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The Diastereospecific Synthesis of New 2',3'-*Cis*-α-Fused Carbocyclic Nucleosides

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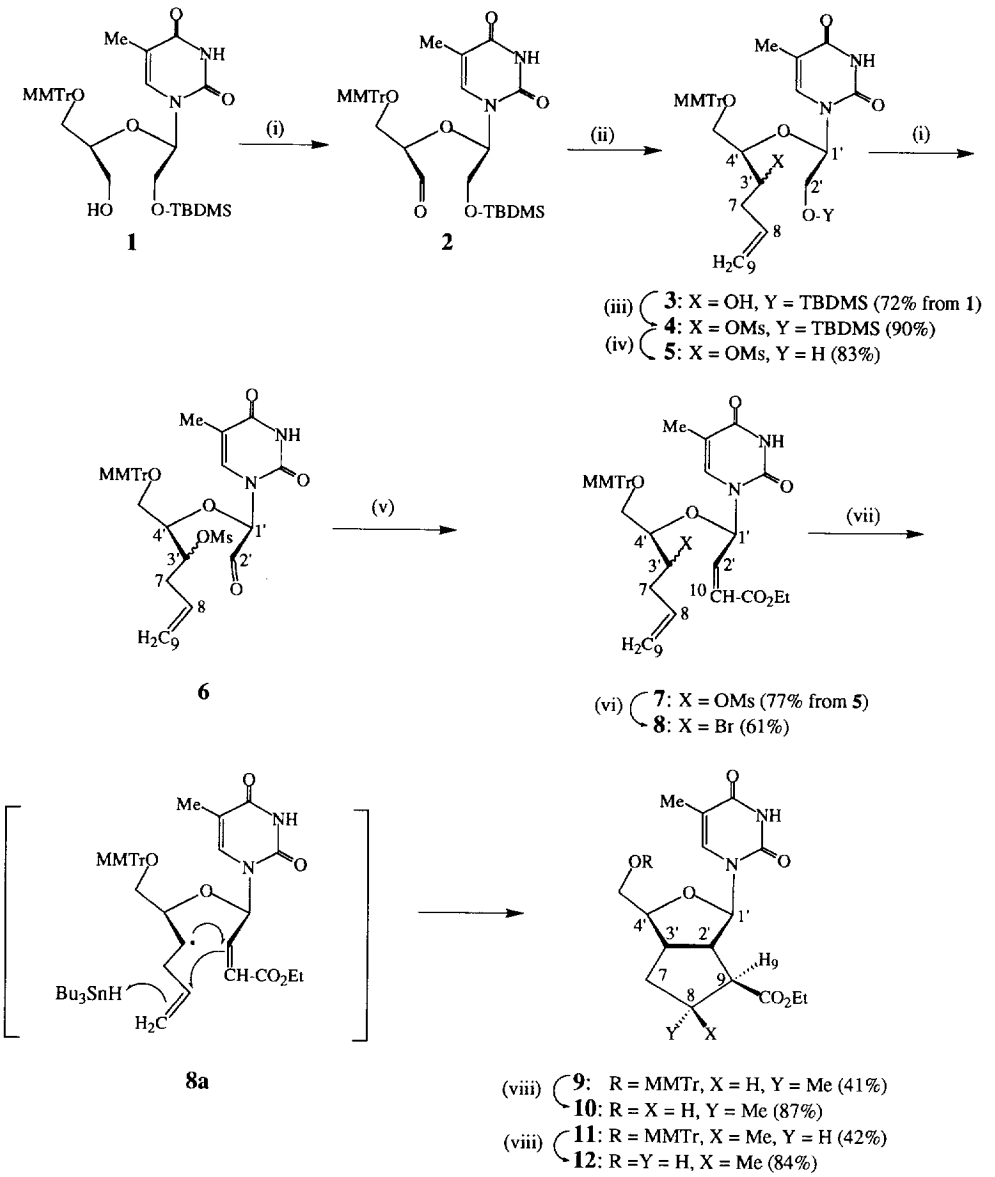
Abstract. *The first diastereospecific synthesis of [3.3.0]- and [3.4.0]-α-cis-fused-carbocyclic nucleosides* ***10, 12 and 20****, starting directly from 2'-O-(TBDMS) or 3'-O-(TBDMS) derivatives of 5'-O-MMTr-2',3'-seco-ribo-thymidines,* ***1 and 13*** *(ref. 4), have been reported. The key steps involve the unsymmetrical modification of the 2'- and 3'-hydroxyls in seco-nucleosides* ***1 and 13*** *and their diastereospecific recyclisation to the furanose-fused carbocyclic rings using either radical cyclization [****1*** *→* ***2*** *→* ***3*** *(72%)→* ***4*** *(90%)→* ***5*** *(83%)→* ***6*** *→* ***7*** *(77%)→* ***8*** *(61%)→* ***9*** *(41%) and* ***11*** *(42%);* ***9*** *→* ***10*** *(87%) &* ***11*** *→* ***12*** *(84%)] or Diels-Alder reaction [****13*** *→* ***14*** *→* ***15*** *(91%)→* ***16*** *(80%)→* ***17*** *→* ***18*** *(36%)→* ***19*** *(69%)→* ***20*** *(84%)].*

Modified sugars in nucleosides or oligonucleos(t)ides have attracted considerable interest because they provide the unique possibility to engineer molecules which mimic or interfere with specific biological functions. Several carbohydrate modified nucleosides have been found to possess antitumour,[1] or antiviral[2,3] activity. The major problems encountered in this exercise are the drug-resistance and the toxicity. It has, however, been suggested that the problem of the drug-resistance can be partly overcome by administering a "cocktail" of drugs with low toxicity against a pathogen-specific target enzyme. In the above venture, clearly the development of new synthetic methods is an important step in the discovery of new types of candidate drugs. In this respect, the development of new synthetic methodologies affording various types of 2',3'-dideoxynucleoside analogues against HIV-specific reverse transcriptase still remains an important goal. Despite the availability of various methods to synthesise 2',3'-dideoxy analogous, the methods for obtaining simple 2',3'-*C*-annulated nucleosides are relatively few,[9b, 9d, 13] and therefore, the development of these stereospecific methodologies have been deemed an important and challenging task. On the other hand, the synthesis of the 2',3'-fused heterocyclonucleosides are readily obtainable by any of the following methodologies: (i) the free radical cyclisation reaction of the 2'-*O(N)*- or 3'-*O(N)*-allyl ethers of nucleosides to give bicyclic tetrahydrofurane[5] or pyrrolidine[6] derivatives. Similarly, the free radical cyclization of 2'- or 3'-allyldimethylsilyl ethers[7] and alkynyldimethylsilyl ethers[8] were used for the construction of the 6- or 7-membered rings with oxygen and silicon, which could be opened up to give 2'- or 3'-*C*-branched nucleosides; (ii) the conjugate Michael addition reaction of the 2',3'-dideoxy-2',3'-didehydro-3'-phenylselenonyl-uridine with ambident nucleophiles gave different kinds of 3-, 4-, 5- or 6-membered heterocycles fused at the 2' and 3'-sugar carbons;[9] (iii) the cycloaddition reaction of the 2',3'-dideoxy-2',3'-didehydro-3'-nitro-thymidine with



Reagents: (i) DCC/DMSO/Cl_2CHCO_2H; (ii) CH_2=CH-CH_2MgBr; (iii) MsCl/Py; (iv) NH_4F/MeOH; (v) Ph_3P=$CHCO_2Et$/THF; (vi) LiBr/DMF; (vii) Bu_3SnH/toluene; (viii) 90% AcOH/H_2O.

