Synthetic Studies on Coenzyme Q_{10}

Part 3[1])

An Improved $C_5 + C_{45}$ Approach to the Stereoselective Synthesis of Coenzyme Q_{10} *via* Metal–Halogen Exchange Strategy

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An efficient and stereoselective approach to the synthesis of coenzyme Q_{10} is described (*Scheme*). The $MeOCH_2$-protected *p*-hydroquinone **4** containing the C_5 (*E*)-allyl (*tert*-butyl)dimethylsilyl ether moiety was obtained *via* a halogen–lithium exchange of the $MeOCH_2$-proctected 2-bromo-5,6-dimethoxy-3-methylhydroquinone **2** and subsequent addition to (*E*)-(^{t}BuMe$_2$Si)-OCH$_2$C(Me)=CHCH$_2$Br (**3**). The reductive desulfonylation of compound **8**, obtained from **4** *via* **5**–**7**, was successfully carried out by employing Li/EtNH$_2$.

Introduction. – During recent work on coenzyme Q_{10} (**1**) [1], we developed two new stereoselective synthetic routes for this vitamin by coupling of the $MeOCH_2$-protected *p*-hydroquinone **6** bearing a C_5-allyl moiety of (*E*)-configuration and the polyprenyl sulfone by *Masaki*'s protocol [1]. The more attrative point of the above methods is that solanesol, a C_{45}-(*all-E*)-polyprenyl alcohol that is readily obtained by extraction from the leaves of tobacco or potato, can be directly utilized in the synthesis of **1**. However, their industrial application is still hampered by the lack of an efficient method for the preparation of compound **6**. In connection with our continued interest in the development of a practical synthetic process for **1**, we now report an efficient and improved synthesis of coenzyme Q_{10} (**1**) starting form the $MeOCH_2$-protected 2-bromo-5,6-dimethoxy-3-methylhydroquinone **2** and {[(2*E*)-4-bromo-2-methylbut-2-enyl]oxy}(*tert*-butyl)dimethylsilane (**3**). The metal–halogen exchange (MHE) applied to **2** followed by the addition of **3** assembled the two parts into the key intermediate **6** needed to complete the synthesis of **1**.

Results and Discussion. – The synthesis of coenzyme Q_{10} was carried out as depicted in the *Scheme*. The known bromide **2** was obtained in an overall yield of 61% from 2,3-dimethoxy-5-methylcyclohexa-2,5-diene-1,4-dione by using the synthetic methodology reported by *Sato* and co-workers [2]. The (*E*)-allyl bromide **3** was readily prepared from 1-hydroxypropan-2-one in 65% overall yield by the procedure developed by *Eberl* and co-workers [3]. The aryllithium intermediate generated from **2** with BuLi in THF at $-78°$ was then allowed to react with the (*E*)-allyl bromide **3** to afford the allyl silyl

[1]) For Parts 1 and 2, see [1].

