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Michael Addition−Aromatization Reaction of Dienylimines Bearing a Leaving Group and Its Application to the Preparation of Thiol-Selective Labeling Reagents Capable of Forming Strong Carbon−Sulfur Bonds

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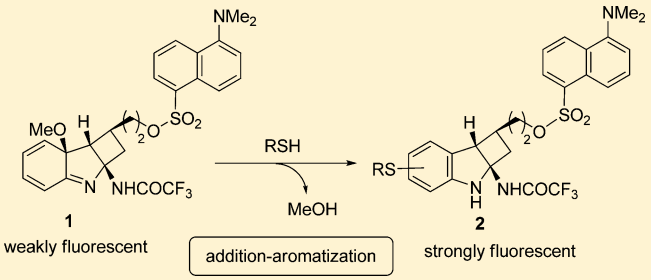
Supporting Information

ABSTRACT: The reaction of a dienylimine with thiols was found to proceed smoothly to afford the corresponding indolines bearing aromatic carbon−sulfur bonds as a result of a Michael addition−aromatization sequence. Furthermore, this reaction was applied to the development of fluorogenic dienylimines that could be used as thiol-selective fluorescent labeling reagents.



INTRODUCTION

Biothiols such as cysteine, homocysteine, and glutathione play an important role in maintaining biological redox homeostasis through the equilibrium of free thiols and oxidized disulfides.[1] As a consequence of their importance, there has been considerable interest in the development of methods for the selective detection of thiols.[2] Thiols have also been used as targets for protein labeling because of their nucleophilicity. The labeling of cysteine residues with thiol reactive reagents is a general approach for the site-specific labeling of proteins,[3] and there is currently substantial interest in the development of different reagents for the labeling of thiols. For example, Apo-AI, which is a major protein component of high-density lipoprotein (HDLs), contains no cysteine in its sequence, whereas Apo-B100, which is an apolipoprotein of low-density lipoprotein (LDLs), possesses a cysteine residue. A thiol-selective fluorescent labeling reagent could therefore be used to label LDLs exclusively in the presence of HDLs. The "response-to-retention" hypothesis proposes that the retention of LDLs by proteoglycans (PGs) is the initiating step in atherosclerosis.[4] With this in mind, the development of compounds allowing for the selective labeling of LDLs could provide useful tools for probing the mechanism of atherosclerosis.

To date, various types of organic reactions have been used for the detection of thiols by fluorescent probes. For example, several different research groups, including those of Maeda and Hilderbrand, designed "off−on" fluorescent probes that were based on the addition−elimination type cleavage of sulfonamides or sulfonate esters.[5] Furthermore, the reductive cleavage of disulfide bonds has also been used for the development of fluorescent sensors.[6] Given that these sulfonamide, sulfonate ester, and disulfide based probes detect thiols via the release of the fluorophore, the thiols to be detected were not connected to the fluorophores. It is therefore not possible for these types of probes to label thiols. Cyclization reactions between aldehydes and aminothiols have been also used for the sensitive detection of cysteine and homocysteine.[7] These types of probes are not generally used for protein labeling experiments because the aminothiol structure is necessary for the initial labeling reactions.

Michael addition reactions to maleimide[8] and other α,β-unsaturated carbonyls[9] have also been studied extensively as thiol reactive probes and tags. These Michael acceptor based probes are known to exhibit high levels of selectivity toward the thiol group. The hydrolysis of maleimide to the corresponding unreactive maleamic acid, however, could compete with the addition of the thiol.[10] Furthermore, the C−S bond could be cleaved though a retro-Michael reaction,[11] with concomitant release of the fluorophore from the target molecule. On the basis of these potential limitations, further research toward the development of a selective fluorescent tag that is capable of forming stronger C−S bonds is still required.

Herein, we report the design and synthesis of the dienylimines **1** as novel thiol labeling reagents (eq 1). These dienylimines were subsequently selectively reacted with thiols according to a Michael type 1,4-addition, followed by aromatization with concomitant elimination of MeOH to

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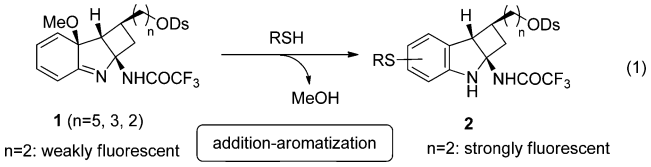
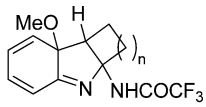


form a strong conjugation product between the fluorophore and the thiols. We have demonstrated that the labeling of thiophenol and octanethiol represents a model study for the detection of biothiols. As a result, these thiols were labeled by fluorescence. In addition, the thiol labeling reagent **1** (n = 2) bearing an ethylene linker increased its fluorescence intensity over the course of the reaction. To the best of our knowledge, there have been very few reports in the literature concerning the use of an addition−aromatization reaction for the labeling of thiols.

RESULTS AND DISCUSSION

Preparation of Dienylimine. For our preliminary experimental work, we investigated the preparation of the dienylimines **3** and their subsequent reaction with thiols.



3a: n=1, **3b**: n=2
3c: n=3, **3d**: n=4

We had previously developed a novel [3,3]-sigmatropic rearrangement involving *N*-trifluoroacetyl enehydrazines for the synthesis of indolines and indoles.[11] In addition, the rearrangement of enehydrazines **4** bearing an *o*-methoxy group on the phenyl ring gave dienylimines **3b**,**c** (Scheme 1). Unfortunately, however, these compounds were formed in low yields. In the case of enehydrazines **4b**,**c**, which contained five- and six-membered rings, respectively, the yields of the corresponding dienylimines **3b**,**c** were 48 and 17%, respectively. These results suggested that the ring size of the enamine moiety in the enehydrazine **4** had a significant impact on the outcome of the rearrangement.

To improve the yield of dienylimine, we further examined the rearrangement−cyclization of enehydrazines **4a**,**d**, which contained four- and seven-membered rings, respectively (Table 1, Scheme 3). The enehydrazines **4a**,**d** were prepared by the condensation reaction of 2-methoxyphenyhydrazine with cyclobutanone or cycloheptanone, followed by the acylation of the respective products with trifluoroacetic anhydride (Scheme 2).[12]

The rearrangement of enehydrazine **4a** bearing a four-membered ring proceeded smoothly in MeCN to afford the two diastereomeric products *cis-syn*-**3a** and *cis-anti*-**3a** in a 51:21 ratio (72% yield), together with indoline **5a** (Table 1, entry 1). Several other solvents were investigated for the transformation, such as toluene, butyronitrile, and trifluoroethanol, but MeCN gave the best yield of the desired dienylimine **3a** (Table 1, entries 2−4).

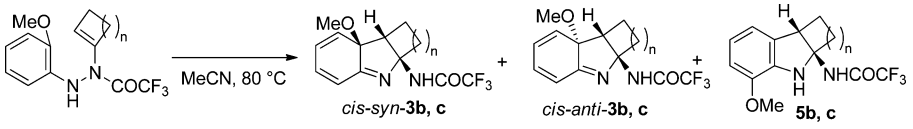
In contrast, the rearrangement of **4d** under the same conditions proceeded with undesired regiochemistry to give indole **5d** as the major product in 47% yield. The desired dienylimine product **3d** was obtained in only 35% yield as a mixture of three diastereomers (Scheme 3).

The results of our preliminary experiments showed that enehydrazine **4a** bearing a four-membered ring was a suitable substrate for the preparation of dienylimine.

Addition of Heteroatom Nucleophiles to Dienylimine. We then proceeded to investigate the nucleophilic addition of a thiol to *cis-syn*-dienylimine **3a** (Scheme 4). It was envisaged that the attack of the thiol could occur at the 3a-, 5-, 6-, or 7-position of dienylimine **3a** to give the corresponding adduct. The *cis-syn*-dienylimine **3a** was dissolved in THF and treated with thiophenol at 0 °C. The 1,4-addition of thiophenol to *cis-syn*-**3a** proceeded smoothly and regioselectively to afford adduct **6** as a mixture of the two diastereomers **6a**,**b** in 70% yield, with indoline **7** in 9% yield. Because the signals of **7** were not observed in the crude ^{1}H NMR spectrum, the indoline **7** was formed by aromatization of **6** during purification. When adducts **6a**,**b** were allowed to stand at room temperature for 15 h, they underwent an aromatization process with concomitant elimination of their methoxy group and migration of the phenylthio group to give the 6-phenylthioindoline **7**. In contrast, the treatment of *cis-syn*-**3a** with thiophenol at room temperature for 13.5 h resulted in the formation of the nonmigrated 5-phenylthioindoline **8** as the major product in addition to 6-phenylthioindoline **7**. Phenol, benzyl alcohol, aniline, and benzylamine were also used as non-thiol-based heteroatom nucleophiles, but the addition reaction did not proceed even at room temperature after 19 h, with only the starting material being recovered.

On the basis of these results, we have proposed a possible reaction pathway for the formation of 5-phenylthioindoline **8** and 6-phenylthioindoline **7** (Scheme 5). The addition of thiophenol would have occurred preferentially at the 5-position of dienylimine **3a** to generate enamine **A** in the reaction system. ^{1}H NMR analysis of the reaction mixture has been used to support the existence of enamine **A** and a trace of imine **6**. Because the product isolated after workup of the reaction mixture was not enamine **A** but imine **6**, it was presumed that the enamine **A** slowly tautomerized to stable imine **6** without the elimination of methanol at 0 °C in the reaction system. In the reaction at room temperature, the intermediate **A** would undergo both the tautomerization to imine **6** (path a) and the aromatization to **8** (path b). The aromatization reaction (path b) proceeded through the elimination of methanol, which

Scheme 1. Conversion of Enehydrazines 4b,c to Dienylimines 3b,c



4b (n=2)	48% (*cis-syn*-**3b** : *cis-anti*-**3b** = 5 : 1)	51% (**5b**)
4c (n=3)	17% (*cis-syn*-**3c** : *cis-anti*-**3c** = 2 : 1)	52% (**5c**)[1)]

[1)] **5c**: indole analog obtained as a result of elimination of trifluoroacetamide

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Scheme 2. Preparation of Enehydrazines 4a,d

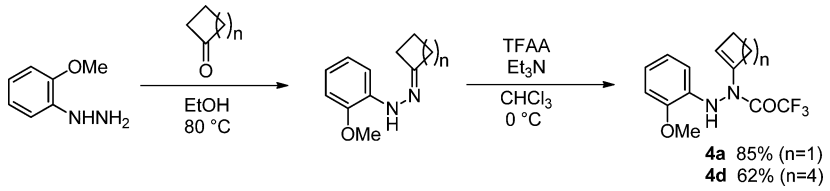
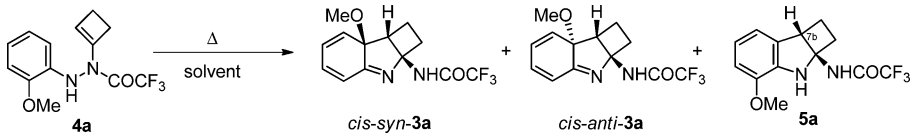
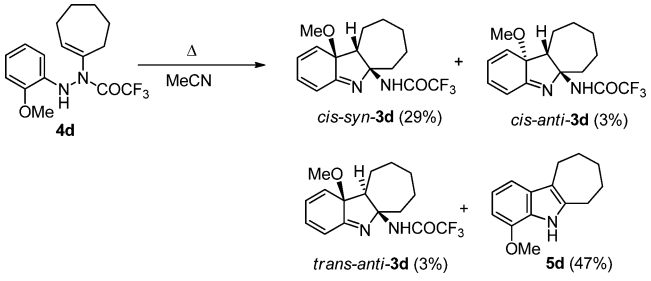


Table 1. Rearrangement–Cyclization Reaction of Enehydrazine 4a



			yield (%)	
entry	solvent (temp (°C))	time (h)	**3a** (*cis-syn*:*cis-anti*)	**5a**
1	MeCN (80)	5	72 (51:21)	27
2	toluene (90)	1	57 (37:20)	39
3	*n*-PrCN (120)	0.5	66 (23:10)	34
4	CF_3CH_2OH (80)	2	56 (45:11)	39

Scheme 3. Rearrangement–Cyclization Reaction of Enehydrazine 4d

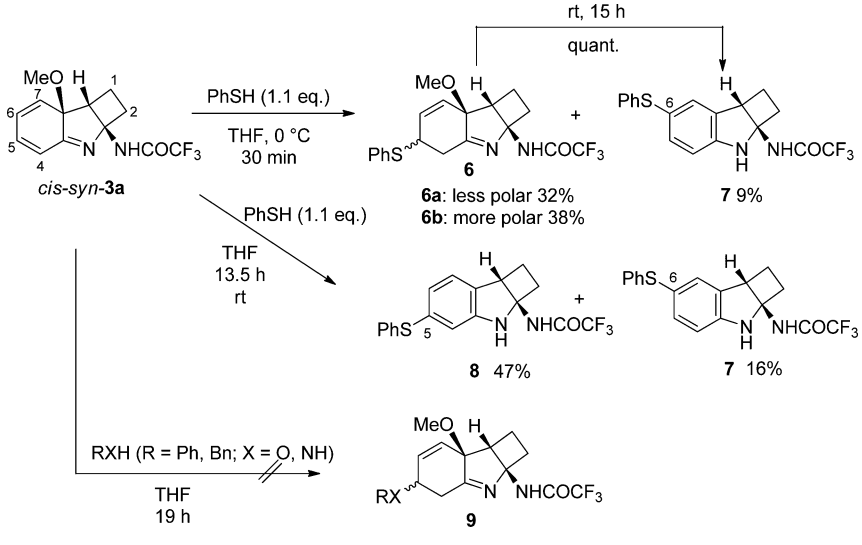


would occur via the deprotonation of the more acidic hydrogen at the 5-position, with the 5-phenylthioindoline **8** being obtained. On the other hand, the imine **6**, which was generated via path a, would give the intermediate thiiranium ion **B** by an S_N2' type displacement reaction. The ring opening of the thiiranium ion **B** followed by an aromatization reaction would then give rise to the observed 6-phenylthioindoline **7**. The result that the isolated imines **6a,b** gave the only 6-phenylthioindoline **7** supported this reaction pathway (**6** → **7**).

