Mendeleev Commun., 2027, **37**, just accepted

Received 15.09.26
Revised 19.10.26

26/8201

Levopimaric acid-derived quinone—triphenylphosphonium hybrids

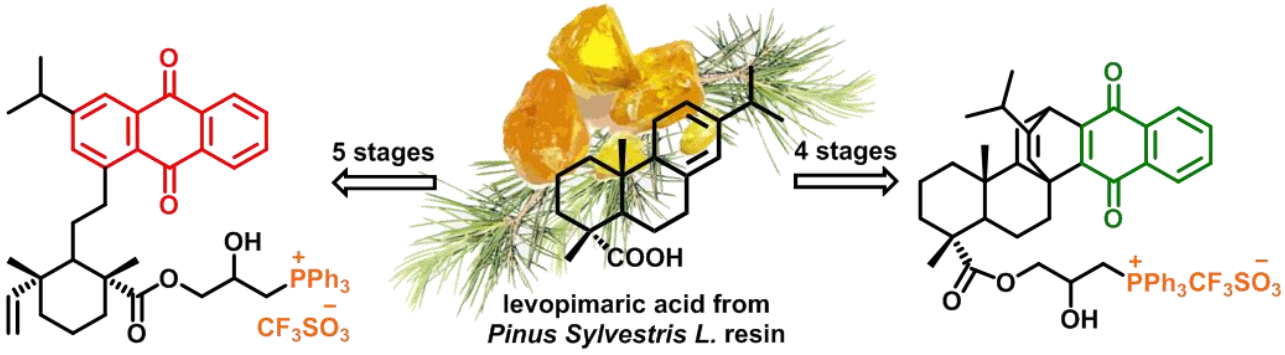
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DOI: 10.71267/mencom.8201

An efficient approach to the synthesis of quaternary phosphonium salts – levopimaric acid derivatives – based on the ring opening of glycidyl esters oxirane ring by P–H-phosphonium salts has been proposed. The key advantage of the method is the preservation of both the terpene scaffold and the quinone fragment under mild acid-catalyzed epoxide ring opening. Based on this approach, a preparative scheme for the synthesis of TPP-conjugated 9,10-anthraquinone derivatives with an overall yield of 63% over 5 steps has been developed.



Keywords: quaternary phosphonium salts, meroterpenes, quinones, glycidyl esters, oxirane ring opening.

Currently, a class of natural and semisynthetic compounds such as meroterpenes is being actively investigated. Interest in them is due to their diverse biological activity: antioxidant, anti-inflammatory, antiviral, antimalarial, immunosuppressive, antiprotozoal, antimicrobial, antitumor and cytotoxic.[1-3] Representatives of this class of compounds possessing a quinone fragment often exhibit high cytotoxic activity. For example, sesquiterpenes from the marine sponge *Pseudoceratina purpurea* containing a benzoquinone moiety showed cytotoxicity against

the multidrug-resistant cancer cell line H69AR (IC_{50} 2.85 ÷ 7.74 μM).[4] The sesquiterpene quinone ilimaquinone, isolated from the sponge *Dactylospongia elegans*, is cytotoxic against a number of tumor cell lines (IC_{50} 1.8 ÷ 2.7 μM).[5] The conjugate of the pentacyclic triterpenoid betulin with 2-chloro-1,4-naphthoquinone showed high cytotoxicity against Colo-829 (IC_{50} 0.13 μM), A549 (IC_{50} 0.77 μM) and C-32 (IC_{50} 1.72 μM) cell lines.[6] Therefore, the search for new methods for the synthesis of quinone-containing meroterpenes is a promising direction. For the construction of such structures, we chose levopimaric acid (LPA) – the main component (up to 27 wt%) of the oleoresin of *Pinus sylvestris* L. The availability of LPA, the ease of obtaining adducts with quinones[7] and their isolation make LPA a convenient platform for the synthesis of potential cytotoxic agents.

