Stereoselective Synthesis of *N,N′*-Diaryl-2,5-dioxopiperazines from Homochiral or Racemic 2-Bromopropananilides†

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N,N′-Diaryl-2,5-dioxopiperazines **8** and **9**, related to the amino acid alanine, are easily obtained by self-cyclocoupling of 2-bromopropananilides **7**. The *cis-(R,R) or cis-(S,S)/trans-(R,S)* distribution is controlled, to varying extents, by starting either from a single enantiomer or racemate and by the promoter, aryl substituent, and solvent. ^{1}H NMR spectra of the members of six diastereomeric couples and X-ray structures of representative products are reported.

2,5-Dioxopiperazines (DOP, diketopiperazines, cyclic dipeptides) are widespread natural peptide derivatives, some of which display biological activity.[1] Simple representatives have been obtained as intended[2] or unexpected products[3] from peptides, amino acids, or amino esters. Esters of hindered amino acids[4] and 2-alkyl-2-(trifluoromethyl) amino acids[5] give little or no DOP, but conversion of 2-aminoisobutyric acid and its esters into DOP occurs.[6] Derivatized DOP yield, in turn, special amino acids on acidolysis.[7] DOP that are N-unsubstituted and/or carrying auxiliary chiral groups at the nitrogens represent useful intermediates in the stereoselective synthesis of C-alkyl amino acids[8] and can catalyze the asymmetric formation of C−C bonds. In particular, cyclo-*(S)*-His-*(S)*-Phe, as well as other DOP, catalyze the formation of excesses of the *R* enantiomer in the Strecker synthesis of hydroxynitriles.[9] Finally, DOP carrying proper groups in the side chains provide rigid frameworks for studying intramolecular photoinduced electron transfer,[10] conformational details,[11] and molecular recognition.[12] The macromolecular self-assembly of DOP tetrapeptides was recently reported.[13]

In previous studies on 2-bromoamides **1**−**3** (Scheme 1), we found that homochiral 2-bromopropanamides (**2**)[14a,d] undergo enantioselective bromide substitution by nitrogen or oxygen nucleophiles, yielding alaninamides **4**, quaternary ammonium amides **5**, or *O*-alkyl lactamides **6**.[14] Base-promoted cyclocoupling of 2-haloacetanilides into *N-N′*-diaryl-DOP[15] and a few *N,N′*-disubstituted-DOP was also reported.[14b,16−18]

Whereas reactions at the carboxylic function normally give DOP bearing the same chirality as the precursors,[19] we expected to observe a composite stereochemical outcome in the synthesis of DOP from chiral 2-haloamides. Accordingly, we prepared chiral nonracemic 2-bromopropananilide and ring-substituted analogs *(S)*-**7a**−**g** or *(R)*-**7a,e** starting from L- or D-alanine[14a,d] as well as racemic *(R,S)*-**7a**−**g** from commercial 2-bromopropanoyl bromide and allowed them to react using NaH (or Ag_2O) as a promoter.

(A). Reactions with NaH in Toluene (Table 1A). Homochiral *(R)*-**7a,e** or *(S)*-**7a**−**e** gave a diastereomeric excess of optically active *cis-(S,S)*-**8a,e** or, respectively, *cis-(R,R)*-**8a**−**e**. The de was highest (8/1) for X = *p*-OMe

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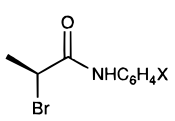
Scheme 1

BrCRR'CONHR" XCHMeCONHR"

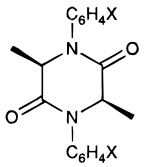
1 R = R' = H **4** X = NRR'

2 R = H R' = Me **5** X = $^{+}$NEt$_3$ CF$_3$SO$_3^{-}$

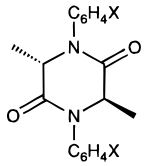
3 R = R' = Me **6** X = OMe



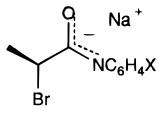
(S)-**7**



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



trans-(R,S)-**9**



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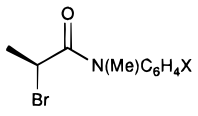

