The Transformations of Terpene Ketones by Oxygen. II. The Base-catalyzed Autoxidation of Pulegone and Fukinone and Their Dihydro Compounds

Akio HORINAKA, Eiyu YO, Otoji MORI, and Keizo NAYA*

Department of Chemistry, Faculty of Science, Kwansei Gakuin University, Uegahara, Nishinomiya, Hyogo 662

(Received November 21, 1978)

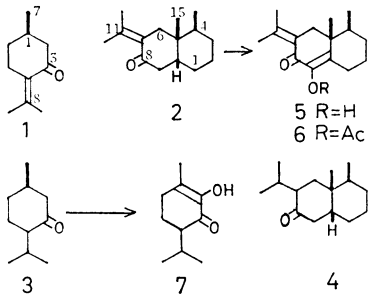
Upon autoxidation in alkaline media, pulegone and fukinone (**2**) gave pairs of hydroxy ketones respectively as the major products; also, hydroxyeremophilone was isolated as its acetate from **2**. On the other hand, their dihydro compounds afforded hydroxy ketones, diosphenols, and acids.

It is well known that enolizable ketones are oxidized rapidly in strongly basic media. This type of autoxidation has been widely applied to the transformations of the naturally occurring terpene ketones and has produced interesting types of substances related to the biosynthesis.[1] It has been pointed out that oxygen attacks at the site of enolization—for example, 3-keto 5β- and the 5α-steroids[2] gave the oxygenation products at the C-4 and C-2 positions respectively.

Since pulegone (**1**) and fukinone (**2**),[3] together with their dihydro derivatives, (**3** and **4**), could be regarded as the logical precursors of the further oxygenated congeners, the autoxidation has been attempted in order to clarify the nature of the products thoroughly.

The autoxidation of **2** and **3** (a mixture of menthone and neomenthone) would be expected to furnish hydroxyeremophilone (**5**)[4] and buccocamphor (**7**),[5] which are found in the oil of *Eremophila mitcelli* and in the essential oils of various *Barosma* or *Mentha* species respectively. In fact, **5** was isolated, but in a poor yield, as the acetate (**6**) from the oxidation mixture. We wish now to report the base-catalyzed autoxidation of the titled compounds and the structural assignments of the products.

The oxidation was carried out under the following three conditions: a) potassium *t*-butoxide/*t*-butyl alcohol; b) potassium *t*-butoxide/*N*,*N*-dimethylformamide, and c) sodium *t*-butoxide/*t*-butyl alcohol, *N*,*N*-dimethylformamide, and tetrahydrofuran in the presence of triethyl phosphite as a reducing reagent.[6] Under the above conditions, **1** and **2** gave pairs of diastereomeric hydroxy ketones, (**8a** and **8b**) and (**9a** and **9b**) respectively. The dihydro analogues, **3** and **4**, gave also pairs of hydroxy ketones, (**10a** and **10b**) and (**11b** and **12**), besides diosphenols (**14** and (**16** and **17**)), and acids (**18** and **19**), respectively. The oxidation products are shown in Table 1, along with their yields based on the consumed starting materials. The acidic products were isolated as the methyl esters.



Hydroxy ketones, **8a**, **8b**, **9a**, and **9b**, were prepared independently from pulegone α- and β-epoxide,[7] and fukinone α- and β-epoxide,[8] respectively by treatment with *p*-toluenesulfonic acid in benzene.[9] They were also found as the minor products among the photosensitized oxygenation products of **1**[10] and **2**.[11] The absolute configuration of **9b** was established by X-ray analysis.[12] The saturated hydroxy ketones, **10a**, **10b**, and **11b**, were obtained by the hydrogenation of the respective hydroxy ketones, **8a**, **8b**, and **9b**. The spectral data of **10a** and **10b** were in good agreement with those given in the literature.[13] It is obvious that a hydroxy ketone, **12**, is the rearranged product from **11b** by the stereospecific acyloin rearrangement[14] in an alkaline medium, though **11b** seems to resist the rearrangement in the aprotic solvent, as in the b) condition. The **12** structure was ascertained by its conversion to the ketone (**13**), which was identical with the authentic sample prepared from **4**.[3] On the other hand, the isomeric hydroxy ketone (**11a**) appears to undergo further oxidation without the subsequent rearrangement.

