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Novel and enantioselective syntheses of (*R*)- and (*S*)-3-hydroxy-4-(2,4,5-trifluorophenyl)butanoic acid: a synthon for sitagliptin and its derivatives

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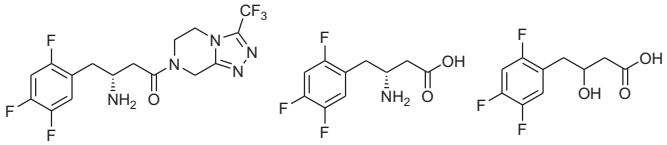
ABSTRACT

A new synthetic strategy for (*R*)- and (*S*)-3-hydroxy-4-(2,4,5-trifluorophenyl)butanoic acid, a building block in the preparation of sitagliptin and its derivatives, was developed. $Pd(OAc)_2$ catalyzed coupling of 2,4,5-trifluoro-1-iodobenzene with allyl alcohol gave 3-(2,4,5-trifluorophenyl)propanal in a yield of 95%. L-Proline catalyzed reaction of the 3-phenylpropanal (in only 1.2 molar equiv) with nitrosobenzene followed by reduction with $NaBH_4$ and Pd/C catalyzed hydrogenation gave (*R*)-3-(2,4,5-trifluorophenyl) propane-1,2-diol with >99% ee and 65% yield. Selective tosylation of primary hydroxyl group of the 1,2-propandiol unit followed by cyanide displacement afforded (*R*)-3-hydroxy-4-(2,4,5-trifluorophenyl)butanenitrile (80%). The nitrile was converted to the title β-hydroxy acid under basic hydrolysis in a yield of 90%. Thus, (*R*)-3-hydroxy-4-(2,4,5-trifluorophenyl)butanoic acid was prepared enantioselectively from the starting material in four steps and 45% overall yield. The reaction sequence was repeated with D-proline as the catalyst to give (*S*)-3-hydroxy-4-(2,4,5-trifluorophenyl)butanoic acid in 45% overall yield and >99% enantiomeric excess.

1. Introduction

Sitagliptin (**1**), a β-amino acid, has been reported to be a potent, competitive, reversible inhibitor of the dipeptidyl peptidase IV (DPP-IV) enzyme, which offers a new mechanism in achieving glycemic control.[1,2] Sitagliptin is constituted from β-amino acid and triazolopyrazine units. Several synthetic methods for the preparation of sitagliptin have been developed by the coupling of β-amino acid **2** with 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]tri-azolo [4,3-*a*]pyrazine units to give **1**. Therefore, syntheses of sitagliptin (**1**) are mainly differentiated from each other by the preparation of β-amino acid **2**, its corresponding ester, or *N*-protected derivatives. The main challenge in this area is to enantioselectively prepare the stereocenter present in the β-amino acid unit.[3]



1 Sitagliptin

2 *(R)*

3a ; ····OH *(R)*
3b ; —OH *(S)*

β-Hydroxy acid **3b** has been used as a key compound in the preparation of β-amino-acid **2**. The use of β-hydroxy acid **3b** in the synthesis of sitagliptin (**1**) was first reported by Merck.[4] The key step of their synthesis is to use (*S*)-$BinapRuCl_2$ to catalyze the asymmetric hydrogenation of the ketone in methyl 4-(2,4,5-trifluorophenyl)-3-oxo-butanoate. Niddam-Hildesheim has recently described an enzymatic method for the preparation of β-hydroxy-acid **2** from the same ketone derivative.[5] Most recently, Kim et al. have also prepared compound **3b** by the arylation of (*S*)-epichlorohydrin with 2,4,5-trifluorophenylmagnesium bromide via a ring opening followed by simple functional group manipulations.[6]

Besides the importance of β-hydroxy acid **3b** in the preparation of β-amino acid **2**, **3b** alone had DPP-IV activity. Zhu et al. have found that imidazopyrazinone derivatives of β-hydroxy acid **3b** also exhibit DPP-IV inhibitory effects.[7] Meanwhile Kong and Liu have also reported that benzopyranyl esters of β-hydroxy acid **3b** have potential as insulin sensitizers in the treatment of diabetes.[8]

In this paper we describe a novel, straightforward and efficient synthesis of both the *R* and *S* enantiomeric forms of β-hydroxy acid **3**, a building block in the preparation of antidiabetic drugs.

