Stereoselective Synthesis of (2*R*,5*R*)- and (2*S*,5*R*)-5-Hydroxylysine

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A stereoselective synthesis of (2*S*,5*R*)-5-hydroxylysine (**1**) and (2*R*,5*R*)-5-hydroxylysine (**17**), based on a concept involving Williams glycine template methodology and (*R*)-hydroxynitrile lyase for the introduction of chirality at the α-position and the side-chain, respectively, is described. This strategy offers an expeditious route towards orthogonally protected 5-hydroxylysines.

Introduction

Collagen is the major structural protein in mammals and is a key molecule in relation to the mechanical strength of tissues such as bone, cartilage, skin, and tendon.[1] One of the amino acids found in collagen is (2*S*,5*R*)-5-hydroxylysine (**1**). It was first discovered by Van Slyke et al. as a constituent of protein hydrosylates.[2] Its structure was elucidated in 1950[3] and, shortly thereafter, Sheehan and Bolhofer presented the first synthesis of D,L-5-hydroxylysine.[4a] Since then, numerous syntheses have been published, all of them giving mixtures of stereoisomers.[4b−4g] Separation of the four stereoisomers has been achieved by fractional crystallization of 5-hydroxylysine derivatives.[5]

Recently, there has been renewed interest in the stereoselective synthesis of 5-hydroxylysine. Adamczyk et al.[6] started from a derivative of (*S*)-glutamic acid and used a diastereomeric separation to obtain a (2*S*,5*R*)-5-hydroxylysine derivative. Kunz et al.[7] reported an interesting approach, combining the Schöllkopf method[8] to create the α-stereogenic centre, and a Sharpless asymmetric aminohydroxylation[9] to generate the β-ethanolamine moiety of 5-hydroxylysine. This strategy provided a stereoselective route for the synthesis of (2*S*,5*S*)-5-hydroxylysine, but was found to be less suitable for preparation of the naturally occurring (2*S*,5*R*)-isomer.[7]

In our research on the synthesis of collagen cross-links,[10] we employed the Williams glycine template[11] for the introduction of the α-stereogenic centres in the synthesis of 5-hydroxylysylnorleucine (HLNL). However, at that time, we were unable to introduce the 5-hydroxyl function of HLNL in a stereoselective manner.[10]

As a result of our continuing research in this area, we report herein the first fully stereoselective synthesis of (2*S*,5*R*)-5-hydroxylysine (**1**) as well as that of a number of orthogonally protected 5-hydroxylysine derivatives. A convergent strategy, similar to that reported previously for HLNL, has been followed.[10]

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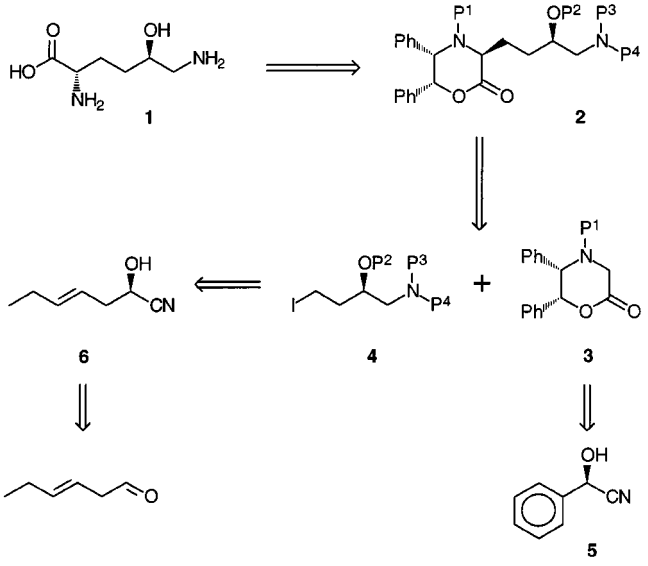
Results and Discussion

The retrosynthesis, depicted in Scheme 1, shows how the orthogonally protected (2*S*,5*R*)-5-hydroxylysine derivatives **2** can be obtained from the enolate of the Williams glycine template **3** through alkylation by electrophiles of type **4**. The latter already contain, in protected form, the β-ethanolamine moiety present in (2*S*,5*R*)-5-hydroxylysine. Template **3** has proved to be an excellent enantioselective reagent for the synthesis of α-amino acids[10−12] and is both commercially available[13] and readily accessible from (*R*)-mandelonitrile (**5**) on a multigram scale.[14] Chiral iodides of type **4** can be synthesized from (*R*)-cyanohydrin **6**, which, in turn, may be obtained through (*R*)-hydroxynitrile lyase[15] mediated addition of HCN[16] to (3*E*)-3-hexenal.



Scheme 1. Retrosynthetic analysis for the synthesis of (2*S*,5*R*)-5-hydroxylysine

In the first step, (3*E*)-3-hexenal was converted into its (*R*)-cyanohydrin **6** (*ee* > 98%, determined as the TBDPS ether) with the aid of purified (*R*)-hydroxynitrile lyase[15] in an aqueous/organic two-phase solvent system.[17] Upon treatment of **6** with TBSCl, *O*-protected cyanohydrin **7a** was obtained (Scheme 2). Conversion into *O*,*N*-protected

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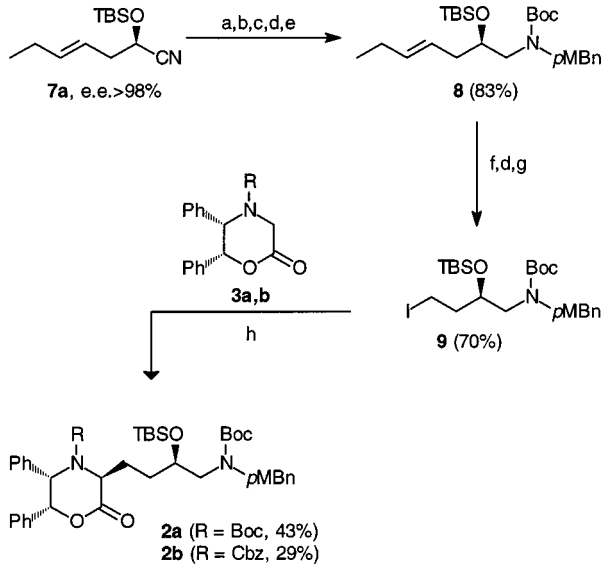
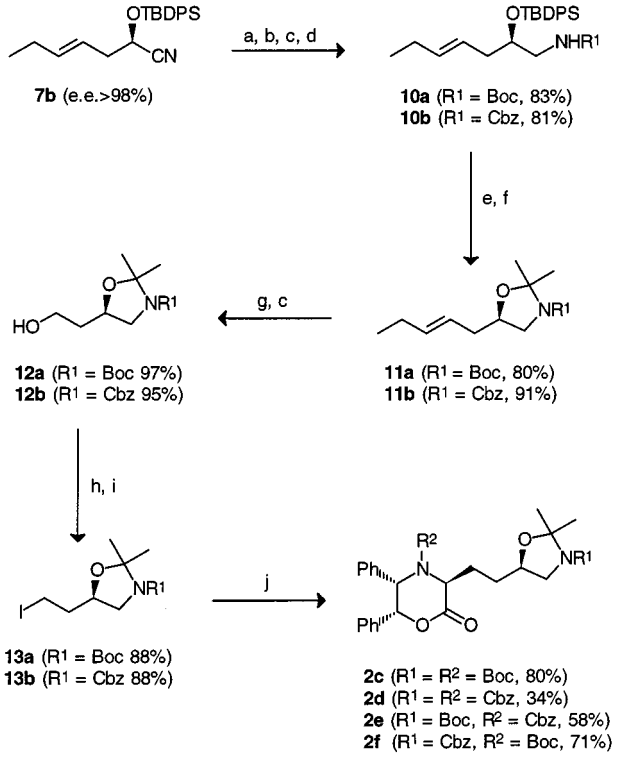
ethanolamine **8** was accomplished by a three-step, one-pot, DIBAL reduction/transimination/$NaBH_4$ reduction procedure,[18] using *p*-methoxybenzylamine (*p*MBn-NH_2) for the transimination with subsequent Boc-protection of the secondary amine. Compound **8** was subjected to ozonolysis, followed by reductive work-up, to afford a primary alcohol. This was then converted to iodide **9** using Garegg's method.[19]



Scheme 2. Synthesis of protected (2*S*,5*R*)-5-hydroxylysine employing the Williams glycine template; reagents: (a) DIBAL, (b) MeOH, (c) *p*MBn-NH_2, (d) $NaBH_4$, (e) Boc_2O, (f) O_3, (g) triiodoimidazole, (h) NaHMDS

In this way, iodide **9** was obtained from cyanohydrin **7a** in 58% overall yield. Alkylation of the Williams glycine template was achieved using a slight modification of Baldwin's method.[12b] Pilot experiments indicated that optimal alkylation results were achieved at temperatures between −50 and −35 °C. The yields, however, were unsatisfactory (29−43%), most probably due to steric factors concerning iodide **9**.[20] It was therefore decided to use a more rigid compound instead of **9**. This demanded several adjustments to the synthesis, as illustrated in Scheme 3. Thus, the TBDPS-protected cyanohydrin **7b** was converted into the *O*,*N*-protected primary amines **10a**,**b**. Subsequent removal of the TBDPS moiety, followed by acid-catalyzed reaction with 2-methoxypropene,[21] afforded oxazolidines **11a**,**b** in excellent yields. Ozonolysis and reductive work-up gave the primary alcohols **12a**,**b** almost quantitatively. When conversion of compounds **12a**,**b** into the corresponding iodides was attempted using triiodoimidazole, no reaction occurred. Alternatively, **12a**,**b** could be converted into their tosylates. After substitution with excess NaI in refluxing acetone, iodides **13a**,**b** were obtained in good overall yields.

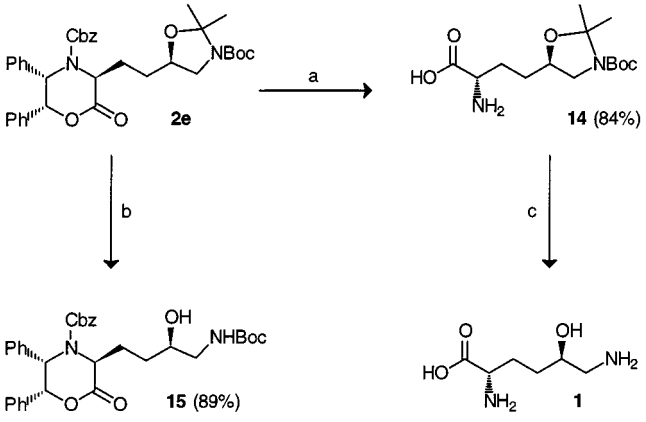
Iodides **13a** and **13b** gave much better yields in the alkylation of Williams glycine templates **3a** and **3b**. In accordance with the literature,[12b] the Boc-protected template **3a** gave higher yields (71−80%) than the Cbz-protected template **3b** (34−58%).