It is known that quinones, being reduced in the mitochondrial electron transport chain, increase ROS levels, which induces apoptosis of tumor cells.[8] Consequently, conjugation of quinones with mitochondria-targeting vector groups may enhance their anticancer properties. The triarylphosphonium moiety is widely used as a vector group.[9,10] Previously, we found convenient routes to TPP-conjugated anthraquinones containing a terpene fragment based on the adduct of LPA with 1,4-naphthoquinone – naphthoquinopimaric acid (NQPA) (Scheme 1, type A)[11] and on the phosphonium derivative of LPA with a polycyclic hydrocarbon skeleton (Scheme 1, type B)[12]. The obtained compounds showed pronounced bactericidal and cytotoxic activity. Thus, the aim of this work is to find a synthetic route to combine a cyclic terpene scaffold and a quinone fragment in one structure (Fig. 1, type C).

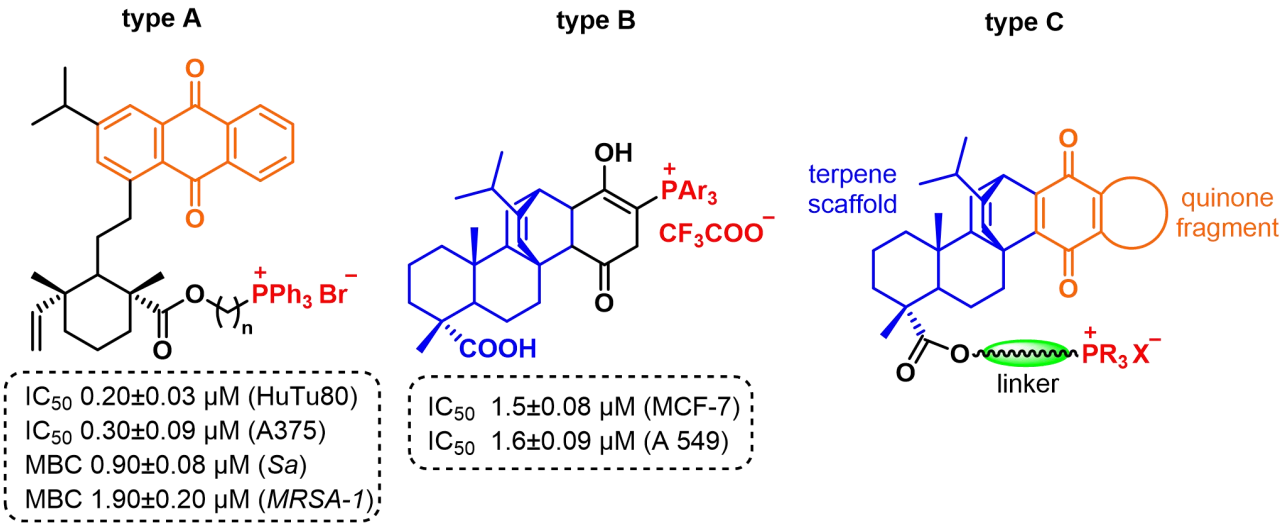


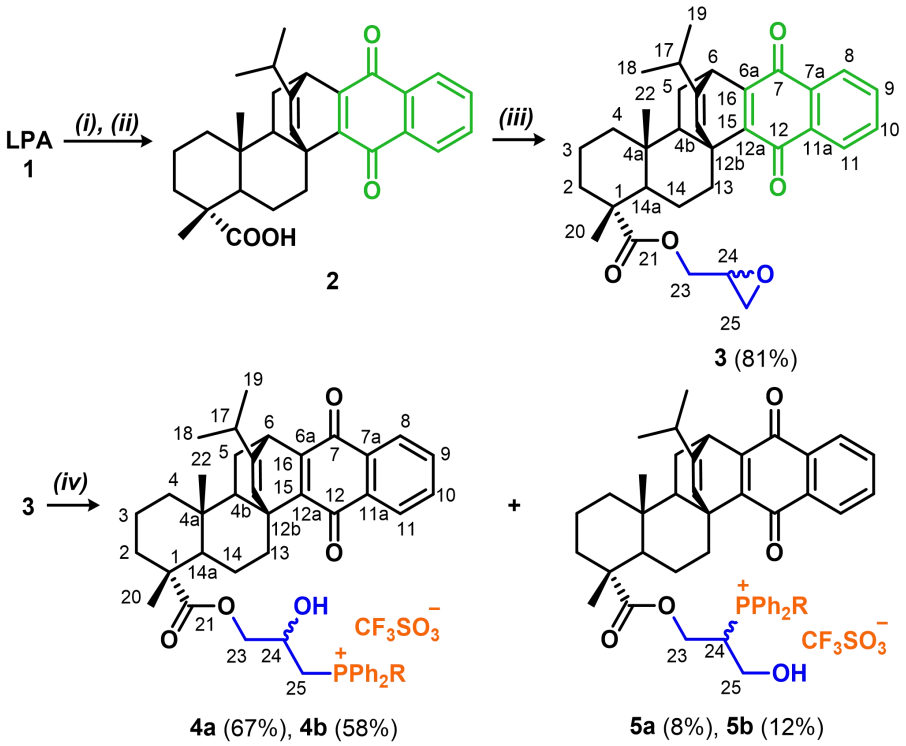
Figure 1 Cytotoxic TPP-conjugated derivatives of levopimaric acid

Dehydronaphthoquinopimaric acid **2** (dehydroNQPA) was chosen as the in this work, since for this substrate the possibility of a reaction between tertiary phosphines and the quinone core is excluded. In this work, a linker approach for conjugating meroterpenes with the TPP fragment was used, which involves linking the phosphonium fragment to the polycyclic scaffold *via* an alkylene,

