## Stereoselective Total Synthesis of (±)-Fukinone

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The eremophilane-type sesquiterpenoid (+)-fukinone, isolated from *Petasites japonicus* Maxim., has been assigned[2] structure and absolute stereochemistry as depicted in **1**. In view of a recent report[3] regarding the synthesis of (±)-9,10-dehydrofukinone, we describe here a simple, stereoselective total synthesis of (±)-fukinone (**1**) *via* a synthetic sequence which fully corroborates the structural and stereochemical assignments.

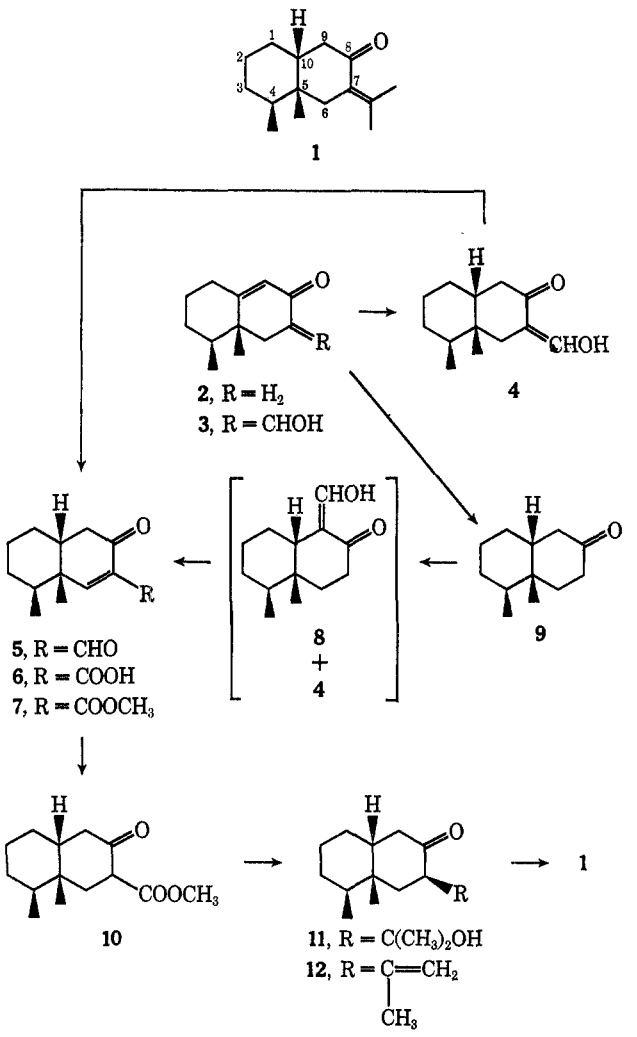
An efficient, stereoselective synthesis of the racemic octalone **2** has already been reported.[4] Conversion of this material into the corresponding hydroxymethylene derivative **3**, followed by catalytic hydrogenation of the latter in ethanolic sodium hydroxide over 10% palladium on charcoal, gave compound **4**, in 84% overall yield. Treatment of **4** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[5] in dioxane for 2 hr afforded, in 60% yield, the crystalline keto aldehyde **5**.

The fact that compounds **4** and **5** possessed the desired stereochemistry was conclusively shown as follows. Hydrogenation of octalone **2** over palladium on charcoal under basic conditions gave, in excellent yield, the cis-fused decalone **9**.[6] This compound was clearly different from the epimeric, trans-fused decalone, obtained from **2** by reduction of the latter with lithium in liquid ammonia.[4] Reaction of **9** with ethyl formate in benzene in the presence of sodium methoxide produced a mixture of hydroxymethylene derivatives **8** and **4** which, as judged by the nmr spectrum, were present in a ratio of approximately 2:3, respectively. Oxidation of this mixture with DDQ[5] in dioxane afforded, albeit in low yield, the unsaturated keto aldehyde **5**. The latter was shown to be identical (ir, nmr, melting point, and mixture melting point) with the keto aldehyde **5** prepared as described previously and thus assured that our synthetic intermediate possessed the desired all-cis stereochemistry.

Oxidation of the keto aldehyde **5** with silver oxide in ethanol–water[7] produced, in 92% yield, the crystalline keto acid **6**. Since treatment of the latter with diazomethane in ether produced a complex mixture of products, esterification was carried out by treatment of **6** with excess methyl iodide in the presence of powdered silver oxide.[8] The resulting keto ester **7**, formed in 92% yield, was subjected to hydrogenation in ethanol over Adams catalyst, affording, in 97% yield, the β-keto ester **10**.

