Enantiospecific Synthesis of (*R*)-3-Amino-4-(2,4,5-trifluorophenyl)butanoic Acid Using (*S*)-Serine as a Chiral Pool

by **Aytekin Köse**, **Özlem Gündoğdu**, **Derya Aktaş**, **Meryem Fıstıkçı**, **Ramazan Altundaş**, **Hasan Seçen***, and **Yunus Kara***

Department of Chemistry, Faculty of Sciences, Atatürk University, TR-25240 Erzurum
(fax: + 90-442-2360948: e-mail: hsecen@atauni.edu.tr, yukara@atauni.edu.tr)

Starting from (*S*)-serine, a new method was developed for the synthesis of the *β*-amino acid part of sitagliptin in ten steps and with an overall yield of 30%. The crucial step of the synthesis was the ring opening of *N*- and *O*-protected (*R*)-aziridin-2-methanol with (2,4,5-trifluorophenyl)magnesium bromide to give *N*- and *O*-protected (*R*)-2-amino-3-(2,4,5-trifluorophenyl)propan-1-ol.

Introduction. – (−)-(*R*)-Sitagliptin (**1**), an inhibitor of dipeptidyl peptidase-IV, has been used as a drug for the treatment of Type-2 diabetes [1][2]. The synthesis of **1** is based on a convergent method consisting of preparation of two components: *β*-amino acid **2** and triazolopyrazine **3** [3] (*Fig.*). In general, an alternative synthesis of **1** mainly focuses on the preparation of **2**.

The preparation of *β*-amino acid **2** can be performed *via* three methods: *i*) synthesis of **2** or its precursors in racemic form, and then chiral resolution; *ii*) synthesis of the relevant achiral precursors and then creation of a stereogenic center by using chiral auxiliaries; *iii*) reacting a trifluorophenyl compound with a suitable enantiomerically pure compound and conversion to **2**. The synthesis performed by *Zeng et al.* [4] and *Tasnadi et al.* [5] are recent examples of method *i*, based on chiral resolution of the racemic mixture. Three generations of *MERCK* [6–8] for synthesis of *β*-amino acid **2** *via* method *ii* are the best examples in which the stereogenic centers are formed by reductions *via* a chiral catalyst or an enzyme. In method *iii*, chiral pools are used for the enantiomerically specific synthesis of **2**. In this context, *Khan et al.* [9] used (*S*)-3,6-diethoxy-2,5-dihydro-2-isopropylpyrazine for synthesis of **2**. In the same manner, *Shen et al.* [10] used (*S*)-(*tert*-butyl) 4-formyl-2,2-dimethyloxazolidine-3-carboxylate as the chiral pool for the preparation of **2**. Recently, *Pan et al.* prepared a chiral aziridine *via* ʟ-homoserine from which they synthesized sitagliptin [11].
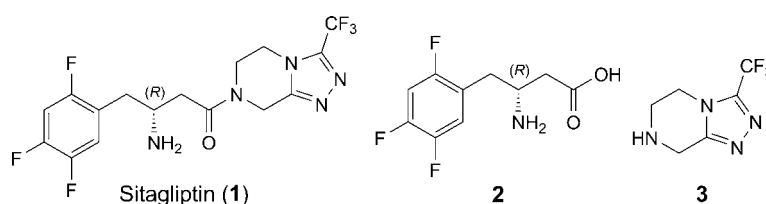

Figure. *Sitagliptin and its components*

In our recent article [12], we described a methodology for the asymmetric synthesis of (*R*)- and (*S*)-3-hydroxy-4-(2,4,5-trifluorophenyl)butanoic acid, a precursor for the *β*-amino acid **2**, *via* D- and L-proline-catalyzed oxyamination. Herein, we report the use of (*S*)-serine, a readily accessible and essential amino acid, for the enantioselective synthesis of *β*-amino acid **2**.

