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Synthesis of Enantiopure 4-Hydroxypipecolate and 4-Hydroxylysine Derivatives from a Common 4,6-Dioxopiperidinecarboxylate Precursor

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tert-Butyl 2-substituted 4,6-dioxo-1-piperidinecarboxylates **4** have been prepared in good yield starting from Boc-Asp-O^{t}Bu and other β-amino acids. By analogy with chiral tetramic acids, their reduction by $NaBH_4$ in CH_2Cl_2/AcOH afforded the corresponding *cis*-4-hydroxy δ-lactams in good yield and stereoselectivity (68−98% de). In the absence of the A(1,3) strain (reduction of 6-substituted 2,4-dioxo-1-piperidines **7**), the *cis*-4-hydroxy isomer was still obtained as the major product but the de values were consistently lower. 4-Hydroxy-6-oxo-1,2-piperidinedicarboxylate **2a**, readily accessible from Boc-Asp-O^{t}Bu (three steps, 63% overall yield), has proven to be an excellent building block for the synthesis of *cis*- and *trans*-4-hydroxypipecolates **17** and **24** (52 and 36% overall yield, respectively) and for the synthesis of a protected 4-hydroxylysine derivative **29** (41% overall yield).

Introduction

The piperidin-2-one ring structure is a common structural feature in many natural products,[1] in synthetic molecules of biological interest[2] (e.g., HIV protease inhibitors,[2a] glycosidase inhibitors,[2b] thrombin inhibitors,[2c] antagonists of the neurokinin-2 receptor,[2d] and fibrinogen receptor antagonists[2e]), as well as in dipeptide surrogates and various constrained peptidomimetics.[3,4] In addition, functionalized piperidin-2-ones are useful and versatile building blocks in organic synthesis. They serve as precursors in the synthesis of key constituents of bioactive molecules such as higher membered lactams,[5] enantiopure substituted piperidines,[6] pipecolic acids,[7] indolizidines,[8] quinolizidine,[9] and isoquinolizidine[10] skeletons as well as δ-amino acids.[11] Therefore, a number of

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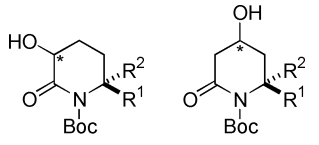
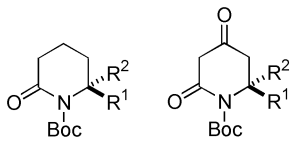
approaches have been investigated for the preparation of substituted δ-lactams in enantiomerically pure form.[12] Although chiral auxiliaries have been utilized with great success,[13] amino acids proved to be particularly useful precursors for the asymmetric synthesis of substituted piperidin-2-ones.

As part of a program dedicated to the synthesis of enantiopure natural and unnatural hydroxylysine derivatives for incorporation into biologically relevant peptides (e.g., glycosylated peptides derived from type II collagen), we became interested in the stereocontrolled synthesis of N-acylated δ-lactams **1** and **2** (R^1 = COOR, R^2 = H), monohydroxylated at the α and *β* positions, and in their use as possible and flexible intermediates for the synthesis of 5- and 4-hydroxylysine derivatives, respectively. This group of lactams has not received much



1 **2**



3 **4**

attention so far. Starting from aspartic acid (Asp) as a cheap and commercially available chiral building block, we recently reported a convenient synthesis of enantiopure (2*S*,5*R*)-5-hydroxy-6-oxo-1,2-piperidinedicarboxylate, a key intermediate in the synthesis of (2*S*,5*R*)-5-hydroxylysine.[14] Asymmetric oxidation of enolates generated from enantiopure 6-oxo-1-piperidinecarboxylate **3** was used to introduce the hydroxyl group at the 5 position.[14] N-acylated δ-lactams such as **3** are particularly useful for two reasons: first, as a consequence of the minimization of pseudoallylic A(1,3) strain,[15] the ring substituent at the *δ* position is believed to adopt a pseudoaxial orientation, thus providing a high diastereofacial bias for further asymmetric transformation. Second, the ring can be opened smoothly by hydrolysis[16] or under reductive conditions[14] to afford substituted δ-amino acids and ϵ-amino alcohols, respectively. We have now investigated 2,4-dioxo-1-piperidinecarboxylates **4** as novel chiral educts for the asymmetric synthesis of enantiopure 4-hydroxy-2-oxo-1-piperidinecarboxylates **2**. Although the corresponding five-membered-ring 2,4-dioxo-1-pyrrolidinecarboxylates (chiral tetramic acid)[17] obtained from Meldrum's acid and N-protected α-amino acids have received considerable attention as precursors in the synthesis of statine [(3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid] derivatives (their stereocontrolled reduction leading exclusively to the *cis*-4-hydroxy derivative), few reports have been made of the synthesis and reactivity of their six-membered counterparts.[18] Two syntheses of 4-hydroxypiperidin-2-ones as a novel entry to compounds incorporating a 4-hydroxypiperidine unit have been published recently.[6h,7a] The approach reported by Davis and coworkers is based on the selective reduction of enantiopure 6-phenylpiperidin-2,4-diones prepared from the corresponding *N*-sulfinyl δ-amino *β*-keto esters and has been applied to the synthesis of alkaloid SS20846 as well as to the naturally occurring *cis*- and *trans*-4-hydroxypipecolic acids.[7a] Although flexible, this method suffers from the need of a chiral *N*-sulfinyl imine as a chiral auxiliary to generate the starting optically pure δ-amino *β*-keto ester. Herein, we report the practical synthesis of *tert*-butyl 2-substituted 4,6-dioxo-1-piperidinecarboxylates **4** starting from Asp and various *β*-amino acids as well as their stereoselective reduction to the corresponding 4-hydroxy derivatives. The reduction of the corresponding 6-substituted 2,4-dioxo-1-piperidine **7** was also studied to determine what the facial selectivity would be in the absence of the A(1,3) strain. 4-Hydroxy-6-oxo-1,2-piperidinedicarboxylate **2a** (R^1 = COO^{t}Bu, R^2 = H), readily accessible in high yield from Boc-Asp-O^{t}Bu, was a useful precursor for the synthesis of 4-hydroxylysine derivatives. In view of the importance of 4-hydroxypipecolic acids as constituents of antibiotics and a number of potential therapeutic agents such as NMDA agonists, HIV protease inhibitors (palinavir), as well as TNF-α-converting enzyme (TACE) inhibitors,[19] we also report an expedient synthesis of enantiopure *cis*-4-hydroxypipecolic acid[20] starting from the same lactam precursor.

Results and Discussion

Synthesis of N-Acylated 4,6-Dioxopiperidines. By analogy with the synthesis of chiral tetramic acids from

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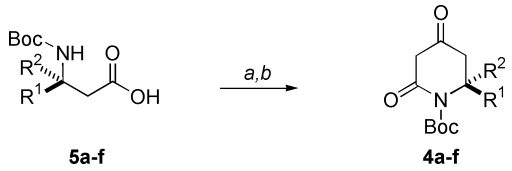
TABLE 1 [a]



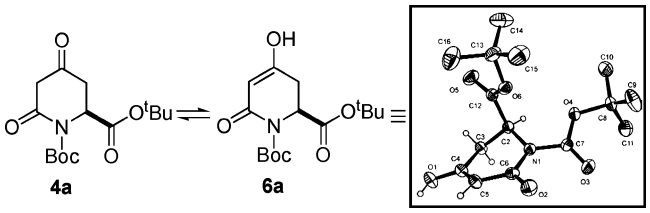
5a-f **4a-f**

compound	R^1	R^2	purified yield (%)
4a	COO^{t}Bu	H	77
4b	COOBn	H	85
4c	H	^{i}Bu	68
4d	H	Bn	87
4e	H	^{i}Pr	63
4f	H	Me	93

[a] (a) Meldrum's acid, EDC, DMAP, CH_2Cl_2; (b) AcOEt, reflux.

α-amino acids,[17] condensation of N-protected 3-aminopropanoic acids with Meldrum's acid in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and DMAP, followed by cyclization at 80 °C in ethyl acetate, provides a convenient and short entry to enantiopure N-acylated 4,6-dioxopiperidines **4**. Dioxopiperidines **4a**−**f** were prepared in good to excellent yields starting from the protected Asp derivatives **5a**,**b** and β^3-amino acids **5c**−**f** (Table 1). While purification of **4b** required chromatography on silica gel,[21] all other compounds (**4a** and **4c**−**f**) were recovered in an analytically pure form by simple crystallization from CH_2Cl_2/pentane.

Dioxopiperidines **4** exist in equilibrium with the thermodynamically stable enol form **6** (Figure 1). Very similar to what is observed with other 1,3-dicarbonyl compounds and N-protected chiral tetramic acids in particular, the keto form **4** exclusively is populated in $CDCl_3$, while ^{1}H and ^{13}C NMR in DMSO-d_6 show only the enol form **6**. X-ray diffraction studies on crystals of **4a** and **4e** grown from AcOEt/hexane reveal the enol tautomers **6a** (Figure 1) and **6e**.[22] Both structures share very similar structural features.



4a **6a**

FIGURE 1. Keto and enol tautomers **4a** and **6a** with the crystal structure of **6a**.

The C2−C12 bond (carboxylate side chain) forms an angle of 5.4(2)° with the normal to the mean plane of the ring atoms in **6a**, confirming the expected axial orientation of the C2 ring substituent because of the minimization of the allylic A(1,3) strain. The piperidine ring in **6a** assumes a sofalike conformation, with the C2 atom deviating by 0.599(3) Å from the least-squares plane defined by the five other atoms. The hydroxyl group at the 4 position, the unique potential strong proton donor of **6a**, is involved in the crystal packing as previously described for **6e**.[22] Strong hydrogen bonds involving this hydroxyl group at C4 and the carbonyl oxygen at position C6 [d(O···O): 2.625(2) Å] as a proton acceptor link the molecules in infinite C(6)[23] chains running along the b axis.

Diastereoselective Reduction Studies. N-acylated chiral tetramic acids can be reduced stereoselectively to the corresponding *cis*-4-hydroxy derivatives either by treatment with $NaBH_4$ in CH_2Cl_2/AcOH[17a−c] or by hydrogenation with PtO_2 (Adam's catalyst) in EtOAc.[17d] Herein, both procedures have been evaluated for the reduction of N-acylated 4,6-dioxopiperidines **4**. Treatment of **4** with $NaBH_4$ in CH_2Cl_2/AcOH (9:1) for 72 h resulted in a quantitative reduction of the keto functionality[24] and gave the expected 4-hydroxylated adduct **2** with de values in the range of 68−98% as determined by HPLC of the crude products (Table 2).

The selectivity of the reaction is significantly influenced by the bulk of the side chain at C2, with the lowest and highest selectivities being observed for the methyl and isopropyl groups, respectively. In the case of the carboxylate side chains, the *tert*-butyl ester group in **4a** exerts a stronger stereodirecting effect than the corresponding benzyl ester. Compounds **2a** and **2c** were obtained in diastereomerically pure form (>99% de) following a single recrystallizaton step (Table 2), and their absolute configuration at C4 was confirmed by X-ray crystal structure determination. Compound **2a** (Figure 2) adopts a chair conformation with atoms N1 and C4 displaced on opposite sides of the C2, C3, C5, and C6 mean plane by −0.355(4) and 0.657(1) Å, respectively. The hydroxyl- and *tert*-butylcarboxylate groups in the 4 and 6 positions of the piperidine ring assume an axial orientation, as can be seen from the angles [5.7(2)° and 16.8(1)°] between the normal to the mean plane of the ring atoms and the bonds C4−O1 and C2−C12, respectively.[25] The rules governing the crystal packing of **6a**

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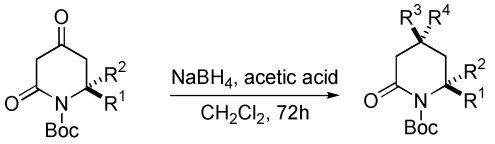
(25) In contrast, the hydroxyl and isobutyl groups in the crystal structure of **2c** assume an equatorial orientation (ref 22).