Scheme 1

ethyl vinyl ether gave bicyclic 2',3'-nitronate;[10] (iv) the 1,3-dipolar cycloaddition reaction of nitrile oxides with 2',3'-dideoxy-2',3'-didehydrothymidine gave 2',3'-isoxazolidine derivatives,[11] or 2'- and 3'-*N*-methylnitrones, upon intramolecular 1,3-dipolar cycloaddition reaction with 3'-*O*- or 2'-*O*-allyl ethers, gave tricyclic 2',3'-tetrahydrofuran derivatives with 3'-spiro isoxazolidine ring;[12] (v) Diels-Alder reaction of the 2',3'-dideoxy-3'-nitro-2',3'-didehydrothymidine with different kind of dienes gave 2',3'-carbocyclic nucleosides;[13] and finally (vi) the intramolecular 1,3-dipolar cycloaddition reaction of modified *seco*-nucleosides gave 2',3'-isoxazolidine nucleosides.[4]

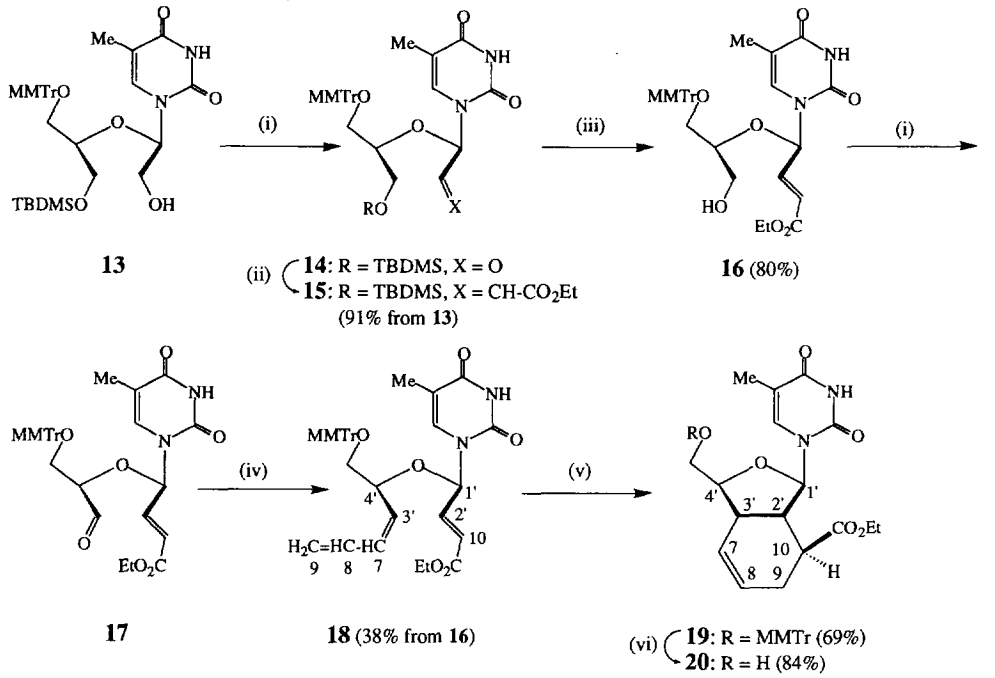
Our latter approach[4] for the synthesis of 2',3'-*cis*-fused nucleosides consisted of the 2'- and 3'-modification of 2',3'-*seco*-nucleosides and its diastereospecific recyclisation. The cheomospecific modification of the 2'- or 3'-primary hydroxyl group of the *seco*-nucleosides proved to be facile in comparison with the corresponding secondary 2'- and 3'-hydroxyl groups of the ribonucleoside. In addition, the subsequent recyclisation of the modified *seco*-nucleoside proved to be stereoselective[4]. As a result, this general approach seemed to us very attractive for the synthesis of hithertofore unknown 2',3'-dideoxy-2',3'-*C*-fused carbocyclic nucleosides. We here report the first stereocontrolled synthesis of 2',3'-dideoxy-[3.3.0]-2',3'-*C*-α-fused-cyclopentanyl nucleosides **10** and **12**, using the stereospecific radical recyclisation of the key diastereomeric mixture of bromo-precursor **8** (**1**→ **2** → **3** → **4**→ **8**). We also report here the first synthesis of 2',3'-dideoxy-[3.4.0]-2',3'-*C*-α-fused-cyclohexenyl nucleoside **20**, using the stereospecific Diels-Alder cyclisation of the precursor **18**, which was prepared by Wittig reaction of the aldehyde **17** with Ph_3P=CH-CH=CH_2, starting from the partially protected *seco*-nucleoside **13**.

Results and Discussion

*(A) Preparation of the pure diastereoisomers of 2',3'-dideoxy-2',3'-C-[3.3.0]-α-fused-cyclopentanyl nucleosides **11** and **12**.* The target 2',3'-*C*-α-fused-cyclopentanyl nucleosides have been synthesized through the radical precursor **8**, which can be conveniently prepared from readily accessible 2'-O-TBDMS-protected 2',3'-*seco*-thymidine **1**.[4] Thus, compound **1** was oxidised (DCC, DMSO, Cl_2CHCO_2H, 2h, RT)[14] into the aldehyde **2**. The crude aldehyde was then directly treated with CH_2=CH-CH_2MgBr[15] to give an inseparable mixture of diastereoisomers of **3** (72%). The 3'-hydroxyl group of **3** was converted to its methanesufonate. The 3'-mesylate served both as a protective group during the subsequent oxidation of 2'-OH to give **6** (*i.e.* **5** → **6**) as well as a leaving group in the substitution reaction at a later step to generate the radical precursor **8** (*i.e.* **7** → **8**). Removal of the 2'-*O*-TBDMS group in **4** was carried out using a NH_4F/MeOH[16] to give **5** (83%), which was oxidised[14] to aldehyde **6**. The crude **6** was then treated with Ph_3P=CH-CO_2Et in THF to give **7** (77% in two steps: **5** → **6**→ **7**). Finally, 3'-methanesulfonyl group in **7** was substituted by Br^- to give the target radical precursor **8** (61%). Compounds **3** - **8** were mixtures of two diastereomers, which was evident from both 1D ^{1}H-NMR and by the proton-proton connectivities in the 2D homonuclear correlation spectroscopy (COSY) (see experimental).

Reaction of **8** with Bu_3SnH and azobisisobutyronitrile (AIBN) in toluene at 95° for 2 h yielded a mixture of two diastereomers **9** and **11**, which were separated in 41 and 42 % yields, respectively. As expected, the free radical generated at C3' through the radical precursor **8**, stereospecifically[4] attacked the sp^2 centre at C2', as shown in the intermediate **8a**, which subsequently underwent a concerted 5-*endo* radical cyclisation to form the fused cyclopentane ring at the α-face of the nucleoside. The diastereospecific formation of the C2'-C3'

covalent bond in **9** was confirmed by the appearance of $^3J_{H2',H3'}$ = 10.4 Hz and also by the H2' (δ 3.04) and H3' (δ 2.88) connectivity in the COSY spectra. Similarly, the detection of full proton-proton coupling network in the cyclopentane ring with the fused furanose ring also confirmed the cyclic nature of the fused cyclopentanyl system *(vide infra)*. The configuration of the [3.3.0]-α-fused furanose-cyclopentane rings in **9** was determined by 1D difference nOe experiments: Saturation of H1' in **9** gives nOe enhancements at H9 (8.2%), H2' (4.4%) and H4' (1.4%). Saturation of 8-Me shows nOe enhancements at H7 (6.2%), H8 (7.2%) and H9 (3.4%) which are consistent with C2'-(*S*), C3'-(*S*), C8-(*R*) and C9-(*S*) configurations. Subsequently, the 5'-*O*-MMTr group from **9** was removed using 90% aq. acetic acid to give **10** (87%), which was again characterised by conformational analysis using a combination of DQF-COSY and NOESY spectra. For compound **11**, we could not extract the essential $^3J_{H2',H3'}$ coupling (not even at 500 MHz) because of the isochronous chemical shifts



Reagents: (i) DCC/DMSO/Cl_2CHCO_2H; (ii) Ph_3P=CH-CO_2Et/THF; (iii) NH_4F/MeOH; (iv) Ph_3P=CH_2-CH=CH_2; (v) toluen (100° C, 12 h); (vi) 90% AcOH.

Scheme 2

of H2', H3' and H9 in a narrow region at δ 2.9, hence we prepared its 5'-deprotected derivative **12** (84%), using the above acidic condition, and characterised it thoroughly by DQF-COSY experiment, which confirmed the presence of $^3J_{H2',H3'}$ = 10.4 Hz, and hence the cyclic fused nature of the system (see Table 1). Additionally, we characterized **12** by NOESY experiment which gave interproton distance informations *(vide infra,* Table 2). Thus a combination of DQF-COSY and NOESY experiments confirmed the structure of **12**, thus proving also the structure of the precursor **11** (C2'-(*S*), C3'-(*S*), C8-(*S*) and C9-(*S*) configurations).

