# 51. A General Method for the Synthesis of 2′-*O*-Modified Ribonucleosides

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A general way for the functionalization of ribonucleosides is described. The method involves the synthesis of the methyl-ribofuranoside derivative **6** equipped with a linker at the 2-hydroxy group (*Scheme 2*). After introduction of the nucleic-acid bases under standard conditions (*Scheme 3*), the resulting β-D-ribonucleosides **8** and **10** are further transformed to derivatives with lipophilic, intercalating, and aminoalkyl residues at the linker moiety. In this way, 2′-modified 5-methyluridines **12**, adenosines **13**, and 5-methylcytidines **15** and **16** were prepared (*Scheme 4*).

**Introduction.** – Antisense oligonucleotides have found widespread use as convenient research tools. They act by selectively inhibiting gene expression at the level of translation [1] [2]. Oligonucleotides are also used to specifically recognize and bind to double-stranded DNA [3] [4]. The goal of inhibiting protein biosynthesis at the level of translation or transcription is hampered by several obstacles. The most severe problems arise from nucleolytic degradation [5] [6] (primarily caused by 3′-exonucleases) as well as inefficient cellular uptake of oligonucleotides [6–8]. A general solution to these drawbacks would raise the possibility of using oligonucleotides as pharmaceutical drugs for the treatment of genetic and viral diseases [9]. Strategies to overcome these problems include chemical modification [1] [10] and/or packing of oligonucleotides into liposomes [11] [12] or nanospheres [13].

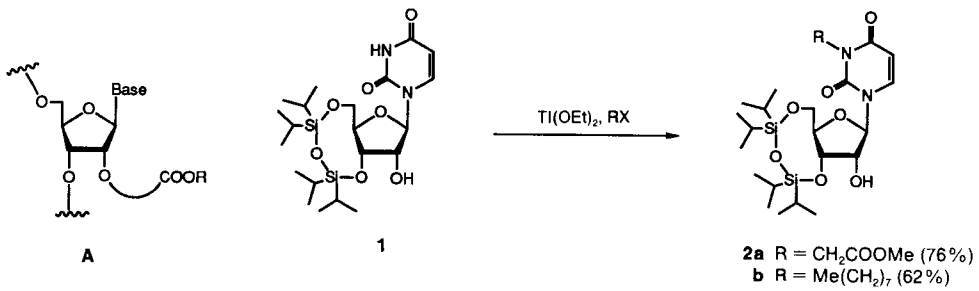
The 2′-position of the nucleoside sugar part can serve as a handle for various substituents such as lipophilic groups [14–20], aminoalkyl chains [20] [21], reporter groups [21], intercalators [22], or cleavage functions. However, selective reaction at the 2′-hydroxy group of ribose is difficult, and efficient alkylations can only be achieved with very reactive electrophiles[1]). Whereas simple derivatives like 2′-*O*-methyl-ribonucleosides were first synthesized [23] and incorporated into oligonucleotides [24] [25] more than 20 years ago, the synthesis of more complex analogues [18–21] was only recently reported. We reasoned that a general solution to this problem could be provided by a 2′-ether-linked aliphatic-acid derivative (see **A**) in *Scheme 1* which could then undergo reaction with different functional groups[2]). For this purpose, haloacetates appeared to be most suitable, since they are highly reactive electrophiles.

**2′-Modified Ribonucleosides.** – Selective alkylation of nucleosides at the sugar moiety usually involve a series of protection/deprotection steps, since reactions at the base

[1]) An exception is adenosine which can be selectively 2′-*O*-alkylated in a simple procedure, see [20] [21].

[2]) During the course of the present work, a patent appeared in which the same approach was followed [26].

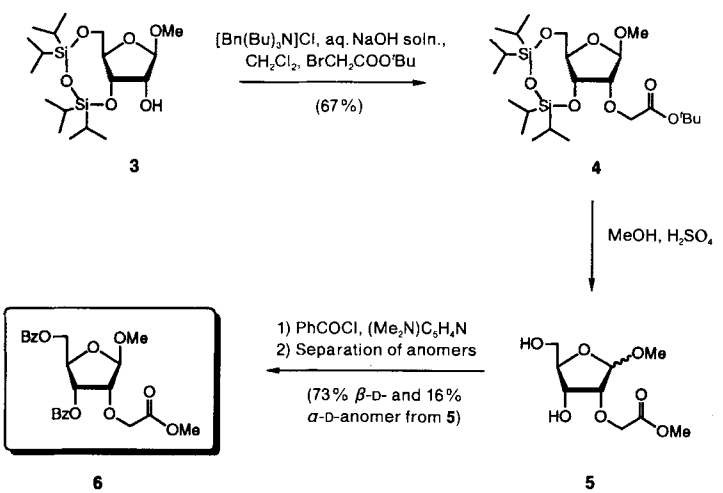
*Scheme 1*




moiety are known to occur readily under a number of conditions [22] [23] [27–29]. Indeed, reaction of nucleoside **1** with alkyl halides in the presence of thallium(II) ethoxide, a smooth *O*-alkylation method used by *Seebach* and coworkers [30] and *Lehn* and coworkers [31] for vicinal diols, afforded exclusively the *N*(3)-alkylated uridine derivatives **2** (*Scheme 1*).

