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Artículo Científico

Allylic oxidation of *ent*-Kaurenic acid, *ent*-Kaurenic acid Methyl Ester and *ent*-Kaurenol

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Resumen:

En este artículo se presenta la oxidación alílica del ácido *ent*-kaurénico, del éster metílico del ácido *ent*-kaurénico y del *ent*-kaurenol. La reacción se realizó utilizando dioxano como solvente, a temperatura ambiente bajo agitación durante 4 horas. Se trató aproximadamente 0,3 mmol de sustrato con 1,2 mmol de SeO_2 y 4,1 mmol de H_2O_2. La oxidación del ácido ent-kaurénico produjo un 56% de ácido *ent*-15α–hidroxi-kaur-16-en-19-oico (**2a**). La oxidación del éster metílico del ácido *ent*-kaurénico dio dos productos: el éster metílico del ácido *ent*-15α–hidroxi-kaur-16-en-19-oico (**2b**, 34%) y el éster metílico del ácido *ent*-15α-16α-epoxi-17-hidroxi-kauran-19-oico (**3a**, 59%). De manera similar la oxidación del *ent*-kaurenol condujo a la formación de dos productos: *ent*-15α,19-dihidroxi-kaur-16-eno (**2c**, 56,7%) y *ent*-15α-16α-epoxi-17,19 -dihidroxi-kaurano (**3b**, 34%). Experimentos realizados usando el doble o la mitad de H_2O_2 manteniendo constante la concentración de SeO_2, no produjeron cambios significativos en la proporción y rendimiento de los productos de oxidación. **Palabras Clave:** Oxidación alílica, óxido de selenio, peróxido de hidrógeno, ácido *ent*-kaurénico, éster metílico del ácido *ent*-kaurénico, *ent*-kaurenol.

Abstract

The allylic oxidation of *ent*-kaurenic acid, *ent*-kaurenic acid methyl ester, and *ent*-kaurenol with SeO_2/H_2O_2 is presented. The reaction was run in dioxan solution at room temperature stirring for 4 hours. About 0.3 mmol of substrate was treated with 1.2 mmol of SeO_2 and 4.1 mmol of H_2O_2. Treatment of *ent*-kaurenic acid afforded 56% of *ent*-15α-hydroxy-kaur-16-en-19-oic acid (**2a**). Treatment of *ent*-kaurenic acid methyl ester afforded two products: *ent*-15α-hydroxy-kaur-16-en-19-oic acid methyl ester (**2b**, 34% yield) and *ent*-15α,16α-epoxi-17-hydroxy-kauran-19-oic acid methyl ester (**3a**, 59% yield). In a similar fashion treatment of ent-kaurenol rendered two products: *ent*-15α,17-dihydroxy-kaur-16-ene (**2c**, 56.7% yield) and *ent*-15α,16α-epoxi-17,19-dihydroxy-kaurane (**3b**, 34% yield). Additional experiments using twice as much or half as much H_2O_2 relative to the amount of SeO_2 did not modify significantly the product ratio neither the yield. **Keywords:** Allylic oxidation, selenium oxide, hydrogen peroxide, *ent*-kaurenic acid, *ent*-kaurenic acid methyl ester, *ent*-kaurenol.

Introduction

Several *ent*-kaurene diterpenoids have been reported to be biologically active. Some authors have reported that poly-oxigenated kaurenes like some compounds isolated from *Isodon* species[1] have antitumor activity. On the other hand Nagashima *et al*[2] concluded that *ent*-11-α-hydroxy-kaur-16-en-15-one induces apoptosis in human leukamia cells and recently it has been found that *ent*-15-oxo-kaur-16-en-19-oic and its 16,17-epoxi derivative inhibit *in vitro* degradation of haemoglobin by *Plasmodium* parasites.[3] The common feature of these compounds is the presence of a methylene-cyclopentanone moiety.

