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A SYNTHETIC APPROACH TO F-ANALOGUES OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS

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SUMMARY

Studies on the synthetic routes to F-analogues of captopril, which is known as an Angiotensin converting enzyme inhibitor, have been undertaken.

INTRODUCTION

Numerous stereocontrolled syntheses of bioactive compounds for Angiotensin converting enzyme inhibitors have been studied over the years [1-10]. However, no studies on their F-analogues with the control of absolute stereochemistry, which are expected to be bioactive compounds, have been undertaken because the introduction of a center of chirality into fluoroorganic compounds often proves to be quite difficult and limited [11-15].

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Recently, we have reported examples of highly stereocontrolled syntheses of fluorinated materials with high optical purity [16-24].

As part of our continuous efforts to develop stereocontrolled synthesis in fluorine chemistry [16-24], we present here some results of synthetic approaches to F-analogues of materials used as Angiotensin converting enzyme inhibitors.

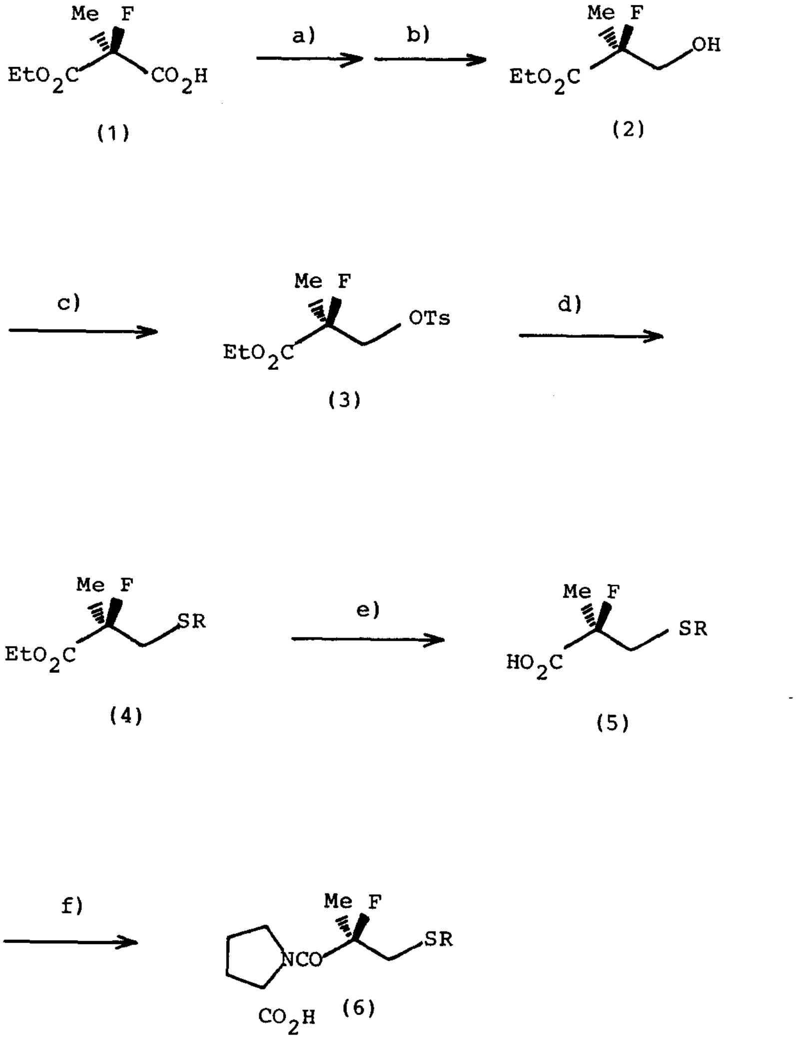
RESULTS AND DISCUSSION

Route to the optically active F-analogues

A brief outline of the synthetic strategies employed in preparing optically active fluorinated derivatives of Angiotensin converting enzyme inhibitor is shown in Scheme I.

