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Ring opening of chiral 2-(1-aminoalkyl)epoxides by aliphatic thiols with total selectivity: synthesis of enantiopure 3-amino-1-(alkylthio)alkan-2-ols

José M. Concellón,* Virginia del Solar, José Ramón Suárez and Elena G. Blanco

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

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Abstract—We have studied the thiolysis of (2*R*,1′*S*)- or (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides **1** or **2** in the presence of $BF_3 \cdot OEt_2$. The ring opening took place at C-3 with complete regioselectivity, affording the corresponding enantiopure (2*R*,3*S*)- or (2*S*,3*S*)-3-amino-1-(alkylthio)alkan-2-ols **3** or **4** in good or high yield. The structures of compounds **3** and **4** have been proposed based on HMBC NMR experiments.

1. Introduction

Thiolysis of epoxides is an efficient and widely used method to obtain β-hydroxy sulfide moieties, which are useful intermediates in organic synthesis. So, β-hydroxy sulfides have been used for the synthesis of allylalcohols,[1] cyclic sulfides,[2] thioketones,[3] a number of important natural products,[4] and a variety of compounds with pharmacological and/or biological activity.[5] In general, the thiolysis of epoxides is achieved by using thiolates under basic conditions[5c,6] or with thiols in the presence of some activating agent.[7] Although some of these methods afforded β-hydroxy sulfides with high regioselectivity[7j,k] an alternative synthesis of enantiopure β-hydroxy sulfides with complete selectivity, in which different diastereoisomers could be available, would be still desirable.

Previously, we reported the synthesis of (2*R*,1′*S*)- or (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides **1** or **2** in enantiopure form.[8] So, compounds **1** were obtained by complete stereoselective reduction of α-amino-α′-chloroketones (easily available from natural α-aminoacids) with $LiAlH_4$. Epoxides **2** were synthesized by highly stereoselective addition reaction of iodomethyllithium, generated in situ (from diiodomethane and methyllithium), to α-aminoaldehydes. Recently, we reported the ring opening of amino epoxides at C-3 by ketones,[9] nitriles,[10] carboxylic acids,[11] and organolithium compounds[12] with total regioselectivity.

In the course of our quest for developing synthetic applications of the enantiopure amino epoxides **1** and **2**, we report herein the reaction of chiral (2*R*,1′*S*)- or (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides **1** or **2** with different thiols, giving the corresponding (2*R*,3*S*)- or (2*S*,3*S*)-3-amino-1-(alkylthio)-alkan-2-ols **3** or **4** in enantiopure form. The opening of the oxirane ring at C-3 proceeded with total regioselectivity. The regiochemistry of the ring opening and, consequently, structure of compounds **3** was unambiguously established by HMBC NMR experiments. The prepared compounds **3** and **4** are precursors of 3-amino vinyl sulfones,[13] starting materials to prepare peptidyl vinyl sulfones, which have been shown to be useful, potent, and selective inhibitors of cysteine proteases.[14]

2. Results and discussion

2.1. Synthesis of (2*R*,3*S*)-3-amino-1-(alkylthio)alkan-2-ols 3

Our first attempts to perform the thiolysis were carried out from amino epoxides **1**, and initially, the attempts to perform the thiolysis of compound **1** were carried out without the presence of an activating agent to open the oxirane ring. In all cases, under several reaction conditions, no reaction was observed and the starting compounds were recovered unchanged. Based on our previous results,[9–11] we used $BF_3 \cdot OEt_2$ to catalyze the ring-opening reactions of **1** with thiols and, after study of the reaction conditions, the best results were obtained by using 3 equiv of thiol in toluene at 70 °C. So, treatment of a solution of (2*R*,1′*S*)-2-(1-aminoalkyl)epoxides **1** in toluene at 70 °C with 3 equiv of different thiols in the presence of $BF_3 \cdot OEt_2$, during 4 h, afforded the

* Corresponding author. E-mail: jmcg@uniovi.es

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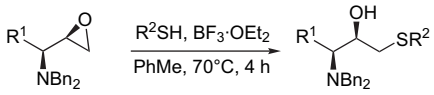
corresponding (2*R*,3*S*)-3-amino-1-(alkylthio)alkan-2-ols **3** in good or high yields and with total selectivity (Scheme 1 and Table 1).



1 **3**

Scheme 1. Synthesis of (2*R*,3*S*)-3-amino-1-(alkylthio)alkan-2-ols **3**.

Table 1. Synthesis of (2*R*,3*S*)-3-amino-1-(alkylthio)alkan-2-ols **3**

Entry	3	R^1	R^2	Yield[a] (%)
1	**3a**	Me	n-C_5H_{11}	74
2	**3b**	Me	Bn	81
3	**3c**	Me	$PhCH_2CH_2$	79
4	**3d**	*i*-Bu	Cy	80
5	**3e**	*i*-Bu	Bn	76
6	**3f**	*i*-Bu	$PhCH_2CH_2$	78
7	**3g**	Bn	n-C_5H_{11}	82
8	**3h**	Bn	Cy	77
9	**3i**	Bn	$PhCH_2CH_2$	78

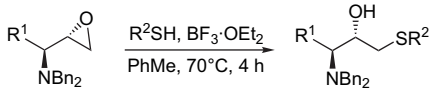
[a] Isolated yield of pure compound **3** after column chromatography based on the starting amino epoxide **1**.

