\beta,1\beta} = J_{2\beta,3\beta} = 3.7$ Hz, H-2*β*), 2.15 (1H, dd, $J_{14\alpha,14\beta} = 11.0$ Hz, $J_{14\alpha,13\beta} = 5.4$ Hz, H-14α), 2.07 (1H, ddd, $J_{13\beta,12\alpha} = 4.9$ Hz, $J_{13\beta,12\beta} = 2.7$ Hz, $J_{13\beta,14\alpha} = 5.4$ Hz, $J_{13\beta,14\beta} \cong 0$ Hz, H-13*β*), 1.86 (dddd, $J_{1\beta,1\alpha} = 13.2$ Hz, $J_{1\beta,2\alpha} = 3.2$ Hz, $J_{1\beta,2\beta} = 3.7$ Hz, $J_{1\beta,3\beta} = 1.1$ Hz, H-1*β*), 1.52 (1H, m*, H-2α), 1.50 (4H, m*, H-11α, H-11*β*, H-12α, and H-12*β*), 1.41 (3H, s, Me-17), 1.34 (3H, s, Me-18), 1.30 (1H, br d, $J_{14\beta,14\alpha} = 11.0$ Hz, $J_{14\beta,13\beta}$

≅ 0 Hz, H-14*β*), 1.20 (1H, dd, $J_{5\alpha,6\alpha}$ = 2.2 Hz, $J_{5\alpha,6\beta}$ = 11.5 Hz, H-5α), 1.15 (3H, s, Me-20), 1.14 (1H, br d, $J_{9\alpha,11\alpha}$ = 7.0 Hz, $J_{9\alpha,11\beta}$ < 0.5 Hz, H-9α), 1.07 (1H, td, $J_{3\alpha,3\beta}$ = $J_{3\alpha,2\beta}$ = 13.2 Hz, $J_{3\alpha,2\alpha}$ = 4.3 Hz, H-3α), 0.86 (1H, td, $J_{1\alpha,1\beta}$ = $J_{1\alpha,2\beta}$ = 13.2 Hz, $J_{1\alpha,2\alpha}$ = 3.9 Hz, H-1α);[43] ^{13}C NMR (pyridine-d_5, 100 MHz), see Table 1; EIMS *m*/*z* 334 $[M]^+$ (100), 319 (10), 316 (65), 301 (25), 289 (44), 271 (38), 255 (32), 159 (26), 151 (35), 149 (29), 147 (34), 145 (33), 137 (52), 136 (57), 135 (56), 133 (44), 131 (34), 125 (31), 123 (71), 121 (44), 119 (44), 109 (58), 107 (63), 43 (82); *anal.* C 71.96%, H 8.89%, calcd for $C_{20}H_{30}O_4$, C 71.82%, H 9.04%.

***ent*-Labda-8(17),12*Z*,14-triene-2α,3*β*-diol (10):**[28] amorphous white solid, mp 74−80 °C; $[\alpha]_D^{20}$ −22.4° (*c* 0.49, $CHCl_3$); IR, ^{1}H and ^{13}C NMR, and mass spectra identical to those reported[2] for the compound isolated from *Croton joufra* [mp 72−74 °C; $[\alpha]_D^{25}$ −18.24° (*c* 0.34, $CHCl_3$)] and for the *ent*-2α-deacetyl derivative of **15** [mp 76−80 °C; $[\alpha]_D^{20}$ −23.7° (*c* 0.313, $CHCl_3$)].[1]

Methyl *ent*-12*β*-hydroxykaur-16-en-19-oate (12):[28] obtained by methylation of **11**; colorless thick oil; $[\alpha]_D^{18}$ −57.1° (*c* 0.621, $CHCl_3$); IR, ^{1}H NMR, and mass spectra identical to those reported previously.[3−6] Lit.: thick oil,[3,5] no $[\alpha]_D$ value has previously been reported.[3−6] For *ent*-12*β*-hydroxykaur-16-en-19-oic acid: $[\alpha]_D^{24}$ −44.7° (*c* 1.0, $CHCl_3$).[5]

