Neoclerodane Diterpenoids from *Scutellaria pontica*†

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Seven novel neoclerodane diterpenoids, scupontins A−G, have been isolated from the Me_2CO extract of the aerial parts of *Scutellaria pontica* (**1**−**7**), together with the known neoclerodanes scutalbin A and scutalpin M. Structures **1**−**7** were established by exhaustive NMR spectroscopic studies and chemical transformations. Scupontins A−D (**1**−**4**, respectively) and scupontins E (**5**) and F (**6**) possess unusual [(3′*S*,3″*S*)-3′-[(3″-acetoxybutyryl)oxy]butyryloxy and [(3′*S*,3″*S*,3‴*S*)-3′-[[3″-[(3‴-hydroxybutyryl)oxy]butyryl]oxy]butyryl]oxy substituents, respectively, attached to the C-19 position of the neoclerodane framework. In the case of the 6α,7β-dibenzoate derivative **7** (scupontin G) its absolute configuration was established by the CD exciton chirality method.

The neoclerodane diterpenes[1] isolated from *Scutellaria* species (Labiatae) are of interest on account of their biological activity as insect antifeedants[2−6] and as antifungal agents against plant pathogenic fungi.[7] In continuation of our studies on *Scutellaria* plants[6,8−10] we report here on the isolation and structure elucidation of seven new neoclerodane derivatives isolated from *Scutellaria pontica* C. Koch.

Results and Discussion

The Me_2CO extract of the aerial parts of *S. pontica* was subjected to extensive chromatography (see Experimental Section) to yield the already known neoclerodane diterpenoids scutalbin A[10] and scutalpin M,[8] together with seven new substances, scupontins A−G, whose structures (**1**−**7**, respectively) were established as follows.

Scupontin A (**1**) had the molecular formula $C_{32}H_{46}O_{12}$, and its IR spectrum showed absorptions for hydroxyl (3470 cm^{-1}), vinyl ether (3090, 1620 cm^{-1}), and ester (1740, 1250 cm^{-1}) groups. The ^{1}H- and ^{13}C-NMR spectra of **1** (Tables 1 and 2, respectively) revealed the presence of two acetoxyl groups (δ_H 2.02 and 1.93, both 3H, s; δ_C 170.6 s, 170.0 s, 21.21 q, and 21.17 q) and two 3-*O*-acylbutyric ester moieties [δ_{H-3} 5.32 qdd and 5.21 br sext, both 1H; δ_{Me-4} 1.30 d and 1.27 d, both 3H, J = 6.2, 6.3 Hz, respectively; δ_C 169.7 s (C-1′), 169.4 s (C-1″), 40.8 t, double signal (C-2′ and C-2″), 67.8 d (C-3′), 67.4 d (C-3″), and 19.89 q and 19.87 q (C-4′ and C-4″); see also Table 1 for the C-2 methylene protons]. In addition, **1** showed characteristic signals of a neoclerodane diterpene [δ_H 0.83 d, 3H, J = 6.5 Hz (Me-17) and 0.95 s, 3H (Me-20); δ_C 16.4 q (C-17) and 14.1 q (C-20)] having a 4α,18-oxirane [δ_H 2.96 dd, 1H, J_{gem} = 3.9 Hz, $J_{18B,3\alpha}$ = 2.3 Hz (H_B-18) and 2.25 d, 1H, J_{gem} = 3.9 Hz (H_A-18); δ_C 62.3 s (C-4) and 48.4 t (C-18)], an esterified 6α-hydroxyl group ($\delta_{H-6\beta}$ 4.63 dd, $J_{6\beta,7\alpha}$ = 11.6 Hz, $J_{6\beta,7\beta}$ = 4.6 Hz; δ_{C-6} 71.9 d), a C-19 acyloxy grouping (δ 4.80 d and 4.39 d, J_{gem} = 12.4 Hz; δ_{C-19} 62.3 t), and a tetrahydrofurofuran moiety involving the C-11−C-16 carbons. The presence of a C-14,C-15 olefinic double bond in this structural part was revealed by the ^{1}H-NMR signals at δ 4.79 (1H, t, $J_{14,13}$ = $J_{14,15}$ = 2.4 Hz, H-14) and 6.45 (1H, t, $J_{15,13}$ = $J_{15,14}$ = 2.4 Hz, H-15), and the carbon atom resonances at δ 101.8 d (C-14) and 146.9 d (C-15). (See Tables 1 and 2 for the remaining proton and carbon resonances of the C-11−C-16 fragment). All the above-mentioned functionalities, except for those of the 3-*O*-acylbutanoates, have been found in several neoclerodane derivatives previously isolated from *Scutellaria* species.[2,3,6−10]

In addition, scupontin A (**1**) possessed a secondary hydroxyl group attached to the neoclerodane nucleus (δ_C 68.7 d, geminal proton as a broad multiplet at δ 3.70, $W_{1/2}$ = 22 Hz). This hydroxyl group must be placed at the C-2 position because the TOCSY spectrum of **1** showed a structural fragment in which the C-1 and C-3 methylene protons, the C-10 methine proton, and the geminal proton of this hydroxyl group are involved. Double resonance experiments indicated that the C-2 hydroxyl group is equatorial, because irradiation at its geminal proton (δ 3.70 m) transformed the signal of the H-3α axial proton (δ 2.10 td, $J_{3\alpha,3\beta}$ = $J_{3\alpha,2\beta}$ = 11.8 Hz, $J_{3\alpha,18B}$ = 2.3 Hz) into a double doublet ($J_{3\alpha,3\beta}$ = 11.8 Hz, $J_{3\alpha,18B}$ = 2.3 Hz), thus establishing a *trans*-diaxial relationship between these two protons.[11]

In agreement with the above conclusions, treatment of **1** with Ac_2O−pyridine yielded a derivative (**8**, $C_{34}H_{48}O_{13}$) for which the IR spectrum was devoid of any hydroxyl absorption and whose ^{1}H-NMR spectrum was identical to that of **1**, except for the presence of an additional acetoxyl group (δ 2.00, 3H, s) and the downfield resonance of the H-2β proton (δ 4.73 m). Comparison of the ^{13}C-NMR spectra of **1** and **8** further supported[11] the presence of a 2α-hydroxyl group in scupontin A [Table 2, acetylation shifts: $\Delta\delta$ + 2.0 ppm

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Table 1. ^{1}H-NMR Spectral Data of Compounds **1**−**3**, **5**, **8**, **10**, and **12**

