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TRITERPENE GLYCOSIDES FROM *Astragalus* AND THEIR GENINS. LXXXI. CHEMICAL TRANSFORMATION OF CYCLOARTANES. VII. SYNTHESIS OF CYCLOSIVERSIGENIN LACTONE*

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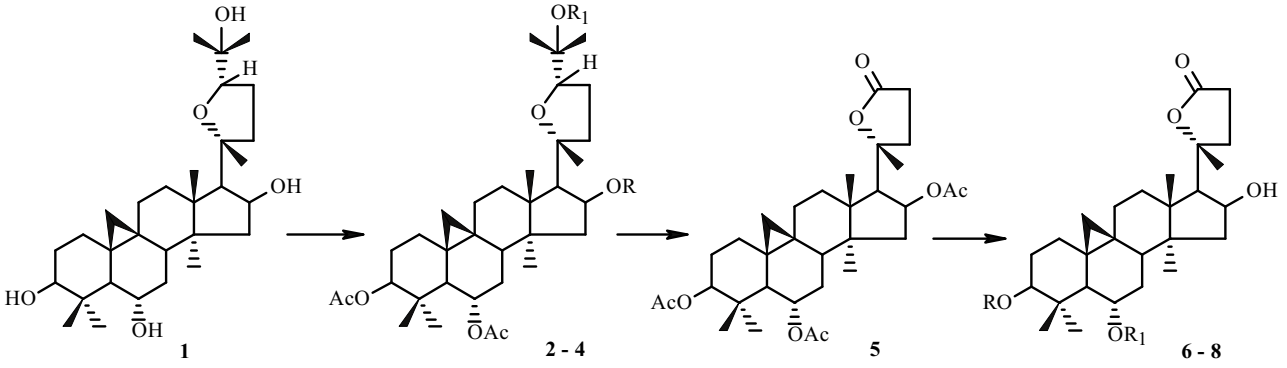
The lactone 20R-25-norcycloartan-3β,6α,16β-triol-20,24-olide was synthesized from cyclosiversigenin.

Key words: *Astragalus*, Leguminosae, cycloartanes, cyclosiversigenin, cyclosiversigenin lactone, PMR, ^{13}C, DEPT, ^{1}H–^{1}H COSY spectra.

We are continuing the chemical transformation of cycloartane methylsteroids and their glycosides [1].

Several cyclosiversigenin glycosides possess cardiotonic activity [2, 3]. Creation of a γ-lactone (butanolide) side chain in order to approximate the structure of cyclosiversioside F to those of cardenolides enhanced the cation-transport activity of cyclosiversioside F lactone compared with the starting glycoside [4]. Therefore, it seemed interesting to prepare a lactone from cyclosiversigenin, which was synthesized in three steps.

Cyclosiversigenin (**1**) was acetylated by acetic anhydride in Py. Column chromatography of the products separated previously produced tetra- (**2**), tri- (**3**), and di- (**4**) acetates of cyclosiversigenin, which were identified by direct comparison with authentic samples [5, 6]. Cyclosiversigenin triacetate (**3**) was oxidized by Jones reagent to produce a lactone ring in the side chain [7]. The oxidation product **5** was the 3,6,16-triacetate of cyclosiversigenin lactone according to the PMR spectrum (C_5D_5N), which exhibited resonances for three acetyls at δ 1.96, 1.98, and 2.02 and clearly resolved resonances of five methyls at 0.76, 0.88, 0.96, 1.08, and 1.36. The structure of **5** was also confirmed by the ^{13}C NMR spectrum (Table 1) where resonances of C-25, C-26, and C-27 were missing and resonances for C-20 and C-24 were observed at 89.33 and 176.44, respectively, characteristic of a 20,24-olide.



