Nucleosides

Part LXIV[1])

Base-Labile Protecting Groups for the Oligoribonucleotide Synthesis

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Dedicated to Prof. Dr. *Edgar Heilbronner* on the occasion of his 80th birthday with best personal wishes

New labile protecting groups for the anticipated synthesis of oligoribonucleotides were developed and introduced *via* their carbonochloridates **8**–**11** at the 5′-*O* position of thymidine (**15**) to form **16**, **18**, **21**, and **24** in good yields (*Schemes 2* and *3*). Similarly, the 5′-*O*-diphenylphosphinoyl(dpp)-protected thymidine derivative **27** was synthesized with diphenylphosphinoyl chloride **14** as the reactive reagent. With the help of the model compounds **16**, **18**, **21**, **24**, and **27**, the deprotection rates of these functions towards base treatment were recorded to evaluate their usefulness as temporary protecting groups in RNA assembly (*Table*). Finally, the relative stability of the 2-(4-nitrophenyl)ethoxycarbonyl (npeoc) protecting group towards bases confirmed its use as a permanent blocking group in our npe/npeoc strategy.

1. Introduction. – Discoveries in the past several years considering RNA, *e.g.* its role as ribozymes [2][3], its application in antisense technology [4][5], or its high binding affinity to specific targets [6–8] increased the demand for synthetic oligoribonucleotides.

The solid-phase synthesis of oligonucleotides has been improved immensely in recent years with the development of phosphoramidite chemistry [9–13]. Compared to DNA, however, the progress in the chemical build-up of RNA has been less fast and remains still less successful since the additional 2′-OH function extends the complexity of an appropriate protecting group strategy. The 2′-*O*-protecting group must remain intact during all the various steps of automated RNA assembly, but should be removed at the end of synthesis under mild conditions to avoid isomerization or cleavage of the internucleotide linkages. Further problems are a reduction in the stepwise condensation yields of the phosphoramidites due to the steric constraints imposed by the additional 2′-*O*-protecting group and the liability of free RNA to enzymatic degradation.

The 2′-OH function of commercially available phosphoramidites is mostly protected with the (*tert*-butyl)dimethylsilyl (tbdms) group, which was introduced by *Ogilvie et al.* [14][15]. Since this group is removed by F^- ions, it is completely compatible with the dimethoxytrityl group, the most common protecting group for the 5′-OH function. However, under the ammoniacal conditions used for the cleavage of the acyl blocking groups of the nucleobases, there is a danger of partial loss of the (*tert*-

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butyl)dimethylsilyl group, which can lead to cleavage of the nucleotide chain [16]. Additional problems are, *e.g.*, the build-up of salt by-products or the steric hindrance of the bulky (*tert*-butyl)dimethylsilyl group.

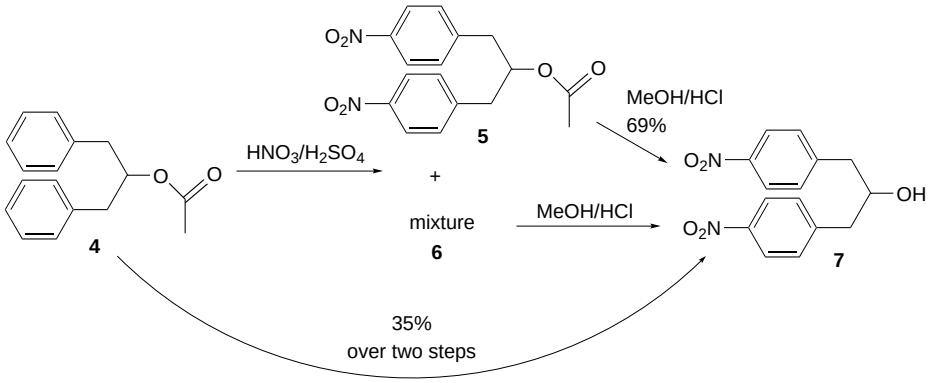
Reese and coworkers introduced acetal protecting groups like the tetrahydro-2*H*-pyranyl [17] or the achiral tetrahydro-4-methoxy-2*H*-pyran-4-yl group [18] for the blocking of the 2′-OH function, which are removed under mild acidic conditions. But especially for the synthesis of longer oligoribonucleotides, the acid-labile acetal function is not sufficiently compatible with the traditional 5′-*O*-trityl groups. As an improvement to this situation, *Reese* and coworkers, furthermore, applied the more stable 1-(2-chloro-4-methylphenyl)-4-methoxypiperidin-4-yl (ctmp) [19][20] and 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl (fpmp) groups [21][22] in combination with the more acid-sensitive 5′-*O*-pixyl function, and just recently the introduction of the 2′-*O*-bis(2-acetoxyethoxy)methyl (Ace) orthoester function in combination with a 5′-*O*-alkoxy-bis(trimethylsilyloxy)silyl group [23] as well as the 2′-*O*-[(triisopropylsilyl)oxy]-methyl (Tom) group [24][25] have also been recommended . Another alternative strategy replaces the acid-labile 5′-*O*-protecting group by base-labile functions to achieve complete compatibility with the 2′-*O*-acetal group. For example, *Gait* and coworkers employed the tetrahydro-4-methoxy-2*H*-pyran-4-yl (thmp) group together with the β-eliminating (9*H*-fluoren-9-ylmethoxy)carbonyl (fmoc) function [26], which is, however, not compatible with the 2-cyanoethyl phosphate protecting group, while *Bergmann* and *Pfleiderer* combined the same acetal group with the 5′-*O*-[2-(dansyl)-ethoxy]carbonyl (danseoc) group [27][28] and the more stable 2-(4-nitrophenyl)ethyl group at the internucleotidic linkage.

In this paper, we report the search of new base-labile protecting groups for the temporary 5′-*O*-protection in oligoribonucleotide synthesis. Their introduction into the 5′-OH function of thymidine led to model substances, which were evaluated regarding their usefulness as new potential protecting groups for RNA assembly.

2. Syntheses. – The syntheses of the new reactive protecting groups were performed from the respective hydroxy compounds, *i.e.*, from 1-phenyl-2-cyanoethanol (=β-hydroxybenzenepropanenitrile; 1pce; **1**), 2-phenyl-2-cyanoethanol (=α-(hydroxymethyl)benzeneacetonitrile; 2pce; **2**), and 2,2-bis(4-nitrophenyl)ethanol ($(np)_2e$; **3**) according to known literature procedures [29–31]. The synthesis of 1,2-bis(4-nitrophenyl)ethanol (=1,3-bis(4-nitrophenyl)propan-2-ol; **7**) began with the nitration of 1-benzyl-2-phenylethyl acetate (**4**) [32] at 0–10° leading to a mixture of nitrated products, whereby the anticipated compound **5** could only partially be crystallized from the reaction mixture by Et_2O (*Scheme 1*). Subsequent acid-catalyzed methanolysis of both the nitrated acetate **5** ($\rightarrow$**7**; 69%) and the remaining oily product mixture **6** gave alcohol **7** in a total yield of 35% over the two steps.

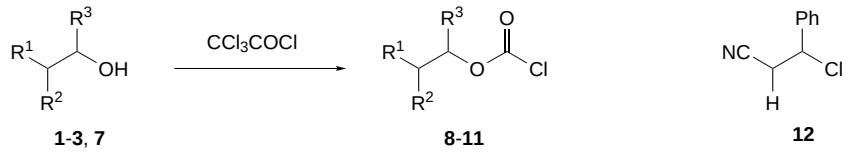
The following reaction of the alcohols **1**–**3** and **7**, respectively, with an excess of diphosgene (1.5–2.5 equiv.) in presence of Et_3N under ice-bath cooling gave the corresponding carbonochloridates **8**–**11** in good yields (73–100%). All efforts to get pure compounds **8** and **9** failed since the carbonochloridate **8** was contaminated with β-chlorobenzenepropanenitrile (**12**; *ca.* 10%) [33] and the starting alcohol **1** (*ca.* 10%), and product **9** contained 20% of α-methylidenebenzeneacetonitrile (**13**) [34–36], formed from **9** by a β-elimination process. Fortunately, these by-products, identified by

Scheme 1

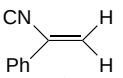


their ^{1}H-NMR data, did not interfere in the following reaction step and thus, no effort was spent on the purification of **8** and **9**, respectively. Since we could not find ^{1}H-NMR data for *β*-chlorobenzenepropanenitrile (**12**) in the literature, this compound was synthesized from hydroxy derivative **1** by reaction with $SOCl_2$ in a yield of 37% ([33]: 47%) to insure positive identification of compound **12**.

