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Facile Synthesis of Optically Active *cis*-2,5-Diphenyl-1,4-Diazabicyclo[2.2.2]octane

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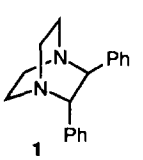
Abstract: Enantiomerically pure (*1R,2R,4R,5R*)- and (*1S,2R,4S,5R*)-2,5-diphenyl-1,4-diazabicyclo[2.2.2]octane (2,5-diphenyl-DABCO) have been prepared and their crystal structures studied. Copyright © 1996 Elsevier Science Ltd

1,4-Diazabicyclo[2.2.2]octane (DABCO) displays interesting catalytic properties due to its strong basicity and nucleophilicity.[1] The Baylis-Hillman reaction and vicinal hydroxylation of olefins by osmium tetroxide[2] is known to be catalyzed by DABCO. Optically active *trans*-2,3-diphenyl DABCO **1** was synthesized in 1991.[3] Later, a variety of *trans*-2,3-disubstituted DABCO's **2** were introduced for the asymmetric version of Baylis-



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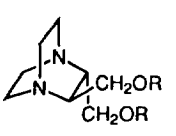

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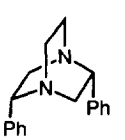

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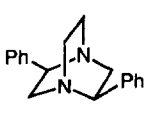

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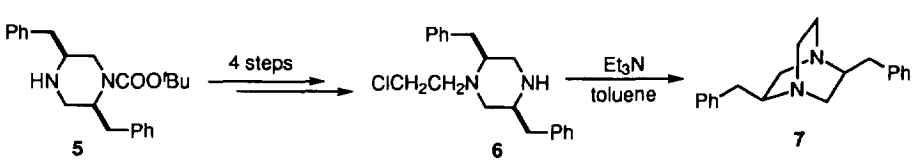
Hillman reaction[4] and of vicinal hydroxylation.[5] The enantiomeric excess (ee) for both reactions was not satisfactory (40 ~ 50 % ee). As a part of our program on the utilization of chiral piperazine derivatives for the enantioselective reactions,[6-8] we have synthesized optically active *cis*-2,5-diphenyl-DABCO, with a view to developing new chemistry of chiral DABCO's. In this paper, we wish to report facile preparation of enantiomerically pure *cis*-2,5-diphenyl-DABCO's **3** and **4** and their X-ray crystallographic structures.

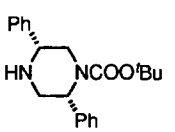
Scheme 1.



5 **6** **7**

Soai *et al*[9] reported a synthesis of optically active *cis*-2,5-dibenzyl-DABCO **7** by the intramolecular cyclization of **6**, which was prepared from **5** in four steps. We have found that the direct alkylation of **8** could give **3** and **4** in one step. Thus, refluxing enantiomerically pure 1-butoxycarbonyl-*2R,5R*-diphenylpiperazine

(5)[7] in 1,2-dibromoethane in the presence of potassium carbonate for 8h gave a diastereomeric mixture of **3** and **4**. Chromatographic separation followed by recrystallization gave pure **3** and **4** in 32 % and 11 % yield respectively. This procedure could give a variety of nonracemic 2,5-disubstituted-DABCO's, since the starting 1-butoxycarbonylpiperazines are easily prepared from optically active amino acids. It is worth noting that possible two diastereomers **3** and **4** were obtained, while an alternative isomer **9** was not obtained from the cyclization of **6**. The structures of **3** and **4** were determined by the X-ray crystallographic analysis[10] since the ^{1}H NMR spectra could not discriminate each other (see experimental section). Crystal structures of **3** and **4** are shown in Figure 1. Diazabicyclo[2.2.2]octane framework of each isomer has a twisted structure (D_3) but not an eclipsed structure (D_{3h}), which corresponds to theoretical calculations and experimental results for bicyclo[2.2.2]octane itself.[11] Both of **3** and **4** possess anticlockwise helicity around the N(1)-N(4) axis (Figure 2). Torsional angles of **3** are larger than those of **4** due to severe repulsive interaction between two endo phenyl rings.