Scheme 3. Synthesis of protected (2*S*,5*R*)-5-hydroxylysines **2c−f**; reagents: (a) DIBAL, (b) MeOH, (c) $NaBH_4$, (d) Boc_2O or Cbz-Cl, (e) TBAF, (f) 2-methoxypropene, (g) O_3, (h) Ts-Cl, (i) NaI, (j) NaHMDS, **3a** or **3b**

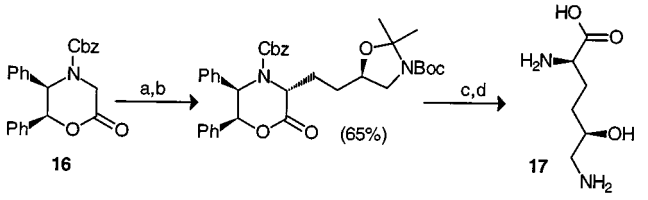
Characterization of compounds **2c−f** was achieved by means of 300 MHz 2D ^1H NMR techniques. Only a single diastereoisomer was observed in each case. This indicates a diastereoselectivity of >96% for the alkylation of the Williams glycine templates.

The versatility of the building blocks **2** is illustrated in Scheme 4. Compound **14**, a suitable intermediate for peptide synthesis, was obtained in 84% yield following reductive deprotection of **2e**. After removal of the isopropylidene moiety in 70% HOAc, *O*-deprotected 5-hydroxylysine **15** was isolated in 89% yield. This compound may well serve as a valuable building block in the synthesis of *O*-glycosylated biologically active compounds.



Scheme 4. Selective deprotection of (2*S*,5*R*)-5-hydroxylysine; reagents: (a) H_2/Pd/C, (b) 70% HOAc, (c) 1.5 M HCl

In order to verify the stereochemistry, compound **14** was deprotected with 1.5 M HCl to obtain **1** (Scheme 4). Both chiral HPLC and ^{1}H NMR analyses of the crude product revealed that the synthesized (2*S*,5*R*)-5-hydroxylysine (**1**) was identical to a commercial sample.[22] By chiral HPLC on a CROWNPACK CR(+) column, we were able to separate (5*R,S*)-hydroxy-D,L-lysine (normal and allo forms, ratio 40:60 according to HPLC) into its four stereoisomers. By analysis of a commercial sample,[22] the (2*S*,5*R*)-5-hydroxylysine peak could be assigned and, by comparison of the peak areas, that of its enantiomer (2*R*,5*S*)-5-hydroxylysine as well. In order to assign the two peaks due to the allo isomers, we alkylated the enantiomer of **3b**, i.e. template **16** (Scheme 5), with iodide **13a**. After deprotection according to the procedure described above, we obtained (2*R*,5*R*)-5-hydroxylysine (**17**), which was eluted as the second peak in the chromatogram of the four isomers. Thus, we were able to establish the order of elution of the four stereoisomers of 5-hydroxylysine on a CROWNPACK CR(+) column as being 2*R*,5*S* → 2*R*,5*R* → 2*S*,5*R* → 2*S*,5*S*. For compounds **1** and **17**, only a single isomer could be detected by HPLC.



Scheme 5. Synthesis of (2*R*,5*R*)-5-hydroxylysine; reagents: (a) NaHMDS, (b) iodide **13a**, (c) H_2/Pd/C, (d) 1.5 M HCl

Conclusion

The synthetic strategy described in this paper offers two expeditious and stereoselective routes towards the synthesis of orthogonally protected 5-hydroxylysines. The first route, leading to TBS-protected 5-hydroxylysines **2a**,**b**, is short, but gives only moderate yields in the final alkylation. The route to **2c−f** is more laborious but offers higher efficiency. As the Williams glycine template is available in both enantiomeric forms and the (*S*)-enantiomers of cyanohydrins **7a**,**b** are also available, either by using an (*S*)-hydroxynitrile lyase[23] in the cyanohydrin synthesis or by inversion of the configuration of (2*R*)-hydroxy-4*E*-heptenenitrile (**6**),[24] all possible stereoisomers of 5-hydroxylysine have become synthetically accessible by this stereoselective route. Protected hydroxylysine **14** is now available for peptide synthesis, while **15** should represent an excellent starting material for *O*-glycosylation reactions.

Experimental Section

General Remarks: TLC analyses were performed on Merck plastic-backed silica gel 60 F_{254} plates. Detection by UV (λ = 254 nm) or by developing with ammonium molybdate (50 g dm^{-3}) and cerium(IV) sulfate (1 g dm^{-3}) in aqueous 10% H_2SO_4 followed by heating to 150 °C, 5% (*w*/*v*) aqueous $KMnO_4$, or Merck ninhydrin spray for TLC followed by heating to 150 °C. Column chromatography was performed on Baker silica gel (0.063−0.200 mm). Solvents for chromatography were distilled before use. Diethyl ether was dried over sodium wire. THF was distilled from $LiAlH_4$. Methanol was dried over molecular sieves (3 Å). Toluene was distilled from and stored over molecular sieves (3 Å). Commercial chemicals were used as received. All reactions were carried out under an inert atmosphere. − Melting points are uncorrected. − ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 instrument, except in the case of compounds **2a−f**, the spectra of which were recorded on a Bruker WM-300 instrument. The latter experiments were performed at elevated temperatures to obtain well-resolved spectra.[25] Unless otherwise stated, samples were examined in $CDCl_3$ solution using TMS as an internal standard for ^{1}H NMR and $CDCl_3$ as internal standard for ^{13}C NMR. Spectra recorded in [D_4]methanol were referenced to residual MeOH/MeOD (δ_H = 4.78, δ_C = 49.0) as internal standard. Spectra recorded in [D_6]DMSO were referenced to (residual protons in) DMSO (δ_H = 2.49, δ_C = 39.5) as internal standard. Enantiomeric excesses (*ee*'s) were determined by HPLC employing a Daicel CHIRALCEL OD column, eluting with hexane (HEX)/2-propanol (IPA) mixtures, or a Daicel CROWNPACK CR(+) column, eluting with aqueous $HClO_4$ solutions. Eluents are specified in each case. − Optical rotations were measured on a Propol automatic polarimeter (Na D line, λ = 589 nm). − ESI-MS was performed on a Perkin−Elmer SCIEX API 165 instrument. ESI-HRMS was performed on a Finnigan MAT 900 instrument.

(3*E*)-3-Hexenal: A solution of 95% (3*E*)-3-hexenol (2.94 g, 27.93 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a suspension of Dess−Martin periodinane[26] (12.90 g, 30.42 mmol) in CH_2Cl_2 (60 mL). After a few minutes, the reaction mixture started to boil and was allowed to do so for about five minutes. The suspension thus obtained was stirred for a further 3 h at room temperature. It was then filtered through a glass frit and the filtrate was washed with saturated aqueous $NaHCO_3$ solution (100 mL) containing $Na_2S_2O_3$ (25 g). The resulting clear solution was dried over $MgSO_4$ and filtered, and the CH_2Cl_2 was removed by distillation (waterbath, max. temp. 60 °C) under argon using a 10 cm Vigreux column. According to ^{1}H NMR spectroscopy, the residue (8.80 g) consisted of a mixture of CH_2Cl_2, diethyl ether, and (3*E*)-3-hexenal in the molar ratio 1.0:1.2:1.2 (estimated 30% *w*/*w* (3*E*)-3-hexenal, ≈ 26.94 mmol). − ^{1}H NMR: δ = 0.97 (t, *J* = 7.3 Hz, 3 H, CH_3), 2.10 (m, 2 H, CH_3CH_2), 3.12 (dd, *J* = 6.6, 2.2 Hz, 2 H, CH_2CHO), 5.58 (m, 2 H, CH=CH), 9.66 (t, *J* = 2.2 Hz, 1 H, CHO). − ^{13}C NMR: δ = 13.1 (CH_3), 25.4 (CH_3CH_2), 46.9 (CH_2CHO), 118.0, 130.6 (C=C), 199.9 (CHO).

(2*R*,4*E*)-2-Hydroxy-4-heptenenitrile (6): NaCN (4.50 g, 91.83 mmol) was dissolved in cold water (45 mL) and the pH was adjusted to 5.2 with citric acid. − (**Caution! Toxic HCN is formed; this operation should be performed in a well-ventilated hood!**). − This HCN buffer was extracted with *tert*-butyl methyl ether (3 × 15 mL) and the combined HCN extracts were placed in a reaction flask. Purified (*R*)-hydroxynitrile lyase[15] (30 mg) was dissolved in 0.1 M citrate buffer (6 mL, pH 5.1) and then added to the HCN extract. At 4 °C, the (3*E*)-3-hexenal solution (*vide supra*) was added and the reaction mixture was stirred overnight at 4 °C. Stirring was then stopped, the aqueous layer was discarded, and the organic layer was dried over $MgSO_4$. After filtration and evaporation of the solvent in vacuo (max. temp. 35 °C), the crude (2*R*,4*E*)-hydroxy-4-heptenenitrile (3.30 g, 94%) was obtained as an orange oil. $[\alpha]_D^{20}$ = +22 (*c* = 1, CH_2Cl_2). − ^{1}H NMR: δ = 1.02 (t, *J* = 7.3 Hz, 3 H,

CH_3), 2.07 (m, 2 H, CH_3CH_2), 2.55 (m, 2 H, CH_2CHO), 4.48 (t, J = 5.8 Hz, 1 H, CHOH), 5.49 (m, 1 H, CH=CH), 5.82 (m, 1 H, CH=CH). − ^{13}C NMR: δ = 13.1 (CH_3), 25.3 (CH_3CH_2), 37.9 (CH_2CH=), 61.0 (CHOH), 119.6 (CN), 120.6, 137.9 (C=C).

(2*R*,4*E*)-2-(*tert*-Butyldimethylsilyl)oxy-4-heptenenitrile (7a): To an ice-cold solution of 97% *tert*-butyldimethylsilyl chloride (2.41 g, 15.51 mmol) and imidazole (1.90 g, 27.94 mmol) in DMF (30 mL) was added crude (2*R*,4*E*)-hydroxy-4-heptenenitrile (1.25 g, 10.00 mmol). After stirring overnight at room temperature, the mixture was poured into water (60 mL) and extracted with diethyl ether (3 × 20 mL). The combined ethereal extracts were washed with water (20 mL) and brine (20 mL). After drying ($MgSO_4$) and evaporation of the solvent, the protected cyanohydrin **7a** was obtained. Purification by column chromatography [silica gel, light petroleum/ethyl acetate, 97.5:2.5) afforded 1.74 g of **7a** (64% based on (3*E*)-3-hexenol] as a colorless oil. $[\alpha]_D^{20}$ = +29 (c = 1, CH_2Cl_2). − ESI-MS: m/z = 262.1 $[M + Na]^+$. − ^{1}H NMR: δ = 0.13 (s, 3 H, CH_3Si), 0.17 (s, 3 H, CH_3Si), 0.89 [s, 9 H, $(CH_3)_3CSi$], 0.99 (t, J = 7.3 Hz, 3 H, CH_3), 2.05 (m, 2 H, CH_3CH_2), 2.46 (t, J = 6.6 Hz, 2 H, $=CHCH_2$), 4.37 (t, J = 6.6 Hz, 1 H, CHOSi), 5.39 (m, 1 H, CH=CH), 5.67 (m, 1 H, CH=CH). − ^{13}C NMR: δ = −5.63, −5.48 [$(CH_3)_2Si$], 13.2 (CH_3), 17.8 [$(CH_3)_3C$], 25.2 [$(CH_3)_3CSi$], 25.6 (CH_3CH_2), 39.4 ($=CHCH_2$), 62.1 (CHOSi), 119.4 (CN), 121.2, 137.6 (C=C).

