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TRITERPENE GLYCOSIDES FROM *Astragalus* AND THEIR GENINS. LXXXVII. CHEMICAL TRANSFORMATION OF CYCLOARTANES. IX. PARTIAL SYNTHESIS OF CYCLOASALGENIN

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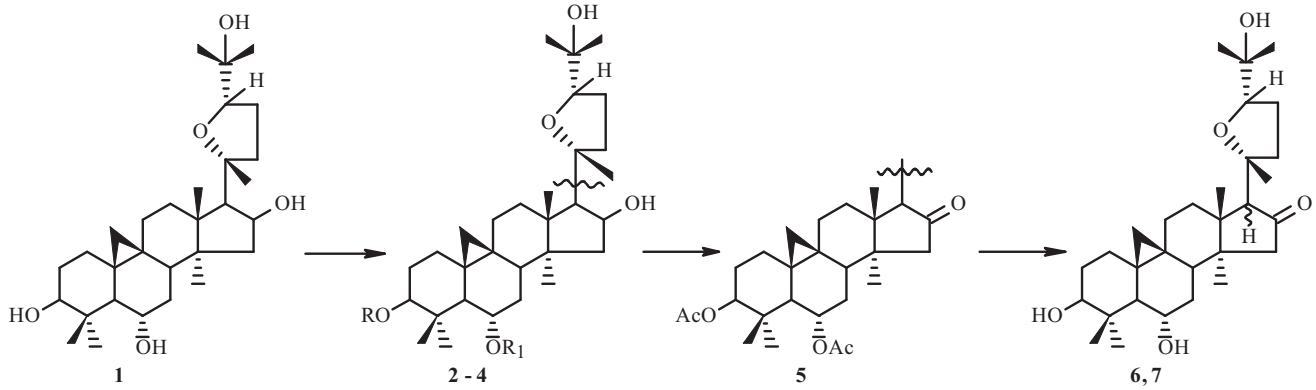
*The natural cycloartane triterpenoid cycloasalgenin, which is 20*R*,24*S*-epoxycycloartan-3*β*,6*α*,25-triol-16-one, was partially synthesized in three steps starting from cyclosiversigenin. In addition to the desired product, its 17-epimer was synthesized. The analogous 17-epimer was also prepared from cycloadsurgenin.*

Keywords: *Astragalus*, Leguminosae, cycloartanes, cycloasalgenin, PMR, ^{13}C NMR, DEPT spectra.

In continuation of the chemical transformation of cycloartane triterpenoids [1], we synthesized partially cycloasalgenin (**6**), which was isolated from *Astragalus zahlbruckneri* Hand.-Mazz. (Leguminosae) in Turkey [2] and described without naming. For convenience, we called it cycloasalgenin. Cycloasalgenin is a 16-keto derivative of cyclosiversigenin. Therefore, we synthesized cycloasalgenin in three steps starting from cyclosiversigenin (**1**).

Cyclosiversigenin was acetylated by acetic anhydride in Py. The 3,6-diacetate (**2**), 6-monoacetate (**3**), and 3-monoacetate (**4**) of cyclosiversigenin, which were previously described [3, 4], were isolated from the reaction products.



1 **2 - 4** **5** **6, 7**

2: R = R$_1$ = Ac
3: R = H, R$_1$ = Ac
4: R = Ac, R$_1$ = H

6: H-17*α*; **7:** H-17*β*

Jones oxidation [5] was used to introduce the C-16 ketone into **2**. This produced **5**, the PMR spectrum of which exhibited at strong field (δ 0.80–1.19) resonances for seven methyls. This indicated that the side chain was retained. The resonance of H-17 in this same spectrum became a singlet at δ 2.85. This was consistent with oxidation of the 16*β*-hydroxyl into a ketone. This was also consistent with the ^{13}C NMR spectrum of **5**, where the C-16 resonance appeared at δ 218.08.

The protecting groups were removed by alkaline hydrolysis of the diacetate of **5**. Ketones **6** and **7** were isolated from the hydrolysis products.

The PMR and ^{13}C NMR spectral data of **6** enabled it to be identified as cycloasalgenin [2]. A compound with an identical structure was obtained during elucidation of the structure of cycloastragenol (cyclosiversigenin) [6].

