2.95-3.25 (m, 4 H, CH_2N), 4.12-4.34 (m, 4 H, benzylic CH_2), 7.40-7.82 (m, 8 H, ArH). Anal. Calcd for $C_{21}H_{30}As_2F_{12}N_2O_{0.25}P_2Pd$: C, 29.3; H, 3.5; N, 3.3. Found: C, 29.1; H, 3.4; N, 3.1.

[*SP*-4-1-[*S*-(*R,*R**)]][5,6,7,8,9,14,15,16,17,18-Decahydro-9,18-dimethyldibenzo[*e*,*l*][1,8,4,11]diazadiarsacyclotetradecine-*As*^{9},*As*^{18},*N*^{6},*N*^{15}]palladium(II) Hexafluorophosphate [(+)-[Pd{(*R*,*R*)-2}]$(PF_6)_2$·0.25MeCOCH$_2$CH$_3$].** This compound was prepared from (*R*,*R*)-**2** and chloropalladate(II) as described above: mp 233-234 °C dec; $[\alpha]_D$ +172° (*c* 0.5, Me_2CO). Anal. Calcd for $C_{21}H_{30}As_2F_{12}N_2O_{0.25}P_2Pd$: C, 29.3; H, 3.5; N, 3.3. Found: C, 29.1; H, 3.6; N, 3.0.

Structural Analyses. Crystal data for both compounds are summarized in Table I. The yellow complex (R_{As},S_{As},*R*)-**20** crystallized from dichloromethane-methanol as elongated (010) plates lying on (001) with pinacoids {101} and {10$\bar{1}$}; orange (R_{As},R_{As},*S*)-**20**·0.5Me_2CO was isolated from acetone solution as almost perfect cubes. A Nicolet XRD P3 four-circle diffractometer[26] was used for the experimental work on the yellow isomer, and a Nicolet four-circle autodiffractometer[27] was used for the orange isomer. The data were corrected for Lorentz and polarization effects. Analytical absorption corrections were applied with transmission factors ranging between 0.473 and 0.647 for (R_{As},S_{As},*R*)-**20**; empirical absorption corrections within the relative range 0.808-1.000 were applied for (R_{As},R_{As},*S*)-**20**·0.5Me_2CO. Atomic scattering factors and anomalous dispersion corrections were taken from ref 28. The structures were solved by the heavy-atom method and refined by least-squares techniques with $\sum w\Delta^2$ minimized; weightings for each reflection were obtained from counter statistics.

Selected molecular dimensions for the two isomers are listed in Table III according to the atom-labeling scheme shown in Figure 1. Final atomic coordinates for the non-hydrogen atoms in the two complexes are given in Table II.

Acknowledgment. We thank Dr. Ward T. Robinson, of the Chemistry Department, University of Canterbury, Christchurch, New Zealand, for recording for us the crystallographic data on compound (R_{As},S_{As},*R*)-**20**.

Supplementary Material Available: Labeling scheme, ORTEP drawings, and tables of bond lengths and bond angles, and atomic and thermal parameters for (R_{As},S_{As},*R*)-**20** and (R_{As},R_{As},*S*)-**20**·0.5Me_2CO (13 pages); tables of observed and calculated structure factors (31 pages). Ordering information is given on any current masthead page.

(27) *Nicolet (Syntex) E-XTL or SHELX Interactive Crystallographic Software Package*; modified by Crystalytics Company, Lincoln, NE.

(28) *International Tables of Crystallography*; Kynoch: Birmingham, England, 1974; Vol. 4.

Total Synthesis of Linear Polyprenoids. 3.[1] Syntheses of Ubiquinones via Palladium-Catalyzed Oligomerization of Monoterpene Monomers

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Abstract: A general methodology for highly regio- and stereoselective Pd(0)-catalyzed, stepwise allylic coupling of bifunctional monomers was developed, representing a practical approach for total synthesis of naturally occurring polyprenoids. As an example, the total synthesis of the cardiovascular agent ubiquinone 10 (coenzyme Q_{10}), as well as shorter ubiquinones, was carried out via selective coupling of monomers easily derived from geraniol that contain either one or two reacting functional end groups. One of these functionalities is a latent allylic electrophile activated by the Pd(0) catalyst and the other is a latent nucleophile activated by an appropriate base. After the desired decaprenyl carbon skeleton of Q_{10} was achieved, the synthesis was completed by removal of the activating groups: Methyl ester was deleted via a highly efficient demethoxycarbonylation procedure involving 4-aminothiophenol and catalytic amounts of cesium carbonate, and the allylic sulfones were deleted by Pd(0)-catalyzed allylic reduction. Finally, oxidation of the aromatic ring to quinone affords ubiquinone 10.

Quinones and hydroquinones with polyprenyl side chains, such as ubiquinones, plastoquinones, phylloquinone (vitamin K_1), and menaquinones (vitamin K_2), are widely distributed in animal and plant tissues.[2] In addition to important biological roles in promoting electron transfer in respiratory chains and photosynthesis, these compounds exhibit various pharmacological activities. Of special interest is ubiquinone 10 (coenzyme Q_{10}, **1**),[3] which is used clinically as a cardiovascular agent and has attracted significant synthetic activity within the past two decades.[4-6] However, because construction of linear polyprenoid chains is still a major synthetic challenge, a practical total synthesis of ubiquinone 10 has not yet been achieved. Available industrial processes for Q_{10} involve either biotechnological[7] or semisynthetic methods, the latter employing solanesol, a nonaprenol extracted from tobacco leaves.[8]

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(1) Part 2: Keinan, E.; Eren, D. *J. Org. Chem.* **1987**, *52*, 3872.

(2) (a) Britton, G. *Nat. Prod. Rep.* **1984**, 68. (b) Cainelli, G.; Cardillo, G. *Acc. Chem. Res.* **1981**, *14*, 89. (c) Crane, F. L. *Annu. Rev. Biochem.* **1977**, *46*, 439. (d) Isler, O.; Schudel, P. *Adv. Org. Chem.* **1973**, *4*, 115. (e) Morton, R. A. *Biol. Rev.* **1971**, *46*, 47. (f) Morton, R. A. *Biochemistry of Quinones*; Academic: New York, 1955. (g) See also ref 3b,c.

(3) For general information concerning ubiquinone 10 see: (a) Yamamura, Y.; Folkers, K.; Ito, Y. *Biochemical and Clinical Aspects of Coenzyme Q_{10}*; Elsevier: Amsterdam: 1977, Vol. I; 1980, Vol. II; 1981, Vol. III; 1983, Vol. IV. (b) Thomson, R. H. *Naturally Occurring Quinones*, 2nd ed.; Academic: New York, 1971. (c) Littaru, G. P.; Ho, L.; Folkers, K. *Int. J. Vitam. Nutr. Res.* **1972**, *42*, 291, 413. (d) Combs, A. B.; Acosta, D.; Folkers, K. *IRCS Med. Sci.: Libr. Compend.* **1976**, *4*, 403. (e) McCormick, D. B., Wright, L. D., Eds. *Methods Enzymol.* **1971**, *18*, 137-562. (f) Bliznakov, E. G.; Hunt, G. L. *The Miracle Nutrient Coenzyme Q_{10}*; Bantam Books: New York, 1987; references cited therein.

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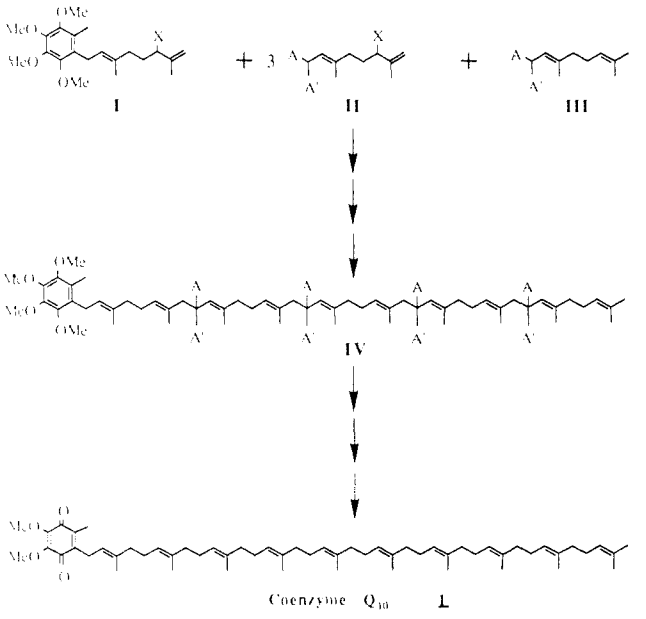
Scheme I



This is, probably, the reason for the currently high cost of Q_{10}.[9]

Considering the problem of linear polyprenoid synthesis as a special case in the general context of producing biopolymers, one ultimately reaches the conclusion that the most general and practical approach, one that will also be applicable for large-scale preparation of various polyprenoid compounds, would be the development of an oligomerization methodology, analogous to widely employed, general approaches to the total synthesis of peptides and polynucleotides. In other words, a set of monomeric units are to be prepared, containing appropriate functional groups. Selective activation of these functionalities would allow controlled coupling of the monomers, leading to the desired polyprenoid carbon skeleton. Obviously, both monomer cyclization and uncontrolled polymerization processes should be avoided.

