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Design and Synthesis of Novel Chiral Pyrrolidine-based Diamines with C_2-Symmetry

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Abstract Novel chiral pyrrolidine-based diamines with C_2-symmetry **2, 3** and their related compounds **4 - 8** were designed and synthesized in optically pure forms Both (+)- and (-)-**2** were prepared from optical active ditosylate **9** **3** was prepared from 3,5-dimethylbenzaldehyde through optical resolution and its absolute stereochemistry was correlated with 2,3-dimethylsuccinate **27** **4** was prepared from (-)-diol **28** **5 - 8** were prepared from **9** and **11**

Design of the chiral ligand for the enantioselective reaction is an important goal in chemical synthesis [1,2] In preliminary communications, we have reported the synthesis of novel C_2-symmetric chiral diamines **2, 3** and their application to the highly enantioselective 1, 2-addition of Grignard reagents to aldehydes[3] and dihydroxylation of olefins by osmium tetroxide [4] Our success is attributable to the formation of sterically confined complexes of metal with chiral ligands In this full account we describe the details of the synthesis of the novel chiral pyrrolidine-based chiral diamines **2, 3** and their related compounds **4 - 8**

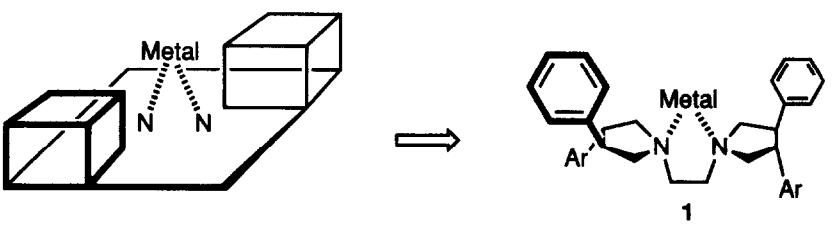

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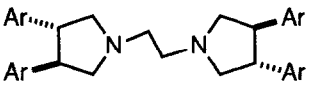
Fig 1 Design of Chiral Diamine

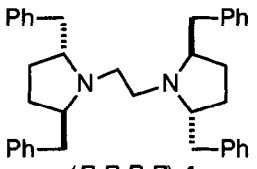
Design of Novel Chiral Diamines

Most successful results in enantioselective asymmetric synthesis are ascribable to the well-defined asymmetric environment constructed with chiral auxiliaries Metal-coordinatable chiral diamines are widely utilized in the stereocontrol of metal-induced reactions [2,5] Our original design of asymmetric environment around a metal chelated with diamine is shown in Fig 1 Two bulky groups are located in symmetry to the metal center to create a chiral environment with C_2-symmetry, which reduce a number of possible conformations in stereodetermining step [6] In order to realize this chiral environment, we employed an optically active *trans*-3,4-diarylpyrrolidine as a chiral component and linked two of them with carbon chain (Fig 2) *trans*-2,5-Disubstituted pyrrolidines are widely used as chiral auxiliaries in diastereoselective asymmetric reactions [7-11] On

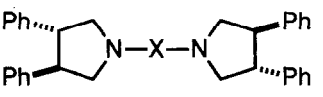
the other hand, *trans*-3,4-disubstituted pyrrolidines has been scarcely utilized in asymmetric synthesis. This type of chiral diamine has the following characters: 1) diamine is expected to work as a bidentated ligand toward a metal reagent; 2) the complex **1** of diamine and metal has an unique structure because of its high symmetry; 3) conformationally rigid aryl groups provide the well-defined chiral environment around metal center, which provide us an expectation of realizing high enantiodifferentiation. We also synthesized analogs of **2**, which have substituents on 2,2',5,5'-position **4**, a trimethylene linker **5**, a 1,2-phenylene linker **6**, a 2,2'-biphenylene linker **7**, and a monodentated amine **8**.



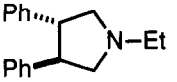
(*R,R,R,R*)-**2**: Ar = Ph
(*R,R,R,R*)-**3**: Ar = 3,5-Xylyl



(*R,R,R,R*)-**4**



(*R,R,R,R*)-**2**: X = CH_2CH_2
(*R,R,R,R*)-**5**: X = $CH_2CH_2CH_2$
(*R,R,R,R*)-**6**: X = 1,2-phenylene
(*R,R,R,R*)-**7**: X = 2,2'-biphenylene



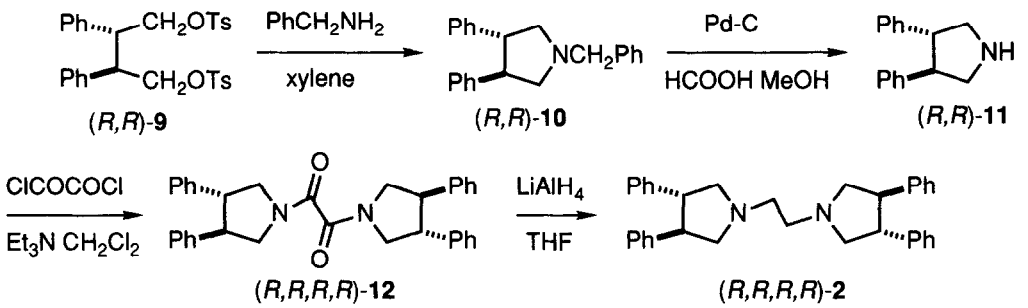
(*R,R,R,R*)-**8**

Fig. 2. Novel Chiral Amines

Synthesis of Chiral Amines

Synthesis of Chiral Diamine 2

Synthetic route of **2** is shown in Fig. 3. (3*R*,4*R*)-Ditosylate **9**[12] was successfully cyclized with benzylamine and the obtained pyrrolidine was hydrogenated with palladium carbon and formic acid to afford (3*R*,4*R*)-diphenylpyrrolidine **11** in 80 % yield. Ethylene linker was introduced by amidation with oxalyl chloride followed by reduction with lithium aluminum hydride to obtain diamine **2** in 85 % yield. As both enantiomers of **9** are available, (*R,R,R,R*)- and (*S,S,S,S*)-**2** were synthesized in the same manner.



(*R,R*)-**9** (*R,R*)-**10** (*R,R*)-**11**

(*R,R,R,R*)-**12** (*R,R,R,R*)-**2**

Fig. 3. Synthesis of **2**

Synthesis of Chiral Diamine 3

Synthetic route of **3** is shown in Fig. 4. 3,5-Dimethylbenzaldehyde **13**[13] and 3,5-dimethylbenzyl cyanide[14] were coupled by potassium cyanide[15] to obtain succinonitrile **14** in 50 % yield. After hydrolysis of the nitrile with sulfuric acid, the desired *dl*-acid **15** was separated from *meso*-diacid through their barium salts and then converted into anhydride **16**. Optical resolution was accomplished in high yield by the separation of diastereomeric amides with (+)-(*R*)-benzylmethylamine. The crude amides mixture was recrystallized from ethanol to give (3*S*,4*S*,α*R*)-amide **17b**, which has higher R_f value on SiO_2 TLC (benzene-acetone, 2/1) and the residue was purified with SiO_2 column chromatography to give (3*R*,4*R*,α*R*)-amide **17a**, which has lower R_f value.

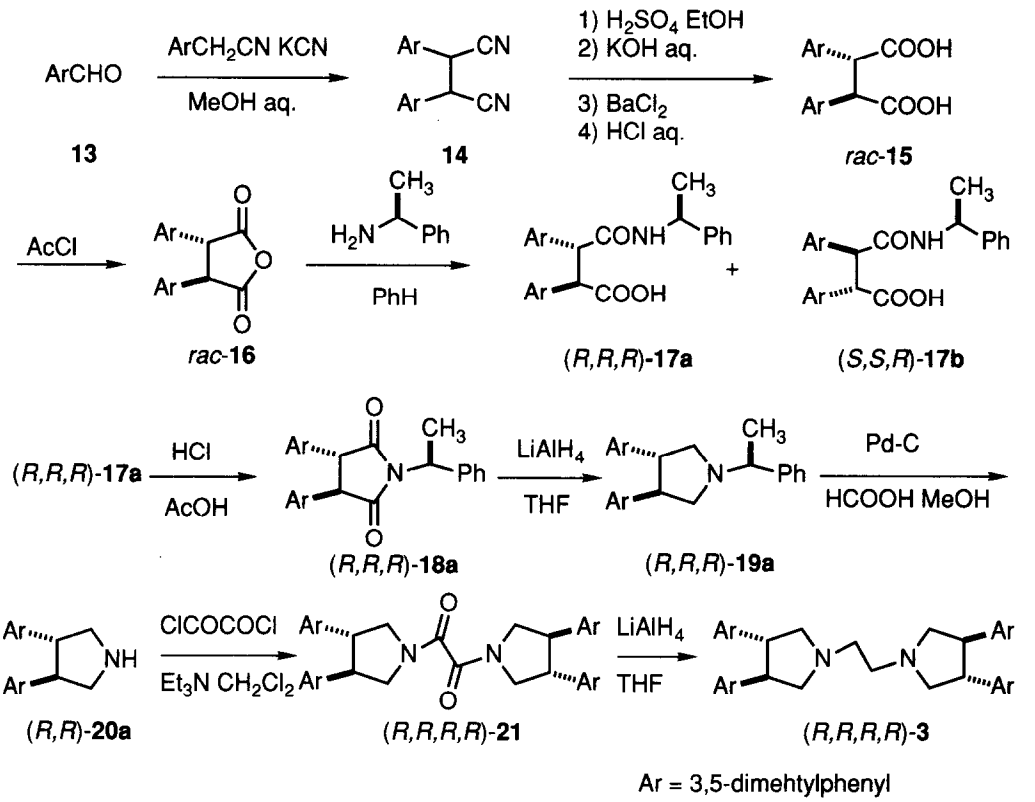


Fig. 4. Synthesis of **3**

The absolute stereochemistry of **17a** was established by chemical method shown in Fig. 5. **17a** was reduced to alcohol **22** through mixed anhydride with sodium borohydride. Lactonization with hydrochloric acid followed by reduction with lithium aluminum hydride gave diol **24**. The hydroxyl group was removed by tosylation followed by hydride reduction. The aryl groups were oxidized with ozone and the resulting dicarboxylic acid was transformed into p-bromophenacyl ester **27** ($[\alpha]_D$ -35°($CHCl_3$)) of known stereochemistry[16] to establish that **17a** has (3*R*,4*R*,α*R*)-configuration.