oxyalkylene or carboxyalkyl linker. The 2-hydroxypropyl fragment, formed upon mild opening of glycidyl esters with tertiary phosphines in acidic media or under the action of P–H-phosphonium salts,[13] was chosen as the linker fragment (Scheme 1). The choice of this approach for quinopimaric acid derivatives is not accidental, since a number of works have shown the possibility of cleavage of the polycyclic scaffold of condensed diterpenes at elevated temperatures via the *retro*-Diels–Alder reaction pathway.[11,14]

To synthesize the glycidyl ester of dehydroNQPA **3**, a literature procedure[15] was adapted (Scheme 1) using racemic epibromohydrin. The obtained ester **3** is a mixture of diastereomers (epimers) in a ratio of d_1 : d_2 ≈ 1 : 1. Next, the oxirane ring was opened by triarylphosphonium triflates (Ph_3P^+–H $CF_3SO_3^-$ or $NpPh_2P^+$–H $CF_3SO_3^-$).

As shown earlier,[13] the oxirane ring opening proceeds stereospecifically with retention of configuration at the chiral atom (in this case, C^{24}). Salts **4a,b** were obtained as a mixture of diastereomers in a 1 : 1 ratio (according to $^{31}P–\{^1H\}$ NMR spectroscopy data). The signals of the diastereomeric salts appear in the characteristic region δ_P 22 ppm. Mass spectrometry data confirm the formation of addition products. In the ^{13}C NMR spectra of the reaction products, the position of the signals of the quinone fragment corresponds to that for dehydroNQPA **2**, which indicates the preservation of the quinone fragment during the reaction (*see Online Supplementary materials*). In the $^{13}C–\{^1H\}$ NMR spectrum, the signals of atoms C^{23}–C^{25} appear with characteristic coupling constants $^3J_{PC}$ 12, $^2J_{PC}$ 5 and $^1J_{PC}$ 55 Hz, respectively.



