A New Approach to Cyclopentenones

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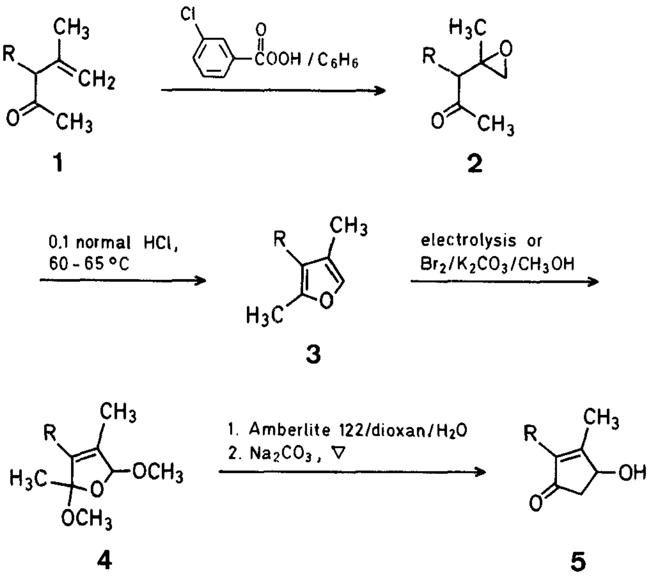
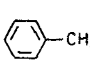
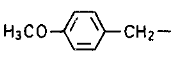
In the course of our investigations to utilize α-substituted mesityl oxides **1** for the synthesis of natural products[2], attention was paid to a cyclization of **1** to obtain cyclopentenones such as dihydrojasmone **(10b)** and allethrolone **(5f)**. Recently, a convenient synthesis of cyclopentenones **10** from the β,γ-unsaturated ketones **1**, based on the addition of bromine to **1** followed by cyclization of the adducts under basic conditions, has been reported[3]. We describe here an alternative synthesis of cyclopentenones **5**, **9**, and **10** by using the new epoxy ketone **2** as a versatile key intermediate.

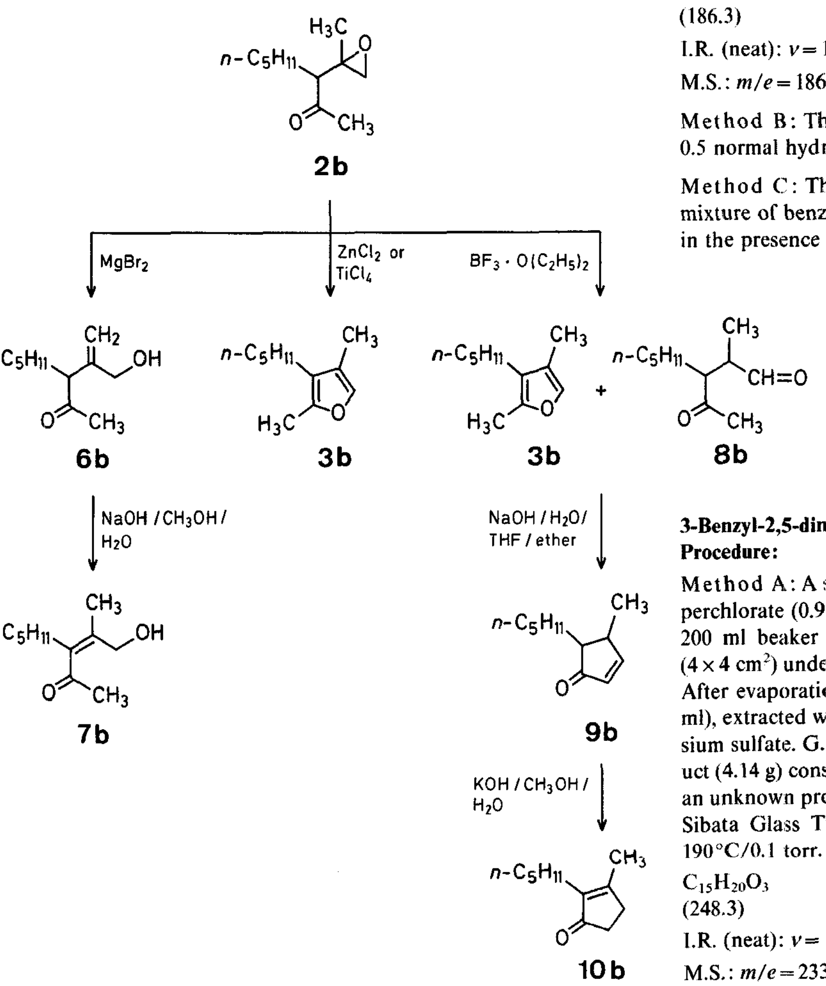
The epoxy ketones **2** were prepared as a diastereoisomeric mixture (1 : 1) by the oxidation of **1**[4] with *m*-chloroperbenzoic acid (Table 1). Reaction of **2** in methanolic hydrogen chloride gave furan **3** as the major product (Table 2). Introduction of dimethoxy moiety into the furan ring in **3** was effectively carried out by electrochemical reaction[5,6] to furnish **4** (Table 3). Addition of bromine to furan **3** in methanol in the presence of potassium carbonate also gave **4**, albeit in lower purity[7,8]. Compounds **4** were converted to cyclopentenones **5** by successive treatment with Amberlite 122 in aqueous dioxan at room temperature, neutralizing the mixture with sodium carbonate and heating to reflux. This two-step method is recommended for ring opening and reconstruction of **4** to give products **5** in high yield.

