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DIASTEREOSELECTIVE REDUCTION OF PERFLUOROALKYLATED α,β-UNSATURATED KETONES WITH BAKER'S YEAST

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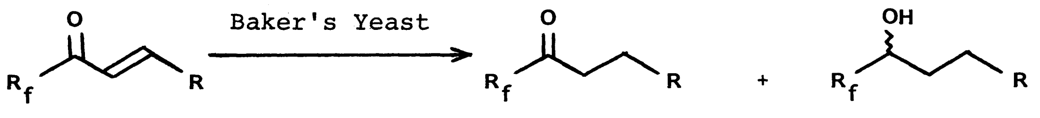
The differentiation of a fluorinated group in the molecule with active fermenting yeast and the double asymmetric induction in some perfluoroalkylated α,β-unsaturated ketones are described.

Asymmetric reduction of a carbonyl group with chiral reductive reagents,e.g., BINAL, Darvon-red, etc., is well known,1) however, our results of the reactions of polyfluorinated alkenyl or alkynyl carbonyl group with those reductive reagents suggest the strong affinity of fluorine atom to metal atoms affording to the racemic carbinols.2,3)

In our previous papers,4,5) we described the utility of microbiological transformation of perfluoroalkylated carbonyl compounds with asymmetric reduction. The stereoselection in microbiological transformation of fluorine compounds constitutes one of the new synthetic approaches to design of fluoroorganic molecules, which represent extension of the synthetic possibility of a wide variety of fluorinated bioactive compounds.

Our continuing studies of microbiological transformation of fluorine compounds, led to search a new approach to diastereoselection.6-10) We now wish to report our observation on the enzymatic utility, which is a new synthetic approach to the diastereoselection with microbiological reduction on the basis of the differentiation of a fluorinated group in the molecule.

The microbiological reduction of α,β-unsaturated ketones with a perfluoroalkyl group, summarized in Tables 1 and 2, lead to the following conclusion. When reaction does take place, the corresponding saturated ketones **1** are mainly obtained from perfluoroalkyl alkenyl ketones, along with small amount of optically active carbinols **2**.



1 2

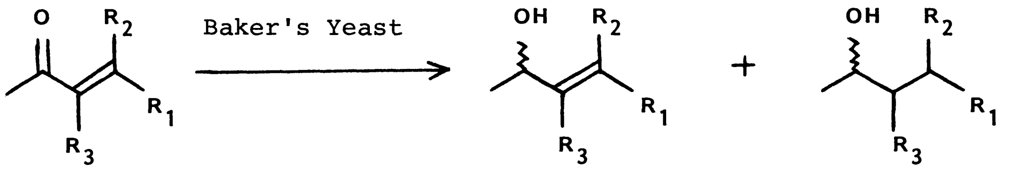
Table 1. Yields and Properties of Saturated Ketones

R_f	R	React. time	Yield/%		Bp θ_m/°C (mmHg)		Optical purity b)
		d	1	2	1	2	2(% ee)
CF_3	Ph	10	74	5	60-62 (5)	75-77 (4)	81
C_2F_5	Ph	10	68	6	86-88 (8)	97-99 (5)	77
C_4F_9	Ph	10	77	3	75-78 (4)	85-88 (2)	78
CF_3	Me	10	46	7	64-67 (65)	78-81 (36)	85
C_2F_5	Me	10	42	9	72-75 (38)	84-86 (18)	79

a) Each structure was determined by means of IR, NMR, and Mass spectral data.

b) The optical purities were determined by ^{19}F NMR after conversion of the carbinols to their diastereomeric esters by optically active perfluorocarboxylic acids which have been developed by our group.11)

However, when the reduction was applied for some ketones with a perfluoroalkyl group attached on carbon-carbon double bond, baker's yeast was found to reduce those particular ketones producing the diastereomer 4 mainly, along with the optically active carbinol 3 after fermenting for 10 d.



3 **4**

Table 2. Yields and Properties of Compounds **3** and **4**

R_1	R_2	R_3	React. time	Yield/%		Bp θ_m/°C (mmHg)		Optical purity	Diastereomeric
			d	**3**	**4**	**3**	**4**	(% ee)a)	ratio b)
CF_3	H	F	2	81	4	74-77 (31)		86	
CF_3	H	F	10	7	67		76-79 (32)		81/19
CF_3	Me	H	2	64	6	86-88 (27)		88	
CF_3	Me	H	10	5	46		83-85 (24)		76/24
C_2F_5	H	F	2	78	3	84-86(14)		90	
C_2F_5	H	F	10	6	51		76-79 (8)		83/27
H	H	CF_3	2	69	2	132-134		93	
H	H	CF_3	10	3	51		84-87 (45)		84/16

a)The optical purities were determined by ^{19}F NMR after conversion of the alcohols to their diastereomeric esters by optically active perfluorocarboxylic acids which have been developed by our group.[11] b) The two diastereomeric ratio was determined by ^{19}F NMR signal intensities.

These results show the carbon-carbon double bond of perfluoroalkyl alkenyl ketones has been reduced more easily than the carbonyl group with active fermenting yeast. Forthermore, no explanation for the diastereomeric assignment is presented at the present time and still await detailed studies.

The present microbiological approach to the diastereoselection is considered to be the new synthetic route to double asymmetric induction in fluorine compounds, and it offers a possibility for microbiological transformation of polyfluoroorganic compounds to versatile bioactive compounds.

In a typical procedure, a suspension of baker's dry yeast (Oriental Yeast Co. LtD., 40 g) and soluble starch (Wako's 1st grade, 60 g) in water (500 ml) was stirred for 1 h at 35-37 °C in Jafermentor (M-100, Tokyo Rikakikai Co.Ltd.). Into the mixture, (Z)-3,5,5,5-tetrafluoro-3-penten-2-one (4.7 g, 30 mmol) was added, and then the whole mixture was stirred at 35-37 °C. After 10 days of the fermenting with stirring, the mixture was subjected to centrifugal separation, and liquid material was poured into 1 M HCl (100 ml) solution. An oily material was extracted with diethyl ether. The ethereal extract was dried over anhydrous magnesium sulfate, and then the solvent was removed. The products were separated by column chromatography on silica gel.

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