Scheme 2

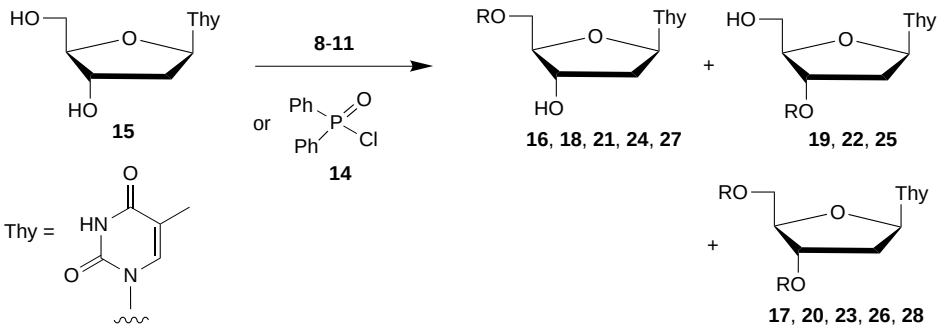


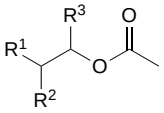
	R^1	R^2	R^3		%
1	CN	H	Ph	**8**	78
2	CN	Ph	H	**9**	73
3	4-NO_2-C_6H_4	4-NO_2-C_6H_4	H	**10**	quant. ([30]: quant.)
7	4-NO_2-C_6H_4	H	4-NO_2-$C_6H_4CH_2$	**11**	95



The introduction of the protecting groups at the 5′-*O*-position of thymidine (**15**) was carried out with a slight excess (1.3 equiv.) of carbonochloridate **8**–**11** and the commercially available diphenylphosphinoyl chloride (**14**), respectively, at low temperature (– 55° (^{i}PrOH/N_2 bath)) in CH_2Cl_2/pyridine, to give the desired 5′-*O*-substituted thymidines **16**, **18**, **21**, **24**, and **27** in yields between 53 and 82%. The 3′,5′-di-*O*-substituted nucleosides **17**, **20**, **23**, **26**, and **28** were formed as by-products in 6–16% yield, and the 3′-*O*-isomers could occassionally also be isolated in small amounts (**19** (5%), **22** (4%), and **25** (3%)). In the case of the (1-phenyl-2-cyanoethoxy)carbonyl (1pceoc) group, it became necessary to neutralize the reaction mixture with acid before workup, since the pyridine concentrated during the evaporation of the solvent caused already cleavage of the 5′-*O*-protecting group.

Scheme 3

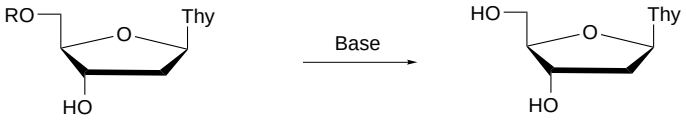


R			5'-*O*-subst.	3'-*O*-subst.	3',5'-di-*O*-subst.
					
R^1	R^2	R^3			
CN	H	Ph	**16** (71%)		**17** (14%)
CN	Ph	H	**18** (68%)	**19** (5%)	**20** (12%)
4-NO_2-C_6H_4	4-NO_2-C_6H_4	H	**21** (74%)	**22** (4%)	**23** (7%)
4-NO_2-C_6H_4	H	4-NO_2-$C_6H_4CH_2$	**24** (82%)	**25** (3%)	**26** (6%)
			**27** (53%)		**28** (16%)

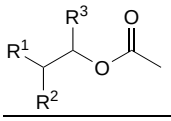
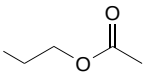
3. Kinetic Studies. – All new protecting groups were tested regarding their cleavage ability towards different bases, mainly 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as well as piperidine and Et_3N (*Table*). The [2,2-bis(4-nitrophenyl)ethoxy]carbonyl ($(np)_2eoc$) function had been developed by *Ramage et al.* [30] as a protecting group in peptide synthesis. Comparatively, we also evaluated the liability of the [2-(4-nitrophenyl)ethoxy]carbonyl (npeoc) group in nucleoside **29** [37], because we use this group together with the 2-(4-nitrophenyl)ethyl (npe) protecting group in our npe/npeoc strategy for the permanent blocking of base and phosphate functions [37–40]. The advantage of this strategy lies in the opportunity to synthesize crude oligomers in a very pure form, since the permanent protecting groups are removed by DBU in an aprotic solvent *via* β-elimination and are washed out while the oligonucleotide is still bound to the solid support.

For the kinetic studies, the appropriate nucleoside was treated with a 10-fold excess of base, usually in MeCN. The only exception was the deprotection reaction of the 5′-*O*-(diphenylphosphinoyl)thymidine (**27**), which had to be run in a protic solvent (*e.g.*, MeOH). In contrast to all other protecting groups, which were removed in a

Table. *Half-Lives of Protected Thymidine Nucleosides in Presence of Base*



16, **18**, **21**, **24**, **27**, **29** **15**

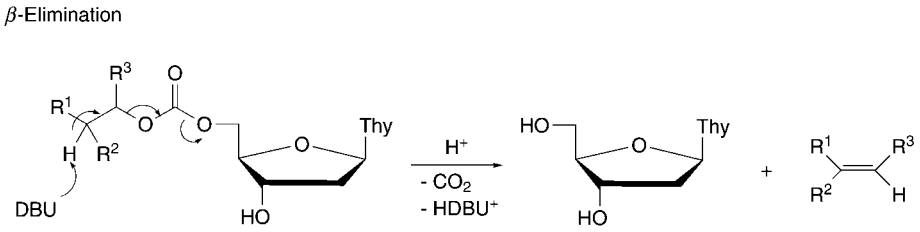
	R			Abbreviation	Base	Concentration [M]	Half-life [$t_{1/2}$]
							
	R^1	R^2	R^3				
16	CN	H	Ph	1pceoc	DBU	0.1	12 s[a]
					piperidine	0.5	47 min[a]
					Et_3N	0.5	15.2 h[a]
18	CN	Ph	H	2pceoc	DBU	0.01	< 15 s[c]
					Et_3N	0.5	< 12 s[c]
21	4-NO_2-C_6H_4	4-NO_2-C_6H_4	H	$(np)_2$eoc	DBU	0.1	12 s[a]
					piperidine	0.5	9.4 min[a]
					Et_3N	0.5	9.8 h[a]
24	4-NO_2-C_6H_4	H	4-NO_2-$C_6H_4CH_2$	nbnpeoc	DBU	0.1	38.6 min[b]
						1	5.3 min[b]
27				dpp	DBU	1	7.3 h[b]
29	4-NO_2-C_6H_4 			npeoc	DBU	0.01	12.2 h[a]
						0.1	94 min[a]
						1	8.7 min[a]

[a]) Calculation of $t_{1/2}$ according to *Method A*. [b]) Calculation of $t_{1/2}$ according to *Method B*. [c]) Complete cleavage within *t*.

β-elimination process by releasing an alkene derivative (see *Scheme 4*), the diphenylphosphinoyl function was cleaved by transesterification in an addition-elimination mechanism initiated by a nucleophilic attack of the MeO^- ion at the P-atom.

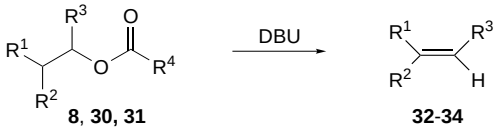
Aliquots were quenched in AcOH/MeCN at defined time intervals, and the mixtures analyzed by HPLC. From the obtained data, we determined the corresponding half-lives ($t_{1/2}$) for the pseudo-first-order reactions. For these calculations, we used two different methods.

Scheme 4

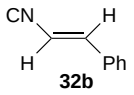


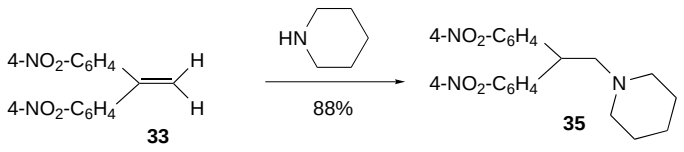
Method A considers the relative amount of protected nucleoside and cleaved protecting group, whereby the difference in extinction coefficient of starting material and resulting alkene derivative **32**–**34** has to be taken into account. For this reason, and to identify the deprotection products clearly by their retention time, compounds **32**–**34** were synthesized from their corresponding carbonochloridates **8** and **31** [37] or acetate **30** [30], respectively, by treatment with DBU according to *Ramage et al.* [30] (*Scheme 5*). Thereby, 3-phenylprop-2-enenitrile (**32**) was obtained as a mixture of its (*Z*)-isomer **32a** and (*E*)-isomer **32b** in a ratio of 3 :7 (by ^{1}H-NMR). The calculation of the half-lives were carried out with the extinction coefficients of this mixture, although the ε-values differ considerably for the (*Z*)-isomer **32a** ($\log \varepsilon_{273} = 4.22$) and the (*E*)-isomer **32b** ($\log \varepsilon_{272} = 4.36$) [41]. But since the calculated kinetic data shall only serve for evaluation, this simplification should be acceptable. The reaction of the 5′-*O*-{[2,2-bis(4-nitrophenyl)ethoxy]carbonyl}thymidine (**21**) with piperidine led to the alkene **33** and a second cleavage product, the ene-piperidine adduct **35** [30]. For an unequivocal identification of compound **35**, reference material was synthesized according to *Ramage et al.* [30] by reaction of 1,1-bis(4-nitrophenyl)ethene (**33**) with piperidine to reveal the same retention time as the product obtained during the kinetic evaluation.

Scheme 5



	R^1	R^2	R^3	R^4		%
8	CN	H	Ph	Cl	**32**	76 (**32a**/**32b** 3:7)
30	4-NO_2-C_6H_4	4-NO_2-C_6H_4	H	CH_3	**33**	70 ([30]: 69)
31	4-NO_2-C_6H_4	H	H	Cl	**34**	54





In those cases, where *Method A* could not be employed for calculation, *Method B* was used, whereby the ratio of the amount of starting nucleoside at a time t and the amount of starting nucleoside at the 0 min time point t_0 was determined.