Design and Synthesis of Thiol Labeling Reagent. The first Michael addition to dienylimine proceeded with high thiol selectivity, and a strong carbon–sulfur bond was formed as a result of the aromatization achieved by the elimination of methanol. On the basis of these results, we proceeded to investigate the preparation of a novel type of thiol labeling reagent (Figure 1).

A linker–fluorophore moiety was introduced at the 1-position of dienylimine because it was envisaged that its placement at this position would have no impact on the reaction with the thiol. In this addition–aromatization reaction, the nitrogen atom of dienylimine was needed for addition of the thiol to an imino group with electron-withdrawing ability. Following the addition–aromatization sequence, the character of the same nitrogen atom would effectively change to become an electron-donating amino group. These changes in the

Scheme 4. Addition of Various Heteroatom Nucleophiles to Dienylimine



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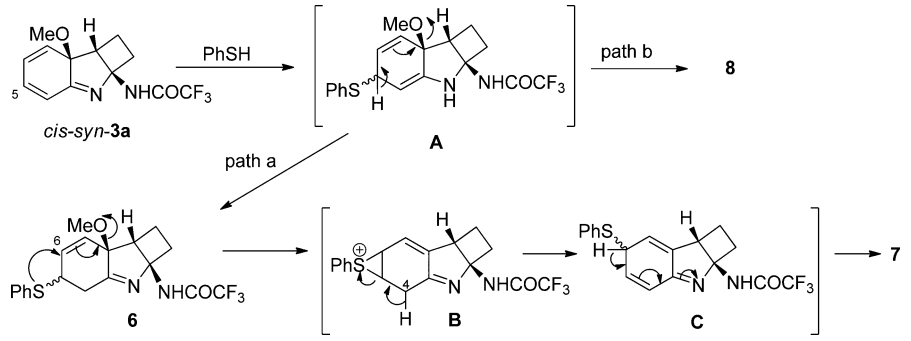
Scheme 5. Possible Reaction Pathways for the Phenylthioindolines 7 and 8



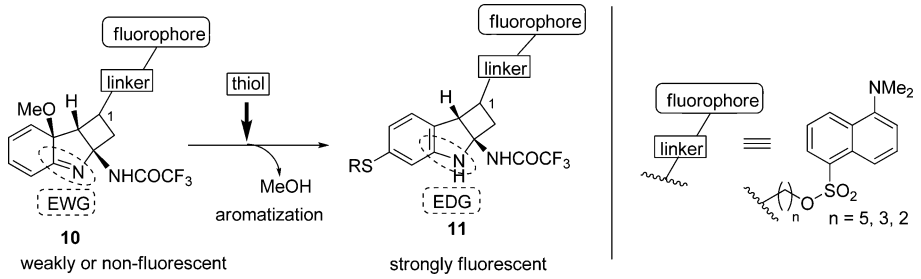
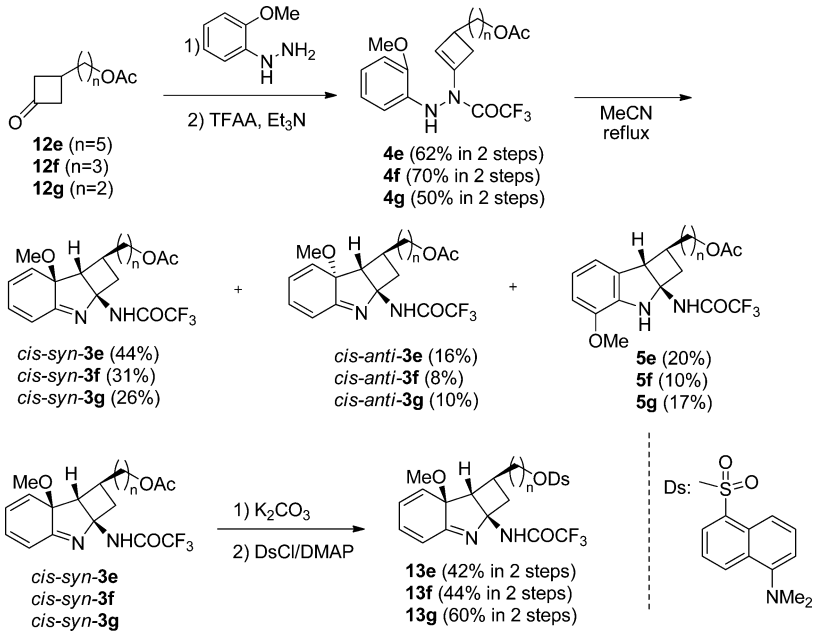


Figure 1. Design of thiol labeling reagent.

Scheme 6. Preparation of the Dienylimines 13e–g



electron density of the conjugated system could affect the fluorescence properties of the system when the fluorophore was close enough to the dienylimine. It was therefore considered that the length of the linker would be an important factor, and we designed and synthesized dienylimine **10** bearing both a dansyl group as a fluorophore and a penta-, tri-, or dimethylene moiety as a linker.

The dansyl group is an electron-donating fluorophore, whereas the dienylimine structure would be able to act as an accepting quencher. The anchoring of the dansyl group to the dienylimine would therefore result in a weakly fluorescent or off fluorescent state as a consequence of a photoinduced electron transfer (PeT) pathway. The resulting product **11** would display a strong fluorescence signal because of the instantaneous shutdown of the electron-transfer pathway.

We initially investigated the synthesis of the dienylimines **13e–g** bearing a dansyl (Ds) oxyalkyl moiety (n = 5, 3, 2) (Scheme 6). The condensation reaction of 2-methoxyphenylhydrazine with a range of cyclobutanones (**12e–g**), which were themselves prepared according to literature procedures,[13] followed by the acylation of the resulting products provided the enehydrazines **4e–g**. The enehydrazines **4e–g** were then heated at reflux in MeCN to give the *cis-syn*-dienylimines **3e–g**, together with the *cis-anti*-dienylimines **3e–g** and the 4-methoxyindolines **5e–g**. Following the deprotection of the acetyl group, the corresponding alcohols were treated with

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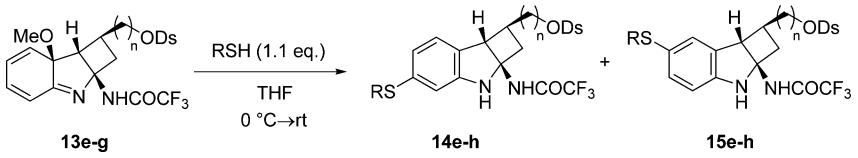
Table 2. Addition–Aromatization Reactions of the Dienylimines 13e–g with Thiols



13e-g 14e-h 15e-h

				yield (%)	
entry	substrate	RSH	time (h)	**14**	**15**
1	**13e** (n = 5)	PhSH	8	33 (**14e**)	29 (**15e**)
2	**13f** (n = 3)	PhSH	8	29 (**14f**)	24 (**15f**)
3	**13g** (n = 2)	PhSH	8	21 (**14g**)	23 (**15g**)
4	**13g** (n = 2)	OctSH	36	19 (**14h**)	24 (**15h**)

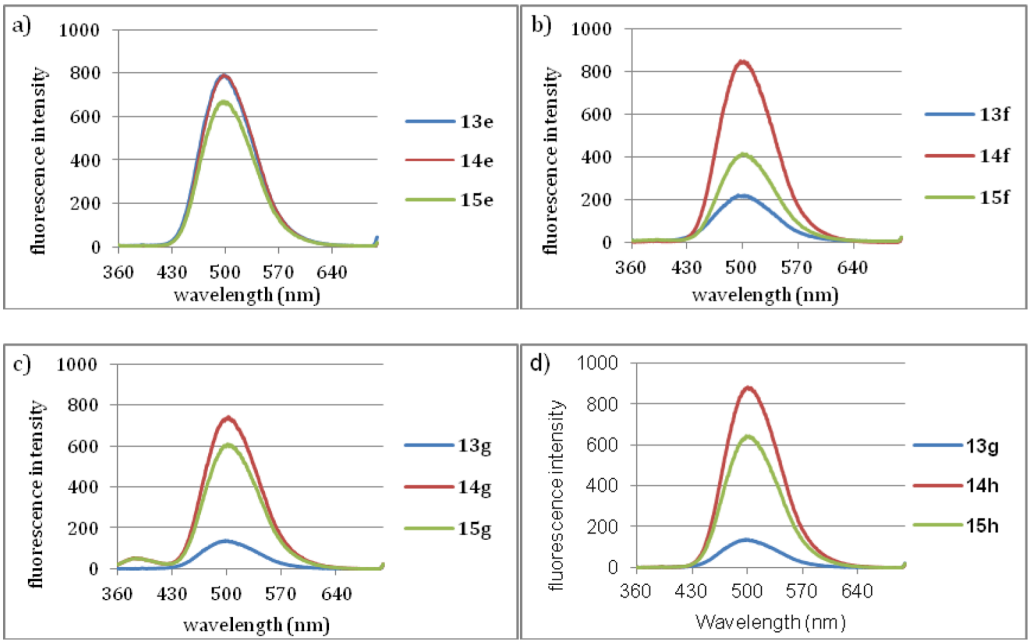


Figure 2. Fluorescence spectra of (a) **13e–15e**, (b) **13f–15f**, (c) **13g–15g**, and (d) **13g–15h**. The concentration was 1.0×10^{-5} M in $CHCl_3$, and the excitation wavelength was 350 nm.

commercially available dansyl chloride in the presence of DMAP to afford the desired dienylimines **13e–g**.

Addition–Aromatization Reaction of Dienylimines 13e–g with Thiol. With the dienylimines **13e–g** in hand, we proceeded to investigate the addition–aromatization reactions with thiophenol and octanethiol (Table 2). When **13e**, bearing a pentamethylene linker, was treated with thiophenol in THF for 8 h, the corresponding addition products **14e** and **15e** were obtained in 33 and 29% yields, respectively (Table 2, entry 1). Dienylimines **13f,g** bearing trimethylene and ethylene linkers, respectively, were also subjected to the addition–aromatization reaction to give **14f,g** and **15f,g** (Table 2, entries 2 and 3). As the length of the linker shortened, the reactivity decreased. The reaction of **13g** with the aliphatic octanethiol gave the corresponding indolines **14h** and **15h** in 19 and 24% yields, respectively, but required a prolonged reaction time (Table 2, entry 4). Given that the indolines **14** and **15** were formed by catching thiols, the sulfenyl part was coupled to the dansyl fluorophore by strong covalent bonds through the indoline moiety bearing an alkyl side chain, and the thiol was not released by a retro-Michael reaction. Dienylimines **13** with a dansyl fluorophore were therefore found to be suitable as thiol-selective labeling reagents.

