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Asymmetric syntheses of (−)-*epi*-pseudoconhydrine and (−)-5-hydroxysedamine based on a *cis*-diastereoselective 1,4-asymmetric induction

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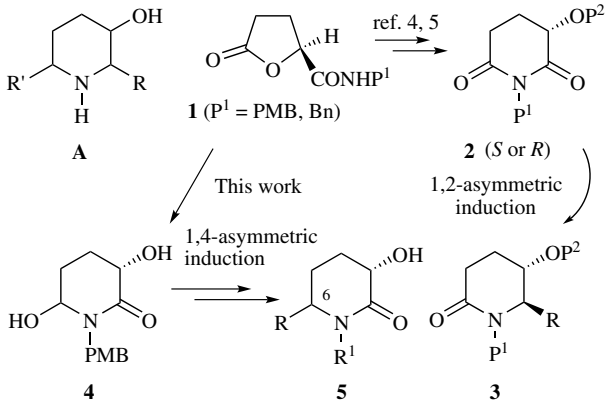
ABSTRACT

The asymmetric syntheses of (−)-*epi*-pseudoconhydrine and (−)-5-hydroxysedamine are reported. The key to these syntheses is an unusual highly *cis*-diastereoselective 1,4-asymmetric induction in the α-amidoallylation of the new chiral building block **15**.

1. Introduction

Due to the presence of the 6-substituted 3-piperidinol (**A** in Scheme 1) as a salient structural feature in a number of bioactive natural products and medicinal agents,[1,2] the asymmetric synthesis of 6-substituted 3-piperidinol containing natural and unnatural bioactive molecules has attracted considerable attention, which has culminated in a number of valuable synthetic strategies.[3] Previously, we had demonstrated that the protected 3-hydroxyglutarimides **2**, easily available from enantiomeric glutamic acid via amido-lactone **1**, can serve as a valuable 3-piperidiol synthon via the C-2 regio- and diastereoselective reductive alkylation of **2** (Scheme 1).[4] Using this method, the asymmetric syntheses of several alkaloids and interesting medicinal agents have been accomplished.[5]

As a continuation of these studies, we sought to explore compound **4** as a new 3-piperidinol building block, which would allow the regioselective introduction of substituents at the C-6 position to provide 6-substituted 3-hydroxypiperidin-2-ones **5** and the corresponding piperidines **A**. The latter is a framework of a number of natural products, such as (+)-pseudoconhydrine[6,7] **6**, (−)-5-hydroxysedamine[8,9] **7**, 5-hydroxypipecolic acid[10] **8**, (−)-cassine[11] **9**, (−)-spectaline[12] **10**, and (−)-prosopinine[13] **11** (Fig. 1). In addition, *cis*-2-carboxymethyl-5-hydroxypiperidine[14] **12** has been considered as a key intermediate for the synthesis of antibiotic 593A, a natural product possessing strong antiviral and antitumor activities.[15] Although a number of 2,5-*trans*-diastereoselective methods have been reported for the synthesis[7] of (+)-pseudoconhydrine **6**, establishment of the 2,5-*cis*-stereochemistry[7a,8,11–13,16] by α-amidoalkylation[17] with high 1,4-asymmetric induction remains a challenging task. For example, in the only asymmetric synthesis of (−)-5-hydroxysedamine **7**, the desired *cis*-diastereomer was formed as the minor diastereomer in 1:9 ratio.[7m] The α-amidoallylation-based approaches to pseudoconhydrine always proceed with *trans*-diastereoselectivity.[7d,l,m] *trans*-Diastereoselection has also been observed in related radical reactions.[7p] Herein we report the synthesis of **15**, its *cis*-diastereoselective α-amidoalkylation with 1,4-asymmetric induction, as well as the asymmetric synthesis of *epi*-pseudoconhydrine[16] **18** and (−)-5-hydroxysedamine[8,9] **7**.



Scheme 1.

2. Results and discussion

As outlined in Scheme 2, we sought to take advantage of the higher reactivity of the lactone carbonyl group of amido-lactone **1** by chemoselective partial reduction with DIBAL-H. The amido-lactol **13** was envisioned to be elaborated further into 6-substituted 3-piperidinol or 6-substituted 3-hydroxypiperidin-2-one **5**. However when lactone-amide **1** was treated with DIBAL-H at −78 °C, **13** was obtained in only 9% yield. A stepwise approach to **4** was then explored.

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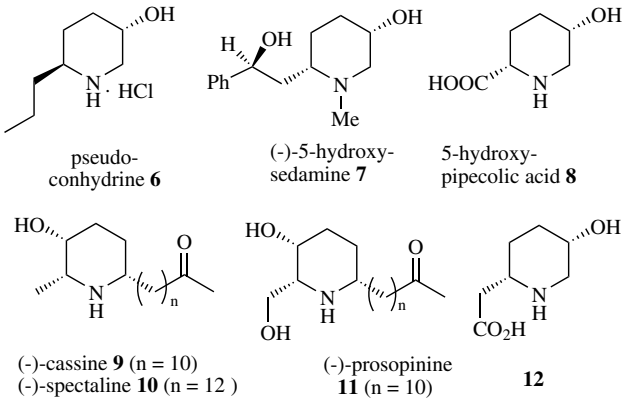
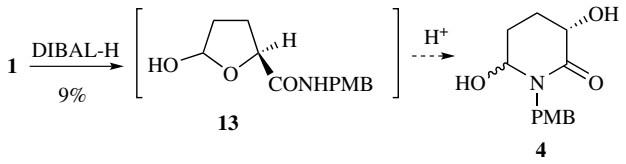
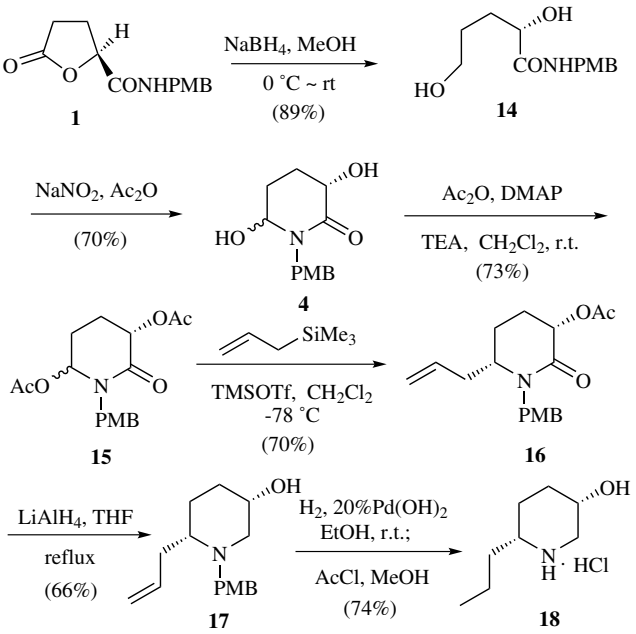


Figure 1.



