HETEROCYCLES, Vol. 75, No. 6, 2008, pp. 1493 - 1501. © The Japan Institute of Heterocyclic Chemistry
Received, 7th January, 2008, Accepted, 18th February, 2008, Published online, 22nd February, 2008. COM-08-11328

STEREOSELECTIVE SYNTHESIS OF A NOVEL CHIRAL PIPERAZINE

Satoshi Kojima,[1,2]* Takashi Chabayashi,[1] Yasuhiro Umeda,[1] Akihisa Iwamoto,[1] Kazuhisa Tanabe,[1] and Katsuo Ohkata[1]

[1]Department of Chemistry, Graduate School of Science, Hiroshima University, 1-3-1 Kagamiyama, Higashi-Hiroshima 739-8526, Japan. [2]Center for Quantum Life Sciences, Hiroshima University, 1-3-1 Kagamiyama, Higashi-Hiroshima 739-8526, Japan. E-mail: skojima@sci.hiroshima-u.ac.jp

Abstract – (2*S*,6*S*)-2,4,6-Tris(phenylmethyl)piperazine was prepared in 11 steps and 53% overall yield from *S*-phenylalanine. Key steps in the synthesis involved reductive amination to introduce an ethoxycarbonylmethyl group on to the secondary nitrogen of the product and selective alkylation to introduce a benzyl group with complete diastereoselectivity.

INTRODUCTION

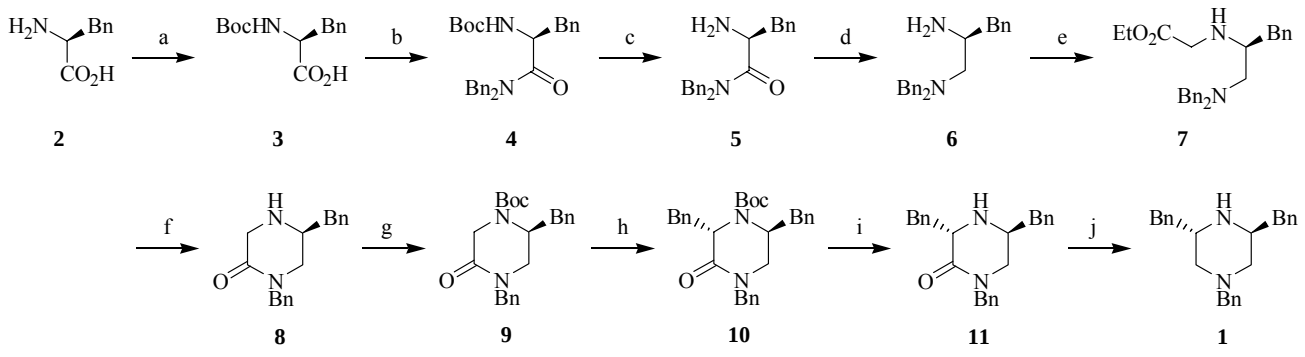
Chiral amines have enjoyed wide application as chiral auxiliaries and chiral ligands in organic synthesis.[1] While cinchona alkaloids have successfully been applied to certain asymmetric reactions as catalysts themselves since the early ’80s,[2] it was not until the seminal widespread application of proline to the aldol reaction[3] and phenylalanine derived chiral 4-imidazolidinone catalysts to the Diels-Alder reaction[4] in 2000, that chiral amines had come to be recognized as catalysts of general applicability. Since then, many novel chiral amines have been designed and prepared as catalysts, thus establishing organocatalysis as one of the mainstream fields in asymmetric synthesis.[5] In connection with projects on total synthesis of natural products, we also have been interested in organocatalysis.[6] In order to develop a group of catalysts of our own, we devised the synthesis of piperazines bearing benzyl groups in the 2 and 6 positions with *trans* relative stereochemistry. Such substitution should be favorable for reducing possible reaction pathways and the installation of the second nitrogen was to enable facile chemical modification at this sight for further functionalization. Not to mention that the compound also has the potential to function as a diamine, a bifunctional compound. The inclusion of benzyl groups was based upon the precedence

