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Note

Synthesis of 3′-C-substituted thymidine derivatives by free-radical techniques: scope and limitations

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Abstract—The scope and limitations of radical-mediated 3′-C-substitution of pyrimidine nucleosides was evaluated with 5′-*O*-(*tert*-butyldimethylsilyl)thymidine or its *tert*-butyldiphenylsilyl analogue having thionoester or thionoamide groups at O-3′, including (methylthio)thiocarbonyl, (phenoxy)thiocarbonyl, (pentafluorophenoxy)thiocarbonyl, and (1-imidazolyl)thiocarbonyl. Their reaction with acrylonitrile, methyl acrylate, and allyltributyltin under radical-generating conditions affords corresponding 3′-C-alkylated products, together with the product of simple deoxygenation at C-3′. The conditions for optimizing the yield of 3′-C-substituted product are presented.

Keywords: Free-radical; Thymidine; Nucleoside; Thionoamide; Thionoester; C-Alkylation

Nucleoside mimetics have held sustained interest over many decades for their potential in the treatment of diseases, as antitumor, antiviral, antibacterial, or antiparasitic agents.[1] Our laboratory has explored synthetic methodology targeted especially toward nucleoside analogues modified in the sugar portion, and to structures having a noncyclized glycon component.[2] The antiviral potential of such mimetics has stimulated much activity, especially in the quest for compounds effective in treating acquired immunodeficiency syndrome (AIDS).[3] Such agents include[3] the reverse-transcriptase inhibitors AZT (Zidovudine), 3TC (Lamivudine), ABC (Abacavir), d4T, ddI, and ddC, which are all 2′,3′-dideoxy nucleoside derivatives. The ability of the human immunodeficiency virus (HIV) to become resistant to a particular drug regimen emphasizes the need for newer agents.[4] In this context we have evaluated synthetic methodology directed toward C-3′-substituted 2′,3′-dideoxy nucleoside derivatives.[5] Examples of such compounds include 3′-fluoro-3′-deoxythymidine,[6] a potent anti-HIV agent in vitro, and C-3′-alkenyl (and alkynyl)-3′-deoxythymidines.[7]

We sought general and high-yielding procedures for C-3′-alkylated 2′,3′-dideoxy nucleosides incorporating a variety of alkyl chains. Possible synthetic approaches to C-3′-substituted nucleoside derivatives include procedures based on the attack of a nucleophile on a pentofuranos-3-ulose derivative, either on a precursor sugar derivative or on a preformed 3′-keto nucleoside. The latter approach often leads simply to the elimination of the nucleoside base, and the former requires an additional synthetic step for covalent attachment of the base. In recent years, free-radical chemistry has been shown to be an attractive alternative for synthesizing C-3′-substituted 2′,3′-dideoxynucleoside analogues directly from a preformed nucleoside, as documented notably in the work of Chu et al.[8] and others,[9,10] who introduced a 3′-*C*-allyl group in a 5′-protected thymidine bearing a thiono substituent at C-3′. The scope and limitations of this approach with respect to other carbon donors remains to be explored.

Our studies have likewise employed thymidine as the precursor, protected at O-5′ by the *tert*-butyldimethylsilyl[11] or *tert*-butyldiphenylsilyl[12] groups, and application of the general strategy of Keck and Yates for allylation of a carbon radical with allyltributyltin[13] and of Giese et al.[14] for C-glycosylation of hexoses with

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acrylonitrile and tributyltin hydride. Optimization of the procedure involved examination of various radical precursors and the evaluation of different trapping agents and experimental conditions.

Thiono groups serving as radical precursors for subsequent C–C bond formation were introduced at O-3′ of the known[11,15] 5′-*O*-*tert*-butyldimethylsilylthymidine (**1**). The crystalline 3′-(methylthio)thiocarbonyl [$CH_3SC(=S)$–] derivative (**2**) was obtained in 84% yield by the successive treatment of **1** with sodium hydride, carbon disulfide, and methyl iodide, and the corresponding 3′-(imidazol-1-yl)thiocarbonyl [$(C_3H_3N_2)C(=S)$–] derivative (**3**) was isolated crystalline in 82% yield by treating **1** with 1,1′-thiocarbonyldiimidazole.

A benzene solution of thionoester **2** and an excess of acrylonitrile (a good radical trapping-agent), was heated under argon, and tri-*n*-butyltin hydride and azobis(isobutanonitrile) (AIBN, as a radical-generating agent), in benzene solution, was added at a controlled rate *via* a syringe pump. Flash chromatography of the reaction mixture revealed three main components. First eluted was a product that appeared to be the carbonyl analogue of thiono precursor **2**, and this was followed by the product of simple 3′-deoxygenation of **2**, identified after the removal of the silyl group, as the known 2′,3′-dideoxy nucleoside. The third fraction, obtained crystalline in 25% yield, was the desired 3′-alkylated product, namely 5′-*O*-*tert*-butyldimethylsilyl-3′-*C*-(2-cyanoethyl)thymidine (**4**). The NMR data (see Tables 1 and 2) for **4** supported the assigned 'down' stereochemistry of the 3′-substituent, as might be expected from favored approach of the carbon addend on the face opposite the large substituents at C-1 and C-4 of the pentofuranose ring. The reaction is evidently stereoselective, but the possibility that the C-3′ epimer might have been present in the reaction mixture cannot be ruled out.

Repetition of the reaction, but using thionocarbamate **3** as the radical precursor instead of **2**, again gave a mixture of products. However, in this instance, the yield of crystalline 3′-*C*-(2-cyanoethyl) derivative **4** was significantly enhanced, to 52%, and it was concluded that thionocarbamate precursor **3** constituted a more effective radical precursor than thionoester **2**.

A further evaluation of thionocarbamate **3** for C-alkylation was conducted under similar conditions, with methyl acrylate as the trapping agent. TLC of the reaction mixture after removal of the 5′-substituent by use of tetrabutylammonium fluoride and chromatographic isolation of the principal component gave 41% of a product whose NMR data the indicated it to be 3′-*C*-(2-methoxycarbonyl)ethyl derivative (**5**) of thymidine.

