A Convenient Dehydration Procedure for the Synthesis of Enantiomerically Pure Cyanohydrins

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Dedicated to Professor Günther Wilke on the occasion of his 75th birthday

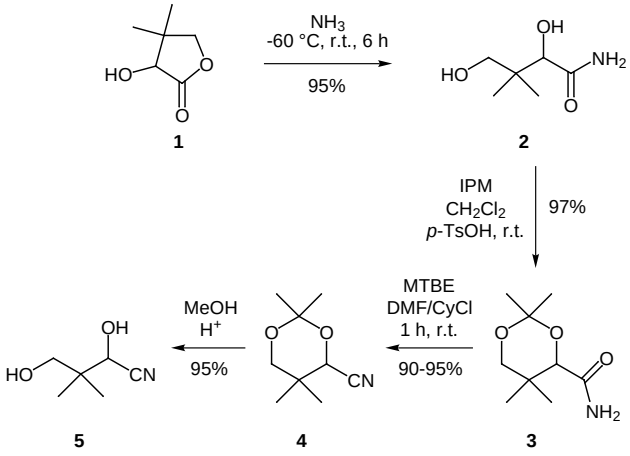
Abstract: Starting from protected α-hydroxy amides, cyanohydrins (α-hydroxy nitriles) are obtained through dehydration by cyanuric chloride/DMF in excellent yield. The advantages of the procedure are the extremely mild reaction conditions that prevent racemization.

Key words: dehydration, cyanuric chloride/DMF adduct, cyanohydrins

Cyanohydrins (α-hydroxy nitriles) are commonly synthesized by the addition of hydrocyanic acid to an aldehyde, as described in several standard textbooks of organic chemistry.[1] Naturally, this method yields racemic mixtures of α-hydroxy nitriles. Starting from an aldehyde, enantiomerically pure α-hydroxynitriles can be obtained using an enzyme (oxynitrilase)[2,3] or by the chiral Lewis acid-catalyzed addition of hydrocyanic acid (or cyanotrimethylsilane) (M = Ti,[4] B,[5] Sn,[6] Re[7]). Cyanohydrins are of particular interest as intermediates since they can readily be converted into a variety of valuable starting materials for synthesis (β-amino alcohols, α-hydroxy ketones, α-hydroxy carboxylic acids).

An alternative method to prepare α-hydroxy nitriles is the dehydration of α-hydroxy amides. We became interested in alternative dehydration methods since all the established procedures give rise to insurmountable problems when conducted on an industrial scale, e.g. expensive reagents, large excess of the cyano component, painstaking workup, toxic solvents, waste problems, etc. The mixture cyanuric chloride/DMF was introduced by Olah and coworkers for the dehydration of aliphatic and aromatic amides to the corresponding nitriles.[8] The potential of this method has so far not been exploited with the notable exception of the synthesis of heterocyclic carbonitriles.[9,10] At around the same time, Rodrigues and Maetz described the preparation of *N*-protected chiral α-amino nitriles from *N*-protected α-amino acid amides using cyanuric chloride/DMF.[11]

Based on our experience with the synthesis of heterocyclic amides we decided to extend our methodology to the dehydration of functionalized amides. We chose cyanohydrins as target molecules for two reasons: on the one hand, there exists a vast experience with enantiomerically enriched cyanohydrines concerning synthesis and analytics, and on the other hand the hydroxy amide precursors are readily available as starting materials. In our model study, the enantiopure α-hydroxy amide was obtained by aminolysis of D- and L- pantolactone **(1)**, respectively (Scheme 1). The hydroxy groups were protected with isopropenyl methyl ether (IPM).[12] Standard procedures for the introduction of a protecting group for the hydroxy functionalities did not yield satisfactory results. Protection with acetone/*p*-TsOH gave only a yield of 35% of the dioxane **3**, while the alternative acetone/orthoester procedure led to only a slight increase of product yield (55%).



Scheme 1

The crucial step, the dehydration of the 1,3-dioxane-4-carboxamide **3** to the nitrile **4**, could be conducted in excellent yields by means of the reaction conditions outlined in Scheme 1. Standard acid-catalyzed deprotection gives the desired cyanohydrin **5**. The key question was whether or not the DMF/cyanuric chloride dehydration would give rise to racemization. In order to determine the enantiomeric ratios it was necessary to separate samples of racemic **3**, **4**, and **5** which were obtained by conducting the reaction sequence starting from D,L-pantolactone **(1)**. The

enantiomeric purity of the intermediates **3** and **4** as well as of the cyanohydrin **5** was determined by gas chromatography on a chiral column. In all cases, complete base line separation was achieved, and the detection limit for one enantiomer under these conditions was estimated to be < 0.05% (Figure 1).

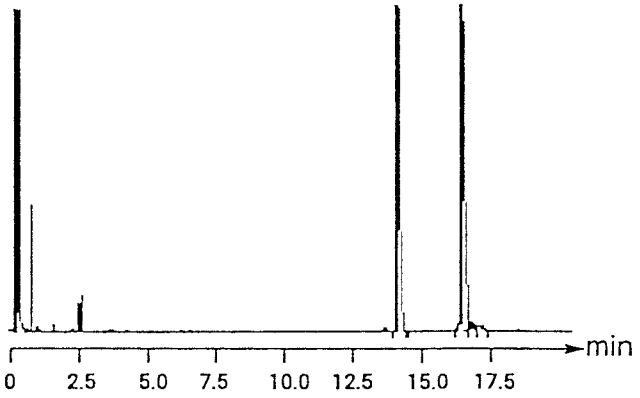


Figure 1 Gas chromatogram of (*R*,*S*)-**5** (chiral stationary phase) after derivatization to the acetate. The GC conditions are described in the experimental part.

