114. Aza-*Claisen* Rearrangement: Synthesis of 5′-Branched 5′-Aminothymidines

by **Jochen Ammenn**[1]), **Karl-Heinz Altmann**[2]), and **Daniel Belluš**[3])*

Corporate Research Units, *Ciba-Geigy AG*, CH-4002 Basel

Dedicated with best personal wishes of *D. B.* to Professor *Oskar Jeger* on the occasion of his 80th birthday

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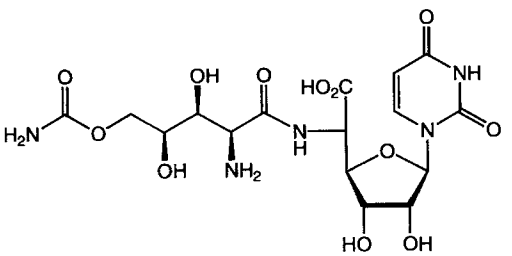
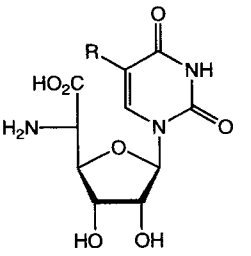
The syntheses of both diastereoisomers of 5′-ethyl-substituted thymidine dimers, the (5′*R*)- and (5′*S*)-configurated **33a** and **33b**, respectively, in which the natural phosphodiester linkage is replaced by an amide group (C(3′)–CH_2CONH–CH(5′)(Et)), are described. Their fully protected derivatives **35a** and **35b**, respectively, are suitable for incorporation into antisense oligonucleotides. Unexpectedly, an attempted Pd^{II}-catalysed aza-*Claisen* rearrangement of trichloroacetimidate **7** provided the diastereoisomerically pure cyclopropane derivative **17**, whose structure was confirmed by X-ray analysis.

Introduction. – Modified nucleosides and nucleotides represent important and also attractive synthetic targets that can be associated with a wide range of biological activities. Although these types of compounds have been traditionally employed mainly as anti-viral and anti-cancer agents [1], modified nucleosides are also constituent parts of a variety of natural products with antibiotic and herbicidal activities [2]. Most recently, they have attracted considerable attention as building blocks for antisense oligonucleotides as a novel class of potential therapeutic agents [3] [4]. One of the particular challenges encountered in the synthesis of naturally occurring nucleoside antibiotics derives from the fact that the nucleoside component frequently possesses a 5′-branched ribose moiety, as, *e.g.*, in polyoxin J and nikkomycin B (*Fig. 1*), thus incorporating an additional chiral center that is not present in natural DNA or RNA building blocks. As for many other sugar-modified nucleosides, 5′-branched 2′-deoxyribonucleosides have also been evaluated as building blocks for antisense oligonucleotides, either in the context of an otherwise unmodified phosphodiester backbone [5] or in combination with amide-modified internucleoside linkages [6]. In particular, it has been demonstrated that the incorporation of 5′-methyl-substituted amide dimer units **1a** and **1b** into oligodeoxyribonucleotides gives rise to substantial changes in RNA-binding properties [6], with modification **1a** ((5′*S*)-configuration) leading to significantly enhanced RNA-binding affinity. In contrast, incorporation of modification **1b** ((5′*R*)-configuration) into the DNA strand of DNA/RNA heteroduplexes results in a dramatic decrease in DNA/RNA duplex stability.

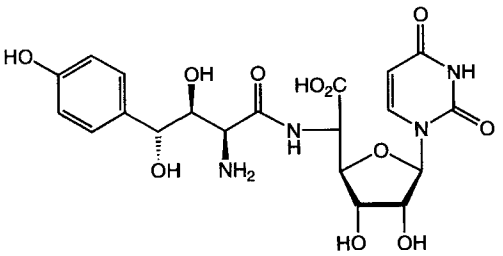
[1]) Present address: TFL (a joint venture of *Ciba*, *Röhm*, and *Stockhausen*), Kirschenallee, D-64275 Darmstadt.
[2]) Present address: *Novartis Pharma AG*, K-136.4.96, CH-4002 Basel.
[3]) Present address: University of Fribourg, CH-1700 Fribourg.



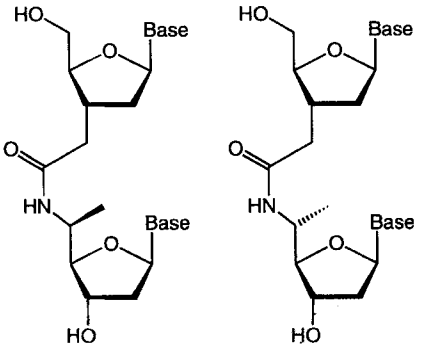
Polyoxin J



R = CH_2OH **Polyoxin C**
R = CH_3 **Deoxypolyoxin C**



Nikkomycin B



1a **1b**

Fig. 1. *Nucleosides possessing a 5′-branched ribose moiety*

Regarding the synthesis of 5′-branched 5′-aminoribonucleoside derivatives, a variety of approaches towards the synthesis of polyoxins C (*Fig. 1*) as the nucleoside components of the polyoxin J and nikkomycin B nucleoside antibiotics have been reported [7–12] that are based on different types of chiral starting materials (*e.g.*, L-serine [7], D-ribose [8], uridine [9], L-threose [10], *myo*-inositol [11]) and involve a diverse number of key transformations to establish the critical chiral center at C(5′) (*e.g.*, nucleophilic addition to a nitro-olefin [8c], asymmetric dihydroxylation of a C=C bond [9], addition of a formyl anion equivalent to an aldehyde [8a], asymmetric aza-*Claisen* rearrangement [8b]). In comparison, only two different approaches have been previously pursued for the synthesis of (5′*S*)-5′-amino-2′-deoxy-5′-methylribonucleosides (as the amino component of dimer units **1a**) [6], one of which involves the (nonselective) addition of methylmagnesium iodide to 'thymidine 5′-aldehyde', whereas the other constitutes a multi-step synthesis that is based on D-glucose as chiral starting material. In both cases, introduction of the 5′-amino group is achieved through a classical functional-group transformation starting from the corresponding secondary alcohol. However, a more versatile alternative for the synthesis of differently 5′-substituted 5′-aminonucleosides could consist in the use of an aza-*Claisen* rearrangement [13] [14] as the key transformation for the installment of the 5′-amino functionality, either at the level of an appropriately protected and functionalized ribose derivative (which would subsequently be elaborated into the de-

sired nucleoside) or directly employing a modified nucleoside as the substrate (*Scheme 1*). Further functionalization of the resulting 5′-vinyl substituent could then lead to a variety of different 5′-substituted 5′-aminonucleosides which would be of considerable interest for structure/affinity studies involving amide-modified oligonucleotides (*cf. Fig. 1*). As to the crucial question of the stereochemistry of the rearrangement step, it should be noted that we have previously demonstrated that the Pd^{II}-catalysed aza-*Claisen* rearrangement of trichloroacetimidates derived from primary allylic alcohols with an adjacent center of chirality can proceed with complete diastereoselectivity [14]. Although this outcome is likely to be related to complexation of the Pd catalyst to an attached protected amino group, it is also conceivable that the chiral sugar moiety in sugar- or nucleoside-derived substrates could lead to a certain degree of diastereoselection.

Scheme 1

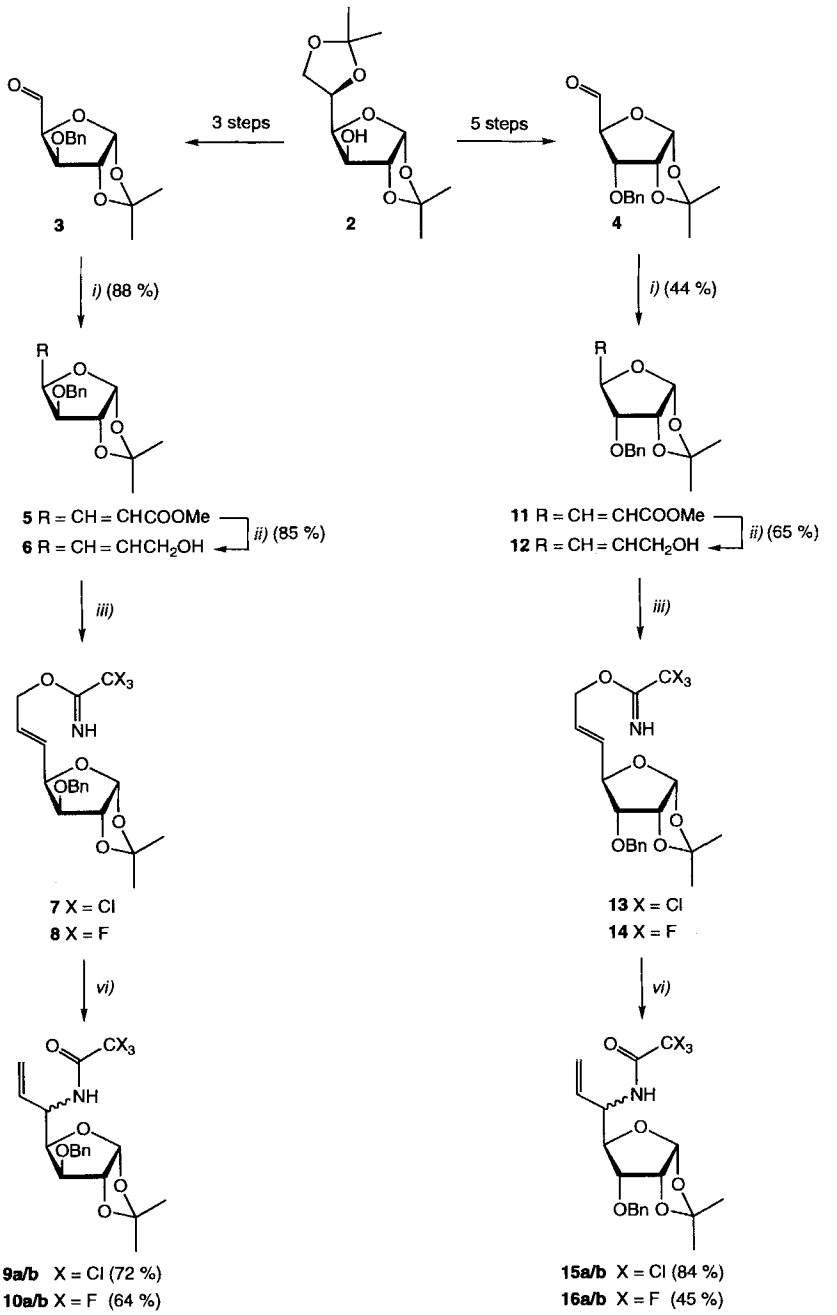
R^1, R^2, R^3, R^4 = H, protected OH; R^5 = H, thymin-1-yl

As indicated above, the thermal rearrangement of an allylic trifluoroacetimidate derived from D-ribose has previously been exploited for the synthesis of thymine-containing deoxypolyoxin C [8b]. However, Pd^{II}- or Hg^{II}-catalysed rearrangments of this type involving sugar-derived substrates have not been previously studied. With nucleoside derivatives, neither thermal nor metal-catalysed reactions have been investigated so far.

In this paper, we now want to report on the thermal as well as metal-catalysed aza-*Claisen* rearrangements of allylic trihaloacetimidates that are derived from D-xylose, D-ribose, and thymidine by chain-extension from the C(5) and C(5′) atom, respectively (*cf. Scheme 1*). Using this methodology, an efficient access to (5′*S*)- and (5′-*R*)-5′-amino-5′-ethylthymidine was established.

Results and Discussion. – Initial experiments served to investigate the effect of neighbouring substituents on the stereoselectivity of the aza-*Claisen* rearrangement. Imidates **7** and **8**, and **13** and **14** (*Scheme 2*), which derived from D-xylose and D-ribose, respectively, were chosen as model substrates. The preparation of **7**, **8**, **13**, and **14** was based on 1,2:5,6-di-*O*-isopropylidene-D-glucose **2** as the common starting material, which was transformed into aldehydes **3** and **4** according to [15]. The aldehydes **3** and **4** were then converted to the α,β-unsaturated esters **5** and **11** by *Wittig* reaction with $Ph_3PCHCOOMe$ in 88 and 44% yield, respectively. Diisobutylaluminium hydride (DIBAH) reduction afforded the allylic alcohols **6** in 85% yield and **12** in 65% yield. Synthesis of the target imidates **7**, **8**, **13**, and **14** was achieved by treatment of the corresponding allylic alcohols with NaH in Et_2O and subsequent addition of the trihalogenoacetonitriles (yields essentially quantitative), with CF_3CN being prepared *in situ* by heating CF_3CONH_2 in the presence of P_2O_5 to 140° [16].

Scheme 2



i) $Ph_3PCHCOOMe$, THF, r.t. 2 h. *ii*) DIBAH, $BF_3 \cdot Et_2O$, CH_2Cl_2, −78°. *iii*) For **7** and **13**: 1. NaH, Et_2O, 0°, 5 min; 2. CCl_3CN, 0°, 15 min, r.t., 30 min; for **8** and **14**: NaH, THF, 0°, 15 min; 2. CF_3CN, −78°, 20 min. *iv*) Xylene, 137°.

The imidates **7**, **8**, **13**, and **14** were submitted to thermally induced aza-*Claisen* rearrangements without purification, producing the trihalogenoacetamides **9**, **10**, **15**, and **16** respectively, in 45–84% yield (see *Table*). These yields pertain to the two-step conversion of the allylic alcohol into the corresponding trihalogenoacetamide. The reactions were generally conducted in refluxing xylene in the presence of 2% of a stabilizer such as 2,6 di(*tert*-butyl)-*p*-cresol (DBPC), which led to significantly improved yields. For example, the yield for the rearrangement of imidate **13** could be raised from 23% without stabilizer to 84% with DBPC. In this thermal study, no significant diastereoselectivity was observed for any of the furanose derivatives investigated, independently of the configuration at C(3) (see *Table*). These findings are in agreement with previous literature reports on the lack of diastereoselectivity in thermally induced aza-*Claisen* reactions involving imidates derived from primary allylic alcohols [14a] [17].

