Synthesis of Crown Ethers Related to Ubiquinones

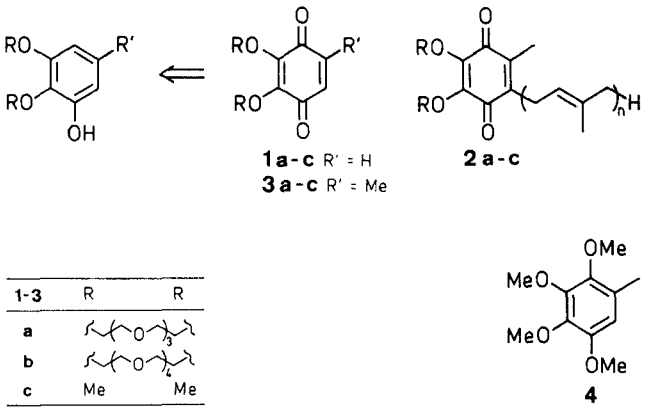
Andreas Merz,* Manfred Rauschel

Institut für Organische Chemie, Universität Regensburg, Universitätsstraße 31, D-8400 Regensburg, Germany

Received 15 October 1992; revised 2 December 1992

Crown ethers in which the two methoxy groups of ubiquinone-0 (2,3-dimethoxy-5-methyl-1,4-benzoquinone) are replaced by oligoethylene glycol bridges have been obtained in five straightforward steps in 35–40% overall yield from 5-methylpyrogallol. A Fremy salt oxidation of a phenolic precursor is used in the final step. The further elaboration of crown ether analogues of ubiquinone-2 was achieved by enol geranylation of cyclopentadiene adducts of the former quinones and subsequent retro-Diels–Alder reaction. The Claisen rearrangement of 2,2-dimethoxy-5-methylphenyl allyl ethers and related crown ethers affords *ortho*- and *para*-allyl-substituted phenols (3:1) that are oxidized to give bisnorubiquinone derivatives and their *ortho*- quinone isomers. All new compounds are characterized by high resolution NMR and mass spectrometry.

In a previous paper we have reported the synthesis of benzoquinone-annelated crown ethers **1a,b**.[1] Because of the structural similarity to the ubiquinone system **2c**, we became interested in the synthesis of related crown ethers **2a,b**. Ubiquinone-10 **2c** (n = 10), also called coenzyme Q, is an important redox carrier in the mitrochondrial respiratory chain and may have pharmacological and dietary significance.[2] Therefore, ubiquinones have attracted much synthetic activity in the past two decades.[3] Structures **2a,b** like other "crowned" natural products[4] may be of interest in biological studies since, in addition to the same redox characteristics as the natural ubiquinones, they have an ion carrier functionality.

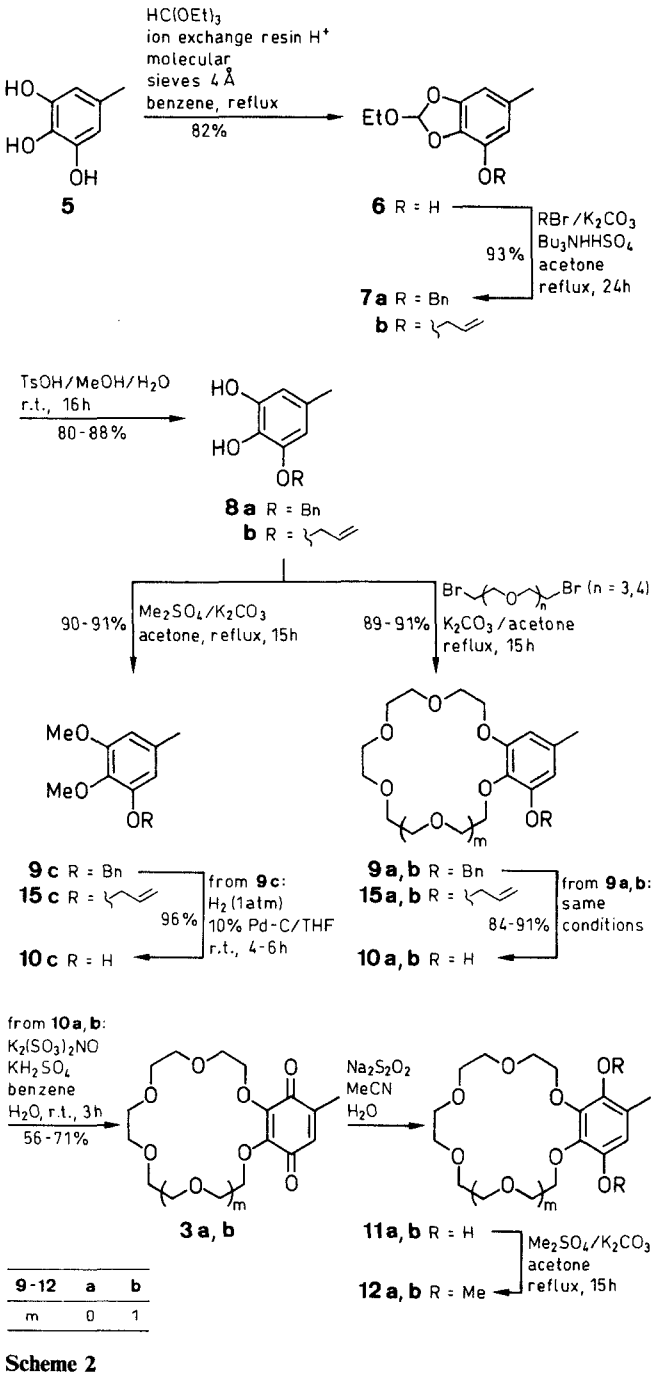


1-3	R	R
a		
b		
c	Me	Me

Scheme 1

Any syntheses of ubiquinones require either 2,3-dimethoxy-5-methyl-1,4-benzoquinone (**3c**), its hydroquinone or ethers thereof, e. g. **4**.[3] All of these intermediates can be connected to an oligoisoprene unit at the free ring position in a variety of ways.

For the synthesis of crown ethers **3a,b** that correspond to the common ubiquinone intermediate, we followed the protective group protocol we had already used for **1a,b**[1] with a Fremy salt [$K_2(SO_3)_2NO$] oxidation of a phenolic precursor in the final step. 5-Methyl-1,2,3-benzenetriol (**5**), available in two steps from trimethoxybenzaldehyde was modified for selective conversion of the three hydroxy groups by protection as the cyclic ortho ester **6** and benzylation at the free 5-OH group to give **7a**. Hydrolysis of the ortho ester **7a** provides the catechol derivative **8a** which now allows crown ether construction at the free hydroxy groups to give **9a,b**. Very good yields in the crown ether ring formation were achieved when oligoethyleneglycol dibromides or dimesylates were used in dry acetone as a solvent and potassium carbonate (K_2CO_3) as a base, tosylates being much less effective. On hydrogenolysis of the benzyl ether function in crude **9a,b**, the crown ethers **10a,b** are obtained in crystalline form. The crystal-



