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Studies toward the oxidative and reductive activation of C–S bonds in 2′-*S*-aryl-2′-thiouridine derivatives

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ABSTRACT

Studies directed toward the oxidative and reductive desulfurization of readily available 2′-*S*-aryl-2′-thiouridine derivatives were investigated with the prospect to functionalize the C2′-position of nucleosides. The oxidative desulfurization-difluorination strategy was successful on 2-(arylthio)alkanoate surrogates, while extension of the combination of oxidants and fluoride sources was not an efficient fluorination protocol when applied to 2′-*S*-aryl-2′-thiouridine derivatives, resulting mainly in C5-halogenation of the pyrimidine ring and C2′-monofluorination without desulfurization. Cyclic voltammetry of 2′-arylsulfonyl-2′-deoxyuridines and their 2′-fluorinated analogues showed that cleavage of the arylsulfone moiety could occur, although at relatively high cathodic potentials. While reductive-desulfonylation of 2′-arylsulfonyl-2′-deoxyuridines with organic electron donors (OEDs) gave predominantly base-induced furan type products, chemical (OED) and electrochemical reductive-desulfonylation of the α-fluorosulfone derivatives yielded the 2′-deoxy-2′-fluorouridine and 2′,3′-dideshydro-2′,3′-dideoxy-2′-fluorouridine derivatives. These results provided good evidence of the generation of a C2′-anion through carbon-sulfur bond cleavage, opening new horizons for the reductive-functionalization approaches in nucleosides.

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1. Introduction

Introduction of fluorine atom(s) into nucleosides dramatically changes their electronic and steric properties, giving them a wide range of biological activity.[1–3] Prominent examples of C2′ fluorinated nucleosides with potent biological activities include anticancer drugs gemcitabine,[4–6] and clofarabine;[7,8] and hepatitis C virus drug sofosbuvir.[9,10] In the last 40 years, numerous methods for the incorporation of fluorine atoms into organic molecules have been developed, as summarized in excellent reviews.[11–16] Despite these developments, construction of the tertiary fluorinated stereocenter at the sugar C2′ (e.g., sofosbuvir) has been still challenging.[17]

Oxidative desulfurization-(di)fluorination is an important fluorination protocol for the preparation of fluoro organic compounds.[16,18] Various reagents or reagent-combinations developed for this approach are known and are based mostly on the combination of an oxidant [e.g., *N*-halosuccinimides (NBS, NIS) or 1,3-dibromo-5,5-dimethylhydantoin (DBH)] and a potentially hazardous fluoride source [e.g., HF-pyridine,[19–21] iodine pentafluoride (IF_5),[22–24] air- and moisture-stable IF_5–pyridine–HF reagent,[25,26] or BrF_3–KHF_2].[27] In addition to these chemical approaches, direct and indirect (with the use of a redox mediator) electrochemical approaches have been developed for some oxidative desulfurization-(di)fluorination reactions, using different sources of fluorinating reagents, either in organic solvents or in Ionic Liquids (ILs).[28–31]

Although, chemical and electrochemical-induced reductive desulfonylation reactions have been known for years,[32–40] in nucleosides they have been limited to reductive dehalogenation or desulfonylation protocols en route to 2′,3′-dideoxy-2′,3′-didehydro nucleosides.[41–47] Reductive desulfonylation/functionalization (including (di)fluorination) strategies in nucleosides are to the best of our knowledge, unknown processes. Our goal was to investigate alternative methodologies for the modification of nucleosides at C2′ position utilizing 2′-*S*-aryl-2′-thionucleosides as convenient

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substrates to access well-known fluoro nucleosides (e.g., gemcitabine or PSI 6130, a core of Sofosbuvir). Herein we report studies on the reactivity of 2′-*S*-aryl-2′-thiouridine substrates (type I, Fig. 1) with respect to oxidation processes and 2′-arylsulfonyl-2′-deoxyuridine (type II) with respect to reductive processes. The oxidative fluorination processes are envisioned to proceed via desulfurization–difluorination of the uridine-2′-thioethers (substrate I, X=H) or desulfurization–fluorination of uridine α-fluorothioethers (substrate I, X=F) using halonium ion (Br^+, I^+) reagents as oxidants and a nucleophilic fluorine source (F^-) for quenching the intermediary C2′-carbocation. The reductive fluorination processes are proposed to proceed via cleavage of the sulfonyl moiety (from substrate II, X=H or F) with single electron transfer reagents or electrochemically and quenching the resultant C2′-carbanion with electrophiles such as F^+, H^+, CH_3^+, etc.

promote the *critical* second fluorination step.[21] The DBH was proven to be more effective than other halogen oxidants (NBS, NIS) in these reactions.[48]

Despite successful desulfurization–difluorination strategy with 2-arylthioalkanoate surrogates, our attempts to extend this protocol to sugars and nucleosides met with only limited success. Thus, treatment of (*S*)-(+)-2-phenylthio-4-benzyloxymethyl-4-butanolide[49] with DBH (4 equiv)/Py.9HF (8 equiv)/CH_2Cl_2/35 °C/15 h gave complex reaction mixture.[48] Also, attempted fluorination of readily available[50] 2′-*S*-aryl-2′-thiouridine analogues of type **6**[51] (Scheme 2) or 2′-*S*-aryl-2′-fluoro-2′-thiouridine analogues of type **8**[51] (Scheme 3) with Py.9HF/DBH failed to give 2′,2′-difluoro products yielding instead 5-brominated[52] products as well as the corresponding sulfoxides and/or α-fluoro sulfoxides, among other byproducts. Installing different protection groups on sugar hydroxyls (Ac, Bn) and EDG (MeO) or EWG (Cl) in phenyl ring as well as changing reaction conditions (e.g., halogen source, temperature, reaction time) did not change the outcome.[48]

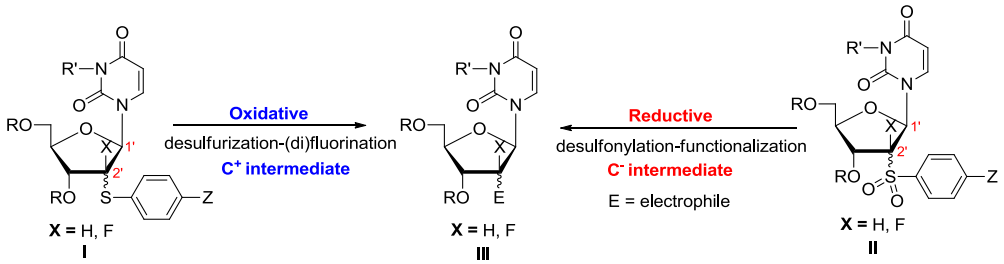


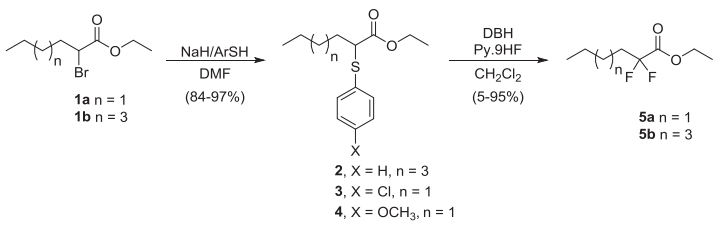
Fig. 1. Proposed pathways for the C2′-functionalization of uridine derivatives.

