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A General Approach to (5*S*,6*R*)-6-Alkyl-5-benzyloxy-2-piperidinones: Application to the Asymmetric Syntheses of Neurokinin Substance P Receptor Antagonist (−)-L-733,061 and (−)-Deoxocassine†

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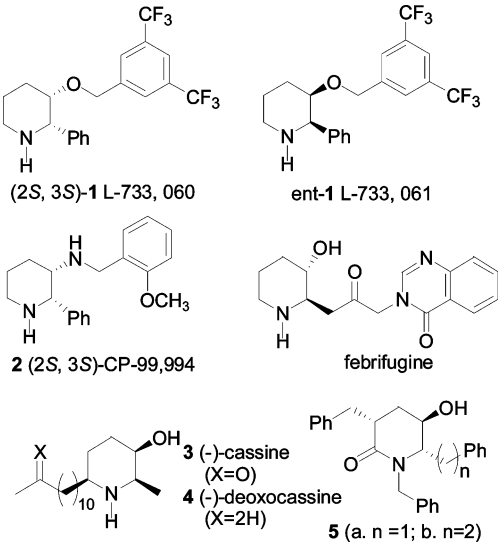
A general approach to (5*S*,6*R*)-6-alkyl-5-benzyloxy-2-piperidinones based on the regio- and diastereoselective reductive alkylation of (*S*)-3-benzyloxyglutarimide **7** is described. This method opens an entrance to chiral nonracemic substituted 3-piperidinols. The versatility of the method is illustrated by the asymmetric syntheses of neurokinin substance P receptor antagonist L-733,061 (ent-**1**), (−)-deoxocassine (**4**), and an inhibitor of HIV proteases (**5a**).

Selectivity, versatility, and flexibility are among the major concern in organic synthesis. Development of multifunctional chiral nonracemic building blocks or synthons has been proven to be a powerful strategy to meet the needs of both the versatility and flexibility.[1] 2-Alkyl-3-hydroxypiperidines, 2,6-dialkyl-3-hydroxypiperidines, and the corresponding 5-hydroxy-2-piperidinones are structural units found in a number of bioactive natural products, drugs, and drug candidates. For example, (+)-L-733,060 (**1**)[2] and (2*S*,3*S*)-CP-99,994 (**2**) are selective and potent neurokinin substance P receptor antagonists, which have been shown to possess potent antiemetic activity (Chart 1); febrifugine and isofebrifugine are well-known antimalarial alkaloids;[3] (−)-cassine (**3**)[4] is a representative of a number of bioactive 2,6-dialkyl-3-piperidinol based alkaloids,[5] and 1,3,6-trisubstituted 5-hydroxy-2-piperidinones such as **5** are potential candidates as inhibitors of HIV proteases.[6]

The important bioactivities, common structural features, and stereochemistry and substituent diversities associated with these piperidines and 2-piperidinones have stimulated the development of 3-piperidinol synthon-based versatile synthetic approaches.[7]

CHART 1. Some Bioactive Piperidines and 2-Piperidinones



Recently, we have embarked on a program aimed at the development of the protected 3-hydroxyglutarimide (*S*)-**6** as a versatile multifunctional chiral nonracemic 3-piperidinol synthon.[8] The studies have culminated in the asymmetric syntheses of neurokinin substance P

† Dedicated to Professor Li-Xin Dai on the occasion of his 80th birthday.

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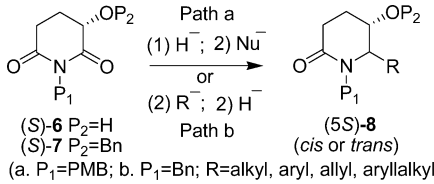
SCHEME 1



receptor antagonists (2*S*,3*S*)-L-733,060 (**1**) and (2*S*,3*S*)-CP-99,994 (**2**)[8a] as well as antimalarial alkaloids (+)-febrifugine and isofebrifugine.[8b] The key point of our method is the regioselective and *cis*-diastereoselective introduction of a phenyl or allyl group at the C-6 of the *N*,*O*-acetal derived from *O*-silyl group protected glutarimide **6** via α-amidoalkylation (**6** to **8**, Scheme 1, path a). To develop a more flexible approach allowing the introduction of various alkyl groups at the C-2 of **6**, required for the syntheses of a variety of piperidine alkaloids and related bioactive compounds, we decided to explore the regio- and stereoselective reductive alkylation approach (**7** to **8**, Scheme 1, path b).[9] The study opens a new access to *trans*-6-alkyl-5-benzyloxy-2-piperidinones **12**, which are valuable precursors for a number of bioactive substituted 5-hydroxy-2-piperidinones[6,10] and substituted 3-piperidinols,[5,7,10] for example, compounds **3** and **4**.

Multigram quantities of (*S*)-3-hydroxyglutarimide **6a** are readily available from (*S*)-glutamic acid as described previously.[8] Protection of the hydroxy group under standard conditions (BnBr, Ag_2O, Et_2O, rt) provided the desired protected (*S*)-glutarimide **7a** {white crystals, mp 74.5−75.0 °C, $[\alpha]^{20}_D$ −53.6 (*c* 1.0, $CHCl_3$)} in 90% yield (Scheme 1). With enantioenriched **7a** easily available in quantity, we then proceeded to study its reaction with Grignard reagents. Addition of methylmagnesium iodide (3 molar equiv) to (*S*)-3-benzyloxy-1-(4-methoxybenzyl)-glutarimide **7a** (THF, −78 °C) yielded **9a** (Scheme 2) as a separable diastereomeric mixture (combined yield 84%). Although the determination of both regio- and diastereoselectivities and tentative attribution of regio- versus diastereoisomers can be made at this stage, only after the subsequent reductive deoxygenation step could we conclude that the methylmagnesium iodide addition to **7a** proceeded in 86:14 regioselectivity (Table 1, entry 1) in favor of the C-2 addition. The major regioisomer **9a**

SCHEME 2

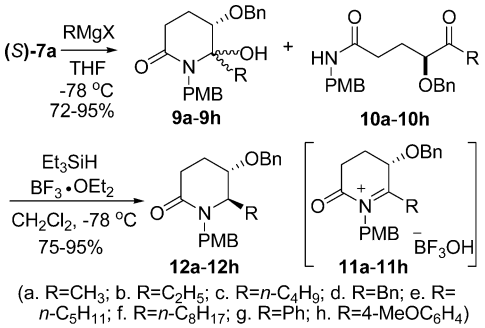
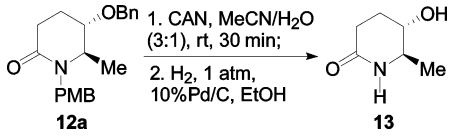


TABLE 1. Results of Reductive Alkylation of 7a According to Procedure Shown in Scheme 2

			selectivities[b]	
entry	R	yield (%)[a]	C_2/C_6	*trans*:*cis*
1	CH_3	**12a** (80)	86:14	92:8
2	C_2H_5	**12b** (79)	88:12	95:5
3	*n*-C_4H_9	**12c** (80)	93:7	95:5
4	Bn	**12d** (73)	97:3	98:2
5	*n*-C_5H_{11}	**12e** (81)	97:3	97:3
6	*n*-C_8H_{17}	**12f** (77)	92:8	96:4
7	Ph	**12g** (80)	92:8	94:6
8	4-$MeOC_6H_4$	**12h** (70)	95:5	96:4

[a] Isolated yield of **12** starting from **7a**. [b] Ratio based on chromatography separation.

SCHEME 3



consisted of two diastereomers in 80:20 ratio. The stereochemistries of diastereomeric **9a** were not assigned (vide infra).

Because the subsequent Lewis acid mediated reductive deoxygenation[11] was considered to proceed via the intermediacy of *N*-acyliminium[12] **11** (Scheme 2), in which the stereochemistry at the C-6 will be destroyed, the diastereomeric mixture **9** was used without separation in the next step. Indeed, in the presence of 3 molar equiv of boron trifluoride etherate, the diastereomers of **9a** were reduced with an excess of triethylsilane (CH_2Cl_2, −78 °C−rt) to yield predominantly *trans*-**12a** (Scheme 2) in a combined yield of 95%. The *trans*/*cis* diastereoselectivity observed in this reaction was 92:8 according to chromatography separation (Table 1, entry 1). The stereochemistry of the major diastereomer **12a** was assigned to *trans* by its conversion into known **13**[10d] (Scheme 3), which was further confirmed by converting **12g** and **12a** to (−)-**1** (L-733,061) and (−)-deoxocassine **4**, respectively (vide infra). The ee of **12a** was determined to be 96.0% on the basis of HPLC analysis on a chiral column.

Encouraged by these results, the reductive alkylations of **7a** with other Grignard reagents were investigated,

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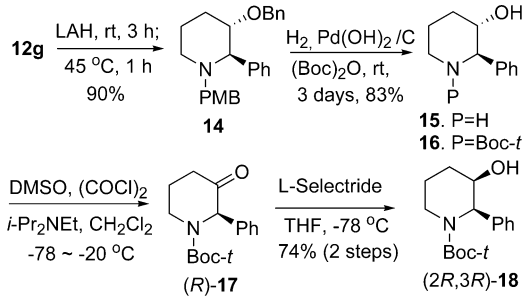
SCHEME 4



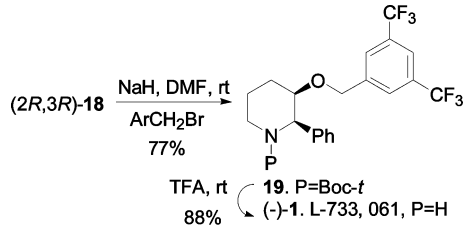
and the results are reported in Table 1. Thus, all of the addition reactions proceed with similar or better C-2 regioselectivity. It is important to note that in a number of cases, substantial amounts of tautomeric ring-opening keto amides products **10** were obtained. Taking into account that tautomers **9** and **10** are interconvertible under acidic conditions, an experimentally expedient protocol for their conversion into **12** would reside on the direct use of the above-mentioned tautomeric mixture in the subsequent reaction. This turned out to be fruitful. In practice, after the Grignard reagent addition to **7a**, the crude was subjected to a short column chromatography to eliminate the C-6 regioisomers and other side products, and all diastereomeric and tautomeric isomers of **9** were collected in one fraction, which without further separation was treated with $Et_3SiH/BF_3{\cdot}OEt_2$ to give the desired 6-alkyl-5-benzyloxy-2-piperidinones **12** in high diastereoselectivities and in good chemical yields (Table 1, entries 2−8).

