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New Stereocontrolled Synthesis of Isomeric *C*-Branched-β-D-Nucleosides by Intramolecular Free-radical Cyclization-Opening Reactions Based on Temporary Silicon Connection†

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Abstract: *Silicon-bearing allyl group tethered to a 2' or 3'-hydroxyl group onto the radical generated at the vicinal 2' or 3' center in the free-radical precursors **11, 15, 19** and **23** were used to promote intramolecular stereocontrolled free-radical-cyclization to give **12a + 12b, 16, 20** and **24** in 60-70% yields. The configuration at the 2' or the 3' center of the allylsiloxane group dictated the stereochemical outcome of the radical cyclization reaction to give cis-fused seven-membered rings in compounds **16, 20** and **24** (from **15, 19** and **23**, respectively) due to relatively long Si-O bond and large C-Si-O bond angle leading to exclusive 7-endo cyclization. The only exception to this was found in the radical-cyclization of **11** in which both cis-fused and trans-fused seven-membered rings **12a** and **12b** were formed as inseparable mixture almost in equal amounts. The seven-membered siloxane ring in the radical-cyclized products **12a + 12b, 16, 20** and **24** were then opened up by a simple oxidation reaction to give different 1,5-diols **13a + 13b, 17, 21** and **25** in high yields. The 5'-O-(4-methoxytrityl) group from **13a + 13b, 17, 21** and **25** was then removed to give pure and isomeric C-branched nucleosides **14a , 14b, 18, 22** and **26**, respectively. The acid catalyzed isomerization of the pentofuranose ring in **17** to a pyranose system in **18** has been concluded on the basis of comparative structural analysis of **17** and **18** by 500 MHz ^{1}H-NMR spectroscopy. The configurations of triol **18** are C-2'(S), C-4'(R), C-5(R), C-6(S), C-7(S) which are also the configurations of the corresponding chiral centers in the precursors **16** and **17**. Note that the acid catalyzed isomerization of furanose in **17** to pyranose ring in **18** has been achieved with full retention of anomeric configuration. The configuration of C-3' in compounds **14a, 14b, 22**, and C-2' in **26** has been elucidated by 1D differential nOe experiments by ^{1}H-NMR spectroscopy at 500 MHz in D_2O solution at 293K. The estimation of the $^3J_{HH}$ coupling constants led us to calculate dihedral angles of **14a, 14b, 17, 18, 22** and **26** using the Karplus-Altona algorithm which have allowed us to define the conformational parameters of their constituent sugar moieties. Molecular mechanics calculations have been subsequently performed on the initial NMR structures of **17** and **18** to give their energy minimized conformations. The structure of **18** has been finally confirmed by estimating proton-proton distances derived from their nOe build-up rates by 2D NOESY experiments at 293K at different mixing times.*

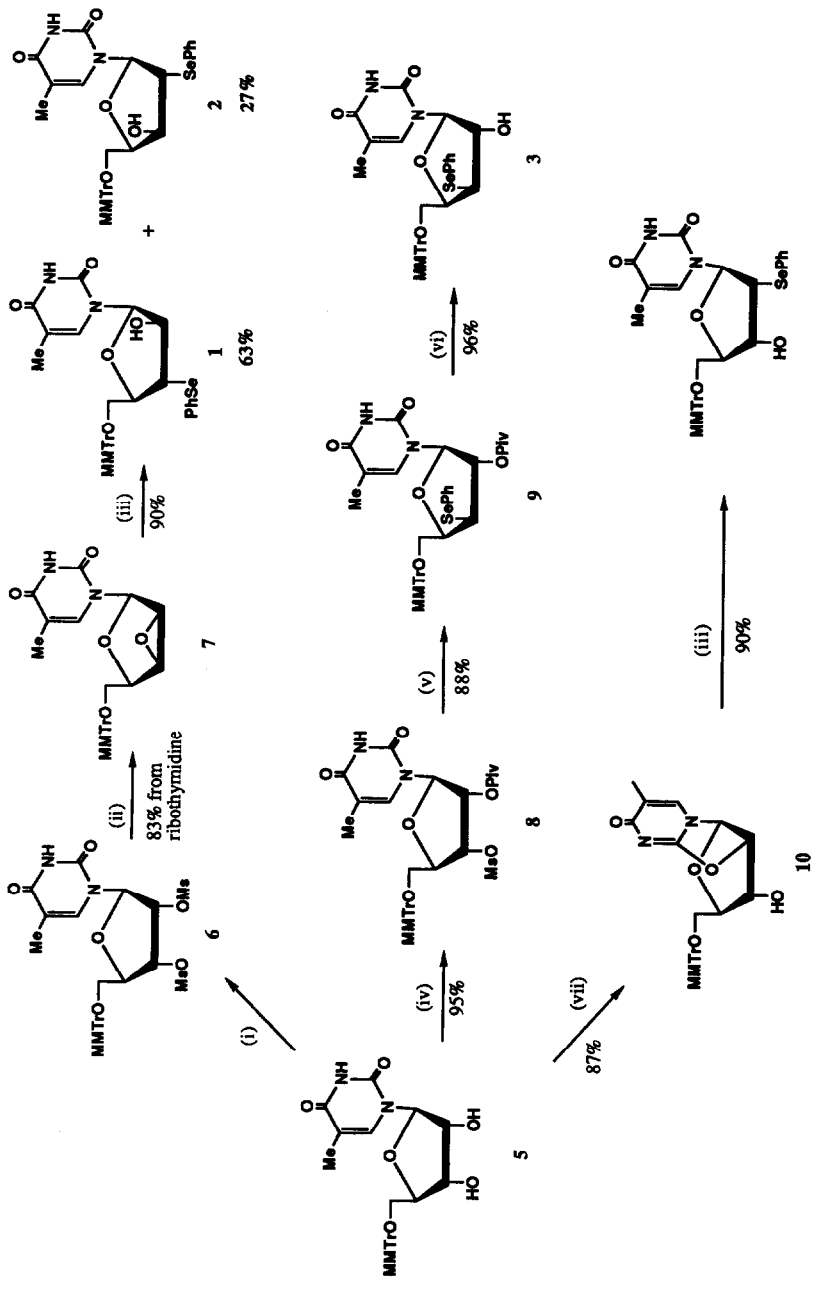
Stereocontrolled intramolecular free-radical cyclization has emerged as a powerful tool for carbon-carbon bond formation in organic synthesis owing to our increasing understanding of the mechanistic behaviour of such reaction over the last decade.[1,2] We have deemed it important for some time now[9,10] that such stereocontrolled intramolecular free-radical cyclization reactions are powerful means for introduction of *C*-branching at 2', 3' or at 5' centers of β-D-nucleosides[4-10]. Development of stereoselective synthesis of *C*-branched nucleosides have drawn much attention because of the fact that some of these *C*-branched nucleosides have been found to produce remarkable antibacterial, antitumor, antiviral activities.[3]

† *Dedicated to the memory of Professor Tohru Ueda*

Intramolecular free-radical cyclization reactions have also the advantage that the condition employed is mild, neutral, and compatible with a number of functional groups compared to the relatively harsh reaction condition employed in the ionic reaction. The starting materials required for the synthesis of free-radical precursors are also easily accessible and stable. In a previous paper, we have already shown that the intramolecular free-radical trapping reaction is an efficient method to functionalize both 2' and 3'-carbons of uridine to give various *cis*-fused furan derivatives through the allyl or propargyl ether tethered to a 2' or 3'-hydroxyl group onto the radical at the vicinal 2' or 3' center.[9] We have also successfully performed intramolecular cyclization reaction of the radical generated at the 3' center by trapping intramolecularly with an olefin or alkyne funtion tethered from the 5'-end by an ether or ester function to give various diastereospecifically pure [3.4.0]-*cis*-fused furo[2,3-c]pyrans or [3.4.0]-*cis*-fused δ-lactones.[10] Note that in the later example it was also possible to orchestrate a smooth conversion of δ-lactones, upon treatment with diluted aqueous ammonia, to the ring-opened *C*-branched *erythro* derivatives through free-radical cyclization and ring-opening sequence. What was clear in these works that more efficient temporary connection of free-radical acceptor, like the unsaturated ester linkage, is necessary in order to demonstrate the generality of our intramolecular free-radical-cyclization-ring-opening methodology for stereospecific syntheses of *C*-branched nucleosides. Recently, silicon connection method has been shown to be synthetically useful because the cleavage of Si-O and Si-C bond of siloxane ring[11-15] can be achieved rather easily, and also due to the fact that the transformable unsaturated silicon-containing reagents are conveniently accessible.[16-19] The choice of temporary silicon connection was also attractive because of wide application of silicon-containing protecting groups in nucleoside chemistry.[20,21] Since Wilt's pioneering work on mechanistic study of silicon-containing radical addition reaction,[22] many papers have been published which deal with the cyclization of silicon-bearing radical (2-sila-3-oxa-5-hexenyl radical and 2-sila-3-oxa-6-heptenyl radical).[23-30] During the progress of this work, three papers[31] have been published which deal with the silicon bearing radical acceptor: vinylsiloxane,[31a] silaketals,[31b] and ethynylsiloxane.[31c]

We herein report our intramolecular free-radical-cyclization-ring-opening methodology for regiospecific or stereospecific syntheses of *C*-branched nucleosides using silicon-bearing allyl group tethered to a 2' or 3'-hydroxyl group onto the radical generated at the vicinal 2' or 3' center in the free-radical precursors: **11**, **15**, **19** and **23**. We chose silicon-bearing allyl group in order to study the applicability of transfer of temporary silicon connection in view of the challenge in the transformation of a 1,2-diol system, as in a simple β-D-nucleoside, to a homologous 1,4-diol or 1,5-diol system(s) due to 6-*exo* or 7-*endo* cyclization, respectively. In this study, we show that, generally, it is the configuration at the 2' or the 3' center of the allylsiloxane group that dictate the stereochemical outcome of the radical cyclization reaction as in **15**, **19** and **23** to give *cis*-fused seven-membered compounds **16**, **20** and **24**, respectively, entirely due to 7-*endo* cyclization. The only exception to this was found in the radical-cyclization of **11** in which both *cis*-fused and *trans*-fused seven-membered rings **12a** and **12b** were formed in an almost equal amounts (NMR) as an inseparable mixture. The seven-membered siloxane ring in the radical-cyclized products **12a** +**12b**, **16**, **20** and **24** were then opened up by a simple oxidation reaction to give different 1,5-diols: **13a** + **13b**, **17**, **21** and **25**. The 5'-*O*-(4-methoxytrityl) group from **13a** + **13b**, **17**, **21** and **25** was then removed to give isomeric *C*-branched nucleosides **14a** , **14b**, **18**, **22** and **26**, respectively, in high yields.

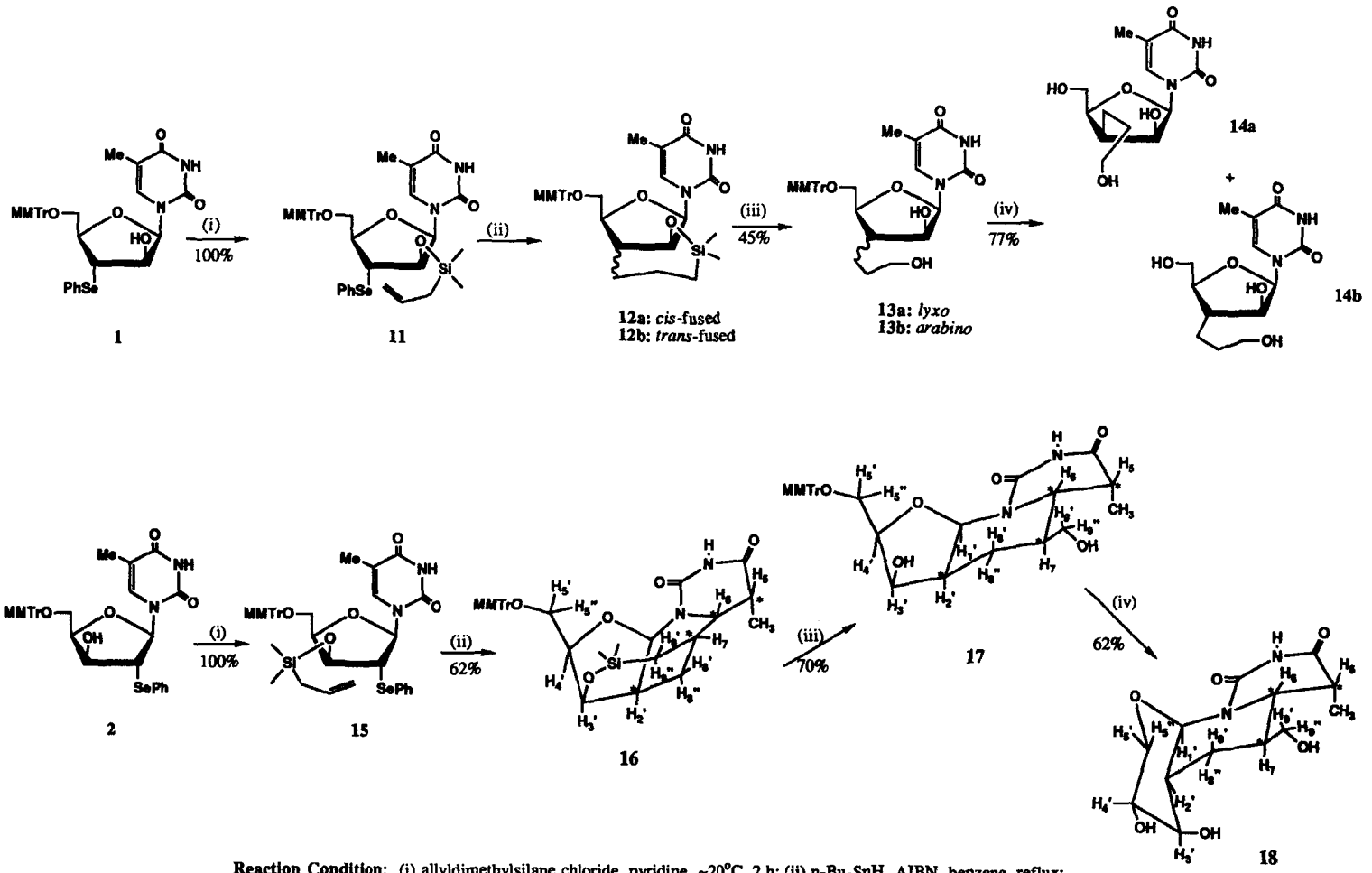
Preparation of free-radical precursors. 1-(5'-*O*-(4-monomethoxytrityl)[MMTr]-3'-deoxy-3'-phenylseleno-β-D-*arabino*furanosyl)thymine **1** and 1-(5'-*O*-(MMTr)-2'-deoxy-2'-phenylseleno-β-D-



