NEW CHIRAL 3-NAPHTHYLAMINOMETHYL-PYRROLIDINES: AN UNEXPECTED EPIMERISATION REACTION

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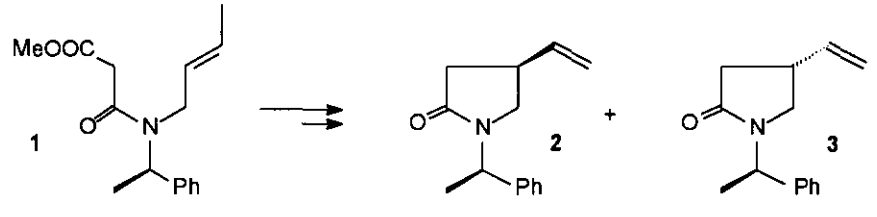
Abstract - New enantiomerically pure 3-naphthylaminomethylpyrrolidines **(8)**, **(9)**, **(14)** and **(15)** were obtained through simple steps starting from chiral 4-ethenylpyrrolidin-2-ones **(2)** and **(3)**. On the other hand, starting from pyrrolidine **(16)**, an epimerisation reaction occurred, which was explained through formation of the bicyclic ammonium salt **(18)**. Nucleophilic addition of Et_2Zn to benzaldehyde, carried out in the presence of **8**, gave (*S*)-1-phenyl-1-propanol in 28% e.e.

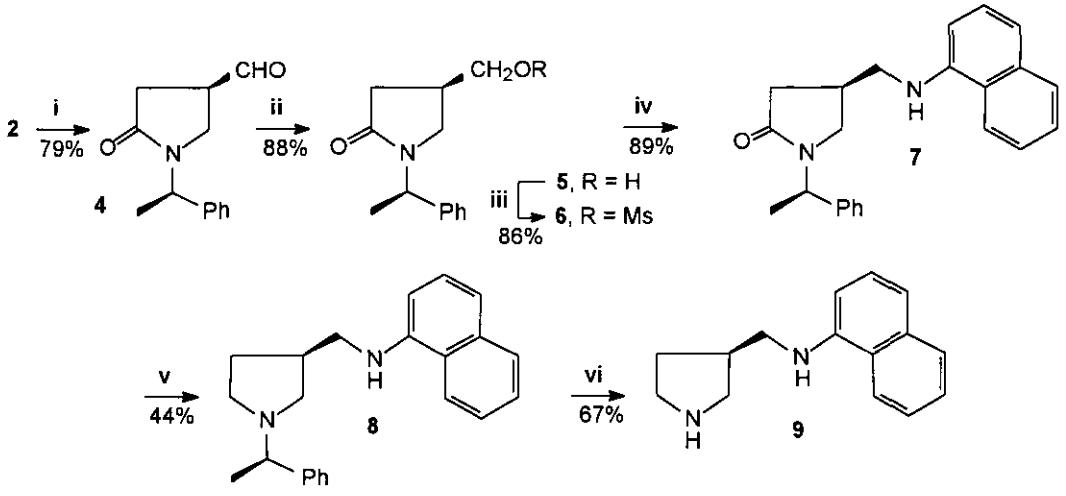
Recently, chiral diamines bearing a pyrrolidine ring have found widespread attention in the chemical and pharmacological fields. In fact, these compounds are known to work as catalysts in a number of reactions, such as nucleophilic additions[1] and kinetic resolutions.[2] On the other hand, much interest arised for such compounds bearing a pyridine nitrogen, owing to their analgesic properties.[3]
Our previous studies on cyclisation of unsaturated acyclic malonamide **(1)** mediated by Mn(III) allowed to prepare 4-ethenylpyrrolidin-2-ones **(2)** and **(3)** with good diastereoselection,[4] and we devised these compounds could be useful starting materials for preparation of chiral diamines which may serve as chiral auxiliaries and ligands in asymmetric synthesis.[1,2]



Scheme 1

Thus, the aldehyde **(4)** was prepared starting from 4-ethenyl derivative **(2)**, and subsequently converted into the corresponding 4-hydroxymethylpyrrolidin-2-one **(5)**.[4] By reaction with methanesulfonyl chloride the mesylate **(6)** was obtained, which then underwent substitution by 1-naphthylamine leading to **7**. By treating this compound with LAH in refluxing THF diamine **(8)** was obtained in moderate yield, together with a substantial amount of the starting material, which was recovered and further reduced to **8**. Finally,