Although the addition of Grignard reagents to glutarimides[13] has been reported as early as 1936,[13a] most of them dealt with symmetric glutarimides, avoiding regioselectivity or stereoselectivity problems. However, in one case, the addition of both phenyllithium and 2-furyllithium to racemic 3-methylglutarimide and its *N*-methyl derivative was reported to give the C-6 addition products.[13d] In the present study, the observed high C-2 regioselectivity (86−97%) of Grignard reagent addition to **7a** could be attributed to both the inductive effect[14] of the C-3 substituent and the (C-3) O-Mg-O (C-2 carbonyl) chelation-induced activating effects.

So far, we have demonstrated that starting from (*S*)-3-hydroxyglutarimide (**6a**), one can access a series of 2-alkyl-3-piperidinols with either (2*S*,3*S*)[8] or (2*R*,3*S*) (vide infra, Scheme 4) stereochemistries. To illustrate the synthetic utility of the method in establishing (2*R*,3*R*) stereochemistry (numbering based on **6a**), we decided to undertake the synthesis of (2*R*,3*R*)-L-733,061 (ent-**1**),[2] the antipode of (2*S*,3*S*)-L-733,060 (+)-**1**.[2] It has been demonstrated that *cis*-2,3-substitution is essential for high-affinity binding to the human NK_1 (hNK_1) receptor.[2b]

Thus, as shown in Scheme 4, lithium aluminum hydride reduction of **12g** (yield 90%), followed by one-pot carbamative debenzylation [H_2, l atm, 20% $Pd(OH)_2$/C, $(Boc)_2O$] led directly to *N-tert*-Boc-2-phenyl-3-piperidinol **16**[2a] {$[\alpha]^{20}_D$ −66.1 (*c* 0.9, $CHCl_3$)} in 83% yield. Swern oxidation[15] [$(COCl)_2$, DMSO, CH_2Cl_2, −78 ∼ −20 °C; *i*-Pr_2NEt] afforded known *tert*-Boc-protected (*R*)-2-phenyl-3-piperidinone **17**,[16] which was reduced immediately with L-Selectride[17] to provide *cis*-(2*R*,3*R*)-**18**[2] {colorless oil, $[\alpha]^{20}_D$ −51.1 (*c* 1.0, $CHCl_3$); lit.[8a] $[\alpha]^{15}_D$ +53.8 (*c* 1.0, $CHCl_3$) for (2*S*,3*S*)-**18**} as the only diastereomer. The overall yield from **16** to **18** was 74%.

SCHEME 5



Etherification (NaH, 3,5-$(CF_3)_2C_6H_3CH_2Br$, DMF, rt, yield 77%) of (−)-**18** gave (−)-**19**[2] {$[\alpha]^{28}_D$ −35.6 (*c* 1.0, $CHCl_3$); lit.[8a] $[\alpha]^{28}_D$ +36.9 (*c* 1.0, $CHCl_3$) for the antipode}, which was then deprotected to afford (−)-L-733,061 (ent-**1**)[2,18] {ent-**1**·HCl mp 213−215 °C. $[\alpha]^{28}_D$ −79.6 (*c* 1.0, MeOH); lit.[2a] mp 215−216 °C. $[\alpha]^{23}_D$ +87.3 (*c* 1, MeOH) for (+)-**1**}(Scheme 5).

The synthesis of (−)-L-733,061 (ent-**1**) served to demonstrate that the method presented here not only allowed preparation of a series of *trans*-(5*S*,6*R*)-6-alkyl-5-hydroxy-2-piperidinones but also opened a flexible entrance to both *trans*-(2*R*,3*S*)- and *cis*-(2*R*,3*R*)-2-alkyl-3-piperidinols, which are key structural features found in a number of bioactive natural or designed piperidines.[4,8,18−20] For example, (*R*)-2-phenyl-3-piperidinone **17** has been used as the key intermediate in the asymmetric synthesis of the antipode of another NK-1 receptor antagonist,[16] and the antipode of **15** has been used as an advanced intermediate in the asymmetric synthesis of natural product *trans*-(2*R*,3*S*)-3-hydroxypipecolic acid,[19] which has also been transformed into (−)-swainsonine,[20] an indolizidine alkaloid possessing potent and specific α-D-mannosidase inhibitory activity.

Next, we turned attention to the synthesis of deoxocassine (**4**)[21] to demonstrate the synthetic versatility of the building block **7a** in introducing the C-6 substituent (numbering based on **6a**). Thus, as shown in Scheme 6, lithium aluminum hydride reduction of **12a** (yield, 84%), followed by one-pot carbamation-debenzylation of **20** [H_2, l atm, 20% $Pd(OH)_2$/C, $(Boc)_2O$, EtOH] led directly to *N-tert*-Boc-2-methyl-3-piperidinol **21** in 79% yield. Fi-

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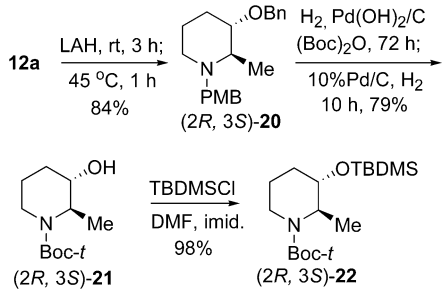
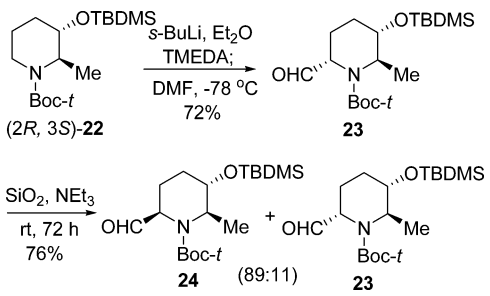
SCHEME 6



SCHEME 7

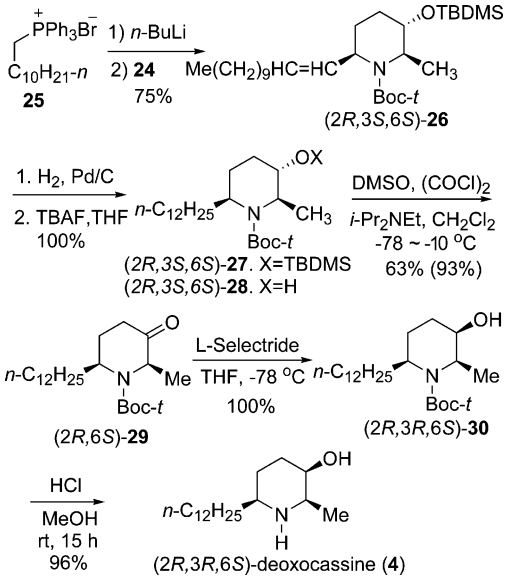


nally, TBDMS ether derivative **22** was obtained upon treatment of **21** with TBDMSCl and imidazole at room temperature.[22]

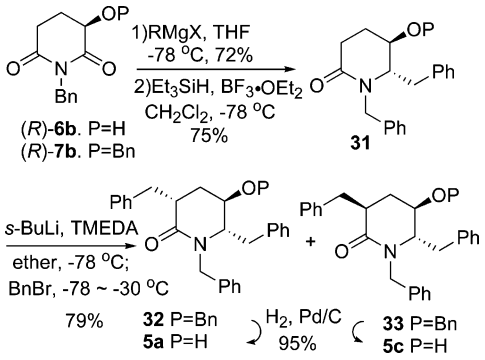
To introduce the C-6 side chain of deoxocassine, Beak's methodology[23] was employed. Thus treatment of **22** with *sec*-butyllithium (1.2 molar equiv) and TMEDA (−30 °C, 1.5 molar equiv) generated in situ the dipole stabilized C-6 carbanion, which was allowed to react with DMF (−78 °C, 10 min). In this way, the desired formylated product **23** was obtained in 94:6 diastereoselectivity and in a combined yield of 72% (Scheme 7). The stereochemistry of the major diastereomer **23** was tentatively assigned as *trans* by analogy with the literature reports.[23] This assignment was confirmed by its epimerization to thermodynamically more stable C_2/C_6 *cis*-diastereomer[23] **24** (vide infra). Treatment of the diastereomeric mixture of **23** with SiO_2 and triethylamine (rt, 72 h) led to an 11:89 diastereomeric mixture of **23** and **24** in favor of C_2/C_6 *cis*-epimer **24**.

Treatment of aldehyde **24** with the Wittig reagent generated in situ from **25** and *n*-butyllithium gave olefin **26** (Scheme 8). Hydrogenation of **26** (H_2, 10% Pd/C, rt, EtOH; yield 100%) followed by deprotection (TBAF, THF, rt, 15 h) provided alcohol **28** in quantitative yield. Inversion of the configuration at the C-3 by Swern oxidation[15] (yield 63%, recovered starting material 30%), followed by L-Selectride reduction[17] provided **30** (yield 100%) as the only diastereomer. Finally, deprotection of **30** under acidic conditions (HCl, MeOH, rt, 15 h) afforded the desired (2*R*,3*R*,6*S*)-deoxocassine (**4**) {mp 47−48 °C; lit.[21a] mp 47.5−48.5 °C. $[\alpha]^{25}_D$ −11.8 (*c* 0.9, $CHCl_3$); lit.[21a] $[\alpha]^{18}_D$ −12.3 (*c* 0.19, $CHCl_3$); lit.[21b] $[\alpha]^{20}_D$ −12.4 (*c* 0.8, $CHCl_3$)} in 96% yield.