Table. *Conditions and Results of Thermally Induced Aza*-Claisen *Rearrangements*

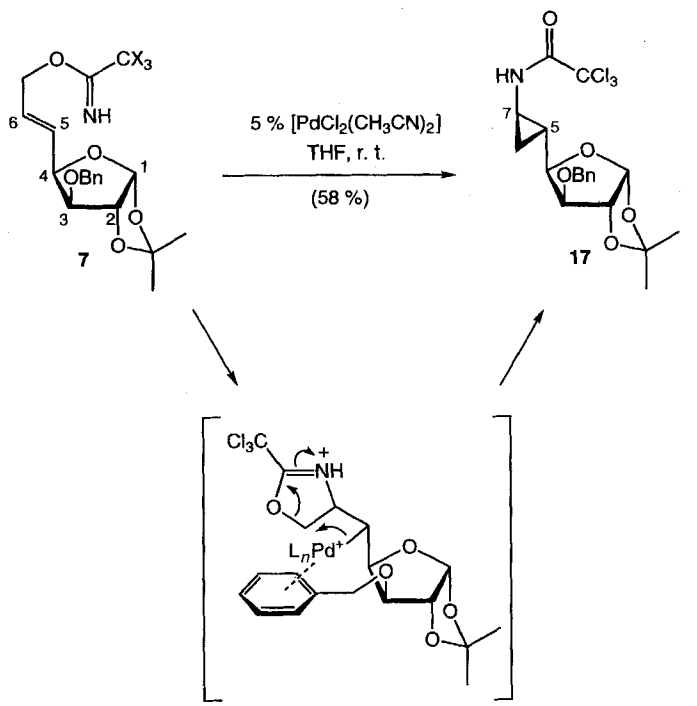
	X	*T* [°C]	*t* [h]	Yield [%]	**a**/**b**		X	*T* [°C]	*t* [h]	Yield [%]	**a**/**b**
9a/**9b**	Cl	137	13	72	1.1:1	**15a**/**15b**	Cl	137	13	84	1:1
10a/**10b**	F	137	81	64	1.5:1	**16a**/**16b**	F	137	81	45	1.2:1

As metal-catalysed aza-*Claisen* rearrangements have been shown to proceed with excellent diastereoselectivity in the synthesis of 1,2-diamino compounds [14], aza-*Claisen* rearrangement of the crude imidates **7**, **8**, **13**, and **14** was also attempted in the presence of $[PdCl_2(MeCN)_2]$ or $[Hg(CF_3COO)_2]$ as potent rearrangement catalysts. Unfortunately, no metal-induced aza-*Claisen* rearrangement was observed for any of these substrates, even in the presence of equimolar or even higher amounts of catalyst, as a precaution against a possible complexation of the catalyst. Unexpectedly, however a novel metal-catalysed cyclization was observed, when *xylo*-trichloroimidate **7** was treated with 5% Pd^{II} catalyst (*Scheme 3*). Cyclopropane derivative **17** was formed diastereoselectively in 58% yield. Formation of **17** occurred faster with higher amounts of $[PdCl_2(MeCN)_2]$, but could not be observed at all with $[Hg(CF_3COO)_2]$. The absolute configuration of **17** was determined by X-ray crystallography (*Fig. 2*)[4]. Since the analogous product was not formed with *ribo*-derivative **13** (3α-OBn group), it may be speculated that neighbouring-group participation of the 3β-OBn group in **7** facilitates the coordination of the Pd-atom with the C=C bond in a way that directs the attack by the imido N-atom to C(6), rather than C(5), thus giving rise to a five-membered-ring transition state prior to formation of the three-membered ring[5]). This novel reaction involves diastereoselective formation of

[4]) X-Ray crystallographic data, including a table of refined atomic coordinates, have been deposited by the editor with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-10/53. Copies of the data can be obtained, free of charge, on application of the director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44-1223-336033 or e-mail: teched@chemcrys.cam.ac.uk).

[5]) Preliminary experiments were conducted to investigate the role of the neighbouring 3β-OBn group. The hypothesis that the 3β-OBn is neccessary for the formation of the three-membered ring was confirmed by rearrangement experiments with similar imidates having other 3β-substituents. With β-positioned MeO, Me_2(thexyl)SiO or hydrogen (3-deoxy-D-xylose) substituents at C(3) of these otherwise identical imidates, neither three-membered-ring formation nor formation of aza-*Claisen* products was observed.

Scheme 3



two new stereogenic centers, while in a conventional aza-*Claisen* rearrangement only one new stereogenic center would have been formed *via* a six-membered-ring transition state.

The lack of stereoselectivity observed for aza-*Claisen* rearrangements of *ribo*- and *xylo*-derivatives **7**, **8**, **13**, and **14** in conjunction with the fact that a number of steps would still be required to convert the resulting rearrangement products **9**, **10**, **15**, and **16**, respectively, into 5′-branched 5′-aminonucleosides led us to investigate an alternative approach to these compounds, involving the aza-*Claisen* rearrangement of nucleoside-derived imidates as the key transformation (*Scheme 4*). For this purpose, thymidine (**18**) was protected in a sequence of reactions (→ **19** → **20** → **21**) to afford primary alcohol **22**. *Moffat* oxidation and addition of (triphenylphosphoranylidene)acetaldehyde to the reaction mixture gave the α,β-unsaturated aldehyde **23** in 77% yield. Reduction with $NaBH_4$ and treatment of the resulting allylic alcohol **24** with NaH and CCl_3CN led to imidate **25** that was submitted to thermally induced aza-*Claisen* rearrangement in refluxing xylene without prior purification. Chromatographical separation of the resulting 1:1 mixture of the diastereoisomeric trichloroacetamides **26a**/**26b** was done only for characterization purposes (combined yield after separation 84%). On larger scale, the mixture was directly reduced with $NaBH_4$ to remove the trichloroacetyl group [18], thus furnishing an 80% yield of an amine mixture **27a**/**27b** which could be more readily separated. The absolute configuration at C(5′) of **27a** and **27b** was determined by the *Mosher* method [19].

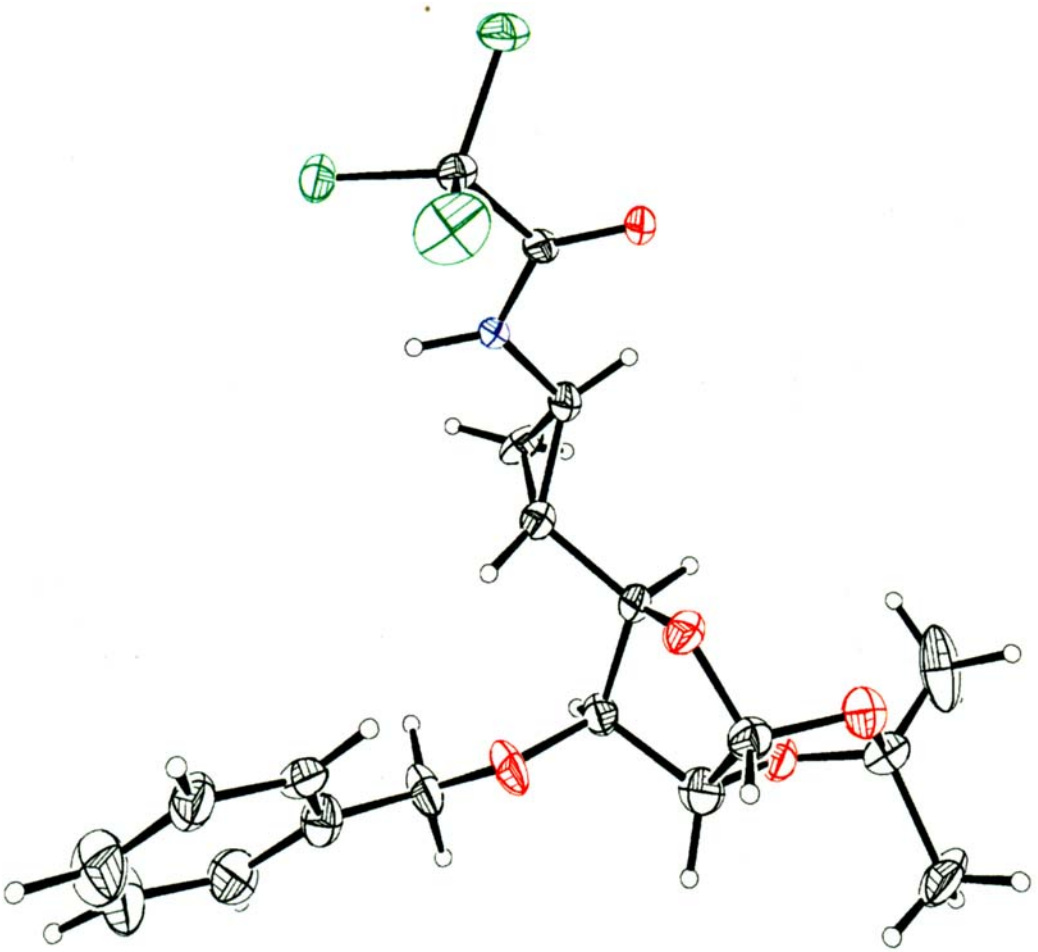
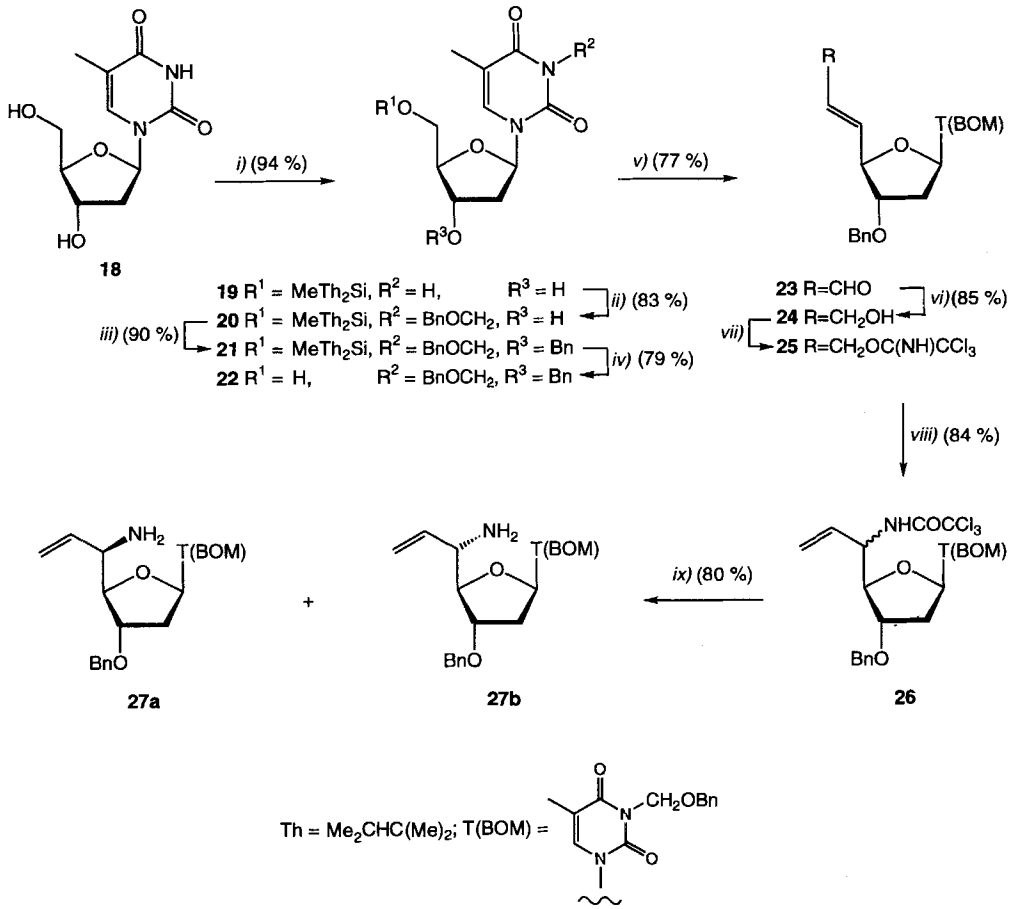


Fig. 2. *X-Ray crystal structure* (ORTEP plot) *of* **17**

In accordance with the results discussed above, for *ribo*- and *xylo*-derivatives **7**, **8**, **13**, and **14**, no aza-*Claisen* products of **25** could be observed at room temperature in the presence of a metal catalyst, in contrast to the easily occurring thermal aza-*Claisen* rearrangement. However, the presence of the bulky thyminyl β-substituent at C(1′) did not induce any diastereoselectivity in the latter rearrangement (see above).

With the 5′-amino-functionalized nucleosides at hand, we now focused on the synthesis of dimers of type **1a** and **1b**. For this purpose, **28** (*Scheme 5*) [20] was converted into the dimethoxytrityl ($(MeO)_2Tr$)-protected activated pentafluorophenyl ester **31** by cleavage of the (t-Bu)Me_2Si protecting group ($\rightarrow$ **29**), reprotection at O–C(5′) with a $(MeO)_2Tr$ group ($\rightarrow$ **30**) in 70% overall yield, and finally reaction of **30** with pentafluorophenyl trifluoroacetate. Although (t-Bu)Me_2Si removal from **28** with Bu_4NF led to problems in the purification of hydroxy acid **29** (removal of Bu_4NF), this route still proved to be more convenient than silyl-ether cleavage from a (t-Bu)Me_2Si-protected dimer.

