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An Easy Access to Protected (4S, 5R)-5-Alkyl-4-hydroxy-2-pyrrolidinones and their Use as Versatile Synthetic Intermediates

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This paper is dedicated to Professor You Wang in memory of his contribution to organic chemistry.

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Abstract: A versatile approach to enantiopure (4S, 5R)-5-alkyl-4-hydroxy-2-pyrrolidinones is described. The key steps involve a regioselective Grignard reagent addition to (S)-malimides, and diastereoselective reductive dehydroxylation of the resulting hemi-azaketals. The flexibility of this methodology has been demonstrated by the synthesis of (2R, 3R)-3-amino-1-benzyl-2-methylpyrrolidine, the parent diamine of antipsychotic agent, emonapride, and the unnatural enantiomer of the β-hydroxy-γ-amino acid residue of hapalosin in lactam form.

2-Pyrrolidinones have been proven to be effective intermediates for the synthesis of pyrrolidine alkaloids and γ-amino acids[2]. For the synthesis of the corresponding hydroxy derivatives in optically active form, easily available (S)-malic acid **1** has been shown to be a valuable chiral pool[3]. In this context, particular attention has been paid to the synthesis of *cis*-disposed 5-alkyl-4-hydroxy-2-pyrrolidinone **3** from (S)-malimide[4] **2,** since this could led to the synthesis of *syn*-β-hydroxy-γ-amino acids[10,11], such as (3S, 4S)-statine[4,7] **4**. The latter is a key component of pepstatin, a naturally occurring aspartyl protease inhibitor. However, the corresponding *anti* oriented (3S, 4R) or (3R, 4S)-β-hydroxy-γ-amino acid residues **7** are also present in many anticancerous and antineoplastic natural products. For example, (3S, 4R, 5S)-isostatine[5] **8** is a component of the didemnins; (3R, 4S, 5S)-dolaisoleuine[6] **9** is a component of Dolastatin 10; and (3R, 4S)-4-methylamino-3-hydroxy-5-phenylpentanoic acid[7] **10** is found in hapalosin[8]. Moreover, *trans*-pyrrolidinones are useful precursor to *cis*-3-aminopyrrolidines[9] **6 (Scheme 1)**.

For the asymmetric synthesis of 2-pyrrolidinones and β-hydroxy-γ-amino acids with general structures **5** and **7**, the most popular method is the one based on the condensation of an L-amino ester or an L-amino aldehyde with an C_2 unit[7,10]. This approach is both efficient and flexible, only in cases where the substituent R in

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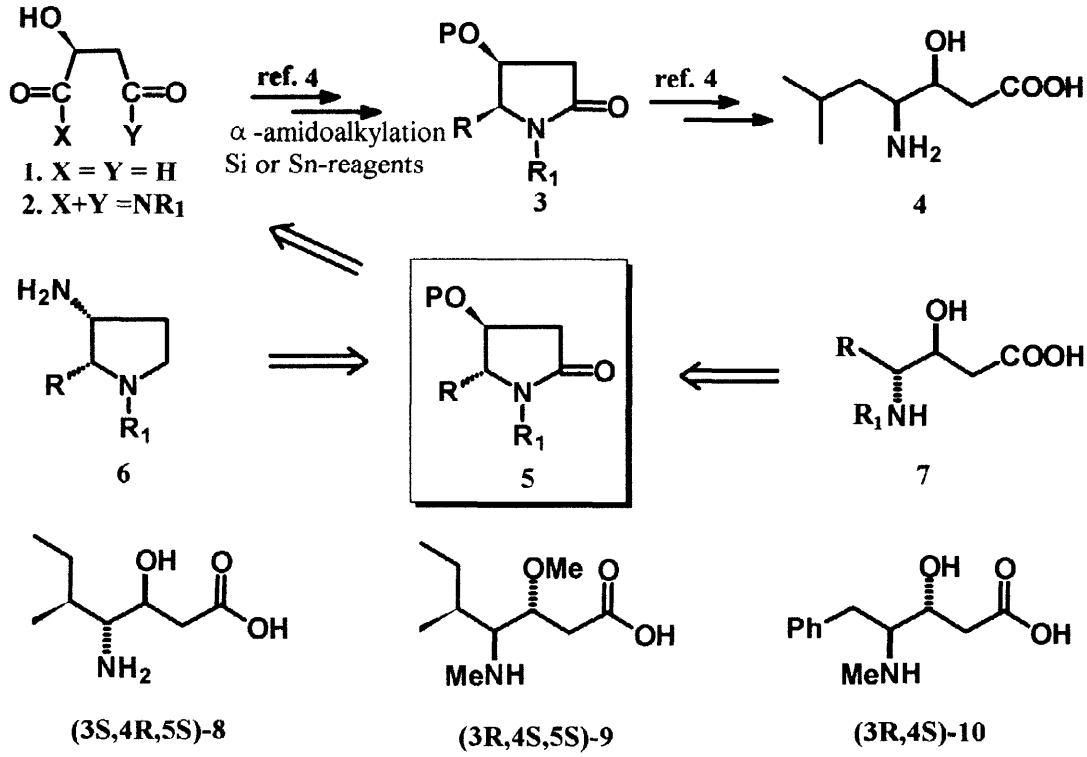
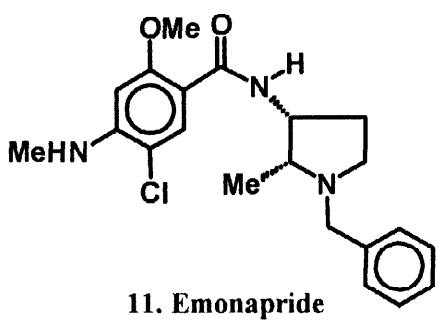
molecules 5 and 7 is corresponded with that found in proteinogenic L-amino acids. As a result, the development of more flexible non-amino-acids-based approaches[5a, 11] to 5 and thus 7 become of importance.

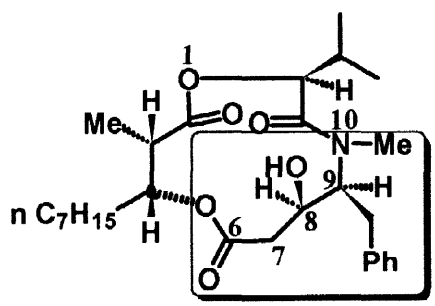
Scheme 1



In a preliminary communication[12] we reported the first asymmetric synthesis of (2R, 3R)-3-amino-1-benzyl-2-methylpyrrolidine **24**, the parent diamine of antipsychotic agent emonapride[13] **11**. Full experimental and spectral data are given in this paper. Moreover, we have extended the method to the synthesis of γ-amino acid fragment of hapalosin in lactam form **32.** Hapalosin **12** is a novel cyclic depsipeptide isolated from the cyanobacterium *Hapalosiphon welwitschii*[8]. It exhibits a higher MDR (multidrug resistance)-reversing activity than verapamil, which was one of the first drugs to be clinically tested for MDR reversal. As a result, the synthesis of hapalosin and its synthetic analogs has attracted much recent attention, four synthetic approaches have been developed[7].