2. Results and discussion

Because of the lack of examples for desulfurization–difluorination reactions of aryl–alkyl thioethers with the arylthio group attached to a secondary internal carbon atom, we initially performed model studies with α-arylthio substituted esters (e.g., **2**; Scheme 1) that mimic the 2′-postion of the ribose in the nucleoside targets (e.g., **I**, X=H). Using the methodology developed by *Haufe* et al.[20,21] we found that treatment of ethyl 2-(phenylthio)octanoate **2** with DBH (3 equiv) and Olah's reagent (Py.9HF, 6 equiv) in CH_2Cl_2 at 35 °C for 2 h, showed 90% conversion to 2,2-difluorooctanoate **5b** (^{1}H NMR, ^{19}F NMR; Scheme 1). The *para*-chlorophenylthio substituted ester **3** provided 2,2-difluorohexanoate **5a** in almost quantitative yield in only 1 h, whereas *para*-methoxyphenylthio ester **4** required 16 h to show 70% conversion to **5a**.[48] These results illustrated that 4-chlorophenyl thioethers were better substrates for these difluorination reactions than corresponding phenyl and 4-methoxyphenyl thioethers, as noted also by Haufe, et al. for the primary alkyl–aryl thioethers.[21] The EDGs on the phenyl ring are believed to stabilize the cationic charge on the resonance-stabilized carbenium–sulfonium ion intermediate and thus promote the first fluorination step; whereas EWGs are assumed to ease the elimination of arylsulfenyl bromide in the last step and therefore

Interestingly, treatment of the 4-methoxyphenyl thioether 6 with NIS (2.1 equiv)/Py.9HF (3 equiv) gave the corresponding 5-iodo 7 (29%) and the α-fluorothioether 8 (12%) products (Scheme 2). Analogous treatment of sulfide 6 with NIS/DAST combination[53,54] produced the mono-α-fluorothioether 8 in 44% isolated yield without 5-halogenation. In contrast, treatment of 6 with DBH (3 equiv)/Py.9HF (6 equiv) generated a complex reaction mixture. These results reiterate the mechanistic assumption that ring activating groups (e.g., OMe) on the aryl ring promote the first fluorination step.

Moreover, treatment of α-fluorothioether **8** with DBH/Py.9HF at −78 °C effected selective bromination of the uracil ring at the C5 position[52] yielding the corresponding 5-bromo derivative **9** as a major product (50%), however with no indication of the *geminal* difluoro product formation (Scheme 3). Interestingly, the α-fluorothioether moiety in **9** remained intact under these *oxidative* conditions. It was previously noted that oxidation of α-fluorothioethers to the α-fluoro sulfoxides with *m*-CPBA required higher temperature and longer reaction time than conversion of the unfluorinated thioethers to the corresponding sulfoxides.[50]



Scheme 1. Desulfurization–difluorinations of α-thioesters **2**–**4**.

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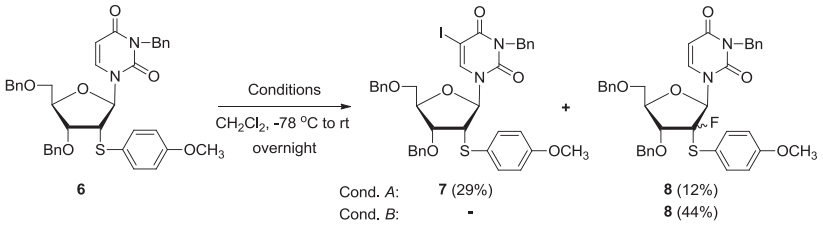
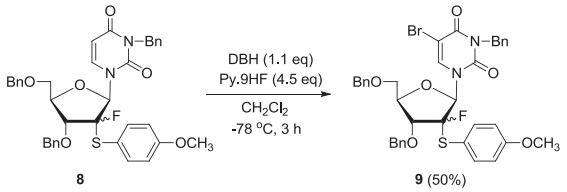


Conditions *A*: NIS (2.1 eq), Py.9HF (3 eq); Conditions *B*: NIS (2.1 eq), DAST (6 eq).

Scheme 2. Attempted fluorination of 2′-*S*-(4-methoxyphenyl)-2′-thiouridine analogue **6**.



Scheme 3. Attempted fluorination of 2′-fluoro-2′-*S*-(4-methoxyphenyl)-2′-thiouridine derivative **8**.

Since the *oxidative* desulfurization–fluorination approaches were not efficient protocols for the utilization of 2′-arylthiouridine derivatives as substrates for the modification of the C2′-position, we turned our attention to the development of a *reductive* desulfonylation approach. This strategy is consisted with the generation of an intermediary carbanion at the C2′-position of uridine derivatives which could be subsequently coupled to an electrophile (e.g., II; Fig. 1). We assumed that such anion could be obtained through cleavage of the C2′-S bond in 2′-arylsulfonyl-2′-deoxyuridine substrates. Moreover, such sulfones derivatives could be conveniently synthesized by simple oxidation of the arylthiouridine substrates used for the oxidative approach.[50,51] Reductive removal of sulfones is usually mediated by highly aggressive metal-containing reducing agents, typically alkali metals, not always compatible with the nucleoside chemistry, as they can cause side reactions on the diverse functional groups present in the molecule.[33] Instead, we opted for the use of recently reported organic electron donors (OEDs)[55–57] that can selectively cleave C–SO_2 bonds by stepwise transfer of two electrons under mild reaction conditions.[35,58] The bispyridinylidene **SED** has a redox potential of $E_{1/2}$ (DMF)=−1.24 V versus SCE (Fig. 2) and efficiently reduces sulfones via the formation of anion intermediates.[58] Its high tolerance to other functional groups, such as ketones, made it particularly suitable for our 2′-deoxyuridine substrates.

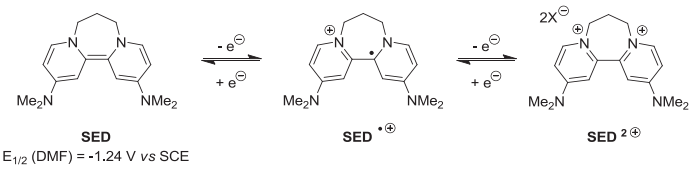
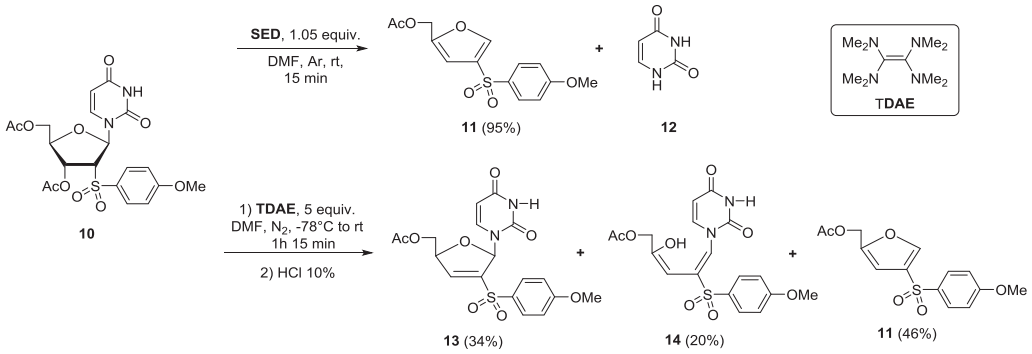


Fig. 2. Redox potential and equilibria of bispyridinylidene **SED** named as "Super-electron donor".