Scheme 4

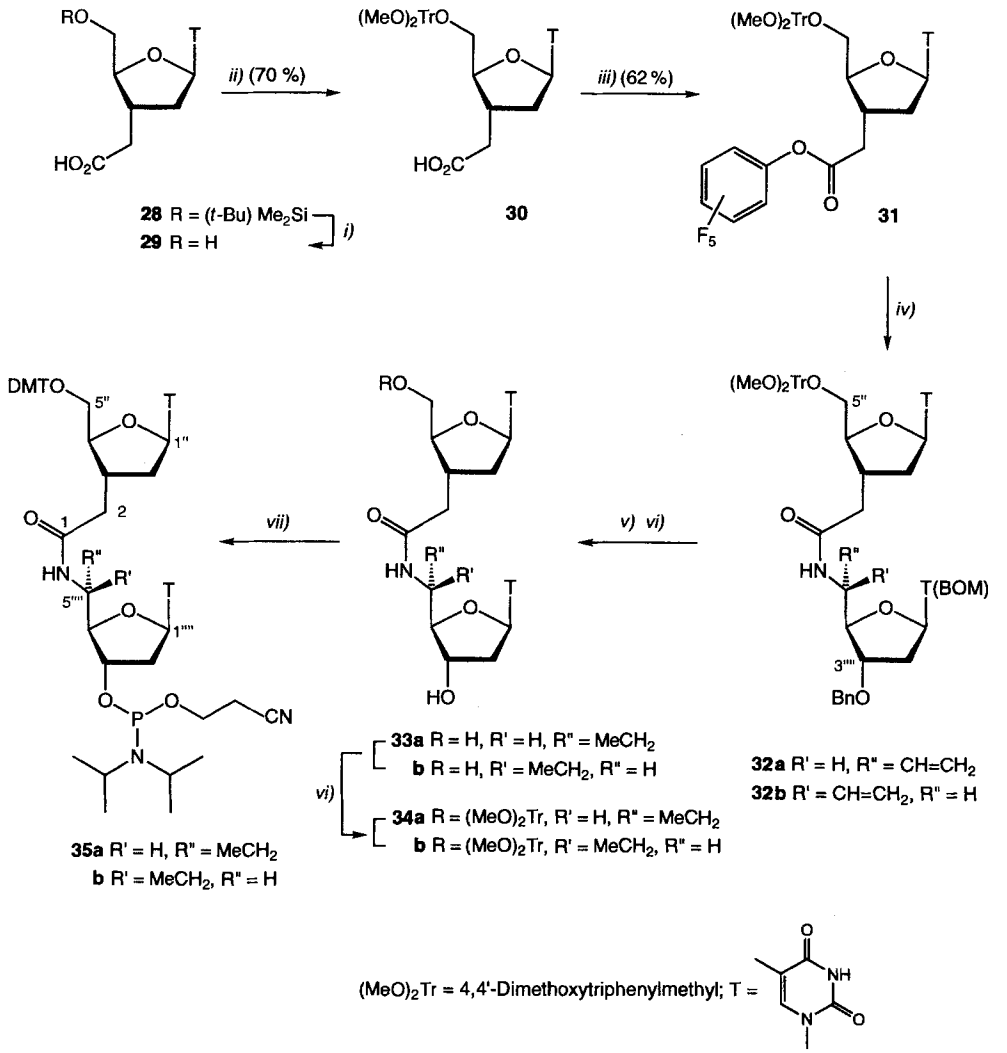


i) $Me_2ThSiCl$, 1*H*-imidazole, DMF, 0°, 1 h. *ii*) $BnOCH_2Cl$, DBU, MeCN, 0°, 2 h. *iii*) 1. NaH, THF, 5 min; 2. BnBr, Bu_4NI, r.t., 12 h. *iv*) Bu_4NF, THF, r.t., 2 h. *v*) 1. DCC, DMSO, H^+, 2 h; 2. $Ph_3PCHCHO$, r.t. 4 h. *vi*) $NaBH_4$, EtOH, 5 min. *vii*) 1. NaH, THF, r.t., 15 min; 2. CCl_3CN, 0°, 15 min, r.t., 30 min. *viii*) Xylene, 137°, 44 h. *ix*) $NaBH_4$, EtOH, r.t., 12 h: **27a**/**27b** 1:1.

Excellent results were obtained for the condensation of pentafluorophenyl ester **31** with amines **27a** and **27b** in the presence of *Hünig*'s base giving **32a** and **32b**, respectively. Complete removal of the benzyl group at C(3'''') and the benzyloxymethyl group at N(3''') by catalytic hydrogenation required addition of 3 equiv. of HCl, which led to loss of the $(MeO)_2Tr$ group at O–C(5'')[6] (→ **33a** and **33b**, resp.). After dimethoxytrityl

[6]) The principals of nucleoside numbering are retained. For convenience, locants 1 and 2 are given to the bridging acetamide moiety, locants 1' to 6' to the 'upper' nucleobase, locants 1'' to 5'' to the 'upper' ribofuranose moiety, locants 1''' to 6''' to the 'lower' nucleobase, and locants 1'''' to 5'''' to heptofuranose moiety (see **35**).

Scheme 5



i) Bu_4NF, THF, r.t. *ii*) $(MeO)_2TrCl$, Et_3N, 4-(dimethylamino)pyridine (cat.), Py, 0°. *iii*) $CF_3COOC_6F_5$, py, DMF, r.t., 16 h. *iv*) **27a** or **27b**, $(i\text{-}Pr)_2EtN$, THF, r.t. 16 h; **32a**: 94%; **32b**: 93%. *v*) H_2, Pd/C, HCl, MeOH, r.t.; **33a**: 78%; **33b**: 77%. *vi*) $(MeO)_2TrCl$, py, 0°, 24 h; **34a**: 66%; **34b**: 65%. *vii*) $[(i\text{-}Pr)_2N]_2POCH_2CH_2CN$, $[(i\text{-}Pr)_2N](CHN_4)$, CH_2Cl_2, r.t., 2 h; **35a**: 86%: **35b**: 88%.

reprotection (→ **34a** and **34b**, resp.) the phosphoramidation afforded compounds **35a** and **35b** which were appropriately functionalized for incorporation into oligonucleotides.

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Experimental Part

General. All temp. quoted are uncorrected. If not indicated otherwise, reagents were commercially available and used without further purification. Solvents were purified and dried according to standard procedures. IR Spectra: *Perkin-Elmer 241 Paragon 1000 FT-IR 25*. NMR Spectra: *Bruker DPX 400* for ^1H, ^{13}C, and ^{31}P; chemical shifts δ in ppm (internal standards), coupling constants J in Hz. Mass spectra: *Finigann-MAT-90* spectrometers. $[\alpha]_D$: *Perkin-Elmer-241* polarimeter (Na 589 nm). TLC: silica gel *60* F_{254} plates from *Merck*. Flash chromatography (FC): silica gel (0.032–0.063 mm) from *Merck*. Combustion analyses were performed at the 'Zentrale Analytik' of *Ciba* in Basel.

1. *Unsaturated Esters* **5** *and* **11** via Wittig *Reaction* (*Method A*). To a soln. of the aldehyde (1 equiv.) in THF (5 ml/mmol), $Ph_3PCHCOOMe$ (1 equiv.) was added at r.t. After stirring for 2 h, the solvent was evaporated.

*Methyl 3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-α-*D*-xylo-hept-5-enfuranuronate* (**5**). According to *Method A*, with **3** (3.81 g, 13.69 mmol): 4.02 g (88%) of **5**, after FC (AcOEt/hexane 1:4). Colourless oil. $[\alpha]_D^{20} = -15.3$ ($c = 0.3$, $CHCl_3$). IR (film): 3065, 3031, 2989, 2951 (C–H); 1723 (C=O); 1437 (CH_2); 1375 (Me). ^1H-NMR ($CDCl_3$): 1.33, 1.50 (2*s*, Me_2C); 3.77 (*s*, MeO); 3.97 (*d*, $J = 4$, H–C(3)); 4.50, 4.63 (2*d*, $J = 13$, $PhCH_2$); 4.63–4.66 (*m*, H–C(2)); 4.80 (*m*, H–C(4)); 6.00 (*d*, $J = 4$, H–C(1)); 6.18 (*dd*, $J = 1, 16$, H–C(6)); 6.96 (*dd*, $J = 5, 16$, H–C(5)); 7.22–7.38 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 26.2, 26.4 (Me); 51.7 (MeO); 72.2 ($PhCH_2$); 79.2, 82.7, 82.8 (C(2), C(3), C(4)); 106.2 (C(1)); 111.9 (Me_2C); 122.8 (C(6)); 127.8, 128.0, 128.1, 128.3, 128.6, 137.0 (arom. C); 141.5 (C(5)); 178.0 (C=O). MS: 333 ($[M - H]^+$), 227 ($[M - PhCH_2O]^+$), 259 ($[M - Me_2CO_2]^+$), 181 ($[M - Me_2CO_2 - Ph]^+$), 169 ($[M - Me_2CO_2 - PhCH_2]^+$), 153 ($[M - Me_2CO_2 - PhCH_2O]^+$). Anal. calc. for $C_{18}H_{22}O_6$ (334.37): C 64.66, H 6.63; found: C 64.66, H 6.79.

*Methyl 3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-α-*D*-ribo-hept-5-enfuranuronate* (**11**). According to *Method A*, with **4** (5.60 g, 20.12 mmol): 2.96 g (44%) of **11**, after FC (AcOEt/hexane 1:4). Colourless oil. $[\alpha]_D^{20} = +45.8$ ($c = 2.3$, $CHCl_3$). IR (film): 3066, 3032, 2990, 2952 (C–H); 1727 (C=O); 1436 (CH_2); 1374 (Me). ^1H-NMR ($CDCl_3$): 1.37, 1.60 (2*s*, 2 Me); 3.53 (*dd*, $J = 4, 9$, H–C(4)); 3.83 (*s*, MeO); 4.53–4.67 (*m*, H–C(3)); 4.58, 4.72 (2*d*, $J = 11$, $PhCH_2$); 5.77 (*d*, $J = 4$, H–C(1)); 6.13 (*dd*, $J = 1, 15$, H–C(6)); 6.93 (*dd*, $J = 4, 15$, H–C(5)); 7.26–7.40 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 25.8, 25.5 (Me); 50.7 (MeO); 71.6 ($PhCH_2$); 76.0, 76.1, 81.0 (C(2), C(3), C(4)); 103.0 (C(1)); 112.3 (Me_2C); 121.0 (C(5)); 127.0, 127.2, 127.6, 136.1 (arom. C); 142.8 (C(6)); 165.5 (C=O). MS: 334 (M^+), 171 ($[M - PhCH_2 - CHCOOMe]^+$). Anal. calc. for $C_{18}H_{22}O_6$ (334.37): C 64.66, H 6.63; found: C 64.67, H 6.71.

2. *Allylic Alcohols* **6** *and* **12** via *DIBAH Reduction* (*Method B*). To a soln. of the unsaturated ester (1 equiv.) in CH_2Cl_2 (10 ml/mmol) was added $BF_3 \cdot Et_2O$ (1.2 equiv.) and 1.2M DIBAH (3.6 equiv.) in toluene at −78°. After stirring for 1 h at −78°, the reaction was quenched with MeOH (0.1 ml/mmol). The mixture was allowed to warm to r.t., poured onto 30% aq. potassium sodium tartrate soln. (30 ml/mmol) and extracted with CH_2Cl_2 (2 × 15 ml/mmol). The org. layer washed with sat. aq. NaCl soln. (30 ml/mmol), dried ($MgSO_4$), and evaporated.

*3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-α-*D*-xylo-hept-5-enfuranose* (**6**). According to *Method B*, with **5** (2.52 g, 7.54 mmol): 1.96 g (85%) of **6**, after FC (AcOEt/hexane 1:4). Colourless oil. $[\alpha]_D^{20} = -61.6$ ($c = 1.7$, $CHCl_3$). IR (film): 3452 (O–H); 3063, 3032, 2988, 2934 (C–H); 1455 (CH_2); 1375 (Me). ^1H-NMR ($CDCl_3$): 1.32, 1.50 (2*s*, 2 Me); 3.87 (*d*, $J = 3$, H–C(2)); 4.17 (*d*, $J = 5$, 2 H–C(5)); 4.53, 4.65 (2*d*, $J = 13$, $PhCH_2$); 4.62–4.70 (*m*, H–C(3), H–C(4)); 5.88 (*ddd*, $J = 1, 7, 16$, H–C(5)); 5.96 (*d*, $J = 3$, H–C(1)); 6.02 (*ddd*, $J = 1, 5, 16$, H–C(6)); 7.23–7.40 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 26.6, 27.2 (Me); 63.4 (C(7)); 72.6 ($PhCH_2$); 81.0, 83.3, 83.7 (C(2), C(3), C(4)); 105.2 (C(1)); 111.0 (Me_2C); 125.4, 134.6 (C(5), C(6)); 128.1, 128.3, 128.9, 137.0 (arom. C). MS: 307 (M^+), 230 ($[M - Ph]^+$), 231 ($[M - Me_2CO_2]^+$), 215 ($[M - PhCH_2]^+$), 141 ($[M - Me_2CO_2 - PhCH_2]^+$). Anal. calc. for $C_{17}H_{22}O_5$ (306.36): C 66.65, H 7.24; found: C 66.37, H 7.28.

*3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-α-*D*-ribo-hept-5-enfuranose* (**12**). According to *Method B*, with **11** (2.12 g, 6.35 mmol): 1.65 g (65%) of **12**, after FC (AcOEt/hexane 1:4). Colourless oil. $[\alpha]_D^{20} = +49.8$ ($c = 2.8$, $CHCl_3$). IR (film): 3474 (O–H); 3030, 2988, 2935 (C–H); 1455 (CH_2); 1374 (Me). ^1H-NMR ($CDCl_3$): 1.35, 1.60 (2*s*, 2 Me); 1.48 (br. *s*, OH); 3.50 (*dd*, $J = 3, 7$, H–C(3)); 4.13 (*d*, $J = 5$, 2 H–C(7)); 4.48 (*t*, $J = 7$, H–C(4)); 4.54–4.58 (*m*, H–C(2)); 4.56, 4.75 (2*d*, $J = 12$, $PhCH_2$); 5.63 (*dd*, $J = 7, 15$, H–C(5)); 5.73 (*d*, $J = 3$, H–C(1)); 6.01 (*dt*, $J = 5, 15$, H–C(6)); 7.28–7.40 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 25.8, 26.1 (Me); 62.2 (C(7)); 71.6 ($PhCH_2$); 76.1, 76.5, 81.3, (C(2), C(3), C(4)); 103.1 (C(1)); 112.4 (Me_2C); 119.0, 133.4 (C(5), C(6)); 126.7, 127.4, 127.5, 127.8, 136.9 (arom. C). MS: 289 (M^+), 230 ($[M - OH]^+$). Anal. calc. for $C_{17}H_{22}O_5$ (306.36): C 66.65, H 7.24; found: C 66.35, H 7.14.

