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Synthesis of Difluoromethanesulfinate Esters by the Difluoromethanesulfinylation of Alcohols

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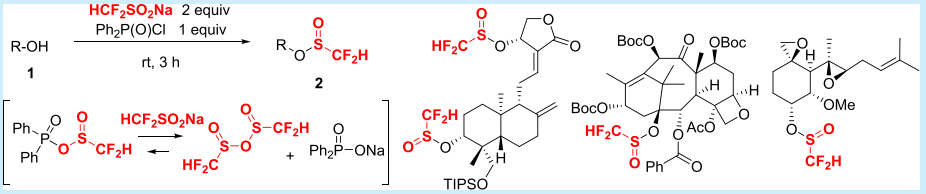

ABSTRACT: Herein, we report the first synthesis of difluoromethanesulfinate esters via the direct difluoromethanesulfinylation of alcohols with HCF_2SO_2Na/$Ph_2P(O)Cl$. Primary, secondary, and tertiary alcohols were converted to the corresponding difluoromethanesulfinate esters in good to excellent yields under mild conditions. The late-stage functionalization of complexed biologically active natural products was also demonstrated. The method was extended to the trifluoromethanesulfinylation of alcohols using CF_3SO_2Na in the presence of a catalytic amount of Me_3SiCl to provide trifluoromethanesulfinate esters.

Organofluorine compounds have gained significant attention in recent decades in the fields of pharmaceuticals and agrochemicals. Although more than 325 fluoro-pharmaceuticals[1] and 424 fluoro-agrochemicals[2] have been registered globally since the 1950s, organofluorine compounds are relatively scarce in nature.[3] In contrast, organosulfur compounds have a long history as components of pharmaceuticals and agrochemicals due to their abundance in natural products.[4] As a result, the trifluoromethylthio (SCF_3) group has become an attractive motif in drug design.[5] Although many SCF_3-containing biologically active compounds have been patented, drug marketing has been limited to agrochemicals, such as monepantel, cefazaflur, toltrazuril, and vaniliprole.[2] Indeed, currently, no SCF_3-containing pharmaceuticals have been approved for human use. This can be partly attributed to the high lipophilicity of the SCF_3 group (π = 1.44)[6] because lipophilicity plays a critical role in determining the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of a drug. Although high lipophilicity contributes to good permeability, broad absorption, and good distribution, it also results in low solubility, poor pharmacokinetics, and high toxicity.[7] Thus, the fine-tuning of the lipophilicity of a drug candidate with minimum structural alterations is of great importance to improving the prospects of clinical success. In this context, difluoromethylthio (SCF_2H) and difluoromethanesulfonyl (SO_2CF_2H) groups have been considered useful tools for the fine adjustment of ADMET properties because both units are hybrids of SCF_3, in addition to being hydrogen-bond donor motifs. Some examples of drug candidates containing SCF_2H/SO_2CF_2H units are shown in Figure 1.[1,2,8]

Inspired by the advantages that the SCF_3/SCF_2H/SO_2CF_2H units can bring to medicinal chemistry, we became interested

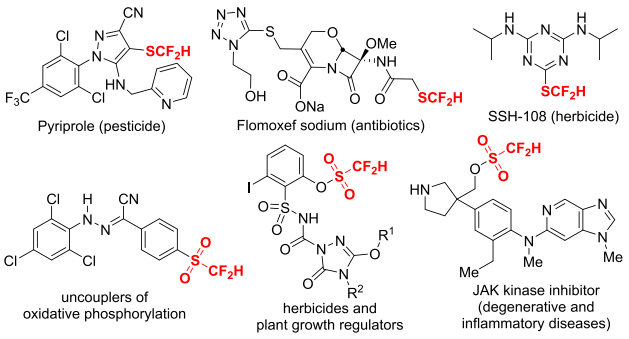

Figure 1. Examples of biologically active SCF_2H- and SO_2CF_2H-containing compounds.

in a new motif, viz., the difluoromethanesulfinyl ($S(O)CF_2H$) group. Due to the presence of a characteristic ionic sulfinyl ($S^+–O^-$) unit, the $S(O)CF_2H$ group possesses a different balance of lipophilicity and hydrophilicity. The estimated log *P* and pK_a values[9] of $PhCH_2O$-SCF_2H, $PhCH_2O$-$S(O)CF_2H$, and $PhCH_2O$-SO_2CF_2H are shown in Table S1. It therefore has potential as a novel tool for fine-tuning the ADMET properties of drug candidates. Although various methods have been reported for the preparation of compounds containing the SCF_3,[5,10] SCF_2H,[11] and SO_2CF_2H[12] groups, the prepara-