2. Results and discussion

Our synthesis started from 2,4,5-trifluoro-1-iodobenzene (**4**). In a recent paper, $Pd(OAc)_2$ catalyzed Heck reaction of 4-fluoro-phenyl iodide with allyl alcohol was reported to give 3-(4-fluorophenyl)

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propanal in good yield.[9] A slight modification of this procedure, compound **4** was reacted with allyl alcohol to give 3-(2,4,5-trifluorophenyl)propanal (**5**) in a yield of 95%. Many recent syntheses incorporated the proline catalyzed enantioselective α-aminoxylation of aldehydes and ketones using nitrosobenzene as the oxygen source.[10] In this reaction, a chiral enamine intermediate is formed followed by reaction with nitrosobenzene to form the corresponding oxyamine enantioselectively.

One of the elegant applications of this method was performed by Talluri and Sudalai[11] in the total synthesis of (*R*)-selegiline using 3-phenylpropanal. In this method, L-proline catalyzed oxyamination of 3-phenylpropanal followed by the reduction of the carbonyl group with $NaBH_4$. Reduction of the O–N bond by Pd/C catalyzed hydrogenation gave (*R*)-3-phenyl-1,2-propandiol.

Employing this method to prepare β-hydroxy acid **3** however, gave suboptimal results. The same reaction conditions were applied to propanal **5**, but only a 30–40% yield of oxyamine **6a** was obtained. Modifying the amounts of L-proline, nitrosobenzene, and aldehyde **5** systematically did not improve the reaction yield nor did extended reaction times.

After these observations, we thought that a minimal amount of water might be crucial for the catalytic cycle of L-proline. The role of H_2O in the proline catalyzed reactions was also reported in previous papers.[12] When we repeated the reaction in wet DMSO (DMSO/H_2O, 97:3), we found that the yield slightly increased. As suggested in previous oxyamination studies,[10] we also screened other solvent systems, such as CH_2Cl_2, $CHCl_3$, and CH_3CN, but no enhancement in yield was achieved. We also observed that the oxyamine **6a** was not very stable on silica gel or standing in the refrigerator. Therefore, the quick filtration of crude oxyamine **6a** through a pad of silica gel with EtOAc and direct reduction of the O–N bond improved the overall yield to 65% from **5**. We also tried to reduce the amount of aldehyde needed as previously described methods require at least 3 equiv of aldehyde. We found that using only 1.2 equiv of aldehyde were enough to achieve the optimal conditions. Furthermore, the use of $CHCl_3$ in the catalytic hydrogenation as a dry HCl producer improved the formation of diol **7a** as a clean product.

We continued our efforts to improve the yield, so we changed the oxyamination reagent to the readily available *p*-nitronitrosobenzene, which is more electrophilic due to its electron poor character. Unfortunately the oxyamination of **5** was repeated with *p*-nitronitrosobenzene in our already established conditions, and it resulted in a lower yield than that achieved with nitrosobenzene.

With **7a** in hand, the primary tosylate was formed selectively at 0 °C, and subsequently displaced with NaCN in DMF to give butanenitrile **9a** in 65% yield. Hydrogen peroxide catalyzed hydrolysis of the nitrile **9a** with aqueous NaOH gave β-hydroxy acid **3a**. The specific optical rotation of the obtained acid **3a** ($[\alpha]_D^{26}$ −8.00) was different from that of **3b** ($[\alpha]_D^{26}$ +16.3), which is well defined in the literature.[4] In order to determine the enantiopurity of carboxylic acid **3a**, we converted **3a** to its ethyl ester **10a** and ran a chiral HPLC analysis, which showed an enantiomeric purity of >99% (Scheme 1).

Applying the same sequence to propanal **5** using D-proline as a catalyst, we successfully obtained diol (*R*)-**7b**, cyanide (*R*)-**9b**, and carboxylic acid (*R*)-**3b**. Interestingly, the specific optical rotation of (*R*)-**3b** was also lower than those reported in the literature: ($[\alpha]_D^{26}$ +9.0). Chiral HPLC of (*R*)-**3b** was analyzed by its corresponding ethyl ester **10b**, which showed its enantiomeric purity to be >99%.

