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SHORT COMMUNICATIONS

# Synthesis of 2-Cyanoethoxy and 2-(1*H*-Tetrazol-5-yl)ethoxy Derivatives of Glycyrrhetic Acid Methyl Ester

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**Abstract**—Cyanoethylation of natural glycyrrhetic acid methyl ester gave the corresponding 3β-*O*-(2-cyanoethyl) derivative which was treated with sodium azide to obtain a novel tetrazolyl derivative of biologically active triterpenoid, methyl 3β-[2-(1*H*-tetrazol-5-yl)ethoxy]-11-oxoolean-12-en-30-oate.

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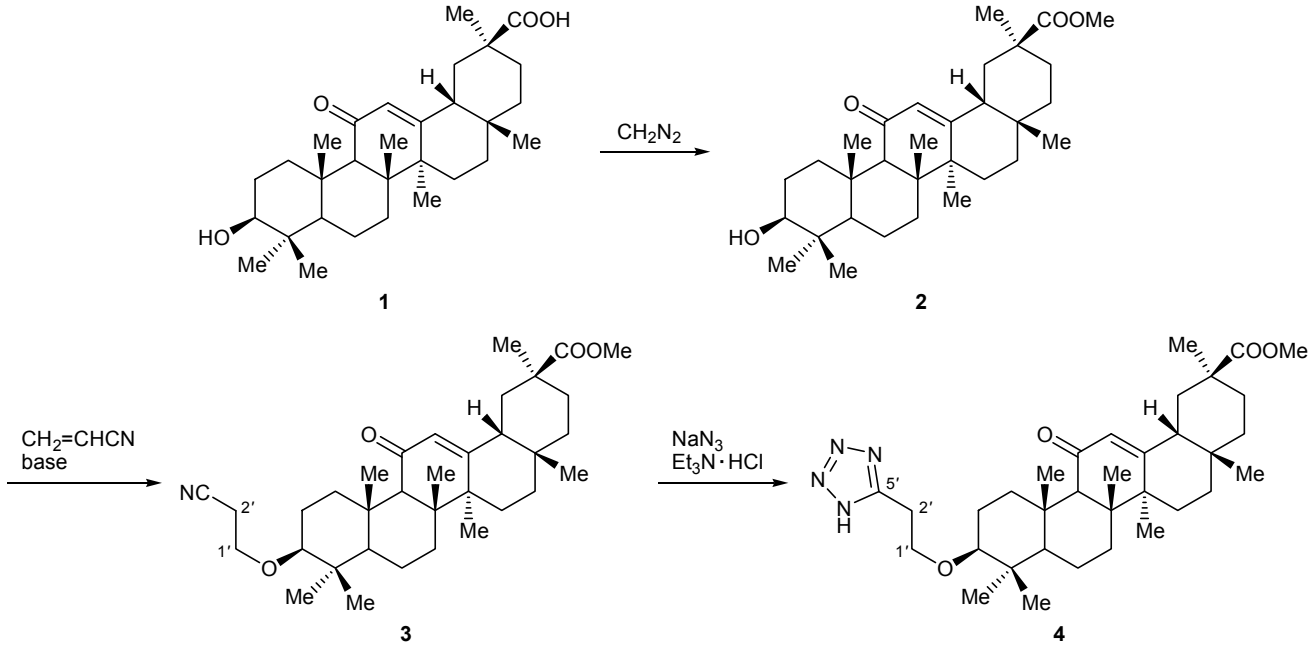
Glycyrrhizic acid and its aglycone, glycyrrhetic acid (**1**), are known due to their biological activity. Extracts of the licorice roots (*Glycyrrhiza glabra* L. and *Glycyrrhiza uralensis* Fisch) have been used for over thousands years in folk medicine. Both the acids themselves [1] and their derivatives [2, 3] were found to exhibit antitumor activity. Glycyrrhizic acid conjugates with amino acids or dipeptides protect cells from cytopathogenic human immunodeficiency viruses [4] and some influenza virus strains [5]. We previously showed that some 3-(2-cyanoethoxy) and 3-[2-(1*H*-tetrazol-5-yl)ethoxy] derivatives of dammarane triterpenoids possess a moderate anti-influenza activity [6, 7].

With the goal of searching for new promising biologically active derivatives of natural triterpenoids, 18β-glycyrrhetic acid methyl ester (**2**) was converted into cyanoethoxy derivative **3** (yield 80%) by cyanoethylation according to Michael. The structure of **3** was confirmed by spectral data, in particular by the presence of C≡N stretching band in the IR spectrum at 2256 $cm^{-1}$, methylene proton signals of the cyanoethyl fragment at δ 2.58, 3.67, and 3.97 ppm in the $^1H$ NMR



spectrum, and CN carbon signal at $\delta_C$ 118.07 ppm in the $^{13}C$ NMR spectrum.

