# Synthetic Studies on Terpenic Compounds. XII.[1] Selective Degradation of the Side Chain in Portulal[2]

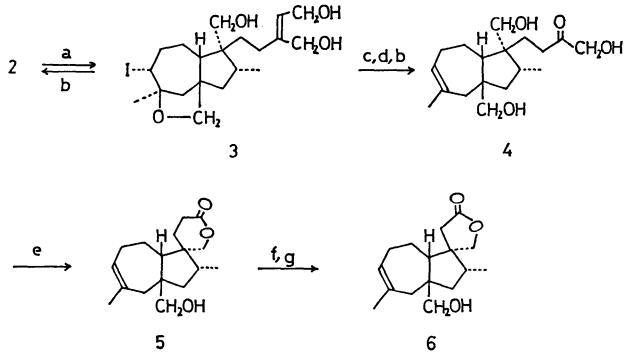
Takashi TOKOROYAMA,* Keizo MATSUO,† and Reizo KANAZAWA††
*Faculty of Science, Osaka City University, Sumiyoshi-ku, Osaka 558*

(Received May 6, 1980)

**Synopsis.** Stepwise degradation of the side chain in portulal has been investigated in connection with synthetic studies. Selective cleavage of the double bond in the side chain was achieved by ozonolysis after protection of the endo-double bond by iodoetherification of the corresponding alcohol. Further degradation led to the formation of the γ-lactone *via* the δ-lactone.

Portulal (**1**), a diterpene isolated from *Portulaca grandflora* Hook as a plant growth regulator, has a unique perhydroazulenoid skeleton with clerodane substitution.[3] In connection with the total synthesis of **1**,[1,4] we examined the products derived from **1** by degradation of its side chain since they might be utilized for confirming the stereochemistry of synthetic intermediates and also as relay compounds. The results of the investigation are given herewith.

The key problem for selective degradation of the side chain lies in the preferential cleavage of the $\Delta^{13,14}$ double bond, since its reactivity and that in the ring hardly differ. We found a solution to this problem by protecting the ring double bond with internal addition of the angular functional group. After several preliminary experiments the iodoetherification of portulol (**2**), obtained by lithium aluminium hydride reduction of **1**,[5] was found to be feasible. Treatment of **2** under specified conditions (Scheme 1) afforded the iodo ether **3** quantitatively. It was found that the latter can be reverted to the former by the reaction with zinc–silver couple[6] or chromium(II) chloride.[7] Ozonolysis of **3** and subsequent treatment of the product with zinc–silver couple gave an α-ketol **4** which was cleaved by periodic acid to yield the δ-lactone **5**, its IR spectrum showing carbonyl absorption at 1740 $cm^{-1}$. Further degradation of **5** to **6** was effected by formylation and subsequent treatment with alkaline hydrogen peroxide. The product showed the carbonyl peak at 1770 $cm^{-1}$ in its IR spectrum. A salient feature in the NMR spectrum was the presence of signals due to vinyl methyl and vinylic protons (δ 1.71 and 5.38, respectively), a singlet (δ 2.39) and an AB quartet (δ 4.09 and 4.23) due to the methylene protons of the spiro-γ-lactone and an AB quartet (δ 3.35 and 3.57) due to the hydroxymethyl protons. A counterpart of the latter AB quartet (δ 3.57) split further with coupling constant of 1.5 Hz, this being observable also in the NMR spectrum of the δ-lactone **5**. The extra splitting might be ascribed to the W-letter coupling with 5α proton, indicating that the free rotation of the angular hydroxylmethyl group is sufficiently restricted and stays in the most stable conformation. Oxidation of **6** with Jones' reagent followed by acid treatment afforded the dilactone **7** which has been correlated with the synthetic intermediate of portulal synthesis.[1] Compound **6** was found to be a pertinent relay compound.




Scheme 1. (a) $I_2$, $NaHCO_3$, THF; (b) Zn-Ag; (c) $O_3$; (d) $Me_2S$; (e) $HIO_4$; (f) $HCO_2Et$, NaH; (g) $H_2O_2$, KOH, MeOH

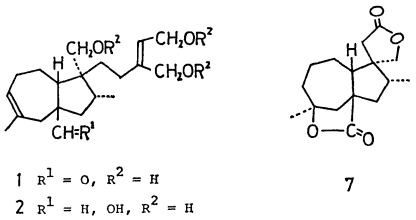



Fig. 1.

## Experimental

Melting points are uncorrected. IR spectra were taken on a JASCO IRA-1 spectrometer as films (liquid) or Nujol mulls (solid), $^1H$ NMR spectra in $CDCl_3$ on a JEOL PS-100 spectrometer and mass spectra on a Hitachi M-52 spectrometer.

