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Synthesis of Chiral Amino Epoxyaziridines: Useful Intermediates for the Preparation of Chiral Trisubstituted Piperidines

José M. Concellón,*,† Estela Riego,† Ignacio A. Rivero,*,‡ and Adrián Ochoa‡

Departamento de Química Orgánica e Inorgánica, Facultad de Química, Universidad de Oviedo, Julián Clavería 8, 33071 Oviedo, Spain, and Centro de Graduados e Investigación del Instituto Tecnológico de Tijuana, Blvd. Industrial s/n, Mesa de Otay, Tijuana, B.C., México 22000

jmcg@sauron.quimica.uniovi.es

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Chiral aminoalkyl epoxyaziridine **1** is synthesized in high yield and diastereoselectivity from L-serine. Ring opening of epoxyaziridine **1** with primary amines is carried out with total chemo- and regioselectivity, affording chiral polyfunctionalized piperidines **8**. The structure of these trisubstituted piperidines is established by NMR studies.

Introduction

Polyfunctionalized chiral building blocks, which are defined as molecules having at least one stereogenic center and more than one chemically differentiated functional group, have played significant roles in asymmetric synthesis and the synthesis of biologically and pharmacologically active molecules,[1] such as functionalized heterocyclic compounds. Therefore, the development of novel synthetic units is highly desired to obtain functional compounds.

In this regard, the piperidine ring systems,[2] and specifically, hydroxylated piperidine alkaloids,[3] constitute a large family of naturally occurring substances, many of which possess important biological activities.[3e] Hence, the development of new methods for the synthesis of these piperidine derivatives in an enantiomerically pure way constitutes an area of current interest.[4]

Recently, we have reported the preparation of the pseudo-C_2-symmetric (2*R*,4*R*)- and (2*S*,4*S*)-*N*,*N*-dibenzyl-1,2:4,5-diepoxypentan-3-amine (amino diepoxides) from serine, in enantiomerically pure form,[5] and the synthesis of chiral amino aziridines from 1-aminoalkyl chloromethyl ketones.[6] On the basis of these methodologies, we wish to report the preparation of a new family of highly functionalized enantiopure compounds, such as (2*S*,1′*R*,2′*R*)-1-benzyl-2-[1′-(dibenzylamino)-2′,3′-epoxypropyl]aziridine **1** (amino epoxyaziridine).[7] Taking into account the different reactivity of oxirane and aziridine rings with nucleophiles, we studied their behavior with primary amines, obtaining functionalized hydroxylated piperidines **8**.

Results and Discussion

Our synthetic strategy to prepare the amino epoxyaziridine **1** was based on the transformation of the ester function of the serine derivative **2** into an aziridine ring and, then, oxirane ring formation from the hydroxyl group (Scheme 1). Thus, as a first step, the α-amino-α′-chloro ketone **3**[5] was prepared from the methyl *N*,*N*-dibenzylated *O*-protected ester **2**,[8] by reaction with in situ generated chloromethyllithium at −78 °C, in high yield (93%, Scheme 1). Treatment of ketone **3** with benzylamine in the presence of $TiCl_4$ at room temperature gave the α-amino ketimine **4**, which was immediately transformed into the amino aziridine **5** by reduction of **4** with $NaBH_4$ at −30 °C, and further treatment with MeLi. That

* To whom correspondence should be addressed. Fax: 34-98-510-34-46.
† Universidad de Oviedo.
‡ Instituto Tecnológico de Tijuana.

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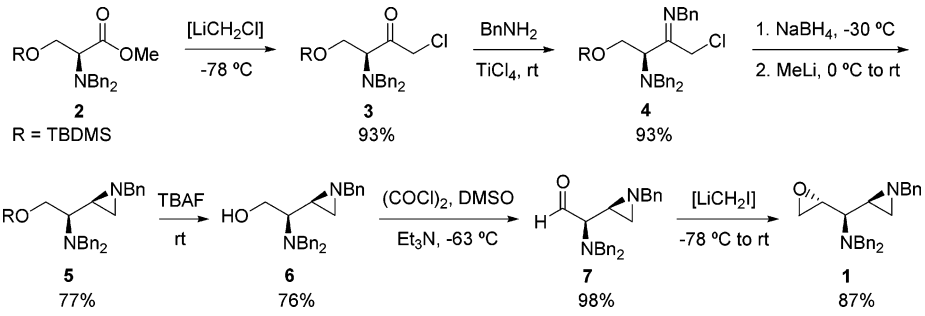
SCHEME 1. Synthesis of Amino Epoxyaziridine 1



reduction process was carried out with total diastereoselectivity (de >95%, ^{1}H NMR 300 MHz).[9]

