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Synthesis of a Hominal Bis(difluoromethyl) Fragment

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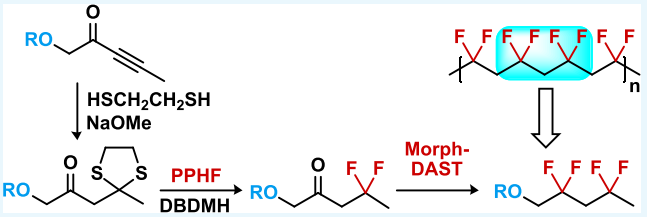
Supporting Information

ABSTRACT: This paper describes the synthesis of a discrete unit of hominal bis(*gem*-CF_2). The controlled introduction of fluorine atoms is a powerful synthetic tool to introduce dipole moments with minimal impact to sterics. Poly(vinylidene difluoride) is a striking example of the influence of fluorine atoms, which impart ferroelectric behavior from the alignment of the dipole moments of CF_2 units; however, it is prepared via direct polymerization of vinylidene difluoride. Thus, a different synthetic pathway is required to produce synthons containing discrete numbers of CF_2 groups in a hominal relation to each other. We found out that, in the case of short chains, the consecutive deoxofluorination of sequentially introduced keto groups is inefficient, as it requires harsh conditions and decreasing yields at each step. To solve this problem, we combined the selective desulfurative fluorination of dithiolanes with pyridinium fluoride and the deoxofluorination of keto groups with morpholinosulfur trifluoride. This strategy is highly reproducible and scalable, allowing the synthesis of the hominal bis(*gem*-CF_2) fragment as a shelf-stable tosylate, which can be used to install discrete chains of hominal bis(*gem*-CF_2) on a variety of synthons and monomers.



INTRODUCTION

The introduction of fluorine atoms into organic compounds has established itself as a powerful tool for tuning their chemical and physical properties with minimal impact to sterics. Fluorination often improves chemical resistance, thermal stability, and biological and optical activities.[1] As a result, C−F bonds can be found in a wide variety of pharmaceuticals,[2,3] agrochemicals, pesticides, surfactants, dyes, and polymeric materials.[4,5]

The unique properties of the fluorine atom have drawn increasing attention to its potential application in the field of organic photovoltaics (OPV), where the introduction of C−F bonds into the monomers of conjugated polymers can significantly improve their performance.[6,7] The systematic introduction of C−F bonds into the backbones of benzodithiophene-[8,9] and thiophene-containing[10−13] conjugated (co)polymers leads to an increase in power conversion efficiencies (PCEs) through a combination of subtle effects.[6] The utility of this approach is evident in the recent work of Zhao et al., where the combination of a fluorinated donor and nonfullerene acceptors enabled OPV devices with PCEs over 13%.[14] In addition to direct backbone fluorination, several studies have examined the effects of introducing fluorinated pendant groups of semifluorinated alkyl chains.[15,16] Such modifications lead to favorable microstructural ordering and remarkably high electron mobilities. There is a growing focus on the electrostatics of pendant groups (i.e., permanent dipoles) in organic materials, from enhancing the dielectric constant of OPV materials[17,18] to stabilizing dopants in thermoelectrics.[19] A striking manifestation of the strong dipole moment created by C−F bonds is ferroelectricity in poly(vinylidene difluoride), which arises from the alignment of CF_2 groups enabled by the $-CH_2CF_2-$ repeat-unit.[20−23]

We are interested in synthesizing discrete chains containing these hominal bis(*gem*-CF_2) (i.e., $CF_2CH_2CF_2$[24]) units that can be attached to small molecules and monomers to tailor their electrostatic properties; however, the synthesis of hominal CF_2 units, in general, has not been widely reported. Typically, such compounds are obtained in the mixture of telomers, as illustrated in Figure 1.

Hauptschein et al. accomplished the telomerization of 1,1-difluoroethylene under thermal conditions, yielding telomer iodides and bromides containing the hominal bis(*gem*-CF_2) fragment.[25] In later work, they prepared fluorocarbon halosulfates, acids, and derivatives that also contained such units.[26] However, in both cases, the hominal bis(*gem*-CF_2) fragment formed in a mixture with perfluorinated moieties. The synthesis also required large autoclaves, long and extensive heating, and difficult fractional distillations for isolation. Similar difficulties were observed by others, via a variety of synthetic approaches: photochemically initiated reactions of bistrifluoromethyl disulfide with olefins,[27] thermal polymerization of SF_5Br with fluoroolefins,[28] modification of other telomers,[29] and telomerization of vinylidene difluoride with α,ω-diiodoperfluoroalkanes[30] and iodoperfluoroalkanes.[31−35]

It is apparently impossible to control the number of CH_2CF_2 units by means of telomerization; a fully synthetic and controllable approach that does not require harsh conditions,

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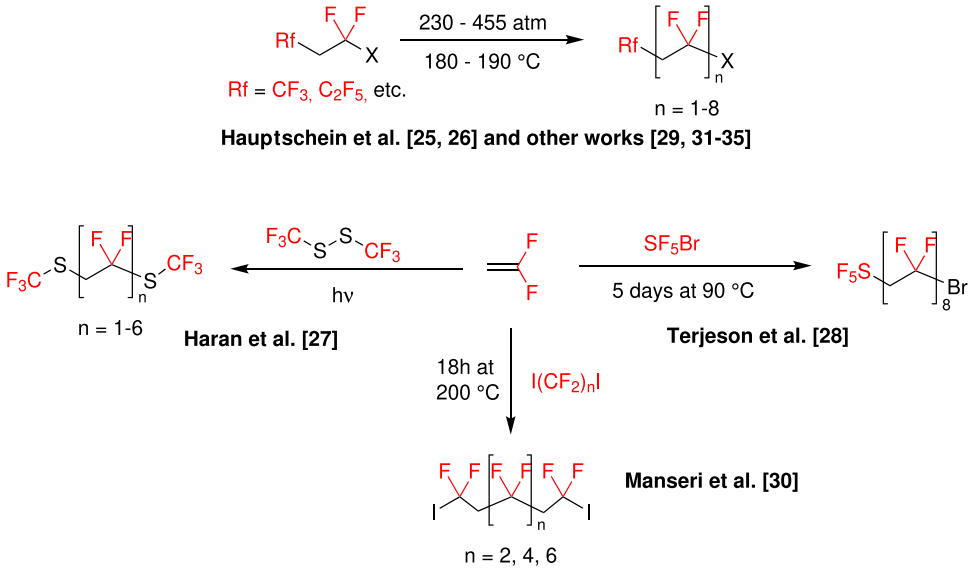

Figure 1. Background for this study: telomerization approach.

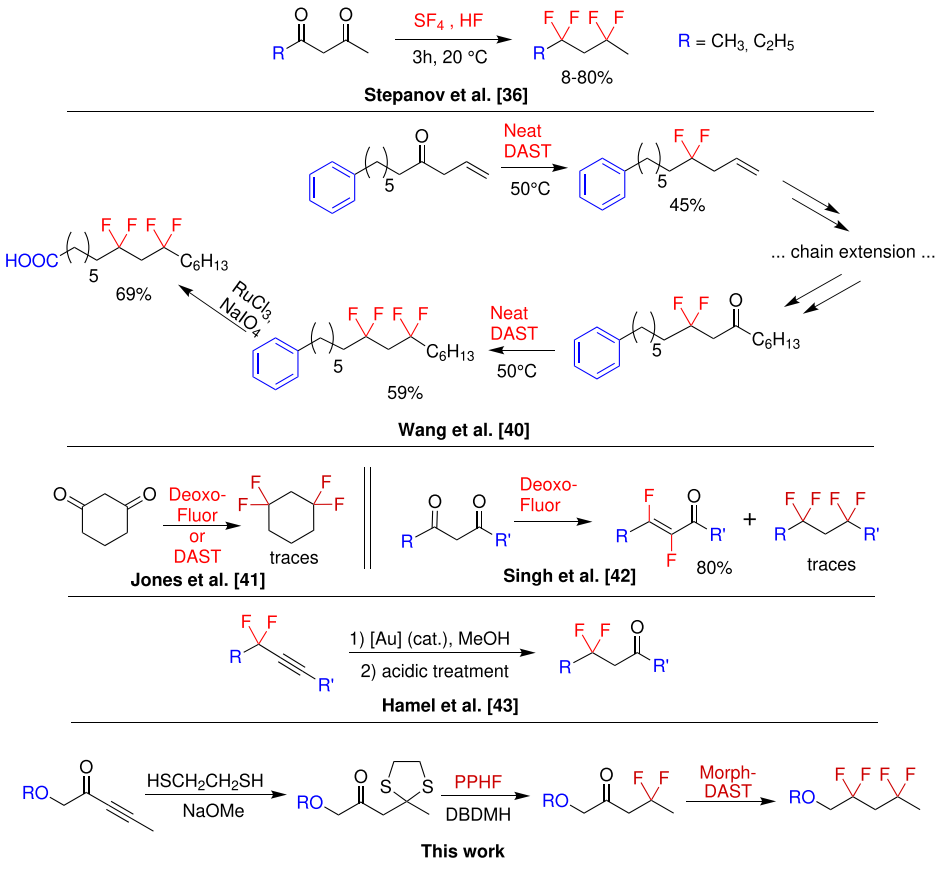

Figure 2. Background for this study: synthetic approaches.

can be performed in a typical laboratory environment, and easily reproduced would be ideal. An overview of such efforts is depicted in Figure 2.

