Synthesis of Precursors to Model Styrene/Methyl Methacrylate Copolymer Radicals. α,α′-Bis(methoxycarbonyl)azoalkanes

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Several symmetrical α,α′-bis(methoxycarbonyl)azoalkanes **4** were prepared in high yield in two steps from the appropriate α-amino esters **13**, or in five steps from 4-substituted 4-phenyl-2-butanones **10**. The sequence involves the generation, separation, and purification of symmetrical N,N′-disubstituted sulfamides **14** followed by oxidative rearrangement under modified Ohme–Schmitz–Preuschhof conditions to yield the title compounds. In the absence of the oxidant, the sulfamides are converted quantitatively into 2,4-disubstituted 3-oxo-1,2,5-thiadiazolidine 1,1-dioxides **15**. In accord with the above methodology, (4*S*)-4-phenyl-2-pentanone was transformed into (2*R*,2′*R*,4*S*,4′*S*)-2,2′-bis(methoxycarbonyl)-4,4′-diphenyl-2,2′-azopentane (**4b**-Ia), the stereochemistry of which was established from that of its precursor (2*R*,2′*R*,4*S*,4′*S*)-*N*,*N*′-bis[2-[2-(methoxycarbonyl)-4-phenylpentyl]]-sulfamide by single-crystal X-ray analysis.

Along with α,α′-dicyanoazoalkanes, α,α′-bis(alkoxycarbonyl)azoalkanes have been of synthetic interest due to their potential use as initiators for radical chain reactions.[1] In simple cases these azo esters have been accessible from the corresponding azo nitriles by acid hydrolysis in alcohols (Pinner reaction).[1,2] In this manner, methyl,[1,2] ethyl, and *n*-butyl azoisobutanoates **2a–c** have been prepared from azoisobutyronitrile (AIBN) (**1**) (Scheme I).[3]

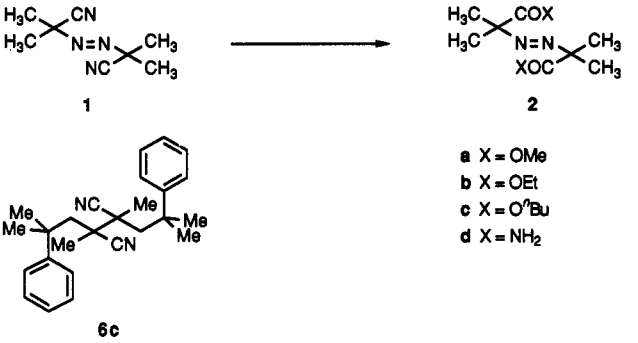
In connection with our work on the mechanism of termination of free-radical chain reactions,[3,4] we required compounds from which we could generate model styrene/methyl methacrylate copolymer radicals. Suitable target compounds, the α,α′-bis(methoxycarbonyl)azoalkanes **4**, should be accessible in principle by hydrolysis of the corresponding α,α′-dicyanoazoalkanes **3**, prepared previously by stereospecific cyanation of the α,α′-dichloroazoalkanes[5] (Scheme II). However, kinetic studies on **4c** [prepared not by hydrolysis but by oxidative coupling (IF_5) of the α-amino ester[6]] have shown that it is significantly less stable than **3c**; thus any hydrolytic method to transform **3** into **4** would need to be very mild.[6]

We report that *all* the desired compounds **4** were successfully prepared by the oxidation of sulfamides **14** derived from α-amino esters. Other attempts based on the hydrolysis of nitriles, nitrilium salts, amides, and hydrazo nitriles were unsuccessful in all but one case.

Results and Discussion

Hydrolyses. Although acid hydrolysis of the methyl imidate obtained from treatment of AIBN (**1**) with methanolic HCl gives the diester **2a**,[2] only the least substituted *meso*-**3a** gave *meso*-**4a**, and then only upon extended exposure (21 days) (Scheme II).

Scheme I



The conversion of nitriles to *N*-alkyl imidates via nitrilium salts has been reported,[7–9] so in principle, acid hydrolysis of these imidates (as in the Pinner reaction[2]) could also yield esters. In a model reaction, 2-propanenitrile was treated with $(i\text{-PrO})_2CH^+BF_4^-$, generated in situ, which yielded the previously unreported 1-methylethyl 2-methyl-*N*-(1-methylethyl)propanimidate (**5b**). The anticipated methyl 2-methyl-*N*-(1-methylethyl)propanimidate (**5a**) was obtained when the reaction was repeated in an excess of methyl formate. However, similar treatment of **3a** with either $Me_3O^+BF_4^-$ or $(i\text{-PrO})_2CH^+BF_4^-$[9] failed to provide **4a**.

The diesters **4** are also accessible, in principle, from diamides.[10] In the case of AIBN (**1**), the diamide **2b** was produced in high yield by using alkaline hydrogen peroxide in DMSO.[11] However, treatment of *meso*-**3c** under a variety of conditions (DMSO/MeOH, DMSO/THF) failed to produce the desired diamide. In THF, decomposition occurred as evidenced by the isolation of one of the two possible diastereoisomers **6c** from the head-to-head radical coupling (Scheme I).

Since hydrolysis of the α,α′-azodinitriles was generally unsuccessful, hydrolysis of the hydrazo dinitriles **7** followed by esterification and oxidation to **4** was attempted (Scheme

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(2) Mortimer, G. A. *J. Org. Chem.* **1965**, *30*, 1632.
(3) Bizilj, S.; Kelly, D. P.; Serelis, A. K.; Solomon, D. H.; White, K. E. *Aust. J. Chem.* **1985**, *38*, 1657 and references therein.
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(8) Borch, R. F. *J. Chem. Soc., Chem. Commun.* **1968**, 442.
(9) Borch, R. F. *J. Org. Chem.* **1969**, *34*, 627.
(10) (a) White, E. H.; Scherrer, H. *Tetrahedron Lett.* **1961**, 758. (b) White, E. H. *J. Am. Chem. Soc.* **1955**, *77*, 6011.
(11) Sawaki, Y.; Ogata, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 793.

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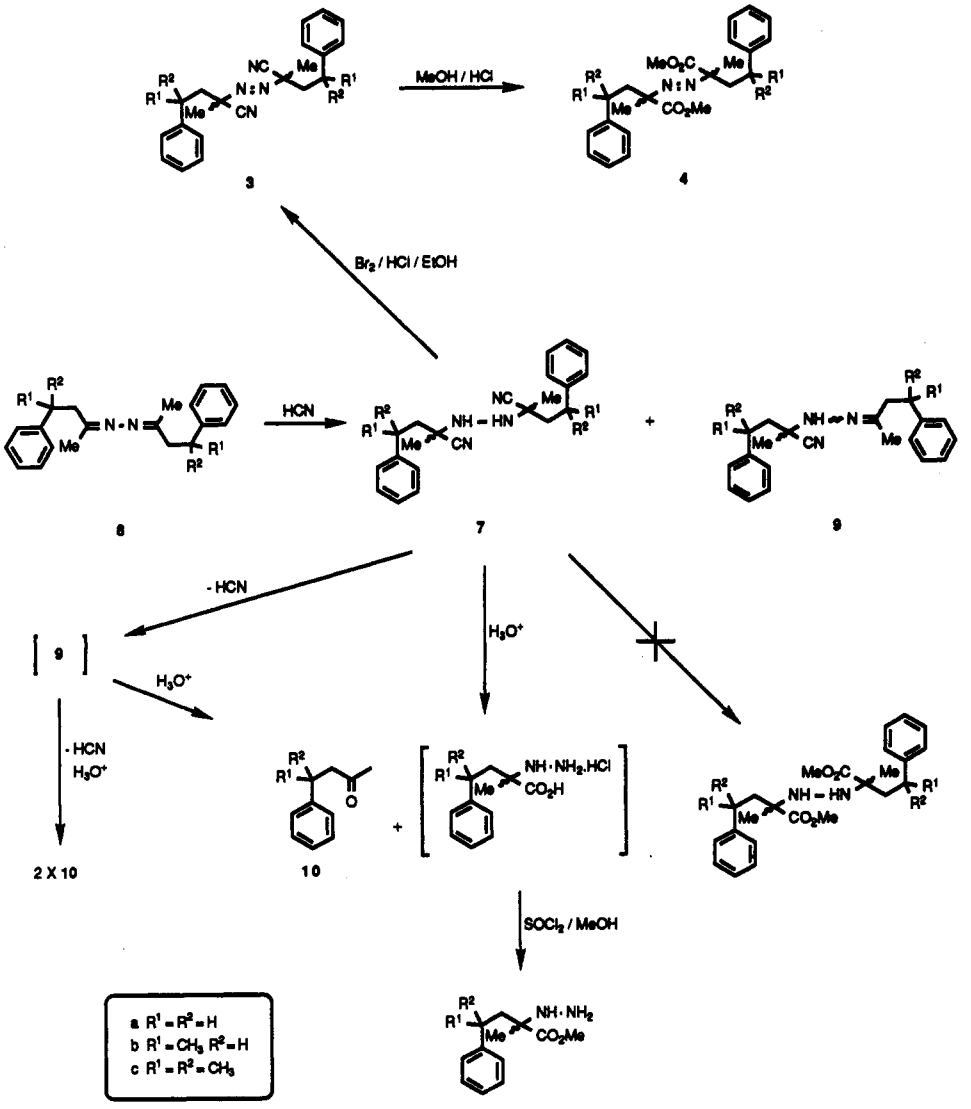
Scheme II



II).[12,13] Treatment of the ketazines **8a,b** with HCN yielded diastereomeric mixtures of **7a** and **7b** and, in the case of **8c**, a mixture of **7c** and **9c**. Hydrolysis of **7a–c** followed by esterification afforded **17a** and **10a** (from **7a**), **10b** (from **7b**), and **10c** (from **7c**).

This tendency of γ-substituted hydrazo nitriles to eliminate HCN rather than undergo hydrolysis has been noted previously by Procházka.[6]

The failure of these hydrolytic procedures to be of general use for the synthesis of α,α′-azo diesters necessitated a different approach utilizing N–N coupling of a preformed α-amino ester.

Coupling of α-Amino Esters: N,N′-Disubstituted Sulfamides. Although one diastereoisomer of **4c** had been prepared in 27% yield by Procházka[6] by the oxidative coupling of the corresponding α-amino ester using IF_5, the procedure was considered unsuitable for the azo esters **3**, due to low yields, difficult workup, and the difficulty of separating diastereoisomers of thermally unstable products. However, the Ohme–Schmitz–Preuschhof procedure for the synthesis of azoalkanes,[14–16] as modified by Timberlake,[17] allows for the coupling of heavily substituted alkylamines in reasonable yields under mild conditions. Under homogeneous conditions the first-formed sulfamides are smoothly transformed into the azo derivative without the isolation of the intermediate thiadiaziridine 1,1-dioxide and the 1,2-dialkylhydrazine.[17] In addition, it was anticipated that the sulfamides would be thermally more stable than the azo diesters, so that separation would best be achieved at that stage.

