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Preparation of trifluoroethyl- and phenyl-protected sulfates using sulfuryl imidazolium salts

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ABSTRACT

Sulfuryl imidazolium salts (SIS's), a new class of sulfating agents, were prepared bearing the trifluoroethyl (TFE) and phenyl groups, two functionalities that have been used for the protection of sulfate monoesters, by subjecting the corresponding sulfonyl imidazoles with methyl triflate. In contrast, SIS's bearing the electron donating neopentyl and isobutyl groups, two moieties that have also been used for the protection of sulfates, were found to be unstable and could not be isolated though SIS's bearing electron donating aryl groups, such as a *p*-methoxyphenyl or *p*-thiomethylphenyl group were readily prepared and are stable compounds. In most instances, TFE-protected phenolic and carbohydrate sulfates were obtained in good yield by reaction of the corresponding SIS's with steroids and carbohydrates. Phenyl-protected carbohydrates were also readily prepared using the corresponding SIS's. Those SIS's having a methyl group at the 2-position of the imidazole ring were, in general, superior sulfating agents to those, which lacked a methyl group at this position. The use of SIS's to prepare TFE-protected sulfates represents a significant improvement of the previous reported procedure, which involved treating unprotected sulfates with trifluorodiazoethane. The TFE protecting group was removed from steroidal sulfates and secondary sulfates in carbohydrates in high yields using NaN_3 in warm DMF, conditions that are less vigorous than those previously reported for removing this group. Deprotection of TFE-protected 6-sulfated carbohydrates using NaN_3 in warm DMF proceeded in lower yields due to partial desulfation.

1. Introduction

Sulfated biomolecules constitute a wide range of compounds, such as sulfated carbohydrates,[1] nucleosides,[2] steroids,[3] pheromones,[4] proteins,[5] and peptides.[6] Their synthesis has become the focus of considerable interest due to the important roles that these molecules play in a wide variety of crucial biological processes. Sulfated compounds are typically constructed using a sulfating agent, such as a sulfur trioxide amine complex.[7] The sulfation step is usually carried out at or near the end of the synthesis due to the highly polar nature of the sulfated products, which makes further manipulations challenging. Moreover, the sulfate group is acid sensitive, which further complicates additional manipulations. Finally, intensive protecting group manipulations are required at the end of the syntheses when preparing sulfated compounds bearing multiple reactive groups, such as sulfated carbohydrates. To overcome these difficulties several groups including ourselves have proposed introducing the sulfate group as a protected sulfodiester at the beginning of the syntheses. This approach was first suggested by Perlin and Penney who examined the phenyl group as a protecting group for sulfated carbohydrates.[8] It was introduced by subjecting the carbohydrate to NaH and then $PhOSO_2Cl$ and is removed by hydrogenation of the benzene ring using Pt_2O/H_2 followed by treatment with base. Proud et al. and later Karst et al., examined the trifluoroethyl (TFE) moiety as a sulfate protecting group in carbohydrates.[9,10a,b] However, Proud et al. reported that they were unable to introduce this group using $TFEOSO_2Cl$ and had to resort to first preparing unprotected sulfate monoesters using pyr/SO_3 followed by treatment with 2,2,2-trifluorodiazoethane, a reagent that must be prepared fresh and is highly toxic and potentially explosive. Moreover, the somewhat harsh conditions that are most commonly employed for its removal, KO*t*-Bu in refluxing HO*t*-Bu, can result in substrate decomposition and consequently low or moderate sulfate deprotection yields.[10b] Both the neopentyl (nPt) and isobutyl (*i*-Bu) groups have been examined as sulfate protecting groups.[11] They are introduced by reacting sodium alkoxides with $ROSO_2Cl$ (R=*i*-Bu or nPt) at −78 °C and removed using nucleophiles such as NaN_3 in warm DMF.[11] Several years ago we reported that the trichloroethyl (TCE) group can be used as a sulfate protecting group.[12] TCE-protected phenyl sulfates can be readily prepared by reacting phenols with readily prepared and stable $TCEOSO_2Cl$ (**1**) and the TCE group easily removed using Zn or Pd/C

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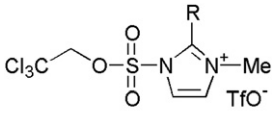
in the presence of ammonium formate.[12] The TCE group is now the most widely used protecting group for aryl sulfates.[13] However, we found that reagent **1** did not work well for introducing TCE-protected sulfate esters into non-phenolic substrates, such as carbohydrates.[14] This led us to develop reagents **2** and **3**, the first examples of sulfuryl imidazolium salts (SIS's) (Fig. 1).[14] These reagents are powerful sulfating agents capable of sulfating phenolic and non-phenolic substrates including carbohydrates in good yield.[14–16] To date, the only SIS's described to date are those bearing the TCE group. In this report we describe the synthesis of SIS's bearing other groups such as the phenyl and TFE groups and determine what groups are compatible with SIS formation. We also show that both phenyl- and TFE-protected sulfates can be introduced using SIS's and also report alternative conditions for TFE removal.