Under the reaction conditions for the dehydration reaction of **3**, the unprotected hydroxy amide **2** is not dehydrated, but the starting material is recovered in 94% yield.

The stability of **2** with regard to racemization was tested in various solvents and at two different temperatures. In polar organic solvents such as 1,4-dioxane, ethyl acetate, and ethanol, the optical rotation of (*R*)- and (*S*)-**2** remained constant over 2 days. In water, however, the optical rotation decreased continuously (see Figure 2). As proved by GC and ^{1}H NMR, this decrease in optical rotation is accompanied by the formation of the ammonium salt **6**, which has the opposite sign of rotation,[13] i.e., while (*S*)-**2** has an $[\alpha]_D^{20}$ of +47.7, the $[\alpha]_D^{20}$ of (*S*)-**6** has a value of −10.13. It has been confirmed that under these conditions no racemization of (*R*)-**1** or (*S*)-**1** takes place.

Finally, an alternative protection scheme for the dehydration was worked out. All reactions so far had employed a protecting group covering both hydroxy functionalities. We were interested in the influence of the secondary hydroxy group on the dehydration reaction. As shown in Scheme 2, we succeeded in selectively protecting the primary hydroxy group using a standard Ph_3CCl procedure. As in the case of the dioxane protection scheme, the dehydration is accomplished in excellent yields at ambient conditions. In contrast to compound **4**, however, the monoprotected cyanohydrin **8** decomposes in the course of a few days, thus rendering the isolation of the pure compound very difficult.

Surprisingly, we found that the melting points of (*R*,*S*)-**2** and (*R*,*S*)-**3** were considerably higher than those of their enantionmerically pure counterparts (*R*)-**2**, (*S*)-**2** and (*R*)-**3**, (*S*)-**3**, respectively. This intriguing behavior prompted us to have a look at the solid state structures of the chiral intermediates. We succeeded in growing crystals suitable for single crystal X-ray diffraction in the case of (*R*,*S*)-**2**, (*R*)-**3**, and (*R*,*S*)-**3**. The conformation of (*R*)-**2** and (*R*)-**3** in the solid state structures of (*R*,*S*)-**2** and (*R*)-**3** are shown in Figures 3 and 4, respectively. All bond lengths and angles are in the range predicted by crystal chemistry. The amide moiety in (*R*)-**2** is perfectly planar, with the sum of angles around the sp^2 C-atom exactly 360°. The six-membered ring in (*R*)-**3** shows an almost ideal chair-like conformation (Cremer−Pople parameters[14] Q = 0.554, θ = 5.5°,

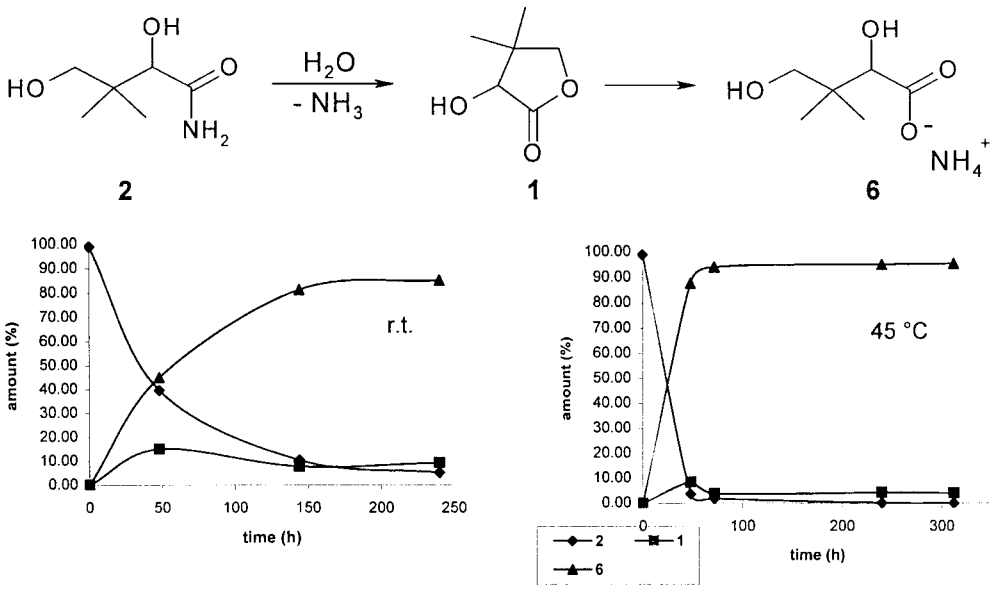
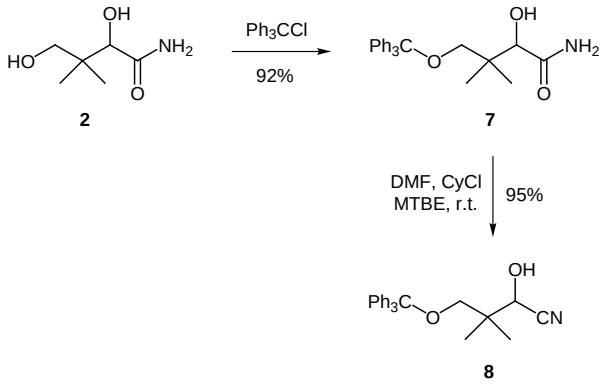


Figure 2 Conversion of (*S*)-**2** to (*S*)-**6** in water at r.t. and 45°C.



