A General and Simple Diastereoselective Reduction by L-Selectride: Efficient Synthesis of Protected (4S,5S)-Dihydroxy Amides

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Abstract: A general approach to (4S,5S)-4-benzyloxy-5-hydroxy-N-(4-methoxybenzyl) amides 10 based on a diastereoselective reduction of (5S,6RS)-6-alkyl-5-benzyloxy-6-hydroxy-2-piperidinones 6 and their tautomeric ring-opened keto amides 7 is described. The reduction with L-Selectride at -20 °C to room temperature afforded the products 10 in excellent yields and moderate to high syn-diastereoselectivities.

Keywords: L-Selectride; 3-hydroxyglutarimide; (4S,5S)-dihydroxyamide

1. Introduction

The (4,5)-dihydroxycarboxylate moiety is a critical framework shared by many bioactive compounds, such as Microcarpalide (1), which is a 10-membered lactone that was isolated from the fermentation broth of an unidentified endophytic fungus by Hemscheidt and co-workers in 2001 [1], and Kalanchosine dimalate (KMC, 2) [2], which is an anti-inflammatory salt from the fresh juice of the aerial parts of Kalanchoe brasiliensis, as well as natural gastroprotective 3,4-dihydroisocoumarins, such as amicoumacin C (3) [3,4] and AI-77B (4) [5,6]. Both the stereochemical variation at C-4, C-5 and the interesting biological activities exhibited by these compounds make them attractive synthetic targets [1,5-7]. A number of methods have been developed for the synthesis of these compounds [8-13], but few methods for the construction of the (4,5)-dihydroxycarboxylate moiety [14-18].
Generally, chiral pool starting materials or Sharpless asymmetric dihydroxylation was used in the construction of the (4,5)-dihydroxycarboxylate moiety.

Figure 1. (4,5)-Dihydroxycarboxylate derivatives.

Previously, we have shown that the protected (S)-3-hydroxyglutarimide 5 may serve as a versatile building block for the asymmetric synthesis of a variety of 2,6-disubstituted 3-hydroxypiperidines [19-23]. A flexible regio- and diastereoselective reductive alkylation method was developed for the conversion of 5 to trans-6-alkyl-5-benzyloxy-2-piperidinone derivatives 8 [20]. Recently, we also developed a chemo- and diastereoselective transformation of the N,O-acetals 6 and their chain tautomers 7, readily derived from protected 3-hydroxyglutarimide 5, into cyclic products (5S,6S/R)-6-alkyl-5-benzyloxy-2-piperidinones 9/8, and anti-10/syn-10 with a combination of boron trifluoride etherate/zinc borohydride in modest chemo- and diastereoselectivities (Scheme 1) [24]. Moreover, the reduction with zinc borohydride in the absence of BF₃•OEt₂ leading exclusively to the formation of the ring-opening products anti-10 in excellent anti-diastereoselectivities was exploited. In addition, we reported the application of this new variation to the asymmetric synthesis of (+)-azimic acid [25].

Scheme 1. The synthesis of 6-alkyl-5-benzyloxy-2-piperidinones.
In the continuation of our interest in the amino acid chiral template-assisted synthesis of natural and unnatural bioactive compounds, as a part of our research program aimed at developing enantioselective syntheses of naturally occurring bioactive compounds, such as Microcarpalide (1), we decided to explore the construction of the (4,5)-dihydroxycarboxylate moiety in order to develop a simple and feasible approach to syn-10, a key intermediate (R = CH=CH₂) for the synthesis of 1. Herein we report a diastereoselective reduction of 6 and 7 employing L-Selectride as the reductive agent to obtain syn-10 (Scheme 2).

2. Results and Discussion

The requisite 6-alkyl-5-benzyloxy-6-hydroxy-2-piperidinones 6, together with their ring-opened keto amide tautomers 7, were prepared via the addition of Grignard reagents to (S)-3-benzyloxyglutarimide 5 under our recently improved conditions [23]. Treatment of the tautomeric mixture of 6a and 7a with 1.2 molar equiv of L-Selectride in THF (−20 °C - rt) yielded syn-10a and anti-10a in a ratio of 86:14 (combined yield: 93%). To explore the generality of the process, a series of hemi-azaketals 6 and their opened keto amide tautomers 7 were investigated using L-Selectride as reductive agent [26-29], and the results are reported in Table 1.

