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Synthesis of 2',3'-*cis* -Fused Pyrrolidino-β-D-nucleosides and Their Conformational Analysis by 500 MHz ^{1}H-NMR

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Abstract. *The unique "off-template" stereoselectivity in the intramolecular free radical cyclization of 3-aza-5-hexenyl endocyclic radical has been demonstrated for the first time through the synthesis of 2',3'-cis-fused pyrrolidino-β-D-nucleosides,* ***19a, 20a, 21a, 22a, 23a, 35a, 36a, 37a and 38a****, which are not hithertofore available by any known procedures. The 2'-linked chiral carbon (C_C) in* ***19a, 20a, 21a*** *and* ***22a*** *has shown 25:1 to 10:1 stereoselectivity depending upon the bulk of its substituent. The 3'-linked chiral carbon (C_C) in* ***35a, 36a*** *and* ***37a****, on the other hand, has shown only 4:1 to 2:1 stereoselectivity. Finally, a full conformational analysis of 2',3'-cis-fused pyrrolidino-β-D-nucleosides* ***19a, 20a, 21a, 22a, 23a, 35a, 36a, 37a*** *and* ***38a*** *is reported using ^{1}H-NMR at 500 MHz. The solution geometry of the furanose and the pyrrolidine rings were studied on the basis of vicinal proton-proton coupling constants using the concept of pseudorotation. The furanose rings in* ***19a - 23a*** *have a geometry biased toward a South-type conformation [70 - 81 % S, 126° < P_S < 131° (C1'-exo-C2'-endo), 28° < Ψ_m < 32°, rms error ±0.05]. In compounds* ***35a - 38a****, the riboses have a conformation biased toward the North-type [~90 % N, 20° < P_N < 38° (C3'-endo) and 27° < Ψ_m < 30°, rms error ±0.05]. In compounds* ***19a - 22a****, the pyrrolidine geometry is biased toward the North-type conformation (C2'-exo), with a phase angle of pseudorotation Q_N ~ -28° and a puckering amplitude Ψ^*_m ~40° (rms error ±0.5). In compounds* ***35a - 37a****, the pyrrolidine has a geometry biased toward a South-type conformation (C2'-endo), with Q_S ~ 175° and Ψ^*_m ~ 39° (rms error ±0.8). The furanose and the pyrrolidine rings share the C2'-C3' bond and have correlated conformations. The pyrrolidine adopts a North-type conformation in* ***19a - 22a*** *when the ribose is in a South-type conformation. In contrast, the pyrrolidine ring adopts a South-type conformation when the ribose is in a North-type conformation (in* ***35a - 37a****). Compounds* ***19a - 23a*** *and* ***35a - 38a*** *show a preference for the γ^+ conformation (~70%). The glycosyl conformation for all pyrrolidine-fused systems was found to be anti.*

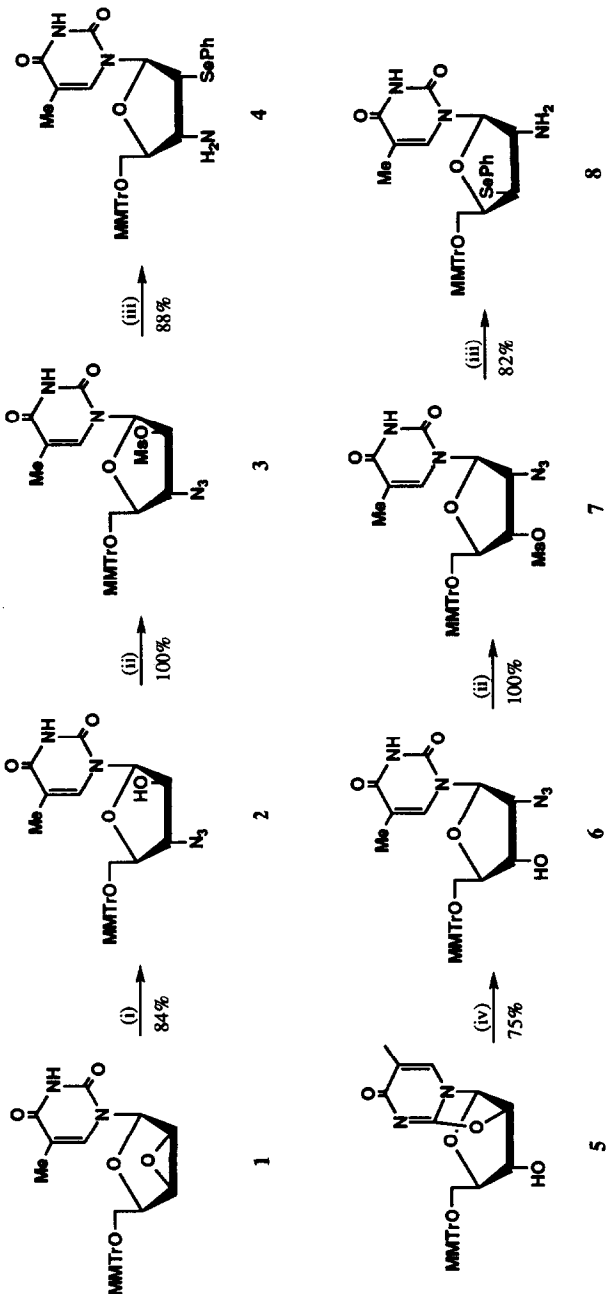
Last decade has witnessed an enormous success in the exploitation of intramolecular free radical cyclization as a powerful tool for carbon-carbon bond formation in organic synthesis,[1] especially for the construction of poly-ring system found in complex natural products.[2] New synthetic methods to produce various structurally modified nucleosides have been also intensely investigated in a search to discover various biologically and pharmaceutically active compounds,[3] especially after the discovery of anti-HIV activities[4a] of several modified nucleosides.[4b,c] The need to search for new therapeutics and to better understand the structural and functional properties of nucleosides and their analogues as well as the

synthetic challenge to generate new categories of modified nucleosides have justified our longstanding interest in the synthesis of *furanose-modified* nucleosides.[5,6]

Recently, we have successfully utilized the intramolecular free radical cyclization methodology[1,2] as a powerful means for the introduction of C-branching at 2'- / 3'-centers of β-D-nucleosides.[6] We have already shown that the intramolecular free radical cyclization reaction[1,2] is an efficient method to functionalize both 2'- and 3'-carbons of uridine to give various *cis*-fused furano derivatives through the generation of endocyclic free-radical at the vicinal 2'- or 3'-center[6a,7] followed by its trapping by the allyl or propargyl group tethered to either 3'- or 2'-hydroxyl group. We herein report stereoselective intramolecular free radical cyclization of 3-aza-5-hexenyl endocyclic radical generated from the 2',3'-dideoxy-2'/3'-allylamino-2'/3'-phenylseleno nucleosides (**14a, 15a, 16a, 17a, 18a, 30a, 31a, 32a, 33a**) to synthesize a new class of hithertofore unknown nucleoside analogue (*i.e.* 2',3'-*cis*-fused pyrrolidino-β-D-nucleosides: **19a, 20a, 21a, 22a, 23a, 35a, 36a, 37a, 38a**) for their biological evaluations and structural study. The synthesis of pyrrolidino nucleosides is also further justified due to the findings that 2'-deoxy-2'-amino and 3'-deoxy-3'-amino ribonucleosides possess unique antibacterial, anticancer and biosynthetic inhibitory activities.[3d] Some polysubstituted pyrrolidines and their fused forms occurring in complex alkaloids also exhibit interesting antibacterial and central nervous system activity, they also show activities against cardiac diseases and hypertensions.[8] The intramolecular cyclization reactions of 1-aza-5-hexenyl radical,[9] and 2-aza-5-hexenyl radical,[10] and 4-aza-5-hexenyl radical[18] have been previously studied in natural product synthesis. The synthetic application of 3-aza-5-hexenyl radical[11-17] has been shown mainly with the simple acyclic radicals in which no "off-template" stereoselectivity has been established. This is the first report of the intramolecular free radical cyclization of 3-aza-5-hexenyl endocyclic radicals demonstrating the unique "off-template" stereoselectivity at a prochiral center.

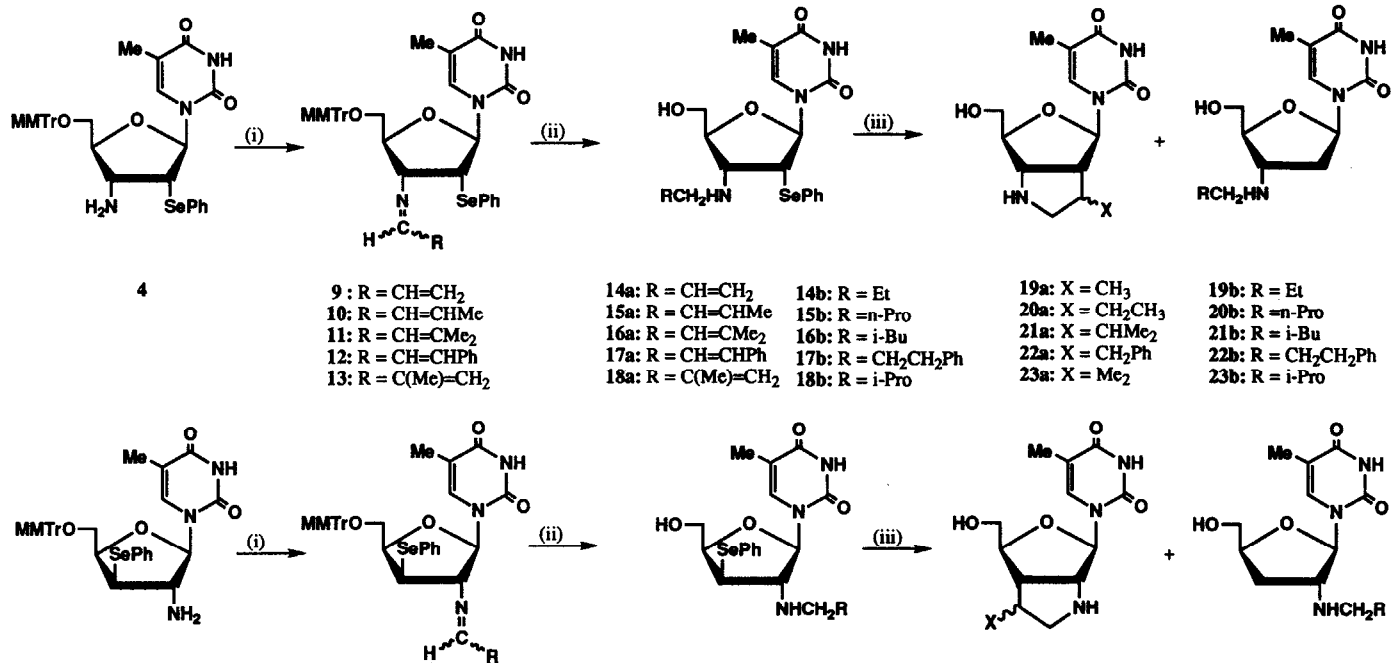
Results and Disscusions

Preparation of free radical precursors. 1-(5'-O-(MMTr)-2',3'-dideoxy-2'-phenylseleno-3'-amino-β-D-ribofuranosyl)thymine **4** was prepared in 88% yield from 1-(5'-O-(MMTr)-2'-methanesulphonyl-3'-deoxy-3'-azido-β-D-arabinofuranosyl)thymine **3** which was synthesized in a high yield through regiospecific epoxide-opening[19] of 1-(5'-O-(MMTr)-2',3'-O-anhydro-β-D-lyxofuranosyl)thymine **1**[20] by azide anion, followed by methanesulphonylation [**1** → **2** → **3** → **4**, (Scheme 1)]. The "one-pot" conversion of **3** → **4** simultaneously involves both the nucleophilic substitution reaction of 2'-methanesulphonyl group by the $PhSe^-$ anion [from $(PhSe)_2$ with $NaBH_4$[6c]] and the reduction of 3'-azido group to 3'-amino by the excess of NaSePh and $NaBH_4$ in THF-EtOH solution at reflux temperature. Clearly, the reagent, $(PhSe)_2/NaBH_4$, has served as a source of both the nucleophile to introduce 2'-phenylseleno group and the reducing agent for the reduction of the 3'-azido group. To the best of our knowledge, this is the first example of such dual transformation achieved simultaneously in one step using $(PhSe)_2/NaBH_4$. It is likely that the strong nucleophicility of $PhSe^-$ anion facilitates the reduction of the 3'-azido group, through the initial attack at the terminal nitrogen of the $R\text{-}N_3$ with the formation of a triazene (RNH-N=N-SePh) which is reduced *in situ* rapidly by the $NaBH_4$ to the primary amine.[21] Similarly, 1-(5'-O-(MMTr)-2',3'-dideoxy-2'-amino-3'-phenylseleno-β-D-xylofuranosyl) thymine **8** was prepared in 82% yield using



Reaction Condition: (i) NaN_3, NH_4Cl, DMF, 120°C, 6–10 h; (ii) MsCl, pyridine, 0–20°C, overnight; (iii) $(PhSe)_2$, $NaBH_4$, EtOH-THF, reflux, overnight; (iv) NaN_3, DMF, 120°C, ~48 h.

