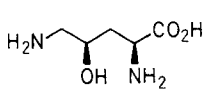
Total Synthesis of the Biphenomycins; II.[1] Synthesis of Protected (2*S*,4*R*)-4-Hydroxyornithines[2]

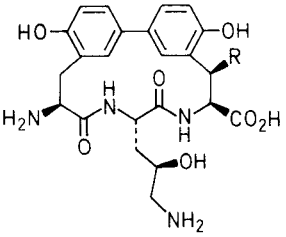
Ulrich Schmidt,* Regina Meyer, Volker Leitenberger, Florian Stäbler, Albrecht Lieberknecht
Institut für Organische Chemie und Isotopenforschung der Universität Stuttgart, Pfaffenwaldring 55, D-7000 Stuttgart 80, Germany

Improved synthetic methods for the preparation of three differently protected (2*S*,4*R*)-4-hydroxyornithines **(10, 16, 24)** have been developed which obviously can be used for the construction of the other stereoisomers. Formation of the corresponding α,β-didehydroamino acid derivatives **(4, 15, 22)** and their enantioselective hydrogenation are the characteristic steps of these syntheses.

(2*S*,4*R*)-4-Hydroxyornithine **(1)** is a component of lower marine animals[3,4] and plants[5,6] and also a metabolite of various enzymatic reactions.[3,4,7-9] The biphenomycins A and B **(2a,b)**,[10] cyclopeptides containing the non-proteinogenic amino acids (*S*,*S*)-diisotyrosine and (2*S*,4*R*)-4-hydroxyornithine, exhibit high antibiotic activities against gram-positive, β-lactam-resistant bacteria.



1

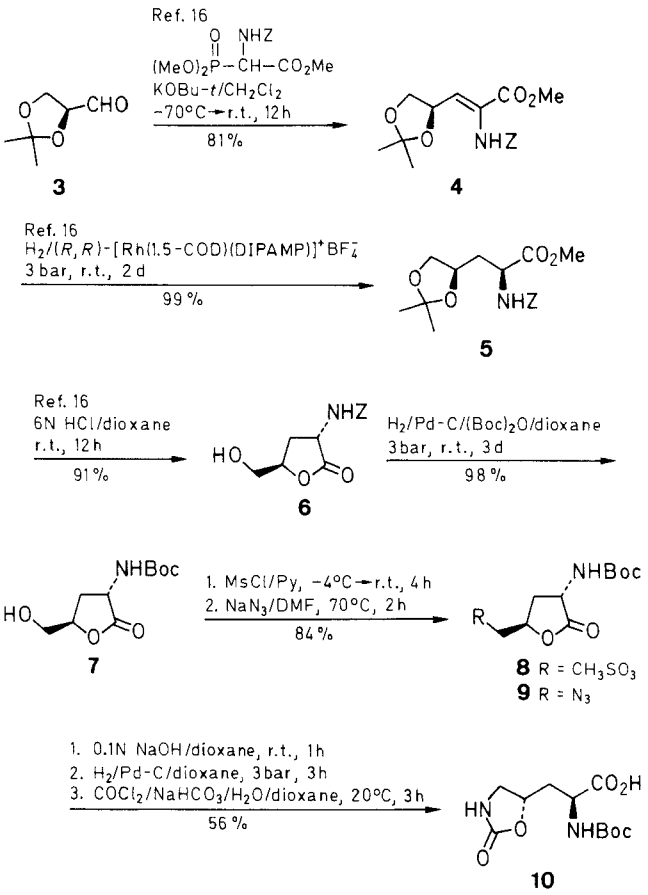


2a R = OH
b R = H

Previously, only non-specific syntheses of the diastereoisomers of racemic γ-hydroxyornithine and their separation were known.[11,12] Thus, (*S*)-γ-oxoornithine was prepared from histidine and subsequently reduced to furnish an *erythro*/*threo* mixture of the isomers which was separated by ion exchange chromatography.[13]

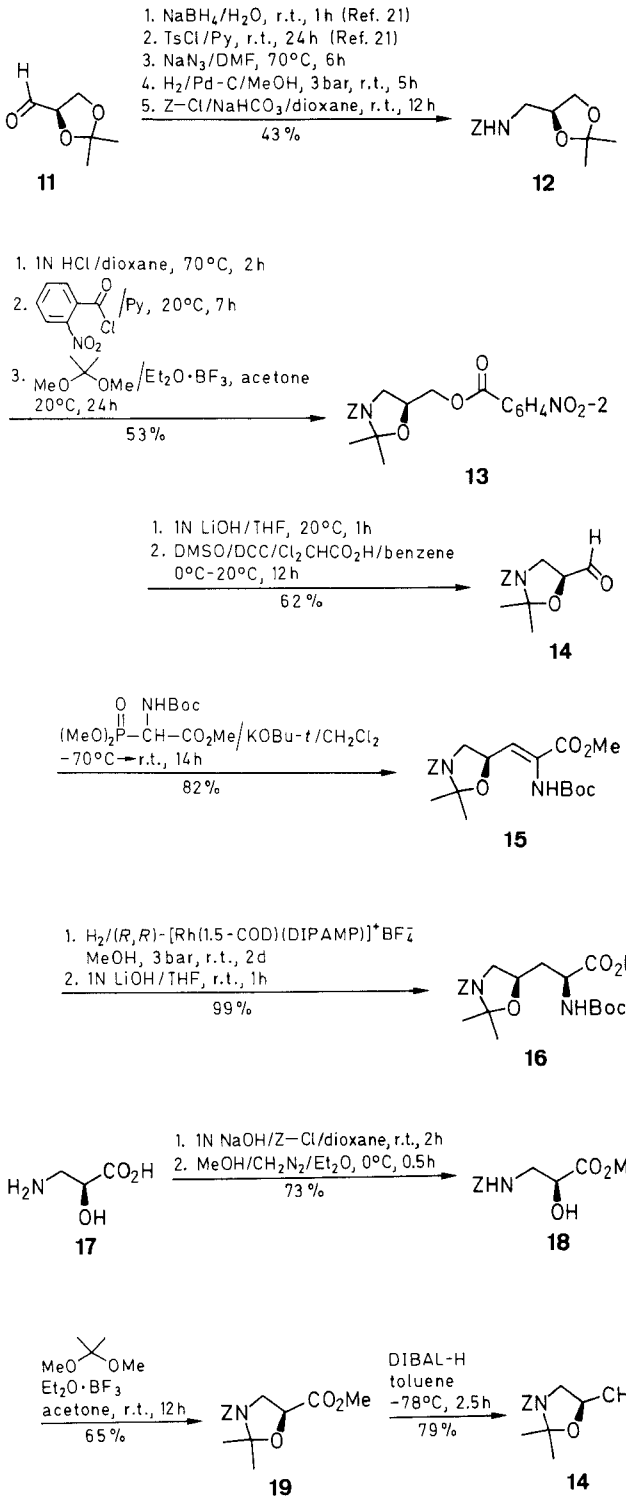
As a preliminary step in our synthesis[1] of biphenomycin B, we have elaborated four stereoselective preparations of (2*S*,4*R*)-4-hydroxyornithines having the δ-amino and γ-hydroxy groups masked by functions which are compatible with the other protected phenolic, amino, and carboxy groups of biphenomycin.

