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An Efficient Preparation and Reactions of [5,6′-Biguaiazulene]-3,3′(5*H*,6′*H*)-dione and 5-Isopropylidene-3,8-dimethyl-1(5*H*)-azulenone: Key Intermediates for the Autoxidation Products of Guaiazulene[1)]

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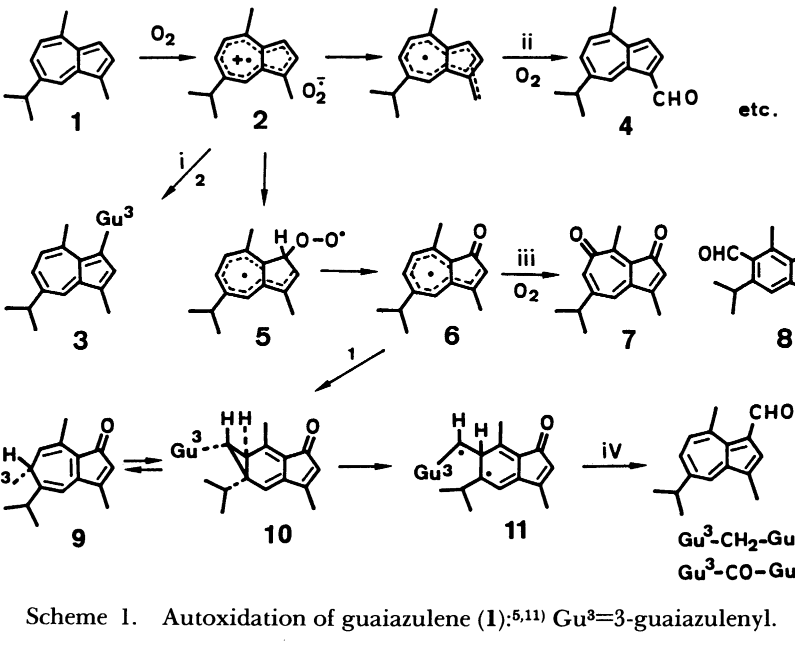
Oxidation of guaiazulene (**1**) with peracetic acid in hexane at 25 °C afforded as high as an 80% yield of the title biguaiazulenedione (**12**), which upon heating at 60 °C under nitrogen gave the title 1-azulenone (**13**) quantitatively. Oxidation of **12** and **13** was studied under various conditions, and these compounds were shown to be highly important key intermediates for a large number of the complex products obtained by autoxidation of **1**.

For the past several years we have undertaken a systematic investigation on autoxidation of various azulenic hydrocarbons and isolated a wide variety of interesting products, whose structures were mostly elucidated.[2—11)] These products can be classified mainly into four groups according to their structural type: i) oxidative coupling products (dimers and trimers), ii) side-chain oxidation products, iii) nucleus-oxidation products (azulenequinones, indenones, naphthalenoids, and benzenoids), and iv) one- carbon-transfer products (formylazulenes, diazulenylmethanes, and ketones). Compounds coupled with substrate azulenes have also been obtained as the secondary products.

In particular, autoxidation of guaiazulene (**1**), which possesses a high, redox potential (E_{pa} 0.71 V vs. SCE),[12)] has been intensively studied under various conditions as a model compound for investigation of oxidation of azulenic hydrocarbons, and a preliminary view on the possible pathways for the extremely complex, competitive reactions has been proposed;[5,11)] see Scheme 1 for intermediates and products **2**—**11** as well as paths i—iv corresponding to the classified structural type mentioned above. We now wish to report herein our study on the reaction of **1** with peracetic acid in hexane, which enabled us to efficiently isolate unique compounds that are considered to be highly important in view of further clarification of complex mechanisms of oxidation of azulenic hydrocarbons.



Scheme 1. Autoxidation of guaiazulene (1):[5,11)] Gu^3=3-guaiazulenyl.