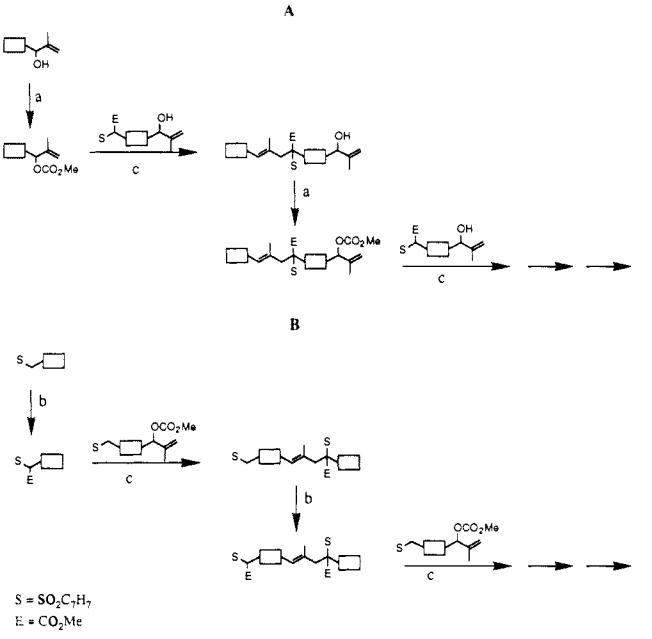
For example, construction of the carbon skeleton of Q_{10} could be envisioned by the appropriate allylic coupling of monomers I–III in Scheme I, yielding the desired decaprenyl carbon skeleton IV. Removal of the activating groups followed by oxidation of the aromatic ring to quinone would lead to the desired product **1**.

Table I. Palladium(0)-Catalyzed Coupling of **3** and **7**[a]

electrophile	leaving group	base	temp, °C	time, h	yield, %	**11a:11b**
7a	OAc	BSA	65	20	54	90:10
7b	$OPO(OEt)_2$	NaH	22	3	67	60:40
7c	OCO_2CMe_3	*t*-BuOK	22	24		
7d	OCO_2Me		22	0.5	88	>97:<3
7e	Cl	NaH	22	1	73	60:40

[a] All reactions were carried out in THF with equimolar quantities of **3** and **7**, $Pd(PPh_3)_4$ (5 mol %), and the base indicated (1.1 equiv). Yields are of isolated products. Ratios of *E*:*Z* isomers were determined by 270-MHz ^1H NMR.

Scheme II[a]



[a] Key: (a) MeOCOCl, diethylaniline, pyridine, benzene, 97%; (b) $(MeO)_2CO$, *t*-BuOK, DMF; (c) $Pd(PPh_3)_4$, THF.

In this paper we report the synthesis of all three monomers and their selective coupling according to the general strategy outlined in Scheme I, resulting in the total synthesis of coenzyme Q_{10} as well as other ubiquinones with shorter side chains.

Results and Discussion

General Strategy. Embarking on an attempt to meet the challenge of polyprenoid synthesis, we designed an oligomerization approach based on the following two principles: (a) All monoterpene monomers are derived from geraniol, a most readily available natural building block. (b) All monomer coupling reactions utilize π-allylpalladium chemistry because of the synthetic advantages associated with Pd(0)-catalyzed allylic alkylation.[10]

As the nucleophilic functionality of the monomers, we have chosen to employ a methine group bearing both methoxycarbonyl and tolylsulfonyl substituents, because the corresponding stabilized carbanion has proven useful as a nucleophilic partner in Pd(0)-catalyzed allylic alkylations.[11] Another advantage associated with these two substituents is their facile removal at the later stages of synthesis. As we obtained satisfactory results with this nucleophilic functionality, it was unnecessary to seek alternative electron-withdrawing groups that might further improve the coupling process.

With respect to the electrophilic end, however, we found strong dependencies of both reactivity and stereoselectivity on the nature

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(5) (a) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1974**, *96*, 8046. (b) Fujita, Y.; Ishiguro, M.; Onishi, T.; Nishida, T. *Synthesis* **1981**, 469. (c) Sato, K.; Inoue, S.; Yamaguchi, R. *J. Org. Chem.* **1972**, *37*, 1889. (d) Raynolds, P. W.; Manning, M. J.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1977**, 499. (e) Chenard, B. L.; Manning, M. J.; Raynolds, P. W.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 378.

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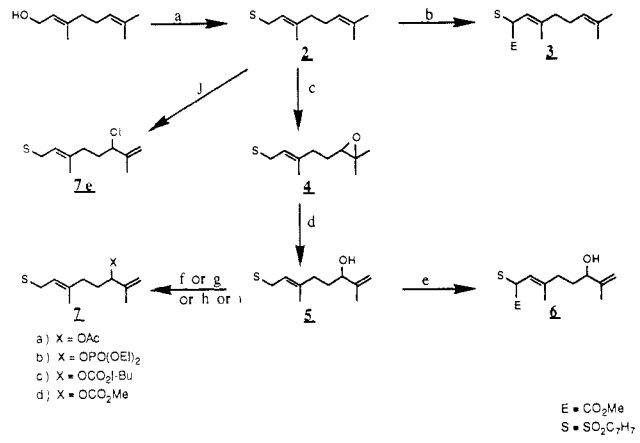
(8) Fukawa, H. Reference 7, p 19.

(9) Coenzyme Q_{10} is the least expensive ubiquinone in the 1988 catalog of Sigma Chemical Co. ($1134/g). The cited prices of Q_6–Q_9 range between $7000 and 22000/g.

(10) (a) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615. (b) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer: Berlin, 1980. (c) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (d) Trost, B. M.; Verhoeven, T. R. *Compr. Organomet. Chem.* **1982**, *8*, 779. (e) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic: London, 1985.

(11) Trost, B. M.; Weber, L.; Strege, P.; Fullerton, T. J.; Dietche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3426.

Scheme III[a]



[a] Key: (a) see ref 12; (b) $(MeO)_2CO$, *t*-BuOK, DMF, −20 °C, 95%; (c) mCPBA, CH_2Cl_2, 79%; (d) $Al(O\text{-}i\text{-}Pr)_3$, toluene, 110 °C, 86%; (e) (1) $(MeO)_2CO$, *t*-BuOK, DMF, −20 °C, (2) MeONa/MeOH, 73% overall; (f) Ac_2O, pyridine, 96%; (g) $(EtO)_2POBr$, collidine, 89%; (h) $(t\text{-}BuOCO)_2O$, CH_2Cl_2, DMAP, 81%; (i) MeOCOCl, diethylaniline, pyridine, benzene, 97%; (j) $Ca(OCl)_2$, CO_2, CH_2Cl_2/H_2O, 77%.

of leaving group X. Therefore, we investigated the influence of various leaving groups on these two factors (vide infra, Table I) and found that methyl carbonate is clearly superior, in that respect, to all other leaving groups examined.

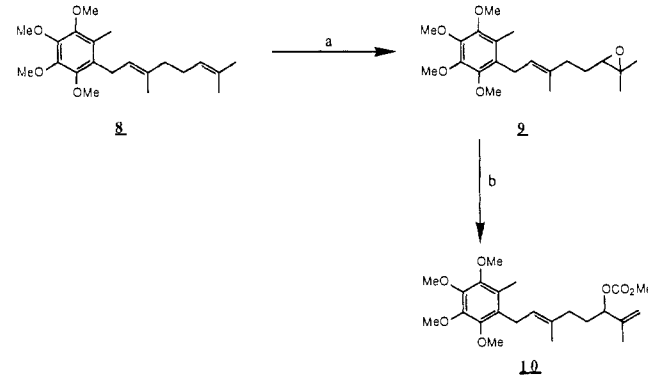
Obviously, palladium-catalyzed formation of C–C bonds is the key process in this synthetic approach. It involves coupling achieved via activation of the allylic electrophile by the Pd(0) complex and activation of the nucleophile by an appropriate base.[10] Therefore, in order to avoid possible cyclization or uncontrolled polymerization of bifunctional monomers having the general structure II, one has to employ the appropriate functionalities and reaction conditions that will not simultaneously activate both ends of the monomer.

