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Total synthesis of polyprenoid natural products via Pd(O)-catalyzed oligomerizations

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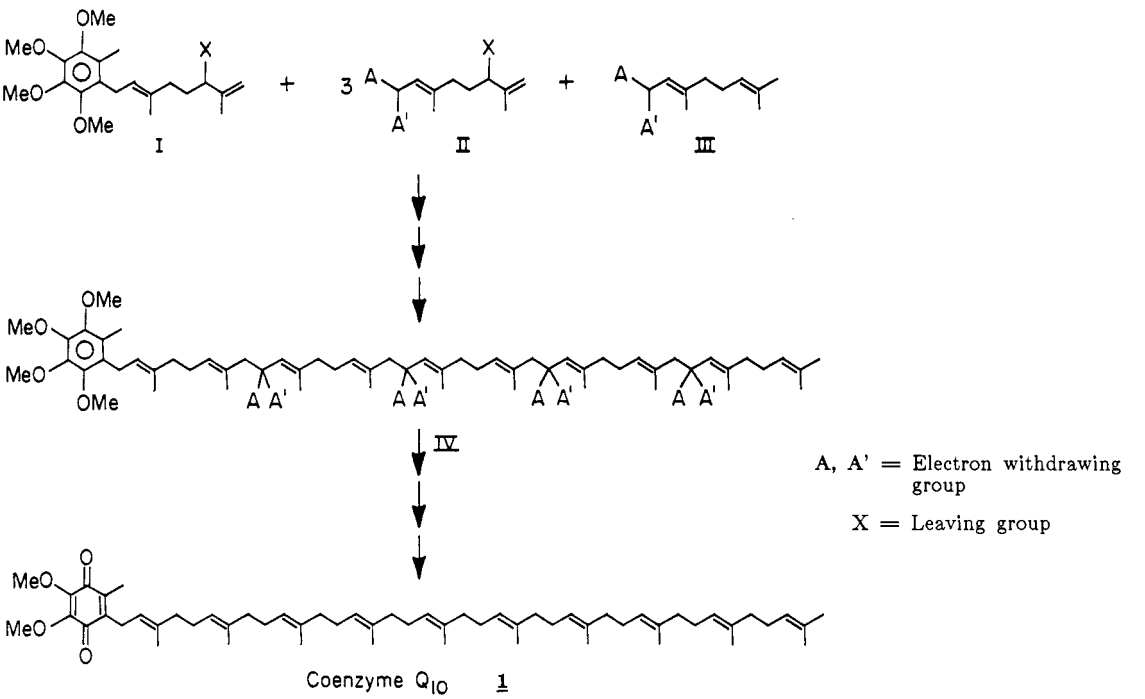
Abstract - A general methodology for highly regio- and stereoselective Pd(0)-catalyzed, stepwise allylic coupling of bifunctional monomers was developed, representing a practical approach for total synthesis of naturally occurring polyprenoids. As an example, the total synthesis of the cardiovascular 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 that is activated by the Pd(0) catalyst and the other is a latent nucleophile activated by an appropriate base. After achieving the desired decaprenyl carbon skeleton of Q_{10}, 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 by Pd(0)-catalyzed allylic reduction. Finally, oxidation of the aromatic ring to quinone affords ubiquinone-10.

INTRODUCTION

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.[1] 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**,[2] which is used clinically as a cardiovascular agent and has attracted significant synthetic activity within the past two decades.[3] 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 or semisynthetic methods, the latter employing solanesol, a nonaprenol extracted from tobacco leaves.

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.

Scheme I



For example, construction of the carbon skeleton of Q_{10} could be envisioned by the appropriate allylic coupling of monomers **I**, **II** and **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**.

Here we report on 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.

