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Quaternary phosphonium salts based on quinopimaric acid

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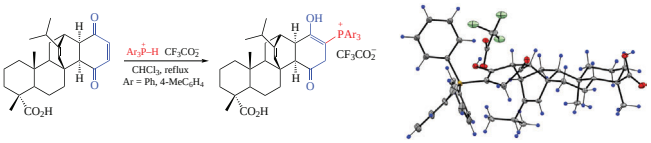
The reaction of quinopimaric acid with P–H-phosphonium salts yielded quaternary phosphonium salts containing enol moiety at the phosphorus atom. The reaction proceeded with high regioselectivity. The structures of the resulting compounds were confirmed by NMR and IR spectroscopy, mass spectrometry, and single-crystal X-ray diffraction.

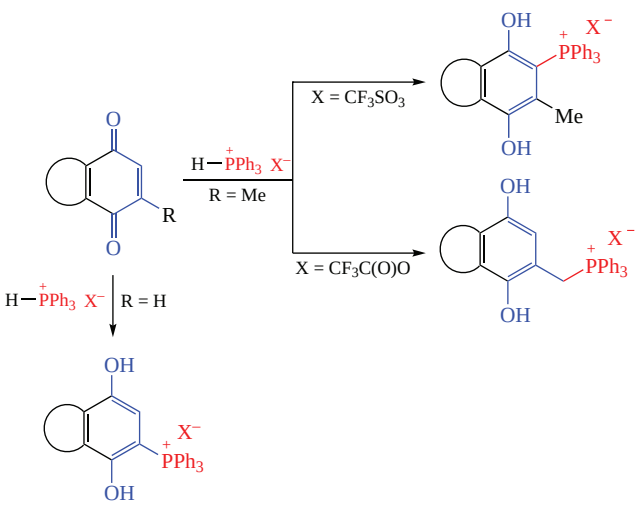


Keywords: phosphonium salts, quinopimaric acid, α,β-unsaturated γ-diketones, quinones, phosphine quaternization, addition reaction.

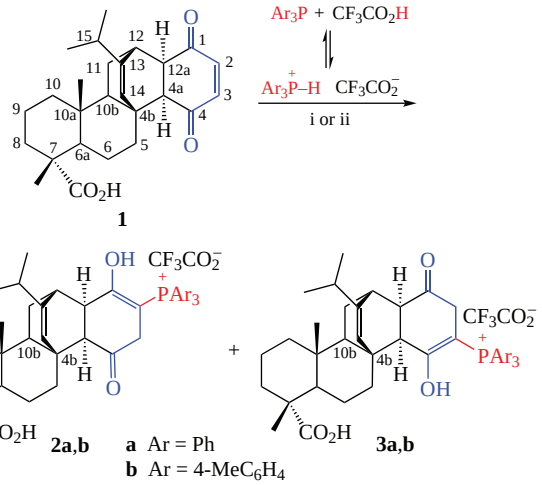
Levopimaric acid (LPA) is contained in up to 27% quantity in the oleoresin of *Pinus silvestris* L. pine. This compound has an exceptional ability among diterpene resin acids to easily undergo the Diels–Alder reaction with quinone-type dienophiles.[1] The adducts of LPA with arenoquinones, including quinopimaric acid (QPA) **1** and its derivatives, have a wide range of biological effects, in particular, anti-inflammatory,[2,3] antiviral,[4,5] anti-hypoxic,[6] choleretic, hepatoprotective,[7] antimicrobial[8] and cytotoxic[9,10] activities. Dihydroquinopimaric acid showed high cytotoxicity against A375 and A2780 tumor cell lines with selectivity indexes of 2.3 and 2.4, respectively.[9] Dihydro-quinopimaric acid amides[11] and oxidized QPA derivatives[12] exhibited antiviral activity against influenza A virus and activity against replication of the nucleic acid of hepatitis C virus (HCV).[5] Oxidized derivatives of dihydroquinopimaric acid and maleopimaric acid were efficient inhibitors of human papillomavirus HPV-11.[5,12] Methyl ester of 1,4-bis(hydroxy-imino)dihydroquinopimaric acid showed high *in vivo* antitumor activity against transplantable solid mammary carcinoma of mice Ca755 and against colon adenocarcinoma AKATOL.[10]

