A Short and Elegant Synthesis of (±)-Streptopyrrolidine

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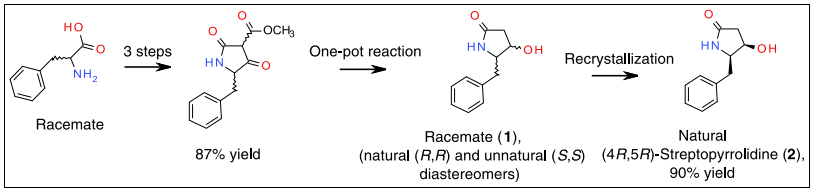

A brief and efficient approach for the synthesis of (±)-5-benzyl-4-hydroxy-2-pyrrolidine (**1**) from phenylalanine racemate is described. The key step is the stereocontrolled reduction of the keto functionality of benzylated pyrrolidinone intermediate (**6**) *via* sodium borohydride in carboxylic acid medium furnishing both (*R*,*R*)- and (*S*,*S*)-configured diastereomers. The natural (*R*,*R*) enantiomer (**2**), however, crystallized out from its racemic mixture. Structure of **2** was confirmed by NMR, IR, elemental analyzer, and single crystal X-ray crystallographic techniques.

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INTRODUCTION

Streptopyrrolidine, (4*R*,5*R*)-5-benzyl-4-hydroxy-2-pyrrolidine (**2**) (Fig. 1), was isolated from the fermentation broth of the deep sea bacterium *Spectromyces* sp. KORDI-3973 by Shin *et al*. [1]. It has been reported to exhibit substantial antiangiogenesis activity with the same potency as the known angiogenesis inhibitor SU11248 [2]. This hydroxypyrrolidine compound is therefore expected to be a significant small molecule bioprobe for sudying angiogenesis [1].

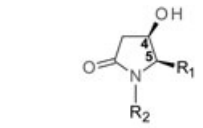
In our continuing efforts toward the synthesis of bioactive pyrrolidine type compounds, our group successfully synthesized some novel substituted 2-pyrrolidinone and spiroisoxazoline compounds [3]. Some of these compounds are shown to exhibit potential anticancer and neuroprotective activities against a panel of normal and cancer cell lines [4]. The 4-hydroxy-2-pyrrolidine ring skeleton in streptopyrrolidine (**2**; Fig. 1) is currently being much investigated in our laboratory due to its significant presence in many biologically active compounds, which include the nootropic drug oxiracetam (Fig. 1). This ring moiety could also act as a versatile intermediate for synthesizing important natural compounds such as the antifungal alkaloid preussin [5] as well as a series of γ-amino acids (GABA). Several research groups had successfully developed asymmetric synthesis of 5-alkyl-4-hydroxy-2-pyrrolidines toward such natural products [6]. Some had specifically synthesized *cis*-5-benzyl-4-hydroxy-2-pyrrolidine as a synthetic intermediate [7] but more recently as the target natural compound (**2**) [8].

Because of its promising bioactivities and unique structure, streptopyrrolidine (**2**) is used as a target molecule in this study. Herein, we report a short and concise synthetic route to racemate (**1**) by using first the convenient way of preparing pyrrolidinone ring moiety *via* condensation and Dieckmann cyclisation, subsequently utilizing a one-pot manner of deacylation and stereocontrolled reduction onto a key intermediate benzylated β,β-diketoester, **6**, as outlined in Scheme 1.

Numerous approaches have been developed for the synthesis of *cis*-5-benzyl-4-hydroxy-2-pyrrolidine [6–8]. However, the absolute configurations of the synthesized 5-benzyl-4-hydroxy-2-pyrrolidines were reported to be (4*S*,5*S*), as there are significant differences in the magnitude of the specific rotation of the synthetic samples [7a, 8] compared with that of the natural compound (**2**) [1]. We verify the structure of our target compound, which crystallized out to be identical to the natural **2** with the correct stereochemistry as the ^{1}H- and ^{13}C-NMR spectral values are the same as those reported by Shin *et al*. [1]. Moreover, single crystal X-ray data have confirmed the absolute configuration of our natural **2** to be (4*R*,5*R*).

