Synthetic Studies on Coenzyme Q_{10}

Part 1

An Efficient and Highly Stereocontrolled Synthesis of Coenzyme Q_{10} *via* a C_5+C_{45} Strategy

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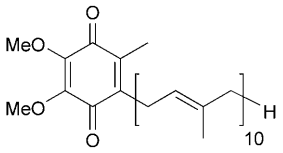
A practical, highly stereoselective ten-step synthesis of coenzyme Q_{10} (**1**) has been accomplished (overall yield *ca*. 28%), starting from commercially available 2,3-dimethoxy-5-methylbenzoquinone (*Scheme*). The introduction of the first side-chain isoprenyl group with (*E*)-configuration (compound **6**) was realized by means of a coupling reaction of the aromatic system **3** with oxirane, followed by *Swern* oxidation and *Wittig* olefination. The tosyl (Ts) group in the sulfone **9** was selectively removed with sodium naphthalenide in THF to afford **1**.

Introduction. – Since its discovery and isolation from the mitochondria of beef heart by *Crane* in 1957, coenzyme Q_{10} (**1**), also known as ubiquinone-10 or vitamin Q_{10}, has been used clinically as a cardiovascular agent [1]. It can also be applied as an antioxidizing [2] and immunomodulating drug, and has a notable effect on cancer treatment [3]. Although a number of methods for the synthesis of coenzyme Q_{10} (**1**) have been developed [4–6], the first industrial approach by *Hideaki Fukawa* at *Nisshin* in 1974 [7], based on direct polyprenylation of hydroquinone monoacetate by *Friedel–Crafts*-type coupling, is still exclusive for the partial synthesis of this vitamin. However, this process is, unfortunately, attended with some unwanted side reactions, especially partial cyclization to a chromanol type compound and (*E*)/(*Z*) isomerization during coupling. Moreover, the coupling yield is very low (20%).



Coenzyme Q_{10} (**1**)

A number of alternative coupling processes have been developed, with various significant improvements. For example, *Sato*'s coupling reaction of 6-bromo-2,3-dimethoxy-5-methylhydroquinone diacetate with π-decaprenylnickel bromide [4b], *Naruta*'s

coupling reaction of 2,3-dimethoxy-5-methylbenzoquinone with decaprenyl(trimethyl)tin [4c], *Terao*'s coupling of a terminally sulfonated prenylhydroquinone bisbenzyl ether with solanesyl bromide [5a], and *Masaki*'s coupling reaction of a protected, terminally brominated prenylhydroquinone with solanesyl *p*-tolylsulfone [5d], among others. Unfortunately, in these cases, problems in controlling the configuration of the C=C bonds have not been fully solved.

Recently, *Lipshutz*'s group [5g][8] reported an efficient and stereoselective coupling strategy in which solanesyl acetylene was activated as a nucleophilic C_{49} vinylalane by treatment with Me_3Al. Although the reported coupling yield is as high as 88%, the use of expensive, toxic, or irritant reagents such as Me_3Al or Cp_2ZrCl_2 restricts the application of this procedure for large-scale preparations.

Several groups have succeeded in the total synthesis of **1** [6]. However, these syntheses are not suitable for commercial exploitation because they comprise more than 20 steps, suffer from relatively low overall yields or use of expensive organometallic catalysts such as Pd^{II} or Zr^{II}. Therefore, an efficient and economical synthesis of **1** is still needed. In this paper, we report a practical and stereoselective method for the total synthesis of coenzyme Q_{10} (**1**), starting from inexpensive, commercially available 2,3-dimethoxy-5-methylbenzoquinone.

