A Convenient Synthesis of 2-Hydroxy-2,6,6-trimethylcyclohexanone: A Versatile Intermediate[1]

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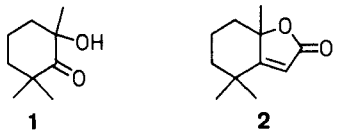
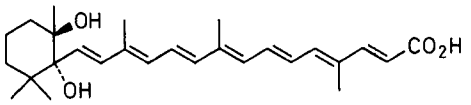
2-Hydroxy-2,6,6-trimethylcyclohexanone (**1**) was obtained in 85–88% yield by the oxidation of β-cyclocitral (2,6,6-trimethyl-1-cyclohexenecarbaldehyde) using 3-chloroperoxybenzoic acid or peracetic acid followed by hydrolysis with methanolic sodium hydroxide.

2-Hydroxy-2,6,6-trimethylcyclohexanone (**1**) is a carotenoid degradation product found in tea,[3] tobacco[4] and a Chinese shrub, *Osmanthus fragrans* Lour.[5] It has also been isolated from the supracaudal scent gland secretion of the red fox[6] and from the seaweed, *Porphyra tenera*.[7] This hydroxy ketone has been used as an intermediate for the synthesis of a bioactive metabolite, dihydroactinidiolide (**2**)[8,9] and azafrin (**3**), a yellow pigment in the traditional food coloring material, azafran.[10] A number of syntheses of **1** are on record; but many of the routes involve multiple steps with a low overall yield[9,11,12] or a cumbersome work up procedure.[13]



1 **2**



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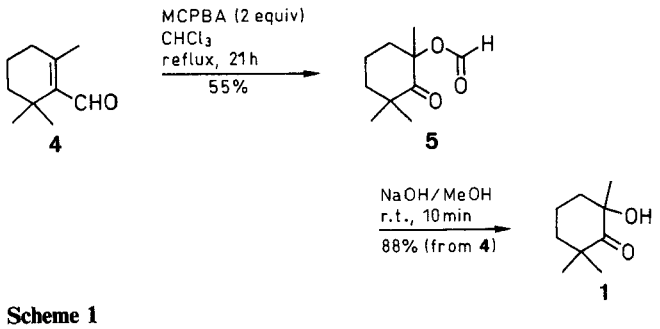
In continuation of our studies on the terpenoids,[1,8] we describe here a facile and high yielding synthesis of **1** starting from a commercially available β-cyclocitral (2,6,6-trimethyl-1-cyclohexenecarbaldehyde, **4**).

Oxidation of α,β-unsaturated aldehydes and ketones with peracids and hydrogen peroxide has been studied extensively.[14,15] Syper[16] found that the reaction of unsaturated aldehydes with hydrogen peroxide in presence of benzeneseleninic acids or 3-chloroperoxybenzoic acid (MCPBA) follows the Baeyer–Villiger oxidation pattern and affords vinyl formates as the principal product. Minor products were identified as formyloxyoxiranes, α-formyloxy ketones, etc.

We have found that the oxidation of β-cyclocitral **4** with two molar equivalents of MCPBA in chloroform under reflux for 21 hours led to the isolation of pure 1,3,3-trimethyl-2-oxocyclohexyl formate (**5**) in 55% yield. Hydrolysis with methanolic sodium hydroxide at room temperature resulted in almost quantitative conversion of **5** to **1** (Scheme 1).

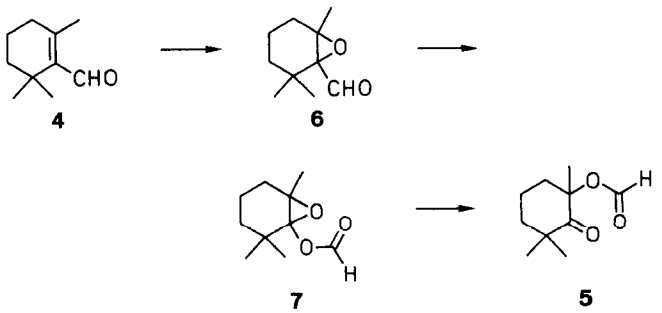


4 **5** **1**

Scheme 1

The proton signals in the $\delta = 7.5–10.5$ region (Table 1) proved useful for a detailed study of the oxidation of **4**. The proton in the formyl group (CHO) is known to resonate between $\delta = 9.0$ and 10.0 while the formyloxy group (OCHO) is characterized by a proton signal at about $\delta = 8.0$. Thus, the compound **5** displays a signal at $\delta = 7.92$ while the corresponding signal for **4** is at $\delta = 10.10$. Valuable structural information is provided by the chemical shifts of the methyl groups. Combined with a knowledge of the molecular weight as determined by the chemical ionization mass spectrometry, the ^{1}H NMR data allowed reliable assignment for the chemical shift of the formyl (or formyloxy) proton (Table 1) in a series of intermediates observed during the oxidation of **4**.

