A Convergent Approach to Coenzyme Q

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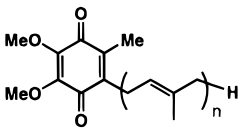
Abstract: Syntheses of coenzyme Q_{3-8} are described, as well as related systems such as plastoquinone-5. Preparation of the higher homologues of the ubiquinones relies on two new conjunctive reagents, or "linchpins", each of which ultimately corresponds to two or three prenyl units. These allow for attachment of a polyprenyl halide at one end, followed by a Ni(0)-catalyzed cross-coupling at the other terminus with a chloromethylated *p*-quinone.

Introduction

Coenzyme Q (**1**) plays an essential role in the orchestration



coenzyme Q_n, **1**

(ubiquinones; $n \leq 12$)

of electron-transfer processes necessary for respiration.[1] Almost all vertebrates rely on one or more forms of this series of compounds which are found in the mitrochondria of every cell (i.e., they are ubiquitous, hence the alternative name "ubiquinones"). Although usually occurring with up to 12 prenoidal units attached to a *p*-quinone headgroup, CoQ_{10} is the compound used by humans as a redox carrier. Oftentimes unappreciated is the fact that when less than normal levels are present, the body must construct its CoQ_{10} from lower forms obtained through the diet, and that at some point in everyone's life span the efficiency of that machinery begins to drop.[2] The consequences of this in vivo deterioration can be substantial; levels of CoQ_{10} have been correlated with increased sensitivity to infection (i.e., a weakening of the immune system), strength of heart muscle, and metabolic rates tied to energy levels and vigor. In some countries (e.g., Japan), CoQ_{10} is treated as a "drug", prescribed especially for those having suffered from heart disease, and is among the leading pharmaceuticals sold. In the United States, however, it is considered a dietary supplement, sold typically in health food stores or through mail order houses at reasonable prices. It is indeed fortunate that quantities of CoQ_{10} are available via a well-established fermentation process,[3] an apparently more cost-efficient route relative to total synthesis. However, for producing lower forms of CoQ, such fermentation processes are either far less efficient or are unknown. Thus, the costs of these materials for research purposes are astonishingly high: e.g., CoQ_6 is ~$22,000/g, and CoQ_9 is over $40,000/g.[4]

Retrosynthetic Analysis

Any synthesis of the ubiquinones (other than CoQ_0; i.e., the quinone alone) must come to grips with the issue of double bond stereocontrol. The all-hydrocarbon nature of the side chains suggests a rather difficult if not unlikely separation of *E*/*Z* mixtures, and it was this particular issue of controlling olefin geometry[5] which gave rise to the sequence ultimately developed. Literature routes which rely on allylic nucleophiles to attach all or partial segments of the polyene chain to a quinone precursor have met with mixed success.[6] Other approaches tend to be highly iterative and linear,[7] or rely on a quinone protection-deprotection scheme for introduction of substituents onto the ring.[8] All share the common feature that many steps are involved, even to arrive at the simpler members of this family of natural products.

An alternative disconnection of **2**, the immediate precursor to **1**, calls for C−C bond formation between a benzylic center

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(1) (a) Thomson, R. H. In *Naturally Occurring Quinones*; Academic Press: N.Y., 1971. (b) Combs, A. B.; Acosta, D.; Folkers, K. *IRCS Med. Sci.: Libr. Compend.* **1976**, *4*, 403. (c) Heller, J. H.; *Perspect. Biol. Med.* **1973**, *16*, 181. (d) Littaru, G. P.; Ho, L.; Folkers, K. *Int. J. Vitam. Nutr. Res.* **1972**, *42*, 291, 413. (e) *Biomedical and Clinical Aspects of Coenzyme Q*; Folkers, K., Yamamura, Y., Eds.; Elsevier: Amsterdam, Vol. 1−4. (f) *Coenzyme Q*; Lenaz, G., Ed., Wiley: New York, 1985. (g) Trumpower, B. L. *Function of Ubiquinones in Energy Conserving Systems*; Academic Press: New York, 1982. (h) Thomson, R. H. *Naturally Occurring Quinones*, 3rd ed.; Academic Press: New York, 1987.

(2) Bliznakov, G. G.; Hunt, G. L. *The Miracle Nutrient Coenzyme Q_{10}*; Bantom Books: New York, 1987.

(3) Sasikala, Ch.; Ramana, Ch. V. *Adv. Appl. Microbiol.* **1995**, *41*, 173.

(4) Sigma-Aldrich Catalog; Sigma-Aldrich: St. Louis, 1998; pp 306−307.

(5) For representative alternative approaches to controlling olefin geometry in polyprenoidal systems, see Mechelke, M. F.; Wiemer, D. F. *Tetrahedron Lett.* **1998**, *39*, 783. Saa, J. M.; Ballester, P.; Deya, P. M.; Capo, M.; Garcias, X. *J. Org. Chem.* **1996**, *61*, 1035. Garcias, X.; Ballester, P.; Capo, M.; Saa, J. M. *ibid.* **1994**, *59*, 5093;

(6) Duralski, A. A.; Watts, A. *Tetrahedron Lett.* **1992**, *34*, 4983. Yanagisawa, A.; Nomura, N.; Noritake, Y.; Yamamoto, H. *Synthesis* **1991**, 1130. Eto, H.; Eguchi, C. *Chem. Lett.* **1988**, 1597. Naruta, Y. *J. Org. Chem.* **1980**, *45*, 4097. Inoue, S.; Yamaguchi, R.; Saito, K.; Sato, K. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 3098.

(7) (a) Eren, D.; Keinan, E. *J. Am. Chem. Soc.* **1988**, *110*, 4356. (b) Mohri, M.; Kinoshita, H.; Inomata, K.; Kotake, H.; Takagaki, H.; Yamazaki, K. *Chem. Lett.* **1986**, 1177. (c) Araki, S.; Sato, T.; Miyagawa, H.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3523. (d) Terao, S.; Kato, K.; Shiraishi, M.; Morimoto, H. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1101. (e) Terao, S.; Kato, K.; Shiraishi, M.; Morimoto, H. *J. Org. Chem.* **1979**, *44*, 868.

(8) Rüttimann, A.; Lorenz, P. *Helv. Chim. Acta* **1990**, *73*, 790. Van Lient, W. B. S.; Steggerda, W. F.; Esmeijer, R.; Lugtenburg, J. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 153.

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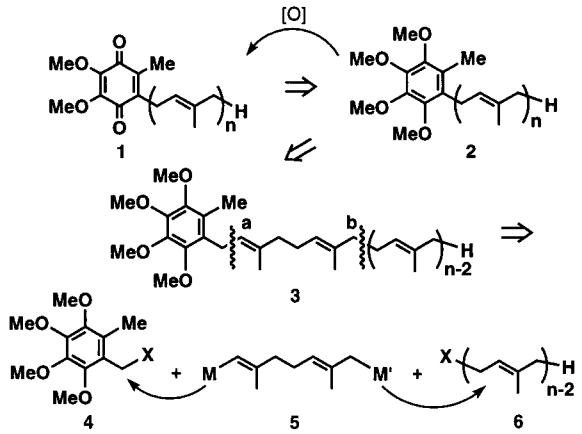
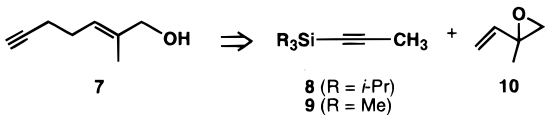
Scheme 1. Retrosynthetic Analysis: The "Linchpin" Approach



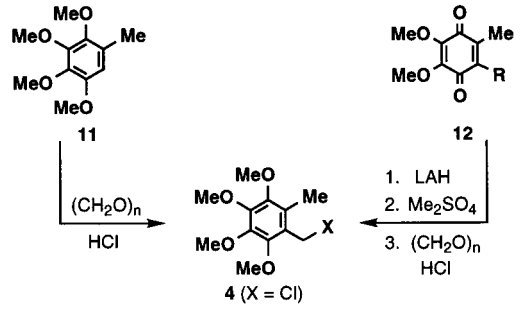
Scheme 2. The Components of Conjunctive Reagent **7**, the Precursor to **5**



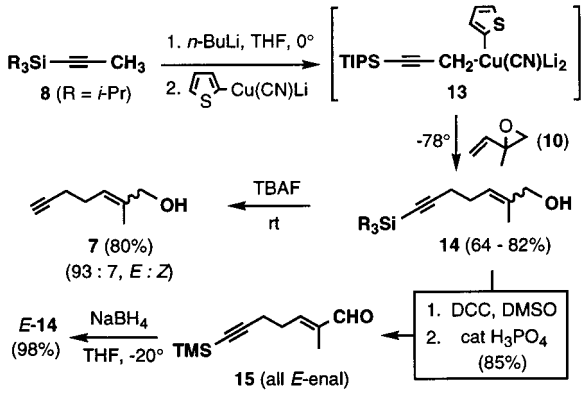
(bond "a" in **3**, Scheme 1) and an *E*-vinylic organometallic. This notion was viewed as particularly attractive in that a transition metal catalyzed cross-coupling to effect this bond formation is likely to retain stereointegrity and produce the required *E* geometry.[9] The remaining hydrocarbon tail could be factored further (bond "b") to include up to four prenyl units (**6**, $n = 3-6$) available in all-*E* form from commercial sources.[10] The conjunctive reagent between these segments becomes the hypothetical vinylic-allylic organometallic **5**, where M and M′ need not be the same and could be generated individually. This "linchpin" unit **5** simplifies to terminal alkyne **7** (Scheme 2), which should be realizable in one pot from coupling of propyne **8** or **9** in metalated form with isoprene oxide **10**. A standard Negishi carboalumination[11] would set the *E* configuration in the vinylalane generated from **7**, while inserting the required methyl appendage. Just which transition metal would best effect the coupling with benzylic halide **4** was not obvious at the outset, since a surprising dearth of precedent for the union of these specific partner types (i.e., a benzylic halide and a vinylalane) continues to this day.[12]

At the other end of linchpin **7**, the corresponding allylic chloride **6** (X = Cl) would be an ideal candidate for subsequent allyl-allyl coupling,[13] where prior art had shown that α,α′ attachments could be highly regioselective, if not regiospecific. This convergent scheme, if successful, would require relatively few steps, and following a known final oxidation to the quinone,[14] would lead to CoQ_n ($n \leq 6$). Higher prenylogues could be envisioned by elongation of **7** and/or geranylgeraniol.[15] In this, a full account of our work in the CoQ area, we detail the successful development and application of this highly convergent strategy, in particular to CoQ_{6-8} for which precursor side-chains are not commercially available.

