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Modular Synthesis of 5-Substituted Thiophen-2-yl *C*-2′-Deoxyribonucleosides

Jan Bárta,[†] Radek Pohl,[†] Blanka Klepetářová,[†] Nikolaus P. Ernsting,[‡] and Michal Hocek*[,†,§]

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Gilead Sciences & IOCB Research Center, CZ-16610, Prague 6, Czech Republic, and Institut für Chemie, Humboldt Universität zu Berlin, Brook-Taylor-Str. 2, D-12489 Berlin, Germany

hocek@uochb.cas.cz

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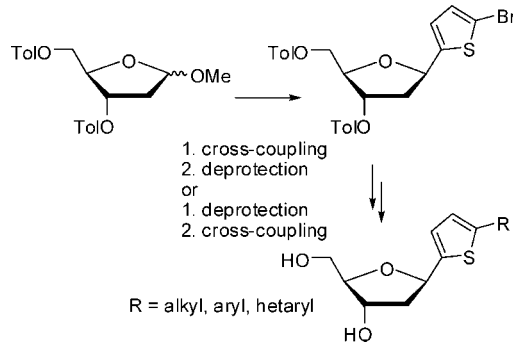

A new modular methodology of preparation of 5-substituted thiophene-2-yl *C*-nucleosides was developed. A Friedel−Crafts-type of C-glycosidation of 2-bromothiophene with toluoyl-protected methylglycoside **2** gave the desired protected 1β-(5-bromothiophen-2-yl)-1,2-dideoxyribofuranose **4a** in 60%. The key intermediate **4a** was then subjected to a series of palladium-catalyzed cross-coupling reactions. The cross-coupling reactions with alkyl organometallics gave β-(5-alkylthiophen-2-yl)-2-deoxyribonucleosides **4** and **7** in moderate yields accompanied by side-products of reduction. On the other hand, cross-couplings with arylstannanes proceeded smoothly to give a series of β-(5-arylthiophen-2-yl)-2-deoxyribonucleosides **4** in good yields. Deprotection of toluoylated nucleosides by NaOMe in MeOH and silylated nucleosides by $Et_3N \cdot 3HF$ gave a series of free *C*-nucleosides **6**. Alternatively, other types of 5-arylthiophene *C*-nucleosides **6** were prepared in one step by the aqueous-phase cross-coupling reactions of unprotected 1β-(5-bromothiophen-2-yl)-1,2-dideoxyribofuranose with boronic acids. Title 5-arylthiophene *C*-nucleosides **6** exhibit interesting fluorescent properties with emission maxima varying from 339 to 396 nm depending on the aryl group attached.

Introduction

C-Nucleosides bearing hydrophobic aryl groups as nucleobase surrogates attracted great attention due to their use in the extension of the genetic alphabet.[1] In oligonucleotide duplexes, they selectively pair with the same of other hydrophobic nucleobases due to increased stacking and favorable desolvation energy as compared to canonical hydrophilic nucleobases.[2] Triphosphates of some of the *C*-nucleosides are efficiently incorporated to DNA by DNA polymerase.[3]

Biaryl *C*-nucleosides are of particular interest because of largely extended stacking and formation of very stable duplexes.[4] Both theoretical calculations[5] and experimental (NMR structure) results[6] confirmed that they form a stacked pair within the B-DNA duplex. On the other hand, incorporation of bulky

[†] Academy of Sciences of the Czech Republic.
[‡] Humboldt Universität zu Berlin.
[§] Phone: +420 220183324. Fax: +420 220183559.

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biaryl *C*-nucleoside into the duplex opposite to the purine or pyrimidine nucleobase causes local disruption of the stacking.[7] Very recently, donor- and acceptor-modified biphenyl *C*-nucleoside-containing oligonucleotide was used[8] for recognition of another hydrophobic modification in the opposite strand or even of a bulge position. Moreover, oligoaryl *C*-nucleosides have been used by Kool et al.[9]for construction of fluorescent oligonucleotide probes. Some related biaryl *N*-nucleosides have been used as nucleoside fleximers[10] and for major groove recognition of the GC pair.[11]

There are several synthetic approaches[12] to *C*-nucleosides: (i) additions of organometallics to ribono- or 2-deoxyribonolactones,[3,13] (ii) coupling of a halogenose with organometallics,[14] (iii) electrophilic substitutions of electron-rich aromatics with sugars under Lewis acid catalysis,[15] or (iv) Heck-type coupling of aryl iodides with glycals.[16] However, none of them is truly general, and many of them suffer from poor selectivity and low yields. Therefore, the development of modular approaches to the synthesis of these important compounds is of great interest.

We are currently involved in development of modular methodologies based on larger scale syntheses of versatile *C*-nucleoside intermediates and their further use for generation of a series of diverse derivatives. We have already developed modular syntheses of 3- and 4-substituted benzene *C*-nucleosides,[17] 6-substituted pyridin-2-yl *C*-nucleosides,[18] and 6-substituted pyridin-3-yl *C*-nucleosides[19] by the preparation of a general halogenated *C*-arylnucleoside intermediate followed by displacement of the bromine for alkyl, aryl, or amino substituents by cross-coupling reactions. Here, we wish to report on a modular synthesis of diverse 5-substituted thiophen-2-yl *C*-nucleosides. Thiophene as a sulfur heterocycle should not be a good H-acceptor in the minor groove, and thus the nucleosides could be used for further studies on the role of the H-bonding for the fidelity of polymerases. Unsubstituted and 5-methylthiophene deoxyribonucleosides were prepared and incorporated to oligonucleotides by Romesberg and found to form stable and selective self-pairs.[20] Moreover, oligoaryl thiophene nucleosides[9] are fluorescent which makes the target aryl-substituted thiophene nucleosides potential candidates for fluorescent labeling of nucleic acids.

Results and Discussion

The two known thiophene *C*-nucleosides were reported[21,20] to be prepared by addition of lithiothiophene to lactol followed by cyclization and deprotection. The first two steps are not stereoselective, and the whole sequence gives ca. 15% overall yields with two difficult separations of epimers. Our selected approach of choice for the synthesis of a series of 5-substituted thiophen-2-yl *C*-nucleosides was based on the synthesis of a suitably protected 5-bromothiophen-2-yl *C*-nucleoside intermediate and on its further synthetic transformations (cross-coupling, amination). To efficiently prepare this key intermediate, we have tried several synthetic pathways based on analogy with some known related nucleosides. After initial unsuccessful attempts on additions of 2-bromo-5-lithiothiphene to protected 2-deoxyribonolactone (in analogy to ref 22) followed by reduction by Et_3SiH in the presence of $BF_3 \cdot Et_2O$ which unfortunately lead only to products of elimination, we have focused on the Friedel−Crafts-type C-glycosidation.[15] 2-Bromothiophene is an electron-rich aromatic system which should be reactive enough for this type of reaction. Applying conditions found in the literature,[15c] either halogenose **1** or methyl glycoside **2** was used as starting material. The reaction of chloro-sugar **1** with 2-bromothiophene **3** in the presence of $BF_3 \cdot Et_2O$ gave the desired β-(5-bromothiophen-2-yl) *C*-nucleoside **4a** in 22% yield and another 22% of undesired α-anomer **5a** (Scheme 1). The same reaction using $AgBF_4$ as Lewis acid gave β-anomer **4a** in improved 54% yield and α-anomer **5a** in 14% yield. The Friedel−Crafts reactions of more stable and easily available methyl glycoside **2** with **3** in the presence of $SnCl_4$ and $AgOCOCF_3$ gave the desired β-*C*-nucleoside **4a** in excellent 60% yield, while the α-anomer **5a** was formed only in 25% yield. The anomers **4a** and **5a** were reasonably well separable by column chromatography using 2.5% ethyl acetate in hexane to efficiently get pure β-anomeric key intermediate **4a** in

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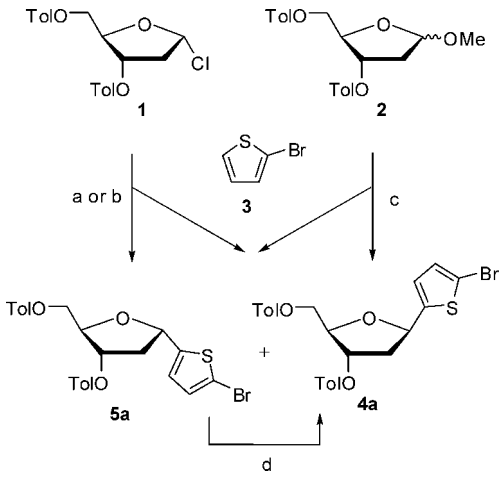
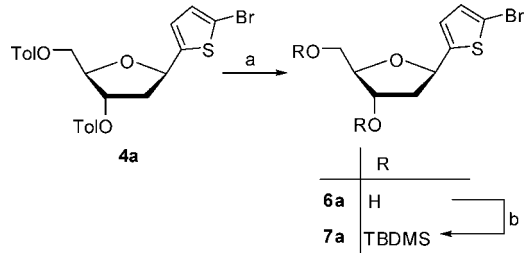
SCHEME 1. Preparation of the Key Intermediate by C-Glycosidation of 2-Bromothiophene[a]



[a] Reagents and conditions: (a) $BF_3 \cdot Et_2O$, DCM, −10 °C, 100 min, **4a** (22%) and **5a** (22%); (b) $AgBF_4$, DCM, −10 °C, 10 min, **4a** (54%) and **5a** (14%); (c) $AgOCOCF_3$, $SnCl_4$, DCM, −20 °C, 10 min, **4a** (60%) and **5a** (25%); (d) TFA, BSA, DCM, 42 °C, 22 h, **4a** (25%).

