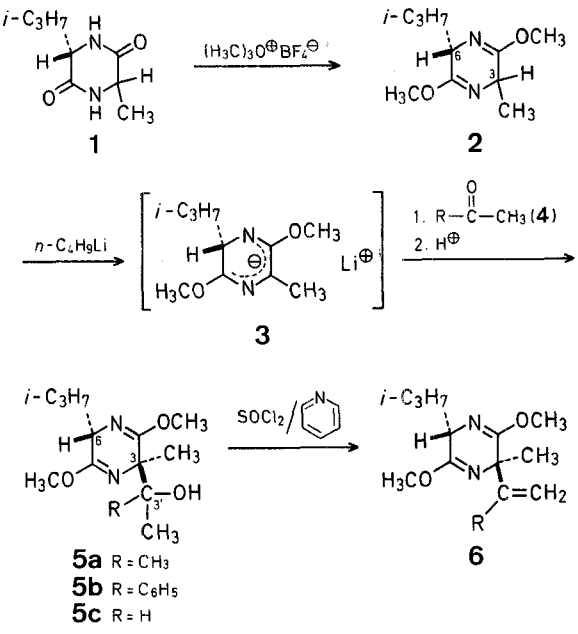

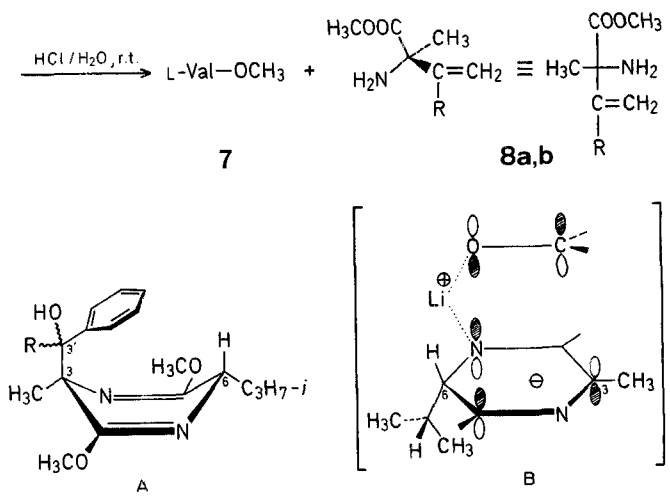

Asymmetric Syntheses via Heterocyclic Intermediates; XIII[1]. Enantioselective Synthesis of (*R*)-α-Alkenylalanine Methyl Esters using L-Valine as Chiral Auxiliary Reagent

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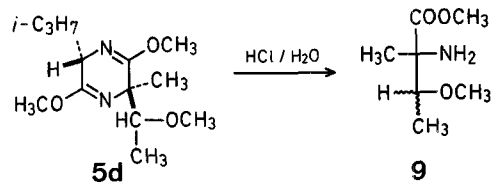
As reported earlier[2], alkyl halides react with the lithiated bis-lactim ether **3** [obtained from cyclo(L-Val-D,L-Ala) **(1)**] with d.e. (=diastereomeric excess=asymmetric induction) >95%. As we have found now, carbonyl compounds **(4)** such as acetone, acetophenone, or acetaldehyde react with **3** also with d.e.>95% to give the (3*R*)-configurated aldol-type adducts **5**. The diastereomeric purity of **5** was established ^{1}H-N.M.R.-spectroscopically using Eu(fod)$_3$ as shift reagent, whereby the methyl singlets could be used for the analysis, or ^{13}C-N.M.R.-spectroscopically, whereby the C-3′-signal could be used. In neither case could the diastereoisomer with the (3*S*)-configuration be detected. The (3*R*)-configuration of **5b** was deduced from the ^{1}H-N.M.R.-spectrum. According to our experience[3], bis-lactim ethers of the type **5** adopt a boat shape for the heterocycle and the "folded conformation" for the hydroxybenzyl group (cf. A for **5b**). Hence, the signal of 6-H suffers an upfield shift[4]. By analogy we assume the (3*R*)-configuration also for **5a** and **5c**.

As expected, the enantioface differentiation at the carbonyl group is weaker. C-3′ Induction amounts to ~5% for **5b** and ~65% for **5c**.

As for the mechanism of carbonyl addition, we postulate the transition state B which is stabilized by HOMO(anion)-LUMO(carbonyl)-attraction (cf. Ref.[3]) and by the chelating power of lithium[5]. Due to the bulky isopropyl group at C-6, "bottom side attack" is favored (cf. B).