Scheme 3. Preparation of Benzylic Fragment **4** (X = Cl)



Scheme 4 . First Generation Synthesis of Linchpin **7**, and Recycling of *Z*-**14** to all-*E*-**14**



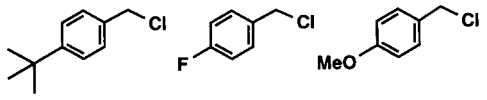
Results

1. Benzylic Fragment 4. Following the protocols delineated by Keinan,[16] pentasubstituted benzene **11** (Scheme 3) was secured, the chloromethylation[17] of which using paraformaldehyde and HCl afforded benzylic halide **4** (X = Cl) as a pale yellow oil. An alternative route was also developed starting with commercially available quinone **12** (R = H). Reduction with LAH in THF followed by di-O-methylation with dimethyl sulfate and then chloromethylation afforded **4** in 62−87% overall yield.

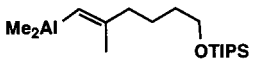
2. Conjunctive Reagent *E*-7. Initially, triisopropylsilylpropyne **8** was lithiated under modified Corey conditions[18a] and combined with our "cuprate in a bottle"[18b] to give mixed thienyl cuprate **13** (Scheme 4). Addition of neat, dry isoprene epoxide **10** afforded allylic alcohol **14** as a 93:7 mix of *E*:*Z* isomers.[19] Unfortunately, these could not be readily separated, and while exposure of the crude product to fluoride (TBAF) cleanly gave alcohols **7**, these too were not amenable to separation. By switching to the corresponding trimethylsilyl analogue **9**, epoxide opening was effected in 85% yield, and although the *E*:*Z* ratio was far worse (∼70:30), the isomers were easily separated by column chromatography leading to linchpin *E*-**7**

(9) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1994.
(10) Obtained from Kuraray Co., Ltd., Kurashiki City, Japan.
(11) Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252. Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639. Matsushita, H.; Negishi, E. *Org. Synth.* **1984**, *63*, 31. Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333.
(12) Negishi, E. I.; Matsushita, H.; Okukado, N. *Tetrahedron Lett.* **1981**, *22*, 2715.
(13) (a) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 8955; *ibid.* **1991**, *113*, 5893. Corey, E. J.; Shieh, W.-C. *Tetrahedron Lett.* **1992**, *33*, 6435. (b) Sato, K.; Inoue, S.; Onishi, A.; Uchida, N.; Minowa, N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 761.
(14) Masaki, Y.; Hasimoto, K.; Sakuma, K.; Kaji, K. *Chem. Pharm. Bull.* **1984**, *32*, 3952.
(15) Altman, I. J.; Ash, L.; Marson, S. *Synthesis* **1974**, 129.
(16) Keinan, E.; Eren, D. *J. Org. Chem.* **1987**, *52*, 3872.
(17) Shunk, C. H.; Wolf, D. E.; McPherson, J. F.; Linn, B. O.; Folkers, K. *J. Am. Chem. Soc.* **1960**, *82*, 5914.
(18) (a) Corey, E. J.; Rucker, C. *Tetrahedron Lett.* **1982**, *23*, 719. (b) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *ibid.* **1987**, *28*, 945. Lipshutz, B. H. In *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed., Wiley: 1994; pp 283−382.
(19) Cahiez, G.; Alexakis, A.; Normant, J. *Synthesis* **1978**, 528.

Table 1. Comparison of Pd(0)- and Ni(0)-Mediated Couplings of Benzyl Chlorides 18−20 with Vinylalane 21



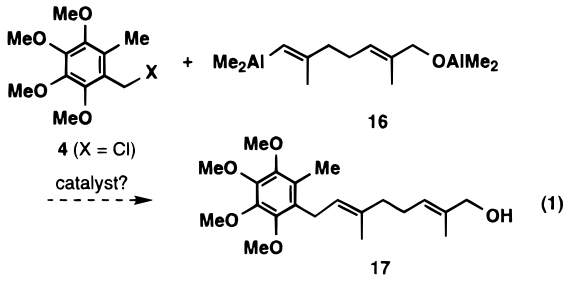
	18	19	20
cat Pd(0):	77	67	54
cat Ni(0):	91	92	84



21

of >98% isomeric purity. The *Z* isomer was converted to the all-*E* form by Moffatt oxidation to the corresponding *Z*-enal, acid-induced isomerization to the favored *E* form **15**, and $NaBH_4$ (heterogeneous in THF) reduction. Overall, the *Z*-**14**-to-*E*-**14** conversion was accomplished in 83% yield.

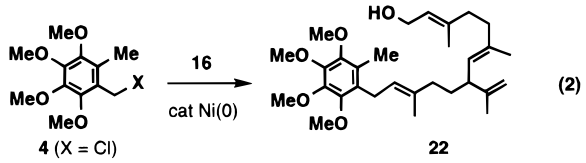
3. Couplings of Vinylalanes with Benzylic Halides. In anticipation of coupling fragment **4** (X = Cl) with the vinylalane derived from *E*-**7** (**16**, eq 1), guidance was sought from the



(1)

literature, specifically with respect to the selection of the transition metal catalyst. Surprisingly, only one report describing such a reaction was uncovered, employing a Pd(0) catalyst with benzyl chloride or bromide together with the vinylalane derived from octyne.[12] Since **4** and **16** are far more functionalized than the literature examples, a brief model study was undertaken using *p*-*tert*-butyl-, *p*-fluoro-, and *p*-methoxybenzyl chlorides (**18**−**20**, respectively; Table 1) together with the vinylalane derived from carboalumination of 1-hexynol TIPS ether, **21**. Following the Negishi recipe (cat $Pd(PPh_3)_4$, room temperature, THF),[12] yields ranged from 54 to 77%, signaling the potential for further inefficiency upon use of the highly substituted and electron-rich "real" educt **4**. Concern for the "yield problem" led us to consider entry into the unchartered domain of related couplings under Ni(0) catalysis, and it was here that considerable success was forthcoming. Starting with commercial $NiCl_2(PPh_3)_2$, reduction to nickel(0) was effected with 2 equiv of *n*-BuLi in THF at ambient temperatures,[20] to which was then initially added PPh_3 (2 equiv) to presumably form $Ni(PPh_3)_4$. This deep, blood-red−brown solution (10 mol %) was then added to a THF solution of each model chloride **18**−**20** containing model vinylalane **21**. Within minutes the desired products had formed and were subsequently isolated in excellent yields. In time, it was found that the additional 2 equiv of PPh_3 which had been added to $NiCl_2(PPh_3)_2$ were not necessary. A more extensive study, as previously reported,[21] lends credence to the generality of this useful aromatic allylation method. Importantly, included in this survey is highly electron-rich benzylic chloride **4**, which reacts with equal rapidity and efficiency (92%) when compared with the corresponding coupling using $Pd(PPh_3)_4$ (67%).

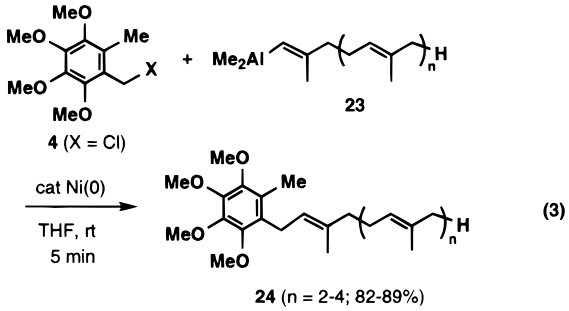
With a firm indication that catalytic Ni(0) should facilitate key bond construction between fragments **4** and **16** (eq 1), it came as a great disappointment to find that yields of coupling product **17** were routinely in the 5−20% category. In time, it was established that while the C−C bond of interest had in fact been made, the allylic aluminum alkoxide in **16** was susceptible to concomitant π-allylnickel formation and subsequent trapping by another equivalent of vinylalane to ultimately give **22** (eq 2). Just recently, the ease with which Ni(0) can cleave allylic



(2)

ethers has been described in terms of new hydroxyl-protecting group chemistry.[22]

4. An Alternative Strategy. Had the desired carbon−carbon bond in **17** been made cleanly, an allyl−allyl coupling was to be pursued, as delineated earlier (cf. Scheme 1, **5** + **6**). The order in which this sequence is carried out, however, does not impact the total number of operations. Thus, by first attaching *E*-**7** to a geranylgeranyl fragment as planned, the offending allylic alcohol would be removed and only a hydrocarbon remains to enter into the Ni(0)-induced coupling. The test of this alternative strategy came in the form of vinylalanes **23** (eq 3). Starting from the chlorides of geraniol, farnesol, and



(3)

geranylgeraniol (**6**, X = Cl, n = 4−6), each could be further elongated with lithiated TMS-propyne. Desilylation and finally carboalumination gave **23.** Coupling with **4** in now standard fashion afforded products **24**, the immediate precursors to CoQ_3, CoQ_4, and CoQ_5, in excellent yields in minutes at room temperature.

5. A Modified Allyl−Allyl Coupling. To arrive at the precursor of CoQ_6, conjunctive reagent *E*-**7** was originally slated for attachment to geranylgeraniol via its chloride derivative **25** (Scheme 5). While conversion of geranylgeraniol to its allylic chloride **26** was essentially quantitative,[23] the anticipated coupling with the corresponding allylbarium[13a] reagent **27** was unsuccessful in our hands. Thus, chloride **26** was converted to sulfone **29** via initial displacement with sulfinate **28** (Scheme 6).[13b] Lithiation, followed by introduction of chloride **25** led to a regio- and stereospecific α,α'-allyl−allyl coupling to give **30** in high isolated yield.[7e] The alternative combination of the anion

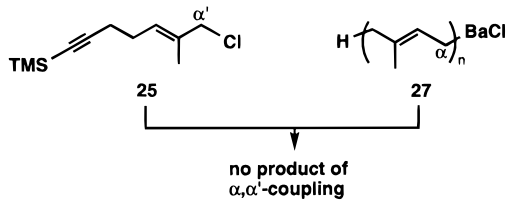
(20) Negishi, E.; Takahashi, T.; Akiyoshi, K. *J. Chem. Soc., Chem. Commun.* **1986**, 1338.

