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TETRAHEDRON: *ASYMMETRY*

A new approach to (*S*)-4-hydroxy-2-pyrrolidinone and its 3-substituted analogues

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Abstract

Successive treatment of a phenyl thioether derived from (*S*)-malic acid with *n*-BuLi, lithium naphthalenide (LN), and electrophiles led to 4-hydroxy-3-substituted 2-pyrrolidinones in one-pot and in high regio- and diastereoselectivity at C-3. *N*-Debenzylation of 1-benzyl-4-hydroxy-2-pyrrolidinone using LN afforded naturally occurring (−)-(*S*)-4-hydroxy-2-pyrrolidinone. (−)-(3*S*,4*S*)-4-Hydroxy-3-methyl-2-pyrrolidinone, the lactam form of the γ-amino acid residue found in marine natural products, bistramides, was prepared by the same method.

The 4-hydroxy-2-pyrrolidinone ring system **1** is present in many biological active compounds (e.g. **2**) and it could act as a versatile intermediate for the syntheses of a wide variety of γ-amino acids (GABA), substituted 2-pyrrolidinones (e.g. **3** and **4**) as well as pyrrolidines. For example, racemic 4-hydroxy-2-pyrrolidinone **1** has been used in the synthesis of nootropic agent oxiracetam **2**;[1] (*R*)-**1** has been converted into two important drugs (*R*)-γ-amino-β-hydroxybutyric acid (GABOB) **5**[2] and (*R*)-carnitine (vitamin B_T) **6**;[2] (*S*)-**1** is a component of *Amanita muscaria* (L. *ex* Fr.);[3] 4-amino-3-hydroxy-2-methylbutyric acid **7** is the γ-amino acid residue found in bistramides A, B, C, D and K, a new class of marine natural products isolated[4] from *Lissoclinum bistratum* with potent cytotoxic, antiproliferative and neurotoxic activities. Consequently, the asymmetric synthesis of both enantiomers of **1** has attracted much current attention.[5,6] In continuation of our efforts[5d,7] to exploit further cheap and easily available (*S*)-malic acid as a useful chiral pool,[8] we wish to report herein a new approach to (*S*)-4-hydroxy-2-pyrrolidinone **1** and its 3-substituted analogues.

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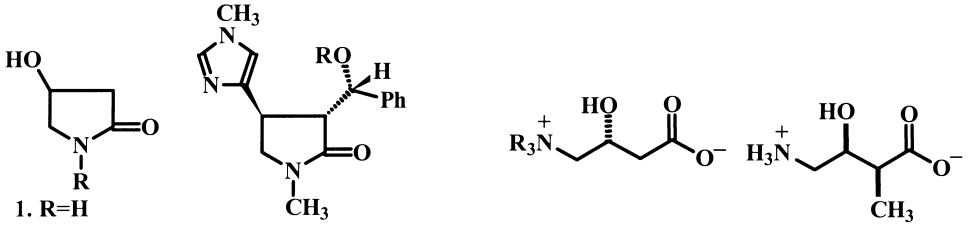
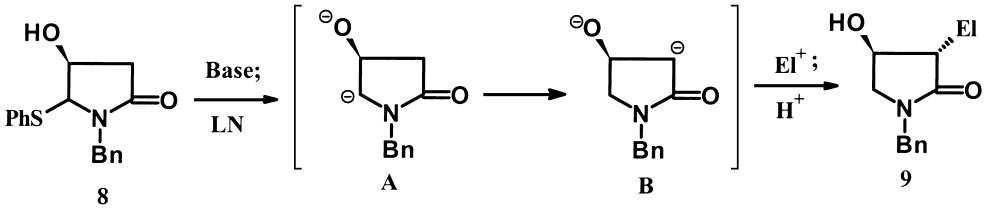


Based on the consideration that in a 1-alkyl-2-pyrrolidinone ring system the protons at C-3 are much more acidic than those at C-5, a one-pot procedure for the synthesis of 2-pyrrolidinones with general structure **9** from phenyl thioether **8** was envisaged (Scheme 1). This approach implicated several successive reactions, namely, *O*-deprotonation, tandem reductive lithiation–proton exchange, nucleophilic reaction and protonation.