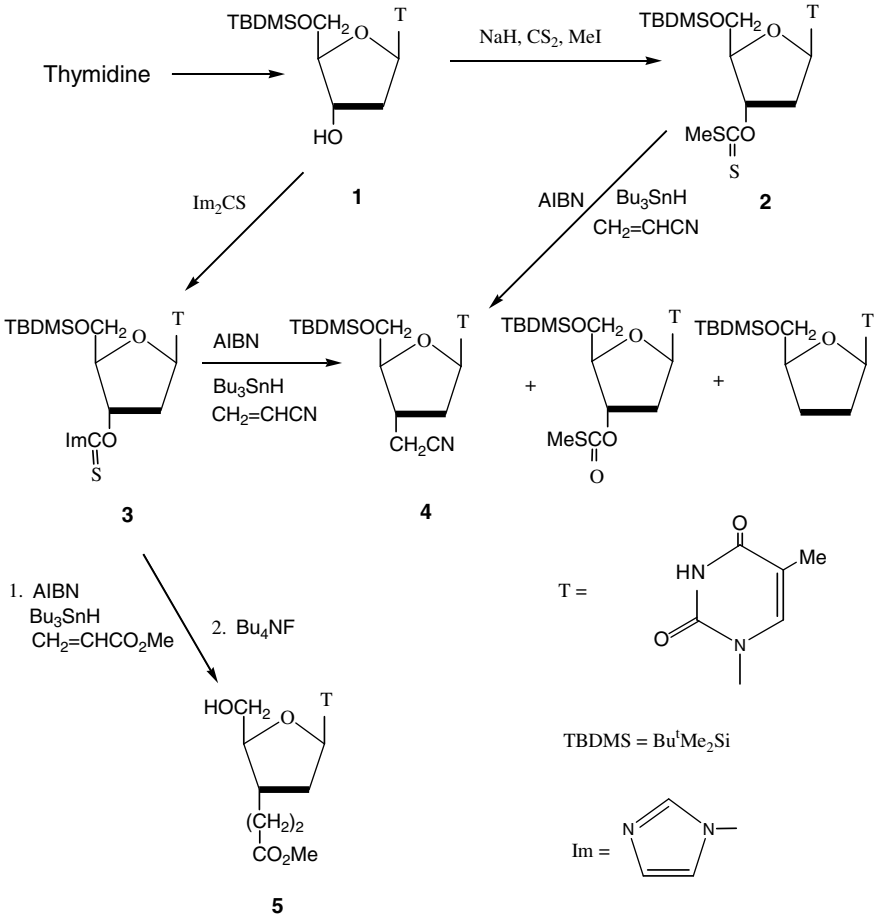

Table 1. ^{1}H NMR chemical-shift data[a] (δ) for compounds **1**–**11**

Compound	Chemical shifts, δ								
	H-1′	H-2′	H-2″	H-3′	H-4′	H-5′	H-5″	H-6	NH
1	6.37 dd	2.36 m	2.11 m	4.46 m	4.04 dd	3.86 m		7.50 d	8.73 s
2[b]	6.43 dd	2.57 m	2.20 m	5.95 d	4.28 m	4.02 dd	3.91 dd		
3	6.46 dd	2.72 dd	2.29 m	5.93 d	4.38 m	4.06 dd	3.97 dd		
4[c]	6.09 dd	2.25 m	2.13 m	2.43 m	3.76 m	3.98 m	3.76 m		
5	6.06 dd				4.01 m	3.75 m			
6	6.39 dd	2.39 ddd	2.20 ddd	4.56 dd	3.99 dd	3.97 dd	3.85 dd	7.48 d	8.41 br
7	6.47 dd	2.66 ddd	2.36 ddd	6.15 dd	4.27 dd	4.09 dd	3.97 dd	7.57 d	8.34 s
8	6.52 dd	2.75 ddd	2.43 d	5.95 dd	4.37 d	4.08 dd	4.08 dd	7.58 dd	8.64 s
9	6.499 dd	2.77 dd	2.48 ddd	6.09 dd	4.36 d	3.65 m		7.59 d	9.17 br
10	6.57 dd	2.77 dd	2.43 ddd	5.95 dd	4.39 d	3.95 m		7.61 d	9.68 br
11	6.12 t	2.10 m		5.05 m	4.06 dd	3.80–3.72 m	2.42 dt	7.52 d	8.83 s

[a] In $CDCl_3$ with Me_4Si as the internal standard.
[b] 2.57 (s, 3H, SMe).
[c] 2.35 (s, 3H, SMe).

Table 2. ^{1}H NMR spin-coupling constants (Hz) for compounds **1**–**11**

Compound	Coupling constants (Hz)						
	$J_{1',2'}$	$J_{1',2''}$	$J_{2',2''}$	$J_{3',4'}$	$J_{4',5'}$	$J_{4',5''}$	$J_{5',5''}$
1	5.8	8.0		2.5	5.0		
2	5.3	9.3		5.9	1.8	2.1	11.4
3	5.3	9.3	14.2	5.9	1.8	2.0	11.4
4	4.6	6.8			2.1	1.8	
5	3.0	7.2					
6[a]	5.9	8.0	8.5		2.9	3.6	12.2
7[b]	5.2	9.4	14.0	6.0	2.0		11.5
8[c]	5.1	9.4	14.1	3.9	1.1		
9[d]	5.2	9.3	14.4				
10[e]	5.1	9.4	14.1	5.9			
11	5.7	5.7	14.5		3.5		11.5

[a] $J_{2',3'}$ 8.5, $J_{2'',3'}$ 2.5 Hz.
[b] $J_{2',3'}$ 5.2, $J_{2'',3'}$ 6.1 Hz.
[c] $J_{2'',3'}$ 6.0 Hz.
[d] $J_{2'',3'}$ 5.2 Hz.
[e] $J_{2'',3'}$ 2.4 Hz.