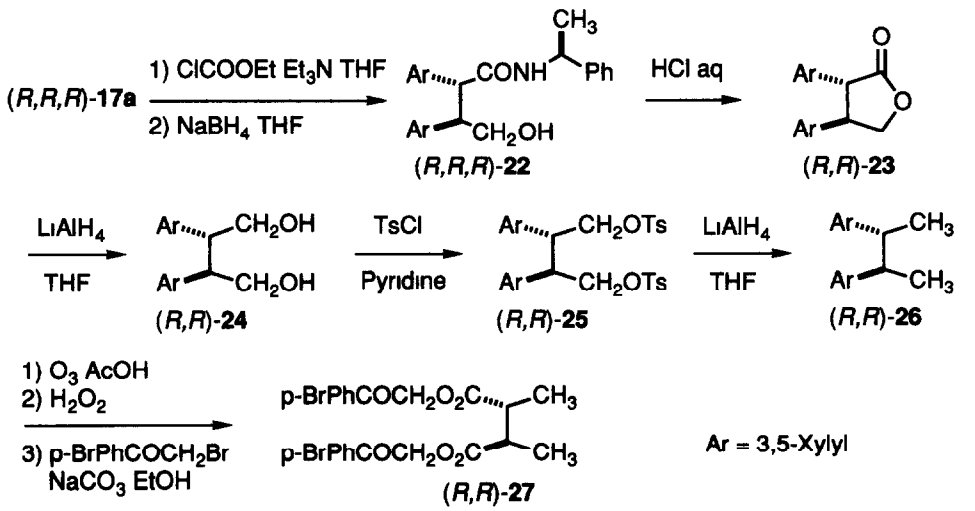


Fig 5 Correlation of the absolute configuration of diamine **3**

Both amide **17a, b** were transformed into 3,4-diarylpyrrolidine **20a,b** by successive imidation, hydride reduction, then catalytic hydrogenation **20b** gives the same physical data as **20a** except the signs of their optical rotation **3** was synthesized from **20a** by amidation with oxalyl chloride followed by hydride reduction

Synthesis of Chiral Diamine 4

(+)-(2*R*,5*R*)-1-Benzylpyrrolidine-2,5-dimethanol **28**[8] was chlorinated with thionyl chloride in dioxane and the crude product was treated with phenylmagnesium bromide to obtain 1,2,5-tribenzylpyrrolidine **29** in 60 % yield Catalytic hydrogenation of **29** with palladium on carbon and formic acid in methanol gave 2,5-dibenzylpyrrolidine **30** in 82 % yield Ethylene linker was introduced by amidation with oxalyl chloride followed by reduction with lithium aluminum hydride to obtain diamine **4** in 85 % yield

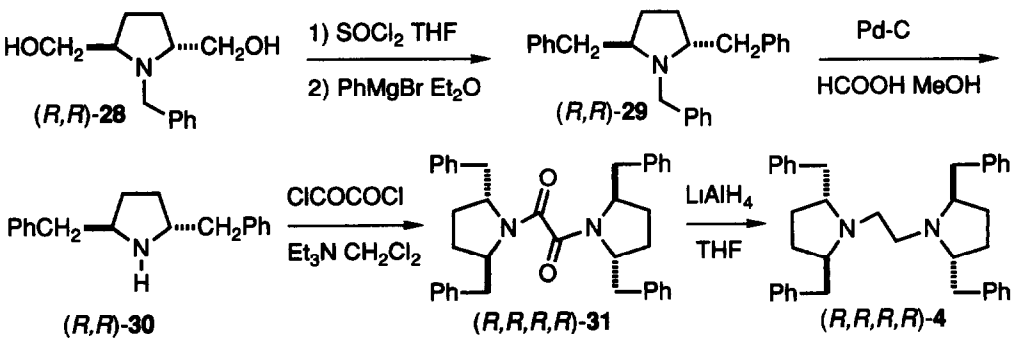


Fig 6 Synthesis of **4**

Synthesis of Amines 5, 6, 7, 8

Diamine **5** having trimethylene linker was synthesized from 3,4-diphenylpyrrolidine **11** by alkylation with dibromopropane in 73 % yield Diamine **6** having 1,2-phenylene linker was synthesized from 1,2-phenylenediamine by alkylation with ditosylate **9** Diamine **7** was synthesized in the same manner as **6** Monoamine **8** was synthesized from 3,4-diphenylpyrrolidine **11** by acetylation followed by hydride reduction

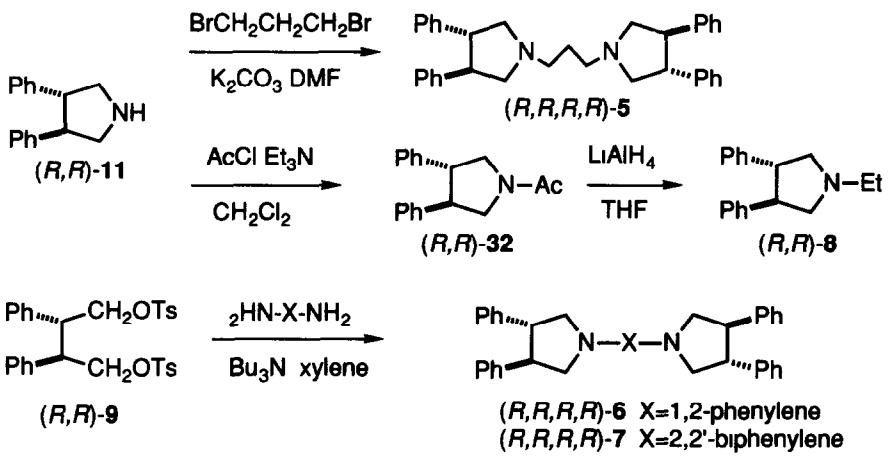


Fig 7 Synthesis of **5, 6, 7, 8**

In summary, novel chiral pyrrolidine-based diamines **2, 3** with C_2-symmetry and their related compounds were synthesized in optically pure forms Diamine **2, 3** were successfully employed in enantioselective 1,2-addition of Grignard reagents to give optically active products in high e e 's, which will be discussed in the following paper

Experimental Section

Melting points were measured using a Buchi 510 melting point apparatus and were not corrected Optical rotations were taken with a JASCO DIP-181 digital polarimeter IR spectra were taken with a JASCO DS-402G infrared spectrometer and expressed in cm^{-1} NMR spectra were taken with a JEOL GSX-400 spectrometer at 400 MHz, or a JEOL FX-100 spectrometer at 100MHz Chemical shift values are expressed in ppm relative to internal tetramethylsilane Abbreviations are as follows s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet, br, broad MS were taken with a JEOL DX-300 mass spectrometer

(3*R*,4*R*)-1-Phenylmethyl-3,4-diphenylpyrrolidine Hydrochloride ((*R*,*R*)-10 HCl) A solution of benzylamine (45 g, 0 42 mol) in xylene (100 ml) was added dropwise to a solution of ditosylate (*R*,*R*)-9[12] (66 g, 0 12 mol) in xylene (400 ml) at 120°C and the whole was stirred under reflux for 10 h After cooling down to room temperature, the resulting precipitate was filtered off and the filtrate was evaporated in vacuo The residue was dissolved in dichloromethane (500 ml) and washed successively with 5 % HCl (200 ml,