2: R = R_1 = Ac; **3, 7:** R = Ac, R_1 = H; **4, 8:** R = R_1 = H; **6:** R = H, R_1 = Ac

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TABLE 1. Chemical Shifts of C Atoms in **1**, **3**, and **5**–**8** ($CDCl_3$, C_5D_5N, δ, ppm)

C atom	**1** ($CDCl_3$)	**3** ($CDCl_3$)	**5** ($CDCl_3$)	**6** ($CDCl_3$)	**7** ($CDCl_3$)	**8** ($CDCl_3$)	**8** (C_5D_5N)
1	32.45	32.76	32.75	32.24	32.02	32.35	32.58
2	31.80	26.88[a]	26.93[a]	30.55	27.05	31.33	31.34
3	78.70	79.85	79.81	78.19	80.38	78.54	78.19
4	41.85	40.45	40.51	41.60	40.69	41.79	42.37
5	53.98	50.01	50.07	50.12	54.11	53.92	53.90
6	69.43	70.57	70.49	71.20	69.06	69.26	68.20
7	38.30	31.68	33.33	33.63	37.98	37.89	38.64
8	47.47	45.30	45.14	45.46	46.77	46.68	46.86
9	21.07	20.96	20.82	20.72	20.94	20.87	21.59
10	29.82	29.53	28.84	29.09	29.58	29.42	30.18
11	26.02	26.26	26.01	25.99	25.95	25.94	26.04
12	33.35	33.25	33.28	33.28	33.26	33.30	33.08
13	45.35	46.38	46.38	45.93	45.81	45.80	45.61[a]
14	46.35	46.51	46.62	46.33	46.19	46.20	45.61[a]
15	46.87	45.57	44.91	47.53	47.60	47.59	48.37
16	73.72	75.97	75.65	73.36	73.34	73.36	71.92
17	57.87	57.34	56.70	57.51	57.39	57.40	57.74
18	21.82	20.76	21.12	21.58	21.82	21.82	20.69
19	30.63	28.17	29.64	30.14	31.42	30.54	30.80
20	87.42	85.89	89.33	90.53	90.68	90.70	90.25
21	28.03	26.88[a]	26.93[a]	30.04	29.93	29.97	29.88
22	34.79	36.69	31.77	32.63	32.46	32.47	32.65
23	26.22	28.02	29.25	29.45	29.40	29.66	29.81
24	81.76	82.11	176.44	177.46	177.62	177.65	177.35
25	72.13	71.22	–	–	–	–	–
26	26.80	24.74	–	–	–	–	–
27	28.16	26.37	–	–	–	–	–
28	20.40	20.29	20.01	20.05	20.16	20.15	19.92
29	28.54	28.68	29.46	27.09	28.37	28.41	29.35
30	15.62	16.57	16.60	15.51	16.65	15.59	16.07
C-3-Ac	–	171.25	171.13	–	171.32	–	–
	–	21.90	21.56	–	21.65	–	–
C-6-Ac	–	170.98	170.73	170.75	–	–	–
	–	22.14	22.11	22.20	–	–	–
C-16-Ac	–	170.82	169.94	–	–	–	–
	–	21.61	21.38	–	–	–	–

[a]Resonances are mutually superimposed within columns.

Lactone **5** was subjected to alkaline hydrolysis with subsequent acidification of the reaction mixture in order to remove the protecting groups. Compounds **6**-**8** were isolated over a column after the usual work up and chromatography of the products.

The PMR spectrum of **6** exhibited a 3H singlet at δ 1.94 that was indicative of one acetyl in the molecule. The acetyl was located on C-6 because the resonance of H-6 underwent a low-field shift and was observed at 4.65. Product **6** was cyclosiversigenin lactone 6-monoacetate.

The PMR spectrum of **7** also contained a resonance for an acetyl but at 1.96. The appearance of the H-3 resonance at low field at 4.70 indicated that the acetyl was retained on C-3 in this product. Compound **7** was cyclosiversigenin lactone 3-monoacetate.

Compound **8** was the target product, i.e., cyclosiversigenin lactone completely freed of protecting groups, according to the PMR spectrum. As expected, the IR spectrum of **8** showed a strong absorption band for hydroxyls at 3380 cm^{-1} and a strong absorption band at 1742 that was characteristic of a γ-lactone.

Thus, the lactone 20*R*-25-norcycloartan-3β,6α,16β-triol-20,24-olide was synthesized in three steps from cyclosiversigenin.