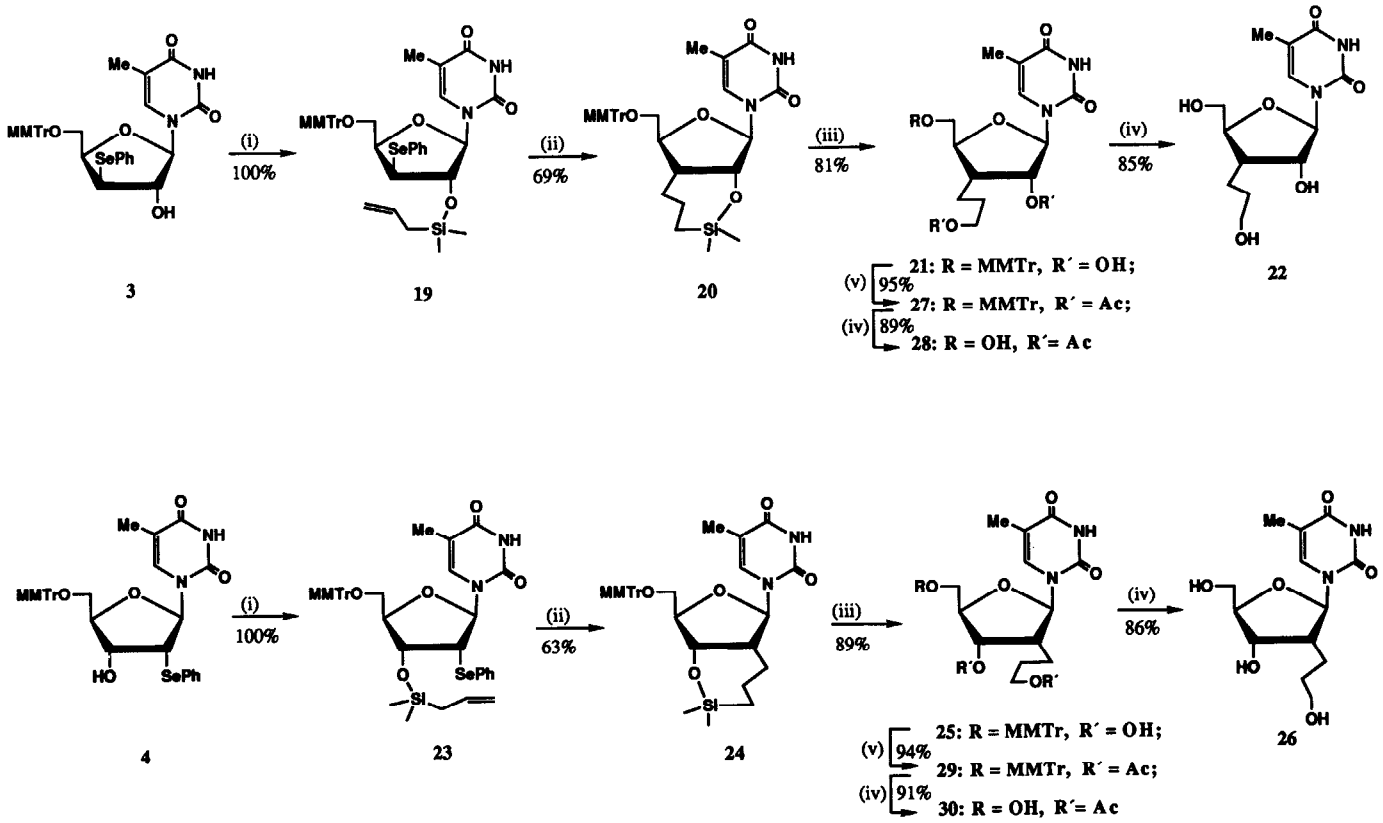
Reaction Condition: (i) MsCl (3 eq), pyridine, ~20°C, overnight; (ii) 1N aqueous NaOH: dioxane(1:1), ~20°C, 6 h; (iii) $(PhSe)_2$, $LiAlH_4$, THF, reflux, 4 h; (iv) (a) PivCl (1.3 eq), pyridine, -10°C, 1.5 h; (b) MsCl (1.5 eq), ~20°C, 6 h; (v) $(PhSe)_2$, $NaBH_4$, EtOH-THF, reflux, overnight; (vi) 1N aq NaOH: dioxane(1:1); (vii) bisimidazole-1-yl-thione, toluene, reflux, 1.5 h.

*xylo*furanosyl)thymine **2** were prepared in 63% and 27% yields, respectively, by the nucleophilic attack of the $PhSe^-$ anion, generated from treatment of $(PhSe)_2$ with $LiAlH_4$ in THF,[7,33] on 1-(5'-*O*-(MMTr)-2',3'-*O*-anhydro-β-D-*lyxo*furanosyl)thymine **7**.[34] 1-(5'-*O*-(MMTr)-2'-deoxy-2'-phenylseleno-β-D-*ribo*furanosyl) thymine **4** was prepared in 90% yield by the nucleophilic attack of the $PhSe^-$ anion from $(PhSe)_2$ with $LiAlH_4$ in THF[8] on 1-(5'-*O*-(MMTr)-2,2'-*O*-anhydro-β-D-*arabino*furanosyl)thymine **10** which was synthesized in 87% yield following Patchett's procedure[35] by treatment of 1-(5'-*O*-(MMTr)-β-D-*ribo*furanosyl)thymine **5** with thiocarbonyl-bis-imidazole in toluene under reflux. When 1-(5'-*O*-(MMTr)-2'-*O*-Pivaloyl-3'-*O*-Methanesulphonyl-β-D-*ribo*furanosyl)thymine **8**,[34,36] prepared in 95% yield from 1-(5'-*O*-(MMTr)-β-D-*ribo*furanosyl)thymine **5**, was subjected to the reaction condition described above [$(PhSe)_2/LiAlH_4$, reflux in THF or dioxane overnight], quite surprisingly, the starting material **8** was recovered almost quantitatively. This reaction however could be performed successfully upon changing the reducing reagent from $LiAlH_4$ to $NaBH_4$. Thus, when compound **8** was treated with the $PhSe^-$ anion generated from treatment of $(PhSe)_2$ with $NaBH_4$[37] in THF-ethanol mixture at reflux overnight, the desired product **9** was obtained in 88% yield. Treatment of compound **9** with aqueous NaOH (1M) in dioxane (1:1, v/v) gave 1-(5'-*O*-(MMTr)-3'-deoxy-3'-phenylseleno-β-D-*xylo*furanosyl)thymine **3** (96%). Compounds **1**, **2**, **3**, **4** were then treated with allylchlorodimethylsilane[32] (1.5 eq) in dry pyridine under argon for 2 h at room temperature to give the free-radical precursors **11**, **15**, **19**, **23**, respectively, in quantitative yields.

Intramolecular free-radical cyclization. A solution of tri-n-butyltin hydride (1.5 eq) and azobisisobutyronitrile (AIBN) in degassed benzene (0.06 M) under an atomosphere of argon was added slowly by a syringe pump into a solution of the free-radical precursors (**11**, **15**, **19**, **23**) in boiling benzene (0.004 M) over 10-14 h. The radical thus generated at 2' or 3'-carbon was efficiently trapped by the double bond of the allylsiloxane tethered at the 3' or 2' hydroxyl group in *ribo*, *arabino*, *lyxo* or *xylo* configuration. In all cases tested, the 7-*endo* cyclized compound was the sole product, no by-product due to the direct reduction of the radical-generating center or 6-*exo* cyclization reaction was detectable. Specific stereoelectronic environments at the α- and β-face of pentofuranose ring of the β-D-nucleoside played crucial roles in the stereochemical outcome of the free-radical addition reaction as we have shown before.[9,10] When the prochiral radical generated at the 2'- or at the 3'-carbon was trapped by the double bond of allyldimethylsilyl ether at the α-face of the nucleoside **19** and **23**, the free-radical cyclization reaction produced single diastereospecific *cis*-fused seven-membered siloxane **20** (69%) and **24** (63%). But when the prochiral radical generated at the 2'- or at the 3'-carbon was trapped by the double bond of allyldimethylsilyl ether at the β-face of the nucleoside **11** and **15**, the outcome of the reaction depends strongly on the position of the radical acceptor at the C2' or C3' center. If the radical acceptor was attached to 2'-oxygen as in **11**, the radical generated at 3'-carbon was trapped to give an *equal amount* of *cis*-fused and *trans*-fused seven-membered siloxanes **12a** and **12b** as judged by NMR. It was subsequently found that, upon our attempts to separate the mixture of **12a** and **12b** by silica gel column chromatography, it is the *trans*-fused seven-membered siloxane ring that decomposed preferentially. This resulted in an enriched amount of the *cis*-fused siloxane **12a** over the *trans*-fused siloxane **12b** in the mixture (10:1 ratio in 35% combined yield) but we failed to separate these two isomers in their pure form despite many attempts. If the radical acceptor was attached to 3'-oxygen as in **15**, the radical generated at 2'-carbon was trapped on the β-face to give an unique tetracyclic product **16** (62%), first, due to efficient 7-*endo* cyclization producing an intermediary secondary radical in the steric proximity of the C5-C6 double bond



Reaction Condition: (i) allyldimethylsilane chloride, pyridine, ~20°C, 2 h; (ii) n-Bu_3SnH, AIBN, benzene, reflux; (iii) 30% H_2O_2(10 eq), KF (2 eq), $KHCO_3$(2 eq), MeOH/THF(1:1), ~20°C, overnight; (iv) 80% aq AcOH, ~20°C, overnight.



Reaction Condition: (i) allyldimethylsilane chloride, pyridine, ~20°C, 2 h; (ii) n-Bu_3SnH, AIBN, benzene, reflux; (iii) 30% H_2O_2(10 eq), KF (2 eq), $KHCO_3$(2 eq), MeOH/THF(1:1), ~20°C, overnight; (iv) 80% aqueous AcOH, ~20°C, overnight; (v) Ac_2O, DMAP, pyridine, ~20°C, overnight.

of thymine, which, in the second step, underwent a tandem free-radical addition-cyclization reaction to give the sole tetracyclic product **16** in a highly stereocontrolled manner.

Oxidative cleavage of Si-C bond of siloxane ring (Tamao oxidation). The siloxane ring can be opened either at the Si-O or Si-C bond. Opening of Si-O bond could be achieved by treatment of fluoride ion, acid or base.[11] Such deprotection conditions are widely used for silicon-containing protecting groups such as t-butyldimethylsilyl (TBDMS).[20] Si-C bond could be cleaved reductively to give new H-C bond,[14,15,23c] and oxidatively to give alcohol.[12] The latter is well known as Tamao oxidation. To demonstrate the free-radical cyclization-ring opening methodology for constructing *C*-branched nucleosides, we are interested in oxidative cleavage of Si-C bond of siloxane ring to produce the 1,5-diol. To test Tamao oxidation system in nucleosides, the pure free-radical cyclization product (**16, 20** or **24**) was used. When a siloxane (**16, 20** or **24**) was treated with the "oxidizing reagent" consisting of 30% H_2O_2 (10 eq), KF (2 eq) and $KHCO_3$ (2 eq) in methanol-THF mixture (v/v 1:1) at room temperature overnight, the diol (**17, 21** or **25**) was obtained in good to excellent yield (70-89%). In all cases, depyrimidination products could be detected in small amounts. The structures of 1,5-diols **21** and **25** were further substantiated by 1,5-di-*O*-acetylation to give compounds **27** and **29**, followed by deprotection of 5'-*O*-MMTr group to give the diacetate **28** and **30** (see Experimental). Since the Tamao oxidation of siloxane ring has been established, we turned to use one-pot procedure of free-radical-cyclization-Tamao oxidation. After the cyclization of the free-radical precursor (**11, 15, 19** or **23**), the crude cyclized product was directly treated with the "oxidizing reagent" at 0°C at room temperature overnight to give the diol (**13, 17, 21** or **25**), after silica gel column purification with ethylacetate as eluent, in 45-58% yield. Note that the epimeric diols **13a** and **13b** produced at this stage were still an equal amount of inseparable mixture as judged by NMR.