Ent-15-oxo-kaur-16-en-19-oic acid was first obtained by hemisynthesis by Cannon *et al*[4] and later was isolated as a natural compound from *Xylopia acutiflora* by Hasan *et al*[5] but it is not readlily available from natural sources. Since in Venezuela *ent*-kaurenic acid can be isolated from several species of *Espeletiinae*,[6] it was considered convenient to explore the possibility of obtaining *ent*-15-hydroxy-16-en-19-oic acid by allylic hydroxylation and this compound could be easily converted into *ent*-15-oxo-

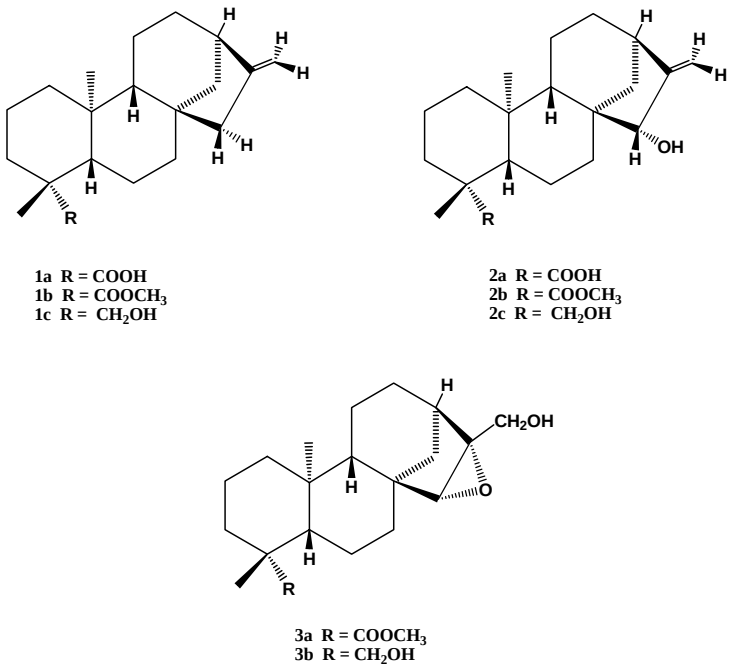

Fig.1. Molecular structures of *ent*-Kaurenic acid (1a), *ent*-kaurenic acid methyl ester (1b), *ent*-kaurenol(1c), and derivatives obtained by allylic oxidation with SeO_2/H_2O_2

kaur-16-en-19-oic acid. kaur-16-en-19-oic acid. In this paper we present results obtained for the allylic hydroxylations of *ent*-kaurenic acid and *ent*-kaurenol using SeO_2 / H_2O_2 as oxidant agent.[7]

Several methods have been described to carry out allylic oxidation. Lead tetraacetate was used by Whitham[8] to obtain derivatives of α-pinene, but the problem with $Pb(AcO)_4$ is that the reaction is performed in acidic medium which causes displacement of the double bond and leads to the formation of isomeric acetates. Active manganese dioxide,[9] chromium trioxide[10] and the acetates of Hg, Ti and Pd have been used[11] with different degree of success, as well as *t*-butyl-hydroperoxide in presence of catalytic amounts of chromium trioxide.[12] After trying some of these reagents we decided to use SeO_2 / H_2O_2.[7] In this paper we present results obtained for the allylic hydroxylations of *ent*-kaurenic acid and *ent*-kaurenol using SeO_2/H_2O_2 as oxidant agent.[7]

Results and Discussions

Kaurenic acid (**1a**) isolated from *Espeletia semiglobulata,* was dissolved in dioxan and stirred with SeO_2 and H_2O_2 at room temperature for 4 hours. Dilution with water and extraction with diethyl ether yielded the crude product which was submitted to flash chromatography over silica gel. Elution with hexane-ethyl acetate (4:1) yielded a white powder which crystallized from MeOH, mp 222-224°C, identical (tlc, ir, nmr, mmp) to *ent*-15α-hydroxy-(-)-kaur-16-en-19-oic acid (**2a**) isolated from *Coespeletia timotensis.*[13] This compound was isolated for the first time from *Espeletia grandiflora* by Piozzi *et al*[14] and it is known by the trivial name of grandiflorolic acid. It was not possible to purify other minor products present.

