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Chemo- and diastereoselective control for a flexible approach to (5*S*,6*S*)-6-alkyl-5-benzyloxy-2-piperidinones

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ABSTRACT

Chemo- and diastereoselective transformation of the *N*,*O*-acetals and their chain tautomers (**4**/**5**), readily derived from protected 3-hydroxyglutarimide **1a**, was studied. It was uncovered that while the reaction with a combination of boron trifluoride etherate/zinc borohydride led to cyclic products (5*S*,6*S*/*R*)-6-alkyl-5-benzyloxy-2-piperidinones **3**/**2**, and **6** in modest chemo- and diastereoselectivities, the reaction of **4**/**5** with zinc borohydride led exclusively to the formation of the ring-opening products **6** in excellent *anti*-diastereoselectivities. On the basis of the latter reaction, a flexible approach to (5*S*,6*S*)-6-alkyl-5-benzyloxy-2-piperidinones **3** was disclosed.

1. Introduction

2,6-Disubstituted piperidin-3-ol is a framework shared by many bioactive alkaloids.[1] As can be seen from Figure 1, 6-substituted 2,3-*cis*-2-methylpiperidin-3-ols constitute a subclass of piperidine alkaloids. Both the stereochemical variation at C-2, C-3, and C-6 positions, and the interesting biological activities exhibited by these alkaloids[1,2] make them attractive synthetic targets.[1,3] A number of methods have been developed for the synthesis of enantio-enriched 2,6-disubstituted piperidin-3-ol alkaloids that share the same '2,3-*cis*' stereochemistry.[4]

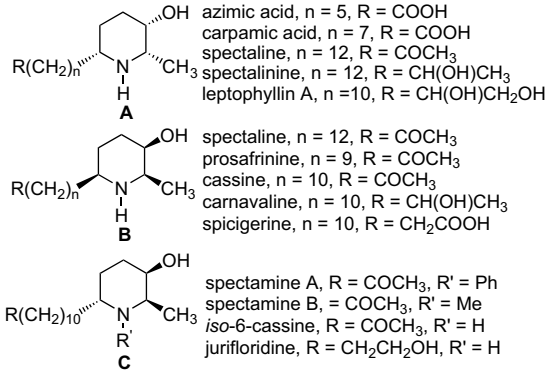
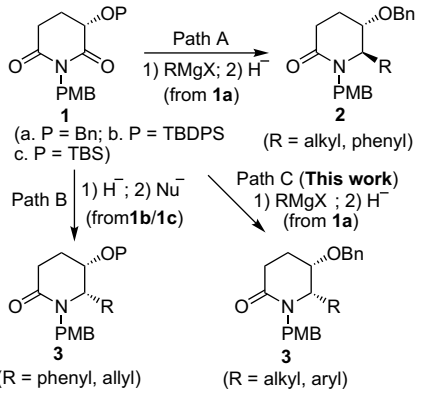


Figure 1. Some naturally occurring 2,6-disubstituted piperidin-3-ol containing alkaloids.

Previously, we have shown that the protected (*S*)-3-hydroxyglutarimides[5] **1** may serve as versatile building blocks for the asymmetric synthesis of a variety of 2,6-disubstituted 3-hydroxypiperidines.[6] A flexible regio- and diastereoselective reductive alkylation[7] method was developed for the conversion of **1a** to *trans*-6-alkyl-5-benzyloxy-2-piperidinone derivatives **2** (Scheme 1, path A).[6c] Although regioselective reduction–stereoselective α-amidoalkylation of **1b** and **1c** allows stereoselective access to the corresponding *cis*-diastereomer[6a,b] (Scheme 1, path B) via either intramolecular aryl/vinyl group delivery,[8] or α-amidoallylation,[6b,9]



Scheme 1. Three approaches for the regio- and diastereoselective conversion of **1** to **2** or **3**.

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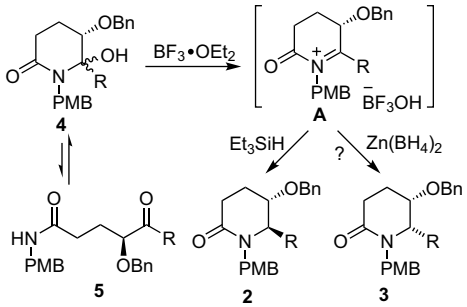
the alkyl groups were limited to aryl, vinyl, and allyl. We report herein a flexible approach to the *cis*-6-alkyl-5-benzyloxy-2-piperidinone derivatives **3** (Scheme 1, path C) using zinc borohydride as a chemo- and diastereoselective control element.

2. Results and discussion

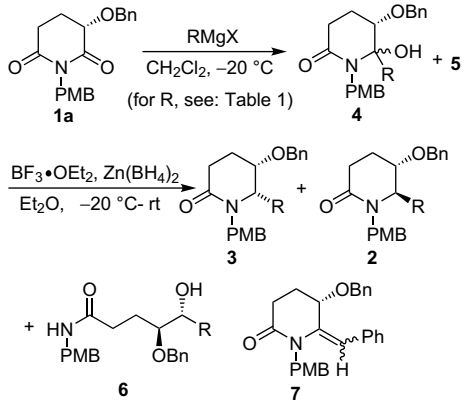
In our previous approach to *trans*-6-alkyl-5-benzyloxy-2-piperidinone derivatives **2**, the *trans*-stereoselectivity was assumed to be resulted from the reduction of the *N*-acyliminium ion intermediate[10] **A** with triethylsilane,[11] a non-chelating hydride donor (Scheme 2). Although the origin of the *trans*-diastereoselectivity in the reduction of the *N*-acyliminium ion intermediates **A** is still unclear, it was naively envisioned that a chelating hydride donor would allow an access to the *cis*-isomer **3**. In view of the frequent use of zinc borohydride[12] as a powerful chelating reducing agent in diastereoselective reductions,[13] it was selected for our investigation.



Scheme 2.

The requisite 6-alkyl-5-benzyloxy-6-hydroxy-2-piperidinones **4**, together with their chain tautomers **5**, were prepared by Grignard reagents addition to (*S*)-3-benzyloxyglutarimide **1a** under our recently improved conditions.[6f] Treatment of both tautomeric and diastereomeric mixture of **4a** and **5a** with 1.5 mol equiv of boron trifluoride etherate, and 3 mol equiv of $Zn(BH_4)_2$ (0.25 M in Et_2O) yielded **3a** and **2a** in a ratio of 88:12 (combined yield: 59%), along with the ring-opening reduced product **6a** (yield: 11%) (Scheme 3). Although the desired 2-piperidinone was formed as a diastereomeric mixture (**3a**/**2a**), to our surprise, only the *anti*-diastereomer **6a** was obtained (Table 1, entry 1). The stereochemistry of the major diastereomer **3a** was assigned to *cis* according to the observed vicinal coupling constants ($J_{5,6}$=4.5 Hz for **3a** and $J_{5,6}$=1.0 Hz for the *trans*-diastereomer **2a**).[6c]

The $BF_3{\cdot}OEt_2$-mediated zinc borohydride reductive deoxygenation reaction was then extended to other tautomeric



Scheme 3.

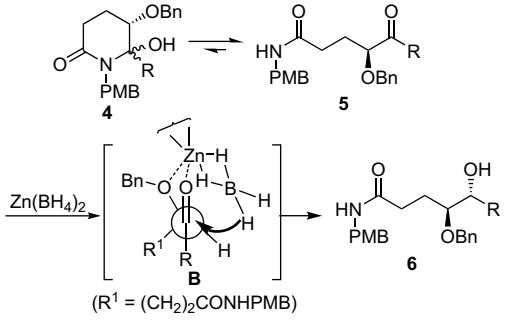
Table 1
Reductive deoxygenation of **4**/**5** according to the procedure shown in Scheme 3

Entry	**4**/**5**		Yield[a] (%)	**3**/**2**	**6**	
				Diastereo-selectivity	Yield[a] (%)	Diastereo-selectivity
1	**a**	R=CH_3	59	88:12[b]	11 (**6a**)	100:0
2	**b**	R=C_2H_5	55	87:13[b]	11 (**6b**)	92:8
3	**c**	R=*n*-C_4H_9	41	85:15[c]	42 (**6c**)	95:5[b]
4	**d**	R=*n*-C_8H_{17}	51	100:0	22 (**6d**)	100:0
5	**e**	R=*n*-$C_{12}H_{25}$	39	100:0	27 (**6e**)	100:0
6	**f**	R=$BnCH_2$	38	100:0	42 (**6f**)	100:0
7	**g**	R=Ph	54	60:40[b]	35 (**6g**)	55:45[b]
8	**h**	R=Bn		Elimination product (**7**), yield: 65%		

[a] Isolated yield.
[b] Ratio based on chromatography separation.
[c] Ratio determined by ^1H NMR analysis.

mixtures **4b–h**/**5b–h**. As can be seen from Table 1, while the yields of 2-piperidinones **3b–h**/**2b–h** are modest or mediocre, the diastereoselectivities are good to excellent except in the case of phenyl derivatives **4g**/**5g**, where the ratio of **3g**/**2g** is only 60:40. Some *anti*-diastereomers were also formed as minor products for the amido diol derivatives **6b** and **6c**. In the case of phenyl derivative, the *syn*/*anti* ratio is only 55:45. When R is a benzyl group (**4h**/**5h**), only the eliminative product **7** was obtained.

