Oligonucleosides with a Nucleobase-Including Backbone

Part 12

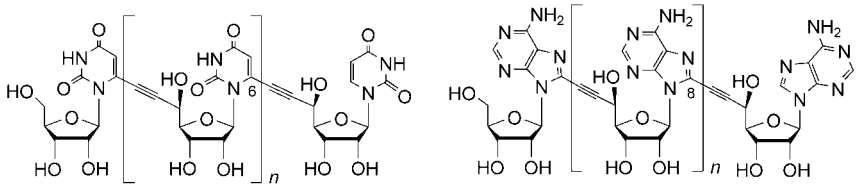
Synthesis of Mixed Ethynylene-Linked Uridine- and Adenosine-Derived Tetramers

by **Simon Eppacher**, **Punit Kumar Bhardwaj**, **Bruno Bernet**, **José Luis Bravo Gala**, **Thomas Knöpfel**, and **Andrea Vasella***

Laboratorium für Organische Chemie, ETH-Hönggerberg, HCI, CH-8093 Zürich

In contradistinction to the corresponding *Grignard* reagent, bis[(trimethylsilyl)ethynyl]zinc reacted with the 5′-oxoadenosine **3** diastereoselectively to the β-D-*allo*-hept-6-ynofuranosyladenine **5**. Lithiation/iodination of the monomeric propargyl alcohol **5** and of the dimeric propargyl alcohol **22** provided the 8-iodoadenosines **7** and **18**, respectively, considerably shortening the synthesis of the dimeric *O*-silylated 8-iodoadenosine **25**. The mixed uridine- and adenosine-derived tetramers **21** and **32** were synthesised. The tetramer **21** was prepared by a linear sequence. *Sonogashira* coupling of **9** and **13** yielded the trimer **16** that was *C*-desilylated to **17**. A second *Sonogashira* coupling of **17** and **19** yielded the tetramer **21**. Tetramer **32** was prepared in higher yields by a convergent route, coupling the acetylene **29** and the iodide **30**. The uridine-derived iodides proved more reactive than the adenosine-derived analogues, and the N^6-unprotected adenosine-derived alkynes were more reactive than their N^6-benzoylated analogues.

Introduction. – We have described the synthesis of uridine-derived pentamers [1][2] and adenosine-derived tetramers [3–5] that are characterised by an ethynylene link between C(5′) of one nucleoside unit and C(6) of an adjacent uracil, or C(8) of a adjacent adenosine moiety (*cf.* **A** and **B**, resp.). Inspection of *Maruzen* models and *Macromodel V. 4.5* (*Amber** force-field, gas phase) [6] force-field calculations suggested that these novel oligonucleotide analogues form autonomous pairing systems and may hybridise with complementary RNA strands [1].



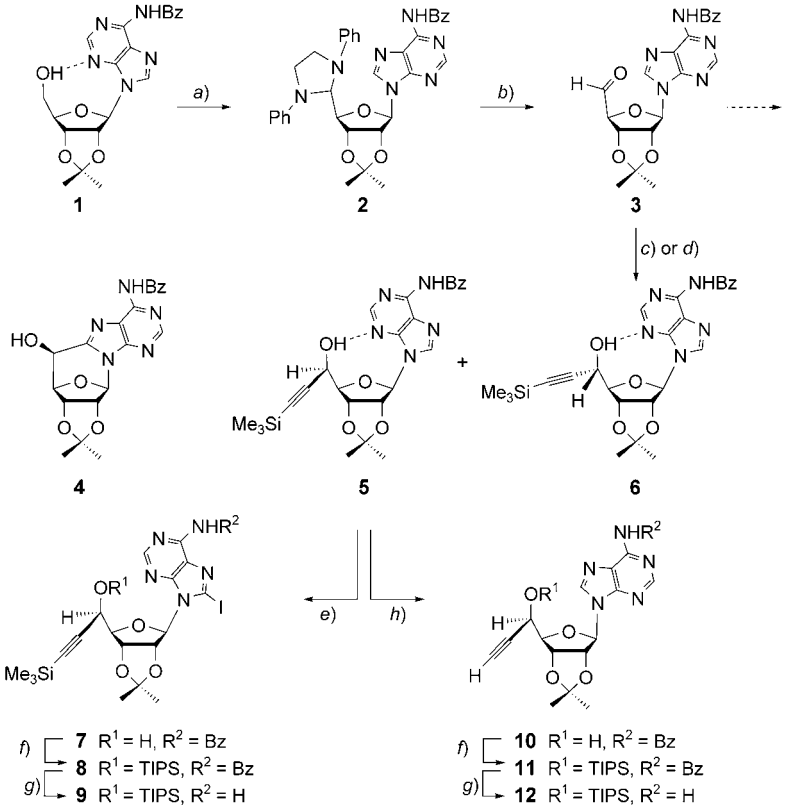
A **B**

The crucial C(5′),C≡C–C(6) and C(5′),C≡C–C(8) bonds of these oligonucleotide analogues were established by a *Sonogashira* coupling [7] between a hept-6-ynofuranosyl-uracil or -adenosine, and a 6-iodouracil or 8-iodoadenosine. Depending on the strategy (linear, convergent, or binomial), this synthesis requires monomeric, dimeric, or oligomeric coupling partners. While the terminal hept-6-ynofuranosyl-uracil and -adenosine derivatives were synthesised in good yields, the required iodides – particularly the adenosine derivatives – were less well accessible.

We now describe an improved synthetic route to iodinated monomers and dimers of adenosine, a diastereoselective addition of bis[(trimethylsilyl)ethynyl]zinc to the aldehyde **3**, the synthesis of two self-complementary tetramers **21** and **32**, and, in this context, the structural effects on the *Sonogashira* coupling.

Results and Discussion. – We reported the preparation of the propargylic alcohols **5** and **6** by addition of $BrMgC{\equiv}CSiMe_3$ to the crude aldehyde **3** [3] (*Scheme 1*). Reproducibility problems during scale-up and the low diastereoselectivity prompted us to re-investigate the preparation of **3** and its reaction with $BrMgC{\equiv}CSiMe_3$. According to *Moffat* and co-workers [8], **3** is obtained in 60% yield by oxidation of **1** [9] with DCC and $Cl_2CHCOOH$ in DMSO, transformation of the crude aldehyde to the *N*,*N*′-diphenylimidazolidine **2**, liberation of the hydrate **3** · H_2O by treatment with

Scheme 1



a) *N*,*N*′-Dicyclohexylcarbodiimide (DCC), Cl_2HCCO_2H, DMSO, then $(PhHNCH_2)_2$, MeOH; 76%. *b*) *Dowex 50W* × *8*, THF/H_2O 1:1, then benzene, reflux, *Dean–Stark* apparatus; 79%. *c*) $BrMgC{\equiv}CSiMe_3$, THF; 40% of **5** and 20% of **6**. *d*) $Zn(C{\equiv}CSiMe_3)_2$, THF; 54% of **5** and 6% of **6**. *e*) Lithium diisopropylamide (LDA), THF, then *N*-iodosucciniimide (NIS), then AcOH; 88%. *f*) Triisopropylsilyl trifluoromethanesulfonate (TIPSOTf), pyridine, CH_2Cl_2; 89% of **8**; 88% of **11**. *g*) $MeNH_2$, PhMe; 85% of **9**; 89% of **12**. *h*) Bu_4NF (TBAF) · 3 H_2O, THF; > 98%.

Dowex 50W × 8, and dehydration to **3** by azeotropic destillation with benzene using a *Dean–Stark* trap[1]).

Addition of $BrMgC{\equiv}CSiMe_3$ to pure **3** at $-15°$ yielded 60% of a 2:1 mixture of **5** and **6**, as independently reported by *Matsuda et al.* [10] (*Scheme 1*). Substitution of $BrMgC{\equiv}CSiMe_3$ by $LiC{\equiv}CSiMe_3$, or the addition of $CeCl_3$ had no influence on the diastereoselectivity. However, addition of 5 equiv. of bis[(trimethylsilyl)ethynyl]zinc (generated from 10 equiv. of $LiC{\equiv}CSiMe_3$ and 5 equiv. of $ZnCl_2$) to **3** at 23° yielded a 9:1 mixture of **5** and **6** in 59% yield[2]). The 8-iodoadenosine **7** was synthesised by introducing the alkynyl substituent after iodination, as attempts to iodinate the triethylsilyl-protected propargyl alcohol **5** did not lead to satisfactory results [3]. However, this synthesis of **7** is rather long, and the intermediate aldehyde (the 8-iodo analogue of **3**) also proved sensitive. For these reasons, we re-investigated the direct iodination of **5** and obtained the desired 8-iodoadenosine **7** in a yield of 88% upon treating **5** with 7 equiv. of LDA. Silylation of **7** with TIPSOTf yielded 89% of the silyl ether **8**, which was *N*-debenzoylated by treatment with $MeNH_2$ in toluene to provide **9** (85%). The coupling partner **12** was obtained in a yield of 78% by *C*-desilylating **5** with TBAF · 3 H_2O to **10**, followed by silylation of HO–C(5′) with TIPSOTf to **11**, and *N*-debenzoylation with $MeNH_2$.

The D-*allo*-hept-6′-ynosyladenines **5**–**12** show a similar conformational preference as related adenosines [3]. The intramolecular H-bond O(5′)–H···N(3) of **7** in $CDCl_3$ is evidenced by the downfield shift of HO–C(5′) (7.06 ppm), the small $J(5',OH)$ and $J(4',5')$ values (<2 Hz), and the (*S*)-conformation ($J(1',2') = 5.3$, $J(3',4') = 0$ Hz; see *Table 2* in the *Exper. Part*). In CD_3OD, the intramolecular H-bond of **10** is mostly replaced by an intermolecular H-bond to the solvent as evidenced by a larger $J(4',5')$ (3.7 Hz) and the (*N*)/(*S*) conformational equilibrium ($J(1',2') = 3.1$, $J(3',4') = 1.9$ Hz), whereas $\delta(H-C(2')) = 5.32$ ppm agrees with both the *syn*-conformation of the intramolecular H-bonded species and an *anti*-conformation. The HO–C(5′) protected iodides **8** and **9** adopt preferentially the (*N*)- ($J(1',2')/J(3',4') = 0.71-0.76$) and completely the *syn*-conformation ($\delta(H-C(2')) = 5.92-5.93$ ppm, $J(4',5') = 8.1-8.4$ Hz), whereas the corresponding *C(8)*-unsubstituted analogues **8** and **9** adopt preferentially the (*S*)- ($J(1',2')/J(3',4') = 1.11-1.16$) and completely the *anti*-conformation ($\delta(H-C(2')) = 5.33-5.35$ ppm, $J(4',5') = 4.7-5.4$ Hz).

