A Useful Route to Both Enantiomers of 1-Amino-2-alkanols: Synthesis of 1-Amino-3-methyl-2-butanol from Valine

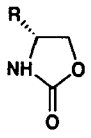
Bernhard Koppenhoefer,*[a] Ulrich Trettin,[a] Andreas Wächtler[b]

[a] Institut für Organische Chemie, Universität Tübingen, Auf der Morgenstelle 18, D-72076 Tübingen, Germany
[b] E. Merck, Frankfurter Str. 250, Postfach 4119, D-27476 Darmstadt, Germany

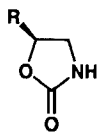
Received 24 September 1993

A multistep synthesis of (*S*)-1-amino-3-methyl-2-butanol (**9**) from D-valine (**3**) is reported. The enantiomeric purity of (*S*)-**9** (97.2 ± 0.2% ee) is determined by GC of the derivative, 5-isopropyloxazolidin-2-one (**2**) on both L- and D-Chirasil-Val. (*R*)-**9** is prepared from L-valine in the same manner; thus, the procedure provides a useful route to both enantiomers of 1-amino-2-alkanols, starting from L- and D-amino acids, respectively.

2-Amino-3-methyl-1-butanol (valinol) (**4**) is a well known chiral auxiliary in asymmetric synthesis. According to Meyers and Evans, suitable derivatives of **4**, such as bicyclic lactams,[1,2] chiral imines,[3,4] and 4-isopropyloxazolidin-2-one (**1**)[5-7] are very effective in diastereomeric bond formation. A number of natural products have been prepared in high enantiomeric purity using this methodology. Inverse substitution of the hydroxy and amino groups in **4** leads to 1-amino-3-methyl-2-butanol (**9**) and 5-isopropyloxazolidin-2-one (**2**), respectively, the prospects of which are yet to be established.



(*R*)-**1**



(*S*)-**2**

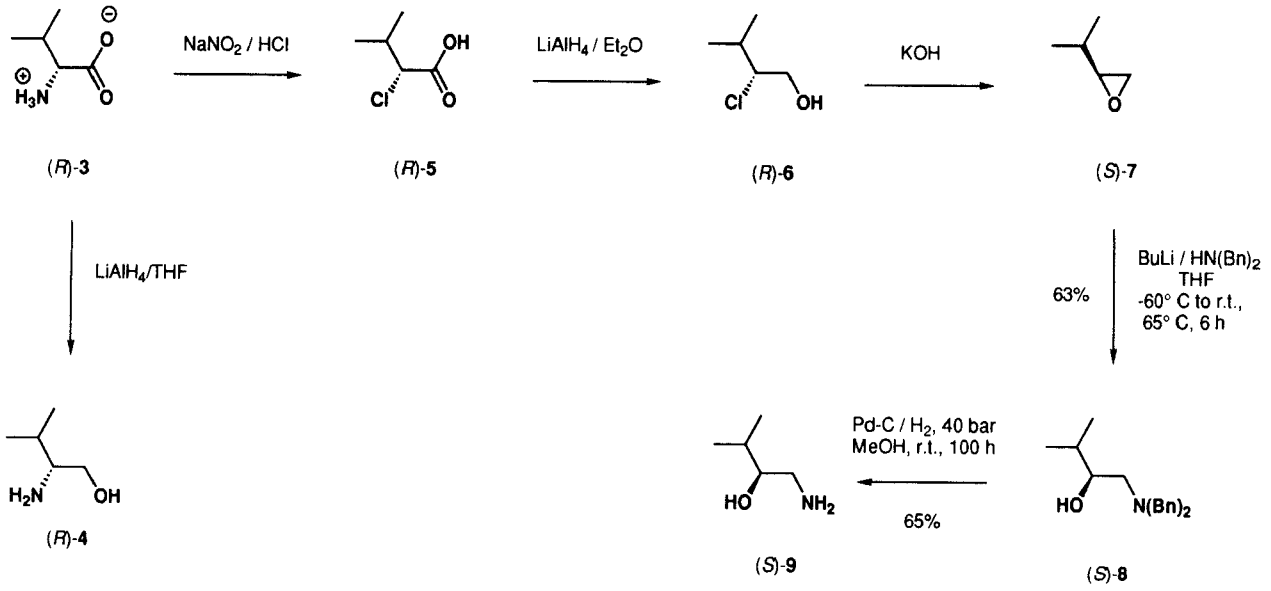
Following an earlier report, (*S*)-1,2-epoxy-3-methylbutane (**7**) was prepared in a three-step synthesis (Scheme) starting from D-valine (**3**).[8,9] The key step in the present work is the ring opening of the epoxide **7** with lithium dibenzylamide at −78 °C to furnish (*S*)-1-(*N*,*N*-dibenzylamino)-3-methyl-2-butanol (**8**). The protecting benzyl groups were removed by hydrogenolytic cleavage with Pd/C[10] to provide (*S*)-1-amino-3-methyl-2-butanol (**9**). For comparison, the (*R*)-enantiomer was prepared in the same manner.

