Synthesis of (*R*)-*tert*-Leucinol by Classical Resolution of the Racemic Mixture**

Karlheinz Drauz,* Wilfried Jahn and Michael Schwarm

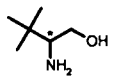
Dedicated to Dr. Wilhelm Schuler on the occasion of his 80th birthday

Abstract: Optically active *tert*-leucinol is an important building block in asymmetric synthesis. However, the (*R*) enantiomer particularly has so far remained difficult to obtain, mainly because of the laborious synthesis of the precursor amino acid, (*R*)-*tert*-leucine. Here we present a new, classical resolution of racemic *tert*-leucinol, which allows straightforward preparation of each, but especially the (*R*) enantiomer, in good yields and high optical purities. The feasibility of the synthesis of useful derivatives is demonstrated by transformation into the corresponding (*R*)-4-*tert*-butyl-2-oxazolidinone.

Keywords
amino alcohols · asymmetric syntheses · chiral auxiliaries · enantiomeric resolution

Introduction

Optically active compounds can be prepared by transformation of precursors from the chiral pool, by fermentation, by the use of suitable enzymes or by asymmetric chemical synthesis. This last area of research has grown considerably over the last two decades and gained more and more importance.[2] Particularly high diastereo- or enantioselectivities have often been achieved by the use of derivatives of optically active *tert*-leucinol (**1**) owing to the sterically demanding *tert*-butyl group, which exerts a pronounced directing influence on reactions at prochiral molecules or functional groups. Oxazolidinone **2**,[3] naphthyloxazoline **3**,[4] ligands for chiral catalysts, such as (phosphinophenyl)oxazoline **4**[5] and similar compounds[6], and various bisoxazolines[7] are examples of such derivatives.



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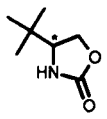

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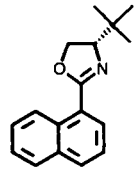

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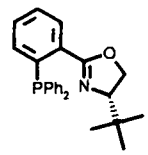

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So far, optically active **1** has been prepared in a multi-step asymmetric synthesis by diastereoselective hydrogenation of a chiral oxazinone derived from α-phenylglycine[8] or, in most cases, by reduction of the corresponding optically active *tert*-leucine (Tle) with one of the established hydride reagents suitable for the reduction of amino acids.[9] However, optically active Tle cannot be synthesized by well-known standard procedures because of its quarternary carbon atom adjacent to the chiral centre. Thus *N*-acetyl- and *N*-chloroacetyl-(*RS*)-Tle are not accepted as substrates by aminoacylase I, although many other acetylated amino acids are converted by this enzyme.[10] Less stereoselective and efficient methods for preparing optically active Tle using amidases, lipases or transaminases are known, but, so far, it has only been possible to produce (*S*)-Tle in high yields and enantiomerically pure form by a cofactor-dependent reductive amination.[11] A few procedures for the chemical resolution of racemic Tle or derivatives thereof[12] and asymmetric syntheses for optically active Tle[13] have also been published. However, there is still no economically acceptable method for the preparation of (*R*)-Tle and, consequently, (*R*)-**1** has remained difficult to obtain up to now.

Results and Discussion

In this paper, we describe a new procedure by which both enantiomers of **1** may be prepared readily and with high optical purity without the use of optically active Tle as starting material. For this purpose, the sodium salt **5** of trimethylpyruvic acid was treated with hydroxylamine hydrochloride to give oxime **6** in 81% yield.[14] This was reduced to (*RS*)-**1** in 71% yield with sodium borohydride/sulfuric acid, which is already known for the reduction of amino acids.[9b]

In the next step, 14 optically active acids were tested for the separation of the enantiomers by fractional crystallization of diastereomeric salts (Table 1). It is interesting that *N*-acylated derivatives of (*S*)-Tle gave crystalline salts particularly enriched with respect to one enantiomer of **1**. *N*-(2-Naphthoyl)-(*S*)-Tle ((*S*)-**7**) gave the best result with regard to yield as well as optical purity. Surprisingly, unlike *N*-acetyl-, *N*-benzoyl- and *N*-(1-naphthoyl)-(*S*)-Tle, (*S*)-**7** formed a salt **8**, containing predomi-

[*] Prof. Dr. K. Drauz, W. Jahn, Dr. M. Schwarm
Degussa AG, ZN Wolfgang, Abt. IC-FE-W
Postfach 1345, D-63403 Hanau (Germany)
Telefax: Int. code + (6181)594312

[**] Amino Acid Transformations. Part 12. Part 11: ref. [1].

