# A Convenient Approach to the Enantiopure (1*S*,2*S*,4*S*,5*S*)- and (1*R*,2*S*,4*R*,5*S*)-2,5-Bis(phenylmethyl)-1,4-diazabicyclo[2.2.2]-octane

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**Cyclodipeptide (3*S*,6*S*)-bis(phenylmethyl)piperazine-2,5-dione was prepared in high yield by heating phenylalanine methyl ester in toluene under reflux. The reduction of this cyclodipeptide with sodium $NaBH_4$-$BF_3$ in DME gave the (2*S*,5*S*)-bis(phenylmethyl)piperazine, which, on heating with ethylene bromide and triethylamine, afforded the title compounds. This method was proved to be generally applicable to the synthesis of $C_2$-symmetric 2, 5-disubstituted-1, 4-diazabicyclo [2. 2. 2] octane from the corresponding natural or unnatural amino acid esters.**

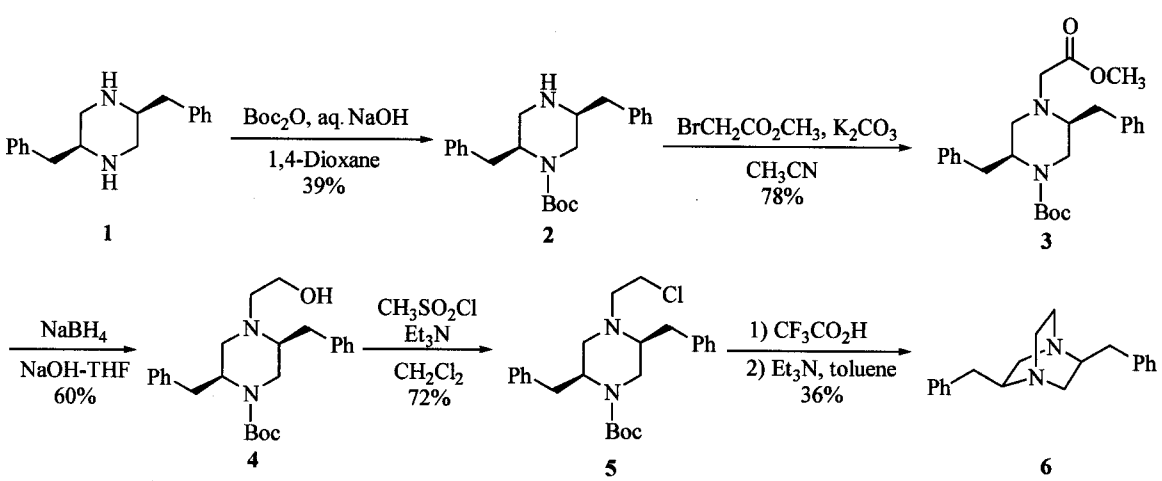
**Keywords** cyclodipeptide, piperazine-1,4-dione, $C_2$-symmetric, preparation

## Introduction

1,4-Diazabicyclo[2.2.2]octane (DABCO) was reported to catalyze organic reactions due to its strong basicity.[1,2] Several chiral *trans*-2,3-disubstituted DABCOs have been synthesized and applied to the asymmetric Baylis-Hillman reaction[3] and vicinal hydroxylation.[4]

The first synthesis of the title compound was reported by Soai[5] from (2*S*,5*S*)-bis(phenylmethyl)piperazine (**1**), as shown in Scheme 1. But this procedure is lengthy, and the overall yield is not so satisfactory. Besides, the reported method for the preparation of **1** is also inconvenient:[6,7] the coupling of phenylalanine methyl ester with *N*-Boc or *N*-Cbz protected phenylalanine gave the protected dipeptide *N*-Boc-/or *N*-Cbz-phenylalanyl-phenylalanine methyl ester, which was then *N*-deprotected by treating with a proper acid such as TFA/or hydrogenolyzed using palladium as the catalyst, and then heated to affect the ring-closure reaction to give the cyclic dipeptide (3*S*,6*S*)-bis(phenylmethyl)-piperazine-2,5-dione (**8**), which was finally reduced to give **1**. The protection of the amino acid and the deprotection of the peptide made the synthesis of the cyclic dipeptide tedious. In our on-going program on asymmetric synthesis, we developed a simple and convenient procedure for the synthesis of the title compound. In this paper, we wish to report this convenient approach to both (1*S*,2*S*,4*S*,5*S*)- and (1*R*,2*S*,4*R*,5*S*)-2,5-bis-(phenylmethyl)-1,4-diazabicyclo[2.2.2]octane.

