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Enantioselective Synthesis of DIANANE, a Novel C_2-Symmetric Chiral Diamine for Asymmetric Catalysis†

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DIANANE (*endo,endo*-2,5-diaminonorbornane) is a novel chiral C_2-symmetric diamine, based on the rigid bicyclo[2.2.1]heptane scaffold. Schiff-base ligands derived from DIANANE have already found use in asymmetric catalysis, e.g., in the highly enantioselective Nozaki−Hiyama−Kishi reaction. We herein describe a practical synthesis of enantiomerically pure DIANANE, starting from norbornadiene in four steps: (i) Pd-MOP catalyzed Hayashi-hydrosilylation/Tamao−Fleming oxidation, (ii) oxidation to norbornane-2,5-dione, (iii) *endo*-selective reductive amination with benzylamine, and (iv) hydrogenolytic debenzylation. None of the steps involves chromatographic purification. For the Tamao−Fleming oxidation, the use of hydrogen peroxide in the form of its urea clathrate instead of aqueous solution proved beneficial. By the above sequence, enantiomerically pure (ee ≥99%) DIANANE was obtained from norbornadiene in 40−50% overall yield. The relative and absolute configuration of DIANANE was confirmed by X-ray crystallography of the DIANANE bis-tosylamide, and of its bis-camphorsulfonamide. Furthermore, the synthesis and X-ray crystal structure of the Schiff-base ligand derived from DIANANE and 3,5-di-*tert*-butyl salicylic aldehyde are reported.

Introduction

In the search for new and ever more efficient chiral transition metal catalysts, the design of novel ligands is one of the major research objectives. Chiral salen ligands are among the so-called "privileged ligands" that effect remarkable enantioselectivity for a broad range of transformations.[1] As one of the first examples, Jacobsen et al.[2] reported in 1990 on the use of the manganese complex of *N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (**1**) for the asymmetric epoxidation of unfunctionalized olefins (Scheme 1). Since then, a variety of transition metal complexes of ligands of this type have been developed for various asymmetric transformations. Among those, chromium Schiff base complexes have been used successfully in Diels−Alder and hetero-Diels−Alder reactions,[3] the kinetic resolution of racemic epoxides,[4] and the Nozaki−Hiyama−Kishi (NHK) reaction.[5] We have recently reported that the Cr-complex of the salen ligand **2**, which is based on *endo,endo*-2,5-diaminonorbornane (DIANANE, **3**) as the diamine component, is a very effective catalyst for the *asymmetric* Nozaki−Hiyama−Kishi (NHK) reaction.[6] DIANANE (**3**) is C_2-symmetric and it has a rigid backbone and a larger N−N distance compared to 1,2-diaminocyclohexane. In the NHK reaction, the Cr complex of the salen ligand **2** provided enantiomeric excesses up to 92% (Scheme 1).[6] Furthermore, substrates such as vinyl triflates and iodides, which are usually not reactive in the catalytic enantioselective NHK reaction using the salen ligand **1**, readily underwent addition to aldehydes to form the expected NHK products. These encouraging results and the great potential of DIANANE (**3**) as a novel C_2-symmetrical diamine prompted us to search for an efficient synthesis of this chiral building block.

Results and Discussion

Our initial synthetic approach toward DIANANE (**3**) started from the known bis-oxime *rac*-**5**[7] of the racemic diketone *rac*-**4**[8] (Scheme 2). We intended to reduce the bis-oxime *rac*-**5** in an *endo*-selective fashion directly to

† Dedicated to Professor Hisashi Yamamoto on the occasion of his 60th birthday.

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(6) Berkessel, A.; Menche, D.; Sklorz, C. A.; Schröder, M.; Paterson, I.; *Angew. Chem.* **2003**, *115*, 1062−1065; *Angew. Chem., Int. Ed.* **2003**, *42*, 1032−1035.

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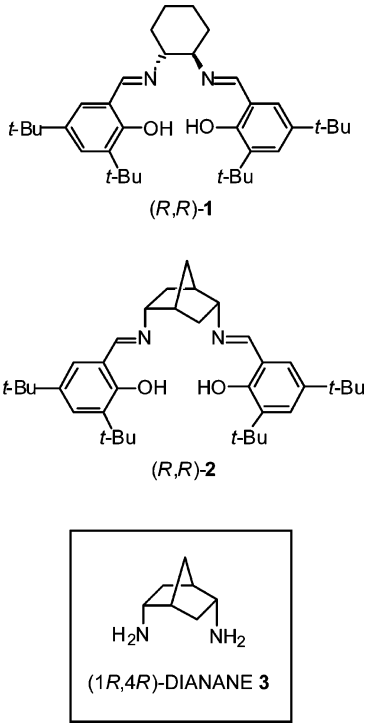
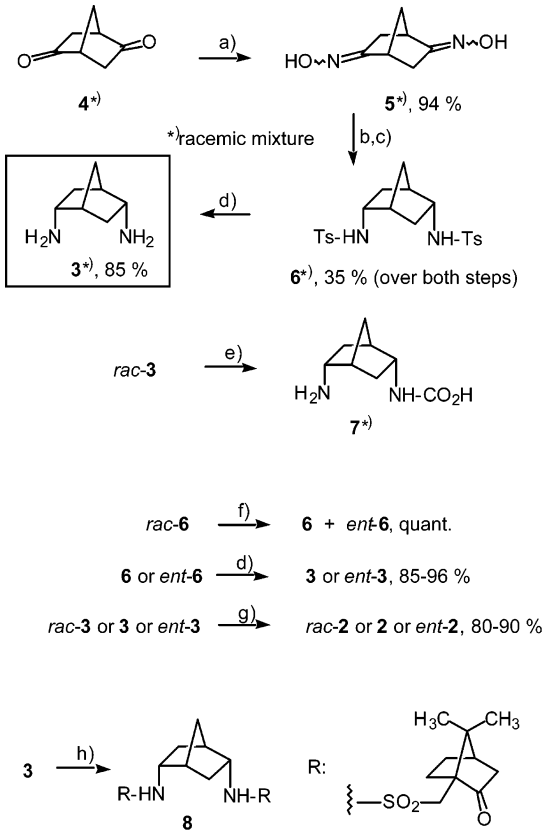
SCHEME 1



racemic DIANANE (*rac*-**3**). Unfortunately, of the numerous reduction conditions tried (catalytic hydrogenation with a variety of heterogeneous catalysts, B- and Al-based hydride reagents), only $NaBH_4$ in combination with $NiCl_2$ gave a reasonable yield of diamine of satisfactory purity (Scheme 2). This reduction product proved to be a mixture of *endo*/*exo*-isomers, the bis-*endo*-diamine *rac*-**3** being the major component (ca. 70%).