Once the aziridine ring was prepared, we proceeded to construct the oxirane cycle through the careful oxidation of the free hydroxyl group in compound **6**, under Swern conditions, and iodomethylation of the resulting α-amino aldehyde **7**, with in situ generated iodomethyllithium at −78 °C. The ring closure of the obtained lithium alcoholate took place spontaneously under these reaction conditions, yielding the product **1** in 87% yield and 93% de (300 MHz ^{1}H NMR).

Since all the intermediate compounds (**3**−**7**) were obtained with a high degree of purity, they could be used without further purification. This allowed the isolation of **1** in good yield (43% after 6 steps).

On the basis of our earlier studies which examined the nonchelation controlled reduction of chiral α-dibenzylamino ketimines[6] and the addition of iodomethyllithium to α-aminoaldehydes,[10] the absolute configuration of amino epoxyaziridine **1** is believed to be (2*S*,1′*R*,2′*R*).[11]

Furthermore, we assumed that synthesis of **1** proceeded with keeping of the integrity of the preexistent asymmetric carbon at the starting material. This assumption is based on previously described preparations of amino aziridines from amino chloromethyl ketones,[6] amino epoxides from α-aminoaldehydes and iodomethyllithium,[10] and amino diepoxides from serine.[12] No racemization took place in these syntheses.[13]

It is noteworthy that all the carbon atoms of epoxyaziridine **1** are differently functionalized. Moreover, the oxirane and the aziridine rings have different reactivity: the oxirane ring is more easily opened by nucleophiles than nonactivated aziridine. Hence, this compound could be used as a new chiral building block in the synthesis of enantiopure compounds. To illustrate this synthetic potential, the amino epoxyaziridine **1** was treated with some primary amines in the presence of lithium perchlorate[14] at room temperature, affording

SCHEME 2. Synthesis of 3-Hydroxy-4,5-diaminopiperidines 8

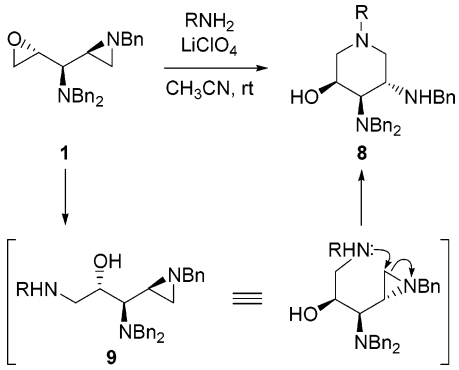


TABLE 1. Synthesis of 3-Hydroxy-4,5-diaminopiperidines 8

entry	product	R	yield (%)[a]
1	**8a**	*n*-propyl	60
2	**8b**	allyl	78
3	**8c**	benzyl	66
4	**8d**	cyclohexyl	70
5	**8e**	(*S*)-Ph(Me)CH	65

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

chiral hydroxylated piperidines **8** as sole products in good yields (Scheme 2, Table 1).

Although no ring activation has been observed in amino aziridines with lithium perchlorate in ring-opening reactions,[15] formation of compounds **8** can be explained by successive openings of the oxirane and the aziridine rings by the amine, at less substituted carbons in compound **1**.

Thereby, the oxirane ring would be opened at the less hindered position according to previous works,[5,14] affording the diamino alcohol **9** (Scheme 2). This intermediate could react through the hydroxyl group (Scheme 3, path a) or through the amine function (Scheme 3, paths b, and c), yielding tetrahydrofurans **A**, pyrrolidines **B**, or piperidines **8**, respectively. However, trisubstituted piperidines **8** were detected as sole reaction products (300 MHz ^{1}H NMR). Therefore, the amine function in intermediate **9** participates in a nucleophilic attack to the aziridine ring at the less hindered position, affording the piperidine ring.