SCHEME 8



SCHEME 9



To illustrate the potential nucleophilic reactivity at the C-5 of **7**, the synthesis of **5a**, a compound belonging to a class of inhibitors of HIV proteases as represented by **5**,[6] was undertaken (Scheme 9). Prepared similarly as described for **12** from (*R*)-3-hydroxyglutarimide (*R*)-**6b**,[8b] **31** was deprotonated with *sec*-butyllithium at −78 °C, and addition of benzyl bromide (−78 to −30 °C, 6 h) afforded a separable diastereomeric mixture **32**/**33** in 9:1 ratio (combined yield, 79%). Both diastereomers **32** and **33** were subjected to hydrogenolysis conditions (H_2, l atm, 10% Pd/C, rt, 3 days) to yield, respectively, **5a** and **5c** in excellent yield. Comparison of ^1H and ^{13}C NMR spectral data of **5a** and **5c** with those reported[6c] allowed conclusion that the major diastereomer obtained during the C-3 benzylation of **31** was **32**.

In summary, we have demonstrated that *N*-protected-3-benzyloxyglutarimide (*S*)-**7** is a versatile 3-piperidinol synthon equivalent; the multiple reactivities possessed by **7** allowed the flexible introduction of a variety of substituents at the *N*-1, C-2, C-5, and C-6 positions of glutarimide **7** in regio- and diastereoselective fashion. Application of the present methodology to the asymmetric syntheses of other bioactive substituted 5-hydroxy-2-piperidinones and 3-piperidinols is under current investigation.

Experimental Section

General Methods. Melting points are uncorrected. Optical rotations were recorded on an automatic polarimeter. IR

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spectra were recorded on a FT-IR spectrophotometer. NMR spectra were recorded in $CDCl_3$ (^1H at 500 MHz and ^{13}C at 125 MHz), and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. HRFABMS spectra were recorded on a FTMS apparatus. Silica gel (300−400 mesh) was used for column chromatography, eluting (unless otherwise stated) with an ethyl acetate/petroleum ether (PE) (60−90 °C) mixture. Dichloromethane, DMF, and diisopropylethylamine were distilled over calcium hydride under N_2. Ether and THF were distilled over sodium benzophenone ketyl under N_2.

(*S*)-3-Hydroxy-1-(4-methoxybenzyl)-2,6-piperidinedione (6a). To a tetrahydrofuran solution (90 mL) of (*S*)-*N*-(4-methoxybenzyl)-tetrahydro-5-oxo-2-furancarboxamide (16.00 mmol), prepared from L-glutamic acid as described previously,[8a] was added a cooled suspension of potassium *tert*-butoxide (7.20 mmol) in anhydrous THF (30 mL) at −78 °C and under nitrogen atmosphere. After 10 min of stirring at −78 °C, the temperature was allowed to arise to −65 °C over 25 min and then adjusted to −50 to −45 °C in 5 min. The reaction was quenched with saturated NH_4Cl at −78 °C. The residue was extracted with EtOAc (3 × 30 mL). The EtOAc extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated to give compound **6a** (yield 70−80%) as white crystals. Mp 98−99 °C (EtOAc); $[\alpha]^{20}_D$ −70.0 (*c* 1.2, $CHCl_3$); IR (film) 3465, 2960, 1730, 1677, 1514, 1338, 1305, 1249, 1177, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 4.90 (s, 2H), 4.22 (ddd, J = 12.9, 5.4, 1.4 Hz, 1H), 3.78 (s, 3H), 3.55 (dd, J = 2.6, 1.4 Hz, 1H), 2.88 (ddd, J = 18.1, 4.8, 2.6 Hz, 1H), 2.66 (ddd, J = 18.1, 12.9, 5.4 Hz, 1H), 2.34 (dddd, J = 12.9, 5.4, 5.4, 2.6 Hz, 1H), 1.88 (dddd, J = 12.9, 12.9, 12.9, 4.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 171.1, 159.1, 130.5 (2C), 128.7, 113.8 (2C), 68.4, 55.2, 43.0, 30.9, 25.2; MS (EI) *m*/*z* 249 (M^+, 100), 203 (28), 121 (20); HRESIMS calcd for $[C_{13}H_{15}NO_4 + Na]^+$ 272.0893, found 272.0897. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.02; N, 5.62. Found: C, 62.58; H, 5.98; N, 5.41.

(*S*)-3-Benzyloxy-1-(4-methoxybenzyl)-2,6-piperidinedione (7a). To a mixture of (*S*)-**6a** (3.500 g, 14.06 mmol) and silver oxide (9.783 g, 42.17 mmol) in dry ether (200 mL) was added benzyl bromide (5.02 mL, 42.13 mmol). The mixture was stirred at room temperature for 10 days. After filtration through silica gel, the solvent was removed under reduced pressure. Flash chromatographic purification on silica gel (eluent EtOAc/PE = 1:8) provided **7a** (4.288 g, 90%) as a waxy solid, which was crystallized from ether to yield **7a** as white crystals. Mp 74.5−75.0 °C; $[\alpha]^{20}_D$ −53.6 (*c* 1.0, $CHCl_3$); IR (film) 2931, 1680, 1513, 1378, 1503, 1248, 1161, 1015 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−6.82 (m, 9H), 4.91 (d, J = 14.5 Hz, 1H), 4.88 (d, J = 14.5 Hz, 1H), 4.83 (d, J = 11.8 Hz, 1H), 4.66 (d, J = 11.8 Hz, 1H), 4.08 (dd, J = 5.9, 5.2 Hz, 1H), 3.78 (s, 3H), 2.93 (ddd, J = 17.7, 7.7, 6.4 Hz, 1H), 2.60 (ddd, J = 17.7, 6.2, 6.2 Hz, 1H), 2.08 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 171.5, 159.0, 137.2, 130.4 (2C), 129.3, 128.5 (2C), 128.0 (3C), 113.8 (2C), 73.9, 72.5, 55.2, 42.4, 29.1, 24.1; MS (EI) *m*/*z* 339 (M^+, 4), 248 (M^+ − Bn, 12), 121 (100), 91 (18); HRESIMS calcd for $[C_{20}H_{21}NO_4 + Na]^+$ 362.1363, found 362.1360. Anal. Calcd for $C_{20}H_{21}NO_4$ C, 70.80; H, 6.19; N, 4.13. Found: C, 70.98; H, 6.29; N, 4.10.

General Procedure for Reductive Alkylation of (*S*)-7a. To a cooled (−78 °C) solution of (*S*)-**7a** (1 molar equiv) in THF (0.1 M) was added dropwise a solution of RMgX in Et_2O (3 molar equiv). The mixture was stirred at −78 °C for 3 h (in the cases of entries 4 and 6−8, the reactions were allowed to slowly warm to −10 °C). The reaction was quenched with saturated NH_4Cl. After extraction with CH_2Cl_2, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent EtOAc/PE = 1:2) to yield **9** and **10**, which were used in the next step without further separation.

To a cooled (−78 °C) solution of a mixture of **9** and **10** (1 molar equiv) in CH_2Cl_2 were added dropwise Et_3SiH (10 molar equiv) and $BF_3{\cdot}OEt_2$ (3 molar equiv) successively. The mixture was stirred at −78 °C for 6 h, then allowed to warm up slowly, and stirred at room temperature overnight. A saturated aqueous $NaHCO_3$ was added, and the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent EtOAc/PE = 1:2) to yield **12**.

(5*S*,6*R*)-5-Benzyloxy-1-(4-methoxybenzyl)-6-methyl-2-piperidinone (12a). Following the general reductive alkylation procedure, **12a** and its diastereomer were obtained in 92:8 diastereomeric ratio and in a combined yield of 80%. (5*S*,6*R*)-**12a** (major diastereomer): R_f 0.35 (EtOAc/PE = 1:1). Colorless oil. $[\alpha]^{20}_D$ +96.9 (*c* 1.3, $CHCl_3$); IR (film) 2990, 2832, 1637, 1470, 1454, 1246, 1176, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−6.78 (m, 9H), 5.41 (d, J = 15.0 Hz, 1H), 4.39 (d, J = 11.9 Hz, 1H), 4.30 (d, J = 11.9 Hz, 1H), 3.83 (d, J = 15.0 Hz, 1H), 3.78 (s, 3H), 3.60 (dq, J = 6.6, 1.5 Hz, 1H), 3.52 (m, 1H), 2.73 (ddd, J = 18.5, 10.7, 8.4 Hz, 1H), 2.42 (ddd, J = 18.5, 6.0, 3.1 Hz, 1H), 2.05 (m, 2H), 1.19 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 158.7, 138.0, 129.2, 129.0 (2C), 128.2 (2C), 127.5, 127.1 (2C), 113.8 (2C), 75.0, 69.8, 55.17, 53.7, 46.6, 27.1, 21.3, 18.3; HRESIMS calcd for $[C_{21}H_{25}NO_3 + H]^+$ 340.1907, found 340.1908. The enantiomeric excess of **12a** is 96.0% as determined by chiral HPLC [100:7:0.3 hexane/dichloroethane/ethanol, λ = 270 nm, t_R 10.9 min for (5*S*,6*R*)-**12a,** 19.0 min for (5*S*,6*S*)-**12a**].