Results and Discussion. – Our synthetic route to **1** is outlined in the *Scheme*. The known hydroquinone **2** was prepared in 97% yield by treatment of 2,3-dimethoxy-5-methylbenzoquinone [9] with $Na_2S_2O_4$ in 1,2-dichloroethane at 40°, using a modified procedure originally developed by *Sato et al.* [10]. Protection of the OH groups of **2** as methoxymethyl (MOM) ethers in EtOH at −20° under N_2 afforded compound **3** in 84% yield. Direct lithiation of the latter was carried out with BuLi in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in hexane at 0°, and subsequent *in situ* coupling with oxirane in THF at −40° gave rise to the desired alcohol **4** in 60% yield. In the absence of TMEDA, lithiation failed.

The next stages involved construction of the (*E*)-configured isoprenyl chain. *Swern* oxidation of **4** afforded the desired aldehyde **5** at −30° in 95% yield. *Wittig* olefination of **5** with the ylide ethyl 2-(triphenylphosphoranylidene)propanoate ($Ph_3P{=}C(Me)CO_2Et$; derived from $BrPh_3PCH(Me)CO_2Et$) in refluxing CH_2Cl_2 provided the ester **6** in 92% yield, with an (*E*)/(*Z*) ratio of 99.3 : 0.7, as determined by GC/MS. The predominant (*E*)-configuration of the C=C bond in **6** was confirmed by a NOESY experiment. NOEs were found between the signals of the Me group at C(2) and the CH_2(4) H-atoms. Next, chemoselective reduction of **6** with $LiAlH_4$ in refluxing THF resulted in the alcohol **7** in 87% yield. Mesylation of the latter with methanesulfonyl chloride (MsCl) and Et_3N in CH_2Cl_2 at −40°, followed by bromination with LiBr in THF, furnished the (*E*)-configured allyl bromide **8** in 95% yield.

We next focused on the coupling between the C_5 side chain in **8** and solanesyl *p*-tolylsulfone (**9**)[1]) for installation of the (all-*E*)-configured C_{50} side chain of coenzyme Q_{10} (**1**). Thus, the sulfone **9** was lithiated with BuLi in HMPA/THF 1 : 5 at −70°, and then

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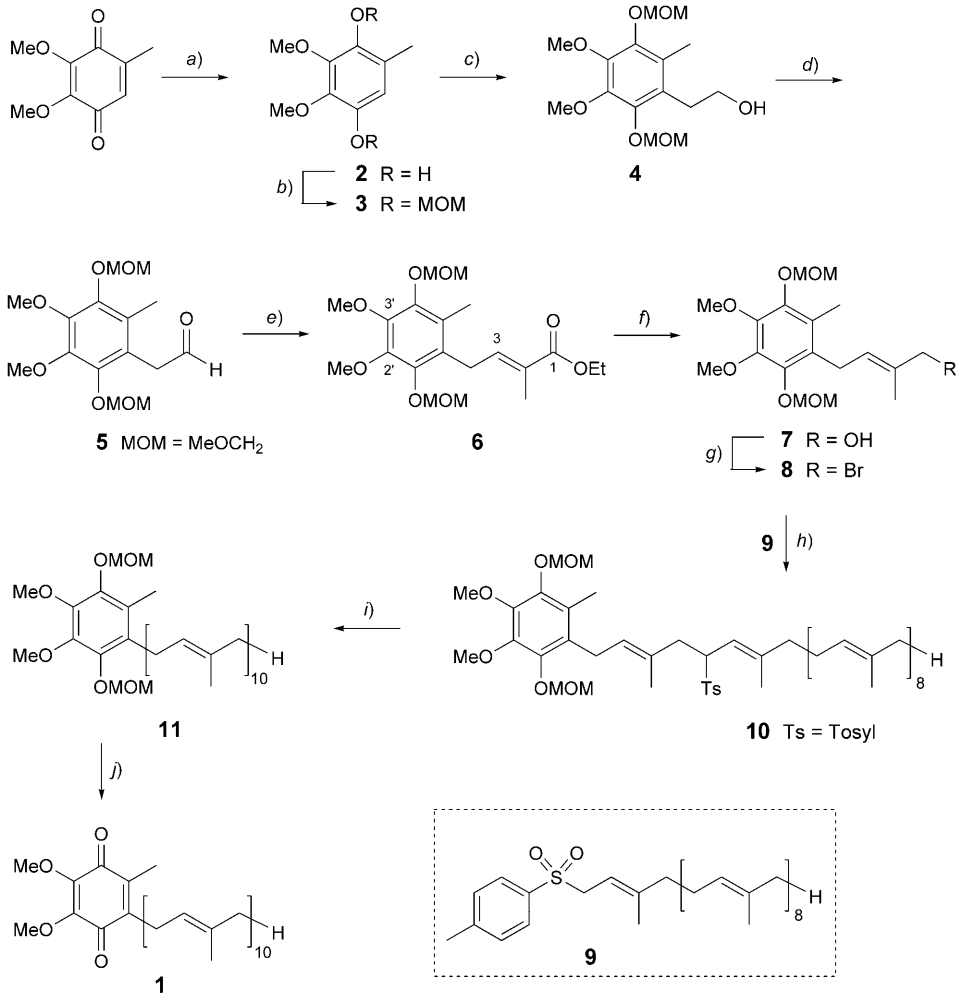
[1]) Systematic name: (2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*)-3,7,11,15,19,23,27,31,35-nonamethylhexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl 4-methylbenzenesulfonate.