SCHEME 2. Protecting Group Manipulations[a]



[a] Reagents and conditions: (a) methanol, MeONa, rt, 24 h, 93%; (b) TBDMSCl, imidazole, rt, 24 h, 94%.

multigram amounts. Nevertheless, we have also tried epimerization of the α-anomeric side product **5a** using a mixture of benzenesulfonic acid (BSA) and trifluoroacetic acid (TFA) in dichloromethane at 40 °C for 22 h to give a mixture containing only 25% of *β*-anomer **4a**. Apparently, the epimerization of **5a** is not an efficient way for preparation of an additional amount of intermediate **4a**.

Subsequent deprotection of intermediate **4a** under Zemplen conditions (NaOMe/MeOH) gave free *β*-*C*-nucleoside **6a** in 93% yield which was further silylated with TBDMSCl to give persilylated intermediate **7a** in 94% yield (Scheme 2).

Having the optimized multigram-scale procedures for the synthesis of the protected 5-bromothiophen-2-yl *C*-nucleosides **4a** and **7a** in hand, we have studied further functional group transformations (Scheme 3, Table 1). At first, we tried to convert bromothiophene nucleoside **4a** to unsubstituted thiophene **4b**. Thus, catalytical hydrogenation of bromothiophene nucleoside **4a** using H_2 under Pd/C in a mixture of EtOH, THF, and H_2O gave the desired thiophene nucleoside **4b** in 95% yield (Table 1). Deprotection under Zemplen conditions afforded the free thiophene nucleoside **6b** in 81% yield.

Then we focused on the introduction of alkyl substituents which were in benzene and pyridine series easily introduced by cross-couplings with trialkylaluminum or alkylzinc halide reagents. Several cross-coupling reactions of either toluoyl- (**4a**) or TBS-protected (**7a**) bromothiophene nucleosides with trialkylaluminums, alkylzinc chlorides, or alkylmagnesium bromides have been tried. However, in most cases, complex unseparable mixture products of cross-coupling **4c**−**4e** or **7c**−**7e** with products of reduction **4b** or **7b** were obtained (Table 1, entries 3−11). For the methylation, the Suzuki−Miyaura reaction of **4a** and **7a** with methylboronic acid has also been tried. While the reaction of toluoyl-protected **4a** gave the mixture of **4c/4b** in a ratio of 6:1, the reaction of TBS-protected **7a** gave the analogous mixture **7c/7b** in 9:1 ratio in acceptable 73% yield. The desired methyl derivatives **4c** or **7c** were not isolable in pure form at this stage, and therefore the mixtures were directly deprotected. Toluoylated nucleosides **4c/4b** were cleaved using NaOMe/MeOH, while the silylated **7c/7b** were deprotected making use of $Et_3N \cdot 3HF$.[23] The resulting mixture of **6b** and **6c** was separable on column chromatography to give the desired 5-methylthienyl *C*-nucleoside **6c** in 39% or 33% overall yield from **4a** or **7a**, respectively. Our further efforts focused on introduction of an ethyl group. However, the Suzuki coupling reaction of **4a** with ethylboronic acid under analogous conditions to methylation gave only the product of reduction, **4b** (entry 8). The Negishi coupling of **7a** with EtZnCl gave an unseparable mixture of desired **7d** and reduced **7b** in excellent yield and a ratio of 4:1 (entry 9). Deprotection followed by separation of the mixture gave the target free nucleoside **6d** in 53% overall yield from **7a**. Finally, benzylation was attempted by reaction of **4a** with BnZnCl giving only the product of reduction in low yield. Ni-catalyzed coupling of **7a** with BnMgCl gave a complex unseparable mixture which was directly deprotected using $Et_3N \cdot 3HF$. Careful column chromatography of the resulting mixture of free nucleosides furnished the desired pure benzylthiophene nucleoside **6e** in acceptable 32% overall yield from **7a**. Apparently, the introduction of alkyl substituents by cross-coupling reactions of **4a** or **7a** is not very practical due to the side-reaction (reduction); however, it is still possible to use it for the synthesis of these compounds.

Then our attention turned to the introduction of aryl and hetaryl groups. Toluoyl-protected *β*-*C*-deoxribonucleoside **4a** was used as a starting compound for the Stille cross-coupling reactions with aryl stannanes in the presence of $PdCl_2$dppf in DMF (entries 12−15). In all cases, the reactions proceeded smoothly to give the target protected biaryl *β*-*C*-nucleosides **4f**−**4i** in good yields. In the case of **4f** and **4i**, even after repeated column chromatography, the products were still impured by stannanes. Therefore, the crude products after chromatography were treated with Me_3Al in toluene to destroy the stannane impurities and rechromatographed to give pure products in ca. 65% yields. Deprotection using MeONa in MeOH gave the free *β*-biaryl-*C*-deoxyribonucleosides **6f**−**6i** in good yields.

Hartwig−Buchwald aminations[24] were performed to introduce N-substituents to thiophene.[25] These reactions were successfully used for amination of halopyridine *C*-nucleosides.[18–19] Lithium bis(trimethylsilyl)amide ($LiN(SiMe_3)_2$) was used as an ammonia equivalent for introduction of the amino group, but reaction gave only products of degradation. It is not surprising since aminothiophenes are known to be very unstable in unprotected form.[26] Therefore, we focused on the introduction of a dimethylamino group. The reaction of **7a** with dimethylamine proceeded only when Pd_2dba_3 catalyst was used in combination with bdtbp as a ligand (entry 18) to give a complex

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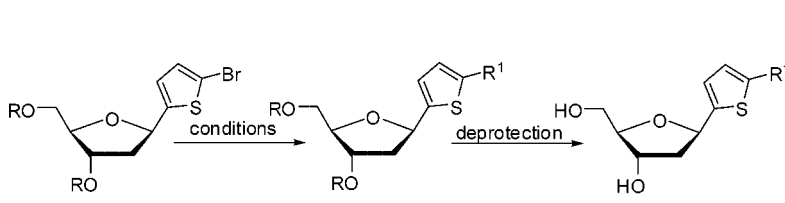
SCHEME 3. Cross-Couplings, Aminations, and Deprotections of 5-Bromothiophene *C*-Nucleosides 4a and 7a



4,6,7	R^1
a	Br
b	H
c	Me
d	Et
e	Bn
f	pyridin-2-yl
g	thiophen-2-yl
h	furan-2-yl
i	2,2′-bipyridin-6-yl
j	NH_2
k	NMe_2

TABLE 1. Reagents, Conditions, and Yields of Reactions

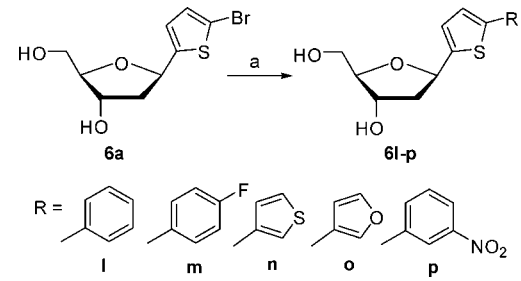
entry	reagent	start compd	catalyst, ligand (base)	solvent	conditions	coupling product	yield (%)	deprot. product	yield (%)
1	H_2	**4a**	Pd/C, Et_3N	THF/EtOH/H_2O	rt, 101 kPa	**4b**	95	**6b**	81
2	H_2	**7a**	Pd/C, Et_3N	THF/EtOH/H_2O	rt, 101 kPa	**7b**	98	**6b**	78
3	Me_3Al	**4a**	$Pd(PPh_3)_4$	THF	12 h/105 °C	**4c/4b**[a]	48 (1:1)		
4	MeZnCl	**4a**	Pd_2dba_3, bdtbp[b]	THF	24 h/70 °C	**4c/4b**[a]	80 (2:1)		
5	$MeB(OH)_2$	**4a**	$Pd(PPh_3)_4$, K_2CO_3	toluene	43 h/115 °C	**4c/4b**[a]	60 (6:1)	**6c**	74
6	$MeB(OH)_2$	**7a**	$Pd(PPh_3)_4$, K_2CO_3	toluene	24 h/115 °C	**7c/7b**[a]	73 (9:1)	**6c**	50
7	EtZnCl	**4a**	Pd_2dba_3, bdtbp	THF	2 h/rt	**4d/4b**[a]	73 (1:2)		
8	$EtB(OH)_2$	**4a**	$Pd(PPh_3)_4$, K_2CO_3	toluene	24 h/115 °C	**4b**[c]	76		
9	EtZnCl	**7a**	Pd_2dba_3, bdtbp	THF	48 h/85 °C	**7d/7b**[a]	93 (4:1)	**6d**	73
10	BnZnBr	**4a**	$Pd(PPh_3)_4$	THF	71 h/60 °C	**4b**	27		
11	BnMgCl	**4a**	$NiCl_2$(dppp)	THF	14 h/85 °C	ni[d]		**6e**	32[e]
12	2-Bu_3Sn-Py[f]	**4a**	$PdCl_2$, dppf[g]	DMF	29 h/115 °C	**4f**	66	**6f**	95
13	2-Bu_3Sn−Th[h]	**4a**	$PdCl_2$, dppf	DMF	16 h/110 °C	**4g**	90	**6g**	93
14	2-Bu_3Sn-Fu[i]	**4a**	$PdCl_2$, dppf	DMF	22 h/120 °C	**4h**	89	**6h**	94
15	6-Bu_3Sn-biPy[j]	**4a**	$PdCl_2$, dppf	DMF	22 h/100 °C	**4i**	64	**6i**	65
16	$LiN(SiMe_3)_2$	**7a**	Pd_2dba_3, P(*t*-Bu)$_3$HBF$_4$		48 h/rt		degrad.		
17	$Me_2NH\cdot HCl$	**7a**	$Pd(OAc)_2$, Josiphos[k], *t*-BuONa	DME	72 h/65 °C		nr		
18	Me_2NH/THF	**7a**	Pd_2dba_3, bdtbp, *t*-BuONa	toluene	7 h/70 °C	**7k**	49[l]		