These results are different with those obtained from the reductive dehydroxylation with $BF_3{\cdot}OEt_2/Et_3SiH$, where no ring-opening products **6** were observed.[6c] The difference can be understood by taking into account of the different chelation properties of the two systems. In the case of reductive dehydroxylation with $BF_3{\cdot}OEt_2/Et_3SiH$, as can be seen from Scheme 2, Lewis acid $BF_3{\cdot}OEt_2$, being a irreversible hydroxyl group abstracting agent, is capable of pushing the tautomeric equilibrium toward the *N*-acyliminium ion intermediate **A**; while the chelating property of $Zn(BH_4)_2$ toward the α-keto ether in tautomers **5** as well as the higher reactivity of $Zn(BH_4)_2$ vis-à-vis the activated ketone carbonyl group (via chelation) can lead to the formation of the ring-opening product **6**. It was envisioned that an inhibition of the formation of the tautomer **5** would decrease the amount of **6** (Scheme 4). Because it was observed that chromatographic separation on silica gel of the Grignard adducts increased the amount of the tautomer **5** in the tautomeric mixture, a modified procedure involving a direct use of the crude adducts was tested. Indeed, when a crude adducts **4a**/**5a** was directly treated with $Zn(BH_4)_2/BF_3{\cdot}OEt_2$ in CH_2Cl_2 (−78 °C to 0 °C), the desired (5*S*,6*S*)-**3a** was obtained in 74% yield. In spite of this, a further investigation on this variation was not pursuit because of the observed modest diastereoselectivity (4:1).

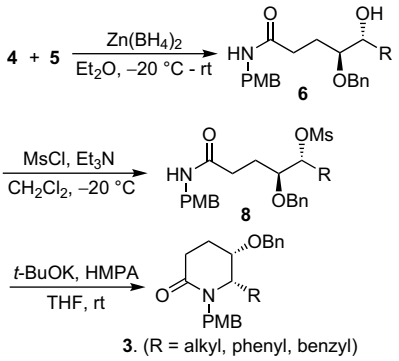


Scheme 4. A plausible $Zn(BH_4)_2$-controlled pathway for the chemo- and *anti*-diastereoselective formation of **6**.

The formation of the ring-opening products **6** in high diastereoselectivity prompted us to develop an alternative approach to piperidinones **3** based on **6** (Table 1). To this end, a switch of cyclic

tautomer **4** to the acyclic tautomer **5** was necessary. In view of the interconvertibility between the two tautomers **4** and **5**, and the observed movement of the equilibrium toward **4** by the $BF_3{\cdot}OEt_2$-promoted exclusive formation of the *N*-acyliminium ion intermediates **A** (Scheme 2), it was envisioned that in the absence of $BF_3{\cdot}OEt_2$, formation of a chelation intermediate between $Zn(BH_4)_2$ and the α-benzyloxy ketone tautomer **5** would enhance both the formation and reduction of **5**, and thus push the equilibrium toward **5** (Scheme 4). In addition, the *anti*-diastereoselectivity[13,14] of the reduction could be predicted by the Cram's five-membered cyclic model,[15]as shown in the transition state **B**.

This turned out to be true. Indeed, when a mixture of **4a** and **5a** was treated with $Zn(BH_4)_2$ in diethyl ether (−20 °C to rt), the desired product **6a** was formed in 82% yield (based on the recovered starting material, 20%) with an *anti*/*syn* diastereoselectivity of 94:6 (Scheme 5, Table 2, entry 1). Except the case of phenyl derivative **6g**, reduction of other homologues gave **6b**–**6j** in yields ranging from 77% to 95%, with 86:14 to 98:2 *anti*/*syn* selectivities (Table 2). The stereochemistry of the major diastereomer **6a** was confirmed by converting **6a** to (5*S*,6*S*)-6-alkyl-5-benzyloxy-2-piperidinone **3a** by mesylation (MsCl, Et_3N, CH_2Cl_2, −20 °C, 1 h) and *t*-BuOK-promoted cyclization (HMPA, THF, rt, 24 h). Following this procedure, 2-piperidinones **3a**–**3j** were prepared and the results are displayed in Table 2.



Scheme 5.

Both the exclusive formation of the ring-opening products **6** from the tautomeric mixtures **4**/**5**, and the high *anti*-diastereoselectivities can be attributed to the formation of the presumed chelating transition state **B** (Scheme 4), which not only switches the equilibrium toward **5**, but also allows the reduction to undergo with a Cram chelation-controlled (*anti*-Felkin-Ahn) manner, producing thus the *anti* (*erythro*) alcohols **6** in good to excellent yields

Table 2
Results of the ring-opening reduction according to the procedure shown in Scheme 5

Entry	Product **6**	Yield[a] (%)	Diastereoselectivity	**3** (% yield)[f]
1	CH_3 (**6a**)	82[b]	94:6[c]	75
2	C_2H_5 (**6b**)	89	94:6[e]	76
3	*n*-C_4H_9 (**6c**)	82	91:9[c]	70
4	*n*-C_8H_{17} (**6d**)	95	98:2[e]	83
5	*n*-$C_{12}H_{25}$ (**6e**)	77	90:10[e]	83
6	$PhCH_2CH_2$ (**6f**)	87	89:11[e]	87
7	Ph (**6g**)	66	65:35[c]	67
8	Bn (**6h**)	85	95:5[c]	81
9	*n*-$C_{16}H_{33}$ (**6i**)	78	86:14[d]	66
10	*i*-Bu (**6j**)	81	97:3[e]	72

[a] Isolated yield.
[b] Based on the recovered starting material: 20%.
[c] Ratio based on chromatography separation.
[d] Ratio based on ^1H NMR analysis.
[e] Ratio based on HPLC analysis.
[f] Isolated yield of **3** starting from **6**.

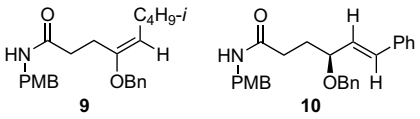


Figure 2.

(Scheme 5). It is to be mentioned that using other reducing systems, *syn*-selective reduction of a related system has been reported.[14] Unexpectedly, the eliminative products **9** and **10** were obtained from the *iso*-butyl and benzyl substituted **6j** and **6h** (Table 2, entries 8, 10, Fig. 2).

3. Conclusion

In conclusion, we were able to demonstrate that through proper selection of Lewis acid-reducing agent combination, both the ring-chain tautomerism of the cyclic *N*,*O*-acetals, derived from the protected 3-hydroxyglutarimide **1a**, and the diastereoselective reduction can be controlled. Taking advantage of the dual role of zinc borohydride both as a bidendate chelating Lewis acid and as a selective reducing agent, a flexible yet stepwise approach to (5*S*,6*S*)-6-alkyl-5-benzyloxy-2-piperidinones **3** was disclosed. The present method is complementary with the boron trifluoride etherate-mediated diastereoselective reduction with triethylsilane, previously developed from these laboratories, that affords (5*S*,6*R*)-6-alkyl-5-benzyloxy-2-piperidinones **2** in excellent chemo- and diastereoselectivities. Application of this method to the asymmetric synthesis of 2,3-*cis*-2,6-disubstituted piperidin-3-ol alkaloids will be reported elsewhere in due course.

