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# Stereospecific, Flexible and Redox-Economic Asymmetric Synthesis of *cis*- and *trans*-3-Hydroxypipecolic Acids and Analogs

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Both *cis*- and *trans*-3-hydroxy-L-pipecolic acids are synthesized from a common chiral intermediate **7** by a short and flexible route. The stereospecific inversion of C-3 was achieved by the formation of an oxazoline followed by acidic ring cleavage. The overall yields are 27 % and 30 %, respectively, in 12 and 10 linear steps. Several versatile chiral building blocks are also accessible by this diastereodivergent synthesis. Unlike the chiral pool approach, our synthetic strategy is not limited by the availability of starting materials.



## Introduction

Multisubstituted chiral piperidines are of pivotal importance to medicinal chemistry and organic synthesis.[1] Hydroxypipecolic acids are an important family of nonproteinogenic cyclic α-amino acids with a chiral substituted piperidine skeleton.[2] Within the 3-hydroxy-L-series, both *cis* (**1**) and *trans* (**2**) isomers are structural units found in diverse natural products and biologically significant molecules such as tetrazomine[3] and febrifugine[4] (Figure 1). In addition, they are also conformationally constrained amino acids relevant to the study of peptide structure and drug design.[5]

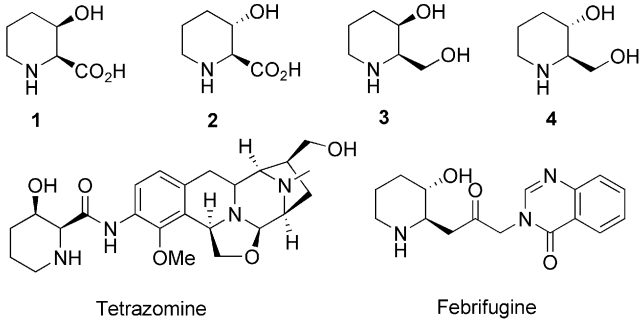
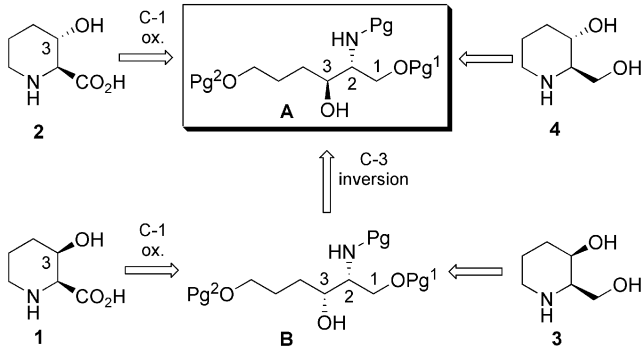



Figure 1. 3-Hydroxypipecolic acids and related structures.

In view of their significance, numerous efforts have been devoted to the synthesis of these chiral scaffolds.[6–8] Most of the reported routes utilized the chiral pool approach,[6] which was inevitably limited by the availability of the starting material, while asymmetric synthesis was rather rare.[7] More importantly, flexible synthetic strategies that are applicable to both **1** and **2** are in demand.[6b,6d,6f,7b,7f] As a part of our ongoing projects on the synthesis of polyhydroxylated alkaloids,[9] herein we report the stereodivergent synthesis of both *cis*- and *trans*-3-hydroxy-L-pipecolic acids as well as their reduced analogues such as **3** and **4**.

We have recently developed an efficient method for the construction of *syn*-vicinal amino alcohols in enantiopure form, which culminated in a facile synthesis of L-(+)-733,060, a 2-phenyl-3-hydroxypiperidine derivative.[9a] Naturally, we envisioned that by replacing the phenyl ring with a carboxylic acid group, this strategy would constitute an efficient synthesis of 3-hydroxypipecolic acids (Scheme 1).




Scheme 1. Retrosynthetic analysis for **1**–**4**.

Although Huang[6a] and Jung[7b] have employed furanyl and *p*-methoxyphenyl, respectively, as masked carboxylic groups, we prefer using a properly protected hydroxymethyl as a latent carboxyl function because it could also provide simple access to 2-hydroxymethylpiperidines **3** and **4** without involving unnecessary adjustment of the oxi-

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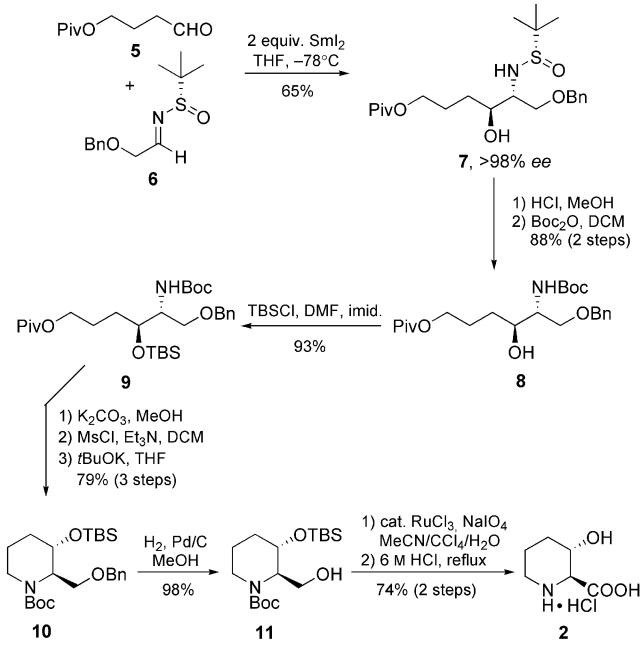
dation state. On the other hand, the C-3 configuration was also fully controllable by this route. The absolute stereochemistry of *anti*-1,2-amino alcohol **A** mapped onto the *trans*-isomer **2**, whereas the *cis*-isomer **1** required **B** by unambiguous inversion of the C-3 hydroxy in **A** at an early stage obviating a late-stage oxidation–reduction sequence,[6f] which was less efficient. Thus, **A** served as the common starting point in our stereospecific, flexible and redox-economic[10] synthesis. In addition, as both enantiomers of *tert*-butanesulfinamide are commercial reagents at affordable prices, switching the chiral auxiliary would easily provide the antipodes of **1**–**4**. Therefore, this strategy represents a comprehensive and unified solution to this class of 2,3-disubstituted piperidines.