100 ml, 100 ml), satd $NaHCO_3$ (200 ml, 100 ml, 100 ml), and brine (100 ml) After drying over Na_2SO_4, the solvent was evaporated in vacuo A solution of the crude product in ether-methanol (1/1, 400 ml) was saturated with HCl gas in ice bath and evaporated in vacuo The residue was recrystallized from ethanol (120 ml) - ether (50 ml) to obtain **(*R*,*R*)-10** HCl (36 g, 86 %) as colorless needles of mp 256-257°C $[\alpha]_D^{20}$ -114° (c=1 04, $CHCl_3$) IR (KBr) 2400, 800, 700 ^{1}H-NMR (100M, $CDCl_3$) δ 3 6-4 0 (6H, m, $CHCH_2$), 4 52 (2H, s, NCH_2Ph), 6 9-7 9 (15H, m, Ph), 13 2 (1H, brs, NH^+) MS m/z 314 (MH^+), 313 (M^+), 236 (M^+-C_6H_6), 222 (M^+-$CH_2C_6H_6$) *Anal* Calcd for $C_{23}H_{23}N$ HCl C, 78 95, H, 6 91, N, 4 00 Found C, 79 16, H, 7 00, N, 3 85

(3*R*,4*R*)-3,4-Diphenylpyrrolidine ((*R*,*R*)-11) A mixture of **(*R*,*R*)-10** (32 g, 0 10 mmol) and Pd-C (10 %, 20 g) in formic acid-methanol (1/1, 200 ml) was stirred for 2 d After the catalyst was removed by filtration, the filtrate was evaporated in vacuo After addition of 15 % NaOH (50 ml), the mixture was extracted with ether (200 ml, 100 ml, 100 ml) The organic layer was washed with brine (50 ml) and dried over Na_2SO_4 Concentration followed by recrystallization from hexane gave **(*R*,*R*)-11** (21 g, 94 %) as colorless prisms of mp 58-59°C $[\alpha]_D^{20}$ -226° (c=1 50, $CHCl_3$) IR (KBr) 3400, 1600, 1490, 1410 ^{1}H-NMR (100M, $CDCl_3$) δ 2 30 (1H, s, NH), 2 9-3 8 (6H, m, $CHCH_2$), 7 13 (10H, s, Ph) MS m/z 223 (M^+) Treating with MeOH-HCl gave **(*R*,*R*)-11** HCl as colorless needles of mp 250°C (dec) $[\alpha]_D^{20}$ -178° (c=0 991, MeOH), *Anal* Calcd for $C_{16}H_{17}N$ HCl C, 73 98, H, 6 98, N, 5 39 Found C, 73 76, H, 7 08, N, 5 39

(3*R*,3'*R*,4*R*,4'*R*)-3,3',4,4'-Tetraphenyl-1,1'-oxalyldipyrrolidine ((*R*,*R*,*R*,*R*)-(12)): Triethylamine (12 ml, 82 mmol) and oxalyl chloride (0 35 ml, 4 1 mmol) were added to a solution of amine **(*R*,*R*)-11** (1 8 g, 8 2 mmol) in dichloromethane (40 ml) at -78°C under Ar atmosphere and the whole was stirred for 10 min at room temperature The reaction mixture was quenched with water (50 ml) and diluted with dichloromethane (100 ml) The organic layer was washed successively with 10 % HCl (20 ml x2), satd $NaHCO_3$ (20 ml), and brine (20 ml), and dried over Na_2SO_4 Concentration followed by recrystallization from chloroform-hexane gave **(*R*,*R*,*R*,*R*)-12** (1 7 g, 86%) as colorless needles of mp 223 5-225 5°C $[\alpha]_D^{20}$ -115°(c=1 60, $CHCl_3$) IR (KBr) 1630, 1600, 1490, 1470 ^{1}H-NMR (100M, $CDCl_3$) δ 3 6 (8H, m, CH_2), 4 2 (4H, m, CH) 7 2 (20H, m, Ph) MS m/z. 500 (M^+) *Anal* Calcd for $C_{34}H_{32}N_2O_2$ C, 81 57, H, 6 44, N, 5 60 Found C, 81 30, H, 6 44, N, 5 70

(3*R*,3'*R*,4*R*,4'*R*)-3,3',4,4'-Tetraphenyl-1,1'-ethylenedipyrrolidine ((*R*,*R*,*R*,*R*)-2) Diamide **(*R*,*R*,*R*,*R*)-12** (2 2 g, 4 4 mmol) was added to a refluxing suspension of $LiAlH_4$ (0.84 g, 22 mmol) in THF and the reaction mixture was stirred under reflux for 2 h Water (0 84 ml), 15% NaOH (0 84 ml), and water (2 5 ml) were successively added to the reaction mixture and the resulting precipitate was filtered off Concentration followed by recrystallization from hexane provided **(*R*,*R*,*R*,*R*)-2** (1 6 g, 77%) as colorless needles of mp 86-87°C $[\alpha]_D^{20}$ -143°(c=1 60, $CHCl_3$) IR (KBr) 2920, 2780, 1600, 1490, 1450, 1150 ^{1}H-NMR (400M, $CDCl_3$) δ 2 77 (2H, dd, *J*=8, 9Hz, NCH_2CH_2N), 2 88 (2H, dd, *J*=8, 9Hz, NCH_2CH_2N), 2 97 (4H, dd, *J*=6, 8Hz, NCH_2CH), 3 24 (4H, dd, *J*=6, 8Hz, NCH_2CH), 3 40 (4H, ddd, *J*=6, 8, 8Hz, CH), 7 1-7 3 (20H, m, Ph) ^{13}C-NMR (100M, $CDCl_3$) δ 53 07 (d), 55 52 (t), 63 11 (t), 126 28 (d), 127 45 (d), 128 38 (d), 143 82 (s) MS m/z 473 (MH^+), 472 (M^+) *Anal* Calcd for $C_{34}H_{36}N_2$ C, 86 40, H, 7 68, N, 5 93 Found C, 86 16, H, 7 72, N, 6 10

(3*S*,4*S*)-1-Phenylmethyl-3,4-diphenylpyrrolidine Hydrochloride ((*S*,*S*)-10·HCl): Benzylamine (24 ml, 0.22 mol) was added dropwise to a solution of ditosylate (*S*,*S*)-9[12] ($[\alpha]_D^{23}$ +4.6°(c=0.24, benzene), 17 g, 0.026 mol) in xylene (200 ml) at 120°C and the whole was stirred under reflux for 24 h. After cooling down to room temperature, the resulting precipitate was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in chloroform (200 ml) and washed successively with 10 % HCl (100 ml x3), satd. $NaHCO_3$ (100 ml x3), and brine (100 ml). After drying over Na_2SO_4, the solvent was evaporated in vacuo. A solution of the crude product in ether-methanol (2/1, 150 ml) was saturated with HCl gas in ice bath and evaporated in vacuo. The residue was recrystallized from ethanol to obtain (*S*,*S*)-10·HCl (5.8 g, 54 %) as colorless needles of mp 250-252°C (dec). $[\alpha]_D^{20}$ +114° (c=1.01, $CHCl_3$). Spectroscopic data were identical with those of (*R*,*R*)-10·HCl. *Anal.* Calcd for $C_{23}H_{23}N$·HCl: C, 78.95; H, 6.91; N, 4.00. Found C, 78.73; H, 6.90; N, 3.74.

(3*S*,4*S*)-3,4-Diphenylpyrrolidine ((*S*,*S*)-11): A mixture of (*S*,*S*)-10 (3.0 g) and Pd-C (10 %, 2.0 g) in formic acid-methanol (1/1, 40 ml) was stirred for 12 h. After the catalyst was removed by filtration, the solvent was evaporated in vacuo. 15 % NaOH (50 ml) was added to the residue and the whole was extracted with ether (100 ml x3). The organic layer was washed with brine (50 ml) and dried over Na_2SO_4. Concentration followed by recrystallization from hexane gave (*S*,*S*)-11 (21 g, 94 %) as colorless prisms of mp 58-59°C. $[\alpha]_D^{20}$ +226° (c=1.50, $CHCl_3$). Spectroscopic data were identical with those of (*R*,*R*)-11. Treating with MeOH-HCl gave (*S*,*S*)-11·HCl as colorless needles of mp 250°C (dec). $[\alpha]_D^{20}$ +179° (c=1.05 MeOH), *Anal.* Calcd for $C_{16}H_{17}N$·HCl: C, 73.98; H, 6.98; N, 5.39. Found C, 73.78; H, 6.97; N, 5.21.

(3*S*,3'*S*,4*S*,4'*S*)-3,3',4,4'-Tetraphenyl-1,1'-oxalyldipyrrolidine ((*S*,*S*,*S*,*S*)-12): Triethylamine (1.3 ml, 9.4 mmol) and oxalyl chloride (0.27 ml, 3.1 mmol) were added to a solution of amine (*S*,*S*)-11 (1.4 g, 6.3 mmol) in dichloromethane (30 ml) at -78°C under Ar atmosphere and the whole was stirred for 10 min at room temperature. The reaction mixture was quenched with water (50 ml) and diluted with dichloromethane (50 ml). The organic layer was washed successively with 10 % HCl (20 ml x2), satd. $NaHCO_3$ (20 ml), and brine (20 ml), and dried over Na_2SO_4. Concentration followed by recrystallization from $CHCl_3$-hexane gave (*S*,*S*,*S*,*S*)-12 (1.4 g, 89 %) as colorless needles of mp 224-225°C. $[\alpha]_D^{20}$ +114°(c=1.60, $CHCl_3$). Spectroscopic data were identical with those of (*R*,*R*,*R*,*R*)-12. *Anal.* Calcd for $C_{34}H_{32}N_2O_2$: C, 81.57; H, 6.44; N, 5.60. Found C, 81.78; H, 6.50; N, 5.51.

