Article

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 (2S,3S)-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 2,6dialkyl-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

CHART 1. Some Bioactive Piperidines and 2-Piperidinones



have stimulated the development of 3-piperidinol synthon-based versatile synthetic approaches.⁷

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

 $^{^{\}dagger}\,\text{Dedicated}$ to Professor Li-Xin Dai on the occasion of his 80th birthday.

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SCHEME 1



receptor antagonists (2S,3S)-L-733,060 (1) and (2S,3S)-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, Ag₂O, Et₂O, rt) provided the desired protected (S)-glutarimide 7a {white crystals, mp 74.5–75.0 °C, $[\alpha]^{20}$ –53.6 (c 1.0, CHCl₃)} 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

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 TABLE 1. Results of Reductive Alkylation of 7a

 According to Procedure Shown in Scheme 2

			selectivities ^b	
entry	R	yield (%) ^a	C2/C6	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	<i>n</i> -C ₅ H ₁₁	12e (81)	97:3	97:3
6	n-C ₈ H ₁₇	12f (77)	92:8	96:4
7	Ph	12g (80)	92:8	94:6
8	4-MeOC ₆ H 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 deoxygenation¹¹ was considered to proceed via the intermediacy of *N*-acyliminium¹² **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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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 Et₃SiH/BF₃·OEt₂ 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 glutarimides¹³ 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 effect¹⁴ 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 highaffinity binding to the human NK₁ (hNK₁) receptor.^{2b}

Thus, as shown in Scheme 4, lithium aluminum hydride reduction of **12g** (yield 90%), followed by one-pot carbamative debenzylation $[H_2, 1 \text{ atm}, 20\% \text{ Pd}(\text{OH})_2/\text{C}, (Boc)_2\text{O}]$ led directly to *N*-tert-Boc-2-phenyl-3-piperi-





dinol **16**^{2a} {[α]²⁰_D -66.1 (*c* 0.9, CHCl₃)} in 83% yield. Swern oxidation¹⁵ [(COCl)₂, DMSO, CH₂Cl₂, -78 ~ -20 °C; *i*-Pr₂NEt] afforded known *tert*-Boc-protected (*R*)-2-phenyl-3-piperidinone **17**,¹⁶ which was reduced immediately with L-Selectride¹⁷ to provide *cis*-(2*R*,3*R*)-**18**² {colorless oil, [α]²⁰_D -51.1 (*c* 1.0, CHCl₃); lit.^{8a} [α]¹⁵_D +53.8 (*c* 1.0, CHCl₃) for (2*S*,3*S*)-**18**} as the only diastereomer. The overall yield from **16** to **18** was 74%.

Etherification (NaH, 3,5-(CF₃)₂C₆H₃CH₂Br, DMF, rt, yield 77%) of (-)-**18** gave (-)-**19**² {[α]²⁸_D -35.6 (*c* 1.0, CHCl₃); lit.^{8a} [α]²⁸_D +36.9 (*c* 1.0, CHCl₃) for the antipode}, which was then deprotected to afford (-)-L-733,061 (ent-1)^{2,18} {ent-1·HCl mp 213-215 °C. [α]²⁸_D -79.6 (*c* 1.0, MeOH); lit.^{2a} mp 215-216 °C. [α]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-(5S,6R)-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-Dmannosidase 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** [H₂, 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



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 methodology²³ 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-diastereomer²³ 24 (vide infra). Treatment of the diastereomeric mixture of **23** with SiO₂ 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 (H₂, 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 oxidation¹⁵ (yield 63%, recovered starting material 30%), followed by L-Selectride reduction¹⁷ provided **30** (yield 100%) as the only diastereomer. Finally, deprotection of 30 under acidic conditions (HCl, MeOH, rt, 15 h) afforded the desired (2R,3R,6S)-deoxocassine (4) {mp 47-48 °C; lit.^{21a} mp 47.5–48.5 °C. [α]²⁵_D –11.8 (*c* 0.9, CHCl₃); lit.^{21a} $[\alpha]^{18}_{D}$ –12.3 (c 0.19, CHCl₃); lit.^{21b} $[\alpha]^{20}_{D}$ –12.4 (c 0.8, $CHCl_3$ in 96% yield.





