168. Synthesis and Characterization of (5′-Deoxyadenosin-5′-yl)cobalamin (= 'Adenosylcobalamin') Analogues Mimicking the Transition-State Geometry of Coenzyme-B_{12}-Dependent Rearrangements

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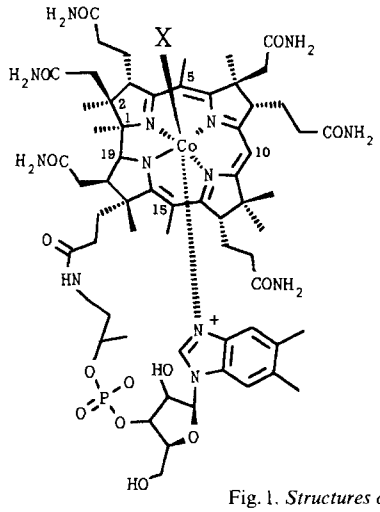
A convergent synthesis of the five novel analogues **1a–e** of (5′-deoxyadenosin-5′-yl)cobalamin (= 'adenosylcobalamin') is described. The analogues **1a–e** carry oligomethylene chains (C_3–C_7) inserted between the central Co-atom and the 5′-O-atom of the adenosine moiety and are thought to mimick the transition-state geometry in coenzyme-B_{12}-catalyzed rearrangement. All five analogues were characterized by NMR, UV, and FAB mass spectrometry.

Introduction. – It is generally accepted that the first step in coenzyme-B_{12}-dependent enzymic rearrangements is the homolytic cleavage of the Co–C bond of the coenzyme. Recently, a substrate synergysm was shown for methylmalonyl-CoA mutase, *i.e.* homolysis of the Co–C bond in the enzyme-coenzyme complex occurs only upon binding of the substrate [1]. On the basis of EPR measurements, it was postulated that in the activated complex, the paramagnetic centres, *i.e.* Co^{II} and the 5′-CH_2 group of adenosine, are at a distance of 6–12 Å [2–4]. Such a drastic change in the coenzyme geometry (and reactivity) must be coupled with a conformational change of the enzyme protein. We devised, therefore, coenzyme-B_{12} analogues mimicking the geometry of the activated complex. In these transition-state or intermediate analogues, the distance between the central Co-atom and the adenosine 5′-O-atom is lengthened by the insertion of a oligomethylene chain. Depending on the length of the chain, the novel analogues are expected to act as more or less strong inhibitors of the coenzyme-B_{12}-dependent reactions by binding to the reactive conformation of enzyme proteins.

Here we describe in detail the synthesis and properties of the (5′-deoxyadenosin-5′-yl)cobalamin (= 'adenosylcobalamin') analogues **1a–e** carrying inserts consisting of 3 to 7 CH_2 groups between the Co-atom and the 5′-O-atom of adenosine.

Results and Discussion. – *Synthesis of the Target [ω-(Adenosin-5′-O-yl)alkyl]cobalamin Derivatives* **1a–e**. On the basis of mechanistic and spectroscopic studies on coenzyme-B_{12}-dependent enzymes the transition-state analogues **1a–e** were devised in which the central Co-atom separated from the 5′-*O*-position of adenosine by insertion of shorter or longer CH_2 chains (C_3 to C_7, see *Fig. 1*). Molecular-mechanics calculations showed that the distance between the Co-centre and the 5′-CH_2 group of adenosine varies



d⁵Ado-Cbl: X = 5′-deoxyadenosin-5′-yl (Coenzyme B_{12})
HO-Cbl: X = OH (Vitamin B_{12b})

1a–e: X = $-(CH_2)_n-O$

(Transition-state analogues)

Fig. 1. *Structures of substituted cobalamins* (X-Cbl)

from 6.9 to 11.9 Å for the zig-zag chain conformers of **1a–e** consisting of 3–7 CH_2 groups, respectively (see *Fig. 2*). Distances in this range were postulated in the activated complex on the basis of EPR measurements [2–4].

To achieve the synthesis of the transition-state analogues a convergent strategy was devised (*Scheme*). Starting from adenosine (**2**) and α,ω-diols **5a–e** (n = 3–7), intermediates **8a–e** (n = 3–7) were prepared which carried an ω-tosyloxy group connected with the 5′-*O*-atom of adenosine through an oligomethylene chain of C_3 to C_7. Although all reaction steps were conventional, some of them required considerable experimentation for finding optimal conditions. The 2′,3′-*O*-isopropylideneadenosine [5] (**3**) and N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine [6–8] (**4**) are known compounds; nevertheless, they were prepared by substantially modified and simplified methods. The protected forms **6a–e** of the α,ω-diols were prepared in moderate yields (39–50%) as colourless oils by an improved method, in analogy with that described for **6d** [9] [10], but involving extractive separation. They showed appropriate ^{1}H-NMR characteristics. Subsequent tosylation of **6a–e** with tosyl chloride in pyridine was accompanied with a high degree of elimination. Thus, tosylation was carried out using only a slight excess of pyridine in dry CH_2Cl_2 as solvent providing the desired α-(tetrahydro-2*H*-pyranyloxy)-ω-tosyloxy derivatives **7a–e** in 65–81% yield which were characterized by ^{1}H- and ^{13}C-NMR spectroscopy. The key step was the attachment of the tosylates **7a–e** to the doubly protected adenosine **4**. This is essentially a simple S_N2 substitution, but the conditions and the quality of the reagents and solvents were crucial. The fully protected chain-lengthened adenosines **8a–e** were obtained in moderate to good yields (60–87%) and characterized by ^{1}H- and ^{13}C-NMR and, in one case (**8d**), by high-resolution mass spectrometry.

The deprotection, and further processing of the intermediates **8a–e**, *via* compounds **9a–e**, **10a–e**, **11a–e**, and **12a–e** is described in detail in the *Exper. Part.* All intermediates were obtained in acceptable yields (56–90%), and their ^{1}H- and ^{13}C-NMR data were consistent with their assumed structures. In the case of compound **10d**, the molecular weight was also confirmed by high-resolution mass spectrometry. The 5′-chain-lengthened adenosine tosylates **12a–e** were then coupled with vitamin B_{12s}. The latter was

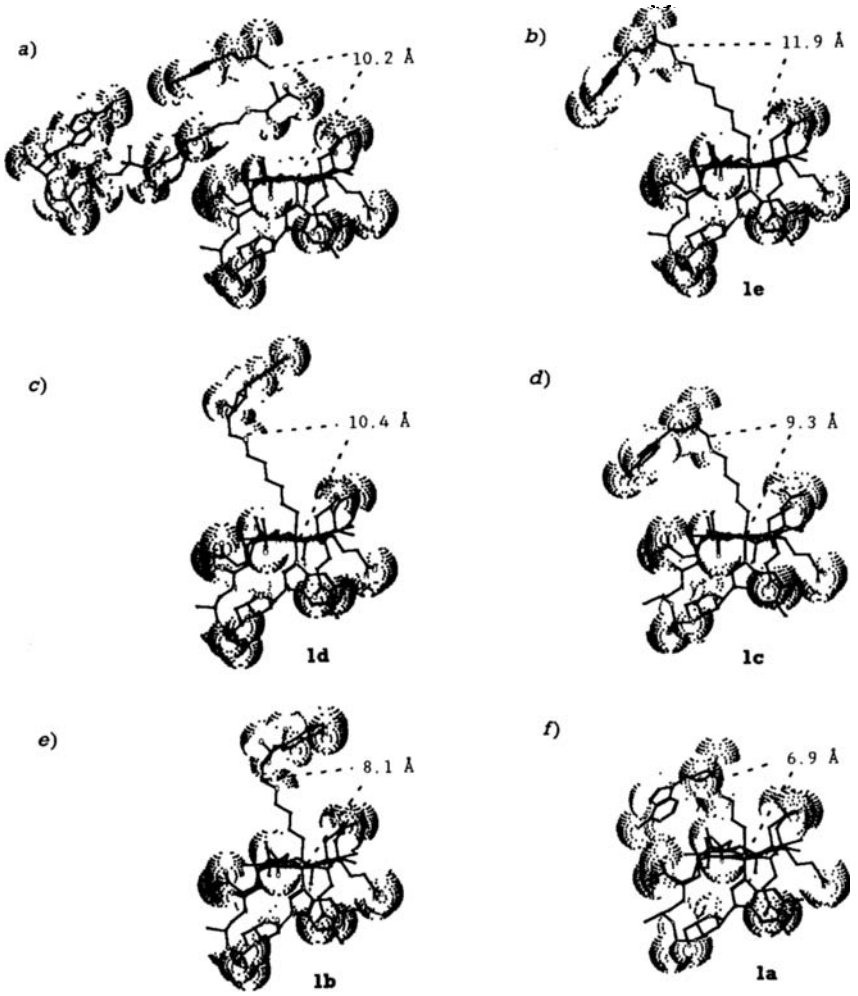
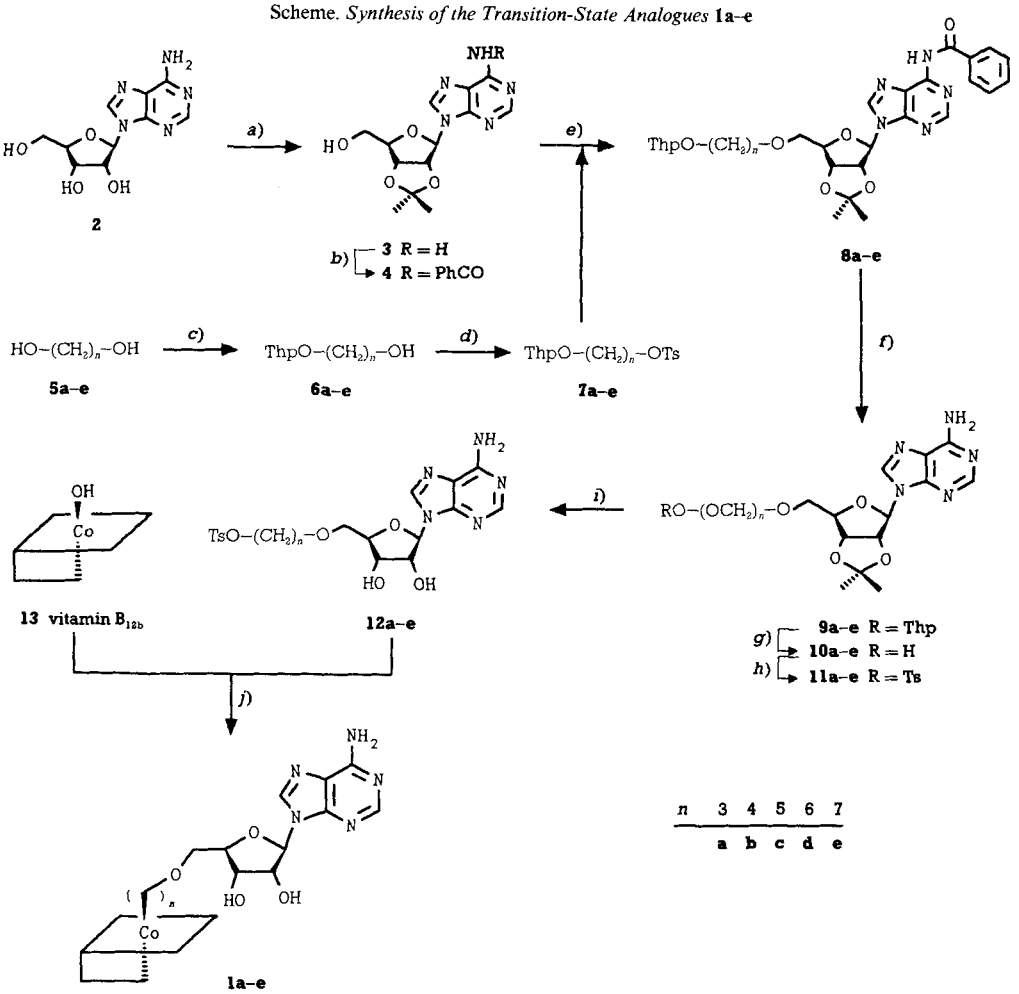


Fig. 2. *Calculated structures and Co–C(5′) distances:* a) *a hypothetical transition state for the methylmalonyl-CoA mutase and* b–f) *transition-state analogues* **1a–e**. Molecular-mechanics calculations were performed on an *IRIS-70-G* computer (*Silicon Graphics*) using PCMODEL 4.0 (*Serena*). X-Ray data of [3-(adenin-9-yl)propyl]cobalamin [17] were applied for building up of the starting structures.

prepared *in situ* from hydroxocobalamin (= vitamin B_{12b}; **13**) by reduction with $NaBH_4$ [11] [12]. In this reaction, pretreatment of the aq. $NaBH_4$ solution with a catalytic amount of a cobalt(II) salt significantly accelerated the rate of the vitamin-B_{12s} formation and increased the yield of the alkylation. After preparative reversed-phase HPLC, the [ω-(adenosin-5′-*O*-yl)alkyl]cobalamins **1a–e** were obtained in 65–80% yield. They were characterized by ^{1}H-NMR spectroscopy and, in the case of **1c**, by a COSY spectrum (see below). Fast-atom-bombardment mass spectroscopy (FAB-MS) confirmed not only the expected molecular weights but, owing to the corresponding fragmentation patterns, also the structures of the analogues **1a–e**. Further characterization and purity determination

Scheme. *Synthesis of the Transition-State Analogues* **1a–e**



a) Acetone, 70% $HClO_4$ soln., 4-Å molecular sieves. *b*) Pyridine, Me_3SiCl; 2. PhCOCl; 3. $MeOH/H_2O$, NaF, H^+. *c*) 3,4-Dihydro-2*H*-pyran, THF, cat. TsOH. *d*) TsCl, pyridine, CH_2Cl_2. *e*) 1. **4**, NaH, DMF; 2. **7**. *f*) Cat. NaOMe, MeOH. *g*) 2M HCl, MeOH. *h*) TsCl, pyridine, CH_2Cl_2. *i*) 10% HCl soln., MeOH, Δ. *j*) 1. **13**, $NaBH_4$, cat. $Co(OAc)_2$, H_2O, 2. **12a–e**, $MeOH/H_2O$.

was achieved by UV/VIS spectra and anal. HPLC. The former varied only slightly and were characteristic for alkylated cobalamins [11] [12]. The retention times (t_R) in the anal. reversed-phase HPLC were in agreement with the expected differences in polarity. A mixture containing vitamin B_{12b} (**13**), coenzyme B_{12}, and all analogues **1a–e** could be cleanly separated into the components with the expected retention times. The analogues **1a–e** are red microcrystalline solids, hygroscopic, and light- and heat-sensitive, but stable when stored in the dark. Aqueous solutions were also stable for days when kept in the dark at 0°.