RESULTS AND DISCUSSION

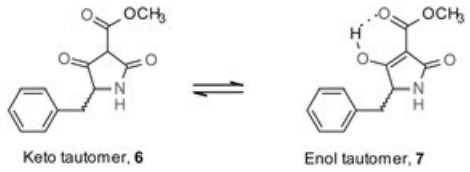
Our synthetic approach to **1** began with the esterification of readily available DL-phenylalanine with thionyl chloride in methanol at 0°C to give the required phenylalanine methyl ester in a quantitative yield, 99% (Scheme 2). Condensation of the methyl ester with methyl malonate potassium salt in an equimolar amount gave an intermediate diester **5** in excellent yield, 94%. The condensation between



R_1 = Bn, R_2 = H (*R*,*R*)-Streptopyrrolidine (**2**)
R_1 = H, R_2 = CH_2CONH_2 Oxiracetam

Figure 1. Chemical structures of (*R*,*R*)-streptopyrrolidine (**2**) and oxiracetam.

Scheme 3. Keto-enol tautomerism of **6**.



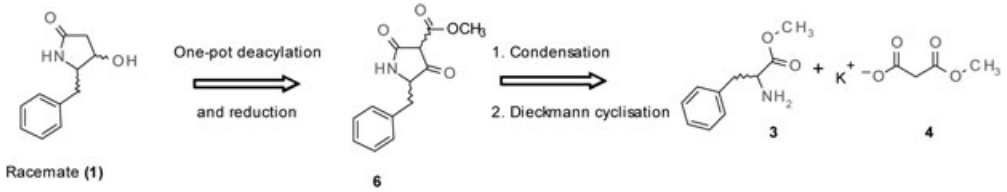
the two reagents was carried out in the presence of dicyclohexylcarbodiimide (DCC), which acts as both a catalyst and a peptide coupling agent, in acetonitrile following the method described by Heinicke [9]. Dieckmann cyclization of diester **5** with sodium methoxide*, in situ* generated from sodium metal and anhydrous methanol in toluene under reflux gave **6**, methyl 5-benzyl-2,4-dioxopyrrolidine-3-carboxylate, as the advanced intermediate toward compound **1** in 87% yield.

As anticipated, in two different solvents of disparate polarities, **6** has shown to exist as either its keto tautomer, **6**, or its enol form, **7** [10]. The β,β-diketoester, **6**, is favored in a more polar solvent, in view of the fact that the reduced polarity of the enol tautomer is induced by the tautomer's intramolecular hydrogen bonding (Scheme 3). The presence of these different tautomers was observed during NMR analysis.

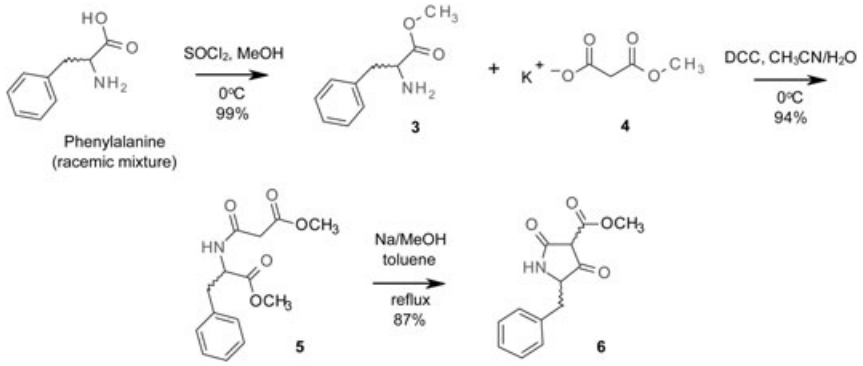
Our synthetic strategy, however, did not require further isolation of the tautomers. Compound **6** was directly subjected to demethoxycarbonylation and reduction in a one-pot reaction manner as described by Poncet *et al.* [7a] (Scheme 4). The diketoester **6** was initially refluxed with sulfuric acid of pH = 1.6 for 10 min to deacylate the methyl ester functionality at C3, then the resulting unpurified benzylated pyrrolidinone was dissolved in a mixture of 1 : 9 ratio of acetic acid-dichloromethane, cooled to 0°C and reduced by sodium borohydride to give racemate **1**, in a quantitative yield. This synthetic strategy furnished both natural (*R*,*R*)-streptopyrrolidine (**2**) and its unnatural (*S*,*S*) configured enantiomer. However, the natural **2** was successfully separated out *via* enantiomeric crystallization, which was obtained by slow evaporation of a methanol-di*iso*propyl ether (1 : 9 *v*/*v*) solution, from its racemic mixture in 90% yield.