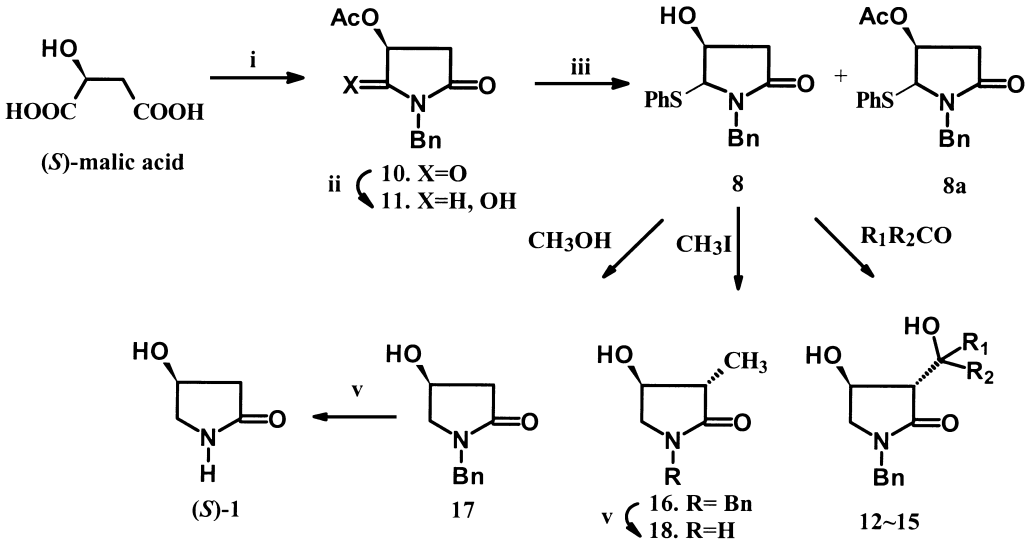


Scheme 1.

1. Results and discussion

The synthesis of the key phenyl thioether **8** started with *O*-acetyl malimide **10**, which was easily prepared from (*S*)-malic acid following a one-pot procedure[7,8b–d] (Scheme 2). Regio- and diastereoselective reduction[8b–d] of **10** with $NaBH_4$ led to *cis*-**11**[8c,d] in good yield (90%). In the presence of a catalytic amount of *p*-TsOH, the reaction of thiophenol with **11** in dry CH_2Cl_2 afforded directly the desired deacetylated thioether **8** in 79% yield and a small amount (11%)[9] of thioether **8a**. The two diastereomers *trans*-**8** and *cis*-**8** (in a ratio of 12:1 in favor of *trans* isomer) are easily separated by flash chromatography. The stereochemistry of *trans*-**8** and *cis*-**8** was assigned according to the observed vicinal coupling constants[7] ($J_{4,5}$=6.2 Hz for *cis*-**8** and $J_{4,5}$=0 Hz for *trans*-**8**).

With thioether **8** in hand, we are now in a position to attempt the novel reductive metallation of phenyl thioether **8**. Although the LN or related system mediated reductive lithiation[10] is a well documented procedure, to the best of our knowledge, none of the reported examples deal with the reactions at position α to the nitrogen of a lactam. We have found that this can be achieved by successive treatment of *trans*-**8** with *n*-BuLi, lithium naphthalenide (LN), and an electrophile. Thus treatment of *trans*-**8** with 1.1 molar equivalents of *n*-BuLi at −78°C, followed by 2.5 molar equivalents of freshly prepared LN and benzaldehyde led to a pair of separable diastereomers **12a**,**b** (ratio 1:1.2 as determined by chromatographic separation, combined yield 74%, Table 1, entry 1) and the reduced product **17** (11% yield). In the same manner, the reaction of transient dianion **B** with *p*-anisaldehyde gave **13a**,**b** (1:1.1, 71%), while when using acetone or cyclohexanone as the electrophile, only one diastereomer **14** (41%) or **15** (40%) was obtained. These results might indicate that the reaction of the transient dianion **B** with carbonyl compounds proceeded with high diastereoselectivity at C-3 (in all examples mentioned above, only one C-3 epimer could be obtained by chromatographic separation in each case), and mediocre



Scheme 2. Reagents and conditions: (i) Huang et al.,[7] Koot et al.,[8c] and Louwrier et al.,[8d] 92%. (ii) Koot et al.,[8c] and Louwrier et al.,[8d] 90%. (iii) PhSH, *p*-TsOH (cat.), CH_2Cl_2, rt; (iv) *n*-BuLi; LN, THF, −78°C, electrophiles (see Table 1); (v) LN, THF, −15 to −10°C

Table 1
Results of the one-pot synthesis of **12–17** from phenyl thioether *trans*-**8**

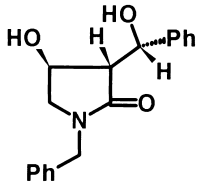
Entry	Electrophile	Product	R_1, R_2 in **12~15**	Yield(%) of **12~16**(ratio)	Yield(%) of **17**
1	PhCHO	**12a/b**	H, Ph	74(1:1.2)[a]	18
2	*p*-$MeOC_6H_4CHO$	**13a/b**	H, C_6H_4OMe-*p*	71(1:1.1)[a]	11
3	$(CH_3)_2CO$	**14**	CH_3, CH_3	41	38
4	$(CH_2)_5CO$	**15**	$(CH_2)_5$	40	14
5	CH_3I	**16**	—	49	22
6	MeOH	**17**	—	—	86.6

a. the diastereomeric ratio was determined by chromatographic separation.

diastereoselectivity at the carbinolic center when using an aldehyde as electrophile. Similarly, the reaction of the dianion **B** with methyl iodide produced **16** (49%) and a small amount of an inseparable mixture consisting of **17** and other unidentified methylated products. Finally, treatment of the dianion **B** with methanol gave lactam **17** in a yield of 86.6%.

