Chiral Azole Derivatives. 4.[1] Enantiomers of Bifonazole and Related Antifungal Agents: Synthesis, Configuration Assignment, and Biological Evaluation

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Azole compounds (such as ketoconazole and bifonazole) have become well-established drugs for the therapy of superficial mycoses.[2] Bifonazole (Mycospor), in particular, is a broad-spectrum antifungal agent, mainly used by topical application in the treatment of fungal skin infections, including nail infections, and also shows antibacterial activity in vitro against some Gram-positive cocci.[3] In the wake of the new regulatory policies,[4] many efforts are currently directed toward the development of enantiomerically pure drugs.[5] However, there is limited information in the literature on the preparation of enantiomers of azole compounds, either by stereoselective synthesis[6] or enantiomeric separation.[7] In particular, only a few examples of enantiopure azole derivatives having the azole moiety directly linked to the stereogenic center have as yet been reported, most likely because of difficulties in their preparation.[8] During the course of our studies on antifungal agents,[9] we became interested in developing methodologies for the preparation of these compounds in homochiral form for subsequent biological evaluation following the new regulatory guidelines. We

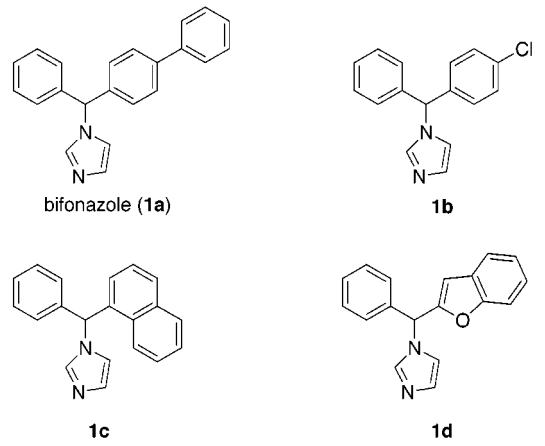

Figure 1.

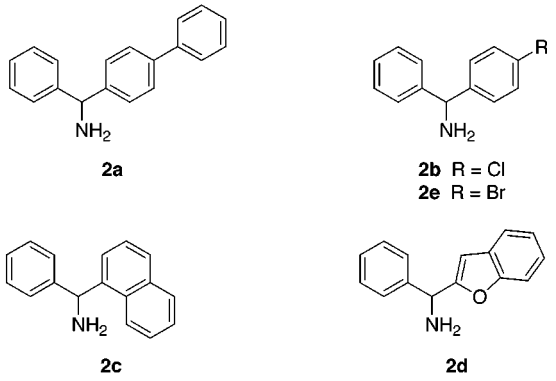

Figure 2.

describe herein the first synthesis, the full stereochemical characterization, and the biological evaluation of both enantiomers of bifonazole (**1a**) and related compounds **1b**−**d** (Figure 1), which have been previously synthesized and tested for their antifungal and/or aromatase inhibiting activity in racemic form.[10−12]

Enantiomerically pure or enriched amines **2a**−**e** (Figure 2) were used as starting material for the synthesis of the target compounds. (*R*)- and (*S*)-**2d** were prepared from (*S*)- and (*R*)-1-phenyl-2-propynylamine (**3**),[13] respectively, by heteroannulation with 2-iodophenol (Scheme 1) following a procedure recently described by us for the preparation of the corresponding alcohols.[14] It is important to point out that, unlike propargyl alcohols, the corresponding propargylamines have not found as yet very extensive application in palladium-mediated het-

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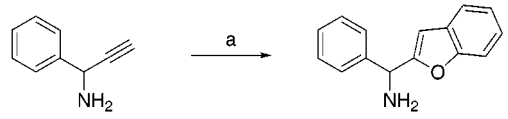
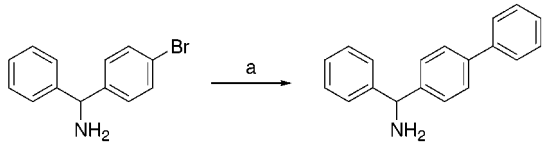
Scheme 1[a]



(*R*)-**3** (98% ee) (*S*)-**2d** (94% ee)
(*S*)-**3** (97% ee) (*R*)-**2d** (93% ee)

[a] Reaction conditions: (a) 2-iodophenol, $PdCl_2(PPh_3)_2$, CuI, TMG, DMF.

