*Chemistry of Natural Compounds, Vol. 35, No. 6, 1999*

# SYNTHESIS OF TRITERPENE ACIDS α-MONOGLYCERIDES AND THEIR CITRATES

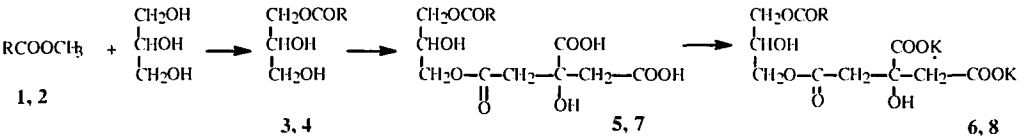
**A. F. Artamonov, F. S. Nigmatullina, M. P. Irismetov, and B. Zh. Dzhiembaev**

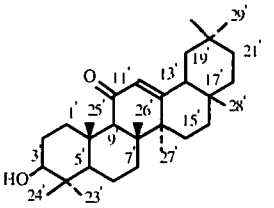
UDC 547.426.21/23:547.597

*α-Monoglycerides of triterpene acids, glycyrrhetic and 18-dehydroglycyrrhetic, and their citrates are synthesized. The structures are confirmed using IR, UV, and $^{1}H$ and $^{13}C$ NMR spectroscopies.*

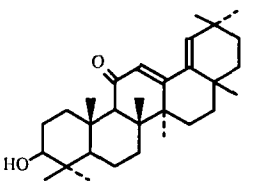
The triterpene acids glycyrrhetic and 18-dehydroglycyrrhetic have broad spectra of biological activity. They exhibit antiinflammatory, bactericidal, antitumor, anti-ulcer, antisclerotic, and other types of activities [1-4]. Therefore, it seemed interesting to prepare esters of triterpene acids with polyatomic alcohols, their citrates, and water-soluble potassium salts of the latter.

The starting glycyrrhetic acid was isolated from licorice roots (*Glycrrhiza glabra* L.). 18-Dehydroglycyrrhetic acid was obtained by modification of glycyrrhetic acid via the Br-derivative [1, 4]. The present article describes the preparation of α-monoglycerides of these acids by transesterification of their methyl esters (**1**, **2**) and glycerine in the presence of a base catalyst (KOH). α-Monoglycerides (**3**, **4**) were isolated from the reaction products using column chromatography on silica gel. Citrates were prepared by reacting the α-monoglycerides (**3**, **4**) with equimolar amounts of citric acid. The citrates (**5**, **7**) were isolated from the reaction products by column chromatography on silica gel. The potassium salts (**6**, **8**) were prepared by neutralization of the citrates with an alcoholic solution of base.




R (**1**, **3**, **5**, **7**)




R (**2**, **4**, **6**, **8**)

Vibrations of the ester C=O group occur at 1725-1735 $cm^{-1}$ in IR spectra of **1-4**; of the conjugated ketone, at 1660-1680 $cm^{-1}$. Vibrations of associated OH groups at 3100-3600 $cm^{-1}$ are also present. The IR spectra of the citrates (**5** and **7**) show vibrations of the second ester C=O at 1740 $cm^{-1}$.

PMR spectra of **3** and **4** contain signals of protons belonging to the glycyrrhetic fragment and to the glycerine moiety. These are a two-proton doublet at 4.1-4.2 ppm for the methylene protons of the acylated alcohol group and a two-proton doublet at 3.6-3.7 ppm for the methylene protons geminal to the hydroxyl. The methine proton of the secondary hydroxyl of glyerine appears as a multiplet at 3.8-4.05 ppm.

The position of the acyl group in **3** and **4** was determined from $^{13}C$ NMR data. The spectrum of unsubstituted glycerine

A. B. Bekturov Institute of Chemical Sciences, Ministry of Science, Academy of Sciences of the Republic of Kazakhstan, Almaty, fax (3272) 61 57 65. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 746-750, November-December, 1999. Original article submitted April 2, 1999.

