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Selective Ring-Opening of Nonactivated Amino Aziridines by Thiols and Unusual Nucleophilic Substitution of a Dibenzylamino Group

José M. Concellón,* Pablo L. Bernad, and José Ramón Suárez

Departamento de Química Orgánica e Inorgánica, Facultad de Química, Universidad de Oviedo, Julián Clavería 8, 33071 Oviedo, Spain

Santiago García-Granda and M. Rosario Díaz

Departamento de Química Física y Analítica, Facultad de Química, Universidad de Oviedo, Julián Clavería 8, 33071 Oviedo, Spain

jmcg@fq.uniovi.es

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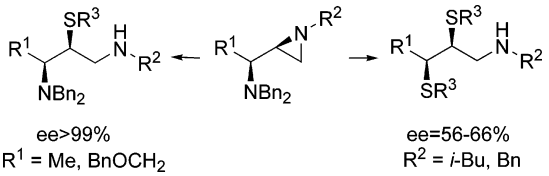

The reaction of chiral 2-(1-aminoalkyl)aziridines **1** with different thiols, in the presence of $BF_3 \cdot Et_2O$, is reported. The obtained products were dependent on the structure of the starting amino aziridines **1**. Thus, enantiopure (2*S*,3*S*)-2-(alkylthio)alkane-1,3-diamines **2** were obtained from aziridines with C-2 substituents with lower steric congestion and partially racemized (2*S*,3*S*)-2,3-bis(alkylthio)alkan-1-amines **3** (ee = 56−66%) from aziridines with larger C-2 subtituents. In both cases, the opening of the nonactivated aziridine ring at C-2 took place with retention of configuration and proceeded with regio- and stereoselectivity at C-2. In the synthesis of **3**, 2 equiv of thiol reacts with **1** and the opening of aziridine ring at C-2 was followed by an unusual displacement of the dibenzylamino group by a second equivalent of thiol. The regiochemistry and relative configuration of compounds **3** was established by single-crystal X-ray analysis. A mechanism is proposed to explain the results obtained.

Introduction

β-(Alkylthio)amines, are important building blocks for the synthesis of various biologically active compounds.[1] In addition, enantiopure 2,3-bis(alkylthio)alkan-1-amines have been used as ligands in palladium-catalyzed asymmetric allylic alkylations.[2] Moreover, aziridine heterocycles are useful starting materials in organic synthesis and have been used to prepare biologically active molecules such as amino acids,[3] alkaloids[4] and heterocycles.[5] The chemical reactivity of aziridines can be explained by considering ring strain in the small heterocycle.[3,6] Consequently, a large number of ring-opening reactions of chiral, activated aziridines have been reported.[3b,7] However, to the best of our knowledge, very few examples of ring opening of nonactivated aziridines have been published.[8] For these reasons, a methodology to prepare chiral 2-(alkylthio)alkane-1-amines and 2,3-bis(alkylthio)alkan-1-amines by ring opening of nonactivated aziridines would be interesting.

Recently, we reported the synthesis of nonactivated enantiopure 2-(1-aminoalkyl)aziridines **1** by reduction of

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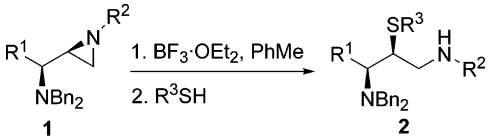
α-amino ketimines derived from 1-aminoalkyl chloromethyl ketones,[9] Subsequently, we have described the highly regio- and diastereoselective ring opening of these aziridines with water,[10] alcohols, carboxylic acids, sodium iodide,[11] and nitriles.[12]

To extend the scope of synthetic applications of enantiopure 2-(1-aminoalkyl)aziridines **1**, we report herein the reaction of **1** with a variety thiols in the presence of BF_3·Et_2O, which took place via a ring opening of the nonactivated aziridine ring, affording a range of products. It seems that the reaction was sensitive to steric hindrance with respect to the amino aziridine reaction partner. Therefore, enantiopure (2*S*,3*S*)-2-(alkylthio)alkane-1,3-diamines **2** were obtained from amino aziridines bearing C-2 subtituents with lower steric congestion and partially racemized (2*S*,3*S*)-2,3-bis(alkylthio)alkan-1-amines **3** (ee= 55−65%) from aziridines with larger C-2 subtituents. In both cases, the opening of the aziridine ring at C-2 proceeded with retention of configuration and took place with regio- and stereoselectivity. In the synthesis of **3**, 2 equiv of thiol reacts with **1** and the opening of aziridine ring at C-2 was followed by an unusual displacement of the dibenzylamino group by the second equivalent of thiol. To the best of our knowledge, no previous S_N2 displacement of dialkylamino groups has been described and only two papers describing the substitution of *N,N*-disulfonylimides by an hydroxyl group have been reported.[13] The regiochemistry and relative configuration of compounds **3** was unambiguously established by single-crystal X-ray analysis, and the enantiomeric purity of compounds **2** and **3** was determined by chiral HPLC (Chiracel OD-RH and OD-H). A mechanism is proposed to explain the obtained results.

Results and Discussion

On the basis of previous papers,[10−12] we have used BF_3·OEt_2 to catalyze the ring-opening reactions of amino aziridines **1** with thiols. Thus, treatment of a solution of amino aziridines **1a**−**c** derived from alanine and *O*-benzyl serine (R^1= Me, $BnOCH_2$), in toluene with 3 equiv of different thiols, in the presence of BF_3·OEt_2 (1.1 equiv) at reflux for 12 h, provided (2*S*,3*S*)-2-(alkylthio)alkane-1,3-diamines **2a**−**e** in good yields (Scheme 1), after standard workup and purification by column chromatography, as shown in Table 1. This transformation appears to be general, and it can be performed with different (cyclic, linear, and phenyl-substituted) aliphatic thiols and with aziridines **1a**−**c** bearing different substituents at the aziridine nitrogen atom (allyl, propyl, and benzyl).