9-12	a	b
m	0	1

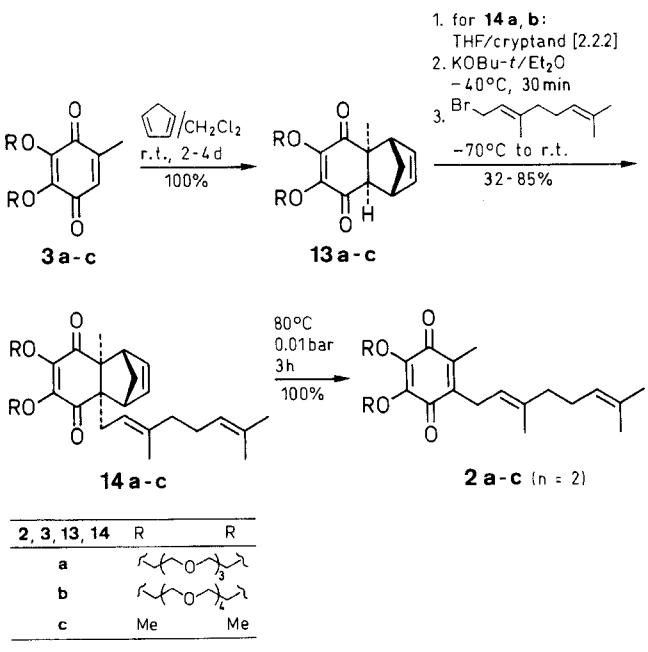
Scheme 2

line, orange colored quinone crown ethers **3a,b** are formed by Fremy's salt oxidation[1,5,6] of **10a,b** in 35–45% overall yield from **5**. Ubiquinone-0, **3c**, can also be prepared by this route in 53% yield from **5**, but an obviously better route to **3c** is the cerium(IV)-oxidation of 2,3,4,5-tetramethoxytoluene (**4**), which recently became available in a two-step procedure from inexpensive *p*-cresol.[7] Compounds **3a,b** can be quantitatively reduced to their hydroquinones **11a,b** by sodium thiosulfite ($Na_2S_2O_2$) in acetonitrile/water and further converted to the dimethyl ethers **12a,b**, structures corresponding to **4**.

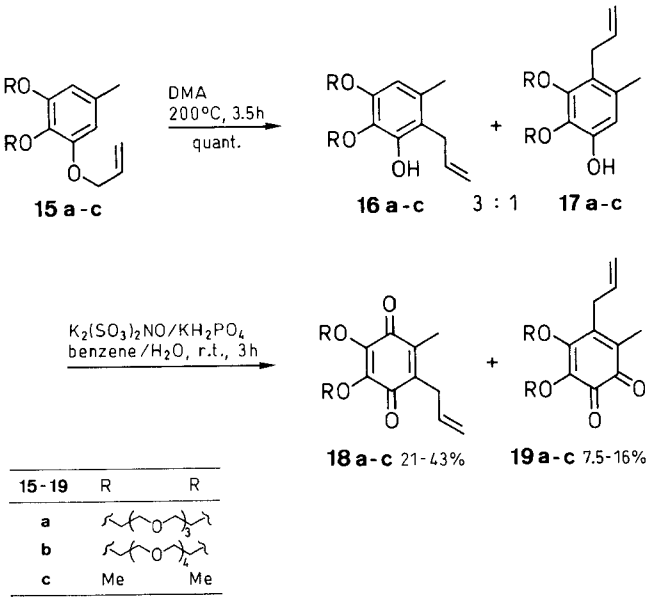
The next goal was the introduction of a linear terpenyl group at the free quinoid, or aromatic position of **3a,b** or **12a,b**, respectively. Preliminary studies using **3c** or **4** as model substrates for geranylation showed that among several published methods,[6,8] the TMEDA promoted lithiation of **4** and subsequent copper(I) cyanide (CuCN) promoted oxidative coupling with geranyl bromide[7] appeared to be the method of choice, giving, in our hands, even better yields than stated in the original work. However, this organometallic pathway as well as *all* other procedures failed for the geranylation of the crown ethers **3a,b**. In search for alternative procedures, we found that in the vitamin K series a Diels–Alder approach for the alkylation had successfully been employed where the free ring position is activated for enolization by intermediate formation of a cyclopentadiene cycloadduct.[9] After alkylation of the enolate, the cyclopentadiene is readily extruded in a *retro*-Diels–Alder reaction. In the model reaction the cycloadduct **13c** of **3c** and cyclopentadiene is converted into the enolate by potassium *tert*-butoxide (KOBu-*t*) in diethyl ether or tetrahydrofuran at low temperatures. C–C-bond formations with various alkyl and alkenyl bromides at the free bridgehead position proceed in high yield. The yield of ubiquinone-2 **2c** (n = 2) is 85–90% after thermal elimination of cyclopentadiene from **14c** at 80 °C/0.1 bar. In the crown ether series, quantitative formation of the cycloadducts **13a,b** was achieved equally well, but the enolization of these enediones and geranylation to **14a,b** again did not occur. We reasoned that this failure might arise from complexation of KOBu-*t* in the crown ether portion of the substrate in a position where it would not be active. Eventually, we found that enolization and subsequent alkylation indeed occurred when a better potassium complex than the crown ether, like cryptand[2.2.2] was present to activate the alcoholate anion.[10] With this protocol, the target crown ethers **2a** and **2b** were finally, after chromatography, obtained as very pure yellow oils in 32 and 50% yield besides unchanged starting materials. Compounds **2a** and **2b** form crystalline complexes with alkali metal ions, e.g. **2a · NaSCN** and **2b · KSCN**.

The selectively protected intermediate **6** offers still another way into a ubiquinone-1 model series: allylation of **6** to **7b** and subsequent elaboration in the same way as in Scheme 2 via **8b** affords the benzocrown allyl ethers **15a,b** and the dimethoxy derivative **15c**. These allyl ethers were subjected to a thermal Claisen rearrangement in dimethylaniline (DMA) as solvent.

The expected Claisen migration of the allyl group into the ortho position was indeed observed, but the crown ethers **16a,b** and the diether **16c** were accompanied by substantial amounts of the products **17a–c** of the para-Claisen rearrangement. When the crude mixtures were oxidized with Fremy's salt, a mixture of *para*- and *ortho*-quinones **18a–c** and **19a–c** was formed that could in all cases be separated by simple column chromatography.



Scheme 3



Scheme 4

The para-Claisen rearrangement is often believed to occur only when there is no free ortho position. There are, however, reported examples of mixed products, when one ortho position is blocked[11,12] and even of phenols with both ortho positions free.[13] Further rearrangement of an allylic substituent from an unsubstituted ortho position into the para position appears possible only if it proceeds faster than the enolization to the *o*-allylphenol. Indeed, an enhancement of solvent polarity was shown to decrease the amount of para-product in certain instances.[13] In the

present examples where the para fraction is unusually high, changing the solvent from DMA to *N*-methylpyrrolidinone,[13] or adding benzoic acid as an acidic catalyst, has no effect on the product ratio. A reasonable explanation for our experimental finding is the rate enhancing effect by the 2-alkoxy group on the undesired rearrangement path, similar to Claisen rearrangements of allyl ester enolates or the oxy-Cope-rearrangement.[14]

Several samples of modified ubiquinone structures synthesized in this work have been tested in in vitro studies of the isolated cytochrome bc_1 heme protein complex.[15] It was shown that natural ubiquinone-10 could be substituted by ubiquinone-2 **2c** (n = 2) and by bisnor-ubiquinone-1 **18c**, as well as simple alkylated derivatives of **3c**. The ubiquinone-like crown ethers that were anticipated to be able to carry fluorescent rare earth cations[16] into tissues could, however, not be incorporated into the reaction center.