(3*S*,3'*S*,4*S*,4'*S*)-3,3',4,4'-Tetraphenyl-1,1'-ethylenedipyrrolidine ((*S*,*S*,*S*,*S*)-2): (*S*,*S*,*S*,*S*)- 12 (0.14 g, 0.28 mmol) was added to a refluxing suspension of $LiAlH_4$ (0.30 g, 7.9 mmol) in THF and the reaction mixture was stirred under reflux for 10 min. Water (0.30 ml), 15% NaOH (0.30 ml), and water (0.90 ml) were successively added to the reaction mixture and the resulting precipitate was filtered off. Concentration followed by recrystallization from hexane provided (*S*,*S*,*S*,*S*)-2 (85 mg, 64 %) as colorless needles of mp 85-87°C. $[\alpha]_D^{20}$ +138°(c=1.60, $CHCl_3$). Spectroscopic data were identical with those of (*R*,*R*,*R*,*R*)-2. *Anal.* Calcd for $C_{34}H_{36}N_2$: C, 86.40; H, 7.68; N, 5.93. Found C, 86.28; H, 7.60; N, 6.01.

3,5-Dimethylbenzaldehyde (13): According to reported procedure,[13] 2-nitropropane (3 5 ml, 3 9 mmol) and 3,5-dimethylbenzyl chloride[17] (5 0 g, 3 2 mmol) were added to a solution of sodium ethoxide (3 5 mmol) in ethanol 30 ml and the whole was stirred under reflux for 2 h The resulting precipitate was filtered off and ether (50 ml), water (30 ml) was added to the filtrate The organic layer was washed with 15 % NaOH (10 ml x2), brine (10 ml) and dried over $MgSO_4$ Distillation (85-94°, 9 mmHg) gave **14** (3 6 g, 83 %) as colorless oil IR (neat) 1700 ^{1}H-NMR (100M, $CDCl_3$) δ 2 36 (6H, s, CH_3), 7 18 (1H, s, p-ArH), 7 40 (2H, s, o-ArH), 9 87 (1H, s, CHO) MS m/z 134 (M^+)

2,3-Bis(3,5-dimethylphenyl)succinonitrile (14): According to reported procedure,[16] a mixture of aldehyde **13** (2 0 g, 15 mmol), 3,5-dimethylbenzyl cyanide[14](2 2 g, 15 mmol), and NaCN (2 2 g, 45 mmol) in aqueous methanol (60 %, 12 ml) was stirred under reflux for 15 h After cooling down to room temperature, the resulting precipitate was collected and recrystallized from benzene to obtain **14** (2 1 g, 50 %) as colorless needles of mp 206-207°C IR (KBr) 2900, 2320, 1600 ^{1}H-NMR (100M, $CDCl_3$) δ 2.32 (12H, s, CH_3), 4 06 (2H, s, CH), 8 81 (4H, s, o-ArH), 8 98 (2H, s, p-ArH) MS m/z 288 (M^+), 262 (M^+-CN) *Anal* Calcd for $C_{20}H_{20}N_2$ C, 83 30; H, 6 99, N, 9.71 Found C, 83.26, H, 7 00, N, 9 61

***trans*-2,3-Bis(3,5-dimethylphenyl)succinic acid (*rac*-15):** A solution of nitrile **14** (50 g, 0 17 mmol) and 98 % H_2SO_4 (500 ml) in ethanol (1000 ml) was stirred under reflux for 2d After cooling down to room temperature, water (500 ml) was added and the mixture was extracted with benzene (500 ml x3) The organic layer was washed with satd $NaHCO_3$ (500 ml x2), brine (500ml), dried over $MgSO_4$, and evaporated in vacuo The mixture of the residue and KOH (30 g) in ethanol (500 ml) was stirred under reflux for 1 h The reaction mixture was evaporated to dryness and the residue was dissolved in hot water (100 ml) A solution of $BaCl_2 \cdot 2H_2O$ (85 g) in hot water (750 ml) was added and the resulting precipitate was collected by filtration 20 % HCl (1000 ml) was added to the precipitate and the whole was stirred for 12 h The colorless powder was collected by filtration and recrystallization gave *rac*-**15** (33 g, 60 %) as colorless needles of mp 254-256°C IR (nujol) 1720 ^{1}H-NMR (100M, DMSO-d_6). 2 10 (12H, s, CH_3), 3 99 (2H, s, CH), 6.78 (6H, s, Ar), 7 40 (2H, s, COOH) MS m/z. 326 (M^+), 283 (M^+-COOH) *Anal* Calcd for $C_{20}H_{22}O_4$ C, 73 60; H, 6 79 Found C, 73 72; H, 6 84.

***trans*-2,3-Bis(3,5-dimethylphenyl)succinic anhydride (*rac*-16):** A mixture of acetyl chloride (200 ml) and diacid (*rac*-**15**) (19 g) was stirred for 12 h at room temperature Concentration followed by recrystallization from benzene-hexane gave *rac*-**16** (14 g, 78 %) as colorless needles of mp 152-153°C IR (KBr) 2840, 1850, 1770, 1600, 1200, 920 ^{1}H-NMR (100M, $CDCl_3$) δ 2 30 (12H, s, CH_3), 4 23 (2H, s, CH), 6 81 (4H, s, o-ArH), 7 00 (2H, s, p-ArH) MS m/z· 308 (M^+) *Anal* Calcd for $C_{20}H_{20}O_3$ C, 77 90, H, 6.54 Found C, 77 93, H, 6 67

(2*R*,3*R*,α*R*)- and (2*S*,3*S*,α*R*)-*N*-(α-Phenylethyl)-3,4-bis(3,5-dimethylphenyl)succinamic acid (17a & b): A solution of anhydride **16** (24 g, 78 mmol) and (-)-(*R*)-α-methylbenzylamine (11 g, 91 mmol) in benzene (250 ml) was stirred for 5 h at the room temperature Concentration followed by recrystallization from ethanol (500 ml) provided (**3*S*,4*S*,α*R*)-17b** (15 g, 42 %) as colorless needles of mp 231-

232°C The mother liquid was evaporated in vacuo and purified with SiO_2 column chromatography (benzene-acetone, 5/1-1/1) to give **(3*S*,4*S*,α*R*)-17b** (2 0 g, 6 %) and **(3*R*,4*R*,α*R*)-17a** (17 g, 48 %) as a caramel

(3*R*,4*R*,α*R*)-17a $[\alpha]_D^{22}$ -152°(c=1 00, $CHCl_3$) IR ($CHCl_3$) 1710, 1660, 1600 ^{1}H-NMR (100M, $CDCl_3$) δ 1 33 (3H, d, *J*=7Hz CH_3), 2 15 (6H, s, CH_3), 2 17 (6H, s, CH_3), 3 91 (1H, d, *J*=10Hz, CH), 4 26 (1H, d, *J*=10Hz, CH), 5 09 (1H, dt, *J*=7,8Hz, CH), 5 71 (1H, d, *J*=8Hz, NH), 6 7-6 8 (6H, m, Xyl), 7 25 (5H, s, Ph) MS m/z 429 (M^+) *Anal* Calcd for $C_{28}H_{31}NO_3$ C, 78 29, H, 7 27, N, 3 26 Found C, 78 02, H, 7 28, N, 3 14

(3*S*,4*S*,α*R*)-17b $[\alpha]_D^{22}$ +218°(c=1 10, $CHCl_3$) IR ($CHCl_3$) 1710, 1665, 1605, (KBr) 1700, 1635, 1600 ^{1}H-NMR (100M, $CDCl_3$) δ 1 41(3H, d, *J*=7Hz, CH_3), 2 14 (6H, s, $ArCH_3$), 2 18(6H, s, $ArCH_3$), 3 97 (1H, d, *J*=10Hz, CH), 4 21 (1H, d, *J*=10Hz, CH), 5 08 (1H, dt, *J*=7,8Hz, CH), 5 66 (1H, d, *J*=8Hz, NH), 6 5-7 3 (11H, m, Ar) MS m/z 429 (M^+) *Anal* Calcd for $C_{28}H_{31}NO_3$ C, 78 29; H, 7 27, N, 3 26 Found C, 78 42; H, 7 38, N, 3 20