For the separation of the desired bis-*endo*-isomer, conversion of the crude mixture to the bis-tosylates and crystallization from methanol proved successful: Under these conditions, the bis-*endo* sulfonamide *rac*-**6** was obtained in 35% yield. The separation of the enantiomers **6** and *ent*-**6** was achieved by preparative HPLC on a Daicel Chiralpak AD column (see the Supporting Information for the X-ray crystal structure of the enantiomerically pure bis-tosylate *ent*-**6**). Detosylation of the sulfonamides **6** and *ent*-**6** (or *rac*-**6**) proceeded smoothly with lithium in liquid ammonia (85%, Scheme 2), affording the enantiomerically pure diamines **3** and *ent*-**3**, respectively (or racemic DIANANE, *rac*-**3**, if racemic bis-tosylate *rac*-**6** was employed). The X-ray crystal structure of DIANANE *ent*-**3** is shown in Figure 1, top. For the determination of the absolute configuration, DIANANE **3** was converted to the bis-(1*S*)-camphorsulfonamide **8** (Scheme 2). X-ray structural analysis of the crystalline bis-sulfonamide **8** unambiguously established the configuration of the DIANANE moiety in **8** to be (1*R*,4*R*) (Scheme 2, see the Supporting Information for the X-ray crystal structure of **8**). We observed that DIANANE *rac*-**3** slowly reacts with carbon dioxide when exposed to air, affording the crystalline carbamic acid *rac*-**7** (Scheme 2). The constitution of the latter was again unambiguously proven by X-ray crystallography (see the Supporting Information for the X-ray crystal structure of the racemic carbamic acid *rac*-**7**). In summary, the synthetic route shown in Scheme 2 allows the preparation of enantiomerically pure DIANANE **3** or *ent*-**3,** but the chromatographic separation step limits the quantities of DIANANE (**3**, *ent*-**3**) accessible by this method.

SCHEME 2[a]



[a] Reaction conditions: (a) $H_2N{-}OH{\cdot}HCl$ (ref 7); (b) $NaBH_4$, $NiCl_2$, 80%; (c) TosCl, NEt_3, crystallization from MeOH; (d) Li, NH_3, −35 °C; (e) air; (f) prep. HPLC on *Daicel* Chiralpak AD; (g) 3,5-di-*tert*-butylsalicylic aldehyde, EtOH; (h) (1*S*)-(+)-camphorsulfonyl chloride, NEt_3.

For the synthesis of larger amounts of both enantiomers of DIANANE, it was necessary to develop an alternative route in which both enantiomers can be generated selectively at an early stage. Scheme 3 summarizes our optimized synthesis of enantiomerically pure DIANANE **3**. Norbornadiene (**9**) served as the starting material. In the first step, norbornadiene (**9**) was subjected to a palladium-catalyzed hydrosilylation with trichlorosilane at −3 °C according to Hayashi et al.[9] The Pd catalyst is generated in situ from bis(allylpalladium chloride) and the axially chiral phosphine ligand [(*R*)-MOP], which is commercially available or can readily be prepared according to literature procedures.[10]

The hydrosilylation is exothermic, and careful temperature control is necessary to keep the proportion of the undesired *meso*-isomer (**11**, Scheme 3) low. The hydrosilylation product was subjected to a Tamao−Fleming oxidation,[9b,d,11] which afforded the bis-*exo*-diol **10** in up

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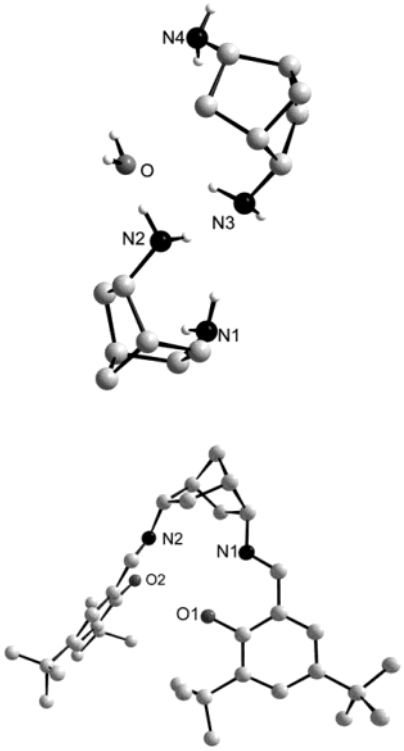
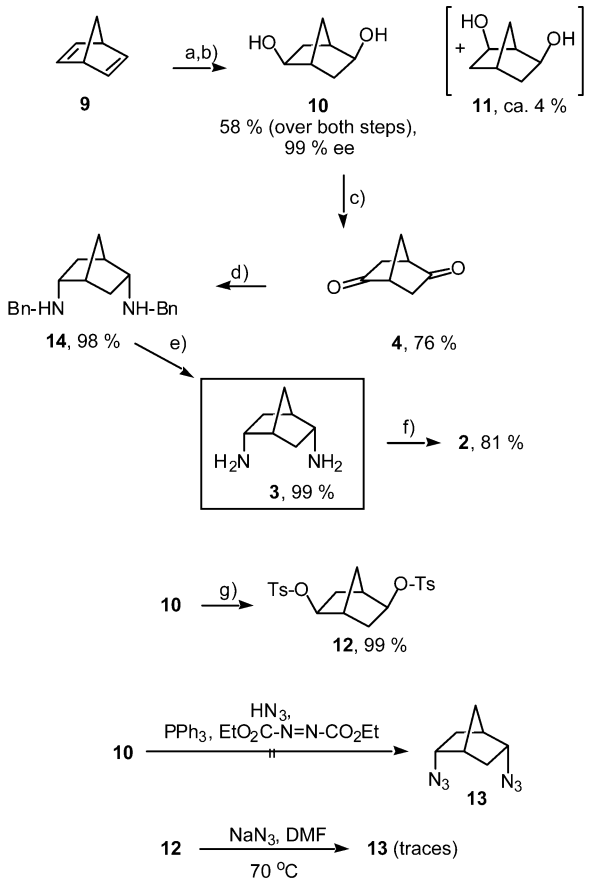


FIGURE 1. X-ray crystal structures of DIANANE hemihydrate (*ent*-**3**, top) and the DIANANE-salen ligand **2** (bottom).

to 58% yield (from norbornadiene). In this oxidation step, the hydrosilylation product is first treated with methanol and triethylamine to convert the chlorosilane into a methyl silicate. Direct oxidation of the bistrichlorosilane with 30% aqueous H_2O_2 in the presence of $KF/KHCO_3$ according to the literature procedure[9b,d] led, in our hands, to rather poor yields of the diol **10**. Optimal yields of the diol **10** (ca. 60%, vide supra) were achieved by using urea−H_2O_2 as the oxidant. Usually, the diol **10** was obtained with an enantiomeric excess of 99%, together with ca. 4% of the *meso*-compound **11**. Clearly, the opposite enantiomer *ent*-**10** can be synthesized in the same way by using (*S*)-MOP as the chiral ligand.