11. Emonapride

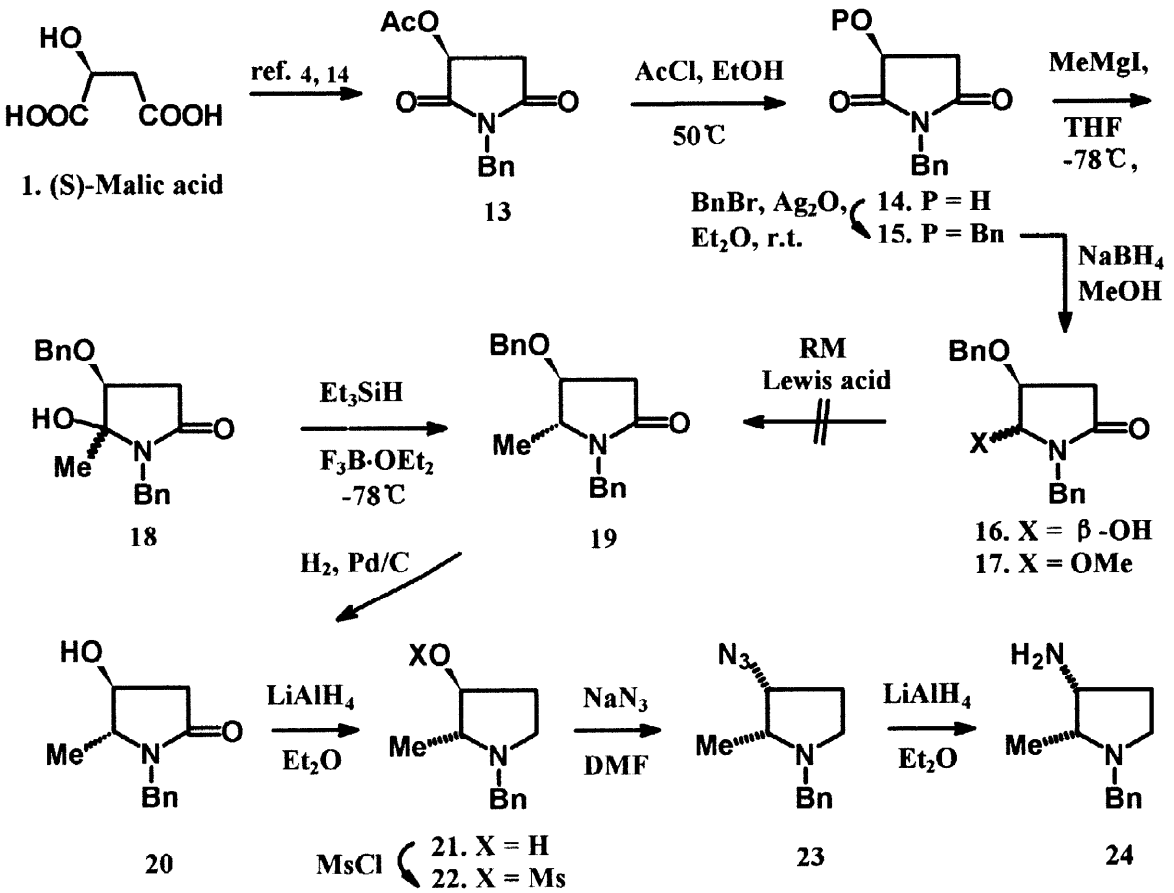


12. Hapalosin

Results and discussion

As shown in **Scheme 2**, *O*-acyl-*N*-benzyl-malimide **13** was readily prepared in one-pot from easily available (S)-malic acid **1** by known method[4,14]. Compound **13** was converted to **14** via acidic ethanolysis (EtOH, AcCl, 50 ℃) followed by *O*-benzylation (BnBr, Ag_2O, Et_2O). Central to our plan was the transformation of **15** to **19**. We first attempted the α-amidoalkylation[15] of 5-methoxy-2-pyrrolidinone **17** obtained from **15** via $NaBH_4$ reduction and acid catalyzed hydroxy-methoxy exchange. However, although the α-amidoalkylation of **17** worked well with silicon reagents[4], stannic reagents, and stabilized carbon nucleophiles[15], similar reaction using more general nucleophiles such as Grignard reagents and cuprates (in the presence of a Lewis acid such as $BF_3{\cdot}OEt_2$, $TiCl_4$, or $ZnBr_2$) were unsuccessful, as has been noted previously in a similar case[16].

Scheme 2



To overcome this difficulty, an alternative approach, taking the advantage of high electrophilicity of the imide carbonyl towards organometallic reagents[17] was adopted. Thus, treatment of methyl magnesium iodide with malimide **15** led smoothly to the desired α-hydroxylactam **18** as a diastereomeric mixture in 52:48 ratio and

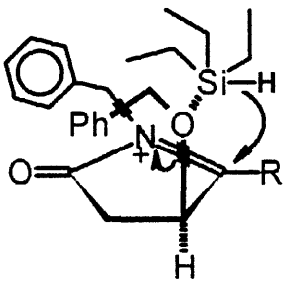
in high regioselectivity which was deduced in the followed step. The stereochemistry of the isomeric **18** were not assigned. The high regioselectivity (>95%) of Grignard reagent addition to more hindered carbonyl α to the C-3 benzyloxy group could be attributed to the complex induced proximity effects (CIPE)[18]. In addition, the explanation proposed by Speckamp[19] to account for the regioselective reduction of *gem*-disubstituted succinimides can also be used to explain the observed regioselectivity. The poor stereoselectivity observed in the Grignard reagent addition might reflect the overall results of the CIPE (*cis*-directing effect) and steric effects (*trans*-directing effect).

The reductive cleavage of the carbon-oxygen bond of hemi-azaketal can be accomplished by ionic hydrogenation[20]. Indeed, when the diastereomeric mixture of **18** was subjected to trifluoroboron etherate mediated triethylsilane reduction[17b,21], *trans*-**19** formed predominately. The *trans* / *cis* diastereoselectivity was more than 95:5 according to chromatographic separation. The *cis*/*trans* stereochemistry of compounds **19** was tentatively assigned according to the observed vicinal coupling constants[4, 6, 10d] ($J_{4,5}$=6.5 Hz for *cis*-**19** and $J_{4,5}$=2.5 Hz for *trans*-**19**). This was further confirmed by converting **19** to *cis*-**24**. A more direct proof was obtained from a single-crystal X-ray crystallographic analysis of compound (4R, 5S)-**32** (**figure 1**). In order to determine the enantiomeric purity of *trans*-(+)-**19**, racemic *trans*-**19** was prepared from (±)-malic acid by following the sequence used for (+)-**19**. (+)-**19** was cofmpared with (±)-**19** by HPLC using a Chiralcel® OB column. The retention times (t_R) for (±)-**19** were 23.5 min and 27.1 min (hexane/*i*-PrOH, 9:1) respectively, and that of (+)-**19** showed only one peak consisting with one of the peak of racemic **19** (t_R=23.5 min) . When racemic **19** was coinjected with (+)-**19**, the peak corresponding to (+)-**19** (t_R=23.5min) was enhanced. Thus, the stereochemistry purity is conserved along the whole sequence from (S)-malic acid to (+)-**19** shown in **Scheme 2**. Extension of this procedure to other Grignard reagents led to corresponding products **19a-d** in similar diastereoselectivity (**Table 1**, Entry 2-5).