(2*R*,3*R*,α*R*)-*N*-(α-Phenylethyl)-2,3-bis(3,5-dimethylphenyl)succimide ((*R*,*R*,*R*)-18a): A solution of **(*R*,*R*,*R*)-17a** (17 g) in conc HCl (50 ml) and acetic acid (200 ml) was stirred under reflux for 24 h The reaction mixture was evaporated in vacuo and the residue was dissolved in ethyl acetate (300 ml) The organic layer was washed successively with water (100 ml x3), satd $NaHCO_3$ (100 ml x3), and brine 100 ml, and then dried over $MgSO_4$ Concentration followed by recrystallization from ethanol (300 ml) gave **(*R*,*R*,*R*)-18a** (10 g, 68 %) as colorless needles of mp 136-137°C, $[\alpha]_D^{22}$ -250 7°(c=1 38, $CHCl_3$) IR (KBr) 1760, 1680, 1600 ^{1}H-NMR (100M, $CDCl_3$) δ 1 88 (3H, d, *J*=7Hz, CH_3), 2 26 (12H, s, CH_3Ar), 3 84 (2H, s, COCH), 5 57 (1H, q, *J*=7Hz, NCH), 6 69 (4H, s, o-ArH), 6 92 (2H, s, p-ArH), 7 3-7 5 (5H, m, Ph) MS m/z 411 (M^+) *Anal* Calcd for $C_{28}H_{29}NO_2$ C, 81 72, H, 7 10, N, 3 40 Found C, 81 66, H, 7 21, N, 3 10

(3*R*,4*R*,α*R*)-*N*-α-Phenylethyl-3,4-bis(3,5-dimethylphenyl)pyrrolidine ((*R*,*R*,*R*)-19a): A solution of **(*R*,*R*,*R*)-18a** (9 0 g, 22 mmol) in THF (50 ml) was added dropwise to a refluxing suspension of $LiAlH_4$ (5 0 g, 30 mmol) in THF (150 ml) and the whole was stirred under reflux for 1 h Water (5 ml), 15% NaOH (5 ml), water (15 ml) were successively added to the reaction mixture and the resulting precipitate was filtered off Concentration followed by SiO_2 column chromatography (hexane-ether, 20/1-10/1) gave crude **(*R*,*R*,*R*)-19a** Treating with picric acid (6 2 g) in dichloromethane and following recrystallization from ethanol (30 ml) gave picrate of **(*R*,*R*,*R*)-19a** (9 3 g) as yellow prisms of mp 148-149 5°C $[\alpha]_D^{25}$ -76 2°(c=1 00, $CHCl_3$) IR (KBr) 1625, 1610, 1535, 1360, 1330, 1310, 1260 ^{1}H-NMR (100M, $CDCl_3$) δ 1 85 (3H, d, *J*=7Hz, CH_3), 2 17 (6H, s, CH_3Ar), 2 22 (6H, s, CH_3Ar), 3 0-4 5 (7H, m, CH_2&CH), 6 7-6 9 (6H, m, Ar), 7 46 (5H, s, Ph), 8 97 (2H, s, pic) *Anal* Calcd for $C_{28}H_{33}N\,C_6H_3N_3O_7$ C, 66 65, H, 5 92, N, 9 14 Found C, 66 42, H, 5 86, N, 9 21 The picrate was treated with NH_4OH in ether to give pure **(*R*,*R*,*R*)-19a** (5 8 g, 69 %) as a caramel $[\alpha]_D^{22}$ -69 7°(c=1 30, $CHCl_3$) IR ($CHCl_3$) 2900, 1600, 1450, 850 ^{1}H-NMR (100M, $CDCl_3$) δ 1 44 (3H, d, *J*=6Hz, CH_3), 2 25 (12H, s, CH_3Ar), 2 6-3 5 (7H, m, CH_2), 6 7-6 8 (6H, m, Ar), 7 2-7 4 (5H, m, Ph) MS m/z 383 (M^+), 368 (M^+-CH_3)

(3*R*,4*R*)-Bis(3,5-dimethylphenyl)pyrrolidine Hydrochloride ((*R*,*R*)-20a HCl): A mixture of **(*R*,*R*)-19a** (5 0 g) and Pd-C (10 %, 5 0 g) in formic acid-methanol (1/2, 60 ml) was stirred for 2 d After the catalyst was removed by filtration, the filtrate was evaporated in vacuo to dryness 15 % NaOH (50 ml) was

added to the residue and the whole was extracted with ether (100 ml x3) The organic layer was washed with brine (30 ml) and dried over K_2CO_3 Concentration followed by treating with MeOH-HCl and recrystallization from benzene-ether gave (***R,R*)-20a** HCl (3 1 g, 76 %) as colorless needles of mp 223-225°C (dec) $[\alpha]_D^{24}$ -175°(c=1 00, MeOH) IR (KBr) 2600-2900, 1590, 1450, 840 ^{1}H-NMR (100M, $CDCl_3$) δ 2 23 (12H, s, CH_3Ar), 3 0-3 9 (6H, m, $CHCH_2$), 6 79 (6H, s, Ar) MS m/z 280 (MH^+), 279 (M^+) *Anal* Calcd for $C_{20}H_{25}N$ HCl C, 76 05, H, 8 30, N, 4 43 Found C, 75 78, H, 8.31, N, 4 50

(3*S*,4*S*,α*R*)-*N*-α-Phenylethyl-2,3-bis(3,5-dimethylphenyl)succinimide ((*S,S,R*)-18b): A solution of **(*S,S,R*)-17b** (200 mg) in conc HCl (1 ml) and acetic acid (5 ml) was stirred under reflux for 15 h. The reaction mixture was evaporated in vacuo and the residue was dissolved in ethyl acetate (30 ml) After washing successively with 10% HCl (10 ml), satd $NaHCO_3$ (10ml x3), and brine (10 ml), the solvent was dried over Na_2SO_4 and evaporated in vacuo Recrystallization from ethanol gave **(*S,S,R*)-18b** (169 mg, 88 %) as colorless needles of mp 125-126°C $[\alpha]_D^{22}$ +73 3°(c=1 04, $CHCl_3$) IR (KBr) 1770, 1680, 1600 ^{1}H-NMR (100M, $CDCl_3$) δ 1 94 (3H, d, *J*=8Hz, CH_3), 2 24 (12H, s, CH_3Ar), 3 86 (2H, s, COCH), 5 55 (1H, q, *J*=8Hz, NCH), 6 65 (4H, s, o-ArH), 6 90 (2H, s, p-ArH), 7 2-7 5 (5H, m, Ph) MS m/z 411 (M^+) *Anal* Calcd for $C_{28}H_{29}NO_2$ C, 81 72, H, 7 10, N, 3 40 Found C, 81 86, H, 7 11, N, 3 36

(3*S*,4*S*)-*N*-α-Phenylethyl-3,4-bis(3,5-dimethylphenyl)pyrrolidine ((*S,S,R*)-19b): A solution of **(*S,S,R*)-18b** (162 mg, 0 39 mmol) in THF (5 ml) was added dropwise to a refluxing suspension of $LiAlH_4$ (81 mg, 2 1 mmol) in THF (10 ml) and the whole was stirred under reflux for 10 min Water (0.08 ml), 15% NaOH (0 08 ml), water (0.24 ml) were successively added to the reaction mixture and the resulting precipitate was filtered off Concentration followed by SiO_2 column chromatography (hexane-ether, 20/1-10/1) followed crude **(*S,S,R*)-19b** Treating with picric acid (95 mg) in dichloromethane and following recrystallization from ethanol (20 ml) gave picrate of **(*S,S,R*)-19b** (122 mg) as yellow prisms of mp 211-212°C (dec) $[\alpha]_D^{25}$ -63 2°(c=1 00, $CHCl_3$) IR (KBr) 1625, 1610, 1560, 1360, 1335, 1310, 1295, 1270 ^{1}H-NMR (100M, $CDCl_3$) δ 1 88 (3H, ,d *J*=7Hz, CH_3CH), 2 13 (6H, s, CH_3Ar), 2 21 (6H, s, CH_3Ar), 2 9-4 5 (7H, m, CH_2&CH), 6 7-6 8 (6H, m, Ar), 7 46 (5H, ,s Ph), 8 97 (2H, s, pic) *Anal* Calcd for $C_{28}H_{33}N$ $C_6H_3N_3O_7$ C, 66 65, H, 5 92, N, 9 14 Found C, 66 74, H, 5 93, N, 9 14 The picrate was treated with NH_4OH in ether to give free amine **(*S,S,R*)-19b** (76 mg, 60 %) as a caramel $[\alpha]_D^{23}$ +101°(c=1 10, $CHCl_3$) IR ($CHCl_3$)· 2900, 1600, 1450, 850 ^{1}H-NMR (100M, $CDCl_3$) δ 1 41 (3H, d, *J*=7Hz, CH_3), 2 25 (12H, s, CH_3Ar), 2 7-3 0 (4H, m, CH_2), 3 1-3 3 (3H, m, CH), 6 80 (3H, s, Ar), 6 85 (3H, s, Ar), 7 2-7 4 (5H, m, Ph) MS m/z 383,(M^+), 368 (M^+-CH_3)

(3*S*,4*S*)-Bis(3,5-dimethylphenyl)pyrrolidine Hydrochloride ((*S,S*)-20b HCl): A mixture of **(*S,S,R*) -19b** (50 mg) and Pd-C (10 %, 30 mg) in formic acid-methanol (1/2, 4 ml) was stirred for 2 d After the catalyst was removed by filtration, the filtrate was evaporated in vacuo to dryness 15 % NaOH was added to the residue and the whole was extracted with ether (20 ml x3) The organic layer was washed with brine and dried over K_2CO_3 Concentration followed by treating with MeOH-HCl and recrystallization from benzene-ether gave **(*S,S*)-20b** HCl salt as needles of mp 222-224°C, $[\alpha]_D^{23}$ +170°(c=0 980, MeOH) Spectroscopic data were identical with those of **(*R,R*)-20a** *Anal* Calcd for $C_{20}H_{25}N$ HCl C, 76 05, H, 8 30, N, 4 43 Found C, 75 88, H, 8 34, N, 4 29

