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A versatile approach to *cis*-5-substituted 4-hydroxy-2-pyrrolidinones: asymmetric synthesis of angiogenesis inhibitor streptopyrrolidine

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ABSTRACT

A concise, flexible, and highly diastereoselective approach to *cis*-5-alkyl-4-hydroxy-2-pyrrolidinones **1** is described. The key step is an ammonium acetate-assisted catalytic hydrogenation of the enamides **9**, derived in two steps from malimides **6a**,**b** as we have described previously. The method was applied to the asymmetric synthesis of streptopyrrolidine **5**, a natural product, which exhibited significant anti-angiogenesis activity.

1. Introduction

Protected *cis*-5-alkyl-4-hydroxy-2-pyrrolidinones **1** are versatile intermediates for the synthesis of bioactive pyrrolidine-containing compounds [e.g., the antifungal alkaloid preussin[1] **2**, novel potential HIV protease inhibitors[2] **3**], and *syn*-β-hydroxy γ-amino acids[3] **4** such as (3*S*,4*S*)-statine **4a**,[3a–k] (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA) **4b**,[3c,6a] and (3*S*,4*S*)-3-amino-5-cyclohexymethyl-2-hydroxyl-pentanoic acid (ACHPA) **4c**[3l,m] (Fig. 1), which are important peptide mimetics.[4] Recently, *cis*-5-benzyl-4-hydroxy-2-pyrrolidinone **5**, named as streptopyrrolidine, was isolated from the fermentation broth of a marine *Streptomyces* sp. KORDI-3973 from the deep sea sediment.[5] It has been demonstrated that streptopyrrolidine **5** significantly blocked the capillary tube formation of the cells at the same potency as a known angiogenesis inhibitor SU11248, and is expected to be a unique small molecule bio-probe for studying angiogenesis.[5]

The structure of streptopyrrolidine **5** has been elucidated by extensive 2D NMR and mass spectroscopic analyses. Its absolute configuration was not deduced due to a significant difference in the magnitude of the specific rotation of the natural product **5** {$[\alpha]_D^{25} = -12$ (*c* 0.05, MeOH)}[5] compared with that of a synthetic sample {$[\alpha]_D^{20} = -44$ (*c* 1.0, MeOH)}.[6a]

Numerous approaches have been developed for the asymmetric synthesis of *cis*-5-alkyl-4-hydroxy-2-pyrrolidinones,[6] including two syntheses[6a,b] of **5** as a synthetic intermediate before its isolation from the natural source. Among the reported methods, the most widely adopted one is based on the stereoselective reduction of tetramic acid derivatives.[3a,l,6a,c,d] However, this method is generally limited to proteinogenic amino acids. Thus the development of complementary non-amino acid-based methods is desirable.

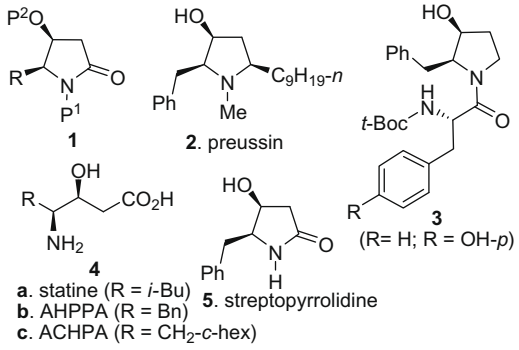
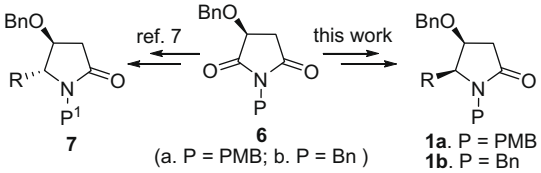


Figure 1.

Previously, we have developed the protected (*S* or *R*)-malimides **6** as versatile chiral building blocks for the asymmetric synthesis of *trans*-5-alkyl-4-hydroxy-2-pyrrolidinones **7** via a highly regio- and diastereoselective reductive alkylation (Scheme 1).[7] In this report, we disclose that malimides **6a**,**b** can also be used for the synthesis



Scheme 1.

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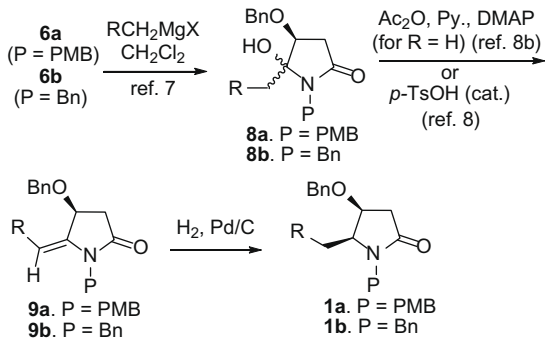
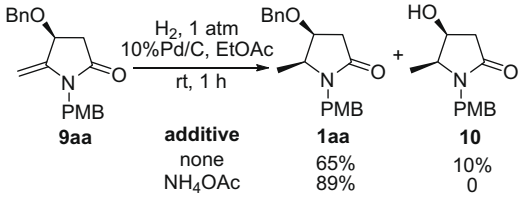
of protected *cis*-5-alkyl-4-hydroxy-2-pyrrolidinones **1a**,**b**. An asymmetric synthesis of streptopyrrolidine **5** is also described.