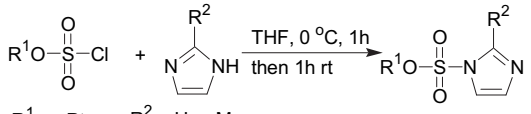
2, R = H
3, R = CH_3

Fig. 1. Sulfuryl imidazolium salts **2** and **3**.

2. Results and discussion

We initially examined the preparation of SIS's bearing moieties that have been studied as sulfate protecting groups such as the TFE, phenyl, isobutyl, and neopentyl groups (Table 1). Thus, sulfuryl chlorides **4**–**7**[8a,11,12,17] were reacted with imidazole or 2-methylimidazole to give compounds **8**–**15**. Compounds **8** and **9** formed by the reaction of imidazole with neopentyl and isobutylsulfuryl chloride were found to be very unstable and decomposed shortly after chromatographic purification. The 2-methylimidazole derivatives of **8** and **9**, compounds **10** and **11**, were slightly more stable yet still decomposed within 6–12 h after chromatography. In contrast those bearing the trifluoroethyl or phenyl groups were readily obtained suggesting that electron withdrawing groups on the ester portion are important for stability and electron donating alkyl groups decrease stability. However, sulfuryl imidazolides bearing electron donating aryl groups can be prepared as exemplified by the known compound **16** (Fig. 2), which has an electron donating

Table 1
Yields of compounds **8**–**15**

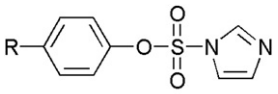


4, R^1 = nPt
5, R^1 = i-Bu
6, R^1 = TFE
7, R^1 = Ph

R^2 = H or Me

Product	R^1	R^2	Yield (%)
8	nPt	H	0[a]
9	*i*-Bu	H	0[a]
10	nPt	CH_3	0[b]
11	*i*-Bu	CH_3	35[b,c]
12	TFE	H	84
13	TFE	CH_3	87
14	Ph	H	75
15	Ph	CH_3	85

[a] Decomposed within 1 h of chromatography.
[b] Decomposed within 6–12 h of chromatography.
[c] Contained 13% DMI as impurity.



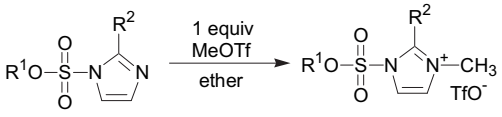
16, R = MeO
17, R = MeS

Fig. 2. Sulfuryl imidizolates **16** and **17**.

methoxy group at the 4-position of the phenyl ring and is readily prepared by reacting 4-methoxyphenol with sulfuryl diimidazole in the presence of a base.[18] We also found that the 4-methylmercapto derivative **17** (Fig. 2) could prepared in a similar manner and is a stable compound.[19]

Attempts to convert **10** and **11** into SIS's by treating them, immediately after purification by chromatography, with MeOTf in Et_2O resulted in the precipitation of a white powder, which rapidly decomposed after filtration and drying under high vacuum. In contrast, subjecting compounds **12**–**15** to methyl triflate in ether resulted in the precipitation of SIS's **20**–**23** as white powders in high yield (Table 2) and can be stored for at least 2 years at −20 °C with showing any detectable decomposition. Although the *p*-methoxyphenyl and *p*-thiomethylphenyl groups have not been employed as sulfate protecting groups we subjected compounds **16** and **17** to MeOTf to determine if SIS's bearing an electron donating group on the phenyl ring could be prepared. As with SIS's **20**–**23**, the resulting SIS's **24** and **25** readily precipitated out of solution and were found to be very stable and can be stored at −20 °C for at least a year without any detectable decomposition.

Table 2
Yields of SIS's **20**–**25**

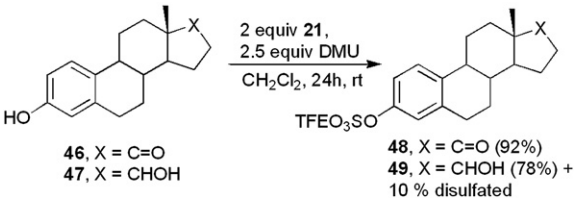


12-17 **18-25**

Product	R^1	R^2	Yield (%)
18	nPt	CH_3	0
19	*i*-Bu	CH_3	0
20	TFE	H	92
21	TFE	CH_3	91
22	Ph	H	92
23	Ph	CH_3	93
24	4-MeOPh	H	90
25	4-MeSPh	H	86

Introduction of TFE-protected sulfates into carbohydrates was examined using SIS's **20** and **21**. Subjecting carbohydrate **26** to 2 equiv **20** in the presence of 2.5 equiv *N*-methyl imidazole (NMI) in THF gave sulfated carbohydrate **36** in a 45% yield. However, switching to 2,6-lutidine as base and performing the reaction in CH_2Cl_2 gave **36** in an 88% yield (entry 1). Using 2 equiv of SIS **21** in the presence of 2.5 equiv 1,2-dimethylimidazole (DMI) in CH_2Cl_2 gave **36** in an 86% yield (entry 2). Carbohydrate **37** was obtained in an 80% yield using SIS **21** and DMI (entry 3). In contrast, carbohydrates **36** and **37** were prepared by Proud et al. in 60% and 51% yields, respectively, using the pyr/SO_3/2,2,2-trifluorodiazoethane methodology.[9] In general, sulfations using SIS **21** and DMI gave higher yields than those using SIS **20** and 2,6-lutidine (entries 3–8). Further studies with SIS **21** using DMI as base revealed that most of the sulfated carbohydrates could be obtained in good yield though in some instances yields were modest even when a considerable excess of SIS and base were used with prolonged reaction times (entries 8 and 10). The TFE-protected sulfate group could be introduced selectively into 2,3-diols of benzylidene acetals in good

