

SELECTIVE  $\alpha$ -OXIDATION OF CYCLIC  $\beta$ -KETOESTERS  
WITH POTASSIUM FLUORIDE AND OXYGEN IN DIMETHYL SULFOXIDE:  
A SYNTHESIS OF KJELLMANIANONE

Hiroshi IRIE<sup>\*</sup>, Jun'ichi KATAKAWA, Masako TOMITA, and Yukio MIZUNO<sup>†</sup>

<sup>\*</sup> Faculty of Pharmaceutical Sciences, Nagasaki University, Bunkyo-machi  
Nagasaki 852

<sup>†</sup> Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku Kyoto 606

Selective oxidation of cyclic  $\beta$ -ketoester groups with potassium fluoride-oxygen in dimethyl sulfoxide provided  $\alpha$ -hydroxy- $\beta$ -ketoesters in fair yields. Application of the oxidation to 5-methoxycarbonyl-3-methoxy-cyclopent-2-enone furnished ( $\pm$ )-kjellmanianone.

In the course of our study concerning a new double Michael annelation for constructing cis-decalin skeleton,<sup>1)</sup> the cis-diketo-diester (1)<sup>1)</sup> was treated with potassium fluoride in dimethyl sulfoxide with an expectation that, provided the second Michael addition in the annelation was reversible, isomerization of the cis-diketo-diester (1) to the corresponding and thermodynamically more stable trans-isomer (2) might take place. However, instead of the trans-diketo-diester (2), the hydroxy-diketo-diester (3) was obtained in low yield as an air oxidation product after stirring the reaction mixture at room temperature for one week. The result led us to study the oxidation of  $\beta$ -ketoester with potassium fluoride-oxygen in dimethyl sulfoxide.

Treatment of the diketo-diester (1) with one molar equivalent of potassium fluoride in dimethyl sulfoxide under oxygen with stirring at 60 °C (bath temperature) overnight gave the hydroxy-diketo-diester (3)<sup>2)</sup> (m.p. 160-162 °C), [ $\nu_{\max}$ (KBr); 3280 (OH), 1738, 1715, and 1685 $\text{cm}^{-1}$  (CO);  $^1\text{H}$ -n.m.r.( $\text{CDCl}_3$ ),  $\delta$ , 1.15 (3H, s.), 3.75 (4H, s, OMe and  $\text{C}_8\text{-H}$ ), and 3.85 (3H, s.)] in 30% yield.<sup>3)</sup> Oxidation of the diketo-diester (4)<sup>1)</sup> in the same manner afforded the hydroxy-diketo-diester (5) (m.p. 175 °C), [ $\nu_{\max}$ (Nujol) 3340 (OH), 1740, 1710, and 1690 $\text{cm}^{-1}$  (CO);  $\delta$ , 1.14 (3H, d,  $J=6.0\text{Hz}$ ), 1.39 (3H, s.), 3.70 (3H, s.), 3.84 (3H, s.), and 4.02 (1H, s.  $\text{C}_8\text{-H}$ )] in 57% yield.

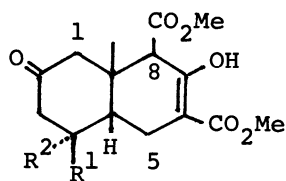
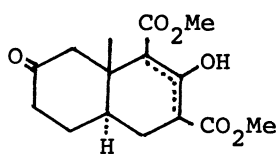


Furthermore, oxidation of the vinylogous  $\beta$ -ketoester (6)<sup>4)</sup> with the same reagent system gave the hydroxy-ketoester (7) (oil) [ $\nu_{\max}$ (neat), 3469 (OH), 1730 and 1650 $\text{cm}^{-1}$  (CO);  $\delta$ , 1.01 (3H, d,  $J=6.5\text{Hz}$ ), 1.30 (3H, t,  $J=7.0\text{Hz}$ ), 1.91 (3H, d,  $J=1.5\text{Hz}$ ), 4.34 (2H, q,  $J=7.0\text{Hz}$ ), and 6.00 (1H, q,  $J=1.5\text{Hz}$ ); Mass  $m/e$  212] and the phenol (8) (oil), [ $\nu_{\max}$ (neat), 3300 (OH) and 1685 $\text{cm}^{-1}$  (CO);  $\delta$ , 1.37 (3H, t,  $J=7.0\text{Hz}$ ), 2.17 (6H, s.), 4.38 (2H, q,  $J=7.0\text{Hz}$ ), and 6.45 (1H, s.)] in 62% and 1% yield, respectively. When the vinylogous  $\beta$ -ketoester (9)<sup>5)</sup> was treated with the same reagent, two hydroxy-ketoesters (10) and (11) were obtained. The  $^1\text{H}$ -n.m.r. spectrum of the former (10) showed a signal at  $\delta$  1.49 (3H, s.) assigned to tert-methyl protons on the carbon bearing a hydroxyl group, whereas the n.m.r. spectrum of the latter (11) exhibited a signal at  $\delta$  1.82 (3H, d,  $J=1.5\text{Hz}$ ) assigned to vinyl methyl protons, these signals suggesting the structures of these oxidation products.