where aryl groups have been found to be effective for stereodetermination via cation-π and π-π interactions, such as in the success particularly enjoyed with the MacMillan catalysts. When we initiated our project, there were no reports to our knowledge on nitrogen containing 6-membered ring heterocycles having benzyl groups with *trans* substitution in regards with the nitrogen atom. A corresponding dibenzyl compound has been known in the pyrrolidine series, which was prepared in scalemic form by optical resolution of racemates.[7] Recently, the successful use of piperazines with C_2-symmetry, in regards with an axis positioned in the center of the 6-membered ring (2,5-disubstituted piperazines), has been reported in the Michael addition reaction.[8] As for the synthesis of *trans* substituted piperazines with 2,6-dimethyl groups, there have been two previous reports.[9,10] Incidentally, 2,6-dimethylpiperazines, though not necessarily trans, are also substructures of substances that have potential of clinical use.[11] Both of the reported syntheses involve the attachment of two chiral moieties of opposite stereochemistry. In contrast to these cases, we use diastereoselective alkylation to introduce the second stereocenter at a late stage of our synthesis, thus leaving the possibility for the stereoselective introduction of other groups at the second stereocenter. Herein, we describe the synthesis of (2*S*,6*S*)-2,4,6-tris(phenylmethyl)piperazine.

RESULTS AND DISCUSSION

The synthetic scheme for (2*S*,6*S*)-2,4,6-tris(phenylmethyl)piperazine is shown in Scheme 1. Using (*S*)-phenylalanine as the starting material, this was treated with $(Boc)_2O$ to give the known *N*-protected **3**. The crude product was treated with ethyl chloroformate in the presence of *N*-methylmorpholine, followed by dibenzylamine to furnish known amide **4**[12] in 89% yield over two steps. Removal of the protecting group with trifluoroacetic acid (TFA) yielded amide **5** also in practically quantitative yield.

The reduction of **5** with the use of a large excess of BH_3-SMe_2 proceeded quantitatively to give diamine **6**. Lowering the amount of reagent to 2.5 equivs still gave rise to the desired product in a yield of 90%. This reaction could also be performed with the less expensive $LiAlH_4$, with a comparable yield of 94%. For



Scheme 1. Reagents and conditions: (a) $(Boc)_2O$, Et_3N, MeOH, 50 °C, 40 min; (b) NMM, $ClCO_2Et$, EtOAc, -15 °C; Bn_2NH, rt, overnight, 89% (2 steps); (c) TFA, CH_2Cl_2, rt, 22 h, 99%; (d) BH_3-SMe_2, THF, rt, 2d, 99% or $LiAlH_4$, THF, reflux, overnight, 94%; (e) EtOCOCHO, $NaBH_4$, AcOH, CH_2Cl_2, rt, 3 h, 95%; (f) 5% Pd/C, H_2, HCl, EtOH, rt, 2.5 h; *p*-TsOH, EtOH, reflux, 10.5 h, 89% (2 steps); (g) $(Boc)_2O$, MeOH, 50 °C, 2 h, 85%; (h) BnBr, KHMDS, -78 °C, 3 h, 95%; (i) TFA, CH_2Cl_2, rt, 15.5 h, 99%; (j) BH_3-SMe_2, THF, rt, 3d, 99% or $LiAlH_4$, THF, reflux, 11.5 h, 87%.

$LiAlH_4$, the reaction had to be carried out under reflux conditions, otherwise (at rt) complex mixtures due to incomplete reaction resulted. Red-Al in THF also gave complex mixtures, whereas $NaBH(OAc)_3$[13] prepared in situ (CH_2ClCH_2Cl, reflux), and BH_3 economically prepared in situ from $NaBH_4$ and $BF_3{\cdot}Et_2O$ did not effect reaction at all. An alternative route involving benzylamine instead of dibenzylamine was also investigated, since the use of this amine would potentially reduce the step involving the removal of a benzyl group in the overall synthesis. However, reduction did not proceed cleanly, in contrast with the amide bearing the dibenzylamine moiety and purification of the product was quite tedious. Furthermore, the subsequent reductive amination of the product was rather messy.

The introduction of an ethoxycarbonylmethyl group to the primary nitrogen atom to give **7** could be carried out by reductive amination in the presence $NaBH(OAc)_3$ with ethyl glycoxylate, generated by periodate cleavage of ethyl tartrate.[14] Attempted alkylation with haloacetates resulted in mixtures and the isolated yield usually did not exceed 30%.