Based on the observed characteristic geminal coupling constants of the methylene protons at C-3 (e.g. **17** and its C-5 alkylated derivatives,[7] J_{gem}=17.5 Hz) and those at C-5 (e.g. compounds **12–16**, J_{gem}=ca. 10 Hz), the regiochemistry of the present one-pot reaction was assigned as shown in structures **12–16**. The stereochemistry at C-3 of compounds **12–16** was assigned by comparison with those obtained by alternative methods.[11,12] A direct stereochemical proof was gained from a single-crystal X-ray crystallographic analysis of compound (1′*S*, 4*R*, 5*S*)-**12b** (Fig. 1).

Thus, we have shown that phenyl thioether *trans*-**8** can serve as a synthetic equivalent to chiron **B** through a one-pot operation. In this procedure, transient dianion **A** was converted to the thermodynamically more stable **B** through proton exchange (Scheme 1). These results open a new approach to



(1'*S*,3*R*,4*S*)-12b

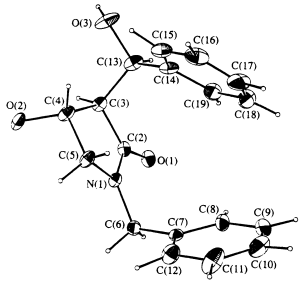


Figure 1. ORTEP plot of compound **12b** (presented as its antipode)

both 3-substituted and 3-unsubstituted 4-hydroxy-2-pyrrolidinones. These 2-pyrrolidinones and their ring opening products are key intermediates for drugs and agrochemicals.[1–6]

We next turned our attention to the synthesis of (*S*)-**1**. For this purpose, it was needed to cleave the amidic *N*-benzyl group in **17**. Although several methods are available to effect the amide *N*-debenzylation,[13,14] the method using dissolved metal in liquid ammonia is the most useful one. Based on the consideration that solvated electrons are the key species responsible for *N*-debenzylation in this type of reaction, it was envisioned that LN would be useful for the same purpose. Thus, treatment of **17** with 6 equivalents of LN led to (*S*)-**1** [mp 156–157°C. $[\alpha]_D^{22}$ −53.9 (*c* 0.5, H_2O)] in 40% yield. Similarly, *N*-debenzylation of **16** using LN afforded **18** [yield 58.7%, mp 135.5–137°C. $[\alpha]_D^{22}$ −58.8 (*c* 0.9, MeOH)], the lactam form of compound *syn*-**7**. Since lactam formation is a useful method for confirming the stereochemistry of the corresponding γ-amino acids,[15] present synthesis of lactam *syn*-**7** would provide a useful reference for the stereochemical assignment of 4-amino-3-hydroxy-2-methylbutyric acid **7**, the γ-amino acid residue (with unknown stereochemistry) found in bistramides A, B, C, D and K.[4] It is also worth mentioning that this amide *N*-debenzylation method presents the advantage of being easy to perform and is apparently the first illustration of LN mediated amide *N*-debenzylation.[16]

In summary, starting from *trans*-**8**, we have developed a concise approach to substituted 2-pyrrolidinones **12**–**17**. Moreover, we also developed a new LN based amide *N*-debenzylation method, which resulted in a new chiral synthesis of naturally occurring (−)-(*S*)-4-hydroxy-2-pyrrolidinone **1** and an asymmetric synthesis of **18** as the lactam form of the γ-amino acid residue found in bistramides.

2. Experimental

Melting points were determined on a Yanaco MP-500 micro melting point apparatus. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR or a Shimadzu IR-408 spectrometer using film NaCl or KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ or D_2O on a Varian unity +500 spectrometer 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 one of the following apparatus: Finnigan Mat-GCQ (direct injection), Hewlett–Packard 5889A or Bruker APEX II FT mass spectrometer and were presented as m/z (% rel. int.). Optical rotations were measured with either a Perkin–Elmer 241 MC or a Perkin–Elmer 341 automatic polarimeter. Elemental analyses were performed by the Micro Analytical Laboratory at either Shanghai Institute of Organic Chemistry or Department of Chemistry, Xiamen University. THF and diethyl ether used in the reactions were dried by distillation over metallic sodium and benzophenone; dichloromethane were distilled over P_2O_5. Silica gel (Qingdao, 400 mesh) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60–90°C) mixtures. (*S*)-4-Acetoxy-1-benzyl-2,5-pyrrolidinedione[7,8c,8d] **10**

and (4*S*,5*S*)-4-acetoxy-1-benzyl-5-hydroxy-2-pyrrolidinone **11** were prepared according to the literature procedures.

