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Synthesis of Furo[2,3-c]pyran-β-D-Nucleosides by Radical-Cyclization & their Conformational Analysis by 500 MHz ^{1}H-NMR Spectroscopy

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Abstract: Free-radical, generated from the 3'-phenylseleno nucleosides as the radical precursors **2 - 5**, *was efficiently trapped intramolecularly by an olefin or alkyne funtion anchored from the 5'-end by an ether function to give various [3.4.0]-cis-fused furo[2,3-c]pyrans* **6 - 9** *(16-34%) along with some reduced products (<10%). Similar intramolecular radical trapping reaction with 5'-O-α,β-ester-linked free radical precursor* **10 - 12**, *under an identical reaction condition, gave [3.4.0]-cis-fused δ-lactones* **13 - 15** *in 10-53% yields without any trace of reduced products. The synthesis of [3.4.0]-cis-fused furo-pyrans* **6 - 9** *from 4-oxo-6-heptenyl radical formed from the precursor* **2 - 5** *and the transformations of* **10 - 12** *to δ-lactones* **13 - 15**, *respectively, constitute first example of intramolecular 6-exo radical cyclization reaction involving the nucleophilic attack of endocyclic ring-radical to the electron-deficient exocyclic unsaturated chain. Smooth conversion of δ-lactones* **14** *and* **15** *to the ring-opened C-branched erythro derivatives* **16** *(95%) and* **17** *(94%), respectively, upon treatment with diluted aqueous ammonia have provided a new methodology for diastereospecific synthesis of 3'-C-branched nucleosides through free-radical cyclization and ring-opening sequence. The structures of furo[2,3-c]pyrans* **6 - 9** *and δ-lactones* **13 - 15** *have been firmly established by detailed 1D differential nOe experiments. Subsequently, we have also analyzed all $^3J_{HH}$ coupling constants at 500 MHz at 0°, 20° and 40°C to estimate all endocyclic dihedral angles using the Karplus-Altona algorithm. Temperature-independent $^3J_{HH}$ clearly show that furo[2,3-c]pyrans* **6 - 9** *and δ-lactones* **13 - 15** *have rigid conformations. Construction of molecular models using the endocyclic torsions of the pentose unit and various dihedral angles of the pyran or δ-lactone unit shows that the pyran ring in [3.4.0]-cis-fused furo-pyrans* **6 - 9** *are in chair conformation and the pentofuranose ring is in North conformation (Figs. 1A & 1B), while the δ-lactone ring in [3.4.0]-cis-fused δ-lactones* **13 - 15** *are in boat conformation and the pentofuranose ring is locked in South conformation (Figs. 1C & 1D). The C*-alkyl substituents in the six-membered ring in both furo[2,3-c]pyrans* **6 - 9** *and in δ-lactones* **13 - 15** *are oriented however in an equatorial position. A comparison of interproton distances obtained from molecular models (Fig. 1A - D), based on $^3J_{HH}$ coupling constants, with those obtained from volumes and intensities of nOe and rOe crosspeaks in the NOESY and ROESY spectra supports the molecular models shown in Fig. 1.*

A number of *C*-branched nucleosides have been found in the nature with considerable biological importance as antibacterial, antitumor or antiviral agents[1-3]. For example, Oxetanocin A, an oxetane containing nucleoside, and several of its analogues with modified 2'-substituent, or with different base moieties, or even replacement of the oxetane ring by the isosteric cyclobutane ring have produced remarkable anti-HIV activities[3]. This has considerably stimulated new research efforts to develop methodologies to synthesize new *C*-branched nucleosides. Methodologies for the preparation of 2'- or 3'-*C*-branched nucleosides can be classified into two different groups: (i) Glycosylation of an appropriately protected base with preconstructed *C*-branched sugar. Problems with such glycosylation approach is that these routes are time-consuming and involve multiple-step synthesis and give anomeric mixtures resulting in poor overall yields[4-15]; (ii) Specific modification of the sugar

ring of the nucleoside itself. Under the latter category, following methods have been developed for specific modifications of the 2'- or 3'-carbon of the sugar ring: (a) Nucleophilic addition to ketonucleosides[16-23], (b)Wittig reaction of ketonucleosides[24, 25], (c) Michael addition to unsaturated nucleosides[26-30], and (d) Nucleophilic opening of epoxy-nucleosides[31-33]. Recently, intermolecular free-radical addition reactions [34-37] have been also used to give 3′-(R & S)-cyano-2′,3′-dideoxynucleosides and 3′-allyl-2′,3′-dideoxy nucleosides. Intramolecular free-radical cyclization reactions have been introduced by us to give diastereospecifically pure [3.3.0]-β-fused-bis-furanonucleosides and a diastereomeric mixture of [3.3.0]-α-fused-bis-furanonucleoside derivatives[38]. Such intramolecular free radical cyclization reactions are useful in the preparation of various *C*-branched nucleosides mainly because of the fact that the condition employed for such reaction is mild and neutral, and compatible with a number of functional groups, and the starting materials required for the synthesis of the free-radical precursor are easily accessible and stable . We herein report a new stereospecific synthesis of 3′-*C*-branched thymidine derivatives by using intramolecular free-radical addition reaction and ring-opening methodology. All the compounds reported herein are new, and have not been hitherto available by any known procedures.

Preparation of free-radical precursors. 1-(3′-deoxy-3′-phenylseleno-β-D-*glycero*-pentofuranosyl) thymine (**1a**) was prepared from thymidine through "3-step-2-pot" reaction sequence using a published procedure in 20 mmol scale in 86% overall yield[39]. Radical precursor **1b** has been subsequently prepared in 93% yield from the easily accessible starting material **1a** by simple removal of the 5'-O-MMTr group by a treatment with 80% aqueous acetic acid at ~20°C overnight. Subsequently, the free-radical precursors **2** - **5** was easily prepared by selective O-alkylation of the 5′-hydroxy group in **1b** with different allyl, or propargyl bromides in THF in presence of sodium hydride at room temperature[38] in excellent yields (80-90%). The acylation of the 5′-hydroxy group in compound **1b** however posed some problem. When compound **1b** was treated with crotonoyl chloride (1.5 - 2.5 eq) in dry acetonitrile in presence of 4-N,N-dimethylaminopyridine (DMAP) (catalytic amount to 2.5 eq) at room temperature, it was found that the reaction strongly depends both upon the amount of DMAP and the reaction time. When excess of DMAP (2.5 eq) was used, the starting material **1b** was consumed within 5 h (Tlc), but only 30% desired product was isolated together with a complex mixture which had lower R_f than compound **1b** on Tlc (10% MeOH in CH_2Cl_2). When a catalytic amount of DMAP (0.2 eq) was used in the latter reaction and the reaction period was prolonged to 4 days, the yield of the desired product could be indeed improved (80%). Acylation of compound **1b** however completely failed to progress when triethylamine was used as a base. Note that the acylation went to completion smoothly at room temperature in 4 h to give compound **11** in a satisfactory yield (85%) when pyridine was used both as a solvent and a base. Acylation of compound **1b** with acrylic chloride using any of the above procedures gave poor yield of the desired product. A satsifactory yield of 5'-acryloyl ester **10** could be however obtained (84%) when a pre-formed mixture of N,N-dicyclohexylcarbodiimide[40] (DCC, 1.5 eq) and acrylic acid (3 eq) in dry CH_2Cl_2 was added within an hour to a suspension of **1b** and NaH at room temperature. Compound **12** was similarly obtained from a reaction of **1b** and 2-hexenoic acid in a good yield (81%) using a procedure described for compound **10**.

Intramolecular free-radical cyclization. We have already shown that a free-radical can be easily generated regiospecifically at the endocyclic 2'- or 3'-carbon of the nucleoside bearing the phenylseleno or phenoxythiocarbonyl group by the reaction of tri-n-butyltin hydride, and such a radical can be efficiently trapped intramolecularly by a distantly located carbon-carbon double bond of a 2'- or 3'-O-allyl group or by a

1a: R = MMTr
1b: R = H
2: R = CH2CH=CH2 (88%)
3: R = CH2CH=C(Me)2 (80%)
4: R = CH2CH=CH(Et) (94%)
5: R = CH2C≡CH (89%)
6: R = Me (16%)
7: R = CH(Me)2 (34%)
8: R = CH2Et (25%)
9: R = H1 = [=CH2] (27%)
10: R = CH=CH2 (84%)
11: R = CH=CH(Me) (85%)
12: R = CH=CH(n-Pr) (81%)
13: R = Me (10%)
14: R = Et (50%)
15: R = CH2(n-Pr) (53%)
16: R = Et (95%)
17: R = CH2(n-Pr) (94%)