Conversion of **7** to heterocycle **8** could be realized by a two step procedure involving the monodebenzylation of the nitrogen atom by hydrogenolysis with Pd/C as catalyst in the presence of HCl followed by intramolecular amidation catalyzed by *p*-TsOH. Only one benzyl group was cleaved off under these hydrogenation conditions. The secondary nitrogen of piperazinone **8** was then protected with a BOC group to give **9**. Although the route is rather lengthy, it was possible to carry out the synthesis up to **9** without the use of chromatographic purification in the case of large scale synthesis.

The introduction of the second stereocenter was carried out using the Williams-Dellaria protocol with KHMDS followed by benzyl bromide to give the trans compound **10** as the exclusive stereoisomer.[15,16] As stated in the reports by these authors, the use of LDA was detrimental and did not give rise to the desired product. Removal of the BOC group with TFA furnished **11**. Reduction of the amide moiety to an amine moiety to give the desired end product **1** could be fulfilled by either BH_3-SMe_2 (87%) or $LiAlH_4$ (94%) in satisfactory yield. The *trans* substitution pattern of **1** was evident from its ^1H NMR, which showed sharp signals for the methylene protons of the benzyl group on 4-nitrogen, whereas the corresponding signals for the benzyl methylene groups attached to the stereogenic carbon centers showed broadened signals, implying interconversion between the the axial and the equatorial benzyl groups on the NMR timescale.

CONCLUSION

In conclusion we have prepared (2*S*,6*S*)-2,4,6-tris(phenylmethyl)piperazine, which has two benzyl groups in 11 steps and 53% overall yield. Although the route is rather lengthy, the first 8 steps could be carried out without chromatographic purification, using recrystallization where necessary or carrying the product to the next step without purification at all. The use of the compound and its derivatives in catalytic

asymmetric reactions is currently underway and the results will be reported in due course.

EXPERIMENTAL

General

Melting points were measured on a Yanaco micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a JEOL JNM–LA500 spectrometer with chemical shifts given from usual standards. High resolution mass spectra were measured on a JEOL JMS-SX102A spectrometer under electron ionization conditions (70 eV) or fast atom bombardment conditions (glycerol as matrix). Elemental analyses (CHN) were carried out on a Perkin–Elmer 2400CHN II elemental analyzer. IR spectra were measured on a HORIBA FT-720 infrared spectrometer. Optical rotations were recorded on a JASCO DIP-370.

THF and ether were freshly distilled from sodium-benzophenone prior to use. Silica gel column chromatography was carried out using Merck 7734 (63-200 mesh) or 9385 (230-400 mesh). Preparative thin layer chromatography was carried out with plates prepared with Merck 7730.

(*S*)-[2-[Bis(phenylmethyl)amino]-2-oxo-1-(phenylmethyl)ethyl]carbamic acid 1,1-dimethylethyl ester (4). To the solution of (*S*)-phenylalanine **2** (13.01 g, 78.78 mmol) in MeOH (100 mL) was added $(Boc)_2O$ (17.18 g, 78.77 mmol), Et_3N (12.1 mL, 85.8 mmol) at rt. After stirring at 50 °C for 40 min, the mixture was concentrated in vacuo. The residue was diluted with EtOAc and quenched with 1 M HCl at 0 °C, and extracted with EtOAc. The organic layer was dried over anhyd. Na_2SO_4 and concentrated in vacuo to give (2*S*)-2-[(1,1-Dimethylethoxy)carbonylamino]-3-phenylpropanoic acid **3** (20.71 g) as a colorless oil.[17] The crude product was used for the next reaction without further purification. R_f = 0.26 (CH_2Cl_2/MeOH = 15:1 v/v).

To the solution of **3** (20.71 g) in EtOAc (180 mL) was added *N*-methylmorpholine (10.8 mL, 98.2 mmol), ethyl chloroformate (9.4 mL, 98 mmol), and dibenzylamine (19.0 mL, 98.2 mmol) slowly at −15 °C. After stirring at 0 °C for 1 h, the solution was allowed to gradually warm up to rt and then it was stirred overnight. Water was added and then the mixture was extracted with EtOAc. The organic layer was washed with sat. aqueous $NaHCO_3$, brine, 1 M HCl, brine, successively. Then the organic layer was dried over anhyd. Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by recrystallization (CH_2Cl_2/toluene) to give **4** (31.23 g, 70.24 mmol, 89%) as a white solid. R_f = 0.83 (SiO_2, CH_2Cl_2/MeOH = 15:1 v/v); mp 108-110 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) 7.36-6.96 (m, 15H), 5.32 (d, *J* = 8.8 Hz), 4.95-4.86 (m, 2H), 4.69 (d, *J* = 14.9 Hz, 1H), 4.36-4.20 (m, 1H), 3.03 (dd, *J* = 7.9, 13.4 Hz, 1H), 2.95 (dd, *J* = 6.1, 13.4 Hz, 1H), 1.40 (s, 9H), 1.18 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 172.6, 155.0, 136.6, 136.5, 136.0, 129.5, 128.8, 128.5, 128.4, 128.3, 127.6, 127.4, 126.9, 126.7, 79.7, 51.6, 49.8, 48.2, 40.0,

