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# Towards Reaction Control: *cis*-Diastereoselective Reductive Dehydroxylation of 5-Alkyl-4-Benzyloxy-5-Hydroxy-2-Pyrrolidinones

**Yu-Huang Wang, Wei Ou, Linfeng Xie, Jian-Liang Ye, and Pei-Qiang Huang*[a]**

**Abstract:** A chemo-, regio-, and stereoselectively controlled reaction is highly desirable, yet challenging in organic synthesis. Diversely substituted *cis* and *trans* isomers of 2-alkyl-3-pyrrolidinols, 5-alkyl-4-hydroxy-2-pyrrolidinones, β-hydroxy-γ-amino acids, and their higher homologues are key structural units found in numerous drugs, drug candidates, and bioactive natural products. Previously, we established a flexible approach to *trans*-5-alkyl-4-benzyloxy-2-pyrrolidinones **14** and *trans*-6-alkyl-5-benzyloxy-2-piperidinones **15**. Herein, we report a direct, flexible, moisture insensitive, and highly diastereoselective approach to the corresponding *cis* diastereomers **16**. This stereocontrolled method is based on the MsOH-mediated (Ms = methane sulfonyl) reductive dehydroxylation of hemiaminal **12** with $NaBH(OAc)_3$. *cis*-5-Alkyl-4-benzyloxy-2-pyrrolidinones **16** are useful building blocks for the syntheses of natural products such as (+)-preussin (**4**) and streptopyrrolidine (**5**) as well as (3*S*,4*S*)-γ-alkyl-β-hydroxy-γ-amino acids (**6**).

**Keywords:** amino acids · diastereoselectivity · natural products · pyrrolidin-2-ones · synthetic methods

## Introduction

Efficiency and selectivity are important goals in organic synthesis.[1] Although a huge number of synthetic strategies are available,[2] the development of efficient and stereoselective reactions and methods remains a major pursuit for many synthetic organic and medicinal chemists.[3–5] The absolute control of chemo-, regio-, and stereoselectivity can significantly enhance the efficiency of a reaction, thus rendering a step-economical synthetic method.[3] In this regard, C–H bond activation,[4] CDC (cross-dehydrogenative coupling),[5] and related methods[5] are typical themes, which have attracted considerable attention. In addition to these examples, systematic studies aimed at reaction control, in general, are expected to gain popularity in the near future. However, the realization of chemo-, regio-, and stereoselective control is still a challenging task, because of the diversity of molecules and the complexity of reactions, caused by the reagent, catalyst, solvent, temperature, and so on.

Diversely substituted 3-pyrrolidinols, 4-hydroxy-2-pyrrolidinones, β-hydroxy-γ-amino acids, and their higher homologues are key structural units found in numerous drugs, drug candidates, and bioactive natural products. For example, nemonapride (**1**) is a potent antipsychotic drug, and (*S*)-ypaoamide (**2**) is a new and broadly acting feeding deterrent. Hapalosin (**3**) has significant multidrug resistance (MDR)-reversing activity, and (+)-preussin (**4**) is a pyrrolidine alkaloid that has potent antifungal activity. Streptopyrrolidine (**5**) is expected to be an angiogenesis inhibitor, and (3*S*,4*S*)-γ-alkyl-β-hydroxy-γ-amino acids (**6**) are pivotal building blocks for peptide mimetics and key subunits of inhibitors of aspartyl and HIV proteases. Furthermore, (2*S*,3*S*)-L-733,060 (**7**) is a selective and potent neurokinin substance P receptor antagonist, and (−)-morusimic acid D (**8**) is an amino acid isolated from the white ripened fruit from *Morus alba*, which is grown in Turkey. Finally, awajanomycin (**9**) has cytotoxic activity against adenocarcinomic human alveolar basal epithelial cells (A549, Scheme 1).

In recent years, we have been engaged in the development of synthetic methods based on the multifunctional building blocks *O*-benzyl (*R*)- or (*S*)-malimides **10** and 3-benzyloxyglutarimides **11**. We have also established a flexible approach to prepare *trans*-5-alkyl-4-benzyloxy-2-pyrrolidinones **14** and *trans*-6-alkyl-5-benzyloxy-2-piperidinones **15** (Scheme 2),[6] which were used as key intermediates in the stereoselective syntheses of several natural products and pharmaceuticals such as nemonapride (**1**),[6c] (*R*)-ypaoamide (**2**),[7] hapalosin (**3**),[8] morusimic acid D (**8**),[9] and awajanomycin (**9**).[10]

To access *cis*-5-alkyl-4-benzyloxy-2-pyrrolidinones, which are useful building blocks for the syntheses of natural products and drugs such as preussin (**4**),[11] streptopyrrolidine (**5**),[12] (2*S*,3*S*)-L-733,060 (**7**), and β-hydroxy-γ-amino acids such as **6a–6c**, two stepwise methods have been developed.[13,14] In view of a step-economical synthesis,[3] a versatile and direct approach to *cis*-5-alkyl-4-hydroxy-2-pyrroli-

[a] Y.-H. Wang, W. Ou, Prof. Dr. L. Xie, Dr. J.-L. Ye, Prof. Dr. P.-Q. Huang
Department of Chemistry and Fujian Provincial Key Laboratory of Chemical Biology
College of Chemistry and Chemical Engineering
Xiamen University, Xiamen, Fujian 361005 (P. R. China)
Fax: (+86) 592-2186400
E-mail: pqhuang@xmu.edu.cn

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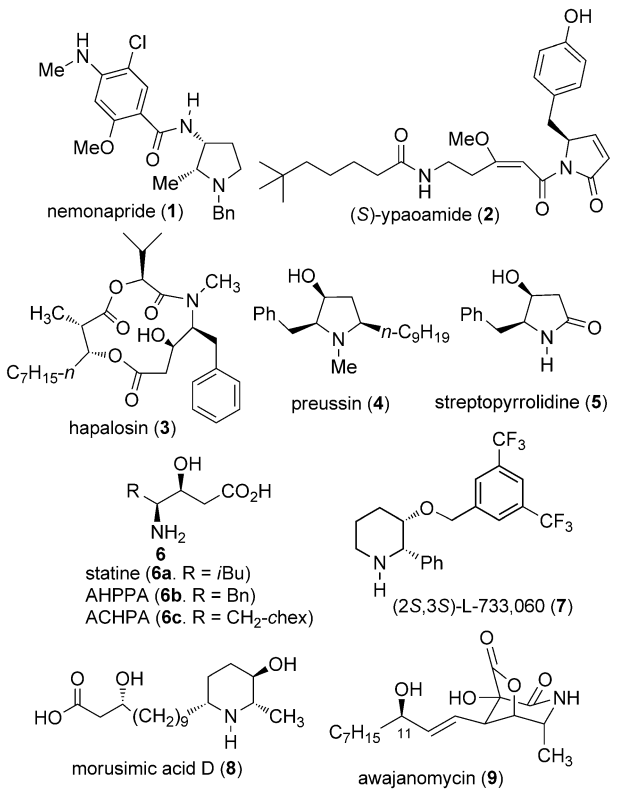
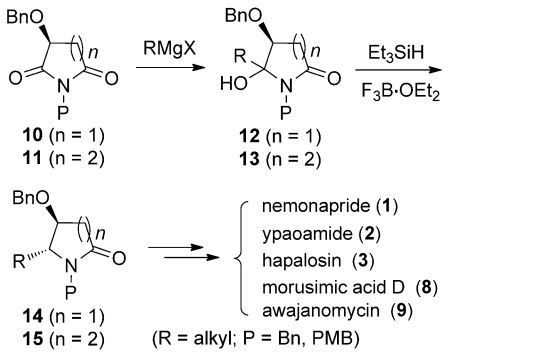



Scheme 1. Some natural products that contain 3-pyrrolidinol, 4-hydroxy-2-pyrrolidinone, β-hydroxy-γ-amino acid, and their higher homologues as key structural units.