The key stereoselectivity was alleged to occur in the final step of the synthetic strategy mediated by the triacetoxyborohydride generated from $NaBH_4$ with excess glacial acetic acid [11]. The incoming hydride comes from the less hindered side of the keto group, away from the benzyl, forcing the hydroxyl to be in *cis*-position to the benzyl substituent (Scheme 5). Therefore, in our system,

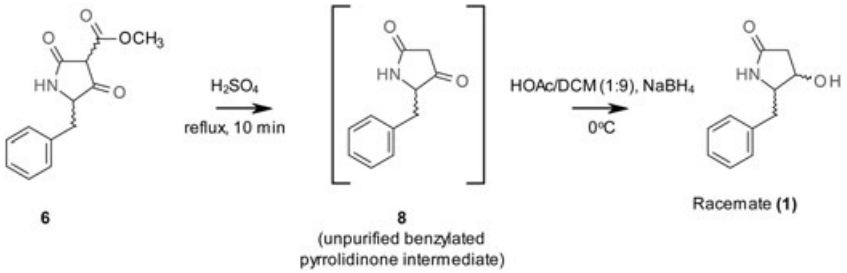
Scheme 1. Synthesis of (±)-streptopyrrolidine (**1**).



Scheme 2. Synthesis of β,β-diketoester **6**.



Scheme 4. One-pot deacylation-reduction of **6**.



such transformation leads to the production of only (*R*,*R*)- and (*S*,*S*)-configured isomers, favoring the formation of the former diastereomer. The presence of both diastereomers was markedly observed in NMR analysis of the oil residue of racemate **1**. The ^{1}H-NMR spectrum shows two separate sets of signals for H-4 and H-5 methines: a set of 4.33 and 3.91 ppm for H-4 and H-5, respectively, in the (*R*,*R*) isomer, and another of 4.20 and 3.76 ppm for the (*S*,*S*) isomer (Fig. 2). The chemical shifts of the H-3 methylene are also distinct: 2.25 and 2.62 ppm for (*R*,*R*); 2.08 and 2.42 ppm for (*S*,*S*). The peak intensity of these signals gave the ratio of (4*R*,5*R*)/(4*S*,5*S*) as 5 : 1 (Fig. 2). For comparison purposes, both ^{1}H-NMR spectra in Figure 2 were obtained in deuterated methanol. They were not measured in deuterated DMSO to avoid any interference from the residual DMSO-d_6 which are at the chemical shifts of 2.48 and 3.28 ppm.

The (4*R*,5*R*)-streptopyrrolidine (**2**) obtained was light yellow crystals with melting point of 134–136°C (lit. Mp 134–135°C [1]). The ^{1}H-NMR spectroscopic data of **2** (Table 1), which were measured in deuterated DMSO, indicate resonances for aromatic protons, two methylenes, two downfield methines at δ 3.68 and δ 4.09, amide NH

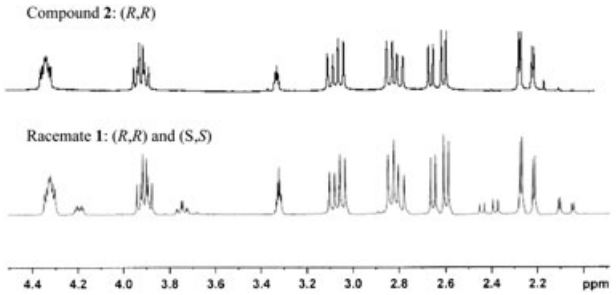


Figure 2. ^{1}H-NMR spectra of **1** and **2** in MeOD.

at δ 7.49, and hydroxy OH at δ 5.13. The nonequivalent protons of C-3 appear to be doublet of doublets at a much upfield region of δ 1.97 (J = 16.5 and 2.7 Hz) and δ 2.38 (J = 16.5 and 6.0 Hz). Likewise, the doublet of doublets of the nonequivalent benzylic protons appear at δ 2.65 (J = 13.5 and 6.0 Hz) and δ 2.95 (J = 13.5 and 7.8 Hz). The olefinic hydrogens of the aromatic ring system appear between δ 7.12 and δ 7.32 as multiplets, indicate the presence of a monosubstituted benzene ring. The ^{13}C spectroscopic data (Table 1) suggest that compound **2** contains one carbonyl carbon, one quaternary aromatic

Scheme 5. Stereocontrolled reduction of **8**.

