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Synthesis and resolution of axially chiral C_2-symmetric 1,1′-binaphthyl-substituted tetramethylethylenediamines[1]

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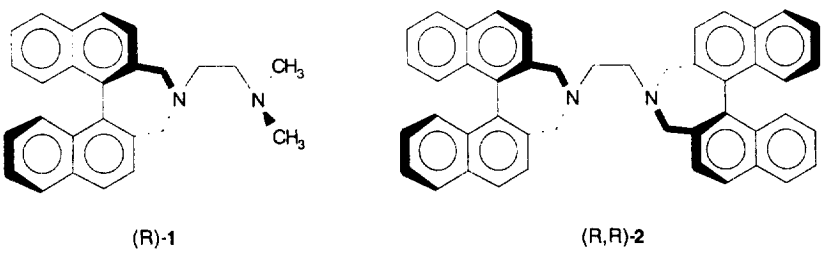
Abstract: The axially chiral TMEDA derivatives **1** and **2** in which tetramethylethylenediamine is substituted respectively by one and two 1,1′-binaphthyl units at their 2,2′-positions, are of interest as chiral catalysts. Experimental details of their preparation in enantiomerically pure form are given. Two different routes have been followed, involving alkylation of both N,N-dimethyl ethylenediamine and ethylenediamine by 2,2′-*bis*-(bromomethyl)-1,1′-binaphthyl either enantiomerically pure as prepared from resolved 1,1′-binaphthyl-2,2′-dicarboxylic acid or racemic, the resulting racemic diamines **1** and **2** being then resolved with dibenzoyl-tartaric acid. © 1997 Elsevier Science Ltd

The diamines **1** and **2** (Figure 1), in which a tetramethylethylenediamine moiety is substituted respectively by one and two 1,1′-binaphthyl units at their 2,2′-positions, were designed in the 80s by D. J. Cram as interesting new potential chiral catalysts for asymmetric induction in reactions of organometallic reagents. We synthesized these compounds and found them to be highly efficient chiral auxiliaries for the stoichiometric catalysis of the addition of alkyllithiums to aldehydes.[2] Chiral complexes of the diamine (*R,R*)-**2** were also shown to be efficient catalysts in polymerization of methacrylate esters.[3]



(R)-**1** (R,R)-**2**

Figure 1. Axially chiral binaphthyl-substituted teramethylethylenediamines with C_2-symmetry.

Rosini *et al.*[4] have recently reported the synthesis of (*S*)-**1** and its use as a stoichiometric catalyst in the enantioselective *syn*-dihydroxylation of olefins by osmium tetroxide, with ees up to 98%. As pointed out by these authors, the diamines **1** and **2** are also likely to be employed as catalytic precursors for stereoselective processes involving transition metal complexes. The potential utility of these compounds for further studies prompts us to publish the experimental details of our preparation of all their enantiomers.

Results and discussion

As previously pointed out,[2] two synthetic approaches were used, both of them involving 2,2′-*bis*-(bromomethyl)-1,1′-binaphthyl **5** as the key intermediate. In a first approach,[4] the enantiomerically pure enantiomers of the dibromide **5** of known absolute configuration (−)-(*S*); (+)-(*R*)

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were prepared from resolved 1,1′-binaphthyl-2,2′-dicarboxylic acid, and reacted with both N,N-dimethylethylenediamine and ethylenediamine to give the enantiomerically pure diamines **1** and **2**. In this way the absolute configurations as well as the maximum specific rotations of **1** and **2** were determined. In the second approach, the same *bis*-alkylation reactions as above, using readily available racemic 2,2′-*bis*-(bromomethyl)-1,1′-binaphthyl, led to the racemic diamines **1** and **2**, which were then resolved to their enantiomerically pure enantiomers, as checked by comparison with the former samples.

Resolution of the diacid (RS)*-4 through a new quinine salt*

The preparation of 1,1′-binaphthyl-2,2′-dicarboxylic acid **4** was carried out as reported in literature.[5] A 6-step sequence starting from 2-methyl-naphthalene led to 1-bromo-2-naphthoic acid methyl ester, which was submitted to Ullmann coupling at 270–280°C for 0.5 h without solvent, in the presence of freshly activated copper bronze (Figure 2).[6] Saponification of the resulting (*R,S*)-**3** as reported[5] led to (*R,S*)-**4**.[7]

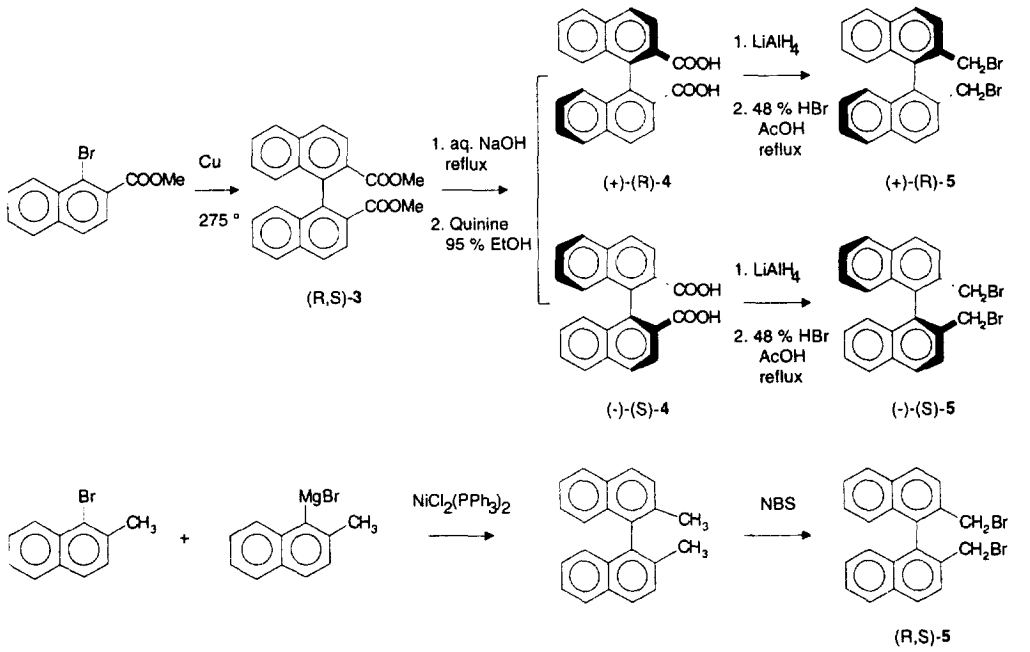

Figure 2. Synthesis of the racemic dibromide (*R,S*)-**5** and its enantiomers.