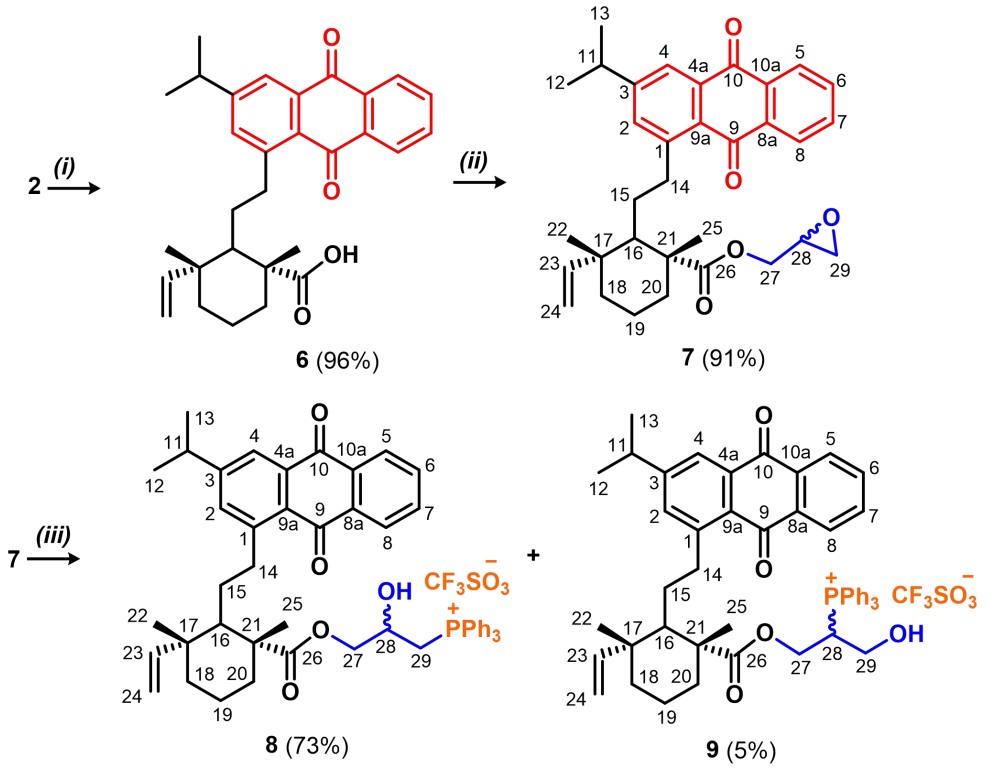
Scheme 1 Reagents and conditions: (*i*) naphthoquinone; $[BMIM]^+PF_6^-$, benzene/hexane (10:1, v:v), r.t., 7 days [16]; (ii) NaOH (10 % aq. sol.), O_2 (atm.), 50-55°C, 1h; HCl (3 % aq. sol.) [11]; (*iii*)

epibromohydrin (*R*/*S*) (3 eq.), K_2CO_3 (3 eq.), DMF, 80°C, 5h.; (*iv*) $RPh_2P^+H\ CF_3SO_3^-$ (0.9 eq.), dry CH_2Cl_2, –10°C → r.t., 72 h., R = Ph (a), Np (b)

It was previously reported that the reaction of epoxide ring opening by P–H-phosphonium salts proceeds regioselectively,[13] however, for substrate **3**, partial epoxide ring opening contrary to the Krasuskii rule is observed (formation of compounds **5**). The products of anti-Krasuskii opening correspond to signals in the $^{31}P–\{^1H\}$ NMR spectrum at about δ_P 24 ppm. The ratio of products **4** and **5** is 17 : 2 in the case of triphenylphosphine (**a**) and 5 : 1 in the case of naphthyldiphenylphosphine (**b**). Attempts to separate products **4** and **5** (chromatography, fractional precipitation) were unsuccessful, however, the target salts were isolated in good yields (**a** 75%, **b** 70%) as mixtures suitable for biological testing. Thus, the presented method allows for the efficient preparation of phosphonium conjugates of dehydroNQPA **2**, without affecting the quinone and terpene fragments.