2. Results and discussion

On the basis of our recent observation that (4*S*)-hemiaminals **8**, prepared by Grignard addition with mailimides[7] **6**, can be subjected to acid-catalyzed dehydration to give stereoselectively the corresponding *E*-enamides **9**,[8] it was envisioned that the hydrogenation of enamides **9** would afford *cis*-5-alkyl-4-hydroxy-2-pyrrolidinones **1** (Scheme 2). Indeed, when enamide **9aa** was subjected to catalytic hydrogenation conditions (H_2, 1 atm, 10% Pd/C), the desired product **1aa** was obtained as a sole diastereomer in 65% yield. However, the concomitantly O-debenzylated byproduct **10** was isolated in about 10% yield (Scheme 3). To suppress this side reaction, we tried the use of ammonium acetate as an additive.[9] To our delight, when the catalytic hydrogenation was run in the presence of ammonium acetate, lactam **1aa** was obtained in 89% yield. The method was extended to other enamides **9ab**, **9ba**–**9bh**, and the results are summarized in Table 1. As can be seen from Table 1, the reactions afforded good to excellent yields, except those with a longer side chain. The enamides bearing longer side chains are less reactive and required longer reaction time, which led to some side products.



Scheme 2.

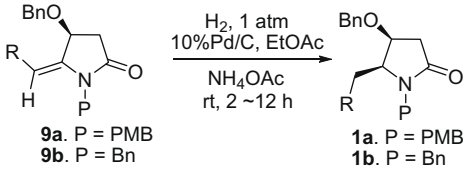


Scheme 3.

The stereochemistry of the products were deduced from the characteristic vicinal coupling constants between the protons H_4 and H_5 ($J_{4,5}$ = 5.5–6.5 Hz),[7c,10] and was confirmed by an X-ray diffraction crystallographic analysis of **1bb** (Fig. 2).

The method was applied to the synthesis[6a,b] of natural product streptopyrrolidine **5** (Scheme 4). Thus the requisite enamide **9ab** was obtained by the *p*-TsOH-mediated dehydration of the known hemiaminal **8ab**.[7e] The ammonium acetate-assisted catalytic hydrogenation of enamide **9ab** afforded lactam **1ab** in excellent yield as the sole diastereomer. N-Deprotection with ceric ammonium nitrate (CAN), followed by O-debenzylation under catalytic hydrogenolysis conditions provided (4*S*,5*S*)-streptopyrrolidine **5** in high overall yield. The synthetic compound shows the same

Table 1
Hydrogenation of enamides **9**



Entry	Enamides **9**			Time (h)	Product **1**[a] (yield%)[b]
	Compd	R	P		
1	**9aa**	H	PMB	2	**1aa** (89)
2	**9ab**	Ph	PMB	4	**1ab** (96)
3	**9ba**	H	Bn	2	**1ba** (92)
4	**9bb**	CH_3	Bn	2	**1bb** (80)
5	**9bc**	*n*-Pr	Bn	2	**1bc** (83)
6	**9bd**	*n*-Bu	Bn	2	**1bd** (72)
7	**9be**	*i*-Pr	Bn	12	**1be** (69)
8	**9bf**	Ph	Bn	4	**1bf** (94)
9	**9bg**	n-C_7H_{14}	Bn	4	**1bg** (73)
10	**9bh**	n-$C_{11}H_{22}$	Bn	4	**1bh** (63)

[a] Only one diastereomer was observed as determined by ^{1}H NMR of the crude.
[b] Isolated yield.

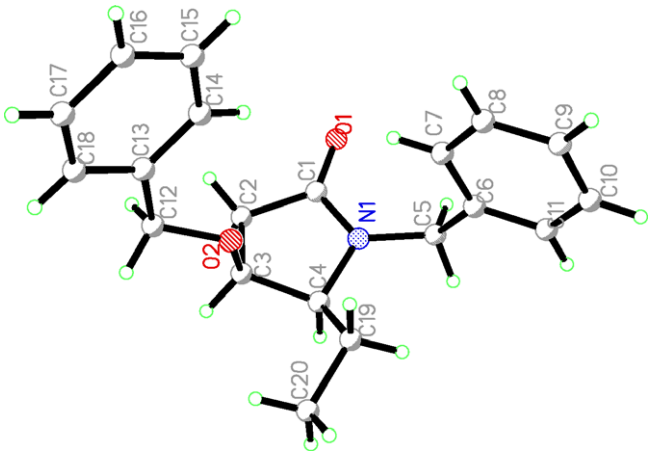
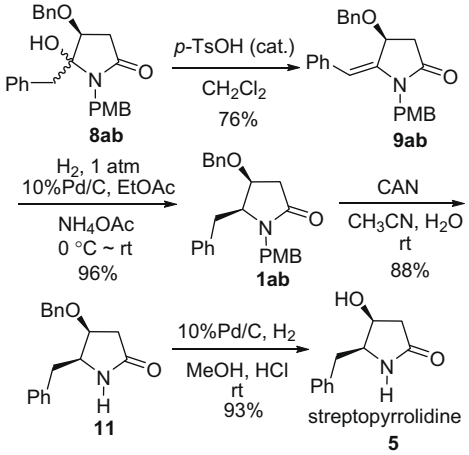


Figure 2. The X-ray structure of compound **1bb**.