Results and Discussion. – As outlined in the *Scheme*, our synthesis started from (*S*)-serine (**4**). The esterification described by *Dubuisson et al.* [13] was applied, and (*S*)-serine methyl ester hydrochloride (**5**) was obtained in good yield (97%). *Ollivier et al.* [14] recently converted (*R*)-serine methyl ester to the (*S*)-isomer of alcohol **8** with the same protecting groups. Applying this methodology to (*S*)-serine methyl ester **5**, we first protected the amino group of **5** and obtained the *N*-Boc-protected compound (*S*)-**6** (92%). The OH group of (*S*)-**6** was protected with (*tert*-butyl)diphenylsilyl (TBDPS) group to give ester (*S*)-**7** (99%). Then, the ester group was reduced by reacting with LiBH$_4$ to give the primary alcohol (*R*)-**8**[1]) (92%) [15]. *Travins* and *Etzkorn* [16] converted *tert*-butyl (3-{[(*tert*-butyl)dimethylsilyl]oxy}-1-hydroxypropan-2-yl)carbamate, a similar compound to (*R*)-**8**, to the corresponding aziridine *via* intramolecular *Mitsunobu* reaction. By a similar method, we also converted alcohol (*R*)-**8** to aziridine (*R*)-**9** (78%). *Zhu et al.* [17] described a method for the regiospecific ring-opening of *N*-protected aziridines with CuBr · SMe$_2$-mediated *Grignard* reagents. By application of this method, we prepared a *Grignard* reagent from 1-bromo-2,4,5-trifluorobromobenzene and treated it in the presence of CuBr · SMe$_2$ with aziridine (*R*)-**9** to obtain (*R*)-**10** (93%). The TBDPS group of (*R*)-**10** was removed by treatment with Bu$_4$NF to afford alcohol (*R*)-**11** (92%). Tosylation of the latter gave (*R*)-**12** (80%), which underwent cyanation by treatment with NaCN, to furnish the nitrile (*R*)-**13** (76%). Nitrile (*R*)-**13** was hydrolyzed with KOH in MeOH/H$_2$O to give (*R*)-**14** (93%). *Khan et al.* [9] used (*R*)-**14** for the synthesis of sitagliptin (**1**) by fusing it to triazolopyrazine **3**, and then they deprotected the *N*-Boc group to give **1**. To determine the enantiomer purity of the acid, (*R*)-**14** was esterified by treatment with SOCl$_2$ and MeOH to give ester (*R*)-**15** (85%). Chiral HPLC analysis of (*R*)-**15** revealed an enantiomer purity of > 99%. The specific optical rotation of ester **15** was + 15.6, which was in good agreement with the value reported in the literature (+ 15.2) [18].

In conclusion, starting from (*S*)-serine, we developed a methodology for the asymmetric synthesis of *N*-Boc-protected (*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoic acid in ten steps and with a 30% overall yield. We also synthesized the *N*- and *O*-protected aziridine **9** for the first time, which can be used as a chiral pool for several synthetic purposes.

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[1]) Although the stereogenic center is not involved in this conversion, the priority of substituents changed and, therefore, the configuration became (*R*).

Scheme. *Synthesis of β-Amino Acid* **14**
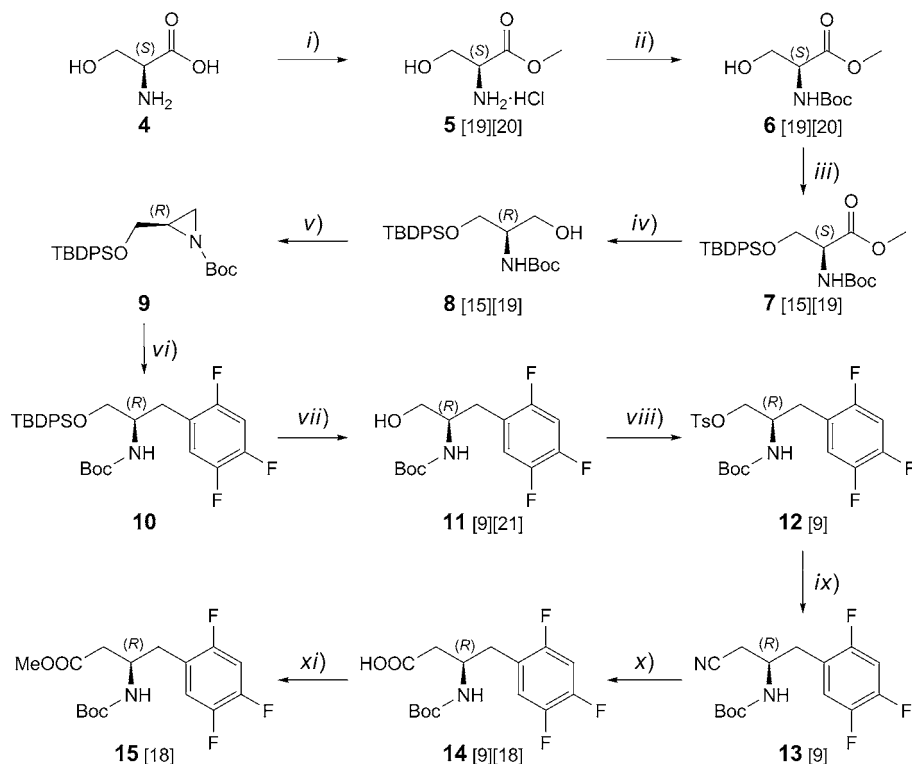
i) SOCl$_2$, MeOH, 0° then reflux, 3 h; 96%. *ii*) Di(*tert*-butyl) dicarbonate (Boc$_2$O), Et$_3$N, CH$_2$Cl$_2$, 0° to r.t., 14 h; 92%. *iii*) (*t*Bu)Ph$_2$SiCl (TBDPSCl), 1*H*-imidazole, CH$_2$Cl$_2$, 0° to r.t., 24 h; 99%. *iv*) LiBH$_4$, THF, 0°, 4 h; 92%. *v*) Ph$_3$P, diisopropyl azodicarboxylate (DIAD), THF, 0°, 1 h; r.t., 18 h; 78%. *vi*) Mg, 1,2-dibromoethane, CuBr·SMe$_2$, 1-bromo-2,4,5-trifluorobenzene, THF, r.t., 5 h; 93%. *vii*) Bu$_4$NF, THF, r.t., 5 h; 92%. *viii*) TsCl, Et$_3$N, CH$_2$Cl$_2$, 1 h; r.t., 18 h; 80%. *ix*) NaCN, DMF, 80°, 19 h; 76%. *x*) 3M KOH$_{(aq)}$, MeOH, reflux (90°), 20 h, then 2M HCl (pH *ca.* 2); 93%. *xi*) SOCl$_2$, MeOH, 0° then reflux, 20 h; 85%.