28.3; ν_{max}(neat)/cm^{-1} 1704, 1639; [α]$_D^{22}$ -10.3 (*c* 1.06, $CHCl_3$); HRMS (EI$^+$) *m/z* calcd for $C_{28}H_{32}N_2O_3$ 444.2413, found: 444.2433.

(2*S*)- 2-Amino-*N*,*N*-bis(phenylmethyl)benzenepropanamide (5). To a solution of **4** (2.50 g, 5.6 mmol) in CH_2Cl_2 (8.0 mL) was added TFA (8.0 mL) at 0 ºC. The mixture was stirred for 1 h at 0 ºC and 20 h at rt. The mixture was concentrated. 1 M $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The organic phase was washed with water and brine, dried over anhyd. Na_2SO_4, filtered and concentrated. Recrystallization from CH_2Cl_2-hexane gave **5** (1.90 g, 99 %) as white crystals. R_f = 0.37 (SiO_2, CH_2Cl_2/MeOH = 15:1 v/v); mp 99-101 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.03 (m, 15H), 4.93 (d, *J* = 14.6 Hz, 1H), 4.31 (d, *J* = 17.4 Hz, 1H), 4.23 (d, *J* = 14.6 Hz, 1H), 4.17 (d, *J* = 17.4 Hz, 1H), 3.92 (t, *J* = 7.0 Hz, 1H), 3.05 (dd, *J* = 7.0, 13.4 Hz, 1H), 2.84 (dd, *J* = 7.0, 13.4 Hz, 1H), 1.80 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 137.7, 136.9, 136.4, 129.4, 129.4, 129.0, 128.5, 128.3, 127.7, 127.4, 126.6, 126.3, 53.4, 49.4, 48.7, 42.9; ν_{max}(neat)/cm^{-1} 3363, 3293, 1619; [α]$_D^{22}$ 32.7 (*c* 1.14, $CHCl_3$); HRMS (EI$^+$) *m/z* calcd for $C_{23}H_{24}N_2O$ 344.1889, found 344.1891; Anal. Calcd for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.22; H, 7.16; N, 8.07.

(2*S*)-2-Amino-3-phenylmethyl-1-[bis(phenylmethyl)amino]propane (6). (Reduction with BH_3-SMe_2) To a solution of **5** (2.50 g, 7.34 mmol) in THF (50 mL) was added dropwise BH_3-SMe_2 (2.0 M in toluene, 39 mL, 78 mmol) at 0 ºC. The mixture was stirred at rt for 2 d. After cooling to 0 ºC the reaction mixture was quenched by the slow addition of 10% HCl (8.0 mL). The mixture was turned basic with 50% NaOH. KOH (15 g) was then added, and the mixture was heated at reflux for 24 h. After cooling to rt, the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over anhyd. Na_2SO_4, filtered and concentrated. Purification by chromatography (SiO_2, CH_2Cl_2/MeOH = 30:1 v/v) gave **6** (2.40 g, 100%) as a yellow oil. R_f = 0.31 (SiO_2, CH_2Cl_2/MeOH = 15:1 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.10 (m, 15H), 3.68 (d, *J* = 14.6 Hz, 2H), 3.49 (d, *J* = 14.6 Hz, 2H), 3.20-3.09 (m, 1H), 2.73 (dd, *J* = 4.9 Hz, 13.4 Hz, 1H), 2.47-2.37 (m, 3H), 1.71 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 139.1, 129.1, 128.9, 128.3, 128.2, 126.9, 126.1, 60.7, 59.0, 50.5, 42.0; ν_{max}(neat)/cm^{-1} 3637, 3374; [α]$_D^{22}$ 54.3 (*c* 1.17, $CHCl_3$); HRMS (EI$^+$) *m/z* calcd $C_{25}H_{28}N_2$ 356.2252, found 356.2245; Anal. Calcd for $C_{25}H_{28}N_2$: C, 83.59; H, 7.93; N, 8.48. Found: C, 83.35; H, 8.07; N, 8.37.

