Synthesis of C(28)-linker derivatives of betulinic acid bearing phosphonate group

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A convenient method for the synthesis of C(28)-linker derivatives of triterpenoids containing a phosphonate group is presented. The method is based on the reaction of triterpenic acids (using betulinic acid as an example) with *O*,*O*-dialkyl-ω-bromoalkane phosphonates in DMF in the presence of K_2CO_3. The target phosphonates are synthesized in a yield of about 80%. The structures and compositions of the synthesized compounds were confirmed by NMR spectroscopy, IR spectroscopy, and elemental analysis.

Key words: triterpenoids, betulinic acid, esters, phosphonates.

Triterpenoids represent a vast class of secondary plant metabolites possessing diverse biological activity.[1] Triterpenoids of the lupane series, in particular, betulinic acid, are being intensively studied in the recent years mainly due to their antiviral activity (especially anti-HIV),[2] as well as anti-inflammatory,[3] anticancer,[4] and other types of biological activity.[5] In several cases, the modified betulinic acid derivatives exhibit much higher activity, including higher cytotoxicity, against tumor cells of various genesis than their unmodified analogues.[6—8]

The mechanism of anticancer effect of betulinic acid remains unclear and, hence, is widely studied. Several explanations were proposed for cytotoxicity of betulinic acid: induction of apoptosis,[9] regulation of autophagy,[10] inhibition of angiogenesis and metastasis,[11] and capability of surmounting resistance of drugs to traditional chemotherapy.[12] A low solubility of betulinic acid in aqueous media and a relatively short half-withdrawal period significantly restrict its therapeutic efficiency and prevent going to extended clinical trials. Diverse methods are presently developed for drug delivery using various carriers, such as liposomes, dendrimers, microcapsules, polymeric micelles, and nanocontainers.[13,14] Phosphonium residues and residues of phosphoric and phosphonic acids of diverse structures are among promising modifying functional groups. Numerous organophosphorus compounds have intrinsic biological activity and, in addition, can impart solubility in physiological media to a target agent, enhance bioaccessibility, and improve transport through cell membranes.[15—19] The introduction of phosphorus-containing groups (phosphates, phosphonates, *etc.*) is used for the synthesis of prodrugs that liberate the active substance under the action of water or due to enzymatic hydrolysis.[20] The examples are known when the introduction of an organophosphorus group into the known drug would enhance the primary activity and also new types of biological activity would appear.[21]

The phosphonate group is met in many structurally diverse molecules with high biological activity, which are considered as stable isosteres of the phosphate derivatives. Among these compounds are antiviral drug Tenofovir,[22] antibiotic Fosfomycin,[23] inhibitors of isoprenoid biosynthesis,[24] inhibitors of tyrosine phosphatase,[25] antimalarial[26] and hypotensive drugs,[27] antiosteoporotic agents Alendronate and Zoledronate,[28] and herbicide Glyphosate.[29] In the recent decade, phosphorus-containing compounds are considered as promising agents in therapeutic approaches to the treatment of infection, tumor, and autoimmune diseases based on the activation and use of γδT-lymphocytes.[30] T-Cells with the T-cellular receptor consisting of γ- and δ-chains (γδTCR) are capable of recognizing non-peptide phosphorylated antigens (phosphoantigens), which induces the regulation of immune response, tissue reparation, maintenance of antigen homeostasis, and mediated by γδT-cells enhancement of anticancer immunity.[31] Phosphoantigens are low-molecular-weight non-peptide compounds containing phosphate or pyrophosphate group, which are permanently expressed in bacterial cells and in cells of plants and animals. One of the classes of compounds activating γδT-cells is formed by bis(phosphonates),[32] especially nitrogen-containing aminobis(phosphonates). The first representatives of aminobis(phosphonates) of betulinic acid were described.[33]