(21) Lipshutz, B. H.; Bulow, G.; Lowe, R.; Stevens, K. L. *J. Am. Chem. Soc.* **1996**, *118*, 5512.

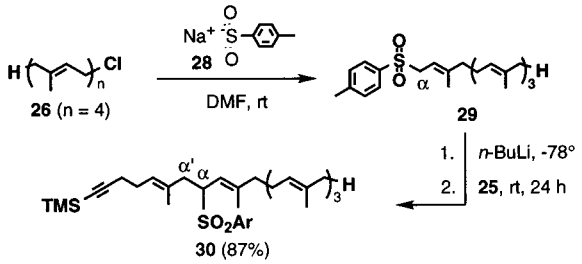
(22) Taniguchi, T.; Ogasawara, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 1136; *Tetrahedron Lett.* **1998**, *39*, 4679.

(23) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339.

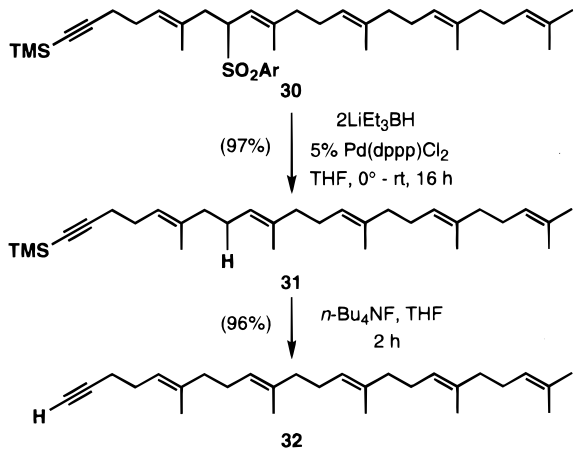
Scheme 5 . Attempted α,α′-Coupling of Chloride **25** with Allylbarium Intermediates **27**



Scheme 6. α,α′-Couplings of Allylic Sulfone **29** and Conjuctive Reagent **25**



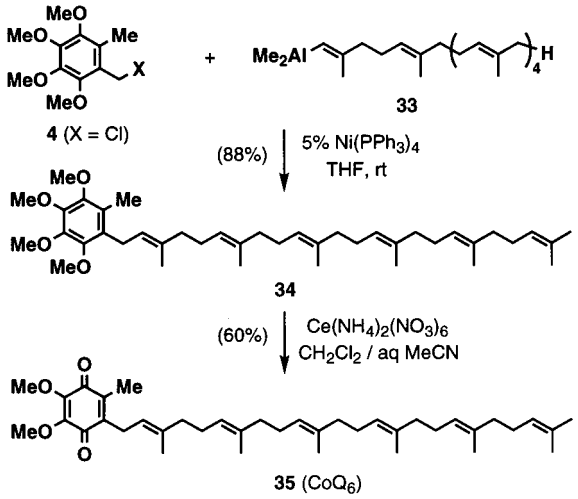
Scheme 7. Synthesis of the CoQ_6 Side-Chain **32**



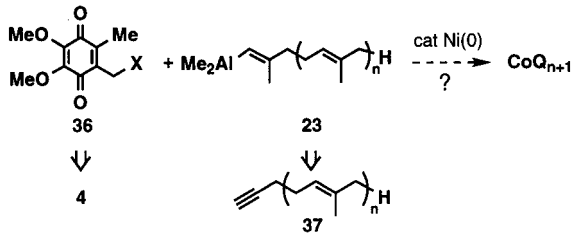
of the sulfone from **25**, and chloride **26**, was neither regio- nor stereospecific in their coupling. Stereospecific catalytic palladium(0) desulfonylation of allylic sulfone **30** to pentaenyne **31** with $LiEt_3BH$[24] followed by fluoride-based removal of TMS gave the CoQ_6 hydrocarbon side-chain precursor **32** in excellent overall yield (Scheme 7).

As anticipated, **32** could be carboaluminated to **33**, which readily participated in the Ni(0) coupling with **4** (X = Cl) to afford **34** in 88% yield (Scheme 8). The final oxidation to CoQ_6 (**35**), however, using ceric ammonium nitrate (CAN),[14] gave only a 60% yield of the ubiquinone. While the explanation for this modest outcome is not clear, the lack of efficiency with this step forced consideration of what in retrospect seems like an obvious question: Why not avoid the final oxidation altogether by using chloromethylated quinone **36** (X = Cl) directly, instead of benzylic chloride **4** (Scheme 9)? Given the limited precedent for benzylic couplings with vinylalanes,[12] it was not surprising that no such Ni(0) couplings of substrates akin to **36** with vinylalanes such as **23** (derived from polyenynes **37**) were known; in fact, chloromethylated quinone **36** (X = Cl) itself was not in the literature.[25]

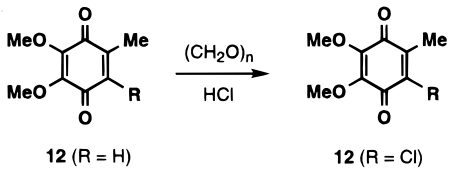
Scheme 8. Synthesis of CoQ_6



Scheme 9. A Direct Approach to CoQ using Chlormethylated Quinone **36** (X = Cl)



6. Couplings of Chloromethylated *p*-Quinones. Although this direct approach to CoQ looked enticing, it was not obvious that such an easily reduced *p*-quinone functional group would cooperate in the presence of Ni(0). That is, while likely that a Ni(II) intermediate prevails in the benzylic system,[26] a sensitive *p*-quinone might respond quite differently, for example, via an SET process should a Ni(I)−Ni(III) cycle be involved.[27] Fortunately, CAN oxidation of **4** took place, affording oily quinone **36** (X = Cl) albeit in modest isolated yields (55−72%). Attempts to chloromethylate quinone **12** (R = H) in the usual fashion (HCHO, HCl) were fruitless, the major product being the chlorinated quinone **12** (R = Cl; eq 4). Reactions in which



(4)

HCl was replaced by other acids (e.g., H_2SO_4) in hopes of forming the hydroxymethylated quinone were not successful.

Relative to their benzylic counterparts, quinones **36** are considerably more reactive toward vinylalanes under Ni(0) catalysis. It was gratifying to find that the chemistry proceeded rapidly and efficiently as desired. Representative couplings included the direct synthesis of plastoquinone-5 (**38**), racemic vitamin K_1 (**39**),[28] and a vitamin K_2 (menaquinone-3, **40**, Figure

(24) Mohri, M.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* **1985**, 451 and references therein.

(25) The corresponding bromomethylated *p*-benzoquinone has been prepared en route to vitamin K; cf. Rüttimann, A. *Chimia* **1986**, *40*, 290.

(26) Ascenso, J. R.; de C. T. Carrondo, M. A. A. F.; Dias, A. R.; Gomes, P. T.; Piedade, M. F. M.; Romao, C. C.; Revillon, A.; Tkatchenko, I. *Polyhedron* **1989**, *8*, 2449.

(27) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047. Morrell, D. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1975**, *97*, 7262. Tsou, T. T.; Kochi, J. K. *ibid.* **1979**, *101*, 6319.

(28) Lipshutz, B. H.; Kim, S.-K.; Stevens, K. L.; Mollard, P. *Tetrahedron* **1998**, *54*, 1241.

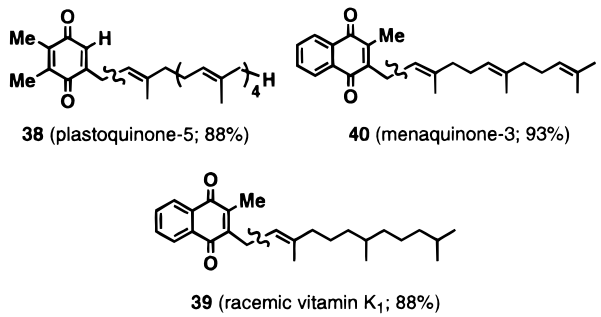


Figure 1. Naturally occurring quinones constructed using chloromethylated *p*-quinone precursors.

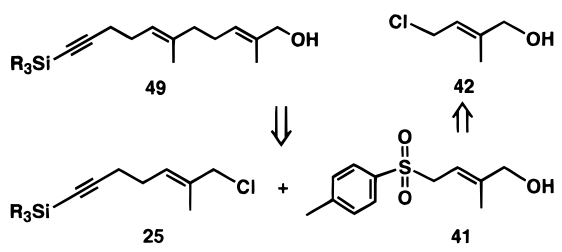
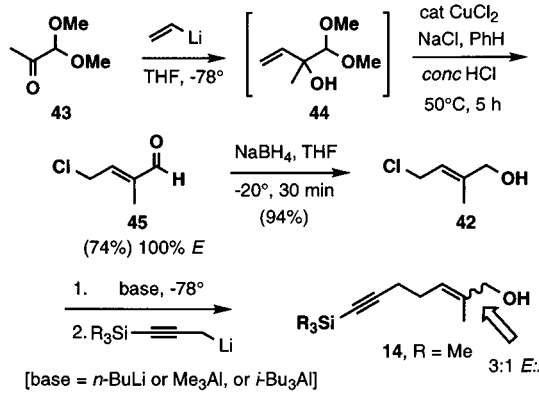


Figure 2.

Scheme 10. Preparation of Allylic Chloride **42**

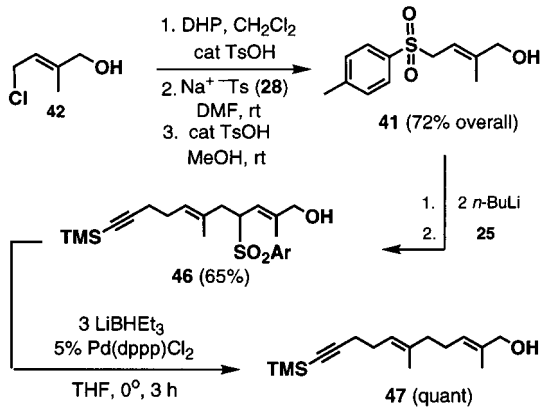


1).[28] Applying this approach to the CoQ_3−CoQ_6 series was rewarding, as couplings took place under mild conditions and in excellent isolated yields (81−93%) using ≤ 5 mol % Ni(0).