SCHEME 1. C-2 Ring Opening of Amino Aziridines 1 (R^1 = Me, $BnOCH_2$) with Thiols



1 **2**

a: R^1 = Me; R^2 = Pr
b: R^1 = Me; R^2 = allyl
c: R^1 = $BnOCH_2$; R^2 = Bn

TABLE 1. C-2 Ring Opening of Aziridines 1 (R^1 = Me, $BnOCH_2$)

entry	product	R^1	R^2	R^3	yield (%)[a]
1	**2a**	Me	Pr	n-C_5H_{11}	76
2	**2b**	Me	Pr	Cy	79
3	**2c**	Me	allyl	$PhCH_2CH_2$	83
4	**2d**	$BnOCH_2$	Bn	Cy	81
5	**2e**	$BnOCH_2$	Bn	Bn	72

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

The reaction of amino aziridines **1a**−**c** derived from alanine and *O*-benzylated serine (R^1= Me, $BnOCH_2$) with thiols was totally regio- and stereoselective, and no mixture of isomers was observed by ^1H and ^{13}C NMR analysis (300 MHz) of crude reaction products **2**, within the limits of NMR assay.

^1H and ^{13}C NMR spectra of compounds **2** showed the incorporation of 1 equiv of thiol to the final product **2a**−**e**. The opening of the aziridine at C-2, with retention of configuration and the structure of compounds **2**, has been proposed on the basis of previous reactions of amino aziridines **1** with H_2O[10] or alcohols[11] in the presence of BF_3·Et_2O and on the single-crystal X-ray analysis of compound **4g** (see below).

The enantiomeric purity of **2b** was determined by chiral HPLC analysis, showing an enantiomeric excess (ee) >99%. To exclude the possibility of coelution of both enantiomers, a racemic mixture of **2b** was prepared and analyzed by HPLC.[14,15]

When the same reaction conditions (3 equiv of thiols, BF_3·OEt_2, and reflux), were applied to amino aziridines derived from phenylalanine and leucine (R^1= Bn, *i*-Bu) **1d**−**f**, different products were obtained and (2*S*,3*S*)-2,3-bis(alkylthio)alkan-1-amines **3** were isolated (Scheme 2 and Table 2). ^1H and ^{13}C NMR spectra of products **3**

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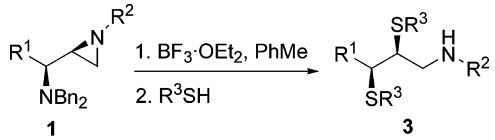
(14) **2b**: Chiracel OD-RH, UV detector 210 nm, 0.3 mL/min, 50 bar, 60:40 MeCN/ClO_4 0.5 M; t_R (min) 45.331 (major enantiomer), 40.851 (minor enantiomer).

(15) Racemic mixture of **2b**, **3f**, and **3g** were prepared by treatment of a racemic mixture of **1a** or **1f** with cyclohexanethiol (**2b** and **3g**) or octane-1-thiol (**3f**), respectively. **1a** and **1f** were obtained by successive transformation of a racemic mixture of ethyl α-dibenzylamino ester derived from alanine (**2b**) or phenylalanine (**3f** and **3g**) into the corresponding chloromethyl ketone (Barluenga, J.; Baragaña, B.; A. Alonso, Concellón, J. M. *J. Chem. Soc*., *Chem. Commun*. **1994**, 969−970), α-chloromethyl ketimine, and aminoaziridine.[9]

SCHEME 2. C-2 Ring Opening of Amino Aziridines 1 (R^1 = Bn, *i*-Bu) with Thiols



1 **3**

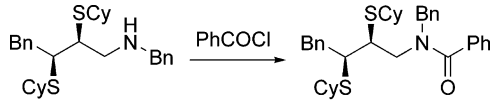
d: R^1 = *i*-Bu; R^2 = allyl
e: R^2 = *i*-Bu; R^2 = Bn
f: R^1 = Bn; R^2 = Bn

TABLE 2. C-2 Ring Opening of Aziridines 1 (R^1= *i*-Bu, Bn)

entry	product	R^1	R^2	R^3	yield (%)[a]
1	**3a**	*i*-Bu	allyl	*n*-C_5H_{11}	49
2	**3b**	*i*-Bu	allyl	$PhCH_2CH_2$	58
3	**3c**	*i*-Bu	Bn	*n*-C_5H_{11}	59
4	**3d**	*i*-Bu	Bn	*n*-C_8H_{17}	61
5	**3e**	*i*-Bu	Bn	Bn	57
6	**3f**	Bn	Bn	*n*-C_8H_{17}	57
7	**3g**	Bn	Bn	Cy	62
8	**3h**	Bn	Bn	$PhCH_2CH_2$	63

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

SCHEME 3. Derivatization of 3g with PhCOCl



3g **4g**

showed the incorporation of two equivalents of thiol in the final products **3a**−**h** and the disappearance of signals corresponding to dibenzylamino group from the starting aminoaziridine **1**. No other regio- or diastereoisomers were observed in the crude reaction products **3a**−**h** by ^1H and ^{13}C NMR analysis (300 MHz).

The enantiomeric excess (ee) of compounds **3f** and **3g** was 66 and 56%, respectively, showing that a partial racemization occurred in the synthesis of compounds **3f** and **3g**. To exclude the possibility of coelution of both enantiomers,[15] a racemic mixture of **3f** and **3g** was prepared and analyzed by HPLC.[16] The ee of compounds **3a**−**e** and **3h** could not be determined by HPLC, due to the coelution of both enantiomers. In this sense, we assume that a partial racemization could also occur in these compounds by analogy with **3f** and **3g**.