The extent of racemization accompanying the ring opening from **7** to **8** and the following hydrogenolysis from **8** to **9** were established by capillary GC on a chiral stationary phase. The determination of the enantiomeric purity of the amino alcohol **9** required derivatization to either 5-isopropyloxazolidin-2-one (**2**) or the preparation of the (*N*,*O*)-bis(trifluoroacetyl) derivative **10**. Each sample was analyzed on both enantiomers of the chiral stationary phase, i.e., L- and D-Chirasil-Val, respectively, to confirm peak identification of the enantiomers, and to increase the reliability of the determination (Figure).

It turned out that both enantiomers of the stationary phase Chirasil-Val produced similar data, with the exceptional situation of a rider peak for (*S*)-**10** on the D-phase. The three valid measurements, ranging from 97.0 to 97.3% ee are in good agreement with the enantiomeric purity of the isopropyloxirane used (97.2% ee).[11] Notably, the ring-opening reaction as the crucial step, due to the regio- and stereoselective S_N2-attack of the amide nucleophile at the carbon atom C-1, proceeds with a high degree of stereocontrol. Thus, the protocol applied opens up a promising "*ex chiral pool*" route to both enantiomers of 1-amino-2-alkanols.

(*S*)-1-(*N*,*N*-Dibenzylamino)-3-methyl-2-butanol (8):

A 500 mL, 4-necked, round-bottomed flask equipped with a magnetic stirrer, reflux condenser, low-temperature thermometer and dropping funnel was charged with dibenzylamine (3.85 g, 19.5 mmol) in anhydr. THF (50 mL) under an atmosphere of dry



Scheme

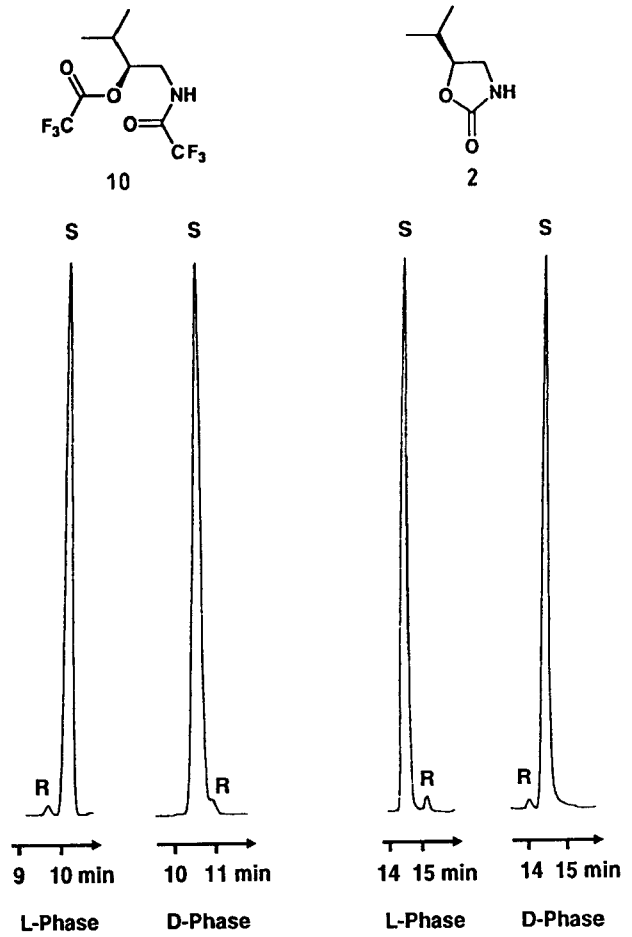


Figure. Left hand: Enantiomeric purity of the Bis-(*N,O*)-TFA derivative (*S*)-**10** on L-Chirasil-Val (97.0% ee) and D-Chirasil-Val (96.6% ee, rider peak); Right hand: 5-Isopropyloxazolidin-2-one [(*S*)-**2**] on L-Chirasil-Val (97.2% ee) and D-Chirasil-Val (97.3% ee). Conditions see experimental part.

N_2. The solution was kept at −78 °C in an acetone/dry ice mixture while a precooled solution of BuLi (12 mL, 1.6 M in hexane) was added over a period of 30 min. Subsequently, a precooled solution of 1,2-epoxy-3-methylbutane (**7**; 2.5 g, 29 mmol) in anhydr. THF (10 mL) was added over another 20 min. The cooling device was removed, and the mixture was stirred for 6 h at 65 °C. A sat. aq solution of NH_4Cl (20 mL) was added, the aqueous layer was separated and extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with 1 N KOH solution (10 mL) and H_2O (10 mL). The aqueous phases were reextracted with Et_2O (2 × 10 mL). After drying (Na_2SO_4), the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (99:1, Et_2O/Et_3N) to give **8** as a pale yellowish oil; yield: 3.5 g (63%) based on dibenzylamine; $[\alpha]_D^{20}$ +24.5° (*c* = 1, MeOH).