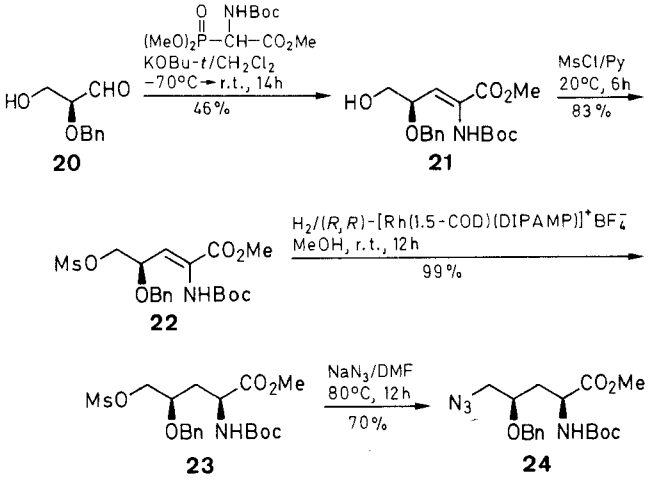
The (2*S*,4*R*)-γ-hydroxyornithine having the δ-amino and γ-hydroxy groups protected by the formation of an oxazolidinone ring was obtained by condensation of (*S*)-isopropylideneglyceraldehyde[14] **(3)** with methyl-2-benzyloxycarbonylamino-2-(dimethoxyphosphoryl)-acetate.[15,16] The resultant didehydroamino acid[16] ($E < 8\%$) was hydrogenated using (*R*,*R*)-[Rh(1,5-COD)(DIPAMP)]$^+BF_4^-$,[17] to furnish the amino acid derivative **5** (ds > 99.5%).[16] After conversion of **5** to the lactone **6**,[16] the benzyloxycarbonyl group was exchanged for a *tert*-butoxycarbonyl group (→ **7**). The azide **9**, obtained via the methanesulfonate **8**, was converted to the oxazolidinone **10** by cleavage of the lactone ring, hydrogenation and subsequent reaction with phosgene. This reaction sequence (Scheme **1**) resulted in the construction of the C_3 unit of γ-hydroxyornithine from the carbonyl group of (*S*)-isopropylideneglyceraldehyde.



On the other hand, the cheaper (*R*)-isopropylideneglyceraldehyde **(11)**[18] is the starting material when the C_5 unit is to be elaborated from the aldehyde function (Scheme **2**). The formyl group was transformed into a benzyloxycarbonylaminomethyl function **12**. A sequence of clean reactions via **13** gave the protected isoserine aldehyde **14** and the didehydroamino acid derivative **15** ($E < 2\%$) was subsequently obtained by condensation with methyl 2-*tert*-butoxycarbonylamino-2-(dimethoxyphosphoryl)acetate.[15] Enantioselective hydrogenation then gave the hydroxyornithine derivative **16** having the δ-amino and γ-hydroxy groups protected as an oxazolidine function (ds > 99.5%; the (2*R*,4*R*)-diastereoisomer could not be detected by HPLC).

The oxazolidine aldehyde **14** is also accessible from (*S*)-malic acid through a three-step transformation to (*S*)-isoserine hydrochloride **17**,[19] esterification to **18**, introduction of the benzyloxycarbonyl group, formation of oxazolidine **19** and reduction of **19** furnished the aldehyde **14**. Further transformations of **14** to the didehydroamino acid derivative **15** and the hydroxyornithine ester derivative of **16** gave rise to a mixture of 75% **16** and 25% of the (2*S*,4*S*)-diastereoisomer which was easily separated by MPLC. We assume that partial epimerization had occurred in the reduction of the ester with diisobutylaluminum hydride (DIBAL-H).





A further synthesis of a differently protected γ-hydroxyornithine derivative starts from (*S*)-2-benzylglyceraldehyde[20] (**20**). Condensation of **20** with methyl 2-*tert*-butoxycarbonylamino-2-(dimethoxyphosphoryl)acetate[15] gave the didehydroamino acid ester **21**. The hydroxy group of **21** was transformed to a methanesulfonate function **22**, subsequent enantioselective hydrogenation furnished **23** and reaction with sodium azide gave a (2*S*,4*R*)-4-hydroxyornithine derivative **24** bearing a δ-azide group as a substitute for the amino group. The (2*R*,4*R*)-diastereoisomer could not be detected in the ^{13}C-NMR spectrum and by HPLC.

Among the modified γ-hydroxyornithines described above, the oxazolidine derivative **16** proved to be the most suitable and hence was the derivative of choice for the biphenomycin synthesis.

We have not yet been able to open the five-membered ring in peptides containing the oxazolidinone amino acid **10** by selective reaction with di-*tert*-butyl dicarbonate and hydrolysis without the cleavage of other amide bonds in the molecule taking place. In contrast, the oxazolidine ring of the γ-hydroxyornithine derivative **16**, as well as those of peptides containing this unit, was easily cleaved by aqueous acetic acid at room temperature.