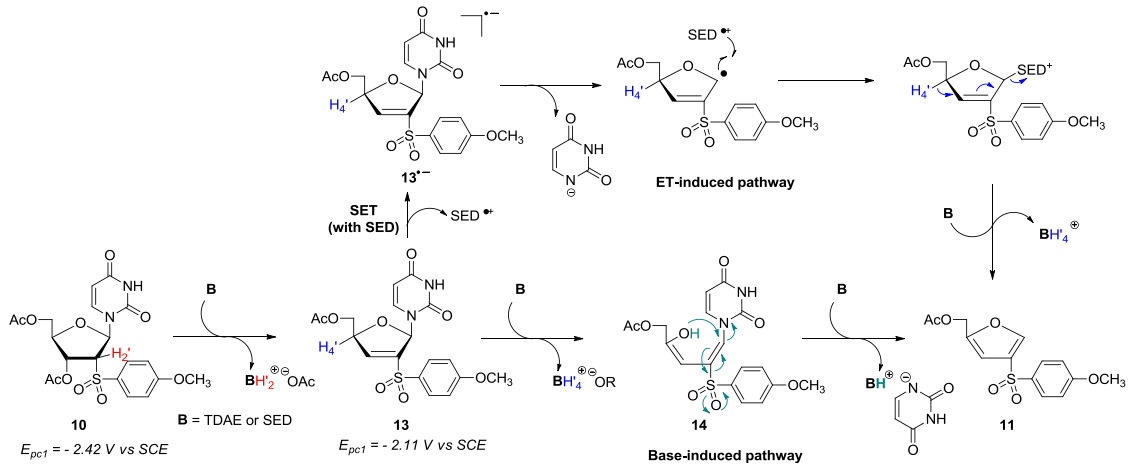
When the 2′-sulfone **10**[50] was treated at rt with the organic reductant **SED**, the reaction cleanly provided the furan product **11** in 95% yield after 15 min (Scheme 4). The uracil base **12** was identified (but not isolated) by ^{1}H NMR in the aqueous phase along with other impurities. To our surprise, cleavage of the C2′–S bond was not observed and the unexpected formation of **11** could not be explained by a sole electron-transfer mechanism. To rationalize this result, we tried the same reaction with a less powerful organic reductant, the commercially available tetrakis(dimethylamino)ethylene (**TDAE**) [$E_{1/2}$ (DMF)=−0.62 V versus SCE]. Treatment of 2′-sulfone **10** with an excess of **TDAE** gave the 3′-acetoxy elimination product **13** (34%), the enol type (open chain sugar) product **14** (20%) and the same furan derivative **11** (46%).

Cyclic voltammetry analysis showed that sulfone derivative **10** could be reduced in two irreversible reduction steps at potentials of −2.42 and −2.64 V versus SCE (Fig. S1, Table S1, Supplementary data), with the first reduction step (E_{pc1}) corresponding to the cleavage of the C2′–S bond with the expulsion of the *p*-methoxybenzenesulfinate. This hypothesis was confirmed by the cyclic voltammetry of an authentic sample[59] of sodium *p*-methoxybenzenesulfinate (Fig. S2). While the reduction potential is in the array of redox potentials that the effective reducing power of **SED** could reportedly attain,[60] the redox potential gap between **TDAE** and **10** (ΔE>1.2 V) clearly indicates that reduction of **10** cannot be achieved by **TDAE**-promoted electron transfer. Since OEDs can act as base or as reducing agent,[61,62] we assumed that **TDAE** initially acted as a base inducing elimination of AcOH by abstracting H2′ to produce **13** (Scheme 5). Judging from the first reduction potential of **13** (E_{pc1}=−2.11 V vs SCE; Table S1, Fig. S3), further reduction of **13** by **TDAE** to produce **11** would also be rather difficult. One can think that **TDAE** is only acting as a base and that **13** suffers from base-induced reactions leading in turn to **14** and **11** (*base-induced pathway*, Scheme 5). The hypothesis of a basic behaviour was supported by the fact that reaction of **10** with 4-dimethylaminopyridine (DMAP) led to the quantitative formation of **11**. On the other hand, in the case of **SED**, a mixed base-/electron transfer-induced mechanism could occur and rapidly lead to **11**. We assumed that under more forced reducing conditions,[60] **13** could be reduced in parallel to the base-induced reactions (*ET-induced pathway*, Scheme 5). Hence, **13** could be reduced by single-electron transfer (SET) leading to glycosidic bond cleavage, followed by trapping of the formed radical by the radical cation of the electron donor (**SED**$^{\bullet+}$).[63] A last base-induced reaction would give **11** and regenerate the **SED**.

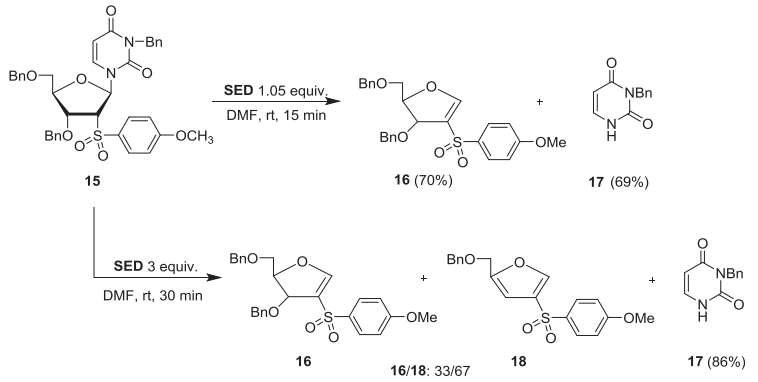
Since the acetyl protection in **10** was base labile in the presence of OEDs, and prone to elimination from the intermediate C2′-carbanion, we also studied benzylated sulfone substrates. However, treatment of the fully benzylated 2′-[(4-methoxyphenyl)sulfonyl] uridine **15**[51] (E_{pc1}=−2.42 V vs SCE; Fig. S1, Table S1) with a stoichiometric amount of **SED** resulted in a similar rapid glycosidic bond cleavage producing the vinyl sulfone **16** (70%) and 3-*N*-benzyluracil **17** (69%; Scheme 6). This result indicated that the basic character of **SED** was probably predominant over its reducing character with substrates bearing a labile α-hydrogen. Treatment of **15** with an excess of **SED** gave two inseparable ribose derivatives: the vinyl sulfone **16** and the furan derivative **18** with possibly the



Scheme 4. Reduction studies of the acetyl-protected sulfone substrate **10** with organic donors.



Scheme 5. Proposed "base-*versus* electron transfer-induced" mechanism for the reaction of **10** with OEDs.



Scheme 6. Reduction studies of benzyl protected sulfone substrate **15** with the **SED**.

latter being formed from **16** under reducing and/or basic conditions as proposed for **10** in Scheme 5.

Since the α-hydrogen of 2′-sulfone substrates were too labile under the desired reductive conditions, α-fluorosulfones **19**[50] and **24**[51] were chosen for the further studies. Thus, treatment of α-fluorosulfone **19** (E_{pc1}=−2.36 V vs SCE; Fig. S4, Table S1) with the **SED** reagent at room temperature gave the mono 3′-deacetylated product **20** (45% conversion) along with unchanged starting material but no further degradation or glycosidic bond cleavage were observed (Scheme 7).[64] The reduction of the sulfonyl moiety was not observed at this temperature. However, known fluorovinyl compound **21**[65] was obtained in 46% yield when **19** was treated with 3 equiv of **SED** at 120 °C. This result indicated that reductive cleavage of the sulfone took place with excess **SED** at high temperature. Controlled-potential electrolysis of **19** in DMF at −1.90 V versus SCE, a potential more positive to the first potential peak measured by cyclic voltammetry (see Table S1), gave, after the consumption of 2.0 F/mole of substrate (1 h, rt), a main fraction that contained **21** and **19** as an inseparable mixture (ratio ~ 8:2), with estimated yield of **21** close to 45% (Scheme 7). Noteworthy to mention that 2′-deoxy-2′-fluoridine **22**, the diacetylated **23** and uracil **12** (albeit in low amount) were also detected in the crude