Treatment of kaurenic acid methyl ester (**1b**) with SeO_2-H_2O_2 in dioxan solution under the same conditions yielded upon purification by flash chromatography two products. The first one eluted with hexane-ethyl acetate (4:1) yielded 32 mg, (34% yield) of a white powder which crystallized from hexane-diethyl ether, mp 114-116°C. The IR of this compound measured as KBr discs showed an OH stretching band at 3540 cm^{-1} and a strong carbonyl band at 1728 cm^{-1} (-$COOCH_3$). Presence of an exocyclic double bond was evidenced by a band at 896 cm^{-1}. The two protons ascribable to this grouping appear as broad singlets at δ 5.13 and δ 5.26 which is a lower field than normally are found in kaurenes (δ 4.70-4.80). On the other hand, the proton located at the same carbon that carries the hydroxyl group appears as a singlet at δ 3.82 which indicates that it is located in the neighborhood of the exocyclic double bond. The mass spectrum of this compound gave a molecular ion at m/z 332 ($C_{21}H_{32}0_3$), and fragment ions at m/z 317 (M^+-CH_3), 314 (M^+-H_2O), 299 [M^+- (CH_3 + H_2O)], 274 (M^+- 58). This last fragmentation involves fission of the C13-C16 bond as well as fission of the C8-C15 bond and transfer of two hydrogen atoms from the rest of the molecule and it is characteristic of kaurenes that have a 15α-hydroxyl group as indicated by Nakano *et al.*[15]

Based on this evidence this compound was identified as *ent*-15 α-hydroxy-kaur-16-en-19 oic acid methyl ester (**2b**). Further elution with hexane-ethyl acetate (4:1) afforded 65 mg (59% yield) of colourless needles upon crystallization from hexane-diethyl ether (3:1), mp 165-166°C. The IR spectrum of this compound showed bands at 3540 cm^{-1} (OH), 1723 cm^{-1} (carbonyl ester) and 1240 cm^{-1} (epoxi moiety). The CH stretching band (3095-3075 cm^{-1}) and CH out of plane deformation band (895 cm^{-1}) typical of the exocyclic double bond of kaurenic acid, was absent. On the other hand the ^{1}H-NMR spectrum indicated that a CH_2OH group was present because it showed two doublets at δ 4.02, 4.05 and δ 3.78, 3.81 which integrated for two protons, and the carbon carrying these protons appeared at 59.1 ppm. A singlet at δ 2.95 was assigned to a proton that forms part of the epoxi moiety. The carbons carrying the epoxi group appeared at 65.1 and 65.2 ppm. Since the rest of the signals were very similar to the signals that belong to rings A, B, and C of *ent*-kaurenic acid methyl ester this product was identified as *ent*-15,16-epoxi-17-hydroxy-kauran-19-oic acid methyl ester (**3a**). This compound has not been reported in the literature.