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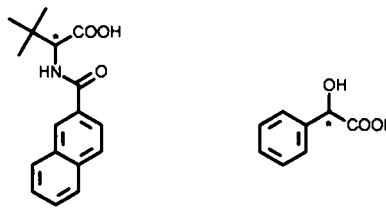
Table 1. Reaction of (*RS*)-**1** with optically active acids [a,b,c,d].

Acid	Solvent	Yield	(*R*)-**1**:(*S*)-**1**
(*R*)-mandelic acid	*i*PrOH	60%	83.2:16.8
(*1R*)-camphor-(10)-sulfonic acid	toluene/MTBE	67%	51.9:48.1
N-formyl-(*S*)-Tle	*i*PrOH	45%	93.9:6.1
after recrystallization	*i*PrOH	33%	98.6:1.4
N-acetyl-(*S*)-Tle	EtOH	54%	36.5:63.5
N-benzoyl-(*S*)-Tle	*i*PrOH	54%	18.6:81.4
N-(1-naphthoyl)-(*S*)-Tle [e]	*i*PrOH	33%	37.1:62.9
N-(2-naphthoyl)-(*S*)-Tle [f]	*i*PrOH	72%	93.7:6.3
second crop		7%	88.5:11.5
after recrystallization	*i*PrOH	70%	98.7:1.3
N-(2,6-dichlorobenzoyl)-(*S*)-Tle	*i*PrOH	55%	69.9:30.1

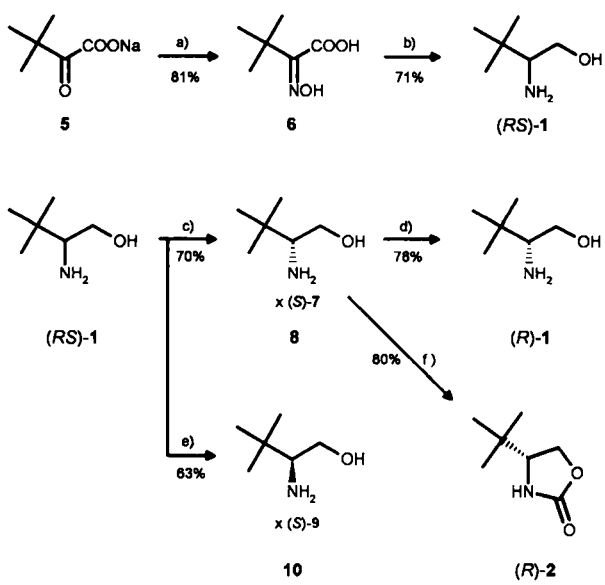
[a] Half an equivalent of the optically active acid was employed per equivalent of (*RS*)-**1** in each experiment. [b] Only the best result has been quoted for each acid. [c] No crystalline salts were obtained with (*S*)-Asp, (*S*)-Glu, (*S*)-pyroglutamic acid, *N*-acetyl-(*S*)-Pro, *N*-acetyl-(2*S*,4*R*)-Hyp and *N*-pivaloyl-(*S*)-Tle. [d] The yields always refer to the amount of one enantiomer in (*RS*)-**1**. [e] *N*-(1-Naphthoyl)-(*S*)-Tle contained roughly 35 mol% naphthaline-1-carboxylic acid as by-product, which could not be separated. [f] The crude product was obtained in two crops, which were pooled and recrystallized.

nantly the (*R*) enantiomer of **1**, which crystallized nicely. After recrystallization, **8** was isolated in 70% yield with an *R*:*S* ratio for **1** of 98.7:1.3. This will be sufficient for most purposes, but further purification can be accomplished by repeated recrystallization, if desired. The remaining *tert*-leucinol (**1**) was isolated from the mother liquor of the crystallization of **8**; it was predominantly (*S*)-configurated. Reaction of (*S*)-mandelic acid ((*S*)-**9**) with **1** gave salt **10** in 63% yield after double recrystallization with an *R*:*S* ratio for **1** of 1.0:99.0 (Scheme 1).