The following analytical instruments were used: Finnigan MAT 90 (EI-MS (70 eV), Varian MAT 311 A (FAB-MS, glycerol matrix, 6 kV); Beckman Acculab 2 (IR); Shimadzu 210 A (UV/Vis, in spectrograde MeCN); Bruker WM 250 or Varian EM 360 (250 or 60 MHz ^{1}H NMR spectra, using TMS as internal standard, in $CDCl_3$ unless otherwise noted). Redox potentials were determined by cyclic voltammetry in MeCN/0.1 M TBAP, using a 3-electrode cell with a Pt working electrode and a Princeton Applied Research Mod. 273 electrochemical system. Melting points (uncorrected) were determined with a Büchi 510 apparatus. Elemental analyses were performed by the analytical laboratory of the University of Regensburg. Satisfactory microanalyses obtained for **3a,b, 6, 8a,b, 9c, 10a–c, 13a–c, 14a,b, 16a,b, 15a–c, 18a–c** and **19a–c**: C ± 0.24, H ± 0.18. Solvents and liquid reagents were purified prior to use by recommended distillation procedures.[17] Geranyl bromide and pentaethylene glycol dibromide were prepared from the diols in > 90% yield and excellent purity by the CBr_4/Ph_3P method.[18]

5-Methyl-1,2,3-benzenetriol (5):
A mixture of 3,4,5-trimethoxybenzaldehyde (Merck No. 821173, 26.0 g, 0.133 mol) and Pd catalyst (10% on carbon, Merck No. 807104, 3.3 g) in AcOH (150 mL) in a laboratory autoclave was pressurized with H_2 at 40 bar for 3 d at r.t. Distillative workup gave 3,4,5-trimethoxytoluene, 23.5 g (97%) as white solid, bp 62–65 °C (0.01 mbar), mp 35–37 °C (Lit.[19] oil).

^{1}H NMR (60 MHz): δ = 2.50 (s, 3 H, $ArCH_3$); 3.79 (s, 9 H, OCH_3); 6.40 (s, 2 H, ArH).

A mixture of trimethoxytoluene (15.0 g, 82.3 mmol), 57% aq HI (d = 1.7, 70 mL) and 30% aq H_3PO_2 (4 mL) was heated in a distillation apparatus equipped with a 18 cm Vigreux column until the distillation of MeI ceased (ca. 4 h). After cooling the mixture was diluted with H_2O (200 mL) and extracted with Et_2O (2 × 50 mL). After washing with $NaHCO_3$ (50 mL) and drying (Na_2SO_4) 11.5 g (96%) of **5** were isolated, mp 127–28 °C, which was used without further purification. Sample recrystallized from benzene: mp 129 °C (Lit.[19] 129 °C).

^{1}H NMR (60 MHz, acetone-d_6): δ = 2.10 (s, 3 H, $ArCH_3$); 6.27 (s, 2 H, ArH); 6.95 (br s, 3 H, OH).

2-Ethoxy-4-hydroxy-6-methyl-1,3-benzodioxole (6):
Compound **5** (10.0 g, 71.4 mmol), $HC(OEt)_3$ (15.8, 0.107 mol), ion exchange resin Amberlite IR 120-plus (0.5 g), powdered molecular sieves 4 Å (4 g) and dry benzene (180 mL, additional 100 mL added during the process) were heated in a distillation apparatus equipped with a 50-cm Vigreux column until 80–100 mL of benzene/EtOH azeotrope (bp 67–75 °C) were collected. The cooled dark red mixture was filtered and distilled. Compound **6** (11.5 g, 82%) was obtained as a viscous oil, bp 145–150 °C/0.01 mbar.

^{1}H NMR (60 MHz): δ = 1.25 (t, 3 H, J = 7 Hz, CH_3-ester); 2.20 (s, 3 H, $ArCH_3$); 3.70 (q, 2 H, J = 7 Hz, CH_2-ester, 5.35 (s, 1 H, OH); 6.30 (s, 2 H, ArH); 6.85 (s, 1 H, methine-H).

4-Benzyloxy-2-ethoxy-6-methyl-1,3-benzodioxole (7a) and 3-Benzyloxy-5-methyl-1,2-benzenediol (8a):
A mixture of **6** (9.0 g, 46.0 mmol), BnBr (7.90 g, 46.0), K_2CO_3 (7 g, 50 mmol), Bu_4NHSO_4 (200 mg) and dry acetone (65 mL) was stirred under reflux for 24 h. Removal of the acetone, addition of H_2O and extraction with CH_2Cl_2 (2 × 30 mL) yields **7a** as a yellowish oil which was used without further purification.

7a: ^{1}H NMR (60 MHz): δ = 1.23 (t, 3 H, J = 7 Hz, CH_3-ester); 2.20 (s, 3 H, $ArCH_3$); 3.73 (q, 2 H, J = 7 Hz, CH_2-ester); 5.20 (s, 2 H, $ArCH_2$); 6.46 (s, 2 H, ArH); 6.86 (s, 1 H, methine-H); 7.37 (m, 5 H, C_6H_5).

A solution of **7a** (11.7 g, 43.3 mmol) and TsOH (300 mg) in 95% aq MeOH (50 mL) is kept at r.t. for 16 h. After neutralization with Na_2CO_3 crude **8a** was obtained by extractive workup with Et_2O/H_2O and purified by filtration through silica gel in MeCN/CH_2Cl_2 to give slightly tan crystals of **8** (8.0 g, 80% based on **6**) mp 49–51 °C.

8a: ^{1}H NMR (250 MHz): δ = 2.23 (t, J = 0.75 Hz, $ArCH_3$); 5.04 (s, 2 H, OH); 6.18 (dd, J = 2.0, 0.75 Hz, 1 H, ArH_6); 6.72 (d, J = 2 Hz, 1 H, ArH_2); 7.37–7.41 (m, 5 H, C_6H_5).

4-Allyloxy-2-ethoxy-6-methyl-1,3-benzodioxole (7b) and 3-Allyloxy-5-methyl-1,2-benzenediol (8b):
In the same procedure as given for **7a** and **8a**, BnBr was replaced by allyl bromide. Starting from **6** (8.0 g, 40 mmol), crude **7b** was obtained (8.9 g, 93%) which was hydrolyzed to give 6.5 g (88%, based on **6**) of **8b**, mp 73–75 °C (from cyclohexane).

7b: IR: ν = 1630 cm^{-1} (C=C).

^{1}H NMR (250 MHz): δ = 1.25 (t, 3 H, J = 7.1 Hz, $ArCH_3$), 2.26 (t, 3 H, J = 0.6 Hz, $ArCH_3$); 3.72 (q, 2 H, J = 7.1 Hz, CH_2-ester); 4.64 (d × t, 2 H, $ArOCH_2$); 5.27 (d × q, 1 H, =CHH-*cis*); 5.39 (d × q, 1 H, =–CHH-*trans*); 6.05 (d × d × t, 1 H, –CH=); 6.35 (q, 1 H, J_{meta} = 1.4 Hz, J_{aliph} = 0.6 Hz); 6.38 (q, 1 H, J_{meta} = 1.4 Hz, J_{aliph} = 0.6 Hz); 6.84 (s, 1 H, methine-H). Coupling constants of the allyl group: $^2J_{allyl}$ = 5.5, $^4J_{allyl}$ = 1.7 (*cis* and *trans*), $^3J_{cis}$ = 10.5, $^3J_{trans}$ = 17.2, $^2J_{gem}$ = 1.7 Hz.