5c P=H 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 (H₂, l atm, 10% Pd/C, rt, 3 days) to yield, respectively, 5a and 5c in excellent yield. Comparison of ¹H and ¹³C 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.

33 P=Bn

 \langle

95%

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-2piperidinones and 3-piperidinols is under current investigation.

Experimental Section

79%

5a P=H

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 CDCl₃ (¹H at 500 MHz and ¹³C at 125 MHz), and chemical shifts are expressed in parts per million (δ) relative to internal Me₄Si. 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 N₂. Ether and THF were distilled over sodium benzophenone ketyl under N₂.

(S)-3-Hydroxy-1-(4-methoxybenzyl)-2,6-piperidinedione (6a). To a tetrahydrofuran solution (90 mL) of (S)-N-(4methoxybenzyl)-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 NH₄Cl at -78 °C. The residue was extracted with EtOAc (3 \times 30 mL). The EtOAc extracts were washed with brine (15 mL), dried over anhydrous Na₂SO₄, and concentrated to give compound 6a (yield 70-80%) as white crystals. Mp 98–99 °C (ÉtOAc); $[\alpha]_{D}^{20}$ –70.0 (*c* 1.2, CHCl₃); IR (film) 3465, 2960, 1730, 1677, 1514, 1338, 1305, 1249, 1177, 1112 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) & 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; $[\alpha]^{20}{}_{\rm D}$ –53.6 (c 1.0, CHCl₃); IR (film) 2931, 1680, 1513, 1378, 1503, 1248, 1161, 1015 cm $^{-1}$; ¹H NMR $(500 \text{ MHz}, \text{CDCl}_3) \delta 7.40-6.82 \text{ (m, 9H)}, 4.91 \text{ (d, } J = 14.5 \text{ Hz},$ 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, CDCl₃) 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 C₂₀H₂₁NO₄ 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 Et₂O (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 NH₄Cl. After extraction with CH₂Cl₂, the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, 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 CH₂Cl₂ were added dropwise Et₃SiH (10 molar

equiv) and BF₃·OEt₂ (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 NaHCO₃ was added, and the aqueous layer was separated and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent EtOAc/PE = 1:2) to yield **12**.

(5S,6R)-5-Benzyloxy-1-(4-methoxybenzyl)-6-methyl-2piperidinone (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%. (5S, 6R)-**12a** (major diastereomer): $R_f 0.35$ (EtOAc/PE = 1:1). Colorless oil. $[\alpha]^{20}_{D}$ +96.9 (*c* 1.3, CHCl₃); IR (film) 2990, 2832, 1637, 1470, 1454, 1246, 1176, 1102 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 [C₂₁H₂₅NO₃ + 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, $\lambda = 270$ nm, $t_{\rm R}$ 10.9 min for (5*S*,6*R*)-**12a**, 19.0 min for (5*S*,6*S*)-**12a**].

(5S,6R)-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,6R)-**12b** (major diastereomer): $R_f 0.35$ (EtOAc/PE = 1:1). Colorless oil. [α]²⁰_D +89.2 (*c* 0.9, CHCl₃); IR (film) 2935, 2879, 1644, 1512, 1463, 1245, 1176, 1091, 1031 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 [C₂₂H₂₇NO₃ + H]+ 354.2064, found 354.2069. Anal. Calcd for C₂₂H₂₇NO₃: C, 74.79; H, 7.65; N, 3.97. Found: C, 74.58; H, 7.96; N, 3.93.

(5S,6R)-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%. (5S,6R)-**12c** (major diastereomer): $R_f 0.40$ (EtOAc/PE = 1:1). Colorless oil. [α]²⁰_D +63.7 (*c* 1.0, CHCl₃); IR (film) 2954, 2933, 2871, 1643, 1512, 1464, 1246, 1175, 1030 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 [C₂₄H₃₁NO₃ + H]⁺ 382.2377, found 382.2373.