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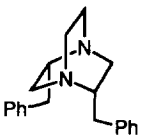

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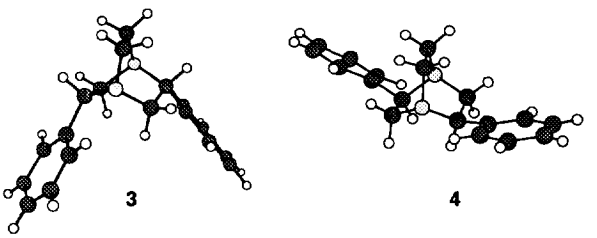
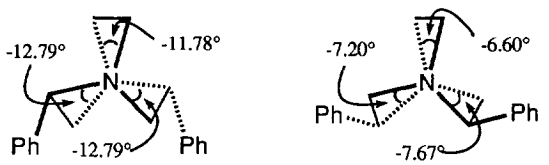
Figure 1. Crystal structures of **3** and **4**.



3 **4**

Figure 2. The views of crystal structures of **3** and **4** across the N(1)-N(4) axis



It is interesting that two isomers **3** and **4** have the opposite absolute stereochemistry at the nitrogen atoms. This is the inherent feature for 2,5-*cis*-disubstituted DABCO, because no stereoisomer on the nitrogen atom can be obtained when 2,3-*trans*-disubstituted piperazine is converted into the diazabicyclo ring system. Utilization of **3** and **4** for asymmetric synthesis is currently under way.

Experimental Section

***(1R,2R,4R,5R)*- and *(1S,2R,4S,5R)*-2,5-diphenyl-1,4-diazabicyclo[2.2.2]octanes 2 and 3.** A mixture

of (*2R,5R*)-1-*tert*-butoxycarbonyl-2,5-diphenylpiperazine (**3**, 510 mg, 1.5 mmol) and $KHCO_3$ (620 mg, 4.5 mmol) in ethylenedibromide (10 ml) was refluxed for 8h. After cooling the reaction mixture was diluted with CH_2Cl_2 and washed with brine, dried over anhydrous Na_2SO_4, and evaporated to give a residue, which was subjected to column chromatography over silica gel. Elution with acetone gave **2** (128 mg, 32 %): mp 208 - 208.5 °C (from AcOEt/CH_2Cl_2); $[\alpha]_D^{18}$ -135.3 (*c* 0.43, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.93 (dd, 2H, *J* = 13.4, 9.0 Hz), 3.08 (s, 4H), 3.25 (ddd, 2H, *J* = 13.4, 9.0, 1.5 Hz), 2.82 (t, 2H, *J* = 9.0 Hz), 7.12 - 7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 47.4, 48.7, 56.4, 126.7, 126.9, 128.4, 141.3; IR (KBr) ν 2880, 1600, 1490, 1175, 810, 725, 700 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.52; H, 7.59; N, 10.60.

Further elution with acetone gave **3** (45 mg, 11 %): mp 153 - 154 °C (from AcOEt/CH_2Cl_2); $[\alpha]_D^{20}$ - 168.9 (*c* 0.45, $CHCl_3$); ^1H NMR (CDCl3, 200 MHz) δ 2.57 (m, 2H), 2.79 (m, 2H), 3.15 (dd, 2H, *J* = 12.9, 8.8 Hz), 3.69 (dd, 2H, *J* = 12.9, 8.8 Hz), 4.08 (t, 2H, *J* = 8.8 Hz), 7.25 - 7.36 (m, 2H), 7.38 - 7.45 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 41.2, 55.1, 56.1, 126.9, 127.1, 128.5, 141.4; IR (KBr) ν 2930, 1495, 1445, 1060, 800, 745, 735, 700 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.42; H, 7,55; N, 10.49.

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10) Compound **3**; monoclinic, space proup C2 with *a* = 10.782(3), *b* = 6.457(4), *c* = 12.027(3) Å, β = 123.17(1)°, ν = 700.9 $Å^3$, Z = 4, *Dcalc* = 1.253 g/cm^3. The structure was refined to *R* = 0.041, *Rw* = 0.048, and *S* = 1.13. Compound **4**; orthorhombic, space group $P2_12_12_1$ with *a* = 9.293(3), *b* = 19.982(10), *c* = 7.647(5)Å, β = 90.00(0)°, ν = 1420.0 $Å^3$, *Z* = 4, *Dcalc* = 1.236 g / cm^3. The structure was refined to *R* = 0.031, *Rw* = 0.033, and *S* = 0.93. Atomic coordinates and amisotropic displacement parameters have been deposited with the Cambridge Crystallographic Centre.
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