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Regioselective Ring Opening of Amino Epoxides with Nitriles: An Easy Synthesis of (2*R*,3*S*)- and (2*S*,3*S*)-1,3-Diaminoalkan-2-ols with Differently Protected Amine Functions

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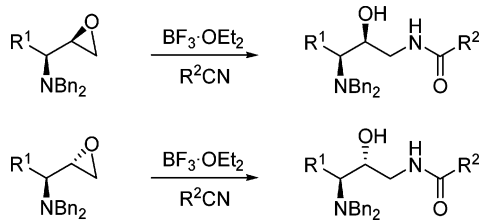

Transformation of enantiopure (2*R*,1′*S*)- or (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides **1** or **2** into the corresponding (2*R*,3*S*)- and (2*S*,3*S*)-1,3-diaminoalkan-2-ols **3** or **4** is described. The opening of the epoxide ring with different nitriles (Ritter reaction) takes place with total selectivity and in high yields in the presence of $BF_3{\cdot}Et_2O$. Interestingly, the two amine groups are differently protected. A mechanism to explain this transformation is proposed.

An important number of peptidomimetic inhibitors of the HIV-1 protease, used for the treatment of AIDS, contains the moiety (2*R*,3*S*)-1,3-diaminoalkan-2-ol,[1] and acylated amines are present in many molecules with pharmacological applications.[2]

In addition, the Ritter reaction of nitriles with different compounds constitutes a simple, convenient, one-step methodology to introduce an acylamino function.[3] In particular, epoxides can be transformed into *N*-acylated 1-amino alcohols.[4] However, to the best of our knowledge, except for the opening of epoxides located in some rings of steroids,[5] few papers have described the use of the Ritter reaction to prepare enantiopure acyclic compounds.[6]

For this reason, a method to prepare efficiently enantiopure (2*R*,3*S*)- or (2*S*,3*S*)-1,3-diaminoalkan-2-ols would be very interesting due to the pharmacological interest of this moiety.

We previously reported an efficient synthesis of enantiopure (2*R*,1′*S*)- or (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides by total stereoselective reduction of the easily available, from natural α-amino acids, α-amino-α′-chloroketones[7] with $LiAlH_4$ or by highly stereoselective addition of in situ generated iodomethyllithium (from diiodomethane and methyllithium) to α-aminoaldehydes, respectively.[8] Very recently, we described the reactions of both amino-epoxides **1** and **2** with different ketones in the presence of $BF_3{\cdot}Et_2O$ to afford the corresponding enantiopure 1,3-dioxolanes.[9] We have also reported the synthesis of enantiopure imidazolines through a Ritter reaction of (2*S*,1′*S*)-2-(1-aminoalkyl)aziridines with nitriles in the presence of $BF_3{\cdot}Et_2O$.[10]

We now report an easy entry to (2*R*,3*S*)- or (2*S*,3*S*)-1,3-diaminoalkan-2-ols **3** or **4** without epimerization by a selective opening of the oxirane ring of (2*R*,1′*S*)- and (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides **1** or **2** with different nitriles in the presence of $BF_3{\cdot}OEt_2$. Interestingly, the two amine groups of the obtained compounds **3** or **4** are differently protected as dibenzylamine and acylamine.

All ring-opening reactions of amino epoxides **1** or **2** with different nitriles were carried out in the presence of $BF_3{\cdot}OEt_2$ to activate the epoxide ring. Initially, the reactions were performed with *syn*-amino epoxides **1**. A solution of compounds **1** in the corresponding nitrile was treated with 1 equiv of $BF_3{\cdot}OEt_2$ and heated at 80 °C for 12 h. Hydrolysis of the reaction mixture led to (2*R*,3*S*)-*N*[1]-acyl-1,3-diaminoalkan-2-ols **3** in good yields (Scheme 1, Table 1).