Finally the epimeric diols **17, 21, 25** were deprotected by treatment of 80% aqueous acetic acid to furnish the *C*-branched nucleosides **18, 22, 26** in 62, 85, 86% yields respectively. The acid catalyzed isomerization of the furanose ring in **17** to pyranose system in **18** has been concluded on the basis of comparative structural analysis of **17** and **18** by 500 MHz ^{1}H-NMR spectroscopy (*vide infra*). The configurations of triol **18** are C-2'(S), C-4'(R), C-5(R), C-6(S), C-7(S) which are also the configurations of the corresponding chiral centers in the precursors **16, 17**. Note that the acid catalyzed isomerization of furanose **17** to pyranose **18** has been achieved with full retention of anomeric configuration. The epimeric mixture of diols **13a** + **13b**, under an identical acidic deprotection condition, gave triols **14a** and **14b** which were separated in pure forms upon silica gel column chromatography [~38% each, R_f (MeOH in CH_2Cl_2, 1:9, v/v)]: **14a** : 0.21; **14b** : 0.1). The absolute configurations of 3'-carbon in compounds **14a** and **14b** were established by 1D differential nOe experiments (*vide infra*).

Following points may be noted from the above results: (i) the free-radical cyclization of 3-oxa-4-sila-6-heptenyl radical without terminal alkene substitutent as in the free-radical precursors **11, 15, 19, 23** makes a definite choice for 7-*endo* cyclization. In all the cases we have studied, the 7-*endo* cyclization product has been obtained as the only detectable product regardless of the type of the tether-site of the radical acceptor. And this is in a good agreement with the trend effected by silicon element in six or seven-membered ring formation by radical cyclization,[24,25,31b] and also with the theoretical prediction for ring formation.[42-44] (ii) The stringent *cis*-cyclization course usually found in intramolecular free-radical addition does not hold tightly here. The formation of epimeric mixture **12a** and **12b** implies that caution should be taken in planning radical addition-cyclization reaction which may lead to the formation of fused rings larger than seven-membered ring.

Table 1: Chemical shifts (δ (ppm)) of compound **14a, 14b, 22, 26** collected from their 500 MHz NMR spectra in D_2O at different temperatures.

chemical shifts (δ (ppm))	compound **14a**			compound **14b**			compound **22**			compound **26**		
	294K	313K	333K	294K	313K	333K	294K	313K	333K	294K	313K	333K
H-1'	5.93	5.91	5.89	6.03	6.00	5.98	5.73	5.73	5.72	5.96	5.93	5.91
H-2'	4.28	4.27	4.26	4.32	4.30	4.28	4.34	4.32	4.32	2.31	2.32	2.30
H-3'	2.70	2.68	2.66	1.97	1.97	1.98	2.04	2.03	2.03	4.41	4.29	4.28
H-4'	4.39	4.38	4.37	3.79	3.78	3.78	4.02	4.00	4.00	4.04	4.02	4.01
H-5'	3.75	3.75	3.76	3.88	3.87	3.86	3.98	3.96	3.93	3.72	3.71	3.71
H-5"	3.68	3.68	3.68	3.75	3.74	3.73	3.75	3.73	3.71	3.72	3.71	3.71
H-6	7.65	7.65	7.64	7.79	7.73	7.68	7.91	7.82	7.75	7.58	7.55	7.51
5-Me	1.85	1.84	1.84	1.83	1.83	1.83	1.80	1.80	1.80	1.84	1.83	1.83
H-α	1.62-1.49	1.61-1.50	1.61-1.51	1.66-1.52	1.61-1.52	1.61-1.52	1.60-1.48	1.58-1.50	1.58-1.51	1.57-1.43	1.59-1.43	1.60-1.44
H-β	1.49	1.50	1.51	1.59-1.52	1.52	1.52	1.48-1.39	1.50-1.37	1.51-1.37	1.54-1.35	1.51-1.35	1.50-1.35
H-γ	3.58	3.57	3.56	3.56	3.56	3.55	3.55	3.54	3.53	3.51	3.49	3.49

Table 2: J-couplings of compound **14a, 14b, 22, 26** collected from their 500 MHz NMR spectra in D_2O at different temperatures.

J-couplings	compound **14a**			compound **14b**			compound **22**			compound **26**		
	294K	313K	333K	294K	313K	333K	294K	313K	333K	294K	313K	333K
$J_{1'/2'}$	3.1	3.1	3.2	5.7	5.7	5.5	0.2	0.3	0.4	9.4	9.2	9.2
$J_{2'/3'}$	4.3	4.1	4.3	7.3	7.3	7.0	4.8	5.1	5.4	5.4	5.5	5.7
$J_{3'/4'}$	8.6	8.7	8.4	7.6	7.3	7.3	9.8	9.8	9.7	1.6	1.8	1.8
$J_{4'/5'}$	2.7	2.8	2.8	1.8	1.7	1.5	2.2	2.5	2.2	4.5	4.7	4.9
$J_{4'/5'}$	5.9	5.7	5.9	4.4	4.7	4.4	3.8	3.7	4.2	4.5	4.7	4.9
$J_{5'/5"}$	12.3	12.2	12.3	12.6	12.7	12.4	13.6	13.1	13.3	a	a	a
$J_{2'/\alpha}$	a	a	a	a	a	a	a	a	a	a	8.9	8.6
J3'/α	9.9	10.0	9.7	7.6	7.3	7.3	9.8	9.8	9.7	a	a	a
Jβ/γ	6.3	6.4	6.3	6.5	6.4	6.5	6.3	6.2	6.2	6.4	6.5	6.5

[a] could not be obtained because of resonance overlap

Table 3: Estimation of γ and Pseudorotational parameters of compound **14a, 14b, 17, 22, 26** calculated from J-couplings obtained at 500 MHz NMR spectra in D_2O at 293K and 313K, 333K and PSEUROT calculations.

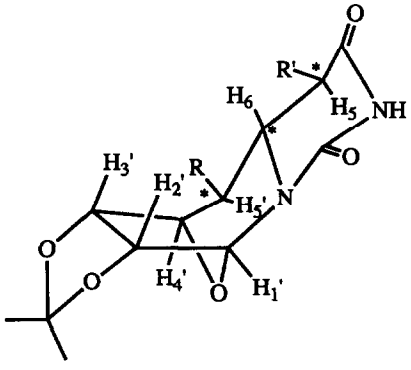
Pseudorotamer parameters	Compound **14a**	Compound **14b**	Compound **17**	Compound **22**	Compound **26**
γ^+	48 %	72 %	54 %	75 %	47 %
γ	3 %	-	35%	-	25 %
γ^t	49 %	28 %	11 %	25 %	28 %
P_N	-10° to 10°	-10°	10-30°	-18°	-10° to 10°
Φ_N	39°	34°	39°	35°	39°
P_S	147°	180 to 200°	140°	-	154°
Φ_S	50°	38°	40°	38°	36°
S-population	86 %	20 %	93 %	0 %	100 %
RMS error	0.03 Hz	0.04 Hz	0.03 Hz	0.6 Hz	0.07 Hz

Table 5 : 1D Differential nOe observed for compound **14a, 14b, 17, 22, 26** at 500 MHz in D_2O at 293K.

Irradiated Proton	OBSERVED nOe [%] FOR VARIOUS COMPOUNDS				
	compound **14a**	compound **14b**	compound **22**	compound **26**	compound **17**
H-6	1' [1.6], 5' [0.9], 5" [1.0]	1' [1.4], 5' [2.2], 5" [2.5], 3' [6.0]	1' [0.9], 2' [1.1], 3' [4.1], 5' [1.7], 5" [1.1]	2' [9.5], 3' [1.2], 5'+5" [1.7]	5 [4.4], 8 [0.5], 9 [-2.0]
H-1'	H6 [1.0], 2' [5.3], 4' [0.6], 3' [4.8]	2' [8.9], 6 [1.2]	6 [1.5], 2' [3.8]	4' [1.0], α+β [3.0]	3' [1.7], 4' [1.7], 2' [3.1], 7 [0.6]
H-2'	3' [4.0], 1' [6.7] α+β [2.7]	3' [2.4], 1' [9.3], α+β [3.7]	3' [6.5], 1' [3.3] 6 [1.4]	α+β [8.0], 3'[8.8], 1' [1.0], 6 [9.4]	3' [4.5], 1' [3.9], 7 [0.7], 8 [1.8]
H-3'	α+β [5.1], 1' [4.0], 2' [5.8], 4' [8.0]	α+β [3.7], 2' [2.3] 5' [1.9], 6 [6.2]	α+β [4.9], 2' [7.2], 4' [1.6], 5' [1.0], 5" [1.1], 6 [4.7]	4' [1.7], 2' [7.6], 6 [1.1], 5'+5" [1.9]	1' [1.4], 2' [3.5], 4' [4.8]
H-4'	5' [4.1], 5" [2.0], 3' [7.2], 1' [0.7]	-	3' [1.5], α+β [1.8], 1' [1.4]	3' [1.5], 1' [0.8], 5'+5" [1.8]	1' [2.1], 3' [4.9], 5' [0.8], 5" [1.7]
H-5'	5" [17.8], 4' [6.5], 6 [2.1]	5" [16.1], 6 [1.9], 3' [1.9]	5" [19.7], 6 [1.3], 3' [1.7]	4' [6.9], 3' [2.1], 6 [2.2]	4' [1.7], 5" [9.9]
H-5"	5' [20.0], 6 [1.5], 4' [4.2]	6 [2.5], 5' [14.9]	5' [20.9], 4' [5.6], 3' [1.7], 6 [1.5]		5' [9.5], 4' [7.3]
H-5					6 [3.6], 9 [2.3], Me^5 [2.8]
H-7					2' [2.7], 9 [4.0], Me^5 [2.5]
H-8					2' [2.9], 9 [2.0], 6 [1.9]
H-9					6 [-1.6]. 5 [2.7], 7 [3.1], 8 [1.2]

Here the steric factor may be responsible for the stereochemical outcome of the reaction. The strong steric repulsion from the aglycone to the silyl ether chain anchored at the 2'-*arabino*-site of compound **11** forced the reaction path to adopt *cis*-cyclization (to **12a**) versus the *trans*-cyclization (to **12b**) in an equally facile manner. This is evident from the fact that **19** or **23** *(cyclization on the α-face)* and especially **15** with the allylsilyl group tethered at C-3' (*cyclization on the β-face* same as **11**) gave only *cis*-cyclization products.

These observations lead us to conclude that *the steric hindrance at the radical-reaction site may have a less important role to play at the transition state than the steric repulsion posed on the tethered radical acceptor olefin in determining the stereochemical-outcome of the intramolecular free-radical cyclization* in **11** and **15**. (iii) It is noteworthy that the reaction of **15** with tri-n-butyltin hydride gave none of the bicyclic compound as in compounds **12**, **20**, and **24**, although the ratio of 2'-reduced product to **16** could be varied as a result of change of concentration of tri-n-butyltin hydride. This suggest that the first radical cyclization is slower than the second in the tandem radical cyclization process leading to **15**. (iv) The diastereoselectivity in the tandem radical cyclization of **15** was impressive: four chiral carbons were formed in a full stereocontrolled manner in one single chemical step, but the mechanistic reason for diastereospecificity is not clear to us. Ueda et al. have demonstrated that the 6-position of pyrimidine base moiety of nucleosides is radiophilic and susceptible to intramolecular free-radical addition.[38-41] In Ueda's system, the 5'-carbon radical added diastereospecifically to the 6-position of the uracil[38,41] or 5-halo-uracil moiety[39] in 2',3'-*O*-isopropylidene urdine derivatives, to give compound **31**. It is noteworthy that the diasterofacial selectivity of the 5'-carbon radical addition to 6-position of the pyrimidine base in Ueda's system[38,39,41] is just reverse of the result in our system, although the hydrogen abstraction of the radical intermediate at the C-5 center gave identical diastereofacial selectivity.[39] We speculate that the coordination of tin hydride to the base moiety may be responsible for the above high diastereofacial selectivity observed at the C-5 of the pyrimidine base.



31a: R = OH, R' = H
31b: R = H, R' = H
31c: R = H, R' = Cl
31d: R = H, R' = Br

*Assignment of configuration of C-3' in compounds **14a**, **14b**, **22**, and C-2' in **26*** : The configuration of C-3' in compounds **14a**, **14b**, **22**, and C-2' in **26** has been elucidated by 1D differential nOe experiments at 500 MHz by ^{1}H-NMR in D_2O solution at 293K. The result of these nOe experiments have been summarized in Table 5. In compound **14a**, H3' has a strong nOe with H2' (5.8%) and H4' (8%), but none with H6. Additionally, we also observed nOe between H1' and H2' (~6%). These suggest that all H1', H2', H3' and H4' are *cis* with respect to each other and remote from H6. This means that the C-2' and C-3' substituents in the pentofuranose moiety in **14a** are in the *lyxo* configuration. In contrast, compound **14b** shows nOe between H3' and H6 (6.2%) and H1' and H2' (~9%). These specific nOe contacts have led us to assign the C-2' and C-3' substituents in the *arabino* configuration in the pentofuranose moiety in **14a**. The *ribo*

Table 4: Dihedral angles (Φ)[1,2] of **17**[3] and **18**[3] from $^3J_{HH}$ couplings obtained at 500 MHz in D_2O at 293K using Karplus-Altona equation.

