Synthetic Studies on Coenzyme Q_{10}

Part 2[1])

An Efficient and Improved Synthesis of Coenzyme Q_{10} *via* the C_5+C_{45} Approach

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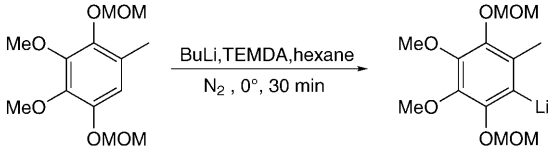
An improved route to coenzyme Q_{10} (**1**) starting from commercially available coenzyme Q_1 is described. The key steps in this synthesis are the SeO_2-mediated oxidation of the protected isoprenylhydroquinone **3** into the (*E*)-allyl alcohol **5** without the formation of undesired stereoisomer 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 Q_{10} (**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 Q_0 (=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 observed[2]). 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 SeO_2-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].

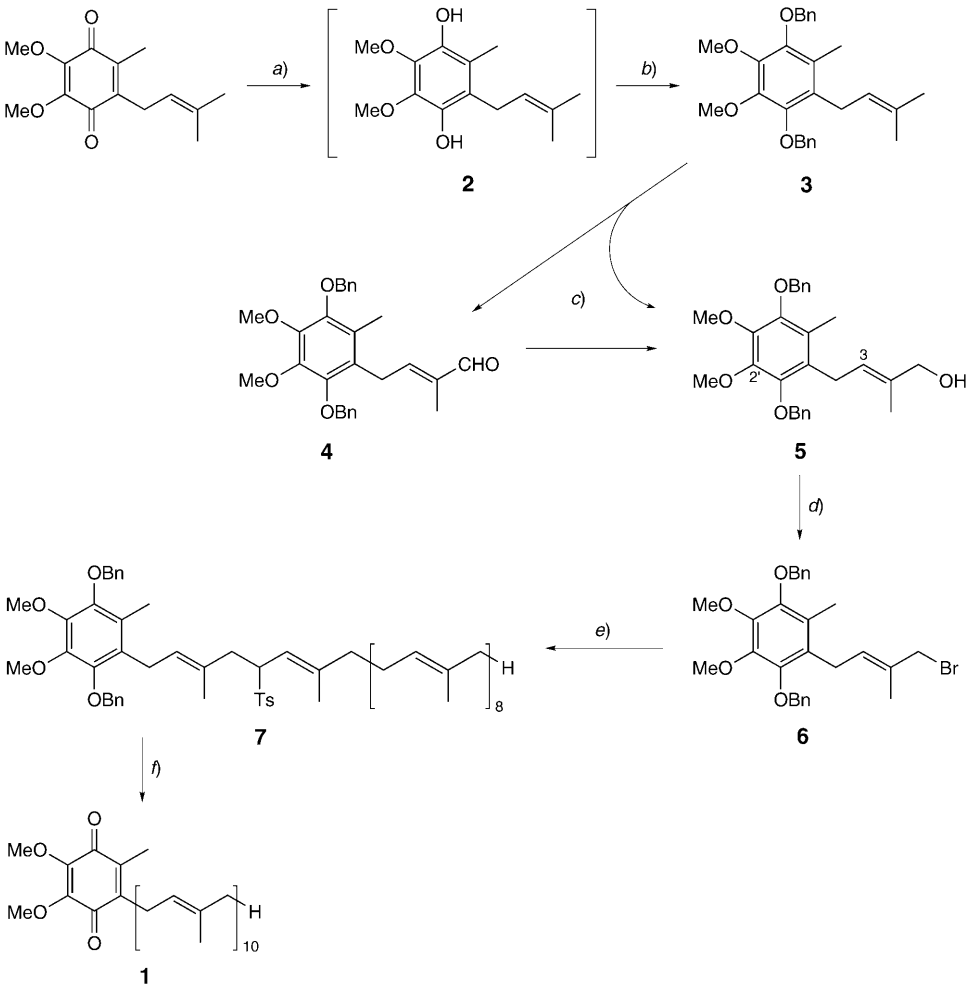
[2]) Only 65% of 1,4-bis(methoxymethoxy)-2,3-dimethoxy-5-methylbenzene was lithiated by BuLi in the presence of *N,N,N′,N′*-tetramethylethane-1,2-diamine (TMEDA).



and stereochemical control in the synthesis of natural products [4]. Herein we describe a practical synthesis of **1** starting from commercially available coenzyme Q_1 (=2,3-dimethoxy-5-methyl-6-(3-methylbut-2-enyl)cyclohexa-2,5-diene-1,4-dione) *via* SeO_2-mediated oxidation of protected isoprenylhydroquinone **3** into the (*E*)-allyl alcohol **5** (*Scheme*).