Resolution of 1,1′-binaphthyl-2,2′-dicarboxylic acid through its quinine salts had been previously reported by Hall and Turner.[5] From equimolar amounts of *anhydrous* (*RS*)-**4** and *anhydrous* quinine in ethanol/ether, the authors obtained a less soluble salt, mp=178°C, $[\alpha]_{546}^{23} = -103.5$ (c 1.1; acetone), leading after decomposition to (−)-(*S*)-**4**, $[\alpha]_{546}^{22} = -125.2$ (c 1; 0.1 M NaOH) and a more soluble salt, mp=184–190°C, $[\alpha]_{546}^{22} = +11.6$ (c 0.99; acetone), leading to (+)-(*R*)-**4**, $[\alpha]_{546}^{22} = +124.2$ (c 1.1; 0.1 M NaOH). However, the efficiency of the resolution was low and the procedure was quite tedious since the salt of higher rotation was not always composed of enantiomerically pure **4**.[8] In our hands, very small experimental differences resulted in a dramatic change concerning salt formation: when (*RS*)-**4** was mixed with 1.1 equivalent mol/mol of commercial quinine in *95% ethanol*, a new quinine salt of the (−)-(*S*)-**4** enantiomer was obtained. Reproducibility in getting this same salt was perfect in numerous experiments realized on either small or medium scale, although variations in the crystallization process were observed. In some cases, crystallization occurred spontaneously after

a short period of time at room temperature, but in other runs, the amount of salt which initially crystallized from 95% EtOH was relatively low. In such cases, the filtrate was concentrated and ether was added in order to get an approximately 1.5:1 Et_2O–95% EtOH solution, which was kept in a refrigerator at +5°C for *ca* one week, to give more salt. Whatever the crystallization process, fast or slow, the amount of salt was always approximately equal to the amount of starting diacid. Although the purity of the salt was already very high at the first crop, it could be repeatedly crystallized from 95% EtOH with high yields because of its excellent crystallinity, making the overall purification process easy and relatively fast. The formation of this new salt, with both melting point mp=202–204°C and specific rotation $[\alpha]_{546}^{25} = +280$ (c 0.6; acetone); $[\alpha]_{546}^{25} = +349$ (c 0.5; chloroform) being completely different from those of the reported one,[5] is believed to be due just to the presence of water, as 95% EtOH is used as the solvent.

The pure salt was decomposed in 1 M KOH/$CHCl_3$ and the aqueous phase was carefully cleaned before acidification, by extraction with $CHCl_3$ and then with ether in order to completely remove chloroform (which could eventually make the specific rotation of the diacid inaccurate by forming clathrates). Extraction with ether directly gave crude crystalline diacid (−)-(*S*)-**4**, with $[\alpha]_{546}^{25} = -126.4$ (c 1; 0.1 M NaOH) corresponding to ≈100% optical purity[9] and with 48% (up to 76%) yield.[10] The other enantiomer was obtained by direct decomposition of the initial mother liquor, by utilizing the much lower solubility in ether of racemic (*R,S*)-**4** compared to its enantiomers. Fractional crystallization from ether led to recovery of almost racemic **4** (10–39% yield) and to (+)-(*R*)-**4**, with $[\alpha]_{546}^{25} = +120.8/+123.5$ (c 1; 0.1 M NaOH) corresponding to 95–97% optical purity[9] and with 52% (up to 90%) yield.[10]

The present resolution procedure, which was found to be very convenient compared to the previous one,[5] is in fact comparable to the procedure of Suda *et al.*[9] through a brucine salt of the diacid **4**, which seems to be excellent and has been reproduced with success by others.[4,11]

Synthesis of 2,2′-bis-(bromomethyl)-1,1′-binaphthyl

The dibromides (+)-(*R*)-**5** and (−)-(*S*)-**5** were prepared as reported[5] from the diacids (+)-(*R*)-**4** and (−)-(*S*)-**4**, respectively. The enantiomerically pure enantiomer (+)-(*R*)-**5** could be obtained by fractional crystallization from methyl ethyl ketone, even from enantiomerically impure (+)-(*R*)-**4**, because of the higher melting point of each enantiomer of **5** (185.5–186.5°C)[5] compared to (*RS*)-**5** (151–155°C)[5] which crystallizes as a conglomerate.[12] Racemic (*RS*)-**5** was readily synthesized from 2-methylnaphthalene, in three steps involving a modification of the aryl–aryl coupling procedure of Kumada *et al.*[13,14] (Figure 2). Efficient procedures for the resolution of this dibromide are now available.[14,15]

Synthesis of the diamines ***1*** *and* ***2***

Treatment of enantiomerically pure (+)-(*R*)-**5** by an excess of N,N-dimethylethylenediamine in refluxing benzene[16] gave enantiomerically pure (−)-(*R*)-**1** with 93% yield, $[\alpha]_{546}^{25} = -409.5$ (c 0.9; abs EtOH), as a white glassy foam which did not crystallize (Figure 3). In the same manner, racemic (*RS*)-**5** gave (*RS*)-**1** with 88% yield, as a crystalline white solid, mp=122.5–124.5°C.

Double N,N-*bis*-alkylation of ethylenediamine using 2 equivalents mol/mol of the dibromide (+)-(*R*)-**5** in the presence of an excess of triethylamine in refluxing benzene was also successful to give enantiomerically pure (−)-(*R,R*)-**2** with 85% yield, $[\alpha]_{546}^{25} = -257.1$ (c 1; $CHCl_3$), as a white solid foam. In the same manner, racemic (*R,S*)-**5** gave the diamine **2** as a mixture of diastereoisomers which were separated by crystallization. The *meso* isomer (*RS*)-**2**, mp=261–264°C, was obtained with 35.3% yield, and the *racemic* isomer (*RS,SR*)-**2**, mp=249–251°C, was isolated with 43.7% yield.

Resolution of the diamines (RS)-*1 and* (RS,SR)-*2 through their salts with (+) and (−) dibenzoyltartaric acid*

When the diamine (*RS*)-**1** was mixed with 2 equivalents (mol/mol) of commercial (−)-dibenzoyltartaric acid monohydrate in 95% ethanol; a salt crystallized out of the solution (Figure 4).

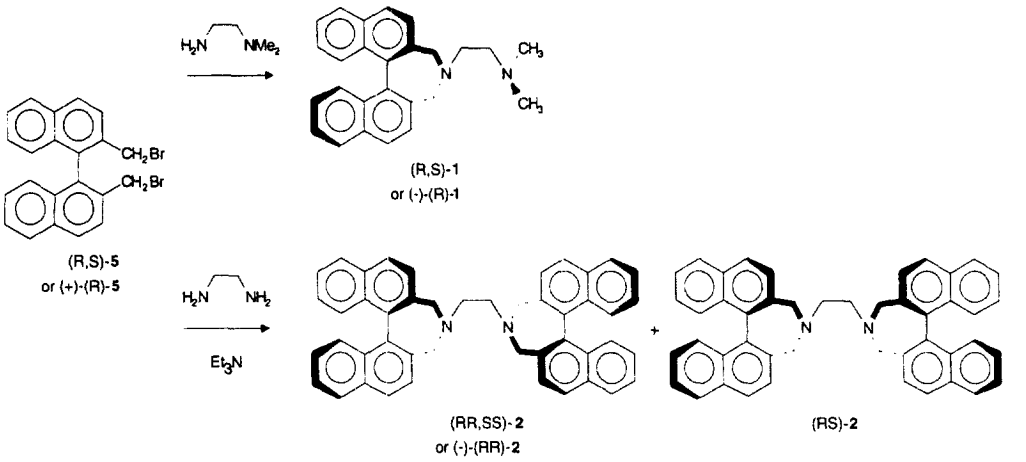

Figure 3. Synthesis of the diamines (−)-(*R*)-**1**, (*RS*)-**1**, (−)-(*R,R*)-**2**, (*RSSR*)-**2** (racemic) and (*R,S*)-**2** (meso).