yield by the slow addition of a solution of DMI to a solution of the carbohydrate and SIS **21** (entries 10–13). The selectivities are consistent with the intrinsic reactivities of the hydroxyl groups of the respective carbohydrates.[16] Using estrone (**46**) and estradiol (**47**) as model aryl substrates it was found that the TFE-protected sulfate group can also be introduced into aryl substrates using SIS **21** in good to excellent yields and relatively good selectivity could be achieved for the phenolic OH in estradiol (Scheme 1).



Scheme 1. Synthesis of TFE-protected estrone and estradiol-3-sulfates.

The synthesis of phenyl-protected sulfated carbohydrates was examined using reagents **22** and **23** and carbohydrates **28**–**31** (Table 4). Using reagent **22**/NMI or **23**/DMI carbohydrates **50** and **51** were obtained in 90–95% yields. In contrast, carbohydrate **51** was prepared in a 75% yield by Penney and Perlin using NaH/$PhOSO_2Cl$.[8a] Carbohydrates **52** and **53**, which were obtained in a modest yield using reagent **22** were obtained in good yield using reagent **23**.

The conditions that are most commonly employed for deprotecting TFE-protected sulfates are refluxing KO*t*-Bu in *t*-BuOH.[9,10b,20] These harsh conditions have severely limited the use of the TFE moiety as a suflate protecting group as the deprotection yields are often low.[10b] As part of our efforts to find more suitable conditions for removing this group we evaluated NaN_3 in warm DMF since these conditions have been used for removing neopentyl groups from sulfates sometimes in very high yield.[11] Subjecting fully protected carbohydrates bearing secondary suflate groups, **37**, **40**, **42**, and **44** to 1.4 equiv of NaN_3 in warm DMF (65–70 °C) for 10–16 h resulted in removal of the TFE group in high yields (Table 5). The crude products were passed through a small silica column using CH_2Cl_2/MeOH or CH_2Cl_2/MeOH/NH_4OH as eluent, which effectively removed any contaminating NaN_3 and gave the desired deprotected sulfates as their sodium or ammonium salts depending on the solvent system used for chromatographic purification. However, deprotections of substrates bearing a primary sulfate group, **36** and **38**, proceeded in lower yields due to competing attack of the azide ion at C-6 followed by partial desulfation. This side reaction was also noted by Karst et al. during the attempted removal of a TFE group from the 6-position of a fully protected disaccharide substrate using KO*t*-Bu in refluxing HO*t*-Bu though it appears that this problem can be reduced or eliminated when free OH groups are present in the substrate.[9,10b] This side reaction was also found to occur during removal of the neopentyl group from neopentyl-protected glucose-3-sulfate though in this case complete loss of the sulfate group occurred.[11] The phenolic sulfates **48** and **49** were deprotected in almost quantitative yield within 1–3 h using 1.4 equiv NaN_3 in DMF at 65–70 °C.

3. Conclusions

In summary, we have shown that SIS's bearing the TFE (compounds **20** and **21**) and phenyl (**22** and **23**) groups, two functionalities that have been used for the protection of suflate groups, can be readily prepared. SIS's bearing the electron donating neopentyl and isobutyl groups, two moieties that have also been used for the protection of sulfates, were found to be unstable and could not be isolated though SIS's bearing an electron-donating *p*-methoxyphenyl or *p*-thiomethylphenyl group were readily prepared and are stable compounds. In most instances, both TFE- and phenyl-protected sulfates were easily prepared using reagents **20**–**23** though reagents **21** and **23** having a methyl group at the 2-position of the imidazole ring were, in general, superior sulfating agents in comparison to reagents **20** and **22**, which lacked a methyl group at this position. In general, the use SIS's **20**–**23** to prepare TFE- or phenyl-protected sulfates represent a significant improvement over the previous approaches to these compounds. Deprotection of carbohydrate substrates bearing a primary sulfate group using NaN_3 in warm DMF proceeded in lower yields due to competing attack of the azide ion at C-6. However the TFE group can be removed from secondary sulfates in carbohydrates and aryl sulfates in excellent yields using NaN_3 in DMF, conditions that we believe are superior to the previous conditions using refluxing KO*t*-Bu in *t*-BuOH. Overall, these results make the TFE group a more viable alternative for sulfate protection.