To extend the scope of this reaction, we performed the reaction of *anti*-amino epoxide **2** with nitriles under the same reaction conditions (Scheme 2, Table 2). In all cases,

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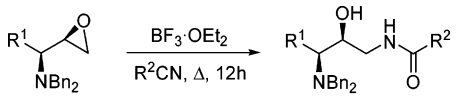
SCHEME 1. Synthesis of (2*R*,3*S*)-1,3-Diaminoalkan-2-ols 3



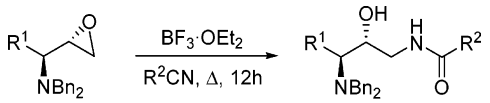
1 3

TABLE 1. Synthesis of (2*R*,3*S*)-1,3-Diaminoalkan-2-ols 3

entry	3	R^1	R^2	yield[a] (%)
1	**3a**	Me	Me	61
2	**3b**	Me	Ph	75
3	**3c**	*i*-Bu	Me	65
4	**3d**	*i*-Bu	Et	63
5	**3e**	Bn	*i*-Pr	75
6	**3f**	Bn	Ph	79

[a] Isolated yield after column chromatography based on the starting amino epoxide **1**.

SCHEME 2. Synthesis of (2*S*,3*S*)-1,3-Diaminoalkan-2-ols 4



2 4

the corresponding (2*S*,3*S*)-1,3-diaminoalkan-2-ols **4** were obtained in good yields and with high selectivity.

The selectivity of the reaction was determined by ^{1}H NMR spectroscopy (300 MHz) of the crude mixture of products, showing the presence of a single diastereoisomer **3** (from aminoepoxide **1**) and a mixture of diastereoisomers **4** (from **2**) in the same relationship as the starting aminoepoxides **2**. The synthesis of diamino alcohols **4** with the same diastereoisomeric excess (de) as the starting amino epoxides **2**[8] indirectly supported the total selectivity of the ring-opening reaction. After purification of compounds **4** by column chromatography, the major diastereoisomer was isolated as a single stereoisomer. Thus, the epoxides **1** or **2** were opened with total regioselectivity and without epimerization by all nitriles investigated to give the (2*R*,3*S*)- or (2*S*,3*S*)-1,3-diaminoalkan-2-ols **3** or **4** exclusively.

The yields of the obtained (2*R*,3*S*)- or (2*S*,3*S*)-1,3-diaminoalkan-2-ols **3** or **4** via Ritter reaction of amino epoxides **1** or **2** are shown in Tables 1 and 2. Analysis of Tables 1 and 2 indicates that the transformation seems to be general; thus, the reaction can be carried out with different nitriles such as aliphatic (linear or branched) and aromatic. In addition, negligible differences in the reaction outcome were observed independently of the epoxide employed (derived from leucine, alanine, and phenylalanine).

It is noteworthy that the different protection of both amine groups in compounds **3** or **4** can be difficult to achieve in some cases.

The mechanism proposed to explain the transformation of **1** or **2** into **3** or **4** is depicted in Scheme 3. Thus, after activation of the oxirane by coordination of the oxygen to the Lewis acid, a ring opening at C-3 by nucleophilic attack of the nitrile would occur, affording the intermediate **6**, which can be hydrolyzed to give compounds **3**. A similar reaction of nitrile with the oxirane at C-2 could produce, after hydrolysis, isomers **8**; however, C-3 attack would be expected to be favored on steric grounds.

TABLE 2. Synthesis of (2*S*,3*S*)-1,3-Diaminoalkan-2-ols 4

entry	4	R^1	R^2	de[a] (%)	yield[b] (%)
1	**4a**	Me	Me	>98 (>98)	64
2	**4b**	Me	Ph	>98 (>98)	76
3	**4c**	*i*-Bu	Et	91 (91)	60
4	**4d**	*i*-Bu	*i*-Pr	89 (91)	61
5	**4e**	Bn	*i*-Pr	90 (92)	62
6	**4f**	Bn	Ph	91 (92)	65

[a] Diastereoisomeric excess determined by ^{1}H NMR analysis of the crude products **4**; de of the starting amino epoxide **2** is given in parentheses. [b] Isolated yield after column chromatography based on the starting amino epoxide **2**.