Attempts to apply the foregoing free-radical procedures using either maleimide, maleic anhydride, or phenylacetylene as the radical trapper proved unsuccessful. With a large excess of maleimide and an extended reaction period, the starting compound was largely recovered.[16] The use of maleic anhydride again returned mostly thionocarbamate **3**, along with the product of simple deoxygenation, the 5′-protected 2′,3′-dideoxythymidine (ddT) derivative. With phenylacetylene, the only product detected was material formed by radical-induced polymerization of phenylacetylene.[16]

The replacement of O-3′ in the thymidine structure by a *C*-allyl group *via* free-radical procedures has been reported by Chu et al.,[8] and Fiandor and Tam,[9] using the 3′-*O*-phenoxythiocarbonyl derivative of compound **1**, and by De Mesmaeker et al.[10] using the *tert*-butyldiphenylsilyl protecting group and the 3′-*O*-(*o*-tolyloxy)thiocarbonyl group. Our studies employed the *tert*-butyldiphenylsilyl protecting group, preparing from thymidine the silyl ether **6** in 82% yield by a modification of a known[12,17] procedure, and **6** was further converted into 3′-thiono derivatives to serve as radical precursors for replacement of the O-3′ substituent by the allyl group. The crystalline 3′-*O*-(methylthio)thiocarbonate (**7**) was obtained from **6** by successive treatment with sodium hydride, carbon disulfide, and methyl iodide. Three additional 3′-thiono compounds were also prepared for comparative evaluation in an effort to maximize yields of 3′-C-alkylated products. Treatment of **6** with phenyl chlorothionoformate–pyridine afforded crystalline 3′-*O*-(phenoxy)thiocarbonate **8**, previously reported[12] as a glass, in 96% yield. Similarly prepared from **6** were the 3′-*O*-(imidazol-1-yl)thiocarbamate **9**, obtained crystalline in 62% yield, and the 3′-*O*-(pentafluorophenoxy)thiocarbonate **10**, also crystalline, in 87% yield.

Each of the four compounds **7**–**10** was evaluated comparatively in reaction with allyltributyltin, with the AIBN initiator generating tributyltin radicals that abstract the thiono group at C-3′ of the 5′-protected nucleoside derivative to generate a radical species at C-3′, which in turn interacts with allyltributyltin to effect allylation at C-3′.

The general procedure for the allylation reaction was adapted from the techniques described by Keck et al.,[18] with careful exclusion of oxygen. Each of the thiono precursors **7**–**10** reacted with allyltributyltin in boiling benzene to produce a mixture of products from which the desired 3′-*C*-allyl product **11** could be isolated as a low-melting crystalline solid, along with the product of simple deoxygenation at C-3′. Compound **11** was earlier described[10] as a foam, prepared from an *o*-tolyl analogue of **8**.

The results are shown in Table 3, where it may be seen that the 1-[5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-3-*O*-[(pentafluorophenoxy)thiocarbonyl]-β-D-*erythro*-pentofuranosyl]thymine radical precursor **10** turned out to be the best precursor among those examined, both in terms of overall yield (89%) and reaction time (2 h). The yield

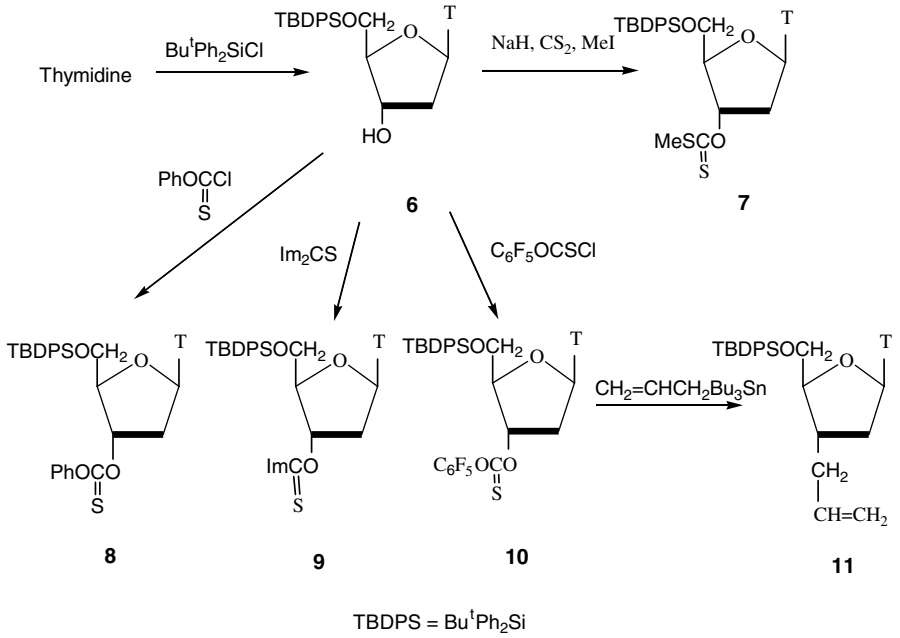

Table 3. Conversion of 3′-hydroxy precursor **6** into 3′-*C*-allyl product **11**

Protect 3′-OH	Yield (%)	Allylation	Yield (%)	Overall yield (%)	Total time (h)
6 → **7**	67	**7** → **11**	22	15	96
6 → **8**	96	**8** → **11**	32	31	70
6 → **9**	62	**9** → **11**	77	48	7
6 → **10**	87	**10** → **11**	90	78	2

of *C*-allyl product **11** ranged from 22% for the (methylthio)thiocarbonate **7**, 32% for the (phenoxy)thiocarbonate **8**, and 72% for the (imidazol-1-yl)thiocarbamate **9**, and all required longer reaction times.

Further functional modification of the allyl group in compound **11** to generate the formylmethyl derivative, and its reduction to the corresponding *C*-(2-hydroxymethyl) derivative has been recorded elsewhere.[19] Although there are conflicting reports as to whether the 5′-deprotected analogue of this derivative possesses antiviral activity,[20,21] it was disclosed[20] to have antitumor activity against four tumor cell lines (L1210, P388, S-180, and CCRF-CEM).

Attempts to prepare 3′-vinyl and 3′-ethynyl analogues of 3′-allyl derivative **11** by similar free-radical procedures were not successful.[19] Although these analogues are accessible[7] by a long synthetic sequence, the current approach offered promise for a simple and brief alternative. However, the procedure used for 3′-C-allylation of pentafluorophenoxythiocarbonyl derivative **10** in reaction with allyltributyltin, repeated under a range of conditions and variation of solvent with either tributylvinyltin or tributylethynyltin led principally to mixtures of the products of simple deoxygenation at C-3′ or removal of the thiono substituent to produce the parent 3′-hydroxy compound **6**; there was no evidence for the formation of C-3′ alkylated products.

In conclusion, this report demonstrates satisfactory procedures for using acrylonitrile and methyl acrylate as radical acceptors for the attachment of a carbon chain at C-3′ of a 5′-protected thymidine *via* a 3′-thiono derivative, and an optimized procedure for C-3′ allylation by the use of a 3′-pentafluorophenoxythionocarbonate precursor. However maleimide, maleic anhydride, and phenylacetylene failed to react under comparable conditions, and the attempted introduction of a vinyl or ethynyl group using tributylvinyltin or tributylethynyltin was likewise unsuccessful.

