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# TRITERPENE GLYCOSIDES OF *Astragalus* AND THEIR GENINS. LXIV. CHEMICAL TRANSFORMATION OF CYCLOARTANES. V. SYNTHESIS OF CYCLOPYCANTHOGENIN FROM CYCLOSIVERSIGENIN

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*The partial synthesis of cyclopycanthogenin, 20R,24S-epoxycycloartan-6α,16β,25-triol-3-one, was developed in four steps from cyclosiversigenin.*

**Key words:** *Astragalus*, cycloartanes, cyclosiversigenin, cyclopycanthogenin, partial synthesis.

In continuation of the chemical transformation of cycloartane triterpenoids [1], we synthesized cyclopycanthogenin (**6**) starting from cyclosiversigenin (**1**). Cyclopycanthogenin is 20R,24S-epoxycycloartan-6$\alpha$,16$\beta$,25-triol-3-one. It has been isolated from *Astragalus pycnanthus* Boriss. (Leguminosae) [2]. The structure of this methylsterol differs from that of cyclosiversigenin in the nature of the C-3 functional groups. The structures of **1** and **6** show that cyclosiversigenin contains a 3$\beta$-hydroxyl whereas cyclopycanthogenin has a 3-ketone. The remaining structural and stereochemical features of **1** and **6** are identical. Therefore, it was interesting to develop a chemical route from cyclosiversigenin to cyclopycanthogenin in order to correlate their structures. We developed a partial synthesis of cyclopycanthogenin starting from cyclosiversigenin, the essence of which consists of selective introduction of the 3-ketone in the latter.

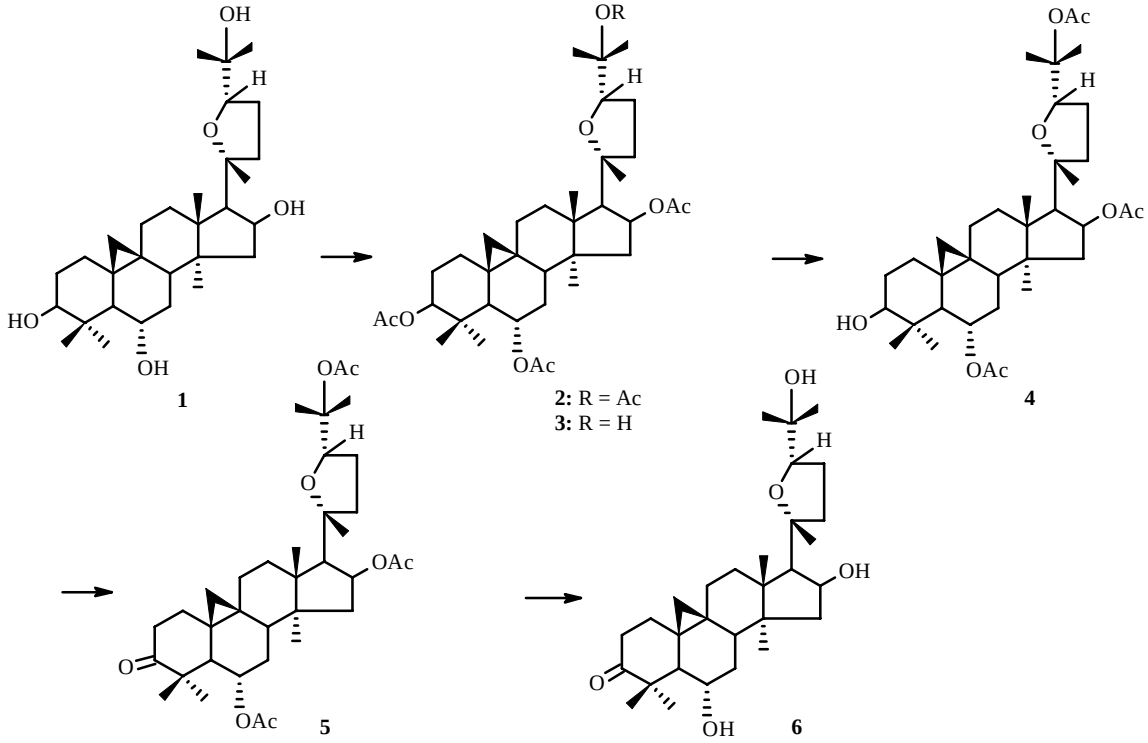


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TABLE 1. $^{13}C$ Chemical Shifts in **1**, **2**, and **6** (δ, ppm, $C_5D_5N$, 0 = TMS)

