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Preparation of Cysteinol Derivatives by Highly Regioselective Ring Opening of Nonactivated Chiral Aziridines by Thiols

Jae Hyun Bae, Seong-Ho Shin, Chan Sun Park, and Won Koo Lee*

Department of Chemistry, Sogang University, Seoul 121-742, Korea

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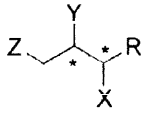
Abstract: Various enantiomerically pure aziridine-2-methanol derivatives **3a-l** were reacted with thiophenol in methylene chloride at room temperature to obtain ring-opening products **4a-l** in high yields with excellent regioselectivity. The reaction procedure is very simple and it provides highly functionalized chiral molecules potentially useful for the synthesis of many biologically important compounds. The reaction rate was found to increase with the acidity of thiols.

Keywords: Amino acids and derivatives; Chiral aziridine; Ring opening

Introduction

Polyfunctionalized chiral units **1** can be found in many biologically active molecules and also they can be precursors for the synthesis of a variety of natural products. The vicinal amino alcohol unit is one of those categories and can be found in molecules such as balanol[1], sphingolipids[2], and bestatin[3]. Various methods have been used for the construction of the β-amino alcohols[4] and one of the efficient ways would be the regioselective ring opening reaction of aziridine-2-methanol derivatives.[5] In general nucleophilic ring opening reactions of substituted aziridines require nitrogen activation with various electron withdrawing groups so that they can stabilize the developing negative charge on the nitrogen during the transition state of the ring opening process.[6]



X, Y, Z = O, N, S

1

We studied the transformation of chiral aziridine-2-methanol derivatives into various amino acid derivatives and we reported the regioselective ring opening of substituted non-activated aziridine-2-methanols by AcOH to provide 2-amino-1,3-propanediols in high yields.[7] The presence of the benzyl substituent on the nitrogen increases the basicity of the lone pair electrons and the nitrogen can easily react with both proton and Lewis acids to produce quaternary ammonium species. As an extension of our research program, we reacted chiral aziridine-2-methanol derivatives with thiols to obtain regioselective ring-opening products in high yields.

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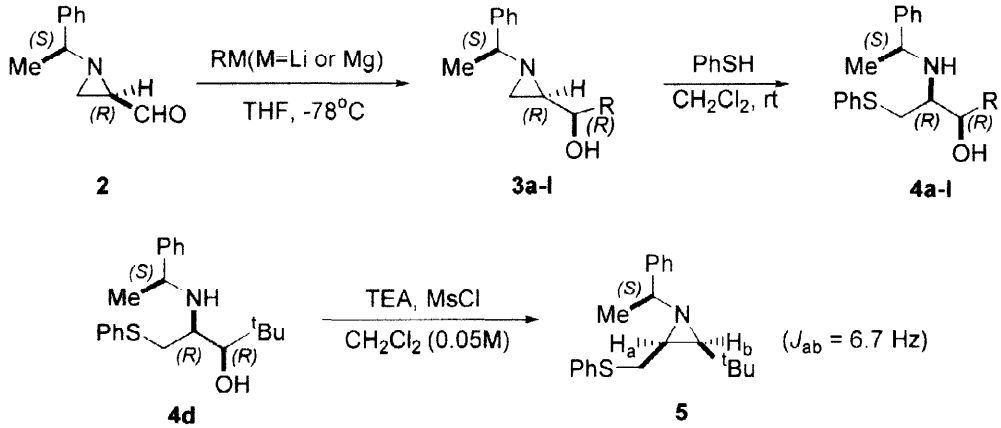
Results and Discussion

We obtained a variety of enantiomerically pure *N*-[(*S*)-(-)-α-methylbenzyl]aziridine-2-methanol derivatives **3** by RM (M= Li or MgX) additions to the corresponding aziridine-2-carboxaldehyde **2**.[8] Since the hydroxy-amino-thiol unit can be found in some HIV protease inhibitors[9], we were interested in ring opening reactions of the aziridine **3** by sulfur nucleophiles. Though there are precedents for ring opening reactions of