The diosphenol, **14**, was positive to a ferric chloride test (black color), exhibiting an UV maximum at 275 nm and a broad IR band at 1670 cm^{-1} characteristic

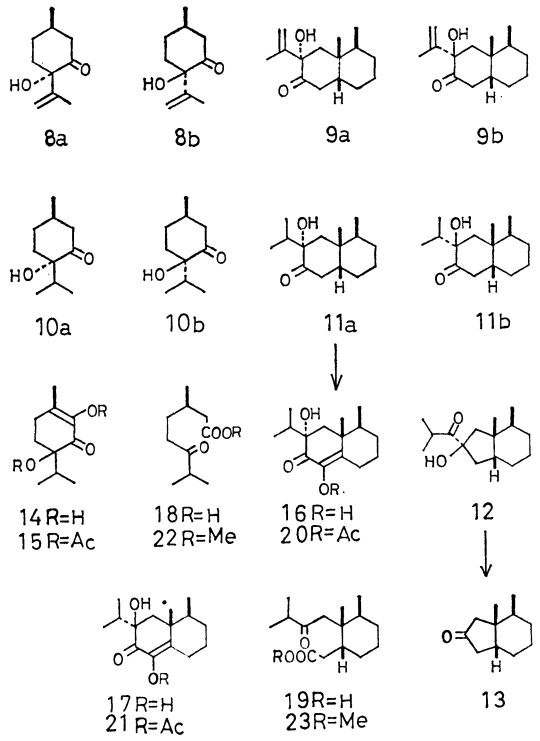
TABLE 1. YIELDS OF OXIDATION PRODUCTS DEPENDING ON THE REACTION CONDITIONS

Condition	Compounds											
	Pulegone (**1**)		Fukinone (**2**)		Dihydropulegone (**3**)				Dihydrofukinone (**4**)			
	Products											
	8a+**8b**	**8a**/**8b**	**9a**+**9b**	**9a**/**9b**	**10a**+**10b**	**10a**/**10b**	**14**	**22**	**11b**	**12**	**16**+**17**	**23**
a	11%	4.2	15%	1	14%	4.5	0%	8%	0%	11%	0%	15%
b	21	3.6	18	0	18	5.6	2	9	7	0	0	6
c	17	1.1	10	0	28	12.8	0	a)	(26)		5	a)

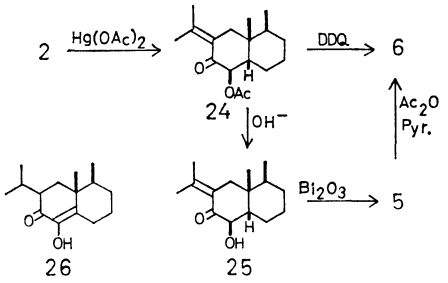
a) Identification could not be done because of the small amount.

of diosphenol. Upon acetylation with acetic anhydride–pyridine, **14** readily afforded its acetate (**15**), whose configuration at C-4 remains to be determined. From **4** we obtained an inseparable mixture of the epimeric diosphenols, **16** and **17**, while the acetate was separated into **20** and **21** by preparative TLC. However, the amount of **21** was too minute for further purification. Upon autoxidation, **11a** gave a diosphenol, **16**, whose acetate was identical with the **20** obtained by the autoxidation of **4**. Accordingly, the configurational assignments to **20** and **21** were established.

The acidic products, **18** and **19**, were isolated as methyl esters (**22** and **23**), after esterification with diazomethane; their structures were confirmed by their preparations from **3** and **4** respectively by the following reaction sequences of Baeyer-Villiger oxidation, alkaline hydrolysis, methylation, and oxidation with chromium trioxide.[15,16] The acidic products are derived from the starting ketone *via* α-hydroperoxy ketones, involving the cleavage of the bond adjacent to the carbonyl group.[17]



Hydroxyeremophilone (**5**) was subjected to considerable decomposition when left standing in the air, and it was carefully isolated as the acetate (**6**) by chromatography on deactivated silica gel. **6** was synthesized from **2** as follows. 9-Acetoxyfukinone (**24**) was obtained by the treatment of **2** with mercury(II) acetate in acetic acid.[18] The PMR spectrum of **24** showed the signal at δ 5.38 (d, J=12 Hz) attributable to the hydrogen attached to the carbon bearing an acetoxyl group. From an examination of the dihedral angle between 9-H and 10β-H, the coupling constant (12 Hz) can be accounted for by the relative orientation of the α-axial 9-H and β-equatorial 9-acetoxyl groups in a steroidal conformation. The treatment of **24** with DDQ in the presence of hydrogen chloride[19] furnished **6** in a poor yield (10%, based on the consumed **24**). Next, the mild alkaline hydrolysis of **24** and the subsequent oxidation of the product (**25**) with bismuth oxide in acetic acid, as shown previously in the oxidation of 2-hydroxypulegone,[19] gave **5**, which was then immediately acetylated with acetic anhydride–pyridine to yield **6**. These two acetates, prepared independently, showed the same R_f value, 0.75 (silica gel; benzene–ethyl acetate, 10: 1), IR, and PMR spectra. Their characteristic IR bands, UV absorption maxima, and specific rotation agree with those given in the literature.[4] There was no sign of the existence of the monoterpene analogue of **5** in the autoxidation products of **1**. The base-catalyzed autoxidation of the terpene ketones under investigation resulted in poor yields of the products, suggesting that the products tend to collapse readily into undesired compounds under the reaction conditions. In spite of the many visualized spots on TLC, attempts to separate the esters derived from the acidic products in the autoxidation of the conjugated ketones, **1** and **2**, were unsuccessful.