8b: ^{1}H NMR (250 MHz): δ = 2.23 (t, 3 H, J = 0.6 Hz, $ArCH_3$); 4.64 (d × t, 2 H, $ArOCH_2$); 5.29 (d × q, 1 H, =CHH-*cis*); 5.38 (d × q, 1 H, =CHH-*trans*); 6.28 (br d, 1 H, ArH_5); 6.05 (d × d × t, 1 H, –CH=); 6.41 (quint, 1 H, $^3J_{Me-ArH}$ = 0.6 Hz, J_{meta} = 1.8 Hz, ArH_7). Coupling constants of the allyl group: $^2J_{allyl}$ = 5.5, $^4J_{allyl}$ = 1.4 (*cis* and *trans*), $^3J_{cis}$ = 10.4, $^3J_{trans}$ = 17.2, $^2J_{gem}$ = 1.4 Hz.

3-Benzyloxy-4,5-dimethoxytoluene (9c) or 3-Allyloxy-4,5-dimethoxytoluene (15c):
Employing a similar alkylation procedure as above, with Me_2SO_4 as a reagent, **8a** and **8b** are converted to their bis-dimethyl ethers **9c** and **15c**, respectively. **9c**: colorless oil, 91% (Kugelrohr distilled).

^{1}H NMR (60 MHz): δ = 2.30 (s, 3 H, $ArCH_3$); 3.85, 3.80 (2 s, 6 H, OCH_3); 5.20 (s, 2 H, $ArOCH_2$); 6.40 (s, 2 H, ArH); 7.40 (m, 5 H, C_6H_5).

15c: colorless oil, 90% (Kugelrohr distilled).

^{1}H NMR (250 MHz): δ = 2.29 (s, 3 H, $ArCH_3$); 3.82, 3.83 (2 × s, 6 H, OCH_3); 4.57 (d × t, 2 H, $ArOCH_2$); 5.26 (d × q, 1 H, =CHH-*cis*); 5.40 (d × q, 1 H, =CHH-*trans*); 6.07 (d × d × t, 1 H, -CH=); 6.39 (s, 2 H, ArH). Coupling constants of the allyl group: $^2J_{allyl}$ = 5.2, $^4J_{allyl}$ = 1.5 (*cis* and *trans*), $^3J_{cis}$ = 10.4, $^3J_{trans}$ = 17.3, $^2J_{gem}$ = 1.5 Hz.

Crown Ether Ring Closures:
If appropriate, the assignment of crown-CH_2 resonances in the ^{1}H NMR spectra used indices "a to e" with increasing distance from the aromatic junction.

The corresponding dioxybenzene derivative (**8a** or **8b**, 10 mmol), together with the appropriate oligoethylene glycol dibromide or dimesylate (10 mmol) was stirred with powdered dry K_2CO_3

(40 mmol) in dry acetone at reflux temperature for 15 h. The acetone was removed in vacuo, H_2O was added and the crown ether was extracted with CH_2Cl_2 (4 × 10 mL). The allyl ethers crystallized on addition of pentane/EtOAc (1:1). The oily benzyl ethers were used without purification for subsequent hydrogenolysis.

14-Benzyloxy-16-methylbenzo-1,4,7,10,13-pentaoxacyclopentadecane **(9a)**: colorless oil, 3.9 g.

^{1}H NMR (60 MHz): δ = 2.20 (s, 3H, $ArCH_3$); 4.3–3.6 (m, 16H, crown-H); 5.05 (s, 2H); 6.31 (s, 2H, ArH); 7.20 (m, 5H, C_6H_5).

17-Benzyloxy-19-methylbenzo-1,4,7,10,13,16-hexaoxacyclooctadecane **(9b)**: colorless oil, 4.3 g.

^{1}H NMR (60 MHz): δ = 2.2 (s, 3H, $ArCH_3$); 3.6–4.3 (m, 20H, crown-H); 5.04 (s, 2H); 6.32 (s, 2H, ArH); 7.2 (m, 5H, C_6H_5).

14-Alloxy-16-methylbenzo-1,4,7,10,13-pentaoxacyclopentadecane **(15a)**: 3.1 g (91%) of colorless crystals, degrad. > 150°C.

^{1}H NMR (250 MHz): δ = 2.26 (s, 3H, $ArCH_3$); 3.83–3.66 (m, 8H, crown d, e); 3.92–3.87 (m, 2H, crown b'); 4.18–4.10 (m, 6H, crown a, b, a'); 4.56–4.52 (d × t, 2H, allyl-H); 5.22 (d × q, 1H, =CHH *cis*); 5.39 (d × q, 1H, =CHH *trans*); 6.05 (d × d × t, 1H, –CH=); 6.37 (br s, 2H, ArH); Coupling constants of the allyl system: $^2J_{allyl}$ = 5.1, $^4J_{allyl}$ = 1.5 (*cis* and *trans*), $^3J_{cis}$ = 10.5, $^3J_{trans}$ = 17.2, $^2J_{gem}$ = 1.5 Hz.

MS (EI 70 eV): *m/z* (%) = 338 ($M^{+\cdot}$, 31), 260 (39), 219 (100), 165 (62).

17-Allyloxy-19-methylbenzo-1,4,7,10,13,16-hexaoxacyclooctadecane **(15b)**: 3.4 g (89%) of colorless crystals, degrad. > 150°C.

^{1}H NMR (250 MHz): δ = 2.27 (s, 3H, $ArCH_3$); 3.74, 3.72, 3.69 (3 × s, 12H, crown-c,d,e); 4.26, 3.92 and 4.12, 3.71 (2 × AA'BB', 8H, crown a, b); 4.53 (d × t, 2H, allyl-H); 5.28–5.23 (d × q, 1H, =CHH *cis*); 5.39 (d × q, 1H, =CHH *trans*); 6.04 (d × d × t, 1H, =CH); 6.37 (br s, 2H, ArH). Coupling constants of the allyl system: $^2J_{allyl}$ = 5.2, $^4J_{allyl}$ = 1.6 (*cis* and *trans*), $^3J_{cis}$ = 10.5, $^3J_{trans}$ = 17.3, $^2J_{gem}$ = 1.6 Hz.

MS (FAB): *m/z* (%) = 421 ($M \cdot K^+$, 9); 405 ($M \cdot Na^+$, 100); 383 ($M \cdot H^+$, 19).

Hydrogenolysis of Benzyl Ether Structures:

The benzyl ethers were hydrogenated at normal H_2 pressure and r.t. in a shaking apparatus using 10% Pd–C (Merck No. 807104) in THF. In typical runs 20 mmol were hydrogenated with 1.5 g catalyst in THF (100 mL) within 4–6 h. Products were recrystallized in EtOAc/pentane mixtures.

14-Hydroxy-16-methylbenzo-1,4,7,10,13-pentaoxacyclopentadecane **(10a)**: 4.6 g (84%), colorless crystals, mp 77–78°C.

^{1}H NMR (250 MHz): δ = 2.23 (s, 3H, $ArCH_3$); 3.69 (s, 4H, crown-c'd'); 4.17/3.92, 4.09/3.85 and 3.76/369 (3 AA'BB'-systems, 3 × 4H, crown-ab,a'b', cd); 5.80 (br s, 1H, OH); 6.24 (d, 1H, ArH_4); 6.41 (d, $^3J_{meta}$ = 1.3 Hz, 1H, ArH_6).

