Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 1, pp. 57-66, 1994
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0957-4166/94 $6.00+0.00

0957-4166(93)E0044-W

EASY PREPARATION OF ENANTIOPURE C_2-SYMMETRICAL AMINOALCOHOLS DERIVED FROM m-XYLYLENE DIAMINE.

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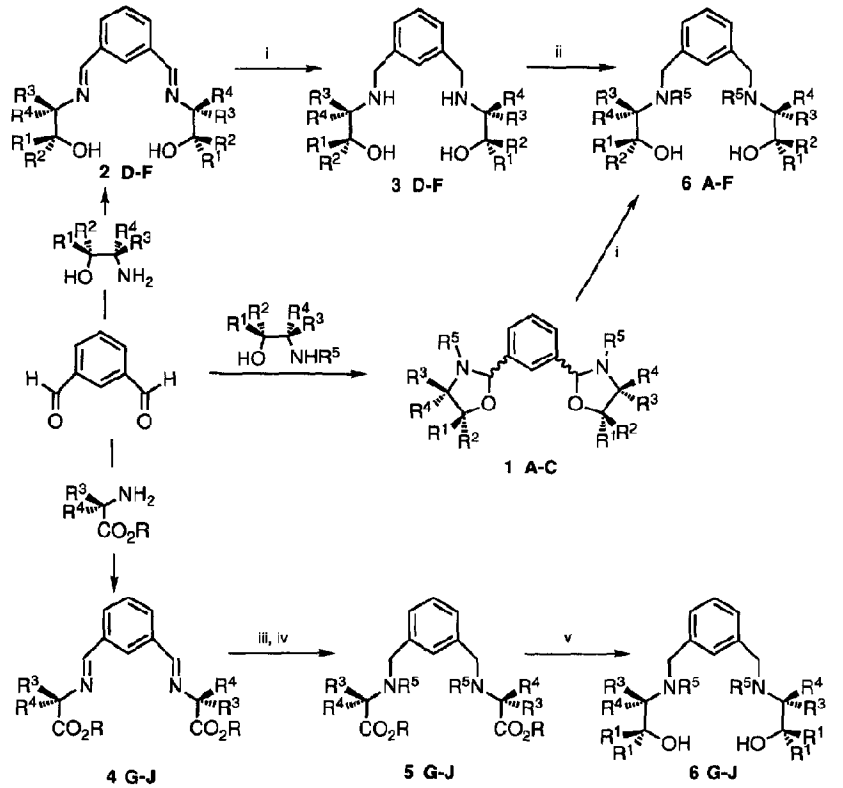
Abstract: The title compounds were prepared by condensation of isophthaldehyde with chiral amino alcohols or α-amino esters in three different ways depending on the substitution pattern. These methods are: for N-substituted amino alcohols, by reduction of the epimeric mixtures of 1,3-oxazolidines formed in the condensation process; for unsubstituted ones, by reduction of the corresponding hydroxy imines, followed by N-alkylation; and for the imines obtained in the condensation with amino esters, by sequential reduction and reaction with methylmagnesium iodide.

Chiral aminoalcohols have been extensively used as modifiers of organometallic reagents for asymmetric reactions,[1-3] and as important materials in the preparation of azacrown derivatives for chiral recognition.[4,5] One of the best rational approaches to the control of the stereoselectivity and the prediction of enantioselectivity is based on the use as ligands molecules possessing only symmetry elements of pure rotation, and the most popular class of such a structures are those having C_2-symmetry.[6,7]

We present here a facile synthesis of polydentate C_2-symmetrical amino alcohols (**6A-J**) that can be used as modifiers of organometallics in catalytic additions and in other type of reactions.[8] Our general method of synthesis is based on the transformation of the condensation products of isophthaldehyde with, readily available, amino alcohols or α-amino esters from chiral pool,[9] and is summarized in the scheme **1**.

We have explored three different ways for the synthesis, depending on the substitution type on the nitrogen in the starting materials, and on the availability of the amino derivative used in the initial condensation.

The most direct access to compounds **6** is represented by the two-step synthesis of **6A-C** from isophthaldehyde in 72-86% total chemical yield. It has been previously described that the condensation of aldehydes with N-alkyl substituted chiral aminoalcohols leads to epimeric mixtures of oxazolidines.[10] Following this methodology, the reaction of isophthaldehyde with the commercially available (+)-(1S,2R)-ephedrine, or the easily prepared (+)-(1S,2R)-N-ethyl- or benzylnorephedrine yields an epimeric (ca. 90:10) mixture of *bis*-1,3-oxazolidines **1A-C**. The diastereomeric constitution at carbon-2 in the heterocycle of these compounds does not constitute a major problem because they are transformed into enantiomerically pure **6A-C** by reduction with lithium aluminium hydride in THF. In the same way, the compound *ent*-**6C** was prepared starting from (-)-(1R,2S)-N-benzylnorephedrine.



compound	6A	6B	6C	*ent*-6C	6D	6E	6F	6G	6H	6I	6J
R											
R^1	Ph	Ph	Ph	H	Ph	Ph	Ph	Me	Me	Me	Me
R^2	H	H	H	Ph	H	H	Ph				
R^3	Me	Me	Me	H	Ph	Ph	H	H	H	Ph	Ph
R^4	H	H	H	Me	H	H	i-Bu	i-Bu	i-Bu	H	H
R^5	Me	Et	Bn	Bn	Me	Et	Me	Me	Et	Me	Et

Scheme 1. *Reagents and conditions*: i; $LiAlH_4$, THF, reflux. ii; R^5-X, Na_2CO_3, CH_3CN, reflux for R^5 = Et, or $HCHO/HCO_2H$, 0°C to 110°C for R^5 = Me. iii; $NaBH_4$, MeOH, R.T. iv; R^5-X, Na_2CO_3, CH_3CN, R.T. v; R^1MgX, Et_2O/THF, 0°C, 2-20 h.

