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Diastereoselective Hydroxylation of 6-Substituted Piperidin-2-ones. An Efficient Synthesis of (2*S*,5*R*)-5-Hydroxylysine and Related α-Amino Acids

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Received May 29, 2002

The synthesis of (2*S*,5*R*)-5-hydroxy-6-oxo-1,2-piperidinedicarboxylates (**5**) and related (3*S*,6*R*)-3-hydroxy-6-alkyl-2-oxo-1-piperidinecarboxylates has been developed. The approach is based on the asymmetric hydroxylation of enolates generated from the corresponding *N*-protected-6-substituted piperidin-2-ones. The utility of **5a** as a precursor in the synthesis of (2*S*,5*R*)-5-hydroxylysine (**1**), an amino acid unique to collagen and collagen-like proteins, has also been demonstrated. (2*S*)-6-oxo-1,2-piperidinedicarboxylates (**6**) required for hydroxylation studies were prepared in 38−74% yield, starting from conveniently protected aspartic acid as inexpensive chiral adduct. Hydroxylation of **6** to **5** proceeds in high yield and excellent diastereoselectivity by treatment of their Li-enolate with (+)-camphorsulfonyloxaziridine at −78 °C. Ring opening of di-*tert*-butyl (2*S*,5*R*)-6-oxo-1,2-piperidinedicarboxylate ((5*R*)-**5a**) under reductive conditions afforded the corresponding 1,2-diol (**17**) in 91%, which was further transformed to (2*S*,5*R*)-5-hydroxylysine in four steps (84%). **17** is also a versatile intermediate in the preparation of *tert*-butyl (2*S*,5*R*)-2-[(*tert*-butoxycarbonyl)amino]-5-hydroxy-6-iodohexanoate (**3**) and *tert*-butyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-[(2*R*)-oxiranyl]-butanoate (**4**), two amino acid derivatives used in the total synthesis of the bone collagen cross-link (+)-pyridinoline (**2a**).

Introduction

Collagen is the major structural protein in mammals and plays an important role in the maintenance of the structural integrity of tissues.[1] Its biosynthesis requires a series of posttranslational modifications such as the hydroxylation of prolyl and lysyl residues and the glycosylation of hydroxylysyl residues. (2*S*,5*R*)-5-Hydroxylysine **1** is one of the amino acids unique to collagen and collagen-like proteins.[2,3] In collagen, hydroxylysine can be glycosylated with either a *β*-D-galactopyrannosyl or an α-D-glucopyrannosyl-(1→2)-*β*-D-galactopyrannosyl residue.[4] The extent of hydroxylation of lysyl residues and glycosylation of hydroxylysyl residues varies markedly among collagen types. Although the exact structural and regulatory roles of hydroxylysines and hydroxylysine-linked carbohydrate units have not been fully elucidated, it is believed that these posttranslational modifications play a major role in the regulation of collagen fibrillogenesis and in the morphology of fibrils.[5] In addition, a peptide derived from type II collagen (CII) and containing a glycosylated hydroxylysyl residue has been identified as an immunodominant T cell epitope involved in collagen-induced arthritis (CIA), a mouse model of rheumatoid arthritis (RA).[6]

The structure of collagen is stabilized by intra- and intermolecular (+)-pyridinoline (**2a**) and (+)-deoxypyridinoline (**2b**) cross-links formed between adjacent lysyl and hydroxylysyl residues. Because of the usefulness of **2** for the diagnosis of osteoporosis and other metabolic bone diseases, as well as difficulties in its isolation from natural sources, a number of approaches to the synthesis of **2a** and **2b** have been proposed in recent years.[7] The preparation of **2a** involves either the use of **1** or the related *tert*-butyl (2*S*,5*R*)-2-[(*tert*-butoxycarbonyl)amino]-

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(2) 5-hydroxylysyl and dihydroxylysyl residues are also found in styelin D, an antimicrobial peptide isolated from hemocytes of ascidian, *Styela clava*: Taylor, S. W.; Craig, A. G.; Fischer, W. H.; Park, M.; Lehrer, R. I. *J. Biol. Chem.* **2000**, *275*, 38417−38426.

(3) *ϵ-N,N,N*-trimethyl-5-hydroxylysine, a (2*S*,5*R*)-hydroxylysine containing a quaternary ammonium salt, is present in the sequence of silaffin-1A$_1$, a silica-precipitating peptide from diatom *Cylindrotheca fusiformis*: Kröger, N.; Deutzmann, R.; Sumper, M. *J. Biol. Chem.* **2001**, *276*, 26066−26070.

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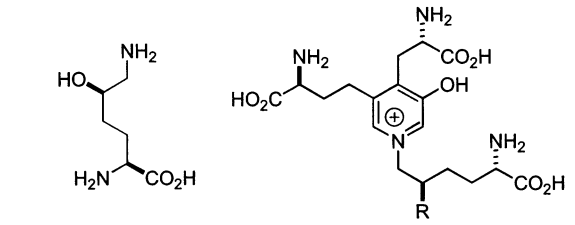
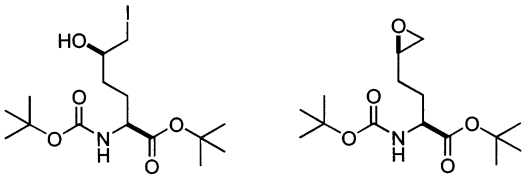
10.1021/jo025950c CCC: $22.00
Published on Web 11/06/2002

5-hydroxy-6-iodohexanoate **3** and *tert*-butyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-[(2*R*)oxiranyl]butanoate **4** as intermediates.



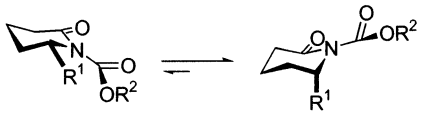
1 **2a R = OH** **2b R = H**



3 **4**

Although (2*S*,5*R*)-5-hydroxylysine (**1**) is commercially available, it is expensive and requires lengthy procedures for protection prior to its use in peptide synthesis (five steps, 37%).[8] (2*S*,5*R*)-5-Hydroxylysine (**1**) is commonly produced by a tedious procedure starting from gelatine acid hydrolysates.[9] Only recently, a few stereoselective approaches to the synthesis of **1** have been investigated. In the strategy developed by Kunz et al.,[10] two successive asymmetric steps were used to create the two stereogenic centers. The 1,2-amino alcohol structure was incorporated by Sharpless asymmetric aminohydroxylation into a homoallyl glycine unit built using the Schöllkopf methodology. Although the method was satisfactory for the preparation of (2*S*,5*S*)-5-hydroxylysine, the yield and diasteroselectivity in favor of **1** were poor. More recently, a 10-step stereoselective synthesis involving the Williams' glycine template methodology and (*R*)-hydroxynitrile lyase for the introduction of the chirality at the 2- and 5-positions, respectively, afforded **1** in ca. 20% yield.[11] Other reported strategies[7a,12] utilized (*S*)-glutamic acid as a starting material. Overall, these methods suffer from limitations including the need for resolutions, lengthy synthetic procedures, and/or separation of diastereomers.

None of the aforementioned syntheses has taken advantage of the α-stereogenic center of the starting α-amino acid to control the stereochemistry while the second stereogenic center at C-5 is introduced. We recently reported a short and stereoselective route to optically active 1,4-disubstituted δ-amino acids that allows the incorporation of various natural and nonnatural side chain functionalities at the α-position.[13] The method involved the alkylation of *N*-Boc-protected-6-alkyl piperidin-2-ones readily prepared from *N*-Boc-protected β^3-amino acids via reduction of the keto functionality of the corresponding β-aminoacyl Meldrum's acid. The high level of 1,4-asymmetric induction achieved during alkylation of the corresponding enolate anion is probably due to the minimization of the allylic A(1,3) strain (see conformation **B**).[14,15] The ring substituent at the 6-position would preferentially adopt an axial conformation, thus providing a high diastereofacial bias in the alkylation step.



A **B**

In the present study, we report an expedient stereoselective synthesis of (2*S*,5*R*)-5-hydroxylysine **1** starting from aspartic acid as inexpensive chiral adduct; the existing α-stereogenic center served for asymmetric induction at C-5. The retrosynthetic analysis is shown in Scheme 1.

Our strategy is based on asymmetric oxidation of enolates generated from piperidinones **6** to the corresponding α-hydroxy carbonyl compounds **5**. We also demonstrate that **5** can serve as a versatile intermediate in the stereoselective synthesis of **3** and **4**.