proton(s)	**1**	**2**	**3**	**5**	**8**	**10**	**12**
H-1α	1.58 (m)[a]	*a*	∼1.65[a]	∼1.60[a]	∼1.60[a]	∼1.60[a]	∼1.60[a]
H-1*β*	2.44 (m)[a]	*a*	∼2.45[a]	∼2.40[a]	∼2.50[a]	∼2.45[a]	∼2.50[a]
H-2α		*a*					
H-2*β*	3.70 (m)[b]	*a*	3.70 (m)[b]	3.70 (m)[b]	4.73 (m)[b]	4.68 (m)[b]	4.67 (dddd)
H-3α	2.10 (td)	*a*	∼2.10[a]	2.12 (td)	2.16 (td)	2.21 (td)	2.21 (td)
H-3*β*	1.40 (ddd)	*a*	∼1.40[a]	∼1.40[a]	∼1.50[a]	∼1.35[a]	1.36 (ddd)
H-6*β*	4.63 (br dd)	4.67 (br dd)	4.62 (br dd)	4.62 (br dd)	4.62 (br dd)	4.63 (br dd)	4.63 (br dd)
H-7α	1.60 (m)[a]	*a*	∼1.60[a]	∼1.60[a]	∼1.60[a]	∼1.65[a]	1.64 (br q)
H-7*β*	1.46 (m)[a]	*a*	∼1.45[a]	∼1.45[a]	∼1.50[a]	∼1.50[a]	1.48 (br dt)
H-8*β*	1.46 (m)[a]	*a*	∼1.45[a]	∼1.45[a]	∼1.50[a]	∼1.40[a]	1.40 (ddq)
H-10*β*	1.58 (dd)	*a*	∼1.60[a]	∼1.60[a]	∼1.60[a]	∼1.60[a]	1.60 (dd)
H-11α	4.01 (dd)	4.01 (dd)	4.09 (dd)	4.02 (dd)	4.01 (dd)	4.15 (dd)	4.15 (dd)
H_A-12	1.63 (br dd)	*a*	∼1.60[a]	∼1.60[a]	∼1.60[a]	∼1.60[a]	∼1.60[a]
H_B-12	1.71 (ddd)	*a*	∼1.65[a]	∼1.70[a]	∼1.70[a]	∼1.90[a]	∼1.90[a]
H-13*β*	3.55(qt)	3.55 (m)[c]	2.87 (m)[d]	3.55 (m)[c]	3.60 (m)[c]	3.25 (m)[d]	3.25 (m)[d]
H_A-14	4.79 (t)	4.80 (t)	*a*	4.79 (t)	4.79 (t)	2.40 (dd)	2.39 (dd)
H_B-14			*a*			2.89 (dd)	2.88 (dd)
H_A-15	6.45 (t)	6.45 (dd)	3.85 (m)	6.45 (dd)	6.43 (dd)		
H_B-15			3.85 (m)				
H-16*β*	6.03 (d)	6.00 (d)	5.65 (d)	6.04 (d)	5.97 (d)	6.01 (d)	6.01 (d)
Me-17	0.83 (3H, d)	0.82 (3H, d)	0.86 (3H, d)	0.83 (3H, d)	0.81 (3H, d)	0.86 (3H, d)	0.86 (3H, d)
H_A-18[e]	2.25 (d)	2.19 (d)	2.25 (d)	2.26 (d)	2.28 (d)	2.29 (d)	2.28 (d)
H_B-18[f]	2.96 (dd)	2.96 (dd)	2.96 (dd)	2.96 (dd)	2.96 (dd)	2.98 (dd)	2.98 (dd)
H_A-19	4.39 (br d)	4.41 (br d)	4.39 (br d)	4.36 (br d)	4.39 (br d)	4.40 (br d)	4.42 (br d)
H_B-19	4.80 (d)	4.84 (d)	4.81 (d)	4.83 (d)	4.84 (d)	4.83 (d)	4.83 (d)
Me-20	0.95 (3H, s)	0.94 (3H, s)	0.94 (3H, s)	0.96 (3H, s)	0.95 (3H, s)	0.95 (3H, s)	0.96 (3H, s)
OH-2α	2.23 (br)		*a*	*a*			
OAc-2α					2.00 (3H, s)	2.01 (3H, s)	2.00 (3H, s)
OAc-6α	1.93 (3H, s)	1.94 (3H, s)	1.93 (3H, s)	1.93 (3H, s)	1.93 (3H, s)	1.95 (3H, s)	1.95 (3H, s)
OAc-3″ or 3‴	2.02 (3H, s)	2.01 (3H, s)	2.02 (3H, s)		2.01 (3H, s)	2.03 (3H, s)	2.02 (3H, s)
H_A-2′	2.54 (dd)	2.54 (dd)	2.54 (dd)	2.54 (dd)	2.53 (dd)	2.54 (dd)	2.55 (dd)
H_B-2′	2.66 (dd)	2.68 (dd)	2.66 (dd)	2.66 (dd)	2.68 (dd)	2.70 (dd)	2.69 (dd)
H-3′	5.32 (qdd)	5.32 (br sext)	5.30 (qdd)	5.33 (br sext)	5.30 (br sext)	5.30 (br sext)	5.30 (br sext)
Me-4′	1.30 (3H, d)	1.29 (3H, d)	1.30 (3H, d)	1.31 (3H, d)	1.28 (3H, d)	1.30 (3H, d)	1.30 (3H, d)
H_A-2″	2.45 (dd)	2.45 (dd)	2.45 (dd)	2.51 (dd)	2.44 (dd)	2.45 (dd)	2.46 (dd)
H_B-2″	2.60 (dd)	2.58 (dd)	2.60 (dd)	2.60 (dd)	2.57 (dd)	2.59 (dd)	2.58 (dd)
H-3″	5.21 (br sext)	5.23 (br sext)	5.21 (br sext)	5.28 (br sext)	5.22 (br sext)	5.23 (br sext)	5.26 (br sext)
Me-4″	1.27 (3H, d)	1.27 (3H, d)	1.27 (3H, d)	1.29 (3H, d)	1.26 (3H, d)	1.27 (3H, d)	1.26 (3H, d)[g]
H_A-2‴				2.55 (dd)			2.45 (dd)
H_B-2‴				2.65 (dd)			2.59 (dd)
H-3‴				4.20 (br sext)			5.24 (br sext)
Me-4‴				1.22 (3H, d)			1.27 (3H, d)[g]

$J_{H,H}$ (Hz)	**1**[h]	**2**[h,i]	**3**[h,j]	**5**[h]	**8**[h]	**10**[h]	**12**[h]
1α,2*β*	*k*	*a*	*k*	*k*	*a*	*k*	12.7
1α,10*β*	10.1	*a*	*a*	*a*	*a*	*a*	12.7
1*β*,2*β*	*k*	*a*	*k*	*k*	*a*	*k*	5.2
1*β*,3*β*	1.8	*a*	*a*	*a*	*a*	*a*	1.6
1*β*,10*β*	2.0	*a*	*a*	*a*	*a*	*a*	2.4
2*β*,3α	11.8	*a*	*k*	11.7	12.2	12.0	12.2
2*β*,3*β*	4.3	*a*	*k*	*k*	*k*	*k*	4.9
3α,3*β*	11.8	*a*	*a*	11.7	12.2	12.2	12.2
6*β*,7α	11.6	11.5	11.2	11.5	11.5	11.5	11.5
6*β*,7*β*	4.6	4.8	4.6	4.5	4.6	4.7	4.7
7α,7*β*	*a*	*a*	*a*	*a*	*a*	*a*	13.7
7α,8*β*	*a*	*a*	*a*	*a*	*a*	*a*	13.0
7*β*,8*β*	*a*	*a*	*a*	*a*	*a*	*a*	4.5
8*β*,17	6.5	6.4	6.4	6.5	6.5	6.5	6.7
11α,12A	4.5	4.8	5.4	4.5	4.6	5.6	5.5
11α,12B	11.7	11.5	11.4	11.7	11.5	11.2	11.2
12A,12B	12.0	*a*	*a*	*a*	*a*	*a*	*a*
12A,13*β*	< 0.3	*k*	*k*	*k*	*k*	*k*	*k*
12B,13*β*	8.1	*k*	*k*	*k*	*k*	*k*	*k*
13*β*,14A	2.4	2.6	*k*	2.7	2.7	4.0	4.0
13*β*,14B			*k*			10.4	10.5
13*β*,15	2.4	2.4	0	2.0	2.1		
13*β*,16*β*	6.2	6.2	5.1	6.2	6.3	5.5	5.5
14A,14B			*a*			18.7	18.7
14A,15A	2.4	2.6	*a*	2.7	2.7		
18A,18B	3.9	3.9	3.9	3.8	3.9	3.9	4.0
18B,3α	2.3	2.3	2.2	2.1	2.2	2.1	2.2
19A,19B	12.4	12.1	12.4	12.2	12.3	12.3	12.5
19A,6*β*	< 0.2	< 0.5	< 0.5	< 0.5	< 0.5	< 0.5	< 0.5
2′A,2′B	15.6	15.7	15.6	15.6	16.0	15.9	16.0
2′A,3′	5.4	5.8	5.4	5.4	5.7	5.7	5.7
2′B,3′	7.7	7.5	7.7	7.7	7.4	7.5	7.5
3′,4′	6.2	6.0	6.3	6.2	6.3	6.3	6.2
2″A,2″B	15.7	15.4	15.7	15.7	15.4	15.3	15.4
2″A,3″	6.1	5.8	6.1	6.1	5.7	5.8	5.7
2″B,3″	7.2	7.5	7.1	7.3	7.5	7.5	7.5
3″,4″	6.3	6.2	6.3	6.3	6.4	6.4	6.2
2‴A,2‴B				15.7			15.5
2‴A,3‴				5.0			5.7
2‴B,3‴				7.9			7.5
3‴,4‴				6.5			6.2

[a] This is an overlapped signal. [b] This signal shows a $W_{1/2}$ = 22 Hz. [c] This signal shows a $W_{1/2}$ = 15 Hz. [d] This signal shows a $W_{1/2}$ = 24 Hz. [e] This is the exo hydrogen with respect to ring B. [f] This is the endo hydrogen with respect to ring B. [g] These assignments may be interchanged. [h] In all compounds the $J_{1\alpha,1\beta}$ value was not measured due to overlapping. [i] In this compound the *J* values that concern the H-2α and H-2*β* protons were not measured due to overlapping of these signals. [j] In this compound *J* values concerning the 2H-14 and 2H-15 protons were not determined. [k] Value was not determined.