Scheme 1



2 **3a-l** **4a-l** **4d** **5**

non-activated aziridines by thiols[10], most ring openings of substituted aziridines by sulfur nucleophiles were studied on activated aziridines.[11] Even with activated aziridines the reactions require a Lewis acid for further activation. However, the nitrogen of the aziridine **3** has a benzyl substituent which makes the ring nitrogen a base sufficiently strong to pick up the proton from the thiol. The proton transfer results in the aziridinium intermediate which is a very labile species. The nucleophile, thiophenolate ion, then attacks the aziridine ring

Table 1. Regioselective Ring Opening of 3a-l by Thiophenol

Entry	R	**Yield of 4** (% isolated)
4a	H	92
4b	Methyl	93
4c	n-Butyl	90
4d	t-Butyl	95
4e	Vinyl	87
4f	1-Hexynyl	85
***4g**	Phenyl	92
4h	2-Methoxyphenyl	93
4i	3-Methylphenyl	92
4j	4-Fluorophenyl	92
4k	1-Naphthyl	95
4l	2-Naphtyl	93

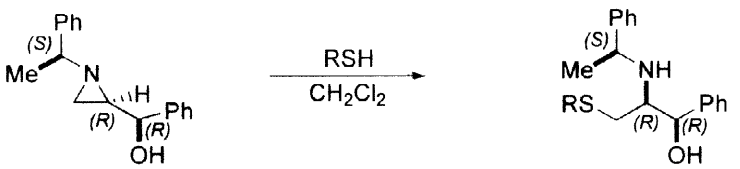
All reactions were completed within 6 h in methylene chloride at rt.
*Reaction was completed in 20 min.

carbon at the less sterically hindered C(3) position to provide ring-opening product **4** in high yields (Scheme 1). The results are summarized in Table 1. The regiochemistry of the ring opening reactions was confirmed by transforming **4d** to the corresponding *cis*-2,3-disubstituted aziridine **5** through an intramolecular cyclization.

The ring opening reactions of **3** with 3 equiv. of thiophenol in methylene chloride proceed smoothly even at room temperature in 3-6 h. The reaction procedure is very simple and the product can be isolated by evaporating the reaction solvent, followed by a short silica gel column chromatography to remove the unreacted thiol.

It was considered that the rate determining step of the ring opening reaction was the proton transfer from the thiol to the ring nitrogen to form the aziridinium intermediate, then the reaction rate would be influenced by the acidity of the thiols. The rate study of the ring opening reactions shows that the reaction rate correlates nicely with the acidity of thiols, and increases with the acidity of thiols (Scheme 2).

Scheme 2. The influence of the acidity of thiols on the reaction rate

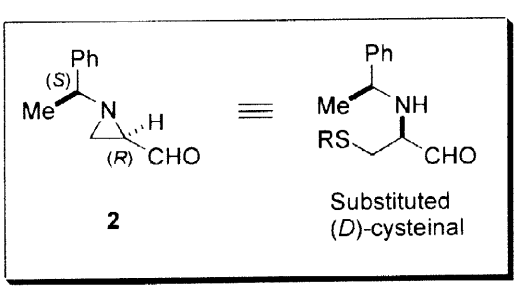


3g **6a-e**

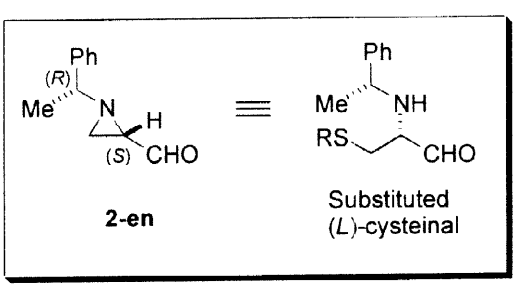
Entry	R	Reaction condition	Yield (% isolated)
6a	Acetyl	< 3 min in CH_2Cl_2 at -78°C	87
6b	4-Nitrophenyl	< 2 min in CH_2Cl_2 at rt	92
6c	4-Chlorophenyl	20 min in CH_2Cl_2 at rt	96
4g	Phenyl	20 min in CH_2Cl_2 at rt	92
6d	Benzyl	8 h in refluxing $CHCl_3$	90
6e	n-Butyl	42 h in refluxing $CHCl_3$	86