Methyl *ent*-12*β*-acetoxy-7*β*-hydroxykaur-15-en-19-oate (13):[28] colorless prisms (EtOAc−*n*-pentane), mp 113−115 °C; $[\alpha]_D^{18}$ −14.8° (*c* 0.446, $CHCl_3$); IR (KBr) ν_{max} 3542, 3021, 2943, 1723, 1708, 1635, 1467, 1437, 1369, 1241, 1155, 1034, 1016, 994, 965, 817 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 5.19 (1H, qd, $J_{15,17}$ = 1.6 Hz, $J_{15,14\beta}$ = 0.8 Hz, H-15), 4.94 (1H, ddd, $J_{12\alpha,11\alpha}$ = 6.9 Hz, $J_{12\alpha,11\beta}$ = 1.0 Hz, $J_{12\alpha,13\beta}$ = 3.2 Hz, H-12α), 3.63 (3H, s, 19-COOMe), 3.60 (1H, dd, $J_{7\alpha,6\alpha}$ = 4.0 Hz, $J_{7\alpha,6\beta}$ = 12.4 Hz, H-7α), 2.48 (1H, br dd, $J_{13\beta,12\alpha}$ = 3.2 Hz, $J_{13\beta,14\alpha}$ = 4.0 Hz, $J_{13\beta,14\beta}$ ≅ 0 Hz, H-13*β*), 2.17 (1H, dddd, $J_{3\beta,3\alpha}$ = 13.5 Hz, $J_{3\beta,2\alpha}$ = 4.2 Hz, $J_{3\beta,2\beta}$ = 3.8 Hz, $J_{3\beta,1\beta}$ = 1.6 Hz, H-3*β*), 2.07 (1H, ddd, $J_{6\alpha,6\beta}$ = 13.1 Hz, $J_{6\alpha,5\alpha}$ = 1.8 Hz, $J_{6\alpha,7\alpha}$ = 4.0 Hz, H-6α), 2.02 (3H, s, 12*β*-OAc), 1.97 (1H, ddd, $J_{11\alpha,11\beta}$ = 17.0 Hz, $J_{11\alpha,9\alpha}$ = 9.9 Hz, $J_{11\alpha,12\alpha}$ = 6.9 Hz, H-11α), 1.95 (1H, br dd, $J_{14\beta,14\alpha}$ = 11.7 Hz, $J_{14\beta,13\beta}$ ≅ 0 Hz, $J_{14\beta,15}$ = 0.8 Hz, H-14*β*), 1.80 (1H, dddt, $J_{2\beta,2\alpha}$ = $J_{2\beta,3\alpha}$ = 13.4 Hz, $J_{2\beta,1\alpha}$ = 13.2 Hz, $J_{2\beta,1\beta}$ = $J_{2\beta,3\beta}$ = 3.8 Hz, H-2*β*), 1.77 (3H, d, $J_{17,15}$ = 1.6 Hz, Me-17), 1.75 (1H, ddd, $J_{6\beta,6\alpha}$ = 13.1 Hz, $J_{6\beta,5\alpha}$ = 12.5 Hz, $J_{6\beta,7\alpha}$ = 12.4 Hz, H-6*β*), 1.70 (1H, dd, $J_{14\alpha,14\beta}$ = 11.7 Hz, $J_{14\alpha,13\beta}$ = 4.0 Hz, H-14α), 1.68 (1H, dddd, $J_{1\beta,1\alpha}$ = 13.2 Hz, $J_{1\beta,2\alpha}$ = 3.5 Hz, $J_{1\beta,2\beta}$ = 3.8 Hz, $J_{1\beta,3\beta}$ = 1.6 Hz, H-1*β*), 1.56 (1H, br s, 7*β*-OH), 1.53 (1H, br dd, $J_{11\beta,11\alpha}$ = 17.0 Hz, $J_{11\beta,9\alpha}$ < 0.5 Hz, $J_{11\beta,12\alpha}$ = 1.0 Hz, H-11*β*), 1.40 (1H, ddddd, $J_{2\alpha,2\beta}$ = 13.4 Hz, $J_{2\alpha,1\alpha}$ = 4.1 Hz, $J_{2\alpha,1\beta}$ = 3.5 Hz, $J_{2\alpha,3\alpha}$ = 4.3 Hz, $J_{2\alpha,3\beta}$ = 4.2 Hz, H-2α), 1.17 (3H, s, Me-18), 1.10 (1H, br d, $J_{9\alpha,11\alpha}$ = 9.9 Hz, $J_{9\alpha,11\beta}$ < 0.5 Hz, H-9α), 1.07 (1H, dd, $J_{5\alpha,6\alpha}$ = 1.8 Hz, $J_{5\alpha,6\beta}$ = 12.5 Hz, H-5α), 0.96 (1H, td, $J_{3\alpha,3\beta}$ = $J_{3\alpha,2\beta}$ = 13.5 Hz, $J_{3\alpha,2\alpha}$ = 4.3 Hz, H-3α), 0.87 (3H, s, Me-20), 0.72 (1H, td, $J_{1\alpha,1\beta}$ = $J_{1\alpha,2\beta}$ = 13.2 Hz, $J_{1\alpha,2\alpha}$ = 4.1 Hz, H-1α); ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; EIMS *m*/*z* 390 $[M]^+$ (10), 375 (1), 372 (1), 348 (2), 330 (18), 315 (12), 312 (32), 287 (14), 271 (13), 253 (14), 237 (24), 162 (45), 145 (56), 144 (49), 131 (33), 123 (89), 121 (42), 119 (48), 109 (80), 107 (66), 43 (100); *anal.* C 70.81%, H 8.69%, calcd for $C_{23}H_{34}O_5$, C 70.74%, H 8.78%.