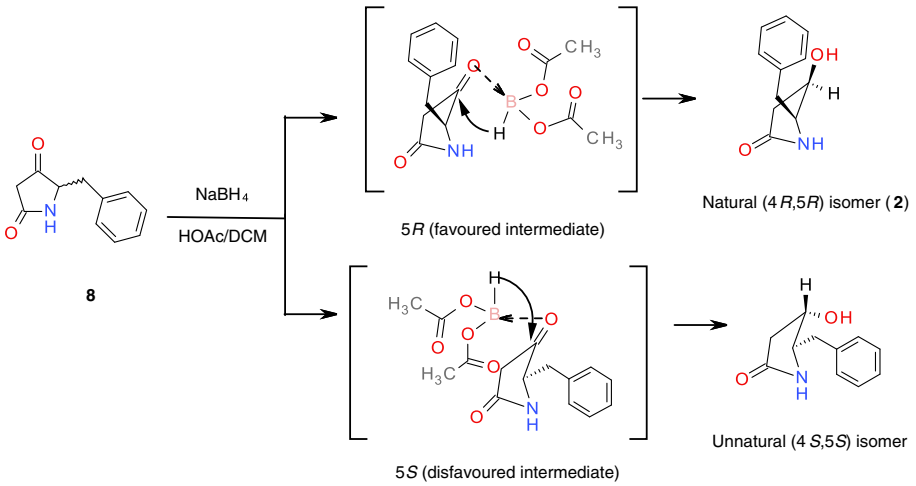


Table 1

^{1}H- and ^{13}C-NMR spectroscopic assignments for **2** in DMSO-d_6.

Position	^{1}H (mult, J = Hz)	^{13}C
NH	7.49 (1H, *s*)	–
2	–	175.36
3	1.97 (1H, *dd*, 16.5, 2.7)	41.20
	2.38 (1H, *dd*, 16.5, 6.0)	
4	4.09 (1H, *m*)	67.39
5	3.68 (1H, *q*, 6.2)	60.53
6	2.65 (1H, *dd*, 13.5, 6.0)	35.00
	2.95 (1H, *dd*, 13.5, 7.8)	
7	–	139.13
8	} 7.15–7.27 (5H, *m*)	129.68
9		128.65
10		126.43
OH	5.13 (1H, *d*, 4.8)	–

carbon, three aromatic methines, two saturated methines, and two methylenes. The ^{1}H-^{1}H COSY spectrum of **2** also shows the correlation between the methine proton H-4 at δ 4.09 and the hydroxyl proton at δ 5.13. These NMR values complement those of the isolated and purified natural streptopyrrolidine as reported by Shin *et al*. [1].

Furthermore, the structure of **2** was confirmed by X-ray investigation. The compound crystallized in monoclinic system with space group P 21/n, a = 5.945(2), b = 9.001 (4), c = 18.712(8), β = 94.100(8), V = 100.4(7) and Z = 4.

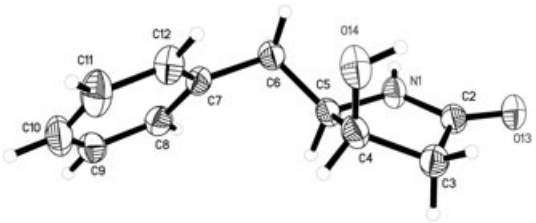


Figure 3. The molecular structure of **2** drawn in the crystals at 50% probability ellipsoid.

The whole molecule is not planar instead the pyrrolidine ring adopts a twist conformation with N1-C5-C4-C3 and N1-C2-C3-C4 torsion angles of −30.99(14)° and −17.58 (17)°, respectively (Fig. 3). The gauche conformation about the C4-C5 bond leads to the formation of (*R,R*) relative configuration as compared to (*S,S*) in the previously reported synthesized compound [7a, 8].