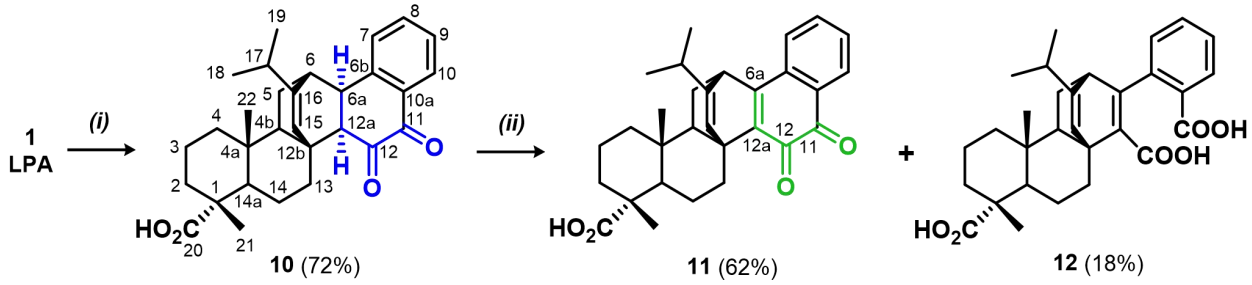
An important achievement of the described approach was its adaptation for the synthesis of conjugates containing the 9,10-anthraquinone fragment (Scheme 2). Such compounds have shown themselves as promising cytotoxic and antibacterial agents.[11] Previously, we obtained a TPP-conjugate containing an anthraquinone fragment by an alternative route,[11] However, the scheme proposed in this work, although it includes one more step, allows to significantly simplify the isolation of the final product (precipitation instead of chromatography) and increases the yield of the target compound over all steps to 63% (versus 39% according to the previously described procedure[11]).

Compound **6** was obtained according to an adapted literature procedure (Scheme 2).[14] Unlike glycidyl ester **3**, in the case of substrate **7**, the epoxide ring opening reaction proceeded more regioselectively (the anti-Krasuskii product constituted only 6% of the major product) and significantly faster (complete conversion was achieved in 18 h instead of 72 h). The formation of the Krasuskii ring opening product **8** is confirmed by $^{13}C–\{^1H\}$ NMR spectroscopy data, where the signals of atoms C^{28} and C^{29} appear with characteristic coupling constants $^2J_{PC}$ 4 and $^1J_{PC}$ 54 Hz, respectively (*see Online Supplementary materials*).



Scheme 2 Reagents and conditions: (*i*) 1,4-dioxane, 130°C, 10h.[14]; (*ii*) epibromohydrin (*R*/*S*) (3 eq.), K_2CO_3 (3 eq.), DMF, 80°C, 5h.; (*iii*) $Ph_3P^+H\ CF_3SO_3^-$ (0.9 eq.), dry CH_2Cl_2, –10°C → r.t., 18 h.

We also attempted to extend the developed approach to substrates containing an *ortho*-naphthoquinone fragment (Scheme 3). The adduct of LPA with 1,2-naphthoquinone **10** was first obtained by B.A. Arbuzov in 1942;[17] in this work, its structure was confirmed by X-ray diffraction (Figure 2). The cycloaddition proceeds stereospecifically to give the *endo*-adduct (in accordance with the *endo*-Alder rule). The cyclohexenedione fragment adopts a twist conformation, the two carbonyl fragments are separated by an angle of 40(1)°, and the C^{10a}–C^{11}–C^{12}–C^{12a} angle is –45.5(9)°. It was shown that diketone **10**, similarly to NQPA,[11] undergoes oxidation under fairly mild conditions to give *o*-quinone **11**. In addition to the target quinone **11**, the formation of a by-product – tricarboxylic acid **12** – was observed during oxidation (yield calculated based on ^{1}H NMR data of the product mixture), which is consistent with literature data on the oxidation of LPA adducts **1** with *o*-quinones.[18,19]



Scheme 3 Reagents and conditions: (*i*) 1,2-naphthoquinone (1 eq.), MeOH, r.t., 24 h. [17]. (*ii*) NaOH (10 % aq. sol.), O_2 (atm.), 50-55°C, 1h; HCl (3 % aq. sol.) [11].