TABLE 2. Reduction of N-Acylated 4,6-Dioxopiperidines 4



dioxopiperidine	R^1	R^2	R^3	R^4	dr[a] of **2**	yield[b] (%)
4a	COO^{t}Bu	H	OH	H	7:93 (0:100)[c]	89 (82)[c]
4b	COOBn	H	OH	H	15:85	85
4c	H	^{i}Bu	H	OH	90:10 (100:0)[d]	93 (71)[d]
4d	H	Bn	H	OH	91:9	91
4e	H	^{i}Pr	H	OH	>99:1	95
4f	H	Me	H	OH	84:16	87

[a] (2*S*,4*R*)-**2**/(2*S*,4*S*)-**2**; ratio determined by analytical C_{18} RP-HPLC of the crude product. [b] Mixture of (2*S*,4*R*)-**2** and (2*S*,4*S*)-**2** obtained after purification of the crude product by a flash column chromatography. [c] Values in parentheses are for (2*S*,4*S*)-**2a** isolated by recrystallization. [d] Values in parentheses are for (2*S*,4*R*)-**2c** isolated by recrystallization.

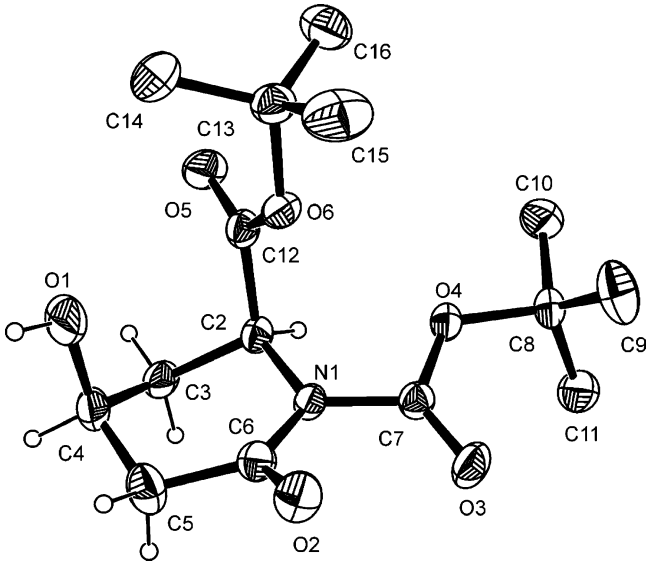
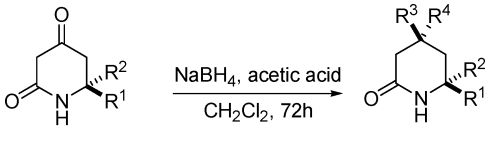


FIGURE 2. ORTEP-3 view of **2a** with the atom numbering scheme and 25% probability displacement ellipsoids. H atoms except those of the piperidine ring are omitted for clarity.

and **2a** are similar to those of the hydrogen-bonded molecules of **2a** forming zigzag C(7) chains.

The reduction of the corresponding **7** in a fashion similar to substituted cyclohexanones[26] is believed to be driven by the torsional effects that favor attack of the hydride reagent across the axial face of the C=O. Dioxopiperidines **7** were prepared in quantitative yield by the treatment of **4** with trifluoroacetic acid, and their reduction was studied under the same conditions for comparison (Table 3). Overall, yields of 4-hydroxylated product **8** were lower. In the absence of the A(1,3) strain, the *cis*-4-hydroxyl isomer is still obtained as the major product, thus confirming attack across the axial face of the C=O, but the de values were lower (58−68%). The stereoselectivity is essentially independent of the bulk

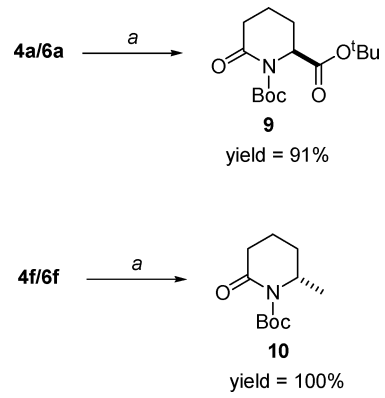
TABLE 3. Reduction of 6-Substituted 2,4-Dioxopiperidine 7



dioxopiperidine	R^1	R^2	R^3	R^4	dr[a] of **8**	yield[b] (%)
7b	COOBn	H	OH	H	21:79	89
7c	H	^{i}Bu	H	OH	82:18	62
7d	H	Bn	H	OH	84:16	86
7e	H	^{i}Pr	H	OH	84:16	49
7f	H	Me	H	OH	80:20	37

[a] (2*S*,4*R*)-**8**/(2*S*,4*S*)-**8**; ratio determined by analytical C_{18} RP-HPLC of the crude product. [b] Mixture of (2*S*,4*R*)-**8** and (2*S*,4*S*)-**8** obtained after purification of the crude product by a flash column chromatography.

SCHEME 1 [a]



[a] (a) PtO_2, H_2, AcOEt, 1 atm.

of the side chain at C6 (Table 3). A similar selectivity (85:15 cis/trans) was reported by Davis and co-workers in the reduction of the related enantiopure (*R*)-6-phenylpiperidine-2,4-dione.[7a]

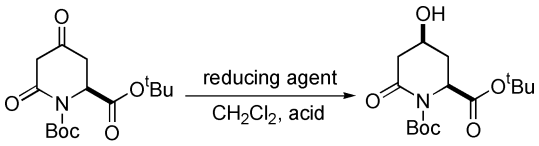
In contrast to N-acylated chiral tetramic acids,[17d] hydrogenation of N-acylated 4,6-dioxopiperidines **4** with Adam's catalyst in EtOAc failed to yield the expected 4-hydroxylated derivatives. Hydrogenation of **4a** and **4f** resulted in the quantitative formation of the fully reduced N-acylated piperidin-2-ones **9**[27] and **10** (Scheme 1). Changing the solvent (THF, $CHCl_3$) or the amount of catalyst (5−15%) did not improve the selectivity of the reaction, and the yields of **2a** and **2f** were consistently below 10%. Monitoring the progression of the reaction by C_{18} RP-HPLC revealed that **9** starts to form immediately. Its amount increased as the starting material was consumed, with the amount of **2a** remaining low. No reaction took place when Adam's catalyst was replaced by Pd on C or by Pearlman's catalyst.

In an attempt to further improve the selectivity of the reduction of **4a** to **2a** with a view to synthesize 4-hydroxypipecolate and 4-hydroxylysine derivatives, other reducing agents (Table 4) were examined. Of all the other borohydride reagents considered, $NaBH_4$ gave the best results. Substituting $NaBH(OAc)_3$ for $NaBH_4$ (entry 2)

(26) Hutchins, R. O.; Su, W. Y.; Sivakumar, R.; Cistone, F.; Stercho, Y. P. *J. Org. Chem.* **1983**, *48*, 3412−3422.

(27) For another route to δ-lactam **9** from **5a** in 74% yield, see ref 14.

TABLE 4. Effect of the Borohydride Reagent and the Carboxylic Acid on the Reduction of 4a



4a **2a**

entry	reducing agent	carboxylic acid	time (h)	dr[a] of **2a**	yield[b] (%)
1	$NaBH_4$	acetic[c]	72	7:93 (>99)[d]	89 (82)[d]
2	$NaBH(OAc)_3$	acetic[c]	72	4:96	61
3	$Me_4NBH(OAc)_3$	acetic[c]	16		0[e]
4	$NaBH_3CN$	acetic[c]	16	25:75	93

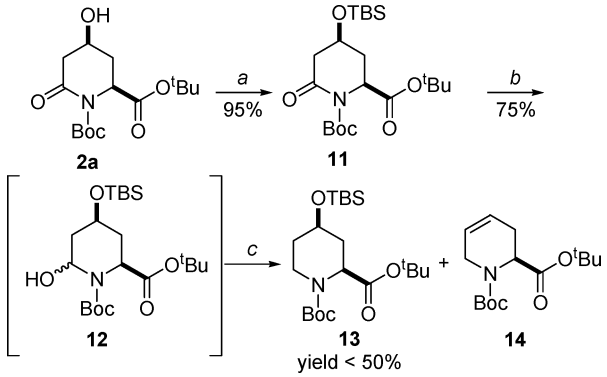
[a] (2*S*,4*R*)-**2a**/(2*S*,4*S*)-**2a**; ratio determined by analytical C_{18} RP-HPLC of the crude product. [b] Mixture of (2*S*,4*R*)-**2a** and (2*S*,4*S*)-**2a** obtained after purification of the crude product by a flash column chromatography. [c] A total of 10% v/v of acetic acid. [d] Values in parentheses are for (2*S*,4*S*)-**2a** isolated by recrystallization. [e] Degradation of the starting material.

improved the stereoselectivity, but the reaction never reached completion. It is worth mentioning that replacing Na^+ with the bulkier Me_4N^+ countercation[28] resulted in complete degradation of **4a**, and no hydroxylated product was obtained (entry 3).[29] When $NaBH_3CN$ was used, the reduction was completed within 16 h, but the de was only 50% (entry 4).

The nature of the carboxylic acid exerts a moderate effect on the stereoselectivity of the reaction (in the Supporting Information). However, pivalic acid gave slightly better results than AcOH (dr 95:5, yield 93%).

(2*S*,4*R*)-4-Hydroxypipecolate and (2*S*,4*S*)-4-Hydroxypipecolate Syntheses. With (2*S*,4*S*)-4-hydroxy-6-oxo-1,2-piperidinedicarboxylate **2a** in hand, we first envisioned its two-step conversion into 4-hydroxypipecolate **17** via the corresponding hemiaminal. This method had previously been reported for the reduction of pyroglutamates to proline derivatives[30] and *N*-Boc-protected piperidin-2-ones to pipecolates[18,30c] in high yields. However, partial reduction of **2a** with $LiEt_3BH$ (super hydride) did not provide the desired hemiaminal but gave the degradation byproducts. Protection of the secondary alcohol prior to the reduction was mandatory. The resulting hemiaminal **12** was isolated in 75% and characterized by ^1H and ^{13}C NMR. The reduction of crude **12** with $Et_3SiH/Et_2O{\cdot}BF_3$ proved to be difficult because of the partial removal of the TBS group. The desired hydroxypipecolate **13** was finally recovered in low yield together with the pipecolate **14** (Scheme 2). Compound **14** was unambiguously characterized by COSY NMR experiments. Because compounds **13** and **14** are extremely close on TLC and almost inseparable by chromatography, this route was not investigated further.