## Results and Discussion

We commenced the synthesis of *trans*-**2** from the asymmetric pinacol-type reductive coupling[11] of aldehyde **5** and α-benzyloxy *tert*-butylsulfinyl imine **6** (Scheme 2). We intended to use benzyl (Bn) and pivaloyl (Piv) groups for the protection of C-1 and C-6 primary alcohols in the coupling product, respectively, for easy and orthogonal removal. As expected, we obtained *anti*-vicinal amino alcohol **7**, possessing two correct stereogenic centers, in good yield (65%) and excellent optical purity (>98% *ee*) as determined by chiral HPLC of the corresponding *N*-benzoyl derivative (see below and the Supporting Information).




Scheme 2. Asymmetric synthesis of **2**.

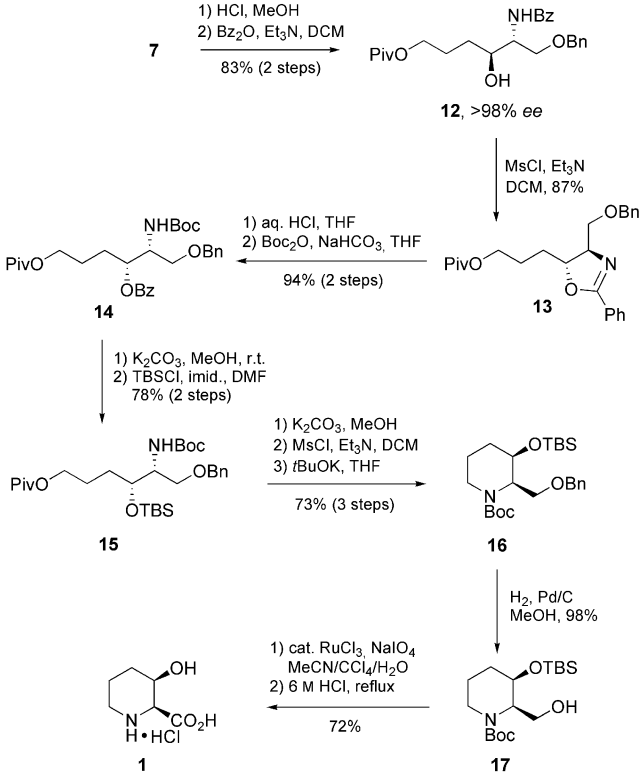
We note that the diastereoselectivity[12] for the coupling using substrate **6**, which has a benzyloxy substitution adjacent to the sulfinyl imine, was higher than that of *tert*-butylsulfinyl benzaldimine reported earlier.[9a] Therefore, there was no need to refine the chromatographed product by further recrystallization to remove inseparable diastereomers (in fact, compound **7** was an oil). This beneficial effect of α-alkoxy substitution might be ascribed to its chelating role for the $Sm^{III}$ species, and might work for other analogous sulfinimine substrates.

The removal of the sulfinyl auxiliary followed by the selective *N*-protection with $Boc_2O$ afforded **8** in high yield (88%). We then blocked the secondary hydroxy by TBS and removed the Piv protection of the terminal primary alcohol by $K_2CO_3$ in refluxing MeOH.[13] Without further purification, we mesylated and subjected the crude product to ring closure using *t*BuOK.[7a] Thus, we obtained **10**, a 2,3-disubstituted piperidine, in a satisfactory yield of 79% over 3 steps. Using NaH as the base required a longer reaction time (48 h); apparently, the potassium derivative was more dissociated than its sodium counterpart. For the ring closure, we also tested the Mitsunobu reaction ($Ph_3P$, DIAD and THF). However, it was less effective, probably due to high steric hindrance around the amino group. Notably, the primary and secondary hydroxyls in **10** were orthogonally protected, which rendered this trifunctional compound a versatile building block. Routine debenzylation afforded 2-(hydroxymethyl)piperidine **11** in near quantitative yield. $Ru^{VIII}$-catalyzed oxidation[14] to the carboxylic acid followed by global deprotection completed the total synthesis of **2** in 10 linear steps with an overall yield of 30%.