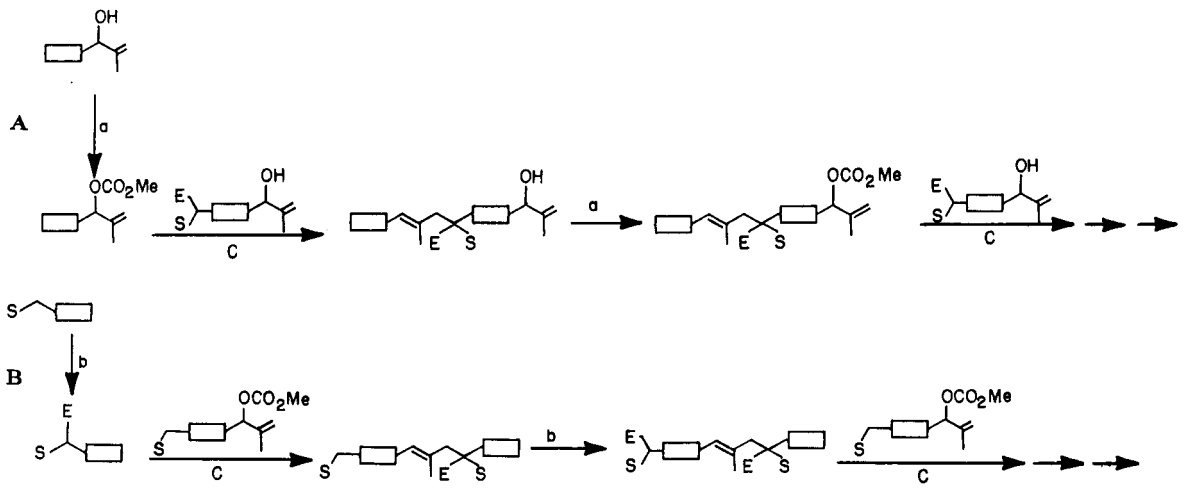
GENERAL STRATEGY

We designed an oligomerization approach that is based on the following two principles: a) all monoterpene monomers are derived from geraniol, a most readily available natural building block, and b) all monomer coupling reactions utilize π-allyl palladium chemistry because of the synthetic advantages associated with Pd(0)-catalyzed allylic alkylation.[4]

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. 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 proceed in two alternative directions, as illustrated by the examples given in Schemes IIA and IIB. The electrophilic functionality in these specific examples is generated by transforming a weak allylic leaving group (alcohol) into a better one (methyl carbonate). The nucleophilic center is created by increasing the level of substitution on the nucleophilic carbon from one electron-withdrawing group (tolylsulfone) to two such groups (sulfone and methyl ester). In these examples,

Scheme II



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 chloroformate or dimethylcarbonate) the approach described in IIA is more practical.

As the nucleophilic functionality of the monomers, we have chosen to employ a methine group bearing both methoxycarbonyl and tolylsulfone substituents, because the corresponding stabilized carbanion has proven useful as a nucleophilic partner in Pd(0)-catalyzed allylic alkylations. 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.

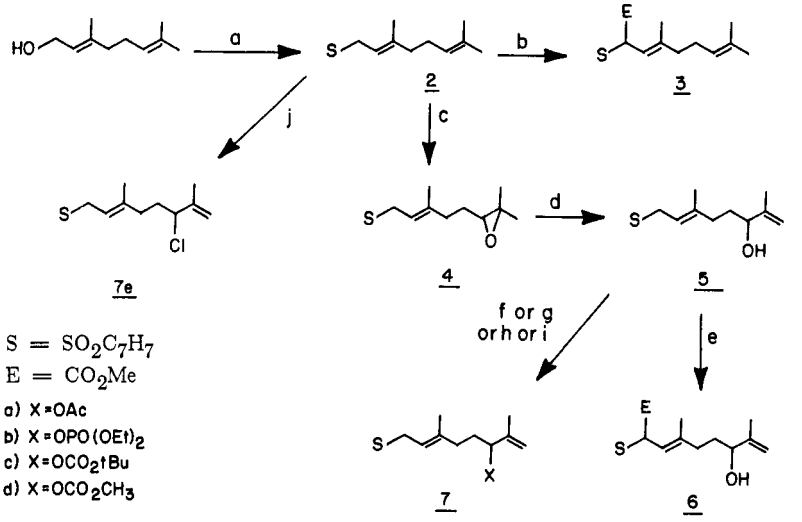
With respect to the electrophilic end, however, we found strong dependencies of both reactivity and stereoselectivity on the nature of allylic leaving group X. Therefore we investigated the influence of various leaving groups on these two factors (vide infra, Table I) and found that methyl carbonate is clearly superior, in that respect, to all other leaving groups examined.