The azidation of cyanoethyl derivative **3** with sodium azide in toluene in the presence of triethylamine hydrochloride afforded a new tetrazolyl derivative of natural glycyrrhetic acid, methyl 3β-[2-(1*H*-tetrazol-5-yl)ethoxy]-11-oxoolean-12-en-30-oate (**4**). The structure of **4** was also confirmed by spectral data. Its IR spectrum lacked C≡N stretching band at 2256 $cm^{-1}$. The $^1H$ NMR spectrum of **4** contained triplet signals of the methylene protons in the tetrazolylethyl substituent in the region δ 3.22–3.97 ppm, and the $^{13}C$ NMR spectrum characteristically displayed signals from the tetrazole carbon atom at $\delta_C$ 154.25 ppm and methylene carbon signals of the tetrazolylethyl fragment at $\delta_C$ 24.79 ($C^{2'}$) and 65.80 ppm ($C^{1'}$).

Glycyrrhetic acid (**1**) was isolated from the licorice roots (*Glycyrrhiza glabra* L.) according to the procedure described in [8]. Compound **1** showed no depression of the melting point (mp 293–296°C) on mixing with an authentic sample. Acid **1** was methylated with a solution of diazomethane in diethyl ether according to [9]. Methyl ester **2** showed no depression of the melting point (mp 248–252°C) on mixing with an authentic sample.

**Methyl 3β-(2-cyanoethoxy)-11-oxoolean-12-en-30-oate (3).** *a*. A mixture of 1.01 g (2.07 mmol) of ester **2**, 2.7 mL (41.4 mmol) of acrylonitrile, 0.008 g of potassium hydroxide, and 0.9 mL (1.03 mmol) of 20% aqueous tetrapropylammonium hydroxide in 16 mL of dioxane was stirred for 2 h at room temperature under argon. The mixture was poured into a mixture of ice with aqueous HCl (pH 2), and the precipitate was filtered off, washed with water until neutral washings, and dried in air. The product was subjected to chromatography on silica gel using hexane–ethyl acetate (4:1) as eluent to isolate 0.25 g (24%) of **3** as colorless crystals with mp 285.5–287.5°C. IR spectrum, ν, $cm^{-1}$: 2256 (C≡N), 1725 (C=O, ester), 1655 (C=O). $^1H$ NMR spectrum, δ, ppm: 0.78 s (3H, $C^{23}H_3$), 0.79 s (3H, $C^{28}H_3$), 1.00 s (3H, $C^{24}H_3$), 1.10 s (3H, $C^{26}H_3$), 1.12 s (3H, $C^{29}H_3$), 1.13 s (3H, $C^{25}H_3$), 1.34 s (3H, $C^{27}H_3$), 2.06 s (1H, 18-H), 2.54 d.d.d (1H, 2′-H, $J$ = 6.4, 6.0, 16.8 Hz), 2.58 d.d.d (1H, 2′-H, $J$ = 6.0, 7.1, 16.8 Hz), 3.50 d.d.d (1H, 1′-H, $J$ = 6.4, 7.0, 9.3 Hz), 3.82 d.d.d (1H, 1′-H, $J$ = 6.4, 7.1, 9.3 Hz), 3.67 s (3H, $OCH_3$), 5.64 s (1H, 12-H). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 16.21 ($C^{25}$), 16.16 ($C^{24}$), 17.23 ($C^6$), 18.53 ($C^{26}$), 22.52 ($C^2$), 23.22 ($C^{27}$), 19.11 ($C^{2'}$), 26.24 ($C^{16}$), 26.31 ($C^{15}$), 28.03 ($C^{23}$), 28.17 ($C^{29}$), 28.37 ($C^{28}$), 30.96 ($^{21}$), 31.67 ($C^{17}$), 32.57 ($C^7$), 36.82 ($C^{10}$), 37.59 ($C^{22}$), 38.68 ($C^1$), 38.95 ($C^4$), 40.94 ($C^{19}$), 43.02 ($C^{14}$), 43.88 ($C^{20}$), 45.25 ($C^8$), 48.22 ($C^{18}$), 51.67 ($OCH_3$), 55.19 ($C^5$), 61.64 ($C^9$), 63.82 ($C^{1'}$), 87.25 ($C^3$), 128.36 ($C^{12}$), 118.07 (CN), 170.12 ($C^{13}$), 176.75 ($C^{30}$), 200.05 ($C^{11}$). Mass spectrum: $m/z$ 560.3720 $[M + Na]^+$. $C_{34}H_{51}NO_4$. Calculated: $M$ 537.38181.