Scheme 2.



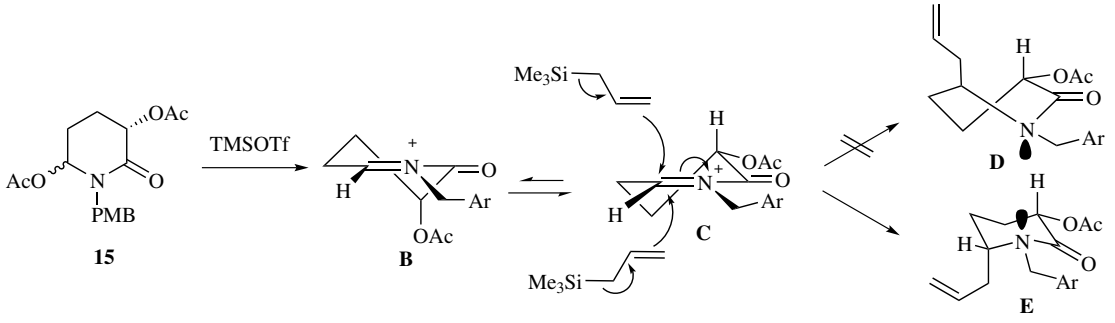
Scheme 3.

The synthesis started from the reduction[18] of the amido-ester **1** by sodium borohydride (Scheme 3). Chemoselective oxidation of the primary hydroxyl group of diol **14** under Bandgar's conditions[19] directly provided the tautomer **4** as a 1:1 diastereomeric mixture in 70% yield. As the acetyl group has been shown to be an excellent neighboring participating group in inducing *trans*-diastereoselective α-amidoallylation,[7d,20] *N*,*O*-acetal **15** was selected as the substrate for investigating α-amidoalkylation.[17] Thus, compound **4** was bis-acetylated (Ac_2O, NEt_3, DMAP, CH_2Cl_2, rt, 24 h) to provide a diastereomeric mixture of 2-piperidinone *N*,*O*-acetal **15**. Due to the lability of **15** and more importantly, on the basis of the consideration that the α-amidoalkylation[17] generally occurs via an *N*-acyliminium intermediate that can be generated from either diastereomer, the diastereomeric mixture of *N*,*O*-acetal **15** was subjected to α-amidoallylation conditions (allyltrimethylsilane, THF, TMSOTf, −78 °C). Indeed, the desired product **16** was obtained as the only isolable diastereomer in 70% yield. The stereochemistry of **16** was determined by ultimate conversion of **16** into the known *epi*-pseudoconhydrine[16] **18** (Scheme 3). Lithium aluminum hydride reduction of **16** ($LiAlH_4$, THF, reflux, 5 h) furnished the corresponding piperidine **17** in 66% yield. Concurrent hydrogenation and *N*-deprotection [$Pd(OH)_2$, 1 atm H_2, EtOH, rt] gave (−)-*epi*-pseudoconhydrine **18**, which was isolated as its hydrochloride salt[16] in 74% yield. The melting point [mp 148.0–148.5 °C (MeOH/Et_2O); lit.[7m] mp 148 °C], specific rotation value {$[\alpha]_D^{20} = -10.2$ (*c* 1.0, EtOH); lit.[7m] $[\alpha]_D^{20} = -9.1$ (*c* 1.0, EtOH)}, and the spectral data of our synthetic material are identical with those reported.[7m]

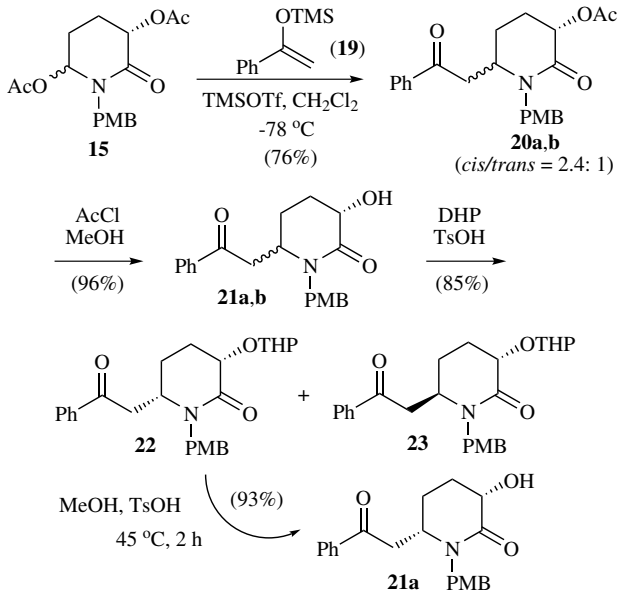
The stereochemical outcome of the α-amidoallylation may be due to, on one hand, the difficulty in forming a bicyclic oxonium intermediate of the more rigid piperidin-2-one ring system,[21] and, on the other hand, the preferential formation of half-chair conformer **C** over conformer **B** (Scheme 4). The allylation of conformer **C** proceeds with stereoelectronic control[22] to give the more favorable chair conformation **E** over twist-boat one **D**.

Next, we turned our attention to the synthesis of (−)-5-hydroxysedamine **7**. Thus, in the presence of TMSOTf, treatment of 1-phenyl-1-(trimethylsilyloxy)ethene **19** with **15** at −78 °C furnished the desired product **20a**,**b** with a 2.4:1 (*cis*/*trans*) diastereoselectivity (Scheme 5). The two inseparable diastereomers **20a** and **20b** were converted, via **21a**,**b**, into the corresponding THP derivatives **22** and **23**, which were easily separated by flash chromatography. Treatment of the major diastereomer **22** with *p*-TsOH in methanol at 45 °C regenerated the alcohol **21a** in 93% yield.