[a] Unseparable mixture. [b] bdtbp = (2-biphenyl)di-*tert*-butylphosphine. [c] Reaction gave only the product of reduction. [d] Not isolated. [e] Overall yield after two steps. [f] 2-Bu_3Sn-Py = 2-tributylstannylpyridine. [g] dppf = 1,1′-bis(diphenylphosphino)ferrocene. [h] 2-Bu_3Sn−Th = 2-tributylstannylthiophene. [i] 2-Bu_3Sn-Fu = 2-tributylstannylfurane. [j] 6-Bu_3Sn-biPy = 6-(tributylstannyl)[2,2′]bipyridine, prepared in situ from 6-bromo-2,2′-bipyridine. [k] Josiphos = (*R*)-(−)-1-[(*S*)-2-(dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine. [l] Product quickly decomposed.

mixture out of which the desired (dimethylamino)thiophene **7k** was isolated in 49% yield. However, compound **7k** was very unstable, and any attempts to deprotect it led to complex mixtures of decomposition products only. Therefore, it can be concluded that Pd-catalyzed aminations are not suitable for introduction of N-constituents in thiophene *C*-nucleosides.

Recently, we became interested in applications of aqueous-phase cross-coupling reactions for direct and efficient functionalizations of unprotected nucleosides.[27] Therefore, we have tested this approach in thiophene *C*-nucleosides. The unprotected *β*-*C*-nucleoside **6a** was used for the aqueous-phase Suzuki−Miyaura cross-coupling reactions with a variety of arylboronic acids in the presence of $Pd(OAc)_2$, TPPTS (P(Ph-$SO_3Na)_3$) ligand, and Cs_2CO_3 as a base (Scheme 4, Table 2). The reactions were performed in a mixture of acetonitrile/water (2:1) for 2−4 h at 90−120 °C to give biaryl *β*-*C*-nucleosides **6l**−**6p** in very good yields (Table 2). This approach is the most efficient to attach an aryl or hetaryl group whenever the corresponding boronic acid is available.

SCHEME 4. Suzuki−Miyaura Reaction[a]



[a] Reagents and conditions: (a) R-$B(OH)_2$, Cs_2CO_3, $Pd(OAc)_2$, TPPTS, H_2O/MeCN (2:1), 2−5 h, 90−120 °C.

TABLE 2. Suzuki−Miyaura Reaction

entry	reagent	conditions	product	yield (%)
1	$PhB(OH)_2$	3 h/90 °C	**6l**	72
2	4-F-$PhB(OH)_2$	4 h/120 °C	**6m**	80
3	3-$ThB(OH)_2$[a]	4 h/120 °C	**6n**	70
4	3-$FuB(OH)_2$[b]	2 h/90 °C	**6o**	78
5	3-NO_2−$PhB(OH)_2$	2 h/90 °C	**6p**	74

[a] 3-$ThB(OH)_2$ = 3-thienylboronic acid. [b] 3-$FuB(OH)_2$ = 3-furylboronic acid.

All compounds were fully characterized, and the crystal structures of **6l** and **6n** were also determined by X-ray diffraction

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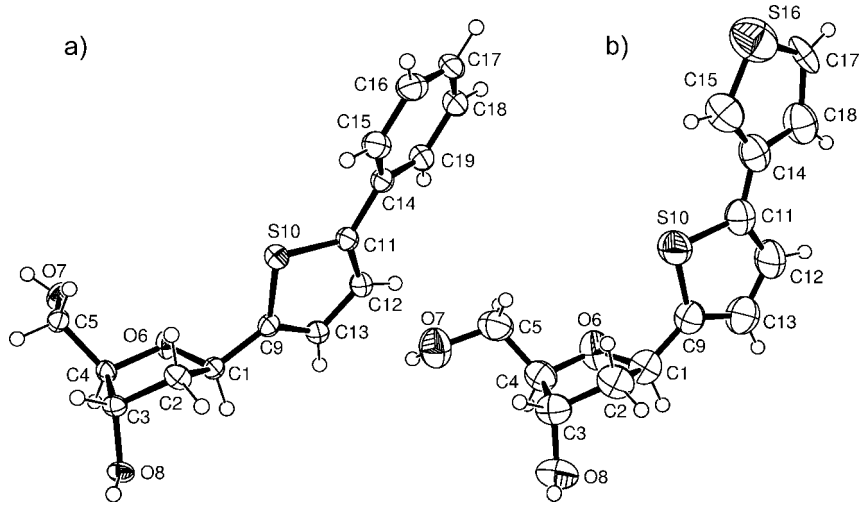

FIGURE 1. ORTEP drawings of crystal structures of **6l** (a) and **6n** (b) with the atom numbering scheme. Thermal ellipsoids are drawn at the 50% probability level.

(Figure 1). Both these *C*-nucleosides in the solid state occur in the expected C2′-endo conformation. No inter- or intramolecular hydrogen bonds were observed to the S10 sulfur atom which confirms our assumption that the thiophene *C*-nucleosides should not form minor-groove H-bonds in the active site of DNA polymerase.

Absorption and fluorescence spectra of the final *C*-nucleosides have been studied. Spectral changes when 1β-(2-thienyl)-2-deoxyribose is substituted at the 5-position of the thiophene moiety by different aryl groups have been observed (Figure 2, Table 3 and Table S1 in Supporting Information). When 1β-(2-thienyl)-2-deoxyribose is substituted at the 5-position of the thiophene moiety by aryl groups, electronic coupling of the two chromophores produces $\pi\pi^*$ absorption bands which peak in the range 280−310 nm. Figure 2a shows the spectra of phenyl and fluorophenyl derivatives **6l** (red) and **6m** (blue). Figure 2b collects the optical spectra when the second moiety is furan, while the analogous dithiophenes are shown in Figure 2c. The conjugated electron system is longer when the extending moiety is connected at its 2-position, which is why **6h** and **6g** have their absorption maxima at $\lambda > 300$ and fluorescence at 360 and 374 nm, respectively, while the corresponding 3-linked analogues **6n** and **6o** are blue-shifted both in absorption and fluorescence (blue curves in Figure 2b,c). Pyridine- and bipyridine-extension **6f** and **6i** leads to the significantly red-shifted spectra in Figure 2d. We did not observe fluorescence from the 5-(3-nitrophenyl)-thiophene derivative **6p** and the bromo-, alkyl-, and amino-substituted derivatives **6a**−**d** and **6k**.

In general, the substitution of the 5-position in thiophene *C*-nucleosides by diverse aryl groups can be used for fine-tuning of the absorption and fluorescent spectral maxima. Compounds **6f**−**6i** having absorption maxima at >300 nm may be good candidates for selective excitation within DNA at these wavelengths. Stokes shifts between absorption and fluorescence peaks are normal ($\approx$5500 cm^{-1}), and mirror symmetry between the $S_1 \leftarrow S_0$ and $S_1 \rightarrow S_0$ bands is observed. The only exception to mirror symmetry is given by **6i**, indicating close-lying bright singlet states. In applications, the exact form of the fluorescence spectrum may be required, for example, when energy transfer rates are to be calculated from the overlap with the acceptor absorption spectrum.[28] For this purpose the fluorescence spectra F($\tilde{\nu}$) are described by a log-normal function[29] (see Supporting Information, Table S1 and equation 1).

Conclusions

A new modular methodology for the synthesis of diverse 5-substituted thiophen-2-yl *C*-2′-deoxyribonucleosides has been developed based on the Friedel−Crafts-type C-glycosidation of 2-bromothiophene followed by functional group transformations of the bromine. It can be easily reduced off to efficiently give unsubstituted thiophene nucleosides (**6b** was prepared in 46% overal yield compared to 15% by the literature procedure[21]). Cross-coupling reactions of protected bromothiophene intermediates with alkylzinc, -magnesium, -aluminum, and/or -boronic acids proceeds usually with simultaneous dehalogenation, and the isolation of the desired alkylthiophene nucleosides is very problematic at the protected stage. However, the separation is achievable after deprotection, so still the method can be relatively efficiently used for the preparation of alkylthiophene *C*-nucleosides (e.g., **6c** was prepared in 22% overal yield compared to 16% by the literature procedure[20]). Hartwig−Buchwald reactions were not suitable for amination of the intermediates due to instability of the aminothiophenes. On the other hand, arylations proceeded very smoothly both using the Stille coupling of protected intermediates with arylstannanes in DMF and using the Suzuki reaction of free nucleoside with arylboronic acids. Most of the 5-aryl- and 5-hetarylthiophene C-nucleosides exhibit fluorescence with emission maxima strongly depending on the nature of the aryl groups. Since the aryl group is attached in the last step(s) via arylstannanes or arylboronic acids (hundereds of diverse reagents of these types are commercially available), the arylation is practical for fine-tuning of the fluorescent properties of the nucleosides. We plan to apply some of these or related nucleosides for incorporation to DNA and/or for fluorescent DNA labeling.