(9) Only one diastereoisomer was visible by ^{1}H and ^{13}C NMR spectra (300 MHz) of compound **5**.

(10) Barluenga, J.; Baragaña, B.; Concellón, J. M. *J. Org. Chem.* **1995**, *60*, 6696.

(11) *N*,*N*-Dibenzylamino carbonyl compounds react with nucleophiles, in absence of Lewis acids, with a nonchelation control. See: Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121.

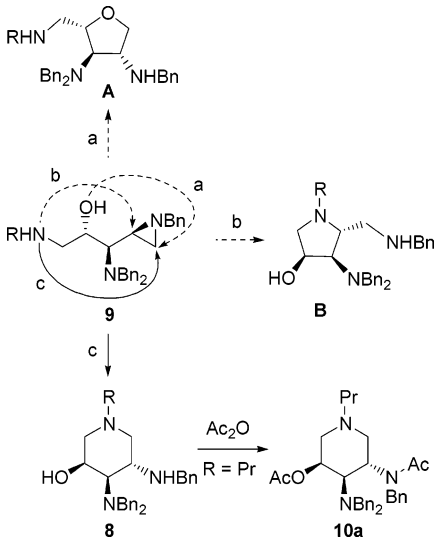
(12) Synthesis of ketone **3** from **2** proceeded with no detectable racemization, which was determined by chiral HPLC in the synthesis of amino diepoxides from serine. See ref 5.

(13) No racemization is observed in the use of *N*,*N*-dibenzylamino carbonyl compounds as electrophiles. See ref 10.

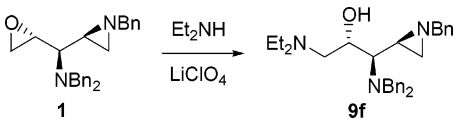
(14) *N*,*N*-Dibenzylamino epoxides are opened with amines, using lithium perchlorate as catalyst: Concellón, J. M.; Cuervo, H.; Fernández-Fano, R. *Tetrahedron* **2001**, *57*, 8983.

(15) Previously, we studied the ring opening of nonactivated aminoaziridines with nucleophiles, using different acids [see: (a) Concellón, J. M.; Riego, E. *J. Org. Chem.* **2003**, *68*, 6407. (b) Concellón, J. M.; Riego, E.; Suárez, J. R. *J. Org. Chem.* **2003**, *68*, 9242], but no reaction was observed in the presence of $LiClO_4$.

SCHEME 3. Probable Products of the Ring Opening of Intermediate 9



SCHEME 4. Ring Opening of 1 with Diethylamine



The structures of ring-opening products were established based on IR and ^{13}C and NOESY NMR experiments. To reject some possible structures of **8**, compound **8a** was acetylated. The IR spectra of this product showed bands at 1735 and 1643 cm^{-1}, characteristic of ester and amide groups, respectively. Consequently, the tetrahydrofuran **A** (Scheme 3) was ruled out, since it would contain two amide functions.

Therefore, the amine group acts as a nucleophile for a second time, as the use of diethylamine can also prove because the corresponding intermediate **9** was isolated (Scheme 4).

On the other hand, two methine groups in the ^{13}C NMR spectrum of **8a** were moved to lower fields in the acetylated derivative (from 63.9 and 51.5 to 67.0 and 55.3 ppm, respectively), which could indicate that the hydroxyl and secondary amine functions could be joined to these carbons. Thus, structure **B** (Scheme 3) would not explain this behavior, and the ring-opening product would correspond to the six-member heterocycle **8**. Moreover, NOESY experiments showed correlation between geminal hydrogens of the C-2 and C-6 methylenes. This correlation is observed in six-member cyclic molecules, due to a conformational equilibrium that produces an exchange of the environment of methylene protons (Figure 1, **I** and **II**).[16] Hence, all these data can support the assigned structures for compounds **8**.