4. Experimental

4.1. General remarks

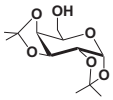
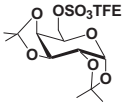
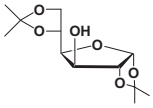
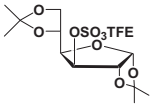
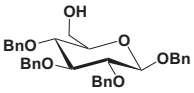
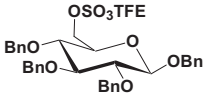
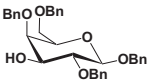
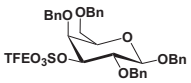
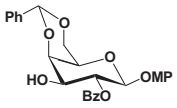
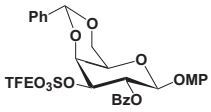
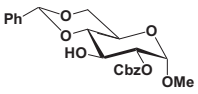
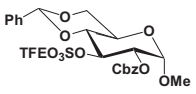
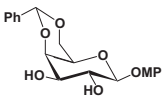
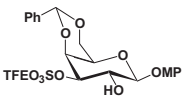
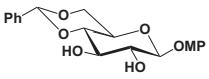
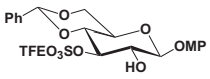
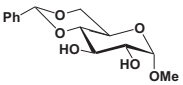
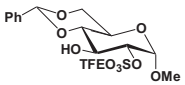
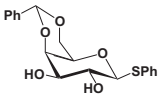
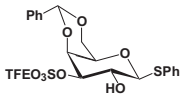
All reactions were carried out under argon with freshly distilled solvents unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium metal in the presence of benzophenone under argon. CH_2Cl_2 was distilled from calcium hydride under nitrogen. Flash chromatography was performed using silica gel 60 Å (234–400 mesh). Chemical shifts (δ) for ^1H NMR spectra are reported in parts per million (ppm) relative to residual solvent peaks ($CDCl_3$, δ 7.24; DMSO-d_6, δ 2.49; CD_3OD δ 3.31) and are reported as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened), integration, coupling constant in hertz, and assignment. Chemical shifts (δ) for ^{13}C NMR spectra are reported in parts per million relative to the residual solvent peaks ($CDCl_3$, δ 77.0, central peak; DMSO-d_6, δ 39.4, central peak; CD_3OD central peak, δ 49.0). Chemical shifts (δ) for ^{19}F spectra are reported in ppm relative to an external fluoroform standard (δ 0.0, $CFCl_3$). All melting points are uncorrected.

4.2. Syntheses

*4.2.1. Representative procedure for the preparation of compounds **11**–**15** (Table 1, compound **13**).* To a solution of 2-methylimidazole (13.6 g, 0.165 mol, 3.0 equiv) in dry THF (60 mL) at 0 °C was added dropwise a solution of reagent **6**[17] (11.0 g, 0.055 mol, 1.0 equiv) in THF (40 mL). The reaction was stirred at 0 °C for 1 h, warmed to room temperature, and stirred for an additional 1 h. The reaction mixture was filtered, the residue was washed with THF, and the filtrate was concentrated under vacuum. The crude residue was purified by flash chromatography (1:2 EtOAc/hexanes) to give **13** as a colorless oil (11.8 g, 87%): ^1H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3H, CH_3), 4.44 (q, 2H, J=7.55 Hz, CH_2), 6.90 (s, 1H),7.24 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 67.2 (q, 1C, J_{CF}=150 Hz, CH_2CF_3), 120.0, 121.0 (q, 1C, J_{CF}=316.5 Hz, CF_3), 128.3, 146.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.5; HRMS (EI^+) m/z calcd for $[C_6H_7F_3N_2O_3S]^+$: 244.0129 $[M]^+$; found: 244.0131.

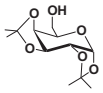
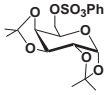
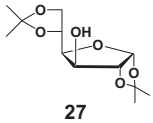
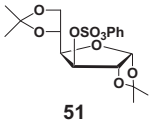
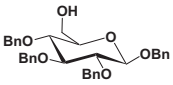
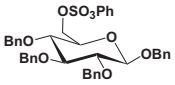
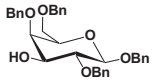
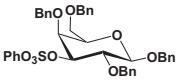
*4.2.2. Representative procedure for the preparation of sulfuryl imidazolium salts (Table 2 compound **21**).* To a solution of compound **13** (9.8 g, 0.04 mol, 1.0 equiv) in dry Et_2O (70 mL) at 0 °C was added methyl triflate (4.6 mL, 0.04 mol, 1.0 equiv) dropwise for 30 min. The reaction was stirred for 3 h at 0 °C during which time a white precipitate formed. The mixture was filtered. The filter cake was washed with cold ether, which afforded compound **21** as a white solid (14.8 g, 91%): ^1H NMR (300 MHz, CD_3OD) δ 2.87 (s, 3H, CH_3-imi), 3.90

Table 3
Synthesis of TFE-protected sulfocarbohydrates with sulfuryl imidazolium salts **20** and **21**

Entry	Substrate	Sulfating agent	Product	Yield (%)
1	 **26**	**20**	 **36**	45,[a] 88[b]
2	**26**	**21**	**36**	86[c]
3	 **27**	**20**	 **37**	70[b]
4	**27**	**21**	**37**	80[c]
5	 **28**	**20**	 **38**	77[b]
6	**28**	**21**	**38**	79[c]
7	 **29**	**20**	 **39**	26[b]
8	**29**	**21**	**39**	58[c]
9	 **30**	**21**	 **40**	80[d]
10	 **31**	**21**	 **41**	52[e]
11	 **32**	**21**	 **42**	75,[f] 89[g]
12	 **33**	**21**	 **43**	89[g]
13	 **34**	**21**	 **44**	85[g]
14	 **35**	**21**	 **45**	78,[f] 91[g]