Scheme 2. The diastereoselective reduction by L-Selectride.

Table 1. Results of reduction according to the procedure shown in Scheme 2.

| Entry | R       | Yield [%] | syn/anti ratio |
|-------|---------|-----------|----------------|
| 1     | CH₃ (10a) | 93        | 6:1⁷         |
| 2     | C₂H₅ (10b) | 97        | 7:1 ⁷        |
| 3     | n-C₄H₉ (10c) | 97        | 7:1 ⁶        |
| 4     | n-C₅H₁₁ (10d) | 95        | 23:2 ⁶       |
| 5     | n-C₈H₁₇ (10e) | 98        | 23:2 ⁶       |
| 6     | n-C₁₂H₂₅ (10f) | 85        | 9:1 ⁷       |
| 7     | n-C₁₆H₃₃ (10g) | 83        | 7:1 ⁷       |
| 8     | i-Bu (10h) | 92        | 3:1 ⁶        |
| 9     | Ph (10i) | 81        | 3:1 ⁷        |
| 10    | Bn (10j) | 92        | 11:2 ⁷       |
| 11    | PhCH₂CH₂ (10k) | 82        | 7:2 ⁷        |

⁷ Isolated yield of 10 starting from 6 and 7. ⁶ Ratio determined by ¹H-NMR analysis. ⁷ Ratio based on HPLC analysis.

As can be seen from Table 1, high yields and modest to high syn-selectivities were obtained for all hemi-azaketals tested. It is interesting to note that modest syn-selectivities were obtained in the case where 6 and 7 bearing i-Bu or Ph (Table 1, entries 8 and 9) as well as PhCH₂CH₂ (Table 1, entry 11).
The stereochemistry of the major diastereomer 10 was assigned to syn-conformer according to the observed vicinal coupling constants [24] ($J_{4,5} = 5.1$ Hz for syn-10a and $J_{4,5} = 4.5$ Hz for anti-10a; $J_{4,5} = 5.2$ Hz for syn-10b and $J_{4,5} = 4.3$ Hz for anti-10b; $J_{4,5} = 5.1$ Hz for syn-10c and $J_{4,5} = 4.2$ Hz for anti-10c; $J_{4,5} = 5.1$ Hz for syn-10e and $J_{4,5} = 4.4$ Hz for anti-10e; $J_{4,5} = 5.1$ Hz for syn-10g and $J_{4,5} = 4.5$ Hz for anti-10g; $J_{4,5} = 6.1$ Hz for syn-10i and $J_{4,5} = 5.1$ Hz for anti-10i). In addition, the stereochemistry of diastereomers syn-10 was confirmed by converting syn-10 to (5$S$,6$R$)-6-alkyl-5-benzyloxy-2-piperidinones 8. For example, syn-10a can be converted to anti-8a in 78% yield by mesylation (MsCl, Et$_3$N, CH$_2$Cl$_2$, $-20\,^\circ$C, 1 h) and t-BuOK-promoted cyclization (HMPA, THF, rt, 24 h) (Scheme 3).

**Scheme 3.** The synthesis of (5$S$,6$R$)-6-methyl-5-benzyloxy-2-piperidinones.

**Figure 2.** A plausible Cram chelation-controlled pathway for the syn-diastereoselective formation of syn-10.

The fact that starting from the tautomeric mixture of 6 and 7 syn-diastereomer 10 was obtained in modest to high diastereoselectivity is in accordance with a Cram model-based mechanism [30-34]. It was envisioned that the hydride to approach C-5 carbon from the same side of the chelate C-4 benzyloxy substituent led to the formation of syn-isomer because of the chelation between lithium ion and oxygen atom of the C-4 oxygen as well as C-5 carbonyl oxygen (Figure 2), which not only switches the equilibrium towards 7, but also allows the reduction to undergo with a Cram chelation-controlled manner.

### 3. Conclusions

In summary, a simple and efficient route to protected (4$S$,5$S$)-dihydroxy amides via the reduction of the tautomeric mixture of 6 and 7 with L-Selectride has been developed. This strategy offers a concise platform for the construction of (4$S$,5$S$)-dihydroxycarboxylate moieties under mild conditions. As
such, this method is complementary, in part, to our previously established anti-diastereoselective method.

