Novel and Stereospecific Synthesis of (2*S*)-3-(2,4,5-Trifluorophenyl)propane-1,2-diol from D-Mannitol

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A stereospecific synthesis of (2*S*)-3-(2,4,5-trifluorophenyl)propane-1,2-diol from D-mannitol has been developed. The reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde with 2,4,5-trifluorophenylmagnesium bromide gave [(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl](2,4,5-trifluorophenyl)methanol in 65% yield as a mixture of diastereoisomers (1:1). The Ph_3P catalyzed reaction of the latter with C_2Cl_6 followed by reduction with Pd/C-catalyzed hydrogenation gave (2*S*)-3-(2,4,5-trifluorophenyl)propane-1,2-diol with >99% ee and 65% yield.

Introduction. – β-Amino acids are used as important precursors in drug and synthetic chemistry. Many approaches have been developed for their efficient synthesis [1]. Sitagliptin (**1**) is a reversible inhibitor of the dipeptidyl peptidase IV (DPP-IV) enzyme [2] and consists of β-amino acid **2** and a triazolopyrazine unit (*Fig.*). Several methods for the synthesis of **1** are known [3]. These methods mainly based on coupling of the β-amino acid and the triazolopyrazine unit and differ by the preparation of the β-amino acid unit. In most concepts, the chiral center has been formed during the

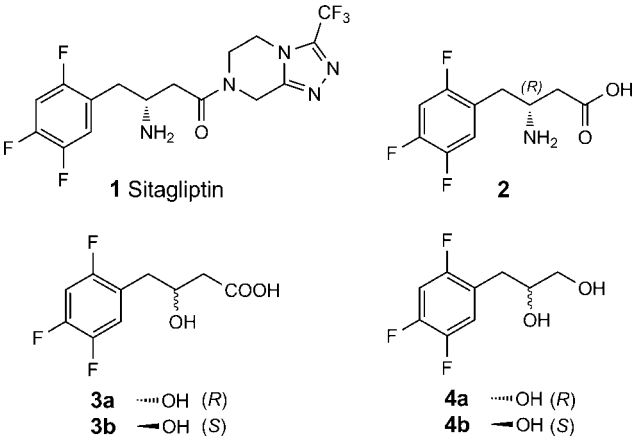


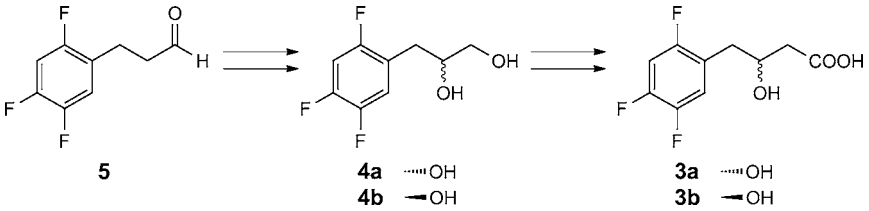
Figure. *Sitagliptin* (**1**)*, β-amino acid* **2***, β-hydroxy acids* **3***, and 1,2-diols* **4**

synthesis. Recently, the synthesis of (*R*)-*β*-amino acid has been realized from a chiral starting material from the chiral pool [4]. In this context, we reported an efficient synthesis of **2** starting from (*S*)-serine, a natural amino acid [5].