(5*S*,6*R*)-6-Benzyl-5-benzyloxy-1-(4-methoxybenzyl)-2piperidinone (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. [α]²⁰_D +79.5 (*c* 1.1, CHCl₃); IR (film) 3024, 2937, 1642, 1512, 1455, 1246, 1175, 1100, 1073, 1030 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 [C₂₇H₂₉NO₃ + H]⁺ 416.2220, found 416.2221. Anal. Calcd for C₂₇H₂₉NO₃: C, 78.07; H, 6.99; N, 3.37. Found: C, 78.36; H, 6.99; N, 3.37.

(5.S,6R)-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%. (5S, 6R)-**12e** (major diastereomer): $R_f 0.40$ (EtOAc/PE = 1:1). Colorless oil. [α]²⁰_D +57.9 (*c* 1.1, CHCl₃); IR (film) 2930, 2859, 1644, 1513, 1463, 1246, 1175, 1073 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 [C₂₅H₃₃NO₃ + 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.

(5S,6R)-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.6R)-**12f** (major diastereomer): $R_f 0.35$ (EtOAc/PE = 1:2). Colorless oil. [α]²⁰_D+55.7 (c 0.5, CHCl₃); IR (film) 2927, 2855, 1644, 1512, 1463, 1246, 1175, 1098, 1035 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); $^{13}\mathrm{C}$ 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.

(5S,6R)-5-Benzyloxy-1-(4-methoxybenzyl)-6-phenyl-2piperidinone (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,6R)-**12g** (major diastereomer): $R_f 0.40$ (EtOAc/PE = 1:2). Colorless oil. [α]²⁰_D +73.1 (*c*1.2, CHCl₃); IR (film) 3061, 3029, 3003, 1644, 1512, 1464, 1451, 1246, 1174 $\rm cm^{-1};$ $^1\rm H$ 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); ¹³C NMR (125 MHz, CDCl₃) 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 C26H27NO3: 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-methoxybenzyl)-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, CHCl₃); IR (film) 2934, 1642, 1612, 1512, 1463, 1248, 1175, 1033 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₇H₂₉NO₄: C, 75.17; H, 6.73; N, 3.25. Found: C, 74.82; H, 6.89; N, 2.92.

(5S,6R)-5-Hydroxy-6-methyl-2-piperidinone (13). To a solution of $12a\ (0.70\ g,\ 2.06\ mmol)$ in $CH_3CN\ (49\ mL)$ and H₂O (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 \times 20 mL). The combined organic layers were washed successively with saturated aqueous sodium bicarbonate (5 \times 5 mL) and brine (5 mL), then dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue and a catalytic amount of TsOH were resolved in CH₂Cl₂ (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 Na₂ŠO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (eluent EtOAc/PE/NH₃/H₂O/ 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 $CH_2Cl_2/EtOH/NH_3 \cdot H_2O = 100$: 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} [α]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; ¹H NMR (500 MHz, CDCl₃) 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, 1.0Hz, 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); ¹³C NMR (125 MHz, CD₃CN) & 172.0, 69.4, 54.6, 28.1, 27.0, 20.4; MS (ESI) m/z130 $(M + H^+, 100).$

(2R,3S)-3-Benzyloxy-1-(4-methoxybenzyl)-2-phenylpi**peridine (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 N2 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 H₂O (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 (CH₂Cl₂/CH₃COCH₃ = 150:1) to afford **14** (1.580 g, 90%) as a waxy solid. $[\alpha]^{25}_{D} + 26.5$ (c 1.1, CHCl₃); IR (neat) 2934, 2858, 2785, 1511, 1453, 1246, 1098 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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.

