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New synthetic approach to mevalonate and mevaldate fluoroanalogues

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Abstract—6,6,6-Tri- and 6,6-difluoromevalonate were synthesized by new method starting from the corresponding β-alkoxyvinyl polyfluoromethyl ketones. Enantiomers of fluoromevalonates were obtained by column chromatography separation of diastereomeric (*S*)-(−)-1-phenylethylamides of fluoromevalonates with the following hydrolysis. Racemic 6,6,6-tri- and 6,6-difluoromevaldates were also prepared.

1. Introduction

Mevalonate (mevalonic acid) **1** and mevaldate **2** (mevaldic acid) (Fig. 1) are important secondary metabolites in the biosynthesis of such important bioregulators as cholesterol, dolichol, ubiquinone, vitamin D, and others.[1] Therefore, the synthesis and biochemical investigation of the fluorinated analogues of these compounds are of interest because replacement of hydrogen by fluorine in natural compounds molecules often leads to biologically active compounds.[2] Previously, several fluorinated mevalonate analogues, such as 6,6,6-trifluoromevalonate **3a**, 6,6-difluoromevalonate **3b**, 6-monofluoromevalonate **3c**, and 4,4-difluoromevalonate **4** and some of their derivatives, were synthesized as racemates.[3] They were shown to be efficient inhibitors of a mevalonate pathway, namely the mevalonate transformation to isopentenyl pyrophosphate; monofluoromevalonate **3c** was found as the most effective inhibitor (K_i = 10 nM).[3c,4]

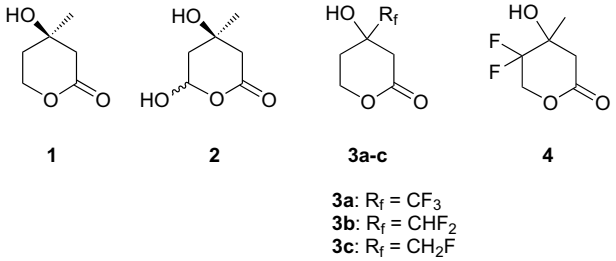

Figure 1. Structures of natural mevalonate **1**, mevaldate **2**, and known fluorinated analogues of mevalonates **3** and **4**.

Inhibition of isopentenyl pyrophosphate synthesis by fluoromevalonates leads to various biological effects. Hence it was shown that fluorinated mevalonates effectively block insect juvenile hormones synthesis.[3b,5] Monofluoromevalonate also shows anticancer activity, which is caused by p21^{ras} oncoprotein synthesis blocking.[6] Moreover, monofluoromevalonate was used in some investigations of biochemical and physiological processes, where mevalonic acid plays an important role.[7]

In spite of the fact that fluorocontaining mevalonates are interesting as biologically active compounds, there are only a few articles, which pay attention to the synthesis of these compounds.[3] Moreover, there is no information with regards to obtaining enantiomerically pure fluoromevalonates (except for single report on the detection of monofluoromevalonate **3c** enantiomers by resolution on analytical chiral GLC)[8] although a configuration of these molecules is probably important because only the (*R*)-enantiomer of mevalonate **1** is found in Nature.[9] Moreover, it was suggested that just one of the fluoromevalonate enantiomers takes part in mevalonate pathway inhibition.[4] At the same time fluorinated analogues of mevaldate are unknown, although it should be expected that they are regulators in the mevalonate pathway also, because mevaldate **2** is a precursor of mevalonic acid **1** in vivo.[10]

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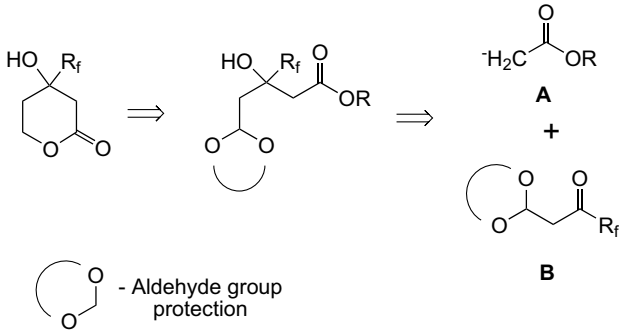
Herein, we report a new synthetic method for obtaining 6,6,6-tri- and 6,6-difluoromevalonates in both racemic and enantimerically pure forms. We also report the synthesis of racemic 6,6,6-tri- and 6,6-difluoromevaldates.

2. Results and discussion

The key step of our retrosynthetic scheme of fluoromevalonate synthesis (Scheme 1) is C–C bond formation between acetate enolate **A** and fluorinated β-ketoaldehyde derivative with protected aldehyde group **B**. The most available fluorinated β-ketoaldehyde derivatives with protected aldehyde group are β-alkoxyvinyl polyfluoromethyl ketones **5**, which are useful building blocks for fluoroorganic synthesis[11] and have been investigated in our laboratory for the synthesis of potential biologically active compounds.[12]



Scheme 1. Retrosynthetic scheme of fluoromevalonate synthesis.

The first reaction in the proposed scheme is C–C bond formation by the addition of *t*-butyl acetate enolate to carbonyl group of enone **5** to give product **6** (Scheme 2). The next step is a mild hydrolysis of the ethoxyvinyl group to give aldehyde **7**; the *t*-butoxycarbonyl group does not hydrolyze under these conditions. Aldehyde **7** can be easily reduced by sodium triacetoxy borohydride to give diol **8**. It should be mentioned that reduction by sodium borohydride, which is standard for similar transformations, gives a poor yield of compound **8**. The last stage of the synthesis of compounds **3** is the removal of the protective *t*-butoxy group with trifluoroacetic acid in dichloromethane. All intermediate compounds **6**–**8** can be purified by column chromatography at each stage, although the scheme proposed allows us to obtain fluoromevalonates **3a**,**b** without the isolation of intermediate products in 56–59% overall yield.

In order to carry out the first stage of fluoromevalonate synthesis in an asymmetric manner, we carried out aldol and Reformatsky[13] reactions with chiral previously synthesized CF_3-enones **5c**–**e** and ketoacetal **9**[14] (Fig. 2). However, the diastereoselectivity of the reactions was low and further attempts to separate diastereomers failed.

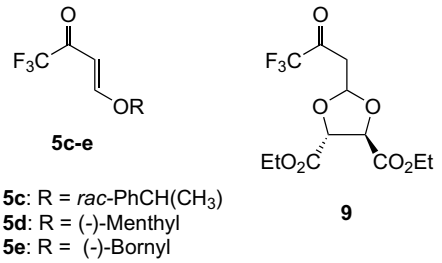


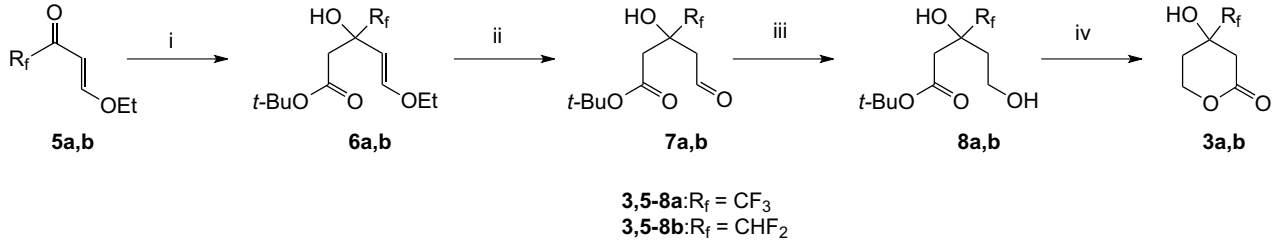
Figure 2. Chiral trifluoroacetyl acetaldehyde derivatives used in asymmetric aldol and Reformatsky reactions.