The structure of compounds **3** and **4**, as depicted in Schemes 1 and 2, was established on the basis of IR, high-resolution mass spectra, ^{1}H and ^{13}C spectra, and HMBC NMR experiments of the obtained diamino alcohols **3** and **4**. Thus, the presence of a broad band ranging between 3336 and 3290 cm^{-1} in the IR spectra of compounds **3** and **4** was assignable to their alcohol function. Moreover, HMBC NMR experiments of **3b** and **4b** showed a correlation between the methylene hydrogens of the C*H*$_2$NCOPh and the carbonyl carbon CH$_2$N*C*OPh, and no interaction between the hydrogen of the C*H*OH and the carbonyl carbon CH$_2$N*C*OPh was observed. Thus, the structure **8** (Scheme 3) would not explain this behavior and this structure was ruled out. Hence, all of these data support the assigned structures for compounds **3** and **4**.

Finally, configurational assignments of compounds **3** or **4** were established taking into account that the original asymmetric centers in the starting amino epoxides **1** or **2** have not been involved in any process; consequently, the absolute configuration of **3** or **4** was (2*R*,3*S*)- or (2*S*,3*S*), respectively.

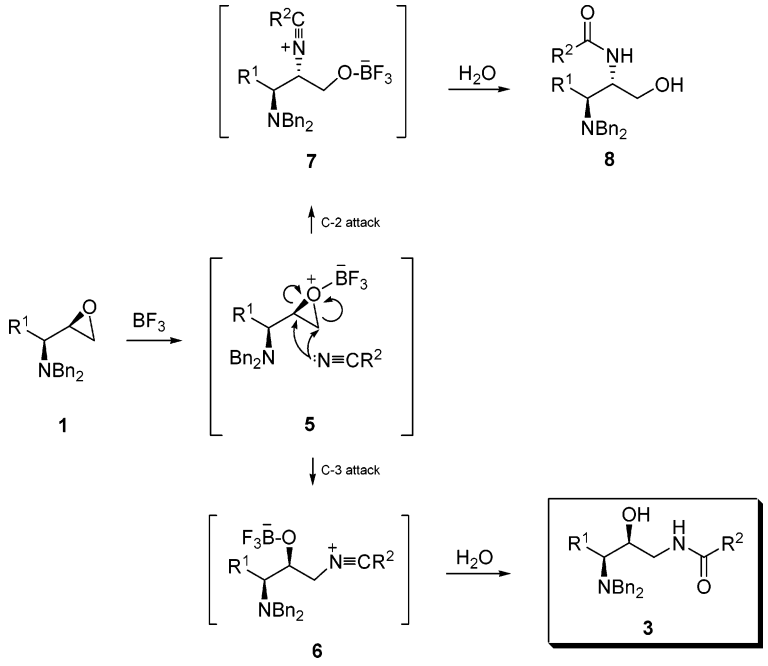
In conclusion, we have described a new and easy synthesis easy of (2*R*,3*S*)- or (2*S*,3*S*)-1,3-diaminoalkan-2-ols, **3** or **4**, without epimerization by the Ritter reaction of (2*R*,1′*S*)- and (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides **1** or **2** with different nitriles in the presence of BF$_3$·OEt$_2$. The opening of the epoxide ring takes place with total regioselectivity, and interestingly, the two amine groups of the obtained compounds **3** or **4** are differently protected as dibenzylamine and acylamine. A mechanism to explain the described transformation has been proposed.

Experimental Section

General Procedure. To a stirred solution of the corresponding amino epoxide **1** or **2** (0.2 mmol) in the corresponding nitrile (1 mL) was added BF$_3$·OEt$_2$ (0.025 mL, 0.2 mmol) at room temperature. After the mixture was stirred at 80 °C for 12 h, an aqueous saturated solution of sodium bicarbonate (5 mL) was added, and the mixture was stirred at room temperature for 5 min. Then, the aqueous phase was extracted with diethyl ether (3 × 5 mL), and the combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated in vacuo. Flash column chromatography on silica gel (hexane/EtOAc 10:1) provided pure compounds **3** and **4**.