Scheme 4.

spectroscopic data as those reported for the natural product.[5] The physical properties of our synthetic product are in agreement

with those reported by Poncet and Castro {white solid, Mp 133–135 °C (CH_2Cl_2/MeOH); lit.[6a] Mp 134–135 °C; $[\alpha]_D^{20} = -43.5$ (*c* 1.0, MeOH); lit.[6a] $[\alpha]_D^{20} = -44$ (*c* 1.0, MeOH); $[\alpha]_D^{20} = -12$ (*c* 0.05, MeOH) for natural product}.[5]

3. Conclusion

In summary, on the basis of our previous results, we have developed a concise, flexible, and highly diastereoselective approach to *cis*-5-alkyl-4-hydroxy-2-pyrrolidinones **1** starting from malimides **6a**,**b**, which constitutes an important extension of the malimide-based synthetic methodology developed from our laboratory. The same sense of specific rotation of our synthetic product compared with that of the natural product allowed determination of the absolute configuration of the natural streptopyrrolidine **5** as (4*S*,5*S*). The difference in magnitude between the synthetic and natural products is attributable to the fact that only 1.54 mg of the natural product was isolated, which prevented an accurate measurement of specific rotation. The ready access to different C-5 substituted *cis*-4-hydroxy-2-pyrrolidinones **1** would find a basis for structure-bioactivity relationship study toward streptopyrrolidine.

4. Experimental

4.1. General

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. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker 400 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by a Bruker Dalton ESquire 3000 plus liquid chromatography-mass spectrometer (direct injection). Optical rotations were measured with Perkin–Elmer 341 automatic polarimeter. Flash column chromatography was carried out with silica gel (300–400 mesh). THF was distilled over sodium benzophenone ketyl under N_2.

4.2. General procedure for the preparation of (4*S*,5*S*)-5-substituted 4-benzyloxy-2-pyrrolidinones 1 from enamides 9

To a mixture of ammonium acetate (2.0 mmol) and 10% Pd/C (20w/w% to enamides **9**) were added successively 5 mL of EtOAc and a solution of enamides **9** (1.0 mmol) in 5 mL of EtOAc. The mixture was stirred under 1 atm of hydrogen for 2–12 h at rt. The mixture was filtered through filter paper. After concentration under reduced pressure, the resulting residue was purified by flash chromatography on silica gel [EtOAc/petroleum ether (P.E.) = 1:2] to give solely *cis*-diastereomers **1** in 63–96% yields.

4.3. (4*S*,5*S*)-1-(4-Methoxybenzyl)-4-(benzyloxy)-5-methyl-2-pyrrolidinone 1aa

To a solution of hemiaminal **8aa**[7e] (500 mg, 1.47 mmol) in CH_2Cl_2 (15 mL) were added pyridine (1.2 mL, 14.7 mmol) and Ac_2O (0.69 mL, 7.3 mmol). The mixture was heated at reflux for 48 h, then cooled to room temperature, diluted with CH_2Cl_2, and washed successively with 1.0 M HCl and water. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel eluting with ethyl acetate/PE (1:5) to give labile enamide **9aa**, which was used in the next step immediately.

Following the general procedure, the hydrogenation of enamide **9aa** (300 mg, 0.93 mmol) for 2 h gave **1aa** (267 mg, 89%) as a colorless oil. $[\alpha]_D^{20} = -19.7$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3030, 2968, 2929, 2867, 1692, 1513, 1454, 1412, 1248 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.5 Hz, 3H, CH_3), 2.58 (d, *J* = 6.5 Hz, 2H, H-3), 3.64 (dq, *J* = 6.5, 6.5 Hz, 1H, H-5), 3.79 (s, 3H, OCH_3), 3.88 (d, *J* = 14.9 Hz, 1H, NCH_2), 4.08 (dt, *J* = 6.5, 6.5 Hz, 1H, H-4), 4.44 (d, *J* = 11.8 Hz, 1H, OCH_2), 4.53 (d, *J* = 11.8 Hz, 1H, OCH_2), 4.96 (d, *J* = 14.9 Hz, 1H, NCH_2), 6.82–6.87 (m, 2H, ArH), 7.11–7.19 (m, 2H, ArH), 7.26–7.38 (m, 5H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 36.5, 43.2, 55.2, 55.8, 71.4, 73.5, 114.0, 127.4, 127.8, 128.4, 128.6, 129.3, 137.6, 159.0, 171.8 ppm; MS (ESI): 348 *m*/*z* (M+Na$^+$); Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.47; H, 6.80; N, 4.34.

4.4. (*S*,*E*)-5-Benzylidene-4-(benzyloxy)-1-(4-methoxybenzyl)-2-pyrrolidinone 9ab

