Total Synthesis of *cis*- and *trans*-3-Hydroxy-D-proline and (+)-Detoxinine†

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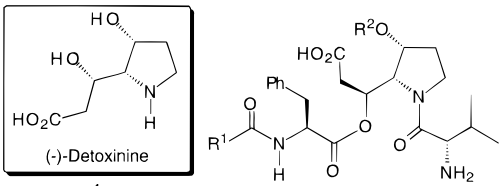
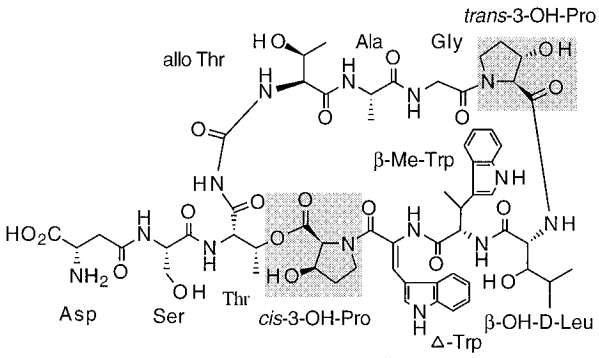
The unnatural enantiomer of the amino acid detoxinine and both diastereomeric 3-hydroxy-D-prolines have been prepared from D-mannitol via the *O*-silylated hydroxyproline **12** as a common key intermediate.

Peptide structures with proline components have received considerable interest over the past few years.[1,2] For instance, detoxinine[3] (**1**) is a constituent of the depsipeptide complex detoxine (**2**) which is a mixture of several components and has been isolated from the fermentation broth of *streptomyces caespitosus* var. *detoxicus 7072 GC1*.



Detoxines are applied as selective antagonists against the cytotoxic activity of the antibiotic blasticidin S, without impeding the antibiotic effect.[4] So far, **1** has been prepared in racemic form[5] or as the natural enantiomer ((−)-**1**).[6]

trans-3-Hydroxy-L-proline has been isolated from mediterranean sponge and from collagen hydrolysates of various sources.[7] Hydroxyproline formation in collagen leads to enhanced stability of the collagen triple helix due to hydrogen bonding between the hydroxyproline's hydroxyl group and the peptide backbone. The elaboration of the biological active (β-turn) structure of the polypeptide antibiotic telomycin[8] (**3**)—produced by streptomyces spp. from florida soil—also depends on *trans*-3-hydroxyproline, which induces strong preferences for this structural motif. Telomycin is the only naturally occuring substance containing the *cis* isomer of 3-hydroxyproline, which stabilizes the second one of the two β-turns.[9] The chirality of the amino acids in the central position ($i + 1$ or $i + 2$) of a turn have a profound effect on the type of turn (I, II, I′, or II′) which is formed.[10] Several syntheses of *cis*- and *trans*-3-hydroxyproline have been described,[11] which among other approaches are based on Dieckmann-type cyclization,[11d] a reductive amination of a suitably substituated amino aldehyde[11b] and on structural manipulations of pyroglutamate,[11c] respectively. In previous papers,[12] we have demonstrated the potential of our D-mannitol-based S_N2-cyclization methodology in the synthesis of optically pure pyrrolidine-type natural products.



Now we extend this approach to the first synthesis of the unnatural detoxinine enantiomer ((+)-**1**) and of the

† Dedicated to Professor Helmut Vorbrüggen on the occasion of his 65th birthday.

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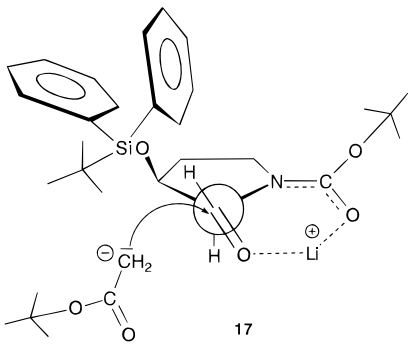
3-hydroxy-D-prolines **23** and **25**, respectively. Retrosynthetic analysis leads to hydroxyproline aldehyde **4** which in turn is to be prepared from the acyclic amine **5** via intramolecular S_N2-displacement. Amine **5** should be accessible from the homoallylic alcohol **6** (Scheme 1).

Synthesis of (+)-Detoxinine. Known alcohol **6**, easily available in three steps from D-mannitol,[12] is converted into azide **9** via standard reactions. Protection of the 1-OH function and mesylation of the 2-OH function generates intermediate **11** with high regioselectivity (Scheme 2).

Staudinger reaction of the azide with triphenylphosphane and base-catalyzed hydrolysis of the phosphine imine releases the free amine which immediately cyclizes under inversion of configuration to stereochemically pure prolinol **12** (Scheme 3). *N*-BOC-protection and desilylation of the primary hydroxyl function furnishes alcohol **13** which is oxidized to aldehyde **14** under Swern conditions.[13] Aldehyde **14** is configurationally stable despite its *cis*-configuration around the five-membered ring and even maintains its configurational integrity during the ester enolate addition, furnishing the hydroxy esters **15** and **16** in a ratio of 10:1. Aldehyde **14** has been prepared by Joullie et al. in racemic form[6b] and shows spectroscopic data similar to ours. In the same publication, the racemic aldehyde was submitted to an aldol addition with Braun's HYTRA reagent,[14] but the diastereoselection was only 2:1 in this case.

The remarkable stereoselectivity in our experiment may be interpreted via a chelate intermediate **17** formed from the lithium cation and the aldehyde and amide oxygens. The silyl protective group prevents any chelate formation with the 4-oxygen and shields the *si*-face of the carbonyl toward the nucleophilic attack.



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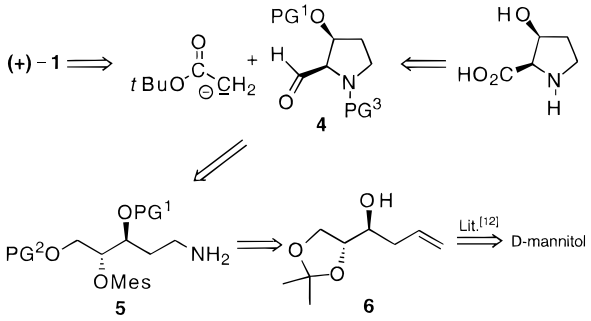
The configuration of **18** is confirmed by an X-ray crystal structure analysis of the corresponding acetonide **19** (Figure 1), which is, moreover, in the form of the enantiomer,[6a] a known compound.

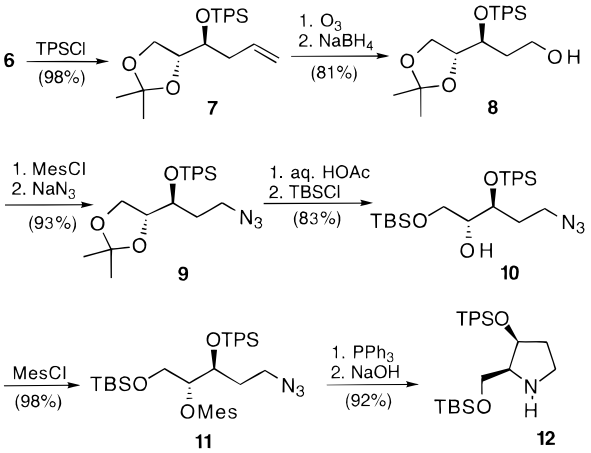
Deprotection of **18** generates free (+)-**1**, identical with the enantiomer[6b] in all spectroscopic data and the absolute value of the optical rotation.

Synthesis of *cis*- and *trans* 3-Hydroxy-D-proline. For the synthesis of *cis*-3-hydroxy-D-proline, the key intermediate **12** was *N*-protected with benzyl carbamate as an acid-resistent protective group. Selective desilylation of the TBS ether with aqueous acetic acid leads to the primary alcohol **20**. Under Swern conditions, the hydroxyl group was smoothly oxidized to aldehyde **21**, which shows two sets of ^{1}H-NMR signals in $CDCl_3$ at room temperature (Figure 2).

