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THE ABSOLUTE STEREOCHEMISTRY OF SENEXDIOLIC ACID AT C-22

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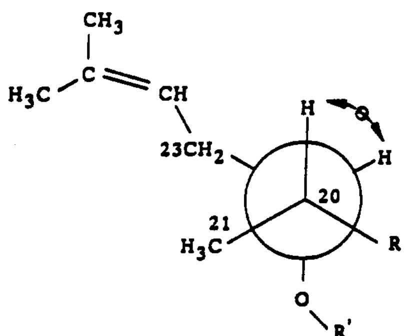
ABSTRACT.—The absolute stereochemistry of senexdiolic acid, a triterpene isolated from *Fomes senex*, *Phellinus torulosus*, and *Phellinus pomaceus*, has been determined as *S* at C-22 by double resonance experiments and chemical correlation with epi-inotodiol [**6**].

In earlier papers on *Phellinus pomaceus* (Pers.: S.F. Gray) Mayre (Hymenochaetaceae) (1,2) we reported the isolation of the sterols ergosta-7,22-dien-3-one and ergosta-7,22-dien-3β-ol as well as the pentacyclic triterpenes friedelin and taraxerol, and β-boswellic, ursolic, phellinic, and javeroic acids. A further investigation of this fungus, this time gathered in the woods of Los Tilos (La Palma), and *Phellinus torulosus* from El Bailadero (Tenerife) afforded the following substances: javeroic acid [**1**], pomacerone [**2**], and senexdiolic acid [**3**].

Senexdiolic acid [**3**], $C_{30}H_{48}O_4$, is a crystalline compound (mp 272–275°) which has been isolated from the fungus *Fomes senex* by Indian chemists (3) who determined its gross structure principally by means of ^{1}H nmr and chemical transformations. Nonetheless, the configuration at C-22 could not be elucidated, and as yet no derivatives suitable for X-ray analysis have been obtained. This paper reports the stereochemistry assigned to C-22 on the basis of double resonance experiments and correlation with epi-inotodiol [**6**].

Compound **3** was methylated and then acetylated to give **4**, $[M]^+$ 486 and **5**, $[M]^+$ 570, respectively. The published (3) ^{1}H-nmr data of **4**, **5** and **9** taken on a 60 MHz spectrometer are far from complete, so a full set of ^{1}H nmr findings run at 200 MHz are given in Table 1 together with first-time data for **3**. Table 2 summarizes the new ^{13}C-nmr data of **9**, **2**, **10**, **4**, and **5**.

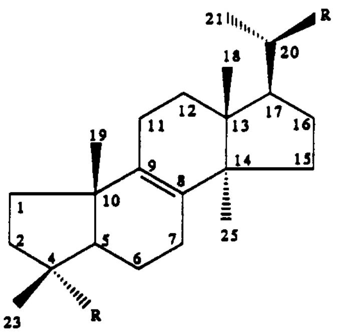
By means of decoupling experiments on the methyl ester **4** the proton H-24 could be correlated with H-26, H-27, and H-23 which in its turn was coupled with H-22. The coupling constant $J_{20,22}$ proved to be 3.1 Hz which, in accordance with the corrected Karplus curve (4), is consistent with the stereochemistry shown in Figure 1. Senexdiolic acid was thus identified as 3β, 22β-dihydroxylanosta-8,24-dien-29-oic acid. If pomacerone [**2**] was reduced with $LiAlH_4$ (dry THF, 6 h, reflux), it yielded a diol **10** with $J_{20\text{-}22}$= 6.5 Hz in line with the stereochemical model mentioned above, the Cram rule, and corrected Karplus curve (presumably