Table 2. ^{13}C-NMR Spectral Data of Compounds **1**-**3**, **5**, **8**, **10**, and **12**

carbon	**1**	**2**	**3**	**5**[a]	**8**	**10**	**12**
C-1	32.1 (t)	22.2 (t)	31.9 (t)	32.0 (t)	28.1 (t)	27.9 (t)	28.0 (t)
C-2	68.7 (d)	25.0 (t)	68.6 (d)	69.0 (d)	70.7 (d)	70.5 (d)	70.7 (d)
C-3	41.0 (t)	32.7 (t)	41.8 (t)	41.5 (t)	38.3 (t)	38.0 (t)	38.1 (t)
C-4	62.3 (s)	64.9 (s)	62.3 (s)		62.1 (s)	61.9 (s)	62.1 (s)
C-5	44.2 (s)	45.5 (s)	44.2 (s)		44.7 (s)	44.4 (s)	44.6 (s)
C-6	71.9 (d)	71.9 (d)	71.9 (d)	72.0 (d)	71.9 (d)	71.5 (d)	71.6 (d)
C-7	33.4 (t)	33.4 (t)	33.4 (t)	33.0 (t)	33.4 (t)	33.1 (t)	33.2 (t)
C-8	36.1 (d)	36.2 (d)	35.6 (d)	36.0 (d)	36.4 (d)	36.1 (d)	36.2 (d)
C-9	39.9 (s)	40.0 (s)	40.3 (s)		40.1 (s)	40.2 (s)	40.3 (s)
C-10	44.5 (d)	48.4 (d)	44.1 (d)	44.5 (d)	44.4 (d)	43.7 (d)	43.8 (d)
C-11	84.2 (d)	84.5 (d)	84.7 (d)	84.0 (d)	84.7 (d)	84.5 (d)	84.6 (d)
C-12	31.3 (t)	31.2 (t)	32.4 (t)	31.0 (t)	31.2 (t)	31.9 (t)	32.0 (t)
C-13	46.0 (d)	46.0 (d)	42.0 (d)	46.0 (d)	46.0 (d)	38.0 (d)	38.1 (d)
C-14	101.8 (d)	101.9 (d)	32.5 (t)	102.0 (d)	101.9 (d)	35.1 (t)	35.3 (t)
C-15	146.9 (d)	146.9 (d)	68.2 (t)	147.0 (d)	146.9 (d)	175.0 (s)	175.0 (s)
C-16	107.6 (d)	107.7 (d)	107.6 (d)	108.0 (d)	107.7 (d)	106.7 (d)	106.8 (d)
C-17	16.4 (q)	16.4 (q)	16.4 (q)	16.0 (q)	16.1 (q)	16.0 (q)	16.2 (q)
C-18	48.4 (t)	48.6 (t)	48.3 (t)	48.0 (t)	48.3 (t)	48.2 (t)	48.3 (t)
C-19	62.3 (t)	61.9 (t)	62.1 (t)	62.0 (t)	61.9 (t)	61.6 (t)	61.7 (t)
C-20	14.1 (q)	14.1 (q)	13.9 (q)	13.5 (q)	14.1 (q)	13.7 (q)	13.9 (q)
2α-0Ac					169.9 (s)	169.8 (s)	170.0 (s)
					21.1 (q)	21.0 (q)	21.1 (q)
6α-OAc	170.0 (s)	170.1 (s)	169.9 (s)		170.0 (s)	170.0 (s)	170.1 (s)
	21.17 (q)	21.1 (q)	21.0 (q)	20.0 (q)	21.2 (q)	21.0 (q)	21.1 (q)
3″- or 3‴-OAc	170.6 (s)	170.1 (s)	170.3 (s)		170.4 (s)	170.5 (s)	170.6 (s)
	21.21 (q)	21.3 (q)	21.0 (q)		21.1 (q)	21.1 (q)	21.3 (q)
C-1′	169.7 (s)	169.9 (s)	169.6 (s)		169.7 (s)	169.6 (s)	169.7 (s)
C-2′	40.8 (t)	41.0 (t)	40.8 (t)	41.0 (t)	40.9 (t)[b]	40.9 (t)	40.9 (t)
C-3′	67.8 (d)	67.6 (d)	67.7 (d)	68.0 (d)	67.6 (d)	67.4 (d)	67.6 (d)
C-4′	19.87 (q)[c]	19.8 (q)	19.8 (q)	19.5 (q)	19.9 (q)	19.7 (q)	19.7 (q)
C-1″	169.4 (s)	169.3 (s)	169.3 (s)		169.2 (s)	169.2 (s)	169.2 (s)
C-2″	40.8 (t)	40.8 (t)	40.8 (t)	41.0 (t)	41.1 (t)[b]	40.7 (t)	40.9 (t)
C-3″	67.4 (d)	67.2 (d)	67.2 (d)	68.0 (d)	67.2 (d)	67.1 (d)	67.5 (d)
C-4″	19.89 (q)[c]	19.9 (q)	19.8 (q)	19.5 (q)	19.9 (q)	19.7 (q)	19.8 (q)
C-1‴							169.1 (s)
C-2‴				41.0 (t)			40.8 (t)
C-3‴				65.0 (d)			67.2 (d)
C-4‴				22.0 (q)			19.9 (q)

[a] Only protonated carbons were measured from the HMQC spectrum; δ_C values for **5** are accurate to ± 0.5 ppm. [b,c] These assignments may be reversed.

for the C-2 α-carbon, and −4.0 and −2.7 ppm for the *β*-carbons (C-1 and C-3, respectively)].

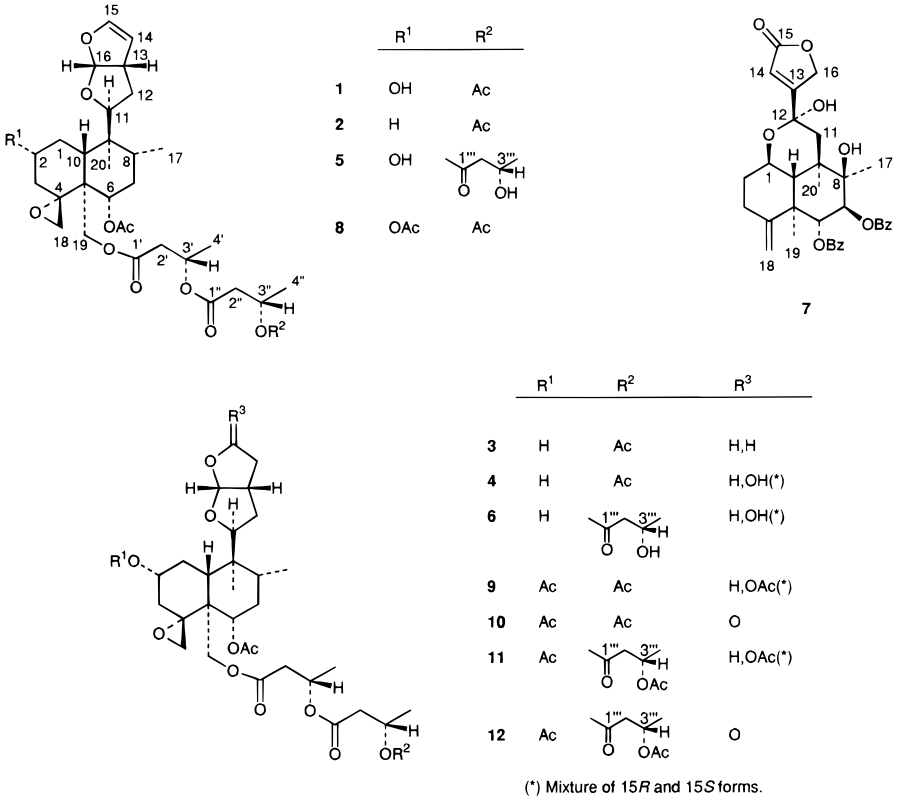
The location of the two acetates and the two 3-*O*-acylbutyrates of scupontin A as well as their arrangement were unambiguously established from the HMBC spectrum. The H-6*β* proton of **1** (*δ* 4.63 br dd) showed a correlation through three bonds with a carbonyl carbon belonging to an acetoxyl group (*δ* 170.0 s), thus establishing that one of the acetates is attached to the C-6α position. This assignment, together with all the above deductions, implied that **1** possesses a [3′-[(3″-acetoxybutyryl)oxy]butyryl]oxy substituent at the C-19 position. This conclusion was corroborated by the TOCSY and HMBC spectra of **1**, which allowed the assignment of both 3-*O*-acylbutyrate fragments (see Tables 1 and 2) and showed connectivities, among others, between the C-19 methylene protons (*δ* 4.39 and 4.80) and the carboxyl carbon of the first 3′-*O*-acylbutyrate (*δ* 169.7 s), between the H-3′ proton (*δ* 5.32) of this substituent and the carboxyl carbon of the second 3″-*O*-acylbutyrate (*δ* 169.4 s), and finally, between the H-3″ proton (*δ* 5.21) of this last group and the carbonyl carbon corresponding to the other acetoxyl group (*δ* 170.6 s) of scupontin A. Moreover, the observed connectivities between the H-3′ and H-3″ protons and the C-1′ and C-1″ carboxyl carbons, respectively, further supported the arrangement of the ester groups. All the ^{1}H- and ^{13}C-NMR data and the TOCSY, HMQC, and HMBC spectra were in complete agreement with structure **1** for scupontin A and allowed the unequivocal assignment of all the protons and carbons of this new diterpenoid (see Tables 1 and 2).

Reduction of **1** with $LiAlH_4$ gave a complex mixture of products from which enantiomerically pure (*S*)-(+)-1,3-butanediol was isolated and identified[12] by its specific rotation value ($[\alpha]^{26}_D$ +29.2°)[13] and gas chromatographic analysis on a chiral column (see Experimental Section), thus establishing a 3′*S*,3″*S* absolute configuration for the [3′-[(3″-acetoxybutyryl)oxy]butyryl]-oxy moiety of scupontin A (**1**).

The absolute configuration of the clerodane part of **1** was not ascertained. However, on biogenetic grounds, it is reasonable to assume that it belongs to the neoclerodane series,[1] like scupontin G (**7**, see below), co-occurring in the same plant, and other diterpenoids previously found in *Scutellaria* species.[6,8,9,14] The molecular rotation values of **1** ($[M]_D$ −196°) and its 2α-*O*-acetyl derivative (**8**, $[M]_D$ −265°) suggested a steroid-like absolute configuration[15] such as in **1** for scupontin A.