2.1. *(4*S,5R*)-1-Benzyl-4-hydroxy-5-thiophenyl-2-pyrrolidinone* trans-***8*** *and the 4*S,*5*S*-isomer* cis-***8***

To a solution of **11** (523 mg, 2.1 mmol) and *p*-toluenesulfonic acid monohydrate (50 mg) in 20 mL of anhydrous CH_2Cl_2 was added thiophenol (0.43 mL, 4.2 mmol). After stirring at rt for 52 h, a saturated aqueous solution of $NaHCO_3$ (9 mL) and brine (5 mL) were added. The mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography (EtOAc:PE 1:1) afforded *trans*-**8** (459 mg, 73%) as a pale yellow oil, *cis*-**8** (38 mg, 6%) as colorless crystals and a small amount of diastereomeric mixture of undeacetylated compound **11** (79 mg, 12%).

trans-**8** (faster eluting isomer): crystallized on standing at low temperature, mp 76.5–77.5°C. $[\alpha]_D^{20}$ −60.8 (*c* 3.0, $CHCl_3$). IR: 3382, 3061, 3032, 2926, 1674, 1583, 1439, 1155, 1252, 1058, 937, 742, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 2.08 (ddd, J=1.0, 6.1, 17.6 Hz, 1H, H-3), 2.18 (dd, J=1.1, 17.6 Hz, 1H, H-3), 4.21 (d, J=14.9 Hz, 1H, $PhCH_2N$), 4.48 (s and dd superimposed, J=1.1, 6.1 Hz, 2H, H-5 and H-4), 5.22 (d, J=14.9 Hz, 1H, $PhCH_2N$), 7.25–7.42 (m, 10H, Ph-H). ^{13}C NMR (125 MHz, $CDCl_3$): 39.04 (C-3), 43.70 (NCH_2Ph), 71.35 (C-5), 73.62 (C-4), 127.65, 128.07, 128.71, 128.98, 129.39 and 130.29 (Ar-*C*H), 134.56 (Ar-C), 135.32 (Ar-CS), 173.11 (C=O). MS (EI): 299 (M^+, 0.1), 190 (M^+−PhS, 57), 172 (5), 109 (7), 92 (9), 91 (100), 65 (17), 51 (3), 39 (5). HRMS calcd for $C_{11}H_{12}NO_2$ (M^+−PhS): 190.0868. Found: 190.0868.

cis-**8** (slower eluting isomer): mp 76–77°C. $[\alpha]_D^{20}$ −18.4 (*c* 1.9, $CHCl_3$). IR: 3408, 3063, 3032, 2931, 2902, 1687, 1605, 1583, 1448, 1382, 1235, 1173, 1086, 748, 707 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 2.19 (dd, J=1.3, 16.8 Hz, 1H, H-3), 2.65 (dd, J=7.6, 16.8 Hz, 1H, H-H), 4.15 (d, J=14.8 Hz, 1H, $PhCH_2N$), 4.51 (ddd, J=6.2, 1.3, 7.6 Hz, 1H, H-4), 4.80 (d, J=6.2 Hz, 1H, H-5), 5.24 (d, J=14.8 Hz, 2H, NCH_2Ph), 7.18–7.44 (m, 10H, Ph-H). ^{13}C NMR (125 MHz, $CDCl_3$): 38.30 (C-3), 44.35 ($PhCH_2N$), 66.33 (C-5), 75.29 (C-4), 127.79, 128.08, 128.24, 128.54, 128.71, 129.35, 131.68, and 133.69 (Ar-CH), 134.61 (Ar-C), 135.53 (ArCS), 171.27 (C=O). MS (EI): 299 (M^+, 0.1), 190 (M^+−PhS, 62), 172 (6), 109 (6), 92 (8), 91 (100), 65 (15), 51 (3), 39 (5). Anal. calcd for $C_{17}H_{17}NO_2S$: C, 68.66; H, 5.68; N, 4.71. Found: C, 68.32; H, 5.70; N, 4.71.