 0009-3130/99/3506-0638$22.00 ©1999 Kluwer Academic/Plenum Publishers

was recorded for comparison. The facts that the signal for C-1, which occupies the α-position relative to the ester, shifts to downfield by 3.5-4.0 ppm whereas that for C-2 of glycerine undergoes a diamagnetic shift of 2.0-2.5 ppm compared with their chemical shifts in unsubstituted glycerine confirm that acylation occurs at the primary hydroxyl. The chemical shift of the C atom of the other primary hydroxyl of glycerine (C-3) changes little (±0.2 ppm).

The chemical shifts of the triterpene acids C atoms in the α-monoglycerides (**3** and **4**), their citrates (**5** and **7**), and the potassium salts (**6** and **8**) agree with the chemical shifts of the corresponding atoms of the starting methyl esters (**1** and **2**) and with those reported in the literature [5].

The $^{13}C$ NMR spectra of **5** and **7** confirm that the free primary hydroxyl of glycerine is acylated because C-3, which is located in the α-position relative to the citric acid ester, shifts to downfield by 3.5-4.0 ppm.

## EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument (KBr pellets); UV spectra, on a Specord UV-Vis spectrophotometer; $^1H$ and $^{13}C$ NMR spectra, on a Mercury-300 instrument at working frequencies 300 and 75 MHz, respectively, in $CDCl_3$ and DMSO-$D_6$ (0 = TMS). The course of reactions was monitored by TLC on Silufol UV-254 plates. Pure compounds were isolated by column chromatography on silica gel.

**Synthesis of α-Monoglycerides of Glycyrrhetic (3) and 18-Dehydroglycyrrhetic (4) Acids.** The methyl ester (10 g, 0.02 mole) of the appropriate acid (**1** and **2**) was heated with glycerine (11.4 g, 0.124 mole) at 200-210°C in the presence of KOH (0.031 g, 0.56 mmole) under an Ar atmosphere for 10 h. The course of the reaction was monitored by TLC on Silufol plates with elution by a $CHCl_3$—$CH_3OH$ (9:1) mixture. The product was extracted with ethylacetate after the reaction was finished, washed with water to remove glycerine, and dried over $MgSO_4$. The solvent was distilled off. α-Monoglycerides **3** and **4** were isolated by column chromatography on silica gel L (0.04-0.1 mm) with elution by $CHCl_3$.

Compound **1**: mp 261-262°C, $R_f$ 0.77 ($CHCl_3$—$CH_3OH$, 9:1).

Found, %: C 76.96, H 9.82. $C_{31}H_{48}O_4$. Calc., %: C 76.75, H 9.90.

IR spectrum (KBr, ν, $cm^{-1}$): 1726 (C=O, ester), 1665 (C=O, conj. ketone), 3100-3600 (–OH).

UV spectrum (EtOH, $\lambda_{max}$, nm): 250 (lg ε 4.04).

$^1H$ NMR (δ, ppm): 21H, $CH_3$ (0.79, s, 6H; 0.99, s, 3H; 1.11, s, 3H; 1.12, s, 3H, 1.14, s, 3H, 1.35, s, 3H); 1.21-1.70 (18H, $-CH_2$); 1.76-2.09 (3H, H-3′, H-5′, H-18′); 2.33 (1H, H-9′), 3.68 (3H, s, $-OCH_3$), 5.65 (1H, H-12′).

$^{13}C$ NMR (δ, ppm): C-1′ 38.73, C-2′ 26.83, C-3′ 78.28, C-4′ 38.73, C-5′ 54.49, C-6′ 17.07, C-7′ 32.33, C-8′ 42.76, C-9′ 61.40, C-10′ 36.65, C-11′ 200.00, C-12′ 128.10, C-13′ 169.00, C-14′ 45.00, C-15′ 25.98, C-16′ 26.05, C-17′ 31.44, C-18′ 47.97, C-19′ 40.63, C-20′ 43.65, C-21′ 30.71, C-22′ 37.34, C-23′ 27.73, C-24′ 15.27, C-25′ 16.02, C-26′ 18.25, C-27′ 23.02, C-28′ 27.97, C-29′ 28.15, C-30′ 176.64, C-31′ 51.47.

