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Synthesis of 2,3-trans Disubstituted Tetrahydrofurans through Sequential Xanthate Radical Addition−Substitution Reactions

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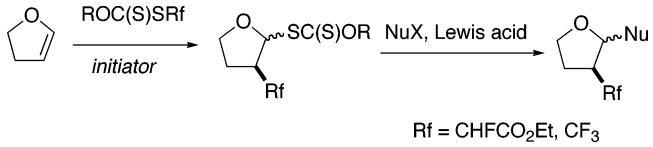

A two-step preparation of 2,3-trans disubstituted tetrahydrofuran derivatives is reported from *S*-alkyl dithiocarbonates. The study of the group transfer reaction from xanthates and alkenes afforded intermediate *S*-alkyl dithiocarbonates. From 2,3-dihydrofuran derivatives, the displacement of the resulting anomeric xanthates with various nucleophiles in the presence of Lewis acid allowed the formation of new carbon−carbon and carbon−heteroatom bonds. This strategy was illustrated by a two-step synthesis of a precursor of modified 2′-β-C-branched nucleoside analogues.

Introduction

Substituted tetrahydrofurans are frequently involved in the synthesis of modified nucleosides or branched-chain sugar nucleosides, which are known to be potent antitumor agents[1] and precursors of modified antisense oligonucleotides.[2] Moreover, nucleosides modified at the 2′-position were used to probe the RNA structure−function relationship,[3] to stabilize RNA duplexes,[4] or to inhibit hepatitis C virus replication.[5] Indeed, these modifications were found to promote a conformational bias toward the C3′-endo (N-type) preferred geometry by an RNA target.[6,7]

In general, modified nucleosides were prepared from substituted tetrahydrofuran derivatives via the formation of a 2-furanyl radical from the corresponding 2-phenylthiocarbonate, thioimidazolate ester, phenylselenanyl, or iodo derivatives.[8] These radicals reacted with olefins in the presence of tributyltin hydride or allyltributyltin to create a new carbon−carbon bond via inter- or intramolecular reactions. However, the nature of the free-radical traps was limited, restricting alkyl group variation at the 2-furanyl position, and multistep chemical modifications were required to prepare new classes of 2′-deoxy-2′-C-branched nucleosides.[9] In this paper, we present an alternative strategy based on the group transfer reactions of *S*-alkyl dithiocarbonates (xanthates)[10] followed by their substitution to prepare 2,3-disubstituted tetrahydrofurans. In particular, the additions of

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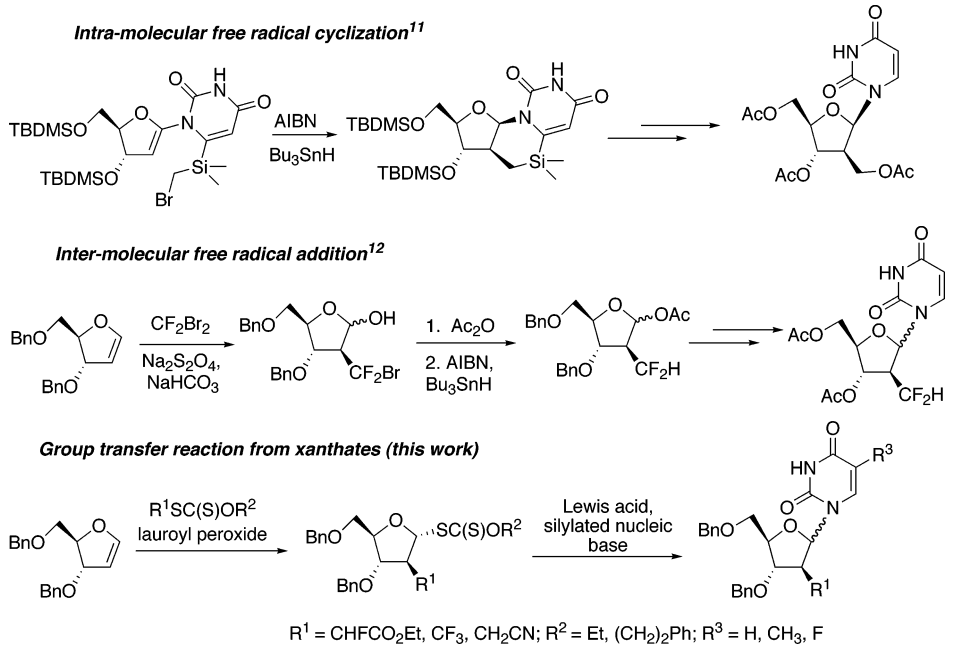
SCHEME 1. Preparation of 2′-C-Branched Nucleosides from Glycal Derivatives



R^1 = $CHFCO_2Et$, CF_3, CH_2CN; R^2 = Et, $(CH_2)_2Ph$; R^3 = H, CH_3, F

alkyl radicals to 2,3-dihydrofuran derivatives using *S*-alkyl dithiocarbonates and the nucleophilic displacements of the resulting anomeric dithiocarbonate function by various nucleophiles to create a new carbon−carbon or carbon−heteroatom bond are described. This two-step radical group transfer reaction nucleophilic substitution sequence should offer a new route for the preparation of 2,3-disubstituted tetrahydrofurans.

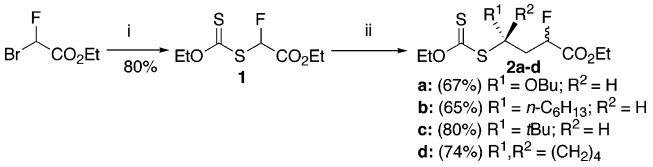
Results and Discussion

Studies related to free-radical additions to substituted dihydrofuran derivatives already containing nucleic bases were known, and the most representative examples were the syntheses of C-branched sugar derivatives through an intramolecular free-radical cyclization (Scheme 1).[11] Alternatively, the introduction of a nucleic base can be achieved at a later stage through the formation of an oxocarbenium ion or by a cyclopropane ring-opening reaction. However, few methods to prepare the corresponding substrates from glycal derivatives were reported (Scheme 1).[12]

This lack of general synthetic methods prompted us to study the use of *S*-alkyl dithiocarbonates to functionalize appropriate 2,3-dihydrofuran derivatives to prepare 2′-deoxy-2′-C-branched nucleosides. To the best of our knowledge, there are no reports on the addition of xanthates onto 2,3-dihydrofurans. The radical group transfer reaction could produce an intermediate anomeric *S*-alkyl dithiocarbonate, which would be helpful for the incorporation of nucleic bases through the Lewis acid promoted formation of an oxocarbenium ion (Scheme 1).

Until recently, only trifluoromethylated xanthates were known, and fluorinated xanthates were relatively difficult to obtain.[13] The introduction of fluorine atoms has been used extensively to modify the biological activities of nucleosides.[14] A preliminary study described the incorporation of fluoromethylcarboxylic ester and trifluoromethyl groups, from the corresponding xanthates, and acyclic or cyclic alkenes.