Conclusions

Since the enantiomer of **2** is easily prepared from (*R*)-(+)-α-methylbenzylamine and an appropriate dibromoester, the *N*-[(*S*)-(-)-α-methylbenzyl]aziridine-2(*R*)-carboxaldehyde **2** and its enantiomer **2-en** can be used as the synthetic equivalents of configurationally stable (*D*)- and (*L*)-cysteinal derivatives, respectively. The above results show that the compound **2** and its enantiomer **2-en** can be used as three-carbon chiral building blocks for the syntheses of structurally diverse sulfur containing chiral molecules.



2



2-en

Experimental

General procedure for the ring opening reactions with thiols: **Preparation of (2*R*)-2-{[(*S*)-α-Methylbenzyl]amino}-3-(thiophenyl)propan-1-ol (4a):** To a solution of [1(*S*)-α-Methylbenzyl)aziridine-2(*R*)-methanol **(3a)** (147 mg, 0.829 mmol) in 4.15 mL of CH_2Cl_2 was added PhSH (274 mg, 2.49 mmol). The mixture was stirred for 6.5 h at room temperature and then the mixture was concentrated in *vacuo*. Purification by silica gel flash chromatography (EtOAc/Hexane 40:60) gave 219 mg (92 %) of the product as a colorless oil. $[\alpha]^{25}_D$= -88.7 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36-7.16 (m, 10H), 3.80 (q, *J* = 6.5 Hz, 1H), 3.46 (dd, *J* = 10.8 Hz, 4.4 Hz, 1H), 3.32 (dd, *J* = 10.8 Hz, 6.0 Hz, 1H), 3.06 (d, *J* = 6.0 Hz, 2H), 2.76-2.68 (m, 1H), 1.30 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.4, 136.2, 129.8, 129.1, 128.7, 127.2, 126.7, 126.4, 63.6, 55.9, 55.8, 35.8, 24.9; HRMS Calcd for $C_{17}H_{21}NOS$: 287.1344, Found: 287.1321

(4b): $[\alpha]^{25}_D$= -134.3 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41-7.21 (m, 10H), 3.80 (q, *J* = 6.5 Hz, 1H), 3.72-3.59 (m, 1H), 3.27 (dd, *J* = 13.6 Hz, 5.0 Hz, 1H), 3.05 (dd, *J* = 3.8 Hz, 13.6 Hz, 1H), 2.44-2.04 (m, 1H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 136.6, 130.0, 129.2, 128.6, 127.3, 127.0, 126.6, 67.6, 59.6, 55.0, 34.5, 24.8, 19.1; HRMS Calcd for $C_{18}H_{23}NOS$: 301.1500, Found: 301.1512

(4c): $[\alpha]^{25}_D$= -105.1 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.19 (m, 10H), 3.80 (q, *J* = 6.5 Hz, 1H), 3.49-3.44 (m, 1H), 3.23 (dd, *J* =13.5 Hz, 5.5 Hz, 1H), 3.07 (dd, *J* = 13.5 Hz, 3.8 Hz, 1H), 2.44 (dd, *J* = 5.7 Hz, 10.1 Hz, 1H), 1.26-0.95 (m, 9H), 0.85-0.78 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 136.6, 130.0, 129.1, 128.5, 127.2, 127.0, 126.5, 71.3, 57.7, 55.1, 34.9, 33.2, 27.5, 24.7, 22.4, 13.7; Anal. Calcd for $C_{21}H_{29}NOS$: C, 73.42; H, 8.51; N, 4.08; S, 9.33. Found: C, 73.38; H, 8.33; N, 4.36; S, 9.26.