Table 1. Preparation of pyrrolidinones **19/31** via the reductive alkylation of (S)-malimides **15/29**

Entry	Regioselective RMgX addition to malimides **15/29**				Stereoselective Reduction	
	Starting Malimides	RMgX	Compounds (Yield, %)	Diastereo-meric Ratio	Compounds (Yield, %)	*cis* : *trans* ratio
1	**15**	MeMgI	**18**(89)	52:48	**19**(90)	4.8:95.2
2	**15**	*n*-BuMgBr	**18a**(94)	66:34	**19a**(86)	3:97
3	**15**	*i*-BuMgBr	**18b**(89)	79:21	**19b**(82)	5.5:94.5
4	**15**	BnMgCl	**18c**(83)	75:25	**19c**(76)	3:97
5	**15**	*p*-$MeOC_6H_5CH_2MgCl$	**18d**(90)	50:50	**19d**(93)	4:96
6	**29**	BnMgCl	**30**(91)	53:47	**31**(85)	5.5:94.5

The fact that starting from a nearly 1:1 diastereomeric mixture of α-hydroxylactam(e.g. **18**), *trans* diastereomer (e.g. **19**) was obtained in high selectivity (*ca.* >95:5) is in accordance with an N-acyliminium based mechanism[4,18]. The surprising high *trans* selectivity might resulted from the chelation between C-4 oxygen and silicon atom as shown in **25**. Thus, the chelation between the hydroxy group of **18** and trifluoroboron etherate led to an N-acyliminium intermediate, the chelation between the C-4 oxygen atom and the triethylsilane directed the hydride to approach C-5 carbon from the same side as the C-4 benzyloxy substituent, producing thus the *trans*-isomer (**Figure 1**). The capacity for silicon atom to form pentavalent organosilicon species is well known[22].



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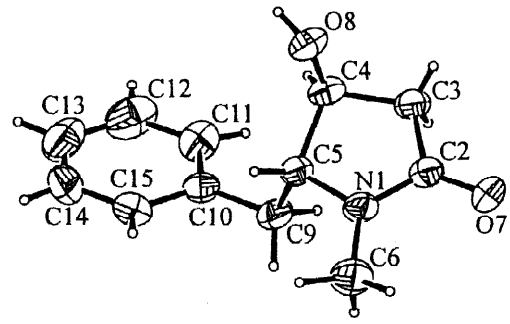


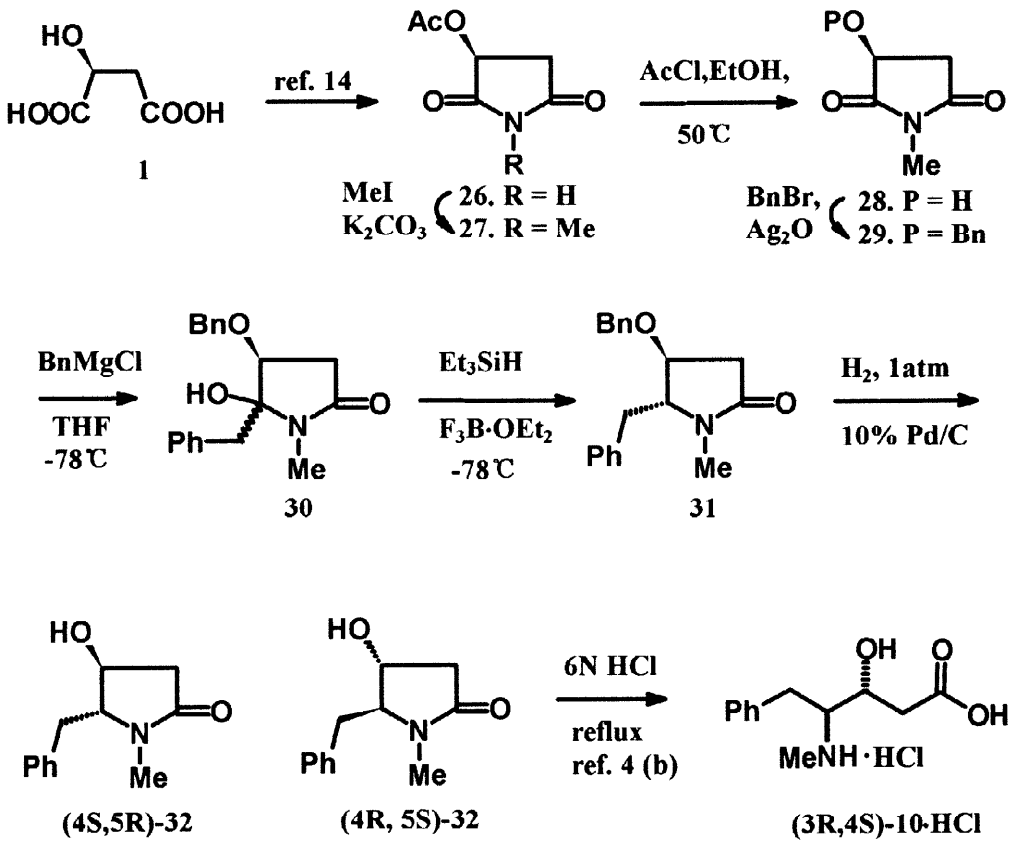
Figure 1

Further conversion of 2-pyrrolidinone **19** to diamine **24** is depicted in **Scheme 2**. Debenzylation of **19** (10% Pd/C, H_2 1 atm , 95% EtOH) yielded β-hydroxylactam (+)-**20** in 95% yield. Amide reduction (LAH, THF, reflux, 92%) followed by *O*-mesylation afforded (-)-**22** in high yields. Mesylate **22** was then subjected to a S_N2 substitution reaction with sodium azide in hot DMF to give β-azido-amine (2R, 3R)-**23** in 87% yield. Lithium aluminium hydride reduction then provided the desired *cis*-(-)-(2R, 3R)-3-amino-1-benzyl-2-methylpyrrolidine **24** in 88% yield. Since racemic **24** has been acylated to give emonapride **11**, our work thus constitutes a formal synthesis of emonapride **11**.