Experimental Part

General. All reagents used were commercially available unless otherwise specified, and all solvents were distilled before use. Specific rotations were measured with a *Bellingham Stanley* ADP polarimeter and a 1-dm tube. HPLC: Chiral column (*CHIRALCEL® OD*) on a *Thermo Finnigan Spectra System P1000* and a polarimetric chiralyser detector. M.p.: *Gallenkamp* melting-point devices. IR Spectra: *PerkinElmer Spectrum One* FT-IR spectrometer. ^{1}H- and ^{13}C-NMR spectra: *Varian 400* and *Bruker 400* spectrometers. HR-MS: electron spray technique (M^+/M^-) from the soln. in MeOH (*Waters LCT Premier*™ *XE UPLC/MS TOF* (Manchester, UK)). Elemental analysis: *Leco CHNS-932* instrument.

Methyl (S)-2-Amino-3-hydroxypropanoate Hydrochloride (= *Methyl* L-*Serinate Hydrochloride*; **5**) [19][20]. To a soln. *of (S)-serine* (**4**; 7.00 g, 66.6 mmol) in 125 ml of MeOH was added slowly SOCl$_2$ (7.25 ml, 11.9 g, 99.9 mmol) at 0°. The resulting soln. was heated at 80° for 3 h. The reaction was quenched and the mixture was concentrated *in vacuo* to give **5** (10.0 g, 96%). White solid. M.p. 161–163° ([20]: 163–165°). ^{1}H-NMR (400 MHz, D$_2$O): 4.65 (br. *s*, NH$_3^+$, OH, HOD); 4.20 (*t*, *J*(2,3) = 3.7, H–C(2)); 4.00,

3.90 (AB, $J_{AB} = 12.4$, $J(2,A) = 4.0$, $J(2,B) = 3.3$, $CH_2(3)$); 3.75 (*s*, MeO). ^{13}C-NMR (100 MHz, D_2O): 169.1 ($C(1)$); 59.5 ($C(3)$); 54.9 ($C(2)$); 54.0 (MeO). Anal. calc. for $C_4H_{10}ClNO_3$ (155.58): C 30.88, H 6.48, N 9.00; found: C 30.90, H 6.24, N 9.07.

*N-[(*tert-*Butoxycarbonyl)]-*L-*serine Methyl Ester* (**6**) [19][20]. To a soln. of **5** (1.00 g, 6.43 mmol) in 15 ml of (dry) CH_2Cl_2 at 0° under N_2 were added Et_3N (1.79 ml, 1.30 g, 12.9 mmol) and Boc_2O (1.40 g, 6.43 mmol) in 5 ml of CH_2Cl_2. The resulting mixture was stirred for 14 h at r.t. The reaction was quenched with H_2O (15 ml), and the mixture was extracted with CH_2Cl_2 (3 × 20 ml). The combined layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by CC (AcOEt/hexane) to give **6** (1.30 g, 92%). Colorless viscous oil. R_f (AcOEt/hexane 1:1) 0.5. $[\alpha]_D^{27} = +11$ ($c = 1$, $CHCl_3$). IR (neat): 3395, 2978, 1744, 1716, 1512, 1457, 1438, 1393, 1368, 1286, 1250, 1214. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.53 (br. *d*, $J(2,NH) = 6.0$, NH); 4.36 (*m*, H–C(2)); 3.93, 3.87 (AB, $J(3a,3b) = 11.0$, $J(3a,OH) = 6.0$, $J(2,3) = 4.0$, $CH_2(3)$); 3.76 (*s*, MeO); 2.82 (*t*, $J(3,OH) = 6.0$, HO–C(3)); 1.43 (*s*, ^tBu). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.6 ($C(1)$); 156.0 (CO of carbamate); 80.5 (Me_3C); 63.7 ($C(3)$); 55.9 ($C(2)$); 52.9 (MeO); 28.5 (Me_3C). Anal. calc. for $C_9H_{17}NO_5$ (219.23): C 49.31, H 7.82, N 6.39; found: C 48.57, H 7.57, N 6.42.