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Results and Discussion

It was briefly reported[10] that treatment of **1** with equimolar peracetic acid in acetic acid at 15 °C for 3 min gave [5,6′-biguaiazulene]-3,3′(5*H*,6′*H*)-dione (**12**, 18% isolated yield) together with **9**[4,11] (20%), **10**[4,11] (10%), and other minor products. However, we have now found out that when the same reaction was carried out in hexane using an excess of 30% peracetic acid at 25 °C for 1 h, **12** was exclusively produced on the evidence of TLC and HPLC; see the reaction conditions summarized in Table 1. Addition of saturated aq sodium carbonate to the reactant afforded **12** as a precipitate in an 80% isolated yield; see the Experimental section for additional spectroscopic data (FAB-MS and ^{13}C NMR) obtained presently to confirm the asymmetrically coupled dimeric structure. The rest of the products isolated from the hexane filtrate and purified by chromatography were **4**,[2,5] **7**,[2,5] **8**,[2,5] **9**, **10**, and 5-isopropylidene-3,8-dimethyl-1(5*H*)-azulenone (**13**), besides a polar resinous substance that remained unidentified (Scheme 2). The yields of these isolated products are summarized in Table 2. Among these products, **13** was newly obtained here in an extremely low yield, but it was prepared efficiently from **12** (see below).

Table 1. Reaction Conditions of Peroxy Acid Oxidation of **1** in Hexane

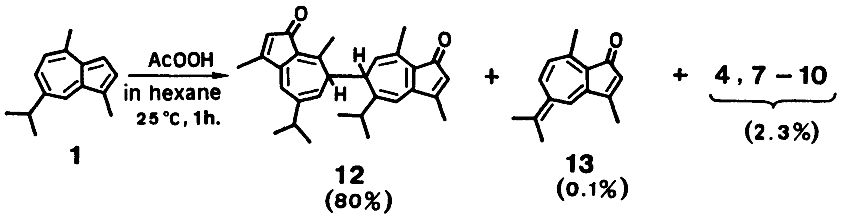
Expt	Temp/ °C	Time/ h	Mole equiv of peracid[a]	Recovered **1**/%
I	25	1	1	70
II	25	1	3	42
III	25	1	6	13

a) Mol equiv of 30% peracetic acid in 40 parts of hexane.

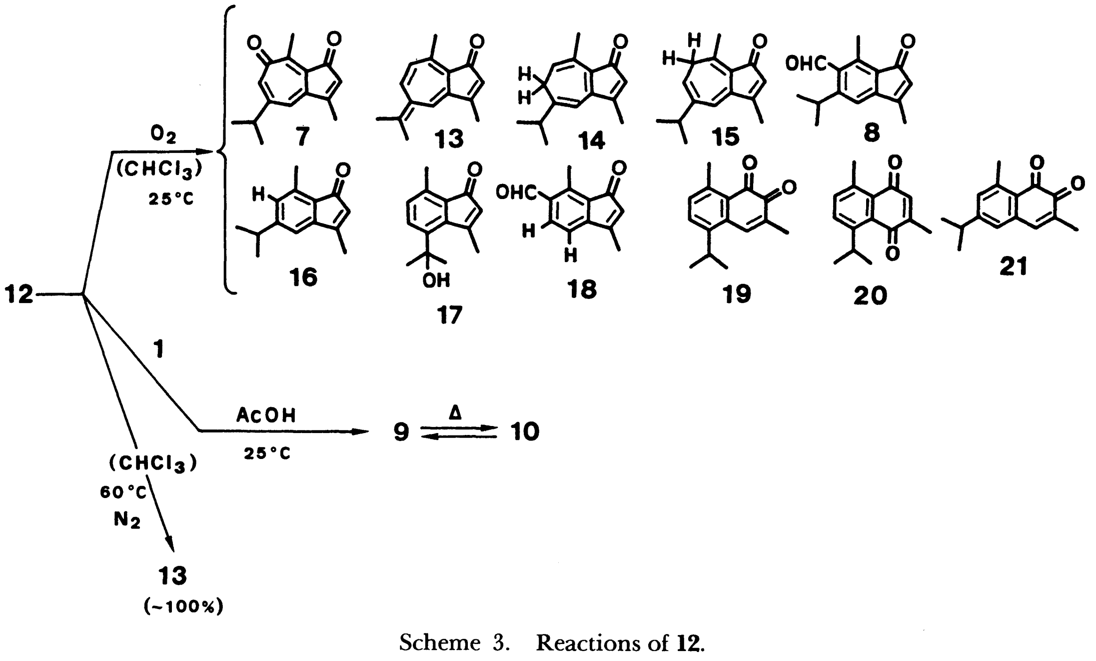
Table 2. Isolated Yield[a]/% of the Oxidation Products from **1**