In Scheme I, the synthetic intermediate is the optically pure hydroxyester (2)[16]. Optically active (S)-(-)-2-fluoro-2-methyl malonic acid monoethyl ester (1)[16] was selectively reduced with N,N-dimethylchloromethyleniminium chloride and sodium borohydride to give good yields of the optically pure (S)-(-)-ethyl 2-fluoro-3-hydroxy-2-methyl propionate (2), $[\alpha]_D$/MeOH -8.87 (c 1.81) >99 %ee. Protection with tosyl chloride followed by treatment of the hydroxyester with a variety of nucleophiles gave (S)-ethyl 2-fluoro-2-methyl-3-substituted propionates (4)(Table 1).

The next step is an enzymatic hydrolysis to obtain the corresponding carboxylic acids (5)(Table 2), and then the condensation reaction with L-proline proceeded to F-analogues of the title materials (6)(Table 3).



Scheme I

a) $Me_2NCHO/COCl_2/CH_2Cl_2$, 0°C b) 2.3 eq. $NaBH_4$/MeCN-THF, -20°c c) TsCl/pyridine d) $RSH/NaH/Et_2O$ e) lipase-MY f) L-proline/1-methyl-2-chloropyridinium iodide/CH_2Cl_2

TABLE 1

Preparation of compounds (4)

Compound No	R	$[\alpha]_D$/MeOH	^{19}F NMR[a] δ ppm	^1H NMR δ ppm	Analysis: Found (Calcd) C	Analysis: Found (Calcd) H
(4a)(nc)	Ph[b]	+4.23 (c 1.25)	71.4(d.d.q)	1.22(CH_3, t, $J_{CH_3-CH_2}$= 8.1 Hz), 1.56(CH_3, d, J_{CH_3-CF}= 23 Hz), 3.30 (H_A, d, J_{H_A-F}= 20 Hz), 3.22(H_B, d, J_{H_B-F}= 22 Hz), 4.10(CH_2, q), 7.27(Ar-H)	59.35 (59.48)	6.01 (6.24)
(4b)(nc)	$PhCH_2$[b]	-54.2 (c 1.08)	73.0(d.d.q)	1.30(CH_3, t, $J_{CH_3-CH_2}$= 7.7 Hz), 1.60(CH_3, d, J_{CH_3-F}= 23 Hz), 2.82 (H_A, d, J_{H_A-F}= 27.3 Hz), 2.84(H_B, d, J_{H_B-F}= 22 Hz), 3.79(CH_2Ph, s), 4.27 (CH_2, q), 7.10-7.46(Ar-H)	61.25 (60.91)	6.54 (6.68)
(4c)(nc)	PhCO[b]	-24.5 (c 1.74)	71.3(d.d.q)	1.29(CH_3, t, $J_{CH_3-CH_2}$= 8 Hz), 1.60 (CH_3, d, J_{CH_3-CF}= 23 Hz), 3.55(H_A, d, J_{H_A-F}= 22 Hz), 3.57(H_B, d, J_{H_B-F}= 22 Hz), 4.20(CH_2, q), 7.11-7.98(Ar-H)	57.54 (57.76)	6.27 (5.59)

[a] From external CF_3CO_2H in $CDCl_3$.

[b] The products were purified by column chromatography on silica gel.

TABLE 2

Preparation of compounds (5)