4. Experimental

4.1. General methods

Melting points were determined on a Yanaco MP-500 micro melting point apparatus and are uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet technique. $^1$H-NMR spectra were recorded in CDCl$_3$ on a Bruker 400 or a Varian unity +500 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in $\delta$ (ppm) units downfield from TMS. Mass spectra were recorded with Bruker Dalton Esquire 3000 plus LC-MS apparatus. Optical rotations were measured with a Perkin-Elmer 341 automatic polarimeter. Elemental analysis was carried out on a Perkin-Elmer 240B instrument. Flash column chromatography was carried out with silica gel (300-400 mesh). THF was distilled over sodium and CH$_2$Cl$_2$ was distilled over P$_2$O$_5$ under N$_2$.

4.2. General procedure for preparation of syn-10

To a cooled (−20 °C) solution of tautomeric mixture 6/7 [20] (1.0 mol equiv) in THF (0.1 M) was added dropwise a solution of L-Selectride (1.2 mol equiv) under argon atmosphere and the mixture was stirred at −20 ~ −10 °C for 1 h. Then, the mixture was allowed to slowly warm to room temperature and was stirred at room temperature overnight. The reaction was quenched with a saturated aqueous NH$_4$Cl. After extraction with CH$_2$Cl$_2$, the combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/Petroleum ether = 1:2), some pure syn-10 and the mixture of syn-10 and anti-10 were obtained.

$(4S,5S)$-4-Benzylxyloxy-5-hydroxy-N-(4-methoxybenzyl)hexanoyl amide (syn-10a): White solid, mp: 74-75 °C; $[\alpha]^{25}_D$: +4.75 (c 1.0, CHCl$_3$); IR (film) $\nu_{max}$: 3407, 3305, 1649, 1513, 1248 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.33-7.25 (m, 5H, Ar-H), 7.15 (d, $J$ = 8.6 Hz, 2H, Ar-H), 6.83 (d, $J$ = 8.6 Hz, 2H, Ar-H), 5.60 (s, 1H, NH), 4.59 (d, $J$ = 11.5 Hz, 1H, OCH$_2$), 4.53 (d, $J$ = 11.5 Hz, 1H, OCH$_2$), 4.32 (dd, $J$ = 14.5, 5.6 Hz, 1H, NCH$_2$), 4.27 (dd, $J$ = 14.5, 5.6 Hz, 1H, NCH$_2$), 3.78 (s, 3H, OCH$_3$), 3.70 (m, 1H, H-4), 3.35 (dd, $J$ = 6.4, 5.1 Hz, 1H, H-5), 2.59 (d, $J$ = 2.8 Hz, 1H, OH), 2.25 (t, $J$ = 7.4 Hz, 2H, H-2), 2.04 (ddd, $J$ = 14.0, 7.4, 4.9 Hz, 1H, H-6), 1.82 (ddd, $J$ = 14.0, 7.4, 6.8 Hz, 1H, H-3), 1.17 (t, $J$ = 6.4 Hz, 3H, CH$_3$); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 172.4 (C=O), 158.9, 138.2, 130.3, 129.1 (2×C), 128.4 (2×C), 127.9 (2×C), 127.8, 114.0 (2×C), 82.1 (C-5), 71.9 (C-4), 68.6 (OCH$_2$), 55.2 (OCH$_3$), 43.0 (NCH$_2$), 31.6, 25.6, 18.9; MS (ESI): 358 [M+H]$^+$, 380 [M+Na]$^+$; Anal calcd for C$_{21}$H$_{27}$NO$_4$: C, 70.56; H, 7.61; N, 3.92. Found C, 70.31; H, 7.76; N, 4.25.