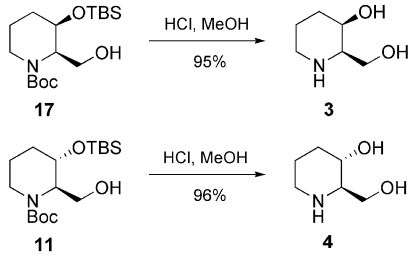
The synthesis of *cis*-**1** is shown in Scheme 3. The deprotection of **7** and subsequent *N*-selective benzoylation produced benzamide **12** (83% over 2 steps). Chiral HPLC analysis of the latter established the *ee* of **7** to be >98%. Considering the difficulty encountered in the removal of *N*-PMB from a 2-substituted piperidine,[9a] this time we employed the simpler benzoyl group instead of the PMB group, and the subsequent transformations of the oxazoline were also totally different from our previous work. Instead of undergoing reductive ring opening to form benzylamine, we hydrolyzed the 2-phenyloxazoline **13** under acidic conditions to give a benzoate,[15] liberating the primary amino group, which we in turn protected with $Boc_2O$ to afford **14**. At this stage, the required stereogenic centers of the target molecule had already been set up unambiguously. We carried out the selective deprotection of the *O*-benzoyl group under mild basic conditions ($K_2CO_3$/MeOH/r.t.) without affecting the primary pivalate, and the resulting secondary alcohol underwent TBS protection to afford **15**, which was actually the C-3 epimer of **9**. In the same vein, we smoothly converted **15** to **16** by a 3-step sequence in a satisfactory yield of 73%. Hydrogenolysis removed the Bn protection for the primary alcohol without incident. After Ru-catalyzed oxidation and global deprotection, we obtained *cis*-3-hydroxy-L-pipecolic acid **1** in 12 linear steps with an overall yield of 27% from the common key intermediate **7**.

The syntheses of the reduced analogs of our title compounds were straightforward (Scheme 4). Global deprotection (2 M HCl/MeOH) of intermediates **17**[6d] and **11**[7a] furnished **3**[16] and **4**,[17] respectively, in excellent yields (>95%). The spectroscopic data of these compounds were also consistent with those reported previously.

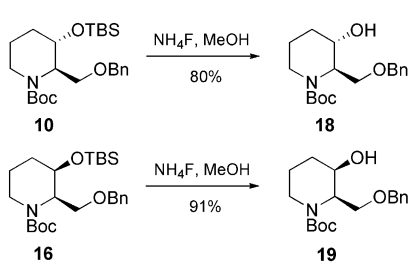



Scheme 3. Asymmetric synthesis of **1**.




Scheme 4. Syntheses of **3** and **4**.

Finally, as depicted in Scheme 5, we smoothly converted intermediates **10** and **16** into useful chiral building blocks **18** and **19**, respectively, upon treatment with inexpensive $NH_4F$[18] in methanol to selectively remove the TBS protection of the C-3 hydroxy group. Only one synthesis of the *cis*-isomer **19** has been documented before, which used phenylglycinol as the chiral auxiliary.[19]




Scheme 5. Syntheses of **18** and **19**.

## Conclusions

In summary, we have accomplished a diastereodivergent asymmetric synthesis of *cis*- and *trans*-3-hydroxy-L-pipecolic acids and their reduced analogs from a common chiral intermediate **7**. The overall yields are 27% and 30% in 12 and 10 linear steps, respectively. Our route featured a stereospecific inversion of a secondary hydroxy group for the construction of *cis*-2,3-disubstituted piperidines. As both enantiomers of *tert*-butanesulfinamide are commercially available at affordable prices, by simple switching the chirality of the sulfinyl auxiliary, enantiomers of all the target molecules are easily accessible. The orthogonally protected compounds **10**, **11** and **16**–**19** can also serve as versatile building blocks for the asymmetric synthesis of related alkaloids.

## Experimental Section

**General Information:** All reactions were performed in oven-dried glassware under an atmosphere of argon. All $^1H$ NMR and $^{13}C$ NMR spectra were recorded at ambient temperature in $CDCl_3$ unless noted otherwise. Chemical shifts are reported in parts per million (ppm) as follows: chemical shift, multiplicity (s singlet, d doublet, t triplet, q quartet, m multiplet, br. broad), coupling constant, and integration. Optical rotations were measured at ambient temperature, and concentrations are reported in g per 100 mL. Melting points are uncorrected. THF was distilled from sodium benzophenone ketyl, $CH_2Cl_2$ and DMF were distilled from $CaH_2$, all other solvents and chemical reagents were used as received. Compound **5**[20] and **6**[21] were prepared according to the literature procedures.

**(4*S*,5*R*)-6-(Benzyloxy)-4-hydroxy-5-[(*S*)-2-methylpropan-2-ylsulfinamido]hexyl Pivalate (7):** To a cooled (–78 °C) solution of $SmI_2$ (30 mmol) in THF (50 mL) under Ar was added dropwise a solution of **5** (3.87 g, 22.5 mmol), **6** (3.795 g, 15 mmol) and *t*BuOH (1.9 mL) in THF (50 mL). The mixture was stirred for 6 h at –78 °C, quenched by saturated aq. $Na_2S_2O_3$, extracted with EtOAc (3 × 50 mL), and the combined organic phases were washed with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes = 1:2 to 1:1) to yield **7** (4.173 g, 65%) as a pale-yellow liquid. $[\alpha]_D^{23}$ = +29.7 (*c* = 1.30, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.38–7.28 (m, 5 H), 4.61–4.42 (AB, $J_{AB}$ = 11.7 Hz, 2 H), 4.09–3.99 (m, 2 H), 3.96 (d, *J* = 8.4 Hz, 1 H), 3.90 (dd, *J* = 9.6, 3.6 Hz, 1 H), 3.79–3.65 (m, 2 H), 3.30 (m, 1 H), 1.91–1.33 (m, 4 H), 1.22 (s, 9 H), 1.16 (s, 9 H) ppm. $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 178.5, 137.4, 128.5, 127.9, 127.8, 73.5, 72.7, 70.2, 64.2, 59.4, 56.0, 38.7, 30.3, 27.1, 25.1, 22.6 ppm. HR-ESI-MS: calcd. for $C_{22}H_{37}NNaO_5S$ $[M + Na]^+$ 450.2290; found 450.2283.

