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LETTERS TO THE EDITOR

Synthesis of Diterpenoid Steviol Derivative Containing a Posphorus–Carbon Bond on the Basis of Pudovik Reaction

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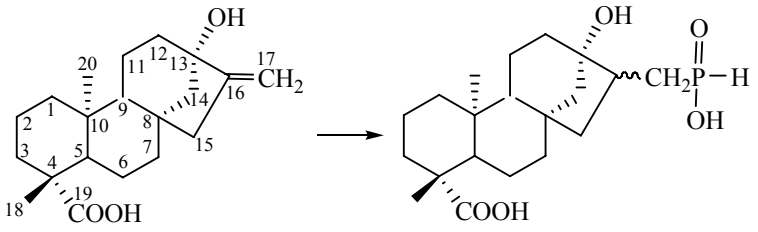
Organophosphorus compounds involving P–C bond (phosphonolipids, phosphonopyruvic acid, phosphinothricin and its analog, etc.) are regarded usually as formal analogs of phosphates, with the difference that their biological properties (for example, anti-microbial, antiviral, anticancer activity, enzyme inhibition, etc.) are much higher and more varied due to certain difficulties of enzymatic degradation of the phosphorus–carbon bond compared with the phosphorus–oxygen bond [1, 2]. Despite this circumstance, there is a significant number of natural metabolites of high biological activity with the phosphorus–carbon bond [3]. Various methods for their preparation including the Arbuzov, Michaelis–Becker, Pudovik, and Abramov reactions have been reported [1, 2]. Isoprenoid phosphorus-containing derivatives with a P–C bond have not been found in natural sources, but the synthesis of these compounds was performed on the basis of secondary metabolites of monoterpenoid (citral, menthane, carane, pinane, bornane derivatives [4–13]), diterpenoid (abietane derivatives [14, 15]) and steroid (cholestane derivatives [16]) series. They were obtained by the Pudovik reaction of unsaturated isoprenoids (limonene, carvomenthone, camphene, α- and β-pinenes) with diethyl phosphite [5, 6]; the reaction of alkali metals arylphosphides with menthyl chloride [7, 8], hydroxy derivatives of maleopimaric and fumaropimaric acids [14, 15] and cholestan-3-one [16]; the reaction of some α,β-unsaturated isoprenoid oxocompounds (citral, carvone, pinocarvone, 3-caren-4-one) and nitriles of monoterpenoid series with three- and dialkylphosphites [4], dibenzylphosphine oxide [9–11] and sodium diethylphosphide [12]; the Diels–Alder reaction of α-phellandrene with *trans*-vinylenebis(diphenylphosphine sulfide) [13].

Continuing the syntheses of organophosphorus derivatives of diterpenoids containing the P–C bond, we pioneered in involving aglycone of *S. rebaudiana* plant glycosides, *ent*-caurane diterpenoid steviol **I** (13-hydroxy-*ent*-caur-16-en-19-oic acid), into the homolytic Pudovik reaction. Diterpenoid **I** was selected as the object for the phosphorylation due to its uniqueness caused by the diverse biological activity [17] and the presence of several reactive centers, making it a promising platform for the drug design. The chemical transformations of diterpenoid **I** were described only in a few studies (see references in [17]). The reason is the ease of conversion of *ent*-caurane hydrocarbon skeleton of steviol **I** into *ent*-beyerane through the Wagner–Meerwein rearrangement. This report is a continuation of a series of papers [18–21] on the development of methods of chemical functionalization of steviol **I** without a change in its *ent*-caurane geometry.

The phosphorylation of steviol **I** was carried out using a large excess of sodium hypophosphite in the presence of triethylborane by analogy with the data [22]. The corresponding phosphonous acid derivative **II** was isolated in 50% yield.

The formation of phosphonous acid **II** was confirmed by the presence of the signals at δ_P 35.5 (intensive) and 31.5 ppm (low-intensive) in the ^{31}P NMR spectrum of the reaction product. In the ^1H NMR spectrum there is a broad doublet at δ 7.06 ppm ($^1J_{PH}$



I **II**

536 Hz) and no singlets at 4.8 and 4.9 ppm, corresponding to the resonance of the double bond protons of steviol **I**. In addition, the IR spectrum has the absorption bands at 1046, 1138, 2326 cm^{-1} corresponding to the stretching vibrations of P–OH, P=O, and P–H bonds, respectively. The presence of low-intensity signal at δ_P 31.5 ppm in the ^{31}P NMR spectrum of the product indicates the formation of ~10% of the second epimer at C^{16}. The products of the rearrangement of *ent*-caurane core of steviol **I** were not found. Thus, another method of the chemical transformation of diterpenoid steviol (phosphorylation of its double bond via the homolytic Pudovik reaction) was developed. It does not affect the geometry of the tetracyclic hydrocarbon skeleton and results in a first *ent*-caurane containing P–C bond.

17-Hydroxyhydrophosphoryl-13-hydroxy-*ent*-cauran-19-oic acid (II). To a solution of $NaH_2PO_2 \cdot H_2O$ (1.06 g, 10 mmol) and steviol **I** (0.1 g, 0.3 mmol) in 20 ml of methanol in an open beaker was added Et_3B (1.0 M. THF, 4 ml, 4 mmol) with stirring. The reaction mixture was stirred for 5 days and concentrated under reduced pressure. The residue was dissolved in water and the unreacted steviol **I** was extracted with diethyl ether (3×50 ml). The aqueous layer was acidified to pH 2–3, the reaction product was extracted with diethyl ether (5×50 ml), the extracts were dried over $MgSO_4$. After removing the solvent, a white powdery residue was isolated. Yield 0.06 g (50%). IR spectrum, ν, cm^{-1}: 1046 (P–OH), 1138 (P=O), 2326 (P–H). ^1H NMR spectrum ($CDCl_3$–CD_3OD), δ, ppm (*J*, Hz): 0.95 s (3H, $C^{20}H_3$), 1.18 s (3H, $C^{18}H_3$), 7.06 d (1H, $^1J_{PH}$ 536, P–H). ^{31}P NMR spectrum (CD_3OD), δ_P, ppm (*J*, Hz): 35.5 d.t ($^1J_{PH}$ 536). Mass spectrum (MALDI-TOF), *m*/*z*: 385 $[M + H]^+$, 407 $[M + Na]^+$, 423 $[M + K]^+$ (calculated: 384.21 $[M]^+$). $C_{20}H_{33}O_5P$.

The NMR spectrum was obtained on a Bruker Avance-600 instrument. The IR spectrum was recorded on a Bruker Vector-22 Fourier spectrometer from KBr pellets. The mass spectrum of matrix-assisted laser desorption/ionization (MALDI) was obtained on a Bruker MALDI TOF Ultraflex III instrument using 2,5-dihydroxybenzoic acid as a matrix.

Steviol **I** was obtained by the oxidative hydrolysis of a Sweta sweetener (Stevian Biotechnology Corp., Malaysia) similar to [19].

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