(2*S*)-2-Amino-3-phenyl-1-[bis(phenylmethyl)amino]propane (6). (Reduction with $LiAlH_4$) To a solution of $LiAlH_4$ (20.6 mg, 0.54 mmol) in THF (2.0 mL) was added **5** (59.9 mg, 0.17 mmol) at 0 °C. After refluxing overnight, the mixture was quenched with H_2O slowly at 0 °C. The precipitate was filtered off and washed with Et_2O. The combined filtrate was washed with brine and dried over anhyd.

Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by preparative TLC (SiO_2, CH_2Cl_2/MeOH, 30:1 v/v) to give **6** (51.4 mg, 94%) as a yellow oil.

(2*S*)-2-(Ethoxycarbonylmethylamino)-3-phenyl-1-[bis(phenylmethyl)amino]propane (7). To a solution of $NaBH_4$ (20.1 mg, 0.38 mmol) in 1,2-dichloroethane (3.0 mL) was added AcOH (0.070 mL, 1.2 mmol) at 0 ºC. The mixture was stirred at rt for 30 min. Then **6** (63 mg, 0.19 mmol) in 1,2-dichloroethane (1.0 mL) was added to the mixture at rt and the mixture was stirred for 3 h. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc. The organic phase was dried over anhyd. Na_2SO_4, filtered, and concentrated. Purification with preparative TLC (SiO_2, CH_2Cl_2/MeOH = 40:1 v/v) gave **7** (75 mg, 95%) as a white solid. R_f = 0.80 (SiO_2, CH_2Cl_2/MeOH = 20:1 v/v), ^{1}H NMR (500 MHz, $CDCl_3$) 7.39-7.19 (m, 13H), 7.16-7.10 (m, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.68 (d, *J* = 13.5 Hz, 2H), 3.45 (d, *J* = 13.5 Hz, 2H), 3.39 (d, *J* = 17.0 Hz, 1H), 3.17 (d, *J* = 17.0 Hz, 1H), 3.05 (br s, 1H), 2.95-2.86 (m, 1H), 2.72 (dd, *J* = 5.7, 13.5 Hz, 1H), 2.61-2.50 (m, 2H), 2.42 (dd, *J* = 4.1, 12.9 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 139.0, 138.9, 129.1, 129.0, 128.3, 128.2, 127.0, 126.1, 60.6, 59.0, 58.0, 56.8, 48.8, 39.5, 14.2; ν_{max}(neat)/cm^{-1} 3054, 1651;HRMS (EI$^+$) *m/z* calcd for $C_{18}H_{20}N_2O$ 416.2464, found 416.2464.

(5*S*)-1,5-Bis(phenylmethyl)-2-piperazinone (8). To a solution of **7** (1.00 g, 2.40 mmol) in 99% EtOH (12 mL) was added conc. HCl (2.3 mL) and 5% Pd/C (330 mg) at rt. After stirring at this temperature for 2.5 h under an atmosphere of hydrogen, excess H_2 was removed. The reaction mixture was filtered through Celite and concentrated *in vacuo*. To the residue was added 99% EtOH (25 mL) and *p*-TsOH (162.4 mg, 0.94 mmol) at rt. After refluxing for 10 h, the mixture was concentrated in vacuo and quenched with sat. aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried over anhyd. Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography (SiO_2, CH_2Cl_2/MeOH = 15:1 v/v) to give **8** (600.8 mg, 89%) as a yellow oil. R_f = 0.26 (SiO_2, CH_2Cl_2/MeOH = 15:1 v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.12 (m, 10H), 4.62 (d, *J* = 14.6 Hz, 1H), 4.56 (d, *J* = 14.6 Hz, 1H), 3.67 (d, *J* = 17.1 Hz, 1H), 3.51 (d, *J* = 17.1 Hz, 1H), 3.21-3.06 (m, 3H), 2.77 (dd, *J* = 5.2, 13.7 Hz, 1H), 2.61 (dd, *J* = 8.5, 13.7 Hz, 1H), 1.90 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 137.0, 136.4, 128.8, 128.6, 128.5, 128.0, 127.3, 126.7, 53.9, 51.9, 49.8, 49.7, 39.4; ν_{max}(neat)/cm^{-1} 3300, 1643; $[\alpha]_D^{22}$ 70.4 (*c* 0.561, $CHCl_3$); HRMS (EI$^+$) *m/z* calcd for $C_{18}H_{20}N_2O$ 280.1576, found 280.1573.