According to the results listed in the *Table*, both the 1pceoc and the $(np)_2$eoc groups are suitable for the temporary protection of the 5′-OH function for the anticipated oligoribonucleotide synthesis. The evaluated half-lives for the deprotection of these functions with DBU (0.1M) are, accordingly, small and considerably shorter than for the npeoc group, which we wish to use for the permanent blocking during RNA assembly. For cleavages with 0.1M DBU, the half-lives of both functions were calculated identically at 12 sec, while the deprotection with piperidine and Et_3N is faster for the $(np)_2$eoc than for the 1pceoc group. However, with half-lives of *ca.* 9 min (0.5M piperidine) and 10 h (0.5M Et_3N), these bases are not useful for the cleavage of the $(np)_2$eoc function as a 5′-*O*-protecting group.

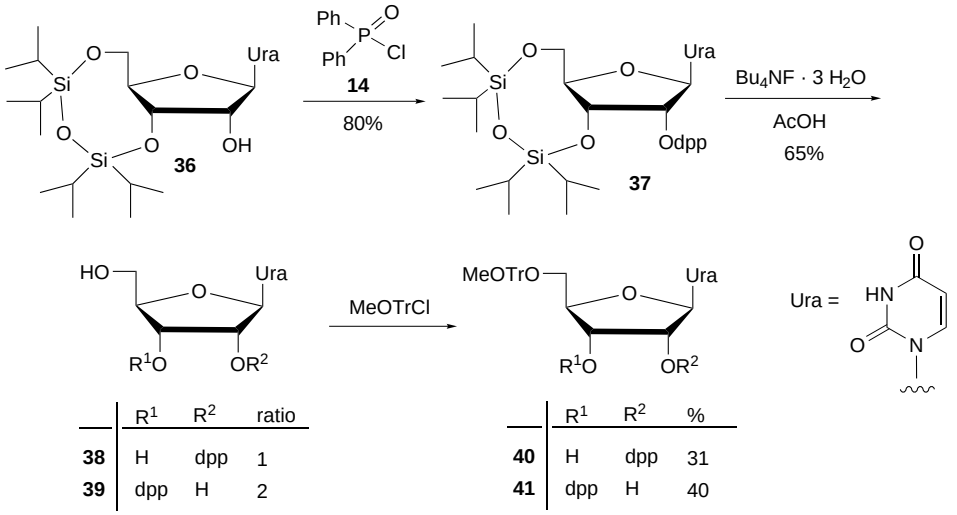
The β-proton of the 1pceoc group is mainly activated only by the cyano function, however, with both the cyano and the phenyl function at C(β), the 2pceoc group becomes extremely base-labile. Thus, even with very dilute DBU (0.01M) or with the weaker Et_3N (0.5M), the deprotection reaction is too fast to record any kinetics. Because of the fact, that some reactions during the synthesis of the monomeric building blocks as well as during the RNA assembly are catalyzed by base, the extreme base liability of the 2pceoc group might cause problems and can not be recommended.

In the case of the nbnpeoc group, the proton at C(β) is activated by only one nitrophenyl function. In this way, the deprotection rate is immensely decreased compared to the $(np)_2$eoc function, where two nitrophenyl groups contribute to the reactivity of H−C(β). With half-lives, recorded in the order of minutes and thus approximately half of the value as for the npeoc group, the nbnpeoc function is not useful for 5′-*O* protection.

This unsuitability also applies to the diphenylphosphinoyl (dpp) function, the half-life of which, in the presence of 1M DBU in MeOH, was evaluated to *ca.* 7 h. However, the dpp group was also tried for the protection of the 2′-OH function in combination with the dimethoxytrityl group as the temporary 5′-*O*-protecting group. As expected, this 2′-*O*-protecting group has the tendency for intramolecular 2′ → 3′-*O*-migration, as found with acyl functions [42–44] which excludes their application as 2′-*O*-protecting groups.

Nevertheless, to examine the migration tendency of the dpp group, it was introduced at the 2′-*O*-position of the 1,1,3,3-tetraisopropyl-1,3-disiloxane-1,3-diyl-(tipds)-protected uridine (**36**) [45] by reaction with diphenylphosphinoyl chloride (**14**) to give **37** (*Scheme 6*). The subsequent cleavage of the tipds function from compound **37** was carried out with Bu_4NF in THF. But even addition of AcOH in order to decrease the basicity of the F-ion could not avoid 2′ → 3′-*O*-migration of the dpp function. The reaction led to a mixture of the 2′-*O*-dpp- and the 3′-*O*-dpp-isomer **38** and **39**, respectively, in a ratio of 1:2 according to ^{1}H-NMR data. Since both isomers showed identical chromatographic properties, the mixture was subsequently tritylated with 2.25 equiv. of monomethoxytrityl chloride, thus achieving better resolution of the product mixture. Indeed, the resulting products were easily separated by flash chromatography, giving the 2′-*O*-dpp-substituted product **40** in 31% yield and the 3′-*O*-dpp-substituted compound **41** in 40% yield, respectively. These findings exclude the dpp group as a sugar protecting group in RNA assembly.

Scheme 6



MeOTr = monomethoxytrityl; dpp= diphenylphosphinoyl

From our results, we can conclude that the 1pceoc and $(np)_2$eoc groups can be considered as potential alternatives for 5′-OH protection in conjunction with 2′-*O*-acetal and npe/npeoc groups in oligoribonucleotide synthesis. The use of the 1pceoc group, however, is advantageous since its carbonochloridate **8** is prepared in only two steps with very good yields. Further studies showing the application of the 1pceoc group in RNA synthesis will be presented in due time.

Experimental Part

General. Products were dried under high vacuum. TLC: precoated silica gel thin-layer sheets *60 F_{254}* from *Merck*. Flash chromatography (FC): silica gel (*Baker*, 30–60 μm); 0.2–0.3 bar. HPLC: pump *L 6000*, autosampler *AS 4000*, *Merck-Hitachi*, UV-detector *Uvikon 730 SLC*, *Kontron*; column *RP 18*, *LiChrospher* 125 × 4 mm, 5 μm, *Merck*; elution: *A*; 0.1M (Et_3NH)OAc buffer (pH 7); *B*; MeCN; gradient: 0% *B* (0–3 min), 0–50% *B* (3–10 min), 50–100% *B* (10–25 min), 100–50% *B* (25–30 min), 50–0% *B* (30–33 min), 0% *B* (33–35 min); flow rate, 1 ml/min. M. p.: *Gallenkamp* melting-point apparatus; no corrections. UV/VIS: *Perkin-Elmer Lambda 5*; λ_{max} in nm (log ε). ^{1}H-NMR: *Bruker AC 250*; δ in ppm rel. to $SiMe_4$ or $CDCl_3$ ((D_6)DMSO) as internal standard.

1. *β-Hydroxybenzenepropanenitrile* (**1**) [29]. A soln. of 1.6M BuLi in hexane (34.5 ml, 55 mmol) in anh. THF (34.5 ml) was cooled under N_2 to −80° (^{i}PrOH/N_2 bath). A soln. of MeCN (2.65 ml, 50 mmol) in dry THF (50 ml) was added dropwise within 8 min and the resulting suspension stirred for 2 h at −80°. After dropwise addition of benzaldehyde (5.31 g, 50 mmol) in anh. THF (50 ml) within 6 min, the cooling bath was removed and the resulting clear soln. stirred for additional 25 min and then poured onto ice/H_2O/conc. HCl soln. (100 g, 60 ml, and 17 ml, resp.). The aq. layer was extracted with Et_2O (3 × 100 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the yellowish residue purified (removal of benzaldehyde) by FC (silica gel (150 g), 14 × 5.5 cm, petroleum ether/AcOEt 7:1 (640 ml), 6:1 (210 ml), 5:1 (300 ml), 4:1 (250 ml), 3:1 (200 ml), 2:1 (300 ml), AcOEt (600 ml)): 7.06 g (96%) ([29]: 78% after distillation) of **1**. Colorless oil. n_D^{20} 1.5394 ([46]: n_D^{20} 1.5388). TLC (petroleum ether/AcOEt 2:1): R_f 0.33. UV (MeOH): 256 (2.53), 212 (sh, 3.74). ^{1}H-NMR ($CDCl_3$): 7.55–7.29 (*m*, Ph); 5.01 (*t*, CH); 2.75 (*d*, CH_2); 2.54 (br. *s*, OH).

2. *1-(4-Nitrobenzyl)-2-(4-nitrophenyl)ethyl Acetate* (**5**). Nitrating acid was prepared by adding 98% sulfuric acid (2 ml) to 60% nitric acid (2 ml) under ice-bath cooling. This mixture was added dropwise to the stirred and ice-cooled oil of 1-benzyl-2-phenylethyl acetate [32] (**4**; 1.27 g, 5.0 mmol) within 15 min, while the temp. was maintained between 0 and 10° (→ slightly yellow mixture). After stirring for further 2 h at r.t., the mixture was poured onto ice (10 g) and the product extracted with Et_2O (25 ml, 2 × 10 ml). The combined org. phase was washed with sat. $NaHCO_3$ soln. (2 × 30 ml), H_2O (3 × 30 ml), and sat. NaCl soln. (30 ml), dried (Na_2SO_4), and evaporated to a light yellow oil. After cooling in the refrigerator, the oil was crystallized from Et_2O in a sonicating bath, and the product was isolated by filtration to give 0.48 g (28%) of **5**. Upon evaporation, the filtrate afforded a yellow oily mixture **6** (1.19 g), containing **5** and other nitrated by-products.