triple bond of a 2'- or 3'-O-propargyl group in a 5-*exo* mode to form five-membered *cis*-fused bicyclic compounds[38]. In the present work, we have taken advantage of the 3'-phenylseleno substituted nucleoside as the generator of the free-radical which is to be trapped by a olefin or alkyne funtion anchored from the 5'-end by an ester or ether function to give various 6-*exo* addition products. Thus, a solution of tri-n-butyltin hydride (1.5 eq) and azoisobutyronitrile (AIBN) in degassed benzene (0.02 M) under an atmosphere of argon was added slowly to a solution of the free-radical precursor (**2** - **5**) in boiling benzene (0.004 M). The radical thus generated at the 3′-carbon was trapped by the double bond of the 5′-O-allyl group intramolecularly to form 5′-ether-linked bicyclic compounds **6** - **9** in low yields (16-34%) along with reduced products (<10%). Similarly, the intramolecular radical trapping reaction with 5'-O-α,β-ester-linked free radical precursor **10** - **12**, under an identical reaction condition as described for **2** - **5**, gave δ-lactones **13** - **15** in 10 -53% yields without detection of any reduced products. It was found that any increase or decrease of the concentration of radical precursors or tri-n-butyltin hydride did not improve the yields of the furo[2,3-c]pyrans. An increase of AIBN, from a catalytic amount up to one equivalent, could somewhat improve the yields of furo[2,3-c]pyrans or δ-lactones especially in the cases of radical precursors with terminally substituted vinyl functions with alkyl group(s) as in compounds **3**, **4**, **11** and **12**. The reason is not clear, but it has been noted in the literature[41] that increase of the amount of radical initiator can sometimes produce an improved radical efficiency. These results may suggest that the new radical intermediate formed upon addition of the 3′-carbon radical to unsaturated bond undergoes both hydrogen abstraction to furnish the furo[2,3-c]pyrans and a competing intermolecular addition to give polymerized product. As a result, unsubstituted vinyl derivatives such as **2** and **10** gave poorer yields of fused bicyclic products **6**, **13**, since it is sterically easier for the transient radical to attack the vinyl group intermolecularly. This steric rational of reactivity of the vinyl function can be substantiated by the fact that the disubstituted vinyl derivative **3** gave better yield of furo[2,3-c]pyran **7** (34%) than other unsubstituted or monosubstituted vinyl derivatives **2**, **4** and **5** to the corresponding products **6**, **8** and **9**. Note that the ester-linked vinyl radical precursors **11** and **12** gave better yields of corresponding [3.4.0]-*cis*-fused δ-lactones **14** and **15** than the ether-linked vinyl radical precursors **3**, **4** and **5** to their bicyclic products **7**, **8** and **9**, respectively. This may be the result of thermodynamically favourable and kinetically rapid 1,5-allylic hydrogen shift in the ether-linked vinyl radical precursors **3**, **4** and **5**[42] producing more by-products compared to the ester-linked vinyl radical precursors **11** and **12** which lack the 5-allylic hydrogen, and therefore gives higher yields of *cis*-fused δ-lactones . Finally, δ-lactones **14** and **15** were treated with diluted aqueous ammonia to give the ring-opened *C*-branched *erythro* derivatives **16** (95%) and **17** (94%), respectively. The methodology described herein has therefore established a diastereospecific synthesis of 3'-*C*-branched nuclesides through free-radical cyclization and subsequent ring-opening sequence.

Stereochemistry of the free-radical cyclization. Following points may be noted regarding the stereochemical outcome of the above free-radical cyclization: (1) The radical generated at 3′-carbon was quenched by 5′-O-unsaturated system at the β-face of the sugar in a *cis* manner (*vide infra* for detailed NMR evidence) in all tested systems (5'-O-allyl, 5'-O-propargyl and 5'-O-α,β-unsaturated ester) to give *cis*-fused furo[2,3-c]pyrans in which the chirality of the 3′-carbon has been preserved exclusively as in the radical precursor. (2) The cyclization gave exclusively 6-*exo*-ring closure products, without any trace of 7-*endo* ring closure products[43]. For example, compound **2** gave *6-exo-trig* cyclized methyl hexanofuranoid derivative **6**, compound **5** gave *6-exo-dig* cyclized methylene hexanofuranoid derivative **9**, and **10** gave *6-exo-trig* cyclized methyl hexanolactone **13**. (3) The stereochemistry of the above nucleophilic free-radical attack to unsaturated

system is however strongly dependent on the nature of 5′-linkage (ether *versus* ester), and in all cases radical cyclization reactions proceeded with full stereospecific control. Different type of 5′-linkage (ether *versus* ester) produced however totally different stereochemical outcome. The 5′-ether linked precursors **2** - **4** gave exclusively *cis*-fused furo[2,3-c]pyrans **6**, **7** and **8**, respectively, in which the configuration of the 3'-branched-carbon (C*) is in S-configuration (*vide infra* for NMR considerations) with the net result that the alkyl group on the 3'-branched-carbon is in *cis* position with respect to H-3′, and occupies *"exo"* position of the ring. The 5′-ester linked precursors **10** - **12** gave also exclusively [3.4.0]-*cis*-fused δ-lactones **13** - **15**, respectively, in which the alkyl group of the 3'-branched-carbon is in R-configuration (*vide infra* for NMR considerations) with the net result that the alkyl group on the 3'-branched-carbon is in *trans* position with respect to H-3′, and thus occupies an *"endo"* position of the ring. From this stereochemical assignments, it clearly emerges that the 3'-*C*-branching in the hydrolyzed products **16** and **17** is in *erythro* configuration.

Mechanistic consideration. Compared to the well-established free-radical cyclization process[44] that gives five-membered ring compounds, its counterpart, six-membered ring cyclization process has been relatively less understood and very little explored for synthetic application[45-50] because of the fact that 6-*exo* cyclization is significantly slower than the 5-*exo* cyclization, and 6-heptenyl radical gives by-product formation due to the thermodynamically favourable 1,5-hydrogen shift[42]. Most of the earlier works which deal with the 6-*exo* free-radical cyclization involve either the 6-heptenyl radical cyclization[45,46], or 2-acetal-6-heptenyl radical cyclization[47-49]. Very recently, Hanessian has reported the intramolecular cyclization of 2-carboxy-6-heptenyl radical [50], generated from α-halo esters, to give the *monocyclic* δ-lactones. Such 6-*exo* cyclization seems to involve a transition state mimicking a distorted chair form of cyclohexane with C(7) occupying a pseudo-equatorial position[50,51]. To the best of our knowledge, there are not any examples of 6-*exo* cyclization reaction of 4-oxo-5-carbo-6-heptenyl radical intermediates such as those generated from the radical precursors **10** - **12** to give [3.4.0]-fused δ-lactones **13** - **15**. While there is a literature example of intramolecular 5-*exo* cyclization of 3-oxo-4-carbo-5-hexenyl radical[52] to give fused γ-lactones, *the transformations of [10 - 12] to [3.4.0]-cis-fused δ-lactones [13 - 15] reported herein constitute the first example of intramolecular 6-exo radical cyclization reaction involving the nucleophilic attack of endocyclic ring radical to the electron-deficient exocyclic unsaturated chain. Similarly, the present example of 6-exo cyclization of 4-oxo-6-heptenyl radical formed from the precursor 2 - 5 constitute the first example of synthesis of [3.4.0]-cis-fused furo-pyrans 6 - 9.*

Assignment of configuration of C-3′ and C at the newly formed ring-junction.* The configuration and conformation of compounds **6** - **9**, and **13** - **15** have been determined by 500 MHz ^{1}H-NMR spectroscopy in $CDCl_3$ solution. The chemical shifts and coupling constants of all protons have been measured at three different temperatures (0°, 20° and 40 °C) for all compounds. We have also performed detailed differential 1D nOe experiments at 20°C in order to assign the spatial proximities of various protons around the pyro[2,3-c]furan ring junction. The observed nOes are shown in Table 5.

(i) *Configuration of C3′ and C**: nOes have been observed (Table 5) between H4' and H3' (~6%), and between H3' and H2" (4 - 6%) in all compounds. Additionally, nOes between H1' and H3' (~1%) have been observed also in compounds **13** - **15**. These specific nOe contacts have led us to assign the H3' to the α-face owing to the *erythro* configuration at C3' for compounds **6** - **9** and **13** - **15**. From this follows that the stereochemistry across the furo[2,3-c]pyran ring junction is *cis*-fused. Note that in none of the compounds studied herein could we observe any nOe between H6 and H3' which also suggest that the H3' is *cis* to H2" and H4'. (ii) *Configuration of C**: In compound **6**, we have observed a weak nOe between H_1 and H3' (1%),

Table 1: Chemical shifts of furo[2,3-c]pyrans **6 - 9 & 13 -15** obtained at 500 MHz NMR spectra in $CDCl_3$ at 293K.

δ (ppm)	Compd. **6**	Compd. **7**	Compd. **8**	Compd. **9**	Compd. **13**	Compd. **14**	Compd. **15**
H-1'	5.85	5.87	5.87	6.08	6.14	6.13	6.13
H-2'	1.99	1.98	2.00	2.39	1.32	1.26	1.26
H-2"	2.61	2.61	2.60	2.51	2.45	2.40	2.41
H-3'	1.81	2.12	1.87	3.11	3.04	3.11	3.09
H-4'	3.97	3.99	3.97	4.16	4.49	4.48	4.48
H-5'	4.33	4.28	4.31	4.37	4.54	4.51	4.51
H-5"	3.63	3.59	3.62	3.67	4.25	4.23	4.23
H1	1.39	1.27	1.34	–	2.77	2.47	2.54
H2	2.91	3.06	2.92	4.16	-	-	-
H3	3.83	3.94	3.94	4.06	–	–	–
CH-alk	0.81	1.57	1.04, 1.24	4.93	1.22	1.35	
C-CH-alk	–	0.92, 0.81	1.16, 1.31	–	–	1.01	1.27 - 1.43
C-C-CH-alk	–	–	0.82	–	–	–	
C-C-C-CH-	–	–	–	–	–	–	0.90
H-6	7.71	7.72	7.73	7.62	7.12	7.10	7.11
5-CH_3-T	1.94	1.94	1.94	1.89	1.93	1.91	1.91

Table 3: Estimation of γ and Pseudorotational parameters of furo[2,3-c]pyrans **6 - 9 & 13 -15** calculated from J-couplings obtained at 500 MHz NMR spectra in $CDCl_3$ at 273K, 293K and 313K and PSEUROT calculations.