Application of this procedure to the preparation of **4** required the synthesis of the α-amino esters **13**. These were prepared by a modified Strecker synthesis from the respective ketones **10**, followed by hydrolysis and esterification (Scheme III). Thus, treatment of the ketones **10** with excess hydrogen cyanide and ammonia gave the corresponding α-amino nitriles **11** quantitatively. The racemic α-amino nitrile **11b** was furnished as a mixture of diastereoisomers [55:45 isomer I/isomer II (these were

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(13) Thiele, J.; Heuser, K. *Justus Liebigs Ann. Chem.* **1896**, *290*, 1.
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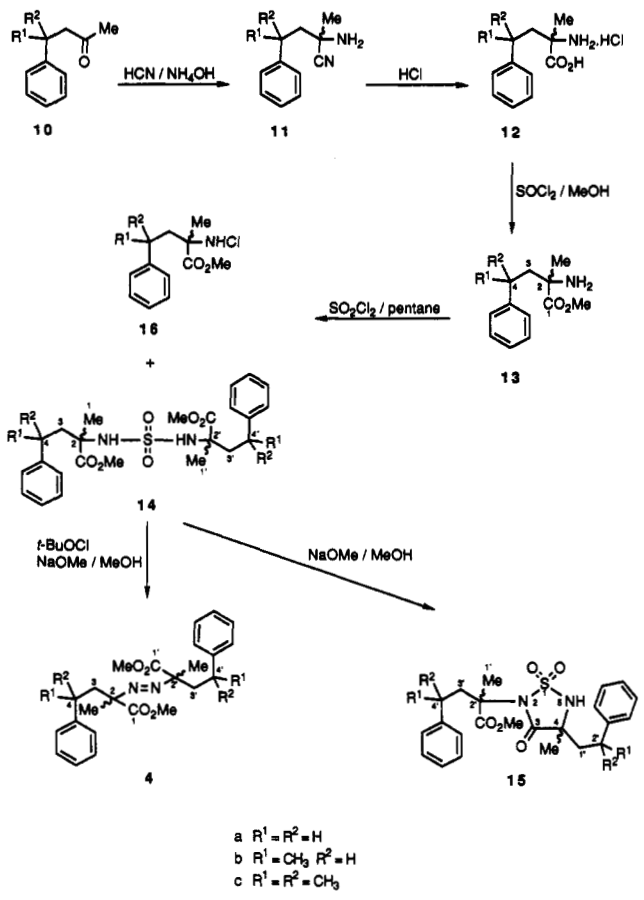
(15) Ohme, R.; Preuschhof, H.; Heyne, H.-U. *Org. Synth.* **1972**, *52*, 11.
(16) Reference 1a, pp 93–96.
(17) Timberlake, J. W.; Hodges, M. L.; Betterton, K. *Synthesis* **1972**, 632.

Scheme III



subsequently shown to be 2*RS*,4*SR*/2*RS*,4*RS*; see below)], and the previously reported nitrile **11c** was isolated as the more stable hydrochloride salt.[5] The crude α-amino nitriles **11** were hydrolyzed to furnish the α-amino acid hydrochloride salts **12** in greater than 80% yields. Racemic **12b** was produced as a mixture of diastereoisomers (55:45 isomer I/II). Fractional recrystallization gave the minor diastereoisomer [isomer II, (2*RS*,4*RS*)-**12b**] in 25% yield. However, the major diastereoisomer could not be purified beyond 82:18 isomer I/II. Exposure of **12** to thionyl chloride/methanol gave the α-amino esters **13** in greater than 80% yields. Esterification of the mixture of **12b** (82:18 isomer I/II) gave a mixture of diastereoisomeric α-amino esters in a similar ratio, which was separated by repeated radial chromatography.

The sulfamides **14** were prepared in 71–85% yields by treatment of 4 equiv of the α-amino esters **13** with SO_2Cl_2 in pentane. It was found that the use of 2 equiv of the α-amino ester as base to neutralize the liberated HCl gave a product superior in purity to that obtained by prior generation of a pyridine–sulfuryl chloride adduct followed by treatment with **13**. Any unreacted α-amino ester was readily recovered, almost quantitatively, from the combined acidic washings. In each case the sulfamide **14a–c** was prepared as a mixture of two diastereoisomers (1:1 by NMR) which was separated by repeated fractional recrystallization and/or by exhaustive radial chromatography. In addition to the sulfamides, small quantities (2–4%) of the *N*-chloroamines (2*RS*,4*RS*)-**16b**, **16c** were isolated in two of the coupling reactions.

Initial efforts to convert the sulfamides to azo diesters under the conditions specified by Timberlake et al.[17] failed. The attempted oxidations using NaH and *t*-BuOCl in pentane gave no azo compounds, possibly due to inefficient mixing under the heterogeneous conditions. However,

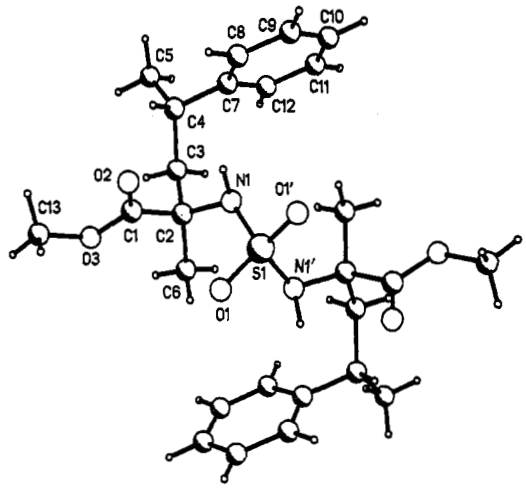


Figure 1. Perspective view and atom labeling of the X-ray structure of the optically active sulfamide **14b**-Ia.

under homogeneous conditions with NaOMe and *t*-BuOCl in methanol at 0 °C, oxidation proceeded smoothly and was complete after 30 min. The azo diesters **4** were produced in almost quantitative yield as colorless oils, most of which crystallized from ether/petroleum ether at low temperature. Precautions were taken to ensure that, during workup, solutions containing the thermally unstable azo diesters were kept below 5 °C, particularly those of **4c**, an isomer of which has been previously reported.[6] The diastereoisomers of **4a** were assigned as meso and *dl* by comparison with *meso*-**4a** prepared above from *meso*-**3a** by the Pinner reaction. Thus, the relative stereochemistry of the precursor sulfamides **14a** was also established.

When **14c** was oxidized with only 1 equiv of *t*-BuOCl, the product isolated was found to be a mixture of **4c** and starting material (ca. 1:1 by NMR) rather than the intermediate thiadiaziridine 1,1-dioxide.[18,19] It would appear that, under these conditions, the formation of the intermediate *N*-chlorosulfamide[19] is rate-determining and, once formed, it rapidly closes to the thiadiaziridine and is subsequently oxidized by *t*-BuOCl. Upon exposure of the mixture to a further equivalent of *t*-BuOCl, the remainder of the sulfamide was smoothly transformed to the azo diester **4c**.

The success of this approach encouraged us to prepare a single, enantiomerically pure diastereoisomer of the target compound most relevant to the styrene/methyl methacrylate copolymer radical precursor, i.e., an enantiomerically pure diastereoisomer of **4b**. Thus the above sequence was applied to (*S*)-4-phenyl-2-pentanone. The α-amino nitrile **11b** was obtained as a mixture of diastereoisomers [55:45 (2*R*,4*S*)/(2*S*,4*S*)] which gave the α-amino acid HCl salt **12b** in a similar ratio upon hydrolysis. Fractional recrystallization of **12b** gave the minor diastereoisomer (2*S*,4*S*)-**12b** in 37% yield, which was esterified to give (2*S*,4*S*)-**13b**. The second (major) diastereoisomer of **12b** could not be purified beyond 95:5 (2*R*,4*S*)/(2*S*,4*S*) and was esterified to give a mixture of α-amino esters **13b**. Repeated radial chromatography subsequently afforded (2*R*,4*S*)-**13b**. Each optically pure diastereoisomer of **13b** (isomer I, II) yielded a single diastereoisomeric sulfamide **14b** (Ia, IIa). The first sulfamide, **14b** isomer Ia (**14b**-Ia), was subjected to single-crystal X-ray analysis, which related all the chiral centers and

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allowed assignment of the absolute stereochemistry as 2*R*,2′*R*,4*S*,4′*S* (Figure 1). Since the conversion of the sulfamides **14** to the α,α′-azo diesters **4** involves no reorganization of the *N*-alkyl substituents[16] (the N–C bond remains intact), this observation unambiguously defines the stereochemistry of this target compound as (2*R*,2′*R*,4*S*,4′*S*)-2,2′-bis(methoxycarbonyl)-4,4′-diphenyl-2,2′-azopentane (**4b**-Ia) as well as those of the second sulfamide isomer (**14b**-IIa) as (2*S*,2′*S*,4*S*,4′*S*)-**14b** and the other diastereomer of the azo diester (**4b**-IIa) as (2*S*,2′*S*,4*S*,4′*S*)-**4b**.

Cyclization of Sulfamides: 3-Oxo-1,2,5-thiadiazolidine 1,1-Dioxides. Treatment of the sulfamides **14** with sodium methoxide in refluxing methanol for 1 h resulted in cyclization to give the previously unreported 2,4-disubstituted 3-oxo-1,2,5-thiadiazolidine 1,1-dioxides **15a–c** in almost quantitative yield (Scheme III). Similar cyclizations have been reported for β-amino esters, which yield six-membered heterocycles.[20,21] In addition, during this investigation, other workers reported the closely related cyclization of *N*-[(methoxycarbonyl)alkyl]-*N*′-methylsulfamides on exposure to base.[22] Although the thiadiazolidines **15** could conceivably close to bicyclic products, they fail to do so.

In conclusion, we have shown that symmetrical α,α′-azo diesters can be prepared under mild conditions in high yields from α-amino carboxylic acid esters. In this way, we have been able to prepare enantiomerically pure (2*R*,2′*R*,4*S*,4′*S*)-2,2′-bis(methoxycarbonyl)-4,4′-diphenyl-2,2′-azopentane, a suitable precursor to model styrene/methyl methacrylate copolymer radicals. The decomposition studies of the α,α′-azo diesters described herein will be reported elsewhere.

Experimental Section

Crystallography. Crystal data and X-ray experimental details for the chiral sulfamide **14b**-Ia are available as supplementary material, as are tabulations of atom coordinates, thermal parameters, and bonding geometry.[23,24] As was found in the structure of another N,N′-disubstituted sulfamide,[25] the molecule adopts a C_2 rather than C_s conformation (in the present case crystallographic C_2 symmetry). This conformation minimizes steric interactions between the nitrogen substituents. As previously observed, the geometry at the nitrogen atom is closer to trigonal planar than to tetrahedral. All intramolecular bonding geometry is normal, and there are no unusually short intermolecular contacts.

Synthesis. General. Melting points are uncorrected. Radial thin-layer chromatography was performed by using a Chromatotron fitted with a 24-cm-diameter glass rotor coated with silica gel 60 PF-254 containing gypsum (Merck). ^1H and ^{13}C NMR spectra were recorded as solutions in $CDCl_3$, unless otherwise indicated. Mass spectra were recorded at 70 eV in the positive ion mode unless otherwise indicated. FAB spectra were recorded in a glycerol matrix. Methanol was distilled from magnesium and stored over 3-Å molecular sieves. Hydrogen cyanide was prepared according to the literature procedure and stored over $CaCl_2$ at −15 °C.[26] Sulfuryl chloride was redistilled and kept in a desiccator. Pentane was of commercial grade and stored over Na wire. Petroleum ether refers to petroleum ether of bp 40–60 °C.

General Procedure for the Synthesis of α-Amino Nitriles (11). The general method outlined by Procházka was followed.[6] A mixture of aqueous ammonia solution (30% w/w) (ca. 4 mL/0.1 mol of ketone) and methanol (5 mL/0.1 mol of ketone) was cooled to −10 °C and saturated with ammonia gas. Liquid HCN (ca. 1.5 equiv) was added to the stirred mixture followed by the ketone (**10**). Ammonia gas was passed through the mixture for a further 30 min, after which time the vessel was securely sealed and the mixture was stirred at 0 °C for 2 h and then at ambient temperature for 2–4 days. The reaction mixture was cooled (−10 °C), and the reaction vessel was cautiously opened. The mixture was extracted with CH_2Cl_2, the organic phase was washed twice with water and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to give the crude α-amino nitrile **11**.

2-Amino-2-methyl-4-phenylbutanenitrile (11a). Reaction of 4-phenyl-2-butanone (**10a**) (37.05 g, 0.25 mol) for 4 days gave **11a** as a yellow liquid (43.45 g, 100%): IR ν_{max} (film) 3371, 3305, 3027, 2979, 2931, 2221, 1602, 1496, 1454, 1378, 753, 702 cm^{-1}; ^1H NMR (400 MHz) δ 7.33–7.28 (m, 2 H), 7.20–7.24 (m, 3 H), 2.86–2.81 (m, 2 H), 1.98–1.94 (m, 2 H), 1.82 (br s, 2 H), 1.53 (s, 3 H); ^{13}C NMR (100 MHz) δ 140.29 (s), 128.62 (d), 128.32 (d), 126.35 (d), 124.17 (s), 49.84 (s), 43.56 (t), 31.07 (t), 27.71 (q); MS (+EI, 70 eV), *m*/*z* (relative intensity) 174 (M^+, 2), 147 (90), 146 (66), 132 (95), 105 (54), 91 (100), 70 (58), 43 (51), 42 (87). Anal. Calcd for $C_{11}N_{14}N_2$: C, 75.8; H, 8.1. Found: C, 75.9; H, 8.4. Hydrochloride salt: mp 137–140 °C dec (lit.[31] mp 140–141 °C).