1. Experimental

1.1. General methods

The solvents were purified and dried as recommended[22] and the evaporation of solvents was performed under diminished pressure at a bath temperature below 40 °C, unless otherwise stated. Melting points were determined with a Fisher–Johns melting point apparatus without correction. Thin-layer chromatography (TLC) was performed on Silica Gel 60 F_{254} (E. Merck) followed by dipping the plates in 5% *p*-anisaldehyde soln, with subsequent heating. Silica Gel 60 (E. Merck) was used for column chromatography. Microanalyses were performed by Atlantic Microlab Inc., Norcross, Ga. ^{1}H NMR and ^{13}C NMR spectra were recorded on the following Bruker instruments, as noted in the tables: AM-250 (250 MHz ^{1}H, 62.5 MHz ^{13}C); AM-300 (300 MHz ^{1}H, 75 MHz ^{13}C); WM-300 (300 MHz ^{1}H,

75 MHz ^{13}C); and AM-500 (500 MHz ^{1}H, 125 MHz ^{13}C). All spectra were recorded at ~25 °C with the spectrometers operating in the Fourier-transform mode. The ^{1}H and ^{13}C spectral assignments were made by comparison with known compounds or with similar structures whose spectral assignments have been published. Decoupling techniques or COSY were also applied to spectral assignments and to determine the coupling constants as necessary. Mass spectra were recorded with Kratos MS-30 or VG70-250s instruments at an ionizing potential of 70 eV.

1.2. Preparation[11,15] of 1-[5-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-β-D-*erythro*-pentofuranosyl]thymine (1)

tert-Butylchlorodimethylsilane (890 mg, 5.90 mmol) was added to a soln of thymidine (1.38 g, 5.70 mmol) and imidazole (780 mg, 11.5 mmol) in *N*,*N*-dimethylformamide (10 mL) at room temperature. After 2 h, the mixture was poured into 50 mL of ice–water in a thin stream with vigorous stirring, and then extracted with CH_2Cl_2 (50 mL × 2). The extracts were combined, dried ($MgSO_4$), and the solvent removed. The residue was triturated with 15 mL of petroleum ether (bp 35–60 °C), and filtration gave 1.78 g of **1** as a white solid. The filtrate was evaporated and the residue adsorbed onto 30 g of silica gel and eluted with 10:1 toluene–1,4-dioxane. Fractions containing the product of R_f 0.67 (1:1 1,4-dioxane–benzene) were combined and after removal of the solvent, afforded a further 80 mg of **1** as a white solid. The combined yield was 1.86 g (5.22 mmol, 92%). Recrystallization from $CHCl_3$–C_6H_6 gave analytically pure **1** as white crystals: mp 197–198.5 °C; lit.[11] mp 198–199 °C; $[\alpha]_D$ +1.65 (*c* 0.80, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): (see Tables 1 and 2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 163.68 (C-4), 150.36 (C-2), 135.44 (C-6), 110.96 (C-5), 87.18 (C-4′), 85.00 (C-1′), 72.63 (C-3′), 63.61 (C-5′), 41.16 (C-2′), 25.95 [C(*C*H$_3$)$_3$], 18.38 [*C*(CH$_3$)$_3$], 12.54 (α-CH$_3$), −5.34 (Si–CH$_3$), −5.44 (Si–CH$_3$).

1.3. 1-[5-*O*-(*tert*-Butyldimethylsilyl)-2-deoxy-3-*O*-[(methylthio)thiocarbonyl]-β-D-*erythro*-pentofuranosyl]thymine (2)

A mixture of **1** (2.80 g, 7.86 mmol), NaH (80% dispersion in mineral oil, 5.60 g), and imidazole (10 mg) in 50 mL of dry tetrahydrofuran was stirred for 30 min at room temperature until no more hydrogen was evolved. Carbon disulfide (5.6 mL, 93 mmol) was added and stirring continued for 1 h at room temperature, followed by the addition of MeI (6.2 mL, 0.10 mol). The resultant mixture was stirred for 30 min at room temperature and then cooled in an ice–water bath. Water was added to the mixture until no more hydrogen was evolved and the product was extracted with 50 mL of Et_2O. The extracts were evaporated and the crude product was purified by flash-column chromatography (50:1 $CHCl_3$–MeOH). The fractions of major product (R_f 0.78, 10:1 $CHCl_3$–MeOH) were collected and the solvent evaporated to give a yellow syrup that was triturated with petroleum ether. Filtration of the pale-yellow solid and drying in vacuo at room temperature gave 2.94 g (6.58 mmol, yield 84%) of compound **2** as white crystals; mp 167–169 °C; $[\alpha]_D$ −38.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): (see Tables 1 and 2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 215.34 (s, C=S), 163.88 (s, C-4), 150.51 (s, C-2), 134.88 (d, C-6), 111.22 (s, C-5), 85.02 (d, C-4′), 84.76 (d, C-1′), 83.90 (d, C-3′), 63.64 (t, C-5′), 38.08 (t, C-2′), 25.85 [q, C(*C*H$_3$)$_3$], 19.20 (q, SCH$_3$), 18.24 (s, *C*(CH$_3$)$_3$), 12.41 (q, α-CH$_3$); −5.44 (q, Si–CH$_3$), −5.51 (q, Si–CH$_3$); EIMS: *m*/*z* 447 [1.34, M+H]$^+$, 339 [7.91, M+H−CH$_3$SC(=S)OH]$^+$, 321 [8.68, M+H−thymine]$^+$. Anal. Calcd for $C_{18}H_{30}N_2O_5S_2Si$ (446.66): C, 48.40; H, 6.77; N, 6.27; S, 14.36. Found: C, 48.41; H, 6.82; N, 6.27; S, 14.46.