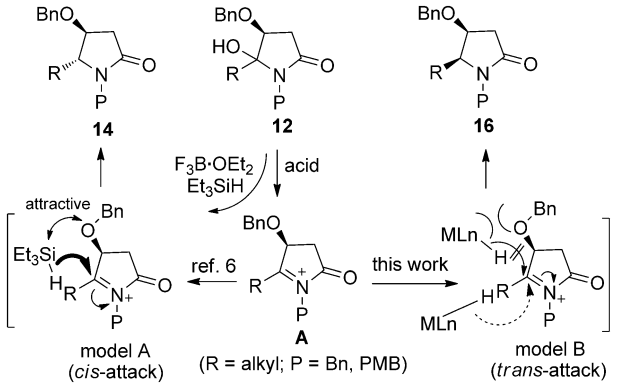

Scheme 2. Our previous flexible approach to *trans*-5-alkyl-4-benzyloxy-2-pyrrolidinones **14** and *trans*-6-alkyl-5-benzyloxy-2-piperidinones **15** and their use in the syntheses of pharmaceuticals and natural products. Bn = benzyl; PMB = *p*-methoxybenzyl.

dinones and *cis*-6-alkyl-5-hydroxy-2-piperidinones is highly desirable.

Keeping reaction control in mind, we herein report an efficient approach to *cis*-(4*S*,5*S*)-5-alkyl-4-benzyloxy-2-pyrrolidinones **16** through a highly *cis*-diastereoselective reductive dehydroxylation of hemiaminals **12**.

## Results and Discussion

We assumed that the reductive dehydroxylation of hemiaminal **12** (Scheme 2) proceeded through *N*-acyliminium intermediate[15] **A** (Scheme 3), and the subsequent reduction



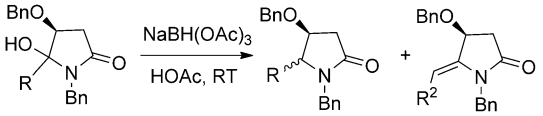

Scheme 3. Two models of diastereoselective control for the diastereodivergent approaches to *trans*- and *cis*-5-alkyl-4-benzyloxy-2-pyrrolidinones.

was controlled under the reaction conditions by the attraction between the reductant $Et_3SiH$ and the OBn group at the C4 position (Scheme 3, model A).[6] Thus, we hypothesized that treating hemiaminals **12** with the alternative reducing system $L_nMH$ would lead to a repulsion between $L_nMH$ and the OBn group in the N-acyliminium intermediate (Scheme 3, model B) and then directly provide *cis*-5-alkyl-4-benzyloxy-2-pyrrolidinones **16**. This hypothesis was partially confirmed by our preliminary studies of the $Me_3SiCl$-mediated $Zn(BH_4)_2$ reductive dehydroxylation of **12**, in which lactams **16** were obained, in most cases, with modest *cis* diastereoselectivities.[16]

On the basis of our preliminary work[16] and in consideration of the cost and moisture-sensitivity of the reducing agent and Lewis acid, we set out to investigate the alternative $NaBH_4$/HOAc reducing system.[17] Hemiaminal **12a** was treated with $NaBH_4$ (8 equiv) in HOAc at room temperature for 6 h, and **16a** was obtained in 94% yield with high *cis* diastereoselectivity (*cis*/*trans* = 91:9). In this case, $NaBH_4$ was treated with HOAc to give $NaBH(OAc)_3$ in situ as the active reducing agent. Therefore, it was not surprising that we obtained **16a** with the same *cis* diastereoselectivity (Table 1, entry 1) upon treating **12a** directly with commercially available $NaBH(OAc)_3$ in HOAc. These promising results prompted us to carry out the remainder of the studies with $NaBH(OAc)_3$ as the reductant to avoid the exothermic effect from the reaction between $NaBH_4$ and HOAc. The results of the reductive dehydroxylation of **12a** in different solvent combinations are summarized in Table 1. Evidently, an improvement in the *cis* diastereoselectivity was observed as the ratio of $CH_2Cl_2$/HOAc increased from 0:1 to 2:1 (Table 1, entries 1–3). However, a further increase in the amount of $CH_2Cl_2$ resulted in

Table 1. Reductive dehydroxylation of hemiaminals **12** with $NaBH(OAc)_3$ in HOAc.




**12** **16 + 14** **17**

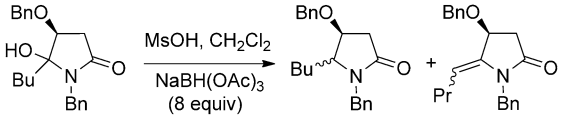
| Entry | Substrate | $R/R^2$ | $CH_2Cl_2$/HOAc [v/v] | **16**/**14**[a] | Yield [%] of **16**+**14**[b] | Yield [%] of **17**[b] |
|---|---|---|---|---|---|---|
| 1 | **12a** | Me/H | 0:1 | 91:9 | 95 | 0 |
| 2 | **12a** | Me/H | 1:1 | 95:5 | 96 | 0 |
| 3 | **12a** | Me/H | 2:1 | 96:4 | 94 | 0 |
| 4 | **12a** | Me/H | 4:1 | 96:4 | 87 | 0 |
| 5 | **12a** | Me/H | 8:1 | 97:3 | 74 | 0 |
| 6 | **12a** | Me/H | 16:1 | 96:4 | 70 | 0 |
| 7 | **12b** | Et/Me | 2:1 | 97:3 | 76 | 19 |
| 8 | **12c** | *i*Bu/*i*Pr | 2:1 | 84:16 | 49 | 40 |
| 9 | **12d** | *n*Bu/*n*Pr | 2:1 | 92:8 | 66 | 30 |

[a] Determined by $^1H$ NMR spectroscopy of the crude product. [b] Yield of isolated product.

lower yields, but nearly the identical *cis* selectivity (Table 1, entries 3–6). Using the optimal reaction conditions, this HOAc-mediated $NaBH(OAc)_3$ reductive reaction was then extended to the higher homologues of **12a**. The reduction of hemiaminals **12b**–**12d** gave the desired reductive dehydroxylation products **16b**–**16d** in modest (Table 1, entry 8) to high (Table 1, entries 7 and 9) *cis* diastereoselectivity. Meanwhile, substantial amounts of **17b**–**17d** were obtained as the side products (Table 1, entries 7–9, ca. 19–40 %).[18] Although the *exo*-dehydration product **17** could be stereoselectively hydrogenated to **16**, as we reported previously,[13] it would be significant to be able to suppress this side reaction.

