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THE SYNTHESIS OF OPTICALLY ACTIVE BUILDING BLOCKS CARRYING AN α,α-DIHALOGENO-β,β,β-TRIFLUOROETHYL GROUP

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SUMMARY

Optically active molecules with α,α-dihalogeno-β,β,β-trifluoroethyl groups were prepared by the microbial hydrolysis of the corresponding esters.

INTRODUCTION

Hydrolytic enzymes have been widely investigated for asymmetric synthesis [1,2]; some work has involved fluorinated compounds [3-9]. As part of our continuing effort to develop stereocontrolled syntheses of fluorinated compounds with high optical purity by use of microorganisms [10-15], we now describe a synthetic approach to optically active molecules possessing α,α-dihalogeno-β,β,β-trifluoroethyl groups

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RESULTS AND DISCUSSION

Preparation of carbinols possessing α,α-dihalogeno-β,β,β-trifluoroethyl groups

Ethyl pentafluoropropionate was converted into the corresponding pentafluoroethyl ketones (1) (Table 1) Reduction of the pentafluoroethyl ketones (1) with lithium aluminium hydride takes place, though the corresponding carbinols are formed in poor yield because halogen was released preferentially from the starting materials. To obtain carbinols (2) bearing the pentafluoroethyl group, sodium borohydride is a suitable reductive reagent (Table 2)

$$CF_3CF_2CO_2Et + RMgX \longrightarrow CF_3CF_2C(O)R \quad (1)$$

$$\xrightarrow{NaBH_4} CF_3CF_2CH(OH)R \quad (2)$$

TABLE 1

Physical properties of $CF_3CF_2C(O)R$

Compound No	R	Yield (%)	bp (℃/mmHg)	Analysis: Found (Calcd) C	H
(1a) (nc)	$PhCH_2CH_2$	39	59-60/9	52 47 (52.39)	3 87 (3.60)
(1b) (nc)	$CH_3(CH_2)_5$	65	67-70/70	46.91 (46 56)	5.29 (5 64)
(1c) (nc)	$CH_3(CH_2)_7$	57	68/30	51.03 (50.77)	6 92 (6 59)

Carbinols (3) bearing the α,α-dichloro-β,β,β-trifluoroethyl group were prepared from the reaction of 1,1,1-trichloro-trifluoroethane and aldehyde by Fujita and his co-workers reported method [16] (Table 2)

$$CF_3CCl_3 + RCHO \xrightarrow{Zn} CF_3CCl_2CH(OH)R \quad (3)$$

TABLE 2

Physical properties of $CF_3CX_2CH(OH)R$

Compound No	R	X	Yield (%)	bp (℃/mmHg)	Analysis: Found (Calcd) C	H
(2a) (nc)	$PhCH_2CH_2$	F	83	64-66/2	52.27 (51 98)	3 87 (4.36)
(2b) (nc)	$CH_3(CH_2)_5$	F	65	73-74/50	45.81 (46.16)	6 79 (6 46)
(2c) (nc)	$CH_3(CH_2)_7$	F	74	110-112/60	50 04 (50 38)	7 04 (7.30)
(3a)	Ph[a]	Cl	60	95/5		
(3b) (nc)	$CH_3(CH_2)_7$	Cl	33	100-102/6	45.08 (44.75)	6 07 (6.49)

[a] Ref. [16]

Preparation of 4,4,5,5,5-pentafluoropentan-1,3-diol (5)

Next in the design of pentafluoroethylated compounds was a synthesis of a 1,3- diol with two types of hydroxy group in the molecule. In the Scheme below is shown a brief outline of the synthetic strategies employed

$$CF_3CF_2CO_2Et + CH_3CO_2Et \xrightarrow{(i\text{-}Pr)_2NLi} CF_3CF_2COCH_2CO_2Et \quad (4)$$

$$\xrightarrow{NaBH_4} CF_3CF_2CH(OH)CH_2CH_2OH \quad (5)$$

Route to optically pure carbinols possessing α,α-dihalogeno-β,β,β-trifluoroethyl groups

Asymmetric hydrolysis of prochiral compounds with enzymes of microbial or animal origin has been extensively studied [17-19]. To establish practical routes to α,α-dihalogeno-β,β,β-trifluoroethylated chiral synthetic tools, we examined this type of asymmetric hydrolysis. The relative reactivity of enantiomers, the extent of hydrolysis ratio and the enantiomeric excess of substrate and product in enzyme-catalyzed kinetic resolutions have been correlated by Chen and co-workers [20, 21].

