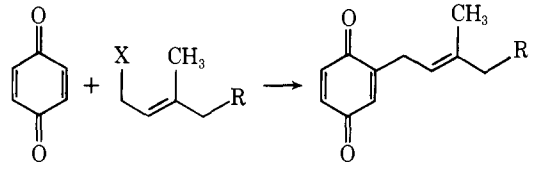
Regiospecific Quinone Isoprenylation. Examples of Remarkably Facile [3,3] Sigmatropic Processes

Sir:

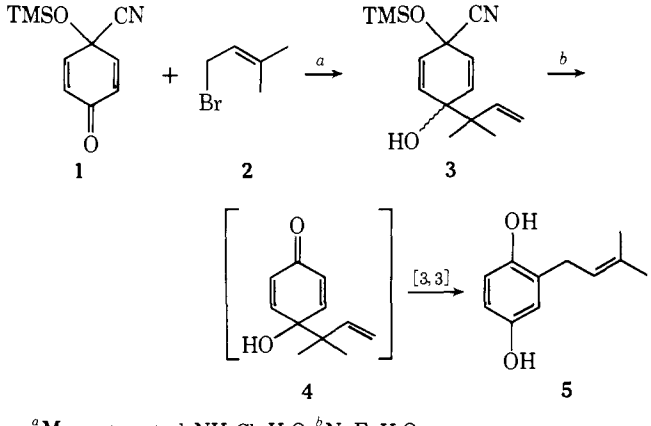
Prenylated quinones are ubiquitous natural products which are involved in diverse biological processes such as blood clotting, electron transport, and oxidative phosphorylation.[1] Invariably, approaches to the synthesis of this class of compounds have focused upon joining the quinoid and prenyl moieties by cross-coupling processes which have met with marginal success.[2-4] A notable exception may be found in the recent work of Rapoport in the synthesis of menaquinones.[3] Herein we wish to disclose a fundamentally different approach to the problem of effecting regiospecific quinone–isoprene coupling (e.g., eq 1, X = halogen).



(1)

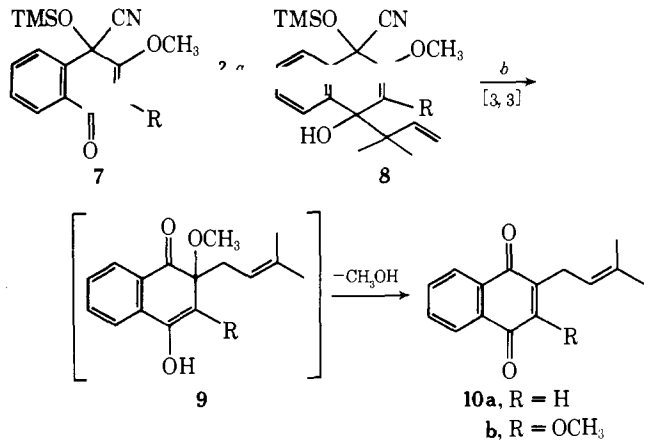
The general series of chemical transformations is outlined in Scheme I. Addition of 1 equiv of the "masked" quinone **1**[5] and 1.2 equiv of allylic bromide **2** in anhydrous ether to ca. 10 equiv of Rieke magnesium[6] in ether–benzene (1:2) at −22° over a 1.5-h period followed by the addition of saturated aqueous ammonium chloride (ca. 1 ml/equiv of quinone) and anhydrous sodium sulfate afforded the expected epimeric masked quinols (**3**) upon filtration and solvent removal. The ^{1}H NMR spectrum of **3** confirmed the illustrated mode of Grignard addition.[7,8] The masked quinols **3** were then deprotected under neutral conditions with aqueous sodium fluoride–THF (25°, 3 h) to give 2-isopentenylhydroquinine (**5**) in 70% yield, mp 96–98 °C,[9] after crystallization from carbon tetrachloride. Alternatively, treatment of **3** with silver fluoride (3 equiv) in aqueous THF (25°, 3 h) resulted in deprotection followed by rearrangement to **5** and oxidation to 2-isopentenyl-*p*-benzoquinone (**6**)[9] in 39% yield. At no point during the conversion of **3** to either **5** or **6** was there evidence for the accumulation of quinol **4** in the reaction. Therefore, the carbon skeletal reorganization that occurs during, or subsequent to, the **3** → **4** transformation must be exceptionally facile and is not a consequence of acid catalysis. Rearrangement, therefore, must either be a symmetry-forbidden [1,2]sigmatropic process with accompanying allylic rearrangement or, more likely, a Cope rearrangement. Since the quinoid nucleus **1** lacks a positional label, the present case fails to distinguish between a formal dienone–phenol rearrangement[10] (1,2-alkyl shift) and Cope rearrangement (1,3-alkyl shift). However, the following related rearrangements, vide infra, implicate the [3,3] sigmatropic process as the rearrangement pathway in the transformation of **4** to **5**.