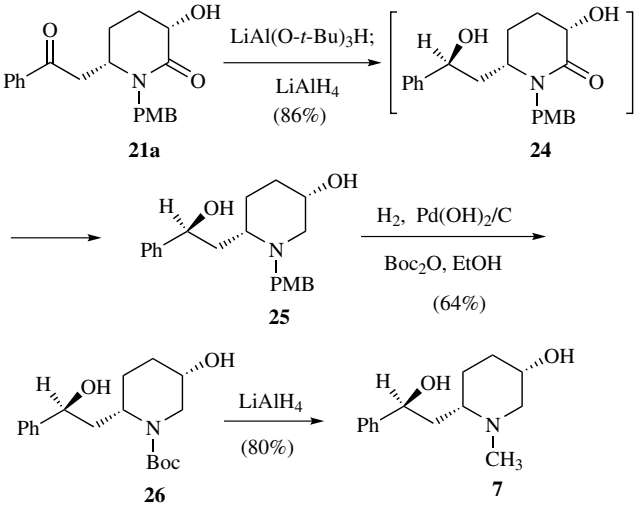
One-pot reduction of the ketone and amide carbonyl groups in **21a** was achieved by successive treatment of **21a** with LiAl(O-*t*-Bu)$_3$H[7m] and lithium aluminum hydride, which gave 5-hydroxysedamine derivative **25** as the only isolable diastereomer in 86% overall yield (Scheme 6). The stereochemistry of compound **25**



Scheme 4.



Scheme 5.



Scheme 6.

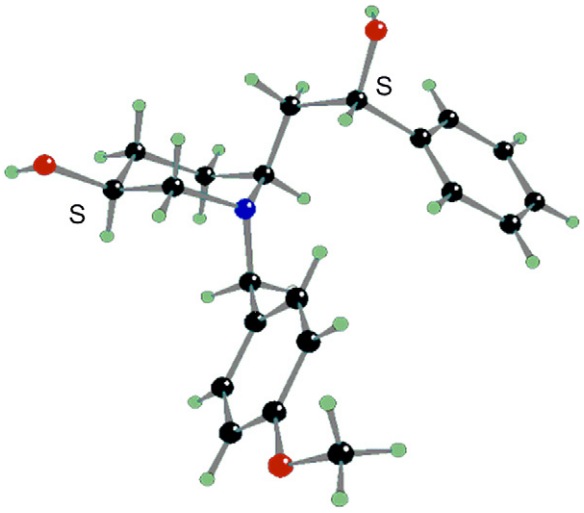
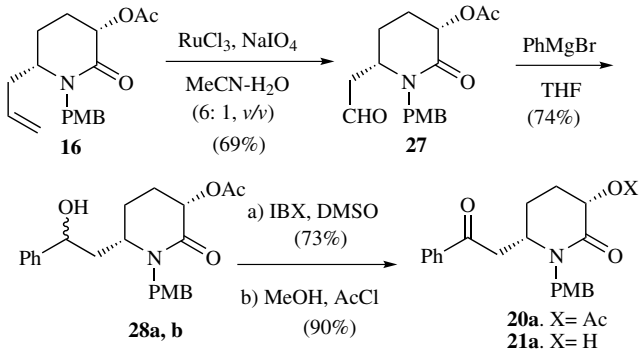


Figure 2. X-ray crystallographic structure of compound **25** (CCDC 673124).



Scheme 7.

was determined by single crystal crystallographic analysis (Fig. 2). The results imply that the major product in the α-amidoalkylation of *N*,*O*-acetal **15** is the *cis*-diastereomer, and the reduction of the ketone **21a** with LiAl(O-*t*-Bu)$_3$H[7m] is highly diastereoselective with the approach of hydride from the less hindered *Re*-face of the carbonyl group.[7m]

To introduce the *N*-methyl group, piperidine **25** was first converted to its *N*-*tert*-Boc derivative **26** by one-pot debenzylation–carbamation [H_2, 1 atm, 20% $Pd(OH)_2$/C, $(Boc)_2O$, EtOH], which led directly to **26** in 64% yield. Then the *N*-Boc group was converted into a *N*-Me group by reducing with lithium aluminum hydride to afford (−)-5-hydroxysedamine **7** {$[\alpha]_D^{20} = -53.4$ (*c* 0.5, MeOH); lit.[8] $[\alpha]_D^{22} = -40$ (*c* 0.3, MeOH), lit.[7f] $[\alpha]_D^{20} = -53$ (*c* 0.3, MeOH); lit.[7m] $[\alpha]_D^{20} = -51.0$ (*c* 2.5, MeOH)} in 80% yield. The ^{1}H and ^{13}C NMR spectral data of our synthetic material are identical with those reported.[8]

To overcome the problem of low stereoselectivity in the formation of compound **20a**, a three-step procedure was developed starting from the allylation products **16** (Scheme 7). Thus Yang's procedure[23] was adopted for the oxidative cleavage of the C–C double bond in compound **16**, which gave the aldehyde **27** in 69% yield. Treatment of the aldehyde **27** with phenyl magnesium bromide produced the alcohol **28** as a diastereomeric mixture in 2.5:1 ratio (combined yield: 74%), which, without separation, was oxidized with *o*-iodoxybenzoic acid (IBX) in DMSO.[24] In this way, compound **20a** was obtained in 73% yield. Treatment of **20a** with a solution of acetyl chloride-containing methanol at room temperature overnight furnished alcohol **21a** in 90% yield, which thus established a highly diastereoselective synthesis of (−)-5-hydroxysedamine **7** via **16**.

3. Conclusions

In summary, we have shown that, in contrast with the generally observed *trans*-diastereoselection in the α-amidoalkylation of *N*,*O*-acetal of piperidine carbamate derivatives, the α-amidoallylation of 2-piperidinone *N*,*O*-acetal **15** is highly *cis*-diastereoselective, affording *cis*-**16** as the only isolable diastereomer; and the similar reaction of **15** with **19** proceeded with a 2.4:1 *cis*/*trans* diastereoselectivity, which is also different from the literature precedents. The observed *cis*-diastereoselective 1,4-asymmetric induction provides an entry into *cis*-6-substituted 3-piperidinol **A**, a skeleton found in several natural products and medicinal agents. The utility of the *cis*-diastereoselective allylation method was demonstrated by the synthesis of (−)-*epi*-pseudoconhydrine **18** and (−)-5-hydroxysedamine **7**. Compound **16** may also be useful for the

synthesis of β-amino acid **12**, a key intermediate for the synthesis of antiviral and antineoplastic antibiotic 593A.

4. Experimental

4.1. General

Melting points were determined (uncorrected) on a Yanaco MP-500 micro-melting point apparatus. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer. NMR spectra were recorded in $CDCl_3$ or in CD_3CN, or in CD_3OD (^1H at 400 or 500 MHz and ^{13}C at 100 or 125 MHz) at room temperature. Mass spectra were recorded on Bruker Dalton Esquire 3000 plus LC–MS (ESI direct injection). Optical rotations were measured with Perkin–Elmer 341 automatic polarimeter. THF used in the reactions was dried by distilling over metallic sodium; dichloromethane was distilled over P_2O_5. Silica gel (Zhifu, 300–400 mesh) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (60–90 °C) mixtures.