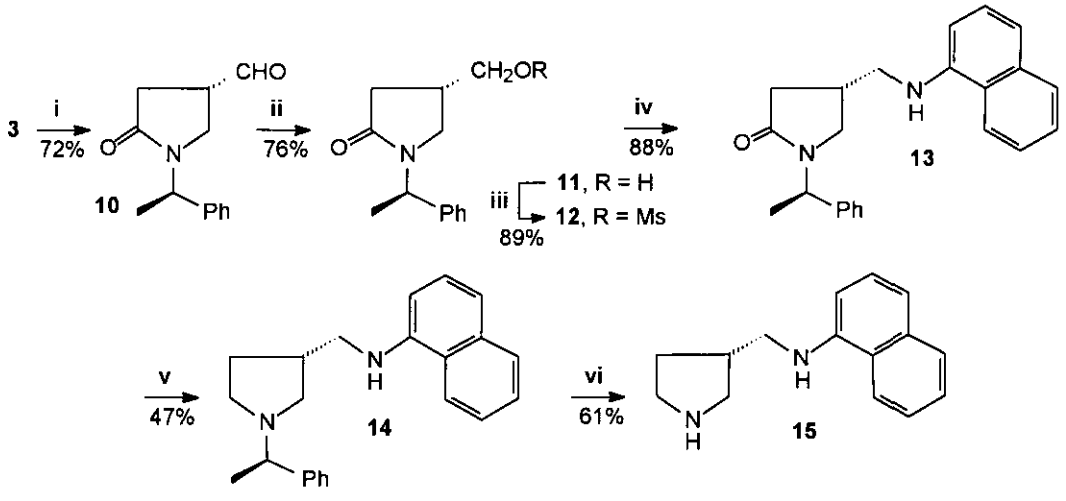
removal of the (*R*)-phenylethyl group was accomplished by treatment of **8** with chloroethyl chlorocarbonate, to give the amine **(9)** in good yield (Scheme 2).[5]



Reagents and conditions: **i.** O_3, -78 °C. **ii.** $NaBH_4$, EtOH. **iii.** $MeSO_2Cl$, Et_3N, DMAP. **iv.** 1-Naphthylamine, 150 °C. **v.** LAH (2 equiv), refluxing THF. **vi.** MeCH(Cl)OCOCl.

Scheme 2

Following the same synthetic pathways, but starting from **3**, amines **(14)** and **(15)** were obtained in comparable yield (Scheme 3).

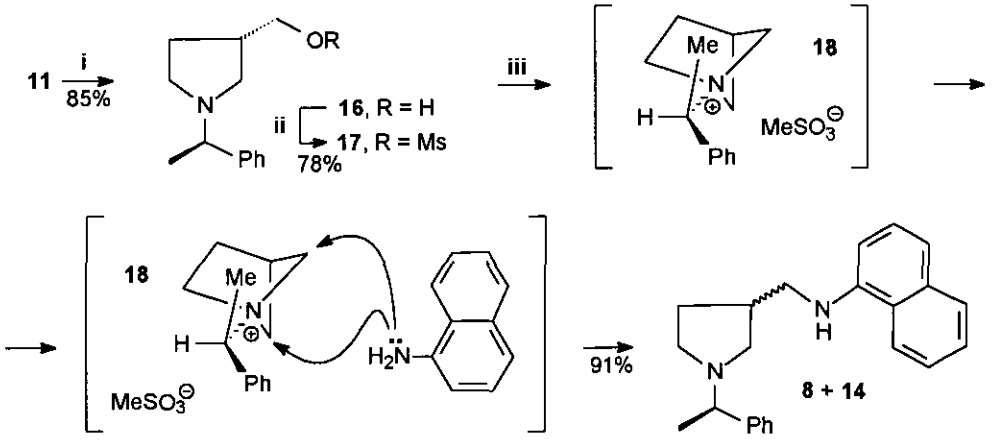


Reagents and conditions: **i.** O_3, -78 °C. **ii.** $NaBH_4$, EtOH. **iii.** $MeSO_2Cl$, Et_3N, DMAP. **iv.** 1-Naphthylamine, 150 °C. **v.** LAH (2 equiv), refluxing THF. **vi.** MeCH(Cl)OCOCl.