**(4*S*,5*R*)-6-(Benzyloxy)-5-(*tert*-butoxycarbonyl)-4-hydroxyhexyl Pivalate (8):** To a solution of **7** (1.498 g, 3.5 mmol) in MeOH (5 mL) was added a methanolic solution of HCl (2 M, 7 mL) at room temperature, stirring was continued for 4 h, and the solution was concentrated under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (10 mL). To this was added $NaHCO_3$ (588 mg, 7.0 mmol) and $Boc_2O$ (1.11 g, 5.3 mmol) at room temperature, and the mixture was stirred overnight, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes = 1:3) to afford **8** (1.303 g, 88%) as a pale-yellow liquid. $[\alpha]_D^{23}$ = –13.5 (*c* = 1.36, $CHCl_3$). $^1H$ NMR

(300 MHz, $CDCl_3$): $\delta$ = 7.38–7.24 (m, 5 H), 5.31 (br. d, $J$ = 6.9 Hz, 1 H), 4.49 (AB, $J_{AB}$ = 11.7 Hz, 2 H), 4.12–3.98 (m, 2 H), 3.78 (br. d, $J$ = 7.5 Hz, 1 H), 3.72–3.56 (m, 3 H), 2.94 (br. d, $J$ = 7.5 Hz, 1 H), 1.95–1.43 (m, 4 H), 1.43 (s, 9 H), 1.17 (s, 9 H) ppm. $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 178.5, 155.8, 137.3, 136.3, 128.5, 128.0, 127.7, 79.6, 73.7, 73.3, 70.2, 64.1, 53.5, 38.7, 30.8, 28.3, 27.2, 25.3 ppm. HR-ESI-MS: calcd.for $C_{23}H_{37}NNaO_6$ $[M + Na]^+$ 446.2519; found 446.2518.

**(4*S*,5*R*)-6-(Benzyloxy)-5-(*tert*-butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)hexyl Pivalate (9):** To a solution of **8** (1.00 g, 2.36 mmol) and imidazole (327 mg, 4.73 mmol) in DMF (8 mL), was added TBSCl (534 mg, 3.55 mmol) in one portion, and the solution was stirred overnight, quenched by $H_2O$, extracted with diethyl ether (2 × 30 mL), and the combined organic phases were washed with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes = 1:20) to afford **9** (1.181 g, 93%) as a colorless liquid. $[\alpha]_D^{23}$ = –7.5 ($c$ = 0.74, $CHCl_3$); NMR peaks were broadened due to the presence of rotamers. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.39–7.24 (m, 5 H), 4.80 (br. d, $J$ = 7.5 Hz, 1 H), 4.50 (AB, $J_{AB}$ = 12.0 Hz, 2 H), 4.03 (t, $J$ = 6.0 Hz, 2 H), 3.90 (m, 1 H), 3.78 (m, 1 H), 3.66 (dd, $J$ = 9.6, 5.1 Hz, 1 H), 3.53 (dd, $J$ = 9.6, 3.9 Hz, 1 H), 1.86–1.45 (m, 4 H), 1.44 (s, 9 H), 1.19 (s, 9 H), 0.88 (s, 9 H), 0.06 (s, 6 H) ppm. $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 178.5, 155.5, 138.1, 128.3, 127.6, 79.2, 73.0, 71.4, 68.5, 64.6, 53.1, 38.7, 30.2, 28.4, 27.2, 25.8, 23.8, 18.0, –4.4, –4.8 ppm. HR-ESI-MS: calcd.for $C_{29}H_{51}NNaO_6Si$ $[M + Na]^+$ 560.3383; found 560.3370.

**(2*R*,3*S*)-*tert*-Butyl 2-(benzyloxymethyl)-3-(*tert*-butyldimethylsilyloxy) Piperidine-1-carboxylate (10):** A mixture of **9** (707 mg, 1.32 mmol) and $K_2CO_3$ (35 mg, 0.25 mmol) in MeOH (14 mL) was refluxed for 10 h and filtered through a short pad of silica gel, which was subsequently rinsed with $CH_2Cl_2$. The combined filtrate was concentrated, redissolved in $CH_2Cl_2$ (40 mL), cooled in an ice bath, and $Et_3N$ (0.36 mL, 2.6 mmol) was added followed by MsCl (0.14 mL, 1.8 mmol). After 1 h at 0 °C, the reaction was quenched by $H_2O$, diluted with $CH_2Cl_2$ (40 mL), washed with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. To a cooled (0 °C) solution of the crude mesylate in THF (25 mL) was added *t*BuOK (295 mg, 2.63 mmol), and the whole was warmed to room temperature over 1 h and stirred at this temperature for another 3 h. The reaction was quenched with sat. aq. $NH_4Cl$, extracted with $CH_2Cl_2$ (2 × 25 mL), and the combined organic phases were washed with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes = 1:20) to afford **10** (452 mg, 79%) as a colorless liquid. $[\alpha]_D^{23}$ = –14.0 ($c$ = 0.90, $CHCl_3$); NMR peaks were broadened due to the presence of rotamers. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.39–7.25 (m, 5 H), 4.53 (AB, $J_{AB}$ = 13.8 Hz, 2 H), 4.33 (br. s, 1 H), 4.13–3.94 (m, 2 H), 3.59–3.44 (m, 2 H), 2.70 (t-like, $J$ = 12.6 Hz, 1 H), 2.00–1.80 (m, 1 H), 1.63–1.52 (m, 2 H), 1.44 (s, 9 H), 1.34–1.23 (m, 1 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H) ppm. $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 155.5, 138.3, 128.3, 127.5, 127.4, 79.1, 72.8, 68.0, 65.2, 56.7 (br), 39.3 (br), 28.4, 27.5, 25.8, 18.9, 18.0, –4.9, –5.0 ppm. HR-ESI-MS: calcd.for $C_{24}H_{41}KNO_4Si$ $[M + K]^+$ 474.2442; found 474.2434.

