Synthesis of C-29-phosphonium derivatives of 3,28-diacetoxylup-20(29)-en-30-oic acid*

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3β,28-Diacetoxylup-20(29)-en-30-oic acid (obtained *via* oxidation of betulin diacetate) enters the addition reaction with P—H-phosphonium salts (triarylphosphonium trifluoroacetates) under mild conditions to afford β-carboxyalkylphosphonium salts. Structure and composition of the resulting compounds were confirmed by NMR and IR spectroscopy, mass spectrometry, and elemental analysis.

Key words: triterpenoids, betulin, triphenylphosphine, phosphonium salts, addition reaction.

Introduction of phosphorus-containing substituents into the structures of practically important substances is widely used to improve their solubility in water and physiological media[1], to increase the current level of their biological activity and to impart them new activities[2,3], to provide fire retardancy to materials[4], *etc*. As demonstrated by numerous examples, delocalized lipophilic cations, among which phosphonium ones[5,6] occupy a special place, display membranotropism and enable mitochondria-targeted drug delivery. Dysfunctions of mitochondria, the main functions of which include supplying cells with energy, control of the reactive oxygen species and launching of the programed cell death,[7] to a greater or lesser extent contribute to various neurodegenerative disorders, cardiovascular diseases, diabetes, obesity, malignant tumors, *etc*.[8—10] that make mitochondria the most important target in therapy of the above diseases. The presence of a positive charge delocalized over aromatic or heteroaromatic rings promotes the penetration of phosphonium conjugates across cellular and mitochondrial lipid membranes and the formation of a significant concentration gradient in the cytosol—mitochondrial matrix system.[11—13] The latter effect is particularly manifested in tumor cells and cardiomyocytes enabling to reach high selectivity in drug delivery exactly to mitochondria of these cells thereby lowering the required therapeutic concentration.[5,6,14—17] There are numerous examples where functionalization of various natural and synthetic compounds with triphenylphosphonium moiety improved their pharmacological properties.[5,18—20] Such an approach has also been widely applied to derivatives of lupane-, oleanane- and ursane-type triterpenoids representing available biologically active compounds isolated from plant raw materials. Among lupane derivatives, phosphonium conjugates of betulin[21—25], betulinic[26—28] and betulonic[28,29] acids and their dihydro derivatives[30] were obtained. Most often, triterpenoid scaffold is modified at the ring A (positions C(2) and C(3)), as well as on positions C(28) and C(19) of isopropylene group.[21—32]

In the present study, a convenient procedure for the preparation of triarylphosphonium derivatives of lupane-type triterpenoids functionalized at the position C(29) has been proposed (Scheme 1). This approach is based on the reaction of stable P—H-phosphonium salts[29,33,34] with diacetoxylup-20(29)-en-30-oic acid **3** as a Michael acceptor, under mild conditions. Using P—H-phosphonium salts obtainable from triarylphosphines and strong protolytic acids makes it possible to retain triterpenoid lupane scaffold, which is labile in acidic media.

To synthesize acid **3**, a two-step procedure has been elaborated based on initial allylic oxidation of diacetoxybetulin (**1**) with selenium dioxide in aqueous solution followed by complete oxidation of the resulting diacetoxylup-20(29)-en-30-al **2** with sodium chlorite. The total yield of acid **3** related to the starting diacetoxybetulin **1** is 55—60%. Unsaturated acid **3** reacts with P—H- phosphonium salts (as exemplified by triphenyl- and tri(*m*-tolyl)-phosphonium trifluoroacetates) under mild conditions to

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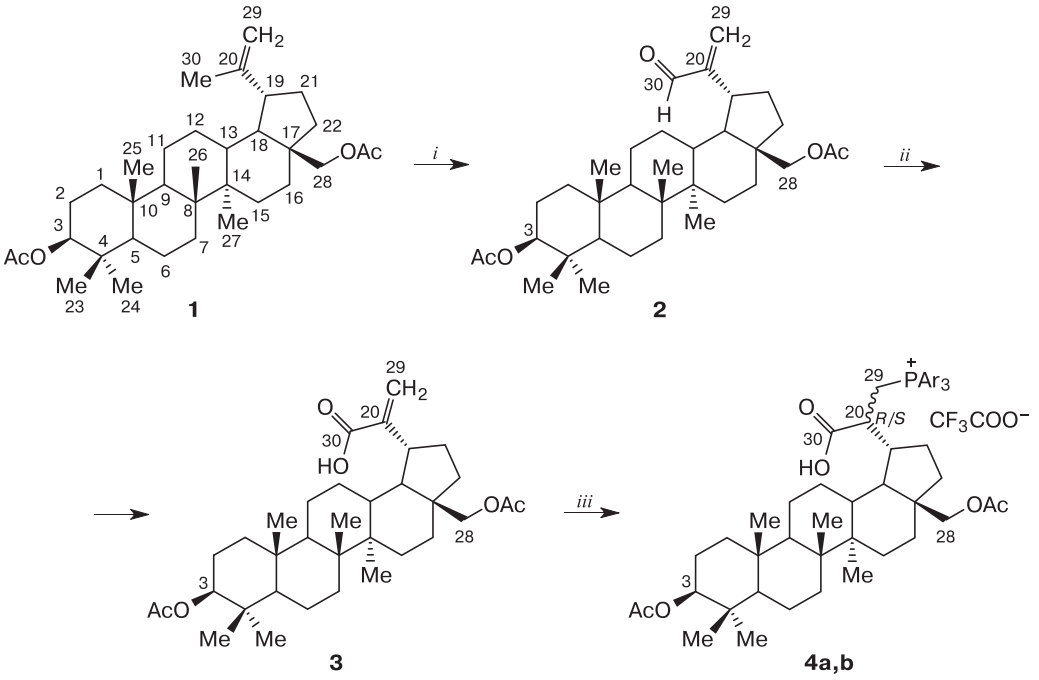
Scheme 1