The product oxidized only at the 9-methylene position, namely, buccocamphor, **7**, and its sesquiterpene analogue (**26**) could not be detected in the reaction mixture of the saturated ketones, **3** and **4**. On the other hand, only **11a** among the hydroxy ketones was found to afford a diosphenol, **16**, in a low yield by autoxidation under the b) reaction conditions, but **11a** could not be found in the autoxidation mixture of **4**. No conclusive proof, therefore, could be obtained as to whether diosphenols, **14**, **16**, and **17**, can be produced *via* hydroxy ketones, **10a,b** and **11a,b** or *via* **7** and **26**. The intermediates presumably suffered rapid oxidation to give the diosphenols.

Finally, it should be noted that the relative ratio of the epimeric 4- or 7-hydroxy ketones is markedly affected by the reaction conditions (Table 1). This may reflect the dependence of the preferential conformation of the enolate anions on the reaction conditions.

Experimental

The IR, UV, and mass spectra were taken with Hitachi EPI-G_3, Shimadzu Spectronic 505, and Hitachi RMU-6 spectrophotometers respectively. The PMR spectra were recorded with a Hitachi R-20B (60 MHz) spectrometer, and the chemical shifts are reported in δ-values, with TMS as the internal reference. The optical rotations were measured with a Perkin-Elmer 141 polarimeter. Analytical and preparative GLC were performed with a Shimadzu GC-1C apparatus on a stainless steel column (ϕ=3 mm). The TLC were run on

silica gel (Merck Kieselgel G). All the melting and boiling points are uncorrected.

General Procedure of Autoxidation. *a) Oxidation Catalyzed by Potassium t-Butoxide in t-Butyl Alcohol*: A ketone (600—800 mg) was dissolved in a solution of 0.5 M potassium *t*-butoxide in *t*-butyl alcohol (20—30 ml). The mixture was stirred vigorously under the bubbling of oxygen at room temperature for 20—40 min, until 1 mol of oxygen has been consumed, and was then diluted with water, acidified with 10% aqueous sulfuric acid, and extracted with ether. The extract was shaken with a saturated sodium hydrogencarbonate solution. The extract was washed with water and dried over sodium sulfate. The removal of the solvent gave an oil, which was subsequently chromatographed on silica gel. Elution with light petroleum–ether (50: 1) or benzene afforded non-acidic products. The sodium hydrogencarbonate solution was acidified with 10% aqueous sulfuric acid and extracted with ether. The extract was treated with diazomethane–etherate. The removal of the solvent gave an oil which was chromatographed on silica gel. Elution with light petroleum–ether (50: 1) gave a methyl ester of the acidic product.

b) Oxidation Catalyzed by Potassium t-Butoxide in N,N-Dimethylformamide: To a solution of potassium *t*-butoxide (*ca.* 9 mmol) in *N,N*-dimethylformamide (15 ml) we added a ketone (600—800 mg). The solution was stirred vigorously under an oxygen atmosphere at −20——10 °C for 4—40 min, until 1 mol of oxygen had been consumed, and was then worked-up in essentially the same manner as Procedure *a*).

c) Oxidation Catalyzed by Sodium t-Butoxide in t-Butyl Alcohol, N,N-Dimethylformamide, and Tetrahydrofuran in the Presence of Triethyl Phosphite: Sodium hydride (300 mg, 50%) was dissolved in *t*-butyl alcohol (2 ml) and *N,N*-dimethylformamide (3 ml). To this solution we added triethyl phosphite (1 ml) in *N,N*-dimethylformamide (3 ml) and then a ketone (0.8—1.0 g) in tetrahydrofuran (7 ml). Oxygen was passed for 1 h into the cooled mixture at −30——20 °C. After the addition of a solution of sodium hydroxide (0.5 g) in methanol–water (2: 1, 15 ml) the reaction mixture was stirred at room temperature for 20 min and then acidified with acetic acid. After the removal of the solvent *in vacuo* and dilution with water, the mixture was extracted with ether. Subsequently, the extract was worked up in a manner similar to that described above.

Autoxidation Products of Pulegone (1) and Dihydropulegone (3).

8a and **8b** were found to be identical with authentic samples[9] by a comparison of the IR and GLC (EGA, 2.6 m; column temperature, 140 °C; H_2-flow rate, 60 ml/min; retention time, **8a**: 9.8 min, **8b**: 13.6 min).