The (5′*S*)-configuration of **4** was evidenced by 1D-NOE experiments in (D_6)DMSO. Irradiation of HO–C(5′) at 6.82 ppm led to a NOE of 1.5% for H–C(3′) and of 8% for H–C(5′), whereas irradiation of H–C(5′) at 5.20 ppm led only to a NOE of 4% for HO–C(5′). The 1,3-oxazine ring of **4** adopts an (*E*)-conformation with O(4′) outside of the common plane, and the furanose ring adopts an E_O conformation as evidenced by $J(1',2') = J(3',4') = 0$ Hz (see *Table 2* in the *Exper. Part*). $J(5,OH) = 5.6$ Hz evidences a fully solvated OH group. The *d* of C(5′) of **4** resonates at the same position as the *d* of C(5′) of the hept-6-ynofuranosyl nucleosides (63 ppm),

---

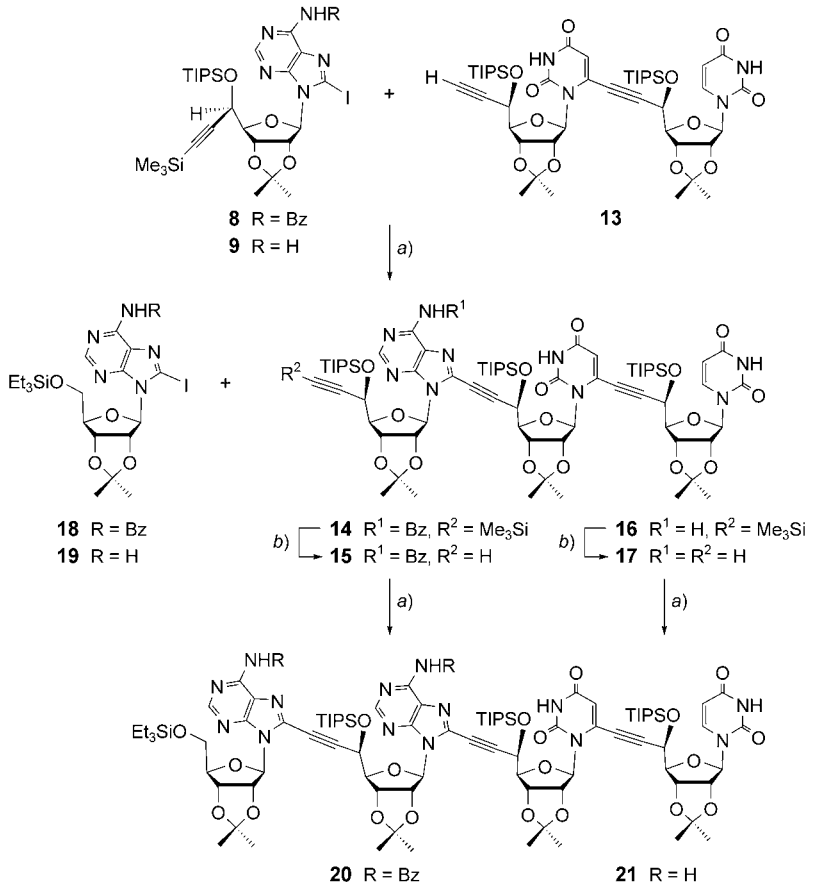
[1]) To obtain the useful but sensitive aldehyde **3**, we had to recrystallise the *N*,*N*′-diphenylimidazolidine **2**, carefully wash **3** · H_2O with H_2O, pre-dry it (100 mbar 45°, 14 h), and perform the dehydration of small amounts of **3** · H_2O in benzene. Neglecting these precautions led to a new, polar, benzene-insoluble product that was identified by ^{1}H- and ^{13}C-NMR spectroscopy, and mass spectrometry as the cyclonucleoside **4**. The (5′*R*)-epimer of **4** was not isolated.

[2]) The selectivity of the addition is in agreement with the *Felkin–Anh* model [11][12].

whereas the *s* of C(8) of **4** (150 ppm) is shifted downfield by *ca.* 8 ppm as compared to the corresponding *d* of **2** and **3** · H_2O (see *Table 3* in the *Exper. Part*).

Considering the poor H_2O solubility of the purely adenosine-derived tetramers [3–5], we aimed at the synthesis of self-complementary oligomers. We first investigated a linear synthesis of the tetramer **21** (*Scheme 2*). *Sonogashira* coupling of the known dimeric uridine-derived acetylene **13** [2] with the 8-iodoadenosine **8** yielded 49% of the mixed trimer **14**; similarly, coupling of **13** with the debenzoylated 8-iodoadenosine **9** gave the mixed trimer **16** (38%). The trimers were *C*-desilylated with $AgNO_3$ and KCN in MeOH/AcOEt to the acetylenes **15** (49%) and **17** (74%), respectively. Coupling the trimer **15** with the 8-iodoadenosine **18** [3] gave only traces of the tetramer **20**, while coupling the debenzoylated trimer **17** with the debenzoylated iodide **19** [4] yielded 50% of the mixed tetramer **21**. This result confirms the higher reactivity of adenosine-

Scheme 2

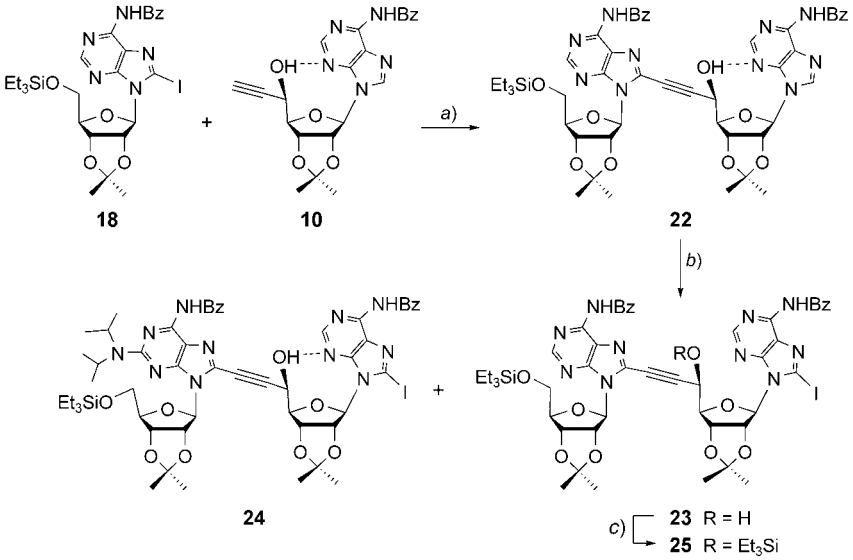


a) [$Pd_2(dba)_3$], CuI, P(fur)$_3$, toluene/Et_3N 1:1; 49% of **14**; 38% of **16**; traces of **20**; 50% of **21**. *b*) $AgNO_3$, MeOH/AcOEt, then KCN; 49% of **15**; 74% of **17**.

derived acetylenes with a free primary NH_2 group as compared to their N^6-benzoylated analogues [4].

For the convergent route to the mixed tetramer **21**, we wished to shorten the synthesis of the known iodinated dimer **25** [5] by lithiation and iodination of **22**, which is accessible in 57% yield by *Sonogashira* coupling of the iodide **18** [3] with the alkyne **10** (*Scheme 3*). When the iodination was performed by treating **22** with 8 equiv. of LDA and NIS, we obtained the desired iodide **23** in 36% yield besides 30% of starting material and 10% of a new product (*Table 1*). It was assigned the structure of the 2-(diisopropylamino)adenosine **24** on the basis of its ^{1}H- and ^{13}C-NMR, and mass spectral data. The analogous iodination in the presence of 16 equiv. of HMPA failed; only starting material was isolated. However, substituting LDA by lithium 2,2,6,6-tetramethylpiperidide in the presence of 16 equiv. of HMPA led in 77% yield to the iodinated dimer **23** without formation of any by-products. The dimeric iodoadenosine **23** was silylated with Et_3SiCl to yield 86% of the silyl ether **25**.

Scheme 3



a) $[Pd_2(dba)_3]$, CuI, $P(fur)_3$, toluene/Et_3N 1:1; 57%. *b*) See *Table 1*. *c*) Et_3SiCl, 1*H*-imidazole, DMF; 86%.

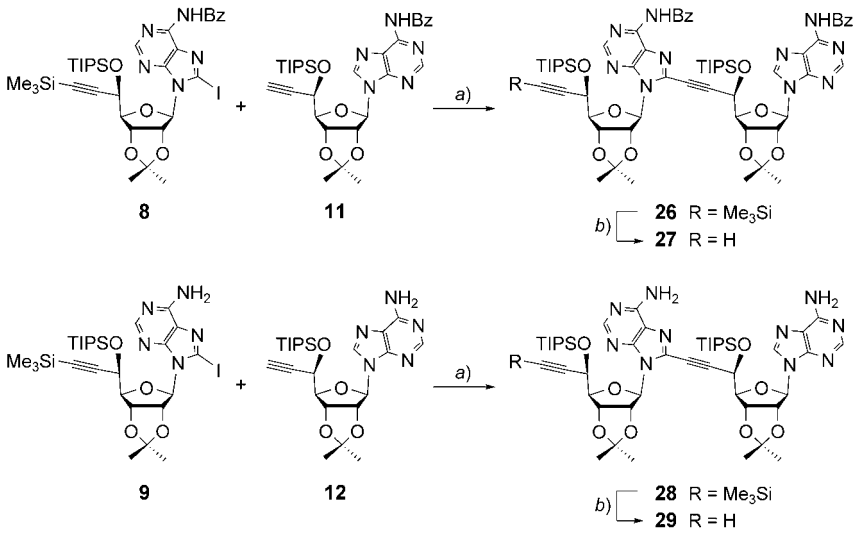
Table 1. *Conditions and Yields in the Iodination of* **22** (LiTMP = lithium 2,2,6,6-tetramethylpiperidide)

Base	NIS	Additive	**22**	**23**	**24**
8 equiv. of LDA	8 equiv.	–	30%	36%	10%
8 equiv. of LDA	8 equiv.	16 equiv. of HMPA	>85%	–	–
8 equiv. of LiTMP	8 equiv.	16 equiv. of HMPA	–	77%	–

An attempt to prepare the mixed tetramer analogue of **20** (Et_3Si protecting group at HO–C(4/III)) by *Sonogashira* coupling of the uridine-derived dimer **13** and the *N*-

benzoylated iodoadenosine **25** failed. Only traces of product were formed[3]) even upon prolonging the duration of the reaction (120 h) in the presence of 0.5 equiv. of [Pd_2dba_3]. This differs significantly from the results of *Gunji* and *Vasella* [5] who showed that coupling of the Et_3Si-protected analogue of **29** (see below and *Scheme 4*) with the dimeric 8-iodoadenosine **25** proceeded in 79% yield to the corresponding tetramer, indicating that the adenosine-derived acetylenes are more reactive than the uracil-derived counterparts. The higher reactivity, in the *Sonogashira* coupling, of the dimeric 6-iodouridine **30** (*Scheme 5*) as compared to the dimeric 8-iodoadenosine **25** is evidenced by the formation, in 51% yield, of the tetramer resulting from the dimeric uridine-derived acetylene **13** and the dimeric uridine-derived iodide **30** [2].

Scheme 4



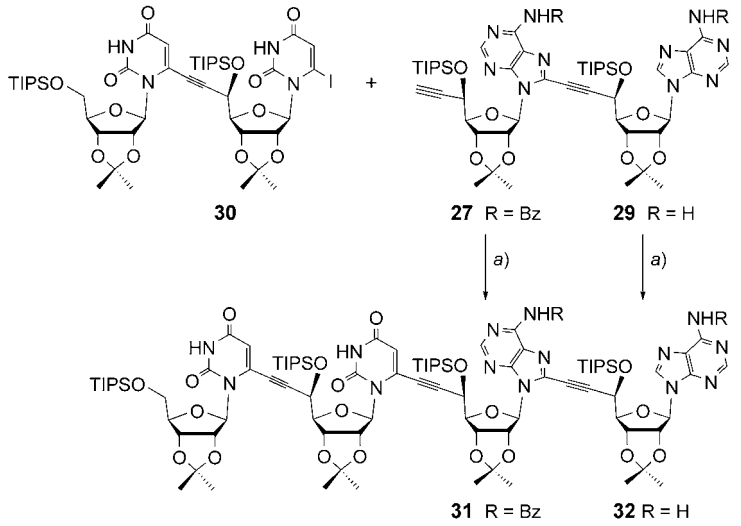
a) [$Pd_2(dba)_3$], CuI, $P(fur)_3$, toluene/Et_3N 1:1; 76% of **26**; 83% of **28**. *b*) $AgNO_3$, MeOH/AcOEt, then KCN; 98% of **27**; 86% of **29**.

Besides the mixed tetramer **21** (*Scheme 2*) with the sequence A(8–7′)aHepA(8–7′)aHepU(6–7′)aHepU (for the nomenclature, see [1]), we wished to synthesise the tetramer **32** (*Scheme 5*) with the complementary sequence U(6–7′)aHepU(6–7′)-aHepA(8–7)aHepA. The dimeric *N*-benzoyladenosine-derived alkyne **27** (*Scheme 4*) was required for a convergent synthesis of **32**. It was obtained in a yield of 74% by coupling the acetylene **11** with the 8-iodoadenosine **8**, followed by *C*-desilylation; similarly, the *N*-debenzoylated dimer **29** was prepared in a yield of 72% by coupling the acetylene **12** and the iodide **9**, and *C*-desilylation.

---

[3]) Workup of an aliquot led to a crude that showed a signal in its MALDI-TOF mass spectrum corresponding to the coupling product.

Scheme 5



a) $[Pd_2(dba)_3]$, CuI, $P(fur)_3$, toluene/Et_3N 1:1; traces of **31**; 69% of **32**.

The tetramer **32** was obtained in 69% yield by *Sonogashira* coupling of the acetylene **29** with the iodide **30** [2], while coupling of the acetylene **27** with **30** yielded only traces of the tetramer **31**, again illustrating the higher reactivity of adenosine derived acetylenes with a free 6-NH_2 group.

