

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 ₂ O ₃ (256.3)	CDCl ₃ : 0.72, 1.13 (2 d); 1.10, 1.40 (2 s); 1.28 (s); 3.99 (d, 6 H)
b	C ₆ H ₅	93	110–120°/0.05	>95 (≈ 5)	C ₁₈ H ₂₆ N ₂ O ₃ (318.4)	CDCl ₃ /C ₆ H ₆ : 0.58, 0.60, 0.93 (3 d); 1.52 (s); 1.66, 1.77 (2 s); 3.02, 3.18 (2 d, 6-H) ^b
c	H	85	60–70°/0.05	>95 (≈ 65)	C ₁₂ H ₂₂ N ₂ O ₃ (242.3)	CDCl ₃ : 0.73, 1.10, 0.91 (3 d); 1.17 (d); 1.35, 1.45 (2 s, epimers)

^a The microanalyses showed the following maximum deviations from the calculated values: C, ±0.14; H, ±0.36.

^b ¹³C-N.M.R. (CDCl₃/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.	[α] _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 ₇ H 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 ₆ H 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 ¹H-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 ¹H-N.M.R. with Eu(fod)₃ using the CH₃-singlets and by ¹³C-N.M.R. using the C—OH signal.

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

(3R,6S)-2,5-Dimethoxy-3-isopropenyl-6-isopropyl-3-methyl- (**6a**) and (3R,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 ¹H-N.M.R. spectrum.

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

(3R,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).

C₁₃H₂₄N₂O₃ calc. C 60.91 H 9.44
(256.3) found 61.05 9.41

¹H-N.M.R. (CDCl₃/TMS_{int}): δ = 1.21, 1.27 (s, epimers, 3-CH₃); 3.29, 3.40 ppm (s, epimers, 3'-OCH₃).

(2R,3SR)-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.

C₇H₁₅NO₃ calc. C 52.16 H 9.38
(161.2) found 52.28 9.43

¹H-N.M.R. (CDCl₃/TMS_{int}): δ = 3.30, 3.36 ppm (2 s, epimers, OCH₃).

- ¹ Part XII: U. Schöllkopf, J. Neubauer, *Synthesis* **1982**, 861.
- ² U. Schöllkopf, U. Groth, K.-O. Westphalen, C. Deng, *Synthesis* **1981**, 969.
- ³ U. Schöllkopf, U. Groth, W. Hartwig, *Justus Liebigs Ann. Chem.* **1981**, 2407.
- ⁴ Cf. Ref.³; alternatively, in the (6*S*,3*S*)-epimer one of the methyl groups of the isopropyl moiety would lead to an upfield shift. This high-field signal is missing in **5b**; cf. U. Groth, *Dissertation*, University of Göttingen, 1981.
- ⁵ This model is similar to the one proposed for the aldol addition: cf.: P. Fellmann, J.-E. Dubois, *Tetrahedron* **34**, 1349 (1978). H. O. House, D. S. Crumrine, A. Y. Teranishi, H. D. Olmstead, *J. Am. Chem. Soc.* **95**, 3310 (1973). C. H. Heathcock et al., *J. Org. Chem.* **45**, 1066 (1980).
- ⁶ For an enantioselective synthesis (e.e. >95%) of (*R*)- β -methylene-phenylalanine methyl ester, cf. U. Schöllkopf, U. Groth, *Angew. Chem.* **93**, 1022 (1981); *Angew. Chem. Int. Ed. Engl.* **20**, 977 (1981).