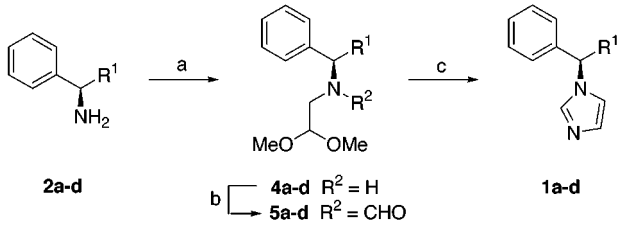
Scheme 2[a]



(*R*)-**2e** (*R*)-**2a**
(*S*)-**2e** (*S*)-**2a**
(>98% ee) (>98% ee)

[a] Reaction conditions: (a) phenylboronic acid, $Pd(OAc)_2$, PPh_3, Na_2CO_3, PrOH, H_2O.

Scheme 3[a]



[a] Reaction conditions: (a) $BrCH_2$ $CH(OMe)_2$, K_2CO_3, DMF; (b) BuOCHO, reflux; (c) $AcONH_4$, AcOH. For simplicity, only the (*S*)-enantiomers are shown. R^1: **a**, 4-biphenylyl; **b**, 4-cholorophenyl; **c**, 1-naphthalenyl; **d**, 2-benzofuranyl (see Table 1).

eroannulation reactions, and to the best of our knowledge, the reaction here reported is the first example involving a chiral nonracemic α-arylpropargylamine. (*R*)-**2d** and (*S*)-**2d** were obtained with only a slight decrease in enantiomeric purity (93% and 94% ee, respectively, as determined by enantioselective HPLC) with respect to the starting amine **3**. Both enantiomers of homochiral amines **2b** (>98% ee), **2c** (80% ee), and **2e** (>98% ee) were prepared according to the literature.[15] The knowledge of the absolute configurations[15b] of (*S*)-(+)-**2c** and (*R*)-(−)-**2c** allowed us to infer the absolute configuration of **2b** and **2e**, by means of the comparison of their circular dichroism (CD) curves (see the Supporting Information). Finally, (*R*)- and (*S*)-**2a** were obtained in high enantiomeric purity (>98% ee) from (*R*)- and (*S*)-**2e** via Suzuki coupling with phenylboronic acid (Scheme 2) and proved to be identical with the compounds obtained through the tedious resolution of the racemic base by means of L-(+)-tartaric acid.[16] Elaboration of **2a**−**d** was carried out through a reaction sequence (Scheme 3) involving N-alkylation with bromoacetaldehyde dimethyl acetal to give **4a**−**d**, followed by N-formylation of **4a**−**d** with butyl formate to afford intermediates **5a**−**d** as a mixture of rotamers in the ratio 2:1. Finally, ring closure by heating in the presence of ammonium acetate/acetic acid provided the final compounds **1a**−**d** in good chemical yield and with high stereoselectivity (Table 1).

Table 1. Preparation of Compounds 4, 5, and 1 (see Scheme 3)