$(4S,5S)$-4-Benzylxyloxy-5-hydroxy-N-(4-methoxybenzyl)heptanoyl amide (syn-10b): White solid, mp: 122-124 °C; $[\alpha]^{25}_D$: +1.86 (c 1.2, CHCl$_3$); IR (film) $\nu_{max}$: 3407, 3306, 1649, 1513, 1248 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.32-7.25 (m, 5H, Ar-H), 7.15 (d, $J$ = 8.7 Hz, 2H, Ar-H), 6.83 (d, $J$ = 8.7 Hz,
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(4S,5S)-4-Benzylmyloxy-5-hydroxy-N-(4-methoxybenzyl)nonanoyl amide (syn-10c): Waxy solid; [α]<sub>D</sub> <sup>25</sup> +1.90 (c 1.5, CHCl<sub>3</sub>); IR (film) ν<sub>max</sub>: 3407, 3305, 1650, 1513, 1248 cm<sup>-1</sup>; 1H-NMR (500 MHz, CDCl<sub>3</sub>): δ 7.35-7.25 (m, 5H, Ar-H), 7.16 (d, J = 8.7 Hz, 2H, Ar-H), 6.84 (d, J = 8.7 Hz, 2H, Ar-H), 5.55 (s, 1H, NH), 4.60 (d, J = 11.5 Hz, 1H, OCH<sub>2</sub>), 4.53 (d, J = 11.5 Hz, 1H, OCH<sub>2</sub>), 4.33 (dd, J = 14.4, 5.6 Hz, 1H, NCH<sub>2</sub>), 4.28 (dd, J = 14.4, 5.6 Hz, 1H, NCH<sub>2</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.52 (m, 1H, H-4), 3.36 (ddd, J = 6.2, 5.1, 5.1 Hz, 1H, H-5) , 2.33 (s, 1H, OH), 2.26 (t, J = 7.4 Hz, 2H, H-2), 2.05 (dd, J = 14.0, 7.4, 5.2 Hz, 1H, H-3), 1.87 (ddd, J = 14.0, 7.6, 7.4 Hz, 1H, H-3), 1.52-1.40 (m, 3H), 1.36-1.25 (m, 3H), 0.89 (t, J = 7.1 Hz, 3H, CH<sub>3</sub>); 13C-NMR (125 MHz, CDCl<sub>3</sub>): δ 172.4 (C=O), 159.0, 138.2, 130.3, 129.2 (2×C), 128.4 (2×C), 127.9 (2×C), 127.8, 114.0 (2×C), 81.1 (C-5), 72.6 (C-4), 72.5 (OCH<sub>2</sub>), 55.3 (OCH<sub>3</sub>), 43.1 (NCH<sub>2</sub>), 33.1, 31.8, 27.9, 23.9, 22.7, 14.0; MS (ESI): 400 [M+H]<sup>+</sup>, 422 [M+Na]<sup>+</sup>, 438 [M+K]<sup>+</sup>; Anal calcd for C<sub>25</sub>H<sub>33</sub>NO< sub>4</sub>: C, 72.15; H, 8.33; N, 3.51. Found C, 72.34; H, 8.36; N, 3.66.

(4S,5S)-4-Benzylmyloxy-5-hydroxy-N-(4-methoxybenzyl)decanoyl amide (syn-10d): Waxy solid; [α]<sub>D</sub> <sup>25</sup> -1.76 (c 2.3, CHCl<sub>3</sub>); IR (film) ν<sub>max</sub>: 3411, 3304, 2931, 1646, 1513, 1248 cm<sup>-1</sup>; 1H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.32-7.26 (m, 5H, Ar-H), 7.15 (m, 2H, Ar-H), 6.82 (m, 2H, Ar-H), 5.85 (s, 1H, NH), 4.59 (d, J = 11.5 Hz, 1H, OCH<sub>2</sub>), 4.52 (d, J = 11.5 Hz, 1H, OCH<sub>2</sub>), 4.32 (dd, J = 14.5, 5.6 Hz, 1H, NCH<sub>2</sub>), 4.28 (dd, J = 14.5, 5.6 Hz, 1H, NCH<sub>2</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.52 (m, 1H, H-4), 3.34 (ddd, J = 5.4, 5.4, 5.2 Hz, 1H, H-5), 2.38 (d, J = 4.3 Hz, 1H, OH), 2.25 (t, J = 7.3 Hz, 2H, H-2), 2.04 (dd, J = 14.0, 7.7, 7.3 Hz, 1H, H-3), 1.87 (ddd, J = 14.0, 7.3, 7.1 Hz, 1H, H-3), 1.50-1.40 (m, 3H), 1.35-1.20 (m, 5H), 0.88 (t, J = 6.8 Hz, 3H, CH<sub>3</sub>); 13C-NMR (100 MHz, CDCl<sub>3</sub>): δ 172.4 (C=O), 159.0, 138.2, 130.4, 129.1 (2×C), 128.4 (2×C), 127.9 (2×C), 127.8, 114.0 (2×C), 81.1 (C-5), 72.6 (C-4), 72.5 (OCH<sub>2</sub>), 55.2 (OCH<sub>3</sub>), 43.0 (NCH<sub>2</sub>), 33.3, 31.8, 26.0, 25.4 (2×C), 22.6, 14.0; MS (ESI): 414 [M+H]<sup>+</sup>, 436 [M+Na]<sup>+</sup>, 458 [M+K]<sup>+</sup>; Anal calcd for C<sub>24</sub>H<sub>33</sub>NO<sub>4</sub>: C, 72.15; H, 8.33; N, 3.51. Found C, 72.34; H, 8.36; N, 3.66.