Scheme 1



4

9 : R = $CH{=}CH_2$
10: R = $CH{=}CHMe$
11: R = $CH{=}CMe_2$
12: R = $CH{=}CHPh$
13: R = $C(Me){=}CH_2$

14a: R = $CH{=}CH_2$ **14b**: R = Et
15a: R = $CH{=}CHMe$ **15b**: R = n-Pro
16a: R = $CH{=}CMe_2$ **16b**: R = i-Bu
17a: R = $CH{=}CHPh$ **17b**: R = CH_2CH_2Ph
18a: R = $C(Me){=}CH_2$ **18b**: R = i-Pro

19a: X = CH_3 **19b**: R = Et
20a: X = CH_2CH_3 **20b**: R = n-Pro
21a: X = $CHMe_2$ **21b**: R = i-Bu
22a: X = CH_2Ph **22b**: R = CH_2CH_2Ph
23a: X = Me_2 **23b**: R = i-Pro

8

24: R = $CH{=}CH_2$
25: R = $CH{=}CHMe$
26: R = $CH{=}CMe_2$
27: R = $CH{=}CHPh$
28: R = $C(Me){=}CH_2$

29a: R = $CH{=}CH_2$ **29b**: R = Et
30a: R = $CH{=}CHMe$ **30b**: R = n-Pro
31a: R = $CH{=}CMe_2$ **31b**: R = i-Bu
32a: R = $CH{=}CHPh$ **32b**: R = CH_2CH_2Ph
33a: R = $C(Me){=}CH_2$ **33b**: R = i-Pro

34a: X = CH_3 **34b**: R = Et
35a: X = CH_2CH_3 **35b**: R = n-Pro
36a: X = $CHMe_2$ **36b**: R = i-Bu
37a: X = CH_2Ph **37b**: R = CH_2CH_2Ph
38a: X = Me_2 **38b**: R = i-Pro

Reaction Condition: (i) RCHO, 4 Å molecular sieve, $(CH_2Cl)_2$, ~20°C; (ii) $NaCNBH_3$, 80% HOAc, ~20°C, overnight; (iii) n-Bu_3SnH, AIBN (cat.), benzene, reflux.

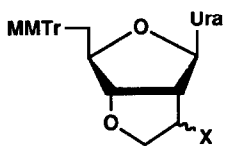
Scheme 2

"$(PhSe)_2/NaBH_4$" system from 1-(5'-O-(MMTr)-2'-deoxy-2'-azido-3'-methanesulphonyl-β-D-ribofuranosyl)thymine **7** which was synthesized in a high yield through the nucleophilic attack of azide anion[22] on 1-(5'-O-(MMTr)-2,2'-O-anhydro-β-D-arabinofuranosyl)thymine **5**[6c] followed by methanesulphonylation [**5** → **6** → **7** → **8**, (Scheme 1)].

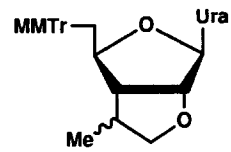
Attempts to perform monoalkylation of 3'/2'-amino group in **4** or **8** under different basic alkylating conditions were not successful in our hands, we therefore turned our attention to the reductive monoalkylation of amino group.[23] It is noteworthy that the reductive monoalkylation of amino group proceeds (**4** / **8** → **9** - **13** or **25** - **28** → **14** - **18** or **30** - **33**) in quite acceptable yield (60-85%) through a "one-pot-two-step" sequence (Scheme 2). This facile conversion however does not work in our hands for the following reaction sequence: **8** → **24** → **29**. The "one-pot-two-step" sequence consists of, first, formation of the imine by reacting the 2'-amino (in **8**) or 3'-amino (in **4**) group with different α,β-unsaturated aldehydes in the presence of 4Å molecular sieve which proceed very well in all cases as indicated by Tlc analysis;[24] second step involves the selective reduction of the 2'- or 3'-imine in **9** - **13** or **24** - **28** by $NaCNBH_3$[25] in acetic acid which also removed 5'-O-MMTr group to give **14** - **18** or **30** - **33**. It is noteworthy that the "overreduction" of α,β-unsaturated imine systems in **9** - **13** or **24** - **28** often give undesired by-products (such as **14b** - **18b** or **30b** - **33b** in 0 - 50% yield based on ^{1}H-NMR, see Experimental part) which is not chromatographically separable from the desired β,γ-unsaturated amino nucleosides (**14a** - **18a** or **30a** - **33a**). Therefore, the mixture of by-product and the β,γ-unsaturated amino nucleoside was subjected to the free-radical reaction step to give the reduced **19b** - **23b** and **35b** - **38b** and the cyclized nucleosides **19a** - **23a** and **35a** - **38a**, which can be easily separated (*vide infra*).

Table 1: "Off Template" Stereoselectivity in the Cyclization of 2'-*verus* 3'-Radicals of Nucleosides.

	2'-endocyclic radical							3'-endocyclic radical			
compd.	**19a** X = Me	**20a** X = Et	**21a** X =i-Pro	**22a** X = Bn	**39a**[6a] X = Me	**39b**[6a] X =Pro	**39c**[6a] X =i-Pro	**35a** X = Et	**36a** X =i-Pro	**37a** X = Bn	**40**[6a] X = Me
major / minor	25:1	27:1	15:1	10:1	8:1	4:1	3:2	4:1	4:1	2:1	2:1



39 a -c



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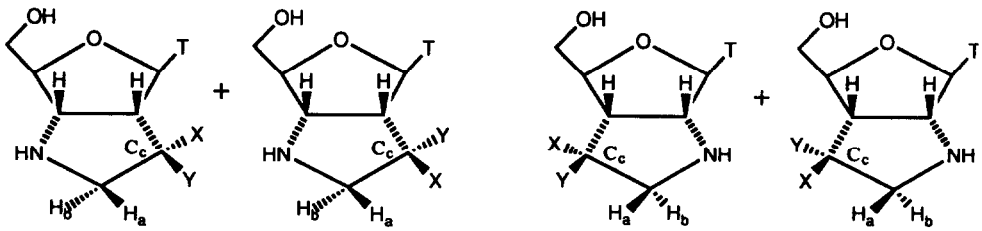
Intramolecular free radical cyclization A solution of tri-n-butyltin hydride (1.5 equiv) and azobisisobutyronitrile (AIBN) in degassed benzene (0.07 M) under an atmosphere of argon was added slowly by a syringe pump into a solution of the free radical precursors (**14**, **15**, **16**, **17**, **18**, **30**, **31**, **32** or **33**) in boiling benzene (~0.01 M) over 2 h. The radical thus generated at 2'- or 3'-carbon was efficiently trapped by the double bond of the allyl group tethered either to the 3'- or 2'-amino group in *ribo* or *xylo* configuration, respectively. The radical efficacy is very high and the efficacy of radical cyclization is almost quantitative. For example, the only product of the radical reaction of pure **17a** was compound **22a**.

The chromatographically homogeneous radical precursors containing by-product due to "overreduction" gave easily separable 2',3'-dideoxy-2'/3'-substituted amino nucleosides (**19b, 20b, 21b, 23b, 35b, 36b, 37b, 38b**) and 2',3'-*cis*-fused pyrrolidino nucleosides (**19a, 20a, 21a, 23a, 35a, 36a, 37a, 38a**) after free radical reaction. Compounds **19a, 20a, 21a, 22a, 35a, 36a, 37a** are all inseparable diastereomeric mixtures due to both axial and equatorial C_c-substituent. They could be however identified spectroscopically (*vide infra*).



19a: X = Me, Y = H
20a: X = Et, Y = H
21a: X = i-Pr, Y = H
22a: X = Bn, Y = H
23a: X = Me, Y = Me

35a: X = Et, Y = H
36a: X = i-Pr, Y = H
37a: X = Bn, Y = H
38a: X = Me, Y = Me

Figure 1: Structure and configuration at the C_c carbon in compounds **19a** - **23a** and **35a** - **38a**. Configurations at the C_c carbon have been determined by 1D differential NOE spectroscopy.

Stereochemistry of the free radical cyclization reaction. It should be noted that (i) 1,2-*cis*-stereochemistry becomes an inevitable outcome due to the five-membered ring-fusion from 3-aza-5-hexenyl endocyclic radical as observed in other 5-hexenyl radical cyclizations.[6, 26-28] The cyclization takes place only in a *cis*-fused manner. Regardless of the configuration of the endocyclic radical generating site, the ring-fusion is governed by the configuration of the anchor-site of the unsaturated system (*i.e.* by the configuration of the 2'- or 3'-amino group). This means that the cyclizations of both *ribo* nucleosides **14a, 15a, 16a, 17a** or **18a** and *xylo* nucleosides **30a, 31a, 32a** or **33a** give only the *ribo* nucleosides **19a, 20a, 21a, 22a, 23a, 35a, 36a, 37a, 38a**. (ii) All intramolecular free radical cyclization reactions reported herein makes a definite choice of 5-*exo* cyclization over 6-*endo* cyclization. Even in the case of quite sterically crowded precursors **18a** or **33a**, the radical reaction gives only 5-*exo* cyclized product **23a** or **38a**, respectively. This is consistent with the work of Padwa *et al.* who have shown that the acyclic 3-aza-5-hexenyl systems, with a large SO_2Ph group on nitrogen, produce exclusively *exo* product, regardless of the substitution of the double bond,[11] which however is in contrast with the theoretical calculation by Spellmeyer and Houk,[29b] who predicted the formation of both 6-*endo* and 5-*exo* products in the intramolecular radical ring closure reaction with substituted olefin. The exclusive formation of the 5-*exo* cyclized products **23a** and **38a** could be due to the result of the complex stereoelectronic factors operating in our system (*vide infra*). (iii) The absolute configuration of the free radical cyclization site has been determined unequivocally by nuclear Overhauser effect (NOE) at 500 MHz (*vide infra*). The 5-*exo* radical ring closure reaction always gives the *cis*-fused product in which the major diastereomer has the C_c-

substituent in the pseudoequatorial geometry in **19a, 20a, 21a, 22a, 35a, 36a, 37a,** although the degree of stereoselectivity for the 2'-endocyclic radical and 3'-endocyclic radical cyclization is considerably different. The configuration of C_c center[31] in the major diastereomers **19a, 20a, 21a, 22a** is R and the configuration of the corresponding center in the minor diastereomer **19a', 20a', 21a', 22a'** is assigned as S

Table 2: ^{1}H-NMR chemical shifts at 500 MHz at 25° C (ppm, referred to TMS set at 0.00 ppm) for the major diastereoisomer of compounds **19a - 23a** and **35a - 38a.**

	19a	**20a**	**21a**	**22a**	**23a**	**35a**	**36a**	**37a**	**38a**
H1'	6.02	6.06	6.04	6.09	5.99	5.61	5.63	5.59	5.61
H2'	2.78	2.86	2.89	2.88	2.36	4.05	4.03	4.08	4.06
H3'	4.04	4.02	4.04	4.04	4.08	2.98	3.07	3.01	2.51
H4'	3.69	3.69	3.82	3.70	3.77	4.12	4.14	4.24	4.10
H5'	3.86	3.85	3.85	3.83	3.84	3.93	4.00	3.86	3.94
H5"	3.75	3.73	3.83	3.74	3.73	3.62	3.66	3.55	3.63
H_a	3.14	3.17	3.17	3.09	2.82	3.23	3.17	3.04	2.83
H_b	2.58	2.59	2.67	2.76	2.74	2.65	2.71	2.72	2.75
C_c-H	2.22	2.07	1.78	2.53	/	2.10	1.85	2.50	/
C_c-Me	1.10	0.87	0.92		1.13	0.97	1.01	0.92	1.07
			0.74		1.05		0.92		1.05
H6	7.37	7.59	7.38	7.25	7.37	7.46	7.56	7.40	7.38
5-Me	1.93	1.93	1.93	1.79	1.93	1.88	1.88	1.87	1.89
C_c-CH_2		1.53	1.78			1.37	1.56	2.89	
								2.61	