*N-[(*tert-*Butoxy)carbonyl]-O-[(*tert-*butyl)(diphenyl)silyl]-*L-*serine Methyl Ester* (**7**) [15][19]. To a soln. of **6** (13.35 g, 60.89 mmol) and $1H$-imidazole (12.43 g, 182.7 mmol) in CH_2Cl_2 (80 ml) was added TBDPSCl (14.25 ml, 15.06 g, 54.80 mmol) at 0° under N_2. *(Note: If the stochiometry alcohol* **6***/TBDPSCl is taken as just 1:1, unreacted TBDPSCl and product* **7** *are inseparable)*. The mixture was stirred at r.t. for 24 h. The reaction was quenched with sat. aq. NH_4Cl (80 ml) and brine (20 ml), and then the mixture was extracted with CH_2Cl_2 (3 × 100 ml). The combined org. layers were dried (Na_2SO_4). The crude product was purified by CC (AcOEt/hexane) to give **7** (25.24 g, 99%). Colorless viscous oil. R_f (AcOEt/hexane 2:8) 0.83. $[\alpha]_D^{25} = +18.6$ ($c = 1$, $CHCl_3$; [15]: $[\alpha]_D^{22} = +14.2$ ($c = 1$, $CHCl_3$)). IR (neat): 3448, 3072, 3050, 2955, 2932, 2889, 2858, 1751, 1719, 1473, 1498, 1473, 1428, 1391, 1366, 1349, 1294, 1251, 1208. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.63–7.60 (*m*, 2 H–C(2',6')); 7.46–7.37 (*m*, 2 H–C(3',4',5')); 5.44 (*d*, $J(2,NH) = 8.4$, NH); 4.41 (*dt*, $J(2,NH) = 8.4$, $J(2,3) = 2.8$, H–C(2)); 4.08, 3.91 (AB, $J(3a,3b) = 10.0$, $J(2,3) = 2.8$, $CH_2(3)$); 3.75 (*s*, MeO); 1.47 (*s*, Me_3CO); 1.05 (*s*, Me_3CSi). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.2 ($C(1)$); 155.4 (CO of carbamate); 135.52, 135.48 (2 $C(2',6')$); 133.0, 132.8 (2 $C(1')$); 129.88, 129.86 (2 $C(4')$); 127.79, 127.77 (2 $C(3',5')$; 79.9 (Me_3CO); 64.6 ($C(3)$); 55.5 ($C(2)$); 52.3 (MeO); 28.4 (Me_3CO); 26.7 (Me_3CSi); 19.3 (Me_3CSi). Anal. calc. for $C_{25}H_{35}NO_5Si$ (457.63): C 65.61, H 7.71, N 3.06; found: C 65.31, H 7.92, N 3.03.

*tert-*Butyl [(2*R*)-1-{[(*tert-*Butyl)(diphenyl)silyl]oxy}-3-hydroxypropan-2-yl]carbamate* (**8**) [15][19]. To a stirred soln. of $LiBH_4$ (1.76 g, 80.8 mmol) in THF (90 ml) was added **7** (12.3g, 26.9 mmol) at 0° under N_2, and the mixture was stirred at the same temp. for 4 h. After completion of the reaction, the solvent was removed *in vacuo*. H_2O (70 ml) was added to the residue at 0°, and the org. phase was extracted with AcOEt (3 × 70 ml). The combined layers were dried (Na_2SO_4). After removal of the solvent, the crude product was purified by CC (AcOEt/hexane) to give **8** (10.67 g, 92%). White solid. R_f (AcOEt/hexane 3:7) 0.53. M.p. 73–75° ([15]: 73°). $[\alpha]_D^{30} = +5.5$ ($c = 1$, $CHCl_3$; [15]: $[\alpha]_D^{22} = +5.2$ ($c = 1$, $CHCl_3$)). IR (KBr): 3677, 3565, 3410, 3284, 3074, 3056, 2998, 2973, 2956, 2929, 2882, 2855, 1685, 1546, 1474, 1428, 1390, 1365, 1309, 1280, 1251. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.66–7.64 (*m*, 2 H–C(2',6')); 7.46–7.37 (*m*, 2 H–C(4'), 2 H–C(3',5')); 5.08 (br. *s*, NH); 3.83–3.67 (*m*, $CH_2(1)$, H–C(2), $CH_2(3)$); 2.51 (br. *s*, OH); 1.45 (*s*, Me_3CO); 1.07 (*s*, Me_3CSi). ^{13}C-NMR (100 MHz, $CDCl_3$): 156.0 (CO); 135.8 (2 $C(2',6')$); 133.1 (2 $C(1')$); 130.2 (2 $C(4')$); 128.1 (2 $C(3',5')$); 80.0 (Me_3CO); 64.4 ($C(3)$); 63.9 ($C(1)$); 53.3 ($C(2)$); 28.6 (Me_3CO); 27.1 (Me_3CSi); 19.5 (Me_3CSi). Anal. calc. for $C_{24}H_{35}NO_4Si$ (429.62): C 66.27, H 6.67, N 2.58; found: C 66.27, H 6.69, N 2.58.