In order to get a method that permits the synthesis of variants with different substituents at the stereocenters we have prepared the *bis*-imino esters **4G** and **4I** by condensation of isophthaldehyde with α-amino esters L-(+)-leucine methyl ester and D-(-)-phenylglycine ethyl ester in good chemical yields. The versatility of these intermediates was shown by their transformation into **5G-H** and **5I-J** respectively by selective reduction of the imine functionality with sodium borohydride in methanol, followed by N-alkylation with methyl or ethyl iodide. The *bis*-aminoalcohols **6G-J** were easily obtained by reaction of the corresponding *bis*-amino esters with methylmagnesium iodide in a mixture of diethyl ether/ THF at 0ºC for 2-20 h.

Surprisingly, attempts to prepare compound **6F** (R^1=R^2= Ph) by the preceeding sequence failed because the reaction of **5G** with phenylmagnesium bromide gave a very complex reaction mixture, where the desired **6F** was only a minor component.

Table 1. Chemical yields for the transformations summarized in Scheme 1.

Compound						Total yield from
1	**2**	**3**	**4**	**5**	**6**	**isophthaldehyde**
1A (quant)[a]					**6A** (80)	(80)
1B (quant)					**6B** (72)	(72)
1C (quant)					**6C** (86)	(86)
ent-**1C** (quant)					*ent*-**6C** (85)	(85)
	2D (quant)	**3D** (77)			**6D** (80)	(62)
					6E (69)	(53)
	2F (quant)	**3F** (50)			**6F** (68)	(34)
			4G (80)	**5G** (67)[b]	**6G** (79)	(42)
				5H (92)[b]	**6H** (80)	(59)
			4I (78)	**5I** (65)[b]	**6I** (73)	(37)
				5J (87)[b]	**6J** (78)	(53)

[a]Quant. means that the crude of the reaction was used in the next step without purification. [b]The yields given refer to the total yields for steps iii and iv.

Instead, compounds **6D-F** were prepared in a different way owing to the availability of the starting chiral aminoalcohols. N-Unsubstituted aminoalcohols react with aldehydes giving mixtures of tautomeric oxazolidines and hydroxy imines, depending on both the structure of the starting compounds and the experimental conditions.[11] In this way we use the commercially available (1S,2R)-2-amino-1,2-diphenylethanol and (S)-2-amino-4-methyl-1,2-diphenylpentanol, prepared by reaction of L-(+)-leucine methyl ester with phenylmagnesium bromide.[12]

Condensation of isophthaldehyde with these N-unsubstituted aminoalcohols gave exclusively hydroxy imines **2D** and **2F**, that were transformed, in good chemical yields, into *bis*-aminoalcohols **3D** and **3F** by

lithium aluminium hydride reduction in THF at reflux. The final **6D** and **6E** (from **3D**) and **6F** (from **3F**) were obtained by N-methylation (formaldehyde, formic acid) or ethylation (ethyl iodide, sodium carbonate). *Bis*-aminoalcohols **6D-F** have been also prepared *via bis*-oxazolidine intermediates. This method implies the prior transformation of the starting N-unsubstituted aminoalcohols into N-monoalkylated ones, but the total yields by this way are lower than that obtained by the hydroxy imino method.

In summary, the methodology described above provides a facile entry to enantiomerically pure C_2-symmetrical *bis*-aminoalcohols by using readily available reagents and very simple reaction conditions. Although the most efficient method is the reductive opening of *bis*-oxazolidines, the choice of the synthetic route will depend on both the availability of the starting materials and the substitution pattern on the final product.

Experimental.

General. Melting points were determined on a Gallenkamp apparatus, in capillary tubes, and are uncorrected. The ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were registered on a Bruker AC 300, using TMS as internal standard. IR spectra were recorded on a Philips PU 9706 Spectrometer, as film or KBr dispersion. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter in a 1 dm. cell, and concentrations are given in g/100 ml. Microanalyses were performed with a Perkin-Elmer 2400-CHN elemental analyzer.

(+)-(1S,2R)-Ephedrine, (+)-(1S,2R)-norephedrine, (-)-(1R,2S)-norephedrine, D-(-)-2-phenylglycine, L-(+)-leucine, (+)-(1S,2R)-2-amino-1,2-diphenylethanol, and isophthaldehyde are commercially available. L-(+)-Leucine methyl ester an D-(-)-2-phenylglycine ethyl ester were prepared by esterification of the corresponding amino acids with anhydrous methanol or ethanol and HCl.[13] (-)-(S)-2-Amino-4-methyl-1,1-diphenylpenthanol was prepared in 62% yield by reaction of (+)-(S)-leucine methyl ester hydrochloride with excess of phenylmagnesium bromide in THF at 0°C for 4 h., and recrystallization.[12]

Condensation of isophthaldehyde with aminoalcohols. General method.

A mixture of a solution of 1.69 g.(12.6 mmol.) of isophthaldehyde and the corresponding aminoalcohol (24 mmol.) in 50 ml. of anhydrous CH_2Cl_2 and 3 g. of molecular sieves was stirred at room temperature until the reaction was finished (TLC, hexane/ethyl acetate: 3/1). The mixture was filtered through a pad of celite, the solvent evaporated on a Rotavapor and the residue, without further purification used in the next step.

^{1}H-NMR analysis shows that in condensations with (+)-(1S,2R)-ephedrine, (+)-(1S,2R)-N-ethyl-, (+)-(1S,2R)-N-benzylnorephedrine and (-)-(1R,2S)-N-benzylnorephedrine the crude of the reactions are constituted by a mixture of *bis*-oxazolidines **1A-C** epimeric at C-2 in the heterocycle; whereas the condensation with N-unsubstituted aminoalcohols, (+)-(1S,2R)-2-amino-1,2-diphenylethanol and (-)-(S)-2-amino-4-methyl- 1,1-diphenylpenthanol leaded to the *bis*-hydroxy imines **2D-F**.