**(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-Butyldimethylsilyloxy)-2-(hydroxymethyl)piperidine-1-carboxylate (11):** A suspension of **10** (376 mg, 0.86 mmol) and 10% Pd/C (40 mg) in MeOH (10 mL) was stirred under a $H_2$ atmosphere at room temperature for 5 h, filtered through celite and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes = 1:4) to afford **11** (292 mg, 98%) as a colorless liquid. $[\alpha]_D^{23}$ = –16.0 ($c$ = 0.74, $CHCl_3$); NMR peaks were broadened due to the presence of rotamers. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 4.18 (m, 1 H), 4.00 (m, 1 H), 3.88 (d, $J$ = 2.7 Hz, 1 H), 3.76–3.57 (m, 2 H), 2.83 (t-like, 1 H), 2.40 (br. s, 1 H), 2.00–1.82 (m, 1 H), 1.68–1.55 (m, 2 H), 1.45 (s, 9 H), 1.40–1.29 (m, 1 H), 0.88 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H) ppm. $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 156.2, 79.6, 65.2, 60.7, 60.0, 39.6, 28.4, 28.2, 25.7, 19.2, 18.0, –4.9, –5.0 ppm. HR-ESI-MS: calcd.for $C_{17}H_{35}NNaO_4Si$ $[M + Na]^+$ 368.2233; found 368.2230.

**(2*S*,3*S*)-3-Hydroxypiperidine-2-carboxylic Acid Hydrochloride (2):** To a well-stirred suspension of **11** (85 mg, 0.25 mmol) and $NaIO_4$ (216 mg, 1.0 mmol) in $CCl_4$ (0.6 mL), MeCN (0.6 mL) and $H_2O$ (0.9 mL) was added $RuCl_3 \cdot 3H_2O$ (2 mg) in one portion, and the mixture was stirred for 1 h at room temperature, diluted with diethyl ether (30 mL), filtered through celite and concentrated under reduced pressure. The residue was refluxed with aq. HCl (6 M, 5.0 mL) for 2 h, cooled and washed with $CH_2Cl_2$ (10 mL). The aqueous phase was concentrated under reduced pressure to afford **2** as a white solid; m.p. 232–234 °C. $[\alpha]_D^{23}$ = +14.5 ($c$ = 0.40, $H_2O$), ref.[6d] $[\alpha]_D^{23}$ = +14.2 ($c$ = 0.95, $H_2O$). $^1H$ NMR (300 MHz, $D_2O$): $\delta$ = 4.15–4.02 (m, 1 H), 3.82 (d, $J$ = 7.8 Hz, 1 H), 3.40–3.27 (m, 1 H), 3.10–2.95 (m, 1 H), 2.05–1.85 (m, 2 H), 1.80–1.55 (m, 2 H) ppm. $^{13}C$ NMR ($D_2O$, 125 MHz): $\delta$ = 171.1, 67.0, 62.2, 44.1, 30.4, 20.1 ppm. HR-ESI-MS: calcd.for $C_6H_{12}NO_3$ $[M + H]^+$ 146.0817; found 146.0813.

**(2*R*,3*S*)-2-(Hydroxymethyl)piperidin-3-ol (4):** To a solution of **11** (74 mg, 0.21 mmol) in MeOH (2 mL), was added a methanolic solution of HCl (2 M, 0.5 mL) at room temperature, stirring was continued for 6 h, and the solution was concentrated under reduced pressure and basified with 2 drops of aq. NaOH (30%). The residue was purified by silica gel flash column chromatography (MeOH/$CH_2Cl_2$ = 1:2) to afford **4** (27 mg, 96%) as a white solid; m.p. 153–154 °C. $[\alpha]_D^{23}$ = +57.0 ($c$ = 0.56, MeOH), ref.[16a] $[\alpha]_D^{23}$ = +58.3 ($c$ = 1.06, MeOH). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 3.86 (AB-d, $J_{AB}$ = 10.8, $J$ = 3.9 Hz, 1 H), 3.54 (AB-d, $J_{AB}$ = 10.8, $J$ = 6.9 Hz, 1 H), 3.35–3.23 (m, 2 H), 3.00–2.92 (m, 1 H), 2.50 (td, $J$ = 12.0, 2.7 Hz, 1 H), 2.38 (ddd, $J$ = 9.6, 7.2, 3.3 Hz, 1 H), 2.06–1.96 (m, 1 H), 1.75–1.65 (m, 1 H), 1.58–1.42 (m, 1 H), 1.40–1.27 (m, 1 H) ppm. $^{13}C$ NMR ($CD_3OD$, 125 MHz): $\delta$ = 69.7, 65.0, 63.8, 46.4, 34.9, 26.2 ppm. HR-ESI-MS: calcd.for $C_6H_{14}NO_2$ $[M + H]^+$ 132.1025; found 132.1019.