SCHEME 2. Ethyl Fluoroacetate Group Transfer Reaction[a]



[a] (i) KSC(S)OEt, 1.5 h, room temperature, EtOH; (ii) $H_2C{=}CR^1R^2$, 30% lauroyl peroxide, $ClCH_2CH_2Cl$, 1 h, reflux.

The synthesis of the xanthate **1** was achieved from the commercially available ethyl bromofluoroacetate (Scheme 2), following known procedure, by a nucleophilic substitution of the bromine atom with *O*-ethyl potassium dithiocarbonate.[10] The substitution reaction proceeded smoothly, and the racemic xanthate **1** was isolated in 80% yield. We noticed that the ease of displacement of the halide depended strongly on the structure; no reaction occurred from ethyl chlorofluoroacetate or bromodifluoroacetate.

The ethyl fluoroacetate group transfer reaction was explored from terminal alkenes (1.1 equiv) and xanthate **1** in the presence of lauroyl peroxide (30%) in refluxing dichloroethane (Scheme 2). After a slow addition of lauroyl peroxide (over 1 h), the mixture was refluxed until complete consumption of the starting materials (monitored by ^{19}F NMR). From all alkenes tested, the reaction was completed after the end of the addition of

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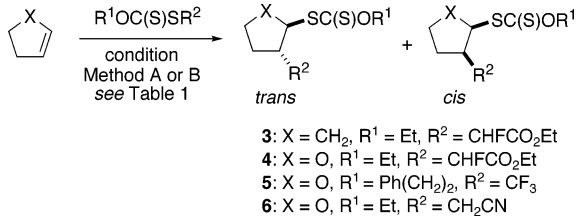
TABLE 1. Group Transfer Reaction from Cyclic Alkenes[a]

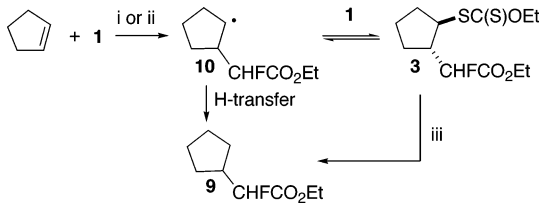
entry	alkene	xanthate $R^1OC(S)SR^2$	method	yield (%)	trans/cis dr	product
1	X = CH_2	**1**: R^1 = Et, R^2 = $CHFCO_2Et$	A B	79 67	>98:2	**3**
2	X = O	**1**	A B	81 73	>98:2	**4**
3	X = O	**7**: R^1 = $Ph(CH_2)_2$, R^2 = CF_3	A B[b]	30 52	>98:2	**5**
4	X = O	**8**: R^1 = Et, R^2 = CH_2CN	B	55	9:1	**6**

[a] Method (A): slow addition of 0.3 equiv of lauroyl peroxide, refluxed $ClCH_2CH_2Cl$, 1−2 h. Method (B): addition of 3 × 0.1 equiv of BEt_3, CH_2Cl_2, room temperature, 1−2 h. [b] Stirring was maintained overnight at room temperature.

SCHEME 3. Xanthate Group Transfer to Cyclic Alkenes



SCHEME 4. Triethylborane-Mediated Group Transfer Reaction



(i) Et_3B (1 M in *n*-hexane), air, CH_2Cl_2, 1 h, room temperature (**3**/**9** ratio = 2:1); (ii) Et_3B (1 M in *n*-hexane), N_2, deoxygenated CH_2Cl_2, 1 h, room temperature (**3**/**9** ratio = 1:0); (iii) Et_3B, air, *n*-hexane, 2 h, room temperature.

lauroyl peroxide, and fluoroesters **2a**−**c** were obtained in fair to good yields as a mixture of diastereomers (1:1 ratio). In no case was reduction through a hydrogen transfer reaction observed, from either the initial or the intermediate radicals. The addition was regioselective, and the fluorocarboxylic ester function was transferred onto the C-terminal. No addition to electron-poor alkenes was observed because of the high electrophilic character of the carboxyfluoromethyl radical, as demonstrated by an unsuccessful attempt to trap the radical with ethyl acrylate.

To approach cyclic structures related to precursors of modified nucleosides, the reactions with cyclopentene and 2,3-dihydrofuran were investigated, in the presence of 30% of lauroyl peroxide (Scheme 3, Table 1). The best results were observed from these alkenes and fluoroxanthate **1** (Table 1, entries 1 and 2) when lauroyl peroxide was added slowly to a mixture of alkene and xanthate (method A). Only two diastereomers were detected in a 1:1 ratio from cyclopentene (X = CH_2), and purification of the crude product afforded product **3** in 79% yield. Similar results were observed from the 2,3-dihydrofuran (X = O) and **1**, and a mixture of two diastereomers of **4** was obtained in 81% yield. Comparison of their H−H coupling constants with those reported in the literature,[12a,15a] supplemented by $^1H\{^{19}F\}$ HOESY NMR experiments, allowed us to assign a 2,3-trans relationship between the xanthate group and the fluorocarboxylic ester function in the structures of **4**. These two isomers of **4** differed only by the relative configuration of the third stereogenic center bearing the fluorine atom. Formation of the 2,3-cis isomers was detected in neither case. These results showed that the group transfer reaction occurred preferentially by the less-hindered face of the intermediate radical in the case of the xanthate **1**.[16] Precedents for high trans selectivity were observed previously during the course of the iodine-atom-transfer addition involving iodofluoroacetate derivatives and cyclic alkenes.[15,17]

Transfer of a trifluoromethyl group from the corresponding xanthate **7**[13a] (Table 1, entry 3) and the 2,3-dihydrofuran has been conducted under identical experimental conditions. The reaction also reached completion after 1 h, and the disubstituted furan **5** was obtained in 30% yield. However, this product was not easy to separate from the lauroyl peroxide. The $^1H\{^{19}F\}$ HOESY NMR experiments indicated that the 2,3-trans isomer **5** was formed as the sole product. In this case, the steric demand of the CF_3 group[18] is strong enough to induce an antitransfer of the dithiocarbonate function.

Because of the difficulty of removing the lauroyl peroxide, triethylborane was tested as an alternative free-radical initiator.[19] Previous work showed that the use of triethylborane often increases the diastereoselectivity of the free-radical addition of xanthates to substituted allylsilanes.[19d] In our first attempt, a solution of triethylborane (0.3 equiv, 1 M in *n*-hexane) was added at room temperature to a solution of xanthate **1** and cyclopentene in dichloromethane under aerobic conditions. NMR analysis of the crude product revealed complete consumption of the xanthate **1** and the formation of the two trans isomers of **3**, together with a third product, **9** (Scheme 4). These were formed in a 1:1:1 ratio. The formation of the byproduct **9** arises from reductive cleavage of isomeric adducts **3** through the formation of the radical **10**, which abstracted a hydrogen atom from the *n*-hexane cosolvent (present in the commercial solution

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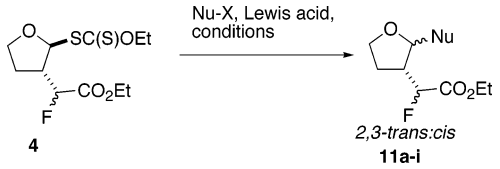
SCHEME 5. Nucleophilic Substitution of Anomeric Dithiocarbonates



of BEt_3), or the excess of alkene. Indeed, addition of triethylborane solution to a solution of xanthates **3** in *n*-hexane, under an air atmosphere, afforded exclusively the fluoroester **9** in 77% yield, after 2 h at room temperature (Scheme 4). These results are in agreement with previous work on the reduction of xanthates by a hydrogen transfer from cyclohexane initiated by peroxides.[20] In the present case, the hydrogen abstraction step from *n*-hexane, which is strongly dependent on the electrophilic character of the radical **10**, was probably favored by the presence of the electron-withdrawing fluoromethylcarboxylate group.