7 **9**

After this procedure, both enantiomers of **1** are now easily available in good yield and high optical purity. If desired, the free amino alcohol can be isolated from the corresponding salt. Thus, reaction of **8** with hydrochloric acid liberated the optically active acid (*S*)-**7**, which was recovered in 99% yield by crystallization. Subsequent experiment showed that as much as 97% of the starting amount of (*S*)-**7** could be recycled from the mother liquor of **8** and from the pure salt **8**. Owing to this almost quantitative rate of recovery, (*S*)-**7** appears to be especially suitable for a classical resolution of a racemic mixture, although it is a rather uncommon resolving agent. After workup of the filtrate, (*R*)-**1** was obtained in 78% yield after distillation. The ratio of enantiomers was determined as 98.7:1.3 *R*:*S*, which is exactly the same as for the starting material, salt **8**.



Scheme 1. a) $H_2NOH \times HCl$, H_2O; b) $NaBH_4/H_2SO_4$, DME; c) *i*PrOH, (*S*)-**7**; d) 1. HCl, H_2O, filtration, 2. aq. NaOH, toluene, 50 °C, separation of layers, 3. evaporation, distillation 89–91 °C/13 mbar; e) workup of mother liquor, *i*PrOH, (*S*)-**9**; f) 1. HCl, H_2O, filtration, 2. aq. NaOH, toluene, 3. ethyl chloroformate, aqueous NaOH, pH 7–8.5, 20–25 °C, 4. 60–65 °C, separation of layers, 5. NaOH, 70–110 °C.

In order to demonstrate the suitability of these salts of optically active *tert*-leucinol for the preparation of derivatives of **1** for asymmetric synthesis, we decided to prepare the oxazolidinone (*R*)-**2**. This was obtained from **8** in 80% yield by alkaline extraction of (*R*)-**1**, acylation with ethyl chloroformate and cyclization with sodium hydroxide in toluene. The optical rotation of (*R*)-**2** ($[\alpha]_D^{20} = +18.8°$, $c = 1$, EtOH) was identical in its absolute value to that of a reference sample of (*S*)-**2**, which had been prepared from (*S*)-Tle. The ratio of enantiomers of (*R*)-**2** was found on analysis to be greater than *R*:*S* = 99.0:1.0. Thus the crystallization of (*R*)-**2** had actually improved the optical purity with respect to the starting material **8** of this reaction sequence. Consequently, other derivatives of **1**, for example **3** or **4**, should also be available from salts **8** or **10** in high enantiomeric purity.

Summary

It was found that, beside the modern methods of asymmetric chemical synthesis and biotransformations, the classical resolution of racemic mixtures via diastereomeric salt pairs still has an important role to play in the preparation of optically active compounds and, as in the case investigated, is the method of choice for the solution of certain problems.

Experimental Section

General: ^1H NMR spectra were recorded at 500 MHz on a Bruker AMX 500, IR spectra on a Perkin–Elmer 1430 infrared spectrophotometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. The elemental analyses were carried out with a Perkin–Elmer 240, Perkin–Elmer 240C or Carlo Erba 1108 elemental analyzer. Melting points were determined with a Reichert–Jung Thermovar apparatus and are not corrected; boiling points were noted during the distillations of the respective compounds. The GC analyses were performed on a DANI 86.10 gas chromatograph with Lipodex E as the stationary phase for **1** and on a Carlo Erba Vega 6000 with L-Chirasil-Val as the stationary phase for **2**, with hydrogen as carrier gas in both cases. Trimethylpyruvic acid was bought from Miles (USA) as aqueous solution with ≈65% content. (*S*)-Tle was produced in-house in accordance with ref. [11]. All other chemicals were obtained from commercial suppliers in technical or reagent grade quality and used without further purification.

Oxime 6: Sodium trimethylpyruvate (**5**) (163.0 g, 1.0 mol, 93.5% purity, prepared from crude trimethylpyruvic acid by addition of an equimolar amount of 50% aqueous NaOH, evaporation of water at 60 °C, addition of acetone, cooling to 5 °C and filtration of the crystalline sodium salt) and hydroxylamine hydrochloride (69.5 g, 1.0 mol) were dissolved in water (450 mL) at 40 °C. Colourless crystals formed on cooling. After being stirred for 1.5 h in an ice-water bath, the crystals were filtered off, washed with ice-cold water (150 mL) and dried in vacuo at 60 °C, then in vacuo over phosphorus pentoxide; yield 117.8 g (81%). M.p. 120–122 °C (decomp.; ref. [14] 121 °C); ^1H NMR (500 MHz, [D$_6$]DMSO, 30 °C, TMS): $\delta = 1.1$ (s, 9H, $C(CH_3)_3$), 11.8 (brs, 1H, OH), 13.1 (brs, 1H, COOH); $C_6H_{11}NO_3$ (145.2): calcd C 49.64, H 7.64, N 9.65; found C 49.75, H 7.89, N 9.71.
The analogous reaction using the original aqueous solution of trimethylpyruvic acid directly gave significantly lower isolated yields of 53–67%.