To a solution of hemiaminal **8ab**[7e] (1.500 g, 1.22 mmol) in dry CH_2Cl_2 (60 mL) was added 75 mg of *p*-TsOH at 0 °C. The reaction mixture was stirred for 2 min., and the reaction was quenched with a saturated aqueous $NaHCO_3$ (5 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:5) to give enamide **9ab** (1.100 g, yield: 76%) as a white solid. Mp 96–98 °C (EtOAc/PE); $[\alpha]_D^{20} = +291.0$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3019, 2926, 1715, 1642, 1345, 1244, 1178, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (d, *J* = 4.0 Hz, 2H, H-3), 3.77 (s, 3H, OCH_3), 4.42 (s, 2H, NCH_2), 4.75 (d, *J* = 15.5 Hz, 1H, OCH_2), 4.80 (d, *J* = 15.5 Hz, 1H, OCH_2'), 4.92 (dt, *J* = 1.0, 4.0 Hz, 1H, H-4), 5.99 (s, 1H, C=CH), 6.83 (m, 2H, ArH), 7.14–7.33 (m, 12H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.2, 43.3, 55.2, 69.5, 71.0, 108.8, 114.1, 126.4, 127.6, 128.0, 128.1, 128.2, 128.4, 128.4(2C), 135.4, 137.0, 141.0, 159.9, 173.1 ppm; MS (ESI): 422 *m*/*z* (M+Na$^+$); HRESIMS calcd for [$C_{26}H_{25}NO_3$+H$^+$]: 400.1913; found: 400.1914.

4.5. (4*S*,5*S*)-5-Benzyl-4-(benzyloxy)-1-(4-methoxybenzyl)-2-pyrrolidinone 1ab

Following the general procedure, the hydrogenation of enamide **9ab** (200 mg, 0.50 mmol) for 4 h gave compound **1ab** (193 mg, 96%) as a white solid. Mp 95–97 °C (EtOAc/PE); $[\alpha]_D^{20} = -5.7$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3062, 3027, 2922, 2875, 2836, 1692, 1513, 1450, 1244, 1174, 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (dd, *J* = 6.4, 16.6 Hz, 1H, H-3), 2.54 (dd, *J* = 5.8, 16.6 Hz, 1H, H-3′), 2.90 (dd, *J* = 6.0, 13.5 Hz, 1H, NCH*CH*$_2$), 3.09 (dd, *J* = 7.8, 13.5 Hz, 1H, NCH*CH*$_2$), 3.63 (d, *J* = 14.9 Hz, 1H, NCH_2), 3.76 (ddd, *J* = 6.0, 6.0, 7.8 Hz, 1H, H-5), 3.80 (s, 3H, OCH_3), 3.95 (ddd, *J* = 5.8, 6.0, 6.4 Hz, 1H, H-4), 4.30 (d, *J* = 11.5 Hz, 1H, OCH_2), 4.45 (d, *J* = 11.5 Hz, 1H, OCH_2), 5.03 (d, *J* = 14.9 Hz, 1H, NCH_2), 6.82–6.86 (m, 2H, ArH), 7.01–7.05 (m, 2H, ArH), 7.07–7.12 (m, 2H, ArH), 7.19–7.36 (m, 8H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.4, 36.6, 43.8, 55.3, 61.6, 71.4, 73.4, 114.0, 126.5, 127.7, 127.8, 128.4(2C), 128.5, 129.3, 129.5, 137.5, 137.9, 159.0, 172.4 ppm; MS (ESI): 424 *m*/*z* (M+Na$^+$); HRESIMS calcd for [$C_{26}H_{27}NO_3$+H$^+$]: 402.2069; found: 402.2065.

4.6. (4*S*,5*S*)-1-Benzyl-4-(benzyloxy)-5-methyl-2-pyrrolidinone 1ba

Following the general procedure, the hydrogenation of enamide **9ba**[8a] (100 mg, 0.34 mmol) for 2 h gave compound **1ba** (93 mg, 92%) as a colorless oil. $[\alpha]_D^{20} = -19.8$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3029, 2975, 2930, 2867, 1691, 1453, 1416, 1124 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 1.20 (d, J = 6.6 Hz, 3H, CH_3), 2.60 (d, J = 6.7 Hz, 2H, H-3), 3.65 (dq, J = 6.5, 6.6 Hz, 1H, H-5), 3.96 (d, J = 15.1 Hz, 1H, NCH_2), 4.10 (dt, J = 6.5, 6.7 Hz, 1H, H-4), 4.44 (d, J = 11.9 Hz, 1H, OCH_2), 4.53 (d, J = 11.9 Hz, 1H, OCH_2), 5.01 (d, J = 15.1 Hz, 1H, NCH_2), 7.21–7.36 (m, 10H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 36.5, 43.8, 56.0, 71.4, 73.5, 127.4, 127.5, 127.8, 127.9, 128.4, 128.6, 136.6, 137.7, 172.0 ppm; MS (ESI): 318 m/z ($M+Na^+$); Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.71; H, 6.75; N, 4.75.

4.7. (4*S*,5*S*)-1-Benzyl-4-(benzyloxy)-5-ethyl-2-pyrrolidinone 1bb

Following the general procedure, the hydrogenation of enamide **9bb**[8a] (100 mg, 0.33 mmol) for 2 h gave compound **1bb** (80 mg, 80%) as white crystals in $CHCl_3$. Mp 80–82 °C; $[\alpha]_D^{20} = -2.7$ (c 1.0, $CHCl_3$); IR (film) ν_{max}: 3030, 2969, 2930, 2871, 1688, 1455, 1424, 1065 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.4 Hz, 3H, CH_3), 1.68–1.80 (m, 2H, CH_2), 2.56 (dd, J = 6.1, 16.8 Hz, 1H, H-3), 2.63 (dd, J = 4.8, 16.8 Hz, 1H, H-3′), 3.48 (ddd, J = 3.9, 6.1, 8.8 Hz, 1H, H-5), 3.97 (d, J = 15.1 Hz, 1H, OCH_2), 4.13 (ddd, J = 4.8, 6.1, 6.1 Hz, 1H, H-4), 4.41 (d, J = 11.7 Hz, 1H, NCH_2), 4.57 (d, J = 11.7 Hz, 1H, NCH_2), 5.02 (d, J = 15.1 Hz, 1H, OCH_2), 7.18–7.38 (m, 10H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.7, 19.9, 37.1, 44.0, 61.6, 71.3, 72.8, 127.4, 127.5, 127.8, 127.8, 128.4, 128.6, 136.7, 137.8, 172.8 ppm; MS (ESI): 332 m/z ($M+Na^+$); Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.20; H, 7.36; N, 4.44.