We, therefore, turned our attention to the ribose derivative **3** [32] [33]. *O*-Alkylation of **3** should be straightforward and would open a general access to a wide variety of different nucleosides, since any base can be introduced later in the synthesis. Alkylation of **3** was carried out under phase-transfer conditions using *tert*-butyl bromoacetate (see *Scheme 2*). The cyclic silyl protecting group resisted the strongly basic conditions well, and only upon prolonged reaction times, 3′-deprotection followed by subsequent alkylation at this position was observed as a minor side reaction besides formation of **4**. Other reagents or reaction conditions, *e.g.* methyl iodoacetate under aprotic conditions in the presence of silver(I) oxide and/or a strong base, also gave the desired product; however, the yields were substantially lower. In the following desilylation of **4**, the *tert*-butyl ester simultaneously underwent transesterification to give methyl ester **5**. After benzoylation,

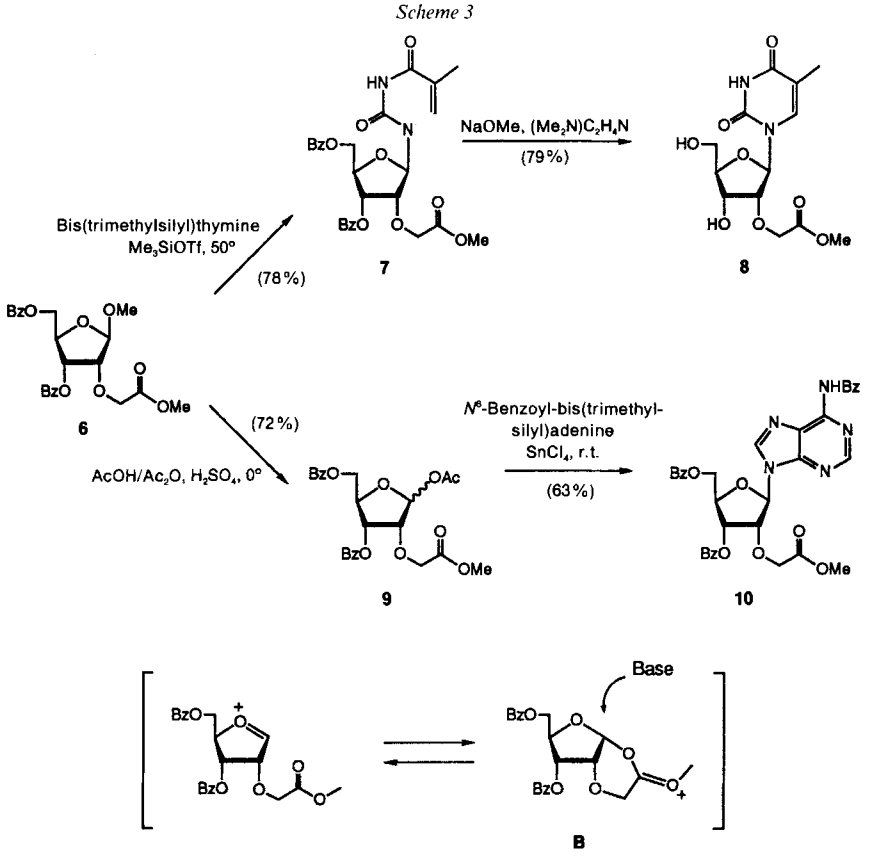
*Scheme 2*



β-D-compound **6** was obtained in 73% yield along with 16% of its α-D-anomer which could be separated by standard column chromatography. The preparation of **6** could easily be carried out on a 1-mole scale starting with (−)-D-ribose without purification of the intermediates in an overall yield of 35–40%.

Introduction of thymine into **6** was best performed in MeCN using 2,4-bis-*O*-(trimethylsilyl)thymine [34] in the presence of trimethylsilyl triflate ($Me_3SiOTf$) [35] (*Scheme 3*). The resulting thymidine derivative **7** was obtained in 78% yield with a high

*Scheme 3*



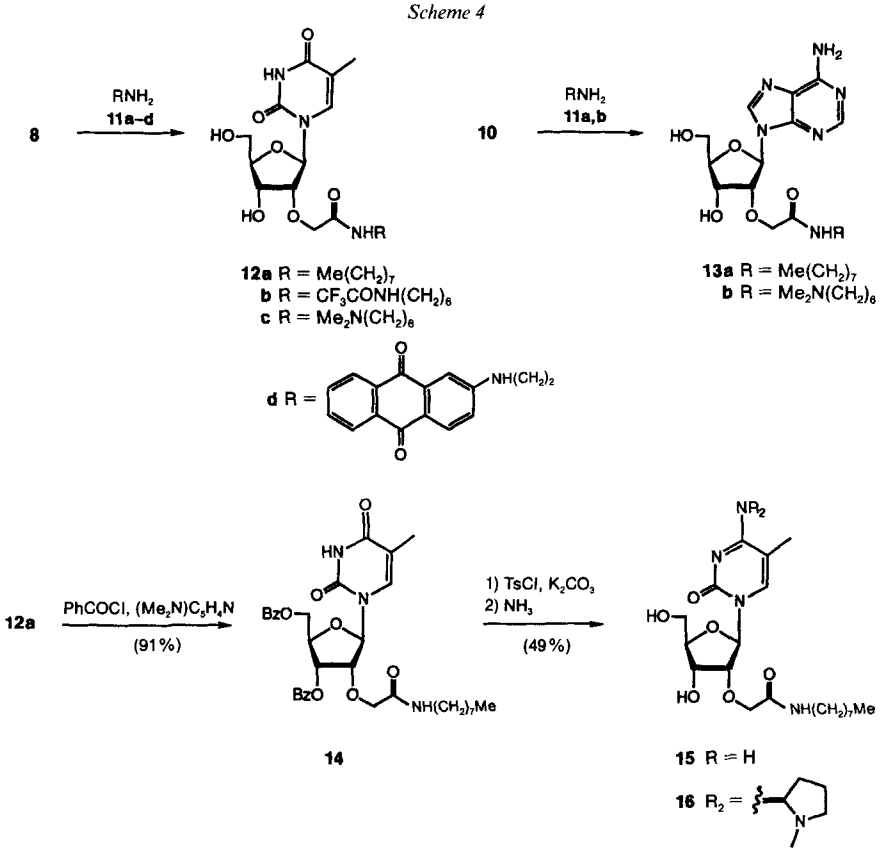

stereoselectivity (β-D/α-D 98:2); another minor unidentified isomer ($\leq 2\%$ by $^1$H-NMR) was also formed. We assume – in analogy to the well known β-preference of the *Hilbert-Johnson* nucleoside synthesis using 2′-*O*-acylated ribofuranosides [36] – that the glycosidation step proceeds through intermediate **B**. The neighboring 2′-ester group electronically stabilizes the oxonium ion, thereby directing the attack of the base from the β-side. Subsequent removal of the 3′- and 5′-benzoate groups gave ester **8**.

