Synthesis of Menaquinones

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Abstract: Various approaches to the synthesis of menaquinones have been studied in which the aromatic component is activated to encourage nucleophilic attack upon a receptive prenyl fragment. Thus alkylation of the potassium salt of 2-methyl-1,4-naphthoquinol or 4-methoxy-3-methyl-1-naphthol with geranyl bromide gave menaquinone-2 in 20 and 45% yield, respectively, following oxidation to the quinone. Hydrogenolysis of the dimethyl ether of 1′-oxymenaquinol-2 (from 2-lithio-3-methyl-1,4-dimethoxynaphthalene and citral) with lithium aluminum hydride–aluminum chloride mixtures gave the desired dimethyl ether of menaquinol-2, but contaminated with its Δ^1 (isomenaquinol) isomer. Argentic oxide demethylation and argentation chromatography achieved separate isolation of menaquinone-2 and isomenaquinone-2. Coupling of geranyl bromide and either the 2-magnesio or 2-cupro-3-methyl-1,4-dimethoxynaphthalene occurred in >90% yield, and menaquinone-2 was obtained after oxidative demethylation in 80% overall yield with 97% trans stereochemistry. Similarly, *all-trans*-menaquinone-9 was obtained from solanesyl bromide in 73% yield. A general resolution of Δ^2-*cis*- and *trans*-menaquinones was achieved with medium pressure liquid chromatography.

Introduction of an isoprenoid functionality into an aromatic nucleus is a general problem in the synthesis of many natural products where in most cases the locus of functionalization and the degree of control over the stereochemical fate of the introduced moiety are of paramont importance. Exemplary of these considerations is the synthesis of a class of naturally occurring quinones known commonly as menaquinones [MK-n, **1b**, and phylloquinone (**1c**)][1,2] in which the polyprenyl side chain at C-3 possesses an all-trans geometry.[3] Introduction of this side chain into the naphthalene nucleus efficiently and with maintenance of trans configuration has presented a continuing challenge for over three decades. The requisite side chains are obtained either naturally[4] from geraniol (C_{10}), farnesol (C_{15}), phytol (C_{20}, $\Delta^{6,10,14}$ saturated), or solanesol (C_{45}), or *via* demanding synthetic routes.[5] In either case, the prenyl component represents the more valuable moiety and thus the one for which the yield should be maximized. In these respects, (a) overall efficiency based upon the prenyl component and (b) maintenance of existing trans stereochemistry, all procedures for menaquinone synthesis have been to some degree, less than successful.

Classically,[6] menaquinones have been prepared by condensation of 2-methyl-1,4-naphthoquinol (**2**) with an appropriate allylic alcohol in the presence of an acid catalyst, the most efficient being boron trifluoride etherate. The resulting menaquinol can then be converted by mild oxidation (O_2, Fe^{+3}, Ag_2O) to the quinone. Overall, these conditions usually avoid side-chain isomerizations and chromanol cyclization and also have been optimized to avoid 2-alkylation[7] but remain fundamentally limited by the inherent instability[8] of the allylic alcohol component to the acidic conditions employed. As a result optimal yields for phylloquinone synthesis rarely exceed 40% and menaquinone examples are reported in less than 20% yield based upon the prenyl component. Preservation of a trans configuration at the Δ^2 position in the product is obtained, and under certain conditions a cis geometry at this position also can be maintained.[6d] Another approach in which the prenyl component is activated as an electrophile not by acid complexing but as an *N*-sulfinylamine ester has been observed to proceed with similar stereospecificity but only in low yield[9] (phylloquinone in 7% yield from phytol).

More recently,[10] activation of the side-chain component as a nucleophile *via* the π-allyl-Ni complex has been utilized to achieve direct addition to a quinone or coupling with a protected 2-methyl-3-bromonaphthoquinol with subsequent oxidation to the corresponding prenylated quinone. Coupling on the bromoquinol in particular has been shown to be applicable to a multiprenyl example (*e.g.*, menaquinone-9 in 37% yield from solanesyl bromide) although retention of trans stereochemistry at the Δ^2 position is incomplete (70:30, trans:cis).[10b]

An approach which is lacking from the literature involves activation of the naphthalenic portion to function as a nucleophile relative to an appropriately functionalized sidechain. Such an approach would avoid entirely acidic conditions which destroy or isomerize the prenyl component and would allow some degree of control over the actual loci of coupling in both the aryl and prenyl component. The latter consideration could be of importance in the synthesis of other prenylated aromatic compounds in which the multiplicity of coupling permutations is greater than that encountered in menaquinone synthesis. Also an activated aromatic nucleophile can potentially yield a more stereospecific coupling product than achievable when disruption of the entire allylic system occurs as in the case with Lewis acid catalysts or π complexes. For these reasons we have investigated this type of coupling reaction as a route to menaquinone synthesis, and our results are discussed below.

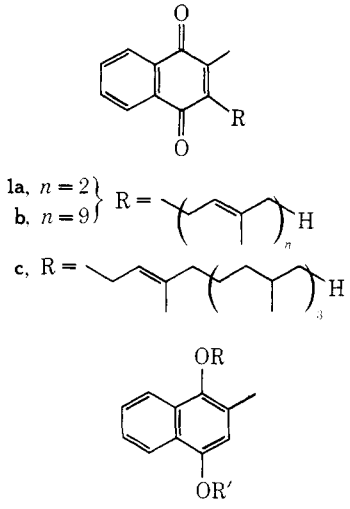
Activation of an aromatic nucleus as a nucleophile can be achieved in several ways, one of the simplest being, in the case of a naphthoquinol, removal of a proton and utilization of the resulting ambident anion in a Claisen alkylation with an appropriately functionalized side chain. In fact, one of the first syntheses of phylloquinone employed this approach by condensing the monosodium salt of 2-methyl-1,4-naphthoquinol (**2**) with phytyl bromide in refluxing benzene.[11,12] Since the exact conditions and yield were never reported and since more recent work suggested appropriate modifications,[13-15] we initiated our investigations into menaquinone synthesis with a reevaluation of this old approach.

As is well known, C- *vs.* O-alkylation of an ambident anion such as the naphthoquinol salt **14** (Scheme I) is profoundly influenced by solvent. In general either nonpolar hydrocarbon solvents[13] or protic solvents[14] are required for preferential C-alkylation while most polar aprotic solvents[15] enable exclusive O-alkylation. In our case a hydrocarbon solvent appeared preferable in that the higher molecular

Table I. Coupling Reactions Leading to Menaquinone-2 and -9 (**1a,b**)

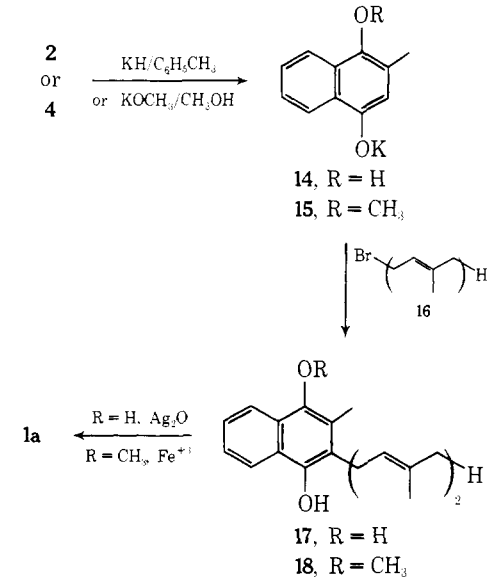
Expt no.	Naphthalene component, equiv	Prenyl component[a]	Intermediate products (yield, %)[b]	Overall yield, % (retention of stereochemistry at Δ^2, %)[c] MK-2	MK-9
1	**14** (1.0) *via* KH	**16**	**17** (n.d.)[d]	17 (97)	
2	**14** (1.0) *via* $KOCH_3$	**16**	**17** (n.d.)	23 (97)	
3	**15** (1.0)	**16**	**18** (n.d.)	45 (97)	
4	**20a** (1.0)	**21**	**24** (92); **25** + **27** (80)	32 (62)	
5	**20a** (1.0)	**23**	**25** (10)		
6	**20a** (1.0)	**16**	**25** (65)		
7	**20b** (1.0)	**16**	**25** (74)		
8	**20c** (1.0)	**23**	**25** (69)		
9	**20c** (1.0)	**16**	**25** (84) + **19** (7)	73 (98)	
10	**20c** (1.1)	**16**	**25** (92) + **19** (8)	80 (98)	
11	**20c** (1.1)	*cis*-**16**[e]	*cis*-**25** (62) + **19** (5)	54 (88)	
12	**20c** (1.25)	**22**	**26** (95) + **19** (8)		73 (99)
13	**20d** (1.0)	**16**	**25** (82) + **19** (7)	71 (98)	

[a] ⩾99% trans stereochemistry at Δ^2 unless otherwise indicated. [b] Values are isolated yields, based upon the prenyl component. [c] % trans (cis) menaquinone/% trans (cis) prenyl component × 100. [d] Not determined = n.d. [e] Derived from 97% *cis*-nerol.