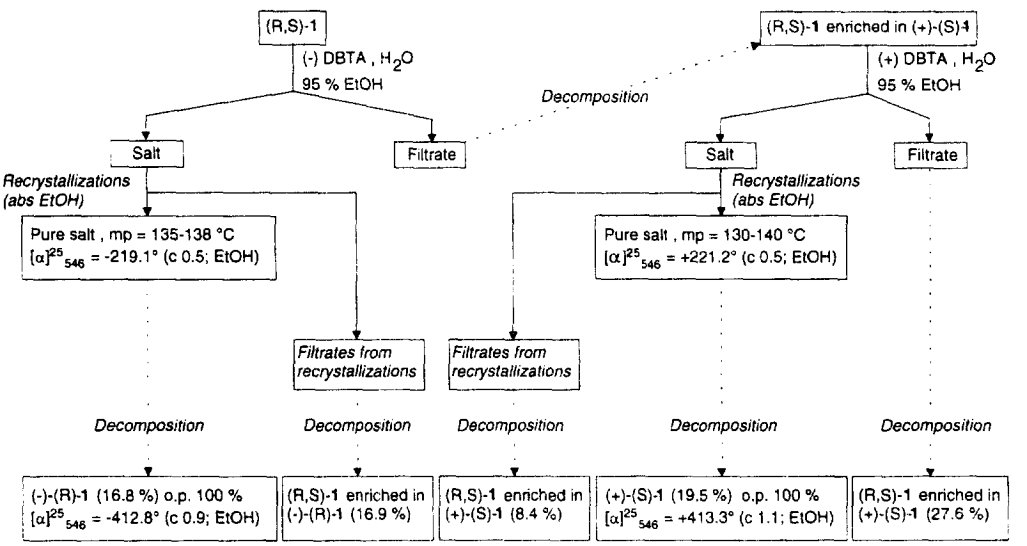

Figure 4. Resolution of the diamine **1**.

Repeated crystallizations from absolute ethanol gave the pure salt, with mp=135–138°C (decomp) and $[\alpha]_{546}^{25} = -219.1$ (c 0.5; abs EtOH). The pure salt was decomposed in 1 M KOH/ether. Careful acid–base extraction of the ether phase directly gave pure (−)-(*R*)-**1**, $[\alpha]_{546}^{25} = -412.8$ (c 0.9; abs EtOH), with 33.5% yield.[10] The filtrate from the first crop was also decomposed to give (*RS*)-**1** enriched in the (+)-(*S*) enantiomer. This mixture was treated with 2 equivalents (mol/mol) of commercial (+)-dibenzoyltartaric acid monohydrate in 95% ethanol. The deposited salt was repeatedly crystallized from absolute ethanol to furnish a pure sample with mp=130–140°C (decomp) and $[\alpha]_{546}^{25} = +221.2$ (c 0.5; abs EtOH). Decomposition of the pure salt as above gave (+)-(*S*)-**1**, $[\alpha]_{546}^{25} = +413.3$ (c 1.1; abs EtOH), with 39.0% yield.[10] Decomposition of the residues from the filtrates of the different recrystallizations of the two salts led to samples of (*RS*)-**1** enriched in either (−)-(*R*) or (+)-(*S*) enantiomers, which could be recycled. Altogether, 89.2% of the starting diamine **1** was recovered.

Although 2 equivalents of dibenzoyltartaric acid monohydrate were used in the resolution, the

obtained (+) and (−) salts had a stoichiometry 1:1 in diacid:diamine, according to their ^{1}H NMR spectrum and to the amount of diamines (+)-(*S*)-**1** and (−)-(*R*)-**1**, respectively, recovered after their decomposition. In another run with only 1.1 equivalent of (−)-dibenzoyltartaric acid monohydrate being used, the same salt as previously obtained crystallized from 95% EtOH, with $[\alpha]_{546}^{25} = -228.9$ (c 0.5; abs EtOH) after purification. This salt was decomposed to give (−)-(*R*)-**1**, $[\alpha]_{546}^{25} = -403.6$ (c 1; abs EtOH), with 44.7% yield.[10] However, in that experiment, a second more soluble salt was isolated from the initial mother liquor, with a melting point mp=130–140°C (decomp) close to the one of the less soluble salt, but a positive specific rotation $[\alpha]_{546}^{25} = +105.3$ (c 0.5; abs EtOH) after purification. Decomposition of this salt gave (+)-(*S*)-**1**, $[\alpha]_{546}^{25} = +405.9$ (c 1; abs EtOH), with 8.5% yield.[10] Therefore, both enantiomers of the diamine **1** can be obtained with the less expensive (−) dibenzoyltartaric acid as single resolving agent, although the recorded low yield in more soluble salt precursor of (+)-(*S*)-**1** makes the procedure unpractical.

Dibenzoyltartaric acid was found to be effective as well in resolving the racemic diamine (*RS,SR*)-**2** (Figure 5). From a solution of this compound and 1.1 equivalent (mol/mol) of (−)-dibenzoyltartaric acid monohydrate in 95% EtOH, kept at room temperature, deposited a salt which was purified by crystallization from 95% EtOH. The pure salt, with mp=169–170°C and $[\alpha]_{546}^{25} = +57.6$ (c 0.5; $CHCl_3$), was decomposed to give (+)-(*S,S*)-**2**, $[\alpha]_{546}^{25} = +256.1$ (c 1.1; $CHCl_3$), obtained as a white solid foam with 41.4% yield.[10]

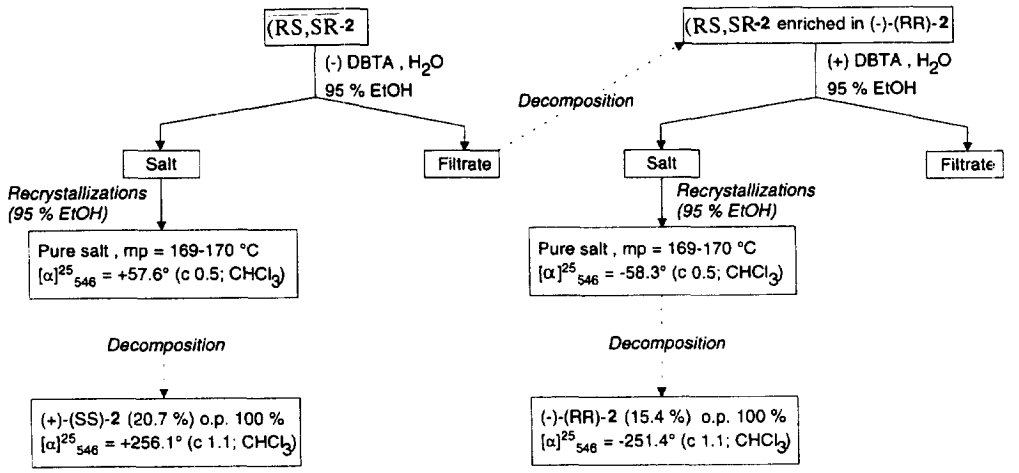

Figure 5. Resolution of the diamine **2**.