4: Ar = Ph (**a**), 3-MeC$_6$H$_4$ (**b**)

Reagents and conditions: *i*. SeO_2, EtOH, H_2O, Δ; *ii*. $NaClO_2$, KH_2PO_4, H_2O_2, Bu^{t}OH, H_2O; *iii*. $Ar_3HP^+CF_3COO^-$, CH_2Cl_2.

afford derivatives **4a,b** as mixtures of epimeric forms in a 1.6 : 1 ratio. The formation of diastereomers in this case is due to appearance of an additional stereogenic center at the C(20) carbon atom.

In the ^{31}P-{^1H} NMR spectra, phosphonium salts **4a,b** are characterized by signals in the range of δ_P 23—24. In their ^{13}C—{^1H} NMR spectra, there are signals of the C(29) carbon atom in the range of δ_C 24—25 appearing as a doublet with $^1J_{P,C}$ = 51.0 Hz, that along with the shape (doublet) of the signals of the P—C_{Ar} carbon atom and the value of $^1J_{P,C}$ = 86.0 Hz confirm the phosphonium nature of the obtained compounds. Structures of all compounds were additionally confirmed using two-dimensional homo- (^1H—^1H COSY) and heteronuclear (^{13}C—^1H HSQC, HMBC) correlation NMR experiments.

As reported in the literature, triphenylposphine can react with α,β-unsaturated carboxylic acids to give betaines.[35,36] In the course of additional experiments we have found that diacetoxylup-20(29)-en-30-oic acid **3** hardly entered the reaction with triphenylphosphine in the absence of strong acids. Hence, prolonged stirring of the mixture of acid **3** with triphenylphosphine provided less than 8% of phospho betaine (according to the ^{31}P—{^1H} NMR data of the reaction mixture).

To summarize, the present study proposes a convenient introduction of triarylphosphonium moiety into lupane-type triterpenoids based on the reaction of diacetoxylup-20(29)-en-30-oic acid, a Michael acceptor, with P—H-phosphonium salts. It was shown that the latter compounds do not promote isomerization of the triterpenoid lupane scaffold.

Experimental

NMR spectra were recorded on a Bruker Avance-400 (^1H, 400 MHz; ^{13}C—{^1H}, 100.6 MHz; ^{31}P—{^1H}, 162.0 MHz) spectrometer at 25 °C. IR-spectra were obtained on a Bruker Tensor 27 apparatus for the sample pellets in KBr. MALDI mass spectra were recorded on a Bruker MALDI-TOF Ultraflex III using 2,5-dihydroxybenzoic acid matrix. Melting points were determined on a Boetius hot-stage. Elemental analysis was performed on a EuroEA 3028-HT-OM Eurovector S.p.A high temperature CHNS-O-analyzer. Compounds were purified and separated using Sepacore X50 (Büchi) flash system. Solvents were purified and dried according to the standard procedures. Betulin diacetate **1** was obtained according to a known procedure.[37]

3β,28-Diacetoxylup-20(29)-en-30-al (2). A mixture of compound **1** (0.5 g, 0.95 mmol) and SeO_2 (0.26 g, 2.37 mmol), ethanol (25 mL), and water (3 mL) was stirred at 100 °C for 6 h. The resulting solution was decanted from the precipitated elemental selenium. Alcohol was evaporated *in vacuo* (15 Torr), the residue was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na_2SO_4, and then evaporated to dryness. The yellow residue was purified by column chromatography using petroleum ether—ethyl acetate mixture