Table 3: ^{1}H-^{1}H coupling constants at 500 MHz (± 0.10 Hz) for the major isomer of **19a - 23a** and **35a - 38a.**

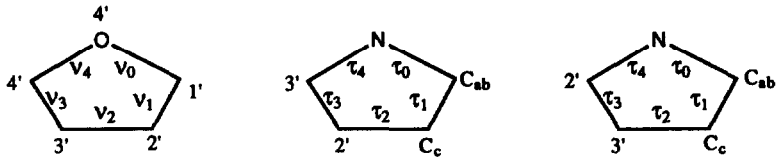
	19a		**20a**		**21a**		**22a**		**23a**	
T(°C)	15°	45°	15°	45°	15°	45°	15°	45°	15°	45°
$J_{1'2'}$	7.0	6.8	7.55	7.4	7.72	7.65	7.72	7.65	7.40	7.2
$J_{2'3'}$	8.8	8.9	8.60	8.7	8.40	8.5	8.42	8.5	8.60	8.6
$J_{3'4'}$	5.96	6.0	5.28	5.35	4.80	4.9	5.26	5.3	5.30	5.3
$J_{4'5'}$	3.16	3.3	2.70	2.9	a	a	a	a	3.0	3.0
$J_{4'5"}$	3.86	4.0	3.80	3.9	4.0	a	a	a	3.8	3.7
$J_{2'c}$	7.5	7.6	7.40	7.55	7.7	7.61				
J_{ac}	6.66	6.8	6.57	6.6	6.0	6.13	6.31	6.25		
J_{bc}	11.58	11.1	11.70	11.8	11.5	11.3	11.22	11.3		
$J_{ab'}$	11.93	11.8	11.70	11.7	11.5	11.3	11.60	11.3	12.0	12.0
	35a		**36a**		**37a**		**38a**			
T(°C)	15°	45°	15°	45°	15°	45°	15°	45°		
$J_{1'2'}$	3.1	2.94	2.45	2.30	3.50	3.30	3.0	3.1		
$J_{2'3'}$	8.00	8.10	7.30	7.35	8.30	8.20	8.0	8.2		
$J_{3'4'}$	8.20	8.26	8.70	8.75	8.40	8.24	8.5	8.3		
$J_{4'5'}$	2.20	2.31	2.10	2.2	2.20	2.4	2.2	2.4		
$J_{4'5"}$	4.20	4.32	3.90	4.05	4.30	4.4	4.1	4.3		
$J_{3'c}$	8.10	8.15	7.80	7.9	8.10	8.1				
J_{ac}	6.84	6.79	7.00	7.0	6.7	6.7				
J_{bc}	11.1	11.0	11.10	11.0	11.2	11.2				
$J_{ab'}$	11.1	11.0	11.10	11.0	11.2	11.3	11.2	11.2		

[a] Could not be measured because of spectral overlap.

(Fig. 1). The configuration of C_c center[31] in the major diastereomers **35a, 36a, 37a** is S and the configuration of the corresponding center in the minor diastereomer **35a', 36a', 37a'** has been assigned as R (Fig. 1). (iv) The cyclization of 2'-endocyclic radical generated from precursors **14a, 15a, 16a, 17a** gives

5~6 times higher "off-template" stereoselectivity than the cyclization of 3'-endocyclic radical from compounds **30a, 31a, 32a** (see Table 1). The improved stereoselectivity at C2'-linked chiral C_c in comparison with C3'-linked chiral C_c found in the cyclization of 3-aza-5-hexenyl endocyclic radical (from **14a, 15a, 16a, 17a, 18a, 30a, 31a, 32a** or **33a**) may be attributed to the finely tuned stereoelectronic factors such as the proximity of the anomeric center to C2', *gauche* effect of the N-substituent and the thymine base in the *anti* orientation. These steric and electronic factors may dictate the formation of the energetically prefered transition state at the C2' which is responsible for the prefered diastereomer formation with the C_c substituent in the equatorial conformation. It can be also seen in Table 1 that the nitrogen analogues show improved "off-template" stereoselectivity than the corresponding oxygen analogues.[6a] (v) The bulk of the C_c-substituent has pronounced effect on the "off-template" stereoselectivity as we can see from Table 1. As the bulk of the substituent X in **19a** (X = Me), **20a** (X = Et), **21a** (X = i-Pro), **22a** (X = CH_2Ph) increases, the "off template" stereoselectivity in the cyclization of 2'-endocyclic radical decreases. The same trend holds in the cyclization of 3'-endocyclic radical, but in a much less pronounced manner (compare **19a, 20a, 21a, 22a** with **39a, 39b, 39c** in Table 1).

Conformational analysis of 19a - 23a and 35a - 38a. The solution geometry of the ribose and pyrrolidine rings in the major diastereomer of **19a - 23a** and **35a - 38a** has been determined from vicinal proton-proton coupling constants (^1H at 500 MHz) using the concept of pseudorotation[32] in which the conformation of a puckered five-membered ring is fully described by two parameters: a phase angle of pseudorotation P and a puckering amplitude Ψ_m. From a survey of X-ray crystallographic studies on nucleosides and nucleotides,[33] it is known that Ψ_m ranges from 35° to 45° with an average of 39°. Two narrow ranges of P values are found. The first range is centered around P = 18° (C3'-*endo* ring conformation) and is denoted as N (North). The second range is centered around P = 162° (C2'-*endo*) and is denoted S (South). In 2',3'-cyclic phosphates, the five-membered cyclic phosphate ring forces the O2'-C2'-C3'-O3' group into near planar arrangement. The puckering amplitude is flattened as indicated by Ψ_m values between 22° and 36°. The pseudorotational parameters were obtained from the J-couplings using the computer program PSEUROT.[34, 35] In solution, the furanose ring exists as an equilibrium of the two rapidly interconverting conformers N and S and four conformational parameters have to be determined, P_N, P_S, Ψ_N, Ψ_S as well as the mole fraction of each conformer. The position of the conformational equilibrium is mainly determined by two factors: the *gauche* effect and the *anomeric* effect. The *gauche* effect is the tendency to adopt the structure in which the O4' and 3'- (and/or 2') substituent are in *gauche* orientation rather than in *trans* orientation. The *anomeric* effect is described as the tendency of the lone pair of the furanose oxygen to be antiperiplanar to the nitrogen of the nucleobase. The pyrrolidine ring has been considered as a substituted proline ring. It has been shown that in solution, the proline ring occur also in an equilibrium between the N and S conformation.[36] Upon introduction of an electronegative substituent at the 4-position of the proline, the equilibrium is displaced toward the S conformation (80 - 90%) due to the *gauche* effect.[36] When the proline ring is fused to be part of a cyclic dipeptide, the proline ring exists in an equilibrium biased toward the N-type conformation.[36] The introduction of an electronegative substituent at the 4-position of proline ring in the cyclic dipeptide results in its complete conformational purity (~100% N).[36] It therefore appears that it is the nature of conformation of the dipeptide ring in the fused proline systems that actually drives the proline conformation.



Ribose ring in **19a - 23a, 35a-38a** Pyrrolidine ring in **19a - 23a** Pyrrolidine ring in **35a - 38a**

ν_0 = [C4'-O4'-C1'-C2']	τ_0 = [C3'-N-C_{ab}-C_c]	τ_0 = [C2'-N-C_{ab}-C_c]
ν_1 = [O4'-C1'-C2'-C3']	τ_1 = [N-C_{ab}-C_c-C2']	τ_1 = [N-C_{ab}-C_c-C3']
ν_2 = [C1'-C2'-C3'-C4']	τ_2 = [C_{ab}-C_c-C2'-C3']	τ_2 = [C_{ab}-C_c-C3'-C2']
ν_3 = [C2'-C3'-C4'-O4']	τ_3 = [C_c-C2'-C3'-N]	τ_3 = [C_c-C3'-C2'-N]
ν_4 = [C3'-C4'-O4'-C1']	τ_4 = [C2'-C3'-N-C_{ab}]	τ_4 = [C3'-C2'-N-C_{ab}]

Figure 2: Nomenclature of the endocyclic torsions for the ribose and the pyrrolidine rings in compounds **19a - 23a** and **35a - 38a**.

(A) Conformation of the furanose ring Three coupling constants $J_{1'2'}$, $J_{2'3'}$ and $J_{3'4'}$ are available to determine the geometry of the furanose ring (Table 3, Figs. 1 and 2), and they were used as an input for the pseudorotational analysis of the ribose using the computer program PSEUROT.[34,37] The large $J_{1'2'}$ in compounds **19a - 23a** indicates a conformational bias toward the South-type. In compounds **35a - 38a**, the small $J_{1'2'}$ suggests that the geometry of the ribose is biased toward an North-type. The coupling constants were measured at 5°, 15° and 45°C. Since very small changes in $^3J_{HH}$ were found at different temperatures, it was necessary to constrain two conformational parameters. A first analysis was performed with P and Ψ_m of the minor conformer fixed in the ranges -60° < P_N < 60° and 20° < Ψ_m < 40°. A second set of calculations were performed with Ψ_m of both conformers fixed in the range 20°-35°. The results of the calculation which gave best rms values are listed in Table 4. The furanose rings in **19a - 23a** have a geometry biased toward a S-type conformation (70 and 81 % S, 126° < P_S < 131° (C1'-*exo*-C2'-*endo*), 28°< Ψ_m < 32°). In compounds **35a - 38a**, the riboses have a conformation biased toward the N-type (~90 %N, 20° < P_N < 38° and 27°< Ψ_m < 30°). The existence of C1'-*exo*-C2'-*endo* conformer in **19a - 23a** was confirmed as to be a real minimum through a grid search in which the phase angle of the major conformer was varied between 90 to 180 ° in steps of 10° while the puckering amplitude was varied between 15 to 45° in steps of 5°. In all calculations, the phase angle and the puckering amplitude of the minor conformer as well as the population of each conformer were optimized in order to minimize the overall rms error which was found at a global minima at P_S = 125°-135°. A similar grid search (P varied beteween -25° and 60° and Ψ_m between 15 and 45°) for **35a - 38a** showed that minimum rms was obtained for 20° < P_N < 40°. It is noteworthy that the puckering of the sugar ring is flattened (25°< Ψ_m < 35°) compared to natural nucleosides[33]. This flattened sugar ring is however a standard structural feature found in X-ray crystal structures of nucleosides and nucleotides with fused five-membered ring bridging C2' and C3' atoms.[7,33,41-60]

(B) Conformation of the pyrrolidine ring In compounds **19a - 22a** and **35a - 37a**, four coupling constants are available to deduce the geometry of the pyrrolidine ring, J_{ab}, J_{bc}, $J_{2'3'}$ and $J_{2'c}$ (in **19a - 22a**) or $J_{3'c}$ (in **35a - 37a**) (Table 3, Figs. 1 and 2). The conformational analysis was performed in the same way

as described previously[38]. The results of the calculation are shown in Table 4. In compounds **19a - 22a**, the pyrrolidine geometry is biased toward the North-type conformation (C2'-*exo*), with a phase angle of

Table 4: Optimized pseudorotational parameters (P, Q, Ψ_m, Ψ^*_m) for the major diastereoisomer of **19a - 23a** and **35a - 38a**

	Ribose[a]				Pyrrolidine[b]			
	P_S	Ψ_m	%S	rms	Q_N	Ψ^*_m	%N	rms
19a	128	28	70	0.049	-28	39	100	0.269
20a	126	31	80	0.035	-27	40	100	0.406
21a	131	32	81	0.035	-29	41	100	0.488
22a	128	33	80	0.035	-27	41	100	0.368
23a	127	32	77	0.022	c	c	c	c
	P_N	Ψ_m	%N	rms	Q_S	Ψ^*_m	%S	rms
35a	29	27	90	0.035	171	37	100	0.872
36a	20	30	93	0.022	178[c]	40	100	0.679
37a	37	27	92	0.021	168	38	100	0.855
38a	31	28	91	0.059	c	c	c	c

[a] Calculation performed with the parameters given in ref. 33. [b] calculated with parameters in ref. 36. [c] It was not possible to determine the conformation of the pyrrolidine ring in compounds **23a** and **38a** where the C_C carbon is bonded to two methyl groups since only two coupling constants are available ($J_{2'3'}$ and $J_{2'C}$ in **23a** and $J_{2'3'}$ and $J_{3'C}$ in **38a**). Since slightly different combinations of P and Ψ_m could be obtained with similar rms values, the ranges for the phase angle of pseudorotation P is ± 5° and for the puckering amplitude ± 2°.

