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Stereoselective synthesis of 4*H*-3,1-benzothiazines via tandem nucleophilic addition/epoxy ring-opening cyclization reactions of 2-(3-phenyloxiranyl)phenyl isothiocyanates

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This paper is dedicated to Professor Juzo Nakayama on the occasion of his 65th birthday and retirement.

Tandem nucleophilic addition/epoxy ring-opening cyclization reactions of 2-(3-phenyloxiranyl)phenyl isothiocyanates to produce 4-hydroxy(phenyl)methyl-4*H*-3,1-benzothiazines were investigated. In the reactions, carbon, sulfur, nitrogen, and oxygen nucleophiles were introduced at the 2-position of the benzothiazines, together with the two adjacent stereogenic centers arising from the epoxy carbon centers. We also found an interesting stereospecific rearrangement of 2-(alkylamino)-4-hydroxy(phenyl)methyl-4*H*-3,1-benzothiazines to 1-alkyl-3-(2-(*trans*-3-phenylthiiran-2-yl)-phenyl)urea.

Keywords: isothiocyanate; epoxide; benzothiazine; thiirane; tandem reaction

1. Introduction

3,1-Benzothiazines have been investigated from a variety of viewpoints, such as development of new synthetic methods (*1–7*), discovery of bioactive compounds (*8*), functional materials (*9*), and their utility as intermediates in organic synthesis (*10*). Although there are many synthetic approaches to 3,1-benzothiazines (*1–5*), a relatively small number of synthetic methods for 4-substituted 4*H*-3,1-benzothiazines having a stereogenic center at the 4-position have been reported so far (*6*, *7*).

From our ongoing interest in the synthesis of nitrogen-containing heterocycles through a tandem methodology of functionalized azacumulenes (*11–14*), we previously demonstrated the tandem nucleophilic addition/intramolecular hetero-Michael addition cyclization (*12*; Equation (1)) and iodocyclization of carbodiimides to give quinazolines and *N*-ring fused benzothiadiazine-*S*,*S*-dioxides (*13*; Equation (2)). Quite recently, we also disclosed a conventional synthesis of 4-aryl-quinoline-2-thiones via the tandem Friedel–Crafts alkenylation/cyclization

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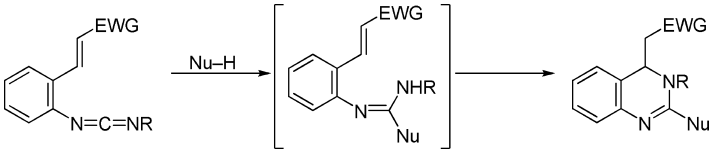
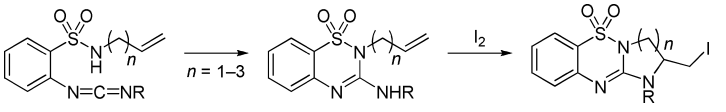
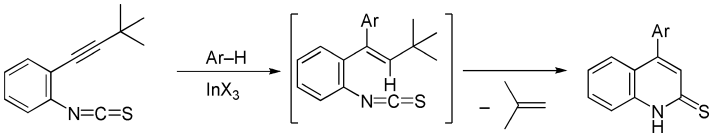
reaction of *o*-alkynylphenyl isothiocyanates (*14*; Equation (3)).



(1)

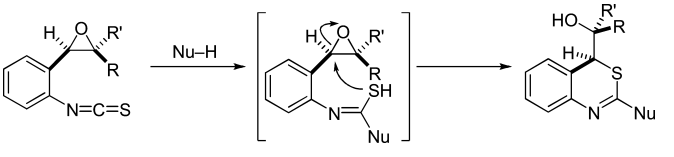


(2)



(3)

In the present work, we focused on the synthesis of 4-substituted 4*H*-3,1-benzothiazines via a tandem method using *ortho*-functionalized phenyl isothiocyanates. Some research groups demonstrated the syntheses of 3,1-benzothiazine derivatives by using the tandem strategy, *i.e.* (i) Friedel–Crafts addition/thiolactonization of 2-isothiocyanatobenzoate to lead to 2-aryl-4*H*-3,1-benzothiazin-4-ones (*2*); (ii) nucleophilic addition/Michael addition of *in situ*-prepared isothiocyanates bearing an *ortho*-substituted α,β-unsaturated carbonyl moiety to lead to 4*H*-3,1-benzothiazin-2-thiones (*7*); (iii) nucleophilic addition/nucleophilic addition of 2-isothiocyanatobenzonitrile to lead to 4-imino-3,1-benzothiazines (*3*); and (iv) nucleophilic addition/nucleophilic substitution reactions of 3-chloro-3-(2-isothiocyanatophenyl) acrylaldehyde (*4*) or 2-bromomethylphenyl isothiocyanate (*5*). In this context, we envisioned that the tandem nucleophilic addition/epoxy-opening cyclization of *N*-(2-oxiranylphenyl) isothiocyanates could lead to 4-hydroxymethyl-4*H*-3,1-benzothiazines in a stereo-controlled manner (Scheme 1). This strategy enables introduction of not only a variety of nucleophiles to the 2-position but also an *R*-substituted hydroxymethyl group to the 4-position with two adjacent stereogenic centers. Here, we report the preliminary results.

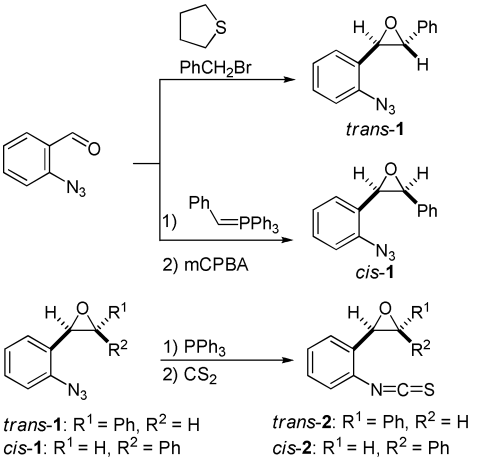


Scheme 1. Tandem nucleophilic addition/epoxy ring-opening cyclization of 2-(oxiranyl)phenyl isothiocyanate leading to 4*H*-3,1-benzothiazines.

2. Results and discussion

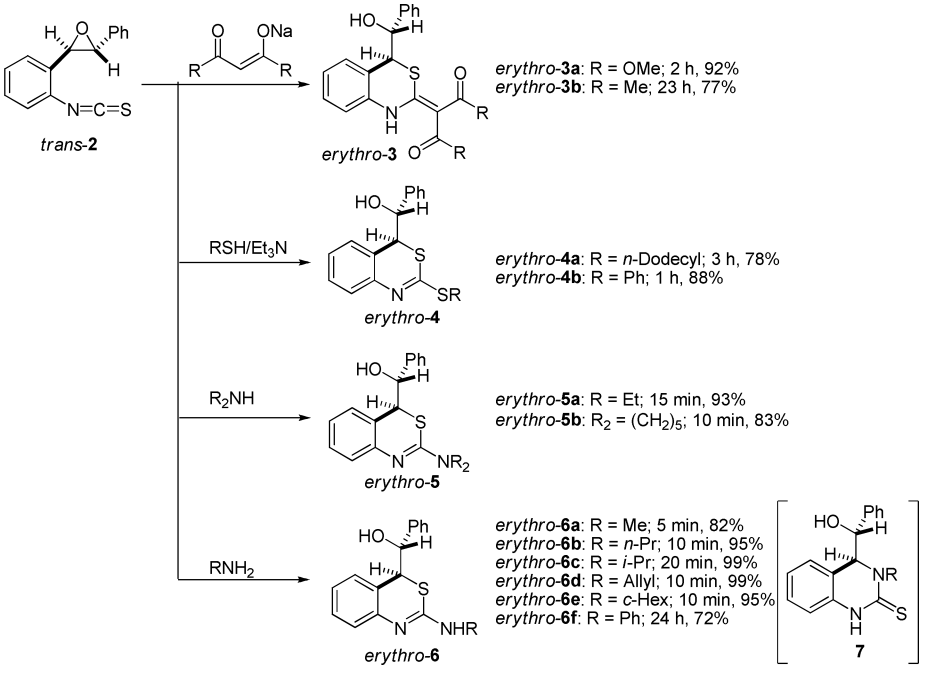
We selected *o*-(3-*trans*- and 3-*cis*-phenyloxiranyl)phenyl isothiocyanates (*trans*- and *cis*-**2**), as substrates for the tandem addition/epoxy ring-opening cyclization. The prerequisite *trans*- and *cis*-oxiranylphenyl azides **1** were prepared from *o*-azidobenzaldehyde (*15*) (Scheme 2). 2-(*trans*-Phenyloxiranyl)phenyl azide (*trans*-**1**) was synthesized via sulfur ylide-mediated epoxidation (Corey–Chaykovsky-type reaction) (*16*) of *o*-azidobenzaldehyde with benzyl bromide, while *cis*-epoxide (*cis*-**1**) was prepared via the Wittig reaction of *o*-azidobenzaldehyde and oxidation