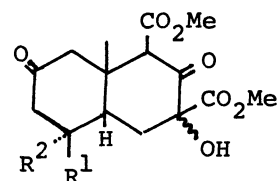
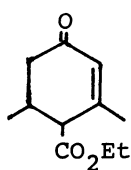
On the other hand, simple conjugated ketones, pulegone and carvone, and open-chain  $\beta$ -ketoesters, ethyl acetoacetate and diethyl propionylmalonate,<sup>6)</sup> gave no oxidation product but resulted in quantitative recovery of the starting materials (revealed by gas chromatographic examination) under the same oxidation conditions. These results indicated that the reagent system ( $\text{KF-O}_2$ -DMSO) was available to selective oxidation of cyclic  $\beta$ -ketoester groups. Addition of triethyl phosphite into the reaction mixture showed a slight improvement of the yield of the corresponding oxidation product.

In order to extend the applicability of the reagent system, the synthesis of kjellmanianone (12) was undertaken. Kjellmanianone (12) was isolated from the brown alga, Sargassum kjellmanianum Yendo, the structure of which was firmly established by X-ray crystallography by Nakayama and his co-workers.<sup>7)</sup> Treatment of 3-methoxycyclopent-2-enone<sup>8)</sup> with lithium diisopropylamide in tetrahydrofuran at  $-70^\circ\text{C}$  followed by methyl chloroformate gave the keto-ester (13) in 20% yield. Oxidation of the keto-ester (13) with the reagent system mentioned above at  $60^\circ\text{C}$  followed by refluxing for 30 min. in the presence of triethyl phosphite furnished ( $\pm$ )-kjellmanianone (12) in 6% yield. The poor yield is probably due to a hydrolysis of the ester group and/or the vinylogous ester group. Eventually, we could overcome the poor yield using 18-crown-6 ether. Thus, the keto-ester (13) was treated with  $\text{KF-O}_2$  in dimethyl sulfoxide in the presence of one molar equivalent of 18-crown-6 ether and triethyl phosphite at room temperature for 3 h to give ( $\pm$ )-kjellmanianone (m.p.  $135\text{--}136^\circ\text{C}$ ) in 60% yield. The  $^1\text{H}$ -n.m.r. ( $\text{CDCl}_3$ ) and i.r. ( $\text{CHCl}_3$ ) spectra of

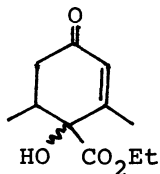


(1)  $R^1=R^2=H$ (4)  $R^1=Me; R^2=H$ 

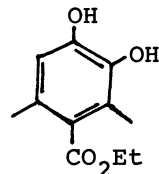
(2)

(3)  $R^1=R^2=H$ (5)  $R^1=Me; R^2=H$ 

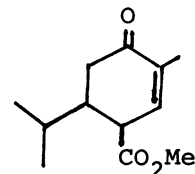
(6)



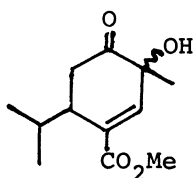
(7)



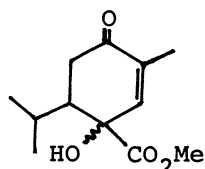
(8)



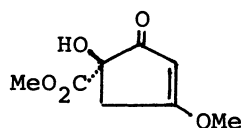
(9)



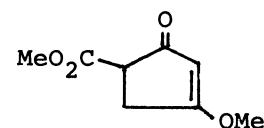
(10)



(11)



(12)



(13)

(±)-kjellmanianone were identical with those of natural kjellmanianone kindly provided by Professor Nakayama (Department of Chemistry, Hiroshima University), indicating accomplishment of the synthesis of (±)-kjellmanianone.

We express our appreciation to Professor M. Nakayama for copies of the n.m.r. and i.r. spectra of kjellmanianone.

#### References and Notes

- 1) H. Irie, J. Katakawa, Y. Mizuno, S. Uda, T. Taga, and K. Osaki, J. Chem. Soc., Chem. Commun., 1978, 717.
- 2) Stereo-structures of the oxidation products, (3), (5), (7), (10), and (11) have not been elucidated so far. We are planning to execute stereo-structure elucidation of these oxidation products by X-ray crystallography.
- 3) The yields shown in this report are the isolated ones after recrystallization, when the products were crystalline.



- 4) M. Mongrain, J. Lafontaine, A. Belanger, and P. Deslongchamps, Can. J. Chem., 48, 3273 (1970).
- 5) The synthesis of the vinylogous  $\beta$ -ketoester (9) was reported at the "22<sup>nd</sup> Symposium on Natural Products", Fukuoka (1979); H. Irie, Y. Mizuno, J. Katakawa, T. Fushimi, T. Taga, and K. Osaki, Abstracts of Papers, p. 212 (1979).
- 6) K. v. Auwers and H. Jacobsen, Justus Liebigs Ann. Chem., 426, 191 (1922).
- 7) M. Nakayama, Y. Fukuoka, H. Nozaki, A. Matsuo, and S. Hayashi, Chem. Lett., 1980, 1243.
- 8) H.O. House and G.H. Rasmusson, J. Org. Chem., 28, 27 (1963).

(Received February 16, 1981)