

Synthetic Studies on Coenzyme Q₁₀

Part 2¹⁾

An Efficient and Improved Synthesis of Coenzyme Q₁₀ via the C₅+C₄₅ Approach

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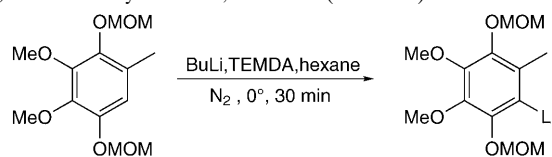
An improved route to coenzyme Q₁₀ (**1**) starting from commercially available coenzyme Q₁ is described. The key steps in this synthesis are the SeO₂-mediated oxidation of the protected isoprenylhydroquinone **3** into the (*E*)-allyl alcohol **5** without the formation of undesired stereoisomer and the one-pot reductive elimination of the phenylsulfonyl and dibenzyl groups in **7** by using naphthalenyllithium.

Introduction. – There is considerable interest in the chemical synthesis of coenzyme Q₁₀ (**1**) due to its unusual structure and biological significance [2] and commercial importance. Although various synthetic routes [3] to **1** have been developed to date, the synthetic strategy implying a terminally functionalized protected isoprenylhydroquinone as a key intermediate seems to be one of the most attractive approach. Our recently proposed route based on (2*E*)-4-[3,4-dimethoxy-2,5-bis(methoxymethoxy)-6-methyl]-2-methylbut-2-en-1-ol allowed us to develop a convenient and highly stereoselective process for **1** starting from coenzyme Q₀ (=2,3-dimethoxy-5-methyl-1,4-benzoquinone) [1]. However, in this process, one important issue became apparent: an incomplete H/Li exchange of the protected hydroquinone was observed²⁾. The overall yield of the thus prepared terminally functionalized protected isoprenylhydroquinone was compromised by this inefficient metalation procedure. The metalation step turned out to be a bottleneck, hampering the scale-up trials. Thus, the development of an efficient and highly regio- and stereoselective preparation of **1** is still in demand.

The SeO₂-mediated terminal oxidation of an isopropylidene moiety to an allyl alcohol is an important strategy towards the formation of an (*E*)-allyl alcohol under regio-

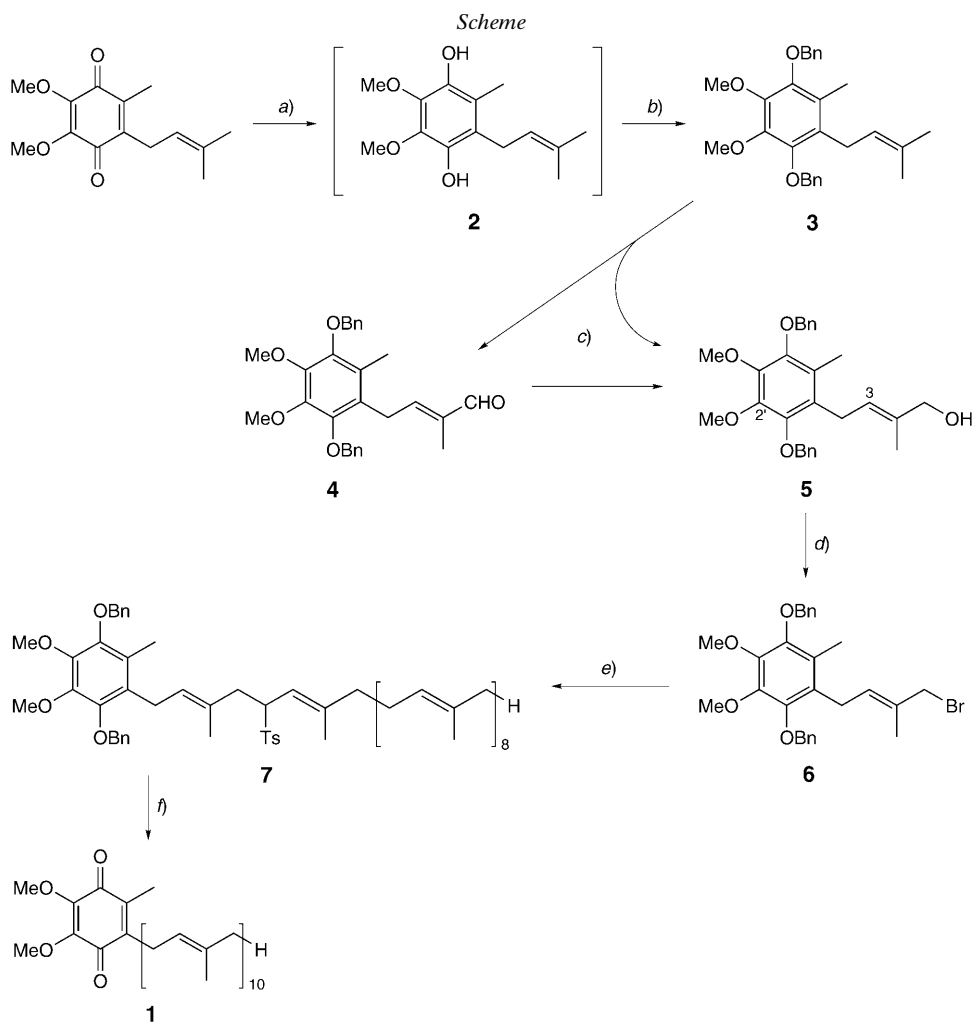
¹⁾ For part 1, see [1].