In order to obtain (±)-fukinone (**1**) from the keto ester **10**, it was only necessary to elaborate the carbomethoxy group of the latter into the isopropylidene functionality. Treatment of **10** with one equivalent of sodium hydride in ether, followed by reaction of the resultant enolate with an excess of ethereal methyllithium[9] gave, after suitable work-up, the desired keto alcohol **11** in 80% yield. Attempted dehydration of **11** by treatment with 1% hydrochloric acid in refluxing methanol produced a product which, as shown by gas–liquid chromatographic analysis, consisted mainly of the decalone **9**, undoubtedly formed *via* a retroaldol reaction. However, treatment of **11** with thionyl chloride in pyridine afforded a product which consisted mainly of (±)-isofukinone (**12**), as shown by ir absorptions at 6.10 and 11.27 μ, characteristic of a terminal double bond, and at 5.85 μ, due to the saturated carbonyl group.

When a solution of (±)-isofukinone (**12**) in dry benzene containing a trace of *p*-toluenesulfonic acid was refluxed for 20 hr, there was obtained a product which consisted mainly of (±)-fukinone (**1**). An analytical sample of the latter was obtained by preparative glc. Although we were unable to secure an authentic sample of (+)-fukinone, our synthetic material exhibited spectral data which was in excellent agreement with the spectral data reported[2] for the

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natural product itself, and the structural assignment is, therefore, fully corroborated.

## Experimental Section

**General.**—Melting points and boiling points are uncorrected. Uv spectra were measured in methanol solution on a Unicam Model SP 800 spectrophotometer. Routine ir spectra were recorded on a Perkin-Elmer Infracord Model 137 spectrophotometer, while comparison spectra were recorded on a Perkin-Elmer Model 421 spectrophotometer. Nmr spectra were determined in deuteriochloroform solution and recorded on Varian Associates spectrometers, Model A-60 and/or Model HA-100. Signal positions are given in the Tiers $\tau$ scale, with tetramethylsilane as an internal standard; the multiplicity, integrated peak areas, and proton assignments are indicated in parentheses. Glc was carried out on an Aerograph Autoprep, Model 700. The following columns (10 ft × 1/4 in., unless otherwise noted) were employed, with the inert, supporting material being 60–80 mesh Chromosorb W in each case: column A, 15% QF-1; column B (10 ft × 3/8 in.), 20% Carbowax 20 M; column C, 3% SE-30; column D (10 ft × 3/8 in.), 30% SE 30. The specific column used, along with column temperature and carrier gas (helium) flow rate (in ml/min), are indicated in parentheses. High-resolution molecular weight determinations were measured on an AEI, type MS-9, mass spectrometer. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia.

**Preparation of Hydroxymethylene Derivative 3.**—To a stirred suspension of sodium methoxide (3.8 g, 70.3 mmol) in 25 ml of dry benzene was added a solution of ethyl formate (5.2 g, 70.3 mmol) in 25 ml of dry benzene. The mixture was cooled to 0° and a solution of octalone **2** (5.0 g, 28.1 mmol) in 25 ml of dry benzene was added. The reaction was stirred, under a nitrogen atmosphere, for 90 min and then allowed to stand at room temperature for an additional 14 hr. To the reaction mixture was added 75 ml of water, the mixture was thoroughly shaken, and the layers were separated. The aqueous solution was washed with ether and then acidified with dilute hydrochloric acid. The resultant mixture was extracted with ether, and the combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated to afford a dark oil which, upon distillation under reduced pressure, afforded 2.5 g (89%, based on unrecovered starting material) of compound **3** as pale yellow crystals, bp 110–112° (0.25 mm). An analytical sample was obtained by vacuum sublimation and exhibited mp 68–71°; uv max 248 mμ (ε 9280), 311 (3860); uv max (NaOH) 242 mμ (ε 13,000), 355 (9620); ir ($CHCl_3$) 6.08, 6.41, 8.42 μ; nmr $\tau$ 0.0 (broad m, 1, =CHOH), 2.62 (s, 1, =CHOH), 4.23 (s, 1, vinyl H), 9.06 (s, 3, tertiary $CH_3$), 9.08 (d, 3, $J$ = 6.5 Hz, secondary $CH_3$).

*Anal.* Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.99; H, 8.73.

