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Asymmetric Syntheses via Heterocyclic Intermediates; XV[1]. Enantioselective Synthesis of (*R*)-(−)-β-Hydroxyvaline using L-Valine or (*S*)-*O*,*O*-Dimethyl-α-methyldopa as Chiral Auxiliary Reagents

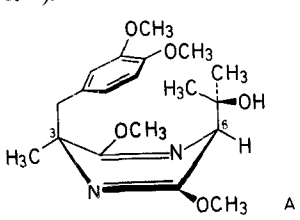
Ulrich SCHÖLLKOPF*, Joachim NOZULAK, Ulrich GROTH

Institut für Organische Chemie der Universität Göttingen, Tammannstraße 2, D-3400 Göttingen, Federal Republic of Germany

Dextrorotatory β-hydroxyvaline has been isolated from an antibiotically active peptide[2]. The compound itself has also been claimed to be biologically active[3]. Its configuration has been assigned (but not proven) as (*S*)-(+) by applying the Clough-Lutz-Jirgenson rule[4].

This communication describes two enantioselective syntheses of (*R*)-(−)-β-hydroxyvaline **(8)** which afford this compound in very high optical purity (probably optically pure[5]) and with predictable configuration. The results prove that the naturally occurring (+)-β-hydroxyvaline does indeed have the (*S*) ≡ L-configuration.

The lithiated bis-lactim ethers **2** or **5** obtained from the bis-lactim ether **1**[6] of cyclo-(L-Val-Gly) or bis-lactim ether **4**[7] of cyclo-[(*S*)-*O*,*O*-dimethyl-α-methyldopa-Gly] were treated with acetone to give the addition products **3** or **6a** with d.e. >95% or ~93%, respectively (d.e. = diastereomeric excess = asymmetric induction). In both cases, the (*R*)-configuration is induced at the new asymmetric center. For **6a**, this follows from the ^{1}H-N.M.R.-spectrum of the crude product. The minor isomer with (3*S*,6*S*)-configuration shows two methyl signals at $\delta = 0.85$ and 0.68 ppm, i.e., at unusually high field strength. This is due to its folded conformation A in which the two methyl groups are located within the shielding cone of the phenyl ring[8]. As for compound **3**, only one diastereoisomer was detected both in the ^{13}C-N.M.R.- and in the ^{1}H-N.M.R.-spectrum [also with Eu(fod)$_3$]; this isomer is the (6*S*,3*R*)-diastereoisomer for (*R*)-(−)-**8** was obtained on hydrolysis (see below).