Having established the synthesis of (2R, 3R)-3-amino-1-benzyl-2-methylpyrrolidine **24**, we turned our attention to extend the method to the synthesis of the γ-amino acid fragment of hapalosin. Due to the current interest in synthetic analogs of hapalosin[7a, b], (S)-malic acid was chosen as starting material which would led to the unnatural enantiomer of **10**. Thus, known *O*-acylmalimide[14] **26** was prepared from (S)-malic acid. N-methylation (MeI, K_2CO_3, acetone, r. t., 15hrs) provided **27** in 86% yield (**Scheme 3**). Deacylation under acidic conditions provided known N-methylmalimide[23] **28**. which was further protected as benzyl ether **29**. Following the reductive alkylation procedure described above (**Scheme 2**), compound (-)-**31** was obtained in high regio and *trans*-stereoselectivity (**Table 1**, entry 6). The coupling constant between protons at C-4 and C-5 positions of the major diastereomer **31** was about 0Hz, corresponding to that needed for the *trans* isomer. *O*-

debenzylation of **31** (1atm H_2, 10% Pd-C, EtOH, r. t.) afforded β-hydroxy lactam (4S, 5R)-**32**. The ^{1}H-NMR spectra of (4S, 5R)-**32** merits comments. The ^{1}H-NMR spectra of (4R, 5S)-**32** obtained from the degradation-lactamization of natural hapalosin **12** indicated that, in $CDCl_3$, **32** existed in two conformers in 6:1 ratio[8]. In CD_3OD, only one conformer was observed, $J_{4,5}$ were found to be 1.6Hz for the major conformer in $CDCl_3$ and 0 Hz for the single conformer in CD_3OD. In our case, however, the ^{1}H-NMR spectra of our (4S, 5R)-**32** showed only one conformer ($J_{4,5}$=0 Hz) either in $CDCl_3$ or in CD_3OD. In order to confirm the proposed structure for **32** and to establish unambiguously the stereochemistry of **32**, a single-crystal X-ray analysis of (4S, 5R)-**32** was performed. The X-ray analysis (**Figure 1**) of **32** unequivocally established the *trans*-relationship between the C-4 hydroxy group and C-5 benzyl substituent. Thus, it was assumed that the conformer equilibrium is acidity dependent, since the acidity in CD_3OD is more important than that in $CDCl_3$. The $CDCl_3$ we used to take ^{1}H-NMR might contain trace of acid. One observation in supporting of this hypothesis is that in the same $CDCl_3$, diastereomers **30** are unstable, while they are stable in deuterated DMSO.

Scheme 3



In view of the easy conversion of (4R, 5S)-**32** to β-hydroxy-γ-amino acid **10**, the hapalosin constituent, just by acidic hydrolysis, the synthesis of (4S, 5R)-**32** thus represents a lactam form of the unnatural 3S, 4R

enantiomer of **10**. More significantly, this approach opened an easy access to a variety of chiral 4-benzyloxy-2-pyrrolidinones **19** ~ **19d (Table 1)**, which could be used as valuable intermediates for new synthetic analogs of β-hydroxy-γ-amino acids.

In summary, we have developed an efficient and general asymmetric alkylation-reduction procedure to *trans*-5-alkyl-4-hydroxy-2-pyrrolidinones. The versatility of this non-amino-acid-based approach to chiral 2-pyrrolidinones **5** was demonstrated by the asymmetric synthesis of (2R, 3R)-**24**, a key intermediate for antipsychotic agent emonapride **11** and (4S, 5R)-**32**, as the lactam form of the unnatural enantiomer of (3R, 4S)-**10**, the γ-amino acid fragment found in hapalosin **12**.

Experimental

Melting points were determined on a Yanaco M-500 micro melting point apparatus and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 681 or with a Shimadzu IR-408 spectrometer using film NaCl or KBr pellet techniques. ^{1}H-NMR spectra were recorded in $CDCl_3$, on one of the following spectrometers: Varian FF80A; Varian Gemini-200; Varian unity+500; Bruker AMX-500, with tetramethylsilane or chloroform as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded at 70 eV ionizing voltage on a Hewlett-Packard 5889A apparatus. MS spectra are presented as m/z (% rel. int.). Optical rotations were measured with a Perkin-Elmer 241 MC automatic polarimeter. Elemental analyses were performed by the Micro Analytical Laboratory at Shanghai Institute of Organic Chemistry. THF and diethyl ether used in the reactions were dried by distillation over metallic sodium and benzophenone; dichloromethane and DMF were distilled over calcium hydride. The course of all of the reactions described could be conveniently monitored by TLC. Silica gel (Qingdao, 400 mesh) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60-90 ℃) mixtures. HPLC analyses were performed with a Chiralcel® OB column, eluting with hexane/*iso*-propanol mixtures, on a Waters HPLC 510 instrument. (S)-4-acetoxy-1-benzyl-2, 5-pyrrolidinedione[4, 14] **13** and (S)-4-acetoxy-2,5-pyrrolidinedione[14] **26** were prepared according to the literature procedures.

(S)-1-benzyl-4-hydroxy-2, 5-pyrrolidinedione (14). To a solution of **13** (1.06g, 4.29mmol) in 150mL of absolute ethanol was added dropwise AcCl (6mL, 90mmol). The mixture was stirred at 50 ℃ for 5h and concentrated *in vacuo*. Benzene was added, then concentrated in vacuo (this procedure was repeated 3 times). Flash chromatography (SiO_2, EtOAc/petroleum ether, 1:1.5) afforded **14** as a white crystalline solid (3.24g, 96% yield). mp 101-102 ℃ (EtOAc). $[\alpha]_D^{25}$ -75.4° (*c* 4.4, $CHCl_3$). IR(KBr, pellet): 3300, 2980, 2920, 1680, 1640, 1540, 1440, 1340, 1275, 1170, 1100, 930, 725, 690cm^{-1}. ^{1}H-NMR($CDCl_3$, 80MHz): 2.63 (dd, J=5.1,

18.3Hz, 1H, H-4), 3.07(dd, J=8.1, 18.3Hz, 1H, H-4), 3.44(s, br, 1H, OH), 4.63(m, H-3, overlapped with next peak), 4.66(s, 2H, $PhCH_2N$), 7.22(m, 5H, C_6H_5). MS: 205(M^+, 100), 187(13), 177(96), 148(22), 132(25), 105(41), 91(96). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.86; H, 5.53; N, 6.66.