The *β*-hydroxy acids **3** have been used as key compounds for the synthesis of **2** (*Fig.*). Furthermore, imidazopyrazinone derivatives of *β*-amino acid **2** [6] and benzopyranyl esters of *β*-hydroxy acid **3b** [7] have shown DPP-IV inhibitory activity. The use of **3b** in the synthesis of the *β*-amino acid moiety **2** of sitagliptin was described by *Hansen et al.* [8]. The synthesis is based on asymmetric hydrogenation of the carbonyl group of methyl 4-(2,4,5-trifluorophenyl)-3-oxobutanoate in the presence of $BinapRuCl_2$ catalysis. *Niddam-Hildesheim* has recently developed the synthesis of the methyl ester of **3b** using an enzymatic method [9]. More recently, *Kim et al.* have also synthesized **3b** starting from (*S*)-epichlorohydrin [10]. In our previous article, we described the stereoselective synthesis of (3*R*)- and (3*S*)-3-hydroxy-4-(2,4,5-trifluorophenyl)butanoic acid (**3**) starting from 3-(2,4,5-trifluorophenyl)propanal [11] (*Scheme 1*). In this method, (2*R*)- and (2*S*)-3-(2,4,5-trifluorophenyl)propane-1,2-diol (**4a** and **4b**, resp.) were first synthesized *via* a D- and L-proline catalyzed oxyamination reaction in which the stereogenic center at the 2-position of the diol was formed.

We report herein a novel and practical stereospecific synthesis of (2*S*)-3-(2,4,5-trifluorophenyl)propane-1,2-diol **4b** from readily available D-mannitol.

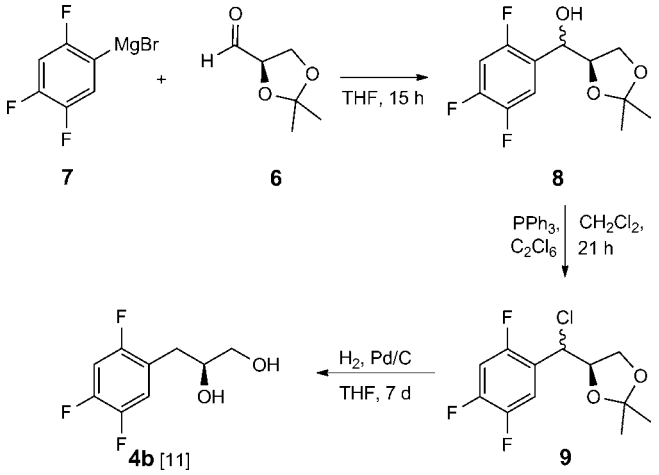
Scheme 1. *Synthesis of β-Hydroxy Acid* **3** [11]



Results and Discussion. – Our synthesis of (4*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**6**) started from D-mannitol using a known method reported in the literature [12]. In this procedure, D-mannitol was ketalized to provide 1,2:5,6-isopropylidene-D-mannitol, and subsequently the 3,4-glycol linkage was cleaved with either $(AcO)_4Pd$ or $NaIO_4$. Then, **6** was used as a chiral pool material. For this purpose, first, 2,4,5-trifluorophenylmagnesium bromide (**7**) was prepared by the reaction of 1-bromo-2,4,5-trifluorobenzene with Mg in the presence of 1,2-dibromoethane. Subsequently, aldehyde **6** was reacted with **7** to give compound **8** in 65% yield as a mixture of diastereoisomers (1:1) (*Scheme 2*).

For practical reasons, the diastereoisomeric alcohols **8** were not isolated, but directly subjected to further reaction. The reduction of the benzylic OH group was carried out by various methods [13]. One of these methods is a direct Pd/C-catalyzed hydrogenation of benzylic ketones or alcohols. However, this methodology was not suitable to reduce the benzylic OH group of **8**. Therefore, we converted alcohol **8** into the corresponding chloride **9** in analogy to the *Appel* method [14], which then was submitted to Pd/C-catalyzed hydrogenation to afford diol **4b** (*Scheme 2*). During the

Scheme 2. *Synthesis of (2S)-3-(2,4,5-Trifluorophenyl)propane-1,2-diol* (**4b**)



reduction of the C–Cl bond by hydrogenation, the ketal group was also removed from the molecule. Thus, the synthesis of the targeted diol was performed from compound **9** in one step.