Product	Expt (reaction conditions)[b]		
	I	II	III
4	0.7	0.2	0.2
7	0.3	0.2	0.1
8	0.7	0.5	0.2
9	1.3	1.6	0.5
10	0.7	0.2	1.3
12	70.5	70.2	80.1
13	0.3	0.2	0.1
RS[c]	20.1	23.3	15.2

a) The yield of each product is based on the consumed **1**. b) Expts I—III correspond to those in Table 1. c) Polar resinous substance.



Scheme 2. Oxidation of **1** with peracetic acid.



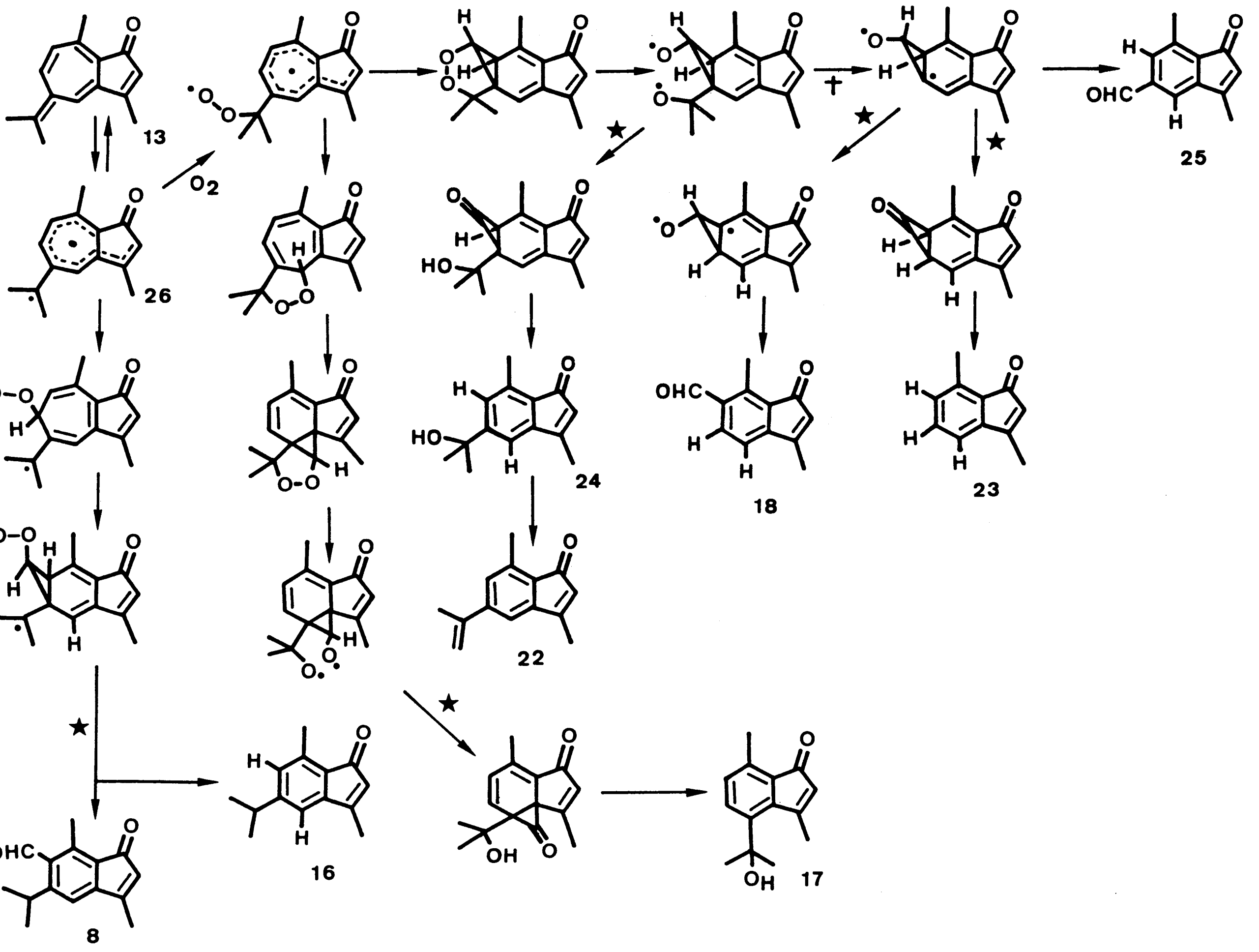
Scheme 3. Reactions of **12**.