Results and Discussion

Piperidinone Synthesis. Several (2*S*)-6-oxo-1,2-piperidinedicarboxylates **6a**−**e** varying at R^2 or R^1 were synthesized for the purpose of studying the stereodirecting effect of the ester substituent at C-2 and the influence of the *N*-protecting groups. Piperidinones **6a**−**d** were prepared from the conveniently protected aspartic acid derivatives **7a**−**d** using a procedure similar to that described previously for the synthesis of *N*-protected 6-alkyl piperidin-2-ones (Scheme 2).[13,16]

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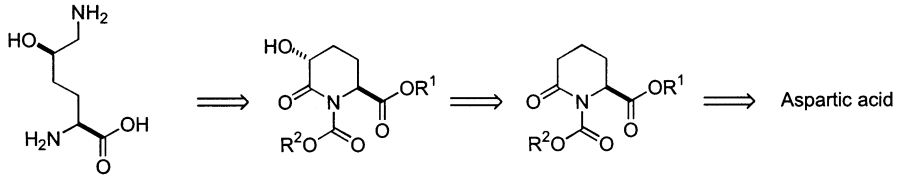
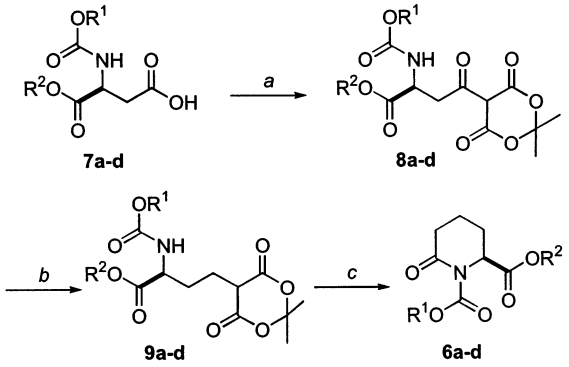
SCHEME 1. Retrosynthesis of (2*S*,5*R*)-5-Hydroxylysine 1



SCHEME 2[a]



	R^1	R^2	Yield, %
6a	^{t}Bu	^{t}Bu	74
6b	^{t}Bu	Bn	71
6c	^{t}Bu	TCE	38
6d	TMSEt	^{t}Bu	70
6e	^{t}Bu	All	99

[a] (a) Meldrum's acid, EDC, DMAP, CH_2Cl_2; (b) $NaBH_4$, CH_2Cl_2/AcOH (10:1); (c) toluene, reflux; (d) H_2, Pd/C, EtOH; (e) allyl bromide, DBU, CH_3CN.

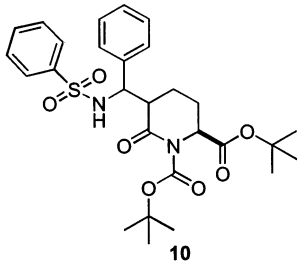
The condensation of **7** with Meldrum's acid afforded **8**, which was used in the next step without further purification. Treatment of **8** with $NaBH_4$ in CH_2Cl_2/AcOH at room temperature resulted in complete reduction of its keto functionality to give **9**. It is likely that **8** first underwent reduction of its ketone functionality to the *β*-hydroxy diester, and that this was followed by dehydration to the unsaturated ester, which is further reduced to **9** via Michael addition of hydride ion.[16]

These compounds were obtained in excellent yield and easily purified by crystallization with the exception of **9d**, for which a flash chromatography was necessary. Decarboxylative ring closure of **9** in toluene at reflux afforded lactams **6** in moderate to good yields after flash chromatography. Additionally, we prepared the piperidinone **6e** in a two-step procedure starting from **6b**. The quantitative reduction of the benzyl ester gave the free carboxylic acid, which was directly protected by reaction with allyl bromide in the presence of DBU to yield **6e**.

Enolate Formation and α-Hydroxylation Studies. Initial oxidation studies were conducted on the enolate of di-*tert*-butyl (2*S*)-6-oxo-1,2-piperidinedicarboxylate **6a**. Various oxidizing agents were evaluated, including Vedejs' MoOPH (MoO_5·HMPA·pyridine) and Davis' oxaziridines [*trans*-(±)-2-(phenylsulfonyl)-3-phenyloxaziridine as well as the two antipodal (+)- and (−)-(10-camphorsulfonyl)oxaziridines].[17,18] **6a** was converted to the corresponding enolate by treatment with 1.1 equiv of LiHMDS or NaHMDS at −78 °C in THF for 2.5 h. The results presented in Table 1 show the influence of the counterion (Li^+ or Na^+) and the conjugated effects of temperature and reaction time for the four electrophiles mentioned above.

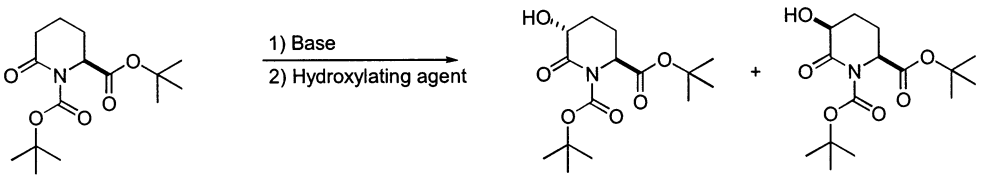
Initial oxidation studies with Vedejs' reagent confirmed the stereodirecting effect of the *tert*-butyl ester substituent. When the lithium enolate of **6a** was treated with MoOPH for 1 h, the corresponding hydroxylated adduct **5a** was obtained in low yield with 76% diastereomeric excess (de). The ratio between the two diastereomers was determined by RP-HPLC of the crude product using a C_{18} column. The major diastereomer, subsequently identified as (5*R*)-**5a**, (vide infra) was isolated in 20% yield (Table 1, entry 1). Recovery of 73% of starting material **6a** suggested that the low yield was attributable to a slow oxidation rate. Attempts to improve the yield by a slow increase of the temperature over a long period of time (entry 2) did not give any hydroxylated product and resulted in nearly complete degradation of **6a**. Similarly, no hydroxylation took place at −78 °C with the more nucleophilic sodium enolate (entry 3). However, performing the experiment with Li-enolate at −50 °C during 0.5 h gave both a dramatic increase in yield and good stereoselectivity (entry 4). Replacing LiHMDS by NaHMDS improved the yield but resulted in lower diastereoselectivity (entry 5 vs 4). In all cases, the remaining starting material made the flash chromatography of **5a** difficult, and a nonnegligible amount of product was lost during purification.

Oxidation of the lithium enolate of **6a** by (±)-PPO for 1 h (entry 6) resulted in the formation of the imino-aldol **10** as the major product together with **5a** in low yield



but 94% de. The imino-aldol **10** was unambiguously characterized by ^{1}H NMR and resulted from the addition of the enolate to the sulfonimine generated from (±)-PPO.[17e−h,18] This side reaction is generally avoided by using sodium enolates. However, in the case of **6a**, replacing the lithium enolate by the sodium enolate (entry 7 vs 6) did not eliminate the imino-aldol but only reduced its amount to the advantage of **5a**. Reduction of the reaction time from 0.5 to 0.25 h (entries 8 vs 7)

TABLE 1. Counterion and Hydroxylating Agent Study for Preparation of 5



6a (5*R*)-**5a** (5*S*)-**5a**

entry	base	electrophile	*T*, °C	time, h	dr[a] of **5a**	purified yield of (5*R*)-**5a**, %
1	LiHMDS	MoOPH[b]	−78	1.0	88:12	20 (73)[c]
2	LiHMDS	MoOPH[b]	−78 → rt	16.0	nd	<5
3	NaHMDS	MoOPH[b]	−78	3.0	–	0
4	LiHMDS	MoOPH[b]	−50	0.5	91:9	77
5	NaHMDS	MoOPH[b]	−50	0.5	83:17	83
6	LiHMDS	(±)-PPO[d]	−78	1.0	97:3	<10
7	NaHMDS	(±)-PPO[d]	−78	0.5	96:4	38
8	NaHMDS	(±)-PPO[d]	−78	0.25	94:6	48
9	NaHMDS	(±)-PPO[d]	−78	3.0	nd	<5
10	LiHMDS	(+)-CSO[e]	−78	0.25	99:1	42 (53)[c]
11	LiHMDS	(+)-CSO[e]	−50	0.25	97:3	77
12	LiHMDS	(+)-CSO[e]	−78	16.0	98:2	92
13	LiHMDS	(−)-CSO[e]	−78	0.25	99:1	21 (78)[c]
14	LiHMDS	(−)-CSO[e]	−50	0.25	97:3	62
15	LiHMDS	(−)-CSO[e]	−78	16.0	98:2	76

[a] (5*R*)-**5a**:(5*S*)-**5a**; ratio determined by analytical C_{18} RP-HPLC of the crude product. [b] MoOPH = MoO_5·pyridine·HMPA. [c] % of recovered starting material. [d] PPO = *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine. [e] CSO = (10-camphorsulfonyl)oxaziridine.

further improved the yield with only a slight decrease of diastereoselectivity. Long reaction times (entry 9) were detrimental for the reaction, and only a mixture of degradation products and starting material was recovered. In all these reactions the presence of the imino-aldol **10** made the purification extremely difficult, and the yields of isolated (5*R*)-**5a** (entries 6−8) do not reflect the actual extent of the reaction. With the aim of circumventing the problem of imino-aldol formation, we next investigated (+)- and (−)-CSO as hydroxylating agents.[17g,h,18] The experiments with (+)- and (−)-CSO were performed in parallel (entries 10−12 vs 13−15) and resulted in very clean reactions (no degradation). In the first series of experiments, the lithium enolate of **6a** was treated at −78 °C for 0.25 h with (+)-CSO or (−)-CSO (entries 10 and 13). Excellent diastereoselectivities but modest yields were obtained as a result of the steric hindrance of CSO. Performing the reaction at −50 °C resulted in better yield and only slightly lower de. The reaction was brought to completion by performing the oxidation at −78 °C overnight (entries 12 and 15). When using (+)-CSO under these conditions (entry 12), the hydroxylation reaction was found to proceed almost quantitatively with a high diastereoselectivity (96% de): (5*R*)-**5a** was isolated in 92% yield. From these experiments with CSO, two general trends can be noted: on one hand, yields are consistently higher with (+)-CSO than with (−)-CSO. On the other hand, (+)- and (−)-CSO do not have opposite effects on the stereochemical course of the reaction.