Compound #	Coupled Protons	1',2'	2',3'	3',4'	4',5'	4',5"	2',8'	2',8"	7,8'	7,8"	7,9'	7,9"	6,7	5,6	5,Me[5]
17	J-couplings [$^3J_{HH}$][1]	3.7	7.4	7.4	5.3	3.2	11.4	4.1	12.5	-	5.4	5.4	10.6	3.3	7.3
	Dihedral angle [ϕ][2]	48°*	-33°*	6°*	#	#	-162°	-54.1°	180°	-	-	-	164.2°	53.7°	–
	MM2 calculations [ϕ][4]	45°	-29°	7°	-58°	-160°	-175°	-57°	-179°	63°	-	-	-177°	51°	–
	AMBER calculations [ϕ][5]	45°	-31°	8°	-54°	-173°	-176°	-55°	-176°	63°	-	-	-178°	50°	–
18	J-couplings [$^3J_{HH}$][1]	1.7	5.0	9.6	5.3	9.7	12.7	4.5	12.7	3.5	5.5	3.8	11.1	3.6	7.4
	Dihedral angle [ϕ][2]	62.2°	-49.8°	-173.4°	-58°	161.4°	180°	-51.6°	180°	58.0°	-	-	174°	51.8°	–
	MM2 calculations [ϕ][4]	62°	-50°	-173°	-58°	-160°	175°	-53°	178°	61°	-	-	174°	52°	–
	AMBER calculations [ϕ][5]	56°	-52°	173°	-54°	-173°	176°	-63°	180°	60°	-	-	-175°	48°	–

1 $^3J_{HH}$ are given at 293K. They were also measured at 283K, 313K and 333K and showed virtually no change in coupling constants

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

3 The chemical shifts of **17** and **18** are as follows at 293K: **17** [δ (ppm)]: 5.63 (H-1'), 2.31 (H-2'), 4.72 (H-3'), 4.14 (H-4'), 3.55 (H-5'), 3.40 (H-5"), 1.24 (H-Me[5]), 2.95 (H-5), 3.74 (H-6), 1.75 (H-7), 1.80 (H-8'), 1.80 (H-8"), 3.60 (H-9'), (H-9"), (MeO), 6.82-7.42 (arom.); **18** [δ (ppm)]: 5.42 (H-1'), 2.19 (H-2'), 3.76 (H-3'), 3.72 (H-4'), 3.88 (H-5'), 3.21 (H-5"), 1.15 (H-Me[5]), 2.84 (H-5), 3.66 (H-6), 1.81 (H-7), 1.46 (H-8'), 1.87 (H-8"), 3.51 (H-9'), 3.61 (H-9"). These chemical shifts were also measured at 283K, 313K and 333K and virtually showed no change. 4 MM2 calculations were performed with dielectric constant of 4. 5 AMBER calculations were performed with distance dependent dielectric constant of 4 gave identical results. * Torsion for predominant South conformer (93%S, from PSEUROT). # At 293K, γ^+ = 54%, γ = 35%, γ^- = 11% which have been calculated on the basis of Ref. 47.

configuration of C-2' and C-3' in **22** is clearly evident from the specific nOe contacts between H6 and H3' (~4%), H2' and H3' (~7%). Substantially stronger nOe contact between H6 and H3' (~4%) and a much weaker nOe between H6 and H2' (~1.2%) result from steric proximity of H3' and H6 owing to the facts that the pentose sugar in **22** is locked in 3'-*endo*, 2'-*exo* puckered mode (*vide infra*) and the glycosidic bond in an *anti* orientation. The *ribo* configuration of C-2' and C-3' in **26** is also clear from the specific nOe contacts between H6 and H2' (9.4%), H2' and H3' (~8%). The reason we see a stronger nOe contact between H6 and H2' (9.4%) and a much weaker nOe between H6 and H3' (~1.1%) is again a result of closer steric proximity of H2' and H6 owing to the facts that the pentose sugar in **26** is locked in 2'-*endo*, 3'-*exo* puckered mode (*vide infra*) and the glycosidic bond in an *anti* orientation. The configurations of all four new or altered chiral centers (C-2', C-5, C-6 & C-7) in compound **17** have been also elucidated by 1D differential nOe experiments. The nOes between H1' and H2' (~3.5%), H2' and H3' (~4%), H3' and H4' (4.8%) suggest the *lyxo* configuration of C-2' and C-3' centers. nOe between H1' and H7 (0.6%), H2' and H7 (2.7%) confirms the S configuration at C-7 center which has been also corroborated on the basis of $^3J_{H6,H7}$ = 10.6 Hz (*trans* coupling corresponds to dihedral angle of 164°, see Table 4 and *vide infra*). The nOes between H6 and H5 (~4%) and H6 and H9'/9" (~1.8%) clearly show that they are all *cis* with respect to each other suggesting an S configuration for C-6 and an R configuration for C-5. This has been also corroborated on the basis of $^3J_{H5,H6}$ = 3.3 Hz (*cis* coupling corresponds to dihedral angle of 54° , see Table 4 and *vide infra*).

Conformation of the furan rings in ***14a, 14b, 17, 22, and 26*** . The conformation of the furan rings in **14a**, **14b**, **17**, **22**, and **26** is described using the pseudorotational concept.[45] 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 **14a**, **14b**, **17**, **22**, and **26** have been calculated from the coupling constants measured at 293K, 313K and 333K, using the program PSEUROT[46] (Table 3). Compounds **14a** (*lyxo*), **17** (*lyxo*) and **26** (*ribo*) have been found to be in an S-type conformation[50] (86, 93 and 100 % respectively at 293K), compounds **14b** (*arabino*) and **22** (*ribo*) were found to be however in an N-type conformation[50] (80 and 100%).

Conformation across C4'-C5' (γ). The population of the γ^+, γ^- and γ^t rotamers were calculated using the Hasnoot-Altona formalism[47] (Table 3).

Comparative structural studies of 17 & 18. The dihedral angles of **17** and **18** have been calculated from the $^3J_{HH}$ coupling constants (Table 4) using the Karplus-Altona equation[48] (1) which includes a correction term to take the influence of the electronegativities of various substituents on $^3J_{HH}$ into account:

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

A perusal of the $^3J_{3',4'}$, $^3J_{4',5'}$, $^3J_{4',5''}$ for **17** and **18** show that the calculated dihedral angles derived from these coupling constants using equation (1) are consistant with the fact that H4'-H5" and H3'-H4' are *trans* diaxial in **18**, while H3'-H4' in **17** is *cis* as expected for a β-D-*lyxo*pentofuranose derivative. Clearly, the *trans* diaxial nature of H4'-H5" and H3'-H4' in **18** is a major piece of structural observation from ^{1}H-NMR data (Table 4) that support the isomerization of the furanose ring in **17** to the pyranose ring in **18** during the acidic deprotection of the 5'-*O*-MMTr group. On the basis of dihedral angles derived from $^3J_{HH}$ coupling constants and molecular model building, it can be seen that the pyranose ring is in a chair conformation (Figs. 1C & 1D) in which 3',4'-hydroxyl groups are in 1,2-diequatorial orientation. Note that the δ(5'-5") is 0.15 ppm for **17** while it is 0.67 ppm for **18**. Most probably the larger δ(5'-5") in **18** is due to preferential

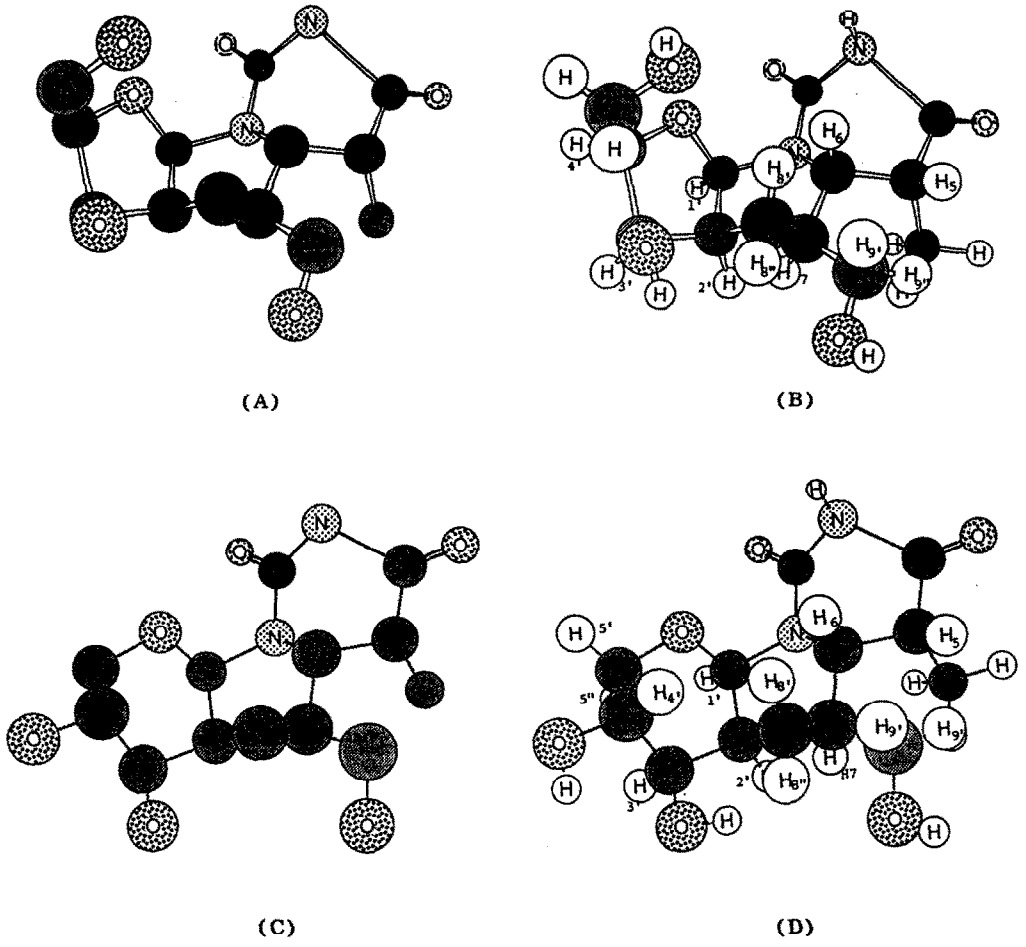


Fig. 1: Molecular models of 1-[5'-*O*-(MMTr)-2'-deoxy-2'-*C*(S),6-*C*(S)-((2-(S)-hydroxymethyl)ethylene)-β-D-*lyxo*furanosyl]-5(R),6(S)-dihydrothymine (**17**) [Figs. 1A & 1B, the 5'-O-MMTr group is not shown] and 1-[2'-deoxy-2'-*C*(S),6-*C*(S)-((2-(S)-hydroxymethyl)ethylene)-β-D-*lyxo*pyranosyl]-5(R),6(S)-dihydrothymine (**18**) [Figs. 1C & 1D] based on dihedral angles calculated by Karplus-Altona algorithm from various $^{3}J_{HH}$ coupling constants shown in Table 4.

downfield shift of the equatorial H-5' over the axial H-5" protons due to combined diamagnetic anisotropy of C-C and C-O bonds inherent in the pyranose system.[49] We have subsequently used other $^3J_{HH}$ coupling constants in the tricyclic pyranoid nucleoside **18** to derive all dihedral angles using equation (1) as shown in Table 4. These data show that the central *cis*-fused piperidine ring in both **17** and **18** is in half-chair/half-boat conformation owing to the planar glycosyl nitrogen (N^1) with H2', H6, H7 and H8' in the axial position and the exocyclic CH_2OH in the equatorial position. The $^3J_{H5,H6}$ coupling constant of 3.6 Hz in the dihydrothymine ring in **18** suggests a dihedral angle of 52° or -56°. In the former, the C^5-Me is placed in the axial orientation and in the later in the equatorial orientation. At this point we resorted to the molecular mechanics study using Allinger's MM2 and Kollman's AMBER all atom force fields as supplied in Macromodel program[51] in order to estimate steric energies involved in the different conformational states. The results of our studies with **17** and **18** are shown in Table 4. Molecular mechanics studies starting with H5-H6 dihedral angles of either 52° or -56° in **18** allowed us to rule out the equatorial orientation of the C^5-Me group corresponding to dihedral angle of -56° on the basis of higher steric energy by ~20 kJ/mole. A similar study also showed that the C^5-Me group in **17** in the axial orientation is favoured over the equatorial orientation by 12 kJ/mol in MM2 ($\varepsilon = 4$) and 38 kJ/mole in AMBER ($\varepsilon = 4r$) calculations.

We have subsequently performed several NOESY experiments at different mixing times (80, 100 and 150 ms) which have enabled us to calculate different interproton distances from the intensities and volumes of the cross peaks which substantiated the pyranoid sugar in **18** beyond any doubt. A comparison of interproton distances obtained from molecular models (Figs. 1C -1D), based on $^3J_{HH}$ coupling constants (*vide supra*), with those obtained from the nOe build-up rates[52] for **18** confirmed its structure [H5-H6 = 2.4Å, H8'-H4' = 2.4Å, C^5-Me-H7 = 2.5Å, H7-H2' = 2.2Å, H1'-H5" = 2.4Å, H1'-H3' = 2.5Å, H1'-H2' = 2.6Å in the model shown in Figs 1C & 1D, corresponding distances calculated by nOe build-up rates[52] are as follows: 2.3Å, 2.2Å, 2.3Å, 2.4Å, 2.4Å, 2.4Å and 2.4Å].

EXPERIMENTAL

^{1}H-NMR spectra were recorded (in δ scale) with Jeol 90Q spectrometer at 90 MHz or at 500 MHz with a Bruker 500 AMX NMR spectrometer, using TMS (0.0 ppm) or CH_3CN (2.00 ppm) as reference. ^{13}C-NMR were recorded at 22.5 MHz using both ^{1}H-coupled and ^{1}H-decoupled or 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, dioxane, benzene, and toluene were freshly distilled from sodium benzophenone ketyl, pyridine was distilled over CaH_2, and ethanol was treated with sodium strips overnight and freshly distilled. 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 atomosphere. ^{1}H- & ^{13}C-NMR assignments of 2'/ 3'-*O*-allylsilyl chain protons and carbons are indicated by H-a (-$SiCH_2$), H-b and H-c or C-a, C-b and C-c and so on from 2'/3'-*O*- direction. And ^{1}H- & ^{13}C-NMR assignments of 2'/ 3'-*C*-branched chain protons and carbons are indicated by H-α, H-β and H-γ or C-α, C-β, and C-γ and so on from 2'/3'-*C*- direction. ^{1}H- & ^{13}C-NMR assignments of compound **16, 17, 18** are indicated by numberings of atoms in Figs **16, 17** and **18**.