Pseudorotamer parameters	Compd. **6**	Compd. **7**	Compd. **8**	Compd. **9**	Compd. **13**	Compd. **14**	Compd. **15**
γ^+	100 %	100 %	100 %	100 %	100 %	100 %	100 %
P_N	18°	14°	28°	-1° to -28°	-10° to +10°	-10° to +10°	-10° to +10°
Φ_N	36°	35°	41°	32° to 26°	38°	38°	38°
P_S	160 to 200°	160 to 200°	160 to 200°	160 to 200°	134°	133°	134°
Φ_S	38°	38°	38°	38°	37°	37°	37°
S-population	8 %	8 %	2 %	36 %	99 %	98 %	99 %
RMS	0.387	0.297	0.531	0.452	0.416	0.465	0.478

Table 4: Calculation of Dihedral angles (Φ)* of the pyran ring of furo[2,3-c]pyrans **6 - 9 & 13 -15** from $^3J_{HH}$ couplings obtained at 500 MHz in $CDCl_3$ at 273K, 293K and 313K using Karplus-Altona equation.

$^3J_{HH}$	Compd. **6**	Compd. **7**	Compd. **8**	Compd. **13**	Compd. **14**	Compd. **15**
	J (Hz) / Φ	J (Hz) / Φ	J (Hz) / Φ	J (Hz) / Φ	J (Hz) / Φ	J (Hz) / Φ
H3'-H1	11.0 160°	12.0 168°	11.0 158°	5.8 -45°	6.7 -41°	6.3 -43°
H1-H3	4.6 -57°	4.6 -57°	4.6 -57°	- -	- –	- –
H1-H2	11.6 -178°	11.6 -178°	11.3 176°	- -	- –	- –
H4'-H5'	0 -86°	0 -86°	0 -86°	0 -86°	0 -86°	0 -86°
H4'-H5"	2.3 46°	2.3 46°	2.0 49°	2.3 46°	2.0 49°	2.1 48°

* Of four possible solutions from the Karplus-Altona equation, only the one which is mutually satisfactory with other torsion has been chosen.

that was not observed for compounds **7** and **8**. For compounds **13, 14** and **15**, on the other hand, the nOe between H_1 and H3' was strong (6 -7%). In compounds **6, 7** and **8**, nOes were observed (Table 5) between H6 and H_1 (4 - 5%) which was absent in compounds **13, 14** and **15**. In addition to these, the nOe between H_1 and H5" which could be observed for **13, 14** and **15** (4 - 5%) was absent in **6, 7** and **8**. For **6, 7** and **8**, we have also noted a weak nOe (~1%) between H_1 and H2'. These observed nOes have led us to assign H_1 to an *endo* face of the pentose ring as a consequence of S configuration of C* for compounds **6, 7** and **8**, and H_1 to an *exo* face of the pentose ring as a consequence of R configuration of C* for **13, 14** and **15**. Note that the configurations of C3' and C* as assigned above is also supported by the chemical shifts of H3' and H_1 (Table 1) in the two groups of compounds (**6, 7, 8** and **13, 14, 15**) with different stereochemistries at C*. The H3' is more shielded in compounds **6, 7** and **8** than in **13, 14** and **15** due to the *cis*-shielding effect of the C*-alkyl substituent in the *exo* orientation (*i.e.* S configuration) in compounds **6, 7** and **8**. Additional proof for the relative stereochemistries at C3'-C* and their assigned configurations has been also obtained from the analysis of ^{3}J-coupling constants (Table 2) between H3' and H_1. The ^{3}J-coupling for compounds **6, 7** and **8** is between 11 and 12 Hz indicating a *trans*-orientation of H3' and H_1 across C3'-C*, while a ^{3}J-coupling of around 6 Hz suggest a *cis*-orientation of H3' and H_1 across C3'-C* in compounds **13, 14** and **15** (*vide infra*).

Conformation of the furan ring. The conformation of the furan ring is described using the pseudorotational concept[53]. The ring geometry is described using two parameters, the phase angle of pseudorotation: P, and the puckering amplitude: ϕ. The ring is known to exist in an equilibrium of two rapidly interconverting conformers denoted by North (C2'-*exo*, C3'-*endo*) (N) and South (C2'-*endo*, C3'-*exo*) (S). The %N and S, the P and ϕ for all our furo[2,3-c]pyrans have been calculated from the coupling constants measured at 0°, 20° and 40 °C, using the computer program PSEUROT[54] (Table 3). Compounds **6, 7** and **8** were found to be in an N-type conformation (92, 92 and 98 % respectively at 293K), compound **9** was found to be in a less predominant N-type conformation (64%). Compounds **13, 14** and **15** were found to be in an S-type conformation (99, 98 and 99 % respectively at 293K).

Conformation across C4'-C5' (γ). The population of the γ^+ rotamer were calculated using the following equation[56] : $\%\gamma^+ = 100(13.3 - (J_{4'5'} + J_{4'5''}))/9.7$. The equation gave 100% γ^+ for all compounds. Assuming that only one rotamer is present, the dihedral angles ϕ[H4'-C4'-C5'-H5'] and ϕ'[H4'-C4'-C5'-H5"] have been calculated to be -86° and 46° , respectively, using equation (1) (Table 3).

Conformation of the pyran ring. Assuming that the pyran ring exists as a single conformer as evident from temperature invariable $^3J_{HH}$, the dihedral angles of the pyran ring have been calculated (Table 4) from the $^3J_{HH}$ coupling constants (Table 2) using the Karplus-Altona equation[55] (1) which includes a correction term to take the influence of the electronegativities of various substituents on $^3J_{HH}$ into account:

$$^3J_{HH} = P_1 \cos^2\phi + P_2 \cos\phi + P_3 + \Sigma\, \Delta\chi_i \{P_4 + P_5 \cos^2(\zeta_i \cdot \phi + P_6 \cdot |\Delta\chi_i|)\} \quad \ldots\ (1)$$

A perusal of these calculated dihedral angles in Tables 3 and 4 show that the conformation of all [3.4.0]-*cis*-fused furo-pyrans **6 - 9** and [3.4.0]-*cis*-fused δ-lactones **13 - 15** are distinctly different and they belong to two different groups of structures. Temperature-independent $^3J_{HH}$ (Table 2) seems to show that they all have rigid conformations. Construction of molecular models (Fig. 1) using the endocyclic torsions of the pentose unit (from P and Φ_m in Table 3), various dihedral angles of the pyran or δ-lactone unit (Table 4) and nOe between H6 and sugar protons (Table 5) immediately show that the pyran ring in [3.4.0]-*cis*-fused furo-pyrans **6 - 9** are in chair conformation, the pentofuranose ring is in North conformation and the thymine is in *anti* orientation (Fig. 1A & 1B), while the δ-lactone ring in [3.4.0]-*cis*-fused δ-lactones **13 - 15** is in boat conformation, the

Table 2: J-couplings of furo[2,3-c]pyrans **6 - 9 & 13 -15** collected from their 500 MHz NMR spectra in $CDCl_3$ at different temperatures.

	Compound **6**			Compound **7**			Compound **8**			Compound **9**			Compound **13**			Compound **14**			Compound **15**		
J-couplings	273K	293K	313K	273K	293K	313K	273K	293K	313K	273K	293K	313K	273K	293K	313K	273K	293K	313K	273K	293K	313K
$J_{1'2'}$	2.2	2.3	2.5	2.4	2.7	2.8	2.1	2.3	2.5	4.0	4.4	4.9	9.7	9.7	9.5	9.5	9.5	9.3	9.5	9.5	9.3
$J_{1'2''}$	7.6	7.6	7.6	7.6	7.6	7.5	7.6	7.6	7.6	6.6	6.5	6.5	5.1	5.1	5.3	5.1	5.1	5.1	5.1	5.1	5.1
$J_{2'2''}$	14.8	14.9	15.0	15.0	14.6	15.0	14.8	14.8	14.6	14.0	14.0	14.1	13.6	13.4	13.6	13.4	13.6	13.6	13.4	13.4	13.6
$J_{2'3'}$	2.1	1.7	2.1	1.8	1.6	1.6	1.4	1.4	1.0	4.0	4.4	5.0	9.5	9.6	9.5	9.5	9.5	9.3	9.2	9.7	9.7
$J_{2''3'}$	7.2	7.2	7.4	7.1	6.8	7.4	7.2	7.2	6.9	7.3	7.6	7.9	8.7	8.7	8.8	8.8	8.7	8.8	8.8	8.7	8.8
$J_{3'4'}$	4.8	4.6	4.8	5.1	5.3	5.5	3.7	3.7	3.3	6.2	6.9	6.9	9.5	9.5	9.6	9.5	9.5	9.5	9.5	9.3	9.5
$J_{4'5'}$	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
$J_{4'5''}$	2.3	2.3	2.3	2.3	2.3	2.3	2.1	2.0	2.3	2.1	2.3	2.3	2.3	2.3	2.3	1.8	2.0	2.1	2.0	2.1	2.1
$J_{5'5''}$	13.4	13.4	13.4	13.2	13.2	13.2	13.4	13.4	13.4	13.2	13.4	13.4	13.2	13.4	13.2	13.2	12.9	13.2	13.1	13.0	12.9
$J_{3'/H1}$	10.9	11.0	11.0	11.9	12.0	11.8	10.9	11.0	10.9	–	–	–	5.8	5.8	5.8	6.7	6.7	6.7	6.3	6.3	6.3
$J_{H1/H3}$	4.8	4.6	4.6	4.6	4.6	4.9	4.6	4.6	4.6	–	–	–	–	–	–	–	–	–	–	–	–
$J_{H1/H2}$	11.6	11.6	11.6	11.6	11.6	11.6	11.3	11.3	11.3	–	–	–	–	–	–	–	–	–	–	–	–
$J_{H2/H3}$	11.6	11.6	11.6	11.6	11.6	11.6	11.3	11.3	11.3	13.4	13.4	13.4	–	–	–	–	–	–	–	–	–
$J_{H1/CH\text{-}alk}$	6.7	6.5	6.7	-	-	-	-	-	-	–	–	–	6.7	6.7	6.7	6.7	6.7	6.7	6.7	6.2	6.5

Table 5: 1D Differential nOe observed for furo[2,3-c]pyrans **6 - 9 & 13 -15** at 500 MHz in $CDCl_3$ at 293K.