**(2*R*,3*S*)-*tert*-Butyl 2-(Benzyloxymethyl)-3-hydroxypiperidine-1-carboxylate (18):** A solution of **10** (34 mg, 0.08 mmol) and $NH_4F$ (38 mg, 1.0 mmol) in MeOH/$H_2O$ (10:1, 2 mL) was heated at 60 °C for 48 h, cooled, diluted with diethyl ether, washed successively with $H_2O$ and brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes = 1:2) to afford **18** (20 mg, 80%) as a colorless liquid. $[\alpha]_D^{23}$ = –33.8 ($c$ = 0.40, $CHCl_3$); NMR peaks were broadened due to the presence of rotamers. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.39–7.25 (m, 5 H), 4.53 (s, 2 H), 4.40 (br. m, 1 H), 4.03 (br. m, 1 H), 3.98 (br. d, $J$ = 12.7 Hz, 1 H), 3.55 (AB, $J_{AB}$ = 10.7 Hz, 2 H), 2.77 (td, $J$ = 13.1, 2.5 Hz, 1 H), 1.96 (br. s, 1 H), 1.90–1.60 (m, 4 H), 1.45 (s, 9 H) ppm. $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 156.0, 138.0, 128.4, 127.6, 127.5, 79.8, 73.0, 67.9, 65.3, 56.8, 39.6, 28.4, 26.5, 18.8 ppm. HR-ESI-MS: calcd.for $C_{18}H_{28}NO_4$ $[M + H]^+$ 322.2018; found 322.2012.

**(4*S*,5*R*)-5-Benzamido-6-(benzyloxy)-4-hydroxyhexyl Pivalate (12):** To a solution of **7** (1.662 g, 3.89 mmol) in MeOH (5 mL) was added a methanolic solution of HCl (2 M, 10 mL) at room temperature, stirring was continued for 4 h, and the solution was concentrated

under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (15 mL), and to this solution was added successively $Et_3N$ (2.33 mL), DMAP (10 mg) and $Bz_2O$ (877 mg, 3.88 mmol) at 0 °C. The solution was warmed to room temperature over 1 h, stirred overnight, diluted with $CH_2Cl_2$ (50 mL), washed successively with sat. aq. $NaHCO_3$ and brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes = 1:2) to afford **12** (1.371 g, 83%) as a pale-yellow liquid. $[\alpha]_D^{23}$ = –16.3 ($c$ = 1.44, $CHCl_3$); HPLC: Chiralpak OD-H column; detected at 214 nm; eluent: *n*-hexane/2-propanol = 80:20 (v/v), flow rate: 0.7 mL/ min, $t_1$ = 7.9 min (major), $t_2$ = 10.6 min (minor). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.77 (d, $J$ = 6.6 Hz, 2 H), 7.55–7.25 (m, 7 H), 7.01 (d, $J$ = 8.1 Hz, 1 H), 4.52 (AB, $J_{AB}$ = 11.7 Hz, 2 H), 4.20 (m, 1 H), 4.14–4.02 (m, 2 H), 3.92 (dd, $J$ = 9.9, 3.3 Hz, 1 H), 3.83–3.70 (m, 2 H), 3.20 (d, $J$ = 8.7 Hz, 1 H), 1.99–1.49 (m, 4 H), 1.17 (s, 9 H) ppm. $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = 178.5, 167.2, 137.1, 131.6, 128.6, 128.5, 127.8, 127.0, 73.8, 73.3, 69.8, 64.0, 52.8, 38.7, 30.9, 27.1, 25.3 ppm. HR-ESI-MS: calcd.for $C_{25}H_{34}NO_5$ $[M + H]^+$ 428.2437; found 428.2437.

**3-[(4*R*,5*R*)-4-(Benzyloxymethyl)-2-phenyl-4,5-dihydrooxazol-5-yl]-propyl Pivalate (13):** To a cooled (0 °C) solution of **12** (1.271 g, 2.98 mmol) and $Et_3N$ (2.4 mL, 16 mmol) in $CH_2Cl_2$ (30 mL) was added dropwise MsCl (0.32 mL, 4.6 mmol), and the mixture was stirred at room temperature overnight, quenched with saturated aq. $NaHCO_3$, and the aq. phase was extracted with $CH_2Cl_2$ (2 × 15 mL). The combined organic phases were washed with $H_2O$ and brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes = 1:4) to afford **13** (1.051 g, 87%) as a colorless liquid. $[\alpha]_D^{23}$ = = +46.7 ($c$ = 0.78, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.94 (d, $J$ = 6.9 Hz, 2 H), 7.51–7.35 (m, 3 H), 7.35–7.25 (m, 5 H), 4.61–4.52 (m, 3 H), 4.17–4.02 (m, 3 H), 3.76 (dd, $J$ = 9.3, 4.5 Hz, 1 H), 3.47 (dd, $J$ = 9.3, 7.8 Hz, 1 H), 1.92–1.71 (m, 4 H), 1.18 (s, 9 H) ppm. $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = 178.4, 164.0, 138.0, 131.3, 128.4, 128.3, 128.2, 127.8, 127.6 (2 C), 82.9, 73.4, 72.1, 71.6, 63.8, 38.7, 31.8, 27.1, 24.5 ppm. HR-ESI-MS: calcd.for $C_{25}H_{32}NO_4$ $[M + H]^+$ 410.2331; found 410.2329.