1.4. 1-[5-*O*-(*tert*-Butyldimethylsilyl)-2-deoxy-3-*O*-[(imidazolyl)thiocarbonyl]-β-D-*erythro*-pentofuranosyl]thymine (3)

A soln of compound **1** (5.70 g, 16.0 mmol) in anhyd THF (15 mL) and 1,1′-thiocarbonyldiimidazole (4.64 g, 90% purity, 23.4 mmol) under argon was boiled under reflux for 2 h. The mixture was then evaporated and the residue subjected to flash chromatography on silica gel (50:1 $CHCl_3$–MeOH) to give a light-yellow syrup (R_f 0.61, 10:1 $CHCl_3$–MeOH), which was triturated with petroleum ether to yield 6.10 g (13.1 mmol, 82% yield) of **3** as a white solid. Recrystallization from $CHCl_3$ and petroleum ether gave **3** as white crystals; mp 105–108 °C; $[\alpha]_D$ −44.0 (*c* 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): (see Tables 1 and 2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 183.11 (s, C=S), 163.79 (s, C-4), 150.56 (C-2), 137.16 (s, C-2 of imidazole), 134.53 (d, C-6), 131.10 (d, C-5 of imidazole), 117.81 (d, C-4 of imidazole), 111.46 (s, C-5), 84.83 (d, C-4′), 84.80 (d, C-1′), 84.25 (d, C-3′), 63.77 (t, C-5′), 38.06 (t, C-2′), 25.85 [q, C(*C*H$_3$)$_3$], 18.26 [s, *C*(CH$_3$)$_3$], 12.47 (q, α-CH$_3$), −5.40 (q, Si–CH$_3$), −5.49 (q, Si–CH$_3$).

1.5. 1-[5-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-(2-cyanoethyl)-2,3-dideoxy-β-D-*erythro*-pentofuranosyl]thymine (4)

1.5.1. From dithiocarbonate 2. A mixture of 500 mg (1.12 mmol) of compound **2** and acrylonitrile (910 μL, 18.0 mmol) in anhyd benzene (20 mL) was heated to reflux under argon. A soln of 0.45 mL (1.67 mmol) of Bu_3SnH and 40 mg of azobis(isobutanonitrile) (AIBN) in 0.7 mL of anhydrous benzene was added *via* a syringe pump at a rate of 0.2 mL/h. The resulting

mixture was boiled under reflux for an additional 2 h. TLC analysis revealed that **2** was still present. Additional acrylonitrile (0.20 mL, 3.96 mmol) was added and a soln (0.50 mL) of benzene containing 350 μL (1.30 mmol) of Bu_3SnH and 40 mg of AIBN was added over 2 h, and boiling was continued for an additional 2 h. However, the amount of **2** present did not decrease appreciably with this further addition. The mixture was cooled to room temperature and evaporated to a syrup, which was subjected to chromatography on silica gel (100:1 $CHCl_3$–MeOH). The first fraction crystallized and was recrystallized from acetone–petroleum ether to afford 1-[5-*O*-(*tert*-butyldimethylsilyl)-3-*O*-(methylthio)carbonyl-2-deoxy-β-D-*erythro*-pentofuranosyl]thymine as white crystals, yield 220 mg (45%), mp 160–162 °C, $[\alpha]_D^{25}$ −0.5 (*c* 0.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 8.06 (s, 1H, NH), 7.51 (d, 1H, H-6), 6.35 (dd, 1H, $J_{1',2'}$ 5.3, $J_{1',2''}$ 9.3 Hz, H-1′), 5.37 (d, 1H, $J_{2',3'}$ H-3′), 4.17 (d, 1H, $J_{3',4'}$ 1.5 Hz, H-4′), 3.91 (d, 2H, *J* 2.0 Hz, H-5′,5″), 2.47 (dd, 1H, J_{gem} 13.9 Hz, H-2′), 2.35 (s, 3H, $COSCH_3$), 2.12 (m, 1H, H-2″), 1.92 (d, 3H, α-CH_3), 0.94 [s, 9H, $C(CH_3)_3$], 0.14 (s, 6H, Si–Me); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 171.63 (s, $OCOSCH_3$), 163.60 (s, C-4), 150.27 (s, C-2), 134.86 (d, C-6), 111.17 (s, C-5), 85.04 (d, C-4′), 84.61 (d, C-1′), 78.13 (d, C-3′), 63.41 (t, C-5′), 38.00 (t, C-2′), 25.84 [q, $C(CH_3)_3$], 18.25 [s, $C(CH_3)_3$], 13.34 (s, SMe), 12.40 (q, α-CH_3), −5.46 (q, SiMe), −5.58 (q, SiMe); EIMS: *m*/*z* 431 (0.5, M^+-1), 93 (100, $CH_3SCO_2H^+$+1). Anal. Calcd for $C_{18}H_{30}N_2O_6SSi$ (430.60): C, 50.20; H, 7.02; N, 6.50; S, 7.45. Found: C, 50.32; H, 7.03; N, 6.55; S, 7.36.

The second fraction gave a crude white solid (26 mg, 7%), which was identified as 1-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-β-D-*erythro*-pentofuranosyl]thymine, as deprotection of the 5′-OH group by treatment of a soln in tetrahydrofuran with 1 M Bu_4NF in tetrahydrofuran for 2 h at room temperature gave 2,3-dideoxy-β-D-*erythro*-pentofuranosylthymine; recrystallized from acetone–petroleum ether it had mp 146–149 °C (lit.[23] mp 145 °C), $[\alpha]_D^{25}$ +27 (*c* 0.62, MeOH); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 163.62 (C-4), 149.87 (C-2), 138.48 (C-6), 108.68 (C-5), 84.70 (C-1′), 80.69 (C-4′), 61.79 (C-5′), 31.57 (C-2′), 24.08 (C-3′), 11.57 (α-CH_3); EIMS: *m*/*z* 227 (24, M^++1), 126 (100, thymine$^+$+1), 101 (84, M^++1−thymine).

The third fraction (140 mg of a crude syrup) was triturated with 10 mL of petroleum ether and 2 mL of Et_2O to yield 110 mg (0.28 mmol, 25%) of **4** as a white solid: mp 117–120 °C; $[\alpha]_D$ +22.0 (*c* 0.25, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): (see Tables 1 and 2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 163.59 (C-4), 150.26 (C-2), 135.23 (C-6), 118.61 (CN), 110.62 (C-5), 85.47 (C-4′), 84.75 (C-1′), 63.10 (C-5′), 38.34 (C-2′), 37.16 (CH_2CN), 28.12 (CH_2CH_2CN), 25.95 [$C(CH_3)_3$], 18.46 [$C(CH_3)_3$], 15.97 (C-3′), 12.60 (α-CH_3), −5.36 (Si–CH_3); EIMS: *m*/*z* 394 [2.31, M+H]$^+$, 336 [1.55, M+H−$CH(CH_3)_3$]$^+$, 268 [31.41, M+H−thymine]$^+$. Anal. Calcd for $C_{19}H_{31}N_3O_4Si$ (393.56): C, 57.99; H, 7.94; N, 10.68. Found: C, 57.77; H, 8.01; N, 10.53.