(2*RS*,4*SR*)- and (2*RS*,4*RS*)-2-Amino-2-methyl-4-phenylpentanenitrile (11b). Reaction of racemic 4-phenyl-2-pentanone (**10b**)[29] (40.56 g, 0.25 mol) for 3 days gave **11b** as a yellow liquid and as a mixture of diastereoisomers [55:45 isomer I (2*RS*,4*SR*)/isomer II (2*RS*,4*RS*)] (47.08 g, 100%): IR ν_{max} (film) 3377, 3309, 3027, 2963, 2932, 2221, 1602, 1494, 1452, 1379, 766, 702 cm^{-1}; ^1H NMR (400 MHz) δ 7.38–7.20 (m, 10 H, Ar, I + II), 3.16 (dqd, 1 H, *J* = 9.0, 7.0, 5.2 Hz, CH, I), 3.05 (dqd, 1 H, *J* = 8.8, 7.0, 5.0 Hz, CH, II), 2.08 (dd, 1 H, *J* = 14.2, 8.8 Hz, C*H*H, II), 2.01 (dd, 1 H, *J* = 14.4, 9.0 Hz, C*H*H, I), 1.98 (dd, 1 H, *J* = 14.4, 5.2 Hz, CH*H*, I), 1.93 (dd, 1 H, *J* = 14.2, 5.0 Hz CH*H*, II), 1.75 (br s, 4 H, NH_2, I + II), 1.44 (s, 3 H, $CH_3C(CN)$, I), 1.36 (d, 3 H, *J* = 7.0 Hz, $CH_3CH(Ph)$, II), 1.35 (d, 3 H, *J* = 7.0 Hz, $CH_3CH(Ph)$, I), 1.24 (s, 3 H, $CH_3C(CN)$, II); ^{13}C NMR (100 MHz) δ 146.03 (s, II), 145.63 (s, I), 128.92 (d, I), 128.72 (d, II), 127.27 (d, I), 127.07 (d, II), 126.91 (d, I), 126.67 (d, II), 124.24 (s, I + II), 49.93 (s, I), 49.49 (s, II), 49.32 (t, II), 48.88 (t, I), 37.67 (d, I), 36.91 (d, II), 29.63 (q, I), 28.11 (q, II), 24.23 (q, II), 24.17 (q, I); MS (+EI, 15 eV), *m*/*z* (relative intensity) 171 (M − NH_3, 15), 161 (22), 160 (12), 147 (14), 146 (100), 133 (13), 118 (10), 105 (20), 57 (13). Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.6; H, 8.6. Found: C, 76.2; H, 8.7.

(2*R*,4*S*)- and (2*S*,4*S*)-2-Amino-2-methyl-4-phenylpentanenitrile (11b). Reaction of (*S*)-(+)-4-phenyl-2-pentanone [(*S*)-**10b**][5] (19.47 g, 0.12 mol) for 4 days gave **11b** as an almost colorless liquid and as a mixture of diastereoisomers (22.60 g, 100%) [55:45 isomer I (2*R*,4*S*)/isomer II (2*S*,4*S*)]. The spectral data were identical with those of the racemic α-amino nitrile prepared above. Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.6; H, 8.6. Found: C, 76.3; H, 8.5.

2-Amino-2,4-dimethyl-4-phenylpentanenitrile Hydrochloride (11c). Reaction of 4-methyl-4-phenyl-2-pentanone (**10c**)[32] (50.5 g, 0.287 mol) for 2 days gave **11c** (58.7 g, 100%). On storage at ambient temperature, **11c** underwent partial elimination of HCN, with reversion to the ketone **10c**, so it was converted to the more stable hydrochloride. The crude α-amino nitrile was diluted with a small volume of dry ethanol, and the solution was chilled in an ice bath. A saturated solution of anhydrous HCl in ether was added dropwise, and with stirring, and the precipitate was filtered and washed with ether to give the hydrochloride as

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a white powder (53.9 g, 78%): mp >300 °C (sealed tube) (lit.[6] mp >350 °C).

General Procedure for the Hydrolysis of α-Amino Nitriles: Synthesis of α-Amino Acid Hydrochloride Salts (12). The crude α-amino nitrile 11 was slowly added with stirring to concentrated hydrochloric acid (ca. 10 mL of HCl/g of nitrile), and the mixture was heated under reflux for 48 h. The reaction mixture was allowed to cool slowly to room temperature and was then chilled in ice. The crude acid salt was filtered, washed with a little cold water, dried, and finally washed by stirring with CH_2Cl_2 and filtering.

2-Amino-2-methyl-4-phenylbutanoic Acid Hydrochloride (12a). Hydrolysis of **11a** (34.85 g, 0.20 mol) and recrystallization of the crude product from water gave **12a** as a white crystalline solid (36.63 g, 80%): mp 255–256.5 °C dec; IR ν_{max} (KBr) 3600–2300 (br), 1745, 1582, 1496, 1167, 1120, 793, 765, 701, 644 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ 8.75 (br s, 4 H), 7.29–7.25 (m, 2 H), 7.18–7.15 (m, 3 H), 2.81–2.73 (m, 1 H), 2.49–2.41 (m, 1 H), 2.15–1.99 (m, 2 H), 1.50 (s, 3 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.61 (s), 140.60 (s), 128.55 (d), 128.21 (d), 126.20 (d), 58.90 (s), 38.81 (t), 29.39 (t), 22.10 (q); MS (+EI, 15 eV), *m/z* (relative intensity) 193 (M – HCl, 5), 176 (13), 149 (11), 148 (100), 131 (5), 91 (12), 89 (31), 88 (30), 36 (6). Anal. Calcd for $C_{11}H_{16}ClNO_2$: C, 57.5; H, 7.0. Found: C, 57.2; H, 7.1. A small amount was treated with dilute aqueous ammonia solution and the product recrystallized from water to give the free α-amino acid as white feathery crystals: mp (sealed tube) 287.5–290 °C dec (lit.[33] mp 287–289 °C dec).

(2*RS*,4*SR*)- and (2*RS*,4*RS*)-2-Amino-2-methyl-4-phenylpentanoic Acid Hydrochloride (12b). The general procedure was modified as follows. A mixture of racemic α-amino nitriles **11b** [55:45 (2*RS*,4*SR*)/(2*RS*,4*RS*)] (47.1 g, 0.25 mol) in concentrated hydrochloric acid (470 mL) was heated at reflux for 48 h. An aliquot was removed, the HCl was evaporated, and the residue was dried in vacuo. ^1H NMR indicated a mixture of diastereoisomers (55:45 I/II). The bulk reaction mixture was allowed to cool slowly to room temperature, and the resulting product was filtered, washed with a little cold water, and recrystallized twice from water to give pure isomer II [(2*RS*,4*RS*)-**12b**] as a white powder (15.09 g, 25%): mp 226–231 °C dec; IR ν_{max} (KBr) 3402, 3325, 2962 (br), 1724, 1503, 1451, 1251, 1233, 770, 707; ^1H NMR (400 MHz, d_6-DMSO) δ 8.51 (br s, 1 H), 7.27–7.14 (m, 5 H), 3.45 (br s, 3 H), 2.95–2.87 (m, 1 H), 2.23 (dd, 1 H, *J* = 14.5, 8.1 Hz), 2.07 (dd, 1 H, *J* = 14.5, 4.4 Hz), 1.28 (s, 3 H), 1.17 (d, 3 H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.24 (s), 146.29 (s), 128.28 (d), 127.13 (d), 126.27 (d), 58.75 (s), 44.61 (t), 34.57 (d), 24.82 (q), 22.57 (q); MS (+EI, 15 eV), *m/z* (relative intensity) 163 (14), 162 (M – HCl – CO_2H, 100), 105 (51), 89 (14), 88 (35), 58 (22), 42 (11), 38 (22), 36 (68). Anal. Calcd for $C_{12}H_{18}ClNO_2$: C, 59.1; H, 7.4. Found: C, 59.0; H, 7.6.

The combined filtrate (73:27 isomer I/II by NMR) was concentrated and recrystallized from water over a period of a week to give a second crop (21.81 g, 36%; 66:34 isomer I/II by NMR). The filtrate, which contained a mixture of diastereoisomeric acids (82:18 isomer I/II) together with ammonium chloride, was concentrated. Recrystallization of the residue failed to increase the purity of isomer I. The residue was taken up in water (100 mL), and the pH was adjusted to 6.5–7 by the addition of dilute aqueous ammonium hydroxide. The free α-amino acid was collected by filtration (17.90 g, 35%). Slow recrystallization from ethanol/water failed to improve further the purity of isomer I. A small sample was acidified to give the hydrochloride [isomer I, (2*RS*,4*SR*)-**12b**; 82% pure by NMR]: ^1H NMR (400 MHz, d_6-DMSO) δ 8.72 (br s, 4 H), 7.29–7.13 (m, 5 H), 3.13–3.04 (m, 1 H), 2.15 (dd, 1 H, *J* = 14.7, 4.9 Hz), 2.09 (dd, 1 H, *J* = 14.7, 8.3 Hz), 1.36 (s, 3 H), 1.14 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, d_6-DMSO) δ 173.13 (s), 147.44 (s), 128.43 (d), 126.73 (d), 126.13 (d), 58.45 (s), 44.90 (t), 33.79 (d), 23.04 (q), 21.91 (q).

(2*R*,4*S*)- and (2*S*,4*S*)-2-Amino-2-methyl-4-phenylpentanoic Acid Hydrochloride (12b). The general procedure was modified as follows. A mixture of (2*R*,4*S*)- and (2*S*,4*S*)-**11b** (21.7 g, 0.115 mol) in concentrated hydrochloric acid (220 mL) was heated at reflux for 60 h. An aliquot was removed, the hydrochloric acid was distilled off, and the residue was dried. ^1H NMR indicated a mixture of diastereoisomers (57:43 I/II). The bulk reaction mixture was allowed to cool slowly to room temperature, and the resulting crystals were filtered, washed with a little cold water, and dried. The product was stirred with ether (120 mL) and filtered to give a white powder. Recrystallization from water gave pure isomer II [(2*S*,4*S*)-**12b**] as white crystals (8.49 g, 30%): mp ca. 160 °C dec; IR ν_{max} (KBr) 3405, 3331, 3027 (br), 1740, 1527, 1214, 1200, 1183, 1131, 770, 699 cm^{-1}. The NMR spectra were identical with those of the racemic acid (2*RS*,4*RS*)-**12b** prepared above. Anal. Calcd for $C_{12}H_{18}ClNO_2$: C, 59.1; H, 7.4. Found: C, 59.0; H, 7.6.

The filtrate from the initial crystallization (80:20 isomer I/II by NMR) was concentrated to ca. 100 mL and allowed to crystallize over 2 days, and the second crop was filtered and dried (6.90 g, 25%; 36:64 isomer I/II by NMR). The filtrate, which contained a mixture of the diastereoisomeric acids (95:5 isomer I/II) together with ammonium chloride, was basified to pH 6.5 by the addition of aqueous ammonium hydroxide, and the free α-amino acid was collected by filtration (8.45 g, 35%; 95:5 isomer I/II). Recrystallization of the acid failed to increase the purity of isomer I beyond 95%. A sample of the α-amino acid was acidified to give the hydrochloride [isomer I, (2*R*,4*S*)-**12b**] as a colorless gum. The NMR spectra were identical with those of the racemic salt (2*RS*,4*SR*)-**12b** prepared above.