(2R,3.5)-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 ditert-butyl dicarbonate (2.13 mL, 9.28 mmol). The mixture was stirred at room temperature and under an atmosphere of H₂ 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 Et₂O to provide **16**^{2a} as white crystals. Mp 67–68 °C. $[\alpha]^{20}_{D}$ –66.1 (*c* 0.9, CHCl₃); IR (neat) 3446, 2931, 1693, 1668, 1417, 1366, 1169, 1128 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₆H₂₃NO₃: C, 69.31; H, 8.30; N, 5.05. Found: C, 69.66; H, 8.51; N, 4.95.

(2R,3R)-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 CH₂Cl₂ (6 mL). The mixture was stirred at -78 °C for 5 min, and a solution of 16 (320 mg, 1.16 mmol) in CH₂Cl₂ (4 mL) was added dropwise. After being stirred at the same temperature for 1 h, *i*-Pr₂NEt (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 CH₂Cl₂ extraction (3 imes 10 mL), the combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, 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, CDCl₃) 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); 13C NMR (125 MHz, CDCl₃) 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 N₂ 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 CH₂Cl₂ (3 × 10 mL), the combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, 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%). [α]²⁰_D -51.1 (*c* 1.0, CHCl₃) {lit.⁴ [α]¹⁵_D +53.8 (*c* 1.0, CHCl₃) for (2*S*,3*S*)-**18**³. The spectral data are identical with those of (2*S*,3*S*)-**18**⁴ HRESIMS calcd for [C₁₆H₂₃NO₃ + 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*)-19² 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. [α]²⁸_D -35.6 (*c* 1.0, CHCl₃) {lit.^{8a} [α]²⁸_D +36.9 (*c* 1.0, CHCl₃) 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 [C₂₅H₂₇NO₃F₆ + 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*)-1² was prepared from (2*R*,3*R*)-19 by a procedure analogue to that used for the preparation of (2*S*,3*S*)-1². Yield 88%. Colorless oil. [α]²⁸_D -79.6 (*c* 1.0, MeOH, hydrochloride) {lit.^{2a} [α]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 $[C_{20}H_{19}\mathrm{NOF_6}+H]^+$ 404.1444, found 404.1470.

(2R,3S)-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 N2 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. [α]²⁵_D -22.0 (c 0.9, CHCl₃); IR (film) 2860, 1511, 1244, 1115, 1103, 1036 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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 = 6.2Hz, 3H), 1.28 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) 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.

(2R,3S)-1-(tert-Butyloxycarbonyl)-3-hydroxy-2-meth**ylpiperidine (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 ditert-butyl dicarbonate (1.60 mL, 6.97 mmol). The mixture was stirred at room temperature under an atmosphere of H₂ 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, H₂, 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, CHCl₃); IR (film) 3434, 2976, 2939, 2869, 1691, 1664, 1414, 1366, 1152 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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.

(2R,3S)-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 \times 10 mL). The combine organic phases were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. Flash chromatographic purification (eluent EtOAc/ PE = 1:15) of the crude provided 22 (866 mg, 98%) as a colorless oil. [α]³⁰_D –11.2 (*c* 1.0, CHCl₃); IR (neat) 2930, 2885, 2857, 1693, 1418, 1365, 1254, 1182, 1086, 1057 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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 = 7.2Hz, 3H) 0.88 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H); 13C NMR (125 MHz, CDCl₃) & 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 [C₁₇H₃₅NO₃- $Si + H]^+$ 330.2459, found 330.2463.

(2R,3S,6R)-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 NH₄Cl (2 mL). The organic layer was separated. The aqueous layer was extracted with Et_2O (5 \times 5 mL), and the combined organic phases were washed with brine (5 mL), dried over anhydrous Na₂SO₄, 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, CDCl₃) & 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); ¹³C NMR (125 MHz, CDCl₃) & 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.

(2R,3S,6S)-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), Et₃N (0.09 mL, 0.06 mmol), EtOAc (1 mL), and petroleum ether (9 mL) was stirred at room temperature and under N₂ 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, CHCl₃); ¹H NMR (500 MHz, CDCl₃) 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); 13C NMR (125 MHz, CDCl₃) 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.