In principle, as is the case in peptide synthesis, chain growth may be carried out in either direction by stepwise activation of the appropriate end functionality, as illustrated by the examples given in Scheme IIA,B. The reactive electrophilic functionality in these specific examples is generated by transforming a poor precursor of π-allylpalladium complex (allylic alcohol) into a better one (allylic methyl carbonate). The required basicity of the nucleophilic partner is achieved by increasing the level of substitution on the nucleophilic carbon from a single electron-withdrawing group (tolylsulfonyl) to two such groups (sulfone and methyl ester). In these examples, generation of both electrophile and nucleophile involves a methoxycarbonylation step. Nevertheless, because acylation at oxygen is much more facile than acylation at carbon (with either methyl chloroformate or dimethyl carbonate) we found the approach described in Scheme IIA to be more practical.

Preparation of Monomers. The synthetic pathways used to prepare monomers II and III are outlined in Scheme III. The simplest monofunctional monomer, **3**, was readily available in three steps from geraniol. Bromination with phosphorus tribromide followed by nucleophilic substitution with sodium *p*-toluenesulfinate yielded geranyl tolyl sulfone (**2**).[12] Treatmenmt of **2** with dimethyl carbonate under basic conditions (potassium *tert*-butoxide) gave monomer **3** in excellent yield.

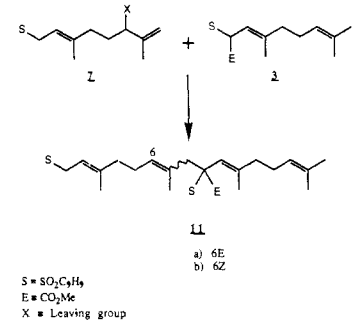
Geranyl tolyl sulfone (**2**) served as the key starting material for preparation of several other monomers. Regioselective epoxidation either with *m*-chloroperbenzoic acid or by an electrochemical approach[13] resulted in epoxide **4** that was isomerized to the desired allylic alcohol **5** via regioselective deprotonation with aluminum triisopropylate in refluxing toluene.[14] Esterification of **5** with acetic anhydride, diethyl phosphorobromidate,[15] di-*tert*-butyl dicarbonate, or methyl chloroformate under basic conditions yielded the corresponding acetate **7a**, diethyl phosphate **7b**, *tert*-butyl carbonate **7c**, or methyl carbonates **7d**, respectively. The allylic chloride **7e** was prepared in 77% yield directly from **2** by reaction with hypochlorous acid.[16]

Scheme IV[a]



[a] Key: (a) mCPBA, CH_2Cl_2, 67%; (b) (1) $Al(O\text{-}i\text{-}Pr)_3$, toluene, 110 °C, 91%, (2) MeOCOCl, diethylaniline, pyridine, benzene, 98%.

Scheme V



The synthesis of the aromatic monofunctional monomer **10** is described in Scheme IV. The synthesis of its precursor, **8**, was described in detail in a previous paper in this series.[1] Starting with **8** and carrying out the sequence of oxidation to **9** and isomerization, followed by acylation in a manner analogous to that described in Scheme III, afforded the desired monomer **10** in satisfactory yield.

Monomer Coupling and Removal of the Activating Groups. Compounds **3** and **7a** were chosen as a representative nucleophile/electrophile couple in our initial studies on the palladium-catalyzed reaction. We began with $Pd(PPh_3)_4$ as the catalyst and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as the nucleophile activator. It soon became evident that this electrophilic partner is insufficiently active, reactions proceeding only under reflux conditions with only moderate yields. We therefore examined the Pd-catalyzed coupling of **3** with monomers **7a–e** bearing various leaving groups (Scheme V; Table I).

Although reactions with the allylic chloride **7e** proceeded significantly faster than with the acetate **7a** and with higher yield, the product was obtained with very poor stereoselectivity. The new double bond was formed as a mixture of *E* and *Z* isomers in a 60:40 ratio, totally unacceptable for polyprenoid synthesis. A situation essentially identical with that of the allylic chloride case was observed with diethyl phosphate.[17] Attempts to employ *tert*-butyl carbonate as a leaving group failed, as essentially no reaction was observed at room temperature within 24 h. However,

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(16) Hegde, S. G.; Vogel, M. K.; Saddler, J.; Hrinyo, T.; Rockwell, N.; Heynes, R.; Oliver, M.; Wolinski, J. *Tetrahedron Lett.* **1980**, 441.
(17) Araki, S.; Sato, T.; Butsugan, Y. *J. Chem. Soc., Chem. Commun.* **1982**, 285.

the easily accessible methyl carbonate was found to be the leaving group of choice due to its high reactivity and because it allows efficient activation of the nucleophile without addition of a base.[18] Additionally, the coupling product **11** was obtained with excellent stereoselectivity, the newly formed trisubstituted double bond possessing an essentially pure *E* configuration (as evident by ^{1}H 270-MHz NMR).

The striking dependence of double-bond geometry on the nature of the leaving group may be rationalized on the grounds of structural flexibility of the allylpalladium intermediate. It is conceivable that equilibrium between η^3- and η^1-allylpalladium complexes would be strongly dependent on the nature of the counteranion.[19] A situation close to pure η^3-allyl complex, where syn geometry is highly favored, would lead to product having pure *E* geometry.[11] However, if the structure of the reactive intermediate is closer to η^1-allylpalladium, then the nature of nucleophilic attack should be closer to an S_N2' mechanism, leading to a mixture of double-bond isomers.

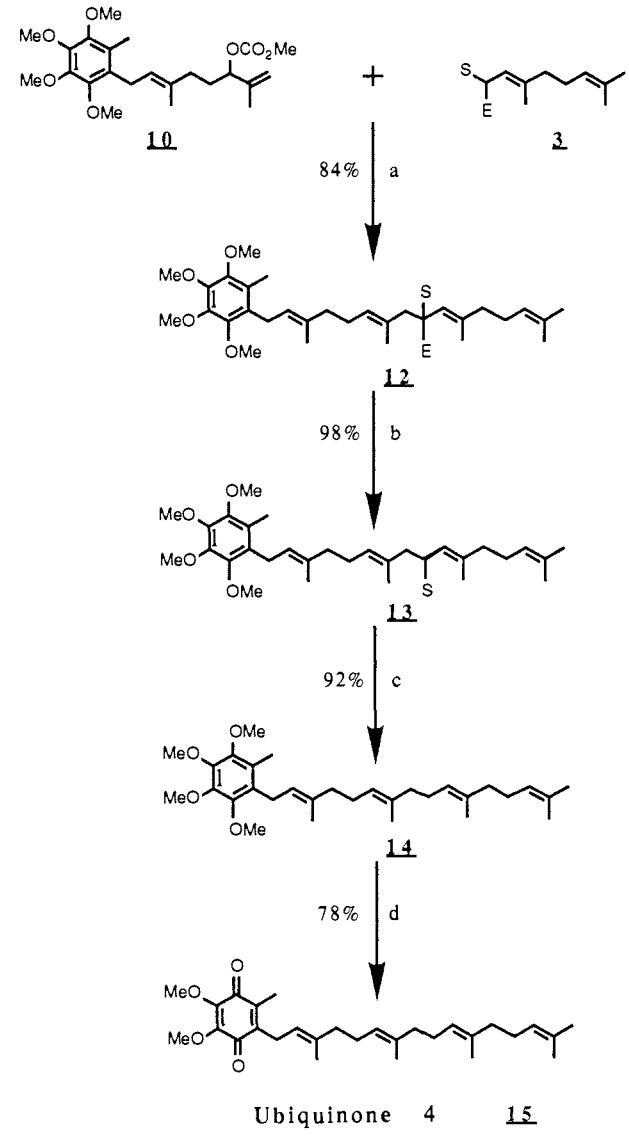
We attempted to enhance catalytic activity of palladium for allylic coupling by investigating various phosphine ligands. Assuming that oxidative addition of the allylic acetate to Pd(0) represents the rate-determining step, we employed electron-donating ligands, which increase palladium nucleophilicity. Moreover, when electron density on the palladium is increased, dissociation[20] of phosphine ligands from the metal should be promoted, increasing its propensity to undergo oxidative addition. As our probe, we chose the reduction of cinnamyl acetate with 1,1,3,3-tetramethyldisiloxane in C_6D_6 (where reactions could be conveniently monitored by ^{1}H NMR) in the presence of 10 mol % of a Pd(0) complex. The relative order of reactivity of the six catalysts examined is represented by the time (minutes) required to achieve 50% conversion.[21] The results were $[Pd[P(p\text{-anisyl})_3]_4$ (16) > $Pd[P(p\text{-tolyl})_3]_4$ (18.5) > $Pd(PPh_3)_3]_4$ (24) > $Pd[P(p\text{-ClPh})_3]_4$ (29) > $^1/_2Pd_2(dba)_3 + 4PPh_3$ (125) > $Pd[P(p\text{-CNPh})_3]_4$ (no reaction).