Methyl *ent*-12*β*-acetoxy-15*β*,16*β*-epoxykauran-19-oate (14):[28] colorless prisms (EtOAc−*n*-hexane), mp 195−196 °C; $[\alpha]_D^{20}$ −17.4° (*c* 1.196, $CHCl_3$); IR (KBr) ν_{max} 3010, 2998, 2951, 1720, 1434, 1363, 1239, 1157, 1029, 990, 851 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 4.97 (1H, ddd, $J_{12\alpha,11\alpha}$ = 4.8 Hz, $J_{12\alpha,11\beta}$ = 1.9 Hz, $J_{12\alpha,13\beta}$ = 4.1 Hz, H-12α), 3.63 (3H, s, 19-COOMe), 2.63 (1H, s, H-15α), 2.23 (1H, t, $J_{13\beta,12\alpha}$ = $J_{13\beta,14\alpha}$ = 4.1 Hz, $J_{13\beta14\beta}$ ≅ 0 Hz, H-13*β*), 2.16 (1H, ddd, $J_{3\beta,3\alpha}$ = 13.3 Hz, $J_{3\beta,2\alpha}$ = 4.2 Hz, $J_{3\beta,2\beta}$ = 3.6 Hz, H-3*β*), 2.01 (3H, s, 12*β*-OAc), 1.82 (1H, m*, H-6α), 1.78 (4H, m*, H-2*β*, H-7*β*, H-11α, and H-14*β*), 1.71 (1H, ddd, $J_{1\beta,1\alpha}$ = 13.4 Hz, $J_{1\beta,2\alpha}$ = 4.2 Hz, $J_{1\beta,2\beta}$ = 3.6 Hz, H-1*β*), 1.63 (1H, m*, H-11*β*), 1.61 (1H, m*, H-6*β*), 1.47 (1H, ddd, $J_{7\alpha,7\beta}$ = 13.3 Hz, $J_{7\alpha,6\alpha}$ = 2.4 Hz, $J_{7\alpha,6\beta}$ = 12.0 Hz, H-7α), 1.43 (3H, s, Me-17), 1.39 (1H, dm, $J_{2\alpha,2\beta}$ = 13.1 Hz, $J_{2\alpha,1\alpha}$ ≅ $J_{2\alpha,1\beta}$ ≅ $J_{2\alpha,3\alpha}$ ≅ $J_{2\alpha,3\beta}$ ≅ 4 Hz, H-2α), 1.23 (1H, br d, $J_{9\alpha,11\alpha}$ = 9.6 Hz, $J_{9\alpha,11\beta}$ < 0.5 Hz, H-9α), 1.16 (3H, s, Me-18), 1.01 (1H, dd, $J_{5\alpha,6\alpha}$ = 1.4 Hz, $J_{5\alpha,6\beta}$ = 11.5 Hz, H-5α), 0.98 (1H, td, $J_{3\alpha,3\beta}$ = $J_{3\alpha,2\beta}$ = 13.3 Hz, $J_{3\alpha,2\alpha}$ = 4.2 Hz, H-3α), 0.93 (1H, dd, $J_{14\alpha,14\beta}$ = 12.0 Hz, $J_{14\alpha,13\beta}$ = 4.1 Hz, H-14α), 0.83 (3H, s, Me-20), 0.79 (1H, td, $J_{1\alpha,1\beta}$ = $J_{1\alpha,2\beta}$ = 13.4 Hz, $J_{1\alpha,2\alpha}$ = 4.1 Hz, H-1α);[43] ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; EIMS *m*/*z* 390 $[M]^+$ (5), 375 (1), 347 (100), 331 (27), 330 (30), 315 (17), 287 (42), 271 (41), 255 (20), 227 (29), 149 (25), 147 (29), 145 (25), 135 (36), 131 (26), 121 (57), 119 (26), 109 (31), 107 (30), 43 (87); *anal.* C 70.81%, H 8.92%, calcd for $C_{23}H_{34}O_5$, C 70.74%, H 8.78%.

Preparation of Compound 10 from Compound 2. A stirred solution of **2** (8 mg, 0.023 mmol) in EtOH (2 mL) was treated with an ethanolic solution of KOH (8%, w/v, 1.5 mL, 2.14 mmol) at room temperature for 18 h. Then, water (10 mL) was added to the reaction and the mixture was extracted with CH_2Cl_2 (10 × 4 mL). The extracts were dried (Na_2SO_4) and filtered, and the solvents removed in vacuo, yielding a residue (4 mg, 0.013 mmol, 56.5%) of pure **10**:[1,2] amorphous white solid, mp 70−78 °C; $[\alpha]_D^{20}$ −21.8° (*c* 0.201, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) and mass spectra identical to those obtained for **3** (see above).