The filtrate from the first crop was decomposed to give (*RS,SR*)-**2** enriched in the (−)-(*R,R*) enantiomer. This sample was treated with 1.1 equivalent (mol/mol) of commercial (+)-dibenzoyltartaric acid monohydrate in 95% ethanol, and the deposited salt was purified by recrystallization from 95% ethanol. The pure salt, with mp=169–170°C and $[\alpha]_{546}^{25} = -58.3$ (c 0.5; $CHCl_3$), was decomposed to give (−)-(*R,R*)-**2**, $[\alpha]_{546}^{25} = -251.4$ (c 1.1; $CHCl_3$), obtained as a white solid foam with 30.7% yield.[10]

Specific rotations of the samples of resolved diamines were found identical, within experimental error, to the ones of the samples obtained from enantiomerically pure dibromide (+)-(*R*)-**5** (Table 1), consistent with resolution of the diamines **1** and **2** to enantiomerically pure state or nearly so. For both compounds, the $[\alpha]$ values were found similar for crude samples obtained after just careful acid–base extraction (see experimental) and for samples being further purified by preparative TLC or GPC. Specific rotations were always determined on samples being previously dried under vacuum (0.1 mm) at 110°C (refluxing toluene) for several hours. In many cases (see Table 1) these samples were also submitted to C,H,N analysis with correct results. We have no explanation for the discrepancy pointed out by Rosini *et al.*,[4] between the value $[\alpha]_{546}^{25}$ of the diamine **1** in the present work, ranging from

Table 1. Specific rotations of the diamines **1** and **2**.[17] (a) Crude product from acid-base extraction; (b) sample purified by preparative TLC; (c) sample purified by GPC; (d) analyzed sample (see experimental)

Entry	Diamine		λ nm c; solvent	589	578	546	436
1	From optically	*(-)-(R)*-**1** [(a)]	1.3; abs EtOH	-339.6	-354.1	-404.8	-650.7
2	pure *(+)-(R)*-**5**	[(b,d)]	0.9; abs EtOH	-342.6	-358.1	-409.5	-657.9
3	From	*(-)-(R)*-**1** [(a)]	0.9; abs EtOH	-345.9	-360.9	-412.8	-663.4
4	resolution	[(c,d)]	0.9; abs EtOH	-338.7	-352.8	-403.6	-650.1
5		*(+)-(S)*-**1** [(a)]	1.1; abs EtOH	+347.0	+361.5	+413.3	+665.0
6		[(c,d)]	0.4; abs EtOH	+334.7	+350.4	+398.3	+640.7
7		*(-)-(R)*-**1** [(a)]	1.0; abs EtOH	-337.9	-352.6	-403.6	-649.6
8		[(c)]	0.5; abs EtOH	-332.3	-345.7	-397.0	-638.6
9		*(+)-(S)*-**1** [(a,d)]	1.0; abs EtOH	+340.6	+355.1	+405.9	+652.8
10	From optically	*(-)-(R,R)*-**2** [(a)]	1.0; $CHCl_3$	-226.8	-234.9	-260.3	-292.2
11	pure *(+)-(R)*-**5**	[(c,d)]	1.0; $CHCl_3$	-223.6	-231.6	-257.1	-287.7
12	From	*(-)-(R,R)*-**2** [(a)]	1.1; $CHCl_3$	-218.0	-226.7	-251.4	-277.4
13	resolution	*(+)-(SS)*-**2** [(a,d)]	1.1; $CHCl_3$	+222.2	+229.8	+256.1	+285.6

397 to 413 (c 0.5 to 1; abs EtOH) for the different samples, and the value $[\alpha]_{546}^{25} = +293$ (c 1.08; abs EtOH) reported by these authors for an almost enantiomerically pure sample of (*S*)-**1**.

In conclusion, the above results demonstrate that all enantiomers of the diamines **1** and **2** can be readily obtained by two different procedures. From a practical point of view, preparation of optically pure **1** by resolution of the racemic diamine through its salts with (+)- and (−)-dibenzoyltartaric acid is a convenient method, while enantiomerically pure **2** should rather be prepared from resolved dibromide **5** in order to avoid the formation of the useless *meso* isomer. Experimental details concerning the use of the diamines **1** and **2** as chiral auxiliaries for the stoichiometric catalysis of addition of alkyllithiums to aldehydes have been previously reported.[2] These diamines should still be interesting compounds for future developments in asymmetric synthesis, according to their expected efficiency as catalysts in a variety of reactions involving organometallic species.

Experimental section

Melting points were recorded on a Thomas Hoover or Fisher-Johns melting point apparatus and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ with a Brücker WP-200 spectrometer at 200 MHz. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane internal standard. Splitting patterns are abbreviated as follows: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet. Optical rotations were taken on a Perkin-Elmer polarimeter, either 141 or 241 MC, in a water jacket 1 dm cell, with designated temperatures, solvents and concentrations. Mass spectra were recorded on a AEI Model MS 9 double focusing spectrometer interfaced by Kratos Co to a Data General Nova 3, at ionizing voltages of 70 eV and 14 eV. Elemental analysis was performed by Spang Microanalytical Laboratory (Eagle Harbor, Michigan) or by Galbraith Laboratories, Inc. (Knoxville, Tennessee). Gel permeation chromatography (GPC) was performed on a 20 ft×0.375 in. (O.D.) column packed with 100 Å Styragel (Water Associates Inc., 35–75 μm mesh, mol. wt. exclusion limit 1500) eluting with CH_2Cl_2.

Resolution of (RS)*-1,1′-binaphthyl-2,2′-dicarboxylic acid 4*

In a one liter erlenmeyer flask were introduced 20.3 g (59 mmol) of desolvated diacid (*RS*)-**4**, prepared as reported[5] (see text), and 400 ml of 95% ethanol. The mixture was heated on a hot plate in order to get a clear boiling solution. In another flask was prepared a solution of commercial quinine

monohydrate (22.3 g; 65 mmol) in 95% EtOH (200 ml), which was also heated to boiling and then rapidly transfered into the hot solution of diacid. The resulting boiling solution was concentrated on the hot plate to 130 ml and allowed to cool to room temperature. Crystallization started after a few minutes and seemed complete after 12 h. After 3 days at room temperature, the crystals were filtered, washed with 95% EtOH and air dried. Yield: 10.2 g. mp=201–203°C. The filtrate was boiled on a hot plate, concentrated to 130 ml and kept at room temperature overnight. No crystallization occured. Diethyl ether (160 ml) was slowly added and the resulting clear solution was kept in a refrigerator (+4°C) with a few previously obtained crystals as seeds. Crystallization occured very slowly. After 9 days, the crystals were filtered, washed with 95% EtOH and air dried. Yield: 8.3 g. mp=202–203°C. The mother liquor was evaporated to dryness *in vacuo* and the residue was vigorously stirred for a few minutes in the presence of aqueous 1 M KOH (150 ml) and $CHCl_3$ (250 ml). The separated chloroform layer was extracted again with 1 M KOH (150 ml). The combined aqueous basic phase was extracted twice with chloroform (150 ml), then with ether (150 ml) in order to get a perfectly clear solution, which was acidified by addition of an excess of 11 M HCl. The resulting precipitate was extracted with ether (500 ml). The ethereal solution was washed twice with water (200 ml), dried over $MgSO_4$, filtered, concentrated (boiling) to *ca* 200 ml and kept in a freezer at −15°C for 3 days. The resulting crystals were filtered, rapidly washed with cold ether, air dried and kept under vacuum (0.1 mm) at 110°C for 24 h, to yield 7.99 g (39.4%) of nearly racemic diacid **4**, $[\alpha]_{546}^{25} = +4.1$ (c 1; 0.1 M NaOH). The ethereal mother liquor was concentrated *in vacuo* to *ca* 5 ml, then kept at room temperature for a few minutes to allow crystallization to proceed, and evacuated. The white crystals were collected by scratching the flask and drying under vacuum (0.1 mm) at 110°C for 24 h, to yield 5.35 g (26.3%) of (+)-(*R*)-**4** with 95.1% optical purity[9]: $[\alpha]_{589}^{25} = +100.4$, $[\alpha]_{578}^{25} = +104.1$, $[\alpha]_{546}^{25} = +120.8$, $[\alpha]_{436}^{25} = +238.6$ (c 1; 0.1 M NaOH); lit.[9] $[\alpha]_{546}^{25} = +127$ (c 1; 0.1 M NaOH). Repeated crystallizations from 95% EtOH of the combined first crops of salt (18.5 g) resulted in almost no change of melting point and specific rotation. Altogether, a sample of 15.3 g of pure salt was obtained. mp=202–204°C. $[\alpha]_{589}^{25} = +279.6$, $[\alpha]_{578}^{25} = +294.0$, $[\alpha]_{546}^{25} = +349.6$, $[\alpha]_{436}^{25} = +765.8$ (c 0.5; chloroform). $[\alpha]_{589}^{25} = +223.4$, $[\alpha]_{578}^{25} = +235.3$, $[\alpha]_{546}^{25} = +280.0$, $[\alpha]_{436}^{25} = +614.6$ (c 0.6; acetone; low solubility; determined for comparison with optical rotation of the reported other salt).[5] The pure salt (15.3 g) was decomposed in chloroform (300 ml)/N KOH (2×200 ml) exactly as above. The diacid obtained after acidification of the clear colorless aqueous phase was extracted with ether (400 ml). The ethereal solution was washed with water (2×300 ml), dried over $MgSO_4$, filtered, concentrated *in vacuo* to ca 5 ml, kept at room temperature for a few minutes to allow crystallization and evacuated. The white crystals were collected and dried under vacuum (0.1 mm) at 110°C for 24 h, to yield 4.84 g (23.9%) of (−)-(*S*)-**4** with ≈100% optical purity:[9] mp=135–150°C (decomp); lit.[9] mp=199–200°C (decomp). $[\alpha]_{589}^{25} = -102.4$, $[\alpha]_{578}^{25} = -108.6$, $[\alpha]_{546}^{25} = -126.4$, $[\alpha]_{436}^{25} = -250.8$ (c 0.94; 0.1 M NaOH); lit.[5] $[\alpha]_{546}^{22} = -125.2$ (c 1; 0.1 M NaOH) for a sample analyzed as **4**, 0.5 H_2O; lit.[9] $[\alpha]_{546}^{25} = -127$ (c 1; 0.1 M NaOH).