MS (EI): *m/z* (%): 298 (M^+, 21); 210 (12); 166 (100); 151 (33); 110 (48); 45 (25).

From the mother liquor, 120 mg (2%) of the homologous crown ether symm.-di(3-hydroxy-5-methylbenzo)-30-crown-10, mp 112–114°C could be isolated.

^{1}H NMR (250 MHz): δ = 3.27 (s, 3H, $ArCH_3$); 4.15/3.84, 4.10/3.71 (2 AA'BB'-systems, 16H + 16H, crown-Ha,d/c,d); 4.95 (br s, 1H, OH); 6.20 (d, 2H, $ArH_{4,4'}$); 6.35 (d, J_{meta} = 0.6 Hz, 2H, $ArH_{6,6'}$).

MS (FAB): *m/z* (%) = 711 ($M \cdot glycerol \cdot K^+$, 9); 635 ($M \cdot K^+$, 96); 619 ($M \cdot Na^+$, 100); 597 ($M \cdot H^+$, 4).

17-Hydroxy-19-methylbenzo-1,4,7,10,13,16-hexaoxacyclooctadecane **(10b)**: 6.0 g (88%), colorless crystals, mp 62–64°C.

^{1}H NMR (250 MHz): δ = 2.23 (s, 3H); 3.59 (s, 4H, crown-He); 3.76–3.63 (m, 8H, crown-Hc, d); 4.27/3.91, 4.17/3.84 (2 AA'BB'-systems, 2 × 4H, crown-Hab/ab'); 6.26 (d, 1H, ArH_4,); 6.40 (d, J_{meta} = 0.6 Hz, 1H, ArH_6); 6.48 (br s, 1H, OH).

MS (EI): *m/z* (%) 342 (M^+, 17); 298 (17); 166 (100); 151 (22); 110 (29); 45 (26).

2,3-Dimethoxy-5-methylphenol **(10c)**: yield 9 g (96%) from 14 g **8**, mp 49–51°C.

^{1}H NMR (60 MHz): δ = 2.25 (s, 3H, $ArCH_3$); 4.20 (s, 6H, OCH_3); 5.15 (br s, 1H, OH); 6.21 (s, 1H, ArH_6); 6.40 (s, 1H, ArH_4).

Claisen Rearrangements of Allyl Phenyl Ethers:

The ethers **15a–c** (1 to 5 mmol) were dissolved in DMA (0.5 mmol/mL) and heated under N_2 at 200°C for 3.5 h and the solvent was removed by Kugelrohr distillation. The conversion was quantitative (by NMR) to mixtures of ortho and para rearrangement products, exhibiting an OH-band at ν = 3400 cm^{-1} in the IR.

15-Allyl-14-hydroxy-16-methylbenzo-1,4,7,10,13-pentaoxacyclopentadecane **(16a)**

17-Allyl-14-hydroxy-16-methylbenzo-1,4,7,10,13-pentaoxacyclopentadecane **(17a)**:

^{1}H NMR of the mixture: **16**: 2.20 (s, 3H, $ArCH_3$); 6.27 (s, 1H, ArH), **17a**: 2.17; 6.56; ratio 3:1.

A small amount of **16a** crystallized: mp 108–109°C (hexane/EtOAc).

^{1}H NMR (250 MHz): δ = 2.20 (s, 3H, $ArCH_3$); 3.34 (d × t, 2H, allyl-H); 3.70 (s, 4H, crown-Hc'd'); 4.24/3.97, 4.13/3.86, 3.76/3.70 (3 AA'BB'-systems, 3 × 4H, crown-Hab, a'b', cd); 4.91 (d × q, 1H, =CHH *trans*); 4.96 (d × q, =CHH– *cis*); 5.91 (s, 1H, OH); 5.92 (d × d × t, –CH=); 6.27 (s, 1H, ArH). Coupling constants of the allyl group: $^2J_{allyl}$ = 5.9, $^4J_{allyl}$ = 1.6 (*cis* and *trans*), $^3J_{cis}$ = 10.3, $^3J_{trans}$ = 17.0, $^2J_{gem}$ = 1.6 Hz.

MS (EI): *m/z* (%) = 338 (M^+, 89); 250 (81); 206 (100); 191 (89).

18-Allyl-17-hydroxy-19-methylbenzo-1,4,7,10,13,16-hexaoxacyclooctadecane **(16b)** *and 20-Allyl-17-hydroxy-19-methylbenzo-1,4,7,10,13,16-hexaoxacyclooctadecane* **(17b)**:

^{1}H NMR of the mixture: **16b**: 2.17 ($ArCH_3$); 6.28 (ArH); **17b**: 2.20 ($ArCH_3$); 6.56 (ArH); ratio 3:1.

A small amount of **16b** was obtained crystalline, mp 92–93°C (hexane/EtOAc).

^{1}H NMR (250 MHz): δ = 2.20 (s, 3H, $ArCH_3$); 3.35 (d × t, 2H, allyl-H); 3.59 (s, 4H, crown-H); 3.73, 3.71–3.59 (AA'+m, 2+6H, crown-H); 4.44/3.87, 4.17/3.82 (2 AA'BB'-systems, 2 × 4H, crown-H); 4.91 (d × q, 1H, =CHH *trans*); 4.93 (d × q, 1H, =CHH *cis*); 5.91 (d × d × t, 1H, –CH=); 6.28 (s, 1H, ArH); 6.39 (s, 1H, OH). Coupling constants of the allyl group: $^2J_{allyl}$ = 5.9 $^4J_{allyl}$ = 1.6 (*cis* and *trans*), $^3J_{cis}$ = 10.3, $^3J_{trans}$ = 16.9, $^2J_{gem}$ = 1.6 Hz.

MS (FAB): *m/z* (%) = 421 ($M \cdot K^+$, 15); 405 ($M \cdot Na^+$, 23); 383 ($M \cdot H^+$ 100).

2-Allyl-5,6-dimethoxy-3-methylphenol **(16c)** *and 4-Allyl-2,3-dimethoxy-5-methylphenol* **(17c)**: yellowish oil, representative ^{1}H NMR signals of the mixture: **16c**: 2.23 ($ArCH_3$); 3.87, 3.83 (OCH_3); 6.30 (ArH). **17c**: 2.18, 3.81, 3.88, 6.56, ratio 3:1.

Fremy Salt Oxidations:

To the well stirred emulsion of a 0.04 M solution of the phenol in benzene or $CHCl_3$ and 0.66 M aq KH_2PO_4 (1:2, vv), solid dry $K_2(SO_3)_2NO$ (Fremy salt, washed with acetone and pentane, 1.0 g, 3.75 mmol per mmol substrate) was added. After 3 h the phases were separated and the aqueous phase was three times extracted with the organic solvent used thus far. The quinones were isolated by crystallization with hexane **(3a–c)** or by column chromatography on silica gel (hexane/Et_2O, 1:1, for **19c**, MeCN/Et_2O, 1:4, for crown ethers **18/19a,b**). From ortho/para mixtures of the allyl quinones the paraquinones are eluted first).

Oxidation of **10a**: *15-Methylbenzo-1,4,7,10,13-pentaoxacyclopentadecane-14,17-dione* **(3a)**: 56%, orange crystals, mp 43–44°C.