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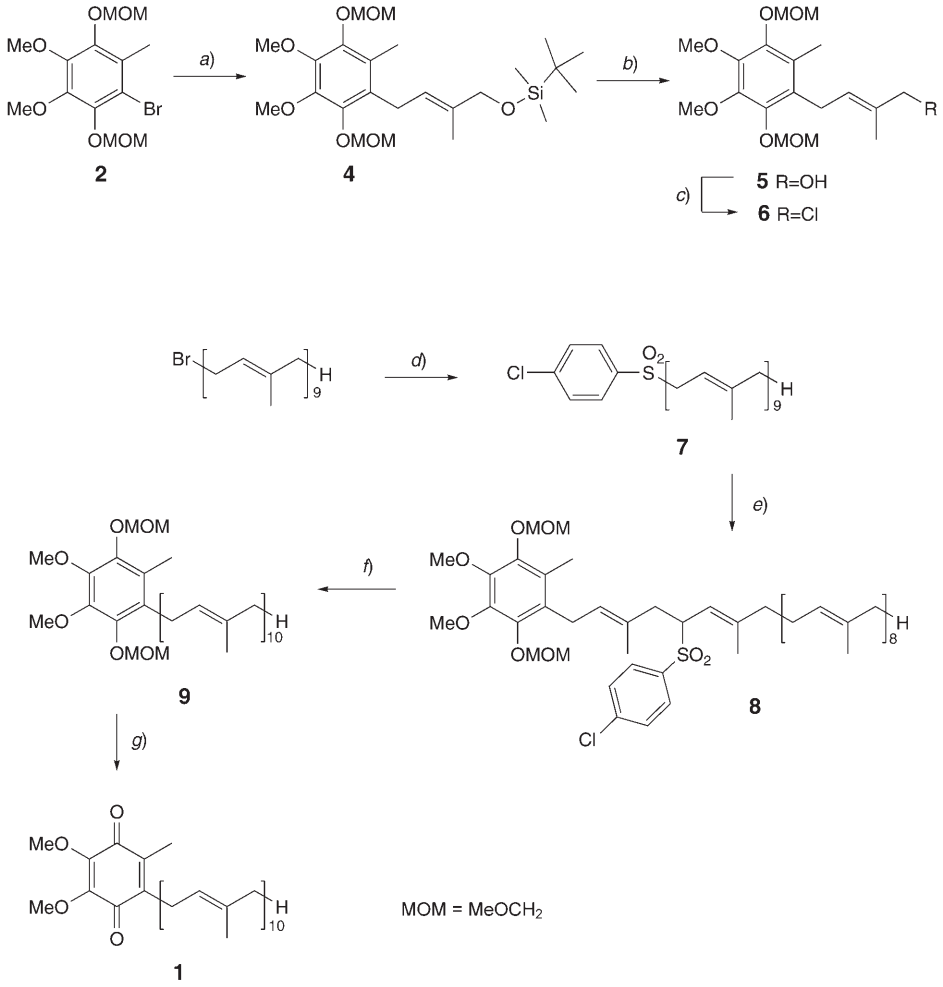
ether **4** in 68% yield with high stereoselectivity ((*E*/*Z*) 99:1, GC/MS). The C=C configuration in **4** was unambiguously established by NOESY experiments (see *Fig.*). The ^{t}BuMe$_2$Si group in **4** was removed by reaction with Bu$_4$NF in THF at 0°. The resulting alcohol **5** was then transformed to the corresponding (*E*)-allyl chloride **6** upon treatment with 2,6-dimethylpyridine, LiCl, and MsCl in DMF at −5°, in 96% isolated yield over two steps. Thus, the preparation of the key intermediate **6** was achieved in 65% yield from **2**.

Scheme



a) 1. BuLi, N_2, −78°, 20 min; 2. (*E*)-(^{t}BuMe$_2$Si)-OCH$_2$C(Me)=CHCH$_2$Br (**3**), −78° → r.t., 2 h, r.t., 5 h; 68%. *b*) Bu$_4$NF, THF, 0°, 40 min. *c*) LiCl, 2,6-dimethylpyridine, DMF, MsCl, −5°, 4 h; 96% over two steps. *d*) Sodium 4-chlorobenzenesulfinate, DMF, r.t., 24 h; 85%. *e*) 1. BuLi, THF/hexamethylphosphoric triamide (HMPA) 8:1, N_2, −70°, 30 min; 2. **6**, −70° → r.t., 2 h, r.t., 1 h; 75%. *f*) 1. EtNH$_2$, Li, THF, −78°, 30 min; 2. isoprene, solid NH$_4$Cl, 86%. *g*) HCl (cat.), MeOH/hexane 2:1, 40°, 3 h; 93%.

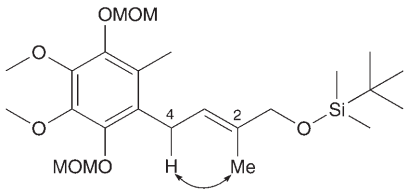


Figure. *NOESY Correlation for compound* **4**

Solanesyl bromide [4], prepared from solanesol, (=(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*, 26*E*,30*E*)-3,7,11,15,19,23,27,31,35-nonamethylhexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-ol) was treated with sodium 4-chlorobenzenesulfinate in DMF at room temperature to give solanesyl 4-chlorophenyl sulfone (**7**) in 85% yield [4]. Coupling of the sulfone **7** through its lithium anion in the presence of chloride **6** afforded the intermediate **8** in 75% yield [5]. Removal of the 4-chlorophenylsulfonyl group in **8** was achieved with Li/$EtNH_2$ in THF at $-78°$ for 30 min, in a similar manner as reported previously [6], to afford the desired product **9** in 86% yield after chromatographic purification. Analysis of the ^{1}H-NMR spectrum and HPLC of the crude product **9** indicated that C=C bond migration from C(6)=C(7) to C(5)=C(6) of the side chain during the desulfonation took place to an extent of only 4%. Deprotection of **9** with conc. HCl in hexane and *in situ* oxidation of the resulting hydroubiquinone by air afforded **1** in 93% yield [1].