Irradiated Proton	OBSERVED nOe [%] FOR VARIOUS COMPOUNDS						
	Compd. **6**	Compd. **7**	Compd. **8**	Compd. **9**	Compd. **13**	Compd. **14**	Compd. **15**
H-1'	2" [4.7]	2" [4.1], 4' [1.8]	2" [4.5], 4' [1.1]		2" [2.5], 3' [1.1]	2" [3.1],3' [1.8],4' [1.2]	2" [3.9], 3' [1.7], 4'
H-2'	2" [23.3], 3', H6 [6.3], CH-alk [2.4], H1 [4.0]	2" [21.0], 3', H6 [7.6], 1' [1.3], CH-alk [2.8], H1 [4.3]	2" [25.4],3' , H6 [6.0], C-CH-alk, H1	1' [2.6], H6 [2.8], CH-alk [2.9]	2" [18.7], H6 [7.0]	2" [17.9], H6 [3.9]	
H-2"	2' [22.9], 4' [2.0] 3' [4.8], 1' [10.3]	2' [17.7], 4' [1.6] 3' [4.1], 1' [12.3]	2' [23.5], 4' [2.4] 3' [3.8], 1' [11.9]	1' [6.9], 3' [4.5]	1' [11.6], 2' [32.3] 3' [7.7]	1' [8.0], 2' [24.7], 3' [7.3], CH-alk	1' [8.5],2' [25.4], 3' [5.3], CH-alk
H-3'	CH-alk [2.3], H1 2" [5.0], 4' [5.5] 2', H2 [1.1]	CH-alk [1.9], C-CH-alk [1.2, 3.4], 2" [9.5], 4' [8.2], H2 [1.2]	CH-alk [1.6], 2" [9.3], 4' [7.1], H2 [1.5]	1' [1.0], 2" [2.7], 4' [5.2], CH-alk [2.4]	1' [3.4], 2" [6.1], 4' [4.7], H1, CH-alk	1' [3.1], 2" [1.6], 4' [7.2], H1 [4.1], C-CH -alk [3.6]	1' [3.0], 2" [2.4], 4' [7.5], H1 [4.5], CH-alk
H-4'	2" [1.1], 5', 5", 3' [6.0], 1' [2.1]	2" [0.9], 5" [4.4], 3' [5.8], 1' [3.6]	2" [0.9], 5', 5", 3' [3.8], 1' [2.0]		1' [3.3], 3' [6.8], 5' 5" [13.7], H1 [3.0]	1' [1.3], 3' [3.2], 5' /5"	1' [3.1], 3' [7.3], 5'/5"
H-5'	5" [22.8], 4'	5" [25.5], 4'	5" [24.8], 4'		4' [?], 5" [31.8]	4', 5"	4' , 5"
H-5"	5' [23.3], 4', H2 [6.0]	5' [29.4], 4' [5.3], H2 [4.1], 3'	5' [26.8], 4' , H2 [4.9], 3'		5' [30.2], H1 [10.3], 4'	5' [14], H1 [8.2] 4'	
H1	H3 [3.2], 3', H6 [5.0], 2' [1.3]	H3 [3.2], 3' [1.0], H6 [5.2], 2' [1.4] CH-alk, C-CH-alk	could not be identified		3', 5" [1.5], CH- alk [11]	3' [7.7], 5" [4.6] CH-alk [13.9], C-CH-alk [2.4]	3' [5.1], 5" [4.5] CH-alk [9.6]
H3	H2 [25.5], H1 [5.8], CH-alk [1.5]	H2 [25.5], H1 [6.4], C-CH-alk [2.9, 1.5]	H2 [81.2], H1 [29.0],				
H2	H3 [25.9], 3' [2.3], 5" [3.6], CH-alk [1.2]	H3 [23.8], 3'[1.0], 5" [2.9], CH-alk	H3 [24.0], 3' [1.3], 5" [3.0], CH-alk [3.2]		3' [1.0], 2', 2" [3.4] H1 [2.2]	H1	
CH-alk	H1 [3.0], 2' [1.0], H3 [0.8], 3' [2.5], H2 [0.9]	C-CH-alk [6.2, 7.3], H1, H2 [1.4]	could not be identified				
C-CH-alk		H3 [1.4, 0.7], CH-alk [3.8, 3.4],3' [1.6, 2.0], H2 [0.6, 1.1]	could not be identified			H1 [1.2], 3' [1.0] CH-alk	
H-6	H1 [4.3], 5-CH_3-T	H1 [4.8], 5-CH_3-T, C-CH-alk [2.1, 1.9]	H1 [4.7], 5-CH_3-T, CH-alk	CH-alk [3.7], 5-CH_3-T, 2' [3.4], 5' [1.8]	2' [5.8], 5-CH_3-T	2' [5.3], 5-CH_3-T 5' [1.2]	2' [3.7], 5-CH_3-T 5' [0.3]
5-CH_3-T	H6	H6	H6	H6	H6	H6	H6

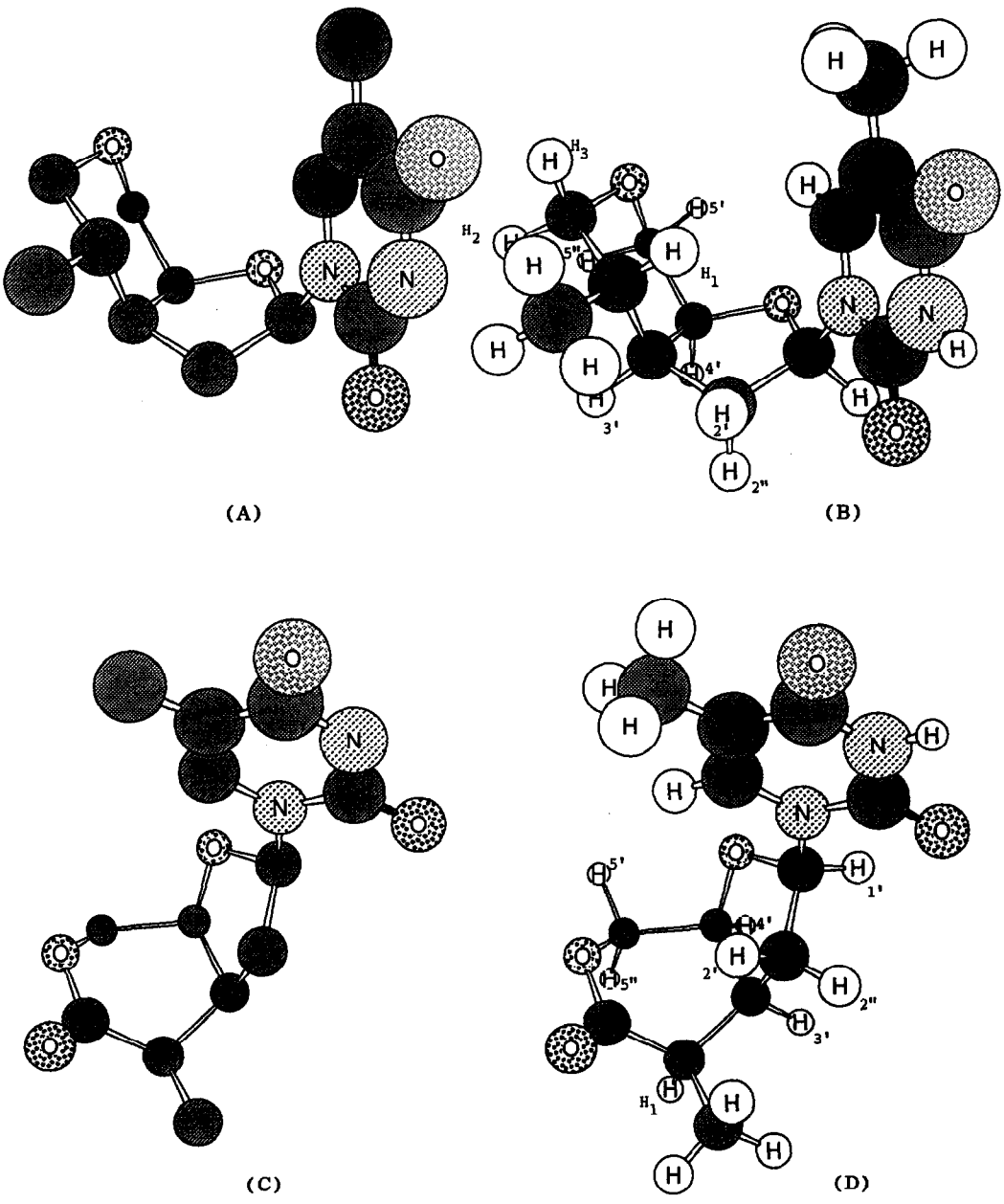

Fig. 1: Molecular models of [3.4.0]-*cis*-fused furo-pyran **6** (Figs. 1A & 1B) and [3.4.0]-*cis*-fused δ-lactones **13** (Figs. 1C & 1D) based on dihedral angles calculated by Karplus-Altona algorithm from various $^{3}J_{HH}$ coupling constants shown in Tables 2-4.