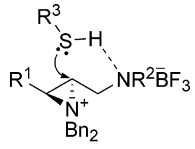
The structure of **3g** was established after transformation into the crystalline *N*-benzoyl derivative **4g** (compounds **3a**−**h** could not be crystallized) by reaction with benzoyl chloride (Scheme 3). The single-crystal X-ray analysis[17] of **4g** permitted us to assign the regiochemistry and the relative configuration of the starting compound **3g**. However, the absolute configuration of the major enantiomer could not be established because compound **3g** was obtained as a 78/22 enantiomeric mixture and we were not able to determine whether the analyzed single-crystal corresponded to the major enantiomer. The structure and relative configuration of the other compounds **3a**−**h**, as depicted in Scheme 2, was assigned by analogy.

It is noteworthy that 2 equiv of thiol reacts with amino aziridines derived from phenylalanine and leucine (R^1 = Bn, *i*-Bu) **1d**−**f**, producing an unusual displacement of the dibenzylamino group and the opening of the aziridine ring. This double nucleophilic displacement (aziridine and dibenzylamino group) can be performed with cyclic and linear aliphatic thiols, which can also bear aromatic substituents (Table 2).

When attempts were made to decrease the amount of thiol to 1 equiv, a mixture (1:1) of **3** and the corresponding diaminoalkanol, as a consequence the ring opening by H_2O[10] during the final hydrolysis of the reaction, were obtained. In addition, when the aziridines **1a**−**c** were treated with an excess of thiol (8 equiv) to produce a double substitution reaction, as in the case of **1d**−**f**, no incorporation of 2 equiv of thiol was observed, and the same final products **2a**−**e** were isolated.

Formation of compounds **2** and **3** may be explained by assuming that, in the first step of the reaction, selective coordination of the Lewis acid with the aziridine nitrogen takes place. This selective coordination of the Lewis acid with the aziridine nitrogen instead of the dibenzylamino group can be justified on steric grounds and has been proved by isolation of the corresponding aziridine−borane complex after treatment of compounds **1** with BF_3·OEt_2 and subsequent reduction with $LiAlH_4$.[18] Presumably, the activated aziridine−Lewis acid complex **5** receives anchimeric assistance from the dibenzylamino group, affording aziridinium salt **6**. Then, the thiol would attack the intermediate **6** at the C-2 position, which would undergo a second inversion of the configuration, yielding amide **7** and, after hydrolysis, the (2*S*,3*S*)-2-(alkylthio)-alkane-1,3-diamines **2** (Scheme 4).

The total regioselectivity observed in the ring opening of intermediate aziridinium salt **6** with different thiols could be explained by the probable formation of a hydrogen bond between thiol and the nitrogen in **6**, shown as **A** in Figure 1. Thus, the C-2 would be the most



A

FIGURE 1. Attack to the aziridinium salt **6** at C-2.

accessible carbon to the sulfur atom of thiol, and the reaction would take place through this carbon, and in addition, the formation of the hydrogen bond would produce an enhancement of the nucleophilicity of thiol. A similar control of the regiochemistry was previously

(16) **3f**: Chiracel OD-H, UV detector 210 nm, 0.6 mL/min, 32 bar, 70:30 hexane/propan-2-ol; t_R (min) 9.153 (major enantiomer), 9.760 (minor enantiomer). **3g**: Chiracel OD-H, UV detector 210 nm, 0.6 mL/min, 33 bar, 98:2 hexane/propan-2-ol; t_R (min) 8.553 (major enantiomer), 7.784 (minor enantiomer).

(17) CCDC-244660 (**4g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or the Cambridge Data Centre, 12, Union Road. Cambridge CB2 1EZ, UK; fax (+44)1223−336.033; or deposit@ccdc.cam.ac.uk).

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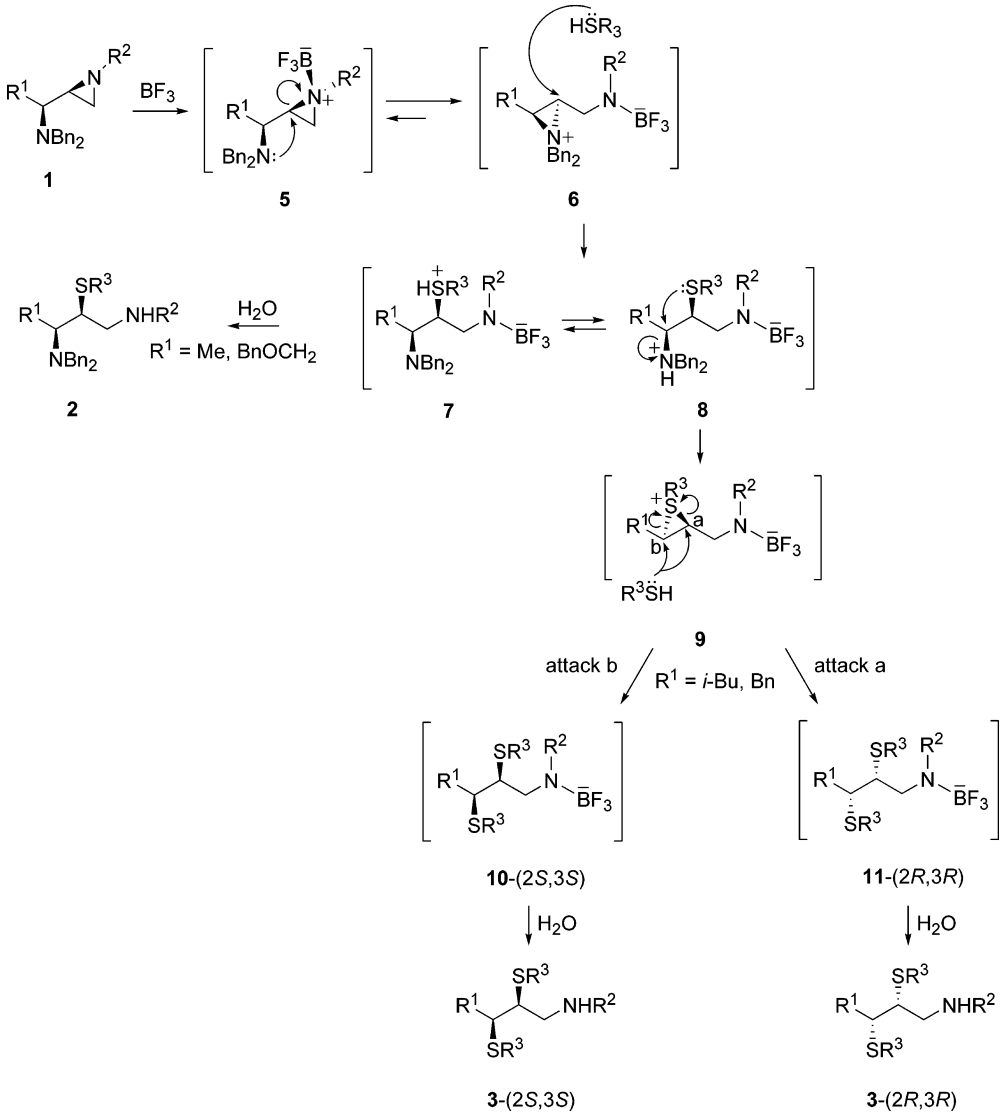
SCHEME 4. Mechanism Proposed