4. Experimental section

4.1. General methods

Melting points were determined on a Yanaco MP-500 micro melting point apparatus and were uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker 400 spectrometer or a Varian Unity 500 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded on a Bruker Dalton ESquire 3000 plus liquid chromatography–mass spectrum (direct injection). HRMS spectra were recorded on a Bruker APEX II FT mass spectrometer, or a Shimadzu LCMS-IT-TOF apparatus. Optical rotations were measured with a Perkin–Elmer 341 automatic polarimeter. Silica gel (300–400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with an ethyl acetate/petroleum ether (PE) (60–90 °C) mixture. Ether and THF were distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2.

4.2. General procedure for the reductive deoxygenation of tautomeric mixture 4/5

To a cooled (−20 °C) solution of tautomeric mixture **4**/**5**[6c,f] (1.0 mol equiv) in THF (0.1 M) was added dropwise a solution of boron trifluoride etherate (1.5 mol equiv) under argon atmosphere and the mixture was stirred at −20 to −10 °C for 30 min. To the resultant mixture was added dropwise a solution of $Zn(BH_4)_2$ (0.25 M, 3 mol equiv) in Et_2O. The mixture was allowed to slowly warm to 0 °C and was stirred at 0 °C overnight. The reaction was quenched with a saturated aqueous 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=1:1) to yield 2-piperidinones **3**/**2** and the ring-opening product **6**.

*4.2.1. (5S,6S)-5-Benzyloxy-1-(4-methoxybenzyl)-6-methyl-2-piperidinone (**3a**)*

Following the general procedure, the reductive deoxygenation of the tautomeric mixture **4a**/**5a** gave a diastereomeric mixture of **3a** and the known **2a**[6c] in 88:12 ratio (combined yield: 59%), along with **6a** as a single diastereomer in 11% yield.

*4.2.1.1. Compound (5S,6S)-**3a**.* R_f=0.35 (EtOAc/PE=1:1), colorless oil. $[\alpha]_D^{25}$ −51.9 (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 1638, 1512, 1450, 1246 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (d, *J*=6.5 Hz, 3H, CH_3), 1.88–2.06 (m, 2H, H-4), 2.47 (ddd, *J*=18.2, 9.4, 8.2 Hz, 1H, H-3), 2.62 (ddd, *J*=18.2, 7.4, 3.8 Hz, 1H, H-3), 3.54 (m, 1H, H-6), 3.60 (ddd, *J*=10.5, 4.6, 4.6 Hz, 1H, H-5), 3.79 (s, 3H, OCH_3), 3.86 (d, *J*=14.8 Hz, 1H, NCH_2), 4.43 (d, *J*=11.8 Hz, 1H, OCH_2), 4.47 (d, *J*=11.8 Hz, 1H, OCH_2), 5.24 (d, *J*=14.8 Hz, 1H, NCH_2), 6.87 (d, *J*=8.7 Hz, 2H, Ar–H), 7.15 (d, *J*=8.7 Hz, 2H, Ar–H), 7.22–7.26 (m, 2H, Ar–H), 7.27–7.35 (m, 3H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 22.0, 29.2, 47.2 (NCH_2), 52.4 (OCH_3), 55.2 (C-6), 70.7 (OCH_2), 74.1 (C-5), 113.9 (2C), 127.5 (2C), 127.7, 128.4 (2C), 129.2 (2C), 129.4, 137.8, 158.9, 169.1 (C=O). MS (ESI): 340 (MH^+, 35), 362 (MNa^+, 100). Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.30; H, 7.29; N, 3.95.

*4.2.1.2. (4S,5R)-4-Benzyloxy-5-hydroxy-N-(4-methoxybenzyl)hexanoyl amide (**6a**) (4S,5R)-**6a** (sole diastereomer).* R_f=0.35 (EtOAc/PE=2:1), white solid, mp: 52–54 °C (EtOAc/PE=1:1). $[\alpha]_D^{25}$ −4.3 (*c* 0.9, $CHCl_3$). IR (film) ν_{max}: 3407, 3305, 1649, 1514, 1248 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (t, *J*=6.3 Hz, 3H, CH_3), 1.84 (ddd, *J*=14.5, 7.4, 6.8 Hz, 1H, H-3), 2.07 (ddd, *J*=14.5, 7.4, 6.3 Hz, 1H, H-3), 2.26 (t, *J*=7.4 Hz, 2H, H-2), 2.10–2.50 (br s, 1H, OH), 3.31 (dt, *J*=4.5, 6.3 Hz, 1H, H-5), 3.74 (ddd, *J*=6.8, 6.3, 4.5 Hz, 1H, H-4), 3.78 (s, 3H, OCH_3), 4.30 (dd, *J*=14.5, 5.6 Hz, 1H, NCH_2), 4.35 (dd, *J*=14.5, 5.6 Hz, 1H, NCH_2), 4.55 (d, *J*=11.5 Hz, 1H, OCH_2), 4.62 (d, *J*=11.5 Hz, 1H, OCH_2), 5.57 (br s, 1H, NH), 6.83 (d, *J*=8.6 Hz, 2H, Ar–H), 7.18 (d, *J*=8.6 Hz, 2H, Ar–H), 7.25–7.33 (m, 5H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 25.6, 31.6, 43.1 (NCH_2), 55.3 (OCH_3), 68.8 (OCH_2), 72.6 (C-4), 82.7 (C-5), 114.1 (2C), 127.9, 127.9 (2C), 128.5 (2C), 129.2 (2C), 130.3, 138.2, 159.0, 172.3 (C=O). MS (ESI): 358 (MH^+, 100). HRESIMS calcd for $[C_{12}H_{23}NO_3+H]^+$: 358.2018; found: 358.2034.

*4.2.2. (5S,6S)-5-Benzyloxy-6-ethyl-1-(4-methoxybenzyl)-2-piperidinone (**3b**)*

Following the general procedure, the reductive deoxygenation of the tautomeric mixture **4b**/**5b** gave a diastereomeric mixture of **3b** and the known **2b**[6c] in 87:13 ratio (combined yield: 55%), and **6b** as a diastereomeric mixture in 92:8 ratio (combined yield: 11%).

*4.2.2.1. Compound (5S,6S)-**3b**.* R_f=0.35 (EtOAc/PE=1:1), colorless oil. $[\alpha]_D^{25}$ −50.9 (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 1642, 1512, 1450, 1246 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, *J*=7.5 Hz, 3H, CH_3), 1.64 (ddd, *J*=14.0, 7.5, 6.6 Hz, 1H), 1.82–2.05 (m, 4H), 2.48 (ddd, *J*=18.2, 8.3, 7.4 Hz, 1H, H-3), 2.63 (ddd, *J*=18.2, 8.4, 5.1 Hz, 1H, H-3), 3.32 (ddd, *J*=11.0, 5.8, 4.7 Hz, 1H, H-6), 3.58 (ddd, *J*=9.6, 5.2, 4.7 Hz, 1H, H-5), 3.79 (d, *J*=14.7 Hz, 1H, NCH_2), 3.81 (s, 3H, OCH_3), 4.38 (d, *J*=11.9 Hz, 1H, OCH_2), 4.42 (d, *J*=11.9 Hz, 1H, OCH_2), 5.40 (d, *J*=14.7 Hz, 1H, NCH_2), 6.85 (d, *J*=8.7 Hz, 2H, Ar–H), 7.14 (d, *J*=8.7 Hz, 2H, Ar–H), 7.17–7.20 (m, 2H, Ar–H), 7.25–7.33 (m, 3H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9 (CH_3), 22.2, 22.5, 28.6, 48.3 (NCH_2), 55.2 (OCH_3), 58.2 (C-6), 70.6 (OCH_2), 73.9 (C-5), 113.9 (2C), 127.1 (2C), 127.5, 128.2 (2C), 129.0 (2C), 129.2, 138.0, 158.7, 169.6 (C=O). MS (ESI): 354 (MH^+, 80), 376 (MNa^+, 100). HRESIMS calcd for $[C_{22}H_{27}NO_3+H]^+$: 354.2069; found: 354.2069.