Fluorescence Property Study. The fluorescent spectra of compounds **13–15** are shown in Figure 2. Dienylimine **13e**, bearing a pentamethylene linker, was strongly fluorescent, and no significant changes were observed in its fluorescence spectra before and after the reaction with thiophenol. In contrast, the fluorescence intensities of the dienylimines **13f,g** were interestingly weaker than that of dienylimine **13e**. As a result, the fluorescence intensities of these compounds increased following their reaction with thiophenol. An increase in the fluorescence intensity was also observed in the reaction of **13g** with aliphatic octanethiol. These results suggested that changes in the fluorescence intensity were occurring as a consequence of the structural change occurring on going from the dienylimine moiety to the indoline nucleus. The closer the distance between the electron donor (dansyl moiety) and the electron acceptor (dienylimine part), the greater the extent to which the fluorescence was quenched. In the case of **13f,g**, the fluorescence intensities of the dansyl group were restored following the reaction of these compounds with thiol.

It was assumed that electrons would flow before and after the reaction, as shown in Figure 3. The fluorescence signals in the

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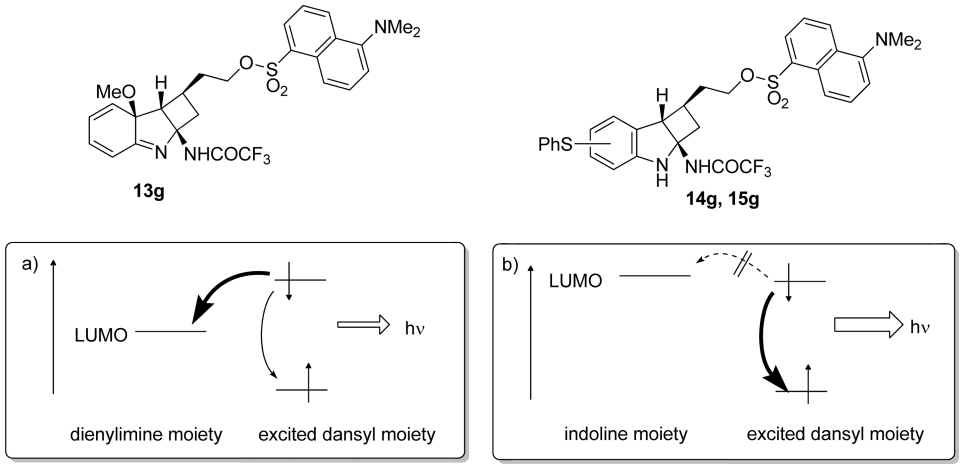

Figure 3. Schematic illustration of (a) d-PeT from the excited dansyl moiety to dienylimine in **13g** and (b) no d-PeT from the excited dansyl moiety to indoline in **14g** and **15g**.

dienylimines **13f,g** were partially quenched, presumably because of donor-excited photoinduced electron transfer (d-PeT) from the fluorophore excited state to the LUMO of the electron-deficient dienylimine moiety.[8a−d,14] The LUMO level of the indoline moiety could be higher than that of dienylimine. Elevation of the LUMO level by raising the electron density could prevent the PeT process from the excited dansyl moiety. Dansyl fluorescence was therefore restored following the addition−aromatization reaction as a consequence of changes in the structure from the electron-deficient dienylimine to the electron-rich indoline. In this PeT process, it is known that the distance from the electron donor to the electron acceptor is a very important parameter. For example, very little fluorescence quenching was observed in the dienylimine **13e** bearing a pentamethylene linker, because the dansyl group was located too far away from the dienylimine moiety.

■ CONCLUSION

In this report, we have presented the addition−aromatization reaction of dienylimines with thiophenol and octanethiol, as well as a basic study of the application of dienylimine in thiol-selective fluorescent labeling reagents. The dienylimine showed a high level of thiol selectivity and formed very strong conjugation products with thiols. Dienylimines bearing dansyl groups as a fluorophore, as well as a polymethylene moiety as a linker, were synthesized as thiol-selective labeling reagents. The fluorescence properties of these materials were subsequently characterized in their reactions with thiophenol and octanethiol. These labeling reagents were able to successfully label thiols through the formation of strong C−S bonds. Labeling reagents bearing an ethylene linker, in particular, showed the most interesting properties, and dienylimine **13g** was partially quenched by a PeT process; its fluorescence intensity increased following its reaction with thiols. Further studies on the structural optimization of dienylimines for the development of more effective fluorescence labeling reagents are currently underway in our laboratory.

■ EXPERIMENTAL SECTION

General Considerations. The melting points are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded at 300 or 500 MHz and at 75 or 125 MHz, respectively. Deuterated chloroform was used as the solvent for the NMR analyses, with tetramethylsilane as an internal reference. Peak assignments were aided by COSY, NOESY, HSQC, and HMBC experiments when necessary. The IR spectra were recorded using chloroform solutions of the samples, except for those which could be run as neat samples. Mass spectra were obtained by an ESI method, except for those collected using EI or APCI, as mentioned for the appropriate spectra. Flash column chromatography (FCC) was performed using SiliaFlash F60. Medium-pressure column chromatography (MCC) was performed using Lober Grösse B (310-25, LiChroprep Si60). PTLC separations were carried out on precoated silica gel plates (E. Merck $60F_{254}$).

General Procedure for the Preparation of *N*-Trifluoroacetylenehydrazines. A ketone (10 mmol) was added to a solution of 2-methoxyphenylhydrazine (10 mmol) in EtOH (25 mL) at room temperature, and the resulting mixture was stirred at reflux for 1−2.5 h. The reaction mixture was then cooled to ambient temperature and concentrated under reduced pressure to give the crude hydrazone, which was dissolved in CH_2Cl_2 (40 mL) and treated sequentially with Et_3N (30 mmol) and TFAA (20 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1−2.5 h and then concentrated under reduced pressure to give the crude product as a residue, which was purified by FCC (hexane/EtOAc 20/1 to 5/1 v/v) to give the enehydrazine **4**.

*Trifluoroacetic acid 1-(1-cyclobuten-1-yl)-2-(2-methoxyphenyl)-hydrazide (**4a**):* white crystals (2.4 g, 85%); mp 60−62 °C (hexane/EtOAc); IR (ν_{max}, cm^{-1}) 3349 (NH), 1717 (CO); ^{1}H NMR (500 MHz) δ 6.95 (1H, td, J = 8.0, 1.5 Hz), 6.91 (1H, td, J = 8.0, 1.5 Hz), 6.86 (1H, dd, J = 8.0, 1.5 Hz), 6.75 (1H, br d, J = 8.0 Hz), 6.62 (1H, s), 5.36 (1H, s), 3.89 (3H, s), 2.82 (1H, br s), 2.70 (1H, br s), 2.26 (2H, br s); ^{13}C NMR (125 MHz) δ 157.6 (q, $COCF_3$), 146.9, 136.6, 134.3, 122.1, 121.3, 116.0 (q, $COCF_3$), 115.7, 113.6, 110.5, 55.7, 31.2, 24.8; HRMS (EI) m/z calcd for $C_{13}H_{13}F_3N_2O_2$ (M^+) 286.0928, found 286.0940.

*Trifluoroacetic acid 1-(1-cyclohepten-1-yl)-2-(2-methoxyphenyl)-hydrazide (**4d**):* yellow oil (2.0 g, 62%). IR (ν_{max} (neat), cm^{-1}) 3350 (NH), 1705 (CO); ^{1}H NMR (500 MHz) δ 6.95−6.89 (1H, m), 6.85 (1H, dd, J = 7.5, 2.0 Hz), 6.80 (1H, dd, J = 7.5, 2.0 Hz), 6.75 (1H, br s), 5.93 (1H, br t, J = 6.5 Hz), 3.87 (3H, s), 2.43−2.09 (4H, br m), 1.73−1.39 (6H, br m); ^{13}C NMR (125 MHz) δ 158.1 (q, $COCF_3$), 147.9, 141.9, 133.8, 128.9, 122.1, 121.1, 116.6 (q, $COCF_3$), 115.7, 110.5, 55.7, 32.1, 31.6, 26.8, 26.2, 25.4; HRMS (EI) m/z calcd for $C_{16}H_{19}F_3N_2O_2$ (M^+) 328.1398, found 328.1405.

Thermal Reaction of *N*-Trifluoroacetylenehydrazines 4a (Entry 1 in Table 1). A solution of enehydrazines **4a** (949 mg, 3.33 mmol) in MeCN (100 mL) was heated at reflux, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was concentrated under reduced pressure to give the crude product as a residue, which was purified by MCC (hexane/EtOAc 10/1 to 2/1 v/v) to give the indoline **5a** (256 mg) and dienylimines *cis-syn*-**3a** (484 mg), and *cis-anti*-**3a** (199 mg) in 27%, 51% and 21% yields, respectively.

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*cis-2a-[(Trifluoroacetyl)amino]-2,2a,3,7b-tetrahydro-4-methoxy-1H-cyclobut[b]indole (**5a**):* yellow crystals; mp 100−102 °C (hexane/EtOAc); IR (ν_{max}, cm^{-1}) 3416 (NH), 1724 (CO); ^1H NMR (500 MHz) δ 6.85 (1H, br s), 6.79 (1H, dd, J = 8.5, 7.0 Hz), 6.71 (2H, br d, J = 8.5 Hz), 4.05 (1H, br dd, J = 9.5, 5.0 Hz), 3.85 (3H, s), 2.97−2.90 (1H, m), 2.71−2.63 (1H, m), 2.60−2.54 (1H, m), 1.94−1.87 (1H, m); ^{13}C NMR (125 MHz) δ 156.3 (q, $COCF_3$), 145.2, 138.2, 132.8, 120.9, 116.4, 115.5 (q, $COCF_3$), 109.8, 76.4, 55.4, 48.1, 34.7, 24.5; HRMS (EI) m/z calcd for $C_{13}H_{13}F_3N_2O_2$ (M^+) 286.0928, found 286.0930. Anal. Calcd for $C_{13}H_{13}F_3N_2O_2$: C, 54.55; H, 4.58; N, 9.79, Found: C, 54.56; H, 4.57; N, 9.81.

*(2aα,7aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,7a,7b-tetrahydro-7a-methoxy-1H-cyclobut[b]indole (cis-syn-**3a**):* white crystals; mp 147−149 °C (hexane/EtOAc); IR (ν_{max}, cm^{-1}) 3417 (NH), 1728 (CO); ^1H NMR (500 MHz) δ 7.31 (1H, br s), 6.58 (1H, br d, J = 9.5 Hz), 6.52 (1H, ddd, J = 9.5, 5.0, 1.0 Hz), 6.45 (1H, ddd, J=9.5, 5.0, 1.0 Hz), 6.11 (1H, dt, J = 9.5, 1.0 Hz), 3.43 (1H, dd, J = 9.5, 7.5 Hz), 3.18 (3H, s), 2.98−2.92 (1H, m), 2.08−1.97 (2H, m), 1.27−1.19 (1H, m); ^{13}C NMR (125 MHz) δ 175.0, 156.3 (q, $COCF_3$), 134.6, 130.7, 129.3, 123.4, 115.6 (q, $COCF_3$), 87.4, 86.3, 51.7, 45.8, 27.7, 14.2; HRMS (EI) m/z calcd for $C_{13}H_{13}F_3N_2O_2$ (M^+) 286.0928, found 286.0942. Anal. Calcd for $C_{13}H_{13}F_3N_2O_2$: C, 54.55; H, 4.58; N, 9.79. Found: C, 54.50; H, 4.42; N, 9.76.

*(2aα,7aβ,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,7a,7b-tetrahydro-7a-methoxy-1H-cyclobut[b]indole (cis-anti-**3a**):* white crystals; mp 160−162 °C (hexane/EtOAc); IR (ν_{max}, cm^{-1}) 3422 (NH), 1728 (CO); ^1H NMR (500 MHz) δ 7.05 (1H, br s), 6.64 (1H, br d, J = 9.5 Hz), 6.55 (1H, ddd, J = 9.5, 5.5, 1.0 Hz), 6.39 (1H, ddd, J = 9.5, 5.5, 1.0 Hz), 6.25 (1H, dt, J = 9.5, 1.0 Hz), 3.22 (3H, s), 3.14 (1H, dt, J = 7.0, 2.5 Hz), 2.54−2.48 (1H, m), 2.37−2.30 (1H, m), 2.23−2.16 (1H, m), 2.04−1.99 (1H, m); ^{13}C NMR (125 MHz) δ 178.6, 156.1 (q, $COCF_3$), 133.4, 132.9, 126.8, 123.0, 115.3 (q, $COCF_3$), 87.4, 84.0, 53.1, 48.5, 31.3, 10.4; HRMS (EI) m/z calcd for $C_{13}H_{13}F_3N_2O_2$ (M^+) 286.0928, found 286.0957. Anal. Calcd for $C_{13}H_{13}F_3N_2O_2$: C, 54.55; H, 4.58; N, 9.79. Found: C, 54.38; H, 4.58; N, 9.79.

