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LETTERS TO THE EDITOR

Dedicated to the 110th anniversary of M.I. Kabachnik's birth

Reaction of Methyl (2-Methylidene)-3-oxolup-20(29)-en-28-oate with Dimethyl Trimethylsilyl Phosphite

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Abstract—A method of phosphorylation of pentacyclic triterpenoids derivatives containing an α,β-unsaturated carbonyl fragment in the ring A was described by the example of the reaction of methyl (2-methylidene)-3-oxolup-20(29)-en-28-oate with dimethyl trimethylsilyl phosphite. Methyl 2-dimethoxyphosphorylmethyl-3-oxolup-20(29)-en-28-oate was obtained as two epimers in a 2 : 1 ratio in a 70% yield.

Keywords: triterpenoid, betulin, betulonic acid, methylidenebetulonate, silyl phosphite

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The use of pentacyclic triterpenoids in targeted chemical modification is becoming increasingly important due to a wide range of biologically valuable properties of these compounds [1]. The most wide-spread scaffolds for targeted modification among pentacyclic triterpenoides are derivatives of oleanane, ursane, and lupane group, which is mainly due to their availability from natural sources. Betulin [lup-20(29)-ene-3β,28-diol] is one of the specimens of the lupane series, its content in the outer birch bark (*Betula pendula L.*, etc.) varies within the range of 10–35% [2] that makes it a unique scaffold for targeted drug design. Betulin exhibits anti-inflammatory [3], anti-viral [4], and antitumor activity [5]. Numerous studies demonstrate that compounds containing the double bonds conjugated with electron-withdrawing groups, so-called Michael acceptors, exhibit high biological activity. The biological effects exhibited by such compounds are related to the ability to activate the system of antioxidant response element Keap1/Nrf2/ARE, induce the expression of antioxidant defense genes and autophagy [6, 7]. Synthesis of antioxidant enzymes based on triterpenoids is of interest due to the presence of Michael acceptors in the structures of these molecules [8].

We have previously shown that the functionalized derivative of betulonic acid **1** containing the Michael acceptor, α,β-unsaturated ketone fragment in the ring A, is capable of easy phosphorylation by triphenylphosphonium triflate with the formation of methyl 3-oxo-2-(2-triphenylphosphonioethyl)lup-20 (29)-en-28-oate triflate **2** as a pair of diastereomers in a 2 : 1 ratio [9] (Scheme 1).

The study of cytotoxicity of compound **2** we performed using cultures of cancer cells (MTT assay) such as human breast adenocarcinoma (MCF-7), human prostate adenocarcinoma (PC-3), and human skin fibroblasts (HSF) as a model of normal cells revealed a noticeable antitumor effect [IC_{50}, μm (±SD): 11.8±1.11 (PC-3), 11.7±1.4 (MCF-7), 19.4±0.4 (HSF); the comparative compound was doxorubicin: 0.35±0.03 (PC-3), 0.06±0.004 (MCF-7), 3.0±0.10 (HSF)], which significantly exceeds the effect of betulin [IC_{50} 148.65±13.09 (PC-3), 227.04±19.42 (MCF-7), 164.4±12.26 μM. (HSF)] [10]. The obtained data suggest the prospect of looking for physiologically active compounds in the series of phosphorylated derivatives of alkylideneterpenoids.