Tetrahedron Letters No. 10, pp 759 - 762, 1976. Pergamon Press. Printed in Great Britain.

# SYNTHESIS OF (R)- AND (S)-4-HYDROXY-2-CYCLOPENTENONES

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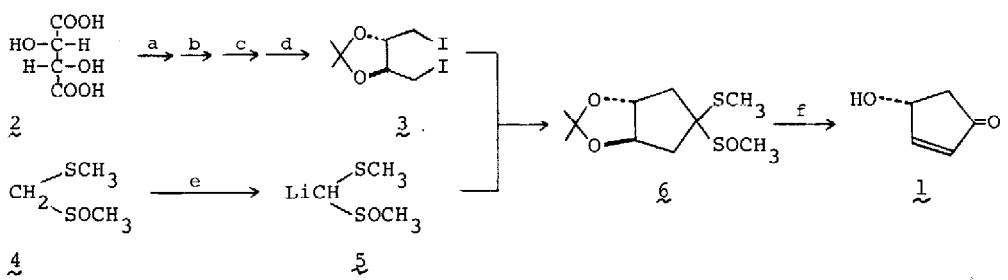
(Received in Japan 8 January 1976; received in UK for publication 28 January 1976)

The double alkylation of 4-hydroxy-2-cyclopentenone and its protected forms is one of the most efficient routes to prostaglandins of E or F series,[1,2] and recently, Stork and Isobe reported an elegant eight-step synthesis of $PGF_{2\alpha}$ starting from (±)-4-cumyloxy-2-cyclopentenone.[3] Then, the use of (R)-4-hydroxy-2-cyclopentenone and its derivatives is desirable for the syntheses of optically active PGE or PGF of natural series. In this letter, we wish to describe the first and unambiguous synthesis of both (R)- and (S)-4-hydroxy-2-cyclopentenones from D- and L-tartaric acids, respectively, and their characterization.

The present pathway for making of (R)-4-hydroxy-2-cyclopentenone (1) was summarized in the accompanying Scheme. First, D-1,4-diiodo-2,3-isopropylidenedioxybutane (3, $[\alpha]_D^{29}$ +16.6°; lit.[4a] $[\alpha]_D^{24}$ +17.5°) was prepared from D-tartaric acid (2) in four steps (total yield: 42%) by the known reactions.[4] Then, the thus-obtained 3 was allowed to react with the lithio derivative (5; 2.3 equiv

Scheme




[a] 2,2-dimethoxypropane/p-toluenesulfonic acid [b] lithium aluminum hydride
[c] p-tosyl chloride/pyridine [d] sodium iodide [e] n-butyllithium [f] 1N sulfuric acid

to 3) of methyl methylthiomethyl sulfoxide (4),[5] followed by acid-hydrolysis. A typical procedure: A hexane solution (42 ml: 60.5 mmol) of n-butyllithium was added at -70° to a solution containing methyl methylthiomethyl sulfoxide (4; 7.485 g: 60.4 mmol), which was stirred at -70° for 1 hr and at -10° for 1 hr. After the dropwise addition of 3 (10.086 g: 26.4 mmol), the resulting mixture was further stirred at -70° for 1 hr and at room temperature for 2 days. A usual work-up (consisting of addition of water, extraction with methylene chloride, and evaporation) gave an oil which was dissolved in ethyl acetate and washed with water to remove the unreacted 4. Drying over anhydrous magnesium sulfate and concentration under reduced pressure afforded a dark reddish oil (5.21 g), which was shown by its NMR spectrum to consist mainly of the cyclization products (6). This oil was dissolved in diethyl ether (300 ml), and then, 1N sulfuric acid (4 ml) was added under ice-cooling. The resulting mixture was stirred at room temperature for 3 days, followed by neutralization with sodium bicarbonate and drying over anhydrous magnesium sulfate. After the removal of the insoluble materials by filtration, the filtrate was evaporated under reduced pressure. The oily residue was column-chromatographed on silica gel (eluted with diethyl ether) to give (R)-4-hydroxy-2-cyclopentenone (1) as an oil (1.357 g, 52.5%). This oil was further purified by distillation under reduced pressure and identified by the following data: a colorless oil; bp 63-64°/0.2 mmHg; $[\alpha]_D^{28}$ +68.6° (in $CHCl_3$, c = 2.48); NMR (in $CDCl_3$): δ 2.20 (1H, d of d, J = 2 and 18 Hz), 2.72 (1H, d of d, J = 6 and 18 Hz), 3.97 (1H, d, J = 6 Hz), 4.98 (1H, m), 6.14 (1H, d of d, J = 2 and 6 Hz), and 7.57 (1H, d of d, J = 3 and 6 Hz); IR (neat): 3375, 1714, and 1588 $cm^{-1}$.[6] Anal. calcd for $C_5H_6O_2$: C, 61.22; H, 6.16. Found: C, 60.91; H, 6.01.

The optical purity of 1 was given by its transformation into the corresponding acetate (7)[8] and the measurement of its NMR spectrum in the presence of tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium [Eu(TFC)$_3$] as a chiral shift reagent. In $CCl_4$ with a ratio: Eu(TFC)$_3$/7 = 0.3, separated methyl signals could be observed as shown in the following Figure. From these results,[9] we estimated the optical purity of the (R)-4-hydroxy-2-

cyclopentenone (1) having $[\alpha]_D^{28} = +68.6^\circ$ as 85%, leading to a specific rotation $[\alpha]_D$ = ca. $+81^\circ$ for optically pure 1.