2, R, R′ = H
3, R, R′ = CH_3
4, R = CH_3; R′ = H
5, R = H; R′ = CH_3
6, R, R′ = $COCH_3$
7, R = $COCH_3$; R′ = H
8, R = H; R′ = $COCH_3$
9, R = $COCH_3$; R′ = CH_3
10, R = CH_3; R′ = $COCH_3$
11, R = $COCH_3$; R′ = $CH_2C_6H_5$
12, R = H; R′ = $CH_2C_6H_5$
13, R = CH_3; R′ = $CH_2C_6H_5$

Scheme I. Reactions Leading to Menaquinone-2 (**1a**) *via* 2-Methyl-1,4-naphthoquinol (**2**) and 4-Methoxy-3-methyl-1-naphthol (**4**)



weight multiprenyl components have limited solubility in methanol–water and could be consumed by competing solvolysis. Also, heterogeneous alkylation in a hydrocarbon solvent has appeared to be the more efficacious reaction.[13a,15]

For model studies geranyl bromide was chosen as the prenyl component and was derived from 99% *trans*-geraniol by treatment with phosphorous tribromide–pyridine, conditions which have been shown to proceed with complete retention of double-bond stereochemistry.[16] The C_{10} unit was chosen as the simplest example of significance to menaquinone synthesis. Not only does the two-prenyl unit allow cis/trans stereochemistry at Δ^2 in the product quinone but it also provides a model for cyclizations and other reactions which might involve a conjunction of the two (Δ^2 and Δ^6) double bonds. In these respects, studies which utilize a C_5 unit or the C_{20} unit derived from phytol can be misleading. The choice of leaving group for the allylic functionality also involved consideration of various factors such as yield, stability, and reactivity. Thus activated esters such as sulfonate[17] and phosphate[18] were rejected because they can only be prepared in low yield and must be used immediately while the allylic halides (Cl or Br) are much more stable and easily available. Purified geranyl bromide could be stored for months at 0° without appreciable decomposition. The enhanced reactivity of the allylic bromide compared to the corresponding chloro compound made it the derivative of choice.

2-Methyl-1,4-naphthoquinol was converted to its monopotassium salt[19] (**14**) with potassium hydride in toluene or by the addition of an equivalent of potassium methoxide in methanol followed by solvent removal. In both cases, reaction with geranyl bromide at room temperature in toluene was complete within 24 hr although upon oxidation menaquinone-2 (**1a**) was obtained in only 20% yield (Table I). The by-products were not identified but clearly one possibility would be 2-alkylation to yield a ketone as was obtained in the Friedel–Crafts alkylation.[20] In order to avoid these complications and to achieve better solubility characteristics utilization of 4-methoxy-3-methyl-1-naphthol (**4**) as the naphthalenic component was investigated.

The efficient preparation of monomethyl ether **4** proved to be more complex than initially assumed. This compound has been prepared by methylation of 2-methyl-1,4-naphthoquinol 4-acetate (**8**) followed by hydrolysis;[21] however, monoacetate **8** is obtained inefficiently *via* selective acetylation of **2**[22] so that the overall process, **2** → **8** → **10** → **4**, is accomplished in less than 10% yield.

We first examined the possibility of synthesizing **4** through either selective methylation or demethylation processes. As has been recently noted[23] the task of achieving monoalkylation of a hydroquinone is difficult without imposing the additional restriction of selectivity. We found this to be the case, in that methylation of **2** with a limiting amount of methyl iodide yielded principally dimethylation. The monomethyl fraction that was isolated contained a preponderance of the undesired 4-methoxy-2-methyl-1-naphthol (**5**), the product also obtained by direct etherification with methanolic HCl.[24a] Similarly, selectivity in demethylation of various aryl methyl ethers has been reported with thioethoxide;[25] however, when either this nucleophile or iodide[26] was applied to dimethyl ether **3**, a mixture of monoethers **4** and **5** was obtained with an unfavorable (**4–5**, 1:4) distribution.

As a result of these failures, a direct though lengthy approach to **4** was employed utilizing as a starting material 2-methyl-1,4-naphthoquinol 1-acetate (**7**) which is easily available by selective hydrolysis of diacetate **6**.[27] After the 4 position was masked as a benzyl ether, ester hydrolysis, methylation of the C-1 phenol, and hydrogenolysis of the benzyl ether yielded monomethyl ether **4** cleanly and in 62% yield from **7**. The only by-product detected in the sequence was some (*ca.* 10%) tetrahydro reduction of the benzenoid ring of **4**. Spectral characteristics of monomethyl ether **4** are quite similar to those obtained for **5** and the two compounds were significantly differentiated only chromatographically with **4** (R_f 0.37, benzene) being somewhat more polar than **5** (R_f 0.57), most probably reflecting the unhindered *vs.* hindered phenolic function.

Salt formation was accomplished conveniently and cleanly with potassium hydride in toluene at 80° in contrast to sodium hydride which reacted only sluggishly at 110°. Consumption of an equivalent of geranyl bromide was complete within an hour at room temperature and the crude product possessed properties expected for coupled product **18**, with only a trace of starting **4** and no O-alkylated material detectable. However, **18** could not be isolated pure, decomposing upon chromatography to yield in part menaquinone-2 (16% yield) probably arising *via* aerial oxidation. On the other hand, if the crude reaction mixture was treated immediately with ferric chloride, menaquinone-2 could be realized in 45% yield. Thus, the Claisen alkylation is somewhat superior to the classical Friedel–Crafts alkylation in efficiency based upon the prenyl component, although this must be balanced by the manipulations necessary to obtain the naphthalene component.

Another method of localizing a negative charge on an aromatic nucleus is through the intermediacy of an appropriately substituted metallo derivative, one example of which is 2-lithio-3-methyl-1,4-dimethoxynaphthalene (**20a**, Scheme II), an intermediate in the synthesis of chlorobiumquinone (**31**).[5a] In this approach **20a** was condensed with citral to yield allylic alcohol **24** (92%). If the 1′-oxy function of **24** could be hydrogenolyzed to give the 1′-methylene, then an efficient menaquinone synthesis would result since argentic oxide (AgO) oxidative demethylation to quinone is facile.[28]

Obviously catalytic hydrogenolysis of the 1′-oxy function of **24** is incompatible with the olefinic side chain; however, lithium aluminum hydride (LAH)–aluminum chloride is reported[29] to hydrogenolyze benzylic–allylic alcohols without concomitant double-bond reduction, which frequently occurs with LAH alone. Indeed, when trans-alcohol **24** was treated with LAH at room temperature significant 2′,3′-dihydro-**24** (**29**) was obtained. However, when the LAH suspension was pretreated with an $AlCl_3$ solution, smooth hydrogenolysis occurred to yield the desired dimethyl ether of menaquinol-2 (**25**) and the $\Delta^{1'}$ by-product **27** as an inseparable mixture in a ratio of 7 to 3. The presence of **27** was deduced from the nmr spectrum which showed a new set of complex vinyl absorptions (δ 6.0–6.6) and a saturated methyl signal at δ 1.15 (J = 6 Hz). Both the yield and product distribution was a function of the LAH–$AlCl_3$ composition so that with a 10% molar excess of LAH optimal yield was obtained with a **25** to **27** ratio of 2.4 to 1. In this manner the presence of vinyl naphthyl ether (**27**) could only be minimized and not avoided.