| C atom | Compound | | |
|---|---|---|---|
| | **1** | **2** | **6** [2] |
| 1 | 32.81 | 32.48 | 31.85 |
| 2 | 31.47 | 27.02 | 35.86 |
| 3 | 78.32 | 79.51 | 216.82 |
| 4 | 42.46 | 40.42 | 50.56 |
| 5 | 54.00 | 49.78 | 53.55 |
| 6 | 68.38 | 70.37 | 69.17 |
| 7 | 38.85 | 31.51 | 38.39 |
| 8 | 47.30 | 45.45 | 48.19 |
| 9 | 20.99 | 20.75 | 21.21 |
| 10 | 29.92 | 28.59 | 28.49 |
| 11 | 26.32 | 26.55 | 26.07 |
| 12 | 33.47 | 33.35 | 33.20 |
| 13 | 45.09 | 46.44 | 45.00 |
| 14 | 46.21 | 46.47 | 46.06 |
| 15 | 46.81 | 45.77 | 47.04 |
| 16 | 73.48 | 75.78 | 73.41 |
| 17 | 58.44 | 57.55 | 58.50 |
| 18 | 21.66 | 21.55 | 22.14 |
| 19 | 31.02 | 29.43 | 31.08 |
| 20 | 87.27 | 85.79 | 87.22 |
| 21 | 28.59 | 27.46 | 28.57 |
| 22 | 34.97 | 37.07 | 34.93 |
| 23 | 26.17 | 25.91 | 26.45 |
| 24 | 81.75 | 81.16 | 81.73 |
| 25 | 71.27 | 82.97 | 71.27 |
| 26 | 27.17 | 22.78 | 27.18 |
| 27 | 28.21 | 22.39 | 28.22 |
| 28 | 20.27 | 20.60 | 20.43 |
| 29 | 29.44 | 26.78 | 28.65 |
| 30 | 16.14 | 16.59 | 20.45 |
| $\underline{CH_3}COO$ | - | 21.85 | - |
| | | 21.69 | |
| | | 21.06 | |
| | | 20.03 | |
| $CH_3\underline{COO}$ | | 170.52 | |
| | | 170.31 | |
| | | 170.24 | |
| | | 170.04 | |

The hydroxyls of cyclosiversigenin were protected by acetylation with acetic anhydride in pyridine. Acetates **2** and **3** were isolated by column chromatography.

The mass spectrum of the less polar acetate **2** has a base peak with *m*/*z* 185. This ion corresponds with the side chain and indicates that the C-25 tertiary hydroxyl is acetylated. A peak for the molecular ion ($[M]^+$ 658) is not observed. The peak with the highest mass number appears at *m*/*z* 643 and corresponds to the ion generated from the molecular ion by elimination of a methyl radical.

Therefore, **2** is cyclosiversigenin tetraacetate. Thus, its IR spectrum lacks hydroxyl absorption bands. These data agree with the $^1H$ and $^{13}C$ NMR spectra of **2**. The $^1H$ NMR spectrum of **2** exhibits signals for four acetoxys at 2.035, 2.087, 2.092, and 2.170 ppm. The $^{13}C$ NMR has signals for the corresponding C atoms (Table 1).

The polar product **3** was identified as the previously described cyclosiversigenin 3,6,16-triacetate [3].

The tetraacetate (**2**) was saponified by methanolic KOH for selective removal of the C-3 acetoxy. The main product of the reaction, **4**, was isolated from the reaction mixture by column chromatography. The $^1$H NMR spectrum of **4** has signals at 1.92, 2.00, and 2.05 ppm for three acetyls. Furthermore, the 1H doublet of doublets with spin—spin coupling constants (SSCC) $^3J_1$ = 11 Hz and $^3J_2$ = 6 Hz for H-3 undergoes a strong-field shift compared with the same signal for **2** and appears at 3.47 ppm. According to this, **4** is cyclosiversigenin 6,16,25-triacetate. Jones oxidation [4] of **4** produced chromatographically pure ketone **5**, which was purified by column chromatography. The IR spectrum of **5** exhibits an absorption band at 1710 cm$^{-1}$, which is characteristic of a six-membered cyclic ketone. As expected, the $^1$H NMR spectrum of **5** lacks resonances for H-3 and exhibits signals for three acetoxys at 1.90, 1.99, and 2.02 ppm. These data define **5** as 20R,24S-epoxycycloartan-6$\alpha$,16$\beta$,25-triol-3-one 6,16,25-triacetate.