4.1.1. (*S*)-*N*-(4-Methoxybenzyl)-2,5-dihydroxypentanamide 14

To a solution of amido-lactone **1** (2.978 g, 11.96 mmol) in MeOH (20 mL) was added $NaBH_4$ (1.363 g, 35.88 mmol) at 0 °C. The mixture was allowed to warm to rt and stirred for 1 h. The reaction was quenched with 10 mL of saturated aqueous $NaHCO_3$ solution and 10 mL of brine at 0 °C. MeOH was removed under reduced pressure. The residue was diluted with water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/MeOH (10:1) to give **14** as a white solid (2.693 g, yield: 89%). Mp 103 °C (EtOAc/PE); $[\alpha]_D^{20} = -23.8$ (*c* 1.0, CH_3OH); IR (film) 3377, 3302, 1610, 1515, 1315, 1108 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.60–1.72 (m, 3H, CH_2CH_2), 1.78–1.93 (m, 1H, CH_2CH_2), 3.61 (t, *J* = 6.3 Hz, 2H, CH_2OH), 3.80 (s, 3H, OCH_3), 4.08 (dd, *J* = 7.0, 3.7 Hz, 1H, COCH), 4.38 (s, 2H, $ArCH_2$), 6.84–6.89 (m, 2H, ArH), 7.19–7.25 (m, 2H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 29.3, 32.5, 43.1, 55.6, 55.7, 62.7, 72.7, 114.9, 129.9, 131.9, 160.4, 177.0 ppm; MS (ESI) *m*/*z* 276 ($M+Na^+$, 100). Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.48; H, 7.50; N, 5.47.

4.1.2. (3*S*,6*R*/*S*)-1-(4-Methoxybenzyl)-3,6-dihydroxypiperidin-2-one 4

To a suspension of diol **14** (500 mg, 1.98 mmol) and $NaNO_2$ (410 mg, 5.94 mmol) in CH_2Cl_2 (5 mL) was added Ac_2O (0.3 mL, 2.97 mmol). After stirring at room temperature for 20 min, the mixture was extracted with ether (2 × 10 mL). The combined organic layers were washed with 5 mL of saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (2:1) to afford **4** (colorless oil, 347 mg, yield: 70%) as a inseparable mixture of two diastereomers in a 1:1 ratio, which was used in the next step without further separation. IR (film) 3373, 1644, 1511, 1246, 1038 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 1.48–2.21 (m, 8H, CH_2CH_2), 2.36 (s, 1H, OH), 3.78 (s, 6H, OCH_3), 3.92 (s, 1H, OH), 3.94 (dd, *J* = 10.2, 7.2 Hz, 1H, NCOCH), 4.03 (d, *J* = 14.9 Hz, 1H, $ArCH_2$), 4.05 (dd, *J* = 14.3, 7.1 Hz, 1H, NCOCH), 4.27 (d, *J* = 14.4 Hz, 1H, $ArCH_2$), 4.24–4.31 (m, 1H, NCH), 4.81 (d, *J* = 14.4 Hz, 1H, $ArCH_2$), 4.75–4.87 (m, 1H, NCH), 5.03 (d, *J* = 14.9 Hz, 1H, $ArCH_2$), 6.83–6.90 (m, 4H, ArH), 7.18–7.24 (m, 4H, ArH) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 24.3, 26.5, 29.1, 29.4, 46.1, 47.0, 55.8 (2C), 68.3, 69.3, 79.3, 80.3, 114.6 (2C), 130.0 (2C), 130.6, 130.7, 159.7, 159.8, 173.6, 173.9 ppm; MS (ESI) *m*/*z*: 274 ($M+Na^+$, 100); HRMS (ESI) calcd for $[C_{13}H_{17}NO_4+H]^+$ 252.1230, found 252.1232.

4.1.3. (3*S*,6*R*/*S*)-3,6-Diacetoxy-1-(4-methoxybenzyl)-2-piperidinone 15

To an ice-bath cooled solution of the diastereomeric mixture of **4** (2.075 g, 8.27 mmol) in CH_2Cl_2 were added successively DMAP (1.052 g, 8.62 mmol), Ac_2O (4.0 mL, 42.25 mmol), and Et_3N (5.9 mL, 42.25 mmol). The mixture was stirred at room temperature overnight. The reaction was quenched with 10 mL of saturated aqueous $NaHCO_3$ solution and 10 mL of water at 0 °C. The organic layer was seperated and the aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (1:1) to afford **15** (colorless oil, 2.022 g, yield: 73%) as an inseparable mixture of two diastereomers in a 2.5:1 ratio, which was used in the next step without further separation. IR (film) 1743, 1677, 1515, 1370, 1229, 1174 cm^{-1}; ^1H NMR (400 MHz, CD_3CN, two diastereomers, **15a/15b** = 2.5:1, data read from the spectrum of the diastereomeric mixture). Compound **15a**: δ 1.76–2.22 (m, 4H, CH_2CH_2), 1.84 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$), 3.69 (s, 3H, OCH_3), 4.09 (d, *J* = 14.9 Hz, 1H, ArCH), 4.70 (d, *J* = 14.9 Hz, 1H, ArCH), 5.26 (dd, *J* = 12.3, 6.2 Hz, 1H, NCOCH), 5.88 (m, 1H, NCH), 6.77–6.85 (m, 2H, ArH), 7.07–7.15 (m, 2H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 21.1, 23.4, 26.7, 48.4, 55.8, 69.7, 81.3, 114.7, 118.3, 130.4, 160.0, 169.2, 170.7, 170.9 ppm. Compound **15b**: δ 1.76–2.22 (m, 4H, CH_2CH_2), 1.86 (s, 3H, $COCH_3$), 2.01 (s, 3H, $COCH_3$), 3.69 (s, 3H, $ArOCH_3$), 4.16 (d, *J* = 14.9 Hz, 1H, $ArCH_2$), 4.68 (d, *J* = 14.9 Hz, 1H, $ArCH_2$), 5.28 (dd, *J* = 12.3, 6.2 Hz, 1H, NCOCH), 5.94 (m, 1H, NCH), 6.77–6.85 (m, 2H, ArH), 7.07–7.15 (m, 2H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 21.2, 23.6, 25.3, 48.3, 55.8, 69.1, 81.2, 114.8, 118.3, 129.9, 130.3, 168.5, 170.6, 170.9 ppm; MS (ESI) *m*/*z* 358 ($M+Na^+$, 100); HRMS (ESI) calcd for $[C_{17}H_{21}NO_6+H]^+$ 336.1442, found 336.1441.