As expected, electron-donating ligands increase reaction rates. However, probably due to enhanced dissociation, they also destabilize the catalyst and reduce its useful lifetime. Accordingly, employment of acceptor ligands such as dibenzylideneacetone (dba) and tris(*p*-cyanophenyl)phosphine effectively stabilize the complex but inhibit catalytic activity. Thus, tetrakis(tri-*p*-tolylphosphine)palladium was found to be the optimal catalyst for our reactions, reaction rates being generally twice as fast as with $Pd(PPh_3)_4$. Nevertheless, due to the generally short reaction times, we employed the latter in most of our reactions.

In order to complete the synthesis, it was necessary to remove the carbomethoxy and tolylsulfonyl groups. It has been reported that, in relatively simple compounds, cleavage of these substituents is rather easy.[11] Nevertheless, we found that when this reaction is to be carried out on a multifunctional system in a single step it becomes nontrivial. We therefore studied the methods for sequential removal of first methoxycarbonyl and then tolylsulfonyl employing two linear diterpene model compounds: geranylgeraniol derivative **11a** and ubiquinone-4 derivative **12**. This study yielded a powerful method for demethoxycarbonylation of the activated methyl esters, employing stoichiometric amounts of 4-aminothiophenol and catalytic quantities of cesium carbonate in hot (85 °C) DMF.[22]

The next step involved reductive removal of the allylic tolylsulfonyl groups, a transformation traditionally performed via dissolving-metal reduction methods (e.g., lithium in ethylamine,[23] sodium in THF/ethanol,[4e] sodium in buffered THF,[11] etc.).

Scheme VI[a]



E = CO_2Me

S = $SO_2C_7H_7$

[a] Key: (a) $Pd(PPh_3)_4$, THF; (b) PATP, Cs_2CO_3, DMF, 85 °C; (c) Super Hydride, $Pd(dppp)Cl_2$, THF, 0 °C; (d) CAN, $MeCN/H_2O/CH_2Cl_2$.

However, these one-electron-transfer reactions are all associated with some inevitable loss of stereochemical integrity at the double bond. This serious drawback made this approach unacceptable for our purpose. A recently reported method for selective reduction of allylic sulfones,[24] utilizing a palladium catalyst, $Pd(dppp)Cl_2$, along with stoichiometric amounts of lithium triethylborohydride, was found applicable in our case, as it caused no apparent isomerization of the double bonds (vide infra).

Total Synthesis of Ubiquinones. Having developed satisfactory methodology for the key steps of our proposed synthetic scheme, we attempted the total synthesis of several ubiquinones. For example, the total synthesis of ubiquinone 4 is outlined in Scheme VI. Pd(0)-catalyzed coupling of **10** to **3** afforded the diterpene skeleton **12** in 84% yield. Demethoxycarbonylation proceeded smoothly to give **13** in 98% yield, and reductive cleavage of the allylic sulfone provided protected ubiquinone 4 (**14**) in 92% yield. Oxidation of the aromatic ring in **14** to the 1,4-quinone was carried out with ceric ammonium nitrate (CAN) according to a known

(18) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523.
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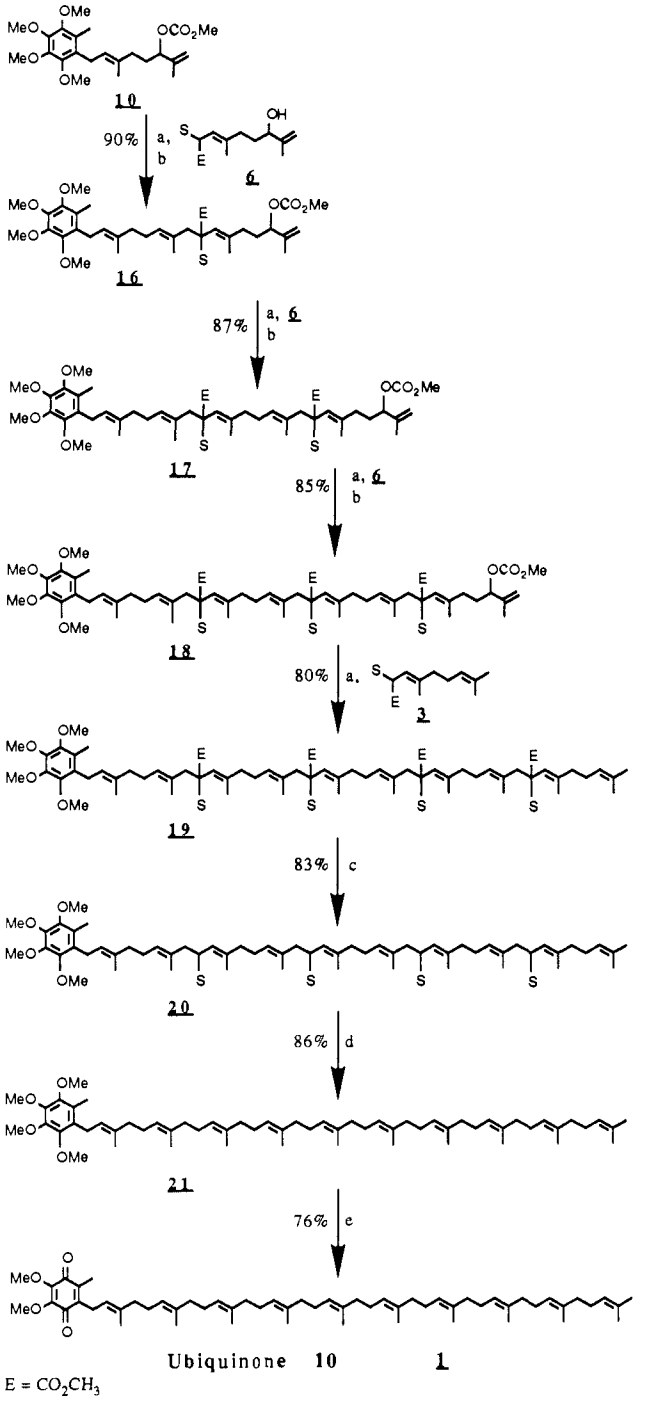
(22) Keinan, E.; Eren, D. *J. Org. Chem.* **1986**, *51*, 3165.
(23) Sato, K.; Inoue, S.; Onishi, A.; Uchida, N.; Minowa, N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 761.
(24) (a) Mohri, M.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* **1985**, 451. (b) See ref 4g.

Scheme VII[a]



[a] Key: (a) $Pd(PPh_3)_4$, THF; (b) MeOCOCl, diethylaniline, pyridine, benzene; (c) PATP, Cs_2CO_3, DMF, 85 °C; (d) Super Hydride, Pd(dppp)Cl_2 THF, 0 °C; (e) CAN, CH_2Cl_2, CH_3CN, H_2O.

procedure,[4a] leading to ubiquinone 4 (**15**) in 78% yield. Overall yield for the four-step sequence was 59%.

The total synthesis of coenzyme Q_{10} was carried out according to the proposed oligomerization, as shown in Scheme VII. Palladium-catalyzed coupling of **10** to **6** and subsequent treatment with methyl chloroformate and diethylaniline resulted in methyl carbonate **16** in 90% yield. The same sequence of coupling to **6** followed by esterification with methyl chloroformate yielded triterpene skeleton **17** in 87% yield. The same sequence was repeated once again, affording the corresponding tetraterpene derivative **18** in 85% yield. Finally, coupling of **18** to **3** resulted in **19**, which possesses the decaprenyl carbon skeleton of ubiquinone-10, in 80% yield.

Demethoxycarbonylation of the four ester groups in **19** proceeded in 83% yield, and reductive cleavage of the four sulfones resulted in the protected ubiquinone **21** in 86% yield. Finally, oxidation of **21** afforded coenzyme Q_{10} in 72% yield. Overall yield for the seven-step sequence was 27.4%. This product was easily recrystallized from ethanol [mp 47 °C (lit.[25] mp 48–49 °C)] and was found to be identical (mixed melting point, ^1H NMR, ^{13}C NMR, IR, HPLC[4b]) with an authentic sample extracted from bovine heart (purchased from Sigma Chemical Co.).

Conclusion

A general methodology for highly regio- and stereoselective Pd(0)-catalyzed stepwise allylic coupling of bifunctional monomers was developed, representing a long-desired, practical approach for total synthesis of naturally occurring polyprenoids. The method was exemplified by the total synthesis of ubiquinone-10 via selective coupling of monomers, easily derived from geraniol. From three different monomers, the synthesis is completed in a short sequence of seven steps with excellent (27.4%) overall yield.