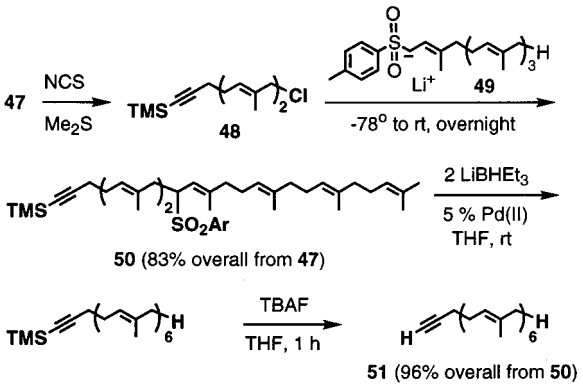
7. Coenzymes Q_7 and Q_8: Elongation of Both Conjunctive Reagent *E*-7 and Geranylgeraniol. On the basis of the original strategy illustrated in Scheme 1, dimetallo conjunctive reagent **5** (representing two prenyl units) and a polyprenoidal halide **6**, X = Cl (1−4 prenyl units) can be combined (along with either **4** or **36**, X = Cl) to afford CoQ_3 to CoQ_6. The higher homologues, however, require the prenylogue of each partner, with which both CoQ_7 and CoQ_8 could be readily synthesized.

Extension of electrophilic chloroenyne **25** to **49** (Figure 2) was based on its attachment to allylic sulfone **41** (in its dianion form). To arrive at the known precursor to **41**, namely *E*-chloro alcohol **42**,[29] glyoxal derivative **43** was treated with vinyllithium at −78° and the crude intermediate 1,2-adduct **44** exposed to catalytic $CuCl_2$ in warm concentrated HCl (Scheme 10). The resulting *E*-chloro aldehyde **45** was then reduced regiospecifically to target **42** with a heterogeneous mixture of $NaBH_4$ in THF at low temperature. Attempts to convert **42** to linchpin *E*-**14** via displacement with lithiated TMS-propyne on an alkoxide derivative (e.g., O−Li, O−$AlMe_2$, or O−Al(*i*-Bu)$_2$) did afford the desired material; however, NMR and GC analyses revealed that the all-*E* stereochemistry in **42** had been compromised, as a 75:25 *E:Z* mix of **14** was obtained. Just how this nontransition metal-based displacement causes the isomerization is unclear.

Scheme 11. Prenylogation of Chloroenyne **25** (R = Me) to **47**



Scheme 12. Synthesis of CoQ_7 Polyenyne Side-Chain **51**



From chloro alcohol **42**, standard THP protection followed by sulfinate displacement with **28** and hydrolysis affords sulfone **41** in good overall yield (Scheme 11). Direct use of **42** in the substitution reaction with **28** did not lead to clean product formation, forcing temporary masking of the hydroxyl moiety. With both **25** and **41** in hand, S_N2 displacement by the dianion of **41** gave the α,α′-coupling product **46** (Ar = C_6H_4-Me-*p*) in 65% yield. Palladium(0)-mediated desulfonylation[16,24] led very efficiently to the new three prenyl unit equivalent **47**. To arrive at the hydrocarbon side-chain needed for CoQ_7, **47** need only be manipulated as seen previously en route to CoQ_6. Thus, chlorination to **48** sets up the α,α′-coupling with anion **49** to efficiently afford **50** (Scheme 12). Desulfonylation and desilylation leads to **51** in 80% overall yield for these four steps.

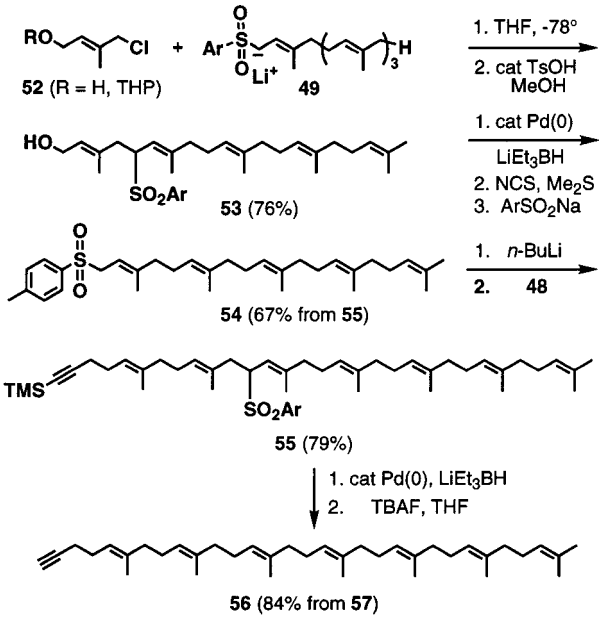
Synthesis of the CoQ_8 side-chain requires prenylation of geranylgeraniol, followed by attachment of this five prenyl unit to conjunctive reagent **48**. Toward this end, known allylic chloride **52** (R = H),[30] as its THP derivative, was coupled with lithio anion **49** to give **53** after THP removal (Scheme 13). Following desulfonylation, alcohol-to-chloride conversion, and aryl sulfone generation, lithiation of resulting sulfone **54** gives a reactive species toward coupling with linchpin **48** to arrive at **55**. Desulfonylation and finally, fluoride treatment, produces all-*E*-polyenyne **56**.

With **51** and **56** now available, the syntheses of CoQ_7 and CoQ_8 are straightforward (Scheme 14). Both **57** and **58** can be formed in excellent yields according to our standard sequence

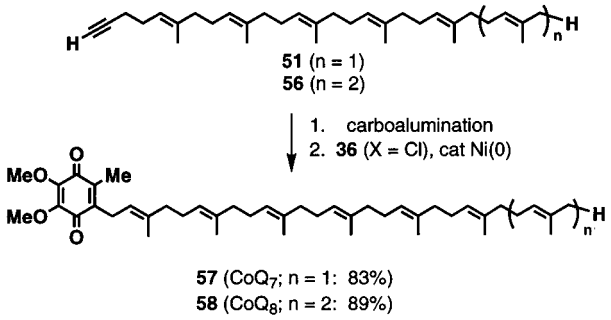
(29) Miyakado, M.; Ohno, N.; Yoshioka, H.; Mabry, T. *Phytochemistry* **1978**, *17*, 143.

(30) Schmid, M.; Gerber, F.; Hirth, G. *Helv. Chim. Acta* **1982**, *65*, 684.

Scheme 13. Preparation of the CoQ_8 Precursor, Polyenyne **56**



Scheme 14. Syntheses of CoQ_7 (**57**) and CoQ_8 (**58**)



of carboalumination and then Ni(0)-catalyzed coupling with quinone **36** (X = Cl).

Discussion

Ni(0) vs Pd(0): Rates, Yields, Cost. While few would argue with the phenomenal success of Pd(0)-catalyzed carbon−carbon bond constructions,[31] it is not by any means a given that this noble metal is preferred among the group 10 triad for all synthetic situations. Indeed, organonickel chemistry continues to assume its place among synthetically useful metals,[32] oftentimes displaying a superior reaction profile. The Ni(0)-mediated cross-couplings described herein between a vinylalane and a benzylic chloride or chloromethylated *p*-quinone represent one case in point. Rates for these couplings, and efficiencies, are greater using Ni(0), while the differential in cost hardly requires comment. To make the process still more attractive, it should be noted that only two phosphines are needed per nickel, as commercially available $NiCl_2 \cdot 2PPh_3$ can be reduced directly. Moreover, it is also our finding that a Ni(0) catalyst can be derived from the components of this Ni(II) complex; that is, by simply mixing $NiCl_2$ with 2 equiv of PPh_3 followed by reduction, the cost of this catalyst precursor drops below $0.30/g. Given that nickel is about half the molecular weight of palladium, another bonus is realized when comparisons are made in cost on a per gram basis.

How Much Ni(0) Is Needed? Originally, couplings of a model vinylalane with a benzylic chloride were effected using 10 mol % Ni(0). Reducing the amount of Ni(0) to 5% gave identical yields, and hence a quick study was conducted to assess catalyst turnover. In fact, no change in yield was noted even at the 0.5 mol % level. Reactions employing lesser quantities were not pursued. While levels this low have been applied to the synthesis of vitamin K_1,[21] most of the couplings en route to CoQ, however, were performed using 2−5 mol % catalyst. This decision was based partly on convenience, but also because of the potential sensitivity of the products toward somewhat longer reaction times which are required as the complexity of the target CoQ increases.

Sulfone-Based α,α′-Couplings. Use of the sulfone moiety[13b] as a control element for the syntheses of polyprenoidal derivatives and their attachment to 2- and 3-unit linchpins allows for facile scale-up of this chemistry beyond the 0.5−1 mmol level used in this work. And while most of the reactions involved in the sequence are high-yielding, it remains unfortunate that the sulfone group is needed at all. Had the allylbarium[13a] route materialized as originally anticipated, the "on" (i.e., sulfonation; **26** + **28**) and "off" (i.e., desulfonylation, with cat Pd(0) + $LiEt_3BH$) steps associated with the elongation of conjunctive reagent **25** or geranylgeraniol would have been eliminated, further streamlining this convergent approach. Nonetheless, the sequence established offers many virtues including brevity and overall efficiency.

Side-Chain Stereochemical Issues. Synthesis of the all-*E* CoQ_n side-chain requires strict maintanence of this key stereochemical feature in each of the C−C bond-forming steps involved. Given that all-*E*-geranylgeraniol is commercially available,[10] confirmation of its stereohomogeneity was readily achieved by analysis using ^{1}H NMR and capillary GCMS, in tandem with literature data.[33] Its elongation to the corresponding all-*E* pentaprenoidal homolog, which relied on the α,α′-coupling of sulfone **29** with allylic chloride **52**, R = THP (Scheme 13), gave the expected all-*E* sulfone **53**. Importantly, **53** was stereochemically unaffected by hydride reduction of its transient π-allylpalladium complex, giving only the desired *E*-olefin geometry, as expected.[16] Likewise, newly derived sulfone **54** ultimately afforded **56**. That the elongation of chloroenyne **25** was based on a similar sulfone coupling (Scheme 11) to arrive at dienyne **47** is attractive in that identical reagents, and essentially identical conditions, can be applied to achieve the desired stereochemical outcome.