(4d): $[\alpha]^{25}_D$= -67.5 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.15 (m, 10H), 3.80 (q, *J* = 6.5 Hz, 1H), 3.23 (dd, *J* =13.4 Hz, 5.7 Hz, 1H), 3.12 (d, *J* = 10.6 Hz, 1H), 3.04 (dd, J = 13.4 Hz, 5.2 Hz, 1H), 2.74 (dd, *J* = 10.0 Hz, 5.7 Hz, 1H), 1.26 (d, J = 6.5 Hz, 3H), 0.67(s, 9H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 136.5, 130.0, 129.2, 128.9, 128.5, 128.1, 127.3, 126.5, 77.6, 55.8, 53.1, 39.0, 34.8, 25.7, 24.0; HRMS Calcd for $C_{21}H_{29}NOS$: 343.1970, Found: 343.1987

(4e): mp 84-85 °C; $[\alpha]^{25}_D$= -127.1 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39-7.21 (m, 10H), 5.70-5.53 (m, 1H), 5.25-5.11 (m, 2H), 4.03-3.96 (m, 1H), 3.79 (q, *J* = 6.5 Hz, 1H), 3.26 (dd, *J* = 13.6 Hz, 5.3 Hz, 1H), 3.03 (dd, J = 13.7 Hz, 4.0 Hz, 1H), 2.58-2.50 (m, 1H), 1.23 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 138.2, 136.6, 130.0, 129.2, 128.7, 127.3, 126.9, 126.5, 117.7, 73.1, 58.0, 55.1, 34.5, 24.6; Anal. Calcd for $C_{19}H_{23}NOS$: C, 72.80; H, 7.40; N, 4.47; S, 10.23. Found: C, 72. 57; H, 7.62; N, 4.65; S, 10.05.

(4f): $[\alpha]^{25}_D$= -80.1 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39-7.16 (m, 10H), 4.29 (d, *J* = 6.9 Hz, 1H), 3.86 (q, *J* = 6.5 Hz, 1H), 3.32 (dd, *J* = 13.9 Hz, 5.5 Hz, 1H), 3.19 (dd, *J* = 13.9 Hz, 4.4 Hz, 1H), 2.75 (dd, *J* = 11.4 Hz, 5.1 Hz, 1H), 2.19-2.13 (m, 2H), 1.48-1.30 (m, 4H), 1.24 (d, *J* = 6.5 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 136.4, 129.6, 129.1, 128.7, 127.3, 126.8, 126.4, 86.7, 78.8, 63.4, 58.8, 55.1, 34.4, 30.3, 24.4, 21.7, 18.1, 13.2; HRMS Calcd for $C_{23}H_{29}NOS$: 367.1970, Found: 367.1974.

(4g): $[\alpha]^{25}_D$= -142.6 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36-7.10 (m, 15H), 4.54 (d, *J* = 7.7 Hz, 1H), 3.75 (q, *J* = 6.5 Hz, 1H), 3.24-3.14 (m, 1H), 2.81-2.69 (m, 2H), 1.21 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 144.4, 141.6, 130.0, 129.2, 129.0, 128.6, 128.3, 127.8, 127.3, 127.0, 126.9, 126.5, 74.2, 60.4, 55.4, 34.7, 24.9; HRMS Calcd for $C_{23}H_{25}NOS$: 363. 1659, Found: 363.1674.

(4h): $[\alpha]^{25}_D$= -117.2 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32-6.74 (m, 14H), 4.93 (d, *J* = 5.6 Hz, 1H), 3.64-3.54 (m, 4H), 3.30-3.18 (m, 1H), 2.98-2.04 (m, 2H), 1.14 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 145.1, 137.0, 130.4, 129.2, 128.9, 128.4, 128.1, 127.6, 126.8, 126.7, 125.9, 120.6, 110.2, 69.1, 57.7, 55.4, 54.7, 35.1, 24.0; HRMS Calcd for $C_{24}H_{27}NO_2S$: 393.1763, Found: 393.1739.

