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J. Nat. Prod., **1992**, 55 (7), 884-898• DOI: 10.1021/np50085a007 • Publication Date (Web): 01 July 2004

Journal of Natural Products
Vol. 55, No. 7, pp. 884-898, July 1992

THE TRANSFORMATION OF GLAUCOLIDE A INTO CADINANOLIDES AND HIRSUTINOLIDES

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ABSTRACT.—Treatment of glaucolide A [**1**] with SiO_2, under conditions normal for the isolation of metabolites from plant material, afforded hirsutinolide-type and cadinanolide-type sesquiterpene lactones previously thought to be natural products. Consequently classification in Vernonieae at the generic level, based on the presence of hirsutinolides and glaucolides, may need to be revised. Also, some structures reported for hirsutinolide-type lactones are in need of revision.

From extensive phytochemical studies on the genus *Vernonia*, which contains more than 1000 species (1), it has been proposed that highly oxygenated germacranolides such as glaucolides and hirsutinolides are characteristic of many species occurring both in the New and the Old World (1–21).

However, this paper deals with the transformation of glaucolide A [**1**], a widespread molecule in *Vernonia*, into hirsutinolides and cadinanolides by Si-gel-catalyzed rearrangement under reaction conditions that closely resemble the usual procedure for isolation of metabolites from plant material. Our results show that both hirsutinolides and cadinanolides can be artifacts produced in the isolation procedure. Such a situation was suggested (16,26) in the transformation of **1** into cadinanolide **3**, and in other cases (22–25), although for 3-oxo-10αH-stilpnomentolide-8-*O*-(5-acetoxysenecionate) (24), a previously known (13) natural product, this was claimed without stereochemical evaluation.

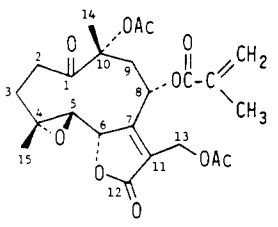
In accordance with these results, utilization of cadinanolide- and hirsutinolide-type lactones as taxonomic markers is no longer reasonable. Consequently, the difference between Vernoniinae and non-Vernoniinae taxa, based on the presence of hirsutinolides, may require revision (1). In addition, we report the unusual reduction products **14**, **15**, and **16**, obtained by treatment of **1** with $NaBH_4$.

RESULTS AND DISCUSSION

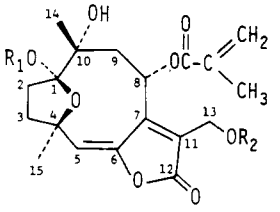
Although there are contradictions concerning the absolute configuration of glaucolides and hirsutinolides (16,25), we assumed the absolute configuration shown in **1** for glaucolide A by analogy with many other sesquiterpene lactones. Hirsutinolide **2** and cadinanolide **3** were obtained when an MeOH solution of **1** was shaken in the presence of Si gel at room temperature for 8 h. Compound **2** was produced when **1** was shaken in the presence of alumina. Hirsutinolides **4**, **5**, and **6** and cadinanolides **7** and **8** were produced when an EtOH solution of **1** was shaken in the presence of Si gel.

Hirsutinolide **2** was identified by comparison of its ^{1}H-nmr (Table 1), ir, and mass spectral data with those reported for 8α-methacryloyloxy-10α-hydroxy-1, 13-bis-*O*-methylhirsutinolide "isolated" from *Vernonia jalcana* (12) after extensive chromatographic separation on Si gel columns. The ^{13}C-^{1}H HETCOR nmr data are given in the Experimental section.

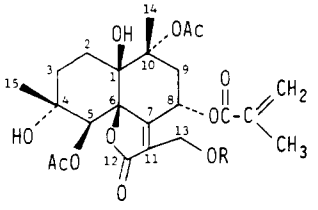
Identification of **3** as vernajalcanolide 8-*O*-methacrylate was achieved by compari-



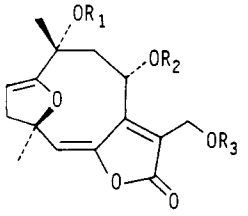
1



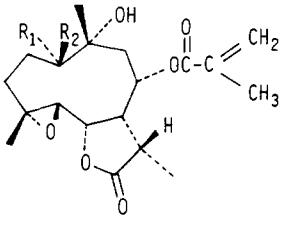
2 R_1=Me, R_2=Me
4 R_1=Et, R_2=Et
6 R_1=H, R_2=Et
9 R_1=H, R_1=Me



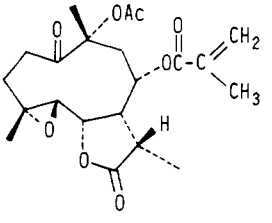
3 R=Me
7 R=Et
8 R=H



5 R_1=H, R_2=COCH(Me)=CH_2, R_3=Et
10 R_1=H, R_2=COEt, R_3=Ac
11 R_1=Ac, R_2=COEt, R_3=Ac



14 R_1=H, R_2=OAc
15 R_1=OAc, R_2=H



16

son with an authentic sample (16). The compound was isolated as white crystals suitable for single crystal X-ray studies. The molecular structure of **3** is illustrated in Figure 1. The results of the X-ray analysis showed a cis fusion between the two six-membered rings, both having an approximate chair conformation. The methyl group and the alcohol, both at C-4, showed α axial and β equatorial orientations, respectively. The acetate moiety at C-5 and the methyl group at C-10 are β-oriented while the acetate and the methacrylate residues at C-10 and C-8, respectively, are α-oriented. The ^{13}C-^{1}H HETCOR nmr data are in the Experimental section.

Comparison of the ^{1}H-nmr data of **2**, **4**, and **6** (Table 1) clearly reveals that these compounds have the hirsutinolide skeleton, the only difference between **2** and **4** being the alkoxy residues at C-1 and C-13, which are methoxyl groups in **2** and ethoxyl groups in **4**. The structure of **6** was deduced as the 8α-methacryloyloxy-10α-hydroxy-13-*O*-ethylhirsutinolide by comparison of its ^{1}H-nmr data with those reported for the 13-*O*-methylhirsutinolide derivative **9** (12) (Table 1).

