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SYNTHESIS OF HALO-SUBSTITUTED FRAMEWORK DERIVATIVES OF QUINOPIMARIC ACID

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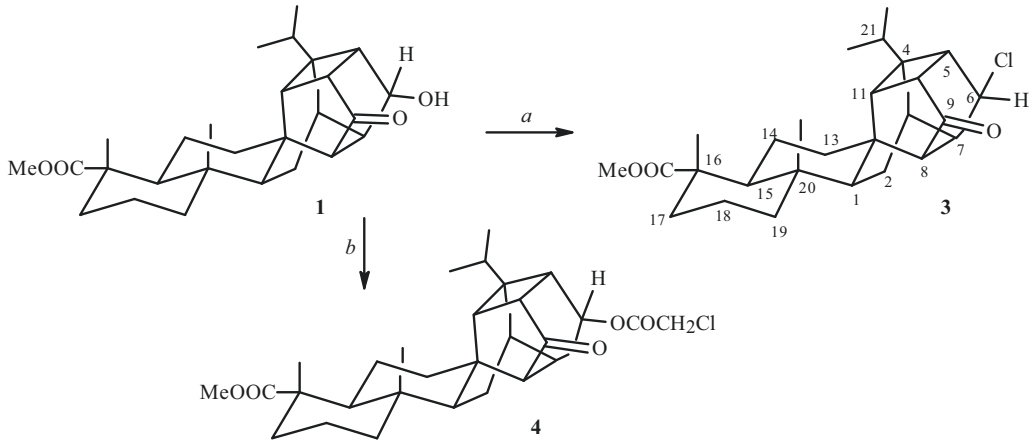
6-Chloro-, 6-chloroacetoxy-, and 16-(2-bromoacetyl)framework derivatives were synthesized from a photoadduct of quinopimaric acid.

Keywords: diterpene acids, framework compounds, halo-derivatives.

Natural diterpene acids of the abietane type comprise plant metabolites isolated from sap of conifers and are of definite interest because of their availability and broad spectrum of biological activity [1]. The principal constituent of *Pinus sylvestris* sap is levopimaric acid (30–35%), which is well known to undergo readily a diene-synthesis reaction [2–5]. Data on the pharmacological activity of levopimaric acid derivatives address mainly compounds prepared by a diene-synthesis reaction with quinones [1]. Adducts from a diene synthesis of levopimaric acid with quinones undergo intramolecular cyclization through the action of UV light to form framework γ-diketones and birdcage compounds [6, 7]. The synthesis of various framework derivatives of diene adducts of *p*-benzoquinone is interesting because of their novel interesting physiological properties (treatment of neurodegenerative disorders and antiviral, antitumor, and other properties) [8].

Introduction into quinopimaric acid of functional groups, e.g., halides, that react with amino- and sulfur-containing groups, is especially successful for peripheral design of framework derivatives of it. Natural halo-containing diterpenoids are few in number. However, the variety of biological activity makes them more and more attractive [9].

Therefore, halides were introduced by two methods into quinopimaric acid framework derivatives, i.e., into the framework and diterpene parts of quinopimaric acid 6-hydroxy-framework derivatives **1** and **2**. The stereochemistry of the hydroxyl in the C-6 position of **1** and **2** was determined based on the stereochemistry of the C-1 position in 1-hydroxyquinopimaric acid, in which the OH group has the β-orientation [10].