In contrast, the formation of **9** was not observed when the reaction was performed in deoxygenated CH_2Cl_2 under an atmosphere of nitrogen. The 2,3-trans products **3** were obtained exclusively and isolated in 67% yield (Table 1, entry 1, method B). In the case of the 2,3-dihydrofuran and other xanthates, similar results were observed. From 2,3-dihydrofuran and xanthate **1**, the 2,3-trans disubstituted furans **4** were isolated in 73% yield (Table 1, entry 2, method B), and reaction performed from the trifluoromethylxanthate **7** afforded the trans adduct **5** in 52% yield (Table 1, entry 3, method B). This method allows also the introduction of another function, as exemplified by the transfer of a cyanomethylene group (Table 1, entry 4). From xanthate **8**,[21] the reaction proceeded smoothly and afforded the 2,3-trans isomers **6** as major products in 55% yield. The fact that the reaction can be performed only in a deoxygenated solvent is not understood clearly, but this suggests that traces of free ethyl radicals seem to be enough to initiate the group transfer process.[22] When the reaction is performed in the presence of air, the equilibrium between the radical **10** and the product **3** is strongly displaced in favor of **10**, probably because of a high concentration of ethyl radicals in the medium.

The study of the displacement of the dithiocarbonate function by a variety of nucleophiles in the presence of Lewis acid was explored from the 2,3-tetrahydrofuran derivatives **4** (Scheme 5). Displacement of the dithiocarbonate function of hemithioacetals by oxygen-containing nucleophiles in the presence of organic or Lewis acids has been studied for the preparation of the corresponding acetals or glycofuranoside derivatives.[13c,23,24] As in the Vorbrüggen glycosylation reaction, these methods are based on the formation of an oxocarbenium ion in situ but have not been used for the introduction of nitrogen- or carbon-containing nucleophiles from anomeric xanthate functions. First, alcohols, such as ethanol and neopentanol (1.1 equiv), were used to explore the selective preparation of hemiacetals. For this study, only one of the two trans diastereomers of tetrahydrofurans **4** was used. Treatment of a single diastereomer, **4**, with alcohols in the presence of silver triflate at −17 °C or 20 °C in toluene[23] led to the formation of a trans/cis mixture of the corresponding hemiacetals in 72−73% yields (Table 2, entries 1 and 2). The reaction was poorly selective, and mixtures of 2,3-trans and -cis isomers **11a** and **11b** were obtained in a 7:3 and 3:2 ratio, respectively, from the ethanol and neopentanol.

Introduction of a carbon-containing nucleophile has been attempted by using organomagnesium reagents (PhMgBr, EtMgBr) in the presence of Lewis acid (AgOTf, $BF_3{\cdot}Et_2O$, $SnCl_4$).[25] Substitution of the xanthate function was not observed in any of these cases. However, carbon−carbon bond formation can be performed from the trans isomers **4** and Me_3SiCN at −78 °C in the presence of $SnCl_4$ (Table 2, entry 3). The resulting 2-cyanotetrahydrofurans **11c** were obtained with a high selectivity and isolated in good yield (83%). The trans and cis adducts were formed in a 93:7 diastereomeric ratio. Other silylated carbon-containing nucleophiles were investigated, including silylketene acetals and silylenol ethers (Table 2, entries 4 and 5). The latter afforded a mixture of 2,3-disubstituted tetrahydrofurans **11d**,**e** in moderate yields (32−36%). The 2,3-trans/cis selectivity was poor from the acyclic silylketene acetal (Table 2, entry 4). In contrast, high diastereoselectivity was observed from the cyclic enol ether (Table 2, entry 5). Only two trans isomers of **11e** were formed as major products when a single trans xanthate **4** was used, as confirmed by $^1H\{^{19}F\}$ HOESY and 2D NOESY NMR experiments. The steric demand of the cyclic enol ether induced a nucleophilic attack of the oxocarbenium ion from the side opposite to the fluoromethylcarboxylate group. This high selectivity could be predicted by a stereoelectronic model.[26c] Carbon−carbon bond formation was attempted by using allylsilane at 0 °C or −78 °C in the presence of AgOTf, $Cu(OTf)_2$, or $SnCl_4$,[26] but corresponding alkylated tetrahydrofurans were detected only as part of a complex mixture.

Nitrogen-containing nucleophiles were investigated, to open a new route to alkylated pyrimidine derivatives (Scheme 5, Table 3). Sodium azide was used to functionalize the *S*-furanyl xanthates **4**, but no reaction occurred in the presence of Lewis acid, even after 3 h in toluene at −17 °C. Nevertheless, the 2-azidotetrafurans **11f** were isolated in 68% yield when Me_3SiN_3 was used as the source of nucleophile (1.5 equiv) in the presence of AgOTf at −17 °C (Table 3, entry 1). The introduction of the azide function was not selective, and a mixture of 2,3-cis and -trans isomers was obtained from the 2,3-trans isomers **4**. With bistrimethylsilyluracil as the nucleophile, the substitution reaction of the xanthate function required the presence of at least a stoichiometric amount of AgOTf, and at −17 °C, *N*-alkyluracil **11g** was isolated in good yield (Table 3, entry 2). A high selectivity was observed, and the 2,3-trans functionalized tetrahydrofurans **11g** were formed as major products, probably because of a nucleic base introduction occurring from the less-hindered face of the oxocarbenium ion. There are precedents for this reaction: displacement of anomeric ribofuranoside carbonates catalyzed by Lawesson's reagent in

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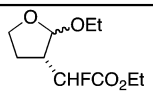
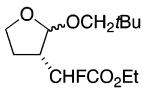
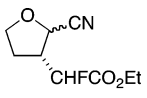
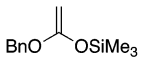
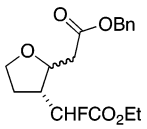
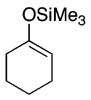
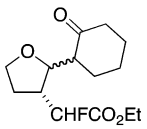
TABLE 2. Carbon−Oxygen and Carbon−Carbon Bond Formation

Entry	Nu-X	Conditions	Lewis acid	Product	Yield (%)	trans/cis dr
1	EtOH	toluene, 20 °C, 15 min	AgOTf	 **11a**	72	7:3
2	tBuCH$_2$OH	toluene, -17 °C, 1 h	AgOTf	 **11b**	73	3:2
3	Me$_3$SiCN	toluene, -78 °C, 2.5 h	$SnCl_4$	 **11c**	83	9:1
4		toluene, -17 °C, 2 h	AgOTf	 **11d**	36	4:1
5		toluene, -17 °C, 1 h	AgOTf	 **11e**	32	>98:2

the presence of silver triflate.[27] Other pyrimidine bases were introduced, and from silylated thymine or 5-fluorouracil, corresponding 2,3-trans tetrahydrofuran derivatives **11h** and **11i** were produced in 83% and 45% yields, respectively (Table 3, entries 3 and 5). In these cases, the use of copper(II) triflate instead of silver triflate was tolerated; however, the substitution reactions were slower and yields were not improved.