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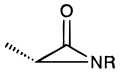

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Table 1. Self-Condensations of *(R)-, (S)-,* or *(R,S)*-2-Bromopropananilides (7) into 1,4-Diaryl-2,5-dioxopiperazines 8 and 9

starting compds		chiral addition	time (h)	products **8** + **9** (%)	products **8/9** (ratio)
	X				
A: Promoter NaH					
(*R*)-**7a**	*p*-OMe		4	98	7.9/1
(*S*)-**7a**	p-OMe		4	95	8.3/1
(*S*)-**7a**	*p*-OMe	(*R,R*)-**8**	4	95	8.5/1
(*S*)-**7a**	*p*-OMe	(*S,S*)-**8**	4	99	8/1
(*S*)-**7a**	*p*-OMe		0.3	71	2.7/1[a]
(*R,S*)-**7a**	*p*-OMe		4	92	1/1.7
(*S*)-**7b**	*p*-Me		11	89	4.5/1
(*R,S*)-**7b**	*p*-Me		11	84	1/2
(*S*)-**7c**	H		15	74	5/1
(*R,S*)-**7c**	H		15	78	1.8/1
(*S*)-**7d**	*p*-Cl		30	93	4.6/1
(*R,S*)-**7d**	*p*-Cl		30	95	2.4/1
(*R*)-**7e**	*m*-Br		18	88	5/1
(*S*)-**7e**	*m*-Br		18	78	5.3/1
(*R,S*)-**7e**	*m*-Br		18	94	2/1
B: Promoter Ag$_2$O/Et$_3$N					
(*S*)-**7c**	H		18	67[b]	2/1
(*S*)-**7e**	*m*-Br		18	69[b]	2/1

[a] At reflux. Balance was given by previously identified[18] O-alkylation product(s). b Balance: 2-triethylammonium propananilide (**5c,e**) (^{1}H NMR spectra).[14d]

and close to 5/1 in all other cases. Racemic *(R,S)*-**7a-e**, in turn, gave 1/2 or 2/1 diastereomeric mixtures of racemic *(R,R),(S,S)-cis*-**8a**−**e** and *trans-(S,R)*-**9a**−**e**. With the racemic reagents, the *cis/trans* ratio varied according to the substitution pattern at the aromatic ring inasmuch as the presence of a methoxy or methyl group favored the *trans* diastereoisomer, whereas unsubstitution or the presence of a halogen atom favored the *cis* diastereoisomer. Even if the diastereomeric distribution in the self-cyclization of 2-bromopropanilides **7** into DOP **8,9** can hardly be compared to the enantiomeric excess induced by DOP in the hydroxynitrile Strecker synthesis,[9] we

Table 2. Self-Condensations of (*R*)-, (*S*)- or (*R,S*)-2-Bromopropananilides (7) into 1,4-Diaryl-2,5-dioxopiperazines 8 and 9. Reactions in THF. Promoter NaH

starting compds		time (h)	products **8** + **9**[a] (%)	products **8/9** (ratio)
	X			
(*S*)-**7a**	*p*-OMe	1	62	3.3/1
(*R,S*)-**7a**	*p*-OMe	1	61[b]	2/1
(*S*)-**7b**	*p*-Me	1	58	3.2/1
(*R,S*)-**7b**	*p*-Me	1	55	2/1
(*S*)-**7c**	H	1	54	3/1
(*R,S*)-**7c**	H	1	53	2/1
(*S*)-**7d**	*p*-Cl	3	45	3/1
(*R,S*)-**7d**	*p*-Cl	3	50	2.5/1
(*S*)-**7e**	*m*-Br	3	54	3/1
(*R,S*)-**7e**	*m*-Br	3	60	2/1
(*S*)-**7f**	*p*-CN	24	49	4/1
(*R,S*)-**7f**	*p*-CN	24	40[c]	3/1

[a] The balance was given by O-alkylation products[18] except for **7f**, where unreacted **7** was also present. [b] Almost identical result was observed in CH_3CN (**8** + **9**: 61%; **8/9**: 1.6/1). [c] At reflux for 15 min, along with some unsaturated products (^{1}H NMR).

tested the produced *cis-(S,S)* or *cis-(R,R)*-DOP **8a** as a potential chirality inducer. No induction became evident. All *cis*-**8** (as well as the diastereomeric *trans*-**9**) are almost insoluble in toluene, suggesting that product solubility does not influence the product distribution (de).