The fluorinated carbinols were converted into esters (6) (Table 3), which were hydrolysed selectively with lipase, to give one optically active form of each carbinol.

The (+)- or (-)-enantiomers were then prepared from the recovered unattacked forms of the esters by hydrolysis using a cellulase Results are summarized in Table 4.

$$CF_3CX_2CH(OH)R^1 \xrightarrow{R^2C(O)Cl} CF_3CX_2CH(OCOR^2)R^1 \quad (6)$$

$$\xrightarrow{\text{lipase}} CF_3CX_2\overset{*}{C}H(OH)R^1 + CF_3CX_2\overset{*}{C}H(OCOR^2)R^1$$

$$\xrightarrow{\text{cellulase}} CF_3CX_2\overset{*}{C}H(OH)R^1$$

The results shown in Tables 3 and 4 clearly demonstrate that optical resolution by asymmetric hydrolysis is a practical method for the synthesis of α,α-dihalogeno-β,β,β-trifluoro ethylated chiral materials.

TABLE 3

Asymmetric hydrolysis of $CF_3CX_2CH(OCOR^2)R^1$ (6) with lipase

Compound No	R^1	R^2	X	Ratio[a] (%)	Time (h)	$[\alpha]_D$/MeOH	O P [b] %ee
(6a)	$PhCH_2CH_2$	CH_3	F	61	43	-15 24(c 1.00)	59
(6b)	$CH_3(CH_2)_5$	CH_3	F	24	5	+3.13 (c 0.94)	17
(6c)	$CH_3(CH_2)_7$	$CH(CH_3)_2$	F	60	186	+9.10 (c 1.02)	50
(6d)	CH_2CH_2OAc	CH_3	F	33	1 5	+39.35(c 1 01)	>97
(6e)	Ph	CH_3	Cl	27	96	+24 88(c 0 99)	92
(6f)	$CH_3(CH_2)_7$	CH_3	Cl	40	150	+24.56(c 1.01)	>80

[a] The hydrolysis ratio was determined by ^{19}F NMR signal intensities. [b] The optical purities were determined by ^{19}F NMR and/or High Presure Liquid Chromatography after conversion of the alcohols to their diastereomeric esters by optically active (R)-α-methoxy-α-trifluoromethylphenylacetic acid chloride.

TABLE 4

Asymmetric hydrolysis of $CF_3CX_2\overset{*}{C}H(OCOR^2)R^1$ (6) with cellulase

Compound No	R^1	R^2	X	Ratio[a] (%)	Time (h)	$[\alpha]_D$/MeOH	O.P.[b] %ee
(6a)	$PhCH_2CH_2$	CH_3	F	87	24	+23 76(c 1 08)	>92
(6b)	$CH_3(CH_2)_5$	CH_3	F	34	48	-4.47 (c 1 34)	24
(6c)	$CH_3(CH_2)_7$	$CH(CH_3)_2$	F	95	30	-14.13(c 1 41)	79
(6d)	CH_2CH_2OAc	CH_3	F	97	15	-39.36(c 1 25)	>97
(6e)	Ph	CH_3	Cl	50	86	-25 01(c 0.99)	93
(6f)	$CH_3(CH_2)_7$	CH_3	Cl	80	36	-19 56(c 1 25)	>65

[a] The hydrolysis ratio was determined by ^{19}F NMR signal intensities. [b] The optical purities were determined by ^{19}F NMR and/or High Presure Liquid Chromatography after conversion of the alcohols to their diastereomeric esters by optically active (R)-α-methoxy-α-trifluoromethylphenylacetic acid chloride.