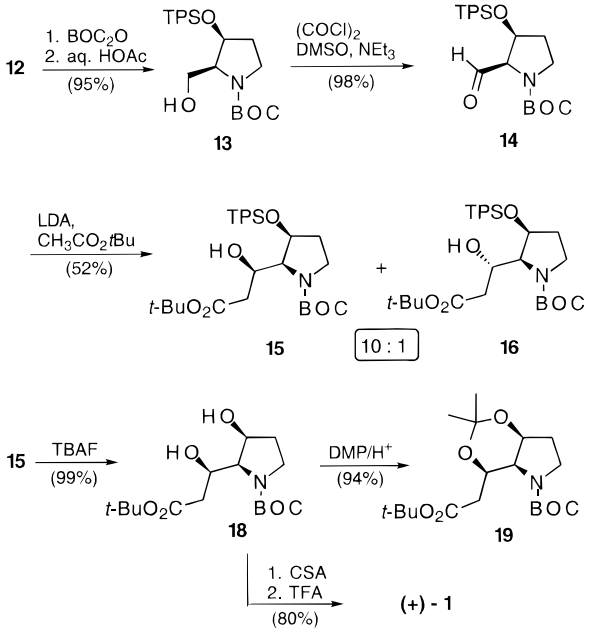
Scheme 1



Scheme 2



Scheme 3



A possible epimerization of the stereogenic center α to the carbonyl group was excluded on the basis of NOE, H,H-COSY 90, and ROESY (short time NOE) experiments which show that the two observed species are rotamers with respect to the carbamate CO−N bond. Interestingly, there is only one set of signals in DMSO-d_6. This demonstrates that the effect is not induced by a steric effect of the benzyl group. Instead, the hindered rotation may be due to a dipolar interaction between the carbamate and the aldehyde. The high polarity of DMSO could interrupt this interaction and thus enhance the rotational freedom of the carbamate. With respect to

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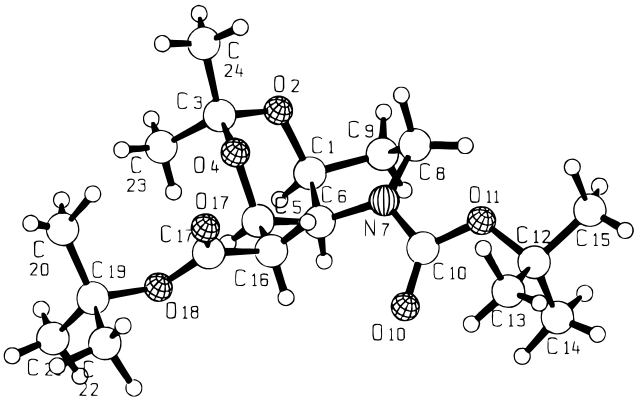
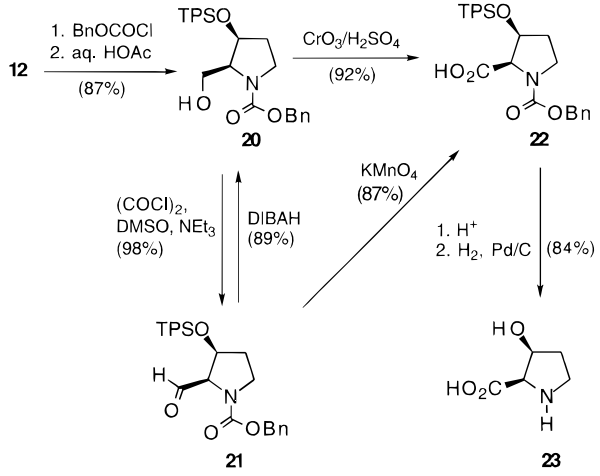
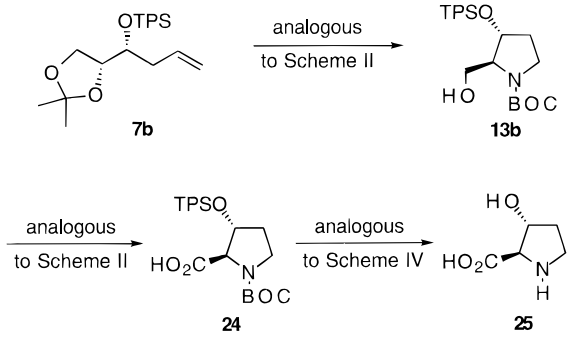


Figure 1. Crystal structure of **19**.

Scheme 4



Scheme 5



potential epimerization of the aldehyde **21**, even a high-temperature ^{1}H-NMR spectrum in DMSO-d_6 did not reveal the appearance of additional signals. There is also chemical evidence for the configurational stability of **21** as both the oxidation to the carboxylic acid **22** and the reduction to alcohol **20** gave isomerically pure material. O- and N-deprotection leads to product **23** in 11 steps with an overall yield of 46%. Deprotection with TBAF gave an inseparable mixture of **23** and ammonium salts (Scheme 4).

The *trans* isomer **23b** was synthesized analogously and with identical yields from alcohol **7b** (Scheme 5) (for data see the supporting information).

In conclusion, we have prepared the unnatural enantiomer of detoxinine ((+)-**1**) from **6** in 11 steps and an overall yield of 25%. The route has also opened an access to the 3-hydroxy-D-prolines **23** and **25** in optically and diastereomerically pure form. The starting material, alcohol **6**, is available in the form of all four diastereomers which renders an unusual stereochemical flexibility to our synthesis.[15] Currently, (+)-**1** is used in detoxine structures to test the change in the physiological activities. Additionally, the incorporation of **23**, **25**, and (+)-**1** in peptidomimetics possibly useful as LHRH antagonists[16] is also being considered.

Experimental Section

General Methods. All reactions were performed in dried and purified solvents and monitored by TLC (plates, Merck 5554). Preparative column chromatography was performed on Merck silica gel 60 F-254, mesh 230−400, with typically 10−30 g of silica gel per gram of substance. NMR spectra were recorded in $CDCl_3$ with TMS as internal standard. Optical rotations were determined at 22 °C in $CHCl_3$ (unless otherwise stated) at 589 nm.

(2*R*,3*S*)-3-*O*-(*tert*-Butyldiphenylsilyl)-1,2-*O*-isopropylidene-5-hexene-1,2,3-triol (7). To a solution of alcohol **6**[12] (45 g, 0.26 mol), imidazole (75 g, 1.1 mol), and a catalytic amount of DMAP (0.4 g) in anhydrous DMF (300 mL) was added *tert*-butyldiphenylsilyl chloride (80 g, 0.29 mol), and the mixture was stirred at rt for 24 h. Then the reaction mixture was treated with H_2O (ca. 10 mL) and stirred for 1 h. The solvents were evaporated, and the residue was partitioned between H_2O (300 mL) and Et_2O (600 mL). The aqueous layer was extracted twice with additional Et_2O. The combined organic layers were washed with brine (300 mL), concentrated in vacuo, and purified by flash column chromatography (hexane/EtOAc, 10:1) to give **7** (105 g, 98%) as a colorless viscous oil: $[\alpha]^{20}_D = +1.1$ ($c = 1.4$, $CHCl_3$); ^{1}H-NMR (250 MHz) $\delta = 1.16$ (s, 9H), 1.40 (s, 3H), 1.43 (s, 3H), 2.24 (m, 2H), 3.88 (dd, $J = 8.0$, 7.5 Hz, 1H), 4.04 (m_c, 2H), 4.20 (dd, $J = 8.3$, 7.5 Hz, 1H), 4.96−5.10 (m, 2H), 5.76−5.92 (m, 1H), 7.40−7.54 (m, 6H), 7.76−7.86 (m, 4H); ^{13}C-NMR (63 MHz) δ 19.39, 25.32, 26.46, 27.01, 38.55, 66.14, 73.05, 77.77, 108.69, 117.45, 127.54, 129.70, 133.58, 133.81, 134.00, 135.98; IR (film, KBr) ν 3072 m, 2959 m, 2858 m, 1472 m, 1380 m, 1370 m, 1212 m, 1112 s (br), 998 m, 915 s, 859 s, 822 s, 740 s, 702 vs, 610 s, 510 cm^{-1}; MS (80 eV, EI, 140 °C) *m*/*z* 395 (5.1), 353 (74.9), 295 (100), 225 (64.3), 199 (28.7), 135 (25.3). Anal. Calcd for $C_{25}H_{34}O_3Si$ (410.6273): C, 73.13; H, 8.35. Found: C, 73.32; H, 8.26.