(4i): $[\alpha]^{25}_{D}$= -133.2 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31-6.89 (m, 14H), 4.49 (d, *J* = 8.1 Hz, 1H), 3.75 (q, *J* = 6.5 Hz, 1H), 3.20 (dd, *J* = 13.6 Hz, 4.8 Hz, 1H), 2.81-2.69 (m, 2H), 2.24 (s, 3H), 1.26 (d, J = 6.5 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 144.5, 141.6, 137.9, 130.0, 129.2, 128.6, 128.5, 128.2, 127.8, 127.6, 127.3, 126.9, 126.5, 124.1, 74.2, 60.4, 55.5, 34.9, 24.9, 21.4; Anal. Calcd for $C_{24}H_{27}NOS$: C, 76.35; H, 7.21; N, 3.71; S, 8.49. Found: C, 76.37; H, 7.46; N, 3.91; S, 8.31.

(4j): $[\alpha]^{25}_{D}$= -130.3 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36-6.87 (m, 14H), 4.50 (d, *J* = 7.8 Hz, 1H), 3.75 (q, *J* = 6.5 Hz, 1H), 3.23-3.13 (m, 1H), 2.78-2.63 (m, 2H), 1.22 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 160.9, 144.4, 137.4, 136.4, 130.1, 129.3, 128.8, 128.6, 128.5, 127.5, 127.0, 126.8, 115.3, 115.0, 73.4, 60.3, 55.2, 34.2, 24.6; Anal. Calcd for $C_{23}H_{24}FNOS$: C, 72.41; H, 6.34; F, 4.98; N, 3.67; S, 8.40. Found: C, 72.75; H, 6.66; N, 3.83; S, 8.50.

(4k): $[\alpha]^{25}_{D}$= -121.5 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.73-6.99 (m, 17H), 5.27 (d, *J* = 6.3 Hz, 1H), 3.65 (q, *J* = 6.5 Hz, 1H), 3.28-3.13 (m, 2H), 2.91-2.80 (m, 1H), 1.17 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.5, 137.3, 136.4, 134.1, 130.8, 129.6, 129.2, 128.7, 128.5, 127.7, 127.1, 126.8, 126.4, 125.7, 125.4, 125.1, 124.1, 72.4, 58.3, 55.8, 35.6, 24.5; Anal. Calcd for $C_{27}H_{27}NOS$: C, 78.41; H, 6.58; N, 3.39; S, 7.75. Found: C, 78.38; H, 6.22; N, 3.55; S, 7.38.

(4l): $[\alpha]^{25}_{D}$= -136.1 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ7.80-7.15 (m, 17H), 4.70 (d, *J* = 8.0 Hz, 1H), 3.77 (q, *J* = 6.5 Hz, 1H), 3.27-3.17 (m, 1H), 2.89-2.75 (m, 2H), 1.23 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.4, 139.1, 136.6, 133.2, 130.1, 129.2, 128.7, 128.4, 128.1, 127.8, 127.7, 127.3, 126.9, 126.6, 126.3, 126.0, 125.9, 124.6, 74.2, 60.3, 55.5, 35.0, 24.8; Anal. Calcd for $C_{27}H_{27}NOS$: C, 78.41; H, 6.58; N, 3.39; S, 7.75. Found: C, 78.35; H, 6.24; N, 3.58; S, 7.41.

Preparation of (2*R*, 3*S*)-2-[(thiophenyl)methyl]-1-[(*S*)-α-methylbenzyl]-3-(*tert*-butyl)aziridine (5): To a solution of **(4d)** (103 mg, 0.30 mmol) in 6.00 mL of CH_2Cl_2 under nitrogen at -78 °C was added triethylamine (152 mg, 1.50 mmol). The mixture was stirred for 10 min and then treated with MsCl (103 mg, 0.899 mmol) at -78 °C. The mixture was warmed up to room temperature, and stirred for 60 h. The mixture was quenched with sat'd aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 mL x 3). The combined organic extracts were dried and silica gel flash chromatography (EtOAc/Hexane 10:90) gave 85 mg (87 %) of the product as a colorless oil. $[\alpha]^{25}_{D}$= -20.0 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45-7.18 (m, 10H), 3.23-3.20 (m, 2H), 2.41 (q, *J* = 6.5 Hz, 1H), 1.70-1.57 (m, 1H), 1.43 (d, *J* = 6.5 Hz, 3H), 1.24 (d, *J* = 6.7 Hz, 1H), 0.71 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145. 2, 137.3, 129.0, 128.8, 128.2, 127.6, 127.2, 125.8, 71.7, 54.6, 43.8, 33.9, 30.9, 28.6, 23.0; HRMS Calcd for $C_{21}H_{27}NS$: 325.1864. Found: 325.1862.