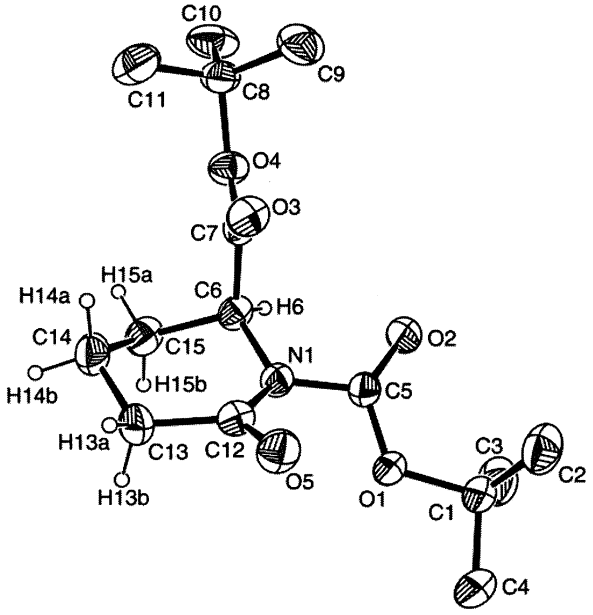


FIGURE 1. Ortep plot of **6a**.

Structural evidence for the high diasterofacial bias in the hydroxylation reaction was obtained by determination of the X-ray crystal structure of **6a.** The structure shown in Figure 1 confirms the expected axial orientation of the C-2 ring substituent resulting from the minimiza-

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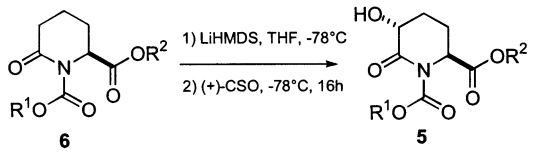
TABLE 2. Influence of the Protecting Groups



compd	R^1	R^2	dr[a] of **5**	purified yield of (5*R*)-**5**, %
5b	tBu	Bn	99:1	88
5c	tBu	TCE	100:0	73
5d	TMSEt	tBu	99:1	87
5e	tBu	All	99:1	89

[a] (5*R*)-**5**:(5*S*)-**5**; ratio determined by analytical C_{18} RP-HPLC of the crude product.

tion of the allylic A(1,3) strain. Its enolate form is believed to adopt a half-chair conformation with the metal coordinating both oxygen atoms O2 and O5 (Figure 1).

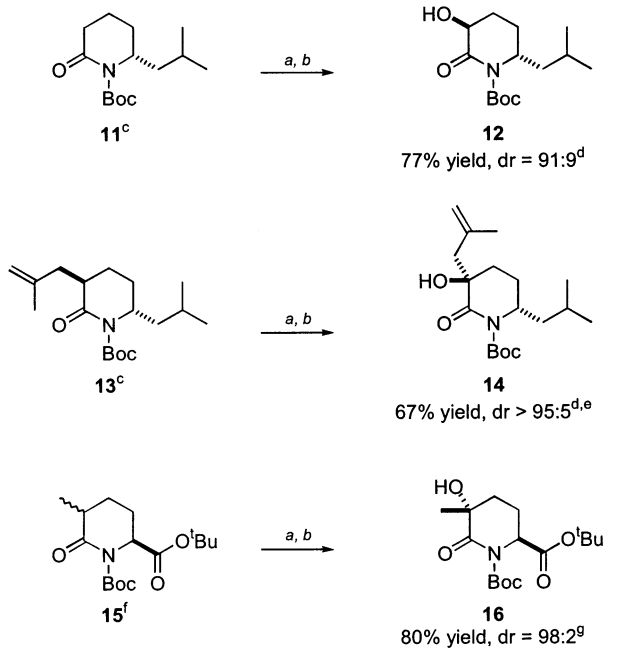
The stereochemical outcome of the reaction was confirmed by X-ray crystal structure analysis of the major diastereomer formed by hydroxylation of **6a**, which was unambiguously assigned to (5*R*)-**5a**.

The influence of R^1 and R^2 in **6a** on the outcome of the hydroxylation reaction was investigated under our optimal conditions: Li-enolate/(+)-CSO/−78 °C/16 h. Results shown in Table 2 indicate that the nature of the ester group R^2 has little influence on yield and stereoselectivity. Only in the case of the trichloroethyl ester protection was the yield found to be consistently lower. The replacement of Boc by Teoc (compound **5d**) had no significant effect.

The hydroxylation reaction of the related 6-alkyl or 3,6-disubstituted piperidinones **11**, **13**, and **15** (Scheme 3) was investigated. When the ester group in **6a** was replaced by a *s*-Bu side chain (**11**), a significant decrease in the diastereoselectivity was observed under our standard conditions with de = 82%. This reaction was not optimized for higher diastereoselectivities. Conversely, high diastereofacial bias was obtained in the hydroxylation of the enolate generated from the piperidin-2-one **13**. The corresponding 3-alkylated-3-hydroxylated adduct **14** was obtained in 67% yield together with 18% of unreacted **13**. In good agreement with the result obtained for **6a**, hydroxylation of the mixture of diastereomers **15** proceeded in good yield and gave **16** as sole diastereomer (dr = 98:2) in 80% yield.

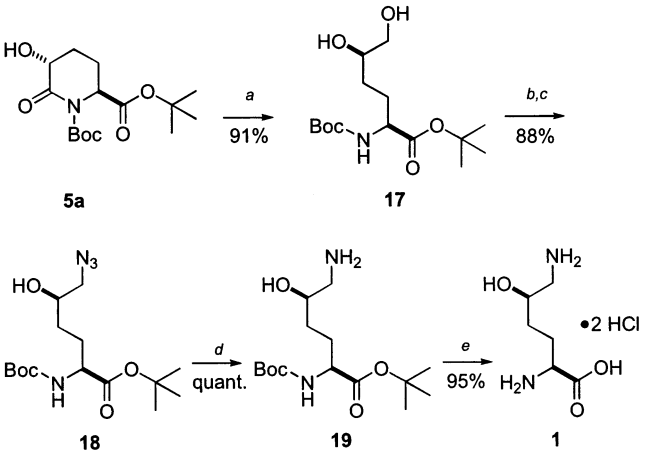
Synthesis of (2*S*,5*R*)-5-Hydroxylysine (1). With pure hydroxylated piperidinone (5*R*)-**5a** in hand, the transformation to the diol **17** then became the key step in our approach to the synthesis of (2*S*,5*R*)-5-hydroxylysine (Scheme 4). We studied methods involving direct ring-opening of (5*R*)-**5a** under reductive condition.[19] Initially, we tried to reduce the lactam function using lithium borohydride in the presence of 1 equiv of water. This procedure, proposed by Penning et al.[21] for the reduction of sterically hindered and alkene-containing acyloxazolidinones, failed to give us the desired product

SCHEME 3[a]



[a] (a) LiHMDS, THF, −78 °C; (b) CSO, −78 °C, 16 h; (c) preparation previously described by us (ref 13); (d) ratio determined by ^{1}H NMR; (e) **14** is the only diastereomer detected; (f) resulting from alkylation of **6a** with MeI, equimolar mixture of diastereomers; (g) ratio determined by C_{18} RP-HPLC of the crude product.

SCHEME 4[a]



[a] (a) $NaBH_4$, EtOH; (b) MsCl, collidine, CH_2Cl_2; (c) NaN_3, DMF; (d) H_2, Pd/C, EtOH; (e) HCl, dioxane.