Stepanov et al. demonstrated one of the first examples of synthetically feasible compounds containing a hominal bis-(*gem*-CF_2) fragment.[36] By treating pentane-2,4-dione with SF_4 for 3 h at 20 °C, they managed to obtain a mixture that contained 8% of 2,2,4,4-tetrafluoropentane and 70% of 4,4-difluoropentan-2-one among other fluorinated products. With increased reaction time (up to 40 h) and the addition of hydrogen fluoride (HF), they observed a shift toward the formation of 2,2,4,4-tetrafluoropentane as a predominant product. The same behavior was observed in the case of 2,2,4,4-tetrafluorohexane from hexane-2,4-dione. Even though this approach seems straightforward, reacting SF_4 and HF in an autoclave is so dangerous as to be forbidden in many (academic) laboratories (such as our own). As a result, more convenient and user-friendly methods of introducing CF_2

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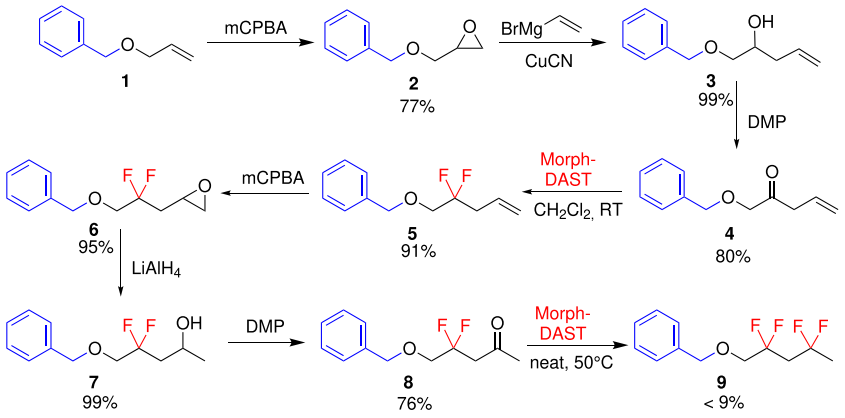
Scheme 1. Consecutive Deoxofluorinations



groups have been developed,[37] largely as a class of dialkylaminosulfur tetrafluorides[38] and pyridinium poly(hydrogen fluoride) (PPHF: 70% hydrogen fluoride, 30% pyridine, also known as Olah reagent).[39]

Significant progress toward the user-friendly synthesis of hominal bis(*gem*-CF_2)-containing compounds using these methods has been done by O'Hagan and co-workers. For example, Wang et al. installed CF_2 groups into a palmitic acid analogue by sequential preparation of appropriate precursor ketones, followed by deoxofluorination using diethylaminosulfur trifluoride (DAST).[40] The conversion to the CF_2 group occurred in modest yields and required neat DAST at elevated temperature. Jones et al. synthesized 2,2-dimethyl-5-phenyl-1,1,3,3-tetrafluorocyclohexane by means of the direct deoxofluorination of a diketone precursor.[41] Attempts to use the same approach in the case of diketones, which did not have dimethyl-substituted methylene between keto groups, were unsuccessful, yielding only complex and intractable products, which could be attributed to the high degree of enolization of such diketones. This behavior of diketones was also noted previously in the work by Singh et al.[42] In both works by Stepanov et al.[36] and Wang et al.,[40] the route to compounds containing the hominal bis(*gem*-CF_2) fragment included the formation of 3,3-difluoroketones as intermediates. 3,3-Difluoroketones themselves are attractive building blocks but are difficult to synthesize; however, recent work by Hamel et al. demonstrated the synthesis of 3,3-difluoroketones via a regioselective gold-catalyzed formal hydration of propargylic gem-difluorides.[43]

Given the relative scarcity of examples of the successful isolation of compounds containing hominal bis(*gem*-CF_2) units, there does not appear to be any reasonable synthetic route to realize our goal of incorporating them into pendant chains. In this work, we demonstrate an approachable, reproducible, and reliable strategy for synthesizing compounds containing the hominal bis(*gem*-CF_2) fragment from the precursor 3,3-difluoroketones. Our strategy is scalable and produces shelf-stable tosylate that can, in principle, be used to introduce hominal bis(*gem*-CF_2) units into any small molecule or monomer.

RESULTS AND DISCUSSION

In our first attempts to synthesize a hominal bis(*gem*-CF_2) fragment, we used a consecutive deoxofluorination approach analogous to that proposed by Wang et al.,[40] as illustrated in Scheme 1. Starting from commercially available allyl benzyl ether (**1**), we performed an epoxidation using *meta*-chloroperbenzoic acid (*m*CPBA), which gave **2** in high yield (77%). This reaction was followed by chain extension with vinylmagnesium bromide and CuCN to produce alcohol **3** in near-quantitative yield (99%), which was oxidized with Dess–Martin periodinane (DMP), leading to the suitable ketone **4** (80% yield). This ketone was then treated with morpholinosulfur trifluoride (Morph-DAST) to introduce the CF_2 group, yielding compound **5**. The deoxofluorination reaction proceeded under mild conditions, requiring 24 h in CH_2Cl_2 at room temperature to achieve a high yield (91%). Morph-DAST was used as our deoxofluorination reagent of choice, as its reactivity was previously reported to be identical to superior over DAST, while possessing higher thermal stability, producing less fumes in laboratory air, and thus being safer to handle.[44−46] To generate the second ketone precursor, compound **5** was epoxidized (*m*CPBA, 95%). The resulting epoxide **6** was reduced with $LiAlH_4$, giving alcohol **7** (99%), which was oxidized with DMP, yielding ketone **8** (76%). Compounds **2**, **3**, **6**, and **7** possess chiral carbon atoms, which lead to obtaining a mixture of stereoisomers of these compounds. However, we carried these compounds through the synthesis, as the stereocenter disappeared when generating the corresponding ketones **4** and **8**. Our attempts to introduce the second CF_2 group by means of deoxofluorination were met with moderate success. Performing the reaction with neat Morph-DAST at 50 °C for 3 days produced a crude product containing compound **9** in poor (9%) yield. Efforts to isolate a completely pure product were unsuccessful.

The low efficiency of the second deoxofluorination step highlights the difficulty in synthesizing the hominal bis(*gem*-CF_2) fragment; the installation of each CF_2 severely deactivates subsequent deoxofluorination reactions, precluding the isolation of more than one CH_2CF_2 unit. In this case, we obtained the product **9** in poor yield. We suspect that the key difference between our work and that of Wang et al.[40] can be attributed to the difference in a keto group environment. Although both contain CF_2 groups in a hominal arrangement, substrate **8** does not possess the long aliphatic chain that is present in palmitic acid, the electron-donating nature of which may have somewhat counteracted the deactivating effect of the first CF_2 group.