1.5.2. Compound 4 from thionocarbamate 3. To a soln of 330 mg (0.71 mmol) of thionocarbamate **4** and acrylonitrile (0.72 mL, 14.3 mmol) in 15 mL of dry benzene boiled under reflux under argon was added a soln of 250 mg (0.93 mmol) of Bu_3SnH and 12 mg of AIBN in 5.0 mL of anhydrous benzene over 5 h *via* a syringe pump at the rate of 1.0 mL/h. The resulting soln was boiled under reflux for an additional 2 h. TLC analysis (10:1 CH_3Cl–MeOH) revealed two major (R_f 0.68 and 0.58) and two minor products (R_f 0.43, 0.35). The solvent was evaporated to give an oil that was resolved by flash chromatography over silica gel. The fraction corresponding to R_f 0.58 contained **4**. The solvent was evaporated and the residue triturated with petroleum ether to give 147 mg (0.37 mmol, 52%) of compound **4** as a white solid.

1.6. 1-[2,3-Dideoxy-3-*C*-(2-methoxycarbonylethyl)-β-D-*erythro*-pentofuranosyl]thymine (5) from thionocarbamate 3

To a soln of thionocarbamate **3** (1.01 g, 2.17 mmol) and methyl acrylate (2.03 g, 23.6 mmol) in 10 mL of anhyd benzene heated to reflux under argon was added a soln of 1.17 mL (4.35 mmol) of Bu_3SnH and 40 mg of AIBN in 7.0 mL of anhyd benzene over a period of 8 h *via* a syringe pump at a rate of 1 mL/h. The resultant soln was boiled for an additional 2 h. TLC monitoring (10:1 $CHCl_3$–MeOH) of the reaction showed a major product at R_f 0.64. After solvent removal, the residue was subjected to flash chromatography over silica gel (25:1 $CHCl_3$–MeOH) to give the R_f 0.64 component (0.930 g) as an oil. Analysis of this fraction revealed the oil to still be a mixture. Deprotection was effected by adding 2.0 mL (2 mmol) Bu_4NF in 30 mL of THF and stirring at room temperature for 30 min. TLC analysis revealed four products (R_f 0.39, 0.35, 0.32, and 0.27; 15:1 $CHCl_3$–MeOH). Removal of solvent followed by flash chromatography on silica gel (15:1 $CHCl_3$–MeOH) gave the homogeneous R_f 0.32 component **5** as a syrup (350 mg, 0.89 mmol, 41%); $[\alpha]_D$ −13 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): (see Tables 1 and 2); ^{13}C NMR (500 MHz, $CDCl_3$): δ 173.43 (s, CO), 163.19 (s, C-4), 150.25 (s, C-2), 136.28 (d, C-6), 110.36 (s, C-5), 88.32 (d, C-4), 85.26 (C-1′), 61.75 (t, C-5′), 51.82 (q, OCH_3), 38.92 (t, C-2′), 36.33 (d, C-3′), 32.29 (t, $CH_2CH_2CO_2CH_3$), 26.97 (t, $CH_2CH_2CO_2CH_3$), 12.52 (α-CH_3). Copies of the ^1H and ^{13}C NMR spectra of compound **5** are recorded in the Supplementary data.

Repetition of this procedure under the same conditions, but with maleimide in the place of methyl acrylate showed no reaction, even after a second addition of

Bu_3SnH and AIBN and further heating for 5 h in boiling benzene, and starting compound **3** was recovered in 84% yield. Similar results were observed when maleic anhydride and phenylacetylene were used in the place of methyl acrylate.[16]

1.7. 1-[5-*O*-(*tert*-Butyldiphenylsilyl)-2-deoxy-β-D-*erythro*-pentofuranosyl]thymine (6)

In a minor modification of the literature procedure,[12,17] *tert*-butylchlorodiphenylsilane (8.375 mL, 31.85 mmol) was added dropwise over 20 min to a 0 °C soln of thymidine (6.24 g, 25.76 mmol) and imidazole (3.725 g, 54.5 mmol) in DMF (37.5 mL) under argon. The mixture was stirred for 2 h and the solvent removed at 90 °C. The resultant yellow syrup was dissolved in $CHCl_3$ (50 mL) and washed with water (40 mL × 2). The $CHCl_3$ layer was dried (Na_2SO_4) and evaporated to furnish a colorless syrup, which was then dissolved in 5:2 ether–MeOH, followed by the addition of hexane (100 mL) with stirring. The resulting soln was cooled to 0 °C, and a white crystalline product formed after 1 h. The crystals were filtered off and washed with hexane to provide a first crop of compound **6**. A second crop of **6** was obtained by concentration of the filtrate, followed by the same purification procedure. The combined yield was 10.22 g (82.5%): mp 162–164 °C; lit.[12] mp 162 °C; R_f 0.38 (ether); $[\alpha]_D$ +55.4 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): (see Tables 1 and 2); ^{13}C NMR ($CDCl_3$): δ 163.96 (C-2), 150.53 (C-4), 135.56, 135.45, 135.30, 132.95, 132.36, 130.16, 130.06, 128.01, 127.97 (aromatic carbons), 128.00 (C-6), 111.30 (C-5), 87.19 (C-4′), 84.77 (C-1′), 72.77 (C-3′), 64.20 (C-5′), 41.02 (C-2′), 27.00 [C(CH_3)$_3$], 19.37 [$C(CH_3)_3$], 12.11 (5-CH_3).

1.8. 1-[5-*O*-(*tert*-Butyldiphenylsilyl)-2-deoxy-3-*O*-[(methylthio)thiocarbonyl]-β-D-*erythro*-pentofuranosyl]thymine (7)