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tion of $S(O)CF_2H$-containing compounds has received little attention,[13] as has the direct introduction of the $S(O)CF_2H$ group.[14] Recently, we achieved the difluoromethylthiolation of carbon nucleophiles through the use of sodium difluoromethanesulfinate (HCF_2SO_2Na) and chlorodiphenylphosphine (Ph_2PCl) in the presence of chlorotrimethylsilane (Me_3SiCl) at a high reaction temperature (Figure 2a).[15] A variety of Csp^2 and Csp^3 nucleophiles, such as indoles, pyrroles, pyrazoles, enamines, ketones, and β-keto esters, were transformed to the corresponding Csp^2 and Csp^3 SCF_2H products in good yields. Even phenols and naphthols, possessing a free OH moiety, were also selectively Csp^2-difluoromethylthiolated on the aromatic ring, while the corresponding O-SCF_2H products were not detected. This reaction required two moles of both HCF_2SO_2Na and Ph_2PCl to generate S-(difluoromethyl)-diphenylphosphinothioate ($Ph_2P(O)$-SCF_2H, **I**), which is the actual reagent involved in the difluoromethylthiolation reaction.

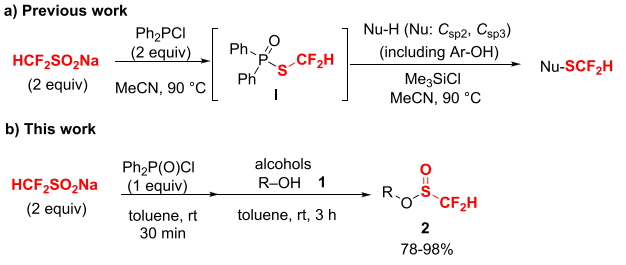


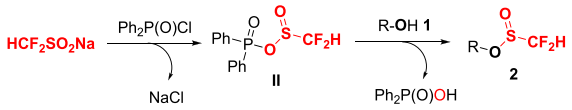
Figure 2. Difluoromethanethiolation vs difluoromethanesulfinylation with HCF_2SO_2Na. (a) Reaction of C-nucleophiles including phenols (previous work). (b) Reaction of alcohols **1** (this work).

Thus, we herein report a new system for the difluoromethanesulfinylation of alcohols to provide previously unknown difluoromethanesulfinate esters (Figure 2b). In the presence of HCF_2SO_2Na and $Ph_2P(O)Cl$, a wide variety of alcohols **1**, including primary, secondary, and tertiary alcohols, are efficiently converted to the corresponding difluoromethanesulfinate esters **2** ($R\text{-}OS(O)CF_2H$) at room temperature in good to excellent yields (Figure 2b). Although trifluoromethanesulfinate esters ($R\text{-}OS(O)CF_3$)[13f,16] and difluoromethanesulfonate esters ($R\text{-}OS(O)_2CF_2H$)[8a,c,13f,17] have been previously reported, to the best of our knowledge, this is the first example of the synthesis of difluoromethanesulfinate esters. The mechanistic details of this transformation are revealed by NMR and LC-MS analyses of the reaction mixtures. The developed method is then extended to the trifluoromethanesulfinylation of alcohols **1** using sodium trifluoromethanesulfinate (CF_3SO_2Na) instead of HCF_2SO_2Na to provide trifluoromethanesulfinate esters **3**.

Based on reactive species **I** determined in our previous study[15] (Figure 2a), we initially envisaged that the ideal reactive species **II** for the difluoromethanesulfinylation reaction could be generated by a 1:1 combination of HCF_2SO_2Na and $Ph_2P(O)Cl$, which subsequently reacts with alcohols **1** to provide difluoromethanesulfinate esters **2** (Scheme 1).