Analogous introduction of adenine into methyl ribofuranoside **6** proved to be more difficult. The reaction of **6** with $N^6$-benzoyl-bis(trimethylsilyl)adenine [37] was very slow, and poor regio- and diastereoselectivity was observed at higher temperatures. Thus, **6** was

first transformed into the acetate derivative **9** (anomer mixture 6:1; *Scheme 3*). Subsequent treatment of **9** with $N^6$-benzoyl-bis(trimethylsilyl)adenine in the presence of tin(IV) chloride [38] at room temperature for one week gave the desired $\beta$-D-isomer **10** in a 6:1 preference over its $\alpha$-D-anomer. Again, higher temperatures led to a dramatic decrease in selectivity of the reaction.

The target compounds could then easily be obtained by reaction of the amines **11a**, **11b** [39], **11c**[3]), or **11d** [41] with either nucleosides **8** or **10** (*Scheme 4*). In this way, it was possible to synthesize the lipophilic derivatives **12a** and **13a** and the nucleosides bearing a protected primary-amine (**12b**), a tertiary-amine (**12c**, **13c**), or an intercalating group (**12d**).

*Scheme 4*




The synthesis of a lipophilic cytidine derivative was realized starting with the 5-methyluridine analogue **12a**, which was benzoylated at the sugar OH groups to give **14**. Tosylation of the base moiety followed by treatment with ammonia [42] gave the cytidine derivative **15** (*Scheme 4*). Since compound **15** was never obtained free from TsOH, it was protected at the $NH_2(4)$ group using the dimethyl acetal of *N*-methylpyrrolidinone [43]

[3]) The preparation of **11c** was previously reported [40]. We chose a slightly different route (see *Exper. Part*).

affording nucleoside **16**, which was purified and characterized. $NH_2(4)$-Protection of cytidine by an *N*-methylpyrrolidine-derived amidine was described and shown to be suitable for automated oligonucleotide synthesis [43].

**Conclusion.** – The present work describes a general method for the preparation of 2′-*O*-substituted ribonucleosides through the use of a glycolic-acid type linker. A variety of thymidine, adenosine, and cytidine derivatives bearing different residues such as lipophilic, intercalating, and amino groups was synthesized in this way. Further elaboration of such modified ribonucleosides, their incorporation into oligonucleotides, and the influence of different groups on the hybridization properties will be described elsewhere.

## Experimental Part

*General.* Anh. solvents were obtained from *Fluka*. Workup stands for addition of org. solvent, washing of the org. phase with the indicated aq. solns. followed by drying ($Na_2SO_4$) and evaporation of the org. solvent on a *Büchi* rotary evaporator. Prep. flash column chromatography (FC) [44]: silica gel *60*, 230–240 mesh (*E. Merck Co.*). UV Spectra: $\lambda$ ($\varepsilon$) in nm. IR Spectra: *Bruker-IFS-66* spectrometer; data in $cm^{-1}$. $^1$H-NMR Spectra: *Bruker-AM-360* (360 MHz) or *Varian-Gemini-200* (200 MHz) spectrometer; chemical shifts in ppm rel. to TMS (= 0 ppm), coupling constants *J* in Hz. Mass spectra: *VG-TS-250* instrument.

*Methyl 3′,5′-O-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)uridine-3-acetate* (**2a**). Thallium(II) ethoxide (16 µl, 0.23 mmol) was slowly added to a soln. of 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine [32] [33a] (**1**; 0.1 g, 0.21 mmol) in DMF (3 ml). After stirring the resulting suspension for 30 min, methyl bromoacetate (22 µl, 0.23 mmol) was added and the mixture stirred for 2 h at r.t. The mixture was filtered through *Celite* and concentrated on a high-vacuum pump. Workup (AcOEt/$H_2O$) and FC (hexane/*t*-BuOMe 2:1) yielded **2a** (86 mg, 76%). IR (film): 3490, 2946, 2868, 1759, 1717, 1671, 1457, 1040. $^1$H-NMR ($CDCl_3$, 360 MHz): 0.85–1.05 (*m*, 28 H); 2.70 (br. *s*, OH); 3.68 (*s*, COOMe); 3.95 (*dd*, *J* = 12, 4, H–C(5′)); 4.03 (*dt*, *J* = 8, 3, H–C(4′)); 4.08 (*d*, *J* = 7, H–C(2′)); 4.16 (*dd*, *J* = 12, 3, H–C(5′)); 4.29 (*dd*, *J* = 7, 8, H–C(3′)); 4.61 (*s*, $NCH_2COO$); 5.69 (*s*, H–C(1′)); 5.71 (*d*, *J* = 8, H–C(5)); 7.65 (*d*, *J* = 8, H–C(6)). MS: 559 (9, $MH^+$), 261 (84), 185 (72), 153 (64), 147 (87), 135 (100).

*3-Octyl-3′,5′-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine* (**2b**). As described for **2a**, with thallium(II) ethoxide (16 µl, 0.23 mmol), **1** (0.1 g, 0.21 mmol), DMF (2 ml), and octyl iodide (42 µl, 0.23 mmol; 3 h at r.t. and 1 h at 80°). FC (hexane/*t*-BuOMe 3:1) yielded **2b** (78 mg, 62%). IR (film): 3450, 2930, 2868, 1710, 1660, 1463, 1040. $^1$H-NMR ($CDCl_3$, 200 MHz): 0.87 (*t*, *J* = 7, $MeCH_2$); 0.9–1.2 (*m*, 28 H); 1.15–1.75 (*m*, 12 H); 3.0 (br. *s*, OH); 3.8–4.25 (*m*, 6 H); 4.35 (*dd*, *J* = 6, 8, H–C(3′)); 5.71 (*d*, *J* = 8, H–C(5)); 5.75 (*s*, H–C(1′)); 7.62 (*d*, *J* = 8, H–C(6)). MS: 599 (86, $MH^+$), 555 (14), 261 (100), 225 (93).