(5 : 1). Yield 0.30 g (58%), m.p. 139—141 °C (chloroform). IR, ν/cm^{-1}: 2946, 2873, 1737 (C=O), 1693 (CH=O), 1636 (=CH_2), 1458, 1391, 1366, 1245 (CH_3CO), 1031, 979, 943, 901 (=CH_2), 753. ^{1}H NMR ($CDCl_3$), δ: 0.72—2.25 (23 H), 0.76 (d, 1 H, H(5), $^3J_{H,H}$ = 9.4 Hz); 0.82 (br.s, 9 H, H(23)—H(25)); 0.93 (3 H, H(27)); 1.01 (3 H, H(26)); 2.04 (s, 3 H, C$\underline{H}_3$C(O)OC(3)); 2.07 (s, 3 H, C$\underline{H}_3$C(O)OC(28)); 2.80 (m, 1 H, H(19), $^3J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 4.3—4.5 Hz); 3.86 (d, 1 H, H_A(28), $^2J_{H,H}$ = 11.0 Hz); 4.27 (d, 1 H, H_B(28), $^2J_{H,H}$ = 11.0 Hz); 4.45 (dd, 1 H, H(3), $^3J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 5.5 Hz); 5.93 (s, 1 H, H_A(29)); 6.28 (s, 1 H, H_B(29)); 9.50 (s, 1 H, H(30)). ^{13}C—{^{1}H} NMR ($CDCl_3$), δ_C: 194.73 (C(30)), 171.48 ($CH_3\underline{C}$(O)OC(28)), 171.02 ($CH_3\underline{C}$(O)-OC(3)), 156.46 (br.s, C(20)), 133.45 (br.s, C(29)), 80.84 (C(3)), 62.38 (C(28)), 55.32 (C(5)), 51.35 (br.s, C(18)), 50.04 (C(9)), 46.55 (C(17)), 42.54 (C(14)), 40.79 (C(8)), 38.33 (C(1)), 37.76 (C(4)), 37.18 (C(13)), 36.99 (C(10)), 36.90—37.10 (br.s, C(19), overlapped with the signal of C(10)), 34.46 (C(22)), 34.07 (C(7)), 31.98 (br.s, C(21)), 29.69 (C(16)), 27.93 (C(23)), 27.42 (C(12)), 26.94 (C(15)), 23.64 (C(2)), 21.32 ($\underline{C}H_3$C(O)OC(3)), 21.04 ($\underline{C}H_3$C(O)OC(28)), 20.77 (C(11)), 18.13 (C(6)), 16.49 (C(24)), 16.10 (C(25)), 15.97 (C(26)), 14.57 (C(27)). Found (%): C, 75.44; H, 9.78. $C_{34}H_{52}O_5$. Calculated (%): C, 75.52; H, 9.69.

3β,28-Diacetoxylup-20(29)-en-30-oic acid (3). Enal **2** (0.3 g, 0.55 mmol) was dissolved in *tert*-butyl alcohol (15 mL). To this solution, 15% H_2O_2 (10 mL), 15 mL of a solution of KH_2PO_4 (1.5 g, 11.02 mmol) in water was added followed by $NaClO_2$ (0.20 g, 2.22 mmol). After stirring for 8 h, *tert*-butyl alcohol was distilled *in vacuo*. To the residue, saturated NH_4Cl solution (100 mL) was added and the mixture was extracted with ethyl acetate (3×30 mL). The organic layer was washed with water, dried over Na_2SO_4, evaporated to dryness *in vacuo* (15 Torr). Yield 0.29 g (95%), m.p. 233—235 °C (*tert*-butyl alcohol). IR, ν/cm^{-1}: 3448 (OH), 2947, 2874, 1737 (C=O), 1716 (COOH), 1625 (=CH_2), 1459, 1391, 1367, 1245 (CH_3CO), 1031, 979, 945, 902 (=CH_2), 750. ^{1}H NMR (CD_3OD), δ: 0.73—2.26 (23 H); 0.77 (d, 1 H, H(5), $^3J_{H,H}$ = 9.7 Hz); 0.84 (br.s, 9 H, H(23)—H(25)); 0.95 (3 H, H(27)); 1.03 (3 H, H(26)); 2.04 (s, 3 H, C$\underline{H}_3$C(O)-OC(3)); 2.08 (s, 3 H, C$\underline{H}_3$C(O)OC(28)); 2.78 (m, 1 H, H(19), $^3J_{H,H}$ = 11.3 Hz, $^3J_{H,H}$ = 5.5 Hz); 3.86 (d, 1 H, H_A(28), $^2J_{H,H}$ = 11.0 Hz); 4.27 (d, 1 H, H_B(28), $^2J_{H,H}$ = 11.0 Hz); 4.46 (dd, 1 H, H(3), $^3J_{H,H}$ = 10.2 Hz, $^3J_{H,H}$ = 5.6 Hz); 5.69 (s, 1 H, H_A(29)); 6.24 (s, 1 H, H_B(29)). ^{13}C—{^{1}H} NMR for compound **4** (CD_3OD), δ: 173.27 ($CH_3\underline{C}$(O)OC(28)), 172.85 ($CH_3\underline{C}$(O) OC(3)), 170.59 (C(30)), 148.50 (br.s, C(20)), 124.07 (br.s, C(29)), 82.43 (C(3)), 63.59 (C(28)), 56.74 (C(5)), 52.18 (br.s, C(18)), 51.49 (C(9), 47.80 (C(17)), 43.78 (C(14)), 42.06 (C(8)), 39.51 (C(1)), 38.84 (C(4)), 38.64 (C(13)), 38.22 (C(10)), 35.31 (C(7)), 35.17 (C(22)), 33.20 (br.s, C(21)), 30.81 (C(16)), 28.61 (C(12)), 28.46 (C(23)), 28.19 (C(15)), 24.66 (C(2)), 22.00 (C(11)), 21.15 ($\underline{C}H_3$C(O)OC(3)), 20.84 ($\underline{C}H_3$C(O)OC(28)), 19.26 (C(6)), 16.98 (C(24)), 16.69 (C(25)), 16.53 (C(26)), 15.18 (C(27)). Found (%): C, 73.19; H, 9.32. $C_{34}H_{52}O_6$. Calculated (%): C, 73.35; H, 9.41.