EXPERIMENTAL

General comments have been published [8]. PMR spectra were recorded on Tesla BS-567A (100 MHz, C_5D_5N, δ, ppm, 0 = HMDS), Bruker AM-300 (300 MHz, C_5D_5N, δ, ppm, 0 = TMS), and Unityplus 400 (400 MHz, $CDCl_3$, δ, ppm, 0 = HMDS) spectrometers; ^{13}C NMR spectra, on Bruker AM-300 (75.5 MHz, C_5D_5N, δ, ppm) and Unityplus 400 (100 MHz, $CDCl_3$, δ, ppm) spectrometers with full C–H decoupling and under DEPT conditions. Chemical shifts of C atoms in the ^{13}C NMR spectrum of **8** in C_5D_5N are given relative to the resonance of the β-C atoms of C_5D_5N, which have chemical shifts δ 123.493 relative to TMS. Chemical shifts of C atoms in ^{13}C NMR spectra in $CDCl_3$ are given relative to the resonance of $CDCl_3$, which resonated at δ 77.36. ^1H—^1H COSY spectra in $CDCl_3$ were obtained on the Unityplus 400 spectrometer. IR spectra in KBr disks were recorded on a Bio-Rad FT-IR Spectrometer 165.

Cyclosiversigenin 3,6,16,25-Tetraacetate (2); 3,6,16-Triacetate (3); and 3,6-Diacetate (4) from 1. Cyclosiversigenin (**1**, 2 g) was acetylated by acetic anhydride (15 mL) in anhydrous Py (15 mL) for 9 d at room temperature, after which the reaction mixture was poured onto ice. The resulting precipitate was filtered off, washed with water, and dried. The products (2.395 g) were separated over a column of silica gel with elution by $CHCl_3$:CH_3OH (50:1) to afford cyclosiversigenin tetraacetate (**2**, 0.2 g), which was identified by direct comparison with an authentic sample [6].

Further elution of the column by the same solvent system produced cyclosiversigenin triacetate (**3**, 1.510 g), mp 211-212°C (MeOH), the NMR spectra of which were identical to those of an authentic sample [5, 6].

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz, 0 = HMDS): 0.31 and 0.53 (2H-19, d, $^2J = 4.7$), 0.78, 0.916, 0.921, 1.02, 1.14, 1.22, 1.23 (7 × CH_3, s), 1.93, 1.96, 1.99 (3 × CH_3COO, s), 2.42 (H-17, d, $^3J = 8$), 3.63 (H-24, dd, $^3J_1 = 8.7$, $^3J_2 = 7.2$), 4.51 (H-3, dd, $^3J_1 = 11.4$, $^3J_2 = 4.6$), 4.65 (H-6, td, $^3J_1 = {}^3J_2 = 9$, $^3J_3 = 4$), 5.35 (H-16, td, $^3J_1 = {}^3J_2 = 8$, $^3J_3 = 5.3$).

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

Continued elution of the column by the same solvent system isolated cyclosiversigenin diacetate (**4**, 0.453 g), mp 228-229°C (MeOH), which was identified by comparison with an authentic sample [5, 6]. The PMR and ^{13}C NMR spectra have been published [1].

20*R*-25-Norcycloartan-3β,6α,16β-triol-20,24-olide 3,6,16-Triacetate (5) from 3. Cyclosiversigenin triacetate (**3**, 1.013 g) in acetone (30 mL) was treated with Jones reagent (0.13 mL) [7], stirred for 25 min at room temperature (24°C), treated with several milliliters of MeOH to destroy the excess of oxidant, poured into water. and extracted with $CHCl_3$. The solid (0.977 g) resulting from the usual work up and evaporation of $CHCl_3$ was chromatographed over a column with elution by $CHCl_3$:CH_3OH (50:1) to afford **5** (710 mg), $C_{35}H_{48}O_8$, mp 181-183°C (MeOH).