Reduction of bis-oxazolidines to aminoalcohols. A solution of the crude reaction mixture of **1A-C** or **2D-F** in anhydrous THF (40 ml.) was added dropwise to a suspension of 0.91 g. (24 mmol) of $LiAlH_4$ in 80 ml. of the same solvent, and refluxed under nitrogen atmosphere for 2-6 h. The solution was cooled to R.T. and sequentially treated with 0.91 ml of H_2O, 2.7 ml of a 15% NaOH solution and 0.91 ml of H_2O, and stirred for

2 h. The white solids were removed by filtration, the solvent of the filtrate was evaporated on the Rotavapor and the residue was purified by recrystallization or by column chromatography (silica gel, hexane/ethyl acetate: 3/1).

The following compounds were prepared by this way:

(-)-(1R,2S)-bis [N-(2-Hydroxy-1,2-diphenyl)-ethyl]-m-xylylenediamine (3D). 77% yield. White solid, m.p. 182-183°C (from toluene). $[\alpha]_D^{23}$= -25.7 (c= 0.7, $CHCl_3$). ^{1}H-NMR (DMSO-d_6): 3.23 (broad s, 4H, *OH* and *NH*); 3.36 (d, 2H, J= 13.4 Hz, C*H*HAr); 3.53 (d, 2H, J= 13.4 Hz, CH*H*Ar); 3.80 (d, 2H, J= 5.9 Hz, *CH*NH); 4.77 (d, 2H, J= 5.9 Hz, *CH*OH); 6.82-7.22 (m, 24 H, H_{arom}). ^{13}C-NMR (DMSO-d_6): 50.7 (CH_2); 67.8 (*CH*NH); 76.6 (*CH*OH); 126.3, 126.9, 127.1, 127.2, 127.4, 127.7, 128.1, 128.4, 128.8 (CH_{arom}); 140.5, 141.1, 143.4 (C_{arom}). Anal. Calcd. for $C_{36}H_{36}N_2O_2$: C, 81.78; H, 6.86; N, 5.30. Found: C, 81.62; H, 6.75; N, 5.15.

(-)-(1S)-bis [N-(1-isobutyl-2-hydroxy-2,2-diphenyl)-ethyl]-m-xylylenediamine (3F). 50% yield. White solid, m.p. 122-123°C (from pentane). $[\alpha]_D^{23}$= -24.1 (c= 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.82 (d, 6H, J= 6.7 Hz, CH_3CHCH_3); 0.84 (d, 6H, J= 6.7 Hz, CH_3CHCH_3); 1.17-1.40 (m, 6H, CHCH_2CH and $CH(CH_3)_2$); 1.48 (broad s, 2H, *NH*); 3.09 (d, 2H, J= 12.3 Hz, C*H*HAr); 3.35 (d, 2H, J= 12.3 Hz, CH*H*Ar); 3.69 (dd, 2H, J_1= 9.5 Hz, J_2= 1.7 Hz, *CH*N); 4.60 (broad s, 2H, *OH*); 6.76-7.70 (m, 24 H, H_{arom}). ^{13}C-NMR ($CDCl_3$): 21.7 (CH_3CHCH_3); 23.8 (CH_3CHCH_3); 25.5 ($CH(CH_3)_2$); 40.5 (CHCH_2CH); 53.7 (CH_2Ar); 62.7 (*CH*N); 78.5 (*C*OH); 125.7, 126.0, 126.3, 126.5, 126.9, 127.9, 128.0, 128.4 (CH_{arom}); 140.3, 145.0, 147.7 (C_{arom}). Anal. Calcd. for $C_{44}H_{52}N_2O_2$: C, 82.46; H, 8.18; N, 4.37. Found: C, 82.23; H, 8.36; N, 4.19.

(+)-(1R,2S)-bis[N-methyl-N-(2-hydroxy-2-phenyl-1-methyl)-ethyl]-m-xylylenediamine (6A). 80% yield. White solid, m. p. 84-85°C (from hexane/ethyl acetate).$[\alpha]_D^{23}$= +27.5 (c= 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 0.98 (d, 6H, J= 6.8 Hz, CH_3CH); 2.17, s, 6H, CH_3N); 2.91 (dq, 2H, J_1= 6.8 Hz, J_2= 4.8 Hz, CH_3*CH*); 3.34 (broad s, 2H, *OH*); 3.58 (s, 4H, CH_2N); 4.84 (d, 2H, J= 4.8 Hz, *CH*OH); 7.00-7.40 (m, 14 H, H_{arom}.). ^{13}C-NMR ($CDCl_3$): 9.5 (CH_3CH); 38.4 (*CH*$_3$N); 58.9 (CH_2); 63.3(CH$_3$*CH*); 73.7 (*CH*OH); 126.1, 126.8, 127.3, 127.8, 129.1 (CH_{arom}); 139.1, 142.7 (C_{arom}.). Anal. Calcd. for $C_{28}H_{36}N_2O_2$: C,77.74; H, 8.39; N, 6.47. Found: C, 77.74; H, 8.15; N, 6.27.

(+)-(1R,2S)-bis [N-ethyl-N-(2-hydroxy-2-phenyl-1-methyl)-ethyl]-m-xylylenediamine (6B). 72% yield. Colorless oil. $[\alpha]_D^{23}$= +22.2 (c= 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 0.96 (t, 6H, J= 7.0 Hz, CH_3CH); 1.00 (d, 6H, J= 6.8 Hz, CH_3CH$_2$); 2.47 (q, 4H, J= 7.0 Hz, CH$_3$*CH*$_2$); 3.08 (dq, 2H, J_1= 6.8 Hz, J_2= 5.3 Hz, CH$_3$*CH*); 3.20 (broad s, 2H, *OH*); 3.43 (d, 2H, J= 14.1 Hz, C*H*HAr); 3.70 (d, 2H, J= 14.1 Hz, CH*H*Ar); 4.71 (d, 2H, J= 5.3 Hz, *CH*OH); 7.00-7.35 (m, 14 H, H_{arom}.). ^{13}C-NMR ($CDCl_3$): 9.8 (CH_3CH); 12.7 (CH_3CH$_2$); 44.3 (CH$_3$*CH*$_2$); 54.5 (CH_2Ar); 59.8 (*CH*CH$_3$); 74.1 (*CH*OH); 126.2, 126.8, 127.0, 127.7, 128.1, 128.7 (CH_{arom}); 139.7, 142.7 (C_{arom}). Anal. Calcd. for $C_{30}H_{40}N_2O_2$: C, 78.22, H, 8.75; N, 6.08. Found: C, 78.09; H, 8.52; N, 5.95.

