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The Simple Synthesis of Cordiachrome B, a Terpenoid Benzoquinone from Cordia Millenii

Takashi Watabe, Yasushi Hosoda, Keiji Okada, and Masaji Oda*
Department of Chemistry, Faculty of Science, Osaka University, Toyonaka, Osaka 560

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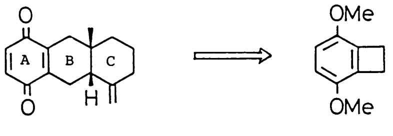
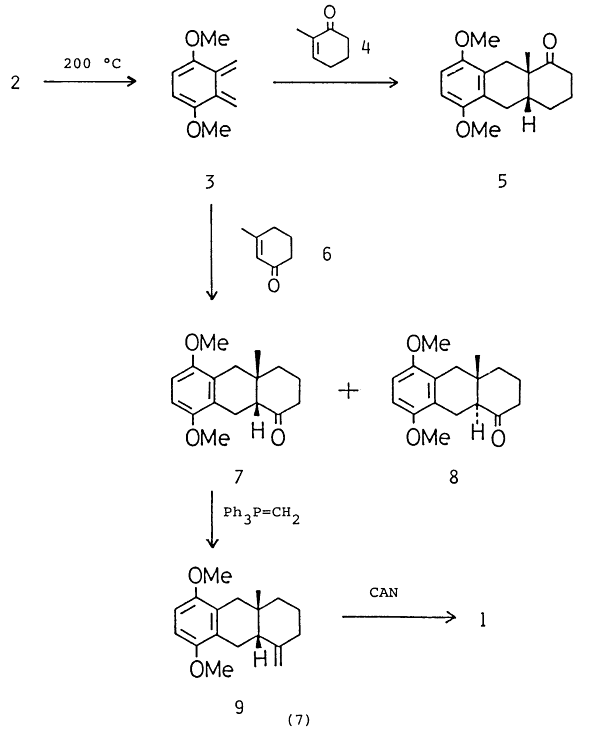
Synopsis. Cordiachrome B, a tricyclic terpenoid *p*-benzoquinone isolated from Cordia millenii, was synthesized in three steps from 1,2-dihydro-3,6-dimethoxybenzocyclobutene employing a Diels-Alder reaction in a key step.

Cordiachrome B (**1**) is a tricyclic sesquiterpene quinone isolated from the heartwood of *Cordia millenii.*[1] Its structure is featured by the cis configuration at the B-C ring juncture, which could be advantageously constructed by a Diels-Alder reaction. In the course of our studies on benzocyclobutene-3,6-quinones,[2] we have prepared 1,2-dihydro-3,6-dimethoxybenzocyclobutene (**2**) which would be a useful synthon for **1** and other polycyclic benzoquinones owing to its thermal isomerization to 1,4-dimethoxy-5,6-dimethylene-1,3-cyclohexadiene (**3**), a reactive *o*-quinodimethane. Generation of **3** through debromination of 3,6-dimethoxy-α,α'-dibromo-*o*-xylene and its trapping with typical dienophiles have been reported by Laduranty et al.;[3] however, the *o*-quinodimethane **3** thus generated seems not suitable for Diels-Alder reactions with weak dienophiles, since it will undergo ring-closure to **2** and oligomerization in competition with the Diels-Alder reaction. This situation would be improved by employing **2** as a synthetic equivalent because **3** can be thermally and reversibly generated from **2** under a high concentration of dienophiles. We here describe the first, short-step synthesis of **1** starting from **2**.



1 2

At first, thermolytic Diels-Alder reaction of **2** with 2-methyl-2-cyclohexen-1-one (**4**) was examined. Reaction of **2** and **4** (5 equivalents) in *o*-dichlorobenzene at 200 °C in an ampoule gave the cycloadduct **5** in a good yield of 75%. Less reactive 3-methyl-2-cyclohexen-1-one (**6**) required somewhat more forced conditions (8.8—10 equivalents of **6** at neat) for satisfactory cycloaddition and afforded a rather complex mixture mainly composed of the desired adduct **7** (16—28% isolated yield) and its trans-isomer **8** (30—40%). The trans adduct **8** was probably formed by epimerization of the cis adduct **7** under the reaction conditions. The higher thermodynamic stability of **8** over **7** was actually demonstrated by smooth epimerization of **7** to **8** on treatment with methanolic sodium hydroxide. Methylenation of **7** with methylenetriphenylphosphorane gave the *exo*-methylene compound **9** in 68% yield without noticeable epimerization. Finally, oxidation of **9** with ammonium cerium(IV) nitrate[4] afforded Cordiachrome B (**1**) in 74% yield. The synthetic quinone **1** was identical with the authentic sample in all respects (Mp, TLC, IR, and ^{1}H NMR).