Table 5: Endocyclic torsion angles ν_2 and τ_3 for the major diastereoisomer of **19a - 22a** and **35a - 37a** calculated from equations 2 and 3, using the conformational parameters P, Ψm, Q and Ψ^*_m of Table 4 (see Fig. 2 for defination of endocyclic torsions).

Compd.	**19a**	**20a**	**21a**	**22a**	**35a**	**36a**	**37a**
ν_2	-17	-18	-21	-20	24	28	22
τ_3	-17	-18	-17	-19	26	31	25

Table 6: Rotamer distribution about the C4'-C5' bond (γ) for the major diastereoisomer of **19a - 23a** and **35a - 38a**.

	19a		**20a**		**21a**		**22a**		**23a**	
T(°C)	15°	45°	15°	45°	15°	45°	15°	45°	15°	45°
γ^+	66	63	71	68	a	a	a	a	68	69
γ^-	9	10	3	5	a	a	a	a	a	
γ^t	25	26	26	27	a	a	a	a	a	
	35a		**36a**		**37a**		**38a**			
T(°C)	15°	45°	15°	45°	15°	45°	15°	45°		
γ^+	71	68	73	73	70	70	72	68		
γ^-	-3	-2	-3	-3	-3	-1	-3	-1		
γ^t	32	33	30	30	33	34	31	33		

[a] Could not be calculated.

pseudorotation of -27° < Q_N < -30° and a puckering amplitude of 39° < Ψ^*_m < 41°. In compounds **35a - 37a**, the pyrrolidine has a geometry biased toward a S-type conformation (C2'-*endo*), with Q_S around 170°-

180° and Ψ^*_m around 37°-40°. All calculations gave a single conformational species (100% N in **19a - 22a** and 100% S in **35a - 37a**). When the amount of minor conformer was fixed to 5 or 10%, the iterations did not converge and gave worse initial rms values. It can therefore be concluded that the pyrrolidine ring adopts exclusively the North conformation in **19a - 22a** and the South conformation in **35a - 37a**.

Interdependence of the geometry of the ribose and the pyrrolidine rings The C2'-C3' bond is part of both the pyrrolidine and furanose rings (Fig. 1) and the corresponding torsion angles are $\nu_2 = \Phi$[C1'-C2'-C3'-C4] for ribose and $\tau_3 = \Phi$[C_c-C2'-C3'-N] in pyrrolidine (Fig. 2). If ν_2 is approximately equal to τ_3, the combination of equations 2 and 3 (see ref. 35) leads to the equation:

$$\Psi^*_m = (\Psi_m \cos P) / (\cos(Q + 144°)) \qquad (4)$$

This equation shows that the geometry of the ribose and pyrrolidine rings are interdependent[7]. Thus, Table 4 shows that the pyrrolidine ring adopts a South-type conformation when the ribose is in a North-type conformation in 35a - 37a. Similarly, when the ribose ring is in a South-type conformation in 19a - 22a, the pyrrolidine adopts a North-type conformation. These correlated conformations of the ribose and the pyrrolidine rings was also found earlier by us for 2'-deoxy-2'-C,3'-O-(1methylethylene)uridine **39a**[7] and 3'-deoxy-3'-C,2'-O-(1methylethylene)uridine **40**[7]. Equations 2^{35} and 3^{35} were used to calculate the torsion angles ν_2 and τ_3 in compounds **19a - 22a** and **35a - 37a**, using the pseudorotational parameters shown in Table 4. The results are summarized in Table 5. It can be seen that for each compound, the calculated torsion angles ν_2 and τ_3 have similar values. These data show that despite the errors associated with the conformational analysis (experimental error in the measurement of the J-couplings, small variation of the J-coupling with the temperature, inaccuracy of the a and b parameters in equations 2 and 3^{35}), the conformational parameters obtained from the pseudorotational analysis are a good representation of the geometry of **19a - 23a** and **35a - 38a** in solution (Fig. 3).

Conformation around the C4'-C5' bond The conformation around the C4'-C5' bond is described as an equilibrium between the three staggered conformations γ^+, γ^- and γ^t. The population of each rotamer was calculated from the $J_{4'5'}$ and $J_{4'5''}$ coupling constants[39]. The results are listed in Table 6. Compounds **19a - 23a** and **35a - 38a** show a preference for the γ^+ conformation, as it is commonly encountered in nucleosides. In case the assignment of H5' and H5" is reversed, the γ^- and γ^t population should be interchanged.

Conclusion

The furanose of **19a - 23a** shows a South-conformation which corresponds to a pseudoequatorial orientation of C_c-substituent and a pseudoaxial orientation of the N-substituent at C3'. This South conformation of the furanose ring is favoured for two main reasons: (i) The *gauche* effect [ϕ(O4'-C4'-C3'-N3') = -116°] *i.e.* the tendency to adopt the structure in which the O4' and 3'-N substituent are in a *gauche* orientation, (ii) the non-electron withdrawing C_c-substituent in a pseudoequatorial location minimize unfavourable steric interactions. These two effects work in a cooperative manner and produce a pronounced effect on the conformation of the sugar ring. In compounds **35a - 38a**, the North conformation of the furanose ring is also dictated by the prefered pseudoaxial location of the nitrogen at C2' giving a

gauche geometry between O4' and N2' [ϕ(O4'-C1'-C2'-N2') = 104°] and the pseudoequatorial orientation of C_c-substituent at C3'. The larger conformational purity of the furanose ring in **35a** - **38a** compared to **19a** - **23a** might be due to the *anomeric* effect. The *anomeric* effect drives the N$\rightleftarrows$ S equilibrium toward the North-type. In **35a** - **38a**, the *anomeric* effect, the *gauche* effect and the pseudoequatorial location of the substituent at C3' are cooperative. In **19a** - **23a**, the *anomeric* effect counteracts the *gauche* effect and the pseudoequatorial location of the substituent at C2'. The furanose ring of 3'-methyl-β-D-xyloadenosine adopts the South-type conformation which corresponds to the pseudoequatorial orientation of 2'-OH (unfavourable) and pseudoequatorial orientation of 3'-Me (favourable).[5d] The two effects are counteractive and it is the steric effect of the methyl group on C3' which actually dictates the conformation of the sugar ring in 3'-methyl-β-D-xyloadenosine.

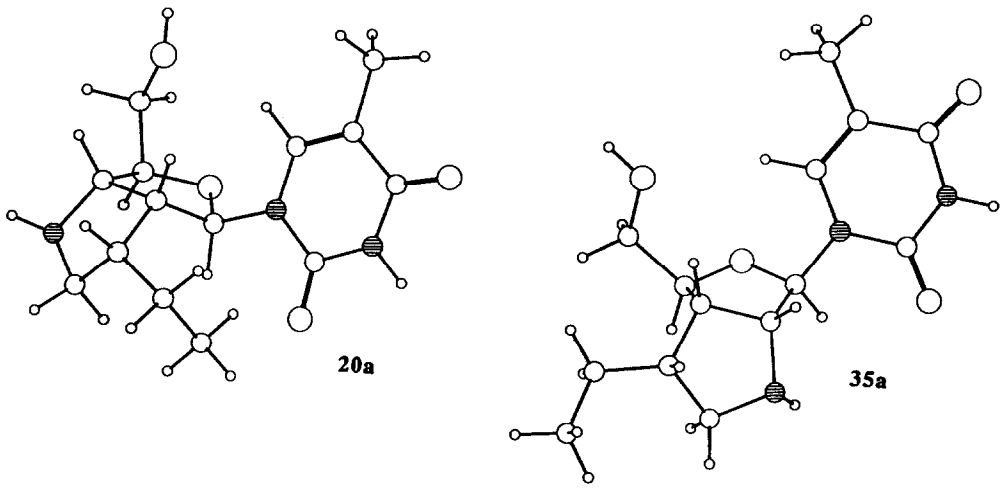


Figure 3: Structure of the major diastereoisomer of **20a** (C_c-configuration is R) and **35a** (C_c-configuration is S). The torsional constraints for structures **20a** and **35a** are based upon the experimental $^3J_{HH}$ (Table 3) which were translated into torsion angles using the generalised Karplus equation (see ref. 32 and 35). These fully NMR constrained structures were energy minimized using the generalized AMBER force field parameters implemented in the computer MacroModel V3.5a. The estimated error in $^3J_{HH}$ of ± 0.1 Hz was used to determine the flat region of ± 3 ° in torsion angles. Inside that region, no energy penalty is paid, while the constraint energy outside the allowed region is calculated by E = V_1 (1 - cos[deviation]). V_1 is a force constant (1000 kJ / mol. rad), and deviation is the deviation in torsion angles from the border of the allowed region. The ribose ring in **20a** is in the South conformation (P = 126°, Ψ_m = 31°), whereas the pyrrolidine ring is in the North conformation (P = -27°, Ψ^*_m = 40°). The C4'-C5' bond is in the γ^+ conformation (C3'-C4'-C5'-O5' = 57°). The glycosidic bond is *anti* (O4'-C1'-N1-C2 = -128°). The ribose ring in **35a** is in the North conformation (P = 29°, Ψ_m = 27°), whereas the pyrrolidine ring is in the South conformation (P = 171°, Ψ^*_m = 37°). The C4'-C5' bond is in the γ^+ conformation [ϕ(C3'-C4'-C5'-O5') = 57°] and the glycosidic bond is *anti* [ϕ(O4'-C1'-N1-C2) = -150°].

It is of interest to compare the geometries of **19a** - **22a** and **35a** - **37a** with those of **39a** and **40** in which the nitrogen at C2' or C3' is replaced by an oxygen atom.[7] The overall conformations of **19a** - **22a** and **39a** and **35a** - **37a** and **40** are very comparable. In **19a** - **22a** and **39a**, the furanose ring adopts preferentially the S-

type conformation while the fused ring at C2' and C3' adopts the N-type conformation. In **35a** - **37a** and **40**, the furanose ring also prefers the North conformation, while the fused ring at C2' and C3' has the South geometry. The higher polarity of the C-O bond compared to C-N bond leads however to a greater preference for O3'-C3'-C4'-O4' *gauche* orientation in **39a** and for O2'-C2'-C1'-O4' *gauche* orientation in **40** which is reflected in the higher South population in **39a** (94% S) and North population in **40** (94% N). The conformational parameters for the solution structures of **35a** - **37a** (Table 4) are found to be very similar to those of the crystal structure of **40** (P = 26°, Ψ_m = 25°; Q = 175°, Ψ^*_m = 33°)[7]. It has been found that the "off-template" stereoselectivity of radical ring-closure reaction by the radical at 2' is larger than at the 3' which is clearly due to different stereochemical environment at C2' and C3'. As the three reactive centers (the planar radical at C2' or C3' and the two carbons of olefin), "situated at the vertices of a slightly obtuse triangle lying within a plane orthogonal to the nodal plane of the π system"[29a] form a transition state, the *anti* conformation of thymine residue exerts a steric and electronic influence at C2'. The energetically most favoured boat-like transition state giving 5-*exo* ring closure has the C-substituent in the equatorial orientation as reflected in the observed stereoselectivity. Clearly, this boat-like transition state is also possible with the C-substituent in the axial orientation, albeit energetically less favoured. As the bulk of the substituent at the terminal olefin increases, one observes poorer stereoselectivity in the ring-closure reactions. The reason for the less bulky groups such as CH_3 or C_2H_5 to exert more stereoselectivity in the ring-closure reactions than the more bulky groups such as (i-C_3H_7 or $PhCH_2$) is essentially due to the fact that the less bulky groups allow the formation of energetically favourable transition state, giving a minimum of steric hindrance, compared to the bulkier groups. As regards the higher stereoselectivity of the ring-closure reaction with nitrogen as the tethering heteroatom compared to oxygen is perhaps because of more restricted rotation across C-N bond producing energetically favoured transition state. It is also likely that a β-substituent (oxygen versus nitrogen to the allylic carbon) can exert stereoelectronic influence on the orientation of the allylic double bond in a specific manner as it has been found, for example, in case of 1-butene in which the eclipsed orientation of methyl substituent with the double bond is energetically favoured.[30]