The dimer **12** is a pale yellow powder and stable at 25 °C as long as it is kept as a solid. When **12** was, however, dissolved in chloroform and allowed to stand at 25 °C under aerobic conditions, it was found to give many products, a majority of which was obtained by autoxidation of **1** (through path iii). The isolated products were various azulenones [**7**[2,5)] (0.4% yield), **13** (30%), **14** (24%), **15** (5%)], indenones [**8**[2,5)] (6%), **16**[2,5)] (22%), **17** (1%), **18**[11)] (2%)], and naphthoquinones [**19**[13)] (2%), **20**[2,5)] (3%), **21** (5%)] (see Scheme 3). In contrast, when dissolved in degassed chloroform[14)] and heated at 60 °C for 1 h under nitrogen, **12** turned out to undergo disruption to afford **13** almost quantitatively.

Compound **13** having a unique structure of quinonemethide is isolable as orange needles but rather unstable. Thus, when dissolved in chloroform and set aside at 25 °C for 1 d in open air, **13** yielded several 1-indenone derivatives **8** (3%), **16** (8%), **17** (1%), **18** (54%), **22** (5%), **23** (1%), **24** (4%), and **25** (1%) (see Scheme 4), some of which had also been produced by autoxidation of **1** (path iii).

The structures of the hitherto unreported compounds **13**—**15**, **17**, and **21**—**25** mentioned above were established by the mass spectrometry and ^{1}H NMR and IR spectroscopy. These spectral data and their assignments are given in the Experimental section. The most probable pathways particularly of the unusual reactions of **13** are then proposed in Scheme 4. It is especially of interest that compounds missing the isopropyl side chain (**18**, **23**) or having an oxidized side chain (**17**, **22**, **24**, **25**) are derived under such extremely mild conditions as those employed presently. This suggests that, at initial stage, **13** is likely to behave like diradical **26** and to react with oxygen competitively at C-6 and the isopropylidene side chain. Then, a series of degradative transformations involving presumably intramolecular hydrogen transfer, acetone cleavage, and decarbonylation proceed to afford various 1-indenones, as illustrated in Scheme 4.

Furthermore, the dimer **12** was shown to react with guaiazulene (**1**) in acetic acid at 25 °C to afford exclusively, at the initial stage, a mixture of **9** (50% yield) and **10** (50%) (Scheme 3). This also provides an important suggestion of a reaction pathway of oxidation of **1**, because both **9** and **10** have been shown[4,11)] to give most of the same one-carbon-transfer products as those directly obtained by autoxidation of **1** (see path



Scheme 4. Autoxidation of **13** in chloroform and possible reaction pathways for the products: *Intramolecular $H^{\bullet}$ transfer; †acetone cleavage.

iv in Scheme 1).

These pieces of evidence described so far are indicative of the 3-guaiazulenone dimer **12** (and presumably the dissociated monomeric radical ketone **6**) and 3-azulenone **13** to be very important key intermediates for the two major reaction pathways (iii and iv in Scheme 1) for the autoxidation of guaiazulene (**1**) and apparently other azulenic hydrocarbons as well. Further studies (including theoretical calculation of the reactivities of these compounds) with regard to the exact reaction mechanisms and selective preparations of desired oxidation products are currently under intensive investigation.