²⁾ Only 65% of 1,4-bis(methoxymethoxy)-2,3-dimethoxy-5-methylbenzene was lithiated by BuLi in the presence of *N,N,N',N'*-tetramethylethane-1,2-diamine (TMEDA).



and stereochemical control in the synthesis of natural products [4]. Herein we describe a practical synthesis of **1** starting from commercially available coenzyme Q₁ (=2,3-dimethoxy-5-methyl-6-(3-methylbut-2-enyl)cyclohexa-2,5-diene-1,4-dione) *via* SeO₂-mediated oxidation of protected isoprenylhydroquinone **3** into the (*E*)-allyl alcohol **5** (Scheme).

Results and Discussion. – Coenzyme Q₁ was prepared in 90% yield from commercially available coenzyme Q₀ according to our previously reported procedure [5].



a) Na₂S₂O₄, H₂O, MeOH, r.t., 3 h. *b*) BnBr, KOH, Bu₄NBr, acetone, reflux, 3 h; 96.0%. *c*) SeO₂, EtOH, reflux, 1 h, then NaBH₄, MeOH; 65.0%. *d*) CBr₄, C₆H₄PPh₂, 0°, 4 h; 95.3%. *e*) Solanesyl *p*-tolyl sulfone, tBuOK, THF/DMF 9:1, -40°, 3 h; 85.3%. *f*) Naphthalenyllithium, THF, -78°, 2 h; 77.0%; 38% (from coenzyme Q₁).

Reduction of coenzyme Q₁ with 40% aqueous Na₂S₂O₄ solution in MeOH, followed by phase-transfer-catalyzed benzylation of the resulting hydroquinone **2** with benzyl bromide in the presence of a catalytic amount of Bu₄NBr and of KOH in acetone under reflux for 3 h furnished the bis(benzyloxy) derivative **3** in 96% yield.

Next, we turned our attention to the efficient stereoselective conversion of **3** into the (*E*)-allyl alcohol **5**. Thus, allylic oxidation of **3** with SeO₂ in EtOH under reflux for 2.5 h gave a mixture of **5** and (*E*)-butenal **4** in the approximate ratio 90:10 (by HPLC and GC/MS of the crude product). Without separation, the crude mixture **5/4** was directly reduced with NaBH₄ in MeOH at room temperature for 30 min to lead to the (*E*)-allyl alcohol **5** in a yield of 65% and (*E*)/(*Z*) ratio of 98:2 (by HPLC). The (*E*)-configuration of **5** was established by NOESY experiments: NOEs were found between the signals of Me–C(2) and the CH₂(4) protons. Bromination of **5** with CBr₄ and polymer-supported triphenylphosphine in CH₂Cl₂ at 0° afforded the (*E*)-allyl bromide **6** in a 95.3% yield. It is worthy to note that the polymer-supported phosphine oxide formed in the reaction can be reduced to the original phosphine without much loss of activity by trichlorosilane according to the method of *Regen* and *Lee* [6].

The coupling of solanesyl *p*-tolyl sulfone (=4-[(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*)-hexatriaconta-2,6,10,14,18,22,26,30,34-nonaenyl]sulfonyl]-4-methylbenzene) with **6** in the presence of potassium ^tBuOK in THF/DMF (9:1) at –40° provided the desired sulfone **7** in 85% yield. The transformation of **7** into **1** was achieved in 77% overall yield via a two-step procedure comprising a one-pot reductive cleavage of the benzyl and arylsulfonyl groups in **7** by treatment with freshly prepared naphthalenyllithium and the air-oxidation of the resulting hydroquinone in hexane at room temperature.

Conclusions. – An effective and convergent process for the preparation of the (*E*)-allyl alcohol **5** via SeO₂-mediated chain-terminal oxidation resulted in a stereoselective synthesis of coenzyme Q₁₀ (**1**) in 38% overall yield starting from commercially available coenzyme Q₁. This method should prove applicable to the synthesis of not only coenzyme Q_{*n*} (*n*=2–12) but also of many other natural products possessing a polyprenyl moiety.