Benzoylation of Compound 10[1,2] to Give *ent*-Labda-8(17),12*Z*,14-triene-2α,3*β*-dibenzoate (16).[28] To a solution of **10** (40 mg, 0.131 mmol) in anhydrous pyridine (4 mL) was added an excess of benzoyl chloride (50 mg, 0.355 mmol), and the reaction mixture was left at room temperature for 5 h. Water (20 mL) was added, and the reaction mixture was stirred for 30 min and then extracted with CH_2Cl_2 (4 × 20 mL). The extract was washed with a saturated aqueous solution of Na_2CO_3 (4 × 10 mL), then with water (2 × 10 mL), and finally dried (Na_2SO_4) and filtered, and the solvents were removed in vacuo. The residue (60 mg) was subjected to column chromatography [Si gel 230−400 mesh, 10 g, petroleum ether−EtOAc (49:1) as eluent], yielding pure **16** (43 mg, 0.084 mmol, 63.8%): amorphous white powder, mp 75−85 °C; $[\alpha]_D^{19}$ +28.2° (*c* 0.305, $CHCl_3$); CD $\Delta\epsilon_{248}$ −6.6, $\Delta\epsilon_{243}$ 0, $\Delta\epsilon_{235}$ +12.5, $\Delta\epsilon_{229}$ 0, $\Delta\epsilon_{224}$ −10.3 (*C* 10^{-3} M, dioxane); IR (KBr) ν_{max} 3087, 2973, 2944, 2857, 1722, 1644, 1602, 1584, 1450, 1314, 1280, 1111, 1069, 1026, 993, 953, 895, 709 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 6.73 (1H, ddd, $J_{14,15A}$ = 10.8 Hz, $J_{14,15B}$ = 17.3 Hz, $J_{14,12}$ = 0.7 Hz, H-14), 5.47 (1H, ddd, $J_{2\beta,1\alpha}$ = 11.5 Hz, $J_{2\beta,1\beta}$ = 4.5 Hz, $J_{2\beta,3\alpha}$ = 10.4 Hz, H-2*β*), 5.25 (1H, d, $J_{3\alpha,2\beta}$ = 10.4 Hz, H-3α), 5.24 (1H, br t, $J_{12,11A}$ = $J_{12,11B}$ = 6.4 Hz, H-12), 5.15 (1H, ddd, $J_{15B,15A}$ = 1.6 Hz, $J_{15B,14}$ = 17.3 Hz, $J_{15B,12}$ = 0.6 Hz, H_B-15, pro-*Z* hydrogen), 5.07 (1H, dt, $J_{15A,14}$ = 10.8 Hz, $J_{15A,15B}$ = $J_{15A,12}$ = 1.6 Hz, H_A-15, pro-*E* hydrogen), 4.91 (1H, q, $J_{17A,17B}$ = $J_{17B,7\alpha}$ = $J_{17B,9\alpha}$ = 1.5 Hz, H_B-17, pro-*E* hydrogen), 4.54 (1H, q, $J_{17A,17B}$ = $J_{17A,7\alpha}$ = $J_{17A,9\alpha}$ = 1.5 Hz, H_A-17, pro-*Z* hydrogen), 2.45 (1H, ddd, $J_{7\beta,7\alpha}$ = 13.0 Hz, $J_{7\beta,6\alpha}$ = 2.4 Hz, $J_{7\beta,6\beta}$ = 4.2 Hz, H-7*β*), 2.39 (1H, dd, $J_{1\beta,1\alpha}$ = 12.4 Hz, $J_{1\beta,2\beta}$ = 4.5 Hz, H-1*β*), 2.35 (1H, ddd, $J_{11B,11A}$ = 17.5 Hz, $J_{11B,9\alpha}$ = 11.2 Hz, $J_{11B,12}$ = 6.4 Hz, H_B-11), 2.25 (1H, ddd, $J_{11A,11B}$ = 17.5 Hz, $J_{11A,9\alpha}$ = 3.2 Hz, $J_{11A,12}$ = 6.4 Hz, H_A-11), 2.06 (1H, br ddd, $J_{7\alpha,7\beta}$ = 13.0 Hz, $J_{7\alpha,6\alpha}$ = 4.0 Hz, $J_{7\alpha,6\beta}$ = 12.0 Hz, H-7α), 1.85 (1H, br dd, $J_{9\alpha,11A}$ = 3.2 Hz, $J_{9\alpha,11B}$ = 11.2 Hz, H-9α), 1.79 (1H, dddd, $J_{6\alpha,6\beta}$ = 12.9 Hz, $J_{6\alpha,5\alpha}$ = 2.8 Hz, $J_{6\alpha,7\alpha}$ = 4.0 Hz, $J_{6\alpha,7\beta}$ = 2.4 Hz, H-6α), 1.75 (3H, d, $J_{16,12}$ = 1.1 Hz, Me-16), 1.52 (1H, dd, $J_{1\alpha,1\beta}$ = 12.4 Hz, $J_{1\alpha,2\beta}$ = 11.5 Hz, H-1α), 1.48 (2H, m, H-5α and H-6*β*, these assignments were in agreement with the HSQC spectrum), 1.09 (3H, s, Me-19), 1.01 (3H, s, Me-18), 0.99 (3H, s, Me-20), 2α-OBz: 7.89 (2H, dd, *J* = 8.4, 1.4 Hz, H-2′ and H-6′), 7.32 (2H, dd, *J* = 8.4, 7.4 Hz, H-3′ and H-5′), 7.44 (1H, tt, *J* = 7.4, 1.4 Hz, H-4′), 3*β*-OBz: 7.96 (2H, dd, *J* = 8.4, 1.4 Hz, H-2″ and H-6″), 7.34 (2H, dd, *J* = 8.4, 7.4 Hz, H-3″ and H-5″), 7.46 (1H, tt, *J* = 7.4, 1.4 Hz, H-4″); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 146.6 (C, C-8), 133.7 (CH, C-14), 132.1 (C, C-13), 130.5 (CH, C-12), 113.6 (CH_2, C-15), 109.3 (CH_2, C-17), 80.6 (CH, C-3), 71.1 (CH, C-2), 56.8 (CH, C-9), 54.4 (CH, C-5), 42.5 (CH_2, C-1), 40.2 (C, C-10), 39.8 (C, C-4), 37.5 (CH_2, C-7), 28.7 (CH_3, C-18), 23.5 (CH_2, C-6), 22.3 (CH_2, C-11), 19.7 (CH_3, C-16), 17.7 (CH_3, C-19), 15.4 (CH_3, C-20), OBz: 166.2 and 166.4 (C, O*C*O*C*$_6H_5$), 132.9 and 132.8 (CH, C-4′ and C-4″), 130.1 and 129.9 (C, C-1′ and C-1″), 129.5 (CH, C-2′, C-6′, C-2″, and C-6″), 128.3 and 128.2 (CH, C-3′, C-5′, C-3″, and C-5″); EIMS *m*/*z* 512 $[M]^+$ (0.1), 390 (1.4), 375 (0.3), 268 (4), 253 (5), 187 (6), 133 (6), 119 (5), 105 (100); *anal.* C 79.40%, H 7.71%, calcd for $C_{34}H_{40}O_4$, C 79.65%, H 7.86%.