The saturated hydroxy ketones (**10a** and **10b**) were found to be identical with the hydrogenation products of **8a** and **8b** respectively by a comparison of the IR and GLC (EGA, 2.6 m; column temperature, 140 °C; retention time, **10a**: 7.5 min, **10b**: 9.4 min); also, their spectral data were in agreement with those given in the literature.[13]

Diosphenol (14): A colorless oil; UV: λ_{max}^{MeOH} 275 nm (ε, 4300); IR(film): 3420, 1705, 1670, 1635 cm^{-1}; PMR(CCl_4): 1.82 (t, J=1.0 Hz, 7-Me), 0.94 and 0.69 (each d, J=6.0 Hz, 9- or 10-Me). **14** (28 mg) was acetylated with acetic anhydride–pyridine in the usual manner to give **15** (15 mg).

Acetate (15): A colorless oil; UV: λ_{max}^{MeOH} 242 nm (ε, 8100); IR (film): 3450, 1750, 1670, 1640, 1200 cm^{-1}; PMR(CCl_4): 3.24 (br s, OH), 2.15 (s, OAc), 1.78 (s, 7-Me), 0.94 and 0.68 (each d, J=6.0 Hz, 9- or 10-Me).

Keto Ester (22): A colorless oil; bp 125—129 °C (bath temperature)/16.5 mmHg†; $[\alpha]_D^{22}$ +9.7° (*c*, 0.51, MeOH); MS: *m/e* 200, M^+, *m/e* 125, base peak; IR(film): 1730, 1710, 1250, 1200, 1160 cm^{-1}; PMR(CCl_4): 3.59 (s, OMe), 1.03 (d, J=7.0 Hz, 9- and 10-Me), 0.89 (d, J=5.0 Hz, 7-Me). **22** was found to be identical with the authentic sample prepared from **3** by a comparison of the IR and GLC (PEG 20M, 2.6 m; column temperature, 146 °C; H_2-flow rate, 58 ml/min; retention time, 24 min) (see below).

Autoxidation Products of Fukinone (2) and Dihydrofukinone (4).

Hydroxy Ketone (9a): Mp 47—53 °C, colorless needles (from pentane); MS: *m/e* 236 M^+, *m/e* 109 base peak; IR(CCl_4): 3480, 3060, 1710, 1635, 902 cm^{-1}; PMR(CCl_4): 4.82 (slightly split s) and 4.65 (s) (12-C=CH_2), 3.27 (s, OH), 1.78 (s, 13-Me), 1.03 (s, 15-Me), 0.87 (d, J=6.0 Hz, 14-Me). **9a** was contaminated by a slight amount of **9b**, but **9a** showed the same physical properties as the authentic sample prepared from fukinone α-epoxide in a comparison of the TLC, IR, and PMR. The preparation of **9a** will be described later.

Hydroxy Ketone (9b): Mp 73.5—74.0 °C, colorless prisms (from pentane); $[\alpha]_D^{23}$ −80° (*c*, 0.99, $CHCl_3$); MS: *m/e* 236 M^+, *m/e* 109 base peak; IR(CCl_4): 3460, 3060, 1705, 1635, 900 cm^{-1}; PMR(CCl_4): 4.85 (slightly split s) and 4.58 (s) (12-C=CH_2), 3.55 (s, OH), 1.84 (d, J=1.0 Hz, 13-Me), 0.89 (s, 15-Me), 0.87 (d, J=6.0 Hz, 14-Me).

Found: C, 76.10; H, 10.10%. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24%. **9b** was found to be identical with the authentic sample prepared from fukinone β-epoxide by a comparison of the IR, PMR, and TLC and by a mixed-melting-point determination.

Hydroxy Ketone (11b): Mp 40.0—41.0 °C, colorless prisms (from pentane); $[\alpha]_D^{23}$ −69° (*c*, 1.0, $CHCl_3$); MS: *m/e* 238 M^+, *m/e* 109 base peak; IR(CCl_4): 3450, 1705 cm^{-1}; PMR (CCl_4): 3.47 (s, OH), 0.99 and 0.64 (each d, J=6.5 Hz, 12- or 13-Me), 0.92 (d, J=6.5 Hz, 14-Me), 0.87 (s, 15-Me).

Found: C, 75.42; H, 10.89%. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00%. **11b** was found to be identical with the hydrogenation product of **9b** by a comparison of the TLC, IR, and PMR and by a mixed-melting-point determination. The preparation of **9b** and **11b** will be described later.

Hydroxy Ketone (12): A colorless oil; $[\alpha]_D^{23}$ +33.7° (*c*, 1.03, $CHCl_3$); MS: *m/e* 238 M^+, *m/e* 109 base peak; IR(CCl_4): 3450, 1693 cm^{-1}; PMR(CCl_4): 3.43 (s, OH), 1.08 (d, J=6.0 Hz, $CHMe_2$), 1.00 (s, 15-Me), 0.81 (d, J=6.0 Hz, 14-Me).