pentofuranose ring is in South conformation and the thymine is in *anti* orientation (Fig. 1C & 1D). It should be however noted that the C*-alkyl substituent in both furo[2,3-c]pyrans **6** - **9** and in δ-lactones **13** - **15** are in an equatorial position. We have subsequently performed several NOESY and ROESY experiments at different mixing times which has enabled us to calculate different interproton distances from the intensities and volumes of the cross peaks shown in Table 6. A comparison of interproton distances obtained from molecular models (Fig. 1A -D), based on $^3J_{HH}$ coupling constants (*vide supra*) with those obtained from NOESY and ROESY spectra (Table 6) supports the molecular structures for both furo[2,3-c]pyrans **6** - **9** and in δ-lactones **13** - **15** shown in Fig. 1.

Table 6 : Comparison of interproton distances obtained from molecular models (Fig. 1A & 1B), based on $^3J_{HH}$ coupling constants (see text) with those obtained from NOESY/ROESY spectra at different mixing times. The distances were calculated by AURELIA[57] from volumes and intensities of the nOe and rOe crosspeaks using the distance between H5'-H5" (1.8 Å) as a reference.

Interproton distances	Molecular Model (Fig. 1A & 1B)	ROESY (80 ms)	NOESY (80 ms)	NOESY (100 ms)	NOESY (200 ms)
H6 - H5'	3.6 Å	3.2 Å	-	-	3.6 Å
H6 - H1	2.5 Å	2.7 Å	2.7 Å	2.8 Å	2.8 Å
H6 - H1'	3.5 Å	3.2 Å	-	-	3.8 Å
H6 - CH_3-T	2.4 Å	-	-	2.5 Å	2.5 Å
H6 - H2'	4.1 Å	-	-	3.3 Å	3.3 Å
H1' - H2'	2.9 Å	2.8 Å	2.5 Å	2.5 Å	2.9 Å
H1' - H2"	2.3 Å	2.5 Å	2.7 Å	2.7 Å	2.6 Å
H1' - H4'	3.2 Å	-	3.5 Å	3.7 Å	3.4 Å
H2' - H2"	1.8 Å	1.5 Å	1.9 Å	2.0 Å	-
H2' - H3'	2.8 Å	-	-	-	-
H2" - H3'	2.4 Å	2.4 Å	2.4 Å	2.5 Å	2.4 Å
H2" - H4'	2.7 Å	2.9 Å	3.0 Å	3.2 Å	2.9 Å
H3' - H4'	2.3 Å	2.3 Å	2.5 Å	2.6 Å	2.5 Å
H3' - H2	2.8 Å	2.7 Å	3.1 Å	3.1 Å	3.0 Å
H4' - H5'	2.7 Å	2.6 Å	2.4 Å	2.3 Å	2.4 Å
H4' - H5"	2.4 Å	2.1 Å	2.5 Å	2.4 Å	2.3 Å
H5" - H2	2.3 Å	2.3 Å	2.4 Å	2.9 Å	2.4 Å
H1 - H3	2.5 Å	2.4 Å	2.4 Å	2.7 Å	2.5 Å
H3 - H2	1.8 Å	1.7 Å	2.0 Å	2.0 Å	2.0 Å

In conclusion, we have shown that free-radical cyclization-ring-opening methodology provides an easy access to *C*-branched nucleoside derivatives with complete stereospecificity. It is due to the D-configuration of the C4', the 5'-substituent successfully dictates the *cis*-fused stereochemistry of both furo[2,3-c]pyrans **6** - **9** and δ-lactones **13** - **15**. The δ-lactones **13** - **15** can be conveniently hydrolyzed giving the 3'-*C*-branched-*erythro*-thymidine derivatives in a stereospecific manner, which are not accessible by any known method. The radical precursors required for such carbon-carbon bond forming reactions in nucleoside derivatives are easily prepared. We believe that this free-radical cyclization-ring-opening methodology will find wider applications in the syntheses of *C*-branched nucleosides.

EXPERIMENTAL

^{1}H-NMR spectra were recorded (in δ scale) with a Jeol 90Q spectrometer at 90 MHz or at 500 MHz with a Bruker 500 AMX NMR spectrometer (for cyclized products) using TMS (0.0 ppm) as the internal standard. ^{13}C-NMR spectra were recorded at 22.5 MHz using both ^{1}H-coupled, ^{1}H-decoupled and INEPT modes. Jeol DX 303 instrument was used for recording high resolution mass spectra. Tlc was carried out using Merck pre-coated silica gel F254 plates. Preparative Tlc was carried out using Merck pre-coated silica gel F254 Plc plates.

The column chromatographic separations were carried out using Merck G60 silica gel. THF and benzene were freshly distilled from sodium benzophenone ketyl, and dichloromethane was distilled from phosphorus pentoxide. All other chemicals were obtained from Aldrich and were used without further purification. All reactions were performed in oven-dried glassware in a dry argon atmosphere. ^{1}H- & ^{13}C-NMR assignments of 5′-O-allyl and 5′-O-ester chain protons and carbons are indicated by H-a (5'-O-CH_2), H-b and H-c or C-a, C-b and C-c and so on from 5′-O- direction. ^{1}H-NMR assignments of compound **6-9** & **13-15** are indicated in Figs **6-9** & **13-15**. In ^{13}C-NMR data, carbon covalently linked with H_1 is termed C_1 and carbon linked with H_2 & H_3 is termed C_2.

1-[2′,3′-dideoxy-3′(R)-phenylseleno-β-D-*glycero*-pentofuranosyl]thymine (1b) Thymidine (4.84 g, 20 mmol) was coevaporated with dry pyridine and redissolved in the same solvent (150 ml). 4-Monomethoxytrityl chloride (7.40 g, 24 mmol) was added and the reaction was allowed to proceed overnight at room temperature. Methanesulfonyl chloride (2.3 ml, 30 mmol) was added at 0 °C, and the reaction was allowed to proceeded for another 6 h at room temperature. The reaction mixture was poured slowly into ice-water (1 L), and the solid was collected by suction, dried by coevaporation with dry toluene, and this was used directly in the following step without any further purification. To a solution of diphenyldiselenide (9.36 g, 30 mmol) in dry THF (100 ml), $LiAlH_4$ (1.14 g, 30 mmol) was added portionwise. After addition, the suspension was boiled under reflux for 10 min, the solid mesylate was then dissolved in dry THF (40 ml) and added dropwise to the above suspension. The reaction mixture was boiled under reflux for 4h, and slowly poured into aqueous saturated ammonium chloride solution, extracted with chloroform. The organic phase was evaporated to dryness and further treated with 80% aqueous acetic acid (150 ml) overnight at room temperature to give crude **1a**. The reaction mixture was evaporated to dryness coevaporated with dry toluene several times. The solid thus obtained was then subjected to flash chromatography to give the pure compound **1b** (6.10 g, 80%). ^{1}H-NMR($CDCl_3$) : 7.87 (q, 1H) H-6; 7.59-7.26 (m, 5H) arom.; 6.10 (dd, $J_{1',2'}$= 6.1 Hz, $J_{1',2''}$= 7.3 Hz, 1H) H-1′; 4.33 (dt, $J_{3',4'}$= 7.1 Hz, $J_{4',5'}$= 3.2 Hz, 1H) H-4′; 3.95 (m, 3H) H-3′, H-5′, H-5"; 2.43 (m, 2H) H-2′; 1.94 (d, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$) : 110.6 (s) C-5; 84.1 (d, J_{CH} = 169.6 Hz) C-1′; 81.6 (d, J_{CH} = 150.5 Hz) C-4′; 63.6 (t, J_{CH} = 142.1 Hz) C-5′; 40.6 (d, J_{CH} = 143.8 Hz) C-3′; 39.5 (t, J_{CH} = 135.9 Hz) C-2′; 12.2 (q, J_{CH} = 129.2 Hz) 5-Me.