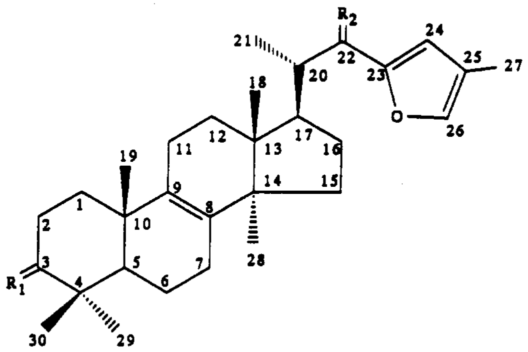
R=lanostane

	θ	$J_{20\text{-}22}$
R′=H	63°	3.1 Hz

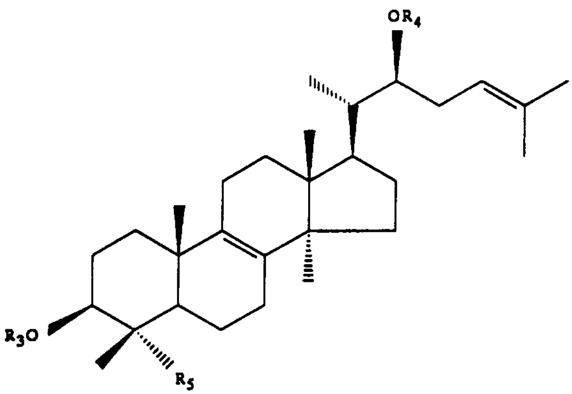
FIGURE 1



1 R=CO_2H
9 R=CO_2Me



2 R_1=R_2=O
10 R_1= OH, H R_2= OH, H



3 R_3=R_4=H, R_5=CO_2H
4 R_3=R_4=H, R_5=CO_2Me
5 R_3=R_4=OAc, R_5=CO_2Me
6 R_3=R_4=H, R_5=Me
7 R_3=R_4=H, R_5=CH_2OH
8 R_3=R_4=H, R_5=CH_2OTs

conforming with inverse stereochemistry at C-22) (Figure 2) (5).

Senexdiolic acid [**3**] was converted into methyl senexdiolate [**4**] and this was reduced with $LiAlH_4$ to yield **7** which, when treated with tosyl chloride, gave the monotosylate **8**. Treatment of **8** with $LiAlH_4$ afforded epi-inotodiol [**6**] with established 22*S* stereochemistry (6,7) and traces of **7**, a sequence which connected **3** and **6** and established the absolute stereochemistry of **3** at C-22 as *S*.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mp's were taken on a Kofler block and uncorrected. Ir spectra were recorded on a Perkin-Elmer 257 spectrometer. ^1H- and ^{13}C-nmr spectra were run on a Bruker WP 200 SY (200 MHz for ^1H nmr and 22.6 MHz for ^{13}C nmr) in $CDCl_3$ or a solution of $CDCl_3$-CD_3OD (1:1). Mass spectra (eims) were obtained on a VG Micromass ZAB-AF with a direct inlet system at 70 eV.

PLANT MATERIAL.—*P. pomaceus* (2.5 kg) and *P. torulosus* (4.5 kg) were dried, ground, extracted, and worked up as described elsewhere (1,2). Plant specimens were deposited in the herbarium of the Faculty of Pharmacy, La Laguna University (voucher numbers TFC Mic 5068 and 6035). Cc on Si gel eluted javeroic acid (220 and 250 mg), pomacerone (135 and 175 mg), and senexdiolic acid (98 and 210 mg) from both extracts.

TABLE 1. ^{1}H-nmr Spectroscopic Data for Compounds **9**, **3**, **4**, and **5** in $CDCl_3$.[a]

Proton	Compound			
	9	**3**[b]	**4**	**5**
H-3	—	3.99 dd (10.3, 5.5)	3.99 dd (11.0, 4.3)	5.17 dd (11.5, 5.0)
Me-18	0.91 s	0.65 s	0.69 s	0.67 s
Me-19	0.94 s	0.94 s	0.98 s	1.02 s
Me-21	1.16 d (6.8)	0.86 d (6.3)	0.92 d (6.3)	0.94 d (6.6)
H-22	—	3.5 dt (6.1, 3.0)	3.64 dt (6.6, 3.1)	4.90 dt (6.5, 3.0)
Me-23	1.20 s	—	—	—
H-24		5.16 t (6.9)	5.16 t (6.3)	5.08 t (7.3)
Me-25	0.71 s	—	—	—
Me-26	—	1.55 s	1.64 s	1.61 s
Me-27	—	1.63 s	1.73 s	1.68 s
Me-28	—	0.80 s	0.86 s	0.88 s
Me-30	—	1.05 s	1.15 s	1.22 s
COOMe	3.63 s	—	3.70 s	3.66 s
COO Me	3.64 s	—	—	—
OAc	—	—	—	1.99 s
OAc	—	—	—	2.02 s

[a]Values in parentheses are coupling constants.
[b]These data were determined in $CDCl_3$-CD_3OD (1:1).

