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STEREOSELECTIVE SYNTHESIS OF CHIRAL 2,3-EPOXYCOMPOUNDS POSSESSING FLUORINATED METHYL GROUPS

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SUMMARY

The preparation of fluoromethylated optically pure trans epoxycompounds [CXF_2-CH(O)-CH-C(O)R, X=F,H or Cl ; R=OEt,Ph,t-Bu, $C(OH)Me_2$] from the corresponding β-hydroxyketones and/or esters is described.

INTRODUCTION

Epoxides are useful precursors for bioactive compounds [1-3] and in our continuing study of stereocontrolled synthetic tools for fluorinated molecules [4-8], we now describe the preparation of chiral 2,3-epoxyketones and/or esters possessing fluorinated methyl groups.

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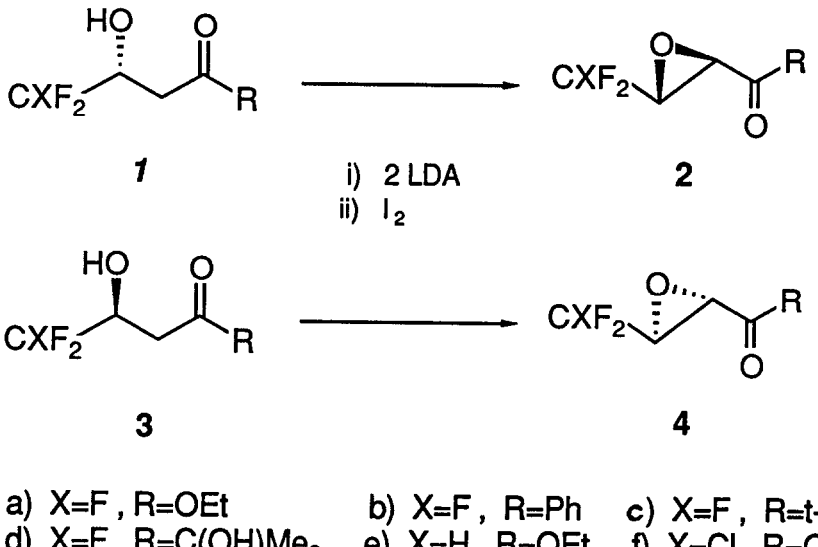
RESULTS AND DISCUSSION

Preparation of trifluoromethylated 2,3-epoxycompounds

The first example of such a reaction, the preparation of the trifluoromethylated (2R,3S)-epoxyester (2a) derived from (R)-(+)-ethyl 3-hydroxy-4,4,4-trifluorobutyrate (1a) has been reported by Seebach and his co-workers [9]. Therefore, we examined the preparation of the enantiomer, the trifluoromethylated (2S,3R)-epoxyester (4a) using their process. (S)-(-)-Ethyl 3-hydroxy-4,4,4-trifluorobutyrate (3a) [4] [>97 %ee $[\alpha]_D$ -20.7 (neat)] was treated with 2 equiv. of lithium diisopropylamide, and then the reaction mixture was subsequently quenched with iodine to produce the (2S,3R)-epoxyester (4a).

The preparation of trifluoromethylated 2,3-epoxyketones derived from the optically active CF_3-β-hydroxyketones was carried out in the same manner, the results being listed in Table 1.



a) X=F, R=OEt b) X=F, R=Ph c) X=F, R=t-Bu
d) X=F, R=C(OH)Me_2 e) X=H, R=OEt f) X=Cl, R=OEt

TABLE 1

Physical properties of CXF_2-CH-CH-C(O)R (O bridging the CH-CH)