(B). Reactions with NaH in THF (Table 2). Compounds reported in Table 1, as well as **7f** (X = *p*-CN) or **7g** (X = *p*-NO_2) (which are insoluble in toluene, as are their sodium salts), have been tested in THF. After hydrogen evolution, the expected **8,9** were formed, along with some previously identified O-alkylation products.[18] *Cis/trans* ratios were close to 3/1 from *(S)*-**7a**−**e** and close to 2/1 from *(R,S)*-**7a**−**e**. The optically active *cis-(R,R)*-**8** from *(S)*-**7** had the same optical activity of the samples obtained in toluene. Starting from the more acidic 2-bromopropananilides **7f,g**, the fast hydrogen evolution was followed by a comparatively slower decay of the intermediate bromoamidate sodium salt (**10**).[14b,c] Accordingly, addition of methyl iodide produced the *N*-methyl derivatives (**11f,g**).[20] Whereas **8f** and **9f** could be eventually obtained from **7f** in modest yield after long reaction times or at reflux, the behavior of **7g** is still under investigation.

(C). Reactions with Ag$_2$O/Et$_3$N (Table 1B). Ag_2O in toluene promotes nucleophilic bromide substitution in 2-bromoamides, with relevant retention of configuration, whereas in the absence of nucleophiles, self-condensation to an O-alkylation product occurs.[14a,d] The system Ag_2O/Et_3N promotes self-cyclization of **7c,e** into *cis-(R,R)*-**8c,e**, the *cis* diastereoisomers prevailing in 2:1 ratio. Competitive formation of previously identified O-self-alkylation product[14a] and quaternary ammonium substitution product (**5c,e**) also takes place.[14d]

X-ray analysis demonstrated that (i) **8c** (X = H) has a *cis* configuration, **8e** (X = *m*-Br) has a *cis-(R,R)* configuration, and **9a** (X = *p*-OMe) is a *trans* centrosymmetric compound. Compounds **8c,e** have slightly puckered *boat* conformations with axial methyls, whereas **9a** has a relatively less flat *chair* conformation with axial methyls. A boat conformation with axial substituents or, respectively, a chair conformation with axial substituents was previously found also for *cis*- or t*rans*-1,3,4,6-tetramethyl-

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2,5-dioxopiperazines, similar to the *N,N′*-unmethylated cyclic dimers: the position over the ring of the parts of the side chains extending beyond Cβ was also studied.[21]

X-ray and ^{1}H NMR data allow us (i) to assume that all *cis*-**8** DOP obtained from *(S)*-**7** have an *R,R* configuration and the ones obtained from *(R)*-**7** have an *S,S* configuration and (ii) to assign the *cis* or *trans* configurations **8a**−**f** and **9a**−**f**. Preliminary experiments showed that pure samples of **8e** or **9e** do not equilibrate upon standing with NaH (toluene, 18 h). However, a sample of **8e**−**9e** equilibrated from [62:38] to [84:16] with LiOH (2 equiv in EtOH−H_2O, reflux, 2 h).[8a]

From the present results, we conclude that the self-condensation of easily available 2-bromopropananilides **7** into **8** + **9** represents a simple access to *N,N′*-diaryl-2,5-dioxopiperazines. The results obtained starting from single enantiomers *(R)*- or *(S)*-**7** with NaH (or Ag_2O) reveal the prevalent formation of the optically active products *cis-(S,S)*-**8** or, respectively, *cis-(R,R)*-**8**. Noteworthy, (i) the *R,R* configurational asset obtained from *(S)*-**7** (arising, in turn, from the natural amino acid) is enantiomeric to the *cis-(S,S)* asset of natural DOP, and (ii) the N^1,N^4-diaryl DOP described here arises from simple reactions which involve no arylation. On the other hand, reactions of racemic *(R,S)*-**7a,e** with NaH in toluene show minor des, but demonstrate a broader dependence of the des upon the ring substituent. The leveling effect by polar solvent and/or temperature increase on the de is reminescent of other stereochemical results.[9]