Conclusions. – In conclusion, a highly efficient synthesis of coenzymeQ_{10} (**1**) has been achieved which has the potential to be used for the large-scale production.

Experimental Part

General. Reagents and chemicals were obtained fom commercial suppliers and used without further purification. THF was distilled from sodium/benzophenone. CH_2Cl_2, Et_3N, DMF, and HMPA were distilled from CaH_2. Petroleum ether for column chromatography (CC) had a b.p. of 30–60°. HPLC: *Shimadzu-LC-10AT* liquid chromatograph with *Spd-10A* UV/VIS detector, working at 270 nm; L_3 column (25 × 4.6 mm); elution with hexane/AcOEt 95:5 at a flow flow rate 2.0 ml/min. M.p.: *WRS-1B* digital metal point apparatus. IR Spectra: *Jasco-FT/IR-4200* spectrometer. NMR Spectra: *Bruker AV 400*. Mass Spectra: *Waters-Quattro-Micromass* spectrometer. GC/MS: *Agilent* GC/MS spectrometer.

*(*tert*-Butyl){[(2*E*)-4-(3,4-dimethoxy-2,5-bis(methoxymethoxy)-6-methylphenyl)-2-methylbut-2-enyl]-oxy}dimethylsilane* (**4**). At −78°, 2.89M BuLi in hexane (1.5 ml) was added dropwise to a soln. of **2** (0.751 g, 2.14 mmol) in THF (15 ml) under N_2. The orange mixture thus obtained was stirred at −78° for additional 20 min. A soln. of **3** (1.19 g, 4.28 mmol) in THF (2.0 ml) was added dropwise, and the resulting mixture was warmed to r.t. within 2 h. After stirring for 5 h at r.t., the mixture was taken up in Et_2O (3 × 50 ml) and washed with 1N aq. HCl (20 ml), H_2O (25 ml), and brine (25 ml), dried (Na_2SO_4), and concentrated. The crude product was purified by CC (SiO_2, petroleum ether/AcOEt 13:1): pure **4** (0.683 g, 67.9%), (*E*)/(*Z*) 99:1 (GC/MS). Colorless oil. IR (film): 2989, 2856, 1471, 1159, 1058, 1027, 837. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.02 (*s*, Me_2Si); 0.87 (*s*, ^{t}BuSi); 1.75 (*s*, Me–C(2)); 2.17 (*s*, Me–C(6′)); 3.40 (*d*, ^3J = 6.8, CH_2(4)); 3.57, 3.58 (2*s*, 2 *Me*OCH_2); 3.85 (2*s*, MeO–C(3′), MeO–C(4′)); 4.0 (*s*, CH_2(1)); 5.04 (*s*, 2 OCH_2O); 5.32 (*t*, ^3J = 6.4, H–C(3)). ^{13}C-NMR (100 MHz, $CDCl_3$): −5.3, −5.0 (Me_2Si); 12.5 (*Me*–C(6′)); 13.6 (*Me*–C(2)); 18.4 (Me_3C); 25.7 (CH_2(4)); 25.9 (Me_3C); 57.4 (2 *Me*OCH_2); 60.9, 60.9 (*Me*O–C(3′), *Me*O–C(4′)); 68.7 (C(1)); 99.3, 99.5 (2 OCH_2O); 123.2 (C(6′)); 126.0 (C(3)); 129.1 (C(1′)); 134.6 (C(2)); 144.4 (C(3′)); 144.8 (C(4′)); 144.9 (C(5′)); 145.3 (C(2′)). EI-MS: 470 (7, M^+), 294 (44), 249 (100), 229 (37), 73 (31). HR-EI-MS: 470.2743 (M^+, $C_{24}H_{42}O_7Si^+$; calc. 470.2700).

