

## Synthesis of Coenzyme Q<sub>10</sub>

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**Abstract: Problem statement:** CoQ<sub>10</sub> is a key compound in ATP synthesis having wide number of health application especially for treating humans suffering from pathophysiological condition. The CoQ<sub>10</sub> presently available in the market is solely derived from fermentation process. A commercially viable synthetic process is yet to be realized. **Approach:** The researchers described a new synthetic route for the preparation of CoQ<sub>10</sub> (1). This new process utilized inexpensive isoprenol as a precursor for the synthesis of an early intermediate with a single isoprene unit. Another key step was the selective oxidation of trans methyl of isoprene unit as a prelude to the expansion of the side chain to decaprenyl group using solanesol. **Results:** Prenylation of 2, 3-dimethoxy-5-methylhydroquinone using isoprenol in presence of a Lewis acid, followed by selective oxidation of trans methyl group of isoprenyl side chain and subsequent allylic bromination yielded a bromide precursor (7). The p-toluenesulfonation of the bromide followed by coupling with solanesyl bromide and de-p-toluenesulfonation yielded dimethyl derivative of the CoQ<sub>10</sub>-quinol. Finally CAN oxidation of dimethyl quinol followed by purification yielded CoQ<sub>10</sub> in 13% overall yield. **Conclusion:** The present process achieved CoQ<sub>10</sub> starting from a relatively inexpensive precursor. Further improvement in the coupling reaction between 8 and solanesyl bromide may lead to a better and viable synthetic process.

**Key words:** Coenzyme Q<sub>10</sub>, isoprenol, sodium-p-toluenesulfinate

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### INTRODUCTION

Coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>), a prominent member of the ubiquinone family, is an essential component of the mitochondrial electron transfer chain, which is required for ATP synthesis and functions as an antioxidant in cell membranes and lipoproteins<sup>[1]</sup>. CoQ<sub>10</sub> is also a powerful antioxidant not only within the mitochondria but also in other organelle membranes containing CoQ<sup>[2]</sup>. CoQ<sub>10</sub> is ubiquitously present in the mammalian tissues, especially in the heart. The fact that the levels of endogenous CoQ<sub>10</sub> in the heart decreases during ischemic heart disease including heart failure prompted clinical trials with CoQ<sub>10</sub> in patients that suffered from heart failure<sup>[3]</sup>. Randomized, double blind, placebo-controlled trials of oral administration of CoQ<sub>10</sub> have confirmed the effectiveness of CoQ<sub>10</sub> in improving angina episodes, arrhythmias and left ventricular function in patients with acute myocardial infarction<sup>[4]</sup>.

CoQ<sub>9</sub> is found in rodents like mice and rats, while CoQ<sub>6</sub>, CoQ<sub>7</sub> and CoQ<sub>8</sub>, are found in yeast and

bacteria<sup>[5,6]</sup>. The majority of CoQ<sub>9</sub> in rat liver is present in its reduced form (ubiquinol), which exerts its antioxidative function<sup>[7]</sup>. Similar to CoQ<sub>10</sub>, CoQ<sub>9</sub> is not merely a compound responsible for energy transduction in mitochondrial membrane in rat heart; it also serves as a functional element in the cells and possesses ability for redox cycling. The CoQ<sub>9</sub> differs from CoQ<sub>10</sub> with respect to the number of isoprenoid units in the tail; CoQ<sub>9</sub> has nine units in contrast to the presence of 10 units in CoQ<sub>10</sub>.

Most of the CoQ<sub>10</sub> is found in mammalian hearts including human myocardium<sup>[7]</sup>. CoQ<sub>10</sub> is not an essential nutrient, because it can be synthesized in the body. High amounts of CoQ<sub>10</sub> can also be found in several food products, including meat, fish, peanuts and broccoli<sup>[8]</sup>. Dietary intake of CoQ<sub>10</sub> is about 2-5 mg day<sup>-1</sup>, which is inadequate for the body under pathophysiological conditions<sup>[2]</sup>. A number of methods have been developed for the synthesis of CoQ<sub>10</sub><sup>[9-26]</sup> since the first industrial approach by Hideki Fukawa at Nisshin in 1974<sup>[27]</sup>.

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The researcher describe herein a novel process for the synthesis of Coenzyme Q<sub>10</sub> as shown in Fig. 1.