$C_{19}H_{25}NO$	calc.	C 80.52	H 8.89	N 4.94
(277.4)	found	80.31	8.71	5.17

^1H NMR ($CDCl_3$): δ = 0.95 (2 d, 6H, $2CH_3$), 1.51 [m, 1H $(CH_3)_2CH$], 2.53 (AB of ABX, 2H, CH_2), 3.48 (m, 1H, OCH), 3.83 (s, 4H, $2CH_2Ph$), 7.35 (m, 10H, $2C_6H_5$).

^{13}C NMR ($CDCl_3$): δ = 17.4, 19.2, 32.7, 58.1, 59.7, 73.7, 128.4–129.9, 140.2.

(*S*)-1-Amino-3-methyl-2-butanol (9):
Compound **8** (3.2 g, 11 mmol) and catalytic amounts of Pd/C in MeOH (50 mL) were stirred at r.t. under an atmosphere of H_2 (40 bar) for 100 h. The course of the reaction was checked by TLC (7:7:2:0.2, *i*-PrOH/hexane/Et_2O/Et_3N) with ninhydrin detection of (*S*)-**9** (R_f = 0.19). The catalyst was filtered off and the solvent removed in vacuo; yield: 0.75 g (65%); $[\alpha]_D^{20}$ +17.3° (*c* = 1, MeOH); 97.2 ± 0.2% ee.

^1H NMR ($CDCl_3$): δ = 0.90, 0.97 (2 d, 6H, $2CH_3$), 1.68 [m, 1H, $(CH_3)_2CH$] 2.6–2.9 (AB of ABC, 2H, CH_2), 3.48 (m, 1H, OCH), 4.6 (s, OH + NH_2).

^{13}C NMR ($CDCl_3$): δ = 17.9, 18.5, 32.1, 44.1, 75.3.

(*S*)-5-Isopropyloxazolidin-2-one (2):
The amino alcohol **9** (5 mg) was converted to **2** with phosgene (1 mL, 20% in toluene) in a 1 mL Reacti-Vial. After 12 h at r.t., the solvent was evaporated in vacuo. The solid residue was taken up in EtOAc and analyzed by GC. Conditions: glass capillary column 20 m × 0.3 mm, deactivated with 1,3-diphenyl-1,1,3,3-tetramethyldisilazane (DPTMDS),[12] coated with either L-[13] or D-Chirasil-Val,[14] inlet pressure: 0.45 atm H_2, split ratio 1:50, oven temperature: 120 °C (L-Phase t_0 = 0.605 min, k'_R = 24.04, k'_S = 23.15, α = 1.039; D-Phase: t_0 = 0.605 min, k'_R = 22.17, k'_S = 23.13, α = 1.043).

(*S*)-1-Amino-(*N,O*)-bis(trifluoroacetyl)-3-methyl-2-butanol (10):
Amino alcohol **9** (5 mg) and $(CF_3CO)_2O$ (0.5 mL) were kept in a tightly closed 1 mL Reacti-Vial. After 2 h at r.t., the volatile components were stripped off with a gentle stream of N_2. The residue was diluted with CH_2Cl_2 and analyzed by GC. Conditions: glass capillary column 20 m × 0.3 mm, deactivated with DPTMDS[12] coated with either L-[13] or D-Chirasil-Val,[14] inlet pressure: 0.45 atm H_2, split ratio 1:50, oven temperature: 70 °C (L-Phase: t_0 = 0.553 min, k'_S = 17.70, k'_R = 16.50, α = 1.072; D-Phase: t_0 = 0.553 min, k'_S = 17.60, k'_R = 18.76, α = 1.065).

We are indebted to Fonds der Chemischen Industrie for financial support.

(1) Meyers, A.I.; Lefker, B.A. *Tetrahedron* **1987**, *43*, 5663.
(2) Meyers, A.I.; Lefker, B.A.; Sowin, T.J.; Westrum, L.J. *J. Org. Chem.* **1989**, *54*, 4243.
(3) Meyers, A.I.; Brown, J.D. *Tetrahedron Lett.* **1987**, *28*, 5283.
(4) Meyers, A.I.; Dickman, D.A.; Bailey, T.R. *J. Am. Chem. Soc.* **1985**, *107*, 7974.
(5) Evans, D.A. *Aldrichim. Acta* **1982**, *15*, 23.
(6) Evans, D.A.; Morissey, M.M.; Dorow, R.L.J. *J. Am. Chem. Soc.* **1985**, *107*, 4346.
(7) Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261.
(8) Koppenhoefer, B.; Schurig, V. *Org. Synth.* **1988**, *66*, 151.
(9) Koppenhoefer, B.; Schurig, V. *Org. Synth.* **1988**, *66*, 160.
(10) Reetz, M.T.; Drewes, M.W.; Schmitz, A. *Angew. Chem.* **1987**, *99*, 1186; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141.
(11) Koppenhoefer, B.; Weber, R.; Schurig, V. *Synthesis* **1982**, 316
(12) Koppenhoefer, B.; Allmendinger, H.; Nicholson, G. *Angew Chem.* **1985**, *97*, 46; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 48.
(13) Bayer, E. *Z. Naturforsch.* **1983**, *38b*, 1281.
(14) Bayer, E.; Allmendinger, H.; Enderle, G.; Koppenhoefer, B *Fresenius' Z. Anal. Chem.* **1985**, *321*, 321.