Compound **2**: mp 210-211°C, $R_f$ 0.74. Found, %: C 77.15, H 9.48. $C_{31}H_{46}O_4$. Calc., %: C 77.06, H 9.53.

IR spectrum (KBr, ν, $cm^{-1}$): 1735 (C=O, ester), 1680 (C=O, conj. ketone), 3000-3500 (–OH).

UV spectrum (EtOH, $\lambda_{max}$, nm): 282 (lg ε 3.92).

$^1H$ NMR (δ, ppm): 21H, $CH_3$ (0.80, s; 0.86, s; 0.87, s; 0.94, s; 0.98, s; 1.19, s; 1.29, s); 1.21-1.73 (16H, $-CH_2$), 2.04 (2H, s, H-3′, H-5′), 2.26 (1H, s, H-9′), 3.67 (3H, s, $-OCH_3$), 5.77 (1H, s, H-19′), 5.79 (1H, s, H-12′).

$^{13}C$ NMR (δ, ppm): C-1′ 38.68, C-2′ 25.56, C-3′ 78.34, C-4′ 38.68, C-5′ 54.72, C-6′ 17.17, C-7′ 35.76, C-8′ 43.12, C-9′ 60.46, C-10′ 36.57, C-11′ 199.95, C-12′ 129.16, C-13′ 162.45, C-14′ 44.82, C-15′ 23.98, C-16′ 24.67, C-17′ 34.36, C-18′ 142.46, C-19′ 123.76, C-20′ 44.04, C-21′ 33.57, C-22′ 37.58, C-23′ 26.79, C-24′ 15.32, C-25′ 16.36, C-26′ 18.04, C-27′ 23.14, C-28′ 27.50, C-29′ 27.71, C-30′ 176.47, C-31′ 51.84.

Compound **3**: 4.6 g (41%), mp 137-140°C, $R_f$ 0.51. Found, %: C 72.53, H 9.34. $C_{33}H_{52}O_6$. Calc., %: C 72.68, H 9.54.

UV spectrum (EtOH, $\lambda_{max}$, nm): 250 (lg ε 3.98).

IR spectrum (KBr, ν, $cm^{-1}$): 1728 (C=O, ester), 1665 (C=O, conj. ketone), 3100-3600 (–OH).

$^1H$ NMR (δ, ppm): glycerine part, 4.14 (2H, d, J = 4 Hz, C-1), 3.81-4.03 (1H, m, C-2), 3.62 (2H, d, J = 4 Hz, C-3); acyl glycyrrhetic acid, 21H, $CH_3$ (0.78, s; 0.97, s; 1.11, s; 1.16, s; 1.22, s; 1.33, s); 1.26-1.63 (18H, $-CH_2$); 1.75-2.14 (3H, H-3′, H-5′, H-18′); 2.25 (1H, s, H-9′); 5.53 (1H, s, H-12′).

$^{13}C$ NMR (δ, ppm): glycerine part, C-1 64.82 (Δδ = +3.50), C-2 69.82 (-2.39), C-3 62.69 (+0.15); acyl glycyrrhetic acid, C-1′ 38.70, C-2′ 27.76, C-3′ 78.36, C-4′ 38.70, C-5′ 54.59, C-6′ 17.20, C-7′ 35.17, C-8′ 42.31, C-9′ 61.45, C-10′ 36.48, C-11′

200.12, C-12′ 123.50, C-13′ 166.18, C-14′ 44.51, C-15′ 26.34, C-16′ 26.73, C-17′ 33.41, C-18′ 44.62, C-19′ 40.00, C-20′ 43.56, C-21′ 31.36, C-22′ 37.18, C-23′ 27.99, C-24′ 15.42, C-25′ 16.24, C-26′ 18.17, C-27′ 20.40, C-28′ 28.15, C-29′ 28.25, C-30′ 178.24.