Finally, configurational assignments of piperidine **8** were established by ^1H NMR coupling constants analysis and NOESY experiments of **8a**,**c**. The H-4 signal (2.39 ppm for **8a**, 2.45 ppm for **8c**) shows $J = 10.6$, 1.8 Hz in **8a** and $J = 10.3$, 1.7 Hz in **8c**, corresponding to a trans relative configuration between H-4 and H-5 and cis for H-4 and H-3. Furthermore, the observation of NOE interactions between H-4 and H-3 and the absence of NOE between H-4 and H-5 support the configuration of piperidines. Therefore, since the original asymmetric center in serine (C-4 in **8**) has not been involved in any process, the absolute configuration of **8** is (3*S*,4*R*,5*S*). This stereochemistry is also in agreement with the proposed ring-opening mechanism.

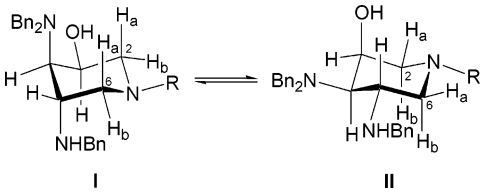


FIGURE 1. Conformational equilibrium of piperidines **8**.

In conclusion, we have described the synthesis of the optically active amino epoxyaziridine **1** with high diastereoselectivity and good yield. The synthetic route is simple, and the starting material (serine) is readily available. Likewise, the usefulness of **1** as a new chiral building block has been proved, affording chiral trisubstituted piperidines in totally chemoselective form.

Experimental Section

(2*R*)-(*Z*)-*N*,*N*-Dibenzyl-3-(benzylimino)-1-[(*tert*-butyldimethylsilanyl)oxy]-4-chlorobutan-2-amine (4). A solution of $TiCl_4$ (0.18 mL, 1.65 mmol) in dry hexane was added dropwise to a stirred solution of **3** (1.30 g, 3 mmol) in dry diethyl ether (30 mL) at 0 °C. Benzylamine (1.31 mL, 12 mmol) was added to the resulting solution over 5 min with stirring. After being stirred at room temperature for 2 h, the mixture was filtered through a pad of Celite and the solvents were removed in vacuo yielding the corresponding crude ketimine **4**. Due to instability of **4** no further purification was attempted, and it was characterized by IR and NMR spectroscopy: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.27 (15 H, m), 4.63 (2 H, d, $J = 16.2$ Hz), 4.30 (1 H, dd, $J = 10.8$, 7.7 Hz), 4.13 (1 H, dd, $J = 10.8$, 5.1 Hz), 3.95 (2 H, d, $J = 10.8$ Hz), 3.90 (2 × 2 H, d, $J = 13.1$ Hz), 3.73 (1 H, dd, $J = 7.7$, 5.1 Hz), 0.98 (9 H, s), 0.15 (3 H, s), 0.12 (3 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.7 (C), 140.0 (C), 139.6 (C), 129.2, 128.2, 128.1, 127.4, 126.9, and 126.5 (6 × CH), 63.0 (CH), 61.2 (CH_2), 54.6 (CH_2), 34.5 (CH_2), 26.0 (CH_3), 18.2 (C), −5.4 (CH_3); IR (neat) 1662.