TABLE 5

^{19}F NMR and ^1H NMR spectral data

Compound No	^{19}F NMR δ ppm	^1H NMR δ ppm
(1a) (nc)	4.9(CF_3), 44.7(CF_2)	2.80(4xH,m), 6 90-7 30(Ar-H)
(1b) (nc)	5 0(CF_3), 44 8(CF_2)	0.97(CH_3), 1 13-2 00(10xH,m)
(1c) (nc)	5.0(CF_3), 44.7(CF_2)	0.90(CH_3), 1 30-2.70(14xH,m)
(2a) (nc)	2.8(CF_3), 43.3(CF_a,d.d, $J_{F\underline{a}-F\underline{b}}$=266, $J_{F\underline{a}-C\underline{H}}$=7 5 Hz), 50 8($CF_b$,d.d, $J_{F\underline{b}-C\underline{H}}$=13.2 Hz)	2 00(3xH), 2.80($C\underline{H}_2CH_2Ph$,m), 3.90(CH,m)
(2b) (nc)	4 0(CF_3), 44.0(CF_a,d.d, $J_{F\underline{a}-F\underline{b}}$=270, $J_{F\underline{a}-C\underline{H}}$=7.5 Hz), 52 3($CF_b$,d d, $J_{F\underline{b}-C\underline{H}}$=16 0 Hz)	1.00(CH_3), 1.20-2 20(10xH,m) 3.20(OH)
(2c) (nc)	4.0(CF_3), 43.6(CF_a,d.d, $J_{F\underline{a}-F\underline{b}}$=268, $J_{F\underline{a}-C\underline{H}}$=7.5 Hz), 52 0($CF_b$,d.d, $J_{F\underline{b}-C\underline{H}}$=16 0 Hz)	0.90(CH_3), 1.20-2.20(14xH,m)

EXPERIMENTAL

General procedure

All microbial hydrolyses were carried out in the "CULSTIR" flask for suspension culture with double arms and jacket (300 ml, Sibata Scientific Technology Ltd.) All commercially available reagents were used without further purification Infrared spectra were obtained by using a JASCO A-102 spectrometer and KBr pellets The ^{1}H(internal Me_4Si) and ^{19}F(external CF_3CO_2H) NMR spectra were recorded by using Varian EM-390 (90 MHz) and Hitachi R-24 (56.5 MHz) spectrometers. Specific rotations were recorded by using a JASCO DIP-140 digital polarimeter. Yields were those of the products actually isolated.

Pentafluoroethyl phenethyl ketone (1a) (nc)

Into a mixture solution of ethyl pentafluoropropionate (9.6 g, 50 mmol) and freshly dried tetrahydrofuran (50 ml), phenethyl magnesium bromide (60 mmol) was added dropwise at a temperature below -70℃. After a further 6 h of stirring below -60 ℃, the reaction mixture was quenched with NH_4Cl. Oily materials were extracted with diethyl ether and then dried over magnesium sulfate. Distillation gave pentafluoroethyl phenethyl ketone (1a) in a yield of 39%, bp 59-60℃/9 mmHg.

Pentafluoroethyl hexyl ketone (1b) (nc)

In the above reaction, hexyl magnesium bromide (60 mmol) was used, and then worked up similarly Distillation gave pentafluoroethyl hexyl ketone (1b) in a yield of 65%, bp 67-70℃/70 mmHg.

Pentafluoroethyl octyl ketone (1c) (nc)

In the same manner, octyl magnesium bromide (60 mmol) was used, and then worked up as usual. Distillation gave pentafluoroethyl octyl ketone (1c) in a yield of 35 %, bp 68 ℃/30 mmHg

1-Pentafluoroethyl 3-phenylpropan-1-ol (2a) (nc)

Into a solution of sodium borohydride (0 35 g, 10 mmol) in ethanol (20 ml), pentafluoroethyl phenethyl ketone (5.05 g, 20 mmol) in ethanol (10 ml) was added dropwise at 0℃. After 4h of stirring at room temperature, the reaction mixture was quenched with saturated NH_4Cl. Oily materials were extracted with diethyl ether and then dried over magnesium sulfate Distillation gave 1-pentafluoroethyl 3-phenylpropan-1-ol (2a) in a yield of 83%, bp 64-66℃/2 mmHg.

1-Pentafluoroethylheptan-1-ol (2b) (nc)

In the above reaction, pentafluoroethyl hexyl ketone (4.64 g, 20 mmol) was used, and then worked up as usual. Distillation gave 1-pentafluoroethylheptan-1-ol (2b) in a yield of 56%, bp 73-74℃/50 mmHg.

1-Pentafluoroethylnonan-1-ol (2c) (nc)

In the above reaction, pentafluoroethyl octyl ketone (5 2 g, 20 mmol) was used, and then worked up as usual Distillation gave 1-pentafluoroethylnonan-1-ol (2c) in a yield of 74%, bp 110-112℃/60 mmHg.

1-(α, α-Dichloro-β, β, β-trifluoroethyl) benzylalcohol (3a) [16]

A mixture of zinc powder (1.5 g-atom), benzaldehyde (2.12 g, 20 mmol) and 1, 1, 1-trichlorotrifluoroethane (2 8 g, 15 mmol) in N, N-dimethylformamide (50 ml) was warmed to 50 ℃. After 3h of heating at that temperature, the reaction mixture was poured into 1N HCl solution. Oily materials were extracted with diethyl ether, and then the solvent was removed. Distillation gave 1-(α, α-dichloro-β, β, β-trifluoroethyl) benzyl alcohol (3a) in a yield of 60%, bp 95 ℃/5 mmHg.