Upon oxidative demethylation the resulting quinone mixture (**1a–28**) could be separated by argentation chromatography into its allyl and vinyl components. The novel vinyl quinone **28** (isomenaquinone-2) was completely characterized and assigned a trans geometry in analogy with other vinyl quinones.[24] The *trans*-vinyl protons apparently because of their close chemical shifts appear as a non-first-order doublet centered at δ 6.35 while the saturated methyl doublet at δ 1.13 (J = 7 Hz) is outstanding. The uv chromophore, λ_{max} 250 nm (ϵ 20,500), 330 (3000), and 370 (2300), is also consistent with the assigned structure.[24] At one time vinyl quinones were proposed as intermediates in oxidative phosphorylation[30a] although such an involvement is now known to be inconsistent with isotope studies.[30b] The above method offers another synthetic entry into this series.[24a]

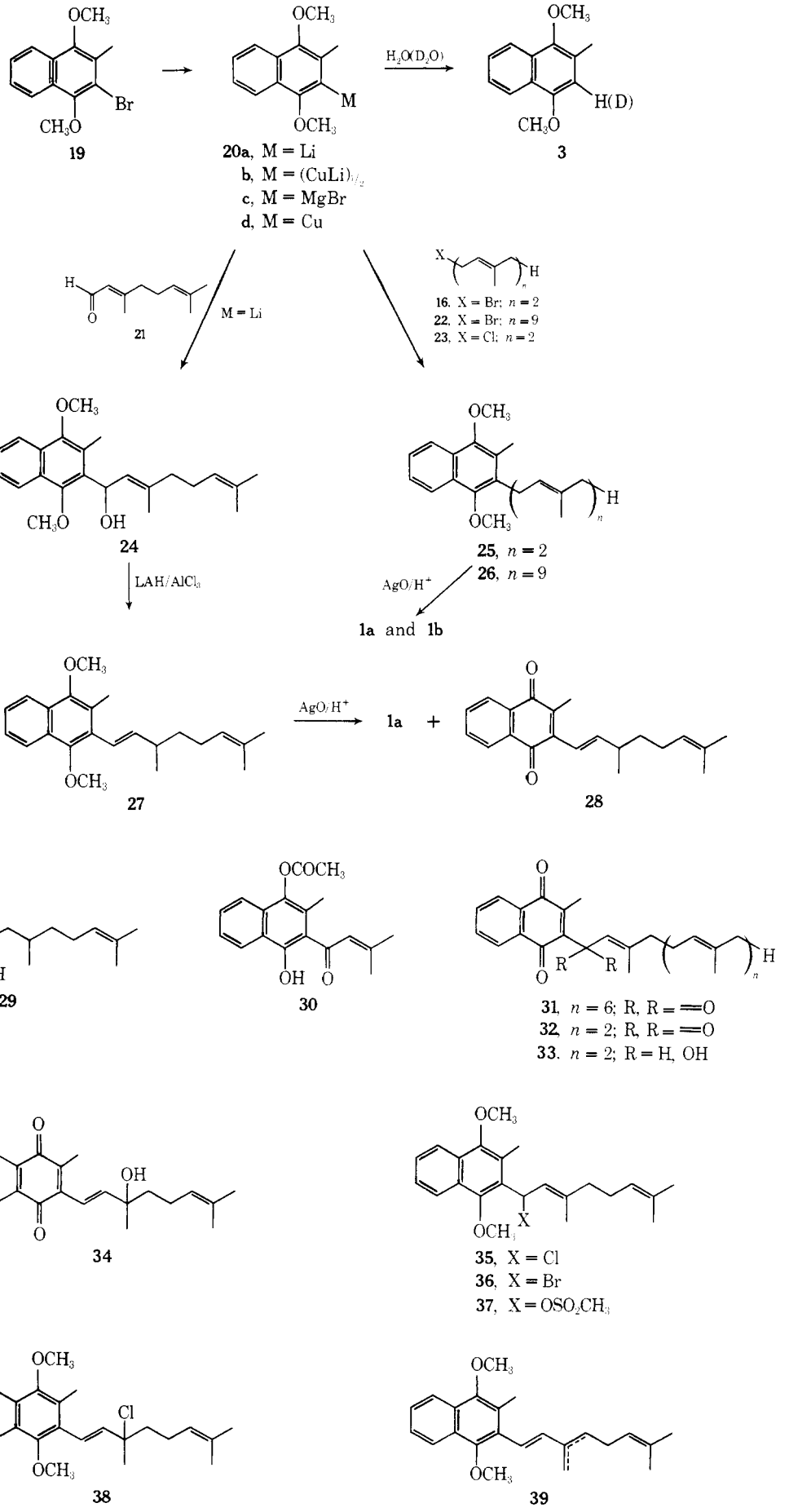
Somewhat puzzling was the apparent discrepancy between the hydrogenolysis above, which appears to proceed through a mesomeric cation intermediate,[29] and the analogous LAH reduction of monoacetate **30** which is reported to yield after oxidation menaquinone-1 with exclusive hydride displacement at C-1′.[31] However, in our hands, 1′-oxomenaquinone-2 (**32**), 1′-oxymenaquinone-2 (**33**), and the rearranged quinone **34** were subjected to LAH reduction–aerial oxidation and in all three cases menaquinone-2 was isolated in low yield but completely free of vinyl isomer **28**.

Returning to the problem at hand, any possibility remaining for achieving allylic reduction without concomitant rearrangement required an activated leaving group such that a milder, SN2-like hydride displacement could be used. However, functionalization of the C-1′ position with a halogen (**35** or **36**) or activated ester (mesylate, **37**) could not be achieved and only chloride displacement gave a product stable enough to be isolated. Thus upon treatment of **24** with carbon tetrachloride–tri-*n*-butylphosphine rearranged chloride **38** was the first formed product by nmr although additional characterization was not possible since on standing or chromatography **38** eliminated HCl to give thiene **39**.

Further treatment of the tertiary chloride with either LAH or lithium triethylborohydride[32] gave only the familiar mixture of **25** and **27**, now contaminated in addition with an equal amount of triene **39**. Further efforts toward menaquinone synthesis *via* aldehyde coupling were abandoned and coupling efforts focused upon utilization of the sidechain functionalized at the alcohol oxidation state thereby obviating the need for a reduction step.

Ample analogy for aryl–allyl coupling of the type we desired exists in the recent literature. For example, phenyllithium and 1-chloro-3-methyl-2-butene couple with exclusive α attack in 80% yield[33] while phenylmagnesium bromide and geranyldiphenyl phosphate form geranylbenzene in 69% yield.[18b] In addition, various non-aryl organometallic species have been used to form new carbon–carbon bonds by displacement upon isoprenoid esters and halides.[34] Rarely, however, have multifunctional organometallic species been used in coupling reactions. The series of 2-metallo-3-methyl-1,4-dimethoxynaphthalenes **20a–d** thus

Scheme II. Reactions Leading to Menaquinone-2 and -9 (**1a,b**) *via* 2-Metallo-3-methyl-1,4-dimethoxynaphthalene (**20a–d**)



seemed particularly attractive for investigation since a wide variety of organometallic functionalities was encompassed, most of which have been useful in achieving coupling with allylic halides. Furthermore, known side reactions such as transmetalation, α- and δ-proton abstraction, and decomposition of the organometallic species can be minimized by judicious choice of naphthalene and prenyl components.

To initiate the study, the various organometallic species **20a–d** were prepared by standard techniques. The preparation of lithio derivative **20a** by transmetalation of butyllithium and 2-bromo-3-methyl-1,4-dimethoxynaphthalene (**19**) has been described previously[5a] and quenching with D_2O led quantitatively to 2-methyl-1,4-dimethoxynaphthalene (**3**) with >99% deuterium incorporation at C-3. Similar formation of **20a** in THF solution at −78° was possible; however, upon warming to room temperature followed by D_2O quenching significant (25%) protium incorporation was observed at C-3 in addition to transmetalation and butyl coupling products. Conversely, Grignard reagent **20c** could only be prepared in THF solution using freshly prepared magnesium filings, and here again deuterium quenching led to **3** with 97% deuterium at the 3 position. The copper derivatives **20b** and **20d** were prepared by treatment of **20a** and **20c** with 0.5 and 1 equiv of cuprous bromide, respectively. Both the latter reagents appeared stable at room temperature, the cuprate being a brownish precipitate in ether suspension while organocopper compound **20d** formed a nearly colorless solution in THF.