**Preparation of Decalone 9.**—To a solution of octalone **2** (1.0 g, 5.62 mmol) in 20 ml of 0.3 *N* ethanolic sodium hydroxide was added 100 mg of 10% palladium on charcoal and the resulting mixture was hydrogenated at room temperature and atmospheric pressure for 15 hr. The reaction mixture was filtered, and the filtrate was neutralized with dilute hydrochloric acid and concentrated. The residue was taken up in ether and the ether solution was washed with brine and dried ($MgSO_4$). Removal of the solvent, followed by distillation of the residual material under reduced pressure, produced 920 mg (92%) of a clear, colorless oil, bp 88–90° (0.35 mm) [lit.[6] bp 75° (0.15 mm)]. Glc analysis (column A, 165°, 85) indicated that this material was greater than 95% pure. An analytical sample of decalone **9** was obtained by preparative glc (column B, 240°, 170) and exhibited $n^{20}D$ 1.4953; ir (film) 5.83, 6.91 μ; nmr $\tau$ 9.04 (s, 3, tertiary $CH_3$), 9.13 (d, 3, $J$ = 6.5 Hz, secondary $CH_3$).

*Anal.* Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.05; H, 11.19.

The 2,4-dinitrophenylhydrazone prepared from decalone **9** exhibited, after recrystallization from ethanol, mp 126–127° (lit.[6] mp 115°).

*Anal.* Calcd for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.14; H, 6.94; N, 15.67.

The semicarbazone derivative and the oxime derivative of decalone **9** were also prepared and exhibited, after recrystallization from ethanol, mp 194–195° (lit.[6] mp 190–191°), and mp 148–148.5° (lit.[6] mp 147–148°), respectively.

**Conversion of Decalone 9 into Hydroxymethylene Derivatives 8 and 4.**—Decalone **9** was converted into a mixture of **8** and **4** *via* a procedure identical with that described above for the preparation of the hydroxymethylene derivative **3**, except that the reaction time in this case was 2 days. From 1.0 g (5.56 mmol) of decalone **9** there was obtained 0.88 g (76%) of a pale yellow oil: bp 105–110° (0.2 mm); uv max 285 mμ (ε 6330); uv max (NaOH) 315 mμ (ε 17,100); ir (film) 6.07, 6.30, 7.32 μ. As judged by the nmr spectrum, this material consisted of a mixture of the hydroxymethylene derivatives **8** and **4**, in a ratio of approximately 2:3, respectively.

*Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.05; H, 9.73.

**Preparation of Keto Aldehyde 5. A. From the Hydroxymethylene Derivative 3.**—A solution of the hydroxymethylene derivative **3** (1.5 g, 7.3 mmol) in 75 ml of 0.3 *N* ethanolic sodium hydroxide containing 150 mg of 10% palladium on charcoal was hydrogenated at room temperature and atmospheric pressure until the desired amount of hydrogen had been absorbed. Work-up as described previously for the preparation of compound **9** afforded 1.5 g (95%) of the crude hydroxymethylene decalone **4**: ir (film) 6.07, 6.30, 7.30 μ; nmr showed no vinyl proton. A solution of compound **4** (200 mg, 0.972 mmol) and DDQ (230 mg, 1.13 mmol) in 15 ml of dry dioxane was stirred at room temperature for 2 hr under an atmosphere of nitrogen. The reaction mixture was diluted with 35 ml of methylene chloride and then filtered through a short column of neutral alumina. The alumina column was further eluted with methylene chloride. The combined eluents were concentrated under reduced pressure and the residue was distilled, bp 180–190° (bath temperature) (0.1 mm), affording a yellow oil which crystallized on standing. Recrystallization from hexane yielded 124 mg (62%) of the desired keto aldehyde **5**: mp 81–83°; uv max 283 mμ (ε 7740); ir ($CHCl_3$) 5.95, 6.23, 7.44 μ; nmr $\tau$ −0.32 (s, 1, CHO), 2.20 (s, 1, vinyl H), 8.74 (s, 3, tertiary $CH_3$), 9.00 (d, 3, $J$ = 6.5 Hz, secondary $CH_3$).

*Anal.* Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.92; H, 9.03.

**B. From the Mixture of Hydroxymethylene Derivatives 8 and 4.**—A solution of the mixture of compounds **8** and **4** (200 mg, 0.972 mmol) and DDQ (225 mg, 1.10 mmol) in 15 ml of dry dioxane was stirred, under an atmosphere of nitrogen, for 2 hr. Upon isolation of the product as described above, there was obtained 30 mg (15%) of the crystalline keto aldehyde **5**. This material was identical (ir, nmr, melting point, mixture melting point) with compound **5** prepared as described above.