The C5/N1/C2/C3/O13 fragment of the pyrrolidinone ring is planar with maximum deviation of 0.032(1) Å for N1 atom from the least square plane. It makes dihedral angle of 59.53° with the benzyl C6/C7/C8/C9/C10/C11/C12 (max deviation 0.025(2) Å for C6 atom) fragment. The bond lengths and angles are in normal ranges [13] with C2-O13 and C4-O14 bond lengths of 1.2257(2) and 1.3403 (11) Å, respectively. In the crystal structure, the molecules are linked by N1-H1A···O13 and O14-H14A···O13 to form centrosymmetric dimers that are linked to form one-dimensional chains along the *a*-axis (Fig. 4). The C-H···*pi* interaction between the methylene hydrogen atom of the pyrrolidinone ring and the benzene centroid is also present.

In conclusion, a short synthesis of natural (4*R*,5*R*)-streptopyrrolidine (**2**) and its unnatural (4*S*,5*S*) configured enantiomer was accomplished by demethoxycarbonylation followed by stereoselective reduction of a key intermediate benzylated β,β-diketoester in a one-pot reaction. The overall yield was 73% over four steps. This synthetic strategy is potentially applicable to members of natural products with a similar ring moiety. Further transformations of (±)-streptopyrrolidine (**1**) toward bioactive natural products are currently underway in our laboratory.

EXPERIMENTAL

General procedures. ^{1}H- and ^{13}C-NMR spectra were measured at 300 and 75 MHz, respectively. All NMR spectra were recorded in deuterated solvents on Varian NMR 300 MHz or Bruker NMR 300 MHz Spectrometers with tetramethylsilane

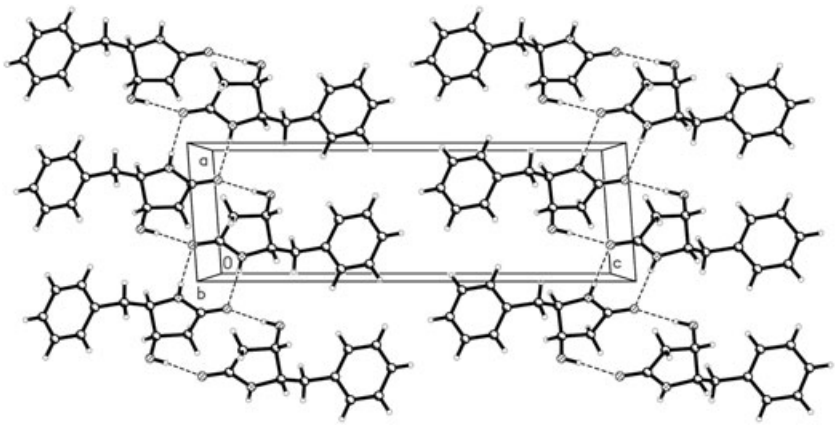


Figure 4. Molecular packing of compound **2** viewed down the *b*-axis. The dashed lines denote the intermolecular hydrogen bonds.

as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Infrared spectra were measured on Varian Excalibur 3100. All samples were run neat on a single refraction ZnSe crystal plate *via* ATR sampling accessory. Elemental analyses were performed on Flash EA 110 instrument. Melting points were determined by either an Electrothermal melting point apparatus or an automatic B-545 melting point apparatus from Büchi and were uncorrected.

Crystals suitable for X-ray investigation were obtained by slow evaporation of a methanol-diethyl ether (1 : 9 *v*/*v*) solution. The measurements were performed at 273(2) or 298(2) K on Bruker SMART APEX CCD diffraction using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Orientation matrix and unit cell parameters were obtained from the setting angles of 25-centers reflection. The structure was solved using direct method and refined by full-matrix least-square method on F^2 using the SHELXTL software package [14]. All non-H atoms were anisotropically refined. The hydrogen atoms were located in a difference Fourier map and then were fixed geometrically and treated as riding atom on the parent C or N atoms, with C-H distances between 0.86 and 0.97 Å.

