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A Trifluoroacetic Acid-labile Sulfonate Protecting Group and Its Use in the Synthesis of a Near-IR Fluorophore

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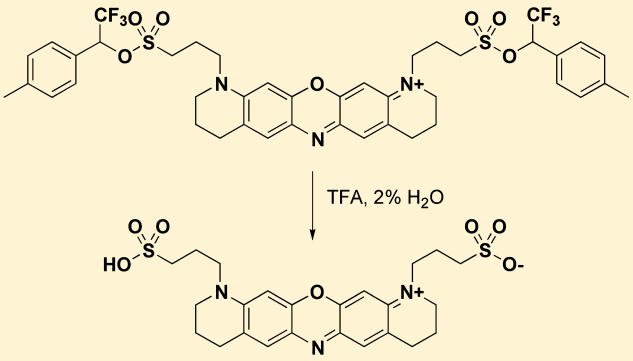
Supporting Information

ABSTRACT: Sulfonated molecules exhibit high water solubility, a property that is valuable for many biological applications but often complicates their synthesis and purification. Here we report a sulfonate protecting group that is resistant to nucleophilic attack but readily removed with trifluoroacetic acid (TFA). The use of this protecting group improved the synthesis of a sulfonated near-IR fluorophore and the mild deprotection conditions allowed isolation of the product without requiring chromatography.



Sulfonation of hydrophobic fluorescent dyes greatly improves both their solubility and fluorescence properties in aqueous media.[1−5] However, sulfonated molecules can be tedious to prepare and purify because their high polarity often necessitates the use of aqueous conditions during synthesis and purification. For example, we found that HPLC was required for purification of sulfonated oxazine near-IR fluorophores such as **1** (Figure 1).[6] On the other hand, purification of stable

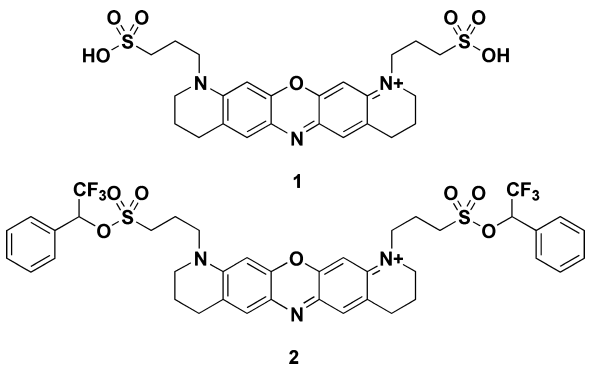


Figure 1. Bis-sulfonate oxazine **1** and bis-sulfonate ester **2**.

sulfonate ester dyes such as **2** was possible via conventional silica gel flash chromatography.[6] Thus, the synthesis of sulfonated molecules could be aided by a protecting group which allows solubility in standard organic solvents and purification by conventional chromatography, but is readily removed in a final cleavage step that does not itself require HPLC purification.

Compared to carboxylates, there are relatively few choices for sulfonate protecting groups.[7] Sulfonate esters are generally highly reactive electrophiles that alkylate a wide range of nucleophilic molecules. Protecting groups currently available for sulfonates all have caveats that limit their general applicability.[8] Isopropyl (iPr) and isobutyl (iBu) sulfonates retain lability to nucleophiles,[9−11] while trichloroethyl (TCE) sulfonates are unstable to mildly basic conditions.[12] Neopentyl (Neo) groups are highly stable to nucleophiles but removal requires either strongly acidic conditions[8,12] or heating in DMF with strong nucleophiles.[11,13] Trifluoroethyl (TFE) sulfonates are stable to both nucleophilic and acidic conditions, but need strongly basic conditions for removal.[8] For our purposes, existing sulfonate protecting groups are either insufficiently stable, require cleavage conditions that are too harsh, and/or deprotection would require subsequent HPLC purification. For example, attempted cleavage of the sulfonate ester dye **2** with NaOH led to dye decomposition.

A convenient cleavage reagent for many protecting groups is trifluoroacetic acid (TFA).[7] While TFA-labile protecting groups for carboxylates, alcohols, amines, and other functionalities are common,[7] most sulfonate esters that are stable to nucleophiles are also stable to TFA.[8] An exception is the "triggered" TFA-labile sulfonate ester protecting group reported by Roberts et al., Neo N−B, which is stable to nucleophiles by virtue of its neopentyl structure.[13] However, cleavage of Neo N−B is a two-step process that requires initial cleavage of a Boc-protected amine followed by neutralization to effect release of the sulfonate. Isolation of the liberated sulfonate requires the chromatographic removal of nonvolatile side-products, and the protecting group itself is not readily available, requiring a four-