Scheme 2

φ = 226.5°) with the carboxamide substituent in the equatorial position. The sum of angles around the sp^2 C-atom is also 360°. The conformation of (*R*)-**3** is very similar in both the solid-state structures of (*R*)-**3** and (*R*,*S*)-**3**; the mean deviation in the six-membered ring is only 0.01 Å, the maximum deviation between the two amide O-atoms is 0.37 Å.

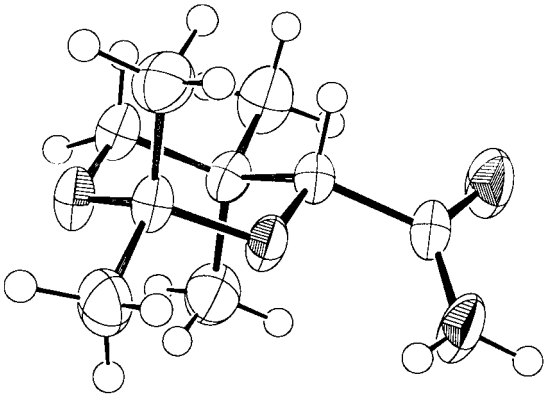


Figure 3 Ortep plot of the structure of (*R*)-**2** in the solid phase of (*R*,*S*)-**2**.

The difference in the melting points of (*R*)-**3** and (*R*,*S*)-**3** is due to the different intermolecular interactions in their solid-state structures. In the case of (*R*)-**3**, the only significant interaction between the 1,3-dioxane-4-carboxamides is a rather long hydrogen bond between NH and a dioxane O-atom (2.16 Å). In the solid state structure of the racemate, however, the (*R*)-molecule forms a hydrogen-bonded dimer with its symmetry-related enantiomer (Figure 5). The stronger intermolecular interaction is probably responsible for the significantly higher melting point of the racemate. In the solid-state structure of (*R*,*S*)-**2**, a quite elaborate hydrogen-bonded supermolecular network is formed by intermolecular interactions between the two hydroxy and the carboxamide moieties (Figure 6).

The starting materials (lactones) were Roche material, the solvents and reagents acetone, cyanuric chloride, CH_2Cl_2, Et_2O, isopropenylmethyl ether, DMF, *tert*-butyl methyl ether, Et_3N, triphenylchloromethane (Fluka), ammonia (Carbagas), hexane, and *p*-TsOH (Merck) were purchased from the respective companies and used without further purification.

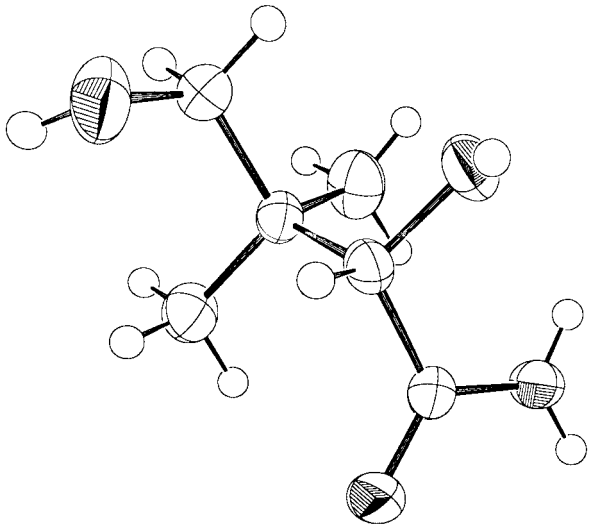


Figure 4 Ortep plot of the structure of (*R*)-**3** in the solid state.

^{1}H NMR spectra (δ, in ppm; *J*, in Hz; relative to internal TMS in $CDCl_3$ and DMSO-d_6 respectively, at 20 °C) were recorded on a Bruker AC 250-E spectrometer. The mass spectra were meassured on a SSQ 7000 mass spectrometer (Finnigan-MAT, Bremen), ionization energy 70 eV, ion source temperature 240 °C, sample introduction directly into the ion source. The mass spectra of compounds **6**, **7**, and **8** were recorded on a Perkin Elmer Sciex API 300 mass spectrometer using a pneumatic-assisted electrospray source (flow injector of 3 μL of an approximately 10 μM/L solution of the sample, flow rate 20 μL/min). The sample was dissolved in a mixture of MeCN and H_2O (containing 10 μM/L of NH_4OAc). Melting points (mp) were observed under a microscope using a Büchi/Tottoli instrument and are not corrected. Boiling points were observed by the method of Siwoloboff. Capillary gas chromatography was performed with a Hewlett-Packard gas chromatograph HP5890 Series II equipped with FI-Detector and an Autosampler 7673 A. Peak integration was done with a Perkin Elmer-Nelson Turbochrom Workstation, Version 6.0.2. The chiral column used was a 15 m fused silica column, coated with 25% heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin in polysiloxanes. Column temperature: 100 °C to 200 °C, programmed at a rate of 2°C/min. Injector port temperature: 210 °C and detection temperature: 250 °C. The carrier gas used was H_2 at 80 kPa. All samples (3 mg) were reacted with Ac_2O in pyridine to the corresponding acetates and injected at a split ratio of approximately 1:40. As depicted in Figure 1, baseline separation was obtained and the detection limit under these conditions for one enantiomer is <0.05%.

The purity of the compounds **6** and **7** was confirmed by SFC on an achiral column (10 m, SB-biphenyl-30, diameter 50 μm, pressure 80–400 atm with a pressure program of 8 atm/min, detector 350 °C, oven temperature 100 °C).

The enantiomeric separation of **6** and **7** was carried out with a micro HPLC on a Phoenix 20CU pump, equipped with a chiral 15 cm column (chiral-OD H, 15 μ), mobile phase 95% hexane/5% *i*-PrOH, flow 4 μL/min, pressure 1.5 mpa, 30 °C, detector UV 215 nm.