The presence of the C-1/C-2 double bond in **5** as well as the ethoxyl substituent at

TABLE 1. ^{1}H-nmr Data of Hirsutinolides **2**, **4**, **6**, and **9**.[a]

Proton	Compound			
	2	**4**[b]	**6**	**9**[c]
H_2-2	2.01 m 2.1 ddd (5,12,6)		2.04 m	
H-5	5.88 s	5.82 s	5.82 s	5.84 sbr
H-8	6.50 m	6.52 dd (9,2)	6.61 dbr (9)	6.56 dbr (9)
H_2-9	2.51 dd (16,9) 2.09 d (16)	2.50 dd (15,9) 2..09 d (15)	2.58 dd (15,9) 2.19 d (15)	2.58 dbr (16) 2.09 dbr (16)
H_2-13	4.53 d (12.5) 4.26 d (12.5)	4.52 d (12) 4.28 d (12)	4.59 d (13) 4.34 d (13)	4.58 dbr (12.5) 4.27 dbr (12.5)
H-14	1.61 sbr	1.56 s	1.58 sbr	1.57 sbr
H-15	1.24 sbr	1.23 s	1.22 sbr	1.22 sbr
MeAcr	6.35 sbr	6.28 s	6.29 sbr	6.28 sbr
	5.68 dq	5.64 dq	5.68 dq	5.67 dq
	1.97 sbr	1.95 sbr	1.94 sbr	1.94 sbr
OMe	3.54 s 3.39 s			3.40 s
OEt		3.80 q 3.55 q 1.21 t 1.18 t	3.59 q 1.21 t	

[a]δ_Hm, in $CDCl_3$, values in parentheses are J.
[b]At 80 MHz.
[c]Values in this column are from Jakupovic *et al.* (12).

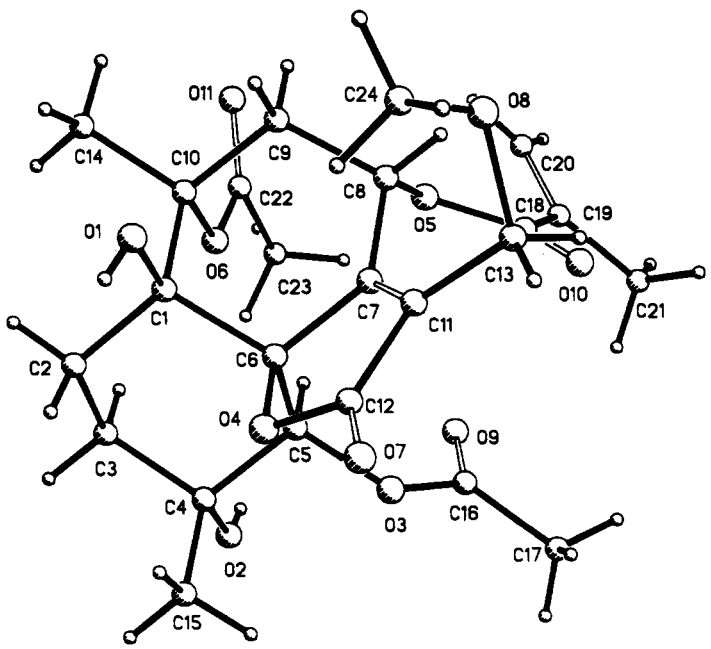


FIGURE 1. Perspective view of the molecular structure of cadinanolide **3**.

C-13 were deduced by comparison of the ^{1}H-nmr data with those of **10** and **11** (Table 2) (27). The stereochemistry of **5** at C-4, C-8, and C-10 follows, with the aid of Dreiding models, from the transformation of **1** into **5**, since these chiral centers are not changed by the reaction. Consequently structures 8–13 in Bohlmann *et al.* (27) and structures 3–7 in Bohlmann *et al.* (28) require revision of the stereochemistry at C-1, C-4, C-8, and/or C-10.

Comparison of the ^{1}H-nmr data of **3**, **7**, and **8** clearly shows that the compounds differ only in the residue at C-13 (Table 3). The lack of a methoxyl signal and the presence of the typical signals of an ethoxyl residue in the ^{1}H-nmr spectrum of **7** revealed that it has an ethoxyl residue at C-13 instead of the methoxyl group present in **3**. The presence of an hydroxyl group at C-13 in **8** is further evidenced by the two-proton H-13 singlet at 4.53 ppm, which in **3** and **7**, both carrying an alkoxy residue, appear as AB systems. The ms spectrum of **8** was in full agreement with its structure. ^{13}C-nmr data for compounds **2**, **3**, and **7** are given in Table 4, and the fractional atomic coordinates of **3** are in Table 5.

Plausible mechanisms to rationalize the transformation of **1** into hirsutinolides (Scheme 1) assume the initial acid-base interaction of the Si gel at the C-4/C-5 oxirane (route A), or at the acetate group at C-13 (route B). Either route consequently forces the release of H-6, the electron denisty at C-6 being delocalized over two alternative routes. Route A involves opening of the epoxide to yield the C-5/C-6 double bond, thus leading to an enol-lactone intermediate like **12**, which undergoes ring closure via nucleophilic attack of the C-4 alkoxy group at the C-1 carbonyl to produce hirsutinolide-type lactones. This route is supported by the fact that epimeric hirsutinolides at C-1 have been "isolated" from *Vernonia* (23,28) and other species (12,29). The other mechanistic route, route B, involves attack of the C-6 anion on C-7, causing expulsion

TABLE 2. ^{1}H-nmr Data of Hirsutinolides **5**, **10**, and **11**.[a]

Proton	Compound		
	5	**10**[b]	**11**[b]
H-2	4.76 dd (3,2)	4.81 dd (3,2)	5.09 dd (3,2)
H_2-3	2.80 dd (15,2) 2.60 dd (15,3)	2.87 dd (16,2) 2.71 dd (16,3)	2.93 dd (16,2) 2.82 dd (16,3)
H-5	5.76 s	5.88 s	6.02 s
H-8	6.55 d (9)	6.26 brd (8)	6.02 s
H_2-9	2.66 dd (9,16) 2.03 d (16)	1.97 dd (1,15) 2.64 dd (8,15)	2.40 dd (2.5,15) 2.72 dd (5,15)
H_2-13	4.50 d (13) 4.36 d (13)	5.02 s	5.07 d (13) 4.87 d (13)
H-14	1.66 s	1.66 s	1.64 s
H-15	1.41 s	1.40 s	1.63 s
OAc		2.08 s	2.12 s 2.03 s
MeAcr	6.27 sbr 5.67 dq 1.98 brs		
OEt	3.56 q 1.23 t		
OCOEt		2.38 dq 1.16 t	2.35 dq 1.14 t

[a]δ_Hm, in $CDCl_3$, values in parentheses are J.
[b]Values in this column are from Bohlmann *et al.* (27).