Methylation of Compound 3 to Give Methyl *ent*-12*β*-Acetoxy-15*β*-hydroxykaur-16-en-19-oate (17).[28] A solution of **3** (25 mg, 0.066 mmol) in Et_2O (50 mL) was treated with an excess of an ethereal solution of CH_2N_2 at room temperature for 3 h. After evaporation of the solvent a residue (25 mg) remained. Crystallization from EtOAc−*n*-pentane yielded **17** (22 mg, 0.056 mmol, 84.8%): colorless plates, mp 128−131 °C; $[\alpha]_D^{20}$ −43.0° (*c* 0.293, $CHCl_3$); IR (KBr) ν_{max} 3444, 3071, 2949, 1726, 1632, 1464, 1376, 1240, 1151, 1017, 908 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.30 (1H, br d, $J_{17B,17A} = 1.1$ Hz, H_B-17, *cis* hydrogen with respect to C-15), 5.23 (1H, br d, $J_{17A,17B} = 1.1$ Hz, H_A-17, *trans* hydrogen with respect to C-15), 4.72 (1H, ddd, $J_{12\alpha,11\alpha} = 4.2$ Hz, $J_{12\alpha,11\beta} = 1.2$ Hz, $J_{12\alpha,13\beta} = 4.4$ Hz, H-12α), 3.83 (1H, s, H-15α), 3.65 (3H, s, 19-COOMe), 2.84 (1H, br t, $J_{13\beta,12\alpha} \cong J_{13\beta,14\alpha} \cong 4.5$ Hz, $J_{13\beta,14\beta} < 0.5$ Hz, H-13*β*), 2.16 (1H, dddd, $J_{3\beta,3\alpha} = 13.3$ Hz, $J_{3\beta,2\alpha} = 4.3$ Hz, $J_{3\beta,2\beta} = 3.8$ Hz, $J_{3\beta,1\beta} = 1.8$ Hz, H-3*β*), 2.15 (1H, br d, $J_{14\beta,14\alpha} = 12.3$ Hz, $J_{14\beta,13\beta} < 0.5$ Hz, H-14*β*), 2.02 (3H, s, 12*β*-OAc), 1.91 (1H, dddd, $J_{6\alpha,6\beta} = 13.6$ Hz, $J_{6\alpha,5\alpha} = 2.1$ Hz, $J_{6\alpha,7\alpha} = 4.0$ Hz, $J_{6\alpha,7\beta} = 3.4$ Hz, H-6α), 1.78 (2H, m*, H-2*β* and H-7*β*), 1.70 (3H, m*, H-1*β*, H-6*β*, and H-11α), 1.61 (1H, br dd, $J_{11\beta,11\alpha} = 16.4$ Hz, $J_{11\beta,9\alpha} < 0.5$ Hz, $J_{11\beta,12\alpha} = 1.2$ Hz, H-11*β*), 1.40 (1H, td, $J_{7\alpha,7\beta} = J_{7\alpha,6\beta} = 13.6$ Hz, $J_{7\alpha,6\alpha} = 4.0$ Hz, H-7α), 1.39 (1H, m*, H-2α), 1.30 (1H, dd, $J_{14\alpha,14\beta} = 12.3$ Hz, $J_{14\alpha,13\beta} = 4.6$ Hz, H-14α), 1.18 (3H, s, Me-18), 1.14 (1H, br d, $J_{9\alpha,11\alpha} = 9.6$ Hz, $J_{9\alpha,11\beta} < 0.5$ Hz, H-9α), 1.04 (1H, dd, $J_{5\alpha,6\alpha} = 2.1$ Hz, $J_{5\alpha,6\beta} = 12.1$ Hz, H-5α), 0.98 (1H, td, $J_{3\alpha,3\beta} = J_{3\alpha,2\beta} = 13.3$ Hz, $J_{3\alpha,2\alpha} = 4.2$ Hz, H-3α), 0.87 (3H, s, Me-20), 0.75 (1H, td, $J_{1\alpha,1\beta} = J_{1\alpha,2\beta} = 13.2$ Hz, $J_{1\alpha,2\alpha} = 4.2$ Hz, H-1α);[43] ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; EIMS *m/z* 390 $[M]^+$ (1), 372 (1), 330 (100), 312 (17), 271 (42), 270 (49), 255 (29), 253 (27), 237 (26), 173 (23), 161 (31), 148 (37), 147 (31), 145 (35), 133 (34), 131 (34), 123 (43), 121 (70); *anal.* C 70.66%, H 8.90%, calcd for $C_{23}H_{34}O_5$, C 70.74%, H 8.78%.