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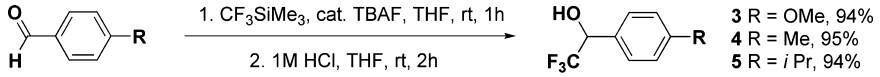
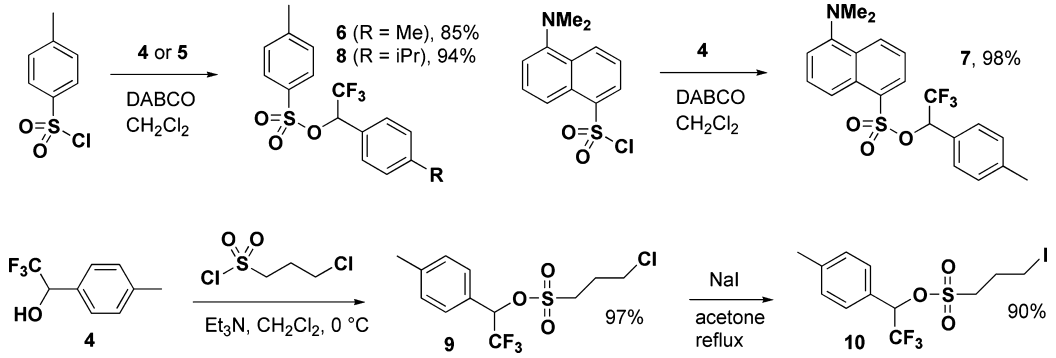
Scheme 1. Ruppert-Prakash Synthesis of Potential Reagents for the Development of Sulfonate Protecting Groups



Scheme 2. Synthesis of TFMT Sulfonate Esters



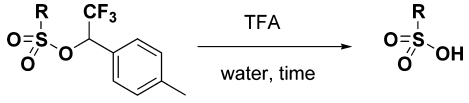
step synthesis from commercially available materials. Other related neopentyl-based protection strategies for sulfonates have similar limitations.[5,14] We therefore sought to develop a sulfonate protecting group which could satisfy three criteria: (i) *intrinsic* TFA-lability not requiring any additional treatment for cleavage to occur; (ii) easy separation of the cleaved sulfonate from any byproducts; and (iii) ready access from commercially available materials.

In a recent survey of commercially available alcohols that could potentially serve as protecting groups for sulfonates, we found that α-trifluoromethylbenzyl (TFMB) sulfonates (as in **2**, Figure 1) are stable to nucleophiles and could function as a scaffold for the design of sulfonate ester protecting groups with engineered lability.[8] For example, we have prepared an esterase-labile sulfonate protecting group by incorporating an acetoxy group into the *para* position.[15] Thus, while TFMB sulfonates themselves are stable to TFA,[8] we hypothesized that electron-rich variants could be created that would be labile to TFA yet retain stability to nucleophiles.

Solvolysis studies of 1-aryl-2,2,2-trifluoromethyl tosylates have shown that the rate of carbocation formation in ionizing solvents is dependent on the nature of the aryl group.[16] We therefore introduced the strongly electron-donating *para*-methoxy group onto the TFMB scaffold by treating *p*-anisaldehyde with $TMSCF_3$ under Ruppert-Prakash conditions[17] to afford **3** (Scheme 1). More weakly electron-donating *p*-methyl and *p*-isopropyl substituents were similarly introduced to yield alcohols **4** and **5**, respectively (Scheme 1). Typically, the Ruppert-Prakash reaction is quenched with HCl to hydrolyze the initially formed TMS ether,[17] followed by chromatographic purification. However, we found that the starting benzaldehydes and trifluoromethylated alcohol products closely elute during flash column purification. Thus, if the reaction is incomplete, purification becomes tedious. We therefore first purified the TMS ether, which was very well resolved from the starting aldehyde by flash chromatography. Subsequent treatment with aqueous acid cleanly cleaved the TMS ether to yield the desired product after extractive workup. We have adopted this improved synthesis protocol for all Ruppert-Prakash reactions with benzaldehydes.

We next tested the suitability of **3**-**5** as sulfonate protecting groups. Reaction of alcohol **3** with sulfonyl chlorides yielded sulfonate esters that were too labile to be easily isolated (e.g., the dansylate and 3-chloropropanesulfonate decomposed during purification on a silica gel column). On the other hand, sulfonate esters **6** and **7** derived from alcohol **4** (Scheme 2) were stable to isolation and to treatment with nucleophiles. Like the corresponding TFMB sulfonate esters,[8] **6** and **7** were quantitatively recovered after 2 h of treatment with 20% piperidine in DMF at room temperature or 4 h of treatment with 1.1 equiv of sodium iodide in refluxing acetone (Table S2, Figure S1, Supporting Information). While stable to nucleophilic attack, the *p*-methyl group is sufficiently electron-donating that sulfonate esters of **4**, dubbed "TFMT" sulfonates, can be cleaved by solvolysis in TFA (Table 1 and

Table 1. TFA Cleavage of Sulfonate Esters 6 and 7



entry	substrate	% water	time (h)	yield (%)
1[a]	**6**	0	2	39
2	7	0	2	84
3[b]	**6**	1	2	41
4	7	1	2	99
5[b]	**6**	1	16	88
6[c]	**6**	2	2	84
7[b]	**6**	3	2	82
8	**6**	5	2	89

[a]Average of $n = 3$. [b]$n = 2$. [c]$n = 4$.