As is shown in Table 1, this transformation appears to be general and it can be performed with different aliphatic thiols (cyclic, linear, and phenyl-substituted) and with amino epoxides **1a–c**, derived from alanine, leucine, and phenylalanine.

The complete regioselectivity was determined by ^1H and ^{13}C NMR analyses (300 MHz) of the crude reaction products, and no regioisomers or byproducts were observed in all reactions, within the limits of NMR assay.

2.2. Synthesis of (2*S*,3*S*)-3-amino-1-(alkylthio)alkan-2-ols 4

To extend the scope of this method, we performed the reaction of *anti*-amino epoxides **2** with thiols, under the same reaction conditions ($BF_3\cdot OEt_2$, toluene, 70 °C, 4 h). In all cases, the corresponding (2*S*,3*S*)-3-amino-1-(alkylthio)-alkan-2-ols **4** were obtained in good yields, with high selectivity, and no important differences were observed in the yields of the reactions from amino epoxide **1** or from **2** (Scheme 2 and Table 2).



2 **4**

Scheme 2. Synthesis of (2*S*,3*S*)-3-amino-1-(alkylthio)alkan-2-ols **4**.

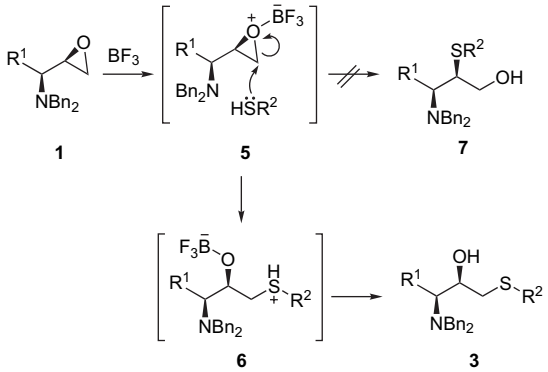
The selectivity of thiolysis of amino epoxides **4** was determined by ^1H and ^{13}C NMR analyses (300 MHz) of the crude reaction products. ^1H and ^{13}C NMR spectral data of the crude reaction products obtained from leucine and phenylalanine show the presence of a mixture of diastereoisomers **4** in the same relationship as the starting amino epoxides **2**. So, the synthesis of (2*S*,3*S*)-3-amino-1-(alkylthio)alkan-2-ols **4** with the same diastereoisomeric excess (de) as the starting amino epoxides **2**[8] was an indirect support of the total selectivity of the ring-opening reaction. After purification of compounds **4** by conventional column chromatography, the major diastereoisomer was isolated as single stereoisomer.

Table 2. Synthesis of (2*S*,3*S*)-3-amino-1-(alkylthio)alkan-2-ols **4**

Entry	4	R^1	R^2	de[a] (%)	Yield[b] (%)
1	**4a**	Me	n-C_5H_{11}	>98 (>98)	77
2	**4b**	Me	Bn	>98 (>98)	79
3	**4c**	*i*-Bu	Cy	89 (91)	72
4	**4d**	*i*-Bu	Bn	90 (91)	71
5	**4e**	Bn	Cy	90 (92)	73
6	**4f**	Bn	$PhCH_2CH_2$	91 (92)	72

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

The structures of compounds **3** and **4**, as depicted in Schemes 1 and 2, were established on the basis of IR, high resolution mass spectra, ^1H and ^{13}C spectra of compounds **3** and **4** and HSQC and HMBC NMR experiments of the obtained diamino alcohols **3b** and **3c**. Thus, the presence of a broad band ranging between 3440 and 3396 cm^{-1} in the IR spectra of compounds **3** and **4** was assignable to their alcohol functionality. Moreover, the HSQC NMR experiments with **3b** and **3c** permitted to establish a correlation between the signals of ^1H with ^{13}C NMR spectra. HMBC NMR experiments of **3b** and **3c** showed correlation between both methylenes bonded to sulfur atom $PhCH_2SCH_2CH(OH)$ and $PhCH_2CH_2SCH_2CH(OH)$, respectively. No interaction between the hydrogen of the *CH*OH and the methylene group bonded to sulfur $PhCH_2S$ or $PhCH_2CH_2S$ was observed. Thus, the structure **7** (Scheme 3) was not according to this HMBC NMR experiment and, consequently, this structure was ruled out. Hence, all of these data support the assigned structures for compounds **3** and **4**. The regiochemistry of the ring opening of amino epoxides by thiols is according to previous reactions of amino epoxides **1** with ketones,[9] nitriles,[10] carboxylic acids,[11] and organolithium compounds.