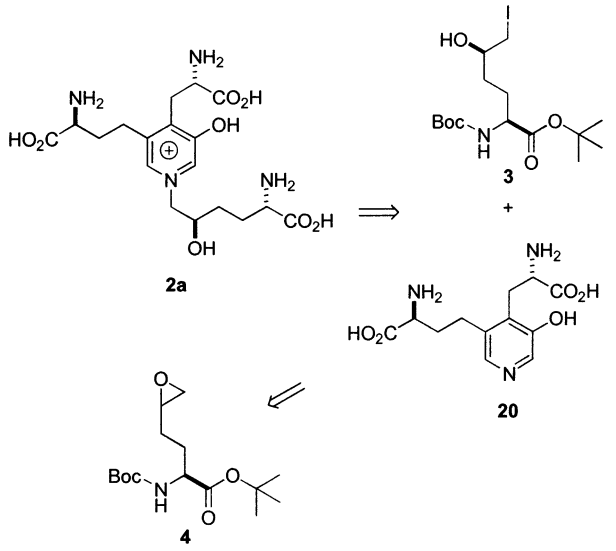
when starting from (5*R*)-**5a**. Protection of the secondary alcohol prior to the reduction did not bring any improvement. However, we found that the *N*-Boc-protected lactam (5*R*)-**5a** could be opened using sodium borohydride in ethanol, the 1,2-diol **17** being formed in high yield (Scheme 4). The protection of the acidic function as the *tert*-butyl ester was mandatory in this step. All attempts to convert lactams **5b** and **5e** to the corresponding diols under these conditions failed and gave degradation

(19) The two-step procedure consisting of ring opening of lactam (5*R*)-**5a** by treatment with LiOH (ref 20) followed by reduction of the newly formed acidic function to the expected diol **17** was not investigated.

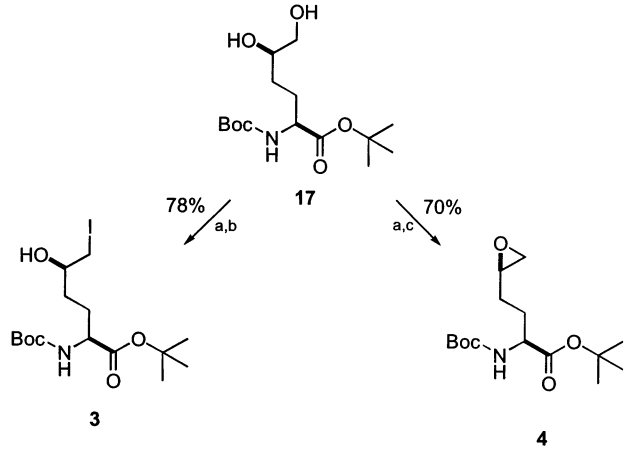
(20) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424−2426.

(21) Penning, T. D.; Djuric', S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307−312.

SCHEME 5



SCHEME 6[a]



[a] (a) MsCl, collidine, CH_2Cl_2; (b) NaI, acetone; (c) K_2CO_3, acetone.

byproducts. The primary alcohol in **17** was selectively mesylated in a very clean reaction,[23] thus averting the need for a purification before the following step. The crude mesylate was quantitatively converted to the 1,2-azido alcohol **18** by nucleophilic substitution with NaN_3. The reduction of the azide function gave the 1,2-amino alcohol Boc-Hyl-O^{t}Bu (**19**), a known precursor of natural hydroxylysine,[7a] in quantitative yield. The final deprotection of the Boc and *tert*-Butyl ester functional groups afforded **1** in an overall yield of 52% starting from the aspartic acid derivative **7a**. The stereoisomeric purity of 5-hydroxylysine (**1**) prepared from (5*R*)-**5a** was determined after derivatization with 1-fluoro-2,4-dinitrophenyl-5-L-alanine amide (Marfey's reagent),[22] by RP-HPLC analysis using a C_{18} column and a linear gradient of 0.1% aqueous TFA and MeOH (30−65% MeOH in 35 min). Under these conditions the four diastereomers of 5-hydroxylysine were baseline separated. Comparison with a commercial sample of (2*S*,5*R*)-5-hydroxylysine revealed that 5-hydroxylysine **1** was 97% pure.

Synthesis of (+)-Pyridinoline Precursors 3 and 4. The total synthesis of (+)-pyridinoline **2a** (Scheme 5), described independently by Waelchli et al. and Adamczyk et al.,[7a,b] involves the construction of an appropriately functionalized 3-hydroxy-4,5-substituted pyridine derivative **20**, followed by the quaternization of nitrogen with the iodo compound **3**. **20** was prepared starting from epoxy amino acid **4** in a biomimetic pathway (Scheme 5). We found that diol **17** was a versatile precursor in the synthesis of related amino acids **3** and **4**, since only two steps were required for the transformation (Scheme 6).

Conclusion

We have reported an efficient methodology for synthesizing enantiopure (2*S*,5*R*)-5-hydroxylysine **1** via the hydroxylation of di-*tert*-butyl (2*S*)-6-oxo-1,2-piperidinedicarboxylate (**6a**). Conveniently protected aspartic acid derivatives **7** as inexpensive chiral adducts were first transformed to the corresponding *N*-protected piperidinones **6** in a simple three-step reaction sequence. Under our optimal conditions—Li-enolate/(+)-CSO/−78 °C/16 h—the hydroxylation reaction of **6** and of related *N*-protected-6-alkyl piperidinones was found to proceed almost quantitatively with high diastereoselectivities (de = 96% in the case of **6a**). Avoidance of allylic A(1,3) strain that forces the carboxylate substituent at C-2 to adopt an axial disposition is believed to be the key factor governing the stereochemical outcome of the reaction. The hydroxylated lactam (5*R*)-**5a** represents a highly versatile chiral synthon which has been used successfully in the synthesis of (2*S*,5*R*)-5-hydroxylysine **1** (eight steps from **7a**, 52% overall yield), as well as in the synthesis of two intermediates required in the total synthesis of bone collagen cross-link (+)-pyridinoline **2a**.

Experimental Section

General. All reactions were performed under an atmosphere of argon. THF was distilled from Na/benzophenone; CH_2Cl_2 was distilled from CaH_2; toluene was distilled over Na. Flash column chromatography was carried out on silica gel (0.063−0.200 mm). HPLC analysis was performed on a Nucleosil C_{18} column (5 μm, 3.9 × 150 mm) by using a linear gradient of A (0.1% TFA in H_2O) and B (0.08% TFA in MeCN) at a flow rate of 1.2 mL/min with UV detection at 214 nm. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz in $CDCl_3$ as the solvent.

Materials. Amino acid derivatives were purchased from Neosystem or Senn Chemicals. Boc-Asp-OBn (**7b**) is commercially available. Boc-Asp-O^{t}Bu (**7a**),[24] Boc-Asp-OTCE (**7c**), and Teoc-Asp-O^{t}Bu (**7d**)[25] were prepared starting from the commercially available Boc-Asp(Bn)-OH. The synthesis of piperidin-2-ones **11** and **13** has already been described.[13] MoOPH,[26] (±)-PPO,[27] and (+)- and (−)-CSO[28] were prepared according to the published procedures.

Preparation of Meldrum's Derivatives 9a−d. EDC (1.5 equiv), DMAP (1.5 equiv), and Meldrum's acid (1 equiv) were added to a 0.25 M solution of PG^1-Asp-OPG^2 in CH_2Cl_2 at 0

(22) Marfey, P. *Carlsberg Res. Commun.* **1984**, *49*, 591−596.
(23) O'Donnell, C. J.; Burke, S. D. *J. Org. Chem.* **1998**, *63*, 8614−8616.
(24) (a) Mathias, L. J. *Synthesis* **1979**, 561−576. (b) Bergmeier, S. C.; Cobas, A. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369−2376.
(25) Shute, R. E.; Rich, D. H. *Synthesis* **1987**, 346−349.
(26) For the preparation of MoOPH, see: Mimoun, H.; Seree de Roch, I.; Sajus, L. *Bull. Soc. Chim.* **1969**, *5*, 1481−1492.
(27) For the preparation of (±)-PPO, see: Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1987**, *66*, 203-210.

°C. The mixture was allowed to reach room temperature, stirred for 3 h, and then washed with 1 N $KHSO_4$. The organic layer was dried over Na_2SO_4 and filtered prior to the addition of CH_2Cl_2 (to afford a 0.05 M solution) and 10% v/v of acetic acid. $NaBH_4$ (3.0 equiv) was added portionwise to the previous solution stirred at room temperature. After 48 h, the mixture was diluted with brine, and the organic layer was washed using water, dried over Na_2SO_4, filtered, and evaporated to afford a residue which was purified by crystallization or by flash chromatography.

***tert*-Butyl (*2S*)-2-[(*tert*-Butoxycarbonyl)amino]-4-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)butanoate (*9a*).** Recrystallization of the crude product from CH_2Cl_2/pentane gave **9a** (5.44 g, yield = 98%): HPLC t_R 10.98 (linear gradient, 30−100% B, 20 min); white crystals; $[\alpha]_D = +11.2$ ($c = 1.0$, $CHCl_3$); mp 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (bd, J = 7.1 Hz, 1H), 4.18 (bs, 1H), 3.77 (bs, 1H), 2.24−2.18 (m, 1H), 2.09−2.01 (m, 2H), 1.83−1.77 (m, 1H), 1.80 (s, 3H), 1.74 (s, 3H), 1.45 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.4 (C), 165.2 (2 C), 155.6 (C), 105.0 (C), 82.3 (C), 79.9 (C), 53.2 (CH), 45.4 (CH), 29.6 (CH_2), 28.6 (CH_3), 28.3 (3 CH_3), 28.0 (3 CH_3), 26.4 (CH_3), 21.8 (CH_2). Anal. Calcd for $C_{19}H_{31}NO_8$: C, 56.84; H, 7.78; N, 3.49. Found: C, 56.84; H, 7.92; N, 3.47.

Benzyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-4-[(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)butanoate (*9b*). Recrystallization of the crude product from CH_2Cl_2/pentane gave **9b** (6.34 g, yield = 95%): HPLC t_R 12.34 (linear gradient, 30−100% B, 20 min); white crystals; $[\alpha]_D = +6.5$ ($c = 1.0$, $CHCl_3$); mp 94−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.30 (m, 5H), 5.17 (m, 2H), 5.16 (m, 1H), 4.37 (m, 1H), 3.73 (m, 1H), 2.25−2.18 (m, 1H), 2.16−2.07 (m, 2H), 1.86−1.81 (m, 1H), 1.80 (s, 3H), 1.74 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.2 (C), 165.1 (C), 165.0 (C), 156.0 (C), 135.3 (C), 128.7 (5 CH), 105.1 (C), 80.4 (C), 67.3 (CH_2), 52.8 (CH), 45.4 (CH), 29.5 (CH_2), 28.6 (CH_3), 28.3 (3 CH_3), 26.5 (CH_3), 21.9 (CH_2).

Trichloroethyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-4-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)butanoate (*9c*). Recrystallization of the crude product from CH_2Cl_2/pentane gave **9c** (3.66 g, yield = 90%): HPLC t_R 11.92 (linear gradient, 30−100% B, 20 min); white crystals; $[\alpha]_D = -8.8$ ($c = 0.9$, MeOH); mp 124−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (bd, J = 7.7 Hz, 1H), 4.87 (d, J = 11.8 Hz, 1H), 4.69 (d, J = 11.8 Hz, 1H), 4.44 (bs, 1H), 3.73 (bs, 1H), 2.29−2.24 (m, 1H), 2.24−2.15 (m, 2H), 1.90−1.85 (m, 1H), 1.81 (s, 3H), 1.74 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.9 (C), 165.1 (2 C), 155.5 (C), 105.2 (C), 94.5 (C), 80.5 (C), 74.4 (CH_2), 53.0 (CH), 45.5 (CH), 29.1 (CH_2), 28.5 (CH_3), 28.3 (3 CH_3), 26.5 (CH_3), 22.0 (CH_2). Anal. Calcd for $C_{17}H_{24}Cl_3NO_8$: C, 42.83; H, 5.07; N, 2.94. Found: C, 43.04; H, 4.87; N, 2.90.

***tert*-Butyl (*2S*)-4-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2-({[(trimethylsilyl)ethoxy]carbonyl}amino)-butanoate (9d).** Purification of the crude product by flash column chromatography gave **9d** (5.35 g, yield = 98%): HPLC t_R 13.10 (linear gradient, 30−100% B, 20 min); colorless oil; $[\alpha]_D = +12.4$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (bd, J = 5.3 Hz, 1H), 4.22 (bs, 1H), 4.14−4.09 (m, 2H), 3.69 (bs, 1H), 2.22−2.13 (m, 1H), 2.09−1.98 (m, 2H), 1.85−1.76 (m, 1H), 1.79 (s, 3H), 1.73 (s, 3H), 1.45 (s, 9H), 0.98−0.94 (m, 2H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.4 (C), 165.1 (2 C), 156.4 (C), 105.0 (C), 82.4 (C), 63.4 (CH_2), 53.6 (CH), 45.5 (CH), 29.5 (CH_2), 28.5 (CH_3), 28.0 (3 CH_3), 26.5 (CH_3), 21.8 (CH_2), 17.7 (CH_2), −1.4 (3 CH_3). Anal. Calcd for $C_{20}H_{35}NO_8Si$: C, 53.91; H, 7.92; N, 3.14. Found: C, 54.15; H, 8.02; N, 3.09.

Preparation of Piperidin-2-ones Derivatives 6a−d. A 0.1 M solution of **9** in dry toluene was refluxed overnight. The solvent was evaporated and the residue dissolved in AcOEt and washed with saturated $NaHCO_3$, brine, and 1 N $KHSO_4$. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (AcOEt/Hex, 2:8) to yield pure **6**.

Di-*tert*-butyl (*2S*)-6-Oxo-1,2-piperidinedicarboxylate (*6a*). Purification of the crude product by flash column chromatography gave **6a** (2.03 g, yield = 76%): HPLC t_R 10.44 (linear gradient, 30−100% B, 20 min); white solid; $[\alpha]_D = -12.3$ ($c = 1.1$, MeOH); mp 46−48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (dd, J = 5.8, 3.6 Hz, 1H), 2.57 (ddd, J = 17.5, 5.6, 4.5 Hz, 1H), 2.47 (ddd, J = 17.4, 9.8, 7.0 Hz, 1H), 2.19−2.13 (m, 1H), 2.05−1.96 (m, 1H), 1.82−1.74 (m, 2H), 1.48 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.6 (C), 170.4 (C), 152.3 (C), 83.2 (C), 82.1 (C), 59.0 (CH), 34.5 (CH_2), 27.9 (6 CH_3), 25.9 (CH_2), 18.3 (CH_2). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 60.30; H, 8.64; N, 4.65.

2-Benzyl 1-*tert*-Butyl (*2S*)-6-Oxo-1,2-piperidinedicarboxylate (6b). Purification of the crude product by flash column chromatography gave **6b** (3.19 g, yield = 75%): HPLC t_R 11.09 (linear gradient, 30−100% B, 20 min); white solid; $[\alpha]_D = -10.2$ ($c = 1.0$, $CHCl_3$); mp 43−44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.29 (m, 5H), 5.22 (d, J = 12.2 Hz, 1H), 5.14 (d, J = 12.2 Hz, 1H), 4.73 (m, 1H), 2.55−2.49 (m, 1H), 2.44 (ddd, J = 17.6, 9.9, 6.8 Hz, 1H), 2.18−2.11 (m, 1H), 2.06−1.97 (m, 1H), 1.77−1.69 (m, 1H), 1.67−1.60 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.4 (C), 170.2 (C), 152.2 (C), 135.3 (C), 128.7 (2 CH), 128.5 (CH), 128.4 (2 CH), 83.6 (C), 67.3 (CH_2), 58.6 (CH), 34.5 (CH_2), 27.9 (6 CH_3), 25.9 (CH_2), 18.3 (CH_2). Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.52; H, 7.01; N, 4.28.

2-Trichloroethyl 1-*tert*-Butyl (*2S*)-6-Oxo-1,2-piperidinedicarboxylate (6c). Purification of the crude product by flash column chromatography gave **6c** (1.00 g, yield = 42%): HPLC t_R 11.87 (linear gradient, 30−100% B, 20 min); white solid; $[\alpha]_D = -1.0$ ($c = 1.1$, MeOH); mp 63−65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (d, J = 11.9 Hz, 1H), 4.87 (dd, J = 6.0, 3.5 Hz, 1H), 4.68 (d, J = 11.9 Hz, 1H), 2.63 (ddd, J = 17.5, 5.8, 4.4 Hz, 1H), 2.53 (ddd, J = 17.5, 9.8, 7.2 Hz, 1H), 2.35−2.28 (m, 1H), 2.21−2.11 (m, 1H), 1.91−1.77 (m, 2H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.1 (C), 169.8 (C), 152.5 (C), 94.5 (C), 84.0 (C), 74.5 (CH_2), 58.3 (CH), 34.5 (CH_2), 28.0 (3 CH_3), 25.8 (CH_2), 18.3 (CH_2). Anal. Calcd for $C_{13}H_{18}Cl_3NO_5$: C, 41.68; H, 4.84; N, 3.74. Found: C, 41.78; H, 4.84; N, 3.81.

2-*tert*-Butyl 1-[(Trimethylsilyl)ethyl] (2*S*)-6-Oxo-1,2-piperidinedicarboxylate (6d). Purification of the crude product by flash column chromatography gave **6d** (2.87 g, yield = 71%): HPLC t_R 13.74 (linear gradient, 30−100% B, 20 min); white solid; $[\alpha]_D = -10.1$ ($c = 1.1$, MeOH); mp 52−54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (dd, J = 5.9, 3.5 Hz, 1H), 4.35−4.30 (m, 2H), 2.59 (ddd, J = 17.3, 5.8, 4.1 Hz, 1H), 2.48 (ddd, J = 17.3, 10.0, 7.1 Hz, 1H), 2.23−2.16 (m, 1H), 2.06−1.97 (m, 1H), 1.85−1.73 (m, 2H), 1.48 (s, 9H), 1.12−1.08 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.4 (C), 170.3 (C), 154.4 (C), 82.3 (C), 65.6 (CH_2), 59.1 (CH), 34.4 (CH_2), 28.0 (3 CH_3), 25.8 (CH_2), 18.3 (CH_2), 17.5 (CH_2), −1.6 (3 CH_3). Anal. Calcd for $C_{16}H_{29}NO_5Si$: C, 55.95; H, 8.51; N, 4.08. Found: C, 55.56; H, 8.44; N, 4.09.