The adducts **5a** and **5b** were dehydrated to the olefinic compounds **6** by treatment with thionyl chloride/pyridine and compounds **6** were hydrolyzed with 0.25 normal hydrochloric acid to give L-Val-OCH$_3$ and (2*R*) methyl 2-amino-2,3-dimethyl-3-butenoate **(8a)** or (2*R*) methyl 2-amino-2-methyl-3-phenyl-3-butenoate **(8b)** (α-methyl-β-methylenephenylalanine methyl ester[6]). Both compounds were enantiomerically pure by N.M.R. standard [Eu(hfc)$_3$].

The acetaldehyde adduct **5c** was *O*-methylated and the resultant **5d** hydrolyzed to a 4.5:1 diastereomer mixture [(2*R*,3*S*) and (2*R*,3*R*)] of methyl 2-amino-3-methoxy-2-methylbutanoate **(9)**, enantiomerically pure at C-2 (the preferred configuration at C-3 was not determined).



Bis-lactim ether **2**[2] was prepared as reported.

Aldol-Type Adducts 5a, b:

A 1.55 normal solution (3.6 ml, 5.5 mmol) of butyllithium in hexane is added by syringe to a stirred solution of compound **2** (0.99 g, 5 mmol) in tetrahydrofuran (10 ml) at −70 °C. After 15 min, a solution of the carbonyl compound **4** (5.5 mmol) in tetrahydrofuran (5 ml) is added and stirring is continued for 2–3 h at −78 °C. Then, a solution of glacial acetic acid (0.33 g, 5.5 mmol) in tetrahydrofuran (2 ml) is added. The solvent is removed in vacuo and the residue shaken with ether (10–15 ml) and water (20 ml). The layers are separated and the aqueous layer is extracted with ether (2 × 10 ml). The ether extract is dried with magnesium sulfate, the solvent evaporated, and the residual product distilled in vacuo.

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Table 1. Aldol-Type Adducts **5**

5	R	Yield [%]	b.p. [°C/torr]	d.e. C-3 (C-3′)	Molecular formula[a]	^{1}H-N.M.R. (TMS_{int}) δ [ppm]
a	CH_3	94	60–70°/0.1	>95	$C_{13}H_{24}N_2O_3$ (256.3)	$CDCl_3$: 0.72, 1.13 (2d); 1.10, 1.40 (2s); 1.28 (s); 3.99 (d, 6H)
b	C_6H_5	93	110–120°/0.05	>95 (≈ 5)	$C_{18}H_{26}N_2O_3$ (318.4)	$CDCl_3/C_6H_6$: 0.58, 0.60, 0.93 (3d); 1.52 (s); 1.66, 1.77 (2s); 3.02, 3.18 (2d, 6-H)[b]
c	H	85	60–70°/0.05	>95 (≈65)	$C_{12}H_{22}N_2O_3$ (242.3)	$CDCl_3$: 0.73, 1.10, 0.91 (3d); 1.17 (d); 1.35, 1.45 (2s, epimers)

[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.14; H, ±0.36.
[b] ^{13}C-N.M.R. ($CDCl_3/TMS_{int}$): δ = 74.11 ppm (C—OH).

Table 2. (*R*)-α-(1-Alkenyl)-alanine Methyl Esters **(8)**

8	R	Yield [%]	b.p. [°C/torr]	%[a] e.e.	$[\alpha]_D^{20}$ (*c*, ethanol)	Molecular formula	^{1}H-N.M.R. ($CDCl_3/TMS_{int}$) δ [ppm]
a	CH_3	—[b]	70–80°/12	>95	− 6.2° (1.0)	$C_7H_{13}NO_2$[c] (143.2)	1.51 (s); 1.73 (s); 1.82 (m); 3.75 (s); 4.95, 5.10 (m)
b	C_6H_5	68	80–90°/0.1	>95	−28.9 (1.2)	$C_{12}H_{15}NO_2$[d] (205.2)	1.55 (s); 3.70 (s); 5.18, 5.45 (s)

[a] Only one enantiomer detectable in the ^{1}H-N.M.R. spectrum using $Eu(hfc)_3$ as shift reagent.
[b] Pure **8a** was isolated by G.L.C. of the 7:3 mixture of **8a**+**7** obtained by bulb-to-bulb distillation.
[c] calc. C 58.72 H 9.15; found 58.78 8.95
[d] calc. C 70.22 H 7.33; found 70.01 7.69

The crude products **5a, b** were analyzed for diastereoisomeric purity by ^{1}H-N.M.R. with $Eu(fod)_3$ using the CH_3-singlets and by ^{13}C-N.M.R. using the C—OH signal.