*tert-*Butyl (2*R*)-2-({[(*tert-*Butyl)(diphenyl)silyl]oxy}methyl)aziridine-1-carboxylate* (**9**). To a soln. of Ph_3P (3.83 g, 14.6 mmol) in THF (60 ml) was added diisopropyl azodicarboxylate (DIAD; 2.83 ml, 2.95 g, 14.6 mmol) at 0° under N_2, and the mixture was stirred at the same temp. for 1 h. After a white precipitate appeared, a soln. of **8** (2.51 g, 5.84 mmol) in THF (10 ml) was added slowly. The resulting mixture was warmed to r.t. and stirred under N_2 for 18 h. After evaporation of the solvent, the residue was purified by CC (AcOEt/hexane) to give **9** (1.88 g, 78%). Colorless viscous oil. R_f (AcOEt/hexane 2:8) 0.82. $[\alpha]_D^{25} = +55$ ($c = 1$, $CHCl_3$). IR (neat): 3448, 3071, 3050, 3000, 2961, 2932, 2893, 2858, 1720, 1589, 1473, 1428, 1392, 1367, 1307, 1257, 1220. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.72 (*dm*, $J = 7.0$, 2

H–C(2′,6′)); 7.46 – 7.38 (*m*, 2 H–C(4′), 2 H–C(3′,5′)); 3.83, 3.68 (*AB*, $J_{AB} = 11.2$, $J(2,3) = 5.2$, CH$_2$(3)); 2.65 – 2.61 (*m*, H–C(2)); 2.25 (*d*, $J(2,3) = 6.0$, H–C(3)); 1.99 (*d*, $J(2,3) = 3.6$, H–C(3)); 1.46 (*s*, *Me*$_3$CO); 1.09 (*s*, *Me*$_3$CSi). ^{13}C-NMR (100 MHz, CDCl$_3$): 162.4 (CO); 135.9 (2 C(2′,6′)); 133.7, 133.5 (2 C(1′)); 133.0 (2 C(4′)); 128.0 (2 C(3′,5′)); 81.3 (*Me*$_3$CO); 64.6 (CH$_2$O); 38.6 (C(2)); 29.5 (C(3)); 28.2 (*Me*$_3$CO); 27.1 (*Me*$_3$CSi); 19.5 (Me$_3$*C*Si). Anal. calc. for C$_{24}$H$_{33}$NO$_3$Si (411.61): C 70.03, H 8.08, N 3.40; found: C 69.83, H 8.17, N 3.45.

tert-*Butyl [(2R)-1-{[(tert-Butyl)(diphenyl)silyl]oxy}-3-(2,4,5-trifluorophenyl)propan-2-yl]carbamate* (**10**). To a slurry of Mg (0.100 g, 4.18 mmol) in THF (10 ml) was added 1,2-dibromoethane (5 mg) under N$_2$. To the mixture was added 1-bromo-2,4,5-trifluorobenzene (0.49 ml, 0.88 g, 4.18 mmol) at r.t., and it was stirred until the disappearance of Mg. This *Grignard* soln. was added *via* cannula to a suspension of **9** (0.86 g, 2.09 mmol) and CuBr · SMe$_2$ (0.21 g, 1.04 mmol) in THF (8 ml) and stirred for 5 h at r.t. under N$_2$. The reaction was quenched with sat. aq. NH$_4$Cl (12 ml), and the org. phase was extracted with AcOEt (3 × 20 ml). After drying (Na$_2$SO$_4$), the solvent was evaporated *in vacuo*, and the residue was purified by CC (AcOEt/hexane) to give **10** (1.06 g, 93%). White solid. R_f (AcOEt/hexane 2 : 8) 0.80. M.p. 90 – 92°. $[\alpha]_D^{25} = +26$ ($c = 1$, MeOH). IR (KBr): 3356, 3072, 3056, 2967, 2932, 2858, 1688, 1524, 1472, 1462, 1425, 1390, 1366, 1333, 1323, 1280, 1242, 1210. ^{1}H-NMR (400 MHz, CDCl$_3$): 7.70 – 7.56 (*m*, 2 H–C(2′,6′)); 7.48 – 7.39 (*m*, 2 H–C(4′), 2 H–C(3′,5′)); 7.04 (*m*, H–C(6′′)); 6.87 (*dt*, $J(H,F) = 10.0$, 6.4, H–C(3′′)); 4.79 (*d*, $J(2,NH) = 8.8$, NH); 4.00 – 3.90 (*m*, H–C(2)); 3.71, 3.62 (*AB*, $J_{AB} = 10.4$, CH$_2$(3)); 2.91, 2.82 (*AB*, $J_{AB} = 13.6$, CH$_2$(1)); 1.40 (*s*, ^{t}Bu); 1.13 (*s*, Me$_3$CSi). ^{13}C-NMR (100 MHz, CDCl$_3$): 156.4 (*ddd*, $J(C,F) = 248.1$, 9.1, 2.4, C(2′′)); 155.5 (CO); 148.9 (*dt*, $J(C,F) = 248.1$, 12.4, 12.4, C(4′′)); 146.7 (*ddd*, $J(C,F) = 242.8$, 12.4, 3.6, C(5′′)); 135.8 (2 C(2′,6′)); 133.3, 133.2 (2 C(1′)); 130.2 (2 C(4′)); 128.1 (2 C(3′,5′)); 122.0 (*dt*, $J(C,F) = 17.8$, 4.7, C(1′′)); 119.2 (*dd*, $J(C,F) = 19.0$, 5.7, C(6′′)); 105.4 (*dd*, $J(C,F) = 28.5$, 20.5, C(3′′)); 79.6 (*Me*$_3$CO); 65.2 (C(1)); 52.3 (C(2)); 31.0 (C(3)); 28.5 (*Me*$_3$CO); 27.2 (*Me*$_3$CSi); 19.6 (Me$_3$*C*Si). Anal. calc. for C$_{30}$H$_{36}$F$_3$NO$_3$Si (543.69): C 67.10, H 8.21, N 3.26; found: C 67.22, H 8.51, N 3.25.