(2R,3S,6S)-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 N₂ 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 CH₂Cl₂ (8 mL). The aqueous layer was extracted with CH_2Cl_2 (3 \times 5 mL), and the combined organic phases were washed with brine (5 mL), dried over anhydrous Na₂SO₄, 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, CHCl₃); IR (neat) 2955, 2927, 2855, 1691, 1364, 1178, 1069 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 H₂ 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%). [α]³⁰_D +10.7 (*c* 0.9, CHCl₃); IR (neat) 2927, 2855, 1690, 1364, 1178, 1063 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 [C₂₉H₅₉NO₃Si + Na]⁺ 520.4156, found 520.4149.

(2R,3S,6S)-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 NH₄Cl solution (1 mL) and water (5 mL) were added successively. The mixture was extracted with CH_2Cl_2 (3 \times 6 mL), and the combined organic layers were washed with brine (3 mL), dried over anhydrous Na₂SO₄, 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, CHCl₃); IR (neat) 3440, 2925, 2854, 1689, 1667, 1407, 1366, 1177 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) & 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.

(2R,3R,6S)-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 CH₂Cl₂ (0.5 mL). After the mixture was stirred at -78 °C for 5 min, a solution of $\mathbf{28}$ (48 mg, 0.13 mmol) in CH₂Cl₂ (1.5 mL) was added dropwise and the stirring was continued for 1 h. To the resultant mixture was added *i*-Pr₂NEt (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 \times 10 mL), the combined organic layers were washed with brine (3 mL), dried over anhydrous Na₂SO₄, 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 N2 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 \times 5 mL), the combined organic layers were washed with brine (3 mL), dried over anhydrous Na₂SO₄, 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, CHCl₃); IR (neat) 3434, 2925, 2854, 1690, 1665, 1406, 1366, 1175 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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 = 7.0Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) 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.

(2R,3R,6S)-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 N₂ 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% NaHCO₃ and extracted with CH_2Cl_2 (3 \times 3 mL). The combined organic layers were washed with brine (1 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (eluent CH₂Cl₂/MeOH/ $NH_3 H_2O = 100.5.1$ gave (2R, 3R, 6S)-deoxocassine 4 (21 mg, 96%) as a white solid. Mp 47-48 °C (lit.^{21a} mp 47.5-48.5 °C). $[\alpha]^{25}_{D} - 11.8 (c \, 0.9, \text{CHCl}_3) \{ \text{lit.}^{21a} [\alpha]^{18}_{D} - 12.3 (c \, 0.19, \text{CHCl}_3); \}$ lit.^{21b} [α]²⁰_D –12.4 (*c* 0.8, CHCl₃)}; IR (neat) 3390, 2924, 2853, 1562, 1466, 1404, 1014 cm^-1; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 [C₁₈H₃₇NO + 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. $[\alpha]^{20}_{\rm D}$ +51 (*c* 1.0, CHCl₃); IR (film) 2927, 1728, 1678, 1343, 1158, 1018; ¹H NMR (500 MHz, CDCl₃) 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, Hz, 1H), 2.03 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) 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 [C₁₉H₁₉NO₃ + H]⁺ 310.1438, found 310.1439.

(5R,6S)-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, CHCl₃); IR (film) 3023, 2941, 1642, 1495, 1453, 1073 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 \times 8 mL), and the combined organic layers were washed with brine (3 mL), dried over anhydrous Na₂SO₄, 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, CHCl₃); IR (film) 3027, 2928, 1637, 1453, 1073 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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, 4.6Hz, 1H), 1.72 (ddd, J = 14.2, 5.5, 5.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) 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, CHCl₃) {lit.^{6a} [α]¹⁵_D +10.9 (c 2, CHCl₃)}; 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, 4.6Hz, 1H), 1.55 (ddd, J = 14.3, 6.8, 6.8 Hz, 1H), 1.62–1.50 (br s, 1H); $^{13}\mathrm{C}$ 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 ¹³C 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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