For improving the yield of **1** we have monitored the oxidation of **4** by ^{1}H NMR spectroscopy using the NMR assignments in Table 1. The initial product of reaction with MCPBA in $CDCl_3$ solution was found to be **6** (Table 2). Further reaction generated the Baeyer–Villiger oxidation product, the epoxy formate **7**[17] (Scheme 2). In course of time, the formation of **5**, and the gradual disappearance of **7** were observed indicating that rearrangement[16,18] of **7** to **5** was proceeding under the acid conditions of the reaction mixture.



4 **6** **7** **5**

Scheme 2

Table 1. ^1H NMR Assignments for Oxidation Intermediates

Compound	CHO	δ, CH_3	M.W.
4	10.10	1.12 (6H), 2.04	152
5	7.92	1.15, 1.22, 1.50	184
6	9.70	1.06, 1.30, 1.34	168
7	8.17	1.10, 1.12, 1.36	184
8	8.07	1.02 (6H), 1.41	168

Table 2. Oxidation of **4** with MCPBA in $CHCl_3$ and the Relative Proportion of Intermediates of Reflux Temperature

Time (h)	4	6	7	5
0.0	0.1	1.0	0.7	0.0
0.5	0.0	1.0	2.0	0.0
2.0	0.0	1.0	9.0	0.0
5.0	0.0	0.0	5.0	1.0
9.0	0.0	0.0	2.0	1.0
21.0	0.0	0.0	0.0	1.0

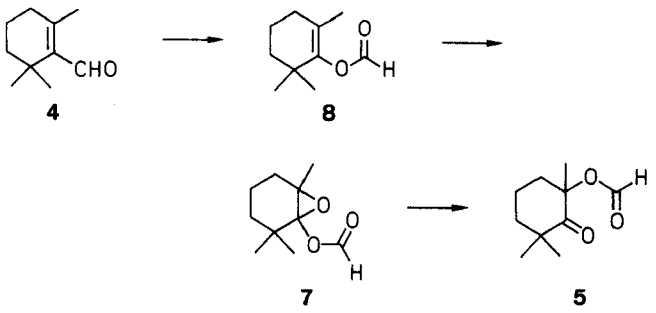
Table 3. Oxidation of **4** with AcOOH in $CDCl_3$ and the Relative Proportion of Intermediates at Room Temperature

Time (h)	4	8	7	5
0.0	9.0	1.0	0.0	0.0
0.2	2.8	1.0	0.0	0.0
0.5	1.2	1.0	0.2	0.0
0.8	0.7	1.0	0.3	0.0
1.0	0.6	1.0	0.4	0.0
1.5	0.6	1.0	0.9	0.0
2.0	0.4	1.0	1.0	0.0
3.0	0.2	1.0	1.2	0.0
6.0	0.0	1.0	3.0	0.0
11.5	0.0	1.0	11.0	0.2
24.0	0.0	1.0	11.0	1.0

The oxidation of **4** with peracetic acid (2 molar equivalents) in chloroform also gave a mixture of the formates **7** and **5**. After 5 hours of reflux, the ratio of **7** and **5** was found to approximately 2:3.

An examination of the product profile during the course of this reaction by ^1H NMR spectroscopy (Table 3) revealed that the initial product is the vinyl formate **8**, which is subsequently epoxidized to **7**. This epoxy formate **7** then rearranges to **5** (Scheme 3). Thus, it appears that although the final product, **5**, obtained during the oxidation of **4** with both MCPBA and peracetic acid is the same, yet the reaction pathways are different. Reaction with MCPBA proceeds with the initial epoxidation of **4** to **6**, whereas its Baeyer–Villiger oxidation is the preferred first step with peracetic acid. Such a variation in the oxidation pathways using MCPBA and peracetic acid was also noticed in non-conjugated enones by Holmes et al.[19]

Table 2 shows the product ratios at different time intervals when **4** was treated with MCPBA as revealed by ^1H NMR spectroscopy. It appears that after 5 hours reflux the



Scheme 3

starting aldehyde **4** and its epoxy derivative, **6**, had completely disappeared. At this stage **7** and **5** were present in 5:1 ratio. Further reflux of the reactants was found unnecessary as the basic hydrolysis of both **5** and **7** results in the target compound, **1**. Consequently, the reaction mixture was treated with methanolic sodium hydroxide to obtain **1** directly.[20] The results were similar when the peracetic acid was used as the oxidant.

β-Cyclocitral (90% purity) was purchased from Sigma Chemical Co. MCPBA (50–60% purity), AcOOH (32% solution in dil. AcOH) and silica gel (250–400 mesh) were purchased from Aldrich Chemical Co. Reagent quality solvents were used without further purification. IR spectra were obtained using Perkin-Elmer 1760 FT-IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were obtained using Bruker AF-200 NMR spectrometer. Chemical ionization mass spectra were obtained using Biospect spectrometer (Scientific Research Instruments Corp. Baltimore, MD).