(2*R*,4*E*)-2-(*tert*-Butyldiphenylsilyl)oxy-4-heptenenitrile (7b): To an ice-cold solution of 97% *tert*-butyldiphenylsilyl chloride (5.92 g, 20.88 mmol) and imidazole (3.17 g, 46.62 mmol) in DMF (40 mL) was added crude (2*R*,4*E*)-hydroxy-4-heptenenitrile (1.90 g, 15.20 mmol). After stirring overnight at room temperature, the mixture was poured into water (100 mL) and extracted with diethyl ether (3 × 30 mL). The combined ethereal extracts were washed with water (30 mL) and brine (30 mL). After drying over $MgSO_4$ and evaporation of the solvent, the protected cyanohydrin **7b** was obtained. Purification by column chromatography afforded 4.41 g [76% based on (3*E*)-3-hexenol] as a colorless oil. $[\alpha]_D^{20}$ = +19 (c = 1, CH_2Cl_2). − HPLC: CHIRALCEL OD, eluent hexane/2-propanol, 99.75:0.25, 1.0 mL/min, UV 254 nm: (*R*)-**10** t_R = 5.48 min, (*S*)-**10** t_R = 8.21 min, *ee* >98%. − ESI-MS: m/z = 364.2 $[M + H]^+$, 386.1 $[M + Na]^+$. − ^{1}H NMR: δ = 0.95 (t, J = 7.3 Hz, 3 H, CH_3), 1.09 [s, 9 H, $(CH_3)_3CSi$], 2.01 (m, 2 H, CH_3CH_2), 2.42 (m, 2 H, $=CHCH_2$), 4.30 (t, J = 6.6 Hz, 1 H, CHOSi), 5.36 (m, 1 H, CH=CH), 5.56 (m, 1 H, CH=CH), 7.40 (m, 6 H, arom.), 7.67 (m, 4 H, arom.). − ^{13}C NMR: δ = 13.4 (CH_3), 19.2 [$(CH_3)_3CSi$], 25.6 (CH_3CH_2), 26.7 [$(CH_3)_3CSi$], 39.4 ($=CHCH_2$), 63.1 (CHOSi), 119.0 (CN), 121.2, 137.9 (C=C), 128.0, 130.4, 131.6, 132.0, 135.7, 135.8 (arom.).

(2*R*,4*E*)-2-(*tert*-Butyldimethylsilyl)oxy-1-(*p*-methoxybenzyl)amino-4-heptene: To a cooled (−80 °C) solution of nitrile **7a** (1.65 g, 6.90 mmol) in dry diethyl ether (50 mL), DIBAL (11.7 mL, 1.0 M in hexane) was added dropwise and the mixture was allowed to warm to −5 °C. After cooling to −95 °C, dry methanol (14 mL) was added followed, after five minutes, by *p*-methoxybenzylamine (3.80 mL, 29.12 mmol). The cooling bath was then removed and the reaction mixture was stirred at room temperature for 2.5 hours. After cooling to −3 °C, $NaBH_4$ (0.69 g, 18.16 mmol) was added. The resulting mixture was stirred overnight at room temperature and then poured into 0.4 M NaOH (75 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aqueous $KHSO_4$ (1 M, 50 mL), NaOH (0.8 M, 40 mL), and brine (40 mL). The organic phase was then dried ($MgSO_4$), filtered, and concentrated in vacuo to yield the crude amine. $[\alpha]_D^{20}$ = −15 (c = 1, CH_2Cl_2). − ESI-MS: m/z = 364.4 $[M + H]^+$. − ^{1}H NMR: δ = 0.12 (s, 3 H, CH_3Si), 0.13 (s, 3 H, CH_3Si), 0.98 [s, 9 H, $(CH_3)_3CSi$], 1.03 (t, J = 7.3 Hz, 3 H, CH_3), 2.06 (m, 2 H, CH_3CH_2), 2.27 (m, 2 H, $=CHCH_2$), 2.68 (m, 2 H, CH_2N), 3.45 (m, 1 H, CHOSi), 3.72 (m, 2 H, $PhCH_2$), 3.87 (s, 3 H, OCH_3), 5.49 (m, 2 H, CH=CH), 6.93 (d, J = 8.8 Hz, 2 H, arom.), 7.33 (d, J = 3.7 Hz, 2 H, arom.). − ^{13}C NMR: δ = −5.3 [$(CH_3)_2Si$], 13.4 (CH_3), 17.8 [$(CH_3)_3CSi$], 25.4 (CH_3CH_2), 25.6 [$(CH_3)_3CSi$], 38.9 ($=CHCH_2$), 53.0 (CH_2N), 54.2 ($PhCH_2$), 54.8 (OCH_3), 71.6 (CHOSi), 113.4, 113.6, 128.8, 132.3, 158.3 (arom.), 124.8, 134.3 (C=C).

(2*R*,4*E*)-2-(*tert*-Butyldimethylsilyl)oxy-1-[(*tert*-butyloxycarbonyl)(*p*-methoxybenzyl)]amino-4-heptene (8): Crude (2*R*,4*E*)-2-(*tert*-butyldimethylsilyl)oxy-1-(*p*-methoxybenzyl)amino-4-heptene (6.90 mmol) was dissolved in CH_2Cl_2 (35 mL). Diisopropylethylamine (3.50 mL, 20.13 mmol) and di-*tert*-butyl dicarbonate (3.00 g, 13.76 mmol) were added and the reaction mixture was stirred for 16 h at room temperature. After evaporation of the solvent, the residual oil was subjected to silica gel chromatography (0 →10% diethyl ether/light petroleum) to afford 2.65 g (83%) of compound **8**. $[\alpha]_D^{20}$ = −23 (c = 1, CH_2Cl_2). − ESI-MS: m/z = 464.4 $[M + H]^+$. − ^{1}H NMR: δ = 0.01 (s, 3 H, CH_3Si), 0.05 (s, 3 H, CH_3Si), 0.91 [s, 9 H, $(CH_3)_3CSi$], 1.12 (t, J = 8.7 Hz, 3 H, CH_3), 1.53 [s, 9 H, $(CH_3)_3CO$], 1.98 (m, 2 H, CH_3CH_2), 2.11 (t, J = 6.6 Hz, 2 H, $=CHCH_2$), 2.85 (m, 2 H, CH_2N), 3.33 (m, 1 H, CHOSi), 3.80 (s, 3 H, OCH_3), 4.21 (d, J = 14.7 Hz, 1 H, $PhCH_2$), 4.63 (d, J = 14.7 Hz, 1 H, $PhCH_2$), 5.42 (m, 2 H, CH=CH), 6.85 (d, J = 8.1 Hz, 2 H, arom.), 7.17 (d, J = 8.1 Hz, 2 H, arom.). − ^{13}C NMR: δ = −4.8 [$(CH_3)_2Si$], 13.5 (CH_3), 17.8 [$(CH_3)_3CSi$], 25.4 (CH_3CH_2), 25.6 [$(CH_3)_3CSi$], 28.3 [$(CH_3)_3CO$], 39.0 ($=CHCH_2$), 51.9 (CH_2N), 54.9 (OCH_3), 60.1 ($PhCH_2$), 71.5 (CHOSi), 113.6, 128.8, 128.9, 130.6, 158.1 (arom.), 124.5, 134.6 (C=C), 155.4 (C=O).

(2*R*)-2-(*tert*-Butyldimethylsilyl)oxy-1-[(*tert*-butyloxycarbonyl)(*p*-methoxybenzyl)]amino-4-butanol: A solution of olefin **8** (2.04 g, 4.40 mmol) in CH_2Cl_2 (100 mL) and MeOH (5 mL) was cooled to −70 °C and ozone was passed through it until a blue color persisted. Stirring was continued for a further 30 min. at −70 °C and then a stream of oxygen was bubbled through the solution to remove the excess ozone. $NaBH_4$ (0.28 g, 7.37 mmol) was added and, after stirring overnight at room temperature, the reaction mixture was poured into water (60 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel column chromatography (0 → 20% ethyl acetate in light petroleum) yielded the title compound as a colorless oil (1.63 g, 84%). $[\alpha]_D^{20}$ = −17 (c = 1, CH_2Cl_2). − ESI-MS: m/z = 440.0 $[M + H]^+$, 462.3 $[M + Na]^+$. − ^{1}H NMR: δ = 0.07 (s, 3 H, CH_3Si), 0.09 (s, 3 H, CH_3Si), 0.91 [s, 9 H, $(CH_3)_3CSi$], 1.46 [s, 9 H, $(CH_3)_3CO$], 1.68 (m, 2 H, CH_2), 1.78 (m, 1 H, CH_2N), 3.09 (m, 1 H, CH_2N), 3.49 (m, 1 H, CHOSi), 3.74 (t, J = 7.3 Hz, 2 H, CH_2OH), 3.80 (s, 3 H, OCH_3), 4.10 (br. s, 1 H, OH), 4.26 (d, J = 16.1 Hz, 1 H, $PhCH_2$), 4.61 (d, J = 15.4 Hz, 1 H, $PhCH_2$), 6.86 (d, J = 8.0 Hz, 2 H, arom.), 7.14 (d, J = 8.0 Hz, 2 H, arom.). − ^{13}C NMR: δ = −5.3 [$(CH_3)_2Si$], 17.8 [$(CH_3)_3CSi$], 25.4 [$(CH_3)_3CSi$], 27.9 [$(CH_3)_3CO$], 37.5 (CH_2), 51.7 (CH_2N), 54.6 (OCH_3), 58.4 ($PhCH_2$), 59.8 (CH_2OH), 68.6 (CHOSi), 79.3 [$(CH_3)_3CO$], 113.4, 127.9, 128.5, 130.0, 158.4 (arom.), 155.4 (C=O).