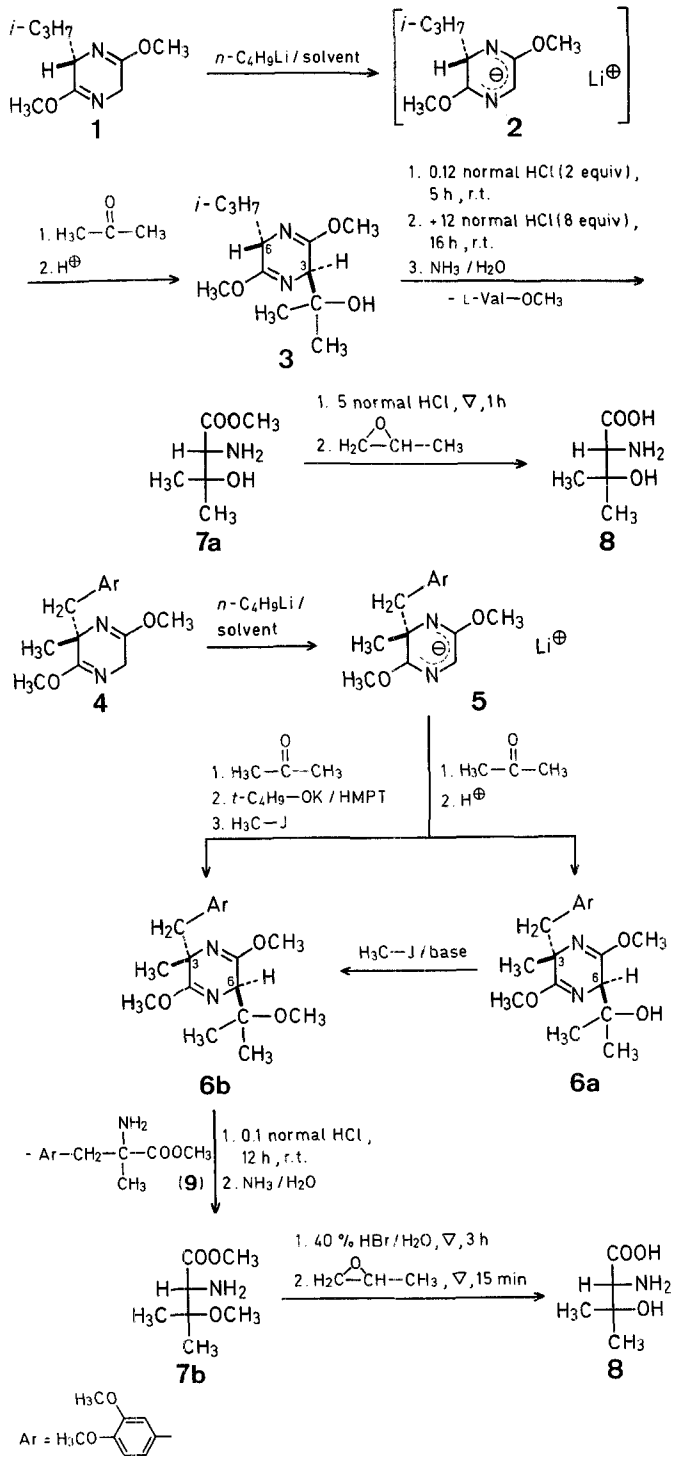


A

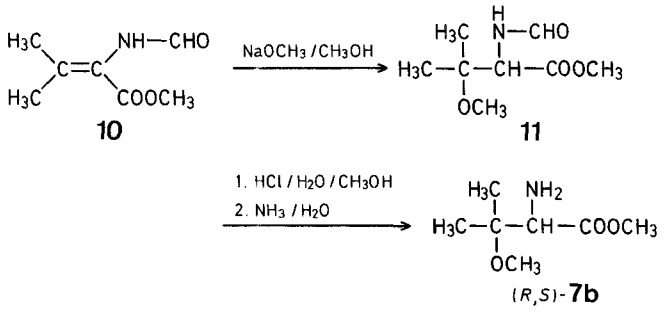
To obtain (*R*)-(−)-β-hydroxyvaline **(8)** from the adducts **3** or **6a**, the following procedures were used.

From **3**: Hydrolysis (under carefully controlled conditions with hydrochloric acid at room temperature) gave methyl L-valinate and methyl (*R*)-β-hydroxyvalinate **(7a)**. The two esters were separated by bulb-to-bulb distillation, and **7a** further hydrolyzed to (*R*)-β-hydroxyvaline **(8)** which was obtained with $[\alpha]_D^{20}$: −11.2° (*c* 1.5, 5 normal HCl).

From **6a**: Prior to hydrolysis, **6a** was *O*-methylated to give **6b** which was cleaved by 0.1 normal hydrochloric acid at room temperature to give (*S*)-*O*,*O*-dimethyl-α-methyldopa methyl ester **(9)** and methyl (*R*)-β-methoxyvalinate **(7b)** [e.e. ~93%, ^{1}H-N.M.R.-spectrometrically determined with Eu(hfc)$_3$]. Both esters were separated by distillation. Compound **7b** was converted into (*R*)-(−)-β-hydroxyvaline **(8)** with aqueous hydrobromic acid ($[\alpha]_D^{20}$: −11.3°, *c* 2.0, 5 normal hydrochloric acid[5]).



For comparison, racemic **7b** (D,L-**7b**) was prepared by treatment of methyl *N*-formyldehydrovalinate[9] **(10)** with sodium methoxide in methanol and hydrolytic deformylation of the resultant compound **11** with hydrochloric acid/methanol.



10 **11** (*R,S*)-**7b**

(3*R*,6*S*)-2,5-Dimethoxy-3-(2-hydroxy-2-propyl)-6-isopropyl-3,5-dihydropyrazine (3):