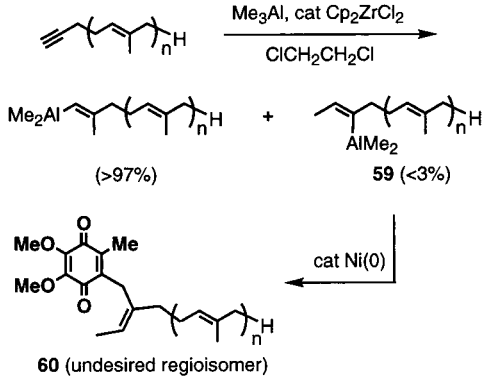
The coupling between polyenynes **37** and either benzylic chloride **4** or chloromethylated *p*-quinone **36** to arrive at *E*-allylated products depends heavily upon the quality of the carboalumination step. A quick study of this inveterate process,[12] conducting the zirconocene-catalyzed vinylalane formation at various temperatures between −50° and room temperature in 1,2-dichloroethane, revealed a modest variation in regiochemistry of Me_3Al addition across the 1-alkyne. Using 1-octyne as a model and adding 1.5 equiv Me_3Al and 0.25 equiv Cp_2ZrCl_2, the external-to-internal ratio of proton-quenched products could be varied from 16 to 33:1, with complete consumption of educt. Fortunately, irrespective of temperature, only *cis* addition occurs. The minor intermediate, which bears the Me_2Al moiety at the internal site (**59**, Scheme 15), is less reactive in subsequent Ni(0)-catalyzed couplings with benzylic substrates such as **4**

(31) Tsuji, J. *Palladium Reagents and Catalysis*; John Wiley and Sons Ltd.: Chichester, 1995.

(32) New Developments in Organonickel Chemistry. Lipshutz, B. H., Luh, T.-Y., Eds.; *Tetrahedron Symposium-in-Print* **1998**, *54*, 1021−1316.

(33) Eis, K.; Schmalz, H.-G. *Synthesis* **1997**, 202. Altman, L. J.; Ash, L.; Marson, S. *ibid*. **1974**, 129.

Scheme 15. Regiochemistry of Carboalumination of CoQ Side-Chain Precursors



(X = Cl). However, in couplings involving the more reactive chloromethylated quinone **36** (X = Cl), both regioisomers react. This observation is manifested in the HPLC analyses of $CoQ_{6,7}$, where 2−3% of the internal vinylalane-derived isomers **60** can be preparatively separated and unequivocally identified by NMR and HRMS data. Recrystallization, for example in the case of CoQ_6, readily removes the undesired oily regioisomer to afford the corresponding all-*E* coenzyme of >99% purity.[34]

The Denoument: New Chemistry. There have been several outgrowths from this adventure in total synthesis of the ubiquinones. Chief among these is the observation that allylated aromatics,[19] including heteroaromatics,[35] of defined *E* stereochemistry can be cleanly generated via the intermediacy of vinylalanes or vinylzirconocenes and chloromethylated aromatic rings as reaction partners. As pointed out many years ago by Kumada regarding aryl halides,[36] and substantiated herein, chloride is the preferred leaving group in these Ni(0)-induced couplings. And while it appears that very little of an inexpensive yet highly reactive catalyst suffices, adding further to the attractiveness of this methodology would be an effective Ni(0) source on a solid support; e.g., the species "nickel-on-charcoal" (Ni/C), such that virtually no waste or potential toxicity issue could arise. Such a catalyst now looks well within our grasp,[37] and its potential for mediating CoQ syntheses is under investigation.

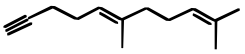
Summary and Conclusions

This study has led to a economically viable route for preparing several of the ubiquinones, especially those which are extremely expensive (CoQ_{6-8}). It takes advantage of two unique disconnections of the target coenzymes, and proceeds via a strictly convergent path using novel conjunctive reagents **25** and **48** as points of attachment for an all-*E* polyprenoidal side chain followed by a key connection to a newly constructed chloromethylated *p*-quinone nucleus.[38] Highlighted is the use of Ni(0)-catalyzed cross-couplings, which showcase nickel as the transition metal of choice in terms of reaction efficiency, rates of couplings, minimization of phosphine, and catalyst expense.

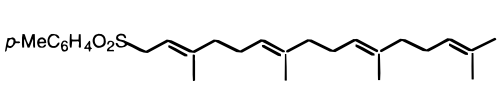
Finally, the focus in this series now shifts back to CoQ_{10}, for its importance as a dietary supplement originally championed by Folkers[1b−d] should not be overlooked. Whether valued as an antioxidant, or as a means of enhancing respiration, metabolism, heart strength, or the immune system, this "miracle nutrient"[2] is attracting increasing attention from the medical community, and may in time be fully recognized as an integral part of our daily nutritional needs. In this regard, Ni(0) catalysis as a means of preparing this neutraceutical synthetically on an industrial scale may figure prominently in the future. Such a process which is economically viable is under development and will be reported in due course.

Experimental Section

Chemicals. 1-Trimethylsilylpropyne is available from Hüls Petrarch. Prenyl alcohol, as well as *E*-geraniol, all-*E*-farnesol, and geranylgeraniol, were obtained from Kuraray Co., in Japan. Zirconocene dichloride was acquired from Boulder Scientific. Sabinsa Corporation supplied both CoQ_0 and solanesol. All other chemicals, including $POCl_3$, $NiCl_2(PPh_3)_2$, $Pd(dppp)Cl_2$, $AlMe_3$, *n*-butyllithium, $LiEt_3BH$, dimethyl sulfate, *N*-chlorosuccinimide, SuperHydride, dihydropyran, 1,2-dichloroethane, TBAF, $ZnCl_2$, 2-methyl-2-vinyloxirane, DCC, 2,3-dimethyl-1,4-hydroquinone, were obtained from commercial sources.



Representative Alkylation of TMS-Propyne; (*E*)-6,10-Dimethylundeca-5,9-diene-1-yne (37, *n* = 2). 1-Trimethylsilylpropyne **9** (3.58 g, 24.2 mmol) was metalated by addition of *n*-BuLi (13.6 mL, 1.69 M in hexanes, 23 mmol) to 64 mL of THF at −78 °C followed by slow addition of the alkyne. After 20 min the reaction was warmed to −20 °C for 20 min prior to recooling to −78 °C. Geranyl chloride (2.28 g, 13.6 mmol) in 15 mL of THF was added slowly to the metalated 1-trimethylsilylpropyne over 5 min and the reaction allowed to stir for 2 h at −78 °C. The reaction was quenched by addition of 40 mL of brine at −78 °C and then warming to room temperature. The layers were separated and the aqueous layer extracted with diethyl ether (3 × 10 mL) and concentrated in vacuo. The residue was taken up in 25 mL of hexanes, dried (anhydrous $MgSO_4$) and concentrated in vacuo. The yellow oil was dissolved in 77 mL of dry EtOH to which anhydrous K_2CO_3 (2.46 g, 17 mmol) was added. After 48 h at room temperature, the reaction mixture was added to 40 mL brine, extracted with hexanes (3 × 40 mL) and the combined organic layers concentrated *in vacuo*. Chromatography of the residue on silica gel (100% petroleum ether), repeated due to poor separation, afforded 1.05 g of a clear oil (44%) after the second chromatography; R_f = 0.39 (petroleum ether); IR 3310, 2967, 2920, 2856, 1668, 1446, 1376, 1108, 835, 631; ^{1}H NMR (400 MHz) δ 5.16 (m, 1H), 5.07 (m, 1H), 2.22−2.15 (m, 4H), 2.06−2.02 (m, 2H), 1.97 (t, 3H), 1.92 (t, J = 2.8 Hz, 1 H), 1.66 (s, 3 H), 1.59 (s, 3 H), 1.58 (s, 3H);^{13}C NMR (100 MHz) δ 136.7, 131.4, 124.2, 122.4, 85.5, 68.0, 39.6, 27.2, 26.6, 25.7, 18.9, 17.7, 16.1; LREIMS *m*/*z* 176(M^+, 2), 161(13), 133(17), 119(6), 105(14), 93(13), 91(36), 81(9), 79(18), 77(13), 69(100), 67(14), 53(13); HRCIMS *m*/*z* calcd for $C_{13}H_{19}$, $(M + H)^+$ 175.1487; found 175.1484.



(*E*,*E*,*E*)-(*p*-Toluenesulfonyl)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-yne (29).[13b] R_f = 0.48 (25% EtOAc/petroleum ether); ^{1}H NMR (500 MHz) δ 7.71 (d, J = 8 Hz, 2H), 7.29 (d, J = 8 Hz, 2H), 5.16 (t, J = 8 Hz, 1H), 5.09−5.02 (m, 3H), 3.76 (d, J = 8 Hz, 2H), 2.42 (s, 3H), 2.06−1.95 (m, 12 H), 1.65 (s, 3H), 1.57 (s, 6H), 1.56 (s,

(34) To further confirm that the isomer present derives from the carboalumination step, all-*E* solanesol was converted to its chloride and elongated via coupling with lithiated TMS-propyne. Removal of the TMS moiety afforded the C_{48} hydrocarbon which was then subjected to carboalumination and then Ni-catalyzed coupling with chloromethylated quinone **36** (X = Cl). Analysis of the resulting CoQ_{10} by HPLC revealed the presence of the same 2−3% of a regioisomer.

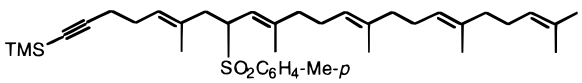
(35) Lipshutz, B. H.; Kim, S.-K.; Mollard, P.; Stevens, K. L. *Tetrahedron* **1998**, *54*, 6999.

(36) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *7*, 1958. Tamao, K.; Kumada, M. In *The Chemistry of the Metal−Carbon Bond*; Hartley, F. R., Ed.; John Wiley: New York, 1987; Vol. 4, p 820.

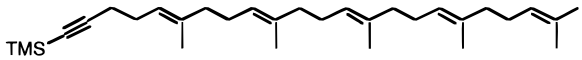
(37) Lipshutz, B. H.; Blomgren, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 5819.

(38) The corresponding *bromo*methylated *p*-quinone (**36**, X = Br) is known; cf. Niiro, Y.; Ueda, H.; Satoh, T.; Matsumoto, H. Japanese Patent WO 95-JP1621 950814.

3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz) δ 146.2, 144.4, 135.9, 135.7, 135.0, 131.2, 129.5, 128.5, 127.3, 124.1, 123.4, 110.5, 56.1, 39.7, 26.8, 26.6, 26.2, 25.7, 21.6, 17.7, 16.2, 16.0; LREIMS *m*/*z* 428(M^+, 2%), 157(13), 69(10); HREIMS *m*/*z* calcd for $C_{27}H_{40}O_2S$, M^+ 428.2749, found 428.2758.