(2*S*,3*S*)-*N*-(3-Dibenzylamino-2-hydroxybutyl)acetamide (3a): colorless oil; $[\alpha]^{25}_D$ = +32.2 (*c* 0.87, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.41−7.23 (m, 10 H), 4.57−4.49 (m, 1 H), 3.86 (d, *J* = 13.8 Hz, 2 H), 3.75−3.57 (m, 2 H), 3.51 (d, *J* = 13.6 Hz, 2 H), 2.81 (apparent qt, *J* = 6.8 Hz, 1 H), 1.95 (s, 3 H), 1.14 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 164.9 (C), 140.1 (2 × C), 128.7 (4 × CH), 128.1 (4 × CH), 126.8 (2 ×

SCHEME 3. Proposed Mechanism



CH), 82.8 (CH), 57.2 (CH_2), 54.9 (CH), 54.7 (2 × CH_2), 14.0 (CH_3), 10.6 (CH_3); MS (70 eV, EI) *m/z* 326 (M^+, <1), 323 (21), 255 (18), 225 (74), 224 (100), 181 (27), 105 (10); HRMS (70 eV) calcd for $C_{20}H_{26}N_2O_2$ (M^+) 326.1994, found 326.1973; IR (neat) 3337, 2932, 1724, 1658, 1495, 1451 cm^{-1}; R_f = 0.29 (hexane/EtOAc 1:1). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.71; H, 7.97; N, 8.46.

(2*S*,3*S*)-*N*-(3-Dibenzylamino-2-hydroxybutyl)benzamide (3b): colorless oil; $[\alpha]^{25}_D$ = −24.0 (*c* 2.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 6.4, 1.7 Hz, 2 H), 7.47−7.19 (m, 13 H), 4.75 (apparent q, *J* = 9.1 Hz, 1 H), 3.98 (dd, *J* = 14.5, 9.6 Hz, 1 H), 3.91 (d, *J* = 13.7 Hz, 2 H), 3.79 (dd, *J* = 14.5, 8.5 Hz, 1 H), 3.59 (d, *J* = 13.7 Hz, 2 H), 2.95 (apparent qt, *J* = 6.9 Hz, 1 H), 1.18 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9 (C), 140.0 (3 × C), 131.1 (CH), 128.7 (4 × CH), 128.2 (2 × CH), 128.1 (4 × CH), 128.0 (2 × CH), 126.7 (2 × CH), 82.6 (CH), 57.7 (CH_2), 55.3 (CH), 54.4 (2 × CH_2), 10.8 (CH_3); MS (70 eV, EI) *m/z* 370 ($M^+ - H_2O$, <1), 224 (22), 211 (46), 210 (12), 105 (100); HRMS (70 eV) calcd for $C_{25}H_{26}N_2O$ ($M^+ - H_2O$, <1) 370.2045, found 370.2057; IR (neat) 3290, 2803, 1718, 1650, 1494, 1451 cm^{-1}; R_f = 0.34 (hexane/EtOAc 3:1). Anal. Calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.26; N, 7.21. Found: C, 77.45; H, 7.18; N, 7.31.

