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Synthesis and X-ray diffraction analysis of coenzyme Q derivatives obtained from natural polyalkoxyallylbenzenes

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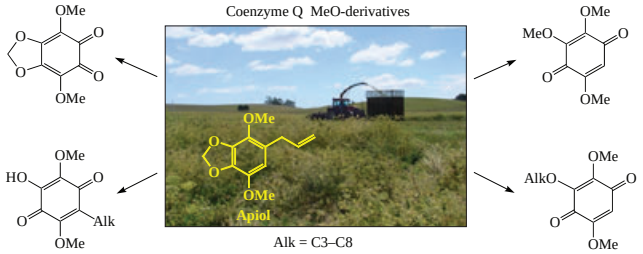
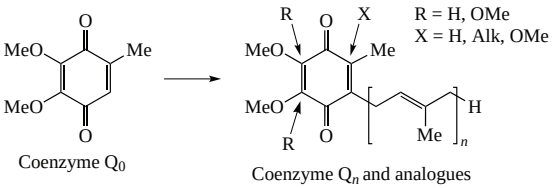
A general synthetic access to methoxy analogues of coenzymes Q bearing functional substituents with various chain lengths at the quinone ring was developed using available natural (polymethoxy)(methylenedioxy)allylbenzenes. The Baeyer–Villiger rearrangement of (methylenedioxy)benzaldehydes into phenols followed by facile oxidation to quinones with the methylenedioxy moiety opening was identified as the key step in the synthesis of the target 1,4- and 1,2-polyalkoxyquinones.



Keywords: allylbenzenes, coenzyme Q, polyalkoxyquinone, (methylenedioxy)benzaldehyde, Baeyer–Villiger rearrangement, formylation, oxidation.

Hydroquinones and 1,4-benzoquinones, such as ubiquinones, plastoquinones, coenzymes, and tocopherols with various lengths of the isoprenoid chains (*n*) and ring substituents (R) are widespread in plants, animals[1,2] and marine organisms.[3] These compounds and their analogues play an important role in the respiratory electron transport chain, have high antioxidant activity; they can regulate mitochondrial membrane permeability and inhibit cancer growth in mammals.[4] The simplest 2,3-dimethoxy-5-methylbenzo-1,4-quinone (coenzyme Q_0, Scheme 1) manifests antitumor properties. In particular, it inhibits the metastasis of breast[5] and skin (melanoma),[6] as well as the ovarian cancer[7] in mice. The quinone chromophore is contained in a number of synthetic drugs and in many natural molecules, so their anticancer activity is the focus of many studies.[8] Naturally occurring 1,2-naphthoquinones, such as β-lapachone,[8] have also been estimated for antitumor effects. In general, *ortho*-quinonoid compounds are even more efficient electrophilic and redox agents in the respiratory chain than *para*-quinonoid ones because of the enhanced electrophilic nature of the vicinal carbonyl groups.[9]

To obtain new antitumor compounds and to study cancer-related physiological processes, there is a need for the syntheses of both 1,4- and 1,2-quinones and hydroquinones with various functional substituents alongside with the isoprenoid chains. The