(2*R*)-2-(*tert*-Butyldimethylsilyl)oxy-1-[(*tert*-butyloxycarbonyl)(*p*-methoxybenzyl)]amino-4-iodobutane (9): The aforementioned alcohol (0.44 g, 1.00 mmol), imidazole (0.14 g, 2.06 mmol), and triiodoimidazole (0.71 g, 1.58 mmol) were co-evaporated with dry toluene (2 × 5 mL). The residue was redissolved in toluene (15 mL) and

triphenylphosphane (1.00 g, 3.81 mmol) was added. The reaction mixture was refluxed for 15 min., after which TLC indicated complete conversion of the starting material. At room temperature, the obtained solids were dissolved by adding acetone (5 mL) and 10% aqueous $NaHCO_3$ (5 mL). The resulting mixture was diluted with diethyl ether (20 mL) and washed with $Na_2S_2O_3$ (10 mL, 1 M) and $NaHCO_3$ (10 mL, 1 M). The ether layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and the residual oil was subjected to silica gel chromatography. Elution with diethyl ether/toluene (0 → 10%) afforded 0.99 g (83%) of iodide **9** as a yellow oil. $[\alpha]_D^{20} = +4.4°$ (*c* = 1, CH_2Cl_2). − ESI-MS: *m*/*z* = 550.5 $[M + H]^+$, 572.2 $[M + Na]^+$. − ^1H NMR: δ = 0.04 (s, 3 H, CH_3Si), 0.09 (s, 3 H, CH_3Si), 0.88 [s, 9 H, $(CH_3)_3CSi$], 1.48 [s, 9 H, $(CH_3)_3CO$], 1.99 (m, 2 H, CH_2), 3.17 (m, 4 H, CH_2, CH_2I), 3.80 (s, 3 H, OCH_3), 3.94 (m, 1 H, CHOSi), 4.31 (d, *J* = 15.4 Hz, 1 H, PhC*H*$_2$), 4.54 (d, *J* = 15.4 Hz, 1 H, PhC*H*$_2$), 6.86 (d, *J* = 8.8 Hz, 2 H, arom.), 7.14 (m, 2 H, arom.). − ^{13}C NMR: δ = −4.8 [$(CH_3)_2Si$], 1.6 (CH_2I), 17.6 [$(CH_3)_3CSi$], 25.5 [(CH_3)$_3$CSi], 28.1 [(CH_3)$_3$CO], 39.2 (CH_2), 50.7 (CH_2N), 51.1 (Ph*C*H$_2$), 54.6 (OCH_3), 70.3 (CHOSi), 79.4 [$(CH_3)_3CO$], 113.6, 128.0, 128.6, 130.4, 158.6 (arom.), 155.2 (C=O).

Alkylation of the Williams Template (General Procedure): The appropriate Williams glycine template (1.50 mmol) and 15-crown-5 (1.60 mL, 8.06 mmol) were co-evaporated twice with toluene and subsequently dissolved in dry THF (30 mL). At −78 °C, sodium bis(trimethylsilyl)amide (1.50 mL, 1.50 mmol, 1 M in THF) was added dropwise. After 5 min., a solution of the appropriate iodide (1.20 mmol) in THF (10 mL) was added dropwise over a period of 5 min. at −70 °C. The mixture was then stirred for 3 h at −50 → −35 °C. The reaction was subsequently quenched by adding a mixture of EtOAc (20 mL) and water (5 mL) and the resulting mixture was allowed to warm to room temperature. After dilution with EtOAc (50 mL), washing with water (20 mL) and brine (20 mL), drying over $MgSO_4$, and evaporation of the solvent, the crude product was obtained. Purification by column chromatography (silica gel, light petroleum/ethyl acetate mixtures) afforded the pure protected hydroxylysines **2**.

***tert*-Butyl (3′*R*,3*S*,5*S*,6*R*)-3-{3′-(*tert*-Butyldimethylsilyloxy)-4′-[*tert*-butyloxycarbonyl(*p*-methoxybenzyl)amino]butyl}-2-oxo-5,6-diphenylmorpholine-4-carboxylate (2a):** From template **3a** (0.54 mmol) and iodide **9** (0.51 mmol), compound **2a** (170 mg) was obtained in 43% yield. $[\alpha]_D^{20} = -13$ (*c* = 0.9, CH_2Cl_2). − ESI-HRMS: *m*/*z* = 775.43876 ± 0.00294 $[M + H]^+$; calcd. 775.43537. − ^1H NMR ([D$_6$]DMSO, 120 °C): δ = 0.06 (s, 3 H, CH_3Si), 0.10 (s, 3 H, CH_3Si), 0.90 [s, 9 H, $(CH_3)_3CSi$], 1.17 [br. s, 9 H, $(CH_3)_3CO$], 1.40 [s, 9 H, $(CH_3)_3CO$], 1.68 (m, 2 H, CH_2), 2.13 (m, 2 H, CH_2), 3.08 (dd, *J* = 6.7, 14.1 Hz, 1 H, CH_2N), 3.28 (dd, *J* = 5.9, 14.1 Hz, 1 H, CH_2N), 3.73 (s, 3 H, OCH_3), 4.03 (m, 1 H, CHOSi), 4.39 (AB, *J* = 15.4 Hz, 2 H, PhC*H*$_2$), 4.76 (t, *J* = 7.2 Hz, 1 H, CHN), 5.17 (d, *J* = 2.8 Hz, 1 H, PhC*H*N), 6.12 (d, *J* = 2.8 Hz, 1 H, PhC*H*O), 6.56 (s, 1 H, arom.), 6.59 (s, 1 H, arom.), 6.88 (d, *J* = 8.7 Hz, 2 H, arom.), 7.16 (m, 10 H, arom.). − ^{13}C NMR ([D$_6$]DMSO, 95 °C): δ = −5.3, −5.2 [$(CH_3)_2Si$], 17.0 [(CH_3)$_3$CSi] 25.2 [(CH_3)$_3$CSi], 27.0, 27.5 [(CH_3)$_3$CO], 29.2, 30.7 (CH_2), 50.2 (CH_2N), 51.1 (OCH_3), 56.3 (C=O*C*HN), 59.9 (Ph*C*HN), 69.5 (CHOSi), 77.8 (Ph*C*HO), 78.6, 79.8 [$(CH_3)_3CO$], 113.6, 125.8, 126.7, 127.1, 127.5, 127.8, 130.0, 134.2, 136.4, 154.6 (arom), 152.4, 158.3 (N−C=O), 168.0 (O−C=O).

Benzyl (3′*R*,3*S*,5*S*,6*R*)-3-{3′-(*tert*-Butyldimethylsilyloxy)-4′-[*tert*-butyloxycarbonyl(*p*-methoxybenzyl)amino]butyl}-2-oxo-5,6-diphenylmorpholine-4-carboxylate (2b): From template **3b** (0.83 mmol) and iodide **9** (0.83 mmol), compound **2b** (197 mg) was obtained in 29% yield. $[\alpha]_D^{20} = -22$ (*c* = 1, CH_2Cl_2). − ESI-MS: *m*/*z* = 809.5 $[M + H]^+$, 831.6 $[M + Na]^+$. − ^1H NMR ([D$_6$]DMSO, 95 °C): δ = 0.06 (s, 3 H, CH_3Si), 0.09 (s, 3 H, CH_3Si), 0.90 [s, 9 H, $(CH_3)_3CSi$], 1.41 [s, 9 H, $(CH_3)_3CO$], 1.69 (m, 2 H, CH_2), 2.17 (m, 2 H, CH_2), 3.07 (dd, *J* = 6.6, 14.6 Hz, 1 H, CH_2N), 3.28 (dd, *J* = 5.9, 14.6 Hz, 1 H, CH_2N), 3.75 (s, 3 H, OCH_3), 4.02 (dd, *J* = 5.8, 11.3 Hz, 1 H, CHOSi), 4.39 (AB, *J* = 15.7 Hz, 2 H, PhC*H*$_2$), 4.80 (dd, *J* = 6.2, 8.0 Hz, 1 H, CHN), 4.98 (s, 2 H, PhC*H*$_2$), 5.30 (d, *J* = 2.9 Hz, 1 H, PhC*H*N), 6.14 (d, *J* = 2.9 Hz, 1 H, PhC*H*O), 6.58 (s, 1 H, arom.), 6.61 (s, 1 H, arom.), 6.90 (d, *J* = 8.8 Hz, 2 H, arom.), 7.13 (m, 16 H, arom.). − ^{13}C NMR ([D$_6$]DMSO, 95 °C): δ = −5.4, −5.3 [$(CH_3)_2Si$], 16.9 [(CH_3)$_3$CSi], 25.0 [(CH_3)$_3$CSi], 27.4 [(CH_3)$_3$CO], 28.8, 30.6 (CH_2), 50.1 (CH_2N), 51.0 (OCH_3), 56.8 (C=O*C*HN), 59.7 (Ph*C*HN), 66.2 (Ph*C*H$_2$), 69.4 (CHOSi), 77.7 (Ph*C*HO), 78.5 [(CH_3)$_3$CO], 113.6, 125.7, 126.6, 126.8, 127.0, 127.3, 127.7, 129.9, 134.0, 135.6, 154.5 (arom.), 148.7, 153.0 (N−C=O), 167.4 (O−C=O).

(2*R*,4*E*)-1-Amino-2-(*tert*-butyldiphenylsilyl)oxy-4-heptene: At −85 °C, DIBAL (20 mL, 1 M in hexane) was added dropwise to a solution of *O*-protected nitrile **7b** (4.29 g, 11.81 mmol) in dry diethyl ether (100 mL). The solution was allowed to warm to −5 °C. After cooling to −95 °C, dry methanol (25 mL) was quickly added, followed by $NaBH_4$ (1.30 g, 34.21 mmol). The cooling bath was then removed and the mixture was stirred at room temperature for 1 h. It was then poured into aqueous 0.6 M NaOH (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield 4.47 g (103%) of the crude amine as a colorless oil. $[\alpha]_D^{20} = -20$ (*c* = 1, CH_2Cl_2). − ESI-MS: *m*/*z* = 368.2 $[M + H]^+$. − ^1H NMR: δ = 0.90 (t, *J* = 8.0 Hz, 3 H, CH_3), 1.07 [s, 9 H, $(CH_3)_3C$], 1.93 (m, 2 H, CH_3CH_2), 2.17 (m, 2 H, =CHC*H*$_2$), 2.65 (m, 2 H, C*H*$_2$NH$_2$), 3.67 (m, 1 H, CHOSi), 5.34 (m, 2 H, C*H*=C*H*), 7.41 (m, 6 H, arom.), 7.66 (m, 4 H, arom.). − ^{13}C NMR: δ = 13.5 (CH_3), 19.1 [(CH_3)$_3$CSi], 25.4 (CH_3CH_2), 26.9 [(CH_3)$_3$CSi], 37.7 (=CH*C*H$_2$), 46.6 (CH_2NH_2), 74.7 (CHOSi), 124.6, 134.4 (C=C), 133.9 (*ipso*), 127.4, 129.5, 135.6, 135.7 (arom.).