*4.2.2.2. (4S,5R)-4-Benzyloxy-5-hydroxy-N-(4-methoxybenzyl)heptanoyl amide (**6b**) (4S,5R)-**6b** (major diastereomer).* R_f=0.35 (EtOAc/PE=2:1), white solid, mp: 66–67 °C (EtOAc/PE=1:1). $[\alpha]_D^{25}$ −5.1 (*c* 1.2, $CHCl_3$). IR (film) ν_{max}: 3409, 3304, 1650, 1513, 1248 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, *J*=7.5 Hz, 3H, CH_3), 1.39–1.61 (m, 2H), 1.83–1.99 (m, 2H), 2.22 (ddd, *J*=15.0, 7.8, 7.2 Hz, 1H, H-2), 2.38 (ddd, *J*=15.0, 6.8, 6.8 Hz, 1H, H-2), 2.73 (s, 1H, OH), 3.36 (ddd, *J*=6.9, 4.7, 4.3 Hz, 1H), 3.67 (ddd, *J*=8.5, 4.3, 4.3 Hz, 1H), 3.78 (s, 3H, OCH_3), 4.26 (dd, *J*=14.4, 5.7 Hz, 1H, NCH_2), 4.32 (dd, *J*=14.4, 5.7 Hz, 1H, NCH_2), 4.45 (d, *J*=11.5 Hz, 1H, OCH_2), 4.56 (d, *J*=11.5 Hz, 1H, OCH_2), 5.80 (br s, 1H, NH), 6.83 (d, *J*=8.7 Hz, 2H, Ar–H), 7.15 (d, *J*=8.7 Hz, 2H, Ar–H), 7.22–7.34 (m, 5H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4, 23.6, 25.4, 31.5, 43.0 (NCH_2), 55.3 (OCH_3), 71.5 (OCH_2), 72.4 (C-4), 80.9 (C-5), 114.0 (2C), 127.8, 127.9 (2C), 128.4 (2C), 129.2 (2C), 130.4, 138.2, 159.0, 173.0 (C=O). MS (ESI): 372 (MH^+, 30), 394 (MNa^+, 100). Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.03; H, 7.55; N, 3.71.

*4.2.3. (5S,6S)-5-Benzyloxy-6-(n-butyl)-1-(4-methoxybenzyl)-2-piperidinone (**3c**)*

Following the general procedure, the reductive deoxygenation of the tautomeric mixture **4c**/**5c** gave a diastereomeric mixture of **3c** and the known **2c**[6c] in 85:15 ratio (combined yield: 41%), and **6c** as a diastereomeric mixture in 95:5 ratio (combined yield: 42%).

*4.2.3.1. Compound (5S,6S)-**3c**.* R_f=0.35 (EtOAc/PE=1:1), colorless oil. $[\alpha]_D^{25}$ −40.7 (*c* 0.6, $CHCl_3$). IR (film) ν_{max}: 1642, 1512, 1456, 1247 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, *J*=6.9 Hz, 3H, CH_3), 1.23–1.43 (m, 4H, 2×CH_2), 1.50–1.60 (m, 1H), 1.78–1.86 (m, 1H), 1.90–2.03 (m, 2H, H-4), 2.47 (ddd, *J*=18.3, 8.1, 8.1 Hz, 1H, H-3), 2.62 (ddd, *J*=18.3, 8.5, 4.8 Hz, 1H, H-3), 3.38 (ddd, *J*=11.0, 5.7, 4.9 Hz, 1H, H-6), 3.64 (ddd, *J*=10.1, 4.9, 4.9 Hz, 1H, H-5), 3.74 (d, *J*=14.7 Hz, 1H, NCH_2), 3.81 (s, 3H, OCH_3), 4.37 (d, *J*=12.7 Hz, 1H, OCH_2), 4.41 (d, *J*=12.7 Hz, 1H, OCH_2), 5.42 (d, *J*=14.7 Hz, 1H, NCH_2), 6.85 (d, *J*=8.5 Hz, 2H, Ar–H), 7.12 (d, *J*=8.5 Hz, 2H, Ar–H), 7.15–7.40 (m, 5H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 23.0, 28.7, 29.1, 29.6, 48.4 (NCH_2), 55.2 (OCH_3), 56.7 (C-6), 70.7 (C-5), 74.2 (OCH_2), 114.0 (2C), 127.5 (2C), 127.7, 128.4 (2C), 129.4 (2C), 130.0, 137.8, 158.9, 169.6 (C=O). MS (ESI): 382 (MH^+, 100). HRESIMS calcd for $[C_{24}H_{31}NO_3+H]^+$: 382.2382; found: 382.2395.

*4.2.3.2. (4S,5R)-4-Benzyloxy-5-hydroxy-N-(4-methoxybenzyl)nonanoyl amide (**6c**) (4S,5R)-**6c** (major diastereomer).* R_f=0.35 (EtOAc/PE=2:1), white solid, mp: 64–65 °C (EtOAc/PE=2:1). $[\alpha]_D^{25}$ −5.7 (*c* 0.9, $CHCl_3$). IR (film) ν_{max}: 3304, 1650, 1513, 1245 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.91 (t, *J*=6.9 Hz, 3H, CH_3), 1.25–1.38 (m, 3H), 1.40–1.55 (m, 3H), 1.92–2.00 (m, 2H), 2.15 (ddd, *J*=14.8, 7.4, 7.4 Hz, 1H, H-2), 2.30 (ddd, *J*=14.8, 6.6, 6.6 Hz, 1H, H-2), 2.52 (s, 1H, OH), 3.39 (dt, *J*=4.2, 7.3 Hz, 1H, H-5), 3.67–3.75 (m, 1H, H-4), 3.75 (s, 3H, OCH_3), 4.20 (dd, *J*=14.4, 5.6 Hz, 1H, NCH_2), 4.27 (dd, *J*=14.4, 5.6 Hz, 1H, NCH_2), 4.38 (d, *J*=11.5 Hz, 1H, OCH_2), 4.51 (d, *J*=11.5 Hz, 1H, OCH_2), 5.65 (br s, 1H, NH), 6.82 (d, *J*=8.7 Hz, 2H, Ar–H), 7.18 (d, *J*=8.7 Hz, 2H, Ar–H), 7.20–7.30 (m, 5H, Ar–H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 22.7, 23.6, 28.3, 31.6, 32.1, 43.1 (NCH_2), 55.3 (OCH_3), 71.0 (OCH_2), 71.6 (C-4), 81.2 (C-5), 114.0 (2C), 127.8, 127.9 (2C), 128.4 (2C), 129.2 (2C), 130.4, 138.2, 159.0, 172.9 (C=O). MS (ESI): 400 (MH^+, 33), 422 (MNa^+, 100), 438 (MK^+, 5). HRESIMS calcd for $[C_{24}H_{33}NO_4+H]^+$: 400.2488; found: 400.2509.

*4.2.4. (5S,6S)-5-Benzyloxy-1-(4-methoxybenzyl)-6-(n-octyl)-2-piperidinone (**3d**)*

Following the general procedure, the reductive deoxygenation of the tautomeric mixture **4d**/**5d** gave **3d** as the sole diastereomer in 51% yield and **6d** as the sole diastereomer in 22% yield.

*4.2.4.1. Compound (5S,6S)-**3d**.* R_f=0.35 (EtOAc/PE=1:2), colorless oil. $[\alpha]_D^{25}$ −30.4 (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 1643, 1513, 1455,

1248 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J=6.9 Hz, 3H, CH_3), 1.20–1.45 (m, 12H), 1.49–1.58 (m, 1H), 1.78–1.87 (m, 1H), 1.90–2.03 (m, 2H, H-4), 2.46 (ddd, J=18.3, 8.4, 7.6 Hz, 1H, H-3), 2.68 (ddd, J=18.3, 8.5, 4.8 Hz, 1H, H-3), 3.37 (dt, J=4.9, 5.9 Hz, 1H, H-6), 3.54 (ddd, J=10.0, 5.2, 4.9 Hz, 1H, H-5), 3.74 (d, J=14.6 Hz, 1H, NCH_2), 3.81 (s, 3H, OCH_3), 4.36 (d, J=12.0 Hz, 1H, OCH_2), 4.41 (d, J=12.0 Hz, 1H, OCH_2), 5.41 (d, J=14.6 Hz, 1H, NCH_2), 6.85 (d, J=8.7 Hz, 2H, Ar–H), 7.12 (d, J=8.7 Hz, 2H, Ar–H), 7.15–7.20 (m, 2H, Ar–H), 7.25–7.35 (m, 3H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 21.9, 22.0, 26.8, 28.1, 28.6, 28.8 (2C), 29.3, 31.2, 47.8 (NCH_2), 54.6 (OCH_3), 56.1 (C-6), 70.1 (OCH_2), 73.5 (C-5), 113.3 (2C), 126.9 (2C), 127.1, 127.6 (2C), 128.5 (2C), 128.8, 137.2, 158.3, 169.0 (C=O). MS (ESI): 438 (MH^+, 100). HRESIMS calcd for $[C_{28}H_{39}NO_3+H]^+$: 438.3008; found: 438.3021.