Other experiments gave the following results in getting always the same quinine salt: (a) (*RS*)-**4**: 34.2 g; salt (95% EtOH/ether 1:1): 27 g. (b) (*RS*)-**4**: 13.5 g; salt (95% EtOH): 13.3 g. (c) (*RS*)-**4**: 9.7 g; salt: 7.1 g (95% EtOH) +2.5 g (95% EtOH/ether). (d) (*RS*)-**4**: 0.17 g; salt (95% EtOH): 0.11 g.

In another illustrative experiment realized a few years later, 55.36 g (142.7 mmol) of (*R,S*)-**4**, EtOH solvate (by ^1H NMR) were divided into three portions. In a first run, 0.36 g of diacid and 0.37 g (1.2 equivalent) of commercial anhydrous quinine were solubilized in boiling 95% EtOH (25 ml). The solution was concentrated to 5 ml and left at room temperature for 24 h with no crystallization observed. Ether (7.5 ml) was slowly added and the flask was scratched with a spatula just previously dropped in the resulting clear solution and air dried. After several days at +4°C, the deposited crystals were collected by filtration (yield 0.43 g; mp=201–204°C). In a second run, solutions of diacid (10 g) in boiling 95% EtOH (150 ml) and quinine (10 g) in boiling 95% EtOH (100 ml) were combined and concentrated to 50 ml, with no crystallization observed after 2 days at room temperature. Ethanol

and water were added in order to get a 90% EtOH solution (90 ml) which was seeded by a few of the former crystals and left at room temperature. Crystallization was completed after 24 h. After one more day at +4°C, the deposited crystals were collected by filtration (yield 9.50 g; mp=203–204°C). In a third run, a solution of diacid (45 g) and quinine (46 g) in boiling 95% EtOH (800 ml) was concentrated to 700 ml. Water (30 ml) was added and the boiling solution allowed to cool to room temperature with no seed. Crystals started to deposit after 2 hours and were collected by filtration after 24 h at room temperature and 24 h at +4°C (yield 42.4 g; mp=206–207°C). The combined filtrates from the first crops of the three runs were concentrated to 250 ml and ether (300 ml) was slowly added. The solution was seeded with a few crystals of salt and was left at +4°C for 10 days to give more crystals (yield 5.9 g; mp=205–207°C). The filtrate was evaporated to dryness and treated with 1 M $KOH/CHCl_3$ for decomposition. Acidification of the aqueous phase followed by extraction with ether, fractional crystallization from ether exactly as above and drying under vacuum (0.1 mm) at 110°C for 24 h, led to nearly racemic diacid **4** (5.0 g; 10.2%) and to (+)-(*R*)-**4** (22.1 g; 45.3%) with 97.2% optical purity:[9] $[\alpha]_{589}^{25} = +103.4$, $[\alpha]_{578}^{25} = +107.6$, $[\alpha]_{546}^{25} = +123.5$, $[\alpha]_{436}^{25} = +245.1$ (c 1; 0.1 M NaOH). The combined crystals of salt from the three runs (58.2 g) were recrystallized from 95% EtOH. The boiling solution was concentrated to *ca* 900 ml and left at room temperature for 2 days, to give 55.3 g of pure salt, with mp=206–207°C and $[\alpha]_{589}^{25} = +276.1$, $[\alpha]_{578}^{25} = +290.3$, $[\alpha]_{546}^{25} = +345.3$, $[\alpha]_{436}^{25} = +758.8$ (c 0.5; chloroform), which was decomposed in the same way as above, to yield 18.6 g (38.1%) of (−)-(*S*)-**4** with 98.8% optical purity:[9] $[\alpha]_{589}^{25} = -99.5$, $[\alpha]_{578}^{25} = -106.8$, $[\alpha]_{546}^{25} = -125.5$, $[\alpha]_{436}^{25} = -249.2$ (c 0.94; 0.1 M NaOH).

Preparation of 2,2′-bis-(bromomethyl)-1,1′-binaphthyl ***5***

Several samples of diacid (+)-(*R*)-**4** (o.p.≈93–96%) obtained from resolution were combined, for a total amount of 13 g (38 mmol). Reduction by a large excess of $LiAlH_4$ in ether as in the literature,[5] led to (*R*)-2,2′-*bis*-(hydroxymethyl)-1,1′-binaphthyl as a crystalline white crude solid (12.09 g; 100%), which was directly treated with 48% HBr in boiling glacial acetic acid, as in the literature,[5] to give 16.51 g (98.2%) of crude dibromide. Repeated crystallization from methyl ethyl ketone until constant melting point and specific rotation led to 11.69 g (70% overall yield from the starting diacid) of pure 2,2′-*bis*-(bromomethyl)-1,1′-binaphthyl (+)-(*R*)-**5** with mp=184.5–185°C; lit.[5] mp=185.5–186.5°C; lit.[18] mp=183.5–185.5°C, and with $[\alpha]_{589}^{25} = +159.2$, $[\alpha]_{578}^{25} = +167.5$, $[\alpha]_{546}^{25} = +196.4°$, $[\alpha]_{436}^{25} = +411.8$ (c 1; benzene) corresponding to 98.2–98.6% optical purity;[5,18] lit.[5] $[\alpha]_{546}^{23} = +199.1$ (c 1; benzene); lit.[18] $[\alpha]_{546}^{29} = +200$ (c 0.9; benzene). By a similar procedure, from 15.4 g (45 mmol) of optically pure diacid (−)-(*S*)-**4** were obtained 14.7 g (100%) of crude (S)-2,2′-*bis*-(hydroxymethyl)-1,1′-binaphthyl and then 17.87 g (90.2%) of recrystallized pure 2,2′-*bis*-(bromomethyl)-1,1′-binaphthyl (−)-(*S*)-**5** with 98.7–99.2% optical purity,[5,18] mp=183.5–184°C; $[\alpha]_{589}^{25} = -160.3$, $[\alpha]_{578}^{25} = -169.0$, $[\alpha]_{546}^{25} = -197.4$, $[\alpha]_{436}^{25} = -414.3$ (c 1; benzene). The preparation of racemic (*RS*)-**5** as in Figure 2 has already been reported.[14]