(5*S*,6*R*)-5-Benzyloxy-6-ethyl-1-(4-methoxybenzyl)-2-piperidinone (12b). Following the general reductive alkylation procedure, **12b** and its diastereomer were obtained in 95:5 diastereomeric ratio and in a combined yield of 79%. (5*S*,6*R*)-**12b** (major diastereomer): R_f 0.35 (EtOAc/PE = 1:1). Colorless oil. $[\alpha]^{20}_D$ +89.2 (*c* 0.9, $CHCl_3$); IR (film) 2935, 2879, 1644, 1512, 1463, 1245, 1176, 1091, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−6.75 (m, 9H), 5.44 (d, J = 14.9 Hz, 1H), 4.36 (d, J = 11.7 Hz, 1H), 4.27 (d, J = 11.7 Hz, 1H), 3.76 (d, J = 14.9 Hz, 1H), 3.74 (s, 3H), 3.67 (m, 1H), 3.32 (m, 1H), 2.69 (ddd, J = 17.1, 8.6, 8.6 Hz, 1H), 2.42 (m, 1H), 2.02 (m, 2H), 1.82 (m, 1H), 1.43 (m, 1H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 158.7, 138.1, 129.3, 129.1 (2C), 128.2 (2C), 127.5, 127.2 (2C), 113.8 (2C), 71.8, 69.7, 59.8, 55.2, 46.8, 27.2, 24.9, 21.5, 10.7; HRESIMS calcd for $[C_{22}H_{27}NO_3 + H]^+$ 354.2064, found 354.2069. Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.79; H, 7.65; N, 3.97. Found: C, 74.58; H, 7.96; N, 3.93.

(5*S*,6*R*)-5-Benzyloxy-6-(*n*-butyl)-1-(4-methoxybenzyl)-2-piperidinone (12c). Following the general reductive alkylation procedure, **12c** and its diastereomer were obtained in 95:5 diastereomeric ratio and in a combined yield of 80%. (5*S*,6*R*)-**12c** (major diastereomer): R_f 0.40 (EtOAc/PE = 1:1). Colorless oil. $[\alpha]^{20}_D$ +63.7 (*c* 1.0, $CHCl_3$); IR (film) 2954, 2933, 2871, 1643, 1512, 1464, 1246, 1175, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−6.70 (m, 9H), 5.45 (d, J = 14.9 Hz, 1H), 4.34 (d, J = 11.7 Hz, 1H), 4.25 (d, J = 11.7 Hz, 1H), 3.78 (s, 3H), 3.73 (d, J = 14.9 Hz, 1H), 3.64 (m, 1H), 3.38 (m, 1H), 2.68 (ddd, J = 18.4, 9.9, 8.6 Hz, 1H), 2.41 (m, 1H), 2.20 (m, 2H), 1.72 (m, 1H), 1.40 (m, 1H), 1.32−1.10 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 158.7, 138.1, 129.4, 129.2 (2C), 128.3 (2C), 127.5, 127.2 (2C), 113.8 (2C), 72.3, 69.8, 58.3, 55.2, 46.8, 31.9, 28.5, 27.2, 22.6, 21.6, 13.9; HRESIMS calcd for $[C_{24}H_{31}NO_3 + H]^+$ 382.2377, found 382.2373.

(5*S*,6*R*)-6-Benzyl-5-benzyloxy-1-(4-methoxybenzyl)-2-piperidinone (12d). Following the general reductive alkylation procedure, **12d** and its diastereomer were obtained in 98:2 diastereomeric ratio and in a combined yield of 73%. (5*S*,6*R*)-**12d** (major diastereomer): R_f 0.30 (EtOAc/PE = 1:2). Colorless oil. $[\alpha]^{20}_D$ +79.5 (*c* 1.1, $CHCl_3$); IR (film) 3024, 2937, 1642, 1512, 1455, 1246, 1175, 1100, 1073, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26−6.70 (m, 14H), 5.45 (d, J = 15.0 Hz, 1H), 4.04 (d, J = 11.8 Hz, 1H), 4.00 (d, J = 11.8 Hz, 1H), 3.71 (d, J = 15.0 Hz, 1H), 3.69 (s, 3H), 3.64 (m, 1H), 3.44 (m, 1H), 3.05

(dd, J = 13.9, 4.6 Hz, 1H), 2.66 (ddd, J = 18.1, 11.6, 7.7 Hz, 1H), 2.54 (dd, J = 13.9, 9.9 Hz, 1H), 2.40 (ddd, J = 18.1, 7.7, 2.1 Hz, 1H), 2.05 (m, 1H), 1.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 158.8, 137.9, 137.4, 129.3 (2C), 129.2, 128.8 (2C), 128.7 (2C), 128.1 (2C), 127.3, 127.2 (2C), 126.8, 113.9 (2C), 71.3, 69.5, 59.5, 55.1, 46.9, 38.8, 27.0, 21.5; HRESIMS calcd for $[C_{27}H_{29}NO_3 + H]^+$ 416.2220, found 416.2221. Anal. Calcd for $C_{27}H_{29}NO_3$: C, 78.07; H, 6.99; N, 3.37. Found: C, 78.36; H, 6.99; N, 3.37.

(5*S*,6*R*)-5-Benzyloxy-1-(4-methoxybenzyl)-6-(*n*-pentyl)-2-piperidinone (12e). Following the general reductive alkylation procedure, **12e** and its diastereomer were obtained in 97:3 diastereomeric ratio and in a combined yield of 81%. (5*S*,6*R*)-**12e** (major diastereomer): R_f 0.40 (EtOAc/PE = 1:1). Colorless oil. $[\alpha]^{20}_D$ +57.9 (*c* 1.1, $CHCl_3$); IR (film) 2930, 2859, 1644, 1513, 1463, 1246, 1175, 1073 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−6.78 (m, 9H), 5.45 (d, J = 14.9 Hz, 1H), 4.34 (d, J = 11.8 Hz, 1H), 4.25 (d, J = 11.8 Hz, 1H), 3.74 (s, 3H), 3.73 (d, J = 14.9 Hz, 1H), 3.64 (m, 1H), 3.38 (m, 1H), 2.69 (ddd, J = 18.6, 9.8, 8.8 Hz, 1H), 2.42 (ddd, J = 18.6, 5.3, 4.3 Hz, 1H), 2.02 (m, 2H), 1.71 (m, 1H), 1.39 (m, 1H), 1.32−1.12 (m, 6H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 158.7, 138.2, 129.3, 129.1 (2C), 128.2 (2C), 127.4, 127.2 (2C), 113.8 (2C), 72.2, 69.7, 58.3, 55.1, 46.8, 32.2, 31.6, 27.1, 26.0, 22.4, 21.5, 13.9; HRESIMS calcd for $[C_{25}H_{33}NO_3 + H]^+$ 396.2533, found 396.2530. Anal. Calcd for $C_{25}H_{33}NO_3$: C, 75.95; H, 8.35; N, 3.54. Found: C, 75.46; H, 8.50; N, 3.41.

(5*S*,6*R*)-5-Benzyloxy-1-(4-methoxybenzyl)-6-(*n*-octyl)-2-piperidinone (12f). Following the general reductive alkylation procedure, **12f** and its diastereomer were obtained in 96:4 diastereomeric ratio and in a combined yield of 77%. (5*S*,6*R*)-**12f** (major diastereomer): R_f 0.35 (EtOAc/PE = 1:2). Colorless oil. $[\alpha]^{20}_D$ +55.7 (*c* 0.5, $CHCl_3$); IR (film) 2927, 2855, 1644, 1512, 1463, 1246, 1175, 1098, 1035 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−6.76 (m, 9H), 5.45 (d, J = 15.0 Hz, 1H), 4.34 (d, J = 11.8 Hz, 1H), 4.25 (d, J = 11.8 Hz, 1H), 3.75 (d, J = 15.0 Hz, 1H), 3.73 (s, 3H), 3.64 (m, 1H), 3.37 (m, 1H), 2.68 (ddd, J = 18.5, 10.3, 8.2 Hz, 1H), 2.40 (ddd, J = 18.5, 9.0, 4.6 Hz, 1H), 2.05 (m, 2H), 1.70 (m, 1H), 1.42−1.00 (m, 13H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 158.8, 138.2, 129.2 (2C), 128.3 (2C), 127.5 (2C), 127.2 (2C), 113.8 (2C), 72.3, 69.8, 58.4, 55.2, 46.9, 32.2, 31.8, 29.4 (3C), 27.2, 26.4, 22.7, 21.6, 14.1; MS (ESI) m/z 438 (M + H$^+$, 100), 460 (M + Na$^+$, 30); HRESIMS calcd for $[C_{28}H_{39}NO_3 + H]^+$ 437.6289, found 437.6280.

(5*S*,6*R*)-5-Benzyloxy-1-(4-methoxybenzyl)-6-phenyl-2-piperidinone (12g). Following the general reductive alkylation procedure, **12g** and its diastereomer were obtained in 94:6 diastereomeric ratio and in a combined yield of 80%. (5*S*,6*R*)-**12g** (major diastereomer): R_f 0.40 (EtOAc/PE = 1:2). Colorless oil. $[\alpha]^{20}_D$ +73.1 (*c* 1.2, $CHCl_3$); IR (film) 3061, 3029, 3003, 1644, 1512, 1464, 1451, 1246, 1174 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−6.76 (m, 14H), 5.65 (d, J = 14.9 Hz, 1H), 4.64 (br s, 1H), 4.44 (d, J = 11.8 Hz, 1H), 4.38 (d, J = 11.8 Hz, 1H), 3.78 (s, 3H), 3.68 (m, 1H), 3.33 (d, J = 14.9 Hz, 1H), 2.82 (ddd, J = 18.5, 11.5, 7.5 Hz, 1H), 2.55 (ddd, J = 18.5, 6.1, 4.1 Hz, 1H), 1.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 158.8, 138.7, 137.8, 129.2, 128.9 (2C), 128.7 (2C), 128.3 (2C), 127.8, 127.6, 127.3 (2C), 126.8 (2C), 113.8 (2C), 76.2, 70.1, 62.6, 55.2, 46.9, 27.2, 20.6. MS (EI) m/z 401 (M$^+$, 50), 262 (100), 121 (35), 91 (36), 77 (10); HRESIMS calcd for $[C_{26}H_{27}NO_3 + H]^+$ 402.2064, found 402.2069. Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.80; H, 6.73; N, 3.49. Found: C, 77.17; H, 6.67; N, 3.74.