(2*S*)-5-Oxo-2,4-bis(phenylmethyl)-1-piperazinecarboxylic acid 1,1-dimethylethyl ester (9). To a solution of **8** (510.9 mg, 1.82 mmol) in MeOH (6.0 mL) was added $(Boc)_2O$ (0.47 mL, 2.2 mmol) and Et_3N (0.41 mL, 2.9 mmol) at rt. After stirring at 50 °C for 2 h, the mixture was quenched with sat.

aqueous NH_4Cl and concentrated in vacuo, and extracted with EtOAc. The organic layer was dried over anhyd. $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by recrystallization (EtOH/H_2O) to give **9** (588.3 mg, 85%) as a white solid. R_f = 0.16 (SiO_2, hexane/EtOAc = 4:1 v/v); mp 112-113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 7.19-7.14 (m, 3H), 6.82-6.77 (m, 2H), 4.92 (d, *J* = 14.3 Hz, 1H), 4.53-4.22 (m, 3H), 3.94 (d, *J* = 18.9 Hz, 1H), 3.46-3.34 (m, 1H), 2.99 (dd, *J* = 1.5, 12.5 Hz, 1H), 2.77 (dd, *J* = 6.1, 13.4 Hz, 1H), 2.64-2.55 (m, 1H), 1.41 (br s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 153.4, 137.2, 136.3, 129.0, 128.8, 128.8, 128.5, 127.9, 126.5, 49.9, 28.2 (5 signals lack due to peak broadening); ν_{max}(neat)/cm^{-1} 1697, 1654; $[\alpha]_D^{22}$ –94.0 (*c* 0.413, $CHCl_3$); HRMS (EI$^+$) *m/z* calcd for $C_{23}H_{28}N_2O_3$ 380.2100, found: 380.2084.

(2*S*,6*S*)-5-Oxo-2,4,6-Tris(phenylmethyl)-1-piperazinecarboxylic acid 1,1-dimethylethyl ester (10). To a solution of **9** (101 mg, 0.26 mmol) in THF (1.0 mL) was added KHMDS (0.5 M in toluene, 0.60 mL, 0.30 mmol) at –78 ºC. The reaction mixture was allowed to warm to 0 ºC. After 30 min the reaction mixture was recooled to –78 ºC and BnBr (0.04 mL, 0.29 mmol) was added. The mixture was stirred at –78 ºC for 3 h. Then brine was added and the mixture was extracted with Et_2O. The organic phase was dried over anhyd. Na_2SO_4, filtrated, and concentrated. Purification by chromatography (SiO_2, hexane/EtOAc = 6:1 v/v) gave **10** (118 mg, 95%) as a white solid. R_f = 0.45 (SiO_2, hexane/EtOAc = 4:1 v/v); mp 138-139 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-6.96 (m, 15H), 6.63-6.55 (m, 1.2H), 6.55-47 (m, 0.8H), 4.78-65 (m, 2H), 4.05-3.95 (m, 1H), 3.86-3.80 (m, 0.6H), 3.80-3.74 (m, 0.4), 3.68-3.64 (m, 0.4H), 3.45-3.40 (m, 0.6H), 3.16 (dd, *J* = 3.1, 13.4 Hz, 1H), 2.88-2.82 (m, 0.6H), 2.82-2.76 (m, 0.4H), 2.47-2.20 (m, 2H), 1.58 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): broadening too extensive for assignment; ν_{max}(neat)/cm^{-1} 1689, 1654; $[\alpha]_D^{22}$ –5.20 (*c* 0.439, $CHCl_3$); HRMS (EI$^+$) *m/z* calcd for $C_{23}H_{28}N_2O_3$ 470.2569, found 470.2578.

