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The Revised Structure of the Antibiotic Tü 1718 B Confirmed by Synthesis

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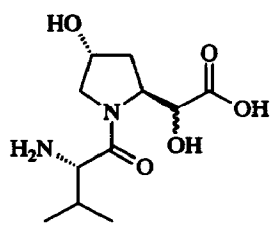
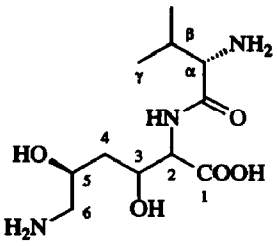
Abstract: The revised structure of the dipeptide antibiotic Tü 1718 B was confirmed by synthesis of two possible diastereoisomers of L-valyl-dihydroxylysine **2**. Comparison of the NMR spectra of the synthetic and natural products indicates (2S,3S,5S)- or (2S,3R,5S)-configuration for the natural product.

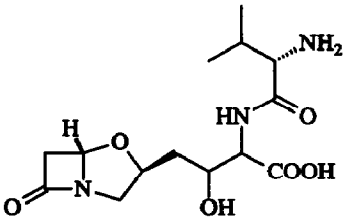
From the culture broth of *Streptomyces antibioticus ssp. antibioticus* Tü 1718 three antibiotically active metabolites have been isolated[1]. Two of them, (2S,5S)-2-(2-hydroxyethyl)clavam (Tü 1718 A_1) and valclavam[2] (Tü 1718 A_2), exhibit (2S,5S)-configuration. In contrast to most other ß-lactam antibiotics and (2R,5R)-clavams, eg. the ß-lactamase inhibitor clavulanic acid, these clavams display a broad spectrum of antifungal activities and an inhibition of their bacteriostatic effects by methionine and its biosynthetic precursors[3]. To the third metabolite, Tü 1718 B, the tentative structure of a L-valyl-dihydroxyhomoproline **1** was assigned[4] and disproved by synthesis[5].



1



2



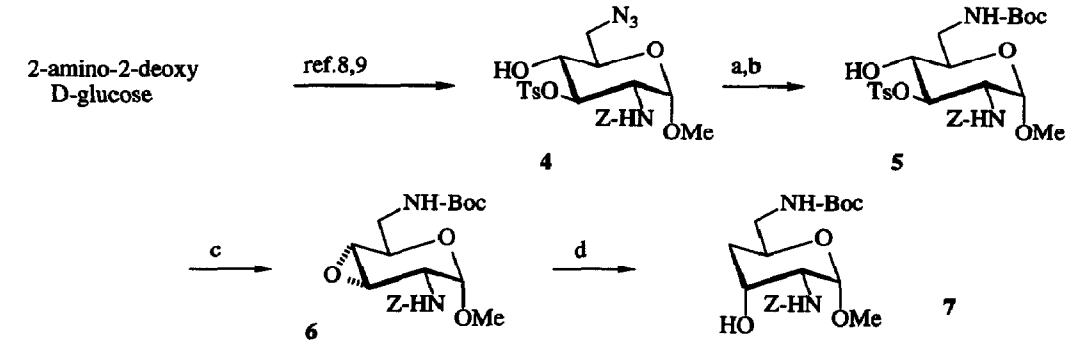
3

The published results of NMR[4] and our own mass spectrometric measurements of the natural product[6] led us come to the conclusion that Tü 1718 B should be represented by a non-cyclic L-valyl-dihydroxylysine structure. Recently, this assumption was confirmed by NMR-spectral investigations of a degradation product of valclavam leading to the revised structures **2** for Tü 1718 B and **3** for valclavam[7]. Thus, we undertook the synthesis of two isomers of **2** to confirm its identity with Tü 1718 B and to determine the correct stereochemistry of the antibiotic. Since the 5-OH function most likely represents a partial structure of the degraded clavam system, a (5S)-configuration could be assumed with respect to the known stereochemistry[8]

of (2S,5S)-2-(2-hydroxyethyl)clavam (Tü 1718 A_1). Our synthetic approach is based on a chiral pool strategy starting from 2-amino-2-deoxy-glucose (Scheme 1).

Reduction of the azido derivative **4**, which was prepared from 2-amino-2-deoxy-glucose by known procedures[9], was carried out with $LiAlH_4$ in THF at low temperature (-20 - -15°C) to avoid side reactions. Without further purification the thus-obtained amine was treated with di-*tert*-butyldicarbonate to afford the protected diamino sugar **5**. The desired deoxygenation at C-4 and inversion at C-3 was accomplished by formation of the epoxide **6**, followed by reduction with $LiAlH_4$. The hydride attack occurs regioselectively at C-4 (> 20:1) to give the *allo*-compound **7**.