To enhance the biological activity of natural compounds, an approach based on modifying molecules with a triphenyl-phosphonium moiety, which provides directed transport to mitochondria, was successfully used in recent years.[13] An efficient method for the synthesis of polyfunctional quaternary phosphonium salts based on the addition of P–H-phosphonium salts to quinones was suggested previously (Scheme 1). This approach allows one to obtain quaternary phosphonium salts containing dihydroxyaryl substituents.[14]

In this work, we have synthesized quaternary phosphonium salts based on natural compounds containing an enedione moiety, the presence of which makes it possible to involve these compounds in reactions with stabilized P–H-phosphonium salts. Thus, QPA **1** was reacted with an equimolar amount of a P–H-



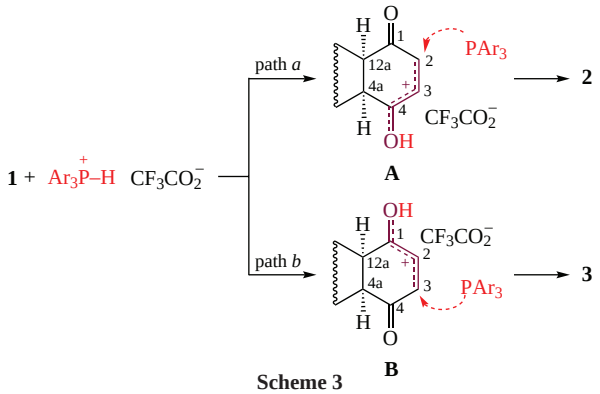
Scheme 1



Scheme 2 *Reagents and conditions*: i, $Ar_3P^+CF_3CO_2^-$, CH_2Cl_2, room temperature, 9 days; ii, $Ar_3P^+CF_3CO_2^-$, $CHCl_3$, 60 °C, 7 h.

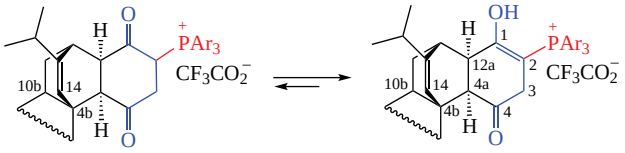
phosphonium salt obtained *in situ* by reaction of triarylphosphines with trifluoroacetic acid (Scheme 2). Regardless of the nature of the phosphine used, the reaction resulted in a mixture of regioisomeric phosphonium salts **2** and **3** (see Scheme 2).

The ^{31}P NMR spectra of the reaction mixtures contain two signals with δ_P 20–21 and 23–24 in ratios of ~10 : 1. The MALDI mass spectra of compounds **2a**, **3a** and ESI mass spectra of compounds **2b**, **3b** show molecular ion peaks with *m/z* 674 and 715, respectively. These data indicate that isomeric compounds are formed, presumably due to phosphine attack at positions 2 or 3 of quinopimaric acid protonated forms **A** and **B** (Scheme 3, pathways *a* or *b*, respectively).



Scheme 3

Replacement of the solvent ($CHCl_3$ instead of CH_2Cl_2) and raising the temperature result, along with a significant reaction acceleration, in an improvement of the regioselectivity giving exclusively isomer **2a** and **2b**.† The ^1H NMR spectra of compounds **2a**,**b** lack the characteristic *AB*-spin proton system of the $C^2=C^3$ double bond that is observed in the spectra of quinopimaric acid, indicating that functionalization at this moiety occurs. The H^{14} proton resonates in the δ 5.4 region, pointing out that the $C^{13}=C^{14}$ double bond is preserved in the reaction. The presence of only one carbonyl carbon signal in the $^{13}C–\{^1H\}$ NMR spectra of compounds **2a**,**b** indicates that the products exist in enolic form (Scheme 4).



2′a,b **2a,b**

Scheme 4

The signals of the C^2 carbon bound to phosphorus appear in the $^{13}C–\{^1H\}$ NMR spectra of compounds **2a**,**b** as doublets in the region of δ_C 75–76. The two-dimensional $^1H–^{13}C$ HSQC hetero-correlation spectrum of compound **2b** (see Online Supplementary Materials) exhibits cross-peaks of the C^3 carbon with the H^{3ax} and H^{3eq} protons (δ_C 39.51 and δ 2.77; δ_C 39.51 and δ 2.07). In the ^1H NMR spectrum, these signals appear as a doublet and a doublet of doublets, respectively, with a characteristic coupling constant $^3J_{HP}$ ~ 14–16 Hz from the phosphorus atom. The two-dimensional $^1H–^1H$ NOESY spectrum of compound **2b** exhibits cross-peaks of the H^{12a} and H^{4a} (δ 3.33 and 3.57), as well as the H^{14} and H^{3ax} protons (δ 5.44 and 2.77).