In conclusion, L- or D-proline catalyzed hydroxylation of aldehyde **5** was achieved in one step without the separation of the oxyamination intermediate. We showed that the use of aldehyde **5** in 1.2 molar equiv was enough to achieve optimal yield. Simple functional group manipulations, such as cyanation and hydrolysis allowed us to obtain either **3a** or **3b** isomers of 3-hydroxy-4-(2,4,5-trifluorophenyl)butanoic acid in high enantiomeric purities (>99%) and in an overall yield of 65%. This protocol is attractive because of the affordable chiral catalysts, the short synthetic sequence, and the good overall yield. All reaction sequences are simple and can be applicable to the large scale synthesis of β-hydroxynitrile **9** and β-hydroxy acid **3**. Aldehyde **5**, synthesized for the first time in this work, may find use as an important starting material in the alternative preparation of sitagliptin or sitagliptin derivatives (Scheme 1).

3. Experimental

3.1. General

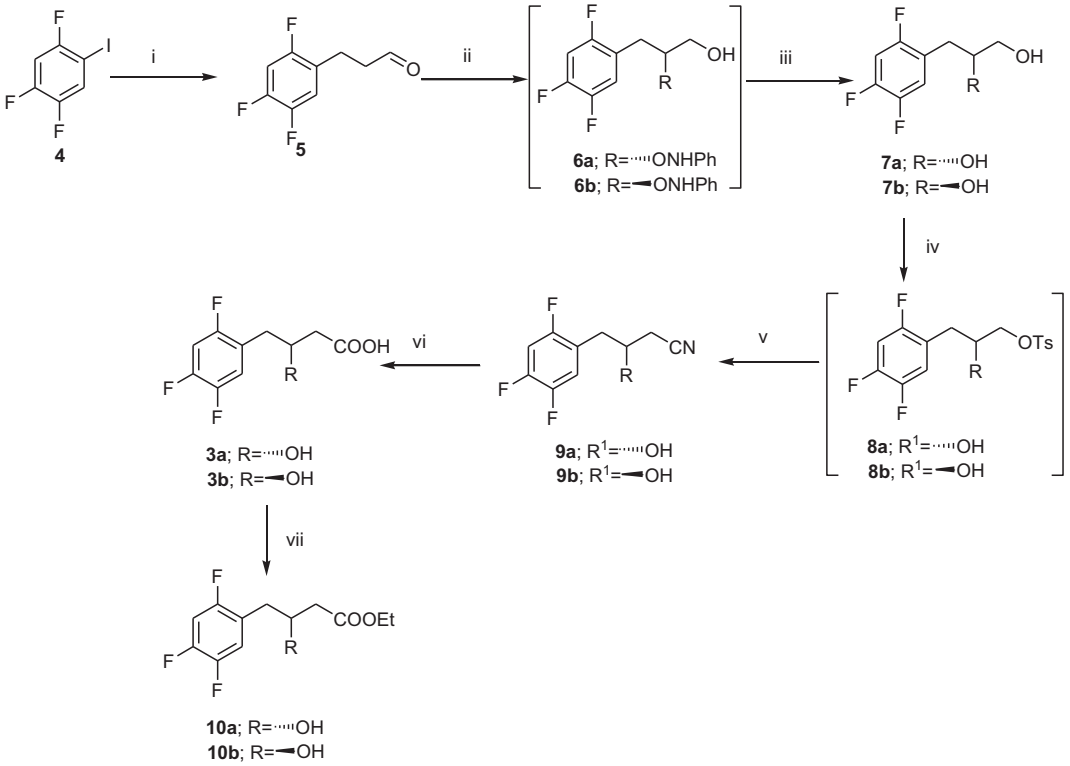
All commercial reagents and chromatography solvents were used as obtained unless otherwise stated. Anhydrous solvents were distilled over appropriate drying agents prior to use. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254}. Fluka Silica gel 60 (0.063–0.2 mm) was used for column chromatography.

Visualization of TLC was accomplished with UV light (254 nm) and by staining with ethanolic PMA (phosphomolybdic acid) solution. HPLC was carried out on a Thermo Finnigan Spectra System P1000 with a chiral column (CHIRALPAK® AS, *n*-hexane/*i*-PrOH, 211 and 220 nm) and a polarimetric chiralyser detector for the rotation of enantiomers. Elemental analyses were performed on a Leco CHNS-932. MS was recorded using a varian GC/MS/MS.

Specific rotations were measured on a Bellingham Stanley ADP 220 589 nm polarimeter in a 1 dm tube. IR spectra were recorded on Perkin–Elmer Spectrum One FT-IR Spectrometer. NMR spectra were recorded using a Varian 400 MHz NMR instrument (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) or a Bruker 400 MHz instrument (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz).