2-Allyl 1-*tert*-Butyl (2*S*)-6-oxo-1,2-piperidinedicarboxylate (6e). Pd/C (150 mg, 10% w/w) was added to a solution of 1.50 g (4.50 mmol) of **6b** in 20 mL of AcOEt at room temperature. The mixture was stirred for 2 h and filtered through Celite. Evaporation of the solvent gave 1.10 g of the free-acid intermediate. The free-acid derivative (1.00 g, 4.11 mmol) and allyl bromide (497 mg, 4.11 mmol) were dissolved in 15 mL of acetonitrile. The mixture was cooled to 0 °C and 751 mg (4.93 mmol) of DBU was added. After stirring for 6 h, acetonitrile was evaporated and the residue was dissolved in AcOEt. The solution was washed with saturated $NaHCO_3$, brine, and 1 N $KHSO_4$. Drying over Na_2SO_4 and evaporation of the filtrate afforded pure **6e** (1.15 g, yield = 99% starting

(28) For the preparation of (+)-CSO and (−)-CSO, see: (a) Bartlett, P. D.; Knox, L. H. *Organic Syntheses;* Wiley: New York, 1973; Collect. Vol. V, pp 196−198. (b) Towson, J. C.; Weismiller, M. C.; Sankar Lal, G. *Org. Synth.* **1990**, *69*, 158−169. (c) Bulman Page, P. C.; Heer, J. P.; Bethell, D.; Lund, A.; Collington, E. W.; Andrews, D. M. *J. Org. Chem.* **1997**, *62*, 6093−6094.

from **6b**): HPLC t_R 8.48 (linear gradient, 30−100% B, 20 min); colorless oil; $[\alpha]_D = -8.9$ ($c = 1.1$, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95−5.85 (m, 1H), 5.34 (dd, $J = 17.2$, 1.4 Hz, 1H), 5.25 (dd, $J = 10.4$, 1.4 Hz, 1H), 4.72 (dd, $J = 5.9$, 3.8 Hz, 1H), 4.66−4.63 (m, 2H), 2.57 (ddd, $J = 17.5$, 6.0, 4.3 Hz, 1H), 2.47 (ddd, $J = 17.5$, 9.9, 6.8 Hz, 1H), 2.21−2.15 (m, 1H), 2.10−2.01 (m, 1H), 1.83−1.67 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.2 (C), 170.2 (C), 152.3 (C), 131.4 (CH), 119.0 (CH_2), 83.6 (C), 66.1 (CH_2), 58.6 (CH), 34.5 (CH_2), 27.9 (3 CH_3), 25.9 (CH_2), 18.3 (CH_2). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.62; H, 7.70; N, 5.01.

General Hydroxylation Procedures.

Enolate Generation. The desired piperidinone derivative was placed in an argon-filled round-bottom flask, dissolved in anhydrous THF to give a ca. 0.3 M solution, and cooled to −78 °C. The indicated base (NaHMDS or LiHMDS; 1.1 equiv) was introduced as a 1.0 M solution in THF via hypodermic syringe. After being stirred for 2.5 h, the desired enolate was ready for hydroxylation.

Enolate Hydroxylation. Procedure A. To the cold enolate solution (−78 °C) prepared as described above was added the indicated amount of crystalline MoOPH (2.0 equiv). The temperature and duration of the hydroxylation reactions were specific to each experiment. The reaction was quenched by introducing a saturated solution of Na_2SO_3 (1 mL/mmol of enolate). The resulting two-phase solution was vigorously stirred for 15 min. The THF was evaporated under reduced pressure and replaced with AcOEt which was washed with water. The organic layer was dried over Na_2SO_4, concentrated, and chromatographed on silica gel (AcOEt/Hex, 3:7).

Procedure B. To the cold enolate solution (−78 °C) prepared as described above was added the indicated amount of oxaziridine (1.5 equiv) dissolved in the minimum volume of THF. The temperature and duration were specific to each experiment. The reaction was quenched by introducing a saturated aqueous solution of NH_4Cl (1 mL/mmol of enolate), and the THF was evaporated under reduced pressure and replaced with AcOEt which was washed with water. The organic layer was dried over Na_2SO_4, concentrated, and chromatographed on silica gel (MeOH/CH_2Cl_2, 2:98).

Di-*tert*-butyl (2*S*,5*R*)-5-Hydroxy-6-oxo-1,2-piperidinedicarboxylate ((5*R*)-5a). Using the best conditions (Table 1, entry 12), (5*R*)-**5a** was obtained as a yellowish oil which was purified by flash column chromatography (640 mg, yield = 92%): HPLC t_R 7.72 (linear gradient, 30−100% B, 20 min); white solid; $[\alpha]_D = -12.1$ ($c = 1.0$, MeOH); mp 88−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (t, $J = 6.4$ Hz, 1H), 4.11 (dd, $J = 9.7$, 7.2 Hz, 1H), 3.61 (bs, 1H), 2.34−2.26 (m, 1H), 2.25−2.16 (m, 1H), 2.13−2.04 (m, 1H), 1.78−1.68 (m, 1H), 1.52 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.8 (C), 169.8 (C), 151.6 (C), 84.2 (C), 82.7 (C), 68.3 (CH), 58.4 (CH), 27.9 (6 CH_3), 26.8 (CH_2), 22.7 (CH_2). Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 56.91; H, 8.20; N, 4.46.

Di-*tert*-butyl (2*S*,5*S*)-5-hydroxy-6-oxo-1,2-piperidinedicarboxylate ((5*S*)-5a): HPLC t_R 7.48 (linear gradient, 30−100% B, 20 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (m, 1H), 4.06 (dd, $J = 11.3$, 6.2 Hz, 1H), 2.34−2.02 (m, 3H), 1.80−1.66 (m, 1H), 1.50 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.6 (C), 170.2 (C), 153.1 (C), 83.9 (C), 82.7 (C), 69.9 (CH), 59.9 (CH), 27.9 (6 CH_3), 26.7 (CH_2), 23.9 (CH_2).

2-Benzyl 1-*tert*-butyl (2*S*,5*R*)-5-hydroxy-6-oxo-1,2-piperidinedicarboxylate (5b). Using the procedure developed for (5*R*)-**5a** (Table 1, entry 12), **5b** was obtained as a yellowish oil which was purified by flash column chromatography (1.81 g, yield = 88%): HPLC t_R 8.39 (linear gradient, 30−100% B, 20 min); colorless oil; $[\alpha]_D = -7.8$ ($c = 1.2$, MeOH); mp 88−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.29 (m, 5H), 5.22 (d, $J = 12.1$ Hz, 1H), 5.15 (d, $J = 12.2$ Hz, 1H), 4.83 (t, $J = 6.3$ Hz, 1H), 4.08 (dd, $J = 9.6$, 6.9 Hz, 1H), 2.27−2.19 (m, 2H), 2.12−2.06 (m, 1H), 1.77−1.68 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.7 (C), 170.7 (C), 151.4 (C), 135.0 (C), 128.8 (CH), 128.7 (2 CH), 128.4 (2 CH), 84.5 (C), 68.3 (CH), 67.6 (CH_2), 58.0 (CH), 27.8 (3 CH_3), 26.7 (CH_2), 22.7 (CH_2). Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.87; H, 6.88; N, 3.95.

2-Trichloroethyl 1-*tert*-Butyl (2*S*,5*R*)-5-Hydroxy-6-oxo-1,2-piperidinedicarboxylate (5c). Using the procedure developed for (5*R*)-**5a** (Table 1, entry 12), **5c** was obtained as a yellowish oil which was purified by flash column chromatography (181 mg, yield = 73%): HPLC t_R 9.45 (linear gradient, 30−100% B, 20 min); white solid; $[\alpha]_D = -17.3$ ($c = 1.0$, MeOH); mp 91−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (d, $J = 11.8$ Hz, 1H), 4.93 (t, $J = 6.5$ Hz, 1H), 4.64 (d, $J = 11.8$ Hz, 1H), 4.15−4.10 (m, 1H), 3.59 (bs, 1H), 2.37−2.26 (m, 2H), 2.23−2.15 (m, 1H), 1.81−1.71 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.3 (C), 169.6 (C), 151.5 (C), 94.4 (C), 84.8 (C), 74.5 (CH_2), 68.3 (CH), 57.6 (CH), 27.9 (3 CH_3), 26.6 (CH_2), 22.5 (CH_2). Anal. Calcd for $C_{13}H_{18}Cl_3NO_6$: C, 39.97; H, 4.64; N, 3.59. Found: C, 40.27; H, 4.65; N, 3.54.

2-*tert*-Butyl 1-[(Trimethylsilyl)ethyl] (2*S*,5*R*)-5-Hydroxy-6-oxo-1,2-piperidinedicarboxylate (5d). Using the procedure developed for (5*R*)-**5a** (Table 1, entry 12), **5d** was obtained as a yellowish oil which was purified by flash column chromatography (90 mg, yield = 87%): HPLC t_R 11.99 (linear gradient, 30−100% B, 20 min); colorless oil; $[\alpha]_D = -10.4$ ($c = 0.8$, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (dd, $J = 6.3$, 6.0 Hz, 1H), 4.37−4.32 (m, 2H), 4.12 (dd, $J = 9.1$, 7.6 Hz, 1H), 3.60 (bs, 1H), 2.25−2.07 (m, 3H), 1.78−1.69 (m, 1H), 1.45 (s, 9H), 1.12−1.06 (m, 2H), 0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.7 (C), 169.7 (C), 153.4 (C), 82.9 (C), 68.2 (CH), 66.6 (CH_2), 58.3 (CH), 27.9 (3 CH_3), 26.6 (CH_2), 22.6 (CH_2), 17.6 (CH_2), −1.6 (3 CH_3).