Oxidation of *ent*-19α-hydroxy-kaur-16-ene (**1c**) with SeO_2-H_2O_2 in dioxan solution yielded after four hours at room temperature a mixture that was purified by flash chromatography rendering two products upon elution with hexane-EtOAc (4:1). The less polar compound 60 mg (56.7% yield) crystallized from hexane, mp 156-157°C, The IR spectrum of this compound showed a broad hydroxyl band centered at 3350 cm^{-1}, and bands at 3042 cm^{-1}, 896 cm^{-1} indicative of the presence of an exocyclic double bond. This evidence was corroborated by the ^{1}H- and ^{13}C-NMR spectra which showed two methylenic protons at δ 5.07 and δ 5.20 bound to C-17 (108.4 ppm), two doublet signals centered δ 3.44 (J=11Hz) and δ 3.74 (J=11Hz) which correspond to the CH_2OH group located at C19 (65.5 ppm), and a singlet at δ 3.80 assigned to the proton attached to C15 (82.9 ppm) at the base of a secondary hydroxyl. The mass spectrum of this compound showed a molecular ion at m/z 304 ($C_{20}H_{32}O_2$), with main fragments at m/z 289 (M^+-CH_3), 286 (M^+-H_2O), 273 (M^+-CH_2OH), 255 (M^+-[CH_2OH+H_2O]). On this evidence this compound was identified as *ent*-15α,19α-dihydroxy-(-)-kaur-16-ene (**2c**) and it was proved to be identical to the same compound previously obtained by Batista *et al*[16] by $LiAlH_4$ reduction of *ent*-15α-acetoxy-kaur-16-en-19-oic acid methyl ester (mp, mmp, tlc, IR, and NMR). Further elution of the column yielded a second product, 38 mg (34% yield) mp 138-140°C. The IR spectrum showed a broad OH stretching band at 3400-3200 cm^{-1} and a deformation band at 1070 cm^{-1}, typical of primary alcohols. The ^{13}C-NMR spectrum showed oxygen carrying carbons at 65.5 ppm, which correlated with protons doublets at δ 3.44 and δ 3.72 (HSQC) and was assigned to the C19 primary hydroxyl group, 65.2 ppm and 65.4 ppm which were assigned to an epoxi moiety at carbons C15-C16, and at 59.4 ppm which was assigned to a primary hydroxyl group at C17 because this carbon correlated (HSQC), with proton doublet signals at δ 3.80 (J=12.8 Hz) and δ 4.04 (J=12.8 Hz). The mass spectrum of this compound showed a molecular ion at m/z 320 ($C_{20}H_{32}O_3$) which indicates the presence of an additional oxygen atom in this compound. The *exo*-cyclic methylenic double bond was absent; therefore the only possible location for the new primary hydroxyl group was C17. On the other hand C16 (65.2 ppm) correlates on the HMBC spectrum with H13, which appears at δ 2.29, and H17. Based on this evidence this compound was identified as *ent*-15,16-epoxi-17,19α-dihydroxy-kaurane (**3b**), a compound that has not been reported in the literature.

The formation of compounds **2a**, **2b**, and **2c** is the result of the allylic hydroxylation of the starting compounds (**1a**, **1b**, and **1c**). On the other hand, formation of **3a** and **3b** could be explained as a consequence of displacement of the exocyclic double bond to carbons 15 and 16. In such event the C-17 methyl would be allylic with respect to the Δ15 double bond and would suffer allylic hydroxylation, finally the double bond would become an epoxide. Why kaurenic acid does not form a 15,16-epoxi-17-hydroxy derivative? It is not possible to affirm that such compound does not form, probably the presence of a free carboxylic acid moiety leads to the formation of other products which make it difficult to isolate the 15,16-epoxide derivative. On the other hand it is interesting to note that oxidation of *ent*-kaurenol produces the 15α-hydroxy derivative in a similar yield as *ent*-kaurenic acid (56.7% and 56% respectively), while oxidation of the *ent*-kaurenic acid methyl ester yielded the epoxi derivative as main product (59% yield).

In order to explore changes in product ratio upon different concentration of H_2O_2 the allylic oxidation of **1b** and **1c** was repeated in the same conditions but using twice as much H_2O_2 or half as much. After work out it was found that both products were formed in about the same proportions.