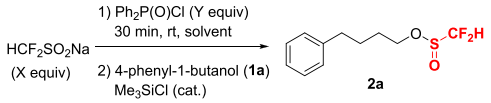
We thus attempted the reaction of alcohol **1a** under the optimal conditions for the difluoromethylthiolation reaction in the presence of Me_3SiCl in MeCN but using $Ph_2P(O)Cl$ instead of Ph_2PCl (Table 1). As expected, the desired difluoromethanesulfinate ester, 4-phenylbutyl difluoromethanesulfinate (**2a**), was obtained in 69% yield (run 1). Subsequent solvent screening (runs 2–5) indicated that

Scheme 1. Generation of Active Species[a]



[a]An expected reactive species **II** was generated from HCF_2SO_2Na and $Ph_2P(O)Cl$ for the difluoromethanesulfinylation process to yield difluoromethanesulfinate esters **2**.

Table 1. Optimization of the Difluoromethanesulfinylation of 1a[a]



run	solvent	additive	X (equiv)	Y (equiv)	yield (%)[b]
1	MeCN	Me_3SiCl	2.0	2.0	69
2	DCE	Me_3SiCl	2.0	2.0	89
3	THF	Me_3SiCl	2.0	2.0	57
4	DMF	Me_3SiCl	2.0	2.0	50
5	toluene	Me_3SiCl	2.0	2.0	93
6	**toluene**	-	**2.0**	**2.0**	**98**
7	toluene	-	1.5	1.5	88
8	toluene	-	1.0	1.0	62
9	**toluene**	-	**2.0**	**1.0**	**90 (89%)**[c]
10	toluene	-	1.5	1.0	78
11	toluene	-	1.2	1.0	64

[a]$Ph_2P(O)Cl$ was added to a solution of HCF_2SO_2Na in the desired solvent (1.0 mL). The mixture was stirred at rt for 30 min. A solution of 4-phenyl-1-butanol (**1a**, 0.2 mmol) in the desired solvent (1.0 mL) and Me_3SiCl (0.02 mmol, 0.1 equiv) were added separately to the mixture and stirred at rt. [b]Yields were determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard. [c]Isolated yield.

toluene (run 5) was the best solvent for this transformation, while DCE (run 2, 89%) is not attractive from the view of green chemistry. Interestingly, the reaction did not require the addition of Me_3SiCl, with the desired compound being obtained in 98% yield in the absence of this reagent (run 6). Although the number of equivalents of both HCF_2SO_2Na and $Ph_2P(O)Cl$ could be reduced to 1.5 and 1.0, the yields also reduced gradually (i.e., 88 and 62%, respectively). The molar ratio of HCF_2SO_2Na to $Ph_2P(O)Cl$ was also varied, and it was found that a high yield was maintained using a 2:1 molar ratio (run 9).

With the optimized conditions in hand (run 9, Table 1), the substrate scope of the reaction was investigated (Scheme 2). Benzyl alcohols (**1b**–**1e**) were converted to the corresponding difluoromethanesulfinate esters (**2b**–**2e**) in good to excellent yields (80–88%). The presence of electron-donating (Me, **1c**), halogen (Br, **2d**), and electron-withdrawing (NO_2, **1e**) substituents was also supported. Primary alcohols (**1f**, **1g**), a secondary alcohol (L-menthol (**1h**)), and a tertiary alcohol (1-adamantanol (**1i**)) were also nicely converted to the corresponding esters (**2f**–**2i**) in high yields (79–98%). Interestingly, the alkene moiety in 9-decen-1-ol (**1g**) remained intact under the conditions employed, and the desired difluoromethanesulfinate ester (**2g**) was obtained in 98% yield.

Late-stage selective functionalization of complexed molecules without an adverse effect on other functional groups in the molecule is a challenge. We thus attempted the

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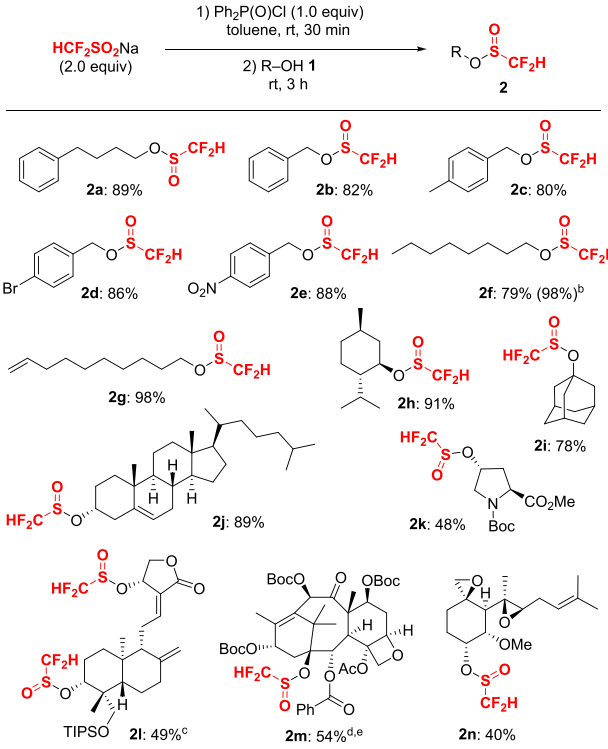
Scheme 2. Substrate Scope for the Difluoromethanesulfinylation of Alcohol 1[a]