*Methyl 2-O-[(*tert*-Butyloxycarbonyl)methyl]-3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-*D*-ribofuranoside* (**4**). Aq. 10N NaOH (250 ml) was added to a soln. of methyl 3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranoside [34] (**3**; 60 g, 0.15 mol) in $CH_2Cl_2$ (1000 ml). The mixture was cooled to 0°, and *tert*-butyl bromoacetate (110 ml, 0.75 mol) and $[Bn(Bu)_3N]Cl$ (117 g, 0.38 mol) were added. After stirring at 0° for 2.5 h, the mixture was extracted 3 times with $H_2O$ (700 ml). The org. layer was evaporated and the residue dissolved in hexane (300 ml). The combined aq. phase was extracted with hexane (1000 ml). The hexane phases were combined, washed ($NH_4Cl$ and NaCl), dried ($Na_2SO_4$), and evaporated to give a yellow oil. FC (hexane/AcOEt 95:5) yielded **4** (51.6 g, 67%). $[\alpha]_D = -67.9$ (*c* = 0.6, MeOH). IR ($CH_2Cl_2$): 2947, 2869, 1745, 1465, 1153, 1055, 1040. $^1$H-NMR ($CDCl_3$, 360 MHz): 1.00–1.15 (*m*, 28 H); 1.48 (*s*, *t*-Bu); 3.33 (*s*, MeO); 3.8–4.1 (*m*, 4 H); 4.23, 4.33 (*AB* of *ABX*, *J* = 15, $OCH_2COO$); 4.47 (*m*, H–C(3)); 4.88 (*s*, H–C(1)). Anal. calc. for $C_{24}H_{48}O_8Si_2$: C 55.3, H 9.3; found: C 55.4, H 9.0.

*Methyl 2-O-[(Methoxycarbonyl)methyl]-*D*-ribofuranoside* (**5**). To a soln. of **4** (19.6 g, 37.5 mmol) in MeOH (200 ml) was added dropwise 98% $H_2SO_4$ soln. (2 ml). The mixture was stirred for 24 h. After treatment with weakly basic anion-exchange resin (*Amberlite IRA-68*, *Fluka*; 120 g), the mixture was filtered and evaporated. The residue was dissolved in $H_2O$ and washed twice with hexane. The aq. phase was evaporated to give **5** (9.2 g; β-D/α-D 4:1) which was used without further purification in the next step.

*Methyl 3,5-Di-O-benzoyl-2-O-[(methoxycarbonyl)methyl]-β-*D*-ribofuranoside* (**6**). To a soln. of crude **5** (8.0 g, 34.0 mmol) in *N*,*N*-dimethylacetamide (150 ml), 4-(dimethylamino)pyridine (10.4 g, 85.1 mmol) was added. After cooling to 0°, benzoyl chloride (9.1 ml, 78.3 mmol) was added dropwise and the mixture stirred at r.t. for 1 h. After workup (AcOEt/$NaHCO_3$), the product was obtained as a mixture of β-D- and α-D-isomers in a ratio 85:15

($^1$H-NMR). FC (*t*-BuOMe/hexane 1:1) yielded β-D-isomer **6** (11.0 g, 73%). $[\alpha]_D = +3.7$ ($c = 1.8$, MeOH). IR ($CH_2Cl_2$): 1757, 1723, 1291, 1110. $^1$H-NMR ($CDCl_3$, 360 MHz): 3.37 (*s*, MeO); 3.65 (*s*, COOMe); 4.15, 4.23 (*AB* of *ABX*, $J = 16$, $OCH_2COO$); 4.26 (*m*, H–C(2)); 4.47, 4.61 (*AB* of *ABX*, $J = 5, 12$, $CH_2(5)$); 4.68 (*m*, H–C(4)); 5.14 (*s*, H–C(1)); 5.52 (*dd*, $J = 6, 8$, H–C(3)); 7.35–7.60 (*m*, 6 H); 8.0–8.1 (*m*, 4 H). Anal. calc. for $C_{23}H_{24}O_9$: C 62.2, H 5.4; found: C 62.3, H 5.4.

Further elution gave the α-D-isomer of **6** (2.4 g, 16%). $[\alpha]_D = +48.8$ ($c = 0.6$; MeOH). IR (film): 2954, 1721, 1270, 1115. $^1$H-NMR ($CDCl_3$, 360 MHz): 3.55 (*s*, $MeO_3$); 3.68 (*s*, COOMe); 4.23 (*s*, $OCH_2COO$); 4.26 (*dd*, $J = 7, 8$, H–C(2)); 4.5–4.7 (*m*, 3 H); 5.20 (*d*, $J = 7$, H–C(1)); 5.51 (*dd*, $J = 4, 8$, H–C(3)); 7.35–7.65 (*m*, 6 H); 8.0–8.15 (*m*, 4 H). Anal. calc. for $C_{23}H_{24}O_9$: C 62.2, H 5.4; found: C 61.9, H 5.2.

*3′,5′-Di-*O*-benzoyl-2′-*O*-[(methoxycarbonyl)methyl]-5-methyluridine* (**7**). At 0° under Ar, **6** (5.0 g, 11.3 mmol) was dissolved in MeCN (50 ml) and treated sequentially with 2,4-bis-*O*-(trimethylsilyl)thymine [34] (4.6 g, 16.9 mmol) and trimethylsilyl trifluoromethanesulfonate (4.4 ml, 22.5 mmol). The resulting mixture was stirred under Ar for 3 h at 50°, then poured into sat. aq. $NaHCO_3$ soln., extracted with AcOEt, dried ($Na_2SO_4$), and evaporated: crude **7** (β-D/α-D 98:2, by $^1$H-NMR). Purification by FC (AcOEt/hexane 3:2) gave pure **7** (4.7 g, 78%). Alternatively, crude 7 could be recrystallized (EtOH/MeOH 3:1) to give pure product in 60–70% yield. M.p. 110–114.5°. $[\alpha]_D = -57.5$ ($c = 1.0$, MeOH). IR (KBr): 3063, 1721, 1694, 1269, 712. $^1$H-NMR ($CDCl_3$, 360 MHz): 1.67 (*s*, Me–C(5)); 3.63 (*s*, COOMe); 4.26 (*AB* of *ABX*, $J = 17$, $OCH_2COO$); 4.57, 4.80 (*AB* of *ABX*, $J = 3, 10$, $CH_2(5')$); 4.60 (*m*, H–C(2′)); 4.69 (*m*, H–C(4′)); 5.53 (*t*, $J = 7$, H–C(3′)); 6.08 (*d*, $J = 5$, H–C(1′)); 7.48 (*m*, 4 H); 7.61 (*m*, 2 H); 8.07 (*m*, 4 H); 8.23 (*s*, 1 H). MS: 539 (2, $M$H$^+$), 413 (8), 160 (40), 105 (100). Anal. calc. for $C_{27}H_{26}N_2O_{10}$: C 60.2, H 4.9, N 5.2; found: C 60.0, H 4.9, N 5.0.