^{1}H-NMR Analysis of the [ω-(Adenosin-5′-O-yl)alkyl]cobalamins **1a–e**. The 1D and 2D COSY ^{1}H-NMR spectra of **1a–e** (n = 3–7) were obtained at 500 MHz under conditions close to those used for the published results on coenzyme $\mathbf{B}_{12}$ (= (5′-deoxyadenosin-5′-yl)cobalamin) [13] [14]. The 1D spectra were measured and processed so as to allow precise integration, and for **1a**, **c**, **e** (n = 3, 5, 7), the results were accurate enough for the determination of the total number of nonexchangeable protons. During sample preparation, it was noted that the analogues **1a** and **1c** with n = 3 and 5, respectively, were much more soluble than the others, and spectroscopic differences between analogues with even or odd n were also found (see below). Our results and the literature data are summarized in *Tables 1* and *2*. The literature signal assignments provided a starting point for our

Table 1. *500-MHz ^{1}H-NMR Data for Coenzyme B_{12} and the Analogues Ado-$(CH_2)_n$-Cbl* **1a–e**, Part 1.[a])[b])

		Chem. shift rel. to TSP[c])					
		CoB_{12}	**1a** (n = 3)	**1b** (n = 4)	**1c** (n = 5)	**1d** (n = 6)	**1e** (n = 7)
Corrin Me							
Me(1^1)	br. *s*	0.47	0.480	0.486	0.504	0.502	0.503
Me(2^1)	*s*	1.36	1.364	1.356	1.375	1.376	1.377
Me(5^1)	*s*	1.45	1.439	2.482	2.473	2.474	2.487
Me(7^1)	*s*	1.70	1.773	1.776	1.767	1.760	1.752
Me(12^1)	*s*	0.87	0.841	0.861	0.767	0.813	0.801
Me′(12^1)	*s*	1.32	1.364	1.337	1.333	1.338	1.332
Me(15^1)	*s*	2.43	2.367	2.305	2.381	2.344	2.388
Me(17^1)	*s*	1.36	1.175	1.117	1.204	1.223	1.265
Corrin CH							
CH(3)	*d*	4.10	4.064	4.12	4.11	4.10	4.150
CH(8)	*dd*	3.29	3.399	3.342	3.396	3.39	3.43
CH(10)	*s*	5.93	5.938	5.893	5.931	5.956	5.953
CH(13)	*dd*	2.89	3.033	2.954	3.012	2.960	2.99
CH(18)	*dd*	2.65	2.64	2.61	2.63	2.64	2.66
CH(19)	*d*	4.24	4.044	4.07	4.080	4.078	4.073
Corrin side-chain CH_2 (a = low field, b = high field)							
CH_2(2^1)	*d* 2.41		2.35, 2.31	2.36, 2.32	2.39, 2.323	2.40, 2.34	2.41, 2.317
CH_2(3^1)	*m* 2.06, 1.96		2.08, 1.98	2.09, 2.00	2.04, 2.00	2.02, 1.99	2.05, 1.97
CH_2(3^2)	*ddd* 2.50		2.52, 2.45	2.53, 2.45	2.57, 2.51	2.54, 2.50	2.54, 2.48
CH_2(7^1)	*d* 2.19, 1.72		2.43, 1.910	2.47, 1.957	2.425, 1.901	2.48, 1.924	2.46, 1.874
CH_2(8^1)	*m* 1.75, 0.81		1.84, 0.83	1.83, 0.82	1.82, 0.82	1.80, 0.82	1.79, 0.84
CH_2(8^2)	*ddd* 1.73, 0.88		1.77, 0.936	1.77, 0.92	1.75, 0.95	1.77, 0.95	1.70, 0.92
CH_2(13^1)	*m* 2.22, 2.00		2.06, 2.01	2.02, 1.97	2.10, 2.00	2.10, 2.01	2.10, 2.00
CH_2(13^2)	*ddd* 2.54		2.61, 2.56	2.53, 2.48	2.53, 2.47	2.54, 2.46	2.54, 2.46
CH_2(17^1)	*ddd* 2.45, 2.06[d])		2.44, 2.05	2.40, 2.02	2.43, 2.05	2.42, 2.04	2.48, 2.04
CH_2(17^2)	*ddd* 1.78[d])		2.42, 1.74	2.35, 1.68	2.40, 1.74	2.40, 1.75	2.43, 1.76
CH_2(18^1)	*dd* 2.65		2.66, 2.61	2.61, 2.61	2.67, 2.62	2.65, 2.60	2.68, 2.64
1-Aminopropan-2-ol (Apr; a = low field, b = high field)							
CH_2(1)(Apr)	*dd* 3.54, 3.16		3.535, 3.189	3.54, 3.191	3.538, 3.203	3.531, 3.205	3.533, 3.188
H–C(2)(Apr)	*m* 4.33		4.353	4.358	4.359	4.36	4.353
Me(3)(Apr)	*d* 1.21		1.213	1.211	1.210	1.205	1.213
Total non-exchangeable H	81		87[e])	89	91[e])	93	95[e])

Table 1 (cont.)

		Chem. shift rel to TSP[c])					
		CoB_{12}	**1a** ($n = 3$)	**1b** ($n = 4$)	**1c** ($n = 5$)	**1d** ($n = 6$)	**1e** ($n = 7$)
(Dimethylbenzimidazolyl)ribose (Dbi-Rib)							
H–C(2)(Dbi)	*s*	6.95	6.929	6.929	6.937	6.932	6.939
H–C(4)(Dbi)	*s*	6.24	6.228	6.229	6.232	6.231	6.230
H–C(7)(Dbi)	*s*	7.16	7.169	7.157	7.162	7.159	7.159
Me–C(5), Me–C(6)(Dbi)	*s*	2.19	2.219	2.215	2.216	2.218	2.213
H–C(1′)(Rib)	*d*	6.26	6.262	6.246	6.254	6.247	6.257
H–C(2′)(Rib)	*dd*	4.23	4.223	4.219	4.227	4.222	4.228
H–C(3′)(Rib)	*ddd*	4.72	4.735	4.726	4.732	4.730	4.730
H–C(4′)(Rib)	*dt*	4.10	4.11	4.10	4.11	4.10	4.110
2 H–C(5′)(Rib)	*dd*	3.88, 3.74	3.900, 3.744	3.889, 3.736	3.898, 3.743	3.89, 3.74	3.895, 3.745
Adenosine (Ade-Rib)							
H–C(2)(Ade)	*s*	8.19	8.267	8.282	8.256	8.285	8.197
H–C(8)(Ade)	*s*	8.00	8.274	8.396	8.314	8.395	8.337
H–C(1′)(Rib)	*d*	5.56	6.002	6.061	6.050	6.098	6.070
H–C(2′)(Rib)	*t(dd)*	4.54	4.685	4.726	4.696	4.659	4.703
H–C(3′)(Rib)	*t(dd)*	3.74	4.245	4.255	4.361	4.360	4.409
H–C(4′)(Rib)	*ddd*	2.54	4.11	4.167	4.204	4.258	4.275
2 H–C(5′)(Rib)	*dd*	1.55, 0.57	3.535, 3.376	3.616, 3.54	3.683, 3.559	3.765, 3.658	3.745, 3.693
Alkyl-Co (Abr)							
CH_2(1″)–Co			1.281, 0.49	1.37, 0.47	1.35, 0.35	1.35, 0.50	1.33, 0.42
CH_2(2″)			0.321, −0.181	0.35, −0.46	0.20, −0.50	0.10, −0.49	0.10, −0.52
CH_2(3″)			3.134, 2.936	1.22, 1.04	0.93, 0.76	0.95, 0.79	0.87, 0.62
CH_2(4″)				3.266, 3.17	1.27	0.95	0.92, 0.86
CH_2(5″)					3.284, 3.22	1.31	0.96, 0.88
CH_2(6″)						3.42	1.34, 1.32
CH_2(7″)							3.42, 3.38

[a]) Data for coenzyme B_{12} (6.5 mg in 0.35 ml of 10 mM phosphate/D_2O, pD 7.0, 20°) are taken from [13]. This work: *ca.* 1–3 mg of analogue **1a–e** in 0.5 ml of 20 mM phosphate/D_2O, pH 7.4, 10°.

[b]) Abbreviations: Apr = 1-aminopropan-2-ol, Dbi = 5,6-dimethylbenzimidazole, Ade = adenine, Rib = ribose, Alk = oligomethylene bridge $(CH_2)_n$ numbered from the Co end. For **1a–e** all assignments were confirmed by observation of the appropriate ^3J, ^4J, or ^5J cross-peaks in the COSY 2D spectra of at least one analogue.

[c]) TSP = trimethylsilyl propionate; shift values with 3 decimal places were determined from 1D spectra (peak picking); values with 2 decimal places (±0.01 ppm) were estimated from the COSY spectrum.

[d]) The specific assignments for $CH_2(17^1)$ and $CH_2(17^2)$ from (= CH_2(55) and CH_2(56), resp. [13]) (based on CH correlations and long-range coupling of C(18) to $CH_2(17^1)$ at *ca.* 2.45 ppm) are probably in error (see text); for the base-off form of coenzyme B_{12} [14], the assignments at pH 2.1 are: $CH_2(17^1)$ at 2.51 and 1.85 and $CH_2(17^2)$ at 2.31 and 1.85 ppm.

[e]) Total proton count confirmed by precise integration.

analysis, and nearly all assignments were independently confirmed through the observation of long-range coupling effects (^4J and ^5J in the corrin and benzimidazole rings) in the COSY spectrum (*Footnote 2* in *Table 2*). Using a 60° mixing pulse, multiplet 'tilt' effects could be observed in many cases which allowed vicinal and geminal couplings to be distinguished. The only literature assignments with which we disagree concern the protons $CH_2(17^1)$ and $CH_2(17^2)$. *Bax* and coworkers [13] assigned protons H_a–$C(17^2)$ and H_b–$C(17^2)$ as being nearly equivalent at 1.78 ppm. However, by reason of the integration

Table 2. *J(H,H) and J(P,H) Coupling Constants for Coenzyme B_{12} and the Analogues* **1a–e**[a])

Coupling	Vicinal and geminal coupling constants in Hz (±0.1)					
	CoB_{12}	**1a** ($n = 3$)	**1b** ($n = 4$)	**1c** ($n = 5$)	**1d** ($n = 6$)	**1e** ($n = 7$)
$CH(3)/H_b–C(3^1)$		10.4				
$CH(8)/CH_2(8^1)$[b])		10.8, 4.9	11.5, 5.2	11.4, 5.1		
$CH(13)/CH_2(13^1)$[b])		9.2, 2.0	7.6, 3.5	9.6, 1.7		9
CH(18)/CH(19)	10.5	10.0		10.1		9.9
$H_a–C(2^1)/H_b–C(2^1)$		–13.3		–12.9		–12.8
$H_a–C(7^1)/H_b–C(7^1)$		–13.5	–13.7	–13.4	–13.6	–13.4
$H_a–C(1)/H_b–C(1)$(Apr)	–13.9	–14.4	–14.4	–14.4	–14.6	–14.4
$H_a–C(1)/H–C(2)$(Apr)	< 0.9	2.7				2.7
$H_b–C(1)/H–C(2)$(Apr)	14.4[c])	6.7	7.0	6.9	6.9	7.1
H–C(2)/Me(3)(Apr)	6.3	6.4	6.4		6.4	6.4
H–C(2)(Apr)/P	7.1	7.0				7.0
H–C(1′)/H–C(2′)(Dbi-*Rib*)	3.0	3.0	3.0	3.0	3.0	3.0
H–C(2′)/H–C(3′)(Dbi-*Rib*)	4.3	4.3	3.9	4.3	4.4	4
H–C(3′)/H–C(4′)(Dbi-*Rib*)	8.9	8.8		8.7		8.7
H–C(3′)(Dbi-*Rib*)/P	7.4	7.4		7.2	7.2	
H–C(4′)/H_a–C(5′)(Dbi-*Rib*)	2.7	2.4	2.4	2.4		
H–C(4′)/H_b–C(5′)(Dbi-*Rib*)	3.9	3.7	3.6	3.8		
$H_a–C(5')/H_b–C(5')$(Dbi-*Rib*)	–13.0	–13.0	–12.9	–13.0		–13.0
H–C(1′)/H–C(2′)(Ade-*Rib*)	3.3	4.7	5.1	4.5	4.3	4.3
H–C(2′)/H–C(3′)(Ade-*Rib*)	5.8	5.0	5.3	4.8	4.7	4.8
H–C(3′)/H–C(4′)(Ade-*Rib*)	6.7	5.2	5.1	5.3	5.2	5.2
H–C(4′)/H_a–C(5′)(Ade-*Rib*)	< 2.0		2.2	2.3	2.6	2.9
H–C(4′)/H_b–C(5′)(Ade-*Rib*)	9.2	6.3		5.3	4.9	4.9
$H_a–C(5')/H_b–C(5')$(Ade-*Rib*)	–9.2	–11.4	–11.2	–11.4	–11.5	–11.5

[a]) See *Footnotes* to *Table 1*; coenzyme B_{12} data is from [14]; in this work, coupling constants were estimated from peak splittings in the 1D spectra wherever possible; the presence of the following long-range couplings was confirmed by COSY cross-peaks for one or more analogues: H–C(4)/H–C(7)(Dbi); H–C(4)/Me–C(5)(Dbi); H–C(4)/Me–C(6)(Dbi); H–C(2)/H–C(4)(Dbi); H–C(2)(Dbi)/H–C(1′)(Rib); H–C(8)(Ade)/H–C(1′)(Rib); $Me(2^1)/H_b–C(2^1)$; $Me(7^1)/H_b–C(7^1)$; $CH(13)/Me(15^1)$; $CH(13)/Me'(12^1)$; $Me(12^1)/Me'(12^1)$; $CH(10)/Me'(12^1)$; $CH(19)/H_a–C(2^1)$.

[b]) Assignments of configuration were not made.