Found: C, 75.41; H, 10.94%. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00%. **12** was found to be identical with the rearranged product of **11b** by a comparison of the IR, PMR, and GLC (SF 96, 35 cm; column temperature, 100 °C; H_2-flow rate, 115 ml/min; retention time, 9.5 min). The rearrangement of **11b** will be described later.

A Mixture of Diosphenols (16 and 17): A colorless oil; bp 116—135 °C (bath temperature)/0.04 mmHg; UV: λ_{max}^{MeOH} 282 nm (ε, 10000); IR(film): 3430, 1660, 1630 cm^{-1}. This mixture (104 mg) was acetylated with acetic anhydride–pyridine in the usual manner. The mixture was then separated into (**20**) and (**21**) by repeated column chromatography on silica gel, with benzene as an eluent, and by subsequent preparative TLC (benzene–ethyl acetate, 10: 1).

Acetate (20): R_f: 0.68, benzene–ethyl acetate, 10: 1; mp 99.5—100.0 °C, colorless prisms (from light petroleum); $[\alpha]_D^{22}$ −80° (*c*, 0.52, $CHCl_3$); IR(KBr): 3450, 1760, 1685, 1635, 1210 cm^{-1}; PMR(CCl_4): 3.11 (br s, OH), 2.18 (s, OAc), 1.27 (s, 15-Me), 0.96 and 0.68 (each d, J=6.0 Hz, 12- or 13-Me), 0.91 (d, J=5.5 Hz, 14-Me).

Found: C, 69.39; H, 8.89%. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90%.

Acetate (21): R_f, 0.73; a colorless oil; $[\alpha]_D^{23}$ +20° (*c*, 0.26, MeOH); UV: λ_{max}^{MeOH} 249 nm (ε, 8200); IR(film): 3450, 1750, 1675, 1635, 1200 cm^{-1}.

Keto Ester (23): Bp 120—122 °C (bath temperature)/0.02

† mmHg=133.322 Pa

mmHg; a colorless oil; $[\alpha]_D^{22}$ +41° (*c*, 0.85, MeOH); MS: *m/e* 237 M^+-31, *m/e* 109 base peak; IR(film): 1735, 1710 cm^{-1}; PMR(CCl_4): 3.56 (s, OMe), 1.01 (s, 15-Me), 0.98 (d, $J=6.5$ Hz, $CHMe_2$), 0.86 (d, $J=7.0$ Hz, 14-Me).

Found: C, 71.40; H, 10.56%. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52%. **23** was found to be identical with an authentic sample prepared from **4** by a comparison of the IR and GLC (PEG 20M, 2.6 m; column temperature, 195 °C; retention time, 14.9 min). The preparation of **23** will be described later.

*Preparation of the Autoxidation Products. Preparation of Hydroxy Ketones (**9a**, **9b**, **11a**, and **11b**).* A solution of fukinone α-epoxide (1.015 g) and *p*-toluenesulfonic acid (250 mg) in dry benzene (270 ml) was stirred at 40 °C for 7 h. Working-up in the usual manner gave a brown oil, which was subsequently chromatographed on silica gel (30 g, Grade II). Elution with light petroleum–ether (50: 1) gave (**9a**) in a 49% yield as the major product. **9b** was obtained in a similar manner from fukinone β-epoxide.

The catalytic hydrogenation of **9a** and **9b** with 10% palladium charcoal gave the saturated hydroxy ketones (**11a** and **11b**) respectively, in quantitative yields.

*Hydroxy Ketone (**9a**)*: Mp 61.5—62.0 °C; colorless needles (from pentane); $[\alpha]_D^{23}$ +91° (*c*, 1.02, $CHCl_3$).

Found: C, 76.26; H, 10.27%. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24%.

*Hydroxy Ketone (**9b**)*: Mp 73.5—74.0 °C; colorless prisms (from pentane); $[\alpha]_D^{23}$ −80° (*c*, 0.99, $CHCl_3$). The further details of **9a** and **9b** will be reported in the succeeding paper on the acid-catalyzed reaction of fukinone epoxides.

*Hydroxy Ketone (**11a**)*: Mp 47—48 °C; colorless prisms (from pentane); $[\alpha]_D^{23}$ +112° (*c*, 1.02, $CHCl_3$); MS: *m/e* 238 M^+, *m/e* 109 base peak; IR(CCl_4): 3480, 1703 cm^{-1}; PMR(CCl_4): 2.89 (s, OH), 0.93 (s, 15-Me), 0.81 (d, $J=6.0$ Hz, 14-Me), 0.91 and 0.70 (each d, $J=6.0$ Hz, 12- or 13-Me).