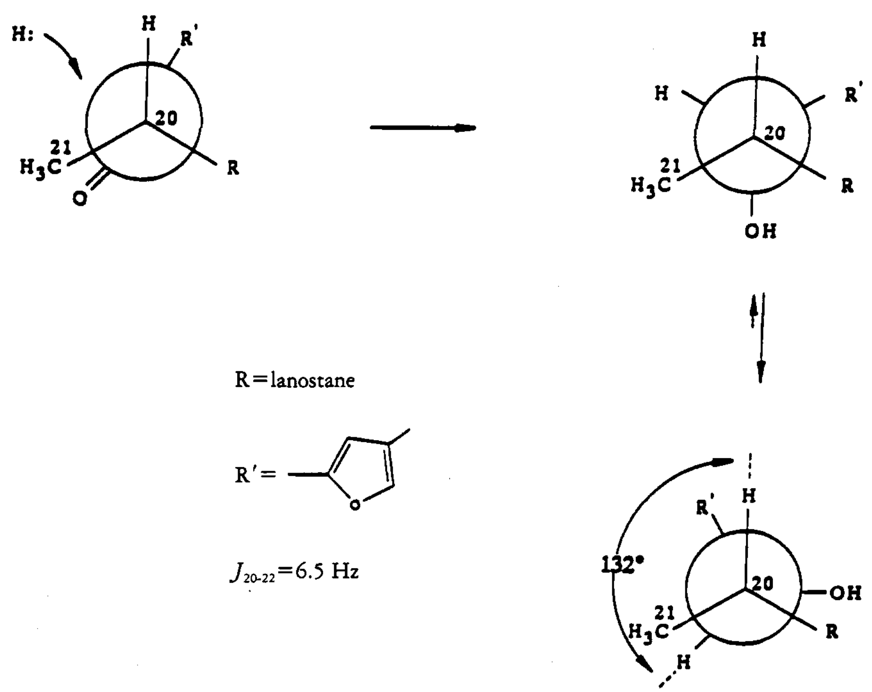


FIGURE 2

TABLE 2. ^{13}C Spectral Data for Compounds **9**, **2**, **10**, **4**, and **5** in $CDCl_3$.

Carbon	Compound				
	9	**2**	**10**	**4**	**5**
C-1	35.91	35.92	35.55	35.11	34.86
C-2	26.71	30.85	27.74	27.18	25.85
C-3	—	217.65	78.94	76.33	76.88[a]
C-4	45.42	47.27	38.86	44.95	36.34
C-5	47.43	46.93	46.90	46.41	46.46
C-6	18.55	19.34	18.23	20.74	20.59
C-7	30.40	27.15	27.79	29.09	26.53
C-8	134.04	133.11	134.16	134.20	133.79
C-9	134.84	135.14	134.55	134.55	134.58
C-10	45.02	36.85	37.00	36.55	34.86
C-11	22.36	20.95	20.94	20.96	20.92
C-12	25.86	26.18	26.50	25.74	23.71
C-13	48.32	44.34	44.80	49.93	44.83
C-14	49.12	49.41	49.45	53.95	49.13
C-15	30.56	31.01	30.81	29.95	26.90
C-16	36.86	34.70	30.88	30.85	30.84
C-17	52.69	51.06	50.35	47.20	47.22
C-18	17.16	17.24	15.69	12.57	13.20
C-19	19.10	18.63	19.12	19.35	19.33
C-20	42.94	44.19	42.83	41.65	39.80
C-21	21.61	21.18	15.77	15.65	15.61
C-22	—	193.55	70.81	73.33	76.99[a]
C-23	—	152.37	155.25	27.07	21.10
C-24	—	119.61	109.52	121.30	120.64
C-25	—	122.53	120.24	134.00	133.38
C-26	—	143.65	138.17	17.90	17.82
C-27	—	9.46	9.77	24.25	24.21
C-28	—	24.26	24.36	25.94	25.75
C-29	—	26.27	27.93	178.00	176.76
C-30	—	16.27	16.27	10.66	11.70
OCOMe	—	—	—	—	170.72
	—	—	—	—	170.11
OCO*Me*	—	—	—	—	21.40[b]
	—	—	—	—	21.10[b]
COOMe	179.82	—	—	—	—
	177.48	—	—	—	—
COO*Me*	51.84	—	—	52.07	52.19
	51.27	—	—	—	—

[a,b]Assignments may be interchanged.