Scheme



a) Sat. aq. $Na_2S_2O_4$, $ClCH_2CH_2Cl$, 40° → r.t., 3 h; 97%. *b*) $MeOCH_2Cl$, EtONa, EtOH, N_2, −20°, 3 h; 84%. *c*) 1. BuLi, TMEDA, hexane, N_2, 0°, 30 min; 2. THF, ethylene oxide, −78°, −40°, 30 min, r.t., 3 h; 60%. *d*) 1. $(COCl)_2$, DMSO, CH_2Cl_2, −78° → −30°, 1 h; 2. Et_3N, r.t., 1 h; 3. 2N HCl; 95%. *e*) $Ph_3P{=}C(Me)CO_2Et$, CH_2Cl_2, reflux, 4 h; 91.7%. *f*) $LiAlH_4$, THF, reflux, 4 h; 87%. *g*) 1. MsCl, Et_3N, CH_2Cl_2, −40°, 1.5 h; 2. LiBr, THF, 0°, 2.5 h; 95.5%. *h*) 1. Compound **9**, BuLi, HMPA/THF 1:5, N_2, −70°, 30 min; 2. −70° → 0°, 2 h; 85%. *i*) 1. $C_{10}H_7Na$, THF, −78°, 30 min; 2. MeOH; 99.8%. *j*) HCl (cat.), MeOH/hexane 2:1, 40°, 3 h; 93%. Overall yield of **1**: 27.9%.

coupled with the bromide **8** in THF to afford the decaprenylated hydroquinone **10** in good yield (85%).

In former syntheses of **1**, the tosyl (Ts) groups were generally removed reductively with dissolved metals [5a–e]; however, loss of stereochemical integrity of the Δ^6 C=C bond has often been observed. When using the protocols reported in [5f] and [11] for

the selective reduction of allylic sulfones, almost no isomerization of the olefinic bond was observed, and the desired hydroquinone **11** was obtained in 89% yield. Unfortunately, this desulfurization procedure is impractical for large-scale synthesis due to the use of expensive and stoichiometric amount of lithium triethylborohydride (Et_3BLiH) as reducing reagent and diphenylphosphinopropane palladium(II) chloride [$PdCl_2$(dppp)] as catalyst. This prompted us to search for an alternative, more-economical process. Fortunately, sodium naphthalenide in THF – prepared from Na and naphthalene at room temperature [12] – smoothly removed the Ts group, affording the hydroquinone **11** in basically quantitative yield (on the basis of HPLC analysis). Finally, simple acid-catalyzed deprotection of the MOM groups in **11**, followed by *in situ* air oxidation in hexane at room temperature afforded the target compound **1** in 93% yield after column chromatography.