[c]) Probably the sum of two coupling constants.

we could clearly see that only 1 H appears near 1.75 ppm, 1 H near 2.05 ppm, and 2 H near 2.45 ppm. In addition, specific correlation peaks for vicinal and geminal couplings involving protons $CH_2(17^2)$ could be distinguished in the COSY spectrum of **1b**.

Considering the data in *Table 1*, we see that the chemical shifts for the (dimethylbenzimidazolyl)ribose moiety change little with chain length *n* and are very close to the values for the natural coenzyme B_{12}. In contrast, the chemical shifts for the adenosine moiety are quite sensitive to the length of the chain due to the expected dependence of anisotropic shielding effects on the distance between the adenosine group and the corrin ring. In coenzyme B_{12} the ribose C(5′) of adenosine is directly bound to Co, whereas in the analogues **1a–e**, it is bound to the ether O-atom of the chain unit, explaining the large difference in shifts of CH_2(5′)(Ade-*Rib*). Large shift differences are also observed for H–C(3′)(Ade-*Rib*) and H–C(4′)(Ade-*Rib*). When we consider the changes in chemical

shift for a given adenosine proton as n is increased, an interesting 'alternating' pattern emerges. *E.g.*, for H–C(8)(Ade) starting with $n = 3$, chemical-shift increments for increasing n are +0.12, −0.08, +0.08, −0.06. A similar pattern is found for H–C(2)(Ade) and H–C(1′)(Ade-*Rib*), while H–C(3′)(Ade-*Rib*) shows +0.01, +0.11, 0.00, +0.05 and H–C(4′)(Ade-*Rib*) a monotonic behaviour with increments of 0.057, 0.037, 0.054, 0.017. The 4 corrin protons CH(3), CH(8), CH(13), and CH(19) which point 'up' in the direction of the adenosine group show significant shift differences for the analogues **1a-e** *vs.* coenzyme B_{12}. The effect is largest for CH(19) which is close to H_a–C(5′)(Ade-*Rib*) (NOE effect) in coenzyme B_{12} [13]. The corrin Me groups Me(12^1)and Me(17^1) also have NOE's with Ade-*Rib* protons in coenzyme B_{12} [13] and show chain-length-dependent shift effects in the analogues. Interesting shift increment patterns are: for Me(12^1), +0.020, −0.094, +0.046, −0.012; for Me(17^1), −0.058, +0.087, +0.019, +0.042; for Me(15^1), −0.062, +0.076, −0.037, +0.044. Again an alternating pattern can be distinguished, and this suggests that the orientation of the adenosine group relative to the corrin ring alternates with increasing methylene chain length, as would be expected, if the chain adopts a relatively stable staggered conformation. It is noteworthy that the solubility of the analogues also shows an alternating pattern with increasing chain length. For the corrin side chains, significant shift perturbations are found only for protons $CH_2(7^1)$ (shown to have NOE's with $CH_2(5^1)$(Ade-*Rib*) coenzyme B_{12} [14]) and H_a–C(13^1) which neighbours the perturbed CH(13).

The coupling-constant data of *Table 2* indicate that the most significant differences between coenzyme B_{12} and the analogues **1a–e** occurs in the Ade-*Rib* moiety. The conformation of the ribose ring and the orientation of $CH_2(5')$ group are different in coenzyme B_{12} due to the steric restrictions on attaching the ribose $CH_2(5')$ directly to the Co-atom. These steric constraints are not present when the methylene chain is used for attachment.

Noteworthy are the differences between the chemical shifts of the geminal protons of each chain CH_2 group depending on their distance from the Co-atom. Thus, in **1c**, the diastereotopic protons of $CH_2(1'')$–Co exhibit a $\Delta\delta$ of *ca.* 1 ppm, and this is also valid for all other analogues. The CH_2 groups in the second ligand sphere of the Co-atom appear at highest field (0.2 and −0.50 ppm, resp.) and show still $\Delta\delta$ values of 0.6–0.7 ppm. The diastereotopy of the CH_2 protons in the third, fourth, fifth, sixth, and seventh ligand spheres is still reflected in the δ values, but is much less pronounced.

General Discussion and Conclusions. – The synthesis and use of artificial coenzyme-B_{12} analogues were reported [12] [15]. (Adeninylalkyl)cobalamins, first synthesized by *Hogencamp* [15], show the closest resemblance to the analogues **1a–e** described here and were found to be competitive inhibitors in respect to coenzyme B_{12} in the diol dehydratase reaction [15]. We expect from the novel analogues **1a–e** a stronger binding ability to coenzyme-B_{12}-dependent enzymes. In contrast to *Hogenkamp*'s analogues, the present ones contain a ribose moiety that should contribute to binding at the active sites and are closer to the structure of the putative transition state. Preliminary kinetic measurements with methylmalonyl-CoA mutase confirmed the inhibitory capabilities of the novel analogues.

It is noteworthy that analogues of adenosine that are extended at the 5′-site by an alkyl group were found in the naturally occurring hopane series [16]. The role of these compounds in the metabolism of the corresponding bacteria is unknown.

The novel [(adenosin-5′-*O*-yl)alkyl]cobalamins may also serve as ligands promoting the crystallization of coenzyme-B_{12}-dependent enzymes. Their detailed biochemical properties and inhibitory behaviour will be published elsewhere.

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Experimental Part

1. *General.* Adenosine, α,ω-alkanediols **5a–e**, 3,4-dihydro-2*H*-pyran, benzoyl chloride, toluene-4-sulfonyl chloride, vitamin B_{12b}, and H_2O-free DMF were products of *Fluka Chemicals*, Switzerland. All sovents were freshly dried and distilled prior to use. HPLC Separations: *Merck-Hitachi-L-6210* pump, *L-4000* UV detector, *D-2500* chromato-integrator, and *Macherey & Nagel* 250 × 4 mm *Nucleosil-10-C_{18}* anal. or *Macherey & Nagel* 250 mm × 1″ *Nucleosil-7-C_{18}* prep. columns. TLC: *Macherey & Nagel* silica gel_{254} plastic plates; solvent systems: *A*, hexane/acetone 2:1; *B*, hexane/acetone 1:1; *C*, CH_2Cl_2/acetone 2:1; *D*, CH_2Cl_2/MeOH 10:1; detection by UV light or heating after 3% ethanolic phosphomolybdic acid treatment. Prep. column chromatography (CC) of the intermediates: vacuum CC [18] or flash chromatography (FC) [19]. M.p.: *Büchi* capillary m.p. instrument; uncorrected. UV/VIS Spectra (λmax(ε) in nm): *Perkin-Elmer-Lambda-2* spectrometer; in 0.05M *Tris* buffer (pH 7.5). NMR Spectra: *Bruker-WM-250* or *AM-400* spectrometers for ^1H and *Bruker-WM-250* spectrometer at 62.90 MHz for ^{13}C and DEPT experiments; $CDCl_3$ solns. containing Me_4Si as internal standard, unless otherwise stated. Detailed ^1H-NMR studies of **1a–e**: at 10° and 500 MHz, *Bruker-AM-500* spectrometer; sample preparation in the dark, adding *ca.* 3 mg of each substance to 0.4 ml of 20 mM phosphate/D_2O buffer and adjusting the pH to 7.4 ± 0.05; **1a** and **1c** dissolved completely, **1b** and **1d**, **e** exhibited much lower solubility (max. 1 mg in 0.5 ml). 1D Spectra: presaturation (3 s) of the residual H_2O resonance, spectral width 7 KHz, 32 K time-domain points, 60° flip angle, 5.3 s repetition time, and 512 transients. Resolution enhancement *via Lorentz-Gauss* lineshape transformation (*Bruker* software) was performed before zero-filling to 64 K and *Fourier* transformation. Precise baseline correction, integration, and peak picking were performed using the *Bruker* software routines. COSY 2D Spectra (magnitude-mode) were obtained for each sample using the following conditions: low-power H_2O presaturation during the relaxation delay (2.5 s) and the evolution period, spectral width 4900 Hz, 2 K time-domain points in t_2, 512 FID's (t_1 points) with 24 transients each, mixing pulse flip angle 60°, initial fixed delay of 20 ms in evolution and detection periods to further suppress H_2O and to provide increased intensity for long-range correlations. The data were zero-filled in t_1 and, after sine-bell window multiplication, were transformed to give 1 *K* × 1 *K* magnitude-mode spectra. EI-MS (electron impact) and FAB-MS (fast-atom bombardment): *Finnigan-MAT-90* high-resolution instrument; EI at 70 eV; samples for FAB as 5% glycerol solns.

2. *2′,3′-*O*-Isopropylideneadenosine* (**3**). A) Adenosine (**2**; 11.0 g, 41.2 mmol), $TsOH \cdot H_2O$ (23.5 g, 124 mmol) and 4 Å molecular sieves (25 g) were mixed in 250 ml of dry acetone and stirred at r.t. After stirring for 2 h (clear soln. → solid precipitate), 12 ml (150 mmol) of pyridine were added (→ precipitate nearly dissolved). The mixture was poured on a 11-cm column (∅12.5 cm) filled with neutral Al_2O_3 and eluted with 1000 ml of dry MeOH. After evaporation of the product-containing fractions, the solid was recrystallized from acetone: 8.5 g (67%) of pure **3**. TLC: R_f 0.47 (*D*). M.p. 218–220° ([5]: 217.5–218° (H_2O)). ^1H-NMR: (250 MHz, (D_6)DMSO): 1.33 (*s*, Me); 1.54 (*s*, Me); 3.54 (*m*, $CH_2(5')$); 4.20 (*m*, CH(4′)); 4.96 (*dd*, *J*(2′,3′) = 6.1, *J*(3′,4′) = 2.5, CH(3′)); 5.23 (*t*, OH); 5.34 (*dd*, *J*(1′,2′) = 3.3, *J*(2′,3′) = 6.1, CH(2′)); 6.11 (*d*, *J*(1′,2′) = 3.3, CH(1′)); 7.34 (br. *s*, NH_2); 8.14 (*s*, CH(2)); 8.32 (*s*, CH(8)). ^1H-NMR (250 MHz, $CDCl_3$): 1.39 (*s*, Me); 1.64 (*s*, Me); 4.79 (*t*, 1 H, $CH_2(5')$); 4.97 (*d*, 1 H, $CH_2(5')$); 4.55 (*s*, CH(4′)); 5.10 (*d*, CH(3′)); 5.21 (*t*, CH(2′)); 5.85 (*d*, CH(1′)); 5.90 (br. *s*, NH_2); 6.60 (*d*, OH); 7.84 (*s*, 1 arom. H); 8.33 (*s*, 1 arom. H).

B) Adenosine (**2**; 5.2 g, 19.5 mmol), 70% $HClO_4$ soln. (1.69 ml, 19.5 mmol), and 4 Å molecular sieves (10 g) were mixed in 100 ml of dry acetone and stirred for 2 h at r.t. (→ precipitate). A soln. of NaOMe (1.2 g) in MeOH (10 ml) was then added in one portion, the resulting mixture heated to boiling and filtrated, the precipitate washed with 3 × 50 ml of hot acetone, and the combined filtrate slow by cooled to 0° 4.12 g (69%) of white crystalline **3**. Anal. data: as described above.

3. *N^6-Benzoyl-2′,3′-*O*-isopropylideneadenosine* (**4**). A) To a soln. of **3** (3.98 g, 13 mmol) in dry pyridine (15 ml), benzoyl chloride (5.48 g, 4.53 ml, 39 mmol) was added dropwise at r.t. over 15 min. After stirring at r.t. for 4 h, 150 ml of CH_2Cl_2 were added. The resulting soln. was washed with 10% HCl soln. (40 ml), sat. $NaHCO_3$ soln. (30 ml),

and brine (30 ml), dried ($MgSO_4$), and evaporated: 7.15 g (95%) of N^6,N^6,5′-O-*tribenzoyl-2′,3′-O-isopropylidene-adenosine*. Yellowish solid. This product was used for the next step without further purification. An anal. sample was obtained by vacuum CC (silica gel (63–200 μm), hexane/acetone 3:1). TLC: R_f 0.68 (*A*). ^{1}H-NMR: 1.40 (*s*, Me); 1.63 (*s*, Me); 4.47–4.67 (*m*, CH_2(5′), CH(4′)); 5.15 (*dd*, *J*(2′,3′) = 6.7, *J*(3′,4′) = 4.0, CH(3′)); 5.51 (*dd*, *J*(1′,2′) = 2.9, CH(2′)); 6.13 (*d*, CH(1′)); 7.24–7.57 (*m*, 3 H_p, 6 H_m); 7.82 (*m*, 4 H_o of $(Bz)_2N$); 7.93 (*m*, 2 H_o of BzO); 8.13 (*s*, CH(8)); 8.54 (*s*, CH(2)).

To a soln. of N^6,N^6,5′-*O*-tribenzoyl-2′,3′-*O*-isopropylideneadenosine (5.79 g, 10 mmol) in EtOH/H_2O 10:1 (60 ml), finely pulverized NaOH (0.6 g, 15 mmol) was added. The mixture was refluxed for 5 min, and after cooling, the soln. was concentrated to 1/10 volume, diluted with H_2O (30 ml), and extracted with CH_2Cl_2 (3 × 40 ml). The extract was washed with H_2O (20 ml) and brine (20 ml), dried ($MgSO_4$), and evaporated and the residue purified by vacuum CC (silica gel, CH_2Cl_2/acetone 3:1): 2.1 g (52%) of **4**. White solid. TLC: R_f 0.40 (*C*). M.p. 133–134° ([6]: 132–133° (EtOH); [7]: 151–153° (EtOH)). ^{1}H-NMR: 1.38 (*s*, Me); 1.63 (*s*, Me); 3.79 (*dd*, *J* = 2.2, 11, 1 H, CH_2(5′)); 3.96 (*dd*, *J* = 2.2, 11, 1 H, CH_2(5′)); 4.52 (br. *s*, CH(4′)); 5.07 (*dd*, *J*(3′,4′) = 3.3, *J*(2′,3′) = 5.8, CH(3′)); 5.22 (*dd*, *J*(1′,2′) = 5.3, CH(2′)); 5.99 (*d*, CH(1′)); 7.38–7.62 (*m*, H_p, 2 H_m); 8.02 (*m*, 2 H_o); 8.15 (*s*, CH(8)); 8.74 (*s*, CH(2)). ^{13}C-NMR: 25.23 (1 Me of Me_2C); 27.46 (1 Me of Me_2C); 62.70 (C(5′)); 81.52 (C(3′)); 83.46 (C(2′)); 86.48 (C(4′)); 93.52 (C(1′)); 114.16 (Me_2C); 124.07 (C(5)); 128.08 (C_o); 128.71 (C_m); 132.82 (C_p); 133.41 (C_{ipso}); 142.64 (C(8)); 150.15 (C(4)); 150.69 (C(6)); 152.23 (C(2)); 165.10 (Ph*C*O).

