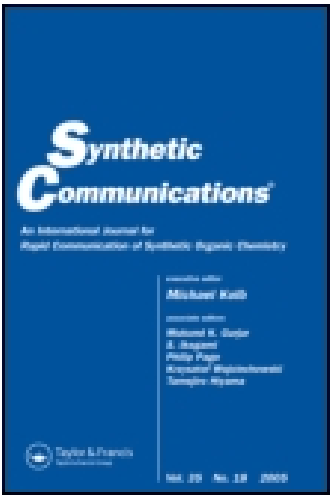


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# A Novel and Convenient Synthesis of Coenzyme $Q_1$

Liang Lu [a] & Fener Chen [a]
[a] Department of Chemistry , Fudan University , 220 Handan Road, Shanghai, 200433, P.R. China
Published online: 10 Jan 2011.

To cite this article: Liang Lu & Fener Chen (2004) A Novel and Convenient Synthesis of Coenzyme $Q_1$ , Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:22, 4049-4053, DOI: 10.1081/SCC-200036578

To link to this article: http://dx.doi.org/10.1081/SCC-200036578

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 22, pp. 4049–4053, 2004

# A Novel and Convenient Synthesis of Coenzyme $Q_1$

**Liang Lu and Fener Chen***

Department of Chemistry, Fudan University, Shanghai, P.R. China



## ABSTRACT

A convenient and efficient synthetic route to Coenzyme $Q_1$ (**6**) starting from 3,4,5-trimethoxytoluene (**1**) is described. The key features of this synthesis include the Diels–Alder reaction of 2,3-dimethoxy-l,4-benzoquinone (**3**) with cyclopentadiene and the introduction of a $C_5$ side chain to 4,5-dimethoxy-2-methyltricyclo[6.2.1.$0^{2,7}$]undeca-4,9-diene-3,6-dione (**4**) under mild conditions, (**6**) was obtained in overall 60% yield.

*Key Words:* Coenzyme $Q_1$; Diels–Alder reaction; Synthesis.

Coenzyme $Q_1$ (**6**) is an important fragment of Coenzyme Q series which function in the electron transport and oxidative phosphorylation processes in mitochondria.[1] Besides its bioactivities, it also acts as a key intermediate in

*Correspondence: Fener Chen, Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, P.R. China; E-mail: rfchen@fudan.edu.cn.

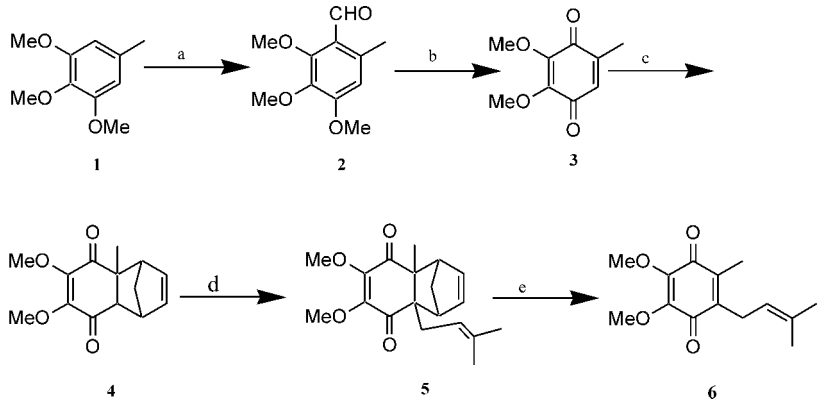


DOI: 10.1081/SCC-200036578 0039-7911 (Print); 1532-2432 (Online)

the synthesis of higher homologs.[2] There have been several attempts to prepare (**6**).[2–4] However, none of them is attractive enough for the large-scale synthesis of (**6**) due to the drawbacks such as the use of some expensive, severe reaction conditions, tedious chromatography separation, etc. Therefore, a convenient and practical method for the synthesis of (**6**) is still in demand. Herein we described a novel and practical synthesis of (**6**) which used a Diels–Alder approach to activate the free quinoid position for alkylation (**Scheme 1**).

Treatment of 3,4,5-trimethoxytoluene (**1**) with $POCl_3$ in DMF at 80°C for 1.5 hr afforded aldehyde (**2**) in 96% yields.[5] In the presence of p-TsOH, (**2**) was oxidized with 30% $H_2O_2$,[6] without separation, and the resulting mixture was oxidized with $Na_2Cr_2O_7$ at r.t. to afford benzoquinone (**3**) as red needle crystals.