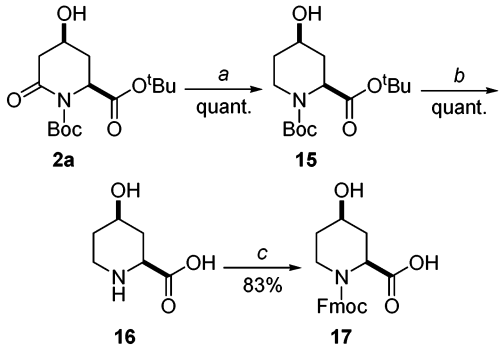
SCHEME 2 [a]



2a **11** **12** **13** **14**

[a] (a) TBSCl, imidazole, CH_2Cl_2; (b) $LiEt_3BH$, THF, −78 °C; (c) Et_3SiH, $Et_2O{\cdot}BF_3$, CH_2Cl_2, −78 °C.

SCHEME 3 [a]



2a **15** **16** **17**

[a] (a) $BH_3{\cdot}SMe_2$, THF, rt; (b) HCl, dioxane; (c) FmocOSu, K_2CO_3, acetone/H_2O.

Alternatively, direct reduction of **2a** with $BH_3{\cdot}SMe_2$ was considered.[31] Although this reagent achieves complete reduction of the lactam functionality in one single step, it has not often been used. The possible reasons could be the need for heating and the long reaction times. Nevertheless, in our hands, lactam **2a** was cleanly reduced in 16 h at room temperature and yielded pure **15** in quantitative yield after workup (Scheme 3).

Simultaneous deprotection of the Boc and *tert*-butyl ester functional groups yielded the (2*S*,4*R*)-4-hydroxypipecolic acid (**16**). Protection of the secondary amine by a (fluorenylmethoxy)carbonyl (Fmoc) group afforded the *cis*-hydroxypipecolate **17** in an overall yield of 52%, starting from the Asp derivative **5a**. Although the synthesis of **17** described in the experimental part is on a relatively small scale (ca. 250 mg), the procedure was also found to be suitable for a larger batch synthesis (10−50 g).

For the preparation of the corresponding *trans*-(2*S*,4*S*)-4-hydroxypipecolate, we initially tried to invert the C4 stereocenter directly on **2a** under Mitsunobu conditions.[32]

(28) $Me_4NBH(OAc)_3$ has been described as an excellent reagent for the reduction of *β*-hydroxy ketones. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

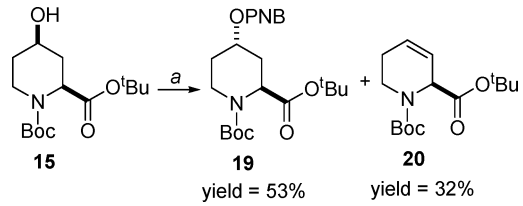
(29) In contrast, the reduction of **4c** with $Me_4NBH(OAc)_3$ resulted in a clean deprotection of the Boc group to give 4,6-dioxopiperidine **8c** in 84% yield. Didierjean, C.; Marin, J.; Wenger, E.; Briand, J. P.; Aubry, A.; Guichard, G. *Acta Crystallogr.* **2003**, in press.

(30) For recent examples, see: (a) Oba, M.; Miyakawa, A.; Nishiyama, K. *J. Org. Chem.* **1999**, *64*, 9275−9278. (b) Oba, M.; Terauchi, T.; Miyakawa, A.; Nishiyama, K. *Tetrahedron: Asymmetry* **1999**, *10*, 937−945. (c) Escribano, A.; Carreño, C.; Garcìa Ruano, J. L. *Tetrahedron Lett.* **1994**, *35*, 2053−2056.

(31) For examples of a lactam ring reduction with $BH_3{\cdot}SMe_2$, see: (a) Courcambeck, J.; Bihel, F.; De Michelis, C.; Quévéler, G.; Kraus, J.-L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1421−1430. (b) Moody, C. M.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3519−3530. (c) Herdeis, C.; Hubmann, H. P. *Tetrahedron: Asymmetry* **1994**, *5*, 351−354. (d) Moody, C. M.; Young, D. W. *Tetrahedron Lett.* **1994**, *35*, 7277−7280. (e) Moody, C. M.; Starkmann, B. A.; Young, D. W. *Tetrahedron Lett.* **1994**, *35*, 5485−5488. (f) Heffner, R. J.; Joullié, M. M. *Tetrahedron Lett.* **1989**, *30*, 7021−7024.

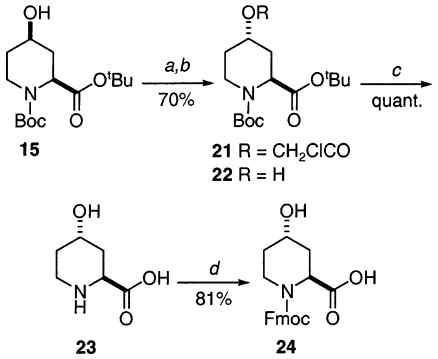
(32) Mitsunobu, O. *Synthesis* **1981**, 1−28.

SCHEME 4 [a]



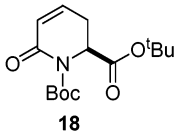
[a] (a) PNBOH, DIAD, PPh_3, THF.

SCHEME 5 [a]



[a] (a) $CH_2ClCOOH$, DIAD, PPh_3, THF; (b) 1 N NaOH, dioxane/H_2O; (c) HCl, dioxane; (d) FmocOSu, K_2CO_3, acetone/H_2O.

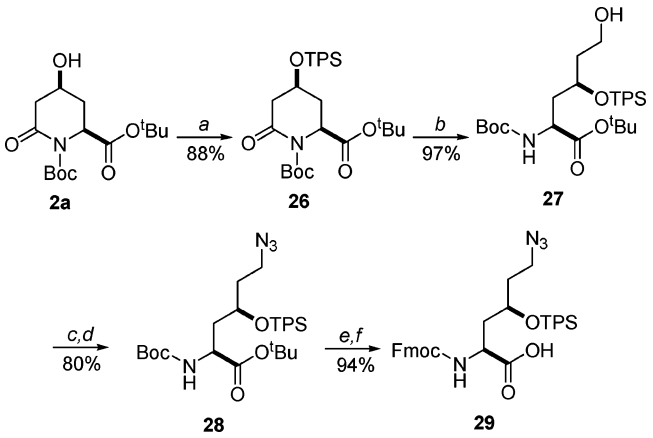
Unfortunately, all of our attempts resulted in β elimination and yielded α,β-unsaturated lactam **18**[33] as the sole product. Starting from *cis*-hydroxypipecolate, the inversion reaction has already been mentioned, but not fully described.[34] Herein, treatment of **15** with *p*-nitrobenzoic acid under Mitsunobu conditions gave the desired pipecolate **19** with an inverted configuration at C4 in 53% yield, together with the 3,4-unsaturated pipecolate **20**. Both pipecolates **19** and **20** were unambiguously characterized by X-ray diffraction studies (Scheme 4 and the Supporting Information).



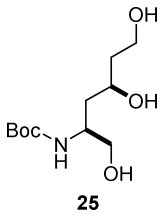
Chloroacetic acid was subsequently found to be the best acid to promote inversion at C4.[35] The Mitsunobu reaction of **15** with chloroacetic acid afforded chloroacetate **21**, which was immediately cleaved under basic conditions to give the corresponding *trans*-4-hydroxypipecolate **22** in 70% yield (two steps). Deprotection of the *N*-Boc and *tert*-butyl ester functional groups yielded (2*S*,4*S*)-4-hydroxypipecolic acid **23**, which was reprotected in **24** with a yield of 57% from **15** (Scheme 5).

(2*S*,4*R*)-4-Hydroxylysine and (2*S*,4*S*)-4-Hydroxylysine Syntheses. In contrast to (2*S*,5*R*)-5-hydroxy-6-oxo-1,2-piperidinedicarboxylate (**1**) (R^1 = COOR, R^2 = H), which could be opened directly using sodium borohydride in ethanol to give the corresponding 1,2-diol in high yield, the ring opening of **2a** under the same conditions failed to give the desired 1,3-diol derivative. Instead, triol **25**, unambiguously characterized by ^1H and ^{13}C NMR, was isolated as the major side product in 32% yield.

SCHEME 6 [a]



[a] (a) TPSCl, imidazole, CH_2Cl_2; (b) $NaBH_4$, EtOH; (c) MsCl, Et_3N, CH_2Cl_2; (d) NaN_3, DMF; (e) TFA/CH_2Cl_2 (1:1); (f) FmocOSu, K_2CO_3, acetone/H_2O.



However, upon protection of the secondary alcohol by a TPS prior to the reduction, the O-protected 1,3-diol **27** could be obtained in 85% yield from **2a**. After purification by filtration through a short plug of silica, the primary alcohol was converted to the corresponding azide by mesylation followed by nucleophilic substitution with NaN_3. The azide can serve as a temporary protection for the amino group of 4-hydroxylysine; the reduction of the azide function being quantitatively and cleanly performed on the solid support at the end of the elongation of the peptidic chain.[36] Selective deprotection of *N*-Boc and *tert*-butyl ester protecting groups in the presence of *tert*-butyldiphenylsilyl directly followed by protection of the primary amine with a Fmoc functionality gave (2*S*,4*R*)-4-hydroxylysine **29**, which was ready for use in a peptide synthesis in 41% overall yield from **5a** (Scheme 6).

Conclusion

Enantiopure N-acylated δ-lactams **1** (R^1 = COOtBu, R^2 = H)[14] and **2a** (this paper), monohydroxylated at the α and β positions, respectively, represent attractive

(33) Enantiopure N-acylated 2-substituted 4,5-unsaturated 6-oxopiperidines are useful building blocks, which can be further transformed in a stereocontrolled manner to give the corresponding 4-substituted derivatives. For the conjugate addition of organocuprate reagents, see refs 6h and 11c. For the conjugate addition of nitroalkanes, see: (a) Hanessian, S.; Seid, M.; Nilsson, I. *Tetrahedron Lett.* **2002**, *43*, 1991−1994.

(34) Bellier, B.; Da Nascimento, S.; Meudal, H.; Gincel, E.; Roques, B. P.; Garbay, C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1419−1424.

(35) The inversion reaction in the presence of formic acid (ref 34) gave a lower yield of the corresponding *trans*-hydroxypipecolate.

(36) (a) Meldal, M.; Juliano, M. A.; Jansson, A. M. *Tetrahedron Lett.* **1997**, *38*, 2531−2534. (b) Lundquist, J. T.; Pelletier, J. C. *Org. Lett.* **2001**, *3*, 781−783.

building blocks for the synthesis of 5- and 4-hydroxylysine derivatives, conveniently protected for a solid-phase peptide synthesis or for further transformations (e.g., glycosylation). Their direct precursors **3** (R^1 = COOtBu, R^2 = H) and **4a** are easily prepared [**3** (R^1 = COOtBu, R^2 = H), 74% yield (three steps);[14] **4a**, 77% yield (two steps)] following a divergent approach starting from the readily available Boc-Asp-O^{t}Bu, which is first condensed with Meldrum's acid. X-ray analyses confirmed that in lactams **3** and **4** the carboxylate side chain at the δ position adopts a quasi-axial orientation (because of the minimization of the pseudoallylic A(1,3) strain), which is useful to differentiate both faces of the molecule in view of subsequent asymmetric transformations. Herein, we found that di-*tert*-butyl (2*S*)-4,6-dioxo-1,2-piperidinedicarboxylate (**4a**) was reduced by $NaBH_4$ in CH_2Cl_2/AcOH in a manner similar to those of the five-membered-ring tetramic acids to afford the corresponding *cis*-4-hydroxylated derivatives **2a** in good yield and selectivity. The ring opening under reductive conditions ($NaBH_4$, EtOH) following protection of the hydroxyl group gave the 1,3-diol **27**, which was further transformed to the 4-hydroxylysine derivative **29**. Alternatively, by treatment with BH_3·SMe_2, **2a** was quantitatively transformed to the enantiopure *cis*-4-hydroxypipecolic acid **16**, an amino acid constituent of natural antibiotics and several drug candidates.