**Scheme 1**

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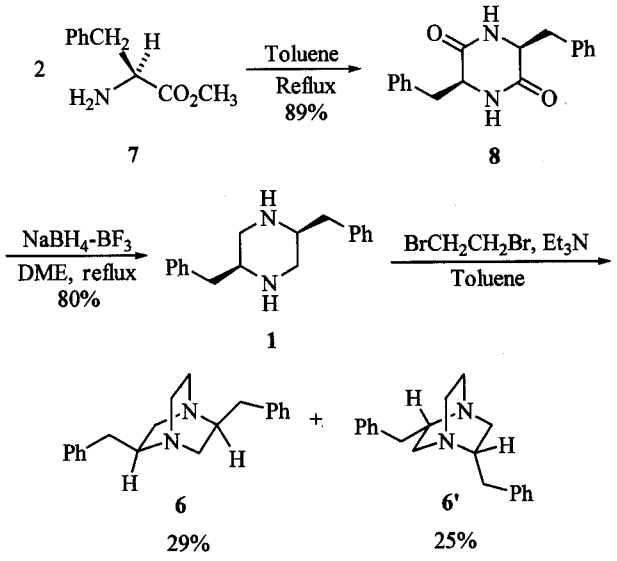
Received December 19, 2002; revised February 19, 2003; accepted March 18, 2003.
Project supported by the Natural Science Foundation of Jiangsu Education Office (No. 01KJB150002).

## Results and discussion

The new approach to (1*S*,2*S*,4*S*,5*S*)- and (1*R*,2*S*,4*R*,5*S*)-2,5-bis(phenylmethyl)-1,4-diazabicyclo[2.2.2]octane **6** and **6'** is shown in Scheme 2. The (3*S*,6*S*)-bis(phenylmethyl)piperazine-2,5-dione (**8**) was prepared from phenylalanine methyl ester **7** in 82.4% yield simply by heating in toluene under reflux. The reduction of **8** was achieved by refluxing it in dimethoxyethane (DME) with sodium borohydride-$BF_3$ under nitrogen atmosphere to give (2*S*,5*S*)-bis(phenylmethyl)-piperazine (**1**). This method is more convenient than the reported methods such as the reduction with $LiAlH_4$ in THF,[8] the reduction with borane in THF,[9] or the reduction with $NaBH_4$-$TiCl_4$ in DME.[10] Treating **1** with 1,2-dibromoethane gave two stereoisomers **6** and **6'**, which are different in the configurations at position 1 and position 4. Since $^1H$ NMR spectra could not discriminate between **6** and **6'**, the structure of **6** was determined by single-crystal X-ray analysis as its dihydrochloride. The ortep view of **6** dihydrochloride is shown in Fig. 1 (the crystal methanol is not shown here). These results are similar to that of the reaction of (2*R*,5*R*)-1-*tert*-butoxycarbonyl-2,5-bis(phenylmethyl)-piperazine with 1,2-dibromoethane, reported by Kaoru Fuji *et al.*, wherein two diastereomers, different in the configurations at position 1 and position 4, formed.[11]

**Scheme 2**




We have also successfully extended this method to the preparation of (1*S*,2*S*,4*S*,5*S*)- and (1*R*,2*S*,4*R*,5*S*)-2,5-bis(2-methylpropyl)-1,4-diazabicyclo[2.2.2]-octane from leucine methyl ester. This means that the new method is generally applicable to the synthesis of $C_2$-symmetric 2,5-disubstituted-1,4-diazabicyclo[2.2.2]octane from the corresponding natural or unnatural amino acid esters.