*4.2.4.2. (4S,5R)-4-Benzyloxy-5-hydroxy-N-(4-methoxybenzyl)tridecanoyl amide (**6d**).* R_f=0.35 (EtOAc/PE=1:1), white solid, mp: 83–84 °C (EtOAc/PE=2:1). $[\alpha]_D^{25}$ −6.7 (*c* 0.8, $CHCl_3$). IR (film) ν_{max}: 3409, 3314, 1638, 1513, 1249 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J=6.8 Hz, 3H, CH_3), 1.20–1.35 (m, 11H), 1.40–1.52 (m, 3H), 1.93 (m, 2H, H-3), 2.22 (ddd, J=15.2, 7.4, 7.4 Hz, 1H, H-2), 2.38 (ddd, J=15.2, 8.2, 6.6 Hz, 1H, H-2), 2.61 (d, J=3.1 Hz, 1H, OH), 3.35 (ddd, J=7.0, 4.4, 4.4 Hz, 1H, H-5), 3.70–3.75 (m, 1H, H-4), 3.78 (s, 3H, OCH_3), 4.26 (dd, J=14.4, 5.5 Hz, 1H, NCH_2), 4.33 (dd, J=14.4, 5.5 Hz, 1H, NCH_2), 4.45 (d, J=11.5 Hz, 1H, OCH_2), 4.57 (d, J=11.5 Hz, 1H, OCH_2), 5.72 (br s, 1H, NH), 6.84 (d, J=8.7 Hz, 2H, Ar–H), 7.15 (d, J=8.7 Hz, 2H, Ar–H), 7.25–7.38 (m, 5H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 23.6, 26.1, 29.3, 29.5, 29.7, 31.6, 31.9, 32.4, 43.1 (NCH_2), 55.3 (OCH_3), 71.0 (OCH_2), 71.6 (C-4), 81.2 (C-5), 114.0 (2C), 127.8, 127.9 (2C), 128.5 (2C), 129.2 (2C), 130.3, 138.2, 159.0, 173.0 (C=O). MS (ESI): 456 (MH^+, 100). Anal. Calcd for $C_{28}H_{41}NO_4$: C, 73.81; H, 9.07; N, 3.07. Found: C, 73.87; H, 8.77; N, 3.06.

*4.2.5. (5S,6S)-5-Benzyloxy-6-(n-dodecyl)-1-(4-methoxybenzyl)-2-piperidinone (**3e**)*

Following the general procedure, the reductive deoxygenation of the tautomeric mixture **4e**/**5e** gave **3e** as the sole diastereomer in 39% yield, and **6e** as the sole diastereomer in 27% yield.

*4.2.5.1. Compound (5S,6S)-**3e**.* R_f=0.35 (EtOAc/PE=1:2), colorless oil. $[\alpha]_D^{25}$ −27.0 (*c* 0.9, $CHCl_3$). IR (film) ν_{max}: 1642, 1513, 1455, 1245 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J=6.8 Hz, 3H, CH_3), 1.18–1.45 (m, 20H), 1.48–1.59 (m, 1H), 1.77–1.88 (m, 1H), 1.88–2.05 (m, 2H, H-4), 2.46 (ddd, J=18.2, 8.4, 7.7 Hz, 1H, H-3), 2.62 (ddd, J=18.2, 8.5, 4.9 Hz, 1H, H-3), 3.37 (dt, J=4.9, 5.9 Hz, 1H, H-6), 3.54 (ddd, J=9.8, 4.9, 4.9 Hz, 1H, H-5), 3.73 (d, J=14.7 Hz, 1H, NCH_2), 3.81 (s, 3H, OCH_3), 4.36 (d, J=12.0 Hz, 1H, OCH_2), 4.40 (d, J=12.0 Hz, 1H, OCH_2), 5.41 (d, J=14.7 Hz, 1H, NCH_2), 6.84 (d, J=8.7 Hz, 2H, Ar–H), 7.12 (d, J=8.7 Hz, 2H, Ar–H), 7.15–7.20 (m, 2H, Ar–H), 7.23–7.32 (m, 3H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 22.5, 22.6, 27.5, 28.7, 29.3, 29.4, 29.5, 29.6 (4C), 29.9, 31.9, 48.4 (NCH_2), 55.2 (OCH_3), 56.7 (C-6), 70.7 (OCH_2), 74.2 (C-5), 113.8 (2C), 127.5 (2C), 127.7, 128.3 (2C), 129.2 (2C), 129.4, 137.8, 158.9, 169.6 (C=O). MS (ESI): 494 (MH^+, 100). Anal. Calcd for $C_{32}H_{47}NO_3$: C, 77.85; H, 9.60; N, 2.84. Found: C, 78.12; H, 9.71; N, 3.08.

*4.2.5.2. (4S,5R)-4-Benzyloxy-5-hydroxy-N-(4-methoxybenzyl)heptadecanoyl amide (**6e**).* R_f=0.35 (EtOAc/PE=1:1), white solid, mp: 66–68 °C (EtOAc/PE=2:1). $[\alpha]_D^{25}$ −3.5 (*c* 2.2, $CHCl_3$). IR (film) ν_{max}: 3306, 1638, 1514, 1250, 1092 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.81 (t, J=6.9 Hz, 3H, CH_3), 1.10–1.25 (m, 19H), 1.30–1.50 (m, 3H), 1.80–1.92 (m, 2H, H-3), 2.16 (ddd, J=14.8, 7.4, 7.4 Hz, 1H, H-2), 2.30 (ddd, J=14.8, 8.0, 6.6 Hz, 1H, H-2), 2.52 (s, 1H, OH), 3.26–3.32 (m, 1H, H-5), 3.63–3.68 (m, 1H, H-4), 3.75 (s, 3H, OCH_3), 4.21 (dd, J=14.4, 5.5 Hz, 1H, NCH_2), 4.27 (dd, J=14.4, 5.5 Hz, 1H, NCH_2), 4.39 (d, J=11.5 Hz, 1H, OCH_2), 4.51 (d, J=11.5 Hz, 1H, OCH_2), 5.65 (s, 1H, NH), 6.79 (d, J=8.7 Hz, 2H, Ar–H), 7.10 (d, J=8.7 Hz, 2H, Ar–H), 7.18–7.30 (m, 5H, Ar–H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.7, 23.6, 26.2, 29.3, 29.6 (6C), 31.6, 31.9, 32.5, 43.1 (NCH_2), 55.3 (OCH_3), 71.1 (OCH_2), 71.6 (C-4), 81.2 (C-5), 114.1 (2C), 127.8, 127.9 (2C), 128.5 (2C), 129.2 (2C), 130.4, 138.2, 159.0, 172.9 (C=O). MS (ESI): 512 (MH^+, 20), 534 (MNa^+, 100), 550 (MK^+, 10). Anal. Calcd for $C_{32}H_{49}NO_4$: C, 75.11; H, 9.65; N, 2.74. Found: C, 75.30; H, 9.40; N, 2.82.

*4.2.6. (5S,6S)-5-Benzyloxy-1-(4-methoxybenzyl)-6-phenylethyl-2-piperidinone (**3f**)*

Following the general procedure, the reductive deoxygenation of the tautomeric mixture **4f**/**5f** gave **3f** as the sole diastereomer in 38% yield, and **6f** as the sole diastereomer in 42% yield.