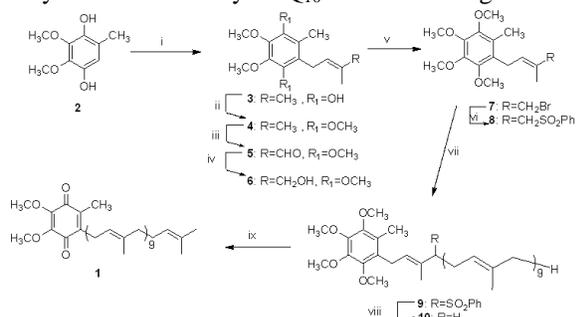


Fig. 1: (i): CCl<sub>4</sub>, 2-methyl-3-buten-2-ol, BF<sub>3</sub>, rt, 96.1%; (ii): NaOH, DMS; 90°C, 78% (iii): SeO<sub>2</sub>, EtOH; (iv): EtOH, NaBH<sub>4</sub>, rt, 65%; (v): THF, Pyridine, PBr<sub>3</sub>, 0°C, 92% (vi): CH<sub>2</sub>Cl<sub>2</sub>, TEA, Sodium p-toluenesulphinate, rt, 83%; (vii): t-BuOK, THF, Solanesolbromide, -20-30°C, 74%; (viii): THF, EtOH, Na, rt, 79%; (ix): CH<sub>3</sub>CN, CH<sub>2</sub>Cl<sub>2</sub>, CAN, 0°C, 72%

## MATERIALS AND METHODS

2, 3-dimethoxy-5-methyl-p-benzoquinone and isoprenol were purchased from Sigma-Aldrich Chemie GmbH, Steinheim, Germany. Sodiumdithionate, dimethylsulphate, sodiumborohydride, phosphoroutribromide, sodium metal, ceric ammonium nitrate were purchased from SD Fine chemicals, TV Industrial estate, Mumbai, India. Selenium dioxide was purchased from Molychem, Souri building, Mumbai, India. All the above chemicals were used as received. Solanesyl bromide was prepared from solanesol, which was isolated from tobacco waste using a known procedure. IR spectra were recorded on a Perkin-Elmer (model spectrum BX) FT-IR instrument in chloroform. <sup>1</sup>H NMR spectra were recorded on Bruker Avance AV 400 MHz Spectrometer and <sup>13</sup>C NMR spectra were recorded on Bruker Avance AV 100MHz Spectrometer. Mass studies were performed on LC-MS system equipped with Agilent 1100 series, LC/MSD detector and 1100 series Agilent HPLC pump. Normal phase silica gel (ACME, 100-200 mesh) was used for column chromatography. Silica gel pre-coated plates (Alugram Sil G/UV<sub>254</sub>) were used for thin layer chromatography using the solvent system CHCl<sub>3</sub>/MeOH (9:1) and visualized by immersing the plate in vanillin sulfuric acid reagent followed by heating at 110°C.

**2, 3-Dimethoxy-5-methyl hydroquinone (2):** 2, 3-dimethoxy-5-methylquinone (6 g, 0.0329 mol) and

48 mL of acetonitrile, 12 mL of water and sodium dithionate (8.6 g, 0.0494 mol) were taken in a round bottom flask. Reaction mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was poured in to ice cold water and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum at 40°C temperature to yield 2 (5.5 g, 90.7%).

**2, 3-Dimethoxy-5-methyl-6-prenylquinol (3):** A mixture of 2, 3-Dimethoxy-5-methylhydroquinone (2, 5.5 g, 0.0298 mol), 28 mL of carbon tetrachloride and 2-methyl-3-buten-2-ol (4.1 g, 0.0476 mol) was taken in a round bottom flask. Under vigorous stirring, BF<sub>3</sub> etherate (0.85 g, 0.00597 mol) was added drop wise to reaction mixture at 0-5°C. Then reaction mixture was allowed to warm up to room temperature and continued the stirring. After 3 h, the reaction mixture was poured into ice cold water and the mixture extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum at 40°C to obtain 3 (8 g, 96.1%).

**2, 3, 4, 5-Tetramethoxy-6-prenyl toluene (4):** 2, 3-dimethoxy-5-prenyl-6-methyl quinol (3, 8 g, 0.03174 mol) and sodium hydroxide (5 g, 0.125 mol) were dissolved in 21 mL of water in a round bottom flask. Dimethyl sulphate (19.9 g, 0.1587 mol) was slowly added to reaction flask at room temperature and the reaction mixture was stirred at 90°C for 2 h. After completion, the reaction mixture was poured in to ice cold water, acidified with 5N H<sub>2</sub>SO<sub>4</sub> and extracted with EtOAc and the organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residue (9 g) was subjected to column chromatography over silica gel using 2% EtOAc/hexane to yield 4 (6.9 g, 78%).

**IR (CHCl<sub>3</sub>) v<sub>max</sub> cm<sup>-1</sup>:** 2933, 1467, 1407, 1350, 1258, 1196, 1100, 1070, 1042, 1015 ; <sup>1</sup>H NMR δ (400 MHz, CDCl<sub>3</sub>): 4.97 (1H, m), 3.83 (3H, s), 3.82 (3H, s), 3.71 (3H, s), 3.71 (3H, s), 3.23 (2H, d, J = 6.80 Hz), 2.07 (3H, s), 1.70 (3H, d, J = 0.8 Hz), 1.61 (3H, d, J = 0.8 Hz); <sup>13</sup>C NMR δ (100 MHz, CDCl<sub>3</sub>): 147.88, 147.69, 144.96, 144.72, 131.30, 129.15, 125.25, 122.94, 61.02, 60.99, 60.61, 25.91, 25.63, 17.86, 11.66; LCMS (ESI, positive scan): m/z 303 (M+Na)<sup>+</sup>.