Scheme 3. Mechanism proposed.

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.

2.3. Mechanism

Scheme 3 shows the proposed mechanism to explain this thiolysis. Formation of compounds **3** may be explained by assuming that, in the first step of the reaction, selective coordination of the Lewis acid with the oxygen takes place. This selective coordination of the Lewis acid with the oxygen instead of the dibenzylamino group can be justified on steric grounds. So, the isolation of the corresponding aziridine–borane complex after treatment of chiral 2-(1-dibenzylaminoalkyl)aziridines with $BF_3 \cdot OEt_2$ and subsequent reduction with $LiAlH_4$[15] was an indirect support of the absence of coordination between $BF_3 \cdot OEt_2$ and the dibenzylamino group. Presumably, the activated oxirane–Lewis acid complex **5** could be attacked at the C-3 position (the most sterically accessible) by the thiol leading to the intermediate **6**, which after hydrolysis could give the (2*R*,3*S*)-3-amino-1-(alkylthio)alkan-2-ols **3**. A similar reaction from amino epoxides **2** with thiols could produce, after hydrolysis, (2*S*,3*S*)-3-amino-1-(alkylthio)alkan-2-ols **4**.

3. Conclusion

We have achieved the synthesis of (2*R*,3*S*)- or (2*S*,3*S*)-3-amino-1-(alkylthio)alkan-2-ols **3** or **4** in enantiopure form and in high yield by the complete regioselective ring opening of amino epoxides **1** or **2** with thiols in the presence of $BF_3 \cdot OEt_2$. The structures of compounds **3** and **4** have been proposed based on the HSQC and HMBC NMR experiments of compounds **3b** and **3c**.

4. Experimental

4.1. General remarks

Reactions which required an inert atmosphere were conducted under dry nitrogen, and the glassware was oven dried. THF was distilled from sodium/benzophenone ketyl immediately prior to use. All reagents were commercially available and were used without further purification. Silica gel for flash chromatography was purchased from Merck (230–400 mesh), and compounds were visualized on analytical thin layer chromatography (TLC) by UV light (254 nm). ^{1}H NMR spectra were recorded at 200 or 300 MHz. ^{13}C NMR spectra and DEPT experiments were determined at 50 or 75 MHz. Chemical shifts are given in parts per million relative to tetramethylsilane (TMS), which is used as an internal standard, and coupling constants *J* are reported in hertz. The diastereoisomeric excesses were obtained from ^{1}H NMR analysis and GC–MS of crude products. GC–MS and HRMS were measured at 70 eV. Only the most important IR absorptions (cm^{-1}) and the molecular ions and/or base peaks in MS are given.

4.2. General procedure for synthesis of 3 and 4

To a stirred solution of the corresponding amino epoxide **1** or **2** (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 (0.6 mmol, 3.0 equiv) at room temperature. After stirring at 70 °C for 4 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 **3** and **4**.

4.2.1. (2*R*,3*S*)-3-(Dibenzylamino)-1-(pentylthio)butan-2-ol (3a). Colorless oil. $[\alpha]_D^{20}$ +8.1 (*c* 2.10, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35–7.28 (m, 10H), 3.93 (s, 4H), 3.68 (br s, 1H), 3.59–3.49 (m, 1H), 3.45–3.31 (m, 1H), 3.18 (apparent qt, *J*=7.0 Hz, 1H), 3.06–2.89 (m, 1H), 2.54 (t, *J*=7.4 Hz, 2H), 1.72–1.58 (m, 2H), 1.47–1.39 (m, 4H), 1.31 (d, *J*=7.0 Hz, 3H), 0.96 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.4 (2×C), 129.2 (4×CH), 128.4 (4×CH), 127.1 (2×CH), 62.3 (CH), 59.0 (CH_2), 54.1 (2×CH_2), 39.7 (CH), 31.2 (CH_2), 30.9 (CH_2), 29.1 (CH_2), 22.3 (CH_2), 18.9 (CH_3), 13.9 (CH_3); MS (70 eV, EI) *m/z* (%) 371 (M^+, <1), 240 (100), 224 (16), 91 (93); HRMS (70 eV) calcd for $C_{23}H_{33}NOS$ (M^+) 371.2283, found 371.2273; IR (neat): 3396, 2928, 2361, 1602, 1494, 1454, 1377 cm^{-1}; R_f=0.34 (hexane/EtOAc 5:1). Anal. Calcd for $C_{23}H_{33}NOS$: C, 74.34; H, 8.95; N, 3.77; O, 4.31; S, 8.63. Found: C, 74.50; H, 8.87; N, 3.80; O, 4.28; S, 8.70.