Methylation of Compound 7 to Give Methyl *ent*-12*β*-Acetoxy-17-oxokaur-15-en-19-oate (19).[28] Treatment of **7** (20 mg, 0.053 mmol) with an excess of CH_2N_2, as described above for obtaining **17**, yielded the methyl ester **19** (16 mg, 0.041 mmol, after crystallization from EtOAc−*n*-pentane, 77.4%): colorless plates, mp 146−149 °C; $[\alpha]_D^{20}$ −39.6° (*c* 0.723, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 249 (3.84) nm; IR (KBr) ν_{max} 2990, 2955, 2730, 2708, 1738, 1713, 1684, 1610, 1444, 1370, 1243, 1208, 1026, 985, 973 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.69 (1H, d, $J_{17,15} = 0.8$ Hz, H-17), 6.60 (1H, d, $J_{15,17} = 0.8$ Hz, H-15), 4.90 (1H, ddd, $J_{12\alpha,11\alpha} = 6.0$ Hz, $J_{12\alpha,11\beta} = 1.2$ Hz, $J_{12\alpha,13\beta} = 4.2$ Hz, H-12α), 3.64 (3H, s, 19-COOMe), 3.07 (1H, t, $J_{13\beta,12\alpha} = J_{13\beta,14\alpha} = 4.2$ Hz, $J_{13\beta,14\beta} = 0$ Hz, H-13*β*), 2.47 (1H, d, $J_{14\beta,14\alpha} = 11.4$ Hz, $J_{14\beta,13\beta} = 0$ Hz, H-14*β*), 2.16 (1H, dddd, $J_{3\beta,3\alpha} = 13.4$ Hz, $J_{3\beta,2\alpha} = 4.2$ Hz, $J_{3\beta,2\beta} = 3.8$ Hz, $J_{3\beta,1\beta} = 1.6$ Hz, H-3*β*), 2.02 (3H, s, 12*β*-OAc), 1.86 (1H, m*, H-6α), 1.82 (1H, m*, H-11α), 1.80 (1H, m*, H-2*β*), 1.74 (1H, m*, H-7*β*), 1.70 (1H, m*, H-6*β*), 1.69 (1H, m*, H-1*β*), 1.69 (1H, td, $J_{7\alpha,7\beta} = J_{7\alpha,6\beta} = 13.0$ Hz, $J_{7\alpha,6\alpha} = 4.0$ Hz, H-7α), 1.61 (1H, br dd, $J_{11\beta,11\alpha} = 17.6$ Hz, $J_{11\beta,9\alpha} < 0.5$ Hz, $J_{11\beta,12\alpha} = 1.2$ Hz, H-11*β*), 1.40 (1H, m*, H-2α), 1.38 (1H, m*, H-14α), 1.23 (1H, br d, $J_{9\alpha,11\alpha} = 9.6$ Hz, $J_{9\alpha,11\beta} < 0.5$ Hz, H-9α), 1.17 (3H, s, Me-18), 1.07 (1H, dd, $J_{5\alpha,6\alpha} = 2.8$ Hz, $J_{5\alpha,6\beta} = 11.6$ Hz, H-5α), 0.98 (1H, td, $J_{3\alpha,3\beta} = J_{3\alpha,2\beta} = 13.4$ Hz, $J_{3\alpha,2\alpha} = 4.2$ Hz, H-3α), 0.87 (3H, s, Me-20), 0.76 (1H, td, $J_{1\alpha,1\beta} = J_{1\alpha,2\beta} = 13.2$ Hz, $J_{1\alpha,2\alpha} = 4.1$ Hz, H-1α);[43] ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; EIMS *m/z* 388 $[M]^+$ (4), 346 (19), 328 (57), 316 (27), 269 (43), 268 (58), 257 (22), 253 (21), 173 (23), 161 (46), 160 (30), 147 (30), 133 (35), 123 (57), 121 (97), 119 (44), 117 (36), 109 (62), 107 (63), 43 (100); *anal.* C 70.93%, H 8.21%, calcd for $C_{23}H_{32}O_5$, C 71.11%, H 8.30%.