*3.1.1. 3-(2,4,5-Trifluorophenyl)propanal (**5**).* To a stirred solution of 2,4,5-trifluoroiodobenzene (**4**) (1.50 g, 5.87 mmol), $Pd(OAc)_2$ (26 mg, 2 mol %), triethylbenzylammonium chloride (1.32 g, 5.79 mmol), and $NaHCO_3$ (0.98 g, 11.7 mmol) in 4 mL of DMF was added allyl alcohol (0.67 g, 0.79 mL, 11.6 mmol) under N_2 atm. The resulting dark brown solution was heated at 45 °C for 20 h. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with EtOAc (3×25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by a silica gel column to give **5** (1.04 g; 95%). Light yellow liquid. (R_f: 0.2, 5:95 EtOAc/hexanes). GC/MS/MS (CI) (150 eV) *m*/*z* (rel intensity, %) 189.1 (M^++1, 13), 144.9 (100). ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.80 (br s, 1H, CHO), 7.04 (ddd, 1H, H-6′, $J_{H,F}$=15.6, 8.4, 6.8 Hz), 6.88 (dt, 1H, H-3′, $J_{H,F}$=10.0, 6.8 Hz), 2.92 (A_2 part of A_2X_2 system, quasi t, 2H, 2×H-3, J=7.2 Hz), 2.78 (X_2 part of A_2X_2 system, quasi t, 2H, 2×H-2, J=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ=200.4 (C-1), 156.1 (ddd, C-2′, $J_{C,F}$=242.7, 9.1, 2.6 Hz), 148.9 (ddd, C-4′, $J_{C,F}$=248.4, 14.1, 12.4 Hz), 146.8 (ddd, C-5′, $J_{C,F}$=243.4, 12.4, 3.7 Hz), 123.8 (ddd, C-1′, $J_{C,F}$=18.1, 5.5, 4.3 Hz), 118.4 (dd, C-6′, $J_{C,F}$=19.0, 5.7 Hz), 105.6 (dd, C-3′, $J_{C,F}$=28.1, 20.6 Hz), 43.7 (C-2), 21.4 (C-3). IR (neat) 3065, 2934, 2829, 2725, 1725, 1632, 1522, 1425, 1388, 1333, 1211, 1152, 1099 cm^{-1}.

*3.1.2. (R)-3-(2,4,5-Trifluorophenyl)propane-1,2-diol (**7a**).* To a solution of 3-(2,4,5-trifluorophenyl)propanal (300 mg, 1.59 mmol) (**5**) in 2 mL of DMSO/H_2O (97:3) was added L-proline (30 mg, 0.26 mmol) at rt. After the reaction mixture was stirred for 3 min, nitrosobenzene (142 mg, 1.33 mmol) was added in one portion to give a green solution. The reaction mixture was stirred for 30 min at 30 °C. After the color of the solution turned orange, the temperature was lowered to 0 °C and diluted with MeOH (4 mL).



Scheme 1. (i) Ally alcohol, $Pd(OAc)_2$ (cat.), $NaHCO_3$, benzyltriethylammonium chloride, DMF, 45 °C, 18 h, 95%. (ii) (a) PhNO, Proline (cat.), DMSO/H_2O (97:3), 30 °C; (b) $NaBH_4$, MeOH, 0 °C; (iii) H_2, Pd/C, $CHCl_3$, EtOH; **5** (L-proline)→**7a**; **5** (D-proline)→**7b**, 65%; (iv) TsCl, NEt_3, CH_2Cl_2, 0 °C, 15 h; (v) NaCN, DMF, 75 °C, 19 h, (**7a**→**9a**; **7b**→**9b**; 65%); (vi) 3 M NaOH, H_2O_2 100 °C, 3 h 90%; (vii) EtOH, H_2SO_4 (cat.), 70 °C, 18 h.

$NaBH_4$ (200 mg, 5.26 mmol) was added carefully. The reaction mixture was stirred for 30 min and then quenched with 15 mL of a saturated $(NH_4)_2SO_4$ solution. The organic phase was extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The solvent was evaporated to give crude **6a** (410 mg). The crude product was submitted to Pd/C catalyzed hydrogenation without further purification and identification.

