Journal of Fluorine Chemistry, *43* (1989) 177–187

Received: June 11, 1988; accepted: December 29, 1988

SYNTHETIC APPROACH TO STEREOISOMERS OF ALLYLIC ALCOHOLS POSSESSING A TRIFLUOROMETHYL GROUP

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SUMMARY

A number of stereoisomers of optically pure allylic alcohols with a trifluoromethyl group [$CF_3CH(OH)CH{=}CHR$; R=Ph, C_6H_{13}] were prepared, utilizing the enantiotopic specificity of asymmetric hydrolysis of their acetates by hydrolases. Their absolute configurations were determined.

INTRODUCTION

The control of the absolute stereochemistry of molecules containing a trifluoromethyl group is of fundamental importance [1-3]. As part of our continuing study of the preparation of new useful fluorinated materials, we have found a simple process to produce stereoisomers of allylic alcohols with a trifluoromethyl group, involving the stereoselective reduction of α-hydroxyalkynes followed by the asymmetric hydrolysis of the acetates of (E)- or (Z)-allylic alcohols by hydrolases.

0022-1139/89/$3.50

RESULTS AND DISCUSSION

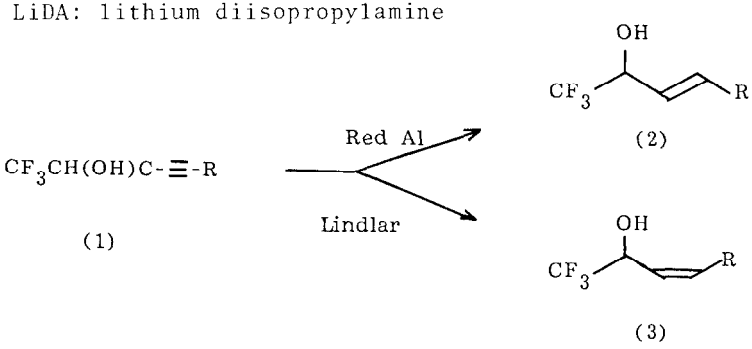
Stereoselective synthesis of (E)- and/or (Z)-allylic alcohols carrying the trifluoromethyl group and their acetates

α-Hydroxyalkynes (1) were prepared by the reaction of trifluoroacetaldehyde with alkynyl lithium compounds. This method is a simple process involving the bubbling of trifluoroacetaldehyde into a solution of the lithium derivative in tetrahydofuran as solvent below -50℃ . These α-hydroxyalkynes were reduced with Red Al [$NaAlH_2(OCH_2CH_2OCH_3)_2$] to give the (E)-allylic alcohols (2) or with a Lindlar/Ca/H_2 system to afford the (Z)-allylic alcohols (3). The resulting carbinols were then converted to the acetates of the title materials with acetyl chloride.

$$CF_3CHO + R\text{-}\equiv\text{-}H \xrightarrow[THF]{LiDA} CF_3CH(OH)C\text{-}\equiv\text{-}R$$

(1)

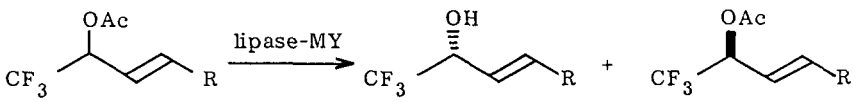
LiDA: lithium diisopropylamine



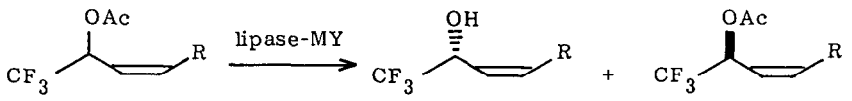
Asymmetric hydrolysis of the acetate derivatives of allylic alcohols with the trifluoromethyl group

The previously reported asymmetric hydrolyses of prochiral compounds using microorganisms suggest that the lipase-MY is suitable for the optical resolution of trifluoromethylated

compounds [4-7]. When the hydrolysis was carried to less than 40% with lipase-MY (Candida cylindracea), the resultant alcohol was greatly enriched in the R (or S) enantiomer. The results shown in Table I clearly demonstrate that asymmetric hydrolysis is a route to the desired trifluoromethylated chiral allylic alcohols, and that the optical purity is sufficiently high for their use as chiral intermediates in fluorine chemistry.