The coupling constants of the ribofuranosyl units in the tetramers **21** in $CDCl_3$ and **32** in $CDCl_3/CD_3OD$ 9:1 differ slightly, but significantly from each other. This allows an unambiguous assignment of H–C(3′) to H–C(5′). The assignment of H–C(1′), H–C(2′), H–C(2), H–C(5), and H–C(8) is based on DQF-COSY spectra of **21** and **32** and on a HMBC spectrum of **32**. Surprisingly, H–C(5/III) of **32** appears as broad *s*.

A comparison of the ^{1}H-NMR data shows that the adenosyl units of the dimers **22**–**29** (**25**–**29** in $CDCl_3$ and **22**–**24** in (D_6)DMSO), the mixed trimers **14**–**17** ($CDCl_3$), and the tetramers **21** ($CDCl_3$) and **32** ($CDCl_3/CD_3OD$ 9:1) possess all a flattened furanose ring ($J(1',2')+J(3',4')=3.8-6.9$ Hz; see *Tables 4*, *6*, *8*, and *10* in the *Exper. Part*). $J(1',2')=0-2.9$ Hz and $J(3',4')=2.1-5.1$ Hz evidence a slight preference for the (*N*)-conformation. The HO–C(5′) protected units II of **22**–**29** and **32**, units III of **14**–**17** and **21**, and unit IV of **21** adopt a *syn*-conformation as evidenced by the downfield shift of H–C(2′) (5.57–5.70 ppm; the solvent and the N^6-protection have a negligible influence on this chemical shift) and the large $J(4',5')$ value (7.3–8.5 Hz for the hept-6-ynofuranosyladenines and 6.0–6.9 Hz for the ribofuranosyladenines). Unit I of the HO–C(5′)-protected iodide **25** also adopts completely the *syn*-conformation (δ(H–C(2′)) = 5.63 ppm, $J(4',5')=8.0$ Hz [4]). The downfield shift of H–C(2′/I) (5.71 ppm) and the large $J(4',5'/I)$ values (7.1–8.5 Hz) of the *C(8/I)*-unsubstituted diamines **28**, **29**, and **32** indicate the complete preference for the *syn*-conformation or an equilibrium between a *syn*-conformer and further conformers leading to similar δ(H–C(2′)) and $J(4',5')$ values. The upfield shift of H–C(2′/I) (5.46–5.49 ppm) and a

smaller $J(4',5'/I)$ value (6.2–6.5 Hz) of the *C(8/I)*-unsubstituted dibenzamides **26** and **27** evidences a 25–40% contribution of the *anti*-conformer in the conformational equilibrium. The complete preference for the *anti*-conformation of the HO–C(5′) protected and 8-unsubstituted monomeric adenosine derivatives and a strongly decreased preference for this conformation of closely related oligomeric adenosines has already been observed [4].

In (D_6)DMSO, HO–C(5′/I) of **22**–**24** is completely solvated as evidenced by $J(5',OH) = 6.0–6.6$ Hz (*cf.* [4][13–15]) and by $J(4',5') = 6.2–8.8$ Hz. Unit I of the iodides **23** and **24** adopts completely the *syn*-conformation ($J(4',5') = 8.0–8.8$ Hz), whereas a *ca.* 35% population of an *anti*-conformation is deduced from $J(4',5'/I) =$ 6.2 Hz of the *C(8/I)*-unsubstituted **22**. In agreement with this finding, H–C(2′/I) of **22** resonates upfield to H–C(2′/I) of **23** (5.51 *vs.* 5.71 ppm). However, the upfield shift of H–C(2′/I) of **24** resonating at 5.47 ppm is surprising; it must be due to the (i-Pr)$_2$N group, and reveals an electronic interaction between the two nucleobases.

The downfield shift for H–C(2′) of the uridyl units II–IV of **14**–**17**, **21**, and **32** (5.16–5.31 ppm; compare with monomeric 6-substituted (5.19–5.30 ppm [1][16]) and 6-unsubstituted uridines (4.72–4.90 ppm [1])) evidences the complete preference for the *syn*-conformation. The steric demand of the uridyl group is smaller than that of the adenyl group, as indicated by $J(4',5'/II)$ of **21** and $J(4',5'/III)$ of **32** (6.1–6.3 Hz). However, $J(4',5'/II)$ of **14**–**17** (8.1–8.3 Hz) has the same size as $J(4',5')$ of the corresponding adenosyl units. H–C(2′/I) of **14** and **15** resonates at 4.93–4.94 ppm and still evidences a preference for the *anti*-conformation, whereas the downfield shift of H–C(2′/I) of **16**, **17**, and **21** (5.21–5.26 ppm) indicates at best a weak contribution of the *anti*-conformer to the conformational equilibrium.

The position of the (i-Pr)$_2$N group of **24** was deduced as follows. In the ^{1}H-NMR range that is typical for the H–C(2) and the H–C(8) signals, we found only one signal corresponding to H–C(2). In the ^{13}C-NMR spectra of **24**, one C(2) gives rise to a *s* at 157.6 ppm, shifted downfield by 5.1 ppm as compared to C(2) of **23**, resonating at 152.5 ppm. The second C(2) resonates as a *d* at 149.73 ppm, shifted by 1.6 ppm to higher fields, as compared to C(2) of **23** (151.3 ppm). The location of the (i-Pr)$_2$N group – at C(2/I) or C(2/II) – was deduced from the FAB-MS. A signal at *m*/*z* 365.9 corresponds to an iodinated, doubly protonated N^6-benzoyladenosine that possesses no (i-Pr)$_2$N group and can be formed only by depurination of unit I. In addition, a signal at *m*/*z* 819.3 corresponds to the remaining ribofuranosyladenine residue possessing the (i-Pr)$_2$N group.

We thank the *ETH-Zürich* and *F. Hoffmann-La Roche AG*, Basel, for generous support.

Experimental Part

General. See [2].

*N^6-Benzoyl-5′-deoxy-2′,3′-*O*-isopropylidene-5′,5′-(*N,N′*-diphenylethylenediamino)adenosine* (**2**). Prepared according to [8] from 27 g of **1** [9]. Yellow crystals. R_f (AcOEt/hexane 2:1) 0.51. M.p. 132–134° ([8]: 132–135°). $[\alpha]_D^{25} = +18.7$ ($c = 1.1$, $CHCl_3$) ([8]: $[\alpha]_D^{23} = +34.8$ ($c = 0.1$, MeOH)). IR ($CHCl_3$): 3405*w*, 3007*m*, 2934*w*, 1708*s*, 1612*s*, 1598*s*, 1502*s*, 1487*w*, 1456*m*, 1082*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 9.51 (br. *s*, NH); 8.05–7.98 (*m*, 2 arom. H); 7.63–7.47 (*m*, 3 arom. H); 7.26–7.13 (*m*, 4 arom. H); 6.81–6.70 (*m*, 6 arom. H); 3.75–3.56 (*m*, CH_2CH_2); 1.49, 1.32 (2*s*, Me_2C). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 164.9 (*s*, C=O); 146.5, 146.4, 133.7 (3*s*); 132.8 (*d*); 129.4 (2*d*); 129.1 (2*d*); 128.8 (2*d*); 128.0 (2*d*); 118.4, 118.3 (2*d*);

Table 2. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Monomeric Adenosine Derivatives* **2**–**4** *and* **7**–**12**

Solvent	**2** $CDCl_3$	**3**·H_2O (D_6)DMSO	**3** (D_6)DMSO	**4** (D_6)DMSO	**7** $CDCl_3$	**8** $CDCl_3$	**9** $CDCl_3$	**10** CD_3OD	**11** $CDCl_3$	**12** $CDCl_3$
H–C(2)	8.72	8.73	8.60	8.65	8.66	8.69	8.18	8.68	8.80	8.31
H–C(8)	7.80	8.62	8.59	–	–	–	–	8.61	8.22	7.98
H–C(1′)	6.16	6.24	6.55	6.42	6.07	6.12	6.07	6.32	6.21	6.31
H–C(2′)	5.15	5.34	5.40	4.76	5.22	5.92	5.93	5.32	5.35	5.33
H–C(3′)	5.20	5.05	5.48	5.07	5.16	5.30	5.27	5.18	5.15	5.15
H–C(4′)	4.63	4.36	4.77	4.73	4.55	4.22	4.18	4.40	4.39	4.33
H–C(5′)	5.74	4.83	9.31	5.20	4.72	4.58	4.53	4.56	4.76	4.74
J(1′,2′)	2.2	2.5	0	0	5.3	2.0	1.9	3.1	2.9	3.1
J(2′,3′)	6.2	6.2	6.2	5.8	5.6	6.2	6.2	6.2	6.2	6.5
J(3′,4′)	4.8	<1	1.9	0	0	2.8	2.5	1.9	2.5	2.8
J(4′,5′)	2.5	5	0	6.2	1.9	8.1	8.4	3.7	5.4	4.7

Table 3. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the Monomeric Adenosine Derivatives* **2**–**4** *and* **7**–**12**

Solvent	**2** $CDCl_3$	**3**·H_2O (D_6)DMSO	**4** (D_6)DMSO	**7** $CDCl_3$	**8** $CDCl_3$	**9** $CDCl_3$	**10** CD_3OD	**11** $CDCl_3$	**12** $CDCl_3$
C(2)	152.9	152.1	151.7	151.9	152.7	153.0	153.5	153.2	153.5
C(4)	149.7	150.5	150.3	149.0	148.6	150.8	151.6	150.0	149.8
C(5)	122.9	125.7	125.5	126.3	125.7	123.0	125.4	123.6	120.4
C(6)	151.3	151.5	151.2	150.9	152.1	154.6	153.4	151.6	156.1
C(8)	141.7	143.2	149.8	103.7	105.4	104.5	144.8	142.2	139.8
C(1′)	88.4	90.4	85.7	96.2	94.4	94.3	93.5	91.5	91.3
C(2′)	83.8	83.8	83.1	81.7	82.8	83.3	85.9	84.1	84.1
C(3′)	80.1	80.8	77.9	80.7	82.4	82.6	82.8	81.4	81.6
C(4′)	87.0	89.3	83.7	87.1	90.1	90.3	90.7	89.3	89.4
C(5′)	73.3	88.9	63.0	63.5	63.6	63.7	63.5	63.4	63.4
C(6′)	–	–	–	101.2	104.2	101.3	82.7	82.0	82.3
C(7′)	–	–	–	92.2	91.2	91.1	76.4	75.1	75.0

115.1 (*s*, Me_2C); 113.6 (2*d*); 113.5 (2*d*); 47.8, 46.8 (2*t*, CH_2CH_2); 27.4, 25.7 (2*q*, Me_2C). FAB-MS (NOBA): 604 (40, $[M+H]^+$).

N^6-*Benzoyl-9-(2,3*-O-*isopropylidene-β*-D-ribo-*pentodialdo-1,5-furanosyl)adenine Hydrate* (**3**·H_2O). A soln. of **2** (18.5 g, 30.6 mmol) in THF/H_2O 1:1 (1.8 l) was treated with *Dowex 50W* (H^+ form, 36 g), stirred at 23° for 1.5 h, and filtered (washing of the resin with 4 × 100 ml of THF). The combined filtrate and washings was concentrated to *ca.* ½ of the volume. The resulting colourless, amorphous solid was filtered off, washed with H_2O, and dried for 24 h at 40° and 100 mbar to afford **3a**·H_2O (13.1 g, 79%). White solid. R_f (AcOEt/hexane 3:1) 0.31. IR (KBr): 3275*s* (br.), 2989*m*, 1702*s*, 1617*s*, 1588*s*, 1523*s*, 1410*s*, 1291*s*, 1263*m*, 1223*m*, 1172*m*, 1157*m*, 1130*m*, 1059*m*. ^{1}H-NMR (200 MHz, (D_6)DMSO): see *Table 2*; additionally, 11.15 (br. *s*, NH); 8.03–8.01 (*m*, 2 arom. H); 7.65–7.60 (*m*, 3 arom. H); 6.28, 6.16 (2*d*, $J=6.2$, 2 HO–C(5′)); 1.53, 1.32 (2*s*, Me_2C). ^{13}C-NMR (75 MHz, (D_6)DMSO): see *Table 3*; additionally, 165.9 (*s*, C=O); 133.5 (*s*); 132.6 (*d*); 128.6 (4*d*); 112.8 (*s*, Me_2C); 26.9, 25.0 (2*q*, Me_2C). HR-MALDI-MS (DHB): 432.093 ($[M-H_2O+Na]^+$, $C_{20}H_{19}N_5NaO_5^+$; calc. 432.128).