4.2.2. (2*R*,3*S*)-1-(Benzylthio)-3-(dibenzylamino)butan-2-ol (3b). Colorless oil. $[\alpha]_D^{20}$ −19.7 (*c* 1.19, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43–7.24 (m, 15H), 3.90–3.72 (m, 6H), 3.62 (dd, *J*=10.4, 5.0 Hz, 1H), 3.40 (apparent t, *J*=9.7 Hz, 1H), 3.07–2.86 (m, 2H), 1.33 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.3 (2×C), 138.1 (C), 129.1 (4×CH), 128.9 (2×CH), 128.4 (2×CH), 128.3 (4×CH), 127.1 (3×CH), 62.2 (CH), 59.1 (CH_2), 54.0 (2×CH_2), 39.0 (CH), 35.2 (CH_2), 18.8 (CH_3); MS (70 eV, EI) *m/z* (%) 391 (M^+, <1), 240 (26), 91 (100); HRMS (70 eV) calcd for $C_{25}H_{29}NOS$ (M^+) 391.1970, found 391.1942; IR (neat): 3420, 3028, 2360, 1602, 1494, 1453, 1376 cm^{-1}; R_f=0.23 (hexane/EtOAc 5:1). Anal. Calcd for $C_{25}H_{29}NOS$: C, 76.68; H, 7.46; N, 3.58; O, 4.09; S, 8.19. Found: C, 76.81; H, 7.53; N, 3.55; O, 4.03; S, 8.11.

4.2.3. (2*R*,3*S*)-3-(Dibenzylamino)-1-(2-phenylethylthio)-butan-2-ol (3c). Colorless oil. $[\alpha]_D^{20}$ −3.3 (*c* 1.14, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42–7.24 (m, 15H), 3.88 (s, 4H), 3.67 (br s, 1H), 3.54 (apparent t, *J*=9.8 Hz, 1H), 3.20 (apparent qt, *J*=6.7 Hz, 1H), 3.00–2.77 (m, 6H), 1.32 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.3 (C), 139.3 (2×C), 129.2 (5×CH), 128.4 (7×CH), 127.2 (2×CH), 126.3 (CH), 62.4 (CH), 58.9 (CH_2), 54.0 (2×CH_2), 39.9 (CH), 35.9 (CH_2), 32.3 (CH_2), 18.5 (CH_3); MS (70 eV, EI) *m/z* (%) 390 (M^+-CH_3, <1), 241 (50), 169 (34), 131 (36), 119 (50), 105 (33), 91 (100), 68 (42); HRMS (70 eV) calcd for $C_{25}H_{28}NOS$ (M^+-CH_3) 390.1892, found 390.1875; IR (neat): 3405, 3028, 2926, 2361, 1603, 1495, 1454, 1375 cm^{-1}; R_f=0.22 (hexane/EtOAc 5:1). Anal. Calcd for $C_{26}H_{31}NOS$: C, 76.99; H, 7.70; N, 3.45; O, 3.94; S, 7.91. Found: C, 76.82; H, 7.78; N, 3.41; O, 3.99; S, 8.00.

4.2.4. (2*R*,3*S*)-1-(Cyclohexylthio)-3-(dibenzylamino)-5-methylhexan-2-ol (3d). Colorless oil. $[\alpha]_D^{20}$ +47.7 (*c* 1.67, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21–7.11 (m,

10H), 3.79 (d, J=13.5 Hz, 2H), 3.77–3.71 (m, 1H), 3.66 (d, J=13.5 Hz, 2H), 3.36–3.24 (m, 2H), 3.02–2.92 (m, 1H), 2.57 (br s, 1H), 2.26–2.25 (m, 1H), 1.85–1.82 (m, 1H), 1.71–1.58 (m, 3H), 1.52–1.43 (m, 2H), 1.25–1.07 (m, 7H), 0.83 (d, J=6.5 Hz, 3H), 0.78 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.6 (2×C), 128.8 (4×CH), 128.4 (4×CH), 127.1 (2×CH), 62.9 (CH), 58.9 (CH_2), 54.8 (2×CH_2), 43.2 (CH), 41.8 (CH), 41.2 (CH_2), 34.3 (CH_2), 33.8 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 25.8 (CH), 25.7 (CH_2), 23.5 (CH_3), 21.7 (CH_3); MS (70 eV, EI) m/z (%) 425 (M^+, <1), 241 (92), 240 (72), 91 (24), 69 (100); HRMS (70 eV) calcd for $C_{27}H_{39}NOS$ (M^+) 425.2752, found 425.2780; IR (neat): 3426, 2929, 2852, 2361, 1495, 1452, 1366 cm^{-1}; R_f=0.39 (hexane/EtOAc 5:1). Anal. Calcd for $C_{27}H_{39}NOS$: C, 75.86; H, 9.06; N, 3.40; O, 3.89; S, 7.79. Found: C, 75.73; H, 8.97; N, 3.43; O, 3.94; S, 7.86.