Efforts to synthesize the *endo*,*endo*-diamine DIANANE **(3)** from the *exo*,*exo*-diol **10** via nucleophilic substitution to the *endo*,*endo*-bis-azide **13**, followed by reduction, were unsuccessful (Scheme 3, bottom). Utilizing a number of variations of the Mitsunobu reaction (HN_3 as the acid component), the expected bisazide **13** could not be prepared. The latter was obtained, however, when the bistosylate **12** (see the Supporting Information for the X-ray crystal structure of the enantiomerically pure bistosylate **12**) was treated with sodium azide in DMF under harsh reaction conditions. The bisazide **13** was formed in trace quantities, together with two unidentified side products, and could not be isolated in pure form. Therefore, this approach was abandoned. Although we never experienced any problems in the course of the above experiments, it should be noted that the azide **13** may be explosive due to its high nitrogen content (ca. 47% by mass). For the thermal behavior of the isomeric bis-*exo*-azide, see ref 12.

SCHEME 3[a]



[a] Reaction conditions: (a) $HSiCl_3$ (2.4 equiv), 0.05 mol % $[Pd(C_3H_5)Cl]_2$, 0.2 mol % (*R*)-MOP, −3 °C; (b) (1) MeOH, NEt_3, (2) KHF_2, H_2O_2·urea; (c) PCC, CH_2Cl_2, rt; (d) Bn-NH_2 (2.5 equiv), $NaBH(OAc)_3$; (e) H_2 (1 atom), Pearlman-catalyst; (f) 3,5-di-*tert*-butylsalicuylic aldehyde, EtOH; (g) TosCl (2.2 equiv), pyridine, 4 °C.

From the enantiomerically pure diketone **4**,[13a,e] which can be easily obtained by either Swern- (79% yield)[13b] or PCC-oxidation (78% yield)[13c,d] of the bis-*exo*-diol **10**, we tried to reach the target molecule DIANANE **(3)** by reductive amination. As the direct amination with NH_4-OAc following a literature procedure[14] did not afford detectable quantities of DIANANE (**3**), we attempted the condensation with benzylamine. In this reaction, the bis-(benzylimine) is readily formed. To exclusively obtain the *endo*/*endo*-bis(benzylamine) **14** (Scheme 3), the in situ reduction of the bisimine had to be *endo*-selective. This was not the case, e.g., for the heterogeneous hydrogenation employing palladium on charcoal as catalyst, which

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TABLE 1. X-ray Crystallographic Data of Compounds (*R*)-2, *rac*-2, (*S*)-3, (*S*)-6, *rac*-6, *rac*-7, (*R*)-8, and (*R*)-12

	(*R*)-2	*rac*-2	(*S*)-3	(*S*)-6	*rac*-6	*rac*-7	(*R*)-8	(*R*)-12
formula	$C_{37}H_{54}N_2O_2$	$C_{37}H_{54}N_2O_2$	$C_{14}H_{28}N_4{\cdot}0.5H_2O$	$C_{21}H_{26}N_2O_4S_2$	$C_{21}H_{26}N_2O_4S_2$	$C_8H_{14}N_2O_2{\cdot}2.5H_2O$	$C_{27}H_{42}N_2O_6S_2$	$C_{21}H_{24}O_6S_2$
M_r	558.82	558.82	261.41	434.57	434.57	163.66	554.75	436.52
cryst dimens [mm^3]	0.20 × 0.01 × 0.10	0.20 × 0.15 × 0.15	0.20 × 0.10 × 0.10	0.20 × 0.15 × 0.15	0.20 × 0.15 × 0.15	0.15 × 0.10 × 0.10	0.15 × 0.15 × 0.15	0.30 × 0.20 × 0.20
cryst syst	monoclinic	monoclinic	tetragonal	triclinic	monoclinic	tetragonal	orthorhombic	orthorhombic
space group	$P2_1$ (no. 4)	$C2/c$ (no. 15)	$P4_2$ (no. 77)	$P1$ (no. 1)	$P2_1/n$ (no. 14)	$I4_1/a$ (no. 88)	$P2_12_12_1$ (no. 19)	$P2_12_12_1$ (no. 19)
a [Å]	10.759(1)	29.976(1)	14.816(2)	14.015(1)	11.612(1)	11.971(1)	11.085(1)	8.478(1)
b [Å]	11.399(1)	12.401(1)	14.816(2)	16.359(1)	10.417(1)	11.971(1)	12.793(1)	12.205(1)
c [Å]	14.881(2)	9.563(1)	6.421(1)	21.349(1)	17.964(1)	30.392(1)	39.330(1)	20.628(1)
α [deg]	90	90	90	103.63(1)	90	90	90	90
β [deg]	109.36(1)	96.17(1)	90	103.49(1)	95.71(1)	90	90	90
γ [deg]	90	90	90	104.56(1)	90	90	90	90
V [Å^3]	1721.9(3)	3534.3(5)	1409.4(3)	4375.8(5)	2162.2(3)	4355.3(5)	5577.4(7)	2134.5(3)
ρ_{calcd} [g·cm^{-3}]	1.078	1.050	1.232	1.319	1.335	1.313	1.321	1.358
Z	2	4	4	8	4	16	8	4
radiation	Mo Kα	Mo Kα	Mo Kα	Mo Kα	Mo Kα	Mo Kα	Mo Kα	Mo Kα
scan mode	φ/ω	φ/ω	φ/ω	φ/ω	φ/ω	φ/ω	φ/ω	φ/ω
$2\Theta_{max}$ [deg]	54	54	54	54	54	54	54	54
unique reflns	6676	3830	2926	37079	4713	2378	12188	4639
obsd reflns [$I > 2\sigma(I)$]	2906	745	1719	25980	3480	1281	6542	3017
R1 (obsd reflns)	0.056	0.063	0.052	0.059	0.038	0.075	0.053	0.040
wR2 (obsd reflns)	0.108	0.174	0.066	0.141	0.089	0.206	0.075	0.071
ρ_{fin}(max) [e·Å^{-3}]	0.214	0.314	0.169	0.367	0.192	0.308	0.187	0.173
CCDC depository no.	224478	224479	224480	224481	224482	224485	224483	224484