Conclusions. – We have developed a novel, efficient, highly stereoselective, and short synthesis of coenzyme Q_{10} (**1**) from commercially available 2,3-dimethoxy-5-methylbenzoquinone. Compound **1** was obtained in ten steps in an overall yield of *ca*. 28%. The method should prove suitable for the large-scale production of this vitamin. Highlights of the synthesis involve stereoselective *Wittig* olefination of the aldehyde **5**, leading to the side-chain functionalized (*E*)-configured synthon **6**, and regioselective reductive desulfurization of compound **10** in the presence of sodium naphthalenide.

Experimental Part

General. THF, Et_2O, hexane and toluene were distilled from sodium benzophenone ketyl, EtOH was distilled from Mg, and CH_2Cl_2, Et_3N, and DMSO were distilled from CaH_2. Petroleum ether (PE) for column chromatography (CC) had a b.p. of 30–60°. *Solanesyl* p-*tolylsulfone* (**9**)[1]) was prepared according to [5c]. HPLC Analyses were performed on a *Shimadzu LC-10AT* liquid chromatograph equipped with a *Spd-10A* UV/VIS detector working at 270 nm, and fitted with an L_3 column (250 × 4.6 mm); elution with hexane/AcOEt 95 : 5 at a flow rate of 2.0 ml/min. Melting points (m.p.) were determined on a *WRS-1B* digital melting-point apparatus. IR Spectra were recorded on a *Nicolet FT-IR 360* spectrophotometer; in cm^{-1}. NMR Spectra were recorded on *Bruker DMX-500* and *Jeol ECA-400* spectrometers; chemical shifts δ rel. to internal Me_4Si, coupling constants *J* in Hz. Mass spectra were recorded on a *HP-5989A* spectrometer; in *m*/*z*. GC/MS: *Finnigan Voyager* spectrometer.

2,3-Dimethoxy-5-methylbenzene-1,4-diol (**2**). To a stirred soln. of 2,3-dimethoxy-5-methylbenzoquinone (8.16 g, 0.11 mol) in 1,2-dichloroethane (150 ml) was added sat. aq. $Na_2S_2O_4$ soln. (*ca.* 100 ml) at 40°, until the red color of the soln. disappeared. The resulting mixture was stirred for 3 h at r.t. under N_2. The aq. layer was extracted with 1,2-dichloroethane (3 × 50 ml), and the combined org. phase was washed with brine (3 × 35 ml), dried (Na_2SO_4), and evaporated under reduced pressure to afford **2** (19.6 g, 97%). Colorless solid. M.p. 76.1–76.5° (lit. m.p. 77–78° [13]). IR (KBr): 3399, 2923, 1601, 1499, 1429, 1371, 1111, 1065, 998, 854. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.18 (*s*, 5-Me); 3.91, 3.88 (2*s*, 2 MeO); 5.20, 5.34 (2*s*, 2 OH); 6.49 (*s*, arom. H).

2,3-Dimethoxy-1,4-bis(methoxymethoxy)-5-methylbenzene (**3**). To a stirred soln. of **2** (8.0 g, 43.4 mmol) in anh. EtOH (200 ml) was added dropwise a first portion of ethanolic EtONa, prepared by dissolving Na (1.10 g, 47.8 mmol) in anh. EtOH (24 ml), followed $MeOCH_2Cl$ (3.85 g, 47.8 mmol) at −20° under N_2. Then, the remaining portions of EtONa (prepared from Na (3.30 g, 143 mmol) in anh. EtOH (72 ml)), was added in three equal portions, each addition being followed by dropwise addition of $MeOCH_2Cl$ (3.85 g, 47.8 mmol). After complete addition of the reagents, the mixture was stirred for 3 h at −20°, filtered, and concentrated under reduced pressure to a final volume of *ca*. 50 ml. Then, 2N aq. KOH soln. (50 ml) was added, and the mixture was extracted with Et_2O (3 × 100 ml). The combined org. phase was washed with 2N aq. KOH soln. (2 × 50 ml) and brine (3 × 50 ml), and dried ($MgSO_4$). The solvent was evaporated *in vacuo* to afford **3** (9.93 g, 84.1%). Yellow oil. IR (film): 2935, 2826, 1588, 1490, 1118, 1072, 987, 925. ^{1}H-NMR (500 MHz,

