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Phosphonium and arsonium salts based on alantolactone

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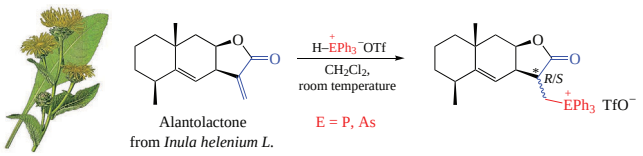
The reaction of alantolactone, a sesquiterpene α,β-unsaturated lactone, with *H*-phosphonium or *H*-arsonium triflates proceeds as P–H or As–H addition at the terminal =CH_2 moiety to afford novel triphenyl(sesquiterpenyl)-phosponium or -arsonium triflates. Their diastereoisomerism at the formed C^{11} chiral center has been simulated by quantum chemical calculations.



Keywords: sesquiterpenes, lactone, alantolactone, addition reaction, phosphonium salts, arsonium salts, quantum chemical calculations.

Dedicated to Academician Mikhail P. Egorov on his 70th anniversary.

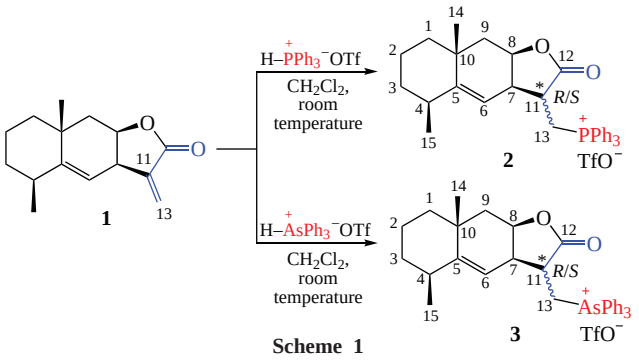
Sesquiterpene lactones (SLs) often incorporate a five-membered α-methylene-γ-lactone moiety that bespeaks a wide range of their biological activity,[1,2] in particular, cytotoxic[3] and antiproliferative[4] ones. Numerous studies[5] have shown that the cytotoxic effect of SLs might be caused by the presence of an exocyclic methylene moiety conjugated with the γ-lactone ring, due to which SL could enter Michael-type addition reactions with biogenic nucleophiles containing sulfhydryl or amino groups. Sesquiterpene lactones also exhibit anti-inflammatory[6] and anti-parasitic[7–10] effects while those containing α-methylene-γ-lactone moiety manifest antimicrobial activities.[11–14]

Alantolactone **1** is a SL representative that belongs to the eudesmane series possessing anti-inflammatory and antitumor activities.[15] Sulfur-[16] and nitrogen-containing[17] derivatives of alantolactone, as well as conjugates with antibiotics[18] were documented. Some alantolactone derivatives show more pronounced cytotoxic and antiproliferative action than the original alantolactone, which demonstrates the prospects of searching for new biologically active agents among its functionalized derivatives.

This work demonstrated the possibility of synthesizing phosphorus- and arsenic-containing alantolactone derivatives. It is known that the triphenylphosphonium[19] and triphenylarsonium[20] moieties can act as the vectors for the targeted delivery of molecules with antitumor properties to the mitochondria of tumor cells. Typically, this approach involves conjugating a biologically active molecule to the triphenylphosphonium moiety *via* alkylene linkers with varying lengths.[21]

The current approach is based on the direct reaction of alantolactone **1** with triphenylphosphonium and triphenylarsonium triflates (Scheme 1). Salts Ph_3P^+H TfO^- and Ph_3As^+H TfO^- were obtained by mixing triphenylphosphine or triphenylarsine with trifluoromethanesulfonic acid in dichloromethane, and then were brought into the reactions with alantolactone **1** *in situ*. Previously, similar approach was successfully tested with derivatives of mono-[22] and triterpenoids[23] and with quinones.[24]