(3*R*,3'*R*,4*R*,4'*R*)-3,3',4,4'-Tetrakis(3,5-dimethylphenyl)-1,1'-oxalyldipyrrolidine ((*R*,*R*,*R*,*R*)-21): Triethylamine (0 44 ml, 3 1 mmol), and oxalyl chloride (0 027 ml, 0 31 mmol) were added to a solution of **(*R*,*R*)-20a** HCl (0 20 g, 0 63 mmol) in dichloromethane (20 ml) at -78°C under Ar atmosphere and the whole was stirred for 10 min at room temperature The reaction mixture was quenched with water (50 ml) and diluted with dichloromethane (100 ml) The organic layer was washed successively with 10 % HCl (20 ml x2), satd $NaHCO_3$ (20 ml), and brine (20 ml), and dried over Na_2SO_4 Evaporation in vacuo followed by recrystallization from benzene-hexane gave **(*R*,*R*,*R*,*R*)-24** (0 15 g, 77 %) as colorless needles of mp 219-221°C (dec) $[\alpha]_D^{25}$ -72 6°(c=1.02, $CHCl_3$) IR (KBr) 1620, 1600, 1380 ^{1}H-NMR (100M, $CDCl_3$) δ 2 23 (24H, s, CH_3), 3 5-4 2 (12H, m, CH&CH_2) 6 79 (12H, s, Ar) MS m/z 612 (M^+) *Anal* Calcd for $C_{42}H_{48}N_2O_2$ C, 82 31, H, 7 89, N, 4 57 Found C, 82 08, H, 7 95, N, 4 53.

(3*R*,3'*R*,4*R*,4'*R*)-3,3',4,4'-Tetrakis(3,5-dimethylphenyl)-1,1'-ethylenedipyrrolidine ((*R*,*R*,*R*,*R*)-3): Diamide **(*R*,*R*,*R*,*R*)-24** (1 6 g, 2 6 mmol) was added to a refluxing solution of $LiAlH_4$ (1 0 g, 26 mmol) in THF (20 ml) and the reaction mixture was stirred under reflux for 2 h After cooling down to room temperature, water (0 84 ml), 15% NaOH (0 84 ml), and water (2 5 ml) were successively added to the reaction mixture and the resulting precipitate was filtered off The filtrate was evaporated in vacuo and the residue was purified by SiO_2 column chromatography (benzene-ether, 5/1-2/1) to afford **3** (1 28 g, 84 %) as a caramel $[\alpha]_D^{22}$ -135°(c=1 07 $CHCl_3$) IR ($CHCl_3$). 1600, 1480, 850 ^{1}H-NMR (100M, $CDCl_3$) δ 2 25 (24H, s, CH_3), 2 7-3 4 (16H, m, CH&CH_2), 6 84 (12H, s, Ar) MS m/z 584 (M^+) Treating with HCl-MeOH gave **3** HCl as a needles of mp 270-300°C (dec) $[\alpha]_D^{22}$ -162°(c=1 02 EtOH) *Anal* Calcd for $C_{42}H_{52}N_2$ 2HCl C, 76 69, H, 8 27, N, 4 26 Found C, 76 43, H, 8 07, N, 4 47

(2*R*,3*R*,α*R*)-*N*-α-Phenylethyl-2,3-bis(3,5-dimethylphenyl)-4-hydroxybutyramide ((*R*,*R*,*R*)-22): Triethylamine (52 mg, 0 51 mmol) and ethyl chlorocarbonate (56 mg, 0 51 mmol) were added to a solution of acid **(*R*,*R*,*R*)-17a** (0 20 g, 0 46 mmol) in THF (5 ml) at 0°C The reaction mixture was stirred for 1 h and the resulting precipitate was filtered off Sodium borohydride (44 mg, 1 2 mmol) was added to the filtrate and the whole was stirred for 1 5 h at room temperature The reaction mixture was quenched with 10 % HCl (10 ml) and the whole was extracted with ethyl acetate (20 ml x 3) The organic layer was washed successively with 10 % HCl (10 ml), 15 % NaOH (10 ml), brine (10 ml) and dried over Na_2SO_4 Evaporation followed by SiO_2 column chromatography (benzene-ethyl acetate, 8/1) afforded **22** (83 mg, 43 %) as a caramel $[\alpha]_D^{20}$ -28 9°(c=0 90, $CHCl_3$) IR ($CHCl_3$) 1640, 3300 ^{1}H-NMR (100M, $CDCl_3$) δ 1.34 (3H, d, *J*=7Hz, CH_3CN), 2 16 (12H, s, CH_3Ar), 2 51 (1H, s, OH), 3 5-4 9 (4H, m, $CHCH_2$), 4 9-5 2 (1H, m, PhCH), 6 20 (1H, d, *J*=10Hz, NH), 6 70 (3H, s, CH_3Ar), 6 82 (3H, s, CH_3Ar), 7 24 (5H, s, Ph) MS m/z 415 (M^+), 397 (M^+-H_2O) HRMS Calcd for $C_{28}H_{33}NO_2$ 415 2675 Found 415 2593

(2*R*,3*R*)-2,3-Bis(3,5-dimethylphenyl)butan-4-olide ((*R*,*R*)-23): A suspension of amide **(*R*,*R*,*R*)-22** (0 18 g) in 10% HCl (20 ml) was stirred under reflux for 1 h The reaction mixture was extracted with $CHCl_3$ (20 ml x 3) and the organic layer was washed with brine (20 ml) and dried over Na_2SO_4 SiO_2 column chromatography (benzene-dichloromethane, 2/1) followed by recrystallization from CCl_4-hexane afforded **(*R*,*R*)-23** (0 13 g, 99 %) as colorless prisms of mp 98°C $[\alpha]_D^{25}$ -233°(c=1 00, $CHCl_3$) IR (KBr)

1770 ^{1}H-NMR (100M, $CDCl_3$) δ 2 27 (12H, s, CH_3Ar), 3 7-3 9 (2H, m, CH_2), 4 2-4 4 (1H, m, CH), 4.6-4 8 (1H, m, CH), 6 8-6 9 (6H, m, Ar) MS m/z 294 (M^+) *Anal* Calcd for $C_{20}H_{22}O_2$ C, 81.60; H, 7 53 Found C, 81 48, H, 7 56

(2*R*,3*R*)-2,3-Bis(3,5-dimethylphenyl)-1,4-butanediol ((*R*,*R*)-24): A mixture of lactone **(*R*,*R*)-23** (0 15 g, 0.51 mmol) and $LiAlH_4$ (0 10 g, 13 mmol) in THF (10 ml) was stirred under reflux for 1 h Water (0 10 ml), 15 % NaOH (0 10 ml), and water (0 30 ml) were successively added to the reaction mixture and the resulting precipitate was filtered off The filtrate was evaporated and the residue was purified by SiO_2 column chromatography (benzene-ethyl acetate, 3/2) followed by recrystallization from benzene-hexane to afford **(*R*,*R*)-24** (0 11 g, 72 %) as a colorless prisms of mp 117-118°C $[\alpha]_D^{20}$ -31 2°(c=1 01, $CHCl_3$). IR($CHCl_3$) 3400, 1600, 1260 ^{1}H-NMR (100M, $CDCl_3$) δ 1 73(2H, s, OH), 2 20 (12H, s, CH_3Ar), 3 18 (2H, t, *J*=4Hz CH), 3 87 (4H, d, *J*=4Hz CH_2), 6.57 (4H, s, o-ArH), 6 76 (2H, s, p-ArH) MS m/z 299 (MH^+), 298 (M^+), 268 (M^+-CH_2O) *Anal* Calcd for $C_{20}H_{26}O_2$· C, 80.50, H, 8 78 Found C, 80 29, H, 9 05

(2*R*,3*R*)-2,3-Bis(3,5-dimethylphenyl)-1,4-butanediol Ditosylate ((*R*,*R*)-25): A solution of diol **(*R*,*R*)-24** (0 12 g, 0 39 mmol) and tosyl chloride (0 23 g, 1.2 mmol) in pyridine (5 ml) was stirred for 2 d at room temperature After adding 10 % HCl (10 ml), the mixture was extracted with ethyl acetate (20 ml x3) The organic layer was washed successively with 10 % HCl (10 ml x 3), satd $NaHCO_3$ (10 ml x 2), brine (10 ml) and dried over $MgSO_4$ Purification by prepTLC (SiO_2, hexane-acetone, 3/1) gave **(*R*,*R*)-25** (14 g, 60 %) as an oil $[\alpha]_D^{22}$ +11°(c=1 00, $CHCl_3$) IR($CHCl_3$)· 1600, 1360, 1180 ^{1}H-NMR (100M, $CDCl_3$) δ 2 14 (12H, s, CH_3Ar), 2 44 (6H, s, CH_3Ar), 3 2-3 4 (2H, m, CH), 3 9-4 2 (4H, m, CH_2), 6 21 (4H, s, o-ArH), 6 82 (2H, s, p-ArH), 7 2-7 4 (4H, m, Ts), 7 6-7 8 (4H, m, Ts) MS m/z· 607 (MH^+), 606(M^+) *Anal* Calcd for $C_{34}H_{38}O_6S_2$ C, 67 30, H, 6 31. Found C, 67 33; H, 6 33