a. $POCl_3$, Py, 0°C, 99%; *b*. $ClCH_2COCl$, $CHCl_3$, 86%

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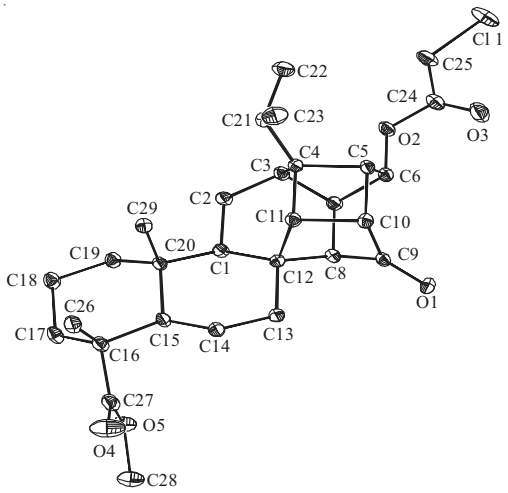
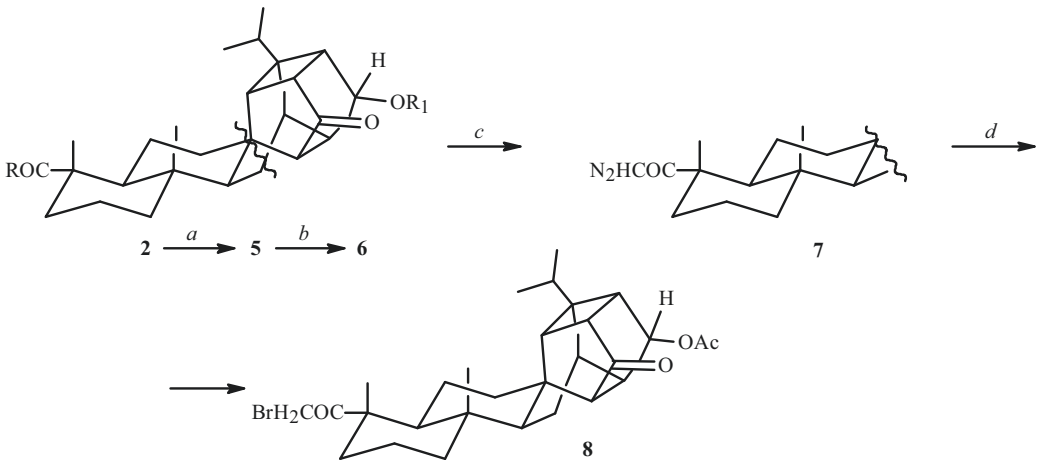


Fig. 1. General view of **4** with atoms represented as 50% probability thermal ellipsoids.



2: R = OH, R_1 = H; **5:** R = OH, R_1 = Ac; **6:** R = Cl, R_1 = Ac
a. Ac_2O; *b*. $(COCl)_2$; *c*. CH_2N_2, CH_2Cl_2, –5°C; *d*. 40% HBr

Exchange of the OH by Cl in ketol **1** was carried out using $POCl_3$ in Py at 0°C and gave a quantitative yield of optically active chloride **3**, $[\alpha]_D^{20}$ +66° (*c* 2.0, $CHCl_3$).

Formation of chloride **3** was proved using NMR spectroscopy and elemental analysis. Thus, the ^{13}C NMR spectrum (J-modulation mode) showed that the doublet for C-6-OH at δ_C 72.41 ppm disappeared and a doublet for C-6-Cl at δ_C 56.95 ppm appeared.

Chloro-substituted ester **4** was obtained by the action of chloroacetyl chloride on ketol **1** under reflux in anhydrous $CHCl_3$. The yield of the 6-chloroacetoxy derivative was 86%. The structure of **4** was confirmed by an x-ray crystal structure analysis (XSA) (Fig. 1).

The ^{13}C NMR spectrum (J-modulation mode) of **4** displayed a weak-field shift of the doublet for C-6-O to δ_C 77.13 ppm, the appearance of a triplet for CH_2Cl at δ_C 40.78 ppm, and a singlet for OCO at δ_C 166.14 ppm.

The halogen was introduced into the diterpene part of the molecule *in situ* in four steps. First, ketol **2** was refluxed in acetic anhydride to protect the hydroxy group. Then, oxalyl chloride reacted with acetate **5** to give acid chloride **6**, treatment of which in CH_2Cl_2 with diazomethane in Et_2O at –5°C gave diazoketone **7**, which was treated without isolation with HBr solution (40%). The yield of bromoketone **8** was 86% in the last step.