The preparation of 1,4-dicarbonyl compounds **8**[9] from **2**, as a direct precursor of cyclopentenones **9** and **10**, was also investigated. For example, **2b** was treated with boron trifluoride etherate to give a 1 : 1 mixture of **3b** and **8b**, which was without purification condensed[9] to **9b** by 5% aqueous sodium hydroxide in 32% yield. The cyclopentenone **9b** was isomerized to dihydrojasmone **(10b)** in quantitative yield[10].



1-5	R	1-5	R
a	i-C_4H_9	d	
b	n-C_5H_{11}	e	
c	n-C_6H_{13}	f	$H_2C{=}CH{-}CH_2{-}$

Furthermore, the following transformations of **2b** with Lewis acid catalysts were carried out. With magnesium bromide, **2b** was converted to **6b** and with zinc chloride or titanium(IV) chloride **2b** gave **3b**. The isomerization of **6b** to **7b** was achieved by treatment with aqueous methanolic sodium hydroxide.



In conclusion, we have shown that the new epoxy ketones **2** can be converted to immediate precursors of several cyclopentenone derivatives, and particularly in the synthesis of 4-hydroxycyclopentenones **5**.

3-Benzyl-4-methyl-4,5-epoxy-2-pentenone (2d); Typical Procedure:

To a solution of 3-benzyl-4-methyl-4-penten-2-one (**1d**; 56.4 g, 0.3 mol) in dichloromethane (800 ml) is slowly added 85% *m*-chloroperbenzoic acid (91 g, 0.45 mol) at 10 °C and allowed to react for 12 h. After filtration of the precipitate formed, the filtrate is carefully and sufficiently washed with 2% aqueous sodium hydrogen carbonate (5 × 500 ml) and dried with magnesium sulfate. Evaporation of the solvent gives a pale yellow liquid which is purified by column chromatography on silica gel (ethyl acetate/hexane, 15/85); yield: 49.1 g (80%). G.L.C. analyses (OV-1, 3m, 150 °C) shows that the **2d** thus obtained consists of a ~46 : 54 mixture of diastereomers.

$C_{13}H_{16}O_2$	calc.	C 76.44	H 7.89
(204.3)	found	76.21	7.73

M.S.: $m/e = 186$ ($M^+ - CH_3$), 173, 171, 144, 129, 91, 43.

3-Benzyl-2,4-dimethylfuran (3d); Typical Procedure:

Method A: A solution of **2d** (40.8 g, 200 mmol) in 0.1 normal methanolic hydrogen chloride (240 ml) and methanol (320 ml) is heated at 65 °C for 6 h. After evaporation of the solvent, the residue is neutralized with solid sodium carbonate (3 g), extracted with ether (3 × 300 ml), and the extract dried with magnesium sulfate. Purification of the product by column chromatography on silica gel (ethyl acetate/hexane, 1/9) affords **3d**; yield: 25 g (67%).

$C_{13}H_{14}O$	calc.	C 83.84	H 7.58
(186.3)	found	83.59	7.40

I.R. (neat): $\nu = 1600$, 1495, 1450, 1275, 1153, 1120 cm^{-1}.

M.S.: $m/e = 186$ (M^+), 171, 157, 143, 128, 109, 95, 91, 43.

Method B: This is carried out similarly to Method A, but by using 0.5 normal hydrogen bromide (20 ml).

Method C: The appropriate compound **2** (25 mmol) dissolved in a mixture of benzene (50 ml) and methanol (10 ml) is refluxed for 13 h in the presence of *p*-toluenesulfonic acid (0.5 mmol).