Found: C, 75.31; H, 10.95%. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00%. For the data of **11b**, see the above description.

*Rearrangement of Hydroxy Ketone (**11b**) with Potassium t-Butoxide in t-Butyl Alcohol.* The hydroxy ketone (**11b**) (22.8 mg) was dissolved in 0.5 M potassium *t*-butoxide–*t*-butyl alcohol and then left at room temperature for 5 min. The reaction mixture was diluted with water, acidified with 10% aqueous sulfuric acid, and extracted with ether. The extract was washed with water and dried over anhydrous sodium sulfate. The subsequent removal of the solvent gave an oil which was chromatographed on silica gel (0.5 g). Elution with light petroleum–ether (100: 1) gave a hydroxy ketone (**12**) (19 mg in an 83% yield).

*Reaction of Hydroxy Ketone (**12**) with Periodic Acid.* The hydroxy ketone (**12**) (60 mg) in ethanol (6 ml) was added to a solution of potassium periodate (150 mg) in 1 M aqueous sulfuric acid (7 ml), and the resulting solution was kept at 45 °C for 9.5 h. The reaction mixture was then diluted with water and extracted with ether. The extract was washed with a saturated sodium hydrogencarbonate solution and then water. The dried extract was evaporated to give an oil, which was subsequently chromatographed on silica gel (1 g). Elution with light petroleum–ether (200: 1) gave a ketone (**13**) (17 mg), which was identical with the authentic sample[3] by a comparison of the IR and GLC (SPE, 2.6 m; column temperature, 150 °C; H_2-flow rate, 32 ml/min; retention time, 17.7 min).

*Autoxidation of Hydroxy Ketone (**11a**).* The hydroxy ketone (**11a**) (280 mg) was stirred into a solution of potassium *t*-butoxide (*ca.* 30 mmol) in *N,N*-dimethylformamide (15 ml). After vigorous stirring in the air for 20 min, the mixture was worked-up in the usual manner gave a yellow oil which was subsequently chromatographed on silica gel (2.5 g). Elution with light petroleum–ether (30: 1) afforded diosphenol (**16**) (20 mg); mp 134.0—135.0 °C, colorless prisms (from light petroleum), $[\alpha]_D^{23}$ +150° (*c*, 1.05, $CHCl_3$); MS: *m/e* 252 M^+, *m/e* 41 base peak; UV: λ_{max}^{MeOH} 282 nm (ε, 11400); IR(KBr): 3480, 3400, 1660, 1630, 1000, 990 cm^{-1}; PMR(CCl_4): 1.21 (s, 15-Me), 0.98 and 0.90 (each d, $J=6.0$ Hz, 12- or 13-Me), 0.71 (d, $J=7.0$ Hz, 14-Me). The acetylation of (**16**) in the usual manner gave an acetate (**20**) which was found to be identical with the authentic acetate prepared from dihydrofukinone (**4**) mentioned above by a comparison of the IR and PMR spectra and by a mixed-melting-point determination.

*Preparation of Keto Ester (**22**) from Dihydropulegone (**3**).* A solution of dihydropulegone (**3**) (232 mg) in chloroform (1 ml) was added, at 0 °C, to a solution of perbenzoic acid (3 mmol equivalent) in chloroform (12.5 ml) in the presence of a catalytic amount of concentrated sulfuric acid. The mixture was then allowed to stand in a refrigerator for 3 days. The reaction mixture was subsequently concentrated, diluted with water, and extracted with ether. The extract was washed successively with a saturated aqueous sodium hydrogencarbonate solution, a saturated aqueous ferrous sulfate solution, and water. The dried extract was evaporated to give an oil which was chromatographed on silica gel (4 g). Elution with benzene gave a lactone as an oil (156 mg, 61%); IR(film): 1710, 1280, 1225 cm^{-1}; PMR(CCl_4): 4.00 (m, CH–O–), 2.45 (d, $J=10$ Hz, CO–CH_2–), 0.98 (d, $J=6.0$ Hz, 7-Me), 0.93 (d, $J=6.0$ Hz, $CHMe_2$).

A solution of the lactone (103 mg) and potassium hydroxide (1 pellet) in methanol (5 ml) was refluxed for 5 h, and then methyl iodide (1.5 ml) was added. After refluxing for a further 3 h, the resulting mixture was concentrated, acidified with 10% aqueous sulfuric acid, and extracted with ether. The dried extract was evaporated to give an oil which was chromatographed on silica gel (2 g) by elution with benzene to furnish a hydroxy ester (76 mg, 62%); IR(film): 3400, 1720 cm^{-1}. The hydroxy ester (36 mg) in pyridine (0.5 ml) was stirred, drop by drop, into a slurry mixture of chromium trioxide (100 mg) in pyridine (1 ml) under cooling, after which the mixture was kept overnight at room temperature under stirring. Subsequent working-up in the usual manner gave a keto ester (**22**) (17 mg, 48%).