*Extraction of Portulal (1).* Portulal was extracted from *Portulaca grandiflora* Hook by essentially the same procedure as that reported.[5] The cut aerial part of the plant was extracted with methanol and the extract concentrated *in vacuo* to about one-fourth of the original volume. The concentrated solution was washed with petroleum ether and then extracted continuously with ether. The ether layer was washed with saturated aq $NaHCO_3$ and dried with anhydrous $Na_2SO_4$, the solvent being removed. The neutral extract thus obtained was chromatographed on a silica-gel column. The crystalline material, eluted with benzene–ethyl acetate (1:1) followed by ethyl acetate, was recrystallized from aq methanol giving portulal **1** as needles, mp 119.5—120 °C.

*Iodo Ether 3.* A solution of $LiAlH_4$ (220 mg, 5.8 mmol) in tetrahydrofuran (20 ml) was added to a solution of **1** (1.359 mg, 4.05 mmol) in anhydrous tetrahydrofuran (30 ml) over a period of 10 min under ice-cooling, After the mixture had been stirred at room temperature for 80

† Present address: Faculty of Pharmaceutical Sciences, Kinki University, Higashiosaka, Osaka 577.

†† Present address: Daiichi Isotope Laboratories, Ltd, Chuo-ku, Tokyo 103.

min, excess reagent was destroyed by the addition of ethyl acetate, water (1.5 ml) and anhydrous $MgSO_4$. Filtration with the aid of Celite and evaporation of the solvent from the filtrate followed by chromatography on a column of silica gel (30 g) afforded portulol (**2**) as a colorless oil (1.388 g), which solidified when cooled. The substance dissolved in a mixture of tetrahydrofuran (30 ml) and water (22 ml) was mixed with aq $NaHCO_3$ (2.298 g, 27.35 mmol) and KI-$I_2$ solution prepared from KI (3.978 g), $I_2$ (1.934 g, 7.61 mmol), and water (25 ml). The mixture was stirred at ambient temperature for 4.5 h. Saturated aq $NaHCO_3$ solution was added to reduce excess iodine, the product isolated by ether extraction giving the iodo ether **3** as a pale yellow oil (1.831 g, 98% overall yield): IR 3360 $cm^{-1}$; $^1H$ NMR 0.98 (3H, d, $J$=6 Hz, $-\underset{|}{C}HC\underline{H}_3$), 1.51 (3H, s, $-O\underset{|}{C}CH_3$). 3.61 (2H, s, $-\underset{|}{C}C\underline{H}_2OH$), 3.79, 3.87 (2H, AB q, $J$=7 Hz, $-CH_2O-$), 4.15 (2H, s, $-\underset{|}{C}=\underset{|}{C}C\underline{H}_2OH$), 4.16 (2H, d, $J$=7 Hz, $-\underset{|}{C}=C\underline{H}CH_2OH$), 4.38 (1H, br s, $-CH_2C\underline{H}I-$), 5.58 (1H, t, $J$=7 Hz, $-\underset{|}{C}=C\underline{H}CH_2OH$).

*Reversion of Iodo Ether* ***3*** *to Portulol (****2****).* *(a) With Zinc-Silver Couple*: A solution of **3** (54 mg, 0.116 mmol) in dry ether (1.5 ml) was treated with zinc-silver couple prepared[6] from silver acetate (0.2 mg) and zinc dust (25 mg) with addition of ethanol (0.25 ml) and acetic acid (1 drop) under reflux for 1.5 h. After filtration, the filtrate was washed successively with dil. HCl saturated aq $NaHCO_3$ and brine, and dried with anhydrous $MgSO_4$. Evaporation of the solvent and purification of the product by silica gel chromatography gave portulol (**2**) (32 mg, 81% yield).

*(b) With* $CrCl_2$: A $CrCl_2$ solution (9 ml, *ca.* 3.7 mmol) was added to an ice-cooled solution of **3** (70 mg, 0.151 mmol) in *N*,*N*-dimethylformamide (8 ml), the mixture being stirred for 1 h. The product was extracted with $CHCl_3$ and the organic layer washed with saturated aq $NaHCO_3$ and brine. Removal of the solvent gave a product which was purified by chromatography (silica gel) to give portulol (**2**) (33 mg, 65% yield).