Methyl 2-amino-3-phenylpropanoate, 3. To a stirred solution of phenylalanine (16.63 g, 100.67 mol) in 118.23 mL of methanol, under ice-cooled condition of −20°C, thionyl chloride (8.05 mL, 110.73 mol) was added dropwise over 10 min and stirred for 30 min. The ice bath was removed and stirred for another 2.5 h. The reaction mixture was then refluxed for 30 min and then evaporated to give the product, methyl 2-amino-3-phenylpropanoate, **3** as white precipitate. The precipitate was filtered and washed with diethyl ether and dried (20.52 g, 99%), m.p. 155°C. IR *v* cm^{-1}: 2994 (N-H), 1745 (C═O), 1148 (C-N), 1233 (C-O); δ_H (D_2O, 300 MHz): 3.13 (1H, dd, *J* = 7.2, 7.5, 7.2, and 7.5 Hz, PhC*H*H), 3.23 (1H, dd, 6.0, 6.3, 6.0, and 6.3 Hz, PhCH*H*), 3.72 Hz (3H, s, OCH_3), 4.32 (1H, t, *J* = 6.6 Hz, NCH), 7.16–7.34 (5H, m, Ar H). ^{13}C (D_2O, 75 MHz): 35.8 (CH_2), 53.5 (OCH_3), 54.0 (CHNH), 128.0–129.3 (aromatic C), 133.6 (quat. aromatic C), 169.9 (C═O); CHN: Found C, 67.48; H, 7.59; N, 8.31; O, 16.62 %; requires C, 67.02; H, 7.31; N, 7.82; O, 17.85 %.

Methyl 3-(1-methoxy-1-oxo-3-phenylpropan-2-ylamino)-3-oxopropanoate, 5. Dicyclohexylcarbodiimide (1.14 g, 5.57 mmol) was added to a solution of phenylalanine methyl ester, **3** (1.00 g, 5.57 mmol) and methyl malonate potassium salt (0.87 g, 5.57 mmol) in acetonitrile/water (13/4 mL) at 0°C and stirred for 2 h. The white precipitate formed was filtered and washed with DCM. The combined filtrates were evaporated, and the residue was partitioned between H_2O and DCM. The DCM fraction was washed with H_2O, dried over anhydrous $MgSO_4$, and evaporated. The white powder was recrystallized from acetone/petroleum ether to give the methyl 3-(1-methoxy-1-oxo-3-phenylpropan-2-ylamino)-3-oxopropanoate, **5** as light yellow oily (1.47 g, 94%), IR *v* cm^{-1}: 3310 (N-H), 1741 (C═O), 1664 (C═O), 1203 (C═O); δ_H ($CDCl_3$, 300 MHz): 3.12 (1H, dd, *J* = 6 and 6 Hz, PhCH*H*), 3.13 (1H, dd, *J* = 5.4 and 5.4 Hz, PhC*H*H), 3. 25 (2H, s, $COCH_2CO$), 3.64 (6H, s, 2 × OCH_3), 4.78 (1H, q, *J* = 6.6, 7.2, and 6.3 Hz, NCH), 7.02–7.25 (5H, m, Ar H), 7.34 (1H, br, s, NH); ^{13}C ($CDCl_3$, 75 MHz): 37.7 (CH_2), 41.0 (CH_2), 52.3 (OCH_3), 52.4 (OCH_3), 53.4 (CHNH), 127.1–129.2 (aromatic C), 135.7 (quat. aromatic C), 164.6 (C═O), 169.1 (C═O), 171.6 (C═O); CHN: Found C, 59.13; H, 6.16; N, 4.75; O, 29.96 %; requires C, 60.21; H, 6.14; N, 5.02; O, 28.64 %.