(2*R*,4*E*)-2-(*tert*-Butyldiphenylsilyl)oxy-1-(*tert*-butyloxycarbonyl)-amino-4-heptene (10a): The aforementioned crude amine (4.47 g) was dissolved in a two-phase system consisting of CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ solution (100 mL). At 5 °C, Boc_2O (8.20 g, 37.61 mmol) was added and the mixture was stirred vigorously overnight at room temperature. The layers were then separated and the aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, light petroleum/ethyl acetate, 98:2 → 95:5) to yield 4.58 g (83%, based on **7b**) of urethane **10a**. $[\alpha]_D^{20} = -7.2$ (*c* = 1, CH_2Cl_2). − ESI-MS: *m*/*z* = 468.5 $[M + H]^+$, 490.4 $[M + Na]^+$. − ^1H NMR: δ = 0.90 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.07 [s, 9 H, $(CH_3)_3CSi$], 1.41 [s, 9 H, $(CH_3)_3CO$], 1.92 (m, 2 H, CH_3CH_2), 2.12 (t, *J* = 6.2 Hz, 2 H, =CHC*H*$_2$), 3.10 (m, 2 H, CH_2N), 3.77 (m, 1 H, CHOSi), 4.66 (br. s, 1 H, NH), 5.32 (m, 2 H, C*H*=C*H*), 7.41 (m, 6 H, arom.), 7.65 (m, 4 H, arom.). − ^{13}C NMR: δ = 13.5 (CH_3), 19.2 [(CH_3)$_3$CSi], 25.5 (CH_3CH_2), 26.9 [(CH_3)$_3$CSi], 28.2 [(CH_3)$_3$CO], 38.3 (=CH*C*H$_2$), 45.3 (CH_2N), 72.6 (CHOSi), 78.5 [(CH_3)$_3$CO], 124.0, 135.1 (C=C), 127.5, 127.6, 129.6, 133.8, 135.6, 135.7 (arom.), 155.6 (C=O).

(2*R*,4*E*)-2-(*tert*-Butyldiphenylsilyl)oxy-1-(benzyloxycarbonyl)amino-4-heptene (10b): The aforementioned crude amine (1.90 g, 5.18 mmol) was dissolved in CH_2Cl_2 (35 mL). Diisopropylethylamine (1.10 g, 8.10 mmol) and *N*-(benzyloxycarbonyloxy)succinim-

ine (2.01 g, 8.10 mmol) were added. After stirring overnight, the mixture was diluted with diethyl ether (50 mL), washed with water, dried ($MgSO_4$), filtered, and concentrated. The residue was applied to a silica gel column and elution with light petroleum/ethyl acetate (98:2 → 90:10) furnished 2.18 g of urethane **10b** (81% yield based on **7b**). $[\alpha]_D^{20} = -2.3$ (c = 1, CH_2Cl_2). − ESI-MS: m/z = 502.3 [M + H]$^+$, 524.4 [M + Na]$^+$. − ^{1}H NMR: δ = 0.89 (t, J = 7.3 Hz, 3 H, CH_3), 1.05 [s, 9 H, $(CH_3)_3CSi$], 1.91 (m, 2 H, CH_3CH_2), 2.13 (m, 2 H, =CHCH_2), 3.20 (m, 2 H, CH_2N), 3.78 (m, 1 H, CHOSi), 5.04 (s, 2 H, PhCH_2), 5.29 (m, 2 H, CH=CH), 7.35 (m, 11 H, arom.), 7.65 (m, 4 H, arom.). − ^{13}C NMR: δ = 13.2 (CH_3), 18.9 [$(CH_3)_3CSi$], 25.2 (CH_3CH_2), 26.6 [$(CH_3)_3CSi$], 37.8 (=$CHCH_2$), 48.0 (CH_2N), 66.0 (PhCH_2), 72.1 (CHOSi), 123.6, 135.4 (C=C), 127.2, 127.3, 127.5, 128.0, 129.4, 133.4, 135.5, 136.4 (arom.), 155.9 (C=O).

(2*R*,4*E*)-1-(*tert*-Butyloxycarbonyl)amino-4-hepten-2-ol: Urethane **10a** (4.58 g, 9.81 mmol) was dissolved in THF (100 mL). At 5 °C, TBAF (4.80 g, 15.24 mmol) was added. The mixture was stirred overnight, after which TLC showed that the starting material had been completely consumed. Evaporation of the solvent and purification of the residue by column chromatography (silica gel, light petroleum/ethyl acetate, 95:5 for elution of Si compounds, 70:30 for elution of the alcohol) yielded 1.85 g (83%) of the title alcohol. $[\alpha]_D^{20} = -5.4$ (c = 1, CH_2Cl_2). − ESI-MS: m/z = 252.1 [M + Na]$^+$. − ^{1}H NMR: δ = 0.98 (t, J = 7.3 Hz, 3 H, CH_3), 1.45 [s, 9 H, $(CH_3)_3CO$], 2.04 (m, 2 H, CH_3CH_2), 2.17 (m, 2 H, =CHCH_2), 2.32 (br. s, 1 H, OH), 3.02 (m, 1 H, CH_2N), 3.30 (m, 1 H, CH_2N), 3.69 (m, 1 H, C*H*OH), 4.91 (br. s, 1 H, NH), 5.42 (m, 1 H, CH=C*H*), 5.57 (m, 1 H, C*H*=CH). − ^{13}C NMR: δ = 13.3 (CH_3), 25.1 (CH_3CH_2), 28.0 [$(CH_3)_3CO$], 37.7 (=$CHCH_2$), 45.5 (CH_2N), 70.4 (CHOH), 79.4 [$(CH_3)_3CO$], 123.9, 134.5 (C=C), 156.4 (C=O).

(2*R*,4*E*)-1-(Benzyloxycarbonyl)amino-4-hepten-2-ol: Prepared from urethane **10b** (2.18 g, 4.35 mmol) as described above. Purification by silica gel column chromatography (light petroleum/ethyl acetate, 90:10 → 60:40) gave the title alcohol in 94% yield (1.08 g). $[\alpha]_D^{20} = -9.0$ (c = 1, CH_2Cl_2). − ESI-MS: m/z = 263.9 [M + H]$^+$, 285.9 [M + Na]$^+$. − ^{1}H NMR: δ = 0.98 (t, J = 7.3 Hz, 3 H, CH_3), 2.11 (m, 5 H, CH_3CH_2, =$CHCH_2$, OH), 3.09 (m, 1 H, CH_2N), 3.37 (m, 1 H, CH_2N), 3.71 (m, 1 H, C*H*OH), 5.11 (s, 2 H, PhCH_2), 5.37 (m, 1 H, CH=C*H*), 5.60 (m, 1 H, C*H*=CH), 7.36 (s, 5 H, arom.). − ^{13}C NMR: δ = 13.2 (CH_3), 25.1 (CH_3CH_2), 37.5 (=$CHCH_2$), 45.8 (CH_2N), 60.0 (PhCH_2), 70.1 (CHOH), 123.8, 135.0 (C=C), 127.5, 127.9, 136.1 (arom.), 156.7 (C=O).

(5*R*,2*E*)-3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-5-(pent-2-enyl)-oxazolidine (11a): (2*R*,4*E*)-1-(*tert*-Butyloxycarbonyl)amino-4-hepten-2-ol (1.85 g, 8.14 mmol) was dissolved in a mixture of CH_2Cl_2 (20 mL) and 2-methoxypropene (3 mL) and pyridinium *p*-toluenesulfonate (58 mg, 0.23 mmol) was added. TLC analysis after 2.5 h showed that the reaction had reached completion. Saturated aqueous $NaHCO_3$ solution (5 mL) was then added and the mixture was stirred for 10 min. The layers were separated and the organic layer was concentrated. Purification of the residue by column chromatography (silica gel, light petroleum/ethyl acetate, 9:1 → 7:3) afforded **11a** (2.12 g, 97%) as a pale-yellow oil. $[\alpha]_D^{20} = -30$ (c = 1, CH_2Cl_2). − ESI-MS: m/z = 270.0 [M + H]$^+$, 291.9 [M + Na]$^+$. − ^{1}H NMR: δ = 0.97 (t, J = 7.3 Hz, 3 H, CH_3), 1.47 [s, 9 H, $(CH_3)_3CO$], 1.54 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 2.02 (m, 2 H, CH_3CH_2), 2.25 (m, 1 H, =CHCH_2), 2.37 (m, 1 H, =CHCH_2), 3.09 (m, 1 H, CH_2N), 3.62 (m, 1 H, CH_2N), 4.07 (m, 1 H, CHO), 5.40 (m, 1 H, CH=C*H*), 5.55 (m, 1 H, C*H*=CH). − ^{13}C NMR: δ = 13.3 (CH_3), 24.3, 26.3 [$(CH_3)_2C$], 25.2 (CH_3CH_2), 28.0 [$(CH_3)_3CO$], 36.0 (=$CHCH_2$), 50.1 (CH_2N), 73.1 (CHO), 79.0 [$(CH_3)_3CO$], 92.8 [$(CH_3)_2C$], 123.1, 134.9 (C=C), 151.4 (C=O).

(5*R*,2*E*)-3-(Benzyloxycarbonyl)-2,2-dimethyl-5-(pent-2-enyl)-oxazolidine (11b): (2*R*,4*E*)-1-(Benzyloxycarbonyl)amino-4-hepten-2-ol was dissolved in a mixture of acetone (10 mL) and 2,2-dimethoxypropane (30 mL). The pH was adjusted to 5.0 using *p*-toluenesulfonic acid. After stirring overnight at room temperature, the reaction mixture was neutralized with triethylamine and the solvents were evaporated. Purification of the residue by silica gel column chromatography (light petroleum/ethyl acetate, 95:5 → 90:10) furnished oxazolidine **11b** (1.20 g, 97%) as a colorless oil. $[\alpha]_D^{20} = -25$ (c = 1, CH_2Cl_2). − ESI-MS: m/z = 304.1 [M + H]$^+$, 326.1 [M + Na]$^+$. − ^{1}H NMR: δ = 0.96 (t, J = 7.3 Hz, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 2.01 (m, 2 H, CH_3CH_2), 2.22 (m, 1 H, =CHCH_2), 2.41 (m, 1 H, =CHCH_2), 3.14 (m, 1 H, CH_2N), 3.70 (m, 1 H, CH_2N), 4.07 (m, 1 H, CHO), 5.13 (s, 2 H, PhCH_2), 5.36 (m, 1 H, C*H*=CH), 5.58 (m, 1 H, CH=C*H*), 7.36 (m, 5 H, arom.). − ^{13}C NMR: δ = 13.3 (CH_3), 24.3 (CH_3), 25.2 (CH_3CH_2), 26.3 (CH_3), 35.8 (=$CHCH_2$), 50.1 (CH_2N), 66.3 (PhCH_2), 73.2 (CHO), 93.1 [$(CH_3)_2C$], 122.9, 135.1 (C=C), 127.5, 128.0, 136.4 (arom.), 151.8 (C=O).