with *m*CPBA. The *trans*- and *cis*-epoxyazides **1**, thus obtained, were subjected to the Staudinger reaction with triphenylphosphine, and an aza-Wittig reaction with carbon disulfide to produce the corresponding *trans*- and *cis*-epoxyphenyl isothiocyanates **2**.



Scheme 2. Preparation of *trans*- and *cis*-epoxyphenyl isothiocyanates **2**.

Initially, we examined the reactions of *o*-(3-*trans*-phenyloxiranyl)phenyl isothiocyanate (*trans*-**2**) with various nucleophiles (Scheme 3). The reaction of *trans*-**2** with dimethyl sodiomalonate was completed within 2 h at room temperature to produce dimethyl (4-*erythro*-hydroxy(phenyl)methyl-1*H*-3,1-benzothiazin-2(4*H*)-ylidene)malonate (*erythro*-**3a**) as a single



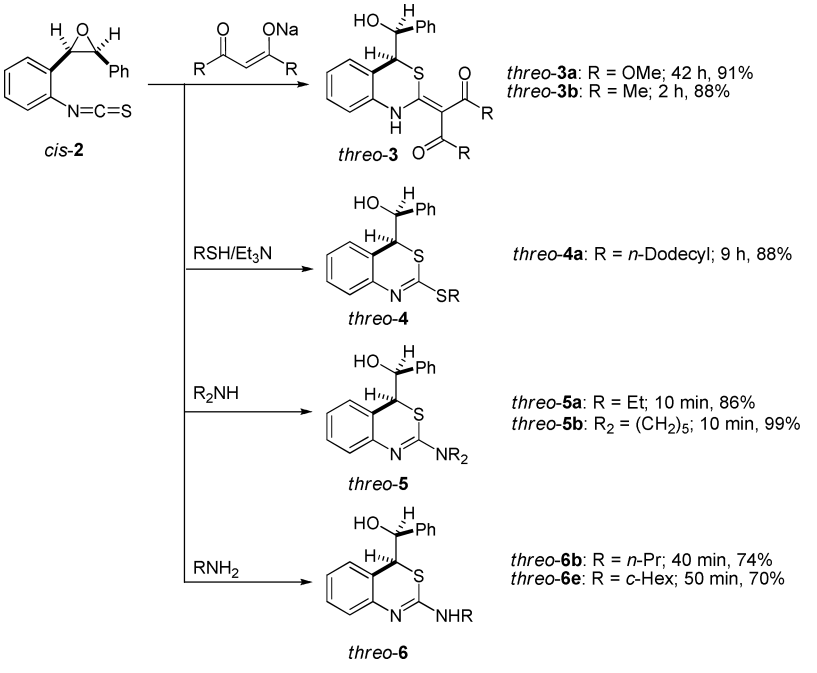
Scheme 3. Reactions of *trans*-epoxyphenyl isothiocyanate **2** with various nucleophiles.

diastereomer in 92% yield. Similarly, sodioacetylacetone reacted with *trans*-**2a** to afford *erythro*-**3b** in 77% yield.

We next investigated the reactions with sulfur nucleophiles, *n*-dodecanethiol or thiophenol, which proceeded at room temperature in the presence of triethylamine to produce 2-thiosubstituted-4*H*-3,1-benzothiazines (*erythro*-**4a,b**).

Secondary amines such as diethylamine and piperidine also reacted with *trans*-**2** rapidly (within 15 min) to produce the corresponding 2-(disubstituted amino)-4*H*-3,1-benzothiazines (*erythro*-**5a,b**) in high yields. In the reaction with a primary amine, an initially formed thiourea intermediate has the ambident nucleophilic center, S and N (see Scheme 1), which then can react at either the sulfur atom or the nitrogen atom to produce benzothiazines **6** or quinazolin-2-thiones **7**, respectively (*17*). As a result, the reaction with primary alkyl amines such as methylamine, *n*-propylamine, isopropylamine, allylamine, and cyclohexylamine yielded 2-alkylamino-4*H*-3, 1-benzothiazines (*erythro*-**6a–e**) in high to excellent yields without formation of quinazolin-2-thiones **7**. Less nucleophilic aniline reacted with *trans*-**2** sluggishly to produce *erythro*-**6f** in 72% yield.

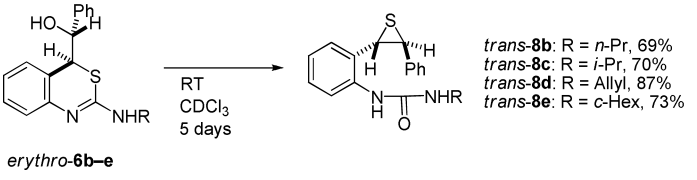
o-(3-*cis*-Phenyloxiranyl)phenyl isothiocyanate (*cis*-**2**) was also treated with selected carbon, sulfur, and nitrogen nucleophiles (Scheme 4). In all the reactions of *cis*-**2**, the nucleophiles participated in the tandem process to provide 2-Nu-substituted 4-*threo*-hydroxy(phenyl)methyl-4*H*-3,1-benzothiazines **3–6** in good to high yields (70–99%). Exclusive formation of the *erythro*- and *threo*-derivatives **3–6** from *cis*- and *trans*-**2**, respectively, indicates that the tandem process proceeds stereospecifically and highly stereoselectively.



Scheme 4. Reactions of *cis*-epoxyphenyl isothiocyanate **2** with various nucleophiles.

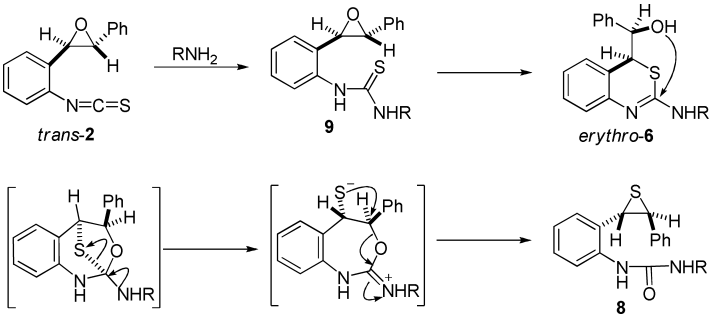
Unexpectedly, we found that 2-(alkylamino)-substituted *erythro*-benzothiazines derivatives (*erythro*-**6b–e**) gradually transformed into *N*-alkyl-*N′*-(2-(*trans*-3-phenylthiiran-2-yl)phenyl)urea derivatives (*trans*-**8b–e**) within 5 days in solution at room temperature (Scheme 5). At a higher temperature, desulfrization of the thiiranes to the corresponding alkenes was observed.