1-[5′-O-allyl-2′,3′-dideoxy-3′(R)-phenylseleno-β-D-*glycero*-pentofuranosyl]thymine (2) *General Procedure of Alkylation:* To a solution of compound **1b** (380 mg, 1.0 mmol) in dry tetrahydrofuran (10 ml) was added sodium hydride (90 mg, 3.0 mmol) and the mixture was stirred ultrasonically for 15 min under argon. Allyl bromide (126 µl, 1.5 mmol) was added with stirring for 5 min at room temperature, then the reaction mixture was heated to reflux for 2 h. The reaction mixture was poured into a saturated solution of ammonium chloride (50 ml), which was extracted with ethyl acetate (2 x 50 ml). The combined extracts were washed with water (50 ml), and dried over $MgSO_4$, All volatile matters were removed in vacuo and the residue was purified on a silica gel column to give compound **2** (370 mg, 88 %). ^{1}H-NMR($CDCl_3$) : 8.75 (br.s., 1H) NH; 7.83 (q, J = 1.2 Hz, 1H) H-6; 7.58-7.25 (m, 5H) arom.; 6.13 (dd, $J_{1',2'}$= 5.9 Hz, $J_{1',2''}$= 8.3 Hz, 1H) H-1′; 5.96-5.79 (m, 1H) H-b; 5.44-5.17 (m, 2H) H-c; 4.46 (dt, $J_{3',4'}$= 7.6 Hz, $J_{4',5'}$= 1.4 Hz, 1H) H-4′; 4.09 (m, 2H) H-a; 3.84 (m, 3H) H-5′, H-5", H-3′; 2.93-2.11 (m, 2H) H-2′, H-2"; 1.92 (d, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$) : 117.6 (t, J_{CH} = 159.5 Hz) C-c; 110.7 (s) C-5; 83.6 (d, J_{CH} = 169.6 Hz) C-1′; 80.3 (d, J_{CH} = 145.6 Hz) C-4′; 72.1 (t, J_{CH} = 143.8 Hz) C-a; 71.9 (t, J_{CH} = 143.8 Hz) C-5′; 41.3 (d, J_{CH} = 148.3 Hz) C-2′; 40.1 (t, J_{CH} = 135.9 Hz) C-2′; 12.4 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB$^-$): calcd. for $(M-H)^-$ 421.0667, found 421.0669.

1-[5′-O-(3-methyl-2-butenyl)-2′,3′-dideoxy-3′(R)-phenylseleno-β-D-*glycero*-pentofuranosyl]thymine (3): The general procedure for alkylation was followed using compound **1b** (760 mg, 2.0 mmol), NaH (80 %, 180 mg, 6.0 mmol) and 4-bromo-2-methyl-2-butene (475 µl, 4.0 mmol) in dry tetrahydrofuran (20 ml) to give compound **3** (721 mg, 80 %). ^{1}H-NMR($CDCl_3$) : 9.14 (br.s., 1H) NH; 7.90 (q, J = 1.2 Hz, 1H) H-6; 7.59-7.25 (m, 5H) arom.; 6.14 (dd, $J_{1',2'}$= 5.9 Hz, $J_{1',2''}$= 8.1 Hz, 1H) H-1′; 5.41 (m, 1H) H-b; 4.44 (dt, $J_{3',4'}$= 7.8 Hz, $J_{4',5'}$= 2.9 Hz, 1H) H-4′; 4.08 (m, 2H) H-a; 3.81 (m, 3H) H-5′, H-5", H-3′; 2.90-2.20 (m, 2H) H-2′, H-2"; 1.92 (d,3H) 5-Me; 1.76 (d, J = 4.4 Hz, 6H) H-d. ^{13}C-NMR ($CDCl_3$) : 120.4 (d, J_{CH} = 148.3 Hz) C-b; 110.6 (s) C-5; 83.6 (d, J_{CH} = 171.9 Hz) C-1′; 80.3 (d, J_{CH} = 148.3 Hz) C-4′; 71.4 (t, J_{CH} = 142.1 Hz) C-a; 67.5 (T, J_{CH} = 140.4 Hz) C-5′; 41.4 (d, J_{CH} = 146.0 Hz) C-3′; 39.9 (t, J_{CH} = 135.9 Hz) C-2′; 25.6 (q, J_{CH} = 129.2 Hz) C-Me(*Me*); 18.0 (q, J_{CH} = 129.2 Hz) C-*Me*(Me); 12.2 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB$^-$): calcd. for $(M-H)^-$ 449.0980, found 449.0992.

1-[5′-O-(2-pentenyl)-2′,3′-dideoxy-3′(R)-phenylseleno-β-D-*glycero*-pentofuranosyl]thymine (4): The general procedure for alkylation was followed using compound **1b** (380 mg, 1.0 mmol), NaH (80 %,

90 mg, 3.0 mmol) and 1-bromo-2-pentene (187 µl, 1.5 mmol) in dry tetrahydrofuran (10 ml) to give compound **4** (420 mg, 94 %). ^{1}H-NMR($CDCl_3$): 9.14 (br. s., 1H) NH; 7.85 (q, J = 1.2 Hz, 1H) H-6; 7.58-7.25 (m, 5H) arom.; 6.14 (dd, $J_{1',2'}$= 5.9 Hz, $J_{1',2''}$= 8.1 Hz, 1H) H-1'; 5.6 (m, 2H) H-b, H-c; 4.43 (dt, $J_{3',4'}$= 8.1 Hz, $J_{4',5'}$= 2.4 Hz, 1H) H-4'; 4.16 (m, 2H) H-a; 3.82 (m, 3H) H-5',H-5", H-3'; 2.90-2.04 (m, 4H) H-2', H-2", H-d; 1.93 (d, 3H) 5-Me; 1.01 (t, J = 7.3 Hz, 3H) H-e. ^{13}C-NMR ($CDCl_3$) : 124.5 (d, J_{CH} = 157.3 Hz) C-b; 110.7 (s) C-5; 83.6 (d, J_{CH} = 169.6 Hz) C-1'; 80.3 (d, J_{CH} = 146.0 Hz) C-4'; 71.6 (t, J_{CH} = 141.5 Hz) C-a; 66.6 (t, J_{CH} = 144.3 Hz) C-5'; 41.4 (d, J_{CH} = 148.3 Hz) C-3'; 40.0 (t, J_{CH} = 135.9 Hz) C-2'; 20.9 (t, J_{CH} = 125.3 Hz) H-d; 14.1 (q, J_{CH} = 125.8 Hz) H-e; 12.4 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB$^-$): calcd. for (M-H)$^-$ 449.0980, found 449.0988.

1-[5'-O-(2-propynyl)-2',3'-dideoxy-3'(R)-phenylseleno-β-D-*glycero*-pentofuranosyl] thymine (5): The general procedure for alkylation was followed using compound **1b** (380 mg, 1.0 mmol), NaH (80 %, 90 mg, 3.0 mmol) and propargyl bromide (223 µl, 2.0 mmol) in dry tetrahydrofuran (10 ml) to give compound **4** (283 mg, 89 %). ^{1}H-NMR($CDCl_3$): 9.21 (br. s., 1H) NH; 7.80 (q, J = 1.2 Hz, 1H) H-6; 7.59-7.25 (m, 5H) arom.; 6.13 (dd, $J_{1',2'}$= 5.6 Hz, $J_{1',2''}$= 7.8 Hz, 1H) H-1'; 4.46 (dt, $J_{3',4'}$= 7.6 Hz, $J_{4',5'}$= 2.7 Hz, 1H) H-4'; 4.26 (dd, 2H) H-a, 4.08-3.74 (m, 3H) H-5', H-5", H-3'; 2.92-2.07 (m, 2H) H-2', H-2"; 2.51 (t, J = 2.4 Hz, 1H) H-c, 1.97 (d, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$) : 110.8 (s) C-5; 83.7 (d, J_{CH} = 173.0 Hz) C-1'; 78.63 (s) C-b; 79.9 (d, J_{CH} = 153.9 Hz) C-4'; 75.3 (d, J_{CH} = 180.8 Hz) C-c; 71.5 (t, J_{CH} = 142.1 Hz) C-5'; 58.2 (t, J_{CH} = 147.7 Hz) C-a; 41.1 (d, J_{CH} = 141.5 Hz) C-3'; 39.8 (t, J_{CH} = 135.9 Hz) C-2'; 12.5 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB$^-$): calcd. for (M-H)$^-$ 419.0511, found 419.0520.

1-[5'-O-(1-oxo-hex-2-ene-1yl)-2',3'-dideoxy-3'(R)-phenylseleno-β-D-*glycero*-pentofuran osyl]thymine (12)*General Procedure of Esterification:*** To a solution of compound **1** (380 mg, 1.0 mmol) in dry tetrahydrofuran (5 ml) was added sodium hydride (80 %, 90 mg, 3.0 mmol) and the mixture was stirred ultrasonically for 30 min under argon, a preformed mixture of DCC (309 mg, 1.5 mmol) and trans-2-hexenoic acid (342 mg, 3.0 mmol) in dry methylene chloride (5 ml) (the pre-mixture was stirred for 15 min.) was then added to the mixture and stirring was continued for 1 h. The reaction mixture was then filtrated and washed with a mixture of ethyl acetate-hexane (6 : 4 , v/v, 100 ml), the filtrate was evaporated to dryness and then subjected to flash chromatography to give compound **12** (384 mg, 81 %). ^{1}H-($CDCl_3$) : 8.98 (br.s., 1H) NH; 7.59-7.27 (m, 6H) H-6, arom.; 7.21-6.88 (m, 1H) H-b; 6.09 (dd, $J_{1',2'}$= 6.4 Hz, $J_{1',2''}$= 6.6 Hz, 1H) H-1'; 5.83 (dt, $J_{a,b}$ = 15.6 Hz, $J_{a,c}$ = 1.5 Hz, 1H) H-a; 4.50 (m, 3H) H-5', H-5", H-4'; 3.95 (m, 1H) H-3'; 3.06-2.01 (m, 2H) H-2', H-2"; 1.93 (d, 3H) 5-Me; 1.74-1.25 (m, 4H) H-c, H-d; 0.94 (t, J = 7.6 Hz) H-e. ^{13}C-NMR ($CDCl_3$) : 120.2 (d, J_{CH} = 161.8 Hz) C-a; 110.8 (s) C-5; 84.3 (d, J_{CH} = 173.0 Hz) C-1'; 79.2 (d, J_{CH} = 151.7 Hz) C-4'; 65.1 (t, J_{CH} = 148.3 Hz) C-5'; 40.4 (d, J_{CH} = 148.3 Hz) C-3'; 39.9 (t, J_{CH} = 135.9 Hz) C-2'; 34.1 (t, J_{CH} = 128.1 Hz) C-c; 21.0 (t, J_{CH} = 126.9 Hz) C-d; 13.5 (q, J_{CH} = 125.8 Hz) C-e; 12.4 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB$^-$): calcd. for (M-H)$^-$ 477.0929, found 477.0896.

