Intermolecular Cycloaddition Reaction of Unactivated Alkenes and *o*-Quinone Methides generated by Electrochemical Oxidation: a Proposed Biomimetic Approach to the Euglobal Skeletons

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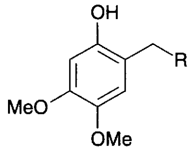
Electrochemical oxidation of *o*-[1-(phenylthio)alkyl]phenols in lithium perchlorate–nitroalkane gives corresponding *o*-quinone methides, which are trapped by unactivated alkenes to form chromanes including euglobal skeletons.

Recently, synthetic methods for the construction of chromane and spirochromane skeletons have been investigated as routes to robustadial dimethyl ethers and their important synthetic intermediates.[1] Natural robustadials (*e.g.* robustadial A **1**, B **2**) and euglobals (*e.g.* euglobal Ia$_1$ **3**, Ia$_2$ **4**), isolated from *Eucalyptus* as antimalarial compounds or inhibitors on Epstein–Barr virus activation,[2] show a variety of cycloadduct structures composed of terpenes and phloroglucinols, which suggest the biogenetic cycloaddition of corresponding terpenes and *o*-quinone methides. Although several methods for the formation of unstable *o*-quinone methides have been reported,[3] further intermolecular reaction with unactivated alkenes has proved difficult.

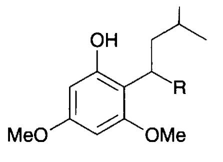
Previously, the lithium perchlorate–nitromethane system was found to accelerate Diels–Alder reaction of quinones generated *in situ* by electrochemical oxidation,[4] and our interest in this area led us to investigate the generation and cycloaddition of unstable intermediates. In the present study, *o*-[1-(phenylthio)alkyl]phenols were converted to the corresponding *o*-quinone methides by electrochemical oxidation in the lithium perchlorate–nitroalkane system, and were then successfully trapped *in situ* by unactivated alkenes to form chromanes, including euglobal Ia$_1$ and Ia$_2$ skeletons.

4,5-Dimethoxy-2-[1-(phenylthio)methyl]phenol **6** and 3,5-dimethoxy-2-[3-methyl-1-(phenylthio)butyl]phenol **8** were obtained from the corresponding *o*-hydroxybenzyl alcohols **5** and **7** by the substitution of thiophenol in the presence of ZnI_2 in CH_2Cl_2.[5] These phenols gave oxidation peaks (**6** 850, **8** 980 mV *vs.* SCE) on CV (0.5 mol dm^{-3} $LiClO_4$ in $MeNO_2$). Anodic oxidation of **6** or **8** (0.07–0.2 mmol) was, therefore, carried out in 15 ml of 0.5 mol dm^{-3} lithium perchlorate–nitromethane or nitroethane solution, containing 4–10 equiv. of alkene, at these peak potentials using a glassy carbon plate (6 × 2 cm) as the anode and a platinum plate (1 × 1 cm) as the cathode, respectively, without separating the two electrodes under Ar. The reaction was quenched at *ca.* 1.2–1.5 F mol^{-1} to afford the desired compounds. Table 1 shows the result of the cycloaddition reaction of the unactivated alkenes with phenols **6** and **8**. For example, anodic oxidation of **6** (20 mg) in the presence of 2-methylbut-2-ene **9** (20 mg) was completed after 4 h to yield cycloadduct **14** in 74% yield. Phenol **6** and cyclohexene **11** gave the *cis* adduct **18** with the rearranged spiro compound **19**. Acid-unstable methylene cyclohexane **12** gave the desired spirochromanes **20** or **21** without isomerization to 1-methylcyclohexene **10**. Furthermore, electrochemical oxidation of **8** with (−)-α-phellandrene **13** yielded **23** and **24**, which correspond to the skeletons of euglobal Ia$_1$ **3** and Ia$_2$ **4**, respectively. The stereochemistry of **23** and **24** was confirmed by differential NOE, and the ^1H and ^{13}C NMR spectra of the terpene moieties were similar to those of **3** and **4**, respectively.† These cycloaddition reactions were stereo- and regio-selective to form the *cis* adducts, whose ether oxygens were attached to the C-1′ position. In addition, compound **13** was attacked from the less hindered side by the *o*-quinone methides generated from **6** or **8**. These selectivities should match those of the biogenesis of natural euglobals.