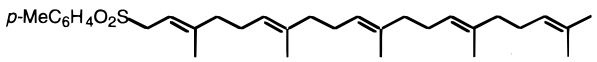


Representative Alkylation of an Allylic Sulfone; (*E*,*E*,*E*,*E*)-6,10,14,18,22-Pentamethyl-8-(*p*-toluenesulfonyl)-1-trimethylsilyltricosa-5,9,13,17,21-pentaen-1-yne (30). *n*-BuLi (4.20 mL of a 2.4 M solution in hexanes, 10.0 mmol) was added dropwise to a solution of geranylgeranyl sulfone **29** (4.28 g, 10.0 mmol) in dry THF (40 mL) at −78 °C. The mixture was stirred at this temperature for 45 min. A solution of allylic chloride **25** (2.11 g, 9.83 mmol) in dry THF (15 mL) was pre-cooled to −78 °C and added dropwise via dry ice-cooled cannula over 5−10 min. The reaction mixture was stirred for 30 min at this temperature, allowed to warm to room temperature, and then stirred for a further 3 h, after which time TLC indicated complete disappearance of the starting material. The mixture was quenched at 0 °C with saturated aqueous ammonium chloride and extracted with Et_2O. The organic layer was washed with water and brine, dried (anhydrous $MgSO_4$), and evaporated in vacuo. Silica gel column chromatography (10% EtOAc/petroleum ether) afforded the coupled sulfone (5.45 g, 90%); R_f = 0.57 (10% EtOAc/petroleum ether); IR 2969, 2921, 2860, 2174, 1446, 1313, 1302, 1250, 1145, 1087, 912, 843, 734, 665; ^{1}H NMR (500 MHz) δ 7.71 (d, J = 8 Hz, 2H), 7.29 (d, J = 8 Hz, 2H), 5.19−5.15 (m, 1H), 5.11−5.08 (m, 2H), 5.05−5.04 (m, 1H), 4.89 (d, J = 10 Hz, 1H), 3.86 (dt, J = 11.5 Hz, J = 3.5 Hz, 1H), 2.87 (d, J = 11.5 Hz, 1H), 2.43 (s, 3 H), 2.26 (dd, J = 13 Hz, J = 11 Hz, 1H), 2.16−2.15 (m, 4H), 2.08−2.04 (m, 4H), 1.99−1.93 (m, 8H), 1.68 (d, J = 1 Hz, 3H), 1.60 (s, 6H), 1.59 (d, J = 1 Hz, 3H), 1.54 (s, 3H), 1.21 (d, J = 1.5 Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (100 MHz) δ 144.9, 144.1, 135.5, 135.0, 134.9, 131.5, 131.1, 129.2, 129.2, 126.4, 124.3, 124.0, 123.4, 117.2, 106.8, 84.4, 63.4, 39.7, 39.6, 37.4, 27.4, 26.7, 26.5, 26.3, 25.6, 21.5, 20.0, 16.4, 16.0, 15.9, 0.1; LREIMS *m*/*z* 606(M^+, 5%), 451(M^+ − SO_2Ar, 100), 377($C_{28}H_{41}^+$, 29); HREIMS *m*/*z* calcd for $C_{38}H_{58}SO_2Si$, M^+ 606.3927, found 606.3928.

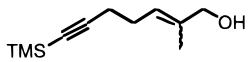


Representative Palladium-Catalyzed Desulfonylation; (*E*,*E*,*E*,*E*)-6,10,14,18,22-Pentamethyl-1-trimethylsilyltricosa-5,9,13,17,21-pentaen-1-yne (31). A mixture of sulfone **30** (2.62 g, 4.32 mmol) and $Pd(dppp)Cl_2$ (0.127 g, 0.216 mmol) in dry THF (30 mL) was cooled to 0 °C. $LiEt_3BH$ (8.46 mL, 1 M solution in THF, 8.36 mmol) was added dropwise over 10 min, whereupon the solution became clear and brown. The mixture was allowed to warm to room temperature over 3 h and then stirred for a further 6 h, after which time a brown precipitate had formed. TLC indicated complete disappearance of the starting material. NaOH (40 mL of a 3 M aqueous solution) was added and the mixture was stirred for 45 min before being poured into saturated aqueous KCN. The mixture was extracted with Et_2O (3×) and the organic layers combined and washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. Silica gel chromatography (5% EtOAc/petroleum ether) afforded the alkyne (1.89 g, 97%); R_f = 0.24 (petroleum ether); IR 2963, 2920, 2855, 2175, 1447, 1383, 1249, 842, 760; ^{1}H NMR (500 MHz) δ 5.17−5.14 (m, 1H), 5.30−5.08 (m, 4H), 2.23−2.22 (m, 4H), 2.09−2.04 (m, 8H), 2.01−1.97 (m, 8H), 1.68 (s, 3H), 1.62 (s, J = 1.5 Hz, 3H), 1.60 (s, 12H), 0.14 (s, 9H); ^{13}C NMR (125 MHz) δ 136.6, 135.0, 134.9, 134.8, 131.2, 124.4, 124.3, 124.2, 124.1, 122.5, 107.4, 84.2, 39.7, 39.7, 39.7, 27.4, 26.8, 26.7, 26.7, 26.6, 25.7, 20.3, 17.7, 16.2, 16.0, 16.0, 0.1; LREIMS *m*/*z* 452(M^+, 1%), 73(70), 69(100); HREIMS *m*/*z* calcd for $C_{31}H_{52}Si$, M^+ 452.3838, found 452.3840.

Representative Desilylation of an Acetylenic Silane; (*E*,*E*,*E*,*E*)-6,10,14,18,22-Pentamethyltricosa-5,9,13,17,21-pentaen-1-yne (32). TBAF (18.75 mL of a 1 M solution in THF, 18.75 mmol) was added dropwise to a solution of TMS-protected alkyne **31** (5.67 g, 12.5 mmol) in THF (40 mL) at 0 °C. The mixture was stirred for 30 min and then poured into ice-cold water and extracted with Et_2O (3×). The combined organic layer was washed with water and brine, dried (anhydrous $MgSO_4$), and evaporated in vacuo. Silica gel column chromatography of the residue (3% EtOAc/petroleum ether) afforded the alkyne (4.58 g, 96%) as a pale yellow oil; R_f = 0.23 (hexanes); IR 3312, 2965, 2922, 2849, 2114, 1446, 1383, 838; ^{1}H NMR (500 MHz) δ 5.19−5.17 (m, 1H), 5.13−5.08 (m, 4H), 2.25−2.18 (m, 4H), 2.11−2.04 (m, 8H), 2.02−1.97 (m, 8H), 1.94 (t, J = 2.5 Hz, 1H), 1.68 (d, J = 1.5 Hz, 3H), 1.62 (s, 3H), 1.60 (s, 12H); ^{13}C NMR (125 MHz) δ 136.7, 135.0, 134.8, 134.8, 131.2, 124.4, 124.2, 124.0, 122.4, 84.5, 68.1, 39.7, 39.6, 27.2, 26.7, 26.7, 26.6, 26.5, 25.7, 18.9, 17.6, 16.1, 16.0, 16.0, 16.0; HREIMS *m*/*z* calcd for $C_{28}H_{44}$, M^+ 380.3443, found 380.3442.

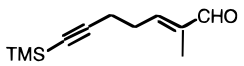


(*E*,*E*,*E*,*E*)-3,7,11,15,19-Pentamethyl-1-(*p*-toluenesulfonyl)eicosa-2,6,10,14,18-pentaene (54). Dimethyl sulfide (0.3 mL, 254 mg, 4.08 mmol) was added dropwise to a solution of *N*-chlorosuccinimide (187 mg, 1.40 mmol) in dry CH_2Cl_2 (7 mL) at 0 °C and the resulting white suspension cooled to −20 °C. A solution of the allylic alcohol prepared from reduction of **53** (200 mg, 0.56 mmol) in dry CH_2Cl_2 (3 mL) previously cooled to 0 °C, was added via cannula. The mixture was warmed to 0 °C and stirred 1.5 h after which TLC showed complete disappearance of the starting material. The mixture was poured onto ice-cold brine and extracted with CH_2Cl_2 (3×), and the collected organic phases were washed (ice-cold brine), dried (anhydrous $MgSO_4$), and evaporated in vacuo. The residue was mixed with sodium *p*-toluenesulfinate (500 mg, 2.81 mmol) and DMF (10 mL) and stirred overnight. The suspension was poured into water and extracted with EtOAc (3×). The combined organic phases were washed (water, brine), dried (anhydrous $MgSO_4$), and evaporated in vacuo. Silica gel chromatography of the residue (10% EtOAc/petroleum ether) afforded the sulfone (225 mg, 81%); R_f = 0.84 (20% EtOAc/petroleum ether); R_f = 0.35 (10% EtOAc/petroleum ether); R_f = 0.13 (5% EtOAc/petroleum ether); IR 2965, 2921, 2854, 1664, 1598, 1447, 1382, 1317, 1236, 1150, 1087, 899, 816, 745, 666; ^{1}H NMR (400 MHz) δ 7.73, 7.32 (AA′XX′, 4H), 5.18 (tq, J = 8 Hz, J = 1 Hz, 1H), 5.15−5.00 (m, 4H), 3.78 (d, J = 8 Hz, 2H), 2.44 (s, 3H), 2.10−1.95 (m, 16H), 1.67 (d, J = 1 Hz, 3H), 1.59, 1.58 (2xbr, 12H), 1.32 (d, J = 1 Hz, 3H); ^{13}C NMR (100 MHz) δ 146.1, 144.3, 135.8, 135.6, 134.9, 134.8, 131.1, 129.5, 128.5, 124.3, 124.2, 124.0, 123.3, 110.4, 56.1, 39.6, 26.7, 26.6, 26.1, 25.6, 21.6, 21.5, 17.6, 16.2, 15.9; LREIMS *m*/*z* 496(M^+, 0.88), 427(3), 217(2), 203(7), 157(16), 135(30), 81(65), 69(100); HREIMS *m*/*z* calcd for $C_{32}H_{48}O_2S$, M^+ 496.3375; found 496.3370.