1-(α,α-Dichloro-β,β,β-trifluoroethyl)nonan-1-ol (3b) (nc)

In the above reaction, octyl aldehyde (2.8 g, 20 mmol) was used, and then worked up as usual. Distillation gave 1-(α,α-dichloro-β,β,β-trifluoroethyl)nonan-1-ol (3b) in a yield of 33 %, bp 100-102 ℃/6 mmHg

^{19}F NMR (CCl_4): δ -3.75(CF_3, s) ppm.

^{1}H NMR (CCl_4): δ 0.73-1.00(CH_3, m), 1.10-1.80(14xH, m), 2.07(OH), 4.05(CH, t, J_{CH-CH_2}= 7.8 Hz)

Preparation of 4,4,5,5,5-pentafluoropentan-1,3-diol (5) (nc)

Ethyl 4,4,5,5,5-pentafluoro-3-oxopentanate (4)

Into the reaction vessel containing lithium diisopropylamide (200 mmol) in diethyl ether (100 ml) was added ethyl acetate (200 mmol) in diethyl ether (30 ml) with a syringe under an atmosphere of argon at -70 ℃, and then the reaction mixture was stirred for 1h at -70 ℃. Into the mixture was added ethyl pentafluoropropionate (19.2 g, 100 mmol) in diethyl ether (40 ml) at that temperature. After stirring for 4h at -70 ℃, the mixture was quenched with saturated NH_4Cl solution. Ethereal layer was separated and dried over magnesium sulfate.
On removal of the solvent, distillation gave ethyl 4,4,5,5,5-pentafluoro-3-oxopentanate (4) in a yield of 57 %,
bp 62-64℃/60 mmHg.
Enol form:
^{19}F NMR (CCl_4): δ 6.5(CF_3, t, $J_{CF_3-CF_2}$= 1.3 Hz), 45.0(CF_2, q) ppm
^{1}H NMR (CCl_4): δ 1.33(CH_3, t, $J_{CH_3-CH_2}$= 7.2 Hz), 4.27(CH_2, q), 5.62(C=C$\underline{H}$, s), 12.0(OH).
Keto form:
^{19}F NMR (CCl_4): δ 5.0(CF_3, s), 44.3(CF_2, s) ppm.
^{1}H NMR (CCl_4): δ 1.33(CH_3, t, $J_{CH_3-CH_2}$= 7.2 Hz), 1.93(CH_2CO, s), 4.27(CH_2, q)
IR (cm^{-1}): 1680(C=C), 1750(C=O), 3200(OH).

Reduction of ethyl 4,4,5,5,5-pentafluoro-3-oxopentanate (4)

Into a solution of sodium borohydride (0 70 g, 20 mmol) in ethanol (20 ml), ethyl 4,4,5,5,5-pentafluoro-3-oxopentanate (5.05 g, 20 mmol) in ethanol (10 ml) was added dropwise at 0℃. After 4h of stirring at room temperature, the reaction mixture was quenched with saturated NH_4Cl Oily materials were extracted with diethylether and then dried over magnesium sulfate. Distillation gave 4,4,5,5,5-pentafluoropentan-1,3-diol(5) in a yield of 86%, mp 59-61℃

^{19}F NMR (CCl_4): δ 4.0(CF_3, s), 43 7($CF_{\underline{a}}F_{\underline{b}}$, d d, $J_{CF_{\underline{a}}-CF_{\underline{b}}}$= 268 Hz), 52.2(CFa$F_{\underline{b}}$, d d) ppm

^1H NMR (CCl_4): δ 0.77(CH_2, m), 3 72(CH_2OH, m), 4.08, 5.35(OH, br), 4 23(CH, m).