The ^{1}H-NMR-spectra were recorded on a Varian T 60 (60 MHz), a Bruker WP 80 (80 MHz) and a Bruker CXP (300 MHz) respectively. Optical rotation values were determined with a Perkin Elmer 241 polarimeter. Melting points (Reichert microscope) are uncorrected. TLC was done on silica gel (Merck Silica 60 F_{254} sheets) and medium pressure column chromatography used Merck LiChroprep Si 60 (15–25 μ). HPLC was done with a LKB Instrument and a silica gel column (Merck Hibar, LiChrosorb Si 60 5 μ).

(2*S*,4*R*)-2-*tert*-Butyloxycarbonylamino-5-hydroxy-4-pentanolide [(3*S*,5*R*)-Dihydro-3-*tert*-butoxycarbonylamino-5-hydroxymethylfuran-2(3*H*)-one; 7]:

To a solution of **6**[16] (9.00 g, 33.9 mmol) in dioxane (150 mL) is added di-*tert*-butyl dicarbonate (7.77 g, 35.6 mmol) and 5% Pd-C (0.50 g). The mixture is hydrogenated at 3 bar for 3 d. The catalyst is filtered off and washed with hot MeOH (500 mL). After evaporation of the solvents the residue is recrystallized from MeOH; yield: 7.69 g (98%); mp 192°C; $[\alpha]_D^{20}$ – 53.1° (*c* = 2.10, DMF).

$C_{10}H_{17}NO_5$	calc.	C 51.94	H 7.41	N 6.06
(231.2)	found	51.96	7.31	5.97

^{1}H-NMR (300 MHz, DMSO-d_6/TMS): δ = 1.39 (s, 9 H), 2.20–2.34 (m, 2 H), 3.47 (ddd, 1 H, *J* = 3.2 Hz, 4.7 Hz, 12.0 Hz), 3.59 (ddd, 1 H, *J* = 2.8 Hz, 4.8 Hz, 12.0 Hz), 4.36 (q, 1 H, *J* = 9.5 Hz), 4.53–4.59 (m, 1 H), 5.12 (t, 1 H, *J* = 5.1 Hz), 7.34 (d, 1 H, *J* = 8.5 Hz).

(2*S*,4*R*)-2-*tert*-Butyloxycarbonylamino-5-methylsulfonyloxy-4-pentanolide [(3*S*,5*R*)-Dihydro-3-*tert*-butoxylcarbonylamino-5-methylsulfonyloxyfuran-2(3*H*)-one, 8]:

To a stirred solution of **7** (7.50 g, 32.4 mmol) in pyridine (80 mL) at – 4°C, methanesulfonyl chloride (5.02 mL, 64.9 mmol) is added dropwise. The mixture is kept at 0°C for 2 h and at r.t. for 2 h and then poured into ice water (300 mL). After extraction with EtOAc (3 × 200 mL) the combined organic layers are washed with sat. aq $KHSO_4$ (300 mL) and sat. aq NaCl (300 mL), dried ($MgSO_4$) and concentrated at reduced pressure to 50 mL. After addition of Et_2O

(300 mL), the precipitated product is isolated by suction filtration; yield: 8.63 g (86%); mp 149°C; $[\alpha]_D^{20} - 44.3°$ (c = 1.06, MeOH).

$C_{11}H_{19}NO_7S$	calc.	C 42.71	H 6.19	N 4.53
(309.3)	found	42.83	6.15	4.40

^{1}H-NMR (300 MHz, DMSO-d_6/TMS): δ = 1.39 (s, 9H), 2.29 (d, 1H, J = 6.1 Hz, 2.32 (d, 1H, J = 6.2 Hz), 3.23 (s, 3H), 4.30 (q, 1H, J = 9.3 Hz), 4.38 (d, 2H, J = 3.9 Hz), 4.84–4.89 (m, 1H), 7.47 (d, 1H, J = 8.3 Hz).

(2*S*,4*R*)-5-Azido-2-*tert*-butyloxycarbonylamino-4-pentanolide [(3*S*,5*R*)-Dihydro-5-azidomethyl-3-*tert*-butoxycarbonylaminofuran-2(3*H*)-one, 9]:

A solution of **8** (8.28 g, 26.8 mmol) and NaN_3 (5.22 g, 80.3 mmol) in DMF (200 mL) is stirred at 70°C for 2 h. After evaporation of the solvent *in vacuo*, the residue is partitioned between CH_2Cl_2 (200 mL) and water (200 mL) and extracted with CH_2Cl_2 (2 × 200 mL). After evaporation the product is purified by silica gel chromatography (petroleum ether (bp 40–60°C)/EtOAc, 1:1); yield: 6.76 g (98%); mp 100°C; $[\alpha]_D^{20} - 84.0°$ (c = 3.34, CH_2Cl_2).

$C_{10}H_{16}N_4O_4$	calc.	C 46.87	H 6.29	N 21.86
(256.3)	found	46.87	6.40	21.95

^{1}H-NMR (300 MHz, $CDCl_3$/TMS): δ = 1.45 (s, 9H), 2.36–2.57 (m, 2H), 3.52 (dd, 1H, J = 3.9 Hz, 13.2 Hz), 3.69 (dd, 1H, J = 3.5 Hz, 13.2 Hz), 4.43–4.46 (m, 1H), 4.75–4.78 (m, 1H), 5.19 (d, 1H, J = 6.0 Hz).