Curiously, however, this rearrangement was almost nonexistent even when a $CDCl_3$ solution of *threo*-**6b** was heated under reflux for several hours.

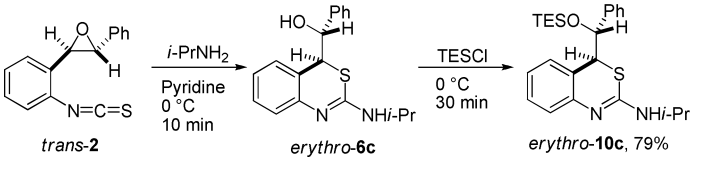


Scheme 5. Formation of *trans*-thiiranes **8b–e** from *erythro*-**6b–e**.

When we looked at the transformation of the initial nucleophilic addition product **9** to the thiirane **8**, we noticed the similarity of this rearrangement to the classical intermolecular reaction between epoxide and thiourea to form thiirane and urea (*18*). Thus, the present rearrangement would proceed intramolecularly in a pathway, as shown in Scheme 6 (*19*). The rearrangement would be initiated by the nucleophilic attack by the hydroxy group to the isothiourea-carbon in **6**, followed by the intramolecular S_N2-type *O*-ring-opening–*S*-ring-closing reaction by the thiolate to produce thiiranes **8** having both inverted stereogenic carbon centers. The protection of the hydroxy group, by the triethylsilyl group of *erythro*-**6c** prepared *in situ* from *trans*-**2**, proved that the *O*-protected *erythro*-**10c** is stable for at least 6 months at room temperature, without conversion to the corresponding thiirane (Equation (4)). This is probably because of the inhibition of the addition to the isothiourea-carbon.



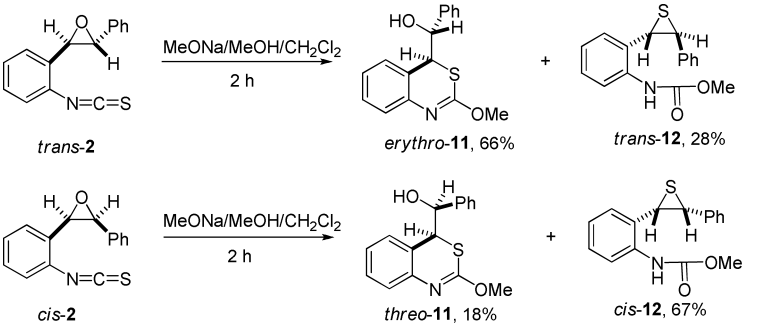
Scheme 6. A possible pathway for the formation of *trans*-thiiranes **8** from *erythro*-**6**.



(4)

Finally, for the synthesis of 2-alkoxy-4*H*-3,1-benzothiazine derivatives, we examined the reaction of epoxyphenyl isothiocyanates **2** with methanol as a nucleophile (Scheme 7). The reactions did not occur without additives or even in the presence of triethylamine at room temperature. However, in the presence of 1.2 equiv of sodium methoxide, the reactions took place. The reaction of *trans*-**2** afforded a mixture of *erythro*-**11** (66%) and *trans*-**12** (28%), while a similar reaction of *cis*-**2** gave a mixture of *threo*-**11** (18%) and *cis*-**12** (67%). The

independent formation of *trans*- and *cis*-thiirane indicates that each reaction from *trans*/*cis*-isothiocyanates **2** to *erythro*/*thr*eo-benzothiazines **11** and to *trans*/*cis*-thiiranes **12** also proceeded in a stereospecific manner.



Scheme 7. Reactions of **2** with sodium methoxide.

3. Conclusion

We have demonstrated the tandem nucleophilic addition/epoxy-opening cyclization of *N*-(2-oxiranylphenyl) isothiocyanates **2** that is a conventional stereo-controlled synthetic approach to functionalized 4*H*-3,1-benzothiazines. Carbon, sulfur, nitrogen, and oxygen nucleophiles were successfully introduced to the 2-position of the 3,1-benzothiazines. We also discovered an interesting stereospecific rearrangement of 4*H*-3,1-benzothiazines to thiiranes.

4. Experimental

4.1. *General*

All melting points were determined on a Yanaco MP apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270-30 or a Horiba FT-710 spectrophotometer. ^{1}H and ^{13}C NMR data were obtained with a JEOL JNM-EX 500, a JEOL JNM-EX 300, or a Bruker AV 600 instrument. Chemical shifts (δ) are quoted in ppm using tetramethylsilane ($\delta = 0$) for ^{1}H NMR and $CDCl_3$ ($\delta = 77.0$) for ^{13}C NMR. Mass spectra were measured on a Bruker Daltonics microTOF spectrometer. Elemental analyses were performed with a Yanaco CHN-CODER MT-6 model. Column chromatography was conducted on silica gel 60 (Kanto Chemical Co.).

4.2. *Preparation of trans-oxiranylphenyl azide 1 (trans-1)*

A solution of *o*-azidobenzaldehyde (2.47 g, 16.8 mmol) in acetonitrile (3 mL) was added to a mixture of tetrahydrothiophene (1.47 mL, 16.8 mmol), benzyl bromide (2.00 mL, 16.8 mmol), and potassium carbonate (2.8 g, 20.2 mmol) in acetonitrile (30 mL) at 0 °C. The mixture was warmed to room temperature, stirred for 3 days, quenched with water, and extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1/4) to yield *trans*-**1** (3.2 g, 80%).

trans-**1**: Yellow solid; mp 46.8–47.2˚C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 3.75 (d, $J = 1.5$ Hz, 1H), 4.13 (d, $J = 1.5$ Hz, 1H), 7.18–7.20 (m, 2H), 7.31–7.39 (m, 7H). ^{13}C NMR (151 MHz, $CDCl_3$, δ): 58.4 (CH), 62.4 (CH), 117.8 (CH), 125.0 (CH), 125.4 (CH), 125.6 (2CH), 126.4 (C), 128.4 (CH), 128.5 (2CH), 129.1 (CH), 136.8 (C), 138.4 (C). IR (KBr): 2113, 1596, 1481 cm^{-1}. Anal. calcd. for $C_{14}H_{11}N_3O$ (237.26): C, 70.87; H, 4.67; N, 17.71. Found: C, 70.86; H, 4.77; N, 17.56.

4.3. *Preparation of cis-oxiranylphenyl azide 1 (cis-1)*

To a stirred solution of benzyltriphenylphosphonium bromide (433 mg, 1.0 mmol) in THF (4 mL) was added a 1.6 M solution of *n*-butyllithium in hexane (0.70 mL, 1.1 mmol) at −15 °C. After stirring for 20 min, a solution of *o*-azidobenzaldehyde (132 mg, 0.9 mmol) in THF (3 mL) was added. After stirring for 30 min at room temperature, the reaction mixture was quenched with water, extracted with dichloromethane, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1/10) to yield a mixture of *cis*- and *trans*-alkenyl azide (134 mg) as a pale yellow amorphous solid, which was used for the next oxidation without further purification.