Scheme 3

Owing to the tedious recycling of pyrrolidin-2-ones **(7)** and **(13)**, an alternative synthesis for these amines was devised. Thus, **11**, was converted into pyrrolidine **(16)** by treating with LAH in refluxing THF. However, when treating methanesulfonate **(17)** with 1-naphthylamine, the product was an equimolar

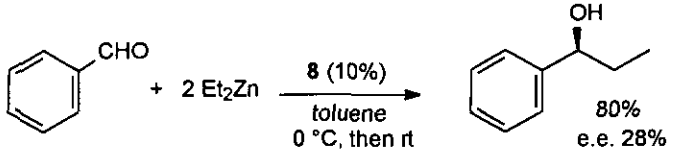
mixture of amines **(8)** and **(14)**, as evidenced by ^{1}H and ^{13}C NMR spectra. In order to explain this result, we postulated the reaction proceeds through the quaternary ammonium salt **(18)**, which arises from an internal substitution reaction. Eventually, this intermediate undergoes non-stereoselective nucleophilic attack by the amine to give an epimeric mixture of **8** and **14**.



***Reagents and conditions*: i.** LAH (2 equiv), refluxing THF. **ii.** $MeSO_2Cl$, Et_3N, DMAP. **iii.** 1-Naphthylamine, 140 °C.

Scheme 4

Amines **(8)** and **(14)** were prepared with the aim to try their activity as chiral catalysts. Thus, in order to ascertain the utility of these compounds, the nucleophilic addition of diethylzinc to benzaldehyde was carried out in the presence of **8**[1] and the reaction afforded (*S*)-1-phenyl-1-propanol in good yield but with only 28% e.e., as determined by specific rotation value of the product (Scheme 5).



Scheme 5

Although the enantiomeric excess is not satisfactory at the present time, modifications of the 3-aminomethyl moiety are currently underway in order to improve the stereoselection.

EXPERIMENTAL

General

Melting points were measured on a Electrothermal IA 9000 apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$ on a Nicolet Fourier Transform Infrared 20-SX spectrophotometer. Diastereomeric ratios were determined by GC analysis using a Chrompack 9001 instrument equipped with a Chrompack 7720 capillary column (50 m x 0.25 mm i.d.; stationary phase CP-Sil-5 CB). ^{1}H and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz, respectively, on a Varian Gemini 200

spectrometer, using $CDCl_3$ as a solvent. Chemical shifts (δ) are reported in ppm relative to TMS and coupling constants (J) in Hz. Assignments were aided by decoupling and homonuclear two-dimensional experiments. Specific rotations were measured on a Perkin Elmer 241 polarimeter. GC-MS analyses were performed with a Hewlett-Packard spectrometer 5890, series II, using a HP-5 capillary column (30 m x 0.25 mm i.d.; stationary phase 5% phenylmethylsilicone). Flash chromatography was performed with silica gel 60 (230-400 mesh). (*R*)-Phenylethylamine, was purchased from Aldrich. Compounds **(2)** and **(3)** were prepared as reported in the literature.[4]

(4*R*,1'*R*)-[1-(1'-Phenylethyl)-2-oxopyrrolidin-4-yl]carboxaldehyde (4)

A solution containing compound **(2)** (4.3 g; 20 mmol) in CH_2Cl_2 (100 mL) was cooled to -78 °C and then O_3 was bubbled until starting material disappeared. Then dimethyl sulphide (DMS, 5 mL) was added and after 3 h the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 50:50), to give **4** (3.4 g; 79%) as a colorless oil. IR ($CHCl_3$): 1715, 1665 cm^{-1}. ^1H NMR: 1.50 (d, 3H, J = 7.2), 2.70 (m, 2H), 3.06 (m, 1H, H_X), 3.09 (dd, 1H, H_A, J_{AX} = 8.4, J_{AB} = 8.4), 3.64 (dd, 1H, H_B, J_{BX} = 2.9, J_{AB} = 8.4), 5.45 (q, 1H, J = 7.2), 7.15 - 7.40 (m, 5 ArH), 9.65 (d, 1H, J = 1.0). ^{13}C NMR: 16.5, 31.9, 41.7, 43.1, 49.9, 127.5, 128.0, 128.3, 129.0, 129.2, 139.9, 171.9, 199.5. $[\alpha]_D$ +73.7° (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 217 (M^+), 202, 188, 160. 146, 118, 105, 91, 77. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.81; H, 6.91; N, 6.40.