EXPERIMENTAL

^{1}H-NMR spectra were recorded (in δ scale) at 90 MHz or at 500 MHz using TMS (0.0 ppm) as reference. ^{13}C-NMR were recorded at 22.5 MHz using both ^{1}H-coupled and ^{1}H-decoupled or INEPT modes. Tlc was carried out using Merck pre-coated silica gel F254 plates. Preparative Tlc was carried out using Merck pre-coated silica gel F254 Plc plates. The column chromatographic separations were carried out using Merck G60 silica gel. THF and benzene was freshly distilled from sodium benzophenone ketyl, pyridine was distilled over CaH_2, and EtOH was treated with sodium strips overnight and freshly distilled. Dichloroethane was dried over 4 Å molecular sieves. CH_3OH was distilled over P_2O_5. 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'-N-allyl chain protons and carbons are indicated by Ha (-NCH_2), Hb and Hc, or Ca, Cb, and Cc and so on from 2'/3'-N-direction. ^{1}H- & ^{13}C-NMR assignments of **19a**, **20a**, **21a**, **22a**, **23a**, **35a**, **36a**, **37a** and **38a** are indicated by numberings of atoms in Fig. 1. One-dimensional diiferential NOE experiments were performed with 50 ms of irradiation time using a decoupling power of 55 dB. NOE difference spectra were obtained upon substraction of on and off resonance spectra. The ^{1}H-NMR chemical shifts for **19a** - **23a** and **35a** - **38a** are listed in Table 2. For each compound, the downfield proton at C5' was assigned as the H5'-proton, whereas the upfield proton was assigned as the H5" proton in accordance with the Remin and Shugar proposal.[40] The diastereotopic protons H_a and H_b were assigned on the basis of the cis-shielding effect of the substituent at the C_c carbon. Thus, H_a absorbs at lower field than H_b if H_a and H_b are respectively transoid

and cisoid to the substituent at C_c (Fig. 1). Table 2 shows that the chemical shift difference between H_a and H_b is 0.5 to 0.65 ppm irrespective of the nature of the substituent at C_c and of the location of the pyrrolidine ring.

1-(5'-O-(MMTr)-2',3'-dideoxy-2'-phenylseleno-3'-amino-β-D-ribofuranosyl)thymine 4: To a solution of **2** (3.6 g, 6.5 mmol) in dry pyridine (40 mL) at 0°C was added methanesulfonyl chloride (1.01 mL, 13 mmol). The reaction mixture was kept at 0°C overnight, quenched with aqueous saturated $NaHCO_3$ (100 mL), and extracted with CH_2Cl_2 (3x50 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated to dryness. The residue (essentially pure **3** as judged by Tlc and NMR) was redissolved in a mixture of THF (70 mL) and EtOH (70 mL) with stirring at rt. To the above solution was added $(PhSe)_2$ (3.04 g, 9.75 mmol) followed by portionwise addition of $NaBH_4$ (1.48 g, 39 mmol). The reaction mixture was then heated at reflux overnight, cooled to rt, quenched carefully with aqueous saturated NH_4Cl (300 mL), and extracted with CH_2Cl_2 (3x100 mL). The combined organic phase was dried ($MgSO_4$), filtered and evaporated to dryness. The foam was purified by silica gel column chromatography to give pure **4** (3.96 g, 88%, Ninhydin test positive). **3** ^{1}H-NMR ($CDCl_3$): δ 8.85 (br. s, 1H) NH, 7.47-6.82 (m, 15H) arom. & H6, 6.18 (d, $J_{1',2'}$ = 5.37 Hz, 1H) H1', 5.19 (dd, $J_{2',3'}$ = 4.64 Hz, 1H) H2', 4.43 (dd, $J_{3',4'}$ = 7.08 Hz, 1H) H3', 3.88 (m, 1H) H4', 3.81 (s, 3H) CH_3O, 3.62 (dd, $J_{4',5'}$ = 3.66 Hz, 1H) H5', 3.38 (dd, $J_{4',5''}$ = 3.66 Hz, $J_{5',5''}$ = 10.98 Hz, 1H) H5", 3.00 (s, 3H) Ms, 1.72 (d, 3H) 5-Me; ^{13}C-NMR ($CDCl_3$): δ 163.2, 149.9, 143.5, 135.4, 134.4, 130.2, 128.1, 128.0, 127.2, 113.2, 110.9, 82.7 (d, J_{CH} = 171.9 Hz), 80.9 (d, J_{CH} = 158.4 Hz), 79.8 (d, J_{CH} = 150.5 Hz), 64.3 (d, J_{CH} = 147.1 Hz), 61.2 (t, J_{CH} = 146.0 Hz), 55.1 (q, J_{CH} = 143.8 Hz), 38.2 (q, J_{CH} = 139.3 Hz), 12.2 (q, J_{CH} = 129.2 Hz). **4** ^{1}H-NMR ($CDCl_3$): δ 8.47 (br. s, 1H) NH, 7.66-6.76 (m, 20H) arom. & H6, 6.35 (d, $J_{1',2'}$ = 7.82 Hz, 1H) H1', 3.95 (m, 3H) H2', H3', H4', 3.80 (s, 3H) CH_3O, 3.43 (m, 2H) H5', H5", 1.63 (br.s, 2H) NH_2, 1.23 (d, 3H) 5-Me; ^{13}C-NMR ($CDCl_3$): δ 163.1, 158.7, 150.3, 143.6, 134.9, 134.5, 130.3, 129.1, 128.2, 127.2, 113.2, 111.0 (s) C5, 88.8 (d, J_{CH} = 168.5 Hz) C1', 87.2 (s) MMTr, 85.6 (d, J_{CH} = 148.3 Hz) C4', 64.0 (t, J_{CH} = 142.1 Hz) C5', 55.2 (q, J_{CH} = 143.8 Hz) MeO, 55.0 (d, J_{CH} = 148.3 Hz), 53.3 (d, J_{CH} = 146.0 Hz), 11.5 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB$^-$): calc. for $(M-H)^-$ 668.1667, found 668.1646.

1-(5'-O-(MMTr)-2',3'-dideoxy-2'-amino-3'-phenylseleno-β-D-xylofuranosyl)thymine 8: A solution of **5** (4.1 g, 8 mmol) and NaN_3 (3.25 g, 50 mmol) in DMF (100 mL) was heated at 120 °C for 48 h and then cooled to rt, evaporated to dryness, partitioned between water and CH_2Cl_2. The organic phase was dried ($MgSO_4$), filtered and evaporated to dryness. The foam was purified by silica gel column chromatography to give pure **6** (3.34 g, 75%). The procedure for the preparation of **4** was followed using **6** (3.05 g, 5.5 mmol) and MsCl (0.86 mL, 11 mmol) in pyridine (40 mL), then $(PhSe)_2$ (2.57 g, 8.25 mmol) and $NaBH_4$ (1.26 g, 33 mmol) in the solution of THF (50 mL) and EtOH (50 mL) to give pure **8** (3.14 g, 82%, Ninhydin test positive). 1H-NMR ($CDCl_3$): δ 7.66 (d, 1H) H6, 7.43-6.81 (m, 19H) arom., 5.86 (d, $J_{1',2'}$ = 6.35 Hz, 1H) H1', 4.56 (m, 1H) H4', 3.87-3.43 (m, 7H) H2', H-3', H5', H5" and CH_3O, 1.88 (br, 2H) NH_2, 1.31 (d, 3H) 5-Me; ^{13}C-NMR ($CDCl_3$): δ 163.6, 158.7, 151.0, 143.3, 135.7, 134.5, 133.6, 130.6, 129.2, 128.7, 127.8, 127.2, 113.0, 111.1 (s) C5, 88.1 (d, J_{CH} = 168.5 Hz) C1', 87.6 (s) MMTr, 79.4 (d, J_{CH} = 148.3 Hz) C4', 64.9 (t, J_{CH} = 142.7 Hz) C5', 62.5 (d, J_{CH} = 142.7 Hz), 55.1 (q, J_{CH} = 143.8 Hz) MeO, 51.3 (d, J_{CH} = 144.9 Hz), 11.5 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB$^-$): calc. for $(M-H)^-$ 668.1667, found 668.1647.

General Procedure for Preparation of Radical Precursors: **1-(2',3'-dideoxy-2'-phenylseleno-3'-amino-3'-N-cinnamyl-β-D-ribofuranosyl)thymine 17:** *Method A.* A solution of **4** (186 mg, 0.268 mmol) in dichloroethane (5 mL) was treated with cinnamaldehyde (68 μL, 0.536 mmol) and 4 Å molecular sieves at rt. The reaction mixture was evaporated to dryness after 2 h, and coevaporated with toluene two times. The foam was subjected to silica gel column chromatography to give **12** (127 mg, 59%) and **4** (73 mg, 38% recovered). The imine **12** (100 mg, 0.124 mmol) thus obtained was redissolved in dry CH_3OH (3 mL) and the solution of $NaCNBH_3$ (7.8 mg, 0.124 mmol) and acetic acid (0.1 mL) in dry CH_3OH (1 mL) was added. The reaction was kept overnight, evaporated to dryness and redissolved in 80% aqueous acetic acid and kept for 7 h. The reaction mixture was evaporated to dryness, extracted between CH_2Cl_2 (3x20 mL) and aqueous saturated $NaHCO_3$ (20 mL). The organic phase was dried ($MgSO_4$), filtered, evaporated to dryness and purified by preparative Tlc to give **17** (54 mg, 81 %). *Method B* (one-pot synthesis). A solution of **4** (208 mg, 0.3 mmol) in dichloroethane (5 mL) was treated with cinnamaldehyde (38 μL, 0.3 mmol) and 4 Å molecular sieves at rt. The reaction mixture was evaporated to dryness after 2 h, and coevaporated with toluene two times. To the above residue was added a solution of $NaCNBH_3$ (19 mg, 0.3 mmol) in aqueous acetic acid (4 mL). After 4 h, water (1 mL) was added and the reaction mixture was kept at rt overnight, evaporated to dryness, extracted between CH_2Cl_2 (3x20 mL) and aqueous saturated $NaHCO_3$ (20 mL). The organic phase was dried ($MgSO_4$), filtered, evaporated to dryness and purified by

preparative Tlc to give pure **17** (120 mg, 74 %). ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.7-6.25 (m, 13H) H6, arom., CH=CH, 6.00 (d, $J_{1',2'}$ = 6.35 Hz, 1H) H1', 4.25 (dd, $J_{2',3'}$ = 6.6 Hz, 1H) H2', 4.05 (m, 1H) H4', 3.80 (m, 2H) H5', H5", 3.65 (m, 1H) H3', 3.40 (d, J = 5.62 Hz, 2H) Ha, 1.70 (d, 3H) 5-Me; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 163.6, 150.3, 137.0, 136.6, 131.8, 129.2, 128.4, 128.0, 127.4, 127.3, 127.1, 126.1, 110.4, 94.2, 84.5, 62.6, 59.1, 51.1, 50.3, 12.2.

1-(2',3'-dideoxy-2'-phenylseleno-3'-amino-3'-N-allyl-β-D-ribofuranosyl)thymine 14a & 1-(2',3'-dideoxy-2'-phenylseleno-3'-amino-3'-N-(n-propyl)-β-D-ribofuranosyl)thymine 14b: General procedure for preparation of radical precursor (Method B) was followed using **4** (139 mg, 0.2 mmol), acrolein (23 μL, 0.3 mmol) and $NaCNBH_3$ (6.3 mg, 0.1 mmol) to give an inseparable mixture of **14a** and **14b** (1:1, 51 mg, 60%). ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.70-6.75 (m, 6H) arom., H6, 6.05 (d, $J_{1',2'}$ = 5.86 Hz, 1H) H1', 5.75 (m) CH=CH_2, 5.15 (m) CH=CH_2, 4.20 (dd, $J_{2',3'}$ = 6.59 Hz) H2', 3.90 (m) H4', H5', H5", 3.55 (m) H3', 3.20 (d, J = 5.62 Hz) Ha, 2.50 (t) Ha, 1.75 (d, 3H) 5-Me, 1.30 (m) Hb, 0.90 (t) Me; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 163.6, 150.3, 137.1, 135.7, 134.8, 129.1, 128.0, 127.3, 116.6, 110.4, 94.2, 94.1, 84.5, 62.6, 59.8, 58.9, 51.3, 50.6, 23.0, 12.2, 11.6.