To a suspension of 1-[5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-β-D-*erythro*-pentofuranosyl]thymine (**6**, 0.961 g, 2.00 mmol) in anhyd THF (7 mL) was added NaH (87.3 mg, 3.64 mmol) with stirring under argon at room temperature. After 30 min, CS_2 (0.42 mL, 6.98 mmol) was added in one portion, followed by MeI (0.28 mL, 4.45 mmol) 30 min later. The reaction was then quenched after 20 min by adding AcOH until no more hydrogen gas was evolved. The mixture was then diluted with 7 mL of ether and filtered. Evaporation of the filtrate gave a yellowish syrup, which upon dissolution in ether yielded a white crystalline solid. Purification of this product on a column of silica gel by gradient elution (from 1:1 ether–hexane to pure ether) afforded compound **7** as white crystals (0.768 g, 1.35 mmol, 67%), mp 133.0–134.5 °C, R_f 0.89 (ether); $[\alpha]_D$ +32.6 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): (see Tables 1 and 2); ^{13}C NMR ($CDCl_3$): δ 215.32 (C=S), 163.99 (C-2), 150.64 (C-4), 135.65, 135.25, 134.89, 132.74, 131.87, 130.28, 130.16, 128.10 (aromatic carbons), 128.07 (C-6), 111.68 (C-5), 84.90 (C-4′), 84.54 (C-1′), 83.52 (C-3′), 77.66 (SCH_3), 64.38 (C-5′), 38.17 (C-2′), 27.03 [C(CH_3)$_3$], 19.39 [$C(CH_3)_3$], 12.08 (5-CH_3); EIMS: *m/z* 571 [1.34, $M+H]^+$, 513 [14.24, $M+H-HC(CH_3)_3]^+$, 405 [48.19, $M+H-CH_3SC(=S)OH-HOC(CH_3)_3]^+$, 307 [21.47, $M+H-CH_3SC(=S)OH-(C_6H_6)]^+$, 279 [79.36, $M+H-CH_3SC(=S)OH-2(C_6H_6)$−thymine]$^+$, 199 [51.06, $(C_6H_5)_2SiOH]^+$. Anal. Calcd for $C_{30}H_{34}N_4O_5SSi$ (570.807): C, 58.92; H, 6.00; N, 4.91. Found: C, 58.63; H, 5.95; N, 4.90.

1.9. 1-[5-*O*-(*tert*-Butyldiphenylsilyl)-2-deoxy-3-*O*-[(phenoxy)thiocarbonyl]-β-D-*erythro*-pentofuranosyl]thymine (8)

To a suspension of 1-[5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-β-D-*erythro*-pentofuranosyl]thymine (**6**, 0.867 g, 1.80 mmol) in anhyd benzene (18 mL) was added phenyl chlorothionoformate (0.249 mL, 1.80 mmol) with stirring under argon at room temperature, and then after 2 min pyridine (0.147 mL, 1.82 mmol) was added in one portion. The temperature was raised to boiling point under reflux, and the reaction was complete after 2 h (a white precipitate of pyridinium chloride formed). The mixture was evaporated and the residue redissolved in $CHCl_3$ (30 mL). The soln was washed with water (30 mL) and the aqueous layer extracted with $CHCl_3$ (5 mL). The combined $CHCl_3$ layers were dried ($NaSO_4$) and evaporated. Flash-column chromatography of the crude product over silica gel with gradient elution (from 3:7 ether–hexane to pure ether) afforded, after evaporation, compound **8** as a white crystalline product (1.066 g, 1.728 mmol, 96%), mp 82.5–84 °C; R_f 0.64 (ether); [lit.[12] glass, R_f 0.79 (93:7 CH_2Cl_2–MeOH)]; $[\alpha]_D$ +36.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): (see Tables 1 and 2); ^{13}C NMR ($CDCl_3$): δ 194.23 (C=S), 153.29 (C-2), 150.31 (C-4), 135.61, 135.23, 134.80, 132.67, 131.80, 130.25, 130.15, 129.62, 128.05 (aromatic carbons), 121.77 (C-6), 111.59 (C-5), 84.75 (C-4′), 84.51 (C-1′), 83.98 (C-3′), 64.69 (C-5′), 38.10 (C-2′), 26.98 [C(CH_3)$_3$], 19.36 [$C(CH_3)_3$], 12.04 (5-CH_3); EIMS: *m/z* 618 [0.02, M+2 H]$^+$, 617 [0.01, $M+H]^+$, 405 [5.62, $M+H-C_6F_5OC(=S)OH-HOC(CH_3)_3]^+$, 279 [22.14, $M+H-C_6H_5OC(=S)OH-HOC(CH_3)_3$−thymine]$^+$, 94 [100, $C_6H_5OH]^+$, 60 [46, $O=C=S]^+$; lit.[12] 617 $[M]^+$, 560 $[M-C_4H_9]^+$.

1.10. 1-[5-*O*-(*tert*-Butyldiphenylsilyl)-2-deoxy-3-*O*-[(imidazolyl)thiocarbonyl]-β-D-*erythro*-pentofuranosyl]-thymine (9)

To a suspension of 1-[5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-β-D-*erythro*-pentofuranosyl]thymine (**6**, 0.723 g,

1.50 mmol) in anhyd THF (15 mL) was added 1,1′-thiocarbonyldiimidazole (0.653 g, 2.97 mmol) with stirring under argon at room temperature, and an additional 0.218 g (0.99 mmol) was added after the temperature of the mixture was lowered to 20 °C. The reaction was complete after 12 h. Silica gel (5 g) was added to the mixture to remove the brownish polar impurity and it was then filtered off through a bed of silica gel. Evaporation of the filtrate afforded **9** as a crystalline product (0.554 g, 0.936 mmol, 62%): mp 174–175 °C; R_f 0.89 (10:1 $CHCl_3$–MeOH); $[\alpha]_D$ +27.3 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): (see Tables 1 and 2); ^{13}C NMR ($CDCl_3$): δ 182.94 (C=S), 163.79 (C-2), 150.60 (C-4), 137.12, 135.55, 135.18, 135.13, 134.44, 132.43, 131.68, 131.06, 130.30, 130.17, 128.07, 128.03 (aromatic and imidazolyl carbons), 117.82 (C-6), 111.80 (C-5), 84.56 (C-4′), 84.47 (C-1′), 83.69 (C-3′), 64.32 (C-5′), 38.01 (C-2′), 26.96 [C(CH_3)$_3$], 19.30 [C(CH_3)$_3$], 12.08 (5-CH_3); EIMS: *m*/*z* 591 [0.04, M+H]$^+$, 405 [33.80, M+H−$C_3H_3N_2C$(=S)OH−HC(CH_3)$_3$]$^+$, 307 [29.65, M+H−$C_3H_3N_2C$(=S)OH−2(C_6H_6)]$^+$, 279 [81.45, M+H−$C_3H_3N_2C$(=S)OH−HC(CH_3)$_3$−thymine]$^+$, 81 [100.00, C_5H_5O]$^+$. Anal. Calcd for $C_{30}H_{34}N_4O_5SSi$ (590.807): C, 61.00; H, 5.80; N, 9.48. Found: C, 60.83; H, 5.82; N, 9.44.