(B) Preparation of pure diastereomer of 2',3'-dideoxy-2',3'-C-[3.4.0]-α-fused-cyclohexenoyl nucleoside ***20.*** For the construction of the furanose-2',3'-*cis*-fused cyclohexene ring, we have chosen to employ Diels-Alder reaction which can be easily carried out under very mild conditions. For the synthesis of the precursor, we initially tried to perform the base-induced elimination reaction of the mesylate group in **4** or **7** to give the triene **18**. All our attempts to perform this were unsuccessful producing intricate mixture of compounds. We could observe only degradation of the starting material because of the instability of the triene **18** in the presence of the base. We therefore employed Wittig reaction of the aldehyde **17**[4] with $Ph_3P{=}CH{-}CH{=}CH_2$[17a] in THF to give **18** in a moderate yield (38%), which was found to be a mixture of *cis* and *trans* stereoisomers. The ratio of the C3'=C7 *cis*-isomer ($J_{3',7}$ = 11.6 Hz) to the C3'=C7 *trans*-isomer ($J_{3',7}$ = 14.5 Hz) was 3 : 2 (^{1}H NMR at 500 MHz). Triene **18** was heated in toluene (100° C, 12 h) to give **19** (69%). The configurations of three new chiral carbons (*i.e.* C2', C3' and C10) formed in the above concerted ring-closure reaction were assigned with the help of 2D NOESY spectra at 500 MHz. We observed the key nOe cross peaks and calculated the interproton distances from the nOe volumes (see experimental) for the following protons: d(H6 - H2') = 2.45 Å, d(H6 - H3') = 2.64 Å, d(H2' - H3') = 2.43 Å and d(H1' - H4') = 2.83Å, which show that the configurations of both C2' and C3' are *S*. These nOes also suggest that the 2',3'-cyclohexene ring is *cis*-fused and is attached at the α-face (*i.e.* "down") of the pentofuranose ring. Furthermore, the proton connectivities of H2' (δ 2.90) and H3' (δ 3.12) in the COSY spectra show that the C2' and C3' covalent bond has indeed been formed and the large $^3J_{H2',H3'}$ coupling constant of 8.2 Hz indicated that the H2' and H3' are *cis*, suggesting a *ribo* configuration of the 2',3'-*cis*-fused carbocyclic ring. The observed volumes of the nOe cross-peaks for H1' - H10 and H4' - H10 suggest that these protons are respectively 2.41 and 2.47Å apart, and hence they are at the same side of the cyclohexene ring, which established the *S* configuration for C10. The configurations of the C2' and C3' centers in compound **19** are in good agreement with the expected transition state of the Diels-Alder reaction. Note that both stereoisomers of **18** (due to *cis* and *trans*-diene moieties) gave only the *ribo* stereoisomer **19** in a stereospecific manner. Clearly, the stereospecificity of the intramolecular Diels-Alder reaction of **18** is owing to the steric repulsions between 5'-*O*-MMTr group and the *cis*-diene moiety in the *cis*-stereoisomer, and between thymine base and the *trans*-diene moiety in the *trans*-stereoisomer, which prevent the formation of any energetically unfavourable[17b] by-products such as *xylo*, *arabino* or *lyxo* derivatives. Finally, 5'-*O*-MMTr group in **19** was removed under acidic condition to give **20** (84%) and its conformation was determined by a combination of 1D spectra at 500 MHz and 2D NOESY spectra.

(C) Assignment of configurations at the new chiral centres as well as the conformational analysis of 2',3'-C-fused nucleosides ***10, 12 and 20.*** The configuration of the new chiral carbons (C9 and C8) formed in the synthesis of compounds **10** and **12** were assigned with the help of 2D NOESY spectra and coupling constants. The DQF-COSY had to be used due to the overlap of the H2', H3' and H9 resonances (see experimental).

In **12** nOes could be observed between H8 and H1' and H4', whereas in **10** the H8 proton showed nOe with H2' and H3', this led us to assign the H8 proton to the β-face (*i.e. R* configuration at C8) in **10** and to the α-face of the sugar (*i.e. S* configuration at C8) in **12**. In compound **10** the nOes between H9 and H1' and H4' led to the conclusion that H9 was on the α-face (*i.e.* C9-*S*). In compound **12** no nOes could safely be assigned to H9 due to its overlap with H2' and H3'. However, the small coupling constant between H2' and H9 (0.7 Hz) indicating a torsional angle close to 90° puts the H9 proton in the α-face (*i.e.* C9-*S*) as it is impossible for the torsional

angle [H2'-C2'-C9-H9] to be close to 90° if H9 is located at the β-face. Note that these assignments puts both 8-methyl group in **10** and **12** in the pseudoequatorial position of the carbocyclic ring.

For compounds **10** and **20** the existence of strong nOe crosspeaks between H6 and H2' and H3' indicates that the glycosyl torsion should be in *anti* conformation. In **12** the overlap of the H2', H3' and H9 resonances makes it impossible to assign any conformation to its glycosyl torsion.

Table 1. Comparison of the experimental coupling constants (^{1}H at 500 MHz) derived torsion angles[a] in **10**, **12** and **20** with those found in the respective molecular models (see Fig. 1)

	Compound **10**				Compound **12**				Compound **20**			
	Experiment		Model		Experiment		Model		Experiment		Model	
Coupling	J_{HH}	ϕ_{HH}	J_{HH}	ϕ_{HH}	J_{HH}	ϕ_{HH}	J_{HH}	ϕ_{HH}	J_{HH}	ϕ_{HH}	J_{HH}	ϕ_{HH}
$J_{1'2'}$	4.7±0.1[b]	126°	5.5	132°	5.2±0.1	130°	6.0	135°	3.9±0.1	121°	4.9	128°
$J_{2'3'}$	10.5±0.2	346°	10.9	351°	10.4±0.4[c]	345°	10.8	350°	8.4±0.2	330°	9.8	339°
$J_{3'4'}$	7.0±0.2	224°	7.5	221°	8.3±0.4	216°	7.6	220°	8.8±0.4	213°	8.2	217°
$J_{3'7}$	7.4±0.4	34°	8.2	29°	7.5±0.2	328°	7.0	325°				
$J_{3'7'}$	7.4±0.4	137°	8.5	143°	1.9±0.2	69°	1.3	76°				
J_{78}	7.4±0.4	326°	6.8	322°	10.4±0.2	154°	11.0	159°				
$J_{7'8}$	10.7±0.2	204°	10.7	204°	6.5±0.2	40°	5.8	44°				
J_{89}	11.0±0.2	156°	11.6	160°	7.1±0.2	322°	6.5	319°				
$J_{2'9}$	8.5±0.2	220°	9.2	217°	0.7±0.4[c]	286°	0.3	280°				
$J_{2'10}$									10.1±0.2	212°	9.6	215°
J_{910}									5.3±0.2	47°	6.1	42°
$J_{9'10}$									9.5±0.2	149°	10.6	156°

[a] The experimental $^3J_{HH}$ (Hz) were obtained from 1D NMR and 2D DQF-COSY at 293 K and theoretical were back-calculated from the energy minimised model structures of compounds **10**, **12** and **20** using the Karplus-Altona equation[18]: $^3J(HH) = P_1\cos^2\phi + P_2\cos\phi + P_3 + \sum \Delta\chi_i\left\{P_4 + P_5\cos^2\left(\xi_i\phi + P_6|\Delta\chi_i|\right)\right\}$, where P_1, P_2 and P_3 are torsion angle terms, whereas P_4-P_7 (P_7 takes into account β substituents) are electronegativity related. The same equation was used to calculate ϕ_{HH} (exp). The error in $^3J_{HH}$ in the above equation is up to ΔJ_{max} = ±1.2 Hz.[18] [b] The different $^3J_{HH}$ error values are owing to the different complexity of the splitting pattern. [c] $^3J_{HH}$ obtained from DQF-COSY, all others are from 1D NMR at 500 MHz. [d] See experimental section for all coupling constants for **10**, **12** and **20**.

The $^3J_{HH}$ measured at 500 MHz for **10**, **12** and **20** were translated into the corresponding proton-proton torsion angles (Φ_{HH}) with the use of the generalised Karplus-Altona equation (see footnote of Table 1),[18] which includes a correction term due to electronegativities of the substituents (Table 1). The structural models of **10**, **12** and **20** have been built with the help of the computer program MacroModel.[19] An all atom AMBER force field[20] as implemented in MacroModel has been used. The Coulombic electrostatic and van der Waals nonbonding cutoffs were both set to 25Å, which exceeds the size of the molecules. Dielectric constant in the distance-dependent dielectric electrostatic treatment was set to 4r. Charges on the individual atoms in **10**, **12** and **20** were assigned by the MacroModel program. The fused bicyclic structures of **10**, **12** and **20** were energy minimised (to derivative convergence of 0.004 kJ mol^{-1}Å^{-1}) with constraints on Φ_{HH} to yield conformers that fulfil all torsion angles derived from $^3J_{HH}$ values (as shown in Table 1). The flat region of ±3° was used in which no energy penalty is paid, whereas the constraint energy outside the allowed region was calculated by E = 1000 kJ mol^{-1} rad^{-1} [1 - cos (deviation)]. The deviations of constrained Φ_{HH} in the final energy minimised conformers of **10**, **12** and **20** presented in Figure 1 were inside ±9° (Table 1), which is within the experimental error limit of $^3J_{HH}$ values and in the assumptions in Karplus-Altona equation.