A 1.55 normal solution (2.7 ml, 4.2 mmol) of butyllithium in hexane is added by syringe to a stirred solution of bis-lactim ether **1**[6] (0.74 g, 4 mmol) in 1,2-dimethoxyethane (glyme) or tetrahydrofuran (8 ml) at −70 °C. The mixture is stirred for 10 min (formation of lithio derivative **2**). Then, a solution of acetone (0.26 g, 4.4 mmol) in glyme (5 ml) is added, stirring at −70 °C is continued for 1 h, a solution of glacial acetic acid (0.25 g, 4.2 mmol) in glyme (2 ml) is added, and the stirred mixture is allowed to warm to room temperature. The solvent is evaporated in vacuo and the residual product **3** is shaken with ether (10–15 ml) + water (20 ml). The layers are separated and the aqueous layer is extracted with ether (2 × 10 ml). The combined ether extract is dried with magnesium sulfate, the ether is evaporated, and the residual product **3** is purified by bulb-to-bulb distillation; yield: 0.95 g (98%); b.p. 75–85 °C (bath)/0.05 torr; d.e. > 95% [according to the ^{1}H-N.M.R. spectrum using Eu(fod)$_3$ and the ^{13}C-N.M.R. spectrum].

$C_{12}H_{22}N_2O_3$	calc.	C 59.48	H 9.15
(242.3)	found	59.60	9.15

I.R. (film): ν = 1690 (C=N); 3100–3500 cm^{-1} (OH).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 0.74, 1.09 [2 d, $CH(CH_3)_2$]; 1.17, 1.33 [2 s, $(\underline{H_3C})_2C$—OH]; 2.33 [dsp, $CH(CH_3)_2$]; 3.60–3.99 (br, OH); 3.75, 3.77 (2 s, OCH_3); 3.96 (dd, J = 3 Hz, ^5J = 3 Hz, 6-H); 4.00 ppm (d, ^5J = 3 Hz, 3-H).

^{13}C-N.M.R. ($CDCl_3$/TMS_{int}): δ = 16.45, 18.96 [$CH(CH_3)_2$]; 25.31, 26.27 [$(H_3\underline{C})_2C$—O]; 60.99 (C-6); 63.85 (C-3); 72.88 [$(H_3C)_2$—$\underline{C}$—O]; 161.78, 164.21 ppm (C=N).

3-(3,4-Dimethoxybenzyl)-2,5-dimethoxy-6-(2-hydroxy-2-propyl)-3-methyl-3,6-dihydropyrazine (6a) or 3-(3,4-Dimethoxybenzyl)-2,5-dimethoxy-6-(2-methoxy-2-propyl)-3-methyl-3,5-dihydropyrazine (6b):

A 1.6 normal solution (6.5 ml, 10 mmol) of butyllithium in hexane is added by syringe to a stirred solution of bis-lactim ether **4** (2.6 g, 8.5 mmol) in tetrahydrofuran (40 ml) at −70 °C. The mixture is stirred for 15 min (formation of lithio derivative **5**). Then, a solution of acetone (0.65 ml, 8.5 mmol) in tetrahydrofuran (10 ml) is added and stirring at −70 °C is continued for 12 h. From this point, different procedures are followed for compounds **6a** and **6b**.

Compound **6a**: The stirred mixture is allowed to warm to room temperature, a solution of glacial acetic acid (0.51 g, 8.5 mmol) in tetrahydrofuran is added, and the solvent is removed in vacuo. The residual crude product **6a** is shaken with phosphate buffer solution (pH 7; 15 ml). The aqueous phase is extracted with ether (4 × 30 ml), the ether extract is dried with magnesium sulfate, the volatile products are removed in vacuo, and the residual product **6a** is purified by bulb-to-bulb distillation; yield: 2.44 g (79%); b.p. 170 °C/0.05 torr.

I.R. (film): ν = 1685 cm^{-1} (C=N).

^{1}H-N.M.R. (CCl_4/C_6H_6): (3*S*,6*R*)-**6a** (~93% in the mixture of diastereoisomers): δ = 1.08, 1.20 ppm [$(H_3\underline{C})_2C$—OH]. (3*S*,6*S*)-**6a**: δ = 0.68, 0.85 ppm [2 s, $(H_3\underline{C})_2C$—OH].

Compound **6b**: The stirred mixture is allowed to warm to 0 °C. Potassium *t*-butoxide (0.95 g, 8.5 mmol) and HMPT (4.8 ml, 27 mmol) are added and the mixture is stirred at 0 °C for 30 min. Then, a solution of methyl iodide (2.41 g, 17 mmol) in tetrahydrofuran (10 ml) is added slowly and stirring is continued for 1 h at 0 °C. The mixture is kept at 40 °C for 24 h, then cooled to room temperature, and poured in ice water (60 ml) + ether (40 ml). The layers are separated and the aqueous layer is extracted with ether (4 × 30 ml). The combined ether extracts are dried with magnesium sulfate and the solvent is removed in vacuo. The residual product **6b** is purified by bulb-to-bulb distillation; yield: 2.8 g (88%); b.p. 160 °C/0.05 torr; d.e. ~ 93%.