4.1.4. (3*S*,6*S*)-6-Allyl-1-(4-methoxybenzyl)-2-oxo-piperidin-3-yl acetate 16

To a cooled (−78 °C) diastereomeric mixture of **15** (1.030 g, 3.07 mmol) and allyltrimethylsilane (1.0 mL, 6.15 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dropwise TMSOTf (0.7 mL, 4.61 mmol) over a period of 15 min. The mixture was stirred for 4 h at the same temperature and then quenched with 5 mL of saturated aqueous $NaHCO_3$ solution. The mixture was warmed up and an additional 5 mL of water was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (1:1) to afford **16** (682 mg, yield: 70%) as a pale yellow oil. $[\alpha]_D^{20} = +44.0$ (*c* 1.0, $CHCl_3$); IR (film) 3075, 2953, 2837, 1744, 1656, 1613, 1513, 1457, 1373, 1303, 1241, 1211, 1176, 1085, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.65–1.70 (m, 2H, CH_2CH_2), 1.83–2.05 (m, 2H, CH_2CH_2), 2.08 (s, 3H, $COCH_3$), 2.20–2.30 (m, 1H, $=CHCH_2$), 2.44–2.50 (m, 1H, $=CHCH_2$), 3.22–3.28 (m, 1H, NCH), 3.72 (s, 3H, OCH_3), 3.80 (d, *J* = 15.0 Hz, 1H, $ArCH_2$), 5.00–5.08 (m, 2H, $=CH_2$), 5.16 (dd, *J* = 7.0, 10.5 Hz, 1H, COCH), 5.24 (d, *J* = 15.0 Hz, 1H, $ArCH_2$), 5.50–5.60 (m, 1H, =CH), 6.76–7.11 (m, 4H, ArH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 22.8, 23.3, 36.2, 47.3, 54.4, 55.2, 69.4, 114.0, 118.4, 129.0, 129.4, 134.0, 159.0, 167.2, 170.3 ppm; MS (ESI) *m*/*z* 340 ($M+Na^+$, 100). Anal. Calcd for $C_{18}H_{23}NO_4$ C, 68.12; H, 7.30; N, 4.41. Found: C, 68.53; H, 7.24; N, 4.27.

4.1.5. (2*R*,5*S*)-2-Allyl-5-hydroxyl-1-(4-methoxybenzyl)-piperidine 17

A suspension of **16** (678 mg, 2.14 mmol) and $LiAlH_4$ (406 mg, 10.69 mmol) in THF (12 mL) was refluxed for 5 h. After cooling to 0 °C, the mixture was diluted with Et_2O (40 mL) and quenched by careful addition of solid $Na_2SO_4{\cdot}10H_2O$. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether/aqueous NH_3 (1:2:0.01) to afford **17** (368 mg, yield: 66%) as a colorless oil. $[\alpha]_D^{20} = -73.9$ (*c* 1.1, $CHCl_3$); IR (film) 3391, 3072, 2931, 2855, 2796, 1639, 1611, 1584, 1511, 1457, 1245, 1176, 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.46–1.58 (m, 2H, CH_2CH_2), 1.68–1.77 (m, 2H, CH_2CH_2), 2.16 (dd, J = 1.7, 11.6 Hz, 1H, NCH_2), 2.35–2.44 (m, 3H, =CHCH_2, NCH_2), 2.40 (s br, 1H, OH, D_2O exchangeable), 2.69–2.75 (m, 1H, NCH), 3.17 (d, J = 13.1 Hz, 1H, $ArCH_2$), 3.73–3.75 (m, 1H, C*H*OH), 3.80 (s, 3H, OCH_3), 4.02 (d, J = 13.1 Hz, 1H, $ArCH_2$), 5.08–5.11 (m, 2H, $=CH_2$), 5.82–5.92 (m, 1H, =CH), 6.82–7.22 (m, 4H, ArH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.8, 30.4, 36.0, 55.2, 56.8, 57.0, 60.0, 65.4, 113.7 (2C), 116.9, 129.9 (2C), 130.8, 135.1, 158.6 ppm; MS (ESI) m/z 262 ($M+H^+$, 100); HRMS (ESI) calcd for $[C_{16}H_{23}NO_2+H]^+$ 262.1802, found 262.1807.

4.1.6. (−)-(2*R*,5*S*)-*epi*-Pseudoconhydrine hydrochloride salt 18

A suspension of **17** (151 mg, 0.58 mmol) and 20% $Pd(OH)_2/C$ (38 mg) in EtOH (6 mL) was stirred under an atmosphere of H_2 for 24 h. The catalyst was filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in water (5 mL) and the pH was adjusted to 1 with 1 M HCl. The mixture was washed with Et_2O (3 mL). The pH was re-adjusted to 14 with a 2 M NaOH solution, and the mixture was extracted with $CHCl_3$ (5 × 4 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in 3 mL of MeOH/AcCl (10:1) and concentrated under reduced pressure. The residue was crystallized from MeOH/Et_2O to afford hydrochloride salt of **18** (77 mg, yield: 74%) as white crystals. Mp 148–148.5 °C (MeOH/Et_2O) [lit.[7m] Mp 148 °C]; $[\alpha]_D^{20} = -10.2$ (*c* 1.0, EtOH) {lit.[7m] $[\alpha]_D^{20} = -9.1$ (*c* 1.0, EtOH)}; IR (KBr) 3411, 2958, 2933, 2871, 2821, 2717, 2542, 2393, 1566, 1442, 1086, 1037 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.96 (t, J = 7.2 Hz, 3H, CH_3), 1.30–1.90 (m, 8H, CH_2CH_2), 3.00–3.30 (m, 3H, NCH, NCH_2), 4.07 (s, 1H, C*H*OH) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 14.1, 19.4, 24.3, 29.7, 36.8, 51.0, 57.9, 62.3 ppm; MS (ESI) m/z 144 ($M+H^+$, 100); HRMS (ESI) calcd for $[C_8H_{17}NO+H]^+$ 144.1383, found 144.1385.