(5*R*)-3-(*tert*-Butyloxycarbonyl)-5-(1-hydroxyethyl)-2,2-dimethyl-oxazolidine (12a): Alkene **11a** (2.10 g, 7.80 mmol) was dissolved in a mixture of CH_2Cl_2 (60 mL) and MeOH (8 mL). At −78 → −72 °C, ozone was passed through the solution until a blue color persisted. The reaction mixture was stirred for a further 30 min. at −75 °C and then oxygen was passed through it for 5 min. Thereafter, $NaBH_4$ (1.45 g, 38.16 mmol) was added and the resulting mixture was allowed to warm slowly to room temperature and then stirred for a further 2 h. Diethyl ether (100 mL) was added and the solution was washed with water (30 mL) and brine (30 mL). After drying ($MgSO_4$) and evaporation of the solvent, column chromatography (silica gel, light petroleum/ethyl acetate, 1:1) of the residue furnished alcohol **12a** (1.85 g, 97%) as a colorless oil. $[\alpha]_D^{20} = -19$ (c = 1, CH_2Cl_2). − ESI-MS: m/z = 246.0 [M + H]$^+$, 268.0 [M + Na]$^+$. − ^{1}H NMR: δ = 1.47 [s, 9 H, $(CH_3)_3CO$], 1.56 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 1.87 (m, 2 H, CH_2), 2.11 (t, J = 5.1 Hz, 1 H, CH_2N), 3.13 (t, J = 9.5 Hz, 1 H, CH_2N), 3.79 (m, 3 H, CH_2OH), 4.25 (m, 1 H, CHO). − ^{13}C NMR: δ = 24.2, 26.2 [$(CH_3)_2C$], 27.9 [$(CH_3)_3CO$], 35.5 (CH_2), 50.6 (CH_2N), 58.2 (CH_2O), 71.1 (CHO), 79.1 [$(CH_3)_3CO$], 92.4 [$(CH_3)_2C$], 151.5 (C=O).

(5*R*)-3-(Benzyloxycarbonyl)-5-(1-hydroxyethyl)-2,2-dimethyl-oxazolidine (12b): Alcohol **12b** was prepared from **11b** as described for **12a**. Yield 1.06 g (95%). − $[\alpha]_D^{20} = -15$ (c = 1, CH_2Cl_2). − ESI-MS: m/z = 280.0 [M + H]$^+$, 301.9 [M + Na]$^+$. − ^{1}H NMR: δ = 1.54 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 1.87 (m, 2 H, CH_2), 2.15 (t, J = 5.1 Hz, 1 H, CH_2N), 3.18 (t, J = 9.5 Hz, 1 H, CH_2N), 3.70 (m, 3 H, CH_2OH), 4.27 (m, 1 H, CHO), 5.13 (s, 2 H, PhCH_2), 7.36 (m, 5 H, arom.). − ^{13}C NMR: δ = 24.3, 26.3 [$(CH_3)_2C$], 35.2 (CH_2), 50.7 (CH_2N), 58.9 (CH_2O), 66.5 (PhCH_2), 71.8 (CHO), 93.3 [$(CH_3)_2C$], 127.5, 128.1, 136.2 (arom.), 151.9 (C=O).

(5*R*)-3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-5-(1-tosyloxyethyl)oxazolidine: Alcohol **12a** (1.11 g, 4.53 mmol) was dissolved in CH_2Cl_2 (30 mL) containing dry triethylamine (1.80 mL, 12.94 mmol). At −10 °C, TsCl (2.10 g, 11.01 mmol) was added and the reaction mixture was stirred at this temperature for 30 min. and then overnight at 4 °C. Thereafter, the solvent was evaporated and the residue was purified by column chromatography (silica gel, light petroleum/ethyl acetate, 9:1 → 3:1) to afford 1.75 g (97%) of the pure tosylate. $[\alpha]_D^{20} = -4.9$ (c = 1, CH_2Cl_2). − HPLC:

CHIRALCEL OD, eluent hexane/2-propanol, 99:1, 1.2 mL/min, UV 254 nm, (*R*)-tosylate t_R = 25.6 min, (*S*)-tosylate t_R = 21.4 min, *ee* 99%. − ESI-MS: *m*/*z* = 400.1 [M + H]$^+$, 422.2 [M + Na]$^+$. − ^{1}H NMR: δ = 1.41 [s, 6 H, $(CH_3)_2C$], 1.46 [s, 9 H, $(CH_3)_3CO$], 1.93 (m, 2 H, CH_2), 2.46 (s, 3 H, C*H*$_3$Ph), 3.01 (t, *J* = 9.5 Hz, 1 H, CH_2N), 3.63 (br. s, 1 H, CH_2N), 4.08 (m, 1 H, CHO), 4.16 (t, *J* = 6.6 Hz, 2 H, CH_2O), 7.35 (d, *J* = 8.0 Hz, 2 H, arom.), 7.80 (d, *J* = 8.8 Hz, 2 H, arom.). − ^{13}C NMR: δ = 21.2 (*C*H$_3$Ph), 24.4, 26.4 [(*C*H$_3$)$_2$C], 28.0 [(*C*H$_3$)$_3$CO], 32.2 (CH_2), 50.3 (CH_2N), 66.8 (CH_2O), 69.7 (CHO), 79.2 [(CH$_3$)$_3$*C*O], 92.7 [(CH$_3$)$_2$*C*], 127.5, 129.6, 132.6, 144.5 (arom.), 151.5 (C=O).

(5*R*)-3-(Benzyloxycarbonyl)-2,2-dimethyl-5-(1-tosyloxyethyl)-oxazolidine: Prepared from **12b** (1.03 g, 3.70 mmol) as described above. Purification by column chromatography (silica gel, light petroleum/ethyl acetate, 98:2 → 3:2) afforded 1.47 g (91%) of the pure tosylate. $[\alpha]_D^{20}$ = −3.8 (*c* = 1, CH_2Cl_2). − ESI-MS: *m*/*z* = 434.1 [M + H]$^+$, 456.1 [M + Na]$^+$. − ^{1}H NMR: δ = 1.45 (s, 3 H, CH_3), 1.54 (s, 3 H, CH_3), 1.95 (m, 2 H, CH_2), 2.44 (s, 3 H, C*H*$_3$Ph), 3.08 (m, 1 H, CH_2N), 3.71 (m, 1 H, CH_2N), 4.07 (m, 1 H, CHO), 4.16 (t, *J* = 6.6 Hz, 2 H, CH_2O), 5.10 (s, 2 H, PhC*H*$_2$), 7.35 (m, 7 H, arom.), 7.78 (d, *J* = 8.0 Hz, 2 H, arom.) − ^{13}C NMR: δ = 21.0 (*C*H$_3$Ph), 24.1, 26.1 [(*C*H$_3$)$_2$C], 31.9 (CH_2), 50.1 (CH_2N), 65.5 (CH_2O), 67.1 (Ph*C*H$_2$), 69.7 (CHO), 93.2 [(CH$_3$)$_2$*C*], 127.3, 127.5, 128.0, 129.4, 132.3, 136.0, 144.4 (arom.), 151.5 (C=O).

(5*R*)-3-(*tert*-Butyloxycarbonyl)-5-(1-iodoethyl)-2,2-dimethyloxazolidine (13a): (5*R*)-3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-5-(1-tosyloxyethyl)oxazolidine (1.10 g, 2.76 mmol) was dissolved in acetone p.a. (40 mL). NaI (1.97 g, 13.13 mmol) was added and the solution was refluxed for 30 min. A white precipitate was formed. TLC analysis revealed complete conversion of the tosylate. The mixture was cooled in an ice bath and filtered. The filtrate was concentrated to dryness and the white solid residue was triturated three times with dry diethyl ether. Evaporation of the ether afforded 1.02 g of a yellow oil, which was purified by column chromatography (silica gel, light petroleum/ethyl acetate, 9:1) to yield 0.90 g (92%) of colorless iodide **13a**. The compound solidified upon storage at −18 °C; m.p. 59−60 °C. − $[\alpha]_D^{20}$ = −1.8 (*c* = 1, CH_2Cl_2). − ESI-MS: *m*/*z* = 355.9 [M + H]$^+$, 377.9 [M + Na]$^+$. − ^{1}H NMR: δ = 1.47 [s, 9 H, $(CH_3)_3CO$], 1.53 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 2.11 (m, 2 H, CH_2), 3.08 (m, 1 H, CH_2N), 3.25 (t, *J* = 6.3 Hz, 2 H, CH_2I), 3.71 (m, 1 H, CH_2N), 4.14 (m, 1 H, CHO). − ^{13}C NMR: δ = 0.68 (CH_2I), 24.5, 26.5 [(*C*H$_3$)$_2$C], 28.2 [(*C*H$_3$)$_3$CO], 36.9 (CH_2), 49.8 (CH_2N), 73.1 (CHO), 79.2 [(CH$_3$)$_3$*C*O], 92.9 [(CH$_3$)$_2$*C*], 151.5 (C=O).

(5*R*)-3-(Benzyloxycarbonyl)-5-(1-iodoethyl)-2,2-dimethyloxazolidine (13b): Prepared from (5*R*)-3-(benzyloxycarbonyl)-2,2-dimethyl-5-(1-tosyloxyethyl)oxazolidine (1.44 g, 3.33 mmol) as described for **13a**. Purification by column chromatography (silica gel, light petroleum/ethyl acetate, 9:1, afforded 1.28 g (96%) of pure iodide **13b**. $[\alpha]_D^{20}$ = −1.8 (*c* = 1, CH_2Cl_2). − ESI-MS: *m*/*z* = 390.0 [M + H]$^+$, 412.1 [M + Na]$^+$. − ^{1}H NMR: δ = 1.54 (s, 3 H, CH_3), 1.56 (s, 3 H, CH_3), 2.11 (m, 2 H, CH_2), 3.14 (m, 1 H, CH_2N), 3.25 (t, *J* = 6.9 Hz, 2 H, CH_2I), 3.78 (m, 1 H, CH_2N), 4.17 (m, 1 H, CHO), 5.11 (s, 2 H, PhC*H*$_2$), 7.36 (m, 5 H, arom.). − ^{13}C NMR: δ = 0.52 (CH_2I), 24.3, 26.3 [(*C*H$_3$)$_2$C], 36.4 (CH_2), 49.7 (CH_2N), 66.2 (Ph*C*H$_2$), 73.1 (CHO), 93.1 [(CH$_3$)$_2$*C*], 125.9, 127.3, 127.5, 128.0, 136.1 (arom.), 151.4 (C=O).