Methyl 5-benzyl-2,4-dioxopyrrolidine-3-carboxylate, 6, as the keto tautomer and methyl 5-benzyl-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate, 7, as the enol tautomer. A solution of methyl 3-(1-methoxy-1-oxo-3-phenylpropan-2-ylamino)-3-oxopropanoate, **5** (1.00 g, 3.58 mmol), in toluene (18 mL) was added to a solution of sodium methoxide, which was prepared from sodium (0.08 g, 3.58 mmol) in dry methanol (3 mL). The mixture was refluxed at 90°C for 6 h under nitrogen. The reaction mixture was cooled and diluted with H_2O and the combined aqueous layers were acidified with concentrated HCl. The product, methyl 5-benzyl-2,4-dioxopyrrolidine-3-carboxylate, **6** slowly precipitated out as light yellow powder (0.76 g, 87%), m.p. 140.4°C. IR *v* cm^{-1}: 3375 (N-H), 1684 (C═O), 1641 (C═O), 1226 (C═O); In deuterated methanol, **6** was present as the keto tautomer; δ_H (CD_3OD, 300 MHz): 2.97 (1H, dd, *J* = 5.7 and 5.7 Hz, PhCH*H*), 3.18 (1H, dd, *J* = 4.2 and 4.2 Hz, PhC*H*H), 3.30 (1H, s, COCHCO), 3.72 (3H, s, OCH_3), 4.38 (1H, t, *J* = 5.1 and 5.1 Hz, NCH), 7.18–7.23 (5H, m, Ar H), ^{13}C (CD_3OD, 75 MHz): 36.5 (CH_2), 50.2 (OCH_3), 58.1 (CHNH), 96.2 (CO*C*HCO), 126.6–129.3 (aromatic C), 135.0 (quat. aromatic C), 164.6 (C═O), 171.7 (C═O), 186.1 (C═O). In deuterated chloroform, methyl 5-benzyl-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic methyl ester was present as the enol tautomer, **7**; δ_H ($CDCl_3$, 300 MHz): 3.77 (1H, dd, *J* = 8.7 and 8.7 Hz, PhCH*H*), 3.28 (1H, dd, *J* = 3.9 and 3.9 Hz, PhC*H*H), 3.78 (3H, s, OCH_3), 4.33 (1H, d, *J* = 5.4 Hz, NCH), 6.16 (1H, br, s, OH), 7.18–7.32 (5H, m, Ar H); ^{13}C ($CDCl_3$, 75 MHz): 37.7 (CH_2), 51.1 (OCH_3), 57.9 (CHNH), 97.9 (CO*C*HCO), 127.2–129.2 (aromatic C), 135.3 (quat. aromatic C), 167.7 (C-O), 187.6 (C═O); CHN: Found C, 63.11; H, 5.19; N, 5.27; O, 26.43 %; requires C, 63.15; H, 5.30; N, 5.67; O, 25.88 %.

Formation of (±)-streptopyrrolidine, 1. A solution of methyl 5-benzyl-2,4-dioxopyrrolidine-3-carboxylate (2.0 g, 8.08 mmol) in 0.025*M* H_2SO_4 (pH = 1.6; 32 mL) was refluxed for 10 min. The solution was rapidly cooled in an ice-bath and extracted three times with ethyl acetate (40 mL). The organic phase was dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The resulting unpurified compound, **8**, was dissolved in acetic acid-dichloromethane (10 : 90; 40 mL), cooled to 0°C, and $NaBH_4$ (0.32 g, 8.40 mmol) was added in three batches. The solvent was removed under reduced pressure furnishing an oily residue, **1**, which consists of both (4*R*,5*R*) and (4*S*,5*S*) isomers. The residue was then recrystallized from methanol-di*iso*propyl ether solution (1 : 9 *v*/*v*) to give the natural (4*R*,5*R*)-5-benzyl-4-hydroxypyrrolidin-2-one (streptopyrrolidine), **2** as light yellow crystals (2.79 g, 90%), m.p. 134–136°C. IR *v* cm^{-1}: 3459 (N-H), 3195 (O-H), 1688 (C═O), 1185 (C-O); δ_H (DMSO-d_6, 300 MHz): 1.97 (1H, dd, *J* = 16.5 and 2.7 Hz, COCH*H*CHOH), 2.38 (1H, dd, *J* = 16.5 and 6.0 Hz, COC*H*HCHOH), 2.65 (1H, dd, *J* = 13.5 and 6.0 Hz, PhCH*H*), 2.95 (1H, dd, *J* = 13.5 and 7.8 Hz, PhC*H*H), 3.68 (1H, q, *J* = 6.6, 5.4, and 6.6 Hz, NCH), 4.09 (1H, m, C*H*OH), 5.13 (1H, d, *J* = 4.8 Hz, COH), 7.15–7.27 (5H, Ar H), 7.49 (1H, s, NH), ^{13}C (DMSO-d_6, 75 MHz): 35.0 (CH_2), 41.2 (CH_2), 60.5 (CHNH), 67.3 (COH), 126.4–129.6 (aromatic C), 139.1 (quat. aromatic C), 175.3 (C═O); CHN: Found C, 69.07; H, 6.84; N, 7.12; O, 16.97 %; requires C, 69.09; H, 6.85; N, 7.32; O, 16.73 %.

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format. This supplementary crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 805759. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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