Alkaline hydrolysis of **5** and subsequent column chromatography produced **6** that was identical to cyclopycanthogenin [2].

## EXPERIMENTAL

**General comments** have been published [1]. The solvent systems benzene—ethylacetate (5:1, 1) and $CHCl_3$—$CH_3OH$ (50:1, 2; 20:1, 3) were used.

$^1$H and $^{13}$C NMR spectra were obtained on UNITYplus 400 and Tesla BS-567A instruments in $C_5D_5N$ and $CDCl_3$.

Mass spectra were recorded in MX-1310 and Kratos MS 25F (UK) instruments at 50 V ionizing potential and 130-170°C.

**Cyclosiversigenin 3,6,16,25-tetraacetate (2) and 3,6,16-triacetate (3) from 1.** Cyclosiversigenin (1 g) was acetylated by acetic anhydride (5 mL) in absolute pyridine (6 mL) for 50 days at 60°C. The solvent was evaporated. The solid was chromatographed over a column using system 1 to afford noncrystalline **2** (758 mg), $C_{38}H_{58}O_9$. IR spectrum (ν, KBr, cm$^{-1}$): 1737, 1247 (esters).

Mass spectrum, *m*/*z* ($I_{rel}$, %): $[M - 15]^+$ 643 (0.8), 598 (10.4), 583 (1.0), 556 (3.1), 538 (26.4), 523 (5.5), 478 (17.6), 463 (6.6), 437 (9.9), 418 (9.9), 403 (8.8), 377 (8.8), 291 (6.6), 271 (7.1), 253 (8.8), 185 (100), 143 (50), 125 (78.6), 107 (28.6).

PMR spectrum (400 MHz, $C_5D_5N$, 0 = TMS, δ, ppm, J/Hz): 0.30 and 0.56 (2H-19, d, $^2J$ = 4.6), 0.91, 1.02, 1.12, 1.31, 1.40, 1.64, 1.64 (7×$CH_3$, s), 2.035, 2.087, 2.092, 2.170 (4×$CH_3COO$, s), 2.54 (H-17, d, $^3J$ = 7.8), 4.19 (H-24, t, $^3J_1$ = $^3J_2$ = 7.5), 4.84 (H-3, dd, $^3J_1$ = 11.5, $^3J_2$ = 4.6), 4.97 (H-6, td, $^3J_1$ = $^3J_2$ = 9.5, $^3J_3$ = 4.3), 5.57 (H-16, td, $^3J_1$ = $^3J_2$ = 7.8, $^3J_3$ = 4.9). Table 1 lists $^{13}$C NMR data.

Further elution of the column by the same system produced **3** (155 mg), mp 211-212°C (methanol) [3].

PMR spectrum (100 MHz, $C_5D_5N$, 0 = HMDS, δ, ppm, J/Hz): 0.18 and 0.44 (2H-19, d, $^2J$ = 4), 0.76, 0.86, 0.97, 1.14, 1.24, 1.26, 1.28 (7×$CH_3$, s), 1.94, 1.96, 2.04 (3×$CH_3COO$, s), 2.44 (H-17, d, $^3J$ = 9), 3.83 (H-24, t, $^3J_1$ = $^3J_2$ = 8), 4.66 (H-3, dd, $^3J_1$ = 10, $^3J_2$ = 4), 4.82 (H-6, td, $^3J_1$ = $^3J_2$ = 10, $^3J_3$ = 4), 5.44 (H-16, m).

**Cyclosiversigenin 6,16,25-triacetate (4) from 2.** Tetraacetate **2** (758 mg) in methanol (25 mL) was treated with $KHCO_3$ (148 mg) in methanol (15 mL) and left at 50°C for one month. The product was poured into water and extracted with $CHCl_3$. The solvent was evaporated. The solid was chromatographed over a column with elution by system 1 to afford noncrystalline **4** (300 mg), $C_{36}H_{56}O_8$. IR spectrum (ν, KBr, cm$^{-1}$): 3525 (OH), 1737, 1250 (esters).