compd	R^1	yield[a] (%)	mp (°C)	ee[b] (%)	$[\alpha]^{23}_D$[c] (*c*)
(*R*)-**4a**	4-biphenylyl	83	yellow oil	ND[d]	+7.9 (1.90)
(*R*)-**4b**	4-chlorophenyl	70	yellow oil	ND	+9.3 (6.92)
(*R*)-**4c**	1-naphthalenyl	83	yellow oil	ND	−25.5 (4.17)
(*R*)-**4d**	2-benzofuranyl	69	yellow oil	ND	−20.1 (1.00)
(*S*)-**4a**	4-biphenylyl	78	yellow oil	ND	−7.6 (1.90)
(*S*)-**4b**	4-chlorophenyl	70	yellow oil	ND	−8.9 (6.90)
(*S*)-**4c**	1-naphthalenyl	89	yellow oil	ND	+26.1 (4.22)
(*S*)-**4d**	2-benzofuranyl	72	yellow oil	ND	+21.3 (1.10)
(*R*)-**5a**	4-biphenylyl	94	yellowish oil	ND	−9.9 (2.01)
(*R*)-**5b**	4-chlorophenyl	94	yellowish oil	ND	+11.0 (2.73)
(*R*)-**5c**	1-naphthalenyl	87	yellowish oil	ND	−32.8 (3.20)
(*R*)-**5d**	2-benzofuranyl	88	yellowish oil	ND	+29.0 (0.88)
(*S*)-**5a**	4-biphenylyl	92	colorless oil	ND	+14.9 (2.02)
(*S*)-**5b**	4-chlorophenyl	79	colorless oil	ND	−10.3 (2.73)
(*S*)-**5c**	1-naphthalenyl	70	colorless oil	ND	+40.2 (3.23)
(*S*)-**5d**	2-benzofuranyl	86	yellowish oil	ND	−27.4 (0.63)
(*R*)-**1a**	4-biphenylyl	68	147−149[e]	>97	−2.8 (1.00)
(*R*)-**1b**	4-chlorophenyl	65	127−130[f]	>98	+8.2 (1.39)
(*R*)-**1c**	1-naphthalenyl	73	81−82[g]	78	+17.0 (1.77)
(*R*)-**1d**	2-benzofuranyl	64	203−205 dec[h]	90	+22.0 (0.60)
(*S*)-**1a**	4-biphenylyl	65	148−150[e]	>97	+3.2 (1.00)
(*S*)-**1b**	4-chlorophenyl	71	126−129[f]	>98	−7.9 (1.13)
(*S*)-**1c**	1-naphthalenyl	71	80−83[g]	78	−17.0 (1.76)
(*S*)-**1d**	2-benzofuranyl	60	201−203 dec[h]	92	−24.1 (0.66)

[a] Yields refer to isolated and purified materials. [b] Determined by enantioselective HPLC (see the Experimental Section). [c] Measured in $CHCl_3$ solution. [d] ND = not determined. [e] Lit.[20] mp 142 °C. [f] As nitrate salt (lit.[10] mp 129−131 °C). [g] Lit.[11] mp 82−83 °C. [h] As hydrochloride salt (lit.[12c] mp 205−207 °C dec).

The enantiomeric excess was determined by enantioselective HPLC on chiral columns Chiralpak AD (**1a**, **1c**, **1d**) and Chiralcel OD (**1b**) using multiple detections: UV/CD and polarimetric (see the Experimental Section for details). An example for compound **1a** is reported in Figure 3.

The enantiomers of compounds **1a**−**d** were tested against *Candida albicans* strains in comparison with the corresponding racemates as well as to fluconazole and amphotericin B as reference standards using the microbroth dilution method.[17] In particular, one laboratory strain of *C. albicans* and two clinical isolates, one of which (L3107 strain) fluconazole-resistant, were used. The results, expressed as minimal inhibitory concentration (MIC, μM), are reported in Table 2. All the tested compounds showed essentially the same antimycotic profile and, quite unexpectedly, in no case was a differential activity between the two enantiomers of each compound observed.[18] This lack of stereoselectivity is not due to racemization of the compounds in the test medium,[19] nor necessarily reflects the insensitivity of the putative fungal target (cytochrome P-450-dependent

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(17) **Biological Assay**. The antimycotic activity against *C. albicans* was evaluated by means of the minimal inhibitory concentration (MIC) using the serial dilution test in a liquid nutrient medium. MIC is defined as the lowest concentration (μg/mL) of tested substance at which there is no macroscopic colonial growth in comparison with a blank experiment after the preset incubation time. Samples were dissolved in a mixture of DMSO/water (1/9, v/v). The medium used was RPMI 1640 broth at pH 7. Inoculum was 10^{-4} CFU/mL from deep frozen yeast stock suspension. Visual reading was performed after 20−24 h of incubation at 35 °C, in humid air.

(18) Analogues of **1d** have proven to inhibit aromatase in enantioselective way (see ref 1).