Table S1, Supporting Information). Inclusion of water as a cation scavenging agent at 2% v/v or greater improves the cleavage yield in the case of the tosyl ester **6**. This may reflect the formation of a tight ion pair that can recombine unless quenched by water.[18] Under these conditions, cleavage is readily achieved in 2 h at room temperature (Table 1), and the pure sulfonate could be conveniently isolated by extraction and evaporation, without requiring chromatography. Tosylate **8** derived from *p*-isopropyl alcohol **5** was also found to be TFA-labile and nucleophile stable, but provided no obvious advantages over TFMT. Finally, the TFMT sulfonate ester is stable to K_2CO_3 in hot DMF and to hot dilute aqueous acidic conditions that cleave acetals and carboxylate esters (2 M HCl/

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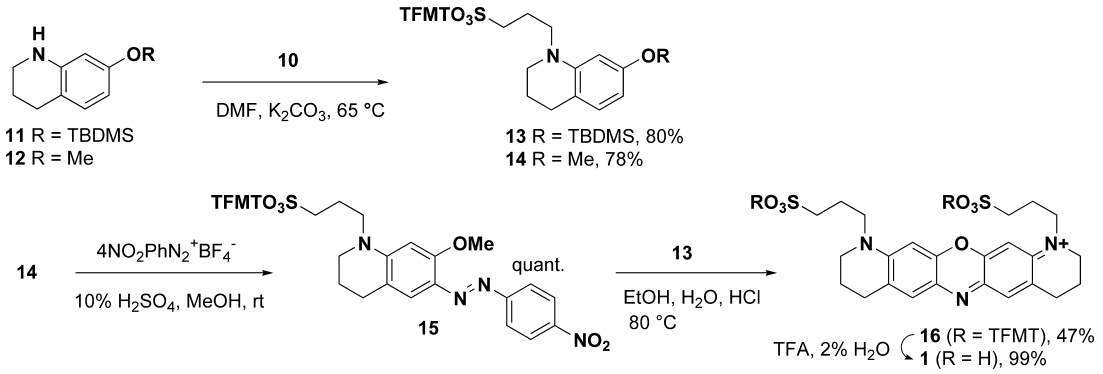
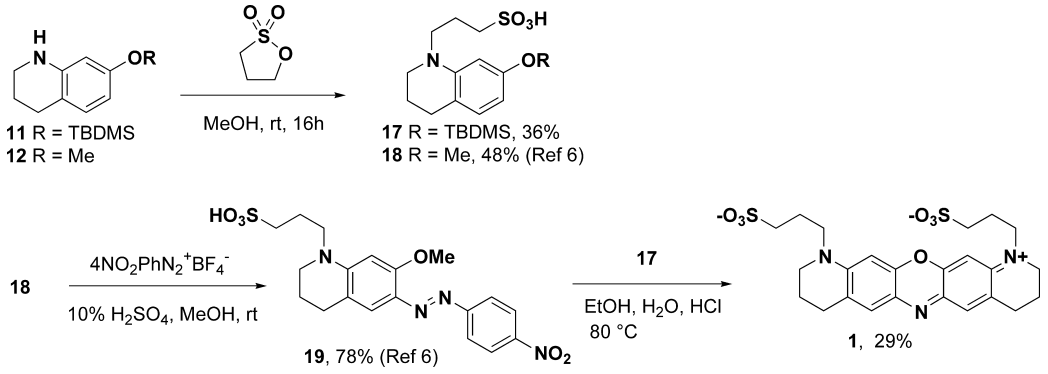
Scheme 3. Synthesis of Bis-sulfonated Oxazine Dye 1 using the TFA-labile TFMT Sulfonate Protecting Group



Scheme 4. Synthesis of Bis-sulfonate Oxazine Dye 1 using 1,3-Propanesultone



acetone, 70 °C),[19] suggesting that TFMT sulfonates could survive similar conditions necessary for oxazine dye synthesis (Table S2, Supporting Information).

Having established that TFMT met our three criteria for a new sulfonate protecting group, we next sought to test its utility in the context of sulfonated near-IR fluorophore synthesis. To access the TFMT-protected sulfonated dyes, we first synthesized the TFMT-protected sulfopropyl iodide **10** (Scheme 2). As with TFMB,[6] the remarkable stability of TFMT sulfonates to nucleophilic attack by iodide is manifestly demonstrated by the selective substitution of the chloride in **9** to cleanly afford **10**. Iodide **10** was then used to alkylate the tetrahydroquinolines **11**[6] and **12**[6] to afford **13** and **14** (Scheme 3). Like TFMB,[6] the TFMT group was stable to these nucleophilic substitution reactions. Similarly, acidic diazonium coupling conditions (10% aqueous H_2SO_4) and dye coupling conditions (hot acetic acid or HCl in refluxing aqueous ethanol) were tolerated, allowing access to the bis-TFMT protected oxazine dye **16** (Scheme 3), which could be purified by silica gel chromatography.

Treatment of the purified bis-TFMT dye **16** with TFA and 2% H_2O at rt for 2h liberated the bis-sulfonate dye **1**. After reaction, the volatiles were removed and the dye was extracted into water and lyophilized. Notably, complete cleavage was observed, and no impurities were introduced (Figure S2, Supporting Information). Compared to the synthesis of the bis-sulfonated oxazine dye **1** using the conventional sulfopropylation reagent 1,3-propanesultone (Scheme 4), the TFMT approach was higher-yielding, easier to perform, and more rapid as all products could be purified by standard silica gel flash chromatography methods rather than HPLC.

In conclusion, TFMT is a new sulfonate protecting group that is readily accessible in a single high-yield step from commercially available materials. TFMT-protected sulfonates are resistant to nucleophilic attack but can be unmasked under relatively mild conditions by treatment with TFA, and the cleavage product separated by extraction and evaporation. The TFMT group thus complements and expands the repertoire of practical and useful sulfonate protecting groups. We have found it to be advantageous for the synthesis and purification of sulfonated oxazine dyes and their intermediates, and anticipate that it will be generally useful for the synthesis of a wide variety of sulfonated molecules. For example, the stability of the TFMT group to 20% piperidine in DMF and facile cleavage by TFA suggests that it may also find application for the synthesis of sulfonated peptides under Fmoc solid-phase peptide synthesis (SPPS) conditions.