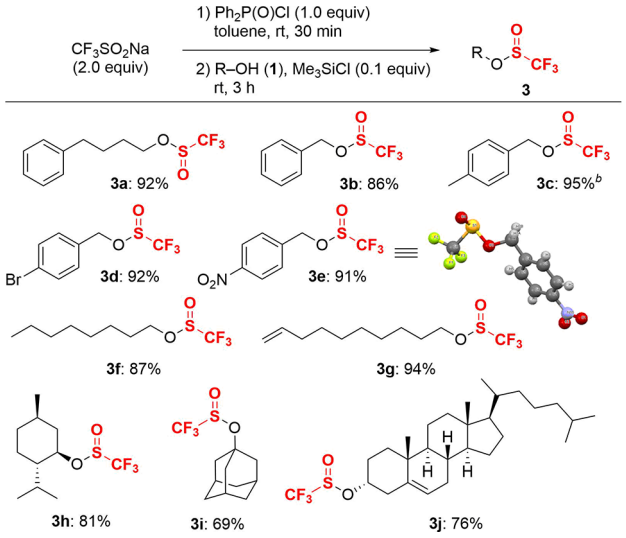
[a]Reaction conditions: $Ph_2P(O)Cl$ (0.2 mmol, 1.0 equiv) was added to a solution of HCF_2SO_2Na (0.4 mmol, 2.0 equiv) in toluene (1.0 mL), and the mixture was stirred at rt for 30 min. A solution of **2** (0.2 mmol) in toluene (1.0 mL) was then added to the mixture and stirred at rt for 3 h. [b]Reaction was conducted with 1.0 g (7.7 mmol) of **1f**. [c]4.0 equiv of $Ph_2P(O)Cl$ and 4.0 equiv of HCF_2SO_2Na were used. [d]2.0 equiv of $Ph_2P(O)Cl$ and 2.0 equiv of HCF_2SO_2Na were used. [e]Yield was determined by ^{19}F NMR of the crude product, due to the instability of **2m**.

difluoromethanesulfinylation of several biologically active complexed molecules under the optimized conditions. Steroid (**1j**) was first examined. The corresponding difluoromethanesulfinate ester **2j** was obtained in good yield without any damage to the multiple stereocenters. 4-Hydroxy-*N*-Boc-proline (**1k**) was next converted to the corresponding sulfinyl ester (**2k**) in 48% yield. For antitumor diterpenoid andrographolide (**1l**), double difluoromethanesulfinylation was observed in two secondary alcohol moieties to furnish the difluoromethanesulfinate diester of andrographolide (**2l**) in 49% yield. The tertiary alcohol of 10-deacetylbaccatin III (**1m**), a synthetic intermediate of anticancer drug Paclitaxel, was converted to the sulfinyl ester (**2m**) in 54% yield. Antiangiogenic fumagillol (**1n**) gave the corresponding difluoromethanesulfinyl ester (**2n**) in 40% yield without opening of the reactive epoxy groups. As indicated, a variety of functional groups such as amino, alkene, conjugated alkene, ketone, oxetane, and epoxide were accommodated in the substrates without affecting the sulfinylation process.

We subsequently considered the syntheses of trifluoromethanesulfinate esters **3**. While the trifluoromethanesulfinylation of alcohols was seminally reported by Hendrickson and coworkers in 1976[16a] and improved by Billard and Langlois et al. in 1999,[16b] we wished to consider our protocol for the trifluoromethanesulfinylation of alcohols **1**. After the brief optimization of reaction conditions (Table S2), we found the reaction in the presence of a catalytic amount of Me_3SiCl to be suitable.