$C_{20}H_{30}N_2O_5$	calc.	C 63.47	H 7.99
(378.5)	found	63.46	7.98

I.R. (film): ν = 1690 cm^{-1} (C=N).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): (3*S*,6*R*)-**6b** (93% in the mixture of diastereoisomers): δ = 1.08, 1.17 ppm [2 s, $(H_3\underline{C})_2C$—OH]. (3*S*,6*S*)-**6b**: δ = 0.92, 1.01 ppm [$(H_3\underline{C})C$—OH].

(*R*)-(−)-β-Hydroxyvaline Methyl Ester [(*R*)-7a]:

The hydrolysis **3**→**7a** is somewhat critical and requires strictly controlled conditions. The crude compound (3*R*,6*S*)-**3** (d.e. > 95%; 0.73 g, 3 mmol) is stirred with 0.12 normal hydrochloric acid (50 ml, 6 mmol) for 5 h at room temperature. Then, 12 normal hydrochloric acid (2 ml, 24 mmol) is added and stirring is continued for 16 h at room temperature. The mixture is extracted with ether (20 ml), the ether extract is discharged, the aqueous layer is concentrated in vacuo (bath temperature 40–60 °C) to a volume of ~3 ml, ether (10 ml) is added, and the pH is adjusted to 8–10 by the addition of concentrated aqueous ammonia with vigorous shaking. The ether layer is separated, the aqueous layer is extracted with ether (5 × 5–10 ml), and the combined ether phase is dried with magnesium sulfate. The ether is evaporated in vacuo and the residual mixture of L-Val-OCH_3 and **7a** is bulb-to-bulb distilled, L-Val-OCH_3 being removed as the forerun. The distillation is repeated; yield of **7a**: 0.26 g (59%); b.p. 70–80 °C (bath)/0.1 torr.

$C_6H_{13}NO_3$	calc.	C 48.97	H 8.90
(147.2)	found	48.99	8.82

I.R. (film): ν = 3150–3550 (NH_2, OH); 1740 (C=O); 1590 cm^{-1} (NH_2).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 1.16, 1.34 (2 s, CH_3); 2.37 (br s, NH_2, OH); 3.36 (s, CH); 3.78 ppm (s, OCH_3).

(*R*)-(−)-β-Methoxyvaline Methyl Ester [(*R*)-7b]:

Compound (3*S*,6*R*)-**6b** (d.e. ~ 93%; 2.1 g, 5.5 mmol) is stirred with 0.1 normal hydrochloric acid (110 ml, 11 mmol) for 12 h at room temperature. The mixture is then extracted with ether (30 ml), the ether extract is discharged, and the aqueous phase is evaporated in vacuo. The residue is dissolved in water (2–3 ml), aqueous 25% ammonia solution (1 ml) is added, and the mixture is extracted with ether (3 × 15 ml). The ether extract is dried with magnesium sulfate, the ether is evaporated, and the residual products **9** and **7b** are separated by bulb-to-bulb distillation, compound **7b** being obtained as the first fraction; yield of **7b**: 0.72 g (81%); b.p. 120 °C (bath/10 torr; e.e. ~ 90% [according to the OCH_3 singlets in the ^{1}H-N.M.R. spectrum using Eu(hfc)$_3$].

$C_7H_{15}NO_3$	calc.	C 52.16	H 9.38
(161.2)	found	52.33	9.29

I.R. (film): ν = 1740 (O—C=O); 1070 cm^{-1} (—C—OCH_3).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 1.21 (s, 3 H, CH_3); 1.26 (s, 3 H, CH_3); 1.82 (2 H, NH_2); 3.22 (s, 3 H, OCH_3); 3.55 (s, 1 H, NC—H); 3.73 ppm (s, 3 H, $COOCH_3$).