(4*R*,1'*R*)-1-(1'-Phenylethyl)-4-hydroxymethylpyrrolidin-2-one (5)

To a solution of aldehyde **(4)** (3.3 g; 15 mmol) in dry ethanol (60 mL) at 0 °C $NaBH_4$ (0.38 g; 10 mmol) was added and solution was stirred for 3 h at 0 °C. Then solid NH_4Cl (3 g) was added and solvent was removed under reduced pressure. To the residue H_2O (10 mL) and ethyl acetate (60 mL) were added and the mixture was extracted with ethyl acetate (3 x 100 mL). The organic layer was then dried (Na_2SO_4) and the residue was purified by silica gel chromatography (ethyl acetate) to give **5** (2.9 g; 88%) as a low-melting solid. IR ($CHCl_3$): 3335, 1668 cm^{-1}. ^1H NMR: 1.51 (d, 3H, J = 7.0), 2.18 - 2.30 (m, 1H), 2.31 - 2.59 (m, 2H), 2.46 (br s, 1H, OH), 3.07 (dd, 1H, H_B, J_{BX} = 7.7, J_{AB} = 10.0), 3.18 (dd, 1H, H_A, J_{AX} = 5.5, J_{AB} = 10.0), 3.54 (dd, 1H, J = 6.7, J = 10.6), 3.62 (dd, 1H, J = 5.6, J = 10.6), 5.46 (q, 1H, J = 7.0), 7.15 - 7.45 (m, 5 ArH). ^{13}C NMR: 16.6, 33.8, 34.9, 45.5, 49.5, 64.9, 127.5, 128.0, 129.0, 140.4, 174.2. $[\alpha]_D$ +152.8° (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 219 (M^+), 204, 160, 146, 132, 128, 105, 91, 77. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.16; H, 7.76; N, 6.35.

(4*R*,1'*R*)-1-(1'-Phenylethyl)-4-methanesulfonyloxymethylpyrrolidin-2-one (6)

To compound **(5)** (4.4 g; 20 mmol) triethylamine (2.7 g; 27 mmol) and *N*,*N*-dimethylaminopyridine (DMAP) (0.3 g) dissolved in ethyl acetate (70 mL) at 0 °C, a solution of methanesulfonyl chloride (2.1 mL; 27 mmol) in ethyl acetate (10 mL) was slowly added. After 3 h at 0 °C the suspension was poured in H_2O-ice and the mixture was extracted with ethyl acetate (3 x 100 mL). The organic layer was dried (Na_2SO_4), the solvent removed under reduced pressure and the residue purified by silica gel chromatography (ethyl acetate) to give **6** (5.1 g; 86%) as a colorless oil. IR ($CHCl_3$): 1678 cm^{-1}. ^1H NMR: 1.53 (d, 3H, J = 7.2), 2.18 - 2.39 (m, 1H), 2.52 - 2.78 (m, 2H), 3.03 (s, 3H), 3.13 (dd, 1H, H_B, J_{BX} = 7.3, J_{AX} = 14.2), 3.19 (dd, 1H, H_A, J_{AX} = 5.6, J_{AB} = 14.2), 4.15 (dd, 1H, J = 7.1, J = 10.4), 4.24 (dd, 1H, J = 5.7, J = 10.4), 5.51 (q, 1H, J = 7.2), 7.25 - 7.41 (m, 5 ArH). ^{13}C NMR: 16.5, 31.4, 34.4, 38.0, 45.1, 49.6, 70.7, 127.6, 128.2, 129.1, 140.1, 172.5. $[\alpha]_D$ +85.0° (c 0.2, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 297 (M^+), 282, 220, 206, 186, 160, 105, 77. Anal. Calcd for $C_{14}H_{29}NO_4S$: C, 56.55; H, 6.44; N, 4.71. Found: C, 56.53; H, 6.41; N, 4.65.