*2′-O-[(Methoxycarbonyl)methyl]-5-methyluridine* (**8**). To a soln. of freshly prepared NaOMe (0.86 mmol) in MeOH (250 ml), were added **7** (9.27 g, 17.2 mmol) and 4-(dimethylamino)pyridine (0.21 g, 1.7 mmol). The suspension was warmed to 50° and stirred for 16 h. The resulting clear yellow soln. was concentrated, the residue dissolved in $H_2O$ (200 ml), washed with $Et_2O$, and the aq. phase concentrated yielding crude **8** (5.12 g, 90%). Recrystallization from MeOH gave pure **8** (4.46, 79%). M.p. (MeOH) 162–164°. $[\alpha]_D = +12.6$ ($c = 1.0$, MeOH). IR (KBr): 3481, 1729, 1705, 1681, 1227. $^1$H-NMR (MeOH, 200 MHz): 1.88 (*s*, Me–C(5)); 3.73 (*s*, COOMe); 3.70–3.90 (*m*, 2 H); 4.03 (*m*, 1 H); 4.13 (*t*, $J = 5$, 1 H); 4.26 (*t*, $J = 5$, 1 H); 4.36 (*s*, $OCH_2COO$); 5.98 (*d*, $J = 4$, H–C(1′)); 7.89 (*s*, H–C(6)). MS: 331 (100, $M$H$^+$), 187 (23), 127 (67). Anal. calc. for $C_{13}H_{18}N_2O_8$: C 47.3, H 5.5, N 8.5; found: C 47.1, H 5.3, N 8.7.

*3,5-Di-*O*-benzoyl-2-*O*-[(methoxycarbonyl)methyl]-β-D-ribofuranosyl Acetate* (**9**). At r.t., **6** (44 g, 100 mmol) was dissolved in $Ac_2O$/AcOH 2:1 (75 ml) and cooled to 0°. Then, 98% $H_2SO_4$ soln. (5 ml) was added dropwise. The mixture was stirred for 20 min at 0°, added slowly into excess sat. aq. $NaHCO_3$ soln. and several times extracted with AcOEt (4 l in total). The combined org. phase was dried ($Na_2SO_4$) and evaporated and the residue purified by FC (hexane/AcOEt 7:3) affording **9** (40.6 g, 86% β-D/α-D 2:1). IR (film): 1751, 1725, 1270, 1112. $^1$H-NMR ($CDCl_3$, 360 MHz): 1.97, 2.19 (2 *s*, Ac); 3.63, 3.68 (2 *s*, COOMe); 4.15–4.80 (*m*, 7 H); 5.51, 5.63 (2 *dd*, 1 H); 6.34 (*s*) and 6.55 (*d*, $J = 7$, 1 H); 7.35–7.70 (*m*, 6 H); 8.00–8.15 (*m*, 4 H). Anal. calc. for $C_{24}H_{24}O_{10}$: C 61.0, H 5.1; found: C 61.0, H 5.1.

*2′-O-[(Methoxycarbonyl)methyl]-*N$^6$*,3′-*O*,5′-*O*-tribenzoyladenosine* (**10**). To a soln. of $N^6$-benzoyl-bis(trimethylsilyl)adenine [37] (11.0 g, 28.6 mmol) in MeCN (200 ml) under Ar was added dropwise at 0° $SnCl_4$ (2.7 ml, 22.9 mmol). Then **9** (9.0 g, 19.1 mmol) was added and the resulting mixture stirred at r.t. After 3 days, a second portion of $SnCl_4$ (2.7 ml, 22.9 mmol) was added and stirring continued for another 4 days. The mixture was then diluted with AcOEt (300 ml) and cautiously poured in vigorously stirred excess sat. aq. $NaHCO_3$ soln. The mixture was extracted several times with AcOEt, the combined org. phase dried ($Na_2SO_4$) and evaporated, and the residue purified by FC (AcOEt/hexane 3:2): **10** (7.8 g, 63%). $[\alpha]_D = -65.1$ ($c = 1.1$, MeOH). IR (KBr): 1723, 1452, 1270, 711. $^1$H-NMR ($CDCl_3$, 200 MHz): 3.50 (*s*, COOMe); 4.14, 4.25 (*AB* of *ABX*, $J = 16$, $OCH_2COO$); 4.62–4.87 (*m*, 3 H); 5.28 (*t*, $J = 5$, H–C(2′)); 5.91 (*t*, $J = 5$, H–C(3′)); 6.37 (*d*, $J = 5$, H–C(1′)); 7.35–7.70 (*m*, 10 H); 7.95–8.15 (*m*, 6 H); 8.24 (*s*, 1 H); 8.68 (*s*, 1 H); 9.14 (*s*, NH). MS: 652 (8, $M$H$^+$), 413 (17), 240 (40), 169 (100). Anal. calc. for $C_{34}H_{29}N_5O_9$: C 62.7, H 4.5, N 10.7; found: C 62.4, H 4.7, N 10.3.

Further elution gave pure α-D-isomer (1.7 g, 14%). $[\alpha]_D = +3.5$ ($c = 1.2$, MeOH). IR (KBr): 1724, 1452, 1269, 711. $^1$H-NMR ($CDCl_3$, 200 MHz): 3.51 (*s*, COOMe); 4.05, 4.10 (*AB* of *ABX*, $J = 16$, $OCH_2COO$); 4.56–4.97 (*m*, 4 H); 5.76 (*t*, $J = 5$, H–C(3′)); 6.88 (*d*, $J = 5$, H–C(1′)); 7.35–7.70 (*m*, 10 H); 7.95–8.15 (*m*, 6 H); 8.41 (*s*, 1 H); 8.82 (*s*, 1 H); 8.99 (*s*, NH). MS: 652 (19, $M$H$^+$), 412 (12), 249 (68), 169 (100).