(S)-1-benzyl-4-benzyloxy-2, 5-pyrrolidinone (15). To a solution of **14** (549mg, 2.78mmol) in 20mL of diethyl ether were added benzyl bromide (0.83mL, 8.42mmol) and silver oxide (1.95g , 8.43mmol). After stirring at dark for two days at room temperature, the mixture was filtered through celite and concentrated in vacuo. Flash chromatography (EtOAc/petroleum ether 1:5, then 1:3) afforded **15** (738mg, 92% yield) as a white solid. mp 76-77.5 ℃ (EtOAc). $[\alpha]_D^{25}$ -34.7° (*c*, 0.7, $CHCl_3$). IR(KBr, pellet): 2980, 2850, 1708, 1440, 1390, 1242, 1310, 1180, 1156, 1130, 1020, 700, 740, 690^{cm-1}. ^{1}H-NMR (200MHz): 2.66(dd, J=4.2, 18.2Hz, 1H, H-4), 2.92(dd, J=8.2, 18.2Hz,1H, H-4), 4.35(dd, J=4.2, 8.2Hz, 1H, H-3), 4.66(s, 2H, $PhCH_2N$), 4.78(d, J=11.7Hz, 1H, $PhCH_2O$), 4.96(d, J=11.7Hz, 1H, $PhCH_2O$), 7.35 (m, 10H, $2C_6H_5$). MS: 296 (MH^+, 3), 189(50), 132(4), 111(20), 91(100). HRMS Calcd for $C_{11}H_{11}O_2N$ (M^+-PhCHO): 189. 0790; Found 189. 0792.

General procedure for the synthesis of (19) from (S)-malimide 15

A solution of **15** (1.50mmol) in anhydrous THF (20mL) was cooled to -78 ℃ under argon, a Grignard reagent (3.0mmol) in diethyl ether was added dropwise. After stirred at -78 ℃ for 1.5h, the reaction was quenched with a saturated aqueous solution of ammonium chloride (12mL) and extracted with dichloromethane (3 × 30mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuum. Filtration through a short pad of silica eluting with ethyl acetate-petroleum ether (60:40) yielded a mixture of two diastereoisomers **18**. The diastereomeric ratio could be obtained either from flash chromatographic separation or from ^{1}H-NMR spectra of the crude mixture.

A mixture of diastereomers **18** (1.20mmol) was dissolved in dry dichloromethane (10mL) under argon. The solution was cooled to -78 ℃, triethylsilane (12mmol) and trifluoroboron etherate (1.4mmol) were added. After stirred at -78 ℃ for 6h, the reaction was quenched by a saturated aqueous sodium bicarbonate and extracted with dichloromethane (3 × 20mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuum. The crude was chromatographied on a column of silica gel with ethyl acetate-petroleum ether (b.p. 60-90 ℃)(60:40) to give *trans*-**19** (yields 76-93%) as colorless oils and trace of *cis*-**19** (**19** ~ **19d**: *trans* : *cis* ≥94.5:5.5).

(+)-(4S, 5R)-1-benzyl-4-benzyloxy-5-methyl-2-pyrrolidinone (19). 90% yield, colorless oil. Following the general procedure for reductive alkylation, *cis* and *trans*-**19** (4.8:95.2) were obtained in a combined yield of 90%. *Trans*-**19**: colorless oil. $[\alpha]_D^{22}$ +77.6 ℃(*c* 0.35, $CHCl_3$). IR (film): 3040, 2975, 2925, 1680, 1600, 1495, 1450, 1360, 1250, 1060, 730, 695cm^{-1}, ^{1}H-NMR(200 MHz): 1.14(d, J=6.6Hz, 3H, CH_3), 2.53(dd, J=3.2, 17.3Hz, 1H, H-3), 2.77(dd, J=6.6, 17.3Hz, 1H, H-3), 3.56, (dq, J=2.5, 6.6Hz, 1H, H-5), 3.80(ddd, J=2.5, 3.2, 6.6Hz, 1H, H-4), 3.98,(d, J=15.3Hz, 1H, $PhCH_2N$), 4.43(d, J=11.7Hz, 1H, $PhCH_2O$), 4.49(d, J=11.7Hz, 1H,

$PhCH_2O$), 5.02(d, J=15.3Hz, 1H, $PhCH_2N$), 7.30(m, 10H, $2C_6H_5$). MS: 295(M^+, 36), 280(1) 189(8), 132(21), 91(100). HRMS Calcd for $C_{19}H_{21}NO_2$: 295.1572. Found: 295.1579.

(+)-(4S, 5R)-1-benzyl-4-benzyloxy-5-butyl-2-pyrrolidinone (19a). 86% yield, colorless oil. $[\alpha]_D^{22}$ +36.9° (*c* 1.0, $CHCl_3$). IR (film): 2956, 2931, 2861, 1684, 1454, 1070, 738, 700cm^{-1}; ^{1}H-NMR (500MHz) : δ 0.85(t, J=7.0Hz, 3H, CH_3), 1.10-1.37, 1.58(2m, 6H, $(CH_2)_3$), 2.54(dd, J=2.0, 17.5Hz,1H, H-3), 2.74(ddd, J=1.0, 6.5, 17.5, 1H, H-3), 3.47(ddd, J=1.5, 3.2, 8.9Hz, 1H, H-5), 3.88(ddd, J=1.5, 2.0, 6.5Hz, 1H, H-4), 3.96(d, J=15.3Hz, 1H, $PhCH_2N$), 4.41(d, J=11.8Hz, 1H, $PhCH_2O$), 4.46(d, J=11.8Hz, 1H, $PhCH_2O$), 5.05(d, J = 15.3 Hz, 1H, $PhCH_2N$), 7.30(m, 10H, $2C_6H_5$). MS: 337(M^+, 12), 280(M^+-Bu, 9), 174(12), 91(100). HRMS Calcd for $C_{22}H_{27}NO_2$: 337.2042. Found: 337.2045.

(+)-(4S, 5R)-1-benzyl-4-benzyloxy-5-(2-methylpropyl)-2-pyrrolidinone (19b). 82% yield, $[\alpha]_D^{22}$ +46.9° (*c* 0.74, $CHCl_3$). IR(film): 3025, 2950, 1680, 1600, 1495, 1440, 1360, 1250, 1065, 740, 700cm^{-1}. ^{1}H-NMR(500MHz): 0.80(d, J=5.0, 3H, CH_3), 0.90 (d, J=6.6Hz, 3H, CH_3), 1.20(m, 1H, CH_2CH), 1.40(m, 1H, CH_2CH), 1.57(m, 1H, $CHMe_2$), 2.54(d, J=17.5Hz, 1H, H-3), 2.75(dd, J=5.5, 17.5Hz, 1H, H-3), 3.48(dd, J=2.7, 10.2Hz, 1H, H-5), 3.84(d, J=5.5Hz, 1H, H-4), 3.93(d, J=15.1Hz, 1H, PhCHN), 4.38(d, J=11.7Hz, 1H, $PhCH_2O$), 4.45(d, J=11.7Hz, 1H, $PhCH_2O$), 5.08(d, J=15.1Hz, 1H, PhCHN), 7.28(m, 10H, $2C_6H_5$). MS: 337(M^+, 11), 280(7), 256(2), 189(57), 91(100). HRMS Calcd for $C_{22}H_{27}NO_2$: 337.2042. Found: 337.2045.