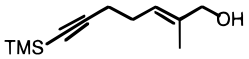


***E*- and *Z*-2-Methyl-7-trimethylsilyl-2-buten-6-yn-1-ol (14, R = TMS).** *n*-BuLi (14.7 mL, 2.45 M in hexanes, 36 mmol) was added dropwise to dry THF (30 mL) at −78 °C. After a few minutes, this mixture was added via a dry ice-cooled cannula to a solution of 1-trimethylsilylpropyne **9** (5.9 mL, 40 mmol) in dry THF (30 mL) at −78 °C. The mixture was stirred for 1 h at this temperature and then for 30 min at −20 °C before being re-cooled to −78 °C. Zinc chloride (36 mL, 0.5 M in THF, 18 mmol) was added dropwise, and the mixture was warmed to 0 °C and allowed to stir for 30 min before being cooled to −78 °C. A solution of CuCN (1.62 g, 18 mmol) and LiCl (1.53 g, 36 mmol) in dry THF (30 mL) was then added dropwise via cannula over 10 min. The cooling bath was removed, and the mixture was allowed to warm to 0 °C and stir further for 20 min at that temperature. A solution of 2-methyl-2-vinyloxirane (1.77 mL, 18 mmol) in THF (10 mL), cooled to 0 °C, was added via cannula over 10 min and the mixture stirred for a further 3 h. The reaction was quenched with saturated aqueous ammonium chloride and then extracted with Et_2O

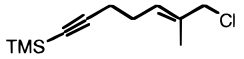
(3×). The organic layers were washed with water and brine, dried (anhydrous $MgSO_4$), and evaporated in vacuo to afford a 71:29 mixture of *E* and *Z* isomers as determined by GC. The isomers were separated by silica gel chromatography (30% EtOAc/petroleum ether, two separations) to afford the desired *E* isomer (1.68 g, 48%) which was >99% isomerically pure. The overall yield of the mixture was determined to be 3.05 g (87%); ***E*-isomer:** R_f = 0.55 (25% EtOAc/petroleum ether); IR 3327, 2956, 2915, 2858, 2171, 1427, 1251, 1043, 1007, 840, 894, 758; ^{1}H NMR (500 MHz) δ 5.48−5.42 (m, 1 H), 4.02 (s, 2 H), 2.27 (m, 4 H), 1.69 (s, 3 H), 0.14 (s, 9 H); ^{13}C NMR (125 MHz) δ 136.2, 123.9, 106.9, 84.6, 68.5, 26.9, 20.0, 13.7, 0.0; LREIMS *m*/*z* 181(M^+, 9), 165(7), 163(7), 135(10), 109(7), 105(9), 96(10), 91(27), 84(21), 75(100), 73(97), 55(17); HREIMS *m*/*z* calcd for $C_{10}H_{17}OSi$, M^+ 181.1049; found 181.1047; ***Z* isomer**: R_f = 0.63 (25%. EtOAc/petroleum ether), ^{1}H NMR (500 MHz) δ 5.31−5.29 (m, 1 H), 4.10 (s, 2 H), 2.28−2.26 (m, 4 H), 1.83 (s, 3 H), 0.13, (s, 9 H); ^{13}C NMR (125 MHz) δ 136.6, 126.2, 107.4, 85.1, 61.33, 26.7, 21.6, 20.4, 0.1.



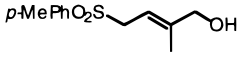
***E*-2-Methyl-7-trimethylsilyl-2-buten-6-yn-1-al (15).** To *Z*-2-methyl-7-trimethylsilyl-2-buten-6-yn-1-ol ***Z*-14** (79 mg, 0.40 mmol) and DCC (293 mg, 1.42 mmol) dissolved in benzene (3 mL) were added DMSO (3 mL) and 85% phosphoric acid (35 mL, 59 mg, 0.51 mmol). After 135 h the reaction was poured onto ice, extracted with petroleum ether (3×), and the combined organic phases were washed (water and brine), dried (anhydrous $MgSO_4$), and evaporated in vacuo. Silica gel chromatography of the residue (5% EtOAc/petroleum ether) yielded 69 mg of the desired 100% *E*-2-methyl-7-trimethylsilyl-2-buten-6-yn-1-al (88%); R_f = 0.48 (5% EtOAc/petroleum ether); R_f = 0.71 (10% EtOAc/petroleum ether); IR 2960, 2176, 1691, 1251, 1042, 844, 760; ^{1}H NMR (400 MHz) δ 6.52 (tq, J = 7 Hz, J = 1 Hz, 1H), 2.56 (q, J = 7 Hz, 2H), 2.43 (t, J = 7 Hz, 2 H), 1.76 (m, 3H), 0.13 (s, 9H); ^{13}C NMR (100 MHz) δ 195.1, 151.8, 140.3, 105.2, 85.8, 27.9, 18.9, 9.3, 0.0; LREIMS *m*/*z* 194(M^+, 1), 193(3), 179(57), 161(10), 149(13), 135-(20), 109(32), 105(50), 75(100).



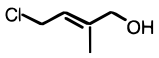
***E*-2-Methyl-7-trimethylsilyl-2-hepten-6-yn-1-ol (*E*-14).** All *E*-2-methyl-7-trimethylsilyl-2-buten-6-yn-1-al ***E*-15** (69 mg, 0.35 mmol) was dissolved in THF (4 mL), cooled to −20 °C and $NaBH_4$ (17 mg, 0.45 mmol) added. After 1 h, 10% HCl was added and the mixture extracted with diethyl ether. The combined organic phases were washed (water, brine), dried (anhydrous $MgSO_4$), and evaporated in vacuo to afford 67 mg (96%) of 100% *E*-2-methyl-7-trimethylsilyl-2-buten-6-yn-1-ol.



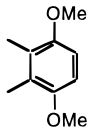
***E*-1-Chloro-2-methyl-7-trimethylsilyl-2-buten-6-yne (25).** To a solution of N-chlorosuccinimide (1.75 g, 13.1 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C was added dropwise, methyl sulfide (1.11 g, 15.15 mmol). The white suspension that resulted was cooled to −20 °C. A solution of *E*-2-methyl-7-trimethylsilyl-2-buten-6-yn-1-ol ***E*-14** (1.98 g, 10.1 mmol) in dry CH_2Cl_2 (10 mL) which had been cooled to 0 °C was added via cannula over 10 min. The mixture was then warmed to 0 °C and stirred for 2.5 h, after which time TLC indicated complete consumption of the starting material. The mixture was poured into ice-cold brine (100 mL) and extracted with CH_2Cl_2 (3×). The organic layers were combined and washed with ice-cold brine, dried ($MgSO_4$), and evaporated in vacuo to afford the allylic chloride (2.11 g, 98%) which was used without purification.



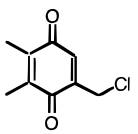
***E*-2-Methyl-4-(*p*-toluenesulfonyl)-2-butenol (41).** A mixture of *E*-4-chloro-2-methyl-2-butenol **42** (537 mg, 4.45 mmol) and DHP (0.42 mL, 387 mg, 4.60 mmol), cooled to 0 °C, was treated with $POCl_3$ (1 drop) for 0.5 h, and then the reagents in excess were removed in vacuo. The residue was stirred overnight with sodium *p*-toluenesulfinate (3.98 g, 22.35 mmol) in DMF (50 mL). The suspension was poured into ice−water and extracted with ethyl acetate (3×). The combined organic phases were then washed (saturated $NaHCO_3$, water, and brine), dried (anhydrous $MgSO_4$), and evaporated in vacuo. The resultant oil was treated with *p*-toluenesulfonic acid (120 mg, 0.63 mmol) in MeOH (30 mL). After 12 h the solution was poured into water and extracted with EtOAc (3×), and the combined organic phases washed (sat $NaHCO_3$, water, and brine) and dried (anhydrous $MgSO_4$). Silica gel chromatography (50% EtOAc/petroleum ether) afforded 760 mg of the title compound (71%); R_f = 0.30 (EtOAc/petroleum ether 1:1); IR 3504, 2921, 2863, 1672, 1597, 1449, 1404, 1301, 1241, 1148, 1085, 1019, 902, 817, 746, 669;^{1}H NMR (400 MHz) δ 7.73, 7.32 (AA′XX′, 4H), 5.49 (tq, J = 8 Hz, J = 1 Hz, 1H), 3.97 (s, 2H), 3.82 (d, J = 8 Hz, 2H), 2.42 (s, 3H), 2.21 (m, 1H), 1.37 (d, J = 1 Hz, 3H); ^{13}C NMR (100 MHz) δ 145.3, 144.6, 135.7, 129.7, 128.3, 110.1, 67.2, 55.6, 21.6, 13.6; LRCIMS (CH_4) *m*/*z* 241(M^+ + 1, 1), 240(M^+, 1), 223(M^+ − 17, 100), 185(7), 157(15), 139(25); HRCIMS (CH_4) *m*/*z* calcd for $C_{12}H_{17}O_3S$, M^+ 241.0898; found 241.0888; calcd for $C_{12}H_{15}O_2S$, M^+ 223.0793; found 223.0787.



***E*-4-Chloro-2-methyl-2-butenol (42).**[29]



2,3-Dimethyl-1,4-dimethoxybenzene. NaOH (3.62 g, 90.5 mmol) was dissolved in 10 mL of H_2O followed by addition of dimethyl sulfate (8.58 mL, 11.4 g, 90.5 mmol). 2,3-Dimethyl-1,4-hydroquinone (5.0 g, 36.2 mmol) was dissolved in 70 mL of ethanol cooled to 0 °C, and the dimethyl sulfate/NaOH solution was added carefully in five portions over 15 min in an exothermic reaction. The dark red solution was stirred for 3.5 h and quenched by addition to 60 mL of ice cold 3 M HCl. EtOAc (50 mL) and Et_2O (20 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (4 × 50 mL) and the ethereal layers subsequently washed with 100 mL 1M HCl, 100 mL H_2O, 80 mL brine and dried (anhydrous $MgSO_4$). Concentration in vacuo gave 5.95 g (98%) of a red solid which was determined to be ∼90% pure by GCMS; R_f = 0.36 (15% EtOAc/petroleum ether); IR (KBr) 2954, 2907, 1599, 1483, 1467, 1437, 1260, 1212, 1116, 1096, 797, 718, 593, 495; ^{1}H NMR (400 MHz) δ 6.67 (s, 1H), 3.79 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz) δ 151.8, 126.6, 107.8, 55.9, 12.0, 11.9; LREIMS *m*/*z* 167(8), 166(69), 152(10), 151(100), 121(16), 108(9), 91(25), 79(11), 77(19), 53(7); HREIMS *m*/*z* calcd for $C_{10}H_{14}O_2$, M^+ 166.0994; found 166.0985.