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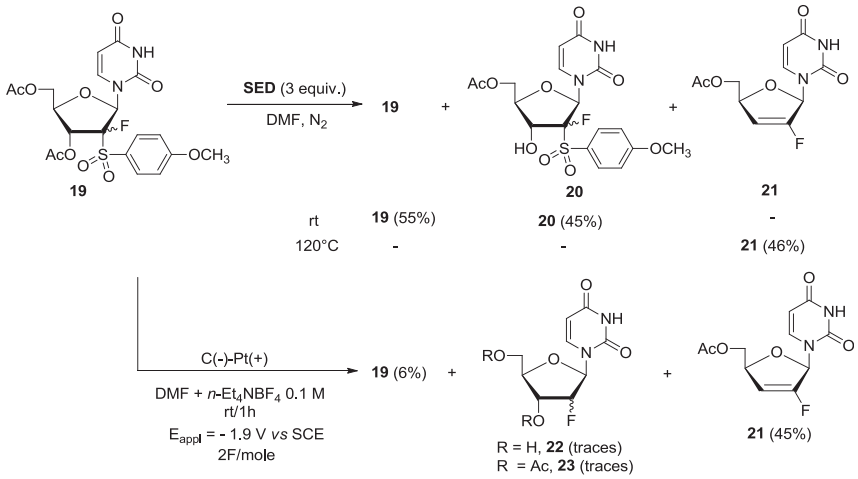


Scheme 7. Reactivity studies of acetyl protected α-fluorosulfone **19** with OED and under electrochemical activation.

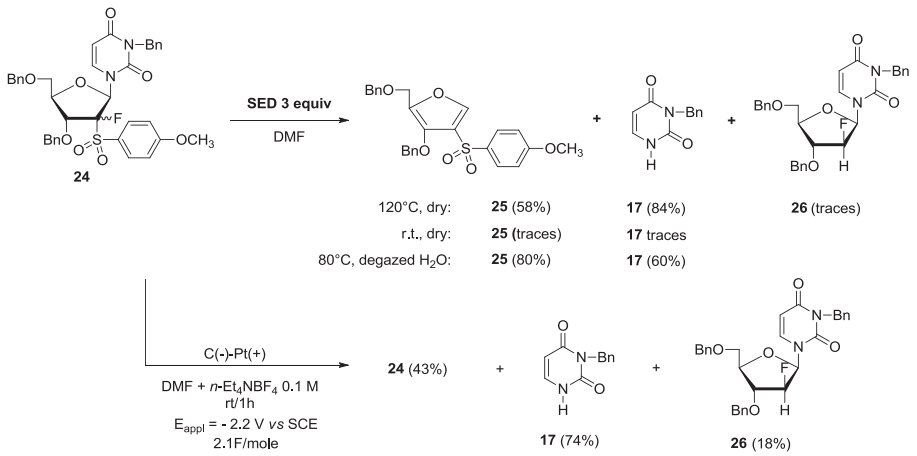
reaction mixture. These results were in line with the profile of products obtained with an excess of the **SED** reagent at 120 °C/3 h, however it offered an alternative milder approach to prepare **21** by a reductive approach. The results with **SED** or the electrochemical activation provided evidence that the C2′ anion was indeed generated through C2′-S bond cleavage. It is important to note that replacement of **SED** with other reducing agents such as samarium iodide did not affect the reduction of the sulfonyl moiety.

To avoid the elimination of the acetate anion from C3′ position, the benzyl protected 2′-α-fluorosulfone derivative **24** was employed to study the reduction of the sulfone moiety with **SED**. However, treatment of **24** with **SED** under analogous conditions (3 equiv; DMF, 120 °C, 3 h) produced a complex reaction mixture (Scheme 8), from which two major products were isolated: furan **25** and 3-*N*-benzyluracil **17**. Also observed by LC-MS was trace amounts of sulfone cleavage product **26**, providing again evidence of the C2′-anion generation, trapped by proton abstraction. Intriguingly, in the furan derivative **25**, sulfone moiety was present and elimination of fluorine was observed. Furan derivative **25** could have been formed from either the reduction of the glycosidic bond followed by base induced fluoride elimination or vice versa. Analogous treatment of **24** with **SED** at room temperature gave only trace amounts of **25** and **17** along with unchanged starting material. Reaction in the presence of deoxygenated water at 80 °C, in order to favour the formation of reduction product **26** (to enhance proton abstraction), did not change the outcome of the reaction. The elimination product **25** and 3-*N*-benzyluracil **17** were obtained in 80% and 60% isolated yields, respectively.

Controlled-potential electrolysis of **24** in DMF at −2.20 V versus SCE, a potential slightly less positive to the first peak potential measured by cyclic voltammetry (see Table S1), gave, after the consumption of 2.1 F/mole of substrate (1 h, rt), **17** in 74% isolated yield and an inseparable mixture containing **24** and **26** (ratio ~ 2.5:1) with also additional products. The estimated yield of **26** was roughly 18%, a yield slightly higher compared to the reaction using the **SED** reagent (Scheme 8). Although the electrolysis did not go to complete conversion of starting material, as opposed to the results obtained with the **SED** reagent, there was no indication of formation of furan **25**. The electrochemical reductive cleavage of **24** seems to be more complex than **19** since generation of more products was observed, but formation of **22**, **23** and **26** under milder electrochemical conditions, is again an attractive starting point for further optimization studies and possible anion trapping.

3. Conclusion

In conclusion, new methods for the modification of nucleosides at the C2′-position via oxidative and reductive activation of carbon-



Scheme 8. Reactivity studies of benzyl protected α-fluorosulfone **24** with **SED** and under electrochemical activation.

sulfur bonds in readily available 2′-thionucleosides were studied. The oxidative desulfurization-difluorination of aryl–alkyl thioethers including 2′-*S*-aryl-2′-thiouridine substrates, using the protocol of Haufe et al. was studied with mixed results. Although successful on 2-(arylthio)alkanoate surrogates, combination of oxidants and fluoride sources was not an efficient fluorination protocol when applied to 2′-thiouridine derivatives, resulting mainly in C5-halogenation of the pyrimidine ring and C2′-monofluorination without desulfurization. Our reductive desulfonylation approach using Organic Electron Donors (OEDs) was hampered by competitive base-induced mechanisms in the case of substrates bearing a labile α-hydrogen, resulting in the elimination of the uracil moieties. On the other hand, reduction of α-fluorosulfone derivatives with OED or by electrochemical activation provided good evidence that the C2′-anion was indeed generated through C2′–S bond cleavage. The major benefit of the electrochemical activation was the milder conditions of the protocol (rt, no base, short time) leading to the formation of 2′,3′-unsaturated-2′-fluorouridine and 2′-fluorinated products. These results open new horizons for the reductive desulfonylation–functionalization strategies, which, although, are still not fully developed in nucleosides, have the potential to be utilized in the synthesis of highly substituted nucleoside analogues including C2′-difluoro analogues.

4. Experimental section

Reagent grade chemicals were used and solvents were dried by reflux and distillation from CaH_2 under N_2 unless otherwise specified, and an atmosphere of N_2 was used for reactions. The MBraun glove box used for some reactions contained dry argon and less than 1 ppm oxygen and water. Reaction progress was monitored by TLC on Merck Kieselgel 60-F_{254} sheets with product detection by 254-nm light. Products were purified by column chromatography using Merck Kiselgel 60 (230–400 mesh) or by automated flash chromatography using a CombiFlash system. UV spectra were recorded with a Varian Cary 100 Bio UV–visible spectrophotometer. ^{1}H (400 MHz), ^{13}C (100.6 MHz), and ^{19}F (376 MHz) NMR spectra were recorded at ambient temperature in solutions of $CDCl_3$ or DMSO-d_6. MS and HRMS spectra were recorded in ESI+ or ESI- mode, unless otherwise noted. The bispyridinylidene SED was synthesized following reported procedure,[58] stored in a glove box and used as a well-defined dark purple solid.