(+)-(4S, 5R)-4-benzyloxy-1,5-dibenzyl-2-pyrrolidinone (19c). 76% yield, colorless oil. $[\alpha]_D^{20}$ +36.4(*c* 1. 2, $CHCl_3$). IR(film): 1694, 1454, 1071cm^{-1}; ^{1}H-NMR(500MHz): 2.44(dd, J=1.6, 17.6Hz, 1H, H-3), 2.51(ddd, J=0.9, 5.6, 17.6Hz, 1H, H-3), 2.54(dd, J=8.6, 13.8Hz, 1H, $CHCH_2Ph$), 2.93(dd, J=4.7, 13.8Hz, 1H, $CHCH_2Ph$), 3.71(ddd, J=1.0, 4.7, 8.6Hz, 1H, H-5), 3.85(ddd, J=1.0, 1.6, 5.6Hz, 1H, H-4), 3.96(d, J=15.3Hz, 1H, NCH_2Ph), 4.09(d, J=11.9Hz, 1H, OCH_2Ph), 4.14(d, J=11.9Hz, 1H, OCH_2Ph), 5.16(d, J=15.3Hz, 1H, NCH_2Ph), 7.00(m, 4H, H-aro.) 7.28(m, 1H, H-aro.). MS: 371(M^+, 0.1), 294(5), 280(39), 174(10), 91(100). HRMS Calcd for $C_{25}H_{25}NO_2$: 371.1886. Found: 371.1902.

(+)-(4S, 5R)-4-benzyloxy-1-benzyl-5-(4-methoxybenzene)-2-pyrrolidinone (19d). 93% yield, colorless. $[\alpha]_D$ +25.6°(*c* 0.6, $CHCl_3$). IR(film): 1690, 1514, 1445, 1250, 1070, 1030, 700cm^{-1}. ^{1}H-NMR(500MHz), 2.45(m, 2H, H-3), 2.51(dd, J=8.1, 13.7Hz, 1H, $PhCH_2$), 2.86(dd, J=4.4, 13.7Hz, 1H, $PhCH_2$), 3.68(dd, J=4.4, 8.1Hz, 1H, H-5), 3.80(s, 3H, OCH_3), 3.85(m, 1H, H-4), 3.96(d, J=15.3, 1H, $PhCH_2N$), 4.15(d, J=11.9, 1H, $PhCH_2O$), 4.17(d, J=11.9, 1H, $PhCH_2O$), 5.16(d, J=15.3, 1H, $PhCH_2N$). MS: 401(M^+, 2), 280(29), 254(11), 91(100). HRMS Calcd for $C_{26}H_{27}NO_3$: 401. 1991. Found: 401. 1983.

(+)-(4S, 5R)-1-benzyl-4-hydroxy-5-methyl-2-pyrrolidinone (20). To a solution of **19** (434mg, 1.47mmol) in 95% ethanol (5mL) was added 156mg of 10% Pd-C. The suspension was placed under 1 atm hydrogen and stirred for a period of 18h. The reaction mixture was filtered through celite. The filtrate was evaporated in vacuo. Flash chromatography (EtOAc/ petroleum ether, 1:2) afforded **20** (286mg, 95%) as a colorless oil.

$[\alpha]_D^{25}$ +83.6 °(*c* 1.0, $CHCl_3$). IR(film): 3350, 3050, 2975, 2925, 1670, 1500, 1430, 1360, 1250, 1170, 1100, 1075, 1040, 735, 695cm^{-1}. ^{1}H-NMR: 1.14(d, J=6.6 Hz, 3H, CH_3), 2.40(dd, J=2.5, 17.0Hz, 1H, H-3), 2.82(dd, J=6.0, 17.0Hz, 1H, H-3), 3.4(d, J=1.0, 6.6Hz, 1H, H-5), 3.99(d, J=15.0Hz, 1H, $PhCH_2N$), 4.07(ddd, J=1.0, 2.5. 6.0Hz, 1H, H-4) 5.00(d, J=15.0Hz, 1H, $PhCH_2N$), 7.3(m, 5H, C_6H_5), MS: 205(M^+, 69), 206(10), 146(29), 132(50), 118(8), 104(16), 91(100). HRMS Calcd for $C_{12}H_{15}NO_2$: 205.1099. Found 205.1090.

(-)-(2R, 3S)-1-benzyl-3-hydroxy-2-methylpyrrolidine (21). A solution of **20** (100mg, 0.49mmol) in 2mL of anhydrous THF was added to $LiAlH_4$ (120mg, 3.4mmol). The suspension was stirred at 65 ℃ for 3h, then chilled with an ice-bath. 0.5ml of H_2O, 0.5ml of an 3M aqueous solution of NaOH, and then 0.5mL of H_2O were added successively and the mixture was extracted with diethyl ether (4 × 15mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo Flash chromatography (MeOH/EtOAc) 1:4) afforded **21** (86mg, 92% yield) as a pale yellow oil. $[\alpha]^{20}_D$ - 73.9° (*c* 3.01, $CHCl_3$). IR (film): 3350, 1450, 1370, 1100, 1050, 750, 700. ^{1}H-NMR δ : 1.25 (d, J = 6.5Hz, 3H, CH_3), 1.79 (m, 1H, 4-H), 2.29 (dd, J = 7.5, 13.8Hz, 1H, H-4), 2.80 (br, 2H, H-5), 3.09 (br, 1H, H-2), 3.68 (d, J = 13.0Hz, 1H, 3-H), 3.92 (d, J = 12.8Hz, 1H, $PhCH_2$), 4.10 (d, J = 12.8Hz, 1H, $PhCH_2$), 7.28 (m, 5H, Ph-H). MS: 191(M^+, 16), 176(M^+-NH_2, 62), 91(100), 65(19), 56(95). HRMS Calcd for $C_{12}H_{17}NO_2$: 191.1310. Found: 191.1326.

(-)-(2R, 3S)-1-benzyl-2-methyl-pyrrolidin-3-yl methanesulfonate (22). To a ice-bath cooled solution of **21** (95mg, 0.5mmol) and a catalytic amount of 4-dimethylaminopyridine in 2mL of dry pyridine was added dropwise methanesulfonyl chloride (0.08mL, 1mmol). The mixture was slowly warmed to room temperature, stirred for 18h, and concentrated under vacuo. 5mL of saturated aqueous $NaHCO_3$ was added. The resulting mixture was extracted with dichloromethane (4 × 10mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Flash chromatography (EtOAc/Petroleum ether, 1:2) afforded **22** (121mg, 93% yield) as a yellow oil. $[\alpha]^{20}_D$ - 51.8° (*c* 0.4, $CHCl_3$). IR (film): 2950, 2770, 1490, 1449, 1350,1175, 960, 740, 700cm^{-1}. ^{1}H-NMR: 1.25(d, J = 6.5Hz, 3H, CH_3), 1.92(m, 1H), 4-H, 2.21(m, 1H, 4-H), 2.44(dd, J = 9.6, 16.7Hz, 1H, 2-H), 2.70(br, 1H, 5-H), 2.92(br, 1H, 5-H), 3.00(s, 3H, CH_3SO_3), 3.33(d, J = 12.8Hz, 1H, $PhCH_2$), 3.99(d, J = 12.8Hz, 1H, $PhCH_2$), 4.74(m, 1H, 3-H), 7.30(m, 5H, Ph-H). MS: 254(M^+-CH_3, 10), 190(29), 91(100), 65(11). HRMS Calcd for $C_{13}H_{19}NO_3S$: 269.1086. Found: 269.1093.