It is remarkable that, of these seven steps, five are catalyzed by palladium complexes. Also notable is the fact that nine of the ten olefinic bonds of the final product participated in transition-metal allylic complexation at some time during the synthesis and could have, on thermodynamic considerations, undergone equilibration of their *E* and *Z* isomers. Nevertheless, all of these double bonds of the synthetic ubiquinone 10 were formed with almost pure *E* geometry, as required for the naturally occurring compound.

Other biologically active linear polyprenoids are currently being synthesized in our laboratories via a similar strategy. In addition, we are studying a novel polymerization methodology based on a transition-metal-catalyzed coupling of bifunctional monomers.[26]

Experimental Section

General Methods. Elemental analyses were carried out at the microanalytical laboratory of the Hebrew University, Jerusalem. Infrared spectra (cm^{-1}) were measured on the neat compounds with an FT-IR Mattson Instruments Sygnus 25. Patterns are designated as follows: br, broad; sh, shoulder; s, strong; w, weak; m, medium. ^1H NMR spectra were measured in deuteriochloroform (unless otherwise cited) on a Bruker WH-270 or Bruker AM-500 NMR spectrometer. All chemical shifts are reported in δ downfield from Me_4Si, and the *J* values are given in hertz. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60, F254, Art. 5549). Column chromatography separations were performed on silica gel (Merck, Kieselgel 60, 230–400 mesh, Art. 9385) under 0.4-atm pressure (flash chromatography). Preparative TLC was performed on glass plates precoated with silica gel (Merck, Kieselgel 60 F-254, Art. 5717). Tetrahydrofuran and diethyl ether were distilled over sodium benzophenone ketyl, DMF was distilled over CaH_2, and dimethylcarbonate was distilled over K_2CO_3.

(2*E*)-3,7-Dimethyl-1-(*p*-tolylsulfonyl)-2,6-octadiene (2). **2** was prepared according to ref 12. The all-trans product was obtained by recrystallization from hexane. NMR: 7.74 (d, *J* = 8.2, 2 H), 7.32 (d, *J* = 8.0, 2 H), 5.17 (t, *J* = 7.6, 1 H), 5.05 (br s, 1 H), 3.79 (d, *J* = 7.9, 3 H), 2.44 (s, 3 H), 2.00 (br s, 4 H), 1.69 (s, 3 H), 1.59 (s, 3 H), 1.34 (s, 3 H).

Methyl (3*E*)-4,8-Dimethyl-2-(*p*-tolylsulfonyl)-3,7-nonadienoate (3). Geranyl tolyl sulfone (**2**)[12] (6.5 g, 22.3 mmol) was dissolved in 40 mL of dry DMF to which was added 10 mL of dry dimethyl carbonate. The solution was cooled to −20 °C, and potassium *tert*-butoxide (5 g) was added. The mixture was stirred at −20 °C for 2 h and at room temperature for 1 h and then quenched with saturated aqueous ammonium chloride, poured into water (250 mL), and extracted with ether (4 × 20 mL). The combined extracts were washed with 1 M HCl, water, and brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by chromatography (silica gel, 10% ethyl acetate in hexane) to give **3** in the form of a colorless oil (7.4 g, 21.2 mmol, 95%). NMR: 7.72 (d, *J* = 8.3, 2 H), 7.33 (d, *J* = 8.0, 2 H), 5.25 (d, *J* = 10.3, 1 H), 5.05 (br s, 1 H), 4.80 (d, *J* = 10.3, 2 H), 3.76 (s, 3 H), 2.45 (s, 3 H), 2.04 (br s, 4 H), 1.69 (s, 3 H), 1.59 (s, 3 H), 1.54 (s,

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(26) Keinan, E.; Haviv, D., to be published.

3 H). IR: 2970–2915, 1744, 1657, 1597, 1438, 1323, 1305, 1149, 1084. Anal. Calcd for $C_{19}H_{26}O_4S$: C, 65.11; H, 7.48. Found: C, 64.97; H, 7.74.

(2*E*)-6,7-Epoxy-3,7-dimethyl-1-(*p*-tolylsulfonyl)-2-octene (4). A solution of *m*-chloroperbenzoic acid (mCPBA; 8 g, 46 mmol) in 100 mL of CH_2Cl_2 was added dropwise over 30 min to a cold (0 °C) solution of **2** (10.2 g, 35.0 mmol) in 100 mL of CH_2Cl_2. The reaction mixture was stirred at 0 °C for 15 min, washed with saturated aqueous $NaHCO_3$ and then with water, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (15% ethyl acetate in hexane), affording 2.1 g of unreacted starting material and 6.8 g of **4** in the form of a colorless oil (22.0 mmol, 79%). NMR: 7.73 (d, J = 8.3, 2 H), 7.32 (d, J = 8.0, 2 H), 5.22 (t, J = 8.0, 1 H), 3.79 (d, J = 7.9, 2 H), 2.66 (t, J = 6.6, 1 H), 2.44 (s, 3 H), 2.15 (dt, J = 7.9, 7.7, 2 H), 1.66–1.49 (m, 2 H), 1.41 (s, 3 H), 1.31 (s, 3 H), 1.25 (s, 3 H). IR: 2955, 2926, 2351, 1653, 1591, 1445, 1376, 1304, 1236, 1142, 1078, 887, 814, 741, 664. Anal. Calcd for $C_{17}H_{24}O_3S$: C, 66.20; H, 7.84. Found: C, 66.21; H, 7.63.

(2*E*)-6-Hydroxy-3,7-dimethyl-1-(*p*-tolylsulfonyl)-2,7-octadiene (5). Epoxide **4** (1.17 g, 3.80 mmol) was dissolved in 50 mL of dry toluene and 10 mL of 0.5 M aluminum triisopropylate in 2-propanol. The solution was refluxed for 20 h, cooled, washed with 20 mL of 2 M HCl and then with water, and dried over $MgSO_4$. The solvent was removed under reduced pressure. Column chromatography (25% ethyl acetate in hexane) yielded alcohol **5** (1.01 g, 3.27 mmol, 86% yield) in the form of a colorless oil. NMR: 7.74 (d, J = 8.1, 2 H), 7.32 (d, J = 8.0, 2 H), 5.22 (t, J = 7.7, 1 H), 4.94 (s, 1 H), 4.85 (s, 1 H), 4.00 (t, J = 6.7, 1 H), 3.79 (d, J = 7.7, 2 H), 2.44 (s, 3 H), 2.14–1.98 (m, 2 H), 1.72 (s, 3 H), 1.66–1.54 (m, 3 H), 1.61 (s, 3 H). IR: 3516 (br), 3068, 2945, 1738, 1652, 1598, 1448, 1291, 1148, 1087, 901, 802, 745.

Methyl (3*E*)-7-Hydroxy-4,8-dimethyl-2-(*p*-tolylsulfonyl)-3,8-nonadienoate (6). Potassium *tert*-butoxide (1.7 g) was added in portions over 30 min to a cold (0 °C) solution of **5** (1.54 g, 5.00 mmol) in 25 mL of dry DMF and 5 mL of dry dimethyl carbonate. The mixture was stirred for 30 min, poured into a 150-mL aqueous solution of NH_4Cl (5 g), and extracted with diisopropyl ether (5 × 20 mL). The combined extracts were washed with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was dissolved in a solution of 0.1 g of sodium methylate in 25 mL of dry methanol and stirred overnight. Solid NH_4Cl (0.15 g) was added, the solvent was removed under reduced pressure, and the product was purified by column chromatography (33% ethyl acetate in hexane) to give **6** as a pale yellow oil (1.34 g, 3.65 mmol, 73%). NMR: 7.72 (d, J = 8.2, 2 H), 7.33 (d, J = 8.3, 2 H), 5.30 (d, J = 10.2, 1 H), 4.94 (s, 1 H), 4.86 (s, 1 H), 4.80 (d, J = 10.4, 2 H), 4.02 (t, J = 5.5, 1 H), 3.75 (s, 3 H), 2.45 (s, 3 H), 2.23–2.01 (m, 2 H), 1.72 (s, 3 H), 1.68–1.55 (m, 3 H), 1.56 (s, 3 H). IR: 3538 (br), 2952, 1742, 1651, 1597, 1437, 1305, 1148, 1084. Anal. Calcd for $C_{19}H_{26}O_5S$: C, 62.27; H, 7.15. Found: C, 62.06; H, 7.42.

