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Asymmetric Synthesis of Both Enantiomers of Acyloxy Methyl 3,3-Difluorolactate

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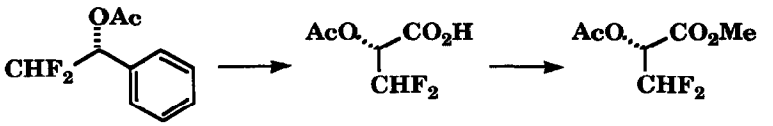
Abstract: Both enantiomers of acyloxy methyl 3,3-difluorolactate are synthsized via enzymatic optical resolution of furanol and transformed into chiral α-hydroxy ketone and diol. The absolute configuration of these materials is determined.

Difluoromethyl substitution on organic molecules often confers bioactivity on these compounds, and can serve as a diagnostic handle for functionalized materials,[1-5] although few developments of methodology and/or reagents suitable for synthesis of such materials in a highly enantioselective manner have been reported. This requires the design and construction of a new type of difluoromethylated chiral building unit. Herein, we would like to describe two pathways based on the enzymatic resolution, giving chiral acyloxy methyl 3,3-difluorolactate. The first route is the oxidation of the acetate derivative of (*R*)-1-phenyl 2,2-difluoroethanol with $RuCl_3$. The second route is the ozonolysis of (*R*)- or (*S*)-furanol possessing a difluoromethyl group.

Recently, we have reported the microbially-based approach for the synthesis of (*R*)- and (*S*)-1-phenyl-2,2-difluoroethanol **1**.[6] Therefore, we have designed the oxidation of the acetate derivative of (*R*)-1-phenyl-2,2-difluoroethanol with $RuCl_3$. The acetate derivative of (*R*)-1-phenyl-2,2-difluoroethanol (>85% ee) was selectively oxidized for 3 weeks with $RuCl_3$ in the solution of H_2O-CH_3CN-CCl_4 to give the optically active compound **2** in 35% yield. The optical purity of **2** (87% ee) was determined by ^{19}F NMR after conversion of the compound to its diastereomeric amides with optically active α-phenethylamine. Esterification of the acid **2** with diazomethane then gave the acetate derivative of (*R*)-(-)-methyl 3,3-difluorolactate **3**. However, there are numerous disadvantages associated with the above approach; e.g., the yield is not high, the oxidation period is too long, efficient control of the conversion ratio is required in order to obtain both enantiomers, and highly enriched products must be prepared at low conversion so that unreacted substrates may be obtained in high optical purity.

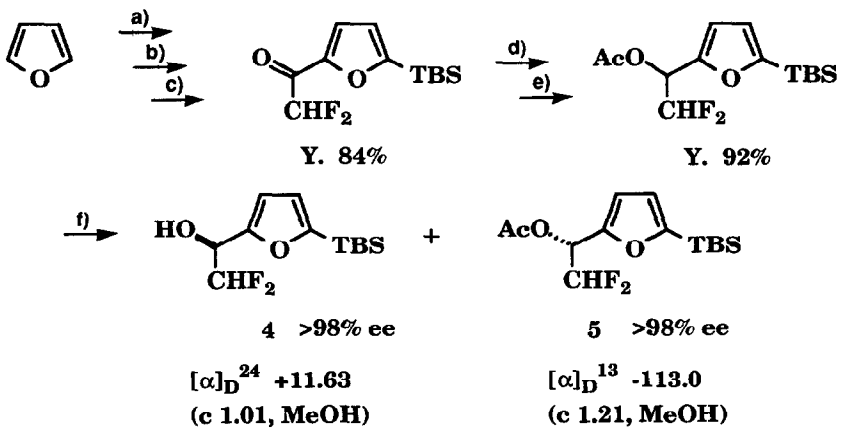


1 2 3

>85% ee 87% ee

To obviate the above disadvantages, we have developed a second route based upon the ozonolysis of (*R*)- and (*S*)-furanols possessing a difluoromethyl group as shown in Scheme 1. Repetitive anion generation with *n*-BuLi and its trapping by appropriate electrophiles such as *tert*-butyldimethylsilyl (TBS) chloride at the first stage and ethyl difluoroacetate at the second stage in a one-pot manner efficiently afforded the ketone. The ketone was then reduced without further purification to furnish the racemic furanol in approximately 77% total yield. The furanol was then subjected to the usual esterification conditions to be converted into the subject for the enzymatic transformation. The asymmetric hydrolysis of the acetate with lipase PS (*Pseudomonas sp.*: Amano Seiyaku Co. Ltd.) produces the the corresponding (*S*)-furanol **4** ($[\alpha]_D^{24}$ +11.63 (c 1.01, MeOH)) in >98% e.e. (enantiomeric excess) at 47% conversion in approximately >85% total yield. The corresponding acetate derivative **5** of the enantiomer with >98% ee was also obtained, whose optical purity would be readily improved by further subjection to the hydrolysis. The ozonolysis of the recovered acetate ($[\alpha]_D^{13}$ -113.0 (c 1.21,MeOH) gave the corresponding (*R*)-acetoxy 3,3-difluorolactic acid,[7] and then the esterification of the acid with diazomethane produced the corresponding methyl acetoxy 3,3-difluorolactate **3**.[8]

Scheme 1

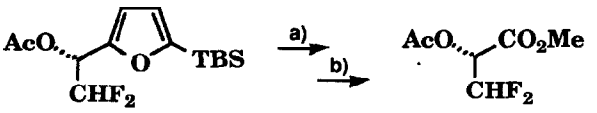


4 >98% ee 5 >98% ee

$[\alpha]_D^{24}$ +11.63 (c 1.01, MeOH) $[\alpha]_D^{13}$ -113.0 (c 1.21, MeOH)

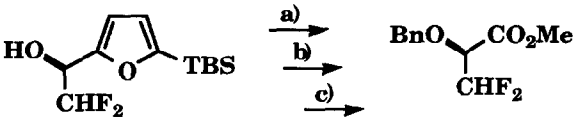
a) *n*-BuLi, THF b) *TBS*-Cl c) CHF_2CO_2Et d) $NaBH_4$ e) CH_3COCl f) lipase PS

(*S*)-Methyl benzyloxy 3,3-difluorolactate ($[\alpha]_D^{19}$ +61.07 (c 1.45, MeOH) was obtained in the same manner.