**Preparation of Keto Acid 6.**—To a solution of keto aldehyde **5** (548 mg, 2.66 mmol) and silver nitrate (953 mg, 5.60 mmol) in 7 ml of ethanol and 5 ml of water was added, over a period of 15 min, a solution of sodium hydroxide (436 mg, 10.90 mmol) in 15 ml of water. The reaction mixture was stirred for a total of 2 hr, and then filtered. The filtrate was concentrated under reduced pressure, diluted with water, washed with ether, acidified with dilute hydrochloric acid, and extracted with ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated. Recrystallization of the residue from hexane–ether afforded 542 mg (92%) of the desired keto acid **6**: mp 65–67°; uv max 245 mμ (ε 6780); ir ($CHCl_3$) 5.75, 6.08, 6.25, 7.00 μ; nmr $\tau$ 2.55 (s, 1, vinyl H), 8.77 (s, 3, tertiary $CH_3$), 9.02 (d, 3, $J$ = 6.5 Hz, secondary $CH_3$).

*Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 70.31; H, 8.22.

**Preparation of Keto Ester 7.**—To a stirred solution of keto acid **6** (262 mg, 1.18 mmol) in 10 ml of methyl iodide was added powdered silver oxide (1.10 g, 4.72 mmol). The reaction mixture was stirred at room temperature for 30 min and then filtered. The filtrate was concentrated and the residue was distilled, affording 257 mg (92%) of the desired keto ester **7**: bp 185–190° (bath temperature) (0.1 mm); $n^{20}D$ 1.5208; uv max 236 mμ (ε 7740); ir (film) 5.78, 5.96, 6.20, 7.00, 7.86, 9.54, 9.98 μ; nmr $\tau$ 2.55 (s, 1, vinyl H), 6.23 (s, 3, $COOCH_3$), 8.82 (s, 3, tertiary $CH_3$), 9.04 (d, 3, $J$ = 6.5 Hz, secondary $CH_3$).

*Anal.* Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.42; H, 8.32.

**Preparation of Carbomethoxy Decalone 10.**—Hydrogenation of the unsaturated keto ester **7** (250 mg, 1.06 mmol) in 10 ml of ethanol at room temperature and atmospheric pressure over Adams catalyst gave, after normal work-up, 242 mg (97%) of the carbomethoxy ketone **10**: $n^{20}D$ 1.5112; uv max 257 mμ (ε 7410); uv max (NaOH) 285 mμ (ε 13,800); ir (film) 5.78, 5.84,

6.02, 6.17, 6.98, 7.75, 8.14, 8.30 μ; nmr τ −2.11 (s, 1, enol H), 6.28 (s, 3, $COOCH_3$), 9.12 (s, 3, tertiary $CH_3$), 9.12 (d, 3, $J$ = 6.5 Hz, secondary $CH_3$).

*Anal.* Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.84; H, 9.30.

(±)-**Fukinone** (1).—To a stirred solution of the carbomethoxy decalone **10** (200 mg, 0.841 mmol) in 2 ml of dry ether at 0° was added 20 mg (0.841 mmol) of sodium hydride. The reaction mixture was stirred for 10 min and 2.15 ml (5.05 mmol) of 2.35 *M* ethereal methyllithium was added over a period of 5 min. The resulting solution was refluxed for 2 hr, diluted with 15 ml of dry ether and then poured into 35 ml of rapidly stirred water. The ether layer was separated, washed with brine, dried ($MgSO_4$), and concentrated to afford 160 mg (80%) of the keto alcohol **11**, ir (film) 2.90, 5.85 μ. The crude alcohol was dissolved in 10 ml of dry pyridine at 0°, 100 μl of thionyl chloride was added, and the resultant solution was stirred for 15 min. The solvent was removed under reduced pressure at 0° and the residual material was taken up in benzene. The benzene solution was washed with water and brine, dried ($MgSO_4$), and concentrated to afford 134 mg of a pale yellow oil. The latter, as shown by glc analysis (column C, 170°, 90), contained mainly (±)-isofukinone (**12**) and exhibited ir (film) absorptions at 5.85, 6.10, and 11.27 μ. A solution of this dehydration product in 15 ml of dry benzene containing a trace of *p*-toluenesulfonic acid was refluxed for 20 hr. The solution was washed with 10% aqueous sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated. Glc analysis (column C, 200°, 85) showed that the residual oil (125 mg) contained approximately 70% (±)-fukinone (**1**), 20% of the decalone **9**, and 10% of an unidentified component. An analytical sample of (±)-fukinone (**1**) was obtained by preparative glc (column D, 230°, 180) and exhibited uv max 251 mμ (ε 6640); ir (film) 5.95, 6.17 μ; nmr τ 8.08 (s, 3, vinyl $CH_3$), 8.24 (s, 3, vinyl $CH_3$), 9.04 (s, 3, tertiary $CH_3$), 9.16 (d, 3, $J$ = 6.5 Hz, secondary $CH_3$). These spectral data are in complete agreement with the spectra data reported[2] for the natural product (+)-fukinone.