Biological Assays. Antimicrobial activities of **1**, **3**−**5**, **7**, **9**, **10**, **12**−**14**, **17**, and **19** were tested against *Staphylococcus aureus* ATCC 25923, *Escherischia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *Candida albicans* CIP 3153A. The minimum inhibitory concentration (MIC) values were determined by the serial broth microdilution method according to NCCLS.[44] The compounds were dissolved in DMSO and graded concentration of broth medium (Mueller-Hinton for bacteria, YMA for the yeast) ranging from 250 to 7.8 μg/mL. Solvent blank was included. Kanamycin was used as positive control (MIC values < 7.8 mg/mL for *S. aureus* and *E. coli* strains).

Acknowledgment. The authors are indebted to Prof. R. Riguera, University of Santiago de Compostela, Spain, for recording the CD spectrum of **14** and helpful discussions. Thanks to Dr. E. S. Martins, "Centro de Botânica do Instituto de Investigação Científica Tropical", Lisbon, Portugal, for the identification of the plant material. The authors are also very grateful to Prof. A. Duarte, Microbiology Laboratory, Faculty of Phamacy, Lisbon University, Portugal, for performing the biological assay. This work was supported by funds from the Spanish "Comisión Interministerial de Ciencia y Tecnología" (CICYT, grant no. AGL 2001-1652) and from Portuguese FCT (I&D no. 8/94), POCTI (QCA III), and Feder Porjects. One of us (C.G.-M.) thanks the Praxis Program for a fellowship (Praxis XXI/BD/18046/98).