Experimental Section

Materials. Boc-Asp-O^{t}Bu (**5a**)[37] was prepared starting from the commercially available Boc-Asp(Bn)-OH. β-Amino acid derivatives **5d**−**g** were prepared by Arndt−Eister homologation of the Boc-protected α-amino acids.[38]

Preparation of 4,6-Dioxopiperidines 4a−**f.** EDC (1.5 equiv), DMAP (1.5 equiv), and Meldrum's acid (1.0 equiv) were added to a 0.25 M solution of acid **5** in CH_2Cl_2 at 0 °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, filtered, and concentrated in vacuo. The residue was dissolved in AcOEt to afford a 0.1 M solution, which was refluxed for 5 h. After being allowed to cool to room temperature, the mixture was washed with 1 N $KHSO_4$ and brine. Drying over Na_2SO_4 and evaporation of the filtrate afforded crude **4**, which was purified by recrystallization or flash chromatography.

Di-*tert*-butyl-(2*S*)-4,6-dioxo-1,2-piperidinedicarboxylate (4a). Recrystallization of the crude product from CH_2Cl_2/pentane gave **4a** (5.82 g, yield = 77%): HPLC t_R 8.14 (linear gradient, 30−100% B, 20 min); yellowish crystals; $[\alpha]_D$ +98.0 (*c* 1.0, $CHCl_3$); mp 124−126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.04 (dd, *J* = 6.8, 2.2 Hz, 1H), 3.50 (d, *J* = 19.5 Hz, 1H), 3.34 (d, *J* = 19.5 Hz, 1H), 2.99 (dd, *J* = 17.5, 2.2 Hz, 1H), 2.81 (dd, *J* = 17.6, 6.8 Hz, 1H), 1.52 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1 (C), 168.9 (C), 165.4 (C), 151.2 (C), 84.6 (C), 83.9 (C), 54.6 (CH), 50.3 (CH_2), 40.9 (CH_2), 27.9 ($3CH_3$), 27.8 ($3CH_3$). Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.36; H, 7.48; N, 4.38.

Di-*tert*-butyl (2*S*)-4-Hydroxy-6-oxo-3,6-dihydro-1,2(2*H*)-pyridinedicarboxylate (6a): ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 4.92 (d, *J* = 1.8 Hz, 1H), 4.81 (dd, *J* = 6.9, 1.7 Hz, 1H), 3.34 (bs, 1H), 3.00 (ddd, *J* = 17.7, 6.9, 1.8 Hz, 1H), 2.59 (dd, *J* = 17.7, 1.7 Hz, 1H), 1.43 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (C), 169.3 (C), 164.5 (C), 152.4 (C), 96.7 (CH), 82.0 (C), 81.8 (C), 55.4 (CH), 30.7 (CH_2), 28.1 ($3CH_3$), 27.9 ($3CH_3$).

2-Benzyl 1-*tert*-Butyl (2*S*)-4,6-Dioxo-1,2-piperidinedicarboxylate (4b). Purification of the crude product by flash column chromatography [AcOEt/Hex/AcOH (5:5:0.1)] gave **4b** (2.19 g, yield = 85%): HPLC t_R 9.05 (linear gradient, 30−100% B, 20 min); colorless oil; $[\alpha]_D$ +76.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 5.24 (dd, *J* = 6.9, 2.0 Hz, 1H), 5.19 (s, 2H), 3.45 (d, *J* = 19.4, Hz, 1H), 3.31 (d, *J* = 19.4 Hz, 1H), 3.04 (dd, *J* = 17.9, 2.0 Hz, 1H), 2.84 (dd, *J* = 17.9, 6.9 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8 (C), 169.9 (C), 165.1 (C), 151.1 (C), 134.5 (C), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.0 (CH), 84.9 (C), 68.3 (CH_2), 53.9 (CH), 50.5 (CH_2), 40.5 (CH_2), 27.8 ($3CH_3$). Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.32; H, 6.07; N, 4.19.

***tert*-Butyl (2*S*)-2-Isobutyl-4,6-dioxo-1-piperidinecarboxylate (4c).** Recrystallization of the crude product from CH_2Cl_2/pentane gave **4c** (2.69 g, yield = 68%): HPLC t_R 8.61 (linear gradient, 30−100% B, 20 min); colorless crystals; $[\alpha]_D$ −78.9 (*c* 1.0, $CHCl_3$); mp 116−119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69−4.63 (m, 1H), 3.45 (d, *J* = 20.7 Hz, 1H), 3.35 (d, *J* = 20.7 Hz, 1H), 2.75 (dd, *J* = 16.8, 5.3 Hz, 1H), 2.65 (dd, *J* = 16.8, 2.6 Hz, 1H), 1.63−1.51 (m, 2H), 1.53 (s, 9H), 1.39−1.30 (m, 1H), 0.92 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4 (C), 166.2 (C), 151.5 (C), 84.1 (C), 50.2 (CH), 49.1 (CH_2), 43.7 (CH_2), 43.0 (CH_2), 27.9 ($3CH_3$), 25.1 (CH), 23.1 (CH_3), 21.5 (CH_3). Anal. Calcd for $C_{14}H_{25}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.80; H, 8.67; N, 5.08.

***tert*-Butyl (2*S*)-2-Benzyl-4,6-dioxo-1-piperidinecarboxylate (4d).** Recrystallization of the crude product from CH_2Cl_2/pentane gave **4d** (567 mg, yield = 87%): HPLC t_R 9.12 (linear gradient, 30−100% B, 20 min); yellowish crystals; $[\alpha]_D$ −92.6 (*c* 1.0, $CHCl_3$); mp 130−132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.24 (m, 3H), 7.16−7.13 (m, 2H), 4.79−4.73 (m, 1H), 3.37 (d, *J* = 20.7 Hz, 1H), 3.26 (d, *J* = 20.8 Hz, 1H), 3.07 (dd, *J* = 13.3, 5.1 Hz, 1H), 2.69 (dd, *J* = 13.3, 9.5 Hz, 1H), 2.64 (m, 2H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2 (C), 166.1 (C), 151.5 (C), 135.9 (C), 129.5 (2CH), 128.9 (2CH), 127.3 (CH), 84.2 (C), 53.5 (CH), 49.1 (CH_2), 42.1 (CH_2), 41.0 (CH_2), 27.9 ($3CH_3$). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.57; H, 7.09; N, 4.51.

***tert*-Butyl (2*S*)-2-Isopropyl-4,6-dioxo-1-piperidinecarboxylate (4e).** Recrystallization of the crude product from CH_2Cl_2/pentane gave **4e** (645 mg, yield = 63%): HPLC t_R 7.32 (linear gradient, 30−100% B, 20 min); white crystals; $[\alpha]_D$ −67.7 (*c* 1.0, $CHCl_3$); mp 101−103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41−4.35 (m, 1H), 3.44 (d, *J* = 20.7 Hz, 1H), 3.33 (d, *J* = 20.7 Hz, 1H), 2.82 (dd, *J* = 17.0, 2.4 Hz, 1H), 2.67 (dd, *J* = 17.0, 5.7 Hz, 1H), 1.80−1.68 (m, 1H), 1.53 (s, 9H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7 (C), 166.2 (C), 152.3 (C), 84.0 (C), 57.1 (CH), 49.2 (CH_2), 41.9 (CH_2), 33.0 (CH), 27.9 ($3CH_3$), 19.6 (CH_3), 19.5 (CH_3). Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.00; H, 8.52; N, 5.37.

***tert*-Butyl (2*S*)-2-Methyl-4,6-dioxo-1-piperidinecarboxylate (4f).** Recrystallization of the crude product from CH_2Cl_2/pentane gave **4f** (625 mg, yield = 93%): HPLC t_R 13.17 (linear gradient, 30−100% B, 20 min); white crystals; $[\alpha]_D$ −108.5 (*c* 1.0, $CHCl_3$); mp 127−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71−4.65 (m, 1H), 3.45 (d, *J* = 20.7 Hz, 1H), 3.33 (d, *J* = 20.7 Hz, 1H), 2.81 (dd, *J* = 16.7, 5.9 Hz, 1H), 2.55 (dd, *J* = 16.6, 2.2 Hz, 1H), 1.53 (s, 9H), 1.31 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2 (C), 165.9 (C), 151.5 (C), 84.1 (C), 49.0 (CH_2), 48.0 (CH), 45.3 (CH_2), 27.9 ($3CH_3$), 20.5 (CH_3). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.96; H, 7.51; N, 6.38.

General Procedure for 4,6-Dioxopiperidine Reduction. The desired dioxopiperidine was placed in an argon-filled round-bottom flask, dissolved in distilled CH_2Cl_2 to give a ca. 0.15 M solution, and cooled to 0 °C. The indicated carboxylic acid was introduced via a hypodermic syringe, and the mixture was stirred for 5 min. The indicated amount of reducing agent was added portionwise, and the mixture was allowed to reach

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room temperature. The reaction time was specific to each experiment. The reaction was quenched by the addition of water and stirred for 10 min. CH_2Cl_2 was evaporated and replaced by AcOEt, and the organic layer was washed with a saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over Na_2SO_4, concentrated, and purified by recrystallization or flash chromatography.

Di-*tert*-butyl (2*S*,4*S*)-4-Hydroxy-6-oxo-1,2-piperidinedicarboxylate (2a). Recrystallization of the crude product from CH_2Cl_2/diisopropyl ether gave **2a** (820 mg, yield = 82%, de > 99%): HPLC t_R 6.19 (linear gradient, 30−100% B, 20 min); colorless crystals; $[\alpha]_D$ −18.0 (*c* 1.0, $CHCl_3$); mp 132−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.61 (dd, J = 6.5, 4.1 Hz, 1H), 4.23 (m, 1H), 2.74 (dd, J = 17.4, 4.8 Hz, 1H), 2.69 (bs, 1H), 2.60 (ddd, J = 17.4, 4.6, 1.6 Hz, 1H), 2.41−2.33 (m, 1H), 2.20 (ddd, J = 14.1, 6.6, 2.9 Hz, 1H), 1.48 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (C), 168.9 (C), 151.8 (C), 83.4 (C), 82.4 (C), 63.9 (CH), 56.2 (CH), 43.2 (CH_2), 32.9 (CH_2), 27.9 ($3CH_3$), 27.8 ($3CH_3$). Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 56.85; H, 7.95; N, 4.44.

2-Benzyl 1-*tert*-Butyl (2*S*,4*S*)-4-Hydroxy-6-oxo-1,2-piperidinedicarboxylate (2b). Purification of the crude product by flash column chromatography [AcOEt/AcOH (10:0.1)] gave **2b** (86 mg, yield = 85%): HPLC t_R 7.87 (linear gradient, 30−100% B, 20 min); colorless oil; $[\alpha]_D$ −19.8 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.30 (m, 5H), 5.19 (d, J = 12.3 Hz, 1H), 5.10 (d, J = 12.3 Hz, 1H), 4.78 (dd, J = 6.6, 3.7 Hz, 1H), 4.28−4.23 (m, 1H), 2.75 (dd, J = 17.4, 4.8 Hz, 1H), 2.63 (ddd, J = 17.5, 3.8, 1.8 Hz, 1H), 2.53−2.44 (m, 1H), 2.22 (ddd, J = 14.2, 6.4, 2.5 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C), 169.0 (C), 151.7 (C), 135.3 (C), 128.5 (2CH), 128.3 (CH), 128.3 (2CH), 83.7 (C), 67.4 (CH_2), 63.5 (CH), 55.5 (CH), 43.0 (CH_2), 32.9 (CH_2), 27.8 ($3CH_3$). Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.76; H, 6.67; N, 3.99.