B) To an ice-cooled soln. of **3** (4.0 g, 13.0 mmol) and 4-(dimethylamino)pyridine (50 mg) in dry pyridine (20 ml), Me_3SiCl (1.76 g, 16.3 mmol, 2.05 ml) was added dropwise over 10 min and the resulting mixture further stirred at r.t. for 1 h. Benzoyl chloride (1.83 g, 13.0 mmol, 1.51 ml) was then added and the mixture cooled to 0° within 10 min. After further stirring at r.t. for 2 h, MeOH/H_2O 6:4 (30 ml), NaF (1.0 g), and Bu_4NCl (100 mg) were added, and stirring at r.t. was continued overnight. The mixture was then diluted with 40 ml of H_2O and the pH adjusted to 2.5 by addition of 5M HCl (*ca.* 40 ml). Extraction with CH_2Cl_2 (4 × 50 ml), washing of the combined extracts with 2M HCl (20 ml), sat. $NaHCO_3$ soln. (30 ml), and brine (30 ml), drying ($MgSO_4$), evaporating, and purifying the residue by vacuum CC as described in *Method A* yielded 3.61 g (68%) of **4**.

4. *ω-[(Tetrahydro-2*H*-pyran-2-yl)oxy]alkan-1-ols* **6a–e**. *General Procedure*. To a soln. of α,ω-alkanediol **5** (0.1 mol) and TsOH (0.1 g) in dry THF (200 ml), 3,4-dihydro-2*H*-pyran (0.1 mol) was added dropwise at 0°. The mixture was stirred at 0° for 1 h and at r.t. for a further h; then 1 ml of Et_3N was added and the solvent evaporated. The residue was taken up in H_2O (15 ml) and MeOH (75 ml) and the bis(tetrahydro-2*H*-pyranyloxy) derivative was removed by extraction with hexane (4–6 × 30 ml). The MeOH was evaporated and the residue diluted with Et_2O (80 ml) washed with H_2O (2–3 × 20 ml) and brine (20 ml), dried ($MgSO_4$), and evaporated: **6** (39–50%), practically homogeneous by TLC.

*3-[(Tetrahydro-2*H*-pyran-2-yl)oxy]propan-1-ol* (**6a**). According to the *General Procedure*, with propane-1,3-diol (**5a**; 19 g, 0.25 mol, 20 ml) and 3,4-dihydro-2*H*-pyran (8.6 g, 0.10 mol, 9.3 ml): 6.2 g (39%) of **6a**. Colourless oil. TLC: R_f 0.47 (*A*), R_f 0.51 (*B*). ^{1}H-NMR: 1.56 (*m*, 2 CH_2); 1.6–1.95 (*m*, 2 CH_2); 2.94 (*t*, OH); 3.45–3.65 (*m*, CH_2O); 3.7–3.96 (*m*, 2 CH_2O); 4.61 ('*t*', OCHO).

*4-[(Tetrahydro-2*H*-pyran-2-yl)oxy]butan-1-ol* (**6b**). According to the *General Procedure*, with butane-1,4-diol (**5b**; 19.7 g, 0.22 mol, 20 ml) and 3,4-dihydro-2*H*-pyran (8.6 g, 0.10 mol, 9.3 ml): 7.9 g (45%) of **6b**. Colourless oil. TLC: R_f 0.49 (*A*), R_f 0.53 (*B*). ^{1}H-NMR: 1.34–1.93 (*m*, 5 CH_2); 2.53 (br. *s*, OH); 3.36–4.0 (*m*, 3 CH_2O); 4.58 ('*t*', OCHO).

*5-[(Tetrahydro-2*H*-pyran-2-yl)oxy]pentan-1-ol* (**6c**). According to the *General Procedure*, with pentane-1,5-diol (**5c**; 10 g, 96 mmol, 10 ml) and 3,4-dihydro-2*H*-pyran (8.3 g, 99 mmol, 9.0 ml): 8.34 g (46%) of **6c**. Colourless oil. TLC: R_f 0.51 (*A*), R_f 0.55 (*B*). ^{1}H-NMR: 1.33–1.91 (*m*, 6 CH_2); 1.98 (br. *s*, OH); 3.32–3.94 (*m*, 3 CH_2O); 4.56 ('*t*', OCHO).

*6-[(Tetrahydro-2*H*-pyran-1-yl)oxy]hexan-1-ol* (**6d**). According to the *General Procedure*, with hexane-1,6-diol (**5d**; 15 g, 0.127 mol) and 3,4-dihydro-2*H*-pyran (10 g, 0.12 mol, 10.9 ml): 12.7 g (50%) of **6d**. Colourless oil. TLC: R_f 0.53 (*A*), R_f 0.57 (*B*). ^{1}H-NMR: 1.35 (*m*, 2 CH_2); 1.4–1.6 (*m*, 4 CH_2); 1.91 (br. *s*, OH); 3.3–3.5 (*m*, CH_2O); 3.58 (*m*, CH_2O); 3.63–3.88 (*m*, 2 CH_2O); 4.54 ('*t*', OCHO).

*7-[(Tetrahydro-2*H*-pyran-2-yl)oxy]heptan-1-ol* (**6e**). According to the *General Procedure*, with heptane-1,7-diol (**5b**; 4.78 g, 36 mmol, 5.0 ml) and 3,4-dihydro-2*H*-pyran (3.0 g, 36.2 mmol, 3.3 ml): 3.6 g (43%) of **6e**. Colourless oil. TLC: R_f 0.54 (*A*), R_f 0.59 (*B*). ^{1}H-NMR: 1.2–1.43 (*m*, 3 CH_2); 1.4–1.9 (*m*, 5 CH_2); 2.49 (br. *s*, OH); 3.26–3.90 (*m*, 3 CH_2O); 4.55 (*m*, OCHO).

5. *ω-[(Tetrahydro-2*H*-pyran-2-yl)oxy] alkyl Toluene-4-sulfonates* **7a–e**. *General Procedure*. To a soln. of **6** (20 mmol) and pyridine (40 mmol) in dry CH_2Cl_2 (40 ml), TsCl (4.76 g, 25 mmol) was added portionwise at r.t. and the resulting mixture stirred for 4 h at r.t. Following dilution with CH_2Cl_2 (60 ml), the soln. was washed with 5% HCl

soln. (20 ml), sat. $NaHCO_3$ soln. (30 ml), and brine (20 ml), dried ($MgSO_4$), and evaporated and the residue purified by vacuum CC (silica gel, hexane/acetone 3:1): **7** (65–81%).

*3-[(Tetrahydro-2*H*-pyran-2-yl)oxy]propyl Toluene-4-sulfonate* (**7a**). According to the *General Procedure*, with **6a** (5.5 g, 34 mmol): 8.3 g (78%) of **7a**. Slightly yellow oil. TLC: R_f 0.51 (*A*), R_f 0.75 (*B*). ^{1}H-NMR: 1.39–1.85 (*m*, 3 CH_2); 1.91 (*m*, CH_2); 2.43 (*s*, *Me*C_6H_4); 3.32–3.50 (*m*, CH_2O); 3.68–3.80 (*m*, CH_2O); 4.14 (*t*, J = 6.5, CH_2OTs); 4.52 ('*t*', OCHO); 7.33, 7.78 (A_2B_2, 4 arom. H). ^{13}C-NMR: 19.43 (C(4) of Thp); 21.57 (*Me*C_6H_4); 25.37 (C(5) of Thp); 29.24 (C(2)); 30.48 (C(3) of Thp); 62.15 (C(3)); 62.76 (C(1)); 67.75 (C(6) of Thp); 98.82 (C(2) of Thp); 127.87 (C_o); 129.85 (C_m); 133.04 (C_p); 144.76 (C_{ipso}).

*4-[(Tetrahydro-2*H*-pyran-2-yl)oxy]butyl Toluene-4-sulfonate* (**7b**). According to the *General Procedure*, with **6b** (7.8 g, 45 mmol): 9.6 g (65%) of **7b**. Colourless oil. TLC: R_f 0.54 (*A*), 0.77 (*B*). ^{1}H-NMR: 1.43–1.92 (*m*, 5 CH_2); 2.44 (*s*, *Me*C_6H_4); 3.25–3.52 (*m*, CH_2O); 3.61–3.87 (*m*, CH_2O); 4.04 (*m*, CH_2OTs); 4.53 (*m*, OCHO); 7.32, 7.77 (A_2B_2, 4 arom. H). ^{13}C-NMR: 19.57 (C(4) of Thp); 21.61 (*Me*C_6H_4); 25.42 (C(5) of Thp); 25.66 (C(3)); 26.00 (C(2)); 30.65 (C(3) of Thp); 62.30 (C(4) of Thp); 66.49 (C(6) of Thp); 70.53 (C(1)); 98.81 (C(2) of Thp); 127.86 (C_o); 129.83 (C_m); 133.14 (C_p); 144.70 (C_{ipso}).

*5-[(Tetrahydro-2*H*-pyran-2-yl)oxy]pentyl Toluene-4-sulfonate* (**7c**). According to the *General Procedure*, with **6c** (8.0 g, 43 mmol): 11.9 g (81%) of **7c**. Slightly yellow oil. TLC: R_f 0.57 (*A*), R_f 0.79 (*B*). ^{1}H-NMR: 1.34–1.90 (*m*, 6 CH_2); 2.43 (*s*, *Me*C_6H_4); 3.26–3.56 (*m*, CH_2O); 3.64–3.99 (*m*, CH_2O); 4.02 (*t*, J = 6.4, CH_2OTs); 4.53 ('*t*', OCHO); 7.34, 7.78 (A_2B_2, 4 arom. H). ^{13}C-NMR: 19.66 (C(4) of Thp); 21.61 (*Me*C_6H_4); 22.23 (C(3)); 25.45 (C(5) of Thp); 28.65 (C(4)); 29.03 (C(2)); 30.72 (C(3) of Thp); 62.36 (C(5)); 67.08 (C(6) of Thp); 70.53 (C(1)); 98.87 (C(2) of Thp); 127.84 (C_o); 129.83 (C_m); 133.15 (C_p); 144.69 (C_{ipso}).

*6-[(Tetrahydro-2*H*-pyran-2-yl)oxy]hexyl Toluene-4-sulfonate* (**7d**). According to the *General Procedure*, with **6d** (4.04 g, 20 mmol): 5.62 g (79%) of **7d**. Colourless oil. TLC: R_f 0.60 (*A*), R_f 0.80 (*B*). ^{1}H-NMR: 1.31 (*m*, 2 CH_2); 1.4–2.0 (*m*, 5 CH_2); 2.44 (*s*, *Me*C_6H_4); 3.25–3.51 (*m*, CH_2O); 3.62–3.93 (*m*, CH_2O); 4.02 (*t*, J = 6.4, CH_2OTs); 4.54 ('*t*', OCHO); 7.34, 7.78 (A_2B_2, 4 arom. H). ^{13}C-NMR: 19.71 (C(4) of Thp); 21.63 (*Me*C_6H_4); 24.77 (C(4)); 25.09 (C(3)); 25.21 (C(5) of Thp); 28.76 (C(5)); 29.48 (C(2)); 30.76 (C(3) of Thp); 62.43 (C(6)); 67.35 (C(6) of Thp); 70.60 (C(1)); 98.92 (C(2) of Thp); 127.87 (C_o); 129.82 (C_m); 133.17 (C_p); 144.68 (C_{ipso}).

*7-[(Tetrahydro-2*H*-pyran-2-yl)oxy]heptyl Toluene-4-sulfonate* (**7e**). According to the *General Procedure*, with **6e** (3.4 g, 15.7 mmol): 4.18 g (72%) of **7e**. Slightly yellow oil. TLC: R_f 0.62 (*A*), R_f 0.82 (*B*). ^{1}H-NMR: 1.27 (*m*, 3 CH_2); 1.4–2.0 (*m*, 5 CH_2); 2.44 (*s*, *Me*C_6H_4); 3.25–3.51 (*m*, CH_2O); 3.62–3.90 (*m*, CH_2O); 4.01 (*t*, J = 6.4, CH_2OTs); 4.55 (*m*, OCHO); 7.34, 7.78 (A_2B_2, 4 arom. H).

6. N^6-*Benzoyl-2',3'-*O*-isopropylidene-5'-*O*-[ω-(tetrahydro-2*H*-pyran-2-yl)alkyl]adenosines* **8a–e**. *General Procedure*. To a soln. of **4** (1.50 g, 3.65 mmol) in dry DMF (15 ml) under Ar, NaH (120 mg, 5 mmol; 70% content) was added. After stirring at 40° for 5 min, **7a** (4.38 mmol) in dry DMF (1 ml) was added and the resulting mixture further stirred at 50° for 2 h. After evaporation of the main bulk of DMF (4–5 Torr), the residue was purified by FC (silica gel, hexane/acetone 2.1): **8** (60–87%).

N^6-*Benzoyl-2',3'-*O*-isopropylidene-5'-*O*-[3-(tetrahydro-2*H*-pyran-2-yl)propyl]adenosine* (**8a**). According to the *General Procedure*, with **4** (0.95 g, 2.3 mmol) and **7a** (0.87 g, 2.76 mmol): 0.76 g (60%) of **8a**. Foamy solid. TLC: R_f 0.46 (*B*), R_f 0.70 (*D*). ^{1}H-NMR: 1.38–1.6 (*m*, 3 CH_2); 1.41 (*s*, Me); 1.6–1.9 (*m*, 2 CH_2); 1.66 (*s*, Me); 3.25–3.9 (*m*, 4 CH_2O); 4.49 (*m*, H–C(4')); 4.56 (*m*, OCHO); 4.97 (*m*, H–C(3')); 5.29 (*m*, H–C(2')); 6.27 (*m*, H–C(1')); 7.45–7.6 (*m*, 2 H_m, H_p); 8.02 (*m*, 2 H_o); 8.28 (*s*, H–C(8)); 8.81 (*s*, H–C(2)); 9.38 (br. *s*, NH). ^{13}C-NMR: 19.61, 19.65 (C(4) of Thp); 25.34 (1 Me of Me_2C); 25.38 (C(5) of Thp); 27.20 (1 Me of Me_2C); 29.72 (C(2")); 30.65 (C(3) of Thp); 62.37, 62.41 (C(3")); 64.02, 64.18 (C(1")); 68.81, 68.92 (C(6) of Thp); 71.07 (C(5')); 81.85 (C(3')); 85.18, 85.22 (C(2')); 86.22 (C(4')); 91.95, 91.99 (C(1')); 98.89, 98.95 (C(2) of Thp); 114.15 (Me_2C); 123.37 (C(5)); 127.93 (C_m); 128.77 (C_o); 132.70 (C_p); 133.70 (C_{ipso}); 141.69 (C(8)); 149.51 (C(4)); 151.41 (C(6)); 152.77 (C(2)); 167.76 (C=O).