N,N-*Dimethylhexane-1,6-diamine* [45] (**11c**). *tert*-Butyl *N*-[6-(dimethylamino)hexyl]carbamate (**18**; 4.5 g, 0.018 mol) was dissolved in AcOEt/3M aq. HCl 1:1 (40 ml) and stirred at r.t. for 15 h. Then the AcOEt layer was separated and the aq. phase evaporated. To the residue was added the minimal amount of 1N NaOH required to obtain a basic soln. The aq. layer was extracted with $CH_2Cl_2$ (5 × 50 ml), the combined org. phase dried ($MgSO_4$),

the solvent evaporated, and the residue distilled (bulb-to-bulb, oven temp. 152°/38 Torr) giving **11c** (1.8 g, 69%). IR (KBr): 3289, 2934, 1576, 1466. $^1$H-NMR ($CDCl_3$, 200 MHz): 1.2–1.6 (*m*, 8 H); 1.59 (*s*, $NH_2$); 2.22 (*s*, $Me_2N$); 2.25 (*t*, *J* = 7, $CH_2NMe_2$); 2.70 (*q*, *J* = 7, $CONHCH_2$). MS: 144 (32, $MH^+$), 128 (17), 114 (52), 58 (100).

*5-Methyl-2′-O-[(*N*-octylcarbamoyl)methyl]uridine* (**12a**). To a soln. of **8** (1.12 g, 3.4 mmol) in abs. EtOH (15 ml) was added octylamine (0.62 ml, 3.7 mmol) and the resulting mixture refluxed for 3 h. Evaporation and drying (100°/0.01 bar, 2 h) gave **12a** (1.44 g, 99%) which was used directly in the next step. For anal. purposes, a small amount was purified by FC (AcOEt/MeOH 93:7). $[\alpha]_D$ = +27.1 (*c* = 0.5, MeOH). UV (25°, $H_2O$): 260 (8300). IR (KBr): 3376, 2927, 1696, 1661, 1118. $^1$H-NMR ($CD_3OD$, 200 MHz): 0.89 (*t*, *J* = 6, $MeCH_2$); 1.2–1.65 (*m*, 12 H); 1.87 (*s*, Me–C(5)); 3.20 (*t*, *J* = 7, $CH_2N$); 3.7–4.35 (*m*, 7 H); 5.93 (*d*, *J* = 2, H–C(1′)); 7.96 (*s*, H–C(6)). MS: 428 (20, $MH^+$), 302 (13), 254 (100), 130 (20).

*5-Methyl-2′-O-{{N-[6-(trifluoroacetamido)hexyl]carbamoyl}methyl}uridine* (**12b**). To a soln. of *N*-(6-aminohexyl)trifluoroacetamide [41] (**11b**; 1.67 g, 7.9 mmol) in MeOH (60 ml), **8** (2.0 g, 6.1 mmol) was added. The resulting mixture was stirred overnight at 50°. Evaporation and FC (MeOH/*t*-BuOMe 1:10) afforded **12b** (1.56 g, 51%). $[\alpha]_D$ = +19.5 (*c* = 2, MeOH). IR (KBr): 3391, 1704, 1660, 1206, 1153. $^1$H-NMR ((D$_6$)DMSO, 360 MHz): 1.18–1.50 (*m*, 8 H); 1.78 (*s*, Me–C(5)); 3.09 (*m*, $CH_2N$); 3.13 (*m*, $CH_2N$); 3.55–3.75 (*m*, $CH_2$(5′)); 3.86–4.15 (*m*, 5 H); 5.19 (*t*, *J* = 5, OH–C(5′)); 5.47 (*d*, *J* = 7, OH–C(3′)); 5.83 (*d*, *J* = 5, H–C(1′)); 7.79 (*s*, H–C(6)); 9.37 (br. *m*, NH); 11.33 (*s*, NH(3)). MS: 511 (63, $MH^+$), 337 (100), 271 (19), 253 (54), 213 (73).

*2′-O-{{N-[6-(Dimethylamino)hexyl]carbamoyl}methyl}-5-methyluridine* (**12c**). To a soln. of *N,N*-dimethylhexane-1,6-diamine [42] (**11c**; 6.5 g, 45 mmol) in MeOH (100 ml), **8** (10.0 g, 30 mmol) was added. The resulting mixture was stirred overnight at 50°. Evaporation and FC (MeOH/AcOEt/$Et_3N$ 30:70:1) afforded **12c** (11.0 g, 83%). $[\alpha]_D$ = +18.4 (*c* = 2.5, MeOH). $pK_{a1}$ = 8.1, $pK_{a2}$ = 11.3. UV (25°, $H_2O$): 260 (7400). IR (KBr): 3385, 2934, 2861, 1696, 1661, 1550, 1468, 1118. $^1$H-NMR ((D$_6$)DMSO, 360 MHz): 1.18–1.45 (*m*, 8 H); 1.77 (*s*, Me–C(5)); 2.09 (*s*, $Me_2N$); 2.16 (*t*, *J* = 7, $Me_2NCH_2$); 3.09 (*m*, $CONHCH_2$); 3.58, 3.71 (*AB* of *ABX*, *J* = 3, 12, $CH_2$(5′)); 3.88 (*m*, H–C(4′)); 3.96 (*m*, H–C(2′)); 3.98, 4.08 (*AB* of *ABX*, *J* = 16, $OCH_2COO$); 4.11 (*m*, H–C(3′)); 5.82 (*d*, *J* = 4, H–C(1′)); 7.80 (*s*, H–C(6)); 7.86 (*t*, *J* = 7, $CH_2NH$). MS: 443 (100, $MH^+$), 317 (5), 299 (4), 269 (27), 201 (22), 187 (15), 155 (13). Anal. calc. for $C_{20}H_{34}N_4O_7$: C 54.3, H 7.7, N 12.7; found: C 54.4, H 7.8, N 12.4.