(*R*)-5-[(*S*)-*N*-*tert*-Butyloxycarbonylalanin-3-yl]-1,3-oxazolidine-2-one (10):

To a stirred solution of **9** (6.00 g, 23.4 mmol) in dioxane (200 mL) is added dropwise 0.1 N aq NaOH (234 mL, 23.4 mmol). The solution is hydrogenated at r.t. in the presence of 5% Pd-C (0.5 g) at 3 bar for 3 h. The catalyst is filtered off, washed with water/dioxane 1:1 (100 mL) and the organic solvent is evaporated *in vacuo*. To the aqueous solution is added Na_2CO_3 (10 g), and slowly a stream of phosgene is passed through the mixture until the aqueous solution becomes neutral. After addition of Na_2CO_3 (10 g), the mixture is treated with phosgene for the second time until pH 7. To the solution is added sat. aq Na_2CO_3 (50 mL) and the aqueous layer is washed with EtOAc (2 × 100 mL). After acidification with aq $KHSO_4$ the aqueous solution is extracted with EtOAc (6 × 100 mL). The combined organic layers are dried ($MgSO_4$) and evaporated to give **10** as a hygroscopic solid which is pure enough for further reactions; yield: 3.60 g (56%); $[\alpha]_D^{20} + 40.6°$ (c = 1.34, dioxane).

$C_{11}H_{18}N_2O_6$	calc.	C 48.17	H 6.62	N 10.21
(274.3)	found	47.93	6.87	8.82

^{1}H-NMR (300 MHz, DMSO-d_6/TMS): δ = 1.38 (s, 9H), 1.92–2.00 (m, 2H), 3.14 (dd, 1H, J = 7.2 H, 8.4 Hz), 3.53 (t, 1H, J = 8.3 Hz), 4.00 (m, 1H), 4.54–4.63 (m, 1H), 7.21 (d, 1H, J = 8.1 Hz), 7.47 (s, 1H), 12.56 (br s, 1H).

(*S*)-4-Benzyloxycarbonylaminomethyl-2,2-dimethyl-1,3-dioxolane (12):

(S)-4-Azidomethyl-2,2-dimethyl-1,3-dioxolane:

To a solution of (*R*)-4-tosyloxymethyl-2,2-dimethyl-1,3-dioxolane[21] (10 g, 34.92 mmol) in DMF (100 mL), NaN_3 (4.54 g, 69.84 mmol) is added and the suspension is stirred at 70°C over 12 h. The mixture is diluted with EtOAc (200 mL) and washed successively with H_2O (2 × 100 mL) and 1 N aq $KHSO_4$ (50 mL). The organic layer is dried ($MgSO_4$), evaporated and Kugelrohr distilled to give (*S*)-4-azidomethyl-2,2-dimethyl-1,3-dioxolane; yield: 4.49 g (82%); bp 50–55°C/0.5 mbar; $[\alpha]_D^{20} - 40.54°$ (c = 44.9, $CHCl_3$).

$C_6H_{11}N_3O_4$	calc.	C 45.85	H 7.05	N 26.74
(157.1)	found	45.61	7.14	27.01

^{1}H-NMR (60 MHz, $CDCl_3$/TMS): δ = 1.37 (s, 3H), 1.48 (s, 3H), 3.35 (d, 2H, J = 5 Hz), 3.60–4.43 (m, 3H).

(S)-4-Benzyloxycarbonylaminomethyl-2,2-dimethyl-1,3-dioxolane **(12)**:

A solution of (*S*)-4-azidomethyl-2,2-dimethyl-1,3-dioxolane (4.49 g, 28.6 mmol) in MeOH (100 mL) is hydrogenated (3 bar) in presence of 5% Pd-C (0.5 g for 5 h). The mixture is filtered and evaporated *in vacuo*.

The crude (*S*)-4-aminomethyl-2,2-dimethyl-1,3-dioxolane (3.07 g, 23.4 mmol) is dissolved in dioxane (10 mL) and $NaHCO_3$ (1.97 g, 23.4 mmol) and benzyl chloroformate (3.32 mL, 23.4 mmol) are added. After 12 h, dioxane is evaporated *in vacuo* and the residue is extracted with Et_2O (2 × 50 mL). The combined organic layers are washed with H_2O (10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The resulting oil is Kugelrohr distilled; yield: 5.27 g, overall yield (70%); bp 145–150°C/1 mbar; $[\alpha]_D^{20} - 2.7°$ (c = 1.04, $CHCl_3$).

$C_{14}H_{19}NO_4$	calc.	C 63.38	H 7.22	N 5.28
(265.3)	found	63.46	7.36	5.11

^{1}H-NMR (80 MHz, $CDCl_3$/TMS): δ = 1.33 (s, 3H), 1.40 (s, 3H), 3.00–4.25 (m, 5H), 5.10 (s, 2H), 5.15 (br s, 1H), 7.45 (s, 5H).

(*S*)-3-Benzyloxycarbonyl-2,2-dimethyl-5-*o*-nitrobenzoyloxymethyl-1,3-oxazolidine (13):

(S)-3-Benzyloxycarbonylamino-1,2-dihydroxypropane:

A solution of **12** 5.27 g (19.86 mmol) in dioxane (15 mL) and H_2O (5 mL) containing 1 N HCl (catalylic amount) is refluxed for 2 h. After evaporation, the solution of the residue in EtOAc (50 mL) is successively washed with 1 N aq $KHCO_3$ (10 mL) and H_2O (10 mL). The organic layer is dried ($MgSO_4$) evaporated and the residue is crystallized from EtOAc/hexane; yield: 4.2 g (94%); mp 60.5°C; $[\alpha]_D^{20} - 9.6°$ (c = 0.94, $CHCl_3$).

$C_{11}H_{15}NO_4$	calc.	C 58.66	H 6.71	N 6.22
(225.24)	found	58.59	6.49	6.24

^{1}H-NMR (80 MHz, $CDCl_3$/TMS): δ = 2.67–3.63 (m, 5H), 4.50 (d, 1H, J = 6 Hz), 4.64 (d, 1H, J = 5 Hz), 5.15 (s, 2H), 7.00 (br s, 1H), 7.35 (s, 5H).