Because the elimination reaction might be favored by the presence of the acetate ion, we envisioned that a stronger acid than HOAc might diminish the elimination pathway. Therefore, we first tested TFA (trifluoroacetic acid) in combination with $NaBH(OAc)_3$ in the reductive dehydroxylation reaction. As expected, in the TFA-mediated reduction of 5-butyl-hemiaminal **12d** with $NaBH(OAc)_3$, the dehydration product **17d** was not obtained. However, the reaction slightly favored the *trans* diastereomer (*cis*/*trans* = 43:57). A subsequent experiment with methane sulfonic acid (MsOH)/$NaBH(OAc)_3$ in $CH_2Cl_2$ ($CH_2Cl_2$/MsOH, v/v = 4:1) proceeded with a modest *cis* diastereoselectivity and an excellent yield (Table 2, entry 1). Increasing the ratio of $CH_2Cl_2$/MsOH had negligible effects on the diastereoselectivity or the yield (Table 2, entries 1–3). Then, we investigated using a 16:1 ratio of $CH_2Cl_2$/MsOH (20 equiv of MsOH). Under these conditions, the reaction proceeded smoothly at lower temperatures; however, the *cis* diastereoselectivity decreased (Table 2, entries 4 and 5). Presumably, the reaction could be an entropy controlled process.[19] Following this temperature-dependent trend, we obtained the highest *cis* diastereoselectivity by heating the reaction mixture at reflux (Table 2, entry 6).

Table 2. Investigation of the conditions for the reductive dehydroxylation of hemiaminal **12d** with $NaBH(OAc)_3$/MsOH.



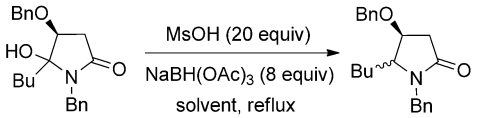

**12d** **16d + 14d** **17d**

| Entry | $CH_2Cl_2$/MsOH | *T* [°C] | (**16d**+**14d**)/**17d** | **16d**/**14d**[a] | Yield [%] of **16d**+**14d**[b] |
|---|---|---|---|---|---|
| 1 | 4:1 | RT | 1:0 | 83:17 | 98 |
| 2 | 8:1 | RT | 1:0 | 84:16 | 97 |
| 3 | ~16:1[c] | RT | 1:0 | 85:15 | 98 |
| 4 | ~16:1[c] | 0 | 1:0 | 80:20 | 98 |
| 5 | ~16:1[c] | −40 | 1:0 | 70:30 | 98 |
| 6 | ~16:1[c] | reflux | 1:0 | 91:9 | 96 |

[a] Determined by $^1H$ NMR spectroscopy of the crude product. [b] Yield of isolated product. [c] MsOH (20 equiv) relative to **12d**.

To improve the diastereoselectivity further, we next tried other solvents with higher boiling points. As outlined in Table 3, a higher *cis* diastereoselectivity (*cis*/*trans* = 95:5) was indeed obtained when the reaction was carried out in $CHCl_3$ (Table 3, entry 2). Besides the boiling point of the

Table 3. Solvents screened for the reductive dehydroxylation of hemiaminal **12d** with $NaBH(OAc)_3$ and MsOH.




**12d** **16d + 14d**

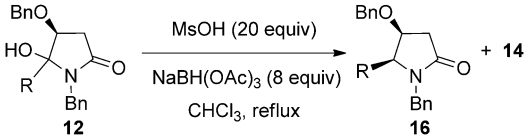
| Entry | Solvent | b.p. [°C] | **16d**/**14d**[a] | Yield [%] of **16d**+**14d**[b] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 40 | 91:9 | 96 |
| 2 | $CHCl_3$ | 61 | 95:5 | 93 |
| 3 | THF | 66 | 93:7[c] | 90 |
| 4 | $CH_3CN$ | 82 | 84:16 | 94 |
| 5 | $ClCH_2CH_2Cl$ | 83 | 94:6[c] | 62 |
| 6 | $PhCH_3$ | 111 | complex | – |

[a] Determined by $^1H$ NMR spectroscopy of the crude product. [b] Yield of isolated product. [c] Determined by HPLC of the crude product.

solvent, other factors such as solvent polarity seemed to be important as well (Table 3, entries 3–5). For example, complex products were obtained by heating the reaction mixture at reflux in toluene (111 °C), but no major products could be identified. Thus, the optimal protocol was defined as the treatment of hemiaminal **12d** with 8 equiv of $NaBH(OAc)_3$ and 20 equiv of MsOH in $CHCl_3$, and then heating the resulting mixture at reflux (Table 3, entry 2).

With these optimized conditions defined, we proceeded to study the reductive dehydroxylation of hemiaminals **12** with various substituents at the C5 position. As outlined in Table 4, the reductive dehydroxylation in $CHCl_3$ of hemiaminals **12a**–**12i**, that contain either a saturated straight-chain alkyl group (Table 4, entries 1–8) or an unsaturated straight-chain alkyl group with a terminal double bond

Table 4. Reductive dehydroxylation of hemiaminals **12a–12i** under the optimal reaction conditions.

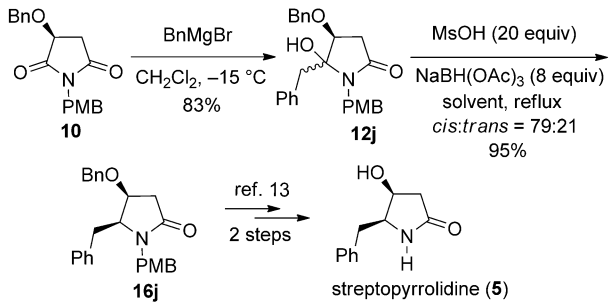



| Entry | Substrate | R | **16**/**14**[a] | Yield [%] of **16**+**14**[b] |
|---|---|---|---|---|
| 1 | **12a** | $CH_3$ | 97:3[c] | **16a**+**14a** (96) |
| 2 | **12b** | $C_2H_5$ | 96:4 | **16b**+**14b** (97) |
| 3 | **12c** | $iC_4H_9$ | 89:11 | **16c**+**14c** (86) |
| 4 | **12d** | $nC_4H_9$ | 96:4 | **16d**+**14d** (93) |
| 5 | **12e** | $nC_3H_7$ | 95:5 | **16e**+**14e** (93) |
| 6 | **12f** | $nC_5H_{11}$ | 96:4 | **16f**+**14f** (92) |
| 7 | **12g** | $nC_7H_{15}$ | 95:5 | **16g**+**14g** (94) |
| 8 | **12h** | $nC_{16}H_{33}$ | 95:5 | **16h**+**14h** (92) |
| 9 | **12i** | $CH_2=CH(CH_2)_3CH_2$ | 96:4 | **16i**+**14i** (96) |

[a] Determined by $^1$H NMR spectroscopy of the crude product. [b] Yield of isolated product. [c] Determined by HPLC of the crude product.