(-)-(2R, 3R)-3-azido-1-benzyl-2-methyl-pyrrolidine (23). A solution of **22** (70mg, 0.26mmol), sodium azide (140mg, 2.15mmol) in 2mL of dry dimethylformamide was heated to 55 ℃ for 28h. The mixture was allowed to cool to room temperature. Brine (2mL) was added and the mixture was extracted with diethyl ether (4 × 6mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (EtOAc/petroleum ether, 1:7) afforded **23** (41mg, 87% yield) as an yellow oil. IR (film): 2930, 2780, 2120, 1495, 1450, 1350, 1250, 1175, 745, 700. ^{1}H-NMR: 1.22 (d, J = 6.5Hz, 3H, CH_3), 1.89 (m, 1H, H-4), 2.13 (br, 2H, H-5), 2.56 (br, 1H, H-2), 2.99 (m, 1H, H-4), 3.16 (d, J = 12.9Hz, 1H, $PhCH_2$), 3.68 (br, 1H,

H-3), 4.02 (d, J = 13.0Hz, 1H, $PhCH_2$), 7.28 (m, 5H, Ph-H).

(-)-(2R, 3R)-3-amino-1-benzyl-2-methylpyrrolidine (24). A solution of **23** (40mg, 0.19mmol) in 1mL of anhydrous tetrahydrofuran was added dropwise to $LiAlH_4$ (22mg, 0.57mmol). The resulting suspension was stirred at 65 ℃ for 4h. A 3M aqueous solution of NaOH (0.2mL) and water (0.5mL) were successively added. The resulting mixture was extracted with dichloromethane (3 × 5mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography ($EtOAc/CH_3OH/NH_3$, 100:10:1) afforded diamine **24** (30mg, 88% yield) as a pale yellow oil. $[\alpha]^{20}_D$ - 88.5°(*c* 0.36, $CHCl_3$). IR (film): 3350, 2950, 1690, 1495, 1450, 1365, 1300, 1120, 1075, 1030, 740, 700cm^{-1}. ^{1}H-NMR: 1.16 (d, J = 6.5Hz, 3H, CH_3), 1.49 (m, 1H, H-4), 2.09 (m, 2H, H-5), 2.19 (s, 2H, NH_2), 2.39 (br, 1H, H-2), 2.92 (m, 1H, H-4), 3.16 (d, J = 13.0Hz, 1H, $PhCH_2$), 3.29 (br, 1H, H-3), 3.99 (d, J = 13.0Hz, 1H, $PhCH_2$), 7.31(m, 5H, Ph-H). MS: 173(M^+-NH_3, 33), 147(26), 132(9), 91(100), 85(22), 71(29), 56(56). HRMS Calcd for $C_{12}H_{15}N$ (M^+-NH_3): 173.1204. Found:173.1215.

(-)-(S)-3-acetoxy-1-methyl-2, 5-pyrrolidinedione (27). To a solution of **26**[14] (1.931g, 12.3mmol) in 200mL of dry acetone was added, under an atmosphere of nitrogen, anhydrous K_2CO_3 (3.73g, 2.7mmol). The suspension was stirred at room temperature overnight, filtered and concentrated in vacuo. To the residue was added dichloromethane, the insoluble material was filtered, the filtrate was concentrated in vacuo, and flash chromatographed to give **27** (1.81g, 86% yield) as a colorless oil. $[\alpha]_D^{22}$ -21.0°(*c* 0.43, $CHCl_3$). IR(KBr, pellet): 2950, 1790, 1750, 1710, 1380, 1250, 1130, 1040, 930, 870, 790 cm^{-1}. ^{1}H-NMR: 400, 2.32(s, 3H, $COCH_3$), 2.68(dd, J=4.8, 18.3Hz, 1H, H-4), 3.06(s, 3H, NCH_3), 3.18(dd, J=8.6, 18.3Hz, 1H, H-4), 5.46(dd, J=4.8, 8.6Hz, 1H, H-3). MS: 171(M^+, 7), 130(9), 129(100), 111(16). HRMS Calcd for $C_7H_9NO_4$: 171.0532. Found, 171.0532.

(-)-(S)-3-hydroxy-1-methyl-2, 5-pyrrolidinedione (28). To a solution of **27** (1.66gm 9.7mmol) in 50mL of absolute ethanol was added dropwise acetyl chloride (2.1mL, 29.1mmol). The mixture was stirred at 50 ℃ for 5h. Concentration in vacuo and flash chromatography (EtOAc/petroleum ether, 1:1) afforded **28** (1.27g, 96% yield) as a white solid. mp 79.5-80 ℃(CH_2Cl_2)(lit[23]., mp 79.5-80 ℃). $[\alpha]_D^{22}$ -78.3°(*c* 1.7, 95% EtOH). [lit[23]., $[\alpha]_D$ -81.3°(*c* 3.5, 95% EtOH)]. IR (KBr, pellet): 3250, 2900, 1720, 1690, 1380, 1280, 1040, 950, 890, 780cm^{-1}. ^{1}H-NMR(500MHz): 2.10(s, 1H, OH), 2.71(dd, J=4.6, 18.2Hz, 1H, H-3), 3.02(s, 3H, CH_3), 3.09(dd, J=8.4, 18.2Hz, 1H, H-3), 4.67(dd, J=4.6, 8.4Hz, 1H, H-4). MS: 129(M^+, 53), 101(36), 58(27). HRMS Calcd for $C_5H_7NO_3$: 129.0426. Found: 129.0431. Anal. Calcd: C, 46.51; H, 5.43; N, 11.09. Found: C, 46.3; H, 5.34; N, 11.08.

(-)-(S)-3-benzyloxy-1-methyl-2, 5-pyrrolidinedione (29). To a solution of **28** (1.148g, 8.9mmol) in 100mL of diethyl ether was added Ag_2O (6.17g, 26.7mmol), and a solution of benzyl bromide(6.35mL, 53.4mmol) in 10mL of diethyl ether. The suspension was stirred at room temperature for 72h in dark. After filtration through celite and concentration in vacuo, the crude was flash chromatographed to afforded **29** (1.56g, 80%) as a white

solid. mp 73-75 ℃. $[\alpha]_D$ -96.2°(*c* 1.9, $CHCl_3$). IR(KBr, pellet): 2920, 1720, 1700, 1440, 1290, 1280, 1110, 1080, 1000, 750, 690cm^{-1}. ^{1}H-NMR(500MHz): 2.67(dd, J=4.0, 18.2Hz, 1H, H-4), 2.97(dd, J=8.2, 18.2Hz, 1H, H-4), 3.02(s, 3H, CH_3), 4.49(dd, J=4.0, 8.2Hz, 1H, H-3), 4.81(d, J=11.6Hz, 1H, PhCH), 5.05(d, J=11.6Hz, 1H, PhCH), 7.38(m, 5H, C_6H_5). MS: 220(M^++1, 0.2), 113(100), 91(70), 85(29). HRMS Calcd for $C_{12}H_{14}NO_3$ [M^++1]: 220.0974. Found: 220.0971.