The chirality of the benzylic C-atom in ketal **9** was lost during the formation of diol **4b**. Hence, the diastereoisomeric mixture **9** was converted into a single enantiomer of **4b**. Analysis of (2*S*)-diol **4b** showed an enantiomeric purity of $>99\%$. The optical rotation of **4b** was found to be $[\alpha]_D^{26} = -36$, which is in perfect agreement with our previously reported value [11]. We think that diol **4b** can be used in syntheses of biological active compounds as a synthon.

Conclusions. – A novel and efficient stereospecific synthesis of (2*S*)-3-(2,4,5-trifluorophenyl)propane-1,2-diol (**4b**) was achieved from easily accessible D-mannitol. This procedure is attractive for the synthesis of chiral diols, β-hydroxy acids and β-amino acids because of its quite simple, economical operation and adaptability to large scale synthesis.

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Experimental Part

General. All reagents used were commercially available unless otherwise specified, and all solvents were distilled before use. HPLC: *Thermo Finnigan Spectra System P1000* with a polarimetric chiralyser detector, with a chiral column (*Chiralcel® OD*). M.p.: *Gallenkamp* melting-point devices, uncorrected. Optical rotations: *Bellingham Stanley* ADP polarimeter with a 1 dm tube. ^{1}H- and ^{13}C-NMR Spectra: *Varian 400* and *Bruker 400* spectrometers; δ in ppm rel. to Me_4Si as internal standard, J in Hz. Elemental analyses: *Leco CHNS-932* instrument.

2,3-O-*Isopropylidene*-D-*glyceraldehyde* (=(4*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde; **6**) was synthesized according to the literature procedure [12].

*[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl](2,4,5-trifluorophenyl)methanol* (**8**; 1:1-mixture of diastereoisomers). To a suspension of Mg (479 mg, 19.9 mmol) in THF (35 ml) was added 1,2-dibromoethane (0.2 ml) and 2,4,5-trifluorobromobenzene (4.2 g, 2.3 ml), and the mixture was stirred vigorously until all of the metallic Mg had reacted resulting in a yellow soln. To this soln. was added a soln. of (4*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**6**; 2 g, 15.4 mmol) in THF (20 ml), and the mixture was stirred for 15 h at r.t. under N_2. After the reaction was completed, a sat. aq. soln. of NH_4Cl (30 ml) was added, then the mixture was extracted with AcOEt (3 × 25 ml). The combined org. layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified *via* silica gel CC with AcOEt/hexane (1:1) to give **8** as a *ca*. 1:1 mixture of diastereoisomers (2.5 g, 65%) as yellow oil (R_f = 1.5, AcOEt/hexane 1:1). ^{1}H-NMR (400 MHz, $CDCl_3$): **8a**: 7.42–7.28 (*m*, H–C(6′)); 6.97–6.89 (*m*, H–C(3′)); 5.12 (*t*, *J* = 2.7, C*H*–OH); 4.35–4.20 (*m*, H–C(4)); 3.97–3.80 (*m*, CH_2(5)); 2.74 (*d*, *J* = 2.7, OH); 1.46 (*s*, Me); 1.38 (*s*, Me). **8b**: 7.42–7.28 (*m*, H–C(6′)); 6.97–6.89 (*m*, H–C(3′)); 4.98 (*t*, *J* = 4.3 C*H*–OH); 4.35–4.20 (*m*, H–C(4)); 3.97–3.80 (*m*, CH_2(5)); 2.97 (*d*, *J* = 4.3, OH); 1.51 (*s*, Me); 1.42 (*s*, Me). ^{13}C-NMR (100 MHz, $CDCl_3$): **8a**: 154.5 (C(2′)); 148.4 (C(4′, 5′)); 123.7 (C(1′)); 116.3 (*dd*, *J*(C,F) = 20, 5, C(6′)); 110.0 (C(2)); 105.4 (*dd*, *J*(C,F) = 28.2, 20.8, C(3′)); 79.1 (C(4)); 67.8 (C(5)); 65.8 (CH–OH); 26.3 (Me); 25.0 (Me). **8b**: 154.5 (C(2′)); 148.4 (C(4′, 5′)); 123.7 (C(1′)); 115.7 (*dd*, *J*(C,F) = 20, 6, C(6′)); 110.3 (C(2)); 105.5 (*dd*, *J*(C,F) = 27.9, 20, (C(3′)); 77.4 (C(4)); 66.4 (C(5)); 64.4 (CH–OH); 26.6 (Me); 25.1 (Me). Anal. calc. for $C_{12}H_{13}F_3O_3$ (262.08): C 54.96, H 5.00; found: C 54.71, H 5.10.

