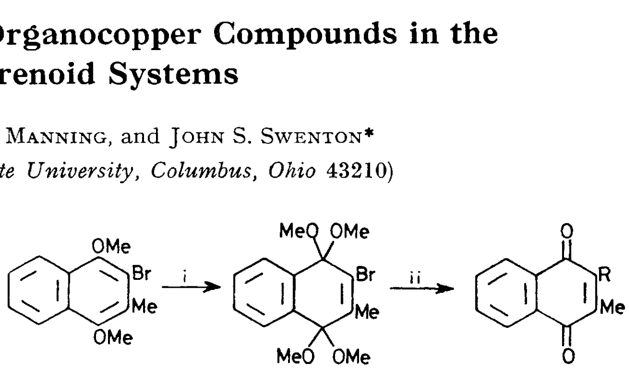
Utilization of Quinone Bisacetal Organocopper Compounds in the Synthesis of Isoprenoid Systems

By Peter W. Raynolds, Michael J. Manning, and John S. Swenton*
(*Department of Chemistry, The Ohio State University, Columbus, Ohio* 43210)

Summary Organocopper derivatives of electrochemically derived quinone bisacetals couple in high yield with allylic halides, allowing an easy synthesis of certain isoprenoid natural products.

We recently reported[1] that 2-lithio-1,1,4,4-tetramethoxycyclohexa-2,5-diene (**1**), efficiently generated by anodic oxidation of 2-bromo-1,4-dimethoxybenzene followed by metallation, reacted with a variety of carbonyl compounds to afford after hydrolysis substituted quinones in good yield. However, this organolithium reagent does not afford acceptable results in reactions with activated halides. We report here (i) the preparation of divinyl copper-lithium reagents formed from congeners of (**1**) which efficiently react with allylic halides and (ii) the utility of these species in the synthesis of vitamin $K_{2(5)}$[2] (**4a**), menaquinone-2[3] (**4b**), vitamin K_1[4] (**4c**), cymopol[5] (**12**), and cymopol monomethyl ether[5] (**11**).

Anodic oxidation of (**2**) in a divided cell as previously described afforded the bisacetal (**3**) in 85% yield.[6] Reaction of the copper–lithium reagent derived from (**3**) [BuLi (1 equiv.), Cu_2I_2 (0·5 equiv.), Me_2S (4 equiv.) in tetrahydrofuran (THF); −60 °C] with prenyl (0·5 equiv.), geranyl (0·5 equiv.), and phytyl bromide (1·0 equiv.) gave (**4a**) (92%), (**4b**) (96%), and (**4c**) (93%), respectively,† after hydrolysis of the crude reaction mixture (1 : 1 THF–1N-HCl; 70 °C; 12 h) and silica gel chromatography.



(2) (3) (4)

a; R = $-CH_2CH{=}CMe_2$
b; R = $-CH_2CH{=}C(Me)CH_2CH_2CH{=}CMe_2$
c; R = $-CH_2CH{=}C(Me)[CH_2CH_2CHMe]_2CH_2CH_2CHMe_2$
Reagents: i, Electrolysis, MeOH–KOH; ii, a, Bu^nLi, b, Cu_2I_2–Me_2S, c, RBr, d, H_3O^+.

The synthesis of cymopol monomethyl ether (**11**), a compound recently isolated from green algae,[5] illustrates the potential of the organocopper chemistry when utilized in conjunction with the regioselective hydrolysis of one acetal function of quinone bisacetals.[6] Anodic oxidation of (**5**) in a single-cell apparatus yielded the bisacetal (**6**) (m.p. 140—141 °C) in 58% yield. The copper–lithium reagent was formed as described above and treated with geranyl bromide (0·5 equiv.) at −20 °C to give (**7**)‡ (84%, oil), showing the expected n.m.r. spectrum. Hydrolysis of one acetal function of (**7**) (9 : 1 THF–0·5N-HCl; −20 °C; 24 h) gave a 4 : 1 mixture of two compounds by n.m.r. analysis. The major product (**8**) is described below. The minor product is tentatively assigned structure (**9**) on the