The Diels–Alder reaction of (**3**) with cyclopentadiene in $CH_2Cl_2$ failed.[7] However the yield is almost quantitative when the above reaction performed in acetic acid. It is known that 4,5-dimethoxy-2-methyltricyclo[6.2.1.$0^{2,7}$]undeca-4,9-diene-3,6-dione (**4**) could be converted into enolate by potassium tert-butoxide in $Et_2O$ or THF at low temperatures. Then C—C bond formations with various alkenyl bromides at the free bridgehead position could proceed.[7] Our attempts to obtain 2-(3-methyl-2-butenyl)-4,5-dimethoxy-7-methyltricyclo[6.2.1.$0^{2,7}$]undeca-4,9- diene-3,6-dione (**5**) via the similar conditions resulted in moderate yield. After many trials, we established optimal conditions for this condensation. Best yield (93%) of the desired product (**5**)




***Scheme 1.*** Reagents and conditions: (a) $POCl_3$, DMF, 80°C, 1.5 hr, 96%. (b) i)30%$H_2O_2$, p-TsOH, 30°C., 2 hr. ii) $Na_2Cr_2O_7$, r.t., 1 hr, 70%. (c) $CH_3COOH$, cyclopentadiene, r.t., 6 hr, 99%. (d) 60% NaH, 1-bromo-3-methyl-2-butene, THF, 0°C, 6 hr, 93%. (e) 85°C 3 hr, 98%.

was obtained when NaH (1.2 eq) was used as the base (**Table 1**). After thermal elimination of (**5**), Coenzyme $Q_1$ was obtained in overall 60% yield.

In conclusion, this method has the advantages of mild conditions, easily accessible starting materials and easiness of separation. It can be a promise method for the industrial synthesis of Coenzyme $Q_1$ and it should provide a general method for synthesizing higher homologs.

## EXPERIMENTAL

Melting points were measured on an WRS-1B digital melting point apparatus without correction. Infra red spectra (IR) were recorded on an Avvatar 360 FT-IR instrument. $^1$HNMR spectra were recorded with a Bruker DMX500 (500 MHz). Chemical shifts (d) were expressed in ppm with the protonated solvent as reference. Mass spectra (MS) were recorded on MAT95 and for the electronic impacts (EI) at 70 eV.

### 2,3,4-Trimethoxy-6-methylbenylaldehyde (2)

To a stirred solution of 3,4,5-trimethoxytoluene (100 g, 0.549 mol) in DMF (100 mL), $POCl_3$ (94.5 g, 0.6 mol) was added dropwise at 40–50°C over a period of 1 hr. The reaction mixture was stirred at 80°C for another 1.5 hr. After being cooled to r.t., the reaction mixture was adjusted to PH = 7 with 10% aq. NaOH. The precipitate was collected by filtration, dried to give (**2**) (110.7 g, 96%) as a white solid.

m.p: 60–61°C (lit.[5] 61–61.5°C). IR: 1686 $cm^{-1}$. $^1$HNMR: d 2.02 (d, 3H), 3.89 (s, 9H), 7.20 (s, 2H), 9.90 (s, 1H). MS (m/z): 210 ($M^+$).

***Table 1.*** Summary of the results obtained from the condensation between (**4**) and 1-bromo-3-methyl-2-butene under the conditions indicated.

| Reaction condition | | | | | |
|---|---|---|---|---|---|
| Base | Ratio of **4** : base | Solvent | Temp. | Time (hr) | Yields of products (%) |
| t-BuOK | 1 : 1.1 | $Et_2O$ | −70°C–40°C | 2 | 66 |
| t-BuOK | 1 : 1.1 | THF | −40°C–20°C | 1.5 | 67 |
| t-BuOK | 1 : 1.2 | THF | −40°C–20°C | 1.5 | 73 |
| 60%NaH | 1 : 1.1 | $Et_2O$ | 0°C | 6 | 81 |
| 60%NaH | 1 : 1.1 | THF | 0°C | 6 | 84 |
| 60%NaH | 1 : 1.2 | THF | 0°C | 6 | 93 |

### 2,3-Dimethoxy-l,4-benzoquinone (3)

To a stirred solution of (**2**) (40 g, 0.204 mol), p-TsOH (13.3 g, 0.08 mol) in methanol (150 mL), 30% $H_2O_2$ (19.2 mL, 0.245 mol) was added dropwise at 30°C over a period of 45 min. The reaction mixture was stirred at 30°C for additional 2 hr. Then $Na_2Cr_2O_7$ (26 g, 0.1 mol) in water (100 mL) was added dropwise at r.t. over 30 min. After stirring for another 1 hr at r.t., the reaction mixture was extracted with petroleum ether (50 mL × 3). The combined organic phase was washed with brine (30 mL × 3) and dried over $Na_2SO_4$, filtered, and evaporated to dryness in vacuo to give (**3**) (26 g, 70%) as red needles.

m.p: 56–58°C (lit.[8] 57–58°C). IR: 1671, 1655 $cm^{-1}$, $^1$HNMR (500 MHz, $CDCl_3$): d 2.04 (d, 3H), 3.99 (s, 3H), 4.00 (s, 3H), 6.40 (q, 1H); EI-MS (m/z): 182 ($M^+$).