(6a) : $[\alpha]^{25}_{D}$= +29.6 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45-7.12 (m, 10H), 4.26 (d, *J* = 7.7 Hz, 1H), 3.95 (q, *J* = 6.5 Hz, 1H), 3.37 (dd, *J* = 13.6Hz, 4.3Hz, 1H), 2.73-2.51 (m, 2H), 2.40(s, 3H), 1.33 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 144.6, 141.2, 128.8, 128.5, 128.1, 127.4, 127.1, 74.9, 59.9, 55.1, 30.6, 28.6, 24.8; Anal. Calcd for $C_{19}H_{23}NO_2S$: C, 69.07; H, 7.04; N, 4.25; S, 9.73. Found: C, 69.35; H, 7.21; N, 4.30; S, 9.36.

(6b): $[\alpha]^{25}_{D}$= -119.1 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.9 Hz, 2H), 7.38-7.13 (m, 12H), 4.60 (d, *J* = 7.0 Hz, 1H), 3.93 (q, *J* = 6.5 Hz, 1H), 3.29-3.19 (m, 1H), 2.92-2.81 (m, 2H), 1.33 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 144.2, 141.4, 128.9, 128.7, 128.2, 127.6, 126.9, 124.1, 74.3, 59.3, 55.3, 32.9, 24.8; HRMS Calcd for $C_{23}H_{24}N_2O_3S$: 394.1351. Found: 394.1343.

(6c): $[\alpha]^{25}_{D}$= -129.4 ° (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29-7.05 (m, 14H), 4.53 (d, *J* = 7.3 Hz, 1H), 3.79 (q, *J* = 6.5 Hz, 1H), 3.19-3.09 (m, 1H), 2.81-2.69 (m, 2H), 1.26 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 141.6, 135.1, 132.5, 131.1, 129.3, 128.7, 128.5, 127.9, 127.4, 126.9, 74.0, 59.9, 55.2, 34.7, 24.6; Anal. Calcd for $C_{23}H_{24}ClNOS$: C, 69.42; H, 6.08; N, 3.52; S, 8.06; Cl, 8.91. Found: C, 69.26; H, 6.47; N, 3.23; S, 8.01.

(6d): $[\alpha]^{25}_{D}$= -157.2 ° (c 1.00, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.29-7.13 (m, 15H), 4.35 (d, *J* = 7.7 Hz, 1H), 3.64 (s, 2H), 3.51 (q, *J* = 6.5 Hz, 1H), 2.63-2.53 (m, 2H), 2.38-2.29 (m, 1H), 1.25 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 141.7, 138.4, 129.0, 128.6, 128.3, 127.7, 127.2, 126.9, 74.2, 59.5, 54.7, 36.7, 31.0, 24.9; HRMS Calcd for $C_{24}H_{27}NOS$: 377.1813. Found: 377.1800

(6e): $[\alpha]^{25}_{D}$= -116.6 ° (c 1.00, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.36-7.17 (m, 10H), 4.44 (d, *J* = 7.7 Hz, 1H), 3.90 (q, *J* = 6.5 Hz, 1H), 2.75-2.61 (m, 2H), 2.50-2.36 (m, 3H), 1.59-1.33 (m, 7H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.6, 141.9, 128.6, 128.2, 127.7, 127.3, 126.9, 74.3, 60.2, 55.4, 33.2, 32.8, 31.9, 25.1, 21.9, 13.7; Anal. Calcd for $C_{21}H_{29}NOS$: C, 73.42; H, 8.51; N, 4.08; S, 9.33. Found: C, 73.62; H, 8.25; N, 3.87; S, 9.37.

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