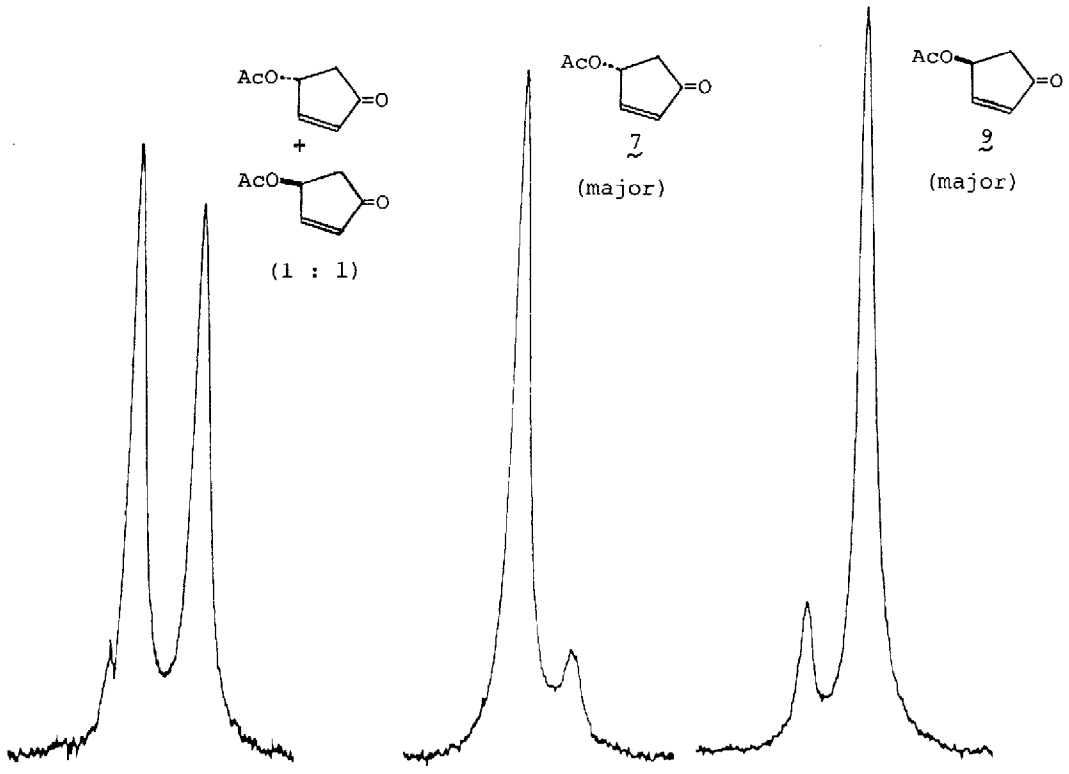
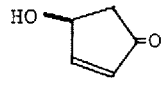



Figure Methyl signals in the NMR spectra of the acetates 7 and 9 in the presence of $Eu(TFC)_3$

(S)-4-Hydroxy-2-cyclopentenone (8), the enantiomer of 1, was also synthesized in a similar manner. L-1,4-Diiodo-2,3-isopropylidenedioxybutane, which was obtained from diethyl L-tartrate in the total yield of 58%, was allowed to react with 5, followed by acid-hydrolysis to give 8 ($[\alpha]_D^{25}$ - 69.0° in $CHCl_3$, c = 2.50).[10] The optical purity was determined to be 86% by measuring the NMR spectrum of the acetate (9) of 8 in the presence of $Eu(TFC)_3$.

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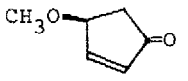
This method is also applicable to the synthesis of optically active 4-methoxy-2-cyclopentenones. Thus, (S)-4-methoxy-2-cyclopentenone (10; $[\alpha]_D^{25}$ $-3.7^{\circ}$ in $CHCl_3$, c = 3.64) was synthesized by the above-mentioned procedure, starting from L-1,4-diiodo-2,3-dimethoxybutane which was obtained from dimethyl L-tartrate by sequential treatment with methyl iodide-silver oxide, reduction with lithium aluminum hydride, tosylation with tosyl chloride-pyridine, and substitution with sodium iodide.[11]



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We are now studying on the synthetic utilities of (R)- and (S)-4-hydroxy-2-cyclopentenones.

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6. These IR and NMR spectra were completely in accord with those of (±)-4-hydroxy-2-cyclopentenone, which was prepared by acid-hydrolysis (2% sulfuric acid; 50-60° for 10 hr) of (±)-4-acetoxy-2-cyclopentenone.[7]
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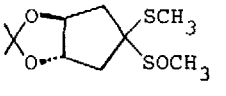
8. By treatment with acetic anhydride-pyridine at room temperature for 14 hr.
9. Since 7 does not undergo any racemization in this acetylation condition, it is reasonable to assume that the optical purity of 7 is approximately equal to that of 1.
10. The specific rotation of (S)-4-hydroxy-2-cyclopentenone (8) rose to $[\alpha]_D^{27}$ $-73.5^{\circ}$ (in $CHCl_3$, c = 2.48), when the cyclization products (11), which were obtained by the reaction of L-1,4-diiodo-2,3-isopropylidenedioxybutane with 5, were purified by column chromatography (on Florisil, eluted with ethyl acetate).



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