tert-*Butyl [(2R)-1-Hydroxy-3-(2,4,5-trifluorophenyl)propan-2-yl]carbamate* (**11**) [9][21]. To a soln. of **10** (0.41 g, 0.75 mmol) in THF (8 ml) was added Bu$_4$NF (0.28 ml, 0.26 g, 0.98 mmol) at r.t. under N$_2$ and stirred for 5 h. The reaction was quenched with sat. aq. NH$_4$Cl (10 ml), and the mixture was extracted with AcOEt (3 × 10 ml). The combined org. layers were dried (Na$_2$SO$_4$). Evaporation of the solvent and chromatography of the residue on CC (AcOEt/hexane) gave **11** (0.21 g, 92%). White solid. R_f (AcOEt/hexane 2 : 8) 0.16. M.p. 126 – 128°. $[\alpha]_D^{25} = +21.6$ ($c = 1$, MeOH). IR (KBr): 3734, 3365, 3078, 3055, 2988, 2935, 2883, 1683, 1524, 1477, 1445, 1424, 1393, 1368, 1335, 1320, 1271, 1253, 1229. ^{1}H-NMR (400 MHz, CDCl$_3$): 7.07 (*m*, H–C(6′)); 6.90 (*dt*, $J(H,F) = 9.6$, 6.4, H–C(3′)); 4.82 (*d*, $J(2,NH) = 7.6$, NH); 3.83 (*m*, H–C(2)); 3.73 – 3.50 (*AB*, CH$_2$(1)); 2.90 – 2.70 (*AB*, CH$_2$(3)); 2.20 (br. *s*, HO–C(1)); 1.39 (*s*, ^{t}Bu). ^{13}C-NMR (100 MHz, CDCl$_3$): 156.4 (*ddd*, $J(C,F) = 242.9$, 9.0, 3.1, C(2′)); 156.0 (CO); 149.0 (*dt*, $J(C,F) = 248.9$, 13.0, C(4′)); 146.9 (*ddd*, $J(C,F) = 246.9$, 12.6, 3.9, C(5′)); 121.6 (*m*, C(1′)); 119.3 (*dd*, $J(C,F) = 18.9$, 6.0, C(6′)); 105.5 (*dd*, $J(C,F) = 28.5$, 20.7, C(3′)); 80.1 (*Me*$_3$C); 64.5 (C(1)); 52.9 (C(2)); 30.4 (C(3)); 28.5 (*Me*$_3$C). Anal. calc. for C$_{14}$H$_{18}$F$_3$NO$_3$ (305.29): C 55.08, H 5.94, N 4.59; found: C 55.01, H 5.41, N 4.67.

(2R)-2-{[(tert-Butoxy)carbonyl]amino}-3-(2,4,5-trifluorophenyl)propyl 4-methylbenzenesulfonate (**12**) [9]. To a soln. of TsCl (1.22 g, 6.39 mmol) in CH$_2$Cl$_2$ (25 ml) was added Et$_3$N (0.89 ml, 0.65 g, 6.39 mmol) at 0° under N$_2$, and stirred for 1 h. Carbamate **11** (1.30 g, 4.26 mmol) was added dropwise. The resulting mixture was stirred at r.t. for 18 h. The solvent was removed under reduced pressure. The crude product was dissolved in CH$_2$Cl$_2$, and hexane was added to precipitate the unreacted TsCl. After filtering the precipitate, the solvent was removed, and the residue was purified by CC (AcOEt/hexane) to give **12** (1.56 g, 80%). White solid. R_f (AcOEt/hexane 3 : 7) 0.66. M.p. 160 – 162°. $[\alpha]_D^{25} = +21.3$ ($c = 1$, MeOH). IR (KBr): 3423, 3054, 3016, 2977, 2934, 1740, 1698, 1634, 1598, 1521, 1462, 1425, 1393, 1360, 1332, 1280, 1265, 1229, 1214. ^{1}H-NMR (400 MHz, CDCl$_3$): 7.77 (*d*, $J(H,F) = 8.2$, H–C(2′,6′)); 7.35 (*d*, $J(H,F) = 8.2$, H–C(3′,5′)); 6.94 – 6.82 (*m*, H–C(3′′), H–C(6′′)); 4.76 (*d*, $J(2,NH) = 8.0$, NH); 4.07 (br. *d*, $J(1a,1b) = 9.6$, H–C(1)); 4.02 (*m*, H–C(2)); 3.94 (*dd*, $J(1a,1b) = 9.6$, $J(1b,2) = 3.2$, H–C(1)); 2.79, 2.75 (*AB*, $J_{AB} = 15.8$, CH$_2$(3)); 2.45 (*s*, Ar*Me*); 1.34 (*s*, ^{t}Bu). ^{13}C-NMR (100 MHz, CDCl$_3$): 156.4 (*ddd*, $J(C,F) = 243.4$, 9.2, 2.6, C(2′′)); 155.1 (CO); 149.2 (*dt*, $J(C,F) = 250.0$, 12.8, 12.8, C(4′′)); 146.8 (*ddd*, $J(C,F) = 243.8$, 12.1, 3.5, C(5′′)); 145.5 (C(1′)); 132.5 (C(4′)); 130.2 (C(2′), C(6′)); 128.2 (C(3′), C(5′)); 120.6 (*dt*, $J(C,F) = 18.2$, 4.6, C(1′′)); 119.1 (*dd*, $J(C,F) = 19.0$, 5.5, C(6′′)); 105.6 (*dd*, $J(C,F) = 28.3$, 20.7,