2-Amino-2,4-dimethyl-4-phenylpentanoic Acid Hydrochloride (12c). Hydrolysis of **11c**·HCl (50.0 g, 0.209 mol) gave **12c** as white crystals (46.1 g, 85%). A small amount was recrystallized from water to give a white powder: mp 244–249 °C dec; IR ν_{max} (KBr) 3159, 2967, 1701, 1638, 1556, 1514, 1383, 1233, 766, 701 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ 7.99 (br s, 4 H), 7.36 (d, 2 H, *J* = 7.5 Hz), 7.28 (t, 2 H, *J* = 7.5 Hz), 7.16 (t, 1 H, *J* = 7.5 Hz), 2.25 (d, 1 H, *J* = 14.7 Hz), 2.17 (d, 1 H, *J* = 14.7 Hz), 1.36 (s, 3 H), 1.32 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 172.97 (s), 149.27 (s), 127.99 (d), 125.71 (d), 125.61 (d), 59.54 (s), 49.97 (t), 37.08 (s), 29.52 (q), 27.96 (q), 23.42 (q); MS (+EI, 15 eV), *m/z* (relative intensity) 221 (M – HCl, 21), 177 (14), 176 (100), 165 (10), 119 (71), 89 (18), 88 (55), 58 (27). Anal. Calcd for $C_{13}H_{20}ClNO_2$: C, 60.6; H, 7.8. Found: C, 60.9; H, 8.1.

General Procedure for the Esterification of α-Amino Acids (12). Synthesis of α-Amino Esters (13). Thionyl chloride (4 equiv) was added, dropwise and with stirring, to dry methanol (ca. 25 mL/0.1 mol of $SOCl_2$) cooled to between 0 and −10 °C. The resulting mixture was added to a suspension of α-amino acid hydrochloride **12** in dry methanol (ca. 1 mL of methanol/mmol of α-amino acid) cooled to between 0 and −10 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for an additional 7–12 days. The excess methanol and thionyl chloride were removed under reduced pressure, and the residue was suspended in CH_2Cl_2 and stirred with 20% aqueous NaOH. The organic phase was separated, and the aqueous phase was extracted with a further portion of CH_2Cl_2. The combined organic phase was washed with water and dried (Na_2SO_4), the solvent evaporated, and the residue distilled (Kugelrohr) to give the pure α-amino ester **13**.

Methyl 2-Amino-2-methyl-4-phenylbutanoate (13a). Treatment of **12a** with methanolic thionyl chloride for 10 days, followed by Kugelrohr distillation (75 °C/0.01 Torr) of the crude product, gave **13a** as a colorless liquid (95% yield): IR ν_{max} (film) 3375, 3311, 3026, 2950, 1731, 1601, 1496, 1454, 1245, 1200, 1116, 748, 700 cm^{-1}; ^1H NMR (400 MHz) δ 7.30–7.25 (m, 2 H), 7.20–7.16 (m, 3 H), 3.71 (s, 3 H), 2.69 (ddd, 1 H, *J* = 13.4, 12.0, 5.3 Hz), 2.53 (ddd, 1 H, *J* = 13.4, 12.0, 5.0 Hz), 2.37 (br s, 2 H), 2.06 (ddd, 1 H, *J* = 13.6, 12.0, 5.0 Hz), 1.93 (ddd, 1 H, *J* = 13.6, 12.0, 5.3 Hz), 1.41, (s, 3 H); ^{13}C NMR (100 MHz) δ 177.68 (s), 141.47 (s), 128.36 (d), 128.30 (d), 125.89 (d), 57.82 (s), 52.22 (q), 42.67 (t), 30.65 (t), 26.36 (q); MS (+EI, 20 eV), *m/z* (relative intensity) 207 (M^+, 4), 149 (11), 148 (100), 103 (9), 102 (16), 91 (13). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.5; H, 8.3. Found: C, 69.2; H, 8.4.

Methyl 2-Amino-2-methyl-4-phenylpentanoate (13b-I) [(2*RS*,4*SR*)-13b]. Esterification of the mixture of racemic α-amino acids **12b** (82:18 isomer I/II), followed by Kugelrohr distillation (75 °C/0.001 Torr), gave a mixture of racemic esters as a colorless liquid (95% yield; 82:18 isomer I/II). The diastereoisomers were separated by radial chromatography (95:5 ether/methanol). The first, major component eluted was distilled,

(33) Goodson, L. H.; Honigberg, I. L.; Lehman, J. J.; Burton, W. H. *J. Org. Chem.* **1960**, *25*, 1920.

as above, to give **13b-I** [(2*RS*,4*SR*)-**13b**] as a colorless liquid: IR ν_{max} (film) 3380, 3310, 2958, 1731, 1494, 1452, 1198, 1130, 763, 701 cm^{-1}; ^1H NMR (400 MHz) δ 7.31–7.26 (m, 2 H), 7.21–7.16 (m, 3 H), 3.61 (s, 3 H), 2.84–2.75 (m, 1 H), 2.06 (dd, 1 H, J = 14.1, 5.7 Hz), 2.03 (dd, 1 H, J = 14.1, 7.8 Hz), 1.53 (br s, 2 H), 1.28 (s, 3 H), 1.21 (d, 3 H, J = 7.1 Hz); ^{13}C NMR (100 MHz) δ 178.07 (s), 147.00 (s), 128.49 (d), 127.03 (d), 126.20 (d), 57.90 (s), 51.98 (q), 48.60 (t), 36.75 (d), 27.51 (q), 24.03 (q); (MS (+EI, 15 eV), m/z (relative intensity), 222 (M + 1, 3), 163 (11), 162 (M – CO_2CH_3, 100), 105 (37), 103 (7), 102 (27), 58 (8). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.6; H, 8.7. Found: C, 70.4; H, 9.0. The second component eluted was **13b-II** [(2*RS*,4*RS*)-**13b**], identical with that prepared below.

13b-II [(2*RS*,4*RS*)-13b]. Esterification of racemic **12b-II** [(2*RS*,4*RS*)-**12b**], followed by Kugelrohr distillation (75 °C/0.001 Torr), gave the racemic ester as a colorless liquid (94% yield): IR ν_{max} (film) 3376, 3312, 2958, 1731, 1494, 1453, 1206, 1126, 763, 701 cm^{-1}; ^1H NMR (400 MHz) δ 7.28–7.24 (m, 2 H), 7.17–7.13 (m, 3 H), 3.18 (s, 3 H), 2.91–2.82 (m, 1 H), 2.29 (dd, 1 H, J = 14.0, 10.0 Hz), 1.82 (dd, 1 H, J = 14.0, 3.8 Hz), 1.64 (br s, 2 H), 1.27 (s, 3 H), 1.24 (d, 3 H, J = 7.1 Hz); ^{13}C NMR (100 MHz) δ 177.42 (s), 145.96 (s), 128.17 (d), 127.41 (d), 126.13 (d), 56.95 (s), 51.62 (q), 48.79 (t), 36.12 (d), 28.08 (q), 24.91 (q); MS (+EI, 15 eV), m/z (relative intensity) 222 (M + 1, 2), 163 (12), 162 (M – CO_2CH_3, 100), 105 (36), 103 (6), 102 (28), 58 (8). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.6; H, 8.7. Found: C, 70.7; H, 8.9.

13b-I [(2*R*,4*S*)-13b]. Esterification of the mixture of enantiomerically pure α-amino acids **12b** (95:5 isomer I/II) gave a mixture of esters as a colorless liquid after Kugelrohr distillation (75 °C/0.001 Torr) (92% yield; 95:5 isomer I/II). The diastereoisomers were separated by radial chromatography (95:5 ether/methanol). The first, major component eluted was distilled, as above, to give **13b-I** [(2*R*,4*S*)-**13b**] as a colorless liquid: $[\alpha]^{25}_D$ –4.0° (*c* 5.0, benzene). The spectral data were identical with those of the racemic ester (2*RS*,4*SR*)-**13b** prepared above. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.6; H, 8.7. Found: C, 70.2; H, 8.5. The second component eluted was **13b-II** [(2*S*,4*S*)-**13b**], identical with that prepared below.

13b-II [(2*S*,4*S*)-13b]. Esterification of **12b-II** [(2*S*,4*S*)-**12b**], followed by Kugelrohr distillation (75 °C/0.001 Torr), gave the ester as a colorless liquid (96% yield): $[\alpha]^{25}_D$ +54.0° (*c* 5.0, benzene). The spectral data were identical with those of the racemic ester (2*RS*,4*RS*)-**13b** prepared above. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.6; H, 8.7. Found: C, 70.5; H, 9.0.

Methyl 2-Amino-2,4-dimethyl-4-phenylpentanoate (13c). Reaction of **12c** for 11 days, followed by Kugelrohr distillation (100 °C/0.04 Torr; lit.[6] 122–124 °C/2 Torr) of the crude product, gave **13c** as a colorless liquid (82% yield): IR ν_{max} (film) 3385, 3330, 2961, 1731, 1454, 1209, 1197, 1140, 1116, 763, 700 cm^{-1}; ^1H NMR (90 MHz) δ 7.40–7.10 (m, 5 H), 3.48 (s, 3 H), 2.31 (d, 1 H, J = 14.5 Hz), 2.12 (d, 1 H, J = 14.5 Hz), 1.57 (br s, 2 H), 1.35 (s, 3 H), 1.32 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR (25 MHz) δ 178.3 (s), 148.2 (s), 128.1 (d), 126.0 (d), 125.8 (d), 57.6 (s), 53.6 (t), 51.8 (q), 37.4 (s), 31.4 (q), 29.9 (q), 28.5 (q); MS (+EI, 15 eV), m/z (relative intensity), 235 (M^+, 2), 177 (13), 176 (100), 120 (9), 119 (98), 103 (9), 102 (69), 84 (11), 58 (21), 49 (14).

General Procedure for the Synthesis of N,N'-Disubstituted Sulfamides (14). A solution of sulfuryl chloride (675 mg, 5 mmol) in pentane (20 mL) was added dropwise to a stirred solution of the α-amino ester **13** (20 mmol) in pentane (40 mL) cooled to 0 °C. The reaction mixture was stirred for 15 min, after which time cold water (100 mL) was added and the reaction mixture was stirred for an additional 15 min. The mixture was extracted with CH_2Cl_2 (120 mL), the organic phase was washed with 1 M HCl (60 mL), followed with water (60 mL), and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to give the crude sulfamide **14** as a colorless, viscous gum. The aqueous phases from the above extraction were combined, basified with 30% (w/v) aqueous NaOH, and extracted with CH_2Cl_2 (2 × 60 mL). The combined organic extract was washed with water (100 mL) and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to recover the excess α-amino ester.

***meso*- and *dl*-*N*,*N*'-Bis[2-[2-(methoxycarbonyl)-4-phenylbutyl]]sulfamide (14a).** Reaction of **13a** with sulfuryl chloride gave **14a** as a mixture of diastereoisomers (71% yield). Exhaustive fractional recrystallization from CH_2Cl_2/petroleum ether gave the two isomers. **14a-I (*dl*-14a)**: colorless prisms; mp 108.8–109.7 °C; IR ν_{max} (KBr) 3287, 1729, 1454, 1320, 1251, 1125, 1003, 737, 698 cm^{-1}; ^1H NMR (400 MHz) δ 7.30–7.25 (m, 4 H), 7.22–7.16 (m, 6 H), 5.59 (s, 2 H), 3.75 (s, 6 H), 2.74 (ddd, 2 H, J = 13.4, 11.8, 5.1 Hz), 2.53 (ddd, 2 H, J = 13.4, 11.7, 5.3 Hz), 2.25 (ddd, 2 H, J = 13.9, 11.7, 5.1 Hz), 2.10 (ddd, 2 H, J = 13.9, 11.8, 5.3 Hz), 1.71 (s, 6 H); ^{13}C NMR (100 MHz) δ 174.93 (s), 140.72 (s), 128.45 (d), 128.42 (d), 126.10 (d), 63.14 (s), 53.01 (q), 41.02 (t), 30.21 (t), 23.45 (q); MS (+EI, 15 eV), m/z (relative intensity) 476 (M^+, 1), 418 (5), 417 (19), 341 (8), 340 (44), 208 (5), 207 (15), 190 (23), 149 (11), 148 (100), 103 (7), 102 (10). Anal. Calcd for $C_{24}H_{32}N_2O_6S$: C, 60.5; H, 6.8. Found: C, 60.2; H, 6.4. **14a-II (*meso*-14a)**: colorless cubes; mp 92.7–93.8 °C; IR ν_{max} (KBr) 3335, 3264, 2998, 2958, 1727, 1454, 1338, 1245, 1214, 1122, 990, 884, 761, 699, 581 cm^{-1}; ^1H NMR (400 MHz) δ 7.29–7.24 (m, 4 H), 7.20–7.15 (m, 6 H), 5.53 (s, 2 H), 3.75 (s, 6 H), 2.72 (ddd, 2 H, J = 13.4, 11.8, 5.2 Hz), 2.55 (ddd, 2 H, J = 13.4, 11.6, 5.3 Hz), 2.23 (ddd, 2 H, J = 13.9, 11.6, 5.2 Hz), 2.12 (ddd, 2 H, J = 13.9, 11.8, 5.3 Hz), 1.69 (s, 6 H); ^{13}C NMR (100 MHz) δ 174.92 (s), 140.78 (s), 128.42 (d), 126.07 (d), 62.99 (s), 52.98 (q), 40.82 (t), 30.18 (t), 23.13 (q); MS (+EI, 15 eV), m/z (relative intensity) 476 (M^+, 4), 418 (9), 417 (39), 341 (6), 340 (30), 208 (9), 207 (33), 190 (30), 149 (11), 148 (100), 103 (10), 102 (7). Anal. Calcd for $C_{24}H_{32}N_2O_6S$: C, 60.5; H, 6.8. Found: C, 60.5; H, 7.1.

