First publ. in: Synthesis (1981), pp. 969-971

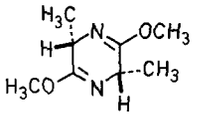
Asymmetric Syntheses via Heterocyclic Intermediates; VIII[1]. Enantioselective Synthesis of (*R*)-α-Methyl-α-amino Acids using L-Valine as Chiral Auxiliary Reagent

Ulrich SCHÖLLKOPF, Ulrich GROTH, Karl-Otto WESTPHALEN, CHUANGZHENG DENG

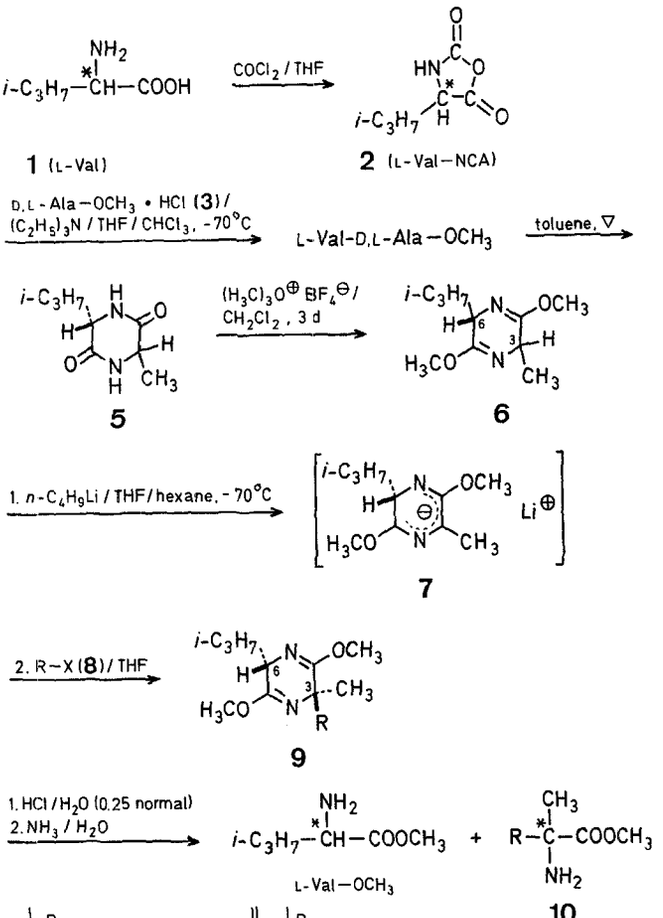
Organisch-Chemisches Institut der Universität Göttingen, Tammannstrasse 2, D-3400 Göttingen, Federal Republic of Germany

Optically active, non-proteinogenic amino acids deserve attention because of their documented or potential biological activity, for instance as pharmaceuticals or enzyme inhibitors.

Recently, we reported on the enantioselective synthesis of α-methyl-α-amino acids starting with the bis-lactim ether of cyclo(L-Ala-L-Ala)[2].

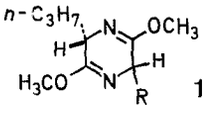


After lithiation, the lithio derivative was alkylated with alkyl halides and the alkylation product subsequently hydrolyzed to L-Ala-OCH_3 and the (*R*)-α-methyl-α-amino acid methyl ester (Type **10**). The diastereoselectivity of the C—C bond-forming alkylation step is 90–95%. Despite the rather high asymmetric induction, this method has the disadvantage that only half of the chiral auxiliary compound (L-Ala) is recovered; the other half is incorporated in the product. This disadvantage is avoided by using the "mixed" bis-lactim ether **6** from cyclo(L-Val-Ala). Lithiation (butyllithium, THF, −70°C) occurs regiospecifically in the alanine part of the molecule. The lithio derivative **7** reacts with alkyl halides **(8)** in unusually high diastereoselectivity (d.e. > 95% in all cases studied) to give the alkylation products **9** in which the alkyl group R has entered *trans* with respect to the isopropyl group at C-6, i.e., *R*-configuration is induced at C-3 of **9** [with D-valine as chiral auxiliary reagent, *S*-configuration would be induced]. Acidic hydrolysis of compounds **9** affords the (*R*)-α-methyl-α-amino acid methyl esters **10** and L-Val-OCH_3. Usually, these two esters can be easily separated by distillation and the chiral auxiliary component L-Val-OCH_3 thus be recovered.