4.2.5. (2*R*,3*S*)-1-(Benzylthio)-3-(dibenzylamino)-5-methylhexan-2-ol (3e). Colorless oil. $[\alpha]_D^{20}$ +14.4 (c 1.26, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37–7.26 (m, 15H), 3.84 (AB syst., J=14.0 Hz, 4H), 3.75–3.71 (m, 2H), 3.70 (d, J=13.1 Hz, 1H), 3.59 (d, J=13.1 Hz, 1H), 3.16–3.06 (m, 1H), 2.98–2.89 (m, 1H), 2.29 (br s, 1H), 1.74–1.36 (m, 3H), 0.87 (d, J=6.6 Hz, 3H), 0.82 (d, J=6.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.6 (2×C), 138.4 (C), 129.0 (5×CH), 128.5 (3×CH), 128.3 (4×CH), 127.1 (3×CH), 61.9 (CH), 59.1 (CH_2), 54.7 (2×CH_2), 43.5 (CH), 41.6 (CH_2), 36.1 (CH_2), 25.2 (CH), 23.2 (CH_3), 21.9 (CH_3); MS (70 eV, EI) m/z (%) 433 (M^+, 7), 402 (34), 238 (100), 219 (48), 218 (39), 137 (39), 92 (75), 68 (35); HRMS (70 eV) calcd for $C_{28}H_{35}NOS$ (M^+) 433.2439, found 433.2452; IR (neat): 3406, 2955, 2361, 1602, 1494, 1454, 1366 cm^{-1}; R_f=0.27 (hexane/EtOAc 5:1). Anal. Calcd for $C_{28}H_{35}NOS$: C, 77.55; H, 8.14; N, 3.23; O, 3.69; S, 7.39. Found: C, 77.69; H, 8.23; N, 3.20; O, 3.73; S, 7.32.

4.2.6. (2*R*,3*S*)-3-(Dibenzylamino)-5-methyl-1-(2-phenylethylthio)hexan-2-ol (3f). Colorless oil. $[\alpha]_D^{20}$ +9.5 (c 1.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24–7.05 (m, 15H), 3.77 (d, J=13.3 Hz, 2H), 3.71 (d, J=13.3 Hz, 2H), 3.68–3.57 (m, 1H), 3.01–2.86 (m, 2H), 2.80–2.69 (m, 3H), 2.58–2.45 (m, 2H), 1.75–1.66 (m, 1H), 1.41–1.35 (m, 1H), 1.29–1.16 (m, 1H), 0.82 (d, J=6.6 Hz, 3H), 0.79 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.4 (C), 139.5 (2×C), 129.0 (4×CH), 128.4 (8×CH), 127.1 (2×CH), 126.4 (CH), 62.3 (CH), 59.1 (CH_2), 54.7 (2×CH_2), 44.1 (CH), 40.9 (CH_2), 36.0 (CH_2), 32.8 (CH_2), 25.6 (CH), 23.5 (CH_3), 21.7 (CH_3); MS (70 eV, EI) m/z (%) 447 (M^+, <1), 240 (100), 91 (21); HRMS (70 eV) calcd for $C_{29}H_{37}NOS$ (M^+) 447.2596, found 447.2618; IR (neat): 3396, 2954, 2362, 1603, 1495, 1454, 1366 cm^{-1}; R_f=0.24 (hexane/EtOAc 5:1). Anal. Calcd for $C_{29}H_{37}NOS$: C, 77.80; H, 8.33; N, 3.13; O, 3.57; S, 7.16. Found: C, 77.68; H, 8.25; N, 3.17; O, 3.52; S, 7.23.

4.2.7. (2*R*,3*S*)-3-(Dibenzylamino)-1-(pentylthio)-4-phenylbutan-2-ol (3g). Colorless oil. $[\alpha]_D^{20}$ +0.80 (c 1.17, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21–7.09 (m, 15H), 3.87 (d, J=13.4 Hz, 2H), 3.79 (d, J=13.4 Hz, 2H), 3.74 (br s, 1H), 3.66–3.60 (m, 1H), 3.04–2.94 (m, 3H), 2.66–2.58 (m, 1H), 2.51–2.49 (m, 1H), 2.09–1.94 (m, 2H), 1.30–1.16 (m, 2H), 1.10–1.05 (m, 4H), 0.74 (t, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.7 (C), 139.5 (2×C), 129.3 (2×CH), 129.1 (4×CH), 128.4 (4×CH), 128.2 (2×CH), 127.2 (2×CH), 126.3 (CH), 62.5 (CH), 59.7 (CH_2), 54.7 (2×CH_2), 48.9 (CH), 39.7 (CH_2), 32.7 (CH_2), 30.9 (CH_2), 29.0 (CH_2), 22.1 (CH_2), 13.9 (CH_3); MS (70 eV, EI) m/z (%) 447 (M^+, <1), 240 (99), 238 (100), 91 (84); HRMS (70 eV) calcd for $C_{29}H_{37}NOS$ (M^+) 447.2596, found 447.2589; IR (neat): 3396, 2928, 2361, 1602, 1494, 1454, 1377 cm^{-1}; R_f=0.29 (hexane/EtOAc 5:1). Anal. Calcd for $C_{29}H_{37}NOS$: C, 77.80; H, 8.33; N, 3.13; O, 3.57; S, 7.16. Found: C, 77.93; H, 8.39; N, 3.09; O, 3.52; S, 7.10.