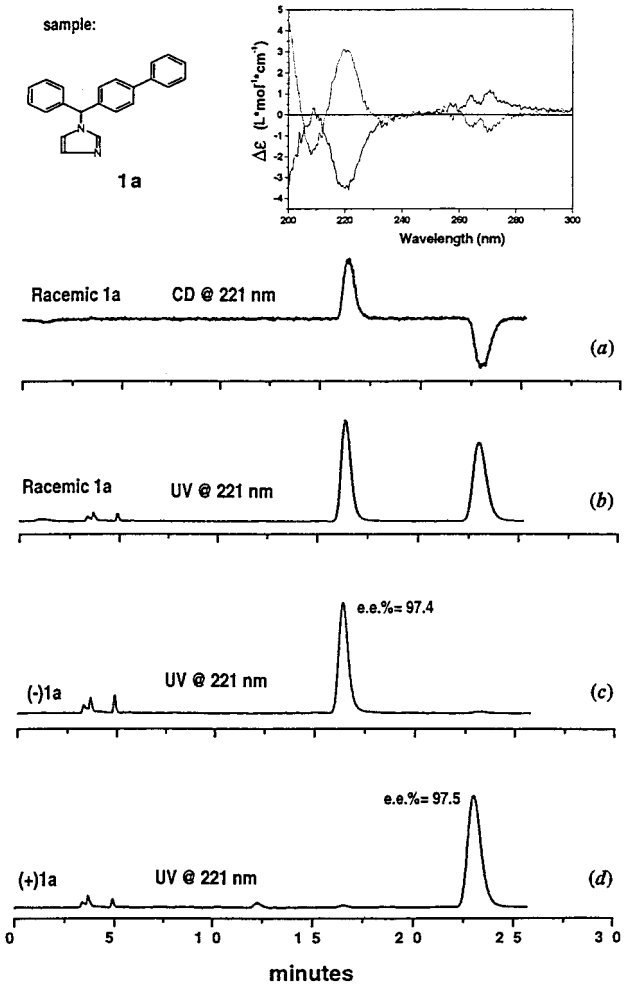

Figure 3. HPLC resolution of the enantiomers of **1a** at 25 °C: column, Chiralpak-AD (250 × 4.6 mm); eluent, *n*-hexane/*i*-PrOH (90/10, v/v); flow rate, 1.0 mL/min. Top: CD spectra of the two enantiomers of **1a** in MeOH. Traces **a** and **b**: CD and UV detection, respectively, of racemic **1a**. Traces **c** and **d**: UV detection of (−)-**1a** (97.4% ee) and (+)-**1a** (97.5% ee), respectively.

Table 2. In Vitro Antimycotic Activity of Compounds 1a−d against *C. albicans* Strains[17]

	MIC (μg/mL)		
compd	*C. albicans* ATCC90028 L3023	*C. albicans* clinical isolate L145	*C. albicans* clinical isolate L3107[a]
(*R*)-**1a**	1	1	>64
(*S*)-**1a**	1	1	>64
(*R,S*)-**1a** (bifonazole)	1	1	>64
(*R*)-**1b**	1	1	32
(*S*)-**1b**	1	2	32
(*R,S*)-**1b**	2	1	64
(*R*)-**1c**	2	2	32
(*S*)-**1c**	1	2	32
(*R,S*)-**1c**	2	1	8
(*R*)-**1d**	2	2	16
(*S*)-**1d**	2	2	16
(*R,S*)-**1d**	1	2	32
fluconazole	0.5	0.5	>64
amphotericin B	0.5	0.5	1

[a] Fluconazole-resistant strain.

lanosterol 14α-demethylase) to the stereochemistry of the inhibitors, but might be the consequence of other phenomena occurring somewhere in the mechanism of action, from uptake by the cells to inhibition of the fungal target enzyme.

Table 3. Thermodynamic Parameters and Elution Order for the Separation of Compounds 1a−d by Enantioselective HPLC

compd	k'_1[a]	α[b]	Pol.[c]	CD[d]
1a	3.96	(−) 1.52	−	(+)
1b	3.21	(−) 1.14	−	(+)
1c	2.10	(+) 1.70	+	(−)
1d	3.55	(+) 1.18	+	(−)

[a] Capacity factor of the first eluted enantiomer. [b] Enantioselectivity factor. [c] Sign of polarimetric detector. [d] Sign of CD detector.

Experimental Section

General Methods. Unless otherwise stated, all reactions were carried out under an argon atmosphere. Reagents were obtained from commercial suppliers and used without further purification. Merck silica gel 60 was used for both column chromatography (70−230 mesh) and flash chromatography (230−400 mesh). Melting points are uncorrected. ^{1}H NMR spectra were measured at 200 MHz. Chemical shifts are reported relative to $CDCl_3$ at δ 7.24 ppm and tetramethylsilane at δ 0.00 ppm. EI low-resolution mass spectra were recorded with an electron beam of 70 eV. Elemental analyses (C, H, N) were performed in house.