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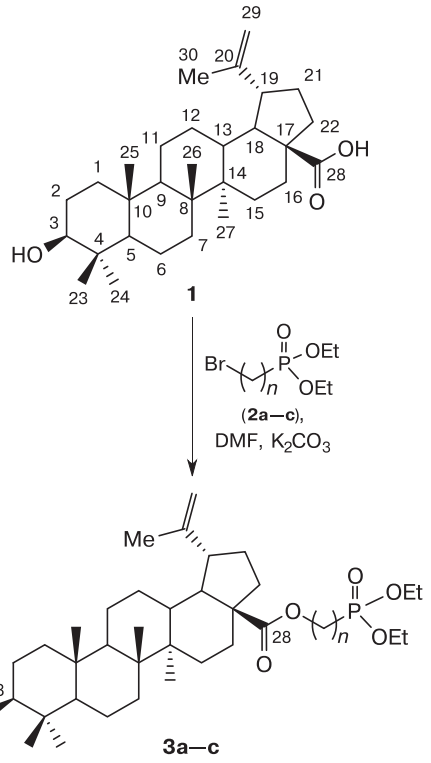
Several approaches to the synthesis of phosphonate-containing triterpenoids of the lupane series are known.[34—37] The phosphorylated derivatives of betulinic and dihydrobetulinic acids, as well as the bevirimate derivatives, are strongly affecting antiviral (anti-HIV) compounds.[34,35,37] Under the Arbuzov reaction conditions, the reaction of 3β,28-diacetoxy-30-bromolup-20(29)-ene with triethyl phosphite affords the phosphonate derivative of lupane triterpenoid in a yield of 76%.[36] The introduction of a phosphonate group into the isopropenyl group of betuline increases the anticancer activity of the target products against cell lines T47D, SNB-19, and C32.[36] We have earlier described a method of introducing the phosphoryl function into the structure of triterpenoids containing the unsaturated carbonyl fragment.[38] The method is based on the reaction of methyl C(2)-methylidene betulonate with dimethyl(trimethylsilyl) phosphite on heating in the presence of $ZnCl_2$. This reaction needs a high temperature and Lewis acids to occur, which is caused, most likely, by steric hindrance of the triterpene platform. The synthesis of intermediate compounds bearing the phosphoryl fragment, which are capable of reacting with triterpenoids under mild conditions, can be an alternative method for phosphonate introduction. Taking into account the aforesaid, it seemed urgent to synthesize new phosphonate derivatives of betulinic acid by its alkylation with ω-haloalkylphosphoryl compounds at the oxygen atom of the carboxyl group C(28)O. The general method for the synthesis of the betulinic derivatives containing the phosphonate group is shown in Scheme 1. The phosphonate group is bonded to the betulinic acid residue at the C(28) position of the triterpenoid cage through the hydrophobic alkylene linker.

Phosphonate fragments were introduced into a molecule of betulinic acid **1** using its reaction with ω-haloalkyl phosphonates **2a—c** in DMF in the presence of K_2CO_3. The reaction occurred under mild conditions (30 °C) for 2—4 h. The yields of target compounds **3a—c** were about 80%. The structures of the products were proved by ^1H, ^{31}P, and ^{13}C NMR spectroscopy.

The ^{31}P NMR spectra of compounds **3a—c** exhibit signals of the phosphorus atoms at δ_P 32. The formation of phosphonates **3a—c** is also proved by the presence of characteristic signals of the protons of the ethoxy group in the ^1H NMR spectra: triplet at δ_H 1.3 and multiplet at δ_H 4.1. The range of δ_H 2.2 exhibits a multiplet of protons of the CH_2P group. The ^{13}C-{^1H} NMR spectra were interpreted with allowance for the spectral data on unsubstituted betulinic acid and ω-haloalkyl phosphonates and also taking into account multiplicity of the signals. The signals in the ^{13}C-{^1H} NMR spectra of compounds **3a—c** are well resolved, which made it possible to reliably compare the spectra with the structures of the synthesized derivatives. The ^{13}C-{^1H} NMR spectra of compounds **3a—c** contain each a single set of characteristic signals of the lupane moiety and corresponding substituents at C(28).