1-(2',3'-dideoxy-2'-phenylseleno-3'-amino-3'-N-crotonyl-β-D-ribofuranosyl)thymine 15a & 1-(2',3'-dideoxy-2'-phenylseleno-3'-amino-3'-N-(n-butyl)-β-D-ribofuranosyl)thymine 15b: General procedure for preparation of radical precursor (Method B) was followed using **4** (208 mg, 0.3 mmol), crotonaldehyde (28 μL, 0.33 mmol) and $NaCNBH_3$ (9.5 mg, 0.15 mmol) to give an inseparable mixture of **15a** and **15b** (2:1, 106 mg, 74%). ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.75-6.80 (m, 6H) arom, H6, 5.90 (d, $J_{1',2'}$ = 6.36 Hz, 1H) H1', 5.50 (m) CH=CHMe, 4.30 (m) H-2', CH=CHMe, 4.00-3.50 (m) H4', H5', H5", H3', 3.15 Ha, 2.50 Ha, 1.75 (d, 3H) 5-Me, 1.70-0.90 (m) Hb, Hc, Hd. ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 163.7, 150.3, 137.0, 134.7, 129.1, 128.3, 127.9, 127.3, 110.3, 93.9, 84.5, 62.6, 59.8, 58.8, 51.0, 50.0, 48.1, 31.9, 29.4, 20.1, 17.6, 13.8, 12.2.

1-(2',3'-dideoxy-2'-phenylseleno-3'-amino-3'-N-(3-methyl-2-butenyl)-β-D-ribofuranosyl)thymine 16a & 1-(2',3'-dideoxy-2'-phenylseleno-3'-amino-3'-N-(3-methyl-butyl)-β-D-ribofuranosyl)thymine 16b: General procedure for preparation of radical precursor (Method B) was followed using **4** (208 mg, 0.3 mmol), 3-methyl-2-butenal (33 μL, 0.33 mmol) and $NaCNBH_3$ (9.5 mg, 0.15 mmol) to give an inseparable mixture of **16a** and a trace of **16b** (95 mg, 65%). ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.62-6.98 (m, 6H) H6, arom., 5.95 (d, $J_{1',2'}$ = 6.34 Hz, 1H) H1', 5.22 (m) Hb, 4.28 (dd, $J_{2',3'}$ = 6.60, 1H) H2', 4.03 (m, 1H) H4', 3.87 (m, 2H) H5', H5", 3.62 (m) H3', 3.25 (d, J = 6.83 Hz) Ha, 1.77 (d, 3H) 5-Me, 1.72, 1.62 (2xs) Me, 0.92, 0.85 (2xs) Me; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 163.8, 150.3, 139.4, 136.2, 135.8, 128.4, 128.2, 127.6, 125.9, 111.3, 90.4, 84.7, 84.2, 83.6, 64.1, 61.9, 57.8, 50.3, 50.2, 44.2, 32.8, 11.9.

1-(2',3'-dideoxy-2'-phenylseleno-3'-amino-3'-N-(2-methyl-2-propenyl)-β-D-ribofuranosyl)thymine 18a & 1-(2',3'-dideoxy-2'-phenylseleno-3'-amino-3'-N-(2-methyl-propyl)-β-D-ribofuranosyl) thymine 18b: General procedure for preparation of radical precursor (Method B) was followed using **4** (208 mg, 0.3 mmol), methacrolein (78 μL, 0.9 mmol) and $NaCNBH_3$ (9.5 mg, 0.15 mmol) to give an inseparable mixture of **18a** and **18b** (4:1, 95 mg, 67%). ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.65-6.80 (m, 6H) arom., H6, 6.00 (m, 1H) H1', 4.80 CH=CH, 4.15 (t, $J_{1',2'}$ = $J_{2',3'}$ = 6.84 Hz) H2', 3.95-3.50 (m) H4', H5', H5", H3', 3.15 Ha, 2.30 Ha, 1.75 5-Me, 1.5-0.9 Hb, Hc; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 163.6, 150.3, 143.0, 137.0, 134.7, 129.1, 127.9, 127.3, 111.5, 110.4, 94.1, 93.9, 84.4, 62.9, 60.2, 59.0, 56.3, 53.8, 51.2, 50.8, 28.5, 20.1, 12.2.

1-(2',3'-dideoxy-3'-phenylseleno-2'-amino-2'-N-crotonyl-β-D-xylofuranosyl)thymine 30a & 1-(2',3'-dideoxy-3'-phenylseleno-2'-amino-2'-N-(n-butyl)-β-D-xylofuranosyl)thymine 30b: General procedure for preparation of radical precursor (Method B) was followed using **8** (139 mg, 0.2 mmol), crotonaldehyde (76 μL, 0.9 mmol) and $NaCNBH_3$ (6.3 mg, 0.1 mmol) to give an inseparable mixture of **30a** and **30b** (3:1, 73 mg, 77%). ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.75-7.10 (m, 6H) arom., H6, 5.75 (d, $J_{1',2'}$ = 5.12 Hz, 1H) H1', 5.32 (m) CH=CHMe, 4.48 (m) H4', CH=CHMe, 3.99 (m) H5', H5", 3.75 (m) H3, 3.52 (m) H2', 2.98 Ha, 2.31 Ha, 1.94 5-Me, 1.57-0.82 (m) Hb, Hc, Hd; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 164.1, 150.7, 136.7, 134.3, 134.1, 129.3, 128.6, 128.5, 128.3, 128.0, 110.8, 89.5, 80.6, 69.1, 67.6, 63.7, 49.1, 48.0, 47.8, 46.8, 31.7, 20.0, 17.6, 13.7, 12.4.

1-(2',3'-dideoxy-3'-phenylseleno-2'-amino-2'-N-(3-methyl-2-butenyl)-β-D-xylofuranosyl)thymine 31a & 1-(2',3'-dideoxy-3'-phenylseleno-2'-amino-2'-N-(3-methyl-butyl)-β-D-xylofuranosyl)thymine 31b: General procedure for preparation of radical precursor (Method B) was followed using **8** (139 mg, 0.2 mmol), 3-methyl-2-butenal (60 μL, 0.6 mmol) and $NaCNBH_3$ (6.3 mg, 0.1 mmol) to give an inseparable mixture of **31a** and **31b** (5:1, 83 mg, 85%). ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.72-7.15 (m) arom., H6, 5.78 (d, $J_{1',2'}$ = 5.37 Hz, 1H) H1', 5.03 (m) CH=CH, 4.47 (m) H4', 4.00 (m) H5', H5", 3.77 (m) H3', 3.51 (m) H2', 2.97 (d, J = 6.35 Hz) Ha, 2.30 Ha, 1.94 5-Me, 1.62, 1.48 Me, 1.60-1.00 (m) Hb, Hc, 0.80, 0.73 Hd; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 164.1, 150.6, 136.7, 135.0, 134.3, 134.0, 129.3, 128.6, 128.0, 121.7, 110.8, 89.5, 80.6, 68.2, 63.6, 47.9, 45.3, 44.8, 38.6, 25.6, 25.4, 22.3, 17.6, 12.4.

1-(2',3'-dideoxy-3'-phenylseleno-2'-amino-2'-N-cinnamyl-β-D-xylofuranosyl)thymine 32a & 1-(2',3'-dideoxy-3'-phenylseleno-2'-amino-2'-N-(3-phenyl-propyl)-β-D-xylofuranosyl)thymine 32b: General procedure for preparation of radical precursor (Method B) was followed using **8** (139 mg, 0.2 mmol), cinnamaldehyde (25 μL, 0.2 mmol) and $NaCNBH_3$ (6.3 mg, 0.1 mmol) to give an inseparable mixture of **32a** and **32b** (6:1, 91 mg, 85%). ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.75-7.15 (m) arom., H6, 6.30-5.75 (m) arom., CH=CHPh, H1', 4.35 (m) H4', 4.00 (m) H5', H5", 3.80-3.50 (m) H3', H2', 3.20 Ha, 2.35 Ha, 1.95 5-Me, 2.00-1.50 Hb, Hc; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 163.9, 150.7, 136.6, 136.4, 134.2, 134.0, 131.8, 129.4, 128.6, 128.4, 128.2, 127.3, 127.1, 126.1, 110.9, 89.4, 80.5, 67.5, 63.8, 49.2, 48.1, 33.0, 31.2, 12.4.

1-(2',3'-dideoxy-3'-phenylseleno-2'-amino-2'-N-(2-methyl-2-propenyl)-β-D-xylofuranosyl)thymine 33a & 1-(2',3'-dideoxy-3'-phenylseleno-2'-amino-2'-N-(2-methyl-propyl)-β-D-xylofuranosyl) thymine 33b: General procedure for preparation of radical precursor (Method B) was followed using **8** (139 mg, 0.2 mmol), methacrolein (78 μL, 0.9 mmol) and $NaCNBH_3$ (6.3 mg, 0.1 mmol) to give an inseparable mixture of **33a** and **33b** (5:1, 65 mg, 68%). ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.75-7.15 (m, 6H) arom., H6, 6.75 (m, 1H) H1', 4.65 (m) CH_2=CH, 4.40 (m) H4', 4.00 (m) H5', H5", 3.70-3.45 (m) H2', H3', 2.90 Ha, 2.10 Ha, 1.95 5-Me, 1.70-0.80 (m) Hb, Hc; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 164.0, 150.6, 142.7, 136.7, 134.2, 134.0, 129.3, 128.7, 128.6, 128.0, 111.4, 110.8, 89.7, 80.6, 69.0, 67.5, 63.7, 54.9, 52.9, 48.2, 47.9, 27.9, 20.2, 12.4.

General Procedure for Radical Cyclization **1-(2',3'-dideoxy-3'-amino-2'-*C*, 3'-*N*-((1-methyl)ethylene)-β-D-ribofuranosyl)thymine 19a & 3'-deoxy-3'-amino-3'-N-(n-propyl)thymidine 19b:** To a boiling solution of **14** (30 mg, 0.065 mmol) in benzene (10 mL) was added a solution of Bu_3SnH (39 μL, 0.14 mmol) and AIBN (5 mg) in benzene (2 mL) over 2 h by a syringe-pump, then the reaction mixture was heated at reflux for another 2 h, evaporated to dryness. The residue was purified by silica gel chromatography to give pure **19a** (inseparable isomeric mixture in a ratio of 25:1, 10 mg, 50.1%, efficacy of radical cyclization 90%) and **19b** (9 mg, 44.8%). For δ and $^3J_{HH}$ of **19a**, see Table 2, 3; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 164.0, 150.1, 136.3 (d, J_{CH} = 178.7 Hz), 111.5, 89.2 (d, J_{CH} = 162.2 Hz, J_{CH} = 146.6 Hz), 64.2 (d, J_{CH} = 144.8 Hz), 61.9 (t, J_{CH} = 144.3 Hz), 52.2 (d, J_{CH} = 137.5 Hz), 52.1 (t, J_{CH} = 137.9 Hz), 37.8 (d, J_{CH} = 131.1 Hz), 12.2 (q, J_{CH} = 129.2 Hz), 11.6 (q, J_{CH} = 126.5 Hz); MS (FAB$^-$): calc. for $(M-H)^-$ 280.1297, found 280.1284. **19b** ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.63 (d, 1H) H6, 6.16 (t, J1',2' = 6.1 Hz, 1H) H1', 3.84 (m, 3H) H4', H5', H5", 3.39 (m, 1H) H3', 2.59 (t, J = 7.32 Hz, 2H) Ha, 2.26 (m, 2H) H2', H2", 1.91 (d, 3H) 5-Me, 1.64-1.25 (m, 2H) Hb, 0.93 (t, J = 7.08 Hz, 3H) Me. ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 136.3 (d, J_{CH} = 179.6 Hz) C6, 110.5 (s) C5, 85.3 (d, J_{CH} = 172.3 Hz) C1', 85.1 (d, J_{CH} = 145.7 Hz) C4', 61.9 (t, J_{CH} = 142.5 Hz) C5', 57.2 (d, J_{CH} = 140.2 Hz) 49.8 (t, J_{CH} = 132.9 Hz) Ca, 38.5 (t, J_{CH} = 133.3 Hz) C2', 22.8 (t, J_{CH} = 126.9 Hz) CH_2, 12.1 (q, J_{CH} = 129.2 Hz) 5-Me, 11.4 (q, J_{CH} = 127.4 Hz) Me. MS (FAB$^-$): calc. for $(M-H)^-$ 282.1454, found 282.1438.