Scupontin B (**2**, $C_{32}H_{46}O_{11}$) is the 2-deoxy derivative of scupontin A (**1**, $C_{32}H_{46}O_{12}$). The IR spectrum of **2** was devoid of hydroxyl absorptions, and the only differences observed between the ^{1}H- and ^{13}C-NMR spectra of **1** and **2** were in agreement with the absence in the latter of the 2α-hydroxyl group of the former [**2**: no signal of the H-2*β* proton downfield; δ_C at 22.2 t (C-1), 25.0 t (C-2), 32.7 t (C-3), 64.9 s (C-4), and 48.4 d (C-10); **1**: $\delta_{H-2\beta}$ 3.70 m; δ_C at 32.1 t (C-1), 68.7 d (C-2), 41.0 t (C-3), 62.3 s (C-4), and 44.5 d (C-10)]. Moreover, the TOCSY and

Chart 1



HMBC spectra of scupontin B were only compatible with a structure such as **2** for this diterpenoid.

The 14,15-dihydro derivative of **1** was also present in the Me_2CO extract of *S. pontica*. This diterpenoid (**3**, scupontin C, $C_{32}H_{48}O_{12}$) showed ^{1}H- and ^{13}C-NMR spectra almost identical to those of **1** (see Tables 1 and 2). The spectroscopic differences between these compounds are due to the presence in **3** of a hexahydrofurofuran moiety[3,6] [C-15 methylene protons at δ 3.85 m, 2H; δ_C 42.0 d (C-13), 32.5 t (C-14), and 68.2 t (C-15)] instead of the tetrahydrofurofuran part of **1** (see above and Tables 1 and 2). As in the case of **1** and **2**, the TOCSY and HMBC spectra of scupontin C confirmed the location and arrangement of its substituents as depicted in formula **3**.

Scupontin D (**4**) was homogeneous on TLC, and its ^{1}H-NMR spectrum (see Experimental Section) showed essentially the same signals as those present in the ^{1}H-NMR spectrum of **1**. The observed differences between the ^{1}H-NMR spectra of **4** and **1** were in agreement with the former being a 1:1 mixture of the C-15 epimers of the 14,15-dihydro-15-hydroxy derivative of the latter. Thus, in **4** the H-11, H-15, and H-16 protons appeared as pairs of signals[10] [δ 4.57 dd and 3.96 dd, 0.5 H each, J = 11.5, 4.1 Hz (H-11α in the 15*S* and 15*R* epimer, respectively); 5.61 and 5.50, 0.5 H each, both br d, J = 4.3, 4.6 Hz, respectively (H-15); 5.81 and 5.76, 0.5 H each, both d, J = 5.4 Hz (H-16)] instead of the single signals corresponding to the H-11, H-15, and H-16 protons of **1** (see above and Table 1); the rest of the spectrum was identical in both compounds.

Treatment of **4** with Ac_2O−pyridine gave **9** as a 7:3 mixture of 15-exo and 15-endo epimers, respectively.[16] Oxidation of **9** with an excess of Jones reagent yielded the 15,16-γ-lactone derivative **10** ($C_{34}H_{48}O_{14}$, ν_{max} 1790 cm^{-1}; δ_{H-16} 6.01, 1H, d, $J_{16,13}$ = 5.5 Hz; δ_{C-15} 175.0 s) by an initial hydrolysis of the acetate group at the C-15 hemiacetalic position, as a consequence of the acidity of the reagent,[6,9,10] followed by oxidation of the resulting 15,16-hemiacetal group to the corresponding γ-lactone.[10] Treatment of the 2α-*O*-acetyl derivative (**8**) of scupontin A with Jones' reagent also yielded **10** by oxidation of a 15,16-hemiacetal, which must have been formed from the 14,15-vinyl ether of the tetrahydrofurofuran moiety of **8**, because it is known[10,17] that the 14,15-double bond of these diterpenoids is very sensitive even to weak acidic conditions. This correlation established the structure depicted in **4** for scupontin D.

Scupontin E (**5**, $C_{34}H_{50}O_{13}$) showed hydroxyl absorption (3460 cm^{-1}) in its IR spectrum. Its ^{1}H- and ^{13}C-NMR spectra (Tables 1 and 2, respectively) were almost identical to those of **1** and the observed differences were consistent with the presence in the former of a third 3-hydroxybutyric ester group [δ_H 2.55, 1H, dd, J = 15.7, 5.0 Hz (H_A-2), 2.65, 1H, dd, J = 15.7, 7.9 Hz (H_B-2), 4.20, 1H, br sext (H-3), and 1.22, 3H, d, J = 6.5 Hz (Me-4); δ_C 41.0 t (C-2), 65.0 d (C-3), and 22.0 q (C-4); see also Tables 1 and 2] instead of one of the acetates of **1** (see above). The attachment of the acetate group of **5** (δ 1.93, 3H, s) at the C-6α-position was in agreement with its unusual upfield resonance due to the shielding effect of the spatially close 4α,18-oxirane, such as in **1**−**4** (see Table 1). Consequently, scupontin E possessed structure **5**.

Like scupontin D (**4**), scupontin F (**6**) was a 1:1 mixture of the C-15 epimers of a 15,16-hemicetal. Its ^{1}H-NMR spectrum (see Experimental Section) was very similar to that of **5**, both showing the same differences as those found between the ^{1}H-NMR spectra of **4** and **1** (see above). Treatment of **6** with Ac_2O−pyridine yielded **11** as a 7:3 mixture of the 15-exo and 15-endo forms, respectively.[16] Reaction of **11** with Jones' reagent gave the 15,16-γ-lactone **12** ($C_{38}H_{54}O_{16}$, ν_{max} 1790 cm^{-1}; δ_{H-16} 6.01, 1H, d, $J_{16,13}$ = 5.5 Hz; δ_{C-15} 175.0 s), which was

Table 3. ^{1}H- and ^{13}C-NMR Spectral Data of Compound **7**

proton(s)	**7**	$J_{H,H}$ (Hz)	**7**	carbon	**7**	carbon(s)	**7**
H-1α	4.39 (td)	1α,2α	5.4	1	65.8 (d)	OBz-6α	
H-2α	2.14 (m)[a]	1α,2β	10.7	2	34.5 (t)	COO	166.0 (s)
H-2β	1.48 (dddd)	1α,10β	10.7	3	30.5 (t)	1′	129.9 (s)
H-3α	2.37 (br td)	2α,2β	13.4	4	152.3 (s)	2′,6′	129.8 (2C, d)
H-3β	2.20 (m)[a]	2α,3α	4.4	5	44.8 (s)	3′,5′	128.3 (2C, d)
H-6β	6.02 (d)	2α,3β	*a*	6	74.7 (d)	4′	133.2 (d)
H-7α	5.84 (d)	2β,3α	13.9	7	75.4 (d)		
H-10β	1.98 (d)	2β,3β	4.6	8	77.0 (s)	OBz-7β	
H-11α	1.65 (d)	3α,3β	13.9	9	40.2 (s)	COO	166.1 (s)
H-11β	2.17 (dd)[b]	3α,18	<0.5	10	46.0 (d)	1″	129.8 (s)
H-14	6.10 (t)	6β,7α	10.0	11	40.0 (t)	2″,6″	129.4 (2C, d)
H_A-16	4.84 (dd)	11α,11β	13.7	12	95.2 (s)	3″,5″	128.1 (2C, d)
H_B-16	4.91 (dd)	11β,OH(12)[c]	2.5	13	172.9 (s)	4″	132.8 (d)
Me-17	1.11 (3H, s)	14,16A	1.9	14	116.1 (d)		
H_A-18	4.64 (br s)	14,16B	1.9	15	173.3 (s)		
H_B-18	4.79 (br s)	16A,16B	18.1	16	70.6 (t)		
Me-19	1.45 (3H, s)	18A ($W_{1/2}$)	2.7	17	19.8 (q)		
Me-20	1.56 (3H, s)	18B ($W_{1/2}$)	1.8	18	105.4 (t)		
OH-8β[c]	1.60 (s)	2′,3′	8.2	19	17.9 (q)		
OH-12α[c]	2.72 (d)	2′,4′	1.4	20	21.4 (q)		
H-2′,6′	7.89 (2H, dd)	2′,5′	~0				
H-3′,5′	7.34 (2H, t)	3′,4′	7.7				
H-4′	7.48 (tt)	2″,3″	8.2				
H-2″,6″	7.74 (2H, dd)	2″,4″	1.4				
H-3″,5″	7.24 (2H, t)	2″,5″	~0				
H-4″	7.39 (tt)	3″,4″	7.7				

[a] These are overlapped signals. [b] This collapsed into a doublet (J = 13.7 Hz) after addition of D_2O. [c] Signal disappeared after addition of D_2O.

also obtained from scupontin E (**5**) by acetylation and subsequent treatment with Jones' reagent (see Experimental Section), thus establishing structure **6** for scupontin F.