(*R*)-(+)-α-(4-Biphenylyl)benzylamine [(*R*)-2a]. Phenylboronic acid (659 mg, 5.4 mmol) was added in one portion to a solution of (*R*)-**2e** (1.35 g, 5.1 mmol) in PrOH (10 mL). The resulting solution was stirred for 30 min at room temperature. Next, $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), Ph_3P (12.3 mg, 0.047 mmol), and 2 N aqueous Na_2CO_3 (3.1 mL, 6.2 mmol) were added successively, and the yellow reaction mixture was refluxed for 6 h. After cooling, the mixture was diluted with water (10 mL) and extracted with EtOAc. The combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by flash chromatography (EtOAc as eluent) to give 1.21 g (91%) of (*R*)-**2a** as white crystals: mp 74−76 °C (from cyclohexane) (lit.[16] mp 78 °C (from diethyl ether)); $[\alpha]^{22}_D$ +13.6 (*c* 2.58, $CHCl_3$). Anal. Calcd for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.41. Found: C, 88.22; H, 6.57; N, 5.20.

(*S*)-(−)-α-(4-Biphenylyl)benzylamine [(*S*)-2a]. Prepared in 90% yield from (*S*)-**2e** following the same procedure described above: $[\alpha]^{22}_D$ −12.8 (*c* 2.50, $CHCl_3$). Physical and chemical data were identical with those described above for the opposite enantiomer.

(*R*)-(−)-α-(2-Benzofuranyl)benzylamine [(*R*)-2d]. To the orange solution obtained by mixing 2-iodophenol (220 mg, 1.0 mmol) and TMG (345 mg, 3.0 mmol) were added successively $PdCl_2(PPh_3)_2$ (35.1 mg, 0.05 mmol), CuI (19.0 mg, 0.1 mmol), and dry DMF (1.0 mL). After 5 min, a solution of (*S*)-**3** (131 mg, 1.0 mmol) in dry DMF (2 mL) was added, and the reaction mixture was stirred at 40 °C for 16 h. After cooling, the reaction was diluted with EtOAc and washed with water (6 × 3 mL). Washings were reextracted with EtOAc, and the combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by flash chromatography (EtOAc/hexanes, 3:1 as eluent) to provide (*R*)-**2d** (156 mg, 70%) as a yellow oil. An analytical sample was prepared by TLC: $[\alpha]^{23}_D$ −10.1 (*c* 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.47−7.15 (m, 9H), 6.48 (s, 1H), 5.39 (br s, 1H), 1.68 (br s, 2H, exchangeable with D_2O). Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.28. Found: C, 80.44; H, 5.96; N, 6.10.

(*S*)-(+)-α-(2-Benzofuranyl)benzylamine [(*S*)-2d]. Prepared in 75% yield from (*R*)-**3** following the same procedure described

(19) Samples dissolved in DMSO/water (1/9, v/v) at pH 7 (phosphate buffer), and stored at 35 °C for 24 h did not show any decrease of the ee value.

(20) *The Merck Index*, 12th ed.; Merck & Co., Inc.,: Whitehouse Station, NJ, 1996; p 1257.

above: $[\alpha]^{23}_D$ +12.0 (*c* 1.22, $CHCl_3$). Physical and chemical data were identical with those described above for the opposite enantiomer.

General Procedure for the Preparation of 4a−d. Bromoacetaldehyde dimethyl acetal (1.5 mmol) and anhydrous K_2CO_3 (1.5 mmol) were added to a solution of the appropriate amine **2** (1 mmol) in dry DMF (2 mL). After being stirred overnight at 120 °C, the reaction mixture was cooled to room temperature, diluted with water, and extracted with EtOAc. The combined extracts were washed with water (4 × 5 mL) and brine and then dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by flash chromatography (Et_2O/hexanes, 1:1 as eluent) to give **4** (Table 1). As an example, the spectroscopic and analytical data of (*R*)-**4a** are reported below. For data referring to the other compounds **4**, see the Supporting Information.