Scheme 1



2, 3: *n* = 4 (**a**), 5 (**b**), 6 (**c**)

The high-field range of the ^{13}C-{^1H} NMR spectra exhibits doublets corresponding to the CH_2P (δ_C 24.4—25.7) and $OCH_2\underline{C}H_3$ (δ_C 16.5) groups with spin-spin coupling constants of 141.0 and 5.9 Hz, respectively. The low-field range exhibits resonance signals of the carbon atoms of the $O\underline{C}H_2CH_3$ (δ_C 61.4, J = 6.5 Hz) and C(3)HOH (δ_C 78—80) fragments and signals of the sp^2-hybridized carbon atoms of the OC(O) group (δ_C 176) and $\underline{C}(29)H_2{=}C$ fragment (δ_C 109).

Thus, in this work we described the convenient method for the introduction of the ω-(dialkoxyphosphoryl)alkyl fragment into the structures of lupane triterpenoids. The method is based on the reactions of triterpenic acids (betulinic acid as an example) with *O*,*O*-dialkyl-ω-bromoalkane phosphonates in DMF in the presence of K_2CO_3. The yields of target phosphonates are about 80%.

Experimental

^1H, ^{13}C, and ^{31}P NMR spectra were recorded at 25 °C on a Bruker Avance-400 instrument (400.0 (^1H), 100.6 (^{13}C), and 162 MHz (^{31}P)) in $CDCl_3$. Chemical shifts are presented relative to signals of residual protons or carbon nuclei of the solvent (δ_H 7.26, δ_C 77.16) and to 85% H_3PO_4 (^{31}P). IR spectra were recorded on a Bruker Tensor 27 instrument for samples in KBr pellets. Melting points were determined on a Boetius heating

stage. Elemental analyses of the compounds were carried out on a EuroEA 3028-HT-OM Eurovector S.p.A high-temperature CHNS-O analyzer. The specific rotation was measured on a Model 341 polarimeter (Perkin Elmer) in a temperature-maintained cell at 20 °C and λ = 589 nm. Solvents were purified and dried according to standard procedures. All solvents used were freshly distilled. Betulinic acid **1** was synthesized using a known procedure[39] from betuline, m.p. 290—293 °C (*cf.* Ref. 36: m.p. 291—292 °C), and the spectral parameters of compound **1** correspond to the earlier published data.[36] Phosphonates **2a—c** were synthesized using a published procedure.[40] The spectral parameters of compounds **2a—c** correspond to the earlier published data.[4]

Synthesis of diethyl phosphonates 3a—c (general procedure). ω-Haloalkyl phosphonate **2a—c** (1.5 mmol) and K_2CO_3 (0.2 g, 1.5 mmol) were added to a solution of betulinic acid **1** (0.5 g, 1.09 mmol) in a mixture of DMF (5 mL) and MeCN (0.5 mL), and the resulting mixture was stirred at 50 °C for 2—4 h. Then the reaction mixture was added to a 10-fold (vol/vol) water excess, and the organics was extracted with $CHCl_3$ (2×15 mL). The combined organic fractions were washed with water, and the solvent was evaporated. The residue was dried *in vacuo* (0.5 Torr) at 80 °C for 1—2 h. Phosphonates **3a—c** were obtained as oils solidifying with time.