EXPERIMENTAL SECTION

General Procedure for Ruppert-Prakash Reactions. Trimethyl(trifluoromethyl)silane (1.4 equiv) was added to a solution of the benzaldehyde (1.0 equiv) in THF (0.5 M). The solution was cooled to 0 °C followed by the dropwise addition of a catalytic amount (~1 drop/mmol) of 1 M tetra-*n*-butylammonium fluoride (TBAF) in THF. The reaction was brought to room temperature and stirred for 1 h. The solution was then concentrated via rotary evaporation and purified by flash column chromatography (0–1% ethyl acetate/hexanes) giving the TMS-protected alcohol as a clear, pale-yellow liquid. This intermediate was dried under vacuum and then dissolved in 1:1 THF–1 M HCl (0.25 M) and stirred for 2 h at room temperature to cleave the TMS ether. The solution was then poured into water and the product was extracted with ethyl acetate. The combined organic phases were washed with 0.1 M HCl, water, brine, and then dried over Na_2SO_4. Removal of solvent in vacuo yielded the product.

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2,2,2-Trifluoro-1-(4-methoxy-phenyl)-ethanol ***3****:*[20] yellow oil (1.4 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, 2H, J = 8.9 Hz), 6.93 (d, 2H, J = 8.9 Hz), 4.97 (q, 1H, J_{HF} = 6.7 Hz), 3.83 (s, 3H), 2.46 (br s, 1H). ^{19}F-NMR (376 MHz, $CDCl_3$): δ −79.0 (d, J = 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 129.1, 126.5, 124.6 (q, $^1J_{CF}$ = 282 Hz), 114.2, 72.5 (q, $^2J_{CF}$ = 32 Hz), 55.5. HRMS (EI) m/z: $[M + H]^+$ Calcd for $C_9H_{10}F_3O_2$: 207.0633, found: 207.0625.

2,2,2-Trifluoro-1-p-tolyl-ethanol ***4****:*[18] pale yellow oil (1.5 g, 95%). The product becomes a soft, off-white solid when stored at 4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, 2H, J = 8.2 Hz), 7.22 (d, 2H, J = 7.9 Hz), 5.02−4.96 (dq, 1H, J = 4.5 Hz, J_{HF} = 6.7 Hz), 2.48 (d, 1H, J = 4.6 Hz), 2.37 (s, 3H). ^{19}F-NMR (376 MHz, $CDCl_3$): δ −78.9 (d, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 131.3, 129.6, 127.6, 124.6 (q, $^1J_{CF}$ = 282 Hz), 72.9 (q, $^2J_{CF}$ = 32 Hz), 21.4. HRMS (EI) m/z: $[M + Na]^+$ Calcd for $C_9H_9F_3ONa$: 213.0503, found: 213.0497.

2,2,2-Trifluoro-1-(4-isopropyl-phenyl)-ethanol ***5****:* pale yellow oil (1.3 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, 2H, J = 8.2 Hz), 7.38 (d, 2H, J = 8.2 Hz), 4.92 (q, 1H, J_{HF} = 6.5 Hz), 4.05 (br s, 1H), 3.11−3.00 (m, 1H), 1.40 (s, 3H), 1.38 (s, 3H). ^{19}F-NMR (376 MHz, $CDCl_3$): δ −78.5 (d, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 131.7, 127.9, 127.0, 124.7 (q, $^1J_{CF}$ = 282 Hz), 72.9 (q, $^2J_{CF}$ = 32 Hz), 34.2, 24.0. HRMS (EI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{14}F_3O$: 219.0997, found: 219.0999.

General Procedure for Sulfonate Ester Formation. Sulfonyl chloride (1.1 equiv) and a trifluoromethyl benzyl alcohol (1 equiv) were dissolved in CH_2Cl_2 (0.7 M). To this solution was added dropwise a solution of DABCO (1.2 equiv) in CH_2Cl_2 (2 M), resulting in precipitate formation. The mixture was then stirred for 4 h at room temperature. The reaction was quenched by the addition of 1 M NaOH (1 mL) resulting in elimination of the precipitate. The solution was diluted into ethyl acetate and extracted with saturated $NaHCO_3$, 0.1 M HCl, water, and brine. The organic phase was then dried over Na_2SO_4 and the solvent was removed via rotary evaporation.

Toluene-4-sulfonic acid 2,2,2-trifluoro-1-p-tolyl-ethyl Ester ***6****:*[18] white solid (1.17 g, 85%). mp 83−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 2H, J = 8.3 Hz), 7.23−7.20 (m, 4H), 7.11 (d, 2H, 7.7 Hz), 5.62 (q, 1H, J_{HF} = 6.4 Hz), 2.40 (s, 3H), 2.33 (s, 3H). ^{19}F-NMR (376 MHz, $CDCl_3$): δ −76.5 (d, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 140.7, 133.3, 129.9, 129.5, 128.3, 128.1, 126.9, 122.5 (q, $^1J_{CF}$ = 281 Hz), 78.3 (q, $^2J_{CF}$ = 34 Hz), 21.8, 21.5. HRMS (EI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{15}F_3O_3SNa$: 367.0592, found: 367.0583.