**2, 3, 4, 5-Tetramethoxy-6-(2-methylbut-2-ene-1-yl)toluene (5) and 2, 3, 4, 5-tetramethoxy-6-(2-methylbut-2-ene-1-ol-4-yl)toluene (6):** To a solution of 2, 3, 4, 5-tetramethoxy-6-prenyl toluene (4, 7.3 g, 0.06576 mol) in ethanol (100 mL) was slowly added

SeO<sub>2</sub> (32.5 g, 0.2959 mol) at room temperature and the reaction mixture was stirred at room temperature for 4 h. After completion of the reaction, the mixture was poured in to ice water and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to obtain a mixture of 5 and 6 (5.5 g, 80%). For identification purpose, a small sample (0.5 g) of the mixture was subjected to silica column chromatography using hexane and ethyl acetate mixtures. The fractions eluted with 15% EtOAc/hexane were monitored, identical fractions combined and evaporated to yield 5 (225 mg). Similarly, the fractions eluted with 30% EtOAc/hexane were monitored and identical fractions combined and evaporated to obtain 6 (150 mg).

**2, 3, 4, 5-Tetramethoxy-6-(2-methylbut-2-ene-1-ol-4yl) toluene (5):** IR (CHCl<sub>3</sub>)  $\nu_{\max}$  cm<sup>-1</sup>: 2932, 1687, 1467, 1407, 1352, 1219, 1104, 1039; <sup>1</sup>H NMR  $\delta$  (400 MHz, CDCl<sub>3</sub>): 9.30 (1H, s), 6.32 (1H, m), 3.84 (3H, s), 3.83 (3H, s), 3.74 (3H, s), 3.72 (3H, s), 3.58 (2H, dd, J = 6.8, 0.8 Hz), 2.07 (3H, s), 1.83 (3H, d, J = 1.2 Hz), <sup>13</sup>C NMR  $\delta$  (100 MHz, CDCl<sub>3</sub>): 195.06, 152.56, 148.07, 147.87, 145.94, 144.88, 138.92, 125.50, 125.28, 61.03, 61.00, 60.96, 60.68, 26.99, 11.93, 9.29; LCMS (ESI, positive scan): m/z 295 (M+H)<sup>+</sup>, m/z 317 (M+Na)<sup>+</sup>, m/z<sup>-1</sup> 333 (M+K)<sup>+</sup>.

**2, 3, 4, 5-Tetramethoxy-6-(2-methylbut-2-ene-1-ol-4yl)toluene (6):** IR (CHCl<sub>3</sub>)  $\nu_{\max}$  cm<sup>-1</sup>: 3432, 2935, 2862, 1466, 1407, 1351, 1219, 1105, 1067, 1039, 1013; <sup>1</sup>H NMR  $\delta$  (400 MHz, CDCl<sub>3</sub>): 5.26 (1H, m), 3.93 (2H, s), 3.83 (3H, s), 3.82 (3H, s), 3.72 (3H, s), 3.70 (3H, s), 3.29 (2H, dd, J = 6.8, 0.8 Hz), 2.07 (3H, s), 1.76 (3H, s), <sup>13</sup>C NMR  $\delta$  (100 MHz, CDCl<sub>3</sub>): 147.93, 147.72, 145.19, 144.75, 134.68, 128.29, 125.23, 124.52, 68.83, 61.02, 60.99, 60.63, 25.51, 13.81, 11.76; LCMS (ESI, positive scan): m/z 319 (M+Na)<sup>+</sup>, m/z 335 (M+K)<sup>+</sup>.

**2, 3, 4, 5-Tetramethoxy-6-(2-methylbut-2-ene-1-ol-4yl)toluene (6):** The mixture of 5 and 6 from the previous reaction (5.5 g, 0.01864 mol) was dissolved in 55 mL of ethanol and treated slowly with sodium borohydride (413 mg, 0.01116 mol) at room temperature and the reaction mixture was stirred at room temperature. After 2 h, the reaction mixture was poured into ice cold water, acidified with 5N HCl and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residue (5 g) was subjected to column chromatography over silica using 5,10,15 and 20% hexane/EtOAc mixtures. The product eluted with 15 and 20% mixtures of EtOAc/hexane were monitored,

combined and evaporated under vacuum to obtain 6 (3.5 g, 65%).