(2*R*,3*S*)-3-*O*-(*tert*-Butyldiphenylsilyl)-1,2-*O*-isopropylidenepentane-1,2,3,5-tetrol (8). Compound **7** (25 g, 61 mmol) in technical MeOH (600 mL) was ozonized at −78 °C until a slightly blue color resulted. Excess ozone was removed by bubbling oxygen through the mixture. $NaBH_4$ (11.6 g, 0.3 mol) was added in seven portions, and the mixture was stirred vigorously until it reached rt. The solvent was removed under reduced pressure, and the residue was dissolved in H_2O (400 mL). After being stirred for 24 h, the mixture was extracted with Et_2O. The combined organic layers were washed with brine, concentrated in vacuo, and purified by flash column chromatography (hexane/EtOAc, 6:1) to give **8** (20.5 g, 81%) as a colorless viscous liquid: $[\alpha]^{20}_D = +1.2$ ($c = 2.6$, $CHCl_3$); ^{1}H-NMR (250 MHz) δ 1.04 (s, 9H), 1.28 (s, 3H), 1.30 (s, 3H), 1.76−1.84 (m, 2H), 2.24 (t(br), $J = 5.0$ Hz, 1H), 3.58 (m_c, 2H), 3.64 (dd, $J = 8.5$, 7.0 Hz, 1H), 3.82 (dd, $J = 11.3$, 6.3 Hz, 1H), 3.98 $J = 8.3$, 6 Hz, 1H), 4.08−4.18 (m, 1H), 7.32−7.44 (m, 6H), 7.64−7.70 (m, 4H); ^{13}C-NMR (63 MHz) δ 19.32, 25.28, 26.29, 26.90, 37.55, 58.95, 67.68, 73.18, 78.52, 109.23, 127.63, 129.85, 13.22, 133.56, 135.83; IR (film, KBr) ν 3445 s (br), 3071 m, 2932 m, 2890 m, 1473 m, 1428 s, 1259 s (br), 1112 s (br), 1074 s (br), 822 s, 703 vs, 611 s, 508 cm^{-1}; MS (80 eV, EI, 250 °C) *m*/*z* 399 (2.7), 357 (1.7), 313 (7.5), 299 (12.2), 269 (48.1), 221 (100), 199 (71.1), 177 (17.8), 135 (20.7). Anal. Calcd for $C_{24}H_{34}O_4Si$ (414.6157): C, 69.53; H, 8.27. Found: C, 69.25; H, 8.01.

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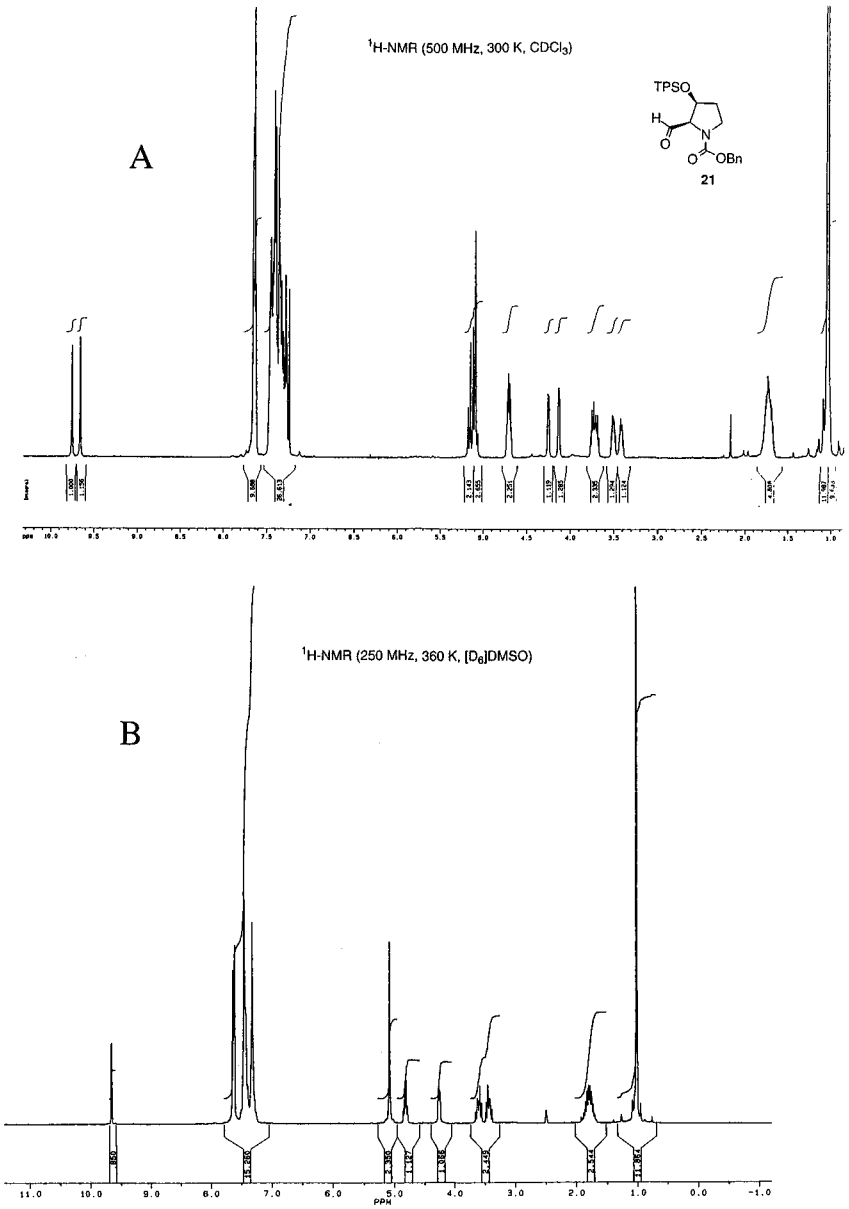

Figure 2. 1H-NMR-spectra of **21** in $CDCl_3$ (A) and DMSO-d_6 (B).

(2*R*,3*S*)-5-Azido-3-*O*-(*tert*-butyldiphenylsilyl)-1,2-*O*-isopropylidenepentane-1,2,3-triol (9). Alcohol **8** (20 g, 48 mmol) in pyridine (100 mL) was treated with methanesulfonyl chloride (7.2 g, 63 mmol) at 0 °C and strirred at rt for 9 h. The mixture was quenched with H_2O (10 mL) and stirred for 1 h. The solvents were removed under reduced pressure, and the residue was filtered through silica gel. The resulting crude product was dissolved in DMF (250 mL), treated with NaN_3 (15.6 g, 240 mmol), and stirred vigorously for 12 h at 65 °C. After the mixture was cooled to rt, H_2O was added and the solution was extracted with ether (4 × 250 mL). The combined organic layers were washed with brine, concentrated in vacuo, and purified by flash column chromatography (hexane/EtOAc, 10:1) to give **9** (19.6 g, 93%) as a colorless oil: $[\alpha]^{20}_D = +15.2$ (c = 3.0, $CHCl_3$); ^{1}H-NMR (250 MHz) δ 1.06 (s, 9H), 1.30 (s, 6H), 1.70−1.94 (m, 2H), 3.32 (dt, J = 7.5, 2.5 Hz, 2H), 3.58 (dd, J = 8, 6.5 Hz, 1H), 3.76 (dd, J = 11.3, 6.3 Hz, 1H), 3.92 (dd, J = 8, 7 Hz, 1H), 4.06 (t, J = 6.3 Hz, 1H), 7.36−7.50 (m, 6H), 7.66−7.76 (m, 4H); ^{13}C-NMR (63 MHz) δ 19.38, 25.19, 26.37, 26.95, 33.02, 47.23, 67.40, 71.96, 78.31, 109.20, 127.65, 127.73, 129.87, 129.94, 133.20, 133.33, 135.79, 135.85; IR (film, KBr) ν 2985 m, 2958 m, 2891 m, 2859 m, 2096 vs, 1590 w, 1473 m, 1428 s, 1380 m, 1370 m, 1262 m, 1112 s, 1075 s (br), 822 s, 741 s, 703 vs, 612 s, 508 s cm^{-1}; MS (80 eV, EI, 120 °C): m/z 424 (2.9), 396 (1.3), 382 (82.0), 338 (7.3), 317 (11.9), 296 (51.8), 267 (14.6), 252 (43.9), 225 (38.1), 218 (20.6), 199 (100), 183 (50.3), 135 (35.7). Anal. Calcd for $C_{24}H_{33}N_3O_3Si$ (439.6285): C, 65.57; H, 7.57; N, 9.56. Found: C, 65.78; H, 7.26; N, 9.41.