(4S,5S)-4-Benzylmyloxy-5-hydroxy-N-(4-methoxybenzyl)tridecanoyl amide (syn-10e): Waxy solid; [α]<sub>D</sub> <sup>25</sup> -2.21 (c 2.3, CHCl<sub>3</sub>); IR (film) ν<sub>max</sub>: 3406, 3304, 2926, 2854, 1646, 1513, 1249 cm<sup>-1</sup>; 1H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.34-7.25 (m, 5H, Ar-H), 7.15 (m, 2H, Ar-H), 6.84 (m, 2H, Ar-H), 5.75 (s, 1H, NH), 4.60 (d, J = 11.5 Hz, 1H, OCH<sub>2</sub>), 4.53 (d, J = 11.5 Hz, 1H, OCH<sub>2</sub>), 4.33 (dd, J = 14.4, 5.6 Hz, 1H, NCH<sub>2</sub>), 4.29 (dd, J = 14.4, 5.6 Hz, 1H, NCH<sub>2</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.51 (m, 1H, H-4), 3.36 (ddd, J = 5.6, 5.6, 5.1 Hz, 1H, H-5), 2.32-2.23 (m, 2H), 2.26 (s, 1H, OH), 2.05 (m, 1H), 1.88 (ddd, J = 14.2, 6.7, 6.7 Hz, 1H), 1.52-1.40 (m, 3H), 1.34-1.20 (m, 11H), 0.88 (t, J = 6.9 Hz, 3H, CH<sub>3</sub>); 13C-
NMR (100 MHz, CDCl₃): δ 172.4 (C=O), 159.0, 138.3, 130.4, 129.2 (2×C), 128.4 (2×C), 127.9 (2×C), 127.8, 114.0 (2×C), 81.2 (C-5), 72.7 (2×C), 72.6 (OCH₂), 55.3 (OCH₃), 43.1 (NCH₂), 33.4, 31.8 (2×C), 29.7, 29.5, 29.3, 26.0, 25.8, 22.6, 14.1; MS (ESI): 456 [M+H]+; Anal calcd for C₂₈H₄₁NO₄: C, 73.85; H, 9.01; N, 3.08. Found C, 73.59; H, 8.98; N, 3.06.

(4S,5S)-4-Benzylxy-5-hydroxy-N-(4-methoxybenzyl)heptadecanoyl amide (syn-10f): White solid, mp: 68-70 °C; [α]²⁵D: -2.63 (c 1.1, CHCl₃); IR (film) νmax: 3423, 3305, 2924, 2853, 1643, 1513, 1248 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ 7.35-7.23 (m, 5H, Ar-H), 7.16 (d, J = 8.2 Hz, 2H, Ar-H), 6.85 (d, J = 8.2 Hz, 2H, Ar-H), 5.70 (s, 1H, NH), 4.61 (d, J = 11.5 Hz, 1H, OCH₂), 4.54 (d, J = 11.5 Hz, 1H, OCH₂), 4.30 (dd, J = 14.5, 5.5 Hz, 1H, NCH₂), 4.30 (dd, J = 14.5, 5.5 Hz, 1H, NCH₂), 3.79 (s, 3H, OCH₃), 3.52 (m, 1H, H-4), 3.35 (m, 1H, H-5), 2.30-2.22 (br s, 1H, OH), 2.26 (t, J = 6.6 Hz, 3H, CH₃), 2.12 (t, J = 7.4 Hz, 2H, H-2), 1.88 (ddd, J = 14.4, 5.5 Hz, 1H, NCH₂), 1.35-1.20 (m, 3H), 1.27-1.18 (m, 1H), 0.92 (d, J = 6.7 Hz, 3H, CH₃); ¹³C-NMR (100 MHz, CDCl₃): δ 172.4 (C=O), 159.1, 138.3, 130.4, 129.2 (2×C), 128.5 (2×C), 127.9 (2×C), 127.8, 114.1 (2×C), 81.2 (C-5), 72.7 (C-4), 72.6 (OCH₂), 55.3 (OCH₃), 43.1 (NCH₂), 33.5, 31.9, 31.8, 29.7 (6×C), 29.4, 26.0, 25.8, 22.7, 14.1; MS (ESI): 512 [M+H]+, 534 [M+Na]+; Anal calcd for C₃₂H₄₉NO₄: C, 75.11; H, 9.65; N, 2.74. Found C, 75.39; H, 9.91; N, 2.86.