(3*S*,5*S*)- 1,3,5-Tris(phenylmethyl)-2-piperazinone (11). To a solution of **10** (112 mg, 0.24 mmol) in CH_2Cl_2 (1.0 mL) was added TFA (1.0 mL) at rt. The mixture was stirred for 1.5 h at rt and then concentrated. 1 M $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The organic phase was dried over anhyd. Na_2SO_4, filtered, and concentrated. Purification by chromatography (SiO_2, CH_2Cl_2/MeOH = 80:1 v/v) gave **11** (88 mg, 99%) as a white solid. R_f = 0.57 (SiO_2, CH_2Cl_2/MeOH = 30:1 v/v); mp = 113-115 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.26 (m, 8H), 7.15-7.02 (m, 5H), 6.73-6.72 (m, 2H) 4.71 (d, *J* = 14.6 Hz, 1H), 4.58 (d, *J* = 14.6 Hz, 1H), 3.76 (dd, *J* = 3.1, 11.0 Hz, 1H), 3.35-3.28 (m, 1H), 3.22 (dd, *J* = 3.1, 13.4 Hz, 1H), 3.18 (dd, *J* = 4.3, 11.6 Hz, 1H), 3.11 (dd, *J* = 9.1, 11.6 Hz, 1H), 2.83 (dd, *J* = 11.0, 13.4 Hz, 1H), 2.74 (dd, *J* = 4.3, 13.4 Hz, 1H), 2.46 (dd, *J* = 9.1, 13.4 Hz, 1H), 1.75 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 137.9, 137.4, 136.7, 129.0, 129.0, 128.8, 128.6, 128.5,

128.1, 127.5, 126.8, 126.2, 59.3, 52.2, 50.0, 49.2, 39.3, 37.6; ν_{max}(neat)/cm^{-1} 3324, 1643; [α]$_D^{22}$ –58.6 (*c* 0.427, $CHCl_3$); HRMS (EI$^+$) *m/z* calcd for $C_{25}H_{26}N_2O$ 370.2045, found 370.2040.

(2*S*,6*S*)-2,4,6-Tris(phenylmethyl)piperazine (1). (Reduction with BH_3-SMe_2) To a solution of **11** (449 mg, 1.2 mmol) in THF (8.0 mL) was added BH_3-SMe_2 (2.0 M in toluene, 6.8 mL, 14 mmol) at rt. The mixture was stirred for 3 d at rt. To the mixture was added 10% HCl (2.0 mL) and a mixture of NaOH and KOH (3.1 g). The mixture was refluxed for 23 h and extracted with EtOAc. The organic phase was dried over anhyd. Na_2SO_4, filtered, and concentrated. Purification with chromatography (SiO_2, CH_2Cl_2/MeOH = 50:1 v/v) gave **1** (374 mg, 87%) as a yellowish solid. R_f = 0.27 (SiO_2, CH_2Cl_2/MeOH, 30:1 v/v); mp 61-62 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-6.95 (m, 15H), 3.58 (d, *J* = 12.8 Hz, 1H), 3.39 (d, *J* = 12.8 Hz, 1H), 3.21-3.19 (m, 2H), 2.80-2.69 (m, 4H), 2.65-2.55 (m, 2H), 2.39-2.27 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 138.6, 129.0, 128.9, 128.3, 128.1, 126.9, 126.0, 63.1, 58.0 (br), 52.6 (br), 39.9 (br); ν_{max}(neat)/cm^{-1} 3320; [α]$_D^{22}$ -37.2 (*c* 0.690, $CHCl_3$); HRMS (EI$^+$) *m/z* calcd for $C_{25}H_{28}N_2$ 365.2252, found 356.2450.

(2*S*,6*S*)-2,4,6-Tris(phenylmethyl)piperazine (1). (Reduction with $LiAlH_4$) To a solution of $LiAlH_4$ (143.0 mg, 3.77 mmol) in THF (3.0 mL) was added **11** (278.1 mg, 0.75 mmol) in THF (5.0 mL) at 0 °C. After refluxing for 11.5 h, the mixture was slowly quenched with a small amount of H_2O at 0 °C. The precipitate was filtered off and washed with Et_2O. The combined filtrate was washed with brine and dried over anhyd. Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by preparative TLC (SiO_2, hexane/EtOAc = 2:1 v/v) to give **1** (252.3 mg, 94%).