Compound No	R	$[\alpha]_D$/MeOH	^{19}F NMR[a] δ ppm	^{1}H NMR δ ppm	Analysis: Found(Calcd) C	Analysis: Found(Calcd) H
(5a)(nc)	Ph[b]	+3.54 (c 0.18)	72.5(d.d.q)	1.60(CH_3, d, $J_{CH_3\text{-}CF}$= 23 Hz), 3.73 (H_A, d, $J_{H_A\text{-}F}$= 21 Hz), 3.74(H_B, d, $J_{H_B\text{-}F}$= 25 Hz), 7.04(Ar-H), 9.82(CO_2H)	56.30 (56.06)	5.01 (5.18)
(5b)(nc)	$PhCH_2$[b]	-32.9 (c 1.14)	72.8(d.d.q)	1.66(CH_3, d, $J_{CH_3\text{-}CF}$= 23 Hz), 2.85(H_A, d, $J_{H_A\text{-}F}$= 21 Hz), 2.88(H_B, d, $J_{H_B\text{-}F}$= 27 Hz), 3.72(CH_2Ph, s), 7.26(Ar-H) 10.45(CO_2H)	52.87 (52.61)	5.48 (5.74)
(5c)(nc)	PhCO[b]	-15.6 (c 1.17)	72.5(d.d.q)	1.69(CH_3, d, $J_{CH_3\text{-}CF}$= 22.7 Hz), 4.37(H_A, d, $J_{H_A\text{-}F}$= 23 Hz), 4.39(H_B, d, $J_{H_B\text{-}F}$= 23 Hz), 7.17-8.21(Ar-H), 11.23(CO_2H)	54.26 (54.54)	4.68 (4.58)

[a] From external CF_3CO_2H in $CDCl_3$.

[b] The products were purified by column chromatgraphy on silica gel.

TABLE 3

Physical properties of compounds (6)

Compound No	R	^{19}F NMR δ ppm	^{1}H NMR δ ppm	Anal. Found (Calcd) % C	H	N
(6a)(nc)	Ph	77.3(d.d.q)	1.68(CH_3, d, $J_{CH_3\text{-}F}$= 24 Hz) 1.85-2.51(3xH, m), 3.17-4.10(4xH), 4.57(1H, m), 7.13-7.60(Ar-H), 10.73(CO_2H)	56.75 (56.55)	5.32 (5.42)	4.87 (4.71)
(6b)(nc)	$PhCH_2$	77.6(d,d,q)	1.64(CH_3, d, $J_{CH_3\text{-}F}$= 23 Hz) 1.87-2.49(3xH, m), 3.10-4.21(6xH), 4.62(1H, m), 7.20-7.55(Ar-H), 10.54(CO_2H)	57.59 (57.86)	5.67 (5.82)	4.75 (4.50)
(6c)(nc)	PhCO	76.9(d,d,q)	1.69(CH_3, d, $J_{CH_3\text{-}F}$= 24 Hz) 1.79-2.54(3xH, m), 3.08-4.30(4xH), 4.59(1H, m), 7.12-7.56(Ar-H), 10.74(CO_2H)	55.63 (55.38)	5.13 (4.96)	4.27 (4.31)

EXPERIMENTAL

(S)-(-)-Ethyl 2-fluoro-3-hydroxy-2-methyl propionate (2)

After a mixture of N,N-dimethylformamide (3.4 ml) and oxalyl chloride (8 ml) in methylene chloride (40 ml) had been stirred for 1h at 0°C, the solvent was removed under dynamic vacuum. Into the reaction vessel, acetonitrile (30 ml) and tetrahydrofuran (100 ml) were added with a syringe under an atmosphere of nitrogen, and then (S)-(-)-2-fluoro-2-methyl malonic acid monoethyl ester (1)[16,17] (6.56 g, 40 mmol, >99 %ee) was added at -30°C. After 1h of stirring at -30°C, a solution of sodium borohydride (3.5 g, 93 mmol) in N.N-dimethylformamide (20 ml) was added slowly at -78°C, cooling with the dry-ice acetone bath. After adding the above solution, the reaction mixture was stirred for 4h at -20°C, and the mixture was quenched with 3N HCl (50 ml). Oily materials were extracted with ethyl acetate, and the organic layer was washed with 1N HCl, 5% aq. $NaHCO_3$, water and brine. On removal of the solvent, distillation gave (S)-(-)-ethyl 3-hydroxy-2-fluoro-2-methyl propionate (4.11 g, 27.4 mmol) in a yield of 69 %, $[\alpha]_D$/MeOH -8.87 (c 1.81), bp 84-85°C/8 mmHg. >99 %ee.