Enantiomerically pure fluoromevalonates were obtained by following enantiomer separation pathway (Scheme 3): the reaction of *rac*-fluoromevalonates **3a** and **3b** with (*S*)-(−)-1-phenylethylamine gave a mixture of diastereomeric amides **10a** and **10b**, easily separated by column chromatography, while further acidic hydrolysis of pure diastereomers (*S*,*S*)- and (*R*,*S*)-**10a**,**b** leads to the corresponding enantiomers (*S*)-**3a**,**b** and (*R*)-**3a**,**b**.

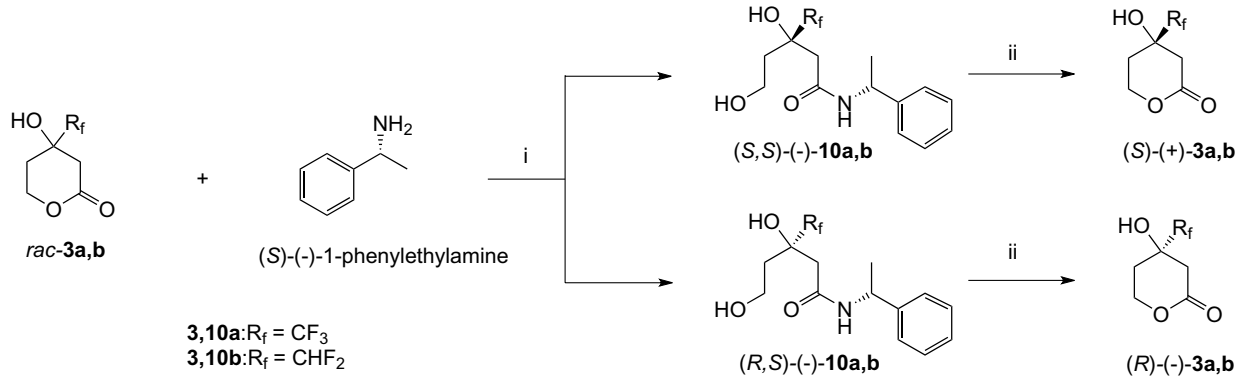
In order to determine the absolute configuration of the resolved enantiomers **3a** and **3b** the X-ray analysis of 6,6,6-trifluoromevalonate (−)-**3b** was performed and it was determined as the (*R*)-enantiomer (Fig. 3).[15] The same configuration corresponds to natural (−)-mevalonate **1** and it can be supposed that (−)-difluoromevalonate (−)-**3b** also has an (*R*)-configuration.

The enantiomeric purity of obtained mevalonates (*S*)- and (*R*)-**3a**,**b** was confirmed by HPLC-analysis of crude amides **11** obtained from fluoromevalonates *rac*-, (*S*)- and (*R*)-**3**, and (*S*)-(−)-ethylnaphtylamine at the same reaction conditions as written above for (*S*)-(−)-1-phenylethylamine (Fig. 4 illustrates HPLC-analysis for **11a**). According to these data practically 100% enantiomeric purity can be supposed for mevalonates (*S*)- and (*R*)-**3a**,**b**.

The synthetic pathway to fluoromevalonates **3** (Scheme 2) can also be used for synthesis of racemic tri- and



Scheme 2. Synthesis of fluorinated mevalonates **3**. Reagents and conditions: (i) LDA, *t*-BuOAc, THF, −78 °C, 79–81%; (ii) 5 M HCl, THF/H_2O, 0 °C, 56–61%; (iii) $NaBH(OAc)_3$, benzene, rt, 76–79%; (iv) CF_3COOH, CH_2Cl_2, rt, 74–81%.



Scheme 3. Fluoromevalonate enantiomers separation. Reagents and conditions: (i) (1) CH_2Cl_2, rt, 24 h, (2) chromatography separation (21–27% yield of each pure diastereomer); (ii) 5 M HCl, H_2O/CH_3CN, reflux, 30 min, 65–75%.

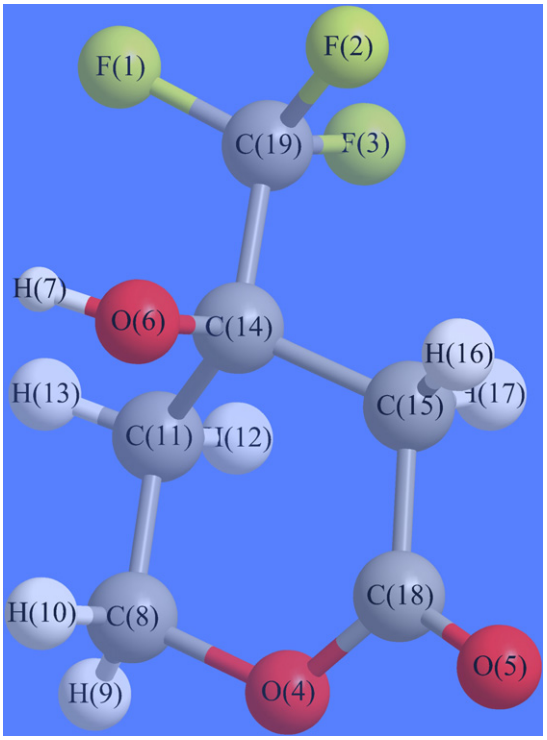


Figure 3. A general view of the X-ray crystallographic structure of compound (*R*)-(−)-**3a**.

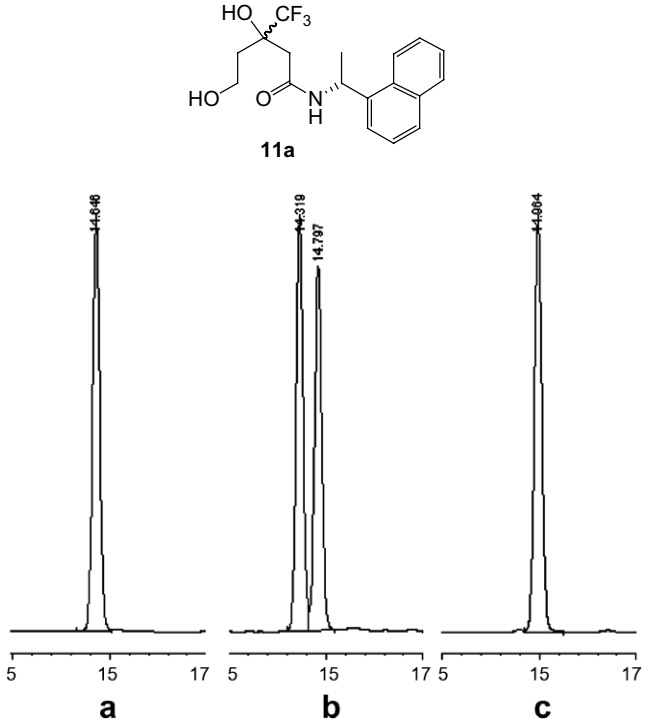
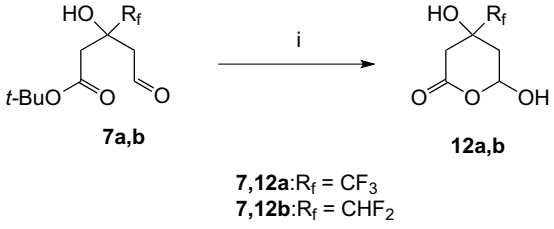


Figure 4. HPLC-analysis chromatograms of amides **11a** obtained from (a) *S*-(+)-**3a**; (b) racemic **3a**; (c) *R*-(−)-**3a**.

difluoromevaldic acids **12a** and **12b** (Scheme 4), which can be obtained from aldehydes **7a** and **7b** by treating with trifluoroacetic acid in good yield.