4-(Diethoxyphosphoryl)butyl-3β-hydroxylup-20(29)-en-28-oate (3a). The yield was 0.579 g (82%), $[\alpha]_D^{20}$ +3.5 (*c* 1, $CHCl_3$). IR, ν/cm^{-1}: 3380, 2925, 2853, 1726, 1642, 1459, 1377, 1318, 1260, 1187, 1159, 1133, 1035, 983, 909, 884, 847, 815, 733. ^{1}H NMR, δ_H: 0.77 (s, 3 H, C(26)H$_3$); 0.84 (s, 3 H, C(25)H$_3$); 0.93 (s, 3 H, C(27)H$_3$); 0.98 (s, 6 H, C(23)H$_3$, C(24)H$_3$); 1.34 (t, 6 H, P(O)(OCH$_2$C$\underline{H}_3$)$_2$, $^3J_{H,H}$ = 7.0 Hz); 1.7 (s, 3 H, C(30)H$_3$); 0.68—2.22 (28 H, protons of lupane cage and (CH$_2$)$_2$ fragment of linker); 2.22—2.26 (m, 2 H, CH$_2$P); 2.97—3.04 (m, 1 H, H(19)); 3.20 (dd, 1 H, H(3), $^3J_{H,H}$ = 11.0 Hz, $^3J_{H,H}$ = 5.0 Hz); 4.07—4.15 (m, 6 H, C(O)OCH$_2$, P(O)(OC$\underline{H}_2$CH$_3$)$_2$); 4.60 (s, 1 H, C(29)H$_a$); 4.70 (s, 1 H, C(29)H$_b$). ^{13}C-{^{1}H} NMR, δ_C: 14.7; 15.3; 16.0; 16.1; 16.5 (d, OCH$_2$C$\underline{H}_3$, $^3J_{P,C}$ = 5.9 Hz); 18.3; 19.3; 20.9; 25.4 (d, CH$_2$P, $^1J_{P,C}$ = 141.6 Hz); 25.5; 27.4; 27.9; 29.5; 29.6; 30.6; 32.1; 34.3; 37.0; 37.2; 38.3; 38.7; 38.8; 40.7; 42.4 (s, C(4)); 47.0; 49.4; 50.6; 55.3 (s, C(5)); 56.5 (s, C(17)); 61.47 (d, O$\underline{C}$H$_2$CH$_3$, $^2J_{P,C}$ = 6.5 Hz); 63.12 (s, $\underline{C}$H$_2$OC(O)); 78.9 (s, C(3)); 109.6 (s, C(30)); 150.6 (s, C(20)); 176.2 (s, C(28)); ^{31}P-{^{1}H} NMR, δ_P: 31.5; Found (%): C, 70.28; H, 10.17. $C_{38}H_{65}O_6P$. Calculated (%): C, 70.34; H, 10.10.

5-(Diethoxyphosphoryl)pentyl-3β-hydroxylup-20(29)-en-28-oate (3b). The yield was 0.578 g (80%), $[\alpha]_D^{20}$ +9.8 (*c* 1, $CHCl_3$). IR, ν/cm^{-1}: 3431, 2944, 2868, 1724, 1641, 1459, 1390, 1377, 1226, 1164, 1134, 1105, 1049, 1029, 967, 883, 754. ^{1}H NMR, δ_H: 0.77 (s, 3 H, C(26)H$_3$); 0.84 (s, 3 H, C(25)H$_3$); 0.93 (s, 3 H, C(27)H$_3$); 0.98 (s, 6 H, C(23)H$_3$, C(24)H$_3$); 1.34 (t, 6 H, P(O)(OCH$_2$C$\underline{H}_3$)$_2$, $^3J_{H,H}$ = 7.0 Hz); 1.7 (s, 3 H, C(30)H$_3$); 0.68—2.20 (30 H, protons of lupane cage and (CH$_2$)$_3$ fragment of linker); 2.22—2.26 (m, 2 H, CH$_2$P); 2.98—3.04 (m, 1 H, H(19)); 3.20 (dd, 1 H, H(3), $^3J_{H,H}$ = 11.0 Hz, $^3J_{H,H}$ = 5.0 Hz); 4.06—4.16 (m, 6 H, C(O)OCH$_2$, P(O)(OC$\underline{H}_2$CH$_3$)$_2$); 4.6 (s, 1 H, C(29)H$_a$); 4.7 (s, 1 H, C(29)H$_b$). ^{13}C-{^{1}H} NMR, δ_C: 14.7; 15.4; 16.0; 16.1; 16.5 (d, OCH$_2$C$\underline{H}_3$, $^3J_{P,C}$ = 5.9 Hz); 18.3; 19.4; 20.9; 22.1; 22.2; 25.6; 25.7 (d, CH$_2$P, $^1J_{P,C}$ = 141.1 Hz); 27.0; 27.2; 27.4; 28.0; 28.3; 29.6; 29.7; 30.6; 32.1; 34.3; 37.0; 37.2; 38.3; 38.8; 38.9; 40.7; 42.4 (s, C(4)); 47.0; 49.4; 50.6; 55.4 (s, C(5)); 56.3 (s, C(17)); 61.5 (d, O$\underline{C}$H$_2$CH$_3$, $^2J_{P,C}$ = 6.5 Hz), 63.6 (s, $\underline{C}$H$_2$OC(O)); 78.9 (s, C(3)); 109.6 (s, C(30)); 150.6 (s, C(20)); 176.1 (s, C(28)); ^{31}P-{^{1}H} NMR, δ_P: 31.95. Found (%): C, 70.54; H, 10.13. $C_{39}H_{67}O_6P$. Calculated (%): C, 70.66; H, 10.19.