Sodium hydrogen carbonate (101 mg, 1.2 mmol) and *m*-chloroperbenzoic acid (259 mg, 1.5 mmol) were added to the mixture of *cis*- and *trans*-alkenyl azides (134 mg) in dichloromethane (3 mL) at 0 °C. After stirring for 5 h, the mixture was quenched with aqueous sodium hydrogen sulfite. The organic layer was separated, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane/hexane = 1/4) to yield *cis*-**1** (86 mg, 36% in two steps) and *trans*-**1** (40 mg, 17% in two steps).

cis-**1**: Yellow solid; mp 83.1–83.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 4.34 (d, $J = 4.3$ Hz, 1H), 4.38 (d, $J = 4.3$ Hz, 1H), 6.94 (d, $J = 7.8$ Hz, 1H), 6.98 (dd, $J = 7.8$, 7.8 Hz, 1H), 7.10–7.20 (m, 6H), 7.29 (d, $J = 7.8$ Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 57.4 (CH), 59.4 (CH), 117.5 (CH), 124.1 (CH), 125.8 (C), 126.5 (2CH), 127.5 (CH), 127.6 (2CH), 128.61 (CH), 128.7 (CH), 134.2 (C), 137.9 (C). IR (KBr): 2129, 1295, 755 cm^{-1}. Anal. calcd. for $C_{14}H_{11}N_3O$ (237.26): C, 70.87; H, 4.67; N. 17.71. Found: C, 70.78; H, 4.81; N, 17.34.

4.4. *Conversion of azides 1 to isothiocyanates 2*

A solution of triphenylphosphine (0.97 g, 3.7 mmol) in dichloromethane (10 mL) was added to a stirred solution of *trans*-**1** (0.88 g, 3.7 mmol) in dichloromethane (15 mL). The mixture was stirred for 2 h at room temperature, and carbon disulfide (10 mL) was added. The mixture was stirred for a day and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1/10) to yield *trans*-**2** (0.69 g, 74%).

trans-**2**: Colorless solid; mp 61.8–62.1 °C. ^{1}H NMR (600 MHz, $CDCl_3$, δ): 3.81 (d, $J = 1.5$ Hz, 1H), 4.17 (d, $J = 1.5$ Hz, 1H), 7.27–7.30 (m, 1H), 7.31–7.33 (m, 2H), 7.34–7.36 (m, 1H), 7.36–7.39 (m, 3H), 7.39–7.43 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 58.9 (CH), 62.5 (CH), 125.4 (CH), 125.7 (2CH), 126.3 (CH), 126.9 (CH), 127.6 (CH), 128.6 (2CH), 129.1 (CH), 130.3 (C), 133.0 (C), 136.1 (C), 137.8 (C). IR (KBr): 2113, 1596, 1481 cm^{-1}. ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{15}H_{11}NNaOS$, 276.0454; found, 276.0447.

cis-**2**: Colorless solid; mp 49.4–50.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.43 (d, $J = 3.9$ Hz, 1H), 4.47 (d, $J = 3.9$ Hz, 1H), 6.96–7.03 (m, 1H), 7.10–7.22 (m, 7H), 7.40 (d, $J = 7.1$ Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 57.7 (CH), 59.3 (CH), 125.2 (CH), 126.3 (2CH), 126.7 (CH), 127.8 (3CH), 128.5 (CH), 128.6 (CH), 129.3 (C), 131.7 (C), 133.6 (C), 137.0 (C). IR

(KBr): 2036, 1488, 894 755 cm^{-1}. ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{15}H_{11}NNaOS$, 276.0454; found, 276.0443.

4.5. *Typical procedure for the reactions with carbon nucleophiles*

trans-Epoxy isothiocyanate (*trans*-**2**) (101 mg, 0.40 mmol) was added to a stirred THF (4 mL) solution of dimethyl sodiomalonate, prepared from 60% sodium hydride (19.2 mg, 0.48 mmol) and dimethyl malonate (55 μL, 0.48 mmol) at −78 °C. The mixture was slowly warmed to 0 °C and stirred for a further 1.5 h. The mixture was quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The organic layers were dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 1/1) to yield *erythro*-**3a** (142 mg, 92%).

erythro-**3a**: Colorless solid; mp 153.2–153.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 2.48 (br s, 1H, OH), 3.73 (s, 3H), 3.76 (s, 3H), 3.91 (d, J = 7.3 Hz, 1H), 4.72 (d, J = 7.3 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 7.09–7.10 (m, 2H), 7.14–7.20 (m, 2H), 7.23–7.34 (m, 4H), 12.4 (s, 1H, N*H*). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 48.8 (CH), 51.6 (CH_3), 51.9 (CH_3), 76.3 (CH), 92.7 (C), 118.5 (CH), 120.3 (C), 124.1 (CH), 126.8 (2CH), 128.0 (2CH), 128.4 (CH), 129.2 (CH), 129.4 (CH), 135.4 (C), 139.5 (C), 160.2 (C), 166.9 (C), 168.5 (C). IR (KBr): 3455, 3023, 1542, 1257 cm^{-1}. ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{20}H_{19}NNaO_5S$, 408.0876; found, 408.0876. Anal. calcd. for $C_{20}H_{19}NO_5S$ (385.43): C, 62.32; H, 4.97; N. 3.63. Found: C, 62.26; H, 5.05; N. 3.62.

erythro-**3b**: Colorless solid; mp 164.2–164.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 2.13 (d, J = 3.9 Hz, 1H, O*H*), 2.37 (br s, 3H), 2.46 (br s, 3H), 4.09 (d, J = 6.9 Hz, 1H), 4.74 (d, J = 6.9 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 7.07–7.13 (m, 3H), 7.18 (dd, J = 7.3, 7.3 Hz, 1H), 7.27–7.38 (m, 4H), 14.7 (s, 1H, N*H*). ^{13}C NMR (76 MHz, $CDCl_3$, δ): 30.2 (CH_3), 31.8 (CH_3), 48.8 (CH), 76.7 (CH), 114.3 (C), 119.5 (CH), 120.7 (C), 125.2 (CH), 126.7 (2CH), 128.2 (2CH), 128.7 (CH), 129.2 (CH), 129.5 (CH), 135.0 (C), 139.5 (C), 161.8 (C), 194.7 (C), 198.7 (C). IR (KBr): 3347, 1658, 1542, 1373 cm^{-1}. ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{20}H_{19}NNaO_3S$, 376.0978; found, 376.0984.

threo-**3a**: Colorless solid; mp 137.2–137.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.04 (s, 1H, O*H*), 3.83 (d, J = 12.4 Hz, 6H), 3.94 (d, J = 8.3 Hz, 1H), 4.59 (d, J = 8.3 Hz, 1H), 6.38 (d, J = 7.3 Hz, 1H), 6.81 (d, J = 7.3 Hz, 1H), 6.90–7.02 (m, 3H), 7.10–7.40 (m, 4H), 12.57 (br s, 1H). ^{13}C NMR (76 MHz, $CDCl_3$, δ): 50.9 (CH_3), 51.7 (CH_3), 52.1 (CH), 74.9 (CH), 93.2 (C), 118.2 (CH), 120.3 (C), 124.0 (CH), 126.6 (2CH), 127.9 (2CH), 128.2 (CH), 128.9 (CH), 129.1 (CH), 135.3 (C), 139.4 (C), 160.5 (C), 167.2 (C), 168.8 (C). IR (KBr): 3432, 3031, 2938, 1689, 1558, 1234 cm^{-1}. ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{20}H_{19}NNaO_5S$, 408.0876; found, 408.0875.

threo-**3b**: Colorless solid; mp 78.7–78.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.39–2.50 (br s, 3H), 2.52–2.61 (br s, 3H), 2.71 (d, J = 2.6 Hz, 1H), 3.97 (d, J = 8.4 Hz, 1H), 4.54 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 7.4 Hz, 1H), 6.85–6.99 (m, 4H), 7.01 (d, J = 7.8 Hz, 1H), 7.14–7.25 (m, 3H). (A peak of one NH proton was not observed.) ^{13}C NMR (126 MHz, $CDCl_3$, δ): 30.0 (CH_3), 31.8 (CH_3), 50.4 (CH), 75.2 (CH), 114.4 (CH), 118.9 (CH), 120.8 (C), 124.9 (CH), 126.5 (2CH), 127.9 (2CH), 128.2 (CH), 128.7 (CH), 129.2 (CH), 134.7 (C), 139.7 (C), 162.1 (C), 194.9 (C), 198.4 (C). IR (KBr): 3332, 2360, 1535, 1365, 1241 cm^{-1}. ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{20}H_{19}NNaO_3S$, 376.0978; found, 376.0990.