1-[5'-O-(1-oxo-prop-2-ene-1yl)-2',3'-dideoxy-3'(R)-phenylseleno-β-D-*glycero*-pentofuran osyl]thymine (10): The general procedure for esterification was followed using compound **1b** (380 mg, 1.0 mmol), NaH (80 %, 90 mg, 3.0 mmol) in dry tetrahydrofuran (5 ml) and the preformed mixture of DCC (309 mg, 1.5 mmol) and acrylic acid (206 µl, 3.0 mmol) in dry methylene chloride (5 ml) to give compound **10** (365 mg, 84 %). ^{1}H-NMR($CDCl_3$) : 9.88 (br.s., 1H) NH; 7.59-7.26 (m, 6H) H-6, arom.; 6.59-5.82 (m, 4H) H-a, H-b, H-1'; 4.54-4.37 (m, 3H) H-5', H-5", H-4'; 4.00 (m, 1H) H-3'; 3.07-2.00 (m, 2H) H-2', H-2"; 1.93 (d, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$) : 110.8 (s) C-5; 84.3 (d, J_{CH} = 176.4 Hz) C-1'; 79.0 (d, J_{CH} = 151.6 Hz) C-4'; 65.4 (t, J_{CH} = 148.3 Hz) C-5'; 40.3 (d, J_{CH} = 152.8 Hz) C-3'; 39.7 (t, J_{CH} = 135.4 Hz) C-2'; 12.4 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB$^-$): calcd. for (M-H)$^-$ 435.0459, found 435.0433.

1-[5'-O-(1-oxo-but-2-ene-1yl)-2',3'-dideoxy-3'(R)-phenylseleno-β-D-*glycero*-pentofuran osyl]thymine (11): To a solution of compound **1b** (380 mg , 1.0 mmol) in dry pyridine (10 ml) was added crotonoyl chloride (121 µl, 1.2 mmol), and the stirred for 4h at room temperature. The reaction mixture was poured into ice-water (100 ml) and extracted with chloroform (3 x 50 ml). The organic phase was evaporated to dryness, coevaporated with toluene, and then subjected to flash chromatography to give the pure compound **11** (383 mg, 85 %). ^{1}H-NMR($CDCl_3$) : 9.22 (br.s., 1H) NH; 7.59-7.25 (m, 6H) H-6, arom.; 7.16-6.84 (m, 1H) H-b; 6.09 (dd, $J_{1',2'}$= 6.3 Hz, $J_{1',2''}$= 6.6 Hz, 1H) H-1'; 5.8 (dq, $J_{a,b}$ = 15.4 Hz, $J_{a,c}$ = 1.7 Hz, 1H) H-a; 4.49 (m, 3H) H-5', H-5", H-4'; 3.95 (m, 1H) H-3'; 3.06-2.01 (m, 2H) H-2', H-2"; 1.93 (d, 3H) 5-Me; 1.87 (m, 3H) H-c. ^{13}C-NMR ($CDCl_3$) : 121.8 (d, J_{CH} = 160.6 Hz) C-a; 110.8 (s) C-5; 84.3 (d, J_{CH} = 174.1 Hz) C-1'; 79.2 (d, J_{CH} = 150.5 Hz) C-4'; 65.1 (t, J_{CH} = 148.3 Hz) C-5'; 40.4 (d, J_{CH} = 151.6 Hz) C-3'; 39.9 (t,

J_{CH} = 135.4 Hz) C-2′; 18.0 (q, J_{CH} = 128.1 Hz) C-c; 12.4 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB⁻): calcd. for (M-H)⁻ 449.0616, found 449.0610.

1-[2',3'-Dideoxy-3'-C,5'-O-carbonyl((1-butyl(R))methylidene)-β-D-*erythro*-pentofuranosyl]thymine (15): *General Procedure for the Free-Radical Cyclization* : A solution of compound **12** (247 mg, 0.519 mmol) in dry benzene (120 ml) was degassed with argon, treated with AIBN (5 mg) and warmed to reflux. A solution of tri-n-butyltin hydride (180 µl, 0.649 mmol, 1.25 eq) and AIBN (85 mg, 0.519 mmol, 1 eq) in dry benzene (40 ml) was added dropwise over 21 h, and the reaction mixture was heated to reflux for additional 2 h. The reaction mixture was cooled to ~20°C and evaporated to dryness. The residue was then treated with hexane (50 ml), extracted with dry acetonitrile (2 x 50 ml). The acetonitrile phase was evaporated to dryness and purified on silica gel column to give compound **15** (88 mg, 53 %). For ^{1}H-NMR, see Tables 1 and 2; ^{13}C-NMR ($CDCl_3$) : 134.1 (d, J_{CH} = 182.0 Hz) C-6; 112.1 (s) C-5; 82.9 (d, J_{CH} = 166.3 Hz) C-1′; 74.7 (d, J_{CH} = 149.4 Hz) C-4′; 68.4 (t, J_{CH} = 151.1 Hz) C-5′; 41.4 (d, J_{CH} = 126.9 Hz) C_1; 37.6 (d, J_{CH} = 131.4 Hz) C-3′; 33.6 (t, J_{CH} = 132.0 Hz) C-2′; 29.0 (t , J_{CH} = 132.0 Hz) CH_2 in n-But; 27.3 (t, J_{CH} = 130.3 Hz) CH_2 in n-But; 22.5 (t, J_{CH} = 128.6 Hz) CH_2 in n-But; 13.7 (q, J_{CH} = 124.7 Hz) CH_3 in n-But; 12.5 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB⁻): calcd. for (M-H)⁻ 321.1451, found 321.1444.

1-[2',3'-Dideoxy-3'-C,5'-O-carbonyl((1-methyl(R))methylidene)-β-D-*erythro*-pentofuranosyl]thymine (13): The general procedure for the free-radical cyclization was followed by using compound **10** (130 mg, 0.299 mmol) in dry benzene (60 ml), tri-n-butyltin hydride (104 µl, 0.375 mmol, 1.25 eq) and AIBN (49 mg, 0.299 mmol) in dry benzene (20 ml), and addition over 14 h to give compound **13** (9 mg, 10 %). For ^{1}H-NMR, see Tables 1 and 2; ^{13}C-NMR ($CDCl_3$) : 134.1 (d, J_{CH} = 183.3 Hz) C-6; 112.2 (s) C-5; 83.0 (d, J_{CH} = 165.0 Hz) C-1′; 74.8 (d, J_{CH} = 152.6 Hz) C-4′; 68.9 (t, J_{CH} = 150.8 Hz) C-5′; 39.8 (d, J_{CH} = 136.0 Hz) C_1; 36.5 (d, J_{CH} = 132.0 Hz) C-3′; 33.9 (t, J_{CH} = 133.3 Hz) C-2′; 13.2 (q, J_{CH} = 128.3 Hz) CH_3; 12.6 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB⁻): calcd. for (M-H)⁻ 279.0981, found 279.0986.

1-[2',3'-Dideoxy-3'-C,5'-O-carbonyl((1-ethyl(R))methylidene)-β-D-*erythro*-pentofuranosyl]thymine (14): The general procedure for the free-radical cyclization was followed by using compound **11** (300 mg, 0.668 mmol) in dry benzene (180 ml), tri-n-butyltin hydride (232 µl, 0.835 mmol, 1.25 eqv.) and AIBN (110 mg, 0.668 mmol) in dry benzene (40 ml), and addition over 20 h to give compound **14** (98 mg, 50 %). For ^{1}H-NMR, see Tables 1 and 2; ^{13}C-NMR ($CDCl_3$) : 134.0 (d, J_{CH} = 173.0 Hz) C-6; 112.1 (s) C-5; 82.9 (d, J_{CH} = 166.3 Hz) C-1′; 74.7 (d, J_{CH} = 151.6 Hz) C-4′; 68.4 (t, J_{CH} = 153.3 Hz) C-5′; 43.1 (d, J_{CH} = 126.8 Hz) C_1; 37.3 (d, J_{CH} = 133.8 Hz) C-3′; 33.5 (d, J_{CH} = 132.0 Hz) C-2′; 20.9 (t, J_{CH} = 128.1 Hz) CH_2 in Et; 12.5 (q J_{CH} = 129.2 Hz) 5-Me; 11.5 (q, J_{CH} = 126.1 Hz) CH_3. MS (FAB⁻): calcd. for (M-H)⁻ 293.1138, found 293.1151.