(R)-(E)-
(2)



(R)-(Z)-
(3)

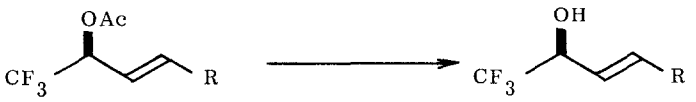
TABLE 1

Asymmetric hydrolysis of acetates to give (R)-enantiomers of compounds (2 and 3)

Compound No	R	Hydrolysis[a] conversion (%)	$[\alpha]_D$/MeOH	Optical[b] purity %ee
(2a)	Ph	35	-13.7 (c 1.02)	94
(3a)	Ph	30	+124.6 (c 1.03)	>99
(2b)	C_6H_{13}	29	+2.09 (c 1.17)	81
(3b)	C_6H_{13}	41	+17.9 (c 1.06)	83

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

The S(or R) enantiomers were prepared from the recovered acetates by hydrolysis using a cellulase (Trichoderma viride) and/or by a chemical method (2 mol/l aqueous K_2CO_3). Results are summarized in Table 2.



(S)-(E)-

(2)

(S)-(Z)-

(3)

TABLE 2

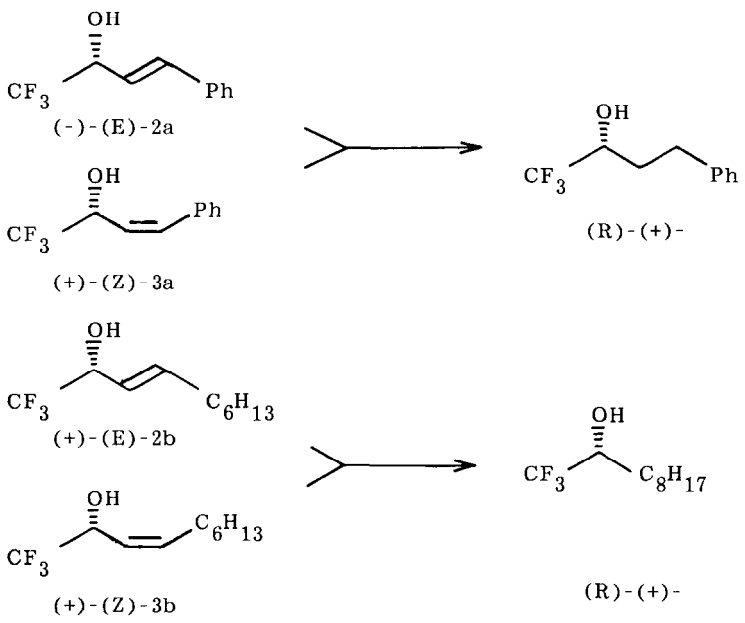
Preparation of (S)-enantiomers

Compound No	R	Hydrolysis[a] conversion (%)	$[\alpha]_D$/MeOH	Optical[b] purity %ee
(2a)	Ph	53	+16.3 (c 1.06)	76
(3a)	Ph	27	-112.2 (c 1.12)	>95
(2b)	C_6H_{13}	44	-2.50 (c 1.00)	>90
(3b)	C_6H_{13}	41	-16.7 (c 1.14)	>97

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

Determination of absolute configuration

We have investigated the absolute configurations of optically active allylic alcohols with trifluoromethyl group in our continuing studies on the preparation of chiral fluorinated molecules. Their absolute configurations were determined by the specific rotation after conversion of the obtained allylic alcohols to the corresponding saturated carbinols by reduction using a PtO_2/H_2 system. The results shown in the Scheme confirm that (-)-(E)-(2a), (+)-(Z)-(3a), (+)-(E)-(2b) and (+)-(Z)-(3b) produced from the asymmetric hydrolysis are the R enantiomers.