ACKNOWLEDGEMENTS

This work was supported in part by Grants-in-Aid for Scientific Research (No. 14540497, 16550098, and 19550042) from the Japan Society for the Promotion of Science. We also acknowledge the Natural Science Center for Basic Research and Development of Hiroshima University for machine time on analytical instruments.

REFERENCES

1. For example see: (a) J. Seyden-Penne, 'Chiral Auxiliaries and Ligands in Asymmetric Synthesis' Wiley, New York, 1995. (b) H. Waldmann, 'Organic Synthesis Highlights II,' ed. by H. Waldmann, VCH, Weinheim, 1995, pp. 49-58. (c) D. Ager, I. Prakash, and D. R. Schaad, *Chem. Rev.*, 1996, **96**, 835. (d) M. D. Groaning and A. I. Meyers, *Tetrahedron*, 2000, **56**, 9843. (e) C. W. Y. Chung and P. H. Toy, *Tetrahedron:Asymmetry*, 2004, **15**, 387. (f) C. Anaya de Parrodi and E. Juaristi, *Synlett*,

2006, 2699.

2. (a) H. Wynberg and E. G. J. Staring, *J. Am. Chem. Soc.*, 1982, **104**, 166. (b) S. France, D. J. Guerin, S. J. Miller, and T. Lectka, *Chem. Rev.*, 2003, **103**, 2985 and references therein.
3. B. List, R. A. Lerner, and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2000, **122**, 2395.
4. K. A. Ahrendt, C. J. Borths, and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2000**, 122**, 4243.
5. For example see: (a) A. Berkessel and H. Gröger, 'Asymmetric Organocatalysis' Wiley-VCH, Weinheim, 2005. (b) H. Pellissier, *Tetrahedron*, 2007, **63**, 9267.
6. S. Kojima, M. Suzuki, A. Watanabe, and K. Ohkata, *Tetrahedron Lett.*, 2006, **47**, 9061.
7. (a) Y. Kawanami,Y. Ito, T. Kitagama,Y. Taniguchi, T. Katsuki, and M. Yamaguchi, *Tetrahedron Lett.*, 1984, **25**, 857. (b) M. Nakajima, K. Tomioka, and K. Koga, *Tetrahedron*, 1993, **49**, 9735.
8. M. T. Barros and A. M. F. Phillips, *Eur. J. Org. Chem.*, 2007, 178.
9. M. Harfenist, D. C. Hoerr, and R. Crouch, *J. Org. Chem.*, 1985, **50**, 1356.
10. J. W. Mickelson, K. L. Belonga, and E. J. Jacobsen, *J. Org. Chem.*, 1995, **60**, 4177.
11. For some recent examples: (a) Y.-L. Zhao, Y.-L. Chen, J.-Y. Sheu, I.-L. Chen, T.-C. Wang, and C.-C. Tzeng. *Bioorg. Med. Chem.*, 2005, **13**, 3921. (b) P. A. Wyman, H. R. Marshall, S. T. Flynn, R. J. King, M. Thompson, P. W. Smith, M. S. Hadley, G. W. Price, C. M. Scott, and L. A. Dawson, *Bioorg. Med. Chem. Lett*,. 2005, **15**, 4708. (c) L. Xu, S. Tao, X. Wang, Z. Yu, M. Wang, D. Chen, Y. Jing, and J. Dong, *Bioorg. Med. Chem.*, 2006, **14**, 5351. (d) E. L. laney, N. P. King, and J. Witherington, *PCT Int. Appl.*, 2007, Patent No. WO 2007113202. (e) M. Guha and A. Kabakibi *U.S. Pat. Appl. Publ.*, 2007, Patent No. US 2007249519.
12. T. Mase, K. Kubota, N. Imanishi, and K. Tomioka, *Jpn. Kokai Tokkyo Koho*, 1993, Patent No. JP 05294915.
13. A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, and R. D. Shah, *J. Org. Chem.*, 1996, **61**, 3849.
14. P. F. Schuda, C. B. Ebner, and S. J. Potlock, *Synthesis*, 1987, 1055.
15. R. M. Williams and M. N. Im, *Tetrahedron Lett.*, 1988, **29**, 6075.
16. J. F. Dellaria Jr. and B. D. Santarsiero, *Tetrahedron Lett.*, 1988, **29**, 6079.
17. E. Ponnusamy, U. Fotadar, A. Spisni, and D. Fiat, *Synthesis*, 1986, 48.