(2*S*,1′*R*)-1-Benzyl-2-{1′-(dibenzylamino)-2′-[(*tert*-butyldimethylsilanyl)oxy]ethyl}aziridine (5). To a −30 °C stirred solution of the ketimine **4** (1.56 g, 3 mmol) in methanol (15 mL) was added $NaBH_4$ (0.23 g, 6.0 mmol). After being stirred at the same temperature for 3 h, the mixture was quenched with a saturated aqueous solution of NH_4Cl (15 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was dissolved in dry THF and treated with MeLi (4.1 mL of 1.5 M solution in diethyl ether, 6.2 mmol). The crude product **5** was examined by ^1H NMR to give a de >95%. Flash column chromatography over silica gel (hexane:ethyl acetate) provided pure compound **5**: R_f 0.30 (hexane/ethyl acetate 10/1); $[\alpha]^{22}_D$ −20.0 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.42−7.23 (15 H, m), 3.88−3.71 (6 H, m), 3.54 (2 H, d, $J = 12.9$ Hz), 2.49 (1 H, q, $J = 5.9$ Hz), 1.82 (1 H, ddd, $J = 6.4$, 5.9, 3.3 Hz), 1.71 (1 H, d, $J = 3.3$ Hz), 1.39 (1 H, d, $J = 6.4$ Hz), 0.96 (9 H, s), 0.07 (6 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.8 (C), 139.2 (C), 128.8, 128.6, 128.3, 127.8, 127.1, and 126.2 (6 × CH), 65.1 (CH_2), 63.8 (CH_2), 61.3 (CH), 54.9 (CH_2), 38.4 (CH), 31.6 (CH_2), 25.8 (CH_3), 18.1 (C), −5.6 (CH_3), −5.7 (CH_3); IR (neat) 3084, 3062, 3028. Anal. Calcd for $C_{31}H_{42}N_2OSi$: C, 76.49; H, 8.07; N, 5.76. Found: C, 76.05; H, 8.21; N, 5.80.

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(2*S*,1′*R*)-1-Benzyl-2-[1′-(dibenzylamino)-2′-hydroxyethyl]-aziridine (6). A solution of **5** (1.46 g, 3 mmol) in THF (30 mL) was stirred with $(Bu_4N)F$ (9 mL of 1 M solution in THF, 9 mmol) at room temperature for 2 h. The reaction mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Removal of the solvent followed by purification by flash column chromatography over silica gel (1/1 hexane/ethyl acetate) provided pure compound **6**: R_f 0.20 (hexane/ethyl acetate 3/1); $[\alpha]^{22}_D$ −57.9 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.21 (15 H, m), 3.60−3.41 (2 H, m), 3.56 (2 × 2 H, d, J = 13.1 Hz), 3.50 (2 H, d, J = 12.8 Hz), 2.72−2.67 (1 H, m), 1.75−1.73 (2 H, m), 1.44 (1 H, d, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.3 (C), 138.4 (C), 128.8, 128.7, 128.3, 127.9, 127.3, and 126.8 (6 × CH), 64.8 (CH_2), 59.5 (CH), 58.7 (CH_2), 53.5 (CH_2), 36.3 (CH), 30.6 (CH_2); IR (neat) 3419. Anal. Calcd for $C_{25}H_{28}N_2O$: C, 80.61; H, 7.58; N, 7.52. Found: C, 80.78; H, 7.49; N, 7.60.

(2*S*,1′*R*)-1-Benzyl-2-[1′-(dibenzylamino)-2′-oxoethyl]aziridine (7). A solution of dry DMSO (0.50 mL, 7.04 mmol) in dry CH_2Cl_2 (2.8 mL) was added dropwise to a −63 °C solution of oxalyl chloride (0.31 mL, 3.52 mmol) in dry CH_2Cl_2 (2.8 mL) over 10 min. The mixture was stirred at the same temperature for 5 min and a solution of **6** (3.2 mmol) in dry CH_2Cl_2 (23 mL) was added within 10 min. The reaction was stirred for an additional 20 min, and then treated carefully with triethylamine (1.4 mL, 16 mmol) in CH_2Cl_2 (5 mL) over 15 min. The mixture was stirred for another 30 min. Water was then added and the aqueous layer was extracted with additional CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with saturated NaCl solution (50 mL), and dried over Na_2SO_4. The solvents were removed in vacuo, yielding the α-aminoaldehyde **7**. Due to instability of the aldehyde **7** no further purification was attempted, and it was characterized by IR and NMR spectroscopy: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.60 (1 H, s), 7.50−7.26 (15 H, m), 3.64 (2 × 2 H, d, J = 13.3 Hz), 3.56 (2 H, d, J = 12.6 Hz), 2.92 (1 H, d, J = 8.0 Hz), 2.01−1.92 (1 H, m), 1.67 (1 H, d, J = 3.3 Hz), 1.61 (1 H, d, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 202.0 (CH), 139.0 (C), 138.6 (C), 129.0, 128.9, 128.4, 128.1, 127.4, and 127.0 (6 × CH), 69.8 (CH), 64.9 (CH_2), 54.8 (CH_2), 34.6 (CH), 31.5 (CH_2); IR (neat) 1695, 1680.