We previously found that, in the nucleophilic substitution of 2-bromopropanamides and -anilides, the stereochemistry (inversion or retention) was controlled, possibly through competitive mechanisms.[14a] A mechanistic investigation[14b] suggested an elusive aziridinone (**12**) as fitting the retention pathway through two consecutive inversions (ring formation and reopening). According to the determination of the absolute configuration of *(R,R)*-**8e** and our assumption that all *cis*-**8** arising from **7** have opposite sp^3 configurations relative to the parent compounds, the main diastereoisomer from the single enantiomeric species formally indicates two self-N-alkylation reactions of the S_N2 type. The possibility that "internal" chiral induction operates in the reaction starting from single enantiomers and the composite influence of the X group on the des calls for further research.

Experimental Section

The 2-bromopropananilides **7a**−**g** were prepared as previously described.[14a,d,22] Their optical purity varied within the limits of 95 ± 3% in comparison with literature data.[22] Compounds *(R,S)*-**7** did not show ^{1}H NMR shifts with tris-3-(trifluoromethylhydroxymethylene)-(+)-camphoratoeuropium-(III) [Eu(tfc)$_3$] or tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octadionato)europium(III) [Eu(dpm)$_3$] or separation upon chromatography on cyclodestrin columns at a difference with compound **2** (R = CH_2Ph) with Eu(tfc)$_3$.[14e] Melting points were determined on a Reichter-Kofler apparatus and are uncorrected. Optical rotations were determined in a polarimeter with a 10 cm cell, operating at 589 nm (sodium D line) at 20 °C. The concentration was 1−2% in chloroform, ethanol, or methanol as indicated. A sonicator Microson XL 2005 with standard microprobe was used for the reactions promoted by Ag_2O. All ^{1}H NMR spectra were recorded on a 200 MHz spectrometer in $CDCl_3$. Chemical shifts are reported as units (ppm) downfield from tetramethylsilane. Mass experiments was performed with a GCMS. TLC was done with precoated plates of silica gel (Merck F-254) using the following solvent systems: R_{f1} = hexane/EtOAc 1/1; R_{f2} = hexane/EtOAc 4/1; R_{f3} = hexane/EtOAc 3/1. **HPLC. Method A.** Analytical: silica column, packed with Eurosphere 100 (250 × 4.6 mm i.d., 5 μm particle size), flow rate 1.0 mL/min. Isocratic elution with a mixture of cyclohexane/EtOAc 40/60. Visualization at 254 nm. Preparative HPLC: Eurosphere 100 silica column (250 × 16 mm i.d., 7 μm particle size), flow rate 15 mL/min. Isocratic elution with the above mixture. **Method B.** Analytical reversed phase HPLC: C_{18} column (150 × 4.5 mm i.d., 5 μm particle size), flow rate 1 mL/min. Preparative reversed phase: C_{18} column (150 × 32 mm i.d., 10 μm particle size), flow rate 30 mL/min. Analytical and preparative processes were carried out by a gradient made up of A = 10% acetonitrile in water and B = 60% acetonitrile in water. A 25 min linear gradient was run from 0% to 50% of B. Visualization at 220 nm. Retention times (t_R) are reported. All elemental analyses gave C, H, N with errors of ±0.5%. All reagents were purchased from Fluka.

***cis-(R,R)- and cis-(S,S)*-3,6-Dimethyl-1,4-bis(*p*-methoxyphenyl)-2,5-dioxopiperazine (8a).** (a) A sample of *(S)*-**7a** (258 mg, 1 mmol; [α] −34.2, $CHCl_3$, lit.[22] [α] −36.8), was added to a suspension of NaH (24 mg, 1 mmol) in toluene (5 mL), and stirring was continued for 4 h. The mixture was washed (H_2O, 3 × 3 mL) and dried (Na_2SO_4). Evaporation to constant weight gave a solid (168 mg, 95%) consisting of *cis-(R,R)*-**8a**/*trans-(S,R)*-**9a** = 8.3/1. HPLC separation (method A) gave (i) pure *cis-(R,R)*-**8a** (t_R 13.2) as colorless prisms (130 mg, 73%): mp 172−74 °C; [α] −2.5 ($CHCl_3$); R_{f1} 0.3; MS *m/z* 354 (M$^+$), 149, 134, 77; ^{1}H NMR δ 1.62 (d, 6H), 3.84 (s, 6H), 4.42 (q, 2H), 6.96-7.23 (m, 8H). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.9. Found: C, 67.91; H, 6.29; N, 7.85. (ii) Pure *trans-(S,R)*-**9a** (t_R 10.9; 9 mg, 5%), see below.