observed in the ring opening of amino aziridines **1** with alcohols and H_2O in the presence of $BF_3{\cdot}Et_2O$.[10,11]

In the case of compounds **1d**−**f** the aminoprotonated alkanethiol group of **8** would produce an intramolecular displacement of the dibenzylamino substituent, affording an intermediate thiiranium salt **9**, which undergoes a reaction with a second equivalent of thiol to yield the dithioether **3**. The ring-opening of thiiranium **9** could take place at C-3 or C-2, producing an enantiomeric mixture of compounds **3**. Assuming that the attack of the second equivalent of thiol with **9** at C-2 is favored for the same reason as before, the major enantiomer would be probably (2*R*,3*R*). The lower regioselectivity observed in the ring opening of **9** with respect to that observed in the reaction of **6** with thiols could be explained by taking into account the higher reactivity of **9** in comparison with **6**. Consequently, the attack of thiol at C-3 could be produced without an enhacement of the nucleophilicity (due to the formation of the hydrogen bond between thiol and the nitrogen atom), affording the enantiomer (2*S*,3*S*).

The different behavior of compounds **1a**−**c** and **1d**−**f** may be explained by assuming that the second nucleophilic substitution in **1d**−**f** can be due probably to the decreased steric congestion that occurs after the displacement of the bulky dibenzylamino group by thiol. In the case of amino aziridines derived from alanine or serine, steric congestion close to the aziridine ring[19] is not released upon the substitution, and in this respect, no transformation of compound **7** into **3** would occur. Thus, the reaction was probably sensitive to steric hindrance with respect to the amino aziridine reaction partner.

In conclusion, we have described the reaction of several chiral, nonactivated amino aziridines **1** with different thiols, affording enantiopure (2*S*,3*S*)-2-alkylthioalkan-1,3-diamines **2** or enantiomeric enriched (2*S*,3*S*)-2,3-bis-(alkylthio)alkan-1-amines **3**, depending on the starting amine aziridines. Starting from amino aziridines derived from phenylalanine or leucine **1d**−**f**, incorporation of 2 equiv of thiol takes place, while for amino aziridines derived from alanine or serine **1a**−**c** only 1 equiv of thiol reacts with **1**. In both reactions the opening of the aziridine ring takes place with total selectivity. A mechanism has been proposed to explain both transformations.

(19) The oxygen atom acts as a separator, which distances the benzyl group from the aziridine ring.

Experimental Section

General Methods. All reactions were carried out under an atmosphere of dry N_2 using oven-dried glassware and syringes. All reagents were purchased in the higher quality available and were used without further purification. $BF_3{\cdot}OEt_2$ was distilled from CaH_2 and toluene was distilled from sodium and stored over activated 4 Å molecular sieves. The solvents used in column chromatography, hexane and EtOAc, were obtained from commercial suppliers and used without further distillation. TLC was performed on aluminum-backed plates coated with silica gel 60 with F254 indicator. Flash column chromatography was carried out on silica gel 60, 230−240 mesh. ^{1}H NMR (200, 300, 400 MHz) and ^{13}C NMR (50.5, 75.5, 100 MHz) spectra were measured at room temperature (except **4g**, where $T = 80$ °C) with tetramethylsilane ($\delta = 0.0$, ^{1}H NMR) or $CDCl_3$ ($\delta = 77.00$, ^{13}C NMR) as internal standard. Carbon multiplicities were assigned by DEPT techniques. Low-resolution electron impact mass spectra (EI-LRMS) were obtained at 70 eV on a HP 5987 A, and the intensities are reported as a percentage relative to the base peak after the corresponding *m/z* value.

General Procedure of Synthesis of Compounds 2 and 3. To a stirred solution of the corresponding amino aziridine **1** (0.2 mmol) in dry toluene (2 mL) were added $BF_3{\cdot}OEt_2$ (0.025 mL, 0.2 mmol) and the corresponding thiol (3 equiv) at room temperature. After stirring at reflux temperature 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_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography on silica gel (hexane/EtOAc 10:1) provided pure compounds **2**. Yields are given in Tables 1 and 2.