Experimental

1β-(5-Bromothiophen-2-yl)-1,2-dideoxy-3,5-di-*O*-toluoyl-D-ribofuranose (4a) and 1α-(5-Bromothiophen-2-yl)-1,2-dideoxy-3,5-di-*O*-toluoyl-D-ribofuranose (5a). To a dried flask containing a

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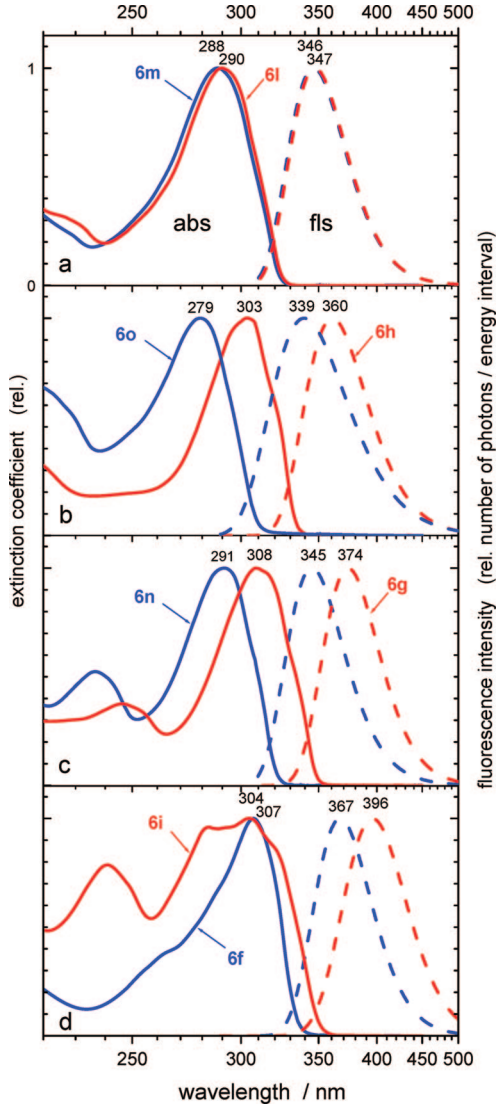

FIGURE 2. Optical spectra of substituted thiophene nucleosides in acetonitrile. Solid lines: absorption. Dashed lines: fluorescence. Peak wavelengths are given as insets.

TABLE 3. Absorption and Fluorescence Band Positions in Acetonitrile

compound	absorption/nm	fluorescence/nm
6f	307	367
6g	308	374
6h	303	360
6i	304	396
6l	290	347
6m	288	346
6n	291	345
6o	279	339
6p	277/295sh[a]	–

[a] sh = shoulder.

solution of the methyl glycoside **2** (4 g, 10.4 mmol) and 2-bromothiophene **3** (3.02 mL, 31.2 mmol) in dry dichloromethane (64 mL) at −20 °C under argon was added $AgOCOCF_3$ (3.45 g, 15.6 mmol) in one portion. After 5 min stirring, $SnCl_4$ (730 μL, 6.24 mmol) was added by syringe, and the mixture was stirred at −20 °C for 10 min. After quenching of the reaction by saturated Na_2CO_3(250 mL), 2% aqueous NH_3 solution (100 mL) was added (for better solubility of Ag and Sn complexes). The mixture was extracted with EtOAc (3 × 70 mL) and washed with saturated $NaHCO_3$ (3 × 50 mL) and saturated NaCl (1 × 100 mL). Then the collected organic layers were dried over $MgSO_4$, and solvents were evaporated under a vacuum. Products were isolated by flash chromatography on silica gel in gradient hexane to hexane/EtOAc (19.5/0.5) to give the desired product **4a** (3.21 g, 60%) followed by α-anomer **5a** (1.34 g, 25%). Compound **4a** was crystallized from isopropanol/heptane to obtain white crystals (mp: 71−72 °C). MS (FAB) *m/z* 515 (M + H). HRMS (FAB) for $C_{25}H_{24}BrO_5S$ [M + H] calculated 515.0528, found 515.0516. ^{1}H NMR (600 MHz, $CDCl_3$): 2.34 (ddd, 1H, J_{gem} = 13.8, $J_{2'b,1'}$ = 10.7, $J_{2'b,3'}$ = 6.0, H-2′b); 2.41 and 2.42 (2 × s, 2 × 3H, CH_3-Tol); 2.56 (ddd, 1H, J_{gem} = 13.8, $J_{2'a,1'}$ = 5.1, $J_{2'a,3'}$ = 1.2, H-2′a); 4.49 (td, 1H, $J_{4',5'}$ = 4.0, $J_{4',3'}$ = 2.0, H-4′); 4.59 (d, 2H, $J_{5',4'}$ = 4.0, H-5′); 5.40 (ddt, 1H, $J_{1',2'}$ = 10.7, 5.1, $J_{1',3}$ = 0.8, $J_{1',3'}$ = 0.5, H-1′); 5.59 (dddd, 1H, $J_{3',2'}$ = 6.0, 1.2, $J_{3',4'}$ = 2.0, $J_{3',1'}$ = 0.5, H-3′); 6.79 (dd, 1H, $J_{3,4}$ = 3.7, $J_{3,1'}$ = 0.8, H-3); 6.89 (d, 1H, $J_{4,3}$ = 3.7, H-4); 7.24 and 7.26 (2 × m, 2 × 2H, H-*m*-Tol); 7.95 (m, 4H, H-*o*-Tol). ^{13}C NMR (151 MHz, $CDCl_3$): 21.64 and 21.67 (CH_3-Tol); 41.6 (CH_2-2′); 64.4 (CH_2-5′); 76.8 (CH-3′); 76.9 (CH-1′); 83.0 (CH-4′); 112.1 (C-5); 125.0 (CH-3); 126.7 and 126.95 (C-*i*-Tol); 129.1 and 129.2 (CH-*m*-Tol); 129.3 (CH-4); 129.67 and 129.69 (CH-*o*-Tol); 143.8 and 144.2 (C-*p*-Tol); 145.5 (C-2); 165.95 and 166.25 (CO). IR spectrum (CCl_4): 3095, 3065, 1726, 1631, 1448, 1377, 1310, 1298, 1268, 1248, 1209, 1178, 1119, 1102 cm^{-1}. α^{20}_D +4.2 (*c* 2.64, $CHCl_3$). Anal. Calcd $C_{25}H_{23}BrO_5S$ (515.4): C, 58.26; H, 4.50. Found: C, 58.02; H, 4.47. Compound **5a**: colorless oil. MS (FAB) *m/z* 515 (M + H). HRMS (FAB) for $C_{25}H_{24}BrO_5S$: [M + H] calculated 515.0528, found 515.0523. ^{1}H NMR (500 MHz, $CDCl_3$): 2.40 (ddd, 1H, J_{gem} = 14.0, $J_{2'b,1'}$ = 4.6, $J_{2'b,3'}$ = 3.0, H-2′b); 2.41 (s, 6H, CH_3-Tol); 2.91 (ddd, 1H, J_{gem} = 14.0, $J_{2'a,1'}$ = 7.7, $J_{2'a,3'}$ = 6.8, H-2′a); 4.52 (dd, 2H, J_{gem} = 11.8, $J_{5'b,4'}$ = 4.7, H-5′b); 4.55 (dd, 2H, J_{gem} = 11.8, $J_{5'a,4'}$ = 4.4, H-5′a); 4.64 (ddd, 1H, $J_{4',5'}$ = 4.7, 4.4, $J_{4',3'}$ = 2.7, H-4′); 5.40 (ddd, 1H, $J_{1',2'}$ = 7.7, 4.6, $J_{1',3}$ = 1.0, H-1′); 5.58 (ddd, 1H, $J_{3',2'}$ = 6.8, 3.0, $J_{3',4'}$ = 2.7, H-3′); 6.74 (dd, 1H, $J_{3,4}$ = 3.7, $J_{3,1'}$ = 1.0, H-3); 6.91 (d, 1H, $J_{4,3}$ = 3.7, H-4); 7.22 and 7.24 (2 × m, 2 × 2H, H-*m*-Tol); 7.76 and 7.94 (2 × m, 2 × 2H, H-*o*-Tol). ^{13}C NMR (125.7 MHz, $CDCl_3$): 21.7 (CH_3-Tol); 40.3 (CH_2-2′); 64.3 (CH_2-5′); 76.0 (CH-3′); 76.8 (CH-1′); 82.2 (CH-4′); 111.6 (C-5); 124.3 (CH-3); 126.7 and 126.95 (C-*i*-Tol); 129.1 and 129.15 (CH-*m*-Tol); 129.5 (CH-4); 129.7 (CH-*o*-Tol); 143.9 and 144.1 (C-*p*-Tol); 148.1 (C-2); 166.1 and 166.25 (CO).