To cope with the apparent narrow scope of the aforementioned consecutive deoxofluorination approach, we decided to change our synthetic strategy, as demonstrated in Scheme 2. First, we reacted previously synthesized epoxide **2**

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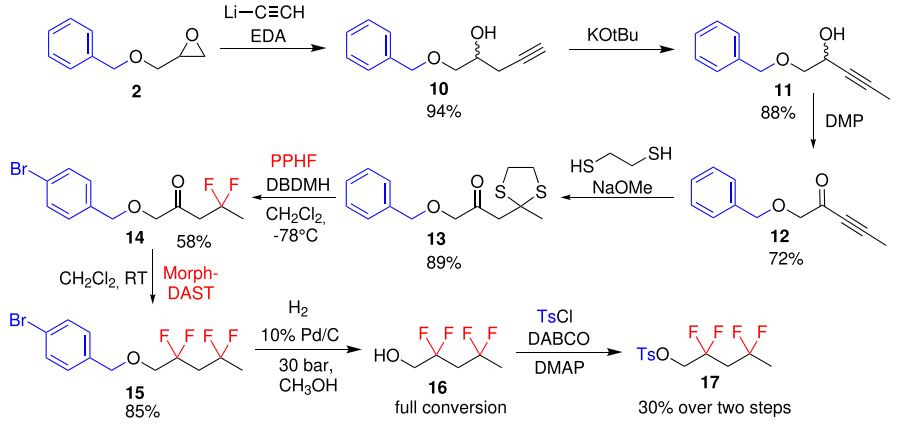
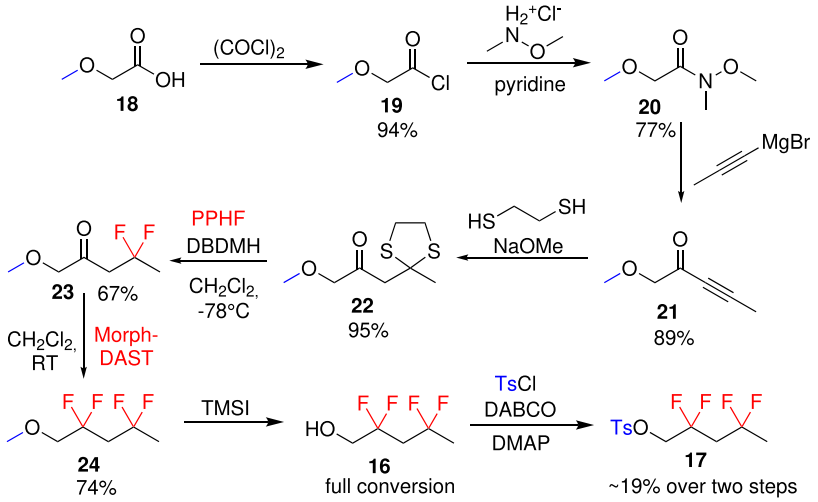
Scheme 2. Combined Desulfurative- and Deoxofluorination Approach with Benzyl Protection



Scheme 3. Combined Desulfurative- and Deoxofluorination Approach with Methyl Protection



with the ethylenediamine complex of lithium acetylide to introduce the propargyl group, yielding alcohol **10** (94%). This compound was then treated with potassium tert-butoxide, to effect the migration of a triple bond, as was demonstrated before by Kadirvel et al.[47] and Li et al.,[48] resulting in the propynyl **11** (88% yield), which was then oxidized with DMP[49] to produce yneone **12** (72% yield). Generating the yneone fragment is a key step, as it was easily converted into β-dithiolane **13** in high yield (89%) using the procedure by Sneddon et al.[50] The dithiolane (thioketal) group acts as an orthogonal protecting group of a parent 1,3-diketone, which simultaneously permits the use of drastically different fluorination techniques on both reaction centers. Using this strategy, we proceeded with desulfurative fluorination of the dithiolane group in **13** with PPHF and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) following the procedure by Sondej and Katzenellenbogen,[51] which resulted in fluorinated product **14**. Because of the use of DBDMH as a source of electrophilic Br^+, during this transformation, the benzyl protecting group was partially brominated. The degree of bromination varied depending on the reaction time and scale; however, it was always significant. The mixture of brominated product **14** and its nonbrominated analogue (58% combined yield after desulfurative fluorination of **13**) was difficult to separate by means of chromatography. However, both compounds demonstrated equal reactivity and were carried through the rest of the synthesis without incident. The second ketone group was then converted into the CF_2 group via deoxofluorination with Morph-DAST under very mild conditions (overnight in CH_2Cl_2), yielding the product **15** in a good yield (85%). One might consider such a smooth transformation to be surprising when taking into account how troublesome was the deoxofluorination of ketone **8**. Indeed, both ketones **8** and **14** have CF_2 groups in a hominal position, which seemingly deactivates deoxofluorination of **8** but does not have major effect on reactivity of **14**. This might be due to the electron-donating effect of the adjacent ether moiety, and we will try to illuminate this phenomenon in our follow-up work.

To generate alcohol **16**, we cleaved the (bromo-)benzyl protecting group of compound **15** with hydrogen gas in an autoclave at 30 bar using palladium on carbon as a catalyst and methanol as a solvent. The deprotection proceeded a bit more slowly than anticipated because the bromines needed to be reduced (forming **9** in situ) before the normal benzyl ether deprotection reaction occurred. Unfortunately, alcohol **16** is extremely volatile, which required some care following the autoclave step; once the autoclave cooled, compound **16** was collected as a cold, methanolic solution and immediately worked up with dichloromethane, without evaporating the solvent. This handling limited the characterization of alcohol **16**, which we could verify by NMR but could not isolate.

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Instead, the resulting crude dichloromethane solution was quickly tosylated, giving the product **17** along with methyl tosylate from the residual methanol from the autoclave mixture. After purification via flash column chromatography, we isolated pure tosylate **17**, which is shelf-stable and considerably less volatile than **16**. As the quantity of alcohol **16** could not be determined accurately (we could only verify full conversion according to ^{19}F NMR), the exact yield of last two steps cannot be reported. However, it is possible to determine the yield of the two-step transformation from compound **15** into the final product **17**, which is 30.7%. We assume that the yield loss is due partly to the (extreme) volatility of the alcohol **16** in addition to the yield of the tosylation reaction itself. To effect the tosylation, we treated the cold crude solution containing **16** and trace amounts of methanol with 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base, along with the catalytic quantity of 4-dimethylaminopyridine (DMAP), followed by the excess amount of 4-toluenesulfonyl chloride. This allowed us to obtain and purify the product **17**; however, while using other procedures (e.g., with NaOH, pyridine, or triethylamine as a base and without DMAP), we either observed very low yields or could not separate the product **17** from the resulting mixture.

To avoid the necessity of using an autoclave and all of the difficulties it created, we investigated the applicability of our strategy to a different substrate, namely, to methoxyacetic acid (**18**). This approach is illustrated in Scheme 3. We started by converting **18** into a Weinreb amide **20** in a two-step process via an intermediate acyl chloride **19** (around 72% two-step yield). The amide **20** was then reacted with 1-propynylmagnesium bromide, yielding the compound **21** (89%). This synthesis was previously reported by Globisch et al.[52] and allowed us to shorten the number of steps, leading to the necessary yneone moiety, which was then treated in a manner similar to that mentioned above. After easily converting it to dithiolane **22** (95% yield), we treated the product with PPHF and DBDMH, resulting in fluorinated compound **23** (67% yield). Although this approach obviates the need for the autoclave and eliminates the bromination of the benzyl protecting group, the intermediates were considerably more volatile, which required care (e.g., when evaporating solvents and storing intermediates between steps) until the final product **17** was isolated. Thus, after producing the compound **23** and deoxofluorinating it with Morph-DAST, we were able to obtain product **24** (74% yield). What followed was the demethylation using iodotrimethylsilane in accordance with Jung et al.,[53] which yielded the aforementioned compound **16** (full conversion by ^{19}F NMR, exact yield could not be determined). Alcohol **16** was promptly tosylated to afford compound **17**. The yield of the two-step transformation from compound **24** into the final product **17** was around 19%, which is lower than for the transformation of **15**. Despite shortening of the synthetic route, this modified strategy proceeded with mixed success, as coping with the volatility of not only the alcohol **16** but also compounds **23**−**24** turned out to be challenging.

CONCLUSIONS

We explored three approaches leading to easy-to-handle and shelf-stable compounds containing a hominal bis(*gem*-CF_2) fragment. While the general strategy involving two consecutive deoxofluorinations of ketones has been demonstrated,[40] it turns out to be quite specific to 1,3-diketones flanked by long alkyl chains. Excluding deprotection, adopting that strategy to our target compound required 8 steps, but failed at last deoxofluorination due to the apparent deactivation of the second deoxofluorination by the first CF_2. To work around this problem and expand the scope of the double difluorination of 1,3-diketones, we combined desulfurative- and deoxofluorinations to obtain the hominal bis(*gem*-CF_2) fragment in good yield in six to seven steps, depending on the protecting group used (e.g., compounds **15** and **24**). The possibility of deoxofluorination of ketones **14** and **23** in the presence of CF_2 groups at the hominal position might be attributed to the influence of the adjacent ether moiety and will be further explored in our upcoming work. While the use of a methyl protective group allowed us to shorten the number of steps and avoid the use of an autoclave, it necessitated working with volatile intermediates. Deprotection of both compounds **15** and **24** followed by the tosylation of intermediate alcohol **16** allows the isolation of the hominal bis(*gem*-CF_2) fragment in the form of product **17**, which can be attached to small molecules and monomers to introduce strong dipole moments in the 1,3 configuration that enables their alignment in an electric field. We believe that such modifications will be useful for affecting the dielectric and molecular doping properties of organic electronic materials.