1-[5'-*O*-(MMTr)-3'-deoxy-3'-phenylseleno-β-D-*arabino*furanosyl]thymine (1) and 1-[5'-*O*-(MMTr)-2'-deoxy-2'-phenylseleno-β-D-*xylo*furanosyl] thymine (2). (a) Ribothymidine[34] (2.58 g, 10 mmol) was coevaporated with dry pyridine to dryness, redissolved in dry pyridine (150 ml), 4-monomethoxytrityl chloride (4.01 g, 13 mmol) was then added to the solution. Stirring was kept at room temperature overnight. Methanesulfonyl chloride (2.33 ml, 30 mmol) was then added to the solution at 0°C.

Stirring was kept for another 7h. The reaction mixture was poured into ice-water, the solid thus formed was collected by filtration, and redissolved in solution of 1N NaOH/dioxane (1:1, v/v) (200 ml), with stirring overnight. The reaction mixture was neutralized by 0.1N HCl to pH 7 to give a white precipitate, Filtration and flash chromatography gave the pure epoxide **7** (4.24 g, 83%). ^{1}H-NMR ($CDCl_3$): 9.50 (br.s, 1H) NH; 7.51- 6.79 (m, 15H) arom., H6; 6.20 (s, 1H) H1'; 4.14 (m, 2H) H2', H3'; 3.88 (m, 1H) H4'; 3.79 (s, 3H) OCH_3; 3.42 (m, 2H) H5', H5"; 1.83 (d, $J_{5,6}$ = 1.2 Hz, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$): 110.8 (s) C5; 86.6 (s) MMTr; 81.2 (d) C1'; 76.5 (d) C4'; 62.0 (t) C5'; 55.7 (d) C2', C3'; 55.1 (q) OCH_3; 12.3 (q) 5-CH_3.(b) To a solution of diphenyldiselenide (3.41 g, 11 mmol) in dry tetrahydrofuran (50 ml) was added lithium aluminium hydride (418 mg, 11 mmol) in small portions under argon at room temperature with stirring.The mixture was subjected to reflux for 10 min to be decolored. A solution of epoxide **7** (4 g, 7.8 mmol) in dry tetrahydrofuran (20 ml) was then added and the stirring was continued at reflux until no starting material was left (ca. 2h). The reaction mixture was then poured slowly with stirring into a saturated aqueous solution of ammonium chloride (100 ml), which was extracted with ethyl acetate (3 x 50 ml). The combined extract was dried over Na_2SO_4, evaporated under vacuum to give an orange oil, which was separated on a silica gel column to give compound **1** (3.3 g, 63%) and compound **2** (1.41 g, 27%). Compound **1**: ^{1}H-NMR ($CDCl_3$): 10.59 (br.s, 1H) NH; 7.66- 6.80 (m, 20H) arom., H6; 6.07 (d, $J_{1',2'}$ = 4.9 Hz, 1H) H1'; 5.02 (br.s, 1H) OH; 4.62 (m, 1H) H2'; 3.96 (m, 1H) H4'; 3.68 (m, 1H) H3'; 3.75 (s, 3H) OCH_3; 3.46 (m, 2H) H5', H5"; 1.47 (d) 5-CH_3. ^{13}C-NMR ($CDCl_3$): 109.0 (s) C5; 86.7 (s) MMTr; 85.2 (d, J_{CH} = 171.9 Hz) C1'; 81.6 (d, J_{CH} = 150.5 Hz) C4'; 76.2 (d, J_{CH} = 152.7 Hz) C2'; 62.4 (t, J_{CH} = 143.8 Hz) C5'; 55.0 (q, J_{CH} = 143.8 Hz) OCH_3; 44.6 (d, J_{CH} = 146.0 Hz) C3'; 11.8 (q, J_{CH} = 129.2 Hz) 5-CH_3. MS (FAB$^-$): calc. for (M-H)$^-$ 669.1508, found 669.1562. Compound **2**: ^{1}H-NMR ($CDCl_3$): 9.67 (br.s, 1H) NH; 6.04 (d, $J_{1',2'}$ = 4.2 Hz, 1H) H1'; 4.28 (m, 2H) H3', H4'; 3.99 (br.s, 1H) OH; 3.86 (m, 1H) H2'; 3.75 (s, 3H) OCH_3; 3.55 (m, 2H) H5', H5"; 1.60 (d, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$): 110.4 (s) C5; 89.9 (d, J_{CH} = 169.6 Hz) C1'; 87.1 (s) MMTr; 80.2 (d, J_{CH} = 147.2 Hz) C4'; 76.1 (d, J_{CH} = 155.0 Hz) C3'; 62.2 (t, J_{CH} = 144.3 Hz) C5'; 55.0 (q, J_{CH} = 143.8 Hz) OCH_3; 50.7 (d, J_{CH} = 151.6 Hz) C2'; 12.0 (q, J_{CH} = 129.2 Hz) 5-CH_3. MS (FAB$^-$): calc. for (M-H)$^-$ 669.1508, found 669.1569.

1-[5'-*O*-(MMTr)-3'-deoxy-3'-phenylseleno-β-D-*xylo*furanosyl]thymine (3). (a) Compound **5** (2.12 g, 4 mmol) was coevaporated with dry pyridine, redissolved in dry pyridine (40 ml), cooled in an ice-salt bath. Pivaloyl chloride (647 µl, 5.2 mmol) was added in one portion. The reaction was left to proceed in the ice-salt bath for 1.5 h. Methanesulfonyl chloride (468 µl, 6 mmol) was then added, and the reaction was left to proceed at room temperature for 6h. The reaction mixture was poured slowly with stirring into ice-water, and the solid thus formed was collected by filtration, subjected to flash chromatography to give the pure compound **8** (2.63 g, 95%). ^{1}H-NMR ($CDCl_3$): 9.20 (br.s, 1H) NH; 7.47-6.85 (m, 15H) arom., H6; 6.24 (d, $J_{1',2'}$ = 6.6 Hz, 1H) H1'; 5.57 (dd, $J_{2',3'}$ = 5.6 Hz, 1H) H2', 5.35 (dd, $J_{3',4'}$ = 2.7 Hz, 1H) H3'; 4.40 (dd, 1H) H4'; 3.80 (s, 3H) OCH_3; 3.54 (dd, $J_{4',5'}$ = 2.4 Hz, $J_{5',5"}$ = 3.9 Hz, 2H) H5', H5"; 2.99 (s, 3H) Ms; 1.41 (d, 3H) 5-Me; 1.25 (s, 9H) Piv. MS (FAB$^-$): calc. for (M-H)$^-$ 691.2325, found 691.2338. (b) To a solution of diphenyldiselenide (608 mg, 1.95 mmol) in dry tetrahydrofuran/ethanol (1:1, v/v, 20 ml) was added sodium borohydride (222 mg, 5.85 mmol) in small portions under argon at room temperature with stirring. The reaction mixture was refluxed to be decolored. A solution of compound **8** (900 mg, 1.3 mmol) in dry tetrahydrofuran (5 ml) was then added and the stirring was continued at reflux overnight. The reaction mixture was poured slowly with stirring into a saturated aqueous solution of ammonium chloride (100 ml), which was extracted with ethyl acetate (3 x 50 ml). The combined extract was evaporated under vacuum to give an oily residue, which was flash chromatogaphed to give the pure compound **9** (867 mg, 88%). ^{1}H-NMR ($CDCl_3$): 8.86 (br.s, 1H) NH; 7.70-6.85 (m, 20H) arom., H6; 6.03 (d, $J_{1',2'}$ = 5.6 Hz, 1H) H1'; 5.71 (dd, $J_{2',3'}$ = 7.3 Hz, 1H) H2'; 4.55 (dt, $J_{3',4'}$ = 7.8 Hz, 1H) H4'; 3.88 (dd, 1H) H3'; 3.81 (s, 3H) OCH_3; 3.65 (m, $J_{4',5'}$ = 3.5 Hz, 2H) H5', H5"; 1.37 (d, 3H) 5-CH_3; 1.13 (s, 9H) Piv. ^{13}C-NMR ($CDCl_3$): 111.4 (s) C5; 87.7 (s) MMTr; 86.1 (d, J_{CH} = 169.6 Hz) C1'; 79.5 (d, J_{CH} = 147.2 Hz) C4'; 79.0 (d, J_{CH} = 162.3 Hz) C2'; 64.5 (t, J_{CH} = 143.8 Hz) C5'; 55.1 (q, J_{CH} = 143.8 Hz) OCH_3; 46.0 (d, J_{CH} = 148.3 Hz) C3'; 26.8 (q, J_{CH} = 128.1Hz) Piv.; 11.5 (q, J_{CH} = 129.2Hz) 5-CH_3. (c) Treatment of compound **9** (825 mg, 1.09 mmol) with a solution of 1N aqueous NaOH/dioxane (1:1, v/v, 40 ml) for 2 h, neutralized with 1N HCl, extracted with chloroform and dried over Na_2SO_4, after flash chromatography, gave compound **3** (700 mg, 96%). ^{1}H-NMR ($CDCl_3$): 10.83 (br.s, 1H) NH; 7.61-6.85 (m, 20 H) arom., H6; 5.79 (d, $J_{1',2'}$ = 3.2 Hz, 1H) H1'; 4.80 (s, 1H) OH; 4.73 (m, 1H) H4'; 4.51 (dd, $J_{2',3'}$ = 4.6 Hz, 1H) H2'; 3.80 (s, 3H) OCH_3; 3.71 (dd, $J_{3',4'}$ = 5.9 Hz, 1H) H3'; 3.51 (m, 2H) H5', H5"; 1.55 (d, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$): 110.4 (s) C5; 91.1 (d, J_{CH} = 171.8 Hz) C1'; 87.3 (s) MMTr; 80.8 (d, J_{CH} = 148.3 Hz) C4'; 80.6 (d, J_{CH} = 152.8 Hz)

C2'; 64.8 (t, J_{CH} = 142.7 Hz) C5'; 55.1 (q, J_{CH} = 143.8 Hz) OCH_3; 48.0 (d, J_{CH} = 147.2 Hz) C3'; 12.0 (q,J_{CH} = 129.2 Hz) 5-CH_3. MS (FAB$^-$): calc. for (M-H)$^-$ 669.1508, found 669.1588.

1-[5'-*O*-(MMTr)-2'-deoxy-2'-phenylseleno-β-D-*ribo*furanosyl]thymine (4). (a) Compound **5** (2.12 g, 4 mmol) was treated with bisimidazole-1-yl-thione (870 mg, 90%, 4.4 mmol) in dry toluene (40 ml) was boiled to reflux for 90 min until no starting material was consumed. The reaction mixture was cooled to room temperature, evaporated to dryness, flash chromatographed to give the pure compound **10** (1.87 g, 91%). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.71 (m, 15H) arom., H6; 6.14 (d, $J_{1',2'}$ = 5.6 Hz, 1H) H1'; 5.25 (d, 1H) H2'; 4.50 (br.s, 2H) H3', H4'; 3.77 (s, 3H) OCH_3; 2.97 (m, 2H) H5', H5"; 1.88 (d, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 173.2 (s), 159.0 (s), 118.6 (s), 90.2 (d, J_{CH} = 179.7 Hz), 89.2 (d, J_{CH} = 166.2 Hz), 87.5 (d, J_{CH} = 152.8 Hz), 86.4 (s), 75.3 (d, J_{CH} = 153.9 Hz), 63.0 (t, J_{CH} = 142.1 Hz), 55.0 (q, J_{CH} = 143.8 Hz), 13.7 (q, J_{CH} = 130.0 Hz). MS (FAB$^-$): calc. for (M-H)$^-$ 511.1869, found 511.1864. (b) To a solution of diphenyldiselenide (1.10 g, 3.52 mmol) in dry dioxane (30 ml) was added lithium aluminium hydride (133 mg, 3.52 mmol) in small portions under argon at room temperature with stirring. The mixture was boiled to reflux for 10 min to be decolored. A solution of compound **10** (1.20 g, 2.34 mmol) in dry dioxane (5 ml) was then added and the stirring was continued at reflux for 6 h. The reaction mixture was cooled to room temperature, slowly poured with stirring into a saturated aqueous solution of ammonium chloride (50 ml), which was extracted with ethyl acetate (3 x 30 ml). The combined extract was dried over Na_2SO_4, evaporated in vacuo to give an oily material, which was chromatographed on silica gel to give the pure compound **4** (1.42 g, 90%). ^{1}H-NMR ($CDCl_3$): 8.85 (br.s, 1H) NH; 7.65-6.80 (m, 20H) arom., H6; 6.53 (d, $J_{1',2'}$ = 9.5 Hz, 1H) H1'; 4.50 (m, 1H) H3'; 4.24 (m, 1H) H4'; 3.97 (dd, $J_{2',3'}$ = 5.1 Hz, 1H) H2'; 3.78 (s, 3H) OCH_3; 3.44 (m, 2H) H5', H5"; 3.29 (1H) OH; 1.22 (d, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$): 111.4 (s) C5; 88.1 (d,J_{CH} = 169.6 Hz) C1'; 87.3 (s) MMTr; 84.9 (d, J_{CH} = 150.5 Hz) C4'; 73.7 (d, J_{CH} = 153.6 Hz) C3'; 64.0 (t, J_{CH}= 142.4 Hz) C5'; 55.1 (q,J_{CH}= 143.8 Hz) OCH_3; 52.6 (d,J_{CH}= 143.8 Hz) C2'; 11.3 (q,J_{CH}= 130.3 Hz) 5-CH_3. MS (FAB$^-$): calc. for (M-H)$^-$ 669.1508, found 669.1546.

