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INTRODUCTION OF CENTER OF CHIRALITY INTO FLUOROCOMPOUNDS BY MICROBIAL TRANSFORMATION OF 2,2,2-TRIFLUOROETHANOL

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2,2,2-Trifluoroethanol is found to be a valuable synthetic tool proceeding to the chiral trifluoromethylated compounds via enantiotopic differentiating reaction and carbon-carbon bond formation with active fermenting baker's yeast.

A current research interest in the living system is the microbial behavior of halogen-containing compounds hardly decomposed by microorganisms.[1-3]

In our previous reports, we have revealed the possibility of microbial transformation of fluorinated compounds under stereocontrol,[4,5] such as the asymmetric induction by reducing the carbonyl group with active fermenting baker's yeast.

$$R_fC(O)R \xrightarrow{\text{baker's yeast}} R_fCH(OH)R$$

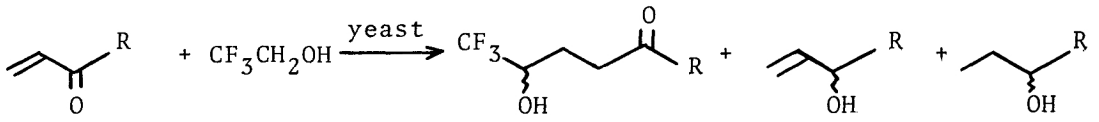
R_f = perfluoroalkyl ; R = alkyl, CH_2CO_2Et

Furthermore, in the recent literature of the fluorine chemistry, considerable attention has been focused on the search of the chiral synthetic tools for the asymmetric synthesis fluorinated bioactive molecules.[6,7]

In our continuing effort to develop the design of the microbial transformation of fluorinated compounds, we now present here some results of the microbial carbon-carbon bond formation by an enantiotopic differentiating reaction using 2,2,2-trifluoroethanol. Among the several practical trifluoromethylated reagents explored up to now, 2,2,2-trifluoroethanol known to act as a suicide inactivator for liver alcohol dehydrogenase[8] seems of particular interest in the commercially available trifluoromethyl group source. The microbial transformation

of 2,2,2-trifluoroethanol summarized in Table 1 leads to the following conclusion.

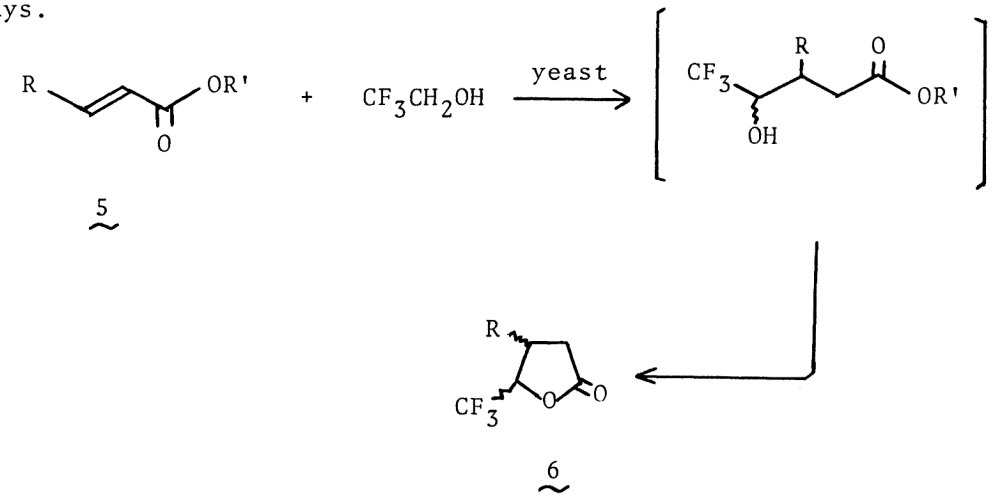
With α,β-unsaturated ketones by our procedure, the microbial transformation takes place according to the following equation.