Scheme

EXPERIMENTAL

1-Phenyl-3-hydroxy-4,4,4-trifluoro-1-butyne (1a) [8]

Into the reaction vessel containing lithium diisopropyl amine (112 mmol) in tetrahydrofuran (100 ml) was added phenylacetylene (10.1g, 100 mmol) in tetrahydrofuran (20 ml) with a syringe under an atmosphere of argon at -50℃, and then the reaction mixture was stirred for 30 min at -50℃. Into the solution was bubbled trifluoroacetaldehyde (110 mmol) at that temperature, and the whole mixture was stirred for 2h at -50 ℃. After quenching with saturated NH_4Cl solution, oily materials were extracted with diethyl ether. On removal of the solvent, distillation gave the corresponding carbinol in a 62% yield, bp 74℃ / 0.3 mmHg (lit [8]; bp 98-100℃/5mmHg)

19F NMR ($CDCl_3$): δ 1.42 (CF_3, d, J_{CF_3-CH} = 6.0 Hz) ppm from ext. CF_3CO_2H.

^1H NMR ($CDCl_3$): δ 2.79 (bs, 1×H), 4.88 (q, 1×H), 7.49 (Ar-H).

IR (KBr): ν 3375 (OH), 2240 (C ≡ C) cm^{-1}.

1-Hexyl-3-hydroxy-4,4,4-trifluoro-1-butyne (1b) (nc)

1-Octyne (10.9g, 100 mmol), trifluoroacetaldehyde (110 mmol) and lithium diisopropyl amine (115 mmol) were used in the same manner, and worked up similarly. Distillation gave 1-hexyl-3-hydroxy-4,4,4-trifluoro-1-butyne in a 66% yield, bp 103℃/2 mmHg.

Analysis. Found : C, 57.86 ; H, 7.59 %

Calcd for $C_{10}H_{15}OF_3$: C, 57.68 ; H, 7.26 %

^{19}F NMR ($CDCl_3$) : δ 2.15 (CF_3, d, J_{CF_3-CH} = 6.6 Hz) ppm.

^1H NMR ($CDCl_3$) : δ 0.89 (m, 3×H), 1.04-1.75 (m, 8×H), 2.05-2.54 (m, 3 ×H), 4.42-4.75 (m, 1×H)

IR (KBr) : ν 3375 (OH), 2240 (C ≡ C) cm^{-1}.

(E)-1-Phenyl-3-hydroxy-4,4,4-trifluoro-1-butene (2a)[4]

Into a solution of Red Al [$NaAlH_2(OCH_2CH_2OCH_3)_2$] (15.6 mmol, 3.4 M in toluene) in freshly dried diethyl ether (20 ml), 1-phenyl-3-hydroxy-4,4,4-trifluoro-1-butyne (1a) (2.0g, 10 mmol) in diethyl ether (10 ml) was added at a temperature below -50 ℃. After 5h of stirring below -50℃, the reaction mixture was quenched with saturated NH_4Cl. Oily materials were extracted with diethyl ether, and then worked up similarly. The products were separated by column chromatography on silica gel using a mixture solution of n-hexane and ethyl acetate (5:1).
^{19}F NMR ($CDCl_3$) : δ 1.12 (CF_3, d, J_{CF_3-H} = 7.9 Hz) ppm.
^1H NMR ($CDCl_3$) : δ 2.72 (br, 1×H), 4.65 (m, 1xH), 6.26 (d.d, $J_{H-H_{vic}}$ = 6.6 Hz), 6.95 (d, $J_{H-H_{trans}}$ = 16.1 Hz), 7.47 (m, Ar-H)
IR (KBr) : ν 3325 (OH), 1655 (C=C) cm^{-1}.

(E)-1-Hexyl-3-hydroxy-4,4,4-trifluoro-1-butene (2b) (nc)

1-Hexyl-3-hydroxy-4,4,4-trifluoro-1-butyne (1b) (2.1g, 10 mmol) and Red Al (16 mmol, 3.4 M in toluene) were used in the same manner, and worked up similarly.
Analysis. Found : C, 56.86 ; H, 8.46 %
Calcd for $C_{10}H_{17}OF_3$: C, 57.13 ; H, 8.15 %
^{19}F NMR ($CDCl_3$) : δ 1.42 (CF_3, d, J_{CF_3-H} = 6.2 Hz) ppm.
^1H NMR ($CDCl_3$) : δ 0.89 (m,3×H), 1.08-1.64(m, 8×H), 1.99-2.26(m, 2×H), 2.32 (1×H), 4.34 (d.q, $J_{H-H_{vic}}$ = 6.0 Hz) 5.51 (d.d, $J_{H-H_{trans}}$ = 15.8 Hz), 6.01 (d.t, $J_{H-H_{vic}}$ = 6.5 Hz)
IR (KBr) : ν 3375 (OH), 1675 (C=C) cm^{-1}.