PMR spectrum (100 MHz, C_5D_5N, δ, ppm, J/Hz, 0 = HMDS): 0.22 and 0.43 (2H-19, d, $^2J = 4$), 0.76, 0.88, 0.96, 1.08, 1.36 (5 × CH_3, s), 1.96, 1.98, 2.02 (3 × CH_3COO, s), 2.57 (H-17, d, $^3J = 7$), 4.70 (H-3 and H-6, m), 5.38 (H-16, m).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz, 0 = HMDS): 0.32 (H-19, d, $^2J = 4.9$), 0.55 (H′-19, d, $^2J = 4.7$), 0.79, 0.92, 0.92, 1.22, 1.44 (5 × CH_3, s), 1.71 (H-5, d, $^3J = 9.8$), 1.93, 1.94, 1.99 (3 × CH_3COO, s), 2.55 (H-17, d, $^3J = 8.6$), 4.51 (H-3, dd, $^3J_1 = 11.3$, $^3J_2 = 4.5$), 4.65 (H-6, td, $^3J_1 = {}^3J_2 = 9.2$, $^3J_3 = 4.5$), 5.31 (H-16, td, $^3J_1 = {}^3J_2 = 8$, $^3J_3 = 6.5$). Table 1 lists the ^{13}C NMR spectrum.

Alkaline Hydrolysis of Cyclosiversigenin Lactone Triacetate (5). A solution of **5** (530 mg) in MeOH (25 mL) was treated with a solution of NaOH (250 mg) in MeOH (25 mL), left at room temperature for 3 d, treated with conc. H_2SO_4 (1 mL), diluted after several minutes with water, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water. The solvent was evaporated. The products (446 mg) were chromatographed over a column with elution by $CHCl_3$:CH_3OH (25:1) to afford monoacetate **6** (160 mg), $C_{29}H_{44}O_6$, mp 240-243°C (MeOH).

PMR spectrum (100 MHz, C_5D_5N, δ, ppm, J/Hz, 0 = HMDS): 0.20 and 0.43 (2H-19, d, $^2J = 4$), 0.82, 1.04, 1.20, 1.20, 1.44 (5 × CH_3, s), 1.94 (CH_3COO, s), 2.42 (H-17, d, $^3J = 8$), 3.40 (H-3, m), 4.65 (H-6, m), 4.84 (H-16, m).

PMR spectrum (400 MHz, CDCl3, δ, ppm, J/Hz, 0 = HMDS): 0.32 and 0.54 (2H-19, d, $^2J = 4.7$), 0.86, 0.87, 0.94, 1.20, 1.44 (5 × CH_3, s), 1.61 (H-5, d, $^3J = 10$), 1.95 (CH_3COO, s), 2.36 (H-17, d, $^3J = 8.6$), 2.97 (H-22, dt, $^2J = 11.7$, $^3J_1 = {}^3J_2 = 10.5$), 3.23 (H-3, dd, $^3J_1 = 11$, $^3J_2 = 4.7$), 4.56 (H-16, q, $^3J_1 = {}^3J_2 = {}^3J_3 = 7.6$), 4.68 (H-6, t, $^3J_1 = {}^3J_2 = 9.6$, $^3J_3 = 4$). Table 1 lists the ^{13}C NMR spectrum.

Continued elution of the column by the same solvent system produced monoacetate **7** (24 mg), $C_{29}H_{44}O_6$, mp 259-260°C (MeOH).

PMR spectrum (100 MHz, C_5D_5N, δ, ppm, J/Hz, 0 = HMDS): 0.20 and 0.47 (2H-19, d, $^2J = 4$), 0.81, 1.10, 1.28, 1.42, 1.42 (5 × CH_3, s), 1.96 (CH_3COO, s), 2.44 (H-17, d, $^3J = 8$), 3.58 (H-6, m), 4.70 (H-3, m), 4.80 (H-16, m).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz, 0 = HMDS): 0.33 and 0.49 (2H-19, d, $^2J = 4.7$), 0.89, 0.98, 1.07, 1.19, 1.45 (5 × CH_3, s), 2.00 (CH_3COO, s), 2.36 (H-17, d, $^3J = 8.5$), 3.47 (H-6, td, $^3J_1 = {}^3J_2 = 9.7$, $^3J_3 = 3.5$), 4.51 (H-3, dd, $^3J_1 = 11.2$, $^3J_2 = 4.6$), 4.57 (H-16, td, $^3J_1 = {}^3J_2 = 8$, $^3J_3 = 6.7$). Table 1 lists the ^{13}C NMR spectrum.