N-(2-dimethylaminoethyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1′,2′-e]azepine (RS)-***1***

A solution of racemic dibromide (*R,S*)-**5** (2.20 g; 5 mmol) and 2-dimethylaminoethylamine (0.88 g; 10 mmol) in benzene (50 ml) was stirred under nitrogen atmosphere and refluxed for 24 h. After cooling to room temperature and addition of 1 M KOH (30 ml), the mixture was extracted with ether (two portions of 100 ml). The organic phase was washed with water (two portions of 50 ml) and 11 M HCl (25 ml) was added. The resulting precipitate was completely solubilized in the acidic aqueous phase after shaking and decantation.[19] The organic phase was extracted with more 11 M HCl (10 ml) and the separated combined aqueous acidic phase was diluted with water to *ca* 150 ml, which led to a gel.[19] Ether (200 ml) was added and the mixture was basicified by slow addition of a large excess of aq. KOH. Vigorous shaking followed by decantation, led to clear colorless phases. The separated ethereal phase was washed with water (two portions of 100 ml), dried over K_2CO_3, filtered and evaporated *in vacuo*, to give 1.71 g (93.4%) of crude (*R,S*)-**1** obtained as a pale yellow glassy

oil which slowly crystallized. This crude sample (as well as similar extraction crude basic parts from several other experiments) was pure by ^{1}H NMR and TLC (SiO_2 or Al_2O_3/THF) and was directly used as starting material for resolution. Trituration in petroleum ether 35–60°C (50 ml) gave a fine white crystalline powder which was filtered, washed with petroleum ether and air dried with vacuum. Weight 1.607 g (87.8%), mp=122.5–124.5°C. Recrystallization from ether led to an analytical sample with mp=123.5–124.5°C. ^{1}H NMR ($CDCl_3$): 7.95–7.21, m, 12H (ArH); 3.72, d (12), 2H and 3.21, d (12), 2H ($ArCH_2N$); 2.77–2.48, m, 4H (CH_2N); 2.29, s, 6H (NMe_2). MS *m/z*: 366 (M^+); 308 (M^+–CH_2NMe_2). Anal. ($C_{26}H_{26}N_2$) calcd. C: 85.21; H: 7.15; N: 7.64; found C: 85.34; H: 7.05; N: 7.63.

*N-(2-dimethylaminoethyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1′,2′-e]azepine (−)-(R)-**1***

From the dibromide (+)-(*R*)-**5** with $[\alpha]_{546}^{25}$ = +196.4 (c 1; benzene) (1.10 g; 2.5 mmol), similar experimental conditions and work-up as above, except the use of dilute instead of concentrated HCl for extraction,[19] led to 0.853 g (93.2%) of crude (extraction basic part) optically pure (−)-(*R*)-**1** with $[\alpha]_{546}^{25}$ = −404.8 (c 1.3; abs. EtOH)[17] (Table 1, entry 1), obtained as a pale yellow solid foam which could not be crystallized and a pale yellow glass after drying.[17] Preparative TLC of an aliquot (Al_2O_3/THF) followed by acid–base extraction of the collected fraction (1 M HCl/ether then aq. KOH/ether),[20] gave an analytical sample with similar specific rotation $[\alpha]_{546}^{25}$ = −409.5 (c 0.9; abs. EtOH)[17] (Table 1, entry 2). ^{1}H NMR ($CDCl_3$): see (*R,S*)-**1**. Anal. ($C_{26}H_{26}N_2$) calcd. C: 85.21; H: 7.15; N: 7.64; found C: 85.05; H: 7.10; N: 7.63.

*Resolution of N-(2-dimethylaminoethyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1′,2′-e]azepine (RS)-**1** to (−)-(R)-**1** and (+)-(S)-**1***

A solution of racemic diamine (*RS*)-**1** (7.34 g; 20 mmol) and commercial (−)-dibenzoyltartaric acid monohydrate (15.05 g; 40 mmol) in 95% EtOH (300 ml) was boiled on a hot plate, filtered on paper, concentrated upon boiling to *ca* 220 ml and kept at room temperature. Crystallization of a white soft solid started after *ca* 2 h and was completed overnight. The crystals were filtered, washed with 95% EtOH and air dried with vacuum for 2 h to give 11.21 g of a white amorphous powder. Two consecutive recrystallizations from abs. EtOH gave 2.97 g of pure salt (white soft solid made of agglomerates of very fine needles) with mp=*ca* 115°C (foaming) to 135–138°C (foam to liquid with decomposition); $[\alpha]_{589}^{25}$ = −182.2, $[\alpha]_{578}^{25}$ = −190.6, $[\alpha]_{546}^{25}$ = −219.1, $[\alpha]_{436}^{25}$ = −371.7 (c 0.53; abs. EtOH). The pure salt (2.97 g) was magnetically stirred for a few minutes in the presence of 1 M KOH (100 ml) and ether (100 ml). The two phases were separated and the aqueous basic phase was extracted with ether (50 ml). The combined ether solution was washed with water (two portions of 100 ml) and then extracted with 11 M HCl (two portions of 20 ml). The combined acidic phase, which remained clear upon dilution into water (200 ml),[19] was washed with ether (100 ml) and then basicified by addition of a large excess of aq. KOH. Addition of ether (200 ml) followed by vigorous shaking gave two clear colorless phases after decantation. The separated ethereal phase was washed with water (two portions of 200 ml), dried over K_2CO_3, filtered and evaporated *in vacuo*, to give 1.23 g (33.5%)[10] of crude, chemically and optically pure (−)-(*R*)-**1** with $[\alpha]_{546}^{25}$ = −412.8 (c 0.9; abs. EtOH)[17] (Table 1, entry 3), obtained as a pale yellow glass after drying.[17] Further purification by GPC, followed by evaporation of dichloromethane from the product containing combined fractions and by acid–base extraction as above (1 M HCl/ether then aq. KOH/ether),[20] gave an analytical sample with similar specific rotation $[\alpha]_{546}^{25}$ = −403.6 (c 0.85; abs. EtOH)[17] (Table 1, entry 4). Anal. ($C_{26}H_{26}N_2$) calcd. C: 85.21; H: 7.15; N: 7.64; found C: 84.97; H: 7.09; N: 7.62. Either crude or purified sample gave similar results in several duplicated asymmetric induction experiments.[2]

The filtrate from the first crop of salt was evaporated and the residue was decomposed in 1 M KOH (150 ml) and ether (150 ml). Acid–base extraction with 1 M HCl/ether then aq. KOH/ether gave 4.079 g (11.1 mmol; 55.6%) of (*RS*)-**1** enriched in (+)-(*S*)-**1**, $[\alpha]_{546}^{25}$ = +141.1 (c 0.5; abs. EtOH), which was treated as above with commercial (+)-dibenzoyltartaric acid monohydrate (8.14 g; 21.6 mmol) in 95% EtOH (400 ml). From the concentrated (to *ca* 160 ml) solution deposited 6.80 g of

salt, which was recrystallized twice from abs. EtOH, to give 3.20 g of pure salt with mp=*ca* 115°C (foaming) to 130–140°C (foam to liquid with decomposition); $[\alpha]_{589}^{25} = +185.5$, $[\alpha]_{578}^{25} = +193.0$, $[\alpha]_{546}^{25} = +221.2$, $[\alpha]_{436}^{25} = +374.3$ (c 0.52; abs. EtOH). Decomposition of the pure salt and acid–base extraction as previously detailed gave 1.43 g (39.0%)[10] of crude, chemically and optically pure (+)-(*S*)-**1** with $[\alpha]_{546}^{25} = +413.3$ (c 1.1; abs. EtOH)[17] (Table 1, entry 5). Further purification by GPC, followed by evaporation of dichloromethane from the product containing combined fractions and by acid–base extraction in the usual manner (1 M HCl/ether then aq. KOH/ether),[20] gave an analytical sample with similar optical rotation $[\alpha]_{546}^{25} = +398.3$ (c 0.4; abs. EtOH)[17] (Table 1, entry 6). Anal. ($C_{26}H_{26}N_2$) calcd. C: 85.21; H: 7.15; N: 7.64; found C: 84.91; H: 7.06; N: 7.54.