(2*R*,3*S*)-5-Azido-1-*O*-(*tert*-butyldimethylsilyl)-3-*O*-(*tert*-butyldiphenylsilyl)pentane-1,2,3-triol (10). Compound **9** (30 g, 68 mmol) was hydrolyzed with a mixture of HOAc/H_2O 6:1 at rt for 24 h. The solvents were removed under reduced pressure, and the residue was dried in vacuo at 40 °C for 6 h to give (2*R*,3*S*)-5-azido-3-*O*-(*tert*-butyldiphenylsilyl)pentane-1,2,3-triol (26.1 g, 96%) as a waxy solid: $[\alpha]^{20}_D = +26.9$ (c = 3.2, $CHCl_3$); ^{1}H-NMR (250 MHz) δ 1.10 (s, 9H), 1.60−1.76 (m, 1H), 1.84 (m_c, 1H), 3.12−3.28 (m, 1H), 3.30−3.42 (m, 1H), 3.48−3.62 (m, 2H), 3.68 (m_c, 1H), 3.86 (dt, J = 6, 5 Hz, 1H), 4−5 (s (br), D_2O-exchange position: 2H), 7.38−7.52 (m, 6 H), 7.66−7.76 (m, 4H); ^{13}C-NMR (63 MHz) δ 19.34, 20.59, 26.95, 31.71, 47.33, 63.14, 71.84, 74.21, 127.75, 127.79, 129.99, 132.86, 133.15, 135.74, 135.76; IR (film, KBr) ν 3405 vs (br), 3072 m, 3050 m, 29.57 m, 2933 m, 2892 m, 2096 vs, 1713 s, 1589 w, 1473 m, 1462 m, 1428 s, 1262 s (br), 1112 vs (br), 823 s, 740 s, 703 vs, 612 cm^{-1}; MS (80 eV, EI, 150 °C) m/z 384 (1.3), 338 (5.5), 296 (20.5), 225 (9.2), 218 (12.0), 199 (100), 183 (17.8), 163 (30.9), 135 (21.4), 91 (13.9). Anal. Calcd for $C_{21}H_{29}N_3O_3Si$ (399.5639): C, 63.13; H, 7.32; N, 10.52. Found: C, 63.44; H, 7.39; N, 10.27. To a solution of the diol (25 g, 63 mmol), imidazole (12.9 g, 190 mmol), and a catalytic amount

of DMAP (0.2 g) in anhydrous THF (750 mL) was added dropwise a solution of *tert*-butyldimethylsilyl chloride (9.9 g, 66 mmol) in THF (220 mL) at 0 °C for 3 h. The reaction mixture was stirred for 24 h until rt was reached. The solution was worked up as described for preparation of compound **7** and purified by flash column chromatography (hexane/EtOAc, 6:1) to give **10** (28.8 g, 89%) as a colorless viscous oil: $[\alpha]^{20}_D = -9.4$ ($c = 2.4$, $CHCl_3$); ^{1}H-NMR (270 MHz) δ 0.00 (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 1.10 (s, 9H), 1.70−1.84 (m, 1H), 1.86−2.00 (m, 1H), 2.46 (d, $J = 2.5$ Hz, D_2O-exchange position: 1H), 3.20−3.48 (m, 3H), 3.56−3.72 (m, 2H), 3.86 (m_c, 1H), 7.36−7.48 (m, 6H), 7.66−7.76 (m, 4H); ^{13}C-NMR (68 MHz) δ −5.57, −5.52, 19.40, 25.76, 26.98, 31.56, 47.46, 64.04, 71.52, 73.83, 127.67, 129.85, 135.78, 135.80; MS (80 eV, EI, 120 °C) *m*/*z* 498 (0.3), 470 (0.8), 456 (32.1), 428 (12.2), 410 (9.2), 378 (7.6), 350 (17.9), 306 (15.5), 296 (29.0), 235 (13.1), 225 (17.5), 199 (100), 195 (30.0), 183 (15.9), 135 (62.8), 73 (76.0). Anal. Calcd for $C_{27}H_{43}N_3O_3Si_2$ (513.820): C, 63.11; H, 8.43; N, 8.18. Found: C, 62.96; H, 8.29; N, 8.41.

(2*R*,3*S*)-5-Azido-1-*O*-(*tert*-butyldimethylsilyl)-3-*O*-(*tert*-butyldiphenylsilyl)-2-*O*-(methylsulfonyl)pentane-1,2,3-triol (11). Compound **10** (28 g, 54 mmol) in pyridine (175 mL) was mesylated as described for compound **9** to give **11** (31.3 g, 98%) as a colorless viscous oil after flash chromatography (hexane/EtOAc, 6:1): $[\alpha]^{20}_D = +21.3$ ($c = 2.8$, $CHCl_3$); ^{1}H-NMR (250 MHz) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 1.12 (s, 9H), 1.24−1.36 (m, 1H), 1.80 (m_c, 2H), 3.00 (s, 3H), 3.12−3.24 (m, 1H), 3.82−3.94 (m, 2H), 4.12 (m_c, 1H), 4.70 (m, 1H), 7.38−7.54 (m, 6H), 7.66−7.80 (m, 4H); ^{13}C-NMR (63 MHz) δ −5.54, 18.19, 19.40, 25.76, 26.92, 32.46, 38.48, 47.40, 61.85, 70.93, 85.45, 127.74, 127.79, 129.97, 130.09, 132.18, 133.28, 135.73, 136.07; MS (80 eV, EI, 200 °C) *m*/*z* 548 (1.0), 534 (1.6), 506 (80.7), 410 (19.4), 351 (9.6), 331 (11.3), 296 (13.4), 277 (100), 240 (10.1), 209 (16.9), 199 (37.4), 135 (50.6), 89 (27.7), 37 (38.7). Anal. Calcd for $C_{28}H_{45}N_3O_5SSi_2$ (591.9176): C, 56.82; H, 7.66; N, 7.10. Found: C, 57.22; H, 8.03; N, 6.99.

(2*S*,3*S*)-2-[(*tert*-Butyldimethylsiloxy)methyl]-3-(*tert*-butyldiphenylsiloxy)pyrrolidine (12). To a solution of **11** (13 g, 25 mmol) in anhydrous THF (200 mL) was added triphenylphosphine (7.9 g, 30 mmol) in eight portions (attention: vigorous N_2 evolution). The mixture was stirred at rt for 7 h and then treated with aqueous 1 M NaOH (2.5 mL) and refluxed for 36 h. The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH/NH_4OH, 95:5:0.5) to give **12** (10.8 g, 92%) as colorless viscous liquid: $[\alpha]^{20}_D = -4.0$ ($c = 2.3$, $CHCl_3$); ^{1}H-NMR (250 MHz) δ 0.06 (s, 6H), 0.88 (s, 9 H), 1.06 (s, 9H), 1.68 (m_c, 2H), 2.70 (s(br), 1H), 2.72−2.82 (m, 1H), 2.96 (dt, $J = 8$, 5.5 Hz, 1H), 3.12 (m_c, 1H), 3.80 (m_c, 2H), 4.44 (dt, J = 5.4, 3.5 Hz, 1H), 7.28−7.46 (m, 6H), 7.62−7.72 (m, 4H); ^{13}C-NMR (63 MHz) δ −5.52, 14.01, 18.03, 19.19, 22.62, 25.84, 26.80, 31.63, 32.25, 43.91, 59.29, 60.22, 66.38, 66.49, 71.92, 72.50, 127.58, 128.41, 129.32, 129.78, 133.36; IR (film, KBr) ν = 3071 w, 2955 m, 2930 m, 2857 s, 1472 m, 1428 m, 1390 w, 1361 w, 1256 s, 1112 s, 1090 s (br), 837 s, 776 m, 740 m, 701 vs, 612 m, 506 s cm^{-1}; MS (80 eV, EI, 100 °C) *m*/*z* 470 (0.5), 469 (1.1), 454 (2.9), 412 (21.9), 324 (100), 295 (5.6), 262 (13.0), 199 (5.6), 183 (8.1), 135 (10.5). Anal. Calcd for $C_{27}H_{43}NO_2Si_2$ (469.8072): C, 69.03; H, 9.23; N, 2.98. Found: C, 69.12; H, 9.09; N, 2.86.