3. *Trichloroacetimidates and Thermally Induced Aza-*Claisen *Rearrangement* (*Method C*). To a suspension of NaH (1.4 equiv.) in Et_2O (1 ml/mmol), the allylic alcohol (1 equiv.) in Et_2O (2 ml/mmol) was added. Stirring was continued for 5 min before CCl_3CN (1.2 equiv.) was added at 0°. Stirring was continued for 15 min at 0° and

30 min at r.t. The mixture was diluted with Et_2O (40 ml/mmol) and poured onto sat. aq. NaCl soln. (10 ml/mmol), dried ($MgSO_4$), and evaporated. The residue was dissolved in xylene (freshly distilled from CaH_2), DBPC (2%) added, and the mixture refluxed.

N-(3-O-Benzyl-1,2-O-isopropylidene-5,6,7-trideoxy-α-D-gluco- and -β-L-ido-hept-6-enfurano-5-yl)trichloroacetamide (**9a** and **9b**, resp.). According to *Method C*, **6** (800 mg, 2.61 mmol) was converted into imidate **7** which was refluxed for 13 h. Evaporation and FC (AcOEt/hexane 1:7) gave 447 mg (38%) of **9a** and 400 mg (34%) of **9b** as colourless oils.

9a: $[\alpha]_D^{20} = -43.4$ ($c = 1.6$, $CHCl_3$). IR (film): 3343 (N–H); 3066, 2990, 2936 (C–H); 1716 (C=O); 1513 (NHC=O); 1456 (CH_2); 1375 (Me); 931 (C=C). ^{1}H-NMR ($CDCl_3$): 1.33, 1.49 (2*s*, 2 Me); 3.96 (*d*, $J = 4$, H–C(3)); 4.23 (*dd*, $J = 4, 6$, H–C(4)); 4.44–4.75 (*m*, H–C(2), H–C(5), PhCH_2); 5.22 (*d*, $J = 11$, H_{cis}–C(7)); 5.32 (*d*, $J = 17$, H_{trans}–C(7)); 5.78 (*ddd*, $J = 4, 11, 17$, H–C(6)); 5.97 (*d*, $J = 3$, H–C(1)); 7.20 (br. *s*, NH); 7.20–7.38 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 26.9, 27.5 (Me); 53.3 (C(5)); 72.9 (PhCH$_2$); 81.0, 82.6, 83.6 (C(2), C(3), C(4)); 93.5 (CCl_3); 105.7 (C(1)); 112.4 (Me_2C); 118.4, 134.5 (C(6), C(7)); 128.4, 128.7, 128.9, 129.2, 129.4, 137.5 (arom. C); 161.8 (CONH). MS: 450 (M^+), 374 ($[M - Ph]^+$), 360 ($[M - PhCH_2]^+$). Anal. calc. for $C_{19}H_{22}Cl_3NO_5$ (450.75): C 50.63, H 4.92, N 3.11; found: C 50.86, H 4.85, N 3.16.

9b: $[\alpha]_D^{20} = +11.4$ ($c = 0.4$, $CHCl_3$). IR (film): 3374 (N–H); 3067, 2989, 2935 (C–H); 1716 (C=O); 1510 (NHC=O); 1456 (CH_2); 1375 (Me); 928 (C=C). ^{1}H-NMR ($CDCl_3$): 1.36, 1.52 (2*s*, 2 Me); 4.12 (*d*, $J = 3$, H–C(3)); 4.34 (*dd*, $J = 3, 5$, H–C(4)); 4.42, 4.68 (2*d*, $J = 10$, PhCH_2); 4.67 (*d*, $J = 3$, H–C(2)); 4.95–5.02 (*m*, H–C(5)); 5.28 (*d*, $J = 11$, H_{cis}–C(7)); 5.35 (*d*, $J = 18$, H_{trans}–C(7)); 5.75 (*ddd*, $J = 6, 11, 18$, H–C(6)); 5.99 (*d*, $J = 3$, H–C(1)); 7.30–7.42 (*m*, 5 arom. H); 8.07 (*d*, $J = 8$, NH). ^{13}C-NMR ($CDCl_3$): 26.2, 26.8 (Me); 53.2 (C(5)); 72.8 (PhCH$_2$); 81.2, 81.8, 83.6 (C(2), C(3), C(4)); 92.7 (CCl_3); 104.9 (C(1)); 111.9 (Me_2C); 117.7, 132.4 (C(6), C(7)); 128.5, 128.6, 128.7, 128.8, 129.0, 135.8 (arom. C); 161.7 (CONH). MS: 450 (M^+), 373 ($[M - H - Ph]^+$), 360 ($[M - PhCH_2]^+$), 344 ($[M - PhCH_2O]^+$). Anal. calc. for $C_{19}H_{22}Cl_3NO_5$ (450.75): C 50.63, H 4.92, N 3.11; found: C 50.39, H 5.01, N 3.27.

N-(3-O-Benzyl-1,2-O-isopropylidene-5,6,7-trideoxy-α-D-allo- and -β-L-talo-hept-6-enfuranos-5-yl)trichloroacetamide (**15a** and **15b**, resp.). According to *Method C*, **12** (793 mg, 2.59 mmol) was converted into imidate **13** which was refluxed for 13 h. Evaporation and FC (AcOEt/hexane 1:7) afforded 490 mg (42%) of **15a** and 490 mg (42%) of **15b** as colourless oils.

15a: $[\alpha]_D^{20} = +39.9$ ($c = 1.9$, $CHCl_3$). IR (film): 3423, 3355 (N–H); 3088, 3064, 2989, 2935 (C–H); 1720 (C=O); 1508 (NHC=O); 1455 (CH_2); 1374 (Me); 928 (C=C). ^{1}H-NMR ($CDCl_3$): 1.36, 1.60 (2*s*, 2 Me); 3.56 (*dd*, $J = 5, 6$, H–C(4)); 4.24 (*dd*, $J = 2, 8$, H–C(3)); 4.52 (*dd*, $J = 2, 5$, H–C(2)); 5.59, 5.76 (2*d*, $J = 12$, PhCH_2); 5.78–5.85 (*m*, H–C(2), H–C(5)); 5.24 (*d*, $J = 11$, H_{cis}–C(7)); 5.28 (*d*, $J = 18$, H_{trans}–C(7)); 5.74 (*d*, $J = 5$, H–C(1)); 5.87 (*ddd*, $J = 6, 11, 18$, H–C(6)); 7.01 (*d*, $J = 9$, NH); 7.28–7.41 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 24.6, 24.9 (Me); 50.0 (C(5)); 70.8 (PhCH$_2$); 77.6, 79.0, 82.4 (C(2), C(3), C(4)); 102.3 (C(1)); 111.7 (Me_2C); 117.7, 131.7 (C(6), C(7)); 126.2, 126.6, 126.7, 134.9 (arom. C); 159.7 (CONH). MS: 450 (M^+), 360 ($[M - PhCH_2]^+$), 119 (CCl_3^+). Anal. calc. for $C_{19}H_{22}Cl_3NO_5$ (450.75): C 50.63, H 4.92, N 3.11; found: C 50.76, H 4.97, N 3.28.

15b: $[\alpha]_D^{20} = +76.2$ ($c = 2.0$, $CHCl_3$). IR (film): 3420, 3342 (N–H); 3088, 3029, 2998, 2935 (C–H); 1715 (C=O); 1505 (NHC=O); 1455 (CH_2); 1374 (Me); 936 (C=C). ^{1}H-NMR ($CDCl_3$): 1.37, 1.61 (2*s*, 2 Me); 3.66 (*dd*, $J = 5, 9$, H–C(4)); 4.18 (*dd*, $J = 4, 9$, H–C(3)); 4.48–4.53 (*m*, H–C(5)); 4.53, 4.78 (2*d*, $J = 12$, PhCH_2); 4.58 (*t*, $J = 4$, H–C(2)); 5.19 (*d*, $J = 18$, H_{trans}–C(7)); 5.22 (*d*, $J = 10$, H_{cis}–C(7)); 5.61 (*ddd*, $J = 7, 10, 18$, H–C(6)); 5.75 (*t*, $J = 4$, H–C(1)); 7.08 (*d*, $J = 8$, NH); 7.31–7.41 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 26.6, 26.8 (Me); 55.1 (C(5)); 72.2 (PhCH$_2$); 77.3, 78.6, 79.2 (C(2), C(3), C(4)); 92.5 (CCl_3); 104.4 (C(1)); 113.5 (Me_2C); 119.8, 131.5 (C(6), C(7)); 128.3, 128.4, 128.6, 128.7, 137.0 (arom. C); 161.2 (CONH). MS: 451 (M^+), 332 ($[M - PhCH_2 - CHCH_2]^+$). Anal. calc. for $C_{19}H_{22}Cl_3NO_5$ (450.75): C 50.63, H 4.92, N 3.11; found: C 50.71, H 5.17, N 3.29.

4. *Trifluoroacetimidates and Thermally Induced Aza-Claisen Rearrangement* (*Method D*). To a suspension of NaH (2 equiv.) in THF (1 ml/mmol), the allylic alcohol (1 equiv.) in THF (2 ml/mmol) was added at 0°. Stirring was continued for 15 min at 0° and the mixture cooled to −78°. CF_3CONH_2 (5.5 equiv.) and powdered P_2O_5 (13.5 equiv.) were heated to 140°. The resulting CF_3CN was passed through a tube and condensed into the cooled mixture of NaH and the allylic alcohol. Stirring was continued for 20 min at −78°. Then, the mixture was allowed to warm to 25°, diluted with Et_2O (50 ml/mmol), washed with sat. aq. NaCl soln. (10 ml/mmol), dried ($MgSO_4$), and evaporated. The residue was dissolved in xylene (freshly distilled from CaH_2), 2% DBPC was added, and the mixture refluxed.

N-(3-O-Benzyl-1,2-O-isopropylidene-5,6,7-trideoxy-α-D-gluco and -β-L-ido-hept-6-enfuranos-5-yl)trifluoroacetamide (**10a**/**10b**). According to *Method D*, **6** (611 mg, 2.00 mmol) was converted into imidate **8** which was refluxed for 81 h. Evaporation and FC (AcOEt/hexane 1:7) afforded 512 mg (64%) of **10a**/**10b** which was not separated.

Colourless oil. IR (film): 3378 (N–H); 3032, 2990, 2936 (C–H); 1725 (C=O); 1538 (NHC=O); 1456 (CH_2); 1376 (Me); 931 (C=C). ^{1}H-NMR ($CDCl_3$): 1.32, 1.34, 1.49, 1.50 (4*s*, 2 Me_2C); 3.94, 4.09 (2*d*, *J* = 3, H–C(3)); 4.18 (*d*, *J* = 6, H–C(4)); 4.27 (2*d*, *J* = 5, 3, H–C(4)); 4.40–4.72 (*m*, PhCH_2); 4.77 (*q J* = 7, H–C(5)); 4.98–5.05 (*m*, H–C(5)); 5.20–5.31 (*m*, 2 H–C(7)); 5.65 (*ddd*, *J* = 6, 10, 18, H–C(6)); 5.65 (*ddd*, *J* = 6, 10, 18, H–C(6)); 5.97, 5.98 (2*d*, *J* = 4, H–C(1)); 6.70–6.78 (*m*, NH); 7.26–7.40 (*m*, 5 arom. H); 7.79–7.82 (*m*, NH). ^{13}C-NMR ($CDCl_3$): 25.0, 25.1, 25.6, 25.7 (Me); 50.3, 50.8 (C(5)); 70.9, 71.5 (PhCH_2); 77.4, 79.0, 79.3, 81.7, 82.4 (C(2), C(3), C(4)); 103.8, 103.9 (C(1)); 110.9 (Me_2C); 117.0, 117.1, 131.0, 132.3 (C(6), C(7)); 126.6, 126.9, 127.0, 127.2, 127.4, 127.5, 127.6, 127.7, 127.8, 134.8, 135.5 (arom. C); 155.6, 156.0 (CONH). MS: 401 (M^+), 386 ([M – $CH{=}CH_2$]$^+$). Anal. calc. for $C_{19}H_{22}F_3NO_5$ (401.38): C 56.86, H 5.52, N 3.49; found: C 56.92, H 5.51, N 3.37.

N-*(3-*O*-Benzyl-1,2-*O*-isopropylidene-5,6,7-trideoxy-*α*-*D*-allo- and -*β*-*L*-talo-hept-6-enfuranos-5-yl)trifluoroacetamide* (**16a**/**16b**). According to *Method D*, **12** (420 mg, 1.37 mmol) was converted into imidate **14** which was refluxed for 81 h. Evaporation and FC (AcOEt/hexane 1:7) afforded 248 mg (45%) of **16a**/**b** which was not separated. Colourless oil. IR (film): 3334 (N–H); 3080, 3033, 2987, 2935 (C–H); 1714 (C=O); 1548 (NHC=O); 1455 (CH_2); 1374 (Me); 913 (C=C). ^{1}H-NMR ($CDCl_3$): 1.38, 1.60 (2*s*, 2 Me); 3.49 (*dd*, *J* = 4, 9, H–C(4)); 3.63 (*dd*, *J* = 4, 9, H–C(4)); 4.14 (*dd*, *J* = 4, 9, H–C(3)); 4.19 (*dd*, *J* = 2, 9, H–C(3)); 4.52–4.87 (*m*, H–C(2), H–C(5)); 4.49, 4.56, 4.75, 4.78 (4*d*, *J* = 12, PhCH_2); 5.12–5.25 (*m*, 2 H–C(7)); 4.77 (*q*, *J* = 7, H–C(5)); 4.98–5.05 (*m*, H–C(5)); 5.20–5.31 (*m*, 2 H–C(7)); 5.64 (*ddd*, *J* = 8, 10, 18, H–C(6)); 5.72 (*t*, *J* = 3, H–C(1)); 5.82 (*ddd*, *J* = 6, 10, 18, H–C(6)); 6.59, 6.65 (2*d*, *J* = 9, NH); 7.30–7.40 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 26.5, 26.7 (Me); 50.6, 53.5 (C(5)); 72.1, 72.4 (PhCH_2); 76.7, 77.2, 77.4, 78.2, 78.4, 79.0 (C(2), C(3), C(4)); 93.5 (CF_3); 104.2, 104.3 (C(1)); 113.6 (Me_2C); 117.2, 117.6, 131.2, 133.2 (C(6), C(7)); 128.3, 128.4, 128.6, 128.7, 120.1, 136.7, 136.9 (arom. C); 156.6, 156.9 (CONH). MS: 401 (M^+), 400 ([M – H]$^+$), 310 ([M – PhCH_2]$^+$), 290 ([M – NCOCF_3]$^+$), 112 (NCOCF_3^+). Anal. calc. for $C_{19}H_{22}F_3NO_5$ (401.38): C 56.86, H 5.52, N 3.49; found: C 56.84, H 5.39, N 3.43.