In the case of **10** nine torsion angles were constrained to mutually consistent values (Table 1) and resulting energy minimised conformer is shown in Figure 1. The pentofuranose moiety in **10** (Fig. 1A) adopts East conformation close to $O_{4'}$-*endo* (P = 86°, Ψ_m = 27°)[21], thymine is *anti* (χ[O4'-C1'-N1-C2] = -154°) and orientation across C4'-C5' is *gauche*$^+$ (γ[O5'-C5'-C4'-C3'] = 59°, experimental $^3J_{4'5'}$ = 2.7 Hz and $^3J_{4'5''}$ = 4.2 Hz show[22] 66% γ^+ and 31% γ^t). The cyclopentane moiety fused to C2'-C3' in **10** adopts C_8-*exo* conformation (P = 128°, Ψ_m = 38°). In the case of **12** torsion angles were constrained to nine mutually consistent values (Table 1). The resulting energy minimised conformer of **12** (Fig. 1B) is characterised by the *anti* orientation of the thymine (χ = -141°), *gauche*$^+$ across C4'-C5' (γ = 60°, experimental $^3J_{4'5'}$ = 2.0 Hz and $^3J_{4'5''}$ = 5.0 Hz give[22] 60% γ^+ and 40% γ^t), East conformation (P = 89°, Ψ_m = 39°)[21] of pentofuranose moiety and C_8-*endo* conformation (P = 52°, Ψ_m = 40°) of cyclopentane moiety fused to C2'-C3'. In both **10** and **12** C8-Me is placed in a pseudoequatorial orientation in consistence with the coupling constants and distance informations (Tables 1 and 2). The energy minimisation of **20** was performed with the constraints on six torsion angles (Table 1). The pentofuranose moiety in **20** (Fig. 1C) adopts East conformation close to $O_{4'}$-*endo*-C4'-*exo* twist conformation (P = 79°, Ψ_m = 27°)[21], thymine is *anti* (χ = -141°) and orientation across C4'-C5' is *gauche*$^+$ (γ = 57°, experimental $^3J_{4'5'}$ = 2.3 Hz and $^3J_{4'5''}$ = 3.3 Hz show[22] 80% γ^+ and 20% γ^t). The cyclohexene moiety

Table 2. Comparison of the experimental distances found in the NOESY spectra in **10**, **12** and **20** with those found in the energy optimised molecular models (see Fig. 1).

	Compound **10**		Compound **12**		Compound **20**	
Distance	Experiment	Model	Experiment	Model	Experiment	Model
H1'-H2'	2.7 Å	2.9 Å	b	2.9 Å	2.8 Å	2.8 Å
H1'-H4'	2.6 Å	2.9 Å	2.3 Å	2.6 Å	2.8 Å	3.0 Å
H1'-H7'	(2.9 Å)	3.7 Å	(3.6 Å)	4.1 Å		
H1'-H8	c	4.6 Å	2.1 Å	2.5 Å		5.3 Å
H1'-H9	2.1 Å	2.2 Å	b	2.3 Å		
H2'-H3'	2.0 Å	2.3 Å	b	2.6 Å	2.4 Å	2.3 Å
H2'-H9	2.6 Å	3.0 Å	b	2.7 Å		
H2'-H8	2.3 Å	3.1 Å	c	3.9 Å		4.8 Å
H3'-H4'	2.6 Å	3.0 Å	b	3.0 Å	2.6 Å	3.1 Å
H3'-H7	2.2 Å	2.2 Å	2.0 Å	2.4 Å	2.4 Å	2.6 Å
H3'-H7'	d	3.0 Å	2.5 Å	2.6 Å		
H3'-H8	2.8 Å	3.0 Å	c	3.9 Å		3.8 Å
H4'-H7'	2.3 Å	2.2 Å	2.1 Å	2.4 Å		
H4'-H8	c	4.6 Å	2.2 Å	2.4 Å		4.3 Å
H4'-H9	2.7 Å	3.5 Å	b	4.0 Å		
H7-H8	2.3 Å	2.5 Å	3.0 Å	3.0 Å		
H7'-H8	(2.3 Å)	3.1 Å	2.3 Å	2.5 Å		
H7'-H9	3.0 Å	2.9 Å	b	4.3 Å		
H8-H9	2.5 Å	3.0 Å	(2.0 Å)	2.5 Å		
H1'-H10					2.5 Å	2.2 Å
H2'-H10					2.8 Å	3.0 Å
H2'-H9'					3.0 Å	3.2 Å
H4'-H10					d	3.5 Å

[a] NOESY spectra were recorded at 293 K at 500.13 MHz and the estimated error in distances is ±0.4 Å (error in the distances is ±0.8 Å if in the parenthesis). [b] It could not be measured due to overlap or is absent. [c] None observed. [d] Satisfactory integration of crosspeak are not possible. A distance within parenthesis is one where the error is large due to noise interference.

fused to C2'-C3' in **20** adopts half-chair/half-boat conformation. The distances in the energy minimised conformers of **10**, **12** and **20** were compared and were found to agree with those calculated from the NOESY spectra (see Table 2).

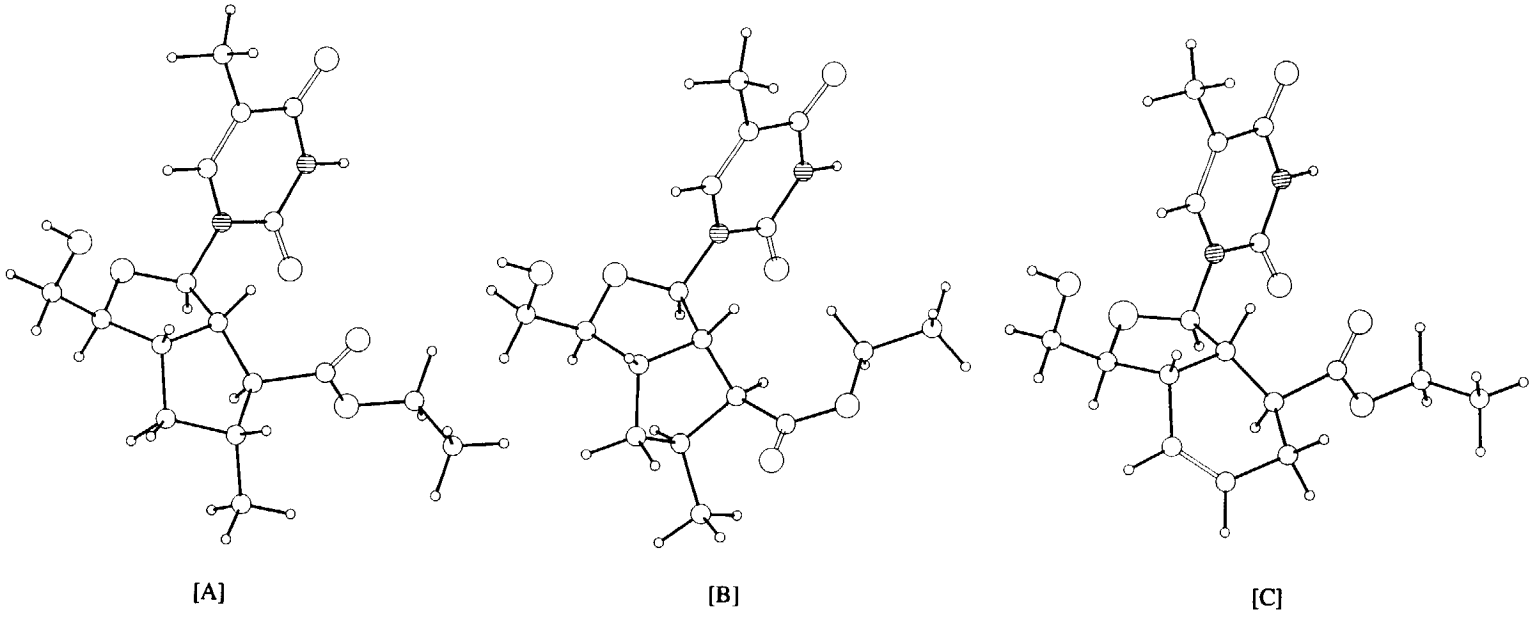


Figure 1. The conformers of **10** (Panel: A), **12** (Panel: B) and **20** (Panel: C) were obtained through energy minimisation with the use of the generalized all atom AMBER force field parameters[20] as implemented in the computer program MacroModel V3.5a[19] with constraints on $\Phi_{H,H}$ to build structures that fulfil torsional angles derived from experimental $^3J_{H,H}$ measured at 500 MHz ^{1}H-NMR (see Table 1) as well as distances from NOESY spectra (Table 2). The pentofuranose ring in **10** (Panel: A) adopts East conformation close to $O_{4'}$-*endo* (P = 86°, Ψ_m = 27°),[21] thymine is *anti* (χ[O4'-C1'-N1-C2] = -154°) and orientation across C4'-C5' is *gauche*$^+$ (γ[O5'-C5'-C4'-C3'] = 59°). The cyclopentane moiety fused to C2'-C3' in **10** adopts C_8-*exo* conformation (P = 128°, Ψ_m = 38°).[21] For the definitions of endocyclic torsion angles to calculate P and Ψ_m for cyclopentane rings in **10** and **12** see ref. 21. The energy minimised conformer of **12** (Panel: B) is characterized by the *anti* orientation of the thymine (χ = -141°), *gauche*$^+$ across C4'-C5' (γ = 60°), East conformation (P = 89°, Ψ_m = 39°) of pentofuranose moiety and C_8-*endo* conformation (P = 52°, Ψ_m = 40°) of cyclopentane moiety fused to C2'-C3'. The pentofuranose moiety in **20** (Panel: C) adopts conformation close to $O_{4'}$-*endo* -C4'-*exo* twist (P = 79°, Ψ_m = 27°), thymine is *anti* (χ = -141°) and orientation across C4'-C5' is in *gauche*$^+$ region (γ = 57°). The cyclohexene moiety fused to C2'-C3' in **20** adopts half-chair/half-boat conformation.