Thermal Reaction of *N*-Trifluoroacetylenehydrazines 4d. A solution of enehydrazines **4d** (3.33 mmol) in MeCN (100 mL) was heated at 82 °C, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was concentrated under reduced pressure to give the crude product as a residue, which was purified by MCC (hexane/EtOAc 10/1 to 2/1 v/v) to give the indole **5d** (335 mg) and dienylimines *cis-syn*-**3d** (316 mg), *cis-anti*-**3d** (33 mg), and *trans-anti*-**3d** (33 mg) in 47, 29, 3, and 3% yields, respectively.

*1,2,3,4,5,6-Hexahydro-7-methoxycyclohept[b]indole (**5d**):* yellow oil; IR (ν_{max} (neat), cm^{-1}) 3472 (NH); ^1H NMR (300 MHz) δ 7.91 (1H, br s), 7.09 (1H, d, J = 7.5 Hz), 6.98 (1H, t, J = 7.5 Hz), 6.56 (1H, d, J = 7.5 Hz), 3.93 (3H, s), 2.80 (4H, dd, J = 11.5, 7.5 Hz), 1.92−1.85 (2H, m), 1.79−1.72 (4H, m); ^{13}C NMR (75 MHz) δ 145.6, 137.1, 130.6, 124.3, 119.3, 114.2, 110.7, 100.9, 55.3, 31.9, 29.5, 28.7, 27.5, 24.9; HRMS (EI) m/z calcd for $C_{14}H_{17}NO$ (M^+) 215.1309, found 215.1319.

*(5aα,10aα,10bα)-5a-[(Trifluoroacetyl)amino]-1,2,3,4,5,5a,10a,10b-octahydro-10a-methoxycyclohept[b]indole (cis-syn-**3d**):* white solid; mp 134−137 °C (hexane/EtOAc); IR (ν_{max} (neat), cm^{-1}) 3407 (NH), 1736 (CO); ^1H NMR (500 MHz) δ 7.23 (1H, br s), 6.57 (1H, br d, J = 9.5 Hz), 6.52 (1H, ddd, J = 9.5, 5.5, 1.0 Hz), 6.43 (1H, ddd, J = 9.5, 5.5, 1.0 Hz), 6.07 (1H, dt, J = 9.5, 1.0 Hz), 3.57 (1H, dd, J = 15.5, 9.5 Hz), 3.16 (3H, s), 2.53 (1H, dd, J = 11.0, 3.0 Hz), 1.84−1.73 (4H, m), 1.58−1.33 (4H, m), 1.23−1.16 (1H, m); ^{13}C NMR (125 MHz) δ 174.7, 155.5 (q, $COCF_3$), 134.4, 130.1, 128.2, 123.0, 115.8 (q, $COCF_3$), 92.7, 86.3, 61.3, 51.5, 34.5, 30.5, 29.1, 26.2, 22.3; HRMS (EI) m/z calcd for $C_{16}H_{19}F_3N_2O_2$ (M^+) 328.1397, found 328.1379.

*(5aα,10aβ,10bα)-5a-[(Trifluoroacetyl)amino]-1,2,3,4,5,5a,10a,10b-octahydro-10a-methoxycyclohept[b]indole (cis-anti-**3d**):* white amorphous; IR (ν_{max} (neat), cm^{-1}) 3440 (NH), 1734 (CO); ^1H NMR (500 MHz) δ 6.66 (1H, dt, J = 9.5, 1.0 Hz), 6.52 (1H, ddd, J = 9.5, 5.5, 1.0 Hz), 6.43 (1H, ddd, J = 9.5, 5.5, 1.0 Hz), 5.98 (1H, dt, J = 9.5, 1.0 Hz), 3.10 (3H, s), 2.69 (1H, ddd, J = 11.0, 8.0, 1.5 Hz), 2.53 (1H, br dd, J = 15.0, 5.0 Hz), 2.12−1.85 (6H, m), 1.45−1.31 (3H, m); ^{13}C NMR (125 MHz) δ 174.0, 155.9 (q, $COCF_3$), 133.3, 130.3, 126.8, 123.8, 115.6 (q, $COCF_3$), 89.9, 81.7, 55.3, 51.7, 34.5, 31.7, 24.6, 23.6, 22.9; HRMS (EI) m/z calcd for $C_{16}H_{19}F_3N_2O_2$ (M^+) 328.1397, found 328.1402.

*(5aα,10aα,10bβ)-5a-[(Trifluoroacetyl)amino]-1,2,3,4,5,5a,10a,10b-octahydro-10a-methoxycyclohept[b]indole (trans-anti-**3d**):* white amorphous; IR (ν_{max} (neat), cm^{-1}) 3351 (NH), 1736 (CO); ^1H NMR (500 MHz) δ 7.24 (1H, br s), 6.68 (1H, dt, J = 9.5, 1.0 Hz), 6.54 (1H, ddd, J = 9.5, 5.5, 1.0 Hz), 6.47 (1H, ddd, J = 9.5, 5.5, 1.0 Hz), 6.02 (1H, dt, J = 9.5, 1.0 Hz), 3.72 (1H, dt, J = 14.5, 4.0 Hz), 3.15 (3H, s), 1.74−2.01 (6H, m), 1.68−1.60 (1H, m), 1.53−1.44 (1H, m), 1.40−1.33 (2H, m); ^{13}C NMR (125 MHz) δ 175.8, 156.1 (q, $COCF_3$), 133.9, 129.7, 128.1, 124.5, 115.8 (q, $COCF_3$), 89.0, 82.1, 57.2, 51.7, 37.4, 25.8, 25.8, 19.5; HRMS (EI) m/z calcd for $C_{16}H_{19}F_3N_2O_2$ (M^+) 328.1397, found 328.1405.

Addition Reaction of PhSH to 3a. PhSH (0.023 mL, 0.22 mmol) was added to a solution of **3a** (57.2 mg, 0.20 mmol) in THF (2 mL) under a N_2 atmosphere at 0 °C, and the resulting mixture was stirred at the same temperature for 30 min. The reaction mixture was then concentrated under reduced pressure to give the crude products as a residue, which was purified by MCC (hexane/EtOAc 10/1 to 1/1 v/v) to give **7** (6.7 mg), the less polar product **6a** (25.4 mg), and the more polar product **6b** (30.3 mg) in 9, 32, and 38% yields, respectively. Compounds **6a**,**b** were converted to **7** after being left to stand at room temperature for 15 h.

*(2aα,5,7aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,4,5,7a,7b-hexahydro-7a-methoxy-5-phenylthio-1H-cyclobut[b]indole (**6a**; less polar product):* colorless oil; ^1H NMR (500 MHz) δ 7.51−7.49 (2H, m), 7.36−7.33 (3H, m), 6.98 (1H, s), 6.19 (1H, dd, J = 10.0, 1.5 Hz), 5.85 (1H, dd, J = 10.0, 2.0 Hz), 3.91−3.86 (1H, m), 3.50−3.47 (1H, m), 3.03 (1H, dd, J = 13.5, 6.5 Hz), 2.99 (3H, s), 3.05−2.95 (1H, m), 2.79 (1H, dd, J = 13.0, 10.5 Hz), 2.13−2.00 (2H, m), 1.08−1.01 (1H, m); ^{13}C NMR (125 MHz) δ 178.4, 155.9 (q, $COCF_3$), 136.0, 133.9, 129.1, 128.4, 126.3, 115.5 (q, $COCF_3$), 87.8, 87.0, 51.6, 46.0, 45.7, 33.0, 30.7, 15.2. HRMS (ESI) m/z: Calcd for $C_{19}H_{20}F_3N_2O_2S$ ($M + H^+$) 397.1198, found 397.1187.

*(2aα,5,7aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,4,5,7a,7b-hexahydro-7a-methoxy-5-phenylthio-1H-cyclobut[b]indole (**6b**: more polar product):* colorless oil; ^1H NMR (500 MHz) δ 7.52−7.50 (2H, m), 7.37−7.31 (3H, m), 6.80 (1H, br s), 6.25 (1H, dd, J = 10.0, 5.0 Hz), 5.94 (1H, dd, J = 10.0, 1.0 Hz), 4.25 (1H, tm, J = 5.0 Hz), 3.60 (1H, dd, J = 9.5, 6.5 Hz), 3.11 (3H, s), 3.08 (1H, dd, J = 13.5, 6.0 Hz), 3.05−2.99 (1H, m), 2.82 (1H, d, J = 14.0 Hz), 2.19−2.09 (2H, m), 1.28−1.21 (1H, m); ^{13}C NMR (125 MHz) δ 176.9, 155.9 (q, $COCF_3$), 133.6, 132.8, 129.3, 128.2, 128.0, 115.5 (q, $COCF_3$), 88.0, 87.3, 51.6, 46.8, 45.0, 31.6, 30.9, 15.0; HRMS (ESI) m/z calcd for $C_{19}H_{20}F_3N_2O_2S$ ($M + H^+$) 397.1198, found 397.1188.

*cis-2a-[(Trifluoroacetyl)amino]-2,2a,3,7b-tetrahydro-6-phenylthio-1H-cyclobut[b]indole (**7**):* white solid; mp 164−167 °C (hexane/EtOAc); IR (ν_{max}, cm^{-1}) 3422 (NH), 1726 (CO); ^1H NMR (500 MHz) δ 7.25 (1H, dd, J = 8.0, 2.0 Hz), 7.17 (1H, br s), 7.23−7.20, 7.16−7.10 (5H, m), 6.94 (1H, br s), 6.62 (1H, d, J = 8.0 Hz), 3.94 (1H, br s), 2.85−2.79 (1H, m), 2.67−2.57 (2H, m), 1.97−1.90 (1H, m); ^{13}C NMR (125 MHz) δ 156.4 (q, $COCF_3$), 150.3, 139.4, 134.9, 132.6, 130.2, 128.9, 127.6, 125.5, 122.0, 115.4 (q, $COCF_3$), 109.8, 76.1, 47.1, 35.2, 24.5; HRMS (EI) m/z calcd for $C_{18}H_{15}F_3N_2OS$ (M^+) 364.0856, found 364.0860.

Addition Reaction of PhSH to 3a. PhSH (0.020 mL, 0.20 mmol) was added to a solution of **3a** (57.2 mg, 0.20 mmol) in THF (2 mL) under a N_2 atmosphere at room temperature, and the resulting mixture was stirred for 13.5 h. The reaction mixture was then concentrated under reduced pressure to give the crude product as a residue, which was purified by MCC (hexane/EtOAc 10/1 to 1/1 v/v) to give **8** (34 mg) and **7** (12 mg) in 47 and 16% yields, respectively.

*cis-2a-[(Trifluoroacetyl)amino]-2,2a,3,7b-tetrahydro-5-phenylthio-1H-cyclobut[b]indole (**8**):* yellow oil; IR (ν_{max} (neat), cm^{-1}) 3302 (NH), 1708 (CO); ^1H NMR (500 MHz) δ 7.43−7.14 (5H, m), 6.96 (1H, d, J = 8.0 Hz), 6.82 (1H, br s), 6.77 (1H, dd, J = 8.0, 2.0 Hz), 6.58 (1H, d, J = 2.0 Hz), 3.96−3.93 (1H, m), 2.87−2.77 (1H, m), 2.66−2.55 (2H, m), 1.97−1.87 (1H, m); ^{13}C NMR (75 MHz) δ 175.6

(q, $COCF_3$), 150.6, 135.8, 135.5, 131.1, 130.6, 129.1, 127.0, 124.4, 122.4, 115.4 (q, $COCF_3$), 111.6, 76.2, 47.0, 34.9, 24.4; HRMS (EI) *m/z* calcd for $C_{18}H_{15}F_3N_2OS$ (M + H^+) 365.0930, found 365.0927.