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TABLE 1. Chemical Shifts of C Atoms in **1**–**9** (100 MHz, 125 MHz, $CDCl_3$, δ, ppm)

C atom	DEPT	**1**	**2**	**3** (C_5D_5N)	**4** (C_5D_5N)	**5**	**6** ($CDCl_3$)	**6** (C_5D_5N)	**7**	**8**	**9**
1	CH_2	32.45	31.78	32.31	31.96	31.70	31.36[a]	31.37[a]	32.20	31.91	31.85
2	CH_2	31.80	25.93	31.15	27.09	25.98	30.52	30.55	31.02	35.65	35.84
3	CH(C)	78.70	79.97	77.18	80.82	79.76	78.58	78.15	78.54	217.68	217.15
4	C	41.85	40.49	41.98	40.87	40.53	41.84	42.37	41.83	50.52	50.50
5	CH	53.98	50.10	50.09	53.74	50.04	53.67	53.85	53.93	53.35	53.90
6	CH	69.43	70.71	71.18[a]	68.00	70.30	68.85	67.88	69.04	69.58	69.92
7	CH_2	38.30	33.28	33.73	38.65	33.46[a]	38.13	38.65	37.98	38.02	38.10
8	CH	47.47	45.15	45.80	47.25	44.44	46.33	45.90	46.00	47.35	47.09
9	C	21.07	21.01	20.67	21.06	20.67	20.64	20.46	20.83	20.76	21.06
10	C	29.82	28.57	29.02	29.40	28.84	29.91	29.97	29.75	28.86	28.92
11	CH_2	26.02	26.18	25.37	26.13	26.64	26.00	26.58	26.08	26.05	26.13
12	CH_2	33.35	33.31	33.22	33.27	33.46[a]	32.26	32.55	32.27	31.72	32.15
13	C	45.35	45.41	45.00	44.95	44.96	44.81	44.98	46.23	44.70	46.20
14	C	46.35	46.27	46.00	46.06	42.50	42.43	42.43	42.16	42.36	42.10
15	CH_2	46.87	46.18	46.39	46.69	51.04	51.43	51.28	51.32	51.80	51.59
16	CH(C)	73.72	73.64	73.30	73.38	218.08	218.71	218.69	217.38	218.90	218.81
17	CH	57.87	57.67	58.21	58.34	65.50	65.50	65.96	65.14	65.56	65.23
18	CH_3	21.82	21.25	21.31	21.64	19.96	20.37	20.10	20.23	20.84	20.71
19	CH_2	30.63	29.39	29.55	30.89	29.46	31.36[a]	31.37[a]	30.53	31.60	31.42
20	C	87.42	87.40	87.18	87.19	84.79	84.80	84.75	83.93	84.77	83.87
21	CH_3	28.03	28.06	28.17	28.15	25.58	25.52[6]	24.99	24.25	25.52	24.25
22	CH_2	34.79	34.75	34.86	34.88	32.08	32.07	32.17	37.92	31.72[a]	37.86
23	CH_2	26.22	26.93	26.43	26.42	26.89	26.67	25.95	25.52	26.68	25.52
24	CH	81.76	81.71	81.62	81.67	82.50	82.37	82.58	88.30	82.27	88.35
25	C	72.13	72.10	71.18[a]	71.22	71.03	71.21	70.81	70.57	71.39	70.57
26	CH_3	26.80	26.85	27.13	27.09	26.84	25.52[6]	26.31	28.36	28.36	28.27
27	CH_3	28.16	26.83	28.55	28.51	25.45	28.36	28.17	28.28	25.48	28.17
28	CH_3	20.40	20.08	19.97	20.17	19.72	19.92	19.49	19.87	20.22*	20.48
29	CH_3	28.54	28.12	27.49	28.82	28.36	28.41	29.32	29.58	28.48	29.62
30	CH_3	15.62	16.59	16.01	16.68	16.60	15.61	16.13	15.60	20.20*	20.14
3-OAc	C	–	171.22	–	170.63	171.17	–	–	–	–	–
	CH_3	–	21.60	–	21.18	21.59	–	–	–	–	–
6-OAc	C	–	170.73	170.31	–	170.71	–	–	–	–	–
	CH_3	–	22.17	21.81	–	22.11	–	–	–	–	–

Resonances denoted by the same letters overlap within columns.
*Assignment of resonances is ambiguous. Assignments of C-26 and C-27 resonances are also interchangeable.

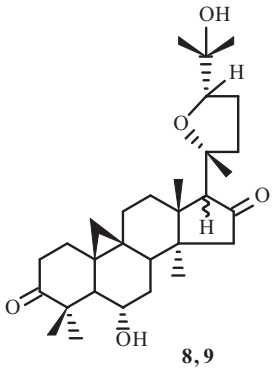
PMR and ^{13}C NMR spectra of **7** showed that the side chain, including the tetrahydrofuran ring, was retained. Also, the resonance for H-17 in the PMR spectrum experienced a high-field shift by 0.23 pm compared with **6** and was observed at δ 2.63.