In our previous studies on 2',3'-*cis* fused furano-[23a] and pyrrolidino-β-D-nucleosides[6] we have shown that the constituent pentofuranose moieties are predominantly in the South type conformations when C3' oxygen or nitrogen substituent is at the α-face. This preference for the South type conformations is due to the gauche effects of [O4'-C4'-C3'-O] and [O4'-C4'-C3'-N] fragments. However, the drive to the South is stronger in furano-β-D-nucleosides (>92%)[23a] than in pyrrolidino-β-D-nucleosides (>70%).[23b] This is consistent with the fact that as the strength of the gauche effect increases with the increase of the electronegativity of the 3'-substituent, the sugar takes up the preferential South conformation.[23b] On the contrary, when C2' oxygen or nitrogen substituent is at the α-face, strong preference for North type sugar conformations was observed in both 2',3'-*cis*-fused furano- (≈100%)[23a] and pyrrolidino-β-D-nucleosides (>80%).[6] The main driving forces towards North pentofuranose conformation are gauche effects of [O4'-C1'-C2'-O] and [O4'-C1'-C2'-N] fragments, respectively and as discussed above the former gauche effect is stronger.[23] In the case of **10** and **12** there are no gauche effects involving O4' and C2' or C3' substituents and the pentofuranose conformation is driven predominantly by the steric effects[23c] which results in the predominance (>85%) of the East type conformation (*vide supra*).

Experimental

^{1}H-NMR spectra were recorded at 270.05 MHz with a JNM-GX 270 spectrometer in δ scale using TMS (0.0 ppm) as an internal reference. ^{13}C-NMR were recorded at 67.80 MHz using both ^{1}H-decoupled or INEPT modes in the same solvent as ^{1}H-NMR. Coupling constants reported in ^{13}C-NMR part are $^1J_{CH}$. UV absorption spectra were recorded with a Varian-Carry 2200 instrument. Jeol DX 303 instrument was used for recording high resolution mass spectra. TLC was carried out using Merck pre-coated silica gel F_{254} plates. The flash column chromatographic separation were carried out using Merck G60 silica gel and gradient of ethanol in dichlormethane.

The ^{1}H-NMR spectra for compounds **10**, **12**, **18**, **19** and **20** were recorded on a Bruker AMX500 NMR spectrometer (^{1}H at 500.13 MHz). The compounds were dissolved in $CDCl_3$ and all spectra were recorded at 293K. The sweep width for all 1D and 2D spectra were 9.5 ppm. The NOESY spectra were recorded in the phase-sensitive mode with a relaxation delay of 3s, using 256 experiments of 4K complex data points (τ_m = 300 ms). The spectra were then zero-filled twice in the F1 dimension and a 2 Hz exponential window in F2 and a π/2 shifted sine^2 window in F1 were applied before Fourier transformation, yielding a final spectra of 2K by 1K real data points. The spectra were integrated using AURELIA (supplied by Bruker) and the distances were calculated using the H7 to H7' crosspeak as a reference distance (1.77 Å) for compounds **10** and **12.** For compound **20** H5' to H5" (1.77 Å). The DQF-COSY spectra of **12** was recorded using 512 experiments of 4K complex data points each with a relaxation delay of 2s. π/4 shifted sine^2 windows were applied in both dimensions and the spectra was zero-filled two times in the F1 dimension before Fourier transformation, giving a final spectra of 2K by 2K data points. For extraction of the coupling constants a projection was taken through the crosspeak of interest, inversely Fourier transformed back to a FID, zero-filled twice and then Fourier transformed again giving a final digital resolution of 0.4 Hz/pt.

1-[5-*O*-MMTr-2-*O*-TBDMS-3-(*R/S*)-*C*-allyl-2,3-*seco*-β-D-ribofuranosyl]thymine (3). Compound **1**[4] (0.84 g, 1.30 mmol) was dissolved in DMSO (3 ml) and treated with DCC (0.80 g, 3.90 mmol) and dichloroacetic acid (80 mg, 0.62 mmol) for 2 h. Then acetic acid (0.1 ml) was added and mixture was dissolved in ethyl acetate (20 ml), filtered and washed with water (4 x 100 ml). Organic phase was dried (Na_2SO_4) and volatiles were removed in vacuo and the residue was coevaporated with toluene and THF. The residue was dissolved in THF (5 ml), the solution was cooled in an ice bath and treated with a solution of CH_2=CH-CH_2MgBr in ether[15] (11.8 ml, 0.11 M). After 10 min, the reaction mixture was quenched with aq. NH_4Cl solution (0.1 M, 2 ml) and extracted with dichlormethane (3 x 20 ml). The organic phase was concentrated and the residue was chromatographed on silica gel to afford a mixture of diastereomers **3** (0.64 g, 72%). ^{1}H-NMR ($CDCl_3$): 8.67 (br s, 1H) NH; 8.53 (br s, 1H) NH; 7.40-7.10 (m, 26H) arom; 6.82 (m, 4H) arom; 5.94 (dd, $J_{1',2'} = J_{1',2''} = 5.4$ Hz, 1H) H1'; 5.92 (dd, $J_{1',2'} = J_{1',2''} = 5.2$ Hz, 1H) H1'; 5.82 (m, 2H) H8; 5.10-4.95 (m. 4H) H9 + H9'; 3.86 (m, 2H) H3'; 3.78 (s, 6H) OMe; 3.71 (m, 4H) H2' + H2"; 3.61 (m, 2H) H4'; 3.30 (dd, $J_{4',5'} = 3.7$ Hz, $J_{5',5''} = 10.5$ Hz, 1H) H5'; 3.20 (m, 5.1 Hz, 3H) H5' + H5" + H5"; 3.06 (d, 4.0 Hz, 1H) OH; 2.77 (d, 5.1 Hz, 1H) OH; 2.42-1.86 (m, 4H) H7 + H7'; 1.69 (d, 1.0 Hz, 6H) 5-CH_3; 0.84 (s, 18H) TBDMS; 0.06 (s, 12H) TBDMS.

1-[5-*O*-MMTr-2-*O*-TBDMS-3-*O*-(*R/S*)-methanesulfonyl-3-*C*-allyl-2,3-*seco*-β-D-ribofuranosyl]thymine (4). 3 (0.63 mg, 0.92 mmol) was coevaporated with pyridine and then dissolved in pyridine (5 ml). Ms-Cl (0.21 ml, 2.75 mmol) was added and reaction mixture was stored overnight at ~5° C. It was quenched with water (2 ml) and extracted with dichlormethane (3 x 20 ml). The organic phase was concentrated and the residue was chromatographed on silica gel to afford mixture of diastereomers **4** (0.63 g, 90%). ^{1}H-NMR ($CDCl_3$): 8.25 (br s, 1H) NH; 8.10 (br s, 1H) NH; 7.38-7.18 (m, 25H) arom; 6.82 (m, 4H) arom; 7.14 (q, 1.2 Hz, 1H) H6; 5.94 (dd, $J_{1',2'} = 4.4$ Hz, $J_{1',2''} = 5.4$ Hz, 1H) H1'; 5.86 (dd, $J_{1',2'} = 4.9$ Hz, $J_{1',2''} = 5.7$ Hz, 1H) H1'; 5.72 (m, 2H) H8; 5.16-4.91 (m, 4H) H9 + H9'; 3.93 (dd, $J_{2',2''} = 11.2$ Hz, 1H) H2'; 3.82 (dd, 1H) H2"; 3.80 (s, 6H) OMe; 3.75 (m, 6H) H3' + H4' + H2' + H2"; 3.26 (m, 3H) H5' + H5' + H5"; 3.04 (dd, $J_{4',5'} = 5.2$ Hz, $J_{5',5''} = 10.5$ Hz, 1H) H5'; 3.01 (s, 3H) Ms; 2.94 (s 3H) Ms; 2.59-2.14 (m, 4H) H7 + H7'; 1.73 (d, 1.1 Hz, 3H) 5-CH_3; 1.69 (d, 3H) 5-CH_3; 0.84 (s, 18H) TBDMS; 0.04 (s, 12H) TBDMS.