IR (KBr): ν = 1655 cm^{-1} (C=O).

UV/Vis: λ (ε): 265 (14300); 410 (885); $E_{1/2}$: –0.61, 1.12 V.

^{1}H NMR (250 MHz): δ = 2.02 (d, J = 1.6 Hz, 3H, $ArCH_3$); 3.76–3.64 (m, 8H, crown-Hcd); 4.48, 3.81 (2 AA'BB' systems, 8H, crown-Hab); 6.40 (q, J = 1.6 Hz, 1H, ArH).

MS (EI): *m/z* (%) = 314 (M^+ + 2H, 7); 312 (M^+, 34); 184 (14); 182 (28); 180 (60); 152 (77).

Oxidation of **10b**: *18-Methylbenzo-1,4,7,10,13,16-hexaoxacyclooctadecane-17,20-dione* **(3b)**: 71%, orange crystals, mp 49–50°C.

IR: ν = 1655 cm^{-1} (C=O).

UV/Vis: λ (ε) = 260 (14140) 395 (850); $E_{1/2}$: −0.57, −1.48 V; UV/Vis: $\lambda(\varepsilon)$ = 260 (14140); 395 (850); $E_{1/2}$: −0.61, 1.12 V.

^{1}H NMR (250 MHz): δ = 2.02 (d, J = 1.6 Hz, 3H, $ArCH_3$); 3.66 (s, 4H, crown-He); 3.71–3.67 (m, 8H, crown-Hcd); 4.47, 3.83 (2 AA'BB' systems, 8H, crown-Hab); 6.41 (q, J = 1.6 Hz, 1H, ArH).

MS (EI): m/z (%) = 368 (M^+ + 2H, 5); 356 (M^+, 23); 312 (2); 268 (7); 224 (3); 182 (24); 181 (35); 180 (55); 152 (81); 96 (80).

Oxidation of **10c**: *2,3-Dimethoxy-5-methyl-1,4-benzoquinone* **(3c)** *(Ubiquinone-0)*: 92%, orange crystals, mp 59°C (Lit.[6,7] 59°C).

Oxidation of **16a/17a** *Mixture:*

15-Allyl-16-methylbenzo-1,4,7,10,13-pentaoxacyclopentadecane-14,17-dione **(18a)**: 21%, orange oil.

IR: ν = 1660, 1650 (C=O), 1640 cm^{-1} (C=C).

UV/Vis: $\lambda(\varepsilon)$ = 273 (5200), 415 (192); $E_{1/2}$ −0.69, −1.35 V.

^{1}H NMR (250 MHz): δ = 2.01 (s, 3H, $ArCH_3$); 3.20 (br d, m, 2H, allyl-H); 3.65–3.535 (narrow AA'BB' system, 8H, crown-Hcd); 4.70/3.71 (2 AA'BB' systems, 4H, crown-Hab); 5.04 (symm.m, 2H, $=CH_2$); 5.51 (d × d × t, 1H, –CH=). Coupling constants of the allyl group: $^2J_{allyl}$ = 6.3, $^3J_{cis}$ = 9.7, J_{trans} = 17.0 Hz.

MS (EI): m/z (%): 354 (M^+ + 2H, 20); 352 (100); 307 (9); 205 (86).

17-Allyl-16-methylbenzo-1,4,7,10,13-pentaoxacyclopentadecane-14,15-dione **(19a)**: 8.5%, dark red oil.

IR: ν = 1640, 1625 cm^{-1} (C=O).

UV/Vis: $\lambda(\varepsilon)$ = 275 (2140); 437 (88); $E_{1/2}$: −0.54, −1.04 V.

^{1}H NMR (250 MHz): δ = 1.94 (s, 3H, $ArCH_3$); 3.27 (br d, 2H, allyl-H); 3.75–3.53 (m, 10H, crown-Hb'cd); 4.25 (AA'part, 2H, crown-Ha'); 4.87, 3.85 (AA'BB' system, 4H, crown-Hab); 5.13–5.05 (symm.m, 2H, $=CH_2$); 5.87–5.76 (m, 1H, −CH=).

MS (EI): m/z (%) = 354 (M^+ + 2H, 11); 352 (M^+, 41); 219 (45); 205 (100).

Oxidation of **16b/17b** *Mixture:*

18-Allyl-19-methylbenzo-1,4,7,10,13,16-hexaoxacyclooctadecane-17,20-dione **(18b)**: 43%, orange oil.

IR: ν = 1655, 1645 (C=O), 1640 cm^{-1} (C=C).

UV/Vis: $\lambda(\varepsilon)$ = 275 (3360); 410 (349); $E_{1/2}$: −0.70, 1.19 V.

^{1}H NMR (250 MHz): δ = 2.01 (s, 3H, $ArCH_3$); 3.22 (br d, 2H, allyl-H); 3.57 (s, 4H, crown-He); 3.63 (narrow AA'BB' system, 8H, crown-Hcd); 4.51, 3.72 (2 AA' BB' systems, 8H, crown-Hab); 5.04 (symm.m, 2H, $=CH_2$); 5.64 (d × d × t, 1H, –CH=). Coupling constants of the allyl group: $^2J_{allyl}$ = 6.5, $^3J_{cis}$ = 9.6, $^3J_{trans}$ = 17.0 Hz.

MS (EI): m/z (%) = 398 (M^+ + 2H, 12); 396 (M^+, 14); 222 (20); 220 (29); 205 (100).

20-Allyl-19-methylbenzo-1,4,7,10,13,16-hexaoxacyclooctadecane-17,18-dione **(19b)**: 16%, dark red oil.

IR: ν = 1640, 1625 cm^{-1} (C=O).

UV/Vis: $\lambda(\varepsilon)$: 260 (49300); 445 (300); $E_{1/2}$: −0.55, 1.05 V.

^{1}H NMR (250 MHz): δ = 1.94 (s, 3H, $ArCH_3$); 3.27 (br d, 2H, allyl-H); 3.80–3.60 (m, 14H, crown-Hb'cde); 4.19 (AA', 2H, crown-Ha'); 4.82, 3.90 (AA'BB', 4Hcrown-Hab); 5.10 (d × m, 1H, =CHH-cis); 5.12 (d × m, 1H, =CHH-*trans*); 5.83 (d × d × t, 1H, –CH=).

MS (EI): m/z (%) = 398 (M^+ + 2H, 60); 396 (M^+, 9); 222 (100).

Oxidation of **16c/17c** *Mixture:*

3-Allyl-5,6-dimethoxy-4-methyl-1,4-benzoquinone **(18c)**: 30%, orange oil

IR: ν = 1660, 1650 (C=O), 1610 cm^{-1} (C=C).

UV/Vis: $\lambda(\varepsilon)$: 274 (14300); 410 (220).

^{1}H NMR (250 MHz): δ = 2.02 (s, 3H, $ArCH_3$); 3.24 (br d, 2H, allyl-H); 4.00, 3.99 (2 s, 6H, OCH_3); 5.06 (symm.m, 1H, $=CH_2$); 5.77 (d × d × t, 1H, –CH=). Coupling constants of the allyl group: $^2J_{allyl}$ = 6.3, $^3J_{cis}$ = 9.8, $^3J_{trans}$ = 17.4 Hz.