TABLE 3. ^{1}H-nmr Data of Cadinanolides **3**, **7**, and **8**.[a]

Proton	Compound		
	3	**7**	**8**
H_2-2	2.36 m 1.70 m	2.38 m 1.68 m	
H_2-3	2.32 m 1.86 m	2.32 m 1.86 m	
H-5	5.87 s	5.87 s	5.81 s
H-8	5.77 dd (2,4.6)	5.84 dd (2,6)	5.76 dd (2,5)
H_2-9	3.47 dd (2,15) 2.10 dd (4.6,15)	3.46 dd (2,15) 2.08 dd (6,15)	3.43 (2,16)
H_2-13	4.53 d (12) 4.26 d (12)	4.55 d (13) 4.31 d (13)	4.53 s
H-14	1.71 s	1.70 s	1.70 s
H-15	1.40 s	1.39 s	1.36 s
OAc	1.94 s	1.94 s	1.94 s
	2.16 s	2.15 s	2.15 s
OMe	3.35 s		
MeAcr	5.98 dq	5.98 dq	5.97 dq
	5.61 dq	5.61 dq	5.67 dq
	1.91 brs	1.91 brs	1.89 brs
OEt		3.46 q	
		1.15 t	

[a] δ_Hm, in $CDCl_3$, values in parentheses are *J*.

of the acetate moiety at C-13 and yielding an enol-α,β-unsaturated lactone like **13**, which then undergoes a nucleophilic Michael-type solvent attack at C-13 and further follows the previously described path to produce hirsutinolide-type lactones with different substituents at C-13. This route explains the transformation of **1** into **2**, **4**, and **6**.

Both routes also explain the formation of C-1 unsubstituted hirsutinolides which must arise from C-1/C-10 epoxy-glaucolides, since both types of molecules have been "isolated" from *Vernonia chamaedrys* (19).

As pointed out by some authors (12), hemiacetal formation between the carbonyl group at C-1 and the C-4 alkoxy residue depends on the stereochemistry of the newly formed C-5/C-6 double bond. Thus, an *E* configuration is adequate for cyclization while a *Z* configuration does not allow ring closure. It has further been suggested (12) that enol-lactones such as **12** could be the biogenetic precursors of cadinanolide-type lactones. However, nucleophilic attack at C-5 in **12** leads to cadinanolide-type lactones. Therefore, intermediate **12** (Scheme 1) seems to explain satisfactorily the transformation of **1** into cadinanolides **3**, **7**, and **8** (12).

Calculations of the electronic structure (39) of **1** provide additional support for the mechanism, since inspection of the atom electron density data (Table 6) revealed that H-6 has the lowest electron density. This is indicative of its relative high "acidity," thus suggesting a high probability of forming a negative charge at C-6. Since some carbon-hydrogen bond distances of **1**, obtained by X-ray diffraction studies (38), showed inconstancies, our calculations were done taking into account the lowest energetic conformation of **1**, obtained after MNDO calculations (39). These facts also explain the reactivity of similar glaucolides which, when treated under mild basic conditions, afford hirsutinolides (12). It is also relevant to notice that the X-ray diffraction study of glaucolide A [**1**] does not allow knowledge of the absolute configuration since no refine-

TABLE 4. ^{13}C-nmr Data of Compounds **2**, **3**, and **7**.

Carbon	Compound		
	2	**3**	**7**
C-1	111.1	89.1	88.9
C-2	33.7	30.3	30.8
C-3	38.2	35.9	35.9
C-4	83.4	89.1	88.9
C-5	125.1	73.2	73.2
C-6	150.6	77.1	76.5
C-7	144.5	157.7	157.2
C-8	66.0	66.3	66.2
C-9	40.3	34.4	34.3
C-10	79.3	84.4	84.3
C-11	132.5	130.1	130.6
C-12	167.5	169.3	169.1
C-13	63.6	63.2	61.5
C-14	25.8	19.6	19.7
C-15	28.2	23.4	23.5
MeAcr	166.0	167.8	167.6
	136.1	136.4	136.4
	126.7	125.6	125.7
	18.2	18.2	18.2
OMe	58.9	58.5	
	51.8		
OAc		170.4	171.3
		171.6	171.7
		23.5	23.4
		20.3	20.4
OEt			66.4
			15.1

ments of the imaginary components of the anomalous scattering terms were reported (38).

The assumption that hirsutinolides and cadinanolides are artifacts formed under isolation conditions is further supported by the fact that species such as *Brocchia cinerea* (30), *Artemisa afra* (31), *Artemisa judaical* (32), *Achillea fragantisima* (33), *Ajania achilleonides* (34), *Spiracantha cornifolia* (35), *Galamensis* ssp. *nairobensis* (36), and some *Pentizia* species (37) contain glaucolides without C-4/C-5 or C-1/C-10 oxiranes or C-1 carbonyl groups and do not contain hirsutinolides or cadinanolides.

In order to evaluate the role of the C-1 carbonyl group of **1** for the proposed mechanism, we studied the reduction of **1** with $NaBH_4$. This reaction afforded mainly **14** and **15**. The major product, **14**, has hydroxyl and ester functions which are evident in the ir spectrum. The presence of one methacrylate residue and only one acetate moiety in **14** was evident in the ^{1}H-nmr and ^{13}C-nmr spectra. Although it is well known that ester residues are normally not affected by the action of $NaBH_4$, the ^{1}H-nmr spectrum of **14** revealed two important facts: one was that the H-8 signal suffered an unusual down-field chemical shift, 5.20 in **1** to 5.81 ppm in **14**, and the other that the singlet at 4.88 ppm is assigned to a proton attached to a carbon atom bearing the acetate residue. These results indicate that **1** suffered a rearrangement to afford **14**. The saturated γ-lactone nature of **14**, indicated in the ir spectrum, is further evident in the ^{1}H-nmr spectrum, where the characteristic signals for H-11, H-13, and H-7 appear at 2.82 ppm as a double triplet, at 1.28 ppm as a three-proton doublet, and at 2.52 as a