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 phosphorous tribromide followed by nucleophilic substitution with sodium *p*-toluenesulfinate yielded geranyltolylsulfone, **2**.[5] Treatment of **2** with dimethyl carbonate under basic conditions (potassium *t*-butoxide) gave monomer **3** in excellent yield.

Geranyltolylsulfone **2** served as the key starting material for preparation of several other monomers. Regioselective epoxidation with either mCPBA or by an electrochemical approach[6] resulted in epoxide **4** that was isomerized to the desired allylic alcohol **5** via regioselective deprotonation with aluminum triisopropylate in refluxing toluene[7]. Esterification of **5** with acetic anhydride, diethyl phosphorobromidate,[8] di-*t*-butyl dicarbonate or methyl

Scheme III

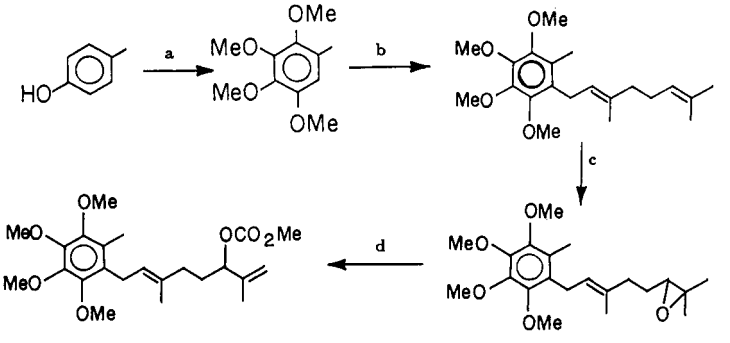


a) See ref. 5. b) $(MeO)_2CO$, tBuOK, DMF, -20°, 95%. c) mCPBA, CH_2Cl_2, 79%. d) $Al(OiPr)_3$, toluene, 110°, 86%. e) 1. $(MeO)_2CO$, tBuOK, DMF, -20°, 2. MeONa/MeOH, 73% overall. f) Ac_2O, pyridine, 96%. g) $(EtO)_2POBr$, collidine, 89%. h) $(tBuOCO)_2O$, CH_2Cl_2, DMAP, 81%. i) MeOCOCl, diethylaniline, pyridine, benzene, 97%. j) $Ca(OCl)_2$, CO_2, CH_2Cl_2/H_2O, 77%.

chloroformate under basic conditions yielded the corresponding acetate **7a**, diethylphosphate **7b**, *t*-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[9].

The synthesis of the aromatic monofunctional monomer **12** is described in Scheme IV. Most of the reported synthetic approaches to the aromatic nucleus of ubiquinones employ highly functionalized aromatic starting materials, such as vanilline, gallic acid, pyrogallol, etc.[10] We found that tetramethoxytoluene **9** can be prepared directly from *p*-cresol (**8**) in a two-step procedure. Tribromination of **8** provided 2,3,6-tribromo-4-methylphenol.[11] Copper-catalyzed methoxylation of the latter, followed by methylation with dimethylsulfate (both carried out in the same pot) yielded 2,3,4,5-tetramethoxytoluene (**9**) in 94% yield.