Methyl senexdiolate [**4**].—Excess ethereal CH_2N_2 was added to **3** (35 mg) in MeOH at room temperature for 30 min, and after evaporation of the solvent, the ester **4** was obtained quantitatively in the form of a colorless solid: mp 203–205°; $[\alpha]_D$ +67.6° (c=0.3, $CHCl_3$); ^1H nmr see Table 1; ^{13}C nmr see Table 2; eims m/z (rel. int.) $[M]^+$ 486 (13), $[M-C_8H_{16}O]^+$ 358 (12), $[M-C_8H_{16}O-H_2O]^+$ 340 (11).

Acetylmethyl senexdiolate [**5**].—Methyl senexdiolate [**4**] (5 mg) was acetylated with Ac_2O/pyridine (0.2 ml of each) for 24 h at room temperature to yield the diacetate **5** (5.2 mg): ^1H nmr see Table 1; ^{13}C nmr see Table 2; eims m/z (rel. int.) $[M]^+$ 570 (11), $[M-CO_2Me]^+$ 511 (15), $[M-CO_2Me-MeCO_2H]^+$ 451 (7), $[M-CO_2Me-2\times MeCO_2H]^+$ 391 (6).

Lanosta-8,23-diene-3,22,29-triol [**7**].—Methyl senexdiolate [**4**] (30 mg) in dry THF (10 ml) was refluxed with $LiAlH_4$ (3 mg) for 3 h. Filtration, drying with Na_2SO_4, and crystallization from MeOH/$CHCl_3$ yielded **7** (20 mg), as needles: mp 206–208°; $[\alpha]_D$ +62.5° [c=0.2, $CHCl_3$-MeOH (1:1)]; ^1H nmr (200 MHz, $CDCl_3$) δ 5.18 (1H, t, J,=6.4 Hz, H-24), 3.78–3.62 (2H, m, H-3, H-22), 3.76 (1H, d, J=10.2 Hz, CH_2OH-29), 3.45

(1H, d, J=10.2 Hz, CH_2OH-29), 1.75 (3H, s, Me-27), 1.66 (3H, s, Me-26), 1.03 (3H, s, Me-28), 0.95 (3H, d, J=6.5 Hz, Me-21), 0.94 (3H, s, Me-30), 0.87 (3H, s, Me-19), 0.72 (3H, s, Me-18); eims *m/z* (rel. int.) $[M]^+$ 458 (10), $[M-Me]^+$ 443 (12), $[M-Me-H_2O]^+$ 425 (12), $[M-Me-H_2O-MeOH]^+$ 393 (2).

TOSYLATION OF COMPOUND **7**.—Compound **7** (20 mg) in dry pyridine (4 ml) was treated with tosyl chloride (15 mg) and left at room temperature for 2 h. The resulting product was extracted with Et_2O, washed with dilute HCl, Na_2CO_3, and H_2O, dried on Na_2SO_4, and subjected twice to preparative tlc in hexane-EtOAc (7:3) to yield the monotosylate **8** (11 mg): ^1H nmr (200 MHz, $CDCl_3$) δ 7.80 (2H, d, J=8.2 Hz, -OTs), 7.30 (2H, d, J=8.2 Hz, -OTs), 5.18 (1H, t, J=6.30 Hz, H-24), 3.99 (1H, d, J=9.7 Hz, CH_2OTs-29), 3.75 (1H, d, J=9.7 Hz, CH_2OTs-29), 3.73–3.62 (2H, m, H-3, H-22), 2.48 (3H, s, Me-Ar), 1.75 (3H, s, Me-27), 1.66 (3H, s, Me-26), 0.97 (3H, s, Me-28), 0.94 (3H, d, J=6.5 Hz, Me-21), 0.88 (3H, s, Me-30), 0.70 (6H, s, Me-18, Me-19), eims *m/z* (rel. int.) $[M-TsOH]^+$ 440 (4), $[M-TsOH-H_2O]^+$ 422 (18), $[M-TsOH-H_2O-Me]^+$ 407 (7).

The monotosylate **8** (10 mg) in THF (5 ml) was refluxed with $LiAlH_4$ (2.5 mg) for 2 h. The resulting product (7 mg) was purified by preparative tlc in hexane-EtOAc (8:2) three times and crystallized from $CHCl_3$/MeOH as needles (5 mg), mp 130–132°, [α]D 42° (c=0.25 in $CHCl_3$): its mp, [α]D, ^1H-nmr, and eims data proved identical to those of epi-inotodiol [**6**].

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