5-Allyl-3,4-dimethoxy-6-methyl-1,2-benzoquinone **(19c)**: 7.5%, red oil.

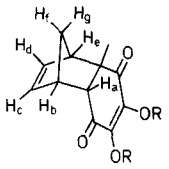
IR: ν = 1640, 1625 cm^{-1} (C=O).

UV/Vis: $\lambda(\varepsilon)$: 275 (5300); 450 (550).

^{1}H NMR (250 MHz): δ = 1.94 (s, 3H, $ArCH_3$); 3.23 (br d, 2H, allyl-H); 3.79 [s, 3H, OCH_3(4)]; 4.18 [s, 3H, OCH_3(3)]; 5.08 (d × m, 1H, =CH-*cis*) 5.10 (d × m, 1H, CHH-*trans*); 6.79 (d × d × t, 1H, −CH=). Coupling constants of the allyl group: $^2J_{allyl}$ = 6.1, $^3J_{cis}$ = 10.6, $^3J_{trans}$ = 16.7 Hz.

Diels–Alder Cycloadditions to the Quinones 3a–c:

To a solution of the quinone (1 mmol) in CH_2Cl_2 (5 mL) was added freshly distilled cyclopentadiene (0.165 mL, 2 mmol) and the mixture was kept at r.t. until the orange color had disappeared (2–4 d). The solvent and excess reagent were removed in vacuo to give the adducts in quantitative yield as yellow oils.



2-Methyl-5,8,11,14,17-pentaoxatetracyclo[19.2.1.0.^{2,20}0.^{4,18}]tetracosa-4(18),22-diene-3,19-dione **(13a)**:

^{1}H NMR (250 MHz): δ = 1.49 (s, 3H, CH_3); 1.67–1.63, 1.55, 1.51 (AB system, $J_{g,h}$ = 9.6 Hz, 2H, H_h, H_g); 2.80 (d, $J_{a,b}$ = 4 Hz, 1H, H_a); 3.07 (m, 1H, H_e); 3.42 (m, 1H, H_b); 3.75–3.62 (m, 8H, crown-Hcd); 3.86–3.77 (CD-part, 4H, crown-Hb); 4.50–4.29 (AB-part of two ABCD systems, 4H, crown-Ha); 6.00 (dd, 1H, H_d, $J_{d,e}$ = 2.9 Hz); 6.13 (dd, 1H, H_c, $J_{b,c}$ = 6.4 Hz, $J_{b,c}$ = 2.8 Hz).

MS (EI): m/z (%) = 378 (M^+, 10); 312 (13); 246 (12); 218 (10); 182 (14); 180 (12); 152 (27); 66 (100).

2-Methyl-5,8,11,14,17,20-hexaoxatetracyclo[22.2.1.0.^{2,23}0.^{4,21}]heptacosa-4(21),25-diene-3,22-dione **(13b)**:

^{1}H NMR (250 MHz): δ = 1.47 (s, 3H, CH_3); 1.67, 1.63, 1.55, 1.51 (AB system, $J_{g,h}$ = 9.6 Hz, 2H, H_h, H_g); 2.80 (d, 1H, H_a, $J_{a,b}$ = 3.9 Hz); 3.07 (m, 1H, H_e); 3.41 (m, 1H, H_b); 3.65 (s, 4H, crown-He); 3.77–3.65 (m, 8H, crown-Hcd); 3.86–3.76 (CD-part, 4H, crown-Hb); 4.48–4.26 (AB-part of two ABCD systems, 4H, crown-Ha); 5.99 (dd, 1H, H_d); 6.14 (dd, 1H, H_c).

MS (EI): m/z (%) = 422 (M^+, 1); 358 (16); 356 (6); 246 (9); 182 (35); 46 (100).

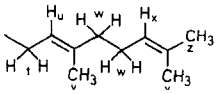
4,5-Dimethoxy-2-methyltricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione **(13c)**:

^{1}H NMR (250 MHz): δ = 1.48 (s, 3H, CH_3); 1.69, 1.65, 1.57, 1.53 (AB system, $J_{g,h}$ = 9.6 Hz, 2H, H_h, H_g); 2.80 (d, 1H, H_a, $J_{a,b}$ = 3.9 Hz); 3.08 (m, 1H, H_e); 3.42 (m, 1H, H_b); 3.93, 3.94 (2 s, 6H, OMe); 6.01 (dd, 1H, H_d); 6.16 (dd, 1H, H_c).

Enol Alkylation of the Diels–Alder Adducts and Subsequent Thermolysis:

2-[(E)-3,7-Dimethyl-2,6-octadienyl]-4,5-dimethoxy-7-methyltricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione **(14c)**:

To a solution of **13c** (500 mg, 2.0 mmol) in dry Et_2O (10 mL), at −70°C, under Ar, freshly sublimed KOBu-*t* (250 mg, 2.2 mmol) was added. After 30 min at −40°C the mixture was again cooled to −70°C and geranyl bromide (2.2 mmol) in Et_2O (3 mL) was added dropwise with a syringe. The mixture was slowly warmed up to r.t. and the product **14c** was isolated by filtration through silica gel: 700 mg (85%) yellow oil.



^{1}H NMR (250 MHz): δ = 1.55–1.43 (m, 1 H, H_h); 1.56 (s, 3 H); 1.58 (s, 3 H, H_z); 1.59 (s, 3 H, H_y); 1.66 (s, 3 H, H_v); 1.81–1.73 (m, 1 H, H_g); 2.11–1.92 (m, 4 H, H_w); 2.75, 2.43 (AB-system × d, 2 H, H_t); 3.10, 3.02 (2 m, Hb, e); 3.91, 3.89 (2 s, 6 H, OMe); 5.07 (m, 2 H, $H_{u,x}$); 6.07 (m, 2 H, $H_{c,d}$).

MS (EI): *m/z* (%) = 384 (M^+, 7); 369 (2); 320 (7); 318 (23); 303 (6); 275 (10); 249 (30); 235 (33); 217 (17); 197 (25); 196 (20); 137 (33); 69 (100); 66 (73); 65 (41).

2-[(E)-3,7-Dimethyl-2,6-octadienyl]-20-methyl-5,8,11,14,17-pentaoxatetracyclo[19.2.1.0.^{2,20}0.^{4,18}]tetracosa-4(18),22-diene-3,19-dione **(14a)**, *2-[(E)-3,7-Dimethyl-2,6-octadienyl]-23-methyl-5,8,11,14,17,20-hexaoxatetracyclo[22.2.1.0.^{2,23}0.^{4,21}]heptacosa-4(21),25-diene-3,22-dione* **(14b)**:

The solution of the crown ether cycloadducts **13a, 13b** and an equimolar amount of cryptand[2.2.2] (2 mmol in 10 mL dry THF) is treated as in the previous protocol. The geranylated crowns (first eluate) are separated from unreacted starting materials by chromatography (Et_2O) on silica gel.

14a: 190 mg (32%), slightly yellow oil.

^{1}H NMR (250 MHz): crown ether protons: δ = 3.68–3.60 (m, 8 H, crown-Hcd); 3.86–3.68 (m, CD-parts, 4 H, crown-Hbb'); 4.31–4.23, 4.19–4.11 (A and B parts of ABCD system, 2 × 1 H, crown-Ha'); 4.54–4.43 (AB part of an ABCD-system, 2 H, crown-Ha); the geranyl and bicycloheptane signals are practically identical with those of **14c**.