### 4,5-Dimethoxy-2-methyltricyclo[6.2.1.$0^{2,7}$]undeca-4, 9-diene-3,6-dione (4)

To a stirred solution of (**3**) (14.1 g, 0.077 mol) in AcOH (30 mL) was added freshly distilled cyclopentadiene (7.2 g, 0.109 mol) and the reaction mixture was stirred at r.t. for 6 hr until the red color has disappeared. The resulting mixture was neutralized with 10% aq.NaOH, extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with brine (30 mL × 3) and dried over $Na_2SO_4$, filtered, and evaporated to dryness in vacuo to give (**4**) (19 g, 99%) as a yellow oil.

IR: 1665 $cm^{-1}$. $^1$HNMR (500 MHz, $CDCl_3$): d 1.48 (s, 3H), 1.54, 1.56, 1.66, 1.67 (AB-System, 2H), 2.80 (d, 1H), 3.08 (m, 1H), 3.42 (m, 1H), 3.91 (s, 3H), 3.94 (s, 3H), 6.01 (dd, 1H), 6.16 (dd, 1H); EI-MS (m/z): 248 ($M^+$).

### 2-(3-Methyl-2-butenyl)-4,5-Dimethoxy-7-methyltricyclo [6.2.1.$0^{2,7}$]undeca-4,9-diene-3,6-dione (5)

To a stirred solution of (**4**) (17.1 g, 0.069 mol) in dry THF (50 mL), at 0°C, 60%NaH (4.13 g, 0.103 mol) was added in portions. Stirring was continued for 30 min at 0°C, then 1-bromo-3-methyl-2-butene (12.32 g, 0.103 mol) in THF (10 mL) was added dropwise at 0°C over 30 min. The reaction mixture was stirred at 0°C for another 6 hr and then poured into cooled water (100 mL), extracted with ethyl acetate (50 mL × 3). The combined organic layer was washed with brine (30 mL × 3) and dried over $Na_2SO_4$, filtered, and evaporated to dryness in vacuo to give (**5**) (20.3 g) as a yellow oil in 93% yield.

IR: 2983, 1663 $cm^{-1}$. $^1$HNMR (500 MHz, $CDCl_3$): d 1.45–1.47 (d, 1H), 1.50 (s, 3H), 1.59 (s, 3H), 1.67 (s, 3H), 1.77–1.79 (d, 1H), 2.39–2.43 (m, 1H), 2.72–2.77 (m, 1H), 3.01–3.09 (d, 2H), 3.87 (s, 3H), 3.91 (s, 3H), 5.07–5.10 (t, 1H), 6.04–6.07 (t, 2H). EI-MS (m/z): 316 ($M^+$).

## Coenzyme $Q_1$ (6)

(**5**) (21.8 g, 0.069 mol) was heated with stirring at 85°C in vacuo (0.01 bar) for 3 hr. The residue was chromatographed on silica gel using hexane-ethyl acetate (6 : 1) to afford Coenzyme $Q_1$ (17.2 g, 98%) as a red oil.

IR: 2946, 1655 $cm^{-1}$. $^1$HNMR (500 MHz, $CDCl_3$): d 1.67 (s, 3H), 1.74 (s, 3H), 2.02 (s, 3H), 3.17 (d, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 4.89 (t, 1H). EI-MS (m/z): 250 ($M^+$).

## REFERENCES


1. (a) Wolstenholme, G.E.W.; O'Connor, C.M. *Ciba Foundation Symposium on Quinones in Electron Transport*; J. & E. Churchill: London, 1961; (b) Wagner, A.F.; Folkers, K. *Vitamins and Coenzymes*; Interscience: New York, 1964; 435; (c) Morton, R.A. *Biochemistry of Quinones*; Academic Press: New York, 1965.
2. Terao, S.; Kato, K.; Shiraishi, M.; Morimoto, H. Synthesis of ubiquinones.2. An efficient preparation of ubiquinone-10. J. Org. Chem. **1979**, *44* (5), 868.
3. Sato, K.; Inoue, S.; Yamaguchi, R. A new synthesis of Coenzyme $Q_1$. J. Org. Chem. **1972**, *37* (12), 1889.
4. Shunk Clifford, H.; Linn Bruce, O.; Wong Emily, L.; Wittreich Paul, E.; Robinson Franklin, M.; Folkers Karl. Synthesis of 6-farnesyl- and 6-phytyl-derivatives of 2,3-dimethoxy-5-methylbenzoquinone and related analogs. J. Amer. Chem. Soc. **1958**, *80* (17), 4753.
5. JP49080031, 1972.
6. Baruah Robindra, N. Preparation of methoxyphenols by oxidation of methoxybenzaldehydes with hydrogen peroxide in presence of *p*-toluenesulphonicm. Ind. J. Chem. **1994**, *33B*, 1103.
7. Merz Andreas; Rauschel Manfred. Synthesis of crown ethers related to ubiquinones. Synthesis **1993**, 797.
8. Sato, K.; Inoue, S.; Sato, H. The synthesis of 2,3-dimethoxy-5-methyl-*p*-benzoquinone. Bull Chem. Soc. Jpn. **1972**, *45*, 3455.


Received in Japan May 24, 2004