yielded a ca. 1:1:1 mixture of the *endo*- and *exo*-isomers. The problem was solved, however, by using triacetoxyborohydride as the reducing agent,[15] which is known to stereoselectively produce *endo*-reduction products for a number of norbornane-like substrates.[15b] Bisimine formation of the diketone **4** and subsequent *endo*-selective reduction could be carried out in one step, providing the bisbenzylamine **14** in 98% yield and with an *endo*-selectivity of 97% (3% of *endo*-*exo*-bisbenzylamine were formed). Debenzylation of **14** by hydrogenolysis with Pearlman's catalyst[16] finally afforded the target molecule DIANANE (**3**) quantitatively. The use of this particular catalyst was crucial because the debenzylation step did not work in a satisfactory manner with standard commercially available palladium-on-charcoal catalysts. However, two palladium-on-charcoal catalysts optimized for hydrogenolytic debenzylation worked just as well as the Pearlman catalyst.[17] Enantiomerically pure DIANANE *ent*-**3** was characterized by X-ray crystallography (in the form of its hemihydrate), and the result is shown in Figure 1, top. As mentioned before, DIANANE **3** tends to form the carbamate **7** upon prolonged contact with air. In practice, we found it convenient to store DIANANE **3** in the bisbenzyl-protected form **14**.

Finally, DIANANE (**3**) was condensed with 2 equiv of 3,5-bis-*tert*-butylsalicylic aldehyde to afford the DIANANE-salen ligand **2** (Schemes 1 and 3). In the course of the crystallization, the few percent of impurities (*meso*-isomer formed in the hydrosilylation of norbornadiene; *exo*-amine formed in the reductive amination step) are lost, and the crystalline Schiff base ligand is ≥99% pure (HPLC, NMR). The Schiff base ligand **2** was subjected to X-ray structural analysis as well, and the result is shown in Figure 1, bottom. In particular the latter crystal structure nicely reveals that the *N*,*N* distance is significantly larger in DIANANE−Schiff base ligands (3.59 Å in **2**) than in those ligands derived from *trans*-1,2-diaminocyclohexane, such as **1** (2.91 Å, Scheme 1).[18]

Conclusion

In this article, we describe a practical synthesis for both enantiomers **3** and *ent*-**3** of DIANANE, starting from readily available norbornadiene (**9**). With large quantities of DIANANE available in both enantiomeric forms, it is expected that this novel C_2-symmetric diamine will find many applications in asymmetric synthesis and catalysis, e.g., in the design of novel salen-type ligands such as **2**.

Experimental Section

General Methods. $HSiCl_3$ was distilled from quinoline. Norbornadiene was passed through neutral alumina (activity I) and subsequently distilled. NEt_3 and pyridine were distilled from CaH_2. Other commercially available reagents were used as purchased. Racemic bicyclo[2.2.1]heptane-2,5-dione-dioxime

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(16) Bernotas, R. C.; Cube, R. V. *Synth. Commun.* **1990**, *20*, 1209−1212.

(17) Catalysts were received from ENGELHARD ITALIANA SPA: (a) Sample code: 43958, 10% Pd on carbon powder, moisture content: 54.66% and (b) Sample code: 43959, 5% Pd on carbon powder, moisture content: 55.00%.

(18) Yoon, J. W.; Yoon, T.-S.; Shin, W. *Acta Crystallogr. Sect. C*: *Cryst. Struct. Commun.* **1997**, *53*, 1685−1687.

was prepared according to a literature method.[7] Axially chiral MOP ligands were prepared according to a literature method.[10] Debenzylation catalysts[17] were kindly provided by Engelhard Inc., NJ. All solvents were distilled prior to use. Dry solvents were freshly distilled under argon from either CaH_2 or Na/benzophenone. Melting points were determined in an open capillary and are uncorrected.

***endo,endo*-2,5-Diaminobicyclo[2.2.1]heptane (*mix*-3, mixture of stereoisomers).** Bicyclo[2.2.1]heptane-2,5-dione-dioxime *rac*-**5** (9.25 g, 60.0 mmol) in dry MeOH (100 mL) was added to a suspension of anhydrous $NiCl_2$ (15.6 g, 120 mmol) in dry MeOH (400 mL) with stirring. The mixture was cooled to −35 °C and $NaBH_4$ (45.0 g, 1.20 mol) was added over a period of 1 h in small portions to maintain a temperature beetween −20 and −35 °C. After completion of the addition, the mixture was allowed to warm to rt and concentrated in vacuo. The dark brown residue was extracted with 15% aq NaOH (100 mL) and CH_2Cl_2 in a liquid/liquid extractor. After 2−3 d the yellow organic suspension was filtered and concentrated in vacuo. Distillation of the residue at 13 mbar, 130 °C, yielded 5.5 g of a colorless oil that solidified upon cooling. This material was shown by GC to be ca. 80% pure and was used in the next step without further purification. GC/MS (capillary column HP-5MS 0.25 mm × 30 m, cross-linked 5% PH ME Siloxane 0.25 μm; He, 1 mL/min; 80 °C, 10 min, 5 °C/min, 100 °C, 10 min, 20 °C/min, 260 °C, 10 min) τ_R 9.8−9.9 min (3 isomers with identical *m*/*z*) 126 M^+, 125 $(M - H)^+$, 109 $(M - NH_3)^+$, 94 (M n -2 $NH_2)^+$, 82 $(C_6H_{10})^+$, 68 $(C_5H_8)^+$.

***endo,endo*-2,5-Bis[4(4-methylphenyl)sulfonylamido]-bicyclo[2.2.1]heptane (*rac*-6).** To a solution of the crude 2,5-diaminobicyclo[2.2.1]heptane *mix*-**3** (9.3 g, 74 mmol) and NEt_3 (22.0 mL, 158 mmol) in dry CH_2Cl_2 (300 mL) at −78 °C was added TosCl (28.6 g, 150 mmol) in small portions with vigorous stirring. The temperature was maintained for 3 h, then the suspension was allowed to warm to rt overnight. The yellow to red brown suspension was washed with 3 × 80 mL of 2 M aq HCl, 2 × 80 mL of H_2O, and 80 mL of brine and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the residue was extracted with a mixture of Et_2O and *n*-pentane (1/1, v/v) several times. The crude product was crystallized from MeOH and treated with activated charcoal in boiling acetic acid. Crystallization from acetic acid and subsequently from MeOH gave 11.1 g (35%) of colorless crystals of *rac*-**6**. Mp 188−190 °C. IR (CsI) 3260, 2964, 1302−1337, 1162, 1092, 813 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.4 Hz, 4H), 7.23 (d, J = 8.4 Hz, 4H), 5.70 (br d, J = 6.9 Hz, 2H), 3.42−3.53 (m, 2H), 2.39 (s, 6H), 2.05−2.10 (m, 2H), 1.50−1.63 (m, 2H), 1.28 (br s, 2H), 1.18−1.26 (m, 2H). ^{13}C NMR (75 MHz, CDCl3) δ 143.3 (s), 137.4 (s), 129.6 (d), 127.1 (d), 54.2 (d), 41.0 (d), 36.9 (t), 28.4 (t), 21.5 (q). MS (FAB) 457 $(M + Na)^+$, 435 $(M + H)^+$, 279 $(M + H - Tos - H_2)^+$, 264 $(M + H - TosNH_2)^+$, 262 $(M + H - TosNH_2 - H_2)^+$. HRMS (ESI) calcd for $C_{21}H_{26}N_2O_4S_2 + H^+$ 435.141, found 435.141. Anal. Calcd for $C_{21}H_{26}N_2O_4S_2$: C, 58.04; H, 6.03; N, 6.45. Found: C, 57.93; H, 5.93; N, 6.41.