(4S,5S)-4-Benzylxy-5-hydroxy-N-(4-methoxybenzyl)heneicosanoyl amide (syn-10g): White solid, mp: 62-64 °C; [α]²⁵D: -1.93 (c 1.1, CHCl₃); IR (film) νmax: 3419, 3302, 2923, 2852, 1655, 1513, 1249 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ 7.33-7.27 (m, 5H, Ar-H), 7.17 (d, J = 8.6 Hz, 2H, Ar-H), 6.85 (d, J = 8.6 Hz, 2H, Ar-H), 5.65 (s, 1H, NH), 4.60 (d, J = 11.5 Hz, 1H, OCH₂), 4.54 (d, J = 11.5 Hz, 1H, OCH₂), 4.33 (dd, J = 14.4, 5.5 Hz, 1H, NCH₂), 4.30 (dd, J = 14.4, 5.5 Hz, 1H, NCH₂), 3.80 (s, 3H, OCH₃), 3.52 (m, 1H, H-4), 3.35 (m, 1H, H-5), 2.30-2.22 (br s, 1H, OH), 2.26 (t, J = 7.4 Hz, 2H, H-2), 2.05 (ddd, J = 14.1, 7.4. 7.4 Hz, 1H, H-3), 1.88 (ddd, J = 14.1, 7.4, 6.8 Hz, 1H, H-3), 1.52-1.40 (m, 3H), 1.35-1.20 (m, 27H), 0.92 (d, J = 6.7 Hz, 3H, CH₃), 0.88 (d, J = 6.7 Hz, 3H, CH₃); ¹³C-NMR (100 MHz, CDCl₃): δ 172.4 (C=O), 159.1, 138.3, 130.4, 129.2 (2×C), 128.5 (2×C), 127.9 (2×C), 127.8, 114.1 (2×C), 81.2 (C-5), 72.8 (C-4), 72.6 (OCH₂), 55.3 (OCH₃), 43.1 (NCH₂), 33.5, 31.9, 31.8, 29.7 (6×C), 29.6 (2×C), 29.4, 26.0, 25.8, 22.7, 14.1; MS (ESI): 568 [M+H]+; Anal calcd for C₃₆H₅₇NO₄: C, 76.15; H, 10.12; N, 2.47. Found C, 76.51; H, 9.91; N, 2.46.