Experimental Part

General. Reagents and chemicals were obtained from commercial suppliers and used without further purification. THF was distilled from Na/benzophenone under N₂. DMF was freshly distilled from CaH₂. Petroleum ether for column chromatography (CC) had a b.p. of 30–60°. Solanesyl *p*-tolyl sulfone was prepared according to [7]. TLC: Aluminium-backed silica gel 60 *F*₂₅₄ plates. Anal. reversed-phase HPLC: *Shimadzu-LC-10AT* liquid chromatograph with *Spd-10A-UV-VIS* detector; *Supelco-C18* 150×4.6 column; mobile phase MeOH/H₂O 3:1, flow rate 1.0 ml/min; detection by UV absorbance at 270 nm. M.p.: *WRS-I-B* digital melting point apparatus; uncorrected. IR Spectra: *Nicolet-FT-IR 360* spectrophotometer; in cm^{–1}. ¹H-NMR Spectra: *Bruker-DMX-500* and *Jeol-ECA-400* spectrometer; chemical shifts δ in ppm rel. to internal Me₄Si, coupling constants *J* in Hz. Mass spectra: *HP-5989A* spectrometer.

1,4-Bis(benzyloxy)-2,3-dimethoxy-5-methyl-6-(3-methylbut-2-enyl)benzene (3). To a stirred soln. of coenzyme Q₁ (7.6 g, 30 mmol) in MeOH (25 ml) was added dropwise a 40% aq. Na₂S₂O₄ soln. until the red color of the soln. disappeared. The mixture was stirred at r.t. for 3 h. The aq. layer was extracted

with 1,2-dichloroethane (3×20 ml) and the combined org. layer washed with ice-water (3×20 ml), dried (Na_2SO_4), and evaporated. The crude hydroquinone **2** was added to a stirred suspension of KOH (3.67 g, 65.5 mmol) and Bu_4NBr (0.1 g) under N_2 , maintaining the temp. at or below 20° . Benzyl bromide (11.1 g, 65.5 mmol) was then added dropwise within 20 min under vigorous stirring, and the mixture was stirred for 3 h under reflux. After cooling to r.t., H_2O (100 ml) was added, the resulting mixture extracted with Et_2O (3×40 ml), the combined org. layer washed with brine (2×100 ml), dried (MgSO_4), and evaporated, and the crude product purified by CC (SiO_2 , petroleum ether): pure **3** (12.36 g, 94%). Colorless oil. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 1.57 (br. s, Me); 1.66 (s, Me); 2.11 (s, Me); 3.38 (d, $J=7.3$, CH_2); 3.94 (s, 2 MeO); 4.94 (s, 2 CH_2O); 5.43 (t, $J=7.3$, $\text{CH}=\text{C}$); 7.26–7.41 (m, 2 Ph). EI-MS: 432 (M^+), 249, 219, 91.

(2E)-4-[2,5-Bis(benzoyloxy)-3,4-dimethoxy-6-methylphenyl]-2-methylbut-2-en-1-ol (**5**). To a stirred suspension of SeO_2 (5.5 g, 46 mmol) in EtOH (100 ml) was added **3** (10 g, 23 mmol) at r.t. The reaction mixture was stirred under reflux for 2 h and filtered. The solvent was evaporated, the residue extracted with Et_2O (3×40 ml), and the combined org. layer washed with brine (2×100 ml), dried (MgSO_4), and evaporated. A soln. of NaBH_4 (0.7 g, 18.4 mmol) in MeOH (150 ml) was added to the residue, and the mixture was stirred for 30 min at 0° . Sat. aq. NH_4Cl soln. was added dropwise, and the aq. layer was extracted with Et_2O . The combined org. layer was washed with sat. aq. NaCl soln. (3×40 ml) and H_2O (3×25 ml), dried (MgSO_4), evaporated and the crude product purified by CC (SiO_2 ; petroleum ether/AcOEt 8:1): pure **5** (6.70 g, 65%). Colorless oil. IR (film): 3410, 2932, 1640, 1455, 1104, 1030, 698. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 1.63 (s, OH); 1.71 (s, Me); 2.30 (s, Me); 3.32 (d, $J=8$, CH_2); 3.95 (s, 2 MeO); 3.97 (s, CH_2); 5.16 (d, $J=15.5$, 2 CH_2); 5.83 (t, $J=7$, $\text{CH}=\text{C}$); 7.15–7.23 (m, 2 Ph). EI-MS: 448 (M^+), 431, 363, 265, 249, 91.