$CDCl_3$): 2.25 (*s*, *Me*Ar); 3.52, 3.59 (2*s*, 2 *Me*OCH_2); 3.87, 3.88 (2*s*, 2 *Me*OAr); 5.05, 5.16 (2*s*, 2 OCH_2O); 6.70 (*s*, arom. H). EI-MS: 272 (M^+), 242, 227, 195, 45.

2-[3,4-Dimethoxy-2,5-bis(methoxymethoxy)-6-methylphenyl]ethanol (**4**). BuLi (5.0 ml of a 1.6M soln. in hexane) was added to a soln. of **3** (1.36 g, 5.0 mmol) in hexane (15 ml) containing TMEDA (1.36 ml) at 0° over 30 min under N_2. The mixture was stirred for an additional 30 min, followed by addition of THF (50 ml). The mixture was cooled to −78°, and a soln. of ethylene oxide (*ca.* 2.20 g, 50 mmol) in THF (15 ml) was added. The resulting mixture was stirred at −40° for 30 min, and thereafter at r.t. for a further 3 h. Then, 2N aq. HCl (25 ml) was added at 0°, and the heterogeneous mixture was stirred for 30 min at this temp. The aq. phase was extracted with Et_2O (3×100 ml), the combined org. phase was washed with brine (3×50 ml), dried ($MgSO_4$), and evaporated *in vacuo.* The crude product was purified by CC (SiO_2; PE/AcOEt 2:1) to afford **4** (0.941 g, 59.6%). Colorless oil. IR (film): 3430, 2937, 1470, 1427, 1103, 1058, 947. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.09 (*s*, OH); 2.24 (*s*, *Me*Ar); 2.98 (*t*, ^3J=6.8, ArCH_2); 3.60 (*s*, 2 *Me*OCH_2); 3.79 (*m*, CH_2OH); 3.85, 3.86 (2*s*, 2 *Me*OAr); 5.05, 5.11 (2*s*, 2 OCH_2O). ^{13}C-NMR (100 MHz, $CDCl_3$): 12.7 (*Me*Ar); 30.5 (C(2)); 57.6 (2 *Me*OCH_2); 61.0 (2 *Me*OAr); 62.3 (C(1)); 99.4, 99.8 (2 OCH_2O); 126.2 (C(1,6) of Ar); 144.2 (C(3) of Ar); 145.2 (C(4) of Ar); 145.5 (C(5) of Ar)); 146.0 (C(2) of Ar). EI-MS: 316 (16, M^+), 239 (15), 210 (34), 209 (100), 45 (78). HR-EI-MS: 316.1516 (M^+, $C_{15}H_{24}O_7^+$; calc. 316.1522).