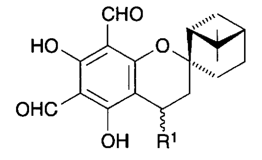
When compounds **6** or **8** were allowed to stand in the presence of alkenes for 48 h, without current and in lithium perchlorate–nitromethane under Ar, scarcely any cycloaddition products were observed. Furthermore, no product was observed after Ag_2O oxidation of **6** or **8** dissolved in the unactivated alkenes. The cycloaddition reaction must, therefore, proceed by one-electron oxidation of the sulfide followed by the elimination of a phenylthio radical to give the corresponding *o*-quinone methides, which subsequently form cycloadducts with alkenes.



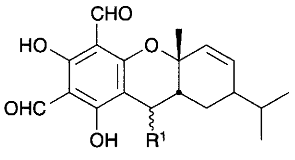
5 R = OH
6 R = SPh



7 R = OH
8 R = SPh



Robustadial A **1** : R^1=7β–CH_2CHMe_2
Robustadial B **2** : R^1=7α–CH_2CHMe_2



Euglobal Ia$_1$ **3** : R^1=7β–CH_2CHMe_2
Euglobal Ia$_2$ **4** : R^1=7α–CH_2CHMe_2

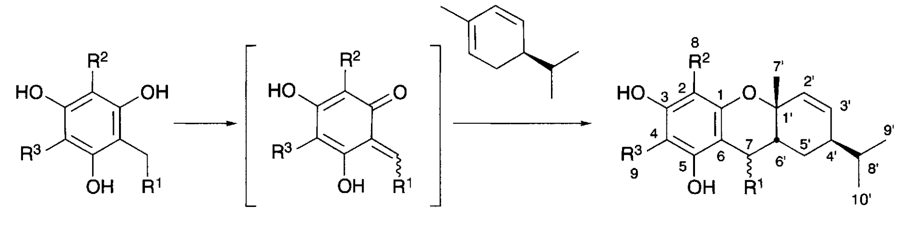
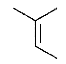
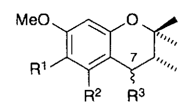
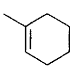
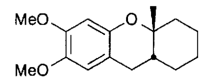
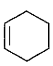
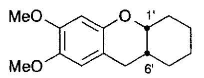
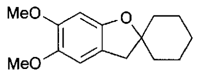
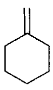
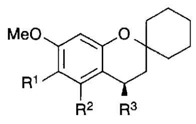
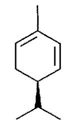
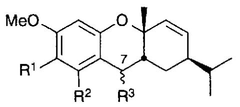
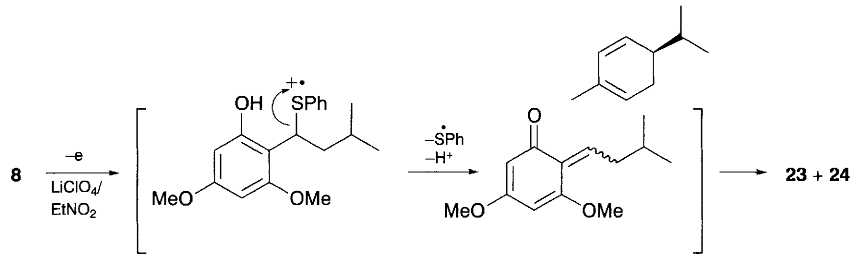