Attempted Addition Reaction of PhOH, $PhNH_2$, BnOH, or $BnNH_2$ to 3a. PhOH (0.019 mL, 0.22 mmol), $PhNH_2$ (0.020 mL, 0.22 mmol), BnOH (0.023 mL, 0.22 mmol), or $BnNH_2$ (0.024 mL, 0.22 mmol) was added to a solution of **3a** (57.2 mg, 0.20 mmol) in THF (2 mL) under a N_2 atmosphere at 0 °C, and the resulting mixture was stirred at the same temperature for 2.5 h. The reaction mixture was then stirred at room temperature for a further 19 h before being concentrated under reduced pressure. Under these reaction conditions, the only starting material was recovered.

Structural Confirmation of Enamine Intermediate A. PhSH (5.0 μL, 0.05 mmol) was added to a solution of **3a** (14.3 mg, 0.05 mmol) in THF-d_8 (1.0 mL) under a N_2 atmosphere at 0 °C, and the resulting mixture was stirred at the same temperature for 30 min. A ^1H NMR spectrum of the reaction mixture was then measured.

Enamine intermediate A (a 1:1 mixture of two diastereoisomers): ^1H NMR (300 MHz, THF-d_8) δ 8.83 ($^1/_2$H, br s), 8.77 ($^1/_2$H, br s), 7.49−7.44 (2H, m), 7.32−7.18 (3H, m), 6.34 ($^1/_2$H, ddd, *J* = 9.5, 2.5, 1.5 Hz), 6.28 ($^1/_2$H, ddd, *J* = 9.5, 4.0, 1.5 Hz), 5.69 ($^1/_2$H, br s), 5.56($^1/_2$H, br s), 5.53 ($^1/_2$H, d, *J* = 9.5 Hz), 5.38 ($^1/_2$H, dd, *J* = 9.5, 2.0 Hz), 5.16 ($^1/_2$H, dd, *J* = 5.5, 2.0 Hz), 5.13 ($^1/_2$H, t, *J* = 2.0 Hz), 4.51 ($^1/_2$H, t, *J* = 4.5 Hz), 4.32 ($^1/_2$H, dd, *J* = 4.5, 2.5 Hz), 3.14−2.93 (1H, m), 3.10 (3/2H, s), 2.90 (3/2H, s), 2.72−2.47 (1H, m), 2.16−2.09 ($^1/_2$H, m), 2.06−1.84 ($^1/_2$H, m), 1.62−1.50 ($^1/_2$H, m), 1.36−1.24 ($^1/_2$H, m), 0.64−0.50 ($^1/_2$H, m).

Preparation of Cyclobutanones 12e−g. Cyclobutanones **12e−g** were prepared from the corresponding alkenyl acetate (18.5 mmol) according to a procedure described in the literature.[12]

*5-(3-Oxocyclobutyl)pentyl acetate (**12e**):* colorless oil (1.43g, 39%); IR (ν_{max}, cm^{-1}) 1784, 1736 (CO); ^1H NMR (300 MHz) δ 4.07 (2H, t, *J* = 7.0 Hz), 3.19−3.09 (2H, m), 2.71−2.62 (2H, m), 2.36 (1H, m), 2.05 (3H, s), 1.67−1.56 (4H, m), 1.42−1.35 (4H, m); ^{13}C NMR (75 MHz) δ 208.5, 171.2, 64.4, 52.5, 36.2, 28.5, 27.9, 25.7, 23.8, 21.0; HRMS (ESI) *m/z* calcd for $C_{11}H_{19}O_3$ (M + H^+) 199.1334, found 199.1329.

*3-(3-Oxocyclobutyl)propyl acetate (**12f**):* colorless oil (1.26 g, 40%); IR (ν_{max}, cm^{-1}) 1784, 1738(CO); ^1H NMR (300 MHz) δ 4.01 (2H, m), 3.22−3.11 (2H, m), 2.74−2.63 (2H, m), 2.46−2.33 (1H, m), 2.06 (3H, s), 1.71−1.61 (4H, m); ^{13}C NMR (75 MHz) δ 241.0, 171.1, 63.9, 52.5, 32.6, 27.4, 23.6, 20.9; HRMS (ESI) *m/z* calcd for $C_9H_{15}O_3$ (M + H^+) 171.1021, found 171.1016.

*2-(3-Oxocyclobutyl)ethyl acetate (**12g**):* colorless oil (1.30 g, 45%); IR (ν_{max}, cm^{-1}) 1785, 1739(CO); ^1H NMR (300 MHz) δ 4.13 (2H, t, *J* = 6.5 Hz), 3.25−3.14 (2H, m), 2.82−2.71 (2H, m), 2.48 (1H, m), 2.06 (3H, s), 1.94 (2H, q, *J* = 6.5 Hz); ^{13}C NMR (75 MHz) δ 206.8, 170.5, 62.6, 52.1, 34.3, 20.6, 20.3; HRMS (ESI) *m/z* calcd for $C_8H_{13}O_3$ (M + H^+) 157.0865, found 157.0860.

Preparation of the Enehydrazine 4e. Cyclobutanone **12e** (1.47g, 7.71 mmol) was added to a solution of 2-methoxyphenylhydrazine (1.07 g, 7.71 mmol) in EtOH (40 mL) at room temperature, and the resulting mixture was stirred at reflux for 2 h. The reaction mixture was then concentrated under reduced pressure to give the crude hydrazone, which was dissolved in CH_2Cl_2 (35 mL) and treated sequentially with Et_3N (3.22 mL, 23.13 mmol) and TFAA (2.14 mL, 15.42 mmol) at 0 °C. The resulting mixture was then stirred at the same temperature for 1.5 h before being concentrated under reduced pressure to give the crude product as a residue, which was purified by flash column chromatography (hexane/EtOAc 10/1 v/v) to give the enehydrazine **4e** (1.98 g) in 62% yield over two steps.

*5-[3-[2-(2-Methoxyphenyl)-1-(2,2,2-trifluoroacetyl)hydrazinyl]-cyclobut-2-en-1-yl]pentyl acetate (**4e**):* brown oil; IR (ν_{max}, cm^{-1}) 3325 (NH), 1720 (CO); ^1H NMR (300 MHz) δ 6.98−6.85 (3H, m), 6.73 (1H, dm, *J* = 6.5 Hz), 6.62 (1H, s), 5.47 (1H, br s), 4.02 (2H, t, *J* = 7.0 Hz), 3.89 (3H, s), 2.92 (1H, br s), 2.51 (1H, br dd, *J* = 11.5, 7.0 Hz), 2.25 (1H, br s), 2.03 (3H, s), 1.63−1.53 (2H, m), 1.40−1.22 (6H, m); ^{13}C NMR (75 MHz) δ 171.3, 157.7 (q, $COCF_3$), 146.8, 136.2, 134.2, 122.0, 121.2, 119.9, 115.9 (q, $COCF_3$), 113.4, 110.4, 64.5, 55.7, 37.7, 36.9, 34.1, 28.5, 27.3, 25.9, 21.0; HRMS (ESI) *m/z* calcd for $C_{20}H_{26}F_3N_2O_4$ (M + H^+) 415.1845, found 415.1823.

Preparation of the Enehydrazine 4f. 2-Methoxyphenylhydrazine (0.88 g, 6.4 mmol) was treated with cyclobutanone **12f** (1.09 g, 6.4 mmol) according to the procedure described above, and the resulting mixture was treated sequentially with TFAA (1.46 mL, 10.5 mmol) and Et_3N (2.19 mL, 15.8 mmol). The crude product was purified by flash chromatography (hexane/EtOAc 3/1 v/v) to give the enehydrazine **4f** (1.73 g) in 70% yield over two steps.

*3-[3-[2-(2-Methoxyphenyl)-1-(2,2,2-trifluoroacetyl)hydrazinyl]-cyclobut-2-en-1-yl]propyl acetate (**4f**):* yellow oil; IR (ν_{max}, cm^{-1}) 3325 (NH), 1722 (CO); ^1H NMR (300 MHz) δ 6.98−6.85 (3H, m), 6.73 (1H, dm, *J* = 6.5 Hz), 6.61 (1H, s), 5.46 (1H, br s), 4.01 (2H, t, *J* = 7.0 Hz), 3.90 (3H, s), 2.95 (1H, br s), 2.55 (1H, br dd, *J* = 11.0, 7.5 Hz), 2.28 (1H, br s), 2.01 (3H, s), 1.62−1.53 (2H, m), 1.47−1.40 (2H, m); ^{13}C NMR (75 MHz) δ 171.1, 157.8 (q, $COCF_3$), 146.8, 136.5, 134.2, 122.0, 121.2, 119.3, 115.9 (q, $COCF_3$), 113.5, 110.4, 64.3, 55.7, 37.3, 30.6, 29.7, 26.8, 21.0; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}F_3N_2O_4$ (M + H^+) 387.1532, found 387.1497.

Preparation of the Enehydrazine 4g. 2-Methoxyphenylhydrazine (1.06 g, 7.7 mmol) was treated with cyclobutanone **12g** (1.20 g, 7.7 mmol) according to procedure described above, and the resulting mixture was treated sequentially with TFAA (1.97 mL, 14.2 mmol) and Et_3N (2.97 mL, 21.3 mmol). The crude product was then purified by flash column chromatography (hexane/EtOAc 3/1 v/v) to give the enehydrazine **4g** (1.43 g) in 50% yield over two steps.

*2-[3-[2-(2-Methoxyphenyl)-1-(2,2,2-trifluoroacetyl)hydrazinyl]-cyclobut-2-en-1-yl]ethyl acetate (**4g**):* yellow oil; IR (ν_{max}, cm^{-1}) 3351 (NH), 1717 (CO); ^1H NMR (300 MHz) δ 6.98−6.85 (3H, m), 6.73 (1H, dm, *J* = 7.0 Hz), 6.62 (1H, s), 5.44 (1H, br s), 4.03 (2H, t, *J* = 6.5 Hz), 3.89 (3H, s), 2.98 (1H, br s), 2.63 (1H, br dd, *J* = 11.5, 7.0 Hz), 2.3525 (1H, br s), 2.00 (3H, s), 1.72 (2H, q, *J* = 6.5 Hz); ^{13}C NMR (75 MHz) δ 171.0, 157.7 (q, $COCF_3$), 146.8, 136.4, 134.1, 122.0, 121.2, 118.9, 115.9 (q, $COCF_3$), 113.4, 110.4, 63.1, 55.6, 36.8, 34.8, 33.0, 20.7; HRMS (ESI) *m/z* calcd for $C_{17}H_{20}F_3N_2O_4$ (M + H^+) 373.1375, found 373.1358.

Thermal Reaction of *N*-Trifluoroacetylenehydrazine 4e. A solution of enehydrazine **4e** (1.97 g, 4.73 mmol) in solvent (30 mL) was heated at 82 °C, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was concentrated under reduced pressure to give the crude product as a residue, which was purified by flash column chromatography (hexane/EtOAc 10/1 v/v) to give the indoline **5e** (391 mg), *cis-syn*-**3e** (862 mg), and *cis-anti*-**3e** (313 mg) in 20, 44, and 16% yields, respectively.

*5-[(1α,2aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,3,7b-tetrahydro-4-methoxy-1H-cyclobut[b]indol-1-yl]pentyl acetate (**5e**):* yellow oil; IR (ν_{max}, cm^{-1}) 3304 (NH), 1715 (CO); ^1H NMR (300 MHz) δ 6.84 (1H, br s), 6.77 (1H, dd, *J* = 8.5, 7.0 Hz), 6.71−6.66 (2H, m), 4.05 (2H, t, *J* = 6.5 Hz), 3.84 (3H, s), 3.70 (1H, d, *J* = 5.5 Hz), 2.70 (1H, ddd, *J* = 12.5, 8.5, 0.5 Hz), 2.60 (1H, dd, *J* = 12.5, 7.5 Hz), 2.14−2.05 (1H, m), 2.04 (3H, s), 1.80−1.59 (4H, m), 1.38−1.25 (4H, m); ^{13}C NMR (75 MHz) δ 171.3, 156.1 (q, $COCF_3$), 145.9, 138.5, 132.1, 120.6, 115.9, 115.4 (q, $COCF_3$), 109.8, 73.6, 64.4, 55.4, 54.2, 40.7, 38.9, 35.9, 28.5, 26.7, 25.7, 21.0; HRMS (ESI) *m/z* calcd for $C_{20}H_{26}F_3N_2O_4$ (M + H^+) 415.1845, found 415.1837.