1-[5-*O*-MMTr-3-*O*-(*R/S*)-methanesulfonyl-3-*C*-allyl-2,3-*seco*-β-D-ribofuranosyl]thymine (5). 4 (0.62 mg, 0.81 mmol) was dissolved in methanol (5 ml) and NH_4F (0.30 g, 8.1 mmol) was added. The reaction mixture was kept standing overnight. Methanol was evaporated and the residue was chromatographed on silica gel to afford mixture of diastereomers **5** (0.44 g, 83%). ^{1}H-NMR ($CDCl_3$): 8.61 (br s, 1H) NH; 8.36 (br s, 1H) NH; 7.32-7.11 (m, 26H) arom; 6.82 (m, 4H) arom; 5.94 (dd, $J_{1',2'} = J_{1',2''} = 4.6$ Hz, 1H) and 5.83 (dd, $J_{1',2'} = J_{1',2''} = 4.7$ Hz, 1H) H1'; 5.72 (m, 2H) H8; 5.18-4.90 (m. 4H) H9 + H9'; 3.78 (s, 6H) OMe; 3.67 (m, 8H) H2' + H2" + H3' + H4'; 3.28 (m, 3H) + 3.07 (m, 1H) H5' + H5"; 3.04 (s, 3H) Ms; 2.98 (s, 3H) Ms; 2.44-2.09 (m, 4H) H7 + H7'; 1.72 (d, 1.1 Hz, 3H) and 1.68 (d, 1.1 Hz, 3H) 5-CH_3.

1-[5-*O*-MMTr-3-*O*-(*R/S*)-methanesulfonyl-3-*C*-allyl-2-deoxy-2-*C*-(*E*-carbethoxymethylidene)-2,3-*seco*-β-D-ribofuranosyl]thymine (7). 5 (0.43 g, 0.66 mmol) was oxidized by DCC/DMSO using a reaction condition described for **3**. The aldehyde **6** was dissolved in THF (5 ml) and treated with Ph_3P=$CHCO_2Et$ (0.69 g, 2.0 mmol). After 20 min. the solvent was evaporated and the residue chromatographed on silica gel to afford mixture of diastereomers **7** (0.36 g, 77%). ^{1}H-NMR ($CDCl_3$): 8.53 (br s, 1H) NH; 8.36 (br s, 1H) NH; 7.72-

7.21 (m, 25H) arom; 6.92 (q, 1.1 Hz, 1H) H6; 6.82 (m, 4H) arom; 6.73 (dd, $J_{1',2'}$ =3.5 Hz, $J_{2',10}$ = 15.6 Hz, 1H) H2'; 6.62 (dd, $J_{1',10}$ = 1.7 Hz, 1H) H1'; 6.29 (dd, 1H) H10; 6.74 (dd, $J_{1',2'}$ =3.8 Hz, $J_{2',10}$ = 15.7 Hz, 1H) H2'; 6.50 (dd, $J_{1',10}$ = 1.6 Hz, 1H) H1'; 6.32 (dd, 1H) H10; 5.75 (m, 2H) H8; 5.17-4.95 (m, 4H) H9 + H9'; 4.26 (q, 7.2 Hz, 4H) $OC\underline{H}_2CH_3$; 3.94 (m, 1H) H3'; 3.85 (m, 1H) H3'; 3.80 (s, 6H) OMe; 3.48 (m, 2H) H4'; 3.29-3.02 (m, 4H) H5' + H5"; 3.01 (s, 3H) Ms; 2.92 (s 3H) Ms; 2.61-2.19 (m, 4H) H7 + H7'; 1.74 (d, 1.1 Hz, 3H) 5-CH_3; 1.72 (d, 3H) 5-CH_3; 1.32 (t, 6H) $OCH_2C\underline{H}_3$.

1-[5-*O*-MMTr-3-deoxy-3-(*R/S*)-bromo-3-*C*-allyl-2-deoxy-2-*C*-(*E*-carbethoxymethylidene)-2,3-*seco*-β-D-ribofuranosyl]thymine (8). **7** (0.34 g, 0.47 mmol) was treated by LiBr (0.40 g, 4.7 mmol) in DMF (5 ml) at 120° C for 2 h. Then the voltiles were removed in vacuo, and the residue was chromatographed on silica gel to afford mixture of diastereomers **8** (0.20 g, 61%) ^{1}H-NMR ($CDCl_3$): 8.35 (br s, 1H) NH; 8.28 (br s, 1H) NH; 7.42-7.14 (m, 24H) arom; 6.82 (m, 4H) arom; 6.89 (q, 1.2 Hz, 1H) H6; 6.87 (q, 1.3 Hz, 1H) H6; 6.71 (dd, $J_{1',2'}$ =3.5 Hz, $J_{2',10}$ = 15.7 Hz, 1H) H2'; 6.61 (dd, $J_{1',10}$ = 1.8 Hz, 1H) H1'; 6.35 (dd, 1H) H10; 6.68 (dd, $J_{1',2'}$ =3.8 Hz, $J_{2',10}$ = 15.7 Hz, 1H) H2'; 6.53 (dd, $J_{1',10}$ = 1.8 Hz, 1H) H1'; 6.36 (dd, 1H) H10; 5.79 (m, 2H) H8; 5.18-5.01 (m, 4H) H9 + H9'; 4.37 (m, 1H) H3'; 4.26 (m, 1H) H3'; 4.25 (q, 7.2 Hz, 4H) $OC\underline{H}_2CH_3$; 3.98 (m, 2H) H4'; 3.78 (s, 6H) OMe; 3.42-3.00 (m, 4H) H5' + H5"; 2.70-2.42 (m, 4H) H7 + H7'; 1.73 (m, 6H) 5-CH_3; 1.31 (t, 6H) $OCH_2C\underline{H}_3$.

1-[5-*O*-MMTr-2,3-dideoxy-2-*C*,3-*C*-((8-(*R*)-methyl-9-(*S*)-ethoxycarbonyl)-trimethylene)-β-D-ribofuranosyl]thymine (9) and **1-[5-*O*-MMTr-2,3-dideoxy-2-*C*,3-*C*-((8-(*S*)-methyl-9-(*S*)-ethoxycarbonyl)-trimethylene)-β-D-ribofuranosyl]thymine (11).** **8** (0.19 g, 0.27 mmol) was dissolved in toluene (3 ml) and treated with Bu_3SnH (1.2 equiv) at 95° C for 2 h. The solvent was evaporated and the residue chromatographed on silica gel to afford **9** (69 mg, 41%) and **11** (71 mg, 42%). **9 :** ^{1}H-NMR ($CDCl_3$): 7.92 (br s, 1H) NH; 7.47-7.22 (m, 13H) arom; 6.83 (m, 2H) arom; 6.02 (d, 4.9 Hz, 1H) H1'; 4.16 (q, 7.2 Hz, 2H) $OC\underline{H}_2CH_3$; 3.98 (m, 1H) H4'; 3.80 (s, 3H) OMe; 3.36 (dd, $J_{4',5'}$ = 3.3 Hz, $J_{5',5''}$ = 10.4 Hz, 1H) H5'; 3.25 (dd, $J_{4',5''}$ = 4.4 Hz, 1H) H5"; 3.04 (ddd, $J_{2',3'}$ = 10.4 Hz, $J_{2',9}$ = 7.7 Hz, 1H) H2'; 2.88 (m, 1H) H3'; 2.50 (dd, $J_{9,8}$ = 10.6 Hz, 1H) H9; 2.36 (m, 1H) H8; 2.11 (ddd, $J_{8,7}$ = 7.3 Hz, $J_{3',7}$ = 13.0 Hz, $J_{7,7'}$ = 14.5 Hz, 1H) H7; 1.59 (d, 1.1 Hz, 3H) 5-CH_3; 1.34 (ddd, $J_{8,7'}$ = 6.8 Hz, $J_{3',7'}$ = 7.7 Hz, 1H) H7'; 1.23 (t, 3H) $OCH_2C\underline{H}_3$; 1.14 (d, 6.3 Hz, 3H) 8-Me. ^{13}C-NMR: 173.7 (s) $\underline{C}OOEt$; 163.2 (s) C4; 149.9 (s) C2; 135.5 (d, 194.3 Hz) C6; 110.7 (s) C5; 90.0 (d, 165.0 Hz) C1'; 85.7 (d, 153.0 Hz) C4'; 63.3 (t, 145.2 Hz) C5'; 60.7 (t, 146.6 Hz) $O\underline{C}H_2CH_3$; 56.0 (d, 138.4 Hz) C2'; 54.7 (d, 135.6 Hz) C3'; 55.1 (q, 143.9 Hz) OMe; 45.2 (d, 141.1 Hz) C9; 42.4 (d, 132.9 Hz) C8; 29.6 (t, 126.0 Hz) C7; 18.6 (q, 126.5 Hz) 8-Me; 14.2 (q, 129.5 Hz) $OCH_2\underline{C}H_3$; 12.0 (q, 122.2 Hz) 5-Me.