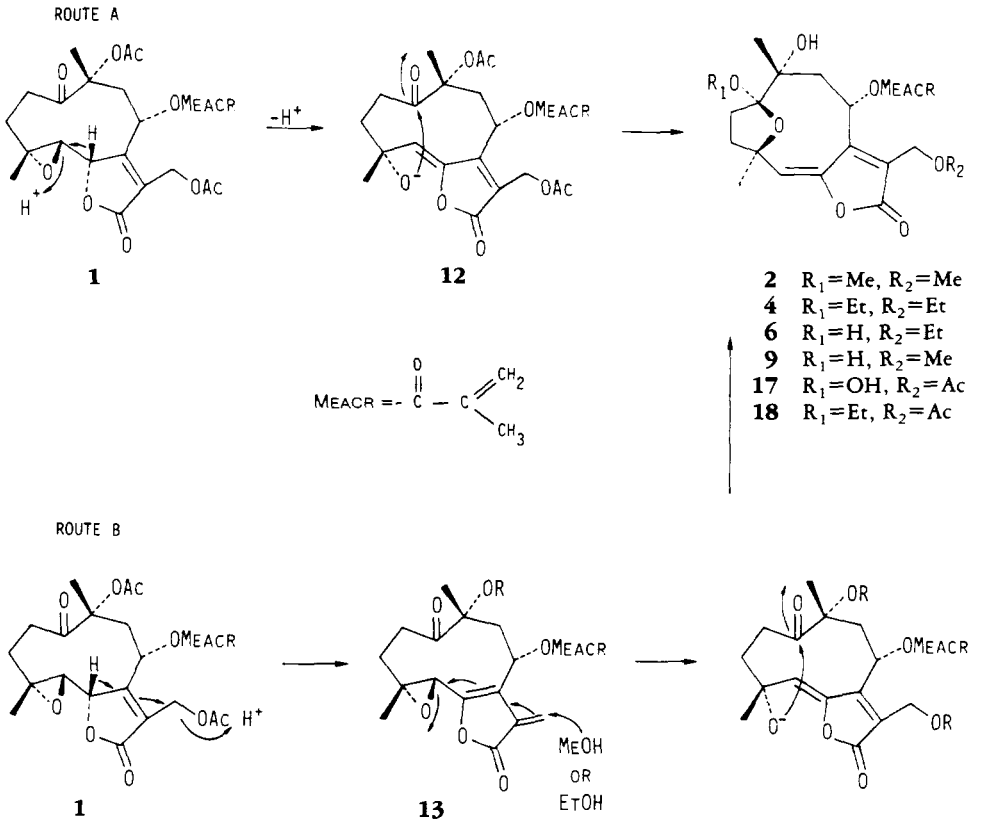
TABLE 5. Experimentally Refined Fractional Atomic Coordinates ($\times 10^4$) of **3**.[a]

Atom	x	y	z
O-1	7628(2)	766(2)	1276(2)
O-2	6505(4)	3907(4)	368(2)
O-3	8275(2)	3614(2)	677(2)
O-4	8156(2)	2330(2)	1602(2)
O-5	8814(2)	1912(2)	−649(2)
O-6	7108(2)	1664(2)	−348(1)
O-7	9256(3)	2302(3)	2315(2)
O-8	10393(3)	704(4)	981(2)
O-9	8311(3)	3912(3)	−451(2)
O-10	9952(2)	2667(3)	−384(2)
O-11	7172(3)	905(2)	−1319(2)
C-1	7353(3)	1415(3)	836(2)
C-2	6489(3)	1725(3)	1068(3)
C-3	6181(3)	2538(3)	735(3)
C-4	6801(3)	3255(3)	818(3)
C-5	7662(3)	2971(3)	563(3)
C-6	7998(3)	2159(3)	879(2)
C-7	8841(3)	1876(3)	629(2)
C-8	8930(3)	1399(3)	−32(2)
C-9	8264(3)	718(3)	−62(2)
C-10	7375(3)	998(3)	117(2)
C-11	9396(3)	1884(4)	1123(3)
C-12	8986(3)	2191(4)	1743(3)
C-13	10296(3)	1602(4)	1112(3)
C-14	6766(3)	260(3)	72(3)
C-15	6814(4)	3599(4)	1535(3)
C-16	8546(3)	4042(3)	121(3)
C-17	9173(4)	4677(4)	318(4)
C-18	9428(3)	2467(4)	−788(3)
C-19	9391(4)	2769(5)	−1504(3)
C-20	9090(5)	2283(5)	−1987(3)
C-21	9757(5)	3601(4)	−1644(4)
C-22	7069(3)	1552(3)	−1035(2)
C-23	6874(4)	2374(4)	−1367(3)
C-24	10157(5)	240(5)	1536(4)

[a]Estimated standard deviations in the last significant digits are shown in parentheses.

double doublet, respectively. The doublet at 3.85 ppm was assigned to H-5, which is attached to a carbon atom bearing an oxygenated function (see Experimental). The stereochemical relationship between H-5, H-6, H-7, H-8, and H-11 was deduced as follows: the value $J_{5,6} = 8$ is indicative of a trans relationship between H-5 and H-6, while the value $J_{7,6} = 6$ shows a cis relationship between H-6 and H-7. Furthermore, the value $J_{7,8} = 0$ shows that the H-7/H-8 dihedral angle is close to 90°. In order to fit these requirements, H-7 and H-11 retain a cis relationship. Taking into account that H-6β and H-8β are not affected by the reaction conditions, it follows that H-5 is α-oriented, while H-7 and H-11 are β-oriented. These assignments were also evident by double irradiation, and the stereostructure of **14** was independently verified by single crystal X-ray diffraction studies.