3-Benzyl-2,5-dimethoxy-2,4-dimethyl-2,5-dihydrofuran (4d): Typical Procedure:

Method A: A solution of **3d** (3 g, 16 mmol) and tetraethylammonium perchlorate (0.92 g, 4 mmol) in methanol (100 ml) is electrolyzed in a 200 ml beaker at room temperature using platinum foil electrodes (4 × 4 cm^2) under constant current (18.7 mA/cm^2) for 4 h (2.78 F/mol). After evaporation of the solvent, the residue is poured into water (20 ml), extracted with ether (4 × 50 ml), and the extract dried with magnesium sulfate. G.L.C. analysis (OV-17, 2m, 200 °C) shows that the product (4.14 g) consists of **4d** (90.3%, 55 : 45 mixture of stereoisomers) and an unknown product (9.7%). Pure **4d** is obtained by distillation using a Sibata Glass Tube Oven GTO-250R; yield: 3.4 g (85%); b.p. 170–190 °C/0.1 torr.

$C_{15}H_{20}O_3$	calc.	C 72.55	H 8.12
(248.3)	found	72.29	7.94

I.R. (neat): $\nu = 1600$, 1497, 1453, 1090, 1000 cm^{-1}.

M.S.: $m/e = 233$ ($M^+ - CH_3$), 217, 205, 201, 185, 157, 129, 91, 43.

Method B: A solution of bromine (2.69 g, 16.8 mmol) in methanol (10 ml) is added dropwise to a mixture of **3d** (3 g, 16 mmol) and potassium carbonate (4.6 g, 33.6 mmol) in methanol (40 ml) at −20 °C and allowed to react for 1 h. Similar work-up of the mixture as described above gives **4d** after distillation; yield: 2.96 g (74%).

2-Benzyl-4-hydroxy-3-methyl-2-cyclopentenone (5d); Typical Procedure:

A mixture of **4d** (20 g, 80 mmol) in water (200 ml)/dioxan (600 ml) and Amberlite 122 catalyst (20 g; whose —SO_3Na moiety is acidified with 1 normal hydrochloric acid and washed with water) is stirred at

Table 1. Epoxy Ketones **2** prepared

Compound **2**	Yield [%]	b.p. [°C]/torr	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
a	77	45°/0.25	$C_{10}H_{18}O_2$ (170.3)	0.78 (d, 6 H, J=6 Hz); 1.09, 1.20 (s, 3 H); 1.20–1.83 (m, 3 H); 2.10, 2.15 (s, 3 H); 2.21–2.66 (m, 3 H)
b	82	59–61°/0.2	$C_{11}H_{20}O_2$ (184.3)	0.83 (t, 3 H, J=6 Hz); 1.14, 1.23 (s, 3 H); 1.10–1.30 (br. s, 8 H); 2.13, 2.18 (s, 3 H); 2.41–2.71 (m, 3 H)
c	75	74–76°/0.3	$C_{12}H_{22}O_2$ (198.3)	0.80 (t, 3 H, J=6 Hz); 1.02, 1.14 (s, 3 H); 1.18–1.50 (m, 10 H); 1.99, 2.05 (s, 3 H); 2.23–2.52 (m, 3 H)
d	80	—[b]	$C_{13}H_{16}O_2$ (204.3)	1.22, 1.30 (s, 3 H); 1.97, 2.12 (s, 3 H); 2.30–3.20 (m, 5 H); 7.10–7.30 (m, 5 H)
e	73	—[b]	$C_{14}H_{18}O_3$ (234.3)	1.20, 1.30 (s, 3 H); 1.97, 2.10 (s, 3 H); 2.33–2.93 (m, 5 H); 3.73 (s, 3 H); 6.70–7.23 (m, 4 H)
f	62	52–57°/4–6	$C_9H_{14}O_2$ (154.2)	1.21, 1.32 (s, 3 H); 2.15, 2.23 (s, 3 H); 2.15–3.10 (m, 5 H); 4.8–6.10 (m, 3 H)

[a] Products **2a, b, d** gave satisfactory microanalyses (C, H; ±0.3). ^{1}H-N.M.R., I.R. and mass spectral data are in agreement with the structure. Products **2c, e, f** were identified by high resolution M.S.

[b] Purified by column chromatography on silica gel (ethyl acetate/hexane, 15 : 85).

