First publ. in: Liebigs Annalen der Chemie 1982, 9, pp. 1756-1757

Asymmetric Syntheses *via* Heterocyclic Intermediates, XI[1)]

Enantioselective Synthesis of (*R*)-(−)-α-Methylserine

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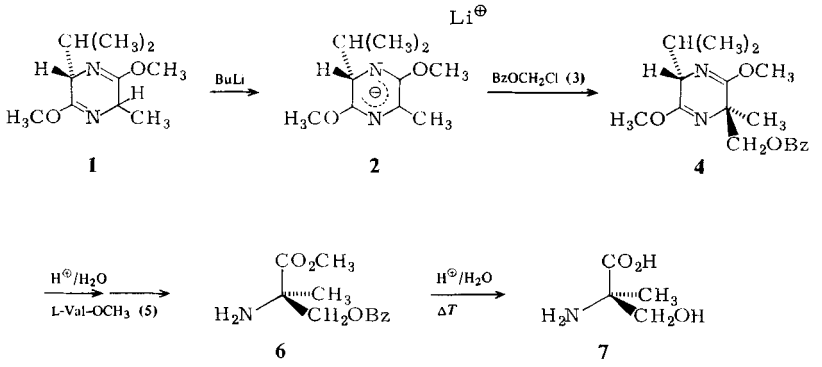
Received May 28, 1982

Asymmetrische Synthesen über heterocyclische Zwischenstufen, XI[1)]. – Enantioselektive Synthese von (*R*)-(−)-α-Methylserin

Die Titelverbindung **7** wurde in enantiomerenreiner Form durch asymmetrische Synthese dargestellt unter Verwendung des Bislactimethers **1** von *cyclo*-(L-Val-DL-Ala) als Ausgangsverbindung.

Optically active nonproteinogenic amino acids are valuable tools in biochemistry to investigate enzyme reaction mechanisms. (*R*)-(−)-α-Methylserine (**7**) was required as a potential inhibitor of the enzyme D-serine dehydratase[2)]. Here we describe an enantioselective synthesis – employing our bis(lactim) ether method[3)] – that provides this uncommon amino acid easily in enantiomerically pure form (both by NMR standard and by rotation). The "mixed" bis(lactim) ether **1**[4)] which contains L-valine as chiral auxiliary was metalated by butyllithium to give the lithium compound **2** which reacts with chloromethyl benzyl ether **3** to afford the (3*R*)-adduct **4** in 91% chemical yield and with d. e.[5)] more than 95% (only one diastereomer was detectable in the ^1H and ^{13}C NMR spectrum). On hydrolysis (0.25 N HCl, room temperature) the adduct **4** is cleaved, liberating methyl L-valinate (**5**), the chiral auxiliary, and (*R*)-(+)-*O*-benzyl-α-methylserine methyl ester (**6**, enantiomerically pure by NMR standard). The two esters are separable by distillation. On heating with 6 N HCl **6** is converted into (*R*)-(−)-α-methylserine (**7**), the target molecule.



1 **2** **4** **6** **7**

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Experimental

(3R,6S)-3-Benzyloxymethyl-3,6-dihydro-6-isopropyl-2,5-dimethoxy-3-methylpyrazine (**4**): A solution of 6.1 ml 1.8 N butyllithium in hexane (11 mmol) was added (syringe) at −70 °C to a solution of 1.98 g (10.0 mmol) **1**[4] in 20 ml of dry THF. After 10 min (formation of **2**) a solution of 1.72 g (11.0 mmol) chloromethyl benzyl ether **3**[6] in 15 ml of THF was added. After 4 h stirring at −70 °C the mixture was allowed to come to room temperature and the solvent evaporated *in vacuo*. The residue was shaken with 20 ml of ether and 20 ml of water, the ether layer separated, and the water layer extracted twice with ether. The combined extracts were dried with $MgSO_4$. Usual workup gave 2.88 g (91%) of **4**; b. p. 140–150 °C/0.1 Torr (bulb-to-bulb distillation). Diastereomerically pure by ^1H and ^{13}C NMR spectra. – IR (film): ν = 1690 cm^{-1} (N=C). – ^1H NMR ($CDCl_3$): δ = 1.24 (s; 3-CH_3), 3.34, 3.72 (AB system; 3-CH_2–O), 4.02 (d; 6-H), 4.47 (s; CH_2Ph). – ^{13}C NMR ($CDCl_3$): δ = 24.03 (3-CH_3), 59.22 (3-C), 61.00 (6-C), 72.88 (CH_2), 76.72 (CH_2Ph).