Mass spectrum, *m*/*z* ($I_{rel}$, %): $[M - 60]^+$ 556 (5.7), 538 (5.1), 514 (3.4), 495 (5.1), 435 (8.5), 394 (3.7), 308 (2.8), 270 (5.1), 217 (8), 185 (76.1), 143 (50), 125 (100).

PMR spectrum (100 MHz, $C_5D_5N$, 0 = HMDS, δ, ppm, J/Hz): 0.19 and 0.50 (2H-19, d, $^2J$ = 4), 0.81, 1.13, 1.19, 1.25, 1.27, 1.50, 1.50 (7×$CH_3$, s), 1.92, 2.00, 2.05 (3×$CH_3COO$, s), 2.44 (H-17, d, $^3J$ = 7.8), 3.47 (H-3, dd, $^3J_1$ = 11, $^3J_2$ = 6), 4.08 (H-24, t, $^3J_1$ = $^3J_2$ = 7), 4.95 (H-6, td, $^3J_1$ = $^3J_2$ = 10, $^3J_3$ = 3), 5.47 (H-16, td, $^3J_1$ = $^3J_2$ = 7.8, $^3J_3$ = 4.7).

PMR spectrum (100 MHz, $CDCl_3$, 0 = HMDS, δ, ppm, J/Hz): 0.31 and 0.50 (2H-19, d, $^2J$ = 4), 0.85, 0.92, 0.92, 1.26, 1.26, 1.35, 1.36 (7×$CH_3$, s), 1.90, 1.94, 1.94 (3×$CH_3COO$, s), 2.35 (H-17, d, $^3J$ = 7.5), 3.22 (H-3, m), 3.94 (H-24, t, $^3J_1$ = $^3J_2$ = 6.3), 4.63 (H-6, m), 5.24 (H-16, m).

**20R,24S-Epoxycycloartan-6$\alpha$,16$\beta$,25-triol-3-one 6,16,25-triacetate (5) from 4.** Triacetate **4** (86 mg) in acetone (15 mL) at -4°C was treated with Jones reagent (0.15 mL) [4] and stirred for 30 min at the same temperature. The reaction was stopped by addition of several drops of methanol. After the usual work up, the product was chromatographed over a column

with elution by system 2 to afford **5** (57 mg), $C_{36}H_{54}O_8$. IR spectrum (ν, KBr, $cm^{-1}$): 1737, 1247 (esters), 1710 (C-3 C=O).

Mass spectrum, *m/z* ($I_{rel}$, %): $[M - 60]^+$ 554 (5.7), 536 (1.1), 512 (4.5), 493 (9.7), 452 (2.3), 433 (15.3), 392 (12.5), 362 (3.4), 306 (4.5), 268 (5.7), 227 (5.1), 217 (13.1), 185 (94.3), 143 (45.5), 125 (100).

PMR spectrum (100 MHz, $C_5D_5N$, 0 = HMDS, δ, ppm, J/Hz): 0.30 and 0.59 (2H-19, d, $^2J = 4$), 0.76, 1.10, 1.19, 1.19, 1.26, 1.49, 1.49 (7×$CH_3$, s), 1.90, 1.99, 2.02 (3×$CH_3$COO, s), 4.07 (H-24, t, $^3J_1 = {}^3J_2 = 7$), 4.80 (H-6, td, $^3J_1 = {}^3J_2 = 10$, $^3J_3 = 4$), 4.42 (H-16, td, $^3J_1 = {}^3J_2 = 8$, $^3J_3 = 5$).

**20R,24S-Epoxycycloartan-6α,16β,25-triol-3-one (6), Cyclopycanthogenin, from 5.** Ketone **5** (50 mg) was dissolved in methanol (10 mL) containing NaOH (30 mg) and held at room temperature for two months. The product was worked up as usual and chromatographed over a column using system 3 to afford **6** (26 mg), mp 233-235°C (methanol), which was identified as cyclopycnanthogenin by its chromatographic mobility on TLC in various solvent systems and comparison with an authentic sample [2] and by spectral data.

## REFERENCES


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