A two-step synthesis of modified 2′-C-nucleoside precursors from protected glycal **12** and xanthate **1** has been developed following this strategy (Scheme 6).[12a,28] The xanthate group transfer reaction was slower than in the previous examples and needed at least 5 h at reflux in the presence of lauroyl peroxide to reach completion. After column chromatography of the crude product, a diastereomeric mixture of 2,3-trans addition products **13** was obtained in 57% yield. These two isomers **13** were obtained in 1:1 ratio and differed only in the configuration of the stereogenic center bearing the fluorine atom, as shown by the $^1H\{^{19}F\}$ HOESY spectrum (Figure 1). The use of triethylborane as a free-radical initiator was less successful, and the reaction needed a longer reaction time to reach completion (overnight at room temperature). Incorporation of the thymine nucleic base was achieved in the presence of silver triflate at 0 °C. After 3 h at 0 °C, a mixture of protected 2′-deoxy-2′-C-β-alkyl nucleoside analogues **14** was obtained in 61% yield. The introduction of the thymine was highly selective, and only the trans products **14** were detected. These were subjected to hydrogenation to lead to the corresponding diol **15**. The $^1H\{^{19}F\}$ HOESY and NOESY NMR experiments allow to us to assign a 1′,2′-trans relationship for compounds **14** and **15** (Figure 1).[29]

Conclusions

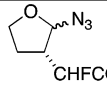
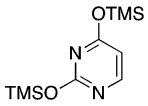
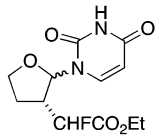
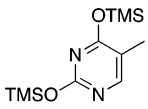
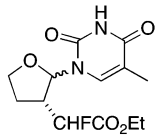
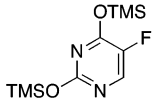
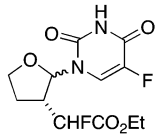
In summary, we have shown that the xanthate group transfer reaction is a useful strategy for the preparation of 2,3-disubstituted tetrahydrofurans through sequential xanthate addition−substitution reactions. In particular, the xanthate group transfer reactions were highly diastereoselective in the case of cyclic alkenes, and the resulting hemithioacetal derivatives can be used as oxocarbenium ion precursors when treated with Lewis acids. This reaction allowed the formation of new carbon−carbon or carbon−heteroatom bonds in one step. This strategy could be applied generally to the preparation of a new generation of modified nucleosides, as illustrated by the two-step preparation of a modified 2′-C-nucleoside precursor **15** from protected glycal derivatives. The intramolecular version of these sequential

(27) (a) Shimomura, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2532−2534. (b) Shimomura, N.; Matsutani, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3100−3106. (c) Shimomura, N.; Mukaiyama, T. *Chem. Lett.* **1993**, 1941−1944.

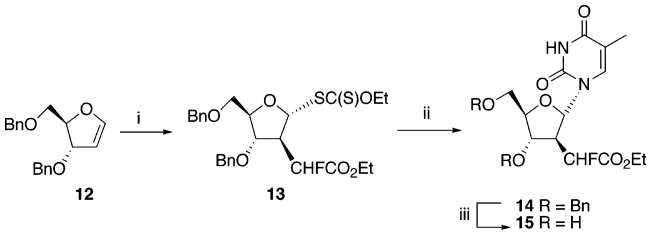
(28) Cameron, M. A.; Cush, S. B.; Hammer, R. P. *J. Org. Chem.* **1997**, *62*, 9065−9069.

(29) Claridge, T. D. W. In *High-Resolution NMR Techniques in Organic Chemistry*; Tetrahedron Organic Chemistry Series; Oxford: Oxford, 1999; Vol. 10, Chapter 8.

TABLE 3. Carbon−Nitrogen Bond Formation

Entry	Nu-X	Conditions	Lewis acid	Product	Yield (%)	trans/cis dr
1	Me_3SiN_3	toluene, -17 °C, 1 h	AgOTf	 **11f**	68	3:2
2		toluene, -17 °C, 2 h	AgOTf	 **11g**	63	9:1
3		toluene, -17 °C, 1.5 h	AgOTf	 **11h**	83	9:1
4		toluene, -17 °C, 4 h	$Cu(OTf)_2$		76	9:1
5		toluene, -17 °C, 1.5 h	AgOTf	 **11i**	45	4:1
6		toluene, -17 °C, 3.5 h	$Cu(OTf)_2$		25	4:1

SCHEME 6. Two-Step Synthesis of a Protected Modified Nucleoside



(i) **1**, lauroyl peroxide (0.3 equiv), $ClCH_2CH_2Cl$, reflux, 5 h (57%); (ii) AgOTf, silylated thymine, toluene, 0 °C, 3 h (61%); (iii) H_2, Pd(C), EtOH, 18 h, room temperature (98%).

xanthate addition−substitution reactions is under investigation to prepare a variety of 2′-α-C-nucleoside derivatives.

Experimental Section

Ethyl Ethoxythiocarbonylsulfanylfluoroacetate (1). Ethylbromofluoroacetate (4.82 g, 26.05 mmol) was added dropwise to a solution of potassium *O*-ethyldithiocarbonate (4.59 g, 28.66 mmol) in absolute ethanol (30 mL) under N_2. The mixture was stirred for 1.5 h at room temperature and extracted with diethyl ether. The organic layer was washed with saturated sodium chloride, dried with anhydrous $MgSO_4$, and evaporated under vacuum. The residue was purified by bulb-to-bulb distillation (80 °C/0.1 mbar) to give

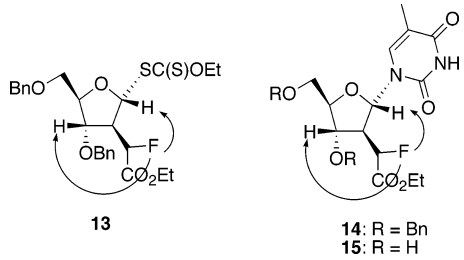


FIGURE 1. $^1H\{^{19}F\}$ HOESY NMR correlation for compounds **13**−**15**.