Scheme I



[a] Mg, saturated NH_4Cl–H_2O. [b] NaF–H_2O

Scheme II

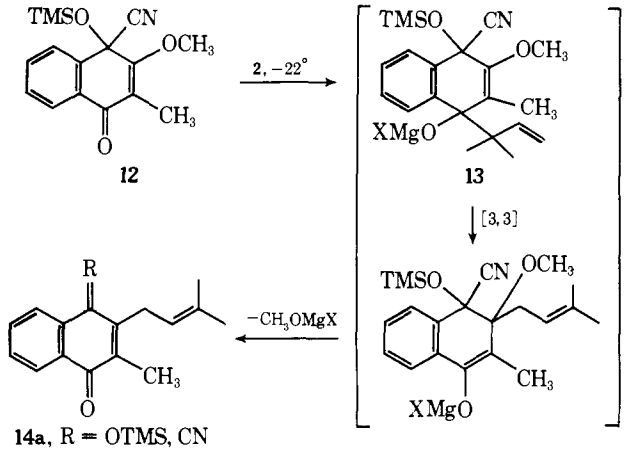


[a] Mg, saturated NH_4Cl–H_2O. [b] AgF–H_2O

Application of this isoprenylation methodology to the synthesis of naturally occurring naphthoquinones[11] helps to resolve the above mechanistic questions. Cyanide-catalyzed addition of trimethylsilyl cyanide, TMSCN, to 2-methoxy-*p*-naphthoquinone[12] (70°, 2 h) afforded the masked quinone **7a:** mp 72–73.5 °C; NMR ($CDCl_3$) δ 0.07 (s, 9 H, Me_3Si), 3.90 (s, 3 H, OMe), 5.80 (s, 1 H, vinyl), 7.31–8.17 (m, 4 H, aromatic) in 82% yield.[5,13] In situ generation and addition of the Grignard reagent derived from bromide **2** as previously described for the preparation of **3** afforded **8a** as an epimeric mixture of alcohols which could be purified by chromatography on Florisil (1.5% ethyl acetate–benzene) in 73% yield. Reaction of **8a** with 1 equiv of AgF in aqueous THF (25°, 3 h) afforded deoxylapachol (**10a**)[14] in 95% yield (Scheme II). Average yields of 67–71% of **10a** based upon **7a** have been obtained without purification of intermediates. This procedure constitutes a substantial yield improvement in the aryl–prenyl coupling method over that reported in earlier syntheses of **10a.**[14] Overall, conversion of **8a** to **10a** must involve: (1) deprotection to quinol derived from **8a;** (2) Cope rearrangement of the quinol to **9a;** and (3) loss of methanol to give **10a** where all three steps proceeded at 25° in 95% yield. The synthesis of lapachol methyl ether (**10b**)[15] from 2,3-dimethoxy-*p*-naphthoquinone (**11**)[16] proceeded in an analogous fashion. Addition of TMSCN to **11** (70°, 2.5 h) afforded **7b** in 86% yield which, upon crystallization (hexane) exhibited the following properties: mp 44.5–45.5 °C; NMR ($CDCl_3$) δ 0.10 (s, 9 H, Me_3Si), 3.82 (s, 3 H, 2-MeO), 4.23 (s, 3 H, 3-MeO), 7.27–8.12 (m, 4 H, aromatic).[13] In situ Grignard addition (ca. −20°) of **2** to **7b** afforded the isolable **8b** which rearranged to lapachol methyl ether (**10b**) upon deblocking with AgF. After chromatography on silica gel (1:1 benzene–hexane), **10b** was isolated in 62% yield, mp 51.5–52 °C.[1]