^{19}F NMR ($CDCl_3$) : δ 84.0 (d.d.q ; J_{F-H} = 18 Hz, J_{F-H} = 21 Hz, J_{F-CH_3} = 23 Hz)

^{1}H NMR ($CDCl_3$) : δ 1.33 (CH_3,t ; $J_{CH_3-CH_2}$ = 7.1 Hz), 1.50

(CH_3,d), 2.67 (OH), 3.77 (CH_2,d), 3.88 (CH_2,d), 4.27 (CH_2,q)

Analysis. Found : C, 47.73 ; H, 7.64 %.
Calcd for $C_6H_{11}O_3F$: C, 48.00 ; H, 7.38 %.

(S)-(-)-Tosylate of (2)

A mixture of (S)-(-)-ethyl 2-fluoro-3-hydroxy-2-methyl propionate (2) (2.0 g, 13 mmol) and tosyl chloride (3.0 g, 16 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. $[\alpha]_D$/MeOH -1.95 (c 1.34).
^{19}F NMR ($CDCl_3$) : δ 82.3 (d.d.q ; J_{F-CH_3} = 19.5 Hz, J_{F-H} = 18.3 Hz, J_{F-H} = 14.7 Hz)
^1H NMR ($CDCl_3$) : δ 1.29 (CH,t ; $J_{CH_3-CH_2}$ = 7.4 Hz), 1.52 (CH_3,d), 2.46 (CH_3,s), 4.13 (CH,d), 4.15 (CH_2,d), 4.18 (CH_2,q), 7.30-7.75 (Ar-H).
Analysis. Found : C, 51.35 ; H, 6.08 %.
Calcd for $C_{13}H_{18}SO_5F$: C, 51.14 ; H, 5.94 %.

(S)-(+)-Ethyl 2-fluoro-2-methyl-3-phenylthiopropionate (4a)(nc)

Into a solution of sodium hydride (0.5 g, 21 mmol) in diethyl ether (20 ml), thiophenol (2.2 g, 20 mmol) was added, and then stirred at room temperature for 30 min. Into the above solution, (S)-(-)-tosylate (3)(5.8 g, 20 mmol) was added. After 24h of stirring at room temperature,the reaction mixture was worked up in the usual manner, giving the product in a 58 % yield, $[\alpha]_D$/MeOH +4.23 (c 1.25).

Compounds (4b) and (4c) were made similarly.

(S)-(+)-2-Fluoro-2-methyl-3-phenylthiopropionic acid (5a)(nc)

A suspension of lipase-MY (*Candida cylindracea* , Meito Sangyo Co. Ltd., 5 g) in distilled water (75 ml), was stirred for 15 min at 40-41°C in the round bottom flask (200 ml). Into the mixture, (S)-(+)-ethyl 2-fluoro-2-methyl-3-phenylthiopropionate (2.4 g, 10 mmol) was added at 40-41°C. After 24 hrs of stirring, the mixture was acidified with 1N HCl and then the precipitates were seperated by filtration. The oily materials were extracted with ethyl acetate, and worked up similarly.

The products were separated by column chromatography using the mixture of n-hexane-ethyl acetate (1:5) as an eluent. $[\alpha]_D$/MeOH +3.54 (c 0.18).

Compounds (5b) and (5c) were made similarly.

Condensation reaction

A mixture solution of (S)-(+)-2-fluoro-2-methyl-3-phenylthiopropionic acid (2.1 g, 10 mmol), L-proline (1.26 g, 11 mmol) and 1-methyl-2-chloropyridinium iodide (3.1 g, 12 mmol) in dichloromethane (20 ml) was refluxed for 3h, and then worked up similarly. The products were separated by column chromatography on silica gel using n-hexane-ethyl acetate (1:5) as an eluent.

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