Compound No	X	R	Yield (%)	$[\alpha]_D$ (c/MeOH)	Analysis C found (calcd)	Analysis H found (calcd)
(2a)	F	OEt	54	+24.6 (1.10)	39.35 (39.14)	4.08 (3.82)
(2b) (nc)	F	Ph	67	+6.20 (1.24)	55.84 (55.57)	3.41 (3.26)
(2c) (nc)	F	t-Bu	61	+14.6 (1.16)	49.27 (48.98)	5.35 (5.65)
(2d) (nc)	F	$C(OH)Me_2$	61	+12.4 (1.04)	44.39 (44.45)	6.53 (6.34)
(2e) (nc)	H	OEt	75	+1.17 (1.14)	43.09 (43.38)	5.04 (4.85)
(2f) (nc)	Cl	OEt	68	+3.57 (1.24)	36.17 (35.92)	3.34 (3.52)
(4a) (nc)	F	OEt	52	-24.2 (1.04)	39.02 (39.14)	3.96 (3.82)
(4b) (nc)	F	Ph	64	-6.30 (1.02)	55.76 (55.57)	3.38 (3.26)
(4c) (nc)	F	t-Bu	66	-14.1 (1.16)	48.64 (48.98)	5.54 (5.65)
(4d) (nc)	F	$C(OH)Me_2$	63	-11.9 (1.28)	44.83 (44.45)	6.27 (6.34)
(4e) (nc)	H	OEt	74	-1.13 (1.09)	43.54 (43.38)	4.67 (4.85)
(4f) (nc)	Cl	OEt	71	-3.68 (1.06)	36.06 (35.92)	3.78 (3.52)

TABLE 2

^1H and ^{19}F-NMR spectra of 2,3-epoxyesters and ketones

Compound No	^1H-NMR ($CDCl_3$) δ (ppm)	^{19}F-NMR[a] δ (ppm)
(2a) or (4a)	1.31 (t, 3H, $J_{CH_3-CH_2}$=7.2 Hz) 3.63 (m, 2H); 4.21 (q, 2H)	-4.58 (d)
(2b) or (4b)	3.67 (dq, 1H, J_{H-H}=2.0 Hz, J_{H-F}=4.8 Hz); 4.32 (d, 1H, J_{H-H}=2.0 Hz); 7.54-7.99 (Ar-H)	-3.73 (d)
(2c) or (4c)	1.26 (s, 9H); 3.47 (dq, 1H, J_{H-H}=1.8 Hz; J_{H-F}=4.8 Hz); 3.89 (d, 1H)	-3.87 (d)
(2d) or (4d)	1.43 (s, 6H); 2.68 (bs, OH); 3.58 (dq, 1H; J_{H-H}=1.8 Hz, J_{H-F}=4.8 Hz)	-0.58 (d)

[a] ppm from CF_3CO_2H in diethyl ether.

Preparation of difluoromethylated 2,3-epoxyesters

We next examined the synthesis of enantiomers of 2,3-epoxyesters possessing the difluoromethyl or chlorodifluoromethyl group. (R)-(+)- or (S)-(-)-ethyl 3-hydroxy-4,4-difluorobutyrate (1e and 3e) and chlorodifluorobutyrate (1f and 3f), >90 %ee, were used in the above system, and the reaction was carried out in the same manner, producing the corresponding (2R,3S)- or (2S,3R)-epoxyesters (2e,4e ; 2f,4f:respectively).

Although the trans/cis ratios (>95 %) have not been clarified in detail because of contamination of some minor products, simple chromatography on silica gel was found to be an effective method for the isolation of pure trans epoxides. The stereochemistries of the epoxides were assigned by using ^{1}H NMR (200 MHz) coupling constants of two epoxy ring protons. The vicinal coupling (J_{H-H}) should be the 1.5-2.0 Hz for the trans protons and 2.0-5.0 Hz for the cis protons [3]. The main product was the trans isomer.

EXPERIMENTAL

Preparation of (2R,3S)-epoxyketone(2b) derived from (R)-(+)-(2-hydroxy-3,3,3-trifluoropropyl)phenyl ketone (1b)

Into a solution of lithium diisopropylamide (25 mmol) in tetrahydrofuran (25 ml) was added (R)-(+)-(2-hydroxy-3,3,3-trifluoropropyl)phenyl ketone (1b) (2.16 g, 10 mmol; >94 %ee, $[\alpha]_D$ +2.58 (c 1.71/MeOH)) [4] in tetrahydrofuran (15 ml) with a syringe under an atmosphere of argon at -78 ℃. After 1h of stirring at -78 ℃, a solution of iodine (3.1 g, 12 mmol) in tetrahydrofuran (25 ml) was added at -78℃. After 4h of stirring at -78℃, the mixture was quenched with 1N HCl until the water layer became neutral. The oily materials were extracted with diethyl ether, and then the ethereal extract was washed with sat. $Na_2S_2O_3$ (100 ml) and sat. NaCl aq. (100 ml), followed by drying with $MgSO_4$. On removal of the solvent, (2R,3S)-epoxyketone

(2b) was separated by column chromatography on silica gel using n-hexane-ethyl acetate (10:1) as an eluent ; yield:1.45 g (67%). IR (cm^{-1}): 1720 (C=O).