2.2. *General procedure for the one-pot synthesis of compounds* ***12***–***17*** *from* trans-***8***

A solution of *trans*-**8** (0.52 mmol) in 1.7 mL of dry THF at −78°C was treated with *n*-BuLi (1.6 M solution in *n*-hexane, 0.57 mmol) and freshly prepared lithium naphthalenide (1.0 M solution in THF, 1.14 mmol). After stirring for 30 min, an electrophile (0.78 mmol) was added. The stirring continued at −78°C for 1 h, and was then allowed to warm to 0°C. A saturated aqueous solution of NH_4Cl was added and the mixture was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography (EtOAc:PE 1:1) afforded the desired product and a small amount of **17** (Table 1).

2.3. *(1′*R,*3*R,*4*S*)-1-Benzyl-4-hydroxy-3-[(1′-phenyl)-hydroxymethyl]-2-pyrrolidinone* ***12a*** *and the (1′*S, *3*R,*4*S*)-isomer* ***12b***

12a (faster eluting isomer): yield 33.8%, white crystals, mp 92–93°C. $[\alpha]_D^{20}$ +44.6 (*c* 1.3, $CHCl_3$). IR: 3350, 2900, 1660, 1480, 1445, 1270, 1040, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 2.10 (s, br, 1H, OH),

2.85 (dd, J=2.4, 4.7 Hz, 1H, H-3), 2.99 (dd, J=4.8, 10.1 Hz, 1H, H-5), 3.32 (dd, J=7.4, 10.1 Hz, 1H, H-5), 4.41 (d, J=15.0 Hz, 1H, $PhCH_2N$), 4.44 (d, J=15.0 Hz, 1H, $PhCH_2N$), 4.47 (ddd, J=4.7, 4.8, 7.4 Hz, 1H, H-4), 5.35 (d, J=2.4 Hz, 1H, CH(OH)Ph), 7.18–7.34 (m, 10H, Ph-H). ^{13}C NMR (75 MHz, $CDCl_3$): 46.36 (C-5), 53.11 (C-3), 58.45 (NCH_2Ph), 65.28 (C-4), 70.80 (Ph*C*HOH), 125.55, 127.64, 127.92, 128.57 and 128.65 (Ar-CH), 135.58 and 141.43 (2×Ar-C), 172.97 (C=O). MS (EI): 297 (M^+, 19), 279 (M^+-H_2O, 10), 190 (28), 174 (34), 131 (10), 106 (11), 91 (100), 77 (12). HRMS calcd for $C_{18}H_{19}NO_3$: 297.1365. Found: 297.1363. Anal. calcd for $C_{18}H_{19}NO_3$: C, 72.73; H, 6.40; N, 4.71. Found: C, 72.86; H, 6.41; N, 4.69.

12b (slower eluting isomer): yield 40.5%, crystallized on standing at low temperature as white crystals, mp 113–114°C. $[\alpha]_D^{20}$ −9.7 (*c* 1.0, $CHCl_3$). IR: 3500, 2800, 1660, 1480, 1450, 1270, 1040, 695 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 2.76 (dd, J=7.1, 9.2 Hz, 1H, H-3), 3.03 (dd, J=6.4, 10.1 Hz, 1H, H-5), 3.30 (dd, J=7.6, 10.1 Hz, 1H, H-5), 4.18 (ddd, J=6.4, 7.1, 7.6 Hz, 1H, H-4), 4.43 (d, J=14.7 Hz, 1H, $PhCH_2N$), 4.48 (d, J=14.7 Hz, 1H, $PhCH_2N$), 4.85 (d, J=9.2 Hz, 1H, CH(OH)Ph), 7.18–7.34 (m, 10H, Ph-H). ^{13}C NMR (75 MHz, $CDCl_3$): 46.24 (C-5), 51.89 (C-3), 56.89 ($NCHPh$), 66.99 (C-4), 74.68 (Ph*C*HOH), 126.68, 127.89, 128.15, 128.66, 128.84 and 128.99 (Ar-CH), 135.41 and 140.33 (2×Ar-C), 173.58 (C=O). MS (EI): 297 (M^+, 19), 279 (M^+-H_2O, 10), 190 (28), 174 (34), 131 (10), 106 (11), 91 (100), 77 (12). HRMS calcd for $C_{18}H_{19}NO_3$: 297.1365. Found: 297.1363.