***tert*-Butyl (2*S*,4*R*)-4-Hydroxy-2-isobutyl-6-oxo-1-piperidinecarboxylate (2c).** Recrystallization of the crude product from CH_2Cl_2/pentane gave **2c** (572 mg, yield = 71%, de > 99%): HPLC t_R 7.51 (linear gradient, 30−100% B, 20 min); colorless crystals; $[\alpha]_D$ +66.3 (*c* 1.0, $CHCl_3$); mp 94−95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18−4.09 (m, 2H), 2.82 (ddd, J = 16.6, 5.7, 1.8 Hz, 1H), 2.59 (m, 1H), 2.48 (dd, J = 16.6, 8.7 Hz, 1H), 2.30−2.21 (m, 1H), 1.71−1.57 (m, 3H), 1.51 (s, 9H), 0.92 (d, J = 4.2 Hz, 3H), 0.90 (d, J = 4.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.0 (C), 152.4 (C), 83.4 (C), 64.1 (CH), 52.6 (CH), 44.8 (CH_2), 43.3 (CH_2), 35.5 (CH_2), 27.9 (3 CH_3), 24.8 (CH), 23.8 (CH_3), 21.2 (CH_3). Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 62.10; H, 9.48; N, 5.22.

***tert*-Butyl (2*S*,4*R*)-2-Benzyl-4-hydroxy-6-oxo-1-piperidinecarboxylate (2d).** Purification of the crude product by flash column chromatography [AcOEt/Hex (6:4)] gave **2d** (92 mg, yield = 91%): HPLC t_R 8.51 (linear gradient, 30−100% B, 20 min); colorless oil; $[\alpha]_D$ +32.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.22 (m, 5H), 4.37−4.28 (m, 1H), 4.19−4.11 (m, 1H), 3.13 (dd, J = 13.0, 4.2 Hz, 1H), 2.95 (dd, J = 13.0, 10.0 Hz, 1H), 2.82 (ddd, J = 16.6, 5.5, 1.5 Hz, 1H), 2.51 (dd, J = 16.6, 7.7 Hz, 1H), 2.33 (bs, 1H), 2.02−1.94 (m, 1H), 1.76−1.67 (m, 1H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (C), 152.5 (C), 137.5 (C), 129.6 (2CH), 128.6 (2CH), 126.7 (CH), 83.6 (C), 64.3 (CH), 55.8 (CH), 43.5 (CH_2), 41.3 (CH_2), 33.8 (CH_2), 28.0 ($3CH_3$). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 67.12; H, 7.71; N, 4.50.

***tert*-Butyl (2*S*,4*R*)-2-Isopropyl-4-hydroxy-6-oxo-1-piperidinecarboxylate (2e).** Purification of the crude product by flash column chromatography [AcOEt/Hex (7:3)] gave **2e** (94 mg, yield = 95%): HPLC t_R 6.00 (linear gradient, 30−100% B, 20 min); white crystals; $[\alpha]_D$ +68.5 (*c* 0.8, $CHCl_3$); mp 56−58 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11−4.01 (m, 1H), 3.95 (dt, J = 9.0, 5.8 Hz, 1H), 2.80 (ddd, J = 16.3, 5.5, 2.4 Hz, 1H), 2.60 (bs, 1H), 2.39 (dd, J = 16.2, 10.4 Hz, 1H), 2.17−2.04 (m, 2H), 1.68−1.57 (m, 1H), 1.50 (s, 9H), 0.91 (d, J = 3.3 Hz, 3H), 0.89 (d, J = 3.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (C), 153.2 (C), 83.6 (C), 64.0 (CH), 58.6 (CH), 43.2 (CH_2), 31.2 (CH_2), 30.7 (CH), 27.8 ($3CH_3$), 18.9 (CH_3), 16.0 (CH_3). Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.96; H, 9.21; N, 5.35.

***tert*-Butyl (2*S*,4*R*)-2-Methyl-4-hydroxy-6-oxo-1-piperidinecarboxylate (2f).** Purification of the crude product by flash column chromatography [AcOEt/Hex (8:2)] gave **2f** (83 mg, yield = 87%): HPLC t_R 11.56 (linear gradient, 5−65% B, 20 min); colorless oil; $[\alpha]_D$ +35.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12−4.05 (m, 2H), 2.79 (ddd, J = 16.4, 7.3, 2.0 Hz, 1H), 2.46 (dd, J = 16.6, 9.0 Hz, 1H), 2.28−2.19 (m, 1H), 2.25 (bs, 1H), 1.72−1.60 (m, 1H), 1.51 (s, 9H), 1.34 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 (C), 152.9 (C), 83.6 (C), 64.0 (CH), 50.1 (CH), 43.0 (CH_2), 38.7 (CH_2), 27.8 ($3CH_3$), 21.8 (CH_3). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.51; H, 8.51; N, 6.05.

Preparation of 4,6-Dioxopiperidines 7b−f. The desired dioxopiperidine was placed in an argon-filled round-bottom flask and dissolved in distilled CH_2Cl_2 to give a ca. 0.15 M solution. The same volume of trifluoroacetic acid was introduced via a hypodermic syringe, and the mixture was stirred for 2 h at room temperature. The solvents were evaporated, and the residue was purified by filtration through a plug of silica.

Benzyl (2*S*)-4,6-Dioxo-2-piperidinecarboxylate (7b). Purification of the crude product by filtration on silica (AcOEt) gave **7b** (106 mg, yield = 99%): TLC R_f 0.22 (AcOEt); white solid; $[\alpha]_D$ +50.2 (*c* 1.1, MeOH); mp 102−103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (bs, 1H), 7.41−7.29 (m, 5H), 5.19 (m, 2H), 4.41−4.36 (m, 1H), 3.33 (d, J = 20.0 Hz, 1H), 3.24 (d, J = 20.0 Hz, 1H), 2.88 (dd, J = 16.9, 5.7 Hz, 1H), 2.72 (dd, J = 16.9, 10.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9 (C), 169.8 (C), 168.8 (C), 134.4 (C), 128.9 (CH), 128.8 (2CH), 128.5 (2CH), 68.2 (CH_2), 50.7 (CH), 47.5 (CH_2), 40.7 (CH_2). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.16; H, 5.47; N, 5.64.

(2*S*)-2-Isobutyl-4,6-dioxopiperidine (7c). Purification of the crude product by filtration on silica [CH_2Cl_2/MeOH (9:1)] gave **7c** (645 mg, yield = 100%): TLC R_f 0.52 [CH_2Cl_2/MeOH (9:1)]; white solid; $[\alpha]_D$ +30.6 (*c* 1.0, MeOH); mp 122−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (bs, 1H), 3.75 (m, 1H), 3.29 (m, 2H), 2.70 (dd, J = 16.3, 4.2 Hz, 1H), 2.34 (dd, J = 16.3, 8.8 Hz, 1H), 1.77−1.68 (m, 1H), 1.56−1.47 (m, 1H), 1.42−1.34 (m, 1H), 0.95 (d, J = 2.7 Hz, 3H), 0.93 (d, J = 2.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5 (C), 170.6 (C), 47.1 (CH), 46.7 (CH_2), 44.5 (CH_2), 44.4 (CH_2), 24.3 (CH), 22.4 (CH_3), 22.1 (CH_3). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 64.16; H, 9.00; N, 8.24.

(2*S*)-2-Benzyl-4,6-dioxopiperidine (7d). Purification of the crude product by filtration on silica (AcOEt) gave **7d** (67 mg, yield = 100%): TLC R_f 0.24 (AcOEt); white solid; $[\alpha]_D$ +9.2 (*c* 1.0, MeOH); mp 156−158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.26 (m, 3H), 7.18−7.15 (m, 2H), 7.06 (bs, 1H), 3.95−3.88 (m, 1H), 3.24 (d, J = 20.1 Hz, 1H), 3.12 (dd, J = 20.1, 0.6 Hz, 1H), 2.87−2.84 (m, 2H), 2.66 (dd, J = 16.2, 4.5 Hz, 1H), 2.43 (ddd, J = 16.1, 8.5, 0.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8 (C), 169.1 (C), 135.4 (C), 129.3 (2CH), 129.0 (2CH), 127.5 (CH), 49.8 (CH), 47.1 (CH_2), 44.0 (CH_2), 42.0 (CH_2). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.96; H, 6.36; N, 6.62.

(2*S*)-2-Isopropyl-4,6-dioxopiperidine (7e). Purification of the crude product by filtration on silica [CH_2Cl_2/MeOH (9:1)] gave **7e** (548 mg, yield = 100%): TLC R_f 0.40 [CH_2Cl_2/MeOH (9:1)]; white solid; $[\alpha]_D$ +35.3 (*c* 1.0, MeOH); mp 88−90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (bs, 1H), 3.53−3.48 (m, 1H), 3.27 (m, 2H), 2.62 (dd, J = 16.1, 4.6 Hz, 1H), 2.45 (dd, J = 16.1, 8.7 Hz, 1H), 1.87−1.78 (m, 1H), 0.99 (d, J = 6.1 Hz, 3H), 0.97 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9 (C), 170.6 (C), 54.4 (CH), 46.6 (CH_2), 41.1 (CH_2), 32.2 (CH), 18.0 (CH_3), 17.7 (CH_3). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.61; H, 8.46; N, 8.75.

(2*S*)-2-Methyl-4,6-dioxopiperidine (7f). Purification of the crude product by filtration on silica [CH_2Cl_2/MeOH (9:1)] gave **7f** (56 mg, yield = 100%): TLC R_f 0.20 [CH_2Cl_2/MeOH (9:1)]; white solid; $[\alpha]_D$ +83.8 (*c* 1.0, MeOH); mp 124−127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (bs, 1H), 3.81−3.75 (m, 1H), 3.22 (m, 2H), 2.64 (dd, J = 16.3, 3.7 Hz, 1H), 2.29 (dd, J = 16.3, 9.7 Hz, 1H), 1.30 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4 (C), 169.5 (C), 47.1 (CH_2), 46.2 (CH_2), 44.4 (CH), 21.3 (CH_3). Anal. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.95; H, 7.11; N, 10.98.

Reduction of 7 into 8. The desired dioxopiperidine **7** was placed in an argon-filled round-bottom flask and dissolved in distilled CH_2Cl_2 to give a ca. 0.15 M solution. A total of 10% v/v of acetic acid was introduced via a hypodermic syringe, and the mixture was cooled to 0 °C. $NaBH_4$ (3 equiv) was added portionwise, and the mixture was allowed to reach room temperature. The reaction was stirred for 72 h and monitored by RP-HPLC. The reaction was quenched by the addition of water and stirred for 10 min. CH_2Cl_2 was evaporated and replaced by AcOEt, and the organic layer was washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over Na_2SO_4, concentrated, and purified by flash chromatography.