Data of **5**: Pale yellow solid. M. p. 139–140°. TLC (petroleum ether/AcOEt 7:3): R_f 0.39. UV (MeOH): 271 (4.33), 211 (sh, 4.20). ^{1}H-NMR ((D$_6$)DMSO): 8.15 (*d*, 4 H *o* to NO_2); 7.50 (*d*, 4 H *m* to NO_2); 5.38–5.26 (*m*, CH); 3.15–2.93 (*m*, 2 CH_2); 1.80 (*s*, Me). Anal. calc. for $C_{17}H_{16}N_2O_6$ (344.3): C 59.30, H 4.68, N 8.14; found: C 59.20, H 4.73, N 8.07.

3. *1-(4-Nitrobenzyl)-2-(4-nitrophenyl)ethanol* (=*1,3-Bis(4-nitrophenyl)propan-3-ol;* **7**). a) *From* **5**: By heating up, a suspension of **5** (0.48 g, 1.39 mmol) in MeOH (5 ml) and conc. HCl soln. (0.1 ml) was dissolved, and the resulting soln. was refluxed for 6 h. The yellow mixture was then poured onto ice (10 g) and the org. phase extracted with AcOEt (3 × 20 ml). The combined org. phase was washed with H_2O (2 × 40 ml) and sat. NaCl soln. (40 ml), dried (Na_2SO_4), and evaporated. The solid residue was crystallized from MeOH (15 ml) to give 292 mg (69%) of **7**.

b) *From Mixture* **6**: A yellow soln. of mixture **6** (1.14 g) in MeOH (5 ml) and conc. HCl soln. (0.1 ml) was heated under reflux for 6 h. The mixture was then poured onto ice (10 g), the org. phase extracted with AcOEt (30 ml, 2 × 20 ml), the combined org. phase washed with H_2O (2 × 40 ml) and sat. NaCl soln. (40 ml), dried (Na_2SO_4), and evaporated, and the brown oil purified by FC (silica gel (25 g), 10.5 × 2.6 cm, toluene (200 ml), toluene/AcOEt 9:1 (200 ml), 8:1 (90 ml), 7:1 (80 ml), 6:1 (70 ml), 5:1 (60 ml)): 152 mg of **7**. Mixture fractions containing **7** were evaporated separately and purified once more by FC (silica gel (15 g), 9.5 × 2.3 cm, toluene/AcOEt 10:1 (220 ml), 9:1 (200 ml)): 81 mg of **7**. Overall yield from 1-benzyl-2-phenylethyl acetate (**4**) 35% of **7**. Colorless needles. M. p. 143–145°. TLC (petroleum ether/AcOEt 2:1): R_f 0.38. UV (MeOH): 276 (4.33), 212 (sh, 4.18). ^{1}H-NMR ((D$_6$)DMSO): 8.15 (*d*, 4 H *o* to NO_2); 7.50 (*d*, 4 H *m* to NO_2); 4.92 (*d*, OH); 4.08–3.92 (*m*, CH); 2.94–2.71 (*m*, 2 CH_2). Anal. calc. for $C_{15}H_{14}N_2O_5$ (302.3): C 59.60, H 4.67, N 9.28; found: C 59.76, H 4.73, N 9.29.

4. *2-Cyano-1-phenylethyl Carbonochloridate* (**8**). Under N_2, a soln. of **1** (1.51 g, 10 mmol) and Et_3N (1.41 ml, 1.03 g, 10 mmol) in dry THF (5 ml) was added dropwise to an ice-cooled, stirred soln. of trichloromethyl carbonochloridate (4.92 g, 3.0 ml, 25 mmol) in dry THF (10 ml) within 10 min. After 10 min, the ice-bath was removed, and stirring was continued at r.t. for 6 h 30 min. The mixture was filtered through a sintered glass funnel, washed with dry THF, and evaporated: 1.91 g of a slightly yellow oil. ^{1}H-NMR: *ca.* 82% of **8** (yield 78%), 10% of *β*-chlorobenzenepropanenitrile (**12**), and 8% of **1**. **8**: TLC (petroleum ether/AcOEt 2:1): R_f 0.82. ^{1}H-NMR ($CDCl_3$): 7.45–7.37 (*m*, Ph); 5.93 (*dd*, CH); 3.08–2.90 (*m*, CH_2).

5. *2-Cyano-2-phenylethyl Carbonochloridate* (**9**). As described in *Exper. 4*, with **2** (1.30 g, 8.85 mmol), Et_3N (1.23 ml, 90 mg, 8.85 mmol), THF (10 ml), trichloromethyl carbonochloridate (2.65 ml, 4.35 g, 22 mmol), and THF (10 ml); addition within 15 min, stirring for 15 min at 0° and 4 h 45 min at r.t.: 1.56 g of a slightly yellow oil, which, according to ^{1}H-NMR data, consists of *ca.* 80% of **9** (yield 73%) and 20% of *α*-methylidenebenzeneacetonitrile (**13**) [34–36], cleaved from **9** by *β*-elimination. **9**: TLC (petroleum ether/AcOEt 2:1): R_f 0.82. ^{1}H-NMR ($CDCl_3$): 7.44–7.35 (*m*, Ph); 4.53 (*d*, CH_2); 4.23 (*t*, CH). Anal. calc. for $C_{9.8}H_{7.8}Cl_{0.8}NO_{1.6}$ (**9**/**13** 80:20) (193.5): C 60.82, H 4.06, N 7.24; found: C 60.61, H 4.22, N 7.50.

6. *2,2-Bis(4-nitrophenyl)ethyl Carbonochloridate* (**10**) [30]. As described in *Exper. 4*, with **3** (1.30 g, 4.51 mmol), Et_3N (0.63 ml, 460 mg, 4.51 mmol), THF (10 ml), trichloromethyl carbonochloridate (0.82 ml, 1.35 g, 6.80 mmol), and THF (8 ml), addition within 10 min, stirring for 10 min at 0° and 3 h 30 min at r.t.: 1.59 g (quant.) ([30]: quant.) of **10**. Pale yellow, cloudy oil which crystallized on cooling in the refrigerator. Almost colorless solid. M.p. 95–97° ([30]: 97–98°). TLC (petroleum ether/AcOEt 2:1): R_f 0.70. UV (MeOH): 271 (4.34), 210 (sh, 4.23). ^{1}H-NMR ($CDCl_3$): 8.21 (*d*, 4 H *o* to NO_2); 7.40 (*d*, 4 H *m* to NO_2); 4.88 (*d*, CH_2); 4.67 (*t*, CH). Anal. calc. for $C_{15}H_{11}ClN_2O_6$ (350.7): C 51.37, H 3.16, N 7.99; found: C 51.37, H 3.30, N 7.94.

7. *1-(4-Nitrobenzyl)-2-(4-nitrophenyl)ethyl Carbonochloridate* (**11**). As described in *Exper. 4*, with **7** (1.00 g, 3.31 mmol), Et_3N (0.46 ml, 340 mg, 3.32 mmol), THF (9 ml), trichloromethyl carbonochloridate (0.8 ml, 1.31 g, 6.63 mmol), and THF (6 ml); addition within 10 min, stirring for 10 min at 0° and 4 h 10 min at r.t.: 1.15 g (95%) of **11**. Colorless solid. M. p. 140–144° (dec.). TLC (petroleum ether/AcOEt 2:1): R_f 0.52. UV (MeOH): 271

(4.33), 211 (sh, 4.20). ^{1}H-NMR ($CDCl_3$): 8.19 (*d*, 4 H *o* to NO_2); 7.37 (*d*, 4 H *m* to NO_2); 5.31 (*quint.*, CH); 3.09 (*d*, 2 CH_2). Anal. calc. for $C_{16}H_{13}ClN_2O_6$ (364.7): C 52.69, H 3.59, N 7.68; found: C 52.84, H 3.75, N 7.71.

8. *β-Chlorobenzenepropanenitrile* (**12**) [33]. A soln. of thionyl chloride (1.2 ml, 1.96 g, 16 mmol) in dry toluene (1.6 ml) was added quickly and dropwise to a soln. of *β*-hydroxybenzenepropanenitrile (**1**; 804 mg, 5.46 mmol) and pyridine (0.32 ml) in dry toluene (15 ml), and the mixture was refluxed for 1.5 h. After cooling to r.t., the mixture was poured onto ice (19 g), the org. phase was extracted with CH_2Cl_2 (3 × 20 ml), the combined org. phase washed with sat. $NaHCO_3$ soln. (2 × 60 ml), dried (Na_2SO_4), and evaporated, and the oil purified by FC (silica gel (40 g), 14.5 × 2.9 cm, petroleum ether/AcOEt 9:1 (200 ml), 8:1 (180 ml), 7:1 (160 ml), 6:1 (140 ml)): 339 mg (37%) ([33]: 47%) of **12**. Colorless oil. TLC (petroleum ether/AcOEt 5:1): R_f 0.58. ^{1}H-NMR ($CDCl_3$): 7.43–7.37 (*m*, Ph); 5.10 (*t*, CH); 3.10, 3.09 (2*d*, CH_2). Anal. calc. for C_9H_8ClN (165.6): C 65.27, H 4.87, N 8.46; found: C 64.96, H 4.98, N 8.33.

