Cyclosadol, Isocyclosadol, and Other Related Triterpene Alcohols Obtained from 24-Methylenecycloartanol by Acid-catalyzed Isomerization

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Synopsis. The acid-catalyzed isomerization of 24-methylenecycloartanol with sulfuric acid afforded cyclosadol (23*E*-Δ^{23}), isocyclosadol (23*Z*-Δ^{23}), and other isomers, including lanostane- and cucurbitane-type isomers with (23*E*)- and (23*Z*)-Δ^{23}- and Δ^{24}-unsaturated side chains. The phytochemical significance of the isomers is discussed.

Our recent study of the acid-catalyzed isomerization of cycloartane (9β,19-cyclolanostane) triterpene alcohols has shown that this isomerization is quite useful in obtaining several lanostane- and cucurbitane [19(10→9β)*abeo*-lanostane]-type isomers.[1] In this study we undertook the isomerization of 24-methylenecycloartanol (24-methylene-9β,19-cyclo-5α-lanostan-3β-ol, **1a**), a cycloartane triterpene alcohol widely distributed in plants,[2,3] in order to prepare several isomers of **1a**. Since **1a** is considered to be the key intermediate of sterol biosynthesis in some plants,[2] the isomerization products which have a structural similarity to **1a** are also considered to be especially worthwhile from the points of view of phytochemistry and sterol biogenesis.

The isomerization of **1a** with sulfuric acid was performed in isopropyl alcohol at 80 °C for 12 h.[1] The compositions of the isomerized products were, after acetylation, carefully determined by GLC to be as follows: Cyclosadol[4-6] [(23*E*)-24-methyl-9β,19-cyclo-5α-lanost-23-en-3β-ol, **1b**, 24%], isocyclosadol [(23*Z*)-24-methyl-9β,19-cyclo-5α-lanost-23-en-3β-ol, **1c**, 7%], cyclobranol[7] (24-methyl-9β,19-cyclo-5α-lanost-24-en-3β-ol, **1d**, 30%), (23*E*)- (**2b**, 2%) and (23*Z*)-24-methyl-5α-lanosta-8,23-dien-3β-ol (**2c**, 1%), 24-methyl-5α-lanosta-8,24-dien-3β-ol (**2d**, 3%), (23*E*)- (**3b**, 12%) and (23*Z*)-24-methyl-5α-lanosta-9(11),23-dien-3β-ol (**3c**, 3%), 24-methyl-5α-lanosta-9(11),24-dien-3β-ol (**3d**, 14%), (23*E*)-24-methyl-10α-cucurbita-5,23-dien-3β-ol (**4b**, 0.5%), 24-methyl-10α-cucurbita-5,24-dien-3β-ol (**4d**, 0.5%), (23*E*)-24-methylcucurbita-5(10),23-dien-3β-ol (**5b**, 2%), and 24-methylcucurbita-5(10),24-dien-3β-ol (**5d**, 1%).

The carbon skeletons of **1**—**5** were established by comparing their ^{1}H NMR spectra with those of **1a** and the relevant compounds described previously.[1] The double bond of the side chains **b** and **c** was found to be located at C-23 by the observation of a mass-fragmentation ion at *m/z* 325 ($M^+-C_7H_{13}-HOAc$) for the acetyl derivatives.[5,6] The configurations of 23*E* (**b**) and 23*Z* (**c**) were established on the basis of the ^{1}H NMR spectra as compared with those of two model olefins, (2*E*)- (**6**) and (2*Z*)-3,4-dimethyl-2-pentene (**7**).[5] The acetyl derivatives with the side chain **d** were established to have a C-24(25) double bond by the ^{1}H NMR, which showed three overlapping olefinic methyl singlets due to the 26-H$_3$, 27-H$_3$, and 28-H$_3$ protons.[7]

Thirteen isomers were obtained by the acid-catalyzed isomerization of **1a**. Among them, two cycloartane isomers, a (23*E*)-Δ^{23}-isomer (**1b**) in *Zea mays*[4-6] and Δ^{24}-isomer (**1d**), have been detected as natural products in several seed-bearing plants,[3] and their possible intermediacy in sterol biosynthesis has been suggested.[2,6] Although the occurrence of the other eleven isomers has not yet been reported, these isomers are also considered to be of significance from the phytochemical and sterol biogenetic points of view. In particular, taking into account the fact that the (23*E*)- and (23*Z*)-isomers of 24-ethylcholesta-5,23-dien-3β-ol both occur as natural products,[8] the occurrence of (23*Z*)-Δ^{23}-compounds such as **1c** can be expected in seed-bearing plants, especially in *Z. mays*. On the other hand, since some 24-methylenated lanostenes, such as **2a** and **3a**, have been detected in some plants,[3] the natural occurrence of several of the lanostane-type isomers prepared in this study can be expected. Some Cucurbitaceae plants have recently been shown to contain 10α-cucurbita-5,24-dien-3β-ol;[9] hence, the occurrence of its higher homologs, such as **4b** and **4d**, is highly probable in these plants.