A summary of the various coupling permutations with geranyl chloride (**23**) and bromide (**16**) is contained in Table I (experiments 5–11 and 13). In most cases[35] complete consumption of the prenyl component occurred and conversion to coupled product **25** was almost quantitative with excess Grignard reagent and geranyl bromide (experiment 10). The only recognizable side reaction was a small amount of transmetalation between **20c/d** and **16** to give bromonaphthalene (**19**) as a contaminant which unfortunately could not be separated from **25.** However, an accurate estimate of the **19:25** ratio could be determined by integration of the corresponding aromatic methyl absorptions. Although difficult to separate at the dimethyl ether stage, the final quinone products, menaquinone-2 and 2-bromo-3-methyl-1,4-naphthoquinone, were readily separable chromatographically.

Optimization of the AgO reaction for menaquinone formation required reduction in the quantity of oxidant from that previously reported.[28] Thus, the yield of MK-2 from this oxidation reached a maximum of 87% with 2.5 equiv of AgO and nitric acid while a maximum conversion yield of 97% (83% direct yield) was obtained with a limiting quantity of oxidant (2.2 equiv). Overall, MK-2 can be realized in 84% yield from geranyl bromide. The determination of stereochemistry introduced at Δ^2 follows.

Although *cis,/trans*-phylloquinones can be separated chromatographically[3] and analyzed quantitatively by integration of the corresponding 3′-methyl absorptions (nmr), *cis*- and *trans*-menaquinone-2 share neither of these features.[6d] The diagnostic 3′-methyl absorption of *cis*-MK-2 overlaps the terminal 7′-transoid methyl signal thus precluding quantitation. For this reason we turned to medium pressure liquid chromatography employing a uv monitor. Using a solvent system adequate for thin-layer chromatography of MK-2 (3% ether in isooctane, R_f 0.35) and a spherical, 20 μ-silica gel absorbent, complete resolution of the *cis*- and *trans*-quinones was obtained.

Assuming equal extinctions for the two isomers, the cis–trans distribution of the various MK-2 products obtained from the above model studies was determined (Table I) and virtually quantitative retention of trans stereochemistry was obtained in all synthetic approaches we have developed except in the quinone derived from experiment 4. In this case the intervention of allylic rearrangement under hydrogenolysis conditions would ensure disruption of the initial stereochemistry. In a more rigorous test of the stereospecificity of the Grignard coupling reaction, neryl bromide (97% cis[16]) was utilized as a substrate and although coupling proceeded in diminished yield most of the original stereochemistry was maintained[36] and 85% *cis*-MK-2 was obtained. Also, since three reactions are involved the loss in stereospecificity cannot be uniquely assigned and may be associated with any or all of the processes.

Synthesis of Menaquinone-9. Having optimized the conditions necessary for efficient and stereospecific multiprenyl quinone synthesis, the elaboration of menaquinone-9 was then accomplished. Solanesol[37] was converted to solanesyl bromide (**22**) by treatment with phosphorous tribromide and pyridine[38] and purified by short-path chromatography to yield crystalline bromide (85%). Coupling with 125 mol % of Grignard reagent **20c** led to dimethyl ether **26** in 95% yield, which was further oxidized to menaquinone-9 with excess (3.0 equiv) AgO in 77% yield.[39] Thus, menaquinone-9 has been realized in 73% overall yield from solanesyl bromide, with 98% trans-$\Delta^{2'}$ geometry as determined by liquid chromatography.

Clearly applicable to the synthesis of other menaquinones, Grignard coupling with allylic halides followed by mild oxidative deprotection of reactive functional groups could well provide a general synthesis of ubiquinones, plastoquinones, and many of the other numerous natural products bearing a prenylated aromatic nucleus. The conjunction of regio- and stereoselectivity as demonstrated here makes this an ideal sequence for such syntheses.

Experimental Section[40]

2-Methyl-1,4-naphthoquinol (2). 2-Methyl-1,4-naphthoquinone (1.72 g, 10 mmol) was suspended in ether (100 ml) and shaken with aqueous $Na_2S_2O_4$ solution (10%) until complete discharge of color. After drying by extraction with saturated NaCl solution the ether phase was evaporated and the residue sublimed (110°, 10 μ) to yield crystalline hydroquinone **2** (1.57 g, 90%): mp 166° dec (lit.[41] mp 181°).

Geranyl Bromide (*trans*-16). Geranyl bromide was prepared from 99% *trans*-geraniol[42] as reported.[43] The crude product was purified by short path distillation (70°, 1 mm) to yield the purified bromide (80%): gc (injector T = 145°, column T = 90°) retention time 29 min plus dehydrohalogenation peaks in variable ratios at retention time 2.7–5.3 min; nmr δ 1.60 (s, cisoid=$C(CH_3)_2$), 1.67 (s, transoid =$C(CH_3)_2$), 1.72 (d, J = 1 Hz, =CCH_3), 2.03 (br, -CH_2CH_2-), 3.95 (d, J = 7 Hz, $BrCH_2$), 5.03 [br, CH=$C(CH_3)_2$], 5.47 (t, J = 7 Hz, $BrCH_2CH$=).

Geranyl Chloride (*trans*-23).[44] A solution of 99% *trans*-geraniol (1.54 g, 10 mmol) in carbon tetrachloride (distilled from P_2O_5, 20 ml) was treated dropwise with tri-*n*-butylphosphine (3.31 g, 16.4 mmol). The reaction mixture was then diluted with petroleum (pet) ether and the solvent phase was decanted from the viscous tri-*n*-butylphosphine oxide. After solvent removal the residue was purified by short-path distillation (70°, 1 mm) to yield pure *trans*-**23** (1.02 g, 60%) as a mobile oil: gc (injector T = 145°, column T = 95°) retention time 17.5 min, (geraniol, retention time 26.5 min); nmr δ 1.60 (s, cisoid=$C(CH_3)_2$), 1.67 (s, transoid=$C(CH_3)_2$), 1.71 (d, J = 1 Hz, =CCH_3), 2.03 (br, -CH_2CH_2-), 4.05 (d, J = 7 Hz, $ClCH_2$) 4.05 (d, J = 7 Hz, $ClCH_2$), 5.05 (br, CH=$C(CH_3)_2$), 5.40 (t, J = 7 Hz, $ClCH_2CH$=); uv 210 nm (ϵ 9860).

Neryl Bromide (*cis*-16). Neryl bromide was prepared from 97% *cis*-nerol[42] as geranyl bromide above: nmr δ 1.60 (s, cisoid=$C(CH_3)_2$), 1.67 (s, transoid=$C(CH_3)_2$), 1.76 (d, J = 1 Hz, =CCH_3), 2.12 (br, -CH_2CH_2-), 3.97 (d, J = 8 Hz, $BrCH_2CH$=), 5.12 (br, CH=$C(CH_3)_2$), 5.53 (t, J = 8 Hz, $BrCH_2CH$=).

Solanesyl Bromide (22). Crude solanesyl bromide was prepared on a 1-mmol scale from solanesol as described.[38] The viscous oil obtained (683 mg) was chromatographed (5% ether–petroleum ether) on a short-path column (*ca.* 1 cm) to yield pure solanesyl bromide as a waxy white solid (589 mg, 85%): mp 41.5–43° (lit.[38] oil); nmr δ 1.63 (s, cisoid=CCH_3), 1.68 (s, transoid=$C(CH_3)_2$), 1.73 (d, J = 1 Hz, $BrCH_2CH{=}CCH_3$), 2.03 (br, CH_2CH_2), 4.02 (d, J = 9 Hz, $BrCH_2$), 5.13 (br, CH=), 5.53 (t, J = 9 Hz, $BrCH_2CH{=}$).