***tert*-Butyl (5′*R*,3*S*,5*S*,6*R*)-3-[2-(3′-*tert*-Butyloxycarbonyl-2′,2′-dimethyloxazolidin-5′-yl)ethyl]-2-oxo-5,6-diphenylmorpholine-4-carboxylate (2c):** From template **3a** (1.50 mmol) and iodide **13a** (1.20 mmol), compound **2c** (560 mg) was obtained in 80% yield; m.p. 69−71 °C. − $[\alpha]_D^{20}$ = −35 (*c* = 1, CH_2Cl_2). − ESI-HRMS: *m*/*z* = 581.3262 ± 0.0008 [M + H]$^+$, calcd. 581.3227. − ^{1}H NMR ([D$_6$]DMSO, 120 °C): δ = 1.21 [br. s, 9 H, $(CH_3)_3CO$], 1.43 [s, 9 H, $(CH_3)_3CO$], 1.45 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.81 (m, 2 H, CH_2), 2.21 (m, 2 H, CH_2), 3.09 (dd, *J* = 8.7, 10.0 Hz, 1 H, CH_2N), 3.68 (dd, *J* = 6.0, 10.0 Hz, 1 H, CH_2N), 4.17 (m, 1 H, CHO), 4.79 (dd, *J* = 6.1, 9.1 Hz, 1 H, CHN), 5.17 (d, *J* = 2.9 Hz, 1 H, PhC*H*N), 6.19 (d, *J* = 2.9 Hz, 1 H, PhC*H*O), 6.57 (s, 1 H, arom.), 6.59 (s, 1 H, arom.), 7.14 (m, 6 H, arom.), 7.27 (m, 2 H, arom.). − ^{13}C NMR ([D$_6$]DMSO, 95 °C): δ = 24.2, 26.0 [(*C*H$_3$)$_2$C], 27.0, 27.5 [(*C*H$_3$)$_3$CO], 29.0, 29.5 (CH_2), 49.7 (CH_2N), 56.0 (C=O*C*HN), 59.7 (Ph*C*HN), 72.1 (CHO), 77.6 (Ph*C*HO), 78.3, 79.8 [(CH$_3$)$_3$*C*O], 92.0 [(CH$_3$)$_2$*C*], 125.7, 126.6, 127.0, 127.3, 134.2 (arom.), 150.8, 152.2 (N−C=O), 167.8 (O−C=O).

Benzyl (5′*R*,3*S*,5*S*,6*R*)-3-[2-(3′-Benzyloxycarbonyl-2′,2′-dimethyloxazolidin-5′-yl)ethyl]-2-oxo-5,6-diphenylmorpholine-4-carboxylate (2d): From template **3b** (0.64 mmol) and iodide **13b** (0.51 mmol), compound **2d** (111 mg) was obtained in 34% yield. $[\alpha]_D^{20}$ = −17 (*c* = 1.4, CH_2Cl_2). − ESI-MS: *m*/*z* = 649.4 [M + H]$^+$, 671.3 [M + Na]$^+$. − ^{1}H NMR ([D$_6$]DMSO, 95 °C): δ = 1.47 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 1.82 (m, 2 H, CH_2), 2.22 (m, 2 H, CH_2), 3.14 (dd, *J* = 8.8, 10.2 Hz, 1 H, CH_2N), 3.66 (dd, *J* = 5.8, 10.2 Hz, 1 H, CH_2N), 4.17 (m, 1 H, CHO), 4.85 (dd, *J* = 6.6, 8.0 Hz, 1 H, CHN), 5.00 (AB, *J* = 12.4 Hz, 2 H, PhC*H*$_2$), 5.12 (s, 2 H, PhC*H*$_2$), 5.29 (d, *J* = 2.9 Hz, 1 H, PhC*H*N), 6.21 (d, *J* = 2.9 Hz, 1 H, PhC*H*O), 6.59 (s, 1 H, arom.), 6.62 (s, 1 H, arom.), 7.22 (m, 18 H, arom.). − ^{13}C NMR ([D$_6$]DMSO, 95 °C): δ = 23.9, 25.8 [(*C*H$_3$)$_2$C], 28.8, 29.4 (CH_2), 49.5 (CH_2N), 56.4 (C=O*C*HN), 59.6 (Ph*C*HN), 65.3, 66.3 (Ph*C*H$_2$), 72.4 (CHO), 77.6 (Ph*C*HO), 92.4 [(CH$_3$)$_2$*C*], 125.7, 126.7, 127.0, 127.4, 134.1, 135.6 (arom.), 151.2, 159.8 (N−C=O), 167.5 (O−C=O).

Benzyl (5′*R*,3*S*,5*S*,6*R*)-3-[2-(3′-*tert*-Butyloxycarbonyl-2′,2′-dimethyloxazolidin-5′-yl)ethyl]-2-oxo-5,6-diphenylmorpholine-4-carboxylate (2e): From template **3b** (0.65 mmol) and iodide **13a** (0.58 mmol), compound **2e** (208 mg) was obtained in 58% yield; m.p. 176−178 °C. − $[\alpha]_D^{20}$ = −25 (*c* = 1, CH_2Cl_2). − ESI-HRMS: *m*/*z* = 637.2902 ± 0.0012 [M + Na]$^+$, calcd. 637.2890. − ^{1}H NMR ([D$_6$]DMSO, 95 °C): δ = 1.46 [s, 12 H, $(CH_3)_3CO$, CH_3], 1.50 (s, 3 H, CH_3), 1.81 (m, 2 H, CH_2), 2.22 (m, 2 H, CH_2), 3.06 (dd, *J* = 8.8, 9.9 Hz, 1 H, CH_2N), 3.66 (dd, *J* = 5.8, 9.9 Hz, 1 H, CH_2N), 4.13 (m, 1 H, CHO), 4.85 (dd, *J* = 6.6, 7.7 Hz, 1 H, CHN), 5.01 (AB, *J* = 12.4 Hz, 2 H, PhC*H*$_2$), 5.30 (d, *J* = 3.0 Hz, 1 H, PhC*H*N), 6.22 (d, *J* = 3.0 Hz, 1 H, PhC*H*O), 6.59 (s, 1 H, arom.), 6.62 (s, 1 H, arom.), 7.08 (m, 7 H, arom.), 7.23 (m, 6 H, arom.). − ^{13}C NMR ([D$_6$]DMSO, 95 °C): δ = 24.1, 26.0 [(*C*H$_3$)$_2$C], 27.5 [(*C*H$_3$)$_3$CO], 28.9, 29.5 (CH_2), 49.7 (CH_2N), 56.4 (C=O*C*HN), 59.7 (Ph*C*HN), 66.3 (Ph*C*H$_2$), 72.1 (CHO), 77.7 (Ph*C*HO), 78.4 [(CH$_3$)$_3$*C*O], 92.0 [(CH$_3$)$_2$*C*], 125.7, 126.6, 126.8, 127.0, 127.4, 134.0, 135.4, 135.6 (arom.), 150.8, 153.0 (N−C=O), 167.5 (O−C=O).

***tert*-Butyl (5′*R*,3*S*,5*S*,6*R*)-3-[2-(3′-Benzyloxycarbonyl-2′,2′-dimethyloxazolidin-5′-yl)ethyl]-2-oxo-5,6-diphenylmorpholine-4-carboxylate (2f):** From template **3a** (1.30 mmol) and iodide **13b** (1.00 mmol), compound **2f** (437 mg) was obtained in 71% yield; m.p. 133−136 °C. − $[\alpha]_D^{20}$ = −28 (*c* = 1, CH_2Cl_2). − ESI-HRMS: *m*/*z* = 637.2905 ± 0.0010 [M + Na]$^+$, calcd. 637.2890. − ^{1}H NMR ([D$_6$]DMSO, 120 °C): δ = 1.19 [br. s, 9 H, $(CH_3)_3CO$], 1.48 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 1.82 (m, 2 H, CH_2), 2.19 (m, 2 H, CH_2), 3.19 (dd, *J* = 8.8, 9.9 Hz, 1 H, CH_2N), 3.78 (dd, *J* = 5.9, 9.9 Hz, 1 H, CH_2N), 4.21 (m, 1 H, CHO), 4.81 (m, 1 H, CHN), 5.11 (s, 2 H, PhC*H*$_2$), 5.17 (d, *J* = 2.9 Hz, 1 H, PhC*H*N), 6.19 (d, *J* = 2.9 Hz, 1 H, PhC*H*O), 6.57 (s, 1 H, arom.), 6.59 (s, 1 H, arom.),

7.24 (m, 13 H, arom.). − ^{13}C NMR ([D$_6$]DMSO, 95 °C): δ = 24.0, 25.9 [(*C*H$_3$)$_2$C], 27.0 [(*C*H$_3$)$_3$CO], 28.9, 29.5 (CH$_2$), 49.6 (CH$_2$N), 56.1 (C=O*C*HN), 59.8 (Ph*C*HN), 65.3 (Ph*C*H$_2$), 72.5 (CHO), 74.6 (Ph*C*HO), 79.9 [(CH$_3$)$_3$*C*O], 92.4 [(CH$_3$)$_2$*C*], 125.7, 126.1, 126.6, 127.0, 127.4, 134.2, 136.3 (arom.), 151.3, 152.3 (N−C=O), 167.9 (O−C=O).

Benzyl (5′*R*,3*R*,5*R*,6*S*)-3-[2-(3′-*tert*-Butyloxycarbonyl-2′,2′-dimethyloxazolidin-5′-yl)ethyl]-2-oxo-5,6-diphenylmorpholine-4-carboxylate: From template **16** (1.29 mmol) and iodide **13a** (1.19 mmol), the title compound (473 mg) was obtained in 65% yield. $[\alpha]_D^{20}$ = +19 (*c* = 1, CH$_2$Cl$_2$). − ESI-HRMS: *m*/*z* = 637.2908 ± 0.0007 [M + Na]$^+$, calcd. 637.2890. − ^{1}H NMR ([D$_6$]DMSO, 95 °C): δ = 1.45 [s, 12 H, (CH$_3$)$_3$CO, CH$_3$], 1.51 (s, 3 H, CH$_3$), 1.82 (m, 2 H, CH$_2$), 2.22 (m, 2 H, CH$_2$), 3.06 (dd, *J* = 8.8, 9.9 Hz, 1 H, CH$_2$N), 3.68 (dd, *J* = 5.8, 9.9 Hz, 1 H, CH$_2$N), 4.13 (m, 1 H, CHO), 4.86 (dd, *J* = 5.1, 9.1 Hz, 1 H, CHN), 5.01 (AB, *J* = 12.8 Hz, 2 H, PhC*H*$_2$), 5.30 (d, *J* = 3.3 Hz, 1 H, PhC*H*N), 6.22 (d, *J* = 3.3 Hz, 1 H, PhC*H*O), 6.58 (s, 1 H, arom.), 6.62 (s, 1 H, arom.), 7.08 (m, 7 H, arom.), 7.24 (m, 6 H, arom.). − ^{13}C NMR ([D$_6$]DMSO, 95 °C): δ = 24.2, 26.0 [(*C*H$_3$)$_2$C], 27.5 [(*C*H$_3$)$_3$CO], 28.9, 29.6 (CH$_2$), 49.7 (CH$_2$N), 56.4 (C=O*C*HN), 59.7 (Ph*C*HN), 66.3 (Ph*C*H$_2$), 72.1 (CHO), 77.6 (Ph*C*HO), 78.3 [(CH$_3$)$_3$*C*O], 92.0 [(CH$_3$)$_2$*C*], 125.7, 126.6, 126.8, 127.0, 127.4, 128.2, 134.1, 135.4, 135.6 (arom.), 150.8, 153.0 (N−C=O), 167.5 (O−C=O).