Benzyl (2*S*,4*S*)-4-Hydroxy-6-oxo-2-piperidinecarboxylate (8b). Purification of the crude product by flash column chromatography [AcOEt/AcOH (10:0.1)] gave **8b** (90 mg, yield = 89%): TLC R_f 0.19 [AcOEt/AcOH (10:0.1)]; colorless oil; $[\alpha]_D$ −1.1 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 6.84 (bs, 1H), 5.17 (m, 2H), 4.17−4.13 (m, 1H), 4.09−4.05 (m, 1H), 3.86 (bs, 1H), 2.58 (dd, J = 17.6, 4.6 Hz, 1H), 2.44−2.38 (m, 1H), 2.31−2.23 (m, 1H), 2.18−2.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (C), 170.8 (C), 135.0 (C), 128.6 (2CH), 128.5 (CH), 128.3 (2CH), 67.5 (CH_2), 63.6 (CH), 51.8 (CH), 39.8 (CH_2), 32.4 (CH_2). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.84; H, 6.05; N, 5.47.

(2*S*,4*R*)-4-Hydroxy-2-isobutyl-6-oxopiperidine (8c). Purification of the crude product by flash column chromatography [CH_2Cl_2/MeOH (9:1)] gave **8c** (63 mg, yield = 62%): TLC R_f 0.36 [CH_2Cl_2/MeOH (9:1)]; white solid; $[\alpha]_D$ +31.4 (*c* 0.8, MeOH); mp 179−180 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 4.01−3.92 (m, 1H), 3.49−3.40 (m, 1H), 2.64−2.56 (m, 1H), 2.20−2.15 (m, 2H), 1.80−1.70 (m, 1H), 1.46−1.26 (m, 3H), 0.94 (d, J = 3.9 Hz, 3H), 0.92 (d, J = 3.9 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.3 (C), 64.0 (CH), 48.1 (CH), 45.4 (CH_2), 40.0 (CH_2), 37.4 (CH_2), 23.8 (CH), 22.0 (CH_3), 21.2 (CH_3). Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 62.83; H, 10.05; N, 8.14.

(2*S*,4*R*)-4-Hydroxy-2-benzyl-6-oxopiperidine (8d). Purification of the crude product by flash column chromatography [CH_2Cl_2/MeOH (9:1)] gave **8d** (78 mg, yield = 86%): TLC R_f 0.32 [CH_2Cl_2/MeOH (9:1)]; white solid; $[\alpha]_D$ +57.3 (*c* 1.0, MeOH); mp 133−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.25 (m, 3H), 7.19−7.15 (m, 2H), 5.84 (bs, 1H), 4.06−3.97 (m, 1H), 3.63−3.54 (m, 1H), 2.88 (dd, J = 13.5, 5.4 Hz, 1H), 2.74−2.63 (m, 2H), 2.27 (dd, J = 17.0, 10.2 Hz, 1H), 2.20−2.15 (m, 1H), 2.55−1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (C), 136.3 (C), 129.2 (2CH), 129.0 (2CH), 127.2 (CH), 64.8 (CH), 51.3 (CH), 43.0 (CH_2), 40.8 (CH_2), 38.0 (CH_2). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.20; H, 7.57; N, 6.76.

(2*S*,4*R*)-4-Hydroxy-2-isopropyl-6-oxopiperidine (8e). Purification of the crude product by flash column chromatography [CH_2Cl_2/MeOH (9:1)] gave **8e** (99 mg, yield = 49%): TLC R_f 0.18 [CH_2Cl_2/MeOH (9:1)]; white solid; $[\alpha]_D$ +35.3 (*c* 1.0, MeOH); mp 149−152 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 4.01−3.90 (m, 1H), 3.32−3.28 (m, 1H), 2.60 (ddd, J = 17.0, 5.7, 2.2 Hz, 1H), 2.13 (ddd, J = 17.0, 10.6, 0.7 Hz, 1H), 2.06−1.98 (m, 1H), 1.88−1.77 (m, 1H), 1.40−1.28 (m, 1H), 0.95 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.8 (C), 64.2 (CH), 55.1 (CH), 40.1 (CH_2), 32.4 (CH_2), 31.5 (CH), 16.9 (CH_3), 15.5 (CH_3). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.34; H, 9.77; N, 8.85.

(2*S*,4*R*)-4-Hydroxy-2-methyl-6-oxopiperidine (8f). Purification of the crude product by flash column chromatography [CH_2Cl_2/MeOH (9:1)] gave **8f** (67 mg, yield = 37%): TLC R_f 0.14 [CH_2Cl_2/MeOH (9:1)]; white solid; $[\alpha]_D$ +83.8 (*c* 1.0, MeOH); mp 181−183 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 4.02−3.92 (m, 1H), 3.53−3.41 (m, 1H), 2.59 (ddd, J = 17.2, 5.7, 2.0 Hz, 1H), 2.18−2.09 (m, 2H), 1.37−1.25 (m, 1H), 1.21 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.3 (C), 63.9 (CH), 45.7 (CH), 39.6 (CH_2), 39.4 (CH_2), 20.9 (CH_3). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 56.05; H, 8.64; N, 10.77.

Di-*tert*-butyl (2*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-oxo-1,2-piperidinedicarboxylate (11). Imidazole (430 mg, 6.32 mmol) and TBSCl (476 mg, 3.16 mmol) were added to a solution of 500 mg (1.58 mmol) of **2a** in 5.0 mL of CH_2Cl_2 at 0 °C. The mixture was allowed to reach room temperature and stirred overnight. After evaporation of the solvent, the residue was dissolved in AcOEt. The solution was washed with 1 N $KHSO_4$, brine, and water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by filtration through a plug of silica [AcOEt/Hex (2:8)] to yield **11** (650 mg, yield = 95%): HPLC t_R 18.16 (linear gradient, 30−100% B, 20 min); $[\alpha]_D$ −29.4 (*c* 1.1, $CHCl_3$); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (dd, J = 7.6, 6.7 Hz, 1H), 4.12−4.03 (m, 1H), 2.74 (ddd, J = 16.6, 5.3, 1.8 Hz, 1H), 2.49 (dd, J = 16.6, 8.5 Hz, 1H), 2.37−2.28 (m, 1H), 2.08−1.96 (m, 1H), 1.50 (s, 9H), 1.46 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (C), 168.9 (C), 152.0 (C), 83.5 (C), 82.2 (C), 64.4 (CH), 56.6 (CH), 44.4 (CH_2), 34.9 (CH_2), 27.9 ($3CH_3$), 27.9 ($3CH_3$), 25.8 ($3CH_3$), 18.1 (C), −4.7 (CH_3), −4.8 (CH_3). Anal. Calcd for $C_{21}H_{39}NO_6Si$: C, 58.71; H, 9.15; N, 3.26. Found: C, 59.01; H, 9.14; N, 3.46.

Di-*tert*-butyl (2*S*,4*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1,2-piperidinedicarboxylate (13). A total of 307 μL of 1 M $LiEt_3BH$ in THF (0.307 mmol) was added to a solution of 110 mg (0.256 mmol) of **13** in 2.0 mL of THF at −78 °C, and the mixture was stirred for 30 min. The reaction was quenched with 0.6 mL of saturated $NaHCO_3$ and allowed to reach 0 °C. H_2O_2 was added via a hypodermic syringe (5 drops), and the mixture was stirred for 30 min at 0 °C. The solvents were evaporated and replaced by CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the intermediate **12**. Crude **12** and Et_3SiH (30 mg, 0.256 mmol) were dissolved in 5.0 mL of CH_2Cl_2 and cooled to −78 °C. $BF_3{\cdot}Et_2O$ (40 mg, 0.282 mmol) was introduced by dropwise addition, and the mixture was stirred for 30 min. Et_3SiH (30 mg, 0.256 mmol) and $BF_3{\cdot}Et_2O$ (40 mg, 0.282 mmol) were consecutively added via a hypodermic syringe, and the mixture was stirred for an additional 2 h. The reaction was quenched by 0.6 mL of a saturated $NaHCO_3$ solution and allowed to reach room temperature. After the addition of a large volume of a saturated $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2. The organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the crude product by flash column chromatography [AcOEt/Hex (1:9)] gave **13** (yield < 50%): TLC R_f 0.36 [AcOEt/Hex (1:9)]; white solid; $[\alpha]_D$ −31.4 (*c* 1.0, $CHCl_3$); appeared as a mixture of two conformers ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.61−4.52 (m, 0.5H) and 4.47−4.38 (m,0.5H), 4.07−4.03 (m, 1H), 3.88−3.68 (m, 1H), 3.40−3.19 (m, 1H), 2.35−2.32 (m, 0.5H) and 2.30−2.26 (m, 0.5H), 1.85−1.77 (m, 1H), 1.61−1.53 (m, 2H), 1.44 (s, 18H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (C), 155.7 (C), 80.7 (C), 79.5 (C), 64.1 (CH), 52.4 (CH), 34.9 (CH_2), 33.1 (CH_2), 32.2 (CH_2), 28.3 ($3CH_3$), 28.2 ($3CH_3$), 26.0 ($3CH_3$), 18.5 (C), −4.8 (CH_3), −4.9 (CH_3). Anal. Calcd for $C_{21}H_{41}NO_5Si$: C, 60.68; H, 9.94; N, 3.37. Found: C, 60.83; H, 10.03; N, 3.37.

Di-*tert*-butyl (2*S*)-3,6-Dihydro-1,2(2*H*)-pyridinedicarboxylate (14). Pure **14** was isolated in low yield (<20%) after flash column chromatography [AcOEt/Hex (1:9)] from the crude product obtained for the preparation of **13**: TLC R_f 0.33 [AcOEt/Hex (9:1)]; colorless oil; $[\alpha]_D$ −9.3 (*c* 1.0, $CHCl_3$);

appeared as a mixture of two conformers ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77−5.71 (m, 1.5H) and 5.64−5.59 (m, 0.5H), 4.94−4.91 (m, 0.5H) and 4.74−4.71 (m, 0.5H), 4.09−3.99 (m, 1H), 3.91−3.66 (m, 1H), 2.66−2.56 (m, 1H), 2.47−2.37 (m, 1H), 1.48 (s, 4.5 H) and 1.46 (s, 4.5H), 1.42 (s, 4.5H) and 1.41 (s, 4.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (C), 155.8 and 155.3 (C), 124.2 and 123.9 (CH), 122.5 and 121.9 (CH), 81.4 and 81.3 (C), 80.0 (C), 53.0 and 51.6 (CH), 42.2 and 41.7 (CH_2), 28.4 ($3CH_3$), 28.0 ($3CH_3$), 26.6 (CH_2).

Di-*tert*-butyl (2*S*,4*R*)-4-Hydroxy-1,2-piperidinedicarboxylate (15). 2a (200 mg, 0.634 mmol) was dissolved in 4.0 mL of anhydrous THF and cooled to 0 °C. BH_3·SMe_2 (301 μL, 3.17 mmol) was introduced via a hypodermic syringe. The mixture was allowed to reach room temperature and stirred overnight. After being cooled to 0 °C, the reaction was quenched by the addition of 1.0 mL of MeOH and stirred for a further 10 min. Evaporation of the solvent gave a residue, which was dissolved in AcOEt. The solution was washed with saturated $NaHCO_3$, water, 1 N $KHSO_4$, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was placed under high vacuum to eliminate the dimethyl sulfide derivatives and gave pure **15** (yield = 100%): TLC R_f 0.30 [AcOEt/Hex (1:1)]; white crystals; $[\alpha]_D$ −54.6 (*c* 0.9, $CHCl_3$); mp 91−93 °C; appeared as a mixture of conformers ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68−4.62 (m, 0.5H) and 4.50−4.43 (m, 0.5H), 4.10−4.06 (m, 1H), 3.85−3.68 (m, 1H), 3.36−3.17 (m, 1H), 2.36−2.31 (m, 1H), 2.10 (bs, 1H), 1.85−1.77 (m, 1H), 1.73−1.54 (m, 2H), 1.42 (bs, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0 (C), 155.6 (C), 81.3 (C), 79.7 (C), 63.1 (CH), 52.2 and 51.1 (CH), 35.9 and 34.9 (CH_2), 33.1 (CH_2), 31.0 (CH_2), 28.3 ($3CH_3$), 27.9 ($3CH_3$). Anal. Calcd for $C_{15}H_{27}NO_5$: C, 59.78; H, 9.03; N, 4.65. Found: C, 59.50; H, 9.14; N, 4.67.