(2*E*)-6-Acetoxy-3,7-dimethyl-1-(*p*-tolylsulfonyl)-2,7-octadiene (7a). Acetylation of **5** with acetic anhydride and pyridine gave **7a** in 96% yield. NMR: 7.74 (d, J = 8.2, 2 H), 7.33 (d, J = 8.2, 2 H), 5.19 (t, J = 8.1, 1 H), 5.09 (t, J = 7.2, 1 H), 4.93 (s, 1 H), 4.90 (s, 1 H), 3.88 (d, J = 8.1, 2 H), 2.44 (s, 3 H), 2.06 (s, 3 H), 2.06–1.87 (m, 2 H), 1.72–1.56 (m, 2 H), 1.71 (s, 3 H), 1.35 (s, 3 H). IR: 2935, 1739, 1656, 1598, 1495, 1448, 1373, 1304, 1243, 1151, 1088, 1020, 903, 818, 746. Anal. Calcd for $C_{19}H_{26}O_4S$: C, 65.11; H, 7.48. Found: C, 64.95; H, 7.33.

(2*E*)-6-(Diethylphosphonooxy)-3,7-dimethyl-1-(*p*-tolylsulfonyl)-2,7-octadiene (7b). Alcohol **5** was reacted with diethyl phosphorobromidate according to the published procedure[15] to give after chromatography (ethyl acetate) the corresponding diethyl phosphate derivative **7b** in 89% yield. NMR: 7.60 (d, J = 8.4, 2 H), 7.42 (d, J = 8.4, 2 H), 5.29 (t, J = 8.0, 1 H), 5.08 (t, J = 8.5, 1 H), 4.96 (s, 1 H), 4.90 (s, 1 H), 4.08 (q, J = 6.8, 4 H), 3.90 (d, J = 8.0, 2 H), 2.45 (s, 3 H), 2.11–1.92 (m, 2 H), 1.78 (s, 3 H), 1.73–1.51 (m, 2 H), 1.41 (s, 3 H), 1.33 (t, J = 6.8, 6 H).

(2*E*)-6-[(*tert*-Butoxycarbonyl)oxy]-3,7-dimethyl-1-(*p*-tolylsulfonyl)-2,7-octadiene (7c). Alcohol **5** (306 mg, 1.00 mmol) was dissolved in 3 mL of CH_2Cl_2 containing a catalytic amount of 4-(dimethylamino)-pyridine. Di-*tert*-butyl dicarbonate (280 mg in 2 mL of CH_2Cl_2) was added over 30 min. The mixture was stirred for 4 h, washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue chromatographed (10% ethyl acetate in hexane) to yield **7c** (330 mg, 0.81 mmol, 81%). NMR: 7.73 (d, J = 8.1, 2 H), 7.32 (d, J = 8.0, 2 H), 5.19 (t, J = 7.6, 1 H), 4.96 (s, 1 H), 4.92 (s, 1 H), 4.85 (t, J = 6.6, 1 H), 3.78 (d, J = 8.0, 2 H), 2.45 (s, 3 H), 2.18–1.91 (m, 2 H), 1.72 (s, 3 H), 1.69–1.51 (m, 2 H), 1.48 (s, 9 H), 1.34 (s, 3 H). IR: 2979, 2930, 2362, 1740, 1454, 1370, 1279, 1152, 1088. Anal. Calcd for $C_{22}H_{32}O_5S$: C, 64.67; H, 7.89. Found: C, 64.56; H, 7.75.

(2*E*)-6-[(Methoxycarbonyl)oxy]-3,7-dimethyl-1-(*p*-tolylsulfonyl)-2,7-octadiene (7d). Alcohol **5** (1.00 g, 3.27 mmol) was dissolved in 15 mL of dry benzene. Dry diethylaniline (0.5 mL) and dry pyridine (0.05 mL) were added, followed by slow addition (1 h) of methyl chloroformate (0.54 mL, 7.00 mmol). The reaction mixture was stirred for 4 h, washed with concentrated NH_4Cl, water, dilute $CuSO_4$, water, and finally brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure. The product (1.16 g, 3.17 mmol, 97% yield) was used without further purification. NMR: 7.73 (d, J = 8.2, 2 H), 7.32 (d, J = 8.2, 2 H), 5.20 (d, J = 7.9, 1 H), 5.00 (s, 1 H), 4.93 (s, 1 H), 3.79 (d, J = 7.8, 2 H), 3.78 (s, 3 H), 2.45 (s, 3 H), 2.04–1.94 (m, 2 H), 1.74–1.58 (m, 3 H), 1.72 (s, 3 H), 1.35 (s, 3 H). IR: 3063, 2959, 1745, 1655, 1599, 1443, 1287, 1247, 1150. Anal. Calcd for $C_{19}H_{26}O_5S$: C, 62.27; H, 7.15. Found: C, 62.56; H, 7.33.

(2*E*)-6-Chloro-3,7-dimethyl-1-(*p*-tolylsulfonyl)-2,7-octadiene (7e). Compound **2** was chlorinated in CH_2Cl_2 according to the published procedure.[16] The product was purified by chromatography (12.5% ethyl acetate in hexane) to yield chloride **7e** in 77% yield. NMR: 7.74 (d, J = 8.3, 2 H), 7.33 (d, J = 8.0, 2 H), 5.22 (t, J = 8.0, 1 H), 5.00 (s, 1 H), 4.90 (s, 1 H), 4.27 (t, J = 7.3, 1 H), 3.80 (d, J = 7.9, 2 H), 2.44 (s, 3 H), 2.16–1.97 (m, 2 H), 1.91–1.80 (m, 3 H), 1.79 (s, 3 H), 1.39 (s, 3 H). IR: 2941, 2355, 1591, 1439, 1302, 1140, 1078, 901, 808, 735, 660. Anal. Calcd for $C_{17}H_{23}ClO_2S$: C, 62.46; H, 7.09. Found: C, 62.42; H, 6.94.

1-[(2*E*)-6-[(Methoxycarbonyl)oxy]-3,7-dimethylocta-2,7-dienyl]-2,3,4,5-tetramethoxy-6-methylbenzene (10). Compound **8**[1] was subjected to the same reaction sequence (epoxidation, epoxide isomerization, acylation) by which **2** was converted into **7d**. Yields of these three steps were 67%, 91%, and 98%, respectively. NMR: 5.05 (t, J = 6.4, 1 H), 4.92 (s, 1 H), 4.89 (s, 1 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.85 (t, J = 5.7, 1 H), 3.78 (s, 6 H), 3.74 (s, 3 H), 3.31 (d, J = 6.5, 2 H), 2.13 (s, 3 H), 2.08–1.90 (m, 2 H), 1.77 (s, 3 H), 1.71 (s, 3 H), 1.73–1.51 (m, 3 H). IR: 3010–2812, 2363, 2208, 1981, 1748, 1655, 1578, 1446, 1271. Anal. Calcd for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11. Found: C, 65.18; H, 8.23.

(2*E*,6*E*,10*E*)-3,7,11,15-Tetramethyl-9-(methoxycarbonyl)-1,9-bis(*p*-tolylsulfonyl)hexadeca-2,6,10,14-tetraene (11a) and (2*E*,6*Z*,10*E*)-3,7,11,15-Tetramethyl-9-(methoxycarbonyl)-1,9-bis(*p*-tolylsulfonyl)hexadeca-2,6,10,14-tetraene (11b). Reaction of **3** and **7** according to Scheme V afforded **11a** and **11b** in yields and ratios indicated in Table I. NMR of **11a**: 7.67 (d, J = 7.6, 4 H), 7.31 (d, J = 7.5, 2 H), 7.28 (d, J = 7.6, 2 H), 5.29 (s, 1 H), 5.15 (t, J = 7.6, 1 H), 5.15 (t, J = 8.1, 1 H), 5.05 (t, J = 7.3, 1 H), 3.76 (d, J = 8.1, 2 H), 3.67 (s, 3 H), 3.11 (d, J = 14.3, 1 H), 2.98 (d, J = 14.3, 1 H), 2.44 (s, 3 H), 2.42 (s, 3 H), 2.09–1.84 (m, 8 H), 1.67 (s, 3 H), 1.59 (s, 3 H), 1.56 (s, 3 H), 1.42 (s, 3 H), 1.33 (s, 3 H). NMR of **11b**: 7.75 (d, J = 7.6, 2 H), 7.73 (d, J = 7.6, 2 H), 7.34 (d, J = 7.6, 2 H), 7.27 (d, J = 7.6, 2 H), 5.18 (s, 1 H), 5.15–5.10 (m, 2 H), 5.03 (t, J = 7.3, 1 H), 3.75 (d, J = 8.5, 2 H), 3.65 (s, 3 H), 3.30 (d, J = 13.4, 1 H), 2.81 (d, J = 13.4, 1 H), 2.45 (s, 3 H), 2.42 (s, 3 H), 2.11–1.86 (m, 8 H), 1.66 (s, 3 H), 1.64 (s, 3 H), 1.58 (s, 3 H), 1.53 (s, 3 H), 1.36 (s, 3 H).