1,4-Bis(benzoyloxy)-2-[(2E)-4-bromo-3-methylbut-2-enyl]-5,6-dimethoxy-3-methylbenzene (**6**). To a soln. of **5** (1.12 g, 2.5 mmol) in CH_2Cl_2 (10 ml) at 0° , successively CBr_4 (1.08 g, 3.25 mmol) and polymer-supported triphenylphosphine (1.25 g, 3.75 mmol) was added. The suspension was stirred at 0° for 4 h and then filtered. The solvent was evaporated and the excess of CBr_4 removed *in vacuo*: pure **6** (1.22 g, 95.3%). Colorless oil. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 1.72 (s, Me); 2.10 (s, Me); 3.35 (d, $J=8$, CH_2); 3.94 (s, CH_2); 3.95 (s, 2 MeO); 5.02 (t, $J=15$, 2 CH_2); 5.83 (t, $J=7$, CH); 7.33–7.43 (m, 2 Ph). EI-MS: 512 (M^+), 431, 340, 249, 91.

1,4-Bis(benzoyloxy)-2-[(2E,6E,10E,14E,18E,22E,26E,30E,34E)-3,7,11,15,19,23,27,31,35,39-decamethyl-5-[(4-methylphenyl)sulfonyl]tetraconta-2,6,10,14,18,22,26,30,34,38-decaenyl]-5,6-dimethoxy-3-methylbenzene (**7**). To a stirred soln. of **6** (5.11 g, 10 mmol) and solanesyl *p*-tolyl sulfone (6.03 g, 8 mmol) in THF/DMF 9:1 (100 ml) was added $t\text{-BuOK}$ (1.58 g, 14 mmol), at -40° under N_2 . Stirring was continued at -40° for 1.5 h, and further at 20° for 1 h. The mixture was poured into sat. aq. NH_4Cl soln. (150 ml) and extracted with Et_2O (3×40 ml), the combined org. layer washed with 1M aq. HCl soln. (3×25 ml) and H_2O (3×25 ml), dried (Na_2SO_4), and evaporated, and the crude product purified by CC (SiO_2 , petroleum ether/AcOEt 8:1): pure **7** (8.08 g, 85.3%). Colorless oil. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 1.51 (s, MeC); 1.68 (s, 8 MeC); 1.67, 1.73 (2s, 2 Me); 1.85–2.16 (m, 8 CH_2CH_2); 2.70 (d, $J=6.5$, CH_2); 3.20 (s, CH_2); 3.40–3.55 (m, CH); 3.91 (s, 2 MeO); 4.83 (d, $J=10.1$, CH_2); 4.89 (s, CH_2); 5.0 (s, $\text{C}=\text{CH}$); 5.10 (s, 2 CH_2O , 9 $\text{C}=\text{CH}$); 7.28 (d, $J=8.2$, Ph); 7.70 (d, $J=8.2$, Ph). MALDI-MS: 1207.8 ($[M+\text{Na}]^+$, $\text{C}_{79}\text{H}_{109}\text{SNaO}_6^+$).

Coenzyme Q_{10} (=2-[(2E,6E,10E,14E,18E,22E,26E,30E,34E)-3,7,11,15,19,23,27,31,35,39-Decamethyltetraconta-2,6,10,14,18,22,26,30,34,38-decaenyl]-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione; **1**). A freshly prepared soln. of 1M naphthalenyllithium in THF (10 mmol, 10 ml) was added dropwise to a soln. of **7** (1.18 g, 1 mmol) in THF at -78° . The mixture was stirred for 2 h at -78° before being warmed up to 0° , quenched with sat. aq. NH_4Cl soln. (20 ml) and extracted with Et_2O (3 ml). The combined org. layer was washed with sat. aq. NaCl soln. (2×15 ml) and H_2O (2×15 ml), dried (Na_2SO_4), and evaporated and the crude product purified by CC (SiO_2 , hexane/THF 9:1). The obtained orange solid was recrystallized from EtOH at 0° : pure **1** (0.67 mg, 77%). Orange crystals. M.p. $48.3\text{--}49^\circ$ ([3d]: m.p. $48\text{--}49^\circ$). Purity $\geq 98.5\%$ (by HPLC). $^1\text{H-NMR}$ (500 MHz, CDCl_3): 1.57, 1.59 (2s, 9 $\text{MeC}=\text{C}$); 1.69 (s, $\text{MeC}=\text{C}$); 1.72 (s, $\text{MeC}=\text{C}$); 2.03 (s, arom. Me); 1.98–2.11 (m, 9 $(\text{CH}_2)_2\text{CH}=\text{C}$); 3.18 (d, $J=6.9$, CH_2); 3.96, 4.01 (2s, 2 MeO); 4.90 (t, $J=7.3$, CH); 5.02–5.14 (m, 9 $\text{C}=\text{CH}$). MALDI-MS: 885.6 ($[M+\text{Na}]^+$, $\text{C}_{59}\text{H}_{90}\text{O}_4\text{Na}^+$).

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