9. *5′-O-[(2-Cyano-1-phenylethoxy)carbonyl]thymidine* (**16**) *and 3′,5′-Bis-O-[(2-cyano-1-phenylethoxy)carbonyl]thymidine* (**17**). After co-evaporation with dry pyridine (3 × 3 ml), thymidine (**15**; 204 mg, 0.84 mmol) was dissolved in dry pyridine (4 ml) and cooled under N_2 to −55° (^{i}PrOH/N_2 bath). A soln. of an oil, containing *ca.* 80% of **8** (230 mg, 1.10 mmol), in dry CH_2Cl_2 (4 ml) was added dropwise within 15 min, and stirring was continued for 6 h at −55 to −20°. Then the mixture was diluted with CH_2Cl_2 (20 ml) and washed with H_2O (20 ml), the aq. layer extracted with CH_2Cl_2 (2 × 20 ml), the combined org. phase dried (Na_2SO_4), evaporated, and co-evaporated with toluene (4 × 10 ml), and the residue submitted to FC (silica gel (20 g), 14 × 2.3 cm, CH_2Cl_2/MeOH 100:1 (101 ml), 100:2 (204 ml), 100:3 (309 ml), 100:4 (208 ml), 100:5 (105 ml)): 250 mg (71%) of **16**. Combined fractions containing **17** were still contaminated with *β*-hydroxybenzenepropanenitrile (**1**) and purified by another FC (silica gel (10 g), 14.5 × 1.4 cm, CH_2Cl_2 (100 ml), CH_2Cl_2/MeOH 100:1 (101 ml), 100:2 (102 ml)): 69 mg (14%) of **17**.

Data of **16**: Colorless foam. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.25. UV (MeOH): 264 (3.98), 213 (sh, 4.25). ^{1}H-NMR ($CDCl_3$): 8.37 (br. *s*, NH); 7.39–7.35 (*m*, Ph (1pceoc)); 7.28, 7.24 (2*s*, H–C(6)); 6.29, 6.26 (2*t*, H–C(1′)); 5.91–5.81 (*m*, CH (1pceoc)); 4.51–4.32 (*m*, H–C(3′), 2 H–C(5′)); 4.13–4.09 (*m*, H–C(4′)); 2.96–2.92 (*m*, CH_2 (1pceoc)); 2.45–2.31 (*m*, H–C(2′), OH–C(3′)); 2.26–2.11 (*m*, H–C(2′)); 1.90, 1.81 (2*s*, Me). Anal. calc. for $C_{20}H_{21}N_3O_7$ (415.4): C 57.83, H 5.10, N 10.12; found: C 57.21, H 5.16, N 9.55.

Data of **17**: Colorless foam. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.49. UV (MeOH): 262 (3.92), 213 (sh, 4.19). ^{1}H-NMR ($CDCl_3$): 8.03 (br. *s*, NH); 7.40–7.35 (*m*, 2 Ph (1cpeoc)); 7.21 (*s*, H–C(6)); 6.33–6.28 (*m*, H–C(1′)); 5.89–5.73 (*m*, 2 CH (1pceoc)); 5.20–5.09 (*m*, H–C(3′)); 4.49–4.29 (*m*, 2 H–C(5′)); 4.19 (*m*, H–C(4′)); 3.03–2.88 (*m*, 2 CH_2 (1cpeoc)); 2.52–2.42 (*m*, H–C(2′)); 2.31–2.26 (*m*, H–C(2′)); 1.91, 1.73 (2*s*, Me). Anal. calc. for $C_{30}H_{28}N_4O_9 \cdot 0.5\ H_2O$ (597.6): C 60.30, H 4.89, N 9.38; found: C 60.65, H 4.89, N 9.25.

10. *5′-O-[(2-Cyano-2-phenylethoxy)carbonyl]thymidine* (**18**), *3′-O-[(2-Cyano-2-phenylethoxy)carbonyl]thymidine* (**19**), *and 3′,5′-Bis-O-[(2-cyano-2-phenylethoxy)carbonyl]thymidine* (**20**). As described in *Exper. 9*, with **15** (201 mg, 0.83 mmol), pyridine (5 ml), **9** (230 mg, 1.10 mmol; oil of *ca.* 80% purity), and CH_2Cl_2 (5 ml); addition within 5 min, stirring for 6 h 30 min at −55 to −10°. Washing with a mixture of H_2O (20 ml) and conc. HCl (3.7 ml). Co-evaporation with H_2O (4 × 10 ml), MeOH (3 × 10 ml), and CH_2Cl_2 (2 × 10 ml). FC (silica gel (20 g), 14 × 2.1 cm, CH_2Cl_2/MeOH 100:1 (101 ml), 100:2 (204 ml), 100:3 (206 ml), 100:4 (104 ml)) gave 233 mg (68%) of **18**, 16 mg (5%) of **19**, and 57 mg (12%) of **20**.

Data of **18**: Colorless foam. TLC: R_f 0.23 (toluene/AcOEt/MeOH 5:4:1). UV (MeOH): 264 (4.01), 213 (sh, 4.24). ^{1}H-NMR ($CDCl_3$): 8.60 (br. *s*, NH); 7.43–7.33 (*m*, Ph (2pceoc)); 7.31, 7.28 (2*s*, H–C(6)); 6.31 (*t*, H–C(1′)); 4.50–4.33 (*m*, CH_2 (2pceoc), H–C(3′), 2 H–C(5′)); 4.25–4.17 (*m*, CH (2pceoc)); 4.14–4.12 (*m*, H–C(4′)); 2.60 (br. *s*, OH–C(3′)); 2.44–2.35 (*m*, H–C(2′)); 2.24–2.13 (*m*, H–C(2′)); 1.92, 1.87 (2*s*, Me). Anal. calc. for $C_{20}H_{21}N_3O_7 \cdot 0.5\ H_2O$ (424.4): C 56.60, H 5.23, N 9.90; found: C 56.89, H 5.14, N 9.88.

Data of **19**: Colorless foam. TLC: R_f 0.30 (toluene/AcOEt/MeOH 5:4:1). UV (MeOH): 263 (3.99), 213 (sh, 4.15). ^{1}H-NMR ($CDCl_3$): 8.93 (br. *s*, NH); 7.42–7.38 (*m*, Ph (2pceoc), H–C(6)); 6.18–6.09 (*m*, H–C(1′)); 5.28 (*m*, H–C(3′)); 4.41 (*d*, CH_2 (2pceoc)); 4.23–4.14 (*m*, CH (2pceoc), H–C(4′)); 3.96–3.83 (*m*, 2 H–C(5′)); 2.88 (br. *s*, OH–C(5′)); 2.59–2.48 (*m*, H–C(2′)); 2.48–2.37 (*m*, H–C(2′)); 1.90 (*s*, Me).

Data of **20**: Colorless foam. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.47. UV (MeOH): 263 (3.98), 212 (sh, 4.32). ^{1}H-NMR ($CDCl_3$): 8.96 (br. *s*, NH); 7.47–7.34 (*m*, 2 Ph (2pceoc), H–C(6)); 6.32 (*t*, H–C(1′)); 5.21–5.14 (*m*, H–C(3′)); 4.48–4.41 (*m*, 2 CH_2 (2pceoc), H–C(5′)); 4.28–4.19 (*m*, 2 CH (2pceoc), H–C(5′)); 4.00–3.91 (*m*, H–C(4′)); 2.50–2.45 (*m*, H–C(2′)); 2.32–2.19 (*m*, H–C(2′)); 1.91, 1.86 (2*s*, Me). Anal. calc. for $C_{30}H_{28}N_4O_9$ (588.6): C 61.22, H 4.80, N 9.52; found: C 61.32, H 5.13, N 9.07.

11. *5′-O-{[2,2-Bis(4-nitrophenyl)ethoxy]carbonyl}thymidine* (**21**), *3′-O-{[2,2-Bis(4-nitrophenyl)ethoxy]carbonyl}thymidine* (**22**), *and 3′,5′-Bis-O-{[2,2-bis(4-nitrophenyl)ethoxy]carbonyl}thymidine* (**23**). As described in *Exper. 9*, with **15** (200 mg, 0.83 mmol), pyridine (5 ml), **10** (376 mg, 1.07 mmol), and CH_2Cl_2 (5 ml); addition

within 20 min, stirring for 6 h 10 min at −55 to −10°. FC (20 g silica gel, 14 × 2.1 cm, CH_2Cl_2/MeOH 100:1 (101 ml), 100:2 (102 ml), 100:3 (103 ml), 100:4 (104 ml), 100:5 (105 ml)) gave 342 mg (74%) of **21** and 19 mg (4%) of **22**. Combined fractions containing product **23** were still contaminated and purified by another FC (silica gel (7 g), 14.5 × 1.4 cm, CH_2Cl_2 (100 ml), CH_2Cl_2/MeOH 100:0.5 (100.5 ml), 100:1 (101 ml), 100:2 (102 ml)): 51 mg (7%) of **23**.