1-[(2*E*,6*E*,10*E*)-9-(Methoxycarbonyl)-14-[(methoxycarbonyl)oxy]-3,7,11,15-tetramethyl-9-(*p*-tolylsulfonyl)hexadeca-2,6,10,15-tetraenyl]-2,3,4,5-tetramethoxy-6-methylbenzene (16). The following description is a representative general procedure for Pd-catalyzed coupling reactions. $Pd(PPh_3)_4$ (17.5 mg, 5 mol %) was added to a solution of **10** (126 mg, 0.30 mmol) and **6** (220 mg, 0.60 mmol) in dry THF (5 mL). After being stirred for 4 h, the reaction was quenched with solid NH_4Cl, solid KCN, and 0.5 mL of water. The solvent was decanted, the remaining solid was washed three times with CH_2Cl_2, and the combined solution was dried over $MgSO_4$. Solvents were removed under reduced pressure and the residue chromatographed (silica gel, 20% ethyl acetate in toluene) to yield an allylic alcohol (195 mg, 0.27 mmol, 91%). To a solution of the latter in dry benzene (3 mL) were added dry diethylaniline (0.15 mL), one drop of dry pyridine, and methyl chloroformate (0.12 mL, 1 mmol). After 4 h the reaction mixture was washed with concentrated NH_4Cl, water, dilute $CuSO_4$, water, and finally brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. Filtration of the residue with CH_2Cl_2 over silica gel and removal of the solvent under reduced pressure afforded **16** (211 mg, 0.27 mmol, 99%). NMR: 7.69 (d, J = 8.2, 2 H), 7.28 (d, J = 8.2, 2 H), 5.33 (s, 1 H), 5.14 (t, J = 9.3, 1 H), 5.01–4.90 (m, 3 H), 3.90 (s, 6 H), 3.88 (s, 3 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.66 (s, 3 H), 3.30 (d, J = 6.5, 2 H), 3.08 (d, J = 15.0, 1 H), 2.89 (d, J = 15.0, 1 H), 2.44 (s, 3 H), 2.17–1.84 (m, 9 H), 2.12 (s, 3 H), 1.73 (s, 3 H), 1.71 (s, 3 H), 1.60 (s, 3 H), 1.55 (s, 3 H), 1.48 (s, 3 H). IR: 3034–2791, 2210, 1739, 1652, 1597.

1-[(2*E*,6*E*,10*E*)-9-(Methoxycarbonyl)-3,7,11,15-tetramethyl-9-(*p*-tolylsulfonyl)hexadeca-2,6,10,14-tetraenyl]-2,3,4,5-tetramethoxy-6-methylbenzene (12). Compounds **3** and **10** were reacted according to the above described procedure. Chromatography (20% ethyl acetate in hexane) yielded **12** in 84% yield. NMR: 7.69 (d, J = 8.2, 2 H), 7.28 (d, J = 8.1, 2 H), 5.18 (s, 1 H), 5.05 (t, J = 8.1, 1 H), 5.03 (t, J = 8.0, 1 H), 5.00 (t, J = 6.7, 1 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.78 (s, 3 H),

3.77 (s, 3 H), 3.66 (s, 3 H), 3.29 (d, J = 6.7, 2 H), 3.09 (d, J = 14.1, 1 H), 2.87 (d, J = 14.1, 1 H), 2.45 (s, 3 H), 2.12 (s, 3 H), 2.08–1.94 (m, 8 H), 1.69 (s, 3 H), 1.62 (s, 3 H), 1.54 (s, 3 H), 1.52 (s, 3 H), 1.42 (s, 3 H). IR: 2932, 1739, 1467, 1408, 1321, 1210, 1144, 1107, 1042. Anal. Calcd for $C_{40}H_{56}O_8S$: C, 68.93; H, 8.10. Found: C, 68.82; H, 8.38.

1-[(2*E*,6*E*,10*E*,14*E*,18*E*)-9,17-Bis(methoxycarbonyl)-22-[(methoxycarbonyl)oxy]-3,7,11,15,19,23-hexamethyl-9,17-bis(*p*-tolylsulfonyl)tetracosa-2,6,10,14,18,23-hexaenyl]-2,3,4,5-tetramethoxy-6-methylbenzene (17). Reaction of **16** and **6** according to the general procedure afforded **17** in 87% yield. NMR: 7.70 (d, J = 8.2, 2 H), 7.68 (d, J = 8.0, 2 H), 7.28 (d, J = 8.4, 2 H), 7.27 (d, J = 8.4, 2 H), 5.33 (s, 2 H), 5.17–5.11 (m, 2 H), 5.01–4.90 (m, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.68 (s, 3 H), 3.65 (s, 6 H), 3.29 (d, J = 7.4, 2 H), 3.15–3.02 (m, 2 H), 2.96–2.79 (m, 2 H), 2.43 (s, 6 H), 2.20–1.82 (m, 13 H), 2.11 (s, 3 H), 1.73 (s, 6 H), 1.59 (s, 9 H), 1.57 (s, 3 H). IR: 3567, 3067, 3035–2862, 1739, 1655, 1597, 1445, 1297.

1-[(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*)-9,17,25-Tris(methoxycarbonyl)-30-[(methoxycarbonyl)oxy]-3,7,11,15,19,23,27,31-octamethyl-9,17,25-tris(*p*-tolylsulfonyl)dotriconta-2,6,10,14,18,22,26,31-octaenyl]-2,3,4,5-tetramethoxy-6-methylbenzene (18). Reaction of **17** and **6** according to the general procedure afforded **18** in 85% yield. NMR: 7.79–7.68 (m, 6 H), 7.36–7.24 (m, 6 H), 5.33 (s, 2 H), 5.25–5.10 (m, 3 H), 5.08–4.96 (m, 4 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.78 (s, 6 H), 3.77 (s, 3 H), 3.69 (s, 3 H), 3.67 (s, 3 H), 3.64 (s, 6 H), 3.30 (d, J = 4.3, 2 H), 3.28–3.01 (m, 3 H), 2.97–2.80 (m, 3 H), 2.43 (s, 9 H), 2.20–1.82 (m, 17 H), 2.12 (s, 3 H), 1.73 (s, 6 H), 1.61 (s, 9 H), 1.58 (s, 3 H), 1.57 (s, 3 H), 1.45 (s, 3 H). IR: 3054, 2994–2937, 1739, 1651, 1597, 1445, 1292, 1217.

1-[(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*,34*E*)-9,17,25,33-Tetrakis(methoxycarbonyl)-3,7,11,15,19,23,27,31,35,39-decamethyl-9,17,25,33-tetrakis(*p*-tolylsulfonyl)tetraconta-2,6,10,14,18,22,26,30,34,38-decaenyl]-2,3,4,5-tetramethoxy-6-methylbenzene (19). The tetraterpene derivative **18** (1.61 g, 1.09 mmol) and **3** (0.46 g, 1.31 mmol) were dissolved in THF (5 mL), $Pd(PPh_3)_4$ (63 mg, 5%) and potassium *tert*-butoxide (20 mg) were added,[27] and the mixture was stirred at room temperature for 4 h. Saturated aqueous NH_4Cl was added and then CH_2Cl_2 (50 mL); the solution was filtered and dried over Na_2SO_4, the solvent was removed under reduced pressure, and the product was purified by flash chromatography (40% ethyl acetate in hexane). Compound **10** was isolated as a very viscous pale yellow oil (1.52 g, 0.87 mmol, 80%). NMR: 7.79–7.65 (m, 8 H), 7.38–7.20 (m, 8 H), 5.35–5.27 (m, 3 H), 5.25–5.09 (m, 5 H), 5.08–4.94 (m, 2 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.67 (s, 3 H), 3.66 (s, 6 H), 3.65 (s, 3 H), 3.29 (d, J = 6.3, 2 H), 3.19–2.98 (m, 4 H), 2.98–2.79 (m, 4 H), 2.43 (s, 12 H), 2.20–1.83 (m, 20 H), 2.13 (s, 3 H), 1.73 (s, 3 H), 1.70–1.50 (m, 24 H), 1.43 (s, 3 H), 1.41 (s, 3 H). IR: 3150–2810, 2363, 2351, 1738, 1651, 1598, 1490, 1318, 1291, 1213, 1084, 1042, 817. Anal. Calcd for $C_{97}H_{120}O_{20}S_4$: C, 66.86; H, 7.40. Found: C, 66.49; H, 7.63.