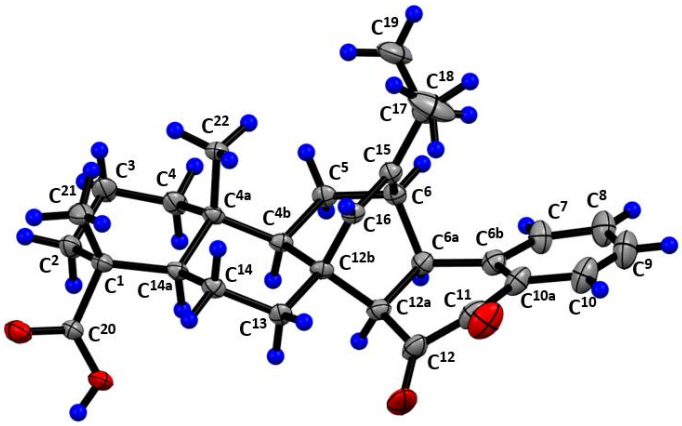
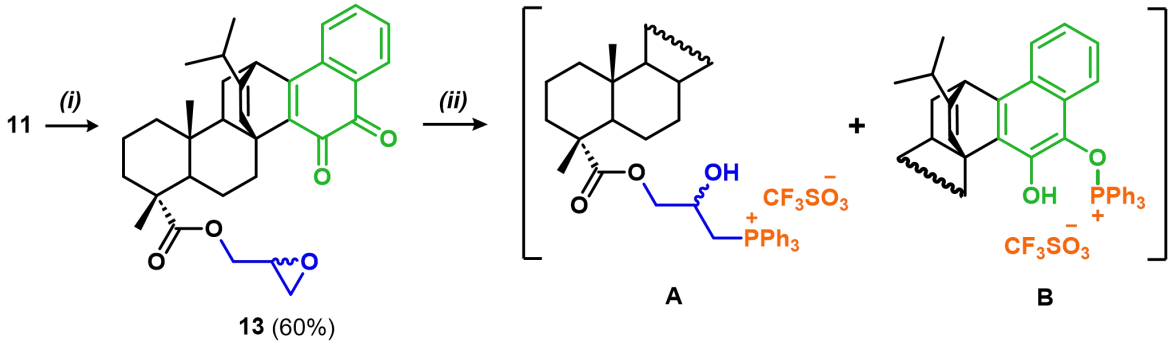


Figure 2 Geometry of the diketone **10** in crystal

Due to the difficulty of separating compounds **11** and **12**, they were subjected to esterification with epibromohydrin without separation (Scheme 4). Ester **13** was isolated in individual form by column chromatography. When glycidyl ester **13** was reacted with triphenylphosphonium triflate (conditions analogous to the preparation of **4** and **8**), it turned out that the reaction at the carbonyl group of the quinone fragment dominates over the target oxirane ring opening (Scheme 4). The ^{31}P NMR spectrum of the reaction mixture contained both signals corresponding to the phosphonium derivative **A** ($\delta_P \approx 22$ ppm) and signals in the region $\delta_P \approx 68$ ppm, characteristic of quasiphosphonium compounds – the product of addition to the quinone carbonyl group (compound **B**). The number of signals indicates the presence in the reaction mixture of products containing only fragment **A** or **B**, as well as both fragments simultaneously. Similar reactions of 1,2-benzoquinones[20,21] and phenanthrenequinone[22] with tertiary phosphines are described in the literature, however, it is interesting that this reaction pathway prevailed for substrate **13**, despite the steric hindrance of this reaction center. The ratio of products **A** : **B** was 1 : 11 (according to ^{31}P NMR spectroscopy data), which makes this approach inapplicable for substrates containing both an *o*-quinone and a glycidyl fragment.



Scheme 4 Reagents and conditions: (*i*) epibromohydrin (*R*/*S*) (3 eq.), K_2CO_3 (3 eq.), DMF, 80°C, 5h.; (*ii*) $Ph_3P^+HCF_3SO_3^-$ (0.9 eq.), dry CH_2Cl_2, –10°C → r.t., 18 h.