4.2.8. (2*R*,3*S*)-1-(Cyclohexylthio)-3-(dibenzylamino)-4-phenylbutan-2-ol (3h). Colorless oil. $[\alpha]_D^{20}$ +1.9 (c 1.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.11 (m, 15H), 3.89 (d, J=13.3 Hz, 2H), 3.78 (d, J=13.3 Hz, 2H), 3.69 (apparent q, J=7.6 Hz, 1H), 3.12–2.98 (m, 3H), 2.66 (dd, J=13.8, 9.4 Hz, 1H), 2.48 (br s, 1H), 1.83–1.68 (m, 2H), 1.56–1.37 (m, 4H), 1.17–0.77 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.9 (C), 139.6 (2×C), 129.3 (2×CH), 129.0 (4×CH), 128.4 (4×CH), 128.1 (2×CH), 127.1 (2×CH), 126.2 (CH), 62.8 (CH), 59.8 (CH_2), 54.9 (2×CH_2), 47.4 (CH), 44.4 (CH), 40.5 (CH_2), 33.9 (CH_2), 33.3 (CH_2), 25.9 (2×CH_2), 25.6 (CH_2); MS (70 eV, EI) m/z (%) 344 ($M^+-C_6H_{11}S$, <1), 312 (48), 238 (70), 91 (100), 69 (42); HRMS (70 eV) calcd for $C_{24}H_{26}NO$ ($M^+-C_6H_{11}S$) 344.2014, found 344.2033; IR (neat): 3425, 2928, 2362, 1603, 1495, 1453, 1363 cm^{-1}; R_f=0.31 (hexane/EtOAc 5:1). Anal. Calcd for $C_{30}H_{37}NOS$: C, 78.38; H, 8.11; N, 3.05; O, 3.48; S, 6.98. Found: C, 78.50; H, 8.17; N, 3.08; O, 3.41; S, 7.05.

4.2.9. (2*R*,3*S*)-3-(Dibenzylamino)-1-(2-phenylethylthio)-4-phenylbutan-2-ol (3i). Colorless oil. $[\alpha]_D^{20}$ +3.3 (c 2.31, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.02 (m, 20H), 3.97 (d, J=13.3 Hz, 2H), 3.88 (d, J=13.3 Hz, 2H), 3.87–3.83 (m, 1H), 3.75 (dd, J=10.5, 8.0 Hz, 1H), 3.21–3.06 (m, 3H), 2.75 (dd, J=13.9, 9.3 Hz, 1H), 2.67–2.61 (m, 2H), 2.56 (br s, 1H), 2.44–2.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.3 (C), 139.7 (C), 139.5 (2×C), 129.3 (2×CH), 129.1 (4×CH), 128.4 (6×CH), 128.3 (4×CH), 127.1 (2×CH), 126.4 (CH), 126.2 (CH), 62.5 (CH), 59.6 (CH_2), 54.8 (2×CH_2), 49.5 (CH), 39.8 (CH_2), 35.7 (CH_2), 34.2 (CH_2); MS (70 eV, EI) m/z (%) 404 ($M^+-C_6H_5$, <1), 240 (44), 241 (100), 238 (28); HRMS (70 eV) calcd for $C_{26}H_{30}NOS$ ($M^+-C_6H_5$) 404.2048, found 404.2058; IR (neat): 3424, 3027, 2360, 1602, 1494, 1453, 1363 cm^{-1}; R_f=0.20 (hexane/EtOAc 5:1). Anal. Calcd for $C_{32}H_{35}NOS$: C, 79.79; H, 7.32; N, 2.91; O, 3.32; S, 6.66. Found: C, 79.64; H, 7.40; N, 2.87; O, 3.37; S, 6.72.

4.2.10. (2*S*,3*S*)-3-(Dibenzylamino)-1-(pentylthio)butan-2-ol (4a). Colorless oil. $[\alpha]_D^{20}$ −7.4 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23–7.13 (m, 10H), 3.79–3.69 (m, 2H), 3.67 (AB syst., J=13.2 Hz, 4H), 2.90 (apparent qt, J=7.2 Hz, 1H), 2.64–2.57 (m, 2H), 2.38 (apparent t, J=7.2 Hz, 2H), 1.50–1.43 (m, 2H), 1.34 (d, J=6.9 Hz, 3H), 1.25–1.10 (m, 4H), 0.79 (t, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.4 (2×C), 129.0 (4×CH), 128.3 (4×CH), 127.1 (2×CH), 63.2 (CH), 59.6 (CH_2), 54.2 (2×CH_2), 39.7 (CH), 31.1 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 22.2 (CH_2), 21.2 (CH_3), 13.9 (CH_3); MS (70 eV, EI) m/z (%) 371 (M^+, <1), 240 (100), 91 (41); HRMS (70 eV) calcd for $C_{23}H_{33}NOS$ (M^+) 371.2283, found 371.2279; IR (neat):

3423, 2928, 2361, 1603, 1494, 1453, 1375 cm^{-1}; R_f=0.35 (hexane/EtOAc 5:1). Anal. Calcd for $C_{23}H_{33}NOS$: C, 74.34; H, 8.95; N, 3.77; O, 4.31; S, 8.63. Found: C, 74.20; H, 8.87; N, 3.81; O, 4.26; S, 8.70.