MS (EI): *m/z* (%) = 516 (M^+, 1); 447 (5); 365 (7); 233 (6); 205 (3); 195 (3); 85 (55); 83 (83); 66 (100); 65 (98).

14b: 410 mg (50%), yellow oil.

^{1}H NMR (250 MHz): crown ether protons: 3.65 (s, 4 H, crown-He) 3.69–3.66 (m, 8 H, crown-Hcd); 3.86–3.69 (m, CD-parts, 4 H, crown-Hbb'); 4.28–4.20, 4.19–4.08 (A and B parts of an ABCD system, 2 × 1 H, crown-Ha'); 4.51–4.43 (AB part of an ABCD-system, 2 H, crown-Ha); the geranyl and bicycloheptane signals are practically identical with those of **14c**.

MS (EI): *m/z* (%) = 558 (M^+, 1); 492 (13); 409 (19); 233 (27); 205 (65); 66 (81); 65 (100).

For the retro-Diels–Alder reactions, the adducts **14a–c** are placed in the distilling bulb of a rotating Kugelrohr apparatus heated at 80 °C for 3 h. The yield of the oily orange quinones is quantitative.

2-[(E)-3,7-Dimethyl-2,6-octadienyl]-5,6-dimethoxy-3-methyl-1,4-benzoquinone, (Ubiquinone-2) (**2c**, *n = 2*): 580 mg, orange oil.

IR: ν = 1660 cm^{-1} (C=O).

UV/Vis: $\lambda(\varepsilon)$ = 270 (2830); 400 (420); $E_{1/2}$: −0.69, 1.49 V.

The 250-MHz-^{1}H NMR data are identical with those in Ref. 6.

MS (EI): *m/z* = 320 (M^+ + 2 H, 8); 318 (M^+, 16); 303 (7); 275 (14); 249 (16); 235 (44); 217 (17); 197 (40); 196 (30); 69 (35); 66 (100).

15-[(E)-3,7-Dimethyl-2,6-octadienyl]-16-methylbenzo-1,4,7,10,13-pentaoxacyclopentadecane-14,17-dione (**2a**, *n = 2*): 143 mg, orange oil.

IR: ν = 1660 cm^{-1} (C=O).

UV/Vis: $\lambda(\varepsilon)$ = 272 (2450); 412 (210); $E_{1/2}$: −0.70, 1.51 V.

^{1}H NMR (250 MHz): δ = 1.58 (s, 3 H, H_z); 1.65 (d, J = 1.1 Hz, 3 H, H_y); 1.72 (d, J = 1.2 Hz, 3 H, H_v); 1.99 (s, 3 H, $ArCH_3$); 2.12–1.94 (m, 4 H, H_w); 3.16 (br d, J = 6.8 Hz, 2 H, H_t); 3.70–3.64 (m, 8 H, crown-Hcd); 4.45–3.82 (AA'BB' system, 8 H, crown-Hab); 5.03, 4.93 (2 br t, J = 6.8 Hz, 2 H, $H_{u,x}$).

MS (EI): *m/z* (%) = 450 (M^+ + 2 H), 448 (M^+, 10), 365 (66); 277 (16); 233 (32); 66 (100).

18-[(E)-3,7-Dimethyl-3,7-octadienyl]-19-methylbenzo-1,4,7,10,13,16-hexaoxacyclooctadecane-14,17-dione (**2b**, *n = 2*): 246 mg, orange oil.

IR: ν = 1660 cm^{-1} (C=O).

UV/Vis: $\lambda(\varepsilon)$: 271 (3220); 415 (330); $E_{1/2}$: −0.69, 1.49 V.

^{1}H NMR (250 MHz): practically identical with the one of **2a**, except for the crown ether resonances: δ = 3.66 (s, 4 H, crown-He); 3.73–3.66 (2 AA'BB' systems, 8 H, crown-Hcd); 4.44, 3.83 (2 AA'BB' systems, 8 H, crown-Hab).

Crystalline complexes, **2a · NaSCN** (mp 230–233 °C, dec) and **2b · KSCN** (mp 245–48 °C, dec) were obtained by stirring CH_2Cl_2 solutions of the complexes over solid salt overnight and precipitating the microcrystalline solids with pentane. The NMR spectra are the same as for the free ligands except that crown ether multiplets are narrower.

Support of this work by the Fonds der Chemischen Industrie is gratefully acknowledged.

(1) Dietl, F.; Gierer, G.; Merz, A. *Synthesis* **1985**, 626.
(2) Yamamura, Y.D.; Folkers, K.; Ito, Y. *Biochemical and Clinical Aspects of Coenzyme Q10*, Elsevier: Amsterdam, 1977, 1980, 1981, 1983, Vols. I–IV.
(3) Eren, D.; Keinen, E. *J. Am. Chem. Soc.* **1988**, *110*, 4356 and literature cited therein, footnotes 4–6.
(4) Vögtle, F.; Jansen, B. *Tetrahedron Lett.* **1976**, 4895.
(5) Scholz, D. *Sci. Pharm.* **1982**, *50*, 78.
(6) Obol'nikova, E.A.; Volkova, O.I.; Samokhvalov, G.I. *Zh. Obshch. Khim.* **1968**, *38*, 453.
(7) Keinan, E.; Eren, D. *J. Org. Chem.* **1987**, *52*, 3872.
(8) Sugihara, H.; Morimoto, H.; Kawamatsu, Y. *Liebigs Ann. Chem.* **1972**, *763*, 128.
Sato, K.; Inoue, S.; Yamaguchi, R. *J. Org. Chem.* **1972**, *37*, 1889.
Sato, K.; Miyamoto, O.; Inoue, S.; Yamamoto, T.; Hirasawa, Y. *J. Chem. Soc., Chem. Commun.* **1982**, 153.
Naruta, Y. *J. Am. Chem. Soc.* **1980**, *102*, 3774.
Naruta, Y. *J. Org. Chem.* **1980**, *45*, 4097.
(9) Rüttimann, A. *Chimia* **1986**, *40*, 290.
(10) Inoue, Y.; Liu, Y.; Hakushi, T., In *Cation Binding by Macrocycles*; Inoue, Y.; Gokel, G.W., Eds.; Marcel Dekker: New York, 1990, pp 5–69.
(11) Marvell, E.N.; Burreson, B.J.; Crandall, T. *J. Org. Chem.* **1965**, *30*, 1030.
(12) Marvell, E.N.; Richardson, B.; Anderson, R.; Stephenson, J.L.; Crandall, T. *J. Org. Chem.* **1965**, *30*, 1032.
(13) Scheinmann, F.; Barner, R.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1603.
(14) Bennett, G.B. *Synthesis* **1977**, 589.
(15) Work done by G. von Jagow and T.A. Link at the Gustav-Emben-Zentrum für Biologische Chemie, Universitätsklinikum der Universität Frankfurt, Theodor-Stern-Kai 7, D-6000 Frankfurt a.M., Germany.
(16) Alpha, B.; Lehn, J.-M.; Mathis, G. *Angew. Chem.* **1987**, *99*, 259; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 266.
(17) Perrin, D.D.; Amarego, W.C.F.; Perrin, D.R. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1980.
(18) Kociensky, R.J.; Carnigliaro, G.; Feldstein, G. *J. Org. Chem.* **1977**, *42*, 354.
(19) Asahima, Y.; Yasue, A. *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 2327.