(7)

Experimental

Melting points were measured on a Mettler FP2 apparatus and are uncorrected. IR spectra were recorded on a Hitachi EPI-G3 grating spectrophotometer. ^{1}H NMR spectra were taken on a Varian XL-100 or JEOL PMX-60SI spectrometer. Column chromatography was performed with Merck Kieselgel 60.

Thermolytic Diels-Alder Reaction of 1,2-Dihydro-3,6-dimethoxybenzocyclobutene (2) with 2-Methyl-2-cyclohexen-1-one (4). A solution of **2** (164 mg, 1.0 mmol) and **4** (550 mg, 5.0 mmol) in *o*-dichlorobenzene (3 cm^3) was heated at 200 °C in an ampoule for 15 h. The solvent and excess **4** were removed in vacuo. Chromatography of the residue on silica gel eluted with hexane-ethyl acetate (95:5 v/v) gave the cycloadduct **5** (205 mg, 75%). Recrystallization from hexane gave colorless prisms; mp 102—103 °C; IR (KBr) 1703, 1599, 1481, 1264, 1080, 952, 808 cm^{-1}; ^{1}H NMR (CDCl$_3$), δ=1.04 (s, 3H), 1.3—3.1 (m, 11H), 3.67 (s, 6H), 6.43 (s, 2H). Found: C, 74.14; H, 8.08%. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H. 8.08%.

Thermolytic Diels-Alder Reaction of 2 with 3-Methyl-2-cyclohexen-1-one (6). A mixture of **2** (492 mg, 3.0 mmol) and **6** (3.0 cm^3, 26.4 mmol) was heated at 210 °C in an ampoule for 22 h. Excess **6** was recovered by distillation in vacuo and the residue was chromatographed on silica gel to give the cis adduct **7** (130 mg, 16%) and trans adduct **8** (327 mg, 40%) in the order of elution. Other minor components were not persued.

Cis adduct **7**: Mp 85—86 °C; IR (KBr) 1710, 1602, 1484, 1260, 1083, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.06 (s, 3H), 1.6—3.5 (m, 11H), 3.68 (s, 3H), 3.75 (s, 3H), 6.52 (s, 2H). Found: C, 74.22; H, 8.06%. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08%.

Trans adduct **8**: Mp 166—168 °C; IR (KBr) 1713, 1600, 1482, 1262, 1083, 945, 808 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.75 (s, 3H), 1.8—3.1 (m, 11H), 3.72 (s, 6H), 6.53 (s, 2H).

Methylenation of The Cis Adduct 7. To a suspension of methyltriphenylphosphonium iodide (545 mg, 1.35 mmol) in dry tetrahydrofuran (8 cm^3) was added a hexane solution of butyllithium (1.25 mmol) under nitrogen atmosphere at 0 °C. A solution of **7** (124 mg, 0.45 mmol) in dry tetrahydrofuran (2 cm^3) was added and the mixture was stirred for 2.5 h during which time temperature was allowed to rise to room temperature. Aqueous ammonium chloride was added and products were extracted with ether. After removal of the solvents, the residue was chromatographed on silica gel to give the exo-methylene compound **9** (84 mg, 70%): Colorless prisms from hexane; Mp 87—88 °C; IR (KBr) 1645, 1602, 1482, 1257, 1088, 890, 794 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.98 (s, 3H), 3.72 (s, 3H), 3.75 (s, 3H), 4.38 (br. s, 1H), 4.62 (br. s, 1H), 6.54 (s, 2H). Found: C, 79.36; H, 8.92%. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88%.

Cordiachrome B(1). To a solution of the compound **9** (84 mg, 0.31 mmol) and 2,6-pyridinedicarboxylic acid *N*-oxide (150 mg, 0.78 mmol) in 20% aqueous acetonitrile (2 cm^3) was added a solution of ammonium cerium(IV) nitrate (425 mg, 0.78 mmol) in 50% aqueous acetonitrile (2 cm^3) at 0 °C. After stirring for 1 h, the mixture was diluted with water and extracted with dichloromethane. Removal of the solvents and chromatographic purification of the product on silica gel column gave **1** as yellow crystals; Mp 63—64 °C (lit,[1] 64—65 °C). The IR and ^1H NMR spectra of the synthetic material were superimposable to those of the authentic sample given from Prof. R. H. Thomson.

The authors are grateful to Prof. Ronald H. Thomson for a generous gift of natural Cordiachrome B and a copy of its ^1H NMR spectrum.

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