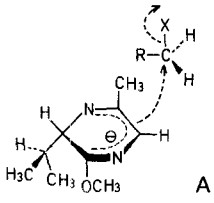
	R		R
a	$-CH_2-C_6H_5$	d	$n-C_7H_{15}$
b	$-CH_2-C_6H_3(OCH_3)_2$	e	$-CH_2-CH=CH_2$
c	$-CH_2-CH=CH-C_6H_5$	f	$-CH_2-C\equiv CH$
		g	$-CH_2-CH=C(CH_3)_2$

The assignment of configuration of compounds **9** is based on the ^{1}H-N.M.R. spectra of **9** and/or on the sign of rotation of the amino acid esters **10** formed on hydrolysis. In the case R = $-CH_2-$Ar, compounds **9** adopt the "folded conformation" in which the aryl ring faces the heterocycle[2,3]. Hence, in the ^{1}H-N.M.R. spectrum, the signal of 6-H experiences a characteristic upfield shift. In case of **9a, b, c**, we prepared the (6*S*,3*S*)-diastereoisomers for comparison by reversing the sequence of group introduction at C-3, starting with the bis-lactim ethers **11a, b, c** and introducing the methyl group with methyl iodide or dimethyl sulfate (d.e.: **9a**, ~85%; **9b**, ~81%; **9c**, ~85%). For **9d–g**, the (3*R*)-configuration is assumed by analogy.



11a,b,c

To explain the unusually high induction of the alkylation step **7**→**9**, we postulate the planar conformation A[5] for the anion of **7** which is attacked by the electrophile **8** predominantly from the less shielded top side.



A

The bis-lactim ether **6** is prepared as follous. L-Valine (**1**) is converted with phosgene into L-Val-NCA (**2**). This compound is condensed with D,L-Ala-OCH_3 to give the dipeptide. L-Val-D,L-Ala-OCH_3 which cyclizes on heating to cyclo(L-Val-Ala) (**5**). This is transformed to the bis-lactim ether **6** with trimethyloxonium tetrafluoroborate[5].

L-Valine *N*-Carboxyanhydride (L-Val-NCA, 2):
Into a stirred suspension of L-valine (**1**; 46.8 g, 0.4 mol) in dry tetrahydrofuran (600 ml), a stream of phosgene is introduced (~30 min) until **1** has completely dissolved. Then, nitrogen is bubbled through the mixture to remove excess phosgene and the solvent is distilled off in vacuo (after another distillation it can be used again). The residual crude product **2** is dissolved in tetrahydrofuran (100 ml) and this solvent is evaporated again to remove hydrogen chloride. The residual still crude product **2** (yield almost quantitative) is dried at 40°C/14 torr and used in the next step without further purification.

Cyclo(L-Val-Ala) (5):
A solution of crude L-Val-NCA (**2**; 58 g, 0.4 mol) in dry tetrahydrofuran (400 ml) is added dropwise to a stirred solution of D,L-alanine methyl ester hydrochloride (**3**; 55.8 g, 0.4 mol) and triethylamine (90.9 g, 0.9 mol) in chloroform (500 ml) at −60° to −70°C, and stirring is continued for 3 h at −70°C and for 30 min at room temperature. Then, triethylamine hydrochloride is filtered off and the filtrate evaporated to dryness in vacuo (40°C). The crude L-Val-D,L-Ala-OCH_3 (**4**) thus obtained is dissolved in toluene (1700 ml), the solution stirred and refluxed for 12 h, and cooled to 0°C. The precipitated product **5** is isolated by suction, washed (on the filter) several times with cold ether, and dried in vacuo at 100°C for ~3 days; yield: 58 g (85%). The product is used in the next step without further purification.

(3*S*,6*S*,*R*)-2,5-Dimethoxy-3-isopropyl-6-methyl-3,6-dihydropyrazine (Bis-lactim Ether 6):
A suspension of cyclo(L-Val-Ala) (**5**; 8.5 g, 50 mmol) and trimethyloxonium tetrafluoroborate (18.5 g, 125 mmol) in dichloromethane (200 ml) is vigorously stirred for 3 days [after 24 h, additional trimethyloxonium tetrafluoroborate (7.4 g, 50 mmol) is added]. To the resultant mixture, a solution of sodium dihydrogen phosphate ($NaH_2PO_4 \cdot 2H_2O$; 28.1 g) and disodium hydrogen phosphate ($Na_2HPO_4 \cdot 2H_2O$; 106 g) in water (500 ml) is added. The layers are separated and the aqueous layer is extracted with dichloromethane (3×50 ml). The combined organic layers are dried with magnesium sulfate, the solvent is evaporated, and the residual product **6** purified by distillation in vacuo; yield: 8.8 g (89%); b.p. 83–85°C/8–10 torr; $[\alpha]_D^{20}$: +82.0° (*c* 1.0, ethanol).