4.1.7. (3*S*,6*R*/*S*)-1-(4-Methoxybenzyl)-6-(2-oxo-2-phenylethyl)-2-oxopiperidin-3-yl acetate 20

To a cooled (−78 °C) solution of 1-phenyl-1-(trimethylsilyloxy)ethene **19** (1.3 mL, 6.10 mmol) and **15** (687 mg, 2.05 mmol) in anhydrous CH_2Cl_2 (8 mL) was added dropwise TMSOTf (0.4 mL, 2.20 mmol). After being stirred for 4 h, the reaction was quenched with 4 mL of saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). 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 chromatography on silica gel eluting with EtOAc/petroleum ether (1:2) to give **20** (colorless oil, 615 mg, yield: 76%) as an inseparable diastereomeric mixture in 2.4:1 ratio. IR (KBr) ν_{max}: 2941, 1744, 1652, 1516, 1453, 1366, 1246, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, two diastereomers, **20a**/**20b** = 2.4:1, data read from the spectrum of the diastereomeric mixture). Compound **20a**: δ 1.80–2.04 (m, 4H, CH_2CH_2), 2.18 (s, 3H, $COCH_3$) 3.30–3.36 (m, 2H, $COCH_2$), 3.76 (s, 3H, OCH_3), 4.00 (d, J = 14.7 Hz, 1H, $ArCH_2$), 4.08–4.20 (m, 1H, NCH), 5.09 (d, J = 14.7 Hz, 1H, $ArCH_2$), 5.13 (dd, J = 7.3, 10.6 Hz, 1H, NCOCH), 6.79–6.84 (m, 2H, ArH), 7.18–7.21 (m, 2H, ArH), 7.42–7.50 (m, 2H, ArH), 7.52–7.61 (m, 1H, ArH), 7.85–7.92 (m, 2H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 23.0, 25.0, 40.5, 47.9, 51.6, 55.0, 69.6, 113.9, 127.8, 128.8, 129.32, 133.43, 136.2, 158.9, 167.5, 170.1, 197.3 ppm. Compound **20b**: δ 1.64–2.34 (m, 4H, CH_2CH_2), 3.12 (dd, J = 8.8, 17.2 Hz, 1H, $COCH_2$), 3.29 (dd, J = 3.7, 17.2 Hz, 1H, $COCH_2$), 3.76 (s, 3H, OCH_3), 4.08–4.20 (m, 1H, NCH), 4.18 (d, J = 14.9 Hz, 1H, $ArCH_2$), 5.00 (d, J = 14.9 Hz, 1H, $ArCH_2$), 5.37 (dd, J = 5.8, 7.6 Hz, 1H, NCOCH), 6.79–6.84 (m, 2H, ArH), 7.18–7.21 (m, 2H, ArH), 7.42 (m, 2H, ArH), 7.52–7.61(m, 1H, ArH), 7.79–7.83 (m, 2H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 24.9, 41.9, 47.5, 51.9, 68.2, 127.7, 128.7, 129.1, 136.1, 158.8, 167.5, 169.9, 196.9 ppm; MS (ESI) m/z 396 ($M+H^+$). Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.39; H, 6.78; N, 3.36.

4.1.8. (3*S*,6*S*)-1-(4-Methoxybenzyl)-6-(2-oxo-2-phenylethyl)-3-(tetrahydro-2*H*-pyran-2-yloxy)piperidin-2-one 22

To a solution of **20** (500 mg, 1.27 mmol) in MeOH (20 mL) was added AcCl (0.7 mL) at 0 °C. The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel eluting with EtOAc/petroleum ether (1:2) to afford a colorless oil (431 mg, yield: 96%). To this material (402 mg, 1.1 mmol) and TsOH (cat.) in anhydrous CH_2Cl_2 (5 mL) was added 3,4-dihydro-2*H*-pyran (DHP, 0.25 mL, 2.75 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h before quenching with 1 mL of saturated $NaHCO_3$ solution, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with EtOAc/petroleum ether (1:2) to afford two main diastereomers **22** (323 mg, yield: 58%) and **23** (145 mg, yield: 26%) as colorless oils. **22**: $[\alpha]_D^{20} = -65.4$ (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max}: 2946, 1681, 1648, 1510, 1444, 1249, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47–2.20 (m, 10H, CH_2CH_2), 3.25 (dd, J = 3.4, 15.4 Hz, 1H, $COCH_2$), 3.35 (dd, J = 9.0, 15.4 Hz, 1H, $COCH_2$), 3.50–3.59 (m, 1H, OCH_2), 3.87 (s, 3H, OCH_3), 3.89 (m, 1H, OCH_2), 3.94 (d, J = 14.7 Hz, 1H, $ArCH_2$), 4.10–4.18 (m, 1H, NCH), 4.27 (dd, J = 6.7, 9.8 Hz, 1H, COCH), 5.12 (d, J = 14.7 Hz, 1H, $ArCH_2$), 5.26 (dd, J = 2.0, 4.7 Hz, 1H, OCHO), 6.80 (m, 2H, ArH), 7.18 (m, 2H, ArH), 7.45 (m, 2H, ArH), 7.6 (m, 1H, ArH), 7.87 (m, 2H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 25.3, 25.4, 30.5, 41.1, 47.6, 51.7, 55.1, 62.9, 71.7, 100.0, 114.0, 127.9, 128.6, 129.1, 129.3, 133.5, 136.4, 158.9, 170.7, 197.5 ppm; MS (ESI) m/z 438 ($M+H^+$). Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.66; H, 7.47; N, 3.01.

4.1.9. (3*S*,6*S*)-1-(4-Methoxybenzyl)-3-hydroxy-6-(2-oxo-2-phenylethyl)piperidin-2-one 21a

From **22**: To a solution of **22** (200 mg, 0.46 mmol) in MeOH (5 mL) was added *p*-TsOH (cat.). After stirring at 45 °C for 2 h, the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel eluting with EtOAc/petroleum ether (1:2) to give **21a** (150 mg, yield: 93%) as a colorless oil.

From **20a**: To a solution of **20a** (77 mg, 0.19 mmol) in MeOH (3 mL) were added three drops of AcCl at 0 °C. The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel eluting with EtOAc/petroleum ether (1:2) to give **21a** (62 mg, yield: 90%) as a colorless oil. $[\alpha]_D^{20} = -10.6$ (*c* 1.1, $CHCl_3$); IR (KBr) ν_{max}: 3423, 2951, 1677, 1628, 1520, 1449, 1242, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.22–1.79 (m, 4H, CH_2CH_2), 3.23 (dd, J = 3.0, 17.6 Hz, 1H, $PhCOCH_2$), 3.33 (dd, J = 9.0, 17.6 Hz, 1H, $PhCOCH_2$), 3.77 (s, 3H, OCH_3), 3.84 (s, 1H, OH, D_2O

exchangeable), 3.99 (d, J = 14.7 Hz, 1H, $ArCH_2$), 4.09 (dd, J = 10.7, 6.5 Hz, 1H, NCOCH), 4.16–4.23 (m, 1H, NCH), 5.04 (d, J = 14.7 Hz, 1H, $ArCH_2$), 6.81 (d, J = 8.6 Hz, 2H, ArH), 7.19 (d, J = 8.6 Hz, 2H, ArH), 7.47 (t, J = 7.8 Hz, 2H, ArH), 7.59 (t, J = 7.4 Hz, 1H, ArH), 7.89 (d, J = 7.4 Hz, 2H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3. 24.9, 41.0, 48.1, 52.2, 55.2, 68.4, 114.1, 128.0, 128.8, 129.3, 133.7, 136.3, 159.1, 172.6, 197.3 ppm; MS (ESI) m/z 354 ($M+H^+$). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.67; H, 7.01; N, 3.57.