Scheme IV



a) 1. Br_2, Fe powder, $CHCl_3$, 76%, 2. $NaOCH_3$, CuCN, DME, 94%. b) *n*-butyl lithium, TMEDA, CuCN, geranyl bromide, THF, 66%. c) mCPBA, CH_2Cl_2, 67%. d) 1. $Al(OiPr)_3$, toluene, 110°, 91%, 2. MeOCOCl, diethylaniline, pyridine, benzene, 98%.

The most common method for direct prenylation of electron-rich aromatic compounds involve Friedel-Crafts allylation under acidic conditions,[12] an approach which is limited by the inherent instability of the allylating agent under the conditions employed and by troublesome side reactions. Another known approach to this coupling is a two-step sequence involving bromination of the available ring carbon, followed by conversion to the corresponding Grignard reagent and coupling to geranyl bromide in the presence of cuprous halide.[13,14]

We modified the latter approach by directly metalating the ring carbon of **9**, thereby bypassing the bromination step.[15] Quantitative metal-hydrogen exchange was achieved employing *n*-butyllithium in hexane and tetramethylethylenediamine (TMEDA). As with the Grignard approach,[14b] the lithiated derivative of **9** failed to couple with geranyl bromide in the absence of copper(I) salts. But even the diaryl cuprate of **9** (formed with 0.5 equivalent of CuI) gave rather poor yields of **10**. However, the mixed cuprate approach (involving one equivalent of either CuI or CuBr and one equivalent of methyl lithium added to lithiated **9**) was more successful, with even better results being obtained using one equivalent of cuprous cyanide, yielding 66% of isolated **10**.[15]

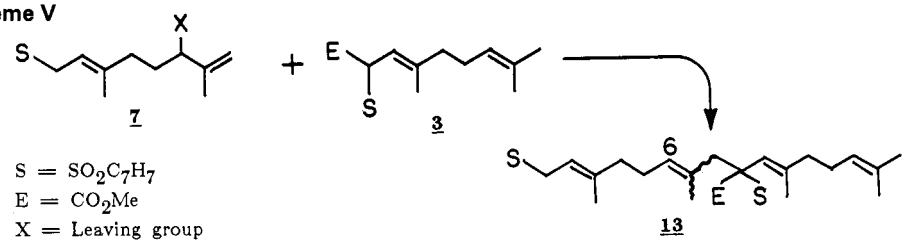
Starting with **10** and carrying out the sequence of oxidation to **11** and isomerization, followed by acylation, in analogous manner to what was described above in Scheme III, afforded the desired monomer **12** in satisfactory yield.

MONOMER COUPLING

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 and 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. An essentially identical situation to that of the allylic chloride case was observed with diethylphosphate.[16] Attempts to employ *t*-butyl carbonate as a leaving group failed, as essentially no reaction was observed at room temperature within 24 hours. Nevertheless, the easily accessible methyl carbonate[17] was found to be the leaving group of choice. In addition to its high reactivity, the coupling product **13** was obtained with excellent stereoselectivity, the newly formed trisubstituted double bond possessing an essentially-pure E configuration (evident by ^1H 270 MHz NMR).

Scheme V



S = $SO_2C_7H_7$
E = CO_2Me
X = Leaving group

a) 6E b) 6Z

Table I: Palladium(0)-catalyzed coupling of 3 and 7.[a]

Electrophile	Leaving group	Base	Temp. (°C)	Time (hr)	Yield (%)	E:Z
7a	OAc	BSA	65	20	54	90:10
7b	$OPO(OEt)_2$	NaH	22	3	67	60:40
7c	OCO_2CMe_3	tBuOK	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 eq). Yields are of isolated products. Ratios of E:Z isomers were determined by 270 MHz ^1H NMR.