*δ-Lactone* ***5***. The iodo ether **3** (2.47 g, 5.32 mmol) dissolved in methanol (100 ml) was ozonized at −70 °C until blue coloration was observed. After the mixture had been left to stand at −70 °C for 15 min, excess ozone was expelled by bubbling of nitrogen gas. Dimethyl sulfide (390 mg, 6.29 mmol) was then added. The mixture was kept at −70 °C for 30 min, the temperature then being allowed to rise by removal of the cooling bath. Evaporation of the solvent gave a crude product which was dissolved in absolute ether (25 ml) and treated with zinc-silver couple (prepared from silver acetate, 14 mg and zinc dust, 2.4 g), ethanol (3 ml) and acetic acid (2 drops) with stirring at room temperature for 16 h. Work-up afforded the ketol **4** as colorless oil (1.6 g). The product dissolved in a mixture of dioxane (40 ml) and water (20 ml) was treated with $HIO_4 \cdot 2H_2O$ (1.7 g, 7.46 mmol) overnight at room temperature. Chloroform extraction and the washing of the extract solution with saturated aq $NaHCO_3$ followed by evaporation of the solvent gave an oil which was purified by silica-gel chromatography. Elution with chloroform-methanol (25:1) gave δ-lactone **5** as a colorless oil: IR ($CHCl_3$) 3470, 1740 $cm^{-1}$; $^1H$ NMR 1.07 (3H, d, $J$=7 Hz, $-\underset{|}{C}HC\underline{H}_3$), 1.71 (3H, br s, $-CH=\underset{|}{C}C\underline{H}_3$), 2.52 (2H, t, $J$=7.5 Hz, $-CH_2C\underline{H}_2CO_2-$), 3.33 (1H, d, $J$=10.5 Hz, $-C\underline{H}_2OH$), 3.56 (1H, dd, $J$=1.5, 10.5 Hz, $-C\underline{H}_2OH$), 4.25 (2H, s, $-CH_2OCO-$) 5.36 (1H, m, $-\underset{|}{C}=C\underline{H}CH_2-$)

*Conversion of δ-Lactone* ***5*** *into γ-Lactone* ***6***. NaH (53 mg, 50% oil dispersion) and ethyl formate (0.5 ml) were added to a solution of **5** (50 mg, 0.18 mmol) in dry benzene (3 ml). After addition of a drop of methanol, the mixture was stirred overnight at room temperature. The reaction mixture was diluted with benzene and shaken with water. The aqueous layer was separated and acidified with dil HCl. Isolation of the product with chloroform extraction gave a yellow oil (50 mg). The formyl derivative thus obtained was dissolved in a mixture of methanol (0.7 ml), water (0.5 ml) and 3 M (1 M=1 mol $dm^{-3}$) NaOH (0.1 ml) and mixed with 3 M NaOH (2 ml) and 30% $H_2O_2$ (0.8 ml). The mixture was stirred at ambient tempearture, 3 M NaOH (2 ml and 3 ml) and 30% $H_2O_2$ (0.4 ml and 2.5 ml) being added after 1.5 and 2.5 h, respectively. The reaction was continued overnight and then worked up. Acidification with dil HCl followed by chloroform extraction and chromatographic purification (silica gel) gave the γ-lactone **6** (25 mg, 53% yield) as a colorless oil: IR ($CHCl_3$) 3500, 1770, 1180, 1030 $cm^{-1}$; $^1H$ NMR 0.97 (3H, d, $J$=6.5 Hz, $-\underset{|}{C}HC\underline{H}_3$), 1.71 (1H, br s, $-CH=\underset{|}{C}C\underline{H}_3$), 2.39 (2H, s, $-CH_2CO_2-$), 3.35 (1H, d, $J$=11 Hz, $-C\underline{H}_2OH$), 3.57 (1H, dd, $J$=1.5, 11 Hz, $-C\underline{H}_2OH$), 4.09, 4.23 (2H, AB q, $J$=10 Hz, $-CH_2OCO-$), 5.38 (1H, m, $-\underset{|}{C}=C\underline{H}CH_2-$).

## References

1) Part XI; T. Tokoroyama, K. Matsuo, H. Kotsuki, and R. Kanazawa, *Tetrahedron*, in press.

2) This work was taken from the doctorate thesis of R. Kanazawa.

3) S. Yamazaki, S. Tamura, F. Marumo, and Y. Saito, *Tetrahedron Lett.*, **1969**, 359.

4) T. Tokoroyama, K. Matsuo, R. Kanazawa, H. Kotsuki, and T. Kubota, *Tetrahedron Lett.*, **1975**, 3651.

5) Y. Abe, E. Taniguchi, M. Eto, and Y. Oshima, *Nogeikagaku-zasshi*, **45**, 169 (1971).

6) J. M. Denis, C. Girrard, and J. M. Conia, *Synthesis*, **1972**, 549.

7) G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4077 (1950).

8) M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis," John Wiley and Sons, New York (1967), Vol. 1, p. 143.