*2′-O-{{N-{2-[(9,10-Dihydro-9,10-dioxoanthracen-2-yl)amino]ethyl}carbamoyl}methyl}-5-methyluridine* (**12d**). A soln. of **8** (2.5 g, 7.5 mmol) in i-PrOH (30 ml) was added to a soln. of 2-[(2-aminoethyl)amino]-anthraquinone [43] (**11d**; 2.0 g, 7.5 mmol) in $CHCl_3$ (30 ml). The resulting mixture was stirred 48 h at 50°. Evaporation and FC (MeOH/*t*-BuOMe/$Et_3N$ 14:86:2) afforded **12d** (3.4 g, 81%). $[\alpha]_D$ = −180 (*c* = 0.25, DMSO). UV (25°, DMSO/$H_2O$ = 1:1): 260 (14800). IR (KBr): 3357, 1688, 1685, 1589, 1294, 1097. $^1$H-NMR ((D$_6$)DMSO, 360 MHz): 1.76 (*s*, Me–C(5)); 3.2–3.4 (*m*, 4 H); 3.65 (*m*, 2 H); 3.8–4.2 (*m*, 5 H); 5.22 (*t*, *J* = 5, 1 H); 5.41 (*d*, *J* = 8, 1 H); 5.83 (*d*, *J* = 4, H–C(1′)); 7.03 (*dd*, *J* = 3, 10, 1 H); 7.32 (*m*, 2 H); 7.8–8.2 (*m*, 6 H). MS: 565 (42, $MH^+$), 391 (35), 352 (100), 267 (54), 250 (65), 236 (70), 181 (44).

*2′-O-[(*N*-Octylcarbamoyl)methyl]adenosine* (**13a**). Octylamine (7.64 ml, 46 mmol) was added to a soln. of **10** (3 g, 4.6 mmol) in abs. EtOH (80 ml) under Ar. After stirring under reflux for 2 days, the mixture was evaporated and the solid residue suspended in AcOEt (20 ml) containing 10% MeOH and stirred for 5 min. The solid was filtered off and dried giving **13a** (1.50 g, 75%). M.p. 168–169° (from MeOH). $[\alpha]_D$ = −36.9 (*c* = 0.6, MeOH). UV (25°, DMSO): 260 (12400). IR (KBr): 3272, 3125, 2926, 1693, 1659. $^1$H-NMR ($CDCl_3$, 200 MHz): 0.89 (*t*, *J* = 7, $MeCH_2$); 1.2–1.8 (*m*, 12 H); 3.24 (*m*, $CH_2NH$); 3.8–4.2 (*m*, 4 H); 4.35–4.5 (*m*, $CH_2$(5′)); 4.82 (*dd*, *J* = 4, 7, 1 H); 5.70 (br. *s*, 2 OH); 5.97 (*d*, *J* = 8, H–C(1′)); 7.85 (*s*, 1 H); 8.33 (*s*, 1 H). MS: 437 (100, $MH^+$), 347 (8), 254 (62).

*2′-O-{{N-[6-(Dimethylamino)hexyl]carbamoyl}methyl}adenosine* (**13c**). *N,N*-Dimethylhexane-1,6-diamine (3.6 g, 25 mmol) was added to a soln. of **10** (1.7 g, 2.5 mmol) in abs. EtOH (30 ml) under Ar. After stirring under reflux for 2 days, the mixture was evaporated and dried for 24 h (50°/0.1 Torr). FC (MeOH/AcOEt/$Et_3N$ 50:50:2) afforded **13c** (0.85 g, 74%). $[\alpha]_D$ = −33.6 (*c* = 1.0, MeOH). UV (25°, $H_2O$): 260 (12900). IR (KBr): 3272, 2933, 1649, 1611, 1570, 1294. $^1$H-NMR ((D$_6$)DMSO, 360 MHz, 120°): 1.2–1.5 (*m*, 8 H); 2.13 (*s*, $Me_2$); 2.21 (*t*, *J* = 7, $Me_2NCH_2$); 3.05 (*q*, *J* = 7, $CH_2NH$); 3.60, 3.71 (*AB* of *ABX*, *J* = 5, 13, $CH_2$(5′)); 4.00 (*s*, $OCH_2COO$); 4.03 (*m*, H–C(4′)); 4.36 (*t*, *J* = 4, H–C(2′)); 4.50 (*t*, *J* = 4, H–C(3′)); 6.06 (*d*, *J* = 6, H–C(1′)); 6.72 (br. *s*, $NH_2$); 8.15 (*s*, H–C(8)); 8.24 (*s*, H–C(2)). MS: 452 (20, $MH^+$), 317 (19), 270 (34), 136 (87), 128 (100).

*3′,5′-Di-O-benzoyl-5-methyl-2′-O-[(*N*-octylcarbamoyl)methyl]uridine* (**14**). To a soln. of **12a** (8.7 g, 20.4 mmol) in *N,N*-dimethylacetamide (200 ml), 4-(dimethylamino)pyridine (6.96 g, 57.0 mmol), and benzoyl chloride (5.9 ml, 51.0 mmol) were added dropwise. The resulting white suspension was stirred overnight. Workup (AcOEt/0.1N HCl/$NaHCO_3$) and FC (AcOEt/hexane 3:1) gave **14** (11.7 g, 91%). $[\alpha]_D$ = −32.0 (*c* = 0.5, MeOH). IR (KBr): 2927, 1723, 1695, 1268, 1096. $^1$H-NMR ($CDCl_3$, 360 MHz): 0.86 (*t*, *J* = 7, $MeCH_2$); 1.05–1.35 (*m*, 12 H); 1.62 (*s*, H–C(6)); 3.09 (*m*, $NHCH_2$); 4.07, 4.14 (*AB* of *ABX*, *J* = 16, $OCH_2COO$); 4.39 (*t*, *J* = 6, H–C(2′)); 4.60, 4.85 (*AB* of *ABX*, *J* = 4, 12, $CH_2$(5′)); 4.70 (*m*, H–C(4′)); 5.57 (*t*, *J* = 7, H–C(3′)); 6.12 (*d*, *J* = 5, H–C(1′)); 6.53 (*m*,

CONH); 7.19 (*s*, H–C(6)); 7.45–7.67 (*m*, 6 H); 8.0–8.1 (*m*, 4 H); 8.24 (*s*, NH(3)). Anal. calc. for $C_{34}H_{44}N_3O_9$: C 63.9, H 6.9, N 6.6; found: C 63.9, H 6.7, N 6.6.