(Z)-1-Phenyl-3-hydroxy-4,4,4-trifluoro-1-butene (3a)[4]

A solution of Lindlar catalyst (0.3g) and 1-phenyl-3-hydroxy-4,4,4-trifluoro-1-butyne (1a) (2.0g, 10 mmol) in hexane (30 ml) was stirred at room temperature under atmosphere of hydrogen. After 3h of stirring under atmosphere of hydrogen, the reaction mixture was quenched with saturated NH_4Cl. Oily materials were extracted with diethyl ether, and then worked up

similarly. The products were separated by column chromatography on silica gel using n-hexane-ethyl acetate (5:1).
^{19}F NMR ($CDCl_3$) : δ 0.92 (CF_3, d, J_{CF_3-H} = 6.2 Hz) ppm.
^1H NMR ($CDCl_3$) : δ 2.41 (br, 1×H), 4.81 (m, 1xH), 5.84 (d.d, $J_{H-H_{vic}}$ = 9.8 Hz), 7.04 (d, $J_{H-H_{trans}}$ = 11.6 Hz), 7.43 (m, Ar-H)
IR (KBr) : ν 3375 (OH), 1640 (C=C) cm^{-1}.

(Z)-1-Hexyl-3-hydroxy-4,4,4-trifluoro-1-butene (3b)(nc)

1-Hexyl-3-hydroxy-4,4,4-trifluoro-1-butyne (1b)(2.1g, 10 mmol) and Lindlar catalyst (0.3g) in hexane (30 ml) were reacted in the same manner, and worked up similarly.
Analysis. Found : C, 57.26 ; H, 7.96 %.
Calcd for $C_{10}H_{17}OF_3$: C, 57.13 ; H, 8.15 %
^{19}F NMR ($CDCl_3$) : δ 1.57 (CF_3, d, J_{CF_3-H} = 6.4 Hz) ppm.
^1H NMR ($CDCl_3$) : δ 0.91 (m,3×H), 1.15-1.65(m, 8×H), 2.00-2.37(m, 2×H), 2.54 (1×H), 4.67 (d.q, $J_{H-H_{vic}}$ = 8.9 Hz) 5.45 (d.d, $J_{H-H_{cis}}$ = 11.3Hz), 5.86 (d.t, $J_{H-H_{vic}}$ = 7.8 Hz)
IR (KBr) : ν 3375 (OH), 1660 (C=C) cm^{-1}.

Preparation of acetate esters

A mixture of (E)-1-phenyl-3-hydroxy-4,4,4-trifluoro-1-butene (2a)(2.0g, 10 mmol), acetyl chloride (14 mmol) and pyridine (2 ml) in dichloromethane (30 ml) was stirred at room temperature. After 10h 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, acetate was purified by column chromatography on silica gel using n-hexane-ethyl acetate (5:1) in 86 % yield.
^{19}F NMR ($CDCl_3$): δ -1.13(CF_3, d, J_{CF_3-H} = 6.8 Hz) ppm.
^1H NMR ($CDCl_3$): δ 2.14(S, 3×H),5.83(d,q, J_{H-H} = 7.2 Hz), 6.14 (d,d, $J_{H-H_{trans}}$ = 15.8 Hz), 6.93 (d, 1 ×H), 7.41 (Ar-H).
IR (KBr): ν 1760(C=O), 1660 (C=C) cm^{-1}.

Other acetate esters were prepared in the same manner.

Asymmetric hydrolysis

A suspension of lipase-MY (candida cylindracea, Meito Sangyo Co. Ltd., 5g) in distilled water (75 ml), was stirred for 15 min at 40-41 ℃ in a round bottom flask (200 ml). Into the mixture, the acetate ester of (E)-1-phenyl-3-hydroxy-4,4,4-trifluoro-1-butene (10 mmol) was added, and then the whole mixture was stirred at 40-41℃. After 2h of stirrring, the flocculant (200 ppm solution prepared from p-713, Dai-ichi Kogyo Seiyaku, 10ml) was added into the stirred mixture for a few minutes. After 1h of stirring, the mixture was acidified with 1N HCl 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. 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 using a mixture of n-hexane-ethyl acetate (5:1).