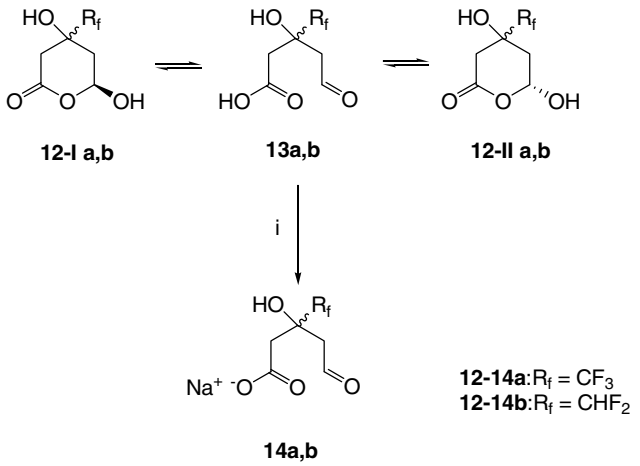
^1H and ^{19}F NMR spectra of obtained fluorinated *rac*-mevaldates **12a** and **12b** were complicated by an equilibrium (Scheme 5) between two diastereomeric lactolic forms **12-I** and **12-II** (whose signals are obviously overlapped, see Sections 4.4.1 and 4.4.3) and acyclic form **13** in various solvents. In order to avoid the equilibrium difficulties in the characterization of fluorinated *rac*-mevaldates **12a** and **12b** we prepared corresponding sodium salts **14a** and **14b** and the NMR-spectroscopic data demonstrate only the opened form **14**.



Scheme 4. Synthesis of fluorinated *rac*-mevaldates **12a** and **12b**. Reagents and conditions: (i) CF_3COOH, CH_2Cl_2, rt, 73–77%.

3. Conclusion

A new method for the synthesis of tri- and difluoromevalonates **3a** and **3b** and tri- and difluoromevaldates **12a** and



Scheme 5. The equilibrium of fluoromevaldates **12a** and **12b** in the solution and salts **14a** and **14b** obtaining. Reagents and conditions: (i) 1 equiv of NaOH, H_2O, rt, 61–64%.

12b starting from the corresponding alkoxy enones **5a** and **5b** has been developed. Enantiomerically pure fluoromevalonates were obtained by a three step method: preparation of diastereomeric (*S*)-(−)-1-phenylethylamides **10a** and **10b**, their chromatographic separation and hydrolysis. The absolute configuration of (*R*)-(−)-6,6,6-trifluoromevalonate (−)-**3a** was determined by X-ray analysis.

4. Experimental

4.1. General

IR spectra were recorded on 'Specord M-80'. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Varian VXR instrument at 300 MHz, Varian Unian Plus at 400 MHz and Bruker Avance DRX at 500 MHz. Chemical shifts were reported in parts per million (ppm). TMS and CCl_3F were used as internal standards for ^{1}H (^{13}C) and ^{19}F, respectively. The conversion of reactions was monitored by TLC-plates (silica gel 60 F_{254}, Merck). Column chromatography was carried out on silica gel 60 (Merck No. 109385, particle size 0.040–0.063). HPLC analysis was performed on Agilent 1100, Diode Array (DA) UV detector, wavelength −254 nm, column ZORBAX SB-C18 5 μm, 9.4 × 250 mm, mobile phase: CH_3CN/H_2O. Injection volume: 10 μL. Starting materials were commercially available (Aldrich, Fluka, Merck). All solvents and liquid reagents were distilled before use. Starting enones **5a**,[11a] **5b**,[11c] chiral enones **5c**–**e**,[14] and ketoacetal **9**[14] were prepared according to literature procedures.

4.2. Synthesis of racemic fluoromevalonates

4.2.1. *tert*-Butyl (*E*)-5-ethoxy-3-hydroxy-3-(trifluoromethyl)-4-pentenoate 6a. A 1.6 M solution of *n*-butyllithium in hexane (0.81 mL) was added dropwise via syringe to a stirred solution of diisopropylamine (0.14 g, 1.4 mmol) in 5 mL of THF at −78 °C under argon. After 15 min the solution of *tert*-butyl acetate (0.20 g, 1.72 mmol) in 2 mL of THF was added and the mixture obtained was stirred at −78 °C for 15 min. The solution of enone **5a** (0.2 g, 1.2 mmol) in 2 mL of THF was then added. After 30 min of stirring at −78 °C, the mixture obtained was warmed to room temperature and was stirred for 2 h. The solution was quenched with brine, the THF phase was separated and the water phase was extracted with ether (3 × 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$. The solvents were removed under vacuum and the residue was purified by flash chromatography (hexane/ethyl acetate, 5:1, $R_f = 0.62$) giving 0.27 g of the resulting product **6a** as a colorless oil (81% yield). ^{1}H NMR ($CDCl_3$): δ_H 1.28 t (3H, CH_2CH_3, $J_{HH} = 7.0$ Hz), 1.46 s (9H, $C(CH_3)_3$), 2.55 d (1H, $CHHCO_2Bu$-*t*, $J_{HH} = 15.4$ Hz), 2.71 d (1H, $CHHCO_2Bu$-*t*, $J_{HH} = 15.4$ Hz), 3.77 q (2H, CH_2CH_3, $J_{HH} = 7.0$ Hz), 4.75 d (1H, C–C*H*=, $J_{HH} = 12.6$ Hz), 5.09 s (1H, O*H*), 6.75 d (1H, =C*H*–O, $J_{HH} = 12.6$ Hz). ^{13}C NMR ($CDCl_3$): δ_C 14.6 (CH_2CH_3), 27.9 ($C(CH_3)_3$), 39.7 (CH_2CO_2Bu-*t*), 65.4 (CH_2CH_3), 73.3 q (*C*–CF_3, $J_{CF} = 29.8$ Hz), 83.1 ($C(CH_3)_3$), 99.7 (C–*C*H=), 124.8 q (CF_3, $J_{CF} = 285.3$ Hz), 151.3 (=*C*H–O), 170.8 (CO_2Bu-*t*). ^{19}F NMR ($CDCl_3$): δ_F −82.87 s (CF_3). IR (CCl_4, cm^{-1}): *v* 3408, 2984, 2936, 1712, 1680, 1656, 1456, 1422, 1392, 1352, 1312, 1164, 1077, 1032. Anal. Calcd for $C_{12}H_{19}F_3O_4$: C, 50.70; H, 6.74. Found: C, 50.59; H, 6.79.