C(3″)); 80.2 (Me$_3$*C*); 70.8 (C(1)); 49.8 (C(2)); 30.7 (C(3)); 28.4 (*Me*$_3$C); 21.9 (Ar*Me*). Anal. calc. for C$_{21}$H$_{24}$F$_3$NO$_5$S (459.48): C 54.89, H 5.26, N 3.05, S 6.98; found: C 54.62, H 5.19, N 3.16, S 7.29.

tert-*Butyl [(2*R*)-1-Cyano-3-(2,4,5-trifluorophenyl)propan-2-yl]carbamate* (**13**) [9]. Compound **12** (138 mg, 0.30 mmol) and NaCN (58.8 mg, 1.20 mmol) were dissolved in 2 ml of DMF. This suspension was heated to 80° for 19 h. DMF was evaporated, and the dark brown residue was subjected to CC (AcOEt/hexane) to give **13** (72.0 mg, 76%). White solid. R_f (AcOEt/hexane 3 : 7) 0.56. M.p. 131 – 133°. [α]$_D^{25}$ = +38 (*c* = 1, CHCl$_3$). IR (KBr): 3326, 2974, 2929, 2246, 1683, 1520, 1421, 1345, 1275, 1226, 1168. ^{1}H-NMR (400 MHz, CDCl$_3$): 7.06 (*ddd*, *J*(H,F) = 15.6, 8.4, 6.8, H–C(6′)); 6.93 (*dt*, *J*(H,F) = 9.6, 6.8, H–C(3′)); 4.84 (*d*, *J*(3,NH) = 7.6, NH); 4.06 (*m*, H–C(3)); 3.01 – 2.85 (*AB*, 2 H–C(2)); 2.74, 2.56 (*AB*, J_{AB} = 16.8, 4.8, CH$_2$(4)); 1.39 (*s*, ^{t}Bu). ^{13}C-NMR (100 MHz, CDCl$_3$): 156.3 (*ddd*, *J*(C,F) = 243.2, 9.2, 2.6, C(2′)); 155.0 (CO); 149.5 (*dt*, *J*(C,F) = 249.4, 12.3, C(4′)); 147.0 (*ddd*, *J*(C,F) = 244.4, 12.5, 3.6, C(5′)); 120.0 (*dt*, *J*(C,F) = 17.9, 5.3, C(1′)); 119.1 (*dd*, *J*(C,F) = 19.1, 5.6, C(6′)); 117.1 (CN); 106.0 (*dd*, *J*(C,F) = 28.2, 20.8, C(3′)); 80.7 (Me$_3$*C*); 47.8 (C(3)); 32.9 (C(2)); 28.4 (*Me*$_3$C); 23.4 (C(4)). HR-ES-MS: 315.1300 ([*M* + 1]$^+$; calc. 315.1315). HPLC: *Chiralyser*, *OD* column; 15% ^{i}PrOH/hexane; 1 ml/min; 254 nm; ee > 99%. Anal. calc. for C$_{15}$H$_{17}$F$_3$N$_2$O$_2$: C 57.32, H 5.45, N 8.91; found: C 57.09, H 5.10, N 8.94.