Synthesis of phosphonium salts 4a,b (general procedure). To a solution of a phosphine (0.36 mmol) in CH_2Cl_2 (2 mL), trifluoroacetic acid (82 μL, 1.08 mmol) was added dropwise, the resulting mixture was stirred for 1 h under Ar atmosphere. Then, a solution of compound **3** (0.1 g, 0.18 mmol) in CH_2Cl_2 (8 mL) was added to the reaction mixture. The resulting solution was stirred under Ar atmosphere for 6 h. The solvent was distilled *in vacuo* (15 Torr), the residue was dissolved in $CHCl_3$ (1 mL) and precipitated with petroleum ether. The solid was filtered off and dried *in vacuo* (15 Torr).

[3β,28-Diacetoxy-30-hydroxy-30-oxolup-29-yl]triphenylphosphonium trifluoroacetate (4a). Yield 0.16 g (95%), diastereomer ratio 1.6 : 1. IR, ν/cm^{-1}: 3448 (OH), 3065, 2949, 2874, 1729 (C=O), 1686 (COOH), 1589, 1485, 1440, 1392, 1250 (CH_3CO), 1197, 1137, 1112, 1030, 998, 979, 945, 902, 798, 747, 722, 691, 608, 541, 506. ^{1}H NMR for epimer **4′a** (CD_3OD), δ: 0.73—2.22 (m, 24 H); 0.86 (br.s, H(27)); 0.87 (br.s), 0.88 (br.s), 0.90 (br.s, 9 H, H(23)—H(25)); 1.05 (br.s, 3 H, H(26)); 2.03 (br.s, 3 H, C$\underline{H}_3$C(O)OC(3)); 2.05 (br.s, 3 H, C$\underline{H}_3$C(O)OC(28)); 2.16 (m, 1 H, H(19)); 2.98 (m, 1 H, H(20)); 3.53 (dd, 1 H, H_A(29), $^3J_{H,H}$ = 14.9 Hz, $^2J_{P,H}$ = 14.9 Hz); 3.76 (br.d, 1 H, H_A(28), $^2J_{H,H}$ = 11.1 Hz); 3.93 (m, 1 H, H_B(29), overlapped with a signal of H_B(29) of epimer **4″a**); 4.33 (d, 1 H, H_B(28), $^2J_{H,H}$ = 11.0 Hz, overlapped with a signal of H_B(28) of epimer **4″a**); 4.44 (m, 1 H, H(3), overlapped with a signal of H(3) of epimer **4″a**); 7.70—7.96 (m, Ph). ^{13}C—{^{1}H} NMR for epimer **4′a** (CD_3OD), δ: 174.58 (C(30)); 173.17 ($CH_3\underline{C}$(O)OC(28)); 172.85 ($CH_3\underline{C}$(O)OC(3)); 162.05 (q, $CF_3\underline{C}OO$, $^2J_{F,C}$ = 32.1 Hz); 136.45 (*p*-C_{Ar}), 134.98 (d, *o*-C_{Ar}, $^2J_{P,C}$ = 10.0 Hz); 131.50 (d, *m*-CAr, $^3J_{P,C}$ = 12.6 Hz); 119.50 (d, *ipso*-C_{Ar}, $^1J_{P,C}$ = 86.3 Hz); 117.77 (q, $\underline{C}F_3COO$, $^1J_{F,C}$ = 292.0 Hz); 82.36 (C(3)), 63.01 (C(28)), 56.62 (C(5)), 51.08 (C(9)), 49.99 (C(18)), 47.51 (C(17)), 45.79 (d, C(19), $^3J_{P,C}$ = 11.9 Hz); 43.98 (C(14)), 43.09 (d, C(20), overlapped with a signal of C(20) of epimer **4″a**); 42.05 (C(8)), 39.46 (C(1)), 38.81 (br.s, C(4)); 38.29 (C(13)); 38.12 (br.s, C(10), overlapped with signals of C(10) and C(13) of epimer **4″a**); 35.24 (C(22)), 34.99 (C(7)), 30.81 (C(16)), 28.45 (C(23)), 27.91 (C(12)), 27.87 (C(15)), 25.83 (d, C(29), $^1J_{P,C}$ = 51.2 Hz); 24.63 (C(2)), 23.70 (C(21)), 21.77 (C(11)), 21.17 ($\underline{C}H_3$C(O)OC(3)), 20.79 ($\underline{C}H_3$C(O) OC(28)), 19.18 (C(6)), 16.98 (C(24)), 16.61 (C(25)), 16.46 (C(26)), 14.99 (C(27)). ^{31}P—{^{1}H}NMR for epimer **4′a** (CD_3OD), δ_P: 23.7.