5-Dimethylamino-naphthalene-1-sulfonic acid 2,2,2-trifluoro-1-p-tolyl-ethyl Ester ***7****:* yellow solid (436 mg, 98%). mp 97−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (d, 1H, J = 8.5 Hz), 8.23 (d, 1H, J = 8.7 Hz), 8.08 (dd, 1H, J = 1.3 Hz, 7.4 Hz), 7.56 (dd, 1H, J = 7.6 Hz, 8.6 Hz), 7.37 (dd, 1H, J = 7.4 Hz, 8.5 Hz), 7.16 (d, 1H, J = 7.1 Hz), 6.98 (d, 2H, J = 8.0 Hz), 6.81 (d, 2H, J = 7.9 Hz), 5.6 (q, 1H, J_{HF} = 6.4 Hz), 2.83 (s, 6H), 2.17 (s, 3H). ^{19}F-NMR (376 MHz, $CDCl_3$): δ −76.3 (d, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 140.3, 132.1, 131.8, 130.4, 130, 129.8, 128.9, 128.2, 126.1, 122.9, 122.5 (q, $^1J_{CF}$ = 281 Hz), 119.7, 115.7, 78.8 (q, $^2J_{CF}$ = 34 Hz), 45.6, 21.3. HRMS (EI) m/z: $[M + H]^+$ Calcd for $C_{21}H_{21}F_3NO_3S$: 424.1194, found: 424.1202.

Toluene-4-sulfonic acid 2,2,2-trifluoro-1-(4-isopropyl-phenyl)-ethyl Ester ***8****:* off-white solid (349 mg, 94%). mp 81−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, 2H, J = 8.4 Hz), 7.20 (d, 2H, J = 8.2 Hz), 7.17 (d, 2H, J = 8 Hz), 7.12 (d, 2H, 8.2 Hz), 5.63 (q, 1H, J_{HF} = 6.4 Hz), 2.92−2.82 (m, 1H), 2.37 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H). ^{19}F-NMR (376 MHz, $CDCl_3$): δ −76.5 (d, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 145.3, 133.4, 129.8, 128.4, 128.1, 127.0, 126.9, 122.5 (q, $^1J_{CF}$ = 281 Hz), 78.5 (q, $^2J_{CF}$ = 34 Hz), 34.1, 24.04, 24, 21.8. HRMS (EI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{19}F_3O_3SNa$: 395.0905, found: 395.0899.

General Procedure for TFA Cleavage of Sulfonate Esters. Sulfonate ester (~0.2 mmol) and water (0−30 μL) were dissolved in TFA (1 mL) and stirred at room temperature for 2−16 h. After rotary evaporation of TFA, the residue was taken up into 80 mL water. The aqueous phase was extracted with ethyl acetate and lyophilized to yield the cleaved tosylate or dansylate.

General Procedure for Determining Stability to 20% Piperdine/DMF. Protected sulfonate (0.1−0.4 mmol) was dissolved in 1 mL of a freshly prepared 20% piperdine/DMF solution and stirred at room temperature for 2 h. The reaction was then poured into 1 M HCl and extracted with ethyl acetate. The combined organic phases were washed with water and brine and then dried over sodium sulfate. The recovered compound was then isolated by removal of the solvent via rotary evaporation.

General Procedure for Determining Stability to NaI in Refluxing Acetone. The protected sulfonate (0.1 mmol) was dissolved in a solution of NaI (16 mg, 0.11 mmol) in 0.2 mL acetone and refluxed for 4 h. The reaction was diluted into 1:1 EtOAc/H_2O and the organic phase was collected. The aqueous phase was further extracted with ethyl acetate and the combined organic phases were washed with brine and dried over sodium sulfate. The compound was then isolated by removal of the solvent via rotary evaporation.

General Procedure for Determining Stability to Potassium Carbonate. K_2CO_3 (0.24 mmol) was added to a solution of the protected sulfonate (0.2 mmol) in DMF (0.4 mL) and the mixture was heated to 65 °C for 24 h. The reaction was then poured into water and acidified with 1 M HCl. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with water and brine and then dried over sodium sulfate. The solvent was removed by rotary evaporation and the recovered material was purified by flash column chromatography (0−10% ethyl acetate/hexanes). Both **6** and **7** were recovered in 92% yield.

Stability of 6 to Hot Dilute Aqueous Acid. Compound **6** (75 mg, 0.22 mmol) was dissolved in a 1 mL solution of 1:1 2 M HCl/acetone and heated to 70 °C for 2 h. The reaction was then poured into ethyl acetate and the organic phase was washed with water and brine and dried over sodium sulfate. The solvent was removed by rotary evaporation and the recovered material was purified by flash column chromatography (0−10% ethyl acetate/hexanes) to return the starting material as a white solid (70 mg, 93%).

3-Chloro-propane-1-sulfonic acid 2,2,2-trifluoro-1-p-tolyl-ethyl Ester ***9****.* Compound **4** (1 g, 5.3 mmol) was dissolved in anhydrous dichloromethane (48 mL) and cooled to 0 °C in an ice bath. Triethylamine (1.46 mL, 10.5 mmol) was then added to the solution. 3-Chloropropanesulfonyl chloride (0.83 mL, 6.8 mmol) dissolved in anhydrous dichloromethane (5 mL) was added dropwise via syringe to the reaction flask at a rate of 20 drops/min. Upon completion of compound addition, the reaction was stirred at 4 °C overnight. The reaction was poured into 1 M HCl and the product was extracted with dichloromethane. The combined organic phases were washed with water, saturated sodium bicarbonate and brine, then dried over sodium sulfate. Removal of the solvent under vacuum resulted in a pale yellow oil. The crude product was purified by flash column chromatography (0−15% ethyl acetate/hexanes) to yield the product as a white solid (1.64 g, 97%). mp 61−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, 2H, J = 8.0 Hz), 7.26 (d, 2H, J = 7.8 Hz), 5.74 (q, 1H, J_{HF} = 6.4 Hz), 3.63−3.54 (m, 2H), 3.27−3.14 (m, 2H), 2.39 (s, 3H), 2.31−2.21 (m, 2H). ^{19}F-NMR (376 MHz, $CDCl_3$): δ −76.3 (d, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.4, 130.0, 128.3, 126.8, 122.5 (q, $^1J_{CF}$ = 281 Hz), 78.3 (q, $^2J_{CF}$ = 35 Hz), 49.8, 42.3, 26.7, 21.6. HRMS (EI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{14}ClF_3O_3SNa$: 353.0202, found: 353.0190.