(+)-(4S, 5RS)-5-benzyl-4-benzyloxy-5-hydroxy-1-methyl-2-pyrrolidione (30). Following the general procedure for the preparation of **19**, and starting from 900mg (4.1mmol) of **29**, two diastereomers **30** were obtained in a combined yield of 91%. Fast eluting isomer (612mg): colorless oil, R_f (EtOAc/PE, 1:1) 0.41. $[\alpha]_D$ +10.0° (*c* 0.43, $CHCl_3$). IR(film): 3300, 2900, 1710, 1700, 1450, 1350, 1260, 1110, 1035, 740cm^{-1}. ^{1}H-NMR (DMSO-d_6, 500MHz): 2.04(dd, J=5.6, 16.4Hz, 1H, H-3), 2.50(dd, J=6.6, 16.4Hz, 1H, PhCH), 2.82(d, J=14.2, 1H, PhCH, 3.76(dd, J=5.6, 6.6Hz, 1H, H-4), 4.18(d, J=11.6Hz, 1H, $PhCH_2O$), 4.22(d, J=11.6Hz, 1H, $PhCH_2O$), 7.2-7.4(m, 10H, $2C_6H_5$). MS: 311(M^+, 0.2), 293(2), 220(36), 91(100). HRMS Calcd for $C_{19}H_{21}NO_3$. 311.1521. Found: 311.1520. Slow eluting isomer, 549mg, R_f (EtOAc/PE, 1:1) 0.27, white solid, mp 112-113.5 ℃. $[\alpha]_D^{22}$ +45.7°(*c* 1.3, $CHCl_3$). IR (KBr, Pellet): 3350, 2900, 1640, 1380, 1110, 940, 690; ^{1}H-NMR(DMSO-d_6, 500MHz): 1.78(dd, J=6.4, 16.4Hz, 1H, H-3), 2.18(dd, J=1.7, 16.4Hz, 1H, H-3), 2.52(d, J=14.2Hz, 1H, PhCH), 2.70(s, 3H, CH_3). 2.80(d, J=14.2Hz, 1H, PhCH), 3.56(dd, J=17, 6.4Hz, 1H, H-4), 3.84(d, J=11.7Hz, 1H, $PhCH_2O$), 3.92(d, J=11.7Hz, 1H, $PhCH_2O$), 7.2-7.4(m, 10H, $2C_6H_5$). MS: 293(M^+-H_2O, (2), 220(5), 187(21), 91(100). HRMS Calcd for $C_{19}H_{19}NO_2$ (M^+-H_2O): 293.1416. Found: 293.1418.

(-)-(4S, 5R)-5-benzyl-4-benzyloxy-1-methyl-2-pyrrolidinone (31). Following the general procedure for the preparation of **19**, and starting from a diastereomeric mixture of **30** (994mg, 3.05mmol), *cis*-isomer (42mg) and *trans*-isomer (719mg) were obtained with a combined yield of 85%. *Cis*-**31**, colorless oil. *Trans*-**31**, colorless oil. $[\alpha]_D^{22}$ -20.6°(*c* 0.5, $CHCl_3$). IR(film): 3040, 2900, 1710, 1370, 1610, 1500, 1445, 1370, 1260, 1205, 1090, 1000, 915, 850, 740cm^{-1}. ^{1}H-NMR(500MHz): 2.34(dd, J=4.2, 16.6Hz, 1H, H-3), 2.38(dd, J=1.2, 16.6Hz, 1H, H-3), 2.61(dd, J=8.3, 13.9Hz, 1H, PhCH), 2.98(dd, J=4.6, 13.9Hz, 1H, PhCH), 3.79(dd, J=4.6, 8.3Hz, 1H, H-5), 3.85(dd, J=1.2, 4.2Hz, 1H, H-4), 4.21(d, J=12.7Hz, 1H $PhCH_2O$), 4.25(d, J=12.7Hz, 1H, $PhCH_2O$), 7.1-7.4(m, 10H, $2C_6H_5$). MS: 295(M^+, 0.4), 204(43), 91(100). HRMS Calcd for $C_{19}H_{21}NO_2$; 295.1572. Found: 295.1561. HRMS Calcd for $C_{12}H_{14}NO_2$(M^+-Bn): 204.1025. Found: 204.1024.

(-)-(4S, 5R)-5-benzyl-4-hydroxy-1-methyl-2-pyrrolidinone (32). To a solution of *cis*-**31** (136mg, 0.46mmol) in 5mL of 95% ethanol was added 10% Pd-C (39mg). The mixture was hydrogenated under 1 atm hydrogen pressure and stirred at room temperature for 72h. At this point the reaction mixture was filtered through celite and the filtrate was evaporated in vacuo. Flash chromatography (EtOAc/PE, 1:1) afforded **32** (89mg, 94%) as a white crystalline solid, mp 118-119 ℃(CH_2Cl_2). $[\alpha]_D^{24}$-64.4°(*c* 0.4, $CHCl_3$). IR(KBr, pellet): 3300, 2900, 1670, 1410, 1000, 720cm^{-1}. ^{1}H-NMR(500MHz): 2.06(s, 1H, OH, disappeared after D_2O exchange), 2.18(d, J=17.5Hz, 1H, H-3), 2.34(dd, J=6.1, 17.5Hz, 1H, H-3), 2.69(dd, J=8.7, 14.0Hz, 1H,

$PhCH_2$), 2.87(s, 3H, CH_3), 2.98(dd, J=4.9, 14.0Hz, 1H, $PhCH_2$), 3.68(dd, J=4.9, 8.7Hz, 1H, H-5), 4.17(d, J=6.1Hz, 1H, H-4), 7.16-7.32(m, 5H, C_6H_5). ^{1}H-NMR(CD_3OD, 500MHz), 2.02(d, J=17.4Hz, 1H, H-3), 2.24(dd, J=5.8, 17.4Hz, 1H, H-3), 2.80(dd, J=7.2, 14.0Hz, 1H, PhCH), 3.68(dd, J=4.7, 7.2Hz, 1H, H-5), 4.12(d, J=5.8Hz, 1H, H-4), 7.2-7.4(m, 5H, C_6H_5). MS: 205(M^+, 2), 114(100), 96(34), 91(6). Anal. Calcd: C, 70.20; H, 7.38; N, 6.82. Found: C, 70.22; H, 7.43; N, 6.85.

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