Preparation of (2R,3S)-epoxyketone(2c) derived from (R)-(+)-(2-hydroxy-3,3,3-trifluoropropyl) tert-butyl ketone (1c)

In the above reaction, (R)-(+)-(2-hydroxy-3,3,3-trifluoropropyl)tert-butyl ketone (1c) (1.96 g, 10 mmol; >95 %ee, $[\alpha]_D$ +18.3 (c 1.03/MeOH), lithium diisopropylamide(24 mmol) and iodine (3.1 g, 12 mmol) were used in the same manner. After 3h of stirring at -78 ℃, the mixture was quenched with 1N HCl until the water layer became neutral. The oily materials were extracted with diethyl ether, and then the ethereal extract was washed with sat. $Na_2S_2O_3$ (100 ml) and sat. NaCl aq. (100 ml), followed by drying with $MgSO_4$. On removal of the solvent, (2R,3S)-epoxyketone (2c) was separated by column chromatography on silica gel using n-hexane-ethyl acetate (10:1) as eluent ; yield: 1.20 g (61%). IR (cm^{-1}): 1715 (C=O).

Preparation of (2R,3S)-epoxyketone (2d) derived from (R)-(+)-(2-hydroxy-3,3,3-trifluoropropyl)(2-trimethylsiloxypropyl)ketone (1d)

In the above reaction, (R)-(+)-(2-hydroxy-3,3,3-trifluoropropyl)(2-trimethylsiloxypropyl)ketone (1d) (2.70 g, 10 mmol; >95 %ee, $[\alpha]_D$ +5.7 (c 1.08/MeOH), lithium diisopropylamide (24 mmol) and iodine (3.1 g, 12 mmol) were used in the same manner. After 4h of stirring at -78 ℃, the mixture was quenched with 1N HCl until the water layer became neutral. The oily materials were extracted with diethyl ether, and then the ethereal extract was washed with sat. $Na_2S_2O_3$ (100 ml) and sat. NaCl aq. (100 ml), followed by drying with $MgSO_4$. On removal of the solvent, (2R,3S)-epoxyketone (2d) was separated by column chromatography on silica gel using n-hexane-ethyl acetate (10:1) as eluent ; yield: 1.21 g (61%). IR (cm^{-1}): 1720 (C=O).

Preparation of (2S,3R)-epoxyester (4a) derived from (S)-(-)-ethyl 3-hydroxy-4,4,4-trifluorobutyrate (3a)

Into a solution of lithium diisopropylamide (24 mmol) in tetrahydrofuran (25 ml) was added (S)-(-)-ethyl 3-hydroxy-4,4,4-trifluorobutyrate (2.0 g, 10 mmol; >97 %ee ; $[\alpha]_D$ (neat) -20.7) in tetrahydrofuran (15 ml) with a syringe under an atmosphere of argon at -78℃. After 1h of stirring at -78℃, a solution of iodine (3.1 g, 12 mmol) in tetrahydrofuran (25 ml) was added at -78℃. After 3h of stirring at -78 ℃, the mixture was quenched with 1N HCl until the water layer became neutral. The oily materials were extracted with diethyl ether, and then the ethereal extract was washed with sat. $Na_2S_2O_3$ (100 ml) and sat. NaCl aq. (100 ml), followed by drying with $MgSO_4$. On removal of the solvent, (2S,3R)-epoxyester (4a) was separated by column chromatography on silica gel using n-hexane-ethyl acetate (10:1) as an eluent ; yield : 0.96 g (52%). IR (cm^{-1}): 1725 (C=O).

Similarly, other 2,3-epoxyketones and ester were prepared in the same manner and the products are listed in the Table 1.