1.11. 1-[5-*O*-(*tert*-Butyldiphenylsilyl)-2-deoxy-3-*O*-[(pentafluorophenoxy)thiocarbonyl]-β-D-*erythro*-pentofuranosyl]thymine (10)

To a suspension of 1-[5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-β-D-*erythro*-pentofuranosyl]thymine (**6**, 2.89 g, 6.0 mmol) in anhyd benzene (100 mL) at room temperature was added pentafluorophenyl chlorothionoformate (1.10 mL, 6.6 mmol) in one portion. Pyridine (0.54 mL, 6.7 mmol), which had been dried over NaOH, was added after stirring for 2 min. The temperature was raised to 80 °C under an argon atmosphere (a white precipitate of pyridine hydrochloride formed). The reaction was complete after refluxing for 2 h. The mixture was evaporated at 70 °C to furnish a porous solid, which was washed with water (50 mL × 3) and then dissolved in $CHCl_3$ (80 mL) and washed with water (50 mL) again. The separated water layer was again extracted with $CHCl_3$ (20 mL). The combined $CHCl_3$ layers were dried (Na_2SO_4) and evaporated to afford a foamy solid. The solid was dissolved in ether and subjected to flash-column chromatography over silica gel with gradient elution (pure hexane to pure ether). Evaporation of the eluate at 70 °C for 2 h, and then at room temperature for 20 h, afforded **10** as a white solid (3.72 g, 0.525 mmol, 87%): mp 80–82 °C; R_f 0.79 (ether); $[\alpha]_D^{25}$ +32.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): (see Tables 1 and 2); ^{13}C NMR ($CDCl_3$): δ 194.25 (C=S), 153.30 (C-2), 150.53 (C-4), 135.61, 135.23, 134.79, 132.67, 131.82, 130.24, 130.15, 129.61, 128.05, 126.80 (aromatic carbons), 121.78 (C-6), 111.63 (C-5), 84.74 (C-4′), 84.51 (C-1′), 83.99 (C-3′), 64.69 (C-5′), 38.10 (C-2′), 26.70 [C(CH_3)$_3$], 19.36 [C(CH_3)$_3$], 12.07 (5-CH_3); EIMS: *m*/*z* 706 (0.06, M$^+$), 649 [11.11, M+H−HOC(CH_3)$_3$]$^+$, 405 [28.43, M+H−C_6F_5OC(=S)OH−HOC(CH_3)$_3$]$^+$, 279 [56.39, M+H−C_6F_5OC(=S)OH−HOC(CH_3)$_3$−thymine]$^+$, 184 [100, C_6F_5OH]$^+$, 60 [46, O=C=S]$^+$. Anal. Calcd for $C_{33}H_{31}F_5N_2O_6SSi$ (706.77): C, 56.08; H, 4.42; N, 3.97. Found: C, 56.19; H, 4.48; N, 3.89.

1.12. 3-*C*-Allyl-1-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-β-D-*erythro*-pentofuranosyl]thymine (11) from pentafluorophenoxythionocarbonate 10

The general procedure of Keck et al.[18] for radical allylation was followed with modifications. A soln of 1-[5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-3-*O*-[(pentafluorophenoxy)thiocarbonyl]-β-D-*erythro*-pentofuranosyl]thymine (**10**, 706.7 mg, 1.000 mmol) and allyltributyltin (1.55 mL, 5.00 mmol) in anhyd benzene (30 mL) was degassed with stirring under vacuum at room temperature, and then charged with argon. The procedure was repeated three times before adding AIBN (90 mg, 0.55 mmol) in one portion under an argon atmosphere. The temperature was increased to reflux and the reaction was complete after 2 h. Two products were visible by TLC analysis. After removal of the solvent at 65 °C, the colorless syrup was chromatographed on a silica gel column *via* gradient elution (from 1:1 ether–hexane to pure ether) to provide a minor fraction of 1-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-β-D-*erythro*-pentofuranosyl]thymine and a major fraction of 1-[3-*C*-allyl-5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-β-D-*erythro*-pentofuranosyl]-thymine, which after evaporation of the eluate, was obtained as a white crystalline product (449 mg, 89.5%): mp 45.0–46.5 °C; R_f 0.72 (ether); $[\alpha]_D$ +40.8 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): (see Tables 1 and 2); ^{13}C NMR ($CDCl_3$): δ 163.90 (C-2), 150.41 (C-4), 135.53, 135.40, 135.36, 135.31, 133.17, 132.76, 130.00, 129.92, 128.91, 127.86, 127.84, 127.54 (aromatic carbons, C-2″ and C-3″), 117.06 (C-6), 110.57 (C-5), 85.53 (C-4′), 84.71 (C-1′), 63.85 (C-5′), 38.17 (C-2′), 37.13 (C-3′), 36.44 (C-1″), 27.00 [C(CH_3)$_3$], 19.38 [C(CH_3)$_3$], 12.15 (5-CH_3); EIMS: *m*/*z* 506 [0.15, M+2H]$^+$, 447 [14.33, M+H−HC(CH_3)$_3$]$^+$, 321 [100.00, M+H−HC(CH_3)$_3$−thymine]$^+$, 199 [49.26, M+H−(C_6H_5)$_2$SiOH]$^+$, 105 [7.12, C_6H_5Si]$^+$. Anal. Calcd for $C_{29}H_{36}N_2O_4Si$ (504.703): C, 69.01; H, 7.19; N, 5.55. Found: C, 69.06; H, 7.21; N, 5.56.

Repetition of this procedure using thiono derivatives **7**, **8**, and **9** gave inferior yields of **11** accompanied by the product of simple deoxygenation at C-3′ and its 3′-hydroxy analogue; details are given elsewhere.[19]

1.13. Attempted synthesis of 3′-vinyl and 3′-ethynyl analogues of 11

Repetition of the procedure used for the conversion of thionoester **10** into 3′-*C*-allyl product **11**, but using tributylvinyltin instead of allyltributyltin and xylene as the solvent led[19] to a mixture of five components, none of which was the desired 3′-*C*-vinyl derivative. Similar results were observed using acetonitrile as the solvent and also with **8** as the precursor and benzene or xylene as the solvent. Likewise, the use of tributylethynyltin under conditions for the conversion of **10** into **11**, with xylene or acetonitrile as the solvent gave mainly the product of deesterification at C-3′, and the use of **8** as the precursor gave a similar result.[19]

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2006.11.015.

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