**2, 3, 4, 5-Tetramethoxy-6-(1-bromo-2-methylbut-2-ene-4yl) toluene (7):** 2, 3, 4, 5-Tetramethoxy-6-(2-methylbut-2-ene-1-ol-4yl) toluene (6, 2 g, 0.006756 mol) was dissolved in 10 mL of tetrahydrofuran and treated with pyridine (0.1 g, 0.001689 mol). PBr<sub>3</sub> (0.66 g, 0.002477 mol) was slowly added to the reaction mixture at 0°C for 15 min. After 30 min, the reaction mixture was poured into ice cold saturated sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residue (2.6 g) was subjected to column chromatography over silica gel using hexane and 2% EtOAc/hexane mixtures. The fractions eluted with 2% EtOAc/hexane mixture were combined and evaporated to obtain 7 (2.2 g, 92%).

IR (CHCl<sub>3</sub>)  $\nu_{\max}$  cm<sup>-1</sup>: 2934, 1466, 1408, 1351, 1200, 1105, 1073, 1039, 1012, 974; <sup>1</sup>H NMR  $\delta$  (400 MHz, CDCl<sub>3</sub>): 5.44 (1H, t, J = 6.8 Hz), 3.89 (2H, s), 3.83 (3H, s), 3.82 (3H, s), 3.72 (3H, s), 3.71 (3H, s), 3.28 (2H, d, J = 6.8 Hz), 2.06 (3H, s), 1.85 (3H, d, J = 0.8 Hz); <sup>13</sup>C NMR  $\delta$  (100 MHz, CDCl<sub>3</sub>): 147.95, 147.78, 145.39, 144.78, 131.75, 129.65, 127.36, 125.27, 61.04, 61.02, 60.98, 60.64, 41.48, 26.23, 14.81, 11.77; LCMS (ESI, positive scan): m/z 361 (M+H)<sup>+</sup>, m/z 383 (M+Na)<sup>+</sup>.

**2, 3, 4, 5-Tetramethoxy-6-(1-p-toluenesulphinyl-2-methylbut-2-ene-4yl)toluene (8):** But-2-ene-2-methyl-1-bromo-4-yl tetramethoxytoluene (1 g, 0.00277 mol) was dissolved in 10 mL of dry dichloromethane treated with triethylamine (0.28 g, 0.00277 mol). Sodium 4-toluene sulphinate (493 mg, 0.00278 mol) was slowly added in portions wise to the reaction mixture and stirred at room temperature for 3 h. Then the reaction mixture was poured in to ice cold water and acidified to pH 4 with 5N HCl and then extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was subjected to column chromatography over silica gel using hexane 5, 10 and 15% EtOAc/hexane mixtures. The fractions eluted with 15% of EtOAc in hexane were monitored and the fractions containing the compound were combined evaporated to afford 8 (1 g, 83.3%).

IR (CHCl<sub>3</sub>)  $\nu_{\max}$  cm<sup>-1</sup>: 2933, 1594, 1463, 1410, 1352, 1309, 1212, 1108, 1040, 970; <sup>1</sup>H NMR  $\delta$  (400 MHz, CDCl<sub>3</sub>): 7.58 (2H, d, J = 8.0 Hz), 7.15 (2H, d, J = 8.0 Hz), 4.85 (1H, t, J = 6.4 Hz), 3.83 (3H, s), 3.80 (3H, s), 3.70 (3H, s), 3.63 (3H, s), 3.61 (2H, s), 3.17 (2H, d, J = 6.8 Hz), 2.32 (3H, s), 1.91 (3H, s), 1.86 (3H, d,

J = 1.2 Hz);  $^{13}\text{C}$  NMR  $\delta$  (100MHz,  $\text{CDCl}_3$ ): 147.84, 147.63, 145.32, 144.67, 144.29, 135.59, 134.29, 129.40, 128.45, 127.18, 125.13, 123.50, 66.14, 61.00, 60.94, 60.89, 60.61, 26.22, 21.49, 16.98, 11.64; LCMS (ESI, positive scan): m/z 435 (M+H) $^+$ .

**Synthesis of 9:** 2, 3, 4, 5-Tetramethoxy-6-(1-p-toluenesulphonyl-2-methylbut-2-ene-4-yl) toluene (1 g, 0.002304 mol) and solanesol bromide (2.4 g, 0.00345 mol) were dissolved in 10 mL of tetrahydrofuran. Separately, potassium ter-butoxide (520 mg, 0.004634 mol) was suspended in 10 mL of tetrahydrofuran and added dropwise to the above solution containing 2, 3, 4, 5-tetramethoxy-6-(1-p-toluenesulphonyl-2-methylbut-2-ene-4-yl)toluene and solanesol bromide at  $-20^\circ\text{C}$ . After 30 min, the reaction mixture was allowed to reach ambient temperature and continued the stirring for 2 h. The contents were then poured in to ice water and the mixture was acidified to pH 4 with 5N HCl and extracted with EtOAc. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum. The residue was subjected to column chromatography over silica gel by eluting with hexane followed by 2 and 5% EtOAc/hexane mixtures. The fractions eluted with 5% EtOAc/hexane were combined and evaporated to yield 9 (1.78 g, 74%).