Preparation of (2R,3S)-epoxyester (2e) derived from (R)-(+)-ethyl 3-hydroxy-4,4-difluorobutyrate (1e)

Into the lithium diisopropylamide (25 mmol) in tetrahydrofuran (25 ml) was added (R)-(+)-ethyl 3-hydroxy-4,4-difluorobutyrate (1e) (1.68 g, 10 mmol); >90 %ee, in tetrahydrofuran (15 ml) with a syringe under an atmosphere of argon at -78℃. After 1h of stirring at -78 ℃, iodine (3.1 g, 12 mmol) in tetrahydrofuran (25 ml) was added at -78℃. After 4h of stirring at -78 ℃, the mixture was quenched with 1N HCl until the water layer became neutral. The oily materials were extracted with diethyl ether, and then the ethereal extract was washed with sat. $Na_2S_2O_3$ and sat. NaCl aq., followed by drying with anhydrous magnesium sulfate. On removal of the solvent, (2R,3S)-epoxyester (2e) was

separated by column chromatography on silica gel using n-hexane-ethyl acetate (10:1): yield 75%: $[\alpha]_D$ +1.17 (c 1.14/MeOH). ^{19}F NMR (Et_2O): δ 46.2 (dt, $J_{F-H_{gem}}$= 52.5, $J_{F-H_{vic}}$= 3.5 Hz) ppm ^1H NMR ($CDCl_3$): δ 1.30 (t, 3H, $J_{CH_3-CH_2}$= 7.2 Hz), 3.45 (1H, $J_{H-H_{trans}}$= 1.1 Hz, C<u>H</u>C(O)), 3.65 (m, 1H, $CHF_2C\underline{H}$), 4.23(q, 2H), 5.67(d.t, 1H, $J_{H-H_{vic}}$= 3.6 Hz, $C\underline{H}F_2$). IR (cm^{-1}): 1725 (C=O).

<u>Preparation of (2S,3R)-epoxyester (4e) derived from (S)-(-)-ethyl 3-hydroxy-4,4-difluorobutyrate (3e)</u>

(S)-(-)-Ethyl 3-hydroxy-4,4-difluorobutyrate (3e) (1.68 g, 10 mmol); >90 %ee, lithium diisopropylamide (25 mmol) and iodine (3.1 g, 12 mmol) were used in the same manner, and then worked up as usual. (2S,3R)-Epoxyester (4e) was separated by column chromatography on silica gel using n-hexane-ethyl acetate (10:1) : yield 74%: $[\alpha]_D$ -1.13 (c 1.09/MeOH). IR (cm^{-1}): 1725 (C=O).

<u>Preparation of (2R,3S)-epoxyester (2f) derived from (R)-(+)-ethyl 3-hydroxy-4-chloro-4,4-difluorobutyrate (1f)</u>

(R)-(+)-Ethyl 3-hydroxy-4-chloro- 4,4-difluorobutyrate (1f) (2.0 g, 10 mmol); >90 %ee, lithium diisopropylamide (25 mmol) and iodine (3.1 g, 12 mmol) were used in the same manner, and then worked up as usual. (2R,3S)-Epoxyester (2f) was separated by column chromatography on silica gel using n-hexane-ethyl acetate (10:1): yield 68% : $[\alpha]_D$ +3.57 (c 1.24/MeOH). ^{19}F NMR (Et_2O): δ -11.5 (dd, J_{F-F}= 168, $J_{F-H_{vic}}$= 8.5 Hz),-14.6 (dd) ppm ^1H NMR ($CDCl_3$): δ 1.29 (t, 3H, $J_{CH_3-CH_2}$= 7.2 Hz), 3.65 (1H, $J_{H-H_{trans}}$= 1.2 Hz, C<u>H</u>C(O)), 3.85 (m, 1H, $CClF_2C\underline{H}$), 4.25(q, 2H) IR (cm^{-1}): 1720 (C=O).

<u>Preparation of (2S,3R)-epoxyester (4f) derived from (S)-(-)-ethyl 3-hydroxy-4-chloro-4,4-difluorobutyrate (3f)</u>

(S)-(-)-Ethyl 3-hydroxy-4-chloro-4,4-difluorobutyrate (3f) (2.0 g, 10 mmol); >90 %ee, lithium diisopropylamide (25 mmol)

and iodine (3.1 g, 12 mmol) were used in the same manner, and then worked up as usual. (2S,3R)-Epoxyester (4f) was separated by column chromatography on silica gel using n-hexane-ethyl acetate (10:1): yield 71% : $[\alpha]_D$ -3.68 (c 1.06/MeOH).
IR (cm^{-1}): 1720 (C=O).

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