N^6-*Benzoyl-9-(2,3*-O-*isopropylidene-β*-D-ribo-*pentodialdo-1,5-furanosyl)adenine* (**3**). A suspension of **3**·H_2O (5 g, 12.9 mmol) in benzene (75 ml) was heated under reflux for 30 min using a *Dean–Stark* condenser and evaporated. The residue was dried *i.v.* to afford **3** (4.8 g, >97%). White foam. IR ($CHCl_3$): 3394*w*, 3041*m*, 2984*w*, 1734*s*, 1712*s*, 1610*s*, 1590*s*, 1503*s*, 1480*m*, 1457*s*, 1385*m*, 1329*m*, 1238*m*, 1211*m*, 1102*m*. ^{1}H-NMR

(300 MHz, (D_6)DMSO): see *Table 2*; additionally, 11.2 (br. *s*, NH); 8.04–8.01 (*m*, 2 arom. H); 7.63–7.51 (*m*, 3 arom. H); 1.52, 1.34 (2*s*, Me_2C). FAB-MS (NOBA): 410 (47, $[M+H]^+$).

(5′S)-N^6-*Benzoyl-8,5′-cyclo-2′,3′*-O-*isopropylideneadenosine* (**4**). Neglecting purification of *N,N′*-diphenylethylenediamine and careful reaction conditions[1]), **4** was obtained as a side product in the preparation of **3**. Heating of **3** in benzene under reflux led to **4**. $[\alpha]_D^{25} = +14.7$ ($c = 0.37$, CH_2Cl_2). IR (CH_2Cl_2): 3386*w*, 3150*w* (br.), 2988*w*, 2937*w*, 1709*s*, 1611*s*, 1582*m*, 1479*s*, 1388*m*, 1328*s*, 1215*m*, 1087*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO): see *Table 2*; additionally, 11.20 (br. *s*, NH); 8.03–8.01 (*m*, 2 arom. H); 7.63–7.59 (*m*, 1 arom. H); 7.55–7.50 (*m*, 2 arom. H); 6.82 (*d*, $J = 5.6$, irrad. at 5.20 → NOE of 4%, HO–C(5′)); 5.20 (irrad. at 6.82 → NOE of 8%, H–C(5′)); 5.07 (irrad. at 6.82 → NOE of 1.5%, H–C(3′)); 1.42, 1.21 (2*s*, Me_2C). ^{13}C-NMR (50 MHz, (D_6)DMSO): see *Table 3*; additionally, 165.6 (*s*, C=O); 133.3 (*s*); 132.5 (*d*); 128.5 (4*d*); 112.6 (*s*, Me_2C); 25.9, 24.5 (2*q*, *Me*$_2$C); 0.2 (*q*, Me_3Si). FAB-MS (NOBA): 410 (100, $[M+H]^+$).

N^6-*Benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-7*-C-*(trimethylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]adenine* (**5**) [3] *and* N^6-*Benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-7*-C-*(trimethylsilyl)-α*-L-talo-*hept-6-ynofuranosyl]adenine* (**6**) [3]. A soln. of (trimethylsilyl)acetylene (3.9 ml, 27.8 mmol) in THF (50 ml) was cooled to 0°, treated dropwise with 3.0M EtMgBr in Et_2O (9.3 ml, 27.9 mmol), stirred at 0° for 15 min and at 23° for 45 min, cooled to −15°, treated dropwise with a soln. of **3** (2.8 g, 6.8 mmol) in THF (50 ml), stirred for 1.5 h, treated with sat. aq. NH_4Cl soln. (50 ml), and allowed to warm to 23°. After evaporation, a soln. of the residue in AcOEt was washed with sat. aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:1) and crystallisation gave **5** (1.4 g, 40%) and **6** (0.7 g, 20%). Data of **5** and **6**: see [3].

N^6-*Benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-7*-C-*(trimethylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]-8-iodoadenine* (**7**). A soln. of (i-Pr)$_2$NH (5.8 ml, 41.4 mmol, distilled from CaH_2) in THF (100 ml) was cooled to −78°, treated dropwise with 1.60M BuLi in hexane (26.0 ml, 41.4 mmol), stirred at −78° for 15 min and at 0° for 15 min, cooled to −78°, treated dropwise with a soln. of **5** (3.2 g, 6.3 mmol) in THF (100 ml), stirred for 2 h, treated dropwise with a soln. of NIS (9.3 g, 41.4 mmol) in THF (100 ml), stirred for 2 h, treated with AcOH (6 ml), and allowed to warm to 23°. After evaporation, a soln. of the residue in AcOEt was washed with sat. aq. $NaHCO_3$ soln., sat. aq. $Na_2S_2O_3$ soln., and brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:1) gave **7** (3.5 g, 88%). White solid. R_f (AcOEt/hexane 1:1) 0.35. $[\alpha]_D^{25} = -84.5$ ($c = 1.0$, CH_2Cl_2). IR ($CHCl_3$): 3403*w*, 3181*m*, 3008*s*, 2181*w*, 1716*m* 1606*s*, 1423*s*, 1320*m*, 1088*s*, 929*m*, 849*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 9.11 (br. *s*, NH); 8.05–7.98 (*m*, 2 arom. H); 7.63–7.47 (*m*, 3 arom. H); 7.06 (*d*, $J = 1.6$, HO–C(5′)); 1.68, 1.39 (2*s*, Me_2C); 0.21 (*s*, Me_3Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 164.4 (*s*, C=O); 133.3 (*s*); 133.0 (*d*); 129.0 (2*d*); 127.9 (2*d*); 114.3 (*s*, Me_2C); 27.8, 25.5 (2*q*, *Me*$_2$C); 0.3 (*q*, Me_3Si). FAB-MS (NOBA): 634 (100, $[M+H]^+$). Anal. calc. for $C_{20}H_{29}N_5O_5Si$ (633.52): C 47.40, H 4.45, N 11.05; found: C 47.39, H 4.56, N 11.17.

N^6-*Benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-7*-C-*(trimethylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]-8-iodoadenine* (**8**). A soln. of pyridine (1.2 ml, 15 mmol, distilled from CaH_2) and **7** (2.0 g, 3.2 mmol) in CH_2Cl_2 (30 ml) was treated dropwise with TIPSOTf (1.77 ml, 6.6 mmol), stirred at 23° for 30 min, washed with brine (3 × 10 ml), dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:2) gave **8** (2.23 g, 89%). Yellow foam. R_f (AcOEt/hexane 1:2) 0.39. $[\alpha]_D^{25} = -3.3$ ($c = 1.0$, $CHCl_3$). UV (MeOH): 290 (23200). IR ($CHCl_3$): 3409*w*, 2893*w*, 2866*w*, 2160*w*, 1710*s*, 1609*s*, 1588*m*, 1461*m*, 1423*s*, 1320*m*, 1095*m*, 846*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 9.13 (br. *s*, NH); 8.01–7.98 (*m*, 2 arom. H); 7.63–7.48 (*m*, 3 arom. H); 1.62, 1.40 (2*s*, Me_2C); 1.10–1.05 (*m*, $(Me_2CH)_3Si$); 0.07 (*s*, Me_3Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 164.8 (*s*, C=O); 133.9 (*s*); 133.1 (*d*); 129.2 (2*d*); 128.1 (2*d*); 114.3 (*s*, Me_2C); 27.2, 25.4 (2*q*, *Me*$_2$C); 18.0 (*q*, $(Me_2CH)_3Si$); 12.4 (*d*, $(Me_2CH)_3Si$); −0.4 (*q*, Me_3Si). FAB-MS (NOBA): 790 (90, $[M+H]^+$).

9-[6,7-Dideoxy-2,3-O-*isopropylidene-5*-O-*(triisopropylsilyl)-7*-C-*(trimethylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]-8-iodoadenine* (**9**). At 25°, a soln. of **8** (600 mg, 0.76 mmol) in dry toluene (35 ml) was treated dropwise with a soln. of 8M $MeNH_2$ in MeOH (1.6 ml, 12.8 mmol), stirred for 2 h, diluted with AcOEt (10 ml), washed with sat. aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 3:1 → 1:1) and crystallisation from AcOEt/hexane gave **9** (441 mg, 85%). Colourless crystals. R_f (AcOEt/hexane 1:1) 0.51. M.p. 159.5–161°. $[\alpha]_D^{25} = -14.6$ ($c = 0.62$, CH_2Cl_2). UV (MeOH): 265 (15000). IR (CH_2Cl_2): 3513*w*, 3402*m*, 2947*m*, 2867*m*, 2172*w*, 1630*s*, 1584*m*, 1467*m*, 1377*m*, 1094*s*, 849*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 5.83 (br. *s*, NH_2); 1.61, 1.39 (2*s*, Me_2C); 1.10–1.05 (*m*, $(Me_2CH)_3Si$); 0.07 (*s*, Me_3Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 114.1 (*s*, Me_2C); 27.2, 25.5 (2*q*, *Me*$_2$C); 18.1 (*q*, $(Me_2CH)_3Si$); 12.5 (*d*, $(Me_2CH)_3Si$); 0.3 (*q*, Me_3Si). HR-MALDI-MS (DHB): 708.182 ($[M+Na]^+$, $C_{27}H_{44}IN_5NaO_5Si_2^+$; calc. 708.187). Anal. calc. for $C_{27}H_{44}IN_5O_5Si_2$ (685.75): C 47.29, H 6.47, N 10.21; found: C 47.19, H 6.33, N 10.10.

N^6-*Benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-β*-D-allo-*hept-6-ynofuranosyl]adenine* (**10**). A soln. of **5** (705 mg, 1.39 mmol) in dry THF (10 ml) was treated with a 1.0M soln. of TBAF in THF (1.42 ml, 1.42 mmol),

stirred for 45 min, treated dropwise with AcOH (0.09 ml), and evaporated. A soln. of the residue in AcOEt was washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 3:1) gave **10** (620 mg, quant.). White foam. R_f (AcOEt/hexane 3:1) 0.18. $[\alpha]_D^{25} = -111.7$ ($c = 0.75$, CH_2Cl_2). UV (MeOH): 279 (20300). IR ($CHCl_3$): 3393*w*, 3300*m*, 3198*m*, 3041*m*, 2989*w*, 1713*s*, 1610*s*, 1456*s*, 1329*m*, 1219*s*, 1089*s*, 957*m*, 851*m*. ^{1}H-NMR (300 MHz, CD_3OD): see *Table 2*; additionally, 8.07–8.04 (*m*, 2 arom. H); 7.65–7.50 (*m*, 3 arom. H); 2.18 (*d*, $J = 2.2$, H–C(7′)); 1.62, 1.39 (2*s*, Me_2C). ^{13}C-NMR (75 MHz, CD_3OD): see *Table 3*; additionally, 166.0 (*s*, C=O); 135.2 (*s*); 134.2 (*d*); 130.1 (2*d*); 129.8 (2*d*); 115.5 (*s*, Me_2C); 27.7, 25.6 (2*q*, Me_2C). FAB-MS (NOBA): 436 (100, $[M+H]^+$).

N^6-*Benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]adenine* (**11**). A soln. of pyridine (0.6 ml, 6.9 mmol, distilled from CaH_2) and **10** (530 mg, 1.22 mmol) in CH_2Cl_2 (100 ml) was treated dropwise with TIPSOTf (0.68 ml, 2.56 mmol), stirred at 23° for 1 h, washed with brine (3 × 10 ml), dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:2) gave **11** (637 mg, 88%). Colourless foam. R_f (AcOEt/hexane 1:1) 0.19. $[\alpha]_D^{25} = -32.2$ ($c = 1.1$, $CHCl_3$). UV ($ClCH_2CH_2Cl$): 280 (23900). IR ($CHCl_3$): 3409*w*, 3304*m*, 2999*w*, 2946*m*, 2893*m*, 2868*m*, 2110*w*, 1709*s*, 1612*s*, 1585*m*, 1456*s*, 1091*s*, 883*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 9.20 (br. *s*, NH); 8.04–7.99 (*m*, 2 arom. H); 7.59–7.45 (*m*, 3 arom. H); 2.42 (*d*, $J = 2.1$, H–C(7′)); 1.64, 1.41 (2*s*, Me_2C); 1.10–1.05 (*m*, $(Me_2CH)_3Si$). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 164.9 (*s*, C=O); 135.6 (*s*); 133.0 (*d*); 129.1 (2*d*); 128.1 (2*d*); 115.0 (*s*, Me_2C); 27.3, 25.4 (2*q*, Me_2C); 18.0 (*q*, $(Me_2CH)_3Si$); 12.4 (*d*, $(Me_2CH)_3Si$). FAB-MS (NOBA): 592 (100, $[M+H]^+$). Anal. calc. for $C_{31}H_{41}N_5O_5Si$ (591.78): C 62.92, H 6.98, N 11.83; found: C 62.92, H 6.92, N 11.65.