1-(2',3'-dideoxy-3'-amino-2'-*C*, 3'-*N*-((1-ethyl)ethylene)-β-D-ribofuranosyl)thymine 20a & 3'-deoxy-3'-amino-3'-N-(n-butyl)thymidine 20b: General procedure for radical cyclization was followed using **15** (90 mg, 0.189 mmol) in benzene (20 mL) and a solution of Bu_3SnH (79 μL, 0.284 mmol) and AIBN (9 mg) in benzene (2 mL) over 2 h to give pure **20a** (inseparable isomeric mixture in a ratio of 27:1, 38 mg, 62.6%, efficacy of radical cyclization 88%) and **20b** (18 mg, 29%). For δ and $^3J_{HH}$ of **20a**, see Tables 2 and 3; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 164.1, 150.1, 136.2 (d, J_{CH} = 179.6 Hz), 111.6, 84.1 (d, J_{CH} = 144.8 Hz), 83.9 (d, J_{CH} = 164.1 Hz), 64.0 (d, J_{CH} = 145.7 Hz), 61.9 (t, J_{CH} = 142.5 Hz), 51.0 (d, J_{CH} = 139.3 Hz), 49.7 (t, J_{CH} = 137.0 Hz), 45.9 (d, J_{CH} = 127.4 Hz), 20.2 (t, J_{CH} = 126.5 Hz), 13.2 (q, J_{CH} = 124.6 Hz),

12.1 (q, J_{CH} = 129.2 Hz); MS (FAB$^-$): calc. for (M-H)$^-$ 294.1454, found 294.1446. **20b** ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.48 (d, 1H) H6, 6.15 (dd, 1H) H1', 3.76-3.5 (m, 4H) H3', H4', H5', H5", 2.60 (t, 2H) Ha, 2.25 (m, 2H) H2', H2", 1.90 (d, 3H) 5-Me, 1.40 (m, 4H) Hb, Hc, 0.90 (t, 3H) Me. MS (FAB$^-$): calc. for (M-H)$^-$ 296.1610, found 296.1612.

1-(2',3'-dideoxy-3'-amino-2'-*C*, 3'-*N*-((1-isopropyl)ethylene)-β-D-ribofuranosyl)thymine 21a & 3'-deoxy-3'-amino-3'-N-(3-methyl-propyl)thymidine 21b: General procedure for radical cyclization was followed using **16** (70 mg, 0.143 mmol) in benzene (15 mL) and a solution of Bu_3SnH (59 μL, 0.21 mmol) and AIBN (7 mg) in benzene (2 mL) over 2 h to give pure **21a** (inseparable isomeric mixture in a ratio of 15:1, 45 mg, 94%, efficacy of radical cyclization 95 %) and **21b** (1 mg, 2.1%). For δ and $^3J_{HH}$ of **21a**, see Table 2, 3; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 164.1, 150.2, 136.1 (d, J_{CH} = 179.6 Hz), 111.7, 84.3 (d, J_{CH} = 145.7 Hz), 84.1 (d, J_{CH} = 165.0 Hz), 64.3 (d, J_{CH} = 147.6 Hz), 62.1 (t, J_{CH} = 142.5 Hz), 52.6 (d, J_{CH} = 128.3 Hz), 50.3 (d, J_{CH} = 138.4 Hz), 48.8 (t, J_{CH} = 138.4 Hz), 26.6 (d, J_{CH} = 128.3 Hz), 22.1 (q, J_{CH} = 122.8 Hz), 12.1 (q, J_{CH} = 129.2 Hz); MS (FAB$^-$): calc. for (M-H)$^-$ 308.1610, found 308.1624.

1-(2',3'-dideoxy-3'-amino-2'-*C*, 3'-*N*-((1-benzyl)ethylene)-β-D-ribofuranosyl)thymine 22a: General procedure for radical cyclization was followed using **17a** (75 mg, 0.14 mmol) in benzene (15 mL) and a solution of Bu_3SnH (58 μL, 0.21 mmol) and AIBN (7 mg) in benzene (2 mL) over 2 h to give pure **22a** (inseparable isomeric mixture in a ratio of 10:1, 50 mg, 93%). For δ and $^3J_{HH}$ of **22a**, see Table 2, 3; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 163.5, 150.2, 139.7, 136.5 (d, J_{CH} = 181.0 Hz), 135.6 (d, J_{CH} = 179.6 Hz), 128.6, 128.5, 128.3, 127.8, 126.2, 126.1, 110.4, 91.7 (d, J_{CH} = 167.7 Hz), 85.4 (d, J_{CH} = 146.6 Hz), 84.7 (d, J_{CH} = 145.7 Hz), 84.4 (d, J_{CH} = 167.7 Hz), 64.6 (d, J_{CH} = 148.5 Hz), 62.7 (t, J_{CH} = 143.1 Hz), 54.5 (d, J_{CH} = 143.0 Hz), 50.8 (t, J_{CH} = 139.3 Hz), 50.4 (d, J_{CH} = 140.2 Hz), 45.4 (d, J_{CH} = 130.0 Hz), 44.7 (d, J_{CH} = 130.1 Hz), 38.9 (d, J_{CH} = 125.6 Hz), 33.1 (t, J_{CH} = 125.6 Hz), 12.3 (q, J_{CH} = 129.2 Hz); MS (FAB$^-$): calc. for (M-H)$^-$ 356.1610, found 356.1602.

1-(2',3'-dideoxy-3'-amino-2'-*C*, 3'-*N*-((1-dimethyl)ethylene)-β-D-ribofuranosyl)thymine 23a & 3'-deoxy-3'-amino-3'-N-(isopropyl)thymidine 23b: General procedure for radical cyclization was followed using **18** (45 mg, 0.0945 mmol) in benzene (10 mL) and a solution of Bu_3SnH (42 μL, 0.15 mmol) and AIBN (5 mg) in benzene (2 mL) over 2 h to give pure **23a** (22 mg, 72.5%, efficacy of radical cyclization 90%) and **23b** (6 mg, 19.7%). For δ and $^3J_{HH}$ of **23a**, see Table 2, 3; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 163.9, 150.2, 136.3 (d, J_{CH} = 179.6 Hz), 111.6, 85.5 (d, J_{CH} = 165.0 Hz), 84.4 (d, J_{CH} = 144.8 Hz), 63.8 (d, J_{CH} = 144.8 Hz), 62.1 (t, J_{CH} = 142.5 Hz), 58.8 (d, J_{CH} = 135.6 Hz), 58.1 (t, J_{CH} = 140.2 Hz), 41.8, 28.1 (q, J_{CH} = 125.6 Hz), 20.7 (q, J_{CH} = 125.6 Hz), 12.2 (q, J_{CH} = 129.2 Hz); MS (FAB$^-$): calc. for (M-H)$^-$ 294.1454, found 294.1422. **23b** ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.58 (d, 1H) H6, 6.16 (dd, J = 5.48 Hz, 6.67 Hz, 1H) H1', 3.92-3.76 (m, 3H) H4', H5', H5", 3.42 (m, 1H) H3', 2.42 (d, J = 6.53 Hz, 2H) Ha, 2.34 (m, 2H) H2', H2", 1.91 (d, 3H) 5-Me, 1.73 (m, 1H) Hb, 0.92 (d, J = 6.67 Hz, 6H) 2xMe; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 164.1, 150.4, 136.3 (d, J_{CH} = 182.4 Hz) C6, 110.5 (s) C5, 85.4 (d, J_{CH} = 171.4 Hz) C1', 85.1 (d, J_{CH} = 146.6 Hz) C4', 62.1 (t, J_{CH} = 142.5 Hz) C5', 57.6 (d, J_{CH} = 139.3 Hz) C3', 55.9 (t, J_{CH} = 131.5 Hz) Ca, 38.7 (t, J_{CH} = 133.3 Hz), C2', 28.2 (d, J_{CH} = 125.6 Hz) Cb, 20.3 (q, J_{CH} = 126.5 Hz) 2xMe, 12.2 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB$^-$): calc. for (M-H)$^-$ 296.1610, found 296.1628.

1-(2',3'-dideoxy-2'-amino-3'-*C*, 2'-*N*-((1-ethyl)ethylene)-β-D-ribofuranosyl)thymine 35a & 1-(2',3'-dideoxy-2'-amino-2'-N-(n-butyl)-β-D-ribofuranosyl)thymine 35b: General procedure for radical cyclization was followed using **30** (55 mg, 0.116 mmol) in benzene (15 mL) and a solution of Bu_3SnH (53 μL, 0.19 mmol) and AIBN (5 mg) in benzene (2 mL) over 2 h to give pure **35a** (inseparable isomeric mixture in a ratio of 4:1, 25 mg, 67.1%, efficacy of radical cyclization 88%)and **35b** (9 mg, 24%). For δ and $^3J_{HH}$ of **35a**, see Tables 2 and 3; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 164.3, 150.7, 137.1 (d, J_{CH} = 183.1 Hz), 110.3, 93.3 (d, J_{CH} = 167.5 Hz), 92.9 (d, J_{CH} = 166.8 Hz), 86.3 (d, J_{CH} = 144.8 Hz), 80.9 (d, J_{CH} = 145.7 Hz), 70.2 (d, J_{CH} = 150.3 Hz), 69.4 (d, J_{CH} = 145.7 Hz), 63.0 (t, J_{CH} = 142.1 Hz), 62.3 (t, J_{CH} = 141.6 Hz), 52.0 (t, J_{CH} = 138.8 Hz), 49.9 (t, J_{CH} = 137.9 Hz), 49.2 (d, J_{CH} = 134.7 Hz), 44.8 (d, J_{CH} = 139.3 Hz), 44.7 (d, J_{CH} = 139.3 Hz), 20.6 (t, J_{CH} = 125.6 Hz), 13.3 (q, J_{CH} = 124.6 Hz), 12.0 (q, J_{CH} = 129.2 Hz); MS (FAB$^-$): calc. for (M-H)$^-$ 294.1454, found 294.1444. **35b** ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.80 (d, 1H) H6, 5.75 (d, $J_{1',2'}$ = 3.42 Hz, 1H) H1', 4.40 (m, 1H) H4', 3.95 (dd, $J_{4',5'}$ = 2.69 Hz, $J_{5',5"}$ = 12.2 Hz, 1H) H5', 3.60 (dd, $J_{4',5"}$ = 3.18 Hz, 1H) H5", 3.39 (m, 1H) H2', 2.65 (t, 2H) Ha, 2.37-1.83 (m, 2H) H3', H3", 1.90 (d, 3H) 5-Me, 1.43 (m, 4H) Hb, Hc, 0.91 (t, 3H) Hd. ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 163.7,

150.6, 136.4 (d, J_{CH} = 180.8 Hz) C6, 110.1 (s) C5, 90.7 (d, J_{CH} = 169.6 Hz) C1', 80.3 (d, J_{CH} = 148.3 Hz) C4', 64.0 (d, J_{CH} = 143.8 Hz) C2', 62.5 (t, J_{CH} = 140.0 Hz) C5', 47.3 (t, J_{CH} = 132.6 Hz) Ca, 31.4 (t, J_{CH} = 132 Hz) CH_2, C3', 20.1 (t, J_{CH} = 128.6 Hz) CH_2, 13.6(q, J_{CH} = 124.7) Me, 12.0 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB^-): calc. for $(M-H)^-$ 296.1610, found 296.1595.