4.2.2. *tert*-Butyl (*E*)-3-(difluoromethyl)-5-ethoxy-3-hydroxy-4-pentenoate 6b. This was synthesized by similar methodology as **6a** from *tert*-butyl acetate (0.20 g, 1.72 mmol) and enone **5b** (0.18 g, 1.2 mmol) giving 0.25 g of **6b** (79% yield) as a colorless oil, $R_f = 0.55$ (hexane/ethyl acetate, 5:1). ^{1}H NMR ($CDCl_3$): δ_H 1.27 t (3H, CH_2CH_3, $J_{HH} = 7.1$ Hz), 1.45 s (9H, $C(CH_3)_3$), 2.46 d (1H, $CHHCO_2Bu$-*t*, $J_{HH} = 15.4$ Hz), 2.62 d (1H, $CHHCO_2Bu$-*t*, $J_{HH} = 15.4$ Hz), 3.74 q (2H, CH_2CH_3, $J_{HH} = 7.0$ Hz), 4.60 s (1H, O*H*), 4.72 d (1H, C–C*H*=, $J_{HH} = 12.6$ Hz), 5.50 dd (1H, CHF_2, $J_{HF} = 57.3$, 55.6 Hz), 6.65 d (1H, =C*H*–O, $J_{HH} = 12.6$ Hz). ^{13}C NMR ($CDCl_3$): δ_C 14.6 (CH_2CH_3), 28.0 ($C(CH_3)_3$), 38.8 (CH_2CO_2Bu-*t*), 65.2 (CH_2CH_3), 72.7 dd (*C*–CHF_2, $J_{CF} = 22.8$, 22.2 Hz), 82.4 ($C(CH_3)_3$), 101.3 (C–*C*H=), 116.4 dd (CHF_2, $J_{CF} = 252.6$, 247.5 Hz), 150.3 (CH=*C*HOEt), 171.3 (CO_2Bu-*t*). ^{19}F NMR ($CDCl_3$): δ_F −131.88 dd (1F, CH*F*F, $J_{FF} = 276.6$, $J_{HF} = 55.6$ Hz), −129.74 dd (1F, CHF*F*, $J_{FF} = 276.6$, $J_{HF} = 57.3$ Hz). IR (CH_2Cl_2, cm^{-1}): *v* 3446, 3060, 2984, 2933, 1705, 1672, 1656, 1454, 1416, 1392, 1368, 1248, 1224, 1200, 1155, 1064, 952. Anal. Calcd for $C_{12}H_{20}F_2O_4$: C, 54.13; H, 7.57. Found: C, 54.21; H, 7.48.

4.2.3. *tert*-Butyl 3-hydroxy-5-oxo-3-(trifluoromethyl)pentanoate 7a. An aqueous solution of hydrochloric acid (5 mL of 5 M) was added to a stirred solution of compound **6a** (0.60 g, 2.11 mmol) in 15 mL of acetonitrile at 0 °C. The mixture obtained was left for 2 h at 0 °C. Then 20 mL of water was added and the mixture was extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with water (15 mL) and a saturated solution of $NaHCO_3$ (2 × 10 mL) after which it was dried with anhydrous $MgSO_4$. The solvents were removed in vacuum and the residue was purified by flash chromatography (hexane/ethyl acetate, 4:1, $R_f = 0.44$) giving 0.37 g of resulting product

as a colorless oil (56% yield). ^{1}H NMR ($CDCl_3$): δ_H 1.48 s (9H, C(CH_3)), 2.65 dd (1H, CHHCHO, J_{HH} = 15.9, 2.6 Hz), 2.66 d (1H, CHHCO$_2$Bu-*t*, J_{HH} = 16.1 Hz), 2.71 d (1H, CHHCO$_2$Bu-*t*, J_{HH} = 16.1 Hz), 2.87 dd (1H, CHHCHO, J_{HH} = 15.9, 2.0 Hz), 5.67 s (1H, OH), 9.86 m (1H, CH=O). ^{13}C NMR ($CDCl_3$): δ_C 27.9 (C(*C*H$_3$)$_3$), 37.5 (*C*H$_2$CO$_2$Bu-*t*), 46.7 (*C*H$_2$CHO), 73.3 q (*C*(OH)CF$_3$, J_{CF} = 29.5 Hz), 83.7 (*C*(CH$_3$)$_3$), 125.0 q (*C*F$_3$, J_{CF} = 285.0 Hz), 170.5 (*C*O$_2$*t*-Bu), 198.9 (*C*HO). ^{19}F NMR ($CDCl_3$): δ_F −82.14 s (CF$_3$). IR (CH_2Cl_2, cm^{-1}): *v* 3375, 3060, 2981, 1727, 1428, 1369, 1248, 1152, 1032. Anal. Calcd for $C_{10}H_{15}F_3O_4$: C, 46.88; H, 5.90. Found: C, 46.69; H, 5.93.

4.2.4. *tert*-Butyl 3-(difluoromethyl)-3-hydroxy-5-oxopentanoate 7b. This was synthesized by similar methodology as **7a** from compound **6b** (0.56 g, 2.11 mmol) giving 0.30 g of product **7b** as a colorless oil (61% yield), R_f = 0.34 (hexane/ethyl acetate, 4:1). ^{1}H NMR ($CDCl_3$): δ_H 1.47 s (9H, C(CH_3)), 2.58 d (1H, CHHCO$_2$Bu-*t*, J_{HH} = 16.1 Hz), 2.65 d (1H, CHHCO$_2$Bu-*t*, J_{HH} = 16.1 Hz), 2.67 d (1H, CHHCHO, J_{HH} = 16.2 Hz), 2.79 d (1H, CHHCHO, J_{HH} = 16.2 Hz), 4.86 s (1H, OH), 5.82 t (CHF$_2$, J_{HF} = 56.0 Hz), 9.84 s (1H, CH=O). ^{13}C NMR: δ_C 27.9 (C(*C*H$_3$)$_3$), 38.1 t (*C*H$_2$CO$_2$Bu-*t*, J_{CF} = 2.4 Hz), 46.7 t (*C*H$_2$CHO, J_{CF} = 1.8 Hz), 72.7 t (*C*–CHF$_2$, J_{CF} = 22.5 Hz), 83.0 (*C*(CH$_3$)$_3$), 115.9 t (*C*HF$_2$, J_{CF} = 249.0 Hz), 170.8 (*C*O$_2$Bu-*t*), 199.8 (*C*HO). ^{19}F NMR: δ_F −131.98 dd (1F, CH*F*F, J_{FF} = 284.3, J_{HF} = 56.0 Hz), −130.94 dd (1F, CHF*F*, J_{FF} = 284.3, J_{HF} = 56.0 Hz). IR (CH_2Cl_2, cm^{-1}): *v* 3568, 3440, 3060, 2982, 2936, 1725, 1426, 1368, 1248, 1155, 1074, 975. Anal. Calcd for $C_{10}H_{16}F_2O_4$: C, 50.42; H, 6.77. Found: C, 50.58; H, 6.68.