4.8. (4*S*,5*S*)-1-Benzyl-4-(benzyloxy)-5-butyl-2-pyrrolidinone 1bc

Following the general procedure, the hydrogenation of enamide **9bc**[8a] (100 mg, 0.30 mmol) for 2 h gave compound **1bc** (83 mg, yield: 83%) as a colorless oil. $[\alpha]_D^{20} = +7.8$ (c 1.0, $CHCl_3$); IR (film) ν_{max}: 3025, 2952, 2935, 2863, 1688, 1456, 1423, 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, J = 6.9 Hz, 3H, CH_3), 1.12–1.38 (m, 4H, $CH_3C_2H_4$), 1.55–1.66 (m, 1H, NCHCH_2), 1.71–1.81 (m, 1H, NCHCH_2'), 2.55 (dd, J = 6.3, 16.8 Hz, 1H, H-3), 2.62 (dd, J = 4.6, 16.8 Hz, 1H, H-3′), 3.46–3.54 (ddd, J = 4.0, 5.9, 9.5 Hz, 1H, H-5), 3.97 (d, J = 15.1 Hz, 1H, NCH_2), 4.09 (ddd, J = 4.6, 5.9, 6.3 Hz, 1H, H-4), 4.39 (d, J = 11.7 Hz, 1H, OCH_2), 4.56 (d, J = 11.7 Hz, 1H, OCH_2), 5.02 (d, J = 15.1 Hz, 1H, NCH_2), 7.18–7.37 (m, 10H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.8, 26.5, 27.3, 37.0, 44.0, 60.6, 71.2, 72.9, 127.4, 127.5, 127.7, 127.8, 128.3, 128.6, 136.6, 137.6, 172.7 ppm; MS (ESI): 360 m/z ($M+Na^+$); HRESIMS calcd for [$C_{22}H_{27}NO_2+H^+$]: 338.2120; found: 338.2122.

4.9. (4*S*,5*S*)-1-Benzyl-4-(benzyloxy)-5-pentyl-2-pyrrolidinone 1bd

Following the general procedure, the hydrogenation of enamide **9bd**[8a] (100 mg, 0.29 mmol) for 2 h gave compound **1bd** (72 mg, 72%) as a colorless oil. $[\alpha]_D^{20} = +7.9$ (c 1.0, $CHCl_3$); IR (film) ν_{max}: 3027, 2957, 2933, 2853, 1695, 1450, 1415, 1099 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, J = 6.8 Hz, 3H, CH_3), 1.13–1.38 (m, 6H, $CH_3C_3H_6$), 1.52–1.68 (m, 1H, NCHCH_2), 1.71–1.83 (m, 1H, NCHCH_2), 2.55 (dd, J = 6.0, 16.8 Hz, 1H, H-3), 2.62 (dd, J = 4.6, 16.8 Hz, 1H, H-3′), 3.50 (ddd, J = 3.9, 6.0, 9.4 Hz, 1H, H-5), 3.97 (d, J = 15.1 Hz, 1H, NCH_2), 4.10 (ddd, J = 4.6, 6.0, 6.4 Hz, 1H, H-4), 4.40 (d, J = 11.7 Hz, 1H, OCH_2), 4.57 (d, J = 11.7 Hz, 1H, OCH_2), 5.02 (d, J = 15.1 Hz, 1H, NCH_2), 7.18–7.34 (m, 10H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.5, 24.9, 26.9, 32.0, 37.1, 44.1, 60.6, 71.3, 73.0, 127.4, 127.6, 127.8, 127.9, 128.4, 128.6, 136.7, 137.7, 172.8 ppm; MS (ESI): 374 m/z ($M+Na^+$); Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.28; H, 8.25; N, 3.81.