Table 2. Substituted Furans **3** prepared

Compound **3**	Method	Yield [%]	b.p. [°C]/torr	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
a	A	62	117–122°/17	$C_{10}H_{16}O$ (152.2)	0.83 (d, 6 H, J=6 Hz); 1.85 (s, 3 H); 2.12 (s, 3 H); 7.0 (s, 1 H)
	B	60			
b	A	68	135–140°/20	$C_{11}H_{18}O$ (166.3)	1.87 (s, 3 H); 2.13 (s, 3 H); 7.0 (s, 1 H)
	B	69			
	C	61			
c	A	66	140–145°/17	$C_{12}H_{20}O$ (180.3)	1.88 (s, 3 H); 2.14 (s, 3 H); 7.0 (s, 1 H)
d	A	67	—[b]	$C_{13}H_{14}O$ (186.3)	1.74 (s, 3 H); 2.17 (s, 3 H); 3.63 (s, 2 H); 7.02 (s, 1 H); 7.1–7.3 (m, 5 H)
e	A	64	—[b]	$C_{14}H_{16}O_2$ (216.3)	1.73 (s, 3 H); 2.17 (s, 3 H); 3.57 (s, 2 H); 3.73 (s, 3 H); ca. 6.72–7.1 (m, 5 H)
f	A	60	48–53°/1.5	$C_9H_{12}O$ (136.2)	1.85 (s, 3 H); 2.15 (s, 3 H); 6.83 (s, 1 H)[c]

[a] Compounds **3a, d** gave satisfactory microanalyses (C, H; ±0.3). ^{1}H-N.M.R., I.R. and mass spectral data are in agreement with the assigned structure. Compounds **3b, c, e, f** were identified by high resolution M.S.

[b] Purified by column chromatography on silica gel (ethyl acetate/hexane, 1 : 9).

[c] Measured in CCl_4.

Table 3. Compounds **4** prepared

Compound **4**	Method	Yield [%]	b.p.[a] [°C]/torr	Molecular formula[b]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
d	A	85	170–190°/0.1	$C_{15}H_{20}O_3$ (248.3)	1.23, 1.28 (s, 3 H); 1.68 (s, 3 H); 2.89, 2.97 (s, 3 H); 3.35, 3.45 (s, 3 H); 5.20, 5.48 (s, 1 H); 7.20 (s, 5 H)
	B	74			
e	A	90	185–200°/0.1	$C_{16}H_{22}O_4$ (278.4)	1.21, 1.28 (s, 3 H); 1.70 (s, 3 H); 2.91, 2.99 (s, 3 H); 3.36, 3.46 (s, 3 H); 5.21, 5.50 (s, 1 H)
	B	77			
f	A	93	—[d]	$C_{11}H_{18}O_3$ (198.3)	1.22, 1.28 (s, 3 H); 1.60 (s, 3 H); 2.81, 2.85 (s, 3 H); 3.20, 3.28 (s, 3 H)[c]

[a] Distilled using a Sibata Glass Tube Oven GTO-250R.

[b] Compound **4d** gave satisfactory microanalyses (C, H; ±0.3). ^{1}H-N.M.R., I.R. and mass spectral data are in agreement with the structure. Compound **4e** was identified by high resolution M.S.

[c] Measured in CCl_4[8].

[d] Purified by column chromatography on silica gel (ethyl acetate/hexane, 25 : 75).

room temperature for 3 h. After filtration of the catalyst, the filtrate is neutralized with solid sodium carbonate (0.5 g) to pH 7.5–8.0 and refluxed for 6 h. Evaporation of the solvent and extraction with ether (3 x 100 ml) yields crude **5d** (17.8 g) which is purified by column chromatography on silica gel (methanol/acetate, 2/98); yield: 12.7 g (78%).

$C_{13}H_{14}O_2$	calc.	C 77.20	H 6.98
(202.3)	found	77.06	6.75

I.R. (neat): $\nu = 3400$, 1700, 1650, 1600, 1498, 1455, 1383 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.02$ (s, 3H, CH_3); 2.25–2.82 (m, 3H, CH_2 and OH); 3.47 (s, 2H, CH_2); 4.62 (d, 1H, CH, $J = 7$ Hz); 7.20 ppm (s, 5 H_{arom}).

By a similar procedure, *4-hydroxy-2-(*p*-methoxybenzyl)-3-methyl-2-cyclopentenone* (**5e**) and *2-allyl-4-hydroxy-3-methyl-2-cyclopentenone* (*allethrolone*; **5f**) are obtained in 83 and 75% yields, respectively.