4.2.5. *tert*-Butyl 3,5-dihydroxy-3-(trifluoromethyl)pentanoate 8a. Acetic acid (0.44 g, 7.33 mmol) was added dropwise to stirring suspension of 0.09 g $NaBH_4$ (2.37 mmol) in 5 mL of benzene under argon. The mixture was refluxed for 1 h and then cooled to 0 °C. A solution of compound **7a** (0.24 g, 0.95 mmol) in 5 mL of benzene was added dropwise and the mixture obtained was stirred for 2 h at room temperature. Then 5 mL of water was carefully added dropwise. The organic layer was separated and water layer was extracted with ether (3 × 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$, the solvents were removed and the residue was purified by flash chromatography (hexane/ethyl acetate, 4:1, R_f = 0.27) giving 0.16 g of resulting product as a colorless oil (79% yield). ^{1}H NMR ($CDCl_3$): δ_H 1.48 s (9H, C(CH_3)), 1.82 ddd (1H, CHHCH$_2$OH, J_{HH} = 14.9, 6.3, 4.5 Hz), 2.12 ddd (1H, CHHCH$_2$OH, J_{HH} = 14.9, 7.2, 4.2 Hz), 2.47 br s (1H, CH$_2$OH), 2.58 d (1H, CHHCO$_2$Bu-*t*, J_{HH} = 16.1 Hz), 2.75 d (1H, CHHCO$_2$*t*Bu, J_{HH} = 16.1 Hz), 3.85–3.96 m (2H, CH_2OH), 5.80 s (1H, CF$_3$COH). ^{13}C NMR ($CDCl_3$): δ_C 27.9 (C(*C*H$_3$)$_3$), 35.6 (*C*H$_2$CH$_2$OH), 37.5 (*C*H$_2$CO$_2$Bu-*t*), 58.1 (*C*H$_2$OH), 74.5 q (*C*–CF$_3$, J_{CF} = 28.5 Hz), 83.2 (*C*(CH$_3$)$_3$), 125.7 q (*C*F$_3$, J_{CF} = 286.1 Hz), 171.3 (*C*O$_2$Bu-*t*). ^{19}F NMR ($CDCl_3$): δ_F −81.81 s (CF$_3$). IR (CH_2Cl_2, cm^{-1}): *v* 3614, 3384, 3060, 2978, 2940, 1705, 1456, 1428, 1372, 1320, 1248, 1184, 1078, 1040. Anal. Calcd for $C_{10}H_{17}F_3O_4$: C, 46.51; H, 6.64. Found: C, 46.70; H, 6.60.

4.2.6. *tert*-Butyl 3-(difluoromethyl)-3,5-dihydroxypentanoate 8b. This was synthesized by a similar methodology as **8a** from compound **7b** (0.2 g, 0.83 mmol) giving 0.15 g of product **8b** as a colorless oil (76% yield), R_f = 0.34 (hexane/ethyl acetate, 4:1). ^{1}H NMR ($CDCl_3$): δ_H 1.47 s (9H, C(CH_3)), 1.76 ddd (1H, CHHCH$_2$OH, J_{HH} = 15.0, 5.9, 4.7 Hz), 1.96 ddd (1H, CHHCH$_2$OH, J_{HH} = 15.0, 6.3, 4.8 Hz), 2.56 d (1H, CHHCO$_2$Bu-*t*, J_{HH} = 16.5 Hz), 2.59 d (1H, CHHCO$_2$*t*Bu, J_{HH} = 16.5 Hz), 2.99 br s (1H, CH$_2$OH), 3.84–3.92 m (2H, CH_2OH), 5.18 s (1H, CHF$_2$COH), 5.77 t (1H, CHF$_2$, J_{HF} = 56.0 Hz). ^{13}C NMR ($CDCl_3$): δ_C 27.9 (C(*C*H$_3$)$_3$), 35.9 (*C*H$_2$CH$_2$OH), 37.6 (*C*H$_2$CO$_2$Bu-*t*), 58.2 (*C*H$_2$OH), 73.8 t (*C*–CHF$_2$, J_{CF} = 21.4 Hz), 82.6 (*C*(CH$_3$)$_3$), 116.7 t (*C*HF$_2$, J_{CF} = 248.1 Hz), 171.6 (*C*O$_2$Bu-*t*). ^{19}F NMR ($CDCl_3$): δ_F −133.00 dd (1F, CH*F*F, J_{FF} = 282.0, J_{HF} = 56.0 Hz), −131.66 dd (1F, CHF*F*, J_{FF} = 282.0, J_{HF} = 56.0 Hz). IR (CH_2Cl_2, cm^{-1}): *v* 3673, 3606, 3448, 3060, 2981, 2936, 1702, 1480, 1426, 1367, 1244, 1155, 1077, 952. Anal. Calcd for $C_{10}H_{18}F_2O_4$: C, 49.99; H, 7.55. Found: C, 49.87; H, 7.56.

4.2.7. Tetrahydro-4-hydroxy-4-(trifluoromethyl)-2*H*-pyran-2-one 3a. Trifluoroacetic acid (1 mL) was added to a solution of compound **8a** (0.50 g, 1.94 mmol) in 10 mL of CH_2Cl_2. The mixture was stirred at room temperature and after 2 h the solvents were evaporated in vacuum and the residue was purified by column chromatography (hexane/ethyl acetate, 2:1, R_f = 0.28) giving 0.29 g of the resulting product as a colorless oil (81% yield). ^{1}H NMR ($CDCl_3$): δ_H 2.06 ddd (1H, CHHCH$_2$O, J_{HH} = 14.7, 4.2, 3.9 Hz), 2.20 ddd (1H, CHHCH$_2$O, J_{HH} = 14.7, 10.7, 5.1 Hz), 2.80 s (2H, CH_2CO$_2$), 4.15 br s (1H, OH), 4.44 ddd (1H, CHHO, J_{HH} = 11.5, 5.1, 4.2 Hz), 4.60 ddd (1H, CHHO, J_{HH} = 11.5, 10.7, 3.9 Hz). ^{13}C NMR ($CDCl_3$): δ_C 28.5 (*C*H$_2$CH$_2$O), 36.8 (*C*H$_2$CO$_2$), 64.8 (*C*H$_2$O), 71.3 q (*C*–CF$_3$, J_{CF} = 31.0 Hz), 124.8 q (*C*F$_3$, J_{CF} = 284 Hz), 168.9 (*C*O$_2$). ^{19}F NMR ($CDCl_3$): δ_F −84.84 s (CF$_3$). IR (CH_2Cl_2, cm^{-1}): *v* 3672, 3564, 3400, 3060, 2984, 2928, 1750, 1480, 1402, 1304, 1228, 1184, 1016, 1000. Anal. Calcd for $C_6H_7F_3O_3$: C, 39.14; H, 3.83. Found: C, 39.01; H, 3.77.

4.2.8. Tetrahydro-4-(difluoromethyl)-4-hydroxy-2*H*-pyran-2-one 3b. This was synthesized by a similar methodology as **3a** from compound **8b** (0.2 g, 0.84 mmol) giving 0.10 g of the resulting product as a colorless oil (74% yield), R_f = 0.54 (CH_2Cl_2/ethyl acetate, 2:1). ^{1}H NMR ($CDCl_3$): δ_H 1.90 ddd (1H, CHHCH$_2$O, J_{HH} = 14.5, 4.5, 3.7 Hz), 2.09 ddd (1H, CHHCH$_2$O, J_{HH} = 14.5, 10.4, 5.1 Hz), 2.64 d (1H, CHHCO$_2$, J_{HH} = 17.5 Hz), 2.72 d (1H, CHHCO$_2$, J_{HH} = 17.5 Hz), 4.00 br s (1H, OH), 4.38 ddd (1H, CHHO, J_{HH} = 11.5, 5.1, 4.5 Hz), 4.66 ddd (1H, CHHO, J_{HH} = 11.5, 10.4, 3.7 Hz), 5.63 t (1H, CHF$_2$, J_{HF} = 56.0 Hz). ^{13}C NMR ($CDCl_3$): δ_C 28.4 (*C*H$_2$CH$_2$O), 36.3 (*C*H$_2$CO$_2$), 65.1 (*C*H$_2$O), 70.7 t (*C*–CHF$_2$, J_{CF} = 22.9 Hz), 115.9 t (*C*HF$_2$, J_{CF} = 248.7 Hz), 170.3 (*C*O$_2$). ^{19}F NMR ($CDCl_3$): δ_F −133.82 dd (1F, CH*F*F, J_{FF} = 284.4, J_{HF} = 56.0 Hz), −132.91 dd (1F, CHF*F*, J_{FF} = 284.4, J_{HF} = 56.0 Hz). IR (CH_2Cl_2, cm^{-1}): *v* 3664, 3572, 3400, 3060, 2981, 2923, 1744, 1560, 1480, 1402, 1368, 1310, 1229, 1168, 11156, 1080, 1008, 981. Anal. Calcd for $C_6H_8F_2O_3$: C, 43.38; H, 4.85. Found: C, 43.30; H, 4.88.