Menaquinone-2 (1a) *via* Alkylation of 2-Methyl-1,4-naphthoquinol Monopotassium Salt (14) with Geranyl Bromide (*trans*-16). With Potassium Hydride. Naphthoquinol **2** (87 mg, 0.50 mmol) was placed in a 2-ml round-bottom vessel under a nitrogen atmosphere, potassium hydride (20.0 mg, 0.50 mmol) was added and the vessel sealed with a serum stopper. Toluene (distilled from sodium, 2.0 ml) was added by syringe and the reaction was stirred at 110° until hydrogen evolution ceased (24 hr). After cooling to room temperature, geranyl bromide (96 μl, 109 mg, 0.50 mmol) was added and the reaction was stirred magnetically for 18 hr after which time gc analysis indicated geranyl bromide (40%) remaining. After 3 days an identical percentage of **16** starting material remained so the reaction was then decomposed with 1 *N* HCl (0.5 ml) and extracted with ether (10 ml). The resulting organic phase was washed with saturated NaCl and oxidized with excess silver (I) oxide to obtain crude quinone, which was chromatographed (5% ether–petroleum ether) to yield 2-methyl-1,4-naphthoquinone (40 mg, 47%) and menaquinone-2 (**1a**) (26 mg, 17%, 96% trans):[45] mp 52–53° (lit.[6d] 51–53°); nmr δ 1.57 (s, cisoid=$C(CH_3)_2$), 1.62 (s, transoid=$C(CH_3)_2$), 1.78 (s, =CCH_3), 2.03 (br, $-CH_2CH_2-$), 2.17 (s, $ArCH_3$), 3.37 (d, J = 7 Hz, $ArCH_2$), 5.05 (br t, J = 7 Hz, CH=), 7.6–8.2 (m, ArH).

With Potassium Methoxide. A 1.00 *M* solution of potassium methoxide in methanol was prepared by adding potassium to absolute methanol under nitrogen and degassed by freezing and thawing under vacuum. Naphthoquinol **2** (87 mg, 0.50 mmol) was placed in a 2-ml vessel under nitrogen atmosphere and the vessel was sealed with a serum stopper. The potassium methoxide solution was added by syringe (0.50 ml, 0.50 mmol) and the methanol then removed. The dry toluene (2.0 ml) was added followed by geranyl bromide (96 μl, 109 mg, 0.50 mmol) and the reaction was stirred magnetically at room temperature for 24 hr. Gc analysis (T = 90°) indicated complete consumption of geranyl bromide; the reaction product was isolated, oxidized, and purified as above to yield 2-methyl-1,4-naphthoquinone (26 mg, 30%) and **1a** (35 mg, 23%).

Selective Demethylation of 2-Methyl-1,4-dimethoxynaphthalene (3). With Lithium Iodide. Anhydrous lithium iodide (670 mg, 5 mmol) was heated at 160° under vacuum for 1 hr. After cooling, 2-methyl-1,4-dimethoxynaphthalene (**3**) (202 mg, 1.00 mmol) and DMF (distilled from and stored over 4Å molecular sieves, 2.5 ml) were added. The reaction was refluxed for 24 hr, then quenched with water and extracted once with ether (50 ml). The ether layer was washed with water, dried over saturated NaCl, and evaporated to yield crude product. Chromatography (benzene) gave a mixture of 4-methoxy-3-methyl-1-naphthol (**4**) and 4-methoxy-2-methyl-1-naphthol (**5**) (94 mg, 50%) which was resolved by further chromatography into **4** (19 mg, 10%) and **5**, (57 mg, 30%) as impure crystalline material. Both could be further purified by recrystallization from benzene–petroleum ether. (**4**): mp 145–147° (lit.[21] mp 150–152°); tlc (benzene) R_f 0.37; nmr δ 2.36 (s, $ArCH_3$), 3.85 (s, $ArOCH_3$), 6.53 (s, 3-ArH), 7.2–8.2 (m, ArH).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4. Found: C, 76.8; H, 6.3.

Monoether **5** proved identical with a sample prepared previously in our laboratories:[24a] mp 101–103°; tlc (benzene) R_f 0.57; nmr δ 2.36 (s, $ArCH_3$), 3.92 (s, $ArOCH_3$), 6.54 (s, 3-ArH), 7.2–8.2 (m, ArH).

With Mercaptide. A solution of ethanethiol (2.22 ml, 1.86 g, 30 mmol) in ether (to 50 ml) was prepared. An aliquot (10.0 ml, 6 mmol) was added to a 25-ml flask containing dimethyl ether (**3**) (202 mg, 1.00 mmol). Butyllithium (5.00 mmol) was then added dropwise with stirring and cooling. After complete addition, solvents and excess ethanethiol were removed by nitrogen sweep followed by a brief evacuation. Then dry DMF (2.5 ml) was added and the mixture was refluxed for 15 min. After cooling 2 *N* HCl (3 ml) was added and the reaction mixture was extracted once with ether. The ether extract was washed, dried over saturated NaCl, and evaporated to yield a crude product which was chromatographed (5–20% ether–benzene) to yield a mixture of monoethers **4** and **5** (122 mg, 65%) in a **4** to **5** ratio of 1 to 3, as estimated by tlc (C_6H_6).

Selective Methylation of 2-Methyl-1,4-naphthoquinol (2). Hydroquinone **2** (174 mg, 1.00 mmol) and anhydrous potassium carbonate (276 mg, 2 mmol) were dried together at 100° for 1 hr under vacuum. Then acetone (stored over 4Å molecular sieves, 2 ml) and methyl iodide (62 μl, 142 mg, 1.00 mmol) were added to the serum stoppered vessel. After heating at 56° for 20 hr, the reaction was added dropwise to 1 *N* HCl (1.0 ml) and the resulting solution was extracted with ether (15 ml). The crude product obtained from evaporation of the ether phase was chromatographed to yield dimethyl ether (**3**) (48 mg, 24%) and a 1:3 mixture of monoethers **4** and **5** (88 mg, 47%).

2-Methyl-4-benzyloxy-1-naphthyl Acetate (11). To 2-methyl-1,4-naphthoquinol 1-acetate (**7**) (1.30 g, 6.00 mmol) and potassium carbonate (1.66 g, 12.0 mmol), dry acetone (18 ml) and benzyl bromide (0.89 ml, 1.28 g, 7.5 mmol) were added and the reaction was refluxed for 24 hr. The salts were removed by filtration and the residue obtained after solvent evaporation was triturated with petroleum ether (10 ml) to obtain crystalline **11** (1.81 g, 98%): mp 105–107°; tlc (20% ether–petroleum ether) R_f 0.38; nmr δ 2.28 (s, $ArCH_3$), 2.43 (s, OAc), 5.19 (s, $-CH_2-$), 6.67 (s, 3-ArH), 7.2–8.4 (m, ArH).

Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.4; H, 5.9. Found: C, 78.0; H, 5.9.

2-Methyl-4-benzoxy-1-naphthol (12). To naphthyl ether ester **11** (1.76 g, 5.75 mmol) and absolute ethanol (10 ml) was added aqueous potassium hydroxide solution (2.0 *N*, 10 ml) and the reaction was heated briefly at 100° until complete solution was achieved. After cooling and neutralizing with aqueous HCl (1.0 *N*, 20 ml) the resulting fluffy precipitate of **12** was obtained by filtration. Crude yield: 1.43 g (90%). An analytical sample was obtained by recrystallization from benzene: mp 80° dec; tlc (benzene) R_f 0.33; nmr δ 2.38 (s, $ArCH_3$), 5.15 (s, $-CH_2-$), 6.64 (s, 3-ArH), 7.2–8.4 (m, ArH).

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.8; H, 6.1. Found: C, 81.5; H, 6.0.