Dihydrojasmone (10b):

To a solution of **2b** (4 g, 22 mmol) in ether (40 ml) is added boron trifluoride etherate (0.7 ml) at −5 °C and allowed to react for 30 min. The mixture is poured into water, extracted with ether (2 x 50 ml), and the extract dried with magnesium sulfate. G.L.C. analyses (PEG-20M or OV-17, 2m, 150 °C) shows that the product (3.92 g) consists of a ~1 : 1 mixture of furan **3b** and aldehyde **8b**. Formation of the aldehyde is confirmed by ^{1}H-N.M.R. spectra (in CCl_4; $\delta = 9.46$ and 9.48 ppm). The crude product is, without purification, added dropwise to a mixture of 5% aqueous sodium hydroxide (15 ml) in tetrahydrofuran (15 ml) and ether (30 ml) at room temperature and allowed to react for 2 h. After neutralization with solid ammonium chloride (1.0 g) the solvent is evaporated and the product distilled to give **3b**; yield: 1.05 g (29%) and **9b**; yield: 1.15 g (32%); b.p. 66–69 °C/0.25 torr. Compound **9b** is characterized spectroscopically.

I.R. (neat): $\nu = 1705$, 1587, 1455, 1375, 1345, 1172 cm^{-1}.

^{1}H-N.M.R. (CCl_4): $\delta = 0.82$ (t, 3H, CH_3, $J = 6$ Hz); 5.87, 5.89 (d, each; 1H, =CH, $J = 6$ Hz); 7.26, 7.28 ppm (d, each; 1H, =CH, $J = 6$ Hz).

Synthesis of dihydrojasmone (**10b**) from **9b** is carried out in quantitative yield by treating with aqueous methanolic potassium hydroxide according to the procedure described previously[9,10].

3-Acetyl-2-methyl-2-octenol (7b):

To a solution of magnesium bromide (~6 mmol) in ether (15 ml), prepared by reacting magnesium (150 mg) and 1,2-dibromoethane (1 ml), is slowly added a solution of **2b** (1.84 g, 10 mmol) in ether (5 ml) at room temperature and stirred for 1 h under a nitrogen atmosphere. The mixture is poured into water (10 ml), extracted with ether (3 x 30 ml), the extract is washed with brine (2 x 10 ml), and dried with magnesium sulfate. Evaporation of the solvent gives crude **6b**; yield: 1.7 g (72%, 78% purity); **6b** could not be further purified due to its thermal instability.

I.R. (neat): $\nu = 3450$, 2950, 2860, 1700, 1360 cm^{-1}.

Crude **6b** (1.67 g) in methanol (15 ml) is added to a 10% aqueous solution of sodium hydroxide (33 ml) at 20 °C and allowed to react for 2 h. After evaporation of methanol, the residue is extracted with ether (3 x 30 ml), the extract is washed with brine (2 x 10 ml), and dried with magnesium sulfate: Crude product (1.62 g) is purified by column chromatography on silica gel (ethyl acetate/hexane, 1 : 3) to give **7b**; yield: 1.27 g (96%).

$C_{11}H_{20}O_2$	calc.	C 71.70	H 10.94
(184.3)	found	71.42	10.69

I.R. (neat): $\nu = 3400$, 2900, 2840, 1670, 1340, 1000 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.8$ (m, 3H, CH_3); 1.27 (br. s, 6H, CH_2); 1.80 (s, 3H, CH_3); 2.23 (br. s, 6H, CH_3CO, CH_2, OH); 4.15 ppm (s, 2H, CH_2O).

M.S.: $m/e = 184$ (M^+), 169, 141, 127, 95, 57, 43, 41.

3-Pentyl-2,4-dimethylfuran (3b) using Lewis Acid Catalysis:

A sample of zinc chloride (1.0 g, 7.3 mmol; freshly prepared by melting in platinum crucible) is placed in a 50 ml flask and dissolved in ether (15 ml) under nitrogen. A solution of **2b** (0.92 g, 5 mmol) in ether (3 ml) is added at 10 °C and stirred for 2 h. The mixture is poured into ice/water (10 ml) and extracted with ether (2 x 15 ml), the extract is washed with 5% aqueous sodium hydrogen carbonate (4 x 10 ml), and dried with magnesium sulfate. After evaporation of the solvent, the residue obtained is purified by column chromatography on silica gel (ethyl acetate/hexane, 1 : 9) to give **3b**; yield: 0.36 g (43%). The high-resolution M.S. proves the assigned structure. Exact mass calculated for $C_{11}H_{18}O$: 166.2626; found: 166.263.

M.S.: $m/e = 166$ (M^+), 161, 137, 109, 95, 43.

A similar reaction of **2b** (5 mmol) in ether (3 ml) with titanium(IV) chloride (5 mmol) in ether (15 ml) at 10 °C for 1 h gives **3b**; yield: 38%.

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