Reduction of scupontins B−F (**2**−**6**, respectively, Chart 1) with $LiAlH_4$, followed by GC analysis of the crude of reactions on a chiral column (see Experimental Section), allowed the identification of enantiomerically pure (*S*)-(+)-1,3-butanediol in all cases. This established a 3*S* absolute configuration for the 3-hydroxybutyric ester groups of these diterpenoids. To the best of our knowledge, this is the first report on the existence of (*S*)-3-hydroxybutyric acid esterifying terpenoid alcohols.

The last of the diterpenoids isolated from the Me_2CO extract of *Scutellaria pontica*, scupontin G (**7**), had the molecular formula $C_{34}H_{36}O_9$, and its IR spectrum showed hydroxyl (3460 cm^{-1}), exocyclic methylene (3080, 1640, 890 cm^{-1}), α,β-unsaturated γ-lactone (3110, 1780, 1640 cm^{-1}), and benzoate group (3070, 1605, 1590, 1745, 1730, 1280, 710 cm^{-1}) absorptions.[8] The UV spectrum of **7** [λ_{max} nm (log ϵ) 227 (4.47) and 273 (3.27)] corroborated the existence of unsaturated chromophores in this diterpenoid. The ^{1}H- and ^{13}C-NMR spectra of **7** (see Table 3) displayed signals for a β-substituted α,β-unsaturated γ-lactone involving the C-13−C-16 carbons[8,18] [δ_H 6.10, 1H, t, J = 1.9 Hz (H-14), 4.84 and 4.91, 1H each, both dd, J_{gem} = 18.1 Hz, $J_{allylic}$ = 1.9 Hz (2H-16); δ_C 172.9 s (C-13), 116.1 d (C-14), 173.3 s (C-15), and 70.6 t (C-16)], as well as for a 8β-hydroxyl group [δ_H 1.11, 3H, s (Me-17), 1.56, 3H, s (Me-20), and 1.60, 1H, s (8β-OH); δ_C 77.0 s (C-8), 40.2 s (C-9), 19.8 q (C-17), and 21.4 q (C-20)], and two benzoyloxy groups (see Table 3) attached to the C-6α and C-7β equatorial positions [δ_H 6.02 and 5.84, 1H each, both d, J = 10.0 Hz (axial H-6β and H-7α protons, respectively); δ_C 74.7 d (C-6) and 75.4 d (C-7)]. These functionalities were identical with those found in scutalpins K and L, two 6α,7β-dibenzoyloxy-8β-hydroxyneoclerod-13-en-15,16-olide derivatives isolated from *Scutellaria alpina*.[8] In addition, scupontin G possessed a 4(18)-exocyclic methylene[11] [δ_H 4.64 and 4.79, 1H each, both br s, $W_{1/2}$ = 2.7, 1.8 Hz, respectively (2H-18); δ_C 152.3 s (C-4) and 105.4 t (C-18)], a Me-19 group[11] (δ_H 1.45, 3H, s; δ_C 17.9 q), and finally a hemiketal function (δ_C 95.2 s) in which the C-12 and C-1 carbons of the neoclerodane framework must be involved, because the C-11 methylene protons of **7** appeared at δ 1.65 and 2.17 as a doublet (J_{gem} = 13.7 Hz) and a double doublet (J = 13.7, 2.5 Hz), respectively, the latter being long-range coupled with the hemiketalic hydroxyl group (δ 2.72, 1H, d, ^4J = 2.5 Hz, see also Table 3). Moreover, the closure of this hemiketal grouping with the C-1β equatorial position was in agreement[19,20] with the chemical shifts and coupling pattern showed by the H-1α and H-10β protons of **7** ($\delta_{H-1\alpha}$ 4.39 td, $J_{1\alpha,2\beta}$ = $J_{1\alpha,10\beta}$ = 10.7 Hz, $J_{1\alpha,2\alpha}$ = 5.4 Hz; $\delta_{H-10\beta}$ 1.98 d, $J_{10\beta,1\alpha}$ = 10.7 Hz; *trans*-diaxial relationship between these protons).

The TOCSY spectrum of **7** confirmed the above-mentioned structural parts and the HMBC spectrum revealed connectivities between the Me-17 protons (δ 1.11 s) and the C-8 and C-9 carbons (δ 77.0 s and 40.2 s, respectively), between the C-18 olefinic protons (δ 4.64 and 4.79) and C-3, C-4, and C-5 (δ 30.5 t, 152.3 s, and 44.8 s, respectively), between the Me-19 protons (δ 1.45 s) and the C-4, C-5, and C-6 (δ 74.7 d) carbons, between the Me-20 protons (δ 1.56 s) and C-8, C-9, and C-10 (δ 46.0 d), as well as correlations of the H-6β proton (δ 6.02 d) with C-4, C-5, C-7 (δ 75.4 d), C-19 (δ 17.9 q), and a carbonyl carbon belonging to a benzoate group (δ 166.0 s), and between the H-7α proton (δ 5.84 d) and C-6 and the carboxyl carbon (δ 166.1 s) of the other benzoate. Moreover, the H-10β proton of **7** (δ 1.98 d) was connected with C-1 (δ 65.8 d), C-2 (δ 34.5 t), C-5, C-6, C-8, C-9, C-19, and C-20 (δ 21.4 q), whereas H-14 (δ 6.10 t) correlated with C-12, C-13, C-15, and C-16 (δ 95.2 s, 172.9 s, 173.3 s, and 70.6 t, respectively) and the H-11α proton (δ 1.63 d) showed connectivities with the C-9, C-10, C-12, and C-20 carbons.

From all the above data it was evident that scupontin G possesses the structure depicted in **7**, except for its absolute stereochemistry and the configuration of the C-12 chiral center. The absolute stereochemistry of scupontin G was established by using the CD exciton chirality method.[21] The 6α,7β-dibenzoyloxy binary system of this compound showed a negative first and a positive second Cotton effect ($\Delta\epsilon_{240}$ −136 and $\Delta\epsilon_{226}$ +62), thus defining a negative chirality and, consequently, a neoclerodane absolute configuration,[1] as it is shown in **7**. For the remaining stereogenic center, C-12, observation of a *W*-type long-range coupling (^4J = 2.5 Hz) between the axial 11β-proton (δ 2.17 dd) and the hydroxyl proton of the 12,1β-hemiketal group (δ 2.72 d) suggested that the C-12 hydroxyl should be in an axial α-orientation and implied a hydrogen bond, probably with the oxygen atom of the 12,1β-hemiketal. The unusual[11,19] downfield resonances of the axial 11β-proton[19] (δ 2.17), deshielded by the axial 8β-hydroxyl group, and the Me-19 protons[11,19] (δ 1.45), which could be shifted downfield by their diaxial spatial relationship with the 12α-hydroxyl group, further supported this point and led to the stereochemical assignment shown in structure **7**.

From a chemotaxonomic point of view, it is of interest to note that scupontins A−F (**1**−**6**, respectively) are the first neoclerodanes isolated from *Scutellaria* species possessing (*S*)-3-hydroxybutyric ester groups,[2,3,6−11,18,22,23] and their arrangement in these diterpenoids is a very unusual structural feature in natural products, although (*R*)-poly(3-hydroxybutanoate) of microbial origin is a well-known and useful compound.[24]

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. CD measurements were made on a JASCO J-715 instrument. IR spectra (KBr) were obtained on a Perkin-Elmer 681 spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ solution using a Varian Unity-500 or a Varian XL-300 apparatus at 500 and 300 MHz, respectively, and chemical shifts are reported with respect to residual $CHCl_3$ (δ 7.25). ^{13}C-NMR spectra were recorded at 125.7 or 75.4 MHz in $CDCl_3$, and chemical shifts are reported with respect to solvent signals (δ_{CDCl3} 77.0). ^{13}C-NMR assignments were determined by HMQC and HMBC spectra. MS were recorded in the positive-FAB mode on a JEOL AX 505 HA instrument. Elemental analyses were made with a Carlo Erba EA 1108 apparatus. Merck Si gel no. 7734 (70−230 mesh) deactivated with 10% H_2O, w/v, was used for column chromatography.

Plant Material. *S. pontica* C. Koch. was cultivated in the Orto Botanico dell'Università di Milano, at Tuscolano, Brescia, Italy. Seeds of the species were provided by the Jardin Botanique de Lausanne, Lausanne, Switzerland. Plant materials were collected in August 1994, and voucher specimens have been deposited in the Herbarium of the Dipartimento di Biologia, University of Milan, Italy.

Extraction and Isolation. Dried and finely powdered aerial parts of *S. pontica* (500 g) were extracted with Me_2CO (3 × 5 L) at room temperature for 1 week. After concentration of the Me_2CO extract *in vacuo* at low temperature (40 °C), 20 g of residue remained. This residue was subjected to dry column chromatography on Si gel with a solvent gradient from 100% petroleum ether (bp 50−70 °C) to 100% EtOAc, and finally with EtOAc−MeOH (9:1). The fraction eluted with EtOAc−petroleum ether (3:2) (120 mg) was subjected to radial chromatography [Si gel disk, CH_2Cl_2−MeOH (24:1) as eluent] to give the following compounds in order of increasing chromatographic polarity: scupontin B (**2**, 6 mg), scutalpin M[8] (16 mg), and scupontin G (**7**, 10 mg). The fraction eluted with EtOAc−petroleum ether (4:1) yielded scutalbin A[10] (23 mg), and the fraction eluted with EtOAc gave scupontin A (**1**, 210 mg). Finally, the fraction eluted with EtOAc−MeOH (9:1) (1.1 g) was rechromatographed [Si gel column, EtOAc−MeOH (49:1) as eluent], yielding the following compounds in order of increasing chromatographic polarity: scupontin C (**3**, 72 mg), scupontin E (**5**, 10 mg), scupontin D (**4**, 420 mg), and scupontin F (**6**, 24 mg).