(1*R*,2*R*,4*R*,5*R*)- and (1*S*,2*S*,4*S*,5*S*)-2,5-Bis[(4-methylphenyl)sulfonylamido]bicyclo[2.2.1]heptane [(*R*)- and (*S*)-6]. The two enantiomers of sulfonamide *rac*-**6** were separated by chiral preparative HPLC on a Daicel Chiralpak AD column (50 mm i.d. × 500 mm L) with *n*-hexane/*i*-PrOH (60/40, v/v), *P* 12 bar, flow 80 mL/min, τ_R 24.0−33.0 min [(*R*)-**6**], 46.5−62.5 min [(*S*)-**6**]. A 100−200 mg sample of *rac*-**6** in 10 mL of hot EtOH were injected per run. The fractions were concentrated in vacuo and the residue was crystallized from MeOH. (*R*)-**6**: Mp 175−176 °C. $[\alpha]^{20}_D$ +12.3 ($CHCl_3$, *c* 1.00). CD (EtOH) $\Delta\epsilon_{205}$ +3.5, $\Delta\epsilon_{223}$ +0.2, $\Delta\epsilon_{233}$ +1.1, $\Delta\epsilon_{248}$ −0.3. Anal. Calcd for $C_{21}H_{26}N_2O_4S_2$: C, 58.04; H, 6.03; N, 6.45. Found: C, 58.11; H, 6.13; N, 6.50. (*S*)-**6**: Mp 174−176 °C. $[\alpha]^{20}_D$ −12.3 ($CHCl_3$, *c* 1.00). CD (EtOH) $\Delta\epsilon_{205}$ −4.0, $\Delta\epsilon_{223}$ −0.4, $\Delta\epsilon_{233}$ −1.8, $\Delta\epsilon_{248}$ +0.1. Anal. Calcd for $C_{21}H_{26}N_2O_4S_2$: C, 58.04; H, 6.03; N, 6.45. Found: C, 58.06; H, 6.02; N, 6.48.

***endo,endo*-2,5-Diaminobicylo[2.2.1]heptane (DIANANE) (*rac*-3).** A flask was charged with the sulfonamide *rac*-**6** (1.31 g, 3.00 mmol), and NH_3 (ca. 150 mL) was condensed at −78 °C with magnetical stirring. The mixture was allowed to warm to −33 °C and solid Li (220 mg, 31.7 mmol) was added gradually. The suspension turned blue and the reaction was quenched after 80 min by dropwise addition of brine (0.5 mL). NH_3 was evaporated and the residue was diluted with H_2O (10 mL) and concentrated in vacuo until the condensation of water was observed. The residue was diluted with H_2O (10 mL), acidified with concentrated HCl, and extracted with CH_2Cl_2. The aqueous phase was concentrated in vacuo until a white precipitate formed. 25% aq NaOH (15 mL) was added and the aqueous solution was extracted with CH_2Cl_2 in a liquid/liquid extractor for 42 h. Concentration of the organic phase yielded 321 mg (85%) of DIANANE *rac*-**3** as a colorless oil or semisolid. Bp 110 °C, 12 mbar. IR (film) 3359, 3282, 2941, 2871, 1604, 1452, 887 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.26−3.30 (m, 2H), 1.95 (br s, 2H), 1.60−1.71 (m, 2H), 1.40 (centered multiplet, 2H), 1.17−1.24 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.7 (d), 43.8 (d), 38.9 (t), 30.2 (t). HRMS (EI) calcd for $C_7H_{14}N_2$ 126.116, found 126.116.

***endo,endo*-(5-Aminobicyclo[2.2.1]heptan-2-yl)carbamic Acid *(rac*-7).** When a solution of DIANANE *rac*-**3** in CH_2Cl_2/MeOH was allowed to stand open to air, off-white crystals of carbamic acid *rac*-**7** precipitated gradually, which were subjected to X-ray structural analysis.

(1*S*,2*S*,4*S*,5*S*)-2,5-Diaminobicylo[2.2.1]heptane (DIANANE, (*S*)-3) by Detosylation of (*S*)-6. The bissulfonamide (*S*)-**6** was subjected to the detosylation procedure described above for *rac*-**6**. As an alternative to the liquid/liquid extraction of the acidified residues from the first extraction, this crude material was treated with a large excess of solid KOH and extracted with CH_2Cl_2 in a Soxhlett extractor. Evaporation of the solvent in vacuo yielded 107 mg (96%) of DIANANE (*S*)-**3** as a colorless oil or semisolid.

(1*S*,1′*S*,4*R*,4′*R*)-*N*,*N*′-(1*R*,2*R*,4*R*,5*R*)-Bicyclo[2.2.1]heptan-2,5-diylbis[7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonamide] [(*R*)-8]. A solution of DIANANE (*R*)-**3** (35 mg, 280 μmol) and NEt_3 (77 μL, 560 μmol) in dry CH_2Cl_2 (10 mL) was cooled to −78 °C and (1*S*)-(+)-camphorsulfonyl chloride (147 mg, 590 μmol) was added. After 1 h, the suspension was allowed to warm to rt and stirred overnight. The reaction mixture was washed with H_2O, 2 M aq HCl (2×), and brine (2×) and dried over $MgSO_4$. A small amount of MeOH was added and the mixture was evaporated until a colorless pecipitation occurred. This material was filtered off and recrystallized twice from MeOH to yield 10 mg (7%) of the product (*R*)-**8** as colorless crystals, suitable for X-ray structural analyis. Mp 204−205 °C. IR (CsI) 3338, 2961, 1742, 1458, 1323, 1142, 1045, 910 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.68−5.71 (m, 2H), 3.80−3.88 (m, 2H), 3.44 (d, J = 15 Hz, 2H), 2.91 (d, J = 15 Hz, 2H), ca. 2.44 (centered multiplet, 2H), ca. 2.44 (centered multiplet, 2H), 2.19−2.27 (m, 2H), 2.09−2.12 (m, 2H), ca. 2.01 (centered multiplet, 2H), ca. 2.00 (centered multiplet, 2H), ca. 1.93 (centered multiplet, 2H), ca. 1.92 (centered multiplet, 2H), 1.51 (br s, 2H), ca. 1.47 (centered multiplet, 2H), ca. 1.44 (centered multiplet, 2H), 1.00 (s, 6H), 0.91 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.7 (s), 59.2 (s), 54.7 (d), 50.3 (t), 48.9 (s), 43.1 (t), 42.7 (d), 42.3 (d), 36.9 (t), 28.6 (t), 27.0 (t), 26.5 (t), 19.9 (q), 19.5 (q). HRMS (ESI) calcd for $C_{27}H_{42}N_2O_6S_2 + Na^+$ 577.237, found 577.238.