(2*S*,3*S*)-*N*^{3},*N*^{3}-Dibenzyl-2-(pentylthio)-*N*^{1}-propylbutan-1,3-diamine (2a): yellow oil; $[\alpha]^{25}_D = +11.3$ (*c* 1.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.22 (m, 10 H), 3.82 (d, J = 13.7 Hz, 2 H), 3.44 (d, J = 13.7 Hz, 2 H), 2.91−2.86 (m, 1 H), 2.73−2.47 (m, 8 H), 2.33−2.24 (m, 1 H), 1.58−1.50 (m, 4 H), 1.38−1.33 (m, 3 H), 1.15 (d, J = 6.8 Hz, 3 H), 1.00−0.91 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7 (2 × C), 128.7 (4 × CH), 128.1 (4 × CH), 126.8 (2 × CH), 61.1 (CH), 56.7 (CH), 54.0 (2 × CH), 49.9 (CH_2), 34.5 (CH_2), 33.0 (CH_2), 30.9 (CH_2), 29.2 (CH_2), 23.5 (CH_2), 22.1 (CH_2), 13.8 (CH_3), 11.9 (CH_3), 9.0 (CH_3); MS (70 eV, EI) *m/z* (%) 333 ($M^+ - C_7H_7$, 2), 225 (60), 224 (100), 181 (22), 91 (97); HRMS (70 eV) calcd for $C_{19}H_{43}N_2S$ ($M^+ - C_7H_7$) 321.2359, found 321.2351; IR (neat) 3309, 3027, 2928, 1494, 1454, 1138 cm^{-1}; R_f = 0.41 (hexane/EtOAc 3:1).

(2*S*,3*S*)-*N*^{3},*N*^{3}-Dibenzyl-2-(cyclohexylthio)-*N*^{1}-propylbutan-1,3-diamine (2b): colorless oil; $[\alpha]^{25}_D = +8.3$ (*c* 1.39, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.24 (m, 10 H), 3.79 (d, J = 13.5 Hz, 2 H), 3.40 (d, J = 13.5 Hz, 2 H), 2.87−2.80 (m, 1 H), 2.69 (dd, J = 12.5, 4.6 Hz, 1 H), 2.63−2.53 (m, 2 H), 2.47 (dd, J = 12.7, 4.0 Hz, 1 H), 2.29−2.21 (m, 2 H), 1.96−1.85 (m, 2 H), 1.74 (br s, 1 H), 1.73−1.46 (m, 3 H), 1.33−1.19 (m, 7 H), 1.12 (d, J = 6.7 Hz, 3 H), 0.94 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8 (2 × C), 128.8 (4 × CH), 128.2 (4 × CH), 126.9 (2 × CH), 61.3 (CH), 56.8 (CH), 54.1 (2 × CH_2), 50.0 (CH_2), 44.2 (CH), 33.7 (CH_2), 33.6 (CH_2), 32.3 (CH_2), 29.6 (CH_2), 26.1 (CH_2), 25.8 (CH_2), 23.6 (CH_2), 12.0 (CH_3), 9.0 (CH_3); MS (70 eV, EI) *m/z* (%) 333 ($M^+ - C_7H_7$, <1), 225 (13), 224 (71), 132 (23), 91 (100), 65 (18); HRMS (70 eV) calcd for $C_{20}H_{33}N_2S$ ($M^+ - C_7H_7$) 333.2359, found 333.2361; IR (neat) 3310, 3028, 2926, 2850, 1494, 1450 cm^{-1}; R_f = 0.25 (hexane/EtOAc 3:1). Anal. Calcd for $C_{27}H_{40}N_2S$: C, 76.36; H, 9.49; N, 6.60. Found: C, 76.23; H, 9.55; N, 6.68.

(2*S*,3*S*)-*N*^{1}-Allyl-*N*^{3},*N*^{3}-dibenzyl-2-(2-phenylethylthio)-butan-1,3-diamine (2c): yellow oil; $[\alpha]^{25}_D = +11.1$ (*c* 0.90, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.20 (m, 15 H), 6.02−5.90 (m, 1 H), 5.27−5.15 (m, 2 H), 3.81 (d, J = 13.5 Hz, 2 H), 3.48−3.36 (m, 3 H), 3.06 (dd, J = 13.9, 6.6 Hz, 1 H), 2.98−2.69 (m, 7 H), 2.52 (dd, J = 12.7, 3.5 Hz, 1 H), 1.14 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.6 (C), 139.5 (2 × C), 136.8 (CH), 128.7, 128.3, 128.2, 126.9, 126.1 (15 × CH), 115.5 (CH_2), 60.1 (CH), 56.1 (CH), 53.9 (2 × CH_2), 50.8 (CH_2), 36.3 (CH_2), 34.5 (2 × CH_2), 8.9 (CH_3); MS (70 eV, EI) *m/z* (%) 353 ($M^+ - C_7H_7$, <1), 224 (76), 215 (39), 196 (27), 91 (100); HRMS (70 eV) calcd for $C_{22}H_{29}N_2S$ ($M^+ - C_7H_7$) 252.1040, found 252.2046; IR (neat) 3306, 3027, 2923, 2803, 1603, 1495, 1453 cm^{-1}; R_f = 0.28 (hexane/EtOAc 3:1). Anal. Calcd for $C_{29}H_{36}N_2S$: C, 78.33; H, 8.16; N, 6.30. Found: C, 78.51; H, 8.06; N, 6.22.