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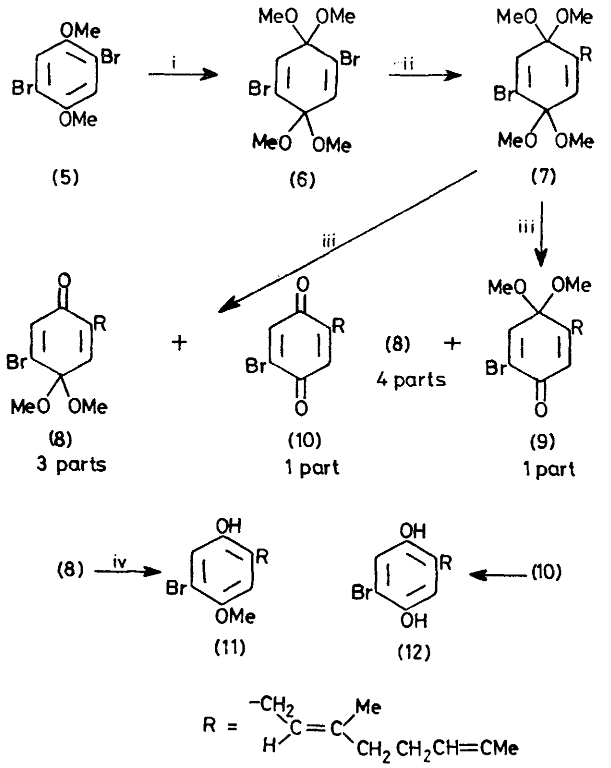
† While the ^1H n.m.r. spectrum suggested no side-chain isomerization in (**4a**—**c**) we cannot exclude the presence of a small amount of *cis*-isomer.

‡ The ^{13}C n.m.r. spectra of (**7**), (**8**), and (**11**) showed no indication of side-chain isomerization in these reactions.



Reagents: i, Electrolysis, MeOH; ii, a, Bu^nLi, b, Cu_2I_2–Me_2S, c, RBr; iii, H_3O^+; iv, Zn–Cu, THF.

basis of n.m.r.§ signals at δ 7·22 (s, 1H), 6·17 (m, 1H), and 3·42 (s, 6H). Since the isomers (**8**) and (**9**) were inseparable, the mixture [or (**7**) itself] was hydrolysed under more vigorous conditions (4 : 1 acetone–0·5N-HCl; room temp.; 2·5 h) to give a 3 : 1 mixture of (**8**)‡ and (**10**). Chromatography on neutral alumina (2% ether–hexane) decomposed the quinone, and (**8**) (73%) was the only product eluted: yellow oil, n.m.r.§ (CCl_4) δ 6·70 (s, 1H), 6·47 (distorted t, *J* 1·5 Hz, 1H), 3·22 (s, 6H), and 2·98 (br. d, *J* 7 Hz, 2H); u.v. (MeOH) 242 nm (ϵ 8170); i.r. (film) 1669 cm^{-1}

The location of the carbonyl group in (**8**) was assigned by n.m.r. analysis of the product of reduction with sodium borohydride after equilibration with D_2O[6] [characterized by n.m.r. analysis§ only: δ 6·73 (d, *J* 3·5 Hz, 1H), 5·58 (m, 1H), 4·42 (br. d, *J* 3·5 Hz, 1H), 3·23 (s, 3H), 3·15 (s, 3H), and 3·02 (br. d, *J* 8 Hz, 2H)]. The vinylic proton *cis* to the bromine, at δ 6·73, is coupled by 3·5 Hz to the adjacent tertiary proton which appears at δ 4·22 as a doublet further broadened by the typically small allylic coupling. This coupling pattern is expected for the reduction product from structure (**8**), and is not consistent with that from structure (**9**).

Zinc-copper couple reduction of (**8**) [Zn–Cu, (2 equiv.), THF–$MeCO_2H$–H_2O (6 : 3 : 1); reflux; 1 h] gave (**11**)‡ [95%; oil; δ (CCl_4)§ 6·87 (s, 1H), 6·58 (s, 1H), 5·09 (br. s, 1H, disappears with EtOD), 3·75 (s, 3H), and 3·20 (d, *J* 7 Hz, 2H); u.v. (MeOH) 297 nm (ϵ 5440)], 3,5-dinitrobenzoate, m.p. 99·5—100·5 °C. Hydrolysis of (**7**) to (**10**) (4 : 1 acetone–0·5N-HCl; room temp.; 24 h) followed by reduction of the crude product with sodium dithionite gave (**12**) (92%), m.p. 59—61 °C,[5] showing the i.r. and n.m.r. absorptions previously described.

The ready availability of these metallated quinone acetals and their high-yield coupling reactions with allylic halides suggest much utility for these reagents in the synthesis of selected isoprenoid systems.

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§ The n.m.r. spectrum also contained multiplets due to the geranyl unit: δ *ca.* 5·3—4·8 (2H), 2·2—1·9 (4H), and 1·8—1·5 (9H).

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