**IR ( $\text{CHCl}_3$ )  $\nu_{\text{max}}$   $\text{cm}^{-1}$ :** 2925, 2854, 1597, 1465, 1406, 1383, 1314, 1219, 1145, 1105, 1086, 1041;  $^1\text{H}$  NMR  $\delta$  (400 MHz,  $\text{CDCl}_3$ ): 7.57 (2H, d, J = 8.0 Hz), 7.15 (2H, d, J = 8.0 Hz), 5.02 (10H, m) 3.82 (3H, s), 3.79 (3H, s), 3.68 (3H, s), 3.58 (3H, s), 2.32 (3H, s), 1.99 (18H, m), 1.90 (20H, m), 1.85 (3H, s), 1.75 (3H, s), 1.60 (6H, s), 1.51 (15H, s), 1.49 (3H, s);  $^{13}\text{C}$  NMR  $\delta$  (100MHz,  $\text{CDCl}_3$ ): 145.24, 144.67, 138.44, 135.31, 134.93, 134.86, 134.15, 129.52, 129.24, 128.87, 124.44, 124.31, 124.25, 118.79, 73.87, 66.32, 60.94, 60.88, 60.58, 39.74, 26.75, 26.70, 25.62, 21.58, 17.63, 16.28, 15.99, 11.54; LCMS (ESI, positive scan): m/z 1046 (M+H) $^+$ .

**2, 3, 4, 5-Tetramethoxy-6-decaprenyltoluene (10):** To a solution of 9 (800 mg, 0.7648 mmol) in 8ml of THF was added ethanol (1.23 g, 0.02676 mol). Sodium (146 mg, 10.707 mmol) pieces were slowly added to the reaction mixture under vigorous stirring at room temperature and continued the stirring for 9 h. Then the reaction was quenched by pouring into ice water and the mixture extracted with EtOAc. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was subjected to column chromatography using hexane and 2% EtOAc/hexane. The fractions eluted with 2% EtOAc/hexane mixture were monitored, identical

fractions combined and evaporated to obtain 10 (540 mg, 79%)

**IR ( $\text{CHCl}_3$ )  $\nu_{\text{max}}$   $\text{cm}^{-1}$ :** 2963, 2925, 2854, 1665, 1465, 1407, 1382, 1352, 1196, 1105, 1043;  $^1\text{H}$  NMR  $\delta$  (400 MHz,  $\text{CDCl}_3$ ): 5.04 (10H, t, J = 6.40 Hz), 3.83 (3H, s), 3.83 (3H, s), 3.71 (3H, s), 3.70 (3H, s), 3.20 (2H, d, J = 6.4 Hz), 2.10 (3H, s), 1.99 (20H, m), 1.91 (18H, m), 1.60 (3H, s), 1.52 (3H, s);  $^{13}\text{C}$  NMR  $\delta$  (100 MHz,  $\text{CDCl}_3$ ): 147.88, 147.70, 135.11, 135.03, 134.91, 134.86, 131.16, 129.79, 124.89, 124.45, 124.30, 124.24, 124.15, 123.43, 123.17, 122.92, 61.02, 60.91, 60.60, 60.56, 40.12, 39.74, 39.72, 27.02, 26.80, 25.62, 23.34, 17.63, 16.21, 11.68, 11.54; LCMS (ESI, positive scan): m/z 915 (M+Na) $^+$ .

**Coenzyme Q<sub>10</sub> (1):** 2, 3, 4, 5-Tetramethoxy-6-decaprenyltoluene (10, 300 mg, 0.00034 mol) was dissolved in a mixture of 1.25 mL of acetonitrile and 1.25 mL of dichloromethane. Ceric ammonium nitrate (560 mg, 0.00102 mole) was slowly added to the reaction mixture at  $0^\circ\text{C}$  followed by 3 mL of aqueous acetonitrile and the reaction mixture was stirred at  $10^\circ\text{C}$ . After 1 h, the reaction mixture was poured in to ice cold water and extracted with EtOAc. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and evaporated under vacuum. The residue was subjected to column chromatography over silica gel using hexane and 2% EtOAc/hexane mixture. The fractions eluted with 2% EtOAc/hexane mixture were monitored, the fraction containing the product combined and evaporated to yield C<sub>6</sub>Q<sub>10</sub> (1, 210 mg, 72%).