Decomposition and usual acid–base extraction of the residues from the filtrates of the various recrystallizations, as shown in Figure 4, led to the following samples of (*RS*)-**1** enriched in either (+)-(*S*)-**1** or (−)-(*R*)-**1**, which were recycled for further resolutions: 1.24 g (16.9%) with $[\alpha]_{546}^{25} = -71.7$ (c 0.96; abs. EtOH); 0.62 g (8.4%) with $[\alpha]_{546}^{25} = +186.6$ (c 1; abs. EtOH) and 2.03 g (27.7%) with $[\alpha]_{546}^{25} = -100.6$ (c 0.8; abs. EtOH).

In another experiment which was not duplicated, (*RS*)-**1** (9.4 g; 25.6 mmol) was combined with only 1.1 equivalent of (−)-dibenzoyltartaric acid monohydrate (10.62 g; 28.2 mmol) in 95% EtOH (250 ml). From the concentrated (to *ca* 125 ml) ethanolic solution deposited the same salt as previously described (11.55 g), which was recrystallized three times from abs. EtOH, to give 5.11 g of pure salt with a similar specific rotation as above: $[\alpha]_{589}^{25} = -189.9$, $[\alpha]_{578}^{25} = -199.0$, $[\alpha]_{546}^{25} = -228.9$, $[\alpha]_{436}^{25} = -388.5$ (c 0.48; abs. EtOH). Decomposition of the pure salt (4.8 g) and acid–base extraction in the usual manner (1 M HCl/ether then aq. KOH/ether), gave 2.09 g (44.4%)[10] of crude, chemically and optically pure (−)-(*R*)-**1** with $[\alpha]_{546}^{25} = -403.6$ (c 0.97; abs. EtOH)[17] (Table 1, entry 7). Further purification by GPC, followed by evaporation of dichloromethane from the product containing combined fractions and by acid–base extraction with 1 M HCl/ether then aq. KOH/ether in the usual manner,[20] gave a sample of similar optical rotation $[\alpha]_{546}^{25} = -397.0$ (c 0.5; abs. EtOH)[17] (Table 1, entry 8). From the filtrate of the first crop of salt, which was standing at room temperature for 24 h, deposited another salt, which was isolated by filtration (weight 1.64 g) and recrystallized twice from 95% EtOH to give 1.45 g of pure more soluble salt with mp=*ca* 130–140°C (foam to liquid with decomposition); $[\alpha]_{589}^{25} = +90.4$, $[\alpha]_{578}^{25} = +93.6$, $[\alpha]_{546}^{25} = +105.3$, $[\alpha]_{436}^{25} = +143.6$ (c 0.49; abs. EtOH). Decomposition of this pure salt (0.9 g) and acid–base extraction (1 M HCl/ether then aq. KOH/ether), gave 0.404 g (8.6%)[10] of crude but analytically and optically pure (+)-(*S*)-**1** with $[\alpha]_{546}^{25} = +405.9$ (c 1; abs. EtOH)[17] (Table 1, entry 9). Anal. ($C_{26}H_{26}N_2$) calcd. C: 85.21; H: 7.15; N: 7.64; found C: 85.04; H: 7.05; N: 7.65.

N-[2-(4,5-dihydro-3H-dinaphtho[2,1-c:1′,2′-e]azepinoethyl)]-4,5-dihydro-3H-dinaphtho[2,1-c:1′,2′-e]azepine (RS)-**2** *(meso) and* (RS,SR)-**2** *(racemic)*

A solution of racemic dibromide (*RS*)-**5** (4.40 g; 10 mmol), ethylenediamine (0.305 g; 5.08 mmol) and triethylamine (5.05 g; 50 mmol) in benzene (150 ml) was stirred under nitrogen atmosphere and refluxed for 4 days. After evaporation of the solvent *in vacuo*, 0.5 M KOH (200 ml) and chloroform (300 ml) were added to the residue. The mixture was magnetically stirred and the decanted yellow clear organic phase was washed with water (two portions of 250 ml), dried over K_2CO_3, filtered and evaporated *in vacuo*. The residue was dissolved in dichloromethane the solution passed through a 100 Å Styragel column for GPC. Elution with dichloromethane (3.7 ml/min) gave a minor peak with Rv=172 ml corresponding to 0.18 g of a polymeric mixture by NMR, and a major peak with Rv=199 ml corresponding to 3.04 g of a diastereoisomeric mixture of diamines **2**, obtained as pale yellow solid foam after evaporation of dichloromethane *in vacuo*. This product was dissolved in benzene (25 ml) and from the resulting clear solution very quickly crystallized a white solid which was filtered, rapidly washed with cold benzene then with ether and air dried with vacuum, to give 1.089 g (35.3%) of pure *meso* diamine (*RS*)-**2**, from which an analytical sample was obtained after recrystallization from benzene/chloroform: mp=261–264°C. ^{1}H NMR ($CDCl_3$): 7.97–7.23, m, 24H (ArH); 3.79, d (12), 4H and 3.27, d (12), 4H ($ArCH_2N$); 2.98–2.60, m, 4H (CH_2N). MS *m/z*: 616 (M^+); 308 ($M^+/2$).

Anal. ($C_{46}H_{36}N_2$) calcd. C: 89.57; H: 5.88; N: 4.54; found C: 89.46; H: 5.91; N: 4.54. The filtrate from the first crop was concentrated until *ca* 15 ml of a clear yellow benzenic solution and ether (*ca* 150 ml) was added, leading to crystallization of a white solid which was filtered, washed with ether and air dried with vacuum, to give 1.346 g (43.7%) of pure *racemic* diamine (*RS,SR*)-**2**, from which an analytical sample was obtained after recrystallization from chloroform: mp=249–251°C. ^{1}H NMR ($CDCl_3$): 8.00–7.22, m, 24H (ArH); 3.77, d (12), 4H and 3.26, d (12), 4H ($ArCH_2N$); 3.03–2.60, m, 4H (CH_2N). MS *m/z*: 616 (M^+); 308 ($M^+/2$). Anal. ($C_{46}H_{36}N_2$) calcd. C: 89.57; H: 5.88; N: 4.54; found C: 89.28; H: 5.85 N: 4.53.