The X-ray crystallographic data of compounds (*R*,*S*)-**2**, (*R*,*S*)-**3**, and (*R*)-**3** were deposited at the Cambridge Crystallographic Data Centre (CCDC).

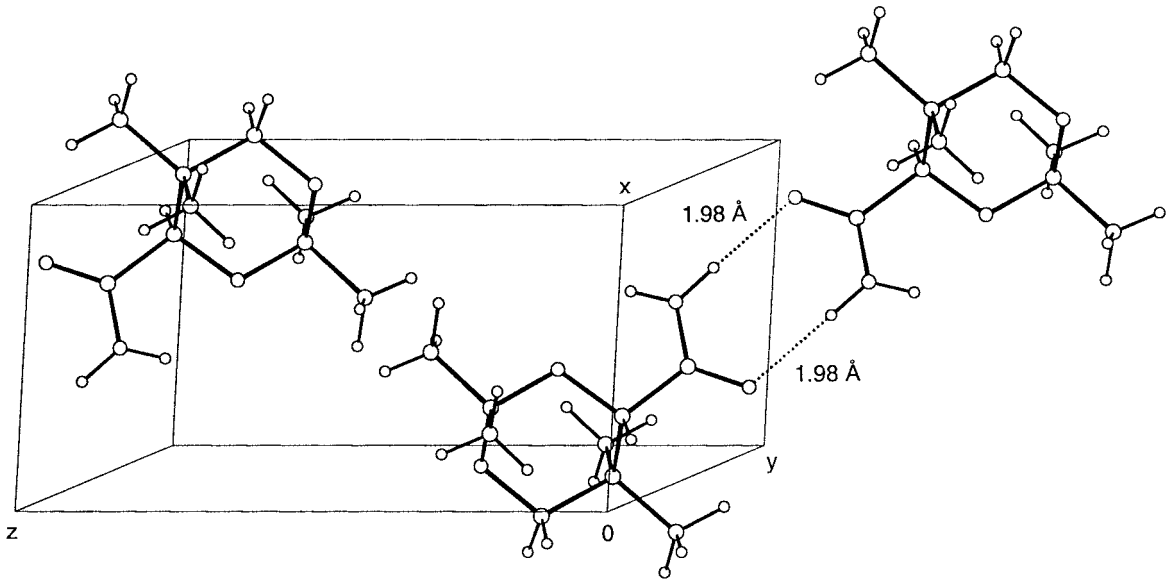


Figure 5 Crystal packing of (*R*,*S*)-**3**, showing the presence of hydrogen-bonded dimers.

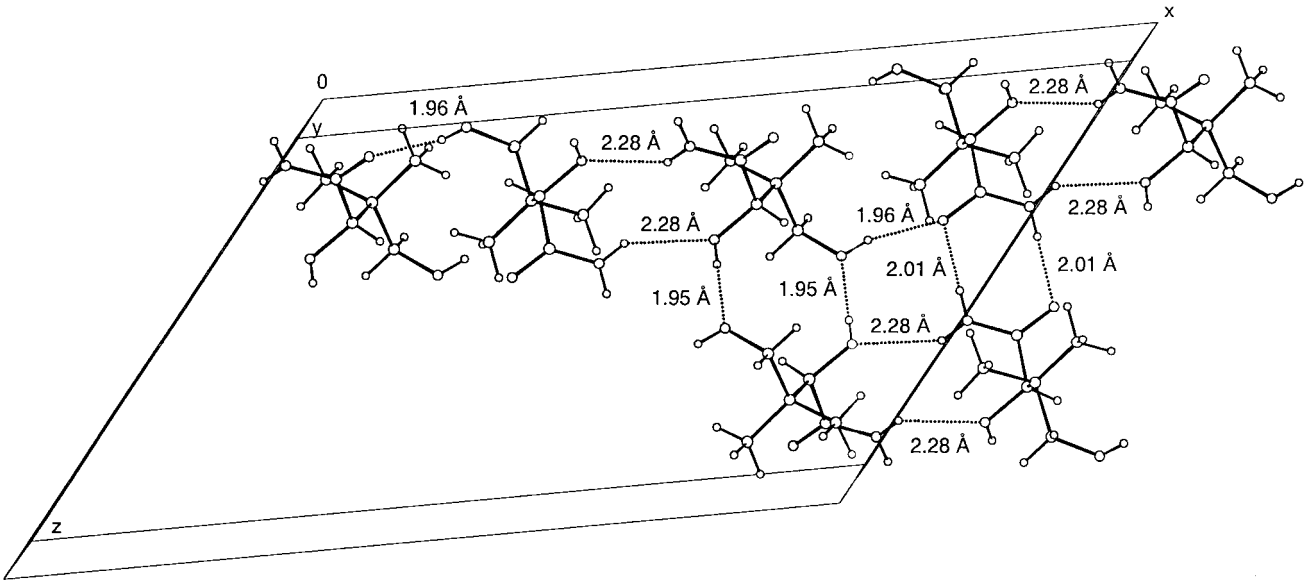


Figure 6 Crystal packing of (*R*,*S*)-**2**, showing the presence of a hydrogen bond network.

(*R*,*S*)-2,4-Dihydroxy-3,3-dimethylbutyramide [(*R*,*S*)-2]; Typical Procedure

D,L-Pantolactone [(*R*,*S*)-**1**; 36.02 g, 277 mmol] was added to liquid ammonia (350 mL) at −60 °C. After 1 h the suspension turned into a clear colorless solution and was then warmed up to r.t. The excess ammonia was evaporated and the resulting colorless solid dried in vacuo; yield: 40.8 g (~100%); mp 128−129.8 °C.