IR (cm^{-1}): 3400(OH)

Analysis Found : C, 31 28 ; H, 3 47 %

Calcd for $C_5H_7O_2F_5$: C, 30.94 ; H, 3.64 %

Preparation of acetate esters (6)

A mixture of 1-pentafluoroethyl 3-phenylpropan-1-ol (2a) (5 1 g, 20 mmol), acetyl chloride (28 mmol) and pyridine (4 ml) in dichloromethane (50 ml) was stirred at room temperature After 12h of stirring, the mixture was quenched with 1N HCl Oily materials were extracted with diethyl ether, and then the organic layer was washed with 5 % aqueous $NaHCO_3$, water and brine. On removal of the solvent, the acetate (6a) was purified by column chromatography on silica gel using n-hexane-ethyl acetate (2:1) as an eluent, in 76 % yield

^{19}F NMR (CCl_4): δ 4 66(CF_3, s), 41 7(C$F_{\underline{a}}$Fb, d.d, $J_{F_{\underline{a}}-F_{\underline{b}}}$= 244, $J_{F_{\underline{a}}-CH}$= 7 3 Hz), 49.3($CF_aF_{\underline{b}}$, d.d, $J_{F_{\underline{b}}-CH}$= 13 0 Hz) ppm

^1H NMR (CCl_4): δ 2 07(5xH, m), 2 62($C\underline{H_2}CH_2Ph$, m), 5.45(CH, m), 7 9-7 4(Ar-H)

IR (cm^{-1}): 1760(C=O)

Other acetate esters (6b, 6d, 6e, 6f) were prepared in the same manner.

Preparation of isobutyl ester (6c)

A mixture of 1-pentafluoroethylnanon-1-ol (2c) (5.24 g, 20 mmol) isobutyryl chloride (28 mmol) and pyridine (5 ml) in dichloromethane (50 ml) was stirred at room temperature. After 15h of stirring, the mixture was quenched with 1N HCl. Oily materials were extracted with diethyl ether, and then the extract was washed with 5 % aqueous $NaHCO_3$, water and brine. On removal of the solvent, isobutyrate (6c) was purified by column chromatography on silica gel using n-hexane-ethyl acetate (5:1) as an eluent, in 87% yield.
^{19}F NMR (CCl_4): δ 4.67 (CF_3, s), 41 8 ($CF_{\underline{a}}F_{\underline{b}}$, d.d, $J_{F_{\underline{a}}-F_{\underline{b}}}$= 268 Hz) 49.3 ($CF_aF_{\underline{b}}$, d.d) ppm.
^1H NMR (CCl_4): δ 0.9 (CH_3, m), 1.30 (19xH, m), 2 60 (2xH, m), 5.5 (CH, m).
IR (cm^{-1}): 1760 (C=O).

Asymmetric hydrolysis

A suspension of lipase P (Amano Seiyaku Co. Ltd , 3 g) in distilled water (75 ml), was stirred for 15 min at 40-41℃ in the "CULSTIR" flask (200 ml). Into the mixture, the acetate ester of 1-pentafluoroethyl 3-phenylpropan-1-ol (2a) (10 mmol) was added, and then the whole mixture was stirred at 40-41℃. After 43h of stirring, the mixture was acidified with 1N HCl and then oily materials were extracted with diethyl ether.
The ethereal extract was dried over anhydrous magnesium sulfate and then the solvent was removed. After determining the hydrolysis ratio by ^{19}F NMR signal intensities using $C_6H_5CF_3$ as an internal standard, the products were separated by column chromatography on silica gel using a mixture of n-hexane-ethyl acetate (5:1) as eluent

Other asymmetric hydrolysis of acetate or isobutyrate derivatives were carried out similarly on the same scale

Synthesis of the other enantiomers

A suspension of cellulase (Trichoderma viride , Yakult Pharmaceutical Industry Co. Ltd., 3 g) in distilled water (60 ml) was stirred for 15 min at 40-41 ℃ in the "CULSTIR" flask (200 ml). Into the mixture, the recovered (+)-acetate derivative of 1-pentafluoroethyl 3-phenylpropan-1-ol (6a) (20 mmol) was added, and then the whole mixture was stirred at 40-41 ℃. After 24h of stirring, the mixture was acidified with 1N HCl and then oily materials were extracted with diethyl ether. The ethereal extract was dried over magnesium sulfate and then the solvent was removed. The products were separated by column chromatography using a mixture of n-hexane-ethyl acetate (5:1) as eluent

The other recovered esters were treated similarly

Determination of optical purity

A mixture solution of (R)-α-methoxy-α-trifluoromethyl-phenylacetic acid chloride (MTPA-Cl) (1 1 mmol), (-)-1-penta-fluoroethyl 3-phenylpropan-1-ol (1 mmol) in pyridine (1 ml) was stirred at room temperature After 1 week of stirring, the whole mixture was poured into water, and then oily materials were extracted with diethyl ether The ethereal extract was washed with 1N HCl, 5% $NaHCO_3$, sat $Na_2S_2O_3$ solution and then brine Renoval of the solvent, the diastereomeric ratio was determined by ^{19}F NMR signal intensities.

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