$C_{10}H_{18}N_2O_2$	calc.	C 60.58	H 9.15
(198.3)	found	60.69	9.17

I.R. (film): $\nu = 1685$ cm^{-1} (C=N).

^{1}H-N.M.R. ($CDCl_3$/TMS): $\delta = 1.41$, 1.42 ppm (d, 3 H, $J = 3$ Hz, 3-CH_3, *trans*/*cis*-**6**).

3-Substituted (3*R*,6*S*)-2,5-Dimethoxy-3-isopropyl-6-methyl-3,6-dihydropyrazines (9); General Procedure:
To a stirred solution of compound **6** (0.6 g, 3 mmol) in dry tetrahydrofuran (7 ml) at −70°C, a 1.55 normal solution (2.1 ml, 3.3 mmol) of butyllithium in hexane is added by syringe and stirring is continued for 15 min. Then, a precooled solution of the alkyl halide **8** (3.3 mmol) in dry tetrahydrofuran (7 ml) is added and stirring is continued for 8–24 h at −70°C. The cooling bath is removed, the solvent evaporated in vacuo, and the residue dissolved in a small amount of ether. The ether solution is shaken with water (10 ml), the water layer is extracted with ether (2×5 ml), and the combined ether phases are dried with magnesium sulfate. The solvent is evaporated in vacuo and the residual crude product **9** purified by bulb-to-bulb distillation. The diastereoisomeric excess (d.e.) of products **9** thus obtained may be assumed to be >95% if only one signal of the 3-CH_3 group is observed in the ^{1}H-N.M.R. spectrum.

I.R. (film): $\nu = 1680$–1690 cm^{-1} (C=N).

Table 1. 3-Substituted (3*R*,6*S*)-2,5-Dimethoxy-3-isopropyl-6-methyl-3,6-dihydropyrazines (**9**) and (3*S*,6*S*)-Analogs

Product	Educt	X in R—X (**8**) [or methylating agent]	Reaction time [h]	Yield [%]	d.e. [%]	b.p./torr[a] [°C]	Molecular formula[b]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
(3*R*,6*S*)-**9a**	**6**	Br	12	68	>95	100–110°/0.1	$C_{17}H_{24}N_2O_2$ (288.4)	1.50 (s, 3-CH_3); 3.18 (d, $J = 3$ Hz, 6-H)
(3*S*,6*S*)-**9a**	**11a**	[CH_3J]	14	82	~85			1.45 (s, 3-CH_3); 3.78 (d, $J = 4$ Hz, 6-H)
(3*R*,6*S*)-**9b**	**6**	Br	12	76	>95	130–140°/0.01	$C_{19}H_{28}N_2O_4$ (348.5)	1.48 (s, 3-CH_3); 3.28 (d, $J = 3$ Hz, 6-H)
(3*S*,6*S*)-**9b**	**11b**	[CH_3 or $(H_3CO)_2SO_2$]	14	74	~80			1.42 (s, 3-CH_3); 3.92 (d, $J = 4$ Hz, 6-H)
(3*R*,6*S*)-**9c**	**6**	Br	8	80	>95	110–120°/0.01	$C_{19}H_{26}N_2O_2$ (314.4)	1.41 (s, 3-CH_3); 3.87 (d, $J = 4$ Hz, 6-H)
(3*S*,6*S*)-**9c**	**11c**	[CH_3J]	14	89	~85			1.36 (s, 3-CH_3); 3.91 (d, $J = 3$ Hz, 6-H)
(3*R*,6*S*)-**9d**	**6**	Br	24	43	>95	110–120°/0.01	$C_{17}H_{32}N_2O_2$ (296.5)	1.36 (s, 3-CH_3); 3.97 (d, $J = 3$ Hz, 6-H)
(3*R*,6*S*)-**9e**	**6**	Br	12	90	>95	100–110°/10	$C_{13}H_{22}N_2O_2$ (238.3)	1.36 (s, 3-CH_3); 3.90 (d, $J = 3$ Hz, 6-H)
(3*R*,6*S*)-**9f**	**6**	Br	8	81	>95	120–120°/10	$C_{10}H_{20}N_2O_2$ (236.3)	1.38 (s, 3-CH_3); 4.05 (d, $J = 3$ Hz, 6-H)
(3*R*,6*S*)-**9g**	**6**	Br	10	94	>95	80–90°/0.1	$C_{15}H_{26}N_2O_2$ (266.4)	1.30 (s, 3-CH_3); 3.87 (d, $J = 3$ Hz, 6-H)

[a] Temperature of bulb-to-bulb distillation.

[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.37; H, ±0.22. Exceptions were (3*R*,6*S*)-**9a** (C, +0.65) and (3*R*,6*S*)-**9d** (C, −0.53).