2,2′-[*endo,endo*-Bicyclo[2.2.1]heptan-2,5-diylbis(nitrilomethylidine)]bis-4,6-di-*tert*-butylphenol (*rac*-2). 2,5-Di-*tert*-butylsalicylaldehyde (1.13 g, 4.83 mmol) was dissolved in dry EtOH (40 mL) and added to a solution of racemic DIANANE *rac*-**3** (290 mg, 2.30 mmol) in dry EtOH (20 mL). After being stirred at rt for 30 min, the solution was heated to reflux and then stirred at rt overnight. The yellow needles formed were filtered off, washed with MeOH, and recrystallized from MeOH/CH_2Cl_2 to yield 1.11 g (86%) of the product *rac*-**2** as bright yellow needles. Mp 286−287 °C. IR (CsI) 2955, 2906, 2873, 1628, 1468, 1439, 1272, 1250, 1069, 880, 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 13.69 (br s, 2H), 8.43 (s, 2H),

7.35 (d, J = 2.3 Hz, 1H), 7.08 (d, J = 2.4 Hz, 2H), 3.80−3.84 (m, 2H), 2.39 (br t, J = 4.0 Hz, 2H), 2.04 (dd, J = 13.5, 4.5, 2H), 1.85−1.94 (m, 2H), 1.71 (s, 2H), 1.41 (s, 18H), 1.30 (s, 18H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.0 (d), 158.1 (s), 139.1 (s), 136.7 (s), 126.5 (d), 125.7 (d), 118.0 (s), 70.4 (d), 44.4 (d), 38.2 (t), 35.1 (s), 34.1 (s), 31.5 (q), 30.2 (t), 29.4 (q). MS (FAB) 571 (M + 12)$^+$, 560 (M + H)$^+$, 559 (M)$^+$, 558 (M − H)$^+$, 543 (M + 2H − H_2O)$^+$, 541 (M − H_2O)$^+$, 503 (M − *t*-Bu)$^+$. Anal. Calcd for $C_{37}H_{54}N_2O_2$: C, 79.52; H, 9.74; N, 5.01. Found: C, 79.48; H, 9.74; N, 4.92.

2,2′-[(1*S*,2*S*,4*S*,5*S*)-Bicyclo[2.2.1]heptane-2,5-diylbis(nitrilomethylidine)]bis-4,6-di-*tert*-butylphenol [(*S*)-2]. 2,5-Di-*tert*-butylsalicylaldehyde (1.41 g, 6.00 mmol) was dissolved in hot EtOH (40 mL) and added to a solution of DIANANE (*S*)-**3** (379 mg, 3.00 mmol) in EtOH (20 mL). After being stirred at rt for 2 h, the mixture was stored at 4 °C overnight. The yellow solid was filtered off and recrystallized from EtOH/CH_2Cl_2 to yield 1.36 g (81%) bright yellow needles of the enantiopure salen (*S*)-**2**. Mp 249−250 °C. $[\alpha]^{20}_D$ −343.7 ($CHCl_3$, *c* 1.00). CD ($CHCl_3$) $\Delta\epsilon_{242}$ +1.6, $\Delta\epsilon_{254}$ +7.5, $\Delta\epsilon_{271}$ −31.8, $\Delta\epsilon_{303}$ −2.0, $\Delta\epsilon_{341}$ −15.5. Anal. Calcd for $C_{37}H_{54}N_2O_2$: C, 79.52; H, 9.74; N, 5.01. Found: C, 79.34; H, 9.62; N, 5.05. (*R*)-**2**: Mp 249−250 °C. $[\alpha]^{20}_D$ +343.7 ($CHCl_3$, *c* 1.00). CD ($CHCl_3$) $\Delta\epsilon_{242}$ −1.9, $\Delta\epsilon_{255}$ −7.5, $\Delta\epsilon_{271}$ +31.9, $\Delta\epsilon_{303}$ +1.7, $\Delta\epsilon_{341}$ +15.0. Anal. Calcd for $C_{37}H_{54}N_2O_2$: C, 79.52; H, 9.74; N, 5.01. Found: C, 79.41; H, 9.61; N, 5.06.

(1*S*,2*R*,4*S*,5*R*)-2,5-Dihydroxybicyclo[2.2.1]heptane [(*S*)-10]. A solution of $[Pd(C_3H_5)Cl]_2$ (14.6 mg, 40.0 μmol) and (*S*)-MOP (78.7 mg, 168 μmol) in benzene (2 mL) was placed into a double-jacketed 50-mL Schlenk flask under Ar. $HSiCl_3$ (19.9 mL, 197 mmol) was added, and the solution was cooled to −3 °C. Norbornadiene (8.34 mL, 82.0 mmol) was added slowly with magnetic stirring. The reaction mixture was stirred at −3 °C for ca. 3 d, until it turned into a pale yellowish solid. The solvent and excess silane were removed in vacuo at rt. The residue was dissolved in 50.0 mL of dry Et_2O under Ar and cooled to 0 °C. A mixture of dry MeOH (59.9 mL, 1.48 mol), dry NEt_3 (80.0 mL, 574 mmol), and dry Et_2O (50.0 mL) was added dropwise. After the solution was stirred at rt overnight, the precipitated salts were filtered off and washed with small quantities of Et_2O. The combined filtrates were concentrated in vacuo to yield a yellowish solid. To this solid was added KHF_2 (32.0 g, 410 mmol), THF (80 mL), MeOH (80 mL), and H_2O_2·urea (57.8 g, 615 mmol). The resulting white suspension was stirred overnight at 60 °C. After addition of a catalytic amount of MnO_2, stirring was continued at rt for 4 h. The solids were filtered off with suction, and the filter cake was washed with MeOH. The combined filtrates were concentrated in vacuo. The residue was dissolved in 100 mL of H_2O and extracted with 5 × 100 mL of a $CHCl_3$/*i*-PrOH mixture (3/1, v/v). The combined organic phases were dried over $MgSO_4$ and evaporated. The remaining white solid was recrystallized from $CHCl_3$/*n*-hexane to give 5.17 g (58% based on norbornadiene) of the diol (*S*)-**10** (99%ee) as thin white crystals, containing ca. 4% of the *meso*-diol (by GC). GC (capillary column WCOT Fused Silica 0.25 mm × 25 m, CP-Chirasil-Dex CB 0.25 μm; He, 1 mL/min; 125 °C, 40 min) τ_R 27.8 min [(*S*)-**10**], 28.5 min [(*R*)-**10**], 36.4 min (**11**). Mp 158 °C. IR (CsI) 3301, 2966, 1458, 1448, 1351, 1091, 743 cm^{-1}. ^{1}H NMR (500 MHz, py-d_6) δ 6.00 (s, 2H), 3.92 (dd, J = 5.0, 3.5 Hz, 2H), 2.41−2.42 (m, 2H), 2.01 (s, 2H), 1.57−1.59 (m, 4H). ^{13}C NMR (125 MHz, py-d_6) δ 73.5 (d), 44.2 (d), 37.7 (t), 31.2 (t). HRMS (EI) calcd for $C_7H_{14}N_2-H_2O$ 110.073, found 110.073.