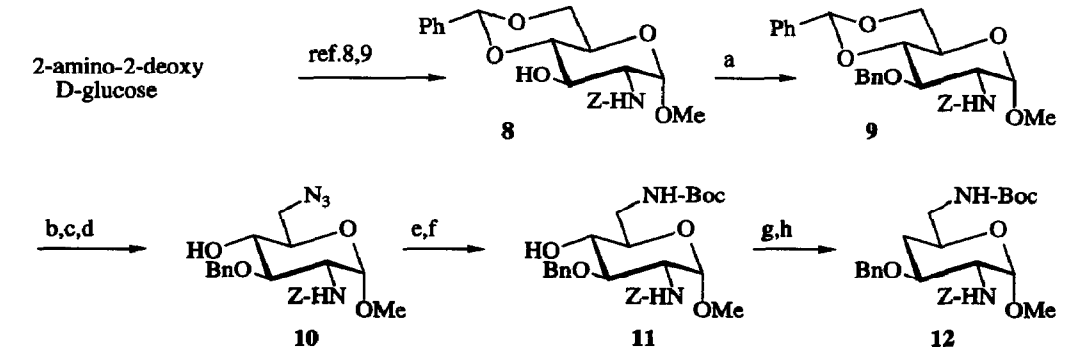
Scheme 1



a: $LiAlH_4$, THF, -15°C; b: $(Boc)_2O$, Na_2CO_3 (67%); c: K_2CO_3, MeOH; d: $LiAlH_4$, THF, -5°C (60%).

The 6-azido-6-deoxy-3-O-benzyl derivative **10** was prepared as described for the 3-O-tosyl derivative **4**[8], with the only difference that the benzylidene derivative **8**, which was prepared from 2-amino-2-deoxy-D-glucose in three steps[8,10,11], was converted to the benzyl ether **9** instead of the tosyl derivative (Scheme 2). Following hydrolysis of the benzylidene acetal, mono-tosylation of the primary hydroxy group and substitution with lithium azide in DMF afforded the azido derivative **10**, from which the Boc-protected amino function was generated as described before. Deoxygenation of the alcohol **11** was achieved by reduction of the tosylate with $NaBH_4$ in DMSO to give the *gluco*-compound **12**.

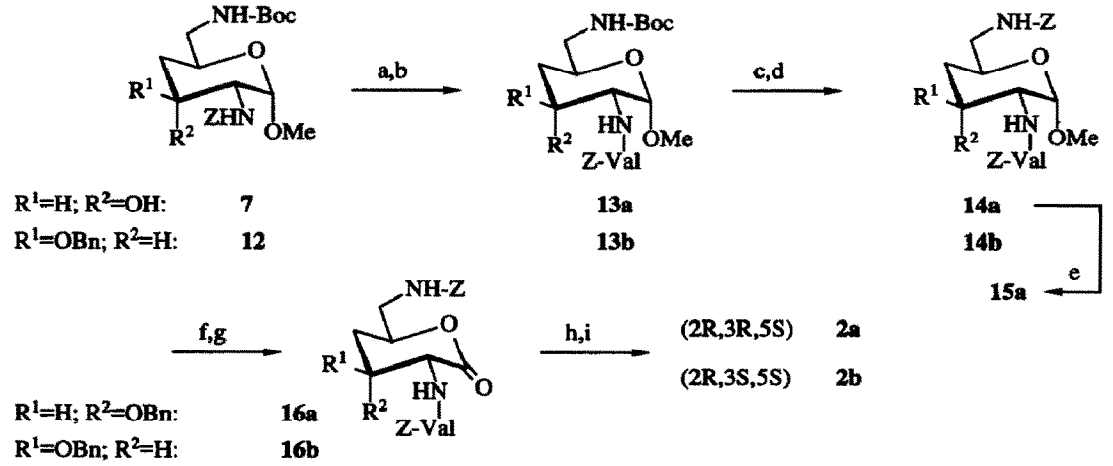
Scheme 2



a: BnBr, BaO, $Ba(OH)_2$, DMF (69%); b: 70% AcOH, 40°C; c: TsCl, pyridine (96%); d: LiN_3, DMF, 75°C (80%); e: $LiAlH_4$, THF, -5°C; f: $(Boc)_2O$, Na_2CO_3 (81%); g: TsCl, pyridine (64%); h: $NaBH_4$, DMSO, 85°C (30%).