*Preparation of Keto Ester (**23**) from Dihydrofukinone (**4**).* A hydroxy ester (**23**)[15] was prepared from dihydrofukinone (**4**) by essentially the same method described above; the subsequent Jones' oxidation gave a keto ester (**23**) in a 58% yield.

*Isolation of Hydroxyeremophilone Acetate (**6**).* Fukinone (**2**) (1.239 g, 5.62 mmol) was dissolved in 0.5 M potassium *t*-butoxide–*t*-butyl alcohol (40 ml), and the mixture was stirred vigorously in the air at room temperature for 3.5 h. Working-up in the usual manner gave a brown oil (1.226 g), which was then chromatographed on deactivated silica gel (Grade II, 24 g). Elution with light petroleum–ether (50: 1) gave a mixture of hydroxyeremophilone (**5**) and (**2**) (327 mg). Subsequent elution with light petroleum–ether (20: 1) afforded a mixture of two epimeric hydroxy ketones (**9a** and **9b**) (77 mg). The mixture of **5** and **2** was immediately treated with acetic anhydride–pyridine. Working-up in the usual manner gave a yellow oil, which was chromatographed on silica gel (Grade II, 5 g). Elution with light petroleum–ether (50: 1) gave **2** (220 mg) and then hydroxyeremophilone acetate (**6**) (35 mg; 5.6% yield based on the **2** consumed), which was recrystallized from light petroleum; mp 53.5—54.0 °C; colorless prisms; $[\alpha]_D^{25}$ +143° (*c*, 1.02, $CHCl_3$); MS: *m/e* 276 M^+, *m/e* 43 base peak; UV: λ_{max}^{MeOH} 285 nm (ε, 7100), 255 nm (ε,

9300); IR(CCl_4): 1760, 1665, 1635, 1203 cm^{-1}; PMR(CCl_4): 2.17 (s, OAc), 2.06 and 1.84 (each s, 12- or 13-Me), 1.01 (s, 15-Me), 0.99 (d, J=6.0 Hz, 14-Me).

Found: C, 73.69; H, 8.41%. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75%.

*Preparation of 9β-Acetoxyfukinone (**24**).* A mixture of fukinone (**2**) (3.446 g, 15.6 mmol) and mercuric acetate (8.45 g, 26.5 mmol) in glacial acetic acid (30 ml) was refluxed for 3.5 h. The resulting dark mixture was decanted to remove the mercury into water and then extracted with ether. The ethereal extract was washed with water and dried over anhydrous sodium sulfate. The removal of the solvent gave a dark viscous oil (3.515 g), which was subsequently chromatographed on silica gel (80 g). Elution with light petroleum–ether (50: 1) afforded the recovered fukinone (**2**) (0.93 g) and 9β-acetoxyfukinone (**24**) (1.357 g, 31%), which was distilled at 130—140 °C (bath temperature)/0.02 mmHg and then crystallized from light petroleum as colorless leaflets; mp 67—68 °C, $[\alpha]_D^{23}$ +160° (*c*, 1.23, $CHCl_3$); MS: *m/e* 278 M^+, *m/e* 28 base peak; UV: λ_{max}^{MeOH} 253 nm (ε, 5800); IR(CCl_4): 1755, 1740, 1707, 1640, 1233 cm^{-1}; PMR(CCl_4): 5.38 (d, J=12 Hz, 9-CH), 2.10 (s, OAc), 1.80 (t, J=1.5 Hz, 12- and 13-Me), 1.00 (s, 15-Me), 0.84 (d, J=6.5 Hz, 14-Me).

Found: C, 73.59; H, 9.38%. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41%. Before crystallization it showed a PMR signal at 5.26 (d, J=5.0 Hz) besides that at 5.38, indicating the existence of a small amount of the 9α-acetoxyl isomer.

*Preparation of Hydroxyeremophilone Acetate (**6**).* a) Into a solution of 9β-acetoxyfukinone (**24**) (303 mg, 1.08 mmol) and DDQ (270 mg, 1.19 mmol) in dry dioxane (20 ml) we bubbled anhydrous hydrogen chloride with stirring for 1 min; the stirring was then continued at room temperature for 4 h. After subsequent filtration and evaporation of the solvent, the residue was taken up in ether, washed with a 1% aqueous sodium hydroxide solution, and water. The evaporation of the solvent gave a viscous light brown oil (211 mg), which was chromatographed on silica gel (Grade II, 6 g). Elution with light petroleum–ether (30: 1) gave the recovered **24** (196 mg) and then hydroxyeremophilone acetate (**6**) (20 mg, 10% based on the **24** consumed).