(2*S*,1′*R*,2′*R*)-1-Benzyl-2-[1′-(dibenzylamino)-2′,3′-epoxypropyl]aziridine (1). To a −78 °C stirred solution of α-aminoaldehyde **7** (1.19 g, 3.2 mmol) and diiodomethane (0.77 mL, 9.6 mmol) in dry THF (10 mL) was added methyllithium (6.4 mL of a 1.5 M solution in diethyl ether, 9.6 mmol) dropwise over 5 min. After being stirred at −78 °C for 30 min, the mixture was allowed to warm to room temperature. Stirring was continued for 1 h and then the reaction was hydrolyzed with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude epoxyaziridine **1** was examined by ^{1}H NMR to give a de of 93%. The crude product was chromatographied on silica gel, which was saturated with triethylamine (3/1 hexane/ethyl acetate) to provide pure compound **1**: R_f 0.43 (hexane/ethyl acetate 3/1); $[\alpha]^{22}_D$ −37.1 (*c* 0.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.50−7.21 (15 H, m), 3.73 (2 × 2 H, d, J = 13.8 Hz), 3.51 (2 H, s), 3.10−3.05 (1 H, m), 2.63 (1 H, dd, J = 5.1, 4.1 Hz), 2.49 (1 H, dd, J = 5.1, 2.8 Hz), 2.26 (1 H, dd, J = 8.5, 4.6 Hz), 1.93−1.84 (1 H, m), 1.62 (1 H, d, J = 3.3 Hz), 1.40 (1 H, d, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.2 (C), 138.8 (C), 138.6 (C), 128.9, 128.6, 128.3, 128.0, 127.3, and 126.6 (6 × CH), 64.9 (CH_2), 61.5 (CH), 54.7 (CH_2), 53.6 (CH), 44.6 (CH_2), 36.0 (CH), 31.3 (CH_2); IR (neat) 3028. Anal. Calcd for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.34; N, 7.29. Found: C, 81.00; H, 7.41; N, 7.17.

General Procedure for the Reaction of (2*S*,1′*R*,2′*R*)-1-Benzyl-2-[1′-(dibenzylamino)-2′,3′-epoxypropyl]aziridine (1) with Amines. To a room temperature stirred solution of **1** (0.38 g, 1.0 mmol) in dry acetonitrile (20 mL) was successively added $LiClO_4$ (0.11 g, 1.0 mmol) and the corresponding amine (1.2 mmol). Stirring was continued at room temperature for 48 h and then the reaction was hydrolyzed with H_2O (30 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was chromatographed on silica gel, which was saturated with triethylamine (3/1 hexane/ethyl acetate) to provide a pure product.

(3*S*,4*R*,5*S*)-5-Benzylamino-4-dibenzylamino-3-hydroxy-1-propylpiperidine (8a): R_f 0.68 (ethyl acetate/hexane 3/1); $[\alpha]^{22}_D$ +33.5 (*c* 0.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.32−7.09 (15 H, m), 4.30 (1 H, br s), 3.86 (2 × 2 H, AB system, J = 14.4 Hz), 3.71 (2 H, AB system, J = 13.2 Hz), 3.20−3.04 (2 H, m), 2.94−2.87 (1 H, m), 2.39 (1 H, dd, J = 10.6, 1.8 Hz), 2.30 (2 H, t, J = 7.8 Hz), 2.00 (1 H, dd, J = 11.4, 0.8 Hz), 1.70 (1 H, t, J = 11.4 Hz), 1.51−1.34 (2 H, m), 0.86 (3 H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 140.3 (C), 140.1 (C), 128.4, 128.3, 128.2, 126.9, and 126.8 (5 × CH), 63.9 (CH), 62.3 (CH), 59.7 (CH_2), 59.1 (CH_2), 58.5 (CH_2), 54.4(CH_2), 52.3 (CH_2), 51.5 (CH), 19.8 (CH_2), 11.6 (CH_3); IR (neat) 3472, 3310**;** MS, *m*/*z* 444 (M^+ + 1, 4), 385 (6), 337 (38), 247 (57), 146 (100).