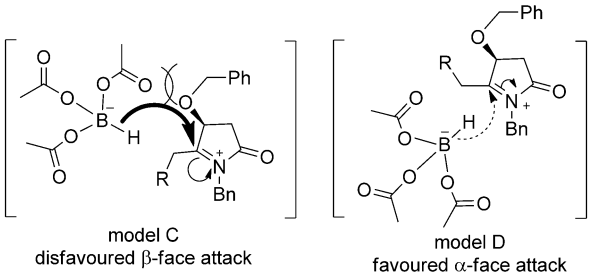
(Table 4, entry 9), resulted in the formation of the desired 5-alkyl-4-benyzloxy-2-pyrrolidinones **16a–16i** in excellent yields and *cis* diastereoselectivity (Table 4, entries 1–9). The tolerance of a side chain with a C=C functionality was noteworthy, because it would allow further functional group transformations.

Next, we extended this newly developed method to the reductive dehydroxylation of compound **12j** (Scheme 4), which contains a PMB (*p*-methoxybenzyl) group, (Scheme 3) to obtain the key intermediate **16j** that is needed for the syntheses of natural products such as streptopyrrolidine and (+)-preussin. Under the same reaction conditions, the desired product **16j** was obtained in an excellent yield, but with modest *cis* selectivity (Scheme 4). As we reported previously,[13] **16j** can be converted into streptopyrrolidine (**5**)[20] through N-deprotection with ceric ammonium nitrate (CAN), followed by O-debenzylation under catalytic hydrogenolysis conditions. In addition, starting from **16j**, (+)-preussin (**4**)[21] can also be readily obtained through an one-pot reductive alkylation of the lactam with *n*-nonylmagnesium bromide,[22] followed by a one-pot debenzylation–urethanation and then a final reduction with $LiAlH_4$.[21s] The current reductive dehydroxylation approach effectively reduced the number of steps to accomplish the total syntheses of these target molecules.




Scheme 4. A formal synthesis of streptopyrrolidine (**5**).

To explain the origin of the *cis* selectivity, we envision a mechanism involving an N-acyliminium ion, which results from the acid-catalyzed dehydroxylation (Scheme 3 and 5).[6] Starting from this presupposition, depicted in Scheme 5, the approach of the hydride from the β face is hindered by the repulsion between the OBn group at the




Scheme 5. Course of the diastereoselective reaction.

C4 position and the bulky $B(OAc)_3$ group (Scheme 5, model C). Thus, model D is favored with the hydride attacking at the C5 position from side opposite to that of the OBn group to give the *cis* isomer. However, as the substituent at the C5 position becomes more bulky, such as in the cases of **12c** (R = *i*Bu) and **12j** (R = Bn), the repulsion between the OBn group at the C4 position and the C5 substituent in the resulting product becomes more severe and leads to a decrease in the *cis* diastereoselectivity.

## Conclusions

In summary, we have developed a direct, flexible, moisture insensitive, and highly diastereoselective approach to *cis*-5-alkyl-4-hydroxy-2-pyrrolidinones **16**. The diastereoselective control in the reductive dehydroxylation of α-hydroxylactams **12** was realized by modifying the reaction variables in the reducing reagent system. Starting from malimide **10**, (+)-preussin (**4**) and streptopyrrolidine (**5**) could be efficiently synthesized through this reductive approach in four and five steps, respectively, with modest selectivity.

## Experimental Section

*General Methods*

Melting points are uncorrected. Optical rotations were recorded on a Perkin–Elmer 341 automatic polarimeter. HRMS FAB spectra were recorded on a 7.0T FT-MS. $^1$H and $^{13}$C NMR spectroscopic data were recorded on a Bruker Avance III spectrometer at 400 and 100 MHz, respectively. Chemical shifts ($\delta$) are reported in ppm and referenced to the internal standard $Me_4Si$ or the solvent signals ($Me_4Si$, 0 ppm for $^1$H NMR; $CDCl_3$, 77.0 ppm for $^{13}$C NMR). Silica gel (300–400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with an ethyl acetate/hexane mixture. Dry THF was distilled over sodium benzophenone ketyl under $N_2$. Dry dichloromethane was distilled over calcium hydride under $N_2$. Other solvents were analytically pure and commercially available.

*General procedure of the preparation of (4S,5S)-5-Substituted-4-benzyloxy-2-pyrrolidinones **16** from hemiaminals **12***

Chloroform (6 mL) was added to a Schlenk tube containing hemiaminals **12a**–**12i** (0.3 mmol) and $NaBH(OAc)_3$ (510 mg, 2.4 mmol). After the tube was sealed, the mixture was heated at reflux and stirred at that temperature. Then, methanesulfonic acid (0.39 mL, 6.0 mmol) was added. After stirring for 1 h, the mixture was cooled to 0 °C and then was quenched with a saturated $NaHCO_3$ solution (6 mL). The mixture was extracted with $CH_2Cl_2$ (3×6 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 a silica gel column (ethyl acetate/hexane = 1:5) to give diastereomers **16a**–**16i** and **14a**–**14i** (86–97 % combined yield; *cis*/*trans*, from 89:11 to 97:3).

*(4S,5S)-1-Benzyl-4-benzyloxy-5-methyl-2-pyrrolidinone (**16a**)*

Following the general procedure, the reduction of hemiaminal **12a** gave **16a** (82.5 mg) as a colorless oil, along with diastereomer **14a** (2.6 mg). The combined yield of two diastereomers (96 %, *cis*/*trans* = 97:3) was determined by HPLC of the crude product. $R_f$ = 0.38 (hexane/EtOAc = 3:1); $[\alpha]_D^{20} = -31.8$ ($c$ = 1.0 in $CHCl_3$), ref. [16] $[\alpha]_D^{25} = -28.5$ ($c$ = 1.0 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.19 (d, $J$ = 6.6 Hz, 3H; $CH_3$), 2.58 (dd, $J$ = 6.7, 17.2 Hz, 1H; H-3), 2.61 (dd, $J$ = 6.7, 17.2 Hz, 1H; H-3), 3.65 (app. quintet, $J$ = 6.6 Hz, 1H; H-5), 3.95 (d, $J$ = 15.2 Hz, 1H; $NCH_2$), 4.10 (app. q, $J$ = 6.7 Hz, 1H; H-4), 4.44 (d, $J$ = 11.8 Hz, 1H; $OCH_2$), 4.53 (d, $J$ = 11.8 Hz, 1H; $OCH_2$), 5.01 (d, $J$ = 15.2 Hz, 1H; $NCH_2$), 7.21–7.36 ppm (m, 10H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 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, 137.6, 172.0 ppm; IR (film): $\tilde{\nu}_{max}$ = 3063, 3029, 2975, 2930, 2867, 1691, 1495, 1453, 1416, 1124 cm$^{-1}$; MS (ESI): $m/z$: 318 $[M+Na]^+$; HRMS (ESI): $m/z$: calcd for $C_{19}H_{21}NO_2Na$: 318.1465 $[M+Na]^+$; found: 318.1471.