(2*S*,3*S*)-*N*-(3-Dibenzylamino-2-hydroxy-5-methylhexyl)acetamide (3c): colorless oil; $[\alpha]^{25}_D$ = +19.1 (*c* 0.86, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.34−7.23 (m, 10 H), 4.70−4.58 (m, 1 H), 3.72 (AB syst., *J* = 13.1 Hz, 4 H), 3.63−3.48 (m, 2 H), 2.66 (apparent q, *J* = 6.6 Hz, 1 H), 1.99 (s, 3 H), 1.88−1.75 (m, 1 H), 1.56−1.48 (m, 1 H), 1.14−0.95 (m, 1 H), 0.88 (d, *J* = 6.7 Hz, 3 H), 0.62 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.8 (C), 140.2 (2 × C), 129.2 (4 × CH), 128.1 (4 × CH), 126.8 (2 × CH), 81.5 (CH), 57.8 (CH), 57.1 (CH_2), 55.0 (2 × CH_2), 36.2 (CH_2), 24.4 (CH), 23.2 (CH_3), 22.2 (CH_3), 14.1 (CH_3); MS (70 eV, EI) *m/z* 353 ($M^+ - CH_3$, <1), 296 (2), 267 (21), 266 (100), 181 (6), 174 (2); HRMS (70 eV) calcd for $C_{22}H_{29}N_2O_2$ ($M^+ - CH_3$) 353.2229, found 353.2267; IR (neat) 3315, 2954, 1741, 1674, 1495, 1454 cm^{-1}; R_f = 0.11 (hexane/EtOAc 3:1). Anal. Calcd for $C_{23}H_{32}N_2O_2$: C, 74.96; H, 8.75; N, 7.60. Found: C, 75.17; H, 8.70; N, 7.51.

(2*S*,3*S*)-*N*-(3-Dibenzylamino-2-hydroxy-5-methylhexyl)propionamide (3d): colorless oil; $[\alpha]^{25}_D$ = +23.6 (*c* 1.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.26 (m, 10 H), 4.70−4.62 (m, 1 H), 3.84−3.57 (m, 6 H), 2.74−2.67 (m, 1 H), 2.37−2.30 (m, 2 H),1.90−1.81 (m, 1 H), 1.57−1.48 (m, 1 H), 1.24 (t, *J* = 7.6 Hz, 3 H), 1.17−1.08 (m, 1 H), 0.92 (d, *J* = 6.7 Hz, 3 H), 0.67 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (C), 140.7 (2 × C), 129.7 (4 × CH), 128.6 (4 × CH), 127.3 (2 × CH), 81.8 (CH), 58.1 (CH_2), 57.7 (CH), 55.5 (2 × CH_2), 36.8 (CH_2), 25.0 (CH), 23.7 (CH_3), 22.8 (CH_3), 22.1 (CH_2), 10.7 (CH_3); MS (70 eV, EI) *m/z* 364 ($M^+ - H_2O$, <1), 267 (16), 266 (100), 181 (4), 174 (3), 132 (3), 119 (3); HRMS (70 eV) calcd for $C_{24}H_{32}N_2O$ ($M^+ - H_2O$) 364.2515, found 364.2495; IR (neat) 3315, 2954, 1737, 1668, 1494, 1454 cm^{-1}; R_f = 0.20 (hexane/EtOAc 3:1). Anal. Calcd for $C_{24}H_{34}N_2O_2$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.57; H, 9.08; N, 7.21.

(2*S*,3*S*)-*N*-(3-(Dibenzylamino-2-hydroxy-4-phenylbutyl)-isobutyramide (3e): colorless oil; $[\alpha]^{25}_D$ = +18.1 (*c* 1.80, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.39−7.18 (m, 15 H), 4.51−4.44 (m, 1 H), 3.98 (d, *J* = 13.5 Hz, 2 H), 3.88−3.76 (m, 1 H), 3.59 (d, *J* = 13.7 Hz, 2 H), 3.52 (dd, *J* = 14.9, 11.5 Hz, 1 H), 3.15 (dd, *J* = 12.0, 4.0 Hz, 1 H), 2.92−2.82 (m, 2 H), 2.57−2.43 (m, 1 H), 1.15 (apparent t, *J* = 7.1 Hz, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.7 (C), 139.6 (2 × C), 139.5 (C), 129.4 (2 × CH), 129.0 (4 × CH), 128.4 (2 × CH), 128.1 (4 × CH), 126.9 (2 × CH), 126.0 (CH), 80.2 (CH), 60.8 (CH), 56.0 (CH_2), 55.5 (2 × CH_2), 32.0 (CH_2), 28.2 (CH), 19.4 (CH_3), 19.3 (CH_3); MS (70 eV, EI) *m/z* 412 ($M^+ - H_2O$, <1), 302 (3), 301 (19), 300 (100), 210 (21), 118 (7); HRMS (70 eV) calcd for $C_{28}H_{32}N_2O$ ($M^+ - H_2O$) 412.2515, found 412.2513; IR (neat) 3327, 2971, 1734, 1653, 1495, 1454 cm^{-1}; R_f = 0.25 (hexane/EtOAc 3:1). Anal. Calcd for $C_{28}H_{34}N_2O_2$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.38; H, 7.84; N, 6.62.