9-[6,7-Dideoxy-2,3-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]adenine* (**12**). At 25°, a soln. of **11** (0.8 g, 1.35 mmol) in dry toluene (30 ml) was treated dropwise with a soln. of 8M $MeNH_2$ in MeOH (1.62 ml, 13.0 mmol), stirred for 4 h, washed with sat. aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated. FC (25 g of silica gel; AcOEt/hexane 3:2 → 3:1) gave **12** (585 mg, 89%). White foam. R_f (AcOEt/hexane 1:1) 0.15. $[\alpha]_D^{25} = -21.7$ ($c = 0.38$, CH_2Cl_2). UV (MeOH): 258 (12300). IR (CH_2Cl_2): 3514*m*, 3403*m*, 3300*w*, 2946*m*, 2868*m*, 1630*s*, 1586*w*, 1470*m*, 1376*m*, 1209*w*, 1097*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 6.24 (br. *s*, NH_2); 2.42 (*d*, $J = 2.2$, H–C(7′)); 1.61, 1.38 (2*s*, Me_2C); 1.10–1.05 (*m*, $(Me_2CH)_3Si$). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 3*; additionally, 114.8 (*s*, Me_2C); 27.3, 25.5 (2*q*, Me_2C); 18.1 (*q*, $(Me_2CH)_3Si$); 12.5 (*d*, $(Me_2CH)_3Si$). HR-MALDI-MS (DHB): 488.262 ($[M+H]^+$, $C_{24}H_{38}N_5O_4Si^+$; calc. 488.269). Anal. calc. for $C_{24}H_{37}N_5O_4Si$ (487.67): C 59.11, H 7.65, N 14.36; found: C 58.94, H 7.78, N 14.29.

N^6-*Benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-7*-C-*(trimethylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]adenin-8-yl-(8 → 7′*-C*)-1-[6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]uracil-6-yl-(6 → 7′*-C*)-1-(6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl)uracil* (**14**). A soln. of **13** [2] (142 mg, 0.15 mmol), **8** (182 mg, 0.23 mmol), $[Pd_2(dba)_3]$ (70 mg, 82 μmol), CuI (16 mg, 84 μmol), and P(fur)$_3$ (20 mg, 86 μmol) in degassed Et_3N/toluene 1:1 (10 ml) was stirred for 24 h at 23° and evaporated. FC (AcOEt/hexane 2:3 → 1:2) gave **14** (120 mg, 49%). Yellow foam. R_f (AcOEt/hexane 1:1) 0.20. ^{1}H-NMR (500 MHz, $CDCl_3$): see *Table 4*; additionally, 9.74 (br. *s*, 2 NH); 9.64 (br. *s*, NH); 8.02–8.00 (*m*, 2 arom. H); 7.59–7.56 (*m*, 1 arom. H); 7.50–7.46 (*m*, 2 arom. H); 1.61, 1.57, 1.55, 1.40, 1.33 (6 H) (5*s*, 3 Me_2C); 1.21–1.04 (*m*, 3 $(Me_2CH)_3Si$); 0.07 (*s*, Me_3Si). HR-MALDI-MS (DHB): 1610.754 ($[M+Na]^+$, $C_{80}H_{117}N_9NaO_{17}Si_4^+$; calc. 1610.754).

N^6-*Benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]adenin-8-yl-(8 → 7′*-C*)-1-(6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl)uracil-6-yl-(6 → 7′*-C*)-1-(6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl)uracil* (**15**). A soln. of **14** (49 mg, 31 μmol) in MeOH/AcOEt 1:1 (8 ml) was treated dropwise with a soln. of $AgNO_3$ (78 mg, 0.46 mmol) in H_2O/MeOH 1:1 (1 ml), stirred at 23° under exclusion of light for 4 h, treated with a soln. of KCN (78 mg, 1.2 mmol) in H_2O (0.3 ml), and stirred for 1 h. After evaporation, a soln. of the residue in AcOEt was washed with brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 2:3) gave **15** (22 mg, 47%). Yellow foam. R_f (AcOEt/hexane 1:1) 0.20. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 4*; additionally, 9.74, 9.64, 8.92 (3 br. *s*, 3 NH); 8.03–8.01 (*m*, 2 arom. H); 7.61–7.46 (*m*, 3 arom. H); 2.29 (*d*, $J = 1.9$, H–C(7′/III)); 1.61, 1.57, 1.55, 1.40, 1.33 (6 H) (5*s*, 3 Me_2C); 1.21–1.04 (*m*, 3 $(Me_2CH)_3Si$). MALDI-MS (IAA): 1540.5 ($[M+Na]^+$).

9-[6,7-Dideoxy-2,3-O-*isopropylidene-5*-O-*(triisopropylsilyl)-7*-C-*(trimethylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]adenin-8-yl-(8 → 7′*-C*)-1-(6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl)uracil-6-yl-(6 → 7′*-C*)-1-(6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl)uracil* (**16**). A soln. of **13** (193 mg, 0.21 mmol), **9** (200 mg, 0.29 mmol), $[Pd_2(dba)_3]$ (80 mg, 80 μmol), CuI (30 mg, 0.16 mmol), and P(fur)$_3$ (37 mg, 0.16 mmol) in degassed Et_3N/toluene 1:1 (30 ml) was stirred for 24 h at 23°. After evaporation, FC (AcOEt/hexane 2:5 → 2:1) gave **16** (116 mg, 38%). Yellow foam.

Table 4. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Mixed Trimers* **14**–**17** *in $CDCl_3$*

	14[a])	**15**[b])	**16**[b])	**17**[b])		**14**	**15**	**16**	**17**
H–C(5/I)	5.80	5.77	6.13	6.08					
H–C(6/I)	7.47	7.44	7.37	7.36					
H–C(1′/I)	5.58	5.59	5.59	5.59	*J*(1′,2′/I)	1.6	1.9	0	1.2
H–C(2′/I)	4.94	4.93	5.21	5.23	*J*(2′,3′/I)	6.3	6.5	6.3	6.6
H–C(3′/I)	4.87	4.88	5.05	5.05	*J*(3′,4′/I)	2.5	2.8	2.7	2.8
H–C(4′/I)	4.34	4.31	4.32	4.31	*J*(4′,5′/I)	6.2	6.2	7.6	7.0
H–C(5′/I)	5.04	5.03	4.99	5.00					
H–C(5/II)	5.85	5.86	5.80	5.81					
H–C(1′/II)	6.14	6.16	6.24	6.24	*J*(1′,2′/II)	< 1	< 1	1.6	1.6
H–C(2′/II)	5.17	5.18	5.23	5.19	*J*(2′,3′/II)	6.2	6.2	6.5	6.4
H–C(3′/II)	5.08	5.08	5.08	5.07	*J*(3′,4′/II)	3.7	3.7	3.2	3.2
H–C(4′/II)	4.25	4.23	4.22	4.20	*J*(4′,5′/II)	8.1	8.1	8.3	8.2
H–C(5′/II)	5.01	5.01	5.03	5.03					
H–C(2/III)	8.78	8.78	8.25	8.25					
H–C(1′/III)	6.33	6.33	6.35	6.34	*J*(1′,2′/III)	1.6	1.9	1.5	1.6
H–C(2′/III)	5.61	5.66	5.61	5.70	*J*(2′,3′/III)	6.2	6.4	6.4	6.4
H–C(3′/III)	5.37	5.36	5.32	5.32	*J*(3′,4′/III)	3.1	3.1	3.2	3.2
H–C(4′/III)	4.19	4.21	4.12	4.14	*J*(4′,5′/III)	8.4	8.1	8.4	8.1
H–C(5′/III)	4.69	4.75	4.60	4.63	*J*(5′,7′/III)	–	2.2	–	2.1
H–C(7′/III)	–	2.29	–	2.26					

[a]) Assignment based on a DQF-COSY spectrum. [b]) Assignment based on selective homodecoupling experiments.

Table 5. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the Trimers* **16** *and* **17** *in $CDCl_3$*

	16	**17**		**16**	**17**
C(2/I–II)	164.8, 162.0	164.8, 162.0	C(2/III)	153.3	153.3
C(4/I–II)	150.6, 149.6	150.6, 149.6	C(4/III)	148.6	148.6
C(5/I)	103.5	103.4	C(5/III)	119.6	119.6
C(5/II)	107.6	107.6			
C(6/I)	142.9	142.9	C(6/III)	155.8	155.8
C(6/II)	137.5	137.5	C(8/III)	134.6	136.6
C(1′/I–II)	96.4, 95.1	96.4, 95.1	C(1′/III)	90.9	90.9
C(2′/I–III)	84.5, 83.9, 83.3	84.5, 83.8, 83.18			
C(3′/I–III)	83.2, 82.9, 82.3	83.18, 82.6, 82.2			
C(4′/I–III)	90.8, 90.7, 90.3	90.7, 90.6, 90.2			
C(5′/I–III)	64.1, 64.0, 63.8	64.1, 64.0, 63.1			
C(6′/I)	102.2	102.2	C(6′/III)	104.9	82.8
C(6′/II)	95.6	95.6			
C(7′/I)	76.4	76.4	C(7′/III)	90.4	73.9
C(7′/II)	74.2	74.2			

R_f (AcOEt/hexane 1:1) 0.33. IR (CH_2Cl_2): 3371*w* (br.), 3200*w*, 2945*m*, 2867*m*, 2235*w*, 2167*w*, 1698*s*, 1636*s*, 1599*w*, 1447*m*, 1383*m*, 1328*w*, 1213*m*, 1096*s*, 1067*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): see *Table 4*; additionally, 11.75, 9.45 (2 br. *s*, 2 NH); 7.07 (br. *s*, NH_2); 1.60, 1.58, 1.55, 1.37, 1.36, 1.35 (6*s*, 3 Me_2C); 1.21–1.06 (*m*, 3 $(Me_2CH)_3Si$); 0.06 (*s*, Me_3Si). ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 5*; additionally, 113.83, 113.66, 113.56

(3*s*, 3 Me_2C); 27.2, 27.1, 26.9, 25.3, 25.1, 24.9 (6*q*, 3 Me_2C); 18.09, 18.03, 17.93 (3*q*, 3 $(Me_2CH)_3Si$); 12.51, 12.46, 12.29 (3*d*, 3 $(Me_2CH)_3Si$); −0.35 (*s*, Me_3Si). HR-MALDI-MS (DHB): 1506.728 ($[M+Na]^+$, $C_{73}H_{113}N_9NaO_{16}Si_4^+$; calc. 1506.728). Anal. calc. for $C_{73}H_{113}N_9O_{16}Si_4$ (1485.09): C 59.04, H 7.67, N 8.49; found: C 59.10, H 7.50, N 8.47.

9-[6,7-Dideoxy-2,3-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]adenin-8-yl-(8 → 7′*-C*)-1-(6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl)uracil-6-yl-(6 → 7′*-C*)-1-(6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl)uracil* (**17**). A soln. of **16** (116 mg, 78 μmol) in MeOH/AcOEt 1:1 (50 ml) was treated dropwise with a soln. of $AgNO_3$ (395 mg, 2.34 mmol) in H_2O (5 ml), stirred at 23° under exclusion of light for 3.5 h, treated with a soln. of KCN (380 mg, 5.9 mmol) in H_2O (6 ml), and stirred for 1 h. After evaporation, a soln. of the residue in AcOEt was washed with brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:1 → 2:1) gave **17** (82 mg, 74%). Colourless crystals. R_f (AcOEt/hexane 1:1) 0.29. IR (CH_2Cl_2): 3370*w* (br.), 3303*w*, 3201*w*, 2945*m*, 2868*m*, 2235*w*, 1698*s*, 1636*m*, 1448*m*, 1383*m*, 1213*m*, 1097*m*, 1067*m*, 882*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): see *Table 4*; additionally, 11.6, 9.4 (2 br. *s*, 2 NH); 7.02 (br. *s*, NH_2); 2.26 (*d*, *J* = 2.2, H−C(7′/III)); 1.60, 1.59, 1.55, 1.37 (6 H), 1.35 (5*s*, 3 Me_2C); 1.21–1.06 (*m*, 3 $(Me_2CH)_3Si$). ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 5*; additionally, 113.91, 113.76, 113.69 (3*s*, 3 Me_2C); 27.18, 27.11, 26.93, 25.23, 25.1, 24.9 (6*q*, 3 Me_2C); 18.08, 18.06, 17.99 (6 C), 17.94, 17.92 (5*q*, 3 $(Me_2CH)_3Si$); 12.5, 12.4, 12.3 (3*d*, 3 $(Me_2CH)_3Si$). HR-MALDI-MS (DHB): 1434.686 ($[M+Na]^+$, $C_{70}H_{105}N_9NaO_{16}Si_3^+$; calc. 1434.688). Anal. calc. for $C_{70}H_{105}N_9O_{16}Si_3$ (1412.91): C 59.51, H 7.49, N 8.92; found: C 59.44, H 7.45, N 8.71.