4.3. Preparation of optically active 6,6,6-tri- and 6,6-difluoromevalonates

4.3.1. Typical procedure of the reaction of fluoromevalonates 3a and 3b with (*S*)-1-phenylethylamine and (1*S*)-1-(1-naphthyl)ethylamine. A solution of either compound **3a** (0.25 g, 1.36 mmol) or **3b** (0.23 g, 1.36 mmol) and (1*S*)-1-phenylethylamine (0.165 g, 1.36 mmol) in CH_2Cl_2 was kept for 48 h at room temperature. The solvent was evaporated in vacuum and diastereomeric amides (*S*)-**10a**,**b** and (*R*)-**10a**,**b** were separated and purified by column chromatography (for **10a**: hexane/ethyl acetate, 2:1, for **10b**: CH_2Cl_2/ethyl acetate, 2:1). A similar procedure was used for the preparation of analytical samples of (1*S*)-1-(1-naphthyl)ethylamides **11a** and **11b**, which was used for HPLC control of the enantiomeric purity of fluoromevalonates **3a** and **3b**.

4.3.2. (3*S*)-3,5-Dihydroxy-*N*-[(1*S*)-1-phenylethyl]-3-(trifluoromethyl)pentanamide (*S*,*S*)-10a. The yield of the product was 0.11 g (27%) as a colorless oil, $R_f = 0.39$ (hexane/ethyl acetate, 2:1), $[\alpha]_D^{25} = -39.4$ (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ_H 1.52 d (3H, C*H*$_3$, $J_{HH} = 6.9$ Hz), 1.82 ddd (1H, C*H*HCH$_2$O, $J_{HH} = 15.0$, 7.1, 3.8 Hz), 2.08 ddd (1H, CH*H*CH$_2$O, $J_{HH} = 15.0$, 7.1, 3.9 Hz), 2.43 d (1H, C*H*HC=O, $J_{HH} = 15.0$ Hz), 2.47 m (1H, CH$_2$I*H*), 2.68 d (1H, CH*H*C=O, $J_{HH} = 15.0$ Hz), 3.90 m (2H, C*H*$_2$IH), 5.13 m (1H, CH$_3$C*H*), 6.16 d (1H, N*H*, $J_{HH} = 6.4$ Hz), 6.66 s (1H, I*H*), 7.28–7.40 m (5H, Ph). ^{13}C NMR ($CDCl_3$): δ_C 21.4 (*C*H$_3$), 35.4 (*C*H$_2$), 38.0 (*C*H$_2$), 49.2 (*C*H$_2$IH), 58.2 (*C*H), 75.1 q (*C*–CF$_3$, $J_{CF} = 28.1$ Hz), 125.8 q (*C*F$_3$, $J_{CF} = 288.0$ Hz), 126.2 (Ph), 127.7 (Ph), 128.8 (Ph), 142.3 (Ph), 170.0 (*C*=O). ^{19}F NMR ($CDCl_3$): δ_F −82.23 s (CF$_3$). IR (CH_2Cl_2, cm^{-1}): *v* 3425, 3304, 3060, 2975, 2321, 1653, 1524, 1496, 1451, 1374, 1323, 1240, 1175, 1136, 1075, 1018, 916. Anal. Calcd for $C_{14}H_{18}F_3NO_3$: C, 55.08; H, 5.94; N, 4.59. Found: C, 55.34; H, 5.89; N, 4.45.

4.3.3. (3*R*)-3,5-Dihydroxy-*N*-[(1*S*)-1-phenylethyl]-3-(trifluoromethyl)pentanamide (*R*,*S*)-10a. The yield of the product was 0.10 g (24%) as a colorless oil, $R_f = 0.33$ (hexane/ethyl acetate, 2:1), $[\alpha]_D^{25} = -54.0$ (*c* 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ_H 1.51 d (3H, C*H*$_3$, $J_{HH} = 7.0$ Hz), 1.77–1.86 m (1H, C*H*HCH$_2$O), 2.05 ddd (1H, CH*H*CH$_2$O, $J_{HH} =$ 14.9, 6.5, 3.4 Hz), 2.48 d (1H, C*H*HC=O, $J_{HH} = 15.0$ Hz), 2.67 d (1H, CH*H*C=O, $J_{HH} = 15.0$ Hz), 2.47 br s (1H, CH$_2$I*H*), 3.89 m (2H, C*H*$_2$IH), 5.13 m (1H, CH$_3$C*H*), 6.35 d (1H, N*H*, $J_{HH} = 6.1$ Hz), 6.52 br s (1H, I*H*), 7.27–7.40 m (5H, Ph). ^{13}C NMR ($CDCl_3$): δ_C 21.5 (*C*H$_3$), 35.5 (*C*H$_2$), 38.5 (*C*H$_2$), 49.1 (*C*H$_2$IH), 58.4 (*C*H), 75.1 q (*C*–CF$_3$, $J_{CF} = 27.7$ Hz), 125.7 q (*C*F$_3$, $J_{CF} = 286.2$ Hz), 126.1 (Ph), 127.6 (Ph), 128.7 (Ph), 142.4 (Ph), 169.7 (*C*=O). ^{19}F NMR ($CDCl_3$): δ_F −82.17 s (CF$_3$). IR (CH_2Cl_2, cm^{-1}): *v* 3424, 3320, 3060, 2976, 2336, 1654, 1525, 1496, 1448, 1375, 1177, 1136, 1077, 1024, 922. Anal. Calcd for $C_{14}H_{18}F_3NO_3$: C, 55.08; H, 5.94; N, 4.59. Found: C, 55.37; H, 5.90; N, 4.49.