IR (nujol): ν = 3415, 3309, 2955, 2872, 2854, 1677, 1481, 1458, 1297, 1277, 1078, 1055, 987, 911, 767, 704 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 0.81 (s, 3 H, CH_3), 0.82 (s, 3 H, CH_3), 3.18 (dd, 1 H, J_{HH} = 4.5 Hz, OCH_2), 3.31 (dd, 1 H, J_{HH} = 4.7 Hz, OCH_2), 3.66 (d, 1 H, J_{HH} = 5.7 Hz, C*H*OH), 4.49 (dd, 1 H, *J* = 4.7 Hz, *J* = 4.5 Hz, OH), 5.23 (d, 1 H, *J* = 5.7 Hz, OH), 7.12 (s, 2 H, $CONH_2$).

MS (70 eV): *m*/*z* (%) = 148 (4, M − H^+) 103 (40), 99 (32), 75 (100).

Anal. ($C_6H_{13}NO_3$): calcd: C, 48.97; H, 8.90; N, 9.52. Found C, 48.95; H, 8.92; N, 9.50.

(*R*)-2,4-Dihydroxy-3,3-dimethylbutyramide [(*R*)-2]

D-Pantolactone [(*R*)-**1**; 48.00g, 370 mmol] was added to liquid ammonia (350 mL) at −60 °C and the reaction was carried out as described above; yield: 51.44 g (91%); colorless solid; mp 94.4−95.2 °C; $[\alpha]_D^{20}$ 49.07.

Anal. ($C_6H_{13}NO_3$): calcd: C, 48.97; H, 8.90; N, 9.52. Found C, 48.84; H, 8.79; N, 9.57.

(S)-2,4-Dihydroxy-3,3-dimethylbutyramide [(*S*)-2]

L-pantolactone [(*S*)-**1**; 35.96 g, 276 mmol] was added to liquid ammonia (350 mL) at −60 °C and the reaction was carried out as described above; yield: 37.15 g (91%); colorless solid; mp 93.8−95.0 °C; $[\alpha]_D^{20}$ −47.7.

Anal. ($C_6H_{13}NO_3$): calcd: C, 48.97; H, 8.90; N, 9.52. Found C, 48.89; H, 9.00; N, 9.35.

(*R*,*S*)-2,2,5,5-Tetramethyl-1,3-dioxane-4-carboxamide [(*R*,*S*)-3]
To a suspension of (*R*,*S*)-**2** (10.00 g, 67.9 mmol) in a mixture of CH_2Cl_2 (150 mL) and acetone (150 mL) at 10 °C were added isopropenyl methyl ether (13.45 mL, 135.8 mmol) and a solution of *p*-TsOH (0.38 g) in acetone (30 mL). The mixture was stirred at r.t. for 1 h and, after filtration, neutralized with Et_3N (~ 1 mL). The clear yellow solution was dried (Na_2SO_4), filtered, and the solvent removed on a rotary evaporator; yield: 12.4 g (98%); colorless solid; mp 122.8−123.4 °C.

IR (nujol): ν = 3483, 3362, 3300, 3246, 3148, 2987, 2961, 2855, 1687, 1649, 1584, 1458, 1382, 1359, 1325, 1292, 1224, 1122, 1041, 972, 867, 771 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 0.92 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 3.18 (d, 1 H, J_{HH} = 9.1 Hz, CH_2), 3.63 (d, 1 H, J_{HH} = 9.1 Hz, CH_2), 3.97 (s, 1 H, OCH), 6.63 (s, 1 H, $CONH_2$), 7.20 (s, 1 H, $CONH_2$).

MS (70 eV): *m*/*z* (%) = 187 (2, M^+), 172 (30), 143 (68), 85 (32), 59 (100).

Anal. ($C_9H_{17}NO_3$): calcd: C, 57.73; H, 9.15; N, 7.48. Found C, 57.84; H, 8.91; N, 7.46.

(*R*)-2,2,5,5-Tetramethyl-1,3-dioxane-4-carboxamide [(*R*)-3]
To a suspension of (*R*)-**2** (17.53 g, 100 mmol) in a mixture of CH_2Cl_2 (150 mL) and acetone (150 mL) at 10 °C were added isopropenyl methyl ether (14.60 mL, 155.3 mmol) and a solution of *p*-TsOH (0.38 g) in acetone (30 mL) and the reaction was carried out as described above; yield: 18.80 g (96%); colorless solid; mp 92.7−94.1 °C; $[\alpha]_D^{20}$ +56.36.

Anal. ($C_9H_{17}NO_3$): calcd: C, 57.73; H, 9.15; N, 7.48. Found C, 57.74; H, 9.15; N, 7.33.

(*S*)-2,2,5,5-Tetramethyl-1,3-dioxane-4-carboxamide [(*S*)-3]
To a suspension of (*S*)-**2** (19.48 g, 132 mmol) in a mixture of CH_2Cl_2 (150 mL) and acetone (150 mL) at 10°C were added isopropenyl methyl ether (18.75 mL; 189.2 mmol) and a solution of *p*-TsOH (0.38 g) in acetone (30 mL) and the reaction was carried out as described above; yield: 24.04 g (97%); colorless solid; mp 92−95 °C; $[\alpha]_D^{20}$ −55.73.

Anal. ($C_9H_{17}NO_3$): calcd: C, 57.73; H, 9.15; N, 7.48. Found C, 57.12; H, 9.22; N, 7.50.