The characteristic spectral data presented above allowed us to unambiguously determine the structure of the molecule's moiety affected in the reaction. The remaining backbone of the molecule remains unchanged and its spectral data match the data for quinopimaric acid reported in the literature.[15]

The existence of compound **2a** in enolic tautomeric form was confirmed by XRD data.‡ Figure 1 shows the geometry of phosphonium salt **2a** in a crystal where the $H–O^1–C^1=C^2$ enolic moiety is clearly visible.

Figure 2 shows the backbone of polycyclic molecule **2a** without hydrogen atoms, trifluoroacetate anion, and phenyl rings at the phosphorus. The six-membered rings forming the rigid bicyclooctene moiety of the molecule exist in *boat* conformation. In the perhydronaphthalene moiety annulated at the $C^{4b}–C^{10b}$ bond, both six-membered heterocycles are arranged in rigidly

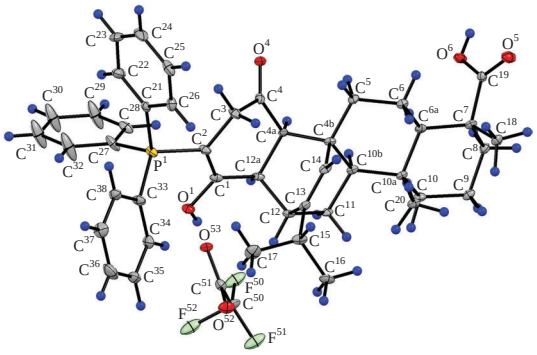


Figure 1 Crystal structure of the phosphonium salt molecule **2a**. The $C^{33–38}$ phenyl group and the trifluoromethyl group are shown in one of the two disordered positions.

† *General procedure for the synthesis of compounds* **2**. An equimolar amount of trifluoroacetic acid (0.04 ml, 0.50 mmol) was added dropwise to a solution of triarylphosphine (0.50 mmol) in $CHCl_3$ (2 ml), and this was heated to 60 °C with stirring under argon. After 10 min, a solution of an equimolar amount of quinopimaric acid (0.21 g, 0.50 mmol) in $CHCl_3$ (4 ml) was added dropwise, and the mixture was refluxed with stirring for 7 h under argon. The solvent was distilled off using a rotary evaporator, the resulting foamy mass was triturated in a light petroleum/acetone mixture (4 : 1, v/v, 10 ml). The products **2a** or **2b** appeared as white powders.

‡ *Crystal data for* **2a**. $C_{46}H_{50}F_3O_6P$ (M = 786.83), monoclinic, space group $P2_1$ at 100(2) K, a = 9.8909(19), b = 10.4252(18) and c = 19.843(4) Å, α = 90°, β = 99.439(5)°, γ = 90°, Z = 2, d_{calc} = 1.295 g cm^{-3}, μ(MoKα) = 0.131 mm^{-1}, F(000) = 890. Crystal size (mm) – 0.10 × 0.12 × 0.51; θ range for data collection (°) = 2.1 < θ < 26. A total of 32537 reflections were collected (7855 independent reflections, R_{int} = 0.068), GOOF 1.174, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0774 and wR_2 = 0.1668, R indices (all data): R_1 = 0.0825, wR_2 = 0.1693, Max. and Min. Resd. Dens. = 0.72/–0.50 (e Å^3), Flack parameter – 0.02(7). XRD of the crystal was performed on a Bruker D8 QUEST automatic three-circle diffractometer with a PHOTON III two-dimensional detector and an IμS DIAMOND microfocus X-ray tube (λ[Mo K$_\alpha$] = 0.71073 Å) under cooling. Data collection and processing of diffraction data were performed using the APEX3 software package.[18] The structure was solved by the direct method using the SHELXT program[19] and refined by the full-matrix least squares method over F^2 using the SHELXL program.[20] All the calculations were performed in the WinGX software package,[21] the calculation of the geometry of the molecules and intermolecular interactions in the crystals was carried out using the PLATON program,[22] and the drawings of the molecules were performed using the MERCURY[23] programs. Non-hydrogen atoms were refined in anisotropic approximation. The phenyl substituent $C^{33}–C^{38}$ was disordered on two positions with 0.51/0.49 occupancy, and the trifluoromethyl group of the acid was disordered on two positions with 0.59/0.41 occupancy. The positions of the hydrogen atoms H(O) were determined using difference Fourier maps, the remaining hydrogen atoms were placed in geometrically calculated positions and all hydrogen atoms were included in the refinement in the 'riding' model.