2-[3,4-Dimethoxy-2,5-bis(methoxymethoxy)-6-methylphenyl]ethanal (**5**). To a stirred soln. of $(COCl)_2$ (1.75 ml, 20.0 mmol) in CH_2Cl_2 (100 ml), was added dropwise a soln. of DMSO (3.0 ml, 40.0 mmol) in CH_2Cl_2 (20 ml) at −60°, and the resulting mixture was stirred for 15 min. Then, a soln. of **4** (3.16 g, 10.0 mmol) in CH_2Cl_2 (25 ml) was added dropwise. The mixture was allowed to warm to −40° over a period of 1 h. Et_3N (11.3 ml, 80.0 mmol) was added, and the resulting soln. was stirred for 1 h at r.t. Then, 2N aq. HCl (87.5 ml) was added, and the aq. layer was extracted with CH_2Cl_2 (3×100 ml). The combined org. phase was washed with brine (3×50 ml), and dried (Na_2SO_4). The solvents were evaporated, and the crude product was purified by CC (SiO_2; PE/AcOEt 2:1) to afford **5** (2.98 g, 94.9%). Colorless oil. IR (film): 2929, 1723, 1468, 1428, 1103, 1060, 973. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.15 (*s*, *Me*Ar); 3.53, 3.60 (2*s*, 2 *Me*OCH_2); 3.77 (*d*, ^3J=1.2, CH_2(2)); 3.87, 3.88 (2*s*, 2 *Me*OAr); 5.07, 5.08 (2*s*, 2 OCH_2O); 9.66 (*s*, H−C(1)). ^{13}C-NMR (100 MHz, $CDCl_3$): 12.0 (*Me*Ar); 41.4 (C(2)); 56.5 (2 *Me*OCH_2); 60.0 (2 *Me*OAr); 98.3, 98.7 (2 OCH_2O); 119.7 (C(6) of Ar); 125.8 (C(1) of Ar); 144.3 (C(3) of Ar); 144.5 (C(4) of Ar); 145.0 (C(2) of Ar); 145.2 (C(5) of Ar); 198.8 (C(1)). EI-MS: 314 (19, M^+), 269 (18), 237 (36), 45 (100). HR-EI-MS: 314.1316 (M^+, $C_{15}H_{22}O_7^+$; calc. 314.1366).

*Ethyl (2*E*)-4-[3,4-Dimethoxy-2,5-bis(methoxymethoxy)-6-methylphenyl]but-2-enoate* (**6**). A mixture of the ylide Ph_3P=C(Me)CO_2Et (2.85 g, 7.88 mmol) and **5** (1.90 g, 6.05 mmol) in CH_2Cl_2 (90 ml) was heated at reflux for 4 h. Sat. aq. NaCl soln. (100 ml) was then added, the aq. layer was extracted with CH_2Cl_2 (3×100 ml), and the combined org. phase was washed with brine (3×50 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave the crude product, which was purified by CC (SiO_2; PE/AcOEt 6:1) to afford pure **6** (2.21 g, 91.7%). The (*E*)/(*Z*) ratio was 99.7:0.3 (GC). Colorless oil. IR (film): 2927, 2854, 1708, 1467, 1427, 1159, 1103, 1023, 974. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.27 (*t*, ^3J=7.3, *Me*CH_2O); 2.00 (*s*, 2-Me); 2.16 (*s*, *Me*Ar); 3.55–3.59 (*m*, 2 *Me*OCH_2, CH_2(4)); 3.86, 3.87 (2*s*, 2 *Me*OAr); 4.17 (*q*, ^3J=7.4, MeCH_2O; 5.06, 5.08 (2*s*, 2 OCH_2O); 6.67 (*t*, ^3J=6.4, H−C(3)). ^{13}C-NMR (100 MHz, $CDCl_3$): 12.7 (*Me*Ar, 2-Me); 14.3 (*Me*CH_2O); 26.9 (C(4)); 57.6 (2 *Me*OCH_2); 60.5 (2 *Me*OAr); 61.0 (MeCH_2O); 99.4, 99.6 (2 OCH_2O); 126.2 (C(6) of Ar); 127.1, 127.7 (C(3), C(1) of Ar); 140.4 (C(2)); 144.4 (C(3) of Ar); 145.2 (C(4) of Ar); 145.4 (C(2.5) of Ar); 168.1 (C(1)). EI-MS: 398 (12, M^+), 353 (15), 321 (23), 263 (28), 235 (15), 45 (100). HR-EI-MS: 398.1934 (M^+, $C_{20}H_{30}O_8^+$; calc. 398.1941).