*5-[(1α,2aα,7aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,7a,7b-tetrahydro-7a-methoxy-1H-cyclobut[b]indol-1-yl]pentyl acetate (cis-syn-**3e**):* colorless oil; IR (ν_{max}, cm^{-1}) 3417 (NH), 1728 (CO); ^1H NMR (300 MHz) δ 7.60−7.42 (1H, br s), 6.56−6.50 (2H, m), 6.50−6.43 (1H, m), 6.10 (1H, dd, *J* = 9.5, 1.0 Hz), 4.04 (2H, t, *J* = 6.5 Hz), 3.17 (3H, s), 3.08 (1H, d, *J* = 7.0 Hz), 2.56 (1H, dd, *J* = 12.5, 8.0 Hz), 2.22−2.13 (1H, m), 2.05 (3H, s), 1.67−1.57 (4H, m), 1.48−1.20 (5H, m); ^{13}C NMR (75 MHz) δ 174.7, 171.1, 156.5 (q, $COCF_3$), 134.6, 130.6, 129.1, 122.9, 115.6 (q, $COCF_3$), 93.1, 85.7, 84.8, 64.3, 51.5, 35.0, 33.7, 28.4, 28.2, 26.6, 25.6, 20.8; HRMS (ESI) *m/z* calcd for $C_{20}H_{26}F_3N_2O_4$ (M + H^+) 415.1845, found 415.1837.

*5-[(1α,2aα,7aβ,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,7a,7b-tetrahydro-7a-methoxy-1H-cyclobut[b]indol-1-yl]pentyl acetate (cis-anti-**3e**):* colorless oil; IR (ν_{max}, cm^{-1}) 3193 (NH), 1724 (CO); ^1H NMR (300 MHz) δ 6.95 (1H, br s), 6.60 (1H, dm, *J* = 9.5 Hz), 6.52

(1H, ddm, J = 9.5, 5.5 Hz), 6.37 (1H, ddm, J = 9.5, 5.5 Hz), 6.27 (1H, dm, J = 9.5 Hz), 4.07 (2H, tm, J = 6.5 Hz), 3.23 (3H, s), 2.81 (1H, m), 2.36−2.33 (2H, m), 2.12−2.04 (1H, m), 2.05 (3H, s), 1.73−1.61 (4H, m), 1.39−1.37 (4H, m); ^{13}C NMR (75 MHz) δ 178.2, 171.2, 156.1 (q, $COCF_3$), 133.4, 133.0, 126.5, 122.3, 115.6 (q, $COCF_3$), 85.1, 84.3, 64.3, 53.0, 52.8, 35.9, 35.1, 28.3, 27.0, 25.6, 24.2, 20.8; HRMS (ESI) m/z calcd for $C_{20}H_{26}F_3N_2O_4$ (M + H$^+$) 415.1845, found 415.1838.

Thermal Reaction of *N*-Trifluoroacetylenehydrazine 4f. Using the same procedure as that described above for the cyclization of enehydrazine **4e**, compound **4f** (1.20 g, 3.12 mmol) was converted to indoline **5f** (120 mg), *cis-syn*-**3f** (373 mg), and *cis-anti*-**3f** (96 mg) in 10, 31, and 8% yields, respectively.

*3-[(1α,2aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,3,7b-tetrahydro-4-methoxy-1H-cyclobut[b]indol-1-yl]propyl acetate (**5f**):* yellow oil; IR (ν_{max}, cm^{-1}) 3416 (NH), 1724 (CO); ^{1}H NMR (300 MHz) δ 6.85 (1H, br s), 6.78 (1H, dd, J = 8.5, 7.0 Hz), 6.72−6.67 (2H, m), 4.66 (1H, br s), 4.06 (2H, t, J = 6.5 Hz), 3.84 (3H, s), 3.73 (1H, d, J = 5.5 Hz), 2.72 (1H, ddd, J = 12.5, 8.5, 1.0 Hz), 2.63 (1H, dd, J = 12.5, 8.0 Hz), 2.19−2.07 (1H, m), 2.04 (3H, s), 1.90−1.54 (4H, m); ^{13}C NMR (75 MHz) δ 171.2, 156.1 (q, $COCF_3$), 144.9, 138.4, 131.9, 120.7, 116.0, 115.4 (q, $COCF_3$), 109.9, 73.6, 64.1, 55.4, 54.1, 40.5, 38.5, 32.3, 26.3, 21.0; HRMS (ESI) m/z calcd for $C_{18}H_{22}F_3N_2O_4$ (M + H$^+$) 387.1532, found 387.1525.

*3-[(1α,2aα,7aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,7a,7b-tetrahydro-7a-methoxy-1H-cyclobut[b]indol-1-yl]propyl acetate (cis-syn-**3f**):* colorless oil; IR (ν_{max}, cm^{-1}) 3182 (NH), 1718 (CO); ^{1}H NMR (500 MHz) δ 8.04 (1H, br s), 6.53 (2H, br d, J = 5.0 Hz), 6.47 (1H, ddd, J = 9.5, 5.0, 2.0 Hz), 6.11 (1H, d, J = 9.5 Hz), 4.03 (2H, td, J = 7.0, 2.0 Hz), 3.17 (3H, s), 3.12 (1H, d, J = 6.0 Hz), 2.60 (1H, dd, J = 12.5, 8.0 Hz), 2.16 (1H, br dd, J = 12.5, 8.0 Hz), 2.05 (3H, s), 1.73−1.66 (2H, m), 1.63−1.51 (2H, m), 1.50−1.41 (1H, m); ^{13}C NMR (125 MHz) δ 175.0, 171.2, 156.6 (q, $COCF_3$), 134.8, 130.6, 129.5, 123.3, 115.7 (q, $COCF_3$), 85.9, 84.8, 64.2, 51.8, 51.7, 34.2, 31.6, 28.3, 26.3, 21.0; HRMS (ESI) m/z calcd for $C_{18}H_{22}F_3N_2O_4$ (M + H$^+$) 387.1532, found 387.1525.

*3-[(1α,2aα,7aβ,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,7a,7b-tetrahydro-7a-methoxy-1H-cyclobut[b]indol-1-yl]propyl acetate (cis-anti-**3f**):* colorless oil; IR (ν_{max}, cm^{-1}) 3193 (NH), 1724 (CO); ^{1}H NMR (500 MHz) δ 7.30 (1H, br s), 6.60 (1H, dt, J = 9.0, 1.0 Hz), 6.53 (1H, ddd, J = 10.0, 5.5, 1.5 Hz), 6.38 (1H, ddd, J = 9.5, 5.5, 1.0 Hz), 6.26 (1H, dt, J = 9.5, 1.0 Hz), 4.10 (2H, td, J = 6.5, 1.0 Hz), 3.22 (3H, s), 2.84 (1H, m), 2.43−2.34 (2H, m), 2.11−2.06 (1H, m), 1.83−1.64 (4H, m); ^{13}C NMR (125 MHz) δ 178.4, 171.2, 156.1 (q, $COCF_3$), 133.5, 132.9, 127.0, 122.9, 115.3 (q, $COCF_3$), 85.3, 84.5, 64.2, 53.2, 53.1, 35.6, 32.4, 26.8, 24.2, 20.9; HRMS (ESI) m/z calcd for $C_{18}H_{22}F_3N_2O_4$ (M + H$^+$) 387.1532, found 387.1527.

Thermal Reaction of *N*-Trifluoroacetylenehydrazine 4g. Using the same procedure as that described above for the cyclization of enehydrazine **4e**, compound **4g** (4.71 g, 12.6 mmol) was converted to indoline **5g** (797 mg), *cis-syn*-**3g** (1.22 g), and *cis-anti*-**3g** (469 mg) in 17, 26, and 10% yields, respectively.

*2-[(1α,2aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,3,7b-tetrahydro-4-methoxy-1H-cyclobut[b]indol-1-yl]ethyl acetate (**5g**):* yellow oil; IR (ν_{max}, cm^{-1}) 3303 (NH), 1714 (CO); ^{1}H NMR (300 MHz) δ 7.63 (1H, br s), 6.77−6.63 (3H, m), 4.66 (1H, br s), 4.13−3.97 (2H, m), 3.80 (3H, s), 3.76 (1H, d, J = 5.0 Hz), 2.72 (1H, dd, J = 12.5, 7.5 Hz), 2.56 (1H, dd, J = 12.5, 7.5 Hz), 2.25−2.12 (1H, m), 2.12−1.89 (2H, m), 1.98 (3H, s); ^{13}C NMR (75 MHz) δ 171.3, 156.2 (q, $COCF_3$), 144.6, 138.6, 131.4, 120.2, 115.8, 115.3 (q, $COCF_3$), 109.8, 73.7, 62.4, 55.1, 53.4, 40.5, 35.6, 34.4, 20.7; HRMS (ESI) m/z calcd for $C_{17}H_{20}F_3N_2O_4$ (M + H$^+$) 373.1375, found 373.1368.

*2-[(1α,2aα,7aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,7a,7b-tetrahydro-7a-methoxy-1H-cyclobut[b]indol-1-yl]ethyl acetate (cis-syn-**3g**):* colorless oil; IR (ν_{max}, cm^{-1}) 3290 (NH), 1715 (CO); ^{1}H NMR (500 MHz) δ 7.39 (1H, br s), 6.49−6.63 (2H, m), 6.46 (1H, ddd, J = 10.0, 5.0, 1.5 Hz), 6.09 (1H, dm, J = 9.5 Hz), 3.96 (2H, m), 3.17 (3H, s), 3.14 (1H, d, J = 6.0 Hz), 2.64 (1H, dd, J = 12.5, 8.5 Hz), 2.21 (1H, dd, J = 12.5, 8.0 Hz), 2.02 (3H, s), 2.06−1.94 (2H, m), 1.58 (1H, m); ^{13}C NMR (125 MHz) δ 175.0, 171.2, 156.6 (q, $COCF_3$), 134.8, 130.6, 129.5, 123.3, 115.7 (q, $COCF_3$), 85.9, 84.8, 64.2, 51.8, 51.7, 31.6, 28.3, 26.3, 21.0; HRMS (ESI) m/z calcd for $C_{17}H_{20}F_3N_2O_4$ (M + H$^+$) 373.1375, found 373.1369.

*2-[(1α,2aα,7aβ,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,7a,7b-tetrahydro-7a-methoxy-1H-cyclobut[b]indol-1-yl]ethyl acetate (cis-anti-**3g**):* pale yellow oil; IR (ν_{max}, cm^{-1}) 3300 (NH), 1721 (CO); ^{1}H NMR (500 MHz) δ 7.88 (1H, br s), 6.59 (1H, dt, J = 9.0, 1.0 Hz), 6.53 (1H, ddd, J = 10.0, 5.5, 1.5 Hz), 6.38 (1H, ddd, J = 9.5, 5.5, 1.0 Hz), 6.27 (1H, dt, J = 9.5, 1.0 Hz), 4.22−4.04 (2H, m), 3.22 (3H, s), 2.93 (1H, m), 2.52−2.42 (1H, m), 2.34 (1H, dd, J = 13.0, 9.0 Hz), 2.18 (1H, ddd, J = 13.0, 4.5, 2.5 Hz), 2.10−1.96 (2H, m), 2.05 (3H, s); ^{13}C NMR (125 MHz) δ 178.6, 171.1, 156.2 (q, $COCF_3$), 133.5, 132.8, 126.9, 122.6, 115.2 (q, $COCF_3$), 85.2, 84.4, 62.7, 53.0, 52.8, 35.2, 34.7, 21.5, 20.9; HRMS (ESI) m/z calcd for $C_{17}H_{20}F_3N_2O_4$ (M + H$^+$) 373.1375, found 373.1369.

Preparation of 13e. K_2CO_3 (290 mg, 2.1 mmol) was added to a solution of *cis-syn*-**3e** (867 mg, 2.1 mmol) in MeOH (20 mL) at 0 °C under an Ar atmosphere, and the resulting mixture was stirred at 0 °C for 4 h. The reaction mixture was then concentrated under reduced pressure to give a residue, which was diluted with H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude product (685 mg). A part of this material (48.5 mg, 0.13 mmol) was then dissolved in CH_2Cl_2 (6.0 mL) before being treated sequentially with pyridine (11 μL, 0.14 mmol), DMAP (7.9 mg, 0.065 mmol), and DsCl (105 mg, 0.39 mmol) at room temperature under an Ar atmosphere. The resulting mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure to give the crude product as a residue, which was purified by flash chromatography (hexane/EtOAc 3/1 v/v) to give **13e** (41.1 mg) in 42% yield over two steps.