^{1}H NMR for epimer **4″a** (CD_3OD), δ: 0.73—2.22 (m, 24 H); 0.86 (br.s, H(27)); 0.87 (br.s), 0.88 (br.s), 0.90 (br.s, 9 H, H(23)—H(25)); 1.05 (br.s, 3 H, H(26)); 2.03 (br.s, 3 H, C$\underline{H}_3$C(O) OC(3)); 2.05 (br.s, 3 H, C$\underline{H}_3$C(O)OC(28)); 2.16 (m, 1 H, H(19)); 2.98 (br.m, 1 H, H(20)); 3.32 (m, 1 H, H_A(29), overlapped with a solvent signal); 3.76 (br.d, 1 H, H_A(28), $^2J_{H,H}$ = 11.1 Hz); 3.93 (m, 1 H, HB(29), overlapped with a signal of H_B(29) of epimer **4′a**), 4.33 (d, 1 H, H_B(28), $^2J_{H,H}$ = 11.0 Hz, overlapped with a signal of H_B(28) of epimer **4a**), 4.47 (m, 1 H, H(3), overlapped with a signal of H(3) of epimer **4′a**); 7.70—7.96 (m, Ph). ^{13}C—{^{1}H} NMR for epimer **4″a** (CD_3OD), δ: 175.55 (C(30)); 173.05 ($CH_3\underline{C}$(O)OC(28)); 172.94 ($CH_3\underline{C}$(O)OC(3)); 162.05 (q, $CF_3\underline{C}OO$, $^2J_{F,C}$ = 32.1 Hz); 136.45 (s, *p*-C);135.32 (d, *o*-C, $^2J_{P,C}$ = 9.9 Hz); 131.54 (d, *m*-C, $^3J_{P,C}$ = 12.6 Hz); 119.45 (d, *ipso*-C, $^1J_{P,C}$ = 86.3 Hz); 117.77 (q, $\underline{C}F_3COO$, $^1J_{F,C}$ = 292.0 Hz); 82.39 (C(3)); 63.15 (C(28)); 56.65 (C(5)); 51.00 (C(9)); 49.90 (C(18)); 47.75 (C(17)); 45.79 (d, C(19), $^3J_{P,C}$ = 11.9 Hz); 44.13 (C(14)); 43.20 (d, C(20), overlapped with a signal of C(20) of epimer **4′a**); 41.94 (C(8)); 39.67 (C(1)); 38.81 (C(4)); 38.14 (br.s, C(10), overlapped with signals of C(10) of epimer **4′a** and C(13) of epimer **4″a**); 38.12(br.s, C(13), overlapped with signals of C(10) and C(13) of epimer **4′a**); 35.24 (C(22)); 35.06 (C(7)); 30.28 (C(16)); 28.45 (C(23)); 27.81 (br.s, C(12), overlapped with a signal of C(15) of epimer **4″a**); 27.81 (br.s, C(15), overlapped with a signal of C(12) of epimer **4″a**); 25.83 (d, C(29), $^1J_{P,C}$ = 51.2 Hz); 24.63 (C(2)), 23.70 (C(21)), 21.69 (C(11)), 21.17 ($\underline{C}H_3$C(O)OC(3)), 20.79 ($\underline{C}H_3$C(O)OC(28)), 19.18 (C(6)),

16.98 (C(24)), 16.53 (C(25)), 16.41 (C(26)), 15.53 (C(27)). ^{31}P—{^{1}H} NMR for epimer **4″a** ($CDCl_3$), δ: 24.5. MALDI MS, *m/z*: 819.8 $[M - CF_3COO]^+$.

[3β,28-Diacetoxy-30-hydroxy-30-oxolup-29-yl]tris(3-methylphenyl)phosphonium trifluoroacetate (4b). Yield 0.16 g (91%), diastereomer ratio 1.6 : 1. IR, ν/cm^{-1}: 3394 (OH), 2947, 2873, 1730 (C=O), 1686 (COOH), 1596, 1482, 1457, 1391, 1248 (CH_3CO), 1202, 1133, 1030, 996, 979, 945, 901, 874, 800, 782, 756, 719, 690, 608, 556, 461. ^{1}H NMR for epimer **4′b** (CD_3OD), δ: 0.73—2.23 (m, 24 H); 0.86 (s, 3 H, H(27)); 0.88 (br.s), 0.88 (br.s), 0.91 (br.s, 9 H, H(23)—H(25)); 1.06 (s, 3 H, H(26)); 2.03 (br.s, 3 H, $C\underline{H}_3C(O)OC(3)$); 2.05 (s, 3 H, $C\underline{H}_3C(O)OC(28)$); 2.14 (m, 1 H, H(19)); 2.47 (s, 3 H, $C_6H_4C\underline{H}_3$); 2.94 (m, 1 H, H(20)); 3.46 (dd, 1 H, $H_A(29)$, $^{3}J_{H,H}$ = 14.9 Hz, $^{2}J_{P,H}$ = 14.9 Hz); 3.75 (br.d, 1 H, $H_A(28)$, $^{2}J_{H,H}$ = 11.0 Hz); 3.91 (m, 1 H, $H_B(29)$, overlapped with a signal of $H_B(29)$ of epimer **4″b**); 4.33 (br.d, 1 H, $H_B(28)$, $^{2}J_{H,H}$ = 11.3 Hz); 4.44 (m, 1 H, H(3), overlapped with a signal of H(3) of epimer **4″b**); 7.50—7.76 (m, Ar). ^{13}C—{^{1}H} NMR for epimer **4′b** (CD_3OD), δ: 174.68 (C(30)), 173.17 ($CH_3\underline{C}(O)OC(28)$), 172.84 ($CH_3\underline{C}(O)OC(3)$), 162.27 (q, $CF_3\underline{C}OO$, $^{2}J_{F,C}$ = 34.6 Hz); 142.10 (d, *m*-$C_{Ar}(2)$, $^{3}J_{P,C}$ = = 12.6 Hz); 137.11 (*p*-C_{Ar}); 134.90 (d, *o*-$C_{Ar}(2)$, $^{2}J_{P,C}$ = 9.9 Hz); 132.14 (d, C_{Ar} (1), $^{2}J_{PC}$ = 9.9 Hz); 131.34 (d, *m*-$C_{Ar}(1)$, $^{3}J_{P,C}$ = 13.6 Hz); 119.50 (br.d, *ipso*-C_{Ar}, $^{1}J_{P,C}$ = 85.6 Hz); 117.91 (q, $\underline{C}F_3COO$, $^{1}J_{F,C}$ = 291.1 Hz); 82.34 (C(3)), 62.99 (C(28)), 56.60 (C(5)), 51.10 (C(9)), 49.99 (C(18)), 47.50 (C(17)), 45.79 (d, C(19), $^{3}J_{P,C}$ = 11.9 Hz); 44.02 (C(14)), 43.08 (d, C(20), overlapped with a signal of C(20) of epimer **4″b**), 42.06 (C(8)), 39.49 (C(1)), 38.81 (C(4)), 38.17 (br.s, C(10), overlapped with signals of C(10) and C(13) of epimer **4″b**), 38.13 (C(13)), 35.25 (C(22)), 35.01 (C(7)), 30.81 (C(16)), 28.44 (C(23)), 27.90 (C(12)), 27.81 (br.s, C(15), overlapped with a signal of C(12) of epimer **4″b**), 25.86 (d, C(29), $^{1}J_{P,C}$ = 51.4 Hz); 24.63 (C(2)), 23.69 (C(21)), 21.93 (C(11)), 21.42 ($C_6H_4\underline{C}H_3$), 21.17 ($\underline{C}H_3C(O)$-OC(3)), 20.79 ($\underline{C}H_3C(O)OC(28)$), 19.18 (C(6)), 16.99 (C(24)), 16.62 (C(25)), 16.46 (C(26)), 15.01 (C(27)). ^{31}P—{^{1}H} NMR for epimer **4′b** (CD_3OD), δ: 23.5.