Data of **21**: Colorless foam. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.39. UV (MeOH): 268 (4.43), 212 (sh, 4.36). ^{1}H-NMR ($CDCl_3$): 8.20 (*d*, 4 H *o* to NO_2); 8.00 (br. *s*, NH); 7.39 (*d*, 4 H *m* to NO_2); 7.18 (*s*, H−C(6)); 6.20 (*t*, H−C(1′)); 4.79–4.73 (*m*, CH_2 (np)$_2$eoc); 4.68–4.61 (*m*, CH (np)$_2$eoc); 4.36–4.34 (*m*, H−C(3′), 2 H−C(5′)); 4.08–4.05 (*m*, H−C(4′)); 2.40–2.30 (*m*, H−C(2′)); 2.20–2.12 (*m*, H−C(2′), OH−C(3′)); 1.81 (*s*, Me). Anal. calc. for $C_{25}H_{24}N_4O_{11} \cdot 0.5\ H_2O$ (565.5): C 53.10, H 4.46, N 9.91; found: C 53.26, H 4.41, N 9.84.

Data of **22**: Colorless foam. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.50. UV (MeOH): 268 (4.42), 211 (sh, 4.36). ^{1}H-NMR ($CDCl_3$): 9.10 (br. *s*, NH); 8.20 (*d*, 4 H *o* to NO_2); 7.42 (*s*, H−C(6)); 7.41 (*d*, 4 H *m* to NO_2); 6.13 (*dd*, H−C(1′)); 5.23–5.21 (*m*, H−C(3′)); 4.75–4.72 (*m*, CH_2 (np)$_2$eoc)); 4.64–4.59 (*t*, CH (np)$_2$eoc); 4.07 (*m*, H−C(4′)); 3.87–3.84 (*m*, 2 H−C(5′)); 2.80 (br. *s*, OH−C(5′)); 2.43–2.33 (*m*, 2 H−C(2′)); 1.86 (*s*, Me). Anal. calc. for $C_{25}H_{24}N_4O_{11} \cdot H_2O$ (574.5): C 52.27, H 4.74, N 9.75; found: C 52.82, H 4.87, N 9.30.

Data of **23**: Colorless foam. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.67. UV (MeOH): 268 (4.58), 211 (sh, 4.47). ^{1}H-NMR ($CDCl_3$): 8.88 (br. *s*, NH); 8.20, 8.19 (2*d*, 8 H *o* to NO_2); 8.39, 7.41 (2*d*, 8 H *m* to NO_2); 7.13 (*s*, H−C(6)); 6.18 (*dd*, H−C(1′)); 5.00–4.97 (*m*, H−C(3′)); 4.84–4.72 (*m*, 2 CH_2 (np)$_2$eoc); 4.70–4.57 (*m*, 2 CH (np)$_2$eoc); 4.33–4.31 (*m*, 2 H−C(5′)); 4.15–4.13 (*m*, H−C(4′)); 2.36–2.33 (*m*, H−C(2′)); 2.14–2.11 (*m*, H−C(2′)); 1.78 (*s*, Me). Anal. calc. for $C_{40}H_{34}N_6O_{17} \cdot 0.5\ H_2O$ (879.7): C 54.61, H 4.01, N 9.55; found: C 54.56, H 4.27, N 9.25.

12. *5′-O-{[1-(4-Nitrobenzyl)-2-(4-nitrophenyl)ethoxy]carbonyl}thymidine* (**24**), *3′-O-{[1-(4-Nitrobenzyl)-2-(4-nitrophenyl)ethoxy]carbonyl}thymidine* (**25**), *and 3′,5′-Bis-O-{[1-(4-nitrobenzyl)-2-(4-nitrophenyl)ethoxy]-carbonyl}thymidine* (**26**). As described in *Exper. 9*, with **15** (401 mg, 1.66 mmol), co-evaporated with pyridine (3 × 5 ml), pyridine (8 ml), **11** (787 mg, 2.16 mmol), and CH_2Cl_2 (7 ml); addition within 15 min at −45°, stirring for 6 h 10 min at −45 to −20°. FC (silica gel (40 g), 14.5 × 2.7 cm, CH_2Cl_2/MeOH 100:1 (202 ml), 100:2 (408 ml), 100:3 (309 ml), 100:4 (104 ml)) gave 770 mg (82%) of **24** and 25 mg (3%) of **25**. Combined fractions containing product **26** were still contaminated and purified by another FC (silica gel (13 g), 17 × 1.3 cm, CH_2Cl_2/MeOH 100:1 (101 ml), 100:2 (102 ml), 100:3 (103 ml)): 83 mg (6%) of **26**.

Data of **24**: Colorless foam. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.37. UV (MeOH): 267 (4.44), 210 (sh, 4.34). ^{1}H-NMR ($CDCl_3$): 8.96 (br. *s*, NH); 8.15, 8.11 (2*d*, 4 H *o* to NO_2); 7.37, 7.33 (2*d*, 4 H *m* to NO_2); 7.22 (*s*, H−C(6)); 6.19 (*t*, H−C(1′)); 5.23 (*quint.*, CH (nbnpeoc)); 4.31–4.15 (*m*, H−C(3′), 2 H−C(5′)); 4.04–3.99 (*m*, H−C(4′)); 3.07–2.97 (*m*, 2 CH_2 (nbnpeoc)); 2.75 (br. *s*, OH−C(3′)); 2.40–2.31 (*m*, H−C(2′)); 2.12–2.02 (*m*, H−C(2′)); 1.87 (*s*, Me). Anal. calc. for $C_{26}H_{26}N_4O_{11} \cdot H_2O$ (588.5): C 53.06, H 4.80, N 9.52; found: C 53.00, H 4.53, N 9.36.

Data of **25**: Colorless foam. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.50. UV (MeOH): 267 (4.45), 211 (sh, 4.40). ^{1}H-NMR ($CDCl_3$): 8.87 (br. *s*, NH); 8.18, 8.15 (2*d*, 4 H *o* to NO_2); 7.41 (*s*, H−C(6)); 7.41, 7.38 (2*d*, 4 H *m* to NO_2); 6.16 (*dd*, H−C(1′)); 5.18 (*quint.*, CH (nbnpeoc)); 5.06–5.03 (*m*, H−C(3′)); 3.87–3.85 (*m*, H−C(4′)); 3.80–3.69 (*m*, 2 H−C(5′)); 3.04 (*d*, 2 CH_2 (nbnpeoc)); 2.63 (br. *s*, OH−C(5′)); 2.39–2.27 (*m*, H−C(2′)); 2.22–2.15 (*m*, H−C(2′)); 1.87 (*s*, Me).

Data of **26**: Colorless foam. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.68. UV (MeOH): 269 (4.64), 212 (sh, 4.54). ^{1}H-NMR ($CDCl_3$): 8.47 (br. *s*, NH); 8.20–8.09 (*m*, 8 H *o* to NO_2); 7.41–7.29 (*m*, 8 H *m* to NO_2); 7.12 (*s*, H−C(6)); 6.15 (*dd*, H−C(1′)); 5.17 (*quint.*, 2 CH (nbnpeoc)); 4.63 (*m*, H−C(3′)); 4.12–3.98 (*m*, 2 H−C(5′)); 3.82 (*m*, H−C(4′)); 3.07–2.98 (2*d*, 4 CH_2 (nbnpeoc)); 2.23–2.16 (*m*, H−C(2′)); 2.01–1.92 (*m*, H−C(2′)); 1.87 (*s*, Me). Anal. calc. for $C_{42}H_{38}N_6O_{17}$ (898.8): C 56.13, H 4.26, N 9.35; found: C 55.80, H 4.54, N 8.99.

13. *5′-O-(Diphenylphosphinoyl)thymidine* (**27**) *and 3′,5′-Bis-O-(diphenylphosphinoyl)thymidine* (**28**). As described in *Exper. 9*, with **15** (202 mg, 0.83 mmol), pyridine (4 ml), diphenylphosphinoyl chloride (**14**; 0.21 ml, 260 mg, 1.10 mmol), and CH_2Cl_2 (3 ml); addition within 10 min at −55°, stirring for 6 h 30 min at −50 to −20°. FC (silica gel (20 g), 14 × 2.1 cm, CH_2Cl_2/MeOH 100:1 (101 ml), 100:2 (204 ml), 100:3 (309 ml), 100:4 (208 ml), 100:5 (105 ml)) gave 197 mg (53%) of **27** and 87 mg (16%) of **28**.

Data of **27**: Colorless foam. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.22. UV (MeOH): 270 (sh, 3.96), 265 (4.00), 261 (sh, 3.98), 219 (sh, 4.39). ^{1}H-NMR ($CDCl_3$): 9.11 (br. *s*, NH); 7.84–7.73 (*m*, 4 H (dpp)); 7.56–7.39 (*m*, 6 H (dpp)); 7.20 (*s*, H−C(6)); 6.29 (*t*, H−C(1′)); 5.72 (br. *s*, OH−C(3′)); 4.62–4.59 (*m*, H−C(3′)); 4.25 (*m*, 2 H−C(5′)); 4.02 (*m*, H−C(4′)); 2.47–2.35 (*m*, H−C(2′)); 2.16–2.05 (*m*, H−C(2′)); 1.57 (*s*, Me). Anal. calc. for $C_{22}H_{23}N_2O_6P$ (442.4): C 59.73, H 5.24, N 6.33; found: C 59.81, H 5.29, N 5.81.