General procedure for silylation of alcohols **1-[5'-*O*-(MMTr)-(2'-*O*-allyldimethylsilyl)-3'-deoxy-3'-phenylseleno-β-D-*arabino*furanosyl]thymine (11).** Compound **1** (930 mg, 1.39 mmol) in dry pyridine (20 ml) was treated with allylchlorodimethylsilane (310 µl, 2.09 mmol) at room temperature under argon for 2 h. The reaction mixture was poured slowly with stirring into ice-water (100 ml), extracted with dichloromethane (3 x 50 ml). The combined extract was dried over Na_2SO_4, evaporated to dryness, coevaporated with dry toluene several times in vacuo at 35 °C to give the essential pure compound **11** in quantitative yield. ^{1}H-NMR ($CDCl_3$): 8.95 (br.s, 1H) NH; 7.61- 6.80 (m, 20H) arom., H6; 6.20 (d, $J_{1',2'}$ = 4.6 Hz, 1H) H1'; 5.78-6.30 (m, 1H) H-b; 4.83-4.65 (m, 2H) H-c; 4.36 (dd, $J_{2',3'}$ = 3.9 Hz, 1H) H2'; 4.12 (dd, $J_{3',4'}$ = 6.1 Hz, $J_{4',5'}$ = 4.6 Hz, 1H) H4'; 3.79 (s, 3H) OCH_3; 3.56 (dd, 1H) H3'; 3.36 (d, 2H) H5', H5"; 1.66 (d, 3H) 5-CH_3; 1.35 (d, J = 7.8 Hz, 2H) H-a; -0.13 (s, 6H) Si-CH_3. ^{13}C-NMR ($CDCl_3$): 114.2 (t, J_{CH} = 158.4 Hz) C-c; 108.8 (s) C5; 86.5 (s) MMTr; 85.0 (d,J_{CH} = 168.5 Hz) C1'; 81.8 (d, J_{CH} = 147.2 Hz) C4'; 76.9 (d, J_{CH} = 152.8 Hz) C2'; 63.5 (t, J_{CH} = 144.9 Hz) C5'; 55.1 (q, J_{CH} = 143.8 Hz) OCH_3; 47.4 (d, J_{CH} = 149.4 Hz) C3'; 24.0 (t, J_{CH} = 122.4 Hz) C-a; 12.0 (q, J_{CH} = 129.2 Hz) 5-CH_3; -2.6 (q, J_{CH} = 119.1 Hz) Si-Me_2. MS (FAB$^-$): calc. for (M-H)$^-$ 767.2, found 767.3.

1-[5'-*O*-(MMTr)-(3'-*O*-allyldimethylsilyl)-2'-deoxy-2'-phenylseleno-β-D-*xylo*furanosyl] thymine (15). The general procedure for silylation of alcohols was followed using compound **2** (900 mg, 1.34 mmol), allylchlorodimethylsilane (298 µl, 2.00 mmol) in dry pyridine (20 ml) to give the pure compound **15** in quantitative yield. ^{1}H-NMR ($CDCl_3$): 8.94 (br.s, 1H) NH; 7.75-6.80 (m, 20H) arom., H6; 6.18 (d, $J_{1',2'}$ = 2.7 Hz, 1H) H1'; 5.67-5.19 (m, 1H) H-b; 4.74 (dd, $J_{3',4'}$ = 3.7 Hz, $J_{4',5'}$ = 0.7 Hz, 1H) H4'; 4.64-4.44 (m, 2H) H-b; 4.17 (dd, $J_{2',3'}$ = 2.0 Hz, 1H) H3'; 3.78 (s, 3H) OCH_3; 3.62-3.09 (m, 3H) H5',H5", H2'; 1.65 (d, 3H) 5-Me; 1.20 (d, J = 8.1 Hz, 2H) H-a; -0.25 (s, 6H) $SiMe_2$. ^{13}C-NMR ($CDCl_3$): 114.3 (t, J_{CH} = 156.1 Hz) C-c; 89.5 (d, J_{CH} = 173.0 Hz) C1'; 86.8 (s) MMTr; 82.0 (d, J_{CH} = 146.0 Hz) C4'; 76.4 (d, J_{CH} = 155.0 Hz) C3'; 62.7 (t, J_{CH} = 143.2 Hz) C5'; 55.1 (q, J_{CH} = 143.8 Hz) OCH_3; 52.7 (d, J_{CH} = 152.7 Hz) C2'; 23.9 (t, J_{CH} = 124.1 Hz) C-a; 12.1 (q, J_{CH} = 129.2 Hz) 5-Me; -2.6 (q, J_{CH} = 119.1 Hz) $SiMe_2$. MS (FAB$^-$): calc. for (M-H)$^-$ 767.2, found 767.3.

1-[5'-*O*-(MMTr)-(2'-*O*-allyldimethylsilyl)-3'-deoxy-3'-phenylseleno-β-D-*ribo*furanosyl] thymine (19). The general procedure for silylation of alcohols was followed using compound **3** (669 mg, 1.0 mmol), allylchlorodimethylsilane (224 µl, 1.5 mmol) in dry pyridine (10 ml) to give the pure compound **19** in quantitative yield. ^{1}H-NMR ($CDCl_3$): 8.82 (br.s, 1H) NH; 7.56-6.76 (m, 20H) arom.,

H6; 5.78 (d, $J_{1',2'}$ = 4.4 Hz, 1H) H1'; 5.65-5.37 (m, 1H) H-b; 4.81-4.67 (m, 2H) H-c; 4.59-4.42 (m, 2H) H4', H2'; 3.71 (s, 3H) OCH_3; 3.67 (dd, $J_{2',3'}$ = 7.6 Hz, $J_{3',4'}$ = 1.7 Hz, 1H) H3'; 3.50 (m, 2H) H5', H5"; 1.45 (d, 2H) H-a; 1.33 (d, 3H) 5-Me, -0.04 (s, 6H) $SiMe_2$. ^{13}C-NMR ($CDCl_3$): 114.1 (t, J_{CH} = 148.8 Hz) C-c; 110.6 (s) C5; 89.1 (d, J_{CH} = 171.9 Hz) C1'; 87.5 (s) MMTr; 80.3 (d, J_{CH} = 147.8 Hz) C4'; 79.8 (d, J_{CH} = 150.5 Hz) C2'; 64.7 (t, J_{CH} = 143.8 Hz) C5'; 55.1 (q, J_{CH} = 143.8 Hz) OCH_3; 49.2 (d, J_{CH} = 148.3 Hz) C3'; 24.3 (t, J_{CH} = 125.8 Hz) C-a; 11.5 (q, J_{CH} = 130.3 Hz) 5-Me; -2.1 (q, J_{CH} = 119.1 Hz) $SiMe_2$.

1-[5'-*O*-(MMTr)-(3'-*O*-allyldimethylsilyl)-2'-deoxy-2'-phenylseleno-β-D-*ribo*furanosyl] thymine (23). The general procedure for silylation of alcohols was followed using compound **4** (960 mg, 1.43 mmol), allylchlorodimethylsilane (320 µl, 2.1 mmol) in dry pyridine (20 ml) to give the pure compound **23** in quantitative yield. ^{1}H-NMR ($CDCl_3$): 8.52 (br.s, 1H) NH; 7.56-6.76 (m, 20H) arom., H6; 6.51 (d, $J_{1',2'}$ = 9.5 Hz, 1H) H1'; 5.93-5.45 (m, 1H) H-b; 4.88-4.71 (m, 2H) H-c; 4.54 (dd, $J_{2',3'}$ = 5.1 Hz, 1H) H3'; 3.96 (dd, $J_{3',4'}$= 1.9 Hz, 1H) H4'; 3.80 (dd, 1H) H2'; 3.72 (s, 3H) OCH_3; 3.44-3.13 (m, $J_{4',5'}$ = 2.2 Hz, 2H) H5', H5"; 1.54 (d, 2H) H-a; 1.16 (d, 3H) 5-Me; 0.07 (s, 6H) $SiMe_2$. ^{13}C-NMR ($CDCl_3$): 114. 2 (t, J_{CH} = 148.6 Hz) C-c; 110.9 (s) C5; 89.6 (d, J_{CH} = 177.5 Hz) C1'; 87.3 (s) MMTr; 85.9 (d, J_{CH} = 149.5 Hz) C4'; 75.3 (d, J_{CH} = 150.5Hz) C3'; 63.5 (t, J_{CH} = 143.8 Hz) C5'; 55.1 (q, J_{CH} = 143.8 Hz) OCH_3; 51.1 (d, J_{CH} = 142.6 Hz) C2'; 24.5 (t, J_{CH} = 122.4 Hz) C-a; 11.4 (q, J_{CH} = 129.2 Hz) 5-Me; -2.0 (q, J_{CH} = 118.0 Hz) $SiMe_2$.

General procedure for radical cyclization. **1-[5'-*O*-(MMTr)-3'-deoxy-2'-*O*,3'-*C*-(1-oxa-2-silatrimethylene)-β-D-*ribo*furanosyl]thymine (20).** To a boiling solution of compound **19** (307 mg, 0.4 mmol) in dry benzene (100 ml) under argon was added slowly a solution of tri-n-butyltin hydride (166 µl, 0.6 mmol) and AIBN (20 mg) in dry benzene (10 ml) by syringe pump over 10 h.After addition of tin solution, the reaction mixture was subjected to reflux for additional 2 h. The reaction mixture was cooled to room temperature, evaporated to dryness in vacuo, partitioned between acetonitrile and hexane. The acetonitrile phase was collected, evaporated to dryness, flash chromatographed to give compound **20** (168 mg, 69%). ^{1}H-NMR ($CDCl_3$): 8.96 (br.s, 1H) NH; 7.72-6.83 (m, 15H) arom., H6; 5.79 (d, $J_{1',2'}$ = 1.4 Hz, 1H) H1'; 4.46 (dd, $J_{2',3'}$ = 5.8 Hz, 1H) H2'; 4.08 (m, 1H) H4'; 3.79 (s, 3H) OCH_3; 3.66-3.08 (m, 2H) H5', H5"; 2.37 (m, 1H) H3'; 1.52 (d, 3H) 5-Me; 1.33 (m, 4H) H-b, H-c; 0.77 (m, 2H) H-a; 0.20 (s, 3H), 0.19 (s, 3H) $SiMe_2$. ^{13}C-NMR ($CDCl_3$): 109.8 (s) C5; 92.4 (d, J_{CH} 173.0 = Hz) C1'; 86.5 (s) MMTr; 84.9 (d, J_{CH} = 147.9 Hz) C4'; 78.0 (d, J_{CH} = 146.0 Hz) C2'; 62.2 (t, J_{CH} = 142.1 Hz) C5'; 55.1 (q, J_{CH} = 143.8 Hz) OCH_3; 43.4 (d, J_{CH} = 133.7 Hz) C3'; 26.7 (t, J_{CH} = 127.5 Hz) C-c; 20.3 (t,J_{CH} = 127.5 Hz) C-b; 17.2 (t, J_{CH} = 115.1 Hz) C-a; 12.0 (q, J_{CH} = 129.2 Hz) 5-Me; -0.7 (q, J_{CH} = 119.1 Hz), -2.2 (q, J_{CH} = 119.1 Hz) $SiMe_2$. MS (FAB$^-$): calc. for (M-H)$^-$ 611.2578, found 611.2554.

1-[5'-*O*-(MMTr)-2'-deoxy-2'-*C*,3'-*O*-(1-oxa-2-silatrimethylene)-β-D-*ribo*furanosyl] thymine (24). The general procedure for radical cyclization was followed using compound **23** (307 mg, 0.4 mmol) in dry benzene (100 ml), tri-n-butyltin hydride (166 µl, 0.6 mmol) and AIBN (20 mg) in dry benzene (10 ml) over 10 h to give compound **24** (154 mg, 63%). ^{1}H-NMR ($CDCl_3$): 8.69 (br.s, 1H) NH; 7.51-6.85 (m, 15H) arom., H6; 6.01 (d, $J_{1',2'}$ = 8.1 Hz, 1H) H1'; 4.57 (dd, $J_{2',3'}$ = 6.8 Hz, 1H) H3'; 4.04 (dd, $J_{3',4'}$ = 3.4 Hz, $J_{4',5'}$ = 2.7 Hz, 1H) H4'; 3.80 (s, 3H) OCH_3; 3.37 (m, 2H) H5', H5"; 2.27 (m, 1H) H2'; 1.70 (m, 4H) H-b, H-c; 1.60 (d, 3H) 5-Me; 0.18, 0.09 (ds, 6H) $SiMe_2$. ^{13}C-NMR ($CDCl_3$): 111.3 (s) C5; 91.7 (d, J_{CH} = 164.0 Hz) C1'; 88.8 (s) MMTr; 85.7 (d, J_{CH} = 147.1 Hz) C4'; 73.1 (d, J_{CH} = 151.7 Hz) C3'; 63.2 (t, J_{CH} = 142.7 Hz) C5'; 55.1 (q, J_{CH} = 143.8 Hz) OCH_3; 51.7 (d, J_{CH} = 131.4 Hz) C2'; 26.0 (t, J_{CH} = 127.5 Hz) C-c; 20.7 (t, J_{CH} = 125.8 Hz) C-b; 16.6 (t, J_{CH} = 118.5 Hz) C-a; 12.0 (q, J_{CH} = 129.3 Hz) 5-Me; -0.9 (q, J_{CH} = 119.0 Hz) , -2.2 (q, J_{CH} = 119.0 Hz) $SiMe_2$. MS (FAB$^-$): calc. for (M-H)$^-$ 611.2578, found 611.2560.