(2*S*,3*S*)-*N*-(3-Dibenzylamino-2-hydroxy-4-phenylbutyl)-benzamide (3f): colorless oil; $[\alpha]^{25}_D$ = +19.9 (c 1.86, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.1, 1.6 Hz, 2 H), 7.44−7.20 (m, 18 H), 4.71 (dt, *J* = 9.3, 3.6 Hz, 1 H), 4.05−3.98 (m, 3 H), 3.81 (dd, *J* = 14.6, 10.1 Hz, 1 H), 3.64 (d, *J* = 13.3 Hz, 2 H), 3.23−3.14 (m, 1 H), 3.02−2.92 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (C), 139.5 (3 × C), 139.4 (C), 131.1 (CH), 129.4 (2 × CH), 129.0 (4 × CH), 128.4 (2 × CH), 128.2 (2 × CH), 128.1 (4 × CH), 127.9 (2 × CH), 126.8 (2 × CH), 126.1 (CH), 80.5 (CH), 61.1 (CH), 57.1 (CH_2), 55.3 (2 × CH_2), 32.3 (CH_2); HRMS (70 eV) calcd for $C_{31}H_{32}N_2O_2$ (M^+) 464.2464, found 464.2457; IR (neat) 3325, 2935, 1730, 1658, 1494, 1453 cm^{-1}; R_f = 0.11 (hexane/EtOAc 3:1). Anal. Calcd for $C_{31}H_{32}N_2O_2$: C, 80.14; H, 6.94; N, 6.03. Found: C, 80.29; H, 6.86; N, 6.15.

(2*R*,3*S*)-*N*-(3-Dibenzylamino-2-hydroxybutyl)acetamide (4a): colorless oil; $[\alpha]^{25}_D$ = +25.1 (*c* 1.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.23 (m, 10 H), 4.57−4.49 (m, 1 H), 3.90−3.38 (m, 6 H), 2.74−2.60 (m, 1 H), 1.91 (s, 3 H), 1.16 (d, *J*

= 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7 (C), 139.6 (C), 139.5 (C), 128.6 (4 × CH), 128.2 (4 × CH), 127.0 (2 × CH), 81.7 (CH), 58.7 (CH_2), 56.9 (CH), 54.3 (2 × CH_2), 13.9 (CH_3), 8.3 (CH_3); MS (70 eV, EI) *m/z* 308 ($M^+ - H_2O$, <1), 225 (21), 224 (100), 181 (11), 132 (5); HRMS (70 eV) calcd for $C_{20}H_{24}N_2O$ ($M^+ - H_2O$) 308.1889, found 308.1894; IR (neat) 3331, 2929, 1739, 1650, 1494, 1453 cm^{-1}; R_f = 0.21 (hexane/EtOAc 3:1). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.71; H, 7.89; N, 8.43.