1-[2',3'-Dideoxy-3'-C,5'-O-((1-methyl(S))ethylene)-β-D-*erythro*-pentofuranosyl]thymine (6): The general procedure for the free-radical cyclization was followed by using compound **2** (240 mg, 0.571 mmol) in dry benzene (150 ml), tri-n-butyltin hydride (198 µl, 0.714 mmol, 1.25 eqv.) and AIBN (94 mg, 0.571 mmol) in dry benzene (40 ml), and addition over 24 h to give compound **6** (24 mg, 16 %). For ^{1}H-NMR, see Tables 1 and 2; ^{13}C-NMR ($CDCl_3$) : 135.4 (d, J_{CH} = 180.9 Hz) C-6; 109.7 (s) C-5; 86.2 (d, J_{CH} = 174.1 Hz) C-1′; 77.7 (d, J_{CH} = 145.7 Hz) C-4′; 72.4 (t, J_{CH} = 135.9 Hz) C_2; 67.8 (t, J_{CH} = 142.7 Hz) C-5′; 40.4 (d, J_{CH} = 134.8 Hz) C-3′; 38.5 (t, J_{CH} = 135.3 Hz) C-2′; 32.3 (d, J_{CH} = 132.3 Hz) C_1; 15.6 (q, J_{CH} = 126.9 Hz) CH_3; 12.6 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB⁻): calcd. for (M-H)⁻ 265.1188, found 265.1198.

1-[2',3'-Dideoxy-3'-C,5'-O-((1-isopropyl(S))ethylene)-β-D-*erythro*-pentofuranosyl]thymine (7): The general procedure for the free-radical cyclization was followed by using compound **3** (314 mg, 0.734 mmol) in dry benzene (180 ml),tri-n-butyltin hydride (254 µl, 0.917 mmol, 1.25 eqv.) and AIBN (120 mg, 0.734 mmol) in dry benzene (40 ml), and addition over 24 h to give compound **7** (67 mg, 34 %). For ^{1}H-NMR, see Table 1 and Table 2; ^{13}C-NMR ($CDCl_3$) : 135.5 (d, J_{CH} = 182.0 Hz) C-6; 109.8 (s) C-5; 85.9 (d, J_{CH} = 173.0 Hz) C-1′; 77.7 (d, J_{CH} = 148.3 Hz) C-4′; 68.0 (t, J_{CH} = 142.7 Hz) C_2; 68.0 (t, J_{CH} = 142.7 Hz) C-5′; 42.4 (d, J_{CH} = 139.3 Hz) C-3′; 39.2 (t, J_{CH} = 134.2 Hz) C-2′; 36.2 (d, J_{CH} = 129.2 Hz) C_1; 28.4 (d, J_{CH} = 139.3 Hz) CH in i-Pr; 21.3 (q, J_{CH} = 125.9 Hz) CH_3 in i-Pr; 17.6 (q, J_{CH} = 125.8 Hz) CH_3 in i-Pr; 12.5 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB⁻): calcd. for (M-H)⁻ 293.1501, found 293.1499.

1-[2',3'-Dideoxy-3'-C,5'-O-((1-n-propyl(S))ethylene)-β-D-*erythro*-pentofuranosyl]thymine (8): The general procedure for the free-radical cyclization was followed by using compound **4** (325 mg, 0.725

mmol) in dry benzene (180 ml), tri-n-butyltin hydride (251 µl, 0.907 mmol, 1.25 eq) and AIBN (119 mg, 0.725 mmol) in dry benzene (40 ml), and addition over 21 h to give compound **8** (53 mg, 25 %). For ^{1}H-NMR, see Table 1 and Table 2; ^{13}C-NMR ($CDCl_3$) : 135.5 (d, J_{CH} = 187.6 Hz) C-6; 109.7 (s) C-5; 86.1 (d, J_{CH} = 171.9 Hz) C-1′; 77.7 (d, J_{CH} = 146.0 Hz) C-4′; 70.9 (t, J_{CH} = 141.0 Hz) C_2; 67.8 (t, J_{CH} = 175.8 Hz) C-5′; 39.1 (d, J_{CH} = 140.4 Hz) C-3′; 38.7 (t, J_{CH} = 134.2 Hz) C-2′; 36.5 (d, J_{CH} = 134.4 Hz) C_1; 33.4 (t, J_{CH} = 126.4 Hz) CH_2 in n-Pr; 19.8 (t, J_{CH} = 125.8 Hz) CH_2 in n-Pr; 13.9 (q, J_{CH} = 125.7 Hz) CH_3 in n-Pr; 12.5 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB$^-$): calcd. for (M-H)$^-$ 293.1501, found 293.1492.

1-[2',3'-Dideoxy-3'-C,5'-O-((1-methylene)ethylene)-β-D-*erythro*-pentofuranosyl]thymine (**9**): The general procedure for the free-radical cyclization was followed by using compound **5** (245 mg, 0.586 mmol) in dry benzene (100 ml), tri-n-butyltin hydride (245 µl, 0.885 mmol) and AIBN (96 mg, 0.586 mmol) in dry benzene (20 ml), and addition over 14 h to give compound **9** (40 mg, 27 %). For ^{1}H-NMR, see Table 1 and Table 2; ^{13}C-NMR ($CDCl_3$) : 131.6 (d, J_{CH} = 178.6 Hz) C-6; 109.7 (s) C-5; 107.0 (t, J_{CH} = 157.3 Hz) CH_2; 84.5 (d, J_{CH} = 173.0 Hz) C-1′; 78.2 (d, J_{CH} = 147.2 Hz) C-4′; 71.2 (t, J_{CH} = 143.8 Hz) C_2, 69.0 (t, J_{CH} = 142.7 Hz) C-5′; 42.6 (d, J_{CH} = 137.0 Hz) C-3′; 39.7 (t, J_{CH} = 135.4 Hz) C-2′; 17.6 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB$^-$): calcd. for (M-H)$^-$ 263.1032, found 263.1035.

1-[2',3'-Dideoxy-3'-C-(1-carboxy-1(R)-propyl)-β-D-*erythro*-pentofuranosyl] thymine (**16**): *General Procedure of Hydrolysis*: Compound **14** (15 mg, 0.051 mmol) was treated with diluted aqueous ammonia (~8%) in methanol (1:1, v/v, 10 ml) at ~20°C for 2 h. The reaction mixture was evaporated to dryness, and subjected to flash chromatography to give compound **16** (15 mg, 95 %). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 8.12 (q, J = 1.2 Hz, 1H) H-6; 6.08 (dd, $J_{1',2'}$= 8.4 Hz, $J_{1',2''}$= 5.7 Hz, 1H) H-1′; 4.24 (m, 1H) H-4′; 3.78 (m, $J_{5',5''}$= 2.4 Hz, $J_{4',5'}$= 3.9 Hz, 2H) H-5′, H-5"; 2.62 (m, 1H) H-3′; 2.25-1.28 (m, 5H) H-2′, H-2", H_1, CH_2 in Et; 1.89 (d, 3H) 5-Me; 0.97 (t, J = 7.1 Hz, 3H) CH_3 in Et. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 136.3 (d, J_{CH} = 181.9 Hz) C-6; 109.1 (s) C-5; 84.1 (d, J_{CH} = 168.2 Hz) C-1′; 79.3 (d, J_{CH} = 148.7 Hz) C-4′; 53.3 (t, J_{CH} = 139.9 Hz) C-5′; 46.3 (d) C_1; 41.9 (d, J_{CH} = 132.1 Hz) C-3′; 34.5 (t, J_{CH} = 134.0 Hz) C-2′; 23.6 (t, J_{CH} = 127.6 Hz) CH_2 in Et; 10.4 (q, J_{CH} = 129.1 Hz) 5-Me; 10.2 (q, J_{CH} = 125.2 Hz) CH_3. MS (FAB$^-$): calcd. for (M-H)$^-$ 311.1243, found 311.1243.

1-[2',3'-Dideoxy-3'-C-(1-carboxy-1(R)-pentyl)-β-D-*erythro*-pentofuranosyl]thymine (**17**): Compound **17**: The general procedure for hydrolysis was followed by using compound **15** (14 mg, 0.0436 mmol) to give compound **17** (13.8 mg, 94 %). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 8.00 (d, J = 1.0 Hz, 1H) H-6; 6.04 (dd, $J_{1',2'}$= 8.5 Hz, $J_{1',2''}$= 5.8 Hz, 1H) H-1′; 4.23 (m, $J_{3',4'}$= 4.2 Hz, 1H) H-4′; 3.83 (m, 2H) H-5′, H-5"; 2.62 (m, 2H) H-3′, H_1; 2.26 (m, 2H) H-2′, H-2"; 1.90 (d, 3H) 5-Me; 1.58-1.26 (m, 6H) CH_2 in n-But; 0.89 (t, J = 5.7 Hz, 3H) CH_3 in n-But. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 137.0 (d, J_{CH} = 182.3 Hz) C-6; 110.3 (s) C-5; 85.1 (d, J_{CH} = 168.0 Hz) C-1′; 79.9 (d, J_{CH} = 149.3 Hz) C-4′; 61.6 (t, J_{CH} = 140.5 Hz) C-5′; 45.4 (d, J_{CH} = 133.3 Hz) C_1; 42.7 (d, J_{CH} = 133.3 Hz) C-3′; 35.2 (t, J_{CH} = 135.2 Hz) C-2′; 31.3 (t, J_{CH} = 126.4 Hz) CH_2 in n-But; 29.4 (t, J_{CH} = 127.0 Hz) CH_2 in n-But; 22.2 (t, J_{CH} = 124.8 Hz) CH_2 in n-But; 13.5 (q, J_{CH} = 125.1 Hz) CH_3 in n-But; 11.8 (q, J_{CH} = 129.4 Hz) 5-Me. MS (FAB$^-$): calcd. for (M-H)$^-$ 339.1556, found 339.1566.

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