(5*S*,6*R*)-5-Benzyloxy-1-(4-methoxybenzyl)-6-(4-methoxyphenyl)-2-piperidinone (12h). Following the general reductive alkylation procedure, **12h** and its diastereomer were obtained in 96:4 diastereomeric ratio and in a combined yield of 70%. (5*S*,6*R*)-**12h** (major diastereomer): R_f 0.35 (EtOAc/PE = 1:2). Colorless oil. $[\alpha]^{20}_D$ +38.5 (*c* 1.0, $CHCl_3$); IR (film) 2934, 1642, 1612, 1512, 1463, 1248, 1175, 1033 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−6.76 (m, 13H), 5.63 (d, J = 15.0 Hz, 1H), 4.58 (br s, 1H), 4.43 (d, J = 11.7 Hz, 1H), 4.38 (d, J = 11.7 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.65 (m, 1H), 3.33 (d, J = 15.0 Hz, 1H), 2.81 (ddd, J = 18.6, 11.7, 7.2 Hz, 1H), 2.54 (ddd, J = 18.6, 6.4, 4.6 Hz, 1H), 1.93−1.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 159.2, 158.8, 137.9, 130.6, 129.3 (2C), 129.0, 128.3 (2C), 128.0 (2C), 127.6, 127.3 (2C), 114.3 (2C), 113.9 (2C), 76.3, 70.2, 62.2, 55.4, 55.2, 46.9, 27.3, 20.6; MS (ESI) m/z 432 (M + H$^+$, 100). Anal. Calcd for $C_{27}H_{29}NO_4$: C, 75.17; H, 6.73; N, 3.25. Found: C, 74.82; H, 6.89; N, 2.92.

(5*S*,6*R*)-5-Hydroxy-6-methyl-2-piperidinone (13). To a solution of **12a** (0.70 g, 2.06 mmol) in CH_3CN (49 mL) and H_2O (14 mL) was added CAN (4.53 g, 8.26 mmol). The resultant mixture was stirred at room temperature for 30 min. H_2O (60 mL) was added, and the aqueous phase was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed successively with saturated aqueous sodium bicarbonate (5 × 5 mL) and brine (5 mL), then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue and a catalytic amount of TsOH were resolved in CH_2Cl_2 (20 mL), and the mixture was stirred at room temperature overnight. The mixture was basified with a saturated sodium bicarbonate solution to reach pH 7. The mixture was extracted with CH_2Cl_2 (2 × 15 mL), and the organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (eluent EtOAc/PE/NH_3/H_2O/MeOH = 100:100:1:5) to yield the *N*-deprotected piperidinone (270 mg, 60%) as a waxy solid.

A suspension of the *N*-deprotected piperidinone (80 mg, 0.37 mmol) and Pd/C (50 mg, 10% Pd) in ethanol (5 mL) was stirred at room temperature and under atmosphere of H_2 for 72 h. The mixture was filtered through Celite, and the solvent was removed under reduced pressure. Flash chromatographic purification on silica gel (eluent CH_2Cl_2/EtOH/NH_3·H_2O = 100:10:1) provided **13** (36 mg, 76%) as colorless crystals. Mp 130−131 °C (EtOAc) (lit.[10d] mp 130−131 °C). $[\alpha]^{26}_D$ +48.5 (*c* 1.0, CH_2Cl_2) [lit.[10d] $[\alpha]^{20}_D$ −49.1 (*c* 1.0, CH_2Cl_2)]; IR (film) 3292, 3196, 2923, 2848, 1652, 1558, 1540, 1457, 1418, 1262, 1075 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (br s, 1H), 3.64 (ddd, J = 8.4, 6.3, 1.0 Hz, 1H), 3.38 (apparent dquint, J = 6.5, 1.0 Hz, 1H), 2.53 (dt, J = 18.1, 6.0 Hz, 1H), 2.38 (ddd, J = 18.1, 9.2, 6.5 Hz, 1H), 2.04 (m, 2H), 1.86 (dddd, J = 13.4, 9.2, 9.2, 6.3 Hz, 1H), 1.26 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 172.0, 69.4, 54.6, 28.1, 27.0, 20.4; MS (ESI) m/z 130 (M + H$^+$, 100).

(2*R*,3*S*)-3-Benzyloxy-1-(4-methoxybenzyl)-2-phenylpiperidine (14). To a cooled (0−5 °C) suspension of lithium aluminum hydride (520 mg, 13.68 mmol) in anhydrous THF (25 mL) was added, under N_2 atmosphere, a solution of **12g** (1.830 g, 4.56 mmol) in THF (5 mL). The mixture was stirred at room temperature for 3 h, then warmed to 40 °C, and stirred at that temperature for 1 h. The mixture was chilled with an ice bath. To the mixture were added successively ether (5 mL), a 10% solution of sodium hydroxide (0.4 mL), and H_2O (0.1 mL). The resultant mixture was stirred at room temperature for 30 min and then filtered through Celite. The filtrate was concentrated at reduced pressure, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/CH_3COCH_3 = 150:1) to afford **14** (1.580 g, 90%) as a waxy solid. $[\alpha]^{25}_D$ +26.5 (*c* 1.1, $CHCl_3$); IR (neat) 2934, 2858, 2785, 1511, 1453, 1246, 1098 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56−6.78 (m, 14H), 4.15 (d, J = 11.5 Hz, 1H), 3.90 (d, J = 11.5 Hz, 1H), 3.77 (s, 3H), 3.67 (d, J = 13.3 Hz, 1H), 3.38 (ddd, J = 11.2, 8.6, 4.4 Hz, 1H), 3.06 (d, J = 8.6 Hz, 1H), 2.88 (m, 1H), 2.79 (d, J = 13.3 Hz, 1H), 2.20 (m, 1H), 1.90 (ddd, J = 13.4, 11.2, 1.7 Hz, 1H), 1.66 (m, 1H), 1.55 (m, 1H), 1.38 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 142.5, 138.6, 131.6, 129.7 (2C), 129.1 (2C), 128.2 (2C), 128.0 (2C), 127.6 (2C), 127.2 (2C), 113.5 (2C), 81.4, 74.0, 71.6, 58.5, 55.2, 52.1, 31.1, 23.5; MS (ESI) m/z 388 (M + H$^+$, 100); HRESIMS calcd for $[C_{26}H_{29}NO_2 + H]^+$ 388.2271, found 388.2267.

(2*R*,3*S*)-1-(*tert*-Butyloxycarbonyl)-3-hydroxy-2-phenylpiperidine (16). To a mixture of **14** (1.200 g, 3.10 mmol) and

20% $Pd(OH)_2/C$ (500 mg) were added ethanol (30 mL) and di-*tert*-butyl dicarbonate (2.13 mL, 9.28 mmol). The mixture was stirred at room temperature and under an atmosphere of H_2 for 72 h. The resultant mixture was filtered through Celite and concentrated under reduced pressure. Flash chromatographic purification on silica gel (eluent EtOAc/PE = 1:4) provided **16** (710 mg, 83%) as a colorless waxy solid, which was crystallized from Et_2O to provide **16**[2a] as white crystals. Mp 67−68 °C. $[\alpha]^{20}_D$ −66.1 (*c* 0.9, $CHCl_3$); IR (neat) 3446, 2931, 1693, 1668, 1417, 1366, 1169, 1128 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.17 (m, 5H), 5.38 (br s, 1H), 4.52 (m, 1H), 4.10 (m, 1H), 2.86 (ddd, J = 13.2, 13.2, 3.2 Hz, 1H), 2.14 (d, J = 6.3 Hz, 1H), 1.92 (qt, J = 13.2, 4.5 Hz, 1H), 1.76 (m, 1H), 1.65−1.57 (m, 1H), 1.45 (s, 9H), 1.43−1.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 138.3, 128.7 (2C), 126.9, 126.4 (2C), 80.1, 67.5, 60.3, 40.0, 28.4, 26.0, 18.9; MS (ESI) *m*/*z* 555 ($2M + H^+$, 100), 278 ($M + H^+$, 45). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.31; H, 8.30; N, 5.05. Found: C, 69.66; H, 8.51; N, 4.95.

(2*R*,3*R*)-1-(*tert*-Butyloxycarbonyl)-3-hydroxy-2-phenylpiperidine (18). Dimethyl sulfoxide (0.25 mL, 3.53 mmol) was added dropwise to a cooled (−78 °C) solution of oxalyl chloride (0.15 mL, 1.71 mmol) in CH_2Cl_2 (6 mL). The mixture was stirred at −78 °C for 5 min, and a solution of **16** (320 mg, 1.16 mmol) in CH_2Cl_2 (4 mL) was added dropwise. After being stirred at the same temperature for 1 h, *i*-Pr_2NEt (0.60 mL, 3.45 mmol) was added, and the mixture was allowed to warm slowly to −25 °C. The resultant mixture was recooled to −78 °C, and a buffer solution of NaOAc−HOAc (2 mL) and water (10 mL) were added successively. After CH_2Cl_2 extraction (3 × 10 mL), the combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed (eluent EtOAc/PE = 1:4) to yield known **17**[16] as a colorless oil (253 mg, yield 80%), which was used in the next step immediately. IR (neat) 2975, 2933, 1722, 1698, 1450, 1410, 1392, 1366, 1167, 1107 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 5.65 (br s, 1H), 4.10 (br s, 1H), 3.30 (m, 1H), 2.51−2.40 (m, 2H), 2.01−1.88 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 155.0, 135.7, 129.0 (2C), 127.7, 125.4 (2C), 80.8, 66.4, 40.2, 37.4, 28.3 (3C), 22.9; MS (EI) *m*/*z* 275 (M^+, 5), 219 (72), 191 (25), 174 (36), 146 (100), 91 (25).