(*R*)-(−)-β-Hydroxyvaline (8):

Hydrolysis **7a**→**8**: Compound (*R*)-**7a** (0.15 g, 1.0 mmol) is heated in boiling 5 normal hydrochloric acid (10 ml) for 1 h. The solvent is then evaporated in vacuo, the residual **8** hydrochloride is dried at 40 °C/0.1 torr for 10 min, and dissolved in hot ethanol (10 ml). Methyloxirane (5 ml) is added, the mixture is refluxed for 10 min, and then cooled to 0 °C. The precipitated product **8** is isolated by suction, washed with cold ether (on the filter), and dried in vacuo over phosphorus pentoxide for 2 days; yield: 0.11 g (83%); $[\alpha]_D^{20}$: −11.2° (*c* 1.5, 5 normal HCl). The product probably is enantiomerically pure. [For physical data and spectra, see below].

$C_5H_{11}NO_3$	calc.	C 45.10	H 8.33
(133.2)	found	45.20	8.34

Cleavage **7b→8:** Compound (*R*)-**7b** (e.e. ~ 90%; 0.32 g, 2.0 mmol) is heated in boiling 40% hydrobromic acid (15 ml) for 3 h. The solvent is then evaporated and the residual crude **8** hydrobromide dried over phosphorus pentoxide. The dried product is dissolved in hot dry ethanol (10 ml), methyloxirane (4 ml) is added, and the mixture is refluxed for 15 min. The precipitated product **8** is isolated by suction, crystallized from water/propanol, and dried over phosphorus pentoxide in vacuo; yield: 0.18 g (66%); m.p. 201 °C; $[\alpha]_D^{20}$: −11.3° (*c* 2.0, 5 normal HCl).

$C_5H_{11}NO_3$	calc.	C 45.11	H 8.26
(133.1)	found	45.00	8.37

I.R. (KBr): ν = 1665 ($COO^{\ominus}$); 1140 cm^{-1} (—C—OH).

^{1}H-N.M.R. (DMSO-d_6/D_2O/TMS_{int}): δ = 1.03 (s, 3H, CH_3); 1.25 (s, 3H, CH_3); 3.27 ppm (s, 1H, NC—H).

(*R,S*)-*N*-Formyl-β-methoxyvaline Methyl Ester (11):
Sodium (0.023 g, 1.0 mmol) is dissolved in dry methanol (40 ml) and methyl 2-formylamino-3-methyl-2-butenoate[9] (**10**; 1.5 g, 9.6 mmol) is added. The mixture is stirred at room temperature for 12 h and is then quenched with glacial acetic acid (0.06 ml, 1.0 mmol). The solvent is evaporated in vacuo and water (15 ml) + dichloromethane (15 ml) are added to the residue. The layers are separated, the aqueous layer is extracted with dichloromethane (3 × 20 ml), and the combined organic extracts are dried with magnesium sulfate. The solvent is removed and the residual product **11** is dissolved in ether (25 ml); the major amount of unreacted educt **10** remains undissolved. For complete crystallization of **10** still present, the ether solution is stored in a refrigerator for 10 h whereupon compound **10** can be removed by suction. The filtrate is evaporated in vacuo and the residual product **11** is purified by bulb-to-bulb distillation; yield: 1.13 g (62%); b.p. 105 °C/0.05 torr.

$C_8H_{15}NO_4$	calc.	C 50.78	H 7.99
(189.2)	found	50.68	7.83

I.R. (film): ν = 1740 (O—C=O); 1670 (NH—C=O); 1070 cm^{-1} (—C—OCH_3).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 1.26 (s, 3H, CH_3); 1.32 (s, 3H, CH_3); 3.24 (s, 3H, OCH_3); 3.77 (s, 1H, NC—H); 3.77 (s, 3H, ester-CH_3); 6.68 (1H, N—H); 8.23 (s, 1H, CHO).

(*R,S*)-β-Methoxyvaline Methyl Ester [(*R,S*)-7b]:
Water (0.075 g, 4.2 mmol) is added to a saturated solution of hydrogen chloride in dry methanol (20 ml), the mixture is cooled to −10 °C, and a solution of compound **11** (0.8 g, 4.2 mmol) in dry methanol (3 ml) is added slowly. Stirring is continued at room temperature for 20 h and then the solvent is evaporated in vacuo. The residual product is dissolved in water (10 ml), aqueous 25% ammonia solution (0.4 ml) is added, and the mixture is extracted with ether (3 × 15 ml). The ether extract is dried with magnesium sulfate, the ether is evaporated, and the residual product is purified by bulb-to-bulb distillation; yield: 0.63 g (93%) (*R,S*)-**7b**. [For chemical and physical data, see (*R*)-**7b**.]

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* Address for correspondence.

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