(2*S*,3*S*)-*N*-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldiphenylsiloxy)-2-(hydroxymethyl)pyrrolidine (13). To an ice-cold solution of **12** (8.5 g, 18 mmol) in 1 M aqueous NaOH/THF 1:3 (500 mL) was added di-*tert*-butyl dicarbonate (11.8 g, 54 mmol) with vigorous stirring for 12 h. The mixture was concentrated in vacuo and partitioned between Et_2O (3 × 250 mL) and H_2O (200 mL), and the combined organic layers were concentrated in vacuo. Excess di-*tert*-butyl dicarbonate was recovered by distillation in vacuo (bp(15torr) 70−73 °C). The crude product was dissolved in acetic acid/H_2O (15:1−15:5, 200 mL) and stirred at rt for 9 h. The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography (hexane/EtOAc, 6:1) to give **13** (7.6 g, 95%) as a colorless oil: $[\alpha]^{20}_D = -11.1$ ($c = 2.7$, $CHCl_3$); ^{1}H-NMR (250 MHz) δ 1.08 (s, 9H), 1.46 (s, 9H), 1.62−1.76 (m, 1H), 1.78−1.94 (m, 1H), 3.04−3.22 (m, 1H), 3.36 (m_c, 1H), 3.76−3.96 (m, 2H), 4.08 (m_c, 1H), 4.20 (m_c, 1H), 4.36−4.48 (m, 1H), 7.36−7.52 (m, 6H), 7.64−7.72 (m, 4H); ^{13}C-NMR (63 MHz) δ −5.62, 14.11, 18.02, 19.18, 22.59, 25.82, 26.84, 32.55, 43.72, 59.22, 60.48, 66.44, 71.33, 72.71, 127.72, 128.32, 129.73, 133.34, 135.63, 154.44; IR (film, KBr) ν 3437 s (br), 3071 m, 2960 m, 2931 m, 2891 s, 2858 s, 1697 vs (br), 1674 vs (br), 1367 s, 1255 m, 1174 vs, 1112 vs, 1041 s, 822 s, 740 s, 702 vs, 610 s, 509 s cm^{-1}; MS (80 eV, EI, 250 °C) *m*/*z* 454 (0.1), 424 (0.1), 398 (0.5), 382 (2.9), 342 (100), 324 (6.0), 290 (6.1), 199 (25.0), 135 (5.8), 91 (4.1), 57 (9.0). Anal. Calcd for $C_{26}H_{37}NO_4Si$ (455.67): C, 68.53; H, 8.18; N, 3.07. Found: C, 68.22; H, 7.78; N, 2.88.

(3*R*)- and (3*S*)-*tert*-Butyl 3-hydroxy-3-((2*S*,3*S*)-3-(*tert*-butyldiphenylsiloxy)-*N*-(*tert*-butoxycarbonyl)-2-pyrrolidinyl)propionate (15) and (16). A cold (−78 °C), well-stirred solution of DMSO (5.6 g, 72 mmol) in CH_2Cl_2 (250 mL) was treated dropwise with oxalyl chloride (3.82 g, 30 mmol). After 30 min, compound **13** was added, and the mixture was stirred for 45 min at −78 °C. NEt_3 (15 g, 150 mmol) was added, and the solution was stirred until rt was reached. The solvents were removed under reduced pressure, and the residue was extracted with Et_2O (3 × 300 mL)−H_2O (1 × 200 mL), dried with $MgSO_4$, and concentrated in vacuo (bath temperature maximum 30 °C). The resulting aldehyde was added dropwise without further purification to a cold (−100 °C) solution of *tert*-butyl acetate (5.8 g, 50 mmol) and LDA (60 mmol) in ether (200 mL). The reaction mixture was stirred at −100 °C for 6 h and at rt for 4 h. The solvents were evaporated in vacuo, and the residue was purified by flash column chromatography (hexane/EtOAc, 6:1) to give **15** (6.7 g, 47%) and **16** (0.68, 4.8%) as colorless viscous oils: **15**: $[\alpha]^{20}_D = -19.2$ ($c = 0.9$, $CHCl_3$); ^{1}H-NMR (270 MHz) δ 1.08 (s, 9H), 1.42 (s, 9H), 1.48 (s, 9H), 1.66−1.82 (m, 1H), 2.02−2.12 (m, 1H), 2.48 (t(br), $J = 12.5$ Hz, 1H), 2.56−2.74 (m, 1H), 3.06−3.26 (m, 2H), 3.34 (dt, J = 11.5, 2 Hz, 1H), 3.80 (m_c, 1H), 4.36 (dt, $J = 10$, 8.7 Hz, 1H), 4.43 (m_c, 1H), 7.34−7.48 (m, 6H), 7.60−7.70 (m, 4H); ^{13}C-NMR (68 MHz) δ −5.32, 18.75, 26.65, 31.81, 43.34, 58.36, 61.15, 65.68, 72.05, 127.77, 128.27, 129.88, 132.83, 133.34, 135.18, 137.00, 154.25, 171.21; IR (film, KBr) ν 3435 s (br), 3069 m, 2961 m, 2931 m, 2891 s, 2858 s, 1695 vs, 1674 vs, 1472 s, 1427 s, 1407 vs, 1367 s, 1255 m, 1174 vs, 1112 vs, 822 s, 740 s, 700 vs, 607 m cm^{-1}; MS (80 eV, EI; 130 °C) *m*/*z* 570 (0.1), 569 (0.1), 551 (1.7), 512 (0.4), 496 (1.5), 465 (9.2), 440 (20.9), 412 (10.1), 400 (35.8), 368 (32.0), 356 (57.4), 324 (48.6), 290 (67.3), 278 (17.5), 199 (64.4), 169 (26.6), 135 (25.7), 113 (38.7), 57 (100). Anal. Calcd for $C_{32}H_{47}NO_6Si$ (569.81): C, 67.45; H, 8.31; N, 2.56. Found: C, 67.32; H, 8.26; N, 2.41. **16**: $[\alpha]^{20}_D = -14.8$ ($c = 1.1$, $CHCl_3$); ^{1}H-NMR (270 MHz) δ 1.14 (s, 9H), 142 (s, 9H), 1.48 (s, 9H), 1.68−1.78 (m, 1H), 1.88−2.02 (m, 1H), 2.36−2.50 (m, 1H), 2.60−2.70 (m, 1H), 3.08 (t, $J = 10$ Hz, 2H), 3.72−3.84 (m, 1H), 4.10 (m_c, 1H), 4.40 (q, $J = 7.5$ Hz, 1H), 4.60 (m_c, 1H), 7.34−7.48 (m, 6H), 7.60−7.70 (m, 4H); IR (film, KBr) ν 3437 s (br), 3068 m, 2960 m, 2931 m, 2891 s, 2858 s, 1695 vs, 1674 vs, 1472 s, 1427 s, 1407 vs, 1367 s, 1255 m, 1174 vs, 1112 vs, 821 s, 738 s, 702 vs, 605 m cm^{-1}; MS (80 eV, EI, 150 °C) *m*/*z* 551 (1.3), 496 (1.7), 465 (12.3), 440 (20.1), 412 (11.3), 400 (38.3), 368 (39.4), 3567 (61.3), 324 (57.3), 290 (73.0), 199 (84.9), 169 (46.7), 135 (27.6), 113 (43.7), 57 (100). Anal. Calcd: C, 67.45; H, 8.31; N, 2.56. Found: C, 66.62; H, 8.16; N, 2.81.