Furthermore, it was shown that the classical approach to quaternary phosphonium salts – the reaction of nucleophilic substitution of halogen in alkyl halides with tertiary phosphines (Scheme S1, *Online Supplementary materials*) – is not applicable for achieving the stated goal, since the main reaction is accompanied by a thermally induced *retro*-Diels–Alder reaction.[11] Carrying out the reaction under milder conditions (reflux in CH_3CN at atmospheric pressure) significantly reduces the rate of nucleophilic substitution of bromine by triphenylphosphine, as demonstrated for ester **S14**. Moreover, under these conditions, the rate of oxidation of triphenylphosphine by residual oxygen of the solvent is comparable to the rate of the target reaction.

Thus, using NQPA **2** as an example, an efficient route to the synthesis of quaternary phosphonium salts containing a terpene scaffold and a 1,4-naphthoquinone fragment, as well as phosphonium salts containing terpene and anthraquinone fragments, has been proposed. On the example of compound **11**, the inapplicability of the described synthetic scheme for obtaining phosphonium conjugates containing a 1,2-naphthoquinone fragment was shown, since in this case the introduction of the phosphonium fragment is complicated by the occurrence of side reactions at the carbonyl group.

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†*Crystal data for* **10**. $C_{30}H_{36}O_4$, plank (0.432 × 0.201 × 0.102 mm3), formula weight 460.59 g mol^{-1}; orthorhombic, P21212 (No. 18), a = 13.4326(8) Å, b = 22.4928(13) Å, c = 9.8103(6) Å, V = 2964.1(3) Å3, Z = 4, Z' = 1, T = 293(2) K, dcalc = 1.032 g cm−3, μ(Mo Kα) = 0.067 mm−1, F(000) = 992; Tmax/Tmin = 0.7580/0.6604; 77972 reflections were collected (2.076° ≤ θ ≤ 25.349°, index ranges: –16 ≤ h ≤ 16, –27 ≤ k ≤ 27, and –11 ≤ l ≤ 11), 5430 of which were unique, R_{int} = 0.0657, R_σ = 0.0243; completeness to θ of 25.349° 99.8 %. The refinement of 312 parameters with no restraints converged to R1 = 0.0725 and wR2 = 0.2108 for 4365 reflections with I > 2σ(I) and R1 = 0.0837 and wR2 = 0.2245 for all data, with goodness-of-fit S = 1.021 and residual electron density ρ_{max}/ρ_{min} = 0.363/–0.195 e $Å^{-3}$, rms 0.046 e $Å^{-3}$; max shift/e.s.d. in the last cycle 0.000. The data were collected on a Bruker D8 QUEST diffractometer with a PHOTON III area detector and an IμS DIAMOND microfocus X-ray tube (Mo Kα radiation). The data reduction package APEX4 were used for data processing. The data were corrected for systematic errors and absorption. The structure was solved by the intrinsic phasing method using SHELXT[23] and refined by the full-matrix least-squares on F2 using SHELXL.[24] Nonhydrogen atoms were refined anisotropically. The hydrogen atoms were inserted at the calculated positions and refined as riding atoms. The unit cell of **10** contains highly disordered solvent molecules, which were treated as a diffuse contribution to the overall scattering without specific atom positions by PLATON/SQUEEZE.[25] Squeezed solvent info is not included in the formulae and related items such as molecular weight and calculated density.

Deposition number CCDC 2576262 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

† For the full description of all synthetic protocols and characteristics of compounds obtained, see *Online Supplementary Materials*.

Authors acknowledge the Russian Science Foundation, grant No. 25-23-00706, for financial support. The measurements have been carried out using the equipment of Distributed Spectral-Analytical Center of Shared Facilities for Study of Structure, Composition and Properties of Substances and Materials of FRC Kazan Scientific Center of the Russian Academy of Sciences and Interdisciplinary Centre for Shared Use of Kazan Federal University.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: *10.71267/mencom.___*

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Received: 15th September 2026; Com. 26/8201