(4*S*,1'*R*)-1-(1'-Phenylethyl)-4-naphthylaminomethylpyrrolidin-2-one (7)

Compound **(6)** (1.9 g; 5.6 mmol) and 1-naphthylamine (5.8 g; 8.4 mmol) under argon atmosphere were heated for 24 h at 150 °C (oil bath). After cooling, to the solid were added first ethyl acetate (100 mL) and then saturated aqueous $NaHCO_3$ (100 mL) and the mixture was then extracted with ethyl acetate (2 x 100 mL). The organic layer was dried (Na_2SO_4), the solvent removed under reduced pressure and the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 50:50), to give 7 (1.7 g; 89%) as a colorless oil. IR ($CHCl_3$): 3350, 1675 cm^{-1}. ^1H NMR: 1.55 (d, 3H, J = 7.2), 2.30 - 2.46 (m, 1H), 2.62 - 2.82 (m, 2H), 3.23 (m, 2H), 3.35 (m, 2H), 4.35 (br s, 1H, NH), 5.55 (q, 1H, J = 7.2), 6.61 (d, 1 ArH, J = 7.0), 7.25 - 7.55 (m, 9 ArH), 7.71 - 7.88 (m, 2 ArH). ^{13}C NMR: 16.7, 31.5, 36.6, 46.8, 48.6, 49,4, 105.0, 118.5, 120.2, 125.4, 126.4, 127.0, 127.6, 128.0, 129.1, 129.2, 134.7, 140.4, 173.6. $[\alpha]_D$ +65.4° (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 344 (M^+), 327, 281, 253, 207, 188, 157, 143, 105, 84. Anal. Calcd for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.16; H, 6.97; N, 8.08.

(3*S*,1'*S*)-1-(1'-Phenylethyl)-3-naphthylaminomethylpyrrolidine (8)

To a solution of **7** (4.71 g; 13.6 mmol) in dry THF (100 mL) under argon atmosphere $LiAlH_4$ (0.5 g; 13.6 mmol) was added and the mixture was refluxed for 4 h. Then methanol (1 mL) and water (5 mL) were added and the mixture was poured into an aqueous saturated solution of Seignette salt (100 mL). The mixture was extracted with ethyl acetate (3 x 100 mL), the organic layer washed with 1 M HCl (100 mL) and, after evaporation under reduced pressure, compound **(7)** (1.9 g; 40%) was recovered. The aqueous layer was then treated with 4 M NaOH until pH 9 and extracted with ethyl acetate (2 x 100 mL). The organic layer was dried (Na_2SO_4) and after removal of the solvent the residue was purified by column chromatography on neutral alumina (cyclohexane:ethyl acetate 95:5) to give **8** (2.0 g; 44%) as a colorless oil. IR ($CHCl_3$): 3345 cm^{-1}. ^1H NMR: 1.55 (d, 3H, J = 7.2), 1.65 - 1.95 (m, 2H), 2.05 - 2.30 (m, 1H), 2.32 - 2.48 (m, 1H), 2.51 - 2.75 (m, 3H), 3.05 - 3.38 (m, 4H), 5.65 (br s, 1H, NH), 6.51 (d, 1 ArH, J = 7.0), 7.18 - 7.55 (m, 9 ArH), 7.75 - 7.88 (m, 1 ArH), 7.95 - 8.05 (m, 1 ArH). ^{13}C NMR: 23.7, 28.8, 30.2, 36.5, 50.1, 53.4, 58.6, 66.6, 103.4, 116.7 120.9, 123.8, 124.8, 126.1, 127.3, 127.4, 127.6, 129.0, 129.1, 134.9, 144.9, 145.7. $[\alpha]_D$ - 87.5° (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 330 (M^+), 315, 253, 225, 187, 172, 156, 128, 105, 91. Anal. Calcd for $C_{23}H_{26}N_2$: C, 83.59; H, 7.93; N, 8.48. Found: C, 83.55; H, 7.87; N, 8.44.