Experimental

Melting points were determined with a Yanagimoto MP-S3 instrument and are uncorrected. Column chromatography was performed with Wako C-300 silica gel. TLC was conducted on plates precoated with silica gel 60F-254 (0.25 mm, Merck) by using 15 : 85 AcOEt-hexane as eluant. HPLC was carried out with Hitachi gel #3011 packed in a Pyrex column (ϕ 5 mm, 500 mm length) with 1 : 9 hexane-MeOH as solvent.

The UV and IR spectra were taken on a Hitachi 323 spectrophotometer and a JASCO IR-A-202 Grating spectrometer, respectively. Mass spectra were taken on a JEOL JMS-HX100 (with a JEOL JMA-DA5000 mass data system) high-resolution instrument and are given in terms of *m/z* (rel intensity) compared with the base peak. NMR spectra were recorded in $CDCl_3$ with a JEOL FX-200 (200 MHz for ^{1}H and 50 MHz for ^{13}C) or JEOL GSX-270 cryospectrometer at 27 °C. The assignments of all signals were made by employing a first-order analysis with the aid of decoupling technique and the parameters were confirmed by a computer-assisted simulation analysis.

Oxidation of Guaiazulene (1). **1**[15] (0.50 g) was added to a stirred solution of peracetic acid [30% aq, 0.64 cm^3, 1.0 mol equiv (for Expt I described in Table 1)] in hexane (20 cm^3). The mixture was stirred at 25 °C for 1 h and then saturated aq sodium carbonate was added. The precipitated solid was filtered off and washed well with water, then with hexane, and finally with ethyl acetate, thus giving pure **12** (105 mg, 71% theoretical yield). The above hexane filtrate and the organic washings were combined, washed thoroughly with water, dried (Na_2SO_4), and evaporated in vacuo. The residue (390 mg) was purified by silica-gel column chromatography first with hexane (to recover unreacted **1**), then with hexane–ethyl acetate (to separate various products), and finally with methanol (to eluate the polar substance) as the eluants. Then, each fraction of the products was further purified by preparative HPLC; when necessary, this chromatographic procedure was repeated.

Expts II and III (Table 1) were conducted under exactly the same procedures as those described above except for using 1.92 and 3.86 cm^3 of 30% peracetic acid in 20 cm^3 of hexane. The yield of each product based on the consumed starting material is summarized in Table 2.

[5,6′-Biguaiazulene]-3,3′(5*H*,6′*H*)-dione (12):[10] A pale yellow powder, mp 138—142 °C (decomp) (lit,[10] 138—142 °C decomp); although some spectral data for this compound were reported[10] the following data to confirm the structure have been obtained in the present study, FAB-MS (matrix, 3-mercapto-1,2-propanediol+NaI) *m/z* 449 (M+23; 3), 427 (M+1; 2), 343 (15), 319 (6), 236 (M/2+23; 20), and 213 (M/2; 100); ^{13}C NMR δ=194.12, 193.57 (C-3, 3′), 162.89, 162.64, 147.90, 147.28, 144.40, 143.66, 141.53, 141.42, 130.29, 129.37, 128.58, 122.87, 122.64, 121.23, 120.35, 45.91, 45.80, 35.55, 22.99, 22.63, 22.45, 22.27, 21.96, 13.73, and 13.69.[16]