^{1}H NMR for epimer **4″b** (CD_3OD), δ: 0.73—2.23 (m, 24 H); 0.83 (s, 3 H, H(27)); 0.88 (br.s), 0.88 (br.s); 0.91 (br.s, 9 H, H(23)—H(25)); 1.04 (s, 3 H, H(26)); 2.03 (br.s, 3 H, $C\underline{H}_3C(O)$-OC(3)); 2.05 (s, 3 H, $C\underline{H}_3C(O)OC(28)$); 2.14 (m, 1 H, H(19)); 2.46 (s, 3 H, $C_6H_4C\underline{H}_3$); 2.94 (m, 1 H, H(20)); 3.18 (m, 1 H, $H_A(29)$, $^{3}J_{H,H}$ = 14.8 Hz, $^{2}J_{P,H}$ = 14.8 Hz); 3.75 (br.d, 1 H, $H_A(28)$, $^{2}J_{H,H}$ = 11.0 Hz); 3.91 (m, 1 H, $H_B(29)$, overlapped with a signal of $H_B(29)$ of epimer **4′b**), 4.33 (br.d, 1 H, $H_B(28)$, $^{2}J_{H,H}$ = 11.3 Hz); 4.47 (m, 1 H, H(3), overlapped with a signal of H(3) of epimer **4″b**); 7.50—7.76 (м, Ar). ^{13}C—{^{1}H} NMR for epimer **4″b** (CD_3OD), δ: 175.69 (C(30)); 173.05 ($CH_3\underline{C}(O)$-OC(28)); 172.95 ($CH_3\underline{C}(O)OC(3)$); 162.27 (q, $CF_3\underline{C}OO$, $^{2}J_{F,C}$ = = 34.6 Hz); 142.13 (d, *m*-$C_{Ar}(2)$, $^{3}J_{P,C}$ = 12.5 Hz); 137.14 (*p*-C_{Ar}); 135.25 (d, *o*-$C_{Ar}(2)$, $^{2}J_{P,C}$ = 9.9 Hz); 132.43 (d, *o*-$C_{Ar}(1)$, $^{2}J_{P,C}$ = 9.9 Hz); 131.39 (d, *m*-$C_{Ar}(1)$, $^{3}J_{P,C}$ = 13.3 Hz); 119.50 (br.d, *ipso*-C_{Ar}, $^{1}J_{P,C}$ = 85.6 Hz); 117.91 (q, $\underline{C}F_3COO$, $^{1}J_{F,C}$ = = 291.1 Hz); 82.41 (C(3)), 63.15 (C(28)), 56.75 (C(5)), 51.10 (C(9)), 49.91 (C(18)), 47.67 (C(17)), 45.79 (d, C(19), $^{3}J_{P,C}$ = = 11.9 Hz); 44.02 (C(14)), 43.16 (d, C(20), overlapped with a signal of C(20) of epimer **4′b**); 41.96 (C(8)), 39.75 (C(1)), 38.81 (C(4)), 38.21 (br.s, C(10), overlapped with signals of C(10) of epimer **4′b** and C(13) of epimer **4″b**); 38.17 (br.s, C(13), overlapped with signals of C(10)), 35.25 (C(22)), 35.15 (C(7)), 30.33 (C(16)), 28.44 (C(23)), 27.81 (br.s, C(12), overlapped with a signal of C(15) of epimer **4′b**); 27.76 (C(15)), 25.86 (d, C(29), $^{1}J_{P,C}$ = 51.4 Hz); 24.63 (C(2)), 23.74 (C(21)), 21.76 (C(11)), 21.51 ($C_6H_4\underline{C}H_3$), 21.17 ($\underline{C}H_3C(O)OC(3)$), 20.79 ($\underline{C}H_3C(O)$ OC(28)), 19.18 (C(6)), 16.99 (C(24)), 16.53 (C(25)), 16.40 (C(26)), 15.44 (C(27)). ^{31}P—{^{1}H} NMR for epimer **4″b** (CD_3OD), δ: 24.2. MALDI MS, *m/z*: 861.9 $[M - CF_3COO]^+$.