$C_{18}H_{26}N_2O_3$ (318.4) Calc. C 67.90 H 8.23 Found C 68.00 H 8.24

(R)-O-Benzyl-α-methylserine methyl ester (**6**): A suspension of 2.54 g (8.00 mmol) **4** in 46 ml of 0.25 N HCl (16 mmol) was stirred at room temperature for 5 d. The mixture was extracted with ether which was discharged. The water layer was evaporated to 5–10 ml *in vacuo*, then ca. 20 ml of ether and – with intensive shaking – conc. ammonia were added until pH = 8–10. The ether layer was separated and the water layer extracted three times with ca. 10 ml of ether. The combined ethereal solution was dried with $MgSO_4$, then the usual workup procedure followed. The residual mixture (**5** and **6**) was bulb-to-bulb distilled and **5** removed as forerun. 1.38 g (81%) **6**; b. p. 100–110 °C/0.1 Torr; $[\alpha]_D^{20}$ = +4.7 (*c* = 1.4, ethanol). – IR (film): ν = 3380, 3310 (NH_2), 1735 cm^{-1} (CO). – ^1H NMR ($CDCl_3$): δ = 1.25 (s; CH_3), 2.06 (s; NH_2), 3.36, 3.70 (AB system; CH_2), 3.68 (s; OCH_3), 4.49 (s; CH_2Ph). – After addition of Eu(hfc)$_3$ the OCH_3 signal was shifted but did not split (e. e. ⩾ 95%).

$C_{12}H_{17}NO_3$ (223.3) Calc. C 64.55 H 7.67 Found C 64.35 H 7.64

(R)-(–)-α-Methylserine (**7**): A solution of 0.45 g (2.00 mmol) **6** was refluxed for 2 h with 20 ml of 6 N HCl. The mixture was evaporated to dryness *in vacuo*, the residual **7** · HCl dried for 15 min at 50 °C/0.1 Torr and dissolved in ca. 20 ml of hot ethanol. Ca. 5 ml of propene oxide was added and the mixture was refluxed for 15 min. After 1 h at 0 °C **7** was isolated by suction, washed (in the filter) with cold ethanol and cold ether and dried for 5 d over P_4O_{10} *in vacuo*: 0.2 g (84%) **7** with m. p. 242–245 (decomp.). Lit.[7]: 235–240 °C, $[\alpha]_D^{20}$ = −3.4 (*c* = 1.2, 6 N HCl), $[\alpha]_D^{20}$ = −6.2 (*c* = 1.0, H_2O). Lit.[7]: $[\alpha]_D^{20}$ = +6.3° for (*S*)-**7** (*c* = 1.0, H_2O). – ^1H NMR (DMSO/D_2O): δ = 1.30 (s; CH_3), 3.47, 3.75 (AB system, J_{AB} = 9 Hz; CH_2).

$C_4H_9NO_3$ (119.1) Calc. C 40.33 H 7.62 Found C 40.50 H 7.57

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[1] X. Communication: *U. Schöllkopf, U. Groth,* and *W. Hartwig,* Liebigs Ann. Chem. **1981**, 2407.

[2] *K. Schnakerz,* University of Würzburg, private communication.

[3] *U. Schöllkopf,* Top. Curr. Chem., in print; cf. Lit.[1] for previous communications on this subject.

[4] *U. Schöllkopf, U. Groth, K.-O. Westphalen,* and *C. Deng,* Synthesis **1981**, 969.

[5] d. e. = diastereomeric excess = asymmetric induction. >95% is assumed if only one stereoisomer is detectable in the NMR spectrum.

[6] *D. S. Connor, G. W. Klein,* and *G. N. Taylor,* Org. Synth. **52**, 16 (1972).

[7] *E. H. Flynn, J. W. Hinman, E. L. Caron,* and *D. O. Woolf, Jr.,* J. Am. Chem. Soc. **75**, 5867 (1953); cf. also *N. Takamura, S. Terashima, K. Achiwa,* and *S. Yamada,* Chem. Pharm. Bull. **15**, 1776 (1967).

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