1 2 3 4

The results shown in Table 1 indicate that the reaction of 1 to 3 and 4 might be the major drawback of these method. However, these reductions proceeded slowly than the case where 2,2,2-trifluoroethanol was absent. The most interesting feature of the above reaction is the formation of optically active carbinols 2 whose structures were assigned by analytical and spectroscopic data. Especially, in ^{19}F NMR spectrum, the signal due to CF_3 group appears as doublet at δ 1.3 ppm from external CF_3CO_2H being split by CHOH hydrogen. The optical purity was determined by ^{19}F NMR after conversion of the alcohols to its diastereomeric ester by optically active perfluorocarboxylic acids which was developed by our group.[9)]

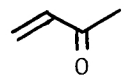
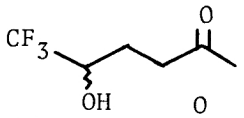
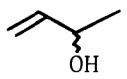
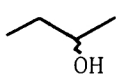
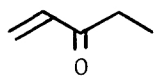
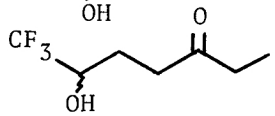
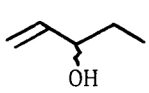
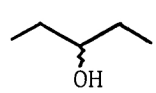
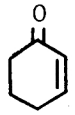
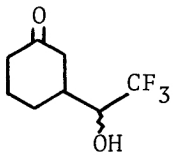
When the microbial transformation was applied for some α,β-unsaturated esters 5, active fermenting baker's yeast was found to proceed to form the lactone 6, along with the reduction of carbon-carbon double bond after fermentation for 7 days.



5 6

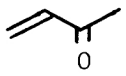
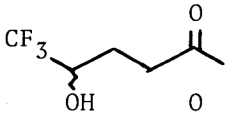
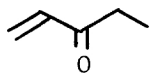
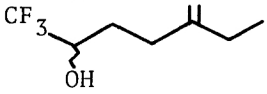
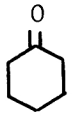
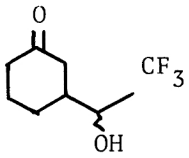
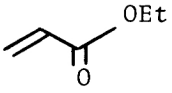
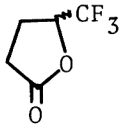
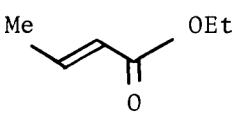
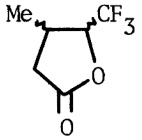
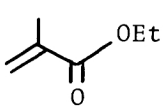
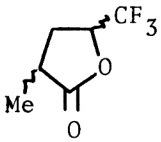
The structure of diastereoisomers of lactones 6 could not be confirmed at the present stage.

Table 1. Coupling Reaction Route to Compounds 2, 3, and 4

Ketone	Yield/%[a] 2		3		4	
		(26)		(18)		(38)
		(41)		(14)		(36)
		(38)		(8)		(43)

a) Yields determined from the relative intensities of GLC signals.

Table 2. Yields and Properties of Compounds 2 and 6

Substrate	Product[a]	Yield/%[b]	Bp Θ_m/°C(mmHg)	α_D (neat)	Optical purity % ee
		26	92-94(5)	-12.1	93
		41	94-97(11)	-11.6	91
		38	76-79(4)	[92/8][c]	
		47	75-78(12)	+13.6	79
		43	78-81(8)	[86/14][c]	
		47	82-85(6)	[83/17][c]	

a) Each structure was determined by means of IR, NMR, and mass spectral data. b) Isolated yield. c) The figures in parentheses give the diastereomeric ratio determined by ^{19}F NMR signal intensities.

The present microbial approach to the carbon-carbon bond formation is considered to be the new synthetic route to asymmetric induction in fluorine containing compounds, and it offers a possibility for the microbial transformation of hardly decomposed fluorinated materials to versatile molecules.

In a typical procedure, a suspension of active fermenting baker's yeast (Oriental Yeast Co. Ltd.) (50 g) and soluble starch (Wako's 1st grade, 75 g) in a buffer solution [600 ml. PH 5.9; prepared from 1/15 M aq. Na_2HPO_4 solution (60 ml) and 1/15 M aq. KH_2PO_4 solution (540 ml)], was stirred for 1 h at 35-36 °C in Jarfermentor (M-100, Tokyo Rikakikai Co. Ltd.). Into the mixture, methyl vinyl ketone (2.1 g, 30 mmol) and 2,2,2-trifluoroethanol (10 g, 100 mmol) was added, and then the whole mixture was stirred at 35-36 °C. After 3 days of stirring, an additional portion of baker's yeast (50 g) and soluble starch (75 g) were added and stirring was continued for 4 days. Into the stirring mixture, the flocculant (200 ppm solution prepared from p-713 ; Dai-ichi Kogyo Seiyaku, 100 ml) was added over a few minute. After 1 h of standing, the mixture was acidified with 3% HCl solution, and then the precipitates were separated by filtration. The oily materials were extracted with diethyl ether. The ethereal extract was dried over anhydrous magnesium sulfate and then the solvent was removed. Distillation gave 6,6,6-trifluoro-3-hydroxy-2-hexanone in a 26% yield.

References

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