The C-17 resonance in the ^{13}C NMR spectrum of **7** also shifted to strong field by 0.36 ppm relative to its position in **6** and appeared at δ 65.14 (Table 1).

These data suggested that C-17 had opposite configurations in **6** and **7**, i.e., the configuration of C-17 in **7** was inverted. Such configuration inversion of C-17 occurred obviously through keto-enol tautomerism during alkaline hydrolysis. Consequently, the subject ketone was a side product, i.e., the 17-epimer of cycloasalgenin, and had the structure 20*R*,24*S*-epoxy-17-*epi*-cycloartan-3β,6α,25-triol-16-one, which is depicted as structure **7**.

Because epimerization at C-17 was observed in the chemistry of cycloartane triterpenoids for the first time, we carried out epimerization of another 16-ketocycloartane, cycloadsurgenin (**8**) [4]. Treatment of **8** with methanolic NaOH under conditions identical to those for preparing **7** formed **9**. Comparison of the PMR and ^{13}C NMR spectra of **7** and **9** showed that the tetrahydrofuran ring in the side chain was retained in **9** and that the side-chain structure was identical in the two compounds. This was consistent with electrospray-ionization mass spectra in positive- and negative-ion mode (MS-ESIPI and

MS-ESINI) of **9**, where quasimolecular ions with *m/z* 509.3 $[M + Na]^+$ and 485.1 $[M - H]^-$ were found. Therefore, **9** was 20*R*,24*S*-epoxy-17-*epi*-cycloartan-6α,25-diol-3,16-dione, i.e., 17-*epi*-cycloadsurgenin.



8, 9

8: H-17α; **9:** H-17β

The configuration inversion of C-17 was also evident in the chemical shifts of side-chain C atoms C-20–C-27.

EXPERIMENTAL

General comments have been published [7]. We used solvent systems $CHCl_3$:MeOH (30:1, 1; 100:1, 2; 90:1, 3; and 50:1, 4).

PMR and ^{13}C NMR spectra were taken in $CDCl_3$ on UNITYplus 400 (Varian) and INOVA 600 (Varian) spectrometers with HMDS and TMS internal standards. ^{13}C NMR spectra were obtained with full C–H decoupling and under DEPT conditions. Chemical shifts of C atoms are given relative to the resonance of the C atom in $CDCl_3$ (δ 77.360). Chemical shifts of C atoms in the ^{13}C NMR spectrum of cycloasalgenin in deuteropyridine are given relative to the resonance of the β-C atoms of deuteropyridine (δ 123.493 vs. TMS).

IR spectra were recorded in KBr disks on a Bio-Rad FT-IR Spectrometer 165.

Electrospray-ionization mass spectra in positive- and negative-ion mode (MS ESIPI and MS ESINI) were obtained in a Waters Alliance 2690-ZQ4000 (LC/MS) spectrometer.

Cyclosiversigenin (1), $C_{30}H_{50}O_5$, mp 239–241°C (MeOH), was prepared as before [4].

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz, 0 = HMDS): 0.31 and 0.45 (d, ^2J = 4.5, 2H-19), 0.89, 0.90, 1.08, 1.16, 1.20, 1.20, 1.23 (s, 7×CH_3), 2.27 (d, ^3J = 7.9, H-17), 2.51 (q, $^3J_1 = {}^3J_2 = {}^2J$ = 11.6, H-22), 3.24 (dd, $^3J_1$ = 11, $^3J_2$ = 4.5, H-3), 3.47 (td, $^3J_1 = {}^3J_2$ = 9.9, $^3J_3$ = 3.4, H-6), 3.68 (t, $^3J_1 = {}^3J_2$ = 7.9, H-24), 4.62 (td, $^3J_1 = {}^3J_2$ = 7.9, $^3J_3$ = 6.3, H-16). Table 1 lists the ^{13}C NMR spectrum.