Data of **28**: Colorless foam. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.32. UV (MeOH): 271 (sh, 4.64), 265 (4.14), 261 (sh, 4.11), 222 (4.60). ^{1}H-NMR ($CDCl_3$): 8.33 (br. *s*, NH); 7.84–7.68 (*m*, 8 H (dpp)); 7.57–7.38 (*m*, 12 H (dpp), H–C(6)); 6.40 (*dd*, H–C(1′)); 5.24 (*m*, H–C(3′)); 4.43 (*m*, H–C(4′)); 4.24 (*m*, H–C(5′)); 4.05–3.96 (*m*, H–C(5′)); 2.57 (*m*, H–C(2′)); 2.17–2.03 (*m*, H–C(2′)); 1.65 (*s*, Me). Anal. calc. for $C_{34}H_{32}N_2O_7P_2 \cdot H_2O$ (660.6): C 61.82, H 5.19, N 4.24; found: C 61.56, H 5.14, N 4.39.

14. *3-Phenylprop-2-enenitrile* (**32**): *(*Z*)-Isomer* **32a** *and (*E*)-Isomer* **32b** [41][47][48]. To a soln. of an oil, containing *ca.* 80% of **8** (3.06 g, 15 mmol), in dry CH_2Cl_2 (50 ml), DBU (6.2 ml, 6.32 g, 41 mmol) was added under CO_2 release in an exothermic reaction. After stirring for 30 min, the mixture was diluted with CH_2Cl_2 (20 ml) and washed subsequently with 2M HCl (2 × 80 ml), H_2O (80 ml), 1M NaOH (2 × 80 ml), and sat. NaCl soln. (2 × 80 ml). The org. layer was dried (Na_2SO_4) and evaporated and the yellow oil submitted to distillation at 119–122°/12–13 mbar ([44]: 121–123°/9 Torr): 1.42 g (76%) of **32** in a ratio **32a**/**32b** 3:7.

Data of **32**: Colorless oil. TLC (petroleum ether/AcOEt 2:1): R_f 0.80. UV (MeOH): 273 (4.29), 215 (sh, 4.16) ([45]: 273 (4.22) for **32a**, 272 (4.36) for **32b**). Anal. calc. for $C_9H_7N \cdot 0.125\ H_2O$ (131.4): C 82.26, H 5.47, N 10.66; found: C 82.35, H 5.56, N 10.9.

Data of **32a**: ^{1}H-NMR ($CDCl_3$): 7.81–7.75 (*m*, 2 H (Ph)); 7.47–7.35 (*m*, 3 H (Ph)); 7.12 (*d*, J = 12.0, PhC*H*CHCN); 5.44 (*d*, J = 12.1, PhCHC*H*CN).

Data of **32b**: ^{1}H-NMR ($CDCl_3$): 7.47–7.35 (*m*, Ph, PhC*H*CHCN); 5.87 (*d*, J = 16.6, PhCHC*H*CN).

15. *1,1-Bis(4-nitrophenylethene)* (*=1,1′-Ethenylidenebis[4-nitrobenzene];* **33**) [30]. On adding DBU (0.456 ml, 465 mg, 3.05 mmol) to a yellow soln. of compound **30** [30] (505 mg, 1.53 mmol) in dry CH_2Cl_2 (4.5 ml), the colour turned immediately dark blue. After stirring for 30 min, the mixture was diluted with CH_2Cl_2 (10 ml) and washed subsequently with 1M HCl (2 × 10 ml), H_2O (10 ml), 2M NaOH (2 × 10 ml), and sat. NaCl soln. (3 × 10 ml). The org. layer was dried (Na_2SO_4) and evaporated and the yellow solid recrystallized from CH_2Cl_2/petroleum ether 6:5 (20 ml): 290 mg (70%) ([30]: 69%) of **33**. Slightly yellow crystals. TLC (petroleum ether/AcOEt 2:1): R_f 0.72. UV (MeOH): 300 (3.78), 216 (sh, 3.75) ([27]: 304). ^{1}H-NMR ($CDCl_3$): 8.22 (*d*, 4 H *o* to NO_2); 7.45 (*d*, 4 H *m* to NO_2); 5.75 (*s*, CH_2). Anal. calc. for $C_{14}H_{10}N_2O_4$ (270.2): C 62.22, H 3.73, N 10.37; found: C 62.50, H 3.81, N 10.37.

16. *(4-Nitrophenyl)ethene* (*=4-Nitro-1-ethenylbenzene*; **34**) [49]. To a soln. of **31** [37] (215 mg, 0.94 mmol) in dry MeCN (94 ml), DBU (1.4 ml, 1.43 g, 9.37 mmol) was added and the mixture stirred overnight for 20 h. The reaction was stopped by adding AcOH (0.536 ml, 9.37 mmol), the mixture diluted with CH_2Cl_2 (20 ml) and washed with H_2O (20 ml), the aq. layer reextracted with CH_2Cl_2 (2 × 20 ml), the combined org. phase washed with sat. $NaHCO_3$ soln. (60 ml), the aq. layer extracted with CH_2Cl_2 (2 × 40 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue purified by FC (silica gel (10 g), 6.5 × 2.1 cm, CH_2Cl_2/MeOH 100:1 (101 ml)): 76 mg (54%) of **34**. Colorless oil. TLC (toluene/AcOEt/MeOH 5:4:1): R_f 0.90. UV (MeOH): 300 (4.14), 219 (3.99) ([46]: 298 (4.14), 218 (4.00)). ^{1}H-NMR ($CDCl_3$): 8.17 (*d*, 2 H *o* to NO_2); 7.52 (*d*, 2 H *m* to NO_2); 6.77 (*dd*, CH); 5.92, 5.48 (2*d*, CH_2).

17. *1-[2,2-Bis(4-nitrophenyl)ethyl]piperidine* (**35**) [30]. To a yellow suspension of **33** (100 mg, 0.37 mmol) in MeCN (3 ml), piperidine (1 ml, 860 mg, 10.1 mmol) was added (→ soln. and colour change to blue). After 5 min stirring, the colour turned yellow again. After 15 min, the mixture was diluted with CH_2Cl_2 (20 ml) and washed with H_2O (20 ml), the aq. layer extracted with CH_2Cl_2 (2 × 20 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the product purified by FC (silica gel (7 g), 14.5 × 1.3 cm, petroleum ether/AcOEt 9:1 (100 ml), 8:1 (90 ml), 7:1 (80 ml), 6:1 (70 ml), 5:1 (60 ml)): 116 mg (88%) of **35**. Orange-red oil. TLC (petroleum ether/AcOEt 2:1): R_f 0.40. UV (MeOH): 275 (4.31), 211 (sh, 4.28) ([27]: 275). ^{1}H-NMR ($CDCl_3$): 8.15 (*d*, 4 H *o* to NO_2); 7.35 (*d*, 4 H *m* to NO_2); 4.40 (*t*, CH (bnpe)); 2.91 (*d*, CH_2 (bnpe)); 2.38 (*m*, 2 CH_2N); 1.46–1.23 (*m*, 3 CH_2). Anal. calc. for $C_{19}H_{21}N_3O_4 \cdot 0.25\ H_2O$ (359.9): C 63.41, H 5.95, N 11.68; found: C 63.54, H 5.96, N 11.39.

18. *Kinetic Studies.* 18.1 *Method A:* Nucleoside **16**, **18**, **21**, or **29**, resp., was treated with 10 equiv. of either DBU/MeCN (0.01, 0.1, and 1M), piperidine/MeCN (0.5M), or Et_3N/MeCN (0.5M) in an attached cap *Eppendorf* tube at r.t. with stirring. At defined time intervals, aliquots (15–350 µl) were quenched in AcOH/MeCN (0.05–0.25M, at least 3 equiv. AcOH per base, end volume of sample 500 µl), and analysed by reversed-phase HPLC. The relative ratio of starting material and cleaved protecting group was detected at 268 or 266 nm. For each experiment, 5–10 time points were taken, plus an assumed 0 min time point. The half-lives ($t_{1/2}$) for the pseudo-first-order reactions were obtained from the graphical plots of $-\ln(1+\varepsilon_{sm}A_{pg}/\varepsilon_{pg}A_{sm})$ *vs.* time, where ε is the extinction coefficient of starting material (ε_{sm}) or cleaved protecting group (ε_{pg}), respectively, at 268 or 266 nm, and A is the area under the peak of starting material (A_{sm}) or cleaved protecting group (A_{pg}), respectively. **15**: t_R 8.25 min. **16**: t_R 12.11 + 12.18 min, ε_{268} 9014. **18**: t_R 12.51 min. **21**: t_R 13.56 min, ε_{268} 24995. **29**: t_R 13.44 min, ε_{266}

18373. **32**: t_R 14.97 + 15.17 min, ε_{268} 19336 (for **32a**/**32b** 3 : 7). **33**: t_R 19.82 min, ε_{268} 11772. **34**: t_R 16.76 min, ε_{266} 5131. **35**: t_R 20.96 min, ε_{268} 19039.