Formation of **8** was proved using NMR spectroscopy and elemental analysis. Thus, the ^{13}C NMR spectrum (J-modulation mode) showed that the singlet for the carboxylic C atom disappeared and two new resonances, a singlet for a CO group at δ_C 206.53 ppm and a triplet for CH_2Br at δ_C 31.99 ppm, appeared.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were taken in 10–20% solutions in deuterated solvent with solvent resonance or $SiMe_4$ as internal standard on Bruker AM-300 (300.13 and 75.47 MHz) and Avance III 500 (500.13 and 125.75 MHz) instruments. Chemical shifts are given on the δ-scale. IR spectra were recorded in a thin layer or nujol suspension on a Shimadzu instrument. Elemental analysis was performed on a Euro EA 3000 analyzer. Optical rotation angles were measured on a PerkinElmer 341 polarimeter (λ 589 nm) at 20°C.

The XSA was carried out on a Bruker Smart Apex2 CCD diffractometer at 100 K (λ Mo Kα-radiation, $2\theta_{max} = 64°$). The dataset of measured intensities was processed using the SAINT and SADABS programs included in the Apex2 program set [11]. The structure was solved by direct methods and refined by anisotropic full-matrix least-squares methods for non-hydrogen atoms over F^2_{hkl}. All calculations were performed on an IBM PC using the SHELXTL program set [12].

The course of reactions was monitored by TLC on Sorbfil PTSKh-AF-A plates. Compounds were detected by spraying plates with H_2SO_4 solution (5%) with subsequent heating to 100–120°C. The eluents were solvent systems $CHCl_3$:MeOH (50:1, 10:1, 5:1). Column chromatography was carried out over standard silica gel 60 (0.063–0.2 mm, 70–230 mesh) (Macherey-Nagel, Germany). Analytical data of all synthesized compounds agreed with those calculated.

Framework quinopimaric acid derivatives **1** and **2** were synthesized as before [13]. The physical and spectral characteristics of **1** and **2** corresponded with the literature data.

Methyl (7*S*,8*S*,16*R*,20*R*)-16,20-Dimethyl-4-isopropyl-6-chloro-9-oxoheptacyclo[10.8.0.0^{3,7}.0^{4,11}.0^{5,10}.0^{8,12}.0^{15,20}] eicosane-16-carboxylate (3). $C_{27}H_{37}ClO_3$. Compound **1** (0.7 g, 1.7 mmol) in anhydrous Py (23 mL) at 0°C was stirred, treated dropwise with $POCl_3$ (1.1 mL, 12 mmol) and stirred at 0°C for 0.5 h and at room temperature for 7 h. The solvent was distilled at reduced pressure. The residue was treated with $CHCl_3$ (20 mL) and washed with HCl solution (1%) and H_2O. The organic phase was dried over Na_2SO_4. The solvent was removed at reduced pressure to afford **3** (0.72 g, 99.9%), mp 114–118°C, $[\alpha]_D^{20}$ +66° (*c* 2.0; $CHCl_3$). IR spectrum (ν, cm^{-1}): 1726, 1460, 1377, 1244, 1194, 1142, 1103, 1053, 974, 754. ^{13}C NMR spectrum ($CDCl_3$ + CD_3OD, δ, ppm): 15.01 (q, Me), 16.25 (q, Me), 16.66 (q, Me), 16.85 (t, C-18), 17.15 (t, C-14), 18.25 (q, Me), 20.81 (t, C-2), 26.31 (d, C-21), 33.29 (t, C-13), 34.17 (d, C-10), 36.40 (s, C-20), 37.27 (t, C-17), 37.60 (t, C-19), 38.33 (s, C-12), 38.80 (d, C-5), 41.45 (d, C-7), 42.35 (d, C-11), 44.83 (d, C-3), 45.27 (d, C-15), 46.86 (s, C-16), 49.30 (d, C-1), 50.61 (s, C-4), 51.66 (q, COO<u>Me</u>), 56.95 (d, C-6), 57.05 (d, C-8), 179.15 (s, COO), 218.45 (s, C=O).