(b) Starting from *(R)*-**7a**, pure *cis-(S,S)*-**8** ([α] +2.6) was obtained.

(c) In similar experiments, pure *cis-(R,R)*-**8** or *cis-(S,S)*-**8** (57 mg, 0.16 mmol) was added along with *(S)*-**7a**. In the first case, the product was a mixture of **8/9** = 8.5/1, after correction for added product; the *cis-(R,R)*-**8** had the same yield and [α] as above. In the second case, the mixture **8/9** = 8/1 gave *cis*-**8** with the same yield but lower optical activity ([α] −1.5).

***trans-(R,S)*-9a** was obtained from *(R,S)*-**7a**. The solid (163 mg, 92%) consisting of **8a/9a** = 1/1.7 was triturated with cyclohexane/EtOAc (2/3); from the solution obtained, **9a** crystallized out overnight (80 mg, 45%). A crystal of **9a** was suitable for X-ray analysis: HPLC, method A (t_R 10.9), R_{f1} 0.25; mp 222−24 °C; ^{1}H NMR δ 1.46 (d, 6H), 3.84 (s, 6H), 4.50 (q, 2H), 6.97−7.26 (m, 8H).

***cis-(R,R)*-3,6-Dimethyl-1,4-bis(*p*-methylphenyl)-2,5-dioxopiperazine (8b)** was obtained as **8a** from *(S)*-**7b** ([α] −34.0, $CHCl_3$, lit.[22] [α] −31.5) along with some **9b** (143 mg, 89%, ratio 4.5/1). HPLC method B (t_R 17.65) yielded **8b** (101 mg, 63%): mp 180−82 °C; [α] −38.0; R_{f1} 0.53; ^{1}H NMR δ 1.62 (d, 6H), 3.66 (s, 6H), 4.64 (q, 2H), 7.12-7.29 (m, 8H). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.68; H, 6.91; N, 8.60.

***trans-(R,S)*-9b**: HPLC (20 mg, 12.4%) t_R 18.50; mp 226−28 °C; R_{f1} 0.59; ^{1}H NMR δ 1.45 (d, 6H), 3.66 (s, 6H), 4.53 (q, 2H), 7.16-7.26 (m, 8H).

***cis-(R,R)*-3,6-Dimethyl-1,4-diphenyl-2,5-dioxopiperazine (8c)** was obtained from *(S)*-**7c** ([α] −33.0, lit.[22] [α] −34.4, $CHCl_3$) with some **9c** (109 mg, 74%; ratio 5/1). HPLC, method B (t_R 13.64) gave **8c**: prisms from toluene (75 mg, 51%); mp 188-89 °C; [α] −30.8; R_{f1} 0.28; ^{1}H NMR δ 1.64 (d, 6H), 4.50 (q, 2H), 7.26-7.50 (m, 10H); MS *m/z* 294 (M$^+$), 119, 104, 77.

(b) A sample of *(S)*-**7e** (258 mg, 1 mmol) was dissolved in toluene (5 mL); Ag_2O (232 mg, 1 mmol) was added. The mixture was sonicated for 18 h at 20 °C and centrifuged. On concentration, the solution gave an oil. Chromatography (SiO_2, hexane/EtOAc 1/1) gave (i) a mixture of **8/9** = 2/1 (98 mg, 67%) and (ii) O-alkylation product.[14a] Methanol eluted 2-triethylammonium propananilide (**5c**).[14d]