2′,3′-O-*Isopropylidene-5′*-O-*(triethylsilyl)adenosin-8-yl-(8 → 7′*-C*)-9-[6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]adenin-8-yl-(8 → 7′*-C*)-1-(6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl)uracil-6-yl-(6 → 7′*-C*)-1-(6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl)uracil* (**21**). A soln. of **17** (40 mg, 28 μmol), **19** [3] (46.5 mg, 85 μmol), $[Pd_2(dba)_3]$ (4 mg, 4.2 μmol), CuI (1.6 mg, 8.2 μmol), and P(fur)$_3$ (1.9 μg, 8.2 μmol) in degassed Et_3N/toluene 1:1 (2 ml) was stirred for 24 h at 23° and evaporated. FC (AcOEt/hexane 2:5 → 2:1) gave **21** (26 mg, 50%). Yellow foam. R_f (AcOEt/hexane 1:1) 0.22. $[\alpha]_D^{25} = +101.8$ (*c* = 0.61, CH_2Cl_2). UV (CH_2Cl_2): 297 (43600). IR (CH_2Cl_2): 3471*w*, 3401*w*, 3317*w*, 3182*w*, 2946*m*, 2868*m*, 1697*s*, 1634*m*, 1602*w*, 1458*m*, 1383*m*, 1328*w*, 1218*m*, 1081*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): see *Table 6*; additionally, 11.60, 8.00 (2 br. *s*, 2 NH); 6.45, 6.35 (2 br. *s*, 2 NH_2); 1.64, 1.58, 1.56, 1.54, 1.45 (6 H), 1.40, 1.38 (7*s*, 4 Me_2C); 1.21–1.06 (*m*, 3 $(Me_2CH)_3Si$); 0.86 (*t*, *J* = 7.8, $(MeCH_2)_3Si$); 0.47 (*q*, *J* = 7.8, $(MeCH_2)_3Si$). ^{13}C-NMR (125 MHz, $CDCl_3$): see *Table 7*; additionally, 113.9, 113.8, 113.7, 113.5 (4*s*, 4 Me_2C); 27.3, 27.2 (2 C), 27.1, 25.6 (2 C), 25.2, 25.1 (6*q*, 4 Me_2C); 17.97 (12 C), 17.93 (2*q*, 3 $(Me_2CH)_3Si$); 13.51, 12.97, 12.76 (3*d*, 3 $(Me_2CH)_3Si$); 6.6 (*q*, $(MeCH_2)_3Si$); 4.2 (*t*, $(MeCH_2)_3Si$). HR-MALDI-MS (DHB): 1853.885 ($[M+Na]^+$, $C_{89}H_{134}N_{14}NaO_{20}Si_4^+$; calc. 1853.887).

N^6-*Benzoyl-2′,3′*-O-*isopropylidene-5′*-O-*(triethylsilyl)adenosin-8-yl-(8 → 7′*-C*)-*N^6-*benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-β*-D-allo-*hept-6-ynofuranosyl]adenine* (**22**). A soln. of **18** [3] (1.79 g, 2.75 mmol), **10** (1.0 g,

Table 6. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Mixed Tetramers* **21** *and* **32** (assignment based on a DQF-COSY spectrum of **21** and **32**, and a HMBC spectrum of **32**)

	21 ($CDCl_3$)				**32** ($CDCl_3$/CD_3OD 9:1)			
	Unit IV	Unit III	Unit II	Unit I	Unit IV	Unit III	Unit II	Unit I
H−C(5)	–	–	5.86	5.84[a])	6.06	6.12[b])	–	–
H−C(2)	8.26	8.28	–	–	–	–	8.19	8.25[c])
H−C(1′)	6.10	6.16	6.34	5.49	6.20	6.10	6.35	6.23 (br.)
H−C(2′)	5.63[d])	5.63[d])	5.31	5.26	5.19	5.16	5.60	5.75 (br.)
H−C(3′)	5.13	5.39	5.00	4.98	4.84	5.00	5.31	5.29
H−C(4′)	4.19	4.29	4.12	4.32	4.11	4.06	4.31	4.46
H−C(5′)	3.69, 3.58	4.88	5.09	5.07	3.84	4.97	5.21	5.02
J(1′,2′)	1.4	0	1.0	1.0	0.9	0.9	1.9	1.8
J(2′,3′)	6.2	6.2	6.5	6.5	6.4	6.3	6.2	6.2
J(3′,4′)	3.9	5.0	3.4	2.9	4.5	5.1	3.2	2.4
J(4′,5′)	6.8, 6.8	7.0	6.3	6.3	6.3, 6.3	6.2	7.6	7.1

[a]) H−C(6/I) at 7.34 ppm. [b]) Broad signal. [c]) H−C(8/I) at 8.11 ppm. [d]) Overlapping signals.

Table 7. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the Tetramers* **21** *and* **32** (assignment of **32** based on a HMBC spectrum)

		21 ($CDCl_3$)	**32** ($CDCl_3/CD_3OD$ 9:1)
C(2/I–IV)	U-Units	164.3, 162.8	163.6 (2 C)
	A-Units	153.2 (2 C)	153.4, 152.6
C(4/I–IV)	U-Units	150.5, 150.3	150.1 (2 C)
	A-Units	148.5 (2 C)	148.8 (I), 148.5 (II)
C(5/I–IV)	U-Units	102.8 (I), 108.7 (II)	109.4, 108.7
	A-Units	119.7, 119.6	119.8, 119.4
C(6/I–IV)	U-Units	143.3 (I), 137.1 (II)	138.0 (IV), 137.3 (III)
	A-Units	155.5, 155.4	155.8 (I), 155.6 (II)
C(8/I–IV)	A-Units	134.9, 134.5	140.7 (I), 133.9 (II)
C(1′/I–IV)		90.5, 90.4, 90.1, 90.0	93.9 (IV), 93.6 (III), 91.4 (I), 90.9 (II)
C(2′/I–IV)		84.0, 83.7, 83.5, 83.3	84.4, 84.0, 83.7, 83.0
C(3′/I–IV)		83.1, 82.6 (2 C), 82.3	82.33 (2 C), 82.26, 81.7 (IV)
C(4′/I–IV)		89.8, 88.4 (3 C)	90.9, 89.9, 89.6, 89.5
C(5′/I–III)		64.3, 64.2, 64.0	64.3 (III), 63.9 (I, II)
C(5′/IV)		63.0	64.4
C(6′/I–III)		97.7, 95.2, 95.0	101.7 (III), 101.5 (II), 95.2 (I)
C(7′/I–III)		74.5, 73.9 (2 C)	75.85 (III), 75.75 (II), 74.5 (I)

2.29 mmol), $[Pd_2(dba)_3]$ (156.6 mg, 0.171 mmol), CuI (45.3 mg, 0.24 mmol), and P(fur)$_3$ (55.7 mg, 0.24 mmol) in degassed Et_3N/toluene 1:1 (100 ml) was stirred for 22 h at 23° and evaporated. FC (AcOEt/hexane 2:1 → 3:1) gave **22** (1.26 g, 57%). Yellow foam. R_f (AcOEt/hexane 3:1) 0.23. $[\alpha]_D^{25} = -82.9$ ($c = 0.53$, $CHCl_3$). UV (CH_2Cl_2): 313 (sh), 302 (sh), 291 (32000). IR ($CHCl_3$): 3397*w*, 3110*w* (br.), 2955*m*, 1713*s*, 1608*s*, 1458*s*, 1331*m*, 1237*m*, 1089*m*. ^{1}H-NMR (500 MHz, (D_6)DMSO): see *Table 8*; additionally, 11.30, 11.20 (2 br. *s*, 2 NH); 8.05–8.03 (*m*, 4 arom. H); 7.67–7.63 (*m*, 2 arom. H); 7.57–7.53 (*m*, 4 arom. H); 6.71 (*d*, $J = 6.0$, HO–C(5′/I)); 1.60, 1.53, 1.38, 1.31 (4*s*, 2 Me_2C); 0.79 (*t*, $J = 7.8$, $(MeCH_2)_3Si$); 0.42 (*q*, $J = 7.8$, $(MeCH_2)_3Si$). ^{13}C-NMR (125 MHz, (D_6)DMSO): see *Table 9*; additionally, 165.5 (*s*, 2 C=O); 133.3, 133.1 (2*s*); 132.5, 132.4 (2*d*); 128.6 (2*d*); 128.5 (2*d*); 128.42 (2*d*); 128.40 (2*d*); 113.4, 113.3 (2*s*, 2 Me_2C); 26.9, 25.2 (2*q*, 2 Me_2C); 6.4 (*q*, $(MeCH_2)_3Si$); 3.7 (*t*, $(MeCH_2)_3Si$). FAB-MS (NOBA): 959 (100, $[M+H]^+$).

Table 8. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Dimeric Adenosine Derivatives* **22**–**24** *in (D_6)DMSO*

	22[a])	**23**[a])	**24**[b])		**22**	**23**	**24**
H–C(2/I)	8.78	8.65	8.49				
H–C(8/I)	8.66	–	–				
H–C(1′/I)	6.39	6.17	6.10	*J*(1′,2′/I)	2.6	2.4	1.8
H–C(2′/I)	5.51	5.71	5.47	*J*(2′,3′/I)	6.2	6.3	6.3
H–C(3′/I)	5.26	5.34	5.15	*J*(3′,4′/I)	2.5	3.2	2.8
H–C(4′/I)	4.39	4.30	4.15	*J*(4′,5′/I)	6.1	8.0	8.8
H–C(5′/I)	4.91	4.88	4.80				
H–C(2/II)	8.76	8.76	–				
H–C(1′/II)	6.25	6.21	6.01	*J*(1′,2′/II)	2.1	2.3	2.9
H–C(2′/II)	5.68	5.62	5.62	*J*(2′,3′/II)	6.3	6.3	6.6
H–C(3′/II)	5.09	5.04	4.87	*J*(3′,4′/II)	3.5	3.5	4.0
H–C(4′/II)	4.16	4.14	4.00	*J*(4′,5a′/II)	6.0	5.9	6.0
H_a–C(5′/II)	3.72	3.73	3.50	*J*(4′,5b″/II)	6.9	6.9	6.0
H_b–C(5′/II)	3.64	3.65	3.46	*J*(5a′,5b″/II)	11.0	10.9	11.3

[a]) Assignment based on a DQF-COSY spectrum. [b]) Assignment based on selective homodecoupling experiments.