References and Notes

(1) Gaspar-Marques, C.; Simões, M. F.; Duarte, A.; Rodríguez, B. *J. Nat. Prod.* **2003**, *66*, 491−496.
(2) Sutthivaiyakit, S.; Nareeboon, P.; Ruangrangsi, N.; Ruchirawat, S.; Pisutjaroenpong, S.; Mahidol, C. *Phytochemistry* **2001**, *56*, 811−814.
(3) Beale, M. H.; Bearder, J. R.; MacMillan, J.; Matsuo, A.; Phinney, B. O. *Phytochemistry* **1983**, *22*, 875−881.
(4) Lewis, N. J.; MacMillan, J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1270−1278.
(5) Bohlmann, F.; Knoll, K.-H.; Robinson, H.; King, R. M. *Phytochemistry* **1980**, *19*, 107−110.
(6) Bohlmann, F.; Jakupovic, J.; King, R. M.; Robinson, H. *Phytochemistry* **1980**, *19*, 863−868.
(7) Biftu, T.; Stevenson, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 360−363.
(8) Star, A. E.; Mabry, T. J. *Phytochemistry* **1971**, *10*, 2817−2818.
(9) Sakakibara, M.; DiFeo, D.; Nakatani, N.; Timmermann, B.; Mabry, T. J. *Phytochemistry* **1976**, *15*, 727−731.
(10) Wollenweber, E.; Wassum, M. *Tetrahedron Lett.* **1972**, *9*, 797−800.
(11) Rodríguez, B.; Martín-Panizo, F. *An. Quím.* **1979**, *75*, 431−432.
(12) Rao, M. M.; Kingston, D. G. I.; Spittler, T. D. *Phytochemistry* **1970**, *9*, 227−228.
(13) Kupchan, S. M.; Sigel, C. W.; Hemingway, R. J.; Knox, J. R.; Udayamurthy, M. S. *Tetrahedron* **1969**, *25*, 1603−1615.
(14) Timmermann, B. N.; Mues, R.; Mabry, T. J.; Powell, A. M. *Phytochemistry* **1979**, *18*, 1855−1858.
(15) Seebacher, W.; Simic, N.; Weis, R.; Saf, R.; Kunert, O. *Magn. Reson. Chem.* **2003**, *41*, 636−638.
(16) Krebs, H. C.; Rakotoarimanga, J. V.; Habermehl, G. G. *Magn. Reson. Chem.* **1990**, *28*, 124−128.
(17) Juell, S. M.-K.; Hansen, R.; Jork, H. *Arch. Pharm. (Weinheim, Ger.)* **1976**, *309*, 458−466.
(18) Several numbering systems are in use for aromadendranes; the one chosen for this paper is that most commonly used (Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, 1991; Vol. 1, p XXV), and it is indicated on formula **1**.
(19) Faure, R.; Ramanoelina, A. R. P.; Rakotonirainy, O.; Bianchini, J.-P.; Gaydou, E. M. *Magn. Reson. Chem.* **1991**, *29*, 969−971.
(20) Ciminiello, P.; Fattorusso, E.; Magno, S.; Mayol, L. *Can. J. Chem.* **1987**, *65*, 518−522.
(21) Rashid, M. A.; Gray, A. I.; Waterman, P. G.; Armstrong, J. A. *J. Nat. Prod.* **1995**, *58*, 618−621.
(22) Wessels, M.; König, G. M.; Wright, A. D. *J. Nat. Prod.* **2001**, *64*, 370−372.
(23) Goldsby, G.; Burke, B. A. *Phytochemistry* **1987**, *26*, 1059−1063.
(24) Gijsen, H. J. M.; Wijnberg, J. B. P. A.; de Groot, Ae. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch., Eds.; Springer-Verlag: Vienna, 1995; Vol. 64, pp 149−193.
(25) Abdel-Mogib, M.; Albar, H. A.; Batterjee, S. M. *Molecules* **2002**, *7*, 271−301.
(26) Fournier, G.; Paris, M.; Dumitresco, S. M.; Pages, N.; Boudene, C. *Planta Med.* **1986**, *52*, 486-488.
(27) A GC analysis[26] of the essential oil of *P. fruticosus* on a fused silica capillary column allowed the identification of 10(14)-aromadendrene, but without defining its absolute configuration.
(28) Since compounds **2**−**17** and **19** belong to the *enantio* series, the *ent*-α- or *ent*-*β*-configuration for a substituent indicates that it is placed, respectively, above or below the plane of the formulas depicted for these substances. Moreover, the α- or *β*-configurations indicated for the assignment of the ^1H NMR spectra of these compounds also refer to this nomenclature throughout the text.
(29) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy. Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983; pp 15−17, 55−103.
(30) Compound **16** showed another Cotton effect ($\Delta\epsilon_{248}$ −6.6) which could be associated with interactions between the benzoates and the 12*Z*,-14-diene chromophore (see ref 29, pp 255−259).
(31) Hutchison, M.; Lewer, P.; MacMillan, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2363−2366.
(32) Liu, G.; Müller, R.; Rüedi, P. *Helv. Chim. Acta* **2003**, *86*, 420−438.

(33) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, 1991; Vol. 2, pp 906−946, 948−956.
(34) Katti, S. B.; Rüedi, P.; Eugster, C. H. *Helv. Chim. Acta* **1982**, *65*, 2189−2197.
(35) Liu, G.; Rüedi, P. *Phytochemistry* **1996**, *41*, 1563−1568.
(36) Fujita, E.; Ochiai, M.; Ichida, I.; Chatterjee, A.; Desmukh, S. K. *Phytochemistry* **1975**, *14*, 2249−2251.
(37) Only eight phyllocladane diterpenoids have been isolated from *Plectranthus* species,[25,32−34] whereas 21 *ent*-kaurane derivatives, including those described in this work (**3**−**9** and **11**), have been found[1,25] in plants belonging to this genus.
(38) Duc, D. K. M.; Fétizon, M.; Lazare, S.; Grant, P. K.; Nicholls, M. J.; Liau, H. T. L.; Francis, M. J.; Poisson, J.; Bernassau, J.-M.; Roque, N. F.; Wovkulich, P. M.; Wenkert, E. *Tetrahedron* **1981**, *37*, 2371−2374.
(39) Bohlmann, F.; Suding, H.; Cuatrecasas, J.; Robinson, H.; King, R. M. *Phytochemistry* **1980**, *19*, 2399−2403.
(40) Herz, W.; Kulanthaivel, P.; Watanabe, K. *Phytochemistry* **1983**, *22*, 2021−2025.
(41) Harrigan, G. G.; Bolzani, V. S.; Gunatilaka, A. A. L.; Kingston, D. G. I. *Phytochemistry* **1994**, *36*, 109−113.
(42) Anam, E. M. *Indian. J. Chem.* **1998**, *37B*, 187−189.
(43) Signals marked with an asterisk appeared as overlapped or partially overlapped multiplets, and their assignments were in agreement with the HSQC spectrum.
(44) Anonymous. In *National Committee for Clinical Laboratory Standards*, 5th ed.; NCCLS: Wayne, PA, 2000; approved standard M7-A5.

NP030490J