1β-(5-Bromothiophen-2-yl)-1,2-dideoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-D-ribofuranose (7a). Imidazole (1.73 g, 25.4 mmol) was added to a solution of **6a** (1.77 g, 6.34 mmol) in dry DMF (30 mL). The mixture was stirred for 5 min, and then TBDMSCl (2.39 g, 15.9 mmol) was added in one portion. The resulting solution was stirred for 15 h at rt. Then, the solvent was evaporated, and the residue was chromatographed on a silica gel column in gradient hexane to hexane/EtOAc (19.5/0.5) to give product **7a** (3 g, 94%) as a colorless oil. MS (FAB) *m/z* 507 (M + H). HRMS (FAB) for $C_{21}H_{40}BrO_3SSi_2$: [M + H] calculated 507.1420, found 507.1415. ^{1}H NMR (500 MHz, $CDCl_3$): 0.08 and 0.09 (2 × s, 2 × 6H, CH_3Si); 0.908 and 0.909 (2 × s, 2 × 9H, $(CH_3)_3C$); 1.98 (ddd, 1H, J_{gem} = 12.7, $J_{2'b,1'}$ = 10.3, $J_{2'b,3'}$ = 5.2, H-2′b); 2.14 (ddd, 1H, J_{gem} = 12.7, $J_{2'a,1'}$ = 5.3, $J_{2'a,3'}$ = 1.6, H-2′a); 3.52 (dd, 1H, J_{gem} = 10.8, $J_{5'b,4'}$ = 6.4, H-5′b); 3.71 (dd, 1H, J_{gem} = 10.8, $J_{5'a,4'}$ = 4.0, H-5′a); 3.92 (ddd, 1H, $J_{4',5'}$ = 6.4, 4.0, $J_{4',3'}$ = 1.8, H-4′); 4.42 (dddd, 1H, $J_{3',2'}$ = 5.2, 1.6, $J_{3',4'}$ = 1.8, $J_{3',1'}$ = 0.6, H-3′); 5.28 (dddd, 1H, $J_{1',2'}$ = 10.3, 5.3, $J_{1',3}$ = 0.8, $J_{1',3'}$ = 0.6, H-1′); 6.73 (dd, 1H, $J_{3,4}$ = 3.8, $J_{3,1'}$ = 0.8, H-3); 6.88 (d, 1H, $J_{4,3}$ = 3.8, H-4). ^{13}C NMR (125.7 MHz, $CDCl_3$): −5.5, −5.4, and −4.7 (CH_3Si); 18.0 and 18.4 ($C(CH_3)_3$); 25.8 and 25.95 ($(CH_3)_3C$); 44.15 (CH_2-2′); 63.8 (CH_2-5′); 74.3 (CH-3′); 76.2 (CH-1′); 88.2 (CH-4′); 111.4 (C-5); 124.45 (CH-3); 129.2 (CH-4); 147.7 (C-2). IR spectrum (CCl_4): 2897, 1471, 1463, 1448, 1407, 1389, 1362, 1257, 1204, 1092, 1054, 971, 939 cm^{-1}. α^{20}_D +2.8 (*c* 4.49, $CHCl_3$).

1β-(5-Methylthiophen-2-yl)-1,2-dideoxy-3,5-di-*O*-toluoyl-D-ribofuranose (4c). Dry toluene (15 mL) was added to an argon-purged flask containing **4a** (500 mg, 0.97 mmol), K_2CO_3 (200 mg,

1.44 mmol), methylboronic acid (116 mg, 1.94 mmol), and $Pd(PPh_3)_4$ (54 mg, 0.05 mmol), and the mixture was stirred under Ar at 115 °C for 43 h. Afterwords, the mixture was cooled to rt and filtered through cellite. Evaporation of the solvent, followed by column chromatography on silica gel in gradient hexane to hexane/toluene (9.7/0.3), afforded the mixture of products **4c/4b** (6:1) (260 mg, 60%) as a colorless oil. For characterization data, see the Supporting Information.

1β-(5-Ethylthiophen-2-yl)-1,2-dideoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-D-ribofuranose (7d). A solution of $ZnCl_2$ (5.7 mL, 0.5 M in THF, 2.84 mmol) was added dropwise to a stirred solution of EtMgBr (2.4 mL, 1 M in THF, 2.36 mmol) in THF (3 mL) during 5 min at 0 °C under Ar, and the stirring was continued for 25 min at 0 °C. This solution was transferred into a solution of **7a** (400 mg, 0.79 mmol), Pd_2dba_3 (36 mg, 0.04 mmol), and bdtbp (24 mg, 0.08 mmol) in THF (5 mL), and the resulting reaction mixture was stirred at rt for 10 min and then at 85 °C for 23 h. The mixture was cooled to rt, poured into saturated NH_4Cl solution (20 mL), and filtered through cellite, and the products were extracted with EtOAc (3 × 20 mL). Evaporation of the organic phase followed by column chromatography on silica gel in gradient hexane to hexane/EtOAc (9.7/0.3) afforded the mixture of products **7d/7b** (4:1) (330 mg, 93%) as a colorless oil. For characterization data, see the Supporting Information.

1β-(5-Benzylthiophen-2-yl)-1,2-dideoxy-D-ribofuranose (6e). A solution of BnMgCl (780 μL, 2 M in THF, 1.55 mmol) was added dropwise to a stirred solution of **4a** (400 mg, 0.78 mmol) and $NiCl_2$(dppp) (42 mg, 0.08 mmol) in THF (4 mL) during 40 min at −20 °C under Ar. The stirring was continued for 10 min to reach rt, and then the mixture was stirred at 85 °C for 14 h. The mixture was cooled to rt and then filtered through cellite, extracted to EtOAc (20 mL), and evaporated. The crude mixture was treated with NaOMe (1 M solution) in MeOH at rt for 24 h, and the residue after evaporation of the solvent was flash-chromatographed on silica gel in gradient EtOAc to EtOAc/MeOH (8/2) to give **6e** (72 mg, 32% after two steps) followed by **6b** (26 mg, 17%) and **6a** (36 mg, 17%) as yellow oils. For characterization data, see the Supporting Information.

General Procedure for the Stille Cross-Coupling Reaction. 2-(Tributylstannyl)hetaryl (1.2−5 equiv) was added dropwise under argon to a stirred solution of **4a** (1 equiv) and $PdCl_2$dppf (5 mol %) in DMF (5.0 mL). The mixture was stirred at 100−120 °C for 16−22 h. The crude reaction mixture was diluted with EtOAc (15 mL), filtered through cellite, and washed with 2 M HCl and brine. The water layers were extracted with EtOAc (3 × 20 mL). Then, the collected organic layers were dried over $MgSO_4$, and solvents were evaporated under a vacuum. The crude product was chromatographed on silica gel in gradient hexane to hexane/EtOAc (9.7/0.3).

1β-[5-(Pyridin-2-yl)thiophen-2-yl]-1,2-dideoxy-3,5-di-*O*-toluoyl-D-ribofuranose (4f). 4f was prepared from **4a** (500 mg, 0.97 mmol) and 2-(tributylstannyl)pyridine (235 μL, 0.85 mmol), by the general procedure (115 °C, 29 h). The crude product after chromatography was further stirred with Me_3Al (470 μL, 2 M in toluene, 0.93 mmol) in toluene (13 mL) at rt for 24 h. The reaction mixture was quenched by saturated Na_2CO_3 (30 mL), washed with saturated $NaHCO_3$ (1 × 50 mL), and extracted with EtOAc (3 × 30 mL). Then, the collected organic layers were dried over $MgSO_4$, and solvents were evaporated under vacuum. Flash chromatography on silica gel eluting hexane to hexane/EtOAc (19.8/0.2) gave pure product **4f** (261 mg, 66%) as a colorless oil. MS (FAB) *m/z* 514 (M + H). HRMS (FAB) for $C_{30}H_{28}NO_5S$: [M + H] calculated 514.1688, found 514.1666. ^{1}H NMR (500 MHz, $CDCl_3$): 2.39 and 2.43 (2 × s, 2 × 3H, CH_3-Tol); 2.45 (ddd, 1H, J_{gem} = 13.8, $J_{2'b,1'}$ = 10.5, $J_{2'b,3'}$ = 6.0, H-2′b); 2.61 (ddd, 1H, J_{gem} = 13.8, $J_{2'a,1'}$ = 5.2, $J_{2'a,3'}$ = 1.3, H-2′a); 4.53 (td, 1H, $J_{4',5'}$ = 4.4, $J_{4',3'}$ = 2.0, H-4′); 4.58 and 4.62 (2 × dd, 2H, J_{gem} = 11.7, $J_{5',4'}$ = 4.4, H-5′); 5.49 (dddd, 1H, $J_{1',2'}$ = 10.5, 5.2, $J_{1',3}$ = 0.7, $J_{1',3'}$ = 0.5, H-1′); 5.63 (dddd, 1H, $J_{3',2'}$ = 6.0, 1.3, $J_{3',4'}$ = 2.0, $J_{3',1'}$ = 0.5, H-3′); 7.05 (dd, 1H, $J_{3,4}$ = 3.7, $J_{3,1'}$ = 0.7, H-3); 7.13 (ddd, 1H, $J_{5,4}$ = 7.4, $J_{5,6}$ = 4.9, $J_{5,3}$ = 1.2, H-5-py); 7.22 and 7.27 (2 × m, 2 × 2H, H-*m*-Tol); 7.44 (d, 1H, $J_{4,3}$ = 3.7, H-4); 7.57 (ddd, 1H, $J_{3,4}$ = 8.0, $J_{3,5}$ = 1.2, $J_{3,6}$ = 1.0, H-3-py); 7.66 (ddd, 1H, $J_{4,3}$ = 8.0, $J_{4,5}$ = 7.4, $J_{4,6}$ = 1.8, H-4-py); 7.97 (m, 4H, H-*o*-Tol); 8.55 (ddd, 1H, $J_{6,5}$ = 4.9, $J_{6,4}$ = 1.8, $J_{6,3}$ = 1.0, H-6-py). ^{13}C NMR (125.7 MHz, $CDCl_3$): 21.6 and 21.7 (CH_3-Tol); 41.6 (CH_2-2′); 64.6 (CH_2-5′); 77.0 (CH-1′); 77.0 (CH-3′); 83.0 (CH-4′); 118.6 (CH-3-py); 121.9 (CH-5-py); 124.2 (CH-4); 125.7 (CH-3); 127.0 and 127.2 (C-*i*-Tol); 129.1 and 129.2 (CH-*m*-Tol); 129.75 and 129.8 (CH-*o*-Tol); 136.5 (CH-4-py); 143.7 and 144.1 (C-*p*-Tol); 144.3 (C-5); 146.1 (C-2); 149.5 (CH-6-py); 152.5 (C-2-py); 166.0 and 166.4 (CO). IR spectrum (KBr): 1716, 1612, 1584, 1565, 1550, 1487, 1454, 1432, 1375, 1271, 1209, 1153, 1105, 1040, 993, 776, 618 cm^{-1}. α^{20}_D −60.8 (*c* 3.13, $CHCl_3$).

