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A NOVEL SYNTHESIS OF CIS-3,4-DISUBSTITUTED CYCLOPENTANONES

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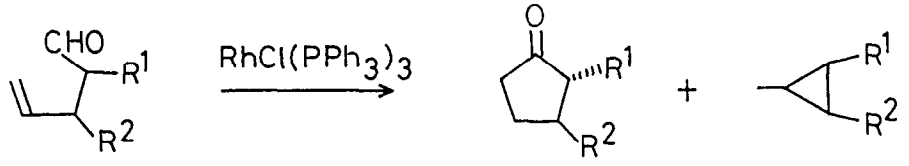
Abstract: A new method for the stereospecific synthesis of cis-3,4-disubstituted cyclopentanones is described.

As a part of synthetic studies on biologically active compounds consisting of five membered ring such as prostaglandins, brefeldin A and methylenomycin A, we undertook the stereospecific synthesis of cis-3,4-disubstituted cyclopentanones. Previously,we reported on the new cyclization reaction[1] (Scheme 1) catalyzed by tris(triphenylphosphine)rhodium[I] chloride (Wilkinson complex), in which 2,3-disubstituted 4-pentenals could be cyclized to 2,3-disubstituted cyclopentanones accompanied by the formation of cyclopropane derivatives under mild conditions. However,the formations of cyclopentanones resulted in unsatisfactory yield. Later, the similar reactions using Rh-complex were independently studied by R.G.Miller[2] and R.C.Larock[3].



Scheme 1

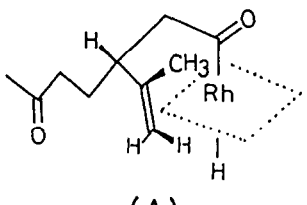
We now wish to describe that 3,4-disubstitued 4-pentenals are stereospecifically converted to cis-3,4-disubstituted cyclopentanone derivatives*1 in fair to good yield. In this case, the formation of cyclopropane derivatives was not observed.

A typical example is as follows. 3(R)-isopropenyl-6-oxo-heptanal(Table I, entry I)(504mg) and Wilkinson complex(825mg) were stirred in CH_2Cl_2 (5ml) for 2.5h at room temperature. After removal of the solvent, the oily residue was dissolved in ether(50ml). The unsoluble material was filtered off, and the filtrate was evaporated off in vacuo to afford the oily residue which was subjected to column chromatography on silica gel. In this way, 3(R),4(R)-3-methyl-4(3'-oxobutyl)cyclopentanone was obtained in 80% yield(423mg) and the trans isomer was not detected.

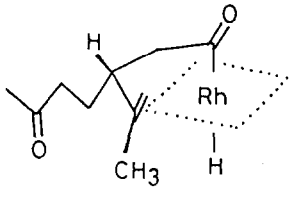
As shown in Table I, even the six membered lactol(entry II and IX) as well as 3,4-disubstituted 4-pentenals proceeded smoothly to yield the cis-3,4-disubstituted cyclopentanones as a sole product. The stereochemistry of product (1) was determined as cis configuration[*2] by comparison of the chemical shift of the C_3-methyl signal in 1(C_3-Me,δ:0.94) with that of 8(C_3-Me,δ:0.97),which was clarified to be cis by the direct conversion into the cis compound (10,Scheme 2, R_1=Me,R_2=COOMe). By similar comparison ,the stereochemistry of 9(C_3-Me,δ:0.97) could be also assigned as cis configuration. The configuration of 3,4-disubstituents in products (2~7) was established to be cis by the chemical correlation with 1, as shown in scheme 2.

The stereospecific formation of cis configuration in this reaction may be understood by taking the stereochemistry of the reaction intermediate into consideration. The two reaction intermediates(A and B) as shown in Fig.I are tentatively proposed. The intermediate(B) is considered to be sterically unfavorable by the repulsion of methyl group and its vicinal substituent. On the other hand, the intermediate A seems to be a preferable form and afford the cis product via the hydrogen migration[*3] and subsequent ring closure to the five membered ring ketone.