Monitoring the Progress of Reactions by ^1H NMR Spectroscopy:
Procedure A: Aliquots (ca. 5.0 mL) of the refluxing mixture containing cyclocitral **4**, MCPBA (or AcOOH) and $CHCl_3$ were withdrawn at specified time intervals, diluted with $CHCl_3$ (10.0 mL) and washed with aq. NaOH (10%) and H_2O successively. After drying (Na_2SO_4), solvent was removed under vacuo and the ^1H NMR spectrum of the residue was taken as $CDCl_3$ solution. Signal intensities of formyl and formate protons (see Table 1) were used to determine the proportion of intermediates. The results are shown in Table 2.

Procedure B: Cyclocitral **4** and AcOOH (or MCPBA) were dissolved in $CDCl_3$. The solution was used directly to study ^1H NMR spectra at specified time intervals. Signal intensities of formyl and formate protons (Table 1) were used to deduce the relative proportion of intermediates (see Table 3).

1,3,3-Trimethyl-2-oxocyclohexyl Formate (5):
A solution of MCPBA (50–60%, 14.0 g, ca. 0.04 mol) in $CHCl_3$ (100 mL) was added slowly to a solution of β-cyclocitral **4** (3.05 g, 0.02 mol) in $CHCl_3$ (10 mL) at its boiling temperature. The mixture was heated under reflux for 21 h and cooled to r. t. The organic layer was washed with aq. NaOH (10%), H_2O, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave **5** (2.7 g, 73%). Further chromatographic purification over silica gel using hexanes/EtOAc (19:1) gave **5** as a colorless oil, yield: 2.0 g (55%).

IR (neat): ν = 1709, and 1723 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 1.15 (3 H, s), 1.22 (3 H, s), 1.50 (3 H, s), 1.60–2.00 (5 H, m), 2.40 (1 H, m), 7.92 (1 H, s).

^{13}C NMR ($CDCl_3$/TMS): δ = 211.9, 159.8, 82.4, 45.2, 38.7, 37.7, 27.1, 26.7, 25.0, 18.5.

CIMS ($CH_4 + NH_4Cl$, 180°C): m/z = 202 $(M + NH_4)^+$, 185 $(M + H)^+$, 138 $(M - HCOOH)^+$.

2-Hydroxy-2,6,6-trimethylcyclohexanone (1):
A solution of MCPBA (50–60%, 14.0 g, ca. 0.04 mol) in $CHCl_3$ (100 mL) was added slowly to a solution of β-cyclocitral **4** (3.05 g, 0.02 mol) in $CHCl_3$ (10 mL) at its reflux temperature. The mixture was heated under reflux for 5 h, cooled to r.t. and washed successively with aq. $NaHSO_3$ (10%), aq. NaOH (10%) and H_2O. Evaporation of the solvent gave colorless oil (ca. 3.7 g), which was hydrolyzed with methanolic NaOH (1%, 100 mL) at r.t. for 10 min. MeOH was removed and the residue was taken in $CHCl_3$ and washed with H_2O. Evaporation of the solvent gave **1** as a colorless oil, yield: 2.8 g (88%).

IR (neat): ν = 3500, and 1700 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 1.15 (3 H, s), 1.21 (3 H, s), 1.40 (3 H, s), 1.60–1.90 (5 H, m), 2.10 (1 H, m), 4.05 (1 H, s, exchangeable with D_2O).

^{13}C NMR ($CDCl_3$/TMS): δ = 218.4, 75.1, 44.1, 40.6, 40.5, 27.1 (2 C), 25.6, 18.6.

CIMS ($CH_4 + NH_4Cl$, 180 °C): m/z = 174 $(M + NH_4)^+$, 157 $(M + H)^+$, 138 $(M - H_2O)^+$.

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(1) Studies on Terpenoids, part 9; for part 8, see
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2,2,6-Trimethyl-7-oxabicyclo[4.1.0]heptan-1-yl formate (**7**): Colorless oil; IR (neat): ν = 1751 cm^{-1};
^1H NMR ($CDCl_3$/TMS): δ = 1.10 (3 H, s), 1.12 (3 H, s), 1.36 (3 H, s), 1.00–1.90 (6 H, m), 8.17 (1 H, s).
^{13}C NMR ($CDCl_3$/TMS): δ = 159.4, 92.8, 66.2, 36.6, 35.0, 30.3, 24.4, 23.7, 20.0, 16.9.
CIMS ($CH_4 + NH_4Cl$, 120 °C): m/z = 202 $(M + NH_4)^+$, 185 $(M + H)^+$, 138 $(M - HCOOH)^+$; (CH_4 + morpholine, 120 °C): m/z = 285 $(M + morpholine)^+$,

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(20) Both **5** and **7** are converted to **1** by hydrolysis. A high yield (88% based on **4**) of the product **1** was obtained by working up the reaction mixture after 5 h.