General Procedure for the Suzuki Cross-Coupling. To an argon-purged flask containing TTPTS (36 mg, 0.06 mmol) and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), a mixture of H_2O/acetonitrile (2:1) (2.5 mL) was added, and the mixture was sonicated for 2 min. This solution was added into a mixture of **6a** (140 mg, 0.5 mmol), boronic acid (0.75 mmol), and Cs_2CO_3 (489 mg, 1.5 mmol) in H_2O/acetonitrile (2:1) (2 mL). The mixture was then stirred at 90 or 120 °C for 2−4 h. After evaporation, the crude product was purified by flash chromatography on silica gel in gradient $CHCl_3$ to $CHCl_3$/MeOH (9.5/0.5).

1β-(5-Phenylthiophen-2-yl)-1,2-dideoxy-D-ribofuranose (6l). 6l was prepared from **6a** and phenylboronic acid (92 mg, 0.75 mmol) by the general procedure (90 °C, 3 h). **6l** (100 mg, 72%) was obtained as a colorless oil and crystallized from isopropanol/heptane to give colorless crystals (mp 145−147 °C). MS (FAB) *m/z* 277 (M + H). HRMS (FAB) for $C_{15}H_{17}O_3S$: [M + H] calculated 277.0898, found 277.0885. ^{1}H NMR (500 MHz, DMSO-d_6): 1.96 (ddd, 1H, J_{gem} = 12.8, $J_{2'b,1'}$ = 10.1, $J_{2'b,3'}$ = 5.6, H-2′b); 2.14 (ddd, 1H, J_{gem} = 12.8, $J_{2'a,1'}$ = 5.5, $J_{2'a,3'}$ = 1.8, H-2′a); 3.38 (dt, 1H, J_{gem} = 11.3, $J_{5'b,4'}$ = 6.0, $J_{5'b,OH}$ = 5.9, H-5′b); 3.46 (dt, 1H, J_{gem} = 11.3, $J_{5'a,OH}$ = 5.3, $J_{5'a,4'}$ = 5.1, H-5′a); 3.77 (ddd, 1H, $J_{4',5'}$ = 6.0, 5.1, $J_{4',3'}$ = 2.3, H-4′); 4.21 (m, 1H, $J_{3',2'}$ = 5.6, 1.8, $J_{3',OH}$ = 3.9, $J_{3',4'}$ = 2.3, $J_{3',1'}$ = 0.5, H-3′); 4.77 (t, 1H, $J_{OH,5'}$ = 5.9, 5.3, OH-5′); 5.12 (d, 1H, $J_{OH,3'}$ = 3.9, OH-3′); 5.23 (ddt, 1H, $J_{1',2'}$ = 10.1, 5.5, $J_{1',3}$ = 0.8, $J_{1',3'}$ = 0.5, H-1′); 7.04 (dd, 1H, $J_{3,4}$ = 3.6, $J_{3,1'}$ = 0.8, H-3); 7.29 (m, 1H, H-*p*-Ph); 7.34 (d, 1H, $J_{4,3}$ = 3.6, H-4); 7.40 (m, 2H, H-*m*-Ph); 7.61 (m, 2H, H-*o*-Ph). ^{13}C NMR (125.7 MHz, DMSO-d_6): 43.6 (CH_2-2′); 62.7 (CH_2-5′); 72.5 (CH-3′); 75.4 (CH-1′); 88.0 (CH-4′); 123.2 (CH-4); 125.4 (CH-*o*-Ph); 125.9 (CH-3); 127.7 (CH-*p*-Ph); 129.3 (CH-*m*-Ph); 134.1 (C-*i*-Ph); 142.5 (C-5); 146.0 (C-2). IR spectrum ($CHCl_3$): 3612, 3336, 3066, 1599, 1549, 1469, 1311, 1091, 1038, 957 cm^{-1}. α^{20}_D +4.2 (*c* 2.36, $CHCl_3$). Anal. Calcd $C_{15}H_{16}O_3S$ (276.4): C, 65.19; H, 5.84. Found: C, 64.82; H, 5.88.

General Procedure for the Zemplen Deprotection. A 1 M NaOMe solution in MeOH (0.2mL, 0.2 mmol) was added to a solution of toluoyl-protected *C*-nucleosides **4a**−**4c** and **4f**−**4i** (0.1 mmol) in MeOH (100 mL), and the resulting solution was stirred overnight at room temperature. Then the solvent was evaporated, and products were isolated by flash chromatography on silica gel in gradient chloroform to chloroform/methanol (19.5/0.5). Some compounds (**6c**, **6f**, **6i**) were repurified by flash chromatography on a reverse-phase C18 column (with linear gradient of H_2O to MeOH).

1β-(5-Bromothiophen-2-yl)-1,2-dideoxy-D-ribofuranose (6a). Compound **6a** was prepared from **4a** (3.52 g, 6.83 mmol) by the general procedure. **6a** (1.77 g, 93%) was obtained as a yellow oil. Crystallization from isopropanol/heptane gave yellow crystals (mp 74−75 °C). MS (FAB) *m/z* 278 (M + H). HRMS (FAB) for $C_9H_{12}BrO_3S$: [M + H] calculated 278.9691, found 278.9684. ^{1}H NMR (500 MHz, DMSO-d_6): 1.88 (ddd, 1H, J_{gem} = 12.8, $J_{2'b,1'}$ = 10.1, $J_{2'b,3'}$ = 5.6, H-2′b); 2.11 (ddd, 1H, J_{gem} = 12.8, $J_{2'a,1'}$ = 5.6, $J_{2'a,3'}$ = 1.8, H-2′a); 3.34 (bddd, 1H, J_{gem} = 11.1, $J_{5'b,4'}$ = 6.0, $J_{5'b,OH}$ = 5.4, H-5′b); 3.42 (bddd, 1H, J_{gem} = 11.1, $J_{5'a,OH}$ = 5.4, $J_{5'a,4'}$ =

4.9, H-5′a); 3.74 (ddd, 1H, $J_{4',5'} = 6.0, 4.9$, $J_{4',3'} = 2.2$, H-4′); 4.18 (bm, 1H, H-3′); 4.75 (bt, 1H, $J_{OH,5'} = 5.4$, OH-5′); 5.11 (bd, 1H, $J_{OH,3'} = 2.8$, OH-3′); 5.19 (dddd, 1H, $J_{1',2'} = 10.1, 5.6$, $J_{1',3} = 0.8$, $J_{1',3'} = 0.6$, H-1′); 6.88 (dd, 1H, $J_{3,4} = 3.7$, $J_{3,1'} = 0.8$, H-3); 7.05 (d, 1H, $J_{4,3} = 3.7$, H-4).^{13}C NMR (125.7 MHz, DMSO-d_6): 43.6 (CH_2-2′); 62.6 (CH_2-5′); 72.5 (CH-3′); 75.5 (CH-1′); 88.0 (CH-4′); 110.3 (C-5); 125.2 (CH-3); 129.95 (CH-4); 148.7 (C-2). IR spectrum (KBr): 3402, 3292, 1632, 1103, 1054, 1444, 1366, 1203, 968, 1071 cm^{-1}. α^{20}_D +21.9 (*c* 1.81, MeOH). Anal. Calcd $C_9H_{11}BrO_3S$ (279.2): C, 38.72; H, 3.97; Br, 28.62. Found: C, 38.51; H, 3.99; Br, 28.85.

1*β*-(5-Thiophen-2-yl)-1,2-dideoxy-D-ribofuranose (6b). Compound **6b** was prepared from **4b** (385 mg, 0.88 mmol) by the general procedure. **6b** (143 mg, 81%) was obtained as a yellow oil. Crystallization from isopropanol/heptane gave colorless crystals (mp 74−75 °C). MS (FAB) *m*/*z* 223 (M + Na). HRMS (FAB) for $C_9H_{13}O_3S$: [M + H] calculated 201.0585, found 201.0582. ^{1}H NMR (500 MHz, DMSO-d_6): 1.92 (ddd, 1H, $J_{gem} = 12.8$, $J_{2'b,1'} = 10.1$, $J_{2'b,3'} = 5.6$, H-2′b); 2.11 (ddd, 1H, $J_{gem} = 12.8$, $J_{2'a,1'} = 5.4$, $J_{2'a,3'} = 1.7$, H-2′a); 3.34 and 3.42 (2 × bm, 2H, H-5′); 3.74 (ddd, 1H, $J_{4',5'} = 6.3, 5.2$, $J_{4',3'} = 2.3$, H-4′); 4.19 (bddd, 1H, $J_{3',2'} = 5.6, 1.7$, $J_{3',4'} = 2.3$, H-3′); 4.78 (bs, 1H, OH-5′); 5.13 (bs, 1H, OH-3′); 5.23 (ddt, 1H, $J_{1',2'} = 10.1, 5.4$, $J_{1',3} = J_{1',3'} = 0.7$, H-1′); 6.96 (dd, 1H, $J_{4,5} = 5.0$, $J_{4,3} = 3.5$, H-4); 7.03 (ddd, 1H, $J_{3,4} = 3.5$, $J_{3,5} = 1.3$, $J_{3,1'} = 0.7$, H-3); 7.42 (dd, 1H, $J_{5,4} = 5.0$, $J_{5,3} = 1.3$, H-5). ^{13}C NMR (125.7 MHz, DMSO-d_6): 43.8 (CH_2-2′); 62.7 (CH_2-5′); 72.5 (CH-3′); 75.3 (CH-1′); 88.0 (CH-4′); 124.65 (CH-3); 125.2 (CH-5); 126.8 (CH-4); 146.2 (C-2). IR spectrum (KBr): 1540, 1442, 1242, 1080, 1053, 1066, 1034, 966, 1322, 1424, 1632 cm^{-1}. α^{20}_D +18.1 (*c* 2.16, MeOH). Anal. Calcd $C_9H_{12}O_3S$ (200.3): C, 53.98; H, 6.04. Found: C, 53.92; H, 6.01.