*5-[(1α,2aα,7aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,7a,7b-tetrahydro-7a-methoxy-1H-cyclobut[b]indol-1-yl]pentyl 5-(dimethylamino)naphthalene-1-sulfonate (**13e**):* yellow oil; IR (ν_{max}, cm^{-1}) 3177 (NH), 1716 (CO); ^{1}H NMR (500 MHz) δ 8.60 (1H, d, J = 8.5 Hz), 8.28 (2H, m), 7.93 (1H, br s), 7.58 (1H, dd, J = 8.5, 8.0 Hz), 7.54 (1H, dd, J = 8.5, 8.0 Hz), 7.20 (1H, d, J = 7.5 Hz), 6.55−6.48 (2H, m), 6.45 (1H, ddd, J = 9.5, 5.0, 2.0 Hz), 6.04 (1H, d, J = 9.5 Hz), 3.97 (2H, td, J = 6.5, 2.0 Hz), 3.15 (3H, s), 2.89 (6H, s), 2.49 (1H, dd, J = 12.5, 8.5 Hz), 2.10 (1H, dd, J = 12.5, 8.5 Hz), 1.62−1.54 (2H, m), 1.54−1.42 (2H, m), 1.39−1.30 (1H, m), 1.28−1.16 (2H, m), 1.16−1.00 (2H, m); ^{13}C NMR (125 MHz) δ 174.9, 156.4 (q, $COCF_3$), 151.7, 134.7, 131.4, 131.3, 130.5, 130.4, 129.8, 129.7, 129.3, 128.6, 123.2, 123.0, 119.3, 115.6 (q, $COCF_3$), 115.4, 85.8, 84.6, 70.7, 51.7, 51.6, 45.4, 45.3, 34.9, 34.0, 28.6, 28.2, 26.2, 25.1; HRMS (ESI) m/z calcd for $C_{30}H_{35}F_3N_3O_5S$ (M + H$^+$) 606.2250, found 606.2242.

Preparation of 13f. Using the same procedure as that described above for the deprotection and dansylation of dienylimine *cis-syn*-**3e**, compound *cis-syn*-**3f** (353 mg, 0.91 mmol) was converted to **13f** (231 mg) in 44% yield over two steps.

*3-[(1α,2aα,7aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,7a,7b-tetrahydro-7a-methoxy-1H-cyclobut[b]indol-1-yl]propyl 5-(dimethylamino)naphthalene-1-sulfonate (**13f**):* yellow oil; IR (ν_{max}, cm^{-1}) 3424 (NH), 1716 (CO); ^{1}H NMR (500 MHz) δ 8.60 (1H, dt, J = 8.5, 1.0 Hz), 8.25−8.23 (2H, m), 7.59 (1H, dd, J = 8.5, 8.0 Hz), 7.54 (1H, dd, J = 8.5, 7.5 Hz), 7.21 (1H, d, J = 7.5 Hz), 7.03 (1H, br s), 6.54 (1H, d, J = 9.5 Hz), 6.49 (1H, ddd, J = 9.5, 5.5, 1.0 Hz), 6.40 (1H, ddd, J = 9.5, 5.5, 1.0 Hz), 5.92 (1H, dt, J = 9.5, 1.0 Hz), 4.01−3.90 (2H, m), 3.13 (3H, s), 3.06 (1H, s), 2.89 (6H, s), 2.38 (1H, dd, J = 12.5, 8.5 Hz), 2.05 (1H, ddd, J = 12.5, 8.5, 1.0 Hz), 1.58−1.46 (4H, m), 1.33−1.24 (1H, m); ^{13}C NMR (125 MHz) δ 175.3, 156.3 (q, $COCF_3$), 151.9, 134.7, 131.6, 131.4, 130.5, 130.2, 129.9, 129.9, 129.6, 128.7, 123.6, 123.0, 119.4, 115.6 (q, $COCF_3$), 115.5, 85.9, 84.4, 70.4, 51.8, 51.7, 45.4, 34.0, 30.9, 28.0, 26.4; HRMS (ESI) m/z calcd for $C_{28}H_{31}F_3N_3O_5S$ (M + H$^+$) 578.1937, found 578.1928.

Preparation of 13g. Using the same procedure as that described above for deprotection and dansylation of dienylimine *cis-syn*-**3e**, compound *cis-syn*-**3g** (372 mg, 1.0 mmol) was converted to **13g** (338 mg) in 60% yield over two steps.

2-[(1α,2aα,7aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,7a,7b-tetrahydro-7a-methoxy-1H-cyclobut[b]indol-1-yl]ethyl 5-(dimethyl-

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*amino)naphthalene-1-sulfonate (**13g**):* yellow oil; IR (ν_{max}, cm^{-1}) 3333 (NH), 1714 (CO); ^1H NMR (500 MHz) δ 8.60 (1H, dm, J = 8.5 Hz), 8.24 (1H, dd, J = 7.5, 1.0 Hz), 8.18 (1H, d, J = 8.5 Hz), 7.54 (1H, dd, J = 8.5, 4.5 Hz), 7.52 (1H, dd, J = 8.5, 4.5 Hz), 7.42 (1H, br s), 7.19 (1H, d, J = 7.5 Hz), 6.54−5.65 (2H, m), 6.45 (1H, ddd, J = 9.5, 4.0, 2.0 Hz), 6.13 (1H, d, J = 9.5 Hz), 4.04 (1H, ddd, J = 11.0, 6.5, 4.5 Hz), 3.88 (1H, ddd, J = 11.0, 7.0, 5.0 Hz), 3.14 (3H, s), 3.07 (1H, d, J = 6.5 Hz), 2.89 (6H, s), 2.42 (1H, dd, J = 11.5, 8.0 Hz), 2.02−1.87 (2H, m), 1.84 (1H, dd, J = 11.5, 8.5 Hz), 1.58 (1H, m); ^{13}C NMR (125 MHz) δ 175.2, 156.5 (q, $COCF_3$), 151.9, 134.9, 131.7, 131.1, 130.5, 130.4, 129.8, 129.8, 129.7, 128.8, 123.2, 123.0, 119.2, 115.6, 115.6 (q, $COCF_3$), 85.9, 84.6, 68.4, 51.8, 51.2, 45.4, 34.2, 33.5, 24.8; HRMS (ESI) m/z calcd for $C_{27}H_{29}F_3N_3O_5S$ (M + H^+) 564.1780, found 564.1775.

Addition−aromatization Reactions of 13e using Thiophenol. PhSH (8.8 μL, 0.086 mmol) was added to a solution of **13e** (51 mg, 0.078 mmol) in THF (2 mL) under an Ar atmosphere at room temperature, and the resulting mixture was stirred for 8 h. The reaction mixture was then concentrated under reduced pressure to give the crude product as a residue, which was purified by PTLC (toluene/EtOAc 1/1 v/v) to give **14e** (18 mg, 33%) and **15e** (16 mg, 29%).

*5-[(1α,2aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,3,7b-tetrahydro-5-phenylthio-1H-cyclobut[b]indol-1-yl]pentyl 5-(dimethylamino)naphthalene-1-sulfonate (**14e**):* yellow oil; IR (ν_{max}, cm^{-1}) 3333 (NH), 1716 (CO); ^1H NMR (500 MHz) δ 8.58 (1H, dd, J = 8.5, 1.0 Hz), 8.26 (1H, dd, J = 7.5, 1.5 Hz), 8.25 (1H, d, J = 9.0 Hz), 7.56 (1H, dd, J = 8.5, 7.5 Hz), 7.53 (1H, dd, J = 8.5, 7.5 Hz), 7.36−7.34 (2H, m), 7.31−7.28 (2H, m), 7.25−7.22 (1H, m), 7.17 (1H, d, J = 7.5 Hz), 6.93 (1H, br s), 6.85 (1H, d, J = 8.0 Hz), 6.72 (1H, dd, J = 7.5, 1.5 Hz), 6.54 (1H, d, J = 1.5 Hz), 4.76 (1H, br s), 3.99 (2H, t, J = 6.5 Hz), 3.46 (1H, d, J = 5.5 Hz), 2.87 (6H, s), 2.67 (1H, ddd, J = 12.0, 8.5, 1.0 Hz), 2.36 (1H, dd, J = 12.0, 8.0 Hz), 2.00−1.93 (1H, m), 1.62−1.44 (4H, m), 1.28−1.22 (4H, m); ^{13}C NMR (125 MHz) δ 156.2 (q, $COCF_3$), 151.8, 150.8, 135.9, 135.3, 131.5, 131.1, 130.4, 129.9, 129.8, 129.2, 128.6, 127.0, 123.9, 123.1, 122.2, 119.4, 115.5, 115.4 (q, $COCF_3$), 111.2, 73.5, 70.7, 53.2, 45.4, 41.1, 38.6, 35.8, 28.6, 26.2, 25.2; HRMS (ESI) m/z calcd for $C_{35}H_{37}F_3N_3O_4S_2$ (M + H^+) 684.2178, found 684.2177.

*5-[(1α,2aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,3,7b-tetrahydro-6-phenylthio-1H-cyclobut[b]indol-1-yl]pentyl 5-(dimethylamino)naphthalene-1-sulfonate (**15e**):* yellow oil; IR (ν_{max}, cm^{-1}) 3335 (NH), 1715 (CO); ^1H NMR (500 MHz) δ 8.57 (1H, d, J = 8.5 Hz), 8.25 (1H, dd, J = 7.0, 1.0 Hz), 8.24 (1H, d, J = 9.0 Hz), 7.55 (1H, dd, J = 8.0, 7.0 Hz), 7.52 (1H, dd, J = 8.0, 7.0 Hz), 7.24−7.08 (7H, m), 7.06 (1H, d, J = 1.5 Hz), 7.00 (1H, br s), 6.59 (1H, d, J = 8.0 Hz), 4.96 (1H, br s), 3.96 (2H, t, J = 7.0 Hz), 3.44 (1H, d, J = 6.0 Hz), 2.87 (6H, s), 2.73 (1H, ddd, J = 12.5, 8.0, 1.0 Hz), 2.35 (1H, dd, J = 12.5, 8.0 Hz), 2.04−1.96 (1H, m), 1.60−1.40 (4H, m), 1.25−1.05 (4H, m); ^{13}C NMR (125 MHz) δ 156.2 (q, $COCF_3$), 151.7, 150.4, 139.9, 134.9, 131.8, 131.4, 130.4, 129.9, 129.8, 128.8, 128.6, 127.5, 125.4, 123.1, 121.6, 119.4, 115.5, 115.4 (q, $COCF_3$), 109.3, 73.4, 70.7, 53.3, 45.4, 41.4, 38.6, 35.8, 28.5, 26.7, 25.1; HRMS (ESI) m/z calcd for $C_{35}H_{37}F_3N_3O_4S_2$ (M + H^+) 684.2178, found 684.2177.

Addition−Aromatization Reactions of 13f using Thiophenol. Using the same procedure as that described above for the addition of thiophenol to **13e**, thiophenol (3.5 μL, 0.034 mmol) was added to compound **13f** (18 mg, 0.031 mmol) to give **14f** (5.9 mg) and **15f** (4.9 mg) in 29 and 24% yields, respectively.

*3-[(1α,2aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,3,7b-tetrahydro-5-phenylthio-1H-cyclobut[b]indol-1-yl]propyl 5-(dimethylamino)naphthalene-1-sulfonate (**14f**):* yellow oil; IR (ν_{max}, cm^{-1}) 3338 (NH), 1715 (CO); ^1H NMR (500 MHz) δ 8.59 (1H, d, J = 9.0 Hz), 8.27 (1H, d, J = 9.0 Hz), 8.26 (1H, dd, J = 7.0, 1.0 Hz), 7.58 (1H, dd, J = 9.0, 8.0 Hz), 7.54 (1H, dd, J = 8.5, 7.5 Hz), 7.37−7.34 (2H, m), 7.32−7.29 (2H, m), 7.26−7.23 (1H, m), 7.20 (1H, d, J = 7.5 Hz), 6.78 (1H, br s), 6.72 (1H, d, J = 8.0 Hz), 6.69 (1H, dd, J = 8.0, 1.5 Hz), 6.52 (1H, d, J = 1.5 Hz), 4.06−4.01 (1H, m), 3.99−3.95 (1H, m), 3.36 (1H, d, J = 6.0 Hz), 2.88 (6H, s), 2.59 (1H, dd, J = 12.5, 8.0 Hz), 2.31 (1H, dd, J = 12.5, 7.5 Hz), 1.90−1.85 (1H, m), 1.67−1.52 (4H, m); ^{13}C NMR (125 MHz) δ 156.1 (q, $COCF_3$), 150.6, 135.7, 135.6, 131.6, 131.4, 131.2, 130.5, 129.9, 129.3, 129.2, 128.7, 127.1, 123.8, 123.1, 122.1, 119.4, 115.5, 115.3 (q, $COCF_3$), 111.2, 73.3, 70.4, 53.0, 45.4, 40.8, 37.9, 31.8, 26.5; HRMS (ESI) m/z calcd for $C_{33}H_{33}F_3N_3O_4S_2$ (M + H^+) 656.1865, found 656.1862.