(2*S*,4*R*)-1-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-4-hydroxy-2-piperidinecarboxylic Acid (17). 15 (250 mg, 0.829 mmol) was placed in a round-bottom flask and dissolved in 2.0 mL of trifluoroacetic acid. The solution was stirred for 2 h at room temperature and checked by TLC. Trifluoroacetic acid was coevaporated with hexane, and the residue was dried under vacuum. Crude **16** was dissolved in 3.0 mL of water. K_2CO_3 (344 mg, 2.49 mmol) and FmocOSu (280 mg, 0.829 mmol) dissolved in 3.0 mL of acetone were consecutively added. After the pH (>9) of the resulting solution had been checked, the mixture was stirred overnight. Acetone was evaporated, and the residual solution was diluted with water. The aqueous solution was acidified with solid $KHSO_4$ prior to the extraction with AcOEt. The organic phase was washed with 1 N $KHSO_4$, dried over Na_2SO_4, and concentrated in vacuo to yield a yellowish oil. Purification of the crude product by flash column chromatography [AcOEt/AcOH (10:0.1)] gave **17** (253 mg, yield = 83%): HPLC t_R 8.77 (linear gradient, 30−100% B, 20 min); white solid; $[\alpha]_D$ −9.5 (*c* 1.0, MeOH); mp 200−201 °C; appeared as a mixture of conformers ^{1}H NMR (300 MHz, CD_3OD) δ 7.82 (d, *J* = 7.3 Hz, 2H), 7.68−7.58 (m, 2H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 4.68 (d, *J* = 5.8 Hz, 0.5H) and 4.53 (d, *J* = 6.7 Hz, 0.5H), 4.47−4.39 (m, 2H), 4.31−4.22 (m, 1H), 4.08−4.03 (m, 1H), 3.87−3.74 (m, 1H), 3.60−3.43 (m, 1H), 2.47−2.38 (m, 1H), 1.92−1.81 (m, 1H), 1.77−1.58 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.2 (C), 158.1 and 157.8 (C), 145.3 (C), 145.2 (C), 145.1 (C), 142.6 (C), 128.8 (2CH), 128.1 (2CH), 126.1 (2CH), 120.9 (2CH), 68.8 (CH_2), 63.7 (CH), 52.5 and 52.2 (CH), 48.4 (CH), 37.1 and 36.8 (CH_2), 34.2 (CH_2), 32.0 and 31.9 (CH_2). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.47; H, 6.09; N, 3.63.

Di-*tert*-butyl (2*S*)-6-Oxo-3,6-dihydro-1,2(2*H*)-pyridinedicarboxylate (18). *p*-Nitrobenzoic acid (239 mg, 1.43 mmol) and PPh_3 (374 mg, 1.43 mmol) were added to a solution of **2a** (300 mg, 0.951 mmol) in 15.0 mL of distilled THF. The mixture was cooled to 0 °C prior to the dropwise addition of a solution of diisopropylazodicarboxylate (DIAD) (288 mg, 1.42 mmol) in 4.0 mL of dry THF. The solution was protected from light and stirred overnight with a slow increase of temperature from 0 °C to room temperature. THF was evaporated and replaced by AcOEt. The solution was washed with saturated $NaHCO_3$, 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** (243 mg, yield = 86%): HPLC t_R 9.30 (linear gradient, 30−100% B, 20 min); colorless crystals; $[\alpha]_D$ +11.6 (*c* 1.0, $CHCl_3$); mp 99−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55−6.50 (m, 1H), 5.88−5.84 (m, 1H), 4.82−4.79 (m, 1H), 2.82−2.73 (m, 1H), 2.71−2.61 (m, 1H), 1.45 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (C), 162.5 (C), 152.1 (C), 139.7 (CH), 126.5 (CH), 83.1 (C), 82.5 (C), 56.2 (CH), 27.9 ($3CH_3$), 27.7 ($3CH_3$), 27.2 (CH_2). Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.13; H, 7.82; N, 4.77.

Di-*tert*-butyl (2*S*,4*S*)-4-[(4-Nitrobenzoyl)oxy]-1,2-piperidinedicarboxylate (19). *p*-Nitrobenzoic acid (83 mg, 0.497 mmol) and PPh_3 (130 mg, 0.496 mmol) were added to a solution of **15** (100 mg, 0.332 mmol) in 5.0 mL of distilled THF. The mixture was cooled to 0 °C prior to the dropwise addition of a solution of DIAD (101 mg, 0.499 mmol) in 1.0 mL of dry THF. The solution was protected from light and stirred overnight with a slow increase of temperature from 0 °C to room temperature. THF was evaporated and replaced by AcOEt. The solution was washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by flash column chromatography [AcOEt/Hex (1:9)] to yield pure **19** (80 mg, yield = 53%): HPLC t_R 17.08 (linear gradient, 30−100% B, 20 min); white crystals; $[\alpha]_D$ −20.5 (*c* 1.0, $CHCl_3$); mp 165−167 °C; appeared as a mixture of two conformers ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.9 Hz, 2H), 8.16 (d, *J* = 8.8 Hz, 2H), 5.04−4.93 (m, 1H) and 4.77−4.71 (m, 1H), 4.19−4.00 (m, 1H), 3.21−3.03 (m, 1H), 2.64−2.53 (m, 1H), 2.16−2.04 (m, 1H), 1.89−1.76 (m, 1H), 1.71−1.57 (m, 1H), 1.48 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (C), 163.8 (C), 155.1 (C), 150.5 (C), 135.6 (C), 130.7 (2CH), 123.5 (2CH), 82.2 (C), 80.4 (C), 70.3 (CH), 55.0 and 54.0 (CH), 40.1 and 39.5 (CH_2), 31.9 (CH_2), 30.5 and 30.4 (CH_2), 28.3 ($3CH_3$), 28.0 ($3CH_3$). Anal. Calcd for $C_{22}H_{30}N_2O_8$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.75; H, 6.96; N, 6.22.

Di-*tert*-butyl (2*S*)-5,6-Dihydro-1,2(2*H*)-pyridinedicarboxylate (20). Pure **20** was isolated in 32% yield after flash column chromatography [AcOEt/Hex (1:9)] of the crude product obtained for the preparation of **19**: TLC R_f 0.52 [AcOEt/Hex (1:9)]; colorless oil; $[\alpha]_D$ −207.9 (*c* 1.1, $CHCl_3$); appeared as a mixture of two conformers ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96−5.87 (m, 1H), 5.82−5.69 (m, 1H), 4.82−4.77 (m, 0.5H) and 4.67−4.62 (m, 0.5H), 4.18−4.12 (m, 0.5H) and 4.03−3.97 (m, 0.5H), 3.11−3.02 (m, 0.5H) and 2.99−2.89 (m, 0.5H), 2.25−2.14 (m, 1H), 2.07−1.93 (m, 1H), 1.44 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7 (C), 155.0 (C), 127.6 and 127.2 (CH), 122.9 and 122.1 (CH), 81.4 (C), 79.9 (C), 56.4 and 55.5 (CH), 38.9 and 37.6 (CH_2), 28.3 ($3CH_3$), 28.0 ($3CH_3$), 24.8 and 24.6 (CH_2). Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.79; H, 9.16; N, 4.88.

Di-*tert*-butyl (2*S*,4*S*)-4-Hydroxy-1,2-piperidinedicarboxylate (22). Chloroacetic acid (141 mg, 1.49 mmol) and PPh_3 (392 mg, 1.49 mmol) were added to a solution of **15** (300 mg, 0.995 mmol) in 10.0 mL of distilled THF. The mixture was cooled to 0 °C prior to the dropwise addition of a solution of DIAD (302 mg, 1.49 mmol) in 5.0 mL of dry THF. The solution was protected from light and stirred overnight with a slow increase of temperature from 0 °C to room temperature. THF was evaporated and replaced by AcOEt. The solution was washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated in vacuo to give **21**. The crude product was dissolved in 1.0 mL of dioxane, and the same volume of water was added. A 1 N NaOH solution was added drop by drop until the pH reached 9. The mixture was stirred for 30 min and checked by TLC. The reaction was quenched by the addition of a large volume of 1 N $KHSO_4$ before extraction with AcOEt. The organic phases were dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by flash column chromatography [AcOEt/Hex (1:1)] to yield **22** (211 mg,

yield = 70%): TLC R_f 0.44 [AcOEt/Hex (1:1)]; colorless oil; $[\alpha]_D$ −38.7 (*c* 1.1, $CHCl_3$); appeared as a mixture of conformers ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (bd, J = 4.9 Hz, 0.5H) and 4.60 (bd, J = 5.5 Hz, 0.5H), 4.03−3.88 (m, 1H), 3.61−3.50 (m, 1H), 2.99−2.84 (m, 1H), 2.69 (bs, 1H), 2.39−2.32 (m, 1H), 1.89−1.80 (m, 1H), 1.60−1.48 (m, 1H), 1.44−1.26 (m, 1H), 1.39 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 and 170.5 (C), 155.4 (C), 81.7 (C), 80.1 (C), 65.9 and 65.7 (CH), 55.2 and 54.2 (CH), 40.5 and 39.9 (CH_2), 35.3 and 35.2 (CH_2), 34.0 and 33.8 (CH_2), 28.2 ($3CH_3$), 27.9 ($3CH_3$). Anal. Calcd for $C_{15}H_{27}NO_5$: C, 59.78; H, 9.03; N, 4.65. Found: C, 59.98; H, 9.22; N, 4.63.