4.3.4. (3*S*)-3-(Difluoromethyl)-3,5-dihydroxy-*N*-((1*S*)-1-phenylethyl)pentanamide (*S*,*S*)-10b. The yield of the product was 0.11 g (29%) as a colorless oil. $R_f = 0.45$ (CH_2Cl_2/ethyl acetate, 2:1), $[\alpha]_D^{25} = -33.2$ (*c* 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ_H 1.48 d (3H, C*H*$_3$, $J_{HH} = 7.1$ Hz), 1.72 dt (1H, C*H*HCH$_2$O, $J_{HH} = 15.3$, 5.4 Hz), 1.91 dt (1H, CH*H*CH$_2$O, $J_{HH} = 15.3$, 5.4 Hz), 2.42 d (1H, C*H*HC=O, $J_{HH} = 15.1$ Hz), 2.50 d (1H, CH*H*C=O, $J_{HH} = 15.1$ Hz), 2.96 br s (1H, CH$_2$I*H*), 3.84 t (2H, C*H*$_2$IH, $J_{HH} = 5.4$ Hz), 5.08 m (1H, CH$_3$C*H*), 5.72 t (1H, C*H*F$_2$, $J_{HF} = 55.6$ Hz), 6.06 s (1H, I*H*), 6.51 d (1H, N*H*, $J_{HH} = 7.0$ Hz), 7.25–7.36 m (5H, Ph). ^{13}C NMR ($CDCl_3$): δ_C 21.5 (*C*H$_3$), 35.6 (*C*H$_2$), 37.8 (*C*H$_2$), 49.1 (*C*H$_2$IH), 58.3 (*C*H), 74.2 t (*C*–CHF$_2$, $J_{CF} = 20.3$ Hz), 116.9 t (*C*HF$_2$, $J_{CF} = 249.1$ Hz), 126.1 (Ph), 127.6 (Ph), 128.8 (Ph), 142.5 (Ph), 170.6 (*C*=O). ^{19}F NMR ($CDCl_3$): δ_F −131.97 dd (1F, CH*F*F, $J_{FF} = 240.8$, $J_{HF} = 55.6$ Hz), −131.27 dd (1F, CHF*F*, $J_{FF} = 240.8$, $J_{HF} = 55.6$ Hz). IR (CH_2Cl_2, cm^{-1}): *v* 3427, 3338, 3060, 3033, 2974, 2933, 1649, 1524, 1496, 1449, 1376, 1224, 1067. Anal. Calcd for $C_{14}H_{19}F_2NO_3$: C, 58.53; H, 6.67; N, 4.88. Found: C, 58.67; H, 6.73; N, 4.81.

4.3.5. (3*R*)-3-(Difluoromethyl)-3,5-dihydroxy-*N*-((1*S*)-1-phenylethyl)pentanamide (*R*,*S*)-10b. The yield of the product was 0.08 g (21%) as a colorless oil. $R_f = 0.42$ (CH_2Cl_2/ethyl acetate, 2:1), $[\alpha]_D^{25} = -45.5$ (*c* 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ_H 1.45 d (3H, C*H*$_3$, $J_{HH} = 7.1$ Hz), 1.72 dt (1H, C*H*HCH$_2$O, $J_{HH} = 14.6$, 5.4 Hz), 1.88 dt (1H, CH*H*CH$_2$O, $J_{HH} = 14.6$, 5.8 Hz), 2.45 d (1H, C*H*HC=O, $J_{HH} = 15.1$ Hz), 2.50 d (1H, CH*H*C=O, $J_{HH} = 15.1$ Hz), 3.46 br s (1H, CH$_2$I*H*), 3.80 m (2H, C*H*$_2$IH), 5.05 m (1H, CH$_3$C*H*), 5.66 t (1H, C*H*F$_2$, $J_{HF} = 55.9$ Hz), 6.00 s (1H, I*H*), 7.03 d (1H, N*H*, $J_{HH} = 7.9$ Hz), 7.20–7.36 m (5H, Ph). ^{13}C NMR ($CDCl_3$): δ_C 21.7 (*C*H$_3$), 35.2 (*C*H$_2$), 38.1 (*C*H$_2$), 49.0 (*C*H$_2$IH), 58.2 (*C*H), 74.2 t (*C*–CHF$_2$, $J_{CF} = 21.5$ Hz), 116.7 t (*C*F$_3$, $J_{CF} = 249.3$ Hz), 126.1 (Ph), 127.5 (Ph), 128.7 (Ph), 142.7 (Ph), 170.6 (*C*=O). ^{19}F NMR ($CDCl_3$): δ_F −131.73 d (CH*F*$_2$, $J_{HF} = 55.9$ Hz). IR (CH_2Cl_2, cm^{-1}): *v* 3427, 3060, 3032, 2971, 2932, 1651, 1525, 1496, 1450, 1376, 1232, 1066. Anal. Calcd for $C_{14}H_{19}F_2NO_3$: C, 58.53; H, 6.67; N, 4.88. Found: C, 58.61; H, 6.66; N, 4.79.

4.3.6. Typical procedure of hydrolysis optically pure (*S*)-(−)-1-phenylethylamides 10a and 10b. A mixture of 5 mL of 4 M hydrochloric acid and the corresponding amide (**10a**: 0.10 g, 0.33 mmol, **10b**: 0.10 g, 0.35 mmol) in 5 mL of acetonitrile was refluxed for 30 min, cooled to room temperature, extracted with diethyl ether (3×10 mL) and the combined organic layers were dried over $MgSO_4$. The solvents were removed in vacuum and the residue was purified by column chromatography (**3a**: hexane/ethyl acetate, 2:1, $R_f = 0.28$, **3b**: hexane/ethyl acetate, 4:1, $R_f = 0.34$).

4.3.7. (4*S*)-4-Hydroxy-4-(trifluoromethyl)tetrahydro-2*H*-pyran-2-one (*S*)-3a. This was obtained from (*S*,*S*)-**10a**. Crystallized from a mixture of diethyl ether/hexane. The yield of the product is 0.045 g (75%). White needles. $[\alpha]_D^{25} = 18.7$ (*c* 1, $CHCl_3$). Mp 62–64 °C. For spectral data see Section 4.2.7.

4.3.8. (4*R*)-4-Hydroxy-4-(trifluoromethyl)tetrahydro-2*H*-pyran-2-one (*R*)-3a. This was obtained from (*R*,*S*)-**10a**. Crystallized from a mixture of diethyl ether/hexane. The yield of the product is 0.04 g (65%). White needles.

$[\alpha]_D^{25} = -17.0$ (c 0.8, $CHCl_3$). Mp 63–65 °C. For spectral data see Section 4.2.7.

4.3.9. (4*S*)-4-Tetrahydro-4-(difluoromethyl)-4-hydroxy-2*H*-pyran-2-one (*S*)-3b. This was obtained from (*S*,*S*)-**10b**. The yield of the product was 0.041 g (71%). Colorless oil. $[\alpha]_D^{25} = +12.2$ (c 0.8, $CHCl_3$). For spectral data see Section 4.2.8.

4.3.10. (4*R*)-4-Tetrahydro-4-(difluoromethyl)-4-hydroxy-2*H*-pyran-2-one (*R*)-3b. This was obtained from (*R*,*S*)-**10b**. The yield of the product is 0.035 g (65%). Colorless oil. $[\alpha]_D^{25} = -10.5$ (c 0.7, $CHCl_3$). For spectral data see Section 4.2.8.

4.4. Preparation of 6,6,6-trifluoromevaldate 12a and 6,6-difluoromevaldates 12b

4.4.1. 6,6,6-Trifluoromevaldate 12a. Trifluoroacetic acid (1 mL) was added to a solution of compound **7a** (0.50 g, 2.07 mmol) in 10 mL of CH_2Cl_2. The mixture was stirred at room temperature and after 2 h, the solvents were evaporated in vacuum and the residue purified by crystallization from benzene to give 0.30 g of the resulting product as a colorless powder (77% yield). Mp 123–124 °C. IR (KBr, cm^{-1}): ν 3429, 2992, 2944, 1684, 1472, 1448, 1384, 1337, 1308, 1257, 1209, 1176, 1120, 1048, 992, 964. Anal. Calcd for $C_6H_7F_3O_4$: C, 36.01; H, 3.53. Found: C, 36.14; H, 3.59. NMR-spectra contain signals of lactols **12-Ia** and **12-IIa** and acyclic form **13a** (the percentage of **13a** is near 30–40% in various solvents such as D_2O, DMSO-d_6, acetone-d_6, etc.).