(*R*)-(+)-α-(4-Biphenylyl)-*N*-(2,2-dimethoxyethyl)benzylamine [(*R*)-4a]: ^{1}H NMR ($CDCl_3$) δ 7.61−7.24 (m, 14H), 4.90 (s, 1H), 4.58 (t, J = 5.6 Hz, 1H), 3.38 (s, 6H), 2.78 (d, J = 5.6 Hz, 2H), 1.86 (s, 1H, exchangeable with D_2O); EIMS *m*/*z* 348 $(M + H)^+$. Anal. Calcd for $C_{23}H_{25}NO_2$: C, 79.50; H, 7.25; N, 4.04. Found: C, 79.26; H, 7.20; N, 3.94.

General Procedure for the Preparation of 5a−d. A solution of the appropriate compound **4** (1 mmol) in butyl formate (20 mL) was refluxed overnight and then evaporated in vacuo. The resulting oily residue was purified by flash chromatography (Et_2O/hexanes, 3:1 as eluent) to provide **5** (Table 1) as a mixture of rotamers in the ratio 2:1 (1.5:1 for **5d**). As an example, the spectroscopic and analytical data of (*R*)-**5a** are reported below. For data referring to the other compounds **5**, see the Supporting Information.

(*R*)-(−)-*N*-[α-(4-Biphenylyl)benzyl]-*N*-(2,2-dimethoxyethyl)formamide [(*R*)-5a]: ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 0.3H), 8.12 (s, 0.7H), 7.58 (d, J = 7.8 Hz, 4H), 7.46−7.20 (m, 10H), 6.99 (s, 0.3H), 6.04 (s, 0.7H), 4.62 (t, J = 5.2 Hz, 0.7H), 3.52 (d, J = 5.3 Hz, 2 × 0.7H), 3.44 (s, 6 × 0.7H), 3.36 (d, J = 5.2 Hz, 2 × 0.3H), 3.12−3.10 (superimposed signals: s, 6 × 0.3H and t, 0.3H); IR 1665 cm^{-1}; EIMS *m*/*z* 376 $(M + H)^+$. Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.90; H, 6.79; N, 3.61.

General Procedure for the Preparation of 1a−d. A solution of the appropriate compound **5** (1 mmol) and $AcONH_4$ (9 mmol) in glacial acetic acid (20 mL) was refluxed for 3 h and then evaporated in vacuo. A saturated aqueous solution of Na_2CO_3 (5 mL) was added to the residue, and the mixture was extracted with EtOAc (3 × 5 mL). The combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by flash chromatography (EtOAc as eluent) to give **1** (Table 1). As an example, the spectroscopic and analytical data of (*R*)-**1a** are reported below. For data referring to the other compounds **1**, see the Supporting Information.

(*R*)-(−)-1-[α-(4-Biphenylyl)benzyl]-1*H*-imidazole [(*R*)-1a]: ^{1}H NMR ($CDCl_3$) δ 7.55−7.11 (m, 16H), 6.87 (s, 1H), 6.54 (s, 1H); EIMS *m*/*z* 311 $(M + H)^+$. Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.12; H, 5.84; N, 9.03. Found: C, 85.27; H, 5.79; N, 8.94.

Assay of Enantiomeric Purity. Enantiomers of compounds **1a−d** were separated by enantioselective HPLC employing the following conditions. Mobile phase: *n*-hexane/*i*-PrOH (90/10, v/v); flow rate, 1.0 mL/min; T = 25 °C. Detectors: UV/CD (**1a**: λ = 221 nm; **1b**, **1c**: λ = 225 nm; **1d**: λ = 245 nm) and ORD in series. Columns: Chiralpak-AD (250 × 4.6 mm) for compounds **1a**, **1c**, and **1d**, Chiralcel-OD (250 × 4.6 mm) for compound **1b**.

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Supporting Information Available: CD curves for compounds (*R*)-(+)-**2b**, (*R*)-(−)-**2c**, (*S*)-(+)-**2c**, (*R*)-(+)-**2e**, and (*S*)-(−)-**2e** as well as spectroscopic and analytical data for compounds **4**, **5**, and **1** (for simplicity, only *R*-enantiomers). This material is available free of charge via the Internet at http://pubs.acs.org.

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