11: ^{1}H-NMR ($CDCl_3$ + CD_3OD): 7.48-7.21 (m, 13H) arom; 6.84 (m, 2H) arom; 5.83 (d, 5.4 Hz, 1H) H1'; 4.12 (m, 2H) $OC\underline{H}_2CH_3$; 3.78 (s, 3H) OMe; 3.70 (m, $J_{3',4'}$ = 4.7 Hz, 1H) H4'; 3.34 (dd, $J_{4',5'}$ = 3.6 Hz, $J_{5',5''}$ = 10.3 Hz, 1H) H5'; 3.30 (dd, $J_{4',5''}$ = 4.6 Hz, 1H) H5"; 2.99 (dd, $J_{2',9}$ = 2.2 Hz, $J_{9,8}$ = 7.2 Hz, 1H) H9; 2.91 (m, 2H) H2' + H3'; 2.51 (m, 1H) H8; 1.72-1.58 (m, 2H) H7 + H7'; 1.72 (d, 1.1 Hz, 3H) 5-CH_3; 1.26 (t, 7.2 Hz, 3H) $OCH_2C\underline{H}_3$; 1.01 (d, 6.8 Hz, 3H) 8-Me. ^{13}C-NMR: 173.5 (s) $\underline{C}OOEt$; 158.5 (s) C4; 143.9 (s) C2; 135.4 (d, 181.9 Hz) C6; 111.3 (s) C5; 89.2 (d, 164.3 Hz) C1'; 84.9 (d, 150.6 Hz) C4'; 64.6 (t, 141.8 Hz) C5'; 60.4 (t, 146.6 Hz) $O\underline{C}H_2CH_3$; 55.1 (q, 143.8 Hz) OMe; 54.0 (d, 134.0 Hz) C2'; 51.9 (d, 132.0 Hz) C3'; 45.2 (d, 136.0 Hz) C9; 37.0 (d, 135.0 Hz) C8; 29.5 (t, 125.7 Hz) C7; 15.4 (q, 125.2 Hz) 8-Me; 14.1 (q, 131.4 Hz) $OCH_2\underline{C}H_3$; 12.0 (q, 122.0 Hz) 5-Me.

1-[2,3-dideoxy-2-*C*,3-*C*-((8-(*R*)-methyl-9-(*S*)-ethoxycarbonyl)-trimethylene)-β-D-ribofuranosyl]thymine (10) **9** (69 mg, 0.11 mmol) was treated 90% aq. acetic acid (3 ml) at RT for 12 h. The solvent was removed in vacuo. The residue was purified by silica gel column chromatography to give **10** (34 mg, 87%). ^{1}H-NMR ($CDCl_3$): 8.13 (br s, 1H) NH; 7.30 (q, 1.2 Hz, 1H) H6; 5.97 (d, 4.7 Hz, 1H) H1'; 4.14 (q, 7.1 Hz, 2H) $OC\underline{H}_2CH_3$; 3.93 (m, 1H) H4'; 3.89 (dd, $J_{4',5'}$ = 2.7 Hz, $J_{5',5''}$ = 11.8 Hz, 1H) H5'; 3.69 (dd, $J_{4',5''}$ = 4.2 Hz, 1H) H5''; 3.05 (ddd, $J_{2',3'}$ = 10.5 Hz, $J_{2',9}$ = 8.5 Hz, 1H) H2'; 2.92 (m, $J_{3',4'}$ = 7.0 Hz, $J_{3',7}$ = $J_{3',7'}$ = 7.4 Hz, 1H) H3'; 2.45 (dd, $J_{9,8}$ = 11.0 Hz, 1H) H9; 2.41 (m, 1H) H8; 2.19 (ddd, $J_{8,7}$ = 7.4 Hz, $J_{3',7}$ = 7.9 Hz, $J_{7,7'}$ = 12.9 Hz, 1H) H7; 1.90 (d, 1.1 Hz, 3H) 5-CH_3; 1.22 (t, 3H) $OCH_2C\underline{H}_3$; 1.20 (ddd, $J_{8,7'}$ = 10.7 Hz, $J_{3',7'}$ = 7.7 Hz, 1H) H7'; 1.15 (d, 6.4 Hz, 3H) 8-Me. ^{13}C-NMR: 173.4 (s) $\underline{C}OO$; 163.2 (s) C4; 149.9 (s) C2; 136.2 (d, 179.6 Hz) C6; 110.9 (s) C5; 90.9 (d, 165.9 Hz) C1'; 87.3 (d, 147.5 Hz) C4'; 63.1 (t, 142.5 Hz) C5'; 60.8 (t, 147.5 Hz) $O\underline{C}H_2CH_3$; 55.7 (d, 140.2 Hz) C2'; 55.0 (d, 136.6 Hz) C3'; 43.8 (d, 140.2 Hz) C9; 42.1 (d, 133.8 Hz) C8; 38.7 (t, 129.2 Hz) C7; 18.6 (q, 125.8 Hz) 8-Me; 14.9 (q, 126.5 Hz) $OCH_2\underline{C}H_3$; 12.4 (q, 129.2 Hz) 5-Me. λ_{max} = 266 nm (EtOH). HRMS (FAB$^-$): calcd. for (M-H)$^-$ 351.1556, found 351.1589.

1-[2,3-dideoxy-2-*C*,3-*C*-((8-(*S*)-methyl-9-(*S*)-ethoxycarbonyl)-trimethylene)-β-D-ribofuranosyl]thymine (12) **11** (71 mg, 0.11 mmol) was deprotected using a reaction condition described for **10** to give **12** (34 mg, 84%). ^{1}H-NMR (500 MHz, $CDCl_3$): 8.43 (br s, 1H) NH; 7.23 (q, 1.1 Hz, 1H) H6; 5.81 (d, 5.2 Hz, 1H) H1'; 4.12 (m, 2H) $OC\underline{H}_2CH_3$; 3.90 (m, $J_{4',5'}$ = 2.0 Hz, 1H) H5'; 3.77-3.68 (m, $J_{3',4'}$ = 8.3 Hz, $J_{4',5''}$ = 5.1 Hz, 2H) H5'' + H4'; 2.98-2.93 (m, $J_{2',3'}$ = 10.4 Hz, $J_{2',9}$ = 0.7 Hz, 3H) H2' + H3' + H9; 2.56 (m, $J_{8,9}$ = 7.1 Hz, 1H) H8; 1.93 (d, 1.1 Hz, 3H) 5-CH_3; 1.74 (ddd, $J_{8,7}$ = 10.4 Hz, $J_{3',7}$ = 7.5 Hz, $J_{7,7'}$ = 12.8 Hz, 1H) H7; 1.62 (ddd, $J_{8,7'}$ = 6.5 Hz, $J_{3',7'}$ = 1.9 Hz, 1H) H7'; 1.25 (t, 7.2 Hz, 3H) $OCH_2C\underline{H}_3$; 1.03 (d, 6.4 Hz, 3H) 8-Me. ^{13}C-NMR: 173.2 (s) $\underline{C}OOEt$; 163.2 (s) C4; 150.2 (s) C2; 135.6 (d, 178.7 Hz) C6; 111.5 (s) C5; 89.6 (d, 164.1 Hz) C1'; 86.2 (d, 145.7 Hz) C4'; 63.4 (t, 145.5 Hz) C5'; 60.5 (t, 147.6 Hz) $O\underline{C}H_2CH_3$; 53.4 (d, 139.3 Hz) C2'; 52.0 (d, 131.0 Hz) C3'; 44.0 (d, 138.4 Hz) C9; 37.2 (d, 157.6 Hz) C8; 36.8 (t, 115.0 Hz) C7; 15.5 (q, 126.5 Hz) 8-Me; 14.2 (q, 126.5 Hz) $OCH_2\underline{C}H_3$; 12.4 (q, 129.2 Hz) 5-Me. λ_{max} = 266 nm (EtOH). HRMS (FAB$^-$): calcd. for (M-H)$^-$ 351.1556, found 351.1525.