4.4.1.1. 4,6-Dihydroxy-4-(trifluoromethyl)tetrahydro-2*H*-pyran-2-ones 12-Ia and 12-IIa. ^{1}H NMR (DMSO-d_6): δ_H 1.84–1.93 m (1H, C*H*HCHO$_2$), 2.14–2.38 m (1H, CH*H*CHO$_2$), 2.75–3.03 m (2H, CH_2CO$_2$), 5.58–5.71 m (1H, CH$_2$C*H*O), 6.69 br s (1H, O*H*), 7.76 br s (1H, I*H*); ^{19}F NMR (DMSO-d_6): δ_F −83.81 s (minor epimer CF_3), −83.72 s (major epimer CF_3).

4.4.1.2. 3-Hydroxy-5-oxo-3-(trifluoromethyl)pentanoic acid 13a. ^{1}H NMR (DMSO-d_6): 2.54–3.04 m (4H, CH_2CHI and CH_2CI$_2$H), 6.70 br s (1H, O*H*), 9.73 s (1H, C*H*O). ^{19}F NMR (DMSO-d_6): δ_F −81.73 s (CF_3).

4.4.2. Sodium 3-hydroxy-5-oxo-3-(trifluoromethyl)pentanoate 14a. A solution of 0.03 g (0.75 mmol) of NaOH in 2 mL of water was added to a solution of **12a** (0.2 g, 1.00 mmol) in 5 mL of water. After 15 min, a water solution was extracted with ethyl acetate (3 × 5 mL) to extract the excess of trifluoromevaldate. The water layer was evaporated and the residue was dried in vacuum giving 0.14 g of the resulting product **14a** as a colorless hydroscopic solid (61% yield). IR (KBr, cm^{-1}): ν 3472, 1723, 1591, 1401, 1288, 1176. ^{1}H NMR (DMSO-d_6): δ_H 2.22 s (2H, CH_2CI$_2$), 2.48 m (1 H, C*H*HCHO), 2.55 dd (1H, CH*H*CHO, $J_{HH} = 15.0$, 2.9 Hz), 9.70 m (1H, C*H*=O), 10.93 br s (1H, I*H*). ^{13}C NMR (DMSO-d_6): δ_C 38.2 (*C*H$_2$), 49.1 (*C*H$_2$), 72.4 q (*C*–CF$_3$, $J_{CF} = 27.6$ Hz), 126.9 q (*C*F$_3$, $J_{CF} = 287.5$ Hz), 173.0 (*C*I$_2$), 198.1 (*C*HI). ^{19}F NMR (DMSO-d_6): δ_F −81.24 s (CF_3). Anal. Calcd for $C_6H_6F_3NaO_4 \cdot 0.5H_2O$: C, 31.18, H, 3.05. Found: C, 31.25; H, 3.00.

4.4.3. 6,6-Difluoromevaldate 12b. This was synthesized by a similar methodology to **12a** from compound **7b** (0.5 g, 2.10 mmol) and 0.28 g of the resulting product **12b** was obtained as a colorless powder by crystallization from benzene (73% yield). Mp 84–86 °C. IR (KBr, cm^{-1}): ν 3448, 2992, 2940, 1684, 1416, 1386, 1368, 1288, 1266, 1208, 1176, 1131, 1082, 1048, 1016, 963, 904. Anal. Calcd for $C_6H_8F_2O_4$: C, 39.57; H, 4.43. Found: C, 39.68; H, 4.48. NMR-spectra contain signals of lactols **12-Ib** and **12-IIb** and acyclic form **13b** (the percentage of **13b** is near 30–40% in various solvents such as D_2O, DMSO-d_6, acetone-d_6, etc.).

4.4.3.1. 4-(Difluoromethyl)-4,6-dihydroxytetrahydro-2*H*-pyran-2-ones 12-Ib and 12-IIb. ^{1}H NMR (DMSO-d_6): δ_H 1.68–1.83 m (1H, C*H*HCHO$_2$), 1.95–2.08 m (1H, CH*H*CHO$_2$), 2.34–2.80 m (2H, CH_2CO$_2$), 5.47–6.20 m (3H, O*H*, C*H*F$_2$, CH$_2$C*H*O$_2$), 7.70 br s (1H, O*H*); ^{19}F NMR (DMSO-d_6): δ_F −132.91 dd (minor epimer, 1F, CH*F*F, $J_{FF} = 279.0$, $J_{HF} = 57.3$ Hz), −133.86 dd (minor epimer, 1F, CHF*F*, $J_{FF} = 279.0$, $J_{HF} = 57.3$ Hz), −134.06 dd (major epimer, 1F, CH*F*F, $J_{FF} = 281.4$, $J_{HF} = 57.3$ Hz), −134.72 dd (major epimer, 1F, CHF*F*, $J_{FF} = 281.4$, $J_{HF} = 57.3$ Hz).

4.4.3.2. 3-(Difluoromethyl)-3-hydroxy-5-oxopentanoic acid 13b. ^{1}H NMR (DMSO-d_6): 2.41–2.80 m (4H, CH_2CHI and CH_2CI$_2$H), 5.71–6.00 m (2H, C*H*F$_2$, O*H*), 9.73 s (1H, C*H*O). ^{19}F NMR (DMSO-d_6): δ_F −132.40 dd (1F, CH*F*F, $J_{FF} = 278.3$, $J_{HF} = 56.0$ Hz), −132.40 dd (1F, CHF*F*, $J_{FF} = 278.3$, $J_{HF} = 56.0$ Hz).

4.4.4. Sodium 3-(difluoromethyl)-3-hydroxy-5-oxopentanoate 14b. This was synthesized by a similar methodology as **14a** from compound **12b** (0.18 g, 1.00 mmol) and 0.13 g of the resulting product **14b** was obtained as a colorless hydroscopic solid (64% yield). IR (KBr, cm^{-1}): ν 3440, 1720, 1592, 1405, 1295, 1064. ^{1}H NMR (DMSO-d_6): δ_H 2.21–2.23 m (2H, CH_2CI$_2$), 2.39 d (1H, C*H*HCHO, $J_{HH} = 14.5$ Hz), 2.49 d (1H, CH*H*CHO, $J_{HH} = 14.5$. Hz), 5.81 t (1H, C*H*F$_2$, $J_{HF} = 56.0$ Hz), 9.72 s (1*H*, C*H*O). ^{13}C NMR (DMSO-d_6): δ_C 39.6 (*C*H$_2$), 48.1 (*C*H$_2$), 72.4 t (*C*–CHF$_2$, $J_{CF} = 20.9$ Hz), 117.8 t (*C*HF$_2$, $J_{CF} = 247.5$ Hz), 174.2 (*C*I$_2$), 198.3 (*C*HI). ^{19}F NMR (DMSO-d_6): δ_F −129.27 dd (1F, CH*F*F, $J_{FF} = 278.3$, $J_{HF} = 56.0$ Hz), −132.18 dd (1F, CHF*F*, $J_{FF} = 278.3$, $J_{HF} = 56.0$ Hz). Anal. Calcd for $C_6H_7F_2NaO_4 \cdot 0.5H_2O$: C, 33.82; H, 3.78. Found: C, 33.70; H 3.85.

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15. Crystallographic data (excluding structure factors) for (*R*)-(−)-**3a** has been deposited with the Cambridge Crystallographic Data Centre as supplementary number CCDC-651852. CCDC-651852 contains the supplementary crystallographic data for this paper. Copies of the data can be obtained, free of charge, on application to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK fax: (+44)-1223-336-033 or e-mail: deposit@ccdc.cam.ac.uk.