4.2.11. (2*S*,3*S*)-1-(Benzylthio)-3-(dibenzylamino)butan-2-ol (4b). Colorless oil. $[\alpha]_D^{20}$ −56.0 (*c* 1.88, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.23–7.10 (m, 15H), 3.70–3.55 (m, 6H), 3.44 (d, *J*=13.7 Hz, 2H), 2.83 (apparent qt, *J*=7.0 Hz, 1H), 2.64–2.57 (m, 1H), 2.42 (br s, 1H), 1.33 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.4 (2×C), 138.1 (C), 128.9 (4×CH), 128.5 (3×CH), 128.3 (4×CH), 127.2 (2×CH), 127.1 (2×CH), 62.9 (CH), 59.0 (CH_2), 54.1 (2×CH_2), 38.2 (CH), 34.9 (CH_2), 21.1 (CH_3); MS (70 eV, EI) *m*/*z* (%) 376 (M^+-CH_3, <1), 240 (96), 219 (39), 169 (40), 131 (49), 119 (38), 91 (60), 69 (100); HRMS (70 eV) calcd for $C_{24}H_{26}NOS$ (M^+-CH_3) 376.1735, found 376.1753; IR (neat): 3425, 3028, 2361, 1602, 1494, 1453, 1374 cm^{-1}; R_f=0.29 (hexane/EtOAc 5:1). Anal. Calcd for $C_{25}H_{29}NOS$: C, 76.68; H, 7.46; N, 3.58; O, 4.09; S, 8.19. Found: C, 76.80; H, 7.54; N, 3.55; O, 4.04; S, 8.11.

4.2.12. (2*S*,3*S*)-1-(Cyclohexylthio)-3-(dibenzylamino)-5-methylhexan-2-ol (4c). Colorless oil. $[\alpha]_D^{20}$ −12.9 (*c* 1.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.21–7.12 (m, 10H), 3.77 (d, *J*=13.7 Hz, 2H), 3.72–3.70 (m, 1H), 3.59 (d, *J*=13.7 Hz, 2H), 2.88–2.81 (m, 2H), 2.68 (apparent q, *J*=6.4 Hz, 1H), 2.49–2.48 (m, 1H), 1.90–1.58 (m, 4H), 1.51–1.48 (m, 2H), 1.23–1.12 (m, 7H), 0.85 (d, *J*=6.5 Hz, 3H), 0.79 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5 (2×C), 129.0 (4×CH), 128.3 (4×CH), 127.1 (2×CH), 63.1 (CH), 59.7 (CH_2), 54.4 (2×CH_2), 44.6 (CH_2), 43.9 (CH), 42.2 (CH), 34.4 (CH_2), 34.3 (CH_2), 26.0 (2×CH_2), 25.6 (CH_2), 24.9 (CH), 23.2 (CH_3), 22.1 (CH_3); MS (70 eV, EI) *m*/*z* (%) 425 (M^+, <1), 240 (25), 238 (100), 91 (35); HRMS (70 eV) calcd for $C_{27}H_{39}NOS$ (M^+) 425.2752, found 425.2764; IR (neat): 3425, 2930, 2361, 1603, 1494, 1451, 1367 cm^{-1}; R_f=0.40 (hexane/EtOAc 5:1). Anal. Calcd for $C_{27}H_{39}NOS$: C, 75.86; H, 9.06; N, 3.40; O, 3.89; S, 7.79. Found: C, 75.98; H, 9.13; N, 3.42; O, 3.94; S, 7.73.