(**1**) in 80% yield as a yellow oil (4.73 g): ^1H NMR (250 MHz, $CDCl_3$) δ 1.33 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.46 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 4.32 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 4.71 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 6.76 (d, $^2J_{HF}$ = 50.4 Hz, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −165.9 (d, $^2J_{HF}$ = 50.4 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.6, 14.0, 63.0, 71.5, 93.5 (d, $^1J_{CF}$ = 232.7 Hz), 165.0 (d, $^2J_{CF}$ = 27.0 Hz), 207.3 (d, $^3J_{CF}$ = 1.3 Hz); IR (NaCl) 1760 cm^{-1}; MS (EI, 70 eV) *m*/*z* (relative intensity) 226 ($M^{+\bullet}$, 3), 227 (M + 1, 9), 166 (100), 138 (80), 137 (34), 120 (44), 93 (12), 45 (29); HRMS (ESI): not analyzable.

General Procedure for the Radical Addition to Olefins. A. Method A (with Lauroyl Peroxide). A solution of xanthate (1 equiv) and olefin (1.1 equiv) in deoxygenated 1,2-dichloroethane was heated to reflux under a nitrogen atmosphere. A solution of lauroyl peroxide (0.3 equiv) in 1,2-dichloroethane was added over

a period of 1 h, and the mixture was refluxed until complete consumption of the xanthate (monitored by ^{19}F NMR). The solvent was evaporated, and the residue was purified by flash chromatography.

B. Method B (with Triethylborane). Three portions of triethylborane (1 M hexane solution, 3 × 0.1 equiv) were added at intervals of 15 min to a mixture of xanthate (1 equiv) and olefin (1.1 equiv) in deoxygenated dichloromethane at room temperature, under a nitrogen atmosphere. The reaction was monitored by ^{19}F NMR, and after complete conversion, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by flash chromatography.

Ethyl 4-Ethoxythiocarbonylsulfanyl-2-fluorodecanoate (2b). Prepared according to method A from **1** (0.30 g, 1.33 mmol), *n*-octene (0.23 mL, 1.46 mmol) in 1,2-dichloroethane (15 mL), and lauroyl peroxide (0.16 g, 0.40 mmol) in 1,2-dichloroethane (3 mL). The reaction was stopped after the end of the addition of lauroyl peroxide. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 98.5:1.5) to afford **2b** as a mixture of two diastereomers (1:1 ratio) (yellow oil, 0.29 g, 65% yield). Major diastereomer: ^1H NMR (250 MHz, $CDCl_3$) δ 0.87 (t, $^3J_{HH}$ = 6.8 Hz, 3H), 1.20−1.36 (m, 11H), 1.42 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.68−1.77 (m, 2H), 2.00−2.35 (m, 2H), 3.82−3.99 (m, 1H), 4.25 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 4.64 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 4.93−5.15 (m, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −191.71 (ddd, $^2J_{HF}$ = 47.1 Hz, $^3J_{HF}$ = 32.9 Hz, $^3J_{HF}$ = 16.5 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.9, 14.0, 22.5, 26.5, 28.9, 31.5, 32.9, 34.9, 37.3 (d, $^2J_{CF}$ = 21.2 Hz), 47.0, 61.6, 69.9, 87.0 (d, $^1J_{CF}$ = 185.5 Hz), 169.4 (d, $^2J_{CF}$ = 23.4 Hz), 213.1. Minor diastereomer: ^1H NMR (250 MHz, $CDCl_3$) δ 0.87 (t, $^3J_{HH}$ = 6.8 Hz, 3H), 1.20−1.36 (m, 11H), 1.42 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.68−1.77 (m, 2H), 2.00−2.35 (m, 2H), 3.82−3.99 (m, 1H), 4.25 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 4.64 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 4.93−5.15 (m, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −190.93 (ddd, $^2J_{HF}$ = 47.1 Hz, $^3J_{HF}$ = 28.2 Hz, $^3J_{HF}$ = 21.2 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.6, 14.0, 22.5, 26.6, 28.9, 31.5, 32.9, 34.9, 36.8 (d, $^2J_{CF}$ = 20.9 Hz), 46.8, 61.6, 69.8, 86.9 (d, $^1J_{CF}$ = 185.6 Hz), 169.3 (d, $^2J_{CF}$ = 23.5 Hz), 213.2; IR (NaCl) 1764 cm^{-1}; MS (EI, 70 eV) *m*/*z* (relative intensity) 339 ([$M^{+\bullet}$ + 1], 6), 305 (19), 217 (85), 197 (34), 123 (100); HRMS (EI, 70 eV) *m*/*z* [M^+] calcd for $C_{15}H_{27}FO_3S_2$ 338.13855, found 338.13678.

Ethyl (2-Ethoxythiocarbonylsulfanyltetrahydrofuran-3-yl)-fluoroacetate (4). Prepared according to method A from **1** (1.00 g, 4.43 mmol), 2,3-dihydrofuran (0.37 mL, 4.87 mmol) in 1,2-dichloroethane (25 mL), and lauroyl peroxide (0.53 g, 1.33 mmol) in 1,2-dichloroethane (5 mL). The reflux was maintained for 30 min after addition of lauroyl peroxide. The residue was purified by flash chromatography (pentane/ethyl acetate 9:1) to afford **4** as a mixture of two trans diastereomers (cis/trans > 2:98, dr trans = 1:1) (yellow oil, 1.06 g, 81% yield). Prepared according to method B from **1** (1.1 g, 4.87 mmol), 2,3-dihydrofuran (0.40 mL, 5.35 mmol), triethylborane (1 M hexane solution) (3 × 0.49 mL, 1.46 mmol) in deoxygenated dichloromethane (20 mL). After the end of BEt_3 addition, the mixture was stirred for 30 min, and the residue was purified by flash chromatography to afford **4** as a mixture of two diastereomers (yellow oil, 1.05 g, 73% yield). First trans diastereomer: ^1H NMR (250 MHz, $CDCl_3$) δ 1.32 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.44 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.96−2.19 (m, 2H), 2.83−2.91 (m, 1H), 3.86−4.12 (m, 2H), 4.28 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 4.63−4.72 (m, 2H), 4.91 (dd, $^2J_{HF}$ = 48.5 Hz, $^3J_{HH}$ = 5.8 Hz, 1H, C*H*F), 6.22 (d, $^3J_{HH}$ = 4.3 Hz, 1H, H_2); ^{19}F NMR (235 MHz, $CDCl_3$) δ −194.50 (dd, $^2J_{HF}$ = 48.5 Hz, $^3J_{HF}$ = 20.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.6, 14.0, 26.9 (d, $^3J_{CF}$ = 4.0 Hz), 46.9 (d, $^2J_{CF}$ = 20.9 Hz), 61.9, 67.5, 69.9, 87.5 (d, $^3J_{CF}$ = 5.0 Hz), 87.9 (d, $^1J_{CF}$ = 189.5 Hz), 167.7 (d, $^2J_{CF}$ = 23.9 Hz), 211.5. Second trans diastereomer: ^1H NMR (250 MHz, $CDCl_3$) δ 1.32 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.44 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 2.03−2.12 (m, 2H), 2.89 (dddt, $^3J_{HF}$ = 24.3 Hz, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 4.7 Hz, $^3J_{HH}$ = 1.2 Hz, 1H), 3.91−4.14 (m, 2H), 4.29 (m, 2H), 4.68 (m, 2H), 5.03 (dd, $^2J_{HF}$ = 48.7 Hz, $^3J_{HH}$ = 4.7 Hz, 1H, C*H*F), 6.14 (d, $^3J_{HH}$ = 4.7 Hz, 1H, H_2); ^{19}F NMR (235 MHz, $CDCl_3$) δ −199.04 (dd, $^2J_{HF}$ = 48.7 Hz, $^3J_{HF}$ = 24.2 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.7, 14.1, 25.9 (d, $^3J_{CF}$ = 3.9 Hz), 47.6 (d, $^2J_{CF}$ = 20.9 Hz), 62.0, 68.3, 70.1, 88.6 (d, $^3J_{CF}$ = 4.4 Hz), 87.9 (d, $^1J_{CF}$ = 190.0 Hz), 168.0 (d, $^2J_{CF}$ = 23.9 Hz), 211.7; IR (NaCl) 1760 cm^{-1}; MS (ESI, 11 eV) *m*/*z* (relative intensity) 319 ([M + Na]$^+$, 25), 197 (100), 177 (30), 175 (7), 155 (7); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{17}FO_4S_2Na$ 319.0450, found 319.0433.