Table 2. α-Methyl-α-amino Acid Methyl Esters (10)

10	Yield [%]	b.p./torr[a] [°C]	$[\alpha]_D^{20}$ (c, ethanol)	e.e. [%]	Molecular formula[b]	I.R. (film) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]
(*R*)-**10a**	79	75–80°/0.05	−2.8° (*c* 1.0 ethanol)	>95	[d]		
(*R*)-**10b**	76	130–140°/0.1	−0.7° (*c* 1.1 ethanol)	>95	[d]		
(*R*)-**10c**	69	110–120°/0.1	−13.2° (*c* 1.1 ethanol)	>95	$C_{13}H_{17}NO_2$ (219.3)	1720	1.40 (s, CH_3)
(*S*)-**10c**[e]	76	120–130°/0.1	+10.6° (*c* 0.8 ethanol)	~85			1.40 (s, CH_3)
(*R*)-**10d**	47[f]	90–100°/0.1	−12.9° (*c* 0.6 ethanol)	>95	$C_{11}H_{23}NO_2$ (201.3)	1730	1.36 (s, CH_3)
(*R*)-**10e**	90[g]		+2.33° (*c* 0.4 ethanol)	>95	$C_7H_{13}NO_2$ (143.2)	1735	1.36 (s, CH_3)
(*R*)-**10f**	87[h]		+2.08° (*c* 0.8 ethanol)	>95	$C_7H_{11}NO_2$ (141.2)	1735	1.39 (s, CH_3)
(*R*)-**10g**	82	100–110°/10	−17.9° (*c* 1.0 ethanol)	94[i]	$C_9H_{17}NO_2$ (171.2)	1735	1.33 (s, CH_3)

[a] Temperature of bulb-to-bulb distillation.

[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.37; H, ±0.22.

[c] Using $Eu(hfc)_3$ as shift reagent.

[d] Identified by comparison of the I.R. and ^{1}H-N.M.R. spectra with those of authentic samples[2].

[e] Prepared from (3*S*,6*S*)-**9c**.

[f] Time required for hydrolysis: 8 days (shaking). 44% of **9d** could be recovered from the ether extract of the acidic aqueous mixture.

[g] 1:1 Mixture of **10e** and L-Val-OCH_3. Product **10e** was isolated by G.L.C. (Chromosorb W, 60/80 mesh, 15% OV 210).

[h] Mixture of **10f** and L-Val-OCH_3. Product **10f** was isolated by G.L.C.

[i] Lower limit. An impurity may possibly mistaken for the (*S*)-enantiomer.

(*R*)-α-Methyl-α-amino Acid Methyl Esters (10) from Hydrolysis of Compounds 9; General Procedure:

A suspension of the compound **9** (2 mmol) in 0.25 normal hydrochloric acid (16 ml, 4 mmol) is stirred at room temperature for 3 days during which time ether (2–3 ml each) is added after 24 h and after 48 h. The solution is extracted with ether (2 × 10 ml) to remove unreacted **9** and is then evaporated to dryness. The residue (**10**·HCl and L-Val-OCH_3·HCl) is dissolved in the minimum amount of water, ether (~20 ml) is added, and then concentrated aqueous ammonia is added with shaking to adjust the mixture to pH 8–10. The ether layer is separated and the aqueous layer extracted with ether (2 × 10 ml). The combined ether layers are dried with magnesium sulfate, the solvent is evaporated in vacuo, and the residual mixture of **10** and L-Val-OCH_3 bulb-to-bulb distilled whereby L-Val-OCH_3 is obtained as the forerun.

Received: May 5, 1981

[1] For Part VII, see: U. Schöllkopf, W. Hartwig, K.-H. Pospischil, H. Kehne, *Synthesis* **1981**, 966.

[2] U. Schöllkopf, W. Hartwig, U. Groth, *Angew. Chem.* **91**, 922 (1979); *Angew. Chem. Int. Ed. Engl.* **18**, 863 (1979).
U. Schöllkopf, W. Hartwig, U. Groth, K. O. Westphalen, *Justus Liebigs Ann. Chem.* **1981**, 696.

[3] For "folded conformations" in other benzyl-substituted heterocycles, cf. A. K. Bose et al., *Heterocycles* **7**, 1227 (1977).

[4] For a discussion, see: U. Groth, *Dissertation*, Universität Göttingen, 1981; details to be published in different context.

[5] Trimethyloxonium tetrafluoroborate was used instead of the cheaper and more reactive triethyl analog (cf. Ref.[1,2]) because the ^{1}H-N.M.R. spectra of the resultant methyl derivatives are simpler than those of the ethyl derivatives (cf. Ref.[3]). Commercial reagents should be cleaned before use.