The molecular structure of **14** is illustrated in Figure 2 and the atomic coordinates are listed in Table 7. The results of the X-ray analysis revealed that **14** is an 11,13-dihy-



SCHEME 1

drogermacran-6,12-olide derivative with the acetate residue and the methacrylate moiety at C-1 and C-8, respectively. The conformation is such that the C-14 and C-15 methyl groups lie syn on the β face of the germacranolide ring and the C-1/C-10 and C-4/C-5 bonds are cross-oriented. The H-6, H-7, H-8, and H-11 atoms are above the approximate plane of the ten-membered ring (i.e., they are β); hence the configuration is H-1α, H-5α, H-6β, H-7β, H-8β, and H-11β. The hydrogen-hydrogen dihedral angles derived from the X-ray analyses of **14** were compared (Table 8) with those deduced from ^{1}H-nmr measurements, their agreement indicating that the conformation of the molecule is similar in the solid state and in solution. Hence, the unusual down-field chemical shifts of H-8β and H-5α in the ^{1}H-nmr spectrum are due to their proximity to the oxygen atoms of the methacrylate residue at C-8, as suggested by the non-bonded distances of 2.34 Å for H-5α/ethereal oxygen and 2.25 Å for H-8β/carbonyl oxygen.

As expected, the stability of **14** in SiO_2 was greater than that of **1**. Furthermore, the data of the electronic structure of **14** (Table 9) shows that the electronic density of H-6 is normal, in full agreement with the assumption that H-6 in **1** is the initial active site for transformations into hirsutinolides and cadinanolides.

The ^{1}H-nmr data of **15** were similar to those for **14** (see Experimental) except for H-1, H-9α, and H-14; their signals in **14** were at 4.98, 2.19 and 1.29 ppm, respectively, while in **15** they were at 5.21, 2.70, and 1.45 ppm, respectively. These facts suggest that the acetate residue at C-1 in **15** is α-oriented. This assumption was confirmed by calculating the dihedral angles between H-1 and H-2α and between H-1 and H-2β, whose values are 40° and 90°, respectively, using a generalized Karplus type equation (40).

TABLE 6. Electronic Data of **1**.

Atom	Electron density[a,b]	Bond	Population analysis[b]
C-1	3.786	C-1/C-2	1.265
C-2	4.040	C-2/C-3	1.299
C-3	3.959	C-3/C-4	1.269
C-4	4.022	C-4/C-5	1.288
C-5	3.953	C-5/C-6	1.311
C-6	3.811	C-6/C-7	1.328
C-7	4.011	C-7/C-8	1.312
C-8	3.802	C-8/C-9	1.260
C-9	3.951	C-9/C-10	1.207
C-10	3.922	C-10/C-14	1.294
C-11	4.140	C-4/C-15	1.332
C-12	3.638	C-7/C-11	1.984
C-13	3.753	C-11/C-12	1.382
C-14	3.938	C-11/C-13	1.346
C-15	3.923	C-2/H-2α	1.331
C-16	3.609	C-2/H-2β	1.258
C-17	4.174	C-3/H-3α	1.416
C-18	3.952	C-3/H-3β	1.403
C-19	3.902	C-5/H-5α	1.471
C-20	3.668	C-6/H-6β	1.398
C-21	3.921	C-8/H-8β	1.326
C-22	3.634	C-9/H-9α	1.428
C-23	3.968	C-9/H-9β	1.220
O-1	6.260	C-4/O-4	0.769
O-4	6.241	C-5/O-4	0.834
O-6	6.270	C-8/O-8	0.865
O-8	6.292	C-10/O-10	0.832
O-10	6.366	C-1/O-1	1.639
O-16	6.323	C-12/O-12	1.646
O-13	6.297	C-16/O-16	1.655
O-20	6.336	C-20/O-20	1.658
O-22	6.323		
H-2β	0.960		
H-2α	0.978		
H-3β	0.973		
H-3α	0.981		
H-5α	0.950		
H-6β	0.945		
H-8β	0.968		
H-9β	0.965		
H-9α	0.970		

[a]Calculated by MNDO.
[b]Some values of the ester residues are not shown.

It is reasonable to assume that migration of the acetate group from C-10 to C-1 in **14** and **15** is caused by nucleophilic attack of the alkoxy group, obtained by reduction of the carbonyl group at C-1, to the acetate moiety at C-10. Although unusual, this migration was also observed when **1** was treated under mild basic conditions to afford bourbonolide-type lactones (12). When **1** was treated under the same reduction conditions used to afford **14** and **15**, but only for 5 min, the reaction yielded **16** as the major component. The stereostructure of **16** was deduced by comparison of its ^{1}H-nmr data with those of **1**, **14**, and **15** (see Experimental). These results suggest initial nucleo-

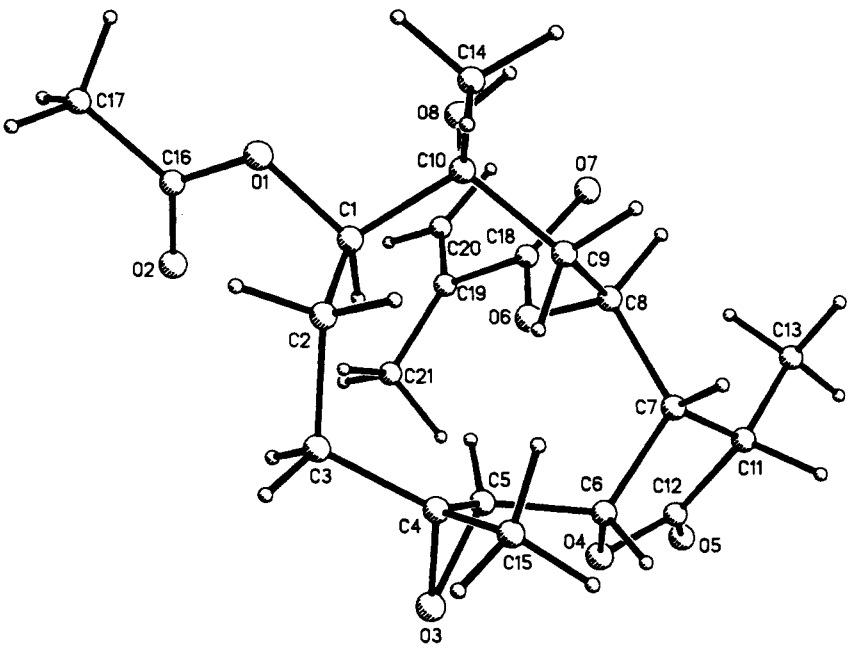


FIGURE 2. Perspective view of the molecular structure of dihydroglaucolide **14**.

philic attack of the hydride at the C-7/C-11 double bond with concomitant expulsion of the acetate residue at C-13, followed by reduction of the carbonyl group at C-1. Although it is uncommon, there are reports (41) of hydrides effecting conjugate reductions.