4.6. *Typical procedure for the reactions with sulfur nucleophiles*

Dodecanethiol (115 μL, 0.48 mmol) and triethylamine (10 μL, 0.07 mmol) were added to a dichloromethane (2 mL) solution of *trans*-epoxy isothiocyanate (*trans*-**2**) (101 mg, 0.40 mmol). The mixture was stirred for 16 h and concentrated under reduced pressure. The residue was purified

by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to yield *erythro*-**4a** (141 mg, 78%).

erythro-**4a**: Colorless solid; mp 46.8–47.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.84–0.93 (m, 3H), 1.26–1.40 (m, 18H), 1.56–1.70 (m, 2H), 2.55 (br s, 1H), 3.00 (ddd, J = 7.5, 7.5, 13.0 Hz, 1H), 3.25 (ddd, J = 7.5, 7.5, 13.0 Hz, 1H), 3.93 (d, J = 8.2 Hz, 1H), 4.44 (d, J = 8.2 Hz, 1H), 7.12 (ddd, J = 1.3, 7.4, 7.4 Hz, 1H), 7.16–7.35 (m, 8H). ^{13}C NMR (76 MHz, $CDCl_3$, δ): 14.1 (CH_3), 22.6 (CH_2), 28.7 (CH_2), 29.1 ($2CH_2$), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.2 (CH_2), 31.8 (CH_2), 50.5 (CH), 75.4 (CH), 120.6 (C), 126.0 (2CH), 127.1 (2CH), 127.9 (2CH), 128.1 (CH), 128.9 (CH), 129.3 (CH), 139.9 (C), 142.8 (C), 158.8 (C). IR (KBr): 3424, 2915, 1535, 956 cm^{-1}. ESI-MS (m/z): $[M+H]^+$ calcd. for $C_{27}H_{38}NOS_2$, 456.2389; found, 456.2387.

erythro-**4b**: Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.19 (br s, 1H), 4.02 (d, J = 8.1 Hz, 1H), 4.53 (d, J = 8.1 Hz, 1H), 7.10–7.25 (m, 5H), 7.28–7.46 (m, 7H), 7.53–7.64 (m, 2H). ^{13}C NMR (76 MHz, $CDCl_3$, δ): 50.7 (CH), 75.6 (CH), 119.9 (C), 126.4 (CH), 126.6 (CH), 127.1 (2CH), 127.9 (2CH), 128.1 (CH), 128.6 (C), 128.9 (3CH), 129.3 (CH), 129.5 (CH), 135.2 (2CH), 139.8 (C), 142.8 (C), 159.9 (C). IR (KBr): 3378, 3062, 1535, 1481, 941 cm^{-1}. ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{21}H_{17}NNaOS_2$, 386.0644; found, 386.0632.

threo-**4a**: Yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.84–0.91 (m, 3H), 1.23–1.28 (m, 17H), 1.56–1.79 (m, 2H), 2.41–2.58 (m, 1H), 2.88–2.96 (br s, 1H, O*H*), 3.03–3.19 (m, 1H), 3.32–3.47 (m, 1H), 3.96 (d, J = 9.0 Hz, 1H), 4.40 (d, J = 9.0 Hz, 1H), 6.25 (d, J = 7.8 Hz, 1H), 6.77–6.89 (m, 1H), 6.91–7.01 (m, 2H), 7.10–7.30 (m, 5H). ^{13}C NMR (76 MHz, $CDCl_3$, δ): 14.1 (CH_3), 22.7 (CH_2), 28.8 (CH_2), 29.1 ($2CH_2$), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 ($2CH_2$), 31.4 (CH_2), 31.9 (CH_2), 53.6 (CH), 74.4 (CH), 120.3 (C), 125.7 (CH), 125.8 (CH), 126.8 (2CH), 127.9 (2CH), 128.1 (CH), 128.6 (CH), 128.9 (CH), 139.6 (C), 142.9 (C), 157.0 (C). IR (KBr): 3440, 2923, 2854, 1704, 1465 cm^{-1}. ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{27}H_{37}NNaOS_2$, 478.2209; found, 478.2209.

4.7. *Typical procedure for the reactions with nitrogen nucleophiles*

Cyclohexylamine (41 μL, 0.4 mmol) was added to a dichloromethane (5 mL) solution of *trans*-epoxy isothiocyanate (*trans*-**2**) (76 mg, 0.30 mmol) at 0 °C. After 10 min, the mixture was concentrated under reduced pressure. The residue was washed with a small amount of hexane to give *erythro*-**6e** (100 mg, 95%).

erythro-**6e**: Colorless solid; mp 155.4–157.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.00–1.29 (m, 3H), 1.30–1.51 (m, 2H), 1.52–1.80 (m, 4H), 1.96–2.10 (m, 2H), 3.88–3.98 (br s, 1H), 4.00 (d, J = 8.4 Hz, 1H), 4.60 (d, J = 8.4 Hz, 1H), 7.05 (dt, J = 1.3, 7.3 Hz, 1H), 7.12 (dd, J = 0.9, 7.9 Hz, 1H), 7.18 (dd, J = 1.5, 7.4 Hz, 1H), 7.26–7.40 (m, 6H). ^{13}C NMR (76 MHz, $CDCl_3$, δ): 24.8 ($2CH_2$), 25.6 (CH_2), 33.0 (CH_2), 33.9 (CH_2), 50.4 (CH), 50.8 (CH), 75.7 (CH), 119.7 (C), 122.9 (CH), 125.2 (CH), 127.0 (CH), 127.2 (2CH), 128.1 (2CH), 128.8 (CH), 129.0 (CH), 140.5 (C), 145.3 (C), 151.8 (C). IR (KBr): 3394, 2931, 1558 cm^{-1}. ESI-MS (m/z): $[M+H]^+$ calcd. for $C_{21}H_{25}N_2OS$, 353.1682; found, 353.1683.

erythro-**5a**: Colorless solid; mp 136–137 °C. ^{1}H NMR ($CDCl_3$, 600 MHz, δ): 1.17 (t, J = 7.0 Hz, 6H), 2.08 (dd, J = 1.0, 3.0 Hz, OH, 1H), 3.40–3.49 (m, 2H), 3.69–3.74 (m, 2H), 4.03 (d, J = 8.6 Hz, 1H), 4.57 (d, J = 8.6 Hz, 1H), 7.03 (dd, J = 7.4, 7.4 Hz, 1H), 7.11 (d, J = 7.4 Hz, 1H), 7.19 (d, J = 7.9 Hz, 1H), 7.29–7.36 (m, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz, δ): 14.1 ($2CH_3$), 43.2 ($2CH_3$), 50.5 (CH), 75.6 (CH), 118.9 (C), 122.4 (C), 125.2 (CH), 127.3 (CH), 128.2 (CH), 128.3 (2CH), 128.5 (2CH), 129.0 (CH), 140.6 (C), 145.9 (C), 152.2 (C). IR (neat): 2969, 2931, 1543 cm^{-1}. ESI-MS (m/z): $[M+H]^+$ calcd. for $C_{19}H_{23}N_2OS$, 327.1526; found, 327.1517.

