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SYNTHETIC APPROACH TO OPTICALLY PURE TRIFLUOROMETHYLATED COMPOUNDS

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SUMMARY

Optically pure (R)- or (S)-O-carbamates of an α,β-unsaturated ester bearing the trifluoromethyl group and the CF_3-analogue of sulcatol were prepared from optically pure (R)-(+)-or (S)-(-)-ethyl 4,4,4-trifluoro-3-hydroxybutanoate.

INTRODUCTION

Research work on the synthesis of biologically interesting amino sugars and natural compounds by several groups has been extensive in recent years [1-8]. However, no stereocontrolled syntheses of their CF_3-analogues, which are expected to be bioactive compounds, have been studied because the introduction of a center of chirality into fluoroorganic compounds often proves to be quite difficult and limited [9-13].

Recently, we have reported examples of highly stereocontrolled syntheses of monofluorinated compounds [14-16]. As part of our continuing study of new useful stereocontrolled syntheses of fluorinated materials with high optical purity [17-20], we present here some results describing a synthetic approach to optically pure (R)- or (S)-O-carbamates of an α,β-unsaturated ester carrying a trifluoromethyl group, which is a precursor of amino sugar analogues, and to optically pure (R)- or (S)-CF_3-analogues of sulcatol.

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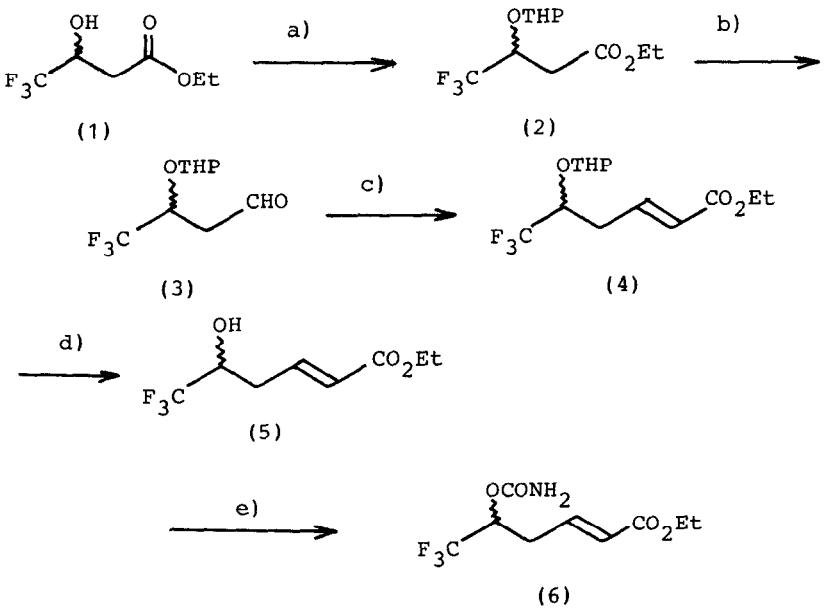
RESULTS AND DISCUSSION

Route to optically pure (R)- or (S)-O-carbamates of an α,β-unsaturated ester

The previously reported optical resolution with asymmetric hydrolysis is a useful and an important design feature achieving desired trifluorinated chiral materials [17].

A brief outline of the synthetic strategies employed in preparing optically pure (R)- or (S)-O-carbamates of an α,β-unsaturated ester with a trifluoromethyl group is shown below.