In summary, we have developed a new convenient, generally applicable method for the preparation of $C_2$-symmetric 2,5-disubstituted-1,4-diazabicyclo[2.2.2]octane from the corresponding natural or unnatural amino acid ester. This method has the advantages of short synthetic route, high yield, and easy-to-operate.

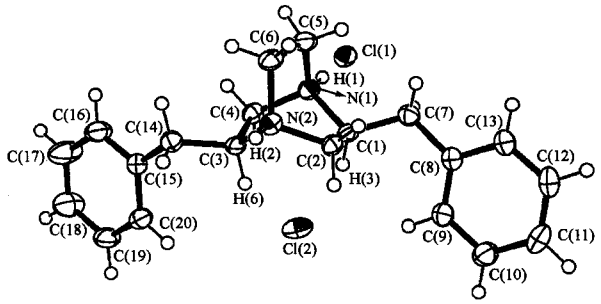



**Fig. 1** X-Ray structure of **6** dihydrochloride.

## Experimental

*General*

Melting points were measured in capillaries and uncorrected. Optical rotations were measured at 589 nm (Na D line) on a WZZ-1 polarimeter. $^1H$ NMR spectra were recorded on a Varian Inova-400 instrument in deuterated chloroform, chemical shifts ($\delta$) were reported relative to tetramethylsilane (TMS). Infrared spectra were recorded on a Nicolet Magna 550 FT-IR spectrometer. Mass spectra were recorded on a Micromass OA-TOF instrument. Elemental analyses were carried out on a Carlo-Erba 1110 analyzer. For preparative column chromatography, silica gel (H60) was used, with the solvent system given in the text. Organic solvents were purified prior to use according to the standard method.

*(3S,6S)-Bis(phenylmethyl)piperazine-2,5-dione* (**8**)

(*S*)-Phenylalanine methyl ester **7** (9.41 g, 52.5 mmol), obtained from the corresponding hydrochloride by dehydrochlorination with saturated solution of sodium bicarbonate, was refluxed in toluene (30 mL), white precipitate began to appear after about 30 min, and the mixture was heated for further 5 h. The mixture was then allowed to cool to r.t. The crystals formed were collected by filtration and washed twice with ether to give 6.37 g of **8**, yield 82.4%. m.p. 308—310 ℃ (lit.[6] 308—310 ℃). IR $\nu_{max}$: 3205, 3086, 1675, 1661, 1497 $cm^{-1}$. Anal. calcd for $C_{18}H_{18}N_2O_2$: C 73.45, H 6.16, N 9.52; found C 73.19, H 6.38, N 9.10.

*(2S,5S)-Bis(phenylmethyl)piperazine* (**1**)

To a suspension of **8** (2.85 g, 9.68 mmol) and $NaBH_4$ (2.48 g, 65.6 mmol) in dry DME (50 mL) was added $BF_3 \cdot Et_2O$ (9.08 g, 64.0 mmol) dropwise under $N_2$ atmosphere while cooling with an ice-water bath. The mixture was refluxed for 12 h, then $NaBH_4$ (1.25 g, 33.0

mmol) and $BF_3 \cdot Et_2O$ (4.68 g, 33.0 mmol) were further added 3 times respectively every 12 h. The reaction mixture was cooled to 0 ℃ and quenched by addition of $H_2O$ (10 mL). The insoluble precipitate was filtered off. The filtrate was made basic with 28% aq. $NH_3$, and was extracted with $CH_2Cl_2$ (20 mL × 3). The combined extracts were dried over anhydrous $Na_2SO_4$. Organic solvents were evaporated and the residue was stirred overnight in 6 mol/L HCl-$CH_3OH$ (3 mL, 18 mmol). After the evaporation of MeOH, the mixture was made basic with 1 mol/L NaOH and extracted with $CH_2Cl_2$. The extract was dried over anhydrous $Na_2SO_4$, evaporated and the residue was treated with 6 mol/L HCl-$CH_3OH$ in $Et_2O$. The crystals formed were collected by filtration to give the dihydrochloride of **1** (2.35 g), yield 71.5%, m.p. 228—230 ℃ (lit.[10] 230—232 ℃). $^1H$ NMR of **1** (as the free base in $CDCl_3$) $\delta$: 1.66 (brs, 2H, NH), 2.78—3.01 (m, 10H), 7.22—7.33 (m, 10H, ArH); IR (KBr) $\nu_{max}$: 3427, 3027, 2921, 1498 $cm^{-1}$. Anal. calcd for $C_{18}H_{24}Cl_2N_2$: C 63.72, H 7.13, N 8.26; found C 63.37, H 7.20, N 8.34.