Table 9. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the Dimeric Adenosine Derivatives* **22**–**24** *in (D$_6$)DMSO* (assignment of **22** and **23** based on a HSQC-GRASP spectrum)

	22	**23**	**24**		**22**	**23**	**24**
C(2/II)	151.7	152.5	157.6	C(2/I)	152.6	151.3	149.73
C(4/II)	150.5	149.2	149.75	C(4/I)	150.5	150.6	149.68
C(5/II)	124.8	127.7	116.8	C(5/I)	125.6	127.9	131.4
C(6/II)	150.7	150.8	151.0	C(6/I)	150.8	152.0	152.5
C(8/II)	135.6	135.6	138.7	C(8/I)	143.1	109.3	112.5
C(1′/II)	89.5	93.0	88.5	C(1′/I)	89.9	89.4	88.9
C(2′/II)	82.5	82.3	82.3	C(2′/I)	83.5	82.4	82.4
C(3′/II)	81.2	81.3	81.5	C(3′/I)	81.3	81.8	80.9
C(4′/II)	87.4	88.2	86.2	C(4′/I)	88.0	87.2	86.6
C(5′/II)	62.6	61.7	61.4	C(5′/I)	61.7	62.6	61.9
				C(6′/I)	96.8	97.3	96.6
				C(7′/I)	73.5	73.1	73.6

N^6-*Benzoyl-2′,3′*-O-*isopropylidene-5′*-O-*(triethylsilyl)adenosin-8-yl-(8 → 7′*-C)-N^6-*benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-β*-D-allo-*hept-6-ynofuranosyl]-8-iodoadenine* (**23**). A soln. of 2,2,6,6-tetramethylpiperidine (TMP; 0.79 ml, 4.48 mmol) in THF (25 ml) was cooled to −78°, treated dropwise with 1.40M n-BuLi in hexane (3.2 ml, 4.5 mmol), stirred at −78° for 15 min and at 0° for 15 min, treated dropwise with HMPA (1.59 ml, 8.96 mmol), cooled to −78°, treated dropwise with a soln. of **22** (540 mg, 0.56 mmol) in THF (2 ml), stirred for 20 min, treated dropwise with a soln. of NIS (980 mg, 4.48 mmol) in THF (2 ml), stirred for 10 min, treated with sat. aq. NH_4Cl soln. (20 ml), and allowed to warm to 23°. After evaporation, a soln. of the residue in AcOEt was washed with sat. aq. $NaHCO_3$ soln., sat. aq. $Na_2S_2O_3$ soln., and brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 2:1) gave **23** (470 mg, 77%). Yellow solid. R_f (AcOEt/hexane 3:1) 0.48. $[\alpha]_D^{25} = -80.3$ ($c = 0.57$, CH_2Cl_2). UV (CH_2Cl_2): 313 (sh), 302 (sh), 293 (46000). IR (CH_2Cl_2): 3392*w*, 3185*w* (br.), 2954*w*, 1714*m*, 1605*s*, 1468*s*, 1326*w*, 1089*m*. ^{1}H-NMR (500 MHz, (D_6)DMSO): see *Table 8*; additionally, 11.35 (br. *s*, 2 NH); 8.05–8.02 (*m*, 4 arom. H); 7.67–7.63 (*m*, 2 arom. H); 7.56–7.53 (*m*, 4 arom. H); 6.62 (*d*, $J = 6.6$, HO–C(5′/I)); 1.61, 1.52, 1.37, 1.29 (4*s*, 2 Me_2C); 0.79 (*t*, $J = 7.8$, ($MeCH_2)_3Si$); 0.42 (*q*, $J = 7.8$, ($MeCH_2)_3Si$). ^{13}C-NMR (125 MHz, (D_6)DMSO): see *Table 9*; additionally, 165.5 (*s*, 2 C=O); 133.2 (2*s*); 132.5 (2*d*); 128.5 (4*d*); 128.4 (4*d*); 113.7, 113.4 (2*s*, 2 Me_2C); 27.1, 26.9, 25.3, 25.2 (4*q*, 2 Me_2C); 6.4 (*q*, ($MeCH_2)_3Si$); 3.7 (*t*, ($MeCH_2)_3Si$). FAB-MS (NOBA): 1085 (100, $[M+H]^+$). Anal. calc. for $C_{48}H_{53}IN_{10}O_{10}Si$ (1085.00): C 53.14, H 4.92, N 12.91; found: C 53.28 H 5.10, N 12.80.

N^6-*Benzoyl-2-(diisopropylamino)-2′,3′*-O-*isopropylidene-5′*-O-*(triethylsilyl)adenosin-8-yl-(8 → 7′*-C)-N^6-*benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-β*-D-allo-*hept-6-ynofuranosyl]-8-iodoadenine* (**24**). The iodination of **22** with 8 equiv. of LDA and NIS gave **23** (36%), **22** (30%), and **24** (10%).

Data of **24**: Yellow solid. R_f (AcOEt/hexane 3:1) 0.71. $[\alpha]_D^{25} = -32.2$ ($c = 0.62$, CH_2Cl_2). IR (CH_2Cl_2): 3367*m*, 2965*w*, 1745*m*, 1693*m*, 1630*m*, 1580*m*, 1509*s*, 1484*m*, 1376*m*, 1334*m*, 1220*m*, 1079*m*. ^{1}H-NMR (400 MHz, (D_6)DMSO): see *Table 8*; additionally, 11.32, 10.77 (2 br. *s*, 2 NH); 8.03–7.99 (*m*, 2 arom. H); 7.96–7.94 (*m*, 2 arom. H); 7.65–7.60 (*m*, 2 arom. H); 6.60 (*d*, $J = 6.5$, HO–C(5′/I)); 7.58–7.49 (*m*, 4 arom. H); 1.54, 1.50, 1.33, 1.27 (4*s*, 2 Me_2C); 1.27–1.18 (*m*, ($Me_2CH)_2N$); 0.89 (*t*, $J = 7.8$, ($MeCH_2)_3Si$); 0.48 (*q*, $J = 7.8$, ($MeCH_2)_3Si$). ^{13}C-NMR (100 MHz, (D_6)DMSO): see *Table 9*; additionally, 165.8, 165.5 (2*s*, 2 C=O); 133.9, 133.8 (2*s*); 132.5, 132.2 (2*d*); 128.47 (2*d*); 128.43 (2*d*); 128.37 (2*d*); 128.33 (2*d*); 113.6, 113.0 (2*s*, 2 Me_2C); 45.7 (*d*, ($Me_2CH)_2N$); 27.0, 26.8, 25.2, 25.0 (4*q*, 2 Me_2C); 20.2, 20.1 (2*d*, ($Me_2CH)_2N$); 6.7 (*q*, ($MeCH_2)_3Si$); 5.9 (*t*, ($MeCH_2)_3Si$). FAB-MS (NOBA): 1184 (100, $[M+H]^+$).

N^6-*Benzoyl-2′,3′*-O-*isopropylidene-5′*-O-*(triethylsilyl)adenosin-8-yl-(8 → 7′*-C)-N^6-*benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triethylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]-8-iodoadenine* (**25**) [5]. A soln. of **23** (330 mg, 0.30 mmol) and 1*H*-imidazole (82 mg, 1.20 mmol) in dry DMF (5.0 ml) was treated dropwise with Et_3SiCl (0.10 ml, 0.60 mmol), stirred for 45 min at 25°, and poured into ice-water (*ca.* 10 ml). After extraction with Et_2O/AcOEt 1:1 (2 × 20 ml), the combined org. layers were washed with brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 2:1) gave **25** (308 mg, 86%). White foam. Data of **25**: see [5].

N^6-*Benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-7*-C-*(trimethylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]adenine-8-yl-(8 → 7′*-C)-N^6-*benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsil-*

yl)-β-D-allo-*hept-6-ynofuranosyl]adenine* (**26**). A soln. of **8** (767 mg, 0.97 mmol), **11** (500 mg, 0.84 mmol), $[Pd_2(dba)_3]$ (80 mg, 0.084 mmol), CuI (22.4 mg, 0.118 mmol), and $P(fur)_3$ (27.2 mg, 0.118 mmol) in degassed Et_3N/toluene 1:1 (30 ml) was stirred for 24 h at 23° and evaporated. FC (AcOEt/hexane 1:1 → 2:1) gave **26** (806 mg, 76%). Yellow foam. R_f (AcOEt/hexane 1:1) 0.21. $[\alpha]_D^{25} = +13.5$ ($c = 0.77$, CH_2Cl_2). UV (CH_2Cl_2): 315 (sh), 302 (sh), 284 (39000). IR (CH_2Cl_2): 3399*m*, 2947*m*, 2868*m*, 2235*w*, 2175*w*, 1712*s*, 1608*s*, 1458*s*, 1331*m*, 1096*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): see *Table 10*; additionally, 9.30, 9.15 (2 br. *s*, 2 NH); 7.99–7.94 (*m*, 4 arom. H); 7.58–7.49 (*m*, 2 arom. H); 7.47–7.43 (*m*, 4 arom. H); 1.65, 1.57, 1.42, 1.35 (4*s*, 2 Me_2C); 1.18–1.03 (*m*, 2 $(Me_2CH)_3Si$); 0.04 (*s*, Me_3Si). ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 11*; additionally, 164.54, 164.46 (2*s*, 2 C=O); 133.7 (2*s*); 132.8 (2*d*); 128.84 (2*d*); 128.82 (2*d*); 127.90 (2*d*); 127.82 (2*d*); 114.92, 114.01 (2*s*, 2 Me_2C); 27.2, 27.1, 25.4, 25.2 (4*q*, 2 Me_2C); 18.0 (*q*, 2 $(Me_2CH)_3Si$); 12.41, 12.38 (2*d*, 2 $(Me_2CH)_3Si$); −0.4 (*q*, Me_3Si). FAB-MS (NOBA): 1253 (100, $[M+H]^+$). Anal. calc. for $C_{65}H_{88}N_{10}O_{10}Si_3$ (1253.73): C 62.27, H 7.07, N 11.17; found: C 62.23, H 7.10, N 10.92.

Table 10. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Dimeric Adenosine Derivatives* **26**–**29** *in $CDCl_3$* (assignment based on selective homodecoupling experiments)

	26	**27**	**28**	**29**		**26**	**27**	**28**	**29**
H–C(2/II)	8.75	8.75	8.22	8.23	H–C(2/I)	8.80	8.80	8.30	8.31
H–C(1′/II)	6.25	6.26	6.19	6.20	H–C(8/I)	8.31	8.30	8.17	8.15
H–C(2′/II)	5.62	5.67	5.57	5.61	H–C(1′/I)	6.25	6.25	6.54	6.44
H–C(3′/II)	5.28	5.28	5.30	5.29	H–C(2′/I)	5.46	5.49	5.71	5.71
H–C(4′/II)	4.17	4.21	4.15	4.19	H–C(3′/I)	5.29	5.31	5.33	5.30
H–C(5′/II)	4.67	4.75	4.69	4.78	H–C(4′/I)	4.49	4.49	4.52	4.51
J(1′,2′/II)	1.8	2.3	1.7	1.9	H–C(5′/I)	5.10	5.13	4.98	4.93
J(2′,3′/II)	5.2	6.4	6.4	6.4	*J*(1′,2′/I)	1.8	2.5	1.7	1.8
J(3′,4′/II)	3.1	3.1	3.1	3.1	*J*(2′,3′/I)	5.1	6.4	6.4	6.3
J(4′,5′/II)	8.1	8.0	8.5	8.0	*J*(3′,4′/I)	3.1	3.1	2.5	2.1
J(5′,7′/II)	–	2.1	–	2.1	*J*(4′,5′/I)	6.2	6.5	8.3	8.5

Table 11. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the Dimeric Adenosine Derivatives* **26**–**29** *in $CDCl_3$*

	26	**27**	**28**	**29**		**26**	**27**	**28**	**29**
C(2/II)	152.9	152.9	153.1	153.0	C(2/I)	153.6	153.6	154.0	153.9
C(4/II)	149.7	149.7	148.7	148.7	C(4/I)	149.8	149.8	149.6	149.1
C(5/II)	122.6	122.6	119.5	119.6	C(5/I)	123.3	123.4	120.3	120.3
C(6/II)	150.3	150.2	155.89	153.9	C(6/I)	151.1	151.0	155.91	155.8
C(8/II)	136.0	136.5	133.7	133.8	C(8/I)	142.5	142.6	140.8	140.7
C(1′/II)	90.9	91.1	90.8	90.9	C(1′/I)	91.1	91.2	91.5	91.5
C(2′/II)	82.8	82.8	83.3	83.2	C(2′/I)	83.9	83.9	83.8	83.7
C(3′/II)	81.5	82.4	82.8	82.56	C(3′/I)	82.5	82.7	82.9	82.64
C(4′/II)	89.1	89.2	90.1	90.0	C(4′/I)	90.1	89.9	90.5	90.2
C(5′/II)	63.6	63.0	63.8	63.1	C(5′/I)	64.0	64.0	64.0	64.0
C(6′/II)	104.5	81.7	105.0	83.1	C(6′/I)	96.0	96.1	94.9	95.0
C(7′/II)	90.6	74.4	90.3	74.6	C(7′/I)	77.3	74.1	74.5	77.3

N^6-*Benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]adenin-8-yl-(8 → 7′*-C)-N^6-*benzoyl-9-[6,7-dideoxy-2,3*-O-*isopropylidene-5*-O-*(triisopropylsilyl)-β*-D-allo-*hept-6-ynofuranosyl]adenine* (**27**). A soln. of **26** (400 mg, 0.32 mmol) in MeOH/AcOEt 1:1 (50 ml) was treated dropwise with a soln. of $AgNO_3$ (544 mg, 3.2 mmol) in H_2O/MeOH 1:1 (20 ml), stirred at 23° under exclusion of light for 6 h, treated with a soln. of KCN (520 mg, 8.0 mmol) in H_2O (2 ml), and stirred for 1.5 h. After evaporation, a soln. of the residue in AcOEt was washed with brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 3:2) gave **27** (370 mg, 98%). Yellow foam. R_f (AcOEt/hexane 2:1) 0.59. $[\alpha]_D^{25} = -3.0$ ($c = 0.7$,