To a solution of **6a** (410 mg) in EtOH (15 mL) were added $CHCl_3$ (0.5 mL; a source of dry HCl) and 40 mg of Pd/C (%10). The reaction flask was purged with hydrogen gas three times before being allowed to stir under a hydrogen balloon for 12 h. Then, the reaction mixture was filtered and the solvent was evaporated. The residue was dissolved in EtOAc (40 mL) and 20 mL of a saturated $(NH_4)_2SO_4$ solution was added. The organic phase was separated and dried over Na_2SO_4 and filtered. Evaporation of the solvent and chromatography of the residue on a silica gel column gave **7a** (177 mg; 65%, according to PhNO). White solid. Mp: 68–69 °C. (R_f: 0.2, 50% EtOAc/hexanes). $[\alpha]_D^{26}$ +36 (*c* 1, EtOH). Anal. Calcd for $C_9H_9F_3O_2$: C, 52.43; H, 4.40. Found: C, 52.43; H, 4.71. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.08 (ddd, 1H, H-6′, $J_{H,F}$=16.0, 8.8, 7.2 Hz), 6.90 (dt, 1H, H-3′, $J_{H,F}$=9.6, 6.8 Hz), 3.94–3.86 (m, 1H, H-2), 3.66 (A part of AB system, dd, 1H, H-1a, $J_{1a,1b}$=11.2 Hz, $J_{1a,2}$=2.9 Hz), 3.46 (B part of AB system, dd, 1H, H-1b, $J_{1a,1b}$=11.2 Hz, $J_{1b,2}$=7.0 Hz), 2.84 (br s, 2H, OH), 2.79 (A part of AB system, dd, 1H, H-3a, $J_{3a,3b}$=14.1 Hz, $J_{2,3a}$=5.2 Hz), 2.71 (B part of AB system, dd, 1H, H-3b, $J_{3a,3b}$=14.1 Hz, $J_{2,3b}$=7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ=156.3 (ddd, C-2′, $J_{C,F}$=242.4 Hz, 9.1, 2.1 Hz), 149.0 (ddd, C-4′, $J_{C,F}$=248.6, 14.2, 12.6 Hz), 146.8 (ddd, C-5′, $J_{C,F}$=243.3, 12.4, 3.1 Hz), 121.4 (ddd, as dt, C-1′, $J_{C,F}$=17.7, 4.9, 4.9 Hz), 119.4 (dd, C-6′, $J_{C,F}$=19.0, 6.1 Hz), 105.5 (dd, C-3′, $J_{C,F}$=28.4, 20.6 Hz), 71.8 (C-2), 66.1 (C-1), 32.4 (C-3). IR (neat) 3256, 2930, 1632, 1518, 1442, 1424, 1377, 1329, 1212, 1150, 1096, 1028, 843 cm^{-1}.

*3.1.3. (S)-3-(2,4,5-Trifluorophenyl)propane-1,2-diol (**7b**).* The procedure above described for **7a** was applied using D-proline in a yield of 65%. White solid. $[\alpha]_D^{26}$ −36 (*c* 1, EtOH).

*3.1.4. (R)-3-Hydroxy-4-(2,4,5-trifluorophenyl) butanenitrile (**9a**).* To a solution of TosCl (493 mg, 2.6 mmol) in CH_2Cl_2 (10 mL) was added NEt_3 (262 mg, 0.36 mL, 2.59 mmol) under N_2 atm at 0 °C. The reaction mixture was stirred for 1 h. After that, a solution of (*R*)-3-(2,4,5-trifluorophenyl)propane-1,2-diol (486 mg, 2.36 mmol) (**7a**) in CH_2Cl_2 (10 mL) was slowly added into this mixture. The reaction mixture was stirred for 15 h at rt. Water was added and the reaction layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was filtered through a pad of silica gel with EtOAc/hexanes to obtain **8a** (657 mg). It was used in the next reaction without further purification and identification.