N^6-*Benzoyl-2',3'-*O*-isopropylidene-5'-*O*-[4-(tetrahydro-2*H*-pyran-2-yl)butyl]adenosine* (**8b**). According to the *General Procedure*, with **4** (0.95 g, 2.3 mmol) and **7b** (0.91 g, 2.76 mmol): 0.95 g (73%) of **8b**. Viscous oil. TLC: R_f 0.49 (*B*), R_f 0.73 (*D*). ^{1}H-NMR: 1.4–2.0 (*m*, 5 CH_2); 1.42 (*s*, Me); 1.65 (*s*, Me); 3.25–3.9 (*m*, 4 CH_2O); 4.53 (*m*, H–C(4'), OCHO); 4.96 (*dd*, J(3',4') = 1.8, J(2',3') = 6.4, H–C(3')); 5.28 (*dd*, J(1',2') = 1.6, H–C(2')); 6.28 (*d*, H–C(1')); 7.4–7.6 (*m*, 2 H_m, H_p); 8.02 ('*d*', 2 H_o); 8.27 (*s*, H–C(8)); 8.79 (*s*, H–C(2)); 9.42 (br. *s*, NH). ^{13}C-NMR: 19.68 (C(4) of Thp); 25.36 (1 Me of Me_2C); 25.36 (C(5) of Thp); 26.24 (C(3")); 26.24 (C(2")); 27.21 (1 Me of Me_2C); 30.69 (C(3) of Thp); 62.42 (C(4")); 67.10 (C(6) of Thp); 70.96 (C(1")); 71.51 (C(5')); 81.84 (C(3')); 85.21 (C(2')); 86.23 (C(4')); 91.94 (C(1')); 98.92 (C(2) of Thp); 114.14 (Me_2C); 123.39 (C(5)); 127.95 (C_m); 128.75 (C_o); 128.75 (C_o); 132.68 (C_p); 133.68 (C_{ipso}); 141.69 (C(8)); 149.52 (C(4)); 151.41 (C(6)); 152.74 (C(2)); 164.79 (C=O).

N^6-*Benzoyl-2',3'-*O*-isopropylidene-5'-*O*-[5-(tetrahydro-2*H*-pyran-2-yl)pentyl]adenosine* (**8c**). According to the *General Procedure*, with **4** (1.23 g, 3.0 mmol) and **7c** (1.23 g, 3.6 mmol): 1.16 g (67%) of **8c**. Foamy solid. TLC:

R_f 0.52 (*B*), R_f 0.75 (*D*). ^{1}H-NMR: 1.2–1.4 (*m*, CH_2); 1.42 (*s*, Me); 1.4–1.9 (*m*, 5 CH_2); 1.66 (*s*, Me); 3.26–3.9 (*m*, 4 CH_2O); 4.55 (*m*, H–C(4′), OCHO); 4.96 (*dd*, *J*(3′,4′) = 1.7, *J*(2′,3′) = 6.6, H–C(3′)); 5.29 (*dd*, *J*(1′,2′) = 1.8, H–C(2′)); 6.28 (*d*, H–C(1′)); 7.4–7.6 (*m*, 2 H_m, H_p); 8.03 ('*d*', 2 H_o); 8.29 (*s*, H–C(8)); 8.82 (*s*, H–C(2)); 9.4 (br. *s*, NH).

N^6-*Benzoyl-2′,3′-*O-*isopropylidene-5′-*O-*[6-(tetrahydro-2*H*-pyran-2-yl)hexyl]adenosine* (**8d**). According to the *General Procedure*, with **4** (1.50, 3.65 mmol) and **7d** (1.56 g, 4.38 mmol): 1.89 g (87%) of **8d**. Viscous oil. TLC: R_f 0.56 (*B*), R_f 0.78 (*D*). ^{1}H-NMR: 1.15–1.4 (*m*, 2 CH_2); 1.42 (*s*, Me); 1.4–1.9 (*m*, 5 CH_2); 1.65 (*s*, Me); 3.28–3.9 (*m*, 4 CH_2O); 4.54 (*m*, H–C(4′), OCHO); 4.96 (*dd*, *J*(3′,4′) = 1.6, *J*(2′,3′) = 6.7, H–C(3′)); 5.28 (*dd*, *J*(1′,2′) = 2.1, H–C(2′)); 6.28 (*d*, H–C(1′)); 7.46–7.64 (*m*, 2 H_m, H_p); 8.04 ('*d*', 2 H_o); 8.30 (*s*, H–C(8)); 8.82 (*s*, H–C(2)); 9.4 (br. *s*, NH). ^{13}C-NMR: 19.69 (C(4) of Thp); 25.36 (1 Me of Me_2C); 25.44 (C(5) of Thp); 25.82 (C(4″)); 25.98 (C(3″)); 27.22 (1 Me of Me_2C); 29.27 (C(5″)); 29.61 (C(2″)); 30.73 (C(3) of Thp); 62.37 (C(6″)); 67.44 (C(6) of Thp); 70.95 (C(1″)); 71.71 (C(5′)); 81.86 (C(3′)); 85.27 (C(2′)); 86.22 (C(4′)); 91.95 (C(1′)); 98.86 (C(2) of Thp); 114.13 (Me_2C); 123.42 (C(5)); 127.95 (C_m); 128.76 (C_o); 132.67 (C_p); 133.69 (C_{ipso}); 141.69 (C(8)); 149.51 (C(4)); 151.45 (C(6)); 152.73 (C(2)); 167.78 (C=O). EI-MS: 595 (04, M^+), 510 (5), 406 (6), 322 (4), 306 (6), 268 (16), 240 (17), 218 (9), 164 (45), 136 (12), 105 (19), 85 (25), 84 (80), 83 (42), 69 (13), 56 (26), 55 (100), 54 (23), 41 (17), 39 (15). HR-MS: 595.2986 (M^+, $C_{31}H_{41}N_5O_7$, calc. 595.3006).

N^6-*Benzoyl-2′,3′-*O-*isopropylidene-5′-*O-*[7-(tetrahydro-2*H*-pyran-2-yl)heptyl]adenosine* (**8e**). According to the *General Procedure*, with **4** (1.23 g, 3.0 mmol) and **7e** (1.33 g, 3.6 mmol): 1.41 g (77%) of **8d**. Viscous oil. TLC: R_f 0.59 (*B*), R_f 0.80 (*D*). ^{1}H-NMR: 1.15–1.4 (*m*, 3 CH_2); 1.42 (*s*, Me); 1.4–1.92 (*m*, 5 CH_2); 1.65 (*s*, Me); 3.3–3.9 (*m*, 4 CH_2O); 4.54 (*m*, H–C(4′), OCHO); 4.96 (*dd*, *J*(3′,4′) = 1.6, *J*(2′,3′) = 6.6, H–C(3′)); 5.28 (*dd*, *J*(1′,2′) = 2.0, H–C(2′)); 6.29 (*d*, H–C(1′)); 7.45–7.6 (*m*, 2 H_m, H_p); 8.03 ('*d*', 2 H_o); 8.29 (*s*, H–C(8)); 8.81 (*s*, H–C(2)); 9.3 (br. *s*, NH).

7. *2′,3′-*O-*Isopropylidene-5′-*O-*[ω-(tetrahydro-2*H*-pyran-2-yl)alkyl]adenosine* **9a–e**. *General Procedure.* A soln. of (3.16 mmol) in MeOH (40 ml) containing NaOMe (0.03 g) was stirred overnight. The product was used in the next step without isolation. An anal. sample (2 ml) was removed and evaporated. The residue was diluted with CH_2Cl_2 (10 ml), the soln. washed with H_2O (2 ml) and brine (2 ml), dried, and evaporated, and the residue purified by FC (silica gel, hexane/acetone 1:1): light yellow viscous oil (85–90%; based on the removed proportion of reaction mixture).

*2′,3′-*O-*Isopropylidene-5′-*O-*[3-(tetrahydro-2*H*-pyran-2-yl)propyl]adenosine* (**9a**). According to the *General Procedure*, with **8a** (740 mg, 1.34 mmol). TLC: R_f 0.18 (*B*), R_f 0.46 (*D*). ^{1}H-NMR: 1.41 (*s*, Me); 1.5 (*m*, 2 CH_2); 1.64 (*s*, Me); 1.78 (*m*, 2 CH_2); 3.3–3.9 (*m*, 4 CH_2O); 4.50 (*m*, H–C(4′), OCHO); 4.98 (*m*, H–C(3′)); 5.30 (*m*, H–C(2′)); 6.18 (*d*, *J* = 1.5, H–C(1′)); 6.25 (br. *s*, NH_2); 8.06 (*s*, H–C(8)); 8.36 (*s*, H–C(2)). ^{13}C-NMR: 19.66 (C(4) of Thp); 25.40 (1 Me of Me_2C); 25.40 (C(5) of Thp); 27.21 (1 Me of Me_2C); 29.78 (C(2″)); 30.67 (C(3) of Thp); 62.38 (C(3″)); 64.15, 64.21 (C(1″)); 68.77, 68.82 (C(6) of Thp); 71.05 (C(5′)); 81.79 (C(3′)); 85.00 (C(2′)); 86.02 (C(4′)); 91.39, 91.44 (C(1′)); 98.93, 98.96 (C(2) of Thp); 114.11 (Me_2C); 119.94 (C(5)); 139.23 (C(8)); 149.47 (C(4)); 153.14 (C(2)); 155.63 (C(6)).

*2′,3′-*O-*Isopropylidene-5′-*O-*[4-(tetrahydro-2*H*-pyran-2-yl)butyl]adenosine* (**9b**). According to the *General Procedure*, with **8b** (900 mg, 1.59 mmol). TLC: R_f 0.23 (*B*), R_f 0.49 (*D*). ^{1}H-NMR: 1.4–1.9 (*m*, 5 CH_2); 1.41 (*s*, Me); 1.64 (*s*, Me); 3.3–3.9 (*m*, 4 CH_2O); 4.52 (*m*, H–C(4′)); 4.55 (*m*, OCHO); 4.97 (*dd*, *J*(3′,4′) = 1.7, *J*(2′,3′) = 6.2, H–C(3′)); 5.32 (*dd*, *J*(1′,2′) = 1.4, H–C(2′)); 6.29 (*d*, H–C(1′)); 6.39 (br. *s*, NH_2); 8.07 (*s*, H–C(8)); 8.37 (*s*, H–C(2)). ^{13}C-NMR: 19.66 (C(4) of Thp); 25.40 (1 Me of Me_2C); 25.43 (C(5) of Thp); 26.29 (C(2″)); 26.29 (C(3″)); 27.21 (1 Me of Me_2C); 30.71 (C(3) of Thp); 62.36 (C(4″)); 67.14 (C(6) of Thp); 70.95 (C(1″)); 71.43 (C(5′)); 81.82 (C(3′)); 85.00 (C(2′)); 86.04 (C(4′)); 91.48 (C(1′)); 98.85 (C(2) of Thp); 114.09 (Me_2C); 119.96 (C(5)); 139.22 (C(8)); 149.46 (C(4)); 153.14 (C(2)); 155.66 (C(6)).

*2′,3′-*O-*Isopropylidene-5′-*O-*[5-(tetrahydro-2*H*-pyran-2-yl)pentyl]adenosine* (**9c**). According to the *General Procedure*, with **8c** (1.14 g, 1.96 mmol). TLC: R_f 0.29 (*B*), R_f 0.51 (*D*). ^{1}H-NMR: 1.15–1.35 (*m*, CH_2); 1.41 (*s*, Me); 1.4–1.9 (*m*, 5 CH_2); 1.64 (*s*, Me); 3.3–3.95 (*m*, 4 CH_2O); 4.52 (*m*, H–C(4′)); 4.58 ('*t*', OCHO); 4.99 (*dd*, *J*(3′,4′) = 1.6, *J*(2′,3′) = 6.4, H–C(3′)); 5.30 (*dd*, *J*(1′,2′) = 1.5, H–C(2′)); 5.77 (br. *s*, NH_2); 6.20 (*d*, H–C(1′)); 8.05 (*s*, H–C(8)); 8.38 (*s*, H–C(2)). ^{13}C-NMR: 19.69 (C(4) of Thp); 22.70 (C(3″)); 25.39 (1 Me of Me_2C); 25.47 (C(5) of Thp); 27.22 (1 Me of Me_2C); 29.21 (C(4″)); 29.45 (C(2″)); 30.75 (C(3) of Thp); 62.40 (C(5″)); 67.36 (C(6) of Thp); 71.00 (C(1″)); 71.61 (C(5′)); 81.84 (C(3′)); 85.13 (C(2′)); 86.13 (C(4′)); 91.67 (C(1′)); 98.87 (C(2) of Thp); 114.09 (Me_2C); 119.98 (C(5)); 139.40 (C(8)); 149.39 (C(4)); 152.96 (C(2)); 155.24 (C(6)).