4.2.13. (2*S*,3*S*)-1-(Benzylthio)-3-(dibenzylamino)-5-methylhexan-2-ol (4d). Colorless oil. $[\alpha]_D^{20}$ −31.6 (*c* 1.23, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–7.13 (m, 15H), 4.52 (apparent q, *J*=7.8 Hz, 1H), 4.34 (apparent t, *J*=8.4 Hz, 1H), 3.85 (apparent t, *J*=8.0 Hz, 1H), 3.53 (s, 4H), 3.52 (d, *J*=13.6 Hz, 1H), 3.28 (d, *J*=13.6 Hz, 1H), 2.96 (br s, 1H), 2.67 (apparent q, *J*=6.6 Hz, 1H), 1.89–1.75 (m, 1H), 1.69–1.59 (m, 1H), 1.31–1.22 (m, 1H), 0.84 (d, *J*=6.5 Hz, 3H), 0.75 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.6 (C), 138.9 (2×C), 129.0 (2×CH), 128.9 (4×CH), 128.5 (4×CH), 128.2 (2×CH), 127.5 (2×CH), 127.0 (CH), 77.2 (CH), 68.9 (CH_2), 58.1 (CH), 54.7 (2×CH_2), 53.8 (CH_2), 35.7 (CH_2), 24.9 (CH), 22.9 (CH_3), 22.8 (CH_3); MS (70 eV, EI) *m*/*z* (%) 433 (M^+, <1), 266 (100), 91 (61); HRMS (70 eV) calcd for $C_{28}H_{35}NOS$ (M^+) 433.2439, found 433.2424; IR (neat): 3422, 3028, 2360, 1602, 1494, 1453, 1376 cm^{-1}; R_f=0.26 (hexane/EtOAc 5:1). Anal. Calcd for $C_{28}H_{35}NOS$: C, 77.55; H, 8.14; N, 3.23; O, 3.69; S, 7.39. Found: C, 77.69; H, 8.07; N, 3.26; O, 3.64; S, 7.46.

4.2.14. (2*S*,3*S*)-1-(Cyclohexylthio)-3-(dibenzylamino)-4-phenylbutan-2-ol (4e). Colorless oil. $[\alpha]_D^{20}$ −67.0 (*c* 1.69, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.09–6.89 (m, 15H), 3.69 (dd, *J*=11.3, 7.0 Hz, 1H), 3.62 (d, *J*=13.6 Hz, 2H), 3.57 (dd, *J*=11.3, 4.8 Hz, 1H), 3.39 (d, *J*=13.6 Hz, 2H), 3.05 (dd, *J*=13.6, 6.4 Hz, 1H), 2.93 (apparent q, *J*=6.8 Hz, 1H), 2.61–2.55 (m, 1H), 2.39 (dd, *J*=13.6, 7.9 Hz, 1H), 1.95–1.92 (m, 1H), 1.74–1.69 (m, 1H), 1.47–1.23 (m, 5H), 1.06–0.81 (m 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.9 (C), 139.4 (2×C), 129.6 (3×CH), 129.0 (4×CH), 128.3 (6×CH), 127.1 (CH), 126.4 (CH), 61.8 (CH), 59.0 (CH_2), 54.0 (2×CH_2), 45.8 (CH), 44.6 (CH), 42.4 (CH_2), 34.0 (CH_2), 33.4 (CH_2), 25.9 (2×CH_2), 25.6 (CH_2); MS (70 eV, EI) *m*/*z* (%) 344 ($M^+-C_6H_{11}S$, 2), 241 (32), 240 (23), 91 (18), 69 (100); HRMS (70 eV) calcd for $C_{24}H_{26}NO$ ($M^+-C_6H_{11}S$) 344.2014, found 344.1989; IR (neat): 3434, 2928, 2361, 1603, 1494, 1452, 1370 cm^{-1}; R_f=0.44 (hexane/EtOAc 5:1). Anal. Calcd for $C_{30}H_{37}NOS$: C, 78.38; H, 8.11; N, 3.05; O, 3.48; S, 6.98. Found: C, 78.24; H, 8.20; N, 3.01; O, 3.43; S, 7.05.

4.2.15. (2*S*,3*S*)-3-(Dibenzylamino)-1-(2-phenylethylthio)-4-phenylbutan-2-ol (4f). Colorless oil. $[\alpha]_D^{20}$ −48.0 (*c* 1.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.04–6.81 (m, 20H), 3.68–3.62 (m, 1H), 3.58 (d, *J*=13.6 Hz, 2H), 3.52 (br s, 1H), 3.34 (d, *J*=13.6 Hz, 2H), 3.06 (dd, *J*=13.8, 5.9 Hz, 1H), 2.84 (apparent q, *J*=6.9 Hz, 1H), 2.58 (apparent q, *J*=5.5 Hz, 1H), 2.44–2.20 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.1 (C), 139.7 (C), 139.3 (2×C), 129.5 (2×CH), 128.9 (4×CH), 128.5 (2×CH), 128.3 (8×CH), 127.0 (2×CH), 126.4 (CH), 126.3 (CH), 61.6 (CH), 58.9 (CH_2), 54.1 (2×CH_2), 47.6 (CH), 41.2 (CH_2), 35.9 (CH_2), 33.5 (CH_2); MS (70 eV, EI) *m*/*z* (%) 481 (M^+, <1), 241 (48), 240 (100), 238 (33); HRMS (70 eV) calcd for $C_{32}H_{35}NOS$ (M^+) 481.2439, found 481.2465; IR (neat): 3440, 3027, 2360, 1602, 1495, 1453, 1364 cm^{-1}; R_f=0.28 (hexane/EtOAc 5:1). Anal. Calcd for $C_{32}H_{35}NOS$: C, 79.79; H, 7.32; N, 2.91; O, 3.32; S, 6.66. Found: C, 79.94; H, 7.40; N, 2.88; O, 3.36; S, 6.60.

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