(2*S*,3*S*)-*N*^{1},*N*^{3},*N*^{3}-Tribenzyl-4-benzyloxy-2-(cyclohexylthio)butan-1,3-diamine (2d): colorless oil; $[\alpha]^{25}_D = -20.4$ (*c* 0.62, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.28 (m, 20 H), 3.98−3.70 (m, 10 H), 3.13−2.93 (m, 2 H), 2.66 (dd, J = 12.5, 6.0 Hz, 1 H), 2.50 (br s, 1 H), 2.00−1.68 (m, 6 H), 1.35−1.30 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1 (C), 139.7 (2 × C), 139.6 (C), 128.8, 128.3, 128.1, 127.0, 126.9 (20 × CH), 59.8 (CH), 59.3 (CH_2), 58.1 (CH), 55.4 (2 × CH_2), 53.0 (CH_2), 51.7 (CH_2), 43.5 (CH), 33.6 (CH_2), 33.5 (CH_2), 31.0 (CH_2), 25.9 (2 × CH_2), 25.6 (CH_2); IR (neat) 3300, 3027, 2927, 2851, 1494, 1452 cm^{-1}; R_f = 0.29 (hexane/EtOAc 3:1). Anal. Calcd for $C_{38}H_{46}N_2OS$: C, 78.85; H, 8.01; N, 4.84. Found: C, 78.97; H, 7.95; N, 4.92.

(2*S*,3*S*)-*N*^{1},*N*^{3},*N*^{3}-Tribenzyl-4-benzyloxy-2-(benzylthio)-butan-1,3-diamine (2e): yellow oil; $[\alpha]^{25}_D = -18.9$ (*c* 1.38, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.23 (m, 25 H), 3.99−3.44 (m, 13 H), 3.10−2.81 (m, 3 H), 2.56 (dd, J = 13.1, 6.1 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.6 (4 × C), 137.9 (C), 129.0, 128.7, 128.5, 128.2, 128.1, 127.0 (25 × CH), 59.4 (CH_2), 59.2 (CH), 57.0 (CH), 55.3 (2 × CH_2), 53.0 (CH_2), 51.4 (CH_2), 35.9 (CH_2), 32.2 (CH_2); MS (70 eV, EI) *m/z* (%) 387 ($M^+ - C_{14}H_{15}$, <1), 240 (47), 223 (30), 132 (31), 91 (100), 65 (27); HRMS (70 eV) calcd for $C_{25}H_{27}N_2S$ ($M^+ - C_{14}H_{15}$) 387.1889, found 387.1876; IR (neat) 3301, 3027, 2923, 1602, 1494, 1454 cm^{-1}; R_f = 0.26 (hexane/EtOAc 3:1). Anal. Calcd for $C_{39}H_{42}N_2OS$: C, 79.82; H, 7.21; N, 4.77. Found: C, 79.99; H, 7.15; N, 4.82.

(2*SR*,3*SR*)-*N*-Allyl-5-methyl-2,3-bis(pentylthio)hexan-1-amine (3a): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97−5.83 (m, 1 H), 5.20−5.06 (m, 2 H), 3.25 (d, J = 6.0 Hz, 2 H), 3.06 (dd, J = 12.0, 4.3 Hz, 1 H), 2.99−2.88 (m, 2 H), 2.59−2.47 (m, 5 H), 1.84−1.80 (m, 1 H), 1.75 (br s, 1 H), 1.64−1.51 (m, 4 H), 1.33−1.21 (m, 9 H), 0.92−0.85 (m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7 (CH), 115.8 (CH_2), 52.2 (CH_2), 51.7 (CH), 49.8 (CH_2), 47.6 (CH), 40.0 (CH_2), 32.7 (CH_2), 32.0 (CH_2), 31.0 (CH_2), 30.9 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 25.4 (CH), 23.3 (CH_3), 22.2 (2 × CH_2), 21.4 (CH_3), 13.9 (2 × CH_3); MS (70 eV, EI) *m/z* (%) 359 (M^+, <1), 256 (14), 186 (36), 152 (100), 117 (47), 70 (46); HRMS (70 eV) calcd for $C_{20}H_{41}NS_2$ (M^+) 359.2680, found 359.2672; IR (neat) 3078, 2956, 2927, 2360, 2342, 1466 cm^{-1}; R_f = 0.55 (hexane/EtOAc 3:1). Anal. Calcd for $C_{20}H_{41}NS_2$: C, 66.79; H, 11.49; N, 3.89. Found: C, 66.91; H, 11.32; N, 3.72.

(2*SR*,3*SR*)-*N*-Allyl-5-methyl-2,3-bis(2-phenylethylthio)-hexan-1-amine (3b): yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.23 (m, 10 H), 6.00−5.90 (m, 1 H), 5.29−5.15 (m, 2 H), 3.33−3.31 (m, 1 H), 3.17−2.82 (m, 11 H), 2.67 (dd, J = 11.4, 8.5 Hz, 1 H), 1.97−1.65 (m, 4 H), 1.37−1.34 (m, 1 H), 0.98 (apparent t, J = 6.7 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3 (CH), 136.6 (2 × C), 128.3, 128.2, 128.0, 126.8, 126.2 (10 × CH), 115.8 (CH_2), 52.1 (CH_2 and CH), 49.8 (CH_2), 47.9 (CH), 40.1 (CH_2), 36.6 (CH_2), 36.4 (CH_2), 34.1 (CH_2), 33.6 (CH_2), 25.4 (CH), 23.2 (CH_3), 21.5 (CH_3); IR (neat) 3315, 3027, 2954, 2924, 2867, 1496, 1454 cm^{-1}; R_f = 0.34 (hexane/EtOAc 3:1). Anal. Calcd for $C_{26}H_{37}NS_2$: C, 73.01; H, 8.72; N, 3.27. Found: C, 73.21; H, 8.61; N, 3.40.