For the introduction of the valine unit both isomers **7** and **12** were subjected to catalytic hydrogenation with Pd/charcoal without loss of the benzyl protecting group of **12** (Scheme 3). The resulting amines were coupled with Z-L-valine in the presence of DCC and 1-hydroxybenzotriazole (HOBt). With respect to the acidic conditions during glycoside hydrolysis, the Boc amino groups of **13a** and **13b** were converted to the Z-derivatives **14a** and **14b** by subsequent treatment with trifluoroacetic acid and benzyl chloroformate. After benzyl protection of the free hydroxy group in **14a**, glycoside cleavage of **15a** and **14b** with diluted p-toluenesulfonic acid provided the anomeric mixtures of the free sugars, which were oxidized with PDC in DMF to give the lactones **16a** and **16b**. Finally, the free dipeptides **2a** and **2b** were obtained by saponification of the lactones and complete deprotection with boron tribromide. Purification was achieved by repeated Sephadex G10 chromatography.

Scheme 3



a: H_2, Pd/C, MeOH; b: Z-Val, DCC, HOBt, THF (**13a**: 61%, **13b**: 85%); c: TFA, CH_2Cl_2, 0°C; d: BnOCOCl, $NaHCO_3$ (**14a**: 61%, **14b**: 73%); e: BnBr, BaO, $Ba(OH)_2$, DMF (61%); f: 2M TsOH, dioxane, 80°C (**a**: 88%, **b**: 36%); g: PDC, DMF (**16a**: 53%, **16b**: 30%); h: 1M NaOH, dioxane; i: BBr_3, CH_2Cl_2 (**2a**: 35%, **2b**: 34%).

Trimethylsilylation of the synthetic products **2** afforded volatile derivatives predominantly containing five trimethylsilyl (TMS) groups, which were investigated by combined gas chromatography/mass spectrometry using electron impact (EI) as well as chemical ionisation (CI). The EI spectrum shows m/z = 622 [M^+ - CH_3] as the ion of highest mass. The correct elemental composition of this ion was confirmed by exact mass measurement under high resolution conditions. The CI spectrum shows m/z = 638 $[M+H]^+$ (46%) and m/z = 566 (45%) indicating a mixture of compounds containing five and four TMS groups, respectively. Apart from small differences in relative signal intensities, the obtained mass spectra of **2a** and **2b** were identical with those of the natural product. These results are strongly supported by comparison of the ^{13}C-NMR spectra (Table 1). From the close correspondence of the chemical shift data and signal splitting of synthetic **2a** and **2b** and natural Tü 1718 B a valyl-dihydroxylysine structure must be concluded. The assignments of the resonances are confirmed by ^1H-^{13}C-COSY NMR measurements in the case of **2a**. Unfortunately, neither **2a** (2R,3R,5S) nor **2b** (2R,3S,5S) seem to represent the correct configuration of the

antibiotic as shown by comparison of the ^{1}H-NMR data (Table 1). Minor deviations of the 2-H and 3-H chemical shift values indicate an incorrect configuration of the synthetic products at these positions. Therefore a (2S,3S,5S)- or (2S,3R,5S)-configuration is more likely to be the correct stereochemistry for the antibiotic Tü 1718 B.

Table 1: Comparison of ^{13}C- and ^{1}H-NMR chemical shift values δ relative to TSP at 0.00 ppm in D_2O at pD = 7 of **2a** and **2b** with Tü 1718 B[4].

Positions	2a	2b	Tü 1718 B	2a	2b	Tü 1718 B
		^{13}C			^{1}H	
C-γ_a-Val	19.6	19.6	19.3	1.04	1.04	1.03
C-γ_b-Val	20.4	20.6	20.2	1.04	1.04	1.05
C-β-Val	32.4	32.6	32.5	2.22	2.22	2.30
C-4	39.4	41.3	40.4	1.73, 1.80	1.62	1.78
C-6	46.6	47.5	46.7	2.95, 3.19	2.92, 3.14	2.97, 3.18
C-α-Val	61.4	61.7	61.0	3.89	3.87	3.90
C-2	62.1	61.7	61.0	4.45	4.25	4.30
C-5	68.2	67.3	67.8	4.07	4.04	4.05
C-3	71.2	70.1	71.3	4.20	4.35	4.25
CO-Val	171.9	172.6	171.7, 177.9	-	-	-
COOH, COO^-	177.6	178.7, 180.7	183.5	-	-	-

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6. We thank Professor G. Jung, University of Tübingen, for a sample of Tü 1718 B
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