The addition of phenylphosphonium triflate to alantolactone **1** occurs through the activated C^{11}=C^{13} carbon–carbon double bond to give phosphonium salt **2** (see Scheme 1) as a mixture of two diastereoisomers d_1 and d_2 in the ratio of 1.0 : 0.14 (the phosphorus signal of diastereoisomer d_1 in the ^{31}P NMR spectrum appears downfield from d_2: δ_P 24.6 and 23.6, respectively). The diastereoisomerism is due to the appearance of new chiral center in structure **2** at C^{11} carbon atom. In the ^{13}C–{^{1}H} NMR spectrum of phosphonium salts **2**, the C^{13}–P^+ carbon resonates as a doublet in the δ_C 19–25 region ($^1J_{PC}$ 54–56 Hz). The carbonyl carbon atom C^{12} appears as a doublet in the δ_C 177–179 region ($^3J_{PC}$ 10–11 Hz), the C^{11} atom as a doublet in the δ_C 39–40 region ($^3J_{PC}$ 4.1 Hz), and the C^7 atom as a doublet in the δ_C 42–44 region ($^3J_{PC}$ 2.2–4.0 Hz).



Scheme 1

The presence of spin–spin coupling of the C^7, C^{11}, C^{12} and C^{13} nuclei with phosphorus along with MALDI mass spectrometry data (*m/z* 495 $[M–CF_3SO_3]^+$) indicate that the triphenylphosphonium moiety is incorporated into the sesquiterpenoid structure.

The analogous reaction of alantolactone **1** with triphenylarsonium triflate occurs under mild conditions (CH_2Cl_2, room temperature) to give arsonium salt **3** as a mixture of two diastereoisomers d_1 and d_2 in the ratio of 1.0:0.7 (^{1}H NMR data). Both diastereoisomers were characterized by ^{13}C and ^{1}H NMR spectroscopy in their mixture. The absence of proton signals for the *exo*-methylidene group $C^{13}H_2$ in the ^{1}H NMR spectrum of arsonium salt **3** and considerable upfield shifts for the C^{11} and C^{13} carbon atoms in the ^{13}C–{^{1}H} NMR spectrum from the δ_C 149–150 and 121–122 regions (in alantolactone) to δ_C 39–40 and 24–26 (the arsonium salt) indicate that structure **3** contains the As–C^{13} bond.

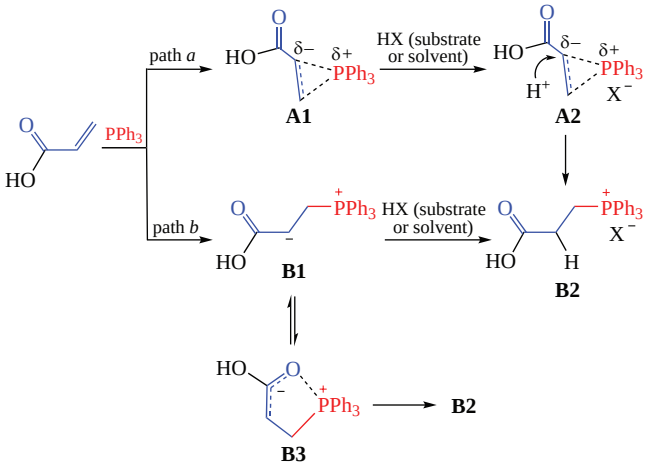
Comparison between the reactions of alantolactone **1** with the P–H-phosphonium salt and the As–H–arsonium salt (see Scheme 1) shows that the phosphonium salt is formed with significantly higher diastereoselectivity than the arsonium salt (*de* 76 and 18%, respectively). This difference may be attributed to the difference in the stability of the resulting diastereoisomeric forms of phosphonium and arsonium salts and to the difference in the mechanism of reactions involving phosphorus and arsenic derivatives.

Table 1 presents data on the relative formation energies of the diastereoisomers of compounds **2** and **3** calculated using the hybrid method B3PW91 of the density functional theory (DFT)[25] and the TZVP extended valence-split basis set[26] with full optimization of all geometrical parameters. It is evident that the difference in the relative energies of the *R* and *S* diastereoisomers in the case of phosphonium derivatives (11*R*)-**2** and (11*S*)-**2** is 18.4 kJ mol^{-1}, while it is 8.0 kJ mol^{-1} for the arsonium derivatives (11*R*)-**3** and (11*S*)-**3**. The possible structures of these compounds according to DFT B3PW91 method are presented in Online Supplementary Materials (Figures S11, S12).