REMOVAL OF THE ACTIVATING GROUPS

In order to complete the synthesis it was necessary to remove the carbomethoxy and tolylsulfone groups. These two electron withdrawing groups were chosen for their effective stabilization of the carbanion partner in Pd(0)-catalyzed allylation[18]. It has been reported that in relatively simple compounds, cleavage of these substituents is rather easy. Nevertheless, we found that when this reaction is to be carried out on a multifunctional system in a single step it becomes nontrivial. It requires a highly efficient, and yet chemoselective, process that transforms each site in nearly quantitative yield while preserving all other functionalities.

We therefore studied the methods for sequential removal of first methoxycarbonyl and then tolylsulfone employing two linear diterpene model compounds: geranylgeraniol derivative **13a** and ubiquinone-4 derivative **14**.

Dealkoxycarbonylation of active esters via S_N2-type dealkylation[19] is certainly the most attractive one-step process for removal of the methyl ester entity, particularly when sterically hindered. The reaction usually involves heating of the substrate in a dipolar aprotic solvent in the presence of a nucleophile. Following Krapcho's original development of this approach,[20] which employed NaCl in dimethylsulfoxide (DMSO), many other nucleophiles have been found applicable,[19] including halides, thiolates, *t*-butoxide, thiocyanate, amines and acetate. By far, the best method is probably that developed by Johnson[21] and modified by Trost and Verhoeven,[22] which employs tetramethylammonium acetate in hot (130°C) DMSO or hexamethylphosphoramide (HMPA) (at 100°C). Unfortunately, a number of the above mentioned procedures, including the tetramethylammonium acetate approach, were not satisfactory for multiple decarboxylation reactions. Only low to moderate yields of the desired products were obtained with model substrates **13a** and **14** (Table II).

In our search for more effective methods, we delved deeper into dealkoxycarbonylation with the thiolate anion. In the literature, this group of weak bases and powerful nucleophiles is employed only infrequently for this purpose, perhaps due to the inconvenience of preparing and storing the required solid sodium or lithium thiolate salts. The procedures described[23] usually require large excesses of thiolate salts which, in addition to their notorious stench, are moisture and oxygen sensitive. In attempting to apply the thiolate approach to the problem at hand, we investigated how four largely-neglected factors influence thiolate-promoted dealkoxycarbonylation: a) the nature of the thiol employed, b) the procedure for generating the corresponding thiolate anion, c) the kind of base used for this purpose, and d) the work-up procedure for efficient removal of by-products, organosulfur compounds in particular.

This study[24] yielded a powerful method for demethoxycarbonylation of the activated methyl esters, employing stoichiometric amounts of 4-aminothiophenol[25] and catalytic quantities of cesium carbonate in hot (85°C) DMF. The superiority of this technique over several other methods was demonstrated in a comparative study on the linear polyprenoid substrates, in which the thiolate/Cs_2CO_3 approach benefited from shorter reaction times, lower temperatures, higher yields and simpler work-up procedures (Table II).

Table II: Comparison of demethoxycarbonylation methods.

Substrate	Nucleophilic reagent	Solvent	Temperature (°C)	Time (hrs)	Yield (%)
14	NaCl, H_2O	DMF	153	15	26
14	NaCN, LiI	DMF	120	15	28
14	CsOAc	DMF	130	24	47
14	Me_4NOAc	HMPA	100	24	62
14	PhSH, Cs_2CO_3	DMF	85	1	73
14	PATP, Cs_2CO_3	DMF	85	1	98
13a	NaCN, LiI	DMF	120	20	58
13a	Me_4NOAc	HMPA	100	7	47
13a	PATP, Cs_2CO_3	DMF	85	1	97