**(2*R*,3*R*)-1-(Benzyloxy)-2-(*tert*-butoxycarbonyl)-6-(pivaloyloxy)-hexan-3-yl Benzoate (14):** A stirred solution of **13** (950 mg, 2.3 mmol) in THF (15 mL) was treated with aq. HCl (2 M, 8 mL) at room temperature for 16 h. The mixture was cooled to 0 °C, basified by the slow addition of $NaHCO_3$ (12.0 g), and diluted with $H_2O$ (40 mL). To this mixture was added a solution of $Boc_2O$ (1.01 g, 4.6 mmol) in THF (9 mL) at room temperature, the mixture was stirred for 2 h, extracted with $CH_2Cl_2$ (50 mL), and the organic phase was washed with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes = 1:4) to afford **14** (1.151 g, 94%) as a colorless liquid. $[\alpha]_D^{23}$ = –9.4 ($c$ = 1.40, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.02 (d, $J$ = 7.5 Hz, 2 H), 7.56 (t, $J$ = 7.8 Hz, 1 H), 7.43 (t, $J$ = 7.8 Hz, 2 H), 7.30–7.20 (m, 5 H), 5.45 (m, 1 H), 4.94 (d, $J$ = 9.6 Hz, 1 H), 4.46 (AB, $J_{AB}$ = 12.3 Hz, 2 H), 4.14–4.00 (m, 3 H), 3.57 (AB-d, $J_{AB}$ = 9.3, $J$ = 3.9 Hz, 1 H), 3.48 (AB-d, $J_{AB}$ = 9.3, $J$ = 5.4 Hz, 1 H), 1.83–1.63 (m, 4 H), 1.35 (s, 9 H), 1.17 (s, 9 H) ppm. $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = 178.4, 166.1, 155.6, 137.6, 133.0, 130.0, 129.7, 128.3 (2 C), 127.7 (2 C), 79.6, 73.4, 73.3, 69.7, 63.8, 52.5, 38.7, 28.2, 28.0, 27.2, 24.6 ppm. HR-ESI-MS: calcd.for $C_{30}H_{41}NNaO_7$ $[M + Na]^+$ 550.2781; found 550.2765.

**(4*R*,5*R*)-6-(Benzyloxy)-5-(*tert*-butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)hexyl Pivalate (15):** A stirred solution of **14** (870 mg, 1.65 mmol) in MeOH (50 mL) was treated with $K_2CO_3$ (1.14 g, 8.3 mmol) at room temperature for 3 h. The mixture was quenched by sat. aq. $NH_4Cl$, extracted with $CH_2Cl_2$ (3 × 30 mL), and the combined organic layers were washed with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes = 1:4) to afford the debenzoylated intermediate (601 mg, 86%) as a colorless liquid. To a solution of the above alcohol (531 mg, 1.26 mmol) and imidazole (174 mg, 2.52 mmol) in DMF (4 mL) was added TBSCl (283 mg, 1.88 mmol) in one portion, and the solution was stirred overnight, quenched by $H_2O$, extracted with diethyl ether (2 × 30 mL), and the combined organic phases were washed with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes = 1:20) to afford **15** (617 mg, 91%) as a colorless liquid. $[\alpha]_D^{23}$ = –2.9 ($c$ = 0.90, $CHCl_3$); NMR peaks were broadened due to the presence of rotamers. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.40–7.23 (m, 5 H), 4.78 (d, $J$ = 9.3 Hz, 1 H), 4.51 (AB, $J_{AB}$ = 12.0 Hz, 2 H), 4.09–3.81 (m, 4 H), 3.52–3.38 (m, 2 H), 1.72–1.50 (m, 4 H), 1.46 (s, 9 H), 1.20 (s, 9 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = 178.4, 155.7, 138.1, 128.3, 127.6, 127.5, 79.2, 73.0, 70.0, 69.3, 64.2, 51.9, 38.7, 30.7, 28.4, 27.2, 25.8, 24.7, 18.0, –4.3, –4.8 ppm. HR-ESI-MS: calcd.for $C_{29}H_{51}NNaO_6Si$ $[M + Na]^+$ 560.3383; found 560.3376.

**(2*R*,3*R*)-*tert*-Butyl 2-(Benzyloxymethyl)-3-(*tert*-butyldimethylsilyloxy)piperidine-1-carboxylate (16):** Starting from **15** (568 mg, 1.06 mmol), following the same procedure as for compound **10**, the crude product was purified by silica gel flash column chromatography (EtOAc/hexanes = 1:20) to afford **16** (336 mg, 73%) as a colorless liquid. $[\alpha]_D^{23}$ = +5.3 ($c$ = 0.66, $CHCl_3$); NMR peaks were broadened due to the presence of rotamers. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.37–7.21 (m, 5 H), 4.72–4.37 (m, 3 H), 4.06–3.62 (m, 4 H), 2.76 (m, 1 H), 1.76–1.56 (m, 2 H), 1.55–1.40 (m, 2 H), 1.46 (s, 9 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = 155.3, 138.7, 128.2, 127.3 (2 C), 79.3, 72.6, 69.4, 64.5, 56.1, 37.4, 29.6, 28.4, 25.7, 24.0, 18.0, –4.9 ppm. HR-ESI-MS: calcd.for $C_{24}H_{41}KNO_4Si$ $[M + K]^+$ 474.2442; found 474.2438.