Electrochemical measurements were performed using an EG & G-Princeton Applied Research 263A all-in-one potentiostat, using a standard three-electrode setup with a glassy carbon electrode (working electrode, diameter=3 mm), platinum wire auxiliary electrode and a non-aqueous Ag/Ag^+ (0.01M $AgNO_3$+0.1M *n*-Bu_4NClO_4) system in MeCN as the reference electrode. All solutions under the study were 0.1 M in the supporting electrolyte *n*-Bu_4NPF_6 (Fluka, electrochemical grade) with the voltage scan rate of 0.2 V s^{-1}. Solutions (2.5 mL) were thoroughly bubbled with dry Ar for 15 min to remove oxygen before any experiment and kept under positive pressure of Ar. Under these experimental conditions the ferrocene/ferricinium couple, used as internal reference for potential measurements, was located at $E_{1/2}$=+ 0.05 V in DMF. Controlled-potential electrolyses were run in a cylindrical divided cell (see Fig. S5) using a porous reticulous carbon electrode (S ~ 2.5 cm^2) as working electrode, a platinum wire as counter electrode separated from the cathodic compartment with a frit glass (porosity 4) and Ag wire as a pseudo reference. Cyclic voltamograms were recorded before the electrolysis and during the electrolysis using a glassy carbon electrode (diameter=1 mm). The solutions containing the substrate and the supporting electrolyte (*n*-Et_4NBF_4 0.1 M) were thoroughly bubbled with dry Ar for 15 min to remove oxygen before any experiment and kept under positive pressure of Ar.

4.1. Ethyl 2-(phenylthio)octanoate (2)

Thiophenol (260 μL, 280 mg, 2.54 mmol) was added to a stirred solution of NaH (60%, dispersion in paraffin liquid; 100.4 mg, 4.18 mmol) in anhydrous DMF (4 mL) at 0 °C. The resulting suspension was stirred at 0 °C for 30 min and at ambient temperature for 30 min, until bubbling (H_2 gas) ceased. The reaction flask was chilled again and ethyl 2-bromooctanoate (540 μL, 630 mg, 2.51 mmol) was added at 0 °C. The resultant clear, colourless solution was stirred at 0 °C for 20 min and at ambient temperature for 2 h, by which time TLC showed exclusive conversion to a slightly more polar spot. Volatiles were evaporated and co-evaporated with toluene (1×) (vacuum pump) and the resulting pale gum was partitioned between $CHCl_3$ (20 mL) and NH_4Cl/H_2O (20 mL). The aqueous layer was extracted with $CHCl_3$ (2×5 mL) and the combined organic phase was washed with $NaHCO_3/H_2O$ (25 mL), brine (25 mL), and dried ($MgSO_4$). Volatiles were evaporated in vacuo and the residue was column chromatographed (10% EtOAc in hexanes) to give **2**[66] (633 mg, 90%) as a pale oil: ^{1}H NMR ($CDCl_3$) δ 7.49–7.46 (m, 2H, Ph), 7.35–7.25 (m, 3H, Ph), 4.16–4.09 (m, 2H, CH_2), 3.66 (dd, *J*=6.6, 8.4 Hz, 1H, H2), 1.96–1.87 (m, 1H, H3), 1.82–1.73 (m, 1H, H3′), 1.51–1.37 (m, 2H, H4, H4′), 1.36–1.26 (m, 6H, H5, H5′, H6, H6′, H7, H7′), 1.19 (t, *J*=7.1 Hz, 3H, CH_3), 0.90 ('t', *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.4, 133.8, 132.7, 128.9, 127.7, 61.0, 50.9, 31.7, 31.5, 28.8, 27.2, 22.5, 14.1, 14.0.

4.2. Ethyl 2-((4-chlorophenyl)thio)hexanoate (3)

Treatment of ethyl 2-bromohexanoate (500 μL, 610.5 mg, 2.74 mmol) with 4-chlorothiophenol/NaH/DMF, as described for **2**, gave **3**[67] as a pale yellow oil (763.6 mg, 97%): ^{1}H NMR ($CDCl_3$) δ 7.41–7.37 (m, 2H, Ph), 7.30–7.26 (m, 2H, Ph), 4.17–4.09 (m, 2H, CH_2), 3.61 (dd, *J*=6.6, 8.4 Hz, 1H, H2), 1.94–1.84 (m, 1H, H3), 1.81–1.69 (m, 1H, H3′), 1.51–1.27 (m, 4H, H4, H4′, H5, H5′), 1.19 (t, *J*=7.1 Hz, 3H, CH_3), 0.91 ('t', *J*=7.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.1, 134.11, 134.10, 132.1, 129.0, 61.1, 51.0, 31.3, 29.4, 22.2, 14.1, 13.8.

4.3. Ethyl 2-((4-methoxyphenyl)thio)hexanoate (4)

Treatment of ethyl 2-bromohexanoate (500 μL, 610.5 mg, 2.74 mmol) with 4-methoxythiophenol/NaH/DMF, as described for **2**, gave **4**[68] as a colourless oil (739.3 mg, 96%): ^{1}H NMR ($CDCl_3$) δ 7.36–7.31 (m, 2H, Ph), 6.78–6.74 (m, 2H, Ph), 4.02 ('q', *J*=7.2 Hz, 2H, CH_2), 3.41 (dd, *J*=6.6, 8.5 Hz, 1H, H2), 1.82–1.75 (m, 1H, H3), 1.68–1.59 (m, 1H, H3′), 1.42–1.32 (m, 1H, H4), 1.30–1.21 (m, 3H, H4′, H5, H5′), 1.10 (t, *J*=7.1 Hz, 3H, CH_3), 0.82 (t, *J*=7.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.2, 160.1, 136.2, 123.4, 114.4, 60.7, 55.2, 51.6, 31.1, 29.3, 22.3, 14.1, 13.8.

4.4. General procedure for the preparation of ethyl difluoroalkanoates (5)

DBH (1.5 mmol) was added to a stirred solution of esters **2** or **3** or (0.5 mmol) and Py.9HF (3 mmol) in CH_2Cl_2 (2 mL) in a polypropylene vessel at ambient temperature. The resulting brown solution was stirred at 35 °C for 2 h (**2**), 1 h (**3**) or 16 h (**4**). The reaction flask was cooled to room temperature, quenched by addition of ice-cold water, diluted with CH_2Cl_2, and neutralized with drop-wise addition of conc. NH_4OH. Organic layer was separated and aqueous layer was back extracted (2×CH_2Cl_2). Combined organic layer was washed with 1N HCl, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give crude difluorinated product **5b** (95% conversion from **2**) or **5a** (95% conversion from **3**; 70% conversion from **4**) as a brown oil, with data as reported.[69]

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5a[69] had: ^{1}H NMR ($CDCl_3$) δ 4.25 (q, $^3J_{H,H}$=7.2 Hz, 2H, CH_2), 2.09–1.88 (m, 2H, H3, H3′), 1.42–1.30 (m, 4H, H4, H4′, H5, H5′), 1.28 (t, $^3J_{H,H}$=7.1 Hz, 3H, CH_3), 0.85 (t, $^3J_{H,H}$=7.2 Hz, 3H, H6, H6′, H6″); ^{13}C NMR ($CDCl_3$) δ 164.4 (t, $^2J_{F,C}$=33.2 Hz, C1), 116.4 (t, $^1J_{F,C}$=249.8 Hz, C2), 63.0 (CH_2), 34.5 (t, $^2J_{F,C}$=23.2 Hz, C3), 23.5 (t, $^3J_{F,C}$=4.3 Hz, C4), 22.2 (C5), 13.9 (CH_3), 13.7 (C6); ^{19}F NMR ($CDCl_3$) δ −105.92 ppm (t, $^3J_{F-H}$=16.8 Hz); GC–MS (t_R=7.5 min) 151 (M^+-Et, 1.1), 87 (100).