Further elution of the column by the same solvent system produced lactone **8** (230 mg), $C_{27}H_{42}O_5$, mp 138-140°C (MeOH).

PMR spectrum (100 MHz, C_5D_5N, δ, ppm, J/Hz, 0 = HMDS): 0.21 and 0.50 (2H-19, d, $^2J = 4$), 0.84, 1.20, 1.28, 1.42, 1.72 (5 × CH_3, s), 2.45 (H-17, d, $^3J = 7$), 3.44 (H-3, m), 3.56 (H-6, m), 4.70 (H-16, q, $^3J_1 = {}^3J_2 = {}^3J_3 = 7$).

PMR spectrum (300 MHz, C_5D_5N, δ, ppm, J/Hz, 0 = TMS): 0.32 and 0.58 (2H-19, d, $^2J = 4$), 0.94, 1.35, 1.39, 1.52, 1.89 (5 × CH_3, s), 2.56 (H-17, d, $^3J = 8.5$), 3.37 (H-22, q, $^2J = {}^3J_1 = {}^3J_2 = 10$), 3.65 (H-3, dd, $^3J_1 = 11$, $^3J_2 = 4$), 3.77 (H-6, td, $^3J_1 = {}^3J_2 = 9$, $^3J_3 = 3$), 4.80 (H-16, q, $^3J_1 = {}^3J_2 = {}^3J_3 = 8.5$). Table 1 lists the ^{13}C NMR spectrum.

PMR spectrum (400 MHz, CDCl3, δ, ppm, J/Hz, 0 = HMDS): 0.32 and 0.46 (2H-19, d, $^2J = 4.4$), 0.88, 0.90, 1.20, 1.20, 1.44 (5 × CH_3, s), 2.36 (H-17, d, $^3J = 8.5$), 3.25 (H-3, dd, $^3J_1 = 11.2$, $^3J_2 = 4.4$), 3.49 (H-6, td, $^3J_1 = {}^3J_2 = 9.7$, $^3J_3 = 3.8$), 4.57 (H-16, td, $^3J_1 = {}^3J_2 = 8.2$, $^3J_3 = 6.8$). Table 1 lists the ^{13}C NMR spectrum.

IR spectrum (KBr, ν, cm^{-1}): 3380 (OH), 1742 (γ-lactone).

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REFERENCES

1. I. M. Isaev, D. A. Iskenderov, and M. I. Isaev, *Khim. Prir. Soedin.*, 591 (2008).
2. Jpn. Pat. No. 57,165,400, "Saponins from *Astragali* root;" *Chem. Abstr.*, **98**, 95652z (1983).
3. Z. A. Khushbaktova, M. A. Agzamova, V. N. Syrov, N. V. Radchenko, N. M. Mirsalikhova, and F. T. Umarova, *Khim. Prir. Soedin.*, 510 (1994).
4. M. I. Isaev, M. A. Agzamova, Z. A. Khushbaktova, Yu. R. Mirzaev, V. N. Syrov, M. B. Gorovits, and N. K. Abubakirov, USSR Pat. Appl. 1,540,245, MKI^3 A 61 K 31/585, C 07 J 17/00; *Otkrytiya, Izobreteniya*, No. 4, 286 (1990).
5. M. I. Isaev, M. B. Gorovits, N. D. Abdullaev, M. R. Yagudaev, and N. K. Abubakirov, *Khim. Prir. Soedin.*, 572 (1981).
6. R. P. Mamedova, M. A. Agzamova, and M. I. Isaev, *Khim. Prir. Soedin.*, 457 (2001).
7. C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).
8. R. P. Mamedova, M. A. Agzamova, and M. I. Isaev, *Khim. Prir. Soedin.*, 453 (2001).