Fig. I

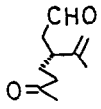
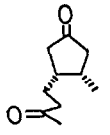
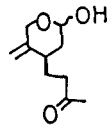
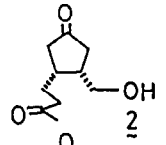
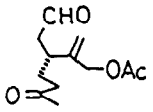
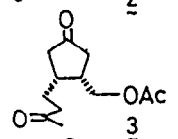
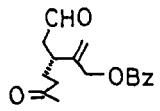
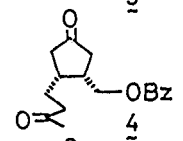
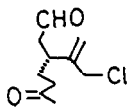
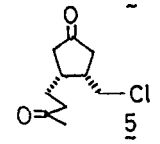
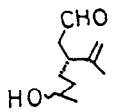
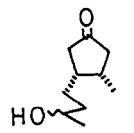
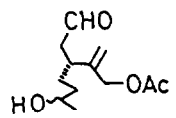
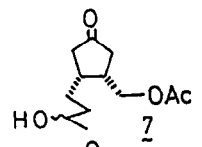
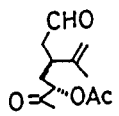
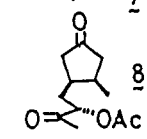
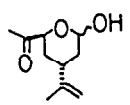
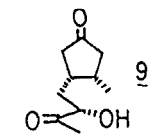


(A)



(B)

Table I

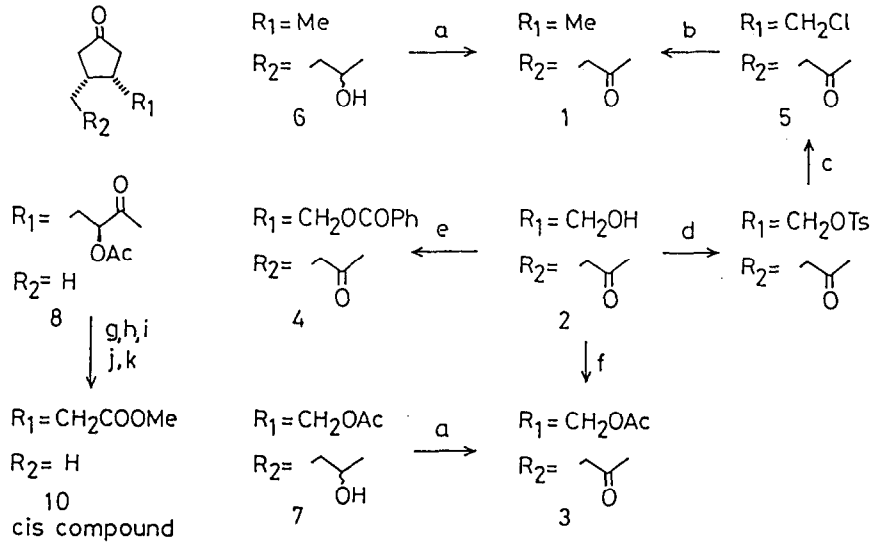
Entry	Aldehyde	React. Cond.	Time(h)	Product	Yield (%)
I		A	2.5	 1	84
II		B	12	 2	50
III		A	2.5	 3	88
IV		A	8	 4	79
V		A	4	 5	73
VI		A	14	 6	62
VII		A	14	 7	53
VIII		A	2.5	 8	85
IX		C	18	 9	49

React. Cond. A) R.T. in CH_2Cl_2 B) reflux in CH_2Cl_2

C) reflux in $CHCl_3$

0.9 mmol of complex and 3 mmol of

4-pentenal in 5 ml of soivent



Reagents : a = Collins oxidation , b = $(Bu)_3SnH$, c = LiCl , d = TsCl / Py , e = PhCOCl / Py , f = Ac_2O / Py , g = $NaBH_4$, h = K_2CO_3 / MeOH , i = $NaIO_4$, j = Jones oxidation , k = CH_2N_2.

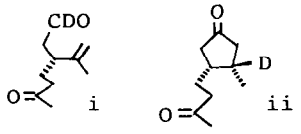
Scheme 2

References and footnotes

*1 The starting materials in entry I-V were synthesized in an optically active form according to Wolinsky's method[4] from d-limonene and (+)-limonen-10-ol, and those in entry VI-IX were synthesized from l-carvon by its slight modification.

*2 In the H^1-NMR spectrum of trans-3-methyl-4-substituted cyclopentanone, the signals of the C_3-Me was observed at δ:1.14-1.20 and at a lower field than that of the corresponding cis configuration[5].

*3 Hydrogen migration from the acylrhodium hydride intermediate(Fig.I A) to the carbon-carbon double bond was demonstrated by similar ring closure of the deuterio-aldehyde(i) to the deuterio-cyclpentanone(ii), in which the location of deuterium was established by the ^{1}H-NMR spectrum. A reaction mechanism of the rhodium-catalyzed cyclization of 4-hexanals was also studied by R.G.Miller[6].



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