*(4S,5S)-1-Benzyl-4-benzyloxy-5-ethyl-2-pyrrolidinone (**16b**)*

Following the general procedure, the reduction of hemiaminal **12b** gave **16b** (86.6 mg) as a white solid, along with diastereomer **14b** (2.9 mg). The combined yield of the two diastereomers (97 %; *cis*/*trans* = 96:4) was determined by $^1$H NMR spectroscopy of the crude product. $R_f$ = 0.34 (hexane/EtOAc = 3:1); m.p. 80–82 °C; $[\alpha]_D^{20} = +13.1$ ($c$ = 1.0 in $CHCl_3$), ref. [16] $[\alpha]_D^{25} = +12.7$ ($c$ = 0.6 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.87 (t, $J$ = 7.4 Hz, 3H; $CH_3$), 1.62–1.83 (m, 2H; $CH_2$), 2.56 (dd, $J$ = 6.4, 16.8 Hz, 1H; H-3), 2.63 (dd, $J$ = 4.8, 16.8 Hz, 1H; H-3′), 3.47 (ddd, $J$ = 3.9, 6.0, 8.8 Hz, 1H; H-5), 3.97 (d, $J$ = 15.2 Hz, 1H; $NCH_2$), 4.13 (ddd, $J$ = 4.8, 6.0, 6.4 Hz, 1H; H-4), 4.41 (d, $J$ = 11.7 Hz, 1H; $OCH_2$), 4.57 (d, $J$ = 11.7 Hz, 1H; $OCH_2$), 5.02 (d, $J$ = 15.2 Hz, 1H; $NCH_2$), 7.18–7.38 ppm (m, 10H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 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; IR (film): $\tilde{\nu}_{max}$ = 3063, 3030, 2969, 2930, 2871, 1691, 1495, 1455, 1424, 1065 cm$^{-1}$; MS (ESI): $m/z$: 332 $[M+Na]^+$; HRMS (ESI): $m/z$: calcd for $C_{20}H_{23}NNaO_2$: 332.1621 $[M+Na]^+$; found: 332.1624.

*(4S,5S)-1-Benzyl-4-benzyloxy-5-isobutyl-2-pyrrolidinone (**16c**)*

Following the general procedure, the reduction of hemiaminal **12c** gave **16c** and **14c** (87 mg, 86 %) as a white solid. The diastereoselectivity of the reaction (*cis*/*trans* = 89:11) was determined by $^1$H NMR spectroscopy of the crude product, which was inseparable by chromatography. $R_f$ = 0.34 (hexane/EtOAc = 3:1); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.75 (d, $J$ = 6.4 Hz, 3H; $CH_3$), 0.87 (d, $J$ = 6.4 Hz, 3H; $CH_3$), 1.29–1.39 (m, 1H; $C_2H_6CH$), 1.54–1.68 (m, 1H; $NCHCH_2$), 1.82 (ddd, $J$ = 4.3, 10.1, 13.8 Hz, 1H; $NCHCH_2$′), 2.54 (dd, $J$ = 5.9, 16.8 Hz, 1H; H-3), 2.64 (dd, $J$ = 3.8, 16.8 Hz, 1H; H-3′), 3.54 (ddd, $J$ = 4.3, 5.3, 9.7 Hz, 1H; H-5), 3.93 (d, $J$ = 15.1 Hz, 1H; $NCH_2$), 4.08 (ddd, $J$ = 3.8, 5.6, 5.9 Hz, 1H; H-4), 4.38 (d, $J$ = 11.5 Hz, 1H; $OCH_2$), 4.56 (d, $J$ = 11.5 Hz, 1H; $OCH_2$), 5.05 (d, $J$ = 15.1 Hz, 1H; $NCH_2$), 7.18–7.38 ppm (m, 10H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 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; IR (film): $\tilde{\nu}_{max}$ = 3063, 3029, 2959, 2932, 2868, 1690, 1495, 1453, 1421, 1088 cm$^{-1}$; MS (ESI): $m/z$: 360 $[M+Na]^+$; HRMS (ESI): $m/z$: calcd for $C_{22}H_{27}NNaO_2$: 360.1934 $[M+Na]^+$; found: 360.1939.

*(4S,5S)-1-Benzyl-4-benzyloxy-5-(n-butyl)-2-pyrrolidinone (**16d**)*

Following the general procedure, the reduction of hemiaminal **12d** gave **16d** (90.4 mg) as a colorless oil, along with diastereomer **14d** (3.8 mg). The combined yield of two diastereomers (93 %; *cis*/*trans* = 96:4) was determined by $^1$H NMR spectroscopy of the crude product. $R_f$ = 0.34 (hexane/EtOAc = 3:1); $[\alpha]_D^{20} = +11.0$ ($c$ = 1.0 in $CHCl_3$), ref. [16] $[\alpha]_D^{20} = +13.1$ ($c$ = 1.2 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.84 (t, $J$ = 6.9 Hz, 3H; $CH_3$), 1.12–1.34 (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′), 3.50 (ddd, $J$ = 4.0, 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, 6.3 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; $NCH_2$), 7.18–7.37 ppm (m, 10H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 13.9, 22.8, 26.5, 27.3, 37.0, 44.0, 60.6, 71.2, 72.9, 127.4, 127.6, 127.8, 127.8, 128.4, 128.6, 136.6, 137.6, 172.7 ppm; IR (film): $\tilde{\nu}_{max}$ = 3065, 3025, 2952, 2935, 2863, 1688, 1493, 1456, 1423, 1092 cm$^{-1}$; MS (ESI): $m/z$: 360 $[M+Na]^+$; HRMS (ESI): $m/z$: calcd for $C_{22}H_{27}NO_2+Na^+$: 360.1934 $[M+Na]^+$; found: 360.1938.

*(4S,5S)-1-Benzyl-4-benzyloxy-5-(n-propyl)-2-pyrrolidinone (**16e**)*

Following the general procedure, the reduction of hemiaminal **12e** gave **16e** and **14e** (90 mg, 93 %) as a white solid. The diastereoselectivity of the reaction (*cis*/*trans* = 95:5) was determined by $^1$H NMR spectroscopy of the crude product, which was inseparable by chromatography. $R_f$ = 0.34 (hexane/EtOAc = 3:1); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.87 (t, $J$ = 7.4 Hz, 3H; $CH_3$), 1.15–1.38 (m, 2H), 1.53–1.63 (m, 1H), 1.67–1.80 (m, 1H), 2.55 (dd, $J$ = 6.4, 16.8 Hz, 1H; H-3), 2.61 (dd, $J$ = 4.7, 16.8 Hz, 1H; H-3), 3.51 (ddd, $J$ = 3.9, 5.8 9.4 Hz, 1H; H-5), 3.97 (d, $J$ = 15.2 Hz, 1H; $NCH_2$), 4.10 (ddd, $J$ = 4.7, 6.0, 6.4 Hz, 1H; H-4), 4.40 (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; $NCH_2$), 7.20–7.40 ppm (m, 10H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 14.3, 18.6, 29.1, 37.0, 44.0, 60.4, 71.3, 73.0, 127.4 (2C), 127.5 (2C), 127.8 (2C), 127.8 (2C), 128.4 (2C), 128.6 (2C), 136.7, 137.6, 172.7 ppm; IR (film): $\tilde{\nu}_{max}$ = 3066, 3030, 2958, 2930, 2870, 1692, 1496, 1454, 1420, 1096 cm$^{-1}$; MS (ESI): $m/z$: 346 $[M+Na]^+$; HRMS (ESI): $m/z$: calcd for $C_{21}H_{25}NNaO_2$: 346.1778 $[M+Na^+]$; found: 346.1782.