3,6-Diacetate (2), 6-Monoacetate (3), and 3-Monoacetate (4) of Cyclosiversigenin from 1. Cyclosiversigenin (1.005 g) was acetylated by acetic anhydride (2.5 mL) in anhydrous Py (5 mL) for 4.5 h at 18°C, after which the mixture was poured into icewater. The resulting precipitate was filtered off, washed with water, and dried. The product was chromatographed over a column using system 1 to afford **2** (550 mg), $C_{34}H_{54}O_7$, mp 234–236°C (MeOH).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz, 0 = HMDS): 0.29 and 0.55 (d, ^2J = 4.8, 2H-19), 0.78, 0.89, 0.93, 1.09, 1.16, 1.18, 1.24 (s, 7×CH_3), 1.70 (d, ^3J = 9.7, H-5), 1.93 (s, CH_3COO on C-6), 1.99 (s, CH_3COO on C-3), 2.27 (d, ^3J = 7.9, H-17), 2.51 (q, $^2J = {}^3J_1 = {}^3J_2$ = 10, H-22), 3.69 (t, $^3J_1 = {}^3J_2$ = 7.4, H-24), 4.51 (dd, $^3J_1$ = 11, $^3J_2$ = 4.6, H-3), 4.62 (td, $^3J_1 = {}^3J_2$ = 7.9, $^3J_3$ = 6.3, H-16), 4.69 (td, $^3J_1 = {}^3J_2$ = 9.2, $^3J_3$ = 4.5, H-6). Table 1 lists the ^{13}C NMR spectrum.

Continued elution of the column by the same solvent system isolated amorphous **3** (130 mg), $C_{32}H_{52}O_6$.

PMR spectrum (400 MHz, C_5D5_N, δ, ppm, J/Hz, 0 = HMDS): 0.17 and 0.44 (d, ^2J = 4.5, 2H-19), 0.85, 1.11, 1.17, 1.18, 1.24, 1.25, 1.46 (s, 7×CH_3), 1.92 (s, CH_3COO), 2.40 (d, ^3J = 7.8, H-17), 2.98 (q, $^2J = {}^3J_1 = {}^3J_2$ = 10.6, H-22), 3.46 (dd, $^3J_1$ = 11.6, $^3J_2$ = 4.6, H-3), 3.75 (dd, $^3J_1$ = 8.9, $^3J_2$ = 5.4, H-24), 4.90 (m, H-16), 4.94 (td, $^3J_1 = {}^3J_2$ = 9.3, $^3J_3$ = 4, H-6). Table 1 lists the ^{13}C NMR spectrum.

Further elution of the column with the same solvent system isolated **4** (120 mg), $C_{32}H_{52}O_6$, mp 243 –245°C (MeOH).

PMR spectrum (400 MHz, C_5D_5N, δ, ppm, J/Hz, 0 = HMDS): 0.18 and 0.44 (d, $^2J = 4$, 2H-19), 0.84, 1.13, 1.17, 1.19, 1.30, 1.46, 1.47 (s, 7×CH_3), 1.96 (s, CH_3COO), 2.40 (d, $^3J = 7.8$, H-17), 2.98 (q, $^2J = {}^3J_1 = {}^3J_2 = 11$, H-22), 3.59 (m, H-6), 3.76 (dd, $^3J_1 = 8.9$, $^3J_2 = 5.5$, H-24), 4.80 (dd, $^3J_1 = 11.6$, $^3J_2 = 4.5$, H-3), 4.89 (m, H-16). Table 1 lists the ^{13}C NMR spectrum.

3β,6α-Diacetoxy-20*R*,24*S*-epoxycycloartan-25-ol-16-one (5) from 2. Diacetate **2** (550 mg) in acetone (100 mL) at –8°C was treated with Jones reagent (0.5 mL) [5] and stirred for 30 min. The excess of oxidant was decomposed by adding to the mixture several milliliters of MeOH. The mixture was poured into water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and evaporated. The solid was chromatographed over a column with elution by system 2 to afford **5** (370 mg), $C_{34}H_{52}O_7$, mp 227–229°C (MeOH).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz, 0 = HMDS): 0.36 and 0.58 (d, $^2J = 4.9$, 2H-19), 0.80, 1.04, 1.08, 1.11, 1.13, 1.19 (s, 7×CH_3), 1.93, 2.00 (s, 2×CH_3COO), 2.85 (s, H-17), 3.67 (dd, $^3J_1 = 8$, $^3J_2 = 5.7$, H-24), 4.53 (dd, $^3J_1 = 11.4$, $^3J_2 = 4.7$, H-3), 4.67 (td, $^3J_1 = {}^3J_2 = 8.9$, $^3J_3 = 4.4$, H-6). Table 1 lists the ^{13}C NMR spectrum.