[a] 2.5 equiv **20**, 2 equiv NMI, THF, 24 h.
[b] 2.0 equiv **20**, 1.1 equiv 2,6-lutidine CH_2Cl_2, 24 h.
[c] 2 equiv **21**, 2.5 equiv DMI, CH_2Cl_2, 24–30 h.
[d] 3 equiv **21**, 4 equiv DMI, CH_2Cl_2, 30 h.
[e] 5 equiv **21**, 6 equiv DMI, CH_2Cl_2, 72 h.
[f] 1.2 equiv **21**, 2 equiv DMI, CH_2Cl_2, 30 h.
[g] 4 equiv **21**, 5 equiv DMI, CH_2Cl_2, 30 h.

Table 4
Synthesis of phenyl-protected sulfocarbohydrates with sulfuryl imidazolium salts **22** and **23**

Entry	Substrate	Sulfating agent	Product	Yield (%)
1	 **26**	**22**	 **50**	90[a]
2	**26**	**23**	**50**	95[b]
3	 **27**	**22**	 **51**	92[a]
4	**27**	**23**	**51**	93[b]
5	 **28**	**22**	 **52**	60[a]
6	**28**	**23**	**52**	80[b]
7	 **29**	**22**	 **53**	51[a]
8	**29**	**23**	**53**	75[b]

[a] 2–2.5 equiv **22**, 2 equiv NMI, THF, 24 h.
[b] 2 equiv **21**, 2.5 equiv DMI, CH_2Cl_2, 24–30 h.

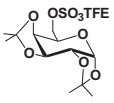
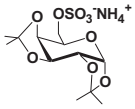
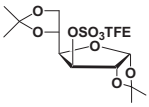
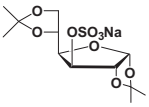
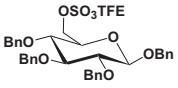
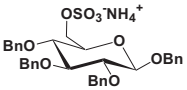
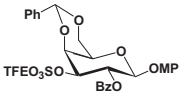
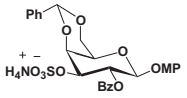
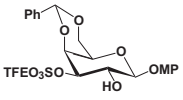
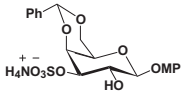
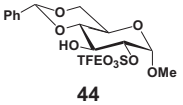
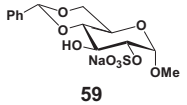
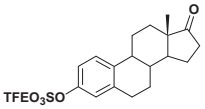
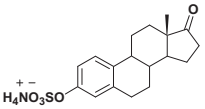
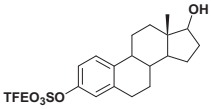
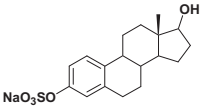
(s, 3H, CH_3), 5.16 (q, 2H, J=7.6 Hz, CH_2), 7.71 (d, 1H, J=2.3 Hz, Himi), 8.01 (d, 1H, J=2.3 Hz, Himi); ^{13}C NMR (75 MHz, CD_3OD) δ 10.4, 35.3, 69.3 (q, 1C, J_{CF}=150 Hz, CH_2CF_3), 120.7, 121.0 (2q, 2C, $2CF_3$, J_{CF}=303, 316.5 Hz, CF_3), 123.6, 148.8; ^{19}F NMR (300 MHz, CD_3OD) δ −75.1,−79.7; HRMS (ESI) m/z calcd for $[C_7H_{10}F_3N_2O_3S]^+$: 259.0364 $[M-OTf]^+$; found: 259.0363.

*4.2.3. Representative procedure for the synthesis of TFE-protected sulfocarbohydrates using reagent **20** and 2,6-lutidine (Table 3, compound **36**).* To a solution of carbohydrate **26** (0.25 g, 0.95 mmol) in CH_2Cl_2 (4.2 mL) at 0 °C (ice bath) was added 2,6-lutidine (0.123 mL, 1.05 mmol, 1.1 equiv) followed by reagent **20** (0.19 g, 0.48 mmol, 0.5 equiv). The reaction was stirred for 1 h at 0 °C and gradually allowed to warm to room temperature. After every 2 h another 0.19 g of reagent **20** was added until the total was equal to 2 equiv and the reaction was stirred overnight for a total of 24 h. The reaction was quenched with water, extracted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated to a crude brown oil. Flash chromatography (1:4, EtOAc/hexanes) gave compound **36** as a white solid (0.28 g, 88%): mp 34–35 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 6H, $2CH_3$), 1.41 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 4.09 (br d, 1H, J=5.6 Hz, H5), 4.15 (dd, 1H, J=7.7, 1.8 Hz, H4), 4.32 (t, 1H, J=4.8 Hz, H2), 4.41 (dd, 2H, J=5.8, 2.5 Hz, H6, H6′), 4.52–4.63 (m, 3H, CH_2CF_3, H3), 5.49 (d, 1H, J=4.6 Hz, H1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 24.7, 25.8, 25.5, 65.6, 66.6 (q, 1C, J_{CF}=150 Hz, CH_2CF_3), 70.1, 70.4, 70.6, 72.5, 96.1, 109.1, 110.1, 121.6 (q, 1C, J_{CF}=303 Hz, CF_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.8; HRMS (ESI) m/z calcd for $[C_{14}H_{22}F_3O_9S]^+$: 423.0937 $[M+H]^+$; found: 423.0952.