(*R*)-3-Naphthylaminomethylpyrrolidine (9)

To a solution of **8** (1.6 g; 5 mmol) in dichloromethane (20 mL) chloroethyl chlorocarbonate (1.4 g; 10 mmol) was added at 0 °C and after 20 min the solvent was removed under reduced pressure. Then to the residue methanol (40 mL) was added and the solution was refluxed for 30 min. Methanol was removed under reduced presssure and to the residue ethyl acetate (100 mL) and 2 M NaOH (50 mL) were added. After extraction with ethyl acetate (2 x 100 mL), the organic layer was dried (Na_2SO_4) and then the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate:methanol:30% NH_4OH 95:4:1) to give **9** (0.76 g; 67%) as a colorless oil. ^1H NMR: 1.45 - 1.52 (m, 1H), 1.95 - 2.15 (m, 2H), 2.43 - 2.65 (m, 1H), 2.83 (dd, 1H, J = 5.5, J = 10.7), 2.91 - 3.08 (m, 1H), 3.14 (dd, 1H, J = 7.7, J = 10.7), 3.24 (d, 2H, J = 6.7), 6.59 (d, 1ArH, J = 7.0), 7.19 - 7.52 (m, 5 ArH), 7.73 - 7.88 (m, 2 ArH). ^{13}C NMR: 30.8, 38.8, 47.1, 49.0, 51.9, 104.4, 117.5, 120.5, 123.8, 125.1, 126.2, 127.2, 129.1, 134.8, 142.2. $[\alpha]_D$ +20.4° (c 0.2, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 226 (M^+), 208, 182, 180, 156, 143, 128, 115, 83, 68. Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.56; H, 8.08; N, 12.44.

(4*S*,1'*R*)-[1-(1'-Phenylethyl)-2-oxopyrrolidin-4-yl]carboxaldehyde (10)

Starting from **3**, the title compound was prepared in 72% yield as a colorless oil following the same procedure as for aldehyde **(4)**. IR ($CHCl_3$): 1713, 1675 cm^{-1}. ^1H NMR: 1.53 (d, 3H, J = 7.2), 2.67 (dd, 1H, J = 9.4, J = 17.1), 2.77 (dd, 1H, J = 5.9, J = 17.1), 3.01 - 3.21 (m, 1H, H_X), 3.29 (dd, 1H, H_A, J_{AX} =

4.5, J_{AB} = 10.1), 3.51 (dd, 1H, H_B, J_{BX} = 8.5, J_{AB} = 10.1), 5.45 (q, 1H, J = 7.2), 7.18 - 7.41 (m, 5 ArH), 9.52 (d, 1H, J = 1.0). ^{13}C NMR: 16.6, 31.8, 42.0, 43.1, 49.8, 127.4, 128,2, 128.9, 139.9, 172.1, 199.4. $[\alpha]_D$ +68.7° (c 0.5, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 217 (M^+), 202, 188, 160. 146, 118, 105, 91, 77. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.93; H, 6.99; N, 6.48.

(4*S*,1'*R*)-1-(1'-Phenylethyl)-4-hydroxymethylpyrrolidin-2-one (11)

Starting from **10**, the title compound was prepared in 76% yield as a white, low melting solid following the same procedure as for **5**. IR ($CHCl_3$): 3345, 1675 cm^{-1}. ^{1}H NMR: 1.53 (d, 3H, J = 7.1), 1.65 (br s, 1H, OH), 2.18 - 2.34 (m, 1H), 2.42 - 2.66 (m, 3H), 2.81 (dd, 1H, H_B, J_{BX} = 4.7, J_{AB} = 10.0), 3.41 (dd, 1H, H_A, J_{AX} = 7.0, J_{AB} = 10.0), 3.43 - 3.57 (m, 2H), 5.48 (q, 1H, J = 7.1), 7.21 - 7.41 (m, 5 ArH). ^{13}C NMR: 16.6, 33.8, 34.8, 45.5, 49.5, 65.1, 127.8, 128.1, 129.1, 140.4, 174.1 $[\alpha]_D$ +78.7° (c 0.5, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 219 (M^+), 204, 160, 146, 132, 128, 105, 91, 77. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.16; H, 7.75; N, 6.36.

(4*S*,1'*R*)-1-(1'-Phenylethyl)-4-methanesulfonyloxymethylpyrrolidin-2-one (12)