4.10. (4*S*,5*S*)-1-Benzyl-4-(benzyloxy)-5-isobutyl-2-pyrrolidinone 1be

Following the general procedure, the hydrogenation of enamide **9be**[8a] (130 mg, 0.39 mmol) for 12 h gave compound **1be** (89 mg, 69%) as a colorless oil. $[\alpha]_D^{20} = +7.3$ (c 1.0, $CHCl_3$); IR (film) ν_{max}: 3034, 2957, 2937, 2867, 1692, 1451, 1412 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (d, J = 6.6 Hz, 3H, CH_3), 0.88 (d, J = 6.6 Hz, 3H, CH_3), 1.29–1.39 (m, 1H, C_2H_6CH), 1.54–1.68 (m, 1H, NCHCH_2), 1.78–1.88 (m, 1H, NCHCH_2'), 2.54 (dd, J = 6.0, 16.8 Hz, 1H, H-3), 2.64 (dd, J = 3.8, 16.8 Hz, 1H, H-3′), 3.54 (ddd, J = 3.8, 5.5, 6.0 Hz, 1H, H-5), 3.93 (d, J = 15.1 Hz, 1H, NCH_2), 4.08 (ddd, J = 4.2, 5.5, 9.5 Hz, 1H, H-4), 4.38 (d, J = 11.6 Hz, 1H, OCH_2), 4.56 (d, J = 11.6 Hz, 1H, OCH_2), 5.06 (d, J = 15.1 Hz, 1H, NCH_2), 7.18–7.38 (m, 10H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 23.7, 24.7, 35.4, 36.8, 44.0, 58.9, 71.2, 73.1, 127.4, 127.5, 127.8, 127.8, 128.4, 128.6, 136.6, 137.6, 172.8 ppm; MS (ESI): 360 m/z ($M+Na^+$); Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 77.92; H, 8.19; N, 4.04.

4.11. (4*S*,5*S*)-1,5-Dibenzyl-4-(benzyloxy)-2-pyrrolidinone 1bf

Following the general procedure, the hydrogenation of enamide **9bf**[8a] (136 mg, 0.37 mmol) for 4 h gave compound **1bf** (130 mg, 94%) as a white solid. Mp 82–84 °C (EtOAc/PE); $[\alpha]_D^{20} = -4.2$ (c 1.0, $CHCl_3$); IR (film) ν_{max}: 3062, 3030, 2918, 2856, 1696, 1500, 1450, 1100 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (dd, J = 6.4, 16.8 Hz, 1H, H-3), 2.56 (dd, J = 5.5, 16.8 Hz, 1H, H-3′), 2.90 (dd, J = 5.9, 13.5 Hz, 1H, NCHCH_2), 3.09 (dd, J = 7.9, 13.5 Hz, 1H, NCHCH_2), 3.71 (d, J = 15.1 Hz, 1H, NCH_2), 3.78 (ddd, J = 5.9, 5.9, 7.9 Hz, 1H, NCH), 3.97 (ddd, J = 5.5, 5.9, 6.4 Hz, 1H, OCH), 4.30 (d, J = 11.5 Hz, 1H, OCH_2), 4.46 (d, J = 11.5 Hz, 1H, OCH_2), 5.07 (d, J = 15.1 Hz, 1H, NCH_2), 7.05–7.11 (m, 4H, ArH), 7.18–7.36 (m, 11H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.4, 36.5, 44.4, 61.8, 71.4, 73.4, 126.5, 127.5, 127.7, 127.8, 127.9, 128.4(2C), 128.6, 129.4, 136.4, 135.5, 137.8, 172.5 ppm; MS (ESI): 394 m/z ($M+Na^+$); Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.78; H, 7.11; N, 3.62.

4.12. (*S*,*E*)-1-Benzyl-4-(benzyloxy)-5-octylidene-2-pyrrolidinone 9bg

To a solution of hemiaminal **8bg** (500 mg, 1.22 mmol) in dry CH_2Cl_2 (12 mL) was added 25 mg of TsOH at 0 °C. The mixture was stirred for 20 min. The reaction was quenched with saturated $NaHCO_3$ (5 mL), and the resultant mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and filtered. After concentration under reduced pressure, the residue was purified by flash chromatography on silica gel (EtOAc/PE = 1: 5) to give enamide **9bg** (260 mg, yield 55%; 92% based on recovered starting material (40%)) as a colourless oil. $[\alpha]_D^{20} = +80.0$ (c 1.0, $CHCl_3$); IR (film) ν_{max}: 3027, 2925, 2848, 1727, 1664, 1454, 1408, 1337, 1205 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 7.0 Hz, 3H, CH_3), 1.13–1.39 (m, 10H, $CH_3C_5H_{10}$), 1.98–2.16 (m, 2H, $C_6H_{13}CH_2$), 2.71 (dd, J = 2.1, 17.8 Hz, 1H, H-3), 2.80 (dd, J = 6.9, 17.8 Hz, 1H, H-3′), 4.47 (d, J = 11.2 Hz, 1H, OCH_2), 4.56 (d, J = 11.2 Hz, 1H, OCH_2), 4.72 (s, 2H, NCH_2), 4.78 (ddd, J = 1.1, 2.1, 6.9 Hz, 1H, H-4), 4.86 (dt, J = 1.1, 7.7 Hz, 1H, C=CH), 7.21–7.40 (m, 10H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 26.7, 29.1(2C), 30.2, 31.7, 36.6, 43.4, 69.9, 70.2, 108.2, 127.0, 127.2, 127.9, 128.1, 128.4, 128.5, 135.9, 137.3, 138.7, 173.0 ppm; MS (ESI): 414 m/z ($M+Na^+$); Anal. Calcd for $C_{26}H_{33}NO_2$: C, 79.76; H, 8.50; N, 3.58. Found: C, 79.98; H, 8.19; N, 3.41.