The previously known compounds, scutalpin M[8] and scutalbin A,[10] were identified by their mp, $[\alpha]_D$, ^{1}H NMR and mass spectra, and by comparison (mixed mp, TLC) with authentic samples.

Scupontin A (1): (11*S*,13*S*,16*S*,3′*S*,3″*S*)-6α-Acetoxy-19-[[3′-[(3″-acetoxybutyryl)oxy)]butyryl]oxy]-4α,18;11,16;15,16-triepoxyneoclerod-14-en-2α-ol: mp 80−95 °C, amorphous solid; $[\alpha]^{20}_D$ −31.5° (*c* 0.225, $CHCl_3$); IR (KBr) ν_{max} 3470 (OH), 3090, 1620 (vinyl ether), 1740, 1250 (ester groups), 2980, 2880, 1450, 1370, 1180, 1140, 1080, 1060, 1030, 1000, 950, 900, 870, 820 cm^{-1}; ^{1}H NMR (500 MHz), see Table 1; ^{13}C NMR (125.7 MHz), see Table 2; positive FABMS *m*/*z* (rel int) 623 $[MH]^+$ (21), 605 $[MH - H_2O]^+$ (51), 545 $[MH - H_2O - AcOH]^+$ (9), 313 (100), 295 (20), 233 (38), 203 (76), 157 (38), 155 (31), 79 (52), 69 (80), 43 (85); *anal.* found C 61.89%, H 7.29%; $C_{32}H_{46}O_{12}$ requires C 61.71%, H 7.45%.

Scupontin B (2): (11*S*, 13*S*, 16*S*, 3′*S*,3″*S*)-6α-Acetoxy-19-[[3′-[(3″-acetoxybutyryl)oxy]butyryl]-oxy]-4α,18;11,16;15,16-triepoxyneoclerod-14-ene: mp 60−70 °C; amorphous solid; $[\alpha]^{20}_D$ −32.6° (*c* 0.221, $CHCl_3$); IR (KBr) ν_{max} 3100, 1620 (vinyl ether) 1740 br, 1250 (ester groups), 2940, 1450, 1370, 1190, 1140, 1080, 1060, 1010, 970, 950, 900, 860 cm^{-1}; ^{1}H NMR (300 MHz), see Table 1; ^{13}C NMR (125.7 MHz), see Table 2; positive FABMS *m*/*z* (rel int) 607 $[MH]^+$ (10), 547 $[MH - AcOH]^+$ (12), 389 (6), 359 (6), 315 (14), 183 (35), 129 (45), 69 (100), 43 (85); *anal.* C 63.06%, H 7.71%, calcd for $C_{32}H_{46}O_{11}$, C 63.33%, H 7.65%.

Scupontin C (3): (11*S*, 13*R*,16*S*, 3′*S*,3″*S*)-6α-Acetoxy-19-[[3′-[(3″-acetoxybutyryl)oxy]butyryl]oxy]-4α,18;11,16;15,16-triepoxyneoclerodan-2α-ol: mp 40−55 °C; amorphous solid; $[\alpha]^{19}_D$ −12.2° (*c* 0.115, $CHCl_3$); IR (NaCl) ν_{max} 3460 (OH), 1740, 1250 (ester groups), 2980, 2880, 1450, 1370, 1190, 1100, 1060, 1030, 930, 900, 880, 840, 820 cm^{-1}; ^{1}H NMR (300 MHz), see Table 1; ^{13}C NMR (75.4 MHz), see Table 2; positive FABMS *m*/*z* (rel int) 625 $[MH]^+$ (3), 607 $[MH - H_2O]^+$ (12), 547 $[MH - H_2O - AcOH]^+$ (4), 375 (4), 315 (22), 113 (100), 69 (98), 43 (38); *anal.* C 61.66%, H 7.87%, calcd for $C_{32}H_{48}O_{12}$, C 61.51%, H 7.75%.

Scupontin D (4): (11*S*,13*S*,15*R* and *S*,16*R*,3′*S*,3″*S*)-6α-Acetoxy-19-[[3′-[(3″-acetoxybutyryl)oxy]butyryl]oxy]-4α,18;11,16-diepoxy-2α-hydroxyneoclerodane 15,16-hemiacetal: thick oil; mixture 1:1 of the 15*R* and 15*S* forms; ^{1}H NMR (300 MHz) δ 5.81 and 5.76 (0.5H each, both d, *J* = 5.4 Hz, H-16), 5.61 (0.5H,

br d, J = 4.3 Hz, H-15), 5.50 (0.5H, br d, J = 4.6 Hz, H-15), 5.32 (1H, br sext, H-3′), 5.21 (1H, br sext, H-3″), 4.80 (1H, d, J = 12.2 Hz, H_B-19), 4.62 (1H, dd, J = 11.6, 4.7 Hz, H-6β), 4.57 (0.5H, dd, J = 11.5, 4.1 Hz, H-11α in the 15*S* epimer), 4.38 (1H, d, J = 12.2 Hz, H_A-19), 3.96 (0.5H, dd, J = 11.5, 4.1 Hz, H-11α in the 15*R* epimer), 3.69 (1H, m, $W_{1/2}$ = 24 Hz, H-2β), 3.07 (0.5H, m, $W_{1/2}$ = 20 Hz, H-13β), 2.96 (1H, dd, J = 3.9, 2.3 Hz, H_B-18), 2.84 (0.5H, m, $W_{1/2}$=20 Hz, H-13β), 2.71−2.40 (4H, m, 2H-2′ and 2H-2″), 2.25 (1H, d, J = 3.9 Hz, H_A-18), 2.01 (3H, s, OAc), 1.93 (3H, s, OAc), 1.29 (3H, d, J = 6.1 Hz, Me-4′), 1.26 (3H, d, J = 6.2 Hz, Me-4″), 0.88 (3H, s, Me-20), 0.90 and 0.86 (1.5H each, both d, J = 6.6 Hz, Me-17).

Scupontin E (5): (11*S*,13*S*,16*S*,3′*S*,3″*S*,3‴*S*)-6α-Acetoxy-19-[[3′-[[3″-((3‴-hydroxybutyryl)oxy]butyryl]oxy]butyryl]oxy]-4α,18;11,16;15,16-triepoxyneoclerod-14-en-2α-ol: mp 50−60 °C, amorphous solid; $[\alpha]^{22}_D$ −5.0° (*c* 0.040, $CHCl_3$); IR (NaCl) ν_{max} 3460 (OH), 1620 (vinyl ether), 1735, 1250 (esters), 2980, 2960, 1450, 1370, 1190, 1100, 1060, 1030, 970 cm^{-1}; ^{1}H NMR (500 MHz), see Table 1; ^{13}C NMR (125.7 MHz), see Table 2 in which only the protonated carbons (measured from the HMQC spectrum) are reported; positive FABMS *m*/*z* (rel int) 667 $[MH]^+$ (8), 649 $[MH - H_2O]^+$ (5), 391 (7), 113 (68), 69 (100), 43 (80); *anal.* C 61.12%, H 7.38%, calcd for $C_{34}H_{50}O_{13}$, C 61.23%, H 7.56%.

Scupontin F (6): (11*S*,13*S*,15*R* and *S*, 16*R*,3′*S*, 3″*S*,3‴*S*)-6α-Acetoxy-19-[[3′-[[3″-[(3‴-hydroxybutyryl)oxy]butyryl]oxy]butyryl]oxy]-4α,18;11,16-diepoxy-2α-hydroxyneoclerodane 15,16-hemiacetal: thick oil; mixture (1:1) of the 15*R* and 15*S* forms; ^{1}H NMR (300 MHz) δ 5.83 and 5.79 (0.5H each, both d, J = 5.4 Hz, H-16), 5.63 (0.5H, br d, J = 4.0 Hz, H-15), 5.52 (0.5H, br d, J = 5.5 Hz, H-15), 5.31 (2H, m, $W_{1/2}$ = 24 Hz, H-3′ and H-3″), 4.83 and 4.80 (0.5H each, both d, J = 12.2, H_B-19), 4.64 (1H, dd, J = 11.2, 4.1 Hz, H-6β), 4.60 (0.5H, dd, J = 11.5, 4.1 Hz, H-11α in the 15*S* epimer), 4.42 and 4.39 (0.5H each, both d, J = 12.2 Hz, H_A-19), 4.21 (1H, br sext, H-3‴), 3.98 (0.5H, dd, J = 11.5, 4.1 Hz, H-11α in the 15*R* epimer), 3.70 (1H, m, $W_{1/2}$=20 Hz, H-2β), 3.10 and 2.85 (0.5H each, both m, H-13β), 2.99 (1H, dd, J = 3.9, 2.2 Hz, H_B-18), 2.70−2.40 (6H, m, 2H-2′, 2H-2″ and 2H-2‴), 2.28 (1H, d, J = 3.9 Hz, H_A-18), 1.94 (3H, s, OAc), 1.30 (3H, d, J = 6.2 Hz, Me-4′), 1.28 (3H, d, J = 6.1 Hz, Me-4″), 1.22 (3H, d, J = 6.3 Hz, Me-4‴), 0.90 (3H, s, Me-20), 0.87 (3H, d, J = 6.4 Hz, Me-17).