*4.2.6.1. Compound (5S,6S)-**3f**.* R_f=0.35 (EtOAc/PE=1:2), colorless oil. $[\alpha]_D^{25}$ −16.5 (*c* 1.2, $CHCl_3$). IR (film) ν_{max}: 1642, 1512, 1455, 1247 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.80–1.90 (m, 1H, H-4), 1.92–2.06 (m, 2H), 2.22 (ddd, J=14.1, 7.8, 4.9 Hz, 1H, H-4), 2.48 (ddd, J=18.2, 8.3, 7.8 Hz, 1H, H-3), 2.65 (ddd, J=18.2, 8.2, 4.9 Hz, 1H, H-3), 2.68 (d, J=8.0 Hz, 1H, $PhCH_2$), 2.72 (d, J=8.0 Hz, 1H, $PhCH_2$), 3.42 (ddd, J=6.2, 4.9, 1.0 Hz, 1H, H-6), 3.58 (ddd, J=10.0, 5.1, 4.9 Hz, 1H, H-5), 3.68 (d, J=14.6 Hz, 1H, NCH_2), 3.80 (s, 3H, OCH_3), 4.36 (d, J=11.9 Hz, 1H, OCH_2), 4.42 (d, J=11.9 Hz, 1H, OCH_2), 5.36 (d, J=14.6 Hz, 1H, NCH_2), 6.80 (d, J=8.7 Hz, 2H, Ar–H), 7.10 (d, J=8.7 Hz, 2H, Ar–H), 7.12–7.15 (m, 2H, Ar–H), 7.18–7.22 (m, 2H, Ar–H), 7.26–7.35 (m, 6H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 28.7, 31.1, 33.3, 48.2 (NCH_2), 55.2 (OCH_3), 55.9, 70.8 (OCH_2), 74.2 (C-5), 113.9 (2C), 126.1, 127.5 (2C), 127.7, 128.4 (2C), 128.5 (4C), 129.2, 129.4 (2C), 137.8, 141.4, 158.9, 169.6 (C=O). MS (ESI): 430 (MH^+, 100). HRESIMS calcd for $[C_{28}H_{31}NO_3+H]^+$: 430.2382; found: 430.2392.

*4.2.6.2. (4S,5R)-4-Benzyloxy-5-hydroxy-N-(4-methoxybenzyl)-7-phenylheptanoyl amide (**6f**).* R_f=0.35 (EtOAc/PE=1:1), white solid, mp: 71–73 °C (EtOAc/PE=1:1). $[\alpha]_D^{20}$ 11.5 (*c* 1.8, $CHCl_3$). IR (film) ν_{max}: 3403, 3305, 1645, 1513, 1248 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.75–1.96 (m, 2H), 2.03 (ddd, J=13.8, 7.2, 6.8 Hz, 1H, H-3), 2.21 (ddd, J=15.3, 9.5, 6.8 Hz, 1H, H-2), 2.38 (ddd, J=15.3, 7.2, 6.6 Hz, 1H, H-2), 2.67 (ddd, J=13.8, 9.5, 6.6 Hz, 1H, H-3), 2.85–2.95 (m, 2H), 3.38 (dt, J=4.3, 7.1, 1H, H-5), 3.68–3.75 (m, 1H, H-4), 3.80 (s, 3H, OCH_3), 4.28 (dd, J=14.5, 5.6 Hz, 1H, NCH_2), 4.35 (dd, J=14.5, 5.6 Hz, 1H, NCH_2), 4.46 (d, J=11.5 Hz, 1H, OCH_2), 4.54 (d, J=11.5 Hz, 1H, OCH_2), 5.72 (br s, 1H, NH), 6.83 (d, J=8.7 Hz, 2H, Ar–H), 7.18 (d, J=8.7 Hz, 2H, Ar–H), 7.20–7.40 (m, 10H, Ar–H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.5, 31.2, 32.3, 34.2, 43.1 (NCH_2), 55.2 (OCH_3), 70.2 (OCH_2), 71.6 (C-4), 81.1 (C-5), 114.0 (2C), 125.7, 127.8, 127.9 (2C), 128.4 (4C), 128.5, 129.2 (2C), 129.4, 130.3, 138.2, 142.1, 159.0, 172.9 (C=O). MS (ESI): 448 (MH^+, 100). HRESIMS calcd for $[C_{28}H_{33}NO_4+H]^+$: 448.2488; found: 448.2493.

*4.2.7. (5S,6S)-5-Benzyloxy-1-(4-methoxybenzyl)-6-phenyl-2-piperidinone (**3g**)*

Following the general procedure, the reductive deoxygenation of the tautomeric mixture **4g**/**5g** gave a diastereomeric mixture of **3g** and the known **2g**[6c] in 60:40 ratio (combined yield: 54%), and **6g** as a diastereomeric mixture in 55:45 ratio (combined yield: 35%).

*4.2.7.1. Compound (5S,6S)-**3g** (major diastereomer).* R_f=0.35 (EtOAc/PE=1:2), colorless oil. $[\alpha]_D^{25}$ −76.4 (*c* 0.9, $CHCl_3$). IR (film) ν_{max}: 1644, 1512, 1246 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.60–1.76 (m, 2H, H-4), 2.58 (ddd, J=18.3, 9.5, 8.7 Hz, 1H, H-3), 2.78 (ddd, J=18.3, 5.4, 5.2 Hz, 1H, H-3), 3.32 (d, J=14.4 Hz, 1H, NCH_2), 3.75–3.82 (m, 1H, H-5), 3.80 (s, 3H, OCH_3), 4.43 (d, J=11.8 Hz, 1H, OCH_2), 4.48 (d, J=11.8 Hz, 1H, OCH_2), 4.57 (d, J=4.9 Hz, 1H, H-6), 5.50 (d, J=14.4 Hz, 1H, NCH_2), 6.82 (d, J=8.7 Hz, 2H, Ar–H), 7.05 (d, J=8.7 Hz, 2H, Ar–H), 7.12 (dd, J=7.8, 1.8 Hz, 2H, Ar–H), 7.19 (dd, J=7.8, 1.8 Hz, 2H, Ar–H), 7.23–7.29 (m, 3H, Ar–H), 7.34–7.40 (m, 3H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 29.6, 47.4 (NCH_2),

55.3 (OCH_3), 61.4, 71.0 (OCH_2), 74.4 (C-5), 114.0 (2C), 127.3 (2C), 127.6, 128.0, 128.2 (2C), 128.4 (2C), 128.7 (2C), 129.0, 129.6 (2C), 136.2, 137.9, 159.0, 169.9 (C=O). MS (ESI): 402 (MH^+, 100), 424 (MNa^+, 30). HRESIMS calcd for $[C_{26}H_{27}NO_3+H]^+$: 402.2069; found: 402.2086.

*4.2.7.2. (4S,5R)-4-Benzyloxy-5-hydroxy-N-(4-methoxybenzyl)-5-phenylpentanoyl amide (**6g**) (major diastereomer).* R_f=0.35 (EtOAc/PE=1:1), white solid, mp: 76–78 °C (EtOAc/PE=2:1). $[\alpha]_D^{25}$ −2.4 (*c* 1.9, $CHCl_3$). IR (film) ν_{max}: 3414, 3315, 1650, 1513, 1248 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.81 (dddd, *J*=14.5, 7.4, 7.0, 3.9 Hz, 1H, H-3), 1.92 (dddd, *J*=14.5, 7.4, 7.1, 1.2 Hz, 1H, H-3), 2.14 (ddd, *J*=14.9, 7.4, 7.4 Hz, 1H, H-2), 2.29 (ddd, *J*=14.9, 7.1, 7.0 Hz, 1H, H-2), 3.00–3.20 (s, 1H, OH), 3.59 (ddd, *J*=5.1, 3.9, 1.2 Hz, 1H, H-4), 3.77 (s, 3H, OCH_3), 4.23 (dd, *J*=14.5, 5.6 Hz, 1H, NCH_2), 4.27 (dd, *J*=14.5, 5.6 Hz, 1H, NCH_2), 4.41 (d, *J*=11.5 Hz, 1H, OCH_2), 4.46 (d, *J*=11.5 Hz, 1H, OCH_2), 4.80 (d, *J*=5.1 Hz, 1H, H-5), 5.68 (br s, 1H, NH), 6.82 (d, *J*=8.7 Hz, 2H, Ar–H), 7.12 (d, *J*=8.7 Hz, 2H, Ar–H), 7.24–7.36 (m, 10H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 31.9, 43.0 (NCH_2), 55.3 (OCH_3), 72.1 (OCH_2), 73.8 (C-4), 82.1 (C-5), 114.0 (2C), 126.5 (2C), 127.5, 127.8, 128.0 (2C), 128.2 (2C), 128.4 (2C), 129.2 (2C), 130.3, 138.0, 140.8, 159.0, 172.9 (C=O). MS (ESI): 420 (MH^+, 15), 442 (MNa^+, 100). Anal. Calcd for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.70; H, 7.04; N, 3.51.