*2.4. (1′*R*,3*R*,4*S*)-1-Benzyl-4-hydroxy-3-[1′-(4-methoxyphenyl)-hydroxymethyl]-2-pyrrolidinone **13a** and the (1′*S*,3*R*,4*S*)-isomer **13b***

13a (faster eluting isomer): yield 33.3%, pale yellow solid, mp 117–119°C. $[\alpha]_D^{20}$ +32.5 (*c* 1.0, $CHCl_3$). IR: 3400, 2950, 1660, 1510, 1440, 1250, 1170, 1025, 800 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 2.85 (dd, J=3.9, 5.8 Hz, 1H, H-3), 3.02 (dd, J=5.5, 10.1 Hz, 1H, H-5), 3.34 (dd, J=7.6, 10.1 Hz, 1H, H-5), 3.80 (s, 3H, OCH_3), 4.47 (s, 2H, $PhCH_2N$), 4.53 (ddd, J=5.5, 5.8, 7.6 Hz, 1H, H-4), 5.37 (d, J=3.9 Hz, 1H, ArCHOH), 6.90 (d, J=8.3 Hz, 2H, $CH_3OC_6H_4$), 7.20 (d, J=8.3 Hz, 2H, $CH_3OC_6H_4$), 7.29–7.34 (m, 5H, Ph-H). ^{13}C NMR (125 MHz, $CDCl_3$): 46.37 (C-5), 52.72 (C-3), 55.30 (NCH_2Ph), 58.32 (CH_3O), 65.68 (C-4), 70.77 (Ph*C*HOH), 114.16, 126.72, 127.68, 128.03 and 128.75 (Ar-CH), 133.24 and 135.73 (2×Ar-C), 159.12 (Ar-COMe). MS (EI): 327 (M^+, 20), 191 (100), 174 (47) 91 (10). HRFABMS calcd for $[C_{19}H_{21}O_4N+H]^+$ 328.1543. Found: 328.1542.

13b (slower eluting isomer): yield 37.4%, pale yellow solid, mp 123–125°C. $[\alpha]_D^{20}$ −14.4 (*c* 1.2, $CHCl_3$). IR: 3400, 2950, 1660, 1510, 1440, 1250, 1170, 1025, 800 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 2.74 (dd, J=7.0, 9.2 Hz, 1H, H-3), 3.02 (dd, J=6.3, 10.1 Hz, 1H, H-5), 3.28 (dd, J=8.0, 10.1 Hz, 1H, H-5), 3.80 (s, 3H, OCH_3), 4.14 (ddd, J=6.3, 7.0, 8.0 Hz, 1H, H-4), 4.42 (d, J=14.7 Hz, 1H, $PhCH_2N$), 4.46 (d, J=14.7 Hz, 1H, $PhCH_2N$), 4.79 (d, J=9.2 Hz, 1H, ArCHOH), 6.90 (d, J=8.3 Hz, 2H, $CH_3OC_6H_4$), 7.18 (d, J=8.3 Hz, 2H, $CH_3OC_6H_4$), 7.27–7.35 (m, 5H, Ph-H). ^{13}C NMR (125 MHz, $CDCl_3$): 46.22 (C-5), 51.92 (C-3), 55.27 (NCH_2Ph), 56.93 (CH_3O), 67.02 (C-4), 74.20 (Ph*C*HOH), 114.28, 127.87, 127.94, 128.15 and 128.82 (Ar-CH), 132.28 and 135.42 (2×Ar-C), 159.68 (Ar-COMe), 173.68 (C=O). MS (EI): 327 (M^+, 11), 191 (100), 174 (47), 91 (12). HRFABMS calcd for $[C_{19}H_{21}O_4N+H]^+$: 328.1543. Found: 328.1545.

*2.5. (3*R*,4*S*)-1-Benzyl-4-hydroxy-3-[(1′-hydroxy-1′-methyl)ethyl]-2-pyrrolidinone **14***

Yield 40.8%, pale yellow oil, $[\alpha]_D^{20}$ −25.4 (*c* 2.3, $CHCl_3$). IR: 3350, 2900, 1655, 1445, 1255, 695 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.29 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 2.57 (d, J=6.5 Hz, 1H, H-3), 3.08 (dd, J=5.6, 10.1 Hz, 1H, H-5), 3.45 (dd, J=7.6, 10.1 Hz, 1H, H-5), 4.32 (ddd, J=5.6, 6.5, 7.6 Hz, 1H,

H-4), 4.41 (d, J=14.9 Hz, 1H, $PhCH_2N$), 4.52 (d, J=14.9 Hz, 1H, $PhCH_2N$), 7.20–7.38 (m, 5H, Ph-H). ^{13}C NMR (125 MHz, $CDCl_3$): 26.50 (CH_3), 27.19 (CH_3), 46.22 (C-5), 53.05 (C-3), 60.10 (NCH_2Ph), 67.33 (C-4), 71.50 (Me_2COH), 127.78, 128.02 and 128.77 (Ar-CH), 135.54 (Ar-C), 173.52 (C=O). MS (EI): 249 (M^+, 13), 231 (M^+-H_2O, 8), 191 (26), 174 (22), 173 (25), 111 (11), 97 (17), 91 (100), 57 (64). HRMS calcd for $C_{14}H_{19}NO_3$: 249.1365. Found 249.1366.