A few mechanisms of reactions of tertiary phosphines with compounds containing activated C=C double bonds are suggested in the literature. Previously, the formation of a cheletropic pre-reaction complex **A1** (Scheme 2, pathway *a*) involving triphenylphosphine and the double bond of the unsaturated substrate followed by the relatively synchronous formation of a covalent P–C bond and protonation of the resulting carbanion center was assumed.[27] However, detailed analysis of kinetic data for reactions of conjugated acids with triarylphosphines in aprotic or weak protolytic solvents (alcohols, aliphatic carboxylic acids) allowed us to make the conclusion on the preferential initial formation of intermediate charged phosphabetaine **B1** (see Scheme 2, pathway *b*) through nucleophilic addition of triarylphosphine to the β-carbon atom followed by intermolecular proton transfer from the substrate or solvent. Moreover, carbanion **B1** can exist in tautomeric equilibrium with phosphonium enolate **B3**[28] which is stabilized by electrostatic interaction between the phosphonium center and the negative charge on the oxygen atom of the conjugated enol.[29] Protonation of enolate **B3** leads finally to phosphonium salt **B2**.

Table 1 Relative energies of diastereoisomers of **2** and **3** (B3PW91/TZVP).

Diastereoisomer	Δ*E*/kJ mol^{-1}	Diastereoisomer	Δ*E*/kJ mol^{-1}
(11*S*)-**2**	0.0	(11*S*)-**3**	0.0
(11*R*)-**2**	18.4	(11*R*)-**3**	8.0



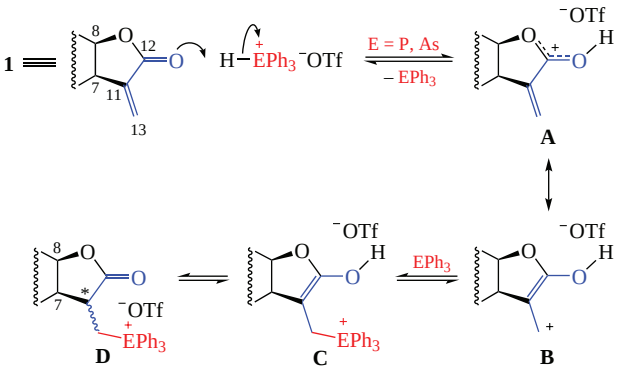
Scheme 2

It has been shown[30] that α-methylene-γ-butyrolactones manifest higher activity in the reaction with tertiary phosphines than acyclic α-substituted unsaturated esters due to the effect of anchimeric assistance caused by the *s-cis*-geometry of the alkene moiety fixed in the ring, which favors the interaction of the phosphonium center with the negative charge on the oxygen atom in the enol (see Scheme 2, structure **B3**).

While the kinetic parameters of the reactions of tertiary phosphines with unsaturated compounds in aprotic or weak protolytic solvents have been described fairly completely, the parameters of similar reactions in the presence of strong acids capable of efficient quaternization of the phosphorus atom (or some other heteroatom) to form P–H-phosphonium salts are not available in the literature. In the presence of strong acids, one should apparently expect the existence of dynamic proton exchange between the phosphorus atom in the phosphine and the oxygen atom in the unsaturated substrate (Scheme 3). In this case, the nucleophilic addition of phosphine to the C=C double bond occurs through the attack of the positively polarized enol **B** that is in resonance stabilization with the acylonium form **A**. The phosphonium enol **C** that is formed undergoes a prototropic isomerization to give salt **D**.

Triphenylarsine has a smaller proton affinity (908.9 kJ mol^{-1}) than triphenylphosphine (972.8 kJ mol^{-1}),[31] which suggests that the nucleophilic properties of the latter are weaker and, as a consequence, the As–H-acid dissociates in solution more strongly than the P–H-acid. In view of this, the prototropic isomerization **C** → **D** (see Scheme 3) in the case of phosphorus can have the form of proton exchange with the P–H-phosphonium salt, while in the case of arsenic, it may occur as direct addition of H^+ to the double bond of the enol.

In summary, a convenient approach to the directed functionalization of sesquiterpene lactones containing an α,β-



Scheme 3

unsaturated moiety with H-phosphonium and H-arsonium salts has been suggested in this work. The addition proceeds diastereoselectively (*de* 18% in the case of the arsonium salt and 76% in the case of the phosphonium salt). The compounds obtained are of interest as new biologically active agents.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.10.006.

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