*2′,3′-*O-*Isopropylidene-5′-*O-*[6-(tetrahydro-2*H*-pyran-2-yl)hexyl]adenosine* (**9d**). According to the *General Procedure* with **8a** (1.80 g, 3.03 mmol). TLC: R_f 0.35 (*B*), R_f 0.54 (*D*). ^{1}H-NMR: 1.15–1.40 (*m*, 2 CH_2); 1.41 (*s*, Me); 1.4–1.9 (*m*, 5 CH_2); 1.64 (*s*, Me); 3.3–3.95 (*m*, 4 CH_2O); 4.52 (*m*, H–C(4′)); 4.57 ('*t*', OCHO); 4.98 (*dd*, *J*(3′,4′) = 1.6, *J*(2′,3′) = 6.3, H–C(3′)); 5.28 (*dd*, *J*(1′,2′) = 1.3, H–C(2′)); 5.8 (br. *s*, NH_2); 6.19 (*d*, H–C(1′)); 8.06

(*s*, H–C(8)); 8.36 (*s*, H–C(2)). ^{13}C-NMR: 19.71 (C(4) of Thp); 25.39 (1 Me of Me_2C); 25.47 (C(5) of Thp); 25.87 (C(4″)); 26.00 (C(3″)); 27.21 (1 Me of Me_2C); 29.33 (C(5″)); 29.61 (C(2″)); 30.76 (C(3) of Thp); 62.38 (C(6″)); 67.50 (C(6) of Thp); 70.96 (C(1″)); 71.68 (C(5′)); 81.84 (C(3′)); 85.11, (C(2′)); 86.10 (C(4′)); 91.58 (C(1′)); 98.85 (C(2) of Thp). 114.05 (Me_2C); 119.94 (C(5)); 139.22 (C(8)); 149.46 (C(4)); 153.11 (C(2)); 155.58 (C(6)). EI-MS: 491 (1.6, M^+), 476 (3), 462 (12), 306 (9), 218 (23), 164 (100), 136 (25), 85 (23), 55 (10), 43 (6). HR-MS: 491.2726 (M^+, $C_{24}H_{37}N_5O_6$, calc. 491.2744).

2′,3′-O-Isopropylidene-5′-O-[7-(tetrahydro-2H-pyran-2-yl)heptyl]adenosine (**9e**). According to the *General Procedure*, with **8a** (1.38 g, 2.27 mmol). TLC: R_f 0.39 (*B*), R_f 0.56 (*D*). ^{1}H-NMR: 1.15–1.40 (*m*, 3 CH_2); 1.42 (*s*, Me); 1.4–1.9 (*m*, 5 CH_2); 1.63 (*s*, Me); 3.3–3.95 (*m*, 4 CH_2O); 4.51 (*m*, H–C(4′)); 4.56 (‘*t*’, OCHO); 4.96 (*dd*, $J(3',4') = 1.7$, $J(2',3') = 6.4$, H–C(3′)); 5.29 (*dd*, $J(1',2') = 1.4$, H–C(2′)); 5.85 (br. *s*, NH_2); 6.19 (*d*, H–C(1′)); 8.06 (*s*, H–C(8)); 8.37 (*s*, H–C(2)). ^{13}C-NMR: 19.75 (C(4) of Thp); 25.40 (1 Me of Me_2C); 25.49 (C(5) of Thp); 25.94 (C(4″)); 26.13 (C(5″)); 27.22 (1 Me of Me_2C); 29.23 (C(3″)); 29.34 (C(6″)); 29.66 (C(2″)); 30.79 (C(3) of Thp); 62.44 (C(7″)); 67.62 (C(6) of Thp); 70.98 (C(1″)); 71.75 (C(5′)); 81.86 (C(3′)); 85.13 (C(2′)); 86.12 (C(4′)); 91.68 (C(1′)); 98.88 (C(2) of Thp); 114.06 (Me_2C); 120.01 (C(5)); 139.31 (C(8)); 149.32 (C(4)); 153.11 (C(2)); 155.39 (C(6)).

8. *5′-O-(ω-Hydroxyalkyl)-2′,3′-O-isopropylideneadenosines* **10a–e**. *General Procedure*. To a MeOH soln. of crude **9** (from 3.65 mmol of **8**, without isolation), 2M HCl (4 ml) was added and the mixture stirred at r.t. for 2 h. After neutralization (pH 7.5) by sat. $NaHCO_3$ soln., the MeOH, was evaporated. The residue was diluted with H_2O to 20 ml, extracted with CH_2Cl_2 (3 × 40 ml), the combined CH_2CO_2 soln. washed with brine (20 ml), dried ($MgSO_4$), and evaporated, and the remaining oil purified by FC (silica gel, CH_2Cl_2/MeOH 20:1): **10** (56–71%; based on **8**) as yellowish semi-solids.

5′-O-(3-Hydroxypropyl)-2′,3′-O-isopropylideneadenosine (**10a**). According to the *General Procedure:* 289 mg (56%; based on **8a**) of **10a**. TLC: R_f 0.28 (*D*). ^{1}H-NMR: 1.40 (*s*, Me); 1.64 (*s*, Me); 1.75 (*m*, CH_2); 3.4–3.75 (*m*, 3 CH_2O); 4.49 (*m*, H–C(4′)); 4.97 (*dd*, $J(2',3') = 6.0$, $J(3',4') = 2.1$, H–C(3′)); 5.29 (*dd*, $J(1',2') = 1.7$, H–C(2′)); 6.18 (*d*, H–C(1′)); 6.5 (br. *s*, NH_2); 8.09 (*s*, H–C(8)); 8.33 (*s*, H–C(2)). ^{13}C-NMR: 25.37 (1 Me of Me_2C); 27.17 (1 Me of Me_2C); 32.19 (C(2″)); 59.68 (C(3″)); 69.19 (C(1″)); 71.04 (C(5′)); 81.58 (C(3′)); 84.99 (C(2′)); 86.03 (C(4′)); 91.35 (C(1′)); 114.23 (Me_2C); 119.74 (C(5)); 139.29 (C(8)); 149.33 (C(4)); 153.24 (C(2)); 155.70 (C(6)).

5′-O-(4-Hydroxybutyl)-2′,3′-O-isopropylideneadenosine (**10b**). According to the *General Procedure*: 368 mg (61%; based on **8b**) of **10b**. TLC: R_f 0.31 (*D*). ^{1}H-NMR: 1.39 (*s*, Me); 1.5–1.8 (*m*, 2 CH_2); 1.66 (*s*, Me); 3.44 (*t*, $J = 6.5$, CH_2(1″)O); 3.5–3.75 (*m*, 2 CH_2O); 4.52 (*m*, H–C(4′)); 4.98 (*dd*, $J(2',3') = 6.3$, $J(3',4') = 2.3$, H–C(3′)); 5.22 (*dd*, $J(1',2') = 1.9$, H–C(2′)); 6.26 (*d*, H–C(1′)); 6.8 (br. *s*, NH_2); 8.20 (*s*, H–C(8)); 8.35 (*s*, H–C(2)). ^{13}C-NMR: 25.38 (1 Me of Me_2C); 26.23 (C(3″)); 27.19 (1 Me of Me_2C); 29.18 (C(2″)); 61.88 (C(4″)); 70.93 (C(1″)); 71.68 (C(5′)); 81.45 (C(3′)); 85.38 (C(2′)); 86.29 (C(4′)); 91.18 (C(1′)); 114.10 (Me_2C); 119.51 (C(5)); 139.10 (C(8)); 149.32 (C(4)); 153.27 (C(2)); 155.82 (C(6)).

5′-O-(5-Hydroxypentyl)-2′,3′-O-isopropylideneadenosine (**10c**). According to the *General Procedure*: 523 mg (68%; based on **8c**) of **10c**. TLC: R_f 0.36 (*D*). ^{1}H-NMR: 1.25–1.65 (*m*, 3 CH_2); 1.40 (*s*, Me); 1.65 (*s*, Me); 3.43 (*m*, CH_2(1″)O); 3.56 (*dd*, $J(4',5') = 3.5$, $J(5'a,5'b) = 10.0$, H_a–C(5′)); 3.63 (*t*, $J = 6.5$, CH_2(5″)); 3.73 (*dd*, $J(4',5') = 2.4$, $J(5'a,5'b) = 10.0$, H_b–C(5′)); 4.53 (*m*, H–C(4′)); 4.97 (*dd*, $J(2',3') = 6.4$, $J(3',4') = 2.2$, H–C(3′)); 5.22 (*dd*, $J(1',2') = 1.6$, H–C(2′)); 5.9 (br. *s*, NH_2); 6.27 (*d*, H–C(1′)); 8.19 (*s*, H–C(8)); 8.40 (*s*, H–C(2)). ^{13}C-NMR: 21.98 (C(3″)); 25.38 (1 Me of Me_2C); 27.19 (C(4″)); 29.22 (1 Me of Me_2C); 32.47 (C(2″)); 62.17 (C(5″)); 71.01 (C(1″)); 71.88 (C(5′)); 81.42 (C(3′)); 85.57 (C(2′)); 86.65 (C(4′)); 91.55 (C(1′)); 114.02 (Me_2C); 119.49 (C(5)); 139.38 (C(8)); 149.40 (C(4)); 153.29 (C(2)); 155.60 (C(6)).

5′-O-(6-Hydroxyhexyl)-2′,3′-O-isopropylideneadenosine (**10d**). According to the *General Procedure*: 871 mg (71%; based on **8d**) of **10d**. TLC: R_f 0.39 (*D*). ^{1}H-NMR: 1.10–1.85 (*m*, 4 CH_2); 1.39 (*s*, Me); 1.66 (*s*, Me); 3.40 (*m*, CH_2(1″)O); 3.52 (*dd*, $J(4',5'a) = 4.2$, $J(5'a,5'b) = 10.9$, H_a–C(5′)); 3.62 (*t*, $J = 6.5$, CH_2(6″)); 3.70 (*dd*, $J(4',5') = 2.4$, $J(5'a,5'b) = 10.9$, H_b–C(5′)); 4.51 (*m*, H–C(4′)); 4.94 (*dd*, $J(2',3') = 6.6$, $J(3',4') = 2.3$, H–C(3′)); 5.21 (*dd*, $J(1',2') = 1.6$, H–C(2′)); 6.23 (*d* + br. *s*, H–C(1′), NH_2); 8.15 (*s*, H–C(8)); 8.34 (*s*, H–C(2)). ^{13}C-NMR: 25.37 (1 Me of Me_2C); 25.39 (C(4″)); 25.75 (C(3″)); 27.19 (C(5″)); 29.50 (1 Me of Me_2C); 32.48 (C(2″)); 61.84 (C(6″)); 70.95 (C(1″)); 71.61 (C(5′)); 81.65 (C(3′)); 85.48 (C(2′)); 86.41 (C(4′)); 91.59 (C(1′)); 113.99 (Me_2C); 119.48 (C(5)); 138.99 (C(8)); 149.39 (C(4)); 153.30 (C(2)); 155.59 (C(6)). EI-MS: 407 (1.6, M^+), 306 (9), 218 (23), 164 (100), 136 (25), 85 (23), 55 (10), 43 (6). HR-MS: 407.2151 (M^+, $C_{19}H_{29}N_5O_5$, calc. 407.2151).

5′-O-(7-Hydroxyheptyl)-2′,3′-O-isopropylideneadenosine (**10e**). According to the *General Procedure*: 611 mg (64%; based on **8e**) of **10e**. TLC: R_f 0.42 (*D*). ^{1}H-NMR: 1.25–1.35 (*m*, 3 CH_2); 1.35–1.65 (*m*, 2 CH_2); 1.41 (*s* Me); 1.66 (*s*, Me); 3.43 (*m*, CH_2(1″)O); 3.56 (*dd*, $J(4',5'a) = 3.7$, $J(5'a,5'b) = 9.8$, H_a–C(5′)); 3.69 (*t*, $J = 6.5$, CH_2(7″)); 3.73 (*dd*, $J(4',5'b) = 1.8$, $J(5'a,5'b) = 9.8$, H_b–C(5′)); 4.53 (*m*, H–C(4′)); 4.97 (*dd*, $J(2',3') = 6.3$, $J(3',4') = 2.2$, H–C(3′)); 5.17 (*dd*, $J(1',2') = 1.6$, H–C(2′)); 6.37 (*d*, H–C(1′)); 6.4 (br. *s*, NH_2); 8.18 (*s*, H–C(8)); 8.37 (*s*,

H–C(2)). ^{13}C-NMR: 25.40 (1 Me of Me_2C); 25.56 (C(4″)); 26.06 (C(5″)); 29.16 (C(3″)); 29.29 (C(6″)); 29.41 (1 Me of Me_2C); 32.51 (C(2″)); 62.05 (C(7″)); 70.85 (C(1″)); 71.56 (C(5′)); 81.46 (C(3′)); 85.68 (C(2′)); 86.28 (C(4′)); 91.47 (C(1′)); 114.02 (Me_2C); 119.40 (C(5)); 138.71 (C(8)); 149.39 (C(4)); 153.34 (C(2)); 155.57 (C(6)).

9. *2′,3′-O-Isopropylidene-5′-O-{ω-[(tol-4-yl)sulfonyloxy]alkyl}adenosines* **11a–e**. *General Procedure*. To a soln. of **10** (2.07 mmol) and dry pyridine (3 mmol) in dry CH_2Cl_2 (5 ml), TsCl (0.47 g, 2.5 mmol) was added and the resulting mixture stirred at r.t. for 6 h. After diluting with CH_2Cl_2 to a volume of 50 ml, the soln. was washed with 5% HCl soln. (10 ml), sat. $NaHCO_3$ soln. (10 ml), and brine (10 ml), dried ($MgSO_4$), and evaporated and the residue purified by CC (silica gel, gradient CH_2Cl_2→CH_2Cl_2/acetone→acetone (600 ml)); **11** (58–70%) as colourless foamy semi-solid.

2′,3′-O-Isopropylidene-5′-O-{3-[(tol-4-yl)sulfonyloxy]propyl}adenosine (**11a**). According to the *General Procedure* with **10a** (250 mg, 0.65 mmol): **11a** (216 mg, 64%). TLC: R_f 0.46 (*D*). ^{1}H-NMR: 1.40 (*s*, Me); 1.63 (*s*, Me); 1.77 (*m*, CH_2); 2.44 (*s*, MeC_6H_4); 3.44 (*t*, J = 6.6, CH_2(1″)O); 3.45–3.65 (*m*, CH_2(5′)); 3.99 ('*t*', CH_2OTs); 4.42 (*m*, H–C(4′)); 4.94 (*dd*, J(2′,3′) = 6.5, J(3′,4′) = 2.7, H–C(3′)); 5.32 (*dd*, J(1′,2′) = 2.3, H–C(2′)); 6.10 (br. *s*, NH_2); 6.14 (*d*, H–C(1′)); 7.31, 7.73 (A_2B_2, 4 arom. H); 7.96 (*s*, H–C(8)); 8.34 (*s*, H–C(2)). ^{13}C-NMR: 21.67 (MeC_6H_4); 25.32 (1 Me of Me_2C); 27.16 (1 Me of Me_2C); 29.99 (C(2″)); 66.92 (C(3″)); 67.26 (C(1″)); 71.10 (C(5′)); 81.68 (C(3′)); 84.70 (C(2′)); 85.93 (C(4′)); 91.44 (C(1′)); 114.22 (Me_2C); 119.93 (C(5)); 127.85 (C_o); 129.86 (C_m); 132.89 (C_p); 139.35 (C(8)); 144.84 (C_{ipso}); 149.39 (C(4)); 153.13 (C(2)); 155.53 (C(6)).