*(2*E*)-4-(3,4-Dimethoxy-2,5-bis(methoxymethoxy)-6-methylphenyl)-2-methylbut-2-en-1-ol* (**5**). $Bu_4NF \cdot H_2O$ (0.39 g, 1.5 mmol) in THF (5 ml) was quickly added to a soln. of **4** (0.47 g, 1 mmol) in THF (20 ml) at 0°. After stirring at 0° for 40 min, the reaction was quenched with an sat. aq. NH_4Cl soln. (15 ml). The aq. phase was extracted with Et_2O (3 × 15 ml), the combined org. phase washed with brine (4 × 10 ml), dried (Na_2SO_4), and concentrated, and the crude product purified by CC (SiO_2, petroleum ether/AcOEt 4:1): pure **5** (0.344 g, 96.6%). Colorless oil. IR (film): 3431, 2924, 1467, 1427, 1393, 1158, 1055, 975. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.63 (*s*, OH); 1.83 (*s*, Me–C(2)); 2.18 (*s*, Me–C(6′)); 3.42 (*d*, ^3J = 6.4, CH_2(4)); 3.58, 3.60 (2*s*, 2 *Me*OCH_2); 3.86 (*s*, MeO–(3′), MeO–C(4′)); 4.00 (*s*, CH_2(1)); 5.05, 5.08 (2*s*, 2 OCH_2O); 5.35 (*t*, ^3J = 5.1, H–C(3)). EI-MS: 356 (27, M^+), 294 (86), 249 (100), 235 (26), 217 (83), 189 (32), 83 (43), 45 (91). HR-EI-MS: 356.1851 (M^+, $C_{18}H_{28}O_7^+$; calc. 356.1835).

*1-[(2*E*)-4-Chloro-3-methylbut-2-enyl]-3,4-dimethoxy-2,5-bis(methoxymethoxy)-6-methylbenzene* (**6**). MsCl (0.2 ml, 2.63 mmol) was added dropwise to a stirred suspension of **5** (0.36 g, 1.01 mmol), 2,6-dimethylpyridine (0.32 ml, 2.73 mmol) and LiCl (0.107 g, 2.53 mmol) in DMF (20 ml) at −5°. After stirring at −5° for 4 h, H_2O (30 ml) was added, the resulting mixture extracted with petroleum ether/Et_2O 1:1 (3 × 40 ml), the combined org. phase washed with H_2O (4 × 30 ml), dried (Na_2SO_4), and concentrated, and the crude product purified by CC (SiO_2, petroleum ether/AcOEt 10:1): pure **6** (0.365 g, 96.8%). Colorless oil. IR (film): 2991, 1159, 1103, 1025, 974, 666. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.89 (*s*, Me–C(3′)); 2.17 (*s*, Me–C(6)); 3.44 (*d*, ^3J = 6.4, CH_2(1′)); 3.56, 3.59 (2*s*, 2 *Me*OCH_2); 3.85, 3.86 (2*s*, MeO–C(3), MeO–C(4)); 4.00 (*s*, $ClCH_2$ (4′)); 5.05, 5.06 (2*s*, 2 OCH_2O); 5.48 (*t*, ^3J = 6.6, H–C(2′)). ^{13}C-NMR (100 MHz, $CDCl_3$): 12.4 (*Me*–C(6)); 14.3 (*Me*–C(3′)); 26.2 (CH_2(1′)); 52.2 (C(4′)); 57.4 (2 *Me*OCH_2); 60.9 (*Me*O–C(3), *Me*O–(4)); 99.3, 99.5 (2 OCH_2O); 125.9 (C(6)); 128.0 (C(2′)); 129.1 (C(1)); 131.6 (C(3′)); 144.34 (C(3)); 144.9 (C(4)); 145.0 (C(5)); 145.3 (C(2)). EI-MS: 376 (1, $M(^{37}Cl)^+$), 374 (3, $M(^{35}Cl)^+$), 294 (44), 249 (100), 217 (38), 91 (14). HR-EI-MS: 376.1452/374.1480 (M^+, $C_{18}H_{27}ClO_6^+$; calc. 376.1467/374.1496).