2-Allyl 1-*tert*-Butyl (2*S*,5*R*)-5-Hydroxy-6-oxo-1,2-piperidinedicarboxylate (5e). Using the procedure developed for (5*R*)-**5a** (Table 1, entry 12), **5e** was obtained as a yellowish oil which was purified by flash column chromatography (890 mg, yield = 89%): HPLC t_R 6.64 (linear gradient, 30−100% B, 20 min); colorless oil; $[\alpha]_D = -9.0$ ($c = 1.0$, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91−5.86 (m, 1H), 5.31 (dd, $J = 17.3$, 1.4 Hz, 1H), 5.28 (dd, $J = 10.4$, 1.4 Hz, 1H), 4.83 (t, $J = 6.5$ Hz, 1H), 4.68−4.64 (m, 2H), 4.13 (dd, $J = 9.3$, 6.4 Hz, 1H), 3.61 (bs, 1H), 2.32−2.24 (m, 2H), 2.18−2.05 (m, 1H), 1.82−1.74 (m, 1H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.6 (C), 170.6 (C), 151.4 (C), 131.2 (CH), 119.4 (CH_2), 84.5 (C), 68.3 (CH), 66.4 (CH_2), 58.0 (CH), 27.9 (3 CH_3), 26.7 (CH_2), 22.7 (CH_2). Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.31; H, 7.19; N, 4.76.

***tert*-Butyl (3*S*,6*R*)-3-Hydroxy-6-isobutyl-2-oxo-1-piperidinecarboxylate (12).** Compound **12** was prepared according to procedure B using (−)-CSO as oxidizing agent. The solution was stirred at −78 °C during 16 h. After the workup, flash column chromatography (MeOH/CH_2Cl_2, 2:98) of the crude product afforded pure **12** (96 mg, yield = 77%): HPLC t_R 9.27 (linear gradient, 30−100% B, 20 min); colorless oil; $[\alpha]_D = +17.2$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33−4.25 (m, 1H), 4.17 (t, $J = 7.9$ Hz, 1H), 3.73 (bd, $J = 1.4$ Hz, 1H), 2.41−2.30 (m, 1H), 2.06−1.99 (m, 1H), 1.77−1.65 (m, 2H), 1.65−1.58 (m, 1H), 1.52 (s, 9H), 1.43 (m, 2H), 0.92 (d, $J = 5.3$ Hz, 3H), 0.90 (d, $J = 5.3$ Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) 174.3 (C), 170.6 (C), 151.9 (C), 83.8 (C), 67.7 (CH), 54.4 (CH), 43.8 (CH_2), 27.8 (3 CH_3), 26.8 (CH_2), 25.0 (CH), 24.2 (CH_2), 23.5 (CH_3), 21.4 (CH_3). Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.82; H, 9.05; N, 5.37.

***tert*-Butyl (3*S*,6*R*)-3-Hydroxy-6-isobutyl-3-(2-methylallyl)-2-oxo-1-piperidinecarboxylate (14).** Compound **14** was prepared according to procedure B using (−)-CSO as oxidizing agent. The solution was stirred at −78 °C during 16 h. After the work up, flash column chromatography (MeOH/CH_2Cl_2, 2:98) of the crude product afforded pure **14** (73 mg, yield = 67%): HPLC t_R 14.68 (linear gradient, 30−100% B, 20 min); colorless crystals; $[\alpha]_D = -31.6$ ($c = 1.0$, $CHCl_3$); mp 42−43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (dd, $J = 2.2$, 1.5 Hz, 1H), 4.73 (dd, $J = 2.0$, 0.8 Hz, 1H), 3.99−3.92 (m, 1H), 3.57 (bs, 1H), 2.39 (d, $J = 10.1$ Hz, 1H), 2.32 (d, $J = 10.2$ Hz, 1H),

2.06−2.00 (m, 1H), 1.75 (s, 3H), 1.72−1.68 (m, 3H), 1.45 (s, 9H), 1.32−1.21 (m, 1H), 1.18−1.05 (m, 1H), 0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 176.3 (C), 153.8 (C), 140.5 (C), 115.7 (CH_2), 83.8 (C), 72.4 (C), 60.9 (CH), 46.8 (CH_2), 36.7 (CH_3), 30.5 (CH_2), 27.6 (3 CH_3), 25.8 (CH_2), 24.0 (CH), 18.6 (CH_2), 12.8 (CH_3), 12.0 (CH_3). Anal. Calcd for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N, 4.30. Found: C, 66.37; H, 9.82; N, 4.38.

Di-*tert*-butyl (2*S*)-5-Methyl-6-oxo-1,2-piperidinedicarboxylate (15). 6a (100 mg, 0.334 mmol) was placed in an argon-filled round-bottomed flask, dissolved in 2.0 mL of anhydrous THF, and cooled to −78 °C. A 1 N solution (0.334 mL) of LiHMDS in THF was introduced by means of a hypodermic syringe. After 2.5 h, 142 mg (1.0 mmol) of MeI was added via a hypodermic syringe. After being stirried at −78 °C during 16 h, the reaction was quenched by adding 0.35 mL of a saturated aqueous solution of NH_4Cl. THF was evaporated under reduced pressure and replaced with AcOEt which was washed with water. The organic layer was dried over Na_2SO_4, concentrated, and chromatographed on silica gel (AcOEt/Hex, 2:8) to give **15** (97 mg, yield = 92%) as an equimolar mixture of diastereomers: HPLC t_R 11.32 (linear gradient, 30−100% B, 20 min); yellowish oil; $[\alpha]_D = -14.8$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (dd, $J = 6.2$, 5.0 Hz, 1H), 4.46−4.45 (m, 1H), 2.51−2.44 (m, 1H), 2.43−2.35 (m, 1H), 2.14−1.80 (m, 8H), 1.45 (s, 9H), 1.44 (s, 9H), 1.40 (s, 9H), 1.40 (s, 9H), 1.18 (d, $J = 2.2$ Hz, 3H), 1.17 (d, $J = 2.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.1 (C), 173.9 (C), 170.8 (C), 170.7 (C), 153.1 (C), 152.7 (C), 83.1 (C), 82.9 (C), 82.0 (C), 82.0 (C), 59.8 (CH), 58.9 (CH), 39.3 (2 CH), 38.1 (CH), 38.0 (CH), 28.0 (3 CH_3), 28.0 (3 CH_3), 27.9 (6 CH_3), 27.2 (CH_2), 26.3 (CH_2), 25.7 (CH_2), 23.6 (CH_2), 17.5 (CH_3), 16.9 (CH_3). Anal. Calcd for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.44; H, 8.93; N, 4.52.

Di-*tert*-butyl (2*S*,5*R*)-5-Hydroxy-5-methyl-6-oxo-1,2-piperidinedicarboxylate (16). Compound **16** was prepared according to procedure B using (+)-CSO as oxidizing agent. The solution was stirred at −78 °C during 16 h. After the workup, flash column chromatography (MeOH/CH_2Cl_2, 2:98) of the crude product afforded pure **16** (84 mg, yield = 80%): HPLC t_R 8.57 (linear gradient, 30−100% B, 20 min); colorless oil; $[\alpha]_D = +44.5$ ($c = 0.9$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (t, $J = 5.7$ Hz, 1H), 3.12 (bs, 1H), 2.25−2.13 (m, 1H), 2.04−1.91 (m, 2H), 1.84−1.79 (m, 1H), 1.49 (s, 9H), 1.46 (s, 9H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 176.0 (C), 170.1 (C), 151.9 (C), 131.2 (CH), 83.8 (C), 82.3 (C), 72.6 (C), 59.8 (CH), 32.3 (CH_3), 28.1 (CH_2), 27.9 (3 CH_3), 22.9 (CH_2). Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.33; H, 8.44; N, 4.06.