erythro-**5b**: Colorless solid; mp 131.0–133.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 1.53–1.70 (m, 6H), 3.60–3.80 (m, 4H), 4.03 (d, $J = 8.5$ Hz, 1H), 4.57 (d, $J = 8.5$ Hz, 1H), 7.05 (dt, $J = 1.1$, 7.4 Hz, 1H), 7.11 (d, $J = 7.3$ Hz, 1H), 7.18 (dd, $J = 1.1$, 7.3 Hz, 1H), 7.27–7.37 (m, 6H). ^{13}C NMR (76 MHz, $CDCl_3$, δ): 24.9 (CH_2), 26.0 ($2CH_2$), 45.7 ($2CH_2$), 50.5 (CH), 75.4 (CH), 119.4 (C), 122.7 (CH), 125.1 (CH), 127.3 (2CH), 128.0 (2CH), 128.1 (CH), 128.6 (CH), 128.8 (CH), 140.7 (C), 145.4 (C), 153.6 (C). IR (KBr): 3239, 2931, 1542, 1234 cm^{-1}. ESI-MS (m/z): $[M+H]^+$ calcd. for $C_{20}H_{23}N_2OS$, 339.1526; found, 339.1526.

threo-**5a**: Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.25 (t, $J = 7.0$ Hz, 6H), 2.92 (br s, 1H), 3.52–3.80 (m, 4H), 3.98 (d, $J = 8.5$ Hz, 1H), 4.45 (d, $J = 8.5$ Hz, 1H), 6.22 (dd, $J = 1.2$, 6.7 Hz, 1H), 6.65 (ddd, $J = 1.2$, 7.3, 7.3 Hz, 1H), 6.96–7.04 (m, 2H), 7.07 (dd, $J = 1.2$, 7.9 Hz, 1H), 7.10–7.25 (m, 4H). ^{13}C NMR (76 MHz, $CDCl_3$, δ): 14.1 ($2CH_3$), 43.5 ($2CH_2$), 53.5 (CH), 74.4 (CH), 118.6 (C), 121.9 (CH), 124.5 (CH), 126.9 (2CH), 127.8 (2CH), 127.9 (CH), 128.2 (CH), 128.4 (CH), 140.0 (C), 145.6 (C), 150.8 (C). IR (KBr): 3417, 2862, 1550, 1465, 1241 cm^{-1}. ESI-MS (m/z): $[M+H]^+$ calcd. for $C_{19}H_{23}N_2OS$, 327.1526; found, 327.1527.

threo-**5b**: Colorless solid; mp 114.4–116.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.60–1.77 (m, 6H), 2.95 (s, 1H), 3.70–3.93 (m, 4H), 4.00 (d, $J = 8.8$ Hz, 1H), 4.46 (d, $J = 8.8$ Hz, 1H), 6.21 (d, $J = 7.5$ Hz, 1H), 6.68 (dd, $J = 7.5$, 7.5 Hz, 1H), 6.98–7.23 (m, 7H). ^{13}C NMR (76 MHz, $CDCl_3$, δ): 24.9 (CH_2), 25.9 ($2CH_2$), 47.7 ($2CH_2$), 53.5 (CH), 74.4 (CH), 118.8 (C), 122.4 (CH), 124.6 (CH), 126.9 (2CH), 127.8 (2CH), 127.9 (CH), 128.3 (CH), 128.4 (CH), 149.9 (C), 145.4 (C), 151.9 (C). IR (KBr): 3401, 2931, 2360, 1542 cm^{-1}. ESI-MS (m/z): $[M+H]^+$ calcd. for $C_{20}H_{23}N_2OS$, 339.1526; found, 339.1523.

erythro-**6a**: Colorless solid; mp 69.0–71.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$, δ): 3.03 (s, 3H), 4.01 (d, $J = 8.3$ Hz, 1H), 4.62 (d, $J = 8.3$ Hz, 1H), 7.07 (t, $J = 7.4$ Hz, 1H), 7.16–7.19 (m, 2H), 7.30–7.38 (m, 6H). (Peaks of one NH and one OH proton were not observed.) ^{13}C NMR (150 MHz, $CDCl_3$, δ): 29.3 (CH_3), 50.5 (CH), 75.8 (CH), 119.6 (C), 123.2 (CH), 125.5 (CH), 127.3 (2CH), 128.1 (2CH), 128.3 (CH), 128.9 (CH), 129.0 (CH), 140.3 (C), 145.3 (C), 150.9 (C). IR (KBr): 3278, 1565, 1211, 902 cm^{-1}. ESI-MS (m/z): $[M+H]^+$ calcd. for $C_{16}H_{17}N_2NaOS$, 285.1056; found, 285.1056.

erythro-**6b**: Pale yellow solid; mp 111.1–113.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.95 (t, $J = 7.4$ Hz, 3H), 1.50–1.70 (m, 2H), 3.40 (t, $J = 6.8$ Hz, 2H), 4.00 (d, $J = 8.4$ Hz, 1H), 4.56 (d, $J = 8.4$ Hz, 1H), 7.00–7.14 (m, 2H), 7.18 (d, $J = 6.2$ Hz, 1H), 7.22–7.40 (m, 6H). ^{13}C NMR (76 MHz, $CDCl_3$, δ): 11.4 (CH_3), 22.9 (CH_2), 44.2 (CH_2), 50.3 (CH), 75.6 (CH), 119.9 (C), 122.9 (CH), 125.2 (CH), 126.9 (CH), 127.2 (2CH), 128.1 (2CH), 128.7 (CH), 128.9 (CH), 140.5 (C), 145.1 (C), 151.7 (C). IR (KBr): 3347, 1565, 1488, 1195 cm^{-1}. ESI-MS (m/z): (m/z): $[M+H]^+$ calcd. for $C_{18}H_{21}N_2OS$, 313.1369; found, 313.1374. Anal. calcd. for $C_{18}H_{20}N_2OS$ (312.43): C, 69.20; H, 6.45; N. 8.97. Found: C, 68.93; H, 6.66; N. 8.82.

erythro-**6c**: Colorless solid; mp 154–155 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 1.21 (d, $J = 6.2$ Hz, 3H), 1.26 (d, $J = 6.2$ Hz, 3H), 4.02 (d, $J = 8.2$ Hz, 1H), 4.29 (septet, $J = 6.4$ Hz, 1H), 4.61 (d, $J = 8.2$ Hz, 1H), 7.06 (dt, $J = 1.3$, 7.3 Hz, 1H), 7.14 (d, $J = 8.1$ Hz, 1H), 7.18 (dd, $J = 1.5$, 7.5 Hz, 1H), 7.29–7.40 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 22.7 (CH_3), 23.5 (CH_3), 44.1 (CH), 50.4 (CH), 75.8 (CH), 119.6 (C), 123.1 (CH), 125.4 (CH), 127.3 (CH), 128.2 (2CH), 128.3 (2CH), 128.9 (CH), 129.1 (CH), 140.4 (C), 145.4 (C), 150.4 (C). IR (KBr): 3409, 2969, 1573, 1203 cm^{-1}. Anal. calcd. for $C_{18}H_{20}N_2OS$ (312.43): C, 69.20; H, 6.45; N, 8.97; Found: C, 69.19; H, 6.65; N, 8.88.

erythro-**6d**: Colorless solid; mp 143–144 °C. ^{1}H NMR (600 MHz, $CDCl_3$, δ): 4.03 (d, $J = 8.6$ Hz, 1H), 4.06–4.16 (m, 2H), 4.63 (d, $J = 8.6$ Hz, 1H), 5.19 (dd, $J = 1.3$, 9.9 Hz, 1H), 5.27 (dd, $J = 1.3$, 17.0 Hz, 1H), 5.93 (ddt, $J = 5.6$, 10.3, 17.0 Hz, 1H), 7.08 (dt, $J = 7.4$ Hz, 1H), 7.13–7.20 (m, 2H), 7.29–7.37 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 44.8 (CH_2), 50.4 (CH), 75.8 (CH), 116.8 (CH), 119.7 (C), 123.4 (CH), 125.4 (CH), 127.3 (CH), 128.2 (2CH), 128.3 (2CH), 128.9 (CH), 129.1 (CH), 134.4 (CH), 140.3 (C), 145.1 (C), 151.3 (C). IR (KBr): 3332,

