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SYNTHESIS AND NUCLEOPHILIC RING-OPENING REACTIONS OF ACTIVATED BICYCLO-[3.1.0]HEXANES.

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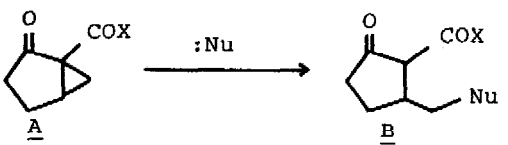
Cyclopropane derivatives are known to be cleft by a variety of nucleophiles, when one of the three-membered ring carbons is substituted with one or more electron-withdrawing substituents.[1] During the course of our study on a novel route to cyclopentanone derivatives, we were interested in the chemistry of 2-oxo-bicyclo[3.1.0]hexanes A bearing electron-withdrawing substituent on 1-position. If the ring-opening reaction by nucleophile occurs selectively at 1-6 bond in A, the resulting B might be used as an intermediate for the synthesis of prostanoids and jasmonoids. This paper deals with the synthesis and ring-opening reaction of A as well as an approach to a key intermediate for prostaglandins.



A B

Methyl 3-oxo-6-heptenoate (1a)[2] was converted to the α-diazo derivative 2a by treatment with p-toluenesulfonyl azide and triethylamine in acetonitrile.[3] Refluxing of 2a in benzene in the presence of anhydrous cupric sulfate gave methyl 2-oxo-bicyclo[3.1.0]hexane-1-carboxylate (3a) in 69% overall yield[4] from 1a: bp 82∿83°C/0.7 mmHg; ν_{max} 1755, 1725 cm^{-1}; nmr(CCl_4) δ: 1.33(t, J=5Hz, 1H), 1.77∿2.73(m, 6H), 3.68(s, 3H). Similar reactions starting from 1b[5] afforded 3b in 37% yield based on 1b: bp 55∿57°C/15 mmHg; ν_{max} 1725, 1690 cm^{-1}; nmr(CCl_4) δ: 1.37(dd, J=4Hz, J=6Hz, 1H), 1.76∿2.70(m, 6H), 2.40(s, 3H).

Treatment of 3a with potassium thiophenoxide in t-butyl alcohol for 1 hr

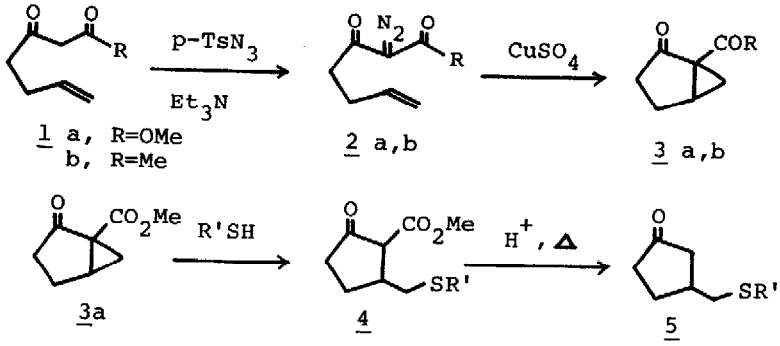
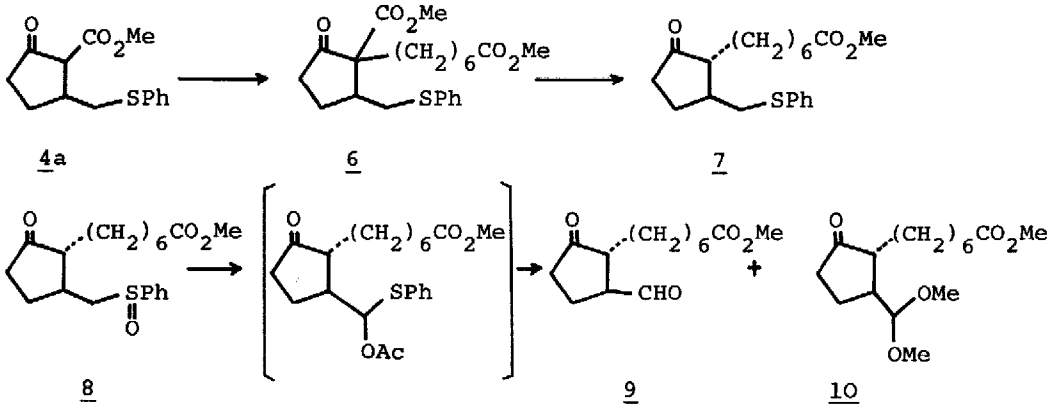