3-Iodo-propane-1-sulfonic acid 2,2,2-trifluoro-1-p-tolyl-ethyl Ester ***10****.* Compound **9** (500 mg, 1.51 mmol) was added to a solution of sodium iodide (906 mg, 6.05 mmol) in acetone (5 mL). The reaction was heated to reflux and stirred for 16 h. After cooling to room temperature, the mixture was filtered to remove sodium chloride and the filtrand was washed with acetone (25 mL). Acetone was removed via rotary evaporation and the resulting residue was extracted between ethyl acetate and water. The organic phase was collected and the aqueous phase was washed with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate, and the solvent removed via rotary evaporation giving a bronze oil. The crude material was purified with flash column chromatography (0−10% ethyl acetate/hexanes) to yield the product as a viscous, pale yellow oil (571 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d,

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2H, J = 8.1 Hz), 7.27 (d, 2H, J = 7.9 Hz), 5.73 (q, 1H, J_{HF} = 6.4 Hz), 3.22−3.07 (m, 4H), 2.39 (s, 3H), 2.33−2.21 (m, 2H). ^{19}F-NMR (376 MHz, $CDCl_3$): δ −76.3 (d, J = 6.4 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 141.5, 130.1, 128.4, 126.8, 122.5 (q, $^1J_{CF}$ = 281 Hz), 78.3 (q, $^2J_{CF}$ = 34 Hz), 53.2, 27.2, 21.6, 2.1. HRMS (EI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{14}F_3IO_3SNa$: 444.9558, found: 444.9520.

3-[7-(tert-Butyl-dimethyl-silanyloxy)-3,4-dihydro-2H-quinolin-1-yl]-propane-1-sulfonic acid 2,2,2-trifluoro-1-p-tolyl-ethyl Ester ***13***. 7-(*t*-Butyldimethylsilyloxy)-1,2,3,4-tetrahydroquinoline **11**[6] (200 mg, 0.76 mmol) was dissolved in DMF (0.8 mL). Compound **10** (641 mg, 1.5 mmol) dissolved in DMF (0.8 mL) and potassium carbonate (120 mg, 0.91 mmol) were added to the solution and the reaction was heated to 70 °C and stirred for 24 h. The reaction was poured into water and acidified to pH 1 with 1 M HCl. The product was extracted with ethyl acetate and the combined organic phases were washed with water and brine and dried over sodium sulfate. The solvent was removed by rotary evaporation and the crude material was purified by flash column chromatography (0−5% acetone/hexanes) to yield a viscous orange oil (337 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, 2H, J = 8.1 Hz), 7.22 (d, 2H, J = 7.9 Hz), 6.78 (d, 1H, J = 8.0 Hz), 6.12 (dd, 1H, J = 2.2 Hz, 8.0 Hz), 6.01 (d, 1H, J = 1.9 Hz), 5.73 (q, 1H, J = 6.4 Hz), 3.33−3.21 (m, 2H), 3.10 (t, 2H, J = 5.5 Hz), 3.12−2.99 (m, 2H), 2.65 (t, 2H, J = 6.3 Hz), 2.38 (s, 3H), 2.07 (p, 2H, J = 7.2 Hz), 1.88−1.82 (m, 2H), 0.98 (s, 9H), 0.19 (s, 6H). ^{19}F-NMR (376 MHz, $CDCl_3$): δ −76.4 (d, J = 6.4 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 155.2, 145.7, 141.3, 130, 129.9, 128.3, 127, 122.6 (q, $^1J_{CF}$ = 281 Hz), 116, 108.2, 103.1, 78.2 (q, $^2J_{CF}$ = 34 Hz), 50.3, 49.7, 49.6, 27.5, 26, 22.5, 21.6, 21.1, 18.5, −4.1. HRMS (EI) m/z: $[M + H]^+$ Calcd for $C_{27}H_{39}F_3NO_4SSi$: 558.2321, found: 558.2305.