(*RS*)-*tert*-Leucinol ((*RS*)-1): The oxime **6** (218.0 g, 1.5 mol) was added portionwise to a stirred suspension of sodium borohydride (171.0 g, 4.5 mol) in 1,2-dimethoxyethane (DME) (1500 mL) at 10–30 °C with vigorous evolution of hydrogen. Then a solution of concentrated sulfuric acid (120 mL, 2.25 mol) in DME (480 mL) was added dropwise over a period of 2.5 h with external cooling. During

this procedure, the temperature rose from 10 °C to 40 °C and, after cooling was stopped, to 55 °C. The mixture was heated to 70 °C and then kept at room temperature for 2 d. Methanol (200 mL) and, subsequently, water (100 mL) were added dropwise, which resulted in vigorous evolution of gas and a final temperature of 60 °C. After evaporation to a thin suspension, addition of ice-water (500 mL) and removal of the organic solvents in vacuo, water (600 mL) and conc. hydrochloric acid (200 mL) were added at 25 °C, which resulted in gas evolution and a rise in temperature to 35 °C. The mixture was stirred for 15 min and then toluene (1500 mL) and 50% aqueous sodium hydroxide (300 mL) were added. The system was heated to 70 °C, the water layer separated and extracted twice with toluene (1 L) at 70 °C. The organic extracts were pooled, treated with Celite, filtered and evaporated to afford 158 g of a yellowish oil, which solidified on cooling. Distillation gave a colourless liquid, which crystallized at room temperature, yield 125.1 g (71%). M.p. 34–35 °C; B.p. 86–95 °C/13 mbar; ^{1}H NMR (500 MHz, [D$_6$]DMSO, 30 °C, TMS): δ = 0.8 (s, 9H, C(CH$_3$)$_3$), 1.3 (brs, 2H, NH$_2$), 2.4 (dd, 1H, C*H*NH$_2$), 3.0 (dd, 1H, C*H*$_2$OH), 3.5 (dd, 1H, C*H*$_2$OH), 4.3 (brs, 1H, OH); $C_6H_{15}NO$ (117.2): calcd C 61.49, H 12.90, N 11.95; found C 61.10, H 13.15, N 11.88.

***N*-(2-Naphthoyl)-(S)-*tert*-leucine ((*S*)-7)**: Over 5 min, a solution of 2-naphthoylchloride (152.4 g, 0.80 mol) in THF (200 mL) was added to a stirred solution of (*S*)-Tle (110.0 g, 0.83 mol) in water (1600 mL). The pH was kept between 7.1 and 7.6 by simultaneous addition of 5 M aqueous sodium hydroxide (in total 330 mL). The reaction mixture was cooled from an initial 28 °C to 22 °C and stirred for 90 min, until the pH remained constant. After evaporation of THF, the suspension was cooled to 10 °C, stirred for 1 h and filtered to remove a solid by-product. The pH of the filtrate was then adjusted to 2.0 by addition of aq. hydrochloric acid (conc. HCl:H$_2$O = 1:1). A thick crystal suspension formed, which was cooled to 10 °C by addition of ice, stirred for 30 min and filtered. The colourless crystals were washed with water and recrystallized twice from toluene (2500 mL and 3000 mL), until the product appeared pure by TLC (diethyl ether:methanol = 10:2). Drying in vacuo at 50 °C afforded 169.4 g (74%) of product. Karl Fischer titration showed a water content of 3.12%. Prolonged drying of (*S*)-7, recovered from salt **8** (see below), in vacuo at 80 °C gave an analytically pure sample. M.p. 161–162 °C; $[\alpha]_D^{20}$ = +39.7 (c = 1.0 in methanol); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 30 °C, TMS): δ = 1.1 (s, 9H, C(CH$_3$)$_3$), 4.5 (d, 1H, C*H*COOH), 7.6 (m, 2H, aromatic H), 8.0 (m, 4H, aromatic H), 8.3 (d, 1H, NH), 8.5 (s, 1H, aromatic H), 12.7 (brs, 1H, COOH); $C_{17}H_{19}NO_3$ (285.3): calcd C 71.56, H 6.71, N 4.91; found C 71.32, H 6.79, N 5.11.