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References

1. C. Dumontet, M. A. Jordan, *Nat. Rev. Drug Discovery*, 2010, **9**, 790; DOI: 10.1038/nrd3253.
2. S. B. Kendall, *Proc. R. Soc. Med.* 1961, **54(5)**, 406.
3. S. Demkowicz, J. Rachon, M. Da´sko, W. Kozak, *RSC Adv.*, 2016, **6**, 7101; DOI: 10.1039/C5RA25446A.
4. I. van der Veen, J. de Boer, *Chemosphere*, 2012, **88**, 1119; DOI: 10.1016/j.chemosphere.2012.03.067.
5. D. C. Rideout, T. Calogeropoulou, J. S. Jaworski, R. Dagnino, M. R. McCarthy, *Anti-Cancer Drug Design*, 1989, **4**, 265.
6. M. P. Murphy, R. A. J. Smith, *Annu. Rev. Pharmacol. Toxicol.*, 2007, **47**, 629; DOI: 10.1146/annurev.pharmtox.47.120505.105110.
7. S. Fulda, L. Galluzzi, G. Kroemer, *Nat. Rev. Drug Discovery*, 2010, **9**, 447; DOI: 10.1038/nrd3137.
8. M. T. Lin, M. F. Beal, *Nature*, 2006, **443**, 787; DOI: 10.1038/nature05292.
9. M. Brownlee, *Diabetes*, 2005, **54**, 1615; DOI: 10.2337/diabetes.54.6.1615.
10. D. Pathania, M. Millard, N. Neamati, *Adv. Drug Delivery Rev.*, 2009, **61**, 1250; DOI: 10.1016/j.addr.2009.05.010.
11. M. P. Murphy, *Biochim. Biophys. Acta*, 2008, **1777**, 1028; DOI: 10.1016/j.bbabio.2008.03.029.
12. J. S. Modica-Napolitano, J. R. Aprille, *Adv. Drug Delivery Rev.*, 2001, **49**, 63; DOI: 10.1016/s0169-409x(01)00125-9.
13. M. Kurtoglu, T. J. Lampidis, *Mol. Nutr. Food Res.*, 2009, **53**, 68; DOI: 10.1002/mnfr.200700457.
14. T. J. Lampidis, Y. Hasin, M. J. Weiss, L. B. Chen, *Biomed. Pharmacother.*, 1985, **39**, 220.
15. J. Zielonka, J. Joseph, A. Sikora, M. Hardy, O. Ouari, J. Vasquez-Vivar, G. Cheng, M. Lopez, B. Kalyanaraman, *Chem. Rev.*, 2017, **117**, 10043; DOI: 10.1021/acs.chemrev.7b00042.
16. V. J. Adlam, J. C. Harrison, C. M. Porteous, A. M. James, R. A. Smith, M. P. Murphy, I. A. Sammut, *FASEB J.*, 2005, **19**, 1088; DOI: 10.1096/fj.05-3718com.
17. I. M. Fearon, S. P. Faux, *J. Mol. Cell. Cardiol.*, 2009, **47**, 372; DOI: 10.1016/j.yjmcc.2009.05.013.