a) dihydropyran/CH_2Cl_2 b) $(i\text{-}Bu)_2AlH$/hexane

c) $(EtO)_2P(O)CH_2CO_2Et$/NaH/toluene d) H^+ e) $ClSO_2NCO$

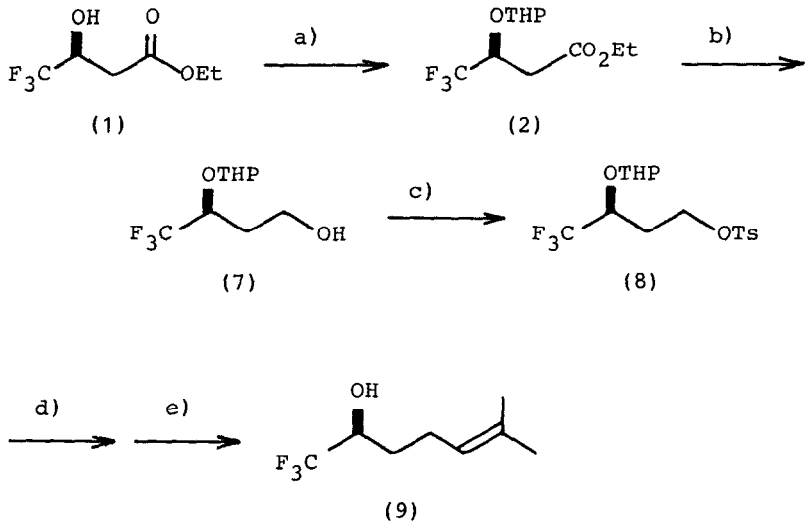
Scheme I

In Scheme I, the synthetic intermediate is optically pure β-hydroxyester (1)[(R)-enantiomer :>98 %ee $[\alpha]_D$ +20.9 (neat); (S)-enantiomer :>97 %ee $[\alpha]_D$ -20.6 (neat)] [17]. Protection with dihydropyrane followed by treatment of the β-hydroxyester with diisobutylaluminium hydride gave the optically active aldehyde. The Wittig-type reaction of aldehyde (3) selectively produced trans-α,β-unsaturated ester (5), which was determined by ^{1}H NMR, the identification being based on the well-established coupling constants for substituted olefins. Treatment of (5), [(R)-enantiomer :>98 %ee $[\alpha]_D$/MeOH +23.7 (c 2.52) ; (S)-enantiomer :>97 %ee $[\alpha]_D$/MeOH -23.5 (c 1.23)] with chlorosulfonylisocyanate and then water gave the optically pure homoallylic carbamate ester (6) with a trifluoromethyl group.

Synthesis of the optically active CF_3-analogue of Sulcatol

An example of the design of an optically active CF_3-analogue of a natural compound is a synthesis of (S)-(+)-Sulcatol, which is known as a pheromone of Gnathotrichus retusus.

In the Scheme II, one of the synthetic intermediate is also optically active compound (1). The protected (R)-(+)-(2) was selectively reduced with lithium aluminium hydride to give good yield of optically pure compound (7), which then reacted with tosyl chloride to give the compound (8) as a potential synthon. Treatment of (8) with cuprate $[(CH_3)_2C{=}CHMgBr\text{-}CuI]$gave the stereocontrolled synthesis for the CF_3-analogue of Sulcatol. The (S)-enantiomer (95 %ee) was also obtained from (S)-(-)-ethyl 4,4,4-trifluoro-3-hydroxybutanoate in the same manner.



a) dihydropyran/CH_2Cl_2 b) $LiAlH_4/Et_2O$ c) TsCl/pyridine
d) $(CH_3)_2C{=}CHMgBr/CuI/Et_2O$ e) H^+

Scheme II

EXPERIMENTAL

(R)-(+)-Ethyl 4,4,4-trifluoro-3-hydroxybutanoate (R)-(1)

A suspension of lipase-MY (*Candida cylindracea* , Meito Sangyo Co. Ltd., 6 g) in buffer solution (120 ml,pH 7.3), prepared from 1/15 M aq Na_2HPO_4 solution (92.2 ml) and 1/15 M aq KH_2PO_4 solution (27.8 ml), was stirred for 15 min at 40-41°C in "CULSTIR" flask for suspension culture with double arms and jacket (300 ml, Sibata Scientific Technology Ltd.). Into the mixture, acetate derivative of ethyl 4,4,4-trifluoro-3-hydroxybutanoate (4.6 g, 20 mmol) was added, and then the whole mixture was stirred at 40-41°C. After 2h of stirring, the flocculant (200 ppm solution prepared from p-713, Dai-ichi Kogyo Seiyaku, 10 ml) was added into the stirred mixture during 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 (34 %) by ^{19}F NMR signal intensities using $C_6H_5CF_3$ as an internal standard, the products were separated by column chromatography using the mixture of n-hexane-diethyl ether (5:1) as an eluent. (R)-(+)-Ethyl 4,4,4-trifluoro-3-hydroxybutanoate , $[\alpha]_D$ +20.9 (neat) ;.98 %ee [lit.[21] $[\alpha]_D$ +20.7 (neat)].

(S)-(-)-Ethyl 4,4,4-trifluoro-3-hydroxybutanoate (S)-(1)

(a) In the above asymmetric hydrolysis, acetate derivative of (1) was hydrolyzed for 6h with lipase-MY, and then (R)-(+)-ethyl 4,4,4-trifluoro-3-hydroxybutanoate (>87 %ee ; hydrolysis ratio 53 %) and the corresponding (S)-acetate derivative were separated by column chromatography.