In the course of synthesizing **17**, we isolated the 3,3-difluoroketones **8**, **14**, and **23**, which are potentially useful building blocks for a variety of applications.[43] By combining deoxofluorination and desulfurative fluorination strategies, we installed the hominal bis(*gem*-CF_2) fragment in the presence of the ketone rather than hydrating a propargylic *gem*-difluoride to form a ketone. Thus, our synthetic strategy expands the scope of the double difluorination of 1,3-diketones and provides an alternative route to the synthesis of 3,3-difluoroketones using accessible and scalable chemistry.

EXPERIMENTAL SECTION

General Information. All reagents were acquired from commercial sources and used without further purification unless stated otherwise. Specifically, Morph-DAST was purchased from Manchester Organics, PPHF (70% hydrogen fluoride, 30% pyridine) was purchased from Sigma-Aldrich, and sodium methoxide (5.4 M (30 wt %) solution in methanol, sealed) was purchased from ACROS Organics. Reactions performed under a nitrogen atmosphere were conducted in flame-dried glassware. All dry solvents were obtained from a solvent purification system, except dimethyl sulfoxide (DMSO), which was purchased from commercial sources. Thin-layer chromatography (TLC) used Merck silica gel 60 F_{254} aluminum plates. Visualization of compounds by TLC was done by irradiation with UV light at 254 nm and iodine or potassium permanganate stain. Column chromatography was performed using SiliCycle SiliaFlash irregular silica gels P60 (40−63 μm, 60 Å) or with a Reveleris X2 flash chromatography system. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR analyses were performed on Agilent Technologies 400/54 Premium Shielded (400 MHz), Varian Oxford AS400 (400 MHz), or Varian Oxford (300 MHz) instrument at 25 °C, using tetramethylsilane as an internal standard. NMR shifts are reported in parts per million (ppm), relative to the residual protonated solvent signals of $CDCl_3$ (δ = 7.26 ppm) or at the carbon absorption in $CDCl_3$ (δ = 77.0 ppm). To determine accurate ^{19}F NMR chemical shifts, $CFCl_3$ (δ = 0.00 ppm) was used as an internal standard. Multiplicities are denoted as

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follows: singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), doublet of doublets (dd), doublet of triplets (dt), doublet of doublet or triplets (ddt), doublet of quartets (dq), doublet of doublet of quartets (ddq), triplet of doublets (td), triplet of doublet of doublets (tdd), triplet of triplets (tt), triplet of triplet of triplets (ttt), quartet of doublets (qd), quartet of triplets of triplets (qtt), and multiplet (m). High-resolution mass spectrometry (HRMS) was performed on Thermo Scientific LTQ Orbitrap XL [Fourier transform mass spectrometry (FTMS)]. Infrared spectra (IR) spectra were recorded on a Thermo Scientific Nicolet iS50 FT-IR spectrometer.

Synthesis. *General Procedure for Epoxidation.* To a stirring solution of an appropriate alkene (1.0 equiv) in CH_2Cl_2 (volume in milliliter (mL) equal to the millimoles (mmol) of alkene) at room temperature and ambient conditions, a solution of *m*CPBA (2.5 equiv) in CH_2Cl_2 (volume in mL equals twice the number of mmol of *m*CPBA) was added. The mixture was left stirring overnight. The resulting mixture was filtered to get rid of formed suspension, and the organic layer was washed successively with aqueous solutions of $NaHSO_3$, $NaHCO_3$, water, and brine, filtering away any formed intermediate precipitate. The combined organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed by rotary evaporation. The resulting product is used without further purification in the next step, unless necessary.

General Procedure for Oxidation of Alcohols. To a 0.3 M solution of an appropriate alcohol (1.0 equiv) in CH_2Cl_2 at 0 °C and in the ambient atmosphere was slowly added Dess−Martin periodinane (DMP) (1.5 equiv), and the resulting mixture was left warming up to room temperature and stirring overnight. The resulting mixture was filtered to get rid of the formed suspension; then, the organic layer was quenched with water and washed with an aqueous saturated $NaHSO_3$ solution and then with a saturated $NaHCO_3$ solution, water, and brine. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The resulting product is used without further purification in the next step, unless necessary.

General Procedure for Dithiolane Formation. This procedure is adapted from the one previously reported by Sneddon et al.[50] Sodium methoxide (5.4 M solution in methanol, 1.3 equiv) was added in one portion to a stirred solution of an appropriate ynone (1 equiv) and ethane-1,2-dithiol (1.1 equiv) in methanol and CH_2Cl_2 (4:1, 0.05 M) at approximately −10 °C. The reaction mixture was stirred overnight, allowing the temperature to rise to ambient temperature. On completion, the reaction was quenched by addition of saturated NH_4Cl solution and extracted with diethyl ether. The organic fractions were washed with water and brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography if necessary.

General Procedure for Deoxofluorination of Ketones. To a 0.5 M solution of an appropriate ketone (1.0 equiv) in CH_2Cl_2 (usually 0.5 M, although molarity might vary and is not a crucial parameter) under an inert atmosphere at 0 °C, Morph-DAST (2.2 equiv) was slowly added. The reaction mixture was allowed to gradually warm up to room temperature and left stirring overnight. Then, it was diluted with additional CH_2Cl_2 and poured dropwise on the stirring mixture of saturated aqueous $NaHCO_3$ and ice. When effervescence was complete, the organic layer was washed with a saturated $NaHCO_3$ solution (until the solution became constantly basic), water, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified using vacuum distillation or column chromatography.

General Procedure for Desulfurative Fluorination of Dithiolanes. A flame-dried three-necked round-bottom borosilicate glass flask, capped with septums, and connected to the Schlenk line, was charged with DBDMH (2.0 equiv) and put under an inert atmosphere. Then, DBDMH was fully dissolved in dry CH_2Cl_2 (approximately 30 mL of CH_2Cl_2 is needed per gram of DBDMH). The mixture was cooled to −78 °C, and PPHF (approximately 1.5 mL/mmol of dithiolane is used) was added via a syringe, making sure that the temperature remains constant. This mixture was stirred for 30 min at −78 °C, followed by the dropwise addition of an appropriate dithiolane (1.0 equiv). The resulting mixture was stirred at a constant temperature of −78 °C for an additional 45 min. It was then carefully poured via a Teflon cannula on the mechanically stirred icy solution of $NaHCO_3$ in the high-density polyethylene vessel, without letting the reaction mixture to warm up. When effervescence was complete and the solution became constantly basic, it was extracted with CH_2Cl_2; washed with saturated $CuSO_4$, water, and brine; dried over Na_2SO_4; and concentrated in vacuo. The resulting crude product was dissolved in a small quantity of CH_2Cl_2 and filtered through silica. Further purification was performed if necessary.

*2-((Benzyloxy)methyl)oxirane (**2**).* According to the General Procedure for Epoxidation, the reaction using ((allyloxy)-methyl)benzene (**1**) (52 mL, 337 mmol) and *m*CPBA (208.00 g, 843 mmol) afforded compound **2** (42.70 g, 260 mmol, 77% yield) as a transparent colorless liquid, which was used in the next step without further purification. If necessary, the product **2** can be distilled at 65 °C and 242 mTorr. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.43−7.24 (m, 5H), 4.59 (q, J = 11.9 Hz, 2H), 3.77 (dd, J = 11.4, 3.0 Hz, 1H), 3.44 (dd, J = 11.4, 5.9 Hz, 1H), 3.19 (ddt, J = 5.9, 4.3, 2.9 Hz, 1H), 2.80 (dd, J = 5.1, 4.1 Hz, 1H), 2.62 (dd, J = 5.1, 2.7 Hz, 1H). ^{13}C NMR (75 MHz, chloroform-*d*) δ 137.9, 128.4, 127.8, 73.3 (d, J = 3 Hz), 70.8, 50.8, 44.3. IR (neat): 3406, 3065, 3030, 3006, 2903, 2861, 1727, 1641, 1595, 1575, 1496, 1453, 1390, 1363, 1295, 1283, 1259, 1206, 1087, 1074, 1027 cm^{-1}. See ref 54 for full characterization.