Results and Discussion. – Coenzyme Q_1 was prepared in 90% yield from commercially available coenzyme Q_0 according to our previously reported procedure [5].

Scheme



a) $Na_2S_2O_4$, H_2O, MeOH, r.t., 3 h. *b*) BnBr, KOH, Bu_4NBr, acetone, reflux, 3 h; 96.0%. *c*) SeO_2, EtOH, reflux, 1 h, then $NaBH_4$, MeOH; 65.0%. *d*) CBr_4, $\bigcirc$-$C_6H_4PPh_2$, 0°, 4 h; 95.3%. *e*) Solanesyl *p*-tolyl sulfone, ^{t}BuOK, THF/DMF 9:1, −40°, 3 h; 85.3%. *f*) Naphthalenyllithium, THF, −78°, 2 h; 77.0%; 38% (from coenzyme Q_1).

Reduction of coenzyme Q_1 with 40% aqueous $Na_2S_2O_4$ 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 Bu_4NBr 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 SeO_2 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 $NaBH_4$ 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 CH_2(4) protons. Bromination of **5** with CBr_4 and polymer-supported triphenylphosphine in CH_2Cl_2 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 ^{t}BuOK 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* SeO_2-mediated chain-terminal oxidation resulted in a stereoselective synthesis of coenzyme Q_{10} (**1**) in 38% overall yield starting from commercially available coenzyme Q_1. 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 N_2. DMF was freshly distilled from CaH_2. 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/H_2O 3:1, flow rate 1.0 ml/min; detection by UV absorbance at 270 nm. M.p.: *WRS-1-B* digital melting point apparatus; uncorrected. IR Spectra: *Nicolet-FT-IR 360* spectrophotometer; in cm^{-1}. ^{1}H-NMR Spectra: *Bruker-DMX-500* and *Jeol-ECA-400* spectrometer; chemical shifts δ in ppm rel. to internal Me_4Si, 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 Q_1 (7.6 g, 30 mmol) in MeOH (25 ml) was added dropwise a 40% aq. $Na_2S_2O_4$ 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 a 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}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, CH=C); 7.26–7.41 (*m*, 2 Ph). EI-MS: 432 (M^+), 249, 219, 91.

*(2*E*)-4-[2,5-Bis(benzyloxy)-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}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, CH=); 7.15–7.23 (*m*, 2 Ph). EI-MS: 448 (M^+), 431, 363, 265, 249, 91.

*1,4-Bis(benzyloxy)-2-[(2*E*)-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}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(benzyloxy)-2-{(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*,34*E*)-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}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}H-NMR (500 MHz, $CDCl_3$): 1.51(*s*, MeC); 1.68 (*s*, 8 MeC); 1.67, 1.73 (2*s*, 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*, C=CH); 5.10 (*s*, 2 CH_2O, 9 C=CH); 7.28 (*d*, *J* = 8.2, Ph); 7.70 (*d*, *J* = 8.2, Ph). MALDI-MS: 1207.8 ($[M+Na]^+$, $C_{79}H_{109}SNaO_6^+$).

Coenzyme Q_{10} (=*2-[(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*,34*E*)-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. 48.3–49° ([3d]: m.p. 48–49°). Purity ≥98.5% (by HPLC). ^{1}H- NMR (500 MHz, $CDCl_3$): 1.57, 1.59 (2*s*, 9 MeC=C); 1.69 (*s*, MeC=C); 1.72 (*s*, MeC=C); 2.03 (*s*, arom. Me); 1.98–2.11 (*m*, 9 $(CH_2)_2CH$=); 3.18 (*d*, *J* = 6.9, CH_2); 3.96 , 4.01 (2*s*, 2 MeO); 4.90 (*t*, *J* = 7.3, CH); 5.02–5.14 (*m*, 9 C=CH). MALDI-MS: 885.6 ($[M+Na]^+$, $C_{59}H_{90}O_4Na^+$).