CH_2Cl_2). UV (CH_2Cl_2): 312 (sh), 302 (sh), 284 (38000). IR (CH_2Cl_2): 3399*w*, 3300*w*, 2946*s*, 2868*m*, 2241*w*, 1712*s*, 1609*s*, 1458*s*, 1331*m*, 1238*m*, 1214*m*, 1097*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): see *Table 10*; additionally, 9.27, 9.07 (2 br. *s*, 2 NH); 8.00–7.98 (*m*, 2 arom. H); 7.96–7.94 (*m*, 2 arom. H); 7.59–7.51 (*m*, 2 arom. H); 7.50–7.45 (*m*, 4 arom. H); 2.30 (*d*, *J* = 2.1, H–C(7′/II)); 1.65, 1.61, 1.43, 1.42 (4*s*, 2 Me_2C); 1.18–1.08 (*m*, $(Me_2CH)_3$Si); 1.08–1.04 (*m*, $(Me_2CH)_3$Si). ^{13}C-NMR (125 MHz, $CDCl_3$): see *Table 11*; additionally, 164.6, 164.5 (2*s*, 2 C=O); 133.7, 133.6 (2*s*); 132.81, 132.80 (2*d*); 128.9 (2*d*); 128.8 (2*d*); 127.9 (2*d*); 127.8 (2*d*); 114.9, 114.1 (2*s*, 2 Me_2C); 27.2, 27.1, 25.4, 25.3 (4*q*, 2 Me_2C); 18.01, 18.00, 17.98, 17.97 (4*q*, 2 $(Me_2CH)_3$Si); 12.41, 12.36 (2*d*, 2 $(Me_2CH)_3$Si). HR-MALDI-MS (DHB): 1203.556 ($[M+Na]^+$, $C_{62}H_{80}N_{10}NaO_{10}Si_2^+$; calc. 1203.550).

*9-[6,7-Dideoxy-2,3-*O*-isopropylidene-5-*O*-(triisopropylsilyl)-7-*C*-(trimethylsilyl)-β-*D*-allo-hept-6-ynofuranosyl]adenin-8-yl-(8 → 7′-*C*)-9-[6,7-dideoxy-2,3-*O*-isopropylidene-5-*O*-(triisopropylsilyl)-β-*D*-allo-hept-6-ynofuranosyl]adenine* (**28**). a) *From* **9** *and* **12**. A soln. of **9** (200 mg, 0.29 mmol), **12** (123.7 mg, 0.25 mmol), $[Pd_2(dba)_3]$ (12 mg, 12.5 μmol), CuI (4.8 mg, 25 μmol), and P(fur)$_3$ (5.8 mg, 25 μmol) in degassed Et_3N/toluene 1:1 (3 ml) was stirred for 16 h at 23° and evaporated. FC (AcOEt/MeOH 1:0 → 10:1) gave **28** (220 mg, 83%).

b) *From* **26**. A soln. of **26** (153 mg, 0.12 mmol) in dry toluene (5 ml) was treated dropwise with a soln. of 8M $MeNH_2$ in MeOH (0.5 ml, 4.0 mmol), stirred for 5 h at 25°, diluted with AcOEt (10 ml), washed with sat. aq. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated. FC (15 g of silica gel; AcOEt/MeOH 1:0 → 10:1) gave **28** (84 mg, 66%). Yellow foam. R_f (AcOEt) 0.27. $[\alpha]_D^{25} = +57.0$ ($c = 0.1$, CH_2Cl_2). UV (CH_2Cl_2): 296 (16700), 264 (21700). IR (CH_2Cl_2): 3512*w*, 3402*m*, 3326*m*, 3199*w*, 2947*s*, 2867*m*, 2173*w*, 1632*s*, 1596*m*, 1468*m*, 1375*m*, 1328*m*, 1212*m*, 1098*s*, 993*m*, 851*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): see *Table 10*; additionally, 6.33 (br. *s*, 2 NH_2); 1.65, 1.56, 1.44, 1.35 (4*s*, 2 Me_2C); 1.30–1.15 (*m*, 2 $(Me_2CH)_3$Si); 0.06 (*s*, Me_3Si). ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 11*; additionally, 114.2, 113.6 (2*s*, 2 Me_2C); 27.1, 27.0, 25.5, 25.2 (4*q*, 2 Me_2C); 18.08, 18.05, 18.04 (6 C) (3*q*, 2 $(Me_2CH)_3$Si); 12.5, 12.4 (2*d*, 2 $(Me_2CH)_3$Si); −0.4 (*q*, Me_3Si). HR-MALDI-MS (DHB): 1067.536 ($[M+Na]^+$, $C_{51}H_{80}N_{10}NaO_8Si_3^+$; calc. 1067.537). Anal. calc. for $C_{51}H_{80}N_{10}O_8Si_3$ (1045.51): C 58.59, H 7.71, N 13.40; found: C 58.63, H 7.72, N 13.37.

*9-[6,7-Dideoxy-2,3-*O*-isopropylidene-5-*O*-(triisopropylsilyl)-β-*D*-allo-hept-6-ynofuranosyl]adenin-8-yl-(8 → 7′-*C*)-9-[6,7-dideoxy-2,3-*O*-isopropylidene-5-*O*-(triisopropylsilyl)-β-*D*-allo-hept-6-ynofuranosyl]adenine* (**29**). A soln. of **28** (170 mg, 0.16 mmol) in MeOH/AcOEt 1:1 (50 ml) was treated dropwise with a soln. of $AgNO_3$ (277 mg, 1.63 mmol) in H_2O/MeOH 1:1 (6 ml), stirred at 23° under exclusion of light for 3.5 h, treated with a soln. of KCN (222 mg, 3.42 mmol) in H_2O (2 ml), and stirred for 1 h. After evaporation, a soln. of the residue in AcOEt was washed with brine, dried (Na_2SO_4), and evaporated. FC (AcOEt/MeOH 1:0 → 10:1) gave **29** (137 mg, 86%). Yellow foam. R_f (AcOEt) 0.27. $[\alpha]_D^{25} = +92.1$ ($c = 1.0$, CH_2Cl_2). UV (CH_2Cl_2): 296 (17000), 264 (19000). IR (CH_2Cl_2): 3513*w*, 3401*m*, 3303*m*, 3194*w*, 2946*m*, 2868*m*, 1631*s*, 1595*m*, 1468*m*, 1375*m*, 1329*m*, 1212*m*, 1099*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): see *Table 10*; additionally, 6.33 (br. *s*, 2 NH_2); 2.31 (*d*, *J* = 2.1, H–C(7′/II)); 1.65, 1.58, 1.44, 1.36 (4*s*, 2 Me_2C); 1.30–1.15 (*m*, $(Me_2CH)_3$Si); 1.15–1.05 (*m*, $(Me_2CH)_3$Si). ^{13}C-NMR (100 MHz, $CDCl_3$): see *Table 11*; additionally, 114.2, 113.8 (2*s*, 2 Me_2C); 27.1, 27.0, 25.4, 25.2 (4*q*, 2 Me_2C); 18.0 (*q*, 2 $(Me_2CH)_3$Si); 12.44, 12.41 (2*d*, 2 $(Me_2CH)_3$Si). HR-MALDI-MS (DHB): 995.497 ($[M+Na]^+$, $C_{48}H_{72}N_{10}NaO_8Si_2^+$; calc. 995.497).

*2′,3′-*O*-Isopropylidene-5′-*O*-(triisopropylsilyl)uridin-6-yl-(6 → 7′-*C*)-1-(6,7-dideoxy-2,3-*O*-isopropylidene-5-*O*-(triisopropylsilyl)-β-*D*-allo-hept-6-ynofuranosyl)uracil-6-yl-(6 → 7′-*C*)-9-[6,7-dideoxy-2,3-*O*-isopropylidene-5-*O*-(triisopropylsilyl)-β-*D*-allo-hept-6-ynofuranosyl]adenin-8-yl-(8 → 7′-*C*)-9-[6,7-dideoxy-2,3-*O*-isopropylidene-5-*O*-(triisopropylsilyl)-β-*D*-allo-hept-6-ynofuranosyl]adenine* (**32**). A soln. of **29** (120 mg, 123 μmol), **30** [2] (190 mg, 185 μmol), $[Pd_2(dba)_3]$ (11.7 mg, 12.3 μmol), CuI (4.7 mg, 25 μmol), and P(fur)$_3$ (5.7 mg, 25 μmol) in degassed Et_3N/toluene 1:1 (25 ml) was stirred for 38 h at 23°, and evaporated. FC (AcOEt/MeOH 1:0 → 10:1) gave **32** (160 mg, 69%). Yellow foam. R_f (AcOEt) 0.24. $[\alpha]_D^{25} = +82.2$ ($c = 1.27$, CH_2Cl_2). IR (CH_2Cl_2): 3475*w*, 3310*w*, 3177*w*, 2946*m*, 2867*m*, 1720*s*, 1646*m*, 1602*m*, 1463*m*, 1432*m*, 1221*m*, 1079*s*, 886*s*. ^{1}H-NMR (500 MHz, $CDCl_3$/CD_3OD 9:1): see *Table 6*; additionally, 1.66, 1.63, 1.52, 1.51, 1.44, 1.41, 1.33, 1.32 (8*s*, 4 Me_2C); 1.26–1.02 (*m*, 4 $(Me_2CH)_3$Si). ^{13}C-NMR (125 MHz, $CDCl_3$/CD_3OD 9:1): see *Table 7*; additionally, 114.33, 114.30, 114.01, 113.60 (4*s*, 4 Me_2C); 27.35, 27.26, 27.18, 26.95, 25.33, 25.31, 25.27, 25.20 (8*q*, 4 Me_2C); 18.00, 17.99, 17.93, 17.90 (4*q*, 4 $(Me_2CH)_3$Si); 12.42, 12.39 (6 C), 12.01 (3*d*, 4 $(Me_2CH)_3$Si). MALDI-MS (DHB): 1895.934 ($[M+Na]^+$, $C_{92}H_{140}N_{14}NaO_{20}Si_4^+$; calc. 1895.934). Anal. calc. for $C_{92}H_{140}N_{14}O_{20}Si_4$ (1874.54): C 58.95, H 7.53, N 10.46; found: C 58.81, H 7.37, N 10.54.

REFERENCES

[1] S. Eppacher, N. Solladié, B. Bernet, A. Vasella, *Helv. Chim. Acta* **2000**, *83*, 1311.
[2] S. Eppacher, N. Solladié, A. Vasella, *Helv. Chim. Acta* **2004**, *87*, 2926.
[3] H. Gunji, A. Vasella, *Helv. Chim. Acta* **2000**, *83*, 1331.
[4] H. Gunji, A. Vasella, *Helv. Chim. Acta* **2000**, *83*, 2975.
[5] H. Gunji, A. Vasella, *Helv. Chim. Acta* **2000**, *83*, 3229.
[6] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440.
[7] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, 1975.
[8] R. Ranganathan, G. Jones, J. Moffatt, *J. Org. Chem.* **1974**, *39*, 290.
[9] S. Chladek, J. Smrt, *Collect. Czech. Chem. Commun.* **1964**, *29*, 214.
[10] A. Matsuda, H. Kosaki, Y. Saitoh, Y. Yoshimura, N. Minakawa, H. Nakata, *J. Med. Chem.* **1998**, *41*, 2676.
[11] M. Chérest, H. Felkin, N. Prudent, *Tetrahedron Lett.* **1968**, 2199.
[12] O. Eisenstein, J. M. Lefour, N. T. Anh, R. F. Hudson, *Tetrahedron* **1977**, *33*, 523.
[13] B. Bernet, A. Vasella, *Helv. Chim. Acta* **2000**, *83*, 995.
[14] L. H. Koole, H. De Boer, J. W. De Haan, C. A. G. Haasnoot, P. van Dael, H. M. Buck, *J. Chem. Soc.*, *Chem. Commun.* **1986**, 362.
[15] P. K. Bhardwaj, A. Vasella, *Helv. Chim. Acta* **2002**, *85*, 699.
[16] A. J. Matthews, P. K. Bhardwaj, A. Vasella, *Helv. Chim. Acta* **2004**, *87*, 2273.

Received September 20, 2004