*1-Chloro-4-[(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*)-3,7,11,15,19,23,27,31,35-nonamethylhexatriaconta-2,6,10,14,18,22,26,30,34-nonaenylsulfonyl]benzene* (**7**). Sodium 4-chlorobenzenesulfinate (2.98 g, 15 mmol) and solanesyl bromide, prepared from solanesol (6.3 g, 10 mmol) and phosphorous tribromide (0.5 ml, 5 mmol), were dissolved in DMF (80 ml). After stirring for 24 h at r.t., the mixture was poured into H_2O (50 ml) and Et_2O (50 ml), the aq. phase extracted with Et_2O (3 × 80 ml), the combined org. phase washed with H_2O (3 × 80 ml), dried (Na_2SO_4), and concentrated, and the crude product recrystallized from EtOH: pure **7** (6.7 g, 85%). White solid. M.p. 49.1–49.6°. IR (KBr): 3087, 3053, 2919, 1664, 1582, 1152, 1089, 767. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.36, 1.60, 1.68 (3*s*, 10 *Me*C=CH); 1.98–2.10 (*m*, 8 $(CH_2)_2$C=C); 3.80 (*d*, ^3J = 7.2, SO_2CH_2); 5.05–5.19 (*m*, 9 C=CH); 7.50 (*d*, ^3J = 8.8, 2 arom. H); 7.50 (*d*, ^3J = 8.8, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.0, 16.3 (8 *Me*C=C); 17.6 (1 *Me*–C(35′)); 25.6 (1 *Me*–C(35′)); 26.1, 26.6–26.7 (8 *CH*$_2$CH=C); 39.6–39.7 (8 *CH*$_2$C(Me)=C); 56.1 (SO_2CH_2(1′)); 110.0 (C(2′)); 123.1–124.4 (8 *C*H=C); 129.2–131.1 (8 *C*(Me)=C); 134.8–135.8 (C(3′), C(2), C(3), C(5), C(6)); 137.2 (C(1)); 145.3 (C(4)); 140.3 (C(1)). ESI-MS: 813.9 (20, $[M(^{37}Cl) + Na]^+$), 812.9 (24), 811.9 (37, $[M(^{35}Cl) + Na]^+$) 475.5 (53), 301.3 (100). HR-MALDI-MS: 813.5353 and 811.5385 ($[M + Na]^+$, $C_{51}H_{77}ClNaO_2S^+$; calc. 813.5303 and 811.5333).

*1-[(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*,34*E*)-5-(4-Chlorophenylsulfonyl)-3,7,11,15,19,23,27,31,35,39-decamethyltetraconta-2,6,10,14,18,22,26,30,34,38-decaenyl]-3,4-dimethoxy-2,5-bis(methoxymethoxy)-6-methylbenzene* (**8**). At −70°, 2.89M BuLi in hexane (0.5 ml) was added dropwise under stirring to a soln. of **7** (0.95 g, 1.2 mmol) in THF/HMPA 8:1 (25 ml), within 30 min under N_2. After stirring at −70° for 30 min, a soln. of **6** (0.258 g, 0.69 mmol) in THF (2 ml) was added dropwise, and the resulting mixture was allowed to warm to r.t. over 2 h. After stirring for 1 h at r.t., H_2O (20 ml) was added, the mixture extracted with Et_2O (3 × 50 ml), the combined org. phase washed with 1N aq. HCl (50 ml) and H_2O (50 ml), dried (Na_2SO_4), and concentrated, and the crude product purified by CC (SiO_2, petroleum ether/AcOEt 8:1): pure **8** (0.59 g, 75.8%). Yellow oil. IR (film): 3050, 2958, 2922, 1664, 1597, 1056, 978, 665. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.23 (*s*, MeC=C); 1.60 (*s*, 8 MeC=C); 1.68, 1.70 (2*s*, 2 MeC=C); 1.85–2.10 (*m*, 8 $(CH_2)_2$CH=C, Me–C(6)); 2.22 (*t*, ^2J = −12.4, ^3J = 12.4, 1 H, CH_2(4′)); 2.88 (*d*, ^2J = −12.4, 1 H, CH_2(4′)); 3.28 (*dd*, ^2J = −15.2, ^3J = 6.4, 1 H, CH_2(1′)); 3.35 (*dd*, ^2J = −15.2, ^3J = 6.4, 1 H, CH_2(1′)); 3.54, 3.57 (2*s*, 2 *Me*OCH_2O); 3.84 (*s*, MeO–C(3), MeO–C(4)); 3.89 (*m*, H–C(5′)); 4.84 (*d*, ^3J = 10.4, H–C(6′)); 5.00, 5.02 (2*s*, 2 OCH_2O); 5.07–5.13 (*m*, 9 C=CH); 7.46 (*d*, ^3J = 8.4, 2 arom. H ($ArSO_2$)); 7.75