5b[69] had: ^{1}H NMR ($CDCl_3$) δ 4.25 (q, $^3J_{H,H}$=7.2 Hz, 2H, CH_2), 2.03–1.91 (m, 2H), 1.45–1.18 (m, 11H), 0.81 (‘t’, $^3J_{H,H}$=6.8 Hz, 3H, H6, H6′, H6″); ^{13}C NMR ($CDCl_3$) δ 164.5 (t, $^2J_{F,C}$=33.0 Hz, C1), 116.4 (t, $^1J_{F,C}$=249.7 Hz, C2), 62.7 (CH_2), 34.5 (t, $^2J_{F,C}$=23.2 Hz, C3), 31.4, 28.7, 22.4, 21.4 (t, $^3J_{F,C}$=4.3 Hz, C4), 13.9; ^{19}F NMR ($CDCl_3$) δ −105.89 ppm (t, $^3J_{F-H}$=17.0 Hz); GC–MS (t_R=7.4 min) 179 (M^+-Et, 60.8), 144 (100).

4.5. 3-*N*-Benzyl-3′,5′-di-*O*-benzyl-5-iodo-2′-*S*-(4-methoxyphenyl)-2′-thiouridine (7) and 3-*N*-benzyl-3′,5′-di-*O*-benzyl-2′-fluoro-2′-*S*-(4-methoxyphenyl)-2′-thiouridine (8)

NIS (95 mg, 0.42 mmol) was added to a stirred solution of **6** (128 mg, 0.2 mmol) and Py.9HF (138 μL, 0.6 mmol) in anhydrous CH_2Cl_2 (3 mL) at −78 °C in a polypropylene vessel and the resulting brown solution was brought to ~5 °C overnight (16 h). Stirring was continued at ambient temperature for 7 h (total reaction time: 23 h). The reaction was quenched by addition of ice-cold water (10 mL), diluted with CH_2Cl_2 (5 mL), neutralized with drop-wise addition of conc. NH_4OH. Organic layer was separated and aqueous layer was back extracted (2×CH_2Cl_2). Combined organic layer was washed with 1N HCl (10 mL), brine (10 mL), dried ($MgSO_4$), and filtered. Volatiles were evaporated in vacuo and the brown residue was column chromatographed (5% → 20% EtOAc in hexanes) to give **7** (44 mg, 29%) as a colourless oil and **8**[51] (2′-*R*/*S*–S, ~1:1; 16 mg, 12%) as a pale-yellow oil.

7 had: UV (MeOH) λ_{max} 253, 283 nm, λ_{min} 246, 273 nm; ^{1}H NMR ($CDCl_3$) δ 7.66–7.63 (m, 2H, Ph), 7.56 (s, 1H, H6), 7.44–7.31 (m, 13H, Ph), 7.12–7.10 (m, 2H, Ph), 6.51 (d, *J*=8.9 Hz, 1H, H1′), 6.33–6.30 (m, 2H, Ph), 5.15 (‘d’, *J*=13.4 Hz, 1H, benzylic), 5.02 (‘d’, *J*=13.3 Hz, 1H, benzylic), 4.68–4.52 (m, 4H, benzylic), 4.33–4.25 (m, 2H, H4′, H3′), 3.76–3.67 (m, 2H, H2′, H5′), 3.66 (s, 3H, OCH_3), 3.51 (dd, *J*=2.0, 10.5 Hz, 1H, H5″); ^{13}C NMR ($CDCl_3$) δ 159.8, 159.1, 150.8, 142.2 (C6), 137.22, 137.16, 136.2, 135.2, 130.4, 128.8, 128.6, 128.4, 128.2, 128.1, 128.06, 127.8, 127.7, 123.0, 114.7, 90.2 (C1′), 82.1 (C3′), 80.7 (C4′), 73.8 (CH_2), 72.3 (CH_2), 70.5 (C5), 68.9 (C5′), 56.4 (C2′), 55.5 (OCH_3), 46.0 (CH_2). HRMS (ESI) *m*/*z* 785.1119 $[M+Na]^+$, calcd for $C_{37}H_{35}IN_2NaO_6S^+$ 785.1133.

Analogous treatment of **6** (128 mg, 0.2 mmol) with NIS (95 mg, 0.42 mmol) and DAST (160 μL, 1.2 mmol) followed by aqueous workup (satd $Na_2S_2O_3$, satd $NaHCO_3$, brine, $MgSO_4$) and column chromatography gave **8**[51] (2′-*R*/*S*–S, ~1:1; 58 mg, 44%) as a pale-yellow oil.

4.6. 3-*N*-Benzyl-3′,5′-di-*O*-benzyl-5-bromo-2′-fluoro-2′-*S*-(4-methoxyphenyl)-2′-thiouridine (9)

Py.9HF (62 μL, 0.27 mmol) was added to a chilled solution of DBH (19 mg, 0.066 mmol) in dry CH_2Cl_2 (1 mL) at −78 °C. The resulting pale solution was stirred at −78 °C for 10 min and a solution of substrate **8** (40 mg, 0.06 mmol) in dry CH_2Cl_2 (2 mL) was added via syringe. The resultant orange solution was stirred at −78 °C for 2 h and was brought to −30 °C over 45 min. The reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with $NaHCO_3/H_2O$ (5 mL), H_2O (5 mL), brine (5 mL), dried ($MgSO_4$). Volatiles were evaporated in vacuo and the yellow residue was column chromatographed (15% EtOAc in hexanes) to give **9** as mixture of diastereomers (2′-*R*/*S*–S, ~4:1) (pale-yellow oil, 22 mg, 50%): UV (MeOH) λ_{max} 253, 280 nm, λ_{min} 239, 271 nm; ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1H, H6), 7.81 (d, *J*=2.1 Hz, 0.2H, Ph), 7.66 (d, *J*=2.2 Hz, 0.8H, Ph), 7.49–7.23 (m, 17H, Ph), 6.78 (d, *J*=8.7 Hz, 0.8H, Ph), 6.75 (d, *J*=8.7 Hz, 0.2H, Ph), 6.44 (d, *J*=13.9 Hz, 0.8H, H1′), 6.27 (br s, 0.2H, H1′), 5.09 (‘d’, *J*=13.6 Hz, 1H, benzylic), 4.92–4.80 (m, 1H, benzylic), 4.73–4.65 (m, 1H, benzylic), 4.62–4.41 (m, 3H, benzylic), 4.18–4.09 (m, 2H, H3′, H4′), 3.92 (s, 0.6H, CH_3), 3.91 (s, 2.4H, CH_3), 3.82–3.72 (m, 1H, H5′), 3.61–3.53 (m, 1H, H5″); ^{19}F NMR ($CDCl_3$) δ −133.52 ppm (br s, 0.8F), −131.57 ppm (br s, 0.2F); ^{13}C NMR ($CDCl_3$) for major isomer: δ 158.4, 157.2, 149.4, 138.1, 137.79, 137.76, 137.3, 136.8, 135.9, 134.1, 134.0, 129.3, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 120.24, 120.23, 112.2, 112.0, 108.7 (d, $^1J_{C2'-F}$=239.1 Hz, C2′), 96.9, 90.4 (d, $^2J_{C1'-F}$=47.3 Hz, C1′), 80.3 (C4′), 79.7 (d, $^2J_{C3'-F}$=17.7 Hz, C3′), 73.5 (CH_2), 73.1 (CH_2), 67.0 (C5′), 56.4 (OCH_3), 45.7 (CH_2). HRMS (ESI) *m*/*z* 755.1182 $[M+Na]^+$, calcd for $C_{37}H_{34}{}^{79}BrFN_2NaO_6S^+$ 755.1197.