3-(7-Methoxy-3,4-dihydro-2H-quinolin-1-yl)-propane-1-sulfonic acid 2,2,2-trifluoro-1-p-tolyl-ethyl Ester ***14***. 7-Methoxy-1,2,3,4-tetrahydroquinoline **12**[6] (100 mg, 0.61 mmol) was dissolved in DMF (0.5 mL). Compound **10** (517 mg, 1.23 mmol) dissolved in DMF (0.8 mL) and potassium carbonate (96 mg, 0.74 mmol) were added to the solution and the reaction was heated to 70 °C and stirred for 24 h. The reaction was poured into water and acidified to pH 1 with 1 M HCl. The product was extracted with ethyl acetate and the combined organic phases were washed with water and brine and dried over sodium sulfate. The solvent was removed by rotary evaporation and the crude material was purified by flash column chromatography (0−10% ethyl acetate/hexanes) to yield a viscous, pale yellow oil (217 mg, 78%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.37 (d, 2H, J = 8.1 Hz), 7.2 (d, 2H, J = 7.9 Hz), 6.76 (d, 1H, J = 8.1 Hz), 6.12 (dd, 1H, J = 2.4 Hz, 8.1 Hz), 6.07 (d, 1H, J = 2.4 Hz), 5.96 (q, 1H, J_{HF} = 6.5 Hz), 3.69 (s, 3H), 3.23−3.02 (m, 4H), 3.01 (t, 2H, J = 5.6 Hz), 2.58 (t, 2H, J = 6.1 Hz), 2.32 (s, 3H), 1.95−1.82 (m, 2H), 1.79−1.73 (m, 2H). ^{19}F-NMR (376 MHz, CD_3OD): δ −78.0 (d, J = 6.5 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 159.5, 145.7, 141.1, 129.5, 128.2, 127.3, 122.9 (q, $^1J_{CF}$ = 280 Hz), 115.3, 100.9, 97.2, 77.8 (q, $^2J_{CF}$ = 34 Hz), 54.4, 49.3, 49.1, 49, 27.2, 22.4, 20.5, 20.2. HRMS (EI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{27}F_3NO_4S$: 458.1613, found: 458.1596.

3-[7-Methoxy-6-(4-nitro-phenylazo)-3,4-dihydro-2H-quinolin-1-yl]-propane-1-sulfonic acid 2,2,2-trifluoro-1-p-tolyl-ethyl Ester ***15***. Compound **14** (105 mg, 0.23 mmol) was dissolved in methanol (2.3 mL). 4-Nitrobenzenediazonium tetrafluoroborate (54 mg, 0.23 mmol) was suspended in 10% sulfuric acid (2.3 mL) with vigorous stirring. The organic solution was added to the aqueous mixture and stirred at ambient conditions for 1 h. The solution was then neutralized with ammonium hydroxide, resulting in a deep red precipitate. The mixture was filtered and the filtrand washed with water to give a blood red solid (140 mg, quantitative). This compound was dried *in vacuo* and used in the next reaction without further purification. NMR of the crude material revealed a contaminant of ammonium tetrafluoroborate salt. A small sample of the compound was therefore desalted by flash column chromatography (0−50% ethyl acetate/hexanes) to obtain NMR. mp 153−155 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, 2H, J = 9.0 Hz), 7.86 (d, 2H, J = 9.0 Hz), 7.58 (s, 1H), 7.37 (d, 2H, J = 7.8 Hz), 7.24 (d, 2H, J = 7.8 Hz), 6.17 (s, 1H), 5.76 (q, 1H, J_{HF} = 6.3 Hz), 3.98 (s, 3H), 3.61−3.47 (m, 2H), 3.31 (t, 2H, J = 5.4 Hz), 3.16−3.05 (m, 2H), 2.72 (t, 2H, J = 5.9 Hz), 2.37 (s, 3H), 2.23−2.11 (m, 2H), 1.92 (p, 2H, J = 5.3 Hz). ^{19}F-NMR (376 MHz, $CDCl_3$): δ −76.3 (d, J = 6.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 157.8, 151, 147.0, 141.5, 134, 130.1, 128.3, 126.7, 124.9, 122.7, 122.6 (q, $^1J_{CF}$ = 281 Hz), 117.8, 116.1, 93.5, 78.5 (q, $^2J_{CF}$ = 34 Hz), 56.7, 50, 49.9, 49.7, 27.4, 22.1, 21.6, 20.7. HRMS (EI) m/z: $[M + H]^+$ Calcd for $C_{28}H_{30}F_3N_4O_6S$: 607.1838, found: 607.1841.

1,11-Bis-[3-(2,2,2-trifluoro-1-p-tolyl-ethoxysulfonyl)-propyl]-3,4,8,9,10,11-hexahydro-2H-13-oxa-6,11-diaza-1-azonia-pentacene Tetrafluoroborate ***16***. Compound **13** (44 mg, 79 μmol) and compound **15** (55 mg, 91 μmol) were dissolved in a solution of ethanol/water/hydrochloric acid (500 μL:50 μL:25 μL) and heated to 80 °C with stirring for 2 h. Solvent was removed via rotary evaporation to give a fluorescent blue residue. The crude material was purified by flash column chromatography (0−10% methanol/dichloromethane) yielding the tetrafluoroborate salt as a blue solid (36 mg, 47%). mp 220−222 °C (dec.); ^{1}H NMR (400 MHz, CD_3OD): δ 7.47 (s, 2H), 7.43 (d, 4H, J = 8.1 Hz), 7.21 (d, 4H, J = 8 Hz), 6.81 (s, 2H), 6.07 (q, 2H, J_{HF} = 6.5 Hz), 3.74−3.61 (m, 4H), 3.55 (t, 4H, J = 5.5 Hz), 3.45−3.33 (m, 4H), 2.90 (t, 4H, J = 6 Hz), 2.28 (s, 6H), 2.15−2.07 (m, 4H), 1.99 (p, 4H, J = 5.5 Hz). ^{19}F-NMR (376 MHz, CD_3OD): δ −78.0 (d, J = 6.5 Hz), −154.58 (s), −154.6 (s) (BF_4^- counterion). ^{13}C NMR (100 MHz, CD_3OD): δ 154.6, 148.7, 141.1, 134.4, 130.8, 129.5, 129.4, 128.2, 127.4, 122.9 (q, $^1J_{CF}$ = 280 Hz), 95.0, 77.7 (q, $^2J_{CF}$ = 34 Hz), 50.64, 50.6, 27.2, 20.6, 20.5, 20.1. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{42}H_{44}F_6N_3O_7S_2$: 880.2525, found: 880.2511.