EXPERIMENTAL

GENERAL.—Nmr measurements were performed in 5 mm (o.d.) sample tubes on either a Varian Associates FT-80A or a XL-300GS spectrometer operated with software version 6.1D. The ^{13}C measurements were Waltz-16 ^{1}H decoupled. The 2D ^{13}C-^{1}H chemical shift correlated spectra were obtained using the standard HETCOR pulse sequence provided by the spectrometer manufacturer.

X-RAY DATA[1].—Data collection for cadinanolide **3** and dihydroglaucolide **14** were done in the θ:2θ scanning mode on a Nicolet R3m four circle diffractometer using CuKα Ni-filtred radiation (λ = 1.54178 Å). The crystal data for **3** and **14** are summarized in Table 10, and their fractional atomic coordinates are given in Tables 5 and 7, respectively. The data measured were corrected for background, Lorentz, and polarization effects, while crystal decay and absorption were negligible. The structures were solved by direct methods using software provided by the diffractometer manufacturer. For structural refinements the non-hydrogen atoms were treated anisotropically, the hydroxyl hydrogen of **3** became evident from ΔF synthesis, and the hydrogen atoms bonded to carbons, included in the structure factor calculation, were refined isotropically. A few reflections were excluded from the final refinement calculations to improve the fit.

ISOLATION OF GLAUCOLIDE A [**1**].—The isolation of glaucolide A [**1**] from *Vernonia morelana* DC. was achieved as reported by Martínez *et al.* (16). Identification was by comparison with an authentic sample (16).

GENERAL PROCEDURE TO OBTAIN HIRSUTINOLIDES AND CADINANOLIDES.—MeOH or EtOH solutions of **1** were shaken in the presence of Si gel at room temperature, the weight ratio of **1** to Si gel being 1:30. The reactions were monitored by tlc. Transformation of **1** was evident within the first hour,

[1]Atomic coordinates for these structures have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, UK.

TABLE 7. Experimentally Refined Fractional Atomic Coordinates ($\times 10^4$) of **14**.[a]

Atom	x	y	z
C-1	4508(3)	−2570(4)	555(2)
C-2	3868(4)	−3452(4)	1031(1)
C-3	3541(4)	−2638(4)	1555(1)
C-4	2156(4)	−1785(4)	1540(2)
C-5	2270(4)	−342(4)	1323(2)
C-6	1030(4)	478(4)	1074(2)
C-7	761(4)	379(4)	454(2)
C-8	2023(3)	−133(4)	104(2)
C-9	2173(3)	−1757(4)	156(1)
C-10	3601(3)	−2492(4)	27(1)
C-11	219(4)	1904(4)	330(2)
C-12	940(4)	2803(4)	757(2)
C-13	303(5)	2502(5)	−241(2)
C-14	3314(4)	−3961(4)	−217(2)
C-15	810(5)	−2614(4)	1561(2)
O-1	5842(2)	−3260(3)	399(1)
C-16	7037(4)	−2836(5)	638(2)
O-2	7090(3)	−1806(5)	929(2)
C-17	8258(4)	−3784(5)	516(2)
O-3	2179(3)	−548(3)	1904(1)
O-4	1370(3)	1975(3)	1183(1)
O-5	1130(4)	4054(3)	764(2)
O-6	3282(2)	651(2)	269(1)
C-18	4035(4)	1338(4)	−118(2)
C-19	5319(5)	2065(5)	121(2)
C-20	6172(6)	2781(5)	−263(3)
C-21	5495(7)	2143(9)	694(3)
O-7	3691(4)	1409(4)	−592(2)
O-8	4438(3)	−1680(3)	−344(1)

[a]Estimated standard deviations in the last significant digits are shown in parentheses.

and reactions were continued until no glaucolide A could be detected. Solutions were filtered, and solvents were removed under vacuum. The residue of each experiment was chromatographed on Si gel using hexane with increasing proportions of EtOAc. Hirsutinolide **2** and cadinanolide **3** were isolated from reactions in MeOH solutions, while hirsutinolides **4**, **5**, and **6**, as well as cadinanolides **7** and **8**, were isolated from reactions in EtOH solutions.

TABLE 8. Hydrogen-Hydrogen Dihedral Angles for **14**.

Atom		X-ray values	Nmr measurement[a]
X	Y		
1	2α	121.5(0)	125
1	2β	−120.4(0.1)	−125
5	6	168.0(0.1)	163
6	7	−24.3(0.1)	29
7	8	73.8(0.1)	74
8	9α	−157.4(0)	−156
8	9β	−40.5(0.1)	−34
7	11	28.0(0.2)	28

[a]Estimated using a generalized Karplus type equation (40).

TABLE 9. Electronic Data of **14**.

Atom	Electron density[a,b]	Bond	Population analysis[b,c]
C-1	3.821	C-1/C-2	1.265
C-2	4.023	C-2/C-3	1.299
C-3	3.987	C-3/C-4	1.269
C-4	4.015	C-4/C-5	1.288
C-5	3.945	C-5/C-6	1.311
C-6	3.848	C-6/C-7	1.328
C-7	4.064	C-7/C-8	1.312
C-8	3.813	C-8/C-9	1.260
C-9	4.033	C-9/C-10	1.207
C-10	3.902	C-10/C-14	1.294
C-11	4.064	C-4/C-15	1.332
C-12	3.670	C-7/C-11	1.984
C-13	3.951	C-11/C-12	1.382
C-14	3.989	C-11/C-13	1.346
C-15	3.941	C-2/H-2α	1.331
C-16	3.588	C-2/H-2β	1.258
C-17	4.160	C-3/H-3α	1.416
C-18	3.918	C-3/H-3β	1.403
C-19	3.964	C-5/H-5α	1.471
C-20	3.640	C-6/H-6β	1.398
C-21	3.953	C-8/H-8β	1.326
O-1	6.343	C-9/H-9α	1.428
O-4	6.247	C-9/H-9β	1.220
O-6	6.269	C-4/O-4	0.769
O-8	6.338	C-5/O-4	0.834
O-10	6.323	C-8/O-8	0.865
O-16	6.360	C-10/O-10	0.832
O-20	6.358	C-1/O-1	1.639
H-2β	0.976	C-12/O-12	1.646
H-2α	0.991	C-16/O-16	1.655
H-3β	0.966	C-20/O-20	1.658
H-3α	0.981		
H-5α	0.918		
H-6β	0.981		
H-8β	0.977		
H-9β	0.996		
H-9α	0.990		

[a]Calculated by MNDO.
[b]Some values of the ester residues are not shown.
[c]Calculated by MINDO/3.