***trans-(R,S)*-9c** was reported.[18]

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***cis-(R,R)*-3,6-Dimethyl-1,4-bis(*p*-chlorophenyl)-2,5-dioxopiperazine (8d)** was obtained as **8a** from *(S)*-**7d** ([α] −33.2; lit.[22] [α] −33.7) with some **9d** (169 mg, 93%, ratio 4.6/1). HPLC, method B (t_R 19.63), gave pure **8d** (115 mg, 63%): [α] +9.0 (EtOH); mp 275−77 °C; R_{f1} 0.54; ^{1}H NMR δ 1.61 (d, 6H), 4.45 (q, 2H), 7.24-7.48 (m, 8H). Anal. Calcd for $C_{18}H_{16}N_2O_2Cl_2$: C, 59.62; H, 4.44; N, 7.71, Cl, 19.52. Found: C, 59.58; H, 4.47; N, 7.69; Cl, 19.42.

***trans-(R,S)*-9d**: HPLC (22 mg, 12%) t_R 20.44; mp 218−20 °C; R_{f1} 0.61; ^{1}H NMR δ 1.46 (d, 6H), 4.53 (q, 2H), 7.20-7.47 (m, 8H).

***cis-(R,R)*-3,6-Dimethyl-1,4-bis(*m*-bromophenyl)-2,5-dioxopiperazine (8e)** (a) was obtained from *(S)*-**7e** ([α] −25.7, lit.[22] [α] −26.5) along with some **9e** (178 mg, 78%, ratio 5.3/1): HPLC (method B; t_R 18.79) prisms from toluene (130 mg, 57%); mp 151−53 °C; [α] −38.0 ($CHCl_3$); R_{f2} 0.39; ^{1}H NMR δ 1.63 (d, 6H), 4.48 (q, 2H), 7.15−7.50 (m, 8H).

(b) Starting from *(R)*-**7e**, pure *cis-(S,S)*-**8e** was obtained (123 mg, 54%): [α] +37.1.

(c) A run using *(S)*-**7e**, Ag_2O, and Et_3N in toluene gave **8e** (51 mg, 35%) and **9e** (25 mg, 17%); the balance consisted of **5e**[14d] and O-alkylation product.[14a]

***trans-(R,S)*-9e** was separated by HPLC (t_R 20.20) from the mixture **8e/9e** (20 mg, 9%): mp 178−81 °C; R_{f2} 0.31; ^{1}H NMR δ 1.47 (d, 6H), 4.54 (q, 2H), 7.14−7.50 (m, 8H).

***cis-(R,R)*-3,6-Dimethyl-1,4-bis(*p*-cyanophenyl)-2,5-dioxopiperazine (8f).** A sample of *(S)*-**7** (253 mg, 1 mmol, [α] −44.8, lit.[22] [α] −45.8) was added to a suspension of NaH (24 mg, 1 mmol) in anhydrous THF (5 mL). After 24 h, THF was eliminated and the residue dissolved in EtOAc and washed with water (3 × 3 mL). The oil was chromatographed (SiO_2, hexane/EtOAc 1/1), and the mixture of **8f**, **9f** (84 mg, 49%, ratio 4/1) was separated by HPLC (method B) to yield **8f** and **9f**. For **8f** (60 mg, 35%): t_R 13.47; [α] +10.0 (MeOH); mp 258−60 °C; R_{f1} 0.25; ^{1}H NMR δ 1.65 (d, 6H), 4.59 (q, 2H), 7.27−7.82 (m, 8H). Anal. Calcd for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.58; H, 4.65; N, 16.2.

***trans-(R,S)*-9f**: HPLC (13 mg, 7%) t_R 12.9; mp 312−14 °C; R_{f1} 0.29; ^{1}H NMR δ 1.50 (d, 6H), 4.62 (q, 2H), 7.42-7.84 (m, 8H).

***(R,S)*-2-Bromo-*N*-methyl-*p*-cyanopropananilide (11f).** A mixture of *(R,S)*-**7f** and NaH in THF was stirred for 1 h, treated with MeI, stirred for 20 min, and centrifuged. Solvent elimination gave an oil that was purified by chromatography (SiO_2, hexane/EtOAc 2/1). Prisms (187 mg, 70%): mp 119−20 °C; R_{f1} 0.47; ^{1}H NMR δ 1.93 (d, 3H), 3.31 (br, 3H), 4.27 (br, 1H), 7.44−7.80 (m, 4H).