(2*SR*,3*SR*)-*N*-Benzyl-5-methyl-2,3-bis(pentylthio)hexan-1-amine (3c): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.24 (m, 5 H), 3.83−3.77 (m, 3 H), 3.11 (dd, J = 11.7, 4.3 Hz, 1 H), 3.02−2.93 (m, 3 H), 2.64 (dd, J = 11.7, 8.8 Hz, 1 H), 2.52 (dd, J = 14.2, 7.1 Hz, 4 H), 1.95 (br s, 1 H), 1.87−1.83 (m, 2 H), 1.61−1.53 (m, 4 H), 1.39−1.12 (m, 6 H), 0.93−0.87 (m, 13

H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2 (C), 128.3 (2 × CH), 128.0 (2 × CH), 126.8 (CH), 53.8 (CH_2), 51.8 (CH), 50.1 (CH_2), 47.6 (CH), 32.7 (CH_2), 32.1 (CH_2), 31.0 (2 × CH_2), 29.7 (CH_2), 29.5 (CH_2), 25.5 (CH), 23.3 (CH_3), 22.2 (3 × CH_2), 21.5 (CH_3), 13.9 (2 × CH_3); MS (70 eV, EI) *m/z* (%) 409 (M^+, <1), 266 (69), 202 (16), 186 (22), 120 (100), 91 (98); HRMS (70 eV) calcd for $C_{24}H_{43}NS_2$ (M^+) 409.2837, found 409.2826; IR (neat) 3027, 2927, 2858, 2360, 2342, 1457 cm^{-1}; R_f = 0.49 (hexane/EtOAc 3:1). Anal. Calcd for $C_{24}H_{43}NS_2$: C, 70.35; H, 10.58; N, 3.42. Found: C, 70.21; H, 10.71; N, 3.31.

(2*SR*,3*SR*)-*N*-Benzyl-5-methyl-2,3-bis(octylthio)hexan-1-amine (3d): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5 H), 3.86 (AB syst., J = 13.4 Hz, 2 H), 3.15 (dd, J = 11.7, 4.1 Hz, 1 H), 3.05−2.96 (m, 2 H), 2.67 (dd, J = 12.1, 2.8 Hz, 1 H), 2.60−2.52 (m, 4 H), 1.93 (br s, 1 H), 1.63−1.59 (m, 5 H), 1.43−1.21 (m, 22 H), 0.97−0.90 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7 (C), 128.8 (2 × CH), 128.5 (2 × CH), 127.3 (CH), 54.3 (CH_2), 52.3 (CH), 50.6 (CH_2), 48.1 (CH), 40.8 (CH_2), 33.3 (CH_2), 32.7 (CH_2), 32.3 (2 × CH_2), 30.6 (CH_2), 30.4 (CH_2), 29.6 (4 × CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.0 (CH), 23.9 (CH_3), 23.1 (2 × CH_2), 22.0 (CH_3), 14.5 (2 × CH_3); MS (70 eV, EI) *m/z* (%) 493 (M^+, <1), 120 (68), 91 (100), 71 (32), 57 (48); HRMS (70 eV) calcd for $C_{22}H_{38}NS$ ($M^+ - C_8H_{17}S$) 348.2719, found 348.2726; IR (neat) 3425, 2955, 2925, 2854, 1453 cm^{-1}; R_f = 0.45 (hexane/EtOAc 3:1). Anal. Calcd for $C_{30}H_{55}NS_2$: C, 72.95; H, 11.22; N, 2.84. Found: C, 73.11; H, 11.10; N, 2.99.

(2*SR*,3*SR*)-*N*-Benzyl-2-methyl-2,3-bis(benzylthio)hexan-1-amine (3e): yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.30 (m, 15 H), 3.67 (d, J = 14.6 Hz, 6 H), 3.06 (dd, J = 12.1, 5.2 Hz, 1 H), 2.98−2.92 (m, 1 H), 2.87−2.81 (m, 1 H), 2.65 (dd, J = 12.1, 8.3 Hz, 1 H), 1.67−1.50 (m, 3 H), 1.34−1.25 (m, 1 H), 0.85 (d, J = 6.3 Hz, 3 H), 0.72 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2 (C), 138.5 (C), 138.4 (C), 128.9, 128.4, 128.3, 128.2, 127.9, 127.0, 126.9, 126.7 (15 × CH), 53.4 (CH_2), 50.3 (CH_2 and CH), 46.1 (CH), 40.6 (CH_2), 36.8 (CH_2), 36.3 (CH_2), 25.1 (CH), 23.0 (CH_3), 21.5 (CH_3); IR (neat) 3061, 3027, 2954, 2925, 2867, 1494, 1453 cm^{-1}; R_f = 0.42 (hexane/EtOAc 3:1). Anal. Calcd for $C_{28}H_{35}NS_2$: C, 74.78; H, 7.84; N, 3.11. Found: C, 74.91; H, 8.02; N, 3.01.

(2*SR*,3*SR*)-*N*-Benzyl-2,3-bis(octylthio)-4-phenylbutan-1-amine (3f): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.24 (m, 10 H), 3.79 (AB syst, J = 14.0 Hz, 2 H), 3.33−3.14 (m, 3 H), 3.04−3.00 (m, 1 H), 2.86−2.77 (m, 2 H), 2.60 (t, J = 7.3 Hz, 2 H), 2.40 (t, J = 7.3 Hz, 2 H), 1.84 (br s, 1 H), 1.66−1.58 (m, 2 H), 1.46−1.27 (m, 22 H), 0.96−0.91 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1 (C), 140.0 (C), 129.2 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 128.0 (2 × CH), 126.8 (CH), 126.2 (CH), 53.6 (CH_2), 51.4 (CH), 51.0 (CH), 50.8 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 31.7 (3 × CH_2), 30.0 (CH_2), 29.6 (CH_2), 29.1 (4 × CH_2), 28.8 (CH_3), 28.7 (CH_2), 22.6 (2 × CH_2), 14.0 (2 × CH_3); IR (neat) 3027, 2927, 2851, 1495, 1448 cm^{-1}; R_f = 0.50 (hexane/EtOAc 3:1). Anal. Calcd for $C_{33}H_{53}NS_2$: C, 78.05; H, 10.12; N, 2.65. Found: C, 78.19; H, 10.01; N, 2.79.