(S)-3-Benzyloxycarbonylamino-2-hydroxy-1-(o-nitrobenzoyloxy)-propane:

To a solution of (*S*)-3-benzyloxycarbonylamino-1,2-dihydroxypropane (2 g, 8.86 mmol) and pyridine (0.71 g, 8.86 mmol) in CH_2Cl_2 (25 mL) at r.t. is added over a period of 5 h, *o*-nitrobenzoyl chloride (1.64 g, 8.86 mmol). After another 2 h the mixture is evaporated *in vacuo* and the solution of the residue in EtOAc (30 mL) is washed successively with 1 N aq $KHSO_4$ (2 × 10 mL) and H_2O (10 mL). The organic layer is dried ($MgSO_4$) and evaporated. Chromatography on silica gel with petroleum ether (bp 40–60°C)/EtOAc (1:1) gives pure product; yield: 2.48 g (75%); $[\alpha]_D^{20} + 15.9°$ (c = 1.13, $CHCl_3$).

$C_{18}H_{18}N_2O_7$	calc.	C 57.75	H 4.85	N 7.48
(374.3)	found	57.76	4.90	7.48

^{1}H-NMR (80 MHz, $CDCl_3$/TMS): δ = 3.13–3.5 (m, 3H), 4.05 (d, 1H, J = 6 Hz), 4.25–4.48 (m, 2H), 5.15 (s, 2H), 5.50 (br t, 1H), 7.40 (s, 5H), 7.55–8.05 (m, 4H).

(S)-3-Benzyloxycarbonyl-2,2-dimethyl-5-o-nitrobenzoyloxymethyl-1,3-oxazolidine **(13)**:

A solution of (*S*)-3-benzyloxycarbonylamino-2-hydroxy-1-(*o*-nitrobenzoyloxy)propane (6.9 g, 18.41 mmol) and 2,2-dimethoxypropane (3.38 g, 36.82 mmol) in acetone (80 mL) containing $Et_2 \cdot BF_3$ (catalytic amount) is stirred at r.t. for 24 h. The mixture is evaporated *in vacuo* and the residue is dissolved in EtOAc (50 mL). The solution is washed with 1 N aq $KHCO_3$ (2 × 10 mL) and H_2O (10 mL) dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography on silica gel with petroleum ether (bp 40–60°C/EtOAc (8:2) gives pure **13**; yield: 6.02 g (79%); $[\alpha]_D^{20} - 9.0°$ (c = 1.1, $CHCl_3$).

$C_{21}H_{22}N_2O_7$	calc.	C 60.86	H 5.35	N 6.74
(414.4)	found	61.03	5.49	6.63

^{1}H-NMR (80 MHz, $CDCl_3$/TMS): δ = 1.55 (s, 3H), 1.63 (s, 3H), 3.25–3.55 (m, 1H), 3.75–4.00 (m, 1H), 4.25–4.58 (m, 3H), 5.15 (s, 2H), 7.38 (s, 5H), 7.50–8.05 (m, 4H).

(*S*)-3-Benzoyloxycarbonyl-5-formyl-2,2-dimethyl-1,3-oxazolidine (14):

(S)-3-Benzyloxycarbonyl-5-hydroxymethyl-2,2-dimethyl-1,3-oxazolidine:

1 N aq LiOH (12.48 mL) is dropped at r.t. to a stirred solution of **13** (5.17 g, 12.48 mmol) in THF (15 mL) and H_2O (5 mL). When saponification is completed (checked by TLC) the reaction mixture is evaporated *in vacuo*. The aqueous suspension of the residue is extracted with Et_2O (2 × 50 mL). The combined organic layers are dried ($MgSO_4$), evaporated and pure product is obtained after Kugelrohr distillation; yield: 3.05 g (92%); bp 140–145°C/1 mbar; $[\alpha]_D^{20}$ −11.6° (*c* = 1.3, $CHCl_3$).

$C_{14}H_{19}NO_4$	calc.	C 63.38	H 7.22	N 5.28
(265.3)	found	63.32	7.34	5.24

^{1}H-NMR (80 MHz, $CDCl_3$/TMS): δ = 1.54 (s, 3 H), 1.63 (s, 3 H), 2.25 (br s, 1 H), 3.37–3.43 (m, 1 H), 3.61–3.81 (m, 3 H), 4.19–4.26 (m, 1 H), 5.11 (br s, 2 H), 7.26–7.36 (m, 5 H).

(S)-3-Benzyloxycarbonyl-5-formyl-2,2-dimethyl-1,3-oxazolidine **(14)**:

To a solution of (*S*)-3-benzyloxycarbonyl-5-hydroxymethyl-2,2-dimethyl-1,3-oxazolidine (2 g, 7.54 mmol) and DCC (2.33 g, 11.31 mmol) in DMSO (20 mL) and benzene (20 mL) at 0°C is added dichloroacetic acid (308 µl, 3.8 mmol). The reaction mixture is stirred for 2 h and hydrolyzed with 1 N aq $KHCO_3$ (10 mL). Filtration from urea is followed by extraction with Et_2O (4 × 25 mL). The combined organic layers are washed with H_2O (5 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The aldehyde **14** can be reacted without further purification; yield: 1.23 g (62%).

^{1}H-NMR (80 MHz, $CDCl_3$/TMS): δ = 1.51–1.90 (m, 6 H), 3.50–4.05 (m, 2 H), 4.38–4.75 (m, 1 H), 5.25 (s, 2 H), 7.55 (s, 5 H), 9.89 (s, 0.5 H).

(*R*)-3-Benzyloxycarbonyl-5-[(*Z*)-2-(*tert*-butoxycarbonylamino)-2-(methoxycarbonyl)vinyl]-2,2-dimethyl-1,3-oxazolidine (15):

To a suspension of KOBu-*t* (0.43 g, 3.8 mmol) in CH_2Cl_2 (2 mL) at −70°C is added methyl 2-*tert*-butoxycarbonylamino-2-(dimethoxyphosphoryl)acetate. After 15 min **14** (1 g, 3.8 mmol) is added. The mixture is kept for 0.5 h at −70°C, then slowly warmed up to r.t. overnight and evaporated *in vacuo*. The solution of the residue in EtOAc is washed with cold water, filtered and evaporated. Chromatography on silica gel of the *E*/*Z*-mixture (1:9) with petroleum ether (bp 40–60°C)/EtOAc (85:15) gives the *Z*-isomer **15**; yield: 1.22 g (74%), $[\alpha]_D^{20}$ −30.3° (*c* = 2.07, $CHCl_3$)

$C_{22}H_{30}N_2O_7$	calc.	C 60.82	H 6.96	N 6.45
(434.5)	found	60.75	7.10	6.40

^{1}H-NMR (80 MHz, $CDCl_3$/TMS): δ = 1.43 (s, 9 H), 1.55 (s, 3 H), 1.63 (s, 3 H), 3.13 (m, 1 H), 3.82 (s, 1 H), 3.8–4.13 (m, 4 H), 3.75–5.0 (m, 1 H), 5.13 (s, 1 H), 6.35 (d, 1 H, *J* = 8 Hz), 6.56 (br s, 1 H), 7.35 (s, 5 H).