2.6. (3R,4S)-1-Benzyl-4-hydroxy-3-(1′-hydroxycyclohex-1′-yl)-2-pyrrolidinone **15**

Yield 40%, pale yellow oil, $[\alpha]_D^{20}$ −24.7 (*c* 2.1, $CHCl_3$). IR: 3350, 2940, 1655, 1490, 1260, 1075, 960, 690 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 1.18–1.82 (m, 10H, $(CH_2)_5$), 2.53 (d, J=6.1 Hz, 1H, H-3), 3.07 (dd, J=5.5, 10.2 Hz, 1H, H-5), 3.44 (dd, J=7.7, 10.2 Hz, 1H, H-5), 4.43 (ddd, J=5.5, 6.1, 7.7 Hz, 1H, H-4), 4.46 (d, J=14.7 Hz, 1H, $PhCH_2N$), 4.51 (d, J=14.7 Hz, 1H, $PhCH_2N$), 7.20–7.37 (m, 5H, Ph-H). ^{13}C NMR (125 MHz, $CDCl_3$): 21.05, 21.23, 25.50, 33.72 and 34.88 (*c*-hex-CH_2), 46.16 (C-5), 52.96 (C-3), 60.34 (NCH_2Ph), 66.83 (C-4), 72.32 (*c*-hex-COH), 127.71, 128.00, and 128.74 (Ar-CH), 135.64 (Ar-C), 173.26 (C=O). MS (EI): 289 (M^+, 6), 271 (M^+-H_2O, 58), 191 (13), 174 (40.6), 111 (11), 97 (17), 91 (100), 71 (38), 57 (60). HRMS calcd for $C_{17}H_{23}NO_3$: 289.1678. Found 289.1676.

2.7. (3S,4S)-1-Benzyl-4-hydroxy-3-methyl-2-pyrrolidinone **16**

Yield 48.5%, pale yellow oil, $[\alpha]_D^{20}$ −47.3 (*c* 0.8, $CHCl_3$). IR: 3350, 2850, 1660, 1485, 1450, 1260, 1075, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 1.23 (d, J=7.3 Hz, 3H, CH_3), 2.44 (dq, J=5.5, 7.3 Hz, 1H, H-3), 3.08 (dd, J=4.6, 10.3 Hz, 1H, H-5), 3.42 (dd, J=6.5, 10.3 Hz, 1H, H-5), 4.03 (ddd, J=4.6, 5.5, 6.5 Hz, 1H, H-4), 4.41 (d, J=14.8 Hz, 1H, $PhCH_2N$), 4.46 (d, J=14.8 Hz, 1H, $PhCH_2N$), 7.19–7.33 (m, 5H, Ph-H). ^{13}C NMR (75 MHz, $CDCl_3$): 13.66 (CH_3), 46.19 (C-5), 52.86 (C-3), 60.09 (NCH_2Ph), 72.19 (C-4), 127.59, 127.96 and 128.69 (Ar-CH), 136.07 (Ar-C), 175.34 (C=O). MS (EI): 205 (M^+, 100), 172 (8), 160 (12), 132 (13), 119 (14), 107 (12), 91 (28). HRFABMS calcd for $[C_{12}H_{15}NO_2+H]^+$: 206.1175. Found: 206.1177.

2.8. (S)-1-Benzyl-4-hydroxy-2-pyrrolidinone **17**

Yield 86.6%, white solid, mp 107.5–109°C, $[\alpha]_D^{20}$ −35.2 (*c* 1.3, $CHCl_3$). IR: 3350, 2910, 1660, 1485, 1440, 1260, 1078, 690 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 2.44 (dd, J=2.3, 17.4 Hz, 1H, H-3), 2.70 (dd, J=6.6, 17.4 Hz, 3H, H-3), 3.18 (dd, J=2.0, 10.9 Hz, 1H, H-5), 3.48 (dd, J=5.6, 10.9 Hz, 1H, H-5), 4.42 (d, J=14.9 Hz, 1H, $PhCH_2N$), 4.45 (m, 1H, H-4), 4.48 (d, J=14.9 Hz, 1H, $PhCH_2N$), 7.18–7.38 (m, 5H, Ph-H). ^{13}C NMR (75 MHz, $CDCl_3$): 41.08 (C-3), 46.28 (C-5), 55.76 (NCH_2Ph), 63.96 (C-4), 127.58, 127.91, and 128.67 (Ar-CH), 135.85 (Ar-C), 173.22 (C=O). MS (EI): 191 (M^+, 100), 172 (28), 146 (36), 118 (19), 104 (22), 91 (48), 65 (11). HRMS calcd for $C_{11}H_{13}NO_2$: 191.0946. Found: 191.0946. Anal. calcd for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.81; N, 7.33. Found: C, 69.01; H, 6.86; N, 7.27.