Compound **8a** (657 mg, 1.82 mmol) and NaCN (268 mg, 5.47 mmol) was dissolved in DMF (6 mL) under N_2 atm. The reaction mixture was stirred for 19 h at 75 °C. After the reaction was completed, the reaction mixture was quenched with H_2O (30 mL) and extracted with EtOAc (3×25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel column to give **9a** (336 mg; 65%). Light yellow oil (R_f: 0.2, %20 EtOAc/hexanes). $[\alpha]_D^{26}$ +2 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.11 (ddd, 1H, H-6′, $J_{H,F}$=15.7, 8.6, 6.9 Hz), 6.94 (dt, 1H, H-3′, $J_{H,F}$=10.0, 6.4 Hz), 4.24–4.12 (m, 1H, H-3), 2.92 (A part of AB system, dd, 1H, H-4a, $J_{4a,4b}$=14.1 Hz, $J_{3,4a}$=4.9 Hz), 2.83 (B part of AB system, dd, 1H, H-4b $J_{3,4b}$=14.1 Hz, $J_{3,4b}$=7.8 Hz), 2.61 (A part of AB system, dd, 1H, H-2a, $J_{2a,2b}$=16.7 Hz, $J_{2a,3}$=4.8 Hz), 2.52 (B part of AB system, dd, 1H, H-2b, $J_{2a,2b}$=16.7 Hz, $J_{2b,3}$=6.5 Hz). 2.39 (br s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ=156.3 (ddd, C-2′, $J_{C,F}$=243.5, 8.9, 2.8 Hz), 149.5 (ddd, C-4′,

$J_{C,F}$=249.8, 14.3, 12.5 Hz), 147.0 (ddd, C-5′, $J_{C,F}$=237.3, 12.3, 3.2 Hz), 120.0 (ddd, C-1′, $J_{C,F}$=17.2, 5.3, 4.1 Hz), 119.6 (ddd, C-6′, $J_{C,F}$=19.1, 5.8, 1.2 Hz), 117.3 (C-1) 105.9 (dd, C-3′, $J_{C,F}$=28.4, 20.7 Hz), 67.4 (C-3), 35.7 (C-4), 25.9 (C-2). IR (neat) 3449, 2929, 2255, 1633, 1520, 1425, 1334, 1212, 1153, 1075 cm^{-1}. HRMS (ES): MH^+, found 216.0631. $C_{10}H_9F_3NO$ requires 216.0636.

*3.1.5. (S)-3-Hydroxy-4-(2,4,5-trifluorophenyl) butanenitrile (**9b**).* The procedure above described for **9a** was applied to diol **7b** to give nitrile **9b** in a yield of 66%. $[\alpha]_D^{26}$ −2 (*c* 1, $CHCl_3$).

*3.1.6. (R)-3-Hydroxy-4-(2,4,5-trifluorophenyl) butanoic acid (**3a**).* To a mixture of nitrile **9a** (440 mg, 2.04 mmol) in 3 M NaOH (12 mL) was added 35% aqueous H_2O_2 (4 mL). The reaction mixture was heated at 100 °C for 3 h. After the reaction was completed, the reaction mixture was cooled to 0 °C. To remove organic impurities, Et_2O (50 mL) was added and the ether phase was dispatched. Then the aqueous phase was acidified with 6 M HCl (ca. pH=1) and was extracted with Et_2O (50 mL), and dried over Na_2SO_4. Filtration and evaporation of the solvent gave **3a** (437 mg, 90%). White solid. Mp 86–87 °C (lit.[4] Mp 84 °C) $[\alpha]_D^{26}$ −8 (*c* 1, $CHCl_3$), (lit.[4]) $[\alpha]_D^{26}$ +16.3 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD) δ=7.24 (ddd, 1H, H-6′, $J_{6'\text{-}F}$=15.6, 8.8, 6.8 Hz), 7.09 (ddd, quasi dt, 1H, H-3′, $J_{3'\text{-}F}$=10.4, 6.4 Hz), 4.25–4.19 (m, 1H, H-3), 2.84 (A part of AB system, dd, 1H, H-4a, $J_{4a,4b}$=13.6 Hz, $J_{3\text{-}4a}$=4.4 Hz), 2.74 (B part of AB system, dd, 1H, H-4b, $J_{4a,4b}$=13.6 Hz, $J_{3,4b}$=7.6 Hz), 2.48 (A part of AB system, dd, 1H, H-2a, $J_{2a,2b}$=15.4 Hz, $J_{2a,3}$=5.2 Hz). 2.42 (B part of AB system, dd, 1H, H-2b, $J_{2a,2b}$=15.4 Hz, $J_{2b,3}$=8 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ=173.9($-CO_2H$), 156.5 (C-2′, ddd, $J_{C,F}$=242.7, 9.4, 2.1 Hz), 148.8 (C-4′, ddd, $J_{C,F}$=246.3, 14.3, 12.7 Hz), 146.6 (C-5′, ddd, $J_{C,F}$=241.1, 12.6, 3.5 Hz), 122.3 (C-1′, ddd, $J_{C,F}$=18.3, 5.8, 4.2 Hz), 119.3 (C-6′, dd, $J_{C,F}$=19.3, 6.2 Hz), 104.9 (C-3′, dd, $J_{C,F}$=29.2, 21.0 Hz), 67.8(C-3), 41.4 (C-2), 35.4(C-4). IR (neat) 3747, 3428, 3064, 2933, 2621, 1714, 1633, 1520, 1426, 1334, 1281, 1212, 1153, 1101 cm^{-1}. HRMS (ES): MH^+, found 235.0570. $C_{10}H_{10}F_3O_3$ requires 235.0582.