Salt 8: (*RS*)-*tert*-Leucinol ((*RS*)-**1**) (175.8 g, 1.5 mol) and (*S*)-7 (214.0 g, 0.75 mol) were dissolved in isopropanol (4.5 L) at 53 °C. While slowly stirred, the mixture was cooled to 39 °C over 6 h, then to 24 °C overnight and to 15 °C in an ice-water bath. The colourless crystals formed were filtered off, washed with 4 × 150 mL of isopropanol and dried; yield 218.3 g (72%). Concentration of the filtrate to 2 L afforded an additional 21.9 g (7%) of product. The total quantity was recrystallized from 4 L of isopropanol, filtered off at 15 °C, washed portionwise with isopropanol (300 mL) and dried; yield 210.6 g (70%). M.p. 184–189 °C; $[\alpha]_D^{20}$ = +41.6 (c = 1.0 in methanol); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 30 °C, TMS): δ = 0.9 (s, 9H, C(CH$_3$)$_3$), 1.0 (s, 9H, C(CH$_3$)$_3$), 2.8 (dd, 1H, C*H*(NH$_3^+$)), 3.6 (ABX system, 2H, CH$_2$), 4.2 (d, 1H, CHCOO$^-$), 7.3 (brs, 4H, NH$_3^+$ + OH), 7.6 (m, 2H, aromatic H), 7.7 (d, 1H, NHCO), 7.9–8.1 (m, 4H, aromatic H), 8.4 (s, 1H, aromatic H); IR (KBr): $\tilde{\nu}$ = 3190 cm^{-1} (NH), 3140, 2960, 1610, 1525, 1375, 1060, 760; $C_{23}H_{34}N_2O_4$ (402.5): calcd C 68.63, H 8.49, N 6.96; found C 68.48, H 8.75, N 7.00; *R*:*S* ratio for **1** (GC, Lipodex E): 98.7:1.3.

Salt 10: The mother liquor of the fractional crystallization was evaporated, the resulting oil dissolved in water (500 mL) and the mixture concentrated to 500 g. At 55 °C, 6 N HCl was used to adjust the pH to 5.5, the solution was seeded with a few crystals of (*S*)-7 and 6 N HCl was added until a pH of 1.8 was reached. The suspension was cooled to 18 °C while being stirred, the crystals filtered off at pH 1.35, washed portionwise with water (250 mL) and dried in vacuo at 75 °C; yield 34.0 g of (*S*)-7. The filtrate was adjusted to pH 7.0 with aqueous NaOH and concentrated to 220 g. 50% aqueous NaOH (45 mL) was added to adjust the pH to 13. After addition of toluene (300 mL), the mixture was warmed to 50–55 °C, the water layer separated and at 55 °C extracted again with toluene (300 mL). The organic extracts were pooled and evaporated. The resulting yellowish oil (98.2 g, 0.82 mol of **1**) was dissolved in isopropanol (3 L), the solution filtered and warmed to 60 °C. (*S*)-**9** (114.0 g, 0.75 mol) was added and dissolved. After production of the first crystals by scratching, the suspension was slowly cooled with stirring, kept at 15 °C for 4 h and filtered. The resulting colourless crystals were recrystallized from isopropanol (1560 mL and a second time from 1500 mL), filtered off, washed and dried; yield 127.3 g (63% with respect to the starting amount of (*RS*)-**1**). M.p. 152–157 °C; $[\alpha]_D^{20}$ = +72.6 (c = 1.0 in methanol); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 30 °C, TMS): δ = 0.9 (s, 9H, C(CH$_3$)$_3$), 2.7 (dd, 1H, CH(NH$_3^+$)), 3.5 (ABX system, 2H, CH$_2$), 4.6 (s, 1H, CHCOO$^-$), 6.8 (brs, 5H, NH$_3^+$ + OH + OH), 7.1 (m, 1H, aromatic H), 7.2 (m, 2H, aromatic H), 7.4 (m, 2H, aromatic H); IR (KBr): $\tilde{\nu}$ = 3430 cm^{-1} (NH), 2970, 1630, 1580, 1515, 1360, 1050, 700; $C_{14}H_{23}NO_4$ (269.3): calcd C 62.43, H 8.61, N 5.20; found C 62.63, H 8.87, N 5.25; *R*:*S* ratio for **1** (GC, Lipodex E): 1.0:99.0.