(3*S*,4*R*,5*S*)-1-Allyl-5-benzylamino-4-dibenzylamino-3-hydroxypiperidine (8b): R_f 0.55 (ethyl acetate); $[\alpha]^{22}_D$ +57.9 (*c* 0.19, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.30−7.10 (15 H, m), 5.85−5.66 (1 H, m), 5.20−5.05 (2 H, m), 4.28 (1 H, t, J = 1.8 Hz), 3.84 (2 × 2 H, AB system, J = 14.7 Hz), 3.70 (2 H, AB system, J = 13.2 Hz), 3.21−3.08 (2 H, m), 3.00 (2 H, d, J = 6.6 Hz), 2.88 (1 H, br s), 2.41 (1 H, dd, J = 10.2, 1.8 Hz), 2.02 (1 H, d, J = 9.8 Hz), 1.73 (1 H, t, J = 11.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.9 (C), 139.7 (C), 134.2 (CH), 128.2, 128.1, 127.9, 126.6, and 126.5 (5 × CH), 117.9 (CH_2), 64.1 (CH), 62.2 (CH), 60.5 (CH_2), 59.5 (CH_2), 58.3 (CH_2), 54.3 (CH_2), 52.2 (CH_2), 51.3 (CH); IR (neat) 3445, 3314, 1639; MS, *m*/*z* 442 (M^+ + 1, 10), 335 (25), 245 (90), 146 (100). Anal. Calcd for $C_{29}H_{35}N_3O$: C, 78.87; H, 7.99; N, 9.52. Found: C, 78.68; H, 8.17; N, 9.50.

(3*S*,4*R*,5*S*)-1-Benzyl-5-benzylamino-4-dibenzylamino-3-hydroxypiperidine (8c): R_f 0.74 (hexane/ethyl acetate 3/1); $[\alpha]^{20}_D$ +33.1 (*c* 0.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39−7.20 (20 H, m), 4.30 (1 H, br s), 3.89 (2 × 2 H, AB system, J = 14.3 Hz), 3.70 (2 H, AB system, J = 13.2 Hz), 3.56 (2 H, AB system, J = 10.1 Hz), 3.20−3.15 (2 H, m), 2.92 (1 H, d, J = 10.2 Hz), 2.47 (1 H, d, J = 10.2 Hz), 2.08 (1 H, d, J = 10.8 Hz), 1.78 (1 H, t, J = 11.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 140.2 (C), 140.0 (C), 137.8 (C), 128.8, 128.4, 128.3, 128.2, 128.0, 127.3, 126.9, and 126.8 (8 × CH), 64.2 (CH), 62.3 (CH), 61.8 (CH_2), 59.6 (CH_2), 58.3 (CH_2), 54.2 (CH_2), 52.1 (CH_2), 51.2 (CH); IR (neat) 3483, 3312; MS, *m*/*z* 492 (M^+ + 1, 6), 385 (42), 295 (100), 146 (73).

(3*S*,4*R*,5*S*)-5-Benzylamino-4-dibenzylamino-1-cyclohexyl-3-hydroxypiperidine (8d): R_f 0.48 (ethyl acetate); $[\alpha]^{22}_D$ +40.9 (*c* 0.09, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.37−7.10 (15 H, m), 4.30−4.20 (1 H, m), 3.84 (2 × 2 H, AB system, J = 14.2 Hz), 3.71 (2 H, AB system, J = 12.8 Hz), 3.18−3.06 (2 H, m), 2.86 (1 H, d, J = 10.6 Hz), 2.50 (1 H, br s), 2.36 (1 H, dd, J = 10.2, 1.8 Hz), 2.24 (1 H, d, J = 11.4 Hz), 1.99 (1 H, t, J = 11.4 Hz), 1.80−1.55 (4 H, m), 1.25−0.98 (6 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.8 (C), 128.2, 128.1, 127.9, 126.6, and 126.5 (5 × CH), 63.7 (CH), 63.3 (CH), 62.7 (CH), 55.6 (CH_2), 54.8 (CH_2), 54.3 (CH_2), 52.3 (CH_2), 52.2 (CH), 29.2 (CH_2), 28.6 (CH_2), 26.1 (CH_2), 25.9 (CH_2), 25.8 (CH_2); IR (neat) 3450, 3313; MS, *m*/*z* 484 (M^+ + 1, 22), 377 (80), 287 (100), 236 (38), 146 (60). Anal. Calcd for $C_{32}H_{41}N_3O$: C, 79.46; H, 8.54; N, 8.69. Found: C, 79.28; H, 8.37; N, 8.50.