Compound **4**: 3.95 g (35.2%), mp 163-165°C, $R_f$ 0.58. Found, %: C 7.83, H 9.08. $C_{33}H_{50}O_6$. Calc., %: C 7.95, H 9.21.

UV spectrum (EtOH, $\lambda_{max}$, nm): 282 (lg ε 3.90).

IR spectrum (KBr, ν, $cm^{-1}$): 1728 (C=O, ester), 1660 (conj. ketone), 3050-3600 (–OH).

$^1$H NMR (δ, ppm): glycerine part, 4.17 (2H, d, J = 4 Hz, C-1), 3.85-4.02 (1H, m, C-2), 3.67 (2H, d, J = 4 Hz, C-3); acyl 18-dehydroglycyrrhetic acid, 21H, $CH_3$ (0.79, 6H, 0.94, 3H, s; 0.98, 3H, s; 1.16, 3H, s; 1.17, 3H, s; 1.31, 3H, s); 2.26 (1H, s, H-9′); 5.74 (1H, s, H-19′), 5.80 (1H, s, H-12′).

$^{13}$C NMR (δ, ppm): glycerine part, C-1 64.99 (Δδ = +3.68), C-2 69.70 (-2.50), C-3 62.72 (+0.18); acyl 18-dehydroglycyrrhetic acid, C-1′ 38.70, C-2′ 25.56, C-3′ 78.28, C-4′ 38.70, C-5′ 54.70, C-6′ 17.17, C-7′ 35.69, C-8′ 43.25, C-9′ 60.50, C-10′ 38.70, C-11′ 200.87, C-12′ 129.36, C-13′ 163.50, C-14′ 44.93, C-15′ 23.98, C-16′ 24.50, C-17′ 34.36, C-18′ 142.48, C-19′ 123.45, C-20′ 44.15, C-21′ 33.59, C-22′ 36.63, C-23′ 26.70, C-24′ 15.42, C-25 16.39, C-26 18.09, C-27′ 20.41, C-28′ 27.59, C-29′ 27.76, C-30′ 176.07.

**Synthesis of Citrates of α-Monoglycerides (5, 7) and Their Potassium Salts (6, 8).** α-Monoglycerides (**3**, **4**, 2.0 g, 0.00367 mole) were heated to 100°C with stirring and treated with citric acid (0.705 g, 0.00367 mole). The temperature was raised to 160°C. The reaction was carried out for 1.5-2 h. Citrates (**5**, **7**) were isolated by column chromatography on silica gel (0.04-0.1 mm) with elution by a $CHCl_3$—$CH_3OH$ mixture (9:1). The citrates (**5**, **7**) were treated at room temperature with stirring with alcoholic KOH (1.7 ml, 5%). The alcohol was removed. The salts (**6**, **8**) were dried under vacuum at 50-60°C until the weight was constant.

Compound **5**: 0.65 g (24.7%), mp 103-106°C, $R_f$ 0.28. Found, %: C 65.25, H 8.13. $C_{39}H_{58}O_{12}$. Calc., %: C 65.18, H 8.08.

IR spectrum (KBr, ν, $cm^{-1}$): 1736, 1745 (C=O, ester), 1680 (C=O, conj. ketone), 3100-3650 (–OH).

UV spectrum (EtOH, $\lambda_{max}$, nm): 249 (lg ε 3.97).

$^1$H NMR (δ, ppm): 21H, $CH_3$ (0.68, s; 0.89, s; 1.03, s; 1.08, s; 1.14, s; 1.24, s; 1.32, s); 2.50 (1H, s, H-9′), 2.78 (4H, s, C-5, C-8), 3.62-3.89 (1H, m, C-2); 3.89-4.13 (4H, br. s, C-1, C-3); 5.34 (1H, s, H-12′).

$^{13}$C NMR (δ, ppm): C-1, 63.93 (Δδ = +2.73); C-2 68.05 (-2.45); C-3 65.46 (+4.01); C-5, C-8 42.42; C-6 72.58; C-4, C-9 170.79; C-7 172.23. Acyl glycyrrhetic acid: chemical shifts correspond to chemical shifts of C atoms of the α-monoglyceride (**3**) and the methyl ester (**1**).