*4.2.4. Representative procedure for the synthesis of TFE-protected sulfocarbohydrates using reagent **21** and DMI (Table 3, compound **40**).* To a solution of carbohydrate **30**[21] (0.3 g, 0.62 mmol) in CH_2Cl_2 (5 mL) at 0 °C (ice bath) were added DMI (0.15 g, 1.56 mmol) and reagent **21** (0.51 g, 1.25 mmol). The ice bath was removed and the reaction allowed to warm to room temperature and then stirred for 30 h. The reaction was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$) and concentrated to crude brown oil. Flash chromatography (1:4, EtOAc/hexanes) gave compound **40** as a white solid (0.32 g, 80%): mp 128–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.6 (br s, 1H, H5), 3.71 (s, 3H, OCH_3), 4.13, 4.41 (AB system, 2H, J=12.5 Hz, H6, H6′), 4.23–4.34 (m, 2H, CH_2CF_3), 4.64 (d, 1H, J=3.3 Hz, H4), 4.99 (dd, 1H, J=10.2, 3.2 Hz, H3), 5.04 (d, 1H, J=7.9 Hz, H1), 5.56 (s, 1H, CHPh), 5.88 (t, 1H, J=9.6 Hz, H2), 6.73, 6.92 (AA′BB′ system, 4H, J=8.7, 8.6 Hz, ArH), 7.47 (m, 8H, ArH), 8.04 (d, 2H, J=7.8 Hz ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 65.9, 67.2 (q, 1C, J_{CF}=150 Hz, CH_2CF_3), 68.3, 68.7, 73.0, 82.1, 101.2, 101.5, 114.4, 119.4, 134.0 (q, 1C, J_{CF}=304.5 Hz, CF_3)126.4, 128.4, 128.6, 129.6, 129.8, 133.6, 136.7, 150.9, 155.9, 164.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.5; HRMS (ESI) m/z calcd for $[C_{29}H_{27}F_3O_{11}SNa]^+$: 663.1124 $[M+Na]^+$; found: 663.1111.

*4.2.5. Representative procedure for the selective sulfation of compounds **42**, **43**, **44**, and **45** (Table 3, compound **45**).* To carbohydrate **35**[22] (0.2 g, 0.55 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C (ice bath) was added reagent **21** (0.45 g, 1.1 mmol), followed by the addition of a solution of DMI (0.26 g, 2.77 mmol) in CH_2Cl_2 (2 mL) for 8 h using a syringe pump. During the addition of the DMI another portion of reagent **21** (0.45 g, 1.1 mmol) was added after 6 h and the ice bath was removed after the initial 1 h. The reaction was left stirring until the reaction was complete by TLC (approx. 30 h). The reaction was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and concentrated to brown crude oil. Flash chromatography (1:4, EtOAc/hexanes) gave compound **45** as a colorless syrup (0.26 g, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (br, 1H, OH), 3.57 (br s, 1H, H5), 3.93 (t, 1H, J=9.5 Hz, H2), 4.03, 4.39 (AB system, 2H, J=12.4 Hz, H6, H6′), 4.41–4.68 (m, 5H, H4, H1, CH_2CF_3, H3), 5.50 (s, 1H, CHPh), 7.29 (m, 8H, ArH), 7.65 (d, 2H, J=7.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.2, 67 (q, 1C, J_{CF}=150 Hz, CH_2CF_3), 68.9, 69.6, 73.4, 84.8, 87.0, 101.1, 123.0 (q, 1C, J_{CF}=305.5 Hz, CF_3),126.3, 128.2, 128.8, 129.1, 129.2, 129.4, 134.0, 137.0; ^{19}F NMR (282 MHz, $CDCl_3$)

Table 5
Deprotection of TFE-protected sulfates with NaN_3

Substrate	Product	Yield (%)
 **36**	 **54**	65
 **37**	 **55**	90
 **38**	 **56**	55
 **40**	 **57**	95
 **42**	 **58**	88
 **44**	 **59**	95
 **48**	 **60**	96
 **49**	 **61**	94

δ −73.8; HRMS (ESI) m/z calcd for $[C_{21}H_{22}F_3O_8S_2]^+$: 523.0708 $[M+H]^+$; found: 523.0720.