(2*RS*,2'*RS*,4*SR*,4'*SR*)- and (2*R*,2'*S*,4*S*,4'*R*)-*N*,*N*'-Bis-[2-[2-(methoxycarbonyl)-4-phenylpentyl]]sulfamide (14b). Treatment of racemic **13b-I** [(2*RS*,4*SR*)-**13b**] with sulfuryl chloride gave the corresponding sulfamide as a mixture of diastereoisomers (1:1 by NMR) (75% yield). A combination of fractional recrystallization (1:5 CH_2Cl_2/petroleum ether) and protracted radial chromatography (CH_2Cl_2), with recycling of the middle fractions, gave the two diastereoisomers. **14b-Ia [(2*RS*,2'*RS*,4*SR*,4'*SR*)-14b]**: fine white needles: mp 86.9–88.4 °C; IR ν_{max} (KBr) 3294, 3266, 2954, 1733, 1717, 1453, 1435, 1323, 1263, 1231, 1133, 1121, 987, 763, 702 cm^{-1}; ^1H NMR (400 MHz) δ 7.33–7.13 (m, 10 H), 4.91 (s, 2 H), 3.64 (s, 6 H), 2.90–2.82 (m, 2 H), 2.31 (dd, 2 H, J = 14.3, 8.4 Hz), 2.07 (dd, 2 H, J = 14.3, 4.9 Hz), 1.41 (s, 6 H), 1.19 (d, 6 H, J = 7.1 Hz); ^{13}C NMR (100 MHz) δ 175.07 (s), 146.90 (s), 128.48 (d), 127.25 (d), 126.23 (d), 62.86 (s), 52.73 (q), 46.41 (t), 36.10 (d), 24.01 (q), 23.98 (q); MS (+EI, 70 eV), m/z (relative intensity) 445 (M – CO_2CH_3, 20) 163 (11), 162 (96), 145 (14), 106 (9), 105 (100), 102 (43), 91 (9), 58 (12), 42 (14). Anal. Calcd for $C_{26}H_{36}N_2O_6S$: C, 61.9; H, 7.2. Found: C, 61.8; H, 7.2. ***meso*-14b-Ib [(2*R*,2'*S*,4*S*,4'*R*)-14b]**: colorless cubes; mp 89.8–91.2 °C; IR ν_{max} (KBr) 3292, 2957, 1729, 1445, 1424, 1335, 1270, 1254, 1150, 1134, 1120, 1094, 761, 700 cm^{-1}; ^1H NMR (400 MHz) δ 7.31–7.15 (m, 10 H), 5.04 (s, 2 H), 3.62 (s, 6 H), 2.89–2.81 (m, 2 H), 2.27 (dd, 2 H, J = 14.3, 8.2 Hz), 2.00 (dd, 2 H, J = 14.3, 5.3 Hz), 1.50 (s, 6 H), 1.18 (d, 6 H, J = 7.1 Hz); ^{13}C NMR (100 MHz) δ 174.92 (s), 146.58 (s), 128.55 (d), 127.12 (d), 126.33 (d), 62.77 (s), 52.66 (q), 47.09 (t), 35.89 (d), 23.79 (q), 23.74 (q); MS (+EI, 70 eV), m/z (relative intensity) 445 (M – CO_2CH_3, 17), 163 (9), 162 (74), 145 (12), 106 (8), 105 (100), 102 (31), 91 (11), 77 (8), 58 (10), 42 (23). Anal. Calcd for $C_{26}H_{36}N_2O_6S$: C, 61.9; H, 7.2. Found: C, 61.6; H, 7.1.

(2*RS*,2'*RS*,4*RS*,4'*RS*)- and (2*R*,2'*S*,4*R*,4'*S*)-*N*,*N*'-Bis-[2-[2-(methoxycarbonyl)-4-phenylpentyl]]sulfamide (14b). Treatment of racemic **13b-II** [(2*RS*,4*RS*)-**13b**] with sulfuryl chloride gave the sulfamide as a mixture of diastereoisomers (1:1 by NMR) (85% yield). The crude viscous gum was taken up in hot CH_2Cl_2, diluted with hot petroleum ether, and allowed to crystallize at ambient temperature. A further two recrystallizations gave racemic **14b-IIa** [(2*RS*,2'*RS*,4*RS*,4'*RS*)-**14b**] as colorless crystals: mp 117.0–118.3 °C; IR ν_{max} (KBr) 3319, 2951, 1736, 1726, 1453, 1427, 1315, 1304, 1261, 1221, 1156, 700 cm^{-1}; ^1H NMR (400 MHz) δ 7.29–7.13 (m, 10 H), 5.48 (s, 2 H), 3.10 (s, 6 H), 3.07–2.98 (m, 2 H), 2.36 (dd, 2 H, J = 14.3, 3.1 Hz), 2.23 (dd, 2 H, J = 14.3, 10.3 Hz), 1.60 (s, 6 H), 1.26 (d, 6 H, J = 7.1 Hz); ^{13}C NMR (100 MHz) 174.07 (s), 145.63 (s), 128.23 (d), 127.72 (d), 126.26 (d), 61.92 (s), 52.39 (q), 46.79 (t), 35.75 (d), 24.71 (q), 24.34 (q); MS (+EI, 70 eV), m/z (relative intensity) 445 (M – CO_2CH_3, 23), 163 (9), 162 (75), 145 (9), 106 (8), 105 (100), 102 (35), 91 (12), 77 (8), 58 (9), 42 (23). Anal. Calcd for $C_{26}H_{36}N_2O_6S$: C, 61.9; H, 7.2. Found: C, 62.0; H, 7.2.

Protracted radial chromatography (CH_2Cl_2) of the residue gave *meso*-**14b-IIb** [(2*R*,2'*S*,4*R*,4'*S*)-**14b**] as an almost colorless, viscous

gum: IR ν_{max} ($CHCl_3$) 3293, 2956, 1730, 1451, 1266, 1219, 1155, 701 cm^{-1}; ^1H NMR (400 MHz) δ 7.29–7.24 (m, 4 H), 7.18–7.13 (m, 6 H), 5.34 (s, 2 H), 3.18 (s, 6 H), 3.01–2.93 (m, 2 H), 2.28 (dd, 2 H, J = 14.4, 3.7 Hz), 2.23 (dd, 2 H, J = 14.4, 9.3 Hz), 1.60 (s, 6 H), 1.25 (d, 6 H, J = 7.1 Hz); ^{13}C NMR (100 MHz) δ 174.00 (s), 145.76 (s), 128.30 (d), 127.54 (d), 126.29 (d), 62.13 (s), 52.36 (q), 46.70 (t), 35.78 (d), 24.76 (q), 24.06 (q); MS (+EI, 12 eV), m/z (relative intensity) 446 (29), 445 (M – CO_2CH_3, 100), 355 (17), 354 (92), 221 (23), 204 (28), 163 (12), 162 (95), 102 (11); exact mass calcd for $C_{26}H_{36}N_2O_6S$ 504.2294, found 504.2296.

The residue was subjected to radial chromatography (CH_2Cl_2) to give a yellow viscous oil (2.1% by mass of the crude sulfamide), which was identified as **methyl (2*RS*,4*RS*)-2-(chloroamino)-2-methyl-4-phenylpentanoate (16b)**: IR ν_{max} (film) 3269, 2956, 1731, 1493, 1453, 1218, 1200, 1121, 764, 701 cm^{-1}; ^1H NMR (400 MHz) δ 7.30–7.25 (m, 2 H), 7.20–7.15 (m, 3 H), 4.77 (s, 1 H), 3.49 (s, 3 H), 2.90–2.81 (m, 1 H), 2.17 (dd, 1 H, J = 14.2, 8.4 Hz), 2.08 (dd, 1 H, J = 14.2, 4.9 Hz), 1.34 (s, 3 H), 1.23 (d, 3 H, J = 7.1 Hz); ^{13}C NMR (100 MHz) δ 173.87 (s), 146.50 (s), 128.38 (d), 127.08 (d), 126.24 (d), 66.92 (s), 52.16 (q), 45.50 (t), 35.84 (d), 24.40 (q), 21.39 (q); MS (+EI, 12 eV), m/z (relative intensity) 221 (11), 220 (M – Cl, 57), 198 (34), 197 (13), 196 (100), 174 (12), 162 (47), 160 (26), 105 (44), 102 (36); exact mass calcd for $C_{13}H_{18}NO_2Cl$ 255.1026, found 255.1027.

(2*R*,2′*R*,4*S*,4′*S*)-*N*,*N*′-Bis[2-[2-(methoxycarbonyl)-4-phenylpentyl]]sulfamide (14b-Ia). Reaction of the enantiomer **13b**-I [(2*R*,4*S*)-**13b**] with sulfuryl chloride gave **14b**-Ia [(2*R*,2′*R*,4*S*,4′*S*)-**14b**] as a colorless, viscous gum (73% yield) which was crystallized from ether/petroleum ether at 0 °C to furnish colorless cubes: mp 106.3–107.4 °C; $[\alpha]^{25}_D$ +18.5° (*c* 4.6, benzene); exact mass calcd for $C_{26}H_{36}N_2O_6S$ 504.2294, found 504.2296. The ^1H and ^{13}C NMR spectra were identical with those of racemic **14b**-Ia prepared above. Anal. Calcd for $C_{26}H_{36}N_2O_6S$: C, 61.9; H, 7.2. Found: C, 62.2; H, 7.5. This sample was subjected to X-ray crystal analysis.

(2*S*,2′*S*,4*S*,4′*S*)-*N*,*N*′-Bis[2-[2-(methoxycarbonyl)-4-phenylpentyl]]sulfamide (14b-IIa). Reaction of the enantiomer **13b**-II [(2*S*,4*S*)-**13b**] gave the optically active sulfamide **14b**-IIa [(2*S*,2′*S*,4*S*,4′*S*)-**14b**] as a colorless, viscous gum (80% yield): $[\alpha]^{25}_D$ +153.9° (*c*, 4.6 benzene); exact mass calcd for $C_{26}H_{36}N_2O_6S$ 504.2294, found 504.2296. The ^1H and ^{13}C NMR spectra were identical with those of racemic **14b**-IIa prepared above.