General Experimental Techniques

Melting points were determined on a Fischer Johns apparatus, and are uncorrected. Optical rotations for solutions in $CHCl_3$ were measured with a JASCO digital polarimeter model DIP-370 using a sodium lamp at 25°C. IR spectra were obtained on a Perkin Elmer FT-IR instrument model 1720X as KBr disks. NMR spectra were recorded with a Bruker Avance DRX 400-MHz instrument

using $CDCl_3$ as solvent. All compounds were characterized by acquisition of ^1H, ^{13}C, DEPT-135, ^1H-^1H COSY, and ^1H-^{13}C correlated experiments. Mass spectra were determined on an HP 5973 MSD instrument equipped with a 5 phenyl-95 methyl-polysiloxane capillary column (30 m, 0.25 mm, 0.25 μm film), at an initial temperature of 250°C, with heating of 5°C/min up to 300°C, using He as carrier gas at 0.9 mL/min. Analytical thin-layer chromatography (TLC) was performed on E. Merck aluminium-backed silica gel (Silica Gel F254) plates. Flash chromatography was performed on silica gel (230-400 mesh, Merck) by gradient elution with hexane-EtOAc mixtures.

*Isolation of ent-kaurenic acid (**1a**).* This compound was obtained from the aerial parts of *Espeletia semiglobulata* collected at Paramo of Piedras Blancas as previously described by Visbal *et al.*[17] Pure *ent*-kaurenic acid crystallized from hexane mp 178-180°C, M^+ m/z 302 ($C_{20}H_{30}O_2$).

*Isolation of ent-kaurenol (**1c**).* This compound was obtained from the aerial parts of *Espeletia semiglobulata* as previously described by Baptista *et al.*[16] Chromatography over silica gel and elution with hexane yielded 0.35 g of pure *ent*-kaurenol, mp 141-142°C, M^+ m/z 288 ($C_{20}H_{32}O$).

Reaction of ent-kaurenic acid with SeO_2/H_2O_2. A dioxan solution of 110 mg (1.2 mmol) of e*nt*-kaurenic acid (**1a**) was stirred with SeO_2 (51 mg, 4.14 mmol) and H_2O_2 (0.45 mL, 30%) at room temperature for 4 hours. At the end of this period water was added and the reaction mixture shaken with diethyl ether. The ether layer was dried over anhydrous Na_2SO_4 and evaporated to dryness, yielding 130 mg of crude product which was submitted to flash chromatography over silica gel (90 g). The column was eluted with hexane-ethyl acetate (4:1). Fractions 31-100 (25 mL each) rendered 65 mg of a white solid which was crystallized from MeOH yielding 63 mg of colourless needles, mp 222-224 °C, $[\alpha]_D^{25}$ -110° (c, 0.60, $CHCl_3$), IR (ν_{max}, cm^{-1}), 3420-2720 (broad band, COOH), 1695 (C=O), 1618 (C=C), 896 (=CH_2). ^1H-NMR ($CDCl_3$, 400 MHz, Table 1); ^{13}C-NMR ($CDCl_3$, 100 MHz, Table 2); MS m/z (%): M^+ 318 ($C_{20}H_{30}O_3$, 81), 303 (M^+-CH_3, 57) 300 (M^+-H_2O, 89), 285 (M^+-[CH_3+H_2O], 86), 260 (M^+- 58, 100), 189 (61), 121 (91), 107 (99). This compound was identical to grandiflorolic acid (**2a**) isolated from *Coespeletia timotensis* (mp, mmp, tlc).[13]

Table 1: ^1H-NMR chemical shifts of e*nt*-15α-hydroxy-kaur-19-oic acid [**2a**]; *ent*-15α-hydroxy-kaur-19-oic acid methyl ester [**2b**]; ent-15α-19α-dihydroxy-kaur-16-ene [**2c**] ; *ent*-15,16-epoxi-17-hydroxy-19-oic acid methyl ester [**3a**]; *ent*-15,16-epoxi-17,19α-dihydroxy-kaurane [**3b**].