(2*S*,3*S*,2′*R*)-*N*-(*tert*-Butoxycarbonyl)-3-hydroxy-2-[1-hydroxy-2-(*tert*-butoxycarbonyl)ethyl]pyrrolidine (18). Alcohol **15** (6.5 g, 11 mmol) in THF (100 mL) was treated with TBAF (4.3 g, 16.7 mmol) and stirred at rt for 16 h. The reaction was quenched by adding H_2O (5 mL). The resulting solution was concentrated in vacuo, and the residue was purified by flash column chromatography (hexane/EtOAc, 1:1) to give **18** (3.6 g, 99%) as colorless powder: $[\alpha]^{20}_D = +1.8$ ($c = 1.4$, $CHCl_3$); ^{1}H-NMR (500 MHz, DMSO-d_6, 80 °C) δ 1.43 (s, 18H; *tert*-butyl groups), 1.58−1.90 (m, 1H; H-4), 1.91−1.99 (m, 1H; H-4), 2.38 (dd, $J = 15$, 8.7 Hz, 1H; H-2″), 2.53 (dd, $J = 15$, 4.5 Hz, 1H; H-2″), 3.31 (ddd, $J = 11.3$, 8.7, 5 Hz, 1H; H-5), 3.37 (dt, $J = 11.3$, 7.5 Hz, 1H; H-5), 3.73 (dd, $J = 7$, 4.5 Hz, 1H; H-2), 4.07 (s(br), 1H; D_2O-exchange position, 3-OH), 4.32 (m_c, 2H; H-2′ and H-3), 4.68 (s(br), 1H; D_2O-exchange position, 2″-OH), determination verified by COSY-experiments; ^{13}C-NMR (68 MHz) δ 27.96, 28.28, 33.00, 39.85, 44.55, 62.07, 68.63,

71.84, 79.93, 81.02, 82.59, 172.73; IR (film, KBr) ν 3362 m, 2979 m, 2936 m, 2894 w, 1738 s, 1720 s, 1702 vs, 1477 m, 1455 m, 1383 s, 1365 s, 1159 s, 1104 m, 1061 m, 1030 m, 975 m, 894 w, 857 w, 773 w cm^{-1}; MS (80 eV, EI, 100 °C) *m/z* 331 (0.2), 215 (0.9), 312 (4.5), 202 (28.9), 186 (12.4), 160 (11.6), 130 (91.6), 113 (36.6), 86 (100), 71 (30.2), 57 (53.1), 43 (35.5). Anal. Calcd for $C_{16}H_{29}NO_6$ (331.41): C, 57.99; H, 8.82; N, 4.23. Found: C, 57.82; H, 8.76; N, 4.45.

(1*S*,5*R*,6*R*)-*N*-(*tert*-Butoxycarbonyl)-3,3-dimethyl-5-(*tert*-butoxycarbonyl)methyl-2,4-dioxa-7-azabicyclo[4.3.0]nonane (19). To a solution of **18** (2.5 g, 7.5 mmol) and dimethoxypropane (3.1 g, 30 mmol) in CH_2Cl_2 (200 mL) was added trifluoroacetic acid (2−3 drops). The solution was stirred for 12 h at rt, and the solvents were evaporated in vacuo. The residue was partitioned between ether (3 × 200 mL) and aqueous phosphate buffer (NaH_2PO_4/Na_2HPO_4, 1:1). The combined organic layers were washed with brine and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/EtOAc, 6:1) and recrystallized with methanol to give **19** (2.6 g, 94%) as colorless needles: Mp 91 °C; $[\alpha]^{20}_D = +99.6$ (c = 1.4, $CHCl_3$) (lit.[6a] for **(−)-19**: mp 90−91 °C, $[\alpha]^{20}_D = -100.0$ (c = 1.8, $CHCl_3$); ^{1}H-NMR (500 HHz, DMSO-d_6, 130 °C) δ 1.29 (s, 3H; CH_3-3), 1.39 (s, 3H; CH_3-3), 1.42 (s, 18H; *tert*-butyl group), 1.74−1.80 (m, 1H; H-9), 1.81−1.87 (m, 1H; H-9), 2.27 (dd, J = 15, 10 Hz, 1H; H-5′), 2.62 (dd, J = 15, 3.8 Hz, 1H; H-5), 3.30 (dt, J = 10, 6.3 Hz, 1H; H-8), 3.64 (ddd, J = 11.3, 7.5, 2.5 Hz, 1H; H-8), 3.78 (dd, J = 5, 4.5 Hz, 1H; H-6), 4.50 (dt, J = 10, 3.8 Hz, 1H; H-5), 4.58 (ddd, J = 5, 5, 2.5 Hz, 1H; H-1); H,H-COSY-90 (500 HHz, DMSO-d_6, 130 °C) crosspeaks: δ_x/δ_y = 1.74−1.80/3.30, 1.74−1.80/3.64, 1.74−1.80/4.58, 1.81−1.87/3.30, 1.81−1.87/3.64, 1.81−1.87/4.58, 2.27/2.62, 2.27/4.50, 2.62/4.50, 3.30/3.64, 3.78/4.50, 3.78/4.58; ^{13}C-NMR (DMSO-d_6, 126 MHz, 130 °C) δ 20.80, 27.46, 27.63, 29.19, 31.74, 38.80, 46.13, 55.42, 67.33, 70.44, 78.70, 79.05, 96.92, 155.25, 169.50; IR (film, KBr) ν 29.86 s, 2835 m, 2900 m, 1720 vs, 1689 vs, 1451 m, 1379 vs, 1365 vs, 1303 s, 1262 s, 1213 s, 1159 vs, 1122 s, 1031 s, 982 s, 954 s, 845 s, 777 m, 547 m cm^{-1}; MS (80 eV, EI, 100 °C) *m/z* 371 (3.9), 356 (2.8), 313 (1.6), 271 (2.9), 244 (12.3), 213 (3.3), 198 (1.5), 184 (5.1), 169 (16.5), 157 (6.1), 122 (2.1), 113 (100), 69 (43.5), 57 (49.7). Anal. Calcd for $C_{19}H_{33}NO_6$ (371.47): C, 61.43; H, 8.94; N, 3.77. Found: C, 61.24; H, 8.96; N, 3.81. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(3*S*)-3-Hydroxy-3[(2*S*,3*R*)-3-hydroxy-2-pyrrolidinyl]propanoic Acid ((+)-1). 18 (0.7 g, 2.2 mmol) in CH_2Cl_2 (100 mL) was treated with a catalytic amount of camphor-10-sulfonic acid and refluxed for 45 min. The resulting mixture was concentrated, filtered through silica gel with CH_2Cl_2/MeOH 94:6 as the eluent, and treated with trifluoracetic acid in MeOH (10%, 100 mL) at rt for 6 h. After being evaporated to dryness, the residue was treated several times with ion exchange resin (Dowex 50W × 4). After removal of the solvent, **(+)-1** (300 mg, 80%) was isolated as colorless powder (mp: 224−227 °C, dec): $[\alpha]^{20}_D = +4.7$ (c = 1.3, H_2O) (lit.[6a] $[\alpha]^{20}_D = -4.8$ (c = 0.5, H_2O); lit.[6b] $[\alpha]^{20}_D = -4.1$ (c = 0.5, H_2O) for **(−)-1**); ^{1}H-NMR (250 MHz, D_2O) δ 2.14 (ddt, J = 13.5, 7.5, 3 Hz, 1H), 2.26 (ddt, J = 13.5, 10.5, 3.5 Hz, 1H), 2.44 (dd, J = 15.5, 8 Hz, 1H), 2.65 (dd, J = 15.5, 3.5 Hz, 1H), 3.40−3.58 (m, 3H), 4.32 (m_c, 1H), 4.50 (dt, J = 3.5, 1.5 Hz, 1H); IR (film, KBr) ν = 3300 vs (br), 2800 s (br), 1640 vs, 1545 m, 1412 s, 1342 s, 1140 m, 1020 m, 843 w, 760 s, 620 s cm^{-1}; MS (80 eV, EI, 120 °C) *m/z* 175 (0.9), 157 (32.7), 139 (12.3), 131 (43.2), 113 (23.2), 95 (5.3), 71 (44.2), 44 (100). Anal. Calcd for $C_7H_{13}NO_4$ (175.18): C, 47.99; H, 7.48; N, 8.00. Found: C, 48.04; H, 7.39; N, 7.84.