Table 1 Cycloaddition reaction of alkenes and *o*-quinone methides

Alkenes	Phenols	Products		Yields (%)
 **9**	6		**14** R^1 = OMe, R^2, R^3 = H	74^a
	8		**15** R^1 = H, R^2 = OMe, R^3 = 7α-isobutyl + **16** R^1 = H, R^2 = OMe, R^3 = 7β-isobutyl	81^b (**15**:**16** = 2:1)
 **10**	6	 **17**		53^a
 **11**	6	 **18** +  **19**		Quant.^{b} (**18**:**19** = 2:1)
 **12**	6		**20** R^1 = OMe, R^2, R^3 = H	48^a
	8		**21** R^1 = H, R^2 = OMe, R^3 = isobutyl	61^a
 **13**	6		**22** R^1 = OMe, R^2, R^3 = H	70^a
	8		**23** R^1 = H, R^2 = OMe, R^3 = 7α-isobutyl + **24** R^1 = H, R$_2$ = OMe, R^3 = 7β-isobutyl	60^b (**23**:**24** = 6:5)

Electrochemical reaction was performed in 0.5 mol dm^{-3} lithium perchlorate dissolved in ^{a} nitromethane, ^{b} nitroethane.



Scheme 1 Proposed biosynthetic reaction of natural robustadials and euglobals

It is suggested that lithium perchlorate–nitroalkane, in addition to the role of electrolyte, effectively promotes the formation of *o*-quinone methide and its cycloaddition with alkenes.

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Footnote

† *Selected data* for **23**: An oil, HRMS *m/z* [M$^+$] found 358.2506 (Calc. for $C_{23}H_{34}O_3$ 358.2506); ^{1}H NMR ($CDCl_3$) δ 0.91 (d, *J* 6.6 Hz, 3H), 0.95 (d, *J* 6.6 Hz, 3H), 0.96 (d, *J* 6.6 Hz), 6H), 1.27 (s, 3H), 1.19–1.73 (m, 5H), 1.94 (m, 1H), 2.02–2.12 (m, 2H), 3.14 (dd, *J* 8.3, 6.0 Hz, 1H), 3.73 (s, 3H), 3.75 (s, 3H), 5.80 (dd, *J* 2.5, 10.4 Hz, 1H), 5.87 (dd, *J* 3.3, 10.4 Hz, 1H), 6.05 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 20.5, 20.7, 22.4, 23.4, 23.6, 25.7, 25.8, 31.3, 32.1, 37.8 (2C), 40.7, 55.1, 55.2, 75.0, 92,1, 94.7, 109.4, 132.4, 133.0, 154.6, 158.9, 159.0; IR (NaCl) ν/cm^{-1} 2960, 1620, 1580, 1200, 1140, 1100; UV–VIS (EtOH) λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 272 (2200); $[\alpha]_D$ −30.2 (*c* 0.1, $CHCl_3$). For **24**: an oil, HRMS *m/z* [M$^+$] found 358.2532 (Calc. for $C_{23}H_{34}O_3$ 358.2506); ^{1}H NMR ($CDCl_3$) δ 0.85 (d, *J* 6.6 Hz, 3H), 0.89 (d, *J* 5.6 Hz, 3H), 0.92 (d, *J* 5.6 Hz, 3H), 0.96 (d, *J* 6.6 Hz, 3H), 1.47 (s, 3H), 1.43–1.73 (m, 6H), 2.00 (m, 1H), 2.08 (m, 1H), 2.76 (dt, *J* 3.7, 8.5 Hz, 1H), 3.73 (s, 3H), 3.76 (s, 3H), 5.45 (dd, *J* 10.3, 1.9 Hz, 1H), 5.70 (dd, *J* 10.3, 3.2 Hz, 1H), 6.05 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 19.9, 20.1, 21.9, 24.0, 26.0, 28.3, 29.9, 31.7, 31.8, 28.6, 42.0, 46.6, 55.17, 55.20, 75.9, 92.1, 94.5, 111.2, 132.6, 133.8, 154.2, 158.2, 158.8; IR (NaCl) ν/cm^{-1} 2960, 1610, 1590, 1200, 1140, 1100; UV-VIS (EtOH) λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) 272 (2000); $[\alpha]_D$ −123.5 (*c* 0.1, $CHCl_3$).

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