4.3. General procedure for the reductive ring-opening of the tautomeric mixture 4/5

To a cooled (−20 °C) solution of the tautomeric mixture **4**/**5** (1 mol equiv) in Et_2O (0.1 M) was added dropwise a solution of $Zn(BH_4)_2$ in Et_2O (3 mol equiv) under argon atmosphere. The mixture was allowed to slowly warm to room temperature and was stirred at that temperature overnight. 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=1:1) to yield **6** as a white solid.

Following the general reductive ring-opening procedure, **6a** and its diastereomer were obtained in 94:6 diastereomeric ratio and in 82% combined yield. Compound **6b** and its diastereomer were obtained in 94:6 diastereomeric ratio and in 89% combined yield. Compound **6c** and its diastereomer were obtained in 91:9 diastereomeric ratio and in 82% combined yield. Compound **6d** and its diastereomer were obtained in 98:2 diastereomeric ratio and in 95% combined yield. Compound **6e** and its diastereomer were obtained in 90:10 diastereomeric ratio and in 77% combined yield. Compound **6f** and its diastereomer were obtained in 89:11 diastereomeric ratio and in 87% combined yield. Compound **6g** and its diastereomer were obtained in 65:35 diastereomeric ratio and in 66% combined yield. Compound **6h** and its diastereomer were obtained in 95:5 diastereomeric ratio and in 85% combined yield. Compound **6i** and its diastereomer were obtained in 86:14 diastereomeric ratio and in 78% combined yield. Compound **6j** and its diastereomer were obtained in 97:3 diastereomeric ratio and in 81% combined yield.

4.4. The physical and spectral data of 6h–6j

The physical and spectral data of **6a**–**6g** are shown in the previous sections, those of **6h**–**6j** in the following sections.

*4.4.1. (4S,5R)-4-Benzyloxy-5-hydroxy-N-(4-methoxybenzyl)-6-phenylhexanoyl amide (**6h**) (4S,5R)-**6h** (major diastereomer)*

R_f=0.35 (EtOAc/PE=2:3), white solid, mp: 75–76 °C (EtOAc/PE=2:1). $[\alpha]_D^{25}$ −5.6 (*c* 1.7, $CHCl_3$). IR (film) ν_{max}: 3408, 3306, 1645, 1513, 1248 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 2.04 (m, 2H, H-3), 2.22 (ddd, *J*=15.2, 7.4, 7.4 Hz, 1H, H-2), 2.41 (ddd, *J*=15.2, 7.5, 6.6 Hz, 1H, H-2), 2.60 (s, 1H, OH), 2.73 (dd, *J*=13.8, 8.8 Hz, 1H, H-6), 2.90 (dd, *J*=13.8, 3.6 Hz, 1H, H-6), 3.38–3.45 (m, 1H, H-5), 3.80 (s, 3H, OCH_3), 3.90–3.98 (m, 1H, H-4), 4.25 (dd, *J*=14.5, 5.6 Hz, 1H, NCH_2), 4.33 (dd, *J*=14.5, 5.6 Hz, 1H, NCH_2), 4.46 (d, *J*=11.5 Hz, 1H, OCH_2), 4.58 (d, *J*=11.5 Hz, 1H, OCH_2), 5.65 (br s, 1H, NH), 6.82 (d, *J*=8.7 Hz, 2H, Ar–H), 7.15 (d, *J*=8.7 Hz, 2H, Ar–H), 7.20–7.50 (m, 10H, Ar–H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.0, 31.4, 39.1, 43.1 (NCH_2), 55.4 (OCH_3), 71.6 (OCH_2), 72.6 (C-4), 80.4 (C-5), 114.0 (2C), 126.3, 127.8, 127.9 (2C), 128.4 (4C), 129.1 (2C), 129.3 (2C), 130.3, 138.1, 138.7, 159.0, 172.8 (C=O). MS (ESI): 434 (MH^+, 100). Anal. Calcd for $C_{27}H_{31}NO_4$: C, 74.80; H, 7.21; N, 3.23. Found: C, 74.46; H, 7.35; N, 3.25.

*4.4.2. (4S,5R)-4-Benzyloxy-5-hydroxy-N-(4-methoxybenzyl)-heneicosanoyl amide (**6i**) (4S,5R)-**6i** (major diastereomer)*

R_f=0.35 (EtOAc/PE=1:2), white solid, mp: 85–86 °C (EtOAc/PE=1:1). $[\alpha]_D^{25}$ −3.4 (*c* 1.1, $CHCl_3$). IR (film) ν_{max}: 3306, 1637, 1514, 1467, 1250 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, *J*=6.9 Hz, 3H, CH_3), 1.18–1.35 (m, 27H), 1.42–1.55 (m, 3H), 1.88–1.98 (m, 2H, H-3), 2.27 (ddd, *J*=14.6, 7.4, 7.4 Hz, 1H, H-2), 2.41 (ddd, *J*=14.6, 8.2, 6.6 Hz, 1H, H-2), 2.65 (br s, 1H, OH), 3.36 (dt, *J*=4.5, 6.5 Hz, 1H, H-5), 3.70–3.76 (m, 1H, H-4), 3.79 (s, 3H, OCH_3), 4.27 (dd, *J*=14.4, 5.5 Hz, 1H, NCH_2), 4.35 (dd, *J*=14.4, 5.5 Hz, 1H, NCH_2), 4.45 (d, *J*=11.5 Hz, 1H, OCH_2), 4.58 (d, *J*=11.5 Hz, 1H, OCH_2), 5.65 (br s, 1H, NH), 6.84 (d, *J*=8.7 Hz, 2H, Ar–H), 7.18 (d, *J*=8.7 Hz, 2H, Ar–H), 7.8–7.40 (m, 5H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 23.5, 26.2, 29.4, 29.6 (2C), 29.7 (8C), 31.6, 31.9, 32.5, 43.1 (NCH_2), 55.3 (OCH_3), 71.0 (OCH_2), 71.6 (C-4), 81.1 (C-5), 114.0 (2C), 127.8, 127.9 (2C), 128.5 (2C), 129.2 (2C), 130.3, 138.2, 159.0, 172.9 (C=O). MS (ESI): 568 (MH^+, 25), 590 (MNa^+, 100). Anal. Calcd for $C_{36}H_{57}NO_4$: C, 76.15; H, 10.12; N, 2.47. Found: C, 76.26; H, 9.81; N, 2.39.

*4.4.3. (4S,5R)-4-Benzyloxy-5-hydroxy-N-(4-methoxybenzyl)-7-methyloctanoyl amide (**6j**) (4S,5R)-**6j** (major diastereomer)*

R_f=0.35 (EtOAc/PE=2:3), white solid, mp: 56–58 °C (EtOAc/PE=2:1). $[\alpha]_D^{25}$ −5.3 (*c* 1.4, $CHCl_3$). IR (film) ν_{max}: 3415, 3305, 1650, 1513, 1248 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.89 (d, *J*=6.7 Hz, 3H, CH_3), 0.94 (d, *J*=6.7 Hz, 3H, CH_3), 1.22 (ddd, *J*=9.5, 9.0, 3.3 Hz, 1H), 1.39 (ddd, *J*=9.5, 5.1, 4.4 Hz, 1H), 1.75–1.84 (m, 1H), 1.87–1.98 (m, 2H), 2.22 (ddd, *J*=15.2, 7.4, 7.4 Hz, 1H, H-2), 2.37 (ddd, *J*=15.2, 6.8, 6.8 Hz, 1H, H-2), 2.52 (s, 1H, OH), 3.33 (dt, *J*=4.2, 6.0 Hz, 1H, H-5), 3.76 (ddd, *J*=9.5, 4.2, 3.8 Hz, 1H, H-4), 3.78 (s, 3H, OCH_3), 4.26 (dd, *J*=14.4, 5.8 Hz, 1H, NCH_2), 4.33 (dd, *J*=14.4, 5.8 Hz, 1H, NCH_2), 4.45 (d, *J*=11.6 Hz, 1H, OCH_2), 4.58 (d, *J*=11.6 Hz, 1H, OCH_2), 5.80 (br s, 1H, NH), 6.78 (d, *J*=8.5 Hz, 2H, Ar–H), 7.15 (d, *J*=8.5 Hz, 2H, Ar–H), 7.25–7.40 (m, 5H, Ar–H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.0, 23.6, 23.7, 24.8, 31.8, 41.4, 43.1 (NCH_2), 55.3 (OCH_3), 69.0 (OCH_2), 71.7 (C-4), 81.6 (C-5), 114.1 (2C), 127.8, 127.9 (2C), 128.5 (2C), 129.2 (2C), 130.4, 138.3, 159.0, 173.0 (C=O). MS (ESI): 400 (MH^+, 40), 422 (MNa^+, 100), 438 (MK^+, 15). HRESIMS calcd for $[C_{24}H_{33}NO_4+H]^+$: 400.2484; found: 400.2482.