***N*,*N*′-Bis[2-[2-(methoxycarbonyl)-4-methyl-4-phenylpentyl]]sulfamide (14c).** Reaction of **13c** with sulfuryl chloride afforded the crude sulfamide as a mixture of diastereoisomers (1:1 by NMR) (81% yield). The viscous gum was taken up in hot CH_2Cl_2, diluted with petroleum ether, and allowed to crystallize at ambient temperature. The solid was filtered and recrystallized to give **14c**-I as white crystals: mp 93.7–95.2 °C; IR ν_{max} (KBr) 3301, 2998, 2962, 1738, 1720, 1598, 1440, 1346, 1257, 1220, 1154, 1129, 764, 702 cm^{-1}; IR ν_{max} ($CHCl_3$) 3350 (NH), 1730 (C=O) cm^{-1}; ^1H NMR (400 MHz) δ 7.34–7.27 (m, 8 H), 7.20–7.16 (m, 2 H), 4.83 (s, 2 H), 3.40 (s, 6 H), 2.32 (d, 2 H, J = 14.8 Hz), 2.16 (d, 2 H, J = 14.8 Hz), 1.42 (s, 6 H), 1.36 (s, 6 H), 1.31 (s, 6 H); ^{13}C NMR (100 Mz) δ 174.51 (s), 147.45 (s), 128.14 (d), 126.20 (d), 126.01 (d), 62.03 (s), 52.44 (q), 52.36 (t), 37.48 (s), 30.41 (q), 29.65 (q), 24.75 (q); MS (+EI, 70 eV), m/z (relative intensity) 473 (M – CO_2CH_3, 12), 176 (25), 119 (100), 102 (33), 91 (37), 58 (20), 42 (22), 41 (17). Anal. Calcd for $C_{28}H_{40}N_2O_6S$: C, 63.1; H, 7.6. Found: C, 63.3; H, 7.3.

The residue from the initial crystallization (70% isomer II by NMR) was recrystallized from CH_2Cl_2/petroleum ether to give **14c**-II as white, feathery clusters: mp 109.1–110.5 °C; IR ν_{max} (KBr) 3351, 3309, 2957, 1739, 1730, 1720, 1599, 1443, 1252, 1220, 1159, 1123, 985, 767, 700 cm^{-1}; IR ν_{max} ($CHCl_3$) 3353 (NH), 1730 (C=O) cm^{-1}; ^1H NMR (400 MHz) δ 7.35–7.27 (m, 8 H), 7.18–7.14 (m, 2 H), 4.93 (s, 2 H), 3.36 (s, 6 H), 2.45 (d, 2 H, J = 14.9 Hz), 2.20 (d, 2 H, J = 14.9 Hz), 1.42 (s, 6 H), 1.41 (s, 6 H), 1.33 (s, 6 H); ^{13}C NMR (100 MHz) δ 174.60 (s), 147.73 (s), 128.03 (d), 126.35 (d), 125.84 (d), 61.94 (s), 52.51 (q), 51.50 (t), 37.51 (s), 30.79 (q) 29.38 (q), 24.97 (q); MS (+EI, 15 eV), m/z (relative intensity) 474 (29), 473 (M – CO_2CH_3, 94), 399 (12), 196 (18), 177 (14), 176 (100), 174 (10), 167 (19), 120 (10), 119 (98), 102 (53), 58 (31). Anal. Calcd for $C_{28}H_{40}N_2O_6S$: C, 63.1; H, 7.6. Found: C, 63.5; H, 7.3.

The residue from the recrystallization of the sulfamides, seen by NMR to be a mixture of the sulfamides together with a small amount of byproduct, was subjected to radial chromatography (1:1 ether/petroleum ether). The first component eluted was purified further by Kugelrohr distillation (110 °C/0.001 Torr) to give an almost colorless, viscous oil (4.2% by mass of the crude sulfamide), which was identified as **methyl 2-(chloroamino)-2,4-dimethyl-4-phenylpentanoate (16c)**: IR ν_{max} (film) 3265, 2954, 1732, 1600, 1496, 1445, 1372, 1261, 1212, 1126, 765, 700 cm^{-1}; ^1H NMR (400 MHz) δ 7.35–7.17 (m, 5 H), 4.62 (s, 1 H), 3.49 (s, 3 H), 2.21 (d, 2 H, J = 0.5 Hz), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.51 (d, 3 H, J = 0.5 Hz); ^{13}C NMR (100 MHz) δ 174.04 (s), 147.47 (s), 128.05 (d), 126.03 (d), 125.98 (d), 67.46 (s), 52.14 (q), 51.01 (t), 37.46 (s), 30.62 (q), 29.87 (q), 21.38 (q); MS (+EI, 10 eV), m/z (relative intensity) 234 (M – Cl, 100), 212 (12), 210 (36), 174 (44), 119 (18); MS (FAB) 272 (M + 1, ^{37}Cl), 270 (M + 1, ^{35}Cl); Anal. Calcd for $C_{14}H_{20}ClNO_2$: C, 62.3; H, 7.5. Found: C, 62.0; H, 7.1. The second component eluted was a mixture of the partially resolved sulfamides.

General Procedure for the Synthesis of Azo Diesters 4 from N,N′-Disubstituted Sulfamides (14). The sulfamide **14** (1.0 mmol) was dissolved in dry methanol (4 mL) by gentle warming and the solution cooled to 0 °C. Sodium methoxide in methanol (4 mL of a 1.0 M solution; 4.0 mmol) was added, and the reaction mixture was stirred at 0 °C for 0.5 h. In most instances the reaction mixture remained as a colorless solution, but at times a white suspension developed, but dissolved upon addition of the oxidant. A solution of *tert*-butyl hypochlorite (239 mg, 2.2 mmol) in methanol (2 mL) was added, and the reaction mixture was stirred at 0 °C for an additional 1 h. The reaction mixture was poured into cold 5% aqueous HCl solution (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extract was washed with water (50 mL) and dried (Na_2SO_4), the solvent was evaporated under reduced pressure, and the residue was dried in vacuo to give the crude azo diester **4**. Precautions were taken to ensure that, at all times during workup, solutions of the azo diester were kept below 5 °C to prevent decomposition.

Dimethyl *dl*-2,2′-Dimethyl-4,4′-diphenyl-2,2′-azobutanoate (*dl*-4a) (4a-I). Reaction of *dl*-**14a** (477 mg, 1.0 mmol) gave *dl*-**4a** as a pale yellow oil (409 mg, 100%), which was crystallized from ether/petroleum ether at low temperature (–15 °C) as fine white needles: mp 49.0–50.3 °C; IR ν_{max} (KBr) 3027, 2995, 2949, 1730, 1496, 1454, 1238, 1192, 1165, 1111, 701 cm^{-1}; ^1H NMR (400 MHz) δ 7.30–7.25 (m, 4 H), 7.21–7.16 (m, 6 H), 3.71 (s, 6 H), 2.67–2.59 (m, 4 H), 2.32–2.17 (m, 4 H), 1.48 (s, 6 H); ^{13}C NMR (100 MHz) δ 172.88 (s), 141.70 (s), 128.39 (d), 128.33 (d), 125.94 (d), 78.23 (s), 52.04 (q), 38.67 (t), 30.28 (t), 20.37 (q); MS (+EI, 12 eV), m/z (relative intensity) 278 (M – $C_8H_8N_2$, 16), 192 (26), 190 (40), 174 (16), 160 (18), 158 (26), 131 (13), 130 (37), 105 (13), 91 (34), 88 (100); MS (FAB) 411 (M + H). Anal. Calcd for $C_{24}H_{30}N_2O_4$: C, 70.2; H, 7.4. Found: C, 70.0; H, 7.5.

***meso*-4a (4a-II).** Reaction of *meso*-**14a** (477 mg, 1.0 mmol) gave *meso*-**4a** as a white solid (404 mg, 98%) which was recrystallized from ether/petroleum ether at low temperature (–15 °C) to give fine white needles: mp 91.2–92.0 °C dec; IR ν_{max} (KBr) 3027, 2992, 2948, 1735, 1731, 1599, 1453, 1264, 1245, 1189, 1164, 1130, 739, 700 cm^{-1}; ^1H NMR (400 MHz) δ 7.30–7.25 (m, 4 H), 7.20–7.16 (m, 6 H), 3.71 (s, 6 H), 2.66–2.61 (m, 4 H), 2.35–2.18 (m, 4 H), 1.46 (s, 6 H); ^{13}C NMR (100 MHz) δ 172.93 (s), 141.72 (s), 128.40 (d), 128.33 (d), 125.94 (d), 78.17 (s), 52.07 (q), 38.82 (t), 30.24 (t), 20.25 (q); MS (+EI, 12 eV), m/z (relative intensity) 278 (M – $C_8H_8N_2$, 27), 192 (22), 190 (35), 174 (26), 160 (17), 158 (23), 131 (16), 130 (32), 105 (11), 91 (39), 88 (100). Anal. Calcd for $C_{24}H_{30}N_2O_4$: C, 70.2; H, 7.4. Found: C, 70.0; H, 7.4.

Dimethyl 2,2′-Dimethyl-4,4′-diphenyl-2,2′-azopentanoate (4b-Ia) [(2*RS*,2′*RS*,4*SR*,4′*SR*)-4b]. Reaction of racemic **14b**-Ia (505 mg, 1.0 mmol) gave **4b**-Ia as a colorless, viscous oil (422 mg, 96%). Crystallization from petroleum ether (–15 °C) gave colorless prisms (364 mg, 83%): mp 41.4–43.0 °C; IR ν_{max} (KBr) 2961, 2945, 1736, 1493, 1450, 1444, 1377, 1210, 1139, 1072, 765, 701 cm^{-1}; ^1H NMR (400 MHz) δ 7.29–7.23 (m, 4 H), 7.18–7.13 (m, 6 H), 3.33 (s, 6 H), 2.94–2.85 (m, 2 H), 2.39 (dd, 2 H, J = 14.2, 8.6 Hz), 2.23 (dd, 2 H, J = 14.2, 4.9 Hz), 1.29 (s, 6 H), 1.26 (d, 6 H, J = 7.1 Hz); ^{13}C NMR (100 MHz) δ 172.57 (s), 146.81 (s), 128.23 (d), 127.28 (d), 126.07 (d), 78.17 (s), 51.59 (q), 44.48 (t), 35.87 (d), 24.60 (q), 20.14 (q); MS (+EI, 12 eV), m/z (relative intensity) 293 (17), 292 (M – $C_9H_{10}N_2$, 100), 260 (9), 228 (8), 175 (8), 174 (96), 173 (16), 172 (12), 142 (42), 141 (14), 106 (11), 105 (34), 101 (20). Anal.

Calcd for $C_{26}H_{34}N_2O_4$: C, 71.2; H, 7.8. Found: C, 71.3; H, 7.6.

***meso*-4b-Ib [(2*R*,2′*S*,4*S*,4′*R*)-4b].** Reaction of *meso*-**14b**-Ib (505 mg, 1.0 mmol) gave *meso*-**4b**-Ib as an almost colorless oil (437 mg, 100%). The oil was dissolved in petroleum ether (3 mL) and kept at −80 °C overnight. The supernatant was decanted, and the residue was dried in vacuo to give a white powder (431 mg, 98%): mp 59.8–61.8 °C dec. Recrystallization from petroleum ether (−15 °C) gave the pure meso azo diester as colorless cubes: mp 63.2–64.4 °C dec; IR ν_{max} (KBr) 2957, 2930, 1737, 1452, 1374, 1323, 1212, 1138, 1117, 762, 701 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.28–7.24 (m, 4 H), 7.18–7.13 (m, 6 H), 3.34 (s, 6 H), 2.93–2.84 (m, 2 H), 2.41 (dd, 2 H, J = 14.2, 8.4 Hz), 2.29 (dd, 2 H, J = 14.2, 5.1 Hz), 1.26 (s, 6 H), 1.25 (d, 6 H, J = 7.1 Hz); ^{13}C NMR (100 MHz) δ 172.67 (s), 146.87 (s), 128.24 (d), 127.25 (d), 126.06 (d), 78.07 (s), 51.62 (q), 44.60 (t), 35.80 (d), 24.46 (q), 20.14 (q); MS (+EI, 12 eV), m/z (relative intensity) 379 (M − N_2 − OCH_3, 1), 293 (19), 292 (100), 260 (7), 228 (7), 175 (9), 174 (92), 173 (16), 172 (9), 142 (36), 141 (9), 106 (8), 105 (20), 101 (10). Anal. Calcd for $C_{26}H_{34}N_2O_4$: C, 71.2; H, 7.8. Found: C, 71.0; H, 7.6.