Coenzyme Q_0 — Coenzyme Q_n and analogues; Ubiquinone: X = Me, *n* = 10

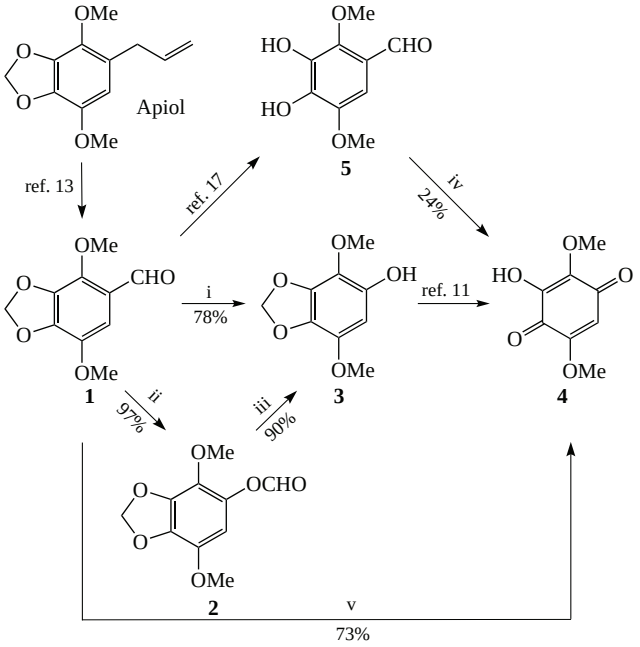
Scheme 1

majority of the syntheses of Q_n coenzymes are based on the incorporation of hydrocarbon chains into an already ready quinone, coenzyme Q_0, by oxidative radical reactions, which have a number of drawbacks (see Scheme 1, ref. 10 and the references therein).

The Baeyer–Villiger rearrangement of aldehydes and ketones with various functional substituents and methylenedioxybenzene moieties into the related phenols that can subsequently be easily oxidized to quinones can serve as a new approach to polymethoxyquinones. It has been shown previously that such polymethoxyphenols can be oxidized with opening of the methylenedioxy moiety to give 1,4-quinones in moderate yields.[11,12] An advantage of this method is the availability of (polymethoxy)(methylenedioxy)benzaldehydes that are easy to prepare from plant allyl(polyalkoxy)benzenes, in particular, from the readily accessible apiol (Scheme 2) that is isolated from the parsley essential oil in 65–70% yields.[13,14]

In this study, the rearrangement of apiol aldehyde **1** under the Baeyer–Villiger conditions using the reported procedure[15] (H_2O_2–H_2SO_4–MeOH) occurs smoothly at room temperature in an up to 15 g scale of the aldehyde (see Scheme 2). Simultaneously, hydrolysis of formate **2** occurs in the reaction mixture, which facilitates the formation of phenol **3** that is isolated in 78% yield. This method is better than the Dallacker technique[12] (H_2O_2–HCOOH) where the yield of aryl formate **2** was 56%, and the yield of isomeric formate in the oxidation of dillapiol aldehyde was 65%. An even higher yield was achieved using selenium dioxide as the catalyst (H_2O_2, Bu^{t}OH).[16] The reaction occurs under milder conditions and allows one to obtain aryl formate **2** in almost quantitative yield (97%), while the overall yield of phenol **3** is 87% in the 30 g scale of the starting apiol aldehyde **1**.

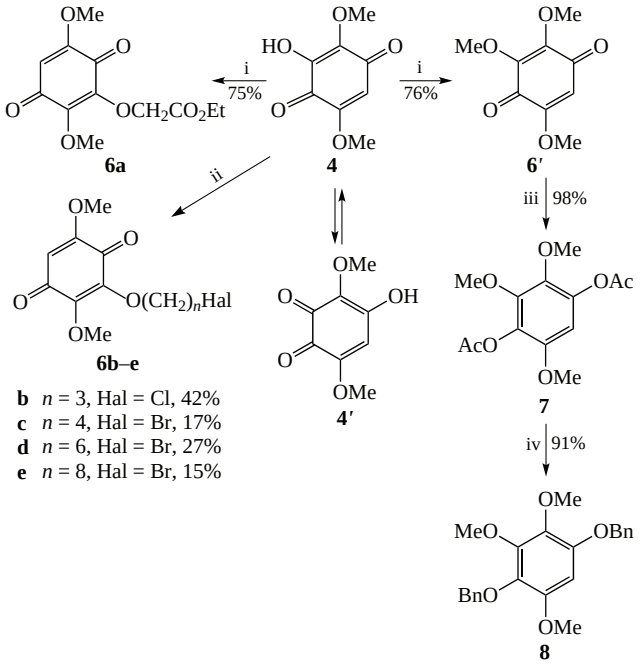
In the case of aldehyde **1** rearrangement in acetic anhydride medium, further oxidation of phenol **3** with opening of the