(+)-(1R,2S)-bis[N-benzyl-N-(2-hydroxy-2-phenyl-1-methyl)-ethyl]-m-xylylenediamine (6C). 86% yield. White solid. m.p. 64-65°C (from hexane/ethyl acetate). $[\alpha]_D^{23}$= +48.5 (c= 1, CH_2Cl_2). ^{1}H-NMR

($CDCl_3$): 1.14 (d, 6H, J= 6.8 Hz, $\underline{CH_3}CH$); 2.52 (broad s, 2H, $\underline{OH}$); 3.07 (m, 2H, $CH_3\underline{CH}$); 3.38 (d, 2H, J= 13.8 Hz, $C\underline{H}HAr$); 3.41 (d, 2H, J= 13.8 Hz, $C\underline{H}HPh$); 3.68 (d, 4H, J= 13.8 Hz, $CH\underline{H}Ar$ and $CH\underline{H}Ph$); 4.70 (d, 2H, J= 6.2 Hz, $\underline{CH}OH$); 6.90-7.30 (m, 24 H, $\underline{H}_{arom}$). ^{13}C-NMR ($CDCl_3$): 9.0 ($\underline{CH_3}$); 54.4 ($\underline{CH_2}Ph$ and $\underline{CH_2}Ar$); 58.2 ($CH_3\underline{CH}$); 75.4 ($\underline{CH}OH$); 126.6, 127.0, 127.3, 127.8, 128.1, 128.6, 129.1 ($\underline{CH}_{arom}$); 139.6, 139.8, 143.1 ($\underline{C}_{arom}$). Anal. Calcd. for $C_{40}H_{44}N_2O_2$: C, 82.15; H, 7.58; N, 4.79. Found: C, 81.93; N, 7.47; N, 4.65.

(-)-(1S,2R)-bis [N-benzyl-N-(2-hydroxy-2-phenyl-1-methyl)-ethyl]-m-xylylenediamine (*ent*-6C). 85% yield. White solid. m.p. 64-65°C (from hexane/ethyl acetate). $[\alpha]_D^{20}$= -47.2(c= 1, CH_2Cl_2). Anal. Calcd. for $C_{40}H_{44}N_2O_2$: C, 82.15; H, 7.58; N, 4.79. Found: C, 82.31; H, 7.50; N, 4.59.

Methylation of amino alcohols 3D *and* 3F. The reaction was carried out by a slight modification of a previous procedure.[14] A mixture of 1.2 ml (1.16 g, 25 mmol) of an 85% aqueous solution of formic acid, 0.79 g (1.5 mmol) of amino alcohol and 1 ml (0.34 g, 12 mmol) of an 36% aqueous solution of formaldehyde, cooled to 0°C, was stirred until the solid was dissolved, and then the clear solution was heated on an oil bath (110-120°C) for 4 h. The mixture was cooled to room temperature and treated with 20 ml of H_2O and a 2N NaOH solution until pH= 10. The suspension was extracted with CH_2Cl_2 (3x 25 ml), washed with H_2O (3x 20 ml) and dried over anhydrous Na_2SO_4. The solid was eliminated by filtration, the solvent eliminated on Rotavapor, and the residue purified by column chromatography (silica gel, hexane/ethyl acetate: 3/1).

By this procedure were prepared the compounds 6D and 6F.

(+)-(1R,2S)-bis [N-methyl-N-(2-hydroxy-1,2-diphenyl)-ethyl]-m-xylylenediamine (6D). 80% yield. White solid. m.p. 129-130°C (from hexane/toluene). $[a]_D^{23}$= +89.3 (c= 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 2.21 (s, 6H, $\underline{CH_3}N$); 2.82 (broad s, 2H, $\underline{OH}$); 3.25 (d, 2H, J= 13.5 Hz, $C\underline{H}HAr$); 3.57 (d, 2H, J= 13.5 Hz, $CH\underline{H}Ar$); 3.60 (d, 2H, J= 6.0 Hz, $\underline{CH}N$); 5.32 (d, 2H, J= 6.0 Hz, $\underline{CH}OH$); 6.80-7.30 (m, 24 H, $\underline{H}_{arom}$). ^{13}C-NMR ($CDCl_3$): 39.0 ($\underline{CH_3}$); 59.3 ($\underline{CH_2}$); 72.6 ($\underline{CH}N$); 74.8 ($\underline{CH}OH$); 126.5, 127.0, 127.2, 127.4, 127.7, 127.8, 128.1, 128.9, 129.5 ($\underline{CH}_{arom}$); 135.9, 138.8, 141.6 ($\underline{C}_{arom}$). Anal. Calcd. for $C_{38}H_{40}N_2O_2$: C, 81.98; H, 7.24; N, 5.03. Found: C, 81.70; H, 7.27, N, 4.86.