4.5. General procedure for the synthesis of (5*S*,6*S*)-2-piperidinones 3 via the cyclization of 6

To a cooled (−20 °C) solution of a mixture of **6** (1.0 mol equiv) and Et_3N (2.0 mol equiv) in CH_2Cl_2 was added dropwise MsCl (1.2 mol equiv) under nitrogen atmosphere. The mixture was stirred at −20 to −10 °C for 2 h. Water 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 the mesylates **8**, which are unstable and were used immediately in the subsequent step.

To a solution of mesylate **8** (1 mol equiv) in THF (0.1 M) and HMPA (2.0 mol equiv) was added dropwise a solution of potassium *tert*-butoxide (1.2 mol equiv) in THF at 0 °C under nitrogen atmosphere. The mixture was allowed slowly to warm to room temperature and was stirred for 48 h. The reaction was quenched with saturated NH_4Cl at 0 °C. 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 (5*S*,6*S*)-2-piperidinones **3** in 66–87% yields (Table 2). The reaction of **8h** gave **9** in 81% yield. The reaction of **8j** gave **10** in 72% yield.

4.5.1. The physical and spectral data of (5S,6S)-2-piperidinones 3a–3g

The physical and spectral data of (5*S*,6*S*)-2-piperidinones **3a**–**3g** are shown in the previous sections.

4.5.2. (5S,6S)-5-Benzyloxy-6-(n-hexadecyl)-1-(4-methoxybenzyl)-2-piperidinone (3i)

Colorless oil. $[\alpha]_D^{25}$ −18.9 (*c* 0.7, $CHCl_3$). IR (film) ν_{max}: 1644, 1512, 1464, 1248 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J*=6.8 Hz, 3H, CH_3), 1.18–1.43 (m, 28H), 1.48–1.60 (m, 1H), 1.77–1.88 (m, 1H), 1.88–2.05 (m, 2H, H-4), 2.48 (ddd, *J*=18.2, 8.1, 8.1 Hz, 1H, H-3), 2.62 (ddd, *J*=18.2, 8.3, 5.0 Hz, 1H, H-3), 3.37 (dt, *J*=4.8, 5.9 Hz, 1H, H-6), 3.54 (ddd, *J*=9.9, 5.1, 4.8 Hz, 1H, H-5), 3.74 (d, *J*=14.6 Hz, 1H, NCH_2), 3.81 (s, 3H, OCH_3), 4.37 (d, *J*=12.2 Hz, 1H, OCH_2), 4.40 (d, *J*=12.2 Hz, 1H, OCH_2), 5.41 (d, *J*=14.6 Hz, 1H, NCH_2), 6.85 (d, *J*=8.5 Hz, 2H, Ar–H), 7.13 (d, *J*=8.5 Hz, 2H, Ar–H), 7.15–7.20 (m, 2H, Ar–H), 7.25–7.32 (m, 3H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.5, 22.7, 27.5, 28.7, 29.3, 29.4, 29.5, 29.6 (3C), 29.7 (5C), 30.0, 31.9, 48.4 (NCH_2), 55.2 (OCH_3), 56.7 (C-6), 70.7 (OCH_2), 74.2 (C-5), 114.0 (2C), 127.5 (2C), 127.7, 128.4 (2C), 129.3 (2C), 129.4, 137.9, 158.9, 169.6 (C=O). MS (ESI): 550 (MH^+, 30), 572 (MNa^+, 100). Anal. Calcd for $C_{36}H_{55}NO_3$: C, 78.64; H, 10.08; N, 2.55. Found: C, 78.26; H, 9.92; N, 2.85.

4.5.3. trans-4-Benzyloxy-N-(4-methoxybenzyl)-7-methyl-4-heptenoylamide (9)

Colorless oil. IR (film) ν_{max}: 1642, 1512, 1246 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (d, *J*=6.7 Hz, 6H, 2×CH_3), 1.55 (ddd, *J*=13.3, 6.7, 6.7 Hz, 1H), 1.89 (dd, *J*=7.5, 6.7 Hz, 2H), 2.41 (t, *J*=7.4 Hz, 2H, H-3), 2.55 (t, *J*=7.4 Hz, 2H, H-2), 3.78 (s, 3H, OCH_3), 4.25 (dd, *J*=14.4, 5.6 Hz, 1H, NCH_2), 4.31 (dd, *J*=14.4, 5.6 Hz, 1H, NCH_2), 4.52 (t, *J*=7.5 Hz, 1H), 4.63 (d, *J*=12.1 Hz, 1H, OCH_2), 4.67 (d, *J*=12.1 Hz, 1H, OCH_2), 5.80 (br s, 1H, NH), 6.82 (d, *J*=8.5 Hz, 2H, Ar–H), 7.13 (d, *J*=8.5 Hz, 2H, Ar–H), 7.25–7.35 (m, 5H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2 (2C), 26.2, 29.5, 34.3, 35.7, 43.1 (NCH_2), 55.3 (OCH_3), 68.6 (OCH_2), 98.4 (C-5), 114.0 (2C), 127.4 (2C), 127.7, 128.4 (2C), 129.2 (2C), 130.5, 137.5, 154.1 (C-4), 159.0, 172.3 (C=O). MS (ESI): 382 (MH^+, 100). HRESIMS calcd for $[C_{24}H_{31}NO_3+H]^+$: 382.2382; found: 382.2377.

4.5.4. trans-(S)-4-Benzyloxy-N-(4-methoxybenzyl)-6-phenylhexanoyl amide (10)

Colorless oil. $[\alpha]_D^{25}$ −61.1 (*c* 1.1, $CHCl_3$). IR (film) ν_{max}: 3303, 1645, 1512, 1248 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.02 (dddd, *J*=13.7, 7.1, 6.6, 0.9 Hz, 2H, H-3), 2.33 (dt, *J*=0.9, 7.1 Hz, 2H, H-2), 3.78 (s, 3H, OCH_3), 3.96 (ddd, *J*=8.0, 7.1, 6.6 Hz, 1H, H-4), 4.25 (dd, *J*=14.4 5.5 Hz, 1H, NCH_2), 4.33 (dd, *J*=14.4, 5.5 Hz, 1H, NCH_2), 4.34 (d, *J*=11.8 Hz, 1H, OCH_2), 4.62 (d, *J*=11.8 Hz, 1H, OCH_2), 5.75 (br s, 1H, NH), 6.11 (dd, *J*=16.0, 8.0 Hz, 1H, H-5), 6.55 (d, *J*=16.0 Hz, 1H, H-6), 6.83 (d, *J*=8.7 Hz, 2H, Ar–H), 7.14 (d, *J*=8.7 Hz, 2H, Ar–H), 7.23–7.40 (m, 10H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.4, 32.6, 43.0 (NCH_2), 55.3 (OCH_3), 70.2 (OCH_2), 79.1 (C-4), 114.0 (2C), 126.5 (2C), 127.6, 127.8 (2C), 127.9 (2C), 128.4 (2C), 128.6 (2C), 129.2, 129.6 130.4, 132.8, 136.3, 138.4, 159.0, 172.4 (C=O). MS (ESI): 416 (MH^+, 5), 438 (MNa^+, 100), 454 (MK^+, 10). Anal. Calcd for $C_{27}H_{29}NO_3$: C, 78.04; H, 7.03; N, 3.37. Found: C, 78.41; H, 7.11; N, 3.36.

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