Scheme 2 *Reagents and conditions*: i, H_2O_2, MeOH, H_2SO_4, 20 °C, 8 h; ii, H_2O_2, SeO_2, Bu^tOH, 50 °C, 2.5 h; iii, MeOH, Et_3N, 20 °C, 45 min, then HCl/CH_2Cl_2, 20 °C; iv, H_2O_2, H_2SO_4, AcOH, 20 °C, 20 h; v, H_2O_2, H_2SO_4, Ac_2O, 20 °C, 4 h.

methylenedioxy moiety occurs simultaneously. As a result, a one-step procedure was developed affording the target 3-hydroxy-2,5-dimethoxybenzo-1,4-quinone **4** in 73% overall yield (see Scheme 2 and Online Supplementary Materials). Preliminary hydrolysis of benzodioxole fragment of compound **1** leading to dihydroxy benzaldehyde **5**[17] did not allowed us to improve the yield of **4** (24%) under standard oxidation conditions.

The *p*-quinone **4** obtained can, in principle, also exist as *o*-quinone **4′** tautomer (Scheme 3) and be methylated at any hydroxy groups. In fact, its methylation with methyl iodide (K_2CO_3, DMF) gave exclusively known[18] 2,3,5-trimethoxybenzo-1,4-quinone **6′** in a high yield. The alkylation with ethyl



b n = 3, Hal = Cl, 42%
c n = 4, Hal = Br, 17%
d n = 6, Hal = Br, 27%
e n = 8, Hal = Br, 15%

Scheme 3 *Reagents and conditions*: i, MeI (or $BrCH_2CO_2Et$), DMF, 20 °C, 48 h; ii, $Hal(CH_2)_nHal$, DMF, 20 °C, 5 h; iii, Zn–AcONa–AcOH–Ac_2O, reflux, 2 h; iv, $PhCH_2Br$, NaOMe, DMF, room temperature, 24 h.

bromoacetate also proceeds readily to furnish product **6a** in reasonable 75% yield while in the case of α,ω-dihaloalkane, the yields of products **6b–e** were markedly lower. Trimethoxyquinone **6′** in an acylating medium is quantitatively reduced with zinc metal to 1,4-diacetoxy-2,3,5-trimethoxybenzene **7**, which can be easily converted to dibenzyloxy derivative **8** (see Scheme 3).

The structure of quinone **6′** was unambiguously proven by single-crystal X-ray diffraction analysis (Figure 1).† The crystal structure is stabilized by π–π C···C interactions along the crystallographic axis *a* (π-stacking, short contacts between neighbouring molecules in the stack are C(3)···C(2), 3.351 Å and C(5)···C(6), 3.366 Å; the distance between C_6 planes of the neighbouring molecules in the stack is 3.30 Å) along with non-covalent C–H···O interactions between the molecules of neighbouring stacks.

Aldehyde **9** synthesized from dillapiol, a parsley seed component,[13] would undergo the similar Baeyer–Villiger oxidation in methanol to give phenol **10** (Scheme 4). However, under standard conditions of oxidative rearrangement of dillapiol aldehyde **9** in acetic anhydride, severe resinification occurs and no products can be isolated. When the reaction time was reduced to 1 h, along with the initial aldehyde, *o*-quinone **11** was isolated in a low yield (15%) without opening the methylenedioxy ring, which did not occur in the case of apiol aldehyde (see Scheme 2). The structure of *o*-quinone **11** was confirmed by single-crystal X-ray diffraction analysis (Figure 2).†

It was reasonable to study the oxidative rearrangement of apiol aldehyde **1** analogues with various substituents at the *ortho*-position, which would provide the availability of coenzyme Q analogues with a methoxy group. 5-Alkoxy(hydroxy) analogues of coenzyme Q are strong coenzyme Q antimetabolites