Ethyl (2-Ethoxythiocarbonylsulfanyl-4-benzyloxy-5-benzyloxymethyltetrahydrofuran-3-yl)fluoroacetate (13). Prepared according to method A from **1** (0.30 g, 1.33 mmol), 1,4-anhydro-2-deoxy-3,5-di-*O*-benzyl-D-*erythro*-pent-1-enitol (0.43 g, 1.46 mmol) in 1,2-dichloroethane (15 mL), and lauroyl peroxide (0.16 g, 0.40 mmol) in 1,2-dichloroethane (3 mL). The solution was refluxed over 5 h after addition of lauroyl peroxide. The residue was purified by flash chromatography to afford **13** as a mixture of two diastereomers (1:1 ratio) (pentane/ethyl acetate 9:1) (pale yellow oil, 0.40 g, 57% yield). First diastereomer (2,3-trans): ^1H NMR (250 MHz, $CDCl_3$) δ 1.26 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.43 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 2.84−3.00 (m, 1H, H_3), 3.42−3.70 (m, 2H), 4.07−4.72 (m, 10H), 4.92 (dd, $^2J_{HF}$ = 49.4 Hz, $^3J_{HH}$ = 6.3 Hz, 1H, C*H*F), 6.34 (d, $^3J_{HH}$ = 2.7 Hz, 1H, H_2), 7.26−7.35 (m, 10H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −194.42 (dd, $^2J_{HF}$ = 49.4 Hz, $^3J_{HF}$ = 18.8 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.7, 14.0, 53.8 (d, $^2J_{CF}$ = 20.6 Hz), 62.1, 68.5, 70.1, 72.4, 73.5, 79.0 (d, $^3J_{CF}$ = 4.1 Hz), 83.0, 86.0 (d, $^1J_{CF}$ = 188.7 Hz), 86.6 (d, $^3J_{CF}$ = 6.3 Hz), 127.8, 127.8, 128.0, 128.4, 128.4, 128.5, 137.7, 167.8 (d, $^2J_{CF}$ = 23.9 Hz), 211.5. Second diastereomer (2,3-trans): ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.43 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 2.84−3.00 (m, 1H, H_3), 3.42−3.70 (m, 2H), 4.07−4.72 (m, 10H), 4.99 (dd, $^2J_{HF}$ = 49.4 Hz, $^3J_{HH}$ = 6.7 Hz, 1H, C*H*F), 6.33 (d, $^3J_{HH}$ = 3.0 Hz, 1H, H_2), 7.26−7.35 (m, 10H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −194.67 (dd, $^2J_{HF}$ = 49.4 Hz, $^3J_{HF}$ = 18.8 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.7, 14.0, 54.2 (d, $^2J_{CF}$ = 20.7 Hz), 62.1, 68.7, 70.1, 72.3, 73.5, 79.2 (d, $^3J_{CF}$ = 3.0 Hz), 83.6, 86.2 (d, $^1J_{CF}$ = 187.9 Hz), 87.9 (d, $^3J_{CF}$ = 6.0 Hz), 127.8, 127.8, 128.0, 128.4, 128.4, 128.5, 137.4, 168.0 (d, $^2J_{CF}$ = 23.9 Hz), 211.8; IR (NaCl) 1758 cm^{-1}; MS (ESI, 19 eV) *m*/*z* (relative intensity) 545 ([M + Na]$^+$, 35), 423 (100), 403 (33); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{31}FO_6S_2Na$ 545.1459, found 545.1444.

General Procedure for the Displacement of the Xanthate Function by a Nucleophile. The nucleophile (1.5 equiv) and then the Lewis acid (1.5 equiv) were added to a solution of **4** (1 equiv) in toluene cooled to −78 °C or −17 °C. The reaction was monitored by TLC (pentane/ethyl acetate 9:1), and after complete conversion, the mixture was filtered and washed with saturated aqueous $NaHCO_3$, dried with anhydrous $MgSO_4$, and evaporated under vacuum. The residue was purified by flash chromatography or by bulb-to-bulb distillation to give the desired products.

Ethyl (2-Cyanotetrahydrofuran-3-yl)fluoroacetate (11c). Prepared from **4** (mixture of 2 trans diastereomers in a 1:1 ratio, 0.50 g, 1.69 mmol), cyanotrimethylsilane (0.34 mL, 2.53 mmol), and tin(IV) chloride (0.30 mL, 2.53 mmol) in toluene (30 mL), at −78 °C for 5 min then at −17 °C for 2.5 h. The mixture was washed with saturated aqueous NaCl, dried with anhydrous $MgSO_4$, and evaporated under vacuum. The residue was purified by flash chromatography (pentane/ethyl acetate 3:7) to give **11c** in 83% yield (0.28 g) as a diastereomeric mixture (cis/trans = 7:93). First diastereomer (trans): ^1H NMR (250 MHz, $CDCl_3$) δ 1.34 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.99−2.31 (m, 2H), 3.06−3.18 (m, 1H, H_3), 3.93−4.09 (m, 2H), 4.32 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 4.71−4.77 (m, 1H, H_2), 4.92 (dd, $^2J_{HF}$ = 49.4 Hz, $^3J_{HH}$ = 5.3 Hz, 1H, C*H*F); ^{19}F NMR (235 MHz, $CDCl_3$) δ −196.35 (dd, $^2J_{HF}$ = 49.4 Hz, $^3J_{HF}$ = 21.2 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.6, 26.2 (d, $^3J_{CF}$ = 4.1 Hz), 47.7 (d, $^2J_{CF}$ = 20.9 Hz), 62.4, 67.4 (d, $^3J_{CF}$ = 5.5 Hz), 69.0, 87.1 (d, $^1J_{CF}$ = 190.6 Hz), 118.1, 167.4 (d, $^2J_{CF}$ = 23.9 Hz). Second diastereomer (trans): ^1H NMR (250 MHz, $CDCl_3$) δ 1.34 (t, $^3J_{HH}$