*(4*R*)-4-[Chloro(2,4,5-trifluorophenyl)methyl]-2,2-dimethyl-1,3-dioxolane* (**9**; 1:1-mixture of diastereoisomers). Ph_3P (892 mg, 3.4 mmol) and hexachloroethane (805 mg, 3.4 mmol) were dissolved in CH_2Cl_2 (20 ml) and stirred for 10 min at r.t. under N_2. Then, a soln. of **8** (638 mg, 2.4 mmol) in CH_2Cl_2 (5 ml) was added. The mixture was stirred at r.t. for 21 h. After completion, checked by TLC, a sat. aq. soln. of NH_4Cl (20 ml) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 ml). The combined org. layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified *via* silica gel CC with AcOEt/hexane (1:1) to give **9** (510 mg, 74%) as yellow oil. (R_f = 0.2, 5:95 AcOEt/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$): **9a**: 7.48–7.42 (*m*, H–C(6′)); 6.98–6.91 (*m*, H–C(3′)); 5.14 (*d*, *J* = 5.9, CH–Cl); 4.50–4.40 (*m*, H–C(4)); 3.99 (*dd*, *J* = 8.8, 6.5, H–C(5)); 3.80 (*dd*, *J* = 8.8, 5.5, H–C(5)); 1.45 (*s*, Me); 1.39 (*s*, Me). **9b**: 7.36–7.29 (*m*, H–C(6′)); 6.98–6.91 (*m*, H–C(3′)); 4.99 (*d*, *J* = 9.1, CH–Cl); 4.50–4.40 (*m*, H–C(4)); 4.22 (*dd*, *J* = 9.2, 5.9, H–C(5)); 4.13 (*dd*, *J* = 9.2, 4.1, H–C(5)); 1.38 (*s*, Me); 1.38 (*s*, Me); ^{13}C-NMR (100 MHz, $CDCl_3$): **9a**: 154.5 (C(2′)); 148.4 (C(4′, 5′)); 125.2 (C(1′)); 117.8 (C(6′)); 111.1 (C(2)); 105.8 (C(3′)); 78.7 (C(4)); 66.8 (C(5)); 54.9 (CH–Cl); 26.9 (Me); 26.5 (Me). **9b**: 154.5 (C(2′)); 148.4 (C(4′, 5′)); 125.7 (C(1′)); 117.8 (C(6′)); 111.0 (C(2)); 105.8 (C(3′)); 78.8 (C(4)); 68.0 (C(5)); 54.4 (CH–Cl); 25.5 (Me); 25.3 (Me). Anal. calc. for $C_{12}H_{12}ClF_3O_2$ (280.05): C 51.35, H 4.31; found: C 51.14, H 4.35.

*(2*S*)-3-(2,4,5-Trifluorophenyl)propane-1,2-diol* (**4b**). To a suspension of Pd/C (20%) in EtOH (10 ml) was added **9** (400 mg, 1.4 mmol). The reaction flask was purged with H_2 gas three times before being allowed to stir under a H_2 atmosphere for 7 d at r.t. Upon completion, the mixture was filtered and concentrated *in vacuo*. The crude product was purified *via* silica gel CC with AcOEt/hexane (1:1) to give **4b** (190 mg, 65%) as white solid. R_f = 0.2, AcOEt/hexane 1:1. M.p.: 68–69°, $[\alpha]_D^{26} = -36$ (*c* = 1, EtOH); see [11].

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