*(4S,5S)-1-Benzyl-4-benzyloxy-5-(n-pentyl)-2-pyrrolidinone (**16f**)*

Following the general procedure, the reduction of hemiaminal **12f** gave **16f** (93.2 mg) as a colorless oil, along with diastereomer **14f** (2.9 mg). The combined yield of two diastereomers (92 %; *cis*/*trans* = 96:4) was determined by $^1$H NMR spectroscopy of the crude product. $R_f$ = 0.34 (hexane/EtOAc = 3: 1); $[\alpha]_D^{20} = +13.9$ ($c$ = 1.0 in $CHCl_3$), ref. [16] $[\alpha]_D^{25} = +14.3$ ($c$ = 1.8 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.84 (t, $J$ = 6.7 Hz, 3H; $CH_3$), 1.15–1.31 (m, 6H; $CH_3C_3H_6$), 1.55–1.64 (m, 1H; $NCHCH_2$), 1.69–1.79 (m, 1H; $NCHCH_2$), 2.56 (dd, $J$ = 6.2, 16.9 Hz, 1H; H-3), 2.62 (dd, $J$ = 4.8, 16.9 Hz, 1H; H-3′), 3.50 (ddd, $J$ = 4.0, 5.9, 9.3 Hz, 1H; H-5), 3.97 (d, $J$ = 15.1 Hz, 1H; $NCH_2$), 4.10 (ddd, $J$ = 4.8, 5.9, 6.2 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 ppm (m, 10H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 13.9, 22.4, 24.9, 26.8, 32.0, 37.0, 44.0, 60.6, 71.3, 72.9, 127.4, 127.6, 127.8, 127.8, 128.4, 128.6, 136.7, 137.7, 172.8 ppm; IR (film): $\tilde{\nu}_{max}$ = 3062, 3030, 2953, 2928, 2858, 1693, 1494, 1454, 1419, 1095 cm$^{-1}$; MS (ESI): $m/z$: 374 $[M+Na]^+$; HRMS (ESI): $m/z$: calcd for $C_{23}H_{29}NNaO_2$: 374.2091 $[M+Na]^+$; found: 374.2098

*(4S,5S)-1-Benzyl-4-benzyloxy-5-(n-septyl)-2-pyrrolidinone (**16g**)*

Following the general procedure, the reduction of hemiaminal **12g** gave **16g** (101.6 mg) as a colorless oil, along with diastereomer **14g** (5.4 mg). The combined yield of two diastereomers (94 %; *cis*/*trans* = 95:5) was determined by $^1$H NMR spectroscopy of the crude product. $R_f$ = 0.34 (hexane/EtOAc = 3:1); m.p. 52–53 °C; $[\alpha]_D^{20} = +15.8$ ($c$ = 1.0 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 0.87 (t, $J$ = 6.9 Hz, 3H; $CH_3$), 1.15–1.32 (m, 10H; $CH_3C_5H_{10}$), 1.54–1.64 (m, 1H; $NCHCH_2$), 1.69–1.79 (m, 1H; $NCHCH_2$), 2.55 (dd, $J$ = 6.4, 16.8 Hz, 1H; H-3), 2.62 (dd, $J$ = 4.8,

16.8 Hz, 1H; H-3′), 3.50 (ddd, $J$=4.0, 5.9, 9.3 Hz, 1H; H-5), 3.97 (d, $J$=15.1 Hz, 1H; $NCH_2$), 4.10 (ddd, $J$=4.8, 5.9, 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; $NCH_2$), 7.19–7.36 ppm (m, 10H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=14.0, 22.6, 25.2, 26.8, 29.1, 29.7, 31.7, 37.0, 44.0, 60.6, 71.3, 73.0, 127.4, 127.6, 127.8, 127.8, 128.4, 128.6, 136.7, 137.6, 172.7 ppm; IR (film): $\tilde{\nu}_{max}$=3063, 3030, 2926, 2855, 1694, 1496, 1454, 1420, 1098 cm$^{-1}$; MS (ESI): $m/z$: 402 [$M$+Na]$^+$; HRMS (ESI): $m/z$: calcd for $C_{25}H_{33}NNaO_2$: 402.2404 [$M$+Na]$^+$; found: 402.2410.

*(4S,5S)-1-Benzyl-4-benzyloxy-5-(n-hexadecyl)-2-pyrrolidinone (**16h**)*

Following the general procedure, the reduction of hemiaminal **12h** gave **16h** (133.3 mg) as a white solid, along with diastereomer **14h** (6.8 mg). The combined yield of two diastereomers (92%; *cis*/*trans*=95:5) was determined by $^1$H NMR spectroscopy of the crude product. $R_f$=0.32 (hexane/EtOAc=3:1); $[\alpha]_D^{20}$=+12.0 ($c$=1.0 in $CHCl_3$), ref. [16] $[\alpha]_D^{25}$=+14.9 ($c$=0.9 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=0.88 (t, $J$=6.8 Hz, 3H; $CH_3$), 1.14–1.34 (m, 28H; $CH_3C_{14}H_{28}$), 1.54–1.64 (m, 1H; NCHC$H_2$), 1.69–1.83 (m, 1H; NCHC$H_2$), 2.54 (dd, $J$=6.3, 16.8 Hz, 1H; H-3), 2.61 (dd, $J$=4.8, 16.8 Hz, 1H; H-3′), 3.50 (ddd, $J$=4.0, 5.9, 9.3 Hz, 1H; H-5), 3.97 (d, $J$=15.1 Hz, 1H; $NCH_2$), 4.09 (ddd, $J$=4.8, 5.9, 6.3 Hz, 1H; H-4), 4.40 (d, $J$=11.7 Hz, 1H; $OCH_2$), 4.56 (d, $J$=11.8 Hz, 1H; $OCH_2$), 5.01 (d, $J$=15.1 Hz, 1H; $NCH_2$), 7.19–7.35 ppm (m, 10H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=14.0, 22.6, 25.2, 26.8, 29.3, 29.4, 29.5, 29.6, 29.6 (2C), 29.7 (4C), 29.8, 31.9, 37.0, 44.0, 60.6, 71.3, 73.0, 127.4, 127.5, 127.7, 127.8, 128.4, 128.6, 136.7, 137.6, 172.7 ppm; IR (film): $\tilde{\nu}_{max}$=3059, 3030, 2923, 2852, 1695, 1495, 1454, 1417, 1096 cm$^{-1}$; MS (ESI): $m/z$: 528 [$M$+Na]$^+$; HRMS (ESI): $m/z$: calcd for $C_{34}H_{51}NNaO_2$: 528.3812 [$M$+Na]$^+$; found: 528.3819.