4.13. (4*S*,5*S*)-1-Benzyl-4-(benzyloxy)-5-octyl-2-pyrrolidinone 1bg

Following the general procedure, the hydrogenation of enamide **9bg** (200 mg, 0.51 mmol) for 4 h gave compound **1bg** (146 mg, 73%) as a colorless oil. $[\alpha]_D^{20} = +10.4$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3027, 2925, 2860, 1696, 1450, 1420, 1408, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 6.9 Hz, 3H, CH_3), 1.18–1.37 (m, 12H, $CH_3C_6H_{12}$), 1.58–1.68 (m, 1H, $C_7H_{15}CH_2$), 1.71–1.85 (m, 1H, $C_7H_{15}CH_2$), 2.59 (dd, *J* = 6.1, 16.8 Hz, 1H, H-3), 2.66 (dd, *J* = 4.1, 16.8 Hz, 1H, H-3′), 3.54 (ddd, *J* = 4.0, 5.8, 8.6 Hz, 1H, H-5), 4.01 (d, *J* = 15.1 Hz, 1H, NCH_2), 4.13 (ddd, *J* = 4.1, 5.8, 6.1 Hz, 1H, H-4), 4.43 (d, *J* = 11.6 Hz, 1H, OCH_2), 4.60 (d, *J* = 11.6 Hz, 1H, OCH_2), 5.06 (d, *J* = 15.1 Hz, 1H, NCH_2), 7.23–7.40 (m, 10H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.5, 25.1, 26.7, 29.1, 29.3, 29.7, 31.7, 37.0, 43.9, 60.5, 71.2, 72.8, 127.3, 127.5, 127.7, 127.7, 128.3, 128.5, 136.6, 137.5, 172.7 ppm; MS (ESI): 416 *m*/*z* ($M+Na^+$); HRESIMS calcd for [$C_{26}H_{35}NO_2$+H^+]: 394.2746; found: 394.2741.

4.14. (*S*,*E*)-1-Benzyl-4-(benzyloxy)-5-dodecylidene-2-pyrrolidinone 9bh

To a solution of hemiaminal **8bh** (1.0 g, 2.15 mmol) in dry CH_2Cl_2 (21 mL) was added 50 mg of TsOH at 0 °C. The mixture was stirred for 20 min. The reaction was quenched with saturated $NaHCO_3$ (10 mL), then the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and filtered. After concentration under reduced pressure, the resulting residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:5) to give enamide **9bh** (709 mg, yield 74%) as a colorless oil. $[\alpha]_D^{20} = +80.6$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3062, 3030, 2929, 2844, 1723, 1676, 1450, 1408, 1341, 1209, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H, CH_3), 1.05–1.34 (m, 18H, $CH_3C_9H_{18}$), 1.94–2.12 (m, 2H, $C_{10}H_{21}CH_2$), 2.67 (dd, *J* = 2.1, 17.8 Hz, 1H, H-3), 2.76 (dd, *J* = 6.9, 17.8 Hz, 1H, H-3′), 4.45 (d, *J* = 11.2 Hz, 1H, OCH_2), 4.55 (d, *J* = 11.2 Hz, 1H, OCH_2), 4.68 (s, 2H, NCH_2), 4.75–4.71 (ddd, *J* = 1.0, 2.1, 6.9 Hz, 1H, H-4), 4.82 (dt, *J* = 1.0, 7.7 Hz, 1H, C=CH), 7.36–7.17 (m, 10H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 26.7, 29.1, 29.3, 29.4, 29.5, 29.6 (2C), 30.1, 31.8, 36.5, 43.4, 69.9, 70.2, 108.1, 127.0, 127.2, 127.9, 128.0, 128.4, 128.4, 135.8, 137.3, 138.7, 172.9 ppm; MS (ESI): 470 *m*/*z* ($M+Na^+$); Anal. Calcd for $C_{30}H_{41}NO_2$: C, 80.49; H, 9.23; N, 3.13. Found: C, 80.13; H, 9.38; N, 3.13.

4.15. (4*S*,5*S*)-1-Benzyl-4-(benzyloxy)-5-dodecyl-2-pyrrolidinone 1bh

Following the general procedure, the hydrogenation of enamide **9bh** (290 mg, 0.65 mmol) for 4 h gave compound **1bh** (183 mg, 63%) as a colorless oil. $[\alpha]_D^{20} = +10.5$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3026, 2921, 2848, 1696, 1454, 1415, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3H, CH_3), 1.16–1.34 (m, 20H, $CH_3C_{10}H_{20}$), 1.51–1.67 (m, 1H, $C_{11}H_{23}CH_2$), 1.67–1.81 (m, 1H, $C_{11}H_{23}CH_2'$), 2.62 (dd, *J* = 4.5, 16.8 Hz, 1H, H-3), 2.55 (dd, *J* = 6.3, 16.8 Hz, 1H, H-3′), 3.47–3.53 (ddd, *J* = 3.9, 5.8, 8.4 Hz, 1H, H-5), 3.97 (d, *J* = 15.1 Hz, 1H, NCH_2), 4.07–4.12 (ddd, 1H, *J* = 4.5, 5.8, 6.3 Hz, H-4), 4.39 (d, *J* = 11.7 Hz, 1H, OCH_2), 4.56 (d, *J* = 11.7 Hz, 1H, OCH_2), 5.02 (d, *J* = 15.1 Hz, 1H, NCH_2), 7.17–7.35 (m, 10H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 25.2, 26.8, 29.3, 29.4, 29.5, 29.6, 29.6 (2C), 29.7, 31.9, 37.0, 44.0, 60.6, 71.2, 72.9, 127.3, 127.5, 127.7, 127.8, 128.3, 128.6, 136.6, 137.6, 172.7 ppm; MS (ESI): 472 *m*/*z* ($M+Na^+$); Anal. Calcd for $C_{30}H_{43}NO_2$: C, 80.13; H, 9.64; N, 3.11. Found: C, 79.99; H, 9.91; N, 2.79.