(2*S*,4*S*)-1-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-4-hydroxy-2-piperidinecarboxylic Acid (24). 22 (110 mg, 0.365 mmol) was placed in a round-bottom flask and dissolved in 2.0 mL of trifluoroacetic acid. The solution was stirred for 2 h at room temperature and checked by TLC. Trifluoroacetic acid was coevaporated with hexane, and the residue was dried under vacuum. Crude **23** was dissolved in 1.5 mL of water. K_2CO_3 (151 mg, 1.09 mmol) and FmocOSu (123 mg, 0.365 mmol) dissolved in 1.5 mL of acetone were consecutively added. After the pH of the resulting solution was checked, the mixture was stirred overnight. Acetone was evaporated, and the residual solution was diluted with water. The aqueous solution was acidified with solid $KHSO_4$ prior to the extraction with AcOEt. The organic phase was washed with 1 N $KHSO_4$, dried over Na_2SO_4, and concentrated in vacuo to yield a yellowish oil. Purification of the crude product by flash column chromatography [AcOEt/AcOH (10:0.1)] gave **24** (109 mg, yield = 81%): HPLC t_R 8.28 (linear gradient, 30−100% B, 20 min); white solid; $[\alpha]_D$ −8.2 (*c* 1.0, MeOH); mp 65−67 °C; appeared as a mixture of conformers ^{1}H NMR (300 MHz, CD_3OD) δ 7.82−7.80 (m, 2H), 7.65−7.57 (m, 2H), 7.43−7.38 (m, 2H), 7.34−7.29 (m, 2H), 4.91 (d, J = 5.7 Hz, 0.5H) and 4.74 (d, J = 5.7 Hz, 0.5H), 4.48−4.37 (m, 2H), 4.28−4.20 (m, 1H), 4.13−4.05 (m, 0.5H), 4.00−3.91 (m, 0.5H), 3.65−3.56 (m, 1H), 3.16−3.00 (m, 1H), 2.50−2.40 (m, 1H), 1.95−1.83 (m, 1H), 1.60−1.47 (m, 1H), 1.38−1.23 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.0 (C), 157.8 and 157.4 (C), 145.3 and 145.2 (C), 145.1 and 145.0 (C), 142.6 (2C), 128.8 (2CH), 128.1 (2CH), 126.1 and 126.0 (2CH), 120.9 (2CH), 69.0 and 68.9 (CH_2), 66.4 (CH), 55.5 and 55.4 (CH), 48.3 (CH), 41.5 (CH_2), 36.2 and 36.1 (CH_2), 34.8 and 34.7 (CH_2). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.83; H, 6.08; N, 3.61.

***tert*-Butyl *N*-[(1*S*,3*S*)-3,5-Dihydroxy-1-(hydroxymethyl)pentyl]carbamate (25).** $NaBH_4$ (48 mg, 1.27 mmol) was added to a solution of **2a** (80 mg, 0.254 mmol) in 2.0 mL of EtOH at 0 °C. The mixture was allowed to reach room temperature and stirred for 6 h. After being quenched with water, the mixture was stirred for a further 10 min. Evaporation of the solvent gave an oil, 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 [CH_2Cl_2/MeOH (9:1)]. Pure **25** was recovered (20 mg, yield = 32%): TLC R_f 0.42 [CH_2Cl_2/MeOH (9:1)]; colorless oil; $[\alpha]_D$ −11.4 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15 (bd, J = 8.8 Hz, 1H), 4.64 (m, 1H), 3.91−3.80 (m, 3H), 3.72 (dd, J = 10.9, 4.0 Hz, 1H), 3.62 (dd, J = 10.9, 4.6 Hz, 1H), 3.32 (bs, 1H), 2.76 (bs, 1H), 1.96 (bs, 1H), 1.81−1.64 (m, 2H), 1.62−1.55 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4 (C), 80.2 (C), 68.5 (CH), 65.3 (CH_2), 61.8 (CH_2), 49.1 (CH), 40.4 (CH_2), 38.0 (CH_2), 28.3 ($3CH_3$).

Di-*tert*-butyl (2*S*,4*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-6-oxo-1,2-piperidinedicarboxylate (26). Imidazole (432 mg, 6.34 mmol) and TPSCl (872 mg, 3.17 mmol) were added to a solution of 500 mg (1.58 mmol) of **2a** in 20.0 mL of CH_2Cl_2 at 0 °C. The mixture was allowed to reach room temperature and stirred overnight. After evaporation of the solvent, the residue was dissolved in AcOEt. The solution was washed with 1 N $KHSO_4$, brine, and water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by filtration through a plug of silica [AcOEt/Hex (2:8)] to yield **26** (770 mg, yield = 88%): HPLC t_R 17.30 (linear gradient, 50−100% B, 20 min); $[\alpha]_D$ −19.5 (*c* 1.0, $CHCl_3$); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66−7.60 (m, 4H), 7.44−7.38 (m, 6H), 4.30 (dd, J = 8.3, 6.6 Hz, 1H), 4.06−3.97 (m, 1H), 2.65 (ddd, J = 16.6, 5.5, 2.0 Hz, 1H), 2.53 (dd, J = 16.6, 9.0 Hz, 1H), 2.30−2.21 (m, 1H), 2.07−1.97 (m, 1H), 1.47 (s, 9H), 1.45 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (C), 168.7 (C), 151.9 (C), 135.6 (4 CH), 133.4 (C), 133.1 (C), 130.0 (2 CH), 127.8 (4 CH), 83.6 (C), 82.2 (C), 65.0 (CH), 56.6 (CH), 44.0 (CH_2), 34.7 (CH_2), 27.9 ($3CH_3$), 27.8 ($3CH_3$), 26.9 ($3CH_3$), 19.0 (C).

***tert*-Butyl (2*S*,4*S*)-2-[(*tert*-Butoxycarbonyl)amino]-4-[(*tert*-butyldiphenylsilyl)oxy]-6-hydroxyhexanoate (27). 26** (710 mg, 1.28 mmol) was dissolved in 10.0 mL of EtOH and cooled to 0 °C. After the portionwise addition of $NaBH_4$ (242 mg, 6.40 mmol), the mixture was allowed to reach room temperature and stirred overnight. After being quenched by water, the mixture was stirred for a further 10 min. Evaporation of the solvent gave an oil, 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/Hex (4:6)]. Pure **27** was recovered (690 mg, yield = 97%): HPLC t_R 15.66 (linear gradient, 50−100% B, 20 min); colorless oil; $[\alpha]_D$ +4.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.68 (m, 4H), 7.44−7.37 (m, 6H), 5.30 (bd, J = 7.9 Hz, 1H), 4.14−4.04 (m, 2H), 3.63−3.49 (m, 2H), 1.96−1.92 (m, 1H), 1.75−1.71 (m, 1H), 1.57 (m, 2H), 1.42 (s, 9H), 1.36 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (C), 155.3 (C), 135.9 (2CH), 135.8 (2CH), 133.6 (C), 133.2 (C), 129.9 (CH), 129.8 (CH), 127.8 (2CH), 127.7 (2CH), 81.6 (C), 79.5 (C), 69.6 (CH), 50.0 (CH_2), 52.0 (CH), 38.4 (CH_2), 38.3 (CH_2), 28.3 ($3CH_3$), 27.9 ($3CH_3$), 26.9 ($3CH_3$), 19.3 (C). Anal. Calcd for $C_{31}H_{47}NO_6Si$: C, 66.75; H, 8.49; N, 2.51. Found: C, 66.88; H, 8.65; N, 2.56.

***tert*-Butyl (2*S*,4*R*)-6-Azido-2-[(*tert*-butoxycarbonyl)amino]-4-[(*tert*-butyldiphenylsilyl)oxy]hexanoate (28).** A total of 307 μL (1.80 mmol) of DIEA was added to a solution of 670 mg (1.20 mmol) of **27** in 20.0 mL of CH_2Cl_2 at ambient temperature. The solution was cooled to 0 °C, and 139 μL (1.80 mmol) of MsCl was added via a hypodermic syringe. The mixture was allowed to reach room temperature and stirred for 3 h. The reaction was quenched with water, and CH_2Cl_2 was evaporated and replaced by AcOEt. The organic phase was washed with 1 N $KHSO_4$, brine, saturated $NaHCO_3$, and water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in 10.0 mL of DMF. A total of 234 mg (3.60 mmol) of NaN_3 was added to the solution, which was heated to 80 °C for 8 h. After being cooled 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 (1:9)] to yield pure **27** (560 mg, 80%): HPLC t_R 18.55 (linear gradient, 50−100% B, 20 min); $[\alpha]_D$ −10.7 (*c* 1.0, $CHCl_3$); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.67 (m, 4H), 7.44−7.35 (m, 6H), 5.21 (bd, J = 7.6 Hz, 1H), 4.15−4.08 (m, 1H), 3.96−3.92 (m, 1H), 3.16 (t, J = 7.1 Hz, 2H), 1.97−1.83 (m, 2H), 1.75−1.68 (m, 2H); 1.43 (s, 9H), 1.37 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6 (C), 155.3 (C), 135.8 (4CH), 133.6 (C), 133.0 (C), 129.9 (2CH), 127.8 (4CH), 81.7 (C), 79.5 (C), 69.0 (CH), 51.8 (CH), 47.5 (CH_2), 38.6 (CH_2), 35.2 (CH_2), 28.3 ($3CH_3$), 27.9 ($3CH_3$), 26.9 ($3CH_3$), 19.3 (C). Anal. Calcd for $C_{31}H_{46}N_4O_5Si$: C, 63.89; H, 7.96; N, 9.61. Found: C, 63.72; H, 8.11; N, 9.79.

(2*S*,4*R*)-6-Azido-4-[(*tert*-butyldiphenylsilyl)oxy]-2-{[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}hexanoic Acid (29). 28 (200 mg, 0.343 mmol) was dissolved in 2.0 mL of CH_2Cl_2 and cooled to 0 °C. A total of 2.0 mL of TFA was slowly added via a hypodermic syringe, and the solution was stirred for 3 h. The mixture was allowed to reach room temperature and stirred for an additional 3 h. The reaction was checked by TLC [AcOET/pyridine/acetic acid/water (8:2:0.5:1)] and stirred at

room temperature until **28** disappeared. The solution was cooled to 0 °C and quenched with the addition of 50.0 mL of a 1 N NH_4OH solution. The solution was extracted twice with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was dissolved in 5.0 mL of acetone, and the same volume of water was added to the solution. A total of 142 mg (1.03 mmol) of K_2CO_3 and 139 mg (0.412 mmol) of FmocOSu dissolved in 1.0 mL of acetone were added to the solution. The mixture was stirred overnight. Acetone was evaporated and replaced by AcOEt prior to washing the solution with 1 N $KHSO_4$, brine, and water. The crude product was purified by flash column chromatography [AcOEt/Hex/AcOH (3:7:0.1)] to yield **29** (210 mg, 94%): HPLC t_R 15.58 (linear gradient, 50−100% B, 20 min); $[\alpha]_D$ +2.5 (*c* 1.0, MeOH); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.70 (m, 6H), 7.63−7.58 (m, 2H), 7.46−7.29 (m, 10H), 5.57 (bd, J = 6.9 Hz, 1H), 4.51−4.45 (m, 1H), 4.41−4.35 (m, 2H), 4.24−4.20 (m, 1H), 4.07−3.98 (m, 1H), 3.22−3.17 (m, 2H), 2.12−1.94 (m, 2H), 1.81−1.75 (m, 2H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4 (C), 156.1 (C), 143.8 (C), 143.7 (C), 141.3 (2C), 135.9 (2CH), 135.8 (2CH), 133.4 (C), 132.7 (C), 130.1 (CH), 130.0 (CH), 127.9 (2CH), 127.8 (2CH), 127.7 (2CH), 127.1 (2CH), 125.2 (CH), 125.1 (CH), 120.0 (2CH), 68.6 (CH), 67.1 (CH_2), 51.5 (CH), 47.4 (CH_2), 47.1 (CH), 37.4 (CH_2), 35.3 (CH_2), 27.0 ($3CH_3$), 14.2 (C). Anal. Calcd for $C_{37}H_{40}N_4O_5Si$: C, 68.49; H, 6.21; N, 8.64. Found: C, 68.57; H, 6.06; N, 8.40.

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Supporting Information Available: Effect of the nature of the carboxylic acid on the reduction of **4a**, ^{1}H and ^{13}C NMR data for all compounds, view of the crystal packing of **6a** and **2a**, ORTEP plot of compounds **18** and **19**, and X-ray crystallographic data of **2a**, **6a**, **18**, and **19** as CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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