5. N-*[(7R)-3-*O*-Benzyl-5,7-cyclo-1,2-*O*-isopropylidene-5,6,7-trideoxy-*β*-*L*-ido-heptofuranos-7-yl]trichloroacetamide* (**17**). To a suspension of NaH (22 mg, 0.92 mmol) in Et_2O (1 ml), **6** (0.20 g, 0.65 mmol) in Et_2O (4 ml) was added. Stirring was continued for 5 min. Then CCl_3CN (0.08 ml, 0.78 mmol) was added at 0°. Stirring was continued for 15 min at 0° and 30 min at 25°. The mixture was diluted with Et_2O (100 ml) and poured onto sat. aq. NaCl soln. (20 ml), dried ($MgSO_4$), and evaporated. The residue was dissolved in THF (5 ml), [$PdCl_2(MeCN)_2$] (10 mg, 0.04 mmol) added, and the mixture stirred for 3 h. Evaporation and FC (AcOEt/hexane 1:7) afforded 171 mg (58%) of **17**. Colourless oil. $[\alpha]_D^{20} = -33.5$ (*c* = 1.0, $CHCl_3$). IR (film): 3308 (N–H); 2989 (C–H); 1594 (NHC=O); 1455 (CH_2); 1375 (Me). ^{1}H-NMR ($CDCl_3$): 0.80–0.97 (*m*, 2 H–C(7)); 1.32, 1.44 (2*s*, 2 Me); 1.45–1.60 (*m*, H–C(5)); 2.85–2.93 (*m*, 2 H–C(6)); 3.52–3.58 (*m*, H–C(4)); 3.85 (*d*, *J* = 3, H–C(3)); 4.57, 4.78 (2*d*, *J* = 12, PhCH_2); 4.65 (*d*, *J* = 4, H–C(2)); 5.93 (*d*, *J* = 4, H–C(1)); 6.90 (*s*, NH); 7.30–7.40 (*m*, 5 arom. H). ^{13}C-NMR ($CDCl_3$): 11.4 (C(7)); 17.6 (C(5)); 26.2, 26.8 (Me); 29.8 (C(6)); 72.0 (PhCH_2); 81.7, 82.3, 82.8 (C(2), C(3), C(4)); 92.3 (CCl_3); 104.9 (C(1)); 111.7 (Me_2C); 127.7, 128.1, 128.6, 137.3 (arom. C); 162.8 (CONH). MS: 450 (M^+), 374 ([M – Ph]$^+$), 342 ([M – PhCH_2O]$^+$), 334 ([M – CCl_3]$^+$), 305 ([M – CCl_3CONH]$^+$), 242 ([M – CCl_3 – PhCH_2]$^+$). Anal. calc. for $C_{19}H_{22}Cl_3NO_5$ (450.75): C 50.63, H 4.92, N 3.11; found: C 50.89, H 5.07, N 3.19.

X-Ray Structure Analysis of **17** (*Fig. 2*). Amide **17** was crystallized in Et_2O/pentane 1:1. Reflection intensities were collected at r.t. on a *Philips-PW1100* diffractometer using graphite monochromator and MoK_α radiation. The structures were solved by direct-method strategies using the program SHELXS-86. Anisotropic least-squares refinement was carried out using the program CRYSTALS. Fractional coordinates are deposited in the *Cambridge Crystallographic Data Base*.

6. *Aza*-Claisen *Rearrangement of Nucleoside-Derived Imidates. 5'-*O*-[Dimethyl(1,1,2-trimethylpropyl)silyl]-thymidine* (**19**). To a soln. of **18** (6.00 g, 24.76 mmol) in DMF (100 ml), 1*H*-imidazole (1.77 g, 26.01 mmol) and dimethyl(thexyl)silyl chloride (= chlorodimethyl(1,1,2-trimethylpropyl)silane; 4.65 g, 26.01 mmol) were added at 0°. After stirring for 15 min at 0°, the mixture was allowed to warm to r.t., stirred for 1 h, and poured onto H_2O (200 ml). The aq. layer was extracted with AcOEt (3 × 200 ml) and the org. layer washed with H_2O (100 ml) and sat. aq. NaCl soln. (100 ml), dried ($MgSO_4$), and evaporated. FC (AcOEt/hexane 3:2) gave 8.98 g (94%) of **19**. White solid. $[\alpha]_D^{20} = +7.0$ (*c* = 0.5, $CHCl_3$). IR (KBr): 3560 (OH); 3174 (NH); 3059, 2959, 2867 (C–H); 1698 (C=O); 1473 (CH_2); 1377 (Me). ^{1}H-NMR ($CDCl_3$): 0.00 (*s*, Me_2Si); 0.82 (*s*, Me_2C); 0.87 (*d*, *J* = 7, Me_2CH); 1.49 (*sept*. *J* = 7, Me_2CH); 1.77 (*s*, Me–C(5)); 1.93 (*ddd*, *J* = 6, 7, 15, 1 H–C(2')); 2.24 (*ddd*, *J* = 2, 6, 15, 1 H–C(2')); 2.74 (*d*, *J* = 4, H–C(3')); 3.70 (*dd*, *J* = 3, 12, 2 H–C(5')); 3.90 (*d*, *J* = 3, H–C(4')); 4.30 (br. *s*, OH); 6.22 (*t*, *J* = 7, H–C(1')); 7.31 (*s*, H–C(6)); 9.09 (br. *s*, NHH). ^{13}C-NMR ($CDCl_3$): –3.3, 3.4, (Me_2Si); 12.6 (*Me*–C(5)); 18.4, 18.5, 20.2, 20.4 (*Me*$_2$C, *Me*$_2$CH); 25.3 (Me_2C); 33.9 (Me_2CH); 41.0 (C(2')); 63.4 (C(5')); 72.6, 84.8, 87.7 (C(1'), C(3'), C(4')); 111.0 (C(5)); 135.3 (C(6)); 150.4, 163.8 (C(2), C(4)). MS: 385 (M^+), 369 ([M – OH]$^+$), 225

($[M - OSiMe_2CMe_2CHMe_2]^+$). Anal. calc. for $C_{18}H_{32}N_2O_5Si$ (384.55): C 56.22, H 8.39, N 7.28; found: C 56.09, H 8.29, N 7.26.

3-[(Benzyloxy)methyl]-5'-O-[dimethyl(1,1,2-trimethylpropyl)silyl]thymidine (**20**). To a soln. of **19** (8.50 g, 22.10 mmol) in MeCN (300 ml), DBU (1,2-diazabicyclo[5.4.0]undec-7-ene; 4.71 g, 30.95 mmol) and (benzyloxy)methyl chloride (4.85 g, 30.95 mmol) were added at 0°. After stirring for 3 h at 0°, the mixture was allowed to warm to r.t. and poured onto sat. aq. NH_4Cl soln. (200 ml). The aq. layer was extracted with AcOEt (3 × 200 ml) and the org. layer washed with sat. aq. NaCl soln. (100 ml), dried ($MgSO_4$), and evaporated. Flash chromatography (AcOEt/hexane 3:2) afforded 9.26 g (83%) of **20**. Colourless oil. $[\alpha]_D^{20} = +6.0$ ($c = 0.9$, $CHCl_3$). IR (KBr): 3467 (OH); 3067, 2959, 2868 (C–H); 1709, 1662 (C=O); 1467 (CH_2); 1363 (Me). ^{1}H-NMR ($CDCl_3$): 0.00 (*s*, Me_2Si); 0.72 (*s*, Me_2C); 0.75 (*d*, $J = 7$, Me_2CH); 1.50 (*sept.*, $J = 7$, Me_2CH); 1.78 (*s*, Me–C(5)); 1.90 (*ddd*, $J = 6$, 7, 15, 1 H–C(2')); 2.21 (*ddd*, $J = 2$, 6, 15, 1 H–C(2')); 3.64 (*dd*, $J = 3$, 6, 2 H–C(5')); 3.86 (*quint.*, $J = 3$, H–C(4')); 4.30 (*dt*, $J = 3$, 6, H–C(3')); 4.56, 5.33 (2*s*, CH_2O, OCH_2N); 6.19 (*dd*, $J = 6$, 7, H–C(1')); 7.10–7.30 (*m*, 5 arom. H, H–C(6)). ^{13}C-NMR ($CDCl_3$): –3.0, –2.8 (Me_2Si); 14.0 (*Me*–C(5)); 19.2, 19.3, 20.9, 21.2 (Me_2C, Me_2CH); 26.1 (Me_2C); 34.7 (Me_2CH); 41.9 (C(2')); 64.1 (C(5')); 71.3, 73.0 (CH_2O, OCH_2N); 73.2, 86.2, 87.6 (C(1'), C(3'), C(4')); 110.9 (C(5)); 128.4, 128.8, 128.9, 129.0, 134.9 (arom. C); 138.8 (C(6)); 151.7, 164.3 (C(2), C(4)). MS: 505 (M^+), 315 ($[M - (CO)_2NCH_2OCH_2Ph]^+$), 172 ($[M - (CO)_2NCH_2OCH_2Ph - SiMe_2 - CMe_2CHMe_2]^+$). Anal. calc. for $C_{26}H_{40}N_2O_6Si$ (504.70): C 61.88, H 7.99, N 5.55; found: C 61.84, H 8.22, N 5.44

3'-O-Benzyl-3-[(benzyloxy)methyl]-5'-O-[dimethyl(1,1,2-trimethylpropyl)silyl]thymidine (**21**). To a suspension of NaH (371 mg, 15.46 mmol) in THF (50 ml), **20** (6.00 g, 11.89 mmol) in THF (200 ml) was added within 10 min at r.t. After 10 min, BnBr (2.44 g, 14.27 mmol) and Bu_4NI (210 mg, 0.06 mmol) were added. After stirring was continued for 16 h, the mixture was diluted with Et_2O (400 ml) and poured onto H_2O (200 ml). The org. layer was washed with sat. aq. NaCl soln. (200 ml), dried ($MgSO_4$), and evaporated. FC (AcOEt/hexane 1:4) afforded 6.37 g (90%) of **21**. Colourless oil. $[\alpha]_D^{20} = +35.2$ ($c = 1.3$, $CHCl_3$). IR (film): 3065, 2958, 2867 (C–H); 1711, 1668 (C=O); 1464 (CH_2); 1362 (Me). ^{1}H-NMR ($CDCl_3$): 0.00, 0.02 (2*s*, Me_2Si); 0.70–0.82 (*m*, Me_2C, Me_2CH); 1.42–1.52 (*m*, Me_2CH); 1.80 (*s*, Me–C(5)); 1.80–2.45 (*m*, 2 H–C(2')); 3.62, 3.74 (2*dd*, $J = 2$, 11, 2 H–C(5')); 4.02–4.08 (*m*, H–C(3'), H–C(4')); 4.37, 4.48 (2*d*, $J = 12$, $PhCH_2$); 4.60, 5.39 (2*s*, CH_2O, OCH_2N); 6.22 (*dd*, $J = 6$, 9, H–C(1')); 7.10–7.32 (*m*, 10 arom. H, H–C(6)). ^{13}C-NMR ($CDCl_3$): –2.8, –2.6 (Me_2Si); 14.0 (*Me*–C(5)); 19.2, 19.3, 21.0, 21.1 (Me_2C, Me_2CH); 26.1 (Me_2C); 34.7 (Me_2CH); 38.6 (C(2')); 64.1 (C(5')); 71.3, 72.1, 72.9 (CH_2O, OCH_2N, $PhCH_2O$); 79.5, 85.9, 86.4 (C(1'), C(3'), C(4')); 111.9 (C(5)); 128.4, 128.5, 128.7, 128.8, 129.0, 129.3, 138.2, 138.8 (arom. C); 134.8 (C(6)); 151.7, 164.3 (C(2), C(4)). MS: 595 (M^+), 517 ($[M - Ph]^+$), 489 ($[M - PhCH_2O]^+$), 473 ($[M - PhCH_2OCH_2]^+$), 143 ($[SiMe_2CMe_2CHMe_2]^+$). Anal. calc. for $C_{33}H_{46}N_2O_6Si$ (594.82): C 66.64, H 7.79, N 4.71; found: C 66.68, H 7.76, N 4.73.

3'-O-Benzyl-3-[(benzyloxy)methyl]thymidine (**22**). To a soln. of **21** (6.00 g, 10.09 mmol) in THF (200 ml), Bu_4NF (3.34 g, 10.59 mmol) was added at r.t. After stirring for 2 h, the mixture was diluted with Et_2O (400 ml) and poured onto H_2O (200 ml). The org. layer was washed with sat. aq. NaCl soln. (200 ml), dried ($MgSO_4$), and evaporated. FC (AcOEt/hexane 2:3) afforded 3.61 g (79%) of **22**. White solid. $[\alpha]_D^{20} = +28.3$ ($c = 1.5$, $CHCl_3$). IR (KBr): 3452 (O–H); 3072, 3031, 2950, 2908 (C–H); 1702, 1637 (C=O); 1471 (CH_2); 1366 (Me). ^{1}H-NMR ($CDCl_3$): 1.92 (*s*, *Me*–C(5)); 2.32 (*ddd*, $J = 7$, 8, 14, 1 H–C(2')); 2.42 (*ddd*, $J = 3$, 7, 14, 1 H–C(2')); 3.76 (*dq*, $J = 3$, 11, 1 H–C(5')); 3.93 (*dt*, $J = 3$, 11, 1 H–C(5')); 4.16 (*dd*, $J = 3$, 7, H–C(3')); 4.28 (*q*, $J = 3$, H–C(4')); 4.52, 4.58 (2*d*, $J = 12$, $PhCH_2$); 4.72, 5.40 (2*s*, CH_2O, OCH_2N); 6.24 (*t*, $J = 7$, H–C(1')); 7.23 (*s*, H–C(6)); 7.26–7.30 (*m*, 10 arom. H). ^{13}C-NMR ($CDCl_3$): 13.3 (*Me*–C5)); 37.1 (C(2')); 62.9 (C(5')); 70.5, 71.6, 72.2, (CH_2O, OCH_2N, $PhCH_2O$); 78.6, 85.1, 88.1 (C(1'), C(3'), C(4')); 112.0 (C(5)); 128.1, 128.7, 129.0, 136.0, 137.0, 138.8 (arom. C); 135.8 (C(6)); 152.0, 163.0 (C(2), C(4)). MS: 453 (M^+), 437 ($[M - OH]^+$), 345 ($[M - PhCH_2O]^+$). Anal. calc. for $C_{25}H_{28}N_2O_6$ (452.50): C 66.36, H 6.24, N 6.19; found: C 66.05, H 6.26, N 6.21.