= 7.2 Hz, 3H), 1.99−2.31 (m, 2H), 3.06−3.18 (m, 1H, H_3), 3.93−4.09 (m, 2H), 4.32 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 4.71−4.77 (m, 1H, H_2), 4.86 (dd, $^2J_{HF}$ = 49.4 Hz, $^3J_{HH}$ = 6.0 Hz, 1H, C*H*F); ^{19}F NMR (235 MHz, $CDCl_3$) δ −194.85 (dd, $^2J_{HF}$ = 49.4 Hz, $^3J_{HF}$ = 21.2 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.0, 27.4 (d, $^3J_{CF}$ = 4.1 Hz), 47.5 (d, $^2J_{CF}$ = 20.1 Hz), 62.4, 66.6 (d, $^3J_{CF}$ = 6.2 Hz), 68.9, 87.6 (d, $^1J_{CF}$ = 189.3 Hz), 118.1, 167.4 (d, $^2J_{CF}$ = 23.9 Hz). Third diastereomer (cis): ^{19}F NMR (235 MHz, $CDCl_3$) δ −194.37 (dd, $^2J_{HF}$ = 47.1 Hz, $^3J_{HF}$ = 11.8 Hz); IR (NaCl) 1759 cm^{-1}; MS (EI, 70 eV) *m*/*z* (relative intensity) 201 ($M^{+\bullet}$, 2), 175 (81), 173 (81), 155 (76), 127 (35), 106 (83), 102 (87), 73 (100), 53 (85); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_9H_{12}FNO_3Na$ 224.0699, found 224.0688.

Ethyl [2-(5-Methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-tetrahydrofuran-3-yl]fluoroacetate (11h). 11h was isolated in 83% yield (0.42 g, pentane/ethyl acetate 3:7) (white solid, mp 96 °C) (cis/trans = 1:9) starting from **4** (mixture of two trans diastereomers in 64:36 ratio, 0.50 g, 1.69 mmol), *O*,*O*′-bistrimethylsilylthymine (0.69 g, 2.53 mmol), and silver triflate (0.65 g, 2.53 mmol) in toluene (30 mL). The yellow mixture was stirred in the dark at −17 °C for 1.5 h. By using copper(II) triflate (0.37 g, 1.01 mmol) as a Lewis acid for 3.5 h, **11h** was isolated in 76% yield (cis/trans = 1:9). First diastereomer (trans): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.91 (d, $^4J_{HH}$ = 1.0 Hz, 3H), 2.09−2.20 (m, 2H), 3.10−3.25 (m, 1H), 4.17−4.37 (m, 4H), 5.05 (dd, $^2J_{HF}$ = 48.1 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, C*H*F), 5.87 (d, $^3J_{HH}$ = 5.1 Hz, 1H, $H_{1'}$), 7.05 (m, 1H), 9.73 (sbr, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −197.99 (dd, $^2J_{HF}$ = 48.1 Hz, $^3J_{HF}$ = 22.6 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.4, 13.9, 27.8 (d, $^3J_{CF}$ = 3.3 Hz), 46.4 (d, $^2J_{CF}$ = 19.9 Hz), 62.2, 69.4, 88.3 (d, $^1J_{CF}$ = 188.7 Hz), 88.9 (d, $^3J_{CF}$ = 5.7 Hz), 110.8, 136.7, 150.2, 163.9, 168.0 (d, $^2J_{CF}$ = 23.9 Hz). Second diastereomer (trans): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, $^3J_{HH}$ = 7.3 Hz, 3H), 1.92 (d, $^4J_{HH}$ = 1.0 Hz, 3H), 2.23−2.34 (m, 2H), 3.10−3.25 (m, 1H), 3.88−4.08 (m, 4H), 4.90 (dd, $^2J_{HF}$ = 47.6 Hz, $^3J_{HH}$ = 5.7 Hz, 1H, C*H*F), 6.19 (d, $^3J_{HH}$ = 6.9 Hz, 1H, $H_{1'}$), 7.07 (m, 1H), 9.63 (sbr, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −203.67 (dd, $^2J_{HF}$ = 47.6 Hz, $^3J_{HF}$ = 33.9 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.6, 14.1, 27.3 (d, $^3J_{CF}$ = 4.3 Hz), 44.7 (d, $^2J_{CF}$ = 20.1 Hz), 62.2, 68.3, 87.2 (d, $^1J_{CF}$ = 186.2 Hz), 88.9 (d, $^3J_{CF}$ = 5.7 Hz), 110.3, 134.8, 150.5, 163.8, 167.5 (d, $^2J_{CF}$ = 23.9 Hz). Third diastereomer (cis): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.93 (d, $^4J_{HH}$ = 1.0 Hz, 3H), 2.27−2.34 (m, 2H), 3.10−3.25 (m, 1H), 4.03−4.37 (m, 4H), 5.38 (dd, $^2J_{HF}$ = 48.6 Hz, $^3J_{HH}$ = 2.9 Hz, 1H, C*H*F), 5.94 (d, $^3J_{HH}$ = 4.5 Hz, 1H, $H_{1'}$), 7.18 (m, 1H), 9.94 (sbr, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −202.89 (dd, $^2J_{HF}$ = 48.6 Hz, $^3J_{HF}$ = 35.3 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.5, 14.0, 23.5 (d, $^3J_{CF}$ = 5.2 Hz), 45.1 (d, $^2J_{CF}$ = 19.4 Hz), 62.2, 68.8, 85.9 (d, $^1J_{CF}$ = 188.7 Hz), 88.9 (d, $^3J_{CF}$ = 5.7 Hz), 110.3, 135.7, 151.1, 164.1, 168.1 (d, $^2J_{CF}$ = 23.9 Hz); IR (KBr) 1751, 1685 cm^{-1}; MS (EI, 70 eV) *m*/*z* (relative intensity) 300 ($M^{+\bullet}$, 5), 175 (18), 155 (100), 127 (40), 109 (11), 55 (13); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{17}FN_2O_5Na$ 323.1019, found 323.1009. Anal. Calcd for $C_{13}H_{17}FN_2O_5$: C, 52.00; H, 5.71; N, 9.33. Found: C, 52.37; H, 6.12; N, 9.28.