**(2*R*,3*R*)-*tert*-Butyl 3-(*tert*-Butyldimethylsilyloxy)-2-(hydroxymethyl)piperidine-1-carboxylate (17):** A suspension of **16** (240 mg, 0.55 mmol) and 10% Pd/C (30 mg) in MeOH (8 mL) was stirred under a $H_2$ atmosphere at room temperature for 5 h, filtered through celite and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes = 1:4) to afford **17** (187 mg, 98%) as a colorless liquid. $[\alpha]_D^{23}$ = –15.9 ($c$ = 1.20, $CHCl_3$), ref.[6d] $[\alpha]_D^{25}$ = –16.0 ($c$ = 0.70, $CHCl_3$); NMR peaks were broadened due to the presence of rotamers. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 4.55–4.30 (m, 1 H), 4.14–3.78 (m, 3 H), 3.71 (m, 1 H), 2.85–2.43 (m, 2 H), 1.83–1.54 (m, 4 H), 1.47 (s, 9 H), 0.91 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = 156.0, 80.0, 70.8, 59.3, 56.6, 38.0, 28.9, 28.4, 25.7, 23.9, 18.0, –4.8, –5.1 ppm. HR-ESI-MS: calcd.for $C_{17}H_{35}NNaO_4Si$ $[M + Na]^+$ 368.2233; found 368.2228.

**(2*S*,3*R*)-3-Hydroxypiperidine-2-carboxylic Acid Hydrochloride (1):** Starting from **17** (98 mg, 0.28 mmol), following the same procedure as for compound **2**, virtually pure product **1** (30 mg, 72%) was obtained as a white solid. $[\alpha]_D^{23}$ = –24.5 ($c$ = 0.60, $H_2O$), ref.[6d] $[\alpha]_D^{23}$ = –25 ($c$ = 1.3, $H_2O$); $^1$H NMR (300 MHz, $D_2O$): $\delta$ = 4.42 (s, 1 H), 3.93 (s, 1 H), 3.29 (m, 1 H), 2.88 (m, 1 H), 1.93–1.73 (m, 2 H), 1.73–1.50 (m, 2 H) ppm. $^{13}$C NMR ($D_2O$, 125 MHz): $\delta$ = 171.6, 65.1, 62.0, 45.0, 29.7, 17.1 ppm. HR-ESI-MS: calcd.for $C_6H_{12}NO_3$ $[M + H]^+$ 146.0817; found 146.0810.

**(2*R*,3*R*)-2-(Hydroxymethyl)piperidin-3-ol (3):** Starting from **17** (82 mg, 0.24 mmol), following the same procedure as for compound **4**, the crude product was purified by silica gel flash column chromatography ($MeOH/CH_2Cl_2$ = 1:2) to afford **3** (30 mg, 95%) as a colorless liquid. $[\alpha]_D^{23}$ = –12.2 (*c* = 0.30, $H_2O$), ref.[16a] $[\alpha]_D^{21}$ = –12.4 (*c* = 2.51, $H_2O$); $^1H$ NMR (500 MHz, $D_2O$): $\delta$ = 4.61 (s, 1 H), 4.37–4.26 (m, 2 H), 3.68 (d, *J* = 13.0 Hz, 1 H), 3.47 (m, 1 H), 3.30 (m, 1 H), 2.55–2.47 (m, 1 H), 2.45–2.30 (m, 2 H), 2.18–2.12 (m, 1 H) ppm. $^{13}C$ NMR ($D_2O$, 125 MHz): $\delta$ = 67.4, 64.3, 61.7, 46.6, 32.3, 21.8 ppm. HR-ESI-MS: calcd.for $C_6H_{14}NO_2$ $[M + H]^+$ 132.1025; found 132.1017.

**(2*R*,3*R*)-*tert*-Butyl 2-(Benzyloxymethyl)-3-hydroxypiperidine-1-carboxylate (19):** A solution of **16** (47 mg, 0.11 mmol) and $NH_4F$ (52 mg, 1.4 mmol) in $MeOH/H_2O$ (10:1, 2 mL) was heated at 60 °C for 36 h, cooled, diluted with diethyl ether, washed successively with $H_2O$ and brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/hexanes = 1:2) to afford **19** (31 mg, 91%) as a colorless liquid. $[\alpha]_D^{23}$ = –38.9 (*c* = 0.76, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.39–7.25 (m, 5 H), 4.62 (br. m, 1 H), 4.54 (AB, $J_{AB}$ = 12.0 Hz, 2 H), 3.90 (m, 1 H), 3.89 (dd, *J* = 9.8, 7.4 Hz, 1 H), 3.82 (dt, *J* = 11.5, 5.0 Hz, 1 H), 3.67 (dd, *J* = 9.7, 6.1 Hz, 1 H), 3.07 (br. s, 1 H), 2.66 (t-like, *J* = 12.8 Hz, 1 H), 1.88 (m, 1 H), 1.66 (m, 1 H), 1.57 (m, 1 H), 1.47 (m, 1 H), 1.44 (s, 9 H) ppm. $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 154.9, 137.7, 128.4, 127.7, 127.6, 79.8, 73.2, 69.5, 66.6, 53.2, 39.0, 28.8, 28.4, 23.9 ppm. HR-ESI-MS: calcd.for $C_{18}H_{28}NO_4$ $[M + H]^+$ 322.2018; found 322.2016.

**Supporting Information** (see also the footnote on the first page of this article): $^1H$ and $^{13}C$ NMR spectra for the new compounds **7**–**10**, **12**–**16**, and **18**.

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