*N-{2-(4,5-dihydro-3H-dinaphtho[2,1-c:1′,2′-e]azepinoethyl)}-4,5-dihydro-3H-dinaphtho[2,1-c:1′,2′-e]azepine (−)-(*R,R*)-2*

A solution of the dibromide (+)-(*R*)-**5** (5.95 g; 13.5 mmol), ethylenediamine (0.422 g; 7 mmol) and triethylamine (7 g; 70 mmol) in benzene (200 ml) was refluxed with stirring under nitrogen atmosphere for 4 days. After cooling to room temperature, ether (*ca* 400 ml) was added, the organic phase was washed with five 200 ml portions of water, dried over K_2CO_3, filtered and concentrated *in vacuo*. The resulting clear yellow benzenic solution (*ca* 20 ml) was diluted with ether (600 ml) and vigorously stirred in the presence of 0.5 N HCl (150 ml). The resulting white precipitate of (−)-(*R,R*)-**2**, 2 HCl[19] was filtered, washed with ether, air dried and transferred in a 1 liter erlenmeyer flask. Ether (400 ml) and 0.5 N KOH (200 mml) were added and the mixture was magnetically stirred at room temperature for several hours, until complete dissolution of the precipitate was observed. The two phases were separated, the ethereal solution was washed with water (3×150 ml), dried over K_2CO_3, filtered and evaporated *in vacuo*. The resulting diamine (−)-(*RR*)-**2** (3.70 g; 88.9%) with $[\alpha]_{546}^{25} = -260.3$ (c 1; $CHCl_3$)[17] (Table 1, entry 10), was obtained as a yellow solid foam. Further purification by GPC (100 Å Styragel; CH_2Cl_2) followed by another acid–base extraction[20] through the salt (−)-(*R,R*)-**2**, 2 HCl as above, led to 3.53 g (84.8%) chemically and optically pure diamine (−)-(*R,R*)-**2** as a pale yellow solid foam which couldn't be crystallized, with $[\alpha]_{546}^{25} = -257.1$ (c 1; $CHCl_3$)[17] (Table 1, entry 11). ^{1}H NMR ($CDCl_3$): see (*RR,SS*)-**2**. MS *m/z*: 616 (M^+); 308 ($M^+/2$). Anal. ($C_{46}H_{36}N_2$) calcd. C: 89.57; H: 5.88; N: 4.54; found C: 89.48; H: 5.83; N: 4.67.

Another run starting from (+)-(*R*)-**5** (4.4 g; 10 mmol), ethylenediamine (0.34 ml; 5 mmol) and triethylamine (5.05 g; 50 mmol) in benzene (150 ml) gave after the same extraction procedure, 2.467 g (80.1%) of crude (−)-(*R,R*)-**2**, pure by NMR and TLC (Al_2O_3; CH_2Cl_2), with $[\alpha]_{546}^{25} = -255.1$ (c 1; $CHCl_3$).[17]

Resolution of racemic N-{2-(4,5-dihydro-3H-dinaphtho[2,1-c:1′,2′-e]azepinoethyl)}-4,5-dihydro-3H-dinaphtho[2,1-c:1′,2′-e]azepine (RS,SR)-*2 to (−)-*(R,R)-*2 and (+)-*(S,S)-*2*

0.899 g (1.46 mmol) of racemic diamine (*RR,SS*)-**2** were combined with commercial (−)-dibenzoyltartaric acid monohydrate (0.628 g; 1.67 mmol) in 95% EtOH (750 ml). The mixture was heated on a hot plate and the resulting clear boiling solution was filtered on paper, concentrated upon boiling to *ca* 300 ml and kept at room temperature. The resulting crystals were filtered, washed with 95% EtOH and air dried. A single crystallization of the obtained white crystalline powder (0.511 g) from 95% EtOH gave 0.383 g of pure salt with mp=169.5–170°C (decomp); $[\alpha]_{589}^{25} = +54.0$, $[\alpha]_{578}^{25} = +54.4$, $[\alpha]_{546}^{25} = +57.6$, $[\alpha]_{436}^{25} = +12.2$, $[\alpha]_{365}^{25} = ca\ -730$ (c 0.5; $CHCl_3$). The pure salt was dissolved in chloroform (150 ml), the solution was extracted with three 100 ml portions of M KOH, washed with water (2×200 ml), dried over $MgSO_4$, filtered and and evaporated *in vacuo*, to give 0.186 g (41.4%)[10] of crude, analytically and optically pure diamine (+)-(*S,S*)-**2**, obtained as a white solid foam, with $[\alpha]_{546}^{25} = +256.1$ (c 1.1; $CHCl_3$)[17] (Table 1, entry 13). Anal. ($C_{46}H_{36}N_2$) calcd. C: 89.57; H: 5.88; N: 4.54; found C: 89.44; H: 5.79; N: 4.63. The filtrate from the first crop was evaporated to dryness *in vacuo*. The residue was dissolved in chloroform (100 ml) and decomposed with M KOH as above to give 0.552 g (61% of the initial amount) of diamine **2** enriched in the (*R,R*) enantiomer, with $[\alpha]_{546}^{25} = -130.51$ (c 1; $CHCl_3$). This sample (0.520 g; 0.844 mmol) was dissolved in boiling

95% EtOH (100 ml). The boiling solution was filtered on paper and combined with a hot solution of commercial (+)-dibenzoyltartaric acid monohydrate (0.351 g; 0.935 mmol) in 95% EtOH (50 ml). The resulting solution was concentrated on a hot plate to *ca* 85 ml and kept at room temperature for 24 h. The deposited salt (0.397 g), with mp=167–168.5°C (decomp) and $[\alpha]_{546}^{25} = -50.3$ (c 0.5; $CHCl_3$), was recrystallized two times from 95% EtOH to give 0.251 g of pure salt, with mp=169–169.5°C (decomp); $[\alpha]_{589}^{25} = -52.7$, $[\alpha]_{578}^{25} = -56.0$, $[\alpha]_{546}^{25} = -58.3$, $[\alpha]_{436}^{25} = -13.3$, $[\alpha]_{365}^{25}$=*ca* +720 (c 0.5; $CHCl_3$). The pure salt (0.220 g) was dissolved in chloroform (150 ml), the solution was extracted with three 100 ml portions of M KOH, washed with water (2×200 ml), dried over $MgSO_4$, filtered and evaporated *in vacuo*, to give 0.138 g (30.7%)[10] of crude, chemically and optically pure diamine (−)-(*R,R*)-**2**, obtained as a white solid foam, with $[\alpha]_{546}^{25} = -251.4$ (c 1.1; $CHCl_3$)[17] (Table 1, entry 12).

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17. Optical rotations of the diamines **1** and **2** were always determined on samples being previously dried under vacuum (0.1 mm) at 110°C (refluxing toluene) for several hours.
18. Fitts, D. D.; Siegel, M.; Mislow, K. *J. Am. Chem. Soc.* **1958**, *80*, 480–486.
19. Racemic (*RS*)-**1** is insoluble in dilute aqueous HCl (giving a gel-like precipitate) but is well soluble in 37% HCl (giving a clear yellow solution), whereas (−)-(*R*)-**1** or (+)-(*S*)-**1** are well soluble in both dilute and concentrated HCl. The hydrochloride salts of (*RS*)-**2**, (*RS,SR*)-**2** and (−)-(*R,R*)-**2** are all insoluble in both dilute and concentrated HCl.
20. The samples of optically pure diamines **1** and **2** recovered by direct evaporation of CH_2Cl_2 solutions after purification by GPC were not completely soluble in Et_2O and could be partly decomposed to brown tars when dried under vacuum (0.1 mm) at 110°C for 12 hours. Such decomposition was never observed for samples recovered by evaporation of Et_2O solutions, which gave a pale yellow

solid foam or glass after drying in the same conditions. For this reason, the samples purified by GPC (or TLC) were always submitted again to an acid–base extraction with first dilute HCl (0.5–1 M), then neutralization of the resulting solution (for **1**) or precipitate (for **2**) by an excess of dilute KOH and extraction with Et_2O.

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