Hirsutinolide **2**.—Compound **2** was obtained from the fractions eluted with hexane-EtOAc (3:2): mp 76–78°; R_f 0.61; uv (MeOH) λ max nm (ε) 202 (11000), 282 (17500); ir ($CHCl_3$) ν max cm^{-1} 3580, 1780, 1740, 1630; $^{13}C/^{1}H$ heteronuclear shift correlation 75.4 (300 MHz) $CDCl_3$ 18.22 (1.97), 25.8 (1.24), 28.2 (1.61), 33.7 (2.01), 38.2 (2.29), 40.3 (2.51), 51.8 (3.54), 58.9 (3.39), 6.36 (4.26 and 4.53), 66.0 (6.5), 125.1 (5.88), 126.7 (5.68 and 6.35); ms (70 eV) *m/z* (rel. int.) $[M]^+$ 408 (3), 290 (10), 232 (90), 188 (45), 69 (100).

Cadinanolide **3**.—Compound **3** was isolated from the fractions eluted with hexane-EtOAc (1:1) and identified by comparison with an authentic sample (16): R_f 0.47 [hexane-EtOAc (1:4)]; $^{13}C/^{1}H$ heteronuclear shift correlation 75.4 (300 MHz) $CDCl_3$ 18.2 (1.91), 19.6 (1.71), 20.3 (1.93), 23.4 (1.40), 23.4 (1.40), 23.5 (2.16), 30.3 (2.31), 34.4 (2.10 and 3.47), 35.9 (1.83 and 2.36), 58.5 (3.34), 63.2 (4.24 and 4.52), 66.3 (5.76), 73.2 (5.88), 125.6 (5.61 and 5.98).

Hirsutinolide **4**.—Compound **4** was obtained from the fractions eluted with EtOAc-hexane (4:1): R_f

TABLE 10. Crystal Data, Collection and Refinement Parameters.

	Compound	
	3	**14**
A. Crystal parameters		
chemical formula	$C_{24}H_{32}O_{11}$	$C_{21}H_{30}O_8$
molecular weight	496.52	410.46
crystal system	tetragonal	tetragonal
space group	$P4_12_12$	$R4_1$
crystal size, mm	0.26 × 0.26 × 0.48	0.28 × 0.28 × 0.80
crystal color	white	white
cell constants		
a, Å	16.011(9)	9.376(1)
b, Å	16.011(9)	9.376(1)
c, Å	19.539(9)	24.405(6)
cell volume, Å^3	5008.47	2145.46
ρ (calc), g/cm^3	1.32	1.26
Z	8	4
F(000), e$^-$	2111.78	879.91
B. Data collection parameters		
μ, cm^{-1}	8.91	7.70
scan width, below $K_{\alpha 1}$, above $K_{\alpha 2}$, deg	1.0–1.0	1.0–1.0
2θ limits, deg	2–50	3–105
scan speed (variable), deg min^{-1}	3–30	3–30
exposure time, h	79.7	12.2
total no. reflections collected	4927	1468
no. unique reflections	4430	1268
Structure refinement		
reflections for final refinement	2944	1260
parameters refined	323	268
R (F), %	7.29	3.85
R (W), %	6.98	5.92
goodness of fit for the last cycle	1.129	1.040
final G	0.0015	0.0035
residual election density (e$^-$/Å^3)	0.48	0.19

0.61 [hexane-EtOAc (1:1)]; ir ($CHCl_3$) ν max cm^{-1} 3562, 1758, 1740, 1630; ms (70 eV) *m/z* (rel. int.) $[M]^+$ 436 (0.7), 375 (1), 328 (1.2), 188 (26), 69 (100).

Hirsutinolide **5**.—Compound **5** was obtained from the fractions eluted with EtOAc-hexane (3:2): mp 108–110°; R_f 0.45 [hexane-EtOAc (3:2)]; ir ($CHCl_3$) ν max cm^{-1} 3562, 1758, 1720, 1635.

Hirsutinolide **6**.—Compound **6** was obtained from the fractions eluted with EtOAc-hexane (3:2): R_f 0.51 [hexane-EtOAc (3:2)]; ir ($CHCl_3$) ν max cm^{-1} 3544, 1757, 1723, 1634; ms (70 eV) *m/z* (rel. int.) $[M]^+$ 408 (4.5), 275 (10), 234 (22), 148 (28), 69 (100), 43 (85).

Cadinanolide **7**.—Compound **7** was isolated from the fractions eluted with EtOAc-hexane (1:1): mp 167–169°; R_f 0.47 [hexane-EtOAc (1:1)]; ir ($CHCl_3$) ν max cm^{-1} 3591, 1758, 1739, 1640; $^{13}C/^1H$ heteronuclear shift correlation 75.4 (300 MHz) $CDCl_3$ 15.1 (1.17), 18.2 (1.91), 19.7 (1.70), 20.4 (1.94), 23.4 (2.15), 23.5 (1.39), 34.3 (2.08 and 3.46), 61.5 (4.31 and 4.55), 66.2 (5.84), 66.4 (3.50), 76.5 (5.85), 125.7 (5.61 and 5.98); ms (70 eV) *m/z* (rel. int.) 380 (0.3), 378 (1.5), 100 (16), 69 (27), 43 (100), 41 (22).

Cadinanolide **8**.—Compound **8** was isolated from the fractions eluted with EtOAc-hexane (1:4): mp 220–223°; R_f 0.50 (EtOAc); ir ($CHCl_3$) ν max cm^{-1} 3596, 1759, 1740, 1635; ms (70 eV) *m/z* (rel. int.) 404 (0.2), 379 (0.2), 276 (10), 99 (57), 43 (100).

REDUCTION OF GLAUCOLIDE A.—A solution of glaucolide A [**1**] (500 mg) in THF (25 ml) was added, with stirring, to a suspension of $NaBH_4$ (500 mg) in THF (25 ml) at 0°. The mixture was stirred at

room temperature for 30 min and diluted with EtOAc. After usual workup it gave a residue which was chromatographed over Si gel, using hexane with increasing proportions of EtOAc, to afford dihydrogermacranolides **14** and **15**. Dihydroglaucolide **16** was isolated when the reaction was stirred only 5 min at room temperature.