*1-(Benzyloxy)pent-4-en-2-ol (**3**).* To a stirred solution of **2** (26.00 g, 158 mmol) and CuCN (1.41 g, 15.83 mmol) in dry tetrahydrofuran (THF) (120 mL) under an inert atmosphere, a 1 M THF solution of vinylmagnesium bromide (238 mL, 238 mmol) was added dropwise at −78 °C. The mixture was allowed to gradually warm up to room temperature and stirred for additional 3 h before it was quenched with a saturated aqueous NH_4Cl solution (100 mL). Layers were separated, the aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined extracts were washed with brine (50 mL) and dried over Na_2SO_4. Evaporation of the solvent gave the product **3** (30.31 g, 158 mmol, 100% yield) as a golden oil. The product was used in the next step without further purification. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.37−7.25 (m, 5H), 5.83 (ddt, J = 17.2, 10.2, 7.1 Hz, 1H), 5.20−5.04 (m, 2H), 4.55 (s, 2H), 3.88 (qd, J = 6.7, 3.3 Hz, 1H), 3.51 (dd, J = 9.5, 3.4 Hz, 1H), 3.38 (dd, J = 9.5, 7.4 Hz, 1H), 2.50 (s, 1H), 2.27 (t, J = 6.8 Hz, 2H). ^{13}C NMR (75 MHz, chloroform-*d*) δ 138.0, 134.3, 129.2−127.1 (m), 117.7, 73.9, 73.4, 69.7, 37.9. IR (neat): 3416, 3066, 3030, 3006, 2904, 2861, 1727, 1641, 1595, 1575, 1496, 1453, 1390, 1363, 1295, 1283, 1259, 1206, 1087, 1074, 1027 cm^{-1}. See ref 54 for full characterization.

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*1-(Benzyloxy)pent-4-en-2-one (**4**).* According to the General Procedure for Oxidation of Alcohols, the reaction using **3** (30.00 g, 156 mmol) and DMP (99.00 g, 234 mmol) afforded compound **4** (23.60 g, 124 mmol, 80% yield) as a yellowish oil. The product was used in the next step without further purification. Note that efforts to further purify the compound **4** using column chromatography or distillation were unsuccessful, due to the migration of the double bond. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.42−7.29 (m, 5H), 6.02−5.84 (m, 1H), 5.24−5.09 (m, 2H), 4.59 (s, 2H), 4.10 (s, 2H), 3.26 (dt, J = 6.9, 1.4 Hz, 2H). ^{13}C NMR (75 MHz, chloroform-*d*) δ 206.4, 137.1, 129.7, 128.5, 128.1, 127.9, 119.2, 74.6, 73.4, 44.0. IR (neat): 3065, 3031, 2981, 2949, 2864, 1724, 1642, 1604, 1575, 1497, 1455, 1437, 1423, 1389, 1322, 1295, 1283, 1258, 1207, 1098, 1028 cm^{-1}. HRMS [FTMS + probe electrospray ionization (pESI)] m/z: ([M + Na]$^{+}$) calcd for $C_{12}H_{14}O_2Na$ 213.0886; found 213.0889.

*(((2,2-Difluoropent-4-en-1-yl)oxy)methyl)benzene (**5**).* According to the General Procedure for Deoxofluorination of Ketones, the reaction using **4** (20.00 g, 16.53 mL, 105 mmol) and Morph-DAST (40.50 g or 30.8 mL, 231 mmol) after distillation of a crude product at 53 °C and 282 mTorr afforded compound **5** (20.23 g, 95 mmol, 91% yield) as a transparent colorless liquid. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.42−7.28 (m, 5H), 5.80 (ddt, J = 17.3, 10.2, 7.2 Hz, 1H), 5.29−5.20 (m, 2H), 4.62 (s, 2H), 3.63 (t, J = 12.3 Hz, 2H), 2.74 (tdt, J = 16.5, 7.2, 1.3 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 137.3, 129.0 (t, J = 6 Hz), 128.5, 128.0, 127.8, 122.1 (t, J = 243 Hz), 120.6, 73.8, 69.9 (t, J = 32 Hz), 38.4 (t, J = 25 Hz). ^{19}F NMR (376 MHz, chloroform-*d*) δ −104.36 (tt, J = 16.5, 12.2 Hz). IR (neat): 3087, 3067, 3032, 2985, 2920, 2872, 1703, 1645, 1498, 1455, 1431, 1368, 1339, 1284, 1254, 1209, 1179, 1161, 1105, 1046, 1029 cm^{-1}. Anal. Calcd for $C_{12}H_{14}F_2O$: C, 67.91; H, 6.65. Found: C, 67.69; H, 6.54. HRMS (FTMS + pESI or APCI) m/z: compound was suffering from ion suppression.

*2-(3-(Benzyloxy)-2,2-difluoropropyl)oxirane (**6**).* According to the General Procedure for Epoxidation, the reaction using **5** (9.60 g, 45.2 mmol) and *m*CPBA (27.9 g, 113 mmol) after purifying the crude product via flash chromatography (silica gel, hexane/ethyl acetate gradient separation) afforded **6** (9.77 g, 42.8 mmol, 95% yield) as a transparent colorless liquid. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.41−7.29 (m, 5H), 4.64 (s, 2H), 3.76−3.68 (m, 2H), 3.17−3.07 (m, 1H), 2.80 (t, J = 4.5 Hz, 1H), 2.53 (dd, J = 5.0, 2.6 Hz, 1H), 2.21 (ddt, J = 18.0, 14.2, 5.6 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 137.2, 128.5, 128.0, 127.8, 124.6−119.0 (m), 73.8, 70.4 (dd, J = 32, 31 Hz), 46.4 (dd, J = 7, 6 Hz), 46.2, 37.5 (t, J = 24 Hz). ^{19}F NMR (376 MHz, chloroform-*d*) δ −101.71 to −103.53 (m), −103.53 to −106.09 (m). The multiplet signals can be recognized as: −102.33 (qd, J = 15.5, 11.4 Hz), −103.02 (dtd, J = 16.8, 14.2, 12.0 Hz), −104.30 (tt, J = 17.5, 11.8 Hz), −104.99 (tdd, J = 17.2, 13.3, 10.1 Hz). IR (neat): 3064, 3032, 3006, 2930, 2875, 1954, 1497, 1454, 1420, 1371, 1338, 1257, 1204, 1106, 1073, 1028 cm^{-1}. HRMS (FTMS + pESI) m/z: ([M + H]$^{+}$) calcd for $C_{12}H_{14}F_2O_2Na$ 251.0854; found 251.0854.

*5-(Benzyloxy)-4,4-difluoropentan-2-ol (**7**).* To a 1 M solution of $LiAlH_4$ (43.8 mL, 43.8 mmol) in diethyl ether, a solution of **6** (5.00 g, 21.91 mmol) in diethyl ether (20 mL) at −10 °C was added dropwise. The resulting mixture was allowed to gradually warm up to room temperature overnight while stirring. Afterward, the resulting mixture was diluted with additional diethyl ether and carefully poured on icy water. The organic layer was washed with 1 N HCl, water, and brine; dried; and concentrated in vacuo, affording the product **7** (5.00 g, 21.7 mmol, 99% yield) as a yellowish oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.40−7.28 (m, 5H), 4.63 (d, J = 1.8 Hz, 2H), 4.16 (dqd, J = 9.5, 6.3, 3.3 Hz, 1H), 3.71 (dd, J = 13.5, 11.8 Hz, 2H), 2.84 (s, 1H), 2.24−2.04 (m, 2H), 1.24 (d, J = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 136.9, 128.6, 128.1, 127.9, 126.0−118.2 (m), 73.9, 70.9 (t, J = 33 Hz), 62.6 (dd, J = 6, 4 Hz), 43.3 (t, J = 23 Hz), 23.9. ^{19}F NMR (376 MHz, chloroform-*d*) δ −100.64 (ddq, J = 257.4, 16.9, 13.4 Hz), −104.26 (dtt, J = 257.6, 18.4, 12.6 Hz). IR (neat): 3419, 2972, 2933, 2876, 1498, 1455, 1405, 1376, 1329, 1283, 1207, 1184, 1103, 1028, 1000 cm^{-1}. HRMS (FTMS + pESI) m/z: ([M + H]$^{+}$) calcd for $C_{12}H_{17}F_2O_2$ 231.1191; found 231.1190.