1-Methoxy-2-methyl-4-benzyloxynaphthalene (13). Naphthyl benzyl ether (**12**) (1.38 g, 5.23 mmol), anhydrous potassium carbonate (1.45 g, 10.5 mmol), and dry acetone (16 ml) were mixed. Methyl iodide (0.655 ml, 1.49 g, 10.5 mmol) was added and the reaction was refluxed (14 hr). Petroleum ether (950 ml) was then added, the salts were removed by filtration, the filtrate was evaporated, and the residue was dissolved in 1 ml of benzene followed by petroleum ether (20 ml). Crystallization occurred at 4° to yield **13** (1.23 g, 85%); mp 106–108°; tlc (benzene) R_f 0.69; nmr δ 2.38 (s, $ArCH_3$), 3.82 (s, OCH_3), 5.15 (s, $-CH_2-$), 6.61 (s, 3-ArH), 7.2–8.4 (m, ArH).

Anal. Calcd for $C_{19}H_{18}O_2$: C, 82.0; H, 6.5. Found: C, 81.9; H, H, 6.7.

4-Methoxy-3-methyl-1-naphthol (4). Methyl benzyl ether (**13**) (925 mg, 3.33 mmol), with 10% Pd/carbon (286 mg) in ethyl acetate (20 ml), was hydrogenated at atmospheric pressure for 38 hr. Catalyst was removed by centrifugation and the crude product obtained by solvent evaporation was determined to contain *ca.* 10% of a methyl ether impurity [nmr δ 2.16 (s, $ArCH_3$), 3.67 (s, $ArOCH_3$), 6.40 (s, 3 ArH) and tlc (10% ether–benzene) R_f 0.77] presumed to be the tetrahydroderivative of **4.** Crystallization from benzene–petroleum ether gave pure **4** as a greyish solid (473 mg, 75%), as characterized above.

Menaquinone-2 *via* Alkylation of the Potassium Salt of 4 (15) with *trans* 16. Methyl ether **4** (83 mg, 0.45 mmol) and potassium hydride (17.6 mg, 0.45 mmol) under nitrogen and in 1.6 ml of toluene were stirred at 110° until hydrogen evolution ceased (1 hr). After cooling to room temperature geranyl bromide (*trans*-**16,** 77 μl, 87 mg, 0.40 mmol) was added and the reaction was stirred for 24 hr. The reaction was diluted with petroleum ether (*ca.* 5 ml) and the salts were removed by centrifugation. The solvents were then evaporated and, under nitrogen, ether (1.0 ml), 95% ethanol (1.0 ml), and aqueous ferric chloride (1.0 *M*, 1.0 ml, 1.0 mmol) were added sequentially. The resulting heterogeneous reaction was

stirred for 15 min and then partitioned between petroleum ether and water. The organic phase was evaporated and the crude product chromatographed (5% ether/pet ether) to yield pure MK-2 (55 mg, 45%, 96% trans).

2-Metallo-3-methyl-1,4-dimethoxynaphthalenes (20a–d). 2-Lithio-3-methyl-1,4-dimethoxynaphthalene (**20a**) was prepared as previously described.[5a] A 0.5-mmol preparation was quenched with deuterium oxide (0.5 ml) and the crude product was obtained by extraction with petroleum ether. Nmr integration of the 3-aromatic proton *vs.* the 5,6,7,8 protons indicated 99% deuterium at the 3 position.

Lithium di(3-methyl-1,4-dimethoxy-2-naphthyl)cuprate (**20b**) was prepared by adding cuprous bromide (MCB, 36 mg, 0.25 mmol) to a preparation of **20a** (0.50 mmol, 0.5 *M*). After vigorous stirring for 15 min a brownish precipitate of cuprate **20b** formed. This was utilized without further purification or characterization.

3-Methyl-1,4-dimethoxynaphthyl-2-magnesium bromide (**20c**) was prepared by the action of freshly prepared magnesium filings (12.0 mg, 0.50 mmol) on 2-bromo-3-methyl-1,4-dimethoxynaphthalene[46] (141 mg, 0.50 mmol) in dry THF (1.0 ml). A clear solution was obtained after 3 hr stirring at room temperature. This preparation was quenched with deuterium oxide (0.5 ml) and the 2-methyl-1,4-dimethoxynaphthalene so obtained was determined by nmr integration as above to contain 97% deuterium at the 3 position. Further efforts to reduce the moisture content of the system failed to raise this percentage incorporation so it was assumed that proton abstraction from some other position in the molecule was occurring.

The above prepared Grignard reagent (0.50 mmol) was treated with cuprous bromide (72 mg, 0.50 mmol) and after brief stirring a gelatinous precipitate formed which upon further stirring gave a homogeneous clear solution of 2-cupro-3-methyl-1,4-dimethoxynaphthalene (**20d**). The reagent was not further characterized.

***trans*-2-Methyl-3-(1-oxy-3,7-dimethyl-2,6-octadienyl)-1,4-dimethoxynaphthalene (24).** *trans*-**24** was prepared from 99% *trans*-citral and **20a** as previously described for *cis*-/*trans*-citral.[5a] The compound so prepared proved indistinguishable (tlc and nmr) from the cis–trans mixture of **24.**

Hydrogenolysis of 24. With Lithium Aluminum Hydride. A suspension of lithium aluminum hydride (38 mg, 1.0 mmol) in dry ether (2.5 ml) was prepared and *trans*-**24** (177 mg, 0.5 mmol) was added in ether solution (2.5 ml). The reaction was stirred for 1 hr and the product was isolated by addition to wet ether. The ether solution was washed with 2 *N* sulfuric acid and water and then dried over magnesium sulfate. Crude product obtained upon solvent evaporation was chromatographed (30% ether/pet ether) to recover **24** (159 mg, 90%) containing by nmr 25% *trans*-2-methyl-3-(1-oxy-3,7-dimethyl-6-octenyl)-1,4-dimethoxynaphthalene (**29,** saturated absorptions, δ 0.7–1.4); **29** and **24** were inseparable chromatographically.

With Lithium Aluminum Hydride–Aluminum Chloride. A suspension of lithium aluminum hydride (38 mg, 1.0 mmol) in dry ether (2.5 ml) was treated with a solution of aluminum chloride (121 mg, 0.91 mmol) in ether (4.5 ml). *trans*-**24** (177 mg, 0.5 mmol) was then added in ether (2.5 ml) and the reaction vessel was sealed with a serum stopper and heated at 40° for 16 hr. Isolation as before gave crude product which was chromatographed (5% ether–petroleum ether) to yield a mixture of *trans*-2-methyl-3-(3,7-dimethyl-2,6-octadienyl)-1,4-dimethoxynaphthalene (**25**) and *trans*-2-methyl-(3,7-dimethyl-1,6-octadienyl)-1,4-dimethoxynaphthalene (**27**) as a colorless oil (134 mg, 80%): tlc (5% ether–petroleum ether) R_f 0.58; nmr (CCl_4) **25** δ 1.57, 1.63 (s, $=C(CH_3)_2$), 1.80 (s, $=CCH_3$), 2.00 (m, $-CH_2CH_2-$), 2.31 (s, $ArCH_3$), 3.53 (d, J = 6 Hz, $ArCH_2$), 3.85 (s, $ArOCH_3$), 5.05 (m, CH=), 7.2–8.2 (m, ArH), and **27** δ 1.15 (d, J = 7 Hz, $-CH(CH_3)-$), 2.35 (s, $ArCH_3$), 6.1–6.6 (m, -CH=CH-). The mixture was estimated to contain 70% of **25** by interation of aromatic methyl absorptions.

***trans*-2-Methyl-3-(3-chloro-3,7-dimethyl-1,6-octadienyl)-1,4-dimethoxynaphthalene (38).** *trans*-**24** (106 mg, 0.3 mmol) in dry CCl_4 (1 ml, distilled from phosphorous pentoxide) was treated with tri-*n*-butylphosphine (78 μl, 64 mg, 0.315 mmol). Immediately a slight opalescence developed and after an hour the reaction was partitioned between petroleum ether and water. Crude product was obtained as a colorless oil by evaporation of the petroleum ether phase: nmr δ 1.80 (s, $-C(CH_3)Cl-$), 2.38 (s, $ArCH_3$), 3.75, 3.80 (s, $ArOCH_3$), 5.10 (br, CH=), 6.40, 6.70 (d, J = 16 Hz, -CH=CH-), 7.2–8.2 (m, ArH). Chromatography (5% ether–petroleum ether) gave triene mixture **39** (89 mg, 88%) again as a colorless oil: tlc (5% ether–petroleum ether) R_f 0.58; nmr δ 1.67, 1.71 (s, $=C(CH_3)_2$), 1.93, 1.98 (d, J = 1.5 Hz, $=C(CH_3)$), 2.39 (s, $ArCH_3$), 2.9 (m, $-CH_2-$), 3.71, 3.78 (s, $ArOCH_3$), 4.9–6.7 (m, CH=), 7.0–8.0 (m, ArH); mass spectrum *m/e* 336 (M^+, 5%), 334 (5), 270 (40), 239 (100), 230 (50), 215 (40). Chloride **38** was also converted to triene **39** upon standing ($t_{1/2}$ = 12 hr).