*5-Methyl-2-O-[(N-octylcarbamoyl)methyl]cytidine* (**15**). To a soln. of **14** (6.0 g, 9.4 mmol) in 1,2-dichloroethane (60 ml), $K_2CO_3$ (2.6 g, 18.9 mmol) and TsCl (2.34 g, 12.2 mmol) were added. The mixture was stirred under reflux overnight, the resulting suspension cooled to r.t. and filtered, and the filtrate cooled in an ice-bath and saturated with $NH_3$. After stirring for 1 h, the precipitate was removed and the filtrate evaporated. The residue was redissolved in MeOH (100 ml) and the resulting soln. again saturated with $NH_3$ at 0°. The vessel was then sealed and the mixture stirred at r.t. for 24 h. Evaporation and FC (AcOEt/MeOH/$Et_3N$ 80:20:1) yielded **15** (1.95 g, 49%). $[\alpha]_D = +25.9$ ($c = 0.5$, MeOH). UV (25°, $H_2O$): 260 (7300). IR (KBr): 3346, 2927, 2856, 1662, 1604, 1123. $^1$H-NMR ($CD_3OD$, 360 MHz): 0.89 (*t*, $J = 7$, $MeCH_2$); 1.2–1.6 (*m*, 12 H); 1.93 (*s*, Me–C(5)); 3.22 (*t*, $J = 7$, $CH_2NH$); 3.41 (*m*, H–C(4')); 3.78, 3.97 (*AB* of *ABX*, $J = 12, 3$, $CH_2$–(5')); 4.03 (*m*, 1 H); 4.2–4.35 (*m*, 3 H); 5.92 (*d*, $J = 3$, H–C(1')); 7.98 (*s*, H–C(6)). MS: 449 (100, $[M + Na]^+$), 427 (5, $MH^+$), 345 (13), 254 (67), 148 (38).

*5-Methyl-N$^4$-(N-methylpyrrolidin-2-ylidene)-2'-O-[(N-octylcarbamoyl)methyl]cytidine* (**16**). Under Ar, **15** (1.6 g, 3.8 mmol) was dissolved in MeOH (10 ml) and *N*-methylpyrrolidinone dimethyl acetal [45] (2.0 g, 13.9 mmol) added. The yellow soln. was stirred for 2 h at r.t. Evaporation and FC (AcOEt/MeOH/$Et_3N$ 80:20:1) gave **16** (1.49 g, 78%). White foam. $[\alpha]_D = +100.0$ ($c = 0.5$, MeOH). IR (KBr): 3350, 2926, 1660, 1577, 1500, 1298. $^1$H-NMR ($CDCl_3$, 360 MHz): 0.88 (*t*, $J = 7$, 3 H); 1.1–1.6 (*m*, 12 H); 1.97 (*s*, Me–C(5)); 2.06 (*m*, 2 H); 3.07 (*s*, MeN); 3.0–3.3 (*m*, 4 H); 3.48 (*t*, $J = 7$, 2 H); 3.81, 3.98 (*AB* of *ABX*, $J = 12, 2$, $CH_2$(5')); 4.1–4.4 (*m*, 5 H); 5.63 (*d*, $J = 4$, H–C(1')); 7.05 (*t*, $J = 5$, NH); 7.55 (*s*, H–C(6)). MS: 508 (28, $MH^+$), 254 (20), 207 (100), 191 (21).

tert-*Butyl* N-*(6-Bromohexyl)carbamate*. A soln. of *tert*-butyl *N*-(6-hydroxyhexyl)carbamat [47] in toluene (150 ml) was slowly added to a mixture of $PPh_3$ (18.6 g, 0.07 mol), $CBr_4$ (23.5 g, 0.07 mol), and toluol (400 ml). The resulting heterogeneous mixture was stirred overnight at r.t. Filtration and evaporation gave a yellow oil which was diluted with $Et_2O$ and stored overnight at 4°. The precipitate was removed by filtration and the filtrate evaporated. FC (hexane/AcOEt 4:1) of the residue gave **17** (12.0 g, 93%). IR (KBr): 3353, 2934, 1696, 1174. $^1$H-NMR ($CDCl_3$, 200 MHz): 1.3–1.6 (*m*, 6 H); 1.44 (*s*, *t*-Bu); 1.85 (*m*, 2 H); 3.11 (*q*, $J = 7$, $CH_2NH$); 3.40 (*t*, $J = 7$, $CH_2Br$); 4.52 (br. *s*, NH). MS: 282 (17), 280 (20, $MH^+$), 226 (100), 224 (100), 182 (27), 180 (34), 100 (52), 57 (100).

tert-*Butyl* N-*[6(dimethylamino)hexyl]carbamate*. $Me_2NH$ (33% in EtOH; 76.8 ml, 0.42 mol) was added to a soln. of *tert*-butyl *N*-(6-bromohexyl)carbamate (12 g, 0.042 mol) in EtOH (50 ml). The resulting yellow soln. was stirred for 4 h at 45°. Evaporation and workup (AcOEt/brine) gave **18** (8.94 g, 86%). IR (KBr): 3350, 2975, 2934, 1715, 1176. $^1$H-NMR ($CDCl_3$, 200 MHz): 1.2–1.6 (*m*, 8 H); 1.46 (*s*, *t*-Bu); 2.22 (*s*, $Me_2N$); 2.25 (*t*, $J = 7$, $CH_2NMe_2$); 3.12 (*q*, $J = 7$, $CONHCH_2$); 4.53 (br. *s*, NH). MS: 245 (100, $MH^+$), 243 (74), 189 (68), 187 (40).

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