1*β*-(5-Methylthiophen-2-yl)-1,2-dideoxy-D-ribofuranose (6c). Compound **6c** was prepared from a mixture of **4c/4b** (254 mg, 0.57 mmol) by the general procedure. Chromatography gave **6c** (89 mg, 74%) and **6b** (10 mg, 9%) as yellow oils. Product **6c** did not crystallize. Lyophilization gave a yellow amorphous solid (mp 39−41 °C). MS (FAB) *m*/*z* 215 (M + H). HRMS (FAB) for $C_{10}H_{15}O_3S$: [M + H] calculated 215.0742, found 215.0750. ^{1}H NMR (500 MHz, CD_3OD): 2.09 (ddd, 1H, $J_{gem} = 13.2$, $J_{2'b,1'} = 10.2$, $J_{2'b,3'} = 5.7$, H-2′b); 2.18 (ddd, 1H, $J_{gem} = 13.2$, $J_{2'a,1'} = 5.5$, $J_{2'a,3'} = 1.9$, H-2′a); 2.43 (d, 3H, $^4J = 1.2$, CH_3); 3.56 (dd, 1H, $J_{gem} = 11.6$, $J_{5'b,4'} = 5.6$, H-5′b); 3.61 (dd, 1H, $J_{gem} = 11.6$, $J_{5'a,4'} = 5.3$, H-5′a); 3.88 (ddd, 1H, $J_{4',5'} = 5.6, 5.3$, $J_{4',3'} = 2.4$, H-4′); 4.30 (dddd, 1H, $J_{3',2'} = 5.7, 1.9$, $J_{3',4'} = 2.4$, $J_{3',1'} = 0.6$, H-3′); 5.26 (dd, 1H, $J_{1',2'} = 10.2, 5.5$, H-1′); 6.60 (dq, 1H, $J_{4,3} = 3.4$, $^4J = 1.2$, H-4); 6.81 (dq, 1H, $J_{3,4} = 3.4$, $^5J = 0.4$, H-3). ^{13}C NMR (125.7 MHz, CD_3OD): 15.25 (CH_3); 44.6 (CH_2-2′); 64.1 (CH_2-5′); 74.3 (CH-3′); 77.55 (CH-1′); 89.0 (CH-4′); 125.6 (CH-4); 125.9 (CH-3); 140.7 (C-5); 143.9 (C-2). IR spectrum (KBr): 1216, 1374, 1491, 1559, 3069, 3401 cm^{-1}. α^{20}_D +20.4 (*c* 2.20, MeOH). Anal. Calcd $C_{10}H_{14}O_3S$ (214.3): C, 56.05; H, 6.59. Found: C, 55.68; H, 6.52.

1*β*-[5-(Pyridin-2-yl)thiophen-2-yl]-1,2-dideoxy-D-ribofuranose (6f). Compound **6f** was prepared from **4f** (402 mg, 0.78 mmol) by the general procedure. **6f** (206 mg, 95%) was obtained as a colorless oil which was crystallized from isopropanol/heptane to give colorless crystals (mp 106−108 °C). MS (FAB) *m*/*z* 278 (M + H). HRMS (FAB) for $C_{14}H_{16}NO_3S$: [M + H] calculated 278.0851, found 278.0842. ^{1}H NMR (500 MHz, DMSO-d_6): 1.95 (ddd, 1H, $J_{gem} = 12.8$, $J_{2'b,1'} = 10.1$, $J_{2'b,3'} = 5.3$, H-2′b); 2.15 (ddd, 1H, $J_{gem} = 12.8$, $J_{2'a,1'} = 5.5$, $J_{2'a,3'} = 1.8$, H-2′a); 3.37 (dd, 1H, $J_{gem} = 11.1$, $J_{5'b,4'} = 6.3$, H-5′b); 3.46 (dd, 1H, $J_{gem} = 11.1$, $J_{5'a,4'} = 5.1$, H-5′a); 3.78 (ddd, 1H, $J_{4',5'} = 6.3, 5.1$, $J_{4',3'} = 2.2$, H-4′); 4.22 (bm, 1H, H-3′); 4.77 (bs, 1H, OH-5′); 5.12 (bs, 1H, OH-3′); 5.24 (dd, 1H, $J_{1',2'} = 10.1, 5.5$, H-1′); 7.06 (dd, 1H, $J_{3,4} = 3.8$, $J_{3,1'} = 0.8$, H-3); 7.25 (ddd, 1H, $J_{5,4} = 7.3$, $J_{5,6} = 4.8$, $J_{5,3} = 1.2$, H-5-py); 7.62 (d, 1H, $J_{4,3} = 3.8$, H-4); 7.80 (ddd, 1H, $J_{4,3} = 8.0$, $J_{4,5} = 7.3$, $J_{4,6} = 1.7$, H-4-py); 7.86 (ddd, 1H, $J_{3,4} = 8.0$, $J_{3,5} = 1.2$, $J_{3,6} = 0.9$, H-3-py); 8.49 (ddd, 1H, $J_{6,5} = 4.8$, $J_{6,4} = 1.7$, $J_{6,3} = 0.9$, H-6-py). ^{13}C NMR (125.7 MHz, DMSO-d_6): 43.7 (CH_2-2′); 62.7 (CH_2-5′); 72.6 (CH-3′); 75.55 (CH-1′); 88.0 (CH-4′); 118.55 (CH-3-py); 122.4 (CH-5-py); 124.8 (CH-4); 125.6 (CH-3); 137.3 (CH-4-py); 143.4 (C-5); 148.8 (C-2); 149.5 (CH-6-py); 152.1 (C-2-py). IR spectrum (KBr): 3409, 2904, 1699, 1632, 1584, 1550, 1486, 1429, 1058, 1029, 995, 970 cm^{-1}. α^{20}_D +4.4 (*c* 2.70, $CHCl_3$). Anal. Calcd $C_{14}H_{15}NO_3S$ (277.3): C, 60.63; H, 5.45; N, 5.05; S, 11.56. Found: C, 60.25; H, 5.34; N, 4.71.

1*β*-(5-(Thiophen-2-yl)thiophen-2-yl)-1,2-dideoxy-D-ribofuranose (6g). Compound **6g** was prepared from **4g** (681 mg, 1.31 mmol) by the general procedure. **6g** (345 mg, 93%) was obtained as a colorless oil which was crystallized from isopropanol/heptane to give colorless crystals (mp 84−85 °C). MS (FAB) *m*/*z* 283 (M + H). HRMS (FAB) for $C_{13}H_{15}O_3S_2$: [M + H] calculated 283.0463, found 283.0454. ^{1}H NMR (500 MHz, DMSO-d_6): 1.93 (ddd, 1H, $J_{gem} = 12.8$, $J_{2'b,1'} = 10.2$, $J_{2'b,3'} = 5.6$, H-2′b); 2.13 (ddd, 1H, $J_{gem} = 12.8$, $J_{2'a,1'} = 5.6$, $J_{2'a,3'} = 1.8$, H-2′a); 3.36 (ddd, 2H, $J_{gem} = 11.3$, $J_{5'b,4'} = 6.1$, $J_{5'b,OH} = 6.0$, H-5′b); 3.44 (ddd, 2H, $J_{gem} = 11.3$, $J_{5'a,OH} = 5.1$, $J_{5'a,4'} = 5.0$, H-5′a); 3.76 (ddd, 1H, $J_{4',5'} = 6.1, 5.0$, $J_{4',3'} = 2.2$, H-4′); 4.20 (m, 1H, $J_{3',2'} = 5.6, 1.8$, $J_{3',OH} = 3.9$, $J_{3',4'} = 2.2$, $J_{3',1'} = 0.5$, H-3′); 4.76 (dd, 1H, $J_{OH,5'} = 6.0, 5.1$, OH-5′); 5.11 (d, 1H, $J_{OH,3'} = 3.9$, OH-3′); 5.22 (dddd, 1H, $J_{1',2'} = 10.2, 5.6$, $J_{1',3} = 0.8$, $J_{1',3'} = 0.5$, H-1′); 6.99 (dd, 1H, $J_{3,4} = 3.6$, $J_{3,1'} = 0.9$, H-3); 7.07 (dd, 1H, $J_{4,5} = 5.1$, $J_{4,3} = 3.6$, H-4-thienyl); 7.12 (d, 1H, $J_{4,3} = 3.6$, H-4); 7.25 (dd, 1H, $J_{3,4} = 3.6$, $J_{3,5} = 1.2$, H-3-thienyl); 7.48 (dd, 1H, $J_{5,4} = 5.1$, $J_{5,3} = 1.2$, H-5-thienyl). ^{13}C NMR (125.7 MHz, DMSO-d_6): 43.65 (CH_2-2′); 62.61 (CH_2-5′); 72.5 (CH-3′); 75.4 (CH-1′); 88.0 (CH-4′); 123.45 (CH-4); 123.9 (CH-3-thienyl); 125.4 (CH-5-thienyl); 125.6 (CH-3); 128.5 (CH-4-thienyl); 135.7 (C-5); 136.85 (C-2-thienyl); 145.6 (C-2). IR spectrum (KBr): 1092, 1049, 1028, 1472, 1351, 1208, 970, 1427, 1081 cm^{-1}. α^{20}_D +11.7 (*c* 2.77, MeOH). Anal. Calcd $C_{13}H_{14}O_3S_2$ (282.4): C, 55.29; H, 5.00. Found: C, 54.91; H, 4.97.