*3.1.7. (S)-3-Hydroxy-4-(2,4,5-trifluorophenyl) butanoic acid (**3b**).* The procedure above described for **3a** was applied to nitrile **9b** to give carboxylic acid **3b** in a yield of 90%. White solid. $[\alpha]_D^{26}$ +8 (*c* 1, $CHCl_3$).

*3.1.8. (R) Ethyl 3-hydroxy-4-(2,4,5-trifluoro-phenyl)butanoate (**10a**).* (*S*)-3-Hydroxy-4-(2,4,5-trifluorophenyl)butanoic acid (**3a**) (51 mg) was dissolved in EtOH (3 mL) and 2 drops of H_2SO_4 was added. The reaction mixture was heated at 70 °C for 18 h. After the reaction was completed, the reaction mixture was cooled to rt and concentrated in vacuo. The residue was diluted with 10 mL of H_2O and extracted with 15 mL of EtOAc. The organic phase was dried over Na_2SO_4. After filtration, the solvent was removed in vacuo to afford **10a** (48 mg, 86%). Light yellow oil (R_f: 0.86, %50 EtOAc/hexanes) $[\alpha]_D^{26}$ −13 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.12 (ddd, 1H, H-6′, $J_{H,F}$=17.2, 8.8, 6.2 Hz),6.90 (dt, 1H, H-3′, $J_{H,F}$=9.7, 6.8 Hz), 4.28–4.20 (m, 1H, H-3), 4.17 (q, 2H, OCH_2CH_3, *J*=7.0 Hz), 3.17 (br s, 1H, −OH), 2.78 (quasi d, 2H, 2×H-4, $J_{3,4}$=6.4 Hz), 2.52 (A part of AB system, dd, 1H, H-2a, $J_{2a,2b}$=16.8 Hz, $J_{2a,3}$=3.2 Hz), 2.43 (B part of AB system, dd, 1H, H-2b, $J_{2a,2b}$=16.8 Hz, $J_{2b,3}$=9.2 Hz), 1.27 (t, 3H, OCH_2CH_3, *J*=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ=172.7 (s, −CO), 156.2 (C-2′, ddd, $J_{C,F}$=242.6, 9.2, 2.6 Hz), 149.0 (C-4′, ddd, $J_{C,F}$=260.9, 14.3, 12.4 Hz), 146.8 (C-5′, ddd, $J_{C,F}$=243.1, 12.4, 3.4 Hz), 121.3 (C-1′, ddd, $J_{C,F}$=18.0, 5.6, 4.2 Hz), 119.6 (C-6′, ddd, $J_{C,F}$=19.0, 6.0, 1.2 Hz), 105.4 (C-3′, dd, $J_{C,F}$=28.8, 20.7 Hz), 67.8(C-3), 61.1 (OCH_2CH_3), 40.6 (C-2), 35.2(C-4), 14.3 (OCH_2CH_3). IR (neat) 3722, 3483, 3055, 2983, 2933, 1732, 1633, 1520, 1425, 1334, 1268, 1210, 1190, 1152, 1099, 1030 cm^{-1}. HRMS (ES): MH^+, found 263.0899. $C_{12}H_{14}F_3O_3$ requires 263.0895.

*3.1.9. (S) Ethyl 3-hydroxy-4-(2,4,5-trifluoro-phenyl)butanoate (**10b**).* The procedure above described for **10a** was applied to nitrile **3b** to give carboxylic acid **10b** in a yield of 86%. Light yellow oil (R_f: 0.86, % 50 EtOAc/hexanes) $[\alpha]_D^{26}$ +13 (*c* 1, $CHCl_3$).

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.01.095.

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