The substrate scope of the difluoromethanesulfinylation was then examined for the same series of alcohols **1** to afford the corresponding trifluoromethylsulfinate esters **3** in good to excellent yields (Scheme 3). Primary, secondary, and tertiary

Scheme 3. Substrate Scope for the Trifluoromethylsulfinylation of Alcohols 1[a]



[a]Reaction conditions: $Ph_2P(O)Cl$ (0.2 mmol, 1.0 equiv) was added to a solution of CF_3SO_2Na (0.4 mmol, 2.0 equiv) in toluene (1.0 mL), and the mixture was stirred at rt for 30 min. A solution of **2** (0.2 mmol) in toluene (1.0 mL) and Me_3SiCl (0.02 mmol, 0.1 equiv) were then added to the mixture and stirred at rt for 3 h. [b] Yield of **3c** was determined by ^{19}F NMR of the crude product.

alcohols, including steroid **1j** and diterpenoid **1k**, were efficiently converted to the desired esters (**3h**−**3k**) over a reaction time of 3 h. The structure of **3e** was also determined unequivocally by X-ray crystallography.

^{19}F NMR spectroscopy (Figure 3 and Figure S1 of the Supporting Information (SI)) was then carried out for HCF_2SO_2Na; no peak was observed due to its low solubility in *d*-toluene (Figure 2a). When $Ph_2P(O)Cl$ was added to the solution, a sharp doublet appeared at −118.2 ppm (J = 56.4 Hz) within 10 min (Figure 2b), although this signal disappeared upon the addition of alcohol **1a**. At this point, product **2a** was newly detected as a clear AB quartet (−123.5 and −125.9 ppm, J = 272.1 and 53.6 Hz) (Figure 2c). The sharp doublet observed at −118.2 ppm was therefore considered the active species for this transformation. Furthermore, a new doublet appeared at −125.3 ppm (J = 56.4 Hz), which was confirmed to be $HCF_2S(O)OH$ **4** by further ^{19}F NMR experiments (Figures S2 and S3 in the SI). Interestingly, the doublet at −125.3 ppm then slowly disappeared spontaneously over several hours, as discussed later.

Based on the ^{19}F NMR analysis and an additional LC-ESI-MS (Figure S4 in the SI), a plausible reaction mechanism was determined, as shown in Figure 3. More specifically, in this mechanism, the first mole of HF_2CSO_2Na reacts with $Ph_2P(O)Cl$ to form the initial intermediate $Ph_2P{-}O{-}S(O)CF_2H$ **II** (detected by LC-ESI-MS) and eliminate NaCl, as detected

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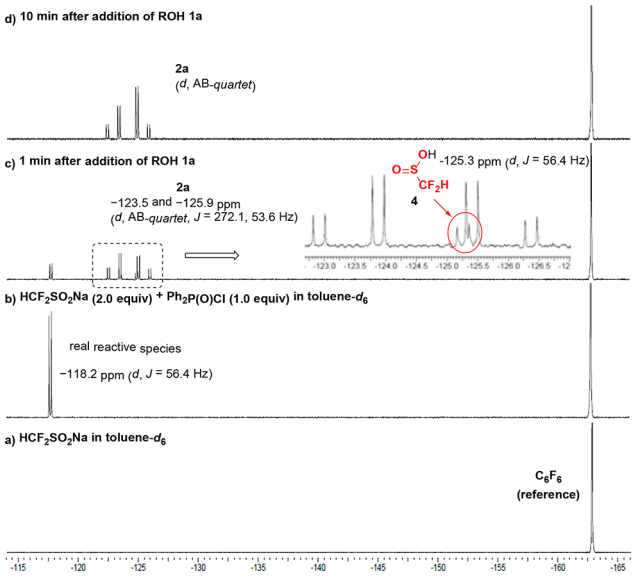
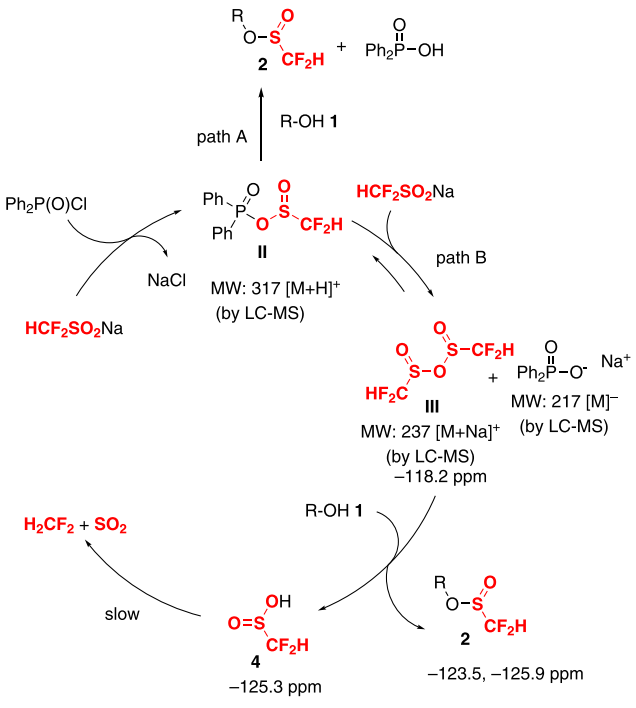