(2*R*,3*R*)-2,3-Bis(3,5-dimethylphenyl)-1,4-butane ((*R*,*R*)-26): A mixture of tosylate **(*R*,*R*)-25** (0 13 g, 0.22 mmol) and $LiAlH_4$ (50 mg, 1 3 mmol) in THF (5 ml) was stirred under reflux for 1 h After adding 10 % HCl (5 ml), the mixture was extracted with ether (10 ml x 3) The organic layer was washed successively with 10 % HCl (10 ml), satd. $NaHCO_3$ (10 ml), brine (10 ml) and dried over $MgSO_4$. Purification by SiO_2 column chromatography (CCl_4) afforded **26** (48 mg, 83 %) as an oil $[\alpha]_D^{22}$ -80.0(c=0.980, $CHCl_3$) IR($CHCl_3$) 1600, 1450, 1380 ^{1}H-NMR (100M, $CDCl_3$) δ 1 17 (6H, d, *J*=7Hz, CH_3CH), 2 25 (12H, s, CH_3Ar), 2 8-3 0 (2H, m, CH), 6 7-6 8 (6H, m, Ar) MS m/z 266 (M^+) HRMS Calcd for $C_{20}H_{26}$ 266 2031 Found 266.1964

(2*R*,3*R*)-Bis(4-Bromophenacyl) 2,3-Dimethylsuccinate ((*R*,*R*)-27): Ozone gas was bubbled into a solution of **(*R*,*R*)-26** (48 mg, 0 10 mmol) in acetic acid (20 ml) for 10 h at room temperature 35 % Hydrogen peroxide (20 ml) was added to the reaction mixture and the whole was stirred for 12 h at room temperature. Platinum black was added to the mixture to decompose excess hydrogen peroxide and then filtered off. The filtrate was evaporated in vacuo to dryness Sodium carbonate (31 mg, 0 29 mmol) in water (1 ml) and 4-bromophenacyl bromide (163 mg, 0 59 mmol) in ethanol (15 ml) was added to the residue and the whole was stirred under reflux for 3 h The mixture was evaporated and diluted with ethyl acetate (20 ml) The organic layer was washed with water (10 ml), brine (10 ml) and dried over $MgSO_4$ Purification by prepTLC (benzene-

acetone, 4/1) followed by recrystallization from benzene afforded (*R,R*)-**27** (3 8 mg) as colorless prisms of mp 185°C $[\alpha]_D^{23}$ -35°(c=0 38, $CHCl_3$) IR (Nujol) 1740, 1700 ^{1}H-NMR (100M, $CDCl_3$) δ 1 34 (6H, d, *J*=7Hz, CH_3), 3 0-3 2 (2H, m, CH), 5 32 (4H, s, CH_2), 7 5-7 8 (8H, m, Ar) MS m/z 538 (M^+), 540 (M^++2), 542 (M^++4) *Anal* Calcd for $C_{22}H_{20}O_6Br_2$· C, 48.92, H, 3 73 Found C, 49 08, H, 3 66

(2*R*,5*R*)-1,2,5-Tribenzylpyrrolidine ((*R,R*)-29) Thionyl chloride (20 ml, 0 26 mol) was added dropwise to a solution of diol (*R,R*)-**28**[8] (19 g, 0 086 mol) in dioxane (200 ml) at 0°C and the whole was stirred for 12 h at room temperature The solvent was evaporated and the residue was suspended in THF (800 ml) Phenylmagnesium bromide (0 52 mol) in ether (300 ml) was added to the suspension and the mixture was stirred under reflux for 4 h After cooling to the room temperature, the whole was poured onto brine 300 ml and filtered through celite pad The organic layer of the filtrate was washed with brine and dried over $MgSO_4$. After evaporating the solvent, the residue was purified with SiO_2 column chromatography (hexane-ether, 20/1) followed by recrystallization from MeOH to obtain (*R,R*)-**29** (17 7 g, 60 %) as colorless needles of mp 50-51°C $[\alpha]_D^{20}$ +113°(c=1 00, $CHCl_3$) IR (KBr) 1600, 1490, 1450, 730, 700 ^{1}H-NMR (100M, $CDCl_3$) δ 1 2-1 9(4H, m, CH_2CH_2), 2 33 (2H, dd, *J*=5, 7Hz, $PhCH_2C$), 2 9-3 3 (4H, m, CH_2&CH), 3 84 (1H, d, *J*=7Hz, $PhCH_2N$), 4 13 (1H, d, *J*=7Hz, $PhCH_2N$), 6 9-7 5 (15H, m, Ph) MS m/z 341 (M^+), 264 (M^+-Ph), 250 (M^+-CH_2Ph) *Anal* Calcd for $C_{25}H_{27}N$ C, 87 93, H, 7 97, N, 4 10 Found C, 88 07, H, 8 08, N, 4 12

(2*R*,5*R*)-2,5-Dibenzylpyrrolidine Hydrochloride ((*R,R*)-30 HCl) A mixture of (*R,R*)-**29** (2 0 g, 5 8 mmol) and Pd-C (10 %, 1.2 g) in formic acid-methanol (1/3, 20 ml) was stirred for 12 h at room temperature After the catalyst was removed by filtration, the solvent was evaporated in vacuo 15 % NaOH (20 ml) was added to the residue and the whole was extracted with ether (20ml x 3) The organic layer was washed with brine (20 ml) and dried over Na_2SO_4 Concentration followed by treating with EtOH-HCl and recrystallization from acetone to obtain **30**·HCl (1 2 g, 82 %) as colorless needles of mp 179-180°C $[\alpha]_D^{20}$ -29 0°(c=1 02, EtOH) IR (KBr) 2800, 1600, 1580, 1490, 1410, 750, 700 ^{1}H-NMR (100M, $CDCl_3$) δ 1 5-2 1 (4H, m, CH_2CH_2), 2 99 (2H, dd, *J*=7, 7Hz, CH_2Ph), 3 54 (2H, dd, *J*=7, 7Hz, CH_2Ph), 3 8-4 1 (2H, m, CH), 7 20 (10H, s, Ph) MS m/z· 252 (MH^+), 251 (M^+), 160 (M^+-CH_2Ph) *Anal* Calcd for $C_{18}H_{21}N$ HCl C, 75 11, H, 7 70, N, 4 87 Found C, 74 89, H, 7 89, N, 4 94

(2*R*,2'*R*,5*R*,5'*R*)-2,2'5,5'-Tetrabenzyl-1,1'-oxalyldipyrrolidine ((*R,R,R,R*)-31) Triethylamine (0 44 ml, 1 2 mmol) and oxalyl chloride (0 017 ml, 0 20 mmol) were added to a solution of (*R,R*)-**30** HCl (0 10 g, 0 40 mmol) in dichloromethane (5 ml) at -78°C under Ar atmosphere and the whole was stirred for 10 min at room temperature The reaction mixture was quenched with water (50 ml) and diluted with dichloromethane (100 ml) The organic layer was washed successively with 10 % HCl (10 ml x3), satd $NaHCO_3$ (10 ml x3), and brine (15 ml),and dried over $MgSO_4$ Concentration followed by recrystallization from benzene-hexane gave (*R,R,R,R*)-**31** (0 15 g, 77 %) as colorless needles of mp 238°C $[\alpha]_D^{20}$ +44°(c=1 00, $CHCl_3$) IR (KBr) 1620, 1570, 1550, 1370, 720, 690 ^{1}H-NMR (100M, $CDCl_3$) δ 1 5-1 9 (8H, m, CH_2CH_2), 2 42 (2H, dd, *J*=6, 7Hz, CH_2Ph), 2 64 (2H, dd, *J*=6, 7Hz, CH_2Ph), 3 01 (2H, dd, *J*=2, 6Hz, CH_2Ph), 3 42 (2H, dd, *J*=2, 6Hz, CH_2Ph), 4 4-4 6 (2H, m, CH), 7 1-7 3 (20H, m, Ph) MS m/z 556 (M^+), 465 (M^+-CH_2Ph) *Anal* Calcd for $C_{38}H_{40}N_2O_2$ C, 81 98; H, 7 24, N, 5 03 Found C, 81.84, H, 7 35, N, 5 14