Methyl (16*R*,20*R*)-6-[(2-Chloroacetyl)oxy]-4-isopropyl-16,20-dimethyl-9-oxoheptacyclo [10.8.0.0^{3,7}.0^{4,11}.0^{5,10}.0^{8,12}.0^{15,20}]eicosane-16-carboxylate (4). $C_{29}H_{39}ClO_{5-}$. Methyl ester of **1** (1.0 g, 2.43 mmol) in anhydrous $CHCl_3$ (20 mL) was treated with chloroacetyl chloride (1 mL) and refluxed for 15 h. The solvent was evaporated. The residue was purified by column chromatography over silica gel using $CHCl_3$–MeOH (50:1). Yield 86%, mp 204–205°C ($CHCl_3$), $[\alpha]_D^{20}$ +73° (*c* 2.0; $CHCl_3$). IR spectrum (ν, cm^{-1}): 1738, 1721, 1462, 1375, 1275, 1254, 1165, 1140, 1103, 1028, 988, 785. ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.34 (q, Me), 16.64 (q, Me), 17.07 (q, Me), 17.21 (t, C-18), 17.56 (t, C-14), 18.57 (q, Me), 21.11 (t, C-2), 26.62 (d, C-21), 33.60 (t, C-13), 35.01 (d, C-10), 36.69 (t, C-17), 37.57 (s, C-20), 37.90 (t, C-19), 38.37 (s, C-12), 39.10 (d, C-5), 40.36 (d, C-7), 40.78 (t, CH_2Cl), 42.55 (d, C-11), 43.74 (d, C-3), 45.41 (d, C-15), 47.10 (s, C-16), 49.57 (d, C-1), 50.77 (s, C-4), 51.94 (q, COO<u>Me</u>), 57.10 (d, C-8), 77.13 (d, C-6), 166.14 (s, OCO), 178.99 (s, COO), 216.31 (s, C=O). A CIF file containing complete information on the structure was deposited in the CCDC (No. 948487) (http://www.ccdc.cam.ac.uk/deposit).

(7*S*,8*S*,16*R*,20*R*)-6-(Acetyloxy)-4-isopropyl-16,20-dimethyl-9-oxoheptacyclo [10.8.0.0^{3,7}.0^{4,11}.0^{5,10}.0^{8,12}.0^{15,20}]eicosane-16-carboxylate (5). $C_{29}H_{40}O_5$. A mixture of **2** (1.3 g, 3.15 mmol) in Ac_2O (6 mL) was refluxed for 1 h and evaporated to dryness. The residue was dissolved in $CHCl_3$ (30 mL), washed with H_2O (2 × 10 mL), and dried over Na_2SO_4. The solvent was removed at reduced pressure to afford the acetate (1.36 g), quantitative yield, mp 68–69°C, $[\alpha]_D^{20}$ +65° (*c* 2.1; $CHCl_3$). IR spectrum (ν, cm^{-1}): 1747, 1732, 1462, 1377, 1236, 1194, 1142, 1103, 1051, 752. ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.16 (q, Me), 16.30 (q, Me), 16.76 (q, Me), 16.81 (t, C-18), 17.49 (t, C-14), 18.41 (q, Me), 20.94 (q, <u>Me</u>CO), 21.01 (t, C-2), 26.43 (d, C-21), 33.48 (t, C-13), 34.86 (d, C-10), 35.69 (s, C-20), 37.37 (t, C-17), 37.57 (t, C-19), 38.24 (s, C-12), 38.91 (d, C-5), 40.36 (d, C-7), 42.37 (d, C-11), 43.64 (d, C-3), 45.44 (d, C-15), 47.94 (s, C-16), 48.94 (d, C-1), 50.53 (s, C-4), 57.05 (d, C-8), 75.02 (d, C-6), 169.78 (s, <u>C</u>OMe), 174.00 (s, COO), 216.46 (s, C=O).