Starting from **11**, the title compound was prepared in 89% yield as a white solid following the same procedure as for **6**. mp 76 °C. IR ($CHCl_3$): 1675 cm^{-1}. ^{1}H NMR: 1.53 (d, 3H, J = 7.1), 2.16 - 2.28 (m, 1H), 2.58 - 2.87 (m, 3H), 2.83 (s, 3H), 3.50 (dd, 1H, H_A, J_{AX} = 7.8, J_{AB} = 10.4), 3.92 (dd, 1H, J = 7.3, J = 9.8), 4.70 (dd, 1H, J = 5.5, J = 9.8), 5.51 (q, 1H, J = 7.1), 7.25 - 7.44 (m, 5 ArH). ^{13}C NMR: 16.4, 31.2, 34.5, 37.7, 44.9, 49.5, 70.7, 117.6, 127.6, 128.2, 129.2, 140.2, 172.5. $[\alpha]_D$ +106.0° (c 0.5, $CHCl_3$).GC-MS (EI, 70 eV): *m/z* 297 (M^+), 282, 220, 206, 186, 160, 105, 77. Anal. Calcd for $C_{14}H_{29}NO_4S$: C, 56.55; H, 6.44; N, 4.71. Found: C, 56.51; H, 6.39; N, 4.67.

(4*R*,1'*R*)-1-(1'-Phenylethyl)-4-naphthylaminomethylpyrrolidin-2-one (13)

Starting from **12**, the title compound was prepared in 88% yield as a colorless oil following the same procedure as for **7**. IR ($CHCl_3$): 3345, 1668 cm^{-1}. ^{1}H NMR: 1.55 (d, 3H, J = 7.2), 2.24 - 2.42 (m, 1H), 2.65 - 2.93 (m, 3H), 3.05 - 3.35 (m, 2H), 3.52 (dd, 1H, H_A, J_{AX} = 7.8, J_{AB} = 10.4), 4.38 (br s, 1H, NH), 5.58 (q, 1H, J = 7.2), 6.51 (d, 1 ArH, J = 7.0), 7.22 - 7.53 (m, 9 ArH), 7.60 - 7.71 (m, 1 ArH), 7.75 - 7.85 (m, 1 ArH). ^{13}C NMR: 16.5, 31,2, 36.6, 46.5, 48.0, 49.4, 104.9, 118.4, 120.1, 125.3, 126.3, 126.9, 127.6, 127.7, 128.1, 129.1,134.8, 140.6, 143.1, 173.6. $[\alpha]_D$ +84.4° (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 344 (M^+), 329, 327, 281, 253, 207, 188, 157, 143, 105, 84. Anal. Calcd for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.14; H, 7.09; N, 8.10.

(3*R*,1'*R*)-1-(1'-Phenylethyl)-3-naphthylaminomethylpyrrolidine (14)

Starting from **13**, the title compound was prepared in 47% yield as a colorless oil following the same procedure as for **8**. IR ($CHCl_3$): 3355 cm^{-1}. ^{1}H NMR: 1.48 (d, 3H, J = 7.1), 1.65 - 1.88 (m, 1H), 2.01 - 2.21 (m, 1H), 2.30 - 2.45 (m, 1H), 2.52 - 2.83 (m, 3H), 2.85 - 2.95 (m, 1H), 3.18 - 3.42 (m, 2H), 3.25 (q, 1H, J = 7.1), 5.51 (br s, 1H, NH), 6.55 (d, 1 ArH, J = 7.0), 7.18 - 7.53 (m, 9 ArH), 7.75 - 8.85 (m, 1 ArH), 7.94 - 8.05 (m, 1 ArH). ^{13}C NMR: 20.1, 28.2, 30.2, 31.4, 52.7, 56.3, 67.8, 125.5, 126.3, 126.4, 126.5, 126.8, 128.7, 129.0, 129.2, 129.6, 130.0, 130.3, 134.8, 136.4. $[\alpha]_D$ +69.6° (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 330 (M^+), 315, 253, 225, 187, 172, 156, 128, 105, 91. Anal. Calcd for $C_{23}H_{26}N_2$: C, 83.59; H, 7.93; N, 8.48. Found: C, 83.51; H, 7.90; N, 8.43.

(*S*)-3-Naphthylaminomethylpyrrolidine (15)

Starting from **14**, the title compound was prepared in 61% yield as a colorless oil following the same procedure as for **9**. $[\alpha]_D$ -20.2 ° (c 0.2, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 226 (M^+), 208, 182, 180, 156, 143, 128, 115, 83, 68. Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.64; H, 7.97;

N, 12.42.