*5-(Benzyloxy)-4,4-difluoropentan-2-one (**8**).* According to the General Procedure for Oxidation of Alcohols, the reaction using **7** (4.50 g, 19.5 mmol) and DMP (12.43 g, 29.3 mmol) afforded **8** (3.38 g, 14.8 mmol, 76% yield) as an orange oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.40−7.27 (m, 5H), 4.58 (s, 2H), 3.77 (t, J = 12.8 Hz, 2H), 3.11 (t, J = 15.7 Hz, 2H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 201.9 (t, J = 5 Hz), 137.1, 128.5, 128.0, 127.8, 120.7 (t, J = 244 Hz), 73.8, 70.2 (t, J = 32 Hz), 47.0 (t, J = 24 Hz), 31.3 (t, J = 2 Hz). ^{19}F NMR (376 MHz, chloroform-*d*) δ −100.97 (tt, J = 15.7, 12.7 Hz). IR (neat): 3065, 3033, 2925, 2875, 1719, 1497, 1454, 1445, 1369, 1335, 1253, 1208, 1179, 1096, 1028, 1006 cm^{-1}. HRMS (FTMS + pESI) m/z: ([M + Na]$^{+}$) calcd for $C_{12}H_{14}F_2O_2Na$ 251.0854; found 251.0853.

*4-(((2,2,4,4-Tetrafluoropentyl)oxy)methyl)benzene (**9**).* Under an inert atmosphere, neat Morph-DAST (0.321 mL, 2.410 mmol) was slowly added to **8** (0.10 g, 0.44 mmol). The mixture was heated up to 50 °C for 4 h and then left stirring at room temperature (for approximately 72 h). The process was controlled daily via ^{19}F NMR of the quenched samples, and Morph-DAST was added until the conversion was complete. Then, the reaction mixture was diluted with CH_2Cl_2 and carefully poured on icy water (100 mL). After effervescence was complete, the organic layer was washed with saturated $NaHCO_3$ solution (till the solution became constantly basic), water (50 mL), and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. An attempt of purifying the resulting crude mixture via flash chromatography (silica gel, hexane/ethyl acetate gradient separation) was made; however, only small quantity of product **9** along with unknown impurities was recovered (0.01 g, 0.04 mmol, 9.12% crude yield). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.41−7.33 (m, 5H), 4.63 (s, 2H), 3.69 (t, J = 12.7 Hz, 2H), 2.73−2.52 (m, 2H), 1.73 (t, J = 19.0 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 137.0, 128.5, 128.1, 127.8, 121.5−118.6 (m), 73.9, 71.2−69.9 (m), 42.0−40.6 (m), 24.1 (t, J = 27 Hz). ^{19}F NMR (376 MHz, chloroform-*d*) δ −85.68 (qtt, J = 19.1, 14.8, 7.8 Hz), −102.85 (ttt, J = 13.1, 8.2, 4.2 Hz). IR (neat): 3090, 3066, 3033, 3008, 2925, 2868, 1819, 1455, 1426, 1397, 1281, 1230, 1173, 1114, 1100, 1059, 1029 cm^{-1}. HRMS (FTMS + pESI, or APCI) m/z: compound was suffering from ion suppression.

*1-(Benzyloxy)pent-4-yn-2-ol (**10**).* This procedure is adapted from the one previously reported by Li et al.[48] To a stirred solution of **2** (15.00 g, 91 mmol) in dry DMSO (20 mL) at 0 °C, a solid powder of lithium acetylide ethylenedi-

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amine complex (15.83 g, 146 mmol) was added in several portions. The reaction mixture was stirred at 0 °C for 3 h and then left warming up to room temperature overnight. Afterward, it was quenched with brine (30 mL) and acidified with 10% aqueous solution of HCl. The resulting mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layer was washed with $NaHCO_3$, water, saturated LiCl, and brine; dried over Na_2SO_4; and concentrated in vacuo. Obtained crude product **10** (16.30 g, 86 mmol, 94% yield) as a yellowish liquid was used in the next step without further purification. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.39−7.28 (m, 5H), 4.57 (s, 2H), 3.98 (qd, J = 6.4, 4.0 Hz, 1H), 3.61 (dd, J = 9.5, 3.9 Hz, 1H), 3.52 (dd, J = 9.5, 6.5 Hz, 1H), 2.54−2.48 (m, 1H), 2.46 (dd, J = 6.3, 2.7 Hz, 2H), 2.03 (t, J = 2.7 Hz, 1H). ^{13}C NMR (75 MHz, chloroform-*d*) δ 137.8, 128.5, 127.8, 127.7, 80.2, 73.5, 72.8, 70.6, 68.8, 23.5. IR (neat): 3416, 3290, 2916, 2862, 2359, 2242, 2118, 1496, 1453, 1362, 1309, 1252, 1205, 1099, 1073, 1027 cm^{-1}. See ref 47 for full characterization.

*1-(Benzyloxy)pent-3-yn-2-ol (**11**).* This procedure is adapted from the one previously reported by Li et al.[48] To a DMSO (10 mL) solution of **10** (5.00 g, 26.3 mmol) under ambient conditions was added potassium *tert*-butoxide (5.90 g, 52.6 mmol) as a DMSO (40 mL) solution. The reaction was stirred at room temperature for 2 h before quenching sequentially with brine and HCl (5 M). The aqueous layer was extracted with diethyl ether, and the combined organic fractions were washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo to afford **11** (4.40 g, 23.13 mmol, 88% yield) as a dark yellow liquid, which was used in the next step without further purification. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.40−7.27 (m, 5H), 4.64−4.57 (m, 2H), 4.53 (tq, J = 4.3, 3.1, 2.2 Hz, 1H), 3.61 (dd, J = 9.8, 3.5 Hz, 1H), 3.52 (dd, J = 9.8, 7.7 Hz, 1H), 2.31 (s, 1H), 1.84 (d, J = 2.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 137.7, 128.5, 127.9, 127.8, 82.1, 73.9, 73.4, 61.8, 3.6. IR (neat): 3290, 3063, 3030, 2917, 2862, 1497, 1454, 1421, 1390, 1362, 1310, 1252, 1206, 1099, 1073, 1028 cm^{-1}. See ref 47 for full characterization.

*1-(Benzyloxy)pent-3-yn-2-one (**12**).* According to the General Procedure for Oxidation of Alcohols, the reaction using **11** (4.39 g, 23.08 mmol) and DMP (14.68 g, 34.6 mmol) afforded **12** (3.16 g, 16.79 mmol, 72.8% yield) as an orange liquid, which was used in the next step without further purification. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.44−7.27 (m, 5H), 4.63 (s, 2H), 4.18 (s, 2H), 2.02 (s, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 184.9, 137.1, 128.5, 128.0, 128.0, 93.2, 78.1, 75.7, 73.3, 4.2. IR (neat): 3031, 2919, 2865, 2216, 1687, 1670, 1496, 1454, 1257, 1187, 1119 cm^{-1}. See ref 55 for full characterization.

*1-(Benzyloxy)-3-(2-methyl-1,3-dithiolan-2-yl)propan-2-one (**13**).* According to the General Procedure for Dithiolane Formation, the reaction using sodium methoxide (7.65 mL of 5.4 M solution in methanol, 41.3 mmol), **12** (5.98 g, 31.8 mmol), and ethane-1,2-dithiol (3.29 g, 34.9 mmol) afforded **13** (7.97 g, 28.2 mmol, 89% yield) as an orange liquid, which was used in the next step without further purification. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.38−7.28 (m, 5H), 4.58 (s, 2H), 4.07 (s, 2H), 3.35−3.25 (m, 4H), 3.21 (s, 2H), 1.87 (s, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 205.4, 137.1, 128.5, 128.0, 127.9, 75.6, 73.3, 61.8, 53.7, 39.6, 32.0. IR (neat): 3061, 3029, 2966, 2920, 2861, 1722, 1584, 1496, 1453, 1423, 1388, 1369, 1333, 1277, 1245, 1205, 1140, 1100, 1027 cm^{-1}. HRMS (FTMS + pESI) m/z: ([M + Na]$^+$) calcd for $C_{14}H_{18}O_2S_2Na$ 305.0640; found 305.0643.