(*R*)-3-Benzyloxycarbonyl-5-[(*S*)-*N*-*tert*-butoxycarbonylalanin-3-yl]-2,2-dimethyl-1,3-oxazolidine (16):

(R)-3-Benzyloxycarbonyl-5-[(S)-2-(tert-butoxycarbonylamino)-2-(methoxycarbonyl)ethyl]-2,2-dimethyl-1,3-oxazolidine:

A solution of **15** (1.27 g, 2.92 mmol) in isopropyl alcohol (100 mL) containing (*R,R*)-[Rh(1.5-COD)(DIPAMP)]$^+BF_4^-$ (20 mg) is hydrogenated (3 bar) at r.t. over 3 d. The mixture is evaporated and the residue chromatographed on silica gel with petroleum ether (bp 40–60°C)/EtOAc (1:1); yield: 1.26 g (99%); $[\alpha]_D^{20}$ +9.1° (*c* = 1.09, $CHCl_3$).

$C_{22}H_{32}N_2O_7$	calc.	C 60.54	H 7.39	N 6.42
(436.5)	found	60.32	7.44	6.23

^{1}H-NMR (300 MHz, $CDCl_3$/TMS): δ = 1.44 (s, 9 H), 1.50 (s, 3 H), 1.58 (s, 3 H), 2.01–2.18 (m, 2 H), 3.10–3.17 (m, 1 H), 3.67–3.85 (m, including s at 3.74, 4 H), 4.08–4.21 (m, 1 H), 3.33–4.37 (br s, 1 H), 5.15–25 (m, 2 H), 5.31 (br s, 1 H), 7.27–7.41 (m, 5 H).

^{13}C-NMR (75 MHz): δ = 172.47, 155.22, 152.19, 136.66, 128.53, 128.36, 128.05, 127.93, 94.11, 80.09, 70.80, 66.55, 52.39, 51.30, 50.57, 35.84, 28.32, 26.16, 24.21.

(R)-3-Benzyloxycarbonyl-5-[(S)-N-tert-butoxycarbonylalanin-3-yl]-2,2-dimethyl-1,3-oxazolidine **(16)**:

To a solution of (*R*)-3-benzyloxycarbonyl-5-[(*S*)-2-(*tert*-butoxycarbonylamino)-2-(methoxycarbonyl)ethyl]-2,2-dimethyl-1,3-oxazolidine (1.26 g, 2.9 mmol) in THF (15 mL) and H_2O (2 mL) is dropped 1 N aq LiOH (2.9 mL). When saponification is complete (CD control), THF is distilled off and the remaining water solution is washed with Et_2O (5 mL). The water layer is acidified and extracted with EtOAc (3 × 10 mL). The combined layers are dried ($MgSO_4$) and evaporated *in vacuo*; yield: 1.2 g (~100%); $[\alpha]_D^{20}$ +2.22° (*c* = 0.32, $CHCl_3$).

$C_{21}H_{30}N_2O_7$	calc.	C 59.70	H 7.16	N 6.63
(422.5)	found	59.46	7.30	6.43

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.36 (s, 9 H), 1.43 (s, 3 H), 1.51 (s, 3 H), 1.93–2.10 (m, 2 H), 3.10 (br m, 1 H), 3.64–3.75 (m, 1 H), 4.14–4.30 (m, 2 H), 5.02 (s, 2 H), 5.28 (d, 1 H, *J* = 6.6 Hz), 7.27 (s, 5 H), 9.19 (br s, 1 H).

Methyl (*S*)-*N*-(Benzyloxycarbonyl)isoserinate (18):

(S)-N-(Benzyloxycarbonyl)isoserine:

A stirred solution of isoserine hydrochloride[19] (**17** · HCl) (6.84 g, 48 mmol) in 1 N aq NaOH (170 mL) is cooled to 0°C and a solution of benzyl chloroformate (10.2 g, 59 mmol) in dioxane (30 mL) is added dropwise over a period of 30 min. Stirring is continued for 2 h at r.t., then dioxane is evaporated at reduced pressure and the aqueous layer is first extracted with Et_2O and next acidified at 0°C with 1 N aq $KHSO_4$ (50 mL). The mixture is extracted with EtOAc (3 × 150 mL). The combined organic layers are dried ($MgSO_4$) and concentrated at reduced pressure yielding the crude product as a colorless solid. This solid is washed with Et_2O (70 mL) and dried ($MgSO_4$); yield: 8.4 g (74%); mp 129°C; $[\alpha]_D^{20}$ +9.2° (*c* = 1.05, MeOH).

$C_{11}H_{13}NO_5$	calc.	C 55.23	H 5.48	N 5.85
(239.2)	found	55.18	5.41	5.71

^{1}H-NMR (80 MHz, DMSO-d_6/TMS): δ = 3.25 (m, 2 H), 4.05 (dd, 1 H, *J* = 7 Hz), 5.03 (s, 2 H), 5.1–7.0 (2 H), 7.0–7.3 (br s, 1 H), 7.35 (s, 5 H).