	2a	**2b**	**2c**	**3a**	**3b**
1a	0.76	0.83	0.79	0.79	0.83
1b	1.92	1.83	1.81	1.94	1.85
2a	1.87	1.79	1.59	1.87	1.58
2b	1.42	1.44	1.44	1.43	1.44
3a	2.14	2.16	1.76	2.15	1.77
3b	1.03	1.02	0.94	1.03	0.96
5	1.09	1.06	0.96	1.10	0.96
6a	1.77	1.85	1.71	1.77	1.69
6b	1.92	1.63	1.32	1.93	1.24
7a	1.76	1.75	1.76	1.76	1.77
7b	1.92	1.47	1.53	1.39	1.53
9	1.01	1.16	1.03	1.02	1.18
11a	1.59	n.a	1.59	1.57	1.58
11b	1.37	1.56	n.a	1.36	n.a
12a	1.59	1.62	1.71	1.57	1.63
12b	1.36	1.56	1.56	1.35	1.58
13	2.73	2.29	2.73	2.73	2.29
14a	1.87	1.58	1.56	1.88	1.58
14b	1.43	1.13	1.02	1.43	1.08
15	3.81	2.95	3.8	3.79	2.90
17a	5.20	4.04	5.20	5.20	4.04
17b	5.07	3.80	5.07	5.07	3.80
18	1.25	1.17	0.97	1.18	0.98
19a	-	-	3.74	-	3.72
19b	-	-	3.44	-	3.44
20	0.95	0.81	1.01	0.84	0.99
OCH_3	-	3 .64	-	3.65	

Table 2: ^{13}C-NMR chemical shifts of e*nt*-15α-hydroxy-kaur-19-oic acid [**2a**]; *ent*-15α-hydroxy-kaur-19-oic acid methyl ester [**2b**]; ent-15α-19α-dihydroxy-kaur-16-ene [**2c**] ; *ent*-15,16-epoxi-17-hydroxy-19-oic acid methyl ester [**3a**]; *ent*-15,16-epoxi-17,19α-dihydroxy-kaurane [**3b**].

	2a	**2b**	**2c**	**3a**	**3b**
C	**ppm**	**ppm**	**ppm**	**ppm**	**ppm**
C-1	40.8	40.7	40.6	40.9	40.5
C-2	19.2	18.3	18.0	19.0	18.1
C-3	37.9	38.1	35.6	38.1	35.6
C-4	43.7	43.8	38.6	43.8	38.6
C-5	57.1	57.0	56.1	56.7	56.6
C-6	21.0	21.1	19.6	20.7	19.2
C-7	35.4	35.1	35.6	35.6	36.1
C-8	47.8	47.7	47.8	43.2	43.3
C-9	53.4	53.3	54.1	49.4	50.5
C-10	39.9	39.6	39.5	39.3	39.3
C-11	18.4	19.1	18.2	18.2	18.2
C-12	32.7	32 .5	32.7	26.5	26.5
C-13	42.4	42.3	42.3	35.7	35.7
C-14	36.3	36.2	32.7	37.0	31.9
C-15	82.8	82.7	82.9	65.2	65.4
C-16	160.3	160.3	160.3	65.1	65.2
C-17	108.4	108.2	108.4	59.1	59.2
C-18	29.1	28.7	27.0	28.7	27.1
C-19	183.6	178.3	65.5	178.2	65.5
C-20	15.9	15.8	18.2	15.2	17.9
O-CH_3	-	51.1	-	51.3	-

*Reaction of ent-kaurenic acid methyl ester (**1b**) with SeO_2/H_2O_2.* The methyl ester of *ent*-kaurenic acid (100 mg, 0.32 mmol) in dioxan (10 mL) was stirred with SeO_2 (46 mg) and H_2O_2 (0.41 mL, 30%) at room temperature for 4 h. Work up by dilution with water and ether extraction (10 mL x 3) gave a crude product which was submitted to flash chromatography over silica gel (70 g) eluting with hexane-EtOAc (4:1). Fractions 1-4 (50 mL each) yielded 32 mg of **2b** which crystallized from MeOH, mp 114-116°C, IR (ν_{max}, KBr cm^{-1}): 3540, 3060, 1728, 1618, 1250, 896. ^{1}H-NMR (Table 1). ^{13}C-NMR (Table 2). MS m/z (%): M^+ 332 ($C_{21}H_{32}O_3$, 42), 317 (M^+-CH_3, 30), 314 (M^+- H_2O, 37), 299 (M^+- [CH_3 + H_2O], 65), 274 (M^+- 58, 100), 255 (97), 239 (48), 189 (40), 121 (69), 107 (52). Further elution with hexane-EtOAc 4:1 yielded 65 mg of **3a**, mp 165-166°C, IR (ν_{max}, cm^{-1}) 3421, 2940, 2844, 1732, 1230, 1146. ^{1}H-NMR (Table 1). ^{13}C-NMR (Table 2). MS m/z (%): M^+ 348 ($C_{21}H_{32}0_4$,15), 330 (M^+-H_2O, 29), 317 (M^+-CH_3OH, 37), 289 (M^+- $COOCH_3$, 42), 274 (64), 267 (45), 207 (52), 121 (100), 107 (69).