*(3*R*)-3-{[(*tert-*Butoxy)carbonyl]amino}-4-(2,4,5-trifluorophenyl)butanoic Acid* (**14**) [9] [18]. Compound **13** (250 mg, 0.79 mmol) was dissolved in 10 ml of 3M KOH in H$_2$O and 8 ml of MeOH. The resulting mixture was heated to 90° for 20 h. After removal of the solvent under reduced pressure, H$_2$O (15 ml) was added to the residue, and the org. phase was extracted with AcOEt (20 ml). The aq. layer was acidified to pH of *ca.* 2 with 2M HCl. The org. material was extracted with AcOEt (3 × 30 ml) and dried (Na$_2$SO$_4$). The solvent was evaporated under reduced pressure, and the crude was purified by CC (SiO$_2$; CH$_2$Cl$_2$/MeOH 4 : 1) to give **14** (245 mg, 93%). White solid. M.p. 121 – 123° ([18]: 124 – 125°). [α]$_D^{25}$ = +21 (*c* = 1, CHCl$_3$; [18]: [α] = +32.3 (*c* = 1, CHCl$_3$)). IR (KBr): 3364, 2984, 2938, 2499, 1695, 1529, 1423, 1354, 1274, 1232, 1207, 1153, 1055. ^{1}H-NMR (400 MHz, CD$_3$OD): 7.17 (*ddd*, *J*(H,F) = 16.0, 8.8, 7.2, H–C(6′)); 7.06 (*dt*, *J*(H,F) = 10.0, 6.8, H–C(3′)); 4.98 (br. *s*, NH); 4.17 – 4.08 (*m*, H–C(3)); 2.92, 2.67 (*AB*, J_{AB} = 13.4, 9.2, 4.8, CH$_2$(2)); 2.55 – 2.44 (*AB*, 2 H–C(4)); 1.33 (*s*, ^{t}Bu). ^{13}C-NMR (100 MHz, CD$_3$OD): 173.4 (COOH); 156.7 (*dd*, *J*(C,F) = 242.2, 9.3, C(2′)); 156.3 (CO of carbamate); 148.9 (*dt*, *J*(C,F) = 246.8, 12.5, C(4′)); 146.5 (*ddd*, *J*(C,F) = 241.1, 12.5, 3.5, C(5′)); 122.3 (*dt*, *J*(C,F) = 18.1, 4.1, C(1′)); 119.3 (*dd*, *J*(C,F) = 19.2, 5.9, C(6′)); 105.0 (*dd*, *J*(C,F) = 29.0, 21.1, C(3′)); 79.7 (Me$_3$*C*); 38.9 (C(3)); 33.3 (C(2)); 27.5 (*Me*$_3$C); 27.2 (C(2)). Anal. calc. for C$_{15}$H$_{18}$F$_3$NO$_4$ (333.30): C 54.05, H 5.44, N 4.20; found: C 54.07, H 5.26, N 4.15.

*Methyl (3*R*)-3-{[(*tert-*Butoxy)carbonyl]amino}-4-(2,4,5-trifluorophenyl)butanoate* (**15**) [18]. To a soln. of **14** (77.0 mg, 0.23 mmol) in MeOH (10 ml) at 0° was added SOCl$_2$ (0.03 ml, 41.6 mg, 0.35 mmol). The ice-bath was removed, and the resulting soln. was heated to reflux and stirred for 20 h. The solvent was removed under reduced pressure. The residue was purified by CC (MeOH/CH$_2$Cl$_2$ 1 : 19) to give **15** (68.0 mg, 85%). White solid. R_f (MeOH/CH$_2$Cl$_2$ 1 : 19) 0.50. M.p. 90 – 92° ([18]: 88 – 88.5°). [α]$_D^{25}$ = +15.6 (*c* = 1, MeOH; [18]: [α] = +15.2 (*c* = 1, MeOH)). IR (KBr): 3356, 3062, 2995, 2955, 1736, 1676, 1527, 1422, 1324, 1290, 1213, 1158. ^{1}H-NMR (400 MHz, CDCl$_3$): 7.03 (*ddd*, *J*(H,F) = 16.0, 8.8, 7.2, H–C(6′)); 6.87 (*dt*, *J*(H,F) = 9.6, 6.8, H–C(3′)); 5.14 (*d*, *J*(3,NH) = 8.4, NH); 4.20 – 4.05 (*m*, H–C(3)); 3.68 (*s*, MeO); 2.90 – 2.76 (*AB*, CH$_2$(2)); 2.56, 2.50 (*AB*, J_{AB} = 16.2, 5.6, 5.4, CH$_2$(4)); 1.35 (*s*, ^{t}Bu). ^{13}C-NMR (100 MHz, CDCl$_3$): 171.8 (*C*OOMe); 156.2 (*ddd*, *J*(C,F) = 242.8, 9.0, 2.5, C(2′)); 155.0 (CO of carbamate); 148.8 (*dt*, *J*(C,F) = 248.6, 14.1, C(4′)); 146.6 (*ddd*, *J*(C,F) = 243.1, 12.4, 3.6, C(5′)); 121.3 (*ddd*, *J*(C,F) = 18.2, 5.4, 4.1, C(1′)); 119.0 (*dd*, *J*(C,F) = 19.0, 6.0, C(6′)); 105.3 (*dd*, *J*(C,F) = 28.5, 20.7, C(3′)); 79.5 (Me$_3$*C*); 51.7 (MeO); 47.7 (C(3)); 37.8 (C(2)); 33.0 (C(4)); 28.2 (*Me*$_3$C). HPLC: *Chiralyser*, *OD* column; 5% ^{i}PrOH/hexane; 1 ml/min; 254 nm; ee > 99% enantiomeric excess. Anal. calc. for C$_{16}$H$_{20}$F$_3$NO$_4$: C 55.33, H 5.80, N 4.03; found: C 55.23, H 5.92, N 3.86.

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