4.1.10. (3*S*,6*S*)-1-(4-Methoxybenzyl)-6-((*S*)-2-hydroxy-2-phenylethyl)piperidin-3-ol 25

To a solution of **21a** (120 mg, 0.34 mmol) in anhydrous THF (10 mL) was added $LiAlH(O\text{-}t\text{-}Bu)_3$ (260 mg, 1.02 mmol) at room temperature, and the mixture was refluxed for 4 h. After cooling to room temperature, $LiAlH_4$ (129 mg, 3.4 mmol) was added and the mixture was refluxed for another 4 h. After cooling to room temperature, the reaction was quenched by careful addition of powdered $Na_2SO_4{\cdot}10H_2O$, and the mixture was stirred until a white precipitate formed. The mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with EtOAc/petroleum ether (2:1) to give **25** as colorless crystals (100 mg, yield: 86%). Mp 144–145 °C (EtOAc/petroleum ether). $[\alpha]_D^{20} = -59.3$ (c 1.0, $CHCl_3$); IR (KBr) ν_{max}: 3394, 2942, 1611, 1515, 1445, 1242, 1065, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33–1.55 (m, 3H, CH_2CH_2), 1.80–1.90 (m, 1H, CH_2CH_2), 1.95–2.10 (m, 1H, PhCHCH_2), 2.19–2.30 (m, 1H, PhCHCH_2), 2.69–2.78 (m, 1H, NCH_2), 2.82 (m, 1H, NCH), 3.04–3.12 (m, 1H, NCH_2), 3.79 (s, 3H, OCH_3), 3.80 (d, J = 12.7 Hz, 1H, $ArCH_2$), 3.86 (d, J = 12.7 Hz, 1H, $ArCH_2$), 3.87 (tt, J = 10.0, 5.0 Hz, 1H, C*H*OH), 4.75 (dd, J = 10.6, 2.0 Hz, 1H, PhCH), 6.85–6.91 (m, 2H, ArH), 7.18–7.38 (m, 7H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1. 29.9, 38.4, 51.4, 55.2, 56.5, 57.7, 62.7, 75.03, 125.5, 127.0, 128.2, 130.0, 130.1, 144.96, 158.9 ppm; MS (ESI) m/z 342 ($M+H^+$). Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.74; H, 8.02; N, 3.95.

4.1.11. (2*S*,5*S*)-*tert*-Butyl 5-hydroxy-2-((*S*)-2-hydroxy-2-phenylethyl)piperidine-1-carboxylate 26

A suspension of **25** (80 mg, 0.18 mmol), 20% $Pd(OH)_2/C$ (30 mg), and Boc_2O (0.16 mL, 0.70 mmol) in EtOH (5 mL) was stirred under an atmosphere of H_2 overnight. After filtration of the catalyst, the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with EtOAc/petroleum ether (1:1) to afford **26** (48 mg, yield: 64%) as a colorless oil. $[\alpha]_D^{20} = -62.4$ (c 0.8, $CHCl_3$). IR (KBr) ν_{max}: 3390, 2929, 2863, 1656, 1415, 1361, 1253, 1150, 1058; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H, $(CH_3)_3$), 1.60–1.94 (m, 4H, CH_2CH_2), 1.98–2.32 (m, 2H, PhCHCH_2), 2.57 (m, 1H, NCH_2), 3.48–3.66 (m, 1H, NCH), 3.90–4.20 (m, 1H, NCH_2), 4.20–4.44 (m, 1H, NCH_2CH), 4.65–4.80 (m, 1H, PhCH), 7.20–7.40 (m, 5H, PhH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3. 28.4, 29.7, 39.6, 45.9, 47.3, 67.1, 72.5, 80.3, 125.7, 127.4, 128.4, 144.4, 155.2 ppm; MS (ESI) m/z 344 ($M+Na^+$); HRMS (ESI) calcd for $[C_{18}H_{27}NO_4+H]^+$ 322.2013, found 322.2016.

4.1.12. (−)-Hydroxysedamine 7

To a solution of **26** (40 mg, 0.12 mmol) in anhydrous THF (3 mL) was added $LiAlH_4$ (45 mg, 1.20 mmol) at room temperature, and the mixture was refluxed for 4 h. After cooling to room temperature, the reaction was quenched by careful addition of powdered $Na_2SO_4{\cdot}10H_2O$, and the mixture was stirred until a white precipitate formed. The mixture was filtered through a Celite pad and the filtrate concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH (10:1) to give **7** as a colorless oil (23 mg, yield: 80%). $[\alpha]_D^{20} = -53.4$ (c 0.5, MeOH) {lit.[8] $[\alpha]_D^{22} = -40$ (c 0.3, MeOH); lit.[7f] $[\alpha]_D^{20} = -53$ (c 0.3, MeOH); lit.[7m] $[\alpha]_D^{20} = -51.0$ (c 2.5, MeOH)}; IR (KBr) ν_{max}: 3365, 2934, 2859, 2793, 1661, 1453, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40–1.75 (m, 4H, CH_2CH_2), 1.89 (ddd, J = 14.3, 5.7, 2.8 Hz, 1H, PhCHCH_2), 2.16 (ddd, J = 14.3, 10.4, 7.8 Hz, 1H, PhCHCH_2), 2.46 (s, 3H, NCH_3), 2.56 (dd, J = 12.8, 3.6 Hz, 1H, NCH_2), 2.68–2.76 (m, 1H, NCH), 2.85 (dd, J = 12.8, 7.2 Hz, 1H, NCH_2), 3.90 (tt, J = 7.3, 3.6 Hz, 1H, NCH_2CH), 4.85 (dd, J = 10.4, 2.8 Hz, 1H, PhCH), 7.20–7.45 (m, 5H, PhH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 128.3, 127.2, 125.5, 73.7, 63.7, 59.6, 57.4, 42.7, 39.7, 30.2, 24.3 ppm; MS (ESI) m/z 236 ($M+H^+$); HRMS (ESI) calcd for $[C_{14}H_{21}NO_2+H]^+$ 236.1645, found 236.1648.