(-)-bis [N-methyl-N-(1-isobutyl-2-hydroxy-2,2-diphenyl)-ethyl]-m-xylylenediamine (6F). 68% yield. White solid. m.p. 126-127°C (from hexane). $[\alpha]_D^{23}$= -105.7 (c= 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.93 (d, 6H, J= 6.3 Hz, $\underline{CH_3}CHCH_3$); 1.09 (d, 6H, J= 6.3 Hz, $CH_3CH\underline{CH_3}$); 1.46 (m, 2H, $(CH_3)_2\underline{CH}$); 1.70 (m, 4H, $CH\underline{CH_2}CH$); 2.03 (s, 6H, $\underline{CH_3}N$); 3.61 (d, 2H, J= 13.0 Hz, $C\underline{H}HAr$); 3.69 (d, 2H, J= 13.0 Hz, $CH\underline{H}Ar$); 3.82 (dd, 2H, J_1= 11.0 Hz, J_2= 2.2 Hz, $C\underline{H}N$); 5.60 (broad s, 2H, $\underline{OH}$); 7.10-7.60 (m, 24 H, $\underline{H}_{arom}$). ^{13}C-NMR ($CDCl_3$): 21.2 ($\underline{CH_3}CHCH_3$); 24.2 ($CH_3CH\underline{CH_3}$); 26.1 ($(CH_3)_2\underline{CH}$); 37.5 ($CH\underline{CH_2}CH$); 38.3 ($\underline{CH_3}N$); 61.6 ($\underline{CH_2}N$); 68.4 ($\underline{CH}N$); 78.8 ($\underline{C}OH$); 126.5, 126.9, 127.2, 127.3, 127.8, 127.9, 128.5, 129.0 ($\underline{CH}_{arom}$); 139.5, 144.5, 146.1 ($\underline{C}_{arom}$). Anal. Calcd. for $C_{46}H_{56}N_2O_2$: C, 82.59; H, 8.44; N, 4.19. Found: C, 82.77; H, 8.49; N, 4.32.

Alkylation with alkyl iodides.[15] A mixture of aminoalcohol or aminoester (3 mmol), the corresponding alkyl iodide (24 mmol) and Na_2CO_3 (24 mmol) in 50 ml of acetonitrile was stirred at room temperature for 24 h

(for methyl iodide) or refluxed for 48 h (for ethyl iodide). The solid was separated by filtration, the filtrate was concentrated under reduced pressure and the residue purified by column chromatography (silica gel, hexane/ethyl acetate: 5/1).

Following this method the compound **6E** was prepared from **3D**.

(+)-(1R,2S)-bis [N-ethyl-N-(2-hydroxy-1,2-diphenyl)-ethyl]-m-xylylenediamine (6E). 69% yield. White solid. m. p. 59-60ºC. $[\alpha]_D^{23}$= +22.8(c= 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.91(t, 6H, J= 7 Hz, $\underline{CH_3}CH_2$); 2.34 (m, 2H, $CH_3C\underline{H}H$); 2.50 (broad s, 2H, $\underline{OH}$); 2.66 (m, 2H, 2H, $CH_3C\underline{H}H$); 3.21 (d, 2H, J= 14.2 Hz, $C\underline{H}HAr$); 3.72 (d, 2H, J= 14.2 Hz, $C\underline{H}HAr$); 3.87 (d, 2H, J= 7.1 Hz, $N\underline{CH}Ph$); 5.23 (d, 2H, J= 7.1 Hz, $HO\underline{CH}Ph$); 6.80-7.30 (m, 24 H, $\underline{H}_{arom}$). ^{13}C-NMR ($CDCl_3$): 11.2 ($\underline{CH_3}$-CH_2); 43.3 (CH_3-$\underline{CH_2}$); 54.1 ($\underline{CH_2}Ar$); 70.2 ($\underline{CH}N$); 73.1($\underline{CH}OH$); 126.8, 127.2, 127.4, 127.7, 127.9, 128.0, 128.2, 128.4, 129.5 ($\underline{CH}_{arom}$); 136.2, 139.5, 141.9 ($\underline{C}_{arom}$). Calc. for $C_{40}H_{44}N_2O_2$: C, 82.15; H, 7.58; N, 4.79. Found: C, 81.32; H, 7.47; N, 4.53.

Condensation of isophthaldehyde with α-amino esters. General procedure.

A mixture of a solution of 2.82 g (21 mmol) of isophthaldehyde and the corresponding amino ester (40 mmol) in 100 ml of anhydrous CH_2Cl_2, and 3 g of molecular sieves was stirred at R. T. for 2h. The molecular sieves were separated by filtration and the solvent was evaporated under reduced pressure. The residue, without further purification, was used in the next step. Diimines **4G** and **4I** prepared by this procedure were identified by their spectral data, that are as follows:

4G. ^{1}H-NMR ($CDCl_3$): 0.90 (d, 6H, J= 6.0 Hz, $\underline{CH_3}CHCH_3$); 0.95 (d, 6H, J= 6.1 Hz, $CH_3CH\underline{CH_3}$); 1.58 (m, 2H, $(CH_3)_2\underline{CH}$); 1.86 (m, 4H, $CH\underline{CH_2}CH$); 3.74 (s, 6H, $\underline{CH_3}O$); 4.11 (t, 2H, J= 6.9 Hz, $\underline{CH}N$); 7.30-8.20 (m, 4H, $\underline{H}_{arom}$); 8.33 (s, 2H, $\underline{CH}$=N). IR (film): 1730, 1635 cm.$^{-1}$

4I. ^{1}H-NMR ($CDCl_3$): 1.23 (t, 6H, J= 7.1 Hz, $\underline{CH_3}CH_2$); 4.20 (q, 4H, J= 7.1 Hz, $CH_3\underline{CH_2}$); 5.21 (s, 2H, $\underline{CH}Ph$); 7.20-8.20 (m, 14 H, $\underline{H}_{arom}$); 8.35 (s, 2H, $\underline{CH}$=N). IR (film): 1730, 1635 cm.$^{-1}$