Experimental

The melting points are uncorrected. The argentic TLC (silica gel-$AgNO_3$, 4:1) was developed 4 times with

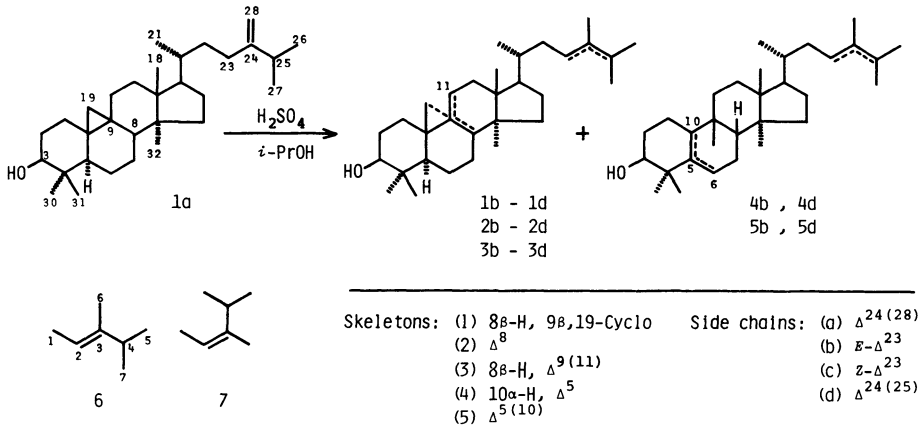

Table 1. Melting points, chromatographic data, and relative intensities (in percent) of selected mass-spectral fragments of the acetates of some new triterpene alcohols

Acetate	Mp θ_m/°C	R_c TLC	RRT HPLC	RRT GLC	m/z 482	467	439	422	407	398	379	355	353	339	325	300	297	295	288	273
1c	131—133	0.85	0.95	2.04	23	17	—	100	70	—	40	4	23	—	55	34	13	8	—	—
2b	112—114	0.86	0.82	1.77	36	100	—	2	73	—	7	7	—	—	10	—	5	5	—	—
2c	—	0.86	0.80	1.72	25	100	—	5	67	—	4	5	—	—	10	—	4	5	—	—
2d	153—155	1.01	0.89	2.12	46	100	—	4	77	4	2	2	—	2	—	—	2	2	—	—
3b	149—151	0.40	0.85	2.02	15	44	27	5	39	—	5	100	—	—	29	—	12	22	—	—
3c	—	0.40	0.83	1.95	17	59	21	2	64	—	6	100	—	—	34	—	8	19	—	—
3d	170—172	0.42	0.92	2.43	33	76	6	12	100	63	6	55	—	8	—	—	10	16	—	—
4b	128—130	0.58	0.63	1.59	7	9	—	31	22	—	—	—	—	—	14	—	9	5	100	64
4d	179—181	0.78	0.68	1.94	3	3	—	15	12	8	—	—	—	3	—	—	3	2	100	56
5b	163—165	0.82	0.62	1.40	12	33	—	100	83	—	8	—	—	—	42	8	8	2	—	—
5d	200—202	1.02	0.67	1.74	15	34	—	100	83	—	10	—	—	15	—	5	10	5	—	—