(*R*)-*tert*-Leucinol ((*R*)-1): Concentrated hydrochloric acid (50 mL) was added dropwise to a stirred suspension of **8** (201.3 g, 0.5 mol) in water (1300 mL). After being warmed to 50 °C, the mixture was stirred until the pH was constant at 1.65 for 15 min. On cooling to 5 °C, the pH dropped to 1.05. After 30 min, the colourless crystals were filtered off, washed with ice-cold water (1 L) and dried in vacuo at 80 °C to afford 141.5 g (99%) of recovered (*S*)-7, which was analytically pure (see above). The filtrate was adjusted to pH 7.5 with 10 M aqueous sodium hydroxide, concentrated to 146 g and exactly divided into two parts. One half was used to prepare (*R*)-**2** (see below), the other half for the isolation of (*R*)-**1**, as follows. One half of the above filtrate (73 g, containing 0.25 mol of (*R*)-**1**) was concentrated to 60 g and, after addition of toluene (100 mL), adjusted to pH 13.0 with 10 M aqueous sodium hydroxide. After being heated to 50 °C, the water layer was separated and extracted again with 75 mL toluene at 50 °C. The pooled organic extracts were treated with sodium sulfate, filtered and evaporated to give 24.2 g of an almost colourless oil. Distillation afforded a colourless, hygroscopic oil, which crystallized at room temperature, yield 22.9 g (78%). B.p. 89–91 °C/13 mbar; $[\alpha]_D^{20}$ = −38.1 (c = 2.0 in ethanol; ref. [9a] + 37 (c = 1 in ethanol for (*S*)-**1**); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 30 °C, TMS): δ = 0.8 (s, 9H, C(CH$_3$)$_3$), 1.3 (brs, 2H, NH$_2$), 2.3 (dd, 1H, C*H*NH$_2$), 3.0 (dd, 1H, C*H*$_2$OH), 3.5 (dd, 1H, C*H*$_2$OH), 4.3 (brs, 1H, OH); $C_6H_{15}NO$ (117.2): calcd C 61.49, H 12.90, N 11.95; found C 61.48, H 13.64, N 12.08; *R*:*S* ratio for **1** (GC, Lipodex E): 98.7:1.3.

Oxazolidinone (*R*)-2: Water (27 mL) and toluene (200 mL) were added to the second 73 g of the above filtrate (containing 0.25 mol of (*R*)-**1**). Ethyl chloroformate (25 mL, 0.26 mol) was added dropwise at 20–25 °C. The pH was kept between 7.0 and 8.5 by addition of 10 M aqueous sodium hydroxide. After being heated to 60–65 °C at pH 8.0, the aqueous layer was separated. The toluene layer was distilled under vacuum to remove water. Finely granulated sodium hydroxide (0.4 g) was added at 70 °C. The mixture was then slowly heated to 110° to give 40 mL distillate containing the ethanol formed during the cyclization. After this had been cooled to 65 °C, a solution of glacial acetic acid (0.6 mL in 10 mL water) was added, the system was stirred for a few minutes, the aqueous layer separated, the toluene layer washed again with water (15 mL) and finally separated at 65 °C. Again the toluene solution was distilled to remove water, then concentrated to 120 mL, filtered hot and cooled while being stirred. Colourless crystals formed, which were filtered off after 30 min at 5 °C, washed with cold toluene and dried in vacuo at 50 °C; yield 28.6 g (80%). M.p. 119–120 °C; $[\alpha]_D^{20}$ = +18.8 (c = 1.0 in ethanol); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 30 °C, TMS): δ = 0.8 (s, 9H, C(CH$_3$)$_3$), 3.5 (dd, 1H, C*H*NH)), 4.1 (ABX system, 2H, CH$_2$), 7.8 (brs, 1H, NH); $C_7H_{13}NO_2$ (143.2): calcd C 58.71, H 9.15, N 9.78; found C 59.04, H 9.56, N 10.05; *R*:*S* ratio for **1** (GC, L-Chirasil-Val): >99.0: <1.0.

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