Compound **16** The general procedure for radical cyclization was followed using compound **15** (307 mg, 0.4 mmol) in dry benzene (100 ml), tri-n-butyltin hydride (166 µl, 0.6 mmol) and AIBN (20 mg) in dry benzene (10 ml) over 14 h to give compound **16** (151 mg, 62%). ^{1}H-NMR ($CDCl_3$): 7.87 (br.s, 1H) NH; 7.51-6.82 8 (m, 14H) arom.; 6.25 (d, $J_{1',2'}$ = 9.5 Hz, 1H) H1'; 4.43 (dd, $J_{2',3'}$ = 4.9 Hz, $J_{3',4'}$ = 2.4 Hz, 1H) H3'; 3.95 (dd, $J_{5,6}$ = 5.9 Hz, $J_{6,7}$ = 10.5 Hz, 1H) H6; 3.83 (dd, 1H) H4'; 3.79 (s, 3H) OCH_3; 3.55 (m, 2H) H5'; H5"; 2.99 (dt, $J_{5\text{-Me-}5}$ = 7.6 Hz, 1H) H5; 2.68 (m, 1H) H2'; 1.76 (m, 1H) H-8; 1.32 (d, 3H) 5-Me; 1.27 (m, 1H) H-7; 0.89 (m, 2H) H-9; 0.30, 0.07 (ds, 6H) $SiMe_2$. ^{13}C-NMR ($CDCl_3$): 86.2 (s) MMTr; 84.4 (d, J_{CH} = 167.4 Hz) C1'; 81.5 (d,J_{CH} = 144.9 Hz) C-4'; 73.7 (d, J_{CH} = 153.9 Hz) C3'; 60.9 (t, J_{CH} = 145.5 Hz) C5'; 55.1 (q, J_{CH} = 143.8 Hz) OCH_3; 52.7 (d, J_{CH} = 147.1 Hz) C-2'; 41.8

(d,J_{CH} = 124.7 Hz) C-5; 39.4 (d, J_{CH} = 123.6 Hz) C-6; 30.6 (d, J_{CH} = 141.5 Hz) C-7; 28.0 (t, J_{CH} = 126.9 Hz) C-8; 22.6 (t, J_{CH} = 121.9 Hz) C-9; 12.2 (q, J_{CH} = 129.2 Hz) 5-Me; 1.22 (q, J_{CH} = 119.3 Hz), 0.36 (q, J_{CH} = 119.1 Hz) $SiMe_2$. MS (FAB^-): calc. for $(M-H)^-$ 611.2578, found 611.2578.

1-[5'-*O*-(MMTr)-3'-deoxy-2'-*O*,3'-*C*-(1-oxa-2-silatrimethylene)-β-D-*lyxo*furanosyl] thymine (12a) & 1-[5'-*O*-(MMTr)-3'-deoxy-2'-*O*,3'-*C*-(1-oxa-2-silatrimethylene)-β-D-*arabino*furanosyl]thymine (12b) The general procedure for radical cyclization was followed using compound **11** (307 mg, 0.4 mmol) in dry benzene (100 ml), tri-n-butyltin hydride (166 μl, 0.6 mmol) and AIBN (20 mg) in dry benzene (10 ml) over 14 h to give compound **12** (86 mg, 35%) as a mixture of **12a** and **12b** (10:1). MS (FAB^-): calc. for $(M-H)^-$ 611.2578, found 611.2548.

General procedure for oxidative cleavage of Si-C bond of radical cyclization products by Tamao oxidation

1-[5'-*O*-(MMTr)-3'-deoxy-3'-*C*-(ω-hydroxypropyl)-β-D-*ribo*furanosyl]thymine (21). *Method A* To a solution of compound **20** (140 mg, 0.23 mmol) in THF/MeOH (1:1, 3 ml) was added potassium fluoride (26 mg, 0.45 mmol), potassium bicarbonate (45 mg, 0.45 mmol), and 30% hydrogen peroxide (230 μl, 2.3 mmol) at room temperature. The reaction mixture was stirred at room temperature overnight, and poured into ice-water (50 ml), extracted with chloroform (3 x 20 ml). The combined extract was dried over Na_2SO_4, evaporated to dryness in vacuo. The residue was subjected to flash chromatography to give compound **21** (107 mg, 81%). *Method B* (one-pot method). The general procedure for radical cyclization was followed using compound **19** (360 mg, 0.469 mmol) in dry benzene (100 ml), tri-n-butyltin hydride (195 μl, 0.70 mmol) and AIBN (20 mg) in dry benzene (10 ml) over 10 h. The reaction mixture was evaporated to dryness. To a solution of the crude product derived from radical cyclization in THF/MeOH (1:1, 6 ml) at 0°C was added potassium fluoride (116 mg, 2 mmol), potassium bicarbonate (100 mg, 1 mmol) and 30% hydrogen peroxide (510 μl, 5 mmol). The reaction mixture was stirred at room temperature overnight, and poured into ice-water (50 ml), extracted with chloroform (3 x 20 ml). The combined extract was dried over Na_2SO_4, evaporated to dryness in vacuo. The residue was separated on a silica gel column with ethyl acetate as eluent to give compound **21** (153 mg, 57%). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.92 (q, 1H) H6; 7.46-6.85 (m, 14H) arom.; 5.70 (s, 1H) H1'; 4.28 (d, $J_{2',3'}$ = 4.6 Hz, 1H) H2'; 4.12 (dt, $J_{3',4'}$ = 10.0 Hz, 1H) H4'; 3.80 (s, 3H) OCH_3; 3.60 (t, J = 5.86 Hz, 2H) H-γ; 3.36 (m, $J_{4',5'}$ = 3.2 Hz, 2H) H5', H5"; 2.29 (m, 1H) H2'; 1.57 (m, 4H) H-β, H-α; 1.37 (d, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$): 110.2 (s) C5; 93.0 (d, J_{CH} = 175.2 Hz) C1'; 86.5 (s) MMTr; 84.4 (d, J_{CH} = 150.5 Hz) C4'; 76.4 (d, J_{CH} = 153.9 Hz) C2'; 62.3 (t, J_{CH} = 140.4 Hz) C5'; 61.7 (t, J_{CH} = 142.1 Hz) C-γ; 55.0 (q, J_{CH} = 143.8 Hz) OCH_3; 40.8 (d, J_{CH} = 125.8 Hz) C3'; 30.5 (t, J_{CH} = 128.1 Hz), 19.8 (t, J_{CH} =125.8 Hz) C-β, C-α; 12.0 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB^-): calc. for $(M-H)^-$ 571.2444, found 571.2416.

1-[5'-*O*-(MMTr)-2'-deoxy-2'-*C*-(ω-hydroxypropyl)-β-D-*ribo*furanosyl]thymine (25). *Method A* . The general procedure for oxidative cleavage of Si-C bond of radical cyclization products by Tamao oxidation was followed using compound **24** (137 mg, 0.22 mmol), potassium fluoride (26 mg, 0.45 mmol), potassium bicarbonate (45 mg, 0.45 mmol), and 30% hydrogen peroxide (224 μl, 2.2 mmol) in THF/MeOH (1:1, 3 ml) at room temperature overnight to give compound **25** (112 mg, 89%). *Method B* (one-pot method). The general procedure for radical cyclization was followed using compound **23** (360 mg, 0.469 mmol) in dry benzene (100 ml), tri-n-butyltin hydride (195 μl, 0.70 mmol) and AIBN (20 mg) in dry benzene (10 ml) over 10h. The reaction mixture was evaporated to dryness. To a solution of the crude product derived from radical cyclization in THF/MeOH 1:1, 6 ml) at 0°C was added potassium fluoride (116 mg, 2 mmol), potassium bicarbonate (100 mg, 1 mmol) and 30% hydrogen peroxide (510 μl, 5 mmol). The reaction mixture was stirred at room temperature overnight, and poured into ice-water (50 ml), extracted with chloroform (3 x 20 ml). The combined extract was dried over Na_2SO_4, evaporated to dryness in vacuo. The residue was separated on silica gel column with ethyl acetate as eluent to give compound **25** (156 mg, 58%). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.61 (q, 1H) H6; 7.43-6.85 (m, 14H) arom.; 6.10 (d, $J_{1',2'}$ = 9.3 Hz, 1H) H1'; 4.41 (d, $J_{2',3'}$ = 4.9 Hz, 1H) H3'; 4.13 (t, $J_{4',5'}$ = 1.2 Hz, 1H) H4'; 3.80 (s, 3H) OCH_3; 3.66 (t, J = 5.1 Hz, 2H) H-γ; 3.42 (t, 2H) H5', H5"; 2.34 (m, 1H) H2'; 1.63 (m, 2H) H-β, H-α; 1.38 (d, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$): 111.4 (s) C5; 87.7 (d, J_{CH} = 164.0 Hz) C1'; 87.1 (s) MMTr; 85.8 (d, J_{CH} = 149.4 Hz) C4'; 72.8 (d, J_{CH} = 151.6 Hz) C3'; 64.2 (t, J_{CH} = 141.0 Hz) C5'; 61.7 (t, J_{CH} = 143.8 Hz) C-γ; 55.0 (q,J_{CH} = 143.8 Hz) OCH_3; 49.6 (d, J_{CH} = 125.8 Hz) C2';

30.0 (t, J_{CH} = 127.5 Hz), 19.7 (t, J_{CH} = 130.3 Hz) C-β, C-α; 11.4 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB⁻): calc. for (M-H)⁻ 571.2444, found 571.2451.

1-[5'-*O*-(MMTr)-2'-deoxy-2'-*C*(S),6-*C*(S)-((2-(S)-hydroxymethyl)ethylene)-β-D-*lyxo* furanosyl]-5(R),6(S)-dihydrothymine (17): *Method A* . The general procedure for oxidative cleavage of Si-C bond of radical cyclization products by Tamao oxidation was followed using compound **16** (118 mg, 0.19 mmol), potassium fluoride (22 mg, 0.38 mmol), potassium bicarbonate (38 mg, 0.38 mmol), and 30% hydrogen peroxide (200 µl, 1.9 mmol) in THF/MeOH (1:1, 3 ml) at room temperature overnight to give compound **17** (76 mg, 70%). *Method B* (one-pot method). The general procedure for radical cyclization was followed using compound **15** (307 mg, 0.40 mmol) in dry benzene (100 ml), tri-n-butyltin hydride (165 µl, 0.60 mmol) and AIBN (20 mg) in dry benzene (10 ml) over 14h. The reaction mixture was evaporated to dryness. To a solution of the crude product obtained from radical cyclization in THF/MeOH (1:1, 6 ml) at 0°C was added potassium fluoride (93 mg, 1.6 mmol), potassium bicarbonate (80 mg, 0.8 mmol) and 30% hydrogen peroxide (408 µl, 4 mmol). The reaction mixture was stirred at room temperature overnight, and poured into ice-water (50 ml), extracted with chloroform (3 x 20 ml). The combined extract was dried over Na_2SO_4, evaporated to dryness in vacuo. The residue was separated on silica gel column with ethyl acetate as eluent to give compound **17** (103 mg, 45%). For ^{1}H-NMR, see Table 4; ^{13}C-NMR ($CDCl_3$): 87.8 (s) MMTr; 80.3 (d, J_{CH} = 166.2 Hz) C1'; 76.0 (d, J_{CH} = 146.0 Hz) C4'; 73.5 (d, J_{CH} = 149.4 Hz) C3'; 63.4 (t, J_{CH} = 139.3 Hz) C5'; 62.9 (t, J_{CH} = 146.0 Hz) C-9; 55.1 (q, J_{CH} = 143.8 Hz) OCH_3; 52.6 (d, J_{CH} = 143.8 Hz) C2'; 39.8 (d, J_{CH} = 141.5 Hz) C5; 37.2 (d, J_{CH} = 138.2 Hz) C6; 36.3 (d, J_{CH} = 128.1 Hz) C-7; 21.4 (t, J_{CH} = 135.4 Hz) C-8; 11.0 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB⁻): calc. for (M-H)⁻ 571.2444, found 571.2468.

1-[5'-*O*-(MMTr)-3'-deoxy-3'-*C*-(ω-hydroxypropyl)-β-D-*lyxo*furanosyl]thymine (13a) & 1-[5'-*O*-(MMTr)-3'-deoxy-3'-*C*-(ω-hydroxypropyl)-β-D-*arabino*furanosyl]thymine (13b). *Method B* (one-pot method). The general procedure for radical cyclization was followed using compound **11** (307 mg, 0.40 mmol) in dry benzene (100 ml), tri-n-butyltin hydride (165 µl, 0.60 mmol) and AIBN (20 mg) in dry benzene (10 ml) over 14h. The reaction mixture was evaporated to dryness. To a solution of the crude product obtained from radical cyclization in THF/MeOH (1:1, 6 ml) at 0°C was added potassium fluoride (93 mg, 1.6 mmol), potassium bicarbonate (80 mg, 0.8 mmol) and 30% hydrogen peroxide (408 µl, 4 mmol). The reaction mixture was stirred at room temperature overnight, and poured into ice-water (50 ml), extracted with chloroform (3 x 20 ml). The combined extract was dried over Na_2SO_4, evaporated to dryness in vacuo. The residue was separated on silica gel column with ethyl acetate as eluent to give an inseparable mixture (1:1) of compounds **13a, 13b**.(104 mg, 45%). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.62-6.83 (m, 15H), 5.97 (m, 1H), 4.52 (m, 2H), 3.75 (s, 1.5H), 3.71 (s, 1.5H), 3.46 (m, 4H), 2.44 (m, 1H), 1.60-1.36 (m, 7H). MS (FAB⁻): calc. for (M-H)⁻ 571.2444, found 571.2478.