To a cooled (−78 °C) solution of **17** (190 mg, 0.69 mmol) in anhydrous THF (6 mL) was added dropwise, under N_2 atmosphere, a solution of L-Selectride (1 M in THF, 1.00 mL, 1.00 mmol), and the mixture was stirred at −78 °C for 2 h. The reaction was quenched by successive addition of a saturated aqueous ammonium chloride (1 mL) and water (6 mL). After extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (eluent EtOAc/PE = 1:4) of the crude then yielded known (2*R*,3*R*)-**18**[2] as a colorless oil (177 mg, yield 93%). $[\alpha]^{20}_D$ −51.1 (*c* 1.0, $CHCl_3$) {lit.[4] $[\alpha]^{15}_D$ +53.8 (*c* 1.0, $CHCl_3$) for (2*S*,3*S*)-**18**}. The spectral data are identical with those of (2*S*,3*S*)-**18**.[4] HRESIMS calcd for $[C_{16}H_{23}NO_3 + Na]^+$ 300.1570, found 300.1560.

(2*R*,3*R*)-1-(*tert*-Butyloxycarbonyl)-2-phenyl-3-[(3,5-bis(trifluoromethyl)benzyl)oxy]piperidine (19). Compound (2*R*,3*R*)-**19**[2] was prepared from (2*R*,3*R*)-**18** by a procedure analogue to that used for the preparation of (2*S*,3*S*)-**19**.[2] Yield 77%. Colorless oil. $[\alpha]^{28}_D$ −35.6 (*c* 1.0, $CHCl_3$) {lit.[8a] $[\alpha]^{28}_D$ +36.9 (*c* 1.0, $CHCl_3$) for (+)-**19**}. The spectral data of (2*R*,3*R*)-**19** are identical with those of (2*S*,3*S*)-**19**.[8a] HRESIMS calcd for $[C_{25}H_{27}NO_3F_6 + Na]^+$ 526.1787, found 526.1812.

(2*R*,3*R*)-2-Phenyl-3-[(3,5-bis(trifluoromethyl)benzyl)oxy]piperidine (−)-(1). (−)-(2*R*,3*R*)-**1**[2] was prepared from (2*R*,3*R*)-**19** by a procedure analogue to that used for the preparation of (2*S*,3*S*)-**1**[2]. Yield 88%. Colorless oil. $[\alpha]^{28}_D$ −79.6 (*c* 1.0, MeOH, hydrochloride) {lit.[2a] $[\alpha]^{23}_D$ +87.3 (*c* 1.0, MeOH)}. The spectral data of (−)-(2*R*,3*R*)-**1** are identical to the reported values.[2a] HRESIMS calcd for $[C_{20}H_{19}NOF_6 + H]^+$ 404.1444, found 404.1470.

(2*R*,3*S*)-3-Benzyloxy-1-(4-methoxybenzyl)-2-methylpiperidine (20). To a cooled (0−5 °C) suspension of lithium aluminum hydride (813 mg, 21.39 mmol) in anhydrous THF (25 mL) was added, under N_2 atmosphere, a solution of **12a** (1.45 g, 4.28 mmol) in THF (5 mL). The mixture was stirred at room temperature for 3 h, then warmed to 45 °C, and stirred at that temperature for 1 h. The mixture was chilled with an ice bath. To the mixture were added successively ether (15 mL), a 10% solution of sodium hydroxide (0.8 mL), and H_2O (0.1 mL). The resultant mixture was allowed to attain room temperature and stirred for 30 min before being filtered through Celite. After being concentrated at reduced pressure, the residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:1) to afford **20** (1.17 g, 84%) as a pale yellow oil. $[\alpha]^{25}_D$ −22.0 (*c* 0.9, $CHCl_3$); IR (film) 2860, 1511, 1244, 1115, 1103, 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−6.82 (m, 9H), 4.62 (d, J = 11.6 Hz, 1H), 4.47 (d, J = 11.6 Hz, 1H), 3.96 (d, J = 13.5 Hz, 1H), 3.78 (s, 3H), 3.22 (d, J = 13.5 Hz, 1H), 3.13 (ddd, J = 8.0, 4.2, 1.6 Hz, 1H), 2.69 (ddd, J = 11.2, 3.5, 3.5 Hz, 1H), 2.32 (dq, J = 6.2, 1.6 Hz, 1H), 2.11 (ddd, J = 16.5, 8.0, 3.7 Hz, 1H), 1.96 (ddd, J = 11.2, 11.2, 2.8 Hz, 1H), 1.65 (ddd, J = 16.5, 7.6, 4.2 Hz, 1H), 1.43 (m, 1H), 1.32 (d, J = 6.2 Hz, 3H), 1.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 138.8, 131.0, 130.2 (2C), 128.3 (2C), 127.8 (2C), 127.4, 113.5 (2C), 80.1, 71.0, 60.8, 57.1, 55.2, 51.1, 29.1, 22.8, 15.5; MS (ESI) *m*/*z* 326 ($M + H^+$, 100); HRESIMS calcd for $[C_{21}H_{27}NO_2 + H]^+$ 326.2114, found 326.2120.

(2*R*,3*S*)-1-(*tert*-Butyloxycarbonyl)-3-hydroxy-2-methylpiperidine (21). To a mixture of **20** (1.10 g, 3.38 mmol) and 20% $Pd(OH)_2/C$ (560 mg) were added ethanol (10 mL) and di-*tert*-butyl dicarbonate (1.60 mL, 6.97 mmol). The mixture was stirred at room temperature under an atmosphere of H_2 for 72 h. The mixture was filtered over Celite and concentrated under reduced pressure to afford a crude, which was resubjected to hydrogenolysis conditions (10% Pd/C, 300 mg, EtOH, rt, H_2, 1 atm, 10 h). The mixture was filtered through Celite again and concentrated under reduced pressure. Flash chromatographic purification on silica gel (eluent EtOAc/PE = 1:4) provided **21** (580 mg, 79%) as a colorless oil. $[\alpha]^{30}_D$ −25.9 (*c* 0.9, $CHCl_3$); IR (film) 3434, 2976, 2939, 2869, 1691, 1664, 1414, 1366, 1152 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.30 (m, 1H), 3.95 (m, 1H), 3.72 (m, 1H), 2.85 (ddd, J = 13.2, 13.2, 2.6 Hz, 1H), 1.95 (br s, 1H), 1.83 (m, 1H), 1.72 (m, 2H), 1.45 (s, 9H), 1.40 (m, 1H), 1.12 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 79.6, 68.7, 53.0, 38.3, 28.4 (3C), 25.5, 19.1, 14.5; MS (ESI) *m*/*z* 216 ($M + H^+$, 100); HRESIMS calcd for $[C_{11}H_{21}NO_3 + H]^+$ 216.1594, found 216.1592.

(2*R*,3*S*)-1-(*tert*-Butoxycarbonyl)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpiperidine (22). A mixture of **21** (580 mg, 2.70 mmol), imidazole (370 mg, 5.44 mmol), TBDMSCl (815 mg, 5.40 mmol), and a catalytic amount of DMAP in DMF (18 mL) was stirred at room temperature overnight. Water (60 mL) was added, and the aqueous phase was extracted with Et_2O (5 × 10 mL). The combine organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash chromatographic purification (eluent EtOAc/PE = 1:15) of the crude provided **22** (866 mg, 98%) as a colorless oil. $[\alpha]^{30}_D$ −11.2 (*c* 1.0, $CHCl_3$); IR (neat) 2930, 2885, 2857, 1693, 1418, 1365, 1254, 1182, 1086, 1057 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.20 (m, 1H), 3.98 (m, 1H), 3.62 (m, 1H), 2.78 (ddd, J = 13.4, 13.4, 2.6 Hz, 1H), 1.90 (dddd, J = 13.6, 13.6, 8.6, 4.2 Hz, 1H), 1.66 (dddd, J = 13.6, 13.6, 3.7, 2.2 Hz, 1H), 1.55 (m, 1H), 1.44 (s, 9H), 1.30 (m, 1H), 1.07 (d, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 78.8, 69.0, 53.0, 38.0, 28.4 (3C), 26.7, 25.7 (3C), 19.3, 18.0, 14.7, −5.0, −5.1; MS (ESI) *m*/*z* 330 ($M + H^+$, 100), 352 ($M + Na^+$, 15); HRESIMS calcd for $[C_{17}H_{35}NO_3Si + H]^+$ 330.2459, found 330.2463.

(2*R*,3*S*,6*R*)-1-(*tert*-Butoxycarbonyl)-5-[(*tert*-butyldimethylsilyl)oxy]-6-methylpiperidine-2-carboxyaldehyde

(23). To a cooled (−78 °C) solution of **22** (600 mg, 1.83 mmol) in dry ether (10 mL) were added TMEDA (0.41 mL, 2.74 mmol) and *s*-BuLi (1.3 M in heptane, 1.7 mL, 2.21 mmol). The mixture was slowly warmed to −30 °C, stirred at that temperature for 30 min, and then recooled to −78 °C again. To the resulting mixture was added dropwise DMF (0.28 mL, 3.61 mmol) in dry ether (1 mL). The resultant mixture was stirred for 10 min at −78 °C and then quenched with saturated aqueous NH_4Cl (2 mL). The organic layer was separated. The aqueous layer was extracted with Et_2O (5 × 5 mL), and the combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatographic purification (eluent EtOAc/PE = 1:15) provided **23** (465 mg, 72%; diastereoselectivity = 94:6) as a colorless oil. $[\alpha]^{30}_D$ −70.6 (*c* 1.1, $CHCl_3$); IR (neat) 2954, 2931, 2707, 1733, 1685, 1395, 1366, 1173 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.36 (s, 1H), 4.06 (m, 1H), 3.75 (m, 1H), 3.70 (m, 1H), 2.02 (m, 1H), 1.76 (m, 1H), 1.60 (m, 2H), 1.45 (s, 9H), 1.09 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 155.3, 80.9, 68.8, 58.3, 53.7, 28.3 (3C), 25.7 (3C), 23.9, 18.7, 18.0, 16.2, −5.0 (2C); MS (ESI)-*m*/*z* 358 (M + H^+, 100), 380 (M + Na^+, 20); HRESIMS calcd for $[C_{18}H_{35}NO_4Si + H]^+$ 358.2408, found 358.2405.