1*β*-[5-(Furan-2-yl)thiophen-2-yl]-1,2-dideoxy-D-ribofuranose (6h). Compound **6h** was prepared from **4h** (164 mg, 0.33 mmol) by the general procedure. **6h** (82 mg, 94%) was obtained as a yellow oil which was crystallized from isopropanol/heptane to give yellow crystals (mp 105−107 °C). MS (FAB) *m*/*z* 267 (M + H). HRMS (FAB) for $C_{13}H_{15}O_4S$: [M + H] calculated 267.0691, found 267.0696. ^{1}H NMR (500 MHz, CD_3OD): 2.12 (ddd, 1H, $J_{gem} = 13.1$, $J_{2'b,1'} = 10.0$, $J_{2'b,3'} = 5.8$, H-2′b); 2.25 (ddd, 1H, $J_{gem} = 13.1$, $J_{2'a,1'} = 5.6$, $J_{2'a,3'} = 2.0$, H-2′a); 3.60 (dd, 1H, $J_{gem} = 11.7$, $J_{5'b,4'} = 5.5$, H-5′b); 3.64 (dd, 1H, $J_{gem} = 11.7$, $J_{5'a,4'} = 5.3$, H-5′a); 3.60 (ddd, 1H, $J_{4',5'} = 5.5, 5.3$, $J_{4',3'} = 2.5$, H-4′); 4.34 (dddd, 1H, $J_{3',2'} = 5.8, 2.0$, $J_{3',4'} = 2.5$, $J_{3',1'} = 0.6$, H-3′); 5.34 (dddd, 1H, $J_{1',2'} = 10.0, 5.6$, $J_{1',3} = 0.8$, $J_{1',3'} = 0.6$, H-1′); 6.47 (dd, 1H, $J_{4,3} = 3.4$, $J_{4,5} = 1.9$, H-4-furyl); 6.53 (dd, 1H, $J_{3,4} = 3.4$, $J_{3,5} = 0.8$, H-3-furyl); 6.97 (dd, 1H, $J_{3,4} = 3.7$, $J_{3,1'} = 0.8$, H-3); 7.11 (d, 1H, $J_{4,3} = 3.7$, H-4); 7.47 (dd, 1H, $J_{5,4} = 1.9$, $J_{5,3} = 0.8$, H-5-furyl). ^{13}C NMR (125.7 MHz, CD_3OD): 44.8 (CH_2-2′); 64.1 (CH_2-5′); 74.3 (CH-3′); 77.4 (CH-1′); 89.2 (CH-4′); 105.9 (CH-3-furyl); 112.7 (CH-4-furyl); 123.0 (CH-4); 126.3 (CH-3); 134.4 (C-5); 143.0 (CH-5-furyl); 145.7 (C-2); 150.8 (C-2-furyl). IR spectrum (KBr): 3148, 3073, 2909, 1632, 1539, 1504, 1447, 1092, 1051, 1030, 969 cm^{-1}. α^{20}_D +10.0 (*c* 1.81, MeOH). Anal. Calcd $C_{13}H_{14}O_4S$ (266.3): C, 58.63; H, 5.30. Found: C, 58.26; H, 5.53.

1*β*-[5-([2,2′]Bipyridin-6-yl)thiophen-2-yl]-1,2-dideoxy-D-ribofuranose (6i). Compound **6i** was prepared from **4i** (150 mg, 0.25 mmol) by the general procedure. **6i** (59 mg, 65%) was obtained as a colorless oil which was crystallized from isopropanol/heptane to give colorless crystals (mp 152−154 °C). MS (FAB) *m*/*z* 355 (M + H). HRMS (FAB) for $C_{19}H_{19}N_2O_3S$: [M + H] calculated 355.1116, found 355.1122. ^{1}H NMR (600 MHz, CD_3OD): 2.18 (ddd, 1H, $J_{gem} = 13.2$, $J_{2'b,1'} = 10.1$, $J_{2'b,3'} = 5.8$, H-2′b); 2.30 (ddd, 1H, $J_{gem} = 13.2$, $J_{2'a,1'} = 5.6$, $J_{2'a,3'} = 1.9$, H-2′a); 3.65 and 3.69 (2 × dd, 2H, $J_{gem} = 11.6$, $J_{5',4'} = 5.3$, H-5′); 3.96 (td, 1H, $J_{4',5'} = 5.3$, $J_{4',3'} = 2.5$, H-4′); 4.37 (dddd, 1H, $J_{3',2'} = 5.8, 1.9$, $J_{3',4'} = 2.5$, $J_{3',1'} = 0.7$, H-3′); 5.39 (ddt, 1H, $J_{1',2'} = 10.1, 5.6$, $J_{1',3} = J_{1',3'} = 0.7$, H-1′); 7.08 (dd, 1H, $J_{3,4} = 3.7$, $J_{3,1'} = 0.7$, H-3); 7.44 (ddd, 1H, $J_{5',4'} = 7.5$, $J_{5',6'} = 4.8$, $J_{5',3'} = 1.2$, H-5′-bipy); 7.60 (d, 1H, $J_{4,3} =$

3.7, H-4); 7.79 (dd, 1H, $J_{5,4} = 7.8$, $J_{5,3} = 0.9$, H-5-bipy); 7.88 (dd, 1H, $J_{4,3} = J_{4,5} = 7.8$, H-4-bipy); 7.96 (ddd, 1H, $J_{4',3'} = 8.0$, $J_{4',5'} = 7.5$, $J_{4',6'} = 1.8$, H-4′-bipy); 8.16 (dd, 1H, $J_{3,4} = 7.8$, $J_{3,5} = 0.9$, H-3-bipy); 8.51 (ddd, 1H, $J_{3',4'} = 8.0$, $J_{3',5'} = 1.2$, $J_{3',6'} = 1.0$, H-3′-bipy); 8.63 (ddd, 1H, $J_{6',5'} = 4.8$, $J_{6',4'} = 1.8$, $J_{6',3'} = 1.0$, H-6′-bipy). ^{13}C NMR (151 MHz, CD_3OD): 44.9 (CH_2-2′); 64.1 (CH_2-5′); 74.4 (CH-3′); 77.7 (CH-1′); 89.3 (CH-4′); 119.6 (CH-5-bipy); 119.9 (CH-3-bipy); 122.7 (CH-3′-bipy); 125.35 (CH-5′-bipy); 125.6 (CH-4); 126.7 (CH-3); 138.7 (CH-4′-bipy); 139.0 (CH-4-bipy); 145.5 (C-5); 149.3 (C-2); 150.0 (CH-6′-bipy); 153.5 (C-6-bipy); 156.4 (C-2-bipy); 157.1 (C-2′-bipy). IR spectrum (KBr): 3374, 3055, 1591, 1578, 1475, 1382, 1226, 1066, 1049, 1029, 997, 803 cm^{-1}. α^{20}_D −5.5 (*c* 2.16, MeOH). Anal. Calcd $C_{19}H_{18}N_2O_3S$ (354.4): C, 64.39; H, 5.12; N, 7.90. Found: C, 64.04; H, 5.16; N, 7.51.

Single Crystal X-Ray Structure Analysis. The diffraction data of single crystals of **6l** (colorless, 0.07 × 0.37 × 0.50 mm) and **6n** (brownish, 0.09 × 0.30 × 0.77 mm) were collected on an Xcalibur X-ray diffractometer with Cu Kα ($\lambda = 1.54180$ Å) at 150 K (**6l**) and 295 K (**6n**). Both structures were solved by direct methods with SIR92[30] and refined by full-matrix, least-squares methods based on *F* with CRYSTALS.[31] The hydrogen atoms were located in a difference map, but those attached to carbon atoms were repositioned geometrically and then refined with riding constraints, while all other atoms were refined anisotropically in both cases.

Crystal data for **6l**: $C_{15}H_{16}O_3S_1$, monoclinic, space group $P2_1$, $a = 5.7250(2)$ Å, $b = 9.9297(3)$ Å, $c = 11.9718(4)$ Å, $\beta = 100.190(3)°$, $V = 669.83(4)$ Å^3, $Z = 2$, $M = 276.35$, 10 484 reflections measured, 2655 independent reflections. Final $R = 0.0278$, $wR = 0.0324$, GoF = 1.0293 for 2508 reflections with $I > 2\sigma(I)$ and 174 parameters.

Crystal data for **6n**: $C_{13}H_{14}O_3S_2$, monoclinic, space group $P2_1$, $a = 5.1041(1)$ Å, $b = 8.2609(1)$ Å, $c = 15.5067(1)$ Å, $\beta = 93.3987(8)°$, $V = 652.68(2)$ Å^3, $Z = 2$, $M = 282.38$, 9848 reflections measured, 2589 independent reflections. Final $R = 0.0565$, $wR = 0.0678$, GoF = 0.9786 for 2211 reflections with $I > 2\sigma(I)$ and 165 parameters.

CCDC 674694 (**6l**) and 674695 (**6n**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Supporting Information Available: General experimental, alternative ways of preparation of **4a**, detailed experimental procedures, and characterization data for compounds **4b**,**c**,**g**−**i**, **6b**−**e**,**m**−**p**, **7b**−**d**,**k**, experimental details of fluorescence measurements and table of log-normal parameters, and copies of all NMR spectra and cif files for **6l** and **6n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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