General procedure for acetylation of diols. **1-[5'-*O*-(MMTr)-2'-*O*-acetyl-3'-deoxy-3'-*C*-(ω-acetoxypropyl)-β-D-*ribo*furanosyl]thymine (27).** Treatment of compound **21** (50 mg, 0.087 mmol) in dry pyridine (2 ml) with acetic anhydride (1 ml) and DMAP (3 mg) at room temperature overnight, after chromatography, to give the compound **27** (55 mg, 96%). ^{1}H-NMR ($CDCl_3$): 8.85 (br.s, 1H) NH; 7.66 (q, 1H) H6; 7.49-6.85 (m, 14H) arom.; 5.87 (d, $J_{1',2'}$ = 1.7 Hz, 1H) H1'; 5.55 (dd, $J_{2',3'}$ = 5.9 Hz, 1H) H2'; 4.03-3.97 (m, 3H) H4', H-γ; 3.80 (s, 3H) OCH_3; 3.74-3.14 (m, 2H) H5', H5"; 2.56 (m, 1H) H3'; 2.15 (s, 3H), 1.99 (s, 3H) 2 x Ac; 1.49 (d, 3H) 5-Me; 1.34 (m, 4H) H-β, H-α. ^{13}C-NMR ($CDCl_3$): 110.8 (s) C5; 89.6 (d, J_{CH} = 171.9 Hz) C1'; 86.8 (s) MMTr; 83.8 (d, J_{CH} = 148.3 Hz) C4'; 77.2 (d, J_{CH} = 159.5 Hz) C2'; 63.8 (t, J_{CH} = 145.5 Hz) C-γ; 62.0 (t, J_{CH} = 142.7 Hz) C5'; 55.1 (q, J_{CH} = 143.8 Hz) OCH_3; 40.5 (d, J_{CH} = 130.3 Hz) C3'; 26.6 (t, J_{CH} = 127.5 Hz), 21.3 (t, J_{CH} = 127.5 Hz) C-β, C-α; 20.7 (q, J_{CH} = 129.2 Hz) Ac; 20.6 (q, J_{CH} = 129.2 Hz) Ac; 11.9 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB⁻): calc. for (M-H)⁻ 655.2656, found 655.2621.

1-[5'-*O*-(MMTr)-3'-*O*-acetyl-2'-deoxy-2'-*C*-(ω-acetoxypropyl)-β-D-*ribo*furanosyl] thymine (29). Treatment of compound **25** (60 mg, 0.105 mmol) in dry pyridine (3 ml) with acetic anhydride (1.5 ml) and DMAP (5 mg) at room temperature overnight, after chromatography, to give the compound **29** (67 mg, 97%). ^{1}H-NMR ($CDCl_3$): 9.56 (br.s, 1H) NH; 7.57 (q, 1H) H6; 7.42-6.85 (m, 14H) arom.; 6.19 (d, $J_{1',2'}$ = 9.5 Hz, 1H) H1'; 5.47 (d, $J_{2',3'}$ = 5.6 Hz, 1H) H3'; 4.07 (m, 3H) H4'; H-γ; 3.80 (s, 3H) OCH_3; 3.49 (br.s, 2H) H5', H5"; 2.64 (m, 1H) H2'; 2.12(s, 3H), 2.04 (s, 3H) 2 x Ac; 1.65

(m, 4H) H-β, H-α; 1.38 (d, 3H) 5-Me. ^{13}C-NMR ($CDCl_3$): 111.8 (s) C5; 87.4 (d, J_{CH} = 175.2 Hz) C1'; 87.3 (s) MMTr; 83.9 (d, J_{CH} = 150.5 Hz) C4'; 75.2 (d, J_{CH} = 164.0 Hz) C3'; 63.9 (t, J_{CH} = 143.2 Hz) C-γ; 63.6 (t, J_{CH} = 147.7 Hz) C5'; 55.1 (q, J_{CH} = 143.8 Hz) OCH_3; 46.8 (d, J_{CH} = 127.0 Hz) C2'; 26.5 (t, J_{CH} = 128.6 Hz), 20.2 (t, J_{CH} = 128.6 Hz) C-β, C-α; 20.7 (q, J_{CH} = 131.4 Hz) Ac; 11.5 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB^-): calc. for $(M-H)^-$ 655.2656, found 655.2614.

General procedure for deprotection of MMTr group. **1-[3'-deoxy-3'-*C*-(ω-hydroxypropyl)-β-D-*ribo*furanosyl]thymine (22)**: Treatment of compound **21**(38 mg, 0.066 mmol) with 80% aq. acetic acid (3 ml) at room temperature overnight, after chromatography, to give compound **22** (17 mg, 85%). For ^{1}H-NMR, see Tables 1 and 2; ^{13}C-NMR ($CDCl_3$ + CD_3OD): 136.4 (d, J_{CH} = 184.2 Hz) C6; 108.7 (s) C5; 91.5 (d, J_{CH} = 174.1 Hz) C1'; 85.0 (d, J_{CH} = 146.0 Hz) C4'; 75.9 (d, J_{CH} = 153.9 Hz) C2'; 61.1 (t, J_{CH} = 141.0 Hz) C5'; 59.3 (t, J_{CH} = 141.0 Hz) C-γ; 39.3 (d, J_{CH} = 125.8 Hz) C3'; 29.5 (t, J_{CH} = 125.8 Hz), 19.6 (t, J_{CH} = 128.1 Hz) C-β, C-α; 11.2 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB^-): calc. for $(M-H)^-$ 299.1243, found 299.1229.

1-[2'-deoxy-2'-*C*-(ω-hydroxypropyl)-β-D-*ribo*furanosyl]thymine (26): Treatment of compound **25** (40 mg, 0.070 mmol) with 80% acetic acid (3 ml) at room temperature overnight, after chromatography, to give compound **26** (18 mg, 80%). For ^{1}H-NMR, see Tables 1 and 2; ^{13}C-NMR ($CDCl_3$ + CD_3OD): 136.1 (d, J_{CH} = 183.1 Hz) C6; 110.1 (s) C5; 87.6 (d, J_{CH} = 168.5 Hz) C1'; 86.7 (d, J_{CH} = 149.4 Hz) C4'; 71.6 (d, J_{CH} = 149.4 Hz) C3'; 61.6 (t, J_{CH} = 142.1 Hz) C5'; 60.9 (t, J_{CH} = 140.1 Hz) C-γ; 47.9 (d, J_{CH} = 129.2 Hz) C2'; 29.3 (t, J_{CH} = 127.5 Hz), 19.4 (t, J_{CH} = 129.7 Hz) C-β, C-α; 10.8 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB^-): calc. for $(M-H)^-$ 299.1243, found 299.1249.

1-[3'-deoxy-3'-*C*-(ω-hydroxypropyl)-β-D-*lyxo*furanosyl]thymine (14a) & 1-[3'-deoxy-3'-*C*-(ω-hydroxypropyl)-β-D-*arabino*furanosyl]thymine (14b): Treatment of compound **13** (50 mg, 0.087 mmol) with 80% aq. acetic acid (3 ml) at room temperature overnight, after chromatography, to give compound **14a** (10 mg, 38.3%, Rf 0.21 in 10% MeOH/CH_2Cl_2), **14b** (10 mg, 38.3%, R_f 0.10 in 10% MeOH/CH_2Cl_2). Compound **14a:** For ^{1}H-NMR, see Tables 1 and 2; ^{13}C-NMR ($CDCl_3$ + CD_3OD): 137.5 (d, J_{CH} = 184.2 Hz) C6; 107.3 (s) C5; 87.0 (d, J_{CH} = 167.4 Hz) C1'; 80.4 (d, J_{CH} = 148.3 Hz) C4'; 68.9 (d, J_{CH} = 156.1 Hz) C2'; 60.7 (t, J_{CH} = 139.9 Hz) C5'; 60.0 (t, J_{CH} = 143.8 Hz) C-γ; 43.9 (d, J_{CH} = 138.2 Hz) C3'; 29.8 (t, J_{CH} = 126.4 Hz), 19.4 (t, J_{CH} = 126.4 Hz) C-β, C-α; 10.7 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB^-): calc. for $(M-H)^-$ 299.1243, found 299.1241. Compound **14b:** For ^{1}H-NMR, see Tables 1 and 2; ^{13}C-NMR ($CDCl_3$ + CD_3OD): 137.8 (d, J_{CH} = 185.4 Hz) C6; 107.7 (s) C5; 84.6 (d, J_{CH} = 167.4 Hz) C1'; 82.6 (d, J_{CH} = 146.0 Hz) C4'; 75.1 (d, J_{CH} = 150.5 Hz) C2'; 61.0 (t, J_{CH} = 141.5 Hz) C5'; 60.7 (t, J_{CH} = 143.2 Hz) C-γ; 45.3 (d, J_{CH} = 138.5 Hz) C3'; 29.1 (t, J_{CH} = 127.9 Hz), 26.6 (t, J_{CH} = 128.9 Hz) C-β, C-α; 10.8 (q, J_{CH} = 129.1 Hz) 5-Me. MS (FAB^-): calc. for $(M-H)^-$ 299.1243, found 299.1242.

1-[2'-deoxy-2'-*C*(S),6-*C*(S)-((2-(S)-hydroxymethyl)ethylene)-β-D-*lyxo*pyranosyl]-5(R),6(S)-dihydrothymine (18): Treatment of compound **17** (40 mg, 0.070 mmol) with 80% aq. acetic acid (3 ml) at room temperature overnight, after chromatography, to give compound **18** (13 mg, 62%). For ^{1}H-NMR, see Table 4; ^{13}C-NMR ($CDCl_3$ + CD_3OD): 174.0 (s) C4; 154.3 (s) C2; 80.0 (d, J_{CH} = 162.9 Hz) C1'; 73.4 (d, J_{CH} = 150.5 Hz) C4'; 67.4 (d, J_{CH} = 143.4 Hz) C-9; 66.1 (t, J_{CH} = 147.2 Hz) C3'; 62.0 (t, J_{CH} = 141.0 Hz) C5'; 52.3 (d, J_{CH} = 137.1 Hz) C5; 40.1 (d, J_{CH} = 130.3 Hz) C2'; 37.1 (d, J_{CH} = 123.6 Hz) C-7; 36.6 (d, J_{CH} = 135.9 Hz) C6; 19.6 (t, J_{CH} = 132.0 Hz) C-8; 10.1 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB^-): calc. for $(M-H)^-$ 299.1243, found 299.1252.

1-[2'-*O*-acetyl-3'-deoxy-3'-*C*-(ω-acetoxypropyl)-β-D-*ribo*furanosyl]thymine (28). Treatment of compound **27** (40 mg, 0.061 mmol) with 80% aq. acetic acid (3 ml) at room temperature overnight, after chromatography, to give compound **28** (22 mg, 94%). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.56 (q, 1H) H6; 5.69 (d, $J_{1',2'}$ = 1.2 Hz) H1'; 5.43 (dd, $J_{2',3'}$ =6.1 Hz, 1H) H2'; 4.07 (m, 3H) H4'; H-γ; 3.85 (m, $J_{4',5'}$ = 2.7 Hz, 2H) H5', H5"; 2.62 (m, 1H) H3'; 2.16 (s, 3H) Ac; 2.05 (s, 3H) Ac; 1.87 (d, 3H) 5-Me; 1.55 (m, 4H) H-β, H-α. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 136.8 (d, J_{CH} = 184.2 Hz) C6; 110.4 (s) C5; 91.3 (d, J_{CH} = 169.6 Hz) C1'; 85.0 (d, J_{CH} = 148.6 Hz) C4'; 77.7 (d, J_{CH} = 159.5 Hz) C2'; 63.8 (t, J_{CH} = 146.6 Hz) C-γ; 60.8 (t, J_{CH} = 142.7 Hz) C5'; 39.2 (d, J_{CH} = 132.6 Hz) C3'; 26.6 (t, J_{CH} = 128.1

Hz), 21.3 (t, J_{CH} = 126.4 Hz) C-β, C-α; 20.8 (q, J_{CH} = 129.2 Hz), 20.5 (q, J_{CH} =129.2 Hz) Ac; 12.3 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB⁻): calc. for (M-H)⁻ 383.1454, found 383.1460.

1-[3'-*O*-acetyl-2'-deoxy-2'-*C*-(ω-acetoxypropyl)-β-D-*ribo*furanosyl]thymine (30). Treatment of compound **29** (39 mg, 0.059 mmol) with 80% aq. acetic acid (3 ml) at room temperature overnight, after chromatography, to give compound **30** (21 mg, 92%). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.58 (q, 1H) H6; 6.00 (d, $J_{1',2'}$ = 9.3 Hz, 1H) H1'; 5.35 (d, $J_{2',3'}$ = 5.6 Hz, 1H) H3'; 4.05 (m, 3H) H4', H-γ; 3.91 (m, 2H) H5', H5''; 2.58 (m, 1H) H2'; 2.14 (s, 3H) Ac; 2.03 (s, 3H) Ac; 1.92 (d, 3H) 5-Me; 1.55 (m, 4H) H-β, H-α. ^{13}C-NMR ($CDCl_3$ + CD_3OD): 136.2 (d. J_{CH} = 183.0 Hz) C6; 111.5 (s) C5; 89.2 (d, J_{CH} = 168.5 Hz) C1'; 85.0 (d, J_{CH} = 150.5 Hz) C4'; 75.3 (d. J_{CH} = 159.5 Hz) C3'; 63.8 (t, J_{CH} = 146.6 Hz) C-γ; 62.6 (t, J_{CH} = 141.6 Hz) C5'; 46.0 (d, J_{CH} = 128.1 Hz) C2'; 26.2 (t, J_{CH} =128.6 Hz), 20.7 (t, J_{CH} = 126.9 Hz) C-β, C-α; 20.5 (q, J_{CH} = 128.2 Hz) Ac; 12.4 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB⁻): calc. for (M-H)⁻ 383.1454, found 383.1467.

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