(2*R*,2'*R*,5*R*,5'*R*)-2,2'5,5'-Tetrabenzyl-1,1'-ethylenedipyrrolidine ((*R*,*R*,*R*,*R*)-4) Diamide **(*R*,*R*,*R*,*R*)-31** (0 63 g, 1 1 mmol) was added to a refluxing solution of $LiAlH_4$ (0.22 g, 5 5 mmol) in THF (10 ml) and the reaction mixture was stirred under reflux for 20 min After cooling down to the room temperature, ether (30 ml), water (0 22 ml), 15% NaOH (0 22 ml), and water (0 66 ml) were successively added to the reaction mixture and the resulting precipitate was filtered off The filtrate was evaporated in vacuo and the residue was recrystallized from hexane to afford **(*R*,*R*,*R*,*R*)-4** (0 51 g, 84 %) as colorless prisms of mp 84 5-85 5°C $[\alpha]_D^{23}$+129°(c=1 10, $CHCl_3$) IR (KBr) 1600, 1490, 1450, 750, 700. ^{1}H-NMR (100M, $CDCl_3$) δ 1 3-1 8 (8H, m, CH_2CH_2), 2 31 (4H, dd, *J*=5, 8Hz, CH_2Ph), 2 9-3.4 (12H, m, $CHCH_2$), 7 16 (20H, s, Ph) MS m/z 529 (MH^+), 528 (M^+), 437 (M^+-CH_2Ph) *Anal.* Calcd for $C_{38}H_{44}N_2$ C, 86.32, H, 8 39, N, 5 30 Found C, 86.08; H, 8 58, N, 5.34

(3*R*,3'*R*,4*R*,4'*R*)-3,3',4,4'-Tetraphenyl-1,1'-trimethylenedipyrrolidine ((*R*,*R*,*R*,*R*)-5): A solution of **(*R*,*R*)-11**(0 20 g, 0 90 mmol), 1,3-dibromopropane (0 045 ml, 0 44 mmol), and K_2CO_3 (0 13 g, 0.94 mmol) in DMF (5 ml) was stirred under reflux for 3 h The reaction mixture was diluted with ethyl acetate (50 ml) and washed with brine (50 ml x2) After drying over Na_2SO_4, concentration followed by SiO_2 column chromatography (benzene-ethyl acetate, 3/1-1/1) gave **5** (0 16 g, 73 %) as a caramel ^{1}H-NMR (100M) δ· 1.7-3 4 (18H, m, $CHCH_2$), 7 17 (20H, s, ArH) MS m/z 486 (M^+) HRMS calcd for $C_{35}H_{38}N_2$ 486.3033 Found 486 2978 Treated with MeOH-HCl followed by recrystallization gave **5** 2HCl as colorless needles with mp 250-270°C (dec), $[\alpha]_D^{20}$-142°(c=1 00, MeOH) IR (KBr) 3450, 2500, 1600, 1490, 1450 *Anal* calcd for $C_{35}H_{38}N_2$ 2HCl·3/4H_2O· C, 73 35, H, 7 30; N, 4 89 Found C, 73 41, H, 7.03, N, 5.06

(3*R*,3'*R*,4*R*,4'*R*)-3,3',4,4'-Tetraphenyl-1,1'-(1,2-phenylene)dipyrrolidine ((*R*,*R*,*R*,*R*)-6): A solution of tosylate **(*R*,*R*)-9** (1 0 g, 1 8 mmol), o-phenylenediamine (0 10 g, 0 9 mmol), and tri-n-butylamine (2 0 ml, 0 84 mmol) in xylene (10 ml) was stirred under reflux for 3 d Purification of the crude mixture with SiO_2 column chromatography (hexane-benzene, 4/1) gave **(*R*,*R*,*R*,*R*)-6** (0 18 g, 19 %) as a caramel $[\alpha]_D^{25}$-91 2°(c=0.950 $CHCl_3$) IR ($CHCl_3$) 1600, 1590, 1500, 1450, 700 ^{1}H-NMR (400M, $CDCl_3$) δ 3 60 (8H, br), 3 75 (4H, br), 6 95 (2H, br), 7 05 (2H, br), 7 1-7 3(20H, m, Ar) ^{13}C-NMR (100M, $CDCl_3$) δ 51 55 (d), 58 38 (t), 116 47 (d), 121.14 (d), 126 57 (d), 127 68 (d), 128.50 (d), 141 69 (s), 142 19 (s) MS m/z 520 (M^+) Treating with picric acid gave **(*R*,*R*,*R*,*R*)-6** picrate as a yellow needles of mp 178-180°C (dec) $[\alpha]_D^{25}$-74 9° (c=1.10, $CHCl_3$) *Anal* Calcd for $C_{38}H_{36}N_2$ $C_6H_3N_3O_7$ C, 70.48, H, 5 24, N, 9 34 Found C, 70 52, H, 5 30, N, 9 38

(3*R*,3'*R*,4*R*,4'*R*)-3,3',4,4'-Tetraphenyl-1,1'-(2,2'-biphenylene)dipyrrolidine ((*R*,*R*,*R*,*R*)-7): A solution of tosylate **(*R*,*R*)-9** (1 0 g, 1 8 mmol), 2,2'-biphenylenediamine (0 17 g, 0 9 mmol), and tri-n-butylamine (2 1 ml, 18 mmol) in xylene (10 ml) was stirred under reflux for 3 d. Purification of the crude mixture with SiO_2 column chromatography (hexane / benzene = 4 / 1) followed by recrystallization from ethyl acetate gave **(*R*,*R*,*R*,*R*)-7** (0.20 g, 37 %) as a colorless needles of mp 200-201°C $[\alpha]_D^{25}$-27 8° (c=1 05 $CHCl_3$) IR (KBr) 1590, 1490, 1470, 1450, 1440, 1330, 750, 690 ^{1}H-NMR (400M, $CDCl_3$) δ 3 3-3 6 (12H, m), 6 8-6 9 (4H, m), 7 0-7 5 (24H, m) ^{13}C-NMR (100M, $CDCl_3$) δ 52 40 (d), 52 46 (d), 57 59 (t), 58 35 (t), 114 16 (d), 115 13 (d), 118 19 (d), 118 37 (d), 126 83 (d), 127,53 (d), 127 65 (d), 127,83

(d), 127,18 (d), 128 38 (d), 128 73 (d), 129 37 (d), 131 00 (d), 132 47 (d), 133 02 (d), 141 18 (s), 141 46 (s), 146 10 (s), 147 18 (s) MS m/z 596 (M^+) *Anal* Calcd for $C_{44}H_{40}N_2$ C, 88 55, H, 6 76, N, 4 69 Found C, 88 47, H, 6 81, N, 4 70

(3*R*,4*R*)-1-Acetyl-3,4-diphenylpyrrolidine ((*R*,*R*)-32) Triethylamine (0 65 ml, 3 8 mmol) and acetic anhydride (0 35 ml, 4 7 mmol) were added to a solution of **(*R*,*R*)-11** (0 70 g, 3 1 mmol) in dichloromethane (20 ml) at -78°C under Ar atmosphere and the whole was stirred for 10 min at room temperature Water (50 ml) and dichloromethane (100 ml) were added to the reaction mixture The organic layer was washed successively with 10 % HCl (20 ml x2), satd $NaHCO_3$ (20 ml), and brine (20 ml), and dried over Na_2SO_4 SiO_2 column chromatography (benzene-ethyl acetate, 1/1) followed by recrystallization from benzene-hexane gave **32** (0 75 g, 88 %) as colorless needles of mp 144-145°C (dec) $[\alpha]_D^{25}$ -110°(c=1 08, $CHCl_3$) IR (KBr) 1630, 1440, 760, 700 ^{1}H-NMR (100M, $CDCl_3$) δ 2 11 (3H, s, CH_3), 3 4-3 7 (4H, m, CH_2), 3 9-4 3 (2H, m CH), 7 1-7 3 (10H, m, Ar) MS m/z 266 (MH^+), 265(M^+) *Anal* Calcd for $C_{18}H_{19}NO$ C, 81 48, H, 7 22, N, 5 28 Found C, 81 61, H, 7 29, N, 5 41

(3*R*,4*R*)-3,4-diphenyl-1-ethylpyrrolidine ((*R*,*R*)-8): Amide **(*R*,*R*)-32** (0 69 g, 2 6 mmol) was added to the refluxing solution of $LiAlH_4$ (0 70 g, 18 mmol) in THF and the reaction mixture was stirred under reflux for 10 min After cooling down to the room temperature, water (0 70 ml), 15% NaOH (0 70 ml), and water (2 1 ml) were successively added to the reaction mixture and the resulting precipitate was filtered off The filtrate was evaporated in vacuo and the residue was purified with Al_2O_3 column chromatography (benzene) to afford **(*R*,*R*)-8** (0 64 g, 98 %) as a caramel $[\alpha]_D^{20}$-155°(c=1 11, $CHCl_3$) IR ($CHCl_3$) 2800-3000, 1600, 1490, 1450, 1150, 700 ^{1}H-NMR (100M, $CDCl_3$) δ 1 18 (3H, t, *J*=7 Hz, CH_3), 2 5-3 5 (8H, m, CH&CH_2), 7 23 (10H, s, Ar) MS m/z 252 (MH^+), 251 (M^+) Treating with HCl-MeOH gave **7** HCl as needles of mp 234-244° (dec) $[\alpha]_D^{20}$-150°(c=1 01, MeOH) *Anal* Calcd for $C_{18}H_{21}N$ HCl C, 75 11, H, 7 70; N, 4 87. Found C, 75 19, H, 7 73, N, 5 02

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