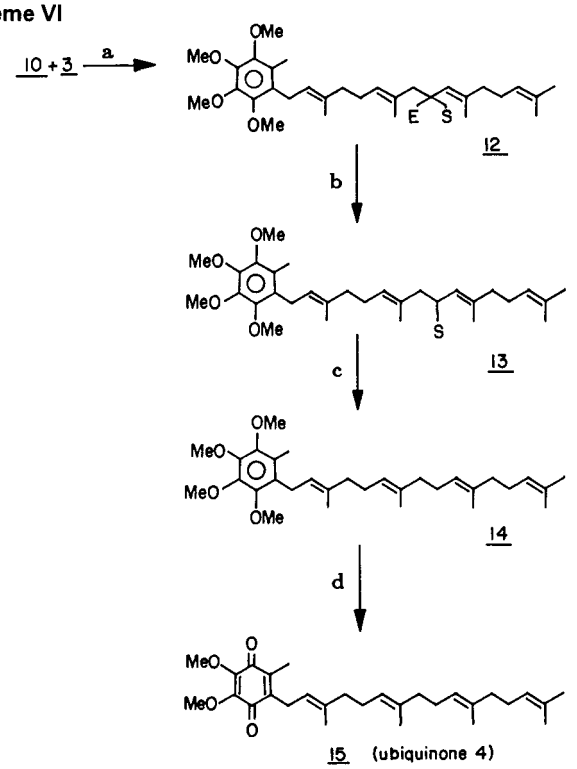
The next step involved reductive removal of the allylic tolylsulfone groups, a transformation which is traditionally performed via dissolving-metal reduction methods (e.g. lithium in ethylamine,[26] sodium in THF/ethanol,[27] sodium in buffered THF,[18] etc.). However, these one-electron transfer reactions 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,[28] utilizing a palladium catalyst, $Pd(dppp)Cl_2$, along with stoichiometric amounts of lithium triethylborohydride, was found applicable in our case. Isolated yields of **16** (Scheme VI) of 92% were obtained with no apparent isomerization of the double bonds.

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.[29]

Pd(0)-catalyzed coupling of **12** to **3** (Scheme VI) afforded the diterpene skeleton **14** in 85% yield. Demethoxycarbonylation proceeded smoothly to give **15** in 98% yield, and reductive cleavage of the allylic sulfone provided protected ubiquinone-4 (**16**) in 92% yield. Oxidation of the aromatic ring in **16** to the 1,4-quinone was carried out with ceric ammonium nitrate (CAN) according to a known procedure,[30] leading to ubiquinone-4 **17** in 81% yield. Overall yield for the four-step sequence was 62%.