*(2*E*)-4-[3,4-Dimethoxy-2,5-bis(methoxymethoxy)-6-methylphenyl]but-2-en-1-ol* (**7**). To a stirred soln. of $LiAlH_4$ (0.315 g, 8.28 mmol) in THF (30 ml) was added a soln. of **6** (1.94 g, 4.87 mmol) in THF (50 ml). The mixture was heated at reflux for 4 h, and then cooled to r.t. AcOEt (10 ml) followed by H_2O (10 ml) were added dropwise, the resulting mixture was filtered, and the aq. layer was extracted with Et_2O (3×50 ml). The combined org. phase was washed with brine (3×35 ml), dried (Na_2SO_4), and evaporated under reduce pressure. The crude product was purified by CC (SiO_2; PE/ AcOEt 3:1) to afford pure **7** (1.51 g, 87.3%). 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*, 2-Me); 2.18 (*s*, *Me*Ar); 3.42 (*d*, ^3J=6.4, CH_2(4)); 3.58, 3.60 (2*s*, 2 *Me*OCH_2); 3.86 (*s*, 2 *Me*OAr); 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: 356.1842 (M^+, $C_{18}H_{28}O_7^+$; calc. 356.1835).

*1-[(2*E*)-4-Bromobut-2-en-1-yl]-3,4-dimethoxy-2,5-bis(methoxymethoxy)-6-methylbenzene* (**8**). To a stirred soln. of **7** (1.78 g, 5 mmol) in CH_2Cl_2 (50 ml) was added Et_3N (1.10 ml, 7.9 mmol) followed by MsCl (0.5 ml, 6.6 mmol) at −40°. After stirring for 1.5 h, a soln. of LiBr (1.74 g, 20 mmol) in THF (40 ml) was added, and the resulting mixture was stirred at 0° for 2.5 h. The mixture was then poured into petroleum ether (PE;

250 ml), washed with H_2O (4×300 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was purified by CC (SiO_2; PE/AcOEt 7:1) to afford pure **8** (2.0 g, 95.5%). Colorless oil. IR (film): 2932, 2828, 1469, 1427, 1393, 1348, 1159, 1057, 1024, 975, 935. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.91 (*s*, Me of side chain)[2]), 2.16 (*s*, *Me*Ar); 3.42 (*d*, ^3J=6.4, ArCH_2); 3.57, 3.59 (2*s*, 2 *Me*OCH$_2$); 3.86, 3.88 (2*s*, 2 *Me*OAr); 3.96 (*s*, BrCH$_2$); 5.05, 5.07 (2*s*, 2 OCH$_2$O); 5.54 (*t*, ^3J=6.0, C=CH of side chain). EI-MS: 420/418 (4, M^+), 294 (25), 263 (25), 249 (64), 233 (5), 217 (17), 45 (100). HR-EI-MS: 420.0966/418.0985 (M^+, $C_{18}H_{27}BrO_6^+$; calc. 420.0971/418.0991).

1-[(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-decaen-1-yl]-3,4-dimethoxy-2,5-bis(methoxymethoxy)-6-methyl-benzene (**10**)[3]). BuLi (1.0 ml of a 1.6M soln. in hexane) was added dropwise to a soln. of *solanesyl* p-*tolylsulfone* (**9**; 0.913 g, 1.19 mmol) and HMPA (2.64 ml) in THF (8.0 ml) at −70° over 30 min under N_2. The resulting yellow mixture was stirred at −70° for 30 min. A soln. of the bromide **8** (0.333 g, 0.795 mmol) in THF (1.0 ml) was added dropwise, and the mixture was warmed up to 0° over a period of 2 h, and finally taken up in Et_2O (3× 50 ml). The mixture was washed with 1N aq. HCl (50 ml) and H_2O (3×25 ml), dried (Na_2SO_4), and the org. layer was evaporated *in vacuo*. The crude product was purified by CC (SiO_2; PE/AcOEt 8:1) to afford pure **10** (0.750 g, 85.3%). Colorless oil. IR (film): 2923, 2854, 1450, 1428, 1146, 1056, 978. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.21 (*s*, MeC=); 1.58–1.60 (br. *s*, 8 MeC=); 1.68, 1.69 (2*s*, 2 *Me*C=); 1.85–2.16 (*m*, 8 (CH$_2$)$_2$CH=, *Me*Ar); 2.22 (*q*, ^2J=−12.8, ^3J=12.4, 1 H of CH$_2$(4) of side chain); 2.42 (*s*, Me of Ts); 2.89 (br. *d*, ^2J=−12.8, 1 H of CH$_2$(4) of Ar); 3.28 (*dd*, ^2J=−15.1, ^3J=6.4, 1 H of CH$_2$(1) of side chain); 3.35 (*dd*, ^2J=−15.1, ^3J=6.4, 1 H of CH$_2$(1) of side chain); 3.53, 3.57 (2*s*, 2 *Me*OCH$_2$O); 3.84 (*s*, 2 *Me*OAr); 3.88 (*m*, H−C(5) of side chain); 4.84 (*d*, ^3J=10.1, C=C(H); 5.00, 5.02 (2*s*, 2 OCH$_2$O); 5.04–5.13 (*m*, 9 C=CH); 7.28 (*d*, ^3J=8.2, 2 arom. H of Ts); 7.69 (*d*, ^3J=8.2, 2 arom. H of Ts). MALDI-MS: 1130 ([M+Na]$^+$, $C_{70}H_{106}NaO_8S^+$).