18.2. *Method B:* Nucleoside **24** or **27** was dissolved in MeCN (for **24**) or MeOH (for **27**), respectively, in an attached cap *Eppendorf* tube. Then, 2–3 aliquots (15–40 µl) were quenched in AcOH/MeCN (0.05–0.25M, end volume of sample 500 µl), and analysed by HPLC for the determination of the area under the peak of starting material at time t_0 (A_0). Then the cleavage reaction was started by addition of 10 equiv. of either DBU/MeCN (for **24**, 0.2 and 2M, end concentration of reaction soln. 0.1 and 1M) or DBU/MeOH (for **27,** 2M, end concentration of reaction soln. 1M) and stirred at r.t.. At defined time intervals, aliquots (15–40 µl) were quenched in AcOH/MeCN (0.05–0.25M, at least 3 equiv. AcOH per base, end volume of sample 500 µl), and analysed by reversed-phase HPLC. The decrease of starting material was detected by 268 nm. For each experiment, 5–10 aliquots were taken. The half-lives ($t_{1/2}$) for the pseudo-first-order reactions were obtained from the graphical plots of $\ln(A_t/A_0)$ *vs.* time, where A_t is the area under the peak of starting material at time *t*. **24**: t_R 15.51 min. **29**: t_R 11.97 min.

19. *2′*-O-*(Diphenylphosphinoyl)-3′,5′*-O-*(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine* (**37**). 3′,5′-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)uridine (**36**) [45] (608 mg, 1.25 mmol) and diphenylphosphinoyl chloride (**14**; 0.485 ml, 600 mg, 2.54 mmol) were stirred in dry pyridine (7.5 ml) overnight for 16 h. Then the mixture was diluted with CH_2Cl_2 (20 ml) and washed with H_2O (20 ml), the aq. phase extracted with CH_2Cl_2 (2 × 20 ml), the combined org. layer dried (Na_2SO_4), evaporated, and co-evaporated with toluene (4 × 10 ml), and the residue purified by FC (silica gel (30 g), 15 × 2.7 cm, CH_2Cl_2/MeOH 100 : 1 (101 ml), 100 : 2 (204 ml), 100 : 3 (206 ml), 100 : 4 (104 ml)): 690 mg (80%) of **37**. Colorless foam. TLC (toluene/AcOEt/MeOH 5 : 4 : 1): R_f 0.38. UV (MeOH): 270 (sh, 3.93), 263 (sh, 4.04), 259 (4.05), 220 (sh, 4.27). ^{1}H-NMR ($CDCl_3$): 8.20 (br. *s*, NH); 7.83 (*m*, 4 H (dpp)); 7.67 (*d*, H–C(6)); 7.53–7.40 (*m*, 6 H (dpp)); 5.86 (*s*, H–C(1′)); 5.62 (*d*, H–C(5)); 5.01 (*dd*, H–C(2′)); 4.42 (*dd*, H–C(3′)); 4.32–4.14 (*m*, H–C(4′), H–C(5′)); 3.98 (*m*, H–C(5′)); 1.06–0.92 (*m*, 4 Me_2CH). Anal. calc. for $C_{33}H_{47}N_2O_8PSi_2$ (686.9): C 57.70, H 6.90, N 4.08; found: C 57.54, H 6.98, N 4.36.

20. *2′*-O-*(Diphenylphosphinoyl)uridine* (**38**) *and 3′*-O-*(Diphenylphosphinoyl)uridine* (**39**). To a soln. of **37** (201 mg, 0.29 mmol) in dry THF (3 ml), AcOH (80 µl, 84 mg, 1.40 mmol) and $Bu_4NF \cdot 3H_2O$ (230 mg, 0.73 mmol) were added. The mixture was stirred for 2 h, then diluted with CH_2Cl_2 (20 ml), and washed with H_2O (20 ml). The aq. phase was extracted with CH_2Cl_2 (2 × 20 ml) and the combined org. layer dried (Na_2SO_4), evaporated, and co-evaporated with H_2O (2 × 10 ml), MeOH (3 × 10 ml), and CH_2Cl_2 (2 × 10 ml). The residue was purified by FC (3 g silica gel, 6 × 1.3 cm, CH_2Cl_2/MeOH 100 : 1 (50.5 ml), 100 : 2 (51 ml), 100 : 3 (51.5 ml), 100 : 4 (52 ml), 100 : 5 (105 ml)): 84 mg (65%) of **38**/**39** 1 : 2. Colorless foam. TLC (toluene/AcOEt/MeOH 5 : 4 : 1): R_f 0.21. Anal. calc. for $C_{21}H_{21}N_2O_7P \cdot H_2O$ (462.4): C 54.55, H 5.01, N 6.06; found: C 54.64, H 4.86, N 6.07.

Data of **38**: ^{1}H-NMR ((D$_6$)DMSO): 11.27 (br. *s*, NH); 7.91–7.75 (*m*, 4 H (dpp)); 7.67–7.41 (*m*, 6 H (dpp), H–C(6)); 6.16 (*d*, H–C(1′)); 5.79 (*d*, OH–C(3′)); 5.48 (*d*, H–C(5)); 5.19 (*t*, OH–C(5′)); 4.63 (*m*, H–C(2′)); 4.10 (*m*, H–C(3′)); 3.98 (*m*, H–C(4′)); 3.53–3.30 (*m*, 2 H–C(5′)).

Data of **39**: ^{1}H-NMR ((D$_6$)DMSO): 11.39 (br. *s*, NH); 7.91–7.75 (*m*, 4 H (dpp)); 7.67–7.41 (*m*, 6 H (dpp), H–C(6)); 5.94 (2*d*, H–C(1′), OH–C(2′)); 5.70 (*d*, H–C(5)); 5.19 (*t*, OH–C(5′)); 4.60 (*m*, H–C(3′)); 4.26–4.21 (*m*, H–C(2′), H–C(4′)); 3.53–3.30 (*m*, 2 H–C(5′)).

21. *2′*-O-*(Diphenylphosphinoyl)-5′*-O-*(monomethoxytrityl)uridine* (**40**) *and 3′*-O-*(Diphenylphosphinoyl)-5′*-O-*(monomethoxytrityl)uridine* (**41**). A mixture **38**/**39** 1 : 2 (80 mg, 0.18 mmol) and MeOTrCl (79 mg, 0.26 mmol) was stirred in dry pyridine (2 ml) overnight for 18 h. After addition of more MeOTrCl (48 mg, 0.15 mmol) and stirring for another 4 h, the mixture was diluted with CH_2Cl_2 (20 ml) and washed with H_2O (20 ml). The aq. phase was extracted with CH_2Cl_2 (2 × 20 ml), the combined org. layer dried (Na_2SO_4), evaporated, and co-evaporated with toluene (4 × 10 ml) and CH_2Cl_2 (2 × 10 ml), and the residue separated by FC (7.5 g silica gel, 14 × 1.5 cm, CH_2Cl_2/MeOH 100 : 1 (101 ml), 100 : 2 (204 ml), 100 : 3 (51.5 ml)): 40 mg (31%) of **40** and 52 mg of **41** (40%).

Data of **40**: Colorless foam. TLC: R_f 0.40 (toluene/AcOEt/MeOH 5 : 4 : 1). UV (MeOH): 271 (sh, 3.93), 265 (sh, 4.01), 259 (4.02), 223 (sh, 4.50). ^{1}H-NMR ($CDCl_3$): 9.37 (br. *s*, NH); 7.94–7.78 (*m*, 4 H (dpp), H–C(6)); 7.59–7.47 (*m*, 6 H (dpp)); 7.31 (*m*, 10 H (MeOTr), 2 H *o* to MeO); 6.86 (*d*, 2 H *m* to MeO); 6.32 (*d*, H–C(1′)); 5.18 (*d*, H–C(5)); 4.78 (*m*, H–C(2′), OH–C(3′)); 4.64 (*m*, H–C(3′)); 4.28 (*m*, H–C(4′)); 3.82 (*s*, MeO); 3.53 (*m*, 2 H–C(5′)). Anal. calc. for $C_{41}H_{37}N_2O_8P$ (716.7): C 68.71, H 5.20, N 3.91; found: C 68.40, H 5.33, N 4.45.

Data of **41**: Colorless foam. TLC (toluene/AcOEt/MeOH 5 : 4 : 1): R_f 0.28. UV (MeOH): 270 (sh, 3.97), 264 (sh, 4.06), 260 (4.06), 222 (sh, 4.49). ^{1}H-NMR ($CDCl_3$): 9.66 (br. *s*, NH); 7.83–7.70 (*m*, 4 H (dpp), H–C(6)); 7.59–7.37 (*m*, 6 H (dpp)); 7.28 (*m*, 10 H (MeOTr)); 7.22 (*d*, 2 H *o* to MeO); 6.84 (*d*, 2 H *m* to MeO); 6.10 (*d*, H–C(1′)); 5.26 (*d*, H–C(5)); 5.03 (br. *s*, OH–C(2′)); 4.82 (*m*, H–C(3′)); 4.48 (*m*, H–C(2′), H–C(4′)); 3.82 (*s*,

MeO); 3.59 (*m*, H–C(5′)); 3.42–3.38 (*m*, H–C(5′)). Anal. calc. for $C_{41}H_{37}N_2O_8P \cdot H_2O$ (734.7): C 67.02, H 5.35, N 3.81; found: C 67.24, H 5.26, N 4.46.

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