(2*R*,3*S*,6*S*)-1-(*tert*-Butoxycarbonyl)-5-[(*tert*-butyldimethylsilyl)oxy]-6-methyl piperidine-2-carboxyaldehyde (24). A mixture of **23** (330 mg, 0.92 mmol), silica gel (500 mg, 300−400 mesh), Et_3N (0.09 mL, 0.06 mmol), EtOAc (1 mL), and petroleum ether (9 mL) was stirred at room temperature and under N_2 atmosphere for 72 h. After filtration, the solvent was evaporated. The residue was chromatographed on silica gel (eluent EtOAc/PE = 1:15) to provide **24** (251 mg, 76%, diastereoselectivity = 89:11) as a colorless oil. $[\alpha]^{30}_D$ +95.6 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.60 (s, 1H), 4.65 (m, 1H), 4.21 (m, 1H), 3.60 (m, 1H), 2.02 (m, 2H), 1.52 (m, 1H), 1.47 (s, 9H), 1.42 (m, 1H), 0.99 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 155.3, 80.3, 68.22, 58.5, 53.3, 28.3 (3C), 25.7 (3C), 22.9, 18.0, 17.8, 15.6, −4.9, −5.1; MS (ESI) *m*/*z* 358 (M + H^+, 100), 380 (M + Na^+, 20); HRESIMS calcd for $[C_{18}H_{35}NO_4Si + H]^+$ 358.2408, found 358.2407.

(2*R*,3*S*,6*S*)-1-(*tert*-Butoxycarbonyl)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-6-undecan-1′-enylpiperidine (26). To a cooled (0 °C) solution of **25** (235 mg, 0.47 mmol) in dry THF (3 mL) was added dropwise *n*-BuLi (2.5 M, 0.19 mL, 0.48 mmol) under N_2 atmosphere. After being stirred at room temperature for 10 min, the mixture was cooled to −78 °C and stirred for 15 min. To the resultant mixture was added aldehyde **24** (110 mg, 0.31 mmol) in THF (2 mL). The solution was stirred for 1 h at −78 °C and warmed slowly to room temperature. The reaction was partitioned between water (5 mL) and CH_2Cl_2 (8 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatographic purification (eluent EtOAc/PE = 1:40) afforded **26** (120 mg, 75%) as a colorless oil. $[\alpha]^{25}_D$ −20.6 (*c* 0.5, $CHCl_3$); IR (neat) 2955, 2927, 2855, 1691, 1364, 1178, 1069 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.60 (dd, J = 10.9, 9.1 Hz, 1H), 5.34 (ddd, J = 10.9, 8.4, 7.2 Hz, 1H), 5.01 (ddd, J = 7.2, 6.1, 2.3 Hz, 1H), 4.17 (dq, J = 7.4, 7.2 Hz, 1H), 3.69 (m, 1H), 2.23 (dddd, J = 13.5, 13.5, 6.1, 3.7 Hz, 1H), 2.15 (m, 2H), 1.87 (dddd, J = 13.5, 13.5, 3.4, 2.3 Hz, 1H), 1.45 (s, 9H), 1.40−1.20 (m, 18H), 1.15 (d, J = 7.4 Hz, 3H), 0.90 (m, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 131.3, 131.2, 78.9, 69.0, 53.5, 46.9, 31.9, 29.8, 29.6 (2C), 29.4 (2C), 29.3, 28.5 (3C), 27.4, 25.7 (3C), 23.6, 22.7, 22.6, 19.6, 18.0, 14.1, −4.9, −5.0; MS (ESI) *m*/*z* 496 (M + H^+, 100); HRESIMS calcd for $[C_{29}H_{57}NO_3Si + Na]^+$ 518.4000, found 518.4002.

(2*R*,3*S*,6*S*)-1-(*tert*-Butoxycarbonyl)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-6-undecanylpiperidine (27). To a suspension of Pd/C (50 mg, 10% Pd) in ethanol was added **26** (75 mg, 0.15 mmol). The mixture was stirred at room temperature and under an atmosphere of H_2 for 24 h. The mixture was filtered through Celite. After being concentrated under reduced pressure, the residue was chromatographed on silica gel column (EtOAc/PE = 1:40) to yield **27** as a colorless oil (75 mg, 100%). $[\alpha]^{30}_D$ +10.7 (*c* 0.9, $CHCl_3$); IR (neat) 2927, 2855, 1690, 1364, 1178, 1063 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.10 (m, 2H), 3.66 (m, 1H), 2.09 (dddd, J = 13.5, 13.5, 6.2, 3.8 Hz), 1.79 (dddd, J = 13.5, 13.5, 3.4, 2.3 Hz, 1H), 1.48 (m, 2H), 1.43 (s, 9H), 1.25 (s, 22H), 1.10 (d, J = 7.3 Hz, 3H), 0.88 (m, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 78.7, 69.1, 53.2, 49.7, 35.4, 31.9, 29.7, 29.7 (5C), 29.3, 28.5 (3C), 27.3, 25.7 (3C), 22.7, 22.1, 20.5, 19.2, 18.0, 14.1, −4.9, −5.0; MS (ESI) *m*/*z* 498 (M + H^+, 100); HRESIMS calcd for $[C_{29}H_{59}NO_3Si + Na]^+$ 520.4156, found 520.4149.

(2*R*,3*S*,6*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-methyl-6-undecanylpiperidine (28). To a solution of **27** (62 mg, 0.12 mmol) in dry THF (2 mL) was added TBAF (1 M in THF, 0.24 mL, 0.24 mmol) at room temperature. The solution was allowed to stir overnight, and then an aqueous NH_4Cl solution (1 mL) and water (5 mL) were added successively. The mixture was extracted with CH_2Cl_2 (3 × 6 mL), and the combined organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed (EtOAc/PE = 1:4) to yield **28** (48 mg, 100%) as a colorless oil. $[\alpha]^{30}_D$ −4.6 (*c* 0.6, $CHCl_3$); IR (neat) 3440, 2925, 2854, 1689, 1667, 1407, 1366, 1177 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.20 (m, 1H), 4.08 (dq, J = 7.1, 6.3 Hz, 1H), 3.75 (m, 1H), 1.96 (m, 1H), 1.85 (m, 2H), 1.58 (m, 1H), 1.45 (s, 9H), 1.40 (m, 2H), 1.26 (m, 20H), 1.16 (d, J = 7.1 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 79.3, 68.6, 53.1, 50.1, 35.2, 31.9, 29.7, 29.6 (5C), 29.3, 28.5 (3C), 27.5, 22.7, 21.1, 20.2, 19.2, 14.1; MS (ESI) *m*/*z* 384 (M + H^+, 100), 406 (M + Na^+, 10); HRESIMS calcd for $[C_{23}H_{45}NO_3 + H]^+$ 384.3472, found 384.3471.

(2*R*,3*R*,6*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-methyl-6-undecanylpiperidine (30). Dimethyl sulfoxide (0.036 mL, 0.51 mmol) was added dropwise to a cooled (−78 °C) solution of oxalyl chloride (0.02 mL, 0.25 mmol) in CH_2Cl_2 (0.5 mL). After the mixture was stirred at −78 °C for 5 min, a solution of **28** (48 mg, 0.13 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise and the stirring was continued for 1 h. To the resultant mixture was added *i*-Pr_2NEt (0.087 mL, 0.50 mmol), and the mixture was allowed to warm slowly to −10 °C. The mixture was recooled to −78 °C, and a buffer solution of NaOAc−HOAc (0.5 mL) and water (5 mL) were added successively. After CH_2Cl_2 extraction (3 × 10 mL), the combined organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed (eluent EtOAc/PE = 1:4) to yield **29** (colorless oil, 30 mg, yield 63%) and the recovered starting material (30%). Compound **29** was used in the next step immediately.

To a cooled (−78 °C) solution of **29** (30 mg, 0.079 mmol) in anhydrous THF (1 mL) was added dropwise, under N_2 atmosphere, a solution of L-Selectride (1 M in THF, 0.16 mL, 0.16 mmol), and the mixture was stirred at −78 °C for 2 h. The reaction was quenched by successive addition of a saturated aqueous ammonium chloride solution (0.5 mL) and water (5 mL). After being extracted with CH_2Cl_2 (3 × 5 mL), the combined organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (eluent EtOAc/PE = 1:4) of the crude then yielded (2*R*,3*R*,6*S*)-**30** as a colorless oil (30 mg, 100%). $[\alpha]^{28}_D$ +6.1 (*c* 1.9, $CHCl_3$); IR (neat) 3434, 2925, 2854, 1690, 1665, 1406, 1366, 1175 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.41 (m, 1H), 3.95 (m, 1H), 3.75 (dq, J = 7.1, 2.0 Hz, 1H), 1.95 (br s, 1H), 1.75−1.56 (m, 4H), 1.49 (m, 2H), 1.46 (s, 9H), 1.26 (m, 20H), 1.14 (d, J = 7.1 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 79.4, 69.9, 50.4, 49.6, 35.0, 31.9, 29.6, 29.6 (5C), 29.3, 28.5 (3C), 27.6, 26.4, 22.9,

22.7, 14.1, 13.5; MS (ESI) *m/z* 406 (M + Na^+, 5), 384 (M + H^+, 100); HRESIMS calcd for $[C_{23}H_{45}NO_3 + H]^+$ 384.3472, found 384.3476.