*Anal.* Calcd for $C_{15}H_{24}O$: mol wt, 220.183. Found (high resolution mass spectrometry): mol wt, 220.181.

**Registry No.**—(±)-**1**, 25828-19-7; (±)-**3**, 25828-20-0; (±)-**4**, 25828-21-1; (±)-**5**, 25828-22-2; (±)-**6**, 25828-23-3; (±)-**7**, 25828-24-4; (±)-**8**, 25828-25-5; (±)-**9**, 25828-26-6; (±)-**10**, 25828-27-7.

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## Catalytic Decomposition of α-Haloalkyl Esters

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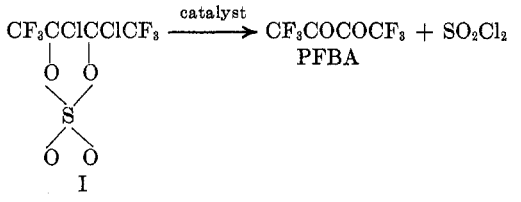
The preparation of perfluorobiacetyl (PFBA) results in the formation of 2,3-dichloro-1,1,1,4,4,4-hexafluorobutane-2,3-diol cyclic sulfate (I) as a coproduct.[1] This material is of little interest of itself; so conversion to PFBA was of interest. This would double the overall yield of PFBA from 2,3-dichloro-1,1,1,4,4,4-hexafluoro-2-butene.

The compound I was not soluble enough in water for hydrolysis to occur at any reasonable rate, but use of a cosolvent, dimethylformamide or dimethyl sulfoxide, resulted in complete hydrolysis. The product was PFBA hydrate. PFBA could then be obtained by dehydration with either fuming sulfuric acid or phosphorous pentoxide. This procedure involves two steps and the best yield obtained was 75%.

It has now been found that I will decompose in the presence of various catalysts to PFBA and sulfuryl




I

chloride in high yield. Compounds which catalyze this reaction are nitrogen or phosphorous derivatives with an unshared pair of electrons which can complex the sulfate. The results of a series of screening runs are given in Table I. In addition, water, alcohols, ethers, esters, and ketones have been in contact with I with no evidence of catalytic decomposition. Dimethylformamide, DMF, was also shown to be an effective catalyst. The use of more than a catalytic amount of DMF allowed the PFBA formed to distill from the solvent free from chlorine and sulfur dioxide.

All of the effective catalysts have an unshared pair of electrons, being nitrogen or phosphorus derivatives. Related compounds which do not have a pair of electrons available for complexation, ammonium chloride and heptafluorobutyramide, do not act as catalysts, and aromatic amines are poor catalysts.

Compounds with active hydrogens, in particular N–H, undergo side reactions apparently forming amine salts which are inactive. Ammonium hydroxide, *tert*-butylamine, and ethanolamine exemplify this behavior.

A reaction of this type has also been observed in the preparation of perfluoroisopropyl acrylate. The preparation of this acrylate has been reported previously with the comment that dimethylformamide would be

$$(CF_3)_2CFOK + CH_2{:}CHCOCl \longrightarrow CH_2{:}CHCOOCF(CF_3)_2 + KCl$$

the best solvent.[2] This recommendation was based on gas chromatographic analysis of the crude reaction mixture. Attempts at this laboratory to use dimethylformamide as the solvent resulted in poor yields. The difficulty was traced to decomposition during distillation with small amounts of DMF in the still kettle. Acrylyl fluoride and hexafluoroacetone were formed.

This reaction, which may be quite general, provides a means of recovering PFBA from I, but solvents such as DMF and *N*-methylpyrrolidone should be avoided in the preparation and use of α-haloalkyl esters.

### Experimental Section

**Hydrolysis of I in a Water–Organic Mixture.**—To 33 g of I was added 20 g of water and 8 g of dimethyl sulfoxide (DMSO). The mixture was heated at 70° for 1.5 hr until the second phase disappeared. Extraction with ether left, after evaporation of the solvent, 26 g of PFBA hydrate and DMSO. No effort was

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