1-[5-*O*-MMTr-3-deoxy-3-*C*-(allylidene)-2-deoxy-2-*C*-(*E*-carbethoxymethylidene)-2,3-*seco*-β-D-ribofuranosyl]thymine (18). **16** (156 mg, 0.26 mmol) was oxidized by DCC/DMSO mixture using a reaction condition described for **3**. Aldehyde **17** was treated by Ph_3P=CH-CH=CH_2[17] (0.26 mmol) in THF (5 ml). The solvent was removed in vacuo. The residue was purified by silica gel column chromatography to give **18** (61 mg, 38%). **18** (*cis*-isomer): ^{1}H-NMR (500 MHz, $CDCl_3$): 7.45-6.80 (m, 13H) arom; 6.82 (m, 2H) arom; 6.76 (dd, $J_{1',2'}$ = 3.4 Hz, $J_{2',10}$ = 15.5 Hz, 1H) H2'; 6.38 (dd, 1H) H1'; 6.33 (dd, 1H) H10; 6.25 (m, $J_{8,9}$ = 16.3 Hz, 1H) H8; 6.24 (m, 1H) H7; 5.28 (m, 1H) + 5.17 (m, 1H) H9 + H9'; 5.17 (m, $J_{4',3'}$ = 8.2 Hz, 1H) H3'; 4.24 (q, 2H) $OC\underline{H}_2CH_3$; 3.80 (s, 3H) OMe; 3.42 (dd, $J_{4',5'}$ = 8.1 Hz, $J_{5',5''}$ = 10.7 Hz, 1H) H5'; 4.36 (m, 1H) H4'; 3.07 (dd, $J_{4',5''}$ = 3.0 Hz, 1H) H5'';1.80 (d, 3H) 5-CH_3; 1.33 (t, 3H) $OCH_2C\underline{H}_3$. **18** (*trans*-isomer): ^{1}H-NMR (500 MHz, $CDCl_3$): 7.45-6.80 (m, 13H) arom; 6.82 (m, 2H) arom; 6.74 (dd, $J_{1',2'}$ = 3.4 Hz, $J_{2',10}$ = 15.6 Hz, 1H) H2'; 6.38 (dd, 1H) H1'; 6.29 (dd, 1H) H10; 6.32 (m, $J_{8,7}$ = 10.5 Hz, $J_{8,9''}$ = 1.7 Hz, 1H) H8; 6.21 (m, $J_{3',7}$ = 14.5 Hz, 1H) H7; 5.39 (m, $J_{4',3'}$ = 8.1 Hz, 1H) H3'; 5.28 (m, 1H) + 5.23 (m, 1H) H9' + H9''; 4.24 (q, 2H)

OCH_2CH_3; 3.80 (s, 3H) OMe; 3.37 (dd, $J_{4',5'}$ = 8.1 Hz, $J_{5',5''}$ = 10.7 Hz, 1H) H5'; 4.90 (m, 1H) H4'; 3.06 (dd, $J_{4',5''}$ = 2.3 Hz, 1H) H5''; 1.80 (d, 3H) 5-CH_3; 1.32 (t, 3H) OCH_2CH_3.

1-[5-*O*-MMTr-2,3-dideoxy-2-*C*,3-*C*-((10-(*S*)-ethoxycarbonyl)-7-butenylene)-β-D-ribofuranosyl]thymine (19): **18** (61 mg, 0.1 mmol) was heated in toluene (3 ml) at 100° C for 12 h. The solvent was removed in vacuo. The residue was purified by silica gel column chromatography to give **19** (42 mg, 69%). ^{1}H-NMR ($CDCl_3$): 7.97 (br s, 1H) NH; 7.61 (q, 1.0 Hz, 1H) H6; 7.48-7.23 (m, 12H) arom; 6.82 (m, 2H) arom; 6.08 (d, 5.1 Hz, 1H) H1'; 5.83 (m, $J_{8,3'}$ = 1.8 Hz, $J_{8,7}$ = 10.0 Hz, $J_{8,9}$ = $J_{8,9'}$ = 3.9 Hz, 1H) H8; 5.49 (m, $J_{3',7}$ = 3.5 Hz, 1H) H7; 4.21 (m, 2H) OCH_2CH_3; 3.87 (ddd, $J_{4',3'}$ = 7.1 Hz, 1H) H4'; 3.80 (s, 3H) OMe; 3.53 (dd, $J_{4',5'}$ = 2.7 Hz, $J_{5',5''}$ = 10.6 Hz, 1H) H5'; 3.30 (dd, $J_{4',5''}$ = 3.2 Hz, 1H) H5''; 3.12 (m, 1H) H3'; 2.90 (ddd, $J_{2',3'}$ = $J_{2',10}$ = 8.2 Hz, 1H) H2'; 2.66 (ddd, $J_{10,9}$ = $J_{10,9'}$ = 6.4 Hz, 1H) H10; 2.43 (m, 2H) H9 + H9'; 1.52 (d, 3H) 5-CH_3; 1.26 (t, 7.1 Hz, 3H) OCH_2CH_3. ^{13}C-NMR: 173.6 (s) COOEt; 163.6 (s) C4; 150.2 (s) C2; 135.7 (d, 177.8 Hz) C6; 126.6 (d) and 124.6 (d) C7 and C8; 111.0 (s) C5; 87.0 (d, 168.6 Hz) C1'; 83.7 (d, 147.6 Hz) C4'; 63.7 (t, 143.0 Hz) C5'; 61.1 (t, 148.0 Hz) OCH_2CH_3; 55.1 (q, 143.9 Hz) OMe; 44.8 (d, 143.0 Hz) C2'; 38.0 (d, 137.7 Hz) C3' + C10; 25.2 (t, 130.1 Hz) C9; 14.1 (q, 126.8 Hz) OCH_2CH_3; 11.8 (q, 128.9 Hz) 5-Me.

1-[2,3-dideoxy-2-*C*,3-*C*-((10-(*S*)-ethoxycarbonyl)-7-butenylene)-β-D-ribofuranosyl]thymine (20): **19** (42 mg, 0.067 mmol) was deprotected using a reaction condition described for **10** to give **20** (20 mg, 84%). ^{1}H-NMR ($CDCl_3$): 8.43 (br s, 1H) NH; 7.40 (q, 1.2 Hz, 1H) H6; 5.96 (d, 3.9 Hz, 1H) H1'; 5.89 (m, $J_{8,3'}$ = 1.7 Hz, $J_{8,7}$ = 10.0 Hz, $J_{8,9}$ = 4.9 Hz, $J_{8,9'}$ = 2.5 Hz, 1H) H8; 5.64 (m, $J_{3',7}$ = 4.0 Hz, $J_{7,9}$ and $J_{7,9'}$ 1.6 and 2.4 Hz, 1H) H7; 4.18 (m, 2H) OCH_2CH_3; 4.02 (m, $J_{4',5'}$ = 2.3 Hz, 1H) H5'; 3.84-3.75 (m, $J_{4',5''}$ = 3.3 Hz, $J_{5',5''}$ = 12.1 Hz, 2H) H4' + H5''; 3.10 (m, 1H) H3'; 2.77 (ddd, $J_{2',3'}$ = 8.4 Hz, $J_{2',10}$ = 10.1 Hz, 1H) H2'; 2.63 (ddd, $J_{10,9}$ = 5.3 Hz, $J_{10,9'}$ = 9.5 Hz, 1H) H10; 2.51-2.06 (m, $J_{9,9'}$ = 17.7 Hz, 2H) H9 + H9'; 1.91 (d, 3H) 5-CH_3; 1.26 (t, 7.2 Hz, 3H) OCH_2CH_3. ^{13}C-NMR: 173.8 (s) COO; 163.4 (s) C4; 150.0 (s) C2; 136.6 (d, 178.7 Hz) C6; 127.0 (d, 166.8 Hz) and 123.8 (d, 162.6 Hz) C7 and C8; 110.9 (s) C5; 89.0 (d, 166.8 Hz) C1'; 84.9 (d, 147.5 Hz) C4'; 62.0 (t, 142.5 Hz) C5'; 61.2 (t, 149.8 Hz) OCH_2CH_3; 44.7 (d, 141.1 Hz) C2'; 39.4 (d, 136.0 Hz) C10; 37.3 (d, 136.1 Hz) C3'; 26.3 (t, 130.6 Hz) C9; 14.0 (q, 127.1 Hz) OCH_2CH_3; 12.4 (q, 129.2 Hz) 5-Me. λ_{max} = 266 nm (EtOH). HRMS (FAB^-): calcd. for $(M-H)^-$ 349.1400, found 349.1411.

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(22) (a) The observed $^3J_{4'5'}$ and $^3J_{4'5''}$ are weighted time-averaged coupling constants related to the couplings of individual conformers and their respective populations. Limiting values for $J_{4'5'}$ and $J_{4'5''}$ in the staggered C4'-C5' rotamers are as follows: γ+ : $J_{4'5'}$ = 2.4 Hz, $J_{4'5''}$ = 1.3 Hz. Rotamer γ^t : $J_{4'5'}$ = 2.6 Hz, $J_{4'5''}$ = 10.5 Hz. Rotamer γ^- : $J_{4'5'}$ = 10.6 Hz, $J_{4'5''}$ = 3.8 Hz. (b) Haasnoot, C.A.G.; de Leeuw, F.A.A.M.; de Leeuw, H.P.M.; Altona, C. *Recl. Trav. Chim. Pays-bas* **1979**, *98*, 576.
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