(b) A suspension of cellulase (*Trichoderma viride*, Yakult Pharmaceutical Industry Co. Ltd., 3 g) in buffer solution (60 ml, pH 7.3), prepared from 1/15 M aq Na_2HPO_4 solution (46.1 ml) and 1/15 M aq KH_2PO_4 solution (13.9 ml), was stirred for 15 min at 40-41°C in "CULSTIR" flask for suspension culture with double arms and jacket (200 ml). Into the mixture, recovered (S)-acetate derivative of ethyl 4,4,4-trifluoro-3-hydroxy-butanoate (1,5 g, 10 mmol) was added and then the whole mixture was stirred at 40-41°C. After 6h of stirring, the flocculant (200 ppm solution, 10 ml) was added into the stirring 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. The products were separated by column chromatography using the mixture of n-hexane-diethyl ether (5:1) as an eluent.
(S)-(-)-Ethyl 4,4,4-trifluoro-3-hydroxybutanoate, $[\alpha]_D$ -20.6 (neat); >97 %ee.

Synthesis of (R)-(+)-(5)

Protection with dihydropyrane

After a mixture of (R)-(+)-ethyl 4,4,4-trifluoro-3-hydroxybutanoate (3.7 g, 20 mmol), dihydropyrane (1.4 g, 20 mmol) and p-toluenesulfonic acid (50 mg) in methylene chloride (40 ml) was stirred for 3.5h at room temperature, the solvent was removed under dynamic vacuum. Distillation gave the compound (2) in a yield of 95 %. bp 71°C/1 mmHg.

Reduction of (2) with diisobutylaluminium hydride

Into the reaction vessel placed the compound (2)(2.6 g, 10 mmol), freshly dried hexane (30 ml) was added with a syringe under atmosphere of argon, and then diisobutylaluminium hydride (11 mmol, 1M in hexane) was added at -70 °C. After adding the reagent, the reaction mixture was stirred for 1h at room temperature, and then the mixture was quenched with sat. NH_4Cl solution. Oily materials were extracted with diethyl ether, and then the ethereal extract was dried over anhydrous magnesium sulfate. On removal of the solvent, distillation gave the corresponding aldehyde in a 86 % yield. bp 58-60°C/1.2 mmHg.
^{19}F NMR ($CDCl_3$) : δ -0.1 (CF_3, d, J_{CF_3-CH} = 8.8 Hz), -0.75 (CF_3, d, J_{CF_3-CH} = 8.8 Hz).
^{1}H NMR ($CDCl_3$) : δ 1.33-2.00 (m, 4xH), 2.67-2.70 (m, 2xH), 3.33-4.00 (4xH), 4.05 (m, 1xH), 4.83 (m, 1xH), 9.80 (CHO).

Wittig-type reaction

Into a mixture solution of sodium hydride (0.27 g, 12 mmol) and toluene (30 ml) under an atmosphere of nitrogen, $(EtO)_2P(O)CH_2CO_2Et$ (3.0 g, 10 mmol) in toluene (10 ml) was added with a syting at 0°C. After 30 min of stirring, aldehyde (3)(1.4 g, 10 mmol) was added at 0°C, the reaction mixture was stirred for 2.5h at room temperature, and then the mixture was quenched with sat. NH_4Cl solution. Oily materials were

extracted with ethyl acetate. On removal of the solvent, the product was purified by column chromatography on silica gel using the n-hexane-ethyl acetate (5:1) as an eluent, in 71 % yield.

^{19}F NMR ($CDCl_3$) : δ -1.08 (CF_3, d, J_{CF_3-CH} = 8.5 Hz), -1.75 (CF_3, d, J_{CF_3-CH} = 8.5 Hz).

^{1}H NMR ($CDCl_3$) : δ 1.20 (CH_3, t), 1.33-2.00 (m, 4xH), 2.56 (CH_2, m), 3.33-4.00 (m, 4xH), 4.17 (CH_2, q), 5.92 (=CH, d, J_{CH-CH} = 12.7 Hz), 6.93 (=CH, m).

(R)-(+)-(5)

A mixture of (4)(2.8 g, 10 mmol), acetic acid (5 ml) and water (20 ml) was stirred for 2h at room temperature. Oily materials were extracted with ethyl acetate and then worked up as usual. (R)-(+)-(5) was purified by column chromatography on silica gel using the n-hexane-ethyl acetate (5:1) as an eluent.

$[\alpha]_D$/MeOH +23.7 (c 2.52); >98 %ee.

^{19}F NMR ($CDCl_3$) : δ +2.8 (CF_3, d, J_{CF_3-CH} = 6.6 Hz).