Reduction of iminoesters with sodium borohydride. The crudes of the condensation reactions were taken in 100 ml of MeOH cooled at 0ºC, and 1.9 g (50 mmol) of powdered $NaBH_4$ were added in portions. The suspension was stirred at that temperature for 2h, and then hydrolysed by addition of 100 ml of a saturated solution of NH_4Cl and allowed to rise to R.T. The solvents were eliminated under reduced pressure, the residue extracted with CH_2Cl_2 (3x 50 ml), and the extract was dried over anhydrous Na_2SO_4; after filtration of the solid, the solvent was removed and the residue purified by column chromatography (silica gel, hexane/ethyl acetate: 3/1). The spectral and analytical data for the reduced compounds are as follows:

(-)-(1S)-bis [N-(1-isobutyl-1-ethoxycarbonyl)-methyl]-m-xylylenediamine (4'G). 80% yield. White solid, m.p. 31-32ºC (from hexane). $[\alpha]_D^{23}$= -51.8 (c= 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.85 (d, 6H, J= 6.2 Hz, $\underline{CH_3}CHCH_3$); 0.91 (d, 6H, J= 6.2 Hz, $CH_3CH\underline{CH_3}$); 1.47 (t, 4H, J= 7 Hz, $CH\underline{CH_2}CH$); 1.71 (s, 2H, $\underline{NH}$); 1.80 (m, 2H, $(CH_3)_2\underline{CH}$); 3.30 (t, 2H, J= 7.1 Hz, $\underline{CH}CO_2Me$); 3.56 (d, 2H, J= 13.0 Hz, $C\underline{H}HAr$); 3.81 (d, 2H, J= 13.0 Hz, $CH\underline{H}Ar$); 3.72 (s, 6H, $\underline{CH_3}OCO$); 7.10-7.30 (m, 4H, $\underline{H}_{arom}$). ^{13}C-NMR ($CDCl_3$):

22.1 ($\underline{CH_3}CHCH_3$); 22.8 ($CH_3CH\underline{CH_3}$); 24.8 ($\underline{CH}(CH_3)_2$); 42.8 ($CH\underline{CH_2}CH$); 51.4 ($\underline{CH_3}OCO$); 52.1 ($\underline{CH_2}Ar$); 59.3 ($\underline{CH}N$); 126.9, 128.0, 128.3 ($\underline{CH}_{arom}$); 140.1 ($\underline{C}_{arom}$); 176.4 ($\underline{CO_2}Me$).

(-)-(1R)-bis [N-(1-ethoxycarbonyl-1-phenyl)-methyl]-m-xylylenediamine (4'I). 78% yield. Colorless oil. $[\alpha]_D^{23}$= -75.9 (c= 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 1.19 (t, 6H, J= 7.1 Hz, $\underline{CH_3}CH_2$); 2.27 (broad s, 2H, $\underline{NH}$); 3.72 (s, 4H, $\underline{CH_2}Ar$); 4.15 (q, 4H, J= 7.1 Hz, $CH_3\underline{CH_2}$); 4.37 (s, 2H, $\underline{CH}Ph$); 7.20-7.50 (m, 14 H, $\underline{H}_{arom}$). ^{13}C-NMR ($CDCl_3$): 13.8 ($\underline{CH_3}$); 51.0 ($CH_3\underline{CH_2}$); 60.6 ($\underline{CH_2}Ar$); 64.2 ($\underline{CH}Ph$); 126.7, 127.2, 127.6, 127.9, 128.2 ($\underline{CH}_{arom}$); 138.0, 139.5 ($\underline{C}_{arom}$); 172.5 ($\underline{CO_2}Et$).

The preceding compounds were transformed into **5G** and **5H** (from **4'G**), and **5I** and **5J** (from **4'I**) respectively by alkylation as described above for aminoalcohols.

(-)-(1S)-bis [N-methyl-N-(1-isobutyl-1-ethoxycarbonyl)-methyl]-m-xylylenediamine (5G). 67% yield. Colorless oil. $[\alpha]_D^{23}$= -94.2 (c= 1.1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.86 (d, 6H, J= 6 Hz, $\underline{CH_3}CHCH_3$); 0.91 (d, 6H, J= 6 Hz, $CH_3CH\underline{CH_3}$); 1.50-2.00 (m, 6H, $CH\underline{CH_2}CH$, and $(CH_3)_2\underline{CH}$); 2.25 (s, 6H, $\underline{CH_3}N$); 3.40 (t, 2H, J= 7.2 Hz, $N\underline{CH}CH_2$); 3.54 (d, 2H, J= 13.6 Hz, $C\underline{H}HAr$); 3.72 (s, 6H, $\underline{CH_3}OCO$); 3.79 (d, 2H, J= 13.6 Hz, $CH\underline{H}Ar$); 7.10-7.30 (m, 4H, $\underline{H}_{arom}$). ^{13}C-NMR ($CDCl_3$): 22.0 ($\underline{CH_3}CHCH_3$); 23.0 ($CH_3CH\underline{CH_3}$); 24.8 ($\underline{CH}(CH_3)_2$); 37.7 ($\underline{CH_3}N$); 38.7 ($\underline{CH_2}CH$); 50.8 ($\underline{CH_3}OCO$); 58.5 ($\underline{CH_2}Ar$); 63.7 ($\underline{CH}N$); 127.3, 128.1, 129.1 ($\underline{CH}_{arom}$); 139.7 ($\underline{C}_{arom}$); 173.4 ($\underline{CO_2}Me$).