(*d*, $^3J = 8.4$, 2 arom. H ($ArSO_2$)). ^{13}C-NMR (100 MHz, $CDCl_3$): 12.4 (*Me*–C(6)); 16.0, 16.3, 16.6 (9 *Me*C=C); 17.7 (1 *Me*–C(39′)); 25.7 (1 *Me*–C(39′)); 26.2 (C(1′)); 26.3, 26.7–26.8 (8 *C*H_2CH=C); 37.4 (C(4′)); 39.7–39.8 (8 *C*H_2C(Me)=C); 57.4 (SO_2*C*H); 60.9 (2 *Me*OCH_2O); 63.7 (*Me*O–C(3), *Me*O–C(4)); 99.4, 99.5 (2 OCH_2O); 117.0 (C(6)); 122.3 (C(6′)); 124.0–124.4, 125.8, 127.0 (9 *C*H=C); 129.8 (C(1)); 128.7, 129.0, 130.8 (4 CH ($ArSO_2$)); 131.2 (C(39′)); 134.9–135.2, 135.8 (8 *C*(Me)=C); 136.5 (C(3′)); 140.2 (C($ArSO_2$)); 144.4(C(3)); 144.8 (C(4), ClC($ArSO_2$)); 145.3 (C(5)); 145.6 (C(2)). ESI-MS: 1151.4 (3, $[M(^{37}Cl) + Na]^+$), 1150.4 (3), 1149.4 (4, $[M(^{35}Cl) + Na]^+$), 411.4 (82), 301.3 (100). HR-MALDI-MS: 1151.6875 and 1149.6907 ($[M + Na]^+$, $C_{69}H_{103}ClNaO_8S^+$; calc. 1151.6930 and 1149.6960).

*1-[(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]-3,4-dimethoxy-2,5-bis(methoxymethoxy)-6-methylbenzene* (**9**). $EtNH_2$ (*ca.* 15 ml) was condensed at $-78°$ into a flask containing a soln. of **8** (1.13 g, 1.0 mmol) in THF (5 ml). Small pieces of Li (*ca.* 70 mg, excess) were added under Ar (→dark blue). After stirring vigorously at $-78°$ for 30 min, the reaction was quenched with isoprene (0.3 ml). Solid NH_4Cl was added until the blue color disappeared. The excess metal was removed with forceps, and the mixture was then diluted with Et_2O (15 ml) and H_2O (20 ml). The aq. phase was extracted with Et_2O (2 × 20 ml), the extract dried (Na_2SO_4), and concentrated, and the crude product purified by CC (SiO_2, petroleum ether/AcOEt 15:1): pure **9** (0.82 g, 86.1%; >96% pure by HPLC). White solid. M.p. 27.9–28.6°. IR (KBr): 2923, 2853, 1450, 1428, 1391, 1349, 1159, 1056, 978. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.58, 1.60, 1.68, 1.75 (4*s*, 11 MeC=C); 1.95–2.10 (*m*, 9 (CH_2)$_2$CH=C); 2.17 (*s*, Me–C(6)); 3.37 (*d*, $^3J = 6.4$, CH_2(1′)); 3.58, 3.60 (2*s*, 2 *Me*OCH_2); 3.86 (*s*, MeO–C(3), MeO–C(4)); 5.04, 5.05 (2*s*, 2 OCH_2O); 5.04–5.13 (*m*, 10 C=CH). MALDI-MS: 975.6 ($[M + Na]^+$, $C_{63}H_{100}NaO_6^+$).

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-decaenyl]-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione*; **1**). A soln. of **9** (0.48 g, 0.50 mmol) in MeOH/hexane 2:1 (60 ml) containing one drop of sat. aq. HCl soln. was stirred at 40° for 4 h. After cooling to r.t., the soln. was neutralized with KOH in MeOH to pH 7. H_2O (10 ml) was added, and the resulting mixture was extracted with hexane (3 × 50 ml). The combined org. phase was washed with H_2O (3 × 25 ml), dried (Na_2SO_4), and concentrated. The crude product, which was accompanied by a small amount of isomeric compounds (3.5% by HPLC), was purified by CC (SiO_2; petroleum ether/AcOEt 15:1): **1** (80.2 mg, 93.0%). Orange oil, which gradually solidified. M.p. 49–49.5° ([16]: m.p. 48–49°). IR (KBr) : 2923, 2853, 1655, 1615, 1450, 1385, 1265, 1155. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.58. 1.60 (2*s*, 9 MeC=C); 1.68 (*s*, MeC=C); 1.74 (*s*, MeC=C); 2.01 (*s*, Me–C(3)); 1.93–2.09 (*m*, 9 (CH_2)$_2$CH=C); 3.18 (*d*, $^3J = 6.9$, CH_2(1′)); 3.98, 4.00 (2*s*, MeO–C(5), MeO–C(6)); 4.93 (*t*, $^3J = 7.3$, C=CH); 5.04–5.13 (*m*, 9 C=CH). MALDI-MS: 885.7 ($[M + Na]^+$, $C_{59}H_{90}NaO_4^+$).

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