2′,3′-O-Isopropylidene-5′-O-{4-[(tol-4-yl)sulfonyloxy]butyl}adenosine (**11b**). According to the *General Procedure*, with **10b** (330 mg, 0.87 mmol): **11b** (311 mg, 67%). TLC: R_f 0.49 (*D*). ^{1}H-NMR: 1.42 (*s*, Me); 1.4–1.8 (*m*, 2 CH_2); 1.65 (*s*, Me); 2.44 (*s*, MeC_6H_4); 3.37 (*t*, J = 6.5, CH_2(1″)O); 3.4–3.7 (*m*, CH_2(5′)); 3.97 (*t*, J = 6.6, CH_2OTs); 4.47 (*m*, H–C(4′)); 4.96 (*dd*, J(2′,3′) = 6.5, J(3′,4′) = 2.5, H–C(3′)); 5.33 (*dd*, J(1′,2′) = 2.1, H–C(2′)); 6.15 (br. *s* + *d*, H–C(1′), NH_2); 7.33, 7.77 (A_2B_2, 4 arom. H); 8.00 (*s*, H–C(8)); 8.34 (*s*, H–C(2)). ^{13}C-NMR: 21.62 (MeC_6H_4); 25.37 (1 Me of Me_2C); 25.41 (C(3″)); 25.61 (C(2″)); 27.18 (1 Me of Me_2C); 70.19 (C(4″)); 70.59 (C(1″)); 70.97 (C(5′)); 81.70 (C(3′)); 84.80 (C(2′)); 86.01 (C(4′)); 91.43 (C(1′)); 114.19 (Me_2C); 119.95 (C(5)); 127.86 (C_o); 129.84 (C_m); 132.99 (C_p); 139.31 (C(8)); 144.75 (C_{ipso}); 149.38 (C(4)); 153.09 (C(2)); 155.56 (C(6)).

2′,3′-O-Isopropylidene-5′-O-{5-[(tol-4-yl)sulfonyloxy]pentyl}adenosine (**11c**). According to the *General Procedure*, with **10c** (490 mg, 1.25 mmol): **11c** (479 mg, 70%). TLC: R_f 0.53 (*D*). ^{1}H-NMR: 1.27 (*m*, CH_2(3″)); 1.35–1.47 (*m*, CH_2(2″)); 1.41 (*s*, Me); 1.60 (*m*, CH_2(4″)); 1.66 (*s*, Me); 2.44 (*s*, MeC_6H_4); 3.34 (*t*, J = 6.2, CH_2(1″)); 3.56 (*dd*, J(4′,5′) = 4.4, J(5′a,5′b) = 10.1, H_a–C(5′)); 3.66 (*dd*, J(4′,5′b) = 2.8, J(5′a,5′b) = 10.1, H_b–C(5′)); 3.98 (*t*, J = 6.6, CH_2OTs); 4.50 (*m*, H–C(4′)); 4.97 (*dd*, J(2′,3′) = 6.3, J(3′,4′) = 2.4, H–C(3′)); 5.31 (*dd*, J(1′,2′) = 2.1, H–C(2′)); 6.19 (*d*, H–C(1′)); 6.22 (br. *s*, NH_2); 7.33, 7.78 (A_2B_2, 4 arom. H); 8.03 (*s*, H–C(8)); 8.36 (*s*, H–C(2)). ^{13}C-NMR: 21.62 (MeC_6H_4); 21.93 (C(3″)); 25.38 (1 Me of Me_2C); 27.19 (1 Me of Me_2C); 28.56 (C(4″)); 28.73 (C(2″)); 70.36 (C(5″)); 70.99 (C(1″)); 71.19 (C(5′)); 81.74 (C(3′)); 84.95 (C(2′)); 86.10 (C(4′)); 91.49 (C(1′)); 114.11 (Me_2C); 119.98 (C(5)); 127.86 (C_o); 129.81 (C_m); 133.06 (C_p); 139.27 (C(8)); 144.70 (C_{ipso}); 149.43 (C(4)); 153.12 (C(2)); 155.62 (C(6)).

2′,3′-O-Isopropylidene-5′-O-{6-[(tol-4-yl)sulfonyloxy]hexyl}adenosine (**11d**). According to the *General Procedure* with **10d** (842 mg, 2.07 mmol): **11d** (686 mg, 58%). TLC: R_f 0.56 (*D*). ^{1}H-NMR: 1.1–1.3 (*m*, 2 CH_2); 1.3–1.47 (*m*, CH_2(2″)); 1.41 (*s*, Me); 1.5–1.7 (*m*, CH_2(5″)); 1.66 (*s*, Me); 2.44 (*s*, MeC_6H_4); 3.37 (*t*, J = 6.4, CH_2(1″)); 3.57 (*dd*, J(4′,5′) = 4.5, J(5′a,5′b) = 10.6, H_a–C(5′)); 3.66 (*dd*, J(4′,5′) = 2.7, J(5′a,5′b) = 10.6, H_b–C(5′)); 3.99 (*t*, J = 6.5, CH_2OTs); 4.50 (*m*, H–C(4′)); 4.96 (*dd*, J(2′,3′) = 6.2, J(3′,4′) = 2.4, H–C(3′)); 5.31 (*dd*, J(1′,2′) = 2.3, H–C(2′)); 5.95 (br. *s*, NH_2); 6.19 (*d*, H–C(1′)); 7.34, 7.78 (A_2B_2, 4 arom. H); 8.04 (*s*, H–C(8)); 8.38 (*s*, H–C(2)). ^{13}C-NMR: 21.63 (MeC_6H_4); 25.14 (C(4″)); 25.37 (1 Me of Me_2C); 25.39 (C(3″)); 27.20 (1 Me of Me_2C); 28.70 (C(5″)); 29.17 (C(2″)); 70.52 (C(6″)); 70.99 (C(1″)); 71.42 (C(5′)); 81.80 (C(3′)); 85.09 (C(2′)); 86.17 (C(4′)); 91.67 (C(1′)); 114.09 (Me_2C); 120.00 (C(5)); 127.88 (C_o); 129.82 (C_m); 133.13 (C_p); 139.36 (C(8)); 144.67 (C_{ipso}); 149.46 (C(4)); 152.97 (C(2)); 155.35 (C(6)).

2′,3′-O-Isopropylidene-5′-O-{7-[(tol-4-yl)sulfonyloxy]heptyl}adenosine (**11e**). According to the *General Procedure*, with **10e** (570 mg, 1.35 mmol): **11e** (497 mg, 61%). TLC: R_f 0.58 (*D*). ^{1}H-NMR: 1.1–1.3 (*m*, 3 CH_2); 1.35–1.5 (*m* CH_2(2″)); 1.42 (*s*, Me); 1.5–1.7 (*m*, CH_2(6″)); 1.67 (*s*, Me); 2.44 (*s*, MeC_6H_4); 3.37 (*t*, J = 6.4, CH_2(1″)); 3.56 (*dd*, J(4′,5′) = 4.5, J(5′a,5′b) = 10.6, H_a–C(5′)); 3.67 (*dd*, J(4′,5′b) = 2.7, J(5′a,5′b) = 10.6, H_b–C(5′)); 3.99 (*t*, J = 6.5, CH_2OTs); 4.51 (*m*, H–C(4′)); 4.97 (*dd*, J(2′,3′) = 6.2, J(3′,4′) = 2.3, H–C(3′)); 5.31 (*dd*, J(1′,2′) = 2.2, H–C(2′)); 6.20 (*d*, H–C(1′)); 6.45 (br. *s*, NH_2); 7.33, 7.78 (A_2B_2, 4 arom. H); 8.07 (*s*, H–C(8)); 8.38 (*s*, H–C(2)). ^{13}C-NMR: 21.61 (MeC_6H_4); 25.18 (C(4″)); 25.38 (1 Me of Me_2C); 25.74 (C(5″)); 27.19 (1 Me of Me_2C); 28.67 (C(6″)); 28.67 (C(3″)); 29.21 (C(2″)); 70.64 (C(7″)); 70.95 (C(1″)); 71.54 (C(5′)); 81.83 (C(3′)); 85.07 (C(2′)); 86.08 (C(4′)); 91.59 (C(1′)); 114.01 (Me_2C); 119.92 (C(5)); 127.86 (C_o); 129.78 (C_m); 133.03 (C_p); 139.18 (C(8)); 144.65 (C_{ipso}); 149.40 (C(4)); 153.08 (C(2)); 155.71 (C(6)).

10. *5'-O-{ω-[(Tol-4-yl)sulfonyloxy]adenosines* **12a–e**. *General Procedure.* Derivative **11** (0.24 mmol) was added to a soln. of 10% HCl soln. (0.2 ml) in MeOH (2 ml) and the mixture heated under reflux for 5 min. The mixture was then cooled to r.t. and analyzed by TLC. This 5 min heating/TLC analysis procedure was repeated several times, until the conversion reached a desired degree. The soln. was then cooled and neutralized with sat. $NaHCO_3$ soln. and evaporated. The residue was diluted to 5 ml with H_2O and extracted with CH_2Cl_2/acetone 5:2 (3 × 4 ml), the combined extract washed with brine (2 ml), dried ($MgSO_4$), and evaporated, and the residue taken up in CH_2Cl_2 (0.5 ml) and purified by FC (silica-gel column (250 × 10 mm), gradient hexane/CH_2Cl_2/acetone 1:1:1→CH_2Cl_2/MeOH 10:1): 10–30% of recovered **11** and 25–46% of **12**.

5'-O-{3-[(Tol-4-yl)sulfonyloxy]propyl}adenosine (**12a**). According to the *General Procedure*, with **11a** (180 mg, 0.35 mmol): 76 mg (46%) of **12a**. Foamy white solid. TLC: R_f 0.32 (*D*). ^{1}H-NMR: 1.88 (*m*, $CH_2(2'')$); 2.38 (*s*, MeC_6H_4); 3.4–3.75 (*m*, $CH_2(1'')$, $CH_2(5')$); 4.08 ('*t*', CH_2OTs); 4.28 (*m*, H–C(4')); 4.41 (*m*, H–C(3')); 4.64 (*m*, H–C(2')); 6.08 (br. *s*, H–C(1')); 6.7 (br. *s*, NH_2); 7.24, 7.70 (A_2B_2, 4 arom. H); 8.06 (br. *s*, H–C(2) or H–C(8)); 8.08 (*s*, H–C(8) or H–C(2)). ^{13}C-NMR: 21.58 (MeC_6H_4); 29.11 (C(2'')); 67.14 (C(3'')); 67.64 (C(1'')); 70.53 (C(5')); 71.16 (C(3')); 75.32 (C(2')); 84.11 (C(4')); 88.86 (C(1')); 119.17 (C(5)); 127.83 (C_o); 129.91 (C_m); 132.71 (C_p); 138.95 (C(8)); 144.92 (C_{ipso}); 148.92 (C(4)); 152.54 (C(2)); 155.50 (C(6)).

5'-O-{4-[(Tol-4-yl)sulfonyloxy]butyl}adenosine (**12b**). According to the *General Procedure*, with **11b** (275 mg, 0.52 mmol): 102 mg (40%) of **12b**. Foamy white solid. TLC: R_f 0.34 (*D*). ^{1}H-NMR: 1.65 (*m*, 2 CH_2); 2.41 (*s*, MeC_6H_4); 3.4–3.55 (*m*, $CH_2(1'')$); 3.55–3.8 (*m*, $CH_2(5')$); 4.02 ('*t*', CH_2OTs); 4.32 (*m*, H–C(4')); 4.43 (*m*, H–C(3')); 4.61 (*m*, H–C(2')); 6.08 (*d*, *J* = 3.4, H–C(1')); 6.65 (br. *s*, NH_2); 7.28, 7.73 (A_2B_2, 4 arom. H); 8.12 (br. *s*, H–C(2) or H–C(8)); 8.17 (*s*, H–C(8) or H–C(2)). ^{13}C-NMR: 21.60 (MeC_6H_4); 25.56 (C(3'')); 25.74 (C(2'')); 70.20 (C(4'')); 70.38 (C(1'')); 70.68 (C(5')); 71.04 (C(3')); 75.50 (C(2')); 84.24 (C(4')); 89.27 (C(1')); 119.26 (C(5)); 127.83 (C_o); 129.88 (C_m); 132.86 (C_p); 138.95 (C(8)); 144.86 (C_{ipso}); 148.79 (C(4)); 152.44 (C(2)); 155.49 (C(6)).

5'-O-{5-[(Tol-4-yl)sulfonyloxy]pentyl}adenosine (**12c**). According to the *General Procedure*, with **11c** (440 mg, 0.80 mmol): 145 mg (36%) of **12c**. Foamy white solid. TLC: R_f 0.38 (*D*). ^{1}H-NMR: 1.30 (*m*, $CH_2(3'')$); 1.51 (*m*, $CH_2(2'')$); 1.69 (*m*, $CH_2(4'')$); 2.40 (*s*, MeC_6H_4); 3.4 (*m*, $CH_2(1'')$); 3.45–3.75 (*m*, $CH_2(5')$); 3.99 (*t*, *J* = 6.4, CH_2OTs); 4.31 (*m*, H–C(4')); 4.43 (*m*, H–C(3')); 4.62 (*m*, H–C(2')); 6.10 (*d*, *J* = 3.0, H–C(1')); 6.7 (br. *s*, NH_2); 7.27, 7.72 (A_2B_2, 4 arom. H); 8.07 (br. *s*, H–C(2) or H–C(8)); 8.18 (*s*, H–C(8) or H–C(2)). ^{13}C-NMR: 21.60 (MeC_6H_4); 21.99 (C(3'')); 28.52 (C(2'')); 28.83 (C(4'')); 70.26 (C(1'')); 70.55 (C(5'')); 71.21 (C(3')); 71.25 (C(5')); 75.57 (C(2')); 84.23 (C(4')); 89.02 (C(1')); 119.22 (C(5)); 127.82 (C_o); 129.85 (C_m); 132.91 (C_p); 139.05 (C(8)); 144.78 (C_{ipso}); 148.34 (C(4)); 152.45 (C(2)); 155.52 (C(6)).