(*R*,*S*)-2,2,5,5-Tetramethyl-1,3-dioxane-4-carbonitrile [(*R*,*S*)-4]
A solution of cyanuric chloride (1.3 g, 10.9 mmol) in *tert*-butyl methyl ether (23 mL) was added to a solution of (*R*,*S*)-**3** (5.00 g, 27.00 mmol) in DMF (8 mL). The mixture was stirred at r.t. for 1 h, in the course of which the solution turned into a yellow suspension. The mixture was neutralized with aq 28% NaOH (6 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (2 × 20 mL). The combined organic phases were washed with distilled water (12.5 mL), dried (Na_2SO_4), and filtered. The solvent was removed on a rotary evaporator to give (*R*,*S*)-**4** as a colorless liquid; yield: 3.53 g (95%); mp −42.7 °C; bp 168.1°C/760 Torr.

IR (KBr): ν = 2996, 2967, 2876, 2250, 1736, 1470, 1396, 1380, 1262, 1242, 1224, 1197, 1157, 1097, 1048, 934, 857 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.98 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 3.48 (d, 1 H, J_{HH} = 9.5 Hz, CH_2), 3.63 (d, 1 H, J_{HH} = 9.5 Hz, CH_2), 4.47 (s, 1 H, CH).

MS (70 eV): *m*/*z* (%) = 170 (8, M-H^+), 154 (85), 143 (10), 94 (38), 59 (92), 56 (50), 43 (100).

Anal. ($C_9H_{15}NO_2$): calcd: C, 63.88; H, 8.93; N, 8.28. Found C, 63.60; H, 8.95; N 8.16.

(R)-2,2,5,5-Tetramethyl-1,3-dioxane-4-carbonitrile [(R)-4]
A solution of cyanuric chloride (5.57 g, 30.2 mmol) in *tert*-butyl methyl ether (110 mL) was added to a solution of (*R*)-**3** (12.6 g, 60.5 mmol) in DMF (25 mL) and the reaction was carried out as described above; yield: 10.31 g (91%); colorless liquid; mp −45.7 °C; bp 148.4 °C/760 Torr; $[\alpha]_D^{20}$ −1.58.

Anal. ($C_9H_{15}NO_2$): calcd: C, 63.88; H, 8.93; N, 8.28. Found C, 63.96; H, 8.79; N, 8.16.

(*S*)-2,2,5,5-Tetramethyl-1,3-dioxane-4-carbonitrile [(*S*)-4]
A solution of cyanuric chloride (7.38 g, 40 mmol) in *tert*-butyl methyl ether (150 mL) was added to a solution of (*S*)-**3** (15.15 g, 80 mmol) in DMF (50 mL) and the reaction was carried out as described above; yield: 12.73 g (94%); colorless liquid; mp −45.8 °C; bp 148.9 °C/760 Torr; $[\alpha]_D^{20}$ +1.80.

Anal. ($C_9H_{15}NO_2$): calcd: C, 63.88; H, 8.93; N, 8.28. Found C, 63.94; H, 8.96; N, 8.45.

(*R*,*S*)-2,4-Dihydroxy-3,3-dimethylbutyronitrile [(*R*,*S*)-5]
Compound (*R*,*S*)-**4** (1.0 g, 5.9 mmol) was dissolved in MeOH (20 mL) and hydrolyzed using Amberlite 15 (0.3 g). After 12 h, the suspension was filtered over speedex, and the bulk of solvent removed at reduced pressure (20 °C/20 mbar, 2 h). After flash-chromatography (silica gel 70−230 mesh, EtOAc) (*R*,*S*)-**5** was obtained as a colorless liquid; yield: 3.6 g (93%).

IR (KBr): ν = 3397, 3242, 2965, 2935, 2904, 2879, 2243, 1474, 1466, 1397, 1371, 1331, 1076, 1043, 1025, 978, 967, 957, 946 911, 865 cm^{-1}.

^1H NMR ($CDCl_3$): *d* = 1.08 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 2.27 (m, 1 H, OH), 3.85 (d, 1 H, J_{HH} = 5.3 Hz, CH_2), 3.54 (d, 1 H, J_{HH} = 5.3 Hz, CH_2), 4.09 (n, 1 H, OH), 4.35 (s, 1 H, CNCH).

MS (70 eV): *m*/*z* (%) = 130 (2, M − H^+) 103 (28), 81 (55), 73 (100), 57 (35), 55 (66), 31 (34).

Anal. ($C_6H_{11}NO_2$): calcd: C, 55.80; H, 8.58; N, 10.85. Found C, 53.79; H, 8.47; N, 9.48.

(*R*)-2,4-Dihydroxy-3,3-dimethylbutyronitrile [(*R*)-5]
A solution of (*R*)-**4** (8.46 g, 50 mmol) in hexane (80 mL) was hydrolyzed by stirring with 37% HCl (0.15 mL). After 2 h distilled water (30 mL) was added. The aqueous phase was extracted with Et_2O (60 mL). The bulk of Et_2O was removed on a rotary evaporator at 40 °C/50 mbar. (*R*)-**5** remained as colorless liquid in a yield of 6.23 g (97%). No meaningful values for optical rotation and elemental analysis could be obtained due to rapid degradation of the samples.

(*S*)-2,4-Dihydroxy-3,3-dimethylbutyronitrile [(S)-5]
A solution of (*S*)-**4** (2 g, 11.2 mmol) in hexane (20 mL) was hydrolyzed by stirring with 37% HCl (0.03 mL). After 2 h distilled water (10 mL) was added. The aqueous phase was extracted with Et_2O (50 mL). The bulk of Et_2O was removed on a rotary evaporator at 40 °C/50 mbar. (*S*)-**5** remained as colorless liquid in a yield of 1.36 g (95%). No meaningful values for optical rotation and elemental analysis could be obtained due to rapid degradation of the samples.