3293, 1635, 1565 cm^{-1}. ESI-MS (m/z): [M+Na]$^+$ calcd. for $C_{18}H_{18}N_2NaOS$, 333.1032; found 333.1022.

erythro-**6f**: Colorless solid; mp 173–175 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.10 (d, J = 8.0 Hz, 1H), 4.70 (d, J = 8.0 Hz, 1H), 7.02–7.23 (m, 4H), 7.26–7.40 (m, 8H), 7.50 (d, J = 7.8 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$, δ): 50.6 (CH), 76.0 (CH), 119.5 (C), 120.6 (CH), 123.6 (CH), 123.9 (CH), 125.9 (C), 126.9 (CH), 127.2 (2CH), 128.2 (2CH), 128.4 (CH), 128.8 (CH), 128.9 (2CH), 129.1 (CH), 129.3 (CH), 140.0 (C), 143.4 (C), 148.4 (C). IR (KBr): 3247, 1550, 1480, 755 cm^{-1}. ESI-MS (m/z): [M+H]$^+$ calcd. for $C_{21}H_{19}N_2OS$, 347.1213; found, 347.1228.

threo-**6b**: Colorless solid; mp 51.6–53.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.00 (t, J = 7.3 Hz, 3H), 1.57–1.75 (m, 2H), 3.38–3.67 (m, 2H), 3.95 (d, J = 8.8 Hz, 1H), 4.48 (d, J = 8.8 Hz, 1H), 6.22 (d, J = 7.3 Hz, 1H), 6.69 (dd, J = 7.3, 7.3 Hz, 1H), 6.92–7.06 (m, 2H), 7.07–7.24 (m, 5H). ^{13}C NMR (76 MHz, $CDCl_3$, δ): 11.5 (CH_3), 22.8 (CH_3), 44.3 (CH_2), 53.7 (CH), 74.5 (CH), 119.4 (C), 122.7 (CH), 124.7 (CH), 126.9 (2CH), 127.9 (2CH), 128.0 (CH), 128.5 (CH), 128.6 (CH), 139.9 (C), 145.1 (C), 150.2 (C). IR (KBr): 3401, 1565, 1473 cm^{-1}. ESI-MS (m/z): [M+H]$^+$ calcd. for $C_{18}H_{21}N_2OS$, 313.1369; found, 313.1372.

threo-**6e**: Colorless solid; mp 114.4–116.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.09–1.54 (m, 5H), 1.55–1.94 (m, 3H), 2.00–2.19 (m, 2H), 3.96 (d, J = 9.0 Hz, 1H), 3.99–4.15 (m, 1H), 4.49 (d, J = 9.0 Hz, 1H), 6.21 (d, J = 7.3 Hz, 1H), 6.67 (dd, J = 7.3, 7.3 Hz, 1H), 6.96–7.04 (m, 2H), 7.07–7.24 (m, 5H). ^{13}C NMR (76 MHz, $CDCl_3$, δ): 24.7 (CH_2), 24.8 (CH_2), 25.6 (CH_2), 33.0 (CH_2), 33.7 (CH_2), 51.1 (CH), 53.7 (CH), 74.4 (CH), 119.4 (C), 122.6 (CH), 124.6 (CH), 126.8 (2CH), 127.9 (2CH), 128.0 (CH), 128.5 (CH), 128.6 (CH), 140.0 (C), 145.0 (C), 149.8 (C). IR (KBr): 3286, 2923, 2854, 1565, 1511 cm^{-1}. ESI-MS (m/z): [M+H]$^+$ calcd. for $C_{21}H_{25}N_2OS$, 353.1682; found, 353.1674.

4.8. *Typical procedure for the rearrangement of erythro-6b–e to yield trans-8b–e*

erythro-**6b** (23.0 mg, 0.074 mmol) was dissolved in chloroform-*d* (0.75 mL). After 5 days, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1/3) to yield *trans*-thiirane (*trans*-**8b**) (15.8 mg, 69%).

trans-**8b**: Colorless solid; mp 114.3–115.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 0.85 (t, J = 7.4 Hz, 3H), 1.34–1.50 (m, 2H), 3.00–3.18 (m, 2H), 4.07 (d, J = 5.2 Hz, 1H), 4.16 (d, J = 5.2 Hz, 1H), 4.70 (br s, 1H) 6.49–6.64 (m, 1H) 7.17 (dd, J = 7.4, 7.4 Hz, 1H), 7.27–7.48 (m, 7H), 7.51 (d, J = 7.8 Hz, 1H). ^{13}C NMR (76 MHz, $CDCl_3$, δ): 11.3 (CH_3), 23.2 (CH_2), 41.8 (CH), 42.1 (CH_2), 43.9 (CH), 125.3 (CH), 125.7 (CH), 127.0 (2CH), 127.5 (CH), 128.0 (CH), 128.7 (2CH), 128.8 (CH), 131.9 (C), 137.2 (C), 138.0 (C), 156.0 (C). IR (KBr): 3430, 3309, 2337, 1635 cm^{-1}. ESI-MS (m/z): [M+Na]$^+$ calcd. for $C_{18}H_{20}N_2NaOS$, 335.1189; found, 335.1182.

trans-**8c**: Colorless solid; mp 154–155 °C. ^{1}H NMR (600 MHz, $CDCl_3$, δ): 1.05 (d, J = 6.4 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H), 3.84–3.92 (m, 1H), 4.05 (d, J = 5.4 Hz, 1H), 4.14 (d, J = 5.4 Hz, 1H), 4.52 (br d, J = 7.4 Hz, 1H), 6.37 (br s, 1H), 7.18 (dd, J = 7.6, 7.6 Hz, 1H), 7.26–7.31 (m, 3H), 7.32–7.35 (m, 3H), 7.38 (d, J = 7.5 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 23.1 (CH_3), 23.2 (CH_3), 42.0 (CH), 42.5 (CH), 43.9 (CH), 125.0 (CH), 125.7 (CH), 126.7 (CH), 127.0 (2CH), 127.7 (CH), 128.1 (CH), 128.8 (2CH), 131.7 (C), 137.3 (C), 138.0 (C), 155.2 (C). IR (KBr): 3324, 1635, 1558 cm^{-1}. ESI-MS (m/z): [M+H]$^+$ calcd. for $C_{18}H_{20}N_2OS$, 313.1369; found, 313.1385.

trans-**8d:** Colorless solid; mp 147.4–178.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.56–3.82 (m, 2H), 4.03 (d, J = 5.3 Hz, 1H), 4.13 (d, J = 5.3 Hz, 1H), 4.52 (br s, 1H), 5.03–5.19 (m, 2H), 5.73–5.82 (m, 1H), 6.32 (br s, 1H), 7.21 (dd, J = 7.4, 7.4 Hz, 1H), 7.28–7.40 (m, 7H), 7.54 (d, J = 7.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 41.8 (CH), 42.8 (CH_2), 43.9 (CH), 115.9

(CH_2), 125.4 (CH), 125.9 (CH), 127.0 (2CH), 127.5 (CH), 128.0 (CH), 128.7 (2CH), 128.8 (CH), 133.9 (C), 134.8 (CH), 137.0 (C), 138.0 (C), 155.8 (C). IR (KBr): 3332, 3293, 1635 cm^{-1}. ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{18}H_{18}N_2NaOS$, 333.1032; found, 333.1024.

trans-**8e:** Colorless solid; mp 171.2–172.5 °C. ^1H NMR (500 MHz, $CDCl_3$, δ): 0.80–1.16 (m, 4H), 1.27–1.38 (m, 2H), 1.59–1.71 (m, 2H), 1.81–1.84 (m, 1H), 1.91–1.94 (m, 1H), 3.51–3.61 (m, 1H), 4.09 (d, $J = 5.4$ Hz, 1H), 4.13 (d, $J = 5.4$ Hz, 1H), 4.30 (br s, 1H), 6.25 (br s, 1H), 7.18 (dd, $J = 7.3$, 7.3 Hz, 1H), 7.27–7.40 (m, 7H), 7.54 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 24.9 (CH_2), 25.5 (CH_2), 29.7 (CH_2), 33.5 (CH_2), 33.6 (CH_2), 42.1 (CH), 43.9 (CH), 49.3 (CH), 125.0 (CH), 125.7 (CH), 127.0 (2CH), 127.7 (CH), 128.1 (CH), 128.7 (2CH), 128.8 (CH), 131.8 (C), 137.3 (C), 138.0 (C), 155.0 (C). IR (KBr): 3309, 2931, 1627 cm^{-1}. ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{21}H_{24}N_2NaOS$, 375.1502; found, 375.1500.