**IR ( $\text{CHCl}_3$ )  $\nu_{\text{max}}$   $\text{cm}^{-1}$ :** 2923, 2853, 1743, 1653, 1611, 1146, 1265, 1201, 1150, 1098, 1023;  $^1\text{H}$  NMR  $\delta$  (400 MHz,  $\text{CDCl}_3$ ): 5.04 (10H, t, J = 6.4 Hz), 3.91 (3H, s), 3.90 (3H, s), 3.12 (2H, d, J = 6.8 Hz), 1.99 (20H, m), 1.94 (3H, s), 1.91 (18H, m), 1.60 (6H, s), 1.53 (3H, s), 1.52 (21H, s);  $^{13}\text{C}$  NMR  $\delta$  (100 MHz,  $\text{CDCl}_3$ ): 183.87, 141.71, 138.85, 137.85, 137.62, 135.15, 134.93, 134.86, 131.17, 125.05, 124.64, 124.44, 124.30, 123.87, 118.92, 61.06, 40.02, 39.74, 39.72, 38.35, 32.00, 29.67, 29.32, 27.00, 26.80, 26.75, 26.71, 26.57, 26.36, 25.63, 25.30, 25.15, 232.38, 17.63, 16.00, 15.97, 11.87, 11.82; LCMS (ESI, positive scan): m/z 863 (M+H) $^+$ , m/z 885 (M+Na) $^+$ , m/z 901 (M+K) $^+$ .

## RESULTS

The synthesis of CoQ<sub>10</sub> was carried out in nine steps as shown in Fig. 1. 2, 3-Dimethoxy-5-methylquinone was reduced to 2 with sodium dithionite in 90.7% yield. The reaction of 2, 3-dimethoxy-5-methylhydroquinone (2) with isoprenol in presence of

BF<sub>3</sub> etherate in carbon tetrachloride yielded the prenylated hydroquinone (3) in 96% yield. The di-O-methylation of the hydroquinone using dimethylsulphate yielded 2, 3, 4, 5-tetramethoxy-6-prenyltoluene (4) in 78% yield. The oxidation of the terminal methyl in the prenyl side chain with selenium dioxide yielded 5 and 6 in 80% overall yield. The mixture of 5 and 6 was subjected to reduction using sodium borohydride to yield the (2E)-4-[2, 3, 4, 5-tetramethoxy-6-methylphenyl] but-2-en-1-ol (6) in 65% yield. The alcohol 6 was converted to the bromide 7 using PBr<sub>3</sub> in 92% yield and then subjected to p-toluenesulfonation using sodium p-toluene sulphinate in dry dichloromethane to give p-toluenesulfinate 8 in 83% yield. The p-toluenesulfinate (8) was nonaprenylated using solanesyl bromide in presence of strong base potassium tert-butoxide to obtain 9 in 74% yield. The reductive de-p-toluenesulfonation of 9 using sodium in ethanol yielded 10 in 79% yield. Finally CAN oxidation of 10 in 1:1 mixture of dichloromethane and acetonitrile, followed by column chromatography and crystallization afforded CoQ<sub>10</sub> (1) in 72% yield.

## DISCUSSION

Coenzyme (CoQ<sub>10</sub>), a member of the ubiquinone family, is an essential component of the mitochondrial electron transfer chain. It is widely being used for cardiac health and also as an antioxidant. It also holds promise as an anticancer agent. The commercial quantities, however, limited as the CoQ<sub>10</sub> in the market is solely derived from the fermentation technology and the available synthetic methodologies are not commercially feasible. The present study has been an attempt towards the cost viable synthesis of CoQ<sub>10</sub>.

A new synthetic route for the preparation of CoQ<sub>10</sub> is described. The key steps include prenylation of the substituted quinol moiety with a relatively inexpensive isoprenol and selective oxidation of trans methyl group in the prenylated intermediate to obtain the substituted prenyl as an essential precursor for the expansion of the side chain to decaprenyl group. The reaction of 2, 3-dimethoxy-5-methylhydroquinone with isoprenol in presence of BF<sub>3</sub> etherate yielded the prenylated hydroquinone (3). It was then subjected to di-O-methylation, followed by oxidation of terminal methyl with selenium dioxide to yield a mixture of 5 and 6. The mixture of 5 and 6 without further separation was subjected to sodium borohydride reduction to yield the (2E)-4-[2, 3, 4, 5-tetramethoxy-6-methylphenyl]but-2-en-1-ol (6). The alcohol was converted to the bromide (7) using PBr<sub>3</sub> and then subjected to p-toluenesulfonation. The p-toluenesulfinate (8) was nona-

prenylated using solanesyl bromide in presence of a strong base to obtain 9. This advanced intermediate 9 was de-p-toluenesulfinated using sodium in ethanol to obtain the dimethyl derivative of CoQ<sub>10</sub> quinol. Finally CAN oxidation of 10 was afforded CoQ<sub>10</sub> (1). The pure CoQ<sub>10</sub> was isolated from the crude reaction mixture using column chromatography followed by crystallization in 13% overall yielded.

## CONCLUSION

CoQ<sub>10</sub> is a potentially useful compound having wide number of health applications especially those related to cardiovascular diseases. Though the CoQ<sub>10</sub> from biotechnology process can able to meet the current demand, no commercially viable synthetic process is available. The present process achieves CoQ<sub>10</sub> starting from relatively inexpensive precursor, called isoprenol. It achieves key synthetic intermediate 8, needed for the expansion of the prenyl chain, through a novel viable process. This is more economical than expanding expensive natural nonaprenyl compound called solanesol by an isoprene unit before coupling to the Q<sub>0</sub> precursor. This process can also be used to produce other CoEnzyme Q compounds having different number of isoprene units per side chain.