1-[(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-decaen-1-yl]-3,4-dimethoxy-2,5-bis(methoxymethoxy)-6-methylbenzene (**11**). To a stirred soln. of **10** (0.553 g, 0.500 mmol) in THF (50 ml) was added dropwise sodium naphthalenide (2.5 ml of a 1M soln. in THF) at −78° over 30 min. The resulting mixture was stirred for 30 min at this temp. Then, the excess sodium naphthalenide was destroyed by addition of MeOH (25 ml). The mixture was warmed to 0°, poured into H_2O (80 ml), and extracted with Et_2O (3×100 ml). The combined org. phase was washed with brine (3×50 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was purified by CC (SiO_2; PE/AcOEt 15:1) to afford **11** (0.475 g, 99.8%; >99.4% pure by HPLC). Colorless solid. M.p. 28.0–28.5°. 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=); 2.17 (*s*, *Me*Ar); 3.37 (*d*, ^3J=6.4, ArCH_2); 3.58, 3.60 (2*s*, 2 *Me*OCH$_2$); 3.86 (*s*, 2 *Me*OAr); 5.04, 5.05 (2*s*, 2 OCH$_2$O); 5.04–5.13 (*m*, 10 C=CH). MALDI-MS: 975.6 ([M+Na]$^+$, $C_{63}H_{100}NaO_6^+$).

Coenzyme Q_{10} (**1**). A soln. of **11** (95.2 mg, 0.10 mmol) in MeOH/hexane 2:1 (30 ml) containing one drop of sat. aq. HCl was stirred at 40° for 4 h. After cooling to r.t., the soln. was neutralized with methanolic KOH to pH 7. Then, 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 evaporated *in vacuo*. The crude product was accompanied by a small amount of isomeric compounds (1.5% by HPLC). Purification by CC (SiO_2; PE/AcOEt 15:1) afforded **1** (80.2 mg, 93.0%). Orange oil, which gradually solidified. M.p. 49–49.5° (lit. m.p. 48–49° [5a]). 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*Ar); 1.93–2.09 (*m*, 9 (CH_2)$_2$CH=); 3.18 (*d*, ^3J=6.9, CH$_2$(1) of side chain); 3.98, 4.00 (2*s*, 2 *Me*OAr); 4.93 (*t*, ^3J=7.3, H−C(2) of side chain); 5.04–5.13 (*m*, 9 C=CH). MALDI-MS: 885.7 ([M+Na]$^+$, $C_{59}H_{90}NaO_4^+$).

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[2]) 'Side chain' = 4-bromo-3-methylbut-2-enyl.

[3]) For clarity (similarity of atom numbering), the less-systematic parent name, (-benzene rather than -sulfone) was chosen.

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Received May 24, 2005