Table 2. ^{1}H NMR data[a] of the acetates of some new triterpene alcohols

Acetate	18-H_3[b]	19-H_3[b,c]	30-H_3[b]	31-H_3[b]	32-H_3[b]	21-H_3[d,e]	26-H_3/27-H_3[d]	28-H[b]	23-H[f]	25-H[g]	Others
1c	0.96	0.34(*d*, 4.4) 0.57(*d*, 3.9)	0.85	0.89	0.89	0.85(5.1)	0.95(6.8)	1.61	5.04(6.8)	2.80(6.8)	—
2b	0.69	1.00	0.88	0.88	0.88	0.84(5.6)	0.99(6.8)	1.55	5.16(6.0)	2.18(6.8)	—
2c	0.69	0.99	0.88	0.88	0.88	0.84(5.1)	0.95(6.8)	1.61	5.03(6.8)	2.80(7.1)	—
2d	0.69	1.00	0.88	0.88	0.88	0.92(4.4)	1.63(*s*)	1.63	—	—	—
3b	0.65	1.07	0.87	0.89	0.74	0.84(5.6)	0.99(6.8)	1.55	5.16(6.0)	2.17(6.8)	5.20(*m*, 11-H)
3c	0.65	1.06	0.87	0.89	0.74	0.84(5.1)	0.95(6.8)	1.60	5.03(6.8)	2.80(7.1)	5.20(*m*, 11-H)
3d	0.65	1.07	0.87	0.89	0.74	0.92(5.8)	1.63(*s*)	1.63	—	—	5.20(*m*, 11-H)
4b	0.81	0.91	1.04	1.04	0.85	0.84(5.6)	0.98(6.8)	1.56	5.16(6.0)	2.19(6.8)	5.50(*d*, 5.5, 6-H)
4d	0.81	0.91	1.04	1.04	0.85	0.92(4.4)	1.62(*s*)	1.62	—	—	5.50(*d*, 5.5, 6-H)
5b	0.79	1.00	0.96[h]	0.93[h]	0.84	0.82(4.9)	0.98(6.3)	1.55	5.14(6.8)	2.17(6.4)	—
5d	0.79	1.00	0.96[i]	0.93[i]	0.84	0.92(4.4)	1.62(*s*)	1.62	—	—	—

a) Given as δ values. Figures in parentheses denote J values in Hz. b) Singlet unless otherwise specified. c) Cyclopropyl methylene signal as for **1c**. d) Doublet if not otherwise specified. e) Assigned with the aid of the lanthanoid-induced-shift techniques.[11] f) Triplet. g) Septet. h) and i) The assignment in each row may be inverted, although that given here is preferred.

CCl_4-CH_2Cl_2 (5:1). The HPLC was carried out on a Partisil 5 ODS-2 column (25 cm×10 mm i.d.) using an UV detector and monitoring at 212 nm (mobile phase, MeOH-H_2O, 98:2). The GLC was performed with a 30 m×0.3 mm i.d. SCOT OV-17 glass capillary column at 260 °C. The R_c-values (relative mobilities) in the argentic TLC and the RRTs (relative retention times) in the HPLC and GLC were expressed relative to cholesteryl acetate (1.00). The MS spectra (70 ev) were taken by means of a probe injection. The ^{1}H NMR spectra (100 MHz) were obtained in a $CDCl_3$ solution, with Me_4Si as the internal standard. The 24-methylenecycloartanol (**1a**)[10] was kindly donated by the Riken Vitamin Co. (Tokyo). The isomerization of **1a** (500 mg) was carried out with conc H_2SO_4 (4 cm^3) in isopropyl alcohol (40 cm^3) while the mixture was being stirred at 80 °C for 12 h. The separation of the isomerization products was performed by the same way as has been described in the previous paper,[1] but the eventual isolation of each product was achieved by HPLC in this study. All of the other techniques used in this study[1] and the full ^{1}H NMR data[5] of **6** (4-H, *septet*, δ= 2.22, J=6.9 Hz; 6-H_3, *s*, δ=1.56) and **7** (4-H, *septet*, δ=2.83, J=6.9 Hz; 6-H_3, *s*, δ=1.59) have been described previously.

The High-resolution MS Data of New Triterpene Alcohols. The molecular ions (M^+) observed in the high-resolution MS for the acetates of the eleven new triterpene alcohols may be described as follows: The acetates of **1c** (*m/z* 482.4104; the molecular formulas of this and the subsequent compounds are $C_{33}H_{54}O_2$, calcd 482.4121), **2b** (*m/z* 482.4085), **2c** (*m/z* 482.4109), **2d** (*m/z* 482.4087), **3b** (*m/z* 482.4096), **3c** (*m/z* 482.4102), **3d** (*m/z* 482.4084), **4b** (*m/z* 482.4146), **4d** (*m/z* 482.4112), **5b** (*m/z* 482.4146), and **5d** (*m/z* 482.4160). The molecular formulas for the fragment ions described in Table 1 were taken from the MS data of the relevant compounds and may be summarized as follows; *m/z* 467 ($C_{32}H_{51}O_2$), 439 ($C_{30}H_{47}O_2$), 422 ($C_{31}H_{50}$), 407 ($C_{30}H_{47}$), 398 ($C_{27}H_{42}O_2$), 379 ($C_{28}H_{43}$), 355 ($C_{24}H_{35}O_2$), 353 ($C_{26}H_{41}$), 339 ($C_{25}H_{39}$), 325 ($C_{24}H_{37}$), 300 ($C_{22}H_{36}$), 297 ($C_{22}H_{33}$), 295 ($C_{22}H_{31}$), 288 ($C_{21}H_{36}$), and 273 ($C_{20}H_{33}$).

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