(-)-(1S)-bis [N-ethyl-N-(1-isobutyl-1-ethoxycarbonyl)-methyl]-m-xylylenediamine (5H). 92% yield. Colorless oil. $[\alpha]_D^{23}$= -146.2 (c= 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.79 (d, 6H, J= 7.1 Hz, $\underline{CH_3}CHCH_3$); 0.87 (d, 6H, J= 7.1 Hz, $CH_3CH\underline{CH_3}$); 1.03 (t, 6H, J= 7.1 Hz, $\underline{CH_3}CH_2$); 1.40-2.00 (m, 6H, $CH\underline{CH_2}CH$ and $(CH_3)_2\underline{CH}$); 2.58 (m, 4H, $CH_3\underline{CH_2}$); 3.46 (m, 2H, $\underline{CH}N$); 3.48 (d, 2H, J= 14.3 Hz, $C\underline{H}HAr$); 3.71 (s, 6H, $\underline{CH_3}OCO$); 3.95 (d, 2H, J= 14.3 Hz, $CH\underline{H}Ar$); 7.10-7.40 (m, 4H, $\underline{H}_{arom}$). ^{13}C-NMR ($CDCl_3$): 13.8 ($\underline{CH_3}CH_2$); 21.6 ($\underline{CH_3}CHCH_3$); 23.0 ($CH_3CH\underline{CH_3}$); 24.4 ($(CH_3)_2\underline{CH}$); 38.9 ($CH\underline{CH_2}CH$); 44.6 ($CH_3\underline{CH_2}$); 50.7 ($\underline{CH_3}OCO$); 54.4 ($\underline{CH_2}Ar$); 59.7 ($\underline{CH}N$); 126.9, 127.7, 128.7 ($\underline{CH}_{arom}$); 140.3 ($\underline{C}_{arom}$); 174.0 ($\underline{CO_2}Me$).

(-)-(1R)-bis [N-methyl-N-(1-ethoxycarbonyl-1-phenyl)-methyl]-m-xylylenediamine (5I). 65% yield. Colorless oil. $[\alpha]_D^{23}$= -39.4 (c= 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.24 (t, 6H, J= 7.1 Hz, $\underline{CH_3}CH_2$); 2.21 (s, 6H, $\underline{CH_3}N$); 3.49 (d, 2H, J= 13.4 Hz, $C\underline{H}HAr$); 3.69 (d, 2H, J= 13.4 Hz, $CH\underline{H}Ar$); 4.20 (q, 4H, J= 7.1 Hz, $CH_3\underline{CH_2}$); 4.31 (s, 2H, $\underline{CH}Ph$); 7.20-7.60 (m, 14 H, $\underline{H}_{arom}$). ^{13}C-NMR ($CDCl_3$): 14.1 ($\underline{CH_3}CH_2$); 38.9 ($\underline{CH_3}N$); 58.3 ($CH_3\underline{CH_2}$); 60.4 ($\underline{CH_2}Ar$); 71.9 ($\underline{CH}Ph$); 127.5, 127.9, 128.0, 128.3, 128.6, 129.2 ($\underline{CH}_{arom}$); 136.6, 138.6 ($\underline{C}_{arom}$); 171.7 ($\underline{CO_2}Et$).

(-)-(1R)-bis [N-ethyl-N-(1-ethoxycarbonyl-1-phenyl)-methyl]-m-xylylenediamine (5J). 87% yield. Colorless oil. ^{1}H-NMR ($CDCl_3$): 1.00 (t, 6H, J= 7.1 Hz, $\underline{CH_3}CH_2N$); 1.27 (t, 6H, J= 7.1 Hz, $\underline{CH_3}CH_2OCO$); 2.64 (q, 4H, J= 7.1 Hz, $CH_3\underline{CH_2}N$); 3.72 (s, 4H, $\underline{CH_2}Ar$); 4.23 (q, 4H, J= 7.1 Hz, $CH_3\underline{CH_2}OCO$); 4.62 (s, 2H, $\underline{CH}Ph$); 7.20-7.45 (m, 14 H, $\underline{H}_{arom}$).

Reaction of amino esters **5G-J** *with methylmagnesium iodide. General method.* To a solution of 2 mmol of the corresponding amino ester in 150 ml of anhydrous THF, cooled on an ice bath, and under nitrogen atmosphere, were dropped 16 ml (16 mmol) of an 1 M solution of methylmagnesium iodide in diethyl ether. The solution was stirred at 0ºC until the reaction was finished (2-20 h) as shown by TLC, then quenched by addition of 40 ml of a saturated solution of NH_4Cl. The mixture was extracted with Et_2O (2x 25 ml), the organic layer was washed with brine and water, and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvents under reduced pressure, the residue was purified by column chromatography (silica gel, hexane/ethyl acetate: 5/1). The spectral and analytical data of the compounds prepared in this way are as follows:

(-)-(1S)-bis[N-methyl-N-(1-isobutyl-2-hydroxy-2,2-dimethyl)-ethyl]-m-xylylenediamine (6G). 79% yield. Colorless oil. $[\alpha]_D^{23}$= -2.4 (c= 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 1.00 (d, 12 H, J= 6.1 Hz, ($\underline{CH_3}$)$_2$CH); 1.14 (s, 6H, $\underline{CH_3}$COHCH$_3$); 1.19 (s, 6H, CH$_3$COH$\underline{CH_3}$); 1.75 (m, 6H, CH$\underline{CH_2}$CH and $\underline{CH}$(CH$_3$)$_2$); 2.31 (s, 6H, $\underline{CH_3}$N); 2.70 (dd, 2H, J_1= 10.0 Hz, J_2= 3.2 Hz, $\underline{CH}$N); 3.66 (d, 2H, J= 13.2 Hz, C$\underline{H}$HAr); 3.92 (d, 2H, J= 13.2 Hz, CH$\underline{H}$Ar); 4.65 (broad s, 2H, $\underline{OH}$); 7.24 (m, 4H, $\underline{H}_{arom}$). ^{13}C-NMR ($CDCl_3$): 21.5, 23.9, 24.9, 28.5 ($\underline{CH_3}$); 26.1 ($\underline{CH}$(CH$_3$)$_2$); 36.2 (CH$\underline{CH_2}$CH); 39.2 ($\underline{CH_3}$N); 61.3 ($\underline{CH_2}$Ar); 70.1 ($\underline{CH}$N); 71.2 ($\underline{C}$OH); 127.2, 128.6 ($\underline{CH}_{arom}$); 139.9 ($\underline{C}_{arom}$). Anal. Calcd. for $C_{26}H_{48}N_2O_2$: C, 74.23; H, 11.50; N, 6.66. Found: C, 74.05; H, 11.37; N, 6.38.