4b-IIa [(2*RS*,2′*RS*,4*RS*,4′*RS*)-4b]. Reaction of racemic **14b**-IIa (505 mg, 1.0 mmol) gave **4b**-IIa as an almost colorless oil (436 mg, 99%). Radial chromatography (2:1 petroleum ether/ether) afforded the pure racemic azo diester (417 mg, 95%): IR ν_{max} (film) 3026, 2957, 1739, 1493, 1453, 1228, 1199, 1138, 763, 700 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.30–7.25 (m, 4 H), 7.21–7.14 (m, 6 H), 3.50 (s, 6 H), 2.95–2.87 (m, 2 H), 2.35 (dd, 2 H, J = 14.0, 7.9 Hz), 2.18 (dd, 2 H, J = 14.0, 5.5 Hz), 1.22 (d, 6 H, J = 6.8 Hz), 1.18 (s, 6 H); ^{13}C NMR (100 MHz) δ 172.93 (s), 147.22 (s), 128.32 (d), 127.24 (d), 126.06 (d), 78.05 (s), 51.69 (q), 44.79 (t), 36.15 (d), 24.17 (q), 21.07 (q); MS (+EI, 12 eV), m/z (relative intensity) 410 (M − N_2, 5), 409 (13), 293 (17), 292 (100), 291 (10), 260 (7), 206 (12), 204 (11), 174 (70), 142 (17), 119 (13), 105 (27), 101 (11). Anal. Calcd for $C_{26}H_{34}N_2O_4$: C, 71.2; H, 7.8. Found: C, 71.1; H, 7.9.

***meso*-4b-IIb [(2*R*,2′*S*,4*R*,4′*S*)-4b].** Reaction of *meso*-**14b**-IIb (505 mg, 1.0 mmol) gave *meso*-**4b**-IIb as an almost colorless oil (440 mg, 100%). Crystallization from petroleum ether (−15 °C) gave the azo diester as colorless cubes (338 mg, 77%): mp 60.2–61.8 °C; IR ν_{max} (KBr) 2982, 2961, 1737, 1470, 1452, 1296, 1244, 1189, 1179, 1144, 1120, 769, 703 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.30–7.25 (m, 4 H), 7.21–7.14 (m, 6 H), 3.49 (s, 6 H), 2.97–2.88 (m, 2 H), 2.38 (dd, 2 H, J = 14.2, 7.8 Hz), 2.16 (dd, 2 H, J = 14.2, 5.6 Hz), 1.21 (d, 6 H, J = 6.8 Hz), 1.19 (s, 6 H); ^{13}C NMR (100 MHz) δ 173.01 (s), 147.23 (s), 128.29 (d), 127.27 (d), 126.04 (d), 77.93 (s), 51.68 (q), 45.23 (t), 36.06 (d), 24.09 (q), 21.12 (q); MS (+EI, 12 eV), m/z (relative intensity) 379 (M − N_2 − OCH_3, 2), 293 (19), 292 (100), 260 (7), 206 (10), 174 (93), 173 (12), 172 (9), 142 (34), 106 (8), 105 (14), 101 (15). Anal. Calcd for $C_{26}H_{34}N_2O_4$: C, 71.2; H, 7.8. Found: C, 71.0; H, 7.4.

4b-Ia [(2*R*,2′*R*,4*S*,4′*S*)-4b]. Reaction of the enantiomer **14b**-Ia [(2*R*,2′*R*,4*S*,4′*S*)-**14b**] (0.81 g, 1.6 mmol) gave the azo diester as an almost colorless oil (0.71 g, 100%): $[\alpha]^{20}_D$ −11.8° (*c*, 2.5 benzene); exact mass calcd for $C_{25}H_{31}O_3$ (M − CH_3N_2O) 379.2273, found 379.2273. The NMR spectra were identical with those of racemic **4b**-Ia prepared above.

4b-IIa [(2*S*,2′*S*,4*S*,4′*S*)-4b]. Reaction of the enantiomer **14b**-IIa [(2*S*,2′*S*,4*S*,4′*S*)-**14b**] (505 mg, 1.0 mmol) gave the azo diester as an almost colorless oil (436 mg, 99%): $[\alpha]^{20}_D$ +31.5° (*c*, 1.6 benzene); exact mass calcd for $C_{25}H_{31}O_3$ (M − CH_3N_2O) 379.2273, found 379.2273. The NMR spectra were identical with those of racemic **4b**-IIa prepared above.

Dimethyl 4,4′-Diphenyl-2,2′,4,4′-tetramethyl-2,2′-azopentanoate (4c-I). Reaction of **14c**-I (533 mg, 1.0 mmol) gave **4c**-I as a white solid (460 mg, 99%). The crude product was dissolved in cold $CHCl_3$, diluted with cold pentane, and left at −15 °C overnight to give colorless cubes (270 mg): mp 73–74 °C dec (lit.[6] mp 74–75 °C); IR ν_{max} (KBr) 2966, 2935, 1737, 1711, 1454, 1442, 1211, 1184, 1150, 1119, 768, 700 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.38–7.36 (m, 4 H), 7.31–7.26 (m, 4 H), 7.18–7.14 (m, 2 H), 3.42 (s, 6 H), 2.56 (d, 2 H, J = 14.7 Hz), 2.47 (d, 2 H, J = 14.7 Hz), 1.34 (s, 6 H), 1.32 (s, 6 H), 0.93, (s, 6 H); ^{13}C NMR (100 MHz) δ 173.10 (s), 148.90 (s), 127.95 (d), 126.07 (d), 125.63 (d), 78.36 (s), 51.60 (q), 49.68 (t), 37.43 (s), 32.28 (q), 28.78 (q), 21.42 (q); MS (+EI, 15 eV), m/z (relative intensity) 466 (M$^+$, 1), 320 (5), 319 (M − $C_9H_{11}N_2$, 14), 221 (7), 220 (49), 219 (10), 120 (43), 119 (100), 118 (15). Anal. Calcd for $C_{28}H_{38}N_2O_4$: C, 72.1; H, 8.2. Found: C, 72.5; H, 7.9.

4c-II. Reaction of **14c**-II (533 mg, 1.0 mmol) gave the azo diester as an almost colorless gum: IR ν_{max} (film) 2959, 1737, 1496, 1454, 1266, 1199, 1155, 1120, 764, 700 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.38–7.27 (m, 8 H), 7.18–7.14 (m, 2 H), 3.43 (s, 6 H), 2.55 (d, 2 H, J = 14.7 Hz), 2.42 (d, 2 H, J = 14.7 Hz), 1.34 (s, 6 H), 1.33 (s, 6 H), 0.92 (s, 6 H); ^{13}C NMR (100 MHz) δ 173.10 (s), 148.85 (s), 127.94 (d), 126.06 (d), 125.62 (d), 78.39 (s), 51.59 (q), 49.59 (t), 37.37 (s), 32.34 (q), 28.69 (q), 21.32 (q); MS (+EI, 12 eV), m/z (relative intensity) 320 (7), 319 (M − $C_9H_{11}N_2$, 19), 221 (13), 220 (76), 219 (12), 120 (51), 119 (100), 118 (11). Anal. Calcd for $C_{28}H_{38}N_2O_4$: C, 72.1; H, 8.2. Found: C, 72.0; H, 8.0.

General Procedure for the Cyclization of Sulfamides. Synthesis of 2,4-Disubstituted 3-Oxo-1,2,5-thiadiazolidine 1,1-Dioxides (15). A solution of the sulfamide **14** (1.0 mmol) and sodium methoxide (4 mmol) in dry methanol (16 mL) was heated under reflux for 1 h. The clear, colorless solution was poured into 5% aqueous HCl solution (40 mL) and extracted with CH_2Cl_2 (2 × 40 mL). The combined extracts were washed with water, dried (Na_2SO_4), and concentrated to furnish the cyclized product **15**.

2-[2-[2-(Methoxycarbonyl)-4-phenylbutyl]]-4-methyl-4-(2-phenylethyl)-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (15a-I) [(2′*RS*,4*RS*)-15a]. Cyclization of racemic **14a**-I (477 mg, 1.0 mmol) yielded **15a**-I as a colorless gum (446 mg, 100%): IR ν_{max} ($CHCl_3$) 3249, 3026, 1735, 1730, 1341, 1309, 1264, 1175, 699 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.31–7.15 (m, 10 H), 4.91 (s, 1 H), 3.74 (s, 3 H), 2.80–2.60 (m, 5 H), 2.58–2.37 (m, 1 H), 2.24 (ddd, 1 H, J = 14.1, 10.9, 5.4 Hz), 2.01 (ddd, 1 H, J = 14.2, 10.9, 6.4 Hz), 1.88 (s, 3 H), 1.52 (s, 3 H); ^{13}C NMR (100 MHz) δ 171.88 (s), 171.27 (s), 140.56 (s), 140.14 (s), 128.68 (d), 128.48 (d), 128.39 (d), 128.36 (d), 126.41 (d), 126.17 (d), 65.70 (s), 65.03 (s), 52.89 (q), 38.94 (t), 36.29 (t), 30.03 (t), 29.78 (t), 23.61 (q), 19.80 (q); MS (+EI, 15 eV), m/z (relative intensity) 444 (M$^+$, 1), 342 (7), 341 (18), 340 (100), 190 (12), 148 (7); exact mass calcd for $C_{23}H_{28}N_2O_5S$ 444.1719, found 444.1720.

15a-II [(2′*RS*,4*SR*)-15a]. Cyclization of *meso*-**14a** (477 mg, 1.0 mmol) yielded **15a**-II as a colorless gum (446 mg, 100%), which crystallized on standing. Recrystallization from ether/petroleum ether gave white, starlike clusters: mp 95.4–96.9 °C; IR ν_{max} (KBr) 3236, 1738, 1697, 1454, 1379, 1346, 1320, 1283, 1192, 1166, 1130, 1013, 695 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.32–7.14 (m, 10 H), 4.85 (s, 1 H), 3.76 (s, 3 H), 2.79–2.60 (m, 5 H), 2.50–2.43 (m, 1 H), 2.22 (ddd, 1 H, J = 14.4, 10.3, 5.5 Hz), 2.05 (ddd, 1 H, J = 14.5, 10.4, 6.6 Hz), 1.87 (s, 3 H), 1.58 (s, 3 H); ^{13}C NMR (100 MHz) δ 171.94 (s), 171.18 (s), 140.45 (s), 139.56 (s), 128.86 (d), 128.49 (d), 128.38 (d), 128.30 (d), 126.68 (d), 126.20 (d), 65.94 (s), 65.25 (s), 52.89 (q), 38.53 (t), 36.43 (t), 30.15 (t), 29.97 (t), 24.02 (q), 19.69 (q); MS (+EI, 15 eV), m/z (relative intensity) 444 (M$^+$, 1), 342 (7), 341 (18), 340 (100), 190 (22), 148 (9); exact mass calcd for $C_{23}H_{28}N_2O_5S$ 444.1719, found 444.1720. Anal. Calcd for $C_{23}H_{28}N_2O_5S$: C, 62.1; H, 6.3. Found: C, 62.5; H, 6.0.

2-[2-[2-(Methoxycarbonyl)-4-phenylpentyl]]-4-(2-phenylpropyl)-4-methyl-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (15b-Ia) [(2′*RS*,2″*SR*,4*RS*,4′*SR*)-15b]. Cyclization of racemic **14b**-Ia (505 mg, 1.0 mmol) yielded racemic **15b**-Ia as a colorless, viscous oil (474 mg, 100%): IR ν_{max} ($CHCl_3$) 3253, 2961, 1745, 1730, 1452, 1337, 1277, 1177, 1135, 702 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.40–7.35 (m, 2 H), 7.30–7.20 (m, 7 H), 7.17–7.13 (m, 1 H), 4.53 (s, 1 H), 3.37 (s, 3 H), 2.97–2.85 (m, 2 H), 2.74 (dd, 1 H, J = 14.2, 8.8 Hz), 2.65 (dd, 1 H, J = 14.2, 3.2 Hz), 2.28 (dd, 1 H, J = 14.9, 3.4 Hz), 2.07 (dd, 1 H, J = 14.9, 10.3 Hz), 1.70 (s, 3 H), 1.36 (s, 3 H), 1.28 (d, 3 H, J = 6.8 Hz), 1.23 (d, 3 H, J = 7.1 Hz); ^{13}C NMR (100 MHz) δ 172.23 (s), 170.65 (s), 146.68 (s), 145.05 (s), 129.51 (d), 128.35 (d), 127.40 (d), 127.22 (d), 126.98 (d), 126.14 (d), 66.27 (s), 65.28 (s), 52.37 (q), 42.95 (t), 40.53 (t), 36.29 (d), 35.29 (d), 26.32 (q), 24.99 (q), 24.64 (q), 20.71 (q); MS (+EI, 15 eV), m/z (relative intensity) 385 (M − CO_2CH_3, 1), 355 (20), 354 (100), 231 (19), 204 (17), 172 (17), 163 (10), 162 (87), 145 (17); exact mass calcd for $C_{25}H_{32}N_2O_5S$ 472.2032, found 472.2034.