CAUTION: In some cases, we experienced an autocatalytic exothermic process, resulting in uncontrolled reaction and higher proportions of the *meso*-isomer. Addition of small amounts of quinoline to the reaction mixture seemed to overcome this problem by quenching any free HCl.

(1*R*,2*S*,4*R*,5*S*)-2,5-Bis[(4-methylphenyl)sulfonyloxy]-bicyclo[2.2.1]heptane [(*R*)-12]. The diol (*R*)-**10** (128 mg, 1.00 mmol) was dissolved in pyridine (2.0 mL) and cooled to 2 °C. TosCl (419 mg, 2.20 mmol) was added and the mixture was allowed to stand at ca. 2 °C for 2 d. The reaction mixture was filtered, and the filtrate was concentrated in vacuo at rt. The residue was treated with a mixture of 2 M aq HCl (5 mL) and extracted with 3 × 5 mL of CH_2Cl_2. The combined organic phases were washed with 2 × 5 mL of 2 M aq HCl and 5 mL of sat. $NaHCO_3$ and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the residue was recrystallized twice from MeOH to yield 430 mg (99%) of colorless crystals of the tosylate (*R*)-**12**. Mp 126−129 °C. IR (CsI) 2976, 1598, 1496, 1442, 1355, 1307, 1175, 1098, 1052, 824 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 4H), 7.31 (d, J = 8.1 Hz, 4H), 4.27 (dd, J = 6.6, 1.8 Hz, 2H), 2.42 (s, 6H), 2.38 (d, J = 5.7 Hz, 2H), 1.59 (s, 2H), 1.51−1.54 (m, 2H), 1.40−1.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7 (s), 134.0 (s), 129.8 (d), 127.6 (d), 82.4 (d), 41.0 (q), 33.8 (t), 31.6 (t), 21.6 (d). $[\alpha]^{20}_D$ +4.0 ($CHCl_3$, *c* 1.00). Anal. Calcd for $C_{21}H_{24}O_6S_2$: C, 57.78; H, 5.54. Found: C, 57.91; H, 5.49.

(1*S*,4*S*)-Bicyclo[2.2.1]heptane-2,5-dione [(*S*)-4]. Diol (*S*)-**10** (5.13 g, 40.0 mmol) and powdered 3 Å molecular sieves (25.0 g) were suspended in CH_2Cl_2 (250 mL). PCC (43.1 g, 200 mmol, 5.00 equiv) was added slowly and the resulting mixture was stirred at rt overnight. Et_2O (250 mL) was added with vigorous stirring, and stirring was continued for 30 min. The mixture was then allowed to stand for 2 h. The liquid was filtered through 50 g of Florisil (80−150 μm). The black residue was extracted with 4 × 50.0 mL of CH_2Cl_2/Et_2O (1/1, v/v) in an ultrasonic bath. The combined extracts were also filtered through the Florisil pad. Evaporation of the combined solutions yielded 3.78 g (76%) of the diketone (*S*)-**4** and the *meso* byproduct as a white solid that was used without further purification (Kugelrohr distillation is possible at 100 °C, 0.12 mbar). The analytical data refer to purified material containing 2.5% of the *meso* byproduct (by GC). GC (capillary column WCOT Fused Silica 0.25 mm × 25 m, CP-Chirasil-Dex CB 0.25 μm; He, 1 mL/min; 100 °C, 30 min) τ_R 18.7 min [(*R*)-**4**], 19.5 min [(*S*)-**4**], 24.6 min (*meso*-diketone). Mp 115−133 °C. IR (CsI) 2966, 1755, 1737, 1409, 964, 712 cm^{-1}. ^{1}H NMR (500 MHz, $CHCl_3$) δ 2.97 (td, J = 6.5, 1.5 Hz, 2H), 2.34−2.39 (m, 2H), 2.13 (td, J = 18.0, 2.0 Hz, 2H), 2.08−2.09 (m, 2H). ^{13}C NMR (125 MHz, $CHCl_3$) δ 212.3 (s), 48.5 (d), 38.9 (t), 36.3 (t). $[\alpha]^{20}_D$ −4.3 ($CHCl_3$, *c* 1.00). Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.48; H, 6.42. (*R*)-**4**: Mp 118−130 °C. $[\alpha]^{20}_D$ +4.2 ($CHCl_3$, *c* 1.00). Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.74; H, 6.50.