3'-O-Benzyl-3-[(benzyloxy)methyl]-5'-deoxy-5'-(2-oxoethylidene)thymidine (= *3-O-Benzyl-1-{3-[(benzyloxy)methyl]-3,4-dihydro-5-methyl-2,4-dioxopyrimidin-1(2H)-yl}-1,2,5,6-tetradeoxy-β-*D-erythro-*hept-5-eno dialdo-1,4-furanose*; **23**). To a soln. of **22** (3.00 g, 6.63 mmol) and dicyclohexyl carbodiimide (5.47 g, 26.52 mmol) in DMSO (60 ml), $CHCl_2COOH$ (427 mg, 3.31 mmol) was added at r.t. After stirring for 3 h, $Ph_3PCHCHO$ (2.12 g, 6.96 mmol) was added, and stirring was continued for 4 h. By addition of oxalic acid (2.09 g, 23.21 mmol) in MeOH (16 ml), the reaction was quenched and the mixture poured onto H_2O (400 ml). The aq. layer was extracted with AcOEt (3 × 200 ml) and the org. layer washed with sat. aq. NaCl soln. (100 ml), dried ($MgSO_4$), and evaporated. FC (AcOEt/hexane 1:2) afforded 2.43 g (77%) of **23**. Colourless oil. $[\alpha]_D^{20} = +58.6$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3064, 3031, 2929, 2870 (C–H); 1714, 1681 (C=O); 1455 (CH_2); 1360 (Me); 978 (C=C). ^{1}H-NMR ($CDCl_3$): 1.95 (*s*, Me–C(5)); 2.21 (*dt*, $J = 7$, 14, 1 H–C(2')); 2.50 (*ddd*, $J = 4, 7, 14$, 1 H–C(2')); 4.26 (*ddd*, $J = 4, 5, 7$, H–C(3')); 4.56, 4.62 (2*d*, $J = 12$, $PhCH_2$); 4.71, 5.50 (2*s*, CH_2O, OCH_2N); 6.25 (*t*, $J = 7$,

H–C(1')); 6.52 (*ddd*, J = 2, 8, 16, CH=C*H*CHO); 6.85 (*dd*, J = 5, 16, H–C(5')); 7.02 (*s*, H–C(6)); 7.22–7.72 (*m*, 10 arom. H); 9.59 (*d*, J = 8, CHO). ^{13}C-NMR ($CDCl_3$): 13.0 (*Me*–C(5)); 37.0 (C(2')); 70.5, 72.2, 72.2 (CH_2O, OCH_2N, PhCH_2O); 80.0, 81.9, 85.9 (C(1'), C(3'), C(4')); 110.8 (C(5)); 127.6, 127.7, 128.2, 128.3, 128.4, 128.5, 128.6, 129.1, 134.6, 135.0, 138.8 (arom. C); 132.4, 132.5 (C(5'), CH=*C*HCHO, C(6)); 163.6 (C(2), C(4)); 193.2 (CHO). MS: 477 (M^+), 279 ([M – CH_2OCH_2Ph – OCH_2Ph]$^+$).

3'-O-Benzyl-3-[(benzyloxy)methyl]-5'-deoxy-5'-(2-hydroxyethylidene)thymidine (**24**). A soln. of **23** (2.20 g, 4.62 mmol) in 90% aq. EtOH (80 ml) was treated with $NaBH_4$ (58 mg, 1.54 mmol) and stirred for 5 min at r.t. The solvent was evaporated and the residue partitioned between AcOEt (200 ml) and H_2O (100 ml). The org. layer was washed with sat. aq. NaCl soln. (50 ml), dried ($MgSO_4$), and evaporated. FC (AcOEt/hexane 1:1) afforded 1.88 g (85%) of **24**. Colourless oil. $[\alpha]_D^{20}$ = + 49.5 (c = 1.3, $CHCl_3$). IR (KBr): 3478 (O–H); 3063, 3030, 2927, 2868 (C–H); 1645 (C=O); 1466 (CH_2); 1360 (Me). ^{1}H-NMR ($CDCl_3$): 1.92 (*s*, Me–C(5)); 2.07 (*dt*, J = 7, 14, 1 H–C(2')); 2.51 (*dd*, J = 4, 7, 14, 1 H–C(2')); 4.01 (*dt*, J = 4, 7, H–C(3')); 4.19–4.23 (*m*, CH=CHCH_2OH); 4.52 (*t*, J = 7, H–C(4')); 4.54, 4.58 (2*d*, J = 12, PhCH_2); 4.70, 5.49 (2*s*, CH_2O, OCH_2N); 5.81 (*ddd*, J = 1, 7, 17, H–C(5')); 5.98 (*ddd*, J = 1, 4, 17, CH=C*H*CH_2OH); 6.24 (*t*, J = 7, H–C(1')); 7.15 (*s*, H–C(6)); 7.23–7.35 (*m*, 10 arom. H). ^{13}C-NMR ($CDCl_3$): 14.0 (*Me*–C(5)); 38.3 (C(2')); 62.8 (CH=CHCH_2OH); 71.3, 72.4, 72.9 (CH_2O, OCH_2N, PhCH_2O); 82.4, 85.1, 89.6 (C(1'), C(3'), C(4')); 111.1 (C(5)); 128.4, 128.8, 128.9, 129.1, 129.3, 129.4, 136.0 (arom. C); 134.7, 135.2, 138.1 (C(5'), CH=*C*HCH_2OH, C(6)); 164.2, 172.0 (C(2), C(4)). MS: 479 (M^+), 463 ([M – OH]$^+$), 385 ([M – OH – Ph]$^+$), 342 ([M – OH – CH_2OCH_2]$^+$), 249 ([M – OH – CH_2OCH_2 – PhCHO]$^+$).

(5'R)- and (5'S)-3'-O-Benzyl-3-[(benzyloxy)methyl]-5'-deoxy-5'-ethenyl-5'-[(trichloroacetyl)amino]thymidine (**26a** and **26b**, resp.). According to *Method C*, **24** (1.49 g, 3.10 mmol) was converted to imidate **25**, which was refluxed in xylene (250 ml) in the presence of DBPC (2%) for 44 h. Evaporation and FC (AcOEt/hexane 1:2) gave 0.81 g (42%) of **26a** and 0.81 g (42%) of **26b** as colourless oils.

(5'S)-Isomer **26a**: $[\alpha]_D^{20}$ = + 31.9 (c = 0.8, $CHCl_3$). IR (KBr): 3318 (N–H); 3064, 3030, 2930, 2870 (C–H); 1714, 1652 (C=O); 1516 (CONH); 1468 (CH_2); 1361 (Me). ^{1}H-NMR ($CDCl_3$): 1.95 (*s*, Me–C(5)); 2.08 (*dt*, J = 7, 14, H–C(2')); 2.48 (*ddd*, J = 4, 7, 14, H–C(2')); 4.11 (*dd*, J = 4, 10, H–C(4')); 4.15 (*dd*, J = 4, 7, H–C(3')); 4.51, 4.58 (2*d*, J = 12, PhCH_2); 4.41–4.63 (*m*, H–C(5')); 4.72, 5.51 (2*s*, CH_2O, OCH_2N); 5.35 (*d*, J = 17, H_{trans} of CH_2=CH); 5.39 (*d*, J = 10, H_{cis} of CH_2=CH); 5.87 (*ddd*, J = 6, 10, 17, CH_2=CH); 6.25 (*t*, J = 7, H–C(1')); 7.02 (*s*, H–C(6)); 7.26–7.43 (*m*, 10 arom. H, NH). ^{13}C-NMR ($CDCl_3$): 13.8 (*Me*–C(5)); 37.4 (C(2')); 55.4 (C(5')); 71.0, 72.4, 72.7 (CH_2O, OCH_2N, PhCH_2O); 78.5, 84.9, 86.1 (C(1'), C(3'), C(4')); 110.9 (C(5)); 119.8, 134.4 (CH_2=*C*H); 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 129.0, 137.4, 138.0 (arom. C); 151.2, 161.9, 163.9 (C(2), C(4), CONH). MS: 622 (M^+), 245 ([thymine–CH_2OCH_2Ph]$^+$), 125 ([thymine]$^+$), 121 ([PhCH_2OCH_2]$^+$). Anal. calc. for $C_{29}H_{30}Cl_3N_3O_6$ (622.93): C 55.92, H 4.85, N 6.75; found: C 55.62, H 5.18, N 6.51.

(5'R)-Isomer **26b**: $[\alpha]_D^{20}$ = + 6.8 (c = 1.0, $CHCl_3$). IR (KBr): 3318 (N–H); 3030, 2927 (C–H); 1708, 1669 (C=O); 1517 (CONH); 1465 (CH_2); 1360 (CH_3). ^{1}H-NMR ($CDCl_3$): 1.78 (*s*, Me–C(5)); 1.91 (*dd*, J = 3, 7, 14, H–C(2')); 2.33 (*dt*, J = 7, 14, 1 H–C(2')); 4.07 (*t*, J = 4, H–C(4')); 4.13 (*dt*, J = 3, 7, H–C(3')); 4.27, 4.31 (2*d*, J = 14, PhCH_2); 4.76, 5.48 (2*s*, CH_2O, OCH_2N); 4.90 (*ddd*, J = 3, 6, 9, H–C(5')); 5.13 (*d*, J = 11, H_{cis} of CH_2=CH); 5.32 (*d*, J = 7, H–C(1')); 5.36 (*d*, J = 18, H_{trans} of CH_2=CH); 5.80 (*ddd*, J = 6, 11, 18, CH_2=C*H*); 7.10–7.50 (*m*, 10 arom. H, H–C(6)); 8.11 (*d*, J = 9, NH). ^{13}C-NMR ($CDCl_3$): 13.5 (*Me*–C(5)); 36.5 (C(2')); 54.9 (C(5')); 71.1, 72.7, 72.8 (CH_2O, OCH_2N, PhCH_2O); 78.8, 85.2, 89.4 (C(1'), C(3'), C(4')); 111.3 (C(5)); 118.5, 134.0, 136.0 (CH_2=*C*H, C(6)); 127.9, 128.1, 128.4, 128.7, 129.1, 137.0 (arom. C); 152.1, 164.2 (C(2), C(4), CONH). MS: 624 ([M + H]$^+$), 516 ([M – PhCH_2O]$^+$), 408 ([M – thymine–CH_2OCH_2Ph]$^+$), 394 ([M – PhCH_2O – PhCH_2OCH_2]$^+$). Anal. calc. for $C_{29}H_{30}Cl_3N_3O_6$ (622.93): C 55.92, H 4.85, N 6.75; found: C 55.60, H 5.08, N 6.46.

(5'R)- and (5'S)-5'-Amino-3'-O-benzyl-3-[(benzyloxy)methyl]-5'-deoxy-5'-ethenylthymidine (**27a** and **27b**, resp.). A soln. of the mixture **26a**/**26b** (700 mg, 1.12 mmol) in EtOH (20 ml/mmol) was treated with $NaBH_4$ (170 mg, 4.50 mmol) and stirred for 12 h at r.t. Evaporation and FC (MeOH/AcOEt 1:24, 0.07% Et_3N) afforded 214 mg (40%) of **27a** and 214 mg (40%) of **27b** as colourless oils.

(5'R)-Isomer **27a**: $[\alpha]_D^{20}$ = + 42.6 (c = 1.0, $CHCl_3$). IR (film): 3364 (N–H); 3065, 2926 (C–H); 1711, 1659 (C=O); 1454 (CH_2); 1360 (Me). ^{1}H-NMR ($CDCl_3$)[6]): 1.92 (*s*, Me–C(5)); 2.00–2.12 (*m*, 1 H–C(2')); 2.45 (*m*, 1 H–C(2')); 3.58 (*t*, J = 7, H–C(3')); 3.94 (*dd*, J = 4, 5, H–C(4')); 4.18 (*q*, J = 4, H–C(5')); 4.50, 4.56 (2*d*, J = 12, PhCH_2); 4.70, 5.49 (2*s*, CH_2O, OCH_2N); 5.20 (*d*, J = 11, H_{cis} CH_2=CH); 5.27 (*d*, J = 18, H_{trans} of CH_2 = CH); 5.87 (*ddd*, J = 7, 11, 18, CH_2=C*H*); 6.25 (*dd*, J = 5, 6, H–C(1')); 7.22–7.40 (*m*, 10 arom. H, H–C(6)). ^{13}C-NMR ($CDCl_3$)[6]): 14.1 (*Me*–C(5)); 38.0 (C(2')); 57.1 (C(5')); 71.3, 72.4, 80.0 (CH_2O, OCH_2N, PhCH_2O); 79.3, 86.6, 87.9 (C(1'), C(3'), C(4')); 111.3 (C(5)); 117.6, 135.3, 138.2 (CH_2=CH, C(6)); 128.4, 128.7, 129.1, 129.3, 139.4 (arom. C); 151.6, 164.1 (C(2), C(4)). MS: 477 (M^+), 400 ([M – Ph]$^+$).