(2*S*,3*S*)-*N*-(Benzyloxycarbonyl)-2-(hydroxymethyl)-3-(*tert*-butyldiphenylsiloxy)pyrrolidine (20). 12 (6 g, 12.8 mmol) and potassium carbonate (8.9 g, 64 mmol) were dissolved in THF/H_2O (3:1, 200 mL) and treated with benzyloxycarbonyl chloride (4.4 g, 26 mmol) at 0 °C under vigorous stirring for 2 h. The reaction mixture was concentrated and partitioned between H_2O (200 mL) and ether (3 × 200 mL). The combined organic layers were washed with brine (30 mL), concentrated in vacuo, and purified by flash column chromatography (hexane/EtOAc, 10:1) to give (2*S*,3*S*)-*N*-(benzyloxycarbonyl)-2-[(*tert*-butyldimethylsiloxy)methyl]-3-(*tert*-butyldiphenylsiloxy)pyrrolidine (7.3 g, 95%) as a colorless viscous liquid: $[\alpha]^{20}_D = -3.1$ (c = 2.9, $CHCl_3$); ^{1}H-NMR (270 MHz) δ 0.00 + 0.04 + 0.06 (three s, all in all 6H), 0.92 + 0.95 (two s, all in all 9H), 1.12 (s, 9H), 1.32 (mc, 1H), 1.74 (m_c, 1H), 2.16−2.32 (m, 1H), 3.2 (quint, J = 9.5 Hz, 1H), 3.48 (t, J = 10 Hz, 1H), 3.46 + 3.76 (two m_c, all in all 1H), 3.92−4.00 (m, 1H), 4.08 (mc, 1H), 4.36 (m_c, 1H), 5.12 (s (br), 2H), 7.28−7.48 (m, 11H), 7.68−7.76 (m, 4H). (rotameric signal split); ^{13}C-NMR (63 MHz) δ −5.65, 14.07, 18.07, 19.17, 22.59, 25.81, 26.81, 31.37, 31.52, 32.20, 43.71, 43.93, 59.26, 60.10, 60.16, 60.48, 66.35, 66.48, 71.90, 72.51, 127.57, 127.85, 127.98, 128.32, 129.77, 133.36, 133.77, 135.56, 135.68, 136.99, 154.57; MS (80 eV, EI, 150 °C) *m/z* 604 (0.2), 603 (0.3), 588 (2.1), 546 (100), 502 (8.6), 410 (5.2), 378 (8.1), 195 (5.9), 91 (67.9). Anal. Calcd for $C_{35}H_{49}NO_4Si_2$ (603.9474): C, 69.61; H, 8.18; N, 2.32. Found: C, 68.98; H, 8.05; N, 2.55. The fully protected amino alcohol (7.0 g, 11.6 mmol) was dissolved in acetic acid/H_2O (15:1−15:5, 200 mL) and stirred at rt for 36 h. The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography (hexane/EtOAc, 6:1) to give **20** (5.45 g, 96%) as a colorless visocus oil: $[\alpha]^{20}_D = -11.2$ (c = 1.3, $CHCl_3$); ^{1}H-NMR (DMSO-d_6, 250 M Hz, 60 °C) δ 1.08 (s, 9H), 1.78 (m_c, 1H), 1.92−2.10 (m, 1H), 3.16−3.28 (m, 1H), 3.32−3.44 (dt, J_1 = 10 Hz, J_2 = 3.5 Hz, 1H), 3.68−3.76 (m, 1H), 3.84 (m_c, 2H), 4.08 (m_c, 1H), 4.44 (dt, J_1 = 8 Hz, J_2 = 7.5 Hz, 1H), 5.06 (s, 2H), 7.24−7.48 (m, 11H), 7.64−7.72 (m, 4H); ^{13}C-NMR (DMSO-d_6, 63 MHz) δ 18.75, 26.65, 31.83, 43.34, 58.36, 61.15, 65.68, 72.05, 127.77, 128.27, 129.88, 132.83, 133.34, 135.18, 137.00, 154.25; IR (film, KBr) ν 3431 m (br), 3071 m, 3050 m, 2959 s, 2931 s, 2892 s, 2858 s, 1696 vs, 1674 vs, 1589 w, 1473 m, 1405 vs (br), 1256 m, 1173 s, 1113 vs, 1086 s, 007 m, 822 s, 703 vs, 612 s, 505 s cm^{-1}; MS (80 eV, EI, 150 °C) *m/z* 424 (0.5), 382 (1.9), 368 (6.8), 342 (21.6), 324 (15.6), 290 (15.5), 264 (86.5), 220 (34.6), 199 (36.4), 135 (16.6), 57 (100). Anal. Calcd for $C_{29}H_{35}NO_4Si$ (489.6853): C, 71.13; H, 7.20; N, 2.86. Found: C, 71.43; H, 7.02; N, 3.23.

(2*R*,3*S*)-*N*-(Benzyloxycarbonyl)-2-formyl-3-(*tert*-butyldiphenylsiloxy)pyrrolidine (21). Alcohol **20** (1.0 g, 2.1 mmol) was oxidized as desribed for **13** to give aldehyde **21** as a colorless oil: $[\alpha]^{20}_D = +71.2$ (c = 1.6, $CHCl_3$); ^{1}H-NMR (500 MHz) δ 1.04 (s, 9 H; $C(CH_3)_3$), 1.72 (m_c, 2 H; 4-H), 3.42+3.51 (two dt, J_1 = 8 Hz, J_2 = 6 Hz, 1 H; 5-H_a), 3.70 + 3.76 (jeein dt, J_1 = 10 Hz, J_2 = 6 Hz, 1 H; 5-H_b), 4.12 + 4.24 (two dd, J_1 = 6 Hz, J_2 = 3.5 Hz, 1 H; 2-H), 4.70 (m_c, 1 H; 3-H), 5.10−5.22 (m, 2 H, benzyl-CH_2), 7.22−7.48 (m, 11 H; aromatic-H), 7.60−7.70 (m, 4 H; aromatic-H), 9.65 + 9.75 (two d, J = 3.5 Hz, 1 H; aldehyde-H); H,H-COSY-90 (500 MHz) crosspeaks δx/δy 1.72/3.42, 1.72/3.51, 1.72/3.70, 1.72/3.76, 1.72/4.70, 3.42/3.70, 3.51/3.76, 4.12/4.70, 4.12/9.65, 4.24/4.70, 4.24/9.75; ^{1}H-NMR (DMSO-d_6, 250 MHz, 60 °C) δ 1.02 (s, 9 H; $C(CH_3)_3$), 1.80 (m_c, 2 H; 4-H), 3.44 (m_c, 1 H; 5-H), 3.60 (m_c, 1 H; 5-H), 4.26 (dd, J_1 = 6 Hz, J_2 = 2 Hz, 1 H; 2-H), 4.82 (dt, J_1 = 6.3 Hz, J_2 = 6 Hz, 1 H; 3-H), 5.08 (s, 2 H; $-CH_2Ph$), 7.24−7.52 (m, 11 H; aromatic-H), 7.60−7.68 (m, 4 H; aromatic-H), 9.66 (d, J = 2 Hz, 1 H; aldehyde-H); ^{13}C-NMR (DMSO-d_6, 63 MHz) δ 18.64, 26.46, 32.34, 33.11, 44.04, 44.50, 66.23, 67.64, 68.06, 74.57, 75.46, 127.25, 127.85, 128.27, 130.07, 131.89, 132.78, 135.17, 136.41, 136.52, 153.65, 154.38; H,H-COSY-90 (DMSO-d_6, 250 MHz) crosspeaks δx/δy 1.80/3.44, 1.80/3.60, 1.80/4.82, 4.26/4.82, 4.26/9.66; IR (film, KBr) ν 3436 s (br), 3070 m, 3047 m, 3032 m, 2954 s, 2931 s, 2891 s, 2858 s, 1700 vs, 1681 vs, 1588 w, 1471 m, 1427 vs, 1359 s, 1112 vs, 823 m, 740 s, 701 vs, 615 s, 505 s cm^{-1}; MS (80 eV, EI, 150 °C) *m/z* 472 (3.9), 446 (23.9), 428 (9.3), 402 (6.3), 338 (2.9), 278 (2.9), 250 (3.0), 234 (11.3), 199 (5.1), 183 (3.5), 135 (5.0), 91 (100). Anal. Calcd for $C_{29}H_{33}NO_4Si$ (487.6695): C, 71.42; H, 6.82; N, 2.87. Found: C, 71.44; H, 6.79; N, 2.92.