*(4S,5S)-1-benzyl-4-benzyloxy-5-(5-hexenyl)-2-pyrrolidinone (**16i**)*

Following the general procedure, the reduction of hemiaminal **12i** gave **16i** (99.8 mg) as a colorless oil, along with diastereomer **14i** (6.2 mg). The combined yield of two diastereomers (96%; *cis*/*trans*=96:4) was determined by $^1$H NMR spectroscopy of the crude product. $R_f$=0.35 (hexane/EtOAc=3:1); $[\alpha]_D^{20}$=+17.0 ($c$=1.0 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=1.15–1.36 (m, 4H; $NCHCH_2C_2H_4$), 1.53–1.65 (m, 1H; NCHC$H_2$), 1.69–1.81 (m, 1H; NCHC$H_2$), 1.93–2.01 (m, 2H; =CHC$H_2$), 2.54 (dd, $J$=6.4, 16.8 Hz, 1H; H-3), 2.61 (dd, $J$=4.8, 16.8 Hz, 1H; H-3′), 3.50 (ddd, $J$=3.9, 6.0, 9.3 Hz, 1H; H-5), 3.97 (d, $J$=15.1 Hz, 1H; $NCH_2$), 4.10 (ddd, $J$=4.9, 6.0, 6.4 Hz, 1H; H-4), 4.39 (d, $J$=11.7 Hz, 1H; $OCH_2$), 4.56 (d, $J$=11.7 Hz, 1H; $OCH_2$), 4.89–4.98 (m, 2H; $=CH_2$), 5.01 (d, $J$=15.1 Hz, 1H; $NCH_2$), 5.74 (tdd, $J$=6.7, 10.2, 17.0 Hz, 1H; =C$H$CH$_2$), 7.19–7.36 ppm (m, 10H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=24.7, 26.7, 29.0, 33.4, 37.0, 44.1, 60.6, 71.3, 72.9, 114.4, 127.4, 127.6, 127.8, 127.8, 128.4, 128.6, 136.6, 137.6, 138.6, 172.7 ppm; IR (film): $\tilde{\nu}_{max}$=3063, 3029, 2926, 2958, 1692, 1495, 1418, 1101 cm$^{-1}$; MS (ESI): $m/z$: 386 [$M$+Na]$^+$; HRMS (ESI): $m/z$: calcd for $C_{24}H_{29}NNaO_2$: 386.2091 [$M$+Na]$^+$; found: 386.2096.

*(4S,5S)-5-Benzyl-4-(benzyloxy)-1-(4-methoxybenzyl)-2-pyrrolidinone (**16j**)*

Following the general procedure, the reduction of hemiaminal **12j** gave **16j** (90.2 mg) as a white solid, along with diastereomer **14j** (24.9 mg). The combined yield of diasterermers (95%; *cis*/*trans*=79:21) was determined by $^1$H NMR spectroscopy of the crude product. $R_f$=0.34 (hexane/EtOAc=3:1); m.p. 95–97°C; $[\alpha]_D^{20}$=−6.2 ($c$=1.0 in $CHCl_3$), ref. [13] $[\alpha]_D^{20}$=−5.7 ($c$=1.0 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=2.48 (dd, $J$=6.5, 16.7 Hz, 1H; H-3), 2.54 (dd, $J$=5.8, 16.7 Hz, 1H; H-3′), 2.90 (dd, $J$=6.0, 13.5 Hz, 1H; NCHC$H_2$), 3.08 (dd, $J$=7.9, 13.5 Hz, 1H; NCHC$H_2$), 3.63 (d, $J$=14.9 Hz, 1H; $NCH_2$), 3.76 (ddd, $J$=6.0, 6.0, 7.6 Hz, 1H; H-5), 3.79 (s, 3H; $OCH_3$), 3.95 (ddd, $J$=5.8, 6.0, 6.5 Hz, 1H; H-4), 4.30 (d, $J$=11.5 Hz, 1H; $OCH_2$), 4.45 (d, $J$=11.5 Hz, 1H; $OCH_2$), 5.02 (d, $J$=14.9 Hz, 1H; $NCH_2$), 6.80–6.86 (m, 2H; Ar-H), 6.99–7.04 (m, 2H; Ar-H), 7.07–7.12 (m, 2H; Ar-H), 7.19–7.36 ppm (m, 8H; Ar-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=33.4, 36.5, 43.7, 55.2, 61.5, 71.4, 73.4, 114.0, 126.5, 127.6, 127.8, 128.4 (2C), 128.5, 129.3, 129.4, 137.5, 137.9, 159.0, 172.4 ppm; IR (film): $\tilde{\nu}_{max}$=3062, 3027, 2922, 2875, 2836, 1692, 1513, 1450, 1244, 1174, 1038 cm$^{-1}$; MS (ESI): $m/z$: 424 [$M$+Na]$^+$; HRMS (ESI): $m/z$: calcd for $C_{26}H_{27}NNaO_3$: 424.1883 [$M$+Na]$^+$; found: 424.1884.

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[1] B. M. Trost, *Science* **1983**, *219*, 245–250.
[2] J. G. de Vries, G. A. Molander in *Science of Synthesis Workbench Edition: Stereoselective Synthesis* (Ed.: P. A. Evans), Thieme, Stuttgart, **2011**, Vols. 1–3.
[3] a) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40–49; b) C.-J. Li, B. M. Trost, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13197–13202; c) T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38*, 3010–3021; d) R. A. Sheldon, *Chem. Soc. Rev.* **2012**, *41*, 1437–1451.
[4] For selected reviews and accounts, see: a) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013–1025; b) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655; c) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788–802; d) B. G. Hashiguchi, S. M. Bischof, M. M. Konnick, R. A. Periana, *Acc. Chem. Res.* **2012**, *45*, 885–898.
[5] a) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344; b) C. J. Scheuermann, *Chem. Asian J.* **2010**, *5*, 436–451; c) C.-J. Li, *Acc. Chem. Res.* **2010**, *43*, 581–590.
[6] For two accounts, see: a) P.-Q. Huang in *New Methods for the Asymmetric Synthesis of Nitrogen Heterocycles* (Eds.: J. L. Vicario, D. Badia, L. E. Carrillo), Research Signpost, Kerala, **2005**, p. 197; b) P.-Q. Huang, *Synlett* **2006**, 1133–1149; for selected examples, see: c) P.-Q. Huang, S.-L. Wang, J.-L. Ye, Y.-P. Ruan, Y.-Q. Huang, H. Zheng, J.-X. Gao, *Tetrahedron* **1998**, *54*, 12547–12560; d) B.-Y. He, T.-J. Wu, X.-Y. Yu, P.-Q. Huang, *Tetrahedron: Asymmetry* **2003**, *14*, 2101–2108.
[7] J. Chen, P.-Q. Huang, Y. Queneau, *J. Org. Chem.* **2009**, *74*, 7457–7463.
[8] C.-F. Dai, F. Cheng, H.-C. Xu, Y.-P. Ruan, P.-Q. Huang, *J. Comb. Chem.* **2007**, *9*, 386–394.
[9] D.-S. Yu, W.-X. Xu, L.-X. Liu, P.-Q. Huang, *Synlett* **2008**, 1189–1192.
[10] a) R. Fu, J.-L. Ye, X.-J. Dai, Y.-P. Ruan, P.-Q. Huang, *J. Org. Chem.* **2010**, *75*, 4230–4243; b) R. Fu, J. Chen, L.-C. Guo, J.-L. Ye, Y.-P. Ruan, P.-Q. Huang, *Org. Lett.* **2009**, *11*, 5242–5245.
[11] a) R. E. Schwartz, J. Liesch, O. Hensens, L. Zitano, S. Honeycutt, G. Garrity, R. A. Fromtling, J. Onishi, R. Monaghan, *J. Antibiot.* **1988**, *41*, 1774–1779; b) J. H. Johnson, D. W. Phillipson, A. D. Kahle, *J. Antibiot.* **1989**, *42*, 1184–1185.
[12] H.-J. Shin, T.-S. Kim, H.-S. Lee, J.-Y. Park, I.-K. Choi, H.-J. Kwon, *Phytochemistry* **2008**, *69*, 2363–2366.
[13] S.-H. Xiang, H.-Q. Yuan, P.-Q. Huang, *Tetrahedron: Asymmetry* **2009**, *20*, 2021–2026.
[14] a) L.-X. Liu, K.-J. Xiao, P.-Q. Huang, *Tetrahedron* **2009**, *65*, 3834–3841; b) K.-J. Xiao, L.-X. Liu, P.-Q. Huang, *Tetrahedron: Asymmetry* **2009**, *20*, 1181–1184.
[15] For recent reviews on the chemistry of *N*-acyliminium ions, see: a) W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *56*, 3817–3856; b) B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi, C. A. Maryanoff, *Chem. Rev.* **2004**, *104*, 1431–1628; c) J. Royer, *Chem. Rev.* **2004**, *104*, 2311–2352; d) A. Yazici, S. G. Pyne, *Synthesis* **2009**, 339–368; e) A. Yazici, S. G. Pyne, *Synthesis* **2009**, 513–541.
[16] Z.-H. Xiao, L.-X. Liu, C. Liu, P.-Q. Huang, *Synth. Commun.* **2011**, *41*, 2036–2043.