(4S,5S)-4-Benzylxy-5-hydroxy-N-(4-methoxybenzyl)-7-methyloctanoyl amide (syn-10h): Waxy solid; [α]²⁵D: -7.34 (c 2.9, CHCl₃); IR (film) νmax: 3410, 3303, 1644, 1513, 1248 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ 7.35-7.23 (m, 5H, Ar-H), 7.15 (d, J = 8.5 Hz, 2H, Ar-H), 6.85 (d, J = 8.5 Hz, 2H, Ar-H), 5.85 (s, 1H, NH), 4.59 (d, J = 11.5 Hz, 1H, OCH₂), 4.53 (d, J = 11.5 Hz, 1H, OCH₂), 4.33 (dd, J = 14.4, 5.8 Hz, 1H, NCH₂), 4.27 (dd, J = 14.4, 5.8 Hz, 1H, NCH₂), 3.78 (s, 3H, OCH₃), 3.65-3.57 (m, 1H, H-4), 3.32 (m, 1H, H-5), 2.37 (d, J = 4.9 Hz, 1H, OH), 2.25 (t, J = 7.2 Hz, 2H, H-2), 2.08-1.98 (m, 1H), 1.93-1.75 (m, 2H), 1.48-1.38 (m, 1H), 1.27-1.18 (m, 1H), 0.92 (d, J = 6.7 Hz, 3H, CH₃), 0.88 (d, J = 6.7 Hz, 3H, CH₃); ¹³C-NMR (100 MHz, CDCl₃): δ 172.4 (C=O), 158.9, 138.2, 130.3, 129.1 (2×C), 128.4 (2×C), 127.9 (2×C), 127.8, 114.0 (2×C), 81.6 (C-5), 72.6 (C-4), 70.6 (OCH₂), 55.2 (OCH₃), 43.0 (NCH₂), 42.3, 31.8, 25.9, 24.5, 23.6, 21.7; MS (ESI): 400 [M+H]+, 422 [M+Na]+, 438 [M+K]+; Anal calcd for C₂₈H₄₃NO₄: C, 72.15; H, 8.33; N, 3.51. Found C, 72.19; H, 8.16; N, 3.29.
(4S,5S)-4-Benzoyloxy-5-hydroxy-N-(4-methoxybenzyl)-5-phenylpentanoyl amide (syn-10i): White solid, mp: 45-47 °C; [α]$_D^{25}$ +14.09 (c 2.7, CHCl$_3$); IR (film) $\nu_{max}$: 3411, 3307, 1655, 1512, 1249 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.36-7.23 (m, 10H, Ar-H), 7.15 (d, J = 8.6 Hz, 2H, Ar-H), 6.86 (d, J = 8.6 Hz, 2H, Ar-H), 5.52 (s, 1H, NH), 4.83 (d, J = 6.1 Hz, 1H, H-5), 4.51 (d, J = 11.5 Hz, 1H, OCH$_2$), 4.46 (d, J = 11.5 Hz, 1H, OCH$_2$), 4.28 (dd, J = 14.4, 5.6 Hz, 1H, NCH$_2$), 4.22 (dd, J = 14.4, 5.6 Hz, 1H, OCH$_2$), 3.77 (s, 3H, OCH$_3$), 3.63 (ddd, J = 6.3, 6.1, 5.2 Hz, 1H, H-4), 3.06 (d, J = 4.0 Hz, 1H, OH), 2.13 (t, J = 7.6 Hz, 2H, H-2), 1.90 (m, 1H, H-3), 1.78 (m, 1H, H-3); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 172.3 (C=O), 159.0, 141.1, 138.0, 130.4, 129.2 (2×C), 128.5 (2×C), 128.3 (2×C), 128.1 (2×C), 127.9 (2×C), 126.8 (2×C), 114.1 (2×C), 82.6 (C-5), 75.8 (C-4), 72.0 (OCH$_2$), 55.3 (OCH$_3$), 43.1 (NCH$_2$), 32.0, 26.5; MS (ESI): 420 [M+H]$^+$, 442 [M+Na]$^+$, 458 [M+K]$^+$; Anal calcd for C$_{26}$H$_{29}$NO$_4$: C, 74.44; H, 6.97; N, 3.34. Found C, 74.49; H, 6.82; N, 3.59.

(4S,5S)-4-Benzoyloxy-5-hydroxy-N-(4-methoxybenzyl)-6-phenylhexanoyl amide (syn-10j): Waxy solid; [α]$_D^{25}$ +2.01 (c 2.6, CHCl$_3$); IR (film) $\nu_{max}$: 3403, 3305, 1644, 1513, 1248, 1030 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.35-7.23 (m, 8H, Ar-H), 7.17-7.12 (m, 4H, Ar-H), 6.83 (d, J = 8.7 Hz, 2H, Ar-H), 5.55 (s, 1H, NH), 4.61 (d, J = 11.5 Hz, 1H, OCH$_2$), 4.54 (d, J = 11.5 Hz, 1H, OCH$_2$), 4.30 (dd, J = 14.5, 5.6 Hz, 1H, NCH$_2$), 4.25 (dd, J = 14.5, 5.6 Hz, 1H, NCH$_2$), 3.82-3.75 (m, 1H, H-4), 3.75 (s, 3H, OCH$_3$), 3.39 (ddd, J = 5.8, 5.8, 5.1 Hz, 1H, H-5), 2.85 (dd, J = 13.8, 4.8 Hz, 1H, H-6), 2.75 (dd, J = 13.8, 8.3 Hz, 1H, H-6), 2.45 (d, J = 5.8 Hz, 1H, OH), 2.23 (t, J = 7.3 Hz, 2H, H-2), 2.07 (dd, J = 14.0, 7.3, 5.6 Hz, 1H, H-3), 1.93 (ddd, J = 14.0, 7.0, 7.0 Hz, 1H, H-3); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 172.4 (C=O), 158.9, 138.6, 138.2, 130.3, 129.3 (2×C), 129.1 (2×C), 128.4 (4×C), 128.0 (2×C), 127.8, 126.3, 114.0 (2×C), 79.8 (C-5), 73.6 (C-4), 72.2 (OCH$_2$), 55.2 (OCH$_3$), 43.0 (NCH$_2$), 39.7, 31.9, 25.7; MS (ESI): 434 [M+H]$^+$, 456 [M+Na]$^+$, 472 [M+K]$^+$; Anal calcd for C$_{27}$H$_{31}$NO$_4$: C, 74.80; H, 7.21; N, 3.23. Found C, 74.83; H, 7.55; N, 3.28.