(3*S*,1'*R*)-1-(1'-Phenylethyl)-3-hydroxymethylpyrrolidine (16)

To a solution of **11** (7.4 g; 30 mmol) in dry THF (100 mL) under argon atmosphere $LiAlH_4$ (1.7 g; 45 mmol) was added and the mixture was refluxed for 7 h. Then methanol (1 mL) and water (5 mL) were added and the mixture was poured into an aqueous saturated solution of Seignette salt (100 mL). The mixture was extracted with ethyl acetate (3 x 100 mL), the organic layer was dried (Na_2SO_4) and after removal of the solvent the residue was purified by column chromatography on neutral alumina (chloroform: aqueous NH_3 95:5) to give **16** (5.2 g; 85%) as a colorless oil. IR ($CHCl_3$): 3350 cm^{-1}. ^1H NMR: 1.37 (d, 3H, J = 6.6), 1.58 (m, 1H), 1.78 (br s, 1H, OH), 1.94 (m, 1H), 2.33 (m, 2H), 2.67 (m, 1H), 3.17 (q, 1H, J = 6.6), 3.47 (dd, 1H, J = 5.1, J = 10.0), 3.63 (dd, 1H, J = 4.5, J = 10.0), 7.15 - 7.41 (m, 5 ArH). ^{13}C NMR: 23.6, 27.2, 39,1, 53.2, 57.3, 65.9, 68.2, 127.5, 128.9,145.3. $[\alpha]_D$ +44.2° (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 205 (M^+), 190, 128, 105, 91. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.01; H, 9.29; N, 6.87.

(3*S*,1'*R*)-1-(1'-Phenylethyl)-3-methanesulfonyloxymethylpyrrolidine (17)

Starting from **17**, the title compound was prepared in 78% yield as a colorless oil following the same procedure as for **6**. ^1H NMR: 1.38 (d, 3H, J = 7.1), 1.40 - 1.58 (m, 1H), 1.91 - 2.12 (m, 1H), 2.35 - 2.68 (m, 4H), 2.99 (s, 3H), 3.21 (q, 1H, J = 7.1), 4.14 (d, 2H, J = 7.4), 7.16 - 7.39 (m, 5 ArH). ^{13}C NMR: 23.4, 27.2, 31.2, 37.8, 52.6, 55.7, 65.8, 73.0, 127.5, 127.6, 128.8, 145.6. $[\alpha]_D$ +27.1° (c 0.5, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 283 (M^+), 268, 206, 188, 172, 118, 105, 91, 77. Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.34; H, 7.47; N, 4.94. Found: C, 59.29; H, 7.39; N, 4.87.

(3*RS*,1'*R*)-1-(1'-Phenylethyl)-3-naphthylaminomethylpyrrolidine (8) and (14)

Compound **(17)** (1.4 g; 5.0 mmol) and 1-naphthylamine (5.8 g; 8.4 mmol) under argon atmosphere were heated for 6 h at 150 °C (oil bath). After cooling, to the solid ethyl acetate (100 mL) and aqueous saturated $NaHCO_3$ solution (100 mL) were added. After extraction with ethyl acetate (2 x 100 mL) the organic layer was dried (Na_2SO_4) and then the solvent removed under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 50:50) to give the diastereomeric amines **(8)** and **(14)** (1.5 g; 91%) as an equimolar unseparable mixture. GC-MS (EI, 70 eV): *m/z* 330 (M^+), 315, 253, 225, 187, 172, 156, 128, 105, 91. Anal. Calcd for $C_{23}H_{26}N_2$: C, 83.59; H, 7.93; N, 8.48. Found: C, 83.51; H, 7.90; N, 8.43.

Addition of Diethylzinc to Benzaldehyde Catalyzed by Diamine (8).

To a solution of benzaldehyde (0.48 g; 4.5 mmol) and diamine **(8)** (0.15 g; 0.45 mmol) in dry toluene (10 mL), diethylzinc (1 M solution in toluene; 9.0 mL; 9 mmol) at 0 °C and then the reaction mixture was stirred for 15 h at rt. A saturated NH_4Cl solution (10 mL) and 1 M HCl (10 mL) were added, and the mixture was extracted with ethyl acetate ((2 x 100 mL). The organic layer was washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 80:20), to give (*S*)-1-phenyl-1-propanol (0.5 g; 80%; 28% e.e.) $[\alpha]_D$ -13.3° (c 1, $CHCl_3$) [lit.,[1] -47.0° (c 5.2, $CHCl_3$)].

ACKNOWLEDGEMENT

We thank C.N.R., Rome, for financial support.

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Received, 1st June, 1999