(*R*)-5 (*R*)-3 >98% ee

a) O_3; quant. b) CH_2N_2, Et_2O $[\alpha]_D^{13}$ -31.78 (c 1.10, MeOH)



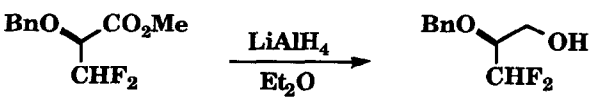
(*S*)-4 (*S*)-6

$[\alpha]_D^{19}$ +10.98 (c 1.25, MeOH); >93% ee

$[\alpha]_D^{19}$ +61.07 (c 1.45, MeOH); >95% ee

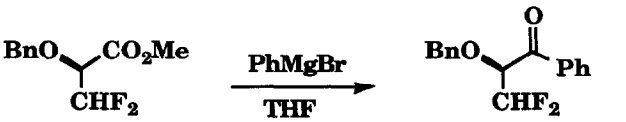
a) $PhCH_2Br$, CH_2Cl_2, NaH, Bu_4NI(cat.); yield (>95%)
b) O_3, MeOH; quant. c) CH_2N_2, Et_2O

The obtained methyl 3,3-difluorolactates **6** would be expected to be useful chiral building blocks for the preparation of functionalized materials with a difluoromethyl group. (*S*)-(+)-Methyl 3,3-difluorolactate **6** was selectively reduced with lithium alminum hydride to give the compound **7** in 89% yield. Furthermore, a derivative of the α-hydroxy ketone **8** was obtained via the Grignard reaction of compound **6** with phenyl magnesium bromide.



(*S*)-6 : >95% ee (*S*)-7 : >95% ee

$[\alpha]_D^{19}$ -17.45 (c 0.850, MeOH)



(*S*)-6 : >95% ee　　Y. 57%　　(*S*)-8 : >95% ee

$[\alpha]_D^{13}$ +58.78

(c 0.874, $CHCl_3$)

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7) (*R*)-(-)-Acetoxy 3,3-difluorolactic acid: ^{1}H NMR ($CDCl_3$); δ 2.24 (3 H, s), 5.37 (1 H, ddd, $J_{H,H}$ = 2.3, $J_{H,F}$ =8.4, 19.4 Hz), 5.4-5.9 (1 H, br), 6.19 (1 H, dt, $J_{H,H}$ =2.2, $J_{H,F}$ =53.5 Hz):^{19}F NMR ($CDCl_3$); δ 32.33 (1 F, ddd, $J_{F,H}$ =21.4, 54.9, $J_{F,F}$ =288.4 Hz), 34.63 (1 F, ddd, $J_{F,H}$ =7.6, 53.4 Hz).

8) (*R*)-(-)-Methyl acetoxy 3,3-difluorolactate: ^{1}H NMR ($CDCl_3$); δ 2.24 (3 H, s), 3.84 (3 H, s), 5.36 (1 H, ddd, $J_{H,H}$ =2.8, $J_{H,F}$ =10.2, 15.7 Hz), 6.13 (1 H, dt, $J_{H,H}$ =2.8, $J_{H,F}$ =53.6 Hz):^{19}F NMR ($CDCl_3$); δ 33.28 (1 F, ddd, $J_{F,H}$ =16.8, 53.4, $J_{F,F}$ =289.9 Hz), 34.43 (1 F, ddd, $J_{F,H}$ =9.2, 53.4 Hz).

9) 2-Benzyloxy-3,3-difluoro-1-propanol: ^{1}H NMR ($CDCl_3$); δ 1.91 (1 H, br), 3.64 (1 H, m), 3.76 (2 H, m), 4.66 (1 H, d, $J_{H,H}$ =11.7 Hz), 4.83 (1 H, d, $J_{H,H}$ =11.7 Hz), 5.85 (1 H, ddd, $J_{H,H}$ =5.0 Hz, $J_{H,F}$ =54.9, 56.0 Hz):^{19}F NMR ($CDCl_3$); δ 33.13 (1 F, ddd, $J_{F,H}$ =12.1, 56.5, $J_{F,F}$ = 296 Hz), 35.28 (1 F, ddd, $J_{F,H}$ =7.6, 54.9 Hz).

10) (1-Benzyloxy 2,2-difluoro)ethyl phenyl ketone: ^{1}H NMR ($CDCl_3$); δ 4.68 (1 H, d, $J_{H,H}$ =11.7 Hz), 3.64 76 (1 H, d, $J_{H,H}$ =11.7 Hz), 4.83 (1 H, ddd, $J_{H,H}$ =4.7, $J_{H,F}$ =54.2, 55.5 Hz), 7.31 (5 H, m), 7.50 (3 H, m), 7.95 (2 H, m):^{19}F NMR ($CDCl_3$); δ 35.96 (1 F, ddd, $J_{F,H}$ =13.0, 55.7, $J_{F,F}$ = 295 Hz), 37.34 (1 F, ddd, $J_{F,H}$ =7.6, 54.2 Hz).