Table I. Yields of β-Keto esters 4 and Cyclopentanone Sulfides 5

	R'	4(%)	5(%)
a	Ph	93*	85
b	$PhCH_2$	78	84**
c	$Me(CH_2)_5$	61	92

* mp 41∿42°C (ether:n-hexane). ** mp 39∿40°C (ether:n-hexane)

at room temperature followed by quenching with 5% hydrochloric acid produced the adduct 4a in 93% yield: ν_{max} 1760, 1730 cm^{-1}; nmr(CCl_4) δ: 1.37∿3.50(m, 8H), 3.68(s, 3H), 7.03∿7.65(m, 5H). Two modes of carbon-carbon bond scission, i.e., the one at 1-5 bond and the other at 1-6 bond, are in principle possible. The former will afford cyclohexanone derivative, while the latter cyclopentanone. Under the above-mentioned conditions, it was found, however, that the latter type of cleavage, i.e., scission at 1-6, occurred selectively. The cyclopentanone structure of the resulting 4a was confirmed by the following degradation, since it was uncertain at this stage due to the presence of keto-enol equilibrium as well as cis-trans isomerism. When the adduct 4a was hydrolyzed and decarboxylated in refluxing 30% aqueous sulfuric acid, there was obtained the cyclopentanone sulfide 5a in 85% yield: ν_{max} 1740 cm^{-1}; nmr(CCl_4) δ: 1.40∿2.62(m, 7H), 2.92(d, J=6.5Hz, 2H), 6.95∿7.33(m, 5H); MS(m/e) 123(CH_2SPh, 73% of base peak). The ir, nmr, and mass spectra of 5a distinctly supported the presence of five-membered ring. The cyclopropane ring in 3a could be cleft selectively with other mercaptides (Table I).



4a 6 7

8 9 10

In order to demonstrate the utility of this new ring-opening reaction, we have now carried out the synthesis of the aldehyde 9 which is known as a precursor for prostaglandins.[6] The β-keto ester 4a was firstly transformed into the corresponding carbanion by treatment with potassium hydride in DMSO[7] under an argon atmosphere and then condensed with methyl 7-iodoheptanoate[8] to provide the diester 6 in 85% yield. Decarboxylation of the diester 6 in refluxing DMF in the presence of lithium iodide[9] afforded the ester 7 in 70% yield: ν_{max} 1740 cm^{-1}; nmr($CDCl_3$) δ: 1.02∿2.41(m, 18H), 2.86, 3.21(AB of ABX, J=13Hz, J=7Hz, J=4Hz, 2H), 3.60(s, 3H), 7.02∿7.41(m, 5H). In general, 2,3-disubstituted cyclopentanones are known to exist in thermodynamically stable trans form.[6,10] The nmr spectrum of 7 exhibited one distinct pair of AB quartets assignable to sulfenyl methylene thus supporting the trans configuration of two side chains in 7. Oxidation of the sulfide ester 7 with m-chloroperbenzoic acid in dichloromethane gave the sulfoxide 8. The sulfoxide 8 was submitted to the standard condition of Pummerer rearrangement (acetic anhydride-sodium acetate).[11] The crude product was directly hydrolyzed in aqueous methanol in the presence of sulfuric acid and mercuric chloride[12] to afford an almost 1:1 mixture of the aldehyde 9 [ν_{max} 2710, 1740 cm^{-1}; nmr(CCl_4) δ: 0.94∿2.95(m, 18H), 3.61(s, 3H), 9.65(d, J=2Hz, 1H)] and its dimethyl acetal 10 in 65% total yield based on 7. The latter acetal could be easily transformed into 9 by refluxing in acetone-water (9:1) in the presence of a catalytic amount of conc. hydrochloric acid.

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