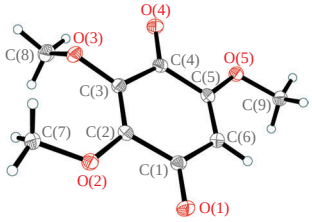


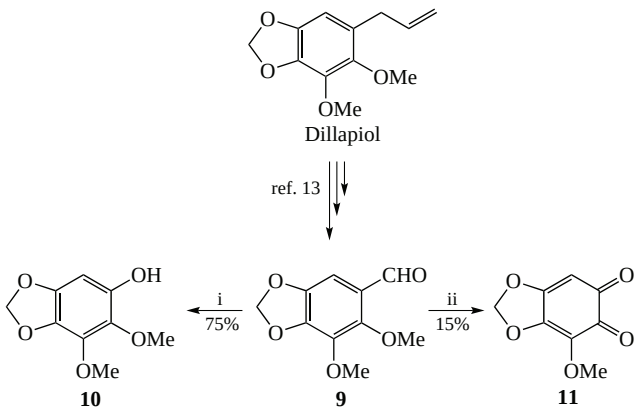
Figure 1 Structure of compound **6′** in a crystal. The thermal vibrations of atoms are represented by ellipsoids in anisotropic approximation (p = 50%).

† *Crystal data for* **6′**. $C_9H_{10}O_5$ (M_r = 198.17), monoclinic, space group $P2_1/c$, at T = 100 K, a = 3.81375(4), b = 27.6180(3) and c = 8.20673(8) Å, β = 97.2112(9)°, V = 857.562(16) Å^3, Z = 4, d_{calc} = 1.535 g cm^{-3}, $F(000)$ = 416, μ = 1.089 mm^{-1}. 9740 reflections (1851 independent reflections, R_{int} = 0.026) were measured and used in the refinement. The refinement converged to R_1 = 0.034 for 1779 observed reflections with $I > 2\sigma(I)$ and wR_2 = 0.100 for all independent reflections, S = 1.079.

Crystal data for **11**. $C_8H_6O_5$ (M = 182.13), monoclinic, space group $C2/c$, at T = 100 K, a = 28.919(6), b = 3.8070(6) and c = 15.564(3) Å, β = 120.323(11)°, V = 1479.1(5) Å^3, Z = 8, d_{calc} = 1.636 g cm^{-3}, $F(000)$ = 752, μ = 0.180 mm^{-1}. 6813 reflections (1632 independent reflections, R_{int} = 0.053) were measured and used in the refinement. The refinement converged to R_1 = 0.071 for 1463 observed reflections with $I > 2\sigma(I)$ and wR_2 = 0.169 for all independent reflections, S = 1.007.

Crystal data for **20**. $C_9H_8O_6$ (M = 212.15), monoclinic, space group $P2_1/c$, at T = 100 K, a = 14.457(3), b = 4.2950(7) and c = 15.367(3) Å, β = 109.88(3)°, V = 897.3(3) Å^3, Z = 4, d_{calc} = 1.571 g cm^{-3}, $F(000)$ = 440, μ = 0.174 mm^{-1}. 6042 reflections (2015 independent reflections, R_{int} = 0.047) were measured and used in the refinement. The refinement converged to R_1 = 0.060 for 1530 observed reflections with $I > 2\sigma(I)$ and wR_2 = 0.179 for all independent reflections, S = 1.134.

CCDC 2210640 (**6′**), 2210768 (**11**) and 2210769 (**20**) contain 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.



Scheme 4 *Reagents and conditions*: i, H_2O_2, MeOH–H_2SO_4, 20 °C, 8 h; ii, H_2O_2, Ac_2O–H_2SO_4, 20–25 °C, 1 h.