*b*. A mixture of 1.00 g (2.06 mmol) of compound **2**, 3.0 mL (45.6 mmol) of acrylonitrile, 0.005 g of potassium hydroxide, and 0.9 mL (1.03 mmol) of 20% aqueous tetrapropylammonium hydroxide in 16 mL of methylene chloride was stirred for 2 h at room temperature under argon. The mixture was poured into a mixture of ice and aqueous HCl (pH 2), and the precipitate was filtered off, washed with water until neutral washings, and dried in air. The two-phase filtrate was extracted with two portions of chloroform, the organic phase was washed with water, dried over $CaCl_2$, and evaporated, and the residue was purified by silica gel chromatography using chloroform–methanol (10:1) as eluent. Yield 0.80 g (80%); the melting point and spectral characteristics of the product were identical to those of a sample prepared as described above in *a*.

**Methyl 3β-[2-(1*H*-tetrazol-5-yl)ethoxy]-11-oxoolean-12-en-30-oate (4).** Compound **3**, 0.50 g (0.93 mmol), was dissolved in 8 mL of anhydrous toluene, and a mixture of 0.61 g (9.3 mmol) of sodium azide and 1.28 g (9.3 mmol) of triethylamine hydrochloride preliminarily dissolved in 5 mL of toluene was added. The mixture was refluxed for 8 h and cooled, the solvent was evaporated, the residue was dissolved in water, and the solution was treated with 10% aqueous HCl. The precipitate was filtered off, washed with water, dried in air, and recrystallized from hexane. Yield 0.28 g (56%), mp 260–262°C. $^1H$ NMR spectrum, δ, ppm: 0.79 s (3H, $C^{28}H_3$), 0.81 s (3H, $C^{23}H_3$), 0.90 s (3H, $C^{24}H_3$), 1.11 s (3H, $C^{26}H_3$), 1.13 s (3H, $C^{25}H_3$), 1.13 s (3H, $C^{29}H_3$), 1.34 s (3H, $C^{27}H_3$), 2.08 d.d.d.d (1H, 18-H, $J$ = 13.5, 4.4, 1.7, 0.8 Hz), 3.25 d.d.d (1H, 2′-H, $J$ = 5.3, 7.0, 15.8 Hz), 3.31 d.d.d (1H, 2′-H, $J$ = 5.3, 6.2, 15.8 Hz), 3.67 d.d.d (1H, 1′-H, $J$ = 5.3, 6.2, 9.3 Hz), 3.69 s (3H, $OCH_3$), 3.97 d.d.d (1H, 1′-H, $J$ = 5.3, 7.0, 9.3 Hz), 5.69 s (1H, 12-H). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 16.23 ($C^{25}$), 16.58 ($C^{24}$), 17.25 ($C^6$), 18.57 ($C^{26}$), 22.73 ($C^2$), 23.21 ($C^{27}$), 24.79 (5′-$CH_2$), 26.24 ($C^{16}$), 26.34 ($C^{15}$), 28.12 ($C^{23}$), 28.19 ($C^{29}$), 28.41 ($C^{28}$), 30.99 ($C^{21}$), 31.71 ($C^{17}$), 32.55 ($C^7$), 36.88 ($C^{10}$), 37.59 ($C^{22}$), 38.68 ($C^1$), 38.84 ($C^4$), 40.98 ($C^{19}$), 43.14 ($C^{14}$), 43.92 ($C^{20}$), 45.36 ($C^8$), 48.31 ($C^{18}$),

51.72 ($OCH_3$), 55.13 ($C^5$), 61.64 ($C^9$), 65.80 ($OCH_2$), 87.56 ($C^3$), 128.20 ($C^{12}$), 154.25 ($C^{5'}$), 170.13 ($C^{13}$), 176.83 ($C^{30}$), 200.61 ($C^{11}$). Mass spectrum: *m*/*z* 603.3894 $[M + Na]^+$. $C_{34}H_{52}N_4O_4$. Calculated: *M* 580.3989.

The IR spectra were recorded in KBr on a Perkin Elmer Spectrum BX spectrometer. The $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker Avance III-400 spectrometer at 400.13 and 100.61 MHz, respectively, using $CDCl_3$ as solvent and reference. The mass spectra were obtained on a Bruker maXis instrument. Silufol plates were used for analytical TLC; eluent hexane (petroleum ether)–ethyl acetate (4:1 or 2:1), spots were visualized by spraying with a 5% solution of 4-methoxybenzaldehyde in ethanol acidified with sulfuric acid, followed by heating at 100–120°C for 2–3 min. The melting points were measured on a PHMK hot stage (Wagetechnik Rapido).

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