Other asymmetric hydrolysis of acetate derivatives were carried out on the same scale and in a similar manner.

Synthesis of (S)-enantiomers

(a) In the above asymmetric hydrolysis, the acetate derivative of (E)-1-phenyl-3-hydroxy-4,4,4-trifluoro-1-butene was hydrolyzed for 6h with lipase-MY, and then (R)-(E)-(-)-1-phenyl-3-hydroxy-4,4,4-trifluoro-1-butene (>80% ee ; hydrolysis ratio 59%) and the corresponding S acetate derivative were separated by column chromatography.

(b) A suspension of cellulase (Trichoderma viride, Yakult Pharmaceutical Industry Co. Ltd., 3g) in buffer solution (60 ml, pH 7.3) was stirred for 15 min at 40-41 ℃ in a round bottom flask (200 ml). Into the mixture, was added the recovered S acetate derivative of (E)-1-phenyl-3-hydroxy-4,4,4-trifluoro-1-butene (10 mmol) and then the whole mixture was stirred at

40-41 ℃. After 6h of stirring, the flocculant (200 ppm solution prepared from p-713, Dai-ichi Kogyo Seiyaku, 10 ml) was added into the stirred mixture over a few minutes. After 1h of stirring, the mixture was acidified with 1N HCl and then the precipitate was 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. The products were separated by column chromatography using a mixture of n-hexane-ethyl acetate (5:1).

Determination of optical purity.

A mixture solution of (R)-(E)-(-)-1-phenyl-3-hydroxy-4,4,4-trifluoro-1-butene (1 mmol) and (R)-α-methoxy-α-trifluoromethylphenylacetic acid chloride(MTPA-Cl) (1.1 mmol) in pyridine (1 ml) was stirred at room temperature. After 24h of stirring, the whole mixture was poured into water, and then oily materials were extracted with diethyl ether. The ethereal layer was washed with 1N HCl, 5% $NaHSO_4$, sat. $Na_2S_2O_3$ solution and then brine. After removal of the solvent, the diastereomeric ratio was determined by ^{19}F NMR signal intensities.

Determination of absolute configuration

Reduction of (E)-(+)-1-hexyl-3-hydroxy-4,4,4-trifluoro-1-butene(2b)

A mixture of (E)-(+)-1-hexyl-3-hydroxy-4,4,4-trifluoro-1-butene (2b) (2.1g, 10 mmol, >81 %ee) and PtO_2 (0.3g) in ethanol (20 ml) was stirred at room temperature under atmosphere of hydrogen. After 24h of stirring, the reaction mixture was quenched with 1N HCl. Oily materials were extracted with diethyl ether, and then worked up similarly. The product was separated by column chromatography on silica gel using a mixture of n-hexane and ethyl acetate (5:1). The eluted (+)-1,1,1-trifluoro-2-decanol was the (R)-enantiomer.
$[\alpha]_D$/MeOH +47.1 (c 1.27) >80%ee [4].

The (z)-(+)-stereoisomer (3b) when reacted similarly gave the same product.

Reduction of (E)-(-)-1-phenyl-3-hydroxy-4,4,4-trifluoro-1-butene(2a)

A mixture of (E)-(-)-1-phenyl-3-hydroxy-4,4,4-trifluoro-1-butene (2a)(2.0 g, 10 mmol, 94 %ee) and PtO_2 (0.3g) in ethanol (20 ml) was stirred at room temperature under an atmosphere of hydrogen. After 24h of stirring, the reaction mixture was quenched with 1N HCl. Oily materials were extractedwith diethyl ether, and then worked up similarly. The resulting (+)-1-phenyl-3-hydroxy-4,4,4-trifluorobutane was the (R)-enantiomer.
$[\alpha]_D$/MeOH +65.7 (c 1.30) >92 %ee [4].

Thc (z)-(+)-stereoisomer (3a) when reacted similarly gave the same product.

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