(-)-(1S)-bis[N-ethyl-N-(1-isobutyl-2-hydroxy-2,2-dimethyl)-ethyl]-m-xylylenediamine (6H). 80% yield. Colorless oil. $[\alpha]_D^{23}$= +43.4 (c= 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 0.99 (d, 12 H, J= 7.2 Hz, ($\underline{CH_3}$)$_2$CH); 1.00 (t, 6H, J= 7.0 Hz, $\underline{CH_3}$CH$_2$); 1.13 (s, 6H, $\underline{CH_3}$CCH$_3$); 1.15 (s, 6H, CH$_3$C$\underline{CH_3}$); 1.50-2.00 (m, 6H, CH$\underline{CH_2}$CH and $\underline{CH}$(CH$_3$)$_2$); 2.50-2.80 (m, 6H, CH$_3\underline{CH_2}$N and $\underline{CH}$N); 3.52 (d, 2H, J= 13.8 Hz, C$\underline{H}$HAr); 4.00 (d, 2H, J= 13.8 Hz, CH$\underline{H}$Ar); 4.62 (broad s, 2H, $\underline{OH}$); 7.25 (m, 4H, $\underline{H}_{arom}$). ^{13}C-NMR ($CDCl_3$): 14.5 ($\underline{CH_3}$CH$_2$); 21.9 ($\underline{CH_3}$CHCH$_3$); 23.6 (CH$_3$CH$\underline{CH_3}$); 24.9 ($\underline{CH_3}$CCH$_3$); 25.8 ($\underline{CH}$(CH$_3$)$_2$); 28.5 (CH$_3$C$\underline{CH_3}$); 36.3 (CH$\underline{CH_2}$CH); 46.9 (CH$_3\underline{CH_2}$); 55.9 ($\underline{CH_2}$Ar); 65.2 ($\underline{CH}$N); 70.4 ($\underline{C}$OH); 127.0, 128.3 ($\underline{CH}_{arom}$); 140.2 ($\underline{C}_{arom}$). Anal. Calcd. for $C_{28}H_{52}N_2O_2$: C, 74.95; H, 11.68; N, 6.24. Found: C, 74.68; H, 11.83; N, 6.04.

(-)-(1R)-bis[N-methyl-N-(2-hydroxy-2,2-dimethyl-1-phenyl)-ethyl]-m-xylylenediamine (6I). 73% yield. Colorless oil. $[\alpha]_D^{23}$= -40.9(c= 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.26 (s, 6H, $\underline{CH_3}$CCH$_3$); 1.29 (s, 6H, CH$_3$C$\underline{CH_3}$); 2.26 (s, 6H, $\underline{CH_3}$N); 3.10 (broad s, 2H, $\underline{OH}$); 3.29 (d, 2H, J= 13.3 Hz, C$\underline{H}$HAr); 3.49 (s, 2H, $\underline{CH}$N); 3.80 (d, 2H, J= 13.3 Hz, CH$\underline{H}$Ar); 7.20-7.40 (m, 14 H, $\underline{H}_{arom}$). ^{13}C-NMR ($CDCl_3$): 27.7 $\underline{CH_3}$CCH$_3$); 29.4 (CH$_3$C$\underline{CH_3}$); 40.6 ($\underline{CH_3}$N); 60.7 ($\underline{CH_2}$Ar); 73.6 ($\underline{C}$OH); 76.0 $\underline{CH}$Ph); 127.2, 127.4, 127.7, 128.2, 129.0, 130.8 ($\underline{CH}_{arom}$); 135.5, 139.7 ($\underline{C}_{arom}$). Anal.Calcd. for $C_{30}H_{40}N_2O_2$: C, 78.22; H, 8.75; N, 6.08. Found: C, 77.99; H, 8.59; N, 6.10.

(-)-(1R)-bis [N-ethyl-N-(2-hydroxy-2,2-dimethyl-1-phenyl)-ethyl]-m-xylylenediamine (6J). 78% yield. White solid, m.p. 95-96ºC. $[\alpha]_D^{23}$= -147.7 (c= 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 1.11 (t, 6H, J= 7.1 Hz, $\underline{CH_3}$CH$_2$); 1.24 (s, 6H, $\underline{CH_3}$CCH$_3$); 1.27 (s, 6H, CH$_3$C$\underline{CH_3}$); 2.28 (m, 2H, CH$_3$C$\underline{H}$HN); 2.70-3.04 (m, 4H, CH$_3$CH$\underline{H}$N and $\underline{OH}$); 3.05 (d, 2H, J= 14.1 Hz, C$\underline{H}$HAr); 3.53 (s, 2H, $\underline{CH}$Ph); 4.18 (d, 2H, J=

14.1Hz, CH*H*Ar); 7.20-7.50 (m, 14 H, *H*arom). ^{13}C-NMR ($CDCl_3$): 13.9 (*C*H_3CH$_2$); 28.2 (*C*H_3CCH$_3$); 29.2 (CH$_3$C*C*H_3); 46.0 (CH$_3$*C*H_2); 56.2 (*C*H_2Ar); 71.7 (*C*HPh); 73.3 (*C*OH); 127.0, 127.7, 128.1, 128.5, 130.8 (*C*Harom); 136.3, 140.6 (*C*arom). Anal. Calcd. for $C_{32}H_{44}N_2O_2$: C, 78.64; H, 9.07; N, 5.73. Found: C, 78.53; H, 9.19; N, 5.62.

Acknowledgements.

Authors thank the financial support provided by the Spanish DGICYT (Project PB89-0356). One of us (M.A.M.) thanks to the Universidad de Valladolid for a predoctoral fellowship.

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(*Received in UK* 12 *October* 1993)