(16*R*,20*R*)-16-(2-Diazoacetyl)-6-(acetyloxy)-4-isopropyl-16,20-dimethyl-9-oxoheptacyclo[10.8.0.0^{3,7}.0^{4,11}.0^{5,10}.0^{8,12}.0^{15,20}]eicosane (7). $C_{29}H_{38}N_2O_4$. A suspension of **5** (0.55 g, 1.25 mmol) in

anhydrous CH_2Cl_2 (20 mL) was stirred under Ar and treated with oxalyl chloride (1 mL) and DMF (5 drops). When the reaction was finished, the solvent and excess of oxalyl chloride were evaporated in vacuo (the bath temperature should not exceed 30°C). Acid chloride **6** was used without further purification. A solution of **6** in anhydrous $CHCl_3$ (20 mL) was added dropwise to a stirred and cooled (–5°C) solution of diazomethane in Et_2O that was prepared from nitrosomethylurea (4.5 g) and stirred at –5°C for 0.5 h. The solvent was distilled at reduced pressure. The yield was quantitative, mp 70–73°C. IR spectrum (ν, cm^{-1}): 2100 (CN_2), 1798 (CO), 1757 (CO), 1724 (CO).

(16*R*,20*R*)-6-(Acetyloxy)-16-(2-bromoacetyl)-4-isopropyl-16,20-dimethyl-9-oxoheptacyclo [10.8.0.0^{3,7}.0^{4,11}.0^{5,10}.0^{8,12}.0^{15,20}]eicosane (8). $C_{29}H_{39}BrO_4$. A solution of **7** (0.64 g, 1.34 mmol) in CH_2Cl_2 (10 mL) was stirred and treated dropwise with HBr solution (40%, 1.34 mL). When gas evolution stopped, the solution was stirred for 1 h and diluted with $CHCl_3$ (30 mL). The organic layer was separated, washed with $NaHCO_3$ solution (5%, 10 mL), and evaporated. The residue was purified using column chromatography over silica gel and $CHCl_3$:MeOH (50:1). Yield 86%, mp 69–70°C, $[\alpha]_D^{20}$ +53° (*c* 1.1; $CHCl_3$). IR spectrum (ν, cm^{-1}): 1744, 1715, 1462, 1377, 1236, 1043, 752. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 0.71 (1H, m, H-18e), 0.72 (3H, d, ^{3}J = 6.4, Me), 0.86 (3H, s, 20-Me), 0.88 (2H, m, H-2e, H-19e), 1.05 (1H, m, H-13e), 1.15 (3H, d, ^{3}J = 6.4, Me), 1.16 (3H, s, 16-Me), 1.18 (1H, m, H-13a), 1.30 (1H, m, H-2a), 1.49 (2H, m, H-14e, H-18a), 1.60 (2H, m, H-1, H-19a), 1.72 (2H, m, H-8, H-14a), 1.90 (3H, s, COMe), 1.92 (1H, m, H-21), 2.18 (1H, s, H-10), 2.38 (1H, m, H-11), 2.50 (2H, s, H-3, H-5), 2.62 (1H, d, J = 8.8, H-7), 4.10 (2H, dd, J = 17.7, 13.3, CH_2Br), 4.70 (1H, s, H-6). ^{13}C NMR ($CDCl_3$, δ, ppm): 15.28 (q, Me), 16.22 (q, Me), 16.74 (q, Me), 16.89 (t, C-18), 17.48 (t, C-14), 18.39 (q, Me), 20.94 (q, MeCO), 21.06 (t, C-2), 26.38 (d, C-21), 31.99 (t, CH_2Br), 33.36 (t, C-13), 34.81 (d, C-10), 36.04 (s, C-20), 37.46 (t, C-17), 37.54 (t, C-19), 38.19 (s, C-12), 38.91 (d, C-5), 40.29 (d, C-7), 42.33 (d, C-11), 43.57 (d, C-3), 45.51 (d, C-15), 48.65 (d, C-1), 50.48 (s, C-16), 52.39 (s, C-4), 57.01 (d, C-8), 74.95 (d, C-6), 169.71 (s, COMe), 206.53 (s, $COCH_2$), 216.37 (s, C=O).

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