Methyl (S)-N-(Benzyloxycarbonyl)isoserinate **(18)**:

A solution of (*S*)-*N*-(benzyloxycarbonyl)isoserine (8.6 g, 36 mmol) in MeOH (70 mL) is cooled to 0°C and treated with a 0.2 N solution of diazomethane in Et_2O (185 mL). After stirring at 0°C for an additional 30 min, excess diazomethane is destroyed by adding AcOH. The MeOH is then evaporated at reduced pressure and the residue dissolved in Et_2O (100 mL). This solution is washed with sat. aq $NaHCO_3$ (100 mL), dried ($MgSO_4$) and evaporated. The colorless oil crystallizes overnight; yield: 8.9 g (98%); mp 43°C; $[\alpha]_D^{20}$ +18.8° (*c* = 1.42, MeOH).

$C_{12}H_{15}NO_5$	calc.	C 56.91	H 5.97	N 5.53
(253.3)	found	57.14	6.06	5.46

^{1}H-NMR (80 MHz, $CDCl_3$/TMS): δ = 3.5 (dd, 2 H, *J* = 6 Hz), 3.5 (br s, 1 H), 3.72 (s, 3 H), 4.15–4.35 (m, 1 H), 5.07 (s, 2 H), 5.1–5.4 (br s, 1 H), 7.35 (s, 5 H).

(*S*)-3-Benzyloxycarbonyl-5-methoxycarbonyl-2,2-dimethyl-1,3-oxazolidine (19):

2,2-Dimethoxypropane (3.33 g, 32 mmol) is added to a solution of ester **18** (4.05 g, 16 mmol) in acetone (70 mL). After the addition of one drop of $Et_2O \cdot BF_3$ in Et_2O the mixture is stirred at r.t. overnight. The solvent is evaporated at reduced pressure and the residue is partitioned between Et_2O (100 mL) and sat. aq $NaHCO_3$ (70 mL). The organic layer is separated, dried ($MgSO_4$) and concentrated at reduced pressure to a yellow oil which is purified by chromatography on silica gel using EtOAc/petroleum ether (bp 40–60°C), (1:1) as eluent; unreacted **18** 1.01 g (25%) is also recovered; yield of **19**: 3.05 g (65%); $[\alpha]_D^{20}$ +15.5° (*c* = 1.11, MeOH).

$C_{15}H_{19}NO_5$	calc.	C 61.42	H 6.53	N 4.78
(293.3)	found	61.36	6.47	4.53

^{1}H-NMR (80 MHz, $CDCl_3$/TMS): δ = 1.55 (s, 3 H), 1.65 (s, 3 H), 3.8 (s, 3 H), 3.6–3.9 (m, 2 H), 4.63 (t, 1 H, *J* = 8 Hz), 5.13 (s, 2 H), 7.35 (s, 5 H).

(*S*)-3-Benzyloxycarbonyl-5-formyl-2,2-dimethyl-1,3-oxazolidine (14):

The protected isoserine ester **19** (3.0 g, 10.2 mmol) is dissolved in dry toluene (50 mL) and cooled under nitrogen to −78 °C. Then a 1 N solution of DIBAL-H in hexane (15 mL) is added dropwise to the mixture keeping the temperature below −65 °C. Stirring is continued for 2.5 h at this temperature, then MeOH (7 mL) is added and the mixture is allowed to warm up to r.t. The solution is stirred with 1 N aq $KHSO_4$ (100 mL) and extracted with EtOAc (2 × 100 mL). The organic layers are combined, dried ($MgSO_4$) and concentrated at reduced pressure yielding the aldehyde as a colorless oil, which can be used without further purification; yield: 2.1 g (79 %).

Methyl (*R,Z*)-4-Benzyloxy-2-*tert*-butoxycarbonylamino-5-hydroxy-2-pentenoate (21):

To a suspension of KOBu-*t* (0.934 g, 8.34 mmol) in CH_2Cl_2 (1 mL) at −70 °C is added methyl 2-*tert*-butoxycarbonylamino-2-(dimethoxyphosphoryl)acetate. After 15 min aldehyde **20**[20] (1 g, 5.56 mmol) is added. Reaction time and workup are the same as described for compound **15**; yield: 900 mg (46 %); $[\alpha]_D^{20}$ −10.12° (c = 1.23, $CHCl_3$).

$C_{18}H_{25}NO_6$	calc.	C 61.52	H 7.17	N 3.99
(351.4)	found	61.39	7.11	3.88

^{1}H-NMR (80 MHz, $CDCl_3$/TMS): δ = 1.42 (s, 9 H), 3.89 (s, 1 H), 3.50–3.80 (m, 5 H), 4.00–4.50 (m, 3 H), 6.30 (d, 1 H, J = 8 Hz), 6.35 (s br, 1 H), 7.35 (s, 5 H).

Methyl (*R,Z*)-Benzyloxy-2-*tert*-butoxycarbonylamino-5-methylsulfonyloxy-2-pentenoate (22):

Methanesulfonyl chloride (0.267 g, 2.34 mmol) in CH_2Cl_2 (2 mL) is dropped to a solution of **21** in pyridine (4 mL). After 6 h stirring at r.t., EtOAc (30 mL) is added and the mixture is washed with 1 N aq $KHSO_4$ (10 mL) and H_2O (10 mL). The organic layer is dried ($MgSO_4$), evaporated and chromatography on silica gel with petroleum ether (bp 40–60 °C)/EtOAc (6:4) gives **22**; yield: 833 mg (83 %); $[\alpha]_D^{20}$ −4.8° (c = 0.82, $CHCl_3$).

$C_{19}H_{27}NO_8S$	calc.	C 53.14	H 6.34	N 3.26
(429.4)	found	53.12	6.25	3.15

^{1}H-NMR (80 MHz, $CDCl_3$/TMS): δ = 1.42 (s, 9 H), 2.99 (s, 3 H), 3.83 (s, 3 H), 4.25–4.75 (m, 5 H), 6.25 (d, 1 H, J = 8 Hz), 6.49 (br s, 1 H), 7.35 (5 H).

Methyl (2*S*,4*R*)-4-Benzyloxy-2-*tert*-butoxycarbonylamino-5-methylsulfonyloxypentanoate (23):

A solution of **22** (0.833 g, 1.94 mmol) dissolved in MeOH (100 mL), containing (*R,R*)-[Rh(1.5-COD)(DIPAMP)$^+$$BF_4^-$ (20 mg) is hydrogenated (3 bar) at r.t. over 3 d. Evaporation and chromatography on silica gel (petroleum ether (bp 40–60 °C)/EtOAc, 1:1) gives **23**; yield: 829 mg (99 %); $[\alpha]_D^{20}$ +42.3° (c = 1.35, $CHCl_3$).