***(R,S)*-2-Bromo-*N*-methyl-*p*-nitropropananilide (11g).** A sample of *(R,S)*-**7g** (273 mg, 1 mmol) was added to NaH (24 mg, 1 mmol) in THF (5 mL). After the mixture was stirred for 18 h, MeI (142 mg, 1 mmol) was added and stirring continued (1 h). Centrifugation and concentration gave an oil. Column chromatography (hexane/EtOAc 3/1) gave prisms (86 mg, 31%): mp 137−39 °C; R_{f3} 0.6; ^{1}H NMR δ 1.79, 1.94 (2d, 3H), 3.34, 3.37 (2s, 3H), 4.31 (br, 1H), 7.49−8.35 (m, 4H).

Crystal data.[23] ***cis*-8c**: $C_{18}H_{18}N_2O_2$, trigonal, $P3_1$ (No. 144), a = 12.846(3) Å, c = 8.138(3) Å, V = 1163.7(6) Å^3, Z = 3, D_{calcd} = 1.26 g cm^{-3}, μ = 0.78 cm^{-1}. Of the 1700 independent reflections, 975 with $I \geq 3\sigma(I)$ were used in the refinement. Full matrix least-squares refinement with all non-hydrogen anisotropic atoms and hydrogen atoms, found in ΔF maps, taken in fixed positions. R (on F) = 0.032, R_w = 0.037. ***cis-(R,R)*-8e**: $C_{18}H_{16}N_2O_2Br_2$, orthorhombic, $P2_12_12_1$ (No. 19), a = 9.197(2) Å, b = 12.594(2) Å, c = 15.708(1) Å, V = 1819.4(4) Å^3, Z = 4, D_{calcd} = 1.65 g cm^{-3}, μ = 44.24 cm^{-1}. Of the 2490 independent reflections, 1205 with $I \geq 2\sigma(I)$ were used in the refinement. Full-matrix least-squares refinement with all non-hydrogen anisotropic atoms and hydrogen atoms in fixed calculated positions. R (on F) = 0.053, R_w = 0.049. ***trans-(R,S)*-9a**: $C_{20}H_{22}N_2O_4$, monoclinic, $P2_1/n$, (No. 14) a = 7.520(1) Å, b = 5.462(2) Å, c = 22.639(2) Å, β = 95.48(1)°, V = 925.7(3) Å^3, Z = 2, D_{calcd} = 1.27 g cm^{-3}, μ = 0.83 cm^{-1}. Of the 2229 unique measured reflections 1410 with $I \geq 2\sigma(I)$ were used in the refinement. Full-matrix least-squares refinement with all non-hydrogen anisotropic atoms and hydrogen isotropic atoms. R (on F) = 0.045, R_w = 0.058.

The data were collected on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated Mo Kα radiation, $\varpi/2\theta$ scan technique. Cell parameters were determined and refined from 25 reflections in the range $10 < \theta < 15°$; three standard reflections monitored every 2 h showed no significant variation during data collection.

All data were corrected for Lorentz and polarization. The data for compound **8e** were also corrected for absorption (ψ scan method, minimum transmission factor = 0.55). The structures were solved by direct methods with the SIR88 system of programs (Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Polidori, G.; Spagna, R.; Viterbo, D. *J. Appl. Crystallogr.* **1989**, *22*, 389). All other calculations were accomplished by the MolEN system of programs (MolEN, *An Interactive Structure Solution Procedure*, Enraf-Nonius; Delft, The Netherlands, 1990).

In order to determine the absolute configuration of compound **8e** both enantiomorphous structures were refined with final disagreement factors of R_1 = 0.53, R_{1w} = 0.049 and R_2 = 0.066, R_{2w} = 0.066 for the two enantiomers, respectively. The correct absolute configuration was assigned to the enantiomer (*R*,*R*) displaying the lower values of the disagreement factors.

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(23) The author has deposited atomic coordinates for *cis*-**8c**, *cis*-(*R*,*R*)-**8e**, and *trans*-(*R*,*S*)-**9a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.