4.9. *Preparation of erythro-10c*

Isopropylamine (30 μL, 0.35 mmol) was added to a stirred pyridine (5 mL) solution of *trans*-**2** (76 mg, 0.3 mmol) at 0 °C. After 10 min, triethylsilyl chloride (100 μL, 0.6 mmol) was added, and the mixture was stirred for 30 min. The mixture was quenched with water, extracted with ethyl acetate, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1/5) to yield *erythro*-**10c** (100 mg, 79%).

erythro-**10c**: Colorless oil. ^1H NMR (600 MHz, $CDCl_3$, δ): 0.18–0.30 (m, 6H), 0.68 (t, $J =$ 7.9 Hz, 9H), 1.22 (d, $J = 6.5$ Hz, 3H), 1.27 (d, $J = 6.5$ Hz, 3H), 3.97 (d, $J = 8.4$ Hz, 1H), 4.22–4.34 (m, 1H), 4.42 (br s, 1H), 4.54 (d, $J = 8.4$ Hz, 1H), 7.05 (ddd, $J = 1.2$, 7.5, 7.5 Hz, 1H), 7.13 (d, $J = 7.5$ Hz, 1H), 7.23 (dd, $J = 1.2$, 7.5 Hz, 1H), 7.26–7.35 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 4.4 ($3CH_2$), 6.5 ($3CH_2$), 22.8 (CH_3), 23.6 (CH_3), 43.9 (CH), 51.4 (CH), 76.3 (CH), 121.3 (C), 122.6 (CH), 124.8 (CH), 127.3 (2CH), 127.7 (2CH), 127.8 (CH), 128.3 (CH), 129.7 (CH), 142.3 (C), 145.1 (C), 150.3 (C). IR (KBr): 2962, 2877, 1573, 1481 cm^{-1}. ESI-MS (m/z): $[M+H]^+$ calcd. for $C_{24}H_{35}N_2OSSi$, 427.2234; found, 427.2234.

4.10. *Typical procedure for the reactions with sodium methoxide*

A solution of sodium methoxide (1.0 M, 0.36 mL, 0.36 mmol) in methanol was added to a stirred solution of *trans*-**2** (76 mg, 0.3 mmol) in dichloromethane (3 mL) at 0 °C. The mixture was stirred for 2 h, quenched with saturated aqueous ammonium chloride, and extracted using dichloromethane. The organic layer was dried over magnesium sulfate, then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/3) to yield *erythro*-**11** (56 mg, 66%) and *trans*-**12** (24 mg, 28%).

erythro-**11**: Colorless solid: mp 88.6–89.0 °C. ^1H NMR (500 MHz, $CDCl_3$, δ): 2.17 (br s, 1H), 3.84 (s, 3H), 4.15 (d, $J = 6.8$ Hz, 1H), 4.66 (d, $J = 6.8$ Hz, 1H), 7.09–7.19 (m, 5H), 7.23–7.32 (m, 4H). ^{13}C NMR (76 MHz, $CDCl_3$, δ): 51.1 (CH), 55.2 (CH_3), 76.6 (CH), 119.4 (C), 125.1 (CH), 126.0 (CH), 127.1 (2CH), 127.9 (2CH), 128.2 (CH), 128.9 (CH), 129.0 (CH), 139.2 (C), 143.3 (C), 159.4 (C). IR (KBr): 3309, 1581, 1203, 755 cm^{-1}. ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{16}H_{15}NNaO_2S$, 308.0716; found, 308.0727.

trans-**12:** Colorless solid; mp 78.7–79.5 °C. ^1H NMR (300 MHz, $CDCl_3$, δ): 3.68 (s, 3H), 4.02 (d, $J = 5.5$ Hz, 1H), 4.15 (d, $J = 5.5$ Hz, 1H), 6.93 (br s, 1H), 7.12 (dd, $J = 7.5$, 7.5 Hz, 1H), 7.26–7.43 (m, 7H), 7.71 (br s, 1H). ^{13}C NMR (76 MHz, $CDCl_3$, δ): 42.7 (CH), 43.3 (CH), 52.5 (CH_3), 122.4 (CH), 124.6 (CH), 127.0 (2CH), 128.1 (2CH), 128.7 (3CH), 136.7 (2C), 137.8 (C), 154.3 (C). IR (KBr): 3324, 2360, 1697, 1527, 1249 cm^{-1}. ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{16}H_{15}NNaO_2S$, 308.0716; found, 308.0728.

threo-**11**: Colorless solid; mp 70.1–72.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 2.97 (br s, 1H), 4.01 (d, $J = 8.9$ Hz, 1H), 4.02 (s, 3H), 4.48 (d, $J = 8.9$ Hz, 1H), 6.32 (d, $J = 7.7$ Hz, 1H), 6.83 (dd, $J = 7.7, 7.7$ Hz, 1H), 6.97–7.00 (m, 2H), 7.17–7.25 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 53.7 (CH), 55.4 (CH_3), 75.4 (CH), 119.7 (C), 124.9 (CH), 125.6 (CH), 126.9 (2CH), 127.9 (2CH), 128.1 (CH), 128.7 (CH), 128.8 (CH), 139.5 (C), 143.0 (C), 158.4 (C). IR (KBr): 3270, 2954, 1727, 1697, 1523, 1280, 1064 cm^{-1}. ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{16}H_{15}NNaO_2S$, 308.0716; found, 308.0720.

cis-**12:** Colorless solid; mp 95.8–96.7 °C. ^{1}H NMR (600 MHz, $CDCl_3$, δ): 3.73 (s, 3H), 4.29 (d, J6.9 Hz, 1H), 4.39 (d, $J = 6.9$ Hz, 1H), 6.33 (br s, 1H), 7.02–7.09 (m, 3H), 7.10–7.14 (m, 3H), 7.20 (ddd $J = 1.0, 7.2, 7.2$ Hz, 1H), 7.34 (br d, $J = 7.2$ Hz, 1H), 7.47 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 41.8 (CH), 43.0 (CH), 52.5 (CH_3), 121.7 (CH), 124.2 (CH), 127.7 (CH), 127.8 (2CH), 128.3 (2CH), 128.5 (CH), 131.9 (CH), 134.5 (C), 136.1 (C), 136.2 (C), 154.1 (C). IR (KBr): 3270, 1689, 1527, 1249, 1064 cm^{-1}. ESI-MS (m/z): $[M+Na]^+$ calcd. for $C_{16}H_{15}NNaO_2S$, 308.0716; found, 308.0716. Anal. calcd. for $C_{16}H_{15}NO_2S$ (285.36): C, 67.34; H, 5.30; N. 4.91; Found C, 67.51; H, 5.65; N, 4.91.

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