Protected (2*S*,5*R*)-5-Hydroxylysine 14: In a hydrogenation flask, compound **2e** (208 mg, 0.34 mmol) was dissolved in a mixture of THF (8 mL) and MeOH (24 mL). The flask was flushed with argon and 10% Pd/C (0.19 g) was added. Hydrogenation was performed at 4.2 bar H$_2$ for 24 h. Thereafter, the solution was filtered through Celite and the filtrate was concentrated to dryness to yield 183 mg of a solid material. Purification by silica gel column chromatography (eluent light petroleum/ethyl acetate, 9:1 → MeOH/ethyl acetate/triethylamine, 3:6:1) gave 86 mg (84%) of protected (2*S*,5*R*)-5-hydroxylysine **14**. $[\alpha]_D^{20}$ = −6.4 (*c* = 0.9, MeOH). − ESI-MS: *m*/*z* = 303.1 [M + H]$^+$, 325.1 [M + Na]$^+$. − ^{1}H NMR (MeOD): δ = 1.34 [s, 9 H, (CH$_3$)$_3$CO], 1.37 (s, 3 H, CH$_3$), 1.41 (s, 3 H, CH$_3$), 1.61 (m, 2 H, CH$_2$), 1.83 (m, 2 H, CH$_2$), 2.92 (dd, *J* = 9.4, 9.5 Hz, 1 H, CH$_2$N), 3.48 (dd, *J* = 5.1, 9.1 Hz, 1 H, CHN), 3.56 (dd, *J* = 5.9, 9.5 Hz, 1 H, CH$_2$N), 4.01 (m, 1 H, CHO). − ^{13}C NMR (MeOD): δ = 24.9, 27.2 [(*C*H$_3$)$_2$C], 28.5 (CH$_2$), 28.7 [(*C*H$_3$)$_3$CO], 29.8 (CH$_2$), 51.9 (CH$_2$N), 55.9 (C=O*C*HN), 74.6 (CHO), 81.3 [(CH$_3$)$_3$*C*O], 94.5 [(CH$_3$)$_2$*C*], 153.7 (N−C=O), 174.2 (O−C=O).

Protected (2*S*,5*R*)-5-Hydroxylysine 15: A suspension of compound **2e** (177 mg, 0.29 mmol) in acetic acid (7 mL) and water (3 mL) was stirred at 30 °C. After 48 h, TLC showed that the conversion was complete. The solvents were evaporated, the residue was suspended in toluene, and the solvent was evaporated once more. This procedure was repeated three times. The residue was then purified by column chromatography (silica gel, light petroleum/ethyl acetate, 9:1 → ethyl acetate/MeOH, 8:2) to yield compound **15** (147 mg, 89%). $[\alpha]_D^{20}$ = −23 (*c* = 1, CH$_2$Cl$_2$). − ESI-MS: *m*/*z* = 597.4 [M + Na]$^+$. − ^{1}H NMR (CDCl$_3$): δ = 1.46 [s, 9 H, (CH$_3$)$_3$CO], 1.73 (m, 2 H, CH$_2$), 2.31 (m, 2 H, CH$_2$), 3.11 (m, 1 H, CH$_2$N), 3.40 (m, 1 H, CH$_2$N), 3.98 (m, 1 H, CHO), 5.00 (m, 3 H, CHN, PhC*H*$_2$), 5.13 (d, *J* = 2.9 Hz, 1 H, PhC*H*N), 5.96 (d, *J* = 2.9 Hz, 1 H, PhC*H*O), 6.59 (s, 1 H, arom.), 6.62 (s, 1 H, arom.), 7.21 (m, 13 H, arom.). − ^{13}C NMR (CDCl$_3$): δ = 28.3 [(*C*H$_3$)$_3$CO], 30.2, 30.6 (CH$_2$), 46.4 (CH$_2$N), 56.0 (C=O*C*HN), 60.7 (Ph*C*HN), 67.9 (Ph*C*H$_2$), 71.9 (CHO), 79.0 (Ph*C*HO), 79.4 [(CH$_3$)$_3$*C*O], 126.4, 126.5, 127.3, 127.4, 127.8, 128.0, 128.2, 128.5, 133.9, 135.3 (arom.), 154.4, 156.6 (N−C=O), 168.5 (O−C=O).

(2*S*,5*R*)-5-Hydroxylysine (1): Protected (2*S*,5*R*)-5-hydroxylysine **14** (16 mg) was dissolved in 1.5 M DCl (0.50 mL) and the resulting solution was allowed to stand at room temperature for 2 h. ^{1}H NMR analysis gave a spectrum identical to that of a commercial (2*S*,5*R*)-5-hydroxylysine sample. − HPLC: Daicel CROWNPACK CR(+), eluent HClO$_4$ (pH 1.0), 0.50 mL/min at 8 °C, detection UV 200 nm: synthesized **1**, t_R = 20.6 min, commercial **1**, t_R = 20.7 min; synthesized (2*R*,5*R*)-5-hydroxylysine (**17**) t_R = 16.5 min, commercial D,L-5-hydroxylysine (peak areas in parentheses): t_R = 11.9 min (19%, 2*R*,5*S*); t_R = 16.2 min (29%, 2*R*,5*R*); t_R = 20.4 min (19%, 2*S*,5*R*); t_R = 22.3 min (30%, 2*S*,5*S*). − ESI-MS: *m*/*z* = 163.2 [M + H]$^+$.

[1] D. R. Eyre, M. A. Paz, P. M. Gallop, *Ann. Rev. Biochem.* **1984**, *53*, 717−748.

[2] [2a] D. D. Van Slyke, A. Hiller, *Proc. Natl. Acad. Sci. USA* **1921**, *7*, 185−186. − [2b] D. D. Van Slyke, A. Hiller,A. Dillon, D. A. MacFadyen, *Proc. Soc. Exp. Biol. and Med.* **1938**, *38*, 548−549.

[3] [3a] J. C. Sheehan, W. A. Bolhofer, *J. Am. Chem. Soc.* **1950**, *72*, 2469−2472. − [3b] S. Bergström, S. Lindstedt, *Arch. Biochem. Biophys.* **1950**, *26*, 323−324.

[4] [4a] J. C. Sheehan, W. A. Bolhofer, *J. Am. Chem. Soc.* **1950**, *72*, 2472−2474. − [4b] J. R. Weisiger, *J. Biol. Chem.* **1950**, *186*, 591−602. − [4c] O. Touster, *J. Am. Chem. Soc.* **1951**, *73*, 491. − [4d] G. Van Zyl, E. E. Van Tamelen, G. D. Zuidema, *J. Am. Chem. Soc.* **1951**, *73*, 1765−1767. − [4e] H. Zahn, L. Zürn, *Chem. Ber.* **1958**, *91*, 1359−1371. − [4f] N. Izumiya, Y. Fujita, M. Ohno, *Bull. Chem. Soc. Jpn.* **1962**, *35*, 2006−2009. − [4g] H. J. Koeners, C. Schattenkerk, J. J. Verhoeven, J. H. van Boom, *Tetrahedron* **1981**, *37*, 1763−1771.

[5] [5a] W. S. Fones, *J. Am. Chem. Soc.* **1953**, *75*, 4865−4866. − [5b] W. S. Fones, *Biochem. Prep.* **1961**, *8*, 62−69.

[6] M. Adamczyk, D. D. Johnson, R. E. Reddy, *Tetrahedron* **1999**, *55*, 63−88.

[7] B. Löhr, S. Orlich, H. Kunz, *Synlett* **1999**, 1139−1141.

[8] U. Schöllkopf, U. Groth, D. Chuanzeng, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 798−799.

[9] G. Li, C. Han-Ting, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451−454.

[10] A. M. C. H. van den Nieuwendijk, J. C. J. Benningshof, V. Wegmann, R. A. Bank, J. M. te Koppele, J. Brussee, A. van der Gen, *Bioorg. & Med. Chem. Lett.* **1999**, *9*, 1673−1676.

[11] R. M. Williams, M. N. Im, *J. Am. Chem. Soc.* **1991**, *113*, 9276−9286.

[12] [12a] D. M. Bender, R. M. Williams, *J. Org. Chem.* **1997**, *62*, 6690−6691. − [12b] J. E. Baldwin, V. Lee, C. J. Schofield, *Synlett* **1992**, 249−251. − [12c] R. M. Williams, *Aldrichimica Acta* **1992**, *25*, 11.

[13] Both enantiomers are available from Aldrich as Cbz-protected and as Boc-protected derivatives.

[14] A. M. C. H. van den Nieuwendijk, E. G. J. C. Warmerdam, J. Brussee, A. van der Gen, *Tetrahedron: Asymmetry* **1995**, *6*, 801−806.

[15] E. Smitskamp-Wilms, J. Brussee, A. van der Gen, G. J. M. van Scharrenburg, J. B. Sloothaak, Recl. Trav. Chim. Pays-*Bas* **1991**, *110*, 209−215.

[16] [16a] J. Brussee, A. C. A. Jansen, A. Kühn, Proc. Symp. Med. Chem., Acta Pharm. Suecica Suppl. 2:479, **1985**. − [16b] F. Effenberger, T. Ziegler, S. Förster, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 458−459. − [16c] J. Brussee, E. C. Roos, A. van der Gen, *Tetrahedron Lett.* **1988**, *29*, 4485−4488. − [16d] P. Zandbergen, J. van der Linden, J. Brussee, A. van der Gen, *Synth. Commun.* **1991**, *21*, 1387−1391. − [16e] E. Kiljunen, L. T. Kanerva, *Tetrahedron: Asymmetry* **1997**, *8*, 1225−1234. − [16f] J. Brussee, A. van der Gen, in *Stereoselective Biocatalysis* (Ed.: R. N. Patel), Marcel Dekker, New York, **2000**, chapter 11, 289−320. − [16g] F. Effenberger, in *Stereoselective Biocatalysis* (Ed.: R. N. Patel), Marcel Dekker, New York, **2000**, chapter 12, 321−342.

[17] W. T. Loos, H. W. Geluk, M. M. A. Ruijken, C. J. Kruse, J. Brussee, A. van der Gen, *Biocatalysis and Biotransformation* **1995**, *12*, 255−266.

[18] P. Zandbergen, A. M. C. H. van den Nieuwendijk, J. Brussee,

A. van der Gen, C. G. Kruse, *Tetrahedron* **1992**, *48*, 3977−3982.
[19] P. J. Garegg, B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866−2869.
[20] The TBDPS analogue of iodide **9** gave alkylation products **2** in 5−10% yield.
[21] S. Thaisrivongs, D. T. Pals, L. T. Kroll, S. R. Turner, H. Fu-Son, *J. Med. Chem.* **1987**, *30*, 976−982.
[22] Available from Fluka: (5*R*)-5-hydroxy-L-lysine dihydrochloride monohydrate; DL-5-hydroxylysine hydrochloride (mixture of DL-normal and DL-*allo* forms).
[23] H. Griengl, A. Hickel, D. V. Johnson, C. Kratky, M. Schmidt, H. Schwab, *Chem. Commun.* **1997**, 1933−1940.
[24] E. G. J. C. Warmerdam, J. Brussee, C. G. Kruse, A. van der Gen, *Tetrahedron* **1993**, *49*, 1063−1070.
[25] R. M. Williams, P. J. Sinclair, D. Zhai, D. Chen, *J. Am. Chem. Soc.* **1988**, *110*, 1547.
[26] [26a] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. − [26b] R. E. Ireland, L. Liu, *J. Org. Chem.* **1993**, *58*, 2899.

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