(5'S)-Isomer **27b**: $[\alpha]_D^{20} = +44.8$ ($c = 0.3$, $CHCl_3$). IR (film): 3375 (N–H); 3031, 2928 (C–H); 1710, 1659 (C=O); 1452 (CH_2); 1360 (Me). ^{1}H-NMR ($CDCl_3$): 1.94 (*s*, Me–C(5)); 2.02 (*ddd*, $J = 7, 9, 14$, 1 H–C(2')); 2.46 (*ddd*, $J = 2, 6, 14$, 1 H–C(2')); 3.60–3.65 (*m*, H–C(5')); 4.03 (*dd*, $J = 3, 4$, H–C(4')); 4.13–4.16 (*m*, H–C(3')); 4.49, 4.55 (2*d*, $J = 12$, PhCH_2); 4.70, 5.49 (2*s*, CH_2O, OCH_2N); 5.23 (*dt*, $J = 1, 10$, H_{cis} of CH_2=CH); 5.27 (*dt*, $J = 1, 16$, H_{trans} of CH_2=CH); 5.90 (*ddd*, $J = 6, 10, 16$, CH_2=C*H*); 6.29 (*dd*, $J = 6, 9$, H–C(1')); 7.23–7.42 (*m*, 10 arom. H, H–C(6)). ^{13}C-NMR ($CDCl_3$): 12.3 (*Me*–C(5)); 36.5 (C(2')); 61.6 (C(5')); 69.5, 70.8, 71.2 (CH_2O, OCH_2N, Ph*C*H_2O); 77.0, 80.6, 85.2 (C(1'), C(3'), C(4')); 109.3 (C(5)); 118.0, 126.0, 133.5, (*C*H_2=*C*H, C(6)); 126.6, 126.7, 127.0, 127.3, 127.5, 127.6, 136.4, 137.4 (arom. C); 149.8, 162.3 (C(2), C(4)). MS: 478 (M^+), 388 ([M – PhCH_2]$^+$), 372 ([M – PhCH_2O]$^+$).

7. *Dimers* **35**. *2-(3'-Deoxythymidin-3'-yl)acetic Acid* (**29**). To a soln. of **28** (4.13 g, 7.91 mmol) in THF (100 ml), Bu_4NF (2.74 g, 8.70 mmol) was added at r.t. After 5 h stirring, the solvent was evaporated. The residue was submitted to 3 successive FC to separate the ammonium salts. Still, the remaining oils contained some ammonium salt that did not interfere with the following reaction. ^{1}H-NMR (D_2O): 1.90 (*s*, Me–C(5)); 2.22–2.70 (*m*, 2 H–C(2'), CH_2COOH, H–C(3')); 3.70–3.93 (*m*, 2 H–C(5'), H–C(4')); 6.15 (*dd*, $J = 5, 8$, H–C(1')); 7.80 (*s*, H–C(6)); 11.16 (br. *s*, COOH). ^{13}C-NMR (D_2O): 15.4 (*Me*–C(5)); 38.1 (C(3')); 41.4, 41.6 (C(2'), *C*H_2COOH); 64.7 (C(5')); 88.7, 89.6 (C(1'), C(4')); 114.5 (C(5)); 141.5 (C(6)); 155.3, 170.2 (C(2), C(4)); 182.7 (COOH). MS: 284 (M^+), 159 ([M – thymine]$^+$), 126 ([thymine + H]$^+$).

2-[3'-Deoxy-5'-O-(dimethoxytrityl)thymidin-3'-yl]acetic Acid (**30**). A mixture of **29** (1.35 g, 4.75 mmol), dimethoxytrityl chloride (1.93 g, 5.70 mmol), Et_3N (673 mg, 6.65 mmol), and 4-(dimethylamino)pyridine (58 mg, 0.48 mmol) in pyridine (10 ml/mmol) was stirred at 0° for 16 h. After evaporation, the residue was dissolved in AcOEt and the soln. washed with H_2O (20 ml/mmol) and sat. aq. NaCl soln. (50 ml), dried ($MgSO_4$), and again evaporated. Flash chromatography (MeOH/AcOEt 1:5, 0.07% NEt_3) afforded 1.95 g (70%) of **30**. Pale yellow foam. ^{1}H-NMR (DMSO): 1.23 (*s*, Me–C(5)); 1.90–3.70 (*m*, 2 H–C(2'), H–C(3'), H–C(4'), 2 H–C(5'), CH_2COOH); 3.72 (*s*, 2 MeO); 6.00 (*dd*, $J = 5, 8$, H–C(1')); 6.85–7.40 (*m*, 13 arom. H); 7.54 (*s*, H–C(6)). ^{13}C-NMR (D_3COD): 13.3 (*Me*–C(5)); 37.5 (C(3')); 40.9, 41.0 (C(2'), *C*H_2COOH); 56.8 (MeO); 65.1 (C(5')); 87.2, 87.4 (C(1'), C(4')); 88.7 (Ar_2Ph*C*); 112.1 (C(5)); 115.1, 129.0, 129.9, 130.4, 132.3, 137.9, 147.0, 167.6 (arom. C); 139.0 (C(6)); 153.3, 161.1 (C(2), C(4)); 180.1 (COOH). MS: 585 (M^+), 283 ([M – MeO), Tr]$^+$), 125 ([thymine]$^+$).

Pentafluorophenyl 2-[3'-Deoxy-5'-O-(dimethoxytrityl)thymidin-3'-yl]acetate (**31**). To a soln. of **30** (1.89 g, 3.23 mmol) and pyridine (382 mg, 4.84 mmol) in DMF (10 ml/mmol), pentafluorophenyl trifluoroacetate (1.35 g, 4.84 mmol) was added at r.t. and the mixture was stirred for 16 h. After dilution with AcOEt (20 ml/mmol), the mixture was washed with H_2O (20 ml/mmol) and sat. aq. $NaHCO_3$ soln. The org. layer was dried ($MgSO_4$) and evaporated and the residue purified by FC (AcOEt/hexane 1:1, 0.07% NEt_3) at 0°: 1.51 g (62%) of **31**. White foam. ^{1}H-NMR ($CDCl_3$): 1.46 (*s*, Me–C5)); 1.60–3.93 (*m*, 2 H–C(2'), H–C(3'), H–C(4'), 2 H–C(5'), CH_2COO); 3.79 (*s*, 2 MeO); 6.20 (*dd*, $J = 5, 8$, H–C(1')); 6.78–7.46 (*m*, 13 arom. H); 7.63 (*s*, H–C(6)); 8.50 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 12.9 (*Me*–C(5)); 35.6 (C(3')); 36.5, 39.3, (C(2'), *C*H_2COO); 56.0 (MeO); 63.7 (C(5')); 84.7, 85.5 (C(1'), C(4')); 87.6 (Ar_2Ph*C*); 111.8 (C(5)); 114.0, 127.9, 128.9, 130.8, 145.1, 159.5, 171.9 (arom. C); 136.1 (C(6)); 151.3, 164.9 (C(2), C(4)); 181.2 (COO). MS: 751 (M^+), 585 ([M – C_6F_5]$^+$), 125 ([thymine]$^+$).

N-{*(5'R)- and (5'S)-3-O-Benzyl-3-[(benzyloxy)methyl]-5'-deoxy-5'-ethenylthymidin-5'-yl*}-*2-[3'-deoxy-5'-O-(dimethoxytrityl)thymidin-3'-yl]acetamide* (= *3'-*{*2-*{{*(5'R)- and (5'S)-3'-O-Benzyl-3-[(benzyloxy)methyl]-5'-deoxy-5'-ethenylthymidin-5'-yl*}*amino*}*-2-oxoethyl*}*-3'-deoxy-5'-O-(dimethoxytrityl)thymidine* (**32a** and **32b**, resp.). To a soln. of **27a,b** (1 equiv.) and **31** (1 equiv.) in THF (10 ml/mmol), (i-Pr)$_2$EtN (1.1 equiv.) was added at 0°. The mixture was allowed to warm to r.t. and stirred for 16 h. Evaporation and FC (AcOEt/hexane 3:1, 0.07% NEt_3) afforded **32a,b** as white foams.

(5'R)-Isomer **32a**: 321 mg, (94%), from **27a** (162 mg, 0.34 mmol), after FC. $[\alpha]_D^{20} = -9.2$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3397 (O–H); 3028, 3013, 2962 (C–H); 1709, 1673, 1657 (C=O); 1466 (CH_2); 1358 (Me). ^{1}H-NMR ($CDCl_3$): 1.48 (*s*, Me–C(5')); 1.92 (*s*, Me–C(5'')); 2.04–2.97 (*m*, 2 H–C(2''), 2 H–C(2'''), H–C(4''), 2 H–C(5'')); 3.24 (*dd*, $J = 4, 11$, 1H, CH_2ONH); 3.45 (*dd*, $J = 2, 11$, 1H, CH_2ONH); 3.75–3.83 (*m*, H–C(3'')); 3.78 (*m*, 2 Me); 4.13 (*dd*, $J = 3, 4$, H–C(4'')); 4.23 (*quint.*, $J = 4$, H–C(3'')); 4.50, 4.55 (2*d*, $J = 12$, PhCH_2); 4.64, 5.46 (2*s*, PhCH_2O, NCH_2O); 4.69–4.76 (*m*, H–C(5'')); 5.18 (*d*, $J = 9$, H_{cis} of CH_2=CH); 5.23 (*d*, $J = 15$, H_{trans} of CH_2=CH); 5.57 (*t*, $J = 7$, H–C(1'')); 5.80 (*ddd*, $J = 5, 9, 15$, CH_2=C*H*); 6.16 (*dd*, $J = 5, 7$, H–C(1'')); 6.80–7.45 (*m*, 23 arom. H); 6.96, 7.62 (2*s*, H–C(6'), H–C(6'')); 8.50 (br.*s*, NH). ^{13}C-NMR ($CDCl_3$): 12.0, 13.3 (*Me*–C5'), Me–C(5''); 35.3 (C(3')); 35.8, 38.3, 38.5 (C(2''), C(2''''), *C*H_2CONH); 52.2, 53.0 (C(3''), C(4'')); 55.2 (MeO); 63.3 (C(5'')); 70.7, 72.3 (PhCH_2O, NCH_2O); 79.3, 84.5, 86.2, 92.9 (C(1''), C(1''''), C(3''''), C(4'''')); 110.5 (C(5'), C(5'')); 116.6 (*C*H_2=CH); 127.1, 127.5, 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 128.6, 130.1, 130.2, 144.4 (arom. C); 135.4 (CH_2=*C*H); 137.3, 137.8 (C(6'), C(6'')); 148.2, 151.0, 158.7, 163.2 (C(2'), C(2''), C(4'), C(4'')); 170.9 (CONH). MS: 1044 (M^+), 954 ([M – PhCH_2]$^+$), 742 ([M – (MeO)$_2$Tr]$^+$).

(5'S)-Isomer **32b**: 350 mg (93%), from **27b** (178 mg, 0.37 mmol), after FC. $[\alpha]_D^{20} = +11.6$ ($c = 1.3$, $CHCl_3$). IR (KBr): 3332 (N–H); 3032, 2930, 2837 (C–H); 1709, 1667 (C=O); 1510 (CONH); 1453 (CH_2); 1361 (CH_3). ^{1}H-NMR ($CDCl_3$)[6]): 0.80–4.70 (*m*, 2 H–C(2''), 2 H–C(2''''), H–C(3''), H–C(3''''), H–C(4''), H–C(4''''), 2 H–C(5''), H–C(5''''), CH_2ONH); 1.47 (*s*, Me–C5')); 1.90 (*s*, Me–C(5''')); 3.77 (*s*, 2 MeO); 4.33, 4.44 (2*d*, $J = 12$, PhCH_2); 4.68, 5.48 (2*s*, PhCH_2O, NCH_2O); 5.24 (*d*, $J = 15$, H_{trans} of CH_2=CH); 5.28 (*d*, $J = 10$, H_{cis} of CH_2=CH); 5.77 (*ddd*, $J = 6$, 10, 15, CH_2=C*H*); 6.10–6.27 (*m*, H–C(1''), H–C(1'''')); 6.78–7.45 (*m*, 23 arom. H); 7.03, 7.58 (2*s*, H–C(6'), H–C(6''')). MS: 1044 (M^+), 954 ([M – PhCH_2^+), 742 ([M – $(MeO)_2$Tr]$^+$).

2-(3'-Deoxythymidin-3'-yl)-N-*[(5'R)- and -(5'S)-5'-deoxy-5'-ethylthymidin-5'-yl]acetamide* (**33a** and **33b**, resp.). H_2 was passed through a mixture of **32a,b**, conc. HCl soln. (3 equiv.), and Pd/C (0.2 equiv.) in MeOH (16 ml/mmol). Evaporation and FC (MeOH/CH_2Cl_2 1:4) gave **33a,b** as white foams.

(5'R)-Isomer **33a**: 129 mg (78%), from **32a** (311 mg, 0.31 mmol), after FC. $[\alpha]_D^{20} = +9.6$ ($c = 1.0$, MeOH). IR (KBr): 3416 (O–H); 2926, 2853 (C–H); 1692, 1680, 1642 (C=O); 1468 (CH_2); 1370 (Me). ^{1}H-NMR (DMSO)[6]): 0.84 (*t*, $J = 7$, *Me*CH_2); 1.10–4.25 (*m*, 2 H–C(2''), 2 H–C(2''''), H–C(3''), H–C(3''''), H–C(4''), H–C(4''''), 2 H–C(5''), H–C(5''''), MeCH_2, CH_2CONH); 1.76, 1.78 (2*s*, Me–C(5'), Me–C(5''')); 5.11 (*t*, $J = 5$, OH–C(5'')); 5.29 (*d*, $J = 4$, OH–C(3'''')); 5.95 (*t*, $J = 5$, H–C(1'')); 6.07 (*t*, $J = 7$, H–C(1'''')); 7.46, 7.86 (2*s*, H–C(6'), H–C(6''')); 7.83 (*d*, $J = 9$, NH); 11.22, 11.27 (2*s*, 2 NH). ^{13}C-NMR (DMSO)[6]): 11.6, 13.1, 13.5 (*Me*–C(5'), *Me*–C(5'''), *Me*CH_2); 25.6 (MeCH_2); 35.3 (C(5'''')); 38.7, 39.3, 40.0 (C(2''), C(2''''), CH_2CONH); 49.8 (C(3'')); 52.5 (C(5'''')); 61.6 (C(5'')); 72.0 (C(4'''')); 85.0, 86.8, 89.0 (C(1''), C(1''''), C(3''''), C(4'')); 109.8, 110.8 (C(5'), C(5''')); 137.4, 137.5 (C(6'), C(6''')); 151.5, 151.6, 165.0 (C(2'), C(2'''), C(4'), C(4''''); 172.3 (CONH). MS: 536 ([M]$^+$), 410 ([M – thymine]$^+$).