(2*R*,3*S*)-*N*-(3-Dibenzylamino-2-hydroxybutyl)benzamide (4b): colorless oil; $[\alpha]^{25}_D$ = +19.5 (*c* 2.93, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.93 (d, *J* = 6.2 Hz, 2 H), 7.49−7.28 (m, 13 H), 4.83−4.71 (m, 1 H), 4.14 (dd, *J* = 15.1, 9.8 Hz, 1 H), 3.86 (d, *J* = 13.6 Hz, 2 H), 3.79 (dd, *J* = 15.0, 7.8 Hz, 1 H), 3.58 (d, *J* = 13.9 Hz, 2 H), 2.90−2.77 (m, 1 H), 1.25 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.5 (C), 139.7 (3 × C), 131.2 (CH), 128.4 (4 × CH), 128.3 (2 × CH), 128.2 (4 × CH), 127.9 (2 × CH), 127.0 (2 × CH), 81.6 (CH), 59.2 (CH_2), 57.0 (CH), 54.3 (2 × CH_2), 8.3 (CH_3); MS (70 eV, EI) *m/z* 388 (M^+, 4), 386 (63), 385 (53), 225 (67), 224 (77), 181 (57), 169 (47), 131 (100); HRMS (70 eV) calcd for $C_{25}H_{28}N_2O_2$ (M^+) 388.2151, found 388.2115; IR (neat) 3375, 2932, 1720, 1650, 1494, 1451 cm^{-1}; R_f = 0.45 (hexane/EtOAc 3:1). Anal. Calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.26; N, 7.21. Found: C, 77.42; H, 7.34; N, 7.13.

(2*R*,3*S*)-*N*-(3-Dibenzylamino-2-hydroxy-5-methylhexyl)propionamide (4c): colorless oil; $[\alpha]^{25}_D$ = +21.5 (*c* 1.93, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39−7.24 (m, 10 H), 4.92−4.81 (m, 1 H), 3.99−3.82 (m, 4 H), 3.52 (d, *J* = 13.9 Hz, 2 H), 3.37 (dd, *J* = 14.2, 7.8 Hz, 1 H), 2.62−2.54 (m, 1 H), 2.29 (q, *J* = 7.4 Hz, 2 H), 2.01−1.87 (m, 1 H), 1.69−1.55 (m, 1 H), 1.18 (t, *J* = 7.6 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H), 0.59 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.3 (C), 139.9 (2 × C), 128.9 (4 × CH), 128.1 (4 × CH), 126.9 (2 × CH), 77.9 (CH), 58.9 (CH_2), 58.8 (CH), 54.4 (2 × CH_2), 34.2 (CH_2), 24.2 (CH), 23.7 (CH_3), 21.7 (CH_3), 21.5 (CH_2), 10.3 (CH_3); MS (70 eV, EI) *m/z* 382 (M^+, 1), 268 (8), 267 (100), 266 (90), 132 (14); HRMS (70 eV) calcd for $C_{24}H_{34}N_2O_2$ (M^+) 382.2620, found 382.2596; IR (neat) 3313, 2953, 1734, 1669, 1495, 1454 cm^{-1}; R_f = 0.18 (hexane/EtOAc 3:1). Anal. Calcd for $C_{24}H_{34}N_2O_2$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.12; H, 9.09; N, 7.46.

(2*R*,3*S*)-*N*-(3-Dibenzylamino-2-hydroxy-5-methylhexyl)isobutyramide (4d): colorless oil; $[\alpha]^{25}_D$ = +29.9 (*c* 1.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.22 (m, 10 H), 4.90−4.83 (m, 1 H), 3.96−3.58 (m, 5 H), 3.51 (d, *J* = 13.7 Hz, 2 H), 3.35 (dd, *J* = 14.3, 7.9 Hz, 1 H), 2.60−2.51 (m, 2 H), 1.94−1.87 (m, 1 H), 1.18 (d, *J* = 6.9 Hz, 6 H), 0.89 (d, *J* = 6.7 Hz, 3 H), 0.56 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (C), 140.0 (2 × C), 128.9 (4 × CH), 128.1 (4 × CH), 126.9 (2 × CH), 77.6 (CH), 59.0 (CH), 58.8 (CH_2), 54.4 (2 × CH_2), 34.1 (CH_2), 28.2 (CH), 24.1 (CH), 23.7 (CH_3), 21.6 (CH_3), 19.7 (CH_3), 19.5 (CH_3); MS (70 eV, EI) *m/z* 396 (M^+, <1), 393 (42), 267 (66), 266 (100), 181 (25), 119 (12); HRMS (70 eV) calc. for $C_{25}H_{36}N_2O_2$ (M^+) 396.2777, found 396.2793; IR (neat) 3320, 2955, 1728, 1662, 1492, 1450 cm^{-1}; R_f = 0.31 (hexane/EtOAc 3:1). Anal. Calcd for $C_{25}H_{36}N_2O_2$: C, 75.72; H, 9.15; N, 7.06. Found: C, 75.54; H, 9.07; N, 7.15.