Scheme VI

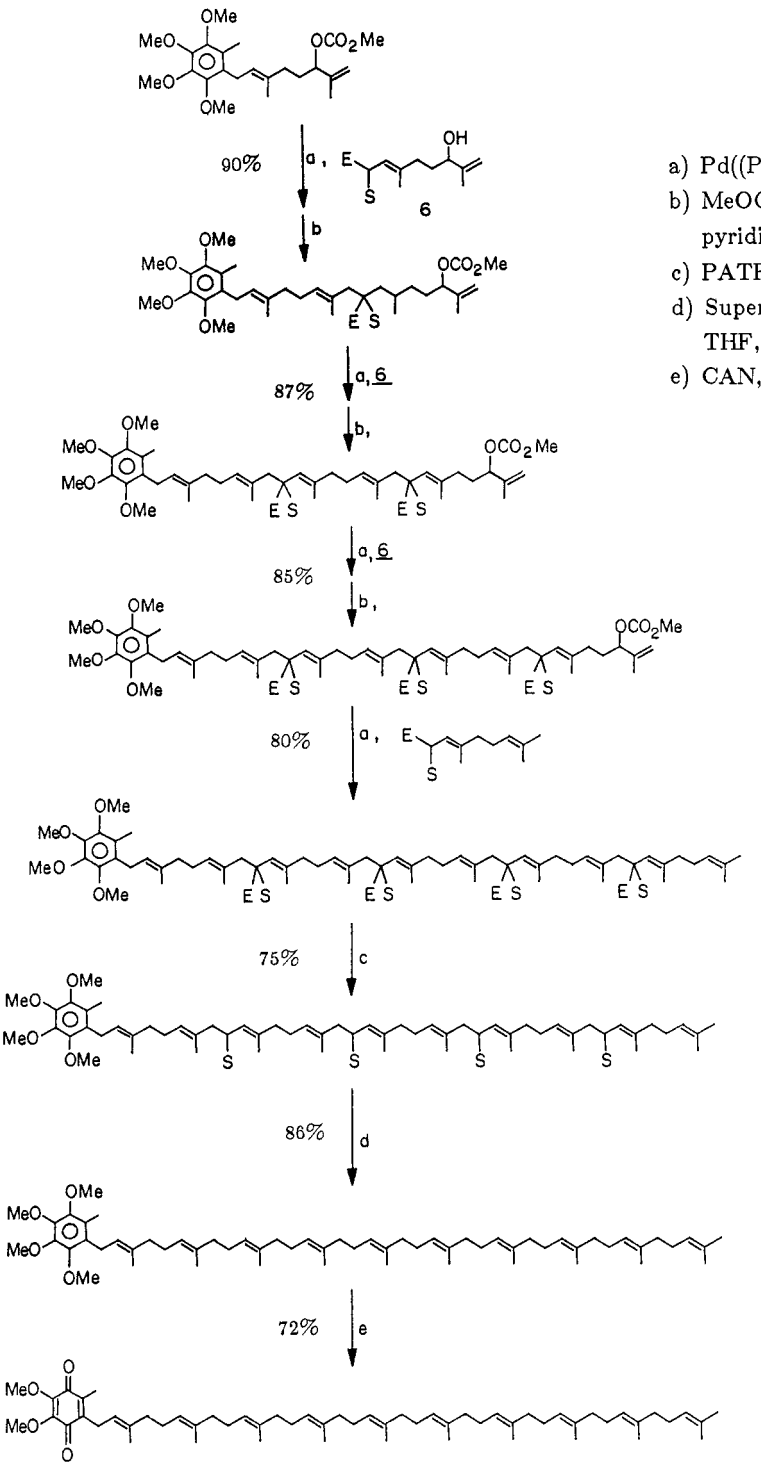


a) $Pd((PPh_3)_4$, THF, 84%.
b) PATP, Cs_2CO_3, DMF, 85°, 98%.
c) Super hydride, $Pd(dppp)Cl_2$, THF, 0°, 92%.
d) CAN, pyridine-2,6-dicarboxylic acid, $MeCN/H_2O$, 81%.

The total synthesis of coenzyme Q_{10} was carried out according to the proposed oligomerization, as shown in Scheme VII. Palladium-catalyzed coupling of **12** to **6** and subsequent treatment with methylchloroformate and diethylaniline resulted in methyl carbonate **18** in 90% yield. The same sequence of coupling to **6** followed by esterification with methylchloroformate yielded the triterpene skeleton **19** in 87% yield. The same sequence was repeated once again, affording the corresponding tetraterpene derivative **20** in 85% yield. Finally, coupling of **20** to **3** resulted in **21**, which possesses the decaprenyl carbon skeleton of ubiquinone-10, in 80% yield.

Demethoxycarbonylation of the four ester groups in **21** proceeded in 75% yield and reductive cleavage of the four sulfones resulted in the protected ubiquinone **23** in 86% yield. Finally, oxidation of **23** afforded coenzyme Q_{10} in 72% yield. Overall yield for the seven step sequence was 24.7%. The final product was purified by recrystallization from ethanol and was found to be identical (melting point, NMR, HPLC) to an authentic sample purchased from Sigma Chemicals Co.

Scheme VII



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. Using three different monomers, the synthesis is completed in a short sequence of seven steps with excellent (24.7%) overall yield.

It is remarkable that out of these seven steps, five are catalyzed by palladium complexes. Also notable is the fact that nine out of the ten olefinic bonds of the final product participated in transition metal 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 preserved pure E geometry, as is 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.[31]

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