Figure 3. ^{19}F NMR experiments in toluene-d_6. (a) HCF_2SO_2Na (2 equiv). (b) The solution of (a) 10 min after the addition of $Ph_2P(O)Cl$ (1 equiv). (c) The solution of (a) 30 min after the addition of alcohol **1a**. (d) The solution of (a) 7 h after the addition of alcohol **1a**.

visually. Although intermediate **II** could be considered the reactive species for the difluoromethanesulfinylation of alcohols **1** (path **A**), this is not the main pathway because the reaction requires 2 equiv of HF_2CSO_2Na for a quantitative conversion. Thus, intermediate **II** rapidly reacts with the second mole of HF_2CSO_2Na to form a more reactive, symmetrical anhydride $(HCF_2S(O))_2O$ **III** (detected by LC-ESI-MS) with the release of $Ph_2P(O)ONa$ (detected as $Ph_2P(O)O^-$ by LC-ESI-MS) via path **B** (Scheme 4). Finally,

Scheme 4. Plausible Reaction Pathway for the Difluoromethanesulfinylation of Alcohols 1 to Esters 2



anhydride **III** (presumably corresponding to the signal at −118.2 ppm) reacts with alcohols **1** at room temperature to furnish the desired sulfinate esters **2** with the release of sulfinic acid, $HCF_2S(O)OH$ **4**. The unstable $HCF_2S(O)OH$ **4** (observed at −125.3 ppm, as confirmed by ^{19}F NMR experiments) slowly decomposes into gaseous SO_2 and H_2CF_2, resulting in the disappearance of the doublet at −125.3 ppm. The observation of >50% of **1a** when only 1 mol of HF_2CSO_2Na was employed (i.e., 62%, run 8, Table 1) could be explained by the contribution of path **A**, which cannot be fully ruled out. However, the use of 2 equiv of HF_2CSO_2Na promotes the complete transformation. Finally, we note that in the trifluoromethanesulfinylation of **1** Me_3SiCl catalytically activates the symmetrical anhydride, $(CF_3S(O))_2O$, which is generated from $Ph_2P(O)Cl$ and 2 equiv of CF_3SO_2Na.

In conclusion, we developed a novel difluoromethanesulfinylation of alcohols based on the $HF_2CSO_2Na/Ph_2P(O)Cl$ system. A variety of previously known difluoromethanesulfinate esters, $ROS(O)CF_2H$, were synthesized in good to excellent yields under mild reaction conditions. The late-stage functionalization of biologically active natural products was also demonstrated. This protocol is the first example of the preparation of difluoromethanesulfinate esters. Our method was also extended to the trifluoromethylsulfinylation transformation using CF_3SO_2Na in the presence of a catalytic amount of Me_3SiCl to afford the corresponding trifluoromethanesulfinate esters, $ROS(O)CF_3$, in good to excellent yields. These systems should be considered novel tools for the direct transformation of biologically attractive alcohols into their di- and trifluoromethanesulfinate esters. Application of this method for the preparation of a drug library is currently under investigation, and the results will be presented in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00688.

Tables S1 and S2, Figures S1−S4, experimental procedures, characterization data, and copies of the NMR spectra for products **2** and **3** (PDF)

Accession Codes

CCDC 2056418 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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‖Y.S. and K.S. contributed equally to this work. All authors have approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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