(*R*)-α-(1-Alkenyl)-alanine Methyl Esters (8a, b):

*(3*R,6S*)-2,5-Dimethoxy-3-isopropenyl-6-isopropyl-3-methyl-* **(6a)** *and (3*R,6S*)-2,5-Dimethoxy-6-isopropyl-3-methyl-3-(1-phenylvinyl)-3,6-dihydropyrazine* **(6b):** A solution of compound **5** (1.0 g of **5a** or 1.27 g of **5b** as an epimer mixture, 4 mmol) and pyridine (1.26 g, 16 mmol) in toluene (10 ml) is added to a stirred solution of thionyl chloride (0.71 g, 6 mmol) in toluene (3 ml) at room temperature. Stirring is continued for 2 days and the mixture then shaken with ether (20 ml) and water (20 ml). The layers are separated and the ether layer is dried with magnesium sulfate. The solvent is evaporated and the residual product purified by bulb-to-bulb distillation.

Compound **6a**; yield: 0.77 g (81%); b.p. 50–60 °C/0.1 torr.

Compound **6b**; yield: 1.1 g (92%); b.p. 110 °C/0.2 torr. The product is contaminated by ~10% of 2,5-dimethoxy-6-isopropyl-3-methylpyrazine.

(R)-*α-(1-Alkenyl)-alanine Methyl Esters* **(8a, b):** A mixture of compound **6** (0.36 g of **6a** or 0.45 g of **6b**, 1.5 mmol) and 0.25 normal hydrochloric acid (12 ml, 3 mmol) is stirred at room temperature for 4 days. After 24, 48, and 72 h, ether (1–2 ml each time) is added. The mixture is extracted with ether (2 × 5–10 ml) and the ether discarded. The water layer is concentrated to 1–2 ml (in vacuo, maximum bath temperature 60–80 °C), ether (~10 ml) is added, and with vigorous shaking, conc. aqueous ammonia is added till pH 8–10. The ether layer is separated and the water layer extracted with ether (3 × 10 ml). The ether extracts are dried with magnesium sulfate, the solvent is evaporated, and the residue distilled (bulb-to-bulb). Product **8a** is obtained as a 7:3 mixture of **8a** and **7** from which pure **8a** can be obtained by G.L.C. (Chromosorb W mesh 60/80, 15% OV 210). Using $Eu(hfc)_3$ as shift reagent, only one enantiomer of **8a, b** can be detected in the ^{1}H-N.M.R. spectrum.

(2*R*,3*S*)- + (2*R*,3*R*)-Methyl 2-Amino-3-methoxy-2-methylbutanoate (9):

*(3*R,6S,3′RS*)-2,5-Dimethoxy-6-isopropyl-3-(1-methoxyethyl)-3-methyl-3,6-dihydropyrazine* **(5d):** A mixture of the 3-(1-hydroxyethyl) compound **5c** (0.48 g, 2 mmol), tetrahydrofuran (10 ml), potassium *t*-butoxide (0.34 g, 3 mmol), and HMPT (1.8 g, 10 mmol) is stirred at 0 °C for 10 min. Then, a solution of methyl iodide (0.57 g, 4 mmol) in tetrahydrofuran is added and stirring is continued for 20 h at 40 °C. The solvent is removed in vacuo, the residue is dissolved in petroleum ether (30 ml), and this solution is extracted with water (5 × 20 ml). The organic layer is dried with magnesium sulfate, the solvent evaporated, and the residual product **5d** purified by bulb-to-bulb distillation; yield: 0.47 g (92%); b.p. 50–60 °C/0.1 torr (bulb-to-bulb).

$C_{13}H_{24}N_2O_3$ (256.3) calc. C 60.91 H 9.44; found 61.05 9.41

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 1.21, 1.27 (s, epimers, 3-CH_3); 3.29, 3.40 ppm (s, epimers, 3′-OCH_3).

*(2*R,3*SR)-Methyl 2-Amino-3-methoxy-2-methylbutanoate* **(9):** A mixture of compound **5d** (0.38 g, 1.5 mmol), 0.25 normal hydrochloric acid (12 ml, 3 mmol), and ether (2–3 ml) is stirred at room temperature for 3 days (after 24 and 28 h, the evaporated ether is replaced by ~1 ml ether). The mixture is extracted with ether (2 × 5 ml), the ether phase discarded, and the aqueous phase worked up as described for **8a, b**; yield: 0.15 g (62%); b.p. 65–75 °C/0.1 torr (bulb-to-bulb). The product is a 4.5:1 mixture of diastereoisomers.

$C_7H_{15}NO_3$ (161.2) calc. C 52.16 H 9.38; found 52.28 9.43

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 3.30, 3.36 ppm (2s, epimers, OCH_3).

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