1-[(2*E*,6*E*,10*E*)-3,7,11,15-Tetramethyl-9-(*p*-tolylsulfonyl)hexadeca-2,6,10,14-tetraenyl]-2,3,4,5-tetramethoxy-6-methylbenzene (13). A 3-mL DMF solution containing **12** (232 mg, 0.33 mmol), *p*-aminothiophenol (PATP) (64 mg), and cesium carbonate (35 mg) was stirred at 85 °C for 1 h. The mixture was then poured into water (20 mL) and extracted with 3 × 10 mL of ether; the combined extracts were washed twice with 1 M HCl (5 mL), water, and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, affording **13** in the form of a nearby colorless oil, which was found to be virtually pure by TLC, NMR, and elemental analysis (206 mg, 98%). NMR: 7.70 (d, J = 8.0, 2 H), 7.29 (d, J = 8.0, 2 H), 5.10 (t, J = 6.5, 1 H), 5.07–4.94 (m, 2 H), 4.87 (d, J = 13, 1 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.88–3.79 (m, 1 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.29 (d, J = 6, 2 H), 2.43 (s, 3 H), 2.12 (s, 3 H), 2.07–1.80 (m, 10 H), 1.73 (s, 3 H), 1.66 (s, 3 H), 1.56 (s, 3 H), 1.50 (s, 3 H), 1.20 (s, 3 H). IR: 2920, 1595, 1410, 1355, 1315, 1300, 1260, 1200, 1140, 1090, 1040, 980, 820, 740, 670. Anal. Calcd for $C_{38}H_{54}O_6S$: C, 71.44; H, 8.52. Found: C, 71.22; H, 8.60.

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-Decamethyl-9,17,25,33-tetrakis(*p*-tolylsulfonyl)tetraconta-2,6,10,14,18,22,26,30,34,38-decaenyl]-2,3,4,5-tetramethoxy-6-methylbenzene (20). Compound **19** (40 mg, 0.023 mmol) was allowed to react with PATP and cesium carbonate in hot DMF according to the above described procedure,[22] affording **20** in the form of a highly viscous oil (29 mg, 0.0191 mmol, 83%). NMR: 7.68 (br d, J = 7.1, 8 H), 7.28 (br d, J = 7.8, 8 H), 5.11–4.92 (m, 6 H), 4.90–4.78 (m, 4 H), 3.86 (s, 6 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.29 (d, J = 7.2, 2 H), 2.94–2.70 (m, 4 H), 2.43 (s, 12 H), 2.35–2.15 (m, 4 H), 2.12 (s, 3 H), 2.08–1.80 (m, 20 H), 1.72 (s, 3 H), 1.68 (s, 3 H), 1.63 (s, 3 H), 1.59 (s, 3 H), 1.51 (s, 6 H), 1.48 (s, 3 H), 1.26 (s, 3 H), 1.20 (s, 9 H). IR: 3658, 3066–2863, 1921, 1731, 1662, 1598, 1273.

1-((2*E*,6*E*,10*E*)-3,7,11,15-Tetramethylhexadeca-2,6,10,14-tetraenyl)-6-methyl-2,3,4,5-tetramethoxybenzene (14). Compound **13** (119 mg, 0.18 mmol) was dissolved in dry THF (2 mL) containing 5 mg of Pd(dppp)Cl_2. The solution was cooled to 0 °C and a solution of lithium triethylborohydride (Super Hydride, Aldrich; 0.4 mL of 1 M solution in THF) was added dropwise over 2 h.[24] The mixture was stirred for an additional 3 h, poured into diisopropyl ether (20 mL), washed with 1 M aqueous solution of NaCN (5 mL), water, and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the product purified by TLC (20% ethyl acetate in hexane) to give **14** (85 mg, 0.17 mmol, 92%). NMR (500 MHz): 5.16–5.05 (m, 3 H), 5.04 (br t, J = 6.22, 1 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.78 (s, 6 H), 3.32 (d, J = 6.37, 2 H), 2.14 (s, 3 H), 2.10–1.93 (m, 12 H), 1.77 (s, 3 H), 1.68 (s, 3 H), 1.59 (s, 3 H), 1.58 (s, 3 H). IR: 2936, 1468, 1408, 1352, 1260, 1197, 1107, 1042, 978.

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)-2,3,4,5-tetramethoxy-6-methylbenzene (21). **21** was prepared from **20** according to the general procedure for sulfone removal; yield was 86%. NMR (500 MHz): 5.11 (br t, J = 6.84, 8 H), 5.08 (qt, J_1 = 7.22, J_2 = 1.07, 1 H), 5.04 (qt, J_1 = 7.63, J_2 = 1.08, 1 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.78 (s, 3 H), 3.78 (s, 3 H), 3.32 (d, J = 6.47, 2 H), 2.14 (s, 3 H), 2.10–2.02 (m, 18 H), 2.01–1.93 (m, 18 H), 1.76 (d, J = 0.52, 3 H), 1.68 (s, 3 H), 1.60 (s, 18 H), 1.59 (s, 9 H), 1.58 (s, 3 H). IR: 2952, 2930, 2859, 1466, 1383, 1353, 1256, 1106, 1097, 1043, 911, 735.

2-((2*E*,6*E*,10*E*)-3,7,11,15-Tetramethylhexadeca-2,6,10,14-tetraenyl)-3-methyl-5,6-dimethoxy-1,4-benzoquinone (15, Ubiquinone 4). Oxidation of **14** according to literature[4a] and chromatography (silica gel, 15% EtOAc in hexane) produced **15** in 78% yield. NMR (500 MHz): 5.092 (qt, J_1 = 5.51, J_2 = 1.27, 1 H), 5.089 (qt, J_1 = 6.79, J_2 = 1.34, 1 H), 5.075 (qt, J_1 = 7.38, J_2 = 1.11, 1 H), 4.935 (qt, J_1 = 7.22, J_2 = 1.16, 1 H), 3.996 (s, 3 H), 3.981 (s, 3 H), 3.185 (d, J = 7.01), 2.08–2.02 (m, 6 H), 2.015 (s, 3 H), 1.99–1.93 (m, 6 H), 1.739 (br s, 3 H), 1.676 (d, J = 0.86, 3 H), 1.597 (br s, 3 H), 1.585 (br s, 3 H), 1.578 (br s, 3 H). IR: 2930, 2854, 1651, 1612, 1452, 1382, 1265, 1205, 1153, 1102, 1024, 949, 753. Anal. Calcd for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31. Found: C, 76.77; H, 9.38.

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)-3-methyl-5,6-dimethoxy-1,4-benzoquinone (1, Ubiquinone 10). Compound **21** was oxidized according to the literature.[4a] Chromatographic purification (silica gel, 15% ethyl acetate in hexane) afforded ubiquinone 10 in 72% yield. Recrystallization from ethanol yielded *all-trans*-ubiquinone 10, mp 47 °C (lit.[25] mp 48–49 °C). NMR (500 MHz): 5.11 (br t, J = 6.9, 8 H), 5.08 (t, J = 8.3, 1 H), 5.06 (t, J = 6.6, 1 H), 4.94 (t, J = 6.6, 1 H), 3.99 (s, 3 H), 3.98 (s, 3 H), 3.18 (d, J = 7.0, 1 H), 2.10–2.01 (m, 22 H), 2.01 (s, 3 H) 2.10–2.01 (m, 22 H), 1.74 (s, 3 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.59 (s, 21 H), 1.58 (s, 3 H). Anal. Calcd for $C_{59}H_{90}O_4$: C, 82.08; H, 10.51. Found: C, 82.13; H, 10.66.

Acknowledgment. We thank the Schmidt Foundation for Applied Research for their generous financial support.

Registry No. 1, 303-98-0; **2**, 53254-60-7; **3**, 114060-22-9; **4**, 114060-23-0; **5**, 68690-36-8; **6**, 114060-24-1; **7a**, 68690-35-7; **7b**, 114060-32-1; **7c**, 114060-33-2; **7d**, 114060-34-3; **7e**, 83110-39-8; **8**, 83036-57-1; **9**, 85228-79-1; **10**, 114060-25-2; **10** (alcohol), 85228-84-8; **11a**, 102779-88-4; **11b**, 114060-35-4; **12**, 102779-87-3; **13**, 102745-41-5; **14**, 114060-26-3; **15**, 4370-62-1; **16**, 114060-27-4; **16** (alcohol), 114060-36-5; **17**, 114060-28-5; **17** (alcohol), 114060-37-6; **18**, 114060-29-6; **18** (alcohol), 114094-40-5; **19**, 114060-30-9; **20**, 114060-31-0; **21**, 94828-17-8.

(27) Due to its high viscosity, compound **18** could not be effectively dried prior to reaction, causing partial destruction of the liberated base. In order to drive reaction to completion, additional base was employed.