(2*R*,3*S*)-*N*-(3-Dibenzylamino-2-hydroxy-4-phenylbutyl)isobutyramide (4e): colorless oil; $[\alpha]^{25}_D$ = +48.5 (*c* 1.25, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32−7.12 (m, 15 H), 4.90−4.79 (m, 1 H), 3.95 (dd, *J* = 14.1, 10.8 Hz, 1 H), 3.72 (AB syst., *J* = 13.9 Hz, 4 H), 3.51 (dd, *J* = 13.6, 8.2 Hz, 1 H), 3.07−2.75 (m, 3 H), 2.62−2.48 (m, 1 H), 1.17 (dd, *J* = 6.9, 0.7 Hz, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.4 (C), 141.0 (C), 140.3 (2 × C), 130.3 (2 × CH), 129.4 (4 × CH), 129.0 (6 × CH), 127.7 (2 × CH), 126.7 (CH), 79.3 (CH), 63.9 (CH), 59.0 (CH_2), 54.7 (2 × CH_2), 31.9 (CH_2), 28.4 (CH), 19.7 (CH_3), 19.6 (CH_3); MS (70 eV, EI) *m/z* 412 ($M^+ - H_2O$, 6), 339 (36), 300 (100), 210 (45), 169 (57), 131 (84); HRMS (70 eV) calcd for $C_{28}H_{32}N_2O$ ($M^+ - H_2O$) 412.2515, found 412.2524; IR (neat) 3336, 2970, 1733, 1652, 1495, 1454 cm^{-1}; R_f = 0.20 (hexane/EtOAc 3:1). Anal. Calcd for $C_{28}H_{34}N_2O_2$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.28; H, 7.87; N, 6.64.

(2*R*,3*S*)-*N*-(3-Dibenzylamino-2-hydroxy-4-phenylbutyl)benzamide (4f): colorless oil; $[\alpha]^{25}_D$ = +5.7 (*c* 3.39, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.0 Hz, 2 H), 7.52−7.21 (m, 18 H), 5.06−4.98 (m, 1 H), 4.21 (dd, *J* = 15.1, 10.1 Hz, 1 H), 3.82 (AB syst, *J* = 13.8 Hz, 4 H), 3.79−3.65 (m, 1 H), 2.23−3.11 (m, 2 H), 3.09−3.94 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (C), 140.0 (C), 139.5 (C), 139.3 (2 × C), 129.4, 129.0, 128.8, 128.6, 128.4, 127.9, 126.6, 125.8 (20 × CH), 79.6 (CH), 63.1 (CH), 59.4 (CH_2), 54.4 (2 × CH_2), 32.1 (CH_2); MS (70 eV, EI) *m/z* 446 ($M^+ - H_2O$, 2), 434 (8), 356 (47), 355 (16), 301 (100); HRMS (70 eV) calcd for $C_{31}H_{30}N_2O$ ($M^+ - H_2O$) 446.2358, found 446.2332; IR (neat) 3319, 2933, 1717, 1652, 1495, 1453 cm^{-1}; R_f = 0.41 (hexane/EtOAc 3:1). Anal. Calcd for $C_{31}H_{32}N_2O_2$: C, 80.14; H, 6.94; N, 6.03. Found: C, 80.30; H, 7.05; N, 5.93.

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Supporting Information Available: ^{13}C NMR spectra of compounds **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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