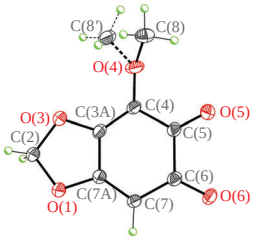
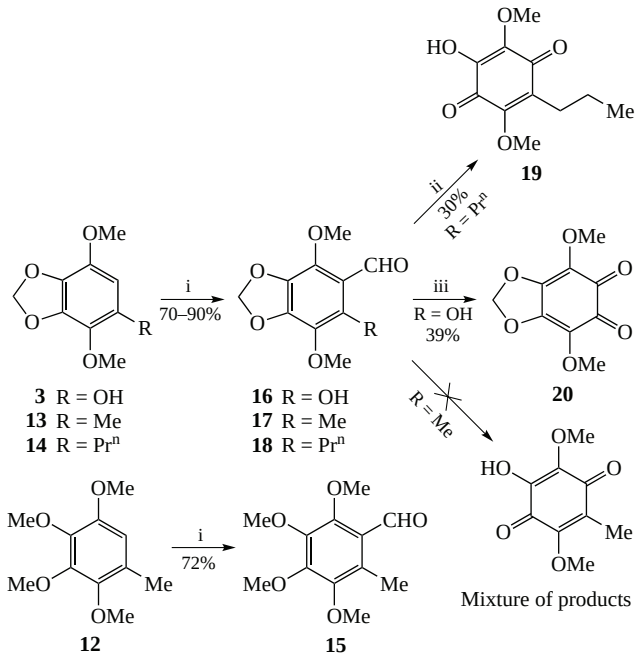


Figure 2 Molecular structure of *o*-quinone **11.** Dashed lines show the alternative position of the disordered methyl substituent.

in the inhibition of succinoxidase and NADH-oxidase.[18–20] The corresponding aldehydes **15**–**18** were obtained by formylation of 2,3,4,5-tetramethoxytoluene **12** as well as alkyl and hydroxy apiol derivatives **3**, **13**, **14** by the previously developed procedure[11] in 73–95% yields (Scheme 5). The structural type **19** is a chemotype of analogues of the natural compound Embelin isolated from *Embelia ribes* (Burm. F.) plants of the *Myrsinaceae* family.[21] Embelin and its derivatives were reported to possess anticancer, antimicrobial, antioxidant, analgesic, anti-inflammatory, anxiolytic, antifertility activities.

In our experiments, propylapiol aldehyde **18** in acetic anhydride medium reacted similarly to unsubstituted aldehyde **1**



Scheme 5 *Reagents and conditions*: i, HCO_2Et, PCl_5, $SnCl_4$, CH_2Cl_2, room temperature, 4 h; ii, H_2O_2, H_2SO_4, Ac_2O, room temperature, 3 h; iii, the same, 2 h.

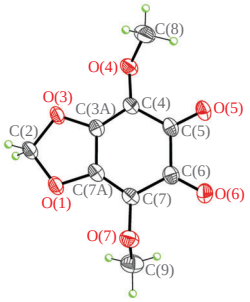


Figure 3 Molecular structure of *o*-quinone **20**.

to yield propylquinone **19** (see Scheme 5). However, the oxidation of methyl derivative **17** fails to give the corresponding quinone, and a mixture of unidentifiable products is formed. Similarly, we failed to isolate any products of oxidation of 2,3,4,5-tetramethoxy-6-methylbenzaldehyde **15**. At the same time, hydroxyapiol aldehyde **16** is oxidized with hydrogen peroxide in methanol to afford dimethoxylated *o*-quinone **20**. The yields of *o*-quinones **11** (15%) and **20** (39%) could not be optimized due to their high reactivity.[22]

The structure of **20** was established by single-crystal X-ray diffraction analysis (Figure 3).† The methoxy substituents in **20** are arranged in an *anti*-periplanar configuration with respect to the plane of the bicyclic moiety. Except for the methyl substituents and methylene group protons, the molecules of *o*-quinones **11** and **20** are almost planar (the RMS deviations of the specified atoms from the plane are 0.027 Å (for **11**) and 0.029 Å (for **20**). A specific feature of molecules **11** and **20** is that they contain very long single bonds (O=)C–C(=O) (C^2_{sp}–C^2_{sp}), namely, 1.571(4) Å (for **11)** and 1.566(4) (for **20**). The molecules in a crystal of **11** form layers parallel to the (100) plane due to C–H···O hydrogen bonds (see Online Supplementary Materials, Figure S2).

In conclusion, a general and simple approach to the synthesis of methoxy- and alkoxy-analogues of coenzymes Q with substituents having various chain lengths based on natural polyalkoxyallylbenzenes has been developed. The methods are scalable to multigram loadings.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.06.032.

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