(3*S*,4*R*,5*S*,1′*S*)-5-Benzylamino-4-dibenzylamino-3-hydroxy-1-(1′-phenylethyl)piperidine (8e): R_f 0.70 (ethyl acetate/methanol 1/1); $[\alpha]^{20}_D$ +50.3 (*c* 0.16, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.40−7.05 (20 H, m), 4.23 (1 H, br s), 3.82 (2 × 2 H, AB system, J = 14.2 Hz), 3.64 (2 H, AB system, J = 13.2 Hz), 3.18−2.98 (3 H, m), 2.97−2.86 (1 H, m), 2.34 (1 H, dd, J = 10.6, 1.6 Hz), 1.99 (1 H, d, J = 11.4 Hz), 1.66 (1 H, t, J = 9.9 Hz), 1.32 (3 H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) 142.1 (C), 139.8 (C), 128.4, 128.1, 128.0, 127.9, 127.2,

126.9, 126.6, and 126.5 (8 × CH), 63.9 (CH), 62.8 (CH), 62.4 (CH), 56.2 (CH_2), 55.3 (CH_2), 54.2 (CH_2), 52.1 (CH_2), 51.6 (CH), 17.8 (CH_3); IR (neat) 3481, 3313; MS, *m*/*z* 506 ($M^+ + 1$, 30), 399 (45), 309 (100), 236 (25), 146 (38). Anal. Calcd for $C_{34}H_{39}N_3O$: C, 80.75; H, 7.77; N, 8.31. Found: C, 81.62; H, 7.51; N, 8.40.

(2*S*,1′*R*,2′*S*)-1-Benzyl-2-[(1′-dibenzylamino-3′-diethylamino-2′-hydroxy)propyl]aziridine (9f): R_f 0.35 (dichloromethane/methanol 9/1); $[\alpha]^{20}_D$ −33.9 (*c* 0.12, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.50−7.15 (15 H, m), 3.78−3.71 (1 H, m), 3.66 (2 × 2 H, AB system, J = 13.8 Hz), 3.55 (2 H, AB system, J = 13.2 Hz), 2.70 (1 H, dd, J = 13.2, 4.0 Hz), 2.59−2.35 (4 H, m), 2.15 (1 H, t, J = 7.8 Hz), 1.97 (1 H, dd, J = 13.2, 10.2 Hz), 2.01−1.91 (1 H, m), 1.76 (1 H, d, J = 3.4 Hz), 1.48 (1 H, d, J = 6.4 Hz), 0.93 (6 H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) 140.0 (C), 138.9 (C), 128.8, 128.6, 128.3, 128.1, 127.7, 127.0, and 126.4 (7 × CH), 67.3 (CH), 64.9 (CH_2), 63.3 (CH), 57.7 (CH_2), 54.9 (CH_2), 46.9 (CH_2), 37.5 (CH), 32.5 (CH_2), 11.9 (CH_3); IR (neat) 3316, 2968; MS, *m*/*z* 458.0 ($M^+ + 1$, 40), 385 (100), 329 (65), 210 (88).

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Supporting Information Available: Experimental details and spectroscopic data for diacetylated compound of **8a**, ^{13}C NMR spectra of **4**−**7**, **1**, **8a**−**e**, and diacetylated **8a**, and NOESY ^{1}H NMR spectra of **8a**,**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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