2.9. (S)-4-Hydroxy-2-pyrrolidinone **1**

A solution of **17** (45 mg, 0.236 mmol) in 2.3 mL of dry THF at −20°C was treated with *n*-BuLi (1.6 M solution in *n*-hexane, 0.22 mL, 0.35 mmol) and freshly prepared lithium naphthalenide (1.5 M solution in THF, 0.94 mL, 1.41 mmol). After stirring at −15 to −10°C for 75 min, the reaction was quenched by MeOH and concentrated in vacuo. Flash chromatography ($CHCl_3$:MeOH 4:1) afforded **1** (9 mg, 38.7%) as a white solid. Mp 156–157°C (lit. for (*S*)-**1**: 153.5–155°C;[3] 155–157°C;[5a] 152–154°C;[5d] for (*R*)-**1**:

157–158°C;[5a] 153–155°C;[2]). $[\alpha]_D^{20}$ −53.9 (*c* 0.6, H_2O) [lit. for (*S*)-**1**: $[\alpha]_D$ −45.8 (H_2O);[3] $[\alpha]_D^{25}$ −55.5 (*c* 1.04, H_2O);[5a] $[\alpha]_D$ −54.8 (*c* 0.48, H_2O)];[5d] $[\alpha]_D^{21}$ −34.5 (*c* 1.4, H_2O)], 60% ee;[5b] for (*R*)-**1**, $[\alpha]_D$ +57.3 (*c*, 1.4, H_2O);[5a] $[\alpha]_D$ +58.6 (*c* 0.36, H_2O).[2] IR: 3246, 3147, 2943, 2929, 1674, 1483, 1408, 1338, 1304, 1065, 968, 744, 685 cm^{-1}. ^1H NMR (500 MHz, D_2O): 2.20 (dd, J=1.7, 17.8 Hz, 1H, H-3), 2.72 (dd, J=6.3, 17.8 Hz, 1H, H-3), 3.29 (dd, J=11.8 Hz, 1H, H-5), 3.65 (dd, J=5.3, 11.8 Hz, 1H, H-5), 4.55 (m, 1H, H-4). ^{13}C NMR (75 MHz, D_2O): 39.56 (C-3), 51.41 (C-5), 66.80 (C-4), 179.36 (C=O). MS (EI): 102 (M^++1, 32), 91 (52), 84 (18), 73 (100), 65 (9). HRFABMS calcd for $[C_4H_7NO_2+H]^+$: 102.0549. Found: 102.0550.

*2.10. (3S,4S)-4-Hydroxy-3-methyl-2-pyrrolidinone **18***

A solution of **16** (85 mg, 0.41 mmol) in 4.1 mL of dry THF at −20°C was treated with *n*-BuLi (1.6 M solution in *n*-hexane, 0.29 mL, 0.46 mmol) and freshly prepared lithium naphthalenide (1.5 M solution in THF, 1.66 mL, 2.49 mmol). After stirring at −15 to −10°C for 2 h, the reaction was quenched by MeOH and concentrated in vacuo. Flash chromatography ($CHCl_3$:MeOH 8:1) afforded **18** (28 mg, 58.7%) as a white solid and recovered starting material **16** (20 mg, 24%). **18**: mp 135.5–136.5°C. $[\alpha]_D^{20}$ −58.8 (*c* 0.9, MeOH). IR: 3232, 3145, 2970, 2929, 1671, 1486, 1461, 1329, 1295, 1122, 976, 832 cm^{-1}. ^1H NMR (500 MHz, D_2O): 1.15 (d, J=7.6 Hz, 3H, CH_3), 2.38 (dq, J=4.6, 7.6 Hz, 1H, H-3), 3.20 (dd, J=4.1, 11.1 Hz, 1H, H-5), 3.66 (dd, J=6.2, 11.1 Hz, 1H, H-5), 4.18 (ddd, J=4.1, 4.6, 6.2 Hz, 1H, H-4). ^{13}C NMR (75 MHz, D_2O): 12.56 (CH_3), 45.19 (C-3), 46.56 (C-5), 73.57 (C-4), 181.65 (C=O). MS (EI): 115 (M^+, 17), 100 (24), 86 (100), 82 (19), 57 (38). HRFABMS calcd for $[C_5H_9NO_2+H]^+$: 116.0706. Found: 116.0706. Anal. calcd for $C_5H_9NO_2$: C, 52.17; H, 7.83; N, 12.17. Found: C, 51.90; H, 7.93; N, 12.11.

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