$C_{19}H_{29}NO_8S$	calc.	C 52.89	H 6.77	N 3.25
(431.5)	found	52.88	6.82	3.15

^{1}H-NMR (80 MHz, $CDCl_3$/TMS): δ = 1.43 (s, 9 H), 1.88–2.25 (m, 2 H), 3.00 (s, 3 H), 3.60 (s, 3 H), 4.00–4.75 (m, 6 H), 5.38 (br s, 1 H), 7.38 (s, 5 H).

Methyl (2*S*,4*R*)-5-Azido-4-benzyloxy-2-*tert*-butoxycarbonylaminopentanoate (24):

DMF (100 mL) containing **23** (0.8 g, 1.85 mmol) and NaN_3 (0.241 g, 3.71 mmol) is stirred at 80 °C over 12 h. The mixture is diluted with EtOAc (200 mL) and washed with 1 N aq $KHSO_4$ and H_2O (100 mL). The organic layer is dried ($MgSO_4$) evaporated and the residue is purified by chromatography on silica gel with petroleum ether (bp 40–60 °C)/EtOAc (8:2); yield: 490 mg (70 %); $[\alpha]_D^{20}$ +40.75° (c = 6.61, $CHCl_3$).

$C_{18}H_{26}N_4O_5$	calc.	C 57.13	H 6.93	N 14.81
(378.4)	found	57.00	6.89	14.70

^{1}H-NMR (300 MHz, $CDCl_3$/TMS): δ = 1.44 (s, 9 H), 2.07–2.11 (m, 2 H), 3.26 (dd, 1 H, J = 4.9 Hz, 12.9 Hz), 3.47–3.52 (m, 1 H), 3.58 (s, 3 H), 3.64–3.71 (m, 1 H), 4.33–4.36 (m, 1 H), 4.45, 4.61 (AB system, 2 H, J_{AB} = 10.9 Hz), 5.28 (d, 1 H, J = 5.7 Hz) 7.26–7.46 (m, 5 H).

^{13}C-NMR (75 MHz, $CDCl_3$/TMS): δ = 172.71, 155.22, 137.41, 128.43, 128.29, 127.97, 80.06, 74.67, 72.11, 53.39, 52.30, 50.98, 35.09, 28.32

This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and BASF AG. We would like to thank Professor V. Jäger, University of Würzburg for a gift of 2-benzylglyceraldehyde.

Received: 7 January 1991

(1) Part I: Schmidt, U.; Meyer, R.; Leitenberger, V.; Lieberknecht, A.; Griesser, H. *J. Chem. Soc., Chem. Commun.*, in press.
(2) Amino Acids and peptides, 78. Synthesis of Biologically Active Cyclopeptides, 20; for part 77 and 19: see Ref. 1
(3) Fujita, Y. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 439.
(4) Makisumi, S. *J. Biochem. (Tokyo)* **1961**, *49*, 284.
(5) Bell, E.A.; Tirimanna, A.S.L. *Nature (London)* **1963**, *197*, 901.
(6) Bell, E.A.; Tirimanna, A.S.L. *Biochem. J.* **1964**, *91*, 356.
(7) Makisumi, S. *J. Biochem. (Tokyo)* **1961**, *49*, 292.
(8) Fujita, Y. *J. Biochem. (Tokyo)* **1961**, *49*, 468.
(9) Makisumi, S. *Mem. Fac. Sci. Kyushu Univ. Ser. C. Chem.* **1964**, *5*, 107.
(10) Ezaki, E.; Iwami, M.; Yamashita, M.; Hashimoto, S.; Komori, T.; Umehara, K.; Mine, Y.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 1453.
Uchida, I.; Shigematsu, N.; Ezaki, M.; Hashimoto, M.; Aoki, H.; Imanaka, H. *Ibid.* **1985**, *38*, 1462.
Uchida, I.; Ezaki, E.; Shigematsu, N.; Hashimoto, M. *J. Org. Chem.* **1985**, *50*, 1342.
Kannan, R.; Williams, D.H. *Ibid* **1987**, *52*, 5435.
Hempel, J.C.; Brown, F.K. *J. Am. Chem. Soc.* **1989**, *111*, 7323.
Brown, F.K.; Hempel, J.C.; Dixon, J.S.; Amato, S.; Mueller, L.; Jeffs, P.W. *Ibid.* **1989**, *111*, 7328.
(11) Talbot, G.; Gaudry, R.; Berlinguet, L. *Can. J. Chem.* **1956**, *34*, 911.
(12) Mizusaki, K.; Yamamoto, H.; Makisumi, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2605.
(13) Mizusaki, K.; Makisumi, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 470.
(14) Hubschwerlen, C. *Synthesis* **1986**, 962.
(15) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53.
(16) Schmidt, U.; Lieberknecht, A.; Kazmaier, U.; Griesser, H., Jung, G.; Metzger, J. *Synthesis* **1991**, 49.
(17) Knowles, W.S.; Sabacky, M.J.; Vineyard, B.D.: Weinkauff, D.J. *J. Am. Chem. Soc.* **1975**, *97*, 2567.
For an improved method for the preparation of the ligand DIPAMP see: Schmidt, U.; Riedel, B.; Griesser, H.; Fitz, C. *Synthesis*, in press.
(18) Fischer, H.O.L.; Baer, E. *Helv. Chim. Acta* **1934**, *17*, 622.
Preparation using $Pb(OAc)_4$, K_2CO_3. Private communication: Mulzer, J. 1983.
(19) Milewska, M.; Polonski, T. *Synthesis* **1988**, 475.
(20) Jäger, V.; Wehner, V. *Angew. Chem.* **1989**, *101*, 512; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 469.
(21) Baer, E., Fischer, H.O.L. *J. Am. Chem. Soc.* **1948**, *70*, 610.