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## REFERENCES

1. Ernster, L. and G. Dallner, 1995. Biochemical, physiological and medical aspects of ubiquinone function. *Biochim. Biophys. Acta*, 1271: 195-204. <http://www.ncbi.nlm.nih.gov/pubmed/7599208>
2. Overvad, K., B. Diamant, L. Holm, G. Holmer, S.A. Mortensen and S. Stender, 1999. Conzyme Q<sub>10</sub> in health and disease. *Eur. J. Clin. Nutr.*, 53: 764-770. <http://www.nature.com/ejcn/journal/v53/n10/abs/1600880a.html>
3. Otani, H., H. Tanaka, T. Inoue, M. Umemoto, K. Omoto, K. Tanaka, T. Sato, T. Osako, A. Masuda, A. Nonoyama and T. Kagawam, 1984. *In vitro* study on contribution of oxidative metabolism of isolated rabbit heart mitochondria to myocardial reperfusion injury. *Circ. Res.*, 55: 168-175.

- <http://circres.ahajournals.org/cgi/content/abstract/5/2/168>
- Singh, R.B., G.S. Wander, A. Rastogi, P.K. Shukla, A. Mittal, J.P. Sharma, S.K. ehrotra, R. Kapoor and R.K. Chopra, 1998. Randomized, double-blind placebo-controlled trial of coenzyme Q<sub>10</sub> in patients with acute myocardial infarction. *Cardiovasc. Drug Ther.*, 12: 347-353. DOI: 10.1023/a:1007764616025
  - Warner, M.G., 2000. Complimentary and alternative therapies for hypertension. *Complementary Health. Pract. Rev.*, 6: 11-19. <http://chp.sagepub.com/cgi/reprint/6/1/11>
  - Matsura, T., K.Yamada and T. Kawasaki, 1992. Difference in antioxidant activity between reduced coenzyme Q<sub>9</sub> and reduced coenzyme Q<sub>10</sub> in the cell: Studies with isolated rat and guinea pig hepatocytes treated with a water-soluble adical initiator. *Biochim. Biphys. Acta*, 1123: 309-315. <http://www.ncbi.nlm.nih.gov/pubmed/1536870>
  - Folkers, K., S. Vadhanavikit and S.A. Mortensen, 1985. Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q<sub>10</sub>. *Proc. Natl. Acad. Sci. USA.*, 82: 901-904. <http://www.pnas.org/content/82/3/901.abstract>
  - Dallner G. and Stocker R., 2005. Coenzyme Q. *Encyclopedia of Dietary Supplements*, Dekker, M. (Ed.). Chapman and Hall/CRC Press/Kluwer, New York, ISBN: 0-8547-5504-4 9, pp: 819.
  - Ruegg, R., U. Gloor, R.N. Goel, G. Ryser, O. Wiss and O. Isler, 1959. Synthese von ubichinon(45) and ubichinon (50). *Helv. Chim. Acta*, 52: 2616. DOI: 10.1002/hlca.19590420733
  - Inoue, S., R. Yamaguchi, K. Saito and K. Sato, 1974. The synthesis of coenzyme Q. *Bull. Chem. Soc. Jap.*, 47: 3098. DOI: 10.1246/bcsj.47.3098
  - Naruta, Y. and K. Maruyama, 1979. Regio and stereocontrolled polyprenylation of quinines. A new synthetic method of coenzyme Q<sub>2</sub>, Q<sub>3</sub> Q<sub>9</sub> and Q<sub>10</sub>. *Chem. Lett.*, 885. DOI: 10.1246/cl.1979.885
  - Yoshizawa, T., H. Toyofuku, K. Tachibana and T. Kuroda, 1982. Regioselective polyprenyl rearrangement of polyprenyl 2, 3, 4, 5-tetrasubstituted phenyl ethers promoted by boron trifluoride. *Chem. Lett.*, 11: 1131-1134. DOI: 10.1246/cl.1982.1131
  - Eto, H. and C. Eguchi, 1988. Novel solvent effect in the practical synthesis of Ubiquinone-10. *Chem. Lett.*, 1597. DOI: 10.1246/cl.1988.1597
  - Van Liemt, W.B.S., W.F. Steggerda, R. Esmeijer and J. Lugtenburg, 1994. Synthesis and spectroscopic characterization of <sup>13</sup>C-labelled ubiquinone-0 and ubiquinone-10. *Recl. Trav. Chim. Pays-Bas.*, 113: 153-161. <http://www.scopus.com/scopus/record/display.url?eid=2-s2.0-0001946801&view=basic&origin=inward&txGid=T371xC8G9sc8FxnM-Q-fBV1%3a2>
  - Terao, S. K. Kato, M. Shiraiishi and H. Morimoto, 1979. Synthesis of ubiquinones. 2. An efficient preparation of ubiquinone-10. *J. Org. Chem.*, 44: 868. DOI: 10.1021/jo01319a051
  - Fujita, Y., M. Ishiguro, T. Onishi and T. Nishida, 1982. A new efficient and stereoselective synthesis of Ubiquinone-10. *Bull. Chem. Soc. Jap.*, 55: 1325. DOI: 10.1246/bcsj.55.1325
  - Sato, K., O. Miyamoto, S. Inoue, T. Yamamoto and Y. Hirasawa, 1982. An efficient stereoselective synthesis of co-enzyme Q<sub>10</sub>. *J. Chem. Soc., Chem. Commun.*, 153. DOI: 10.1039/C39820000153
  - Masaki, Y., K. Hashimoto and K. Kaji, 1984. Synthetic studies on isoprenoidquinones. 1. A facile region and stero controlled synthesis of protected hydroquinones with an omega-hydroxyphenyl or omega-hydroxygeranyl side chain. *Chem. Pharm. Bull.*, 32: 3959. [http://www.journalarchive.jst.go.jp/english/jnlabstract\\_en.php?cdjournal=cpb1958&cdvol=32&noissue=10&startpage=3959](http://www.journalarchive.jst.go.jp/english/jnlabstract_en.php?cdjournal=cpb1958&cdvol=32&noissue=10&startpage=3959)
  - Masaki, Y., K. Hashimoto, K. Sakuma and K. Kaji, 1984. Synthetic studies on isoprenoidquinones. II. Syntheses of Ubiquinone-10, phylloquinone, and Menaquinone-4 by a chain-extending method utilizing terminally functionalized isoprenoidhydroquinones. *Chem. Pharm. Bull.*, 32: 3952. [http://www.journalarchive.jst.go.jp/english/jnlabstract\\_en.php?cdjournal=cpb1958&cdvol=32&noissue=10&startpage=3952](http://www.journalarchive.jst.go.jp/english/jnlabstract_en.php?cdjournal=cpb1958&cdvol=32&noissue=10&startpage=3952)
  - Mohri, M., H. Kinoshita, K. Inomata, H. Kotake, H. Takagaki and K. Yamazaki, 1986. Palladium-catalyzed regio and streoselective reduction of allylic compounds with LiBEt<sub>3</sub>. Application to the synthesis of Co-enzyme Q<sub>10</sub>. *Chem. Lett.*, 15: 1177-1180. DOI: 10.1246/cl.1986.1177
  - Lipshutz, B.H., P. Mollard, S.S. Pfeiffer and W. Chrisman, 2002. A short, highly efficient