Scupontin G (7): (12*R*)-6α,7β-Bis(benzoyloxy)-1β,12-epoxy-8β,12α-dihydroxyneocleroda-4(18),13-dien-15,16-olide: mp 127−129 °C (EtOAc−petroleum ether); $[\alpha]^{22}_D$ −91.1° (*c* 0.836, $CHCl_3$); IR (KBr) ν_{max} 3460 (OH), 3110, 3070, 1605, 1590 (aromatic), 3080, 1640, 890 (exocyclic methylene), 1780 (α,β-unsaturated γ-lactone), 1745, 1730, 1280, 710 (OBz), 2940, 1450, 1320, 1110, 1100, 1070, 1030, 970, 760, cm^{-1}; UV (MeOH) λ_{max} nm (log ϵ) 227 (4.47), 273 (3.27); CD nm ($\Delta\epsilon$) 269 (0), 240 (−136), 231 (0), 226 (+62), 217 (0) (*c* 0.0342, MeOH); ^{1}H NMR (500 MHz, 0.017 M in $CDCl_3$), see Table 3; ^{13}C NMR (125.7 MHz), see Table 3; positive FABMS *m*/*z* (rel int) 589 $[MH]^+$ (5), 571 $[MH - H_2O]^+$ (4), 327 $[MH - H_2O - 2BzOH]^+$ (5), 207 (13), 105 $[Bz]^+$ (100), 77 (18), 43 (12); *anal.* C 69.41%, H 6.23%, calcd for $C_{34}H_{36}O_9$, C 69.36%, H 6.17%.

Preparation of (11*S*,13*S*,16*S*,3′*S*,3″*S*)-2α,6α-Diacetoxy-19-[[3′-[(3″-acetoxybutyryl)oxy]butyryl]-oxy]-4α,18;11,16;15,16-triepoxyneoclerod-14-ene (8) from Scupontin A (1). Treatment of **1** (40 mg) with Ac_2O−pyridine (1:1, 4 mL) at room temperature for 48 h yielded **8** [32 mg after chromatographic purification, Si gel, EtOAc−petroleum ether (1:1) as eluent]. Compound **8**: mp 45−55 °C; amorphous solid; $[\alpha]^{18}_D$ −39.9° (*c* 0.303, $CHCl_3$); IR (KBr) ν_{max} 3100, 1620 (vinyl ether), 1740 br, 1250 (esters), 2980, 2880, 1450, 1370, 1190, 1140, 1090, 1060, 1020, 1010, 950, 905, 870 cm^{-1}; ^{1}H NMR (300 MHz), see Table 1; ^{13}C NMR (75.4 MHz), see Table 2; positive FABMS *m*/*z* (rel int) 665 $[MH]^+$ (8), 605 $[MH - AcOH]^+$ (4), 579 (5), 313 (12), 203 (38), 129 (65), 69 (100), 55 (94), 43 (74), 41 (98); *anal.* C 61.70%, H 7.06%, calcd for $C_{34}H_{48}O_{13}$, C 61.42%, H 7.28%.

Preparation of (11*S*,13*S*,15*R* and *S*,16*R*,3′*S*,3″*S*)-2α,6α-Diacetoxy-19-[[3′-[(3″-acetoxybutyryl)oxy]-butyryl]oxy]-4α,18;11,16-diepoxyneoclerodane 15,16-(15-*O*-Acetyl)hemiacetal (9) from Scupontin D (4). Treatment of **4** (100 mg) with Ac_2O−pyridine (1:1, 10 mL) at room temperature for 48 h gave **9** (96 mg).

Compound 9: mixture (7:3) of the 15*S* (exo) and 15*R* (endo) forms, respectively;[16] ^{1}H NMR (300 MHz) δ 6.37 (0.7H, d, J = 4.8 Hz, H-15 in the 15*S* epimer), 6.28 (0.3H, d, J = 5.8 Hz, H-15 in the 15*R* epimer), 5.80 and 5.79 (0.3H and 0.7H, respectively, both d, J = 5.4 Hz, H-16), 5.37−5.19 (2H, m, H-3′ and H-3″), 4.85 (1H, d, J = 12.3 Hz, H_B-19), 4.65 (2.3H, m, H-2β, H-6β, and H-11α in the 15*R* epimer), 4.41 (1H, d, J = 12.3 Hz, H_A-19), 4.04 (0.7H, dd, J = 11.4, 4.4 Hz, H-11α in the 15*S* epimer), 2.98 (1H, dd, J = 4.0, 2.0 Hz, H_B-18), 2.77−2.40 (4H, m, 2H-2′ and 2H-2″), 2.29 (1H, d, J = 4.0 Hz, H_A-18), 2.03, 2.01, 2.00, and 1.95 (3H each, s, 4OAc), 1.30 (3H, d, J = 6.4 Hz, Me-4′), 1.28 (3H, d, J = 6.3 Hz, Me-4″), 0.97 and 0.95 (0.9H and 2.1H, respectively, both s, Me-20), 0.91 and 0.86 (0.9H and 2.1H, respectively, both d, J = 6.4 Hz, Me-17).

Preparation of (11*S*,13*S*,16*R*,3′*S*,3″*S*)-2α,6α-Diacetoxy-19-[[3′-[(3″-acetoxybutyryl)oxy]butyryl]-oxy]-4α,18;11,16-diepoxyneoclerodan-15,16-olide (10) from Compounds 8 and 9. To a solution of **8** (50 mg) in Me_2CO (10 mL) was added an excess of Jones' reagent[25] at 0 °C with stirring. After 30 min, the excess of Jones' reagent was destroyed by addition of EtOH, and then the reaction mixture was diluted with H_2O (30 mL). Extraction with $CHCl_3$ (4 × 10 mL) and work-up as usual gave a residue (48 mg) from which pure **10** (40 mg) was obtained after chromatography [Si gel, EtOAc−petroleum ether (1:1) as eluent]. Identical treatment of **9** (60 mg) also yielded **10** (32 mg).

Compound 10: mp 60−70 °C, amorphous solid; $[\alpha]^{19}_D$ −25.2° (*c* 0.424, $CHCl_3$); IR (KBr) ν_{max} 1790 (γ-lactone), 1740, 1250 (esters), 2980, 1450, 1370, 1180, 1100, 1060, 1020, 990, 970, 930, 880 cm^{-1}; ^{1}H NMR (300 MHz), see Table 1; ^{13}C NMR (75.4 MHz), see Table 2; positive FABMS *m*/*z* (rel int) 681 $[MH]^+$ (30), 635 (18), 484 (18), 311 (25), 237 (20), 157 (38), 69 (100); *anal.* C 60.09%, H 7.14%, calcd for $C_{34}H_{48}O_{14}$, C 59.97%, H 7.11%.

Preparation of (11*S*,13*S*,15*R* and *S*,16*R*,3′*S*, 3″*S*,3‴*S*)-2α,6α-Diacetoxy-19-[[3′-[[3″-[(3‴-acetoxybutyryl)oxy]butyryl]oxy]butyryloxy-4α,18;11,16-diepoxyneoclerodan 15,16-(15-*O*-Acetyl)hemiacetal (11) from Scupontin F (6). Treatment of **6** (18 mg) with Ac_2O−pyridine (1:1, 4 mL) at room temperature for 48 h gave **11** [18 mg, after chromatographic purification, Si gel, EtOAc−petroleum ether (1:1) as

eluent]. Compound **11**: mixture (7:3) of the 15*S* (exo) and 15*R* (endo) forms, respectively;[16] ^{1}H NMR (300 MHz) δ 6.36 (0.7H, d, J = 4.7 Hz, H-15 in the 15*S* epimer), 6.27 (0.3H, d, J = 5.7 Hz, H-15 in the 15*R* epimer), 5.80 and 5.79 (0.3H and 0.7H, respectively, both d, J = 5.4 Hz, H-16), 5.29 (3H, m, H-3′, H-3″, and H-3‴), 4.84 (1H, d, J = 12.3 Hz, H_B-19), 4.64 (2.3H, m, H-2β, H-6β, and H-11α in the 15*R* epimer), 4.42 (1H, d, J = 12.3 Hz, H_A-19), 4.02 (0.7H, dd, J = 11.5, 4.2 Hz, H-11α in the 15*S* epimer), 2.98 (1H, dd, J = 3.9, 2.1 Hz, H_B-18), 2.70−2.40 (6H, m, 2H-2′, 2H-2″, and 2H-2‴), 2.28 (1H, d, J = 3.9 Hz, H_A-18), 2.02, 2.01, 2.00, and 1.95 (3H each, s, 4OAc), 1.30 (3H, d, J = 6.9 Hz, Me-4′), 1.27 (3H, d, J = 6.2 Hz, Me-4″), 1.26 (3H, d, J = 6.5 Hz, Me-4‴), 0.97 and 0.95 (0.9H and 2.1H, respectively, both s, Me-20), 0.91 and 0.86 (0.9H and 2.1H, respectively, both d, J = 6.4 Hz, Me-17).

