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

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As stereospecific synthesis of (2S)-3-(2,4,5-trifluorophenyl)propane-1,2-diol from \( \delta \)-mannitol has been developed. The reaction of 2,3-\( O \)-isopropylidene-\( \delta \)-glyceraldehyde with 2,4,5-trifluorophenyl-magnesium bromide gave \([(4R)-2,2\text{-dimethyl-1,3-dioxolan-4-yl}](2,4,5\text{-trifluorophenyl})\text{methanol in 65% yield as a mixture of diastereoisomers (1:1). The Pd}_2\text{P catalyzed reaction of the latter with } C\text{Cl}_6\text{ followed by reduction with Pd/C-catalyzed hydrogenation gave (2S)-3-(2,4,5-trifluorophenyl)propane-1,2-diol with } >99\% \text{ ee and 65% yield.}

Introduction. – \( \beta \)-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 \( \beta \)-amino acid 2 and a triazolopyrazine unit (Fig. 1). Several methods for the synthesis of 1 are known [3]. These methods mainly based on coupling of the \( \beta \)-amino acid and the triazolopyrazine unit and differ by the preparation of the \( \beta \)-amino acid unit. In most concepts, the chiral center has been formed during the

![Figure. Sitagliptin (1), \( \beta \)-amino acid 2, \( \beta \)-hydroxy acids 3, and 1,2-diols 4](image-url)
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 benzopyranyle 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 BinapRuCl₂ 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 (3R)- and (3S)-3-hydroxy-4-(2,4,5-trifluorophenyl)butanoic acid (3) starting from 3-(2,4,5-trifluorophenyl)propanal [11] (Scheme 1). In this method, (2R)- and (2S)-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 (2S)-3-(2,4,5-trifluorophenyl)propane-1,2-diol 4b from readily available d-mannitol.

**Results and Discussion.**

Our synthesis of (4R)-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 NaIO₄. 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 benzyl OH group was carried out by various methods [13]. One of these methods is a direct Pd/C-catalyzed hydrogenation of benzyl ketones or alcohols. However, this methodology was not suitable to reduce the benzyl 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
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 (2S)-diol 4b showed an enantiomeric purity of >99%. The optical rotation of 4b was found to be [α]D 36 = −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 (2S)-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 chiraliser 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. 1H- and 13C-NMR Spectra: Varian 400 and Bruker 400 spectrometers; δ in ppm rel. to Me4Si as internal standard, J in Hz. Elemental analyses: Leco CHNS-932 instrument.

2,3-O-Isopropylidene-α-glyceraldehyde (= (4R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde; 6) was synthesized according to the literature procedure [12].
[(4R)-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 (4R)-2,2-dimethyl-1,3-dioxolan-4-carbaldehyde (6; 2 g, 15.4 mmol) in THF (20 ml), and the mixture was stirred for 15 h at r.t. under N₂. After the reaction was completed, a sat. aq. soln. of NH₄Cl (30 ml) was added, then the mixture was extracted with AcOEt (3 x 25 ml). The combined org. layers were dried (Na₂SO₄), 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 (R₁ = 1.5, AcOEt/hexane 1:1). ¹H-NMR (400 MHz, CDCl₃): 8a: 7.42 –7.28 (m, H–C(6')); 6.97 –6.89 (m, H–C(3')); 5.12 (t, J = 2.7, CH–OH); 4.35 –4.20 (m, H–C(4')); 3.97 –3.80 (m, CH₂(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 CH–OH); 4.35 –4.20 (m, H–C(4')); 3.97 –3.80 (m, CH₂(5)); 2.97 (d, J = 4.3, OH); 1.51 (s, Me); 1.42 (s, Me). ¹³C-NMR (100 MHz, CDCl₃): 8a: 154.5 (C(2')); 148.4 (C(4', 5')); 123.7 (C(1')); 116.3 (dd, J(C,CF) = 20, 5, C(6')); 110.0 (C(2')); 105.4 (dd, J(C,CF) = 28.2, 20.8, C(3')); 79.1 (C(4)); 678 (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,CF) = 20, 6, C(6')); 110.3 (C(2')); 105.5 (dd, J(C,CF) = 279, 20, (C(3')); 774 (C(4)); 66.4 (C(5)); 64.4 (CH–OH); 26.6 (Me); 25.1 (Me). Anal. calc. for C₂₉H₂₆F₁₃O₆: C 54.96, H 5.00; found: C 54.71, H 5.10.

(4R)-4-[Chloro(2,4,5-trifluorophenyl)methyl]-2,2-dimethyl-1,3-dioxane (9; 1:1 mixture of diastereoisomers). Ph₂P (892 mg, 3.4 mmol) and hexachloroethane (805 mg, 3.4 mmol) were dissolved in CH₂Cl₂ (20 ml) and stirred for 10 min at r.t. under N₂. Then, a soln. of 8 (638 mg, 2.4 mmol) in CH₂Cl₂ (5 ml) was added. The mixture was stirred at r.t. for 21 h. After completion, checked by TLC, a sat. aq. soln. of NH₄Cl (20 ml) was added and the mixture was extracted with CH₂Cl₂ (3 x 15 ml). The combined org. layers were dried (Na₂SO₄), 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. (R₁ = 0.2, 5.95 AcOEt/hexane). ¹H-NMR (400 MHz, CDCl₃): 9a: 7.48 –7.42 (m, H–C(6')); 6.98 –6.91 (m, H–C(3')); 5.14 (dd, J = 5.9, CH–CI); 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 (dd, J = 9.1, CH–CI); 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). ¹³C-NMR (100 MHz, CDCl₃): 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–CI); 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–CI); 25.5 (Me); 25.3 (Me). Anal. calc. for C₂₉H₂₂Cl₃F₁₂O₅ (280.05): C 51.35, H 4.31; found: C 51.14, H 4.35.

(2S)-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 H₂ gas three times before being allowed to stir under a H₂ 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. R₁ = 0.2, AcOEt/hexane 1:1. M.p.: 68 –69 °C; [α]₁₅ο = −36 (c = 1, EtOH); see [11].

REFERENCES

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