4.7. 5′-*O*-Acetyl-2′,3′-dideoxy-2′,3′-didehydro-2′-[(4-methoxyphenyl)sulfonyl]uridine (13), 1-[5-acetyl-4-hydroxy-2-((4-methoxyphenyl)sulfonyl)-1,3-pentadien-1-yl]uracil (14) and [4-[(4-methoxyphenyl)sulfonyl]furan-2-yl]methyl acetate (11)

TDAE (0.24 mL, 1.04 mmol) was added to a stirred solution of **10** (100 mg, 0.207 mmol) in anhydrous DMF (2 mL) at −78 °C under argon. The reaction mixture was brought to ambient temperature over 1 h 15 min and a 10% HCl solution (2 mL) was then added. The crude was extracted with EtOAC (3×) and the combined organic phase was dried over anhydrous Na_2SO_4. Volatiles were evaporated in vacuo and the residue was column chromatographed (PE 100% → EtOAc/PE 2/1 → EtOAc 100%) to give **11** (29.5 mg, 46%), **14** (17.5 mg, 20%), and **13** (30 mg, 34%), all as colourless oils.

13 had: ^{1}H NMR ($CDCl_3$) δ 9.23 (br, 1H, NH), 7.79–7.75 (m, 2H, Ph), 7.24 (d, *J*=8.4 Hz, 1H, H6), 7.18 (t, *J*=1.6 Hz, 1H, H3′), 7.03–6.99 (m, 3H, Ph, H1′), 5.55 (dd, *J*=2, 8.4 Hz, 1H, H5), 5.12–5.09 (m, 1H, H4′), 4.41 (dd, *J*=4, 12.4 Hz, 1H, H5′), 4.29 (dd, *J*=3.6, 12.4 Hz, 1H, H5″), 3.87 (s, 3H, OCH_3), 2.09 (s, 3H, Ac); ^{13}C NMR (50 MHZ, $CDCl_3$) δ 170.1 (C=O), 164.9 (C^{Ph}), 162.9 (C4), 150.3 (C2), 142.1 (C6), 141.9 (C2′), 139.5 (C3′), 130.8 (CH^{Ph}), 129.1 (C^{Ph}), 115.2 (CH^{Ph}), 103.2 (C5), 87.5 (C1′), 82.8 (C4′), 63.9 (C5′), 56.1 (OCH_3), 20.8 (Ac). HRMS (ESI) *m*/*z* 423.0856 $[M+H]^+$, calcd for $C_{18}H_{19}N_2O_8S^+$ 423.0857.

14 had: ^{1}H NMR ($CDCl_3$) δ 9.00 (br s, 1H, NH), 7.76 (d, *J*=8.8 Hz, 2H, Ph), 7.58 (s, 1H, H1′), 6.97–6.99 (m, 3H, Ph, H6), 5.69 (br, 1H, OH), 5.62 (dd, *J*=1.2, 8.0 Hz, 1H, H5), 4.93–4.79 (m, 1H, H3′), 4.27 (dd, *J*=4.4, 12.4 Hz, 1H, H5′), 4.21 (dd, *J*=4.8, 12.4 Hz, 1H, H5″), 3.86 (s, 3H, OCH_3), 1.95 (s, 3H, Ac); ^{13}C NMR ($CDCl_3$) δ 170.4 (C=O), 164.2 (C^{Ph}), 162.6 (C4), 160.3 (C1′), 150.3 (C2), 140.2 (broad, C6), 131.5 (C^{Ph}), 129.9 (CH^{Ph}), 116.9 (broad, C2′), 114.9 (CH^{Ph}), 103.7 (C5), 88.7 (broad, C3′), 63.4 (C5′), 55.6 (OCH_3), 20.5 (CH_3^{Ac}). HRMS (ESI) *m*/*z* 423.0864 $[M+H]^+$, calcd for $C_{18}H_{19}N_2O_8S^+$ 423.0857; 440.1119 $[M+NH_4]^+$, calcd for $C_{18}H_{22}N_3O_8S^+$ 440.1122.

11 had: ^{1}H NMR ($CDCl_3$) δ 7.93 (d, *J*=0.8 Hz, 1H, H1), 7.85–7.89 (m, 2H, Ph), 6.96–7.00 (m, 2H, Ph), 6.56 (s, 1H, H3), 4.97 (s, 2H, H5, H5′), 3.85 (s, 3H, OCH_3), 2.05 (s, 3H, Ac); ^{13}C NMR ($CDCl_3$) δ 170.3 (C=O), 163.8 (C^{Ph}), 152.4 (C4), 145.7 (C1), 132.9 (C2), 131.1 (C^{Ph}), 129.8 (CH^{Ph}), 114.7 (CH^{Ph}), 108.7 (C3), 57.4 (C5), 55.8 (OCH_3), 20.8 (CH_3^{Ac}); HRMS (ESI) *m*/*z* 328.0852 $[M+NH_4]^+$, calcd for $C_{14}H_{18}NO_6S^+$ 328.0849.

4.8. [4-[(4-Methoxyphenyl)sulfonyl]furan-2-yl]methyl acetate (11) and uracil (12)

In a glove box, **SED** (31 mg, 0.1 mmol) was added to a solution of **10** (50 mg, 0.1 mmol) in anhydrous DMF (4 mL) and the resulting mixture was stirred at ambient temperature for 15 min. Then the

reaction flask was brought out of the glove box and water was added to the crude reaction mixture. The aqueous phase was extracted with CH_2Cl_2 (3×), the combined organic phase was dried over anhydrous Na_2SO_4 and volatiles were evaporated in vacuo to give **11** (29.4 mg, 95%) as a colourless oil.

Acidification of the aqueous phase (pH ~5–6) followed by extraction (2×CH_2Cl_2) gave a white solid. ^{1}H NMR (MeOD) of the white solid revealed the presence of uracil **12** along with other impurities.

4.9. 3,5-Di-*O*-Benzyl-1,2-dideoxy-1,2-didehydro-2-[(4-methoxyphenyl)sulfonyl]ribose (16), 2-[(benzyloxy)methyl]-4-[(4-methoxyphenyl)sulfonyl]furan (18) and 3-*N*-benzyluracil (17)

In a glove box, **SED** (22 mg, 7×10^{-5} mol, 1.05 equiv) was added to a solution of **15** (45 mg, 6.7×10^{-5} mol) in DMF (4 mL) and the reaction mixture was stirred at ambient temperature for 15 min. Then the reaction flask was brought out of the glove box and water was added to the crude reaction mixture. The aqueous phase was extracted with CH_2Cl_2 (3×) and the combined organic phase was dried over anhydrous Na_2SO_4. Volatiles were evaporated in vacuo and the residue was column chromatographed (PE 100%→PE/EtOAc 9/1→EtOAc 100%) to give **16** (22 mg, 70%) as a white gum and **17** (9.4 mg, 69%) as a white solid.

16 had: ^{1}H NMR ($CDCl_3$) δ 7.83–7.79 (m, 2H, Ph), 7.42 (s, 1H, H1), 7.37–7.31 (m, 3H, Ph), 7.26–7.24 (m, 5H, Ph), 7.09–7.07 (m, 2H, Ph), 6.86–6.84 (m, 2H, Ph), 4.86 (d, J=3.2 Hz, 1H, H3), 4.77 (td, J=3.2, 5.6 Hz, 1H, H4), 4.49 (d, J=2.4 Hz, 2H, CH_2), 4.40 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.48 (dd, J=5.6, 10.4 Hz, 1H, H5), 3.40 (dd, J=5.6, 10.4 Hz, 1H, H5); ^{13}C NMR ($CDCl_3$) δ 163.3 (C^{Ph}), 159.7 (C1), 137.4 (C^{Ph}), 137.3 (C^{Ph}), 133.6 (C^{Ph}), 129.8 (2 CH^{Ph}), 128.7 (2 CH^{Ph}), 128.4 (2 CH^{Ph}), 128.1 (3 CH^{Ph}), 128.0 (CH^{Ph}), 127.9 (2 CH^{Ph}), 119.7 (C2), 114.2 (2 CH^{Ph}), 90.3 (C3), 80.7 (C4), 73.7 (CH_2), 70.8 (CH_2), 68.9 (C5), 55.7 (OCH_3); HRMS (ESI) m/z 484.1789 $[M+NH_4]^+$, calcd for $C_{26}H_{30}NO_6S^+$ 484.1788.