15b-Ib [(2′*RS*,2″*RS*,4*SR*,4′*SR*)-15b]. Cyclization of *meso*-**14b**-Ib (505 mg, 1.0 mmol) yielded racemic **15b**-Ib as a colorless, viscous oil (472 mg, 100%) which crystallized on standing. Recrystallization from ether/petroleum ether gave colorless cubes: mp 119.7–121.2 °C; IR ν_{max} (KBr) 3268, 2968, 1730, 1722, 1454, 1375, 1337, 1295, 1278, 1238, 1201, 1180, 1123, 696, 620 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.45–7.40 (m, 2 H), 7.35–7.25 (m, 7 H), 7.21–7.17 (m, 1 H), 4.52 (s, 1 H), 3.38 (s, 3 H), 3.02–2.94 (m, 1 H),

2.80–2.71 (m, 1 H), 2.79 (dd, 1 H, J = 14.2, 9.5 Hz), 2.59 (dd, 1 H, J = 14.2, 2.6 Hz), 2.28 (dd, 1 H, J = 15.1, 3.3 Hz), 2.12 (dd, 1 H, J = 15.1, 10.1 Hz), 1.56 (s, 3 H), 1.45 (s, 3 H), 1.33 (d, 3 H, J = 7.3 Hz), 1.26 (d, 3 H, J = 6.8 Hz); ^{13}C NMR (100 MHz) δ 172.63 (s), 170.75 (s), 146.68 (s), 144.43 (s), 129.82 (d), 128.48 (d), 127.81 (d), 127.28 (d), 126.89 (d), 126.29 (d), 66.56 (s), 65.54 (s), 52.32 (q), 42.89 (t), 41.58 (t), 36.73 (d), 35.62 (d), 26.60 (q), 25.80 (q), 24.90 (q), 19.36 (q); MS (+EI, 15 eV), m/z (relative intensity) 385 (M – CO_2CH_3, 1), 356 (7), 355 (18), 354 (100), 231 (13), 204 (18), 172 (5), 163 (5), 162 (39), 145 (9); exact mass calcd for $C_{25}H_{32}N_2O_5S$ 472.2032, found 472.2034. Anal. Calcd for $C_{25}H_{32}N_2O_5S$: C, 63.5; H, 6.8. Found: C, 63.7; H, 6.7.

15b-IIa [(2′*RS*,2″*RS*,4*RS*,4′*RS*)-15b]. Cyclization of racemic **14b**-IIa (505 mg, 1.0 mmol) yielded racemic **15b**-IIa as a colorless, viscous oil (474 mg, 100%): IR ν_{max} ($CHCl_3$) 3255, 2960, 1745, 1736, 1730, 1452, 1336, 1296, 1186, 1136, 701 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.30–7.26 (m, 2 H), 7.24–7.16 (m, 7 H), 7.12–7.08 (m, 1 H), 3.74 (s, 1 H), 3.70 (s, 3 H), 3.03 (dd, 1 H, J = 14.3, 9.3 Hz), 2.98–2.85 (m, 2 H), 2.24 (dd, 1 H, J = 14.6, 9.6 Hz), 2.20 (dd, 1 H, J = 14.3, 2.1 Hz), 1.94 (dd, 1 H, J = 14.6, 4.4 Hz), 1.74 (s, 3 H), 1.22 (d, 3 H, J = 6.8 Hz), 1.21 (d, 3 H, J = 6.8 Hz), 0.79 (s, 3 H); ^{13}C NMR (100 MHz) δ 171.91 (s), 171.81 (s), 147.06 (s), 145.45 (s), 128.67 (d), 128.35 (d), 127.34 (d), 127.16 (d), 126.58 (d), 126.06 (d), 65.34 (s), 64.23 (s), 52.76 (q), 43.24 (t), 40.86 (t), 35.36 (d), 35.11 (d), 26.82 (q), 24.43 (q), 21.47 (q), 19.73 (q); MS (+EI, 12 eV), m/z (relative intensity) 356 (6), 355 (21), 354 (M – C_9H_{10}, 100), 204 (10), 162 (21); exact mass calcd for $C_{25}H_{32}N_2O_5S$ 472.2032, found 472.2034.

15b-IIb [(2′*RS*,2″*SR*,4*SR*,4′*RS*)-15b]. Cyclization of *meso*-**14b**-IIb (505 mg, 1.0 mmol) yielded racemic **15b**-IIb as a white solid (470 mg, 99%). Recrystallization from ether/petroleum ether gave colorless prisms (388 mg, 82%): mp 130.6–131.8 °C; IR ν_{max} (KBr) 3304, 2955, 1740, 1724, 1372, 1337, 1284, 1260, 1198, 1136, 770, 706 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.39–7.34 (m, 2 H), 7.31–7.25 (m, 3 H), 7.22–7.17 (m, 3 H), 7.12–7.09 (m, 2 H) 3.68 (s, 3 H), 3.45 (s, 1 H), 3.06 (dd, 1 H, J = 14.7, 9.8 Hz), 2.97–2.90 (m, 1 H), 2.88–2.79 (m, 1 H), 2.13 (dd, 1 H, J = 14.7, 1.7 Hz), 1.80 (s, 3 H), 1.79 (dd, 1 H, J = 14.9, 3.4 Hz), 1.37 (s, 3 H), 1.21 (d, 3 H, J = 7.1 Hz), 1.20 (d, 3 H, J = 7.1 Hz), 0.91 (dd, 1 H, J = 14.9, 10.7 Hz); ^{13}C NMR (100 MHz) δ 172.57 (s), 171.96 (s), 147.13 (s), 144.97 (s), 129.18 (d), 128.39 (d), 127.50 (d), 127.24 (d), 126.83 (d), 126.13 (d), 65.05 (s), 64.10 (s), 52.70 (q), 43.07 (t), 40.79 (t), 35.11 (d), 35.00 (d), 27.19 (q), 24.25 (q), 21.63 (q), 19.41 (q); MS (+EI, 12 eV), m/z (relative intensity) 385 (M – CO_2CH_3, 1), 356 (7), 355 (18), 354 (M – C_9H_{10}, 100), 231 (7), 205 (5), 204 (24), 163 (5), 162 (40), 145 (7); exact mass calcd for $C_{25}H_{32}N_2O_5S$ 472.2032, found 472.2034. Anal. Calcd for $C_{25}H_{32}N_2O_5S$: C, 63.5; H, 6.8. Found: C, 63.6; H, 6.7.

15b-Ia [(2′*R*,2″*S*,4*R*,4′*S*)-15b]. Cyclization of the enantiomer **14b**-Ia [(2*R*,2′*R*,4*S*,4′*S*)-**14b**] (505 mg, 1.0 mmol) gave **15b**-Ia [(2′*R*,2″*S*,4*R*,4′*S*)-**15b**] as a colorless, viscous gum (473 mg, 100%): $[\alpha]^{25}_D$ +83.2° (*c*, 1.9 benzene); exact mass calcd for $C_{25}H_{32}N_2O_5S$ 472.2032, found 472.2034. The NMR spectra were identical with those of racemic **15b**-Ia prepared above.

15b-IIa [(2′*S*,2″*S*,4*S*,4′*S*)-15b]. Cyclization of the enantiomer **14b**-IIa [(2*S*,2′*S*,4*S*,4′*S*)-**14b**] (505 mg, 1.0 mmol) gave **15b**-IIa [(2′*S*,2″*S*,4*S*,4′*S*)-**15b**] as a colorless, viscous gum (472 mg, 100%): $[\alpha]^{25}_D$ –40.1° (*c*, 1.2 benzene); exact mass calcd for $C_{25}H_{32}N_2O_5S$ 472.2032, found 472.2034. The NMR spectra were identical with those of racemic **15b**-IIa prepared above.

2-[2-[2-(Methoxycarbonyl)-4-methyl-4-phenylpentyl]]-4-methyl-4-(2-methyl-2-phenylpropyl)-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (15c-I). Cyclization of **14c**-I (533 mg, 1.0 mmol) gave **15c**-I as a colorless, viscous gum (502 mg, 100%). Crystallization from ether/petroleum ether gave colorless cubes (434 mg, 87%): mp 122.0–124.0 °C; IR ν_{max} (KBr) 3255, 2971, 1744, 1729, 1333, 1272, 1174, 766, 702 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.47–7.42 (m, 4 H), 7.39–7.29 (m, 5 H), 7.20–7.15 (m, 1 H), 4.52 (s, 1 H), 3.42 (s, 3 H), 2.89 (d, 1 H, J = 14.0 Hz), 2.79 (d, 1 H, J = 14.0 Hz), 2.34 (d, 1 H, J = 15.3 Hz), 2.30 (d, 1 H, J = 15.3 Hz), 1.43 (s, 3 H), 1.38 (s, 3 H), 1.35 (s, 3 H), 1.30 (s, 3 H), 1.28 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR (100 MHz) δ 172.79 (s), 170.44 (s), 147.00 (s), 146.04 (s), 129.51 (d), 127.98 (d), 127.43 (d), 126.24 (d), 125.92 (d), 125.78 (d), 67.38 (s), 63.79 (s), 52.12 (q), 47.39 (t), 46.28 (t), 37.32 (s), 37.02 (s), 34.38 (q), 31.36 (q), 29.80 (q), 27.52 (q), 24.79 (q), 20.02 (q); MS (+EI, 12 eV), m/z (relative intensity) 382 (M – C_9H_{10}, 1), 270 (2), 219 (18), 218 (100), 159 (11), 119 (35), 118 (8); exact mass calcd for $C_{27}H_{36}N_2O_5S$ 500.2345, found 500.2345. Anal. Calcd for $C_{27}H_{36}N_2O_5S$: C, 64.8; H, 7.2. Found: C, 64.7; H, 7.2.

15c-II. Cyclization of **14c**-II (533 mg, 1.0 mmol) gave **15c**-II as a white foam (500 mg, 100%): IR ν_{max} ($CHCl_3$) 3257, 2967, 1744, 1730, 1337, 1279, 1176, 1123, 701 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.42–7.34 (m, 6 H), 7.32–7.26 (m, 3 H), 7.19–7.14 (m, 1 H), 4.45 (s, 1 H), 3.41 (s, 3 H), 2.88 (s, 2 H), 2.41 (d, 1 H, J = 15.1 Hz), 2.26 (d, 1 H, J = 15.1 Hz), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 6 H), 1.27 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (100 MHz) δ 172.39 (s), 170.86 (s), 147.17 (s), 146.43 (s), 129.32 (d), 128.01 (d), 127.19 (d), 126.23 (d), 125.88 (d), 125.72 (d), 67.29 (s), 64.05 (s), 52.25 (q), 47.12 (t), 45.05 (t), 37.40 (s), 37.17 (s), 34.44 (q), 31.46 (q), 29.99 (q), 26.53 (q), 25.41 (q), 21.73 (q); MS (+EI, 15 eV), m/z (relative intensity) 382 (M – C_9H_{10}, 2), 219 (15), 218 (81), 159 (12), 133 (9), 120 (10), 119 (100), 118 (21), 57 (10), 56 (9); exact mass calcd for $C_{27}H_{36}N_2O_5S$ 500.2345, found 500.2345.

Supplementary Material Available: Experimental details of crystallography, X-ray analysis, and tables of crystallographic data for **14b**-Ia and experimental details for the synthesis of compounds **2d**, *dl*-**3a**, **4a**, **5a**,**b**, **6c**, **7a**–**c**, **8a**,**b**, **9c**, and **17a** (12 pages). Ordering information is given on any current masthead page.