4.1.13. (3*S*,6*S*)-1-(4-Methoxybenzyl)-2-oxo-6-(2-oxoethyl)piperidin-3-yl acetate 27

To a stirring mixture of compound **16** (114 mg, 0.36 mmol) and an aqueous solution of $RuCl_3$ (0.25 mL, 0.0125 mmol, 3.5 mol %) in MeCN (6 mL) and distilled water (1 mL) was added portionwise $NaIO_4$ (154 mg, 0.72 mmol) over a period of 5 min at room temperature. After stirring for 2 h, the reaction was quenched with saturated aqueous solution of $Na_2S_2O_3$, and the two layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/petroleum ether (2:1) to afford **27** (79 mg, yield: 69%) as a colorless oil. $[\alpha]_D^{20} = +51.0$ (c 1.0, $CHCl_3$); IR (film) 2951, 1744, 1663, 1512, 1366, 1244, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.89–1.76 (m, 1H, CH_2CH_2), 2.01–1.90 (m, 1H, CH_2CH_2), 2.14–2.01 (m, 2H, CH_2CH_2), 2.16 (s, 3H, $COCH_3$), 2.89–2.84 (m, 2H, CH_2CHO), 3.79 (s, 3H, OCH_3), 3.94 (d, J = 14.8 Hz, 1H, $ArCH_2$), 4.03–3.97 (m, 1H, NCH), 5.08 (d, J = 14.8 Hz, 1H, $ArCH_2$), 5.13 (dd, J = 10.2, 7.3 Hz, 1H, NCOCH), 6.90–6.81 (m, 2H, ArH), 7.21–7.13 (m, 2H, ArH), 9.69 (s, 1H, CHO) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 22.9, 25.2, 46.3, 47.9, 49.6, 55.2, 69.5, 114.1, 128.6, 129.4, 159.1, 167.2, 170.2, 199.2 ppm; MS (ESI) m/z 374 [$(M+MeOH+Na)^+$, 100]. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.50; H, 6.22; N, 4.10.

4.1.14. (3*S*,6*S*,2′*R*/*S*)-1-(4-Methoxybenzyl)-6-(2-hydroxy-2-phenylethyl)-2-oxopiperidin-3-yl acetate 28a,b

To a cooled (−20 °C) solution of **27** (40 mg, 0.125 mmol) in THF (3 mL) was added dropwise 0.3 mL of a 0.5 M solution of PhMgBr in THF (0.15 mmol). After stirring at −20 °C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl (3 mL) and the mixture was extracted with Et_2O (3 × 5 mL). 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 eluting with EtOAc/petroleum ether (2:1) to afford **28** (colorless oil, 37 mg, yield: 74%) as a mixture of two diastereomers in 2.5:1 ratio, which was used in the next step without further separation. IR (film) 3382, 2952, 2855, 1731, 1636, 1461, 1378, 1237; ^1H NMR (400 MHz, $CDCl_3$, two diastereomers, **28a/28b** = 2.5:1, data read from the spectrum of the diastereomeric mixture). Compound **28a**: δ 1.79–2.20 (m, 6H, CH_2CH_2 and NCHCH_2), 2.12 (s, 3H, $COCH_3$), 3.66–3.74 (m, 1H, NCH), 3.77 (d, J = 14.5 Hz, 1H, $ArCH_2$), 3.79 (s, 3H, $ArOCH_3$), 4.86 (d, J = 8.7 Hz, 1H, PhCH), 5.20 (dd, J = 10.1, 7.8 Hz, 1H, NCOCH), 5.26 (d, J = 14.5 Hz, 1H, $ArCH_2$), 6.78–6.87 (m, 2H, ArH), 7.15–7.21 (m, 2H, ArH), 7.28–7.43 (m, 5H, ArH) ppm. Compound **28b**: δ 1.79–2.20 (m, 6H, CH_2CH_2 and NCHCH_2), 2.14 (s, 3H, $COCH_3$), 3.25–3.34 (m, 1H, NCH), 3.61 (d, J = 14.5 Hz, 1H, $ArCH_2$), 3.77 (s, 3H, $ArOCH_3$), 4.64 (d, J = 6.8 Hz, 1H, PhCH), 5.20 (dd, J = 10.1, 7.8 Hz, 1H, NCOCH), 5.24 (d, J = 14.5 Hz, 1H, $ArCH_2$), 6.71–6.78 (m, 2H, ArH), 6.88–6.93 (m, 2H, ArH),

7.28–7.41 (m, 5H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, diastereomeric mixture) **28**: δ 21.0, 23.0, 23.1, 23.9, 25.0, 40.0, 40.7, 41.1, 47.0, 47.3, 52.0, 52.3, 69.3, 71.5, 72.6, 113.9, 125.5, 125.9, 128.0, 128.2, 128.7, 128.9, 129.0, 129.3, 129.6, 129.7, 143.6, 144.0, 158.9 (2C), 161.5, 167.0, 167.1, 170.4 ppm; MS (ESI) m/z 420 ($M+Na^+$, 100%). Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.38; H, 7.09; N, 3.49.

4.1.15. (3*S*,6*S*)-1-(4-Methoxybenzyl)-6-(2-oxo-2-phenylethyl)-2-oxopiperidin-3-yl acetate 20a

To a solution of **28a**,**b** (37 mg, 0.1 mmol) in DMSO (3 mL) was added *o*-iodoxybenzoic acid (IBX, 52 mg, 0.19 mmol). After stirring at room temperature for 2 h, the reaction mixture was diluted with Et_2O (5 mL) and quenched with H_2O (3 mL). The mixture was filtered, through a pad of Celite and washed with Et_2O. The organic layer was separated, 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 eluting with EtOAc/petroleum ether (1:1) to afford **20a** (27 mg, yield: 73%) as a colorless oil. $[\alpha]_D^{20} = +6.9$ (c 1.4, $CHCl_3$); IR (film) 3386, 2929, 1735, 1652, 1507, 1454, 1364, 1233, 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80–1.88 (m, 1H, CH_2CH_2), 1.89–2.00 (m, 1H, CH_2CH_2), 2.03–2.11 (m, 2H, CH_2CH_2), 2.14 (s, 3H, $COCH_3$), 3.23–3.38 (m, 2H, $PhCOCH_2$), 3.73 (s, 3H, $ArOCH_3$), 3.95 (d, 1H, J = 14.7 Hz, $ArCH_2$), 4.10–4.18 (m, 1H, NCH), 5.07 (d, 1H, J = 14.7 Hz, $ArCH_2$), 5.09 (dd, 1H, J = 10.6, 7.5 Hz, NCOCH), 6.76–6.82 (m, 2H, ArH), 7.13–7.18 (m, 2H, ArH), 7.40–7.47 (m, 2H, ArH), 7.52–7.59 (m, 1H, ArH), 7.81–7.87 (m, 2H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 23.1, 25.2, 40.6, 48.1, 51.7, 55.2, 69.8, 114.1, 128.0, 128.8, 128.9, 129.5, 133.6, 136.4, 159.1, 167.4, 170.4, 197.5 ppm. MS (ESI) m/z 418 ($M+Na^+$, 100%).

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