*1-((4-Bromobenzyl)oxy)-4,4-difluoropentan-2-one (**14**).* According to the General Procedure for Desulfurative Fluorination of Dithiolanes, the reaction using DBDMH (6.54 g, 22.87 mmol), PPHF (25 mL, 277 mmol), and **13** (3.23 g, 11.44 mmol) afforded a crude product **14** as an orange liquid. It contained the mixture of 1-((4-bromobenzyl)oxy)-4,4-difluoropentan-2-one and 1-(benzyloxy)-4,4-difluoropentan-2-one (2.07 g; which when calculated for 1-((4-bromobenzyl)oxy)-4,4-difluoropentan-2-one is 6.74 mmol, 58.9% yield). This mixture was used in the next step without further purification. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.39−7.31 (m, 5H), 4.54 (s, 2H), 4.12 (d, J = 4.5 Hz, 2H), 3.05 (td, J = 14.7, 6.3 Hz, 2H), 1.73 (t, J = 18.9 Hz, 3H). ^{13}C NMR (75 MHz, chloroform-*d*) δ too low intensity of the signals. ^{19}F NMR (376 MHz, chloroform-*d*) δ −85.15 to −85.43 (m). Attempts to purify and separate the crude product **14** using flash column chromatography (silica gel, hexane/ethyl acetate gradient separation) went with moderate success, as mostly 1-((4-bromobenzyl)oxy)-4,4-difluoropentan-2-one was isolated, which still contained impurities. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.49 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 4.54 (s, 2H), 4.13 (s, 2H), 3.05 (t, J = 14.7 Hz, 2H), 1.73 (t, J = 18.9 Hz, 3H). ^{13}C NMR (151 MHz, chloroform-*d*) δ 201.7, 135.9, 131.7, 129.5, 128.5, 122.1, 75.6, 72.7, 50.2 (d, J = 17 Hz), 46.6 (t, J = 27 Hz), 30.2, 23.6 (t, J = 27 Hz). ^{19}F NMR (376 MHz, chloroform-*d*) δ −85.84 (qt, J = 22.8, 16.4 Hz). IR (neat): 3057, 2927, 2856, 1733, 1677, 1593, 1488, 1403, 1305, 1266, 1229, 1203, 1190, 1111, 1069, 1012 cm^{-1}. HRMS (FTMS + pESI) m/z: ([M + Na]$^+$) calcd for $C_{12}H_{13}BrF_2O_2Na$ 330.9939; found 330.9941.

*1-Bromo-4-(((2,2,4,4-tetrafluoropentyl)oxy)methyl)-benzene (**15**).* According to the General Procedure for Deoxofluorination of Ketones, the reaction using **14** (2.07 g, 6.74 mmol) and Morph-DAST (1.974 mL, 14.83 mmol) after purifying the crude product via flash chromatography (silica gel, hexane/ethyl acetate gradient separation) afforded compound **15** (1.88 g, 5.71 mmol, 85% yield) as a colorless transparent oil. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.49 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 4.57 (s, 2H), 3.68 (t, J = 12.7 Hz, 2H), 2.61 (p, J = 15.4 Hz, 2H), 1.72 (t, J = 19.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 138.7, 134.3, 132.0, 126.3−120.4 (m), 124.6, 75.8, 73.4 (tt, J = 31, 2 Hz), 43.9 (tt, J = 28, 25 Hz), 26.8 (tt, J = 27, 2 Hz). ^{19}F NMR (376 MHz, chloroform-*d*) δ −85.86 (qtt, J = 19.2, 14.8, 7.6 Hz), −102.62 (ttt, J = 15.7, 12.6, 7.7 Hz). IR (neat): 3006, 2951, 2922, 2877, 1723, 1594, 1488, 1396, 1381, 1279, 1240, 1172, 1121, 1097, 1069, 1012, 968, 943, 921, 872, 827, 795, 714, 674 cm^{-1}. Anal. Calcd for $C_{12}H_{13}BrF_4O$: C, 43.79; H, 3.98. Found: C, 43.75; H, 4.05. HRMS (FTMS + pESI or APCI) m/z: compound was suffering from ion suppression.

*2,2,4,4-Tetrafluoropentan-1-ol (**16**).* Solution of **15** (0.43 g, 1.31 mmol) in methanol (10 mL) together with 10% palladium on carbon (0.14 g, 0.131 mmol) and few drops of HCl were mixed in an autoclave. The system was closed and left stirring in the hydrogen atmosphere at 30 bar pressure for 24 h. Afterward, the autoclave was cooled with ice and the cold solution was dissolved in CH_2Cl_2 (50 mL), filtered through silica, then promptly washed with cold water and brine, dried over Na_2SO_4, and concentrated in vacuo (without putting pressure below 800 mbar, to avoid losses of alcohol due to its volatility). Then, 2.72 g of crude solution of **16** was obtained in

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CH_2Cl_2 and methanol. The full conversion of **15** to **16** was confirmed by ^{19}F NMR, and to avoid further loss of the product, the crude solution was promptly used in the next step without further purification. For calculations, the quantity of alcohol **16** was used as if the yield is 99% (0.2 g, 1.249 mmol). ^1H NMR (400 MHz, chloroform-*d*) δ 3.82 (t, J = 13.0 Hz, 2H), 2.61 (p, J = 15.3 Hz, 2H), 1.74 (t, J = 19.0 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ too low intensity of the signals. ^{19}F NMR (376 MHz, chloroform-*d*) δ −85.81 to −86.78 (m), −104.16 to −106.39 (m).

*2,2,4,4-Tetrafluoropentyl 4-Methylbenzenesulfonate (**17**).* To a stirred solution of crude **16** (0.20 g, 1.249 mmol) from the previous step were added *N*,*N*-dimethylpyridin-4-amine (DMAP, 0.015 g, 0.125 mmol) and DABCO (0.28 g, 2.498 mmol) at 0 °C in CH_2Cl_2 (2.5 mL), followed by 4-methylbenzene-1-sulfonyl chloride (0.29 g, 1.56 mmol), and the resulting solution was sealed and left warming up to room temperature and stirring overnight. Then, it was washed with water, 1 N HCl, $NaHCO_3$, 1 N KOH, and brine; dried; and concentrated. The resulting crude product was purified using flash chromatography (silica gel, hexane/ethyl acetate gradient separation), affording compound **17** (0.126 g, 0.40 mmol) as a transparent yellowish oil. ^1H NMR (400 MHz, chloroform-*d*) δ 7.86−7.75 (m, 2H), 7.37 (d, J = 8.1 Hz, 2H), 4.19 (t, J = 12.0 Hz, 2H), 2.55 (p, J = 15.2 Hz, 2H), 2.46 (s, 3H), 1.67 (t, J = 19.0 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 148.3, 134.6, 132.7, 130.7, 126.4−121.0 (m), 123.2−117.9 (m), 70.7 (tt, J = 35, 3 Hz), 43.8 (tt, J = 28, 24 Hz), 26.8 (tt, J = 27, 2 Hz), 24.4. ^{19}F NMR (376 MHz, chloroform-*d*) δ −86.76 (qtt, J = 19.0, 14.9, 7.9 Hz), −102.54 (ttt, J = 15.6, 12.0, 7.7 Hz). IR (neat): 3007, 2959, 2929, 1598, 1451, 1397, 1368, 1243, 1190, 1174, 1096, 1021 cm^{-1}. Anal. calcd for $C_{12}H_{14}F_4O_3S$: C, 45.86; H, 4.49; S, 10.20. Found: C, 46.77; H, 4.67; S, 10.13. HRMS (FTMS + pESI) m/z: ($[M + NH_4]^+$) calcd for $C_{12}H_{18}F_4O_3S_1N_1$ 332.0938; found 332.0944.

As the quantity of alcohol **16** could not be determined accurately, the exact yield of last two steps cannot be reported. However, it is possible to determine the yield of the two-step transformation from compound **15** (0.43 g, 1.306 mmol) into the final product **17** (0.126 g, 0.401 mmol), which is 30.7%.

We assume that the yield loss is due to the volatility of the alcohol **16** and the specific tosylation procedure. When applied for other substrates (e.g., 2-(2-ethoxyethoxy)ethanol), the average yield of this tosylation procedure is 60%, which means an approximate yield of 51% after an autoclave. Interestingly, the use of other procedures for tosylation of alcohols (e.g., with NaOH, pyridine, or triethylamine as a base and without DMAP) did not allow us to separate the pure product **17**.