(1*S*,2*S*,4*S*,5*S*)-2,5-Dibenzylaminobicylo[2.2.1]heptane [(*S*)-14]. Glacial acetic acid (12.0 mL, 208 mmol) was added dropwise to a suspension of $NaBH_4$ (2.45 g, 65.0 mmol) in dry CH_2Cl_2 (200 mL) and the resulting mixture was heated to reflux for 30 min. A mixture of diketone (*S*)-**4** (3.23 g, 26.0 mmol) in dry CH_2Cl_2 (50.0 mL) and $BnNH_2$ (7.09 mL, 65.0 mmol) was added dropwise at rt. After being stirred for 6 h the reaction was quenched by the addition of 5% aq NaOH (51.8 mL, 65.0 mmol). The mixture was extracted with 3 × 150 mL of 2 M aq HCl and the combined aqueous phases were basified by the addition of solid NaOH to pH 9. The resulting suspension was extracted with 3 × 150 mL of Et_2O and the combined organic phases were dried over $MgSO_4$. After concentration in vacuo a colorless oil remained, which solidified slowly. This material was purified by Kugelrohr distillation at 150 °C, 3 × 10^{-3} mbar, to yield 7.79 g (98%) of the product (*S*)-**14** as a colorless solid. Mp 48−49 °C. IR (CsI) 3228, 3029, 2955, 2870, 2797, 1648, 1560, 1496, 1456, 1345, 1143, 1103, 1030, 995, 729, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.14−7.27 (m, 10H), 3.60 (dd, J = 12.9, 9.0 Hz, 4H), 3.06 (td, J = 10.2, 3.9 Hz, 2H), 2.21 (br t, J = 4.2 Hz, 2H), 1.60−1.69 (m, 4H), 1.40 (s, 2H), 1.31 (dd, J = 12.6, 4.2 Hz, 2H). ^{13}C NMR (75 MHz, $CHCl_3$) δ 140.6 (s), 128.3 (d), 128.2 (d), 126.8 (d), 58.4 (d), 52.5 (t), 39.8 (d), 38.2 (t), 29.2 (t). $[\alpha]^{20}_D$ −15.7 ($CHCl_3$, *c* 1.00). Anal. Calcd for $C_{21}H_{26}N_2$: C, 82.31; H, 8.55; N, 9.14. Found: C, 82.39; H, 8.57; N, 9.13. (*R*)-**14**: Mp 43−49 °C. $[\alpha]^{20}_D$ +14.5 ($CHCl_3$, *c* 1.00). Anal. Calcd for $C_{21}H_{26}N_2$: C, 82.31; H, 8.55; N, 9.14. Found: C, 81.18; H, 8.52; N, 9.17.

(1*S*,2*S*,4*S*,5*S*)-2,5-Diaminobicylo[2.2.1]heptane DIANANE [(*S*)-3] by Hydrogenolysis of (*S*)-14. A suspension of the bisbenzylamine (*S*)-**14** (1.53 g, 5.00 mmol) and $Pd(OH)_2$ (15−20% on activated charcoal with 50% H_2O, 1.41 g) in EtOH (50 mL) was stirred under H_2 atmospheric pressure (balloon). After the solution was stirred for 24 h, debenzylation was found to be complete by GC/MS. The catalyst was filtered off and the solution was concentrated in vacuo to afford 625 mg (99%) of DIANANE (*S*)-**3** as a colorless oil that crystallized upon cooling to 4 °C to yield colorless needles. Mp ca. 20 °C. GC/MS (capillary column HP-5MS 0.25 mm × 30 m, cross-linked 5% PH ME Siloxane 0.25 μm; He, 1 mL/min; 100 °C, 5 min, 20 °C/min, 200 °C, 15 min, 20 °C/min, 280 °C, 10 min) τ_R 5.1 min (**3**: 126 (M^+), 109 ($M - NH_3$)$^+$, 94 ($M - 2\ NH_2$)$^+$, 82 (C_6H_{10})$^+$, 68 (C_5H_8)$^+$), 12.4 min (mono-N-Bn-**3**: 216 (M^+, 172 ($C_{12}H_{14}N$)$^+$, 132 ($C_9H_{10}N$)$^+$, 125 ($M - C_7H_7$)$^+$, 106 (C_7H_8N)$^+$, 91 (C_7H_7)$^+$), 28.5 min (**14**: 306 (M^+, 215 ($M - C_7H_7$)$^+$, 201 ($M - C_7H_7N$), 91 (C_7H_7)$^+$). GC (capillary column CP-Chirasil-Dex CB 0.25 mm × 25 m, WCOT Fused Silica 0.25 μm; He, 1 mL/min; 150 °C, 40 min) τ_R 22.7 min (bis-TFA-amide of (*S*)-**3**), 23.3 min (bis-TFA-amide of (*R*)-**3**), 24.6 min (bis-TFA-amide of meso compound). IR (film) 3353, 3276, 2944, 2872, 1652, 1594, 1456, 1386, 898 cm^{-1}. ^1H NMR (300 MHz, MeOH-d_4) δ 3.22 (td, J = 3.3, 1.5 Hz, 2H), 1.99 (br t, J = 4.5 Hz, 2H), 1.64−1.75 (m, 2H), 1.42 (dd, J = 1.5, 1.5 Hz, 2H), 1.10−1.17 (m, 2H). ^{13}C NMR (75 MHz, MeOH-d_4) δ 54.1 (d), 44.8 (d), 39.5 (t), 30.1 (t).

Purity Determination of 2,2′-[(1*S*,2*S*,4*S*,5*S*)-Bicyclo-[2.2.1]heptane-2,5-diylbis(nitrilomethylidine)]bis-4,6-di-*tert*-butylphenol [(*S*)-2] Obtained from the Above Amine [(*S*)-3]. The enantiopure salen (*S*)-**2** was prepared from DIANANE (*S*)-**3** obtained by debenzylation of (*S*)-**14** according to the above procedure. In the recrystallized product, the corresponding *meso*-salen could not be detected by NMR. HPLC analysis revealed that less than 0.2% of the *meso*-salen is present in the recrystallized salen (*S*)-**2**. HPLC (MN EC 250/4 Nucleodur 100-5 C18 EC; CH_3CN, 0.4 mL/min; 60 min; UV, 220−400 nm) τ_R 38.2 min (**2**), 49.5 min (*meso*-salen). UV (HPLC) 230, 266, 332 nm (for both peaks). Mp 250 °C. $[\alpha]^{20}_D$ −343.7 ($CHCl_3$, *c* 1.00). Anal. Calcd for $C_{37}H_{54}N_2O_2$: C, 79.52; H, 9.74; N, 5.01. Found: C, 79.34; H, 9.91; N, 5.05. (*R*)-**2**: Mp 250 °C. $[\alpha]^{20}_D$ +344.7 ($CHCl_3$, *c* 1.00). Anal. Calcd for $C_{37}H_{54}N_2O_2$: C, 79.52; H, 9.74; N, 5.01. Found: C, 79.34; H, 9.55; N, 5.04.

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Supporting Information Available: X-ray analyses of compounds (*R*)-**2**, *rac*-**2**, (*S*)-**3**, (*S*)-**6**, *rac*-**6**, *rac*-**7**, (*R*)-**8**, and (*R*)-**12**. This material is available free of charge via the Internet at http://pubs.acs.org. X-ray crystallographic data for compounds (*R*)-**2**, *rac*-**2**, (*S*)-**3**, (*S*)-**6**, *rac*-**6**, *rac*-**7**, (*R*)-**8**, and (*R*)-**12** were collected as summarized in the table. The table also states the depository numbers at the Cambridge Crystallographic Data Centre. From there, the full set of data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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