Hydrogenolysis of 38. With Lithium Aluminum Hydride. Benzylic allylic chloride (**38**) was prepared on a 0.5-mmol scale as above and added in ether solution (2 ml) to a suspension of lithium aluminum hydride (30 mg, 0.8 mmol) in ether (2 ml). After stirring for 1 hr the reaction mixture was partitioned between wet ether–2 *N* sulfuric acid. Crude product obtained from the ether extract was chromatographed (5% ether–petroleum ether) to yield a purified oil (116 mg, 70%) containing **25:27:39** in a 40:32:28 ratio as determined by nmr integration of the corresponding aromatic methyl absorptions.

With Lithium Triethylborohydride. Lithium hydride (119 mg, 15 mmol) and dry tetrahydrofuran (distilled from lithium aluminum hydride, 19 ml) were mixed and triethylborane in hexane (Texas Alkyls, 0.79 g/ml, 16.8% TEB, 11.1 ml, 15 mmol) was added. The reagent was stirred overnight and the titer of the resulting solution of lithium triethylborohydride was assumed (0.50 *M*). Chloride **38,** prepared on a 0.5-mmol scale, was dissolved in petroleum ether (1.0 ml) and treated with the lithium triethylborohydride solution (3 ml, 1.5 mmol). After stirring for 2 hr the reaction was partitioned between petroleum ether and water and the crude product obtained from evaporation of the petroleum ether phase was chromatographed (5% ether–petroleum ether) to yield a nonpolar fraction (120 mg, 71%) containing **25:27:39** in a 38:28:34 ratio.

Attempted Preparation of 2-Methyl-3-(1-bromo-3,7-dimethyl-2,6-octadienyl)-1,4-dimethoxynaphthalene (36). Allylic alcohol **24** (177 mg, 0.50 mmol) and pyridine (53 mg, 0.67 mmol) were dissolved in petroleum ether (1.0 ml) and phosphorous tribromide (61 mg, 0.23 mmol) in petroleum ether (1.0 ml) was added dropwise by syringe to the cooled (−10°) mixture. After 1 hr the reaction was partitioned between petroleum ether and water and the crude product was obtained from the petroleum ether phase (131 mg). By nmr this contained only triene mixture **39.**

Allylic alcohol **24** (106 mg, 0.30 mmol) and tri-*n*-butylphosphine (61 mg, 0.30 mmol) were mixed in 1 ml of dry acetonitrile and CBr_4 (105 mg, 0.32 mmol) was added. After an hour the reaction mixture was partitioned between petroleum ether and water. The crude petroleum ether soluble product was obtained and again by nmr contained only triene **39.**

Attempted Preparation of 2-Methyl-3-(1-methylsulfonyloxy-3,7-dimethyl-2,6-octadienyl)-1,4-dimethoxynaphthalene (37). Allylic alcohol **24** (177 mg, 0.5 mmol) was dissolved in petroleum ether (3.0 ml) and mesyl chloride (39 μl, 57 mg, 0.50 mmol) was added. The reaction was cooled to 0° and triethylamine (69 μl, 51 mg, 0.50 mmol) was added dropwise with stirring over 10 min. A white precipitate of the amine hydrochloride formed. The reaction mixture was partitioned between petroleum ether and water and crude product was obtained from the petroleum ether phase. By nmr it contained only triene **39.**

***cis*-/*trans*-Menaquinone-2 (*cis*-/*trans*-1a) and *trans*-2-Methyl-3-(3,7-dimethyl-1,6-octadienyl)-1,4-naphthoquinone (28).** Dimethoxynaphthalene mixture **25/27** (56 mg, 0.166 mmol) obtained from the lithium aluminum hydride–aluminum chloride hydrogenolysis of *trans*-**24** above and argentic oxide (51.5 mg, 0.415 mmole) were mixed in dioxane (1.7 ml)/water (0.17 ml) and nitric acid (6.2 *N*, 70 μl, 0.43 mmol) was added. After complete solution the reaction mixture was partitioned between petroleum ether and water, and crude product was obtained from the petroleum ether phase. This was chromatographed on kieselgel impregnated with silver nitrate (20%) and Rhodamine-6G (0.1%) (4% ether in 1:1 toluene–cyclohexane) to yield *cis*-/*trans*-**1a** as a yellow oil (25 mg, 44%, 62% trans): tlc (5% ether in 1:1 toluene–cyclohexane, silver nitrate impregnated kieselgel) R_f 0.37; uv 243 nm (ϵ 17,850), 248 (19,150), 260 (17,500), 270 (17,050), 326 (3020); nmr as reported.[6c] *trans*-**28** was also obtained from the same chromatography as a yellow oil: tlc (5% ether in 1:1 toluene–cyclohexane, silver ni-

trate impregnated kieselgel) R_f 0.50; uv 250 nm (20,500), 282 (7160), 330 (3000), 370 (2300); nmr δ 1.13 (d, J = 7 Hz, $CH(CH_3)$), 1.63, 1.70, (s, $=C(CH_3)_2$), 2.27 (s, $ArCH_3$), 5.13 (br, CH=), 6.37 (d, J = 4 Hz, -CH=CH-), 7.5-8.2 (m, ArH).

Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.8; H, 7.8. Found: C, 81.7; H, 7.5.

Menaquinone-2 (1a) from 1'-Oxomenaquinone-2 (32), 1'-Oxymenaquinone-2 (33), and 2-Methyl-3-(3'-oxy-3',7'-dimethyl-1',6'-octadienyl)-1,4-naphthoquinone (34). *cis-/trans*-1'-oxomenaquinone-2[5a] (179 mg, 0.56 mmol) dissolved in dry tetrahydrofuran (1.0 ml) was added dropwise to a refluxing solution of lithium aluminum hydride (60 mg, 1.5 mmol) in tetrahydrofuran (5 ml). After an additional hour of reflux the reaction was cooled and added to wet ether-2 *N* sulfuric acid. Oxygen was bubbled into the ether solution to obtain the crude quinone which was chromatographed (8% ether-petroleum ether) to obtain *cis-/trans*-MK-2 (**1a**) as a yellow oil (25 mg, 15%, stereochemistry not determined).

The above procedure was repeated with quinone allylic alcohols **33** and **34**,[5a] and product **1a** was obtained in 12 and 14% yield, respectively (stereochemistry not determined).

Menaquinone-2 (1a) *via* Coupling of 2-Metallo-3-methyl-1,4-dimethoxynaphthalene (20a-d) with Geranyl Chloride (*trans*-23), Geranyl Bromide (*trans*-16), and Neryl Bromide (*cis*-16). Experiment 5 (Table I). Lithio reagent **20a** was prepared on a 0.5-mmol scale, geranyl chloride (106 μl, 86 mg, 0.50 mmol) was added, and the reaction vessel was sealed *in vacuo*. The reaction was heated at 50° for 68 hr after which the vessel was opened and the geranyl chloride remaining (80%) determined by gc analysis. The reaction mixture was diluted with petroleum ether, the salts were removed by centrifugation, and crude product was obtained by evaporation of solvents. Chromatography (3% ether/pet. ether) gave the dimethyl ether of menaquinone-2 (**25**, 17 mg, 10%) and dimethoxynaphthalene (**3**) (62, mg, 62%).