CCDC 2294136 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

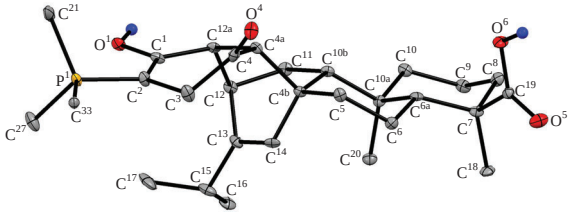


Figure 2 Conformation of the polycyclic backbone of the phosphonium salt molecule **2a**. To simplify the picture, the hydrogen atoms and the trifluoroacetate anion are omitted, and only carbon atoms bound to phosphorus are shown instead of the phenyls.

fixed *chair* conformations. The methyl groups at C^7 and C^{10a} occupy the axial positions, while the O^1H hydroxycarbonyl group is located in an equatorial position. The deviations of C^{18} and C^{20} atoms from the $C^{6a}C^7C^9C^{10}$ plane, which is planar to within ±0.012(6), are –1.351(6) and 2.176(6) Å. The equatorially located C^6, C^{10b} and C^{19} atoms deviate from this plane by –0.544(6), –0.239(5) and 0.930(6) Å. The deviations of the axially arranged C^{14} and C^{20} atoms from the $C^5C^6C^{10b}C^{10a}$ plane, which is planar to within ±0.008(6), are –2.092(5) and –1.445(6) Å. The cyclohexenone ring annulated at the C^{4a}–C^{12a} bond of the bicyclooctene moiety contains three $C^1C^{12a}C^{4a}C^4$, $C^3C^2C^1C^{12a}$ and $C^3C^4(O^4)C^{4a}$ four-atom moieties that are planar to within ±0.019(6), ±0.001(7) and ±0.005(6) Å. The C^2 and C^3 atoms deviate to the same side from the $C^1C^{12a}C^{4a}C^4$ plane by different distances, namely –0.371(6) and –0.783(7) Å; the C^4 and C^{4a} atoms are also located on the same side of the $C^3C^2C^2C^1C^{12a}$ plane at different distances of –0.356(6) and 0.410(5) Å. These data indicate that the annulated cyclohexenone ring exists in an asymmetric *boat* conformation. The dihedral angle between the $C^3C^2C^1C^{12a}$ and $C^1C^{12a}C^{4a}C^4$ planes is 18.0(4)°.

To determine the reasons for the predominant formation of phosphonium salts containing a phosphorus atom at the C^2 carbon atom, quantum-chemical calculations of the effective charges on the atoms were performed for QPA. The calculations were carried out using the B3PW91 hybrid density functional theory (DFT) method[16] and the expanded split valence basis set TZVP[17] with full optimization of all geometrical parameters. The charges on selected QPA atoms are presented in Table S1 (see Online Supplementary Materials). The calculations show that the charge on the C^2 atom is more negative than that on the C^3 atom, which suggests that the nucleophile would add to the protonated form of quinopimaric acid (see Scheme 3).

In conclusion, a convenient synthesis of functionalized phosphonium salts based on the addition of P–H-phosphonium salts to enedione derivatives (using quinopimaric acid as an example) was accomplished under mild conditions, which provided functionalization of natural and semi-synthetic compounds sensitive to thermal effects in high yields. A specific feature of quinopimaric acid as a substrate in this reaction is that the phosphonium salt formed is stabilized in enolic form, which is not observed in the case of the addition of tertiary phosphines to Michael acceptors with simpler structures.

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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.2024.01.034.

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