(4S,5S)-4-Benzoyloxy-5-hydroxy-N-(4-methoxybenzyl)-7-phenylheptanoyl amide (syn-10k): Waxy solid; [α]$_D^{25}$ -7.35 (c 1.9, CHCl$_3$); IR (film) $\nu_{max}$: 3411, 3306 2932, 1645, 1513, 1248, 1030 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.40-7.20 (m, 10H, Ar-H), 7.15 (d, J = 11.5 Hz, 1H, OCH$_2$), 4.61 (d, J = 11.5 Hz, 1H, OCH$_2$), 4.54 (d, J = 11.5 Hz, 1H, OCH$_2$), 4.30 (dd, J = 14.5, 5.6 Hz, 1H, NCH$_2$), 4.25 (dd, J = 14.5, 5.6 Hz, 1H, NCH$_2$), 3.82-3.75 (m, 1H, H-4), 3.75 (s, 3H, OCH$_3$), 3.39 (ddd, J = 5.8, 5.8, 5.1 Hz, 1H, H-5), 2.85 (dd, J = 13.8, 4.8 Hz, 1H, H-6), 2.75 (dd, J = 13.8, 8.3 Hz, 1H, H-6), 2.45 (d, J = 5.8 Hz, 1H, OH), 2.23 (t, J = 7.3 Hz, 2H, H-2), 2.07 (dd, J = 14.0, 7.3, 5.6 Hz, 1H, H-3), 1.93 (ddd, J = 14.0, 7.0, 7.0 Hz, 1H, H-3); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 172.9 (C=O), 158.9, 138.6, 138.2, 130.3, 129.3 (2×C), 129.1 (2×C), 128.4 (4×C), 128.0 (2×C), 127.8, 126.3, 114.0 (2×C), 79.8 (C-5), 73.6 (C-4), 72.2 (OCH$_2$), 55.2 (OCH$_3$), 43.0 (NCH$_2$), 39.7, 31.9, 25.7; MS (ESI): 434 [M+H]$^+$, 456 [M+Na]$^+$, 472 [M+K]$^+$; Anal calcd for C$_{28}$H$_{33}$NO$_4$: C, 74.80; H, 7.21; N, 3.23. Found C, 74.83; H, 7.55; N, 3.28.

4.3. The synthesis of (5S,6R)-2-Piperidinone 8a via the cyclization of 10a

To a cooled (−20 °C) solution of a mixture of 10a (182 mg, 0.51 mmol) and Et$_3$N (0.14 mL, 1.00 mmol) in CH$_2$Cl$_2$ (5 mL) was added dropwise MsCl (0.047 mL, 0.61 mmol) under a nitrogen
atmosphere. The mixture was stirred at $-20 \sim -10 \, ^\circ C$ for 1 h. Water was added and the aqueous layer was separated and extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/P.E. = 1:2) to yield the mesylate 11 (202 mg), which is unstable and was used immediately in the next step. To a solution of mesylate 11 (202 mg, 0.43 mmol) in THF (3 mL) and HMPA (0.15 mL, 0.86 mmol) was added dropwise a solution of potassium tert-butoxide (58 mg, 0.52 mmol) in THF (2 mL) at 0 $^\circ C$ under nitrogen atmosphere. The mixture was allowed slowly warming to room temperature and was stirred for 24 h. The reaction was quenched with saturated NH$_4$Cl at 0 $^\circ C$. The aqueous layer was separated and extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent EtOAc/P.E. = 1:2) to yield (5$S$,6$R$)-8a (135 mg, 78% yield). For the data of (5$S$,6$R$)-8a see [20].

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Sample Availability: Samples of the compounds 10a-10k are available from the authors.

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