5-Isopropylidene-3,8-dimethyl-1(5*H*)-azulenone (13): Orange needles, mp ca. 135 °C (darkened); R_f 0.30; UV λ_{max} (MeOH) 209, 244sh, 265, 300sh, 389, 400sh, and 488sh nm; IR ($CHCl_3$) 1680 cm^{-1} (C=O); EI-MS *m/z* 212 (M$^+$; 100), 197 (95), 183 (5), 169 (17), 153 (12), 141 (14), 128 (9), and 115 (6); ^{1}H NMR δ=1.89, 1.92 (3 H each, 2 s, Me_2C-5), 2.18 (3 H, d, $J\simeq1.0$ Hz, Me-3), 2.37 (3 H, s, Me-8), 5.62 (1 H, d, J=13.0 Hz, H-7), 6.15 (1 H, qd, $J\simeq1.0$, 0.3 Hz, H-2), 6.43 (1 H, dd, J=13.0, 2.0 Hz, H-6), and 6.52 (1 H, dd, J=2.0,$\simeq$0.3 Hz, H-4). Found: *m/z* 212.1210. Calcd for $C_{15}H_{16}O$: M, 212.1201.

Reactions of 12. A. Under Aerobic Conditions: A solution of **12** (100 mg) in chloroform (10 cm^3) was allowed to stand at 25 °C for 1 d in open air. After evaporation of the solvent and purification of the residue by chromatography, the following products were obtained: **7**[2,5] (0.4% yield), **8**[2,5] (5.7%), **13** (30.4%), **14** (24.1%), **15** (5.1%), **16**[2,5] (21.5%), **17** (1.0%), **18**[11] (1.7%), **19**[13] (2.2%), **20**[2,5] (3.2%), and **21** (4.8%).

3(6*H*)-Guaiazulenone (14): Pale yellow needles; R_f 0.55; EI-MS *m/z* 214 (M$^+$; 100) 199 (46), 184 (6), 172 (80), 171 (80), 156 (28), 143 (62), 129 (37), 128 (34), and 115 (8), the fragmentation pattern closely resembled that of **15** (see below); ^{1}H NMR, the sample was not stable enough for the measurement of the spectrum.

3(5*H*)-Guaiazulenone (15): Pale yellow needles; R_f 0.55; EI-MS *m/z* 214 (M$^+$; 46), 199 (45), 184 (5), 172 (38), 171 (100), 156 (12), 143 (18), 128 (12), and 115 (5). ^{1}H NMR δ=1.07 (6 H, d, J=7.0 Hz, Me_2C-7), 2.196 (3 H, d, J=1.5 Hz, Me-1), 2.41 (3 H, s, Me-4), 2.484 (1 H, sept, J=7.0 Hz, CH-7), 2.73 (2 H, d, J=7.0 Hz, H-7), 5.40 (1 H, td, J=7.0, 2.0 Hz, H-6), 5.91 (1 H, q, J=1.5 Hz, H-2), and 6.34 (1 H, d, J=2.0 Hz, H-8). Found: *m/z* 214.1366. Calcd for $C_{15}H_{18}O$: M, 214.1357.

4-(1-Hydroxy-1-methylethyl)-3,7-dimethyl-1*H*-inden-1-one (17): Pale yellow oil; R_f 0.18; IR ($CHCl_3$) 3600—3200 (OH) and 1700^{-1}(C=O); EI-MS 216 (M$^+$; 22), 201 (35), 198 (100), 183 (83), 173 (6), 169 (6), 159 (74), 155 (31), 141 (6), 128 (22), 115 (15), 100 (6), 93 (11), 77 (6), 59 (6), 51 (5), and 43 (34); ^{1}H NMR δ=1.69 (6 H, s, Me_2C-4), 1.728 [1 H, s, C(OH)-4], 2.51 (3 H, br s, Me-7), 2.61 (3 H, d, J=1.5 Hz, Me-3), 5.75 (1 H, q, J=1.5 Hz, H-2), 6.95 (1 H, br d, J=8.0 Hz, H-6), and 7.216 (1 H, d, J=8.0 Hz, H-5). Found: *m/z* 216.1089. Calcd. for $C_{14}H_{16}O_2$: M, 216.1150.