2-Chloromethyl-5,6-dimethyl-[1,4]-benzoquinone. 2,3-Dimethyl-1,4-dimethoxybenzene (3.0 g, 18.0 mmol), paraformaldehyde (1.36 g, 39.71 mmol) and 20 mL concentrated HCl were combined, and the flask was fitted with a gas bubbler and connected to an aqueous $NaHCO_3$ trap. HCl gas was generated by slow addition of concentrated H_2SO_4 to NH_4Cl. HCl was bubbled into the reaction mixture for 10 min. After 1.5 h, the reaction was quenched by addition of 90 mL of H_2O and 30 mL of Et_2O. The layers were separated, and the aqueous phase was extracted with diethyl ether (2 × 50 mL) and EtOAc (2 × 50 mL). The pooled organics were washed with water (100 mL) and

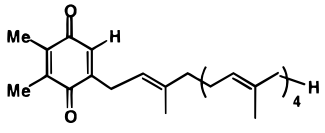
brine (50 mL), dried (anhydrous $MgSO_4$), and concentrated in vacuo to give a green-brown solid. Silica gel chromatography (2.5% EtOAc/petroleum ether) gave 2.46 g (63.5%) of an off white solid as an inseparable mixture of the mono-, di-, and non-chloromethylated products. The crude chloromethylquinone (1.94 g) was dissolved in 15 mL of CH_3CN and cooled to 0 °C. Ceric ammonium nitrate (11.65 g) was dissolved in 33 mL of H_2O and 20 mL of CH_3CN and cooled to 0 °C prior to slow addition to the hydroquinone mixture. After 25 min, 20 mL of Et_2O was added, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organics were washed with brine until the aqueous layer was colorless (6 × 20 mL). The solution was dried (anhydrous $MgSO_4$), concentrated in vacuo, and chromatographed on silica gel (5% EtOAc/petroleum ether), collecting 1.31 g of a bright yellow solid (78%); $R_f = 0.49$ (15% EtOAc/petroleum ether); IR 3434, 3271, 2952, 1650, 1619, 1425, 1381, 1317, 1266, 1238, 1103, 737; ^{1}H NMR (400 MHz) δ 6.80 (t, $J = 1.2$ Hz, 1H), 4.35 (d, $J = 1.2$ Hz, 2 H), 1.98 (dt, $J = 3.6$ Hz, $J = 1.2$ Hz, 6 H); ^{13}C NMR (400 MHz) δ 186.9, 185.7, 143.1, 141.3, 140.9, 133.3, 39.4, 12.2, 12.1; LREIMS *m*/*z* 186($M^+ + 2$, 33), 184(M^+, 100), 158(34), 156(96), 150(41), 141(11), 122(11), 121(53), 120(21), 107(25), 101(16), 93(48), 92(11), 91(54), 79(28), 77(40), 68(10), 67(55), 65(11), 54(27), 54(42), 52(12), 51(31); HREIMS *m*/*z* calcd for $C_9H_9O_2Cl$, M^+ 184.0291; found 184.0283.

Ni(0)-Catalyzed Couplings: CoQ$_n$. The general procedure consists of the preparation of two distinct species: a carboaluminated alkyne and the Ni(0) catalyst which, when combined with the chloromethylated CoQ nucleus, gives the cross-coupled product.

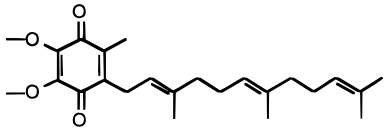
Carboalumination. Using standard syringe/septa procedures, Cp_2ZrCl_2 (98 mg, 0.33 mmol) was combined with $AlMe_3$ (990 μL, 2.0 M in hexanes, 1.98 mmol), cooled to 0 °C and 90% of the solvent removed in vacuo. The resulting white solid was dissolved in 1.0 mL of $ClCH_2CH_2Cl$, warmed to room temperature for 10 min and recooled to 0 °C. The alkyne (0.66 mmol, 1.33 equiv) was added neat or dissolved in a minimum amount of $ClCH_2CH_2Cl$ via cannula. Additional $ClCH_2CH_2Cl$ was then added, bringing the total volume of $ClCH_2CH_2Cl$ up to 1.5 mL. After 4 h, or when the reaction is judged complete by GC, the solvent is removed in vacuo and 3 mL of freshly distilled hexanes added and then removed in vacuo. Hexanes (3 mL) were again added, the solids were allowed to precipitate, and the supernatant was cannulated away from the solids and the washing repeated with an additional 3 mL of hexanes. The vinylalane solution was concentrated in vacuo and the pale yellow oil dissolved in THF (3.0 mL) and cooled (−23 °C).

Ni(0) Catalyst. To a solution of $NiCl_2(PPh_3)_2$ (9.8 mg, 0.015 mmol) in THF (1.0 mL) was added dropwise slowly *n*-BuLi (18 μL, 1.64 M in hexanes, 0.030 mmol) giving a red-black solution of the active Ni(0) catalyst.

Cross-Coupling. The cross coupling was effected by addition of chloromethylated *p*-quinone **36** (115 mg, 0.5 mmol), dissolved in a minimum of THF, via cannula to the precooled vinylalane solution prepared above, followed immediately by addition of the Ni(0) complex. Additional THF is added to bring the total volume of THF up to 5.0 mL. The reaction is followed by TLC by removing 20 μL aliquots and quenching into a biphasic system of $CHCl_3$ and citric acid·H_2O (3 g/10 mL). After 1 h the reaction was quenched at −23 °C by addition of 10 mL of $CHCl_3$ and 3.0 g of citric acid monohydrate dissolved in 10 mL of water followed by 20 min of vigorous stirring. The layers were then separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were washed once with saturated brine solution (10 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo and flash chromatographed on silica gel (5−10% EtOAc/petroleum ether) to give CoQ$_n$ as a red oil or solid.



Plastoquinone-5 (38). The alkyne precursor **37** ($n = 4$, 206 mg, 0.66 mmol), $AlMe_3$ (990 mL, 2.0 M in hexanes, 1.98 mmol), Cp_2ZrCl_2 (96 mg, 0.33 mmol) and $ClCH_2CH_2Cl$ (1.2 mL) were used in the carboalumination procedure described above. $NiCl_2(PPh_3)_2$ (9.8 mg, 0.015 mmol), *n*-BuLi (18.4 mL, 1.62 M in hexanes, 0.03 mmol) and THF (1.0 mL) were used to prepare the Ni(0) catalyst by the procedure described above. 1-Chloromethyl-5,6-dimethyl-*p*-quinone (90 mg, 0.48 mmol) and THF (4.0 mL) were used in the cross-coupling following the procedure above. After 1 h at −23 °C, 10 mL of Et_2O was added, the solution was filtered through a pad of Celite/Na_2SO_4·10H_2O (1:1 mixture) and rinsed (3 × 30 mL) with Et_2O. Concentration in vacuo to a yellow oil followed by silica gel chromatography (2.5% EtOAc/petroleum ether) yielded 205.7 mg of a yellow oil (88%); $R_f = 0.41$ (15% EtOAc/petroleum ether); IR 3421, 2963, 2922, 2855, 1650, 1617, 1444, 1381, 1316, 1101, 882; ^{1}H NMR (400 MHz) δ 6.5 (t, $J = 1.2$ Hz, 1H), 5.08 (m, 4H), 3.09 (d, $J = 7.6$ Hz, 2H), 1.99 (m, 22H), 1.64 (s, 3H), 1.59 (s, 3H), 1.56 (s, 12H); ^{13}C NMR (100 MHz) δ 187.7, 187.6, 147.0, 140.9, 140.5, 1339.6, 135.3, 134.9, 134.8, 132.0, 131.1, 12224.4, 124.22, 124.18, 1223.8, 118.1, 39.7, 39.6, 27.4, 26.7, 26.63, 26.59, 26.4, 25.6, 17.6, 16.1, 16.01, 15.96, 15.95, 12.3, 11.9; Anal. Calcd for $C_{33}H_{48}O_2$: C, 83.20; H, 10.08. Found: C, 83.42; H, 10.36.



Representative Coupling to CoQ$_n$ and Related Quinones; CoQ$_3$ (1, $n = 3$). The alkyne precursor **37** ($n = 2$, 116.2 mg, 0.66 mmol), $AlMe_3$ (990 μL, 2.0 M in hexanes, 1.98 mmol), Cp_2ZrCl_2 (98.0 mg, 0.34 mmol) and $ClCH_2CH_2Cl$ (1.5 mL) were used in the carboalumination procedure described above. $NiCl_2(PPh_3)_2$ (9.7 mg, 0.015 mmol), *n*-BuLi (18 μL, 1.64 M in hexanes, 0.030 mmol), and THF (1.0 mL) were used to prepare the Ni(0) catalyst by the procedure described above. Chloromethylquinone **36** (115.6 mg, 0.50 mmol) and THF (4.0 mL) were used in the cross-coupling described above. Silica gel chromatography (10% EtOAc/petroleum ether) yielded 162 mg of a red oil (84%); $R_f = 0.35$ (15% EtOAc/petroleum ether); IR 2965, 2926, 1649, 1611, 1450, 1380, 1287, 1264, 1204, 1153, 1102, 1022, 947, 743; ^{1}H NMR (400 MHz) δ 5.04 (m, 2H), 4.91 (t, $J = 7.2$ Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.16 (d, $J = 7.2$ Hz, 2H), 2.03−1.91 (m, 11H), 1.71 (d, $J = 0.8$ Hz, 3H), 1.64 (d, $J = 0.8$ Hz, 3H), 1.55 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz) δ 184.7, 183.9, 141.7, 138.8, 137.6, 131.3, 124.3, 123.8, 118.9, 61.1, 39.7, 26.7, 26.4, 25.7, 25.3, 17.6, 16.3, 16.0, 11.9; LREIMS *m*/*z* 386(M^+, 4), 249(18), 235(47), 217(18), 197(35), 196(18), 189(11), 91(11), 81(19), 69(100), 43(24); HREIMS *m*/*z* calcd for $C_{34}H_{34}O_4$, M^+ 386.2457; found 386.2456.

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Supporting Information Available: Experimental details and full spectral data for all new compounds not given in the Experimental Section (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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