b) An aqueous potassium hydroxide solution (*ca.* 1.8%) was added, over a period of 2 weeks under a nitrogen atmosphere, to a solution of **24** (281 mg, 1.01 mmol) in methanol (10 ml), in the presence of 1 drop of 1% phenolphtalein in ethanol, at such a rate that the solution was kept faintly alkaline. The reaction mixture was then diluted with water and extracted with ether. The extract was worked-up in the usual manner to give a pale yellow oil (165 mg), which was subsequently chromatographed on silica gel (Grade II, 7 g). Elution with benzene gave 9β-hydroxyfukinone (**25**) (144 mg, 61%); a colorless oil; $[\alpha]_D^{23}$ +122° (*c*, 0.68, $CHCl_3$); UV: λ_{max}^{MeOH} 252 nm (ε, 4500); IR(CCl_4): 3460, 1760 (sh), 1708 (sh), 1692, 1640 cm^{-1}; PMR(CCl_4): 4.17 (d, J=11 Hz, 9α-H), 3.50 (s, OH), 1.87 (d, J=1.5 Hz) and 1.81 (d, J=1.0 Hz) (12- and 13-Me), 0.95 (s, 15-Me), 0.83 (d, J=6.0 Hz, 14-Me).

A mixture of **25** (109 mg, 0.46 mmol) and bismuth oxide (111 mg, 0.24 mmol) in glacial acetic acid (2 ml) was stirred at 120 °C for 10 min. The solution was decanted to remove the bismuth metal into water (20 ml) and then extracted with ether. The subsequent working-up as usual gave a brown oil, which was subjected to preparative TLC to afford **5** (64 mg, 59%). Its acetate (**6**) was obtained in the usual manner.

The authors wish to thank the staff of the Research Laboratory, Toyo Jozo, Co., Ltd., for the microanalysis and MS measurements, and the Institute of Food Chemistry for the measurement of the MS spectra.

References

1) D. H. R. Barton, E. J. Bailey, and J. Elks, *Proc. Chem. Soc.*, **1960**, 214; D. H. R. Barton, S. K. Pradham, S. Sternhell, and J. F. Templeton, *J. Chem. Soc.*, **1961**, 255.

2) B. Camarino, B. Patelli, and R. Sciaky, *Tetrahedron Lett.*, **1961**, 554.

3) K. Naya, I. Takagi, Y. Kawaguchi, Y. Asada, Y. Hirose, and N. Shinoda, *Tetrahedron*, **24**, 5871 (1968).

4) C. Djerassi, R. Mauli, and L. H. Zalkow, *J. Am. Chem. Soc.*, **81**, 3424 (1959).

5) "Rodd's Chemistry of Carbon Compounds," 2nd ed, Elsevier Publishing Co., Amsterdam (1968), Vol. IIB, p. 202.

6) J. N. Gardner, F. E. Carlon, and O. Gnoj, *J. Org. Chem.*, **33**, 3294 (1968).

7) W. Reusch and P. Mattison, *Tetrahedron*, **23**, 1953 (1967); G. W. K. Cavil and C. D. Hall, *Tetrahedron*, **23**, 1119 (1967).

8) K. Kobayashi, Y. Yamamoto, H. Miyanaga, and K. Naya, 23th National Meeting of the Chemical Society of Japan, Tokyo, April 1970, Abstr. No. 18337.

9) W. Reusch, D. F. Andersen, and C. K. Johnson, *J. Am. Chem. Soc.*, **90**, 4988 (1968).

10) K. H. Schulte-Elte, M. Gadola, and B. L. Muller, *Helv. Chim. Acta*, **54**, 1870 (1971).

11) K. Naya and J. Yamamoto, 14th Symposium on the Chemistry of Terpenes, Essential Oils, and Aromatics, Symposium Paper (1970), p. 114.

12) An account will soon be published elsewhere.

13) T. Suga, T. Shishibori, and T. Matsuura, *J. Org. Chem.*, **32**, 965 (1967).

14) "Molecular Rearrangement," ed by P. de Mayo, Interscience Publishers, New York (1963), pp. 18, 801, 1114.

15) M. Kawai and K. Naya, *Chem. Lett.*, **1972**, 389.

16) R. Schollinger and W. Treibs, *Chem. Ber.*, **94**, 2978 (1961).

17) W. von E. Doering and R. M. Haines, *J. Am. Chem. Soc.*, **76**, 482 (1954); T. J. Wallace, H. Pobiner, and A. Schriesheim, *J. Org. Chem.*, **30**, 3768 (1965).

18) R. H. Reitsema, *J. Am. Chem. Soc.*, **79**, 4465 (1957).

19) H. J. Ringold and A. Turner, *Chem. Ind. (London)*, **1962**, 211.