*4.2.6. Representative procedure for the synthesis of TFE-protected estrone and estradiol-3-sulfates (Scheme 1, compound **49**).* To a solution of estradiol (**47**, 0.3 g, 1.1 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C (ice bath) was added reagent **21** (0.43 g, 1.1 mmol) followed by the addition of a solution of DMI (0.26 g, 2.75 mmol) in CH_2Cl_2 (2 mL) for 6 h using a syringe pump. During the addition of the DMI another portions of reagent **21** (0.43 g, 1.1 mmol) was added after 4 h and the ice bath was removed after the initial 1 h. The reaction was left stirring until the reaction was complete by TLC (approx. 24 h). The reaction was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and concentrated to brown crude oil. Flash chromatography (1:4, EtOAc/hexanes) gave compound **49** as a colorless syrup (0.373 g, 78% of the monosulfated estradiol+0.065 g, 10% of the disulfated derivative): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (s, 3H, CH_3), 1.21–1.52 (m, 7H), 1.60 (s, 1H), 1.73 (m, 1H), 1.93 (m, 2H), 1.98 (m, 1H), 2.14 (m, 1H), 2.33 (d, 1H, J=13.0 Hz), 2.92 (t, 1H, J=3.6 Hz), 3.71 (t, 1H, J=8.4 Hz, H17), 4.64 (q, 2H, J=7.6.0 Hz, CH_2CF_3), 7.03 (s, 1H, ArH), 7.06 (d, 1H, J=8.5 Hz, ArH), 7.31 (d, 1H, J=8.5 Hz, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0, 23.1, 26.1, 26.8, 29.5, 30.5, 36.6, 38.1, 38.2, 43.1, 44.1, 50.0, 67.5 (q, 1C, J_{CF}=150 Hz, CH_2CF_3), 81.7, 117.7, 120.8, 121.2 (q, 1C, J_{CF}=308 Hz, CF_3), 127.1, 139.4, 140.4, 147.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.3; HRMS (EI^+) m/z calcd for $[C_{20}H_{25}F_3O_5S]^+$: 434.1375 $[M]^+$; found: 434.1364.

*4.2.7. Representative procedure for synthesis of phenyl-protected sulfocarbohydrates using sulfuryl imidazolium salt **23** (Table 4, compound **50**).* To a solution of carbohydrate **26** (0.25 g, 0.96 mmol) in CH_2Cl_2 (4.2 mL) at 0 °C (ice bath) was added 2-methylimidazole (0.23 mL, 2.4 mmol) followed by reagent **23** (0.77 g, 1.92 mmol). The reaction was stirred for 1 h at 0 °C and gradually allowed to warm to room temperature. The reaction was stirred overnight (24 h), then diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$) and concentrated to a crude brown oil. Flash chromatography (1:4, EtOAc:hexanes) gave compound **50** as a white solid (0.38 g, 95%): mp 77–79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (2s, 6H, $2CH_3$), 1.42 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 4.15 (t, 1H, J=6.6 Hz, H5), 4.21 (dd, 1H, J=7.8, 1.8 Hz, H4), 4.32 (dd, 1H, J=4.8, 2.4 Hz, H2), 4.47–4.56 (dd, 2H, J=5.8, 2.5 Hz, H6, H6′), 4.62 (dd, 1H, J=7.7, 2.2 Hz, H3), 5.51 (d, 1H, J=4.9 Hz, H1), 7.32 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 24.8, 25.9, 25.9, 65.7, 70.2, 70.5, 70.6, 72.3, 96.1, 109.0, 109.8, 121.4, 127.4, 129.8, 150.3; HRMS (EI) m/z calcd for $[C_{17}H_{21}O_9S]^+$: 401.0906 $[M-CH_3]^+$; found: 401.0905.

*4.2.8. Representative procedure for the deprotection of TFE-protected sulfates with sodium azide (Table 5, compound **57**).* To a solution of carbohydrate **40** (0.1 g, 0.156 mmol) in DMF (1 mL) was added sodium azide (0.014 g, 0.21 mmol) and the reaction was heated at 70 °C (oil bath) for 10 h after which no starting material was detected by TLC. The solvent was removed by rotary evaporation. Flash chromatography of the residue (20:4:1 CH_2Cl_2/MeOH/NH_4OH) afforded **57** as a white solid (0.085 g, 95%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.60 (s, 3H, OCH_3), 3.91 (br s, 1H, H5), 4.08 (AB system, 2H, J=12.4 Hz, H6, H6′), 4.62 (m, 2H, H4, H3), 5.35 (m, 2H, H1, H2), 5.60 (s, 1H, CHPh), 6.76, 6.86 (AA′BB′ system, 4H, J=8.7, 8.6 Hz, ArH), 7.04 (br, 4H, NH_4), 7.47 (m, 6H, ArH), 7.59 (t, 1H, J=7 Hz, ArH), 7.95 (d, 2H, J=7.8 Hz ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.8, 66.5, 68.6, 70.0, 73.8, 74.6, 99.6, 100.3, 115.0, 118.1, 126.7, 128.4, 128.9, 129.2, 129.9, 130.5, 133.5, 138.8, 151.2, 155.1, 165.5; HRMS (ESI^-) m/z calcd for $[C_{27}H_{25}O_{11}S]^+$: 557.1118 $[M-H]^-$; found: 557.1126.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.11.085. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. Kovensky, J. *Curr. Med. Chem.* **2009**, *16*, 2338.
2. (a) Schroeder, F. C.; Taggi, A. E.; Gronquist, M.; Malik, R. U.; Grant, J. B.; Eisner, T.; Meinwald, J. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 14283; (b) Kaysser, L.; Eitel, K.; Tanino, T.; Siebenberg, S.; Matsuda, A.; Ichikawa, S.; Gust, B. *J. Biol. Chem.* **2010**, *285*, 12684.
3. D'Auria, M. V.; Minale, L.; Riccio, R. *Chem. Rev.* **1993**, *93*, 1839.
4. Hoye, T. R.; Dvornikovs, V.; Fine, J. M.; Anderson, K. R.; Jeffrey, C. S.; Muddiman, D. C.; Shao, F.; Sorensen, P. W.; Wang, J. *J. Org. Chem.* **2007**, *72*, 7544.
5. Seibert, C.; Sakmar, T. P. *Biopolymers* **2008**, *90*, 459.