(*S*)-Ammonium Pantoate [(*S*)-6]
The stability measurements and conversion of **2** were carried out in the following way:

A solution of **2** (2 g, 13.6 mmol) in H_2O (40 mL) was stirred at r.t. or 45 °C. Samples for GC were taken every 30 min for 4 h, then every 60 min for 4 h, and finally every 8 h, dried and silylated (BSTFA) for GC measurements. After complete conversion the mixture was concentrated (45 °C/20 mbar). The crude product was stirred with Et_2O (20 mL), filtered and dried (40 °C/10 mbar); yield: 1.8 g (80%).

IR (nujol): ν = 3359, 3239, 2922, 2854, 2253, 2178, 1932, 1738, 1564, 1462, 1376, 1317, 1287, 1189, 1155, 1069, 1040, 1022, 959, 943, 883, 821, 725, 734 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 0.71 (s, 3 H, CH_3), 0.77 (s, 3 H, CH_3), 3.06 (d, 1 H, *J* = 10.6 Hz, CH_2), 3.27 (s, 1 H, OH), 3.35 (d, 1 H, *J* = 10.9 Hz, CH_2), 6.5 (br s, 4 H, NH_4^+).

MS (ion spray): *m*/*z* = 147,1 (M^-).

Anal. ($C_6H_{15}NO_4$): calcd: C, 43.63; H, 9.15; N, 8.48. Found C, 43.77; H, 9.22; N, 8.18.

(*R*,*S*)-2-Hydroxy-3,3-dimethyl-4-trityloxybutyramide [(R,S)-7]
To a suspension of (*R*,*S*)-**2** (3.0 g, 20.4 mmol) in Et_3N (6 mL) and CH_2Cl_2 (10 mL) was added a solution of triphenylchloromethane (5.9 g, 20.5 mmol) in CH_2Cl_2 (50 mL) at 5 °C. The mixture was heated to r.t. and stirred for 3 h. After hydrolysis with H_2O (60 mL), the phases were separated, the organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by recrystallization from Et_2O/hexane; yield: 7.7 g (93%). The purity according to SFC was 98%; mp 121−122 °C.

IR (nujol): ν = 3459, 3449, 3191, 3083, 3002, 2976, 2854, 1968, 1689, 1671, 1665, 1597, 1492, 1463, 1375, 1100, 1080, 1007, 976 958, 899 cm^{-1}.

^1H NMR, ($CDCl_3$): δ = 0.98 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 3.02 (d, 1 H, *J* = 9.0 Hz, OCH_2), 3.16 (d, 1 H, *J* = 9.0 Hz, OCH_2), 3.71 (d, 1 H, *J* = 4.5 Hz, $CH_)$, 4.11 (d, 1 H, *J* = 4.5 Hz, OH), 5.11 (s, 1 H, NH_2) 6.15 (s, 1 H, NH_2) 7.25−7.45 (m, 15 H_{arom}).

MS (ion spray): *m*/*z* = 428.5 (MK^+), 412.3 (MNa^+), 243 (CPh_3^+).

Anal. ($C_{25}H_{27}NO_3$): calcd: C, 77.09; H, 6.99; N, 3.60. Found C, 77.31; H, 6.97; N, 3.68.

(*R*)-2-Hydroxy-3,3-dimethyl-4-trityloxybutyramide [(*R*)-7]
The reaction of (*R*)-**2** with triphenylchloromethane was carried out as described above. (*R*)-**7** was obrained as a colorless solid in a yield of 7.6 g (92%). The purity according to SFC was 98.5%; er: *R*/*S* = 99.2:0.8; mp 123−124°C; $[\alpha]_D^{20}$ 11.0 (*c* = 0.95g/100 mL, EtOH).

Anal. ($C_{25}H_{27}NO_3$): calcd: C, 77.09; H, 6.99; N, 3.60. Found C, 76.82; H, 6.88; N, 3.67.

(*S*)-2-Hydroxy-3,3-dimethyl-4-trityloxybutyramide (*S*)-7
The reaction of (*S*)-**2** with triphenylchloromethane was carried out as described above. (*S*)-**7** was obtained as a colorless solid in a yield of 7.7 g (93%). The purity according to SFC was 99.2%; er: *R*/*S* = 99.2:0; mp 126−127 °C; $[\alpha]_D^{20}$ −11.2 (*c* = 0.95g/100 mL, EtOH).

Anal. ($C_{25}H_{27}NO_3$): calcd: C, 77.09; H, 6.99; N, 3.60. Found C, 76.88; H, 7.09; N, 3.64.

(*R*,*S*)-2-Hydroxy-3,3-dimethyl-4-trityloxbutyronitrile [(*R*,*S*)-8]; Typical Procedure
A solution of cyanuric chloride (0.8 g, 4.3 mmol) in *tert*-butyl methyl ether (15 mL) was added to a solution of (*R*,*S*)-**7** (3.4 g, 8.7 mmol) in DMF (4.5 mL). The mixture was stirred at r.t. for 1 h, in the course of which the solution turned into a yellow suspension. To the mixture was added H_2O (15 mL), and the aqueous phase was extracted with *tert*-butyl methyl ether (2 × 30 mL). The combined organic phases were washed with distilled water (30 mL), dried (Na_2SO_4), and filtered. The solvent was removed on a rotary evaporator. Crude (*R*,*S*)-**8** was obtained as pale yellow solid and purified by recrystallization from acetone/hexane; yield: 3.08 g (95%).