Experiment 7. Lithium dinaphthylcuprate (**20b**) (0.5 mmol) was prepared and geranyl bromide added (96 μl, 108 mg, 0.50 mmol). After stirring for 17 hr the reaction mixture was partitioned between petroleum ether and water and crude product then obtained upon evaporation of the organic solvent. This was chromatographed as above to yield **25** (125 mg, 74%) and **3** (15 mg, 15%).

Experiment 10. Grignard reagent **20c** (0.55 mmol, 1.1 *M*) was prepared and geranyl bromide (0.50 mmol) was added. After 17 hr the reaction mixture was diluted with petroleum ether, the salts were removed by centrifugation, and the solvents were evaporated to give the crude product. This was chromatographed to yield an inseparable mixture of **25** (156 mg, 92%) and 2-bromo-3-methyl-1,4-dimethoxynaphthalene (**19**, 11 mg, 8%) in addition to **3** (7 mg, 7%). The determination of the **25**/**19** ratio was performed by integration of the corresponding aromatic methyl absorptions (δ 2.38 and 2.52, respectively).

Dimethyl ether mixture **25-19** (84.5 mg, 0.254 mmol) and argentic oxide (68.2 mg, 0.55 mmol) were mixed and dioxane (2.5 ml)/water (0.25 ml) added. Addition of nitric acid (6.2 *N*, 92 μl, 0.57 mmol) accomplished the oxidation. The reaction was then partitioned between petroleum ether (19 ml) and water (2 ml); and the organic phase was extracted with water (2 × 3 ml) and then evaporated. The residue was chromatographed (4% ether-petroleum ether) to yield recovered **25-19** (12 mg, 14%) and *trans*-**1a** (60 mg, 83%, 97% trans). The conversion yield based upon recovered starting material was 97%.

Experiment 11. A mixture of *cis*-**25-19** was obtained by coupling of Grignard reagent **20c** with neryl bromide (*cis*-**16**) followed by purification as above. *cis*-**25**: nmr δ 1.7 (m, $=C(CH_3)_2$ and $=C(CH_3)$), 2.2-2.3 (m, $-CH_2CH_2-$), 2.38 (s, $ArCH_3$), 3.57 (d, J = 6 Hz, $ArCH_2$), 3.90 (s, $ArOCH_3$), 5.0-5.3 (br, CH=), 7.3-8.2 (m, ArH).

Dimethyl ether mixture *cis*-**25-19** (34 mg, 0.10 mmol) and argentic oxide (27 mg, 0.22 mmol) were mixed and dioxane (1 ml)/water (0.1 ml) was added. With the exclusion of light, nitric acid (6.2 *N*, 38 μl, 0.23 mmol) was added and the product was obtained by isolation and purification as before to yield *cis*-menaquinone-2 as a yellow oil (24 mg, 82%, 85% cis). Spectral properties (uv and nmr) were coincident with those previously reported.[6d]

Experiment 13. Organocopper reagent **20d** was prepared (0.5 mmol) and geranyl bromide (**16**, 0.50 mmol) was added resulting in an immediate precipitate of cuprous bromide. After stirring for 1 hr the reaction was diluted with petroleum ether and the product was isolated as above to yield a **25-19** mixture (**25**, 138 mg, 82%; and **19**, 10 mg, 7%) and naphthalene **3** (4 mg, 4%).

The **25-19** mixture was oxidized as above with argentic oxide (2.5 equiv) and nitric acid (2.6 equiv) to yield *trans*-menaquinone-2 (87%, 97% trans). Based upon recovered starting material the conversion yield was 92%.

Experiments 6, 8, and 9 were performed in an analogous manner to those reported above.

***all-trans*-2-Methyl-3-(3,7,11,15,19,23,27,31,35-nonamethyl-2,6,10, 14,18,22,26,30,34-hexatriacontanonenyl)-1,4-dimethoxynaphthalene (26).** Grignard reagent **20c** (0.37 mmol, 0.62 *M*) was prepared and solanesyl bromide (**22**, 208 mg, 0.30 mmol) was added. After standing for 18 hr the salts were precipitated with petroleum ether and the residue obtained by solvent evaporation was chromatographed to yield the dimethyl ether of menaquinol-9 (**26**, 232 mg, 95%) contaminated with bromonaphthalene (**19**) (7 mg, 8%). A sample of **26** was obtained as a waxy solid by recrystallization from petroleum ether: mp 58-59.5°; tlc (3 % ether-isooctane) R_f 0.42; nmr δ 1.63 (s, $=C(CH_3)$), 1.83 [s, $=C(3\text{-}CH_3)$], 2.04 (s, $-CH_2CH_2-$), 2.38 (s, $ArCH_3$), 3.57 (d, J = 6 Hz, $ArCH_2$), 3.88 (s, $ArOCH_3$), 4.9-5.3 (br, CH=), 7.3-8.2 (m, ArH).

Anal. Calcd for $C_{58}H_{86}O_2$: C, 85.4; H, 10.6. Found: C, 85.4; H, 10.9.

***all-trans*-Menaquinone-9 (1b).** The dimethyl ethers of menaquinol-9 (**26**, 163 mg, 0.20 mmol) and argentic oxide (62 mg, 0.50 mmol) were mixed in dioxane (3.0 ml) and water (0.20 ml). Nitric acid (6.2 *N*, 84 μl, 0.52 mmol) was added and the reaction was stirred until complete solution. The reaction mixture was then partitioned between petroleum ether (10 ml) and water (2 ml) and the organic phase washed with water (2 × 3 ml) and evaporated. The residue was chromatographed to yield starting material (**26**, 35 mg, 22%) and *all-trans*-menaquinone-9 (**1b**, 110 mg, 70%, 98% Δ^2-trans, 89% conversion yield): mp 58-59° (lit.[6c] mp 58-59°); tlc (3% ether-isooctane) R_f 0.38; nmr δ 1.65 [s, $=C(CH_3)$], 1.82 [s, $=C(3\text{-}CH_3)$], 2.03 (s, $-CH_2CH_2-$), 2.20 (s, $ArCH_3$), 3.40 (d, J = 7 Hz, $ArCH_2$), 4.9-5.3 (br, CH=), 7.5-8.2 (m, ArH).

Complete consumption of starting material was observed when the above reaction was repeated using oxide (3.0 equiv) and nitric acid (3.1 equiv) and quinone **1b** was obtained in 77% yield.

References and Notes

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Biosynthesis of Corrins. I. Experiments with [^{14}C]Porphobilinogen and [^{14}C]Uroporphyrinogens

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Abstract: Previous work in the area of corrin biosynthesis is summarized, and the results of administering regiospecifically synthesized versions of [8-^{14}C]porphobilinogen (PBG) and [^{14}C]uroporphyrinogen (uro'gens) of types I–IV to resting cells of *Propionibacterium shermanii* are discussed in terms of the distribution of radioactivity in vitamin B_{12} (cyanocobalamin). The development of satisfactory feeding conditions, isolation procedures, and some improvement for the synthesis of intermediates are described.

Vitamin B_{12} (cyanocobalamin, **1**), one of nature's most complex nonprotein structures ($C_{63}H_{88}N_{14}O_{14}PCo$), has presented a formidable challenge at every stage of its investigation. The isolation of the crystalline "antipernicious anemia factor" from liver by Folkers[1] and Smith[2] in 1948 marks the beginning of chemical studies[3-5] which culminated in 1955 with Hodgkin's X-ray diffraction analysis.[6] In 1958, the coenzyme **2** was characterized by Barker[7] and its structure again deduced by X-ray diffraction (Hodgkin).[8] The discovery of the cobalt–carbon bond in turn opened up a whole new area of research on the remarkable rearrangements catalyzed by the coenzyme. The recent achievement[9] of the total synthesis of vitamin B_{12} represents the solution of yet another outstanding problem posed by the complex functional and stereochemical array contained in the corrin nucleus. The same structural and stereochemical features of **1** also constitute a major problem in considering the possible mode of biosynthesis of corrins (as **3**), for although it has been known for almost 20 years that vitamin B_{12} shares the "early" part of heme, chlorophyll and tetrapyrrole biosynthesis in that it is built up *via* the succinate–glycine/δ-aminolevulinate sequence,[10] the point at which the "cobalt" route divides from the "iron" and "magnesium" pathways was unknown at the outset of our investigation. From