Ethyl [2-(5-Methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-4-benzyloxy-5-benzyloxymethyltetrahydrofuran-3-yl]fluoroacetate (14). 14 was isolated in 61% yield (0.12 g; pentane/ethyl acetate 3:2) (colorless oil) (dr = 46:54) starting from **13** (mixture of two trans diastereomers in 47:53 ratio) (0.20 g, 0.38 mmol), *O*,*O*′-bistrimethylsilylthymine (0.16 g, 0.57 mmol), and silver triflate (0.15 g, 0.57 mmol) in toluene (10 mL). The yellow mixture was stirred in the dark at 0 °C for 3 h. Major diastereomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.16 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.82 (d, $^4J_{HH}$ = 1.0 Hz, 3H), 3.05 (dq, $^3J_{HH}$ = 5.5 Hz, $^3J_{HF}$ = 25.4 Hz, 1H), 3.49 (m, 2H), 4.03−4.25 (m, 3H), 4.39−4.54 (m, 5H), 4.98 (dd, $^2J_{HF}$ = 47.9 Hz, $^3J_{HH}$ = 4.9 Hz, 1H, C*H*F), 6.11 (d, $^3J_{HH}$ = 6.0 Hz, 1H, $H_{1'}$), 7.14−7.32 (m, 11H), 8.82 (sbr, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −196.89 (dd, $^2J_{HF}$ = 47.9 Hz, $^3J_{HF}$ = 25.9 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.5, 13.9, 53.4 (d, $^2J_{CF}$ = 19.9 Hz), 62.3, 69.5, 72.5, 73.6, 80.0 (d, $^3J_{CF}$ = 3.1 Hz), 83.8, 85.8 (d, $^3J_{CF}$ = 5.7 Hz), 86.1 (d, $^1J_{CF}$ = 190.0 Hz), 111.3, 127.8, 127.9, 128.0, 128.2, 128.5, 128.6, 136.3, 137.1, 137.4, 150.0, 163.6, 167.7 (d, $^2J_{CF}$ = 23.3 Hz). Minor diastereomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.83 (d, $^4J_{HH}$ = 0.9 Hz, 3H), 2.85 (dq, $^3J_{HH}$ = 4.9 Hz, $^3J_{HF}$ = 26.2 Hz, 1H), 3.48 (m, 2H), 4.03−4.25 (m, 3H), 4.39−4.54 (m, 5H), 5.13 (dd, $^2J_{HF}$ = 48.2 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, C*H*F), 6.14 (d, $^3J_{HH}$ = 5.3 Hz, 1H, $H_{1'}$), 7.14−7.32 (m, 11H), 9.01 (sbr, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −196.03 (dd, $^2J_{HF}$ = 48.2 Hz, $^3J_{HF}$ = 28.2 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.6, 13.9, 55.2 (d, $^2J_{CF}$ = 20.1 Hz), 62.1, 69.6, 72.3, 73.6, 79.7 (d, $^3J_{CF}$ = 2.8 Hz), 85.1, 85.6 (d, $^1J_{CF}$ = 186.8 Hz), 86.4 (d, $^3J_{CF}$ = 5.0 Hz), 111.4, 127.8, 127.9, 128.0, 128.2, 128.5, 128.6, 135.1, 137.0, 137.4, 150.5, 163.7, 167.8 (d, $^2J_{CF}$ = 23.9 Hz); IR (NaCl) 1689 cm^{-1}; MS (ESI, 8 eV) *m*/*z* (relative intensity) 527 ($M^{+\bullet}$ + 1, 54), 401 (100), 311 (14), 293 (26), 185 (20), 169 (3), 127 (2); HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{32}FN_2O_7$ 527.2194, found 527.2192.

Ethyl [2-(5-Methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-4-hydroxy-5-hydroxymethyltetrahydrofuran-3-yl]fluoroacetate (15). A solution of **14** (84 mg, 0.16 mmol) (mixture of two diastereomers in 44:56 ratio) in absolute ethanol (5 mL) with 10% Pd/C (100 mg) was stirred under H_2 overnight at room temperature. The solution was filtered and concentrated. The resulting solid was purified by filtration on silica gel to give a white solid in 98% yield (54 mg) (dr = 44:56). Major diastereomer: ^{1}H NMR (400 MHz, MeOD) δ 1.32 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.93 (d, $^4J_{HH}$ = 1.2 Hz, 3H), 3.21 (ddt, $^3J_{HF}$ = 28.2 Hz, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 2.8 Hz, 1H, $H_{2'}$), 3.67 (m, 1H), 3.82 (t, $^2J_{HH}$ = $^3J_{HH}$ = 2.4 Hz, 1H), 4.06−4.39 (m, 4H), 5.39 (dd, $^2J_{HF}$ = 47.1 Hz, $^3J_{HH}$ = 3.2 Hz, 1H, C*H*F), 6.04 (d, $^3J_{HH}$ = 6.8 Hz, 1H, $H_{1'}$), 7.55 (m, 1H); ^{19}F NMR (235 MHz, MeOD) δ −204.96 (dd, $^2J_{HF}$ = 47.1 Hz, $^3J_{HF}$ = 28.2 Hz); ^{13}C NMR (62.9 MHz, MeOD) δ 13.3, 15.0, 54.7 (d, $^2J_{CF}$ = 19.1 Hz), 63.8, 64.0, 71.6 (d, $^3J_{CF}$ = 3.4 Hz), 87.0, 87.2 (d, $^1J_{CF}$ = 186.2 Hz), 88.0 (d, $^3J_{CF}$ = 4.4 Hz), 112.9, 138.5, 153.4, 167.1, 170.5 (d, $^2J_{CF}$ = 23.3 Hz). Minor diastereomer: ^{1}H NMR (400 MHz, MeOD) δ 1.24 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.96 (d, $^4J_{HH}$ = 1.2 Hz, 3H), 2.96 (dddd, $^3J_{HF}$ = 28.2 Hz, $^3J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 5.2 Hz, $^3J_{HH}$ = 3.2 Hz, 1H, $H_{2'}$), 3.63 (m, 1H), 3.85 (t, $^2J_{HH}$ = $^3J_{HH}$ = 2.4 Hz, 1H), 4.06−4.39 (m, 4H), 5.35 (dd, $^2J_{HF}$ = 47.1 Hz, $^3J_{HH}$ = 2.8 Hz, 1H, C*H*F), 6.06 (d, $^3J_{HH}$ = 5.2 Hz, 1H, $H_{1'}$), 7.63 (m, 1H); ^{19}F NMR (235 MHz, MeOD) δ −203.13 (dd, $^2J_{HF}$ = 47.1 Hz, $^3J_{HF}$ = 28.2 Hz); ^{13}C NMR (62.9 MHz, MeOD) δ 13.2, 15.2, 56.9 (d, $^2J_{CF}$ = 19.6 Hz), 62.8, 63.0, 70.9 (d, $^3J_{CF}$ = 5.1 Hz), 86.4 (d, $^3J_{CF}$ = 5.0 Hz), 86.9 (d, $^1J_{CF}$ = 188.1 Hz), 88.3, 112.9, 140.1, 152.9, 167.2, 170.5 (d, $^2J_{CF}$ = 23.3 Hz); IR (KBr) 1686 cm^{-1}; MS (ESI, 8 eV) *m*/*z* (relative intensity) 347 ($M^{+\bullet}$ + 1; 41), 221 (100), 185 (16), 173 (33), 153 (11), 127 (53); HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{20}FN_2O_7$ 347.1255, found 347.1250.

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Supporting Information Available: Preparation of compounds **2a**, **2c**,**d**, **3**, **5**, **6**, **9**, **11a**,**b**, **11d**−**g**, and **11i**; selected ^{1}H and ^{13}C NMR spectra of compounds **1**, **2a**−**d**, **3**−**6**, **9**, **11c**−**i**, and **13**−**15**; and 2D HOESY or NOESY NMR experiments of compounds **3**−**6**, **11c**, **11e**, **11h**, and **13**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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