*2-Methoxyacetyl Chloride (**19**).* This procedure is adapted from the one previously reported by Globisch et al.[52] Dimethylformamide (20 μL, catalytic amount) and oxalyl chloride (66.7 mL, 762 mmol) were added to a solution of 2-methoxyacetic acid (45 mL, 586 mmol) in CH_2Cl_2 (300 mL) at 0 °C under an inert atmosphere, and the solution was stirred for 3 h. The solvent was removed in vacuo to give **19** (60.00 g, 553 mmol, 94% yield) as a pale yellow oil, which was used without further purification.

*N,2-Dimethoxy-N-methylacetamide (**20**).* This procedure is adapted from the one previously reported by Globisch et al.[52] *N*,*O*-Dimethylhydroxylamine hydrochloride (59.30 g, 608 mmol) and pyridine (98 mL, 1216 mmol) were added to a crude solution of **19** (60.00 g, 553 mmol) in CH_2Cl_2 (400 mL) under an inert atmosphere, and the solution was stirred at room temperature for 18 h before quenching with saturated $NaHCO_3$; extracting with CH_2Cl_2; and washing with water, 1 N HCl, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give **20** (57.00 g, 428 mmol, 77% yield) as a transparent colorless liquid. If the product purity is unsatisfactory, it can be distilled at 43 °C and 727 mTorr. ^1H NMR (400 MHz, chloroform-*d*) δ 3.84 (s, 2H), 3.34 (s, 3H), 3.07 (s, 3H), 2.81 (s, 3H). See ref 52 for full characterization.

*1-Methoxypent-3-yn-2-one (**21**).* This procedure is adapted from the one previously reported by Globisch et al.[52] To a solution of **20** (20.00 g, 150 mmol) in THF (200 mL) at −78 °C was added 0.5 M THF solution of prop-1-yn-1-ylmagnesium bromide (451 mL, 225 mmol), and the resulting mixture was stirred overnight at room temperature. The reaction was quenched with aqueous NH_4Cl solution (150 mL) and extracted with ethyl acetate (3 × 70 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo, affording compound **21** (15.00 g, 134 mmol, 89% yield) as a yellowish liquid. If the product purity is unsatisfactory, it can be distilled at 74 °C and 9.69 Torr. ^1H NMR (300 MHz, chloroform-*d*) δ 4.07 (s, 2H), 3.39 (s, 3H), 1.99 (s, 3H). See ref 52 for full characterization.

*1-Methoxy-3-(2-methyl-1,3-dithiolan-2-yl)propan-2-one (**22**).* According to the General Procedure for Dithiolane Formation, the reaction using sodium methoxide (18.55 mL of 5.4 M solution in methanol, 93 mmol), **21** (8.00 g, 71.3 mmol), and ethane-1,2-dithiol (7.39 mL, 78 mmol) afforded compound **22** (14.00 g, 67.9 mmol, 95% yield) as a yellowish liquid, which was used in the next step without further purification. ^1H NMR (300 MHz, chloroform-*d*) δ 3.96 (s, 2H), 3.36 (s, 3H), 3.34−3.19 (m, 4H), 3.13 (d, J = 2.3 Hz, 2H), 1.82 (s, 3H). ^{13}C NMR (75 MHz, chloroform-*d*) δ 205.4, 78.1, 61.8, 59.3 (d, J = 3 Hz), 58.2, 53.5, 39.6, 31.9. IR (neat): 2965, 2921, 2821, 1722, 1446, 1423, 1368, 1335, 1277, 1197, 1105, 1072, 1034 cm^{-1}. HRMS (FTMS + pESI) m/z: ($[M + H]^+$) calcd for $C_8H_{15}O_2S_2$ 207.0508; found 207.0506.

*4,4-Difluoro-1-methoxypentan-2-one (**23**).* According to the General Procedure for Desulfurative Fluorination of Dithiolanes, the reaction using DBDMH (13.86 g, 48.5 mmol), PPHF (45 mL, 499 mmol), and **22** (5.00 g, 24.23 mmol) after distillation of a crude product at 41 °C and 19.8 Torr or filtering the CH_2Cl_2 solution through silica afforded compound **23** (2.50 g, 16.43 mmol, 67.8% yield) as a yellow liquid. Precautions have to be taken when working with product **23**, as the rapid weight loss could be observed due to its volatility. ^1H NMR (400 MHz, chloroform-*d*) δ 4.06 (s, 2H), 3.43 (s, 3H), 3.04 (t, J = 14.7 Hz, 2H), 1.73 (t, J = 18.9 Hz, 3H). ^{13}C NMR (75 MHz, chloroform-*d*) δ 202.0, 121.5 (t, J = 240 Hz), 78.1, 59.3 (d, J = 6 Hz), 46.4 (t, J = 27 Hz), 23.5 (t, J = 26 Hz). ^{19}F NMR (376 MHz, chloroform-*d*) δ −85.36 (qt, J = 18.9, 14.8 Hz). IR (neat): 3001, 2926, 2853, 2830, 1734, 1640, 1451, 1391, 1353, 1280, 1226, 1202, 1117, 1094, 1062, 1042 cm^{-1}. HRMS (FTMS + pESI) m/z: ($[M + Na]^+$) calcd for $C_6H_{10}F_2ONa$ 175.0541; found 175.0541.

*2,2,4,4-Tetrafluoro-1-methoxypentane (**24**).* According to the General Procedure for Deoxofluorination of Ketones, the reaction using **23** (2.5 g, 16.43 mmol) and Morph-DAST (6.33 g or 4.81 mL, 36.2 mmol) afforded compound **24** (2.14 g, 12.26 mmol, 74.6% yield) as a dark yellow liquid. If the product purity is unsatisfactory, it can be purified using column chromatography (CH_2Cl_2, R_f = 0.84). Precautions have to be taken when working with product **24**, as the rapid weight loss could be observed due to its volatility. ^1H NMR (400 MHz,

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chloroform-*d*) δ 3.60 (t, J = 12.8 Hz, 2H), 3.44 (s, 3H), 2.57 (p, J = 15.4 Hz, 2H), 1.71 (t, J = 19.0 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 126.8−120.4 (m), 75.7 (tt, J = 31, 2 Hz), 62.4, 43.8 (tt, J = 28, 24 Hz), 26.7 (tt, J = 27, 2 Hz). ^{19}F NMR (376 MHz, chloroform-*d*) δ −85.51 (qtt, J = 19.1, 14.9, 7.7 Hz), −102.47 (ttt, J = 16.3, 13.0, 8.1 Hz). IR (neat): 2934, 2855, 1706, 1675, 1635, 1394, 1174, 1114 cm^{-1}. HRMS (FTMS + pESI or APCI) m/z: compound was suffering from ion suppression.

*2,2,4,4-Tetrafluoropentan-1-ol (**16**).* To an ice-cold stirred solution of **24** (0.40 g, 2.30 mmol) in $CDCl_3$ (1.5 mL) in a sealed vessel with a septum cap under an inert atmosphere, trimethylsilyl iodide (1.15 g, 0.78 mL, 5.74 mmol) was slowly added. The resulting solution was stirred at room temperature, until the full conversion of **24** to **16** was confirmed by ^{19}F NMR (took 36 h), after which it was quenched with methanol. The resulting mixture was extracted with ether and washed with $NaHSO_3$, water, $NaHCO_3$, and brine. Combined organic layers were dried and gently concentrated (without lowering the pressure below 800 mTorr), affording the crude solution containing **16**. ^{1}H NMR (400 MHz, chloroform-*d*) δ 3.83 (t, J = 13.0 Hz, 2H), 2.61 (p, J = 15.2 Hz, 2H), 1.73 (t, J = 19.1 Hz, 3H). ^{13}C NMR (75 MHz, chloroform-*d*) δ too low intensity of the signals. ^{19}F NMR (376 MHz, chloroform-*d*) δ −85.99 to −86.49 (m), −104.88 to −105.29 (m). Precautions have to be taken when working with product **16**, as the rapid weight loss could be observed due to its volatility. To avoid further loss of the product, the crude solution was used without further purification in a tosylation reaction according to the above-mentioned procedure. The total crude amount (0.34 g, 2.12 mmol, 92% yield) was used for calculations. As the amount of alcohol **16** could not be determined accurately, the exact yield of the demethylation step cannot be reported. However, it is possible to determine the yield of the two-step transformation from compound **24** (0.40 g, 2.297 mmol) into the final product **17** (0.12 g, 0.764 mmol), which is 19.88%, and is lower than that determined through the benzyl protection route.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b02131.

^{1}H, ^{13}C, and ^{19}F NMR spectra of compounds **2**−**17** and **20**−**24** (PDF)

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Notes

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