*(1R,2S,4R,5S)- and (1R,2S,4R,5S) bis-(phenylmethyl)-1,4-diazabicyclo[2.2.2]octane* **6** *and* **6′**

A mixture of **1** (1.00 g, 3.75 mmol), triethylamine (0.81 g, 8.00 mmol) and 1,2-dibromoethane (0.20 mL, 0.43 g, 2.30 mmol) in toluene (10 mL) was heated under reflux for 12 h, and then cooled to r.t. The reaction mixture was brought to pH = 9—10 with 1 mol/L aq. NaOH, the organic phase was separated. The aqueous phase was extracted with chloroform (15 mL × 3). The combined organic phase was dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. The residue was applied to a column and eluted with chloroform/methanol ($V/V$ = 50:1) to give **6** and **6′**.

**6** pale yellow oil, 0.34 g, yield 29%, $[\alpha]_D^{20}$ + 104 (*c* 0.8, methanol) (lit.[5] $[\alpha]_D^{24}$ + 104.1, *c* 4.06, methanol). $^1H$ NMR (chloroform-*d*) $\delta$: 2.49—2.57 (m, 2H, PhCH**H** × 2), 2.65—2.75 (m, 4H, 2-, 5-, 7- and 8-CH**H**), 2.89—2.96 (m, 6H, 2- and 5-CH**H**, 3- and 6-CH, PhCH**H** × 2), 3.03—3.09 (m, 2H, 7- and 8-CH**H**), 7.17—7.29 (m, 10H, ArH); MS *m/z* (%): 292.19 (73, $M^+$), 250.16 (8), 201.13 (100), 160.11 (20), 146.16 (25), 117.07 (29), 91.05 (31). Dihydrochloride, white crystals, m.p. 188—190 ℃. IR $\nu$: 3455, 3070, 2988, 2240, 1499 $cm^{-1}$. Anal. calcd for $C_{20}H_{26}Cl_2N_2$: C 65.75, H 7.17, N 7.67; found C 65.48, H 7.42, N 7.63.

**6′** pale yellow oil, 0.29 g, yield 25%, $[\alpha]_D^{20}$ + 134 (*c* 0.8, methanol); $^1H$ NMR $\delta$: 2.69—2.78 (m, 10H), 2.89—3.00 (m, 4H), 7.20—7.33 (m, 10H, ArH); MS *m/z* (%): 292.19 (71, $M^+$), 250.16 (9), 201.13 (100), 160.11 (21), 146.16 (25), 117.07 (32), 91.05 (35). Dihydrochloride, white hygroscopic crystals, m.p. 136—138 ℃; picrate, yellow crystals, m.p. 158—160 ℃. Anal. calcd for $C_{32}H_{30}N_8O_{14}$: C 51.20, H 4.03, N 14.93; found C 50.87, H 4.01, N 14.91.

*X-Ray crystallography*

**6** dihydrochloride (50 mg) was dissolved in methanol (4 mL). After standing for a week, suitable crystals formed. A crystal of (+)-(1*R*,2*R*,4*R*,5*R*)-2,5-bis-(phenylmethyl)-1,4-diazabicyclo[2.2.2]octane dihydrochloride was mounted on a glass fiber. All measurements were made on a Rigaku with graphite monochromated Mo Kα radiation.

Of the 7689 reflections that were collected, 2355 were unique ($R_{int}$ = 0.02), and equivalent reflections were merged. The structure was solved by direct method using the SIR92.

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(E0212191 PAN, B. F.; ZHENG, G. C.)