Analogous treatment of **15** (50 mg, 7.5×10^{-5} mol) with **SED** (64 mg, 2.2×10^{-4} mol, 3 equiv) in DMF (4 mL) for 30 min at room temperature gave **18** as a mixture with **16** (colourless oil; 7.4 mg; ratio of **16**:**18** is 33/67) and **17** (13 mg, 86%) as a white solid.

18 had: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.93 (s, 1H, H1), 7.91–7.84 (m, 2H, Ph), 7.36–7.30 (m, 5H, Ph), 7.01–6.96 (m, 2H, Ph), 6.49 (s, 1H, H3), 4.53 (s, 2H, CH_2), 4.42 (s, 2H, H5), 3.86 (s, 3H, OCH_3); MS (ESI) m/z 376.17 $[M+NH_4]^+$, calcd for $C_{19}H_{22}NO_5S^+$ 376.12.

4.10. 5′-*O*-Acetyl-2′,3′-didehydro-2′,3′-dideoxy-2′-fluorouridine (21)

In a glove box, **SED** (68 mg, 0.24 mmol, 3 equiv) was added to a stirred solution of **19** (40 mg, 0.08 mmol) in anhydrous DMF (4 mL) and the resulting dark brown solution was stirred at 120 °C for 18 h. Reaction flask was brought out of the glove box, and 10% HCl solution was added to the crude reaction mixture. Aqueous layer was extracted with CH_2Cl_2 (2 ×). Combined organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give a brown solid. Et_2O was added to the solid and was filtered. Filtrate was concentrated in vacuo to give **21** (<10 mg, ~46%) along with other impurities. ^{1}H NMR of the black solid (DMSO-d_6) showed similar peaks to the ones obtained for the oxidized form of the **SED** (**SED**$^{2+}$).[58]

21[65] had: ^{1}H NMR ($CDCl_3$) δ 8.47 (br s, 1H, NH), 7.52 (dd, J=1.0, 8.1 Hz, 1H, H6), 6.90–6.88 (m, 1H, H1′), 5.78 (d, J=8.1 Hz, 1H, H5), 5.69 (m, 1H, H3′), 5.06–5.02 (m, 1H, H4′), 4.35–4.21 (m, 2H, H5′,5″), 2.11 (s, 3H, Ac); ^{19}F NMR ($CDCl_3$) δ −133.76 (t, J=4.6 Hz, F2′); MS (EI) m/z 271.09 $[M+H]^+$, calcd for $C_{11}H_{12}FN_2O_5^+$ 271.07.

4.11. 3-(Benzyloxy)-2-[(benzyloxy)methyl]-4-[(4-methoxyphenyl)sulfonyl]furan (25)

In a glove box, **SED** (62 mg, 0.22 mmol, 3 equiv) was added to a solution of **24** (50 mg, 7.3×10^{-5} mol) in anhydrous DMF (4 mL) and the resulting solution was stirred at 120 °C for 3 h. Reaction flask was brought out of the glove box, and water was added to the crude reaction mixture. The aqueous phase was extracted with CH_2Cl_2 (3×) and the combined organic phase was dried with Na_2SO_4. Volatiles were evaporated in vacuo and the residue was column chromatographed (PE/EtOAc 9/1→EtOAc 100%) to give **25** (19.6 mg, 58%) as a white gum and 3-*N*-benzyluracil (**17**; 12.4 mg, 84%) as white solid.

Analogous treatment, in a glove box, of **24** (58.3 mg, 8.5×10^{-5} mol) with **SED** (72 mg, 0.25 mmol, 3 equiv) at ambient temperature for 4 h showed only trace amounts of **25** and **17** on TLC. Addition of degassed water (0.5 mL, 500 mg, 27.75 mmol) followed by heating at 80 °C for 30 min gave, after workup and silica gel chromatography, **25** (31.7 mg, 80%) and **17** (10.1 mg, 60%).

25 had: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.94–7.87 (m, 2H, Ph), 7.83 (s, 1H, H1), 7.37–7.24 (m, 10H, Ph), 6.95–6.88 (m, 2H, Ph), 5.07 (s, 2H, CH_2), 4.41 (s, 2H, CH_2), 4.17 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.6 (C3), 144.8 (C1), 142.4 (C^{Ph}), 140.7 (C^{Ph}), 137.4 (C^{Ph}), 136.2 (C^{Ph}), 132.8 (C4), 130.0 (CH^{Ph}), 128.55(CH^{Ph}), 128.53 (CH^{Ph}), 128.48 (CH^{Ph}), 128.0 (CH^{Ph}), 127.9 (CH^{Ph}), 125.6 (C2), 114.3 (CH^{Ph}), 77.3 (CH_2), 72.4 (CH_2), 61.1 (CH_2), 55.7 (OCH_3). HRMS (ESI) m/z 482.1632 $[M+NH_4]^+$, calcd for $C_{26}H_{28}NO_6S^+$ 482.1632.

4.12. General procedure for the electrolysis of 19 and 24

Under argon was introduced in the cathodic compartment, 10 mL of an anhydrous DMF solution containing *n*-Et_4NBF_4 0.1M and 2.5 mL of the same solution in the anodic compartment (see Fig. S5 for the cell). The cathodic solution was deoxygenated with argon bubbling for 15 min and then was introduced **19** or **24**. Solution was stirred and deoxygenated further for 10 min. A cyclic voltamogram was then recorded using a glassy carbon electrode in order to determine the reduction potential of starting material. A constant potential of −2.21 V for **19** or −2.51 V for **24** was then applied at room temperature, with an initial current close to 12–18 mA. The progress of the electrolysis was followed by cyclic voltammetry. After 2.0–2.1 F/mole of starting material (1 h), the electrolysis was stopped and quenched with an aqueous NH_4Cl solution and extracted with EtOAc (3×), the combined organic phase were washed with H_2O (3×), dried over Na_2SO_4 and filtered. Concentration *under vacuo* left a residue that was purified by silica gel chromatography.

From 0.09 g (0.180 mmol) of **19**, 75.1 mg of a viscous yellow oil was obtained as a crude product. Column chromatography (5% MeOH in $CHCl_3$) gave a fraction (31.2 mg) that contained an inseparable mixture of **21** and **19** (ratio 8:2) with estimated yields of **21** (45%) and **19** (6%) from ^{1}H and ^{19}F NMR. Further elution gave traces amount of **22** and **23** along with other fluorinated impurities as confirmed by mass spectrometry and NMR.

From 0.09 g (0.131 mmol) of **24**, 89.6 mg of a viscous yellow oil was obtained as crude product. Column chromatography (5% MeOH in $CHCl_3$) gave a fraction (50 mg) that contained an inseparable mixture of **24** and **26** (ratio ~ 2.5:1) with estimated yields of **24** (43%) and **26** (18%) from ^{1}H and ^{19}F NMR. Further elution gave **17** (74%) in addition to other fluorinated impurities.

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Supplementary data

Supplementary data (These data include experimental procedures and characterization data for 2′-thiouridine precursors **6**, **8**, **15**, and **24** as well as Table S1 and Figs. S1–S5 for the cyclic voltammetry experiments with **10**, **13**, **15**, **19** and **24**) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.02.063.

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