20*R*,24*S*-Epoxycycloartan-3β,6α,25-triol-16-one (6) (cycloasalgenin) and 20*R*,24*S*-Epoxy-17-*epi*-cycloartan-3β,6α,25-triol-16-one (7) from 5. Diacetate **5** (100 mg) was treated with NaOH in MeOH (20 mL, 0.1%), left for 7 d at room temperature, acidified by adding H_2SO_4, and poured into water. The products were extracted by EtOAc. The EtOAc extract was washed with water and evaporated. The solid was chromatographed over a column with elution by system 3 to afford **7** (24 mg), $C_{30}H_{48}O_5$.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz, 0 = HMDS): 0.37 and 0.49 (d, $^2J = 4.5$, 2H-19), 0.91, 1.03 (s, 2×CH_3), 1.049 (d, $^4J = 0.8$, CH_3-28), 1.09, 1.19, 1.20, 1.25 (s, 4×CH_3), 1.94 (d, $^2J = 18$, H-15α), 2.07 (dq, $^2J = 18$, $^4J = 0.8$, H-15β), 2.63 (s, H-17), 2.64 (td, $^2J = {}^3J_1 = 11.8$, $^3J_2 = 8.4$, H-22), 3.26 (dd, $^3J_1 = 11.2$, $^3J_2 = 4.5$, H-3), 3.50 (td, $^3J_1 = {}^3J_2 = 9.4$, $^3J_3 = 4$, H-6), 3.89 (dd, $^3J_1 = 10.5$, $^3J_2 = 6$, H-24). Table 1 lists the ^{13}C NMR spectrum.

Continued elution of the column by the same solvent system isolated **6** (30 mg), $C_{30}H_{48}O_5$, mp 214 –215°C (MeOH).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz, 0 = HMDS): 0.36 and 0.49 (d, $^2J = 4.3$, 2H-19), 0.91, 1.04, 1.09, 1.11, 1.13, 1.19, 1.21 (s, 7×CH_3), 1.34 (d, $^3J = 9.3$, H-5), 2.04 (s, 2H-15), 2.86 (s, H-17), 3.27 (dd, $^3J_1 = 11$, $^3J_2 = 4.5$, H-3), 3.49 (td, $^3J_1 = {}^3J_2 = 9.5$, $^3J_3 = 4$, H-6), 3.67 (dd, $^3J_1 = 8.5$, $^3J_2 = 5.5$, H-24).

Table 1 lists the ^{13}C NMR spectrum.

PMR spectrum (400 MHz, C_5D_5N, δ, ppm, J/Hz, 0 = HMDS): 0.21 and 0.48 (d, $^2J = 4{,}4$, 2H-19), 0.94 (dd, $^4J_1 = 0.9$, $^4J_2 = 0.7$, CH_3-28), 1.08, 1.13, 1.16, 1.25, 1.36 (s, 5×CH_3), 1.61 (d, $^3J = 9.4$, H-5), 1.78 (s, CH_3-29), 1.96 (dq, $^2J = 17.8$, $^4J = 0.7$, H-15α), 2.09 (dq, $^2J = 17.8$, $^4J = 0.9$, H-15β), 2.95 (s, H-17), 3.55 (dd, $^3J_1 = 11.5$, $^3J_2 = 4.7$, H-3), 3.66 (td, $^3J_1 = {}^3J_2 = 9.4$, $^3J_3 = 3.7$, H-6), 3.73 (dd, $^3J_1 = 8$, $^3J_2 = 5.8$, H-24).

Table 1 lists the ^{13}C NMR spectrum.

20*R*,24*S*-Epoxy-17-*epi*-cycloartan-6α,25-diol-3,16-dione (9) from 8. Cycloadsurgenin (**8**, 30 mg) was dissolved in methanolic NaOH (10 mL, 0.1%), left at room temperature for 7 d, poured into water, and extracted with EtOAc. After the usual work up and evaporation of solvent, the solid was chromatographed over a column using system 4 to afford **9** (12 mg), $C_{30}H_{46}O_5$.

IR spectrum (KBr, ν_{max}, cm^{-1}): 3445 (OH), 1735 (>C=O on C-16), 1703 (>C=O on C-3).

MS-ESIPI (*m*/*z*): 509.3 $[M + Na]^+$; MS-ESINI (*m*/*z*): 485.1 $[M - H]^-$.

PMR spectrum (600 MHz, $CDCl_3$, δ, ppm, J/Hz, 0 = TMS): 0.52 and 0.70 (d, $^2J = 4.2$, 2H-19), 1.04, 1.13, 1.16, 1.23, 1.26, 1.34, 1.37 (s, 7×CH_3), 2.71 (s, H-17), 3.56 (td, $^3J_1 = {}^3J_2 = 9.6$, $^3J_3 = 2.4$, H-6), 3.89 (dd, $^3J_1 = 10.2$, $^3J_2 = 5.4$, H-24).

Table 1 lists the ^{13}C NMR spectrum.

Continued elution with the same solvent system isolated **8** (10 mg).

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