^{1}H NMR ($CDCl_3$) : δ 1.30 (CH_3, t, $J_{CH_3-CH_2}$ = 7.1 Hz), 2.50 (2xH), 3.47 (CH, d), 4.03 (1xH, br), 4.22 (CH_2, q), 6.02 (=CH, d, J_{CH-CH} = 17 Hz), 7.00 (=CH, d.t, J_{CH-CH_2} = 7.1 Hz).

IR (cm^{-1}) : 3450 (OH), 3000, 1710 (C=O), 1660, 980 (trans-CH=CH).

Analysis : Found : C, 45.35 ; H, 5.13 %.

Calcd for $C_8H_{11}O_3F_3$: C, 45.29 ; H, 5.23 %.

Synthesis of (S)-(-)-enantiomer was carried out the same scale and manner. $[\alpha]_D$/MeOH -23.5 (c 1.23) ; >97 %ee.

O-Carbamate of α,β-unsaturated ester

Into a mixture solution of chlorosulfonyl isocyanate (1.3 g, 12 mmol) and methylene chloride (20 ml), (R)-(+)-(5)(2.1 g, 10 mmol) was added at -78°C, and then the mixture was allowed to warm to room temperature. After 30 min of stirring at room temperature, water was added into the mixture solution, and then

the whole was heated at 70°C for 5h. Oily materials were extracted with ethyl acetate, and the extract was dried over anhydrous magnesium sulfate and then the solvent was removed. O-Carbamate was purified by column chromatography using the mixture of n-hexane-diethyl ether (5:1) as an eluent. (yield. 82 %)

^{19}F NMR ($CDCl_3$) : δ -0.58 (CF_3, d, J_{CF_3-CH} = 7.0 Hz).

^{1}H NMR ($CDCl_3$) : δ 1.07 (CH_3, t, $J_{CH_3-CH_2}$ = 7 Hz), 2.67 (CH_2, m), 4.13 (CH_2, q), 4.67 (3xH, br), 5.88 (=CH, d, J_{CH-CH} = 17 Hz), 6.78 (=CH, d.t, J_{CH-CH_2} = 7 Hz).

IR (cm^{-1}) : 3475 (NH_2), 3390 (NH_2), 3050, 1750 (C=O), 1670, 1610, 995 (trans-CH=CH).

Analysis : Found : C, 44.58 ; H, 5.26 %.

Calcd for $C_9H_{12}O_4F_3$: C, 44.82 ; H, 5.02 %.

Synthesis of (R)-tosylate (8)

Reduction of (2) with lithium aluminium hydride

Into the vessel placed lithium aluminium hydride (12 mmol), freshly dried diethyl ether (30 ml) was added with a syringe under atmosphere of argon, and then the optically active compound (2)(2.6 g, 10 mmol) was added at -70°C. After adding the reagent, the reaction mixture was stirred for 3h at room temperature, and then the mixture was quenched with sat. NH_4Cl solution. The ethereal solution was separated, and then was dried over anhydrous magnesium sulfate. On removal of the solvent, the product was purified by column chromatography on silica gel using n-hexane-diethyl ether (5:1) as an eluent, in 86 % yield.

IR (cm^{-1}): 3410 (OH).

(R)-Tosylate (8)

A mixture of compound (7)(2.2 g, 10 mmol) and tosyl chloride (2.5 g, 13 mmol) in pyridine (20 ml) was stirred at room temperature. After 3h of stirring, the mixture was poured into

water, and then oily materials were extracted with ethyl acetate Tosylate was purified by column chromatography on silica gel using n-hexane-diethyl ether (5:1) as an eluent, in 95 % yield.

(R)-CF_3-analogue of Sulcatol derived from (R)-tosylate (8)

Into a solution of cuprate (20 mmol) in freshly dried diethyl ether (20 ml), (R)-tosylate (8)(5 mmol) in diethyl ether (20 ml) was added slowly at room temperature. After 24 h of stirring at that temperature, the reaction mixture was poured into water, and then the ethereal layer was separated. (R)-CF_3-analogue of Sulcatol was purified by column chromatography on silica gel using the mixture solution of n-hexane-diethyl ether (5:1) as an eluent.

^{19}F NMR ($CDCl_3$) :δ +2.5 (CF_3, d, J_{CF_3-CH} = 6.5 Hz).

^1H NMR ($CDCl_3$) :δ 1.68-1.70 (2xCH_3), 2.50 (2xH), 2.86 (2xH), 3.48 (CH, d), 4.06 (1xH, br), 6.86 (=CH, t, J_{CH-CH_2} = 7.0 Hz).

Analysis : Found : C, 52.65 ; H, 7.31 %.

Calcd for $C_8H_{13}OF_3$: C, 52.74 ; H, 7.19 %.

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