*3-[(1α,2aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,3,7b-tetrahydro-6-phenylthio-1H-cyclobut[b]indol-1-yl]propyl 5-(dimethylamino)naphthalene-1-sulfonate (**15f**):* yellow oil; IR (ν_{max}, cm^{-1}) 3324 (NH), 1714 (CO); ^1H NMR (500 MHz) δ 8.56 (1H, d, J = 8.5 Hz), 8.28−8.24 (2H, m), 7.56 (1H, dd, J = 8.5, 7.5 Hz), 7.51 (1H, dd, J = 8.5, 7.5 Hz), 7.26−7.21 (3H, m), 7.17 (1H, d, J = 7.0 Hz), 7.15−7.11 (3H, m), 6.95 (1H, d, J = 1.5 Hz), 6.84 (1H, br s), 6.57 (1H, d, J = 8.0 Hz), 4.90 (1H, br s), 4.06−4.01 (1H, m), 3.98−3.92 (1H, m), 3.27 (1H, d, J = 5.5 Hz), 2.86 (6H, s), 2.66 (1H, dd, J = 13.0, 9.0 Hz), 2.29 (1H, dd, J = 12.0, 7.5 Hz), 1.94−1.86 (1H, m), 1.26−1.24 (4H, m); ^{13}C NMR (125 MHz) δ 156.3 (q, $COCF_3$), 151.9, 150.3, 139.4, 135.0, 131.6, 131.3, 131.2, 129.9, 129.8, 129.7, 128.9, 128.7, 127.5, 125.5, 123.1, 121.7, 119.4, 115.5, 115.4 (q, $COCF_3$), 109.4, 73.2, 70.3, 53.0, 45.4, 41.1, 38.0, 31.9, 26.4; HRMS (ESI) m/z calcd for $C_{33}H_{33}F_3N_3O_4S_2$ (M + H^+) 656.1865, found 656.1862.

Addition−Aromatization Reactions of 13g using Thiophenol. Using the same procedure as that described above for the addition of thiophenol to **13e**, thiophenol (9.7 μL, 0.095 mmol) was added to compound **13g** (49 mg, 0.087 mmol) to give **14g** (12 mg) and **15g** (13 mg) in 21 and 23% yields, respectively.

*2-[(1α,2aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,3,7b-tetrahydro-5-phenylthio-1H-cyclobut[b]indol-1-yl]ethyl 5-(dimethylamino)naphthalene-1-sulfonate (**14g**):* yellow oil; IR (ν_{max}, cm^{-1}) 3192 (NH), 1716 (CO); ^1H NMR (500 MHz) δ 8.61 (1H, dt, J = 8.5, 1.0 Hz), 8.26 (1H, dd, J = 7.5, 1.0 Hz), 8.18 (1H, dt, J = 8.5, 1.0 Hz), 7.55 (1H, dd, J = 8.5, 7.5 Hz), 7.47 (1H, dd, J = 8.5, 7.5 Hz), 7.40−7.37 (2H, m), 7.35−7.31 (2H, m), 7.29−7.24 (1H, m), 7.15 (1H, dd, J = 7.5, 1.0 Hz), 6.87 (1H, d, J = 7.5 Hz), 6.73 (1H, dd, J = 7.5, 1.5 Hz), 6.72 (1H, br s), 6.55 (1H, d, J = 1.5 Hz), 4.57 (1H, br s), 4.10−4.05 (1H, m), 3.99−3.94 (1H, m), 3.63 (1H, d, J = 5.5 Hz), 2.89 (6H, s), 2.43 (2H, t, J = 7.5 Hz), 2.18−2.07 (2H, m), 1.96−1.90 (1H, m); ^{13}C NMR (125 MHz) δ 156.2 (q, $COCF_3$), 151.8, 150.4, 135.8, 135.7, 131.6, 131.3, 130.6, 129.9, 129.8, 129.4, 129.2, 128.7, 127.1, 124.3, 123.0, 123.0, 122.6, 119.3, 115.6, 115.3 (q, $COCF_3$), 111.5, 73.4, 68.7, 52.8, 45.4, 40.1, 35.3, 34.7; HRMS (ESI) m/z calcd for $C_{32}H_{31}F_3N_3O_4S_2$ (M + H^+) 642.1708, found 642.1706.

*2-[(1α,2aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,3,7b-tetrahydro-6-phenylthio-1H-cyclobut[b]indol-1-yl]ethyl 5-(dimethylamino)naphthalene-1-sulfonate (**15g**):* yellow oil; IR (ν_{max}, cm^{-1}) 3334 (NH), 1715 (CO); ^1H NMR (500 MHz) δ 8.58 (1H, dt, J = 8.5, 1.0 Hz), 8.24 (1H, dd, J = 7.5, 1.0 Hz), 8.19 (1H, d, J = 8.5 Hz), 7.51 (1H, dd, J = 8.5, 7.5 Hz), 7.49 (1H, dd, J = 8.5, 7.5 Hz), 7.26−7.22 (2H, m), 7.18−7.16 (4H, m), 7.14−7.11 (2H, m), 6.78 (1H, br s), 6.60 (1H, d, J = 8.0 Hz), 4.78 (1H, br s), 4.07 (1H, dt, J = 10.5, 5.5 Hz), 3.93 (1H, ddd, J = 10.5, 8.0, 5.5 Hz), 3.61 (1H, d, J = 5.5 Hz), 2.89 (6H, s), 2.52 (1H, dd, J = 13.0, 9.0 Hz), 2.45 (1H, dd, J = 13.0, 8.0 Hz), 2.23−2.15 (1H, m), 2.10−2.03 (1H, m), 1.97−1.90 (1H, m); ^{13}C NMR (125 MHz) δ 156.2 (q, $COCF_3$), 151.8, 150.1, 139.3, 135.1, 131.7, 131.3, 131.1, 130.6, 130.0, 129.8, 129.8, 128.9, 128.8, 127.8, 125.6, 123.1, 122.4, 119.2, 115.6, 115.3 (q, $COCF_3$), 109.7, 73.4, 68.5, 52.9, 45.4, 40.4, 35.3, 34.7; HRMS (ESI) m/z calcd for $C_{32}H_{31}F_3N_3O_4S_2$ (M + H^+) 642.1708, found 642.1703.

Addition−Aromatization Reactions of 13g using Octanethiol. Using the same procedure as that described above for the addition of thiophenol to **13e**, octanethiol (14 μL, 0.081 mmol) was added to compound **13g** (45 mg, 0.073 mmol) and the reaction mixture was stirred at room temperature for 36 h to give **14h** (9.4 mg) and **15h** (12 mg) in 19 and 24% yields, respectively.

*2-[(1α,2aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,3,7b-tetrahydro-5-octylthio-1H-cyclobut[b]indol-1-yl]ethyl 5-(dimethylamino)-naphthalene-1-sulfonate (**14h**):* yellow oil; IR (ν_{max}, cm^{-1}) 3325 (NH), 1714 (CO); ^1H NMR (500 MHz) δ 8.61 (1H, dt, J = 8.5, 1.0 Hz), 8.26 (1H, dd, J = 7.5, 1.0 Hz), 8.19 (1H, dt, J = 8.5, 1.0 Hz), 7.55 (1H, dd, J = 8.5, 7.5 Hz), 7.49 (1H, dd, J = 8.5, 7.5 Hz), 7.19 (1H, dd, J = 7.5, 1.0 Hz), 6.88 (1H, d, J = 7.5 Hz), 6.74 (1H, br s), 6.70 (1H, dd, J = 7.5, 1.5 Hz), 6.59 (1H, d, J = 1.5 Hz), 4.11−4.05 (1H, m), 3.99−3.94 (1H, m), 3.61 (1H, d, J = 5.5 Hz), 2.90 (6H, s), 2.87 (2H, d, J = 7.5 Hz), 2.45 (2H, dm, J = 7.5 Hz), 2.18−2.05 (2H, m), 1.96−

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1.89 (1H, m), 1.65 (2H, qn, J = 7.5 Hz), 1.42 (2H, m), 1.32−1.23 (8H, m), 0.88 (3H, m); ^{13}C NMR (125 MHz) δ 156.2 (q, $COCF_3$), 151.8, 150.1, 131.6, 131.1, 130.6, 129.9, 129.8, 128.7, 128.0, 124.1, 123.1, 120.4, 119.3, 115.6, 115.3 (q, $COCF_3$), 109.8, 73.5, 68.7, 52.8, 45.4, 40.1, 35.3, 34.7, 33.8, 31.8, 29.3, 29.2, 29.2, 29.1, 28.9, 22.7, 14.10; HRMS (ESI) m/z calcd for $C_{34}H_{43}F_3N_3O_4S_2$ (M + H^+) 678.2647, found 678.2643.

*2-[(1α,2aα,7bα)-2a-[(Trifluoroacetyl)amino]-2,2a,3,7b-tetrahydro-6-octylthio-1H-cyclobut[b]indol-1-yl]ethyl 5-(dimethylamino)-naphthalene-1-sulfonate (**15h**):* yellow oil; IR (ν_{max}, cm^{-1}) 3337 (NH), 1714 (CO); ^{1}H NMR (500 MHz) δ 8.61 (1H, dt, J = 8.5, 1.0 Hz), 8.26 (1H, dd, J = 7.5, 1.0 Hz), 8.21 (1H, d, J = 8.5 Hz), 7.55 (1H, dd, J = 8.5, 7.5 Hz), 7.52 (1H, dd, J = 8.5, 7.5 Hz), 7.19 (1H, d, J = 7.5 Hz), 7.15 (1H, dd, J = 8.0, 1.0 Hz), 7.12 (1H, br d, J = 1.5 Hz), 6.79 (1H, br s), 6.54 (1H, d, J = 8.0 Hz), 4.11−4.05 (1H, m), 3.98−3.91 (1H, m), 3.65 (1H, d, J = 5.5 Hz), 2.89 (6H, s), 2.80 (2H, t, J = 7.5 Hz), 2.45 (2H, d, J = 8.0 Hz), 2.21−2.12 (1H, m), 2.12−2.05 (1H, m), 1.97−1.89 (1H, m), 1.58 (2H, qn, J = 7.5 Hz), 1.38 (2H, qn, J = 7.5 Hz), 1.30−1.20 (8H, m), 0.88−0.84 (3H, m); ^{13}C NMR (125 MHz) δ 156.3 (q, $COCF_3$), 151.8, 148.8, 132.3, 131.6, 131.2, 131.1, 130.6, 129.9, 129.8, 129.8, 127.7, 125.9, 123.1, 119.3, 115.6, 115.3 (q, $COCF_3$), 109.6, 73.5, 68.7, 53.0, 45.4, 40.2, 36.3, 35.2, 34.7, 31.8, 29.4, 29.2, 29.2, 28.8, 22.7, 14.1; HRMS (ESI) m/z calcd for $C_{34}H_{43}F_3N_3O_4S_2$ (M + H^+) 678.2647, found 678.2639.

Fluorescence Spectra Measurement. Compounds **13e−g**, **14e−h**, and **15e−h** were dissolved in $CHCl_3$ at a concentration of 1.0×10^{-5} M, and their fluorescence spectra were measured using an F-7000 spectrofluorimeter (Hitachi) with a 1 × 1 cm quartz cell. The excitation wavelength was set at 350 nm. The slit widths of the excitation and emission were set at 2.5 nm.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H and ^{13}C NMR spectra for all of the new compounds, COSY and NOESY spectra of *cis-syn*-**3a**, *cis-anti*-**3a**, **5a**, *cis-syn*-**3d**, *cis-anti*-**3d**, *trans-anti*-**3d**, **7**, and **8**, and HSQC and HMBC spectra of compounds **7** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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