4.16. (4*S*,5*S*)-5-Benzyl-4-(benzyloxy)-2-pyrrolidinone 11

To a solution of compound **1ab** (383 mg, 0.95 mmol) in CH_3CN (29.7 mL) and H_2O (3.3 mL) was added CAN (2.618 g, 4.78 mmol), and the mixture was stirred at room temperature for 5 h. To the resulting mixture was added H_2O (60 mL), and the mixture was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed successively with saturated aqueous sodium bicarbonate and brine (5 mL), dried over anhydrous Na_2SO_4, and filtered. After concentration under reduced pressure, the resulting residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 125:1) to give compound **11** (236 mg, 88%) as a white solid. Mp 157–158 °C (EtOAc/PE); $[\alpha]_D^{20} = -35.6$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3284, 2906, 2879, 1703, 1653, 1260 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.55 (d, *J* = 5.6 Hz, 2H, H-3), 2.85 (dd, *J* = 9.8, 13.7 Hz, 1H, $NCHCH_2$), 3.08 (dd, *J* = 4.7, 13.7 Hz, 1H, $NCHCH_2'$), 3.97 (ddd, *J* = 4.7, 5.7, 9.8 Hz, 1H, H-5), 4.29 (ddd, *J* = 5.6, 5.6, 5.7 Hz, 1H, H-4), 4.51 (d, *J* = 11.7 Hz, 1H, OCH_2), 4.65 (d, *J* = 11.7 Hz, 1H, OCH_2), 5.60 (br s, 1H, NH), 7.18–7.44 (m, 10H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.5, 36.7, 59.6, 71.5, 75.1, 126.7, 127.7, 127.9, 128.5, 128.8, 129.1, 137.5, 137.9, 174.5 ppm; MS (ESI): 304 *m*/*z* ($M+Na^+$); HRESIMS calcd for [$C_{18}H_{19}NO_2$+Na^+]: 304.1313; found: 304.1321.

4.17. (4*S*,5*S*)-5-Benzyl-4-hydroxy-2-pyrrolidinone (streptopyrrolidine 5)

To 75 mg of 10% Pd/C was added a solution of compound **11** (150 mg, 0.534 mmol) in 10 mL of dry methanol. Then 2–3 drops of HCl (2 M) were added into the mixture. The mixture was stirred under 1 atm of hydrogen for 12 h at rt. It was filtered through filter paper. After concentration under reduced pressure, the resulting residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 25: 1) to give streptopyrrolidine **5** (95 mg, 93%) as a white solid. Mp 133–135 °C (CH_2Cl_2/MeOH) (lit.[6a] Mp 134–135 °C); $[\alpha]_D^{20} = -43.5$ (*c* 1.0, MeOH) {lit. $[\alpha]_D^{25} = -12$ (*c* 0.05, MeOH);[5] $[\alpha]_D^{20} = -44$ (*c* 1.0, MeOH)[6a]}; IR (film) ν_{max}: 3278, 2917, 1682, 1449, 1262, 1063; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (dd, *J* = 2.4, 17.2 Hz, 1H, H-3), 2.65 (dd, *J* = 6.0, 17.2 Hz, 1H, H-3′), 2.84 (dd, *J* = 9.0, 13.7 Hz, 1H, $NCHCH_2$), 3.04 (dd, *J* = 5.7, 13.7 Hz, 1H, $NCHCH_2$), 3.22 (d, *J* = 6.0 Hz, 1H, OH), 3.85–3.92 (ddd, *J* = 5.7, 5.7, 9.0 Hz, 1H, H-5), 4.44 (ddd, *J* = 2.4, 5.7, 6.0 Hz, 1H, H-5), 5.84 (br s, 1H, NH), 7.22–7.37 (m, 5H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.3, 40.9, 60.8, 68.6, 126.8, 128.9, 129.0, 137.7, 175.8 ppm; ^1H NMR (500 MHz, DMSO-d_6) δ 1.97 (dd, *J* = 2.6, 16.5 Hz, 1H, H-3), 2.38 (dd, *J* = 5.9, 16.5 Hz, 1H, H-3′), 2.65 (dd, *J* = 6.1, 13.5 Hz, 1H, $NCHCH_2$), 2.96 (dd, *J* = 8.0, 13.5 Hz, 1H, $NCHCH_2'$), 3.67 (ddd, *J* = 5.7, 6.1, 8.0 Hz, 1H, H-5), 4.10 (ddd, *J* = 2.6, 5.7, 5.9 Hz, 1H, H-4), 5.14 (d, *J* = 5.0 Hz, 1H, OH), 7.17–7.22 (m, 1H, ArH), 7.24–7.30 (m, 4H, ArH), 7.53 (br s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 34.6, 40.9, 60.1, 66.9, 126.0, 128.2, 129.2, 138.7, 174.8 ppm; MS (ESI): 214 *m*/*z* ($M+Na^+$); HRESIMS calcd for [$C_{11}H_{13}NO_2$+H^+]: 192.1025; found: 192.1024.

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