IR (KBr): ν = 3459, 3087, 3060, 3038, 2967, 2876, 2245, 1958, 1729, 1672, 1597, 1490, 1447, 1321, 1182, 1077, 1009, 932, 898, 764, 702 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.04 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 3.09 (d, 1 H, *J* = 10.0 Hz, CH_2), 3.28 (d, 1 H, *J* = 9.5 Hz, CH_2), 3.55 (d, 1 H, *J* = 7.5 Hz, CH), 4.32 (d, 1 H, *J* = 7.75 Hz, OH), 7.19−7.43 (m, 15 H_{arom}).

MS (ion spray): *m*/*z* = 410.5 (MK^+), 394.3 (MNa^+) 372.4 (MH^+), 243.3 (CPh_3^+).

Anal. ($C_{25}H_{25}NO_2$): calcd: C, 80.83; H, 6.78; N, 3.77. Found C, 80.60; H, 6.95; N, 3.61.

(*R*)-2-Hydroxy-3,3-dimethyl-4-trityloxybutyronitrile [(*R*)-8]
The dehydration reaction of (*R*)-**7** with cyanuric chloride was carried out as described above. (*R*)-**8** resulted as a pale yellow solid in 95% yield; $[\alpha]_D^{20}$ −5.06 (*c* =1.03g/100 mL, EtOH). The compound still contained 0.1% water and 2.6% hexane, as determined by Karl Fischer titration and GC integration, respectively.

Anal. ($C_{25}H_{25}NO_2$): calcd: C, 80.83; H, 6.78; N, 3.77. Found C, 81.19; H, 6.89; N, 3.06.

(*S*)-2-Hydroxy-3,3-dimethyl-4-trityloxybutyronitrile [(*S*)-8]
The dehydration reaction of (*S*)-**7** with cyanuric chloride was carried out as described above. (*S*)-**8** resulted as a pale yellow solid in 95% yield; $[\alpha]_D^{20}$ +7.19 (*c* = 1.069/100 mL, EtOH). The compound still contained 0.1% water and 2.2% hexane, as determined by Karl Fischer titration and GC integration, respectively.

Anal. ($C_{25}H_{25}NO_2$): calcd: C, 80.83; H, 6.78; N, 3.77. Found C, 80.47; H, 6.91; N, 3.04.

Crystal Structure Determinations
All measurements were performed on an Enraf Nonius Mach 3 four-circle diffractometer at room temperature using graphite-monochromatized Mo-Kα radiation (λ = 0.7107 Å), and the reflection intensities were collected using ω-scans. The structures were solved using direct methods (SHELXS86[15]), all non-hydrogen atoms were refined anisotropically, all the hydrogen atoms were located from difference Fourier-maps and refined isotropically without constraints (SHELXL93[16]).

Crystal Structure Data of (*R*,*S*)-2
Suitable crystals were obtained by recrystallization from EtOH. Unit cell parameters were obtained by least-squares refinement of the 2θ values of 24 reflections with $10 \le \theta \le 14°$: monoclinic, space group C2/c (No.15), a = 21.334(2), b = 7.006(1), c = 13.557(1) Å, β = 129.20(1)°, V = 1570.4(3) $Å^3$, Z = 8, $\rho_{calc.}$ = 1.245 gcm^{-3}, μ = 0.10 mm^{-1}, F(000) = 640. Number of unique reflections: 1388 ($0 \le \theta \le 25°$), of which 947 [$F_o > 4\sigma(F_o)$] were used for the determination and refinement of the structure. The refinement converged at R_1 = 0.038 (R_1= 0.73 and R_2 = 0.120 for all 1388 reflections) (wR_2 = 0.120, number of variables 143) with the largest difference peak and hole at 0.15 and −0.19 $eÅ^{-3}$, respectively.

Crystal Structure Data of (*R*,*S*)-3
Suitable crystals were obtained by recrystallization from hexane. Unit cell parameters were obtained by least-squares refinement of the 2θ values of 21 reflections with $7 \le \theta \le 14°$: triclinic, space group P-1 (No.2), a = 6.707(1), b = 8.059(1), c = 10.955(2) Å, α = 99.92(1), β = 98.77(1), γ = 111.85(1)°, V = 526.0(1) $Å^3$, Z = 2, $\rho_{calc.}$ = 1.182 gcm^{-3}, μ = 0.09 mm^{-1}, F(000) = 204. Number of unique reflections: 1843 ($0 \le \theta \le 25°$), of which 1100 [$F_o > 4\sigma(F_o)$] were used for the determination and refinement of the structure. The refinement converged at R_1 = 0.040 (R_1 = 0.095 and R_2 = 0.184 for all 1843 reflections)(wR_2 = 0.184, number of variables 186) with the largest difference peak and hole at 0.16 and -0.16 $eÅ^{-3}$, respectively.

Crystal Structure Data of (*R*)-3

Suitable crystals were obtained by recrystallization from hexane. Unit cell parameters were obtained by least-squares refinement of the 2θ values of 25 reflections with $10 \le \theta \le 14°$: orthorhombic, space group $P2_12_12_1$ (No.19), a = 7.709(2), b = 10.847(2), c = 12.545(1) Å, V = 1049.0(3) Å^3, Z = 4, $\rho_{calc.}$ = 1.186 gcm^{-3}, μ = 0.09 mm^{-1}, F(000) = 408. Number of unique reflections: 1211 ($0 \le \theta \le 26°$), of which 890 ($F_o > 4\sigma(F_o)$) were used for the determination and refinement of the structure. The refinement converged at R_1 = 0.042 (R_1 = 0.072 and R_2 = 0.127 for all 1211 reflections) (wR_2 = 0.127, number of variables 186) with the largest difference peak and hole at 0.18 and −0.27 eÅ^{-3}, respectively.

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