Compound **6**: 0.53 g (95%), mp 215-218°C. Found, %: C 58.90, H 6.97, K 9.76. $C_{39}H_{56}O_{12}$. Calc., %: C 58.94, H 7.05, K 9.82.

IR spectrum (KBr, ν, $cm^{-1}$): 1735, 1743 (C=O, ester), 1680 (C=O, conj. ketone), 3100-3600 (–OH).

UV spectrum (EtOH, $\lambda_{max}$, nm): 250 (lg ε 3.96).

Chemical shifts of protons in the $^1$H NMR and of C atoms in the $^{13}$C NMR of the potassium salt (**6**) correspond to those of the citrate (**5**) and the α-monoglyceride (**3**).

Compound **7**: 0.66 g (25%), mp 112-115°C, $R_f$ 0.38. Found, %: C 65.28, H 7.75. $C_{39}H_{56}O_{12}$. Calc., %: C 65.36, H 7.82.

IR spectrum (KBr, ν, $cm^{-1}$): 1730, 1745 (C=O, ester), 1680 (C=O, conj. ketone), 3000-3600 (–OH).

UV spectrum (EtOH, $\lambda_{max}$, nm): 282 (lg ε 3.89).

$^1$H NMR (δ, ppm): 21H, $CH_3$ (0.69, s; 0.88, s; 0.92, s; 1.14, s; 1.17, s; 1.31, s); 2.38 (1H, s, H-9′), 2.67 (4H, s, C-5, C-8); 3.75-3.92 (1H, m, C-2); 3.92-4.13 (4H, br. s, C-1, C-3), 5.53 (1H, s, H-19′), 5.59 (1H, s, H-12′).

$^{13}$C NMR (δ, ppm): C-1 63.98 (Δδ = +2.78); C-2 68.25 (-2.25); C-3 65.30 (+3.85); C-5, C-8 42.38; C-6 72.57; C-4, C-9 170.78; C-7 172.12.

Acyl 18-dehydroglycyrrhetic acid: chemical shifts correspond to those of C atoms of the α-monoglyceride (**4**) and the methyl ester (**2**).

Compound **8**: 0.54 g (96%), mp 194-197°C. Found, %: C 59.14, H 6.76, K 9.75. $C_{39}H_{54}K_2O_{12}$. Calc., %: C 59.09, H 6.82, K 9.84.

IR spectrum (KBr, ν, $cm^{-1}$): 1725, 1740 (C=O, ester), 1675 (C=O, conj. ketone), 3000-3600 (–OH).

UV spectrum (EtOH, $\lambda_{max}$, nm): 281 (lg ε 3.86).

Chemical shifts of protons in the $^1$H NMR and C atoms in the $^{13}$C NMR of the potassium salt (**8**) correspond to those of the citrate (**7**) and the α-monoglyceride (**4**).

## REFERENCES


1. G. A. Tolstikov and M. I. Goryaev, *Glycyrrhetic Acid*, Nauka, Alma-Ata (1966), Vol. 71, p. 81.
2. *Problems in the Study and Use of Licorice in the USSR*, Nauka, Moscow-Leningrad (1966), pp. 167, 180.
3. Materials of the International Scientific-Practical Conference "Processing of Medicinal Raw Materials and Production of Phytopreparations for Medicine and Agriculture," Almaty (1966), pp. 116, 118.
4. M. P. Irismetov, *Synthesis and Biological Activity of Derivatives of Glycyrrhetic Acid, Solasodine, and Diosgenin* [in Russian], Author's Abstract of a Doctoral Dissertation in Chemical Sciences, Almaty (1993).
5. G. A. Tolstikov, L. M. Khalilov, L. A. Baltina, R. M. Kondratenko, A. A. Panasenko, and E. V. Vasil'eva, *Khim. Prir. Soedin.*, 645 (1985).