1-(2',3'-dideoxy-2'-amino-3'-*C*, 2'-*N*-((1-isopropyl)ethylene)-β-D-ribofuranosyl)thymine 36a & 1-(2',3'-dideoxy-2'-amino-2'-N-(3-methyl-butyl)-β-D-ribofuranosyl)thymine 36b: General procedure for radical cyclization was followed using **31** (75 mg, 0.153 mmol) in benzene (16 mL) and a solution of Bu_3SnH (64 μL, 0.23 mmol) and AIBN (7 mg) in benzene (2 mL) over 2 h to give pure **36a** (inseparable isomeric mixture in a ratio of 4:1, 39 mg, 76.5%, efficacy of radical cyclization 90.7%) and **36b** (8 mg, 15.6%). For δ and $^3J_{HH}$ of **36a**, see Tables 2 and 3; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 164.4, 150.7, 137.2 (d, J_{CH} = 183.3 Hz), 136.9 (d, J_{CH} = 183.3 Hz), 110.1, 93.3 (d, J_{CH} = 168.6 Hz), 92.1 (d, J_{CH} = 167.7 Hz), 87.4 (d, J_{CH} = 148.5 Hz), 81.5 (d, J_{CH} = 143.9 Hz), 70.7 (d, J_{CH} = 147.6 Hz), 70.3 (d, J_{CH} = 149.4 Hz), 62.6 (t, J_{CH} = 141.6 Hz), 61.5 (t, J_{CH} = 141.6 Hz), 51.6, 51.3, 50.4, 48.6 (t, J_{CH} = 137.9 Hz), 47.0 (d, J_{CH} = 136.55 Hz), 43.5 (d, J_{CH} = 140.2 Hz), 31.2 (d, J_{CH} = 127.4 Hz), 26.8 (d, J_{CH} = 121.9 Hz), 22.2 (q, J_{CH} = 122.8 Hz), 21.9 (q, J_{CH} = 122.7 Hz), 21.0 (q, J_{CH} = 122.8 Hz), 20.5 (q, J_{CH} = 122.6 Hz), 12.0 (q, J_{CH} = 129.2 Hz); MS (FAB^-): calc. for $(M-H)^-$ 308.1610, found 308.1626; **36b** ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.80 (d, 1H) H6, 5.75 (d, $J_{1',2'}$ = 3.18 Hz, 1H)H1', 4.40 (m, 1H) H4', 3.95 (dd, $J_{4',5'}$ = 2.69 Hz, $J_{5',5''}$ = 12.2 Hz, 1H) H5', 3.60 (dd, $J_{4',5''}$ = 3.20 Hz, 1H) H5", 3.40 (m, 1H) H2', 2.65 (t, J = 6.08 Hz, 2H) Ha, 2.38-1.64 (m, 2H) H3', H3", 1.90 (d, 3H) 5-Me, 1.49-1.26 (m, 3H) Hb, Hc, 0.90 (d, J = 6.10 Hz, 6H) 2xMe. ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 136.4 (d, J_{CH} = 177.5 Hz) C6, 110.1 (s) C5, 90.7 (d, J_{CH} = 168.5 Hz) C1', 80.3 (d, J_{CH} = 149.4 Hz) C4', 64.1 (d, J_{CH} = 143.8 Hz) C2', 62.5 (t, J_{CH} = 142.6 Hz) C5', 45.8 (t, J_{CH} = 133.7 Hz) Ca, 38.5 (t, J_{CH} = 124.7 Hz) CH_2, 31.5 (t, J_{CH} = 132.0 Hz) CH_2, 25.9 (d, J_{CH} = 121.0 Hz) CH, 22.2 (q, J_{CH} = 124.7 Hz) Me, 12.0 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB^-): calc. for $(M-H)^-$ 310.1767, found 310.1762.

1-(2',3'-dideoxy-2'-amino-3'-*C*, 2'-*N*-((1-benzyl)ethylene)-β-D-ribofuranosyl)thymine 37a & 1-(2',3'-dideoxy-2'-amino-2'-N-(3-phenyl-propyl)-β-D-ribofuranosyl)thymine 37b: General procedure for radical cyclization was followed using **32** (64 mg, 0.119 mmol) in benzene (15 mL) and a solution of Bu_3SnH (53 μL, 0.19 mmol) and AIBN (6 mg) in benzene (2 mL) over 2 h to give pure **37a** (inseparable isomeric mixture in a ratio of 2:1, 36 mg, 79%, efficacy of radical cyclization 93%)and **37b** (7 mg, 15.3%). For δ and $^3J_{HH}$ of **37a**, see Tables 2 and 3; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 164.3, 150.7, 139.9, 139.6, 137.2 (d, J_{CH} = 183.3 Hz), 137.0 (d, J_{CH} = 183.0 Hz), 128.6 128.4, 128.0, 126.3, 126.2, 110.4, 93.6 (d, J_{CH} = 166.8 Hz), 93.0 (d, J_{CH} = 166.8 Hz), 86.2 (d, J_{CH} = 148.5 Hz), 80.7 (d, J_{CH} = 144.8 Hz), 70.1 (d, J_{CH} = 148.5 Hz), 69.3 (d, J_{CH} = 146.6 Hz), 63.1 (t, J_{CH} = 142.1 Hz), 62.3 (t, J_{CH} = 142.1 Hz), 52.1 (t, J_{CH} = 138.8 Hz), 50.0 (t, J_{CH} = 137.5 Hz), 45.5 (d, J_{CH} = 133.5 Hz), 45.3 (d, J_{CH} = 133.8 Hz), 44.2 (d, J_{CH} = 133.8 Hz), 39.1 (t, J_{CH} = 127.4 Hz), 33.8 (t, J_{CH} = 127.0 Hz), 12.0 (q, J_{CH} = 129.2 Hz); MS (FAB^-): calc. for $(M-H)^-$ 356.1610, found 356.1612; **37b** ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.71 (d, J = 1.22 Hz, 1H) H6, 7.30-7.20 (m, 5H) arom., 5.71 (d, $J_{1',2'}$ = 3.42 Hz, 1H) H1', 4.40 (m, 1H) H4', 3.95 (dd, $J_{4',5'}$ = 2.68 Hz, 1H) H5', 3.64 (dd, $J_{4',5''}$ = 3.42 Hz, $J_{5',5''}$ = 12.2 Hz, 1H) H5", 3.40 (m, 1H) H2', 2.75-2.57 (m, 4H) Ha, Hc, 2.36-1.66 (m, 2H) H3', H3", 1.89 (d, 3H) 5-Me, 1.31 (m, 2H) Hb. ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 163.0, 150.6, 136.4 (d, J_{CH} = 179.0 Hz) C6, 128.2, 125.7, 110.2 (s) C5, 91.0 (d, J_{CH} = 169.6 Hz) C1', 80.3 (d, J_{CH} = 148.3 Hz) C4', 63.8 (d, J_{CH} = 141.6 Hz) C2', 62.7, (t, J_{CH} = 141.0 Hz) C5', 47.1 (t, J_{CH} = 132.0 Hz) Ca, 33.2 (t, J_{CH} = 124.1 Hz) CH_2, 31.6 (t, J_{CH} = 132.6 Hz) CH_2, 31.1 (t, J_{CH} = 130.3 Hz) CH_2, 12.1 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB^-): calc. for $(M-H)^-$ 358.1767, found 358.1786.

1-(2',3'-dideoxy-2'-amino-3'-*C*, 2'-*N*-((1-dimethyl)ethylene)-β-D-ribofuranosyl)thymine 38a & 1-(2',3'-dideoxy-2'-amino-2'-N-(2-methyl-propyl)-β-D-ribofuranosyl)thymine 38b: General procedure for radical cyclization was followed using **33** (50 mg, 0.105 mmol) in benzene (10 mL) and a solution of Bu_3SnH (44 μL, 0.158 mmol) and AIBN (5 mg) in benzene (2 mL) over 2 h to give pure **38a** (26 mg, 77.1%, efficacy of radical cyclization 90%) and **38b** (5 mg, 14.7%). For δ and $^3J_{HH}$ of **38a**, see Table 2, 3; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 164.4, 150.6, 137.1 (d, J_{CH} = 181.5 Hz),110.3, 93.6 (d, J_{CH} = 168.6 Hz), 82.1 (d, J_{CH} = 144.8 Hz), 70.1 (d, J_{CH} = 147.6 Hz), 62.8 (t, J_{CH} = 141.6 Hz), 57.8 (t, J_{CH} = 139.3 Hz), 52.3 (d, J_{CH} = 139.3 Hz), 41.1, 28.0 (q, J_{CH} = 124.6 Hz), 20.6 (q, J_{CH} = 125.6 Hz), 11.9 (q, J_{CH} = 128.3 Hz); MS (FAB^-): calc. for $(M-H)^-$ 294.1454, found 294.1467; **38b** ^{1}H-NMR ($CDCl_3$+CD_3OD): δ 7.77 (d, J = 1.22 Hz, 1H) H6, 5.73 (d, $J_{1',2'}$ = 3.17 Hz, 1H) H1', 4.42 (m, 1H) H4', 3.97 (dd, $J_{4',5'}$ = 2.68 Hz, $J_{5',5''}$ = 12.21 Hz, 1H) H5', 3.65 (dd, $J_{4',5''}$ = 3.42 Hz, 1H) H5", 3.38 (m, 1H) H2', 2.45 (d, 2H) Ha, 2.36-1.65 (m,

3H) H3', Hb, H3", 1.90 (d, 3H) 5-Me, 0.91 (d, J = 6.35 Hz, 6H) 2xMe; ^{13}C-NMR ($CDCl_3$+CD_3OD): δ 163.4, 150.5, 136.4, (d, J_{CH} = 177.5 Hz) C6, 110.5 (s) C5, 91.0 (d, J_{CH} = 169.6 Hz) C1', 80.4 (d, J_{CH} = 148.3 Hz) C4', 64.1 (d,J_{CH} = 141.6 Hz) C2', 62.6, (t, J_{CH} = 142.1 Hz) C5', 55.4 (t, J_{CH} = 135.4 Hz) Ca, 31.6 (t, J_{CH} = 132.0 Hz) C3', 28.0 (d, J_{CH} = 125.8 Hz) Cb , 20.3 (q, J_{CH} = 124.7 Hz) 2xMe, 12.1 (q, J_{CH} = 129.2 Hz) 5-Me. MS (FAB$^-$): calc. for (M-H)$^-$ 296.1610, found 296.1599.

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shown in Fig. 1. The fact that the proton at C_c showed a NOE with the H_a but not with the H_b proton confirm that the enhancement observed is due to spatial proximity and not due to the effect of the J-couplings (the $^3J_{bc}$ coupling is always larger than the $^3J_{ac}$ coupling). ***Configuration at C_c Center of the Minor Diatereoisomer in 19a - 23a and 35a - 38a*** The configuration at C_c was determined only for **22a**. In **22a**, a NOE was observed at H1' upon saturation of the proton at C_c, which indicates that the C_c carbon has the S configuration.

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35. The translation of J-couplings to P and Ψ_m is achieved in three steps. (i) The generalized Karplus equation relates the vicinal proton-proton coupling constants with the corresponding proton-proton torsion angles ϕ_{HH} and takes into account the effect of substituent electronegativity and orientation; (ii) The proton-proton torsion angles ϕ_{HH} are related to the corresponding endocyclic torsion angles ν_i by the equation:

$$\phi_{HH} = a + b\nu_i \qquad (1)$$

The nomenclature for the endocyclic torsion angles ν_0-ν_4 in riboses and τ_0-τ_4 in pyrrolidine is shown in Figure 2. In trigonal symmetry approximation, b is 1, a is 0 for *cis* proton and ± 120 for *trans* proton. However, in five-membered rings, the bond angles deviated from tetrahedral values, there is a deviation from trigonal projection symmetry and the parameters a and b which are characteristic of each pair of vicinal protons, differs from the standard values (ref. 33). (iii) The endocyclic torsion angles ν_i are translated into the phase angle of pseudorotation P and the puckering amplitude Ψ_m according to the equation:

$$\nu_i = \Psi_m \cos(P + (i-2)\,144^\circ) \qquad \text{with } i = 1\text{-}4 \qquad (2)$$

For the pyrrolidine ring, the relation between the phase angle of pseudorotation Q, the puckering amplitude Ψ^*_m and the endocyclic torsion angles τ_0-τ_4 is given by:

$$\tau_i = \Psi^*_m \cos(Q + (i-2)\,144^\circ) \qquad \text{with } i = 1\text{-}4 \qquad (3)$$

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38. Two sets of calculation were performed: (1) The parameters Q and τ of the minor conformer were fixed betwen $100^\circ < P < 220^\circ$ and $25^\circ < \Psi^*_m < 45^\circ$, while the parameters Q and Ψ^*_m of the major conformers were optimized to minimize the overall root mean square error (rms). (2) The puckering amplitude of both conformers were fixed between 25 and 45 °, while their phase angle were optimized. For each calculation, two sets of a and b parameters in equation 1 were tried. In the first case, a was set to 0, ± 120 ° depending on the location of the proton while b was set to 1. In the second case, the a and b parameters calculated by Altona *et al.* for unsubstituted prolines were used (see reference 36). Lower rms values (0.1-0.2 Hz) were obtained when the a and b parameters derived for proline rings were used. It should be kept in mind however that none of these two sets of parameters is absolutely correct for our pyrrolidine system because of different substituents in our fused pyrrolidine ring.
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