(5'S)-Isomer **33b**: 141 mg (77%), from **32b** (345 mg, 0.34 mmol), after FC. $[\alpha]_D^{20} = +16.5$ ($c = 0.2$, MeOH). IR (KBr): 3421 (O–H); 2969, 2933 (C–H); 1671 (C=O); 1549 (CONH); 1475 (CH_2); 1372 (Me). ^{1}H-NMR (DMSO)[6]): 0.82 (*t*, $J = 7$, *Me*CH_2); 1.22–4.25 (*m*, 2 H–C(2''), 2 H–C(2''''), H–C(3''), H–C(3''''), H–C(4''), H–C(4''''), 2 H–C(5''), H–C(5''''), MeCH_2CH_2CONH); 1.76, 1.78 (2*s*, Me–C(5'), Me–C(5''')); 4.97 (*t*, $J = 5$, OH–C(5'')); 5.10 (*d*, $J = 4$, OH–C(3'''')); 5.87 (*t*, $J = 5$, H–C(1'')); 5.98 (*dd*, $J = 6$, 9, H–C(1'''')); 7.40, 7.88 (2*s*, H–C(6'), H–C(6''')); 7.90–8.00 (*m*, NH); 11.24, 11.33 (2*s*, 2 NH). ^{13}C-NMR (DMSO)[6]): 11.5, 13.3, 13.5 (*Me*–C(5'), *Me*–C(5'''), *Me*CH_2); 24.5 (MeCH_2); 35.5 (C(5'''')); 38.8, 39.1, 39.8 (C(2''), C(2''''), CH_2CONH); 52.5, 52.6 (C(3''), C(5'''')); 61.9 (C(5'')); 71.9, 84.8, 85.0, 86.7, 89.2 (C(1''), C(1''''), C(3''''), C(4''), C(4'''')); 109.9, 110.9 (C(6'), C(6''')); 137.0, 137.5 (C(5'), C(5''')); 151.5, 151.7, 164.8, 165.0 (C(2'), C(2'''), C(4'), C(4''''); 172.1 (CONH). MS: 536 (M^-).

N-*[(5'R)- and (5'S)-5'-Deoxy-5'-ethylthymidin-5'-yl]-2-[3'-deoxy-5'*-O-*(dimethoxytrityl)thymidin-3'-yl]acetamide* (**34a** and **34b**, resp.). A mixture of **33a,b** (1 equiv.) and dimethoxytrityl chloride (2.5 equiv.) in pyridine (16 ml/mmol) was stirred at 0° for 24 h. After evaporation, the residue was dissolved in CH_2Cl_2 (30 ml/mmol) and the soln. washed with sat. aq. NaCl soln. (20 ml/mmol), dried ($MgSO_4$), and evaporated. FC (MeOH/CH_2Cl_2 1:12, 0.07% Et_3N) afforded **34a,b** as pale yellow foams.

(5'R)-Isomer **34a**: 114 mg (66%), from **33a** (110 mg, 0.21 mmol), after FC. $[\alpha]_D^{20} = +3.4$ ($c = 1.0$, MeOH). IR (KBr): 3400 (O–H); 3018, 2944, 2839 (C–H); 1710, 1691, 1680, 1666 (C=O); 1468 (CH_2); 1366 (Me). ^{1}H-NMR (CD_3OD)[6]): 0.93 (*t*, $J = 8$, *Me*CH_2); 1.39 (*s*, Me–C(5')); 1.87 (*s*, Me–C(5''')); 1.40–1.50, 1.61–1.72 (2*m*, MeCH_2); 2.13–2.42 (*m*, 2 H–C(2''), 2 H–C(2''''), 2 H–C(5'')); 2.89–3.00 (*m*, H–C(4'')); 3.28–3.37, 3.44–3.49 (2*m*, CH_2CONH); 3.70–3.74 (*m*, H–C(4'''')); 3.73 (*s*, 2 MeO); 3.84–3.91 (*m*, H–C(3'')); 3.91–3.99 (*m*, H–C(5'''')); 4.24–4.29 (*m*, H–C(3'''')); 6.04–6.09 (*m*, H–C(1''), H–C(1'''')); 6.80–7.47 (*m*, 13 arom. H, H–C(6'), H–C(6''')). ^{13}C-NMR (CD_3OD)[6]): 10.3, 11.7, 11.8 (*Me*–C(5'), *Me*–C(5'''), *Me*CH_2); 25.4 (MeCH_2); 35.9 (C(5'''')); 38.6, 38.9, 39.6 (C(2''), C(2''''), CH_2CONH); 53.0 (C(3'')); 55.1 (MeO); 63.3 (C(5'')); 72.4, 85.3, 85.9, 87.0, 87.3, 88.4 (C(1''), C(1''''), C(3''''), C(4''), C(4''''), Ar_2Ph*C*); 113.6, (C(6'), C(6''')); 110.0, 111.6, 127.5, 128.3, 128.8, 130.8, 138.6, 144.4, 159.6 (arom. C); 137.0, 138.5 (C(5'), C(5''')); 145.4, 151.6, 165.5, 165.7 (C(2'), C(2'''), C(4'), C(4''')); 173.3 (CONH). MS: 837 ([M – H]$^+$), 534 ([M – $(MeO)_2$Tr – H]$^+$).

(5'S)-Isomer **34b**: 137 mg (65%) from **33b** (135 mg, 0.25 mmol), after FC. $[\alpha]_D^{20} = -21.7$ ($c = 2.3$, $CHCl_3$). IR (KBr): 3392 (O–H); 3011, 2839 (C–H); 1689 (C=O); 1510 (CONH); 1468 (CH_2). ^{1}H-NMR ($CDCl_3$)[6]): 0.78–4.40 (*m*, 2 H–C(2''), 2 H–C(2''''), H–C(3''), H–C(3''''), H–C(4''), H–C(4''''), 2 H–C(5''), H–C(5''''), MeCH_2, CH_2CONH); 1.47 (*s*, Me–C(5')); 1.87 (*s*, Me–C(5''')); 3.76 (*s*, 2 MeO); 6.06–6.17, 6.22–6.31 (2*m*, H–C(1''), H–C(1'''')); 6.76–7.65 (*m*, 13 arom. H, H–C(6'), H–C(6''')). ^{13}C-NMR ($CDCl_3$)[6]): 9.8, 12.0, 12.7 (*Me*–C(5'), *Me*–C(5'''), *Me*CH_2); 24.3 (MeCH_2); 35.7 (C(5'''')); 38.1, 38.7, 39.2 (C(2''), C(2''''), CH_2CONH); 46.0 (C(3'')); 55.2 (MeO); 63.7 (C(5'')); 72.5, 84.4, 85.3, 86.7, 87.6, (C(1''), C(1''''), C(3''''), C(4''), C(4'''')); 98.6 (Ar_2Ph*C*); 110.8, 111.4 (C(6'), C(6''')); 113.3, 128.0, 128.2, 130.2, 144.5, 158.6 (arom. C); 135.3, 135.5 (C(5'), C(5''')); 150.9, 164.2, 164.6 (C(2'), C(2'''), C(4'), C(4''')); 171.5 (CONH). MS: 837 ([M – H]$^+$), 534 ([M – $(MeO)_2$Tr – H]$^+$).

(5'R)- and (5'S)-5'-Deoxy-5'-{{2-[3'-deoxy-5'-O-(dimethoxytrityl)thymidin-3'-yl]acetyl}amino}-5'-ethylthymidine 3'-[2-Cyanoethyl Diisopropylphoshoramidite] (**35a** and **35b**, resp.). To a soln. of amide **34a,b** (1 equiv.) and diisopropylammonium 1*H*-tetrazolide (5 equiv.) in CH_2Cl_2 (30 ml/mmol), 2-cyanoethyl tetraisopropylphosphorodiamidite (3 equiv.) was added at r.t. The mixture was stirred for 2 h before it was diluted with CH_2Cl_2 (50 ml/mmol), washed with sat. aq. $NaHCO_3$ soln. (20 ml/mmol), dried ($MgSO_4$), and evaporated. The residue was dissolved in CH_2Cl_2 (10 ml/mmol) and the soln. stirred and treated at once with pentane (100 ml/mmol). The resulting white solid was filtered and dried *in vacuo*.

(5'R)-Isomer **35a**: 117 mg (86%), from **34a** (110 mg, 0.13 mmol). $[\alpha]_D^{20} = -25.1$ ($c = 1.4$, $CHCl_3$). IR ($CHCl_3$): 3392 (N–H); 3014 (C–H); 1690 (C=O); 1509 (CONH); 1465 (CH_2). ^{1}H-NMR ($CDCl_3$, 2 diastereoisomers)[6]): 0.84–0.97 (*m*, *Me*CH_2); 1.12–1.23 (*m*, 2 *Me*$_2$CH); 1.10–2.95 (*m*, 2 H–C(2''), 2 H–C(2'''), H–C(3''), 2 H–C(5''), 2 H–C(6''), CH_2CN); 1.48 (*s*, Me–C(5')); 1.92 (*s*, Me–C(5''')); 3.26–3.32, 3.45–3.52 (2*m*, CH_2CONH); 3.53–4.48 (*m*, H–C(3'''), H–C(4''), H–C(4'''), H–C(5'''), 2 Me$_2$C*H*, CH_2CH_2OP); 3.78 (*s*, 2 MeO); 5.53 (*t*, $J = 7$, H–C(1''')); 6.20–6.27 (*m*, H–C(1'')); 6.80–7.61 (*m*, 13 arom. H, H–C(6'), H–C(6'''), NH). ^{13}C-NMR ($CDCl_3$, 2 diastereoisomers)[6]): 10.5, 10.6, 12.0, 12.2 (*Me*–C(5'), *Me*–C(5'''), *MeCH*$_2$); 20.3–20.5 (*CH*$_2$CH$_2$OP); 24.5 (*d*, $J = 9$, *Me*$_2$CH); 26.0, 26.1 (Me*C*H$_2$); 35.7, 35.9 (C(5''')); 37.3, 38.2, 38.9 (C(2''), C(2'''), *C*H$_2$CONH); 51.3, 51.6 (C(3'')); 55.2 (MeO); 58.2 (*d*, $J = 20$, CH$_2$*C*H$_2$OP); 63.9, 64.0 (C(5'')); 73.9, 74.0, 84.3, 84.9, 86.7 (C(1''), C(1'''), C(3'''), C(4''), C(4''')); 91.4 (Ar$_2$Ph*C*); 110.8, 111.0 (C(6'), C(6''')); 117.9 (CN); 113.3, 127.0, 128.0, 128.2, 130.2, 131.7, 139.7, 144.5, 158.6 (arom. C); 135.6, 135.9 (C(5'), C(5''')); 150.4, 150.5, 150.7, 150.8, 163.8, 163.9, 164.0 (C(2'), C(2'''), C(4'), C(4''')); 170.7, 170.8 (CONH). ^{31}P-NMR ($CDCl_3$, 2 diastereoisomers): 150.3, 150.5. MS: 1036 (M^+), 819 ([M – PO(N(i-Pr)$_2$) (OCH$_2$)$_2$CN]$^+$).

(5'S)-Isomer **35b**: 140 mg (88%) from **34b** (128 mg, 0.15 mmol). $[\alpha]_D^{20} = -7.0$ ($c = 1.9$, $CHCl_3$). IR ($CHCl_3$): 3020, 2934 (C–H); 1685 (C=O); 1508 (CONH); 1465 (CH_2); 1365 (Me). ^{1}H-NMR ($CDCl_3$, 2 diastereoisomers)[6]): 0.88–4.62 (*m*, 2 H–C(2''), 2 H–C(2'''), H–C(3''), H–C(3'''), H–C(4''), H–C(4'''), 2 H–C(5''), H–C(5'''), 2 H–C(6''), *Me*CH_2, Me$_2$C*H*, (CH$_2$)$_2$CN, CH_2CONH); 1.48 (*s*, Me–C(5')); 1.92 (*s*, Me–C(5''')); 3.79 (*s*, 2 MeO); 6.05–6.40 (*m*, H–C(1''), H–C(1''')); 6.81–7.64 (*m*, 13 arom. H, H–C(6'), H–C(6'''), NH). ^{13}C-NMR ($CDCl_3$, 2 diastereoisomers)[6]): 10.2, 10.6, 12.0, 12.0, 12.7 (*Me*–C(5'), *Me*–C(5'''), *MeCH*$_2$); 20.0–20.6 (*CH*$_2$CH$_2$OP); 22.9, 23.0 (C(6''')); 24.1, 24.5, 24.6, 24.6 (*Me*$_2$CH); 35.6, 35.7 (C(5''')); 38.3–38.8 (C(2''), C(2'''), *C*H$_2$CONH); 43.2, 43.3 (C(3'')); 55.2 (MeO); 57.5 (CH$_2$*C*H$_2$OP); 63.9 (C(5'')); 76.7, 84.3, 84.9, 85.4, 86.7, 87.3 (C(1''), C(1'''), C(3'''), C(4''), C(4''')); 111.4 (C(6'), C(6''')); 119.5 (CN); 113.2, 127.0, 128.0, 128.2, 130.1, 130.2, 135.2, 135.7, 135.8, 158.6 (arom. C); 135.5, 135.6 (C(5'), C(5''')); 150.3, 150.5, 150.6, 163.7, 163.8, 164.0 (C(2'), C(2'''), C(4'), C(4''')); 171.0, 171.7 (CONH). MS: 1036 (M^+), 819 ([M – PO(N(i-Pr)$_2$) (OCH$_2$)$_2$CN]$^+$).

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