- synthesis of coenzyme Q<sub>10</sub>. *J. Am. Chem. Soc.*, 124: 14282-14283. DOI: 10.1021/ja021015v
22. Min, J.H., J.S. Lee, J.D. Yang and S. Koo, 2003. The Friedel-Crafts allylation of a prenyl group stabilized by a sulfonemioety: Expeditious syntheses of ubiquinones and menaquinones. *J. Org. Chem.*, 68: 7925-7927. DOI: 10.1021/jo0350155
  23. Eren, D. and E. Keinan, 1988. Total synthesis of linear polyprenoids. 3. Syntheses of ubiquinones via palladium-catalyzed oligomerization of monoterpene monomers. *J. Am. Chem. Soc.*, 110: 4356-4362. DOI: 10.1021/ja00221a040
  24. Keinan, E. and D. Eren, 1988. Total synthesis of polyprenoid natural products via Pd(0)-catalyzed oligomerizations. *Pure Applied Chem.*, 60: 89-98. <http://media.iupac.org/publications/pac/1988/pdf/6001x0089.pdf>
  25. Yanagisawa, A., N. Nomura, Y. Nortitake and H. Yamamoto, 1991. Highly S<sub>N</sub>2', (E)-, and antiselective alkylation of allylic phosphates. Facile synthesis of coenzyme Q<sub>10</sub>. *Synthesis*, 12: 1130-1036. <http://cat.inist.fr/?aModele=afficheN&cpsidt=5179286>
  26. Negishi, E.I., S.Y. Liou, C.D. Xu and S.Q. Huo, 2002. A novel, highly selective and general methodology for the synthesis of 1,5-diene-containing oligoisoprenoids of all possible geometrical combinations exemplified by an iterative and convergent synthesis of Coenzyme Q<sub>10</sub>. *Org. Lett.*, 4: 261-264. DOI: 10.1021/oL010263d
  27. Folkers, K. and Y. Yamaura, 1984. Biomedical and clinical aspects of coenzyme Q. *Proceedings of the International Symposium on Coenzyme Q*, Oct. 24-26, Martinsried, Munich, West Germany, pp: 432. <https://www.alibris.com/search/books/isbn/9780444803801>