(2*R*,3*S*)-*N*-(Benzyloxycarbonyl)-3-(*tert*-butyldiphenylsiloxy)pyrrolidine-2-carboxylic Acid (22). Alcohol **20** (5.2 g, 10.6 mmol) dissolved in acetone (100 mL) was treated dropwise with Jones reagent (freshly prepared from CrO_3 (1 g), H_2SO_4 (1.4 g) and H_2O (6 mL)) under vigorous stirring at

0 °C until a lasting orange color was obtained. 2-Propanol (1 mL) was added, and the mixture was filtered through Celite and washed with acetone/HOAc 20:1. The solvents were evaporated, and the residue was purified by flash column chromatography (CH_2Cl_2/ MeOH/HOAc 94:5:1) to give **22** (4.9 g, 92%) as colorless brittle foam: $[\alpha]^{20}_D = -35.9$ (c = 1.8, $CHCl_3$); ^{1}H-NMR (250 MHz) δ 0.96 (s, 9H), 1.70 (m_c, 1H), 1.92−2.08 (m, 1H), 3.16 (dd, J_1 = 17.5 Hz, J_2 = 10 Hz, 1H), 3.60 (m_c, 1H), 4.22−4.48 (m, 2H), 4.86−5.10 (m, 2H), 7.12−7.40 (m, 11H), 7.56−7.70 (m, 4H), 9.72 (s (br), 1H); ^{13}C-NMR (63 MHz) δ 18.99, 26.71, 31.27, 32.07, 43.82, 44.03, 62.43, 62.76, 67.11, 72.63, 73.43, 127.51, 127.73, 127.78, 128.37, 129.98, 132.47, 133.26, 133.44, 135.71, 135.83, 136.35, 154.35, 154.78, 175.16, 175.61; IR (film, KBr) ν 3441 m (br), 3070 m, 3056 s, 3032 m, 2932 s, 2894 s, 2858 s, 1712 vs (br), 1428 vs, 1361 s, 1194 m, 1113 s, 1054 s, 999 m, 920 m, 855 m, 823 m, 724 s, 703 vs, 612 s, 503 s cm^{-1}; MS (EI, 80 eV, 200 °C) m/z 684 (1.2), 472 (0.5), 446 (15.9), 418 (4.1), 402 (22.7), 374 (7.0), 338 (3.9), 310 (3.6), 278 (6.2), 266 (2.9), 234 (4.8), 199 (18.0), 135 (4.8), 91 (100), 65 (1.3). Anal. Calcd for $C_{29}H_{33}NO_5Si$ (503.6689): C, 69.16; H, 6.60; N, 2.78. Found: C, 69.47; H, 6.41; N, 2.69.

***cis*-(2*R*,3*S*)-3-Hydroxyproline (23).** Acid **22** (2.5 g, 5 mmol) was dissolved in CH_2Cl_2/CF_3CO_2H 100:1 (130 mL) and refluxed for 36−48 h. The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH/HOAc; 85:15:1) to give (2*R*,3*S*)-*N*-(benzyloxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid (1.2 g, 92%) as a colorless brittle foam: $[\alpha]^{20}_D = +31.5$ (c = 1.1, MeOH); ^{1}H-NMR (D_2O/CD_3OD, 500 MHz, 90 °C) δ 2.55 (m_c, 1 H; 4-H_a), 2.67 (m_c, 1H; 4-H_b), 4.07−4.12 (m, 1H; 5-H_a), 4.18−4.24 (m, 1H; 5-H_b), 4.89 (d, J = 10 Hz, 1H; 2-H), 5.15 (q, J = 10 Hz, 1H; 3-H), 5.73 (s (br), 2 H; benzyl-CH_2), 7.94−8.06 (m, 5 H; aromatic-H); H,H-COSY-90 (D_2O/CD_3OD, 500 MHz, 90 °C) crosspeaks δx/δy 2.55/2.67, 2.55/4.07−4.12, 2.55/4.18−4.24, 2.55/5.15, 2.67/4.07−4.12, 2.55/4.18−4.24, 2.67/5.15, 4.07−4.12/4.14−4.24, 4.89/5.15; ^{13}C-NMR (D_2O/CD_3OD, 126 MHz, 90 °C) δ 32.71, 45.25, 66.38, 68.00, 72.08, 128.33, 128.88, 129.39, 137.49, 157.08, 176.68; IR (film, KBr) ν 3392 vs (br), 3093 m, 3037 m, 2983 m, 2960 m, 1685 vs (br), 1600 vs (br), 1433 vs, 1363 s, 1209 s, 1138 s, 973 m, 914 m, 837 m, 800 m, 721 s, 697 s cm^{-1}; MS (80 eV, EI, 250 °C) m/z 249 (1.3), 221 (3.4), 219 (6.3), 159 (11.5), 149 (7.3), 108 (70.6), 91 (100), 79 (35.4), 77 (25.0), 65 (12.6), 51 (12.2), 44 (66.5). Anal. Calcd for $C_{13}H_{15}NO_5$ (265.2652): C, 48.86; H, 5.70; N, 5.28. Found: C, 58.82; H, 5.72; N, 5.32. (2*R*,3*S*)-*N*-(Benzyloxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid (0.4 g 1.5 mmol) was dissolved in MeOH/H_2O 3:1 (50 mL), and a catalytic amount of Pd−C (10%) was added. The mixture was treated with H_2 (1 atm) with vigorous stirring for 3 h at rt. The solvents were removed under reduced pressure, and the residue was filtered through Celite and washed with MeOH/H_2O 3:1. The solvents were evaporated and the residual solid was crystallized from aqueous ethanol to give **23** (170 mg, 91%) as a colorless powder: mp 242−253 °C dec (lit.[11d], mp 245−255 °C); $[\alpha]^{20}_D$ = +93.4 (c = 1.3, H_2O) (lit.[11b], $[\alpha]^{20}_D$ +89.0 (c = 0.7, H_2O)); ^{1}H-NMR (D_2O, 500 MHz) δ 2.02−2.10 (m, 1H), 2.14−2.24 (m, 1H), 3.34 (dt, J = 11.5, 2.9 Hz, 1H), 3.49 (dt, J = 10.6, 7.8 Hz, 1H), 4.00 (d, J = 4.0 Hz, 1H), 4.63 (m, 1 H), ^{13}C-NMR (D_2O, 126 MHz) δ 36.34, 46.54, 70.55, 74.41, 171.84; IR (film, KBr) ν 3250 s, 3080 m, 2849 m, 1630 vs, 1580 s, 1469 s, 1410 m, 1380 m, 1290 m, 1109 m, 870 s cm^{-1}; MS (80 eV, EI, 250 °C) m/z 86 (100), 74 (14.3), 69 (41.2), 57 (6.6). Anal. Calcd for $C_5H_9NO_3$ (131.0582): C, 45.80; H, 6.92; N, 10.68. Found: C, 45.47; H, 6.52; N, 10.45.

Supporting Information Available: ^{1}H-NMR, ^{13}C-NMR, IR, optical rotation data, mass spectral data, and elemental analyses of **7b**, **9b**, **10b**, **11b**, **13b**, **24**, and **25** and preparation procedures of **24** and **25** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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