5'-O-{6-[(Tol-4-yl)sulfonyloxy]hexyl}adenosine (**12d**). According to the *General Procedure*, with **11a** (643 mg, 1.14 mmol): 148 mg (25%) of **12d**. Foamy white solid. TLC: R_f 0.41 (*D*). ^{1}H-NMR: 1.23 (*m*, 2 CH_2); 1.47 ('*t*', CH_2); 1.55 ('*t*', CH_2); 2.41 (*s*, MeC_6H_4); 3.42 (*t*, *J* = 6.1, $CH_2(1'')$); 3.55–3.75 (*m*, $CH_2(5')$); 3.96 (*t*, *J* = 6.7, CH_2OTs); 4.34 (*m*, H–C(4')); 4.44 ('*t*', H–C(3')); 4.58 ('*t*', H–C(2')); 6.10 (*d*, *J*(1',2') = 4.0, H–C(1')); 6.6 (br. *s*, NH_2); 7.30, 7.75 (A_2B_2, 4 arom. H); 8.08 (br. *s*, H–C(8)); 8.18 (*s*, H–C(2)). ^{13}C-NMR: 21.61 (MeC_6H_4); 25.14 (C(4'')); 25.50 (C(3'')); 28.68 (C(5'')); 29.30 (C(2'')); 70.26 (C(6'')); 70.65 (C(1'')); 71.35 (C(3')); 71.50 (C(5')); 75.78 (C(2')); 84.47 (C(4')); 89.28 (C(1')); 119.31 (C(5)); 127.84 (C_o); 129.83 (C_m); 132.99 (C_p); 138.40 (C(8)); 144.74 (C_{ipso}); 148.85 (C(4)); 152.41 (C(2)); 155.49 (C(6)).

5'-O-{7-[(Tol-4-yl)sulfonyloxy]heptyl}adenosine (**12e**). According to the *General Procedure*, with **11e** (461 g, 0.80 mmol): 163 mg (38%) of **12e**. Foamy white solid. TLC: R_f 0.43 (*D*). ^{1}H-NMR: 1.2 (*m*, 3 CH_2); 1.55 (*m*, 2 CH_2); 2.41 (*s*, MeC_6H_4); 3.43 ('*t*', $CH_2(1'')$); 3.55–3.8 (*m*, $CH_2(5')$); 3.98 (*t*, *J* = 6.7, CH_2OTs); 4.33 (*m*, H–C(4')); 4.46 (*m*, H–C(3')); 4.64 (*m*, H–C(2')); 6.13 (*d*, *J*(1',2') = 2.7, H–C(1')); 6.7 (br. *s*, NH_2); 7.30, 7.75 (A_2B_2, 4 arom. H); 8.08 (br. *s*, H–C(8)); 8.20 (*s*, H–C(2)). ^{13}C-NMR: 21.60 (MeC_6H_4); 25.22 (C(4'')); 25.83 (C(3'')); 28.67 (C(5'')); 28.76 (C(2'')); 29.36 (C(6'')); 70.27 (C(7'')); 70.73 (C(1'')); 71.28 (C(3')); 71.65 (C(5')); 75.71 (C(2')); 84.36 (C(4')); 89.08 (C(1')); 119.23 (C(5)); 127.84 (C_o); 129.83 (C_m); 133.02 (C_p); 139.02 (C(8)); 144.72 (C_{ipso}); 148.85 (C(4)); 152.44 (C(2)); 155.55 (C(6)).

11. *[ω-(Adenosin-5'-O-yl)alkyl]cobalamins* (**1a–e**). *General Procedure* [11][12]. To a soln. of vitamin B_{12b} (**13**; 103 mg, 0.075 mmol) and 2 mg of cobalt(II) acetate in 4 ml of deoxygenated H_2O, a soln. of $NaBH_4$ (28 mg, 0.75 mmol) and cobalt(II) acetate (0.5 mg) in 1 ml of deoxygenated H_2O was added under Ar (cherry coloured→brown, then greenish gray) and the resulting soln. stirred at r.t. for 20 min. Then a soln. of **12** (0.10 mmol) in 2 ml of deoxygenated MeOH was added (greenish brown→deep red) and the mixture stirred at r.t. in the dark for 45 min. The soln. was then diluted with 5 ml of 1% AcOH/H_2O and extracted with 50% phenolic CH_2Cl_2 (3 × 2 ml). The combined phenolic extracts were diluted with Et_2O (50 ml), and the resulting precipitate was filtered off and washed with dry CH_2Cl_2 (2 × 30 ml). Redissolving (with 6 ml of MeOH) and repeating the precipitation with 50 ml of Et_2O yielded crude **1** (81–88%) as light and heat sensitive, hygroscopic, red solids. The crude products were purified by prep. HPLC (λ 280 nm, *v* = 6 ml/min; eluents: 0.01% CF_3COOH/H_2O (*A*) and MeOH (*B*), using a

linear gradient of 30–70% *B* in *A* within 25 min). Typically, a 50-mg portion of crude **1** in 30% MeOH/H_2O (5 ml) was applied onto the column in one run. The product-containing fractions were evaporated in the dark giving the desired pure **1** with 65–80% recovery (direct chromatographic workup of the reaction mixtures without the above described extractive treatment can also be done).

[3-(Adenosin-5'-O-yl)propyl]cobalamin (**1a**). According to the *General Procedure*, with **13** (103 mg, 0.075 mmol) and **12a** (48 mg, 0.10 mmol). Purification by HPLC yielded 98.1 mg (80%) of pure **1a**. Anal. HPLC (v = 0.8 ml/min, λ 280 nm): t_R 11.4 min (0–1 min, 30% *B* in *A*; 1–25 min, 30–70% *B* in *A*; *A*, 0.02M NaH_2PO_4; *B*, MeOH); t_R 12.6 min (0–1 min, 30% *B* in *A*; 1–25 min, 30–70% *B* in *A*; *A*, 0.01% (v/v) CF_3COOH/H_2O; *B* MeOH). UV/VIS: 262.4 (25300), 288.8 (13600), 316.8 (10800), 342.4 (9900), 518.0 (6700). FAB-MS: peak abundance around $[M + H]^+$ (rel. to the most intensive peak of this group): 1637 (6), 1638 (100), 1639 (88), 1640 (83), 1641 (18); fragmentation (the most intensive peaks from the relevant peak groups, normalized to the most intensive peak of the spectrum): 1638 (0.08), 1331 (1), 1070 (0.3), 972 (0.7), 277 (8), 225 (21), 185 (91), 93 (100).

[4-(Adenosin-5'-O-yl)butyl]cobalamin (**1b**). According to the *General Procedure*, with **13** (103 mg, 0.075 mmol) and **12b** (49 mg, 0.10 mmol). Purification by HPLC gave 85.4 mg (69%) of pure **1b**. Anal. HPLC (v = 0.8 ml/min, λ 280 nm): t_R 12.6 min (0–1 min, 30% *B* in *A*; 1–25 min, 30–70% *B* in *A*; *A*, 0.02M NaH_2PO_4; *B*, MeOH); t_R 13.3 min (0–1 min, 30% *B* in *A*; 1–25 min, 30–70% *B* in *A*; *A*, 0.01% (v/v) CF_3COOH/H_2O; *B*, MeOH). UV-VIS: 262.6 (26400), 289.0 (14100), 315.6 (11600), 345.0 (10700), 513.2 (7200). FAB-MS: peak abundance around $[M + H]^+$ (rel. to the most intensive peak of this group): 1651 (3), 1652 (95), 1653 (100), 1654 (47), 1655 (19), 1656 (3); fragmentation (most intensive peaks from the relevant peak groups normalized to the most intensive peak of the spectrum): 1653 (0.3), 1331 (2), 1070 (0.5), 972 (0.2), 369 (3), 277 (10), 185 (98), 93 (100).

[5-(Adenosin-5'-O-yl)pentyl]cobalamin (**1c**). According to the *General Procedure*, with **13** (138 mg, 0.10 mmol) and **12c** (66 mg, 0.13 mmol): 148 mg (88%) of crude **1c**. Purification of crude **1c** (120 mg) by HPLC resulted in 92.6 mg of pure **1c**. Anal. HPLC (v = 0.8 ml/min, λ 280 nm): t_R 13.3 min (0–1 min, 30% *B* in *A*; 1–25 min, 30–70% *B* in *A*; *A*, 0.02M NaH_2PO_4; *B*, MeOH); t_R 14.2 min (0–1 min, 30% *B* in *A*; 1–25 min, 30–70% *B* in *A*; *A*, 0.01% (v/v) CF_3COOH/H_2O; *B*, MeOH). UV/VIS: 262.8 (27400), 289.2 (14500), 314.8 (12400), 344.6 (10700), 511.2 (7500). FAB-MS: peak abundance around $[M + H]^+$ (rel. to the most intensive peak of this group): 1665 (7), 1666 (100), 1667 (87), 1668 (52), 1669 (19), 1670 (1); fragmentation (most intensive peaks from the relevant peak groups, normalized to the most intensive peak of the spectrum): 1666 (0.2), 1331 (2), 1070 (0.8), 972 (1.8), 338 (10), 185 (89), 93 (100).

[6-(Adenosin-5'-O-yl)hexyl]cobalamin (**1d**). According to the *General Procedure*, with **13** (103 mg, 0.075 mmol) and **12d** (52 mg, 0.10 mmol): 102.4 mg (81%) of crude **1d**. Purification of a 51-mg portion by HPLC resulting 40.9 mg of pure **1d**. Anal. HPLC (v = 0.8 ml/min, λ 280 nm): t_R 14.6 min (0–1 min, 30% *B* in *A*; 1–25 min, 30–70% *B* in *A*; *A*, 0.02M NaH_2PO_4; *B*, MeOH); t_R 15.3 min (0–1 min, 30% *B* in *A*; 1–25 min, 30–70% *B* in *A*; *A*, 0.01% (v/v) CF_3COOH/H_2O; *B*, MeOH). UV/VIS: 262.8 (26800), 289.2 (14200), 316.4 (12000), 345.4 (10600), 512.2 (7400). FAB-MS: peak abundance around $[M + H]^+$ (rel. to the most intensive peak of this group): 1680 (85), 1681 (100), 1682 (30), 1683 (2); fragmentation (most intensive peaks from the relevant peak groups, normalized to the most intensive peak of the spectrum): 1681 (12), 1331 (100), 1070 (31), 972 (28), 352 (56), 185 (54), 147 (58), 136 (83), 93 (59).

[7-(Adenosin-5'-O-yl)heptyl]cobalamin (**1e**). According to the *General Procedure*, with **13** (138 mg, 0.10 mmol) and **12e** (70 mg, 0.13 mmol): 137.2 mg (81%) of crude **1e**. Purification of a 35-mg portion by HPLC resulted in 22.6 mg of pure **1e**. Anal. HPLC (v = 0.8 ml/min, λ 280 nm): t_R 15.8 min (0–1 min, 30% *B* in *A*; 1–25 min, 30–70% *B* in *A*; *A*, 0.02M NaH_2PO_4; MeOH); t_R 16.5 min (0–1 min, 30% *B* in *A*; 1–25 min, 30–70% *B* in *A*; *A*, 0.01% (v/v) CF_3COOH/H_2O; *B*, MeOH). UV/VIS: 262.6 (28900), 289.2 (15400), 314.8 (13300), 344.8 (11300), 512.0 (8000). FAB-MS: peak abundance around $[M + H]^+$ (rel. to the most intensive peak of this group): 1693 (26), 1694 (84), 1695 (100), 1696 (8), fragmentation (most intensive peaks from the relevant peak groups, normalized to the most intensive peak of the spectrum): 1695 (0.3), 1331 (2.5), 1070 (1), 972 (3.6), 366 (6), 225 (25), 133 (100), 93 (18).

REFERENCES

[1] Y. Zhao, P. Such, J. Rétey, *Angew. Chem.* **1992,** *104,* 212; *ibid. Int. Ed.* **1992,** *31,* 215.
[2] G. R. Buettner, R. E. Coffmann, *Biochim. Biophys. Acta* **1977,** *480,* 495.
[3] J. F. Boas, P. R. Hicks, J. R. Pilbrow, *J. Chem. Soc., Faraday Trans. 2* **1978,** *74,* 417.
[4] B. M. Babior, T. H. Moos, W. H. Orme-Johnson, H. Beinert, *J. Biol. Chem.* **1974,** *249,* 4537.
[5] A. Hampton, *J. Chem. Soc.* **1961,** *83,* 3640.
[6] S. Chladek, J. Smrt, *Collect. Czech. Chem. Commun.* **1964,** *29,* 214.
[7] R. S. Ranganathan, G. H. Jones, J. G. Moffat, *J. Org. Chem.* **1964,** *39,* 290.
[8] H. R. Kriecheldorf, M. J. Fehrle, *Makromol. Chem.* **1980,** *181,* 2571.
[9] S. Sakane, K. Maruoka, H. Yamamoto, *Tetrahedron* **1986,** *42,* 2203.
[10] A. Katoh, T. Lu, B. Devadas, S. P. Adams, J. I. Gordon, G. W. Gokel, *J. Org. Chem.* **1991,** *56,* 731.
[11] D. Dolphin, *Methods Enzymol.* **1971,** *18c,* 34.
[12] H. P. C. Hogenkamp, W. H. Pailes, C. Brownson, *Methods Enzymol.* **1971,** *18c,* 57.
[13] M. F. Summers, L. G. Marzilli, A. Bax, *J. Am. Chem. Soc.* **1986,** *108,* 4285.
[14] A. Bax, L. G. Marzilli, M. F. Summers, *J. Am. Chem. Soc.* **1987,** *109,* 566.
[15] T. Toraya, K. Ushio, S. Fukui, H. P. C. Hogenkamp, *J. Biol. Chem.* **1977,** *252,* 963.
[16] G. Flesch, M. Rohmer, *Eur. J. Biochem.* **1988,** *175,* 405.
[17] T. G. Pagnano, L. G. Marzilli, M. M. Flocco, C. Tsai, H. L. Carell, J. P. Glusker, *J. Am. Chem. Soc.* **1991,** *113,* 531.
[18] L. Poppe, L. Novák, *Magy. Kém. Lapja* **1985,** *40,* 366.
[19] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978,** *43,* 2923.