6. Tomishima, M.; Ohki, H.; Yamada, A.; Makib, K.; Ikeda, F. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2886.
7. For a recent review on the chemical synthesis of sulfated carbohydrates see: Al-Horani, R. A.; Desai, U. R. *Tetrahedron* **2010**, *66*, 2907.
8. (a) Penney, C. L.; Perlin, A. S. *Carbohydr. Res.* **1981**, *93*, 241; (b) Abdel-Makil, M. M.; Perlin, A. S. *Carbohydr. Res.* **1989**, *190*, 39; (c) Abdel-Makil, M. M.; Perlin, A. S. *Carbohydr. Res.* **1989**, *189*, 123.
9. Proud, A. D.; Prodger, J. C.; Flitsch, S. L. *Tetrahedron Lett.* **1997**, *41*, 7243.
10. (a) Karst, N. A.; Islam, T. F.; Linhardt, R. J. *Org. Lett.* **2003**, *5*, 4839; (b) Karst, N. A.; Islam, T. F.; Avci, F. Y.; Lindhardt, R. J. *Tetrahedron Lett.* **2004**, *45*, 6433.
11. Simpson, L. S.; Widlanski, T. S. *J. Am. Chem. Soc.* **2006**, *128*, 1605.
12. Liu, Y.; Lien, I. F. F.; Ruttgaizer, S.; Dove, P.; Taylor, S. D. *Org. Lett.* **2004**, *6*, 209.
13. (a) Fukuda, T.; Ohta, T.; Saeki, S.; Iwao, M. *Heterocycles* **2010**, *80*, 841; (b) Bunschoten, A.; Kruijtzer, J. A. W.; Ippel, J. H.; de Haas, C. J. C.; van Strijp, J. A. G.; Kemmink, J.; Liskamp, R. M. J. *Chem. Commun.* **2009**, 2999; (c) Li, X. S.; Robertson, L. W.; Wehmler, H. J. *Chem. Cent. J.* **2009**, *3*, 5; (d) Ali, A. M.; Hill, B.; Taylor, S. D. *J. Org. Chem.* **2009**, *74*, 3583; (e) Chen, J.; Yu, B. *Tetrahedron Lett.* **2008**, *49*, 1682; (f) Lu, C. P.; Ren, C. T.; Wu, S. H.; Chu, C. Y.; Lo, L. C. *Chembiochem* **2007**, *8*, 2187; (g) Furstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2006**, *128*, 8087; (h) Yamaguichi, T.; Fukada, T.; Ishibashi, F.; Iwao, M. *Tetrahedron Lett.* **2006**, *47*, 3755; (i) Furstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2005**, *127*, 11620; (j) Ahmed, V.; Ispahany, M.; Ruttgaizer, S.; Guillemette, G.; Taylor, S. D. *Anal. Biochem.* **2005**, *340*, 80; (k) Gunnarsson, G. T.; Riaz, M.; Adams, J.; Desai, U. R. *Bioorg. Med. Chem.* **2005**, 1783.
14. Ingram, L. J.; Taylor, S. D. *Angew. Chem., Int. Ed.* **2006**, 3503.
15. Ingram, L. J.; Desoky, A.; Ali, A. M.; Taylor, S. D. *J. Org. Chem.* **2009**, *74*, 6479.
16. Desoky, A.; Taylor, S. D. *J. Org. Chem.* **2009**, *74*, 9406.
17. Charalambous, J.; Frazer, M. J.; Gerrard, W. *J. Chem. Soc.* **1964**, 5480.
18. Albaneze-Walker, J.; Raju, R.; Vance, J. A.; Goodman, A. J.; Reeder, M. R.; Liao, J.; Maust, M. T.; Irish, P. A.; Espino, P.; Andrews, D. R. *Org. Lett.* **2009**, *11*, 1463.
19. See the Supporting data.
20. Karst et al. have also reported that, in certain instances, the TFE groups could also be removed using NaOMe/MeOH (see Ref. 10b). However, these conditions are not general as Proud et al. (see Ref. 9) as well as Karst et al. (see Ref. 10b) have shown that some TFE-protected sulfated carbohydrates are fairly resistant to these conditions even at reflux.
21. Jacquinet, J.-C. *Carbohydr. Res.* **2004**, *339*, 349.
22. Ellervik, U.; Magnusson, G. *J. Org. Chem.* **1998**, *63*, 9314.