6-(Diethoxyphosphoryl)hexyl-3β-hydroxylup-20(29)-en-28-oate (3c). The yield was 0.575 g (78%), $[\alpha]_D^{20}$ +2.2 (*c* 1, $CHCl_3$). IR, ν/cm^{-1}: 3421, 2941, 2868, 1723, 1642, 1454, 1390, 1376, 1317, 1221, 1164, 1134, 1104, 1030, 964, 884, 733. ^{1}H NMR, δ_H: 0.75 (s, 3 H, C(26)H$_3$); 0.81 (s, 3 H, C(25)H$_3$); 0.91 (s, 3 H, C(27)H$_3$); 0.96 (s, 6 H, C(23)H$_3$, C(24)H$_3$); 1.31 (t, 6 H, P(O)(OCH$_2$C$\underline{H}_3$)$_2$, $^3J_{H,H}$ = 7.0 Hz); 1.67 (s, 3 H, C(30)H$_3$); 0.66—2.18 (32 H, protons of lupane cage of (CH$_2$)$_4$ fragment of linker); 2.19—2.23 (m, 2 H, CH$_2$P); 2.96—3.02 (m, 1 H, H(19)); 3.17 (dd, 1 H, H(3), $^3J_{H,H}$ = 11.0 Hz, $^3J_{H,H}$ = 5.1 Hz); 4.02—4.12 (m, 6 H, C(O)OCH$_2$, P(O)(OC$\underline{H}_2$CH$_3$)$_2$); 4.6 (s, 1 H, C(29)H$_a$); 4.7 (s, 1 H, C(29)H$_b$). ^{13}C-{^{1}H} NMR, δ_C: 14.7; 15.3; 16.0; 16.1; 16.4 (d, OCH$_2$C$\underline{H}_3$, $^3J_{P,C}$ = 5.9 Hz); 18.3; 19.3; 20.9; 22.3; 22.4; 25.55; 25.64 (d, CH$_2$P, $^1J_{P,C}$ = 140.8 Hz); 27.4; 28.0; 28.5; 29.6; 30.0; 30.2; 30.7; 32.2; 34.4; 37.0; 37.2; 38.3; 38.8; 38.9; 40.7; 42.4 (s, C(4)); 47.0; 49.4; 50.5; 55.4 (s, C(5)); 56.5 (s, C(17)); 61.4 (d, O$\underline{C}$H$_2$CH$_3$, $^2J_{P,C}$ = 6.5 Hz); 63.7 (s, $\underline{C}$H$_2$OC(O)); 78.9 (s, C(3)); 109.5 (s, C(30)); 150.6 (s, C(20)); 176.1 (s, C(28)). ^{31}P-{^{1}H} NMR, δ_P: 32.2. Found (%): C, 70.88; H, 10.23. $C_{40}H_{69}O_6P$. Calculated (%): C, 70.97; H, 10.27.

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