*Reaction of ent-kaurenol (**1c**) with SeO_2/H_2O_2. Ent*-kaurenol (100 mg, 0.35 mmol) in dioxan (10 mL) was stirred with SeO_2 (46 mg) and H_2O_2 (0.41 mL, 30%) at room temperature for 4 h. Work up by dilution with water and ether extraction (10 mL x 3) gave a crude product which was submitted to flash chromatography over silica gel (70 g). Elution with hexane-diethyl ether (25 mL fractions) yielded from fractions 1-3 a white powder (**2c**, 60 mg) which crystallized from hexane-diethyl ether, mp 156-157°C, $[\alpha]_D^{25}$ -47° (c 0.56 , $CHCl_3$), IR (KBr, ν_{max} cm^{-1}): 3350, 3042, 2910, 1650, 1050, 1000, 900; ^{1}H-NMR (Table 1). ^{13}C-NMR (Table 2). MS m/z (%): M^+ 304 (7), 289 (M^+-CH_3, 15), 286 (M^+-H_2O), 273 (M^+-31, 44), 255 (100), 109 (38), 81 (38). Further elution yielded from fractions 4-7 a white powder (**3b**, 38 mg) which crystallized from hexane-diethyl ether (3:1) mp 138-140°C. IR (KBr, ν_{max} cm^{-1}): 3550, 3420, 2929, 2843, 1062, 1028. ^{1}H-NMR (Table 1). ^{13}C- NMR (Table 2). MS m/z (%): 320 ($C_{20}H_{32}O_3$, 9), 302 (M^+- H_2O, 22), 289 (M^+-CH_3OH, 92), 271 (M^+- {H_2O + CH_3OH), 246 (50), 207 (100), 123 (69), 109 (59), 91 (66).

*Reaction of ent-kaurenic acid methyl ester (**1b**) with different proportions of SeO_2 and H_2O_2.* The methyl ester of *ent*-kaurenic acid (100 mg, 0.32 mmol) in dioxan (10 mL) was stirred with SeO_2 (46 mg) and 0.20 mL of 30% H_2O_2 (half as much as before) at room temperature for 4 h. Work up as previously described and purification by flash chromatography yielded 30 mg of **2b** and 62 mg of **3a**. When the oxidation of 100 mg of **1b** was made with 46 mg of SeO_2 and 0.92 mL of H_2O_2 (twice as much), 31 mg of **2b** and 60 mg of **3a** were obtained.

*Reaction of ent-kaurenol (**1c**) with different proportions of SeO_2 and H_2O_2.* *ent*-Kaurenol (100 mg, 0.32 mmol) in dioxan (10 mL) was stirred with SeO_2 (46 mg) and 0.20 mL of 30% H_2O_2 (half as much) at room temperature for 4 h. Work up as previously described and purification by flash chromatography yielded 55 mg of **2c** and 34 mg of **3b**. When the oxidation of 100 mg of **1c** was made with 46 mg of SeO_2 and 0.92 mL of H_2O_2 (twice as much), 56 mg of **2c** and 35 mg of **3b** were obtained.

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