(2*R*,3*R*,6*S*)-3-Hydroxy-2-methyl-6-undecanylpiperidine (Deoxocassine, 4). A 0.5 M solution of HCl in MeOH (1 mL) was added to **30** (30 mg, 0.079 mmol), and the resulting solution was stirred under N_2 atmosphere and at room temperature overnight. The solvent was removed under reduced pressure. To the resultant residue was added water (2 mL). The mixture was basified with 5% $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were washed with brine (1 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (eluent CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$ = 100:5:1) gave (2*R*,3*R*,6*S*)-deoxocassine **4** (21 mg, 96%) as a white solid. Mp 47−48 °C (lit.[21a] mp 47.5−48.5 °C). $[\alpha]^{25}_D$ −11.8 (*c* 0.9, $CHCl_3$) {lit.[21a] $[\alpha]^{18}_D$ −12.3 (*c* 0.19, $CHCl_3$); lit.[21b] $[\alpha]^{20}_D$ −12.4 (*c* 0.8, $CHCl_3$)}; IR (neat) 3390, 2924, 2853, 1562, 1466, 1404, 1014 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.63 (m, 1H), 3.40−2.96 (br s, 1H), 2.88 (dq, *J* = 6.4, 1.4 Hz, 1H), 2.65 (m, 1H), 1.95 (m, 1H, NH), 1.58−1.38 (m, 4H), 1.26 (s, 22H), 1.21 (d, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 67.5, 57.5, 56.1, 35.9, 31.9, 31.7, 29.7, 29.6 (5C), 29.6, 29.3, 25.7, 25.0, 22.7, 17.9, 14.1; MS (ESI) *m/z* 284 (M + H^+, 100); HRESIMS calcd for $[C_{18}H_{37}NO + H]^+$ 284.2948, found 284.2952.

(*R*)-1-Benzyl-3-benzyloxy-2,6-piperidinedione ((*R*)-7b). Following the procedure described for (*S*)-**7a**, this compound was prepared from (*R*)-**6b** in a yield of 90%. (*R*)-**7b**: waxy solid. $[\alpha]^{20}_D$ +51 (*c* 1.0, $CHCl_3$); IR (film) 2927, 1728, 1678, 1343, 1158, 1018; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29−7.15 (m, 10H), 4.88 (d, *J* = 13.5 Hz, 1H), 4.82 (d, *J* = 13.5 Hz, 1H), 4.73 (d, *J* = 11.5 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.00 (t, *J* = 5.2 Hz, 1H), 2.86 (ddd, *J* = 18.0, 7.5, 7.5 Hz, 1H), 2.53 (ddd, *J* = 18.0, 6.0, 6.0 Hz, 1H), 2.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 171.4, 137.1, 137.0, 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.0 (2C), 127.4 (2C), 73.8, 72.4, 42.9, 29.0, 24.0; MS (ESI) 310 (M + H^+, 80), 332 (M + Na^+, 100); HRESIMS calcd for $[C_{19}H_{19}NO_3 + H]^+$ 310.1438, found 310.1439.

(5*R*,6*S*)-5-Benzyloxy-1,6-dibenzyl-2-piperidinone (31). Following the general reductive alkylation procedure as described for **7a**, the reductive alkylation of (*R*)-**7b** led to **31** and its diastereomer in 96:4 diastereomeric ratio and in a combined yield of 54%. (5*R*,6*S*)-**31**: colorless oil. $[\alpha]^{15}_D$ −86.1 (*c* 1.1, $CHCl_3$); IR (film) 3023, 2941, 1642, 1495, 1453, 1073 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26−7.00 (m, 15H), 5.56 (d, *J* = 15.3 Hz, 1H), 4.12 (d, *J* = 12.3 Hz, 1H), 4.09 (d, *J* = 12.3 Hz, 1H), 3.86 (d, *J* = 15.3 Hz, 1H), 3.70 (ddd, *J* = 9.8, 4.6, 1.9 Hz, 1H), 3.51 (m, 1H), 3.12 (dd, *J* = 14.0, 4.6 Hz, 1H), 2.75 (ddd, *J* = 18.1, 11.6, 7.5 Hz, 1H), 2.61 (dd, *J* = 14.0, 9.8 Hz, 1H), 2.47 (ddd, *J* = 18.1, 5.5, 1.5 Hz, 1H), 2.12 (m, 1H), 2.02 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 137.8, 137.4, 137.2, 128.9 (2C), 128.8 (2C), 128.5 (2C), 128.2 (2C), 128.0 (2C), 127.4 (2C), 127.30, 127.2, 126.9, 71.3, 69.6, 60.0, 47.6, 38.8, 27.1, 21.5; MS (ESI) *m/z* 386 (M + H^+, 100), 408 (M + Na^+, 10); HRESIMS calcd for $[C_{26}H_{27}NO_2 + H]^+$ 386.2114, found 386.2107.

(3*R*,5*R*,6*S*)-5-Benzyloxy-1,3,6-tribenzyl-2-piperidinone (32) and (3*S*,5*R*,6*S*)-5-Benzyloxy-1,3,6-tribenzyl-2-piperidinone (33). To a cooled (−78 °C) solution of (5*R*,6*S*)-**31** (100 mg, 0.26 mmol) and HMPA (0.09 mL, 0.52 mmol) in anhydrous ether (2.5 mL) was added *s*-BuLi (1.3 M in heptane, 0.20 mL, 0.26 mmol) under nitrogen atmosphere, and the mixture was stirred for 30 min. To the resulting mixture was added dropwise BnBr (0.06 mL, 0.52 mmol), and the stirring was continued at the same temperature for 2 h and then at −35 °C for 3 h. Saturated aqueous ammonium chloride (1 mL) and water (5 mL) were added successively. The mixture was extracted with ether (3 × 8 mL), and the combined organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatograph (eluent EtOAc/PE = 1:3) of the crude yielded **32** and **33** (97 mg, diastereomeric ratio = 90:10, combined yield 79%). Major diastereomer (**32**): colorless oil. $[\alpha]^{15}_D$ −32.7 (*c* 0.5, $CHCl_3$); IR (film) 3027, 2928, 1637, 1453, 1073 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−6.90 (m, 20H), 5.50 (d, *J* = 14.8 Hz, 1H), 4.04 (d, *J* = 12.6 Hz, 1H), 4.01 (d, *J* = 12.6 Hz, 1H), 3.88 (d, *J* = 14.8 Hz, 1H), 3.68 (m, 1H), 3.54 (dd, *J* = 13.7, 3.9 Hz, 1H), 3.48 (m, 1H), 2.97 (dd, *J* = 13.7, 4.8 Hz, 1H), 2.83 (dd, *J* = 13.9, 11.2 Hz, 1H), 2.67 (dd, *J* = 13.9, 8.9 Hz, 1H), 2.56 (m, 1H), 2.02 (ddd, *J* = 14.2, 7.3, 4.6 Hz, 1H), 1.72 (ddd, *J* = 14.2, 5.5, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 140.4, 137.9, 137.2, 129.4, 129.0 (3C), 128.8 (3C), 128.6, 128.3, 128.2, 128.1 (3C), 127.5, 127.4 (3C), 127.3 (2C), 126.9, 126.1, 113.8, 73.1, 70.1, 60.6, 48.2, 38.8, 38.5, 26.7, 22.6; MS (ESI) *m/z* 476 (M + H^+, 100), 498 (M + Na^+, 30); HRESIMS calcd for $[C_{33}H_{33}NO_2 + H]^+$ 476.2584, found 476.2586.

(3*R*,5*R*,6*S*)-1,3,6-Tribenzyl-5-hydroxy-2-piperidinone (5a). To a mixture of **32** (92 mg, 0.19 mmol) and Pd/C (60 mg, 20% Pd) was added methanol (2 mL) and formic acid (0.2 mL), and the mixture was stirred for 10 h. The mixture was filtered through Celite and concentrated. The residue was purified by flash chromatography on silica gel (eluent EtOAc/PE = 1:3) to provide **5a** (56 mg, 75%) as white crystals. Mp 145−146 °C (EtOAc/PE). $[\alpha]^{15}_D$ +23.1 (*c* 1.6, $CHCl_3$) {lit.[6a] $[\alpha]^{15}_D$ +10.9 (*c* 2, $CHCl_3$)}; IR (film) 3386, 2924, 1607, 1493, 1452, 1080 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20−7.00 (m, 15H), 5.39 (d, *J* = 14.9 Hz, 1H), 3.74 (d, *J* = 14.9 Hz, 1H), 3.72 (m, 1H), 3.42 (dd, *J* = 13.7, 4.3 Hz, 1H), 3.38 (m, 1H), 2.90 (dd, *J* = 14.0, 5.4 Hz, 1H), 2.79 (dd, *J* = 13.7, 10.4 Hz, 1H), 2.65 (dd, *J* = 14.0, 8.2 Hz, 1H), 2.49 (m, 1H), 1.95 (ddd, *J* = 14.3, 7.5, 4.6 Hz, 1H), 1.55 (ddd, *J* = 14.3, 6.8, 6.8 Hz, 1H), 1.62−1.50 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 140.1, 137.2, 137.1, 129.5 (2C), 129.1 (2C), 128.8 (2C), 128.7 (2C), 128.4 (2C), 128.2 (2C), 127.5, 127.0, 126.2, 66.8, 64.1, 48.3, 39.4, 38.6, 38.4, 30.0; MS (ESI) *m/z* 386 (M + H^+, 90), 408 (M + Na^+, 100); HRESIMS calcd for $[C_{26}H_{27}NO_2 + H]^+$ 386.2114, found 386.2109.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **1**, **4**, **5a**, **7a**, **7b**, **12a**−**h**, **13**, **14**, **16**, **18**−**24**, **26**−**28**, and **30**−**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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