1β-Acetyloxy-8α-methacryloxy-10α-hydroxyl-11,13β-dihydrogermacran-6α,12-olide [**14**].—White crystal: R_f 0.50 (EtOAc), mp 208°; ir ($CHCl_3$) ν max cm^{-1} 3596, 1759, 1740, 1635; ^1H nmr (300 MHz, $CDCl_3$) δ 1.28 (d, $J=7$, 3H, H-13), 1.29 (s, 3H, H-15), 1.46 (s, 3H, H-14), 1.63–1.70 (m, 2H, H-2), 1.93 (s, 3H, H-19), 2.04 (s, 3H, *Me*COO), 2.18 (m, 1H, H-3), 2.20 (m, 1H, H-9), 2.52 (dd, $J=6$, 9, 1H, H-7), 2.82 (qt, $J=9$, 7, 1H, H-11), 3.85 (d, $J=8$, 1H, H-5), 4.40 (dd, $J=8$, 6, 1H, H-6), 4.98 (d, $J=6$, 1H, H-1), 5.56 (brs, 1H, H-18), 5.81 (dd, $J=9$, 8, 1H, H-8), 6.06 (brs, 1H, H-18′); ms (70 eV) *m/z* (rel. int.) 404 (0.2), 379 (0.2), 276 (10), 99 (57), 43 (100); ^{13}C nmr (75.4 MHz, $CDCl_3$) δ 9.6 (C-13), 16.8 (C-15), 18.5 (C-19), 21.0 (*Me*COO), 24.7 (C-14), 29.6 (C-2), 37.5 (C-11), 38.3 (C-3), 39.1 (C-9), 47.0 (C-7), 59.1 (C-5), 61.5 (C-6), 64.5 (C-4), 65.2 (C-8), 72.6 (C-10), 80.5 (C-1), 126.3 (C-18), 135.2 (C-17), 166.3 (C-16), 170.6 (*Me*COO), 176.9 (C-12); $^{13}C/^1H$ heteronuclear shift correlation 75.4 (300 MHz) $CDCl_3$ 9.6 (1.28), 16.3 (1.29), 18.5 (1.93), 21.0 (2.09), 24.7 (1.46), 29.6 (1.63 and 1.70), 37.5 (2.82), 38.3 (2.18), 39.1 (1.95 and 2.2), 47.0 (2.52), 61.5 (4.40), 65.2 (5.81), 126.3 (5.56); ms (70 eV) *m/z* (rel. int.) $[M-18]^+$ 392 (1.94), 350 (30), 220 (10), 71 (22), 69 (60), 43 (100).

1α-Acetoyloxy-8α-methacryloxy-10α-hydroxyl-11,13β-dihydrogermacran-6α,12-olide [**15**].—White crystal: R_f 0.47 (EtOAc); mp 185–188°; ir ($CHCl_3$) ν max cm^{-1} 3500, 1768, 1725, 1640; ^1H nmr (300 MHz, $CDCl_3$) δ 1.22 (d, $J=7$, 3H, H-13), 1.45 (s, 3H, H-14), 1.52 (s, 3H, H-15), 1.87 (s, 3H, H-19), 2.01 (s, 3H, *Me*COO), 2.18 (m, 1H, H-3), 2.52 (dd, $J=6$, 9, 1H, H-7), 2.70 (dd, $J=6$, 14, 1H, H-9), 2.82 (qt, $J=9$, 7, 1H, H-11), 3.85 (d, $J=8$, 1H, H-5), 4.40 (dd, $J=8$, 8, 1H, H-6), 5.21 (d, $J=6$, 1H, H-1), 5.56 (brs, 1H, H-18), 5.81 (dd, $J=9$, 8, 1H, H-8), 6.06 (brs, 1H, H-18′); ms (70 eV) *m/z* (rel. int.) 404 (0.2), 379 (0.2), 276 (10), 99 (57), 43 (100); ^{13}C nmr (75.4 MHz, $CDCl_3$) δ 9.6 (C-13), 16.8 (C-15), 18.5 (C-19), 21.0 (*Me*COO), 24.7 (C-14), 29.6 (C-2), 37.5 (C-11), 38.3 (C-3), 39.1 (C-9), 47.0 (C-7), 59.1 (C-5), 61.5 (C-6), 64.5 (C-4), 65.2 (C-8), 72.6 (C-10), 80.5 (C-1), 126.3 (C-18), 135.2 (C-17), 166.3 (C-16), 170.6 (*Me*COO), 176.9 (C-12); $^{13}C/^1H$ heteronuclear shift correlation 75.4 (300 MHz) $CDCl_3$ 9.6 (1.22), 16.8 (1.52), 18.5 (1.87), 21.0 (2.01), 24.7 (1.45), 29.6 (1.63 and 1.70), 37.5 (2.82), 38.3 (2.18), 39.1 (1.95 and 2.2), 47.0 (2.52), 61.5 (4.40), 65.2 (5.81), 126.3 (5.56); ms (70 eV) *m/z* (rel. int.) $[M-18]^+$ 392 (1.94), 350 (30), 220 (10), 71 (22), 69 (60), 43 (100).

11,13β-Dihydroglaucolide A [**16**].—Oily compound: ir ($CHCl_3$) ν max cm^{-1} 1780, 1740, 1725, 1635; ^1H nmr (80 MHz, $CDCl_3$) δ 1.32 (d, $J=7$, 3H, H-13), 1.45 (s, 3H, H-14), 1.55 (s, 3H, H-15), 1.94 (s, 3H, H-19), 2.05 (s, 3H, *Me*COO), 2.90 (d, $J=8$, 1H, H-5), 4.32 (dd, $J=8$, 6, 1H, H-6), 4.90 (brd, $J=8$, 1H, H-8), 5.64 (brs, 1H, H-18), 6.10 (brs, 1H, H-18); ms (70 eV) *m/z* (rel. int.) 335 (15), 323 (0.2), 220 (10), 99 (18), 95 (15), 69 (86), 43 (100).

ACKNOWLEDGMENTS

Partial financial support from CoNaCyT, CoSNET, and Proyectos Estratégicos-SEP is acknowledged.

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Received 24 October 1991