***tert*-Butyl (2*S*,5*R*)-2-[(*tert*-Butoxycarbonyl)amino]-5,6-dihydroxyhexanoate (17).** $NaBH_4$ (935 mg, 24.75 mmol) was added to a solution of 1.56 g (4.95 mmol) of α-hydroxy lactam (5*R*)-**5a** in 20 mL of absolute ethanol at 0 °C. The mixture was allowed to reach room temperature and stirred for 4 h. After being quenched with water, the mixture was stirred for a further 10 min. Evaporation of the solvent gave a solid, which was dissolved in AcOEt. The solution was washed with water and dried over Na_2SO_4. Evaporation of the filtrate afforded an oil which was subjected to filtration through a silica pad (AcOEt/AcOH, 99:1). Pure **17** was recovered (1.44 g, yield = 91%): HPLC t_R 5.85 (linear gradient, 30−100% B, 20 min); $[\alpha]_D = +12.2$ ($c = 1.1$, $CHCl_3$); waxy white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (bd, 1H), 4.15−4.10 (m, 1H), 3.92 (bs, 2H), 3.69−3.63 (m, 1H), 3.56 (dd, $J = 11.0$, 2.9 Hz, 1H), 3.38 (dd, $J = 11.0$, 7.3 Hz, 1H), 1.93−1.86 (m, 1H), 1.68−1.59 (m, 1H), 1.47−1.42 (m, 2H), 1.41 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.0 (C), 155.8 (C), 82.0 (C), 79.9 (C), 71.7 (CH), 66.6 (CH_2), 53.8 (CH), 29.3 (CH_2), 28.7 (CH_2), 28.3 (3 CH_3), 28.0 (3 CH_3). Anal. Calcd for $C_{15}H_{29}NO_6$: C, 56.41; H, 9.15; N, 4.39. Found: C, 56.20; H, 9.42; N, 4.35.

***tert*-Butyl (2*S*,5*R*)-6-Azido-2-[(*tert*-Butoxycarbonyl)-amino]-5-hydroxyhexanoate (18).** Collidine (6.0 mL, 45.10 mmol) was added to a solution of 1.44 g (4.51 mmol) of the 1,2-diol **17** in 90 mL of CH_2Cl_2 at ambient temperature. The solution was cooled to 0 °C and 568 mg (4.96 mmol) of MsCl dissolved in 5.5 mL of CH_2Cl_2 was added. After being stirred for 20 h at 0 °C, the reaction was quenched with water (35 mL), the phases were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with 1 N $KHSO_4$, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in 20 mL of DMF. NaN_3 (586 mg, 9.02 mmol) was added to the solution, which was heated to 80 °C for 8 h. After being allowed to cool to room temperature, water was added to the solution, which was extracted twice with AcOEt. The combined organic layers were washed with water, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by flash column chromatography (AcOEt/Hex, 3:7) to yield pure **18** (1.37 g, yield = 88%): HPLC t_R 10.07 (linear gradient, 30−100% B, 20 min); colorless oil; $[\alpha]_D = +13.8$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (bd, 1H), 4.21−4.14 (m, 1H), 3.76 (bs, 1H), 3.39−3.36 (m, 1H), 3.26 (dd, $J = 12.4$, 4.0 Hz, 1H), 3.21 (dd, $J = 12.4$, 6.6 Hz, 1H), 1.96−1.87 (m, 1H), 1.69−1.58 (m, 1H), 1.53−1.48 (m, 2H), 1.42 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.7 (C), 155.8 (C), 82.2 (C), 80.0 (C), 70.4 (CH), 57.0 (CH_2), 53.5 (CH), 29.8 (CH_2), 29.6 (CH_2), 28.3 (3 CH_3), 28.0 (3 CH_3). Anal. Calcd for $C_{15}H_{28}N_4O_5$: C, 52.31; H, 8.19; N, 16.27. Found: C, 52.32; H, 8.42; N, 16.09.

(2*S*,5*R*)-5-Hydroxylysine Dihydrochloride (1). Palladium on activated carbon (5 mg, 10% Pd) was added to a solution of 100 mg (0.29 mmol) of **18** in 2 mL of ethanol. The mixture was vigorously stirred at room temperature for 4 h under an atmosphere of hydrogen and filtered through Celite. Evaporation of the solvent gave **19** in quantitative yield as a colorless oil. The residue was dissolved in 2 mL of a 4 N solution of HCl in dioxane and stirred at room temperature for 2 h. Evaporation of the solvent gave **1** (65 mg, yield = 95%), a white solid.

Determination of the Stereomeric Purity of 1. Compound **1** (1 mg) was dissolved in 1 mL of 50% (v/v) aqueous acetonitrile containing 0.4% (v/v) of triethylamine. A 200 μL aliquot of this solution was mixed with 200 μL of Marfey's reagent in acetone (2.5 mg in 1 mL). The mixture was thermostated at 40 °C for 2 h and diluted to 1.0 mL with water prior to injection. The same procedure was repeated using the commercially available (2*S*,5*R*)-5-hydroxylysine and a commercial mixture of the four diastereoisomers. HPLC analysis was performed on a Nucleosil C_{18} column (5 μm, 3.9 × 150 mm) by using a linear gradient (30−65% B, 35 min) of A (0.1% TFA in H_2O) and B (MeOH) at a flow rate of 1.0 mL/min with UV detection at 214 nm: D,L-5-hydroxy-D,L-lysine, t_R 23.93, 25.92, 27.57, 28.36 min; commercial **1**, t_R 27.59 min; synthesized **1**, t_R 27.59 min.

***tert*-Butyl (2*S*,5*R*)-2-[(*tert*-Butoxycarbonyl)amino]-5-hydroxy-6-iodohexanoate (3).** Collidine (0.83 mL, 6.26 mmol) was added to a solution of 200 mg (0.626 mmol) of **17** in 11.0 mL of CH_2Cl_2 at ambient temperature. The solution was cooled to 0 °C and 79.0 mg (6.88 mmol) of MsCl dissolved in 0.75 mL of CH_2Cl_2 was added. After being stirred for 20 h at 0 °C, the reaction was quenched with water, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic extracts were washed with 1 N $KHSO_4$, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in 10 mL of acetone, and 188 mg (1.252 mmol) of NaI was added to the solution, which was refluxed for 16 h. Acetone was evaporated and replaced by AcOEt. The solution was washed with water, dried over Na_2SO_4, filtered, and evaporated under vacuo. The crude product was purified by flash column chromatography (AcOEt/Hex, 2:8) to yield pure **3** (210 mg, yield = 78%): HPLC t_R 10.82 (linear gradient, 30−100% B, 20 min); colorless oil; $[\alpha]_D = +14.7$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (bd, 1H), 4.18−4.14 (m, 1H), 3.55−3.49 (m, 1H), 3.26 (m, 2H), 3.18 (dd, $J = 10.1$, 5.9 Hz, 1H), 1.94−1.86 (m, 1H), 1.68−1.51 (m, 3H), 1.41 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$)

171.6 (C), 155.7 (C), 82.2 (C), 79.9 (C), 70.6 (CH), 53.5 (CH), 31.9 (CH_2), 29.7 (CH_2), 28.4 (3 CH_3), 28.1 (3 CH_3), 15.4 (CH_2). Anal. Calcd for $C_{15}H_{28}INO_5$: C, 41.97; H, 6.57; N, 3.26. Found: C, 42.04; H, 6.69; N, 3.28.

***tert*-Butyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-4-[(2*R*)-oxiranyl]butanoate (4).** Collidine (0.83 mL, 6.26 mmol) was added to a solution of 200 mg (0.626 mmol) of **17** in 11.0 mL of CH_2Cl_2 at ambient temperature. The solution was cooled to 0 °C and 79.0 mg (6.88 mmol) of MsCl dissolved in 0.75 mL of CH_2Cl_2 was added. After being stirred for 20 h at 0 °C, the reaction was quenched with water, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic extracts were washed with 1 N $KHSO_4$, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in 3 mL of methanol. K_2CO_3 (173 mg, 1.252 mmol) was added to the solution, which was stirred at room temperature during 4 h. The mixture was filtered, and the solvent was evaporated and replaced by AcOEt. The solution was washed with water and brine, dried over Na_2SO_4, filtered, and evaporated under vacuo. The crude product was purified by filtration through a plug of silica (AcOEt/Hex, 3:7) to yield **4** (132 mg, yield = 70%): HPLC t_R 9.93 (linear gradient, 30−100% B, 20 min); white solid; $[\alpha]_D = +18.3$ ($c = 1.0$, $CHCl_3$); mp 43−45 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (bd, 1H), 4.15−4.12 (m, 1H), 2.88−2.84 (m, 1H), 2.70 (dd, $J = 4.9$, 4.0 Hz, 1H), 2.43 (dd, $J = 4.9$, 2.7 Hz, 1H), 1.95−1.87 (m, 1H), 1.72−1.63 (m, 1H), 1.60−1.52 (m, 2H), 1.40 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.6 (C), 155.4 (C), 82.0 (C), 79.6 (C), 53.7 (CH), 51.7 (CH), 47.0 (CH_2), 29.2 (CH_2), 28.4 (CH_2), 28.3 (3 CH_3), 28.0 (3 CH_3). Anal. Calcd for $C_{15}H_{27}NO_5$: C, 59.78; H, 9.03; N, 4.65. Found: C, 59.64; H, 9.30; N, 4.91.

Acknowledgment. J.M. thanks the CNRS and Neosystem for a predoctoral fellowship.

Supporting Information Available: Ortep plot of compound (5*R*)-**5a**. X-ray crystallographic file of (5*R*)-**5a** and **6a**. ^{1}H and ^{13}C spectra for all compounds reported. RP-HPLC traces of (5*S*)-**5a** and **5d**. RP-HPLC traces of **1**, commercial (2*S*,5*R*)-5-hydroxylysine, and 5-hydroxylysine (four diastereomers) after derivatization with Marfey's reagent. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025950C