(2*SR*,3*SR*)-*N*-Benzyl-2,3-bis(cyclohexylthio)-4-phenylbutan-1-amine (3g): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.30 (m, 10 H), 3.81 (s, 2 H), 3.34−3.13 (m, 3 H), 3.05 (ddd, J = 9.1, 7.2, 1.9 Hz, 1 H), 2.87−2.78 (m, 2 H), 2.76−2.63 (m, 1 H), 2.36−2.33 (m, 1 H), 1.99−1.54 (m, 11 H), 1.41−1.14 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2 (C), 140.1 (C), 129.2 (2 × CH), 128.2 (2 × CH), 128.0 (2 × CH), 127.9 (2 × CH), 126.8 (CH), 126.1 (CH), 53.5 (CH_2), 51.4 (CH_2), 49.6 (CH), 49.3 (CH), 44.4 (CH), 44.0 (CH), 39.9 (CH_2), 34.2 (2 × CH_2), 33.8 (CH_2), 33.6 (CH_2), 26.0 (2 × CH_2), 25.9 (CH_2), 25.8 (2 × CH_2), 25.6 (2 × CH_2); MS (70 eV, EI) *m/z* (%) 467 (M^+, 2), 352 (34), 238 (92), 236 (52), 232 (40), 130 (43), 120 (100), 55 (22); HRMS (70 eV) calcd for $C_{29}H_{41}NS_2$ (M^+) 467.2675, found 467.2661; IR (neat) 3062, 3027, 2925, 2854, 1495, 1454 cm^{-1}; R_f = 0.53 (hexane/EtOAc 3:1). Anal. Calcd for $C_{29}H_{41}NS_2$: C, 74.46; H, 8.83; N, 2.99. Found: C, 74.61; H, 8.72; N, 2.91.

(2*SR*,3*SR*)-*N*-Benzyl-2,3-bis(phenylethylthio)-4-phenylbutan-1-amine (3h): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.10 (m, 20 H), 3.77 (AB syst, J = 14.2 Hz, 2 H), 3.29−3.24 (m, 2 H), 3.15 (dd, J = 11.9, 6.1 Hz, 1 H), 3.05.3.02 (m, 1 H), 2.95−2.64 (m, 10 H), 1.78 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3 (C), 140.2 (C), 140.1 (C), 139.7 (C), 129.2, 128.4, 128.3, 128.0, 126.9, 126.3, 126.2 (20 × CH), 53.5 (CH_2), 51.6 (CH), 51.2 (CH), 50.1 (CH_2), 39.2 (CH_2), 36.5 (CH_2), 36.3 (CH_2), 34.1 (CH_2), 34.0 (CH_2); MS (70 eV, EI) *m/z* (%) 467 ($M^+ - C_8H_9S$, 5), 300 (41), 120 (64), 105 (29), 91 (100), 65 (26); HRMS (70 eV) calcd for $C_{25}H_{19}NS$ ($M^+ - C_8H_9S$) 374.1937, found 374.1951; IR (neat) 3061, 3026, 2919, 2846, 1603, 1493, 1454 cm^{-1}; R_f = 0.37 (hexane/EtOAc 3:1). Anal. Calcd for $C_{33}H_{37}NS_2$: C, 77.45; H, 7.29; N, 2.74. Found: C, 77.33; H, 7.36; N, 2.82.

Prepartion of Compound 4g. To a stirred solution of the amino aziridine **3g** (70 mg, 0.15 mmol) in dry THF (2 mL) was added PhCOCl (0.019 mL, 0.16 mmol) at room temperature. After stirring 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_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography on silica gel (hexane/EtOAc 20:1) provided pure compounds **4g** (76 mg, 89% yield).

(2*SR*,3*SR*)-1-*N*-Benzyl-*N*-[2,3-bis(cyclohexylthio)-4-phenylbutyl)]benzamide (4g): white solid; mp 72−76 °C; ^{1}H NMR (400 MHz, C_6D_6, T = 80 °C) δ 7.55−7.16 (m, 15 H), 4.90 (s, 2 H), 4.47−4.35 (m, 1 H), 3.72 (dd, J = 15.4, 3.9 Hz, 2 H), 3.50−3.43 (m, 2 H), 3.08−3.03 (m, 1 H), 2.71−2.66 (m, 1 H), 2.02−1.87 (m, 4 H), 1.76−1.65 (m, 4 H), 1.53−1.15 (m, 12 H); ^{13}C NMR (100 MHz, C_6D_6, T = 80 °C) δ 171.6 (C), 140.4 (C), 137.9 (C), 137.6 (C), 129.5, 129.0, 128.6, 128.5, 128.1, 126.3 (15 × CH), 50.0 (CH), 49.8 (CH_2), 47.8 (CH), 44.7 (CH), 44.3 (CH), 40.3 (CH_2), 34.5 (2 × CH_2), 34.1 (CH_2), 34.0 (CH_2), 26.0 (3 × CH_2), 25.8 (4 × CH_2); IR (neat) 3452, 2928, 2852, 1634, 1495, 1447, 1414 cm^{-1}; R_f = 0.65 (hexane/EtOAc 3:1). Anal. Calcd for $C_{36}H_{45}NOS_2$: C, 75.61; H, 7.93; N, 2.45. Found: C, 75.78; H, 7.79; N, 2.55.

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Supporting Information Available: ^{13}C NMR spectra of compounds **2**, **3**, and **4g**. This material is available free of charge via Internet at http://pubs.acs.org.

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