6-Isopropyl-3,8-dimethyl-1,2-naphthoquinone (21): Pale yellow needles; R_f 0.55; EI-MS *m/z* 228 (M$^+$; 18), 185 (100), 157 (22), and 128 (8); ^{1}H NMR δ=1.225 (6 H, d, J=7.0 Hz, Me_2C-6), 2.27 (3 H, d, J=1.5 Hz, Me-3), 2.58 (3 H, br s, Me-8), 3.52 (1 H, sept, J=7.0 Hz, CH-6), 5.76 (1 H, q, J=1.5 Hz, H-4), 7.48 (1 H, d, J=2.0 Hz, H-5), and 7.61 (1 H, br d, J=2.0 Hz, H-7). Found: *m/z* 228.1148. Calcd for $C_{15}H_{16}O_2$: M, 228.1150.

B. Under Anaerobic Conditions: A solution of **12** in degassed chloroform was heated at 60 °C for 1 h under nitrogen, followed by the same work-up, giving **13** quatitatively (by TLC and HPLC).

C. In the Presence of 1: A solution of **12** (166 mg) and **1** (300 mg) in acetic acid (15 cm^3) was allowed to stand at 25 °C for 1 h, followed by the same work-up, giving **9**[4] (50% yield) and **10**[4] (50%).

Reaction of 13. A solution of **13** (100 mg) in chloroform (10 cm^3) was allowed to stand at 25 °C for 1 d in open air, followed by the same work-up as above, giving **8**[2,5] (3.0% yield), **16**[2,5] (7.8%), **17** (1.0%), **18**[11] (53.8%), **22** (5.0%), **23** (1.0%), **24** (4.4%), and **25** (1.0%).

5-Isopropenyl-3,7-dimethyl-1*H*-inden-1-one (22): Pale yellow needles; R_f 0.78; EI-MS *m/z* 198 (M$^+$; 100), 183 (98), 169 (11), 155 (86), 139 (8), 128 (18), and 115 (13).

3,7-Dimethyl-1*H*-inden-1-one (23): Pale yellow needles, R_f 0.78; EI-MS *m/z* 158 (M$^+$; 100), 129 (37), and 115 (44).

5-(1-Hydroxy-1-methylethyl)-3,7-dimethyl-1*H*-inden-1-one (24): Pale yellow oil; R_f 0.18; EI-MS *m/z* 198 (M$^+$ $-H_2O$; 100), 183 (98), 169 (11), 155 (86), 139 (8), 128 (18), and 115 (13).

3,7-Dimethyl-1-oxo-1*H*-indene-5-carbaldehyde (25): Pale yellow needles; R_f 0.49; EI-MS *m/z* 186 (M$^+$; 100), 157 (20), 143 (3), 129 (30), and 115 (30).

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14) On setting aside this solution at room temperature, a well-resolved, hyperfine ESR spectrum became observable, suggesting a splitting of **12** into a certain radical species, probably the monomeric radical **6**, under anaerobic conditions. We are very grateful to Dr. Yozo Miura (Osaka City Univ.) for the measurement of the ESR spectrum. Full analysis of the spectrum for the structural proof is currently in progress and the result will be reported in a future paper.

15) Guaiazulene (**1**) is commercially available from Konan Kako, Co. (Osaka): Blue-violet prisms, mp 31 °C.

16) In addition to these data, we were puzzled to observe optical activity for **12**:$[\alpha]_D^{21}$ -6.98 ($CHCl_3$, $c=0.5$). Details of this unexpected fact is currently being studied and the result will be reported elsewhere.

Note added to Proof. After this paper was accepted for publication, Professor Toyonobu Asao (Tohoku University, Sendai) has kindly informed us that his newly synthesized 3-guaiazulenol gives, on being allowed to stand in ether, an oxidative dimeric product which he considers identical with our specimen **12**. On the basis of 600 MHz ^{1}H NMR (with 2D mode, in C_6D_6) data, he has assigned the product to be a ca. 10:8 mixture of meso and enantiomers of [5,5′-biguaiazulene]- 3,3′(5*H*,5′*H*)-dione. For the NMR measurement the specimen was dissolved in C_6D_6 (sparingly soluble) by prolonged heating and the IR spectrum (KBr) of his specimen appears to be slightly different from ours. Nevertheless, we are further checking our structure proposed for **12**.