1,11-Bis-(3-sulfo-propyl)-3,4,8,9,10,11-hexahydro-2H-13-oxa-6,11-diaza-1-azonia-pentacene Tetrafluoroborate ***1*** *by TFA Cleavage of* ***16***. Compound **16** (12 mg, 12 μmol) and water (20 μL) was dissolved in trifluoroacetic acid (1 mL) and stirred at room temperature for 2 h. TFA was removed via rotary evaporation and the residue was dissolved in water (60 mL). The aqueous phase was extracted with ethyl acetate (1 × 40 mL, 4 × 20 mL) and lyophilized to give the pure blue compound as a tetrafluoroborate salt (8.1 mg, 99%). mp 365−367 °C (dec.); ^{1}H NMR (400 MHz, D_2O): δ 6.99 (s, 2H), 6.6 (s, 2H), 3.5 (br s, 8H), 2.86 (t, 4H, J = 7.4 Hz), 2.62 (br s, 4H), 1.99 (p, 4H, J = 7.0 Hz), 1.82 (br s, 4H). ^{19}F-NMR (376 MHz, D_2O): δ −150.9 (s), −151.0 (s) (Tetrafluoroborate counterion). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{24}H_{30}N_3O_7S_2$: 536.1525, found: 536.1507.

*3-[7-(tert-Butyl-dimethyl-silanyloxy)-3,4-dihydro-2H-quinolin-1-yl]-propane-1-sulfonic acid monohydrate (****17****).* 7-*t*-Butyldimethylsiloxy-1,2,3,4-tetrahydroquinoline **11**[6] (214 mg, 0.812 mmol) and 1,3-propanesultone (200 mg, 1.6 mmol) were dissolved in methanol (1.6 mL) and stirred overnight at room temperature. The solvent was removed via rotary evaporation and the crude material was purified by flash column chromatography (10% methanol/dichloromethane) to yield a yellow-white solid (119 mg, 36%). mp 202−204 °C (dec.); ^{1}H NMR (400 MHz, CD_3OD): δ 6.73 (d, 1H, J = 8.0 Hz), 6.14 (br s, 1H), 6.05 (dd, 1H, J = 1.8 Hz, 8 Hz), 3.35 (t, 2H, J = 7.2 Hz), 3.27 (t, 2H, J = 5.5 Hz), 2.88 (t, 2H, J = 7.5 Hz), 2.64 (t, 2H, J = 6.3 Hz), 2.07 (p, 2H, J = 7.6 Hz), 1.9 (p, 2H, J = 6.3 Hz), 0.97 (s, 9H), 0.17 (s, 6H). ^{13}C NMR (100 MHz, CD_3OD): δ 155, 154.8, 145.5, 129.4, 116.3, 103.4, 50.5, 49.2, 49.1, 27.2, 25.2, 22.1, 21.9, 18, −5.2. HRMS (EI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{32}NO_4SSi$: 386.1821, found: 386.1821.

1,11-Bis-(3-sulfo-propyl)-3,4,8,9,10,11-hexahydro-2H-13-oxa-6,11-diaza-1-azonia-pentacene Trifluoroacetate ***1***. Compound **17** (43 mg, 110 μmol) and 3-[7-Methoxy-6-(4-nitro-phenylazo)-3,4-dihydro-2H-quinolin-1-yl]-propane-1-sulfonic acid **19**[6] (48 mg, 110 μmol) were dissolved in a solution of ethanol: water: hydrochloric acid (1 mL: 100 μL: 50 μL) and heated to 80 °C with stirring for 2 h. The solvent was removed via rotary evaporation to give a fluorescent blue residue. The crude material was purified to 99% purity by HPLC over a C18 column to yield a blue solid (22 mg, 29%). Solvent A and B were respectively aqueous 0.1% trifluoroacetic acid and acetonitrile/0.1% trifluoroacetic acid. The flow rate during purification was 5 mL/min. The absorbance detector was set at 294, 306, 383, 607, and 660 nm. Elution of the compound was obtained via the following method: 15% B for 5 min, 15−50% B over 35 min, 50−100% B over 5 min, 100% B for 10 min. mp 365−367 °C (dec.); ^{1}H NMR (400 MHz, D_2O): δ 6.72 (s, 2H), 6.44 (s, 2H), 3.38 (br s, 8H), 2.81 (t, 4H, J = 6.8

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Hz), 2.48 (br s, 4H), 1.91 (br s, 4H), 1.73 (br s, 4H). ^{19}F-NMR (376 MHz, D_2O): δ −76.1 (s) (TFA counterion). ^{13}C NMR (100 MHz, D_2O): δ 153.9, 147.9, 132.4, 129.4, 129.2, 95.2, 51.4, 50.7, 48.0, 26.9, 21.7, 20.2. HRMS (EI) m/z: $[M - 2H]^-$ Calcd for $C_{24}H_{28}N_3O_7S_2$: 534.1368, found: 534.1348.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra for all compounds; Supporting Tables and HPLC Figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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