  

[17] W. Gribble, *Chem. Soc. Rev.* **1998**, *27*, 395–404, and refs. [1] and [2] cited therein.

[18] a) X. Zhou, P.-Y. Zhang, J.-L. Ye, P.-Q. Huang, *C. R. Chim.* **2008**, *11*, 5–18; b) X. Zhou, P.-Q. Huang, *Synlett* **2006**, 1235–1239.

[19] For some entropy-controlled reactions, see: a) V. Jagannadham, S. Steenken, *J. Am. Chem. Soc.* **1988**, *110*, 2188–2192; b) T. Nishida, A. Miyafuji, Y. N. Ito, T. Katsuki, *Tetrahedron Lett.* **2000**, *41*, 7053–7058; c) T. Sugimura, K. Hagiya, Y. Sato, T. Tei, A. Tai, T. Okuyama, *Org. Lett.* **2001**, *3*, 37–40; d) M. Lombardo, S. Fabbroni, C. Trombini, *J. Org. Chem.* **2001**, *66*, 1264–1268; e) O. Benali, M. A. Miranda, R. Tormos, S. Gil, *J. Org. Chem.* **2002**, *67*, 7915–7918; f) T. Tei, Y. Sato, K. Hagiya, A. Tai, T. Okuyama, T. Sugimura, *J. Org. Chem.* **2002**, *67*, 6593–6598; g) R. Saito, S. Naruse, K. Takano, K. Fukuda, A. Katoh, Y. Inoue, *Org. Lett.* **2006**, *8*, 2067–2070; h) R. A. Moss, M. Zhang, *Org. Lett.* **2008**, *10*, 4045–4048; i) Y. Sohtome, B. Shin, N. Horitsugi, R. Takagi, K. Noguchi, K. Nagasawa, *Angew. Chem.* **2010**, *122*, 7457–7461; *Angew. Chem. Int. Ed.* **2010**, *49*, 7299–7303.

[20] For a selected synthesis of streptopyrrolidine, see: a) A. Duris, A. Daich, D. Berkes, *Synlett* **2011**, 1631–1637; b) W. Huang, J. Y. Ma, M. Yuan, L. F. Xu, B. G. Wei, *Tetrahedron* **2011**, *67*, 7829–7837; c) D. K. Mohapatra, B. Thirupathi, P. P. Das, J. S. Yadav, *Beilstein J. Org. Chem.* **2011**, *7*, 34–39; d) see ref. [13].

[21] For selected synthesis of (+)-preussin, see: a) C. S. Pak, G. H. Lee, *J. Org. Chem.* **1991**, *56*, 1128–1133; b) M. Shimazaki, F. Okazaki, F. Nakajima, T. Ishikawa, A. Ohta, *Heterocycles* **1993**, *36*, 1823–1836; c) W. Deng, L. E. Overman, *J. Am. Chem. Soc.* **1994**, *116*, 11241–11250; d) H. Yoda, H. Yamazaki, K. Takabe, *Tetrahedron: Asymmetry* **1996**, *7*, 373–374; e) I. Kadota, S. Saya, Y. Yamamoto, *Heterocycles* **1997**, *46*, 335–348; f) R. Verma, S. K. Ghosh, *Chem. Commun.* **1997**, 1601–1602; g) T. Bach, H. Brummerhop, *Angew. Chem.* **1998**, *110*, 3577–3579; *Angew. Chem. Int. Ed.* **1998**, *37*, 3400–3402; h) R. Verma, S. K. Ghosh, *J. Chem. Soc., Perkin Trans. 1* **1999**, 265–270; i) K. Y. Lee, Y. H. Kim, C. Y. Oh, W. H. Ham, *Org. Lett.* **2000**, *2*, 4041–4042; j) J. J. Caldwell, D. Craig, S. P. East, *Synlett* **2001**, 1602–1604; k) M. Okue, H. Watanabe, T. Kitahara, *Tetrahedron* **2001**, *57*, 4107–4110; l) D. K. Dikshit, L. N. Goswami, V. S. Singh, *Synlett* **2003**, 1737–1739; m) P. Q. Huang, T. J. Wu, Y. P. Ruan, *Org. Lett.* **2003**, *5*, 4341–4344; n) S. Canova, V. Bellosta, J. Cossy, *Synlett* **2004**, 1811–1813; o) F. A. Davis, J. H. Deng, *Tetrahedron* **2004**, *60*, 5111–5115; p) M. B. Bertrand, J. P. Wolfe, *Org. Lett.* **2006**, *8*, 2353–2356; q) F. A. Davis, J. Zhang, H. Qiu, Y. Z. Wu, *Org. Lett.* **2008**, *10*, 1433–1436; r) J. A. Draper, R. Britton, *Org. Lett.* **2010**, *12*, 4034–4037; s) K.-J. Xiao, Y. Wang, K.-Y. Ye, P.-Q. Huang, *Chem. Eur. J.* **2010**, *16*, 12792–12796; t) R. Chowdhury, S. K. Ghosh, *Synthesis* **2011**, 1936–1945.

[22] K.-J. Xiao, J.-M. Luo, K.-Y. Ye, Y. Wang, P.-Q. Huang, *Angew. Chem.* **2010**, *122*, 3101–3104; *Angew. Chem. Int. Ed.* **2010**, *49*, 3037–3040.

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