The appropriate masked quinone **12** which may serve as a general precursor to the menaquinones[3] was prepared from the requisite naphthoquinone[16] in 93% yield: mp 56–57 °C (hexane); NMR: ($CDCl_3$) δ 0.00 (s, 9 H, Me_3Si), 2.00 (s, 3 H, Me), 4.17 (s, 3 H, MeO), 7.33–8.16 (m, 4 H, aromatic).[13] Under identical conditions, in situ Grignard addition of **2** to **12** at −22° followed by aqueous ammonium chloride quench afforded **14a** directly which, by analogy to the earlier cases, must have proceeded via 1,2-carbonyl addition followed by Cope rearrangement of the magnesium alkoxide **13.** This apparent low temperature [3,3] sigmatro-

Scheme III



pic process is no longer surprising in light of our recent studies on related rearrangements[17] and illustrates a potential bond reorganization which can occur if appropriate temperature control is not maintained during carbonyl addition. Deblocking **14a** with AgF under standard conditions afforded vitamin $K_{2(5)}$ (**14b**) in 71% overall yield after chromatography on silica gel (1:1 hexane–benzene).[18]

As a consequence of the excellent regioselectivity that has been observed in the addition of TMSCN to *p*-quinones,[5] a variety of *p*-allyl quinols are now accessible. Based upon the course of related Cope rearrangements[19] it is expected that unsymmetrically substituted *p*-allyl quinols will undergo allylic rearrangement in a predictable fashion leading to unsymmetrically prenylated benzoquinones. Aside from the synthetic consequences of this approach to quinone prenylation, the observation of exceptionally facile allyl-*p*-quinol Cope rearrangements should be viewed as good precedent for the possible reinterpretation of the mechanism of related allyl quinol rearrangements[20] and other reactions which may proceed through such intermediates.[4b,20b]

Acknowledgment. We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for support of this research.

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Chemistry of Superoxide Ion. III. Quenching of Singlet Oxygen[1]

Sir:

Since McCord and Fridovich discovered that the enzymic function of erythrocuprein is the dismutation of superoxide radical to give hydrogen peroxide and oxygen,[2] numerous studies have appeared on the toxic effects of superoxide in biological systems.[3-7] Toxic effects have been attributed to hydroxyl radicals formed by reaction of superoxide with hydrogen peroxide, and it has also been reported that, although singlet oxygen does not appear to be a product of the enzyme-catalyzed dismutation of superoxide,[8,9] it may be produced in the uncatalyzed dismutation in aqueous solution.[8,10,11] Several authors have also reported that *no* singlet oxygen is produced in this process.[12,13]

$$2O_2\cdot^- + 2H^+ \rightarrow H_2O_2 + O_2\ (^1\Delta_g \text{ or } ^3\Sigma_g^-)$$

Krinsky found that human polymorphonuclear leukocytes kill a colorless mutant strain of *Sarcina lutea* more readily than a carotenoid-containing strain;[14] since carotenoids are powerful quenchers of singlet oxygen,[15] Krinsky postulates that singlet oxygen, perhaps produced by the dismutation of superoxide in leukocytes, may be an active bactericidal species.

Because of the interest in this topic, we undertook a quantitative study of the yield of singlet oxygen produced by the dismutation of tetramethylammonium superoxide[1] in organic solvents with added water, using various olefinic traps.[16,17] The results were erratic, depending on the acceptor and on the concentration of superoxide ion. It occurred to us that a possible explanation for the erratic results is that $O_2\cdot^-$ could quench singlet oxygen by electron transfer, according to the reaction shown below, and that this reaction might well be very rapid.

$$^1O_2 + O_2\cdot^- \rightarrow O_2\cdot^- + {}^3O_2 + 22 \text{ kcal}$$

In order to determine whether this reaction was occurring, we have studied the kinetics of photooxygenation of diphenylisobenzofuran (F) with added tetramethylammonium superoxide,[21,27] using the technique of Young[18] as used previously by our group.[19,20] The kinetic scheme for the reaction of the fluorescent F (rate constant k_R) with singlet oxygen, in competition with the quenching of singlet oxygen by $O_2\cdot^-$ (k_Q) and decay of $^1O_2$ (k_d) is as shown in eq 1.