Preparation of (11*S*,13*S*,16*R*,3′*S*,3″*S*,3‴*S*)-2α,6α-Diacetoxy-19-[[3′-[[3″-[(3‴-acetoxybutyryl)oxy]butyryl]oxy]butyryl]oxy]-4α,18;11,16-diepoxyneoclerodan-15,16-olide (12) from Compound 11 and Scupontin E (5). Treatment of **11** (15 mg) with Jones' reagent,[25] as previously described for obtaining **10**, yielded **12** [8 mg, after chromatographic purification, Si gel, EtOAc−petroleum ether (1:1) as eluent].

Scupontin E (**5**, 3 mg) was treated with Ac_2O−pyridine, and the peracetate, without characterization, was treated with Jones' reagent[25] giving 1 mg of a compound identical (^{1}H NMR and TLC) with **12**.

Compound **12**: mp 50−60 °C, amorphous solid; $[\alpha]^{22}_D$ −15.5° (*c* 0.071, $CHCl_3$); IR (KBr) ν_{max} 1790 (γ-lactone), 1735, 1250 (esters), 2980, 1450, 1370, 1190, 1100, 1060, 1025, 990, 970, 930 cm^{-1}; ^{1}H NMR (500 MHz), see Table 1; ^{13}C NMR (125.7 MHz), see Table 2; positive FABMS *m*/*z* (rel int) 767 $[MH]^+$ (10), 580 (8), 447 (7), 233 (17), 141 (22), 115 (65), 69 (100); *anal.* C 59.26%, H 7.21%, calcd for $C_{38}H_{54}O_{16}$, C 59.50%, H 7.10%.

(*S*)-(+)-1,3-Butanediol from Scupontin A (1). To a solution of **1** (100 mg) in anhydrous THF (20 mL) was added a solution of $LiAlH_4$ (400 mg) in THF (50 mL). The mixture was refluxed during 4 h, cooled at −20 °C, and a saturated aqueous solution of Na_2SO_4 was added dropwise to the reaction mixture. The white precipitate was filtered through a pad of Celite, and the solids washed with abundant CH_2Cl_2−MeOH mixture (3:1). The residue (75 mg) obtained by evaporation of the solvents was subjected to column chromatography (Si gel, EtOAc as eluent) giving 21 mg of the less polar constituent (TLC) of the reduction mixture. This compound, a colorless thick oil, showed IR and ^{1}H-NMR spectra identical with those reported[12] for (±)-1,3-butanediol, and it had $[\alpha]^{26}_D$ +29.2° (*c* 0.963, $CHCl_3$) [lit.[13] for (*S*)-(+)-1,3-butanediol: $[\alpha]^{20}_D$ +30 ± 2°]. Comparison with an authentic sample[13] of (*S*)-(+)-1,3-butanediol by GC (HRGC MEGA 2 Series Fisons instrument) using a chiral capillary column (SE-54/heptakis-2,3-di-*O*-pentyl-β-cyclodextrin; length 25 m, diameter 0.25 mm; temperature: column 70 °C, injector 250 °C) confirmed the identity.

(*S*)-(+)-1,3-Butanediol from Scupontins B−F (2−6). A sample of each compound (**2**, 2 mg; **3**, 20 mg; **4**, 50 mg; **5**, 2 mg; and **6**, 8 mg) was treated with $LiAlH_4$ as described for **1**. The reduction mixtures were analyzed by GC as above and enantiomerically pure (*S*)-(+)-1,3-butanediol was identified in all the samples.

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References and Notes

(1) Although the hydrocarbon skeleton of these diterpenoids is biogenetically derived from an *ent*-labdane, and they should be named *ent*-clerodanes, we prefer to use the term neoclerodane proposed by Rogers et al. (Rogers, D.; Unal, G. G.; Williams, D. J.; Ley, S. V.; Sim, G. A.; Joshi, B. S.; Ravindranath, K. R. *J. Chem. Soc., Chem. Commun.* **1979**, 97−99) because it is the nomenclature used in the majority of the articles published on this subject since 1979.
(2) Anderson, J. C.; Blaney, W. M.; Cole, M. D.; Fellows, L. E.; Ley, S. V.; Sheppard, R. N.; Simmonds, M. S. J. *Tetrahedron Lett.* **1989**, *30*, 4737−4740.
(3) Cole, M. D.; Anderson, J. C.; Blaney, W. M.; Fellows, L. E.; Ley, S. V.; Sheppard, R. N.; Simmonds, M. S. J. *Phytochemistry* **1990**, *29*, 1793−1796.
(4) Blaney, W. M.; Cuñat, A. C.; Ley, S. V.; Montgomery, F. J.; Simmonds, M. S. J. *Tetrahedron Lett.* **1994**, *35*, 4861−4864.
(5) Cuñat, A. C.; Díez-Martín, D.; Ley, S. V.; Montgomery, F. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 611−620.
(6) Rodríguez, B.; de la Torre, M. C.; Rodríguez, B.; Bruno, M.; Piozzi, F.; Savona, G.; Simmonds, M. S. J.; Blaney, W. M.; Perales, A. *Phytochemistry* **1993**, *33*, 309−315.
(7) Cole, M. D.; Bridge, P. D.; Dellar, J. E.; Fellows, L. E.; Cornish, M. C.; Anderson, J. C. *Phytochemistry* **1991**, *30*, 1125−1127.
(8) de la Torre, M. C.; Rodríguez, B.; Bruno, M.; Piozzi, F.; Savona, G.; Vassallo, N.; Servettaz, O. *Phytochemistry* **1995**, *38*, 181−187.
(9) Rodríguez, B.; de la Torre, M. C.; Rodríguez, B.; Gómez-Serranillos, P. *Phytochemistry* **1996**, *41*, 247−253.
(10) Bruno, M.; Piozzi, F.; Rodríguez, B.; de la Torre, M. C.; Vassallo, N.; Servettaz, O. *Phytochemistry* **1996**, *42*, 1059−1064.
(11) Esquivel, B.; Flores, E.; Hernández-Ortega, S.; Toscano, R. A. *Phytochemistry* **1995**, *38*, 175−179.
(12) For the IR and ^{1}H NMR spectral data of (±)-1,3-butanediol see *The Aldrich Library of Infrared Spectra;* Pouchert, C. J. Ed., Aldrich Chemical: Milwaukee, WI, 1981; 71G; and *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra*; Pouchert, C. J.; Behnke, J., Eds., Aldrich Chemical: Milwaukee, WI, 1993; Vol. 1, 196A and B.
(13) *Fluka Catalogue*; Fluka Chemie AG: Buchs, Switzerland, 1995; p 283; compound no. 18 938.
(14) Bozov, P. I.; Malakov, P. Y.; Papanov, G. Y.; de la Torre, M. C.; Rodríguez, B.; Perales, A. *Phytochemistry* **1993**, *34*, 453−456.
(15) Fieser, L. F.; Fieser, M. *Steroids*; Reinhold Publishing: New York, 1959; pp 177−180, and references therein.
(16) Acetylation of a 1:1 mixture of the C-15 epimers of **4** and **6** gave a 7:3 mixture of the C-15 epimers of **9** and **11**, respectively, in which the 15-exo form (15*S* in **9** and **11**) was the major constituent. This behavior may be attributed to the easy esterification of the more sterically accessible 15*R*-exo form in **4** and **6**, and to the existence of an equilibrium between the opened and closed forms of the 15,16-hemiacetal.
(17) Barton, D. H. R.; Cheung, H. T.; Cross, A. D.; Jackman, L. M.; Martin-Smith, M. *J. Chem. Soc.* **1961**, 5061−5073.
(18) de la Torre, M. C.; Rodríguez, B.; Bruno, M.; Malakov, P. Y.; Papanov, G. Y.; Piozzi, F.; Savona, G. *Phytochemistry* **1993**, *34*, 1589−1594.
(19) Chen, T.-B.; Galinis, D. L.; Wiemer, D. F. *J. Org. Chem.* **1992**, *57*, 862−866.
(20) Huneck, S.; Asakawa, Y.; Taira, Z.; Cameron, A. F.; Connolly, J. D.; Rycroft, D. S. *Tetrahedron Lett.* **1983**, *24*, 115−116.
(21) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy. Exciton Coupling in Organic Stereochemistry;* University Science Books: Mill Valley, CA, 1983.
(22) Merritt, A. T.; Ley, S. V. *Nat. Prod. Rep.* **1992**, *9*, 243−287.
(23) Rodríguez-Hahn, L.; Esquivel, B.; Cárdenas, J. *Prog. Chem. Org. Nat. Prod.* **1994**, *63*, 107−196.
(24) Mori, K.; Miyake, M. *Tetrahedron* **1987**, *43*, 2229−2239.
(25) Kleinfelter, D. C.; Schleyer, P. R. *Org. Synth.* **1962**, *42*, 79−82.

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