18. J. A. Jara, V. Castro-Castillo, J. Saavedra-Olavarria, L. Peredo, M. Pavanni, F. Jana, M. E. Letelier, E. Parra, M. I. Becker, A. Morello, U. Kemmerling, J. D. Maya, J. Ferreira, *J. Med. Chem.*, 2014, **57**, 2440; DOI: 10.1021/jm500174v.
19. T. A. Prime, F. H. Blaikie, C. Evans, S. M. Nadtochiy, A. M. James, C. C. Dahm, D. A. Vitturi, R. P. Patel, C. R. Hiley, I. Abakumova, R. Requejo, E. T. Chouchani, T. T. Hurd, J. F. Garvey, C. T. Taylor, P. S. Brookes, R. A. J. Smith, M. P. Murphy, *Proc. Natl. Acad. Sci. U. S. A.*, **106**, 10764; DOI: 10.1073/pnas.0903250106.
20. M. Millard, D. Pathania, Y. Shabaik, L. Taheri, J. Deng, N. Neamati, *PLoS One*, 2010, **5**, e13131; DOI: 10.1371/journal.pone.0013131.
21. O. V. Tsepaeva, A. V. Nemtarev, T. I. Abdullin, L. R. Grigor´eva, E. V. Kuznetsova, R. A. Akhmadishina, L. E. Ziganshina, H. K. Cong, V. F. Mironov, *J. Nat. Prod.*, 2017, **80**, 2232; DOI: 10.1021/acs.jnatprod.7b00105.
22. Pat RF 2665922 (2018); *Byull. Izobr.* [*Bulletin of Inventions*], 2019, 25.
23. Y. Ye, T. Zhang, H. Yuan, D. Li, H. Lou, P. Fan, *J. Med. Chem.*, 2017, **60**, 6353; DOI: 10.1021/acs.jmedchem.7b00679.
24. A. Yu. Spivak, J. Keiser, M. Vargas, R. R. Gubaidullin, D. A. Nedopekina, E. R. Shakurova, R. R. Khalitova, V. N. Odinokov, *Bioorg. Med. Chem.*, 2014, **22**, 6297; DOI: 10.1016/j.bmc.2014.07.014.
25. I. S. Antipin, O. V. Tsepaeva, A. V. Nemtarev, T. I. Abdullin, L. R. Grigor´eva, E. V. Kuznetsova, R. A. Akhmadishina, V. F. Mironov, *Eur. J. Clin. Inv.*, 2018, **48(S1)**, 97; DOI: 10.1111/eci.12926.
26. I. S. Antipin, D. V. Ponomaryov, L. R. Grigor´eva, T. I. Salikhova, R. Ali, T. Dang, O. V. Tsepaeva, A. V. Nemtarev, T. I. Abdullin, V. F. Mironov, *Eur. J. Clin. Inv.*, 2019, **49(S1)**, 61; DOI: 10.1111/eci.13108.
27. A. Yu. Spivak, D. A. Nedopekina, R. R. Khalitova, R. R. Gubaidullin, V. N. Odinokov, Yu. P. Bel´skii, N. V. Bel´skaya, V. A. Khazanov, *Med. Chem. Res.*, 2017, **26**, 518; DOI: 10.1007/s00044-016-1771-z.
28. D. A. Nedopekina, R. R. Gubaidullin, V. N. Odinokov, P. V. Maximchik, B. Zhivotovsky, Yu. P. Bel'skii, V. A. Khazanov, A. V. Manuylova, V. Gogvadze, A. Yu. Spivak, *Med. Chem. Commun.*, 2017, **8**, 1934; DOI: 10.1039/c7md00248c.
29. O. V. Tsepaeva, A. V. Nemtarev, V. F. Mironov, *J. Org. Chem.*, 2017, **53**, 614 [O. V. Tsepaeva, A. V. Nemtarev, V. F. Mironov, *Russ. J. Org. Chem.* (*Engl. Transl.*), 2017, **53**, 621; DOI: 10.1134/S1070428017040212.
30. A. Yu. Spivak, D. A. Nedopekina, E. R. Shakurova, R. R. Khalitova, R. R. Gubaidullin, V. N. Odinokov, Yu. P. Bel´skii, N. V. Bel´skaya, S. A. Stankevich, E. V. Korotkaya, V. A. Khazanov, *Russ. Chem. Bull.*, 2013, **62**, 188; DOI: 10.1007/s11172-013-0028-y.
31. O. V. Tsepaeva, A. V. Nemtarev, T. I. Abdullin, E. V. Kuznetsova, V. F. Mironov, *Russ. J. Gen. Chem.*, 2018, **88**, 1944]; DOI: 10.1134/S1070363218090335.
32. E. Chrobak, E. Bebenek, M. Kadela-Tomanek, M. Latocha, C. Jelsch, E. Wenger, S. Boryczka, *Molecules*, 2016, **21**, 1123; DOI: 10.3390/molecules21091123.
33. N. R. Khasiyatullina, V. F. Mironov, S. K. Gumerova, A. D. Voloshina, A. S. Sapunova, *Mendeleev Commun.*, 2019, **29**, 435; DOI: 10.1016/j.mencom.2019.07.027.
34. N. R. Khasiyatullina, A. M. Vazykhova, Y. K. Voronina, V. F. Mironov, *Russ. J. Gen. Chem.*, 2017, **87**, 1934; DOI: 10.1134/S1070363217090079.
35. V.I. Galkin, Yu. V. Bakhtiyarova, N. A. Polezhaeva, I. V. Galkina, R. A. Cherkasov, D. B. Krivolapov, A. T. Gubaidullin, I. A. Litvinov, *Russ. J. Gen. Chem.*, 2002, **72**, 376; DOI: 10.1023/A:1015435432082.
36. V. I. Galkin, Yu. V. Bakhtiyarova, N. A. Polezhaeva, I. V. Galkina, R. A. Cherkasov, D. B. Krivolapov, A. T. Gubaidullin, I. A. Litvinov, *Russ. J. Gen. Chem.*, 2002, **72**, 384; DOI: 10.1023/A:1015487416152.
37. L. Pohjala, S. Alakurtti, T. Ahola, J. Yli-Kauhaluoma, P. Tammela, *J. Nat. Prod.*, 2009, **72**, 1917; DOI: 10.1021/np9003245.

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