REFERENCES

[1] X. J. Yu, F. E. Chen, H. F. Dai, X. X. Chen, Y. Y. Kuang, B. Xie, *Helv. Chim. Acta* **2005**, *88*, 2575.

[2] K. Folkers, Y. Yamamura, R. H. Tohomson, 'Biomedical and Clinical Aspects of Coenzyme Q', Vol. 3, Elsevier/North-Holland Biomedical Press, Amsterdam-New York-Oxford, 1981; F. L. Carane, R. Barr, 'Methods in Enzymology', Eds. D. B. McCormick, L. D. Wright, Academic Press, New York, 1971.

[3] a) R. Rüegg, U. Gloor, R. N. Goel, G. Ryser, O. Wiss, O. Isler, *Helv. Chim. Acta* **1959**, *52*, 2616; b) S. Inoue, R. Yamaguchi, K. Saito, K. Sato, *Bull. Chem. Soc. Jpn.* **1974**, *47*, 3098; c) Y. Naruta, K. Maruyama, *Chem. Lett.* **1979**, 885; d) S. Terao, K. Kato, M. Shiraishi, H. Morimoto, *J. Org. Chem.* **1979**, *44*, 868; e) Y. Naruta, *J. Org. Chem.* **1980**, *45*, 4095; f) Y. Fujita, M. Ishiguro, T. Onishi, T. Nishida, *Synthesis* **1981**, 469; g) K. Sato, O. Miyamoto, S. Inoue, T. Yamamoto, Y. Hirasawa, *J. Chem. Soc., Chem. Commun.* **1982**, 153; h) T. Yoshizawa, H. Toyofuku, K. Tachibana, T. Kuroda, *Chem. Lett.* **1982**, 1131; i) M. Mohri, H. Kinoshita, K. Inomata, H. Kotake, H. Takagaki, K. Yamazaki, *Chem. Lett.* **1986**, 1177; j) H. Eto, C. Eguchi, *Chem. Lett.* **1988**, 1597; k) B. H. Lipshutz, G. Bulow, F. Fernandez-Lazaro, S. K. Kim, R. Lowe, P. Mollard, K. L. Stevens, *J. Am. Chem. Soc.* **1999**, *121*, 11664; l) B. H. Lipshutz, P. Mollard, S. S. Pfeiffer, W. Chrisman, *J. Am. Chem. Soc.* **2002**, *124*, 14282; m) E. Niggishi, S. Y. Liou, C. D. Xu, S. Q. Huo, *Org. Lett.* **2002**, *4*, 261; n) B. H. Lipshutz, A. Lower, V. Berl, K. Schein, F. Wetterich, *Org. Lett.* **2005**, *7*, 4095; o) Q. Li, K. Gu, X. H. Chang, *Chin. J. Org. Chem.* **2005**, *25*, 1494; p) P. Bovicelli, R. Antonioletti, M. Barontini, G. Borioni, R. Bernini, E. Mincione, *Tetrahedron Lett.* **2005**, *46*, 1255.

[4] K. B. Sharpless, R. F. Lauer, *J. Am. Chem. Soc.* **1972**, *94*, 7154; M. A. Umbreit, K. B. Sharpless, *J. Am. Chem. Soc.* **1977**, *99*, 5526; L. M. Stephenson, D. R. Speth, *J. Org. Chem.* **1979**, *44*, 4683; M. Haruna, K. Ito, *J. Chem. Soc., Chem. Commun.* **1981**, 483; M. Philip, B. Frank, *Tetrahedron Lett.* **1989**, *30*, 3637; A. Gerard, B. D. Mireille, A. Robert, M. Michele, C. Manuel, R. Hector, V. Gonzalo, P. Thierry, *Synth. Commun.* **1997**, *27*, 45; P. Sandrine, H. Curtis, W. B. Srabani, B. David, L. F. Alex, *Tetrahedron Lett.* **1998**, *39*, 6139.

[5] L. Lu, F. E. Chen, *Synth. Commun.* **2004**, *34*, 4049.

[6] S